NATIONAL CANCER INSTITUTE
Center for Cancer Research

Pediatric Oncology Branch

DATE: May 19, 2018

TO: CTEP PIO, CTEP, NCI, NIH

Chairperson, NCI Central Institutional Review Board (NCI CIRB)

FROM: Udo Rudloff, MD

Principal Investigator
POB, CCR, NCI

SUBJECT: Amendment 4 to NCI protocol number 10050 entitled, "A Phase II Study of Selumetinib (AZD6244) for the Treatment of Advanced Pancreas Cancer harboring KRAS G12R Mutations"

The primary purpose of this amendment is to update protocol CAEPR and consent Selumetinib risk language. Additionally, please, note, as part of the implementation of version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE), the CAEPR list for selumetinib, which was previously in CTCAE 4.0 language, has been migrated to CTCAE 5.0 language.

Patients and their providers are able to send their tumor tissue for somatic gene mutation profiling to Foundation Medicine which performs rapid genotyping on multiple NGS platforms. It issues a CLIA report which is in line with study guidelines and makes the patients, without the need for further screening, immediately eligible for starting treatment with selumetinib. In this regard, we clarified in the protocol that test result from CLIA certified laboratory, confirming somatic KRAS G12R mutation can be used for confirmation of patient's eligibility and to decrease the number of patients screened.

We also have updated dosing delays/dose modifications of selumetinib for the management of grade 2 AST/ALT elevations to give patients who only have a transient brief AST/ALT under appropriate lab monitoring the possibility to return to DL 0. However, should a grade 2 or greater AST/ALT elevation again occur after restarting selumetinib or return to DL 0, the patient can only continue on DL -1. The AST/ALT elevations we observed were very transient. To eliminate ambiguity as to how often patients can return to higher dose levels after resolution of low grade ALT/AST elevations or other related lab abnormalities, we amended Section 6: Upon two recurrences of DLT necessitating dose reduction, no further attempts to return to higher dose level after resolution to ≤Grade 1 will be made.

Finally, we simplified eligibility criteria with regard to total bilirubin levels now using cutoff elevated versus not elevated above institutional normal (different institutions have different definitions and cutoffs), and defining AEs as elevated above institutional accepted normal levels.

Editorial changes have been made throughout the document for clarity.

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
1	Stats	The trial has expected outcome data for many of the first 7 patients. Changing the statistical plan at this point decreases the statistical rigor of the final analysis. This has been discussed several times with CTEP biostatisticians and CTEP leadership and we do not favor any changes to the 2-stage design for the trial. If there is not an objective response in the first 7 patients, the trial should not proceed to a second stage. If there appears later to be a signal for prolonged stable disease in these first-stage patients, this can be discussed with CTEP and AstraZeneca. **Response: We agreed not to change statistical plan.**

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

#	Section	Comments
2	4.2.2	Specimen Tracking Training: According to section 9.1.1 all sample tracking will be managed at NCI. Please confirm, and if this text is unnecessary, please delete. **Response: Samples collected at NCI only will be additionally tracked in NCI as described in section 9.1.1. Procedures described in Section 4.2.2 will be also followed.**
3	Table 9	ctDNA Blood Collection: the link should be labeled Appendix H rather than Appendix G. It does jump to the correct section. **Response: This has been corrected in Section 9**

III. Recommendations:

#	Section	Comments
	7.3.3	In the third paragraph, please replace, "Death due to progressive disease should be reported as Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)" under the system organ class (SOC) of the same name." with the following: "Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." **Response: This has been replaced in Section 7.3.3 Expedited Reporting Guidelines**
	4.1	At the time of the next amendment please replace 4.1.1 and 4.1.2 using the following templated text and reformat section 4.1 accordingly:

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td></td><td>
Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.
<table>
<tr><th>Documentation Required</th><th>IVR</th><th>NPIVR</th><th>AP</th><th>A</th></tr>
<tr><td>FDA Form 1572</td><td>✔</td><td>✔</td><td></td><td></td></tr>
<tr><td>Financial Disclosure Form</td><td>✔</td><td>✔</td><td>✔</td><td></td></tr>
<tr><td>NCI Biosketch (education, training, employment, license, and certification)</td><td>✔</td><td>✔</td><td>✔</td><td></td></tr>
<tr><td>HSP/GCP training</td><td>✔</td><td>✔</td><td>✔</td><td></td></tr>
<tr><td>Agent Shipment Form (if applicable)</td><td>✔</td><td></td><td></td><td></td></tr>
<tr><td>CV (optional)</td><td>✔</td><td>✔</td><td>✔</td><td></td></tr>
</table>
An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

</td></tr>
</table>

#	Section	Comments
		Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >. **Response: This has been replaced in the Section 4.1 Investigator and Research Associate Registration with CTEP**
	4.2	At the time of the next amendment please replace 4.2 using the following templated text: This study is supported by the NCI Cancer Trials Support Unit (CTSU). Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following: • An active Federal Wide Assurance (FWA) number • An active roster affiliation with the Lead Network or a participating organization • A valid IRB approval • Compliance with all protocol specific requirements. In addition, the site-protocol Principal Investigator (PI) must meet the following criteria: • Active registration status • The IRB number of the site IRB of record listed on their Form FDA 1572 • An active status on a participating roster at the registering site Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. **Response: This has been replaced in the section 4.2 Site Registration**
	8.1.2.1	At the time of the next amendment please delete these sections and replace with the following updated language:

#	Section	Comments
		Agent Ordering and Agent Accountability NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution. Study agent must be ordered after patient is registered to the treatment arm as no starter supplies are being provided for this study. Submit agent requests 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. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management. **Response: This has been replaced in section 8.1.2 Agent Ordering and Agent Accountability**
	8.1.2.4	At the time of the next amendment please delete and replace with the following updated language: Useful Links and Contacts • CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/ • NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov • PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm • PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP • CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/ • CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov • IB Coordinator: IBCoordinator@mail.nih.gov • PMB email: PMBAfterHours@mail.nih.gov • PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET). **Response: This has been replaced in Section 8.1.2.4 Useful links and Contacts**

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td>4.1.1,
4.1.2</td><td>
Please delete the information in these 2 subsections and replace with the following language, in accordance with the Registration and Credential Repository initiative.

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

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• Added to a site roster
</td></tr>
</table>

#	Section	Comments
		• Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN • Act as the site-protocol PI on the IRB approval • Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL). Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >. **Response: This has been replaced in Section 4.1 Investigator and Research Associate Registration with CTEP**
	4.2	**Please revise the following paragraph as specified.** Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following: ~~an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.~~ • An active Federal Wide Assurance (FWA) number • An active roster affiliation with the Lead Network or a participating organization • A valid IRB approval • Compliance with all protocol specific requirements. In addition, the site-protocol Principal Investigator (PI) must meet the following criteria: • Active registration status • The IRB number of the site IRB of record listed on their Form FDA 1572 • An active status on a participating roster at the registering site **Response: This has been replaced in section 4.2 Site Registration**
	4.2.2	**Please delete the following bullet point.** • CTSU Transmittal Sheet (optional) **In addition, while 10050 has been identified as a Specimen Tracking study, and the following information is required to be included in this section.** • Specimen Tracking Training ▪ At least one individual at each participating site will need to complete the Theradex-led training ▪ Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal

#	Section	Comments
		▪ The training is a one-time only requirement per individual ▪ This training will need to be completed before the first patient enrollment at a given site ▪ Peter Clark is the main point of contact at Theradex for the training (802-456-8735, PClark@theradex.com). Nafeesa Sarakhawas is the backup contact (609.480.2693, NSarakhawas@theradex.com). **Response: This has been corrected in section 4.2.2 Requirements For 10050 Site Registration**
	4.3.4	**Please revise the following bullet point as indicated.** • To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type. **Response: This has been updated in Section 4.3.4 OPEN/IWRS User Requirements**
	12.2	**Please revise the sentence below as specified.** Data collection for this study will be done through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA, ~~(~~Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the ind ividual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.. **Response: This has been replaced in Section 12.2 Data Reporting**
	12.2.1	**Please update the Theradex email address to CTMSSupport@theradex.com** **Response: This has been updated in section 12.2.1 Method**

ADDITIONAL CHANGES:

1. **Document header**. The version date has been updated.
2. **TITLE** page: branch affiliation, room number and fax number of Dr. Rudloff have been updated, Cara Kenney has been removed from the list of NIH Associate investigators, Santhana Webb, Linda Sciuto and Rasa Viliams have been added to the list; Cara Kenney has been removed and Santhana Webb has been added as Study coordinator/Referral contact, Tatiana Beresnev has been removed as Responsible Data Manager, identification of amendment has been added, version date has been updated.

3. In the **Design:** of PRECIS and Section **5 TREATMENT PLAN** the clarification about selumetinib administration in regard to meals have been done.
4. **TABLE OF CONTENTS** has been updated
5. In the Section **3.1.4** we made clarification, that patients are eligible, if they already have KRAS mutation status confirmation.
6. In the Section **3.1.8 Patients must have normal organ and marrow function as defined below**: the correction has been made to allow participation of subjects with total bilirubin below institutional limits.
7. In the Section **4.2.3 Submitting Regulatory Documents** suite number of CTSU regulatory office has been corrected.
8. In the Section **4.3 Patient Registration** reference to Harris (HOIS) has been removed as the company has been renamed.
9. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 has been replaced with version 5.0 in Sections **6 DOSING DELAYS/DOSE MODIFICATIONS**, Section **7.2 Adverse Event Characteristics**, and Section **12.1 Study Oversight**
10. In the Section **6 DOSING DELAYS/DOSE MODIFICATIONS** we updated table with Summary of dose holding/interruptions and dose de-escalation recommendations for selumetinib.
11. In the Section **7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS** CAEPR for Selumetinib has been updated.
12. Section **7.7.3 Non-compliance (NIH Definition)** with NIH definition of non-compliance has been added as the clinical director now requires reports of this event.
13. Section **7.7.4 NCI Clinical Director Reporting** has been updated per current NCI clinical director reporting requirements.
14. Reference to Appendix I and clarification about KRAS mutation test have been added in Section **9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES**.
15. Shipping address has been updated in Section Shipping instructions for Participating sites
16. The **STUDY CALENDAR** has been updated to explain screening KRAS mutation test.
17. Section **STATISTICAL CONSIDERATIONS** has been updated to explain new number of patients screened.
18. **Appendix I: Cancer Gene Mutation-Standard Panel** has been added.

NCI Protocol #: 10050

Local Protocol #: 17C0144

ClinicalTrials.gov Identifier: NCT03040986

TITLE: A Phase II Study of Selumetinib (AZD6244) for the Treatment of Advanced Pancreas Cancer harboring KRAS G12R Mutations

Corresponding Organization: National Cancer Institute LAO-NCI

Principal Investigator: Udo Rudloff, MD, PhD, POB/CCR/NCI ([A-F])
10 Center Drive, CRC Room 2B38D
Bethesda, MD 20892
Phone: 240-760-6238
Fax: 301-480-2462
Udo.Rudloff@nih.gov

Participating Organizations:

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO

NIH Associate Investigators: Anish Thomas, DTB/CCR/NCI ([A-F])
10 Center Drive, Room 4-5330
Bethesda, MD 20892-1906
Phone: 240-760-6241
Email: anish.thomas@nih.gov

Santhana Webb, OCD/CCR/NCI ([A-C, E-F])
10 Center Drive, Room 8D44F
Bethesda, MD 20892-1906
Phone: 240-858-3165
Email: santhana.webb@ mail.nih.gov

Linda Sciuto, OCD/CCR/NCI ([A-C, E-F])
10 Center Drive, Room 8D48
Bethesda, MD 20892-1906
Phone: 240-760-6117
Email: lsciuto@mail.nih.gov

Rasa Vilimas, OCD/CCR/NCI ([A-C, E-F])
10 Center Drive, Room 8D44
Bethesda, MD 20892-1906
Phone: 240-858-3158
FAX: 301-480-2462
Email: rasa.viliams@nih.gov

Statistician:

Seth Steinberg, Ph.D. ([E-F])
Head, Biostatistics and Data Management Section
Office of the Clinical Director, Center for Cancer Research
National Cancer Institute
9609 Medical Center Drive, Room 2W334, MSC 9716
Bethesda, MD 20892
Phone: 240-276-5563
steinbes@mail.nih.gov

Study Coordinator/ Referral Contact:

Santhana Webb, R.N. ([A-C, E-F])
10 Center Drive, Room 8D44F
Bethesda, MD 20892-1906
Phone: 240-858-3165
Fax: 301-480-2462
Email: santhana.webb@nih.gov

Roles

A. Obtain information by intervening or interacting with living individuals for research purposes
B. Obtaining identifiable private information about living individuals
C. Obtaining the voluntary informed consent of individuals to be subjects
D. Makes decisions about subject eligibility
E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
G. Some/all research activities performed outside NIH

NCI-Supplied Agent:

Drug Name:	AZD6244 hydrogen sulfate (Selumetinib) (NSC 748727)
IND #:	
Sponsor	DCTD, NCI
Manufacturer	AstraZeneca

Protocol Type / Version # / Version Date: Amendment 4/Version 1/ May 19, 2018

PRÉCIS

Background:

- It is expected that in 2020 pancreas cancer will rank 2nd in cancer-related deaths in the U.S. having surpassed colon and breast cancer.
- Patients with advanced pancreas cancer have few available treatment options and an overall poor prognosis.
- The vast majority of pancreatic cancers (up to ≥94%) harbor mutations of the KRAS gene, and there is ample preclinical evidence that KRAS mutations are an essential driver of pancreas cancer development and progression, essential for the unique metabolomic and transcriptomic landscape of pancreatic cancers, involved in pancreatic cancer stem cell formation, as well as in mediation of resistance to chemo- and molecular therapy.
- KRAS mutational isoforms and regulators of MAPK signaling are a prognostic biomarker for outcome in pancreas cancer. KRAS G12R mutation status predicts response to selumetinib inhibition in a large panel of pancreas cancer cell lines.
- Pre-clinical evidence, both in a large panel of cell lines and in patient-derived xenotransplantation models, suggests that selumetinib (AZD6244) has activity against pancreas cancers harboring KRAS G12R mutations.
- This study tests the hypothesis if patients with advanced pancreas cancer with a unique KRAS mutational isoform respond to the MEK inhibitor selumetinib (AZD6244) and if genetic or protein expression information derived from treated patients distinguishes patients responding to the drug from patients progressing under treatment.

Objectives:

- Determine the objective response rate to selumetinib administered as 75 mg orally twice daily on a continuous schedule in patients with advanced pancreas cancer harboring KRAS G12R mutations.

Eligibility:

- Patients must have histologically confirmed locally advanced or metastatic pancreas cancer
- Patients must have confirmed somatic KRAS G12R mutation as determined by sequence analysis of matched normal DNA from any specimen obtained from the individual (prior CLIA genotyping results from surgical resection specimens are acceptable).
- Patients must not have had chemotherapy, molecular therapy with erlotinib, radiation therapy, or experimental biological or molecular therapy for at least 4 weeks prior to starting study medication. Patients who received FOLFIRINOX must be 6 weeks from the last administration of therapy. Patients must have recovered from any acute toxicity related to prior therapy or surgery, to a grade 1 or less unless specified.
- Age ≥18 years.

Design:

- Patients will be screened for the presence of KRAS gene mutations in their tumor and only patients who harbor KRAS G12R mutations will be enrolled in the treatment phase of the study.
- Selumetinib (AZD6244) will be administered as an oral dose of selumetinib sulfate 75 mg twice daily (in the morning and evening) taken two hours after a meal and one hour before the next meal. Selumetinib will be given continuously; one cycle equals 28 +/- 2 days.
- Up to 25 eligible patients (allowing for a staged accrual of initially 10 patients who will receive selumetinib and are evaluable after the 1st cycle) will be treated over 3-4 years and the trial will be completed over 4 to 5 years, allowing for completion of follow-up.

SCHEMA

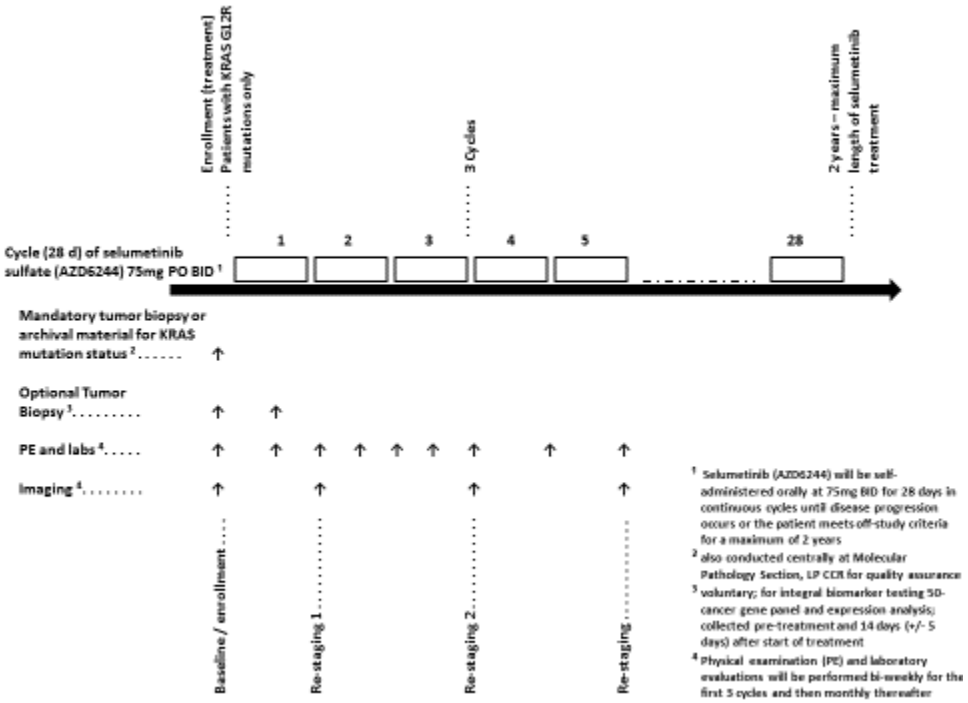

Enrollment (treatment) Patients with KRAS G12R mutations only
3 Cycles
2 years – maximum length of selumetinib treatment
Cycle (28 d) of selumetinib sulfate (AZD6244) 75mg PO BID [1]
1
2
3
4
5
28
Mandatory tumor biopsy or archival material for KRAS mutation status [2]
Optional Tumor Biopsy [3]
PE and labs [4]
Imaging [4]
Baseline / enrollment
Re-staging 1
Re-staging 2
Re-staging
[1] Selumetinib (AZD6244) will be self-administered orally at 75mg BID for 28 days in continuous cycles until disease progression occurs or the patient meets off-study criteria for a maximum of 2 years
[2] also conducted centrally at Molecular Pathology Section, LP CCR for quality assurance
[3] voluntary; for integral biomarker testing 50-cancer gene panel and expression analysis; collected pre-treatment and 14 days (+/- 5 days) after start of treatment
[4] Physical examination (PE) and laboratory evaluations will be performed bi-weekly for the first 3 cycles and then monthly thereafter

TABLE OF CONTENTS

1 OBJECTIVES

1.1 Primary Objective

1.1.1 Determine the objective response rate to selumetinib administered as 75 mg orally twice daily on a continuous schedule in patients with advanced pancreas cancer harboring KRAS G12R mutations.

1.2 Secondary Objectives

1.2.1 To determine the progression free survival of patients with locally advanced, unresectable and stage IV pancreas cancer treated with selumetinib monotherapy.

