8.1.1 Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)	**Revised to include:** **Revised "How Supplied" text**

This submission is in response to Mr. Howells' May 23, 2022 notice regarding updates to the trametinib tablet formulation pharmaceutical information.

NCI Protocol #: *9525*

Local Protocol #: *13-505*

TITLE: An open label, two-part, phase Ib/II study to investigate the safety, pharmacokinetics, pharmacodynamics, and clinical activity of the MEK inhibitor trametinib and the BCL2-family inhibitor navitoclax (ABT-263) in combination in subjects with KRAS or NRAS mutation-positive advanced solid tumors

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NCI Supplied Agent(s):
Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)
Navitoclax; NSC 750238)

IND#: 119585

IND Sponsor: DCTD, NCI

Other Agent(s): *N/A*

Investigational Agent	**IND#**	**IND Sponsor**
N/A		

Investigational Device	**IDE#**	**IDE Sponsor**
N/A		

Protocol Type / Version # / Version Date: *Amendment 21; Version 23, Revised* July 22, 2022

SCHEMA

Study Design

This study is a two-part Phase 1b/Phase 2 clinical trial of the MEK inhibitor trametinib in combination with the BCL2-family inhibitor navitoclax.

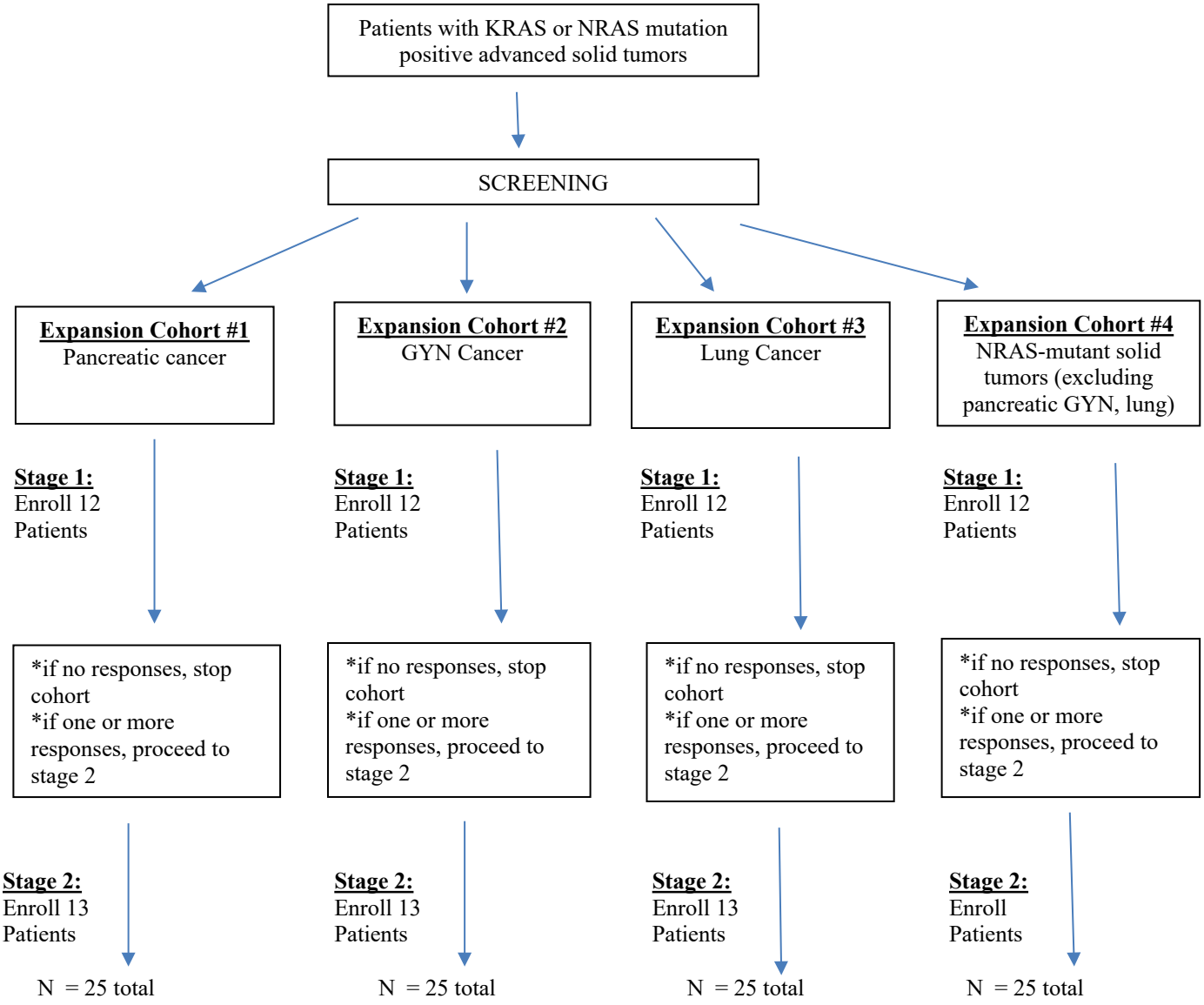
In Part 1 (Phase 1b), this study aims to determine the maximal tolerated dose (MTD) of trametinib and navitoclax that can be given safely in combination in order to determine a recommended phase 2 dose (RP2D). Patients with advanced or metastatic solid tumors that have been determined to harbor KRAS or NRAS mutations by CLIA-approved laboratory assay will be eligible. Prior therapy for advanced or metastatic disease will be allowed. Pharmacokinetic (PK) assays will be carried out to assess the interaction of these two drugs, and these data will be correlated with clinical toxicities as dose escalation is undertaken. Paired pre-treatment and on-treatment tumor biopsies will be obtained to assess the pharmacodynamic response to therapy.

Part 2 is a single-arm Phase 2 study of trametinib in combination with navitoclax at the RP2D determined in the Phase 1b trial above. Patients with KRAS mutation or NRAS mutations positive solid tumors will be enrolled into up to 4 different disease-specific expansion cohorts. These will include expansion cohorts for patients with KRAS or NRAS mutation-positive: (1) Pancreatic cancer, (2) GYN cancer, (3) lung cancer, (4) all other NRAS-mutant solid tumor types exclusive of pancreatic, GYN, and lung cancers.

Part 1 (Phase 1b)

Dose Escalation Schedule		
Dose Level	**Dose**	
	Trametinib (mg) PO daily	Navitoclax **(mg) PO daily**
Level 1	1	150
Level 2	1.5	150
Level 3	1.5	200
Level 4	2	200
Level 5	2	250
Level 6	2	300
Level 7	2	325

Part 2 (Phase 2)



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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 *Part 1 (Phase 1b) Primary objectives*

To determine the dose-limiting toxicities of trametinib in combination with navitoclax, and the maximal doses at which both drugs can be safely administered together.

1.1.2 *Part 2 (Phase 2) Primary objectives*

To determine the response rate of the combination of trametinib and navitoclax in subjects with KRAS or NRAS mutation-positive advanced or metastatic solid tumors in disease-specific expansion cohorts.

To confirm the safety and tolerability of trametinib and navitoclax in combination at the recommended phase 2 dose (RP2D) determined in the Phase 1b portion.

1.2 Secondary Objectives

1.1.3 *Part 1 (Phase 1b) Secondary Objectives*

To determine the pharmacokinetics of both drugs administered together.

To assess for evidence of response to therapy.

To evaluate the pharmacodynamic response to therapy in tumor biopsies

1.1.4 *Part 2 (Phase 2) Secondary Objectives*

To evaluate the pharmacodynamic response to therapy in tumor biopsies (first 15 patients enrolled overall)

2. BACKGROUND

2.1 Study Diseases

KRAS and NRAS mutation-positive advanced solid malignancies: RAS family members are the most frequently mutated oncogenes in human cancer. KRAS mutations occur in ~20% of all cancers, with particularly high frequency in pancreatic (~90%), colorectal (~40%), and lung

(~30%) cancers (Malumbres et al., 2003; Montagut et al., 2009). NRAS mutations are present in melanoma (~20%) and colorectal cancer (~10%). However, no effective therapies exist for RAS-mutant cancers, largely because RAS itself has proven difficult to target directly with small molecules (Young et al., 2009). Targeting single RAS effector pathways (e.g. MEK) has also failed to induce clinical responses (Rinehart et al., 2004; Adjei et al, 2008), likely because RAS activates multiple critical effector pathways, such as the MEK-ERK, PI3K-AKT, and NF-κB pathways (Montagut et al., 2009).

2.2 CTEP IND Agent(s)

2.2.1 Trametinib Dimethyl Sulfoxide (GSK1120212B)

The RAF-MEK-ERK pathway plays a critical role in multiple cellular functions. Activation of the pathway can result from activation/mutations of the upstream receptor tyrosine kinases (RTKs) and RAS, or upregulation/mutations in RAF and MEK. Upon activation, RAF acts as the MAPK kinase and activates MAPKK (MEK1/2), which in turn catalyze activation of the effectors ERK1/ERK2. Once activated, ERK1/2 translocate into the nucleus and phosphorylate a number of effector proteins and transcriptional factors that regulate cell proliferation, motility, differentiation, and survival.

Trametinib is one of the several MEK inhibitors in clinical development. On May 29, 2013, the U.S. Food and Drug Administration (FDA) approved trametinib for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutations as detected by an FDA-approved test (U.S. Food and Drug Administration, 2013). On January 10, 2014, the Food and Drug Administration granted accelerated approval to trametinib and dabrafenib for use in combination to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test (U.S. Food and Drug Administration, 2014).

Experience to date indicates that MEK is a valid target. In a phase III trial comparing trametinib with dacarbazine or paclitaxel in patients with BRAF V600E or V600K mutant metastatic melanoma, trametinib demonstrated a significantly better response rate, progression-free survival, and overall survival (Flaherty *et al.*, 2012). However, single agent activities are limited. Extensive research is underway to identify the patient selection markers and develop rational combination strategies. Preclinical studies have provided strong rationale and proof of principle for combination of MEK inhibitors with RTK inhibitors (EGFR or IGF-1R) (Gopal *et al.,* 2010; Ebi *et al.,* 2011), PI3K/AKT inhibitors (Engelman *et al.,* 2008; Hoeflich *et al.,* 2009), and mTOR inhibitors. On the other hand, the optimal dose/schedule and patient selection criteria for combination regimens have not been defined. Phase 1 results for a number of combinations have been reported, including AZD6244 + MK2206 (Tolcher *et al.,* 2011) and GDC-0973 + GDC-094 (MEK + PI3K inhibitor) (Bendell *et al.,* 2011).

The most up-to-date preclinical and clinical study information for trametinib can be found in the GSK1120212 (trametinib) Investigator's Brochure (2013).

2.2.1.1 Mechanisms of Action and Preclinical Data with Trametinib

Trametinib is a dimethyl sulfoxide (DMSO) solvate compound (ratio 1:1) with potent, allosteric and ATP non-competitive inhibition of MEK1/2 (IC_{50} of 0.7 and 0.9 nM against MEK1 and MEK2, respectively) (Gilmartin *et al.,* 2011). Trametinib inhibited MEK1/2 kinase activity and prevented RAF-dependent MEK phosphorylation (S217 for MEK1), producing prolonged pERK1/2 inhibition. Trametinib showed better potency against unphosphorylated MEK1/2 (u-MEK1/2) when compared with preactivated diphosphorylated MEK (pp-MEK), suggesting that u-MEK affords a higher affinity binding site for trametinib than does pp-MEK.

The specificity of trametinib was confirmed against a panel of 183 kinases, including MEK5 (the closet kinase homolog to MEK1/2), CRAF, BRAF, ERK1, and ERK2 (Yamaguchi *et al.,* 2011). Trametinib demonstrated equal potency against activated MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of RAF-mediated MEK1 activation (IC_{50} = 0.60 nM) over pMEK1 kinase activity (IC_{50} = 13 nM) (Investigator's Brochure, 2012a).

BRAF-mutant Colo205, A375P F11s, and HT-29 human tumor xenograft mouse models showed the most significant mean tumor growth inhibition (TGI) (80% to 87%) at 3.0 mg/kg trametinib, with multiple complete and partial tumor regressions. In the Colo205 model, tumor regression was observed even at a dose of 0.3 mg/kg (Yamaguchi *et al.,* 2011). Two KRAS-mutant xenograft models, HCT-116 and A549, also showed significant TGI (83% and 75%) but without significant tumor regressions (Gilmartin *et al.,* 2011). As predicted by cell proliferation assays, tumor xenograft lines with wild-type (wt) RAF/RAS (PC3, BxPC3, and BT474) were much less sensitive, showing only modest TGI (44-46%) with no tumor regressions.

Pharmacodynamic studies were performed in mice treated with trametinib for 14 days (Gilmartin *et al.,* 2011). In the A375P F11s xenograft model, the first dose of trametinib (3 mg/kg) significantly reduced pERK for more than 8 hours on Day 1. pERK inhibition was more sustained (over 24 hours) after the Day 7 dose, probably due to an increase in the steady-state levels of trametinib after repeated doses. The average C_{max} in blood was 1,410 nM on Day 7, with an estimated half-life ($t_{1/2}$) of 33 hours. In addition, immunohistochemistry (IHC) also confirmed inhibition of cell proliferation (reduced Ki67) and G1 cell cycle arrest (elevated p27Kip1/CDKN1B) following 4 days of treatment.

2.2.1.2 Clinical Pharmacokinetics (PK) and Activity of Trametinib

FTIH Phase 1 Trial of Trametinib Monotherapy (MEK111054)
There are 3 parts in this ongoing study. Part 1: The dose-escalation portion involves administration of trametinib (repeat doses of 0.125 mg to 4.0 mg) to patients with solid tumors or lymphoma in one of three schedules - (1) QD for 21 days followed by 7 days without drug, (2) loading dose on Day 1 or Day 1-2, followed by QD with the designated dose, or (3) QD dosing without a drug holiday. Part 2: cohort expansion at the recommended phase 2 dose (RP2D) for pancreatic cancer, melanoma, NSCLC, CRC, or any BRAF mutation-positive cancer. Part 3: expansion to characterize the biologically active range of trametinib via analysis of pharmacodynamic biomarkers (biopsies or FDG-PET).

The dose escalation part and some of the cohort expansion components have been completed. The MTD of trametinib was established as 3 mg QD, but the recommended phase 2 dose (RP2D) was chosen at 2 mg QD based on tolerability of repeated cycles (Infante *et al.,* 2010).

PK and metabolism of trametinib:
PK measurements were conducted under fasting conditions. After a single dose (Day 1), AUC_{0-24} and C_{max} values were dose-proportional up to 6 mg, lower than dose proportional following 8 mg, and greater than dose proportional following the 10 mg dose. Median T_{max} was 1.5 hours.

After repeat doses (Day 15), trametinib accumulated with a mean accumulation ratio of 6.6 at the RP2D of 2 mg QD. Between-subject variability in exposure ranged from 27-50% for C_{max} and 20-41% for AUC_{0-24} across all dosing regimens. The effective $t_{1/2}$ was approximately 4.5 days, and steady state was reached by approximately Day 15. Trametinib had a small peak:trough ratio of ~2 (Infante *et al.,* 2010). At 2 mg QD on Day 15, mean AUC_{0-24} was 376 ng•h/mL and C_{max} 23 ng/mL, and the mean trough concentrations ranged from 10.0 to18.9 ng/mL. The long half-life and small peak:trough ratio of trametinib allowed constant target inhibition within a narrow range of exposure.

Drug-drug interactions:
Trametinib is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways (Investigator's Brochure, 2012a). The deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Trametinib has an overall low potential for drug-drug interactions.

Pharmacodynamic effect and biomarkers:
The relationship between dose and tumor biomarkers such as pERK, Ki67, and p27, were evaluated in patients with BRAF or NRAS mutation-positive metastatic melanoma

(Investigator's Brochure, 2012a). In general, increasing exposures and/or doses provided greater pharmacodynamic effects. The median change observed at a dose of 2 mg QD was 62% inhibition of pERK, 83% inhibition of Ki67, and a 175% increase in p27.

Antitumor Activity of Trametinib Monotherapy
In the FTIH phase 1 trial, 14 patients with BRAF-mutant melanoma received trametinib at 2 mg QD (2 mg/day continuously, or 2 mg for 21 days followed by a 1 week break). The overall objective response rate (ORR) was 43% (6/14), including 2 complete responses (CRs) (Investigator's Brochure, 2012a). In 9 patients with BRAF wt melanoma, 2 patients achieved a partial response (PR), and 3 stable disease (SD) (Infante *et al.,* 2010). In 26 evaluable pancreatic cancer patients, there were 2 PRs (1 PR was KRAS mutation-positive) and 11 SD (2 achieved ≥20% tumor reduction) (Messersmith *et al.,* 2011). Among the 27 CRC patients (without selection of RAS or RAF mutations), 8 SD were observed.

In a phase 3 trial, patients with unresectable stage IIIC or IV cutaneous melanoma with a BRAF V600E or V600K mutation were randomized (2:1) to trametinib (2 mg, PO, QD) or chemotherapy (dacarbazine or paclitaxel) (Flaherty *et al.*, 2012). There were 322 patients in the intention-to-treat (ITT) population, of whom 273 (85%) were in the primary efficacy population (patients with $BRAF^{V600E}$-positive cancer who did not have brain metastases at baseline). In the ITT analyses, the ORR was 22% in the trametinib group and 8% in the chemotherapy group; the median duration of PFS was 4.8 months in the trametinib group as compared with 1.5 months in the chemotherapy group; and the 6-month OS rate was 81% in the trametinib group and 67% in the chemotherapy group.

Antitumor Activity of Trametinib in Cancer Other Than Melanoma
In a phase 1/2 monotherapy study, acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients were given trametinib at dose levels from 1-2 mg QD. Drug-related AEs in 45 patients were similar to that observed in patients with solid tumors, and 2 mg PO QD was selected for further investigation in this patient population. Twelve patients (23%) withdrew due to an AE, including cardiac failure (2) and infection (2). Efficacy was reported in 39 patients (Borthakur *et al.,* 2010). The best response in 13 patients with KRAS or NRAS mutations included 3 CRs (23%), 7 SD (54%), and 1 PD (progressive disease) (5%). In 26 patients with wild-type RAS or an unknown mutation, there were 2 PRs (8%).

2.2.1.3 Trametinib Safety Profile

A **Comprehensive Adverse Events and Potential Risks (CAEPR)** list using NCI Common Terminology Criteria for Adverse Events (CTCAE 5.0) terms is included in Section 7.1 of the protocol.

Based on available AE data from clinical studies involving trametinib to date, the most common toxicities are rash and diarrhea. Rash and diarrhea are common, class-effect

toxicities for MEK inhibitors. In addition, visual impairment and left ventricular ejection fraction (LVEF) reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with trametinib as well as other MEK inhibitors.

AEs of special interest:
Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (*i.e.*, have been observed with other MEK inhibitors) or are potentially life-threatening (Investigator's Brochure, 2013). The following sections provide integrated summaries for these AEs across different clinical trials, with emphasis on trials using trametinib as monotherapy, especially at the RP2D of 2 mg.

Refer to dose modification guidelines for the toxicities for which they are addressed in Section 6.

Rash: Rash was a common AE observed across different dose levels and in different combinations (Investigator's Brochure, 2013). At the 2 mg dose, rash was seen in 27% to 78% of patients in different trials. Of the ~370 subjects with rash AEs at the 2 mg monotherapy dose (including crossover subjects) in five studies, the majority of rash AEs were grades 1 or 2 (24% to 73%); 0% to 9% of patients experienced grade 3 rash AEs, and four patients had a grade 4 rash AE.

In a randomized phase 3 trial of trametinib vs. chemotherapy, the overall incidence of skin toxicity (including rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema) was 87% in patients treated with trametinib and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients on the trametinib arm, most commonly for secondary infections of the skin. The median time to onset of skin toxicity was 15 days (range: 1 to 221 days), and median time to resolution was 48 days (range: 1 to 282 days). Dose reduction was required in 12% for skin toxicities, and permanent discontinuation of trametinib was required in 1% of patients.

Diarrhea: At the 2 mg monotherapy dose, 33% to 58% of patients in five trials had diarrhea (Investigator's Brochure, 2013). Of ~320 subjects (including crossover subjects) with diarrhea at this dose, the majority of diarrhea AEs were grade 1 or 2 in severity (33% to 56% of all study patients); 17 patients had grade 3 diarrhea, and none had grade 4 diarrhea.

Visual disorders: At the 2 mg monotherapy dose, 4% to 21% of the patients in five trials experienced visual disorders (Investigator's Brochure, 2013). Of the 85 total subjects (including crossover subjects) experiencing visual disorders at this dose level, the majority of visual disorders were grades 1 or 2 (4% to 20% of all study patients); six patients experienced grade 3 visual disorders, and one patient experienced a grade 4

visual disorder.

- *Retinal Pigment Epithelial Detachment (RPED):* Also known as chorioretinopathy, RPED is a visual impairment due to fluid accumulation under the retina and causes blurry vision. There were five cases of RPED, previously termed central serous retinopathy, reported from the integrated trametinib safety population consisting of subjects treated with trametinib 2 mg once daily from five studies (Investigator's Brochure, 2013). As of 23 June 2013, 14 cases of RPED were reported across the entire trametinib program amongst subjects treated with trametinib either as monotherapy or in combination with other anti-cancer agents (including cases from a MEK/BRAF combination study).

- *Retinal vein occlusion (RVO):* As of 23 June 2013, a total of four cases of RVO were reported across the entire trametinib program (including one case from a MEK/BRAF combination study) (Investigator's Brochure, 2013). All cases of RVO occurred in one eye only. Study drug was stopped at time of diagnosis in all cases. There was a decrease of visual acuity in two subjects with central RVO (CRVO) while the other two subjects had no meaningful decrease of visual acuity. In the two subjects with CRVO, local treatment with intravitreal injections of anti-VEGF antibodies was initiated within 2 weeks after RVO diagnosis, and visual acuity improved in one subject and restored to baseline conditions in another subject, at the time of the data cutoff. Three of these four cases were considered related to study treatment by the investigators.

Hepatic disorders: Abnormalities of liver enzymes and bilirubin have been observed with administration of trametinib (Investigator's Brochure, 2013). However, assessment of these cases was often confounded by co-morbid conditions (such as biliary obstruction), concomitant use of other potentially hepatotoxic drugs, and liver metastases. At the 2 mg monotherapy dose, 8% to 34% of patients in five trials had LFT abnormalities. Of the 96 total patients (including crossovers) with LFT changes, the majority were grade 1 or 2 in severity (4% to 20% of all study patients); 26 had grade 3 events, and 6 patients had grade 4 events.

Cardiac-related AEs: At the 2 mg monotherapy dose, 3% to 21% of the subjects in six studies had cardiac-related AEs (Investigator's Brochure, 2013). Of the 65 total subjects (including crossover subjects) experiencing cardiac-related AEs at the 2.0 mg monotherapy dose in five of the studies, the majority of cardiac-related AEs were grades 1 or 2 in severity (0% to 16% of all study subjects); 18 subjects had grade 3 cardiac-related AEs, and no subjects had Grade 4 cardiac-related AEs in any study. No subject in one study, which evaluated the effect of repeat oral dosing of trametinib 2 mg QD on cardiac repolarization in subjects with solid tumors, had cardiac-related AEs. One study subject receiving trametinib 2 mg QD had grade 5 (fatal) acute cardiac failure, with evidence of massive tumor invasion of the heart; this AE was considered not drug-related by the investigator.

In the phase 3 trial of trametinib vs. chemotherapy in patients with melanoma (MEK114267), cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased LVEF) occurred in 7% (14/211) of patients treated with trametinib, and in no patients in the chemotherapy arm. Cardiomyopathy was identified within the first month of treatment in five of these 14 patients; median onset of cardiomyopathy was 63 days (range: 16 to 156 days). Cardiomyopathy resolved in 10 of these 14 (71%) patients. Cardiac monitoring should be included in trametinib protocols, to include LVEF assessment by echocardiogram or MUGA scan at baseline, one month after initiation of trametinib and then at 2- to 3-month intervals while on treatment. Refer to dose modification guidelines for cardiac AEs in the event of LVEF decline or symptomatic cardiac AEs.

Pneumonitis: At the 2 mg monotherapy dose, 0% to 4% of the subjects in five studies had pneumonitis (Investigator's Brochure, 2013). Of the nine total subjects (including crossovers) experiencing pneumonitis AEs at this dose, three subjects had grade 1 or 2 pneumonitis and six subjects had grade 3 pneumonitis.

