March 11, 2019
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 #19 to EAY131-K1, *Phase 2 Study of JNJ-42756493 (Erdafitinib) in Patients with Tumors with FGFR Amplifications.*

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 Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

This addendum is in response to Dr. S. Percy Ivy February 22, 2019 Request for Rapid Amendment for Erdafitnib (JNJ-42756493).

The following revisions to EAY131-K1 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	3.3	Updated the Erdafitnib CAEPR list with version 2.2, January 04, 2019.

The following revisions to EAY131-K1 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date.
2.	What possible risks can I expect from taking part in this study?	Updated the possible risks language and the Erdafitnib risk list with version 2.2 January 04, 2019.

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

We request review and approval of this addendum to EAY131-K1 so ECOG-ACRIN may activate it promptly.

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

Thank you.

Sincerely,

Pamela Cogliano

Senior Director, Protocol Development

Enclosure

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

EAY131-K1

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol K1: Phase 2 Study of JNJ-42756493 (Erdafitinib) in Patients with Tumors with FGFR Amplifications

JNJ-42756493 (ERDAFITINIB) TREATMENT SUBPROTOCOL CHAIR:	Alain Mita, MD
JNJ-42756493 (ERDAFITINIB) TREATMENT SUBPROTOCOL CO-CHAIR:	Ingrid Mayer, MD
JNJ-42756493 (ERDAFITINIB) TRANSLATIONAL CHAIR:	Heather Cheng, MD, PhD

Version Date: March 11, 2019

NOTE: This subprotocol (EAY131-K1) should be used in conjunction with the MATCH Master Protocol (EAY131).

SUBPROTOCOL ACTIVATION DATE

Incorporated in Addendum #13
Addendum #16
Addendum #19

Agent	IND#	NSC#	Supply
JNJ-42756493 (Erdafitinib)	IND Sponsor: DCTD, NCI IND#[redacted]	781558	NCI Supplied

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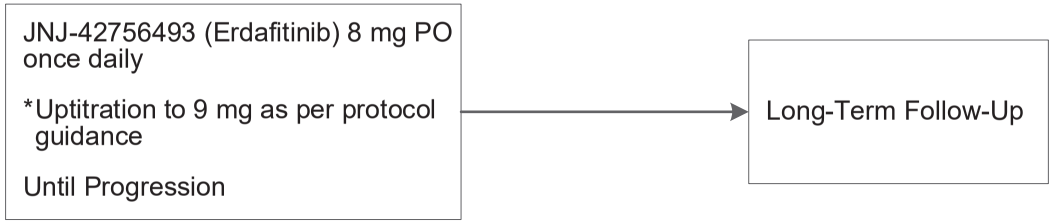
Schema



Cycle = 28 days
Accrual Goal: 35
*Refer to Section 3.1

1. Introduction

1.1 JNJ-42756493 (Erdafitinib)

1.1.1 The FGFR Signaling in Malignancy

The fibroblast growth factor receptors (FGFR) are tyrosine kinases that are present in many types of endothelial and tumor cells and are shown to play an important role in tumor cell growth, survival, and migration as well as in maintaining tumor angiogenesis. Over-expression of FGFRs, or inappropriate activation through point mutation, chromosomal translocation, or aberrant splicing, has been implicated in many forms of human malignancies. These FGFR abnormalities have been associated with neoplastic progression in multiple cancer types, including breast, lung, prostate, endometrial, gastric, and urothelial carcinoma. Therefore, targeting FGFRs represents an attractive strategy for the development of cancer treatment options by simultaneously inhibiting tumor cell growth, survival, and migration, as well as tumor angiogenesis. Four different FGFRs have been identified: FGFR1, FGFR2, FGFR3, and FGFR4. Fibroblast growth factor receptor signaling is activated as a result of being bound by fibroblast growth factors (FGFs), their natural ligands. The binding of FGF to FGFR results in receptor dimerization and subsequent activation of downstream signaling pathways. Activated FGFR stimulates tyrosine phosphorylation and activation of a number of signaling molecules including FGFR substrate 2 (FRS2). The phosphorylation of FRS2 leads to activation of the Grb2/Sos1 complex and subsequent activation of the mitogen-activated protein kinase pathway. This signaling pathway contributes to FGFR-mediated cell proliferation and migration. The activation of another FRS2 downstream pathway, phosphoinositide 3-kinase pathway, is involved in cell motility and survival. The FGF/FGFR signaling pathway has unequivocally been demonstrated to be important for many biological processes critical for the growth of some tumor cells.

1.1.2 JNJ-42756493 (Erdafitinib): Structure, Physical Chemical and Pharmacological Properties

JNJ-42756493-AAA, referred to as JNJ-42756493, has a molecular weight of 446.54 and a molecular formula of C25H30N6O2. The full chemical name is N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine. JNJ-42756493 has a pKa1 and pKa2 of 9.1 (secondary amine moiety) and 1.9 (quinoxaline moiety), respectively, and a log P of 4.39 (pH12.0).

JNJ-42756493 is a potent, oral pan-FGFR tyrosine kinase inhibitor with IC50 values in the low nanomolar range for all members of the FGFR family (FGFR1 to 4). It has demonstrated potent inhibition of cell proliferation with IC50 values ranging from <1 to <1000 nM in FGFR pathway-activated cancer cell lines including squamous non-small cell lung cancer (NSCLC), gastric, breast, hepatocellular cancer (HCC), endometrial, bladder, multiple myeloma, and acute myeloid leukemia. Non-FGFR driven cell lines require significantly higher drug

concentration for inhibition of cell proliferation to be observed. Target inhibition and pathway modulation have been demonstrated in cellular models at active cellular concentrations. Brief exposure to JNJ-42756493 has been demonstrated to result in long-term target inhibition. JNJ-42756493 has been shown to have in vivo antitumor activity in mouse xenograft models of FGFR-driven gastric, bladder, and squamous NSCLC tumor models, and in patient-derived xenografts from squamous NSCLC, gastric, breast, and hepatocellular tumors

JNJ-42756493 is supplied as a 1-mg (G-013), a 5-mg (G-014) and a 20-mg (G015) oral capsules or as 2-mg (G-016), 3-mg (G-017), 4-mg (G-019), and 5-mg (G-018) oral film coated tablets. In addition, JNJ-42756493 oral film-coated tablets with a different coating is being developed: 3-mg (G-023), 4-mg (G-024) and 5-mg (G-025).

Additional information may be found in the Investigator's Brochure.

1.1.3 Animal Pharmacokinetics, Metabolism and Toxicology

JNJ-42756493 showed an intermediate to high permeability in Caco-2 cells and is subject to P-glycoprotein (P-gp) efflux. In animals, JNJ-42756493 is a high clearance molecule with a moderate volume of distribution and a short elimination half-life. Bioavailability of JNJ-42756493 was low in mice and rats, and high in dogs (when dosed as a formulation in 20% hydroxypropyl-β-cyclodextrin (HP-βCD)). The bioavailability increased dose dependently due to nonlinear kinetics in animals. The nonlinear kinetics is probably due to the saturation of the first pass metabolism in animals, and is not observed at clinical doses in man. The free fraction in man was between 0.55% and 0.74%. In animals, the free fraction ranged from 2.2% (nude rat) to 13.7% (dog). JNJ-42756493 is highly bound to α1-acid glycoprotein (α1-AGP). In rats, a fast and extensive distribution to the tissues was shown with highest tissue exposures being observed in lung and liver. The most important metabolic pathways both in vitro in (animal and human) hepatocytes and in vivo (rat) were ring closed structures, probably resulting from O-demethylation and incorporation of a carbon atom to form a seven membered ring (M4 and M7), O-demethylation (M6) followed by glucuronidation (M2), and the O-demethylation of M4 and M7 (M1), followed by addition of one oxygen (M9). All human metabolites were covered by the toxicology species. There was a good correlation between the metabolite patterns in vivo and in vitro. CYP3A4 can be considered the dominant CYP450 enzyme involved in the microsomal metabolism of JNJ-42756493. Other enzymes could be involved as well. In both rat and dog, fecal excretion of drug-related material was higher than urinary excretion. JNJ-42756493 shows weak inhibition potential towards CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A reflected in IC50 values >15μM. The mechanism based inhibition (MBI) potential of JNJ42756493 towards CYP3A4 activity was weak.