1.2.2 To evaluate the safety of selumetinib in patients with advanced pancreas cancer

1.2.3 To determine the impact of additional genetic alterations on the response to selumetinib in pancreas cancer harboring KRAS G12R mutations

1.2.4 To develop a clinically applicable biomarker predicting response to selumetinib in pancreas cancer harboring KRAS G12R mutations

2 BACKGROUND

2.1 Study Disease

2.1.1 Pancreas cancer – a disease with dire need for improved treatments

The grave unmet medical need for improved treatments in pancreas cancer is well documented by

A. a 5-year overall survival rate of 7% which has not substantially changed over the last 3 decades
B. regulatory approval of only 2 cytotoxic chemotherapy combination regimens (FOLFIRINOX and gemcitabine+abraxane) since the approval of gemcitabine in 1996 extending overall survival by a few months in the combination treatment arms
C. a current lack of any effective precision medicine molecular therapy options

It is expected that in 2020 pancreas cancer will rank 2nd in cancer-related deaths in the U.S. having surpassed colon and breast cancer.[1] Following a U.S. Congressional request, NCI has responded in 2010 with a NCI National Pancreas Cancer Action Plan detailing, among other priorities and updates, the development of novel innovative therapy options tailored to the unique biology of pancreas cancer as priorities in the future fight against this disease.[2]

There are no effective molecular therapy options available in pancreas cancer. The anti-EGFR small molecule inhibitor erlotinib (Tarceva) received regulatory approval in 2007 following the large phase III Canadian NCIC CTG PA.3 trial.[3] This study randomized patients afflicted by advanced pancreas cancer (23.5% locally advanced; 76.5% stage IV) to either gemcitabine vs gemcitabine plus erlotinib. An increase in OS and PFS of 14 days (2 weeks) in the gemcitabine+erlotinib group was observed. While statistically significant, actual prescribing of erlotinib by practicing physicians has declined due to skepticism of its clinical relevance. However, considering the positive signal in this large trial it is likely that there is a subset of patients which may benefit from anti-EGFR therapy. Consecutive biomarker studies however, in particular KRAS wild type mutation status (following the strong predictive value of KRAS wt status for anti-EGFR therapy by cetuximab or panatumumuab in colorectal cancer) or EGFR amplification status failed to predict a subset of patients with a robust response or improved outcome receiving erlotinib

treatment.[4] These results are mirrored by the large phase III Southwest Oncology Group–Directed Intergroup Trial S0205 trial of gemcitabine vs gemcitabine+cetuximab in advanced pancreas cancer patients: there was a trend towards an improvement of quality-of-life indicators at early measurement points in the gemcitabine+cetuximab arm, however no correlative biomarker studies are available to identify a subset enriched for improved outcome.[5] Thus, findings in NCIC CTG PA.3 and SWOG Intergroup S0205 on a total of 1,335 patients suggest that there may be a subset(s) of patients who may benefit from an anti-EGFR, or a similar molecular therapy approach, but that the lack of an accurate biomarker, or understanding of aberrant EGFR signaling, including its effector MAPK pathway, currently prevents these patients from receiving improved therapy options, and possibly better outcome, in this rapidly fatal disease.

Some of the currently most promising molecular, or precision medicine, therapy approaches pursued in pancreas cancer to date include, for example, the administration PARP inhibitors in BRCA-mutant pancreas cancer (the DNA damage repair genes BRCA1 and 2 are affected by somatic variants in 5-7% of pancreas cancers), the administration of the chemotherapy agent oxaliplatinum to patients selected based on a recent genomic DNA damage repair response signature,[6] or the 5-hyaluranic acid inhibitor PEGPH20 in combination with gemcitabine to increase delivery of gemcitabine to the tumor following lowering of interstitial pressures and 'break of the stromal barrier'.[7]

In this regard, and as a landmark study in the field, pancreas cancer clinical research has spearheaded a first-in-time first-in-human effort of genotype-directed molecular therapy using whole genome sequencing (WGS).[8] Investigators of the recently released Precision Medicine for Advanced Pancreas Cancer: The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) Trial attempted to identify druggable mutations in pancreas cancer tumor genomes by WGS and treat patients with small molecule inhibitors based on these findings. This study initially raised concerns about the feasibility of acquiring suitable tumor specimens for molecular analysis and returning high-quality actionable genomic data within a clinically acceptable timeframe: an inability to obtain a biopsy or insufficient tumor content in the available specimen were common reasons for patient exclusion from molecular analysis while deteriorating performance status prohibited a number of patients from proceeding in the study. However, a number of somatic variants which triggered a pre-determined signal for molecular therapy were identified including KRAS wild type mutation status, HER2 amplifications, BRCA1 or 2 mutations or somatic variants in ATM1 or other rare variants attesting to the feasibility of this strategy.[8] No clinical outcome data are currently available. This precision medicine concept even now extends onto selecting patients with BRCA variants or 'BRCA-like' variant signatures or with immunogenic signatures based on large-scale gene expression profiling for immunotherapies like immune checkpoint inhibitors or anti-CSF/CSFR1 therapy targeting tumor associated macrophages.[9, 10]

2.1.2 The KRAS mutational landscape in pancreas cancer

The vast majority of pancreatic cancers (up to ≥94%) harbor mutations of the KRAS gene, and there is ample preclinical evidence that KRAS mutations are an essential driver of pancreas cancer development and progression, essential for the unique metabolomic and transcriptomic landscape of pancreatic cancers, involved in pancreatic cancer stem cell formation, as well as in mediation of resistance to chemo- and molecular therapy.[9-11] That there is considerable heterogeneity within KRAS mutant pancreas cancers, with substantial implications for guiding therapy, has been

shown in vitro in elegant synthetic lethality studies, and in correlative tissue studies defining classical and quasi-mesenchymal subtypes guiding response to gemcitabine or erlotinib therapy.[12, 13]

KRAS mutations affecting codon 12 comprise of nearly all KRAS mutations in pancreas cancer. KRAS G12R mutations are after KRAS G12D and G12V the 3rd most common KRAS isoform mutations in pancreas cancer comprising of up to 20% of KRAS mutations in some studies.[14] Overall both, affected codons, namely codon 12, 13, and 61 of the KRAS oncogene, and nucleotide substitutions of affected codons are highly specific and differ between the three 'KRAS cancers' pancreas cancer, colon cancers, and NSCLC. **Figure 1** shows distribution of KRAS mutational isoforms derived from large-scale genotyping efforts including NCIs TCGA initiative across pancreas, colon, and non-small cell lung cancer. KRAS G12R mutations (highlighted in orange, lower panel) are highly unique for pancreas cancer as they are exceedingly rare, or non-existent, in other cancers (1% in thyroid cancers, <2% in NSCLC, <2% in colon cancers of all KRAS mutant cancers).

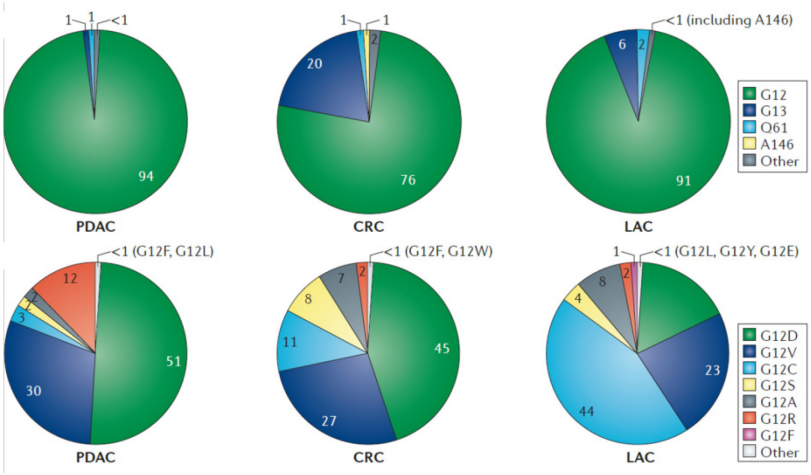


Figure 1. KRAS mutations vary across different epithelial cancers including pancreas cancer (PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; LAC, lung adenocarcinoma). Upper panel, codons affected by somatic variants in the KRAS oncogene across different cancer, lower panel, distribution of KRAS mutational isoforms of codon 12 (from Cox AD et al. 2014).

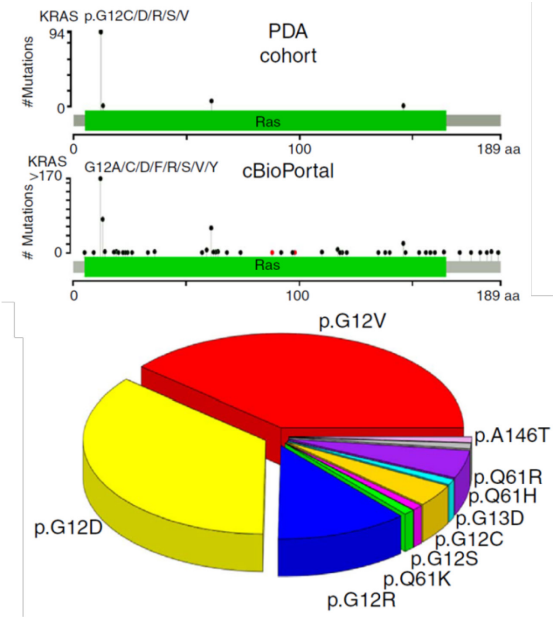


Figure 2. KRAS mutation profile in PDAC (top) and in other cancers (cBioPortal, bottom). Pie chart of KRAS mutational isoforms in pancreas cancer, percentage of KRAS G12R mutations in blue (from Witkiewicz AK et al. 2015).

2.1.3 KRAS mutational isoforms and regulators of MAPK signaling are a prognostic biomarker for outcome in pancreas cancer

KRAS mutational status per see (KRAS wild type versus KRAS mutant) as well as KRAS mutational isoform status are associated with different clinical outcomes in pancreas cancer.[11, 15] **Figure 3** shows the improved outcome, including overall survival, of stage IV pancreas cancer patients with KRAS G12V mutations compared to G12D and G12R mutations measured in biopsy specimens, **Figure 4** shows the improved overall survival of KRAS Q61 mutations to non-Q61 mutations in surgical resection specimens of a recent large exomic sequencing study of >100 pancreatic cancer specimens.[11, 15] These studies showed that patients affected by tumors without KRAS mutations have better outcomes compared to patients afflicted by pancreas cancers harboring KRAS mutations and that different Kras mutational isoforms are associated with different effector states of MAPK signaling. These observations are affirmed by findings in our laboratory: using the SEER Pancreas Cancer Tissue Microarray (TMA) and a TMA with pancreas cancer biospecimens constructed from NIH patients, we identified the scaffolding kinase "connective tissue enhancer of KSR" (CNKSR1), a major regulator of MAPK pathway signaling - identified within a large RNAi kinome screen as a major mediator of resistance to MEK inhibition in the MEK-resistant cell line YAPC -, as a novel prognostic biomarker. Pancreas cancer patients with high CNKSR1 expression (measured as 2+ or 3+) versus patients with low CNKSR1 expression (0 or 1+) had significantly improved overall survival following resection of their tumors. Thus, KRAS mutational isoforms likely vary in their impact on pancreas cancer biology and pancreas cancer progression due to different mechanisms of action and signal transduction dependencies.

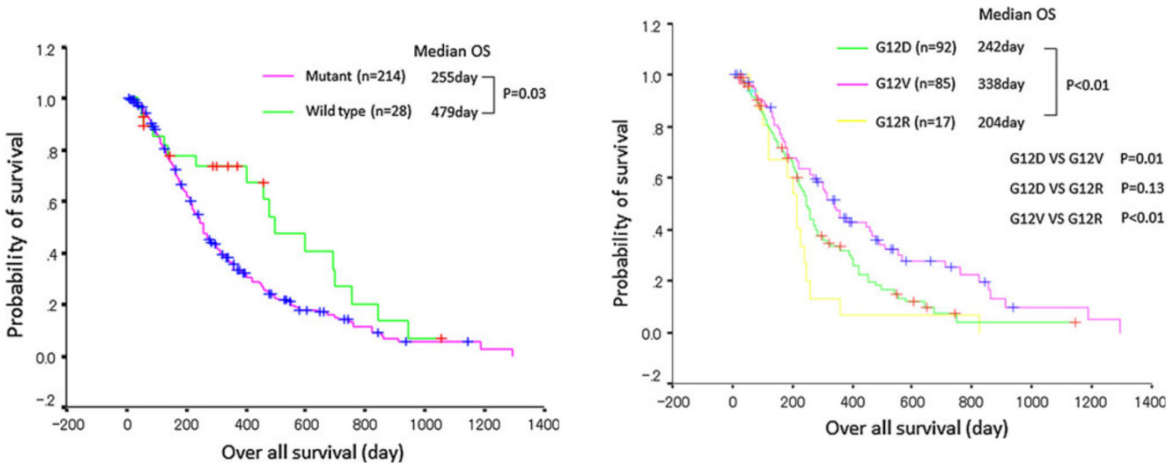


Figure 3. Impact of KRAS wild type status (left), and KRAS mutation subtype (KRAS G12V, G12D, and G12R, right) on overall survival of patients with advanced pancreas cancer (from Ogura T et al. 2013).

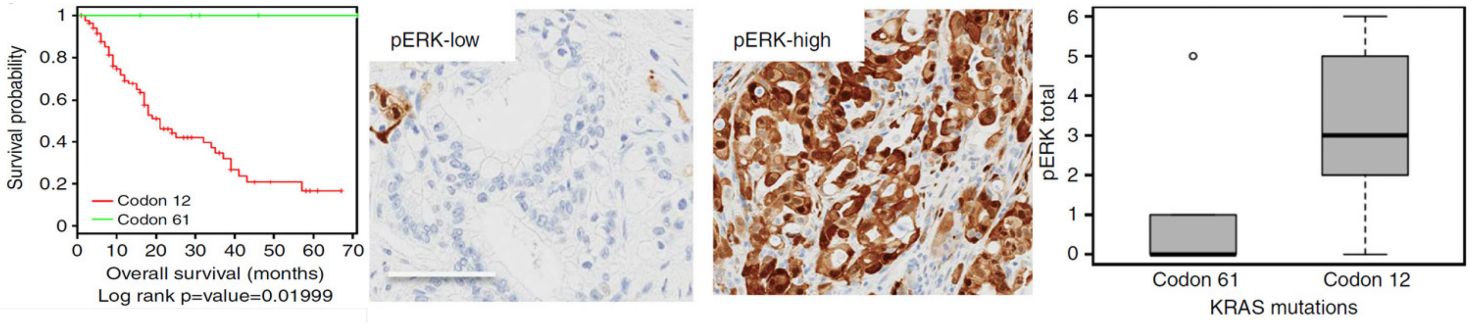


Figure 4. Kaplan-Meier analysis of KRAS codon 12 vs codon 61 mutations (left). Different KRAS mutational isoforms are associated with unique downstream signaling. phospho-ERK levels measured by immunohistochemistry in KRAS codon 61 versus codon 12 mutational subtype are shown (right) (from Witkiewicz AK et al. 2015).

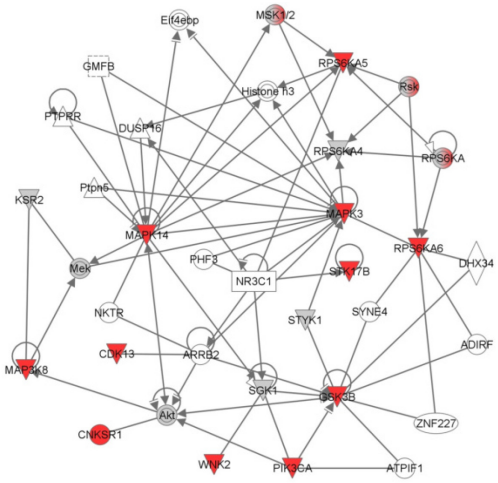


Figure 5. RNAi screen in pancreatic cancer cell line YAPC. Top candidates are enriched in known protein-protein interactions as determined by IPA. This screen targeting a set of 704 genes, which included the human kinome, identifies modulators of selumetinib response in the MEK-resistant network was generated through an IPA core analysis of the 17 genes scoring with 2 active siRNAs. The analysis considered only known direct relationships between genes, and used the 704 genes represented in the screen as background. Top candidates highlighted in red. The network was the top scoring IPA network (score = 29).

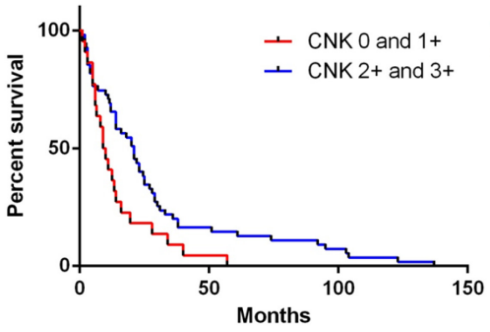


Figure 6. Expression levels of the MAPK pathway regulator CNKSR1 identified via RNAi screening of selumetinib treated vs untreated cells have prognostic value for the outcome of surgically resected pancreas cancer patients (Log-rank (Mantel-Cox) test; p=0.0151)

2.1.4 KRAS G12R mutation status predicts response to selumetinib inhibition in a large panel of pancreas cancer cell lines

Figure 7 shows waterfall plots of response to selumetinib in a panel of 52 authenticated pancreatic cell lines as measured by activity area and IC50. KRAS mutation status is shown for each cell line, cell lines harboring KRAS G12R mutations are highlighted in red. To demonstrate a 'class-effect' and to exclude that observed profile is unique to selumetinib, cell lines were also treated with MEK162 (Novartis) and the ERK inhibitor VTX-11e yielding a similar sensitivity profile (data not shown). **Figure 7** shows the summary of comparisons of sensitivity profiles of KRAS G12R versus non-G12R pancreas cancer cell lines as scatter plots using activity area (measure of efficacy and potency, or 1-AUC, left) and IC50 (potency, right): pancreas cancer cell lines harboring KRAS G12R mutations are 3 – 10 times more sensitive than cell lines harboring other KRAS mutational isoforms. To validate these findings in an independent set of cell lines, the cell line encyclopedia panel from the Broad Institute was interrogated for cell lines with known RAS mutation status and data on treatment with selumetinib.[16] All pancreas cancer cell lines treated in the discovery panel were removed. Due to the paucity of cell lines with KRAS G12R mutations in non-PDAC histologies, the G12R group comprised of 4 cell lines (thyroid cancer, NSCLC). When compared to non-KRAS G12R mutant KRAS cell lines from a diverse group of different non-PDAC histologies, cell lines harboring KRAS G12R mutations were again more sensitive than non-KRAS G12R lines (**Figure 8**, right).[16] To confirm the validity of our activity area measurements in the

pancreas cancer panel, similar scatter plots were derived from the Broad Institute pancreas cancer cell line panel treated with selumetinib. KRAS G12R harboring cell lines, like in our panel (92% overlap of used cell lines; only 3 KRAS G12R lines), were again the most sensitive subgroup (data not shown).

These in vitro findings in PDAC are further affirmed by a recent study with the MEK inhibitor MEK162 in 29 pancreatic cancer lines, some of them also present in our larger panel: cell lines with the electrically charged amino acid substitution aspartic acid for glycin at codon 12 (KRAS G12D) were statistically significantly more sensitive compared to cell lines harboring KRAS codon mutations leading to the hydrophobic insertion of valine for glycin (KRAS G12V) (**Figure 9**). While this panel only contained two KRAS G12R mutant cell lines (introducing an arginine (ARG) at codon 12), which precluded a statistical comparison, their median IC50 was equally low than the one of the KRAS G12D-mutant cell lines (**Figure 9**).[17] These, and above findings suggest that the electrically charged arginine or aspartate introduced by the G12R and G12D variant triggers unique pertubations in the interactions with RAS binding partners like other kinases or regulatory proteins like scaffolding proteins or phosphatases which govern select responses to small molecule inhibition. Signal transduction pertubations unique to KRAS mutational isoforms have recently been shown in a detailed phosphoproteomic analysis of KRAS-isogenic cell lines.[18]

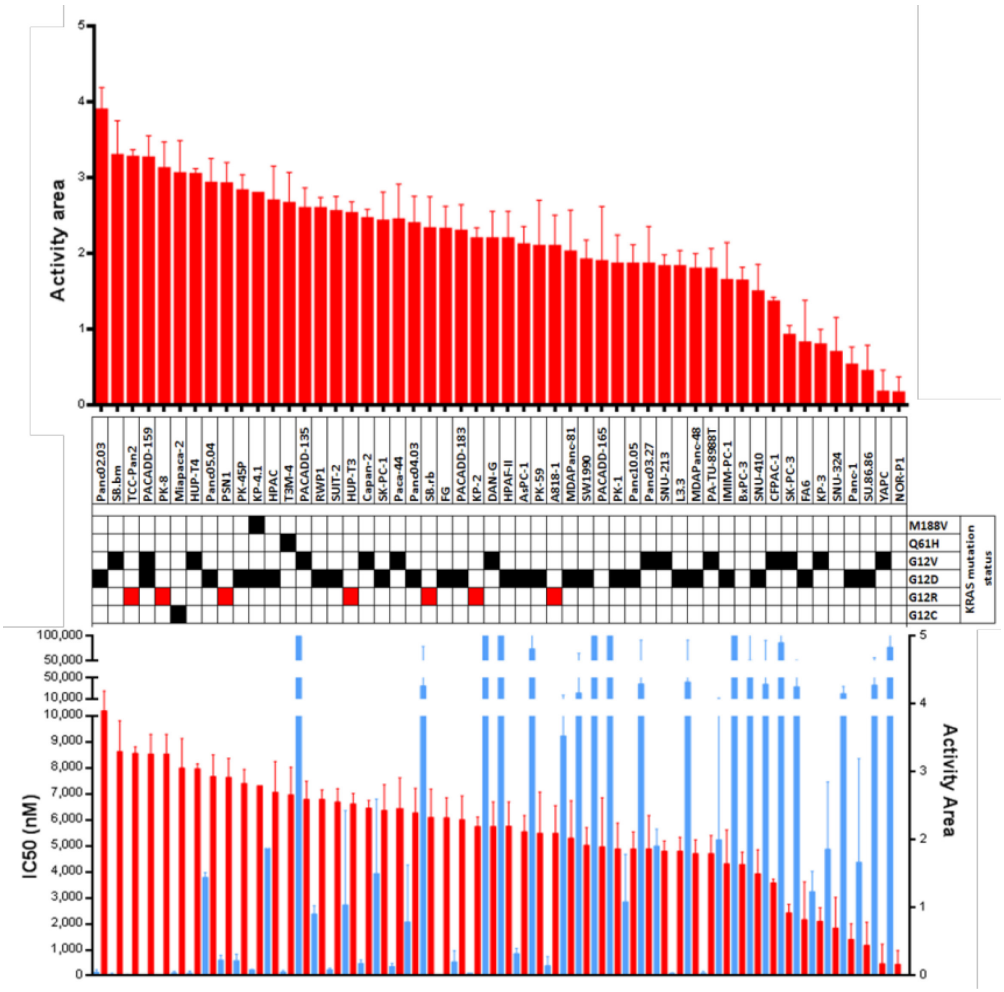


Figure 7. In vitro sensitivity of selumetinib in 52 authenticated pancreatic cancer cell and tissue culture lines. Activity area capturing maximum response for each cell line (red bar, top), KRAS mutation status (mid, KRAS G12R mutations highlighted in red), and comparison to potency measurements (IC50, blue bars, bottom) are shown.

