A Phase II Trial of Vemurafenib in Combination with Sorafenib to Treat Patients with Advanced KRAS Mutated Pancreatic Cancer. Targeting RAF Dimers to Suppress Oncogenic RAS Signaling
(The Dr. Nate Nieto Study)

Protocol #: HRI-Vemurafenib-Sorafenib-001

NCT05068752
IND Exempt

Sponsor
HonorHealth Research Institute

Principal Investigator
Erkut H. Borazanci, MD, MS
HonorHealth Research Institute
10510 North 92nd Street
Scottsdale, AZ 85258
Phone: 480-323-1350
Email: eborazanci@honorhealth.com

Lead Scientific Investigator
Haiyong Han, PhD
Translational Genomics Research Institute (TGen) An Affiliate of City of Hope
445 North Fifth Street
Phoenix, AZ 85004
Email: hhan@tgen.org

Consulting Investigator
Daniel D. Von Hoff, MD, FACP, FASCO, FAACR
HonorHealth Research Institute
10510 North 92nd Street
Scottsdale, AZ 85258

Translational Genomics Research Institute (TGen) An Affiliate of City of Hope
445 North Fifth Street
Phoenix, AZ 85004
Phone: 602-343-8492
Email: dvh@tgen.org

CONFIDENTIALITY STATEMENT

<table>
<tr><td colspan="2">Consulting Investigator
Talia Golan, MD
Sheba Medical Center - Israel
Pancreatic Cancer Center
Phone: 972-77-997-2480
Email: Talia.golan@sheba.health.gov.il</td></tr>
<tr><td>Clinical Sub-Investigator
Gayle S. Jameson, ACNP-BC, AOCN
HonorHealth Research Institute
10510 North 92nd Street
Scottsdale, AZ 85258
Phone: 480-323-1350
Email: gjameson@honorhealth.com</td><td>Clinical Sub-Investigator
Lana Caldwell
HonorHealth Research Institute
10510 North 92nd Street
Scottsdale, AZ 85258
Email: lcaldwell@honorhealth.com</td></tr>
<tr><td>Scientific Sub-Investigator
Richard G. Posner, PhD
Northern Arizona University
Flagstaff AZ, 86011
Phone: 928-606-2805
Email: Richard.Posner@nau.edu</td><td>Scientific Sub-Investigator
William S. Hlavacek, PhD
Theoretical Biology & Biophysics Group
Los Alamos National Laboratory
Los Alamos, NM 87545
Phone: 505-665-1355 (office)
Email: wish@lanl.gov</td></tr>
<tr><td>Scientific Sub-Investigator
Boris N. Kholodenko, PhD, D.Sc., MRIA
University College Dublin - Belfield
Dublin 4, Ireland
Phone: +353-1-716-6304
Email: boris.kholodenko@ucd.ie</td><td>Scientific Sub-Investigator
Walter Kolch, MD, FRSE, MRIS
Systems Biology Ireland & Conway Institute
University College Dublin, Ireland
Phone: 00353-1-716 6303
Email: walter.kolch@ucd.ie</td></tr>
<tr><td>Scientific Sub-Investigator
Oleksii S. Rukhlenko, PhD
Systems Biology Ireland
University College Dublin, Ireland
Email: oleksii.rukhlenko@ucd.ie</td><td></td></tr>
<tr><td colspan="2">Biostatistician
Denise J. Roe, DrPH.
The University of Arizona Cancer Center
1515 North Campbell Avenue
Campus PO Box 245024
Levy Building 1933
Tucson, AZ 85724
Phone: 520-626-2281
Email: droe@email.arizona.edu</td></tr>
</table>

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INVESTIGATOR'S PROTOCOL AGREEMENT

Study Title: A Phase II Trial of Vemurafenib in Combination with Sorafenib to Treat Patients With Advanced KRAS Mutated Pancreatic Cancer. Targeting RAF Dimers to Suppress Oncogenic RAS Signaling (The Dr. Nate Nieto Study)
Protocol No.: HRI-Vemurafenib-Sorafenib-001

Version 3 dated 28 Mar 2023

I confirm that my staff and I have carefully read and understand this protocol. I/we agree to comply with the procedures and terms of the study specified herein. In particular, I/we have agreed to:

- Abide by all obligations stated on Form FDA 1572 and on other document(s) required by local regulatory authority.
- Retain records and documents related to this trial for at least 7 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 7 years have elapsed since the formal discontinuation of clinical development of the investigational products.
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- Maintain confidentiality and assure security of HonorHealth Research Institute (HRI) confidential documents.
- Obtain Institutional Review Board (IRB) approval of the protocol, any amendments to the protocol, and periodic re-approval as required, and to keep the IRB informed of adverse events and periodically report the status of the study to them.
- Not implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the IRB, except where necessary to eliminate an immediate hazard to the subjects or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Assure that each patient enrolled into the trial has read, understands, and has signed the Informed Consent.
- Ensure that I and all persons assisting me with the study are adequately informed and trained about the investigational drug and of their study-related duties and functions as described in the protocol.
- Make prompt reports of serious adverse events (SAEs), AESIs, pregnancies, and deaths (within 1 business day of becoming aware of the event) to HRI Oncology Drug Safety as indicated in Section 8 of the protocol.
- Assure access to study monitors.

- Prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.
- Arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to the Sponsor.
- Cooperate fully with any study-related GCP audit as performed by quality assurance group specified by the sponsor.
- Abide by the stipulations in the Disclosure of Data section and the manuscript preparation/authorship guidelines established at the outset of the study.

Investigator's Printed Name: _____

Investigator's Signature and Date: _____

SAE REPORTING REQUIREMENTS

All SAEs, AESI, and pregnancies must be reported on Medwatch Form 3500A within 24 hours/ 1 business day of becoming aware of the event, to HonorHealth Oncology Drug Safety Team after the Investigator recognizes/classifies the event as a SAE, AESI, or pregnancy.

The completed MedWatch Form 3500A with accompanying SAE Coversheet should be sent to the Oncology HRI Drug Safety, at the contacts as specified below. Refer to Section 8 for more details.

HonorHealth will be responsible for reporting SAEs, AESI, and pregnancies to Bayer and Genentech as per Section 8.12.

HonorHealth Oncology Drug Safety Team
Phone: 480-323-1350
Fax: 480-323-1560
Email: OncologyDrugSafety@honorhealth.com

List of Abbreviations	
AE	Adverse Event
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BID	Twice a day (from Latin "b*is in die")*
BRAF	Proto-oncogene B-Raf
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA-125	Cancer antigen 125
CA 19-9	Carbohydrate antigen 19-9
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
CNS	Central Nervous System
CO2	Bicarbonate
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor Deoxyribonucleic Acid
CTEP	Cancer Therapy Evaluation Program
DHHS	Department of Health and Human Services
DILI	Drug Induce Liver Injury
DNA	Deoxyribonucleic Acid
DTC	Differentiated Thyroid Cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ERK	Extracellular Signal-Related Kinase
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HCC	Hepatocellular Carcinoma
HIPAA	Health Insurance Portability and Accounting Act
HRI	HonorHealth Research Institute
ICF	Informed Consent Form
ICH	International Conference of Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous

KRAS	KRAS gene
LDH	Lactate Dehydrogenase
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NS	Normal Saline
OS	Overall Survival
PD	Progressive Disease
PDA	Pancreatic Ductal Adenocarcinoma
PFS	Progression free survival
P-gp	P-glycoprotein
PO	By mouth (from Latin *"per os")*
PR	Partial Response
pRBC	Packed Red Blood Cells
PT	Prothrombin Time
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SPF	Sun Protection Factor
SD	Stable Disease
TGen	Translation Genomics Research Institute
ULN	Upper Limit of Normal
UVA	Ultraviolet A
UVB	Ultraviolet B
WOCBP	Women of Childbearing Potential

TRIAL SCHEM

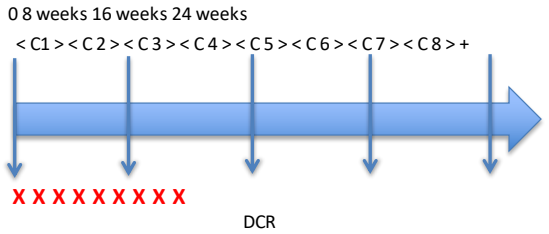
Patients with metastatic advanced RAS mutated refractory pancreatic cancer where the patient has progressed on ≥ 2 prior chemotherapy regimens for their advanced disease.

Vemurafenib
480 mg PO BID daily*
+
Sorafenib
200 mg PO AM and 200 mg PO PM daily**

X 28 days
(1 cycle)

Tumor Assessment every 8 weeks + CA19-9 (or CA 125, or CEA if not expressers of CA 19-9)

Study treatment continues until disease progression or unacceptable toxicity



Key Study Endpoints:

- Disease control rate (DCR)- CR+PR+SD at 16 weeks
- Safety
- Progression Free Survival (PFS)
- Overall Survival (OS)
- Changes in plasma free DNA mutated KRAS – Blood collected at baseline and prior to each cycle (X)

*Vemurafenib Dose level-1 will be 240 mg PO BID
** Sorafenib Dose level-1 will be 200 mg PO daily

TRIAL SYNOPSIS

Title and Number: A Phase II Trial of Vemurafenib in Combination with Sorafenib to Treat Patients With Advanced KRAS Mutated Pancreatic Cancer. Targeting RAF Dimers to Suppress Oncogenic RAS Signaling (The Dr. Nate Nieto Study)
Protocol No. HRI-Vemurafenib-Sorafenib-001
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Sponsor:
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Principal Investigator:
Erkut H. Borazanci, MD, MS – HonorHealth Research Institute, Scottsdale, AZ

Consulting Investigator:
Daniel D. Von Hoff, MD, FACP, FASCO, FAACR – HonorHealth Research Institute, Scottsdale, AZ and Translational Genomics Research Institute (TGen), an Affiliate of City of Hope

Talia Golan, MD – Sheba Medical Center, Israel

Clinical Phase:
Phase II

Objectives:

Primary: To determine the efficacy by the disease control rate (CR+ PR +Stable at 16 weeks) of the combination of the type I½ RAF inhibitor (RAFi) Vemurafenib in combination with the type II RAFi Sorafenib in patients with KRAS mutated refractory pancreatic cancer.
Note: Type I inhibitors bind to the active protein kinase conformation (DFG-ASP “in” αC helix “in”). Type I½ inhibitors bind to a DFG-ASP “in” and αC helix “out” inactive conformation. Type II RAF inhibitors trap kinases in the DFG-ASP “out” αC helix “in” inactive conformation (Roskowski, 2016, Rukhlenko 2018).

Secondary:

1. To confirm the safety of giving Vemurafenib + Sorafenib to patients with advanced pancreatic cancer

2. To determine the clinical activity of Vemurafenib + Sorafenib as defined progression free survival (PFS) and overall survival (OS) rate.

3. To utilize circulating tumor DNA (ct DNA) in plasma to give qualitative (mutations) and to some extent quantitative (amount of ct DNA) information regarding BRAF and KRAS. This will be measure at baseline and just before each cycle.

4. To measure phospho ERK and phospho AKT in plasma to determine if the treatment has hit the intended target (Takano et al. 2010, Petricoin 2009). This will be measure at baseline and just before each cycle

Exploratory:

- To evaluate changes in phospho ERK and phospho AKT in tumor tissue.

Trial Design:
Open Label, Single Arm Trial

Number of Patients:
Between 7 and 12 evaluable patients

In the first stage 7 evaluable patients will be accrued. If there are zero patients with disease control (CR+ PR +Stable at 16 weeks) in these first 7 evaluable patients, the study will be stopped. Otherwise, 5 additional evaluable patients will be accrued for a total of 12 evaluable patients.

An evaluable patient is defined as one that receives any number of doses of both agents (Vemurafenib + Sorafenib) and has a scan after at least 2 cycles of treatment.

Name & Dose of Drugs:

- Vemurafenib will be given 480 mg PO BID daily x 28 days = 1 cycle Dose level -1 will be 240 mg PO BID

- Sorafenib will be given 200 mg PO BID daily x 28 days = 1 cycle (Dose level -1 will be 200 mg PO daily)

Note: All doses are to be taken without food. Doses can only be taken one hour before or 2 hours after a meal.

Patient Population:
Patients with metastatic advanced KRAS mutated refractory pancreatic cancer where the patient has progressed on ≥ 2 prior chemotherapy regimens for their advanced disease.

Endpoints:

Primary: disease control rate (defined as CR + PR + Stable at 16 weeks) using RECIST 1.1 criteria.

Secondary:

- Safety of giving vemurafenib + sorafenib in this population of patients
- Progression free survival (PFS)
- Overall survival (OS)
- Identify whether or not the drug combination resulted in changes in plasma free DNA mutated KRAS, BRAF, phospho ERK and phospho AKT

Exploratory:

- Changes in phospho ERK and phospho AKT in tumor tissue.

Inclusion Criteria:

1. Be able to understand and be willing to sign the written informed consent for the trial. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.

2. Be ≥ 18 years of age on day of signing informed consent.
3. Histologically confirmed cancer of the pancreas (KRAS mutated) with metastases and progression on at least ≥ 2 prior treatment regimens for their disease.
4. Known mutation status of KRAS and BRAF kinases. For those patients in which this has not previously been determined, the patient must have an archival tumor specimen (primary or metastatic stie) available to submit to confirm KRAS and BRAF status.
5. Have a performance status of 0 or 1 on the ECOG performance scale.
6. Demonstrate adequate organ function as defined below:
    a. Absolute neutrophil count ≥1,500/mm3
    b. Platelet concentration ≥ 60 x 10^9/L
    c. Hemoglobin ≥ 8.5 g/dL. Criteria must be met without erythropoietin dependency and without packed red blood cells (pRBC) transfusion within the last 2 weeks.
    d. Serum creatinine < 1.5 X institutional ULN.
    e. Total bilirubin ≤ 2.5 mg/dL
    f. Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) < 5 × ULN
    g. Prothrombin time (PT) ≤ 60 seconds or International Normalized Ratio (INR) ≤ 2.3
7. Female participants of childbearing potential must have a negative serum pregnancy test performed within 24 hours prior to receiving first dose of trial medication. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
8. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP)
    OR
    b. A WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 30 days after the last dose of trial treatment.
9. Male participants must agree to use contraception during the treatment period and for at least 30 days after the last dose of trial treatment and refrain from donating sperm during this period.
10. Patient must have QTC of ≤500ms.
11. Subject must be able to swallow and retain oral medication**.**
12. **Measurable disease per RECIST 1.1**

Exclusion Criteria:

1. Is currently participating and receiving trial therapy or has participated in a trial of an investigational agent and received trial therapy or used an investigational device within 2 weeks of the first dose of this trials' treatment.
2. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Cycle 1/Day 1 or who has not recovered (i.e.

NCI-CTC AE Version 5.0 ≤ Grade 1 at the time of signing informed consent) from adverse events due to a previously administered agent(s).

