DATE: February 25, 2021

TO: CTEP Protocol and Information Office

FROM: [redacted], MD

SUBJECT: Amendment in response to review of amendment 13 comments for the request for amendment (RA) from Dr. [redacted], NCI, dated February 1, 2021 and eligibility correction.

SUMMARY OF CHANGES – Protocol

I. Comments Requiring a Response – Major Issues including Administrative & Editorial Issues:

#	Section	Comments
1.	3.1.3.4	Please make the correction in proteinuria lab range from < to **≤ 1+** as recommended per SOC#3. **PI Response: This correction has been made.**
2.	8.1	Please update navitoclax (ABT-263) pharmaceutical information as follow: Mode of Action: ~~Navitoclax disrupts the interactions between antiapoptotic Bcl-2 family proteins and their counterparts. Navitoclax induces cancer apoptosis by inhibiting the antiapoptotic Bcl-2 family proteins Bcl-XL, Bcl-2, Bcl-w, and Bcl-B~~. 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 ~~off-white~~ light pink powder How Supplies: ~~Abbot Laboratories~~ AbbVie supplies and the DCTD/NCI distributes navitoclax as 25 mg and 100 mg film coated tablets packaged in 28-Count and 30-Count high-density polyethylene (HDPE) bottles, respectively. 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. Navitoclax inactive ingredients: Copovidone, Vitamin E polyethylene glycol succinate, colloidal silicon dioxide, croscarmellose sodium, sodium stearyl fumarate (coating, 25 mg: iron oxide red ~~E172~~ or iron oxide yellow, polyvinyl

#	Section	Comments
		alcohol, polyethylene glycol 3350, talc, titanium dioxide; and 100 mg: iron oxide yellow ~~E172~~ or oxide red, polyvinyl alcohol, polyethylene glycol 3350, talc, titanium dioxide). Approximate Solubility: Navitoclax free base is practically insoluble in water~~. and freely soluble in Phosal 53 MCT with 10 % ethanol.~~ Patient Care Implications: ~~Thrombocytopenia has been the primary dose limiting toxicity in the clinical development of navitoclax. Patients must be careful when taking herbal products or over-the counter (57) drugs especially, OTC drugs that treat multisymptoms such as for cough & cold. These medications may contain aspirin or ibuprofen, which may affect platelets function~~ For trials using single agent navitoclax, female patients of childbearing potential must agree to use highly effective methods of contraception throughout the study and for 30 days after the last dose of study treatment. For clinical studies with navitoclax in combination, use of contraception may be longer and male subjects may need to use contraceptive methods. It is unknown whether navitoclax is excreted in human milk; thus, breastfeeding is not allowed. **PI Response: These corrections have been made.**

II. Request for Amendment

#	Section	Comments
1.	Header, Title Page	Updated protocol version date.
2.	7.1	Updated Navitoclax CAEPR to Version 2.5, January 4, 2021, with the following changes: • Added New Risk: • Also Reported on Navitoclax Trials But With Insufficient Evidence for Attribution: Abdominal distension; Cardiac arrest; Chest wall pain; Disease progression; Edema trunk; Enterocolitis; Gastrointestinal disorders - Other (laryngeal hemorrhage); Gastrointestinal disorders - Other (pneumatosis coli); Generalized muscle weakness; Hemoglobin increased; Hyperkalemia; Hyperuricemia; Investigations - Other (elevated LFTs); Malaise; muscle weakness; Pancreatitis; Stroke; Syncope; Weight gain

		• Increase in Risk Attribution:
		  • Changed to Less Likely from Also Reported on Navitoclax Trials But With Insufficient Evidence for Attribution: Lymphocyte count decreased
		
		• Decreased in Risk Attribution:
		  • Changed Also Reported on Navitoclax Trials But With Insufficient Evidence for Attribution from Less Likely: Abdominal pain; Anemia; Constipation; Dyspepsia; Electrocardiogram QT corrected interval prolonged; Flatulence; Headache; Hypokalemia; White blood cell decreased

III. Changes requested by the PI

#	Section	Comments
3.	3.1.3.4	Corrected the typo for proteinuria from < to ≤ 1+ based on the investigator brochure for vistusertib.

SUMMARY OF CHANGES – Consent Form

#	Section	Comments
1.	Header	Updated protocol version date.

2.	Possible Side Effects of Navitoclax	Changes to the drug risks of Navitoclax:
		• Decreased in Risk Attribution:
		  • **Changed to Rare** from Occasional: Infection, especially when white blood cell count is low
		  • Changed to Also Reported on Navitoclax Trials But With Insufficient Evidence for Attribution from Occasional (i.e. **removed** from the Risk Profile): Anemia which may require blood transfusion; Belly pain, Constipation; Heartburn; Passing gas; Change in heart rhythm; Headache

NCI Protocol #: 10070

Local Protocol #: ETCTN10070

ClinicalTrials.gov Identifier: NCT03366103

TITLE: Phase 1/2 study of navitoclax plus vistusertib in patients with relapsed small cell lung cancer (SCLC) and other solid tumors

Phase 1 closed to accrual: 12/19/19
Now Open for Phase 2

Corresponding Organization: **LAO-MD017** / JHU Sidney Kimmel Comprehensive Cancer Center LAO

Principal Investigator: [redacted], MD, PhD
Johns Hopkins University
Viragh Building, [redacted]
201 N. Broadway
Baltimore, MD 21287
[redacted]

Participating Organizations (Phase 1)

LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO

Participating Organizations (Phase 2)

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO

Statistician:

[redacted]
Johns Hopkins University
Oncology Biostatistics
550 North Broadway, [redacted]

Protocol Contact:

[redacted], CCRC
Johns Hopkins University SKCCC
201 N. Broadway Street, [redacted]
Baltimore, MD 21287
[redacted]

NCI-Supplied Agent(s): Navitoclax (NSC 750238), Vistusertib (AZD2014; NSC 787289)

IND #: [redacted]

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Original / Version 1 / December 5, 2016
Revision / Version 2 / February 16, 2017
Revision / Version 3 / March 9, 2017
Revision / Version 4 / June 14, 2017
Revision / Version 5/ September 5, 2017
Revision / Version 6/ September 29, 2017
Revision / Version 7/ October 18, 2017
Amendment / February 9, 2018
Amendment / May 7, 2018
Amendment / July 25, 2018
Amendment / February 26, 2019
Amendment / June 19, 2019
Amendment / August 20, 2019
Amendment / May 18, 2020 (Disapproved)
Amendment / July 06, 2020
Amendment / September 20, 2020
Amendment / February 15, 2021 (Disapproved)
Amendment / February 25, 2021

SCHEMA

This is a single-arm, open label, Phase 1/2 study of navitoclax plus vistusertib in patients with recurrent SCLC and other solid tumors. The phase 1 portion of the study is a dose escalation in patients with all solid tumors. All patients will receive navitoclax in combination with vistusertib daily.

Dose Escalation Schedule		
Dose Level	**Dose**	
	Navitoclax* by mouth, once a day	**Vistusertib by mouth, twice a day**
Level -1	150 mg	25 mg
Level 1	150 mg	35 mg
Level 2	250 mg	35 mg
Level 3	325 mg	35 mg
Level 4	325 mg	50 mg
* To reduce the incidence of significant thrombocytopenia, all patients will receive a 7 day lead-in dosing of navitoclax 150mg po once a day prior to C1D1. At any time after 7 days of navitoclax, if the platelet count is >50,000 and stable or increasing, subjects can dose escalate to the navitoclax dose defined in the cohort level and start vistusertib. Cycle 1 day 1 is defined as the first day both study drugs are taken.		

The phase 2 portion of this study is now open and includes patients with recurrent small cell lung cancer only. Patients will receive navitoclax plus vistusertib at the RP2D established in the dose escalation portion of the study. The RP2D determined from the Phase 1 portion was Level 1: navitoclax 150 mg by mouth once a day plus vistusertib 35 mg by mouth twice a day.

Mandatory biopsies and blood samples will be collected for correlative studies. Approximately 37 patients will be enrolled in the phase 2 portion of this study.

Phase 2 Dose	
Navitoclax* by mouth, once a day	**Vistusertib by mouth, twice a day**
150 mg	35 mg
* To reduce the incidence of significant thrombocytopenia, all patients will receive a 7 day lead-in dosing of navitoclax 150 mg po once a day prior to C1D1. At any time after 7 days of navitoclax, if the platelet count is > 50,000 and stable or increasing, subjects can dose escalate to the navitoclax dose defined in the cohort level and start vistusertib. Cycle 1 day 1 is defined as the first day both study drugs are taken.	

Per the drug manufacturer AstraZeneca, clinical supply of Vistusertib (AZD2014) will expire on August 31, 2021 (based on the planned expiration date extension), and there will be no additional drug available for clinical use after that date. All patients must complete their last treatment on

or before August 31, 2021, and the study will be closed to accrual and treatment to coincide with this expiration date.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Phase 1

1.1.1 Primary Objectives

1.1.1.1 To evaluate the safety and tolerability of the combination of navitoclax and vistusertib in patients with advanced solid tumors

1.1.1.2 To determine the maximum tolerated dose (MTD), dose limiting toxicities (DLT), and recommended phase 2 doses (RP2D) of navitoclax and vistusertib

1.1.2 Secondary Objectives

1.1.2.1 To evaluate the pharmacokinetics of navitoclax and vistusertib when administered together

1.1.2.2 To observe and record anti-tumor activity. Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2 Phase 2

1.2.1 Primary Objective

1.2.1.1 To determine the objective response rate (ORR), defined as complete plus partial response, of the combination of navitoclax and vistusertib in patients with recurrent SCLC

1.2.2 Secondary Objectives

1.2.2.1 To confirm the safety and tolerability of navitoclax and vistusertib at the RP2D

1.2.2.2 To estimate progression free survival (PFS) and overall survival (OS) of the combination of navitoclax and vistusertib at the RP2D

1.2.2.3 To estimate disease control rate (DCR) of the combination of navitoclax and vistusertib at the RP2D. The DCR is defined as the sum of CR, PR, and SD divided by the total number of patients in the phase 2 part of the study.

1.2.3 Correlative Objectives

1.2.3.1 To assess pharmacodynamic changes in levels of phosphorylated 4EBP1 (p4EBP1) the ratio of p4EBP1 to total (p4EBP1/4EBP1) in paired pre-treatment and on-treatment biopsies at the RP2D

1.2.3.2 To correlate changes in BAX and MCL-1 with response

1.2.3.3 To estimate the baseline inter-patient variability in p4EBP1, pS6, BAX, and MCL-1.

1.2.3.4 To explore exposure-response relationships between navitoclax and vistusertib exposure and the pharmacodynamic endpoints (safety, efficacy, and laboratory correlatives).

2. BACKGROUND

2.1 Small Cell Lung Cancer

Small cell lung cancer (SCLC) represents 15% of all lung cancers and accounts for nearly 30,000 deaths in the US annually (2). Etoposide plus cisplatin was established as the standard of care for SCLC in the 1980s and can confer high response rates as initial therapy (3). Recurrence and death, however, is nearly universal; the overall survival of patients diagnosed with advanced SCLC is 8-10 months, a statistic that has not changed significantly in over 30 years (4). New therapies are critically needed.

2.1.1 BCL-2 inhibition in SCLC

Over-expression of the anti-apoptotic protein, BCL-2, is observed in > 60% of SCLC cases and correlates with therapy resistance (5, 6). ABT-737 and its orally bioavailable derivative, navitoclax, are high affinity BH3 mimetics that bind to BCL-2, BCL-xL and BCL-w (but spare MCL-1) and displace proteins bound to the BH3 domains of these anti-apoptotic proteins. We and others have demonstrated that ABT-737 can induce dramatic responses in BCL-2 expressing SCLC cell lines in vitro and in vivo (7, 8). In phase I/II clinical trials, however, navitoclax, had only limited single-agent activity in patients with relapsed SCLC (9, 10) and was difficult to combine with cytotoxic chemotherapy due to myelosuppression. The dose limiting toxicity of navitoclax was thrombocytopenia due to on-target inhibition of BCL-xL in circulating platelets (11), which could be attenuated by graduated lead-in dosing (9).

2.1.2 Combined BCL-2 and mTOR inhibition in SCLC PDX models

There is increasing evidence that co-targeting survival and growth pathways is effective in multiple tumor types. Combinatorial activity of PI3K/AKT/mTOR and BCL-2 inhibitors has been demonstrated preclinically in several tumor types including lymphoma, leukemia, breast cancer and SCLC (12-16). In two recent manuscripts we have reported that the combination of BCL-2/BCL-xL inhibitors, ABT-737 or navitoclax, with mTOR inhibitors led to potent induction of cell death and tumor regression in multiple preclinical in vivo models of SCLC including cell line xenografts, patient-derived xenografts (PDXs) and a genetically engineered mouse model (GEMM) (15, 16).

Gardner et al., modeled ABT-737 resistance in SCLC PDXs and demonstrated that the mTOR inhibitor, rapamycin, can enhance ABT-737 activity in BCL-2 expressing SCLC models (15). In this study, several PI3K/mTOR inhibitors, including rapamycin, everolimus and AZD8055, were synergistic with ABT-737 in SCLC cell lines in vitro. Furthermore, rapamycin enhanced ABT-737 cytotoxicity in vivo resulting in rapid and durable tumor regressions in BCL-2 expressing PDXs derived from patients with chemotherapy-naïve (LX47, Fig. 1A) and recurrent (LX48, Fig. 1B) SCLC. In contrast, in a BCL-2 low PDX (LX33) treatment with rapamycin resulted in tumor growth inhibition (15); ABT-737 did not add significantly to the effect of rapamycin (Fig. 1C).

Two pro-apoptotic BCL-2 family members required for ABT-737 mediated cell death (17), BAX and BAK, were increased in the rapamycin and ABT-737/rapamycin arms (Fig. 1D, red box). Increased BAX expression, without opposition from BCL-2 (due to ABT-737), is a possible explanation for the synergistic effects of ABT-737 and rapamycin.