Furthermore, data from isogenic SW48 colon cancer cell lines show that cells with a KRAS G12R allele are highly sensitive to selumetinib compared to SW48 cells with hemiallelic KRAS G12D mutations (**Figure 10**).[19] In this colon cancer model, isogenic KRAS G12V mutations displayed similar sensitivity to selumetinib as KRAS G12R mutations, and a detailed recent phosphoproteomic analysis of these isogenic SW48 cell lines has yielded unique signatures associated with individual KRAS mutations.[19]

In summary, irrespective of source pancreas cancer panel (Rudloff lab vs [16]), activity measure (activity area vs IC50), pancreas cancer vs non-pancreas cancer histology, or type of MEK inhibitor (selumetinib vs MEK162) KRAS G12R mutation status consistently identified most sensitive group of cell lines.

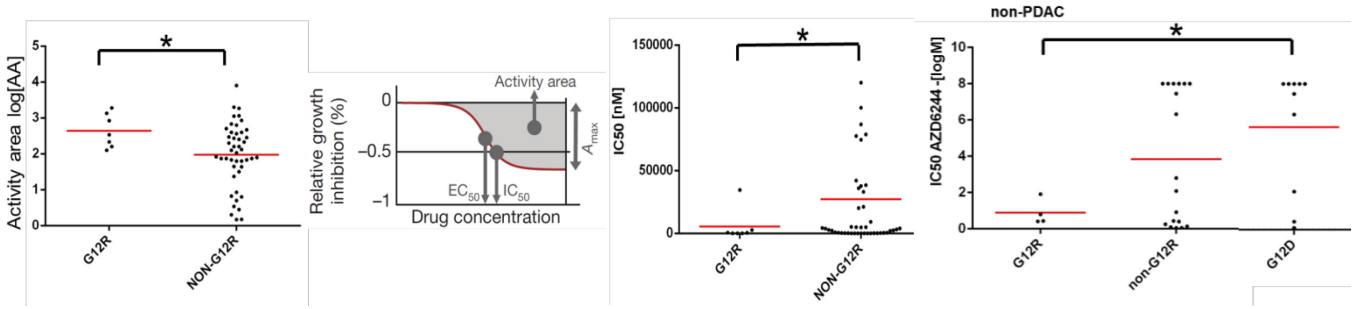


Figure 8. Average activity (AA) area (sum of differences between measured Ai at concentration i and A = 0, excluding positive A values: AA = Σi[0-min(0,Ai/100)] (left) and IC50s (middle, in nM) of PDAC cell lines; Mann Whitney test, 2-tailed, p≤0.05 indicated as *). Scatter plots of independent set (obtained from Barretina J et al, 2012) of non-PDAC cell lines with known KRAS mutation status and treated with selumetinib (right).

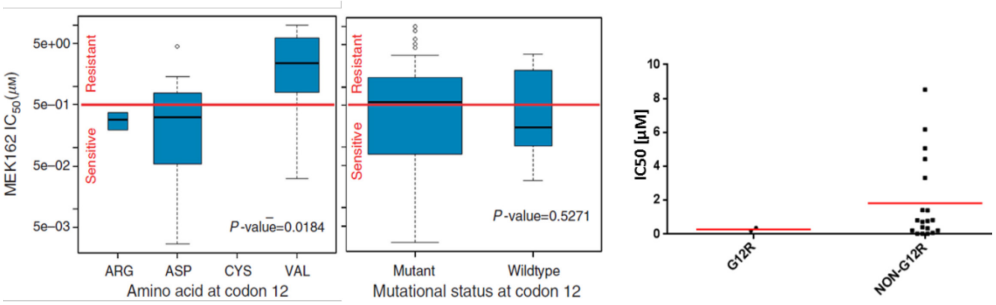


Figure 9. Sensitivity profile of PDAC lines treated with MEK162 and measured by IC50 by KRAS mutational subtypes (ARG, KRAS G12R, ASP, G12D, CYS, G12C, and VAL, G12V; left) and KRAS mutant vs wild type status (middle). Scatter blot of G12R vs non-G12R KRAS-mutant pancreas cancer cell lines, right. (Hamadi H et al., 2015)

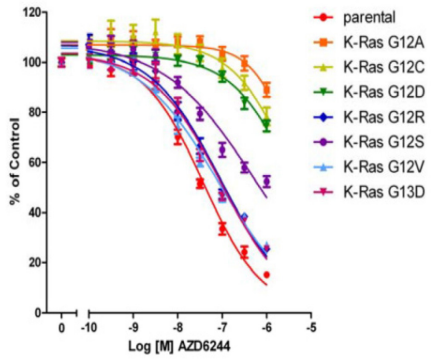


Figure 10. Codon 12 KRAS mutations govern response to MEK therapy using selumetinib in the isogenic SW48 KRAS (+/-) colon cancer in vitro model (Troiani T et al., 2014).

2.1.5 Decreased WNT and RhoGTPase signaling component expression in KRAS G12R-mutant cells compared to KRAS non-G12R cells

Extensive phospho-immunoblotting failed to identify pathways selectively up- or downregulated in the KRAS G12R cell lines (data not shown). Pathways not altered in KRAS G12R compared to KRAS non-G12R lines include the MAPK pathway measured by phospho-RSK, ERK, and MEK, the PI3K-AKT pathway measured by pAKT, pS6, and p4E-BP1, as well as EGFR and HER3 signaling. RAS activation measured by GTP loading did also not differ significantly between the

isoforms. To probe into transcriptional differences between the KRAS isoforms, gene expression profiles of the three cohorts (at least >6 cell lines per mutational isoform) were compared. **Figure 11** shows supervised cluster analysis of 208 differentially expressed genes (DEGs) between the 3 groups. Using these 208 DEGs RNASeq data from TCGA Pancreas Cancer specimens showed weak separation on Principal Component Analysis suggesting DEG set is associated with KRAS isoform mutation status also in patient tissues (**Figure 12**). Gene set enrichment analysis on DEGs identified components of WNT signaling, including the novel KRAS effector Yes- associated protein 1 (YAP1) shown to be able to bypass KRAS oncogene addiction in pancreas cancer, as well as RhoGTPase signaling (Table 1; adjusted p values by multiple comparisons are shown) to be reduced in KRAS G12R harboring pancreas cancer cell lines.[20, 21]

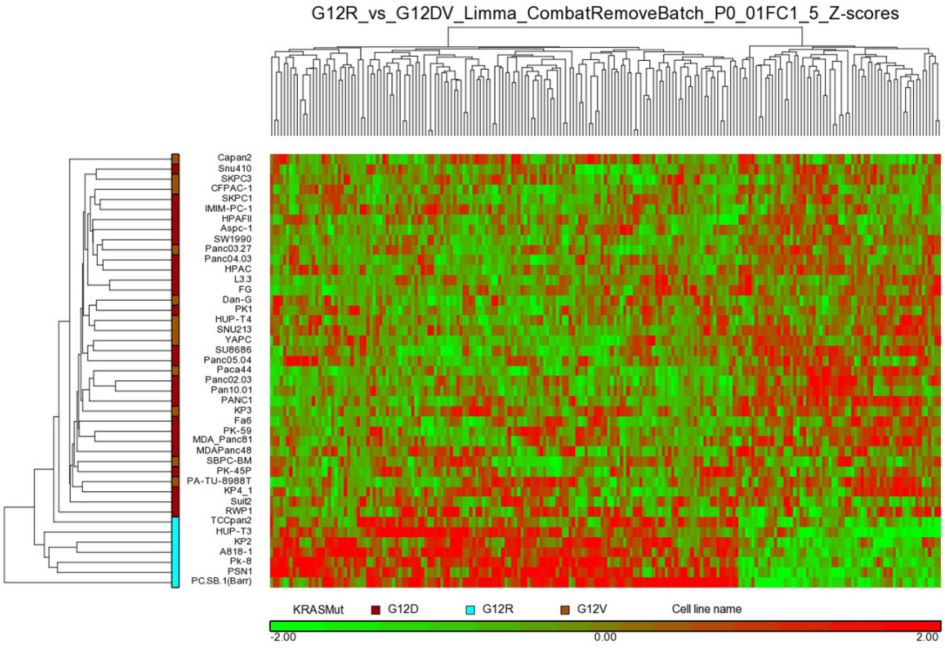
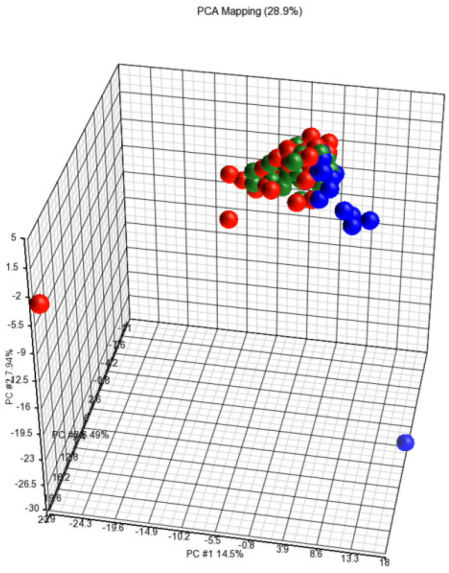


Figure 11. 208 Differentially expressed gene (DEG) sets between KRAS G12R (blue), G12D (red), and G12V (brown) pancreas cancer cell lines. DEGs were also validated in independent CCLE pancreas cancer cell line data set: 151 of top 272 DEGs identified by above comparison were validated



Database:biological process Name:regulation of Wnt receptor signaling pathway ID:GO:003011

C=183; O=4; E=0.46; R=8.76; rawP=0.0011; adjP=0.0818

Index	UserID	Value	Gene Symbol	Gene Name	EntrezGene	
1	10413	NA	YAP1	Yes-associated protein 1	10413	E
2	6496	NA	SIX3	SIX homeobox 3	6496	E
3	30851	NA	TAX1BP3	Tax1 (human T-cell leukemia virus type I) binding protein 3	30851	E
4	81847	NA	RNF146	ring finger protein 146	81847	E

Database:biological process Name:Cdc42 protein signal transduction ID:GO:0032488

C=21; O=2; E=0.05; R=38.15; rawP=0.0012; adjP=0.0818

Index	UserID	Value	Gene Symbol	Gene Name	EntrezGene	
1	55785	NA	FGD6	FYVE, RhoGEF and PH domain containing 6	55785	ENS
2	30851	NA	TAX1BP3	Tax1 (human T-cell leukemia virus type I) binding protein 3	30851	ENS

Database:biological process Name:regulation of Rho GTPase activity ID:GO:0032319

C=88; O=3; E=0.22; R=13.66; rawP=0.0014; adjP=0.0818

Index	UserID	Value	Gene Symbol	Gene Name	EntrezGene	
1	55785	NA	FGD6	FYVE, RhoGEF and PH domain containing 6	55785	ENS
2	30851	NA	TAX1BP3	Tax1 (human T-cell leukemia virus type I) binding protein 3	30851	ENS
3	10565	NA	ARFGEF1	ADP-ribosylation factor guanine nucleotide-exchange factor 1 (brefeldin A-inhibited)	10565	ENS

Figure 12. Principal Component Analysis of the 208 DEG set identified by supervised clustering of pancreas cancer cell line panel applied to randomly selected TCGA gene expression sets (n≥10 for each KRAS mutational isoform). Moderate separation of KRAS G12R specimens (blue) from KRAS G12D (red) and G12V (green) cases.

These findings were validated using a novel technique made available by NCIs Ras Program to my laboratory: siREN screening silences signaling nodes in cancer cell lines and assesses loss-of-function on cell biology. A large siREN screen was carried out in >20 of our cell lines with the three different KRAS mutational isoforms, which showed different signal transduction dependencies in the KRAS G12R vs non KRAS G12R lines: KRAS G12R-harboring cell lines showed different dependency on RhoGTPase signaling, previously identified by comparative gene expression analysis (**Figure 13**). Another vulnerability in KRAS G12D/V and not G12R cells includes regulation of metabolism, in particular glycolysis and hexokinase metabolism, with KRAS G12R able to tolerate loss of these metabolic pathways.

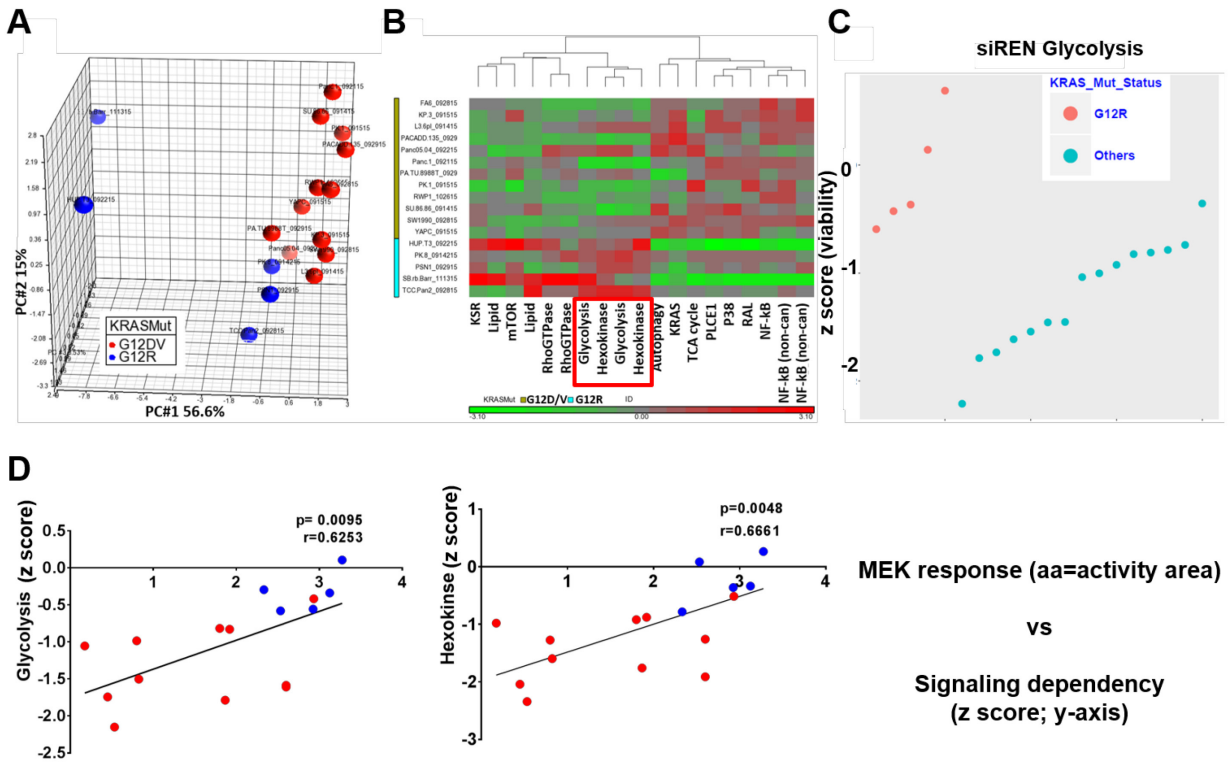


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Figure 13. Different survival cues of intracellular signaling hubs in KRAS G12R vs non-G12R cell lines is associated with response to MAPK pathway inhibition. **A**, Principal component analysis shows near perfect separation of KRAS G12R (blue) from KRAS G12D/V cells. **B**, Supervised cluster analysis by measured cell viability upon knockdown of individual signaling nodes. KRAS G12R cell lines retain viability upon loss of glycolysis and RhoGTPase signaling vs non-KRAS G12R lines, **C**, Response of KRAS G12R vs G12D/V cell lines to loss of glycolysis signaling (z score viability; $p<0.05$, 2-tailed t test). **D**, Response to MEK inhibition (measured by activity area upon 10-dose drug response testing; x-axis) correlates with redundancy of metabolic programs (baseline z score; siREN screen; y-axis); Pearson's coefficient test).

Correlating drug response with lethality upon loss-of-function of 48 individual signaling hubs during siREN screening revealed, among others, strong correlations between dependency on glycolytic function and resistance to MEK inhibition in non-KRAS G12R cell lines and redundancy of glycolysis and sensitivity upon MAPK inhibition (**Figure 13**). Indeed, baseline metabolic profiling of KRAS G12R vs non-G12R cell lines using the XF Extracellular Flux Analyzer (SeaHorse XF® Analyzer) revealed greater glycolytic plasticity upon glycolytic stress in KRAS G1R vs non-KRAS G12R cells (**Figure 14**) as well as increased glucose uptake and lactate production (data not shown). Upon MAPK inhibition, KRAS G12R cell lines do develop metabolic survival dependencies, in particular dependencies on glutamine metabolism (**Figure 14**). These findings, overall, suggest that non-KRAS G12R cell lines derive survival cues from metabolic programs including glycolysis, small GTPase signaling, and others whereas cells with KRAS G12R isoform mutations, to a larger degree, depend on intact MAPK pathway signal transduction cues (**Figure 14**).