Good Laboratory Practice (GLP) repeat dose toxicology studies up to 3 months of duration were conducted in rats and dogs with once daily or intermittent administration of JNJ-42756493. The no observed

adverse effect level (NOAEL) in the 3-month rat study was 4 mg/kg/day in males and below 4 mg/kg/day in females based on the cornea atrophy and the diffuse atrophy of the exorbital lacrimal gland at 4 mg/kg/day in females. At 4 mg/kg/day, JNJ-42756493 Cmax and AUC0-24h values were 6.98 ng/mL and 26.3 ng•h/mL in male rats, and 13.4 ng/mL and 45.2 ng•h/mL in female rats at the end of the 3-month treatment period. The NOAEL in the 3-month dog study was below 0.5mg/kg/day based on the lacrimal gland atrophy in males and females from 0.5 mg/kg/day onwards. At 0.5 mg/kg/day, JNJ-42756493 Cmax and AUC0-24h values were 21.6 ng/mL and 172 ng•h/mL in maledogs, and 15.9 ng/mL and 92 ng•h/mL in female dogs at the end of the 3-month treatment period. The majority of clinical pathology and target organ changes observed in the rat and dog were attributed to exaggerated pharmacology of JNJ-42756493 evidenced by cartilage (chondroid) dysplasia, soft tissue mineralization and atrophy of gland and epithelial structures. Eye-related findings, notably thinning of the corneal epithelium (seen in rats) and lacrimal gland atrophy (seen in rat and dog), and changes to haircoat and nails were only seen in the 3month studies. There was no clear benefit of an intermittent (7 days on/7 days off) dosing regimen versus a daily dosing regimen in animals. In the 1-month studies, complete recovery was seen in the mammary gland (rat) whereas chondroid dysplasia and soft tissue mineralizations were shown to be slowly and partially reversible; except for the aorta mineralizations in dogs that did not show recovery after a 4-week washout period. JNJ-42756493 showed no genotoxic potential in the standard panel of GLP genotoxicity tests. JNJ-42756493 was classified as a very severe eye irritant at a high concentration (20% w/w) in the in vitro bovine corneal opacity and permeability (BCOP) test. At clinically relevant concentrations, JNJ42756493 did not induce vascular irritation in the standard hen's egg chorioallantoic membrane (HETCAM) test in vitro. JNJ-42756493 was evaluated in mice as having skin sensitizing potential. Although JNJ-42756493 exhibited a positive reaction in the 3T3 Neutral Red uptake phototoxicity test in vitro, no evidence of cutaneous phototoxicity was observed in a pigmented rat study.

JNJ-42756493 is an intrinsic human ether-à-go-go-related gene (hERG) blocker with a proarrhythmic liability, which translates into a prolonged repolarization (QTc) after intravenous (i.v.) dosing in the anesthetized dog and guinea-pig and after oral (p.o.) dosing in the conscious dog. Because clear and consistent effects on QTc were found in anesthetized dogs and guinea pigs at levels above 771 ng/mL (unbound fraction of 81.4 ng/ml), clinical exposures exceeding this level will have a substantially increased risk of serious cardiac toxicity. In a modified Irwin’s test in rats, JNJ-42756493 showed minimal neurofunctional aberrations (impaired wire maneuvers and flaccid body tone) from 8 mg/kg (mean Cmax =12.1 ng/mL), considered an indirect effect of JNJ-42756493 treatment.

1.2 Supporting Preliminary Data

1.2.1 First-In-Human Study

Janssen conducted a phase 1 FIH study in patients with advanced cancer, including a subgroup of patients demonstrating FGFR aberrations, with several expansion cohorts and 2 schedules (daily and a 7 day on, 7 day off schedule).[1] The recommended dose on the daily schedule was 9 mg; recommended dose on the intermittent schedule was 10 mg. AUC was dose-proportional and apparent T1/2 was fairly long (50-60h). Among 23 response-evaluable patients with tumor FGFR pathway alterations, four confirmed partial responses and one unconfirmed partial response were seen in patients with glioblastoma and urothelial and endometrial cancer, all with FGFR2 and FGFR3 translocations. Median duration of response was 7.2 months and median PFS was 5.1 months. Common adverse events include hyperphosphatemia (manageable with treatment interruption), dry skin and nail toxicities. Drug-related gr ≥3 AEs were onycholysis, paronychia, and hand-foot syndrome. DLT: 1 at 12 mg (Gr 3 LFT elevation).

In this study (Study EDI1001), 125 subjects (98%) experienced a TEAE; 68 subjects (54%) experienced a Grade 3 or higher TEAE. The 5 most common adverse events (35% or greater) in the total population are hyperphosphatemia, dry mouth, asthenia, constipation, and stomatitis. Other commonly observed effects include skin and nail changes, which are considered adverse drug reactions. Grade 3 or higher TEAEs were reported for 65 subjects (51%). The most common were elevated aspartate aminotransferase and hyponatremia, reported for 7 subjects each. Ten (10) subjects (8%) had treatment-emergent adverse events that resulted in discontinuation of treatment. General physical health deterioration was the only event that led to discontinuation by more than 1 subject. Adverse events of special interest include events that are class effects of FGFR inhibitors and have been experienced by patients treated with other FGFR inhibitors. These events include skin, mucosal, and nail changes and hyperphosphatemia, fatigue, and reversible retinal pigment epithelial detachment (RPED or central serous retinopathy[CSR]). Fifty subjects (39%) were reported with serious adverse events. The most frequently reported serious events (by 5 or more subjects) were general health deterioration, dyspnea, and intestinal obstruction. A total of 16 subjects have discontinued from Study EDI1001 due to death. Of these, 13 deaths were within 30 days of last dose. The primary cause of most deaths within 30 days was progressive disease (9/13 subjects). For 3 subjects, the primary cause of death was an adverse event. These were not drug related, and were anemia and sepsis in 1 subject, pulmonary edema in 1 subject, and cerebral hemorrhage in 1subject

In patients, JNJ-42756493 exhibited dose-related increase in Cmax and AUC and time-independent PK within the dose range of 0.5 mg to 12 mg, both after single and multiple daily dosing. Median Tmax observed ranged from 2 to 4 hrs (JNJ-42756493 as capsule). JNJ-42756493 is highly bound to plasma proteins such as α1-Acid

Glycoprotein (α1-AGP). In patients, free fractions of JNJ-42756493 in human plasma were small (average~0.36%). JNJ-42756493 is a P-glycoprotein (P-gp) substrate. In vitro data suggested the metabolism of JNJ-42756493 was limited, leading to a low amount of metabolites being formed. CYP3A4 is the dominant CYP450 enzyme involved. Long terminal phase halflife of JNJ-42756493 (>50 hrs) in plasma was observed resulting in approximately 3-fold accumulation of Cmax and AUC following multiple daily dosing.

A poster at ESMO2016 presented data in urothelial carcinoma (UC) patients from the same Phase 1 study. Thirty pts with UC were treated at 2 mg QD (n=1), 9 mg QD (n=12), 10 mg ID (n=15), 12 mg QD (n=1), or 12 mg ID (n=1). Across these dose levels, median treatment duration was 3.3 months (mo). The most common drug-related AEs were hyperphosphatemia (53%), dry mouth (47%), diarrhea (43%), and dry skin (43%); all of these were grade 1 or 2 severity, except for 1 case of grade 3 hyperphosphatemia (3%) and 2 cases of grade 3 diarrhea (7%). The most common grade ≥ 3 AEs were anemia (17%), hand-foot syndrome (13%), and stomatitis (11%). Among FGFR-mutated or translocated, response evaluable UC pts (as of 06 Jun 2016), 7/11(63.6%) pts were treated at 9 mg QD and achieved PR with median duration of response of 7.2 mo (95% CI 3.8, 15.3), and 4/13 (30.8%) pts were treated at 10 mg ID and achieved PR.