Embryofetal toxicity: Based on its mechanism of action, trametinib can cause fetal harm when administered to a pregnant woman. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Incidence of common AEs reported from a phase III trial of trametinib vs. chemotherapy in patients with advanced melanoma:

Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, or current evidence of Class II or greater congestive heart failure (New York Heart Association) were excluded from this trial. Selected adverse reactions (AR) occurring in patients receiving trametinib as compared to patients in the chemotherapy arm are listed as below:

Table: Selected adverse reactions (ARs) occurring in ≥10% of patients receiving trametinib AND at a higher incidence than in the chemotherapy arm (high in the trametinib arm compared with chemotherapy by ≥5% in overall incidence or by ≥2% grade 3 or 4 AEs)

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Adverse Reactions	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Pruritis	10	2	1	0

Paronychia	10	0	1	0
Gastrointestinal disorders				
Diarrhea	43	0	16	2
Stomatitis	15	2	2	0
Abdominal pain	13	1	5	1
Vascular disorders				
Lymphedema	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage	13	<1	0	0

Table: Percent-patient incidence of laboratory abnormalities occurring at a higher incidence in patients treated with trametinib versus chemotherapy (between-arm difference of ≥5% [all grades] or ≥2% [grades 3 or 4])

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Preferred term	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Increased aspartate aminotransferase (AST)	60	2	16	1
Increased alanine aminotransferase (ALT)	39	3	20	3
Hypoalbuminemia	42	2	23	1
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

Other clinically important adverse reactions observed in ≤10% of patients (n=329) treated with trametinib were: nervous system disorders (dizziness, dysgeusia), ocular disorders (blurred vision, dry eye), infections and infestations (folliculitis, rash pustular, cellulitis), cardiac disorders (bradycardia), gastrointestinal disorders (xerostomia), and musculoskeletal and connective tissue disorders (rhabdomyolysis).

2.2.1.4 Clinical Experience with the Combination of Trametinib + Dabrafenib

Trametinib has previously been evaluated in combination with other targeted therapies. Experience with the combination of trametinib and the BRAF inhibitor dabrafenib is summarized below. Preliminary data on 45 patients participating in the phase 1/2 study of dabrafenib and trametinib, BRF113220, have been reported (Infante *et al.*, 2011).

PK:
The plasma levels of dabrafenib were higher in combination with trametinib as compared to that with monotherapy. Geometric mean Day 15 AUC of dabrafenib in combination ranged from 3539 to 5187 ng•hr/mL, and the AUC observed in the monotherapy study was 2619 ng•hr/mL. Further data are required to understand this difference.

PK of trametinib did not appear to be affected by the addition of dabrafenib. Preliminary results showed that the geometric mean dose-normalized $AUC_{0-\tau}$ (CV%) for trametinib

(dose normalized for the 2.0 mg QD dose) in combination with dabrafenib at 150 mg BID was 302 ng•hr/mL (n=17; 35%) on Day 15. Historical PK data from the trametinib FTIH study (MEK111054) indicated a mean Day 15 $AUC_{0-\tau}$ (CV%) of 360 ng•hr/mL (31%).

Safety and the RP2D for the combination of trametinib and dabrafenib
One DLT of a recurrent grade 2 neutrophilic panniculitis occurred, and pyrexia was common (51%). The RP2D was 150 mg BID dabrafenib plus 2 mg QD trametinib (both agents at the RP2D for single agent). Of the 137 patients enrolled, 32 patients were treated at the RP2D. SAEs experienced by more than one patient include: pyrexia (5%), hypotension (4%), nausea (3%), and 2% of patients had a constellation of AEs including vomiting, dehydration, or renal failure. The only grade 4 AE was a sepsis-like syndrome with fever/hypotension. Grade 3 AEs included generalized rash (n=2, 4%) and neutropenia (n=2, 4%). Skin toxicity (rash) occurred in 9 (20%) patients. Of note, the rate of SCC was 2% in this study. A single case of grade 5 hyponatremia was reported. Other common AEs are listed in the table below.

Summary of selected AEs experienced by ≥5% of patients regardless of causality in BRF113220 (treated at RP2D)

AE Term	Dose Escalation Cohort (150mg BID/2 mg QD) (n=31)
Any AE, n (%)	24 (77)
Pyrexia	10 (32)
Rash	4 (13)
Dermatitis acneiform	1 (3)
Hypotension	4 (13)

Activity
Among 77 evaluable patients with melanoma who had not received prior BRAF inhibitors, there were 43 responses (56%), including 4 CRs (5%) and 39 PRs (51%) (Weber *et al.*, 2012). Twenty-nine patients experienced SD, and three patients experienced PD. Patients were treated on four escalating dose levels of dabrafenib/trametinib (mg BID/mg QD): 75/1, 150/1, 150/1.5, 150/2. The confirmed RR for each dose level, respectively, was 67% (n=6), 64% (n=22), 48% (n=25), and 54% (n=24). Median PFS (months) for each of the first three dose levels, respectively, was 8.7, 8.3, and 5.5; PFS data are not mature for the fourth (150/2) dose level. Overall PFS was 7.4 months.

Currently, the randomized phase 2 portion (Part C) of the study of dabrafenib with or without trametinib has enrolled 162 patients as of September 1, 2011 (Investigator's Brochure, 2012b).

2.2.1.5 Clinical Experience with the Combination of Trametinib + GSK2141795 (AKT inhibitor) (TAC113886)

Trametinib has previously been evaluated in combination with other targeted therapies. Experience with the combination of trametinib and the AKT inhibitor GSK2141795 is summarized below. Twenty-three patients with advanced solid tumors received the combination using a zone-based escalation procedure enabling evaluation of multiple combination doses in parallel cohorts (Kurzrock *et al.,* 2011). While the RP2D for single agent for single agent trametinib and GSK2141795 are 2 mg/d and 75 mg/d, dose reductions were required for the combination. DLTs include grade 2 AST and ALT elevation, and grade 3 chest pain with sustained ventricular tachycardia; all DLTs were reversible with drug interruption. The most common AEs (≥10%) included nausea (26%), AST elevation (22%; grade 3/4, 9%), fatigue (22%) and rash (22%). Three MTDs were defined for variable dose ratios: 2 mg trametinib + 25 mg GSK2141795; 0.5 mg trametinib + 75 mg GSK2141795; and 1.5 mg trametinib + 50 mg GSK2141795. Three of 13 evaluable patients (unselected) had tumor shrinkage of 8% (ovarian), 16% (endometrial), and 17% (ovarian) after 8 weeks on study. The dose regime of 1.5 mg trametinib + 50 mg GSK2141795 will be considered for further development. Additional trials to explore alternate schedules (*e.g.*, intermittent) and pharmacodynamic markers are ongoing.

2.2.2 Navitoclax

Navitoclax is a novel small molecule Bcl-2 (B-cell lymphoma-2) family protein inhibitor that binds with high affinity to multiple anti-apoptotic Bcl-2 family proteins including Bcl-X_L (inhibition constant [K_i]<0.5 nM), Bcl-2 (K_i<1.0 nM), Bcl-w (K_i<1.0 nM), and Bcl-B (K_i<5.0 nM) (Investigator's Brochure, 2011).

The Bcl-2 family of genes encodes a group of closely-related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 homology (BH) domains (Cory and Adams, 2002; Borner 2003; Cory *et al*., 2003; Willis *et al*., 2003). The anti-apoptotic family members (Bcl-X_L, Bcl-2, Bcl-w, A-1, and Mcl-1) are characterized by four BH domains that are designated BH1-4. The pro-apoptotic proteins are subdivided into multidomain proteins (Bax and Bak) and the BH3-only proteins (Bad, Bik, Bid, Bim Hrk, Bmf, Noxa, and Puma). The interplay between these three groups of proteins serves as the gateway to the intrinsic apoptosis pathway.

The pro-apoptotic proteins Bax and Bak are direct mediators of apoptosis and are absolutely required for the initiation of the mitochondrial apoptosis pathway (Lindsten *et al.*, 2000; Wei *et al.*, 2001; Degenhardt *et al.*, 2002). Anti-apoptotic Bcl-2 family proteins (*e.g.*, Bcl-2 and Bcl-X_L) inhibit cytochrome c release by blocking Bax/Bak activation (Adams and Cory, 2001). The exact mechanism of action of Bcl-2 and Bcl-X_L has not been completely elucidated; however, it is known that it requires the ability to bind the pro-apoptotic Bcl-2 family members, and that the ratio of pro-apoptotic to anti-

apoptotic proteins is associated with cell survival (Yang and Korsmeyer, 1996; Fadeel *et al.*, 1999; Tsujimoto and Shimizu, 2000).

In contrast to other known oncogenes, Bcl-2 does not stimulate cellular proliferation, but rather inhibits programmed cell death by protecting cells from a wide variety of pro-apoptotic stimuli, including cytokine withdrawal, irradiation, cytotoxic drugs, heat, and deregulated oncogenes (Korsmeyer, 1999). Antiapoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, and are therefore compelling targets for antitumor therapy. Over expression of certain antiapoptotic Bcl-2 proteins is associated with increased tumor resistance to chemotherapy; thus, inhibition of these proteins might enhance response to such therapies and overcome resistance.

Based on data from company-sponsored studies in relapsed/refractory lymphoid malignancies, SCLC, and other solid tumors, the RP2D for single-agent studies in these indications should include a 7-day lead-in of navitoclax 150 mg PO, followed by 325 mg on Days 1-21 of a 21-day cycle. A phase 1 trial in CLL has obtained a RP2D of a 7-day lead-in of 100 mg/day followed by 250 mg on Days 1-21 of a 21-day cycle (Roberts *et al*., 2012).

Nonclinical Efficacy Studies

Preclinical models of therapy-resistant lymphoma support the biologic relevance of the Bcl-2 family of proteins in the pathogenesis of B-cell lymphomas. In three flank models of B-cell lymphoma (DoHH-2, WSU-DLCL2, and GRANTA-519) known to express high levels of Bcl-2, significant monotherapy activity was noted when navitoclax was administered at an oral dose of 100 mg/kg/day, once daily (QD) × 17 days (Investigator's Brochure, 2011). Tumor growth inhibition in these models ranged from 40% to 54% as compared to vehicle treated controls. The WSU-DLCL2 line had been isolated from a patient whose disease progressed following chemotherapy, radiation therapy, and bone marrow transplantation, and is reputed to be a model of therapy-resistant lymphoma.

Navitoclax has been tested *in vitro* against 68 cell lines spanning diverse tumor types and was found to display potent (concentration achieving 50% effect [EC_{50}] <1 μM) single-agent activity against small cell lung cancer (SCLC), follicular lymphoma, and leukemia-derived cell lines (Investigator's Brochure, 2011). These included 10 of 22 cell lines representing multiple leukemia and lymphoma types spanning both B-cell and T-cell malignancies, and 7 of 22 SCLC cell lines. In a panel (n=23) of cell lines examined by the Pediatric Preclinical Testing Program (PPTP), IC_{50} values of <1 μM were observed in 9 cell lines, including 3 acute lymphoblastic leukemia (ALL), 2 rhabdomyosarcoma, and 1 Ewing's sarcoma cell line (Lock *et al*., 2008). In addition, strong synergism was observed with DNA-damaging and antimitotic agents across multiple cell lines and tumor types (Investigator's Brochure, 2011). Strong synergism with DNA-damaging agents (etoposide, carboplatin) as well as with the proteasome inhibitor bortezomib was

observed in the A549 non-small cell lung cancer (NSCLC) cell line. Interestingly, in some cases, the degree of synergism was dependent on the ratio of the two compounds. For example, the synergism between navitoclax and carboplatin increased as the ratio of navitoclax to carboplatin decreased.

To assess the ability of navitoclax to directly induce apoptosis, the time course of caspase-3 activation was monitored in H146 cells as a function of navitoclax concentration (Investigator's Brochure, 2011). Navitoclax induced a concentration-dependent increase in caspase-3 activation with an EC_{50} of approximately 100 nM. Caspase-3 activity is rapidly induced in response to navitoclax treatment with near maximum activity by 6 hours. This is consistent with the time course for which cytotoxicity is observed in this cell line. Other apoptotic markers (cytochrome c release, phosphatidylserine externalization) were elevated in a navitoclax -dose-dependent manner, further supporting the hypothesis that navitoclax induces apoptosis, likely mediated through Bcl-2 family proteins.
Navitoclax was found to be active in 8 of 9 xenograft models of established SCLC, in which tumors were allowed to grow to an average volume of 200 to 250 mm^3 prior to initiation of therapy (Investigator's Brochure, 2011). When delivered at a dose of 100 mg/kg/day orally (PO) for 21 consecutive days, navitoclax exhibited highly significant activity in 3 models (H1963, H889, and H146). Complete tumor regression was observed in half of the mice bearing H146 tumors and all of the mice bearing either H889 or H1963 tumors. Significant antitumor activity, including partial responses (PRs; ≥50% shrinkage), was observed in an additional 5 models (H1417, H128, H211, H510, and H345). Using the same dose and schedule, navitoclax was also active against larger (440 mm^3), more vascular H146 tumors, inducing complete tumor regression in 3 of 10 mice and 1 confirmed tumor cure.

In panels of murine tumor xenograft models examined by the PPTP, single-agent navitoclax prolonged the event-free survival (EFS) period in 5 of 6 ALL models as well as in 9 of 35 solid tumor xenograft models examined (Lock *et al*., 2008). Complete responses (CRs) were seen in a B-precursor ALL xenograft and in both T-cell xenografts. Solid tumors that showed improved EFS included 2 of 5 rhabdomyosarcoma, 2 of 5 osteosarcoma, 2 of 6 neuroblastoma, 1 of 5 Ewing sarcoma, and 1 of 3 Wilms' tumor models, as well as the only ependymoma model tested.

Efficacious doses of navitoclax were determined from dose-response studies in the H146 SCLC flank tumor model after daily (Days 1-21) PO dosing of navitoclax. A dose of 50 mg/kg/day elicited tumor regression in 6 of 9 mice (2 CRs, 4 PRs) and was defined as the minimally efficacious dose. A dose of 100 mg/kg/day induced a high percentage of complete tumor regressions and was identified as the target dose. At the 200 and 300 mg/kg/day doses, 20% of the mice were cured, as no tumor was evident by histopathological examination at 125 days after inoculation. Plasma and tissue drug concentrations were determined following multiple (n = 3) QD PO dosing in the same strain of mouse utilized in the efficacy study. From this study, the minimally efficacious

plasma exposure for navitoclax in mice, as expressed by area under the concentration-time curve (AUC), was 53 μg•hr/mL, and the target AUC was 88 μg•hr/mL. Based on these data and on PK modeling, the predicted efficacious plasma exposure in humans is a maximum plasma concentration (C_{max}) of 6.5 μg/mL.

Nonclinical Toxicology

The primary effects of navitoclax on the hematopoietic systems of both rats and dogs were decreased circulating platelets and lymphocytes (Investigator's Brochure, 2011). These effects were dose-dependent and reversible, as were any effects secondary to platelet depletion. The decreased circulating lymphocytes consisted of CD4 and CD8 T cells in rats and dogs, with a primary effect seen on B cells in dogs. Other observed hematopoietic effects included reversible decreases in total white blood cell count and eosinophil count, primarily in the rat.

Macroscopic and microscopic changes indicative of lymphoid depletion occurred in lymphoid tissues at ≥30 mg/kg/day in rats and at ≥3 mg/kg/day in dogs, and were consistent with reductions in circulating lymphocytes (Investigator's Brochure, 2011). Affected lymphoid organs included lymph nodes and spleen (rats and dogs), thymus (rats only), and Peyer's patch (dogs only). Partial to complete reversibility of all effects on lymphoid tissue was noted.

Navitoclax had no clear adverse CNS effects in the rat and mouse at an intraperitoneally (IP) injected dose of 5 mg/kg (Investigator's Brochure, 2011). At doses of 10 mg/kg IP and higher, mild to moderate sedation occurred and latency to sleep increased after barbital injection. At doses of 25 mg/kg IP and higher, body temperature decreased as sedation became more pronounced. At 100 mg/kg IP, loss of traction was observed. Navitoclax produced no relevant effects on neurobehavioral function through the highest dose of 15 mg/kg (plasma concentrations of 137.9 ± 27.5 μg/mL).

Navitoclax does not pose a genotoxic risk, as it was negative in all genetic toxicity studies, and no effect on embryo-fetal development in rats or rabbits was observed (Investigator's Brochure, 2011).

In the Segment I male rat fertility study, navitoclax -related changes were limited to small and/or soft testes, decreased testis and epididymis weights, hypospermatogenesis, and reduced sperm motility and sperm counts at 30 mg/kg/day (top dose) following approximately 70 days of once daily oral dosing (Investigator's Brochure, 2011). In addition, time- and dose-dependent navitoclax -related effects were observed on the rat ovary. Ovarian atrophy (associated with ~58% decreased ovarian weights) was observed at the highest dose of 100 mg/kg in the 6-month study, characterized by reduction or absence or corpora lutea and reduction in number of developing follicles. Decreases in ovarian weights (up to ~29%) were observed at the lower doses in the 6-month study and in the shorter duration studies of 2 and 13 weeks in duration. These weight changes were

considered not to be adverse due to the absence of associated histopathologic findings. However, no effect on reproductive performance was observed in male or female rats. No impairment of fertility was observed in the female rat Segment I study at up to 100 mg/kg/day (high dose). In Segment II embryo-fetal development studies, once daily oral doses of navitoclax in time-mated female rats (high dose, 100 mg/kg/day) and rabbits (high dose, 200 mg/kg/day) were not teratogenic and did not have any effect on the embryo/fetal viability of offspring.

Clinical Safety Profile

Navitoclax is being investigated as a single agent and as a component of combination therapy. Trial M10-454, a biocomparison study, is fully enrolled. Additionally, three phase 1/2a studies have completed and published safety and tolerability data from the phase 1 dose-escalation portions of the studies, and have transitioned to the phase 2a portions of the study:

- M06-814, in patients with relapsed or refractory lymphoid malignancies (Wilson *et al*., 2010).
- M06-822, in patients with small-cell lung cancer (SCLC), pulmonary carcinoid, and other solid tumors (phase 1), and in patients with SCLC (phase 2a) (Gandhi *et al*., 2011; Rudin *et al*., 2012).
- M06-873, in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) (Roberts *et al*., 2012).

Thrombocytopenia has been the primary dose-limiting toxicity (DLT) in the clinical development of navitoclax. This has been observed nonclinically and is thought to be due to the pharmacodynamic effect of drug action (inhibition of the platelet-expressed homolog Bcl-X_L, leading to apoptosis) (Investigator's Brochure, 2011). Grade 3/4 thrombocytopenia was observed in 29 out of 55 patients in trial M06-814 (Wilson *et al*., 2010); 5 out of 47 patients in the phase 1 portion of trial M06-822 and 16 out of 39 SCLC patients in the phase 2a portion (Gandhi *et al*., 2011; Rudin *et al*., 2012); and 8 out of 29 patients in trial M06-873 (Roberts *et al*., 2012). Grade 4 thrombocytopenia and neutropenia were reversible via temporary suspension or dose reduction of navitoclax, and filgrastim for persistent grade 4 thrombocytopenia.

In all three trials, platelet count decreases occurred both on an intermittent dosing schedule (navitoclax administered PO QD on 14 consecutive days of a 21-day cycle) and on a continuous schedule (21 out of 21 days). Platelet counts reached their nadir soon (1-3 days) after the first dose of navitoclax, but with a rebound occurring even during the dosing period (Wilson *et al*., 2010; Gandhi *et al*., 2011). This recovery is thought to be due to a compensatory upregulation of megakaryocyte platelet production. As a result, clinical studies now employ a 7-day lead-in period at a reduced dose of navitoclax prior to administration of the full dose in Cycle 1. Use of the lead-in dose before a continuous dosing schedule has helped to reduce acute platelet nadirs and the incidence of grade 4 thrombocytopenia during the first cycle, allowing higher doses than were obtainable on

the intermittent (14/21) schedule (Wilson *et al*., 2010; Roberts *et al*., 2012). However, severe thrombocytopenia was observed during later cycles in 4 of 7 patients in the 250 mg and 300 mg continuous-dosing cohorts; as with thrombocytopenia observed in Cycle 1, these events were reversible with dose reduction or granulocyte colony-stimulating factor (G-CSF) administration (Roberts *et al*., 2012).

Other frequently reported AEs include anemia, neutropenia, infection, diarrhea, nausea, and fatigue (Investigator's Brochure, 2011; Wilson *et al*., 2010; Gandhi *et al*., 2011; Roberts *et al*., 2012). Although decreases in circulating neutrophils were not observed in nonclinical toxicity studies, neutropenia has been noted in some patients both early (Cycles 1-5) and late (Cycles 7-14) in the CLL monotherapy study M06-873 (Roberts *et al*., 2012). Preliminary analysis of early clinical data demonstrates an apparent trend in decreasing baseline-normalized ANC nadirs with increasing navitoclax dose, C_{max}, or AUC. As such, neutropenia is considered an adverse drug reaction, attributed to navitoclax administration; in the CLL study it was reversible with dose reduction or G-CSF administration.

Grade 1 and 2 gastrointestinal AEs may be due to the vehicle used in the liquid formulation; nausea and vomiting have been managed with antiemetics, and diarrhea with diphenoxylate and atropine (Wilson *et al*., 2010). Anorexia is also considered an adverse drug reaction as it is consistent with the other identified gastrointestinal toxicities.

Other AEs of interest include elevation in liver enzymes, which has limited some subjects' dosing. As such, liver function tests should be routinely monitored during the conduct of navitoclax studies.

Some investigators have reported QTc prolongation as non serious adverse events (Investigator's Brochure, 2011). Many of these subjects were heavily pretreated with cardiotoxic drugs. Based on nonclinical evaluation, it is unknown or unlikely that QTc prolongation is related to navitoclax administration; however, further clinical QTc investigation is planned. Additionally, metabolic changes such as hyperuricemia, hyperkalemia, and increased lactate dehydrogenase (LDH) values have been reported and are consistent symptoms of tumor lysis syndrome (TLS). One serious adverse event of TLS was reported; however, with continued treatment with prophylaxis, no further events of TLS have been reported. A treatment management strategy for subjects experiencing TLS is discussed in Section 6.

The following recommended phase 2 doses (RP2D) were independently determined based on their respective safety and tolerability results:

- M06-814 (lymphoid malignancies): 7-day lead-in dose of 150 mg/day followed by 325 mg QD (21/21 days) (Wilson *et al*., 2010).
- M06-822 (SCLC and other solid tumors): 7-day lead-in dose of 150 mg/day followed by 325 mg QD (21/21 days) (Gandhi *et al*., 2011).
- M06-873 (CLL): 7-day lead-in dose of 100 mg/day followed by 250 mg QD

(21/21 days) (Roberts *et al*., 2012).

Clinical Pharmacokinetics

Pharmacokinetic (PK) data were obtained for the intermittent (14/21) dosing schedules in trials M06-814, M06-822, and M06-873, and for the continuous (21/21) dosing schedule in trial M06-873. M06-814 also tested for food effects on PK parameters. Overall, the absorption of navitoclax after oral dosing was relatively slow, with C_{max} achieved around 6-9 hours after first dose. Exposure (C_{max} and AUC_{0-24}) was approximately dose-proportional over a range of doses from 10 mg/day through 475 mg/day. There were no significant differences in PK values between disease groups (general lymphoid malignancies, SCLC, and CLL) (Investigator's Brochure, 2011). Individual study results are summarized below.

Trial M06-814: Peak concentration was observed approximately 9 hours after dosing, with a terminal plasma half-life ($t_{1/2}$) of approximately 17 hours, with first-order elimination kinetics (Wilson *et al*., 2010). Exposure was dose-proportional over a range of 10 mg/day to 440 mg/day, with an interpatient variability in exposure of 40%. The dose-normalized C_{max} and AUC_{0-24} of a non-fasting dose was about 20% higher than a fasting dose among subjects in the 10 mg through 440 mg cohorts. Dosages ≥315 mg/day met the minimum plasma exposure predicted to be in the therapeutic range based on animal models. After a fasting dose, the oral clearance of navitoclax averaged about 4.4 L/h across all dose levels (Investigator's Brochure, 2011). Navitoclax was not detected in urine, indicating little to no renal excretion.