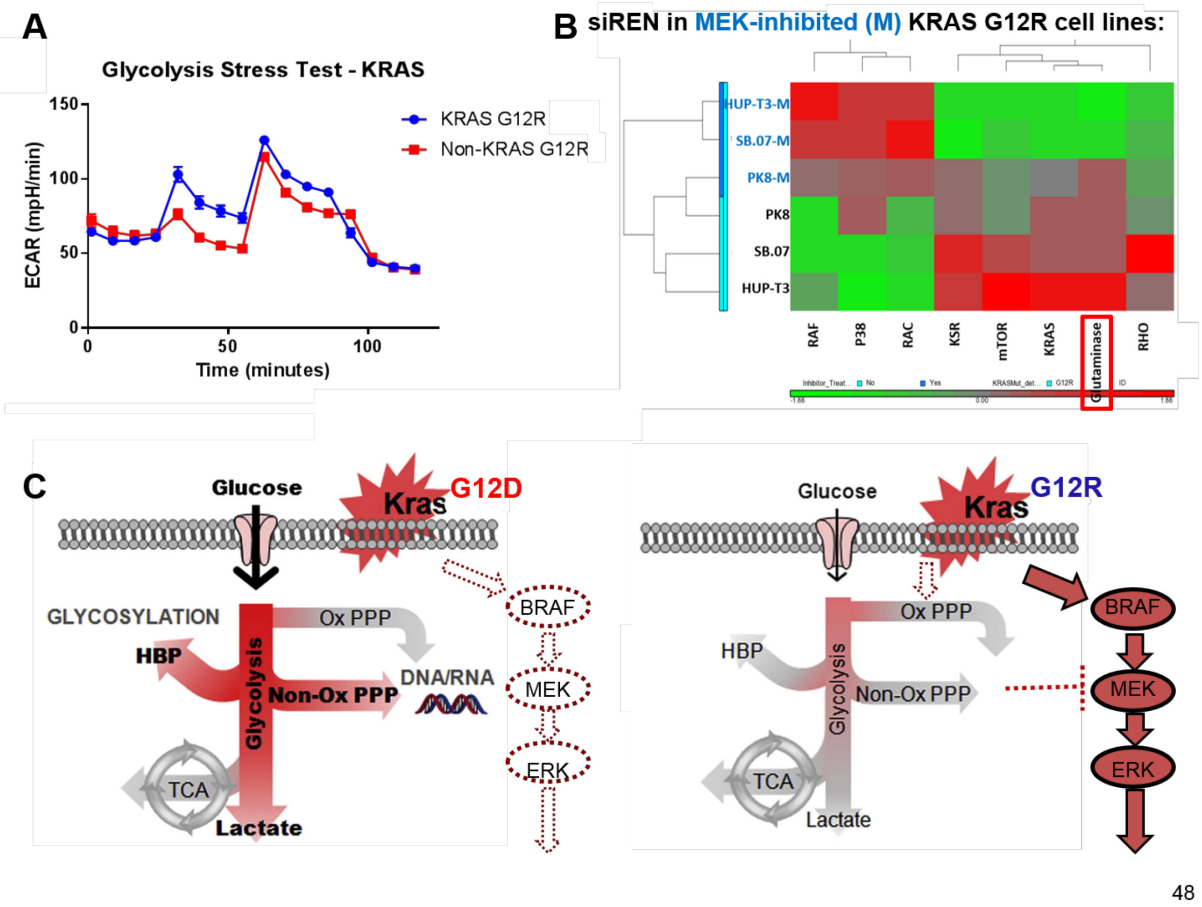


Figure 14 Different metabolic programming in non-KRAS G12R (red) versus KRAS G12R harboring (blue) pancreas cell lines. **A**, Glycolytic function measured by XF Extracellular Flux Analyzer (SeaHorse XF® profiling) in glucose-starved conditions. Increased rate of glycolysis but reduced glycolytic reserve (glycolytic capacity minus rate of glycolysis) in KRAS G12R vs non-KRAS G12R cell lines. **B**, Upon MEK inhibition, KRAS G12R-harboring cell lines recruit metabolic survival programs including glutamine metabolism. **C**, select survival programs in non-KRAS G12R (left) versus KRAS G12R-harboring (right) pancreas cancer cell lines.

2.1.6 Patient-derived xenotransplants from human pancreatic tumors harboring KRAS G12R mutations are selectively sensitive to MEK inhibition with selumetinib (AZD6244)

PDX models derived from human cancers have distinct advantages over other advanced preclinical model like the more commonly used xenotransplantation of human cancer cell lines or genetically engineered mouse models (GEMM) of cancer. These include, among others, the inherent clonal heterogeneity of human cancers as well as the inclusion of tumor-educated stroma into the model, both major determining factors of cancer biology and drug response. **Figure 15** shows selective reduction of tumor growth in a PDX model of pancreas cancer harboring a KRAS G12R mutation (left) compared to KRAS G12D mutation shown on the right. Analysis of downstream effector pathways in PDX models both at baseline and after treatment with selumetinib by reverse phase protein microarray (RPMA) shows increased induction of the cell cycle inhibitor p27kip in the KRAS G12R model compared to the KRAS G12D tumors (**Figure 16).** ().

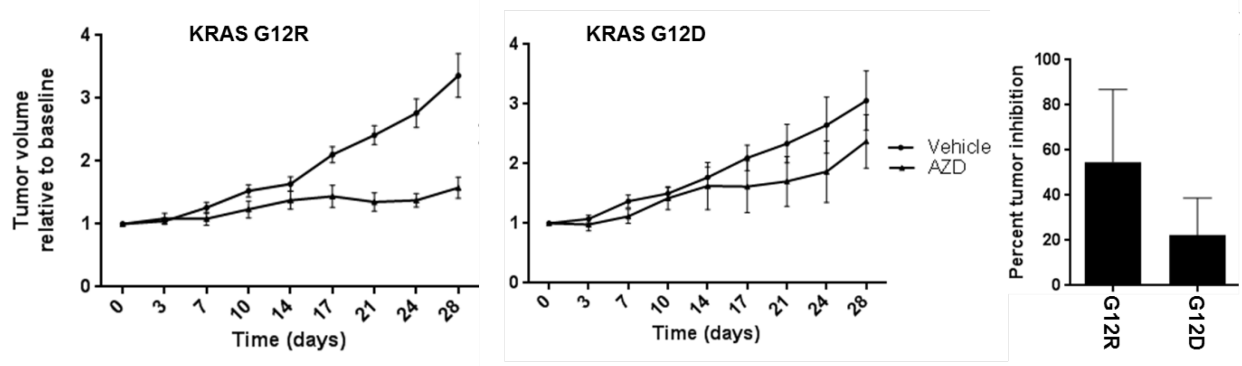


Figure 15 Patient-derived xenografts harboring KRAS G12R (left) and KRAS G12D (right) mutations treated with 35mg/kg selumetinib (AZD6244) twice daily 5 out of 7 days for 4 weeks.

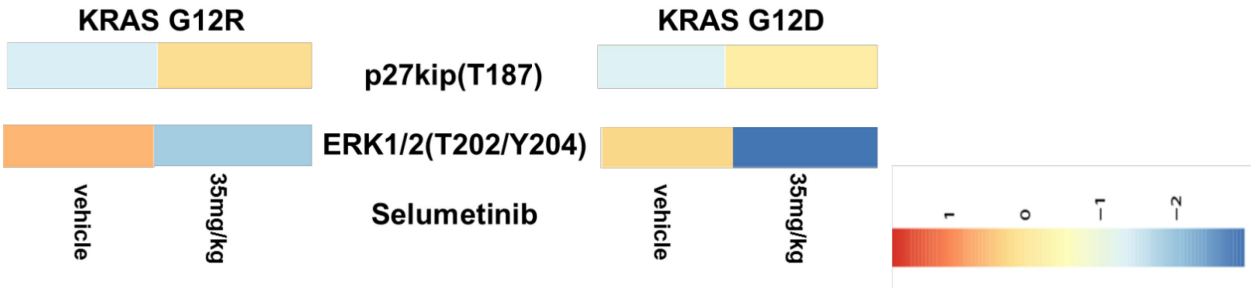


Figure 16 Two-fold increased induction of the cell cycle inhibitor p27kip upon selumetinib treatment in the KRAS G12R PDX (left) versus KRAS G12D model. Reverse phase protein microarray normalized to loaded total protein of n=3 tumors, log[intensity] normalized to total protein

2.1.7 How does this study impact future trials/practice of molecular therapy in pancreas cancer

Similar to trametinib in BRAF-mutant metastatic cutaneous melanoma or selumetinib in ongoing trials of ocular melanoma, KRAS-mutant thyroid cancers, or selumetinib in combination with chemotherapy in non-small cell lung cancer, the proposed study aims to establish a role for this class of agents in pancreas cancer as well as a role for a precision medicine approach guided by different KRAS-mutational isoforms both in pancreas cancers, and possibly other KRAS-driven cancers. For example, it would support a general more differentiated approach to KRAS-driven cancers selecting patients by KRAS mutational isoform status. In this regard, it would support signals from a retrospective pooled analysis of randomized trials in colorectal cancer or a prospective randomized phase II study in non-small cell lung cancer. In a pooled retrospective analysis of 579 chemotherapy-refractory colorectal cancer patients randomized in the clinical trials NCIC CTG/AGITG CO.17, BOND, MABEL, EMR202600, EVEREST, or SALVAGE to the addition of the EGFR inhibitor cetuximab, De Rook and colleagues examined the impact of KRAS mutation status, including isoforms affected KRAS codon 12 versus 13, on overall survival and response to cetuximab. **Figure 17** shows improvement in OS in patients randomized to receive cetuximab in the KRAS G13 but not in the more common KRAS G12D group. Response to cetuximab in colorectal cancer patients harboring KRAS G13 mutations was similar to response in KRAS wild type patients, the currently used biomarker to select patients for anti-EGFR therapy in stage IV disease.

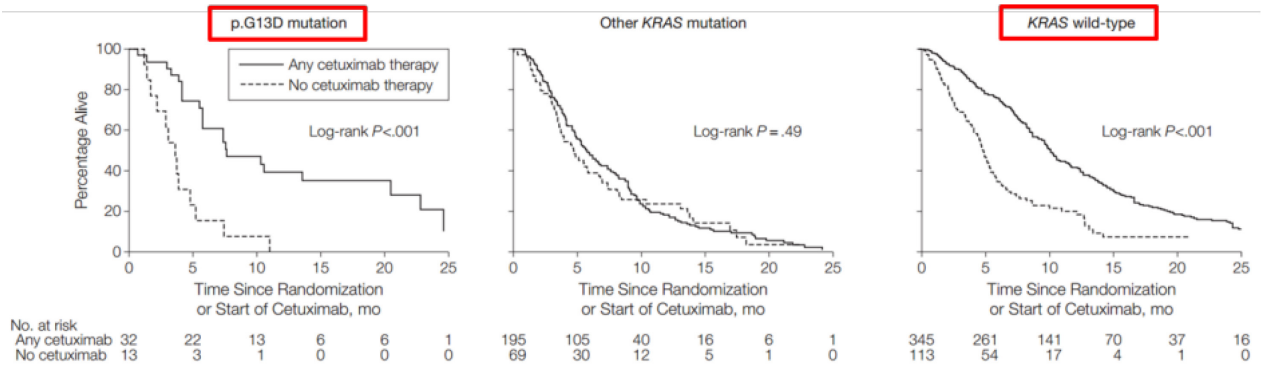


Figure 17. Retrospective correlative tissue analysis of RCTs NCIC CTG and AGITG CO.17 Trial in colorectal cancer patients randomized to anti-EGFR treatment with cetuximab vs supportive care shows improved outcome in KRAS G13-mutant tumors similar to KRAS wild type cancers (from DeRook W, 2010, JAMA).

Similarly, to the above study, the impact of KRAS codon G12 isoform mutation status on response to MEK inhibition has been studied retrospectively in a large randomized phase II study of KRAS-mutant non-small cell lung cancer patients randomized to second line docetaxol vs docetaxol plus selumetinib. There was a trend, statistically significant for progression-free survival and objective response rates, towards improved clinical outcome in KRAS G12C and G12V-mutant lung cancer patients which was not observed in lung cancer patients harboring other KRAS mutational isoforms like KRAS G12A. **Figure 18** shows impact of the addition of selumetinib to docetaxol on overall survival and progression-free survival in chemotherapy-refractory lung cancer patients stratified by KRAS isoform mutation status.

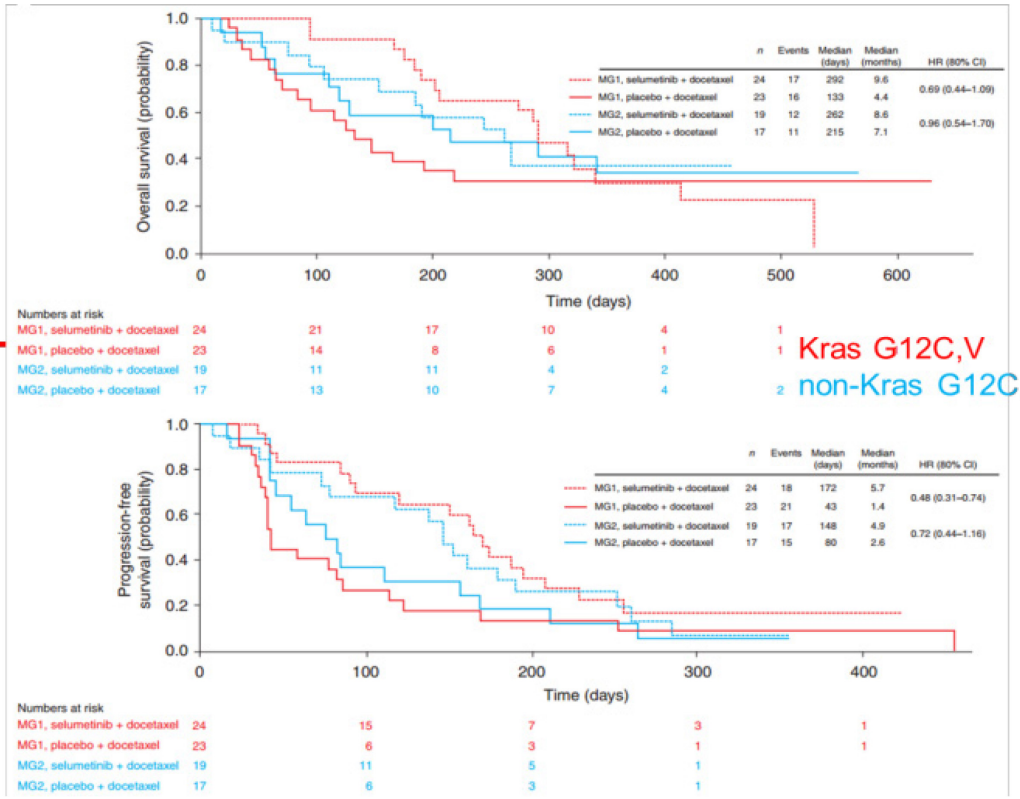


Figure 18 In patients receiving selumetinib +docetaxel and harboring KRAS G12C or G12V mutations there were trends towards greater improvement in OS, PFS and ORR compared with other KRAS mutations. Overall survival, top; progression-free survival, bottom) (from Jänne PA, 2015, Br J Cancer).

Selumetinib has been compared in a randomized phase II study in unselected pancreas cancer to the 2nd-line chemotherapy agent capecitabine and shown not to have any advantage over capecitabine.[22] Similar to the Canadian NCIC CTG PA.3 phase III study with erlotinib these had been unselected patients and patients which had received at least gemcitabine and often additional chemotherapy therapy before. Furthermore, in the above randomized phase II clinical trial of advanced pancreas cancer patients (n=37 selumetinib; n=32 capecitabine) overall survival (OS) was chosen as primary endpoint with no capture of response rates.[22] No retrospective genotyping on tissues was performed.

The weak positive signal with the anti-EGFR inhibitor in the NCIC CTG PA.3 trial, the early data with selumetinib in NSCLC patients,[23] our preclinical studies as well preclinical studies from other investigators now suggest a previously underappreciated heterogeneity of KRAS mutational isoform signaling which drives cancer biology and might harbor important information for clinical decision making. Thus, this study, in case positive, would

(1) add a possibly novel treatment option in a disease void of effective therapies and patients desperate for treatments,

(2) support enhanced efforts into KRAS mutational isoform-directed molecular therapy, both in pancreas and other cancers with frequent KRAS mutations. Considering the high prevalence of KRAS mutations in common cancers like NSCLC, colon, thyroid, or triple

negative breast cancer, a positive finding might trigger a number of studies on KRAS-mutational genotype directed therapies,[14]

(3) support future molecular therapy studies in pancreas cancer attempting to exploit less common low-frequency somatic mutations in this disease like BRAF (3%; vemurafenib), PI3KCA (1%; GDC-0941, BKM120), CDK4 (4%; PD-0332991), or BRCA gene family mutations (3%; mitomycin-C, olaparib).[11]

2.2 CTEP IND Agent

2.2.1 AZD6244 (selumetinib)

AZD6244 (ARRY-142886; selumetinib) is a potent, selective, orally (PO) available, and non-ATP competitive small molecule inhibitor of the mitogen-activated protein (MAP) kinase kinase, MEK1/2 (AZD6244 Investigator's Brochure, Edition #15 (March 30, 2015).[24] AZD6244 inhibits the activity of purified MEK by 50% at 10-14 nmol/L (IC_{50}), and is inactive or only minimally active at 10 mcmol/L against epidermal growth factor receptor (EGFR), ERBB2, p38α, ERK2, and MAPKK 6 kinases. AZD6244 is metabolized to biologically active N-desmethyl AZD6244, which is approximately 3- to 5-fold more active than the parent compound.

The RAS/RAF/MEK/ERK signaling pathway plays a central role in the regulation of many cellular processes including proliferation, survival, differentiation, apoptosis, motility, and metabolism.[25, 26] This pathway is one of the most important and best understood MAP kinase signal transduction pathways, activated by a diverse group of extracellular signals including integrins, growth factor receptors (*i.e.,* EGFR, platelet-derived growth factor receptor [PDGFR], and insulin-like growth factor-1 receptor), and cytokines. Activated RAS triggers the phosphorylation and activation of RAF kinase, which then phosphorylates MEK1 and MEK2 on two serine residues. Activated MEK phosphorylates its only known substrates, ERK1 and ERK2. Phosphorylated ERK (pERK) dimerizes and translocates to the nucleus where it is involved in several important cellular functions, including cell proliferation.[27]

Overexpression of growth factors or growth factor receptors involved in the RAS/RAF/MEK/ERK pathway and activating genetic mutations of the signaling proteins may lead to uncontrolled proliferation and tumor formation. For example, RAS genes are the most frequently mutated oncogenes detected in human tumors). RAS proteins are guanine nucleotide binding proteins that activate RAF proteins when bound to GTP. Cancer-associated mutations in RAS proteins stabilize the GTP-bound form of RAS, thereby providing a constitutive signal downstream in the cascade. In addition to being found in almost all pancreatic adenocarcinomas, RAS mutations are found in ~40% of colorectal carcinomas (CRC), 20-25% of lung adenocarcinomas, and also in some breast or ovarian cancers. *BRAF* mutations have also been observed in many human cancers, particularly melanoma (30-60%), thyroid cancer (30-50%), CRC (5-20%), and ovarian cancer (~30%).[24, 26] These mutations in *BRAF* usually involve gain-of-function substitutions that render the kinases constitutively active. Also, studies of primary tumor samples and cell lines have shown constitutive activation or overactivation of the MAP kinase pathways in cancers of the pancreas, colon, lung, ovary, biliary tract, and kidney.[28] Therefore, agents targeting the RAS/RAF/MEK/ERK pathway may inhibit oncogenic signaling in tumor cells.

Nonclinical Studies

Efficacy

In vitro studies have shown that AZD6244 is a potent and selective inhibitor of MEK with IC_{50} of 10-14 nM (AZD6244 Investigator's Brochure, Edition #15 (March 30, 2015). Significant biochemical activity has not been detected when tested at 10 mcmol/L against a diverse panel of >300 other molecules, including enzymes, receptors, kinases, transporters, and ion channels. The effects of AZD6244 on ERK phosphorylation and cell viability were determined in a panel of cell lines with known RAF and RAS mutant status. AZD6244 inhibited ERK1 and ERK2 phosphorylation with IC_{50} 0.0018-0.0408 mcmol/L. In cell viability assays, IC_{50} values ranged from <10 nM to >10 μM and most of the cell lines that were sensitive to selumetinib contained either a BRAF or RAS gene mutation. Two metabolites of AZD6244 (N-desmethyl AZD6244 and an amide AZD6244) have been identified. The N-desmethyl metabolite was found to be 3-to 5-fold more potent inhibitor than the parent compound in cellular ERK phosphorylation and cell viability inhibition assays. In contrast, the AZD6244 amide metabolite was up to 50-fold less active than AZD6244 and therefore is unlikely to significantly contribute to biological activity of AZD6244. In tumor cell viability inhibition assays, N-desmethyl metabolite was ≥5-fold more potent than AZD6244 in inhibiting cell viability.

Significant suppression of tumor growth in response to AZD6244 treatment was observed in several xenograft mouse models derived from a range of tumor types including melanoma, breast, pancreatic, lung, colon, and hepatocellular carcinomas.[29-32] In papillary thyroid cancer models, AZD6244 effectively inhibited tumor growth, both *in vitro* and *in vivo*, particularly in tumor cells carrying activating *BRAF* gene mutations.[33] In the Calu-6 lung cancer xenograft model, AZD6244 suppressed tumor growth at doses of 10, 25, or 100 mg/kg given twice daily (BID), and the minimal effective dose was identified as 0.75 mg/kg administered BID.[30] In this model, MEK activity was inhibited as assessed by determination of pERK levels in tumor. Studies using human CRC xenograft models demonstrated that AZD6244 inhibited tumor growth by inhibition of cell proliferation in SW620 model and by induction of apoptosis in Colo205 model. *In vivo* studies with mutant *KRAS* positive (*KRAS*$^{+}$) human cancer xenografts have demonstrated the potential for using AZD6244 in combination with a number of cytotoxic and targeted agents, including docetaxel, irinotecan, gemcitabine, pemetrexed, gefitinib, cediranib, rapamycin, cisplatin, and temozolomide (AZD6244 Investigator's Brochure, Edition #15 (March 30, 2015).