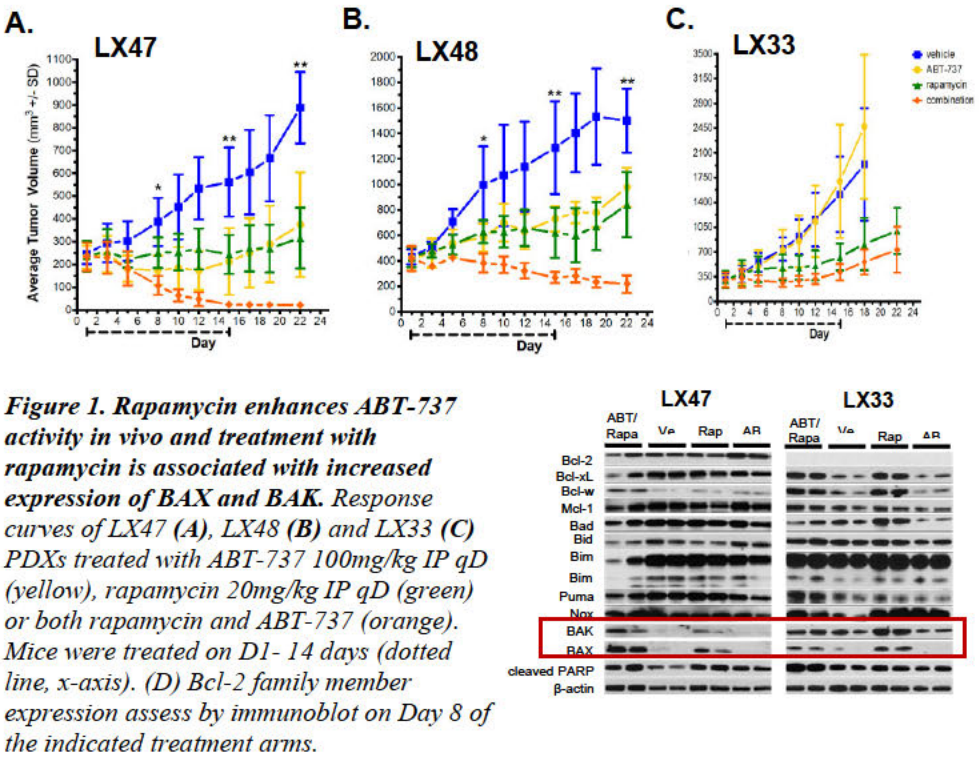

Figure 1. Rapamycin enhances ABT-737 activity in vivo and treatment with rapamycin is associated with increased expression of BAX and BAK. *Response curves of LX47* ***(A)****, LX48* ***(B)*** *and LX33* ***(C)*** *PDXs treated with ABT-737 100mg/kg IP qD (yellow), rapamycin 20mg/kg IP qD (green) or both rapamycin and ABT-737 (orange). Mice were treated on D1- 14 days (dotted line, x-axis). (D) Bcl-2 family member expression assess by immunoblot on Day 8 of the indicated treatment arms.*

Combined BCL-2 and TORC1/2 catalytic inhibitors are effective in SCLC xenograft models

Allosteric mTOR inhibitors, such as rapamycin, target only TORC1 and have largely exhibited limited single agent activity. One hypothesis underlying the limited clinical activity is that selective inhibition of TORC1 without engagement of TORC2 may result in activation of Akt through the S6K-IRS1 feedback loop and via mTORC2-mediated phosphorylation of AKT. AZD8055 and AZD2014 (vistusertib) are TORC1/2 catalytic inhibitors designed to improve upon these shortcomings of rapalogs.

Faber et al., has recently reported the efficacy of combined BCL-2 family inhibition and mTOR catalytic inhibition in multiple models of SCLC (16). The authors showed that the combination of navitoclax and AZD8055 potently induced increased apoptosis in a panel of SCLC cell lines in vitro and in vivo. A combinatorial effect and durable effect was also seen in BCL-2 low lines (Fig. 2), which was not observed with ABT-737 and rapamycin. One possible explanation for this difference is that the catalytic inhibitors, and not the rapalogs, potently reduce phosphorylation of 4EBP1. This in turn leads to decreased eIF4E activity, which reduces cap-dependent translation. MCL-1 transcripts

are particularly affected by this, and indeed MCL-1 protein levels drop significantly in response to catalytic TORC inhibition in SCLC cell lines (16). This MCL-1 reduction is thought to complement the BCL-2 and BCL-xL inhibitory effects of navitoclax, thereby facilitating BIM-mediated apoptosis. The authors found that in a SCLC PDX model, combination navitoclax and AZD8055 significantly repressed tumor growth and led to tumor regressions, compared to either drug alone (16) (Fig. 2c). When combined with navitoclax (or ABT-737), TORC1/2 catalytic inhibitors have comparable activity to rapamycin in BCL-2 expressing SCLC models and appear to be superior to rapamycin BCL-2 low xenografts.

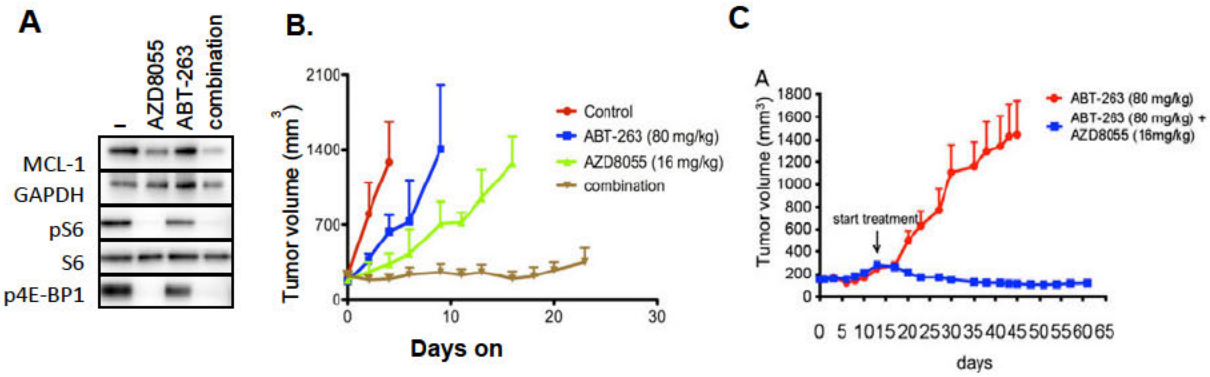

Figure 2. Activity of combination navitoclax (ABT-263) and AZD8055 in BCL-2 low-expressing line H82 and a SCLC PDX. ***(A)*** *H82 cell relative protein levels after 16 hour treatment with no drug (-), AZD8055 500 nM, ABT-263 1 uM, or combination AZD8055 500 nM and ABT-263 1 uM.* ***(B)*** *Human H82 cells were grown as xenograft tumors in Nu/Nu mice and when tumors were 100-200 mm^3 mice were randomized into treatment cohorts as indicated.* ***(C)*** *SCLC PDXs were treated with ABT-263 or ABT263 plus AZD8055.*

Navitoclax plus TORC1/2 inhibitor causes tumor regressions in an autochthonous model of SCLC

Faber et al., further tested the activity of combination navitoclax and AZD8055 in a p53; Rb1 conditional inactivation GEMM model of SCLC (18) . Tumors in this GEMM mimic the histologic features, acquired genetic alterations, and metastatic dissemination of human SCLC (16, 19). In this model, treatment with navitoclax and AZD8055 led to significant tumor stabilizations and regressions compared to either drug alone or no treatment in this model (Fig. 3). The activity of this combination in the GEMM model adds to the xenograft data by demonstrating activity in autochthonous tumors arising in the context of an intact immune system and tumor microenvironment.

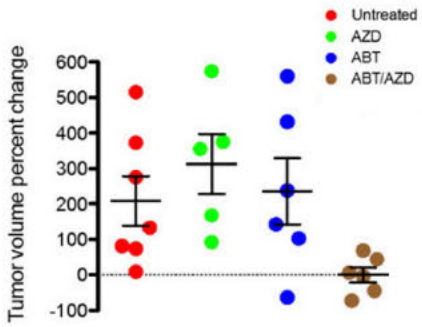

Figure 3. Activity of combination navitoclax (ABT-263) and AZD8055 in GEMM of SCLC. *Mice harboring homozygous floxed alleles of p53 and Rb1 were administered intratracheal adenovirus expressing Cre recombinase. Animals were monitored until they developed a lung tumor measurable by MRI and then were randomized to receive no treatment, AZD8055 16 mg/kg PO daily (6 days per week), ABT-263 80 mg/kg PO daily 6 days per week, or combination AZD8055 16 mg/kg and ABT-263 80 mg/kg PO daily 6 days per week. After 21 days of treatment, animals were re-imaged by MRI and tumor volume percent change was calculated. The percent tumor volume for each animal is plotted as a single circle, with black bars indicating mean and SEM.*

Summary

Taken together these data demonstrate that this combinatorial strategy meets a stringent criterion for preclinical efficacy and has significant translational potential. Our preclinical data support a cohesive model in which SCLC malignant cells with BIM expression rely on BCL-2, BCL-xL and MCL-1 to prevent apoptosis. Inhibition of BCL-2 and BCL-xL with navitoclax, in addition to induction of BAX expression and reduction of MCL-1 protein levels by TORC catalytic inhibition, results in potent induction of apoptosis and tumor regressions. Assessing intra-tumoral levels of relevant biomarkers to assess this model in patients treated with navitoclax and vistusertib will be critical for formulating a mechanistic understanding of tumor responses.

2.2 CTEP IND Agent (Navitoclax)

2.2.1 Navitoclax (ABT-263)

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) (ABT-263 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 (20-23). 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 (24-26). Anti-apoptotic Bcl-2 family proteins (*e.g.*, Bcl-2 and Bcl-X_L) inhibit cytochrome c release by blocking Bax/Bak activation (27). 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 (28-30).

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 (31). Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, and are therefore compelling targets for antitumor therapy. Overexpression of certain anti-apoptotic 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.

2.2.1.1 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 (ABT-263 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 (ABT-263 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 (32). In addition, strong synergism was observed with DNA-damaging and antimitotic agents across multiple cell lines and tumor types (ABT-263 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 (ABT-263 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 (ABT-263 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 (33) period in 5 of 6 ALL models as well as in 9 of 35 solid tumor xenograft models examined (32). 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.

2.2.1.2 Nonclinical Toxicology

The primary effects of navitoclax on the hematopoietic systems of both rats and dogs were decreased circulating platelets and lymphocytes (ABT-263 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 (ABT-263 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 (ABT-263 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 (ABT-263 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 (ABT-263

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.

2.2.1.3 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 (34).
- 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) (9, 10).
- M06-873, in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) (35).

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) (ABT-263 Investigator's Brochure, 2011). Grade 3/4 thrombocytopenia was observed in 29 out of 55 patients in trial M06-814 (34); 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 (9, 10); and 8 out of 29 patients in trial M06-873 (35). Grade 4 thrombocytopenia and neutropenia were reversible via temporary suspension or dose reduction of navitoclax, and filgrastim for persistent grade 4 neutropenia.

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 (9, 34). 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 (34, 35). 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 (35).

Other frequently reported AEs include anemia, neutropenia, infection, diarrhea, nausea, and fatigue (ABT-263 Investigator's Brochure, 2011) (9, 34, 35). 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 (35). 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 (34). 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 nonserious adverse events (ABT-263 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 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.

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) (34).
- M06-822 (SCLC and other solid tumors): 7-day lead-in dose of 150 mg/day followed by 325 mg QD (21/21 days) (9).
- M06-873 (CLL): 7-day lead-in dose of 100 mg/day followed by 250 mg QD (21/21 days) (36).

2.2.1.4 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) (ABT-263 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 (34). 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 (ABT-263 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 (9). 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 (35). 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.

2.2.1.5 Clinical Efficacy

Trial M06-814: Overall, 21 of 46 patients with assessable adenopathy showed some reduction in tumor size (34). 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 (34). 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 (9). 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 (10). 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 (35). 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.

2.2.1.6 Planned starting dose for Phase 1

For this combination trial with vistusertib, the initial dose of navitoclax will be 150mg daily, which is less than 50% of the phase 2 dose of 325mg daily. The 150mg daily dose was the starting dose in the combination trial of trametinib and navitoclax. If this is found to be tolerable when combined with 35mg of dose level 1 of vistusertib, the dose of navitoclax will then be escalated to 250mg, and 325mg daily. A lead-in dose of 150mg daily will be used for the first week in all dosing cohorts.

2.3 Other Agent (Vistusertib)

2.3.1 Vistusertib (AZD 2014)

Vistusertib is an inhibitor of the kinase activity of mammalian Target of Rapamycin (mTOR) serine threonine kinase, which plays a critical role in regulating cellular energy sensing, growth and metabolism. Deregulation of mTOR signaling is observed in many tumor types (37, 38), and mutations or loss of function of several upstream regulators, have been reported in most types of human tumor (39, 40).

The mTOR kinase forms two distinct multiprotein complexes called mTORC1 and mTORC2. Rapamycin and its analogues (rapalogs) are potent inhibitors of mTORC1 and have shown to be clinically effective in certain cancer types, such as endometrial cancer, mantle cell lymphoma, renal cell carcinoma and breast cancer. However, resistance to rapamycin and its analogues have been shown to limit their response rates in clinical studies. Vistusertib is a selective inhibitor of mTOR kinases and unlike rapalogs inhibits signaling of both mTORC1 and mTORC2 complexes (41). Vistusertib is therefore molecularly differentiated from rapamycin and its analogues.

2.3.1.1 Preclinical Studies

In addition to its dual inhibition of mTORC1 and mTORC2, vistusertib achieves a more profound inhibition of mTORC1 and shows a broader range of growth inhibitory activity in vitro across tumor types compared to rapalogs. Additionally, vistusertib has been found to be particularly effective in estrogen receptor-positive (ER+) breast cancer cell lines. Vistusertib delivers efficacy in a number of different tumor types in pre-clinical mouse models, particularly in breast cancer models which are sensitive or resistant to endocrine therapy.

2.3.1.2 Key Safety Findings

At the data cut-off (DCO) October 5, 2015 (Investigator's Brochure AZD2014, Version 7), clinical data were available for the clinical study program for vistusertib from 3 Phase 1 and 1 Phase 2a AstraZeneca sponsored studies. These were designed to assess the safety, tolerability, PK and preliminary efficacy of vistusertib. There were also 10 ongoing ESR studies.

As of DCO of October 5, 2015, 547 patients have been enrolled in studies with vistusertib; 252 in AZ-sponsored studies, and 295 in externally sponsored collaborative research (ESCR) studies. A total of 465 patients have received vistusertib; 252 in AZ-sponsored studies, and approximately 213 in ESCR studies.

Two AstraZeneca-sponsored Phase 1 studies were designed to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of vistusertib. Several doses and dosing schedules of vistusertib have been explored in both the monotherapy and combination studies including:

- D2270C00001: monotherapy in patients with advanced cancer. This study is now complete and Clinical Study Report (CSR) is available.
- D2270C00005: in combination with fulvestrant in patients with metastatic breast cancer.
- D2270C00008 (Japan PK) monotherapy in patients with advanced solid malignancies
- D2274C00001 (STORK) in combination with paclitaxel to patients with relapsed or refractory squamous non-small cell lung cancer (sqNSCLC) after at least one line of therapy
- D2270C00011 (TAX-TORC) in combination with paclitaxel in patients with solid tumors

Monotherapy
In Study D2270C00001 the following dosing was explored:

Dosing schedule	Doses explored	Defined MTD
Intermittent weekly BD dosing (2 consecutive days, 2 days on, 5 days off)	100 mg, 125 mg 170 mg, 225 mg	125 mg (2 consecutive days, 2 days on, 5 days off)
Continuous BD dosing	25 mg, 50 mg, 70 mg, 100 mg	50 mg
Continuous QD dosing	75 mg, 100 mg, 125 mg, 175 mg	100 mg

BD- twice daily dosing, QD- once daily dosing, MTD- maximum tolerated dose.

86.7 % of patients experienced at least 1 adverse event (AE) considered related to vistusertib by the reporting investigator. The most common AEs related to study treatment (occurring in ≥15% patients overall across all cohorts) were fatigue (58.5%), nausea (48.1%), mucositis (29.6%), diarrhea (28.1%), rash (27.4%), decreased appetite (22.2%), vomiting (21.5 %) and hyperglycemia (15.6%). Dose limiting toxicities (DLTs) reported at non-tolerated doses were fatigue, diarrhea, mucositis, nausea, vomiting and rash. During the study, 55/135 (40.7%) patients had a serious adverse event (SAE), and 24/135 (17.8%) had a treatment-related SAE. One patient died due to an AE of pulmonary embolism during the study; this was deemed unrelated to treatment by the investigator. 26 patients (19.3%) reported at least 1 AE leading to discontinuation. The most common AEs leading to discontinuation of vistusertib (reported in ≥4 patients overall) were fatigue (7.4%), nausea (4.4%), decreased appetite (3.0%), diarrhea (3.0%), mucositis (3.0%), rash (3.0 %), and vomiting (3.0%).