Note: Patients with ≤ Grade 2 neuropathy and ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the trial.

3. Previous BRAF inhibitor use such as vemurafenib, GSK2118436 or sorafenib.
4. If patient received major surgery, and has not yet recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
5. Previously untreated or concurrent cancer that is distinct in primary site or histology from pancreatic cancer except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before study entry. All cancer treatments must be completed at least 3 years prior to study entry (i.e., signature date of the informed consent form).
6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
7. Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v5.0] on repeated measurement) despite optimal medical management.
8. Active of clinically significant cardiac disease including:
    a. Congestive heart failure New York Heart Association (NYHA) > Class II. (Appendix D)
    b. Active coronary artery disease (CAD)
    c. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
    d. Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.
9. Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
10. Has an active infection requiring systemic therapy.
11. Evidence or history of bleeding diathesis or coagulopathy
12. Patient with any pulmonary hemorrhage/bleeding event of NCI-CTCAE v5.0 ≥ Grade 2 within 4 weeks before initiating study treatment; any other hemorrhage/bleeding event of NCI-CTCAE v5.0 ≥ Grade 3 within 4 weeks before initiating study treatment.

13. Patient with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) within 6 months of informed consent.
14. Presence of a non-healing wound, non-healing ulcer, or bone fracture.
15. History of organ allograft (including corneal transplant).
16. Known or suspected allergy or hypersensitivity to any of the study drugs (sorafenib, and or vemurafenib) study drug classes, or excipients of the formulations given during the course of this trial.
17. All patients with known diagnosis of Neurofibromatosis Type 1 or other known RAS-opathies
18. Patients with uncontrolled seizures
19. Treatment with medications that have known risk of QTc interval prolongation or Torsades de Pointe (TdP) within 14 days or 5 half-lives before dose of either drug is given in this study and for the duration of the study. Refer to Appendix E1 for medications with a known risk of TdP.
20. Treatment with a strong or moderate CYP3A inducers (e.g, phenytoin, carbamazepine, phenobarbital, St. John's Wort [hypericum perforatum], dexamethasone at a dose of greater than 16 mg daily, or rifampin [rifampicin], and/or rifabutin) or inhibitors within 28 days before dose of either drug is given in this study and for the duration of the study. Refer to Appendix G.
21. Malabsorption or other significant bowel or stomach resections
22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
23. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
24. Inability to comply with the protocol and/or not willing or not available for follow-up assessments required to assess toxicity

Statistical Methods:

Between 7 and 12 evaluable patients total will be entered into this study. To obtain that number of evaluable patients we estimate up to 24 patients will possibly be enrolled. An evaluable patient is defined as one that receives at least one dose of doses of both agents (vemurafenib + sorafenib) and has a scan after at least 2 cycles of treatment.

After the adjustment based upon the NTF from May 13, 2022, we will examine 5 more patients at a reduced dose. If at least one patient of the five demonstrated a partial response (overall response rate of $\geq$ 20%), we will proceed with enrolling 7 more patients. Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 0% will be tested against a one-sided alternative. In the first stage, n=5 patients will be accrued. If there are zero patients with a response (either a PR or CR) in these 5 patients, the study will be stopped. Otherwise, 7 additional patients will be accrued for a total of 12. The null hypothesis will be rejected if 3 or more patients have a response (either PR or CR) in 12 patients.

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1. BACKGROUND AND RATIONALE

1.1. Disease Background and Introduction

Pancreatic cancer continues to be a very lethal disease. It was estimated that in 2021, 60,430 Americans (31,950 men and 28,480 women) would be diagnosed with pancreatic ductal adenocarcinoma (PDA), and 48,220 will die from the disease. Pancreatic cancer accounts for about 3% of all cancers in the US and about 8% of all cancer deaths (Siegel et al. 2021).

Furthermore it is projected that by 2030, PDA will be the second leading cause of death from cancer in the US. Worldwide, PDA is the twelfth most common cancer, accounting for an estimate of > 300,000 deaths a year (Rahib 2014).

Detection of pancreatic cancer has been notoriously very late in the disease and therefore the 5-year survival rate is only 9%. Right now, the only potential cure for pancreatic cancer is surgical resection (if the disease is caught early). However only 10-20% of PDA patients are diagnosed with localized, surgically resectable disease. Even with the advances made over the past decade in the surgical resection of PDA, the 5- year survival after resection and adjuvant chemotherapy approaches 30% (Strobel 2019), and unfortunately most (~ 80%) have reoccurrence of their cancer within 2 years of resection, and those reoccurrences are almost universally fatal (Kleef 2016).

The prognosis for this disease is poor despite diagnostic progress and new chemotherapeutic regimens. Current treatment regimens for advanced PDA although offering modest improvements in progression-free survival (PFS) and overall survival (OS), are clearly inadequate in achieving long term survival in these patients.

Additional treatment strategies are desperately needed. In this study we propose a combination of two commercially available drugs a type I½ RAF inhibitor and a type II RAF inhibitor. As will be seen below this approach is based on some very solid science.

It has been established that 90% of pancreatic cancer patients harbor somatic oncogenic point mutations in KRAS (90%). The oncogenic KRAS mutation has been shown to be the major event in pancreatic cancer; it confers permanent activation of the KRAS protein, which acts as a molecular switch to activate various intracellular signaling pathways and transcription factors inducing cell proliferation, migration, transformation and survival.

The presence of mutated KRAS correlates with a worse prognosis for patients with pancreatic cancer whether or not they undergo surgical resection.

The RAS/RAF/MEK/extracellular signal-related kinase (ERK) pathway is pivotal for cell proliferation and survival and is frequently hyperactivated in tumors. Virtually all pancreatic cancers are KRAS mutated and therefore that pathway is a prime target for

drug development. Clinically used RAF inhibitors are ineffective in RAS mutant tumors because they enhance homo- and heterodimerization of RAF kinases, leading to paradoxical activation of ERK signaling. We built a next-generation mechanistic dynamic model to analyze combinations of structurally different RAF inhibitors, which can efficiently suppress MEK/ERK signaling (Kholodenko, 2015 and Rukhlenko 2018). This rule-based model of the RAS/ERK pathway integrates thermodynamics and kinetics of drug-protein interactions, structural elements, posttranslational modifications, and cell mutational status as model rules to predict RAF inhibitor combinations for inhibiting ERK activity in oncogenic RAS and/or BRAFV600E backgrounds. Predicted synergistic inhibition of ERK signaling was corroborated by experiments in mutant NRAS, HRAS, and BRAFV600E cells, and inhibition of oncogenic RAS signaling was associated with reduced cell proliferation and colony formation.

1.2. Rationale of Clinical Trial

We lost a dear friend, Dr. Nate Nieto, an incredible microbiologist to advanced pancreatic cancer at the young age of 44. Nate's colleagues, caregivers and friends (some listed here as coinvestigators,) who are experts in Systems Biology and Advanced Analytics, have banded together to provide the best possible fresh, systems-based science to attack pancreatic cancer.

As an overview, this study aims to combine two RAF inhibitors (RAFi) to suppress oncogenic RAS signaling to ERK and overcome the notorious resistance to RAFi caused by RAF dimerization (Kholodenko 2015; Rukhlenko et al., 2018). This is an entirely new approach against RAS mutated pancreatic cancer.

1.3. Study Agent(s) Background and Associated Known Toxicities

1.3.1. Vemurafenib

Vemurafenib is a type I½ RAF inhibitor. Vemurafenib is also an orally available inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. Vemurafenib inhibits other kinases in vitro such as; CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, and FGR at similar concentrations. At steady state, Vemurafenib exhibits linear pharmacokinetic within the 240 mg to 960 mg dose range.

There has been a tremendous amount of clinical experience with Vemurafenib. The most common adverse events include (≥30%): arthralgias, rash, alopecia, fatigue, photosensitivity reactions, nausea, pruritus and skin papillomas. Special precautions from the package insert include new primary cutaneous malignancies, new non-cutaneous squamous cell carcinomas, tumor promotion in BRAF wild-type melanoma patients, serious hypersensitivity reactions (anaphylaxis and Drug Reaction with Eosinophilia and Systemic Symptoms - DRESS syndrome), Stevens-Johnson syndrome and toxic epidermal necrolysis, QT prolongation, hepatotoxicity, photosensitivity (advise patients to avoid sun exposure), uveitis, harm to the fetus, radiation sensitization and recall, and

renal failure. Vemurafenib is currently approved for patients with BRAF V600E mutated melanoma as well as for patients with BRAF V600E mutated Erdheim-Chester disease.

1.3.2. **Sorafenib**

Sorafenib is a kinase inhibitor that inhibits multiple intracellular (CRAF, BRAF and mutant BRAF) and many surface kinases (KIT, FLT3, RET, RET/PTC, VEGFR-1, VEGFR-2, VEGFR-3 and PDGFR-β). It is currently FDA approved for the treatment of patients with hepatocellular carcinoma, advanced renal cell carcinoma and locally recurrent or metastatic, progressive differentiated thyroid carcinoma refractory to radioactive iodine treatment. Sorafenib is a type II BRAF kinase inhibitor (traps their target kinases in an inactive so-called DFG-out state occupying a hydrophobic pocket adjacent to the ATP binding site (Kufareva and Abagyan 2008). The agent has had very extensive clinical trials. No trials with Sorafenib as a single agent in patients with advanced pancreatic cancer have been reported. However, Sorafenib has been added to a gemcitabine+cisplatin combination in patients with advanced pancreatic cancer with no indication for improving the response rate or median progression free survival over what was achieved with chemotherapy alone.

A single arm phase II trial by Kindler and colleagues (Kindler 2012) of gemcitabine+sorafenib also didn't appear promising. However, the hypothesis to be tested in the present study is that the addition of this type II kinase inhibitor to the type I½ kinase inhibitor Vemurafenib will produce responses in patients. This type of design is based on the very solid science of Kholodenko (2015) and Rukhlenko et al (2018).

Sorafenib's most common adverse reactions include: diarrhea, fatigue, infection, alopecia, hand-foot syndrome, rash, weight loss, anorexia, nausea, gastrointestinal and abdominal pain, hypertension and hemorrhage. The most dangerous of these include: cardiac ischemia (2.7%), bleeding from varices (2.4%), and hypertension (9.4%) (need to take BP weekly for the first 6 weeks). The rash and hand-foot reactions are generally grade 1-2. Rare events include: gastrointestinal perforation, wound healing complications, QT interval prolongation, a 0.06% incidence of hepatic failure and death, and impairment of thyroid stimulating hormone suppression in patients with Differentiated Thyroid Carcinoma. Patients can experience a rise in amylase or lipase (without pancreatitis) and hypophosphatemia (13%), anemia (44%), thrombocytopenia (12%), hypocalcemia (12%) and hypokalemia (5%).

1.4. Clinical Experience with Reported Phase I Trial with Vemurafenib + Sorafenib

Preclinical experiments with Vemurafenib plus Sorafenib in a Vemurafenib resistant melanoma cell line demonstrated a synergistic effect of Sorafenib+Vemurafenib (Srivastava and Moorthy, 2019). The MD Anderson team (Kato et al, 2015) have reported an initial phase I clinical trial of Vemurafenib plus Sorafenib to overcome BRAF resistance (NCT0153136). They established the safe doses in this heavily treated population (76% had had prior BRAF or MEK inhibitors). Their MTD was 720mg PO BID of Vemurafenib

and for Sorafenib 400mg AM PO and 200mg PM PO (n=24 patients). Toxicities included: grade 3 hypertension (n=1), grade 3 headaches (n=1), grade 3 rash (n=2), and grade 3 depression (n=1). Five responses were noted (some who had prior PanRAF ERK and MEK inhibitors): 1 melanoma, 1 adenocarcinoma of the lung and 2 ovarian cancers. Of note, patients had a change in the amount of BRAF mutant DNA corresponding with their clinical course. Again, the MTD for the regimen was Vemurafenib 720mg PO BID and Sorafenib 400mg AM and 200mg PM (Kato et al 2015 and Janku, personal communication). Their study documented that this combination can be given safely with substantial efficacy. Of note, in their study is that unfortunately there were no patients with adenocarcinoma of the pancreas on the study.
Amendment 3 of this study adjusts the starting dose of vemurafenib to 480 mg po bid and sorafenib to 200 mg po bid based upon toxicity seen in the first 3 patients who have completed 1 cycle of therapy. Of the first 3 patients who completed cycle 1 dosing the exposure of the combination was 57%- both agents; 64% Vemurafenib and 53% sorafenib; and 80% both agents. The reason for dose holding was due to 2 instances of a grade 3 rash and 1 instance of a grade 3 hypertension.

2. HYPOTHESIS

The addition of a type I½ RAF inhibitor to a type II RAF inhibitor will have clinical activity against KRAS mutated advanced pancreatic cancer.

3. STUDY OBJECTIVES

3.1. Primary Objectives

To determine the efficacy (disease control rate- CR+PR+ Stable at 16 weeks) of the combination of the type I½ RAF inhibitor (RAFi) Vemurafenib in combination with the type II RAFi Sorafenib in patients with advanced KRAS mutated refractory pancreatic cancer.

[Note: Type I inhibitors bind to the active protein kinase conformation (DFG-ASP “in” αC helix “in”). Type I½ inhibitors bind to a DFG-ASP “in” and αC helix “out” inactive conformation. Type II RAF inhibitors trap kinases in the DFG-ASP “out” αC helix “in” inactive conformation (Roskowski, 2016, Rukhlenko 2018)].

3.2. Secondary Objectives

- To confirm the safety of giving Vemurafenib + Sorafenib to patients with advanced pancreatic cancer.

- To determine the clinical activity of Vemurafenib + Sorafenib as defined Progression free survival (PFS) and Overall survival (OS) rate.

- To utilize circulating tumor DNA (ct DNA) in plasma to give qualitative (mutations) and to some extent quantitative (amount of ct DNA) information

regarding BRAF and KRAS. This will be measured at baseline and just before each cycle

- To measure phospho ERK and phosphor AKT in plasma samples to determine if the treatment has hit the intended target (Takano et al. 2010, Petricoin 2009). This will be measured at baseline and just before each cycle.

3.3. Exploratory Objectives

- To evaluate changes in phospho ERK and phospho AKT in tumor tissue.

3.4. Endpoints

3.4.1. Primary Endpoint

- Disease control rate (defined as CR+PR+SD x16 weeks) using RECIST criteria.