1.2.2 Phase 2 Experience

Janssen performed a phase 2 study (NCT02365597) in urothelial cancer; (such patients have a reasonably high incidence of alterations with FGFR/TACC mutations, and are screened for “certain FGFR translocation or mutations at a central lab; the exact variants are not public) using 2 dosing regimens.[2] Regimen 1 is JNJ-42756493 (erdafitinib) 10 mg dose, 7 days on/7 days off (with option to up-titrate to 12 mg 7 days on/7 days off) in 28 day cycles; Regimen 2 is JNJ-42756493 (erdafitinib) 6 mg dose, once daily (with option to up-titrate to 8 mg) in 28 day cycles. The RP2D was chosen to be 8 mg daily for 28 days. Thus the RP2D is 8 mg continuously. The study is currently ongoing and efficacy results have not been presented. As of 3 June 2016, 50 subjects have been treated in this study; 24 subjects in the 10 mg intermittent dosing regimen and 26 subjects in the 6 mg continuous dosing regimen. Twenty (20) subjects have discontinued treatment, 7 subjects (14%) due to progression of disease and 5 subjects (10%) due to adverse events. Thirty (30) subjects (60%) are continuing to receive treatment.

Two other studies are currently being conducted in Asian patients only, one dose escalation and one phase 2 study in HCC patients. Results of these studies are not available.

1.3 Rationale for 8 mg starting and 9 mg up-titration dose:

Selected dose regimen: Choice of the Sustained Dosing Regimen: 8 mg Daily with Flexibility to Up-titrate to 9 mg Daily.

Pharmacokinetics: At the 8 mg dose, based on pharmacokinetic simulations, the expected mean unbound Cavg plasma concentrations in patients during the 28

day cycle period is 3.4 ng/mL. The mean unbound average plasma concentration of urothelial cancer patients with clinical activity (partial responses) in the Phase 1 study was 2.5 ng/mL, which is also consistent with the preclinical target window. Antitumor activity is anticipated to correlate with preclinical AUC for unbound drug (AUCu), and at the 8 mg dose level, 90% of patients will have unbound trough plasma concentrations and AUCu levels within the target window (0.6 to 2.4 ng/mL) by Day 3. Thus, 8 mg daily is predicted to generate continuously efficacious drug concentrations for the vast majority of patients.

Pharmacodynamics: Hyperphosphatemia is a common drug-induced toxicity due to renal tubular FGFR inhibition and, thus, it can serve as a pharmacodynamics marker of drug activity. Dose dependent elevations in serum phosphate occurred in all patients starting at 4 mg daily. Because this represents a target-mediated drug effect, one of the Phase 1 study goals was to select a dose regimen that consistently induced manageable hyperphosphatemia but did not exceed a critical level requiring cessation of therapy, which in the Phase 1 study was 7 mg/dL. Emerging data from the ongoing Phase 1 study indicates that a phosphate increase of at least 35% over baseline level may be associated with anti-tumor response. Therefore a pharmacodynamics objective of 50% increase in phosphate level over baseline was felt to be appropriate. Considering the median phosphate level of 3.6 mg/dL at baseline in the Phase 1 study, and of 3.3 mg/dL at baseline in the Phase 2 study (IA1 data) an increase of at least 50% for the majority of subjects would correspond to an absolute phosphate level of around 5.5 g/dL (which is also 35% over the phosphate ULN). Subjects achieving a phosphate level of less than 5.5mg/dL by the end of first cycle dosing period (day 28) would be considered to have had inadequate PD effect and would be candidates for dose escalation to 9 mg daily to achieve an optimum PD effect (phosphate range 5.5-7mg/dL).

Overall, emerging pharmacokinetic/pharmacodynamics (PK/PD) modeling suggests that approximately 60% of subjects would have serum phosphate levels < 5.5 mg/dL (on Day 28) when dosed with 6 mg and would potentially benefit from dose up-titration. Additionally, by Day 28 approximately 13% of subjects may reach a phosphate level ≥ 7 mg /dL and thus need an unscheduled interruption of up to 7 days to maintain the phosphate level in the target range of 5.5 to <7 mg/dL.

Clinical safety: The 8 mg daily dose is the continuous regimen that, based on modelling, would likely be well tolerated without significant treatment interruptions (approximately 10% to 15% anticipated early interruptions) and for which the majority of subjects would tolerate the sustained dose of 8 mg once daily. Escalation on Day 15 of the first treatment cycle of daily dose from 8 mg QD to 9 mg QD in the subjects with both phosphate below 5.5 mg/dL (suboptimal pharmacodynamics effect; about 40% of subjects), and without significant drug related toxicity (Grade ≥2 toxicity or Grade ≥1 central serious retinopathy or retinal pigment epithelial detachments) is unlikely to significantly change the overall tolerability profile.

Clinical activity: Assessment of clinical activity at the 6 mg dose and in up-titrated subjects at IA1 is limited by the paucity of treated subjects, but 3 PR were observed in 14 subjects with phosphate level below 5.5 mg/dL and 4 PR in 7 subjects with phosphate level over 5.5 mg/dL, pointing to the potential importance of attaining full pharmacodynamics effect. Hence the aim is to bring a maximal number of subjects within the target phosphate range of 5.5 mg/dL to

less than 7 mg/dL in order to attain maximal sustained inhibition of target, and thereby allow for potential optimization of efficacy, given the observed correlation thus far between clinical response and the pharmacodynamics effect on phosphate. Selective dose escalation to 9 mg for optimization of the pharmacodynamics effect in approximately 40% of subjects is likely to increase the potential for clinical activity without significantly increasing dose interruptions or toxicity. In addition, the mean dose intensity of the continuous 8 mg regimen (with flexibility to up-titrate) based on PK/PD model based simulations is likely to be 6.7 mg /day, which would be close to the 6.8 (±2.37) mg/day as observed with the 9 mg daily schedule in Phase 1 as compared to the observed 5.4 (± 0.63) mg/day reported with the 6 mg daily schedule in Phase 1, thereby increasing the potential for clinical activity.

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).

_____ 2.1.2 Patients must have FGFR Amplification as determined via the MATCH Master Protocol and described in Appendix II. See Appendix II for information on the FGFR mutations 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 JNJ-42756493 (erdafitinib) or compounds of similar chemical or biologic composition.

_____ 2.1.5 Patients with current evidence of corneal or retinal disorder/keratopathy are excluded.

_____ 2.1.6 Patients must not be currently using medications that can elevate serum phosphorous and/or calcium levels.

2.1.6.1 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.

2.1.6.2 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.

_____ 2.1.7 Patients with a history of Hyperphosphatemia will be excluded.

_____2.1.8 Patients may not have received strong inhibitors or potent inducers of CYP3A within 2 weeks before the first dose of study treatment. Patients with inability to discontinue treatment with a strong CYP3A4 and/or CYP2C9 inhibitor or inducer prior to start of treatment are excluded.

_____ 2.1.9 Patients who have previously received treatment with a FGFR-targeted inhibitor are excluded. Such inhibitors include AZD4547, BGJ398, BAY1163877 and LY2874455). Prior non-selective FGFR inhibitor treatment (e.g. Pazopanib, dovitinib, ponatinib, brivanib, lucitanib, lenvatinib) are allowed.

_____2.1.10 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.

_____ 2.1.11 Patients with transitional cell carcinoma of the bladder and /or urothelial tract are not eligible. These patients are encouraged to enroll in the ongoing disease-specific studies.

_____2.1.12 Patients with impaired renal function (glomerular filtration rate [GFR] < 60 mL/min) are excluded. GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula).

_____ 2.1.13 Patients with persistent phosphate level > ULN during screening (within 14 days of treatment and prior to Cycle 1 Day 1) and despite medical management are excluded.

_____ 2.1.14 Patients with a history of or current uncontrolled cardiovascular disease as stated below are excluded:

- Unstable angina, myocardial infarction, or known congestive heart failure Class II-IV within the preceding 12 months; cerebrovascular

accident or transient ischemic attack within the preceding 3 months, pulmonary embolism within the preceding 2 months.

- Any of the following: sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes, cardiac arrest, Mobitz II second degree heart block or third degree heart block; known presence of dilated, hypertrophic, or restrictive cardiomyopathy.

_____ 2.1.15 Patients with impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions are excluded.

_____ 2.1.16 Female subjects (of child-bearing potential and sexually active) must use medically acceptable methods of birth control (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of the study, and for 4 months after the last intake of study drug. Male subjects (with a partner of child-bearing potential) must use a condom with spermicide when sexually active and must not donate sperm from the first dose of study drug until 5 months after the last dose of study drug.