Trial M06-822: Peak concentration was observed approximately 7 hours after dosing, with a $t_{1/2}$ of approximately 15 hours (Gandhi *et al*., 2011). Exposure (C_{max} and AUC_{0-24}) was dose-proportional over a range of 10 mg/day to 475 mg/day. Interpatient variability in dose-normalized C_{max} and AUC_{0-24} was about 40%, and values were similar between fasting and non-fasting conditions. Peak-to-trough plasma concentration ratio was close to twofold at steady state. Dosages ≥225 mg/day met the minimum plasma exposure predicted to be in the therapeutic range based on animal models.
Trial M06-873: Peak concentration was observed approximately 6-8 hours after dosing in both the intermittent and continuous dosing cohorts (Roberts *et al*., 2012). Exposure was dose-proportional over a range of 10 mg/day to 250 mg/day in the intermittent cohort, and interpatient variability in AUC was 46% for intermittent and continuous cohorts. No consistent trend was observed in dose-normalized steady-state trough concentrations over time. Navitoclax exposure did not demonstrate any correlation with age, sex, body weight, body surface area, renal function, or total bilirubin levels.

Clinical Efficacy

Trial M06-814: Overall, 21 of 46 patients with assessable adenopathy showed some reduction in tumor size (Wilson *et al*., 2010). Ten of these patients achieved a PR of at

least a 50% reduction in tumor size, and these responders had median progression-free survival (PFS) of 455 days. Responses occurred over the entire range of doses, with the exception of 20 and 200 mg/day, and in several tumor types. Responses were recorded after a median of 3.5 cycles (range 2–10).

CLL and small lymphocytic lymphoma (SLL), diseases of B-cell accumulation, showed the greatest sensitivity to treatment (Wilson *et al*., 2010). Seven patients with leukemic counts of >5000 cells/μL achieved at least a 50% reduction in their leukemia cells, and eight of 16 patients with measurable adenopathy, including bulky adenopathy, achieved a PR of at least a 50% reduction in lymph-node size. For all 20 patients with CLL or SLL, median PFS was 246 days, and median overall survival had not been reached at time of the report. Measurable tumor reduction was also noted in six of 16 patients with follicular lymphoma. Overall, the 16 patients with FL had a median PFS of 88 days, and no patient with FL had died at time of the report.

Trial M06-822: Of the 38 patients who were evaluable for response in the phase 1 portion (23 with SCLC or pulmonary carcinoid), eight had stable disease (SD; five SCLC and three atypical pulmonary carcinoid) and one patient with SCLC remained on study for 13 months (Gandhi *et al*., 2011). One patient with SCLC had a PR that was sustained for longer than 35 months (at the time of report); this patient had a localized recurrence after first-line treatment with progressive disease on second-line therapy before study entry. Overall, among patients with disease control, the median number of prior therapies was three (range, 1–5 prior therapies). The majority of patients with disease control were those treated at the highest dose levels and the median duration of disease control was 5 months (range, 2–35 months).

In the phase 2a portion of the trial, out of 39 SCLC patients, only 1 PR (ORR 2.6%) and 9 SD were observed (Rudin *et al*., 2012). Thirteen patients were not evaluable for response. Median PFS was 1.5 months (95% confidence interval [CI], 1.4–1.7) and median OS was 3.2 months (95% CI, 2.3–8.1).

Trial M06-873: Nine of 29 CLL patients achieved a PR (objective response rate [ORR] 31%), five on the intermittent-dosing (14/21) cohort and four on the continuous-dosing cohort (Roberts *et al*., 2012). SD was the best response in 18 patients and was sustained for at least 6 months in eight patients. Among the 26 patients who received doses of navitoclax sufficient to achieve sustained exposure of biologically active concentrations (≥110 mg/day), the ORR was 35%. Clinical benefit appeared durable, since seven patients had SD features for more than 12 months from commencement of therapy. The median PFS and the median time to disease progression were both 25 months.

Among seven patients with fludarabine-refractory disease receiving ≥110 mg/day, one achieved a PR and five had overall SD while demonstrating some antitumor efficacy with either a more than 50% reduction in peripheral blood lymphocytosis and/or a substantial reduction in lymphadenopathy. The median PFS of fludarabine-refractory patients was

25 months. Among nine patients with bulky lymphadenopathy receiving navitoclax at doses ≥110 mg/day, three achieved a PR and six had SD while demonstrating some tumor reduction. Similarly, three of nine patients with del (17p) CLL treated with navitoclax at ≥110 mg/day achieved a PR, and their median PFS has not been reached.

2.3 *Other Agent(s)*

N/A

2.4 Rationale

Previously, our laboratory and others showed that simultaneous targeting of more than one RAS effector pathway (specifically the MEK-ERK (MAPK) and PI3K-AKT pathways) caused marked responses in KRAS-driven mouse tumor models (Engelman et al., 2008; She et al., 2010). While these data support the promise of combination therapy strategies, toxicity has prevented dosing both medications at or near their maximally-tolerated doses when used in combination (LoRusso et al., 2012; Bedard et al., 2012; Speranza et al., 2012). Thus, potent and continuous suppression of the MEK and PI3K pathways may not be possible in patients with currently available agents. Furthermore, this approach may be effective only in a subset or KRAS-mutant cancers. Consequently, additional effective combination therapy strategies for KRAS-mutant cancers are critically needed.

A large-scale screening study of >600 cell lines with >100 targeted compounds identified MEK inhibitors as the most effective agents in KRAS-mutant cell lines (Garnett et al., 2012). However, while MEK inhibition alone leads to decreased proliferation in most KRAS mutant cancers, MEK inhibitors alone typically fail to induce a cell death response (Corcoran et al., 2013). This observation likely explains why MEK inhibitors have often led to stable disease in KRAS-mutant cancer patients (Infante et al., 2010), but have rarely, if ever, led to true objective tumor responses. Still, because of their potent growth inhibitory effects and their ability to cause disease stabilization in patients with KRAS mutant cancers, MEK inhibitors are a promising backbone for potential combination strategies for KRAS mutant cancers.

Recently, we conducted a pooled shRNA-drug screen to identify promising partners for combination therapy with MEK inhibitors in KRAS mutant cancers (Corcoran et al., 2013). The top hit from this screen was the anti-apoptotic gene BCL-XL. Pharmacologic inhibition of BCL-XL with the BH3 mimetic navitoclax in combination with a MEK inhibitor led to pronounced apoptosis in the vast majority of 30 KRAS mutant cancer cell lines from different tumor types (pancreas, colorectal, and lung). Apoptosis induction was significantly greater with this inhibitor combination than with either agent alone. Mechanistically, we observed that MEK inhibition alone led to dramatic upregulation of the pro-apoptotic protein BIM. However, immunoprecipitation studies revealed that these increased BIM levels were bound and inhibited by BCL-XL. However, addition of navitoclax blocked the inhibitory interaction of BCL-XL and

BIM, thus "freeing" these elevated levels of BIM protein to promote apoptosis.

In vivo, the combination of navitoclax and a MEK inhibitor led to dramatic tumor regressions in 5 independent KRAS mutant cancer models, and to significantly greater anti-tumor effect than either agent alone. We observed dramatic tumor regressions of established tumors in 3 independent KRAS mutant tumor xenograft models and in 2 genetically-engineered KRAS-driven mouse models of lung cancer (one with mutant p53 and one with wild-type p53). Analysis of treated tumor tissue showed dramatic induction of cell death only in tumors treated with the combination of navitoclax and a MEK inhibitor. These results represent some of the most impressive in vivo preclinical efficacy observed to date with any therapeutic strategy in KRAS mutant cancers.

NRAS activates the same key downstream pathways as KRAS, and NRAS mutant cancers also represent a molecular subtype with few effective treatments. NRAS mutant cancers have shown increased sensitivity to single-agent MEK inhibitors, when compared to KRAS mutant cancers—for example, the MEK inhibitor binimetinib recently exhibited a 15% confirmed response rate in NRAS mutant melanoma patients and extended survival relative to standard chemotherapy. Still, most patients fail to respond and combination therapy strategies are needed.

Thus, we hypothesize that the combination of navitoclax and a MEK inhibitor (trametinib) is a promising novel targeted therapy combination strategy with the potential to lead to tumor responses in patients with KRAS or NRAS mutant cancers of several different tissue types, including melanoma, pancreatic, colorectal, GYN, and lung cancers.

2.5 Correlative Studies Background

2.5.1 Pharmacokinetic Studies

While the pharmacokinetics of trametinib and navitoclax given as single agents is well-understood, this study will evaluate the pharmacokinetics of these agents when given in combination. During the Phase 1b portion of the study, subjects will have blood drawn pre-dose, and 2h, 4h, 6h, 8h, and 23h after dosing on (1) day 7 of a 7-day navitoclax single-agent lead-in dosing period and (2) again after 14 days of combination dosing. Pre-dose (0h) levels of trametinib and navitoclax will also be measured on day 1 of cycles 2, 4, 8 and 12. Plasma concentrations of trametinib will be determined through established procedures by GSK, and concentrations of navitoclax will be determined through established procedures by AbbVie. These studies will be used to determine whether trametinib and navitoclax interact from a pharmacokinetic standpoint, and will be used to determine the maximum observed plasma drug concentration (Cmax), area-under-the concentration-time-curve from zero (pre-dose) to 24 hours (AUC(0-24)), pre-dose (trough) drug concentration for trametinib and navitoclax, and t1/2. Since it is not yet clear whether the single-agent MTDs of these compounds can reached when these agents are dosed in combination, measuring the plasma drug concentrations achieved at

each dose level provide a valuable comparison of the drug exposure achieved at a given dose level to what is known to be achieved at the single-agent MTD.

2.5.2 Pharmacodynamic Studies

This study will incorporate pharmacodynamic analyses to evaluate the effects of trametinib and navitoclax given in combination on key cellular signaling pathways and on the induction of apoptosis and inhibition of tumor cell proliferation. Paired pre-treatment and on treatment core biopsies will be obtained from all patients in the Phase Ib portion of the trial and the first 15 patients enrolled on the Phase 2 portion of the trial (minimum of 4 patients from each of cohorts 1, 2 and 3 will be biopsied), if these patients have lesions that can be safely biopsied without unacceptable risk or discomfort to the patient. Pre-treatment biopsies will be obtained between days -21 and -1 of treatment, and the on-treatment biopsy will be obtained on day 22 (+/-7 days) for patients in the Phase 1b and Part 2 schedule A, and on day 15 (+/-7 days) for patients in the Phase 1b and Part 2 schedule B. Core biopsies of the same tumor lesion will be obtained at each time point. Both fresh frozen and formalin-fixed paraffin-embedded cores will be obtained at each time point.

Paired biopsies will be used to assess the pharmacodynamic response to therapy in these patients. Markers to be assessed will include proteins or mRNAs involved in MAPK or BCL2 family signaling (e.g. phospho-ERK, phospho-S6, or MAPK phosphatases such as DUSP6/MKP1) to evaluate pathway inhibition, markers of tumor cell proliferation (e.g. Ki67), and markers of apoptosis and cell death (e.g. Cleaved caspase-3). For each patient, the change in marker level between the pre-treatment and on-treatment (day 15) biopsies will indicate the effects of treatment on each marker. Other potentially important biomarkers identified in emerging laboratory investigations may also be evaluated.

Biopsies from patients in the Phase Ib portion of the trial will provide an evaluation of the effects of each cohort's dose level on signaling pathway inhibition, inhibition of tumor cell proliferation, and induction of tumor cell death. This will provide an important metric as to the extent of target inhibition at each given dose level. Paired biopsies obtained from the first 15 patients enrolled in the Phase 2 portion of the trial (minimum of 4 patients from each of cohorts 1, 2 and 3 will be biopsied) will provide a more detailed assessment of the pharmacodynamic effects of therapy at the RP2D and will offer the potential to correlate pharmacodynamic effects with tumor response and patient outcome.

2.5.3 Predictive Biomarker Analysis in Pre-Treatment Biopsies

Given the molecular heterogeneity of KRAS and NRAS mutant cancers, no single therapeutic regimen is expected to be effective in all patients. Therefore, molecular characterization of archived or pre-treatment tumor biopsy tissue for each patient enrolled on this trial will provide a critical opportunity to identify valuable biomarkers to predict which patients are more or less likely to respond to treatment.

2.5.3.1 Mutational Analysis

Extensive tumor mutational analysis of 1000 genes will be performed for each patient using a next-generation genotyping platform employed as part of standard oncology care at the Massachusetts General Hospital Cancer Center. Mutations in key pathways that might affect the likelihood of a patient's tumor to respond to therapy (e.g. PIK3CA, PTEN, p53, etc.) will be correlated with objective tumor response or PFS. Additional in-depth genomic analyses, including copy number analyses, may also be performed.

2.5.3.2 Biomarker Expression Analysis

We also plan analysis of selected protein and mRNA biomarkers identified in previous (and future) laboratory studies. For example, our initial laboratory studies (Corcoran et al., Cancer Cell, 2013) have suggested that KRAS mutant cancers that express markers of epithelial differentiation (e.g. E-cadherin) are more likely to respond to this therapy that cancers expressing markers of mesenchymal differentiation (e.g. vimentin). Thus, E-cadherin and vimentin levels will be assessed by immunohistochemistry in archived or pre-treatment biopsies. Also, baseline levels of specific BCL2 family apoptotic proteins, including BCL-XL, MCL1, and BIM, have also been shown to predict responsiveness to this therapy in laboratory models. These markers will also be assessed. Biomarker levels will be correlated with response rate or PFS and may help identify which subpopulation of KRAS or NRAS mutant cancer patients are more or less likely to response therapy.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically- or cytologically-confirmed diagnosis of KRAS or NRAS mutation-positive malignancy that is metastatic or unresectable and for which standard curative measures do not exist or are no longer effective. Patients must have activating mutations affecting codons 12, 13, 61, or 146 as determined in a CLIA certified lab to be eligible for this study.

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

3.1.3 Participants must have received at least one line of prior systemic chemotherapy and must have experienced documented radiographic progression or intolerance on this therapy.

3.1.4 Paired pre-treatment and post-treatment biopsies are required for all patients on Part 1 and first 15 patients in Part 2. Participants must have available archival tumor tissue (at least 20 unstained slides.) If archival tissue is not available or is found not to contain tumor tissue, a fresh biopsy is required. If a patient is having a tumor biopsy, less than 20 unstained slides are acceptable with approval of the PI. Biopsies will only be performed in a given patient if they are not deemed to involve unacceptable risk based on the sites of disease and other concurrent medical conditions.

3.1.5 Age ≥18 years.

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

3.1.6 ECOG performance status ≤1 (see Appendix A).

3.1.7 Life expectancy of greater than 3 months

3.1.8 Able to swallow and retain orally-administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

3.1.9 All prior treatment-related toxicities must be CTCAE v4 grade ≤1 (**except alopecia**) at the time of enrollment. This requirement to return to ≤ grade 1 does not apply to immune checkpoint inhibitor related endocrinopathies (e.g. thyroiditis, hypophysitis, etc.) that necessitate hormone replacement therapy including, but not limited to levothyroxine, cortisol, and testosterone. CTCAE v5.0 will be utilized beginning April 1, 2018.

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

- Leukocytes ≥3,000/mcL
- Absolute neutrophil count (ANC) ≥1,200/mcL (subjects may be treated with hematopoietic growth factors to achieve or maintain this level)
- Hemoglobin ≥9 g/dL
- Platelets ≥100x10^9/L
- Albumin ≥2.5 g/dL
- Total bilirubin ≤1.5x institutional ULN (patients with Gilbert's syndrome may have serum bilirubin >1.5×ULN)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5x institutional ULN

- Serum creatinine ≤1.5 mg/dL *OR* calculated creatinine clearance (Cockroft-Gault formula) ≥50 mL/min *OR* 24-hour urine creatinine clearance ≥50 mL/min
- Prothrombin time (PT)/International normalized ratio (INR) and partial thromboplastin time (PTT) ≤1.2x institutional ULN
- Left ventricular ejection fraction ≥ institutional lower limit of normal (LLN) by ECHO or MUGA

3.1.11 The effects of trametinib and navitoclax on the developing human fetus are unknown. For this reason, women of child-bearing potential and men with a female partner of child bearing potential must agree to use adequate contraception using ***one of the methods listed below*** prior to study entry, for the duration of study participation, and up to 4 months following completion of therapy.

- total abstinence from sexual intercourse (minimum one complete menstrual cycle prior to study drug administration);
- Vasectomized male subject or vasectomized partner of female subjects;
- Hormonal contraceptives (oral, parenteral, transdermal or vaginal ring) for at least 3 months prior to study drug administration; if the subject is currently using a hormonal contraceptive, she should also use a barrier method during this study and for 1 month after study completion;
- intrauterine device (IUD);
- double-barrier method: male condom plus diaphragm or vaginal cap with spermicide (contraceptive sponge, jellies or creams);

Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception. Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms for the duration of the study and for 4 months following completion of therapy.

Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to initiation of treatment. Women will be considered not of childbearing potential if they are surgically sterile (bilateral oophorectomy or hysterectomy) and/or post-menopausal (amenorrheic for at least 12 months).

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. The potential hazard to the fetus should be explained to the patient and partner (as applicable).

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 History of another malignancy.

Exception: Patients who have been disease-free for 3 years, or patients with a history of completely resected non-melanoma skin cancer or any carcinoma in situ and/or patients with indolent second malignancies, are eligible. Consult the CTEP Medical Monitor if unsure whether second malignancies meet the requirements specified above.

3.2.2 History of interstitial lung disease or pneumonitis.

3.2.3 Any major surgery, extensive radiotherapy (>15 days of treatment), chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within 21 days prior to first dose of study treatment and/or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to first dose of study treatment.

3.2.4 Use of other investigational drugs within 28 days (or five half-lives, whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of study drug(s)and during the study.

3.2.5 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

Exception: Patients with brain metastases will be allowed on study if they have clinically controlled neurologic symptoms, defined as surgical excision and/or radiation therapy followed by 21 days of stable neurologic function and no evidence of CNS disease progression as determined by CT or MRI within 21 days prior to the first dose of study drug.

3.2.6 Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to trametinib, or excipients or to dimethyl sulfoxide (DMSO), or to compounds of similar chemical or biologic composition to navitoclax.

3.2.7 Current use of a prohibited medication. The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on study treatment. (note: megestrol [Megace] if used as an appetite stimulant is allowed).
- Concurrent treatment with bisphosphonates is permitted; however, treatment must be initiated prior to the first dose of study therapy. Prophylactic use of bisphosphonates in patients without bone disease is not permitted, except for the treatment of osteoporosis.
- Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including, but not limited to, St. John's wort, kava, ephedra [ma huang], ginkgo

biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).
- Due to the expected dose-limiting toxicity of thrombocytopenia, the following concomitant medications are not allowed during navitoclax administration: Warfarin, clopidogrel (Plavix), ibuprofen, tirofiban (Aggrastat), and other anticoagulants, drugs, or herbal supplements that affect platelet function are excluded, with the exception of low-dose anticoagulation medications (such as heparin) that are used to maintain the patency of a central intravenous catheter. Aspirin will not be allowed within 7 days prior to the first dose of navitoclax or during navitoclax administration. However, subjects who have previously received aspirin therapy for thrombosis prevention may resume a low dose (*i.e.*, maximum 100 mg QD) of aspirin if platelet counts are stable ($\geq$50,000/mm^3) through 6 weeks of navitoclax administration. All decisions regarding treatment with aspirin therapy will be determined by the investigator in conjunction with the medical monitor.

3.2.8 Preclinical studies indicate that navitoclax is metabolized by CYP3A4, is a moderate inhibitor of CYP2C8, and is a strong inhibitor of CYP2C9. Therefore, caution should be exercised when dosing navitoclax concurrently with CYP2C8 and CYP2C9 substrates. Common CYP2C8 substrates include paclitaxel, statins, and glitazones, whereas CYP2C9 substrates include phenytoin and warfarin. When possible, investigators should switch to alternative medications or monitor the patients closely (particularly in the case of medications that have a narrow therapeutic window such as warfarin. Use of warfarin is specifically prohibited while on study). CYP3A inhibitors such as ketoconazole and clarithromycin are not allowed 7 days prior to the first dose of navitoclax or during navitoclax administration.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

Patient instructions and information of possible drug interactions, contained in Appendix D, will be given to all patients upon enrollment in this study.

3.2.9 History or current evidence/risk of retinal vein occlusion (RVO).

3.2.10 History or evidence of cardiovascular risk including any of the following:

- LVEF<LLN.
- A QT interval corrected for heart rate using the Bazett's formula QTcB $\geq$480 msec.
- History or evidence of current clinically significant uncontrolled arrhythmias (exception: patients with controlled atrial fibrillation for >30 days prior to enrollment

are eligible).
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.
- History or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) functional classification system
- Treatment-refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy.
- Known cardiac metastases.
- Patients with intra-cardiac defibrillators.

3.2.11 Known Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (patients with chronic or cleared HBV and HCV infection are eligible). Patients with Human Immunodeficiency Virus (HIV) are not eligible if on anti-retroviral medications.

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

3.2.13 Subject has an underlying condition predisposing them to bleeding or currently exhibits signs of clinically significant bleeding.

3.2.14 Subject has a recent history of non-chemotherapy-induced thrombocytopenic-associated bleeding within 1 year prior to the first dose of study drug.

3.2.15 Subject has a significant history of cardiovascular disease (*e.g.*, MI, thrombotic or thromboembolic event in the last 6 months).

3.2.16 Pregnant women or nursing mothers. Animal reproductive studies have not been conducted with trametinib or navitoclax. Therefore, the study drug must not be administered to pregnant women or nursing mothers.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	6		+	5		=	11	
Not Hispanic or Latino	61		+	58		=	119	
Ethnic Category: Total of all subjects	67	(A1)	+	63	(B1)	=	130	(C1)

Racial Category						
American Indian or Alaskan Native	1	+	1	=	2	
Asian	7	+	6	=	13	
Black or African American	8	+	7	=	15	
Native Hawaiian or other Pacific Islander	2	+	1	=	3	
White	49	+	48	=	97	
Racial Category: Total of all subjects	67 (A2)	+	63 (B2)	=	130 (C2)	
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Dana Farber Harvard Cancer Center (DF/HCC) institutions (Massachusetts General Hospital and Dana Farber Cancer Institute) will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Complete the IWRS protocol-specific eligibility checklist online using the eligibility assessment documented in the participant's medical record to generate a subject number and a RAVE eCRF page for the patient and receive confirmation email.

4. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

5. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

6. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3 Investigator and Research Associated Registration with CTEP

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

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

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

- Act as the site-protocol PI on the IRB approval.

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm >. **Error! Hyperlink reference not valid.**For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov mailto:>.

5. TREATMENT PLAN

5.1 Agent Administration

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

to clinic staff at the end of each course (28-day cycle).

Vomited doses of both trametinib and navitoclax will not be made up. Each medication should be taken approximately 24 hours after the time that same medication was taken, with an allowable window of +/- 8 hours. Doses of each medication should be taken at least 16 hours after the prior day's dose of that same medication. For days on which subjects will undergo an on-treatment biopsy or any other procedure which required the subject to be NPO, Navitoclax should be taken in the a.m. with Jello at least two hours before the scheduled procedure. Trametinib and navitoclax doses should not be crushed, chewed, or dissolved.

5.1.1 Treatment plan for Part 1 (Phase 1b)

Dosing levels for Part1 of the study are listed below in **Table 5.1** and dose escalation will proceed as outlined in Figure 5.1. Agents will be dosed daily in a 28-day cycle according to the description outlined in **Table 5.2**. A 28-day cycle has been used in previous combination studies with trametinib, such as the study combining trametinib and dabrafenib, summarized in section 2.2.1.4. Subjects will be assessed for toxicities and safety at weekly intervals during the first 28-day cycle, at two week intervals during cycle two, and monthly thereafter. Subjects will undergo radiographic assessments of tumor response every 2 cycles (8 weeks +/- 1 week). The schema for dose escalation is shown below in **Table 5.3**, utilizing standard Phase 1 cohorts of 3 subjects per dose level. The occurrence of 1 dose limiting toxicity (DLT; defined in Section 5.2) will prompt expansion of a given dose level to 6 subjects. The occurrence of 2 DLTs in a given dose level will indicate that the maximal tolerated dose (MTD) has been exceeded, and expansion of the prior dose level to 6 subjects will occur, if not already performed. Patients will be replaced if they are not evaluable for the DLT window. The dose of each agent to be used for Part 2 (Phase 2) of the study (the recommended Phase 2 dose (RP2D)) will be the highest dose level at which no more than 1 subject out of 6 experiences a DLT. Dose escalation will proceed until the MTD/RP2D have been determined, or until the RP2D of each compound individually (2mg daily for trametinib; 325mg daily for navitoclax) is reached (represented by dose level 7). If the MTD is reached before dose level 7, alternative dosing schemes will be considered by the investigators in which trametinib is dosed intermittently in an effort to reduce toxicity (denoted as Schedule C). If necessary, the exact details of these alternative dosing schemes will be designed at a future date through a protocol amendment.