Although most patients experienced an AE, the drug was considered to be well tolerated with easily manageable side effects by the investigators. A total of 68 patients (50.4%) experienced an AE of Common Terminology Criteria for Adverse

Events (CTCAE) grade 3, 1 patient (1.3%) had a CTCAE grade 4 AE, and 1 patient (1.3%) had a CTCAE grade 5 AE (incidence rates include DLTs at non-tolerated doses). 15 (12%) patients on doses below the MTD experienced AEs that led to the discontinuation of vistusertib and no patients on a dose below the MTD for the QD continuous and intermittent (2 consecutive days, 2 days on, 5 days off) dosing schedules reported any AEs which led to discontinuation. AEs that defined the drug's non-tolerability were generally reversible within a week of stopping treatment with vistusertib. 105 patients (77.8%) had a duration of treatment (including periods of dose interruption) of >3 months. 1 patient had duration of treatment of 18 months.

The change from the continuous dosing at a dose of 50 mg BD to the intermittent (2 consecutive days, 2 days on, 5 days off) dosing of vistusertib at a dose of 125 mg BD was accompanied by an increase in the incidence of nausea from 20/41 (48.8%) to 9/13 (69.2 %) and diarrhea from 18/41 (44.0%) to 9/13 (69.2 %), however, it reduced the incidence of rash from 20/41 (48.8%) to 2/13 (15.4%)] and mucositis from 18/41 (43.9%) to 4/13 (30.8%). The 125 mg 2 consecutive days, 2 days on, 5 days off schedule did not have any AE's associated with discontinuation with vistusertib, compared to the continuous 50 mg BD schedule, for which 18/41(43.9 %) patients discontinued treatment as a result of an AE.

T wave changes on ECG have been observed in 9 selected patients of the total 135 included in study D2270C00001**:** 4 patients had AE of T wave inversion reported by Investigator. Additional 5 patients' ECG were assessed by GSP/MSD as potentially significant as the T wave changes were persistent on treatment and did not resolve at end of study. However, the above mentioned ECG findings do not indicate a clinically significant ECG abnormality when the pre-clinical CV safety profile of the study compound and the clinical context of the observed ECG changes are taken into the final clinical consideration.

Study D2270C00005: Combination with Fulvestrant (42)

In Study D2270C00005 in the following vistusertib dosing was explored:

Dosing schedule	Doses explored	Recommended dose/ defined MTD
Intermittent BD dosing (2 consecutive days, 2 days on 5 days off)	125 mg, 170 mg	125 mg (2 consecutive days, 2 days on 5 days off), under fasting and fed conditions
Continuous BD dosing	35 mg, 50 mg	50 mg
Continuous QD dosing	75 mg, 100 mg	75 mg

BD- twice daily dosing, QD- once daily dosing, MTD- maximum tolerated dose

At the MTD doses the most frequently reported AEs related to vistusertib (reported in ≥15% patients overall) were fatigue, nausea, rash, diarrhea, decreased appetite,

vomiting, hyperglycemia, mucositis, pruritus, headache, anemia, asthenia, dry skin, constipation, dizziness and skin hyperpigmentation. Due to low numbers in Study D2270C00005 50 mg BD continuous dosing with fulvestrant group, headache, asthenia, constipation, dizziness and skin hyperpigmentation are included in this list despite only affecting 2 patients (2/13, 15.4% of the group). The most frequently reported AEs of CTCAE Grade 3 or higher (reported in >1 patient at an MTD, irrespective of causality) were rash, fatigue, nausea, infections, mucositis, vomiting, anemia, diarrhea, hyperglycemia, and hypophosphatemia.

At MTD doses, no SAE MedDRA term was reported in more than 1 patient. The SAEs in the continuous dosing groups of 50 mg BD plus fulvestrant and 75 mg QD plus fulvestrant were pulmonary embolism, infections, neutropenia, renal impairment, and spinal compression fracture. The SAEs in the intermittent dosing group of 125 mg BD plus fulvestrant were vomiting, nausea, hypercalcemia, diarrhea, infections, colitis, enteritis and subdural hematoma. Two patients had causally-related SAEs: 1 patient (75 mg QD) had CTCAE Grade 4 febrile neutropenia; and 1 patient (125 mg BD) had CTCAE Grade 3 nausea, Grade 3 vomiting, and Grade 3 diarrhea. All these SAEs were considered by the investigator to be related to vistusertib but not fulvestrant.

There was one death due to an AE in the Study D2270C00005 MTD of 75 mg QD + fulvestrant (continuous dosing). This was an AE of sepsis of unknown etiology which was deemed unrelated to treatment by the investigator.

Combination with Paclitaxel

Study D2270C00011 **(**TAX-TORC) Vistusertib is being explored in combination with paclitaxel in patients with squamous cell lung cancer and epithelial ovarian cancer in an Externally Sponsored Collaborative Research (ESCR) study. The paclitaxel dose is 80 mg/m^2 administered weekly for six consecutive weeks followed by a one week treatment interruption. In order to maximize exposure to vistusertib at the same time as paclitaxel, the dose of 50 mg BD vistusertib, 3 days on, 4 days off, in combination with 80 mg/m2 weekly paclitaxel (6 weeks on, 1 week off) was selected for further exploration.

In Study D2270C00011 22 patients had an SAE ≥CTCAE Grade 3; diarrhea (reported in 4 patients), and fatigue, pneumothorax, sepsis, small intestinal obstruction, and urinary tract infection (each reported in 2 patients) were the only CTCAE ≥Grade 3 SAEs that were reported in more than 1 patient. Ten patients had at least 1 SAE that was considered to be related to study treatment (1 patient with fatigue, 1 patient with fatigue and mucosal inflammation, 1 patient with rash macular and rash maculopapular [both considered to be related to vistusertib only], 1 patient with febrile neutropenia and diarrhea, 3 patients with diarrhea [2 events considered to be related to vistusertib only], 1 patient with urinary tract infection, gastrointestinal toxicity and pneumonitis, and 2 patients with bronchitis). Seven patients had SAEs that resulted in discontinuation of study drug: 1 patient (25 mg BD) with pneumothorax and

cerebrovascular accident; 1 patient (25 mg BD) with dyspnea; 1 patient (50 mg BD, 3 days on and 4 days off) with device-related sepsis; 1 patient (50 mg BD, 3 days on and 4 days off) with pulmonary edema, urinary tract infection, gastrointestinal toxicity and pneumonitis; 1 patient with bronchitis (50 mg BD); 1 patient with hemoptysis (25 mg BD); and 1 patient with bronchitis, small intestinal obstruction, and ascites (50 mg BD 3 days on 4 days off).

Three patients died due to AEs in Study D2270C00011. One patient died as a result of bronchitis which was thought to be related to both vistusertib and to paclitaxel. One patient died following chest sepsis and pneumonia, thought to be related to paclitaxel only. One patient died as a result of hemoptysis and disease progression, thought to be unrelated to either drug.

Study D2274C00001 (STORK) Only 4 patients of the 5 patients dosed (n=5) had reported AEs. Abdominal pain and peripheral neuropathy (each reported in 2 patients) are the only MedDRA preferred terms to have been reported in more than 1 patient. The AEs at CTCAE Grade 3 and above were mucositis, diarrhea, and acute respiratory failure. AEs thought to be causally-related to vistusertib were fatigue, diarrhea, mucositis, pruritus, asthenia, abdominal pain, and anemia. There were two SAEs (chronic obstructive pulmonary disease and acute respiratory failure) and these occurred in the same patient, neither of these was thought to be causally-related to vistusertib. There have been no deaths in this study. This study was terminated early.

Summary of Safety Findings

Vistusertib Monotherapy and in combination with Fulvestrant
The overall safety findings at vistusertib MTDs in small numbers of patients in non-randomized Phase 1 trials in monotherapy and in combination with fulvestrant were very similar and the main AEs observed are consistent with AEs already reported for other mTOR inhibitors: rash, pruritus, mucositis, fatigue, nausea, vomiting, diarrhea, constipation and decreased appetite. However, at intermittent dosing schedules, vistusertib showed a different safety profile compared to continuous dosing schedules. At intermittent dosing schedules (125 mg BD 2 days on and 5 days off) the main AEs reported, which also led to dose discontinuation in 1 patient, were nausea and vomiting. There was also a marked reduction in rash at intermittent dosing schedules (from 69.2% to 16.2% in combination and 48.8% to 15.4% in monotherapy), pruritus (61.5% to 13.5% in combination and 34.1% to 0% in monotherapy) and mucositis (from 69.2% to 29.7% in combination therapy and 43.9% to 30.8% in monotherapy). Interestingly, there were no cases of pneumonitis observed with this intermittent monotherapy schedule (compared with 2.4% and 7.7% in the continuous monotherapy and combination therapies respectively). Thus, the intermittent dosing schedules, showing similar efficacy at least in combination with fulvestrant offer an important new development option for a mTOR kinase inhibitor with a different safety profile, especially for combinations with other agents.

Vistusertib in combination with Paclitaxel

AstraZeneca recently reviewed preliminary unvalidated safety and efficacy data from these two studies (D2274C00001 (STORK) and D2270C00011 (TAX-TORC)). In the STORK study there were no new safety signals or significant changes to the expected safety profile of vistusertib. However, data from both of these studies in sqNSCLC patients, who commonly have a large number of comorbidities, suggested that the vistusertib 50 mg BD (3 days on 4 days off per week) in combination with weekly paclitaxel (6 weeks on, 1 week off) dose level did not appear to be an acceptable regimen because of discontinuations due to rapid disease progression and/or AEs. In addition, data suggested that the vistusertib 50 mg BD in combination with weekly paclitaxel dose level of the STORK study did not demonstrate acceptable efficacy in sqNSCLC patients, with only stable disease observed (for between approximately 2 to 6 months) as best response in 4/11 patients (no objective response was observed).

AstraZeneca considered these data to represent a change in the benefit:risk profile of the vistusertib 50 mg BD (3 days on 4 days off per week) in combination with weekly paclitaxel (6 weeks on, 1 week off) dose level in sqNSCLC patients. Therefore, AstraZeneca decided not to further evaluate the 50 mg BD in combination with weekly paclitaxel dose level in sqNSCLC patients.

2.3.1.3 Key Efficacy Findings

In D2270C00001 (monotherapy in patients with advance cancer) at the 50 mg BD dose in a total of 40 patients, 2 patients had an objective response; 1 patient with pancreatic acinar cell type cancer and 1 patient with ER+ breast cancer had confirmed RECIST PR and received vistusertib treatment for 175 and 206 days, respectively. In addition, 12 patients in the 50 mg BD group, and 4 patients each in the 100 mg QD and 125 mg intermittent cohort achieved stable disease.

In D2270C00005 (combination with fulvestrant), as of the DCO (October 5, 2015) vistusertib in combination with fulvestrant has demonstrated encouraging response rate data in this Phase I setting at MTDs for both the continuous and intermittent dosing schedules (42). There were partial responses (confirmed and unconfirmed) at every MTD dose group, 3/11 (27.3%) with a confirmed response rate of 2/11 (18.2%) in the 50 mg BD continuous dosing group, 3/13 (23.1%) with a confirmed response rate of 2/13 (15.4%) in the 75 mg QD continuous dosing group, and 3/20 (15.0%) with a confirmed response rate of 1/20 (5.0%) in the 125 mg BD intermittent dosing group.

Additional information on the best objective responses in all patients and patients with measurable disease at baseline, is included in Table 20 in Section 5 of the IB edition 7.

2.3.1.4 Clinical Pharmacokinetics

The pharmacokinetics of vistusertib has been studied following single and repeat administration of a solution and tablet formulation in cancer patients. QD, BD and

intermittent dosing (2 consecutive days, 2 days on, 5 days off) have been investigated.

Solution: The single dose PK data showed that vistusertib administered as a solution formulation was orally available and rapidly absorbed, with median time to reach maximum plasma concentration (T_{max}) between 0.50 h and 1.0 h (range 0.27 h to 2.1 h) across the 25 mg to 125 mg dose range. Plasma levels declined in a biphasic manner and terminal half-life ($t_{½,\lambda z}$) was short and variable between patients (mean between 2.5 h and 3.8 h across the 25 mg to 125 mg dose range; individual range 0.82 h to 8.0 h). Single dose exposure (AUC) increased greater than proportionally to dose across the range investigated, with a 5-fold increase in dose from 25 mg to 125 mg giving approximately a 13-fold increase in AUC and a 9-fold increase in C_{max}.

Tablets: Single dose PK data following administration of the tablet formulation showed that absorption of the tablet was slower relative to the solution. This was shown by a comparatively lower C_{max} and a slightly longer T_{max} (median between 1.0 h and 3 h and range from 0.5 h to 6.2 h) across the 50 mg to 225 mg dose range investigated (more information is available in the AZD 2014 IB version 7, Figure 2 and Table 5).

In summary, vistusertib is orally available, rapidly absorbed when administered as a tablet and has a short terminal half-life. There is a greater than dose proportional increase in exposure (AUC) to vistusertib across the dose range investigated with a corresponding decrease in oral clearance (CL/F). At higher doses (>100 mg) the apparent clearance decreases (CLss/F < CL/F for the same dose) following repeat dosing, with a corresponding increase in terminal half-life. The mechanism for this and clinical relevance has not been fully elucidated. Absorption of vistusertib is delayed following administration with food (delayed T_{max} and reduction in C_{max}) relative to the fasted state, but the extent of exposure (AUC) appears comparable.

Pharmacokinetics and drug metabolism in humans

Vistusertib is a substrate and weak inhibitor of various cytochrome P450 isoenzymes and drug transporters in vitro. In addition, vistusertib is a weak inducer of CYP3A4 in vitro. The clinical relevance of these findings has not been fully evaluated. There are specific exclusion criteria and co-medication guidance in place to avoid potential pharmacokinetic drug interactions (the AZD 2014 Investigator's Brochure, version 7, and section 5.3.2 for further information).

2.3.1.5 Pharmacodynamics

In study D2270C00001, phosphorylation of markers of S6 and 4EBP1 (TORC1) was reduced in 8/8 and 3/7 evaluable tumor biopsies respectively and phosphorylation of the marker of AKT (TORC2) was reduced in 3/4 evaluable tumor biopsies, following vistusertib treatment.

2.3.1.6 Planned starting dose for Phase 1

Vistusertib is available for administration as a tablet for use in clinical studies and is presented as three strengths: 10, 25 or 50 mg. Continuous and intermittent dosing schedules have been explored and the intermittent schedule has shown an improved safety profile compared to the continuous dosing schedule in non-randomized studies. For this combination trial with navitoclax, the initial dose of vistusertib will be 35mg BID; based on the preclinical data presented in section 2.4, continuous dosing of vistusertib was recommended. If a continuous BID regimen of vistusertib is not tolerated even at the 25 mg dose level, then an alternative schedule of BID for 2 days on/5 days off will be explored as suggested by AstraZeneca.