3.4.2. Secondary Endpoint

- Safety of giving Vemurafenib + Sorafenib in this population of patients
- Progression free survival
- Overall survival
- Identify whether or not the drug combination resulted in changes in plasma free DNA mutated KRAS, BRAF, phospho ERK, phospho AK

3.4.3. Exploratory Endpoint

- Changes in phospho ERK and phospho AKT in tumor tissue

4. STUDY POPULATION

4.1. Inclusion Criteria

1. Be able to understand and be willing to sign the written informed consent for the trial. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Histologically confirmed cancer of the pancreas (KRAS mutated) with metastases and progression on at least ≥ 2 prior treatment regimens for their disease.
4. Known mutation status of KRAS and BRAF kinases. For those patients in which this has not previously been determined, the patient must have an archival tumor specimen (primary or metastatic stie) available to submit to confirm KRAS and BRAF status.
5. Have a performance status of 0 or 1 on the ECOG performance scale.
6. Demonstrate adequate organ function as defined below:
    a. Absolute neutrophil count ≥1,500/mm3
    b. Platelet concentration ≥ 60 x 10^9/L

c. Hemoglobin ≥ 8.5 g/dL. Criteria must be met without erythropoietin dependency and without packed red blood cells (pRBC) transfusion within the last 2 weeks.
d. Serum creatinine < 1.5 X institutional ULN.
e. Total bilirubin ≤ 2.5 mg/dL
f. Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) < 5 × ULN
g. Prothrombin time (PT) ≤ 60 seconds or International Normalized Ratio (INR) ≤ 2.3

7. Female participants of childbearing potential must have a negative serum pregnancy test performed within 24 hours prior to receiving first dose of trial medication. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
8. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP)
    OR
    b. A WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 30 days after the last dose of trial treatment.
9. Male participants must agree to use contraception during the treatment period and for at least 30 days after the last dose of trial treatment and refrain from donating sperm during this period.
10. Patient must have QTC of ≤500ms.
11. Subject must be able to swallow and retain oral medication**.**
12. **Measurable disease per RECIST 1.1**

4.2. Exclusion Criteria

1. Is currently participating and receiving trial therapy or has participated in a trial of an investigational agent and received trial therapy or used an investigational device within 2 weeks of the first dose of this trials' treatment.
2. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Cycle 1/Day 1 or who has not recovered (i.e. NCI-CTC AE Version 5.0 ≤ Grade 1 at the time of signing informed consent) from adverse events due to a previously administered agent(s).

    Note: Patients with ≤ Grade 2 neuropathy and ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the trial.

3. Previous BRAF inhibitor use such as vemurafenib, GSK2118436 or sorafenib.
4. If patient received major surgery, and has not yet recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
5. Previously untreated or concurrent cancer that is distinct in primary site or histology from pancreatic cancer except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before

study entry. All cancer treatments must be completed at least 3 years prior to study entry (i.e., signature date of the informed consent form).

6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
7. Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v5.0] on repeated measurement) despite optimal medical management.
8. Active of clinically significant cardiac disease including:
    a. Congestive heart failure New York Heart Association (NYHA) > Class II. (Appendix D)
    b. Active coronary artery disease (CAD)
    c. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
    d. Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.
9. Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
10. Has an active infection requiring systemic therapy.
11. Evidence or history of bleeding diathesis or coagulopathy
12. Patient with any pulmonary hemorrhage/bleeding event of NCI-CTCAE v5.0 ≥ Grade 2 within 4 weeks before initiating study treatment; any other hemorrhage/bleeding event of NCI-CTCAE v5.0 ≥ Grade 3 within 4 weeks before initiating study treatment.
13. Patient with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) within 6 months of informed consent.
14. Presence of a non-healing wound, non-healing ulcer, or bone fracture.
15. History of organ allograft (including corneal transplant).
16. Known or suspected allergy or hypersensitivity to any of the study drugs (sorafenib, and or vemurafenib) study drug classes, or excipients of the formulations given during the course of this trial.
17. All patients with known diagnosis of Neurofibromatosis Type 1 or other known RAS-opathies
18. Patients with uncontrolled seizures
19. Treatment with medications that have known risk of QTc interval prolongation or Torsades de Pointe (TdP) within 14 days or 5 half-lives before dose of either drug is given in this study and for the duration of the study. Refer to Appendix E1 for medications with a known risk of TdP.

20. Treatment with a strong or moderate CYP3A inducers (e.g, phenytoin, carbamazepine, phenobarbital, St. John's Wort [hypericum perforatum], dexamethasone at a dose of greater than 16 mg daily, or rifampin [rifampicin], and/or rifabutin) or inhibitors within 28 days before dose of either drug is given in this study and for the duration of the study. Refer to Appendix G.
21. Malabsorption or other significant bowel or stomach resections
22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
23. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
24. Inability to comply with the protocol and/or not willing or not available for follow-up assessments required to assess toxicity

5. STUDY TREATMENT

5.1. Treatment Dosage and Administration

The specific study drugs, formulation, dosage, administration, and schedule are detailed in Tables 1 and 2 and the sections that follow. Study treatment will be administered on an outpatient basis. Each treatment cycle will be 4 weeks (28 days in duration).

The commercial product for each study drug will be supplied for this trial. Vemurafenib will be provided by Genentech, and Sofaranib will be provided by Bayer. Refer to Section 9 for Drug Treatment Information and link to prescribing information (package inserts).

Table 1: Study Drugs

Agent	Formulation	Dose	Route	Schedule	Cycle Length
Vemurafenib	240 mg tablets	480 mg	PO	BID	28 days
Sorafenib	200 mg tablets	200 mg	PO	BID	28 days

Table 2: Study Drug Dose Levels

	Vemurafenib	Sorafenib
Dose level 1 (starting dose)	480 mg PO BID	200 mg po bid
Dose level -1	240 mg PO BID	200 mg daily

5.2. Administration of Vemurafenib + Sorafenib

Patients will be asked to take the specified number of tablets for their prescribed dose on an empty stomach at a regular time each day with water. Doses should be taken either one hour prior or two hours after a meal. Approximately 12 hours should elapse between doses.

5.3. Toxicities and Dosing Delays / Dose Modifications

Any patient who receives study treatment on this trial will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Schedule of Events (Appendix A). Toxicity will be graded according to the NCI CTCAE, Version 5 which is available at:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

For any dose interruptions, re-initiation of study treatment may be delayed for a maximum of 28 days to allow recovery from any toxicity. In exceptional cases where subjects are responding, re-initiation of therapy after missing > 28 consecutive days of treatment may be considered on a case-by-case basis after confirmation with the Principal Investigator.

Treatment related toxicities will be attributed by investigators, and causality will be assessed individually for each of the study drugs in the combination regimen, both Vemurafenib and Sorafenib (Refer to Section 8.4).

Dose modifications and treatment delays based on observed drug-related toxicity will be performed as described in Sections 5.3.1. and 5.3.2 and will follow the prescribing information:

Vemurafenib
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf)

Sorafenib
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021923s020lbl.pdf)

In the event that either Vemurafenib or Sorafenib is to be discontinued due to toxicity, both drugs are to be discontinued and the patient is to have off treatment procedures completed (Section 6.3). The patient is to be followed for 30 days after withdrawal from study treatment for adverse events (Section 6.4), and every 3 months until study completion for survival status.

5.3.1. **Vemurafenib and Sorafenib Dose Modifications**

Vemurafenib and sorafenib should be withheld for Grade 3 or greater adverse reactions due to study treatment. Upon recovery to Grade 0-1, restart vemurafenib and sorafenib at a reduced dose (dose level -1) as follows:

- Vemurafenib 240 mg twice daily plus sorafenib 200 mg daily for first appearance of Grade 3 or greater adverse reactions.
- Stop therapy for second appearance of Grade 3 or greater

If dose reductions below Vemurafenib 240 mg twice daily or sorafenib 200 mg po daily are indicated, the patient will be withdrawn.

Vemurafenib should be discontinued for any of the following:

- Grade 4 adverse reaction, first appearance (if clinically appropriate) or second appearance
- QTc prolongation > 500ms and increased by > 60s from pre-treatment values.

Temporary interruption of sorafenib is recommended in patient undergoing major surgical procedures.

Table 3: Adverse Reactions Requiring Dose Modification of Sorafenib

Adverse Reaction	CTCAE Grade	Action	Dose reduce and resume sorafenib
Cardiovascular Events			
Cardiac ischemia and/or infarction	Grade 2 and above	Permanently discontinue	Do not resume
Congestive heart failure	Grade 3	Interrupt [a] until ≤ Grade 1	Decrease to 200mg daily
	Grade 4	Permanently discontinue	Do not resume
Hemorrhage requiring medical intervention	Grade 2 and above	Permanently discontinue	Do not resume
Hypertension	Grade 2 asymptomatic and diastolic pressure 90-99mmHg	Treat with anti-hypertensive therapy	Continue sorafenib dosing as scheduled and closely monitor blood pressure
	Grade 3	Interrupt until symptoms resolve and diastolic blood pressure < 90mmHg	Treat with anti-hypertensives. Decrease to 200 mg daily when resumed.

			If further reduction is needed patient is to be withdrawn.
	Grade 4	Permanently discontinue	Do not resume
Gastrointestinal Perforation	Any grade	Permanently discontinue	Do not resume
QT Prolongation	Monitor electrolytes and ECG. If QTc is >500ms or for an increase from baseline of 60ms or greater	Interrupt Correct electrolyte abnormalities (magnesium, potassium, calcium)	Use medical judgement before restarting
Severe DILI	≥ Grade 3 ALT in the absence of another cause[c] AST/ALT > 3xULN with bilirubin > 2x ULN in the absence of another cause[c]	Permanently discontinue	Do not resume
Non-hematological toxicities	Grade 2	Treat on time	Decrease to 200 mg daily
	Grade 3		
	1st occurrence	Interrupt until ≤ Grade 2	Decrease to 200 mg daily
	No improvement within 7 days or 2ndoccurrence	Interrupt until ≤ Grade 2	do not resume
	3rd occurrence	Permanently discontinue	Do not resume
Dermatological toxicities	Grade 2: Painful erythema and swelling of the hands of feet and/or discomfort affecting the patient's normal activities		
	1st occurrence	Continue sorafenib and consider topical therapy for symptomatic relief	If no improvement after 7 days follow steps below.
	No improvement within 7 days at reduced dose or 2nd or 3rd occurrence	Interrupt until toxicity resolves to Grade 0-1	Decrease to 200 mg daily[d]
	4th occurrence	Permanently discontinue	Do not resume

	Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities or daily living		
	1st occurrence	Interrupt until toxicity resolves to Grade 0-1	Decrease to 200 mg daily[d]
	2nd occurrence	Interrupt until toxicity resolves to Grade 0-1	Do not resume [d]
	3rd occurrence	Permanently discontinue	Do not resume

ULN – upper limit of normal; DILI – drug induced liver injury

a. If no recovery after 28-day interruption, treatment will be discontinued unless the patient is deriving clinical benefit
b. If more than two dose reductions are required, treatment will be discontinued
c. In addition, any grade Alkaline phosphatase increase in the absence of known bone pathology and Grade 2 or worse Bilirubin increase; Any 1 of the following: INR ≥ 1.5, Ascites and/or encephalopathy in the absence of underlying cirrhosis or other organ failure considered to be due to DILI.
d. When dose reduction is necessary for Grade 2 or 3 dermatologic toxicities, after at least 28 days of treatment on a reduced dose of sorafenib, the dose of sorafenib may be increased by one dose level from the reduced dose. Approximately 50% of patients requiring dose reduction for dermatologic toxicity are expected to meet the criteria for resumption of the higher dose and roughly 50% of patients resuming the previous dose are expected to tolerate the higher dose (that is, maintain the higher dose level with recurrent Grade 2 or higher dermatologic toxicity).

5.4. Concomitant Medications / Treatments

Necessary supportive measures for optimal medical care may be given throughout the study, including IV antibiotics to treat infections, blood components, and antiemetics. Additional care will be administered as indicated by the treating physician and the patient's medical need. No concomitant cytotoxic therapy, whether conventional or investigational, will be allowed during this study. All concomitant medications and supportive therapy must be recorded on the appropriate CRF.

The use of grapefruit or grapefruit juice and St. John's Wort (hyperforin) is prohibited during study treatment. The treating investigator is to discuss this with the patient prior to initiating study treatment and will review list of all medications and supplements during the course of the study.

Medications with a known risk of TdP are prohibited during the course of the study. Refer to Appendix F1. Use caution with medications with a possible risk of TdP or a conditional risk of TdP. Refer to Appendix F2 and F3.

Radiotherapy may be allowed while the patient is enrolled in this study if given to help palliate a specific symptom (e.g. bone pain, brain metastases, etc.).

5.5. Concomitant Therapies Requiring Caution

5.5.1. Vemurafenib

- **Strong CYP3A4 inhibitors**: Coadministration of a strong CYP3A4 inhibitor increased vemurafenib plasma concentration and may lead to increased toxicity. Avoid coadministration of vemurafenib with strong CYPA4 inhibitors, if this is unavoidable consider dose reduction of vemurafenib, if clinically indicated. Refer to Appendix G, Table 1 for a compiled list of CYP3A4 inhibitors.
- **Strong CYP3A4 inducers**: Coadministration of vemurafenib with rifampin, a strong CYP3A4 inducer, decreased vemurafenib plasma concentration and may result in decrease efficacy. Avoid coadministration of vemurafenib with strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampin for the duration of the study. Refer to Appendix G, Table 2 for a compiled list of CYP3A4 inducers.
- **CYP1A2 Substrates**: Coadministration of vemurafenib with tizanidine, a sensitive CYP1A2 substrate, increased tizanidine systemic exposure by 4.7-fold. Avoid concomitant use of vemurafenib with drugs having a narrow therapeutic window that are primarily metabolized by CYP1A2. If coadministration cannot be avoided, monitor closely for toxicities, and consider a dose reduction of concomitant CYP1A2 substrates. Refer to Appendix H for a compiled list of CYP1A2 major substrates.
- **P-gp Substrates**: Coadministration of vemurafenib with digoxin, a sensitive P-glycoprotein (P-gp) substrate, increased digoxin systemic exposure by 1.8-fold. Avoid concurrent use of P-gp substrates known to have narrow therapeutic indices. If use of these medications is unavoidable, consider dose reduction of P-gp substrate.
- **Warfarin**: INR (International Normalization Ratio) monitoring should be considered when Vemurafenib is used concurrently with warfarin.

5.5.2. Sorafenib

- **Strong CYP3A4 inhibitors**: Ketoconazole, a strong inhibitor of CYP3A4 and P-glycoprotein, administered at a dose of 400mg once daily for 7 days did not alter the mean AUC of a single oral dose of sorafenib 50mg in healthy volunteers. Refer to Appendix G, Table 1 for a compiled list of CYP3A4 inhibitors.
- **Strong CYP3A4 inducers**: Rifampin, a strong CYP3A4 inducer, administered at a dose of 600mg once daily for 5 days with a single oral dose of sorafenib 400mg in healthy volunteers resulted in a 37% decrease in the mean AUC of

sorafenib. Avoid concomitant use of strong CYP3A4 inducers (such as carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, St. John's wort), when possible because these drugs can decrease the systemic exposure to sorafenib. Refer to Appendix G, Table 2 for a compiled list of CYP3A4 inducers.