Pharmacokinetic/Pharmacodynamic Studies

Two oral formulations of AZD6244 have been tested in preclinical pharmacology studies: the original mix-and-drink formulation (AZD6244 free-base), and the AZD6244 hydrogen sulfate salt (capsule) formulation (AZD6244 Hyd-Sulfate) (AZD6244 Investigator's Brochure, Edition #15 (March 30, 2015). The former requires reconstitution of the AZD6244 free-base crystalline powder in the 25% (w/v) Aqueous Captisol® (sulfobutyl ether β-cyclodextrin) (SBE-CD) solution. While systemic exposure was demonstrated in the rat and monkey studies with AZD6244 free-base, the exposure was not dose-proportional; bioavailability was decreasing with increasing dose. This is likely a reflection of dose-limited absorption due to limited solubility of AZD6244 free-base. However, AZD6244 hydrogen sulfate produced approximately proportional exposures with dose in the mouse and monkey, and allowed higher exposures than AZD6244 free-base. There was no/minimal accumulation of AZD6244, whether dosed with AZD6244 free-base or AZD6244 hydrogen sulfate on multiple dosing in the mouse, rat, or monkey. N-desmethyl metabolite was not detectable in rat and at only trace levels in the monkey, but was produced in mouse at

circulating levels around 2-12% of parent compound. Studies in rats and mice indicate that AZD6244 is widely distributed, although concentrations were generally lower in tissue than blood. High levels of protein binding (93.7%-99.7%) were observed in all preclinical species tested and in humans (98.4%). There was no evidence of AZD6244-related material binding to melanin and minimal penetration into the central nervous system (CNS).

AZD6244 is metabolized in human hepatocytes by cytochrome P450 (CYP enzymes) 1A2, 2C19 and 3A4, with CYP1A2 being the enzyme primarily responsible for the formation of the N-desmethyl metabolite. Glucuronidation appears to be a significant clearance mechanism for AZD6244 and the N-desmethyl metabolite. It is a weak inducer of CYP 3A, 1A, and 2C9. AZD6244 does not inhibit CYP 1A2, 2C8, 2C19, 2D6, and 3A4. It was a weak inhibitor of CYP2C9 (IC_{50} 44.7 mcM). N-desmethyl AZD6244 does not inhibit CYP 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, but is a weak inhibitor of 1A2 (IC_{50} of 18.9 mcM). In the rat, mouse, and monkey, fecal excretion was the predominant route after oral and intravenous dosing.

Toxicologic Studies

Toxicity of AZD6244 was evaluated in the acute dosing (one or two doses on a single day) and continuous daily dosing studies (for a 1 month and 6 months) in Sprague-Dawley rats and cynomolgus monkeys (AZD6244 Investigator's Brochure, Edition #15 (March 30, 2015). The repeat-dose study in rats indicated that the agent was well tolerated but produced soft stools and gastrointestinal mucosal mineralization associated with increased serum phosphorus and decreased albumin. Tissue mineralisation was not apparent in cynomolgus monkeys when dosed for up to 1 month with AZD6244 free-base or for up to 6 months with AZD6244 hydrogen sulfate. However, mineralization was seen in multiple tissues (cornea, kidney, liver, myocardium, skeletal muscle, and glandular stomach) in mice dosed with AZD6244 hydrogen sulfate for up to 1 month, and in the liver of a small number of mice dosed up to 6 months. Twice daily (BID) oral dosing with AZD6244 free-base for 1 month in monkeys produced diarrhea, dehydration, and electrolyte imbalance, in some animals associated with renal toxicity. Dosing with AZD6244 hydrogen sulfate (0.5, 1.5, and 4 mg/kg BID) for up to 6 months in monkeys was also associated with fluid and/or red-colored feces, but with no notable gastrointestinal (GI) tract or renal pathology.

AZD6244 and its N-desmethyl metabolite showed no evidence of mutagenic potential, but AZD6244 produced an increase in micronucleated immature erythrocytes in mice, predominantly via an aneugenic mode of action. AZD6244 showed enhanced cytotoxicity in the presence of ultraviolet (UV) light. Reproductive toxicology data in mice indicate that AZD6244 can have adverse effects on embryofetal development and survival at dose levels that were not toxic to mothers.

In summary, preclinical studies demonstrated that AZD6244 exposures can be significantly enhanced by using AZD6244 hydrogen sulfate, compared to AZD6244 free-base. In 6-month toxicology studies, AZD6244 exposures, expressed as area under the concentration-time curve from time 0 h to 12 h (AUC_{0-12}), achieved with AZD6244 hydrogen sulfate at high dose levels (4 mg/kg BID in monkeys and 20 mg/kg BID in mice) were approximately 3-fold and 15-fold higher in primates and mice, respectively, when compared with those achieved in man at 75 mg BID AZD6244 hydrogen sulfate. At the NOAEL of 1.5 mg/kg BID from 1-month and 6-month studies in primates, exposures were generally similar to those seen in man after dosing at 75 mg BID AZD6244 hydrogen sulfate. Exposure achieved in the 6-month mouse study at the low dose level

of 1 mg/kg BID was slightly below that seen to date in man after dosing with AZD6244 hydrogen sulfate (75 mg BID). Preclinical pharmacology studies suggest an acceptable safety profile for administering AZD6244 free-base or AZD6244 hydrogen sulfate to cancer patients.

Clinical Experience

Pharmacokinetics

AZD6244 plasma PK parameters of AZD6244 hydrogen sulfate were similar after single and multiple dosing, suggesting a minimal accumulation over time after BID dosing (AZD6244 Investigator's Brochure, Edition #15 (March 30, 2015). The AZD6244 exposure parameters, *i.e.,* the maximum plasma concentration (C_{max}) and the AUC were approximately dose-proportional across the 25- to 100-mg BID dose range after single (day 1) or multiple dosing studied on days 1, 8, 15, and 22. The geometric mean values of exposure parameters were: C_{max}=369-1483 ng/mL and AUC_{0-12}=1361-7055 ng·h/mL on day 1, and C_{max}=458-1365 ng/mL and AUC_{0-12}=1515-4758 ng·h/mL on day 8. AZD6244 was absorbed relatively quickly across all dose levels, with a median time-to-reach C_{max} (t_{max}) of 1.5 hours. Following the peak, AZD6244 concentration declined multi-exponentially with a mean terminal elimination half-life ($t_{1/2}$) ranging from 5 to 7 hours, which was consistent across dose levels. The apparent volume of distribution at steady state (V_{ss}/F) and apparent clearance (CL/F) also remained largely consistent across the dose range, with mean values ranging from 87 to 126 L and 12 to 19 L/h, respectively. The plasma PK profile of the AZD6244 active metabolite, N-desmethyl AZD6244, was similar to that of AZD6244, although exposure was much lower, achieving C_{max} and AUC values generally <15% of the parent compound, in each patient. The median t_{max} was approximately 1.5 hours and $t_{1/2}$ ranged from 9-13 hours. The AZD6244 amide metabolite showed increased exposure on multiple dosing indicating some accumulation. Given the 3-to 5-fold greater potency of the N-desmethyl metabolite compared to AZD6244 shown by the *in vitro* cell-based ERK phosphorylation assay, the N-desmethyl AZD6244 is likely to contribute to pharmacodynamic effects. In contrast, AZD6244 amide, which was approximately 40- to 50-fold less active than AZD6244 in this assay, is unlikely to contribute significantly to AZD6244 biological activity. Nevertheless, both metabolites will be measured in all future AstraZeneca-sponsored clinical studies of AZD6244 hydrogen sulfate.

The capsule formulation significantly improved oral bioavailability compared the free-base formulation, although large inter-patient variability was noted. The estimated oral bioavailability of capsule relative to the free-base suspension based on a dose-normalized AUC_{0-24} was 263% (90% confidence interval [CI]=214%-322%). The geometric mean values of exposures obtained for AZD6244 hydrogen sulfate at the maximum tolerated dose (MTD) of 75 mg BID (AUC_{0-24}=6335 and 5448 ng·h/mL on day 1 and 8, respectively, and C_{max}=1207 and 1439 ng/mL on day 1 and 8, respectively) were statistically significantly higher than those obtained at the MTD of AZD6244 free-base (100 mg BID); the relative estimated exposures by hydrogen sulfate *vs.* free-base were 197% (90% CI=161 to 242%) for AUC_{0-24} and 252% (90% CI=182 to 348%) for C_{max}.

A food effect study involving administration of AZD6244 hydrogen sulfate to patients with advanced solid malignancies under fasting conditions and with a high-fat meal indicated a statistically significant effect of food on the exposure of AZD6244. Geometric mean C_{max} and AUC values were reduced by approximately 62% and 19%, respectively, under fed conditions.

Therefore, for further clinical studies, it is recommended that AZD6244 be taken on an empty stomach (*i.e.*, no food other than water can be taken) at least 2 hours after a meal and 1 hour before the next meal. AZD6244 capsule should be taken with water.

At a population level, plasma exposure of AZD6244 (C_{max} and AUC) appeared to be increased in healthy volunteers of Asian descent by approximately 1.5- to 2-fold, in non-Japanese Asians and Japanese Asians, respectively, compared with Western healthy volunteers. However, the AZD6244 PK was highly variable and there was overlap in the range of exposure experienced by Asian and Western subjects.

There is no evidence of PK interactions between docetaxel, dacarbazine, temsirolimus, or erlotinib and AZD6244.

Efficacy

Four randomized phase 2 monotherapy studies comparing efficacy of AZD6244 free-base formulation (100mg BID) to standard chemotherapy regimens in patients with solid tumors (melanoma, pancreatic cancer, CRC, and NSCLC) did not demonstrate superior efficacy of AZD6244 over standard chemotherapy agents (AZD6244 Investigator's Brochure, Edition #15 (March 30, 2015). Several objective responses were observed in melanoma patients with mutant BRAF tumors and in patients with mutant KRAS NSCLC.

Although statistical significance in overall survival (OS) was not achieved, a statistically significant improvement was seen in progression-free survival (PFS) for AZD6244 in combination with docetaxel in patients with mutant KRAS NSCLC (P=0.014)[34] and for AZD6244 in combination with dacarbazine in patients with mutant BRAF cutaneous melanoma (P=0.021),[35] when compared to the respective chemotherapy/placebo groups. Clinical activity of AZD6244 hydrogen sulfate monotherapy was demonstrated in uveal melanoma.[36]

Safety

The tolerability profile of AZD6244 free-base at 100 mg BID was similar to that of AZD6244 hydrogen sulfate at 75 mg BID (AZD6244 Investigator's Brochure, Edition #15 (March 30, 2015). The most common AEs associated with AZD6244 are acneiform rash, diarrhea, nausea, vomiting, peripheral edema, and fatigue. Stomatitis, dry skin, and pyrexia have also been commonly reported in the AZD6244 studies. Dose escalation of selumetinib was limited mainly by the occurrence of rash and diarrhea.

Events consistent with central serous retinopathy/retinal pigment epithelial detachment have been reported in a small number of patients receiving treatment with AZD6244, generally in combination with other novel targeted anticancer agents.

Mild (generally grade 1) elevations in serum liver transaminases have been recorded within the first week of starting treatment with AZD6244 and levels tend not to increase further beyond the first month of continued dosing. Mild increases in serum phosphate and in calcium phosphate product have been reported.

Dyspnea and exertional dyspnea have been reported in patients receiving AZD6244. The majority of these events have occurred in patients with lung or pleural disease due to their underlying malignancy. There have been reports of pneumonitis-type events, including symptoms of shortness of breath, fatigue, cough and/or fever, in a small number of patients receiving AZD6244, but

pneumonitis-AZD6244 association has not been established. Studies of AZD6244 should include guidance for the management and investigation of new or worsening dyspnea or symptoms of pneumonitis-type events that are not attributed to the patient's underlying cancer.

Increases in systolic or diastolic blood pressure, sometimes exceeding the threshold for therapeutic intervention, have been observed in studies with AZD6244. Asymptomatic reductions in left ventricular ejection fraction (LVEF) to below 55% have been observed in a small number of patients during AZD6244 treatment and evidence of reversibility while on continuous dosing was demonstrated in some patients. Studies of AZD6244 should include baseline and symptom-triggered echocardiography assessments and guidance for the management and investigation of decreases of LVEF. Review of electrocardiogram (ECG) parameters has shown no evidence of QT interval corrected according to Fridericia's formula (QTcF) prolongation during treatment with AZD6244.

Increased creatine phosphokinase (CPK) levels have been reported in a small number of patients with advanced cancer receiving AZD6244. A relationship between selumetinib and increased CK levels has not been established.

2.3 Rationale

Patients with advanced pancreas cancer have few available treatment options and an overall poor prognosis. Pre-clinical evidence, both in a large panel of cell lines and in patient-derived xenotransplantation models, suggests that selumetinib (AZD6244) has activity against pancreas cancers harboring KRAS G12R mutations.

This study tests the hypothesis

(1) if patients with advanced pancreas cancer with a unique KRAS mutational isoform respond to the MEK inhibitor selumetinib (AZD6244) and
(2) if genetic or protein expression information derived from treated patients distinguishes patients responding to the drug from patients progressing under treatment

2.4 Correlative Studies Background

The rationale for the chosen correlative tissue is derived from the observation that (1) additional inherent somatic gene perturbations, either within the targeted signal transduction pathway or affecting other pro-survival cell functions, frequently mediate resistance to targeted agents. Examples of relevance to the MEK inhibition in KRAS G12R mutant pancreas cancer are for example concomitant mutations of the PI3K-AKT-mTOR pathway or gene amplifications in the cyclin or cyclin kinase regulating genes. The immediately available information on variant status in 50 additional common known cancer genes as part of the applied gene panel allows immediate correlation and possible identification of common genetic mechanisms of resistance. The correlation of CNKSR1 expression status, measured by IHC, with response to selumetinib is a direct translation of our laboratory efforts; we have shown that CNKSR1, a scaffolding kinase and regulator of MAPK kinase signaling, mediates in preclinical models resistance to MAPK pathway inhibition. Circulating tumor DNA (ctDNA) analysis is capable of accurately determining tumor progression, prognosis, and assisting in targeted therapy development via prediction of response when applied prospectively in later studies.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed locally advanced or metastatic pancreas cancer.

3.1.2 Patients must have received at least 6 months 5-FU- or gemcitabine-based treatments for pancreas cancer (FOLFIRONOX, FOLFOX, 5-FU+ nal-IRI (MM-398; nanoliposomal irinotecan), or 5-FU (including capecitabine), gemcitabine-based gemcitabine plus abraxane, gemcitabine monotherapy among others).

3.1.3 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional techniques or as ≥10 mm (≥1 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section **11** for the evaluation of measurable disease.

3.1.4 Patients must have CLIA confirmed somatic KRAS G12R mutation as determined by sequence analysis of matched normal DNA from any specimen obtained from the individual. Patients must provide test result from CLIA certified laboratory, confirming somatic KRAS G12R mutation or archival tumour sample for KRAS analysis or be willing to undergo mandatory screening biopsy.

3.1.5 Patients must not have had chemotherapy, molecular therapy with erlotinib, radiation therapy, or experimental biological or molecular therapy for at least 4 weeks prior to starting study medication. Patients who received FOLFIRINOX must be 6 weeks from the last administration of therapy. Patients must have recovered from any acute toxicity related to prior therapy or surgery, to a grade 1 or less unless specified.

3.1.6 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of AZD6244 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.7 ECOG performance status ≤1 or Karnofsky ≥70%, (see **Appendix A**).

3.1.8 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥75,000/mcL
– hemoglobin (Hgb)	≥9.0 g/dL
– total bilirubin	below or within normal institutional limits
– AST(SGOT)/ALT(SGPT)	<3× institutional upper limit of normal
– creatinine	≤ institutional upper limit of normal
OR	
– creatinine clearance	>60 mL/min/1.73 m^2 by either Cockcroft-Gault formula or 24-hour urine collection analysis

3.1.9 Patients must be willing to return to the Clinic for follow-up visits.

3.1.10 The effects of AZD6244 on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 4 weeks after dosing with AZD6244 ceases. Women of child-bearing potential must have a negative pregnancy test within 14 days prior to study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the patient should inform her treating physician immediately. Please note that the AZD6244 manufacturer recommends that adequate contraception for male patients should be used for 12 weeks post-last dose due to sperm life cycle.

Note: Selumetinib is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with selumetinib, breastfeeding should be discontinued if the mother is treated with selumetinib.

3.1.11 Ability to understand and the willingness to sign a written informed consent document or patients with Impaired Decision Making Capacity (IDMC) if they are represented by a Legally Authorized Representative (LAR).

3.1.12 Patient must be able to reliably swallow oral medications.

3.2 Exclusion Criteria

3.2.1 Patients who have received prior treatment with tyrosine kinase inhibitors (e.g. erlotinib), or anti-EGFR agents (e.g. cetuximab, panitumumab).

3.2.2 Patients currently receiving any medication known to induce central serous chorioretinopathy which in the opinion of the Principal Investigator, would make the administration of study drug hazardous.

3.2.3 Patients with active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment)

3.2.4 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.5 Any underlying medical condition which, in the opinion of the principal investigator, will make the administration of study drug hazardous or obscure the interpretation of adverse events

3.2.6 Patients who are receiving any other investigational agents.

3.2.7 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. No additional workup is needed to exclude brain metastases if the patient is asymptomatic or has no history of brain metastases.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to AZD6244 or other agents used in study.

3.2.9 Previous MEK, RAS, or RAF inhibitor use.

3.2.10 Patients with the following cardiac conditions are excluded:

- Uncontrolled hypertension (blood pressure [BP] of ≥150/95 despite medical support/management)
- Acute coronary syndrome within 6 months prior to starting treatment
- Uncontrolled angina – Canadian Cardiovascular Society grade II-IV despite medical support/management
- Heart failure NYHA Class II or above (for the NYHA Classification refer to **Appendix B**)
- Prior or current cardiomyopathy (within 6 months) including but not limited to the following:
    - Known hypertrophic cardiomyopathy
    - Known arrhythmogenic right ventricular cardiomyopathy
    - Abnormal ejection fraction (echocardiogram [ECHO]) <= 53% (if a range is given then the upper value of the range will be used) or cardiac MRI
    - Previous moderate or severe impairment of left ventricular systolic function (LVEF <45% on echocardiography or equivalent on Multi-Gated Acquisition Scan [MUGA]) even if full recovery has occurred. Echo and additional cardiac studies not indicated unless clinically symptomatic or patient has significant cardiac history.
    - Severe valvular heart disease
    - Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest
    - Fridericia's corrected QT interval (QTcF) >= 450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (*e.g.*, heart failure, hypokalemia, family history of long QT interval syndrome) are excluded. The use of medication(s) that can prolong QTc interval is prohibited while treated on this study. For a comprehensive list of agents that prolong QTc refer to a frequently-updated medical reference, such as https://www.crediblemeds.org/everyone/composite-list-all-qtdrugs.

3.2.11 Patients with known ophthalmologic conditions, such as:

3.2.11.1 Current or past history of central serous retinopathy

3.2.11.2 Current or past history of retinal vein occlusion

3.2.11.3 Known intraocular pressure (IOP) > 21 mmHg (or ULN adjusted by age) or uncontrolled glaucoma (irrespective of IOP); patients with controlled glaucoma and increased IOP who do not have meaningful vision (light perception only or no light perception) may be eligible after discussion with the study chair

3.2.11.4 Subjects with any other significant abnormality on ophthalmic examination (performed by an ophthalmologist) should be discussed with the study chair for potential eligibility

3.2.11.5 Ophthalmological findings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor or strabismus) or long-standing orbito-temporal PN (such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study.

3.2.12 Patients with refractory nausea and vomiting, chronic gastrointestinal (GI) diseases (*e.g.*, inflammatory bowel disease) or significant bowel resection.

3.2.13 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with AZD6244. HIV-positive patients not on antiviral therapy with undetectable viral loads and CD4 counts >300, and after confirmation of eligibility after discussing with the Study chair are eligible.

3.3 Inclusion of Women and Minorities

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

4 REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	

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

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

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

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

4.2 Site Registration

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status

- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the *10050* protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-NCI, and protocol #10050.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 10050 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Specimen Tracking Training
  - At least one individual at each participating site will need to complete the Theradex-led training
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal
  - The training is a one-time only requirement per individual
  - This training will need to be completed before the first patient enrollment at a given site
- Peter Clark is the main point of contact at Theradex for the training (802-456-8735,

PClark@theradex.com). Nafeesa Sarakhawas is the backup contact (609.480.2693, NSarakhawas@theradex.com)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office

1818 Market Street, Suite 3000

Philadelphia, PA 19103

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

4.2.4 Checking **Site** Registration Status

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

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 NCI Central Registration (NCI Site Only)

Registration will be a two-part process as patients are screened on this protocol. Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. To initially register a subject after the participant has signed the consent, complete the top portion the registration Eligibility Checklist from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) indicating that the patient is being registered for screening and send via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. Once eligibility is confirmed after completion of screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and email the completed registration checklist to the CRO at NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will

call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Subjects that do not meet screening criteria should be removed from the study per the procedure below.