2.4 Correlative Studies Background

2.4.1 Navitoclax and Vistusertib Pharmacokinetics

In cancer patients, navitoclax exposure is dose proportional over the dose range proposed in this trial (34). Navitoclax pharmacokinetics is best described by a two-compartment model with slow absorption (i.e., a lag-absorption with a one transit compartment) and linear elimination between doses of 10 and 475 mg (43). The T_{max} occurs at 9 hr with a 17 hr half-life. Age has a significant effect on apparent clearance with an estimated value of 5.5, 3.7, and 3.0 L/hr for a 30, 60, or 90 yo patient. Lastly, the pharmacokinetics were linked with thrombocytopenia (pharmacodynamics effect) by an E_{max} model utilizing a semiphysiological model with a progenitor compartment with maturation to a circulating platelet thus linking the known DLT of navitoclax to the drug exposure. A mass balance study demonstrated ~90% of the navitoclax is excreted in the feces with ~50% being metabolites (7 metabolites have been identified) (44). Navitoclax is metabolized by CYP3A4 and is a moderate inhibitor of CYP2C8 and a strong inhibitor of CYP2C9 (ABT-263 Investigator's Brochure, 2011). Navitoclax is also reported to be a P-glycoprotein (ABCB1) substrate (45). Despite being primarily metabolized by CYP3A4, the pharmacokinetic of navitoclax were not altered when administered with the strong CYP3A4 inhibitor, ketoconazole (46). However, when administered with the strong CYP3A4 inducer rifampin, navitoclax AUC was decreased by 40% but the half-life was not altered (44).

Vistusertib (AZD2014 Investigator's Brochure version 7, 2016) was selected from a series of dual mTORC1 and mTORC2 inhibitors due to its superior pharmacokinetic profile in rodents and minimal metabolism via human hepatocytes (47). Vistusertib is metabolized by CYP3A4 and CYP3A5 and is substrate for and inhibited by the P-glycoprotein (ABCB1) and BCRP (ABCG2) transporters (AZD2014 Investigator's Brochure version 7, 2016). Vistusertib is a weak inhibitor of CYP2C8, CYP 2C9, CYP2C19, and CYP2D6 but unlikely to cause clinically relevant drug-drug interactions (AZD2014 Investigator's Brochure version 7, 2016). Vistusertib induced CYP3A4 mRNA in a concentration-dependent manner in human hepatocytes but the clinical relevance has not been determined or estimated (AZD2014 Investigator's Brochure version 7, 2016). Patients on moderate to strong inducers and/or inhibitors of CYP3A4/5

and P-glycoprotein (ABCB1) and BCRP (ABCG2) are excluded in other trials (mTORC1/mTORC2 Kinase Inhibitor AZD2014 in Previously Treated Glioblastoma Multiforme https://clinicaltrials.gov/ct2/show/NCT02619864).

There is a potential for a drug-drug interaction between CYP3A4 with navitoclax as a substrate and vistusertib as a weak inducer. Since navitoclax will need to be given for 1 week prior to the combination to attenuate thrombocytopenia, a formal drug-drug interaction trial design will not be performed. A full pharmacokinetic profile of navitoclax at steady-state will be proposed in this trial to assess for a drug-drug interaction. Additionally, navitoclax and vistusertib trough concentrations will be assessed over the course of the first cycle. The navitoclax concentrations will be used to correlate with thrombocytopenia. We will incorporate the expansion to a full pharmacokinetic profile for navitoclax and vistusertib if toxicities are frequent and severe with the combination.

2.4.2 Reverse Phase Protein Array

Our preclinical data supports a mechanism in which exposure to mTOR inhibitors results in changes in BCL-2 family member expression and sensitizes tumors to navitoclax. Specifically, we observed that mTOR inhibition resulted in increased expression of proapoptotic proteins (BAX and BAK) and decreased expression of the antiapoptotic protein, MCL-1; either of these perturbations could render cells more sensitive to the effects of a BCL-2 inhibitor such as navitoclax. Here we hypothesize that at the RP2D of navitoclax plus vistusertib, paired pre-treatment and on-treatment tumor biopsies will demonstrate the following pharmacodynamic responses: decreased phosphorylation of the TORC1 targets 4EBP1 S6K, decreased MCL-1 protein levels, increased BAX or BAK protein levels, and increased apoptosis. We further hypothesize that these changes will correlate with response to the drug combination.

As BCL-2 proteins and the mTOR pathway are generally regulated at the protein level we will use reverse phase protein array (RPPA) as our integrated assay for this study. RPPA utilizes a small amount of tissue to assess the levels of over 180 proteins and phospho-proteins including BCL-2 family members, PI3K/AKT/mTOR proteins and proteins involved in cell death. The utility of RPPA has been documented in multiple studies based on cell lines and patient samples. The MD Anderson Cancer Center RPPA core and our translational science collaborator, Dr. [redacted], have extensive experience in this technology and application in preclinical and clinical studies for a spectrum of cancers including SCLC.

Using RPPA we will compare mTOR pathway activation and BCL2 protein levels at baseline then after a 2 week exposure to vistusertib and navitoclax at the RP2D. Paired pre-treatment and on treatment core biopsies will be mandatory for patients on the phase 2 portion of the trial. Fresh biopsies are optional for patients on the Phase 1 portion of the trial. As described above, these samples will provide the opportunity to correlate pharmacodynamic effects with tumor response and pharmacokinetic parameters at the RP2D. Pre-treatment biopsies will be obtained during screening, and on-treatment

biopsies will be obtained on Cycle 1 Day 15 (+/-7days). Vistusertib is a potent ATP-competitive inhibitor of both TORC1 and TORC2 complexes and produces dose-dependent inhibition of phosphorylation of 4EBP1, S6K and AKT in vivo. The differential intensity of phospho-4EBP1 or p-S6 in pre-treatment compared with on-treatment tissue samples may serve as marker to assess PD effect of vistusertib on inhibition of TORC signaling.

Assessing tumor levels of these potential biomarkers in patients treated with navitoclax plus vistusertib will be critical for formulating a mechanistic understanding of tumor responses and we believe that paired tumor biopsies can be obtained safely. In our recent Hopkins institutional experience ~ 50% of study biopsies for patients with advanced SCLC were obtained from outside the thorax at sites including liver, adrenal gland and lymph nodes. For patients whose tumors are localized to the lung, our endobronchial and transthoracic biopsy complication rates (primarily pneumothorax) are 5-10%. We feel that these numbers are representative of academic institutions, particularly those that would participate in this study. Our protocol specifies that we will only attempt to collect tumor samples if patients have tumor sites amenable to biopsy; the risk of pneumothorax will be heavily considered when determining whether a tumor site is amenable to biopsy.

2.4.3 Tissue and plasma biomarkers of efficacy (exploratory biomarkers)

2.4.3.1 Tumor Tissue Studies

When available, optional extra or leftover tissue samples (archival or fresh) will be studied to identify biomarkers associated with drug activity. Potential studies include analyses that would complement the results from the RPPA analyses(including gene expression and IHC) and whole-exome sequencing on pre-treatment tumors for identification of genomic correlates of response using methodologies developed by the Velculescu group (48-50). High priority targets would include BCL-2 family members (e.g., BIM, BAX, BCL-2, BCL-all, MCL-1) and of the PI3K/mTOR pathway, including RICTOR amplification.

2.4.3.2 Optional Blood Studies

The Velculescu group has developed non-invasive genomic approaches in order to determine somatic mutations that detect residual disease in the patient's circulation (51-54). Using optional blood samples collected prospectively after initiation of navitoclax plus vistusertib, we will determine whether measurements of cancer-specific genomic alterations in circulating tumor DNA (ctDNA) can predict disease progression prior to conventional CT imaging. Tumor-specific mutations found in the circulation after disease progression will be compared to the genomic profile of the recurrent tumors and we will confirm the presence of matching resistance mutations in ctDNA.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Phase 1 Specific Eligibility Criteria

3.1.1.1 Patients must have histologically or cytologically confirmed malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

3.1.2 Phase 2 Specific Eligibility Criteria

3.1.2.1 Patients must have histologically or cytologically confirmed small cell lung cancer whose disease has relapsed or progressed after ≥ 1 prior therapy, one of which must have been a platinum doublet. Pathology confirmation must be done at SKCCC or at the local participating site.

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

3.1.2.3 Subjects must be willing to undergo 2 sets of core needle biopsies (pre-treatment and on-treatment), if there are lesions amenable to biopsy. An optional core biopsy will be requested at progression.

3.1.3 General Eligibility Criteria

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

3.1.3.2 ECOG performance status ≤ 1 (Karnofsky ≥70%, see Appendix A)

3.1.3.3 Life expectancy of greater than 12 weeks.

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

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- hemoglobin ≥ 9.0 g/dL
- platelets ≥100,000/mcL
- aPTT, PT ≤ 1.2 x ULN
- total bilirubin ≤ 1.5 x ULN (patients with Gilbert's syndrome may have serum bilirubin > 1.5 ULN)
- AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN if no demonstrable liver

	metastases or ≤ 5 x ULN in the presence of liver metastases
– creatinine	≤ 1.5 x ULN and concurrent creatinine clearance (CrCl) ≥ 50mL/min/1.73 m^2 for patients with Cr > 1.5 x ULN
– proteinuria	≤ 1+ on dipstick testing (if 2+ seen on first test, retest ≥ 24 hours later)

3.1.3.5 Patients with a history of central nervous system (CNS) metastases must have documentation of stable or improved status based on brain imaging for at least 2 weeks after completion of definitive treatment and within 2 weeks prior to first dose of Study Drug, off or on a stable dose of corticosteroids.

3.1.3.6 Patients must have completed chemotherapy, biological or radiotherapy ≥ 3 weeks prior to entering the study.

3.1.3.7 Patients must have recovered to ≤ grade 1 adverse events or to ≤ grade 2 alopecia and sensory neuropathy due to prior treatment.-

3.1.3.8 Patients must be able to understand and willing to sign a written informed consent document.

3.1.3.9 Patients must be able to swallow pills.

3.1.3.10 The effects of navitoclax and vistusertib on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study participation, and up to 90 days following completion of therapy. For women this should include one highly effective method of contraception and one barrier method, as defined below.

Highly effective methods include:

- total abstinence from sexual intercourse (minimum one complete menstrual cycle prior to study drug administration);
- vasectomized partner;
- medroxyprogesterone acetate depot injection;
- placement of a copper-banded intrauterine device (IUD) or intrauterine system (IUS);
- bilateral tubal ligation.

Barrier methods include:

- condom;
- occlusive cap (e.g. diaphragm or cervical/vault caps) with spermicide.

Please note: use of other oral, injected or implanted hormonal methods of contraception cannot be considered highly effective as it is currently unknown whether vistusertib may reduce their effectiveness. Periodic abstinence, the rhythm

method, and the withdrawal method are not acceptable methods of 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 90 days following completion of therapy.

Women of childbearing potential must have a negative urine 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. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of navitoclax and/or vistusertib administration.

3.2 Exclusion Criteria

3.2.1 Phase 2 Specific Exclusion Criteria

3.2.1.1 Prior treatment with a TORC1, dual TORC1/2 inhibitor, or BCL-2/xL inhibitor

3.2.1.2 Patients with active malignancies other than SCLC or patients with prior curatively treated malignancy at high risk of relapse during the study period with the exception of localized squamous or basal cell skin cancers.

3.2.2 Phase 1 and General Exclusion Criteria

3.2.2.1 Major surgery within 21 days of starting protocol treatment.

3.2.2.2 Patients who are receiving any other investigational agents.

3.2.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to navitoclax or vistusertib

3.2.2.4 Patients receiving anticoagulation or anti-platelet therapy are excluded due to the risk of thrombocytopenia with navitoclax.

- Excluded agents include heparin or low molecular weight heparin, warfarin, clopidogrel, ibuprofen and other NSAIDS, tirofiban, 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 (≥50,000/mm3) 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.

3.2.2.5 Patients with an underlying condition predisposing them to bleeding or currently exhibiting signs of clinically significant bleeding.

3.2.2.6 Patients with a recent history of non-chemotherapy-induced thrombocytopenic-associated bleeding within 1 year prior to the first dose of study drug.

3.2.2.7 Patients with a significant history of cardiovascular disease or procedures within the preceding 6 months (*e.g.*, MI, coronary artery bypass graft placement, angioplasty, vascular stent, angina pectoris, ventricular arrhythmias requiring continuous therapy, congestive heart failure New York Heart Association (NYHA) Grade ≥ 2, thrombotic or thromboembolic event).

3.2.2.8 Any of the following cardiac criteria:
- Mean resting corrected QT interval (QTc using Fredericia's formula (QTcF)) > 470 msec obtained from 3 electrocardiograms
- Congenital or family history of long or short QT syndrome, Brugada syndrome, known history of QTc prolongation or Torsades de Pointes within 12 months of entering the study
- Abnormal echocardiogram at baseline (left ventricular ejection fraction [LVEF] < 40% and shortening fraction [SF] < 15%.

Drugs which have an increased risk for QTc prolongation should be avoided; for a list of these drugs, please refer to http://crediblemeds.org/

3.2.2.9 Patients with uncontrolled Type 1 or Type 2 diabetes. Vistusertib belongs to a class of drugs that causes hyperglycemia. In order to assess toxicity, patients with an elevated risk of hyperglycemia should be excluded from study.

3.2.2.10 Patients currently receiving medications or herbal supplements of the classes below are ineligible. Patients are eligible if they stop use of these compounds at least 1 week prior to receiving any treatment on this protocol or as specified in protocol section 5.3.1.1, 5.3.2.1 and 5.3.2.2.
- potent inhibitors or inducers of CYP3A4/5 (CYP3A4 inhibitors such as ketoconazole and clarithromycin are not allowed 7 days prior to the first dose of navitoclax and during navitoclax administration)
- strong or moderate inhibitors of Pgp or BRCP1
- sensitive substrates of CYP2C9 (i.e. phenytoin and warfarin)
- substrates of certain drug transporters (OATP1B1, OATP1B3, MATE1 or MATE2K)

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as Facts and Comparisons or Lexicomp; medical reference texts such as the Physicians' Desk Reference may also provide this information.

3.2.2.11 Pregnant women are excluded from this study because navitoclax and vistusertib have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with navitoclax and vistusertib breastfeeding should be discontinued if the mother is treated with navitoclax and vistusertib

3.2.2.12 Patients positive for human immunodeficiency virus (HIV) are not excluded from this study, but HIV-positive patients must have:

- A stable regimen of highly active anti-retroviral therapy (HAART) that does not include strong or moderate CYP3A4 inducers or inhibitors
- No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
- A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based test

3.2.2.13 Any hematopoietic growth factors (e.g., filgrastim [granulocyte colony-stimulating factor; G-CSF], sargramostim [granulocyte-macrophage colony-stimulating factor; GM-CSF]) within 14 days prior to receiving study treatment.

3.2.2.14 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.

3.2.2.15 Patients who have received a live, attenuated vaccines within 4 weeks of first dose of drug

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications (*e.g.*, Roster Update Management System [RUMS], OPEN, Rave,),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

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

4.2 Site Registration

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

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation,
- IRB-signed CTSU IRB Certification Form, and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Asssurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select LAO-LAO-MD017, and protocol number 10070,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Requirements For 10070 Site Registration:

- For Phase 2 of the study: Internal site initiation visit (SIV) conducted by the site study PI with the site research team
  -SIV checklist and sign-in sheet must be completed and signed by site study PI and sent back to the Protocol Liaison of the lead LAO.

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → Regulatory Submission.

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

4.2.4 Checking **Site** Registration Status

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

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen
- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

4.3.2 OPEN/IWRS User Requirements

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

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

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.3.3 Patient Enrollment Instructions

In order to verify eligibility, the following documents should be submitted to the Study Coordinator of the Lead Organization at least 48 hours prior to treatment initiation:

- Complete Request for Registration Form
- Signed consent form and eligibility checklist
- Recent physical exam note, including performance status
- Screening labs/urinalysis/pathology report
- Screening imaging report/EKG/ ECHO

After approval by the Lead Organization, the patient may be enrolled in OPEN.