- **Neomycin**: Neomycin administered as an oral dose of 1g three times daily for 5 days decreased the mean AUC of sorafenib by 54% in healthy volunteers administered a single oral dose of sorafenib 400mg. The effects of other antibiotics on the pharmacokinetics of sorafenib have not been studied.
- **Drugs that increase Gastric pH**: The aqueous solubility of sorafenib is pH dependent, with higher pH resulting in lower solubility. However, omeprazole, a proton pump inhibitor, administered at a dose of 40mg once daily for 5 days did not result in a clinically meaningful change in sorafenib single dose exposure. No dose adjustment of sorafenib is considered necessary.
- **Effect of sorafenib on other drugs**: Sorafenib 400mg twice daily for 28 days did not increase the systemic exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), and omeprazole (CYP2C19 substrate).

5.6. Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, OR
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator

5.7. Duration of Follow-up

Patients will be followed for adverse events for 30 days following the last dose of study treatment. Patients will be followed for survival status every 3 months until study completion (this may be completed through medical record review or follow up phone calls).

5.8. Removal of Subjects from Protocol Therapy

Patients will be removed from study treatment when any of the criteria listed in Section 5.6 apply. The reason for study removal and the date the patient was removed will be documented in the Case Report Form. The patient should complete the end of treatment visit and followed-up per protocol (Sections 6.5, 6.5).

5.9. Subject Replacement

Patients who receive any number of doses of both agents (Vemurafenib + Sorafenib) and has a scan after at least 2 cycles of treatment will not be replaced. Therefore, any

patient that does not meet this criteria will be replaced in order to achieve 7 evaluable patients.

6. STUDY PROCEDURES

6.1. Screening / Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 28 days prior to initiated study treatment unless otherwise stated. The screening procedures include:

- Informed Consent
- Medical History -To include concurrent baseline conditions (using NCI CTCAE, version 5.0), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
- ECOG Performance Status (Appendix B)
- Review inclusion / exclusion criteria
- Vital Signs (blood pressure, pulse, respiratory rate, and temperature)
- Complete physical examination including height (cm) and weight (kg)
- Concomitant medication notation to include all medications taken in the last 30 days
- Hematology: CBC with differential and platelet count
- Serum chemistries: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase, albumin, LDH, total protein, and electrolytes (sodium, potassium, chloride, CO2, magnesium, calcium). In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin. Calculate creatinine clearance (the Cockcroft-Gault equation may be used to calculate the creatinine clearance at any of the time points in this protocol)
- Coagulation: PT, INR
- CA19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Serum pregnancy test for WOCBP within 72 hours prior to the first dose of study treatment.
- Electrocardiogram (ECG)
- Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is required to exclude brain metastases if clinically indicated only. If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. (RECIST 1.1 criteria Section 7.1)
- Blood for correlative analysis - 3 X 10 mL

- Confirm KRAS and BRAF mutation status by tissue biopsy. For those patients in which the mutation status of KRAS and BRAF kinases has not previously been determined, the patient must have an archival tumor specimen (primary or metastatic site) available to submit to confirm KRAS and BRAF status. The results of the mutation status are required for determining patient's eligibility for this trial.

6.2. Optional Tissue Collection

As part of participation in this trial, subjects will be provided the option to consent to the collection of tumor tissue for Reverse Phase Protein Array (RPPA) analysis.

For those patients that consent to the optional tissue collection for RPPA analysis, tissue will be collected from a newly obtained core or excisional biopsy of a tumor lesion if performed recently (within 30 days prior to study treatment on Day 1) and during their participation in the study should they be scheduled for a biopsy as part of their routine care through the follow-up period.

Tissue samples will be centrally analyzed by Theralink. Details for processing and shipping of the tissue will be provided in the Trial Lab Manual.

6.3. Procedures During Treatment (Cycle is 28 Days)

Patients must begin Cycle 1 within 28 days of signing the informed consent document and after the screening assessments. All assessments should be performed within 72 hours of each specified time parameter, with the exception of Cycle 1 in which assessments must be conducted within 24 hours (except those noted), or if medical or scheduling conditions require a delay.

6.3.1. Day 1 of Each Cycle

- Inclusion/exclusion review (Cycle 1 only)
- Directed Physical exam
- Vital Signs (blood pressure, pulse, respiratory rate, and temperature)
- Measurement of weight (kg) and BSA calculation prior to dosing
- ECOG Performance Status
- Hematology: CBC with differential and platelet count
- Serum chemistries: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, CO2, magnesium, calcium). In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin. Calculate creatinine clearance (Cockcroft-Gault equation)
- Coagulation: PT, INR – only required for patients on warfarin
- Serum Pregnancy Test
- ECG (Cycles 1 through 3, then every 3 cycles 6, 9, 12 etc.)
- Blood for correlative analysis- 3 X 10 mL (cycle 2 and beyond)
- AEs using the NCI CTCAE 5.0

- Concomitant medication notation
- Distribute study medications to the patient and provide the Patient Study Drug Diary (Appendix E) and provide instructions to the patient to return on day 1 of each cycle.
- Cycle 2 and beyond: Complete Drug Accountability (Per Section 9.4): Collect previous cycle study medications and review the completed Patient Study Drug Diary with the patient and address any discrepancies with the patient.

6.3.2. Days 8, 15 and 22 of Cycle 1

- Directed physical exam
- Vital Signs (blood pressure, pulse, respiratory rate, and temperature)
- ECOG Performance Status
- Hematology: CBC with differential and platelet count
- Serum chemistries: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, CO2, magnesium, calcium). In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin. Calculate creatinine clearance (Cockcroft-Gault equation)
- ECG (Cycle 1/ Day 15 only)
- AEs using the NCI CTCAE 5.0
- Concomitant medication notation

6.3.3. Tumor Assessments Every 2 Cycles (Every 8 Weeks)

- Tumor measurements per RECIST 1.1 (before C3, C5, C7 etc.). Tumor measurements may be obtained at the discretion of the principal investigator if clinically indicated.
- CA19-9 (or CA 125, or CEA if not expressers of CA 19-9) before C3, C5, C7 etc.)

In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments earlier if there is a strong clinical suspicion of disease progression, in order to either confirm or refute the clinical impression.

Reassessment of the extent of tumor should be made by the same imaging methods used to establish baseline tumor measurements.

6.4. Off Treatment Visit – to be Completed 14-28 (+/-2) Days From the Last Dose of Study Treatment

- Directed physical exam, if deemed necessary
- Weight (kg)
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)

- ECOG Performance status
- Hematology: CBC with differential and platelet count
- Serum chemistries: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, CO2, magnesium, calcium). In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin. Calculate creatinine clearance (Cockcroft-Gault equation).
- Coagulation: PT, INR– only required for patients on warfarin
- CA19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Serum pregnancy if applicable
- Blood for correlative analysis- 3 X 10 mL
- AEs using the NCI CTCAE 5.0
- Concomitant medication notation
- Complete Drug Accountability (Per Section 9.4): Collect all previously distributed study medications and review the completed Patient Study Drug Diary with the patient and address any discrepancies with the patient.
- Confirm contact information for patient and a designated family member, and primary care physician and remind patient of follow-up telephone contact that will be conducted 30 days after the last dose of study treatment and then every 3 months for survival status.

6.5. Follow-up Procedures

Patients will be followed for 30 days after completion of (or early withdrawal from) study treatment for adverse events.

Patients will be followed for survival end points every 3 months until study completion (may be done through medical record review or follow up phone calls). Receipt of second line therapy will be recorded.

6.6. Study Treatment Discontinuation

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The patient should complete the end of treatment visit and required followed-up per protocol (Sections 6.3, 6.4) when possible.

The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient is unable to comply with protocol requirements;
- Patient demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator and approval by PI);

- Patient experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges continuation on the study would not be in the subject's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Lost to follow-up. If a research patient cannot be located to document survival after a period of 1 year, the subject may be considered "lost to follow-up." All attempts to contact the patient during the one year must be documented.

7. MEASUREMENT OF EFFECT

7.1. Disease Control Rate

Disease control rate (defined as CR + PR + Stable x16 weeks) will be evaluated using the RECIST criteria (version 1.1, 2009) proposed by the RECIST committee.

These response criteria are widely recognized and accepted as the standard criteria for determining response in patients with solid tumors.

https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

All patients who have measurable disease according to the RECIST criteria and who have their disease re-evaluated will be evaluable for response.

For the purposes of this study, patients should be reevaluated for response approximately every 2 cycles.

7.2. Safety / Tolerability

Analyses will be performed for all subjects having received at least one dose of study therapy. The study will use the CTCAE version 5.0 for reporting of non-hematologic adverse events.

The incidence of all AEs (regardless of causality) and all treatment-related AEs (those AEs thought to be suspected related to study drug) will be summarized by NCI CTCAE version 5.0 term and maximum grade. The incidence of AEs that lead to discontinuation of study drug will also be summarized. Listings of patients who discontinue study drug due to an AE and patients with SAEs and deaths will be presented.

Vemurafenib + Sorafenib dose administration data will be listed and any dose interruptions and dose reductions will be summarized.

7.3. Progression Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from study treatment initiation (C1/D1) to first documentation of objective tumor progression or to death due to any

cause. In the absence of previous documentation of objective tumor progression will be censored at the last date the patient was known to be progression-free in those who do not have objective tumor progression and who are: 1) still on study at the time of an analysis; 2) are given anti-tumor treatment other than the study treatment; or 3) are removed from study follow-up prior to documentation of objective tumor progression.

7.4. Survival

Survival is defined as the time from initiation of study treatment (C1/D1) to date of death. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive.

8. ADVERSE EVENTS

8.1. Adverse Event Monitoring

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Investigators should refer to the Safety Information section of the current Investigator Brochures for sorafenib and vemurafenib, for the expected side effects of the study drugs.

Therapeutic monitoring should be performed following dose selection or modification of study drug in a manner consistent with the local clinical standard of care. In general, subjects should be closely monitored for side effects of all concomitant medications regardless of the path of drug elimination.
All concomitant medications must be recorded in the subject's source documentation.

Subjects must be carefully monitored for AEs. This monitoring also includes clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, intensity, and relationship to the study drug, or other chemotherapy/treatment.

8.2. Adverse Event Definition

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (Section 8.3), including signs or symptoms associated with pancreatic cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)

- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

8.2.1. Serious Adverse Event Definition

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization (see section 8.5.2.5).
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drugs.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

8.3. Adverse Event Reporting

The study period during which AEs and SAEs as described in Section 8.2 where the patient has been exposed to study treatment must be reported. Reporting period begins at the time of initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

8.4. Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (assessed for each Sorafenib and Vemurafenib separately, see Section 8.4.1), and actions taken to study drug (8.4.2).

8.4.1. Causal Relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information.

The causality assessment should be done separately for each study treatment.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guidelines to the attributions and causal relationship:

Attribution	**Causal Relationship**
Possibly Related Probably Related Definitely Related	Yes- Related
Not Related Unlikely Related	No- Not Related

Yes (Possibly, Probably, Definitely)
There is a plausible temporal relationship between the onset of the AE and administration of the study treatment (assessed for each Sorafenib and Vemurafenib separately) and the AE cannot be readily explained by the subject’s clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study treatment or with similar treatments; and/or the AE abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re- challenge.

No (Not related, Unlikely)
Evidence exists that the AE has an etiology other than the Sorafenib and Vemurafenib (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study treatment (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Inserts (Refer to Section 9).

Unexpected adverse events are those not listed in the Package Inserts or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the Package Inserts. For example, under this definition, hepatic necrosis would be unexpected if the Package Inserts only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

8.4.2. **Action Taken with Study Treatment**

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

8.4.3. **Outcome**

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

8.4.4. **Assessment of Severity of Adverse Events**

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Below Table 4. should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE**.**

Table 4: Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]

5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

8.5. Procedures for Eliciting, Recording and Reporting Adverse Events

8.5.1. Eliciting Adverse Events

8.5.2. Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

8.5.2.1. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.5.2.2. Progressive Disease

If progressive disease leads to signs and symptoms that meet the criteria for an SAE (i.e., hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE and not the underlying progressive disease.

8.5.2.3. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 8.3), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

8.5.2.4. Pre-Existing Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

8.5.2.5. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study
- The admission is not associated with an AE. (e.g. social hospitalization for purposes of respite care).

8.5.2.6. Laboratory Abnormalities

An isolated laboratory abnormality that is assigned grade 4, according to CTCAE definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE or Adverse Events of Special Interest (AESIs-Section 8.7). CTCAE grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

8.6. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 30 days after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 30 days after the last dose of study drug, a report should be completed and expeditiously submitted to HRI Drug Safety/Bayer/Genentech. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be

classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

Female patients of childbearing potential should be advised to use contraception during the treatment and at least 30 days after the last dose of study treatment. Women must refrain from donating eggs during this same period.

8.7. Adverse Events of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
  - Treatment-emergent ALT or AST > 3 X ULN in combination with total bilirubin > 2 X ULN
  - Treatment-emergent ALT or AST > 3 X ULN in combination with clinical jaundice
- Acute Kidney Injury
- Cutaneous Squamous Cell Carcinomas
- Non cutaneous Squamous Cell Carcinomas
- Pancreatitis
- Liver injury
- Progression of RAS Mutant Malignancies
- QT Prolongation
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

8.8. Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to HRI Oncology Drug Safety:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

8.9. Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

8.10. Post-Study Adverse Events

For studies involving collection of survival data the investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug or study discontinuation/termination, whichever is earlier) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject including pregnancy occurring in the partner of a male study subject who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by all parties during this period half yearly to ensure successful transmission of single case reports.

8.11. Adverse Event Requiring Expedited Reporting

HonorHealth will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the study drug (Sorafenib and Vemurafenib).

The definition of serious adverse events (SAEs) is given in Section 8.2 and Adverse Events of Special Interest (AESIs) in Section 8.7.

All SAEs, AESI, and pregnancies must be reported on Medwatch Form 3500A within 24 hours/ 1 business day of becoming aware of the event, to HonorHealth Oncology Drug Safety Team after the Investigator recognizes/classifies the event as a SAE, AESI, or pregnancy.

The completed MedWatch Form 3500A along with the accompanying SAE Coversheet should be sent to the HRI Oncology Drug Safety contacts as specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below.

MedWatch 3500A (Mandatory Reporting) form is available at:
https://www.fda.gov/media/69876/download

HonorHealth Drug Safety Team	
Phone:	480-323-1350
Fax:	480-323-1560
Email:	OncologyDrugSafety@honorhealth.com

HonorHealth will be responsible for reporting SAEs, AESI, and pregnancies to Bayer and Genentech as per Section 8.12.

8.11.1. **Medwatch 3500A Reporting Guidelines**

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

8.11.2. **Follow-up Information**

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports. Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

8.12. HonorHealth Reporting to Genentech and Bayer

HonorHealth will forward quarterly listings of non-serious AEs originating from the Study to Bayer/Genentech.