_____ _____

Physician Signature Date

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

3. JNJ-42756493 (Erdafitinib) Treatment Plan

3.1 Administration Schedule

JNJ-42756493 (erdafitinib) is administered orally at least 1 hour before eating or at least 2 hours after a meal at the prescribed dose (flat dose) daily continuously, for 28 days of every 28-day cycle.

At start, JNJ-42756493 (erdafitinib) is administered orally at the dose of 8 mg throughout the first 14 days of a 28-day cycle.

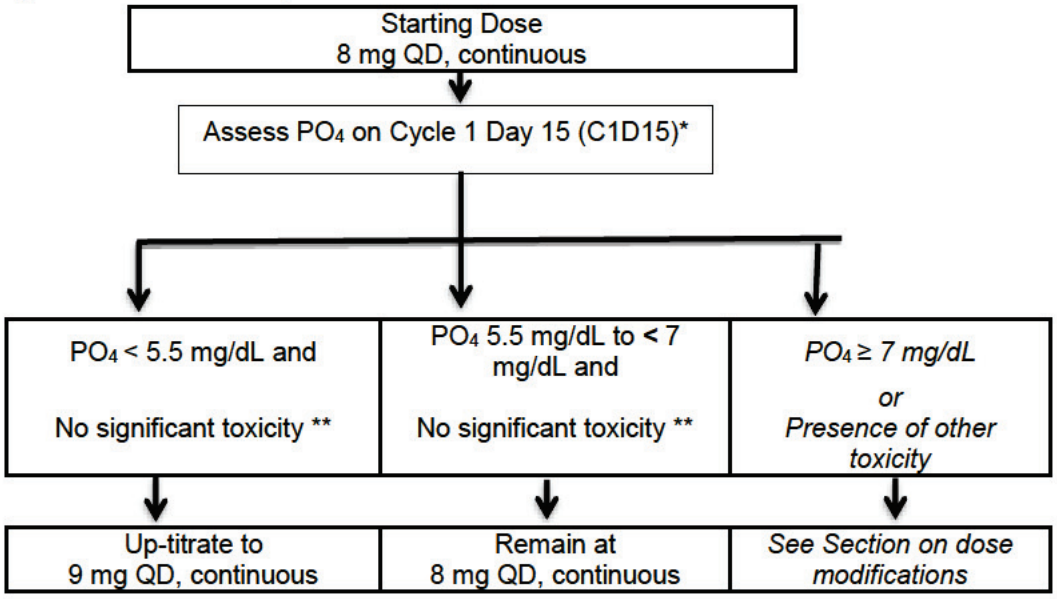
Rev. Add16

Dose Up-titration Guidelines

For subjects, treatment will be up-titrated or maintained based on phosphate level measured on Cycle 1 Day 15, and taking into account observed toxicity to that day, as described in Figure 1. The up-titrated dose would be given starting on Cycle 1 Day 15, for the remainder of the treatment.

Further treatment modification or termination will be based on toxicity as described below. For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity, specific recommendations in the management guidelines are provided below.

Figure 1: Dose Up-titration



* PO4 assessments are done as per T&E; dose up-titration decision is based on C1D15 assessment and up-titrated dose to be administered starting C1D15.

** Drug related toxicity during Cycle 1 as determined by investigator. At any time during treatment with study drug, dose interruptions/modifications would be managed by investigator as clinically indicated. Specific recommendations on dose reductions and toxicity management are provided throughout Section 3.4.

Tablets should be taken with 8 ounces of water and swallowed intact. Each dose should be taken at least 1 hour before eating or at least 2 hours after a meal, at approximately the same time each day. Subjects should avoid consuming grapefruit or Seville oranges while on study treatment due to CYP450 3A4/5 inhibition.

JNJ-42756493 (erdafitinib) should be administered daily at approximately the same time, and the interval between two consecutive doses should be approximately 24 hours. Missed doses for any reason (including vomiting following drug administration) can be taken up to 6 hours after the scheduled time. If it has been more than 6 hours since the missed dose, then that dose should be skipped.

Repeat cycles until progression.

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 K1

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 K1 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 JNJ-42756493 (erdafitinib), or within 28 days of the subject's last dose of JNJ-42756493 (erdafitinib), 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.
- **Ocular events**: Any grade 3 or higher ocular event of any type occurring must be reported via CTEP-AERs in the timeframe outlined in Section 5.3.6 of the EAY131 MASTER protocol for the specific grade being reported.
- **Liver Events:** Any liver adverse event that meets the criteria listed below, with no other explanation for the abnormality, must be reported via CTEP-AERs in the timeframe outlined in

Section 5.3.6 of the EAY131 MASTER protocol for the specific grade being reported.

- ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN (> 35% direct bilirubin) (or ALT ≥ 3 x ULN and international normalized ratio [INR] > 1.5, if INR measured). Exception to the bilirubin elevation is made if the subject has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.
- ALT ≥ 5 x ULN for 2 weeks or ALT >8 ULN.
- ALT ≥ 3 x ULN if associated with the appearance or worsening of symptoms of liver injury, hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
- Persistent elevation of ALT ≥ 3 x ULN for ≥ 4 weeks or if ALT elevation cannot be monitored.

- **Hy's law criteria:** If the following criteria are met, then it must must be reported via CTEP-AERs in the timeframe outlined in Section 5.3.6 of the EAY131 MASTER protocol for the specific grade being reported
  - (ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN (> 35% direct bilirubin) with no evidence of ALP elevation or ALT ≥ 3 x ULN and INR > 1.5 and no alkaline phosphatase [ALP] elevation).

EAY131 – Subprotocol K1 specific expedited reporting exceptions:

For Subprotocol K1, 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 <u>secondary malignancy</u> 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.

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3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for JNJ-42756493 (Erdafitinib, NSC 781558)

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 417 patients.* Below is the CAEPR for JNJ-42756493 (Erdafitinib).

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.

Version 2.2, January 04, 2019[1]

Adverse Events with Possible Relationship to Erdafitinib (JNJ-42756493) (CTCAE 5.0 Term) [n= 417]			**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		***Dry eye (Gr 2)***
	Keratitis		
Eye disorders - Other (central serous retinopathy)[2]			
	Eye disorders - Other (eye disorders)[3]		
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		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***

Adverse Events with Possible Relationship to Erdafitinib (JNJ-42756493) (CTCAE 5.0 Term) [n= 417]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INFECTIONS AND INFESTATIONS			
	Conjunctivitis		
	Paronychia		***Paronychia (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
Hyperphosphatemia			***Hyperphosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 2)***
	Respiratory, thoracic and mediastinal disorders - Other (nasal dryness)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
Dry skin			***Dry skin (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
	Pruritus		
Skin and subcutaneous tissue disorders - Other (nail disorder)[4]			***Skin and subcutaneous tissue disorders - Other (nail disorder)[4] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (skin fissures)		

[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]Central serous retinopathy includes: chorioretinopathy, retinal detachment, retinal oedema, detachment of retinal pigment epithelium, detachment of macular retinal pigment epithelium, retinopathy and vitreous detachment.

[3]Eye disorders includes, but is not limited to eye disorder with redness and irritation of the eye, maybe associated with increased tearing of the eyes, itchy eyes, and inflamed eyes.

[4]Nail disorder includes, but is not limited to, onycholysis, onychalgia, onychoclasis, nail dystrophy, nail loss, nail bed bleeding, nail bed inflammation, nail discomfort, nail discoloration, and nail ridging.