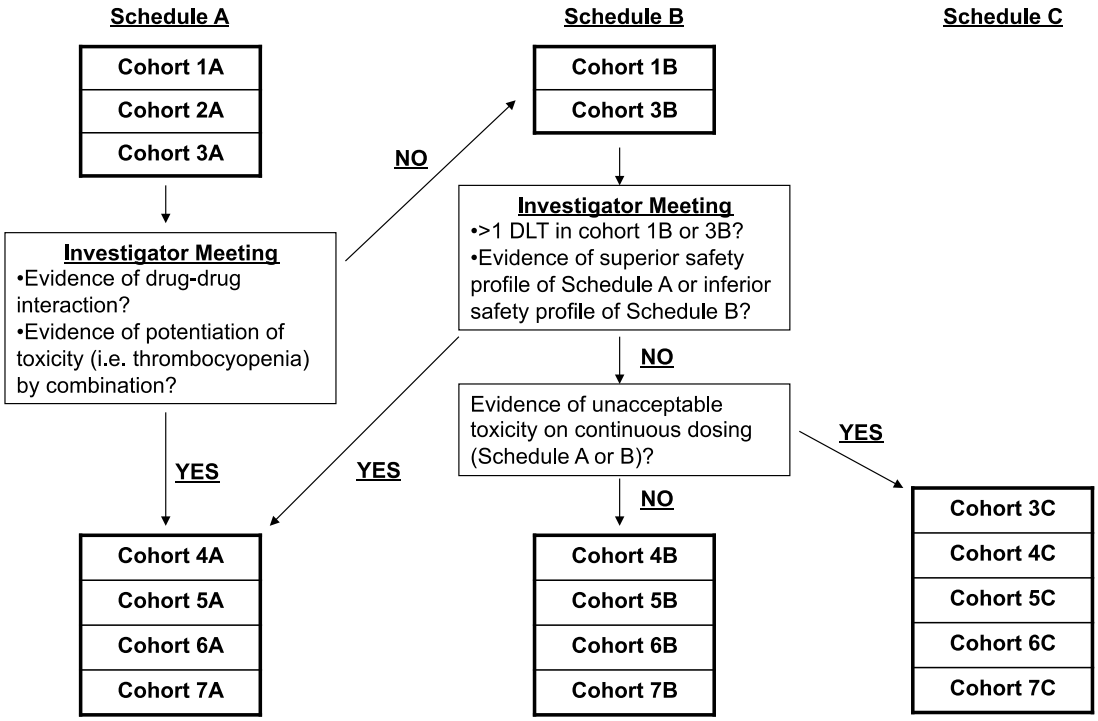
Table 5.1: Dosing Levels for Part 1 (Phase 1b)

Dose Escalation Levels		
Dose Level	**Dose**	
	Trametinib (mg) PO daily	Navitoclax **(mg) PO daily**
Level 1	1	150

Level 2	1.5	150
Level 3*	1.5	200
Level 4*	2	200
Level 5*	2	250
Level 6*	2	300
Level 7*	2	325

*Dose levels 3-7 will include a 7-day lead-in dosing period for navitoclax at 150 mg PO daily.

Figure 5.1: Dose Escalation Schema for Part 1 (Phase1b)



To reduce the incidence of significant thrombocytopenia associated with navitoclax dosing, a 7-day lead-in dosing period will be used for dose levels in which the target dose of navitoclax is greater than 150 mg daily (dose levels 3-7). Subjects will begin with navitoclax dosed at 150 mg PO daily and will escalate to the navitoclax dose defined in the cohort dose level after the 7th day of lead-in dosing if the subject's platelet count is ≥50,000/mm^3 and the patient has no evidence of clinically significant bleeding, defined as grade 2 or higher hemorrhage regardless of platelet count. If the subject's platelet count on the 7th day of lead-in dosing is <50,000mm^3, then the dose of navitoclax will be maintained at 150 mg daily for an additional 7 days. If the platelet count is <50,000mm^3 after 14 days at the lead-in dose, then the lead-in dose will become the subject's dose for the duration of the study.

Two different schedules relating to the lead-in dosing period will be evaluated during Part 1 of this study. Schedule A will administer the 7-day lead-in dosing period of navitoclax as a single agent, prior to the initiation of trametinib dosing. Schedule B will begin the 7-day lead-in dosing period of navitoclax simultaneously with the initiation of trametinib dosing. Since potential drug interactions between trametinib and navitoclax are not yet defined, and since it is not yet known

whether trametinib might potentiate the thrombocytopenia associated with navitoclax dosing, Schedule A (single agent lead-in) provides a potentially safer avenue for initial investigation of this combination. However, since navitoclax has not exhibited convincing single agent activity in pre-clinical models of KRAS mutant cancers (Corcoran et al., 2013), while trametinib has demonstrated activity in patients with KRAS mutant cancers (Infante et al, 2010; Messersmith et al., 2011), Schedule B may be preferable from an efficacy standpoint, as it does not delay the initiation of trametinib. Therefore, it will be important to determine if any meaningful differences in safety and tolerability exist between Schedules A and B. Schedule C (alternative dosing schedule with intermittent trametinib dosing) will be evaluated if unacceptable toxicity is observed during dose escalation on Schedules A or B. Schedules A, B and C are outlined below:

Schedule A
Cycle 1 ONLY

Treatment day:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
							T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
L	L	L	L	L	L	L	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Cycle 2 and Subsequent Cycles

Treatment day:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Schedule B
Cycle 1 ONLY

Treatment day:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
L	L	L	L	L	L	L	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Cycle 2 and Subsequent Cycles

Treatment day:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Schedule C
Cycle 1 ONLY

Treatment day:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
T	T	T	T	T	T	T	T	T	T	T	T	T	T														
L	L	L	L	L	L	L	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Cycle 2 and Subsequent Cycles

Treatment day:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
T	T	T	T	T	T	T	T	T	T	T	T	T	T														
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

T = trametinib dose defined by Phase 1b dose level or RP2D
L = lead-in dose of navitoclax (150 mg daily).
N = Navitoclax dose defined by Phase 1b dose level or RP2D. **Note: as described above, after 7 days of navitoclax at the lead-in dose of 150 mg daily (L), dose will be escalated to the dose defined by the Phase 1b dose level or the RP2D (A), only if subject's platelet count is ≥50,000/mm^3 and the patient has no evidence of clinically significant bleeding, defined as grade 2 or higher hemorrhage regardless of platelet count. If the subject's platelet count on the 7th day of lead-in dosing is <50,000mm^3, then the dose of navitoclax will be maintained at 150 mg daily for an additional 7 days. If the platelet count is <50,000mm^3 after 14 days at the lead-in dose, then the lead-in dose will become the subject's dose for the duration of the study.**

Evaluation of dosing Schedules A and B will be performed according to the schema in **Figure 5.1.** Since it is not yet known whether drug interactions might occur between trametinib and

navitoclax or whether trametinib might potentiate the thrombocytopenia associated with navitoclax dosing, Schedule A (single agent lead-in) will be evaluated first. Since the thrombocytopenia associated with navitoclax is typically most profound during the first few days of dosing, Schedule A represents a safer initial approach.

Dose levels 1-3 will be enrolled according to Schedule A (i.e. dosing cohorts 1A, 2A, 3A). After completion of dose level 3A, if dose escalation is warranted per the criteria outlined in **Table 5.3** above, an investigator meeting will be held with NCI/CTEP and pharmaceutical collaborators to review safety data. Pharmacokinetic data will be reviewed to evaluate for any evidence of drug interaction, and adverse event data will be reviewed to evaluate for any potentiation of toxicity (in particular, thrombocytopenia) by the combination. If significant safety concerns are noted, dose escalation will proceed for the remainder of the study according to Schedule A (i.e. to dosing cohort 4A, 5A, 6A, 7A). If no significant safety concerns are noted, and it is deemed safe to proceed, dosing will return to dose level 1 according to schedule B (i.e. dosing cohort 1B). Dose escalation will then proceed according to Schedule B to dosing cohort 3B. Since both dose levels 2 and 3 involve beginning with 150 mg navitoclax and 1.5 mg trametinib, it is not necessary to evaluate dose levels 2 and 3 both according to schedule B, as both would test the safety of initiating navitoclax and trametinib simultaneously at these same doses. Therefore, dose escalation will proceed directly from cohort 1B to cohort 3B. If >1 DLT is experienced within dosing cohort 1B or within 3B, then Schedule B will be abandoned, and dose escalation will proceed with dosing cohort 4A. If dosing cohort 3B is completed with ≤1 DLT, then a second investigator meeting will be held with NCI/CTEP and pharmaceutical collaborators to review safety data. Pharmacokinetic data will be reviewed to evaluate for any evidence of drug interaction, and adverse event data will be reviewed to evaluate for any potentiation of toxicity (in particular, thrombocytopenia) by the combination. If the investigators and NCI/CTEP and pharmaceutical collaborators agree that Schedule B demonstrates a comparable or improved safety profile relative to Schedule A, then dose escalation will proceed according to Schedule B (i.e. to dosing cohort 4B, 5B, 6B, 7B) until the RP2D is determined. However, if evidence of drug interaction exists, or if the investigators and NCI/CTEP and pharmaceutical collaborators agree that Schedule A demonstrates a superior safety profile, particularly as it relates to navitoclax-associated thrombocytopenia, then dosing will proceed for the remainder of the study according to Schedule A (i.e. to dosing cohort 4A, 5A, 6A, 7A) until the RP2D is determined. If, however, unacceptable toxicity (either >1 DLT or toxicity not meeting criteria for DLT, but deemed to be unacceptable by investigators) is observed at a given dose level independent of schedule A or B, then and alternative dosing schedule (Schedule C) will be explored with intermittent trametinib dosing (days 1-14 only of each 28 day cycle), beginning at the last dose level completed. With Protocol Version 10 (dated 8/9/16), there will be no further Dose Escalation on Schedule A or B.

Table 5.2: Schedule of Agent Administration

Schedule A and B:

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Trametinib	*Take on empty stomach, >1 hour before meal or >2 hours after meal*	** *tablet(s)*	*PO daily, >1 hour before meal or >2 hours after meal*	*Days 1-28*	*28 days (4 weeks)*
Navitoclax*	*Take with food.*	** *tablet(s)*	*PO in the a.m.*	*Days 1-28*	
** For days on which subjects will undergo an on-treatment biopsy, Navitoclax should be taken in the a.m. with Jello at least two hours before the scheduled biopsy.* ***Doses as appropriate for assigned dose level.*					

Schedule C:

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Trametinib	*Take on empty stomach, >1 hour before meal or >2 hours after meal*	** *tablet(s)*	*PO daily in the p.m., >1 hour before meal or >2 hours after meal*	*Days 1-14*	*28 days (4 weeks)*
Navitoclax*	*Take with food.*	** *tablet(s)*	*PO in the a.m.*	*Days 1-28*	
** For days on which subjects will undergo an on-treatment biopsy, Navitoclax should be taken in the a.m. with Jello at least two hours before the scheduled biopsy.* ***Doses as appropriate for assigned dose level.*					

Table 5.3: Dose Escalation Criteria for Part 1 (Phase 1b)

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**

0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Patients will be replaced if they are not evaluable for the DLT window.

5.1.2 Treatment Plan for Part 2 (Phase 2)

For the Phase 2 portion of the study, patients will be dosed at the RP2D defined in Part 1 of this study in 28-day cycles. The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course (28-day cycle). Patients will receive a 7-day lead-in dosing period of navitoclax at 150 mg PO daily according the Schedule (Schedule A vs. Schedule B) by which the RP2D was defined, as described in the previous subsection. As in Part 1, subjects will begin with navitoclax dosed at 150 mg PO daily and will escalate to the navitoclax dose defined in the cohort dose level after the 7th day of lead-in dosing if the subject's platelet count is ≥50,000/mm^3 and the patient has no evidence of clinically significant bleeding, defined as grade 2 or higher hemorrhage regardless of platelet count. If the subject's platelet count on the 7th day of lead-in dosing is <50,000mm^3, then the dose of navitoclax will be maintained at 150 mg daily for an additional 7 days. If the platelet count is <50,000mm^3 after 14 days at the lead-in dose, then the lead-in dose will become the subject's dose for the duration of the study.

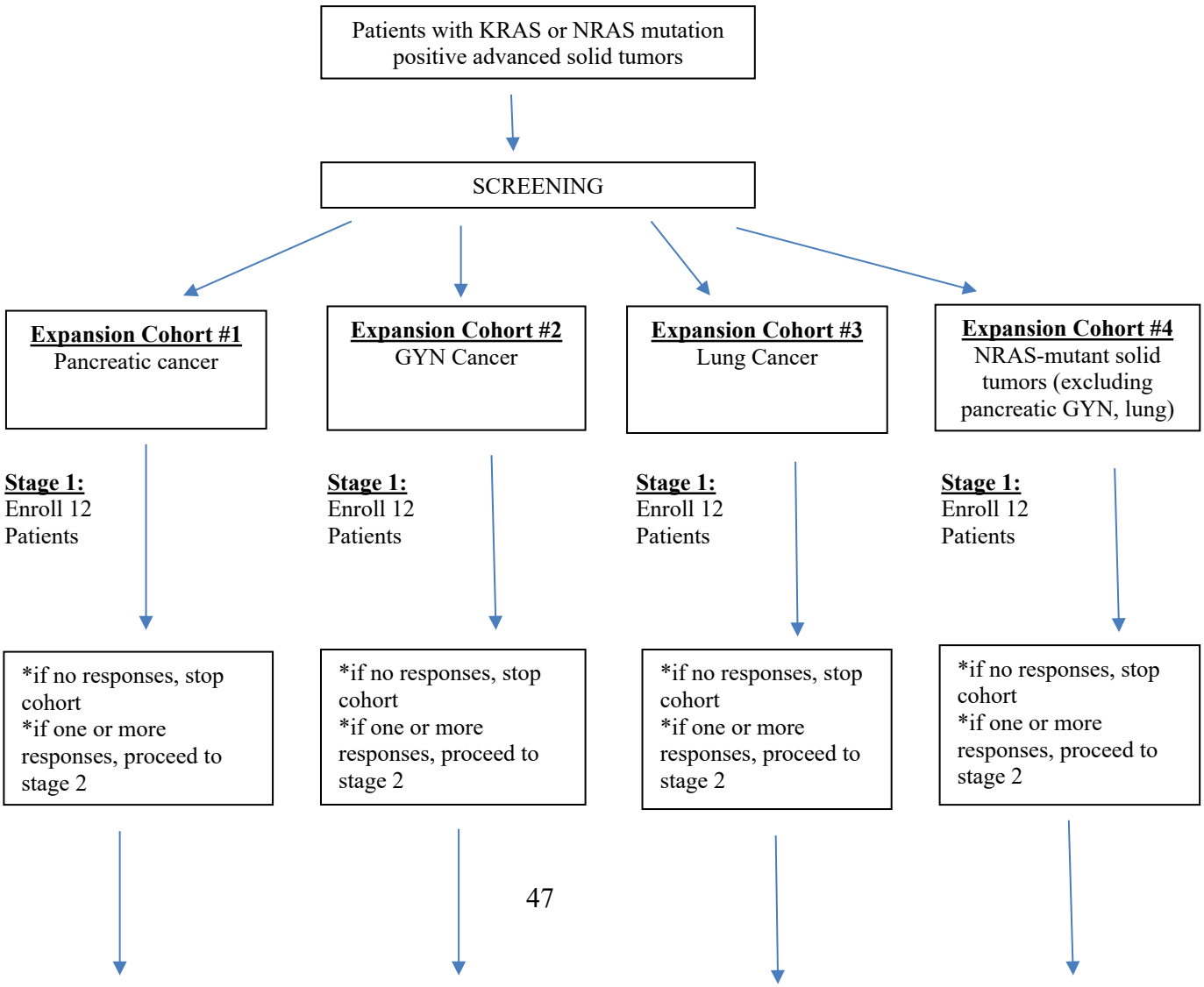
In Part 2 of the study, patients with KRAS or NRAS mutation-positive advanced solid tumors will be enrolled into one of the following four expansion cohorts, according to tumor type:

Expansion cohort #	**Description**

Expansion cohort 1	KRAS or NRAS mutation-positive pancreatic cancer
Expansion cohort 2	KRAS or NRAS mutation-positive GYN cancer
Expansion cohort 3	KRAS or NRAS mutation-positive lung cancer
Expansion cohort 4	NRAS mutation-positive solid tumors of all other types (excluding pancreatic, GYN, and lung)

Patients will be enrolled to each expansion cohort according to the schema below. A total of 12 patients will be enrolled in each expansion cohort. If no objective tumor responses (partial or complete responses, as defined in section 11.1.4) are seen in the first 12 patients enrolled in a given cohort, the cohort will close. If at least one objective tumor response is observed in a given cohort, an additional 13 patients (for a total of 25 patients) will be enrolled to that cohort. Statistical considerations are discussed in more detail in Section 13. Patients will be assessed weekly for toxicity and safety during the first 28-day cycle and monthly thereafter. Patients will undergo radiographic assessment of tumor response every 2 cycles (8 weeks).

Part 2 (Phase 2)



Stage 2: Enroll 13 Patients	**Stage 2:** Enroll 13 Patients	**Stage 2:** Enroll 13 Patients	**Stage 2:** Enroll Patients
N = 25 total	N = 25 total	N = 25 total	N = 25 total

5.1.3 Trametinib

The effect of food on trametinib absorption is unknown. On PK days, the current recommendation is to administer trametinib on an empty stomach 1 hour (+/- 5 minutes) before navitoclax (which should be taken with food.) On non-PK days, the medications do not necessarily need to be taken in this sequence, but trametinib should always be taken on an empty stomach (defined at least one hour +/- 5 minutes before and/or two hours after food,) and navitoclax should always be taken with food. However, patients are encouraged to keep to the same schedule used on PK days as part of their daily administration, if possible. The recommendation to administer trametinib fasting may change based on emerging data.

5.1.4 Navitoclax

The recommended starting dose for combination studies of navitoclax is 150 mg PO daily.

5.1.5 Other Agent(s)

N/A

5.1.6 Other Modalities or Procedures

N/A

5.1.7 Investigational Imaging Agent Administration

N/A

5.2 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) is based on the CTEP Active Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). CTCAE v5.0 will be utilized beginning April 1, 2018. DLT refers to toxicities experienced during the first 42 days of treatment. A DLT will be defined as follows:

- Any grade 4 toxicity

- Grade 3 fatigue, persistent for more than 7 days
- Grade ≥ 3 nausea, diarrhea, or vomiting despite maximum supportive care and persisting more than 72 hours
- Grade ≥ 3 neutropenia with fever > 38.5°C
- Grade 3 thrombocytopenia with clinically significant bleeding. Clinically significant bleeding will be defined as any bleeding requiring transfusion, hospitalization, or medical or surgical intervention. Clinically significant bleeding will only be considered a DLT if it is associated and attributable to study drug induced thrombocytopenia.
- Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >10% from baseline with confirming assessment within 7 days.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Dose escalation will proceed within each cohort according to the scheme shown in **Table 5.3** above. Dose-limiting toxicity (DLT) is defined above.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Trametinib

Because there is a low potential for interaction of trametinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.3.2 Navitoclax

Potential issues with navitoclax include drug-drug interactions and thrombocytopenia. See the navitoclax supportive care guidelines (Section 6) currently included in all company-sponsored protocols for managing thrombocytopenia (with platelet transfusion recommendations), lymphopenia, and tumor lysis syndrome.

In adult monotherapy clinical studies, reductions in circulating platelet counts were observed in an expected, dose-dependent predictable manner, with the nadir occurring 3-5 days after the first dose of navitoclax followed by a subsequent recovery during ongoing dosing. This effect is reversible with interruption of study drug. Platelets recover towards baseline with continued dosing, but may not necessarily reach baseline levels. **Therefore, adequate platelet monitoring should be obtained, including after initiation of navitoclax therapy and when platelet counts are noted to be <50,000/mm^3** (see also Section 6.2). Attenuated lead-in dosing appears to ameliorate the risk of early grade 4 thrombocytopenia, and continuous dosing

mitigates major swings in circulating platelet counts.

Colony stimulating factors (G-CSF, GM-CSF) or human erythropoietin will be considered during administration of navitoclax if deemed necessary by the investigator.

The following concomitant medications are not allowed during navitoclax administration due to mechanistic-based platelet toxicities from navitoclax: Warfarin, Clopidogrel (Plavix), ibuprofen, tirofiban (Aggrastat), and other anticoagulants, drugs, or herbal supplements that affect platelet function. Administration of heparin to keep subject's infusion lines patent is allowed. Low-dose anticoagulation medications that are used to maintain the patency of a central intravenous catheter are allowed.

Aspirin will not be allowed within 7 days prior to the first dose of navitoclax or during navitoclax administration. However, subjects who have previously received aspirin therapy for thrombosis prevention, may resume a low dose (*i.e.*, maximum 100 mg QD) of aspirin if platelet counts are stable ($\geq$50,000/mm^3) through 6 weeks of navitoclax administration. All decisions regarding treatment with aspirin therapy will be determined by the investigator in conjunction with the medical monitor.

Disulfiram is not allowed due to potential drug interactions.

Navitoclax is a moderate inhibitor of the activity of cytochrome P450 (CYP) isoenzyme CYP2C8 (IC_{50} = 3.4 μM or 3.3 μg/mL) and is a potent inhibitor of CYP2C9 activity (IC_{50} = 1.0 μM or 0.97 μg/mL). At the expected biologically effective plasma concentration of about 3 to 5 μM (3–5 μg/mL), navitoclax is likely to inhibit the metabolism of drugs that are substrates for CYP2C8 and CYP2C9. Clinically relevant CYP2C8 substrates include paclitaxel, statins, and glitazones, whereas phenytoin and warfarin are substrates of CYP2C9. Co-dosing with CYP2C8 and CYP2C9 substrates should be undertaken with caution.

Navitoclax is metabolized in the liver by CYP3A4. Strong CYP3A4 inducers/inhibitors are NOT allowed. Weak or moderate inhibitors/inducers are allowed, but should be used with caution. CYP3A4 inhibitors such as ketoconazole and clarithromycin are not allowed 7 days prior to the first dose of navitoclax or during navitoclax administration.

5.4 Duration of Therapy

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

- Disease progression,
- Intercurrent 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 patient unacceptable for further treatment in the judgment of the investigator.
- The study reaches its planned stopping date, which will be 2 years after the last patient's first dose of study drugs. However, in the event that a patient or patients have an excellent response to therapy that is ongoing at the time of this planned stopping date, the possibility of continuing treatment for the patient(s) in question will be subject to discussion.

5.5 Duration of Follow Up

Patients will be followed until the resolution or stabilization of all study-related toxicity and for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

When a situation arises that requires dose interruption or discontinuation of one of the study drugs based on the criteria outlined below, the other study drug should be continued as indicated according to the protocol until the patient meets criteria for removal from study as outlined in Section 5.4.

6.1 Trametinib Dose Modifications

The table below outlines the dose levels to be used for any necessary trametinib dose modifications:

Dose Level	Trametinib Dose/Schedule
0	2 mg QD
-1	1.5 mg QD

-2	1 mg QD
-3	0.5 mg QD

A maximum of two trametinib dose level reductions are allowed. If a third dose level reduction is required, treatment will be permanently discontinued.

6.1.1 Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections

Trametinib Treatment Modification for Clinically Significant Toxicities Likely to be Related to Trametinib in the judgment of investigator (This section is not for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, or visual changes. Refer to other sections for these specific AEs).		
CTCAE v4 Grade *	**Management Guideline**	**Dose Modification**
Grade 1	Monitor as clinically indicated. Provide supportive care according to institutional standards	Continue trametinib at current dose level.
Grade 2 (tolerable)		• Interrupt treatment until resolution to grade 1 or baseline. • Upon resolution, restart treatment at current dose level.
Grade 2 (intolerable) and Grade 3		• Interrupt treatment until resolution to grade 1 or baseline. • Upon resolution to baseline or grade 1, restart with one level of dose reduction • If the Grade 3 toxicity recurs, interrupt trametinib; When toxicity resolves to Grade 1 or baseline, restart trametinib **reduced by another dose level**
Grade 4		Permanently discontinue trametinib.
Trametinib should be discontinued if treatment delay is ≥21 days due to toxicities. If the investigator concludes that continued trametinib will benefit a patient, the study chair and CTEP Medical Monitor may be consulted for the possibility of resuming trametinib, provided that toxicities have resolved to baseline or grade 1.		