HonorHealth will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed MedWatch form should be sent to the Bayer/Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below.

Bayer Safety Global Pharmacovigilance – USA
Bayer Ref #: IRR-US-000177
Phone: 888-842-2937
Fax: 973-709-2185
Email: DrugSafety.GPV.US@bayer.com

Genentech SAE Reporting
Genentech Ref# ML-42826
Phone: 800-334-0290
Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

Product Complaints without AE should call via PC Hotline Number:
800-334-0290 (M-F: 5am to 5pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Type of Report	Timelines
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

Case Transmission Verification of Single Case Reports

- The parties will verify that all single case reports have been adequately received by Bayer and Genentech via HonorHealth emailing Bayer and Genentech a

Quarterly line-listing documenting single case reports sent by HonorHealth to Bayer and Genentech in the preceding time period.

- The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.
- If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.
- Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by HonorHealth to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Bayer and Genentech

9. DRUG / TREATMENT INFORMATION

9.1. Vemurafenib

Package Insert:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf

Other names for the drug:

- Zelboraf®;
- propane-1-sufonic acid {3-[5-(4-chlorphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide
- C23H18ClF2N3O3S molecular weight 489.9.

Classification - type of agent: A kinase inhibitor

Mode of action: Vemurafenib is a low molecular weight, orally available, inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. Vemurafenib also inhibits other kinases in vitro such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5 and FGR at similar concentrations. Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib has anti-tumor effects in cellular and animal models of melanomas with mutated BRAF V600E.

Storage and stability: Vemurafenib tablets are to be stored in their original container with lids tightly closed at room temperature 20ºC-25 ºC (68 ºF-77 ºF). Storage temperature excursions are permitted between 15ºC-30 ºC (59ºF-86 ºF).

Protocol dose: 480 mg PO (2 x 240mg tablets) BID

Preparation: No preparation required.

Route of administration for this study: Oral

Availability: Provided by Genentech free of charge.

Patient Counseling Information:

- Advise the patient to read the FDA-approved patient labeling (Medication Guide) before starting vemurafenib.
- Advise the patient to avoid consuming grapefruit and grapefruit juice while take vemurafenib during study treatment as this may raise the levels of vemurafenib and could make side effects worse.
- Advise the patient to avoid the use of St. John's Wort while taking vemurafenib during study treatment as this may lower the levels of the drug, which can make it less effective.
- Vemurafenib increases the risk of developing new primary cutaneous malignancies. Patients should be advised of the importance of contacting their healthcare provider immediately for any changes in their skin.
- Anaphylaxis and other serious hypersensitivity reactions can occur during treatment and upon re-initiation of treatment with vemurafenib. Patients should be advised to stop taking vemurafenib and to seek immediate medical attention for symptoms of anaphylaxis and hypersensitivity.
- Severe dermatological reactions can occur in patients receiving vemurafenib. Patients should be advised to stop taking vemurafenib and to contact their health-care provider for severe dermatologic reactions.
- Vemurafenib can prolong QT interval, which may result in ventricular arrhythmias. Patients should be advised of the importance of monitoring their electrolytes and the electrical activity of the heart (via and ECG) during treatment with vemurafenib.
- Liver injury leading to functional hepatic impairment, including coagulopathy or other organ dysfunction, can occur with vemurafenib. Patients should be advised of the importance of laboratory monitoring of their liver during treatment with vemurafenib and to contact their health-care provider for relevant symptoms.
- Vemurafenib can cause mild to severe photosensitivity. Patients should be advised to avoid sun exposure, wear protective clothing, use a broad-spectrum UVA/UVB sunscreen and lip balm (SPF≥30) when outdoors to help protect against sunburn.
- Ophthalmologic reactions can occur in patients treated with vemurafenib. Patients should be advised to contact their health care provider immediately for ophthalmologic symptoms.

- Due to potential risk to a fetus woman of child-bearing potential must use effective contraception during treatment with vemurafenib and for 2 weeks after their last dose.
- If a female patient confirms or suspects pregnancy during the study, they should contact their healthcare provider immediately. Any confirmed pregnancy is to be reported within 24 hours as per Section 8.6.
- If a male patient's sexual partner becomes pregnant during the study, they should contact their healthcare provider immediately. Any confirmed pregnancy is to be reported within 24 hours as per Section 8.6.
- Female patients should be advised not to breastfeed during treatment with vemurafenib and for 2 weeks following the final dose.
- Radiation sensitization and recall can occur in patients treated with radiation prior to, during, or after treatment with vemurafenib. Patients should be advised to inform their health care provider if they have had or are planning to receive radiation therapy. Radiotherapy may be allowed while the patient is enrolled in this study if given to help palliate a specific symptom (e.g. bone pain, brain metastases, etc.
- Renal failure can occur in patients treated with vemurafenib. Patients should be advised of the importance of monitoring serum creatinine prior to and during treatment with vemurafenib.
- Advise patients to contact their health care provider for symptoms of Dupuytren's contracture or plantar fascial fibromatosis

9.2. Sorafenib

Package Insert:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021923s020lbl.pdf

Other names for the drug(s):

- Nexavar
- Sorafenib tosylate
- 4-(40{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}ogebixt)N2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate
- C21H16ClF3N4O3 x C7H8O3S

Classification - type of agent: Kinase inhibitor

Mode of action: Sorafenib is a kinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib was shown to inhibit multiple intracellular (c-CRAF, ARAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, RET/PTC, VEGFR-1, VEGFr-2, VEGFR-3, and PDGFR-β). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis. Sorafenib inhibited tumor growth of HCC, RCC and DTC human tumor xenografts in immunocompromised mice. Reductions in

tumor angiogenesis were seen in models of HCC and RCC upon sorafenib treatment and increases in tumor apoptosis were observed in models of HCC, RCC and DTC.

Storage and stability: The tablets should be stored in a dry place at 25 ºC (77 ºF). Storage temperature excursions are permitted between 15ºC-30 ºC (59 ºF-86 ºF).

Protocol dose: 200mg (one tablet) PO am and 200mg (one tablet) PO pm

Preparation: No preparation is required

Route of administration for this study: Oral

Availability: Provided by Bayer free of charge.

Patient Counseling Information:

- Patients should be advised to read the FDA approved patient labelling guide prior to starting treatment with sorafenib.
- Discuss with patients that cardiac ischemia and/or infarction and congestive heart failure, have been reported during sorafenib treatment and that they should immediately report any episodes of chest pain or other symptoms of cardiac ischemia or congestive heart failure.
- Inform patients with a history of prolonged QT interval that sorafenib can worsen the condition.
- Inform patients that sorafenib can increase the risk of bleeding and that they should promptly report any episodes of bleeding.
- Inform patients that bleeding, or INR elevations have been reported in some patients taking warfarin while on sorafenib and that their INR should be monitored regularly.
- Inform patients that hypertension can develop during sorafenib treatment, especially during the first six weeks of therapy and that blood pressure should monitored regularly during treatment.
- Patients should be advised of the possible occurrence of hand-foot skin reaction and rash during sorafenib treatments and the measures they should take.
- Patients should be advised that cases of gastrointestinal perforation have been reported in patients taking sorafenib.
- Patients should be informed that temporary interruption of sorafenib is recommended in patients undergoing major surgical procedures due to potential wound healing complications.
- Sorafenib can cause hepatitis which may result in hepatic failure and death. Patients should be advised that liver function tests should be monitored regularly during treatment and that they should report symptoms of hepatitis.

- Due to potential risk to a fetus woman of child-bearing potential must use effective contraception during treatment and for 6 months after the last dose of sorafenib. Male patients with female partners of reproductive potential or who are pregnant must use effective contraception during treatment with sorafenib and for 3 months after receiving their last dose.
- If a female patient confirms or suspects pregnancy during the study, they should contact their healthcare provider immediately.
- Patients on sorafenib should not breastfeed while taking the medication and for 2 weeks after receiving their last dose.
- If a patient misses a dose of sorafenib, the next dose should be taken at the regularly scheduled time; they should not double the dose. Patients should be instructed to contact their healthcare provider immediately if they take too much sorafenib.

9.3. Return and Retention of Study Drug

Institutional pharmacy standard operating procedures will be followed for retention, storage, and destruction of study drug.

9.4. Drug Accountability

Patients will be instructed to complete a study drug diary and return along with the study medication bottles on Day 1 visit of each cycle for drug accountability. Drug accountability will be completed by delegated study personnel at minimum of once per cycle by reviewing both the patient completed drug diary and the returned study medication. Study personnel will document any missed doses in the source documents and review this with both the patient and the treating investigator. Study personnel will provide additional reinstruction to the patient and implement additional drug accountability throughout a cycle as needed.

10. CORRELATIVES / SPECIAL STUDIES

10.1. Trial Specimens

Blood specimens will be collected for plasma DNA to determine target engagement before, during and after treatment. This will be measured at baseline and just before each cycle of treatment. The site will collect blood samples (3 X 10 mL) at screening, Day 1 of each treatment cycle, and at the off treatment study visit.

Please see Laboratory Manual for details on blood collection and processing guidelines.

10.2. Assay Methodology

Blood samples will be collected and processed for plasma at baseline and just before each treatment cycle. Plasma will be used to analyze circulating tumor DNA (ctDNA) to give qualitative (mutations) and to some extent quantitative (amount of ctDNA) information regarding BRAF and KRAS.

Blood samples will be collected and processed for serum at baseline and just before each treatment cycle. Serum will be analyzed using the Bio-plex suspension array using specific antibodies and flow cytometry as per the methods developed by Takano et al. 2010 to measure phopho ERK to determine if the treatment has hit the intended target.

Tissue samples
For those patients that consent to the optional tissue collection for RPPA analysis, tissue will be collected from a newly obtained core or excisional biopsy of a tumor lesion if performed recently (within 30 days prior to study treatment on Day 1) and during their participation in the study should they be scheduled for a biopsy as part of their routine care during their participation in the study through the follow-up period.

Tissue samples will be analyzed using Reverse Phase Protein Array (RPPA).

10.3. Specimen Banking
Any blood samples remaining after the trial specified analyses is completed will be transferred to and stored at HonorHealth if the patient consented for use of their remaining samples for future research purposes at HonorHealth's discretion. This includes the original specimen collected from the patient as well as derivatives created from the original specimen (DNA, RNA).

11. STATISTICAL CONSIDERATIONS

11.1. Study Design / Study Endpoints
This is a phase II open-label, single arm trial, with the identity of the treatment known to the patients, Investigators, and Sponsor.

11.2. Sample Size and Accrual
Between 7 and 12 evaluable patients total will be entered into this study. To obtain that number of evaluable patients we estimate up to 24 patients will possibly be enrolled. An evaluable patient is defined as one that receives at least one dose of both agents (vemurafenib + sorafenib) and has a scan after at least 2 cycles of treatment. We are hoping for a disease control rate of ≥40%. Simon’s two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, n=7 patients will be accrued. If there are zero responses in these 7 patients, the study will be stopped. Otherwise, 5 additional patients will be accrued for a total of 12. The null hypothesis will be rejected if 3 or more responses are observed in 12 patients. This design yields a type I error rate of 0.0188 and power of 0.9077 when the true response rate is 40%. (Jung et al, 2004).

11.3. Data Analyses Plans

11.3.1. Analysis of the Conduct of the Trial

Enrollment, major protocol deviations, and discontinuations for the trial will be summarized using a CONSORT diagram.

11.3.2. **Patient Disposition**

A detailed description of patient disposition will include:

- A summary of data on patient discontinuation from treatment.
- A summary of data on overall qualification status of all patients.
- An account of all identified protocol deviations.

All patients enrolled in the study will be included in the summation. An evaluable patient is any patient who has received any number of doses of both agents (vemurafenib + sorafenib) and has a scan after at least 2 cycles of treatment. The number of patients who do not qualify for analysis, who die or discontinue before treatment begins, will be specified.

11.3.3. **Analysis of Patient Characteristics**

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions
- Prior therapies
- Concomitant medications and treatments
- Other patient characteristics will be summarized as appropriate.

11.3.4. **Statistical Analysis**

The primary efficacy analysis will focus on the disease control rate (CR + PR + SD at 16 weeks). Secondary endpoints include progression-free survival (PFS) and overall survival (OS). The efficacy analysis will only be conducted on patients who have received any number of doses of both agents (vemurafenib + sorafenib) and have a scan after at least 2 cycles of treatment.

Objective responses will be evaluated using the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1). Changes (i.e. improvements) in tumor measurements from baseline values will be assigned a status of CR or PR or SD. Objective response measurements will comprise the sum of CR plus PR. The overall response rate, as well as the rates for the individual categories of response (i.e. CR, PR, SD, and PD), will be estimated by the percentage of patients achieving these criteria with exact 95% binomial confidence intervals.

Progression-free survival is defined as the interval from the date of study treatment initiation (C1/D1) to the earliest date of documented evidence of recurrent or progressive disease, or the date of death due to any cause, whichever occurs first. Overall survival will be measured from the date of study treatment initiation (C1/D1) to the date of death

due to any cause, or the date of last contact (censored observations). For the estimation of progression-free and overall survival a Kaplan-Meier analysis will be performed.

Longitudinal measurements of circulating tumor DNA (ctDNA) and phospho ERK will be visualized using plots for each evaluable patient. These measurements will be transformed using a logarithmic transformation, if necessary, to remove skewness. Significant changes across time will be assessed using linear mixed effects models, to account for the correlation among the measurements within an individual. If the observed change is non-linear, nonlinear mixed effects models will be used.

11.3.5. **Safety and Tolerance Analysis**

All patients who received at least one dose of any of the study medications will be included in the safety analyses. Vemurafenib + Sorafenib dose administration data will be listed and any dose interruptions and dose reductions will be summarized.

The incidence of all AEs (regardless of causality) and all treatment-related AEs (those AEs thought to be suspected related to study drug) will be summarized by NCI CTCAE version 5.0 term and maximum grade. The incidence of SAEs and AEs that lead to discontinuation of study drug will also be summarized. Listings of patients who discontinue study drug due to an AE and patients with SAEs and deaths will be presented. Narratives will be provided for patients who experience an SAE.

11.4. Stopping Rules

The study can be stopped early based on the following criteria:

- Per PI or sponsor discretion
- If none of the first 7 evaluable patients have disease control (CR+ PR +SD at 16 weeks)

12. STUDY MANAGEMENT

12.1. Ethics

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, and in full compliance with the World Medical Association Declaration of Helsinki and its most recent amendments.

12.2. Institutional Review Board (IRB) Approval

Before study initiation, this protocol and informed consent form will be submitted for review and approval to the IRBs charged with oversight for the clinical sites. In addition, any form of proposed advertising and advertising text for patient recruitment must be

reviewed and approved by (Sponsor) prior to submission to the IRB. The Investigator will forward to (Sponsor) -nominated designee a copy of the IRB's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in 21 CFR 56 of the Code of Federal Regulations, as well as those of the applicable regulatory bodies in all other participating countries outside of the U.S.