Adverse events reported on Erdafitinib (JNJ-42756493) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Erdafitinib (JNJ-42756493) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy)

CARDIAC DISORDERS - Sinus tachycardia

EYE DISORDERS - Blurred vision; Eye disorders - Other (blepharitis); Eye disorders - Other (blindness unilateral); Eye disorders - Other (corneal erosion); Eye disorders - Other (corneal infiltrates); Eye disorders - Other (eyelid edema); Eye disorders - Other (foreign body sensation in eyes); Eye disorders - Other (lagophthalmos); Eye disorders - Other (macular degeneration); Eye disorders - Other (metamorphopsia); Eye disorders - Other (ocular hyperemia); Eye disorders - Other (xanthopsia); Eye pain; Night blindness; Papilledema; Photophobia; Vision decreased

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Dysphagia; Gastrointestinal disorders - Other (intestinal obstruction); Salivary duct inflammation

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; General disorders and administration site conditions - Other (general physical health deterioration); Non-cardiac chest pain; Pain

INFECTIONS AND INFESTATIONS - Herpes simplex reactivation; Infections and infestations - Other (clostridum difficile colitis); Infections and infestations - Other (lower respiratory tract infection); Infections and infestations - Other (oral herpes); Sepsis; Urinary tract infection

INVESTIGATIONS - Alkaline phosphatase increased; Creatinine increased; GGT increased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastases to spine)

NERVOUS SYSTEM DISORDERS - Lethargy; Somnolence

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hypoxia; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (respiratory distress)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Eczema; Hyperkeratosis; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (cutaneous calcification); Skin and subcutaneous tissue disorders - Other (skin exfoliation); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin and subcutaneous tissue disorders - Other (skin toxicity); Skin atrophy; Skin hyperpigmentation; Skin ulceration

VASCULAR DISORDERS - Hypotension; Thromboembolic event

NOTE: Erdafitinib (JNJ-42756493) 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 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

Dose Modifications and Dose Delays

Treatment can be modified or terminated based on toxicity as described in Table 1. For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity, specific recommendations in the management guidelines are provided below.

Table 1: Dose Modification Guidelines

Toxicity Grade	Action	Dose Modification After Resolution of Adverse Event
1	None	Continue same dose
2	None or consider interruption	If interrupted, restart at same dose or 1 dose lower, if necessary.
3	Interrupt drug	Restart at 1 or 2 doses lower if recovery (to ≤ Grade 1 or back to baseline for non-hematologic toxicity) is within 28 days. Discontinue drug if unresolved for >28 days.
4	Interrupt drug or discontinue	Discontinue*

For general toxicity management:

- Subjects with any grade of toxicity (Grade 1 to 4) should be provided symptomatic treatment when applicable.
- Subjects should follow the guidelines in Table 2 for dose reduction recommendations and may have more than 1 dose reduction.
- If JNJ-42756493 (erdafitinib) must be withheld for more than 28 days for a drug-related adverse event that fails to resolve to acceptable level (e.g., ≤ Grade 1 non-hematologic toxicity or back to baseline), treatment with JNJ-42756493 (erdafitinib) should be discontinued with the exception noted below.*
- If the subject achieves calcium-phosphate product > 70 mg^2/dL^2 for 2 consecutive weeks despite phosphate lowering therapy or > 90 mg^2/dL^2 any time during treatment despite phosphate lowering therapy, JNJ-42756493 (erdafitinib) should be withheld until recovery to calcium-phosphate product < 55 mg^2/dL^2. Treatment may be reintroduced at the first reduced dose level.
- In all cases of clinically significant impaired wound healing or imminent surgery or potential bleeding complications, it is recommended that dose administration be interrupted, appropriate clinical laboratory data be carefully monitored, and supportive therapy administered, where applicable. Dose

administration may be restarted when it is considered safe and at an appropriate dose, according to the investigator's assessment.

*Exception: if a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator.

Dose reduction levels are provided in Table 2,

Table 2: Dose Schedule and Dose Reductions - 8 mg Once Daily (QD) dosing, continuous daily dosing in 28-day cycles

Category	If dose is 8 mg:	If dose uptitrated to 9 mg:
1st dose reduction	6 mg	8 mg
2nd dose reduction	5 mg	6 mg
3rd dose reduction	4 mg	5 mg
4th dose reduction	**stop**	4 mg
5th dose reduction		**stop**

Liver Event Safety Stopping Criteria

Liver chemistry threshold stopping criteria have been established to provide safety to the subjects and to better assess the etiology of the liver event during the development of new investigational products. The liver chemistry stopping criteria include any of the following:

- ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN (> 35% direct bilirubin) (or ALT ≥ 3 x ULN and international normalized ratio [INR] > 1.5, if INR measured). Exception to the bilirubin elevation is made if the subject has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.
- ALT ≥ 5 x ULN for 2 weeks or ALT > 8 ULN.
- ALT ≥ 3 x ULN if associated with the appearance or worsening of symptoms of liver injury, hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
- Persistent elevation of ALT ≥ 3 x ULN for ≥ 4 weeks or if ALT elevation cannot be monitored.

The liver chemistry should be repeated within 2 to 3 days. If any of the chemistry stopping criteria are met and there is no other explanation for the abnormalities, the study drug must be STOPPED, and the event reported as a serious adverse event if applicable. If Hy's law criteria (ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN (> 35% direct bilirubin) with no evidence of ALP elevation or ALT ≥ 3 x ULN and INR >1.5 and no alkaline phosphatase [ALP] elevation) are met, then the event should be reported as a serious adverse event.

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Liver Event Follow-Up Requirements

For subjects meeting any of the liver chemistry stopping criteria, the following procedures should be followed:

- Re-assess liver chemistries within 72 hours. Monitor liver chemistries (ALT, AST, alkaline phosphatase, bilirubin, including bilirubin fractions and INR) 1

to 2 times weekly until resolution, stabilization, or return to subject's baseline values. Monitor clinical condition closely.

- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, or known hepatotoxins.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Check the viral hepatitis serology as appropriate and include:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B core antibody (IgM);
  - Hepatitis C RNA;
  - Hepatitis E IgM antibody (appropriate for subjects traveling outside North America);
  - Cytomegalovirus IgM antibody; and
  - Epstein-Barr viral capsid antigen IgM antibody (or equivalent test).
- Anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease

Liver Event Re-challenge Requirements

If a subject meets the liver event stopping criteria, the study drug should not be re-administered. In the case in which Hy's law is not met and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator. Prior to re-introduction, the investigator should obtain written permission from the study medical monitor and the IRB. The investigator should also have the subject re-consent, explaining that re-introduction of study drug could lead to liver damage, which may be serious and/or may even result in death.

Guidelines for the Management of Elevated Phosphate Levels

Guidelines for the clinical management of elevated serum phosphate levels are presented in Table 3.

Table 3: Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Medical Management
All subjects in the study	Continue JNJ-42756493 (erdafitinib) treatment.	Restriction of phosphate intake to 600 – 800 mg/day.
5.5-6.9 mg/dL (1.8-2.2 mmol/L)	Continue JNJ-42756493 (erdafitinib) treatment.	Restriction of phosphate intake to 600 – 800 mg/day. May consider sevelamer 800 mg to 1,600 mg 3 times a day (with food)
7.0-9.0 mg/dL (2.3-2.9 mmol/L)	Withhold [a] JNJ-42756493 (erdafitinib) treatment until serum phosphate level returns to < 5.5 mg/dL. Re-start treatment at the same dose level. A dose reduction may be implemented for persistent [b] hyperphosphatemia (≥ 7 mg/dL) if clinically necessary	Restriction of phosphate intake to 600 – 800 mg/day. Sevelamer 800 to 1,600 mg 3 times a day with food until phosphate level is < 5.5 mg/dL.
> 9.0 mg/dL (> 2.9 mmol/L)	Withhold [a] JNJ-42756493 (erdafitinib) treatment until serum phosphate level returns to < 5.5 mg/dL. Re-start treatment at the first reduced dose level. A second dose reduction may be implemented if needed or clinically indicated for persistent [b] hyperphosphatemia (≥ 7 mg/dL) at every cycle	Restriction of phosphate intake to 600 – 800 mg/day. Sevelamer up to 1,600 mg 3 times a day with food AND Acetazolamide 250 mg 2 or 3 times a day only until serum phosphate level returns to < 5.5 mg/dL.
> 10.0 mg/dL (> 3.2 mmol/L) and/or significant alteration in baseline renal function and/or Grade 3 hypocalcemia	JNJ-42756493 (erdafitinib) should be discontinued permanently. (In situations where the subject is having clinical benefit and the investigator and the sponsor's medical monitor agree that re-starting drug is in the best interest of the subject, the drug may be re-introduced at 2 dose levels lower if appropriate[c]. Follow other recommendations described above.)	Medical management as clinically appropriate.