4.3.4 OPEN/IWRS Questions?

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

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

5.1.1 Phase 1: Dose Escalation

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 (see Appendices C and D). The medication diary will be returned to clinic staff at the end of each 28-day treatment cycle.

Eligible subjects will be treated with daily oral navitoclax and daily oral vistusertib given in a 28-day cycle following the dose- escalation scheme in the table below.

Dose Escalation Schedule

Dose Level	Dose	
	Navitoclax* by mouth, once a day	**Vistusertib by mouth, twice a day**
Level -1	150 mg	25 mg
Level 1	150 mg	35 mg
Level 2	250 mg	35 mg
Level 3	325 mg	35 mg
Level 4	325 mg	50 mg

* To reduce the incidence of significant thrombocytopenia, all patients will receive lead-in dosing of navitoclax 150mg po once a day prior to C1D1. At any time after 7 days of navitoclax, if the platelet count is >50,000 and stable or increasing, subjects can dose escalate to the navitoclax dose defined in the cohort level and start vistusertib. Cycle 1 day 1 is defined as the first day both study drugs are taken.

The RP2D will be defined as the highest dose level at which < 33% of the dose cohort (0 of 3 or 1 of 6) experiences DLT during 1 cycle. During the phase 1 portion of this study, the RP2D was determined to be navitoclax 150 mg by mouth daily plus vistusertib 35 mg by mouth twice a day.

5.1.2 Phase 2

Eligible subjects will be treated with navitoclax and vistusertib at Dose Level 1: navitoclax 150 mg by mouth once a day plus vistusertib 35 mg by mouth twice a day.

Per the drug manufacturer AstraZeneca, clinical supply of Vistusertib (AZD2014) will expire on August 31, 2021 (based on the planned expiration date extension), and there will be no additional drug available for clinical use after that date. All patients must complete their last treatment on or before August 31, 2021, and the study will be closed to accrual and treatment to coincide with this expiration date.

5.1.3 Dosing Instructions

Navitoclax should be taken once a day by mouth on a 28-day cycle. Navitoclax should be taken with food. Navitoclax should be swallowed whole; patients should be instructed not to split, crush or chew the tablets. If vomiting occurs after taking Navitoclax, the dose should not be retaken.

To reduce the incidence of significant thrombocytopenia, all patients will receive 7 days of lead-in dosing of navitoclax 150mg po once a day prior to C1D1. At any time after 7 days of navitoclax, if the platelet count is >50,000 and stable or increasing, subjects can dose escalate to the navitoclax dose defined in the cohort level and start vistusertib. C1D1 dosing should be held for clinically significant bleeding. Cycle 1 day 1 is defined as the first day both study drugs are taken.

Vistusertib: where possible all doses of vistusertib should be taken at approximately the same times each day. Twice daily doses should be taken approximately 12 hours apart. If vomiting occurs within 30 minutes after vistusertib dosing, or later if the tablet(s) can be identified in the vomit content, the patient can re-take a new tablet(s).

Should a patient miss a scheduled dose of either agent, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the tablets on time.

5.1.3.1 Food restrictions

- Navitoclax should be given with food
- Vistusertib can be given with or without food.
- Sugary and fatty foods should be kept to a minimum in the meals prior to taking a dose of vistusertib
    - Large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g. grapefruit juice or marmalade) should be avoided whilst taking vistusertib. No more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily is allowed

5.1.3.2 Sunlight-protection measures

Patients should be advised of the need for sunlight protection measures such as use of sunscreen and sunglasses, as well as avoidance of sunbeds/tanning booths, during administration of vistusertib, and should be advised to adopt such measures for a period of three months after receiving their final dose of vistusertib.

5.2 Dose Escalation and Definition of Dose-Limiting Toxicity

5.2.1 Definition of Dose Limiting Toxicity

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).

The occurrence of any of the following toxicities during cycle 1 will be considered a dose-limiting toxicity (DLT), if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

- ≥ Grade 3 non-hematologic toxicity
  - Except nausea, vomiting or diarrhea that can be controlled by appropriate medical intervention or prophylaxis and that resolves to grade 0-1 within 48 hours with medical intervention
  - Except electrolyte toxicities that can be corrected to grade 0-1 or baseline within 48 hours after holding treatment
- ≥ Grade 3 rash attributed to the combination will be considered a DLT if grade 3 despite maximal medical management (including oral antibiotic, topical or oral steroids) for > 72 hours
- Febrile neutropenia; grade 4 neutropenia; grade 4 anemia; grade 4 thrombocytopenia; or thrombocytopenic bleeding
- Pneumonitis > grade 2
- Delay in starting cycle 2 of ≥ 14 days due to toxicity of any grade related to one or more protocol drugs
- Dose intensity in cycles beyond cycle 1 will be considered in the assessment of the recommended phase II dose
- To be evaluable for a DLT, 75% of dose must have been administered in cycle 1 unless a DLT has occurred.

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

5.2.2 Dose Escalation Schema

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

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.

5.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of navitoclax and/or vistusertib with other concomitantly administered drugs, 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 for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

5.3.1 Navitoclax

Because there is a potential for interaction of navitoclax with other concomitantly administered drugs, 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 for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

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.

5.3.1.1 Cytochrome P450

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. 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).

Navitoclax is metabolized in the liver by CYP3A4. CYP3A4 inhibitors such as ketoconazole and clarithromycin are not allowed 7 days prior to the first dose of navitoclax or during navitoclax administration.

5.3.1.2 Thrombocytopenia

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. 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: 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 (≥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.

5.3.1.3 Disulfiram

Disulfiram is not allowed due to potential drug interactions

5.3.1.4 Protein binding

Narrow therapeutic index drugs with high protein binding (>99.8%) should be avoided.

5.3.2 Vistusertib (AZD 2014)

Because there is a potential for interaction of vistusertib with other concomitantly administered drugs, 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 for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

5.3.2.1 Cytochrome P450

Vistusertib is a substrate of P450 CYPs 3A4 and 3A5 and drug transporters Pgp (MDR1) and BCRP, *in vitro*. Concomitant treatment with strong or moderate inhibitors of these enzymes/transporters may increase exposure to vistusertib. Conversely, strong or moderate inducers of CYP3A may decrease the exposure to vistusertib. Strong or moderate inhibitors or inducers of CYP3A4/5, Pgp (MDR1) and BCRP are excluded.

- If a patient requires short-term administration of a restricted CYP3A4/5, Pgp or BCRP inhibitor vistusertib treatment must be withheld for three days prior to administration and not restarted until the concomitant therapy has been discontinued for the appropriate time period (at least 1 week for competitive inhibitors and 2 weeks for time-dependent inhibitors).
- If a patient requires short-term administration of a restricted CYP3A4/5, Pgp (MDR1) or BCRP isoenzyme inducer this should be clearly documented in the Case Report Form (CRF) and may then be permitted, but the Investigator will be informed that this could lead to lower levels of study drug and a potential reduction in clinical efficacy.

5.3.2.2 Substrates of Drug Transporters: OATP1B1, OATP1B3, MATE1 or MATE2K

If a patient requires short term administration of restricted substrates of OATP1B1, OATP1B3, MATE1 or MATE2K vistusertib treatment must be withheld for 3 days prior to the first administration and not restarted until the concomitant therapy has been discontinued for at least 3 half-lives.

5.3.2.3 QTc prolongation

Drugs which have an increased risk for QTc prolongation should be avoided; for a list of these drugs, please refer to http://crediblemeds.org/

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
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

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

5.5 Duration of Follow Up

Phase 1: Patients will be followed for 30 days to document related toxicities after removal from study or until death, whichever occurs first.

Phase 2: Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients who are taken off study for any reason other than disease progression or death will continue to reimaging studies approximately every 8 weeks until disease progression, start of new therapy or death. Patients will be followed in clinic or by telephone approximately every 12 weeks until death or 2 years from registration whichever comes first, for purposes of survival follow-up.

6. DOSING DELAYS/DOSE MODIFICATIONS

Best supportive care and treatment will be allowed for each subject (antiemetics, antibiotics, transfusions, nutritional support, pain control, *etc.*) with the exceptions noted in Section 5.4 (General Concomitant Medication and Supportive Care Guidelines) and in the subsections below. Colony stimulating factors (G-CSF, GM-CSF) or human erythropoietin will be considered during administration of navitoclax if deemed necessary by the investigator. If a patient must discontinue one agent due to toxicities, they are permitted to continue on the other agent on study. If one agent is discontinued, management of adverse events due to the remaining agent continue as outlined below.

6.1 Phase 1

6.1.1 Dose de-escalation of Navitoclax

Dose Level	Starting Dose (once a day)	Dose Reduction 1
-1	150 mg	None*
1	150 mg	None*
2	250 mg	150mg
3	325 mg	250mg
4	325 mg	250mg

6.1.2 Dose de-escalation of Vistusertib

Dose Level	Starting Dose (twice daily)	Dose Reduction 1
-1	25 mg	None*
1	35 mg	25 mg
2	35 mg	25 mg
3	35 mg	25 mg
4	50 mg	35 mg

*Alternate dose de-escalation schemes will be discussed with the CTEP sponsors and industry collaborators.

6.1.3 Management of Thrombocytopenia

6.1.3.1 Dose Reduction and Interruption

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

C1D1 dosing should be delayed for clinically significant bleeding.

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 manual reading and a separate peripheral draw.

Thrombocytopenia	Management for navitoclax	Management for vistusertib
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	No change in dose
Grade 3	Hold until < Grade 2. Resume at one dose level lower, if indicated.*	No change in dose
Grade 4	Off protocol therapy	Hold until < Grade 2. Resume at one dose level lower, if indicated.
*Patients requiring a delay of >2 weeks should go off protocol therapy.		

For any clinically significant bleeding event, defined as grade 2 or 3 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.

Patients with grade 4 bleeding events should be discontinued from the study.

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.

6.1.3.2 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.

6.1.4 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.

Neutropenia	Management for navitoclax	Management for vistusertib
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until < Grade 2. Resume at one dose level lower, if indicated.*	No change in dose
Grade 4	Hold until < Grade 3. Resume at one dose level lower.*	Hold until < Grade 2. Resume at one dose level lower, if indicated.*
*Patients requiring a delay of >2 weeks should go off protocol therapy.		

6.1.5 Management of Febrile Neutropenia

Standard management practices for febrile neutropenia should be followed.

Febrile Neutropenia	Management for navitoclax	Management for vistusertib
Grade 3	Hold until infection is resolved, antibiotics are no longer required and ANC < Grade 2. Resume at	Hold until infection is resolved, antibiotics are no longer required and ANC < Grade 2. Resume at

Febrile Neutropenia	Management for navitoclax	Management for vistusertib
	one dose level lower, if indicated.*	one dose level lower, if indicated.*
Grade 4	Hold until infection is resolved, antibiotics are no longer required and ANC < Grade 2. Resume at one dose level lower, if indicated.*	Hold until infection is resolved, antibiotics are no longer required and ANC < Grade 2. Resume at one dose level lower, if indicated.*
*Patients requiring a delay of >2 weeks should go off protocol therapy.		

6.1.6 Management of EKG Changes

Patients who develop persistent, confirmed T wave repolarization abnormalities (inversion or flattening) on regularly scheduled ECGs may be referred for a cardiology opinion and should have the following assessments performed:

- ECHO/MUGA as clinically indicated and end of study and/or safety follow-up visit if any abnormal LV function was diagnosed.
- ECG at safety follow-up visit
- Troponin measurement as clinically indicated and at end of study

6.1.7 Management of Liver Function Test Abnormalities

Evidence of abnormal liver function should be monitored as per the protocol guidelines. Increased levels of AST, ALT, or serum bilirubin should trigger an investigation of the cause which may include viral infection or disease progression with liver infiltration. The Investigator should consider whether the abnormal liver function meets the criteria for expedited reporting; see Section 13.2.

Adverse Event	Management for navitoclax	Management for vistusertib
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until G ≤ 2 and reduce 1 dose level if related to navitoclax. If there is a treatment delay >2 weeks, discontinue navitoclax.	Hold until G ≤ 2, then rechallenge at the same dose. If subject develops G3 liver function abnormalities again, hold until ≤ 2, reduce 1 dose level.
Grade 4	Hold until grade ≤ 2, reduce 1 dose level.	Hold until grade ≤ 2, reduce 1 dose level.
*Patients requiring a delay of >2 weeks should go off protocol therapy.		

6.1.8 Management of other adverse events

Adverse Event	Management for navitoclax	Management for vistusertib
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Reduce 1 dose level if related to navitoclax. If there is a treatment delay >2 weeks, discontinue navitoclax.	Reduce 1 dose level if related to vistusertib. If there is a treatment delay >2 weeks, discontinue vistusertib.
Grade 4	Hold until grade ≤ 2, reduce 1 dose level.	Hold until grade ≤ 2, reduce 1 dose level.
*Patients requiring a delay of >2 weeks should go off protocol therapy.		

6.2 Phase 2

6.2.1 Dose de-escalation of Navitoclax

There are no dose reductions of navitoclax in Phase 2. If navitoclax is discontinued, vistusertib may be continued.

6.2.2 Dose de-escalation of Vistusertib

Vistusertib may be dose reduced once. If further dose reduction is indicated, the subject will discontinue vistusertib. If vistusertib is discontinued, navitoclax may be continued.

Dose Level	Dose (twice daily)
1	35 mg
-1	25 mg

6.2.3 Management of Thrombocytopenia

6.2.3.1 Dose Reduction and Interruption

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

C1D1 dosing should be delayed for clinically significant bleeding.

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 manual reading and a separate peripheral draw.

Thrombocytopenia	Management for navitoclax	Management for vistusertib
≤ Grade 1	No change in dose.	No change in dose.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	No change in dose.
Grade 3	Discontinue navitoclax.	No change in dose
Grade 4	Discontinue navitoclax.	Hold until ≤ Grade 1. Resume at one dose level lower.

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

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.

6.2.3.2 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.

6.2.4 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.

Neutropenia	Management for navitoclax	Management for vistusertib
≤ Grade 1	No change in dose.	No change in dose.
Grade 2	No change in dose.	No change in dose.
Grade 3	Discontinue navitoclax.	No change in dose.
Grade 4	Discontinue navitoclax.	Hold until < Grade 2. Resume at one dose level lower.

6.2.5 Management of Febrile Neutropenia

Standard management practices for febrile neutropenia should be followed.

Febrile Neutropenia	Management for navitoclax	Management for vistusertib
Grade 3	Discontinue navitoclax.	Hold until infection is resolved, antibiotics are no longer required and ANC < Grade 2. Resume at one dose level lower.
Grade 4	Discontinue navitoclax.	Hold until infection is resolved, antibiotics are no longer required and ANC < Grade 2. Resume at one dose level lower.

6.2.6 Management of EKG Changes

Patients who develop persistent, confirmed T wave repolarization abnormalities (inversion or flattening) on regularly scheduled ECGs may be referred for a cardiology opinion and should have the following assessments performed:

- ECHO/MUGA as clinically indicated and end of study and/or safety follow-up visit if any abnormal LV function was diagnosed.
- ECG at safety follow-up visit
- Troponin measurement as clinically indicated and at end of study

6.2.7 Management of Liver Function Test Abnormalities

Evidence of abnormal liver function should be monitored as per the protocol guidelines. Increased levels of AST, ALT, or serum bilirubin should trigger an investigation of the cause which may include viral infection or disease progression with liver infiltration. The Investigator should consider whether the abnormal liver function meets the criteria for expedited reporting; see Section 13.2.