In addition, the Investigator will be responsible for forwarding to Sponsor nominated designee a description of the IRB board members (including profession and affiliation) or a United States (US) Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet FDA and other appropriate regulatory requirements. In addition, the labeling for all approved study drugs should be submitted to the IRB for informational purposes.

12.3. Informed Consent

Written informed consent of the patient to participate in the study must be obtained and documented by the Investigator in accordance with the FDA regulations set forth in 21 CFR 50 as well as the applicable regulatory bodies in all other participating countries outside the United States.

The Investigator must provide the patient with a copy of the informed consent form in a language understandable to the patient. Written consent should be obtained before any protocol-required procedures are performed, including any procedure not part of normal patient care (e.g., withdrawal of current medications).

Changes made by a participating site to the recommended informed consent must be forwarded to HRI/Triligent for approval prior to submission to the corresponding IRB. A copy of the signed informed consent will be given to the patient or their legal representative and a copy must be retained in the Investigator's study records.

12.4. Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are patient to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

12.5. Reporting to Regulatory Authorities, Ethics Committees and Investigators

HonorHealth will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where

applicable.

HonorHealth will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

12.6. Annual Reports and Study Close-Out

Any study report submitted to the IRB by the Sponsor-Investigator should be copied to Bayer and Genentech. This includes all IRB annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Bayer and Genentech per the terms detailed in the contract.

12.7. Investigator Obligations

12.7.1. Form FDA 1572

The Investigator must provide a fully executed Form FDA 1572. Any additions to the study must be provided via a new fully executed Form FDA 1572. Others should follow FDA guidance “Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs”.

12.7.2. Curriculum Vitae

The Investigator must provide his/her current signed and dated curriculum vitae and a current signed and dated curriculum vitae for each sub-Investigator listed on Form FDA 1572. Current signed and dated curriculum vitae is defined as updated within 2 years of study start up.

12.7.3. Investigator Protocol Agreement

The Investigator must sign the Investigator’s Protocol Agreement. The original must be kept on file at the Investigator site and a copy provided to HRI. The completed Investigator’s Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator’s Protocol Agreement must be signed if and when a protocol amendment is issued by (Sponsor/CRO).

12.7.4. Financial Disclosures

The Investigator and sub-Investigator(s) must complete a Clinical Investigator Financial Certification/Disclosure Statement to report financial interests and arrangements that may be of concern to FDA per 21 CFR 54.

12.7.5. Laboratory Certifications and Normal Ranges

The Investigator will indicate on the Form FDA 1572 the name and location of any local laboratories that will be used for laboratory assessments. The Investigator will provide a copy of all clinical laboratory certifications, certification numbers, and dates of certifications, and. Normal ranges for all laboratory tests will be included with all reported results. Updated versions of these documents must be provided to HRI appropriate. In the event the clinical laboratory is changed during the study HRI will be promptly notified,

and the Form FDA 1572 will be updated. Appropriate documentation will be submitted to HRI to verify the certification of the new laboratory.

All radiology facilities being utilized outside the investigative site must be pre-approved by HRI.

12.7.6. **Confidentiality**

The Investigator and any other study personnel involved in this study shall not disclose, or use for any purposes (other than for the performance of this study), any data, records, or other information (hereinafter collectively "information") disclosed to the Investigator or other study personnel. Such information shall remain the confidential and proprietary property of HRI and shall be disclosed only to the Investigator or other designated study personnel.

The obligation of non-disclosure shall not apply to the following:

- Relevant disclosure to potential study participants for the purpose of obtaining informed consent;
- Information after such time that it is or becomes publicly available through no fault of the Investigator or other study personnel; and,
- Information after such time that it is disclosed to the Investigator by a third party entitled to disclose such information.
- If the study site is a 'covered site' under the definitions of the Health Insurance Portability and Accounting Act (HIPAA), the Investigator will ensure that the patient consents to the use of data by HRI/Bayer/Genentech and its designees for the purposes of regulatory submissions, study publications, and drug approval.

12.8. Source Documentation

Source documents serve as the evidence of the existence of the patient and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed by the Sponsor or assigned clinical monitor.

Data captured on the eCRFs is to be transcribed from source document and must be consistent with any discrepancies explained and documented.

12.9. Case Report Forms

All the clinical data will be captured by the site on electronic case report forms (eCRFs). The eCRFs will be used for all consented patients. The investigator and trained trial personnel will enter and edit the data via a secure network, with secure identification and password requirement. A complete electronic audit trial will be maintained. The investigator will be required to provide approval of all data to confirm accuracy. Copies of the eCRFs will be provided to the investigator at the conclusion of the trial.

HRI will monitor the study to verify study data, medical records, and eCRFs in accordance with current ICH GCP guidelines as well as other applicable regulations and guidelines.

12.10. Data Management and Monitoring / Auditing

Data monitoring procedures will be carried out by an HRI appointed monitor and will be performed on a regular basis to comply with Good Clinical Practice guidelines.

Review of the case report forms, cross-reference with source documentation (including radiology review), review of study related regulatory documents and logs (e.g., enrollment, study site staff training and delegation) and review of drug infusion records will be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements. At the conclusion of the monitoring visit, the site monitor will meet with the site staff to discuss and request specific corrections to the case report forms, and/or request clarification, and/or additional source documentation. The Principal Investigator and Clinical Research Coordinator responsible for the study will be provided with a follow-up letter for resolution of the findings.

The HRI monitor will complete a written monitoring report. The report will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The Principal Investigator will be expected to submit any Corrective Action Plans, in writing.

12.10.1. Data Safety and Monitoring

An independent Data Safety and Monitoring Committee (DSMC) will be formed to evaluate the safety and effectiveness of the study medication for each subject. The DSMC will also review all SAEs and AESIs reported by each site. The DSMC will review study data to determine if endpoints are being met and if the study can continue with or without changes to the protocol or if the study should be terminated immediately due to safety concerns or lack of data to support study endpoints. Findings and recommendations of the DSMC will be reported to the Sponsor after each meeting.

12.11. Record Retention

In accordance with applicable regulatory requirements, following closure of the study, the Investigator will maintain a copy of all site study records in a safe and secure location. HRI will inform the Investigator of the time period for retaining these records in order to comply with applicable regulatory requirements.

HRI reserves the right to terminate the study for refusal of the Investigator and/or investigational site to comply with any requirements stated in this study protocol.

13. REFERENCES

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APPENDICES

Appendix A: Schedule of Events

Assessment	Screening Within 28 Days	Cycle 1					Cycle 2 +				Prior to Cycles 3, 5, 7, etc.	Off Treatment Visit [11]	Follow-up
		Day 1		Day 8	Day 15	Day 22	Day 1						
Window												14-28 (± 2 days) of last dose	30 days of last dose, then every 3 months
Signed informed consent	X												
Review inclusion/exclusion	X	X											
Medical history[1]	X												
Complete Physical Exam	X												
Direct Physical Exam		X[2]		X[3]	X	X	X[3]					X	
Height (cm)	X												
Weight (kg)	X	X[2]					X[3]					X	
BSA calculation		X[2]					X						
Vital signs[4]	X	X[2]		X[3]	X	X	X[3]					X	
ECOG PS	X	X[2]		X[3]	X	X	X[3]					X	
CT/ MRI scan / tumor measurements[5]	X										X		
ECG[6]	X	X			X		X[6]						
CBC w/differential & PLTs	X	X[2]		X[3]	X	X	X					X	
Serum chemistries[7]	X	X[2]		X[3]	X	X	X					X	
PT/INR	X	X[2, 8]					X[8]					X[8]	
CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)	X										X	X	
Serum pregnancy	X	X[2]					X					X	
Confirm KRAS, BRAF Mutation Status [13]	X												
Blood for correlative analysis (3 X 10 mL)	X						X					X	
Optional Tumor Tissue [15]	X	<----------X---------->											
Concomitant medications[9]	X	X		X	X	X	X					X	
Adverse events[10]		X		X	X	X	X					X	
Contact Information Review	X	X										X	X
Telephone follow-up[12]													X

Drug Accountability- (Section 9.4)		X					X				X	
TREATMENT												
Vemurafenib[14]		X ---------->					X ---------->					
Sorafenib[14]		X ---------->					X ---------->					

Schedule of Events footnotes:

1. To include concurrent baseline conditions (using NCI CTCAE, version 5.0), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
2. Should be performed < 24 hours prior to the initiating study treatment day on C1/D1.
3. Should be performed within 72 hours prior to treatment on day 1 of each cycle beyond cycle 1.
4. Vitals signed include blood pressure, pulse, respiratory rate and temperature.
5. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, a brain scan is required to exclude brain metastases if clinically indicated only. If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. (see RECIST 1.1 criteria in Section 7.1). Follow-up scans are due every 2 cycles (prior to cycle 3, 5, 7, etc.)
6. ECG (Cycles 1 through 3, then every 3 cycles 6, 9, 12 etc.)
7. To include glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium). In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin. Calculate creatinine clearance (Cockcroft-Gault equation)
8. PT/INR required only for patients on warfarin.
9. To include all medications and supplements taken within 30 days prior to study enrollment. The use of grapefruit juice and St. John's Wort (hyperforin) is prohibited during study treatment. The treating investigator is to discuss this with the patient prior to initiating study treatment and will review list of all medications and supplements during the course of the study.
10. Patient will be followed until resolution of any drug-related AE or SAE occurring during the study, including, within 30 days of last administration of study medication, or when the patient begins alternative therapy; whichever is sooner.
11. Off Treatment -Early Termination assessments can be completed 14-28 (+/- 2) days from the last dose of study treatment.
12. Follow-up assessments for survival in person or by telephone will be conducted in all patients 30 days after the last dose of study treatment and then every 3 months until study completion (may be done through medical record review or follow up phone calls). Receipt of second line therapy will be recorded.
13. Confirm KRAS and BRAF mutation status. For those patients in which the mutation status of KRAS and BRAF kinases has not previously been determined, the patient must have an archival tumor specimen (primary or metastatic site) available to submit to confirm KRAS and BRAF status. The results of the mutation status are required for determining patients eligibility for this trial
14. Patients will be asked to take the specified number of tablets for their prescribed dose on an empty stomach at a regular time each day with water. Doses should be taken either one hour prior or two hours after a meal. Approximately 12 hours should elapse between doses.
15. For those patients that consent to the optional tissue collection for RPPA analysis, tissue will be collected from a newly obtained core or excisional biopsy of a tumor lesion if performed recently (within 30 days prior to study treatment on Day 1) and during their participation in the study should they be scheduled for a biopsy as part of their routine care during their participation in the study through the follow-up period

Appendix B: ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982;5:649-655.

Appendix C: Revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0

(PUBLISHED 27 NOVEMBER 2017)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 can be viewed on-line at the following NCI web site:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix D: New York Heart Association (NYHA)

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
Class	**Objective Assessment**
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

Appendix E: Medications with Risk of QT Prolongation and TdP (Torsades de Pointes)

Data obtained from CredibleMeds https://crediblemeds.org/new-drug-list/

Table E1 - Medications with a KNOWN risk of TdP
Table E2 - Medications with a POSSIBLE risk of TdP
Table E3 - Medications with a CONDITIONAL risk of TdP

Table F1-Medications with a known risk of TdP (These drugs prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended)			
Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Aclarubicin (Only on Non US Market)	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer	Cancer
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Arrhythmia
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox	Anti-cancer	Cancer (leukemia)
Astemizole (Removed from US Market)	Hismanal	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection
Bepridil	Vascor	Antianginal	Angina Pectoris (heart pain)
Cesium Chloride	Energy Catalyst	Toxin	Alternative therapy cancer
Chloroquine	Aralen	Antimalarial	Malaria
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Nausea, Schizophrenia, many others
Chlorprothixene (Only on Non US Market)	Truxal	Antipsychotic	Schizophrenia
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection

Cisapride (Removed from US Market)	Propulsid	GI stimulant	Increase GI motility
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace	Antiarrhythmic	Arrhythmia
Dofetilide	Tikosyn	Antiarrhythmic	Arrhythmia
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic	Nausea, vomiting
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq	Antiarrhythmic	Arrhythmia
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam,	Antidepressant, SSRI	Depression (major), anxiety disorders

	Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil		
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Arrhythmia
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection
Gatifloxacin (Removed from US Market)	Tequin	Antibiotic	Bacterial infection
Grepafloxacin (Removed from US Market)	Raxar	Antibiotic	Bacterial infection
Halofantrine (Only on Non US Market)	Halfan	Antimalarial	Malaria
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation
Hydroquinidine (Dihydroquinidine) (Only on Non US Market)	Serecor	Antiarrhythmic	Arrhythmia
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, Anti-inflammatory	Malaria, SLE, rheumatoid arthritis
Ibogaine (Only on Non US Market)		Psychedelic	Narcotic addiction, unproven
Ibutilide	Corvert	Antiarrhythmic	Arrhythmia
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection
Levomepromazine (Methotrimeprazine)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia

(Only on Non US Market)			
Levomethadyl acetate (Removed from US Market)	Orlaam	Opioid agonist	Narcotic dependence
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva	Antipsychotic	Schizophrenia
Meglumine antimoniate (Only on Non US Market)	Glucantime	Antiparasitic	Leishmaniasis
Mesoridazine (Removed from US Market)	Serentil	Antipsychotic	Schizophrenia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Nifekalant (Only on Non US Market)	Shinbit	Antiarrhythmic	Arrhythmia
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin	Anti-cancer	Cancer
Papaverine HCl (Intra-coronary)		Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap	Antipsychotic	Tourette's Disorder
Probucol (Removed from US Market)	Lorelco	Antilipemic	Hypercholesterolemia

Procainamide	Pronestyl, Procan	Antiarrhythmic	Arrhythmia
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Arrhythmia
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic	Bacterial infection
Sevoflurane	Ultane, Sojourn	Anesthetic, general	Anesthesia
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Arrhythmia
Sparfloxacin (Removed from US Market)	Zagam	Antibiotic	Bacterial infection
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Terfenadine (Removed from US Market)	Seldane	Antihistamine	Allergic rhinitis
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss	Vasoconstrictor	Septic shock
Terodiline (Only on Non US Market)	Micturin, Mictrol	Muscle relaxant	Bladder spasm
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa	Anti-cancer	Cancer (thyroid)