* CTCAE v5.0 will be utilized beginning April 1, 2018.

6.1.2 Trametinib Dose Modification for Rash

Rash is a frequent AE observed in patients receiving trametinib (Investigator's Brochure, 2012a). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors (Balagula *et al.*, 2010; Lacouture *et al.*, 2011).

The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the study chair or the CTEP Medical Monitor may be required.

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
Prevention/Prophylaxis[a]	• Avoid unnecessary exposure to sunlight. • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (*e.g.*, glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. • Topical steroids and antibiotics should be applied at least twice daily, starting on Day 1 of study treatment, to body areas such as face, chest, and upper back. • Use mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (*e.g.*, clindamycin) or oral antibiotics (*e.g.*, doxycycline 100 mg BID, minocycline 100 mg BID).
Symptomatic Care[b]	• Pruritic lesions: Cool compresses and oral antihistamine therapies. • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream. • Desquamation: Thick emollients and mild soap. • Paronychia: Antiseptic bath, local potent corticosteroids in addition to antibiotics; if no improvement, consult dermatologist or surgeon. • Infected lesions: Appropriate bacterial/fungal culture-driven systemic or topical antibiotics.
[a] Rash prophylaxis is recommended for the first 6 weeks of study treatment. [b] Patients who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management.	

Trametinib Dose Modification Guidelines and Management for Rash		
Rash Severity	**Management Guideline**	**Dose Modification**
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue trametinib. • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib by one dose level**.[3]

Trametinib Dose Modification Guidelines and Management for Rash		
Rash Severity	**Management Guideline**	**Dose Modification**
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• **Reduce trametinib by one dose level.** • If rash recovers to ≤ grade 1 within 2 weeks, increase dose to previous dose level. • If no recovery to ≤ grade 1 within 2 weeks, interrupt trametinib until recovery to ≤ grade 1. • **Restart trametinib at reduced dose level.**[3]
Grade ≥3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[2] • Consult dermatologist.	• Interrupt trametinib until rash recovers to ≤ grade 1. • **Restart with trametinib reduced by one dose level.**[3,4] • If no recovery to ≤ grade 2 within 4 weeks, **permanently discontinue trametinib**.
1. Rash prophylaxis is recommended for the first 6 weeks of study treatment. 2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone priopionate 0.5% cream. 3. Approval of CTEP Medical Monitor is required to restart study treatment after >4 weeks of interruption. 4. Trametinib may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.		

6.1.3 Trametinib Dose Modifications for Visual Changes

Trametinib is known to be associated with visual adverse events. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions (RVO)). For events of visual changes (regardless of severity) for which an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Patients are required to have a standard ophthalmic exam performed by an ophthalmologist at baseline and any time patients report visual disturbance. The exam will include best corrected visual acuity, tonometry slit lamp biomicroscopic examination, visual field examination, and indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

Guidelines regarding management and dose reduction for visual changes and/or ophthalmic examination findings considered to be related to study treatment are provided in the tables below.

Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1[b]	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • <u>If RPED suspected or diagnosed:</u> see RPED dose modification table below (following this table); **report as SAE.** • <u>If RVO diagnosed:</u> **Permanently discontinue trametinib and report as SAE.**
Grade 2 and Grade 3	• Consult ophthalmologist immediately	• Interrupt trametinib • If RPED and RVO excluded, restart trametinib at same dose level after visual AE is ≤ grade 1. If no recovery within 3 weeks, discontinue trametinib • <u>If RPED diagnosed</u>, see RPED dose modification table below; **report as SAE.** • <u>If RVO diagnosed:</u> **Permanently discontinue trametinib and report as SAE**
Grade 4	• Consult ophthalmologist immediately • Report as SAE	• Interrupt trametinib • If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose <u>after</u> discussion with CTEP medical monitor • **If RVO or RPED diagnosed, permanently discontinue trametinib**

Abbreviations: RPED = retinal pigment epithelial detachment; RVO= retinal vein occlusion; SAE = serious adverse event

a: Refers to CTCAE Version 4.0 'Eye disorders – Other, specify'. CTCAE v5.0 will be utilized beginning April 1, 2018.

b: If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily • If no recovery within 4 weeks, permanently discontinue trametinib.

a: Refers to CTCAE Version 4.0 'Retinopathy'. CTCAE v5.0 will be utilized beginning April 1, 2018.

6.1.4 Trametinib Dose Modification for Diarrhea

Episodes of diarrhea have occurred in patients receiving trametinib (Investigator's Brochure, 2012a). Other frequent causes of diarrhea may include concomitant medications (*e.g.*, stool softeners, laxatives, antacids, *etc.*), infections by *C. difficile* or other pathogens, or partial bowel obstruction. Those conditions should be excluded.

Guidelines regarding management and dose modification for diarrhea considered related to trametinib are provided in the table below.

Management and Trametinib Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 1 or 2	• Diet: Stop all lactose containing products; eat small meals, BRAT-diet (bananas, rice, apples, toast) recommended. • Hydration: 8-10 large glasses of clear liquids per day (*e.g.*, Gatorade or broth). • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea >48 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Add budesonide or other second-line therapies (octreotide, or tincture of opium) and oral antibiotics.	• Continue trametinib. • If diarrhea is grade 2 for > 48 h, interrupt trametinib until diarrhea resolves to grade ≤1. • Restart trametinib at the same dose level • If treatment delay is > 21 days, discontinue trametinib.

Management and Trametinib Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Interrupt trametinib until diarrhea resolves to ≤ grade 1. • Restart with trametinib reduced by one dose level.[4] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue trametinib**. • If treatment delay is >21 days, discontinue trametinib.
1. **Uncomplicated diarrhea** defined by the absence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. 2. **Complicated diarrhea** defined by the presence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. 3. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea. 4. Escalation of trametinib to previous dose level is allowed after consultation with the medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.		

6.1.5 Trametinib Dose Modification for Liver Chemistry Changes

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	Treatment modifications and assessment/monitoring
ALT ≥3x ULN but <5x ULN and TB <2x ULN, without symptoms considered related to liver injury or hypersensitivity and who can be monitored weekly for 4 weeks	May continue study drug. Report as SAE if CTEP-AERS reporting criteria are met. If liver chemistry stopping criteria are met any time, proceed as described below. MONITORING: Repeat LFT (ALT, AST, ALK, bilirubin) until they return to normal/baseline or stabilise (LFT may be every 2 weeks after 4 weeks if ALT <3x ULN and TB <2 ULN).

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	Treatment modifications and assessment/monitoring
Criteria for discontinuing study drug: When any of the liver stopping criteria below is met, discontinue trametinib ALT ≥3xULN and bilirubin ≥2x ULN or >35% direct bilirubin [1, 2] ALT ≥ 3xULN and INR >1.5, if INR measured[2] (INR threshold does not apply if subject is on anticoagulant) ALT ≥5x ULN ALT ≥3x ULN persists for ≥4 weeks ALT ≥3x ULN and cannot be monitored weekly for 4 weeks ALT ≥3x ULN associated with symptoms[3] (new or worsening) believed to be related to liver injury or hypersensitivity	Immediately discontinue study treatment. Do not restart/rechallenge unless approved by CTEP trametinib medical monitor. *[* Report as SAE if: 1) CTEP-AERS reporting criteria are met, or 2) patients meet criteria 1-2. Perform liver event ASSESSMENT AND WORKUP (see below). Monitor the subject until liver chemistries resolve, stabilize, or return to baseline (see MONITORING below). *[* MONITORING: *In patients stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities):* Repeat liver chemistries (ALT, AST, ALK, bilirubin) and perform liver event follow-up assessments within 24 hours. Monitor subjects twice weekly until LFT return to normal/baseline or stabilize. A specialist or hepatology consultation is recommended. *In patients stopping for criteria 3-6:* Repeat LFT and perform liver event follow up assessments within 24-72 hrs Monitor subjects weekly until LFTs return to normal/baseline or stabilize. ASSESSMENT and WORKUP: Viral hepatitis serology.[4] If possible, obtain blood sample for PK analysis.[5] Serum CPK and LDH. Fractionate bilirubin, if total bilirubin ≥2x ULN. CBC with differential to assess eosinophilia. Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). Record alcohol use. *Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities)*: Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	Treatment modifications and assessment/monitoring
	immunoglobulin G (IgG or gamma globulins). Serum acetaminophen adduct HPLC assay (in subjects with likely acetaminophen use in the preceding). If there is underlying chronic hepatitis B (e.g. positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.[6] Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.
Footnotes: 1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, which indicates direct bilirubin elevations and suggesting liver injury. 2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3x ULN and INR >1.5 (if INR measured) may indicate severe liver injury (possible "Hy's Law"). INR measurement is not required, and the threshold value stated will not apply to subjects receiving anticoagulants. 3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia) 4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody 5. PK sample is desired if feasible. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. 6. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal *et al.*, 2005).	

6.1.6 Trametinib Dose Modification for Pneumonitis

Pneumonitis has been observed in patients receiving trametinib. To reduce the risk of pneumonitis, patients will be monitored closely for symptoms and evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in the tables below.

Pneumonitis Guidelines for Trametinib Monotherapy		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	• CT scan (high-resolution with lung windows) recommended. • Work-up for infection. • Monitoring of oxygenation via pulse-oximetry recommended. • Consultation with pulmonologist recommended.	Continue trametinib at current dose.
Grade 2	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests: If < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL recommended. • Symptomatic therapy including corticosteroids if clinically indicated.	• Interrupt trametinib until recovery to grade ≤1. • If AE resolved to grade ≤1 and relationship to trametinib is equivocal, restarting trametinib with one dose reduction may be considered, after discussion with the medical monitor. • If treatment delay is > 4 weeks, **permanently discontinue trametinib**.
Grade 3	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL if possible. • Symptomatic therapy including corticosteroids as clinically indicated.	• Interrupt trametinib until recovery to grade ≤1. • If AE resolved to grade ≤1 and relationship to trametinib is equivocal, restarting trametinib with one dose reduction may be considered, after discussion with the medical monitor. • If treatment delay is >4 weeks, **permanently discontinue trametinib**.
Grade 4	Same as grade 3.	**Permanently discontinue trametinib.**
Abbreviations: BAL = bronchoalveolar lavage; CT = computed tomography.		

6.1.7 Trametinib Dose Modification for Reduced Left Ventricular Ejection Fraction

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib. Therefore, ECHOs or MUGAs must be performed in regular intervals outlined in the Study Calendar. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s).

Trametinib Dose Modification Guidelines and Stopping Criteria for LVEF Decrease		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt trametinib and repeat ECHO within 2 weeks.[a] • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): – Consult with the CTEP trametinib medical monitor and request approval for restart. – Restart treatment with trametinib at reduced dose by one dose level.[b] – Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If LVEF **does not** recover within 4 weeks: – Consult with cardiologist. – Permanently discontinue trametinib. – Report as SAE – Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution. – Consult with the CTEP medical monitor.[d]
Symptomatic[c]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%.	• **Permanently discontinue trametinib.** • **Report as SAE.** • **Consult with cardiologist.** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.
[a] If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later. [b] Escalation of trametinib to previous dose level can be considered in LVEF remains stable for 4 weeks after restarting of trametinib. Approval from the CTEP medical monitor is required. [c] Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.		

6.1.8 Trametinib Dose Modification for QTc Prolongation

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec or • uncorrected QT>600 msec or • QTcB>530 msec for subjects with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to Grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits.

	• Review concomitant medication usage for a prolonged QTc. • Restart at current dose level[b] • **If event does not resolve or recurs after restarting, permanently discontinue study treatment**

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula

a: Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period (within one hour), and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.

b: If the QTc prolongation resolves to Grade 1 or baseline, the subject may resume study treatment if the investigator and CTEP medical monitor agree that the subject will benefit from further treatment.

6.1.9 Trametinib Dose Modification for Hypertension

Increases in blood pressure (BP) have been observed in patients receiving trametinib. Recommendations for BP monitoring and management are provided below.

Monitoring: All BP assessments should be performed under the following optimal conditions:

- The subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor.
- The subject is relaxed comfortably for at least 5 minutes.
- Restrictive clothing has been removed from the cuff area, and the right cuff has been selected.
- The subject's arm is supported so that the middle of the cuff is at heart level.
- The subject remains quiet during the measurement.
- In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the two readings averaged to obtain a final BP measurement. The averaged value should be recorded in the eCRF.
- Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the study calendar. Ideally, subsequent blood pressure assessments should be performed within 1 week.

Management and Trametinib Dose Modification for Hypertension		
Event	**Management Guideline**	**Dose Modification**
Definitions used in the table: - Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. - Well-controlled hypertension: Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits. - Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range. - Asymptomatic hypertension: SBP >140 mmHg and/or DBP >90 mmHg in the absence of the above symptoms.		
(Scenario A) • Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	Continue trametinib at the current dose.
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt trametinib if clinically indicated. • Once BP is well-controlled, restart trametinib reduced by one dose level.[a]
(Scenario C) • Symptomatic hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt trametinib. • Once BP is well-controlled, restart trametinib reduced by one dose level.[a]
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	Permanently discontinue trametinib.
a: Escalation of trametinib to previous dose level can be considered if BPs remain well-controlled for 4 weeks after restarting of trametinib. Approval from the CTEP medical monitor is required.		

6.2 Navitoclax Dose modifications

The table below outlines the dose levels to be used for any necessary navitoclax dose modifications:

Dose Level	Navitoclax Dose/Schedule
6	325 mg QD
5	300 mg QD
4	250 mg QD
3	200 mg QD
2	150 mg QD
1	100 mg QD

A maximum of three navitoclax dose level reductions are allowed. If a fourth dose level dose reduction is required, navitoclax will be permanently discontinued.

If navitoclax is held > 21 days, it should be discontinued.

6.2.1 Management of Thrombocytopenia

6.2.1.1 Dose Reduction and Interruption

Navitoclax accelerates apoptosis of circulating platelets, which differs from typical chemotherapy-induced thrombocytopenia related to myelosuppression.

All decisions regarding continued navitoclax dosing for individual subjects will be determined by the investigator, as appropriate. These decisions should be guided by the following:

Additional platelet counts should be performed every other day or at the discretion of the investigator for a platelet count on any given day that is less than 50,000/mm^3.

Administration of navitoclax will be interrupted or discontinued for any pre-dose platelet count <25,000/mm^3. A platelet count <25,000/mm^3 should be confirmed the same day by a separate peripheral blood draw and sent also for a peripheral blood smear.

For any clinically significant bleeding event, defined as grade 2 or higher hemorrhage regardless of platelet count, navitoclax should be withheld, and:

- Once the toxicity recovers to an acceptable grade level (*i.e.*, ≤grade 1 bleeding and/or platelet count is ≥50,000/mm^3 and stable or increasing), navitoclax may be restarted at a reduced dose of DL –1.
- If the toxicity recurs at the dose levels above, navitoclax should once again be interrupted. Once the toxicity recovers to an acceptable grade level, navitoclax may be restarted at reduced dose of DL –2.
- If the toxicity recurs at the dose levels above, navitoclax should once again be interrupted. Once the toxicity recovers to an acceptable grade level, navitoclax may be restarted at DL –3 or stopped altogether.

After any grade 4 platelet count <25,000/mm^3 is observed for the first time per month in a

subject, serial PK samples will be collected. PK samples will be collected as soon as possible after the grade 4 platelet count is determined and then 24 and 48 hours after the event.

Limited human clinical data are available to understand the response to infusion of exogenous platelets in the presence of circulating drug levels. Data from a single dose and a 28-day multiple dose, nonclinical studies in dogs demonstrate that under conditions of navitoclax plasma concentrations exceeding concentrations in the clinic (>10 μg/mL) and rapid platelet apoptosis, platelet infusions do not have a measurable effect on circulating platelet counts. However, under conditions of lower navitoclax plasma concentrations (<10 μg/mL), platelet infusions do result in an increase in circulating platelet counts. This response appears to be more consistent and of greater duration as navitoclax plasma concentrations decline. Although the administration of multiple platelet transfusions may produce a sustained increase in circulating platelets, post-transfusion platelet kinetics should be monitored when clinically indicated.
If platelet transfusions are required in response to active bleeding, dosing of navitoclax should be suspended. It should be noted that platelet response with transfusions may not follow typical platelet kinetics of thrombocytopenia as with typical chemotherapy-induced myelosuppression. Procedures consistent with local institutional blood banking guidelines regarding platelet transfusions should be followed.

6.2.1.2 Platelet Transfusion Recommendations

If a platelet transfusion is deemed necessary, the investigator should be aware of the following:

- Due to the rapid apoptotic effect of navitoclax on mature platelets, the initial increase in platelet counts post-transfusion(s) may be smaller and the duration of response may be shorter. For this reason, the most recently collected donor platelets should be transfused.
- A post-transfusion platelet count should be obtained within 10 to 60 minutes.
- Additional transfusions may be necessary to achieve the desired platelet response.

6.2.2 Management of Lymphopenia

There is a potential for lymphopenia in this study. Anti-infective prophylaxis should be implemented at the investigator's discretion, including appropriate prophylaxis for viral, fungal, bacterial, or *Pneumocystis carinii Pneumonia* (PCP) infections. Potential for drug-drug interactions should be considered. See description of excluded and cautionary medications. Given the potential for increased thrombocytopenia associated with many of the agents used for PCP prophylaxis, investigators should consult with the principal investigator prior to initiating PCP prophylaxis.

6.2.3 Management of Neutropenia

Standard management practices for neutropenia should be followed. Preliminary data analysis from the ongoing phase 1 studies in subjects with CLL demonstrates an apparent trend in decreasing baseline-normalized absolute neutrophil count (ANC) nadir with increasing doses,

C_{max}, or AUC.

6.2.4 Management of Tumor Lysis Syndrome

In subjects with various tumor types, there is a potential for tumor lysis in the presence of risk factors such as bulky disease, elevated pre-treatment LDH levels, elevated leukocyte count, and dehydration. Adequate hydration, careful monitoring of laboratory values, and use of an agent to reduce the uric acid level should be considered for subjects at high risk in the first 4 weeks. For subjects who are at high risk during subsequent weeks, please consider the same management plan.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. AEs will be collected and reported from the start of study treatment (first dose of study drug) and until the end of the follow up period as defined in section 5.5. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The subset of AEs (SPEER) is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 968 patients.* Below is the CAEPR for Trametinib dimethyl sulfoxide (GSK1120212B).

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

7.1.1 CAEPRs for CTEP IND Agents

7.1.1.1 CAEPR for Trametinib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for

Trametinib dimethyl sulfoxide (GSK1120212B, NSC 763093)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1111 patients.* Below is the CAEPR for trametinib dimethyl sulfoxide (GSK1120212B).

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

Version 2.6, October 10, 2019[1]

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
	Sinus bradycardia		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
		Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	
	Eye disorders - Other (visual disorders)[2]		
		Papilledema	
	Periorbital edema		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
Generalized edema[3]			***Generalized edema[3] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[4]		
INFECTIONS AND INFESTATIONS			
	Folliculitis		***Folliculitis (Gr 2)***
	Lung infection		
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	CPK increased		
	Ejection fraction decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypoalbuminemia		
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Nail changes		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])	
Skin and subcutaneous tissue disorders - Other (rash)[5]			***Skin and subcutaneous tissue disorders - Other (rash)[5] (Gr 3)***
		Stevens-Johnson syndrome[6]	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event (venous)	
	Vascular disorders - Other (hemorrhage)[7]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Visual disorders include visual disturbance that can be associated with conjunctival hemorrhage, corneal graft rejection, cyclitis, eye nevus, halo vision, iritis, macular edema, retinal hemorrhage, visual acuity reduced, visual impairment, and vitreous detachment.

[3]Generalized edema includes edema, lymphedema, and edema limbs.

[4]Hypersensitivity (allergic reactions) may present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.

[5]Skin and subcutaneous tissue disorders - Other (rash) may include rash, rosacea, rash acneiform, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrhoeic dermatitis, dermatitis psoriasiform, rash follicular, skin fissures, and skin chapped.

[6]Stevens-Johnson syndrome has been observed in patients treated with trametinib and dabrafenib combination.

[7]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage), and fatal intracranial hemorrhages have been reported.

Adverse events reported on trametinib dimethyl sulfoxide (GSK1120212B) trials, but for which

there is insufficient evidence to suggest that there was a reasonable possibility that Trametinib dimethyl sulfoxide (GSK1120212B) caused the event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy, sinus tachycardia
EYE DISORDERS - Corneal ulcer; Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Photophobia
GASTROINTESTINAL DISORDERS – Ascites; Duodenal ulcer; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric hemorrhage; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage; Ileus; Obstruction gastric; Pancreatitis; Small intestinal obstruction;
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); Localized edema; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS – Cholecystitis; Hepatic failure; Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy)
INFECTIONS AND INFESTATIONS - Biliary tract infection; Catheter related infection; Device related infection; Endocarditis infective; Enterocolitis infectious; Hepatitis viral; Infections and infestations - Other (abscess limb); Infections and infestations - Other (necrotizing fasciitis); Infections and infestations - Other (oral infection); Pharyngitis; Sepsis; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Lymphocyte count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia;
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (compression fracture); Myalgia; Neck Pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria; Hematuria; Proteinuria; Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension;

Note: Trametinib dimethyl sulfoxide (GSK1120212B) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for Navitoclax

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Navitoclax (ABT-263, NSC 750238)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 934 patients.* Below is the CAEPR for Navitoclax (ABT-263).

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

Version 2.6, November 16, 2021[1]

Adverse Events with Possible Relationship to Navitoclax (ABT-263) (CTCAE 5.0 Term) [n= 934]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Febrile neutropenia		
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all

Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[3]Peripheral neuropathy includes Peripheral motor neuropathy and Peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC.

Adverse events reported on Navitoclax (ABT-263) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Navitoclax (ABT-263) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia
CARDIAC DISORDERS - Cardiac arrest; Sinus bradycardia
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Constipation; Dyspepsia; Enterocolitis; Flatulence; Mucositis oral; Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Edema trunk; Fever; Flu like symptoms; Malaise
HEPATOBILIARY DISORDERS - Hepatic pain
INFECTIONS AND INFESTATIONS - Infections[2]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Hemoglobin increased; Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Generalized muscle weakness; Muscle cramp; Myalgia; Neck pain; Pain in extremity
NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia; Headache; Nervous system disorders - Other (burning sensation); Nervous system disorders - Other (neuropathy peripheral)[3]; Stroke; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Oropharyngeal pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Pruritus; Rash maculo-papular
VASCULAR DISORDERS - Hypotension

Note: Navitoclax (ABT-263) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting.

CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (Cancer Therapy Evaluation Program Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

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

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

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

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** in the system organ class (SOC) "General disorders and administration site conditions". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.3.4 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the **Pregnancy Information Form** should be completed and faxed along with any additional medical information to **301-230-0159.** The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

7.3.4.1 **Pregnancy**

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3** "***Pregnancy, puerperium and perinatal conditions - Other (Pregnancy)***" under the ***Pregnancy, puerperium and perinatal conditions*** SOC.
- There is a possibility that the sperm of male patients treated on studies involving possible teratogenic agents may have been damaged. For this reason, pregnancy in partners of men on study should also be reported and followed as described in this section.
- Pregnancy should be followed until the outcome is known.

7.3.4.2 **Pregnancy Loss**

- Pregnancy loss is defined in CTCAE as "***Death in Utero.***"
- Any Pregnancy loss should be reported expeditiously, as **Grade 4** "***Pregnancy Loss***" under the ***Pregnancy, puerperium and perinatal conditions*** SOC.
- A Pregnancy loss should **NOT** be reported as a Grade 5 event under the ***Pregnancy, puerperium and perinatal conditions*** SOC, as currently CTEP-AERS recognizes this event as a patient death.

7.3.4.3 **Death Neonatal**

- Neonatal death, defined in CTCAE as "**A disorder characterized by cessation of life occurring during the first 28 days of life**" that is felt by the investigator to be at

least possibly due to the investigational agent/intervention, should be reported expeditiously.