Adverse Event	Management for navitoclax	Management for vistusertib
≤ Grade 1	No change in dose.	No change in dose.
Grade 2	No change in dose.	No change in dose.
Grade 3	Discontinue navitoclax.	Hold until G ≤ 2, then rechallenge at the same dose. If subject develops G3 liver function abnormalities again, hold until ≤ 2, reduce 1 dose level.
Grade 4	Discontinue navitoclax.	Hold until grade ≤ 2, reduce 1 dose level.

6.2.8 Management of other adverse events

Adverse Event	Management for navitoclax	Management for vistusertib
≤ Grade 1	No change in dose.	No change in dose
Grade 2	No change in dose.	No change in dose
Grade 3	Discontinue navitoclax.	Reduce 1 dose level if related to vistusertib. If there is a treatment delay >2 weeks, discontinue vistusertib.
Grade 4	Discontinue navitoclax.	Hold until grade ≤ 2, reduce 1 dose level.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

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 648 patients. Below is the CAEPR for navitoclax (ABT-263).

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. 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 CAEPR for CTEP IND Agent

7.1.1.1 CAEPR for Navitoclax (ABT-263, NSC 750238)

Version 2.5, January 4, 2021[1]

Adverse Events with Possible Relationship to Navitoclax (ABT-263) (CTCAE 5.0 Term) [n= 648]			**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		

	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
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Constipation; Dyspepsia; Enterocolitis; Flatulence; Gastrointestinal disorders - Other (laryngeal hemorrhage); Gastrointestinal disorders - Other (pneumatosis coli); Mucositis oral; Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Disease progression; Edema limbs; Edema trunk; Fever; Flu like symptoms; Malaise; Pain
INFECTIONS AND INFESTATIONS - Infections[2]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Hemoglobin increased; Investigations - Other (elevated LFTs); Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Myalgia; 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.

7.1.2 Adverse Event List for Vistusertib (AZD2014, NSC 787289)

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 483 patients.* Below is the CAEPR for Vistusertib (AZD2014).

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 2.4, April 6, 2020[1]

Adverse Events with Possible Relationship to Vistusertib (AZD2014) (CTCAE 5.0 Term) [n= 483]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
GASTROINTESTINAL DISORDERS			
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
Nausea	Mucositis oral		***Mucositis oral (Gr 2)*** ***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
		Hypokalemia	
		Hypophosphatemia	

Adverse Events with Possible Relationship to Vistusertib (AZD2014) (CTCAE 5.0 Term) [n= 483]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Pruritus		
Rash maculo-papular			***Rash maculo-papular (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.

Adverse events reported on vistusertib (AZD2014) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that vistusertib (AZD2014) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
GASTROINTESTINAL DISORDERS - Abdominal pain; Dry mouth; Gastroesophageal reflux disease; Oral pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever; Malaise
INFECTIONS AND INFESTATIONS - Bronchial infection; Fungemia; Infections and infestations - Other (lower respiratory tract infection); Shingles
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion related reaction
INVESTIGATIONS - Blood lactate dehydrogenase increased; Cholesterol high; Creatinine increased; Investigations - Other (liver enzymes increased); Lymphocyte count decreased; Platelet count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (progressive disease)

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Lethargy; Seizure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Photosensitivity
VASCULAR DISORDERS - Thromboembolic event

Note: Vistusertib (AZD2014) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for SAE reporting only. This study will continue to utilize CTCAE version 4.0 for routine toxicity reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 and 5.0. A copy of the CTCAE version 4.0 and 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 (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

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

original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

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

7.3.3 Expedited Reporting Guidelines

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

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

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

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.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** of the following outcomes:
1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of

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

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

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

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

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

- All Grade 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

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported**

expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.

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

7.5 Secondary Malignancy

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

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

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

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

7.6 Second Malignancy

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

8. PHARMACEUTICAL INFORMATION

8.1 CTEP IND Agents

8.1.1 Navitoclax (ABT-263; NSC 750238)

Chemical Name: 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 the DCTD/NCI distributes navitoclax as 25 mg and 100 mg film coated tablets packaged in 28-Count and 30-Count high-density polyethylene (HDPE) bottles, respectively.

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.

Navitoclax inactive ingredients: 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).

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 to between 15-25°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability

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

Route of Administration: Oral.

Method of Administration: Take navitoclax tablets with food.

Potential Drug Interactions: Navitoclax metabolizes via CYP3A4. It is a moderate inhibitor of CYP2C8 and a strong inhibitor of CYP2C9. Use caution when navitoclax is administered with drugs of CYP3A4 inhibitors/inducers, CYP2C8 and CYP2C9 substrates. Concomitant use of strong CYP3A4, CYP2C8, CYP2C9 substrates/inhibitors/inducers or drugs with narrow therapeutic window (e.g., warfarin) should be avoided. Use alternative medications if possible.

Patient Care Implications: For trials using single agent navitoclax, female patients of childbearing potential must agree to use highly effective methods of contraception throughout the study and for 30 days after the last dose of study treatment. For clinical studies with navitoclax in combination, use of contraception may be longer and male subjects may need to use contraceptive methods.

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

Availability: Navitoclax is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Navitoclax is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Vistusertib (NSC 787289)

Other Names: AZD2014

Classification: mTOR kinase inhibitor

Approximate Solubility: Vistusertib has solubility of >14.8 mg/mL in Simulated Gastric Fluid (pH 1.7) and 0.018 mg/mL in Sorensen's phosphate buffer (pH 6.8). The pKa of vistusertib is 6. The melting point of vistusertib is approximately 239°C.

Mode of Action: Vistusertib is an inhibitor of the kinase activity of mammalian Target of Rapamycin (mTOR) serine threonine kinase, which plays a critical role in regulating cellular energy sensing, growth and metabolism.

Description: Crystalline powder.

How Supplied: Vistusertib is supplied by AstraZeneca and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as film-coated tablets available in 10 mg (plain, round, biconvex, yellow), 25 mg (plain, round, biconvex, yellow), and 50 mg (plain, round biconvex, or oval, yellow) strengths. Tablets contain vistusertib,

mannitol, microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate. The tablet film coat comprises polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc and yellow iron oxide. Each high density polypropylene (HDPE) bottle contains 40 tablets.

Storage: Store at room temperature below 30°C (86°F). If a storage temperature excursion is identified, promptly return vistusertib to room temperature below 30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability

Stability: Based on the planned expiration extension, clinical supply of Vistusertib (AZD2014) will expire on August 31, 2021. Supplies can be used until the terminal lot shelf life dating of August 31, 2021 is reached or the NCI inventory is exhausted.

Route of Administration: Oral administration. Vistusertib can be given with or without food.

Potential Drug Interactions: Vistusertib is metabolized by CYP3A/5 and is substrate for Pgp (MDR1) and BCRP transporters. Vistusertib is a weak inhibitor of CYPs 2C8, 2C9, 2C19, 2D6, and transporters OATP1B1, OATP1B3, MATE1, and MATE2K in vitro. "Co-medications which are moderate or strong inhibitors or inducers of CYP3A4/5, Pgp (MDR1) and BCRP, or sensitive substrates of CYPs 2C8, 2C9, 2C19, 2D6, or the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K, should be avoided."

8.2 Agent Ordering, Accountability and Investigator Brochure Availability

8.2.1 NCI-supplied agents may be requested by the responsible investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP

Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

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

8.2.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.2.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- Registration and Credential Repository (RCR): https://ctepcore.nci.nih.gov/rcr/
- RCR Help Desk: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Overview

Mandatory research bloods will be obtained in the phase 1 and phase 2 portions of this study for integrated correlative studies including navitoclax and vistusertib pharmacokinetic profiles. Mandatory tumor biopsies will be obtained in the Phase 2 portion of this study for integrated correlative biomarker studies.

9.1.1 Blood Samples

During both Phase 1 and Phase 2, mandatory PK blood samples will be obtained at the time points as outlined above and on the Study Calendar. In the event that a subject cannot have all blood samples or volume needed at a single visit, the samples and/or remaining samples should be collected at the next possible visit.

Optional blood samples will be obtained pretreatment, on treatment and at progression for exploratory studies.

9.1.2 Tissue Samples

In Phase 2, mandatory tumor biopsies will be obtained pretreatment and on treatment as outlined in the study calendar. Optional biopsies will be requested at progression and for patients on the Phase 1 portion of the study. In the event that a subject cannot undergo a second biopsy for any reason, including refusal, or the baseline biopsy was unsuccessful or inevaluable, the subject can continue to be treated per study protocol.

Subjects will undergo a direct or image-guided research biopsy procedure. FNA and on-site cytopathologic evaluation, where appropriate, will be done for sample/site adequacy followed by core biopsies for collection of tissue for the research correlates outlined. The biopsy site will be clearly documented in the records; baseline and each follow-up biopsy will preferentially be done in the same organ site. Approximately 4-6 core biopsy specimens will be obtained with each biopsy as outlined; the cytopathology slide will also be retained and submitted, if performed. If a subject discontinues the study prior to a planned follow-up biopsy, an attempt should be made to collect the next scheduled biopsy when the decision is made to discontinue and prior to initiation of additional treatment, if possible.

The study staff will be notified when a biopsy is taking place. If core biopsy is not possible, other methods may be approved in advance by the Protocol Chair/designee.

9.1.3 Handling and Shipping of Tissue Specimens

A unique subject identifier will be assigned to each subject by the coordinating center and will be used to label the samples. The protocol scientific investigator(s) analyzing the samples will be blinded as to the direct subject identifiers.

A **PK Sheet** will be provided for specific handling and processing instructions; this document is available on the CTSU website under the Case Report Forms tab.

Sites should contact the laboratory before shipping specimens to ensure the laboratory is open and receiving specimens.

Research bloods and biopsies will be sent to Johns Hopkins to the laboratories of Drs. [redacted] and [redacted] as described in the PK Sheet. After shipping, samples, and associated data, will be stored at Johns Hopkins unless the subject withdraws consent.

9.2 Integrated Correlative Studies

9.2.1 Navitoclax Pharmacokinetic Profile

Background: This assay will be utilized to determine navitoclax concentrations and ultimately the drug exposure. There is a potential for a drug-drug interaction between CYP2C8 with navitoclax as a moderate inhibitor and vistusertib as a substrate. Since navitoclax will need to be given for 1 week prior to the combination to attenuate thrombocytopenia, a formal drug-drug interaction trial design will not be performed. Navitoclax concentrations will be used to correlate with any thrombocytopenia. We will incorporate the expansion to a full pharmacokinetic profile for navitoclax if toxicities are frequent and severe with the combination.

Method: Navitoclax blood levels will be measured by LC-MS/MS. The bioanalytical method for determining navitoclax in human plasma has been developed and validated utilizing liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) techniques. The analytical method was be validated as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (58). Navitoclax was extracted from plasma using acetonitrile precipitation. Chromatographic separation was achieved with a ACQUITY UPLC® BEH C_{18} column (1.7 µm 2.1 x 50 mm) and isocratic elution with an acetonitrile-water-formic acid mobile phase over a 3 min total analytical run time. An AB Sciex 4500 triple quadrupole mass spectrometer operated in positive electrospray ionization mode was used for the detection of navitoclax. The assay range was 5-5,000 ng/mL and proved to be accurate (89.5-104.9%) and precise (CV ≤ 11.0%). Long-term frozen plasma stability for navitoclax at -70°C has been determined for at least 211 d and is on-going.

Analysis: For navitoclax, individual PK parameters will be estimated for C_{max}, AUC, $T_{1/2}$, apparent Cl/F and apparent V/F using non-compartmental or compartmental PK methods with the software WinNonlin. Advanced population PK methods may be employed to assess the link between drug exposure and biological effects and efficacy. Steady-state trough concentrations will also be calculated. The PK parameters will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. The PK parameters (i.e., T1/2, C) will be compared across dose level using nonparametic statistical testing techniques. Exploratory correlative studies with

pharmacodynamic (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics. Significance for comparisons will be at the $p<0.05$ level. All p values for secondary endpoints will be two-sided.

9.2.1.1 Collection of Specimens

Blood samples (~6 mL) will be taken into heparin tubes at designated time points, and immediately placed on ice.

- Phase 1 portion: Blood samples will be taken at the following time points: Day -7 pretreatment, C1D1 pretreatment, C1D1 6 hours post-dose, C1D8 pretreatment, C1D15 pretreatment and 1, 2, 3, 4, 6 and 8 hours post-dose, C1D16 pre-treatment and C2D1 pretreatment.
- Phase 1 portion (expanded): If there are multiple DLTs (tolerability issues) an additional 7 samples will be collected at the following time points: on D-7 at 1, 2, 3, 4, 6 and 8 hours after administration, and D-6 pre-treatment (~24 hr after D-7 administration). This is in addition to the 12 samples listed above for the standard Phase 1 portion.
- Phase 2 portion: Blood samples will be taken at the following time points: Day -7 pretreatment, C1D1 pretreatment, C1D8 pretreatment, C1D15 pretreatment and C2D1 pretreatment.

If a participant misses a dose of navitoclax or vistusertib during Cycle 1 prior to Cycle 1 Days 15/16 and will continue on treatment, Dr. [redacted] should be contacted to determine the optimal timing of the PK collection, which may no longer occur on Cycle 1 Days 15/16. Since navitoclax and vistusertib are to be administered continuously, the adjustment may occur in the date of the collection but not the 8 samples to be obtained. The exact timing will depend on the duration of interruption and proximity to Cycle 1 Days 15/16. In some circumstances, the PK collection may be waived due to difficulties in re-scheduling the PK.

9.2.1.2 Handling of Specimens

At each time point, ~6 mL of peripheral blood will be collected in a green-top heparin vacutainer (Becton Dickinson Catalog # 367878, Franklin Lakes, NJ).

1. Obtain venous blood by standard phlebotomy technique from a peripheral access point. NOTE: Suggest using a minimum 18G needle to avoid sample hemolysis.
2. Fill-up the tubes as much as possible until blood flow stops.
3. GENTLY invert each tube several times (8-10 times) immediately after collection to avoid sample hemolysis.
4. Place samples immediately **on ice** after collection; samples must be processed **within 30 minutes**.

Processing instructions:

1. Invert sample 8-10 times immediately before processing.
2. Centrifuge at 2500-3000 rpm for 10 minutes in swinging bucket (SW) or 15 minutes in a fixed angel (FA) rotor at 4ºC in a refrigerated centrifuge. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.

3. Carefully remove tube from centrifuge.
4. Using a pipette, transfer equal aliquots of plasma into 2-3 labeled 2 mL cryovials, not exceeding ~1 mL per cryovial.
5. Label samples as navitoclax PK, including study number (NCI10070), unique patient ID (assigned by the consortium), initials, date of collection, draw time, and time point.
6. Store plasma samples at -70ºC or below until shipment or transfer to Johns Hopkins.

9.2.1.3 Shipping of Specimens

Specimens should be stored through the duration of navitoclax correlative studies (through C2D1) and shipped as a batch by participant (more than one participant/shipment is acceptable if the site has >1 participant on-study). A participant's samples should be shipped to the APC lab within 6 months of the first sample's collection date. (i.e., if D-7 sample is collected on 1/1/2017, all of that participant's samples should be at the APC lab by 7/1/2017). The APC lab may contact the study team to request shipment off-schedule. The navitoclax and vistusertib pharmacokinetic specimens can be shipped in the same shipment.