Table F2. Medications with a possible risk of TdP			
These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended.			
Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Abarelix (Only on Non US Market)	Plenaxis	GnRH Antagonist	Cancer (prostate)
Alfuzosin	Uroxatral	Alpha-1 adrenergic blocker	Benign prostatic hyperplasia
Alimemazine (Trimeprazine) (Only on Non US Market)	Nedeltran, Panectyl, Repeltin, Therafene, Theraligene, Theralen, Theralene, Vallergan, Vanectyl, Temaril	Antihistamine	Allergy
Apalutamide	Erleada	Nonsteroidal antiandrogen	Cancer (prostate)
Apomorphine	Apokyn, Ixense, Spontane, Uprima	Dopamine agonist	Parkinson's disease
Aripiprazole	Abilify, Aripiprex	Antipsychotic, atypical	Schizophrenia, depression (adjunct)
Artemether/Lumefantrine	Coartem	Anti-malarial	Marlaria
Artenimol/piperaquine (Only on Non US Market)	Eurartesim	Antimalarial	Malaria
Asenapine	Saphris, Sycrest	Antipsychotic, atypical	Schizophrenia
Atomoxetine	Strattera	CNS stimulant	ADHD
Bedaquiline	Sirturo	Antibiotic	Tuberculosis, Multi-drug resistant
Bendamustine	Treanda, Treakisym, Ribomustin, Levact	Anti-cancer	Cancer (Leukemia, lymphoma)

Benperidol (Only on Non US Market)	Anquil, Glianimon	Antipsychotic	Schizophrenia
Betrixaban	Bevyxxa	Anticoagulant	Anticoagulant
Bortezomib	Velcade, Bortecad	Proteasome inhibitor	Cancer (multiple myeloma,lymphoma)
Bosutinib	Bosulif	Anti-cancer	Cancer (leukemia)
Buprenorphine	Butrans, Belbuca, Bunavail, Buprenex, Subutex, Suboxone, Zubsolv	Opioid agonist	Narcotic addiction and pain
Cabozantinib	Cometriq	Anti-cancer	Cancer (renal cell)
Capecitabine	Xeloda	Anti-cancer	Cancer (GI, Breast)
Carbetocin (Only on Non US Market)	Pabal, Lonactene, Duratocin	Uterotonic	Uterine atony
Ceritinib	Zykadia	Anti-cancer	Cancer (Lung)
Clofazimine (Only on Non US Market)	Lamprene	Antibiotic	Leprosy
Clotiapine (Only on Non US Market)	Entumine	Antipsychotic, atypical	Psychosis
Clozapine	Clozaril, Fazaclo, Versacloz	Antipsychotic, atypical	Schizophrenia
Cobimetinib	Cotellic	Anti-cancer	Cancer (Melanoma)
Crizotinib	Xalkori	Anti-cancer	Cancer (Non-small cell lung cancer, metastatic)
Cyamemazine (Cyamepromazine) (Only on Non US Market)	Tercian	Antipsychotic	Schizophrenia, sedation
Dabrafenib	Tafinlar	Anti-cancer	Cancer (melanoma)
Dasatinib	Sprycel	Anti-cancer	Cancer (leukemia)
Degarelix	Firmagon, Ferring	Anti-androgen	Cancer (prostate)
Delamanid (Only on Non US Market)	Deltyba	Antibiotic	Tuberculosis, Multi-drug resistant

Desipramine	Pertofrane, Norpramine	Antidepressant, Tricyclic	Depression
Deutetrabenazine	Austedo	Vesicular monamine transporter 2 inhibitor	Chorea (Huntington's disease)
Dexmedetomidine	Precedex, Dexdor, Dexdomitor	Sedative	Sedation
Dextromethorphan/Quinidine	Nuedexta	Unknown	Pseudobulbar affect
Dolasetron	Anzemet	Antiemetic	Nausea, vomiting
Efavirenz	Sustiva	Antiviral	HIV/AIDS
Eliglustat	Cerdelga	Glucosylceramide synthase inhibitor	Gaucher's disease
Encorafenib	Braftovi	BRAF inhibitor	Cancer (Melanoma)
Entrectinib	Rozlytrek	Anti-cancer	Cancer (Lung)
Epirubicin	Ellence, Pharmorubicin, Epirubicin Ebewe	Anti-cancer	Cancer
Eribulin mesylate	Halaven	Anti-cancer	Cancer (breast, metastatic)
Ezogabine (Retigabine)	Potiga, Trobalt	Anticonvulsant	Seizures, Partial
Felbamate	Felbatol	Anticonvulsant	Seizures
Fingolimod	Gilenya	Sphingosine phospate receptor modulator	Multiple Sclerosis
Fluorouracil (5-FU)	Adrucil, Carac, Efudex, Efudix	Anti-cancer	Cancer
Flupentixol (Only on Non US Market)	Depixol, Fluanxol	Antipsychotic	Schizophrenia
Gemifloxacin	Factive	Antibiotic	Bacterial infection
Gilteritinib	Xospata	Antineoplastic	Cancer (Acute Myeloid Leukemia)
Glasdegib	Daurismo	Anti-cancer	Cancer (Acute myeloid leukemia)

Granisetron	Kytril, Sancuso, Granisol	Antiemetic	Nausea, vomiting
Hydrocodone - ER	Hysingla™ ER, Zohydro ER	Analgesic	Pain, severe
Iloperidone	Fanapt, Fanapta, Zomaril	Antipsychotic, atypical	Schizophrenia
Imipramine (Melipramine)	Tofranil	Antidepressant, Tricyclic	Depression
Inotuzumab ozogamicin	Besponsa	Anti-cancer	Cancer (acute lymphocytic leukemia}
Isradipine	Dynacirc	Antihypertensive	Hypertension
Ivosidenib	Tibsovo	IDH1 inhibitor	Cancer (Acute myeloid leukemia)
Ketanserin (Only on Non US Market)	Sufrexal	Antihypertensive	Hypertension
Lacidipine (Only on Non US Market)	Lacipil, Motens	Calcium channel blocker	Hypertension
Lapatinib	Tykerb, Tyverb	Anti-cancer	Cancer (breast, metastatic)
Lefamulin	Xenleta	Antibiotic	Community acquired pneumonia
Lenvatinib	Lenvima	Anti-cancer	Cancer (Thyroid)
Leuprolide (Leuprorelin)	Lupron, Eligard, Viadur, Carcinil, Enanton, Leuplin, Lucrin, Procren, Prostap	Anti-androgen	Cancer (prostate)
Levetiracetam	Keppra	Anti-seizure	Epilepsy
Levomethadone (levamethadone) (Only on Non US Market)		Opioid	Opiate withdrawal syndrome
Lithium	Eskalith, Lithobid	Antimanic	Bipolar disorder
Lofexidine	Lucemyra	Alpha-2-adrenergic agonist, central	Opioid withdrawal syndrome

Lopinavir/Ritonavir	Kaletra, Aluvia	Antiviral	HIV/AIDS
Lumateperone	Caplyta	Antipsychotic, atypical	Schizophrenia
Lurasidone	Latuda	Antipsychotic, atypical	Schizophrenia, biopolar disorder and others
Maprotiline	Ludiomil	Anti-depressant, Tetracyclic	Depression
Melperone (Only on Non US Market)	Bunil, Buronil, Eunerpan	Antipsychotic, atypical	Schizophrenia
Memantine	Namenda XR	NMDA receptor antagonist	Alzheimer's disease
Mianserin (Only on Non US Market)	Tolvon	Anti-depressant	Depression
Midostaurin	Rydapt	Anti-cancer	Cancer (Acute myeloid leukemia)
Mifepristone	Korlym, Mifeprex	Progesterone antagonist	Pregnancy termination
Mirabegron	Myrbetriq	Beta3 adrenergic antagonist	Bladder spasm
Mirtazapine	Remeron	Antidepressant, Tetracyclic	Depression
Moexipril/Hydrochlorothiazide	Uniretic, Univasc	Antihypertensive	Hypertension, diuresis
Necitumumab	Portrazza	Anti-cancer	Cancer (Lung)
Nicardipine	Cardene	Antihypertensive	Hypertension
Nilotinib	Tasigna	Anti-cancer	Cancer (leukemia)
Norfloxacin	Noroxin, Ambigram	Antibiotic	Bacterial infection
Nortriptyline	Pamelor, Sensoval, Aventyl, Norpress, Allegron, Noritren, Nortrilen	Antidepressant, Tricyclic	Depression
Nusinersen	Spinraza	Antisense oligonucleotide	Spinal Muscular Atrophy
Ofloxacin	Floxin	Antibiotic	Bacterial infection
Oliceridine	Olinvyk	Analgesia	Pain
Osilodrostat	Isturisa	Aldosterone synthase inhibitor	Cushing's Disease

Osimertinib	Tagrisso	Anti-cancer	Cancer (EGFR pos. NSC Lung cancer)
Oxytocin	Pitocin, Syntocinon	Oxytocic	Labor stimulation
Ozanimod	Zeposia	Immunomodulation	Multiple Sclerosis
Paliperidone	Invega, Xepilon	Antipsychotic, atypical	Schizophrenia
Palonosetron	Aloxi	Antiemetic	Nausea, vomiting
Panobinostat	Farydak	Histone deacetylase inhibitor	Cancer, Multiple myeloma
Pasireotide	Signifor	Somatostatin analog	Cushings Disease
Pazopanib	Votrient	Anti-cancer	Cancer (renal cell, sarcoma)
Perflutren lipid microspheres	Definity, Optison	Imaging contrast agent	Diagnostic adjunct
Perphenazine	Trilafon, Etrafon/Triavil, Decentan	Antipsychotic	Schizophrenia
Pilsicainide (Only on Non US Market)	Sunrythm	Anti-arrhythmic	Arrhythmia
Pimavanserin	Nuplazid	Antipsychotic, atypical	Psychosis, Parkinson's Disease
Pipamperone (Only on Non US Market)	Dipiperon, Propitan, Dipiperal, Piperonil, Piperonyl	Antipsychotic	Schizophrenia
Pitolisant (Tiprolisant)	Wakix	Histamine 3 antagonist/inverse agonist	Narcolepsy
Pretomanid		Antitubercular	Tuberculosis, extensively drug resistant
Primaquine phosphate		Antimalarial	Malaria
Promethazine	Phenergan	Antipsychotic / Antiemetic	Nausea, vomiting
Prothipendyl (Only on Non US Market)	Dominal, Largophren, Timoval,	Antipsychotic	Schizophrenia

	Timovan, Tumovan		
Remimazolam	Byfavo	Sedative	Sedation
Ribociclib	Kisqali	Anti-cancer	Cancer (breast)
Rilpivirine	Edurant, Complera, Eviplera, Juluca	Antiviral	Viral infection (HIV/AIDS)
Romidepsin	Istodax	Histone deacetylase inhibitor	Cancer (lymphoma)
Rucaparib	Rubraca	PARP inhibitor	Cancer
Saquinavir	Invirase(combo)	Antiviral	Viral infection (HIV/AIDS)
Selpercatinib	Retevmo	Kinase inhibitor	Lung cancer
Sertindole (Only on Non US Market)	Serdolect, Serlect	Antipsychotic, atypical	Schizophrenia, anxiety
Siponimod	Mayzent		Multiple Sclerosis
Sorafenib	Nexavar	Anti-cancer	Cancer (liver, renal cell, metastatic thyroid)
Sunitinib	Sutent	Anti-cancer	Cancer (GIST, renal cell, pNET)
Tacrolimus	Prograf, Prograf, Advagraf, Protopic	Immunosuppressant	Immune suppression
Tamoxifen	Nolvadex, Istubal	Anti-cancer	Cancer (breast)
Tazemetostat	Tazverik	Anti-cancer	Epithelioid sarcoma
Telavancin	Vibativ	Antibiotic	Bacterial infection
Telithromycin	Ketek	Antibiotic	Bacterial infection
Tetrabenazine	Nitoman, Xenazine	Vesicular Monoamine Transporter 2 Inhibitor	Chorea (Huntington's disease)
Tiapride (Only on Non US Market)	Tiapridal, Italprid, Sereprile, Tialaread, Tiaryl, Tiaprim, Tiaprizal,	Selective D2, D3 dopamine antagonist	Alcoholism, withdrawal

	Sereprid, Tiapridex		
Tipiracil/Trifluridine	Lonsurf	Anti-cancer	Cancer (Metastatic colorectal)
Tizanidine	Zanaflex, Sirdalud	Muscle relaxant	Muscle spasticity
Tolterodine	Detrol, Detrusitol	Muscle relaxant	Bladder spasm
Toremifene	Fareston	Estrogen agonist/antagonist	Cancer (breast, metastatic)
Tramadol	Crispin, Ralivia ER, Ralivia Flashtab, Tramadolum, Tramal, Tramodol, Tridural, Ultram, Ultram ER, Zydol, Ixprim, Zaldiar, Topalgic	Analgesic	Pain
Trimipramine	Surmontil, Rhotrimine, Stangyl	Antidepressant, Tricyclic	Depression
Tropisetron (Only on Non US Market)	Navoban, Setrovel	Antiemetic	Nausea, vomiting
Valbenazine	Ingrezza	Vesicular monamine transporter 2 inhibitor	Tardive Dyskinesia
Vardenafil	Levitra	Phosphodiesterase 5 inhibitor	Erectile dysfunction
Vemurafenib	Zelboraf	Anti-cancer	Cancer (melanoma)
Venlafaxine	Effexor, Efexor	Antidepressant, SNRI	Depression
Vorinostat	Zolinza	Histone deacetylase inhibitor	Cancer (lymphoma)
Zotepine (Only on Non US Market)	Losizopilon, Lodopin,	Antipsychotic, atypical	Schizophrenia

	Setous, Zoleptil		
Zuclopenthixol (Zuclopentixol) (Only on Non US Market)	Cisordinol, Clopixol, Acuphase	Antipsychotic	Psychosis

Table F3. Medications with a possible risk of TdP These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended.			
Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Abarelix (Only on Non US Market)	Plenaxis	GnRH Antagonist	Cancer (prostate)
Alfuzosin	Uroxatral	Alpha-1 adrenergic blocker	Benign prostatic hyperplasia
Alimemazine (Trimeprazine) (Only on Non US Market)	Nedeltran, Panectyl, Repeltin, Therafene, Theraligene, Theralen, Theralene, Vallergan, Vanectyl, Temaril	Antihistamine	Allergy
Apalutamide	Erleada	Nonsteroidal antiandrogen	Cancer (prostate)
Apomorphine	Apokyn, Ixense, Spontane, Uprima	Dopamine agonist	Parkinson's disease
Aripiprazole	Abilify, Aripiprex	Antipsychotic, atypical	Schizophrenia, depression (adjunct)
Artemether/Lumefantrine	Coartem	Anti-malarial	Marlaria
Artenimol/piperaquine (Only on Non US Market)	Eurartesim	Antimalarial	Malaria
Asenapine	Saphris, Sycrest	Antipsychotic, atypical	Schizophrenia
Atomoxetine	Strattera	CNS stimulant	ADHD
Bedaquiline	Sirturo	Antibiotic	Tuberculosis, Multi-drug resistant