NOTE: These are general guidelines that are based on emerging data and consensus experience of participating investigators and/or the experts in the field. The treating physicians must use clinical judgment and local standard of care to decide the best way to manage phosphate elevation. If Sevelamer hydrochloride (renagel) is not available, use of other phosphate binders (non-calcium containing) based on the local standard is recommended, including Sevelamer carbonate (Renvela) or lanthanum carbonate (Fosrenol). These guidelines will be updated based on emerging data. Additional information on phosphorous in foods by class of food can also be found at www.permanente.net/homepage/kaiser/pdf/42025.pdf. Additional information for phosphate management and diet can be found the National Kidney Foundation website (http://www.kidney.org/atoz/content/phosphorus.cfm)

Table 3: Guidelines for Management of Serum Phosphate Elevation

a Drug interruptions for hyperphosphatemia suggested to be 7 days duration

b Persistent hyperphosphatemia is considered to be more than 1 sequential phosphate value of >=7 mg/dL

c If a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator. Prior to re-introduction, the investigator should obtain written permission from the study medical monitor and the IRB. The investigator should also have the subject re-consent, explaining that re-introduction of study drug could lead to increased risk of recurrent toxicities. (please see Section 16.2.3 for details)

Guidelines for the Management of Dry Mouth and Stomatitis

Guidelines for the clinical management of dry mouth (xerostomia) and stomatitis are provided in Table 4 and Table 5, respectively.

- **General Prophylaxis:**
  - Good oral hygiene
  - Use a soft toothbrush
  - Avoidance of spicy, acidic, hard, and hot food and beverages
  - Use of mild-flavored toothpastes
  - Use of saline-peroxide or salt and soda mouthwashes 3 or 4 times per day
  - Water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth)

Table 4: Guidelines for the Management of Dry Mouth (Xerostomia)

Grade and Definition	Study Drug Management	Medical Management
Grade 1: symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow > 0.2 mL/min	Continue study drug at current dose.	Sorbitol lozenges PRN
Grade 2: moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min	Continue study drug at current dose.	Sorbitol lozenges PRN and Cevimeline 30 mg TID or Pilocarpine 5 mg TID
Grade 3: inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva less than 0.1 ml/min	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition.	Sorbitol lozenges PRN and Cevimeline 30 mg TID or Pilocarpine 5 mg TID

Table 4: Guidelines for the Management of Dry Mouth (Xerostomia)

Grade and Definition	Study Drug Management	Medical Management
	When resolved to ≤ Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue study drug.	Evaluation and therapy as clinically indicated

Table 5: Guidelines for the Management of Mucositis

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Asymptomatic or mild symptoms; interventions not indicated	Continue study drug at current dose.	Topical steroid moderate strength and lidocaine 2-5% jelly or solution QID
Grade 2: Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Continue study drug at current dose. Consider study drug holding if no improvement in 1 week. When resolves to ≤ Grade 1 or baseline, restart at same or 1 dose level below in consultation with the medical monitor.	Dexamethasone solution (3.3 mg/5 mL) swish and spit QID and lidocaine 2-5% jelly or solution QID
Grade 3: Severe pain; interfering with oral intake	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤ Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Dexamethasone solution (3.3 mg/5 mL) swish and spit QID and lidocaine 2-5% jelly or solution QID
Grade 4: life threatening consequences, urgent intervention indicated	Discontinue study drug.	Evaluation and therapy as clinically indicated

Guidelines for the Management of Dry Skin and Skin Toxicity

Guidelines for the management of dry skin are provided in Table 6.

- **General prophylaxis:**
  - Avoid unnecessary exposure to sunlight and excessive use of soap.
  - Avoid bathing in excess; use tepid rather than hot water.
  - Use moisturizers regularly; apply thick, alcohol-free and oil-in-water based emollient cream on exposed and dry areas of the body.
  - Avoid perfumed products, bubble bath, perfumed soaps, and take breaks from shaving.

- Use broad spectrum sunscreen with a skin protection factor (SPF) ≥15.
- Wear cotton clothes next to skin rather than wool, synthetic fibers, or rough clothing.
- Use occlusive alcohol-free emollient creams (jar or tub) for treatment of mild/moderate xerosis.
- For scaly areas, use exfoliants (ammonium lactate 12% or lactic acid cream 12%).

Table 6: Guidelines for Management of Dry Skin

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Dry skin covering less than 10% body surface area (BSA) and no associated erythema or pruritus	Continue study drug at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles.
Grade 2: Dry skin covering 10 to 30% BSA and associated with erythema or pruritis with limited instrumental activities of daily living (IADL)	Continue study drug at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles. Use zinc oxide 13-40% at night for areas with fissures.
Grade 3: Dry skin covering > 30% BSA and associated with pruritis; limiting self-care activities of daily living (ADL)	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤ Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Use topical steroid ointment or cream* BID and zinc oxide 13-40% at night for areas with fissures.
Grade 4: Dry skin with life-threatening consequences, urgent intervention indicated	Discontinue study drug.	Evaluation and therapy as clinically indicated
* Topical Steroid Ointments: Clobetasol 0.05%, Betamethasone 0.05%, Fluocinonide 0.05%		

Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia)

Guidelines for management of nail discoloration/loss/ridging (onycholysis/onychodystrophy) are provided in Table 7. Guidelines for the management of paronychia are provided in Table 8.

- **General Prophylaxis:**
  - Good hygienic practices, keep fingers and toes clean.
  - Keep nails trimmed
  - Use gloves for housecleaning and gardening to minimize damage and prevent infection

- Nail polish and imitation fingernails should not be worn until the nails have grown out and returned to normal
- Wearing comfortable shoes (wide sized shoes with room for the toes)
- Trimming nails but avoiding aggressive manicuring

Table 7: Guidelines for Management of Nail Discoloration/Loss/Ridging (Onycholysis/Onychodystrophy)

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Asymptomatic; clinical or diagnostic observations only	Continue study drug at current dose,	Over the counter nail strengthener OR poly-urea urethane nail lacquer (Nuvail) OR diethylene glycol monoethylether nail lacquer daily (Genadur)
Grade 2: Symptomatic separation of the nail bed from the nail plate or nail loss, limiting instrumental ADLs	Continue study drug at current dose. Consider study drug holding if no improvement in 1 to 2 weeks. When resolves to ≤ Grade 1 or baseline, restart at same or 1 dose level below in consultation with the medical monitor.	For signs of infection (periungal edema/erythema/ tenderness and/or discharge), obtain bacterial cultures, and then start the following: • treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim (Bactrim®) DS BID) AND • topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily)
Grade 3: Severe nail tip pain, symptomatic separation of the nail bed from the nail plate or nail loss, significantly limiting IADLs	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤ Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Silver nitrate application weekly AND topical antibiotics AND vinegar soaks.[a] For signs of infection (periungal edema/erythema/ tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/trimethoprim (Bactrim®) DS BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological and/or surgical evaluation.
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue study drug	Evaluation and therapy as clinically indicated

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B

Table 8: Guidelines for Management of Paronychia

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Nail fold edema or erythema; disruption of the cuticle	Continue study drug at current dose.	Topical antibiotics AND vinegar soaks[a]
Grade 2: Nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Continue study drug at current dose. Consider study drug holding if no improvement in 1 to 2 weeks. When resolves to ≤ Grade 1 or baseline, restart at same or 1 dose level below in consultation with the medical monitor	Topical antibiotics AND vinegar soaks[a] AND topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) For signs of infection (periungal edema/erythema/tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim (Bactrim) DS BID).
Grade 3: Operative intervention indicated; IV antibiotics indicated; limiting self care ADL	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤ grade 1 or base line, restart at one dose level below in consultation with the medical monitor.	Vinegar soaks[a] AND consider nail avulsion For signs of infection (periungal edema/erythema/tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim (Bactrim) DS BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological and/or surgical evaluation.
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue study drug.	Evaluation and therapy as clinically indicated

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B

Guidelines for Eye Toxicity Associated With Vision Changes

If a subject experiences an event of confirmed new corneal or retinal abnormality while on study drug, the event should be reported as an adverse event of special interest (if Grade 1 or 2) or a serious adverse event (if Grade 3 or higher) as appropriate. Any new and clinically significant symptoms, such as but not limited to, blurred vision, partial or complete loss of vision, double vision, floaters or color spots or halos around light, change in color or night vision, photophobia, ocular pain or stinging sensation, or foreign body sensation should be further evaluated and managed per the guidelines below.