4.3.2 Off Study Procedure (NCI Site Only)

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov>.

4.3.3 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

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

4.3.4 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form

4.3.5 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Following registration, patients should begin protocol KRAS G12R mutation testing within 5 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's

registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

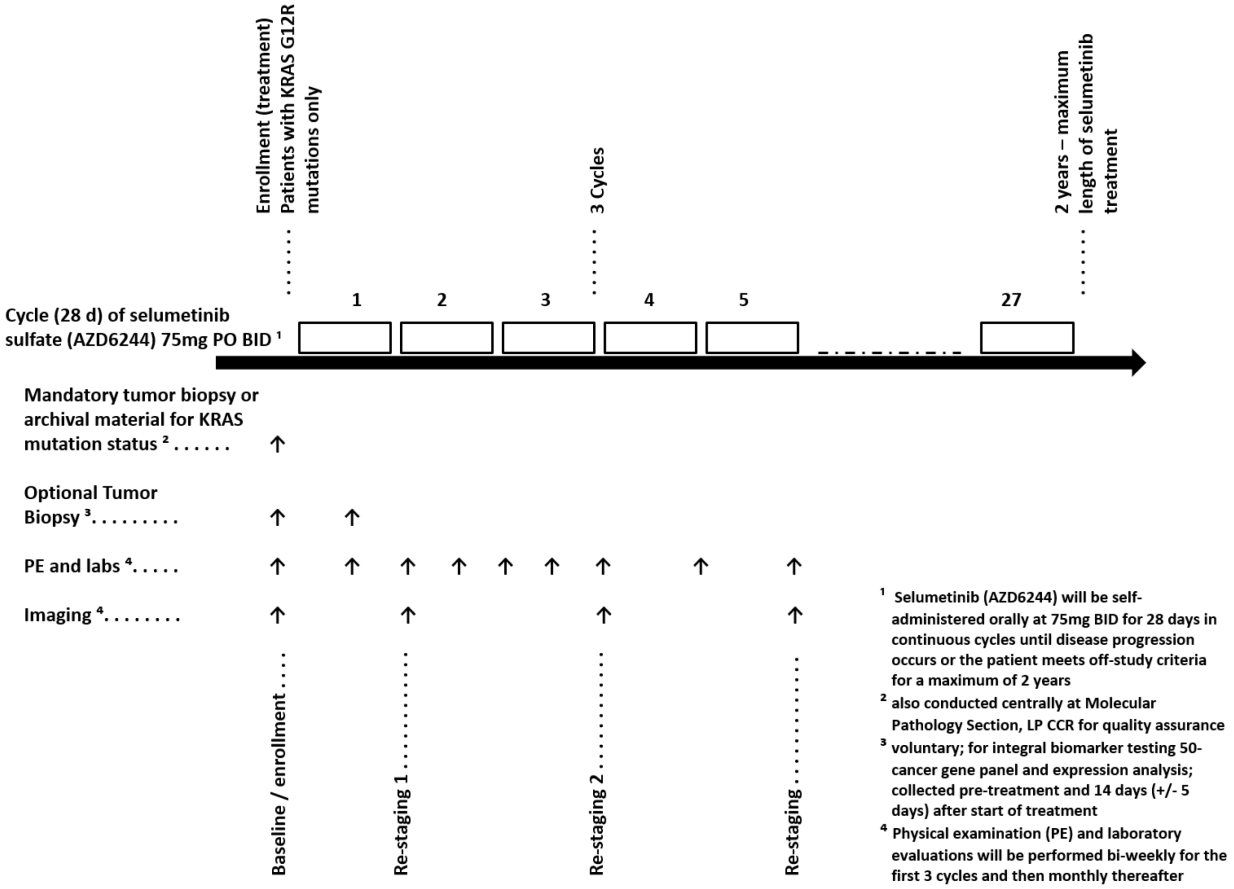
5 TREATMENT PLAN

Patients will be screened for the presence of KRAS gene mutations in their tumor and only patients who harbor KRAS G12R mutations will continue onto the treatment phase of the study. Please see section **10** for screening procedures.

Selumetinib (AZD6244) will be administered as an oral dose of selumetinib sulfate 75 mg twice daily (in the morning and evening) taken two hours after a meal and one hour before the next meal. Selumetinib will be given continuously; one cycle equals 28 +/- 2 days.

Up to 24 evaluable patients (allowing for a staged accrual of initially 7 patients who will receive selumetinib and are evaluable after the 1st cycle) will be treated over 2 years and the trial will be completed over 2(-4) years, allowing for completion of follow-up.

The primary objective of the trial will be to determine whether selumetinib (AZD6244) monotherapy in advanced pancreas cancer patients harboring KRAS G12R mutations is able to be associated with a response rate (PR +CR) that can rule out 5% (p0=0.05) in favor of an improved response rate of 30% (p1=0.30).



5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section **7**. Appropriate dose modifications are described in Section **6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 AZD6244 Hydrogen Sulfate Administration

All new NCI-sponsored trials with AZD6244 will use the hydrogen sulfate salt (capsule) formulation. Treatment will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section **7**. Appropriate dose modifications for AZD6244 hydrogen sulfate are described in Section **6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1.1 AZD6244 hydrogen sulfate will be administered at a dose of 75 mg orally twice a day, approximately 12 hours apart. For the evaluation purposes, a cycle will be defined as 28 +/- 2 days. Detailed instructions for storage and handling are provided in Section **8** (Pharmaceutical Information) of the protocol.

- Patients will be provided with a Medication Diary for AZD6244 (**Appendix D**), instructed in its use, and asked to bring the diary with them to each appointment. A new copy of the Medication Diary will be given to patients whose dose is reduced due to adverse events (AEs).
- AZD6244 capsules should be swallowed whole with a glassful of water twice a day, approximately 12 h apart, on an empty stomach – no food or drink other than water for 2 hrs prior to dosing and 1 h after dosing (*i.e.*, AZD6244 should be taken at least 2 h after a meal and 1 h before the next meal).

5.1.1.2 Follow up for certain AEs should be performed to better characterize the effects of AZD6244 therapy:

- Patients experiencing **edema** should have cardiac ejection fraction (EF) measurements, serum chemistry (including electrolytes and albumin), and routine urinalysis.
- Patients with symptoms consistent with **cardiac** impairment (*e.g.,* congestive cardiac failure, edema, or dyspnea) should have EF measurements (MUGA scan or echocardiography) at the time of the event as well as other routine investigations. Decreases in left ventricular ejection fraction (LVEF) from baseline (if known) may be investigated according to the algorithm described in **Appendix E**.
- **Respiratory** events (pulmonary edema) should be followed up with an electrocardiogram, EF measurement, and chest X-ray. All new dyspnea AEs or worsening of pre-existing dyspnea AEs should be followed according to the dyspnea management algorithm (**Appendix F**).

- Oxygen saturation will be measured at baseline and again following any **respiratory event**.
- Patients experiencing **visual disturbances** should undergo a complete ophthalmologic examination, including a slit lamp examination.

5.2 General Concomitant Medication and Supportive Care Guidelines

- Because there is the potential for drug-drug interaction through the cytochrome P450 enzyme system (CYP), the case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The enzymes in question are CYP 1A2/3, 2C9, 2C19, 3A4/5, and UGT1A1. AZD6244 hydrogen sulfate (selumetinib) is metabolized by these enzymes and may be affected by other drugs that inhibit or induce these enzymes. The proteins in question are P-gp and BCRP. AZD6244 hydrogen sulfate (selumetinib) is a substrate of BCRP and P-gp transporters and may be affected by other drugs that inhibit or induce these transporters. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. **Appendix C** (Patient Drug Information Handout and Wallet Card) should be provided to patients and their caregivers.
- The patient's smoking history should be documented in the CRF, including the number of packs smoked/day (if a smoker).
- Diarrhea can generally be controlled with the following regimen: loperamide (4 mg orally [PO]) at onset of symptoms, followed by 2 mg loperamide every 2 hours while awake (or 4 mg PO every 4 hours while sleeping) up to a maximum of 16 mg loperamide per day.
- The nausea and vomiting that may occur with AZD6244 administration can generally be managed through the use of appropriate simple supportive measures (*e.g.,* prochlorperazine). To date, 5 HT_3 antagonists have not been routinely required.
- Patients should avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.
- Because AZD6244 capsules contain significant amounts of vitamin E, the following precautions apply:
    - Patients should not take supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interrupt blood coagulation processes.
    - High doses of vitamin E have been reported to potentiate the anticoagulant activity of coumadins such as warfarin. Patients who are taking concomitant coumarin anticoagulant medications should have their INR or anticoagulant assessment conducted more frequently after starting AZD6244 therapy. The dose of anticoagulant should be adjusted according to these anticoagulant measurements.
- Reproductive toxicology data indicate that AZD6244 has the potential for adverse effects on embryofetal development and survival. Therefore, AZD6244 should not be

administered to pregnant or breast-feeding women and conception while on treatment must be avoided. Female patients of child-bearing potential will be required to use reliable methods of contraception for the duration of the study and until 4 weeks after the last dose of AZD6244. Male patients with sexual partners who could become pregnant (*i.e.,* women of child-bearing potential) should use acceptable methods of contraception for 12 weeks after completing the study to avoid pregnancy and/or potential adverse effects.

5.3 Duration of Therapy

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

- Completion of 27 cycles of study therapy
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from study therapy
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator (patient non-compliance)
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

5.4 Duration of Follow Up

Patients will be followed for 52 weeks through a telephone interview every 2 months after removal from study therapy or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Progression Free Survival (PFS) will be captured as the duration of time from start of treatment to time of progression or death, whichever occurs first. After progression and coming off treatment, patients will be followed for 52 weeks through a telephone interview every 2 months or until death, whichever occurs first.

6 DOSING DELAYS/DOSE MODIFICATIONS

General guidelines for treatment modifications at the time of re-treatment:

Adverse Events: All adverse events in this trial will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 - a complete listing is available at the CTEP website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Dose adjustments will be made according to the guidelines below, with dose levels defined as follows:

Dose Level (DL)	***Agent*** **Dose**
0	Selumetinib 75 mg twice daily
-1*	Selumetinib 50 mg twice daily
-2*	Selumetinib 75 mg once daily

Summary of dose holding/interruptions and dose de-escalation recommendations for selumetinib in case of selumetinib-related adverse events (graded according to NCI-CTCAE v5.0)

General Adverse Events	Action
Non-hematological, Grade 1 or 2	Continue selumetinib therapy at full dose prescribed. Apply maximum supportive care recommendations. If prolonged duration of Grade 2 adverse event (≥7 days) is affecting quality of life, decrease dose to DL -1, if symptoms persist and continue to affect quality of life for ≥ 7 more days, a second dose reduction to DL -2 will be allowed.
Non-hematological, Grade 3 or 4 (excluding cardiac and hepatobiliary events)	Apply maximum supportive care recommendations. Hold selumetinib therapy until recovery to Grade ≤ 1 (up to 14 days). For NCI-CTCAE v5.0 Grade 3 or 4 interstitial pneumonitis or Grade 4 rash manifested as toxic epidermal necrolysis (e.g. Stevens-Johnson Syndrome etc.) selumetinib must be permanently discontinued If recurrence of adverse event after drug hold/ interruptions is observed, and maximum supportive care measures applied, hold drug once again until recovery to Grade ≤ 1 (up to 14 days) and restart drug at DL-1. If adverse event recurs, a second dose reduction to DL -2 will be allowed after symptoms recover to Grade ≤ 1.
Non-hematological, Grade 3 or 4 adverse events NOT resolved to	Action (discontinue or resume selumetinib therapy) in individual cases after discussions with the

Grade ≤ 1 within a maximum of 2 weeks from last planned administration	Sponsor. Up to 2 reductions (DL-1 and DL-2) will be considered after maximum supportive care recommendations are introduced.
Cardiac Adverse Events	
Cardiac (Severity corresponding to NYHA criteria)	Selumetinib therapy to be discontinued permanently in case of symptomatic NYHA class III and IV CHF. Selumetinib therapy to be held, continued, or resumed accordingly for patients with NYHA class I or II CHF.
Hepatobiliary Adverse Events	
Grade 3 AST/ALT* and Grade 2 total bilirubin elevation	Hold selumetinib for 2 weeks; restart drug at DL-1 if events resolved to ≤Grade 1. If Grade 3 events recur after dose reduction, then discontinue selumetinib.
Grade 2 AST/ALT or Grade 1 total bilirubin elevation	Reduce selumetinib by one dose level for 2 weeks. Labs should be done every week until resolution of AST/ALT elevations to ≤Grade 1 and elevated bilirubin levels to normal. At the end of the 2 weeks the dose level may be increased if the toxicity resolves to ≤Grade 1 for AST/ALT elevations or to normal for bilirubin. If toxicity doesn't resolve to ≤Grade 1 for AST/ALT elevations or to normal for bilirubin, then continue with the reduced dose. Upon two recurrences of these adverse events, necessitating dose reduction, no further attempts to return to higher dose level after resolution to ≤Grade 1 will be made.
Grade 4 events	Discontinue selumetinib
* retest within 3 days from the first occurrence and then weekly to determine if ALT elevation persists **Note:** In case of multiple short interruptions of dose due to either adverse events or drug supply or other reasons the sum of days without selumetinib treatment should not exceed 21 days in any 90 day treatment period.	

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2 **and**

7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Selumetinib (AZD6244 hydrogen sulfate [NSC 748727]), AZD6244 (NSC 741078)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol-specific exceptions to expedited reporting to NCI (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 969 patients.* Below is the CAEPR for Selumetinib (AZD6244).

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

Version 2.6, January 4, 2018[37]

Adverse Events with Possible Relationship to Selumetinib (AZD6244) (CTCAE 5.0 Term) [n= 969]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Febrile neutropenia[38]	
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	***Left ventricular systolic dysfunction (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea[39]			***Diarrhea[39] (Gr 3)***
	Dry mouth		
	Mucositis oral		***Mucositis oral (Gr 3)***

Adverse Events with Possible Relationship to Selumetinib (AZD6244) (CTCAE 5.0 Term) [n= 969]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema face		***Edema face (Gr 2)***
Edema limbs			***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Pain		
INFECTIONS AND INFESTATIONS			
	Paronychia		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	CPK increased		***CPK increased (Gr 3)***
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		

Adverse Events with Possible Relationship to Selumetinib (AZD6244) (CTCAE 5.0 Term) [n= 969]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		
Rash acneiform			***Rash acneiform (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
	Hypertension		

[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]Febrile neutropenia/neutropenic infection has been observed primarily in trials combining Selumetinib (AZD6244) and docetaxel.

[3]SBE-CD (Captisol®, vehicle) in the mix and drink formulation is known to cause soft stools and/or diarrhea in rats and dogs; however, it is possible that some of these findings might be related to exacerbation of the vehicle effect by Selumetinib (AZD6244).

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC

Adverse events reported on AZD6244 (selumetinib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD6244 (selumetinib) caused the adverse event:

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

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Atrioventricular block first degree; Cardiac disorders - Other (Takatsubo cardiomyopathy syndrome); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Heart failure; Myocardial infarction; Palpitations; Pericardial effusion; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia

CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (physeal dysplasia)

EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Extraocular muscle paresis; Eye disorders - Other (bilateral macular edema); Eye disorders - Other (black haze in line of vision); Eye disorders - Other (chalazion); Eye disorders - Other (elevated intraocular pressure); Eye disorders - Other (retinal bleeding); Eye disorders - Other (spotty vision; itchy vision); Flashing lights; Floaters; Optic nerve disorder; Papilledema; Photophobia; Retinal detachment; Retinopathy; Uveitis

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Bloating; Cheilitis; Colitis; Dyspepsia;

Dysphagia; Esophagitis; Flatulence; Gastric hemorrhage; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (pneumatosis coli); Gingival pain; Ileal stenosis; Oral hemorrhage; Rectal hemorrhage; Stomach pain; Upper gastrointestinal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Facial pain; Flu like symptoms; Localized edema; Malaise; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure Hepatobiliary disorders - Other (liver dysfunction/failure [clinical])

INFECTIONS AND INFESTATIONS – Infection[4]

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Hemoglobin increased; INR increased; Lipase increased; Lymphocyte count increased; Serum amylase increased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperphosphatemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (elevated calcium phosphorus product); Metabolism and nutrition disorders - Other (sensation of warmth)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Joint range of motion decreased; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (bilateral stiffness hands and feet [intermittent]); Musculoskeletal and connective tissue disorder - Other (joint swelling); Musculoskeletal and connective tissue disorder - Other (muscle weakness neck); Musculoskeletal and connective tissue disorder - Other (neck myopathy); Myalgia; Myositis; Neck pain; Pain in extremity; Rhabdomyolysis

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl. cysts and polyps) - Other (Merkel cell carcinoma); Tumor pain

NERVOUS SYSTEM DISORDERS - Aphonia; Cognitive disturbance; Concentration impairment; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Leukoencephalopathy; Memory impairment; Spinal cord compression; Nervous system disorders - Other (spinal cord compression); Oculomotor nerve disorder; Paresthesia; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delusions; Depression; Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal inflammation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchopulmonary hemorrhage; Epistaxis; Hoarseness; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pulmonary edema; Sore throat; Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Scalp pain; Skin and subcutaneous tissue disorders - Other (skin fissures); Skin ulceration; Stevens-Johnson syndrome; Urticaria

VASCULAR DISORDERS - Flushing; Hypotension; Lymphedema; Thromboembolic event

Note: AZD6244 (selumetinib) 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.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section **7.1.1**) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers).

The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section **7.3.3**).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

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

7.3.3 Expedited Reporting Guidelines

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

Note: A death on study requires both routine and expedited reporting, regardless of

causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

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

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

An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization
≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization
≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

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

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

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

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

7.7 Reporting to the NCI Clinical Director (NCI Site Only)

7.7.1 Definitions

7.7.1.1 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.7.1.2 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.7.2 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.7.3 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.7.4 NCI Clinical Director Reporting

Deaths that occur within 30 days of completing treatment or receiving a research intervention should be reported via email to the Clinical Director. If a death occurs after 30 days, it should be reported only if the death is at least possibly related to the research treatment or intervention.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at dahutw@mail.nih.gov and to CCRsafety@mail.nih.gov within one business day of learning of the death.

All Unanticipated Problems, Serious Protocol Deviations, UADEs and Serious or continuing non-compliance must be reported to the NCI CD.

- To report these events, please send an email to the NCI CD at CCRsafety@mail.nih.gov. The report that is submitted to the outside IRB can be used to report to the NCI CD..

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section **7.1**.

8.1 CTEP Agent

8.1.1 AZD6244 hydrogen sulfate (NSC 748727)

8.1.1.1 Chemical Name: 5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-[(2-hydroxyethoxy)carbamoyl]-1-methyl-1H-benzimidazol-3-ium hydrogen sulfate

8.1.1.2 Other Names: Selumetinib hydrogen sulfate; ARRY-142886

8.1.1.3 Classification: Mitogen-activated protein kinase kinase (MEK) inhibitor

8.1.1.4 CAS Registry Number: 606143-52-6

8.1.1.5 Molecular Formula: $C_{17}H_{15}BrClFN_4O_3 \bullet H_2SO_4$ M.W.: 555.76

8.1.1.6 Solubility: Very low aqueous solubility (3.4 mcg/mL at pH 7.4)

8.1.1.7 Mode of Action: AZD6244 is a selective mitogen-activated protein kinase (MEK) inhibitor. By inhibiting MEK, AZD6244 inhibits ERK phosphorylation, which may inhibit oncogenic growth signaling in tumor cells by targeting the RAS/RAF/MEK/ERK pathway. The RAS/RAF/MEK/ERK pathway is an important mediator of many cellular processes including proliferation, survival, differentiation, apoptosis, motility, and metabolism.

8.1.1.8 How Supplied: Astra Zeneca supplies and CTEP, DCTD, NCI distributes AZD6244 hydrogen sulfate. The agent is supplied as size 4 hydroxypropylmethylcellulose (HPMC) capsules available in 25 mg (blue) strengths. Capsules are packaged in white, high density polyethylene (HDPE) containers with induction-seals and child-resistant closures. Each bottle contains 60 capsules.