Bendamustine	Treanda, Treakisym, Ribomustin, Levact	Anti-cancer	Cancer (Leukemia, lymphoma)
Benperidol (Only on Non US Market)	Anquil, Glianimon	Antipsychotic	Schizophrenia
Betrixaban	Bevyxxa	Anticoagulant	Anticoagulant
Bortezomib	Velcade, Bortecad	Proteasome inhibitor	Cancer (multiple myeloma,lymphoma)
Bosutinib	Bosulif	Anti-cancer	Cancer (leukemia)
Buprenorphine	Butrans, Belbuca, Bunavail, Buprenex, Subutex, Suboxone, Zubsolv	Opioid agonist	Narcotic addiction and pain
Cabozantinib	Cometriq	Anti-cancer	Cancer (renal cell)
Capecitabine	Xeloda	Anti-cancer	Cancer (GI, Breast)
Carbetocin (Only on Non US Market)	Pabal, Lonactene, Duratocin	Uterotonic	Uterine atony
Ceritinib	Zykadia	Anti-cancer	Cancer (Lung)
Clofazimine (Only on Non US Market)	Lamprene	Antibiotic	Leprosy
Clotiapine (Only on Non US Market)	Entumine	Antipsychotic, atypical	Psychosis
Clozapine	Clozaril, Fazaclo, Versacloz	Antipsychotic, atypical	Schizophrenia
Cobimetinib	Cotellic	Anti-cancer	Cancer (Melanoma)
Crizotinib	Xalkori	Anti-cancer	Cancer (Non-small cell lung cancer, metastatic)
Cyamemazine (Cyamepromazine) (Only on Non US Market)	Tercian	Antipsychotic	Schizophrenia, sedation
Dabrafenib	Tafinlar	Anti-cancer	Cancer (melanoma)
Dasatinib	Sprycel	Anti-cancer	Cancer (leukemia)

Degarelix	Firmagon, Ferring	Anti-androgen	Cancer (prostate)
Delamanid (Only on Non US Market)	Deltyba	Antibiotic	Tuberculosis, Multi-drug resistant
Desipramine	Pertofrane, Norpramine	Antidepressant, Tricyclic	Depression
Deutetrabenazine	Austedo	Vesicular monamine transporter 2 inhibitor	Chorea (Huntington's disease)
Dexmedetomidine	Precedex, Dexdor, Dexdomitor	Sedative	Sedation
Dextromethorphan/Quinidine	Nuedexta	Unknown	Pseudobulbar affect
Dolasetron	Anzemet	Antiemetic	Nausea, vomiting
Efavirenz	Sustiva	Antiviral	HIV/AIDS
Eliglustat	Cerdelga	Glucosylceramide synthase inhibitor	Gaucher's disease
Encorafenib	Braftovi	BRAF inhibitor	Cancer (Melanoma)
Entrectinib	Rozlytrek	Anti-cancer	Cancer (Lung)
Epirubicin	Ellence, Pharmorubicin, Epirubicin Ebewe	Anti-cancer	Cancer
Eribulin mesylate	Halaven	Anti-cancer	Cancer (breast, metastatic)
Ezogabine (Retigabine)	Potiga, Trobalt	Anticonvulsant	Seizures, Partial
Felbamate	Felbatol	Anticonvulsant	Seizures
Fingolimod	Gilenya	Sphingosine phospate receptor modulator	Multiple Sclerosis
Fluorouracil (5-FU)	Adrucil, Carac, Efudex, Efudix	Anti-cancer	Cancer
Flupentixol (Only on Non US Market)	Depixol, Fluanxol	Antipsychotic	Schizophrenia
Gemifloxacin	Factive	Antibiotic	Bacterial infection

Gilteritinib	Xospata	Antineoplastic	Cancer (Acute Myeloid Leukemia)
Glasdegib	Daurismo	Anti-cancer	Cancer (Acute myeloid leukemia)
Granisetron	Kytril, Sancuso, Granisol	Antiemetic	Nausea, vomiting
Hydrocodone - ER	Hysingla™ ER, Zohydro ER	Analgesic	Pain, severe
Iloperidone	Fanapt, Fanapta, Zomaril	Antipsychotic, atypical	Schizophrenia
Imipramine (Melipramine)	Tofranil	Antidepressant, Tricyclic	Depression
Inotuzumab ozogamicin	Besponsa	Anti-cancer	Cancer (acute lymphocytic leukemia}
Isradipine	Dynacirc	Antihypertensive	Hypertension
Ivosidenib	Tibsovo	IDH1 inhibitor	Cancer (Acute myeloid leukemia)
Ketanserin (Only on Non US Market)	Sufrexal	Antihypertensive	Hypertension
Lacidipine (Only on Non US Market)	Lacipil, Motens	Calcium channel blocker	Hypertension
Lapatinib	Tykerb, Tyverb	Anti-cancer	Cancer (breast, metastatic)
Lefamulin	Xenleta	Antibiotic	Community acquired pneumonia
Lenvatinib	Lenvima	Anti-cancer	Cancer (Thyroid)
Leuprolide (Leuprorelin)	Lupron, Eligard, Viadur, Carcinil, Enanton, Leuplin, Lucrin, Procren, Prostap	Anti-androgen	Cancer (prostate)
Levetiracetam	Keppra	Anti-seizure	Epilepsy
Levomethadone (levamethadone) (Only on Non US Market)		Opioid	Opiate withdrawal syndrome

Lithium	Eskalith, Lithobid	Antimanic	Bipolar disorder
Lofexidine	Lucemyra	Alpha-2-adrenergic agonist, central	Opioid withdrawal syndrome
Lopinavir/Ritonavir	Kaletra, Aluvia	Antiviral	HIV/AIDS
Lumateperone	Caplyta	Antipsychotic, atypical	Schizophrenia
Lurasidone	Latuda	Antipsychotic, atypical	Schizophrenia, biopolar disorder and others
Maprotiline	Ludiomil	Anti-depressant, Tetracyclic	Depression
Melperone (Only on Non US Market)	Bunil, Buronil, Eunerpan	Antipsychotic, atypical	Schizophrenia
Memantine	Namenda XR	NMDA receptor antagonist	Alzheimer's disease
Mianserin (Only on Non US Market)	Tolvon	Anti-depressant	Depression
Midostaurin	Rydapt	Anti-cancer	Cancer (Acute myeloid leukemia)
Mifepristone	Korlym, Mifeprex	Progesterone antagonist	Pregnancy termination
Mirabegron	Myrbetriq	Beta3 adrenergic antagonist	Bladder spasm
Mirtazapine	Remeron	Antidepressant, Tetracyclic	Depression
Moexipril/Hydrochlorothiazide	Uniretic, Univasc	Antihypertensive	Hypertension, diuresis
Necitumumab	Portrazza	Anti-cancer	Cancer (Lung)
Nicardipine	Cardene	Antihypertensive	Hypertension
Nilotinib	Tasigna	Anti-cancer	Cancer (leukemia)
Norfloxacin	Noroxin, Ambigram	Antibiotic	Bacterial infection
Nortriptyline	Pamelor, Sensoval, Aventyl, Norpress, Allegron, Noritren, Nortrilen	Antidepressant, Tricyclic	Depression
Nusinersen	Spinraza	Antisense oligonucleotide	Spinal Muscular Atrophy
Ofloxacin	Floxin	Antibiotic	Bacterial infection

Oliceridine	Olinvyk	Analgesia	Pain
Osilodrostat	Isturisa	Aldosterone synthase inhibitor	Cushing's Disease
Osimertinib	Tagrisso	Anti-cancer	Cancer (EGFR pos. NSC Lung cancer)
Oxytocin	Pitocin, Syntocinon	Oxytocic	Labor stimulation
Ozanimod	Zeposia	Immunomodulation	Multiple Sclerosis
Paliperidone	Invega, Xepilon	Antipsychotic, atypical	Schizophrenia
Palonosetron	Aloxi	Antiemetic	Nausea, vomiting
Panobinostat	Farydak	Histone deacetylase inhibitor	Cancer, Multiple myeloma
Pasireotide	Signifor	Somatostatin analog	Cushings Disease
Pazopanib	Votrient	Anti-cancer	Cancer (renal cell, sarcoma)
Perflutren lipid microspheres	Definity, Optison	Imaging contrast agent	Diagnostic adjunct
Perphenazine	Trilafon, Etrafon/Triavil, Decentan	Antipsychotic	Schizophrenia
Pilsicainide (Only on Non US Market)	Sunrythm	Anti-arrhythmic	Arrhythmia
Pimavanserin	Nuplazid	Antipsychotic, atypical	Psychosis, Parkinson's Disease
Pipamperone (Only on Non US Market)	Dipiperon, Propitan, Dipiperal, Piperonil, Piperonyl	Antipsychotic	Schizophrenia
Pitolisant (Tiprolisant)	Wakix	Histamine 3 antagonist/inverse agonist	Narcolepsy
Pretomanid		Antitubercular	Tuberculosis, extensively drug resistant
Primaquine phosphate		Antimalarial	Malaria
Promethazine	Phenergan	Antipsychotic / Antiemetic	Nausea, vomiting

Prothipendyl (Only on Non US Market)	Dominal, Largophren, Timoval, Timovan, Tumovan	Antipsychotic	Schizophrenia
Remimazolam	Byfavo	Sedative	Sedation
Ribociclib	Kisqali	Anti-cancer	Cancer (breast)
Rilpivirine	Edurant, Complera, Eviplera, Juluca	Antiviral	Viral infection (HIV/AIDS)
Romidepsin	Istodax	Histone deacetylase inhibitor	Cancer (lymphoma)
Rucaparib	Rubraca	PARP inhibitor	Cancer
Saquinavir	Invirase(combo)	Antiviral	Viral infection (HIV/AIDS)
Selpercatinib	Retevmo	Kinase inhibitor	Lung cancer
Sertindole (Only on Non US Market)	Serdolect, Serlect	Antipsychotic, atypical	Schizophrenia, anxiety
Siponimod	Mayzent		Multiple Sclerosis
Sorafenib	Nexavar	Anti-cancer	Cancer (liver, renal cell, metastatic thyroid)
Sunitinib	Sutent	Anti-cancer	Cancer (GIST, renal cell, pNET)
Tacrolimus	Prograf, Prograf, Advagraf, Protopic	Immunosuppressant	Immune suppression
Tamoxifen	Nolvadex, Istubal	Anti-cancer	Cancer (breast)
Tazemetostat	Tazverik	Anti-cancer	Epithelioid sarcoma
Telavancin	Vibativ	Antibiotic	Bacterial infection
Telithromycin	Ketek	Antibiotic	Bacterial infection
Tetrabenazine	Nitoman, Xenazine	Vesicular Monoamine Transporter 2 Inhibitor	Chorea (Huntington's disease)
Tiapride (Only on Non US Market)	Tiapridal, Italprid, Sereprile, Tialaread, Tiaryl,	Selective D2, D3 dopamine antagonist	Alcoholism, withdrawal

	Tiaprim, Tiaprizal, Sereprid, Tiapridex		
Tipiracil/Trifluridine	Lonsurf	Anti-cancer	Cancer (Metastatic colorectal)
Tizanidine	Zanaflex, Sirdalud	Muscle relaxant	Muscle spasticity
Tolterodine	Detrol, Detrusitol	Muscle relaxant	Bladder spasm
Toremifene	Fareston	Estrogen agonist/antagonist	Cancer (breast, metastatic)
Tramadol	Crispin, Ralivia ER, Ralivia Flashtab, Tramadolum, Tramal, Tramodol, Tridural, Ultram, Ultram ER, Zydol, Ixprim, Zaldiar, Topalgic	Analgesic	Pain
Trimipramine	Surmontil, Rhotrimine, Stangyl	Antidepressant, Tricyclic	Depression
Tropisetron (Only on Non US Market)	Navoban, Setrovel	Antiemetic	Nausea, vomiting
Valbenazine	Ingrezza	Vesicular monamine transporter 2 inhibitor	Tardive Dyskinesia
Vardenafil	Levitra	Phosphodiesterase 5 inhibitor	Erectile dysfunction
Vemurafenib	Zelboraf	Anti-cancer	Cancer (melanoma)
Venlafaxine	Effexor, Efexor	Antidepressant, SNRI	Depression
Vorinostat	Zolinza	Histone deacetylase inhibitor	Cancer (lymphoma)

Zotepine (Only on Non US Market)	Losizopilon, Lodopin, Setous, Zoleptil	Antipsychotic, atypical	Schizophrenia
Zuclopenthixol (Zuclopentixol) (Only on Non US Market)	Cisordinol, Clopixol, Acuphase	Antipsychotic	Psychosis

Appendix F: Table 1.Compiled list CYP3A4 inhibitors [US FDA (2019);Flockhart (2007)]

This table is prepared to provide examples of clinical index inducers and is not intended to be an exhaustive list.

	Strong inhibitors	Moderate inhibitors	Weak inhibitors	Inhibitor Strength TBD
CYP3A4	boceprevir, clarithromycin cobicistat, danoprevir and ritonavir[c], elvitegravir and ritonavir[c], grapefruit juice[a], idelalisib, indinavir and ritonavir[c], itraconazole, ketoconazole, lopinavir, nefazadone, nelfinavir, ribociclib, ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) [c], posaconazole, ritonavir[c], saquinavir and ritonavir[c], telaprevir, tipranavir and ritonavir[c], telithromycin, troleandomycin, voriconazole	aprepitant, ciprofloxacin, conivaptan[b], crizotinib, cyclosporine, diltiazem[d], dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit juice, imatinib, netupitant/palonosetron, tofisopam[e], verapamil	atomoxetine, chlorzoxazone, cilostazol, cimetidine, clotrimazole, esomeprazole, fosaprepitant, lesinurad, istradefylline, ivacaftor, lomitapide, omeprazole, pantoprazole, ranitidine, ranolazine, ticagrelor	amiodarone, chloramphenicol, delaviridine, diethyl-dithiocarbamate (DDTC), gestodene[e], mibefradil[e], mifepristone, norfloxacin, star fruit

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
[b] The classification is based on studies conducted with intravenously administered conivaptan.
[c] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
[d] Diltiazem increased AUC of certain sensitive CYP3A substrates (e.g., buspirone) more than 5-fold.” [US FDA (2019)]
[e] Off the US market; not approved in US
Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.”[US FDA (2019)]

Appendix G continued: Table 2. Compiled list of CYP3A4 inducers [US FDA (2019); Flockhart (2007)]

This table is prepared to provide examples of clinical index inducers and is not intended to be an exhaustive list.

	Strong inducers	Moderate inducers	Weak inducers	Inhibitor Strength TBD
CYP3A	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[(a)]	bosentan, efavirenz, etravirine, nafcillin, phenobarbital, primidone, rifabutin	armodafinil, modafinil, rufinamide, oxcarbazepine	brigatinib, nevirapine, pioglitazone

[(a)] The effect of St. John's wort varies widely and is preparation dependent.

Note: Strong, moderate, and weak inducers are drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%, ≥50% to <80%, and ≥20% to <50%, respectively." [US FDA (2019)]

References:

1. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). https://drug-interactions.medicine.iu.edu. Accessed 11/04/20.

2. US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. Accessed 11/04/20.