All subjects should have monthly Amsler grid tests and an initial ophthalmological examination performed at Screening by an ophthalmologist, which should include assessment of visual acuity, tonometry, fundoscopy (examination of both central and peripheral zones should be performed); where available, an Optical Coherence Tomography (OCT) should be performed. A follow-up

ophthalmological examination should be performed as clinically necessary based on the findings of the monthly Amsler grid tests*** and clinical assessment. It is assumed that about 30% patients will require follow-up full ophthalmological examinations.

If Central Serous Retinopathy (CSR)/Retinal Pigment Epithelial Detachments (RPED) is suspected, an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected Retinal Vein Occlusion (RVO). It is also recommended that color fundus photos or OCT images be obtained and stored in the subject's records for future reference. In subjects with suspected retinal pathology such as CSR or RVO, a consultation with a retina specialist should be considered.

*** Observation of wavy, broken or distorted lines, or a blurred/missing area of vision is equivalent to a positive Amsler grid test. For any positive Amsler grid test, subject should be referred for full ophthalmologic exam within 7 days.

Table 9: Guidelines for Management of Eye Toxicity

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only Or abnormal Amsler grid test	Refer for an ophthalmologic examination. If an ophthalmologic exam cannot be performed within 7 days, withhold treatment of JNJ-42756493 until an examination can be performed. If there is no evidence of eye toxicity on ophthalmologic examination, continue JNJ-42756493 therapy at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as central serous retinopathy (CSR)/ retinal pigment epithelial detachments (RPED), withhold JNJ-42756493 until signs and symptoms have resolved. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologic examination, resume JNJ-42756493 therapy at the next lower dose level after consultation with the medical monitor.[a] Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence then re-escalation can be considered in consultation with the medical monitor.[a]	Refer the subject for an ophthalmologic examination. For retinal pathology perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Immediately withhold JNJ-42756493 therapy. If there is no evidence of drug-related corneal or retinal pathology on ophthalmologic examination, withhold JNJ-42756493 until signs and symptoms have resolved. Resume JNJ-42756493 therapy at the next lower dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as CSR/RPED, withhold JNJ-42756493 until signs and symptoms have resolved, stabilized, or subject is lost to follow-up or withdraws consent (which ever happens first). If toxicity is Grade 2 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume JNJ-42756493 therapy at the next lower dose level after consultation with the medical monitor.	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 3: Severe or	If the toxicity is Grade 3, report as a serious adverse	

Table 9: Guidelines for Management of Eye Toxicity

Grade and Definition	Study Drug Management	Medical Management
medically significant but not immediate sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	event and permanently discontinue JNJ-42756493. If however the toxicity is Grade 3 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks and the subject is having clinical benefit, and the investigator and the sponsor's medical monitor agree that re-starting drug is in the best interest of the subject, then JNJ-42756493 therapy may be resumed at 2 dose levels lower if appropriate.[a] Monitor for recurrence using appropriate investigations every 1 to 2 weeks for a month and as clinically appropriate thereafter. For cases of recurrence consider permanent discontinuation.	
Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue treatment with JNJ-42756493. Report as a serious adverse event and monitor resolution of the event until complete resolution, stabilization or the subject is lost to follow-up or withdraws consent (which ever happens first).	Promptly refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. Follow specific treatment per the ophthalmologist's recommendation.

[a] If a subject has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the subject considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the medical monitor is in agreement with this assessment. With appropriate re-consenting, the subject can be retreated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator. Prior to re-introduction, the investigator should obtain written permission from the study medical monitor and the IRB. The investigator should also have the subject re-consent, explaining that re-introduction of study drug could lead to increased risk of recurrence. (please see section 16.2.3 for details)

Guidelines for the Management of Dry Eye

- **General considerations:** Avoid unnecessary exposure to sunlight, use sunglasses in bright light.
- **Prophylactic management:** Frequent use of artificial tear substitutes is strongly recommended.
- **Reactive management**:
  - Withhold JNJ-42756493 for Grade 3 toxicity
  - Artificial tear substitutes if not started, every 4 to 6 hours
  - Hydrating /lubricating eye gels and ointments
  - Severe treatment-related dry eye should be evaluated by an ophthalmologist

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

4.1 Therapeutic Parameters for JNJ-42756493 (Erdafitinib) Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving JNJ-42756493 (erdafitinib) 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
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]				
Ophthalmologic exam[L]	X	X			X	
Phosphate Levels[M]			X			
Tumor biopsy and blood sample for MATCH Master Protocol[E]				X	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).

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). Serum tumor markers are not required on Cycle 1, Day 15. 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 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 must be conducted in person. The Toxicity Assessment is not required prior to Cycle 1, but is required on cycle 1 day 1, cycle 1 day 15 and on day 1 of 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.

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.

L. All subjects should have monthly Amsler grid tests and an initial ophthalmological examination performed at Screening by an ophthalmologist, which should include assessment of visual acuity, tonometry, fundoscopy (examination of both central and peripheral zones should be performed); where available, an Optical Coherence Tomography (OCT) should be performed. A follow-up ophthalmological examination should be performed as clinically necessary based on the findings of the monthly Amsler grid tests and clinical assessment. It is assumed that about 30% patients will require follow-up ophthalmological examinations.

When Central Serous Retinopathy (CSR)/Retinal Pigment Epithelial Detachments (RPED) is suspected, an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected Retinal Vein Occlusion (RVO). It is also recommended that color fundus photos or OCT images be obtained and stored in the subject's records for future reference. In subjects with suspected retinal pathology such as CSR or RVO, a consultation with a retina specialist should be considered.

Amsler grid testing will be administered by the treating physician or nurse on Day 1 of each 28-day cycle. Observation of wavy, broken or distorted lines, or a blurred/missing area of vision is equivalent to a positive Amsler grid test. For any positive Amsler grid test, subject should be referred for full ophthalmologic exam within 7 days. However, if the subject has an abnormal Amsler grid test at baseline (during Screening), then a repeat ophthalmic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler Grid test at Screening, or the subject has developed new clinical symptoms.

M. For subjects, treatment will be up-titrated or maintained based on phosphate level measured on Cycle 1 Day 15, and taking into account observed toxicity to that day, as described in Figure 1. The up-titrated dose would be given starting on Cycle 1 Day 15.

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.

Ordering instructions for Cycle 1:

Once a patient is registered to Arm K1, the site should request Cycle 1 supplies through OAOP consisting of the following:

- 2 bottles of 4 mg tablets and 2 bottles of 3 mg tablets

This quantity provides enough JNJ42756493 (erdafitinib) to complete Cycle 1 at either the:

- Starting dose of 8 mg on Days 1 - 28, or
- Starting dose of 8 mg on Days 1 – 14 and the up-titrated dose of 9 mg on Days 15 – 28.

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Once it is determined whether the patient's dose will be up-titrated following completion of the Day 15 evaluation (including the patient's phosphate based on sections 3 and 4.1), a clinical drug request for the appropriate Cycle 2+ supplies should be submitted in OAOP per the usual ordering procedure.

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).

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 on this protocol.

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 JNJ-42756493 (NSC 781558)

5.1.1 Other Names:

Erdafitinib

5.1.2 Classification:

pan-FGFR tyrosine kinase inhibitor

5.1.3 Mode of Action:

JNJ-42756493 is an oral pan-FGFR tyrosine kinase inhibitor that has demonstrated potent inhibition of cell proliferation in FGFR pathway-activated cancer cell lines.

5.1.4 Storage and Stability:

Storage: Store intact bottles at controlled room temperature 15°C to 30°C (59 to 86°F).

If a storage temperature excursion is identified, promptly return JNJ42756493 to 15°C to 30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf life dating is printed on the bottle label.

5.1.5 Dose Specifics

JNJ-42756493 (erdafitinib) tablets will be administered orally once a day on a continuous daily dosing schedule on a 28-day cycle. Dose reductions are allowed according to Section 3.4.