AZD6244 hydrogen sulfate capsules contain a dispersion of drug in d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS; a water soluble form of vitamin E). Each 25 mg capsule contains 35.9 mg TPGS.

Daily Vitamin E intake based on the daily adult dose of AZD6244

Dose	Vitamin E amount
75 mg twice a day (3 x 25 mg x 2)	215.4 mg

8.1.1.9 Storage: Store the AZD6244 hydrogen sulfate capsules at controlled room temperature (20°C-25°C). Brief excursions are permitted between 15°C and 30°C.

8.1.1.10 Stability: Stability studies are ongoing.

If a storage temperature excursion is identified, promptly return AZD6244 hydrogen sulfate to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

8.1.1.11 Route of Administration: Oral. Do not eat or drink (except water only) for 2 hours prior to dosing and 1 hour after dosing selumetinib (AZD6244 hydrogen sulfate) capsules. AZD6244 capsules should be taken with water only.

8.1.1.12 Potential Drug Interactions: High vitamin E doses may potentiate warfarin's anticoagulant activity. Monitor PT/INR more frequently in patients receiving both warfarin and AZD6244 hydrogen sulfate capsules.

Avoid concomitant intake of supplemental vitamin E.

AZD6244 hydrogen sulfate is primarily metabolized by CYP 1A2 to form the active N-desmethyl metabolite; in addition, CYP 1A3 and UGT1A1 form glucuronide conjugates. CYP 2C9, 2C19, 3A4/5 can also metabolize the parent agent; however, as observed during in vitro studies using a pan-CYP inhibitor, other available pathways contribute to AZD6244 metabolism. Use caution in patients who are taking strong inducers or inhibitors of these CYP or UGT enzymes.

AZD6244 is also a substrate of BCRP and P-gp transporters. Use caution in patients who are taking strong inducers or inhibitors of either transport protein.

AZD6244 hydrogen sulfate is a weak inducer of CYP enzymes 3A, 1A and 2C9 and a weak inhibitor of CYP2C9 and both BCRP (breast cancer resistance protein) and OATP1B1 transporters. It did not inhibit OCT1 or P-glycoprotein. The N-desmethyl metabolite is a weak inhibitor of CYP1A2. In vitro data suggest that AZD6244 hydrogen sulfate is unlikely to cause clinically relevant drug-drug interactions by these mechanisms.

8.1.1.13 Patient Care Implications: Study participants should be counseled to avoid excessive sun exposure and use adequate sun protection measures if sun exposure is anticipated during the study.

Availability

AZD6244 hydrogen sulfate is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

AZD6244 hydrogen sulfate is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section **12.4**).

8.1.2 Agent Ordering and Agent Accountability

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

Study agent must be ordered after patient is registered to the treatment arm as no starter supplies are being provided for this study.

Submit agent requests 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. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

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

8.1.2.3 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 and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.2.4 Useful links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov

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

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Biomarker Name **and Person performing the study**	**Assay** **(CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose**	**Tissue/Body Fluid Tested** **and Timing of Assay**	**Mandatory/ Optional**	**Funding Source(s)**
KRAS Mark Raffeld, Molecular Pathology, Laboratory of Pathology, NCI using the 50 cancer gene deep sequencing assay applied for genetic profiling of solid organ cancers **Appendix I**	Cancer Gene Panel CLIA: Y	Eligibility criterion, KRAS G12R mutation status prerequisite for selumetinib treatment Eligibility determination,	Tissue - either biospy or previous surgical specimen At enrollment * If a biopsy is needed, the site with the most minimal morbidity will harvested at the discretion of the PI. combined with KRAS mutation testing at enrollment (same assay)	Mandatory for patients who do not have KRAS mutation status confirmed	CCR

Biomarker Name **and Person performing the study**	**Assay** **(CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose**	**Tissue/Body Fluid Tested** **and Timing of Assay**	**Mandatory/ Optional**	**Funding Source(s)**
50-cancer gene panel (multiplexed deep sequencing assay to identify somatic variants in tumor specimen) Mark Raffeld, Molecular Pathology, Laboratory of Pathology, NCI	Cancer Gene Panel CLIA: Y	Integrated to identify potential mutations governing resistance to selumetinib in KRAS G12R mutant cancers to identify molecular subgroups predicting response to the investigational agent. This genetic information retrieved from tumors are somatic mutations only. No germline mutation testing will be done.			
CNKSR1 Markku Miettinen, Laboratory of Pathology. NCI	IHC CLIA: N	to identify subgroups of patients responding to the investigational agent to identify biomarkers of response	Tissue from optional screening biopsy at enrollment Tissue from optional CT guided biopsy after 2 weeks on the study	Optional	Dr. Rudloff's lab

Biomarker Name **and Person performing the study**	**Assay (CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose**	**Tissue/Body Fluid Tested** **and Timing of Assay**	**Mandatory/ Optional**	**Funding Source(s)**
Circulating Tumor DNA (ctDNA) Mark Raffeld, Molecular Pathology, Laboratory of Pathology, NCI	CTC (blood) CLIA: N	Integrated to identify biomarkers of response	Blood (to be taken with clinical samples) – 5 ml ctDNA Blood Collection (see **Appendix H**) At enrollment, after 2, 4, 6, and 8 weeks on study and from there monthly	Optional	Dr. Rudloff's lab

9.1 Sample Storage, Tracking and Disposition

9.1.1 NCI Site Only

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

All samples initially will be sent to Blood Processing Core (BPC) for processing and storage until they are distributed to Dr. Rudloff's lab sample analysis as described in the protocol.

9.1.2 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

9.1.2.1 BPC contact information

Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

9.1.2.2 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced

back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the Clinical Center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

9.1.2.3 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

9.1.3 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissues are stored for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed for research conducted in relation to this protocol.

9.1.4 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described in Section above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NCI IRB as soon as he is made aware of such loss. If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the

office of the CCR, NCI.

9.1.5 Shipping instructions for Participating sites

For patients enrolled at Non-NIH sites, the biopsy sample will be sent as a paraffin block together with copy of the original pathology report (or molecular pathology report) to

Santhana Webb
10 Center Drive, Room 8D44F
Bethesda, MD 20892-1906
Phone: 240-858-3165
Fax: 301-480-2462
Email: santhana.webb@nih.gov

Tissue block and matched pathology report will have matching identification number.
Fresh blood will be send on dry ice to

Dr. Yansong Bian
Hatfield Center
CRC-1B 34A
10 CENTER DR
BETHESDA MD 20814
Phone: 301-451-6928
yansong.bian@nih.gov

Samples may be shipped from site of acquisition to site of analysis in batches. Shipping must be by expedited courier on dry ice.
Participating sites should send e-mail with information about planning shipment to Cara Kenney and Yansong Bian 2 days before actual shipment.
Each sample should be labeled with a unique identifier linking the biospecimen to the respective pathology report. A hard copy should be included into the shipment. If a tumor block is not available, unstained slides may also be submitted. 15 unstained slides are preferable.

10 STUDY CALENDAR

Screening evaluations are to be conducted will be obtained within 8 weeks prior to start of enrollment. Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Laboratory evaluation tests may be performed at the NCI or at the local physician. Assays and scans may be taken 5 days earlier or later than scheduled depending on individual needs.

For the evaluation purposes, a cycle will be defined as 28 +/- 2 days (4 weeks). A patient may receive up to 27 cycles (108 weeks).

	Screening	Baseline[h]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wks 13-108[c]	End of Treatment Evaluations[d]	FU[e]
AZD6244			A	A	A	A	A	A	A	A	A	A	A	A	A		

	Screening	Baseline[h]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wks 13-108[c]	End of Treatment Evaluations[d]	FU[e]
hydrogen sulfate																	
Informed consent	X																
Confirmation of diagnosis	X																
Demographics	X																
Medical history	X																
Concurrent meds		X	X----------X														
Physical exam	X	X	X		X		X		X		X		X		X	X	
Vital signs	X	X	X		X		X		X		X		X		X	X	
Height	X																
Weight	X	X	X		X		X		X		X		X		X	X	
Performance status	X	X	X		X		X		X		X		X		X	X	X
CBC w/diff, plts [g] PT, PTT	X	X	X		X		X		X		X		X		X	X	
Serum chemistry [a,g]	X	X	X		X		X		X		X		X		X	X	
EKG	X																
Adverse event evaluation		X----------X														X	X
Tumor measurements		X	Tumor measurements performed after 4 weeks and thereafter are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X	
Radiologic evaluation		X	Radiologic measurements should be performed after 4 weeks and thereafter every 8 weeks.													X	
B-HCG		X[b]															
Tumor biopsy for KRAS mutation status, Cancer gene panel and CNKSR1 by IHC [k]	X unless archived or prior biopsy material availabl e																

	Screening	Baseline[h]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wks 13-108[e]	End of Treatment Evaluations[d]	FU[e]
Tumor biopsy for CNKSR1 by IHC [k]					X[f]												
Blood for Circulating Tumor DNA (ctDNA)[k]		X[f]			X[f]		X[f]		X[f]		X[f]		X[f]		X[f, i]		
Tumor markers CA19-9, CEA, CA 125		X					X				X				X[i]		
Advance Directive[j]		X															

A: AZD6244 hydrogen sulfate: Dose 75 mg twice a day every day.

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase, magnesium, prealbumin

b: Serum pregnancy test (women of childbearing potential).

c: Assessments will be performed once per cycle.

d: Patients will be invited to their study site approximately 30 days following the last dose of study drug. If patents are not able to come or provide lab results from home, they will be asked by phone for performance status, any adverse events and new cancer treatment.

e: Patients will be followed for 52 weeks with a telephone interview for performance status, any adverse events and new cancer treatment every 2 months.

f: Optional

g: The laboratory tests can be performed either at the NIH clinic or at home.

h: Baseline evaluations do not need to be repeated if they were done on screening during appropriate time frame.

i: monthly

j: As

icated in section **13.3**, all subjects enrolled in NIH will be offered the opportunity to complete an NIH Advance Directive form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

k: All research study will be performed at NIH. For shipping instructions, please, see Section **9.1.5.** Not necessary for patients with confirmed KRAS mutation status

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response after the first 4 weeks, then every 8 weeks thereafter. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

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

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with AZD6244.

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over

and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be

guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

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

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

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

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

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

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

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

11.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

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

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

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

11.1.6 Progression-Free Survival

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

12 STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug. The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

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

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

The Study Chair and PIs at all ETCTN Sites will review all obtained data every 6 months.

"The following decision rule to halt the study if – at any of the sites – will be applied at time of review:

1) >= 1 death related to adverse event (not related to progression of disease)
2) >= 3 non-hematological grade 3 or 4 toxicities based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 within first stage of study.

12.2 Data Reporting

Data collection for this study will be done through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave..

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

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

12.2.1 Method

*For studies assigned for **CTMS Routine** Monitoring:*

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

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

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less

than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

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

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

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

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

12.2.3 NCI Data Sharing Plans

Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_X__ De-identified data in an NIH-funded or approved public repository.

_X__ Identified data in BTRIS

_X__ De-identified or identified data with approved outside collaborators under appropriate

agreements.

How and where will the data be shared?

Data will be shared through:

_X__ An NIH-funded or approved public repository. Insert name or names:_____clinicaltrials.gov_____.

_X__ BTRIS (automatic for activities in the Clinical Center)

_X__ Approved outside collaborators under appropriate individual agreements.

_X__ Publication and/or public presentations (de-identified or in accordance with Journal's and institutional policy)

When will the data be shared?

_X__ Before publication.

_X__ At the time of publication or shortly thereafter.

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator"

(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to

restrict NCI's participation in the proposed combination protocol.

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

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

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

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

12.4 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Rationale For Subject Selection

The patients to be entered in this protocol have advanced pancreatic cancer, either locally advanced unresectable pancreatic cancer or stage IV disease with metastatic disease dissemination, and hence have limited life expectancies.

Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared to another. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to gender or to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

13.2 Participation of Children

Because no dosing or adverse event data are currently available on the use of AZD6244 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

13.3 Participation of Subjects Unable to Give Consent (NCI Site Only)

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **13.4**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

13.4 Evaluation of Benefits and Risks/Discomforts

Potential benefits to subjects expected from the trial: As a result of participating in this trial, patients will receive evaluation and treatment of their tumor. This protocol may or may not be helpful for a specific patient, but the results may help the investigators learn about the administration of AZD6244 on a continuing basis. The potential for this research treatment to offer control of the disease is unknown; however, based on information to date, the possibility of an effect on the progression of disease exists. Benefit cannot be promised nor can the chance of benefit be accurately predicted.

Potential risks of selumetinib include the range of side effects outlined in Section **8.1.1.**

13.4.1 Alternative Approaches or Treatments

Patients will be advised verbally and in writing regarding the risks and benefits of this trial, treatment requirements, and alternative approaches to entering the trial. Written consents will be obtained.

13.4.2 Procedures to Eliminate or Minimize Potential Risks

This study may involve unforeseeable risks for patients, such as side effects whose exact nature and severity are unpredictable. Scrupulous care will be taken to minimize such side effects. All patients will be given blood tests, physical examinations, and scans, as described in the monitoring schedule, and must have a local physician to provide long-term care and monitoring for complications. Immediate medical treatment is available at the enrollment site for any patients who suffer physical injury as a result of participation in this study. No compensation is available, but any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

13.4.3 Provisions for Monitoring Data Collection to Ensure Subject Safety

As information is gathered from this trial, clinical results will be shared with patients. Laboratory and clinical data will be frequently gathered and any new significant finding(s) found during the course of the research, which may affect a patient's willingness to participate further, will be explained.

Confidentiality of information concerning participants will be maintained, including in all publications and presentations resulting from this study. Names of participants or material identifying participants will not be released without permission, except as such release is required by law. Records at the National Cancer Institute are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

13.4.4 Biopsies

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the enrollment site. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

13.4.5 Radiation risks

The optional biopsy collected at 2 weeks is for research purposes only and will be done under CT guidance. Subjects undergoing optional biopsy collection will be exposed to 0.80 rem. This amount of radiation is below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee.

13.4.6 Non-Physical Risks of Genetic Research

13.4.6.1 Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Patients will

be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with patients, family members or health care providers.

13.4.6.2 Risk related to possibility that information may be released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

13.4.6.3 Risk to family or relatives

Family members or relatives may or may not want to be aware of familial tendencies or genetic risks of disease which may cause anxiety about possible future health problems.

13.5 Risks/Benefits Analysis

Considering that the drug has been administered to thousands of patients already and has been found safe, the preclinical efficacy data including patient-derived xenotransplanation models and considering that pancreatic cancer is a rapidly fatal disease with few effective treatment option, a gross risk/benefit analysis appears to be in overwhelming favor for potential benefit.

13.6 Consent Process and Documentation

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts, potential benefits and potential alternative therapies will be carefully explained to the patient or the patient's surrogate, and a signed informed consent document will be obtained by the PI, AI or clinical staff fellow. Moreover, any experimental invasive procedure will require a separate consent form.

13.6.1 Telephone Reconsent Procedure (NCI Site Only)

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

14 STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

This is a phase 2 trial in patients with measurable locally advanced or stage IV pancreas cancer patients harboring KRAS G12R mutations are treated with the tyrosine kinase inhibitor selumetinib (AZD6244). All patients eligible for treatment will undergo formal response evaluation after 1 and 3 cycles of therapy and every 2 cycles after that.

14.1.1 Screening

The prevalence of advanced pancreas cancer patients harboring KRAS G12R mutations is 15%. Using an outside organization, Foundation Medicine, potential participants for this trial may be pre-screened for the presence of the KRAS G12R mutation prior to enrolling on this trial. As a result, it is expected that greater than 50% of subjects who are pre-screened and then enrolled onto this trial for further evaluation will be able to be treated on this trial. If this were to apply to the screening population and if 155 patients were screened, there is a 73% probability of identifying at least 21 patients with a KRAS G12R mutation. The primary objective of this trial is to determine if selumetinib monotherapy is able to produce adequate numbers of clinical responses in patients with locally advanced or stage IV metastatic pancreas cancer with KRAS G12R mutations. If so, this regimen will be considered for use in subsequent studies, to determine its role in this disease. Evaluable patients are patients whose response to a treatment can be measured because enough information has been collected (e.g. patients who come off study due to progression of disease, either by RECIST or clinically, due to toxicity, or patient's withdrawal). Inevaluable patients are patients who are lacking this information.

14.1.2 Treatment

The primary objective of this trial is to determine if selumetinib monotherapy is able to produce adequate numbers of clinical responses in patients with locally advanced or stage IV metastatic pancreas cancer with KRAS G12R mutations. If so, this regimen will be considered for use in subsequent studies, to determine its role in this disease.

The study will be conducted using a phase 2 optimal design. The objective of the trial will be to determine whether this novel agent is able to be associated with a response rate (PR + CR) that can rule out 5% (p0=0.05) in favor of an improved response rate of 30% (p1=0.30). Using alpha=0.10 (probability of accepting a poor agent) and beta=0.10 (probability of rejecting a good agent), initially 7 evaluable patients will be enrolled in the study. If after accrual of patient #7 no patient has responded, accrual will be halted until patient #7 becomes evaluable. If 0 of 7 patients respond, then no further patients will be enrolled. If 1 or more of the first 7 evaluable patients enrolled have a clinical response, then accrual will continue until a total of 21 evaluable patients have been enrolled. If 1 to 2 of the 21 has a clinical response, then this will be considered inadequate for further investigation of this regimen. If 3 or more of 21 respond, then this will warrant further investigation in a subsequent trial. Under the null hypothesis (5% response rate), the probability of early termination is 70%.

14.2 Sample Size/Accrual Rate

The accrual ceiling will be set at 60 patients to be screened for the presence of KRAS G12R mutations to allow for treatment of up to 25 patients, which would include up to 3 inevaluable patients. It is expected that 1-2 patients per month will be treated on this trial. Allowing for treatment with this agent over a two year period with follow up, it is expected that the trial will be completed in approximately 3 years.

14.3 Analysis of Secondary Endpoints

Progression-free survival will be calculated using the Kaplan-Meier method.

Toxicity data will be obtained and presented by type and grade of toxicity. Toxicities may be informally compared within patient subsets to estimate the toxicity rate in those subsets.

The association of response to selumetinib (PR as defined by RECIST) and presence of concomitant activating oncogene mutations or loss of tumor suppressor function will be presented descriptively to estimate the response rates according to those characteristics.

Comparisons between the semi-quantitative measurements of CNKSR1 will be made descriptively to estimate the differences of the expression level in pancreas cancer tissues and clinical outcome variables. Similarly, ctDNA levels, and alterations in somatic variants between baseline and repeat profiling (integrated biomarker; voluntary) will be evaluated for change from baseline levels and the estimated changes will be reported.

A variety of other secondary evaluations will be performed. In all cases, the evaluations will be done with exploratory intent, and results will be presented descriptively.

Priority #1 – predictive biomarkers for response to selumetinib in KRAS G12R pancreas cancer patients:

1. Pre-treatment variant profile and response. Presence of variants identified in the 50-cancer gene panel will be compared with response, presenting the results in a 2x2 table with findings reported descriptively.

2. Pre-treatment ctDNA levels will be divided into groups to separate aberrant values from the rest. The cutoffs will be > and <2 standard deviations of the mean, with the cutoffs applied to both ctDNA levels. Based on these groups, resulting in patients with cfDNA transcripts levels >2 SD above the mean, patients with cfDNA transcripts levels <2SD below the mean, and the rest in between, the categorical results will be evaluated and reported relative to response vs. non-response in a descriptive manner.

3. Pre-treatment CNKSR1 staining (scored semi-quantitatively as 0, 1+, 2+, and 3+, per number of treated patients) vs. response or not will be reported in a table.

Priority #2 – longitudinal biomarker measuring response to treatment

1. cfDNA transcript levels will be followed from the start of treatment q2 weeks and the change to pre-treatment will be plotted for each timepoint in a spider plot format. This will be a descriptive presentation only.

2. Variant profile derived from voluntary repeat biopsies will be compared to pre-treatment variant profile and gain of variants (adjusted for similar sequencing depth) will be recorded. This will be a descriptive presentation only.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Asian	4	3	0	0	**7**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	4	3	0	0	**7**
White	20	14	4	3	**41**
More Than One Race	0	0	3	2	**5**
Total	**28**	**20**	**7**	**5**	**60**

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14.4 Reporting and Exclusions

14.4.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with AZD6244.