- A neonatal death should be reported expeditiously as **Grade 4** "***Death neonatal***" under the ***General disorders and administration*** SOC.
- Neonatal death should **NOT** be reported as "***Death neonatal"*** under the ***General disorders and administration SOC***, a Grade 5 event. If reported as such, CTEP-AERS interprets this as a death of the patient being treated.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

7.6 Second Malignancy

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

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agents

8.1.1 Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)

Chemical Name (IUPAC): equimolecular combination of N-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl}phenyl)acetamide with (methylsulfinyl)methane

Other Names: trametinib, Mekinist, GSK1120212, JTP-74057, JTP-78296, JTP-75303

CAS Registry Number: 1187431-43-1

Classification: MEK inhibitor

Molecular Formula: $C_{26}H_{23}FIN_5O_4 \bullet C_2H_6OS$
M.W.: 693.54 (dimethyl sulfoxide solvate), 615.41 (anhydrous parent)

Approximate Solubility: Trametinib dimethyl sulfoxide is almost insoluble in water (<0.0001 mg/mL at 25° C)
Mode of Action: Trametinib dimethyl sulfoxide is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Tumor cells commonly have hyperactivated extracellular signal-related kinase (ERK) pathways in which MEK is a critical component. Trametinib dimethyl sulfoxide inhibits activation of MEK by RAF kinases and MEK kinases.

Description: Trametinib dimethyl sulfoxide is a white to almost white powder.

How Supplied: Novartis supplies and CTEP, NCI, DCTD distributes trametinib as 0.5 mg and 2 mg (as free base) tablets. Tablets may be provided in investigationally-labeled bottles or commercially-labeled bottles.

The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), colloidal silicon dioxide and sodium lauryl sulfate.

The aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow (0.5 mg tablet), iron oxide red (2 mg tablet) and polysorbate 80 (2 mg tablet).

Each investigationally-labeled bottle contains 32 tablets with a desiccant:

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated.
- 2 mg tablets are pink, round, biconvex and film-coated.

Each commercially-labeled bottle contains 30 tablets with a desiccant:

- 0.5 mg tablets are yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face.

- 2 mg tablets are pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face.

Storage: Store tablets at 2°C - 8°C in the original bottle and dispense unopened bottles. Do not open bottles or repackage tablets or remove desiccant. Bottles should be protected from light and moisture.

If a storage temperature excursion is identified, promptly return trametinib to 2°C - 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing. Tablets are only stable for 32 days once bottle has been opened. If multiple bottles are dispensed to a patient in the same visit, please advise the patient to open only one bottle at a time.

Route of Administration: Oral. Take by mouth on an empty stomach, either 1 hour before or 2 hours after a meal.

Potential Drug Interactions

In vitro studies suggest that trametinib dimethyl sulfoxide is not a substrate of CYP enzymes or of human Pgp, BCRP, OATP1B1 or OATP1B3 transporters.

Trametinib dimethyl sulfoxide is a weak CYP2C8 inhibitor and weak CYP3A4 inducer. Drug-drug interactions with sensitive substrates of 2C8 and 3A4 are not anticipated.

Availability

Trametinib dimethyl sulfoxide (GSK1120212B) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Navitoclax (ABT-263; NSC 750238)

Chemical Name or Amino Acid Sequence: Benzamide, 4-[4-[[2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl]-1-piperazinyl]-*N*-[[4-[[(1*R*)-3-(4-morpholinyl)-1-[(phenylthio)methyl]propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]

Other Names: ABT-263

Classification: BCL-2 family protein inhibitor

Molecular Formula: $C_{47}H_{55}ClF_3N_5O_6S_3$ **M.W.:** 974.61 g/mol

Approximate Solubility: Navitoclax free base is practically insoluble in water

Mode of Action: Navitoclax is an orally bioavailable BCL-2 family protein inhibitor that binds with high affinity to multiple antiapoptotic proteins including BCL-X_L, BCL-2, and BCL-W. Antiapoptotic BCL-2 family members are associated with tumor initiation, disease progression, and drug resistance, and compelling targets for oncology drug development.

Description: White to light pink powder.

How Supplied: AbbVie supplies and **t**he DCTD/NCI distributes navitoclax as 25 mg and 100 mg film coated tablets packaged in 28 and 30 count high-density polyethylene (HDPE) bottles, respectively.

Navitoclax inactive ingredients are Copovidone, Vitamin E polyethylene glycol succinate, colloidal silicon dioxide, croscarmellose sodium, sodium stearyl fumarate (coating, 25 mg: iron oxide red or iron oxide yellow, polyvinyl alcohol, polyethylene glycol 3350, talc, titanium dioxide; and 100 mg: iron oxide yellow or oxide red, polyvinyl alcohol, polyethylene glycol 3350, talc, titanium dioxide).

Note: Navitoclax must be dispensed in its original bottle. If need to dispense the exact count to patient, removing extra tablet(s) from the original bottle is allowed. Document the extra tablet(s) as wasted in Oral DARF.

Note: There will be a change of tablet color in future lots of navitoclax in the coming months.

	Previous and Current Lots	Future Lots
25 mg Tablets	Pink	Yellow
100 mg Tablets	Yellow	Pink

Storage: Store intact bottles of navitoclax at room temperature 15^0 – 25^0C (59^0- 77^0F), protect from light.

If a storage temperature excursion is identified, promptly return navitoclax (ABT-263) to 15^0 – 25^0C (59^0- 77^0F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf life stability studies for the intact bottles of navitoclax are on-going.

Route*(s)* of Administration: Oral.

Method of Administration: Take navitoclax tablets with food.

Potential Drug Interactions:

CYP-mediated DDI: Navitoclax metabolizes via CYP3A4. Concomitant use of strong and moderate CYP3A4 inhibitors/inducers should be taken with caution. Use alternative medications if possible.

In vitro studies, navitoclax is a moderate inhibitor of CYP2C8, a strong inhibitor of CYP2C9 and a weak inhibitor of CYP2C19, CYP2D6 and CYP3A4 following a 300 mg QD dose. Use caution when navitoclax is administered with sensitive substrates of CYP2C8 and CYP2C9.

Navitoclax is not an inducer of CYP1A2, CYP2B6, CYP2C9 and CYP3A4 and therefore is not expected to have any potential for DDI via CYP. As for M13, it did not increase CYP1A2, CYP2B6 and CYP3A4 mRNA expression when tested at concentrations up to 30 µM.

Transporter mediated DDI: Navitoclax and M13 (navitoclax metabolite) are inhibitors of OATP1B1/3, with IC_{50} values of 2.0 µM (navitoclax) and 20.8 µM (M13) but do not result in DDI based on the static model (OATP1B1/1B3, R<1.1). Navitoclax may inhibit P-gp and BCRP at therapeutic doses (I_{gut}/IC_{50}>10). Both navitoclax and M13 are P-gp and BCRP substrates but are not OATP1B1/3 substrates.

Navitoclax and M13 are not inhibitors of OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K. M13 is not an inhibitor of P-gp, BCRP, or BSEP in vesicles or in MDCK cells.

Plasma Protein Binding: Navitoclax was highly bound to plasma proteins across species. Protein binding was highest in the human and dog (99.99%) followed by the mouse, rat, and monkey (99.98%). For each species studied, the extent of binding was constant over the entire drug concentration range (10 to 500 µg/mL) and the
binding was independent of gender. The results indicate that navitoclax will be highly bound (99.99%)
to proteins in human plasma at concentrations expected after a therapeutic dosage (Cmax of 6.5 µg/mL).

Patient Care Implications:

Women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) while on treatment with navitoclax (ABT-263) and at up to 30 days after the last dose of navitoclax (ABT-263). Male study subjects who are sexually active with a WOCBP (woman of child-bearing potential), even if the male subject has undergone a successful vasectomy, must agree to use condoms while on treatment and through at least 90 days after the last dose of study drug.

It is unknown whether navitoclax is excreted in human milk; thus, breastfeeding is not allowed.

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NCI Biosketch, Agenda Shipment Form, and Financial Disclosure Form (FDF)

Submit agent request through the PMB Online Agent Ordering Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) (https://ctepcore.nci.nih.gov/iam) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call (240-276-6575) or email PMB (PMBAfterHours@mail.nih.gov) any time. Refer to the PMB's website for specific policies and guidelines related to agent management."

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.

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

8.2 Other Investigational Agent(s)

N/A

8.3 Commercial Agent(s)

N/A

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies and Patient Tumor Biopsies

9.1.1 Validation of KRAS and NRAS mutations

9.1.1.1 Rationale

To ensure the validity and accuracy of KRAS or NRAS mutations in patients enrolled in this study, KRAS and NRAS genotyping will be confirmed centrally at a single institution (Massachusetts General Hospital) using a standardized CLIA-approved clinical genotyping platform. For those patients whose KRAS or NRAS status was not determined initially by this platform, KRAS or NRAS mutation will be confirmed retrospectively using this standardized assay provided that tissue is available for analysis. However, patients will be allowed to enroll in the study prior to retrospective validation, provided they have a documented KRAS or NRAS mutation as determined by a CLIA-approved assay.

9.1.1.2 Procedures and Analysis

KRAS or NRAS mutational status will be confirmed using the CLIA-approved standard clinical genotyping platform used for routine clinical care at the Massachusetts General Hospital, the SNaPshot assay (Dias-Santagata *et al*, 2010). SNaPshot assay will be performed in the Molecular Pathology Laboratory at the Massachusetts General Hospital Cancer Center.

9.1.2 Pharmacodynamic analyses in paired pre-treatment and on-treatment tumor biopsies.

9.1.2.1 Rationale

This study will incorporate ancillary/exploratory pharmacodynamic analyses to evaluate the effects of trametinib and navitoclax given in combination on key cellular signaling pathways and on the induction of apoptosis and inhibition of tumor cell proliferation. Paired pre-treatment and on treatment (day 22 +/- 7 days) core biopsies will be obtained from all patients in the Phase 1b

schedule A portion of the trial, (day 15 +/- 7 days) in the schedule B or C portion, and the first 15 patients enrolled on the Phase 2 portion of the trial (minimum of 4 patients from each of cohorts 1, 2 and 3 will be biopsied), if these patients have lesions that can be safely biopsied without unacceptable risk or discomfort to the patient. Biopsies from patients in the Phase 1b portion of the trial will provide an evaluation of the effects of each cohort's dose level on signaling pathway inhibition, inhibition of tumor cell proliferation, and induction of tumor cell death. This will provide an important metric as to the extent of target inhibition at each given dose level. Paired biopsies obtained from the first 15 patients enrolled in the Phase 2 portion of the trial (minimum of 4 patients from each of cohorts 1, 2 and 3 will be biopsied) will provide a more detailed assessment of the pharmacodynamic effects of therapy at the RP2D and will offer the potential to correlate pharmacodynamic effects with tumor response and patient outcome.

Previous studies incorporating pharmacodynamic analyses of targeted agents (including MEK inhibitors) given in combination have shown that the degree of target and/or pathway inhibition achieved at doses of targeted agents reachable when given in combination (which are often less than the doses achievable when given as single agents, due to additive toxicity) can be incomplete, and thus inadequate to promote efficacy (Speranza et al., 2012). Thus, it will be critical to understand the degree of target and/or pathway inhibition achieved at a given dose level of the combination and at the RP2D, as this may have important implications on the efficacy observed.

9.1.2.2 Procedures and analysis

Given the potential effects of navitoclax on platelets and bleeding risk, platelet count and coagulation studies (INR, PTT) will be checked on the same day prior to any research biopsies performed while patient is taking study drugs. A platelet count of >50,000/m^3 and an INR and PTT in the normal/acceptable range according to institutional guidelines will be required for a patient to undergo tumor biopsy.

Pre-treatment biopsies will be obtained between days -21 and -1 of treatment. When possible, it is preferred, but not required, that the pre-treatment biopsy be performed between days -7 and -1 of treatment in order to most accurately represent the baseline signaling activity prior to treatment. On-treatment biopsies will be obtained after ~2 weeks of combination dosing (day 22 +/- 7 days for Schedule A dosing, day 15 +/- 7 days for Schedule B or C dosing). Core biopsies of the same tumor lesion will be obtained at each time point. A minimum of one core will be formalin-fixed and paraffin-embedded, and a minimum of one core will be flash frozen. Both formalin-fixed paraffin-embedded and flash frozen tissue will be stored in the pathology department at the Massachusetts General Hospital.

Paired biopsies will be used to assess the pharmacodynamic response to therapy in patients treated with trametinib and navitoclax. Markers to be assessed will include proteins or mRNAs involved in MAPK or BCL2 family signaling (e.g. phospho-ERK, phospho-S6, or MAPK phosphatases such as DUSP6/MKP1) to evaluate pathway inhibition, markers of tumor cell proliferation (e.g. Ki67), and markers of apoptosis and cell death (e.g. Cleaved caspase-3).

These ancillary/exploratory analyses will be conducted in the Massachusetts General Hospital Molecular Pathology Biomarker Laboratory. For each patient, the change in marker level between the pre-treatment and on-treatment biopsies will indicate the effects of treatment on each marker. Results will be reported as a % increase or decrease in level of a given marker after treatment initiation (on-treatment biopsy) relative to before treatment (pre-treatment biopsy).

9.1.2.3 Potential risks to patients

The research biopsies performed on this study do carry a low risk of procedure-related complications. To minimize these risks, biopsies will be performed by personnel who are highly-trained and experienced with these procedures (procedures will typically be performed by interventional radiology). In addition, the choice of biopsy site will be based on determination of sites that will have the lowest risk of complication based on sites of disease for the individual patient. Adequate measures will be performed to monitor patients undergoing biopsies. All potential risks associated with these research-purpose biopsies will be discussed verbally and in writing with the patient during the informed consent process upon study enrollment by the study team, and again prior to the procedure by the provider performing the biopsy (typically interventional radiology). Patients will have the choice not to participate in this study if they do not wish to undergo research-related biopsies. Biopsies will only be performed in a given patient if they are not deemed to involve unacceptable risk based on the sites of disease and other concurrent medical conditions. **Given the potential for thrombocytopenia associated with navitoclax, biopsies will only be performed if platelet count is >50,000cells/mm3 and stable and coagulation studies (PT/INR and PTT) are in acceptable range, in accordance to institutional guidelines.**

9.1.3 Identification of potential predictive biomarkers in pre-treatment tumor tissue

9.1.3.1 Rationale

Given the molecular heterogeneity of KRAS and NRAS mutant cancers, no single therapeutic regimen is expected to be effective in all patients. Therefore, molecular characterization of archived or pre-treatment tumor biopsy tissue for each patient enrolled on this trial will provide a critical opportunity to identify valuable biomarkers to predict which patients are more or less likely to respond to treatment. Initially, these analyses will be exploratory and hypothesis-generating in nature, but promising biomarker candidates identified in this study can potentially be assessed in future clinical studies evaluating this therapeutic regimen.

Initial laboratory studies evaluating the combination of BCL-XL and MEK inhibition in KRAS mutant cancer cell lines have identified potential biomarkers of sensitivity. For example, our initial studies (Corcoran et al., 2013) have suggested that KRAS mutant cancers that express markers of epithelial differentiation (e.g. E-cadherin) are more likely to respond to this therapy than cancers expressing markers of mesenchymal differentiation (e.g. vimentin). Thus, E-cadherin and vimentin levels will be assessed by immunohistochemistry in pre-treatment tumor tissues of all patients enrolled on this study and correlated with clinical outcome. Our initial

work has shown that E-cadherin and vimentin can be readily assessed in formalin-fixed paraffin-embedded tissue from KRAS mutant cancer patients (Corcoran et al, 2013).

9.1.3.2 Procedures and analysis

Pre-treatment tumor tissue for analysis will be obtained either from archival tissue remaining from a patients' prior surgery, diagnostic biopsy, or other procedure performed during routine clinical care. These archival tissue blocks will be obtained from the pathology departments of the Massachusetts General Hospital or Dana Farber Cancer Institute, or will be provided by the pathology department of the institution at which the procedure was performed. Alternatively, tissue derived from the study-related pre-treatment biopsy may also be used for this purpose if necessary. At least 20 unstained slides should be obtained. If a patient is having a tumor biopsy, less than 20 are acceptable with PI approval.

9.1.3.3 Mutational analysis

In depth, mutational analysis will be performed using a 1000 gene next-generation sequencing platform employed as part of standard oncology care at the Massachusetts General Hospital Cancer Center. Mutations in these 1000 cancer-related genes that might affect the likelihood of a patient's tumor to respond to therapy will be correlated with clinical outcome. In addition, further in-depth genomic analyses, including copy number analysis, may be performed on selected specimens.

9.1.3.4 Protein and RNA biomarkers

Selected protein and RNA biomarkers identified in previous (and future) laboratory studies will be analyzed in pre-treatment tissues. Based on initial laboratory studies (Corcoran et al, 2013) discussed above, E-cadherin and vimentin protein levels will be assessed by immunohistochemistry in formalin-fixed paraffin-embedded tissues. These analyses will be performed using established clinical testing assays by the Clinical Pathology Laboratory at the Massachusetts General Hospital. Analysis of additional protein and RNA biomarkers, such as baseline levels of BIM, BCL-XL, MCL1, and other apoptotic proteins, will also be performed.

9.1.3.5 Potential risks to patients

The majority of these analyses will involve archival tissue previously obtained through clinical procedures performed as part of routine clinical care. As such, no additional risks will be posed for patients. In the situation where no archival tissue exists, or if archival tissue is not suitable for analysis (e.g. does not contain tumor tissue), then tissue for analysis will be obtained from the protocol related pre-treatment biopsy outlined above in Section 9.1.1. The risks associated with these biopsies are outlined in Section 9.1.1. However, since patients will already be undergoing these biopsies as part of the research study plan, no additional risk will be posed by utilizing the tissue that is collected for these analyses.

9.1.4 Blood collection for cell-free circulating tumor DNA (cfDNA) analysis

9.1.4.1 Rationale

cfDNA analysis represents an increasingly important and noninvasive means of assessing mutations in tumor-derived DNA shed into the bloodstream by tumor cells throughout the patient's body. cfDNA analysis can provide a highly specific means of monitoring tumor burden by tracking the abundance of tumor-derived DNA mutations in the blood throughout treatment. Sequencing of cfDNA can also provide a non-invasive means of performing targeted or comprehensive tumor mutational analysis without the need for a biopsy.

9.1.4.2 Procedures and analyses

20 mL of peripheral blood will be collected in two 10 mL Streck cfDNA tubes at each of the timepoints outlined in the study calendar, including pre-treatment, at various intervals during treatment and at disease progression. Streck tubes containing whole blood can be shipped at room temperature (within 5 days of draw) to:

Corcoran Laboratory
Massachusetts General Hospital Cancer Center
149 13th St, Room 7330
Charlestown, MA 02129

Cell free plasma will be isolated through two serial centrifugations steps, and plasma and blood cell pellet will be aliquoted and frozen. cfDNA will be isolated from 5 mL using a QIAGEN cfDNA kit and will be analyzed by droplet digital PCR (ddPCR) using probes specific to the particular KRAS or NRAS mutation present in each patient's tumor. Serial measurement of KRAS or NRAS mutational abundance in cfDNA throughout treatment will provide a non-invasive and personalized means of monitoring tumor burden, and the change in mutation levels in cfDNA will be correlated with radiographic response. In select patients of interest, such as patients who respond to therapy, but ultimately progress, cfDNA derived from pre-treatment and post-progression plasma may be analyzed by next-generation sequencing methods to identify potential mechanisms of acquired resistance.

9.1.4.3 Risks to patients

All blood for cfDNA analysis will be drawn at the time of routine lab draws for other study-associated blood draws, and thus will not pose significant additional risk to the patient.

9.2 Investigational Device Information

N/A

9.3 Laboratory Correlative Studies

9.3.1.1 ***Pharmacokinetic Studies of navitoclax and trametinib dosed in combination***

While the pharmacokinetics (PK) of trametinib and navitoclax given as single agents is well-understood, this study will evaluate the pharmacokinetics of these agents when given in combination. These studies will be used to determine whether trametinib and navitoclax interact from a pharmacokinetic standpoint, and will be used to determine the plasma drug exposures achievable at a particular combination dose level and at the maximally-tolerated dose and RP2D. The pharmacokinetics and plasma drug levels achieved during combination dosing will have key implications on the potential for efficacy at a given dose level.

During Part 1 (the Phase 1b portion) of the study, subjects will have blood drawn pre-dose (0h), and 2h, 4h, 6h, 8h, and 23h after dosing of navitoclax on (1) day 7 of a 7-day navitoclax single-agent lead-in dosing period and (2) again after 14 days of combination dosing. The exact timing of PK blood draws will thus vary depending on whether navitoclax is being given as a single-agent and whether a subject is following dosing schedule A or B/C (as defined in Section 5.1). The exact timing of PK draws are outlined in table format in section 9.3.1.2 below. Subjects will also have PK blood samples drawn pre-dose on day 1 of cycles 2, 4, 8, and 12.

During Part 2 (the Phase 2 portion) of the study, subjects will have PK blood samples drawn pre-dose on day 1 of cycles 2, 4, 8, and 12. The exact timing of PK draws are outlined in table format in section 9.3.1.2 below.

PK blood samples will be analyzed by AbbVie (for navitoclax) and GSK (for trametinib) according to established procedures, and assessed for the endpoints described in Sections 2.5.1 and 13.4.1.1.

9.3.1.2 Collection of Specimens

PK blood specimens will be drawn according to the schedules below, which vary depending on which study part—Part 1 (Phase 1b) vs. Part 2 (Phase 2)—and which dosing schedule—Schedule A vs. B—to which a given subject has been enrolled.

For the purposes of these dosing schedules:

(1) All blood draw times are relative to administration of navitoclax (0h = pre-dose for navitoclax).
(2) On PK days, trametinib is to be dosed in the morning on empty stomach ONE HOUR (+/- 5 minutes) before navitoclax dose is administered with food. Thus, when a patient is receiving both drugs, an additional trametinib pre-dose (-1h) PK sample will be drawn.
(3) On non-PK days, the medications do not necessarily need to be taken in this sequence, but trametinib should always be taken on an empty stomach (defined as at least one hour +/- 5 minutes before and/or two hours after food,) and navitoclax should always be taken with food. However, patients are encouraged to keep to the same schedule used on PK

days as part of their daily administration, if possible.

Procedures for sample collection are outlined in detail in APPENDIX C.

9.3.1.2.1 Schedule for PK sample collection for Part 1 (Phase 1b) Schedule A

Cycle (C), day (D)	Timing of PK sample blood draws	PK for
C1, D7*	Pre-dose (0h **,) 2h (+/-5 min,) 4h (+/-5min,) 6h (+/- 5 min,) 8h (+/-24 min)	***Navitoclax only***
C1, D8*	Pre-dose trametinib (will represent 23h post dose navitoclax from prior day, +/-1 hr)	***Navitoclax only***
C1, D21[#]	Pre-dose trametinib** (-1h), pre-dose navitoclax (0h**,) 2h (+/-5min,) 4h (+/-5min,) 6h (+/-5min,) 8h (+/-24 min)	Navitoclax and trametinib
C1, D22[#]	Pre-dose trametinib** (-1h) (will represent 23 h post-dose navitoclax from prior day, +/-1hr)	Navitoclax and trametinib
C2, D1	Pre-dose trametinib** (single trough level)	Navitoclax and trametinib
C4, D1	Pre-dose trametinib** (single trough level)	Navitoclax and trametinib
C8, D1	Pre-dose trametinib** (single trough level)	Navitoclax and trametinib
C12, D1	Pre-dose trametinib** (single trough level)	Navitoclax and trametinib

* Navitoclax dosed as single-agent for 7-day lead-in under Schedule A. Thus, these PK assessments will be for navitoclax only. All other PK assessments will be for navitoclax and trametinib.
[#] Represents 14th day of trametinib dosing under Schedule A
** Pre- dose samples should be drawn within 5 minutes of dosing

9.3.1.2.2 Schedule for PK sample collection for Part 1 (Phase 1b) Schedule B

Cycle (C), day (D)	Timing of PK sample blood draws	PK for
C1, D7	Pre-dose trametinib (-1h)**, pre-dose navitoclax (0h)**, 2h (+/-5 min,) 4h (+/-5min,) 6h (+/-5 min,) 8h (+/-24 min)	Navitoclax and trametinib
C1, D8	Pre-dose trametinib – (will represent 23h post-dose navitoclax from prior day, +/- 1 hr)	Navitoclax and trametinib

C1, D14[#]	Pre-dose trametinib (-1h)**, pre-dose navitoclax (0h)**, 2h (+/- 5 min,) 4h (+/-5 min,) 6h (+/- 5 min,) 8h (+/- 24 min)	Navitoclax and trametinib
C1, D15[#]	Pre-dose trametinib (-1h) (will represent 23h post-dose navitoclax from prior day, +/- 1 hr)	Navitoclax and trametinib
C2, D1	Pre-dose trametinib** (single trough level)	Navitoclax and trametinib
C4, D1	Pre-dose trametinib** (single trough level)	Navitoclax and trametinib
C8, D1	Pre-dose trametinib** (single trough level)	Navitoclax and trametinib
C12, D1	Pre-dose trametinib** (single trough level)	Navitoclax and trametinib

** Pre- dose samples should be drawn within 5 minutes of dosing
[#] Represents 14th day of trametinib dosing under Schedule B

9.3.1.2.3 Schedule for PK sample collection for Part 1 (Phase 1b) Schedule C

Cycle (C), day (D)	Timing of PK sample blood draws	PK for
C1, D7	Pre-dose navitoclax (0h), 2h (+/-5 min,) 4h (+/-5min,) 6h (+/-5 min,) 8h (+/-24 min)	Navitoclax and trametinib
C1, D8	Pre-dose navitoclax (0h), (will represent 24h post-dose from prior day)	Navitoclax and trametinib
C1, D14[#]	Pre-dose navitoclax (0h), 2h (+/- 5 min,) 4h (+/-5 min,) 6h (+/- 5 min,) 8h (+/- 24 min)	Navitoclax and trametinib
C1, D15[#]	Pre-dose navitoclax (0h) (will represent 23h post-dose navitoclax from prior day, +/- 1 hr)	Navitoclax and trametinib
C2, D1	Pre-dose navitoclax (single trough level)	Navitoclax and trametinib
C4, D1	Pre-dose navitoclax (single trough level)	Navitoclax and trametinib
C8, D1	Pre-dose navitoclax (single trough level)	Navitoclax and trametinib
C12, D1	Pre-dose navitoclax (single trough level)	Navitoclax and trametinib

[#] Represents 14th day of trametinib dosing under Schedule C
Trametinib dosing is always in the evenings. Timing is not adjusted on PK days

9.3.1.2.4 Schedule for PK sample collection for Part 2 (Phase 2)

Cycle (C), day (D)	Timing of PK sample blood draws	PK for
C2, D1	Pre-dose trametinib	Navitoclax and trametinib
C4, D1	Pre-dose trametinib	Navitoclax and trametinib
C8, D1	Pre-dose trametinib	Navitoclax and trametinib
C12, D1	Pre-dose trametinib	Navitoclax and trametinib

9.3.1.3 Handling of Specimens

Procedures for specimen handling and processing are defined in APPENDIX C.