Please ship 1-2 aliquots to the APC laboratory. Once receipt is confirmed, the back-up aliquot may be shipped. The back-up can be shipped later

Preparing the shipment

- Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH).
- Please organize the samples by Patient and Time point in the box.
- Do not store in plastic bags (they break on dry-ice and labels will detach).
- A copy of each of the pharmacokinetic sample collection forms for the respective patients or a sample list should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them (in addition to sample label) and numbering samples on the sample sheet.
- Note the study number, PI, and the drugs used/to be measured.
- A name, phone number and email address should be included with samples so that receipt can be acknowledged.
- Please notify the lab by telephone (410-502-7192 or 410-955-1129) or fax (410-502-0895) at least 24 hours prior to shipment.

Shipping

- All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state.
- Overnight shipments should occur on Monday through Wednesday (Tuesday is the preferred day) except when the following day is a holiday.

Analytical Pharmacology Core Laboratory*
Attn: NCI10070 Navitoclax/Vistusertib Study Samples
1650 Orleans St. CRB1 Rm 184

Baltimore, MD 21231-1000
Phone: 410-502-7192 or 410-955-1129
Fax: 410-502-0895

9.2.1.4 Sites Performing Correlative Study

ETCTN Central Laboratory: Dr. [redacted], The Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC)

9.2.2 Vistusertib Pharmacokinetic Profile

Background: This assay will be utilized to determine vistusertib concentrations and ultimately the drug exposure. Since navitoclax will need to be given for 1 week prior to the combination to attenuate thrombocytopenia, a formal drug-drug interaction trial design will not be performed. Vistusertib trough concentrations will be assessed over the course of the first cycle to compare to historical controls and correlate with toxicity, efficacy and pharmacodynamics correlatives.

Method: Vistusertib blood levels will be measured by LC-MS/MS. The bioanalytical method for determining vistusertib in human plasma has been developed and validated utilizing liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) techniques. The analytical method was validated as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (58). Vistusertib was extracted from plasma using acetonitrile precipitation. Chromatographic separation was achieved with an ACQUITY UPLC® BEH C_{18} column (1.7 µm 2.1 x 50 mm) and isocratic elution with an acetonitrile-water-formic acid mobile phase over a 3 min total analytical run time. An AB Sciex 4500 triple quadrupole mass spectrometer operated in positive electrospray ionization mode was used for the detection of vistusertib. The assay range was 5-5,000 ng/mL and proved to be accurate (98.7-105.7%) and precise (CV ≤ 10.5%). Long-term frozen plasma stability for vistusertib at -70°C is on-going.

Analysis: Trough concentrations for vistusertib will be obtained to correlate with pharmacodynamics outcomes; a full profile will be employed if there are multiple DLTs (tolerability issues). Steady-state trough concentrations will be calculated. Steady-state trough concentrations will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. Steady-state trough concentrations will be compared across dose level using nonparametric statistical testing techniques. Exploratory correlative studies with pharmacodynamic (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics. Significance for comparisons will be at the $p<0.05$ level.

9.2.2.1 Collection of Specimen(s)

Blood samples (~6 mL) will be taken into heparin tubes at designated time points, and immediately placed on ice.

- Phase 1 portion**:** Blood samples will be taken at the following time points: C1D1 pretreatment, C1D1 2 hours post-treatment, C1D8 pre-treatment, C1D15 pretreatment, C1D15 2 hours post-treatment and C2D1 pretreatment.
- Phase 1 portion (expanded): If there are multiple DLTs (tolerability issues) an additional 8 samples will be collected at the following time points: on C1D15 at 0.5, 1, 1.5, 2, 4, 6 and 8 hours after administration, and C1D16 pre-treatment (~24hr after C1D15 administration). This is in addition to the 4 samples listed above for the standard Phase 1 portion.
- Phase 2 portion**:** Blood samples will be taken at the following time points: C1D1 pretreatment, C1D8 pretreatment, C1D15 pretreatment and C2D1 pretreatment.

9.2.2.2 Handling of Specimens(s)

At each time point, ~6 mL of peripheral blood will be collected in a green-top heparin vacutainer (Becton Dickinson Catalog # 367878, Franklin Lakes, NJ).

1. Obtain venous blood by standard phlebotomy technique from a peripheral access point. NOTE: Suggest using a minimum 18G needle to avoid sample hemolysis.
2. Fill-up the tubes as much as possible until blood flow stops.
3. GENTLY invert each tube several times (8-10 times) immediately after collection to avoid sample hemolysis.
4. Place samples immediately **on ice** after collection; samples must be processed **within 30 minutes**.

Processing instructions:

1. Invert sample 8-10 times immediately before processing.
2. Centrifuge at 2500-3000 rpm for 10 minutes in swinging bucket (SW) or 15 minutes in a fixed angel (FA) rotor at 4ºC in a refrigerated centrifuge. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.
3. Carefully remove tube from centrifuge.
4. Using a pipette, transfer equal aliquots of plasma into 2-3 labeled 2 mL cryovials, not exceeding ~1 mL per cryovial.
5. Label samples as vistusertib PK, including study number (NCI10070), unique patient ID (assigned by the consortium), initials, date of collection, draw time, and time point.
6. Store plasma samples at -70ºC or below until shipment or transfer to Johns Hopkins.

9.2.2.3 Shipping of Specimens

Specimens should be stored through the duration of navitoclax correlative studies (through C2D1) and shipped as a batch by participant (more than one participant/shipment is acceptable if the site has >1 participant on-study). Details on shipments to the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC) can be found in Section 9.3.1.3.

9.2.2.4 Site Performing Correlative Study

ETCTN Central Laboratory: Dr. [redacted], The Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC)

9.2.3 Pharmacodynamic Studies: Reverse Phase Protein Array (RPPA)

Background: RPPA is a quantitative assay that analyzes nanoliter amounts of sample for potentially hundreds of proteins. This antibody-based assay determines levels of protein expression, as well as protein modifications such as phosphorylation, cleavage, and fatty acid modification and allows concordant interrogation of multiple signaling molecules and their functional status. Major strengths include identification and validation of cellular targets, characterization of signaling pathways and networks, as well as determination of on and off target activity of novel drugs. Samples are analyzed for proteins involved in cell cycle progression, apoptosis, functional proteomics, and signaling networks. The integrated information will display the potential biomarkers to predict intracellular signaling networks and functional outcomes affected by therapeutics. RPPA has been used to profile and validate signaling networks in human cancer cell lines and tumor tissue.

Methods**:** Paired pre-treatment and on treatment core biopsies will be obtained from patients on the phase 2 portion of the trial in order to provide the opportunity to correlate pharmacodynamic effects with tumor response and pharmacokinetic parameters at the RP2D. Pre-treatment biopsies will be obtained during screening and on-treatment biopsies will be obtained on Cycle 1 Day 15 (+/-7days).

Protein extracted from snap frozen tissue will be adjusted to a concentration of 1ug/ul, denatured by SDS. The lysates will be serial diluted to define the linear range of each antigen-antibody reaction and will be printed on nitrocellulose-coated slides and probed with validated antibodies (antibody list attached). A Tecan robotic liquid handling system is utilized for serial dilution of cell lysates and sample transfer; a G3 GeneTac arrayer and an Aushon 2470 arrayer for printing of up to 24 (G3) or 100 slides (2470) per run. A Biogenix i600TM and two DAKO Universal Staining systems are used to probe each slide with a different antibody. Each autostainer is capable of staining approximately 60 slides per day under conditions that are specific for each individual antibody. Signals are captured by tyramide dye deposition (CSA System, DAKO).

9.2.3.1 Collection and Handling of Specimens

The time points of collection are provided in the study calendar (Section 10).

Below is a guideline for a recommended procedure.

1. Obtain 3 biopsy cores preferably 16g or 14g needle, 18g minimum – the larger the bore

the better within reason.
2. Samples should be labeled with the NCI protocol number (NCI10070), unique patient ID (assigned by the consortium), "RPPA", initials, date of collection, draw time, and time point.
3. Snap freeze in liquid nitrogen and store at -80 degrees Celsius until shipping.

9.2.3.2 Shipping of Specimen(s)

Biopsy specimens for RPPA should be sent on dry ice to:

[redacted]
Johns Hopkins SKCCC
1550 Orleans Street, CRB2, [redacted]
Baltimore, MD 21287
Tel: [redacted]
Fax: [redacted]

Samples will be sent to Dr. [redacted] lab in batches every 3-6 months

9.2.3.3 Sites Performing Correlative Study

The [redacted] Lab at MD Anderson Cancer Center, Houston, TX

9.3 Exploratory/Ancillary Correlative Studies

When available, archival tissue and fresh biopsies (pretreatment, on-treatment and on progression) and plasma will be studied to identify biomarkers associated with drug activity.

9.3.1 Optional blood and tissue collection for correlative genomic studies

The following samples will be optional for subjects on study:

- Archival tumor tissue: FFPE block (preferred) or 25 x 5 micron slides, cut under DNA/RNA precautions mounted on plus slides. Please do not prebake the slides.
- Fresh tissue biopsy: FFPE or flash frozen samples collected at the time points listed in the Study Calendar (Section 10). Please collect snap frozen samples as described in the laboratory manual
- Peripheral blood: 2 x 10ml collected in **Streck** tubes at time points listed in the Study Calendar (Section 10). Streck tubes can be provided by JHH.

9.3.1.1 Collection and Handling of Optional Blood and Tissue Specimens

A **Laboratory Manual** will be provided for specific handling and processing instructions; this document will be disseminated with the clinical protocol.

Optional peripheral blood handling:
1. At each time point, 2 x 10 mL of peripheral blood will be collected in Streck tube

2. Obtain venous blood by standard phlebotomy technique from a peripheral access point. Suggest using a minimum 21G needle.
3. Fill-up the tubes as much as possible until blood flow stops.
4. GENTLY invert each tube 8-10 times immediately after collection
5. Samples should be labeled with the NCI protocol number (NCI10070), unique patient ID (assigned by the consortium), "Peripheral Blood", initials, date of collection, draw time, and time point.
6. STORE tubes at ambient temperature
7. SHIP at ambient temperature within 3 days of blood collection

9.3.1.2 Shipping of Specimen(s)

Optional Tissue and Blood Specimens should be sent to:

[redacted]
Johns Hopkins SKCCC
1550 Orleans Street, CRB2, [redacted]
Baltimore, MD 21287
Tel: [redacted]
Fax: [redacted]

10. STUDY CALENDAR

Baseline assessments are to be conducted within 4 weeks prior to start of protocol therapy. Unless otherwise indicated, Day 1 assessments may be performed up to 3 days before the scheduled visit. The schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.) with the guidance of the Protocol Chair/designee, as appropriate, and will not be reportable as a deviation unless the endpoints of the study are affected.

The results of Day 1 labs of any cycle need to be reviewed before initiating treatment for that cycle. One cycle is 28 days.

Phase 1 Calendar:

	Base-line	Run-In D(-7)→	C1D1	C1D8	C1 D15	C1 D16	C2D1	C2 D15	C3D1, etc	C3 D15, etc	Off Study
CLINICAL ASSESSMENTS											
Informed consent	X										
Demographics	X										
Medical history	X										
Physical exam	X	X	X	X	X		X	X	X		X
Vital signs, Height (baseline), Weight, O_2 Sat	X	X	X	X	X		X	X	X		X
Performance status	X	X	X	X	X		X	X	X		X
CBC w/diff, platelets	X	X[m]	X	X	X		X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X		X	X	X		X
PT/PTT	X	X	X	X	X		X	X	X		
EKG	X[p]	X	X[o]		X[o]		X		X		
Echocardiogram[b]	X										
Urinalysis	X										
Pregnancy Test[c]	X										
Tumor Assessment /Imaging[d]	X								X		
TREATMENT											
Navitoclax, lead-in dose[e]		X --- X									

	Base-line	Run-In D(-7)→	C1D1	C1D8	C1 D15	C1 D16	C2D1	C2 D15	C3D1, etc	C3 D15, etc	Off Study
Navitoclax, final dose[f]			X ---------- X								
Vistusertib[g]			X ---------- X								
CORRELATIVE STUDIES											
Pharmacokinetics (Phase 1)[h, j]		X	X	X	X	X	X				
Archival Tumor	X										
Fresh Tumor Biopsy[k] (Phase 2, optional for Phase 1)	X				X						X
Plasma for Biomarkers (Optional)	X				X				X[n]		X
OTHER ASSESSMENTS											
Concurrent meds	X	X	X	X	X		X	X	X		X
Symptom/Toxicity Assessment[l]	X	X	X ---------- X								

a: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, LDH, magnesium, phosphate, amylase, and lipase.

b: As described in section 6.6, additional echocardiograms may be performed in the event of abnormal ECGs or if otherwise indicated.

c: For WOCBP (women of childbearing potential) only: A urine pregnancy test is required ≤7 days prior to the first dose of navitoclax

d: CT scan of the chest and other relevant sites will be performed ≤ 4 weeks prior to the start of therapy. For SCLC or other tumor types where brain metastases are common, MRI brain with gadolinium (or CT scan brain with contrast if MRI is contraindicated) should also be performed at Baseline. MRI window is between 2 weeks and start of D-7 Navitoclax lead-in dose.

e: Subjects will receive lead-in dosing of navitoclax at 150mg daily for 7 days prior to C1D1. At any time after 7 days of navitoclax, if the platelet count is >50,000 and stable or increasing, the subject can dose escalate to the navitoclax dose defined in the cohort level and start vistusertib.

f: Dose as assigned; daily by mouth.

g: Dose as assigned, BID by mouth, unless alternative dosing schedule has been used

h: On all PK days specimens will be collected prior to dosing. In addition on C1D1 PK specimens will be drawn at 2 hours after dosing for vistusertib and at 6 hours after dosing for navitoclax. On C1D15, PK specimens will be drawn at 1, 2, 3, 4, 6, and 8 hours after dosing. If there are multiple DLTs (tolerability issues), additional samples will be collected on Day -7 at 1, 2, 3, 4, 6 and 8 hours after dosing, Day -6 pre-dose, C1D15 at 0.5 and 1.5 hours post-dose as described in sections 9.2.1.1 and 9.2.2.1.

i: On all PK days specimens will be collected prior to dosing. If dose is missed during C1D1, Dr. [redacted] should be contacted to determine optimal timing collection.

j: 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.

k: Mandatory fresh tissue will be collected during Phase 2 for integrated biomarker studies at baseline and C1D15. A biopsy at time of progression is optional. Phase 1 participants may opt to provide fresh tissue at any of these time points. We recommend that participating sites follow their institutional guidelines regarding threshold platelet counts required for biopsy and minimal duration between last platelet count and on-study biopsy. General guidelines followed at Hopkins include: a threshold platelet count of 50,000 -70,000 for core biopsy and a maximum of 2 days between last platelet check and biopsy.

	Base-line	Run-In D(-7)→	C1D1	C1D8	C1 D15	C1 D16	C2D1	C2 D15	C3D1, etc	C3 D15, etc	Off Study
l: Adverse event evaluation as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 m: During the run-in period additional platelet counts may be performed at the discretion of the treating investigator or as clinically indicated. n: Plasma for Biomarkers will be collected whenever Disease Assessment imaging is performed. o: EKG to be done prior to dosing and at 2 hours and 6 hours after dosing of navitoclax and vistusertib p: 3 EKGs must be obtained if abnormal QT interval is present during baseline/screening.											