JNJ-42756493 (erdafitinib) dose	Use tablet strengths
8 mg	2 x 4 mg
6 mg	2 x 3 mg
9 mg	3 x 3 mg

5.1.6 How Supplied:

Janssen Pharmaceuticals supplies and CTEP, NCI, DCTD distributes JNJ-42756493. The agent is available as 3 mg (yellow), 4 mg (orange), and 5 mg (brown) film coated tablets. The approximate dimensions of the round tablets are in the table below:

Strength	Diameter (mm)	Thickness (width) (mm)
3 mg	7.7 $\pm$ 0.2	3.7 $\pm$ 0.4
4 mg	8.2 $\pm$ 0.2	4.2 $\pm$ 0.4
5 mg	8.7 $\pm$ 0.2	4.6 $\pm$ 0.4

JNJ42756493 tablets are provided in 30 count bottles made of high density polyethylene (HDPE), with an induction seal and child resistant cap. Tablets must be dispensed in the original container.

Tablet excipients include mannitol, microcrystalline cellulose, meglumine, croscarmellose sodium, magnesium stearate, and Opadry AMB II.

5.1.7 Route of Administration:

Oral. Take tablets at least 1 hour before eating or at least 2 hours after a meal at approximately the same time each day. Tablets must be swallowed whole with 8 ounces of water. Do not crush or chew.

If a dose is missed, it can be taken up to 6 hours after the scheduled time; the subject may return to the normal schedule the following day. If it has been more than 6 hours since the missed dose, then that dose should be skipped and the subject should continue treatment at the scheduled time the next day.

5.1.8 Incompatibilities:

JNJ-42756493 shows weak inhibition potential towards CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. No clinical studies have been conducted yet for JNJ-42756493 regarding the potential for drug-drug interactions in humans.

CYP3A4 and CYP2C9 can be considered the dominant CYP450 enzymes involved in the microsomal metabolism of JNJ-42756493. With CYP2D6 and CYP2C8 can potentially be involved to a minor extent. Caution is to be exercised in combining JNJ-42756493 with strong inhibitors/inducers of CYP3A4/5 and CYP2C9. Subjects should be closely monitored for potential toxicities, and appropriate action, including temporary interruption of JNJ-42756493, as appropriate should be taken.

JNJ-42756493 has intermediate to high permeability with some indication of a P-glycoprotein (P-gp) efflux mechanism. Potent inhibitors of P-gp should be contraindicated.

5.1.9 Side Effects:

See Section 3.3 for side-effects

5.1.10 Nursing/Patient Implications

Female subjects (of child-bearing potential and sexually active) must use medically acceptable methods of birth control prior to study entry and for the duration of the study, and for 4 months after the last intake of study drug. Male subjects (with a partner of child-bearing potential) must use a condom with spermicide when sexually active **and** must not donate sperm from the first dose of study drug until 5 months after the last dose of study drug.

Medically acceptable methods of contraception that may be used by the subject and/or his/her partner include hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, true sexual abstinence, and surgical sterilization (eg, confirmed successful vasectomy or tubal ligation). True sexual abstinence is an acceptable method of contraception and is defined as refraining from heterosexual intercourse during the entire period of the study, including 4 months for females and 5 months for males after the last dose of study drug is given.

No clinically significant QT prolongation or cardiovascular effects have been noted to date. However, consistent QT prolongation was seen across several species in nonclinical studies. Concomitant administration of medications that induce QTc should be used with caution.

All subjects should be closely monitored with special attention to cardiovascular function and evidence of disturbance of phosphate homeostasis and bone pathology and ocular symptoms until sufficient clinical experience is obtained.

Ophthalmological testing should be performed once during screening. Additional exams should be performed as clinically necessary.

6. Translational Studies

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

7. References

1. Tabernero J, Bahleda R, Dienstmann R, et al. Phase I dose-escalation study of JNJ-42756493, an oral pan-fibroblast growth factor receptor inhibitor, in patients with advanced solid tumors. J Clin Oncol 2015; 33(30): 3372-4.
2. Siefker-Radtke AO, Mellado B, Decaestecker K, et al. Ongoing phase 2 study of erdafitinib (JNJ-42756403), a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor in patients (pts) with metastatic or unresectable urothelial carcinoma and FGFR gene alterations [abstract]. In: Proc ESMO 2016; Ann Oncol 2016 (suppl 6) abstract 845TiP

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol K1: JNJ-42756493 (Erdafitinib), FGFR Amplifications

Appendix I

Patient Pill Calendar

Storage: Store intact bottles at controlled room temperature 15°C to 30°C (59 to 86°F).

Pill Calendar Directions

1. Take your scheduled dose of each tablet.
2. If you forget, the missed tablets can be taken up to 6 hours after the scheduled time. If it has been more than 6 hours since the missed dose, that dose will be skipped and you will resume treatment at the next scheduled time.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
4. Tablets must be swallowed whole with 8 ounces of water. Do not crush or chew.
5. Tablets should be taken at least 1 hour before eating or 2 hours after a meal, at approximately the same time each day.
6. Subjects should avoid consuming grapefruit or Seville oranges while on study treatment.

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.

JNJ-42756493 (erdafitinib) dose	Use tablet strengths
3 mg	1 x 3 mg
4 mg	1 x 4 mg
5 mg	1 x 5 mg
6 mg	2 x 3 mg
8 mg	2 x 4 mg
9 mg	3 x 3 mg

JNJ-42756493 (Erdafitinib)

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		3 mg	4 mg	5 mg	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
22								
23								

DAY	Date Month	Day	Year	Time tablets taken	Number of tablets taken 3 mg	4 mg	5 mg	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.)
24								
25								
26								
27								
28								

Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol K1: JNJ-42756493 (Erdafitinib), FGFR Amplifications

Appendix II

Actionable Mutations for Sub-Protocol EAY131-K1

Gene Name	Variant ID	Variant Type	Variant Description	Level of Evidence Code
FGFR1	FGFR1	CNV	Amplification	3
FGFR2	FGFR2	CNV	Amplification	3
FGFR3	FGFR3	CNV	Amplification	3
FGFR4	FGFR4	CNV	Amplification	3

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol K1: JNJ-42756493 (Erdafitinib), FGFR Amplifications

Rev. Add16

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, JNJ42756493 (erdafitinib). 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:

JNJ42756493 interacts with a certain specific enzyme in your liver, and a certain transport protein that helps move drugs in and out of cells. JNJ42756493 may interact with the heart's electrical activity (QTc prolongation).

- The enzymes in question are **CYP3A4 and CYP2C9.** JNJ42756493 is broken down by these enzymes and may be affected by other drugs that inhibit or induce them.
- CYP3A4 and CYP2C9 can be considered the dominant CYP450 enzymes involved in the microsomal metabolism of JNJ-42756493. Caution is to be exercised in combining JNJ-42756493 with inhibitors/inducers of CYP3A4 and CYP2C9. JNJ-42756493 may be affected by drugs that increase or inhibit metabolism of CYP450 3A4 substrates. Therefore, administering JNJ-42756493 with drugs that potently inhibit or induce CYP450 3A4/5 or 2C9 has the potential to change the drug therapeutic effects (inducers) and toxicity (inhibitors).
- The protein in question is **P-glycoprotein.** JNJ-42756493 is moved in and out of cells/organs by this transport protein. Potent inhibitors of P-glycoprotein should be contraindicated.
- No clinically significant QT prolongation or cardiovascular effects have been noted to date. However, consistent QT prolongation was seen across several species in nonclinical studies. Therefore, concomitant administration of medications that induce QTc should be used with caution.

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

JNJ-42756493 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:

JNJ-42756493 must be used very carefully with other medicines that use certain **liver enzymes or 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 **CYP3A4, CYP2C9 or P-glycoprotein.** Concomitant administration of **medications that induce QTc should be used with caution.**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid consuming grapefruit or Seville oranges while taking JNJ-42756493
- 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 JNJ-42756493**.** This clinical trial is sponsored by the NCI. **JNJ-42756493 (erdafitinib)** may interact with drugs that are **processed by your liver, or use certain transport proteins in your** body, or **affects the electrical activity of your heart**. 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.

JNJ-42756493 interacts with specific liver enzymes called CYP3A4 and CYP2C9 and transport protein P-glycoprotein. JNJ42756493 must be used very carefully with other medicines that interact with these enzymes or transporter. Consistent QT prolongation was seen across species in nonclinical studies. Therefore, concomitant administration of medications that induce QTc should be used with caution.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A4, CYP2C9, or P-glycoprotein.
- Avoid consuming grapefruit or Seville oranges while taking study drug
- 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

  _____.