9.3.1.4 Shipping of Specimens

Procedures for specimen shipping are defined in APPENDIX C.

9.3.1.5 Sites Performing Correlative Study

Analysis of PK samples will be performed by AbbVie (for navitoclax) and GSK (for trametinib) according to established procedures, and assessed for the endpoints described in Sections 2.5.1 and 13.4.1.1. Results will be reported to investigators, and data analysis will be performed at DF/HCC in cooperation with AbbVie and GSK.

9.4 Special Studies

N/A

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays, Echocardiogram or MUGA, and ophthalmic examination must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. All study visits have a +/- 3 day window after Cycle 2, Day 1.

Labs obtained on C1, D1 must re-meet eligibility criteria.

Part 1 (Phase 1b) Schedule A

	Pre-Study	C1D1	C1D7	C1D8	C1D15	C1D21	C1D22	C2D1	C2D15	C3D1, C4D1, etc..	Off Study[q]
Trametinib				T	T	T	T	T	T	T	
Navitoclax		L	L	N	N	N	N	N	N	N	
Informed consent [a]	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X									
Physical exam [b]	X	X		X	X		X	X	X	X	X
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X	X		X	X		X	X	X	X	X
Performance status	X	X		X	X		X	X	X	X	X
CBC w/diff, plts	X	X	X		X		X	X	X	X	X
Serum chemistry[d]	X	X	X		X		X	X	X	X	X
PT/PTT	X	X	X				X			X	X
Tumor Markers [e]	X							X		X	X
Urinalysis	X										
EKG [f]	X	X		X	X		X	X	X		
Echocardiogram or MUGA	X	Repeat on C1D28 (up to 5 days prior or on C2D1.) Thereafter, repeat every 12 weeks (use same methodology for baseline and follow up). [g]									
Ophthalmology exam	X	Repeated as needed only if patient experiences vision changes									
Adverse event evaluation		X----------X									X
Radiologic evaluation/Tumor measurements	X	Radiologic measurements (by CT or MRI) should be performed every 8 weeks following Cycle 1 Day 1. Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. [h]									X
B-HCG [i]	X										

Tumor biopsy	X[j]						X[k]				
PK blood draw[l]			X[m]	X[m]		X[n]	X[n]	X[o]		X[l]	
Archival Tissue	X[p]										

T: Trametinib. Dose as assigned; dose first in morning on empty stomach, at least 1 hour before food (there are no hematologic paramaters that must be met to continue dosing with trametinib at the beginning of each cycle.)
N: Navitoclax. Dose as assigned; dose second in morning with food, at least 1 hour after trametinib
L: Lead-in dose of navitoclax. 150 mg daily in morning for 7 days, dosed as above.

a: Informed consent can be signed within 28 days of C1D1.
b: Complete physical exam required pre-study and on Day 1 of each cycle, including head, eye, ear, nose, throat (HEENT,) cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Limited or symptom directed physical exam at the discretion of the investigator is sufficient at all other visits.
c: Vitals should include blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature.
d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
e: Disease-specific tumor markers as appropriate (e.g. CEA, CA-19-9, CA125) should be drawn at specified times provided the patient has elevation of that specific tumor maker prior to study enrollment. Colorectal: CEA; Pancreatic: CEA and CA-19-9; Lung: CEA; Any other tumor types: PI with treating MD can advise which tumor markers are appropriate to follow.
f: EKGs should be done pre-dose at all required time points.
g: ECHO or MUGA to be performed at screening and again on C1D28 (acceptable window C1D23-D29.) Thereafter, exam should be repeated every 12 weeks (+/-1 week.) The same modality used during screening should be used for all follow up exams.
h: Tumor measurements and radiologic evaluation should occur every 8 weeks +/- 1 week. If a patient is on a dose hold, scans should be kept on original schedule and should not be shifted. Patients that have scans which reveal disease progression do not need to repeat end of treatment scans.
i: Serum pregnancy test (women of childbearing potential) must be done within 7 days of C1D1.
j: Pre-study tumor biopsy to occur between days -21 and day-1. When possible, it is preferred, but not required, that the pre-treatment biopsy be performed between days -7 and -1 of treatment in order to most accurately represent the baseline signaling activity prior to treatment. Platelet count and PT/PTT must be checked prior to procedure according to institutional guidelines, and must be in acceptable range as defined in section 9.1.1.2.
k: On treatment biopsy to occur ~2 weeks after trametinib dosing on C1D22 (+/- 7 days.) Platelet count and PT/PTT must be checked prior to procedure on the same day, and must be in acceptable range as defined in section 9.1.1.2.
l: Complete PK schedule detailed in Section 9.3. Additional PK samples (single trough measurements only) required on day 1 of cycles 4, 8, and 12, not represented on this calendar.
m: Includes pre-dose (0h), 2h, 4h, 6h, 8h draws on C1D7 and 23h draw (pre-dose) on C1D8. See section 9.3 for details.
n: Includes pre- trametinib (-1h), pre navitoclax (0h), and 2h, 4h, 6h, 8h post navitoclax draws on C1D21 and 23h draw (pre- trametinib) on C1D22. See section 9.3 for details.
o: Single pre-dose (pre- trametinib and navitoclax) trough on C2D1. See Section 9.3 for details.
p: At least 20 unstained slides are required. If a patient is having a tumor biopsy, less than 20 is acceptable with PI approval.
q: Off study procedures should be performed within 14 days of last dose. Patients will be followed until the resolution or stabilization of all study-related toxicity and for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Part 1 (Phase 1b) Schedule B

	Pre-Study	C1D1	C1D7	C1D8	C1D14	C1D15	C1D22	C2D1	C2D15	C3D1, C4D1, etc..	Off Study[q]
Trametinib		T	T	T	T	T	T	T	T	T	
Navitoclax		L	L	N	N	N	N	N	N	N	
Informed consent [a]	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------								----------X	
Physical exam [b]	X	X		X		X	X	X	X	X	X
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X	X		X		X	X	X	X	X	X
Performance status	X	X		X		X	X	X	X	X	X
CBC w/diff, plts	X	X	X			X	X	X	X	X	X
Serum chemistry [d]	X	X	X			X	X	X	X	X	X
PT/PTT	X	X	X			X		X		X	X
Tumor Markers [e]	X							X		X	X
Urinalysis	X										
EKG [f]	X	X		X		X	X	X	X		
Echocardiogram or MUGA	X	Repeat on C1D28 (up to 5 days prior or on C2D1.) Thereafter, repeat every 12 weeks (use same methodology for baseline and follow up). [g]									
Ophthalmology exam	X	Repeated as needed only if patient experiences vision changes									
Adverse event evaluation		X----------								----------X	X
Radiologic evaluations/ Tumor measurements	X	Radiologic measurements (by CT or MRI) should be performed every 8 weeks following Cycle 1 Day 1. Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. [h]									X

B-HCG	X[i]										
Tumor biopsy	X[j]					X[k]					
PK blood draw[l]			X[m]	X[m]	X[n]	X[n]		X[o]		X[l]	
Archival Tissue	X[p]										

T: Trametinib. Dose as assigned; dose first in morning on empty stomach, at least 1 hour before food (there are no hematologic paramaters that must be met to continue dosing with trametinib at the beginning of each cycle.)
N: Navitoclax. Dose as assigned; dose second in morning with food, at least 1 hour after trametinib
L: Lead-in dose of navitoclax. 150 mg daily in morning for 7 days, dosed as above.

a: Informed consent can be signed within 28 days of C1D1.
b: Complete physical exam required pre-study and on Day 1 of each cycle, including head, eye, ear, nose, throat (HEENT,) cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Limited or symptom directed physical exam at the discretion of the investigator is sufficient at all other visits.
c: Vitals should include blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature.
d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
e: Disease-specific tumor markers as appropriate (e.g. CEA, CA-19-9, CA125) should be drawn at specified times provided the patient has elevation of that specific tumor maker prior to study enrollment. Colorectal: CEA; Pancreatic: CEA and CA-19-9; Lung: CEA; Any other tumor types: PI with treating MD can advise which tumor markers are appropriate to follow.
f: EKGs should be done pre-dose at all required time points.
g: ECHO or MUGA to be performed at screening and again on C1D28 (acceptable window C1 D23-D29.) Thereafter, exam should be repeated every 12 weeks (+/-1 week.) The same modality used during screening should be used for all follow up exams.
h: Tumor measurements and radiologic evaluation should occur every 8 weeks +/- 1 week. If a patient is on a dose hold, scans should be kept on original schedule and should not be shifted. Patients that have scans which reveal disease progression do not need to repeat end of treatment scans.
i: Serum pregnancy test (women of childbearing potential) must be done within 7 days of C1D1.
j: Pre-study tumor biopsy to occur between days -21 and day-1. When possible, it is preferred, but not required, that the pre-treatment biopsy be performed between days -7 and -1 of treatment in order to most accurately represent the baseline signaling activity prior to treatment. Platelet count and PT/PTT must be checked prior to procedure according to institutional guidelines and must be in acceptable range as defined in section 9.1.1.2.
k: On treatment biopsy to occur ~2 weeks after trametinib dosing on day 15 (+/- 7 days.) Platelet count and PT/PTT must be checked prior to procedure on the same day, and must be in acceptable range as defined in section 9.1.1.2.
l: Complete PK schedule detailed in Section 9.3. Additional PK samples (single trough measurements only) required on day 1 of cycles 4, 8, and 12, not represented on this calendar.
m: Includes pre-dose (0h), 2h, 4h, 6h, 8h draws on C1D7 and 23h draw (pre-dose) on C1D8. See section 9.3 for details.
n: Includes pre- trametinib (1h), pre navitoclax (0h), and 2h, 4h, 6h, 8h post navitoclax draws on C1D14 and 23h draw (pre- trametinib) on C1D15. See section 9.3 for details.
o: Single pre-dose (pre- trametinib and navitoclax) trough on C2D1. See Section 9.3 for details.
p: At least 20 unstained slides are required. If a patient is having a tumor biopsy, less than 20 is acceptable with PI approval.
q: Off study procedures should be performed within 14 days of last dose. Patients will be followed until the resolution or stabilization of all study-related toxicity and for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Part 1 (Phase 1b) Schedule C

	Pre-Study	C1D1	C1D7	C1D8	C1D14	C1D15	C1D22	C2D1	C2D15	C3D1, C4D1, etc..	Off Study[q]
Trametinib		T	T	T	T			T		T	
Navitoclax		L	L	N	N	N	N	N	N	N	
Informed consent [a]	X										
Demographics	X										

Medical history	X										
Concurrent meds	X	X----------									X
Physical exam [b]	X	X		X		X	X	X	X	X	X
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X	X		X		X	X	X	X	X	X
Performance status	X	X		X		X	X	X	X	X	X
CBC w/diff, plts	X	X	X			X	X	X	X	X	X
Serum chemistry [d]	X	X	X			X	X	X	X	X	X
PT/PTT	X	X	X			X		X		X	X
Tumor Markers [e]	X							X		X	X
Urinalysis	X										
EKG [f]	X	X		X		X	X	X	X		
Echocardiogram or MUGA	X	Repeat on C1D28 (up to 5 days prior or on C2D1.) Thereafter, repeat every 12 weeks (use same methodology for baseline and follow up). [g]									
Ophthalmology exam	X	Repeated as needed only if patient experiences vision changes									
Adverse event evaluation		X----------									X
Radiologic evaluations/ Tumor measurements	X	Radiologic measurements (by CT or MRI) should be performed every 8 weeks following Cycle 1 Day 1. Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. [h]									X
B-HCG	X[i]										
Tumor biopsy	X[j]					X[k]					
PK blood draw[l]			X[m]	X[m]	X[n]	X[n]		X[o]		X[l]	
Archival Tissue	X[p]										
cfDNA blood draw		X						X		X	X

T: Trametinib. Dose as assigned; **dose in the evening** on empty stomach, at least 1 hour before or two hours after food (there are no hematologic paramaters that must be met to continue dosing with trametinib at the beginning of each cycle.)
N: Navitoclax. Dose as assigned; dose in morning with food
L: Lead-in dose of navitoclax. 150 mg daily in morning for 7 days, dosed as above.

a: Informed consent can be signed within 28 days of C1D1.
b: Complete physical exam required pre-study and on Day 1 of each cycle, including head, eye, ear, nose, throat (HEENT,) cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Limited or symptom directed physical exam at the discretion of the investigator is sufficient at all other visits.
c: Vitals should include blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature.
d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
e: Disease-specific tumor markers as appropriate (e.g. CEA, CA-19-9, CA125) should be drawn at specified times provided the patient has elevation of that specific tumor maker prior to study enrollment. Colorectal: CEA; Pancreatic: CEA and CA-19-9; Lung: CEA; Any other tumor types: PI with treating MD can advise which tumor markers are appropriate to follow.
f: EKGs should be done pre-dose at all required time points.
g: ECHO or MUGA to be performed at screening and again on C1D28 (acceptable window C1 D23-D29.) Thereafter, exam should be repeated every 12 weeks (+/-1 week.) The same modality used during screening should be used for all follow up exams.
h: Tumor measurements and radiologic evaluation should occur every 8 weeks +/- 1 week. If a patient is on a dose hold, scans should be kept on original schedule and should not be shifted. Patients that have scans which reveal disease progression do not need to repeat end of treatment scans.
i: Serum pregnancy test (women of childbearing potential) must be done within 7 days of C1D1.
j: Pre-study tumor biopsy to occur between days -21 and day-1. When possible, it is preferred, but not required, that the pre-treatment biopsy be performed between days -7 and -1 of treatment in order to most accurately represent the baseline signaling activity prior to treatment. Platelet count and PT/PTT must be checked prior to procedure according to institutional guidelines and must be in acceptable range as defined in section 9.1.1.2.
k: On treatment biopsy to occur ~2 weeks after trametinib dosing on day 15 (+/- 7 days.) Platelet count and PT/PTT must be checked prior to procedure on the same day, and must be in acceptable range as defined in section 9.1.1.2.
l: Complete PK schedule detailed in Section 9.3. Additional PK samples (single trough measurements only) required on day 1 of cycles 4, 8, and 12, not represented on this calendar.
m: Includes pre-dose (0h), 2h, 4h, 6h, 8h draws on C1D7 and 24h draw (pre-dose) on C1D8. See section 9.3 for details.
n: Includes pre navitoclax (0h), and 2h, 4h, 6h, 8h post navitoclax draws on C1D14 and 24h draw on C1D15. See section 9.3 for details.
o: Single pre-dose (pre-navitoclax) trough on C2D1. See Section 9.3 for details.
p: At least 20 unstained slides are required. If a patient is having a tumor biopsy, less than 20 is acceptable with PI approval.
q: Off study procedures should be performed within 14 days of last dose. Patients will be followed until the resolution or stabilization of all study-related toxicity and for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Part 2 (Phase 2) Schedule A
(To be used if RP2D is to be given by Schedule A)

	Pre-Study	C1D1	C1D8	C1D15	C1D22	C2D1	C2D15	C3D1, C4D1, etc..	Off Study[p]
Trametinib			T	T	T	T	T	T	
Navitoclax		L	N	N	N	N	N	N	
Informed consent [a]	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X----------							----------X
Physical exam [b]	X	X	X	X	X	X	X	X	X
Vital signs [c]	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X
Serum chemistry [d]	X	X	X	X	X	X	X	X	X
PT/PTT	X	X	X		X			X	X
Tumor Markers[e]	X					X		X	X
Urinalysis	X								
EKG [f]	X	X	X	X	X	X	X		
Echocardiogram or MUGA	X	Repeat on C1D28 (up to 5 days prior or on C2D1.) Every 12 weeks (use same methodology for baseline and follow up). [g]							
Ophthalmology exam	X	Repeated as needed only if patient experiences vision changes							
Adverse event evaluation		X----------							---------- X
Radiologic evaluation/Tumor measurements	X	Radiologic measurements (by CT or MRI) should be performed every 8 weeks following Cycle 1 Day 1. Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study							X

		for progressive disease. [h]							
B-HCG	X[i]								
Tumor biopsy	X[j,k]				X[j,l]				
PK blood draw[m]						X[n]		X[m]	
Archival Tissue	X[o]								

T: Trametinib. Dose as assigned; dose first in morning on empty stomach, at least 1 hour before food (there are no hematologic paramaters that must be met to continue dosing with trametinib at the beginning of each cycle.)
N: Navitoclax. Dose as assigned; dose second in morning with food, at least 1 hour after trametinib
L: Lead-in dose of navitoclax. 150 mg daily in morning for 7 days, dosed as above.

a: Informed consent can be signed within 28 days of C1D1.
b: Complete physical exam required pre-study and on Day 1 of each cycle, including head, eye, ear, nose, throat (HEENT,) cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Limited or symptom directed physical exam at the discretion of the investigator is sufficient at all other visits.
c: Vitals should include blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature.
d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
e: Disease-specific tumor markers as appropriate (e.g. CEA, CA-19-9, CA125) should be drawn at specified times provided the patient has elevation of that specific tumor maker prior to study enrollment. Colorectal: CEA; Pancreatic: CEA and CA-19-9; Lung: CEA; Any other tumor types: PI with treating MD can advise which tumor markers are appropriate to follow.
f: EKGs should be done pre-dose at all required time points.
g: ECHO or MUGA to be performed at screening and again on C1D28 (acceptable window C1 D23-D29.) Thereafter, exam should be repeated every 12 weeks (+/-1 week.) The same modality used during screening should be used for all follow up exams.
h: Tumor measurements and radiologic evaluation should occur every 8 weeks +/- 1 week. If a patient is on a dose hold, scans should be kept on original schedule and should not be shifted. Patients that have scans which reveal disease progression do not need to repeat end of treatment scans.
i: Serum pregnancy test (women of childbearing potential) must be done within 7 days of C1D1.
j: Tumor biopsies to be performed only in first 15 patients enrolled in Part 2.
k: Pre-study tumor biopsy to occur between days -21 and day-1. When possible, it is preferred, but not required, that the pre-treatment biopsy be performed between days -7 and -1 of treatment in order to most accurately represent the baseline signaling activity prior to treatment. Platelet count and PT/PTT must be checked prior to procedure according to institutional guidelines, and must be in acceptable range as defined in section 9.1.1.2.
l: On treatment biopsy to occur ~2 weeks after trametinib dosing on C1D22 (+/- 7 days.) Platelet count and PT/PTT must be checked prior to procedure on the same day, and must be in acceptable range as defined in section 9.1.1.2.
m: Complete PK schedule detailed in Section 9.3. Additional PK samples (single trough measurements only) required on day 1 of cycles 4, 8, and 12, not represented on this calendar.
n: Single pre-dose (pre-trametinib and navitoclax) trough on C2D1.
o: At least 20 unstained slides are required. If a patient is having a tumor biopsy, less than 20 is acceptable with PI approval.
p: Off study procedures should be performed within 14 days of last dose. Patients will be followed until the resolution or stabilization of all study-related toxicity and for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Part 2 (Phase 2) Schedule B
(To be used if RP2D is to be given by Schedule B)

	Pre-Study	C1D1	C1D8	C1D15	C1D22	C2D1	C2D15	C3D1, C4D1, etc…	Off Study[p]
Trametinib		T	T	T	T	T	T	T	
Navitoclax		L	N	N	N	N	N	N	
Informed consent [a]	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X----------X							
Physical exam [b]	X	X	X	X	X	X	X	X	X
Vital signs [c]	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X
Serum chemistry[d]	X	X	X	X	X	X	X	X	X
PT/PTT	X	X	X	X		X		X	X
Tumor Markers [e]	X					X		X	
Urinalysis	X								
EKG [f]	X	X	X	X	X	X	X		
Echocardiogram or MUGA	X	Repeat on C1D28 (up to 5 days prior or on C2D1.) Thereafter, repeat every 12 weeks (use same methodology for baseline and follow up). [g]							
Ophthalmology exam	X	Repeated as needed only if patient experiences vision changes							

Adverse event evaluation		X----------X							X
Radiologic Evaluations/Tumor measurements	X	Radiologic measurements (by CT or MRI) should be performed every 8 weeks following Cycle 1 Day 1. Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. [h]							X
B-HCG	X[i]								
Tumor biopsy	X[j,k]			X[j,l]					
PK blood draw[m]						X[n]		X[m]	
Archival Tissue	X[o]								

T: Trametinib. Dose as assigned; dose first in morning on empty stomach, at least 1 hour before food (there are no hematologic paramaters that must be met to continue dosing with trametinib at the beginning of each cycle.)
N: Navitoclax. Dose as assigned; dose second in morning with food, at least 1 hour after trametinib
L: Lead-in dose of navitoclax. 150 mg daily in morning for 7 days, dosed as above.

a: Informed consent can be signed within 28 days of C1D1.
b: Complete physical exam required pre-study and on Day 1 of each cycle, including head, eye, ear, nose, throat (HEENT,) cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Limited or symptom directed physical exam at the discretion of the investigator is sufficient at all other visits.
c: Vitals should include blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature.
d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
e: Disease-specific tumor markers as appropriate (e.g. CEA, CA-19-9, CA125) should be drawn at specified times provided the patient has elevation of that specific tumor maker prior to study enrollment. Colorectal: CEA; Pancreatic: CEA and CA-19-9; Lung: CEA; Any other tumor types: PI with treating MD can advise which tumor markers are appropriate to follow.
f: EKGs should be done pre-dose at all required time points.
g: ECHO or MUGA to be performed at screening and again on C1D28 (acceptable window C1 D23-D29.) Thereafter, exam should be repeated every 12 weeks (+/-1 week.) The same modality used during screening should be used for all follow up exams.
h: Tumor measurements and radiologic evaluation should occur every 8 weeks +/- 1 week. If a patient is on a dose hold, scans should be kept on original schedule and should not be shifted. Patients that have scans which reveal disease progression do not need to repeat end of treatment scans.
i: Serum pregnancy test (women of childbearing potential) must be done within 7 days of C1D1.
j: Tumor biopsies to be performed only in first 15 patients enrolled in Part 2.
k: Pre-study tumor biopsy to occur between day -21 and day -1. When possible, it is preferred, but not required, that the pre-treatment biopsy be performed between days -7 and -1 of treatment in order to most accurately represent the baseline signaling activity prior to treatment. Platelet count and PT/PTT must be checked prior to procedure according to institutional guidelines, and must be in acceptable range as defined in section 9.1.1.3.
l: On-treatment tumor biopsy to occur after ~14 days of trametinib dosing on day 15 (+/- 7 days). Platelet count and PT/PTT must be checked prior to procedure on same day, and must be in acceptable range as defined in section 9.1.1.3.
m: Complete PK schedule detailed in Section 9.3. Additional PK samples (single trough measurement only) required on day 1 of cycles 4, 8, and 12, not represented on this calendar
n: Single pre-dose (pre-trametinib and navitoclax) trough on C2D1. See Section 9.3 for details.
o: At least 20 unstained slides are required. If a patient is having a tumor biopsy, less than 20 is acceptable with PI approval.
p: Off study procedures should be performed within 14 days of last dose. Patients will be followed until the resolution or stabilization of all study-related toxicity and for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Part 2 (Phase 2) Schedule C
(To be used if RP2D is to be given by Schedule C)