14.4.2 Evaluation of Response

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

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

All conclusions should be based on all eligible patients. Sub analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub analyses may not serve as the basis for drawing

conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

15 REFERENCES

1. Rahib, L., et al., *Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States.* Cancer Res, 2014. **74**(11): p. 2913-21.
2. http://www.cancer.gov/researchandfunding/reports/pancreatic-action-plan.pdf., 2012.
3. Moore, M.J., et al., *Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group.* J Clin Oncol, 2007. **25**(15): p. 1960-6.
4. da Cunha Santos, G., et al., *Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada Clinical Trials Group Study PA.3.* Cancer, 2010. **116**(24): p. 5599-607.
5. Moinpour, C.M., et al., *Pain and emotional well-being outcomes in Southwest Oncology Group-directed intergroup trial S0205: a phase III study comparing gemcitabine plus cetuximab versus gemcitabine as first-line therapy in patients with advanced pancreas cancer.* J Clin Oncol, 2010. **28**(22): p. 3611-6.
6. Waddell, N., et al., *Whole genomes redefine the mutational landscape of pancreatic cancer.* Nature, 2015. **518**(7540): p. 495-501.
7. Provenzano, P.P., et al., *Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma.* Cancer Cell. **21**(3): p. 418-29.
8. Chantrill, L.A., et al., *Precision Medicine for Advanced Pancreas Cancer: The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) Trial.* Clin Cancer Res, 2015. **21**(9): p. 2029-37.
9. Connor, A.A., et al., *Association of Distinct Mutational Signatures With Correlates of Increased Immune Activity in Pancreatic Ductal Adenocarcinoma.* JAMA Oncol, 2016.
10. Bailey, P., et al., *Genomic analyses identify molecular subtypes of pancreatic cancer.* Nature, 2016. **531**(7592): p. 47-52.
11. Witkiewicz, A.K., et al., *Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets.* Nat Commun, 2015. **6**: p. 6744.
12. Singh, A., et al., *A gene expression signature associated with "K-Ras addiction" reveals regulators of EMT and tumor cell survival.* Cancer Cell, 2009. **15**(6): p. 489-500.
13. Collisson, E.A., et al., *Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy.* Nat Med, 2011. **17**(4): p. 500-3.
14. Cox, A.D., et al., *Drugging the undruggable RAS: Mission possible?* Nat Rev Drug Discov, 2014. **13**(11): p. 828-51.
15. Ogura, T., et al., *Prognostic value of K-ras mutation status and subtypes in endoscopic ultrasound-guided fine-needle aspiration specimens from patients with unresectable pancreatic cancer.* J Gastroenterol, 2013. **48**(5): p. 640-6.
16. Barretina, J., et al., *The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity.* Nature, 2012. **483**(7391): p. 603-7.
17. Hamidi, H., et al., *KRAS mutational subtype and copy number predict in vitro response of human pancreatic cancer cell lines to MEK inhibition.* Br J Cancer, 2014. **111**(9): p. 1788-801.
18. Hammond, D.E., et al., *Differential reprogramming of isogenic colorectal cancer cells by*

distinct activating KRAS mutations. J Proteome Res, 2015. **14**(3): p. 1535-46.
19. Troiani, T., et al., *Primary and acquired resistance of colorectal cancer cells to anti-EGFR antibodies converge on MEK/ERK pathway activation and can be overcome by combined MEK/EGFR inhibition.* Clin Cancer Res, 2014. **20**(14): p. 3775-86.
20. Kapoor, A., et al., *Yap1 activation enables bypass of oncogenic Kras addiction in pancreatic cancer.* Cell, 2014. **158**(1): p. 185-97.
21. Azzolin, L., et al., *YAP/TAZ incorporation in the beta-catenin destruction complex orchestrates the Wnt response.* Cell, 2014. **158**(1): p. 157-70.
22. Bodoky, G., et al., *A phase II open-label randomized study to assess the efficacy and safety of selumetinib (AZD6244 [ARRY-142886]) versus capecitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy.* Invest New Drugs, 2012. **30**(3): p. 1216-23.
23. Janne, P.A., et al., *Impact of KRAS codon subtypes from a randomised phase II trial of selumetinib plus docetaxel in KRAS mutant advanced non-small-cell lung cancer.* Br J Cancer, 2015. **113**(2): p. 199-203.
24. Friday, B.B. and A.A. Adjei, *Advances in targeting the Ras/Raf/MEK/Erk mitogen-activated protein kinase cascade with MEK inhibitors for cancer therapy.* Clin Cancer Res, 2008. **14**(2): p. 342-6.
25. O'Neill, E. and W. Kolch, *Conferring specificity on the ubiquitous Raf/MEK signalling pathway.* Br J Cancer, 2004. **90**(2): p. 283-8.
26. Wellbrock, C., M. Karasarides, and R. Marais, *The RAF proteins take centre stage.* Nat Rev Mol Cell Biol, 2004. **5**(11): p. 875-85.
27. Khokhlatchev, A.V., et al., *Phosphorylation of the MAP kinase ERK2 promotes its homodimerization and nuclear translocation.* Cell, 1998. **93**(4): p. 605-15.
28. Hoshino, R., et al., *Constitutive activation of the 41-/43-kDa mitogen-activated protein kinase signaling pathway in human tumors.* Oncogene, 1999. **18**(3): p. 813-22.
29. Breitkreutz, I., et al., *Targeting MEK1/2 blocks osteoclast differentiation, function and cytokine secretion in multiple myeloma.* Br J Haematol, 2007. **139**(1): p. 55-63.
30. Davies, B.R., et al., *AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 kinases: mechanism of action in vivo, pharmacokinetic/pharmacodynamic relationship, and potential for combination in preclinical models.* Mol Cancer Ther, 2007. **6**(8): p. 2209-19.
31. Huynh, H., et al., *Targeted inhibition of the extracellular signal-regulated kinase kinase pathway with AZD6244 (ARRY-142886) in the treatment of hepatocellular carcinoma.* Mol Cancer Ther, 2007. **6**(1): p. 138-46.
32. Tai, Y.T., et al., *Targeting MEK induces myeloma-cell cytotoxicity and inhibits osteoclastogenesis.* Blood, 2007. **110**(5): p. 1656-63.
33. Ball, D.W., et al., *Selective growth inhibition in BRAF mutant thyroid cancer by the mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244.* J Clin Endocrinol Metab, 2007. **92**(12): p. 4712-8.
34. Janne, P.A., et al., *Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study.* Lancet Oncol, 2013. **14**(1): p. 38-47.
35. Robert, C., et al., *Selumetinib plus dacarbazine versus placebo plus dacarbazine as first-line treatment for BRAF-mutant metastatic melanoma: a phase 2 double-blind randomised study.* Lancet Oncol, 2013. **14**(8): p. 733-40.

36. Carvajal, R.D., et al., *Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial.* JAMA, 2014. **311**(23): p. 2397-405.
37. *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.*
38. *Febrile neutropenia/neutropenic infection has been observed primarily in trials combining AZD6244 (selumetinib) and docetaxel.*
39. *SBE-CD (Captisol®, vehicle) in the mix and drink formulation is known to cause soft stools and/or diarrhea in rats and dogs; however, it is possible that some of these findings might be related to exacerbation of the vehicle effect by AZD6244 (selumetinib).*

16 APPENDICES

16.1 Appendix A: Performance Status Criteria

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

16.2 Appendix B: New York Heart Association Classifications

Clinical Evaluation of Functional Capacity of Patients
with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to work**
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

Reference: Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953).

16.3 Appendix C: 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, **selumetinib (AZD6244 hydrogen sulfate)**. This clinical trial is sponsored by the National Cancer Institute (NCI). 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 prescriber need to know:

Selumetinib (AZD6244 hydrogen sulfate) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 1A2, 2C8, 2C9, 2C19, 3A4/5 and UGT 1A1 and 1A3. Selumetinib (AZD6244 hydrogen sulfate) is metabolized by these enzymes and may be affected by other drugs that inhibit or induce these enzymes.
- The proteins in question are P-gp and BCRP. Selumetinib (AZD6244 hydrogen sulfate) is a substrate of BCRP and P-gp transporters and may be affected by other drugs that inhibit or induce these transporters.

March 2016

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

Selumetinib (AZD6244 hydrogen sulfate) interacts with many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them 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 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 prescribers can write prescriptions. You must also tell 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:

Selumetinib (AZD6244 hydrogen sulfate) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 1A2, 2C8, 2C9, 2C19, 3A/5, UGT 1A1 and 1A3, P-gp and BCRP."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Avoid taking extra vitamin E found in vitamins or supplements.
- 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 _____.

March 2016

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **selumetinib (AZD6244 hydrogen sulfate).** This clinical trial is sponsored by the NCI. AZD6244 hydrogen sulfate (selumetinib) interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistant, nurse practitioners, 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.

- Selumetinib (AZD6244 hydrogen sulfate) interacts with CYP 1A2, 2C8, 2C9, 2C19, 3A4/5, UGT 1A1 and 1A3, P-gp, and BCRP, and must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered "strong inducers/inhibitors of CYP 1A2, 2C8, 2C9, 2C19, 3A4/5, UGT 1A1 and 1A3, P-gp and BCRP."
- You should avoid taking extra vitamin E found in vitamins or supplements.
- 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 _____.

16.4 Appendix D: Patient's Pill Diary

CTEP-assigned Protocol #_____

PATIENT PILL DIARY

Today's date _____**Agent** __**AZD6244**_hydrogen sulfate (selumetinib)__

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

1. Complete one form for each cycle of treatment.
2. **AZD6244 capsules** should be stored at room temperature. Keep away from heat sources.
3. You will take **AZD6244** twice each day about 12 hours apart. Take the medicine on an empty stomach (no food or drink other than water for 2 hours before and 1 hour after dosing).

   Morning dose: take_____ mg (____capsules) **AZD6244**. ********** Evening dose: take _____mg (____capsules) **AZD6244**.
4. Record the date, the number of **AZD6244** capsules you swallowed in the morning and again in the evening, and when you swallowed the medicine.
5. If you have any comments or notice any side effects, please record them in the Comments column
6. If you missed your dose or vomited one dose continue selumetinib AZD6244 as per schedule, don't take additional doses to make-up for missed dose. In case you missed multiple doses, please contact your doctor.
6. Discuss with your doctor all other medications you are currently taking, including herbal medicines, as some of these medicines may also interact with selumetinib in a harmful way.
7. Do not take supplemental vitamin E.
8. Please bring this form and your bottles of **AZD6244** when you return for each appointment.

Day	Date	Time of morning dose	Dose taken # of capsule taken	Time of evening dose	Dose taken # of capsule taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						

13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of capsules taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

16.5 Appendix E: Patient handout addressing aggressive management for diarrhea

If you have more than 3 liquid stools –

- Stop all lactose-containing products, alcohol, and high osmolar supplements such as line Ensure, Ensure Plus, Boost, or energy milk shakes
- Drink 8-10 large glasses of clear liquids per day (e.g., Gatorade, broth)
- Eat frequent small meals (bananas, rice, applesauce, toast, plain pasta – BRAT diet)
- Record number of stools and report symptoms like lightheadedness, dizziness, nausea, fever
- Start loperamide; initial dose 4 mg, followed by 2 mg q 4 h or after very unformed stool and contact your doctor
- Re-assess in the next 12 – 24 h

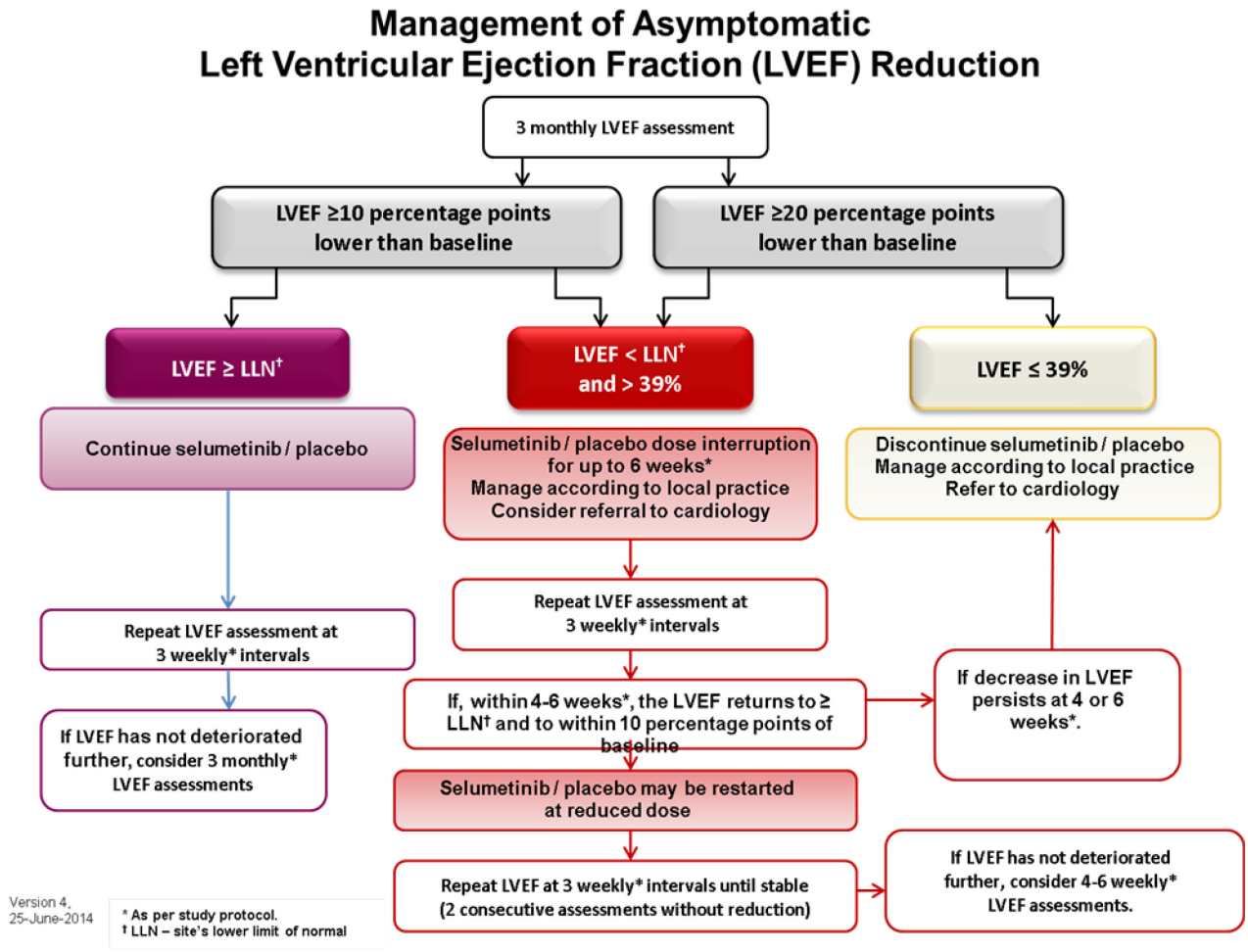
If symptoms improving:

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12 h diarrhea-free interval

If symptoms are not improving:

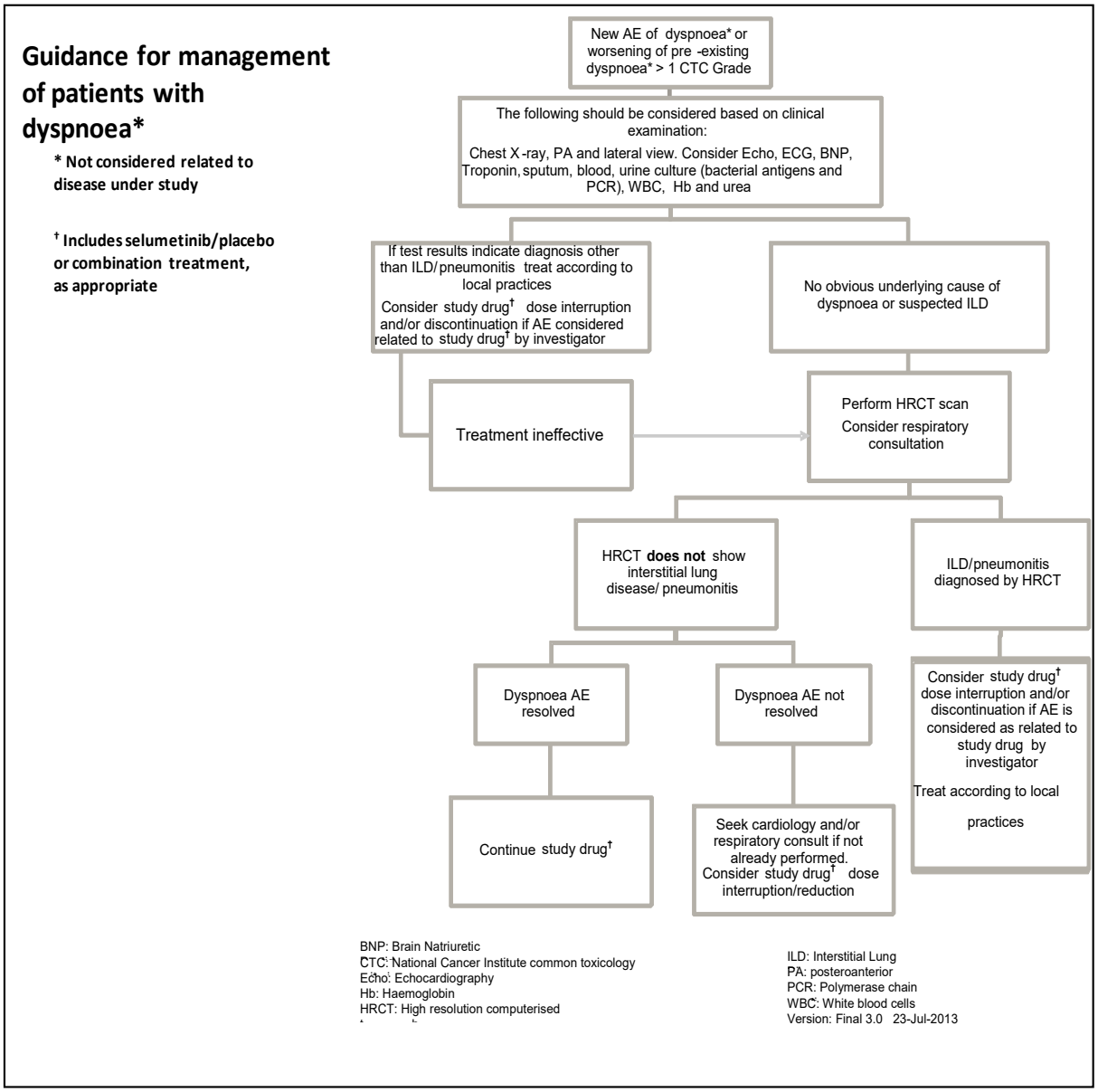
- Go to Emergency Room in the nearest hospital

16.6 Appendix F: Safety Management Algorithm: LVEF Reduction



AstraZeneca Guidance for AZD6244 studies (March 2015)

16.7 Appendix G: Safety Management Algorithm for Dyspnea



AstraZeneca Guidance for AZD6244 studies (March 2015)

16.8 Appendix H Plasma preparation for cell free (cf) DNA extraction using EDTA collection tubes.

10/15/2016

1. Collect up to 5 ml Peripheral Blood in standard EDTA (purple top) collection tube. Record time of blood draw on tube.

2. Bring to lab stat for processing*

3. Centrifuge at 1500 x g for 10 minutes to remove blood cells at 4°C.

4. Transfer supernatant to new nuclease free conical tube carefully taking care not to disturb buffy coat**

5. Centrifuge a second time at 10,000 x g at 4°C to remove any remaining cells and debris.**

6. Carefully transfer supernatant without disturbing the pellet into nuclease free cryotubes (2 ml size) and store at -80°C until DNA extraction.

*processing should occur within 2 hours at room temperature of blood draw or stored at 4°C for up to 24 hours to prevent lysing of blood cells

**It is extremely important, not to disturb the buffy coat after the first spin, and any pellet after the second spin.

Note: this procedure is adapted from published sources and procedures

16.9 Appendix I: Cancer Gene Mutation-Standard Panel

Molecular Diagnostics Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health
Bldg 10 / Room 3S249, (301) 480-8080

Molecular Diagnostics Section Test Directory

Test Name	Assay Description	Assay Type	Specimen Type Accepte	Category/Use
Cancer Gene Mutation-Standard Panel (a multiplex 50 gene panel with next-generation sequencing)	Ion Torrent Cancer Hotspot Panel (CHP2). Targets ~2850 COSMIC hotspot mutations in 50 cancer genes (ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53 VHL)	Qual.	FFPE Tissue	NSCLC, Colorectal Cancer, Bladder Cancer, Melanoma, other / Oncology Clinical Research Protocol