	Pre-Study	C1D1	C1D8	C1D15	C1D22	C2D1	C2D15	C3D1, C4D1, etc…	Off Study[p]
Trametinib		T	T			T		T	
Navitoclax		L	N	N	N	N	N	N	
Informed consent [a]	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X----------X							
Physical exam [b]	X	X	X	X	X	X	X	X	X
Vital signs [c]	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X
Serum chemistry[d]	X	X	X	X	X	X	X	X	X
PT/PTT	X	X	X	X		X		X	X
Tumor Markers [e]	X					X		X	
Urinalysis	X								
EKG [f]	X	X	X	X	X	X	X		
Echocardiogram or MUGA	X	Repeat on C1D28 (up to 5 days prior or on C2D1.) Thereafter, repeat every 12 weeks (use same methodology for baseline and follow up). [g]							

Ophthalmology exam	X	Repeated as needed only if patient experiences vision changes							
Adverse event evaluation		X----------X							X
Radiologic Evaluations/Tumor measurements	X	Radiologic measurements (by CT or MRI) should be performed every 8 weeks following Cycle 1 Day 1. Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. [h]							X
B-HCG	X[i]								
Tumor biopsy	X[j,k]			X[j,l]					
PK blood draw[m]						X[n]		X[m]	
Archival Tissue	X[o]								
cfDNA blood draw		X				X		X	

T: Trametinib. Dose as assigned; dose in evening on empty stomach, at least 1 hour before or two hours after food (there are no hematologic paramaters that must be met to continue dosing with trametinib at the beginning of each cycle.)
N: Navitoclax. Dose as assigned; dose in morning with food
L: Lead-in dose of navitoclax. 150 mg daily in morning for 7 days, dosed as above.

a: Informed consent can be signed within 28 days of C1D1.
b: Complete physical exam required pre-study and on Day 1 of each cycle, including head, eye, ear, nose, throat (HEENT,) cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Limited or symptom directed physical exam at the discretion of the investigator is sufficient at all other visits.
c: Vitals should include blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature.
d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
e: Disease-specific tumor markers as appropriate (e.g. CEA, CA-19-9, CA125) should be drawn at specified times provided the patient has elevation of that specific tumor maker prior to study enrollment. GYN: CA-125; Pancreatic: CEA and CA-19-9; Lung: CEA; Any other tumor types: PI with treating MD can advise which tumor markers are appropriate to follow.
f: EKGs should be done pre-dose at all required time points.
g: ECHO or MUGA to be performed at screening and again on C1D28 (acceptable window C1 D23-D29.) Thereafter, exam should be repeated every 12 weeks (+/-1 week.) The same modality used during screening should be used for all follow up exams.
h: Tumor measurements and radiologic evaluation should occur every 8 weeks +/- 1 week. If a patient is on a dose hold, scans should be kept on original schedule and should not be shifted. Patients that have scans which reveal disease progression do not need to repeat end of treatment scans.
i: Serum pregnancy test (women of childbearing potential) must be done within 7 days of C1D1.
j: Tumor biopsies to be performed only in first 15 patients enrolled in Part 2.
k: Pre-study tumor biopsy to occur between day -21 and day -1. When possible, it is preferred, but not required, that the pre-treatment biopsy be performed between days -7 and -1 of treatment in order to most accurately represent the baseline signaling activity prior to treatment. Platelet count and PT/PTT must be checked prior to procedure according to institutional guidelines, and must be in acceptable range as defined in section 9.1.1.3.
l: On-treatment tumor biopsy to occur after ~14 days of trametinib dosing on day 15 (+/- 7 days). Platelet count and PT/PTT must be checked prior to procedure on same day, and must be in acceptable range as defined in section 9.1.1.3.
m: Complete PK schedule detailed in Section 9.3. Additional PK samples (single trough measurement only) required on day 1 of cycles 4, 8, and 12, not represented on this calendar
n: Single pre-dose (pre-navitoclax) trough on C2D1. See Section 9.3 for details.
o: At least 20 unstained slides are required. If a patient is having a tumor biopsy, less than 20 is acceptable with PI approval.

p: Off study procedures should be performed within 14 days of last dose. Patients will be followed until the resolution or stabilization of all study-related toxicity and for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.
Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with navitoclax and/or trametinib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

11.1.2 Disease Parameters

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

measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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

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

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

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

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but

the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is required in this study.

Conventional CT: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. CT is the preferred imaging modality in this study and should be used as the primary method of disease assessment unless otherwise measurable lesions are not able to be adequately assessed by CT scan, in which case one of the following imaging modalities can be used instead. However, the same imaging modality used at baseline should be used for evaluation of measurable disease throughout the study.

MRI: Use of MRI is acceptable in situations in which lesions are not adequately assessable by conventional CT scanning. Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. The same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

Investigator).

11.1.4.3 Evaluation of Best Overall Response

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

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

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

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

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR

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

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

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

11.1.7 Response Review

For Part 2 (the phase 2 portion) of the study, an expert(s) independent of the study will review all responses at the study's completion.

11.2 Antitumor Effect – Hematologic Tumors

N/A

11.3 Other Response Parameters

N/A

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Information on CTMS reporting is available at http://www.theradex.com/CTMS. Data will be submitted to CTMS at least once every two weeks on the NCI/DCTD case report form or the electronic case report form (ACES).

12.1.2 Responsibility for Data Submission

N/A

12.2 CTEP Multicenter Guidelines

N/A

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

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

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

any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Part 1 (Phase 1b)

Part 1 (Phase 1b) of this study aims to determine the maximal tolerated dose (MTD) of trametinib and navitoclax that can be given safely in combination in order to determine a recommended phase 2 dose (RP2D). Patients with advanced or metastatic solid tumors that have been determined to harbor KRAS or NRAS mutations by CLIA-approved laboratory assay will be eligible. Prior therapy for advanced or metastatic disease will be allowed. Pharmacokinetic (PK) assays will be carried out to assess the interaction of these two drugs, and these data will be correlated with clinical toxicities as dose escalation is undertaken. Paired pre-treatment and on-treatment (day 15) tumor biopsies will be obtained to assess the pharmacodynamic response to therapy. Adverse events and DLT will be reported as defined in Sections 7 and 5.2, respectively. Evaluation of response rate will be performed as defined in Section 11.
Dose escalation will be conducted as outline in **Section 5.1**. The following table shows the probability of escalating the dose for various true, but unknown, rates of unacceptable toxicity.

True DLT Rate	**Probability of Dose Escalation**
10%	91%
20%	71%
30%	49%
40%	31%
50%	17%
60%	8%

13.1.1.1 Primary Objective

- To determine the dose-limiting toxicities of trametinib in combination with navitoclax, and the maximal doses at which both drugs can be safely administered together.

13.1.1.2 Primary Endpoint

- Adverse events

13.1.1.3 Secondary Objectives

- To determine the pharmacokinetics of both drugs administered in combination.
- To assess for evidence of response to therapy.
- To evaluate the pharmacodynamic response to therapy in tumor biopsies.

13.1.1.4 Secondary Endpoints

- Pharmacokinetic Endpoints
  - Maximum observed plasma drug concentration (Cmax)
  - Area-under-the concentration-time-curve from zero (pre-dose) to 24 hours (AUC(0-24)) for trametinib and navitoclax when administered in combination.
  - pre-dose (trough) drug concentration at the end of the dosing interval for trametinib and navitoclax when administered in combination.
  - t1/2 of trametinib and navitoclax when administered in combination.
- Response rate (partial response [PR] + complete response [CR])
- Pharmacodynamic Endpoints: Change in levels (between pre-treatment and day 15 tumor biopsies) of proteins/mRNAs implicated in MAPK or BCL2 family signaling, proliferation markers (Ki67), or apoptosis markers (Cleaved caspase-3)

13.1.2 Part 2 (Phase 2)

Part 2 is a single-arm Phase 2 study of trametinib in combination with navitoclax at the RP2D determined in the Phase 1b trial above. Patients with KRAS or NRAS mutation-positive solid tumors will be enrolled into up to 4 different disease-specific expansion cohorts. These will include expansion cohorts for patients with KRAS or NRAS mutation-positive: (1) Pancreatic cancer, (2) GYN cancer, (3) lung cancer, (4) all other solid tumor types exclusive of pancreatic, GYN, and lung cancers. Part 2 aims to evaluate the efficacy of this regimen in the tumor types above and to further evaluate the safety and toxicity profile of this regimen at the RP2D defined in Part 1 of the study. Paired pre-treatment and on-treatment (day 15) tumor biopsies will be obtained on the first 15 patients enrolled in Part 2 (minimum 4 patients biopsied in each of expansion cohorts 1, 2, and 3) to assess the pharmacodynamic response to therapy. Adverse events will be reported as defined in Section 7. Evaluation of response rate will be performed as defined in Section 11. PFS will be determined as defined in Section 11.1.6.

The primary goal of Part 2 is to evaluate the efficacy of this regimen in patients with various KRAS or NRAS mutation-positive solid tumor. Based on traditional response rates to standard second line chemotherapy in the tumor types being studied (Guglielmi et al, 2007; Conroy et al, 2011), we conclude that a response rate of 15-20% or greater in a given expansion cohort would deem this regimen worthy of further study in that specific patient population. In part 2, patients will be enrolled in 4 expansion cohorts by a two-stage design, as outlined in **Section 5.1**. Initially 12 patients will be enrolled to each cohort in Stage 1. If no responses are observed in a given cohort among the first 12 patients, then that cohort will be stopped for futility. However, if one or more responses are observed in a given cohort, the cohort will proceed to Stage 2, and an additional 13 patients will be enrolled for a total of 25 patients in that cohort. If at least three responses are observed within a completed cohort of 25 patients, the regimen will be considered promising for treating the specific tumor type. This design has a 11% false-positive and a 22% false-negative error rate for testing a 17% vs. a 5% response rate. The probability of early stopping is 54% if the underlying response rate were truly only 5%. In the event that the number of responses observed in a given cohort does not meet the pre-established response criteria defined above, but promising anti-tumor activity is observed (such as prolonged stable disease or tumor regressions that fall short of the RECIST cutoff for partial response), the possibility of further evaluating of this regimen in the specific patient population can be explored through a joint discussion between the investigators, pharmaceutical collaborators, and the NCI-CTEP.

13.1.2.1 Primary Objectives

- To determine the response rate of the combination of trametinib and navitoclax in subjects with KRAS or NRAS mutation-positive advanced or metastatic solid tumors in disease-specific expansion cohorts.
- To confirm the safety and tolerability of trametinib and navitoclax in combination at the RP2D determined in the Phase 1b portion.

13.1.2.2 Primary Endpoints

- Response rate (partial response [PR] + complete response [CR])
- Progression-free survival (PFS)
- Adverse events

13.1.2.3 Secondary Objective

- To evaluate the pharmacodynamic response to therapy in tumor biopsies (first 15 patients enrolled overall, minimum 4 patients biopsied in each of expansion cohorts 1, 2, and 3)

13.1.2.4 Secondary Endpoints

- Pharmacodynamic Endpoints: Change in levels (between pre-treatment and day 15 tumor biopsies) of proteins/mRNAs implicated in MAPK or BCL2 family signaling, proliferation markers (Ki67), or apoptosis markers (Cleaved caspase-3)

13.2 Sample Size/Accrual Rate

13.2.1 Part 1 (Phase 1b)

Depending on whether enrollment also occurs to the B dosing cohorts for dose levels 1-3, overall accrual to Part 1 of this study will likely be between 21-30 patients. It is estimated that between 3-5 patients will be enrolled per month to the phase 1b portion of the study, resulting in an accrual time of between 6-9 months.

13.2.2 Part 2 (Phase 2)

Part 2 of the study will involve four expansion cohorts each enrolling a maximum of 25 patients. Each cohort will enroll a minimum of 12 patients, and will enroll an additional 13 patients (for 25 total patients) if at least one objective tumor response is observed among the first 12 patients (as described above). Therefore, a minimum of 48 patients and a maximum of 100 patients will be enrolled to this part of the study. Based on past accrual rates at DF/HCC for patients with KRAS or NRAS mutation-positive solid tumors, we estimate that between 8-10 patients will be enrolled per month to the phase 2 portion of the study, resulting in an anticipated maximum accrual time of 10-12 months.

13.2.3 Accrual Targets

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	6		+	5		=	11	
Not Hispanic or Latino	61		+	58		=	119	
Ethnic Category: Total of all subjects	67	(A1)	+	63	(B1)	=	130	(C1)
Racial Category								
American Indian or Alaskan Native	1		+	1		=	2	
Asian	7		+	6		=	13	
Black or African American	8		+	7		=	15	
Native Hawaiian or other Pacific Islander	2		+	1		=	3	
White	49		+	48		=	97	
Racial Category: Total of all subjects	67	(A2)	+	63	(B2)	=	130	(C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)	

13.3 Stratification Factors

N/A

13.4 Analysis of Secondary Endpoints

13.4.1 Secondary Endpoints for Part 1 (Phase 1b)

13.4.1.1 Pharmacokinetic Endpoints

The following pharmacokinetic endpoints will be measured and reported for navitoclax and trametinib.

- Maximum observed plasma drug concentration (Cmax)
- Area-under-the concentration-time-curve from zero (pre-dose) to 24 hours (AUC(0-24)) for trametinib and navitoclax when administered in combination.
- pre-dose (trough) drug concentration at the end of the dosing interval for trametinib and navitoclax when administered in combination.
- t1/2 of trametinib and navitoclax when administered in combination.

In particular, in dose levels 1A and 2A, the Cmax and AUC(0-24) for navitoclax will be assessed pre-trametinib (e.g. day 7 of lead-in dose in Schedule A) and after 2 weeks of trametinib co-administration (day 21 of schedule A, 14th day of trametinib dosing) to determine if any increase or decrease in navitoclax levels are observed following initiation of trametinib (indicative of drug interaction).

13.4.1.2 Response Rate

Response rate will be defined and reported as outlined in Sections 11 and Section 13.5.2 below.

13.4.1.3 Pharmacodynamic Endpoints

Change in levels (between pre-treatment and post-treatment tumor biopsies) of proteins/mRNAs implicated in MAPK or BCL2 family signaling (e.g. phosphorylated ERK (P-ERK)), proliferation markers (Ki67), or apoptosis markers (Cleaved caspase-3) will be evaluated in paired tumor biopsies obtained. Results will be reported as a % increase or decrease in level of a given marker after treatment initiation (day 15 biopsy) relative to before treatment (pre-treatment biopsy). For example, the % increase or decrease in the H-score of P-ERK, Ki67, or Cleaved caspase-3 will be reported relative to the pre-treatment biopsy.

13.4.2 Secondary Endpoints for Part 2 (Phase 2)

13.4.2.1 Pharmacodynamic Endpoints

Change in levels (between pre-treatment and post treatment tumor biopsies) of proteins/mRNAs

implicated in MAPK or BCL2 family signaling (e.g. phosphorylated ERK (P-ERK)), proliferation markers (Ki67), or apoptosis markers (Cleaved caspase-3) will be evaluated in paired tumor biopsies obtained. Results will be reported as a % increase or decrease in level of a given marker after treatment initiation (post treatment biopsy) relative to before treatment (pre-treatment biopsy). For example, the % increase or decrease in the H-score of P-ERK, Ki67, or Cleaved caspase-3 will be reported relative to the pre-treatment biopsy.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with navitoclax and/or trametinib.

13.5.2 Evaluation of Response

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

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

All conclusions should be based on all eligible patients. Sub analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all

IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C PK SAMPLING GUIDELINES

1) TRAMETINIB PK

PK studies will be done to assess the biodistribution of trametinib.

Plasma concentrations of trametinib will be measured under the direction of GSK. Analysis will be performed by GSK and the results made available to the investigators.

Specimen Collection

(Details are provided in the "Pharmacokinetic Laboratory Manual" supplied by GSK. Note: This will be disseminated with the clinical protocol and is also available to investigators on request from the coordinating center.)

Specimen Collection Schedule (an example of timepoints of collection is listed below.)

- At each time point, collect 2 mL whole blood PK sample into a properly labeled 2 mL K2EDTA evacuated blood collection tube. Record the date and time each sample is collected. **Note the sampling time and volume of blood collection may differ with specific protocols and/or regimens. (In general, separate aliquots are required for PK studies of individual drugs**)

Schedule for Part 1 (Phase 1b) Schedule A
(All times relative to navitoclax dose, per Section 9.3)

Day of Collection	Planned Collection Time (hr)
C1D7	Pre-dose (0h,) 2hr, 4h, 6h, 8h (for navitoclax only)
C1D8	Pre-dose trametinib (represents 23 hr from prior day for navitoclax only)
C1D21	Pre-trametinib (-1h), pre-navitoclax (0h), 2h, 4h, 6h, 8h (for both navitoclax and trametinib)
C1D22	Pre-trametinib (represents 23h draw, for both navitoclax and trametinib)
C2D1	Pre-trametinib (for both navitoclax and trametinib)
C4D1	Pre-trametinib (for both navitoclax and trametinib)
C8D1	Pre-trametinib (for both navitoclax and trametinib)
C12D1	Pre-trametinib (for both navitoclax and trametinib)

Schedule for Part 1 (Phase 1b) Schedule B
(All times relative to navitoclax dose, per Section 9.3)

Day of Collection	Planned Collection Time (hr)
C1D7	Pre-trametinib (-1h), pre-navitoclax (0h), 2h, 4h, 6h, 8h (for both navitoclax and trametinib)
C1D8	Pre-trametinib (represents 24h draw, for both navitoclax and trametinib)
C1D14	Pre-trametinib (-1h), pre-navitoclax (0h), 2h, 4h, 6h, 8h (for both navitoclax and trametinib)
C1D15	Pre-trametinib (represents 24h draw, for both navitoclax and trametinib)
C2D1	Pre-trametinib (for both navitoclax and trametinib)
C4D1	Pre-trametinib (for both navitoclax and trametinib)
C8D1	Pre-trametinib (for both navitoclax and

	trametinib)
C12D1	Pre-trametinib (for both navitoclax and trametinib)

Schedule for Part 1 (Phase 1b) Schedule C
(All times relative to navitoclax dose, per Section 9.3)

Day of Collection	**Planned Collection Time (hr)**
C1D7	Pre-navitoclax (0h), 2h, 4h, 6h, 8h (for both navitoclax and trametinib)
C1D8	Pre-navitoclax (for both navitoclax and trametinib)
C1D14	Pre-navitoclax (0h), 2h, 4h, 6h, 8h (for both navitoclax and trametinib)
C1D15	Pre-navitoclax (for both navitoclax and trametinib)
C2D1	Pre-navitoclax (for both navitoclax and trametinib)
C4D1	Pre-navitoclax (for both navitoclax and trametinib)
C8D1	Pre-navitoclax (for both navitoclax and trametinib)
C12D1	Pre-navitoclax (for both navitoclax and trametinib)

Schedule for Part 2 (Phase 2)

Day of Collection	**Planned Collection Time (hr)**
C2D1	Pre-navitoclax (for both navitoclax and trametinib)
C4D1	Pre-navitoclax (for both navitoclax and trametinib)
C8D1	Pre-navitoclax (for both navitoclax and trametinib)
C12D1	Pre-navitoclax (for both navitoclax and trametinib)

Specimen Processing Procedures

Immediately after collection, gently invert (do not shake) the evacuated blood collection tube 8-10 times to mix the K_2EDTA anticoagulant with the whole blood. Blood samples *MUST* be placed on wet ice immediately after mixing the blood with the anticoagulant. Blood samples should be processed into plasma within 15 minutes of collection (30 minutes maximum). Centrifuge samples at 2500 to 3000 rpm for 10 to 15 minutes at 4°C to achieve a clear plasma layer over the red cells. The speed and time may be varied according to the make and model of centrifuge used. Immediately transfer plasma into two 1.0 mL Matrix TrackMate ScrewTop tubes (each containing approximately 0.75 mL of plasma) and store at -20°C until shipped. Ship all frozen plasma samples on dry ice, overnight.

Specimen Shipping Instructions

Ship PK samples to:

Covance Laboratories Inc.
3301 Kinsman Boulevard
Madison, WI 53704
Tel 608.241.4471
FAX 608.242.7978

2) NAVITOCLAX (ABT-263) PK

PK studies will be done to assess the biodistribution of navitoclax.

Plasma concentrations of navitoclax will be measured under the direction of AbbVie. Analysis will be performed by AbbVie and the results made available to the investigators.

Navitoclax (ABT-263) PK Samples

The processing of PK samples should be performed as described below:
1. Collect 3 mL blood in a K2EDTA collection tube.
2. Immediately invert tube 8-10 times and place in ice bath or cryoblock until ready to centrifuge.
3. Centrifuge within 1 hour of collection at approximately 1100-1600xg for approximately 10 minutes in a refrigerated centrifuge.
4. Transfer plasma into an appropriately labeled screw-capped polypropylene tube using a plastic

pipette.
5. Freeze at –20°C or colder completing process within 2 hours of collection.
6. Store samples at –20 °C or colder until shipment

Shipping of Specimen(s)

The frozen plasma samples for Navitoclax will be packed in dry ice sufficient to last during transport for 3 days and shipped from the study site to AbbVie according to instructions from AbbVie. An inventory of the samples included will accompany the package. Arrangements will be made with AbbVie for the shipment of samples to:

AbbVie Sample Receiving
R43F/AP13A-2 Room 2310
c/o: Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL 60085
Telephone: 847-937-0889
Telefax: 847-938-9898
E-mail: sample.receiving@abbvie.com

APPENDIX D PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

Patient Name:	**Diagnosis:**	**Trial #:**	
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	Navitoclax (ABT-263)
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	Navitoclax (ABT-263)

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:
Navitoclax (ABT-263) interacts with certain specific enzyme(s) in your liver or other tissues like the gut.

	Explanation
CYP isoenzymes	The enzymes in question are **CYP2C8, CYP2C9, and CYP3A4**. Navitoclax (ABT-263) is a moderate inhibitor of CYP2C8 and strong inhibitor of CYP2C9. Substrates of CYP2C8 or CYP2C9 with a narrow therapeutic window should be used with caution. Navitoclax (ABT-263) is metabolized by CYP3A4 to some extent. Use caution when coadministered with any medications that are considered strong or moderate CYP3A4 inhibitors or inducers. .

These are the things that you need to know:
The study drug navitoclax (ABT-263), may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered substrates of CYP2C8 or CYP2C9 with a narrow therapeutic window, and strong or moderate inhibitors/inducers of CYP3A4.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Make sure your doctor knows to avoid certain prescription medications.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

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(Next page: Patient Drug Interaction Wallet Card)

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EMERGENCY INFORMATION

Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S): Navitoclax (ABT-263)

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

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Tell your doctors **before** you **start** or **stop** any medicines.

Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!

Use caution and avoid the following drugs if possible:

- No St. John's Wort, grapefruit or grapefruit juice can be consumed while taking navitoclax (ABT-263).
- Tell your doctor if you're taking ibuprofen or aspirin.

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

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DRUG INTERACTIONS

Carry this card with you at all times

Navitoclax (ABT-263) interacts with specific enzymes called CYP3A4, CYP2C8 and CYP2C9 and must be used very carefully with other medicines.

Your healthcare providers should be aware of any medicines that are strong or moderate inhibitors / inducers of CYP3A4, or substrates of CYP2C9 or CYP2C8 with a narrow therapeutic window, which should be used with caution.

Before prescribing new medicines, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.

Version AUG/2020

For more information: 1-800-4-CANCER

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For more information: 1-800-4-CANCER

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APPENDIX E MEDICATION DIARIES

Please provide attached medication diaries to participants as appropriate.

APPENDIX F BIOASSAY TEMPLATES

Please include all applicable bioassays.