Phase 2 Calendar:

	Base-line	Run-In D(-7)→	C1D1	C1D8	C1 D15	C1 D16	C2D1	C3D1, etc	Off Treatment[q]	Follow Up[r]
Informed consent	X									
Demographics	X									
Medical history	X									
Physical exam	X	X	X	X	X		X	X	X	
Vital signs, Height (baseline), Weight, O_2 Sat	X	X	X	X	X		X	X	X	
Performance status	X	X	X	X	X		X	X	X	
CBC w/diff, platelets	X	X[m]	X	X	X		X	X	X	
Serum chemistry[a]	X	X	X	X	X		X	X	X	
PT/PTT	X	X	X	X	X		X	X		
EKG	X[p]	X	X[o]		X[o]		X	X		
Echocardiogram[b]	X									
Urinalysis	X									
Pregnancy Test[c]	X									
Tumor Assessment/ Imaging[d]	X							X		X
TREATMENT										
Navitoclax, lead-in dose[e]		X --- X								
Navitoclax[f]			X ---------- X							
Vistusertib[g]			X ---------- X							
Pharmacokinetics[i, j]		X	X	X	X		X			
Archival Tumor	X									
Fresh Tumor Biopsy[k]	X				X				X	
Plasma for Biomarkers (Optional)	X				X			X[n]	X	
OTHER ASSESSMENTS										
Concurrent meds	X	X	X	X	X		X	X	X	
Symptom/Toxicity Assessment[l]	X	X	X	X	X		X	X	X	
Survival status										X

a: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, LDH, magnesium, phosphate, amylase and lipase.

	Base-line	Run-In D(-7)→	C1D1	C1D8	C1 D15	C1 D16	C2D1	C3D1, etc	Off Treatment[q]	Follow Up[r]

b: As described in section 6.6, additional echocardiograms may be performed in the event of abnormal ECGs or if otherwise indicated.

c: For WOCBP (women of childbearing potential) only: A urine pregnancy test is required ≤7 days prior to the first dose of navitoclax.

d: CT scan of the chest and other relevant sites will be performed ≤ 4 weeks prior to the start of therapy. For SCLC or other tumor types where brain metastases are common, MRI brain with gadolinium (or CT scan brain with contrast if MRI is contraindicated) should also be performed at Baseline. MRI window is between 2 weeks and start of D-7 Navitoclax lead-in dose.

e: Subjects will receive lead-in dosing of navitoclax at 150mg daily for 7 days prior to C1D1. At any time after 7 days of navitoclax, if the platelet count is >50,000 and stable or increasing, the subject can start Phase 2 dosing of navitoclax and vistusertib.

f: Dose as assigned; daily by mouth.

g: Dose as assigned, BID by mouth, unless alternative dosing schedule has been used.

h: On all PK days specimens will be collected prior to dosing. In addition on C1D1 PK specimens will be drawn at 2 hours after dosing for vistusertib and at 6 hours after dosing for navitoclax. On C1D15, PK specimens will be drawn at 1, 2, 3, 4, 6, and 8 hours after dosing. If there are multiple DLTs (tolerability issues), additional samples will be collected on Day -7 at 1, 2, 3, 4, 6 and 8 hours after dosing, Day -6 pre-dose, C1D15 at 0.5 and 1.5 hours post-dose as described in sections 9.2.1.1 and 9.2.2.1.

i: On all PK days specimens will be collected prior to dosing. If dose is missed during C1D1, Dr. [redacted] should be contacted to determine optimal timing collection.

j: 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.

k: Mandatory fresh tissue will be collected during Phase 2 for integrated biomarker studies at baseline and C1D15. A biopsy at time of progression is optional. Phase 1 participants may opt to provide fresh tissue at any of these time points. We recommend that participating sites follow their institutional guidelines regarding threshold platelet counts required for biopsy and minimal duration between last platelet count and on-study biopsy. General guidelines followed at Hopkins include: a threshold platelet count of 50,000 -70,000 for core biopsy and a maximum of 2 days between last platelet check and biopsy.

l: Adverse event evaluation as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

m: During the run-in period additional platelet counts may be performed at the discretion of the treating investigator or as clinically indicated.

n: Plasma for Biomarkers will be collected whenever Disease Assessment imaging is performed.

o: EKG to be done prior to dosing and at 2 hours and 6 hours after dosing of navitoclax and vistusertib

p: Triplicate EKG must be obtained for eligibility.

q: Off treatment assessments will be conducted 30 days (+ 14 days) after the last dose of either study drug.

r: For patients taken off study for reasons other than disease progression, will continue imaging studies every 8 weeks until disease progression, start of a new therapy, or 2 years from registration. Survival status will be collected every 12 weeks by clinic or by telephone until 2 years from registration.

11. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated every 8 weeks. In addition to a baseline scan, confirmatory scans will also be obtained 8 (not less than 4) weeks following initial documentation of an 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) (59). 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 vistusertib.

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 (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
Tumor lesions that are situated in a previously irradiated area may only be considered measurable if they are growing on pre-treatment imaging.

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

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published (60-62). In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer (63)

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

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

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

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

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

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

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

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

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

11.1.5 Duration of Response

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

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

11.1.6 Progression-Free Survival (PFS)

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

There is no independent or central review of the radiology assessments planned for this trial. It is the responsibility of each Principal Investigator to ensure that tumor assessments are reported per the RECIST 1.1 criteria outlined above. The Protocol Chair (or her designee) may choose to review select cases.

12. STUDY OVERSIGHT AND 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 Study Oversight

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

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

For a Phase 1/2 trial, enrollment to the Phase 2 portion of the trial will not begin until a protocol amendment has been submitted which summarizes the Phase 1 results, the recommended Phase 2 dose, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the Phase 2 portion can begin.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

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

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

12.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system

and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

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

12.2.1 Method

*For studies assigned for **CTMS Comprehensive** Monitoring:*
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits).

For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

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

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

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

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

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

Further information on data submission procedures can be found in the ETCTN Program

Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.2.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality

12.3 CTEP Multicenter Guidelines

N/A

12.4 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

This is a phase 1/2 study of the combination of navitoclax plus vistusertib for patients with recurrent SCLC and other solid tumors. The primary endpoint of the phase 1 portion is to study the safety and tolerability of the combination in patients with advanced solid tumors. The primary endpoint of the phase 2 portion is to assess the response rate of the combination in patients with recurrent SCLC.

13.1.1 Phase 1: Dose Escalation

The primary endpoint for the dose escalation portion of this trial will be toxicity as graded by CTCAE v.4.0. All patients who start treatment will be included in the summaries of toxicity.

The Phase 1 portion will follow a dose-escalation schema with standard 3+3 design. At least 3 patients must be treated for 4 weeks without the development of a DLT prior to treating a new cohort at a higher dose level. The occurrence of 1 dose-limiting toxicity (DLT) will prompt expansion of a given dose level to 6 subjects. The occurrence of 2 DLTs will mean that the maximal tolerated dose has been exceeded, and expansion of the prior dose level to 6 subjects will occur, if not already performed. Dose escalation will proceed until the MTD is determined, or until the recommended phase 2 dose (RP2D) of each compound individually is reached.

The dose of drugs used for the Phase 2 portion of the trial will be the highest dose level at which no more than 1 subject out of 6 experiences a DLT.

During the Phase 1 portion of the study, 14 subjects were enrolled. Five subjects were deemed not evaluable – 4 did not complete the DLT period and 1 did not comply with the expected study dosing. No DLTs were observed in the first 3 subjects enrolled to Dose Level 1. Two of the three subjects experienced grade 3 elevated ALT/AST at Dose Level 2. Three additional subjects were enrolled to Dose Level 1. No DLTs were observed in these subjects. Based on this information, we determined the RP2D dose to be Dose Level 1: navitoclax 150 mg by mouth once a day plus vistusertib 35 mg by mouth twice a day.

13.1.2 Phase 2

The primary endpoint for the phase 2 portion of this trial will be objective response rate (ORR), defined as the proportion of eligible subjects who have a complete response (CR) or partial response (PR) using RECIST 1.1 criteria. A Simon's optimal two-stage design (57) will be used. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. The alternative hypothesis in this Simon two-stage design is 20%. In the first stage, 12 patients will be accrued. If there are 0 responses in these 12 patients, the study will be stopped. Otherwise, 25 additional patients will be accrued for a

total of 37. The null hypothesis will be rejected if 4 or more responses are observed in 37 patients. This design yields a type I error rate of 10% and power of 90% when the true response rate is 20%. A trial with this Simon optimal design will have a 54% chance of stopping early when the true probability of response is 5% (the null hypothesis) and the expected sample size will be 23.5.

13.2 Sample Size/Accrual Rate

13.2.1 Phase 1

The sample size required to adequately determine the MTD is not driven by statistical considerations. The precise sample size depends on the observed toxicity rate. It is anticipated that a minimum of 6 and a maximum of 24 subjects will be enrolled in the dose escalation portion of the study. The projected accrual rate for this group of patients is expected to be 3 patients per month.

13.2.2 Phase 2

The sample size for the phase 2 portion of the study will be 37 patients. This study will be a multi-institution phase 2 study lead by SKCCC. We expect to enroll 3 patients per month and anticipate full enrollment in 15 months.

PLANNED ENROLLMENT REPORT (Both Phases)

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	4	0	0	**6**
Native Hawaiian or Other Pacific Islander	0	1	0	0	**1**
Black or African American	5	7	0	0	**12**
White	24	30	2	3	**59**
More Than One Race	1	0	0	0	**1**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Total	**32**	**42**	**2**	**3**	**79**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

13.3 Analysis Populations

13.3.1 Phase 1

During the dose escalation portion of the trial, patients who are not evaluable for dose escalation/expansion/de-escalation decisions will be replaced, up to a maximum of 2 patients per dose level. Replacement of greater than 2 patients per dose level will require discussion between the primary investigator, the medical monitor, and other site investigators.

13.3.2 Phase 2

13.3.2.1 Safety population

All patients enrolled in the phase 2 portion of this study will be included in the safety analysis population and considered evaluable for toxicity from the time of their first dose of the study drug(s).

13.3.2.2 Intention-to-treat population

All patients who meet eligibility criteria and receive at least one dose of the study drug will be included in the analysis of the primary and secondary endpoints, even if there are subsequent protocol deviations. When re-evaluation to determine response is not performed, the response category reported will be missing (unknown), however these patients will be included in the denominator for the purposes of the interim and primary objective analyses and be counted as non-responders. Patients will be replaced if they are removed from the study after signing the informed consent but before receiving the study drug.

13.3.2.3 Per-protocol analysis

Additional analyses will be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., missing re-evaluations for response, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). These analyses may not serve as the basis for drawing conclusions concerning treatment efficacy. The reasons for excluding patients from these analyses will be clearly reported.

13.4 Analysis of Primary Endpoints

13.4.1 Phase 1

Safety and tolerability will be analyzed through the incidence of adverse events, serious adverse events, and specific laboratory abnormalities (worst grade). Toxicities will be tabulated by type and grade for all doses and presented using frequencies and percentages based on the NCI CTCAE v4.0. The proportion of DLTs at each dose level will be reported with exact binomial 95% confidence intervals.

13.4.2 Phase 2

All patients who meet eligibility criteria and receive at least one dose of the study drug will be included in the interim and final analysis of the primary objective. 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 8) unknown (not assessable, insufficient data).

Patients in response categories 3-8 will be included in the denominator for the interim and final analyses. The ORR (response categories 1 and 2) will be reported with its corresponding 95% confidence interval.

13.5 Analysis of Secondary Endpoints

13.5.1 Phase 1

The secondary endpoint for the dose escalation portion of this trial is to preliminarily assess whether a bi-directional pharmacokinetic interaction occurs when navitoclax and vistusertib are co-administered.

Descriptive statistics will be provided for selected PK, and PD data by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

For navitoclax and vistusertib, steady-state trough concentrations will be calculated. For vistusertib, individual PK parameters will be estimated for C_{max}, AUC, $T_{1/2}$, apparent Cl/F, and apparent V/F using non-compartmental or compartmental PK methods with the software WinNonlin. Advanced population PK methods may be employed to assess the link between drug exposure and biological effects and efficacy. The PK variables will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. PK parameters (i.e., T½, Cl, and AUC) will be compared across dose level using nonparametic statistical testing techniques. Exploratory correlative studies with pharmacodynamic (biological endpoints, toxicity and efficacy)

will be analyzed using nonparametric statistics. Significance for comparisons will be at the $p<0.05$ level. All p values for secondary endpoints will be two-sided.

Operating characteristics of the 3+3 study design

A summary of the results of a series of simulations for standard 3+3 dose escalation are given below to demonstrate the operating characteristics of this design when the true probabilities of toxicity are varied by scenario. The target probability of DLT with standard 3+3 designs is <30% for all simulations and results are from 1,000 repetitions of the trial.

For each scenario and dose level, the table reports the simulated true toxicity (true tox), the mean number of patients across simulations at a dose level (N pat), the mean number of DLTs across simulations at that dose level (N DLT), the percentage of DLTs at that dose level (sum of DLTs/ sum of patients; % DLT), the percent of time a dose level was the recommended dose (% Recommend), and the overall percentage of time patients were treated at a dose (% Experimentation).

Scenario 1: Highest dose less than 30% is dose level 3:

	true tox	N pat	N DLT	% DLT	% Recommend	% Experimentation
dose 1	0.10	3.81	0.42	0.11	31	33.96
dose 2	0.20	3.66	0.82	0.22	28	32.62
dose 3	0.25	2.46	0.68	0.28	19	21.93
dose 4	0.35	1.29	0.47	0.36	9	11.50
Overall:	**No Recommendation 13%**					
	Mean patients 11.22					
	Mean DLTs 2.39					
	Mean last dose 2.5					

Scenario 2: Highest dose less than 30% is dose level 2:

	true tox	N pat	N DLT	% DLT	% Recommend	% Experimentation
dose 1	0.20	4.08	0.80	0.11	29.1	42.28
dose 2	0.25	3.02	0.77	0.22	25.3	31.33
dose 3	0.35	1.83	0.64	0.28	12.2	18.96
dose 4	0.40	0.72	0.30	0.36	5.0	7.43
Overall:	**No Recommendation 28.4%**					
	Mean patients 9.65					
	Mean DLTs 2.51					
	Mean last dose 2.03					

Scenario 3: Highest dose less than 30% is dose level 1:

	true tox	N pat	N DLT	% DLT	% Recommend	% Experimentation
dose 1	0.25	4.28	1.09	0.26	35.9	53.35

dose 2	0.35	2.51	0.89	0.36	16.2	31.35
dose 3	0.40	0.96	0.40	0.42	4.7	12.01
dose 4	0.45	0.26	0.11	0.41	1.9	3.29

Overall: No Recommendation 41.3%
Mean patients 8.01
Mean DLTs 2.49
Mean last dose 2.47

Scenario 4: Highest dose less than 30% is below dose level 1:

	true tox	N pat	N DLT	% DLT	% Recommend	% Experimentation
dose 1	0.30	4.37	1.31	0.30	29.9	57.90
dose 2	0.35	2.15	0.74	0.34	13.9	28.53
dose 3	0.40	0.82	0.33	0.41	3.8	10.82
dose 4	0.50	0.21	0.10	0.48	1.3	2.75

Overall: No Recommendation 51.1%
Mean patients 7.5
Mean DLTs 2.48
Mean last dose 1.22

Scenario 5: Highest dose less than 30% is above dose level 4:

	true tox	N pat	N DLT	% DLT	% Recommend	% Experimentation
dose 1	0.05	3.27	0.09	0.03	8	23.85
dose 2	0.10	3.63	0.34	0.09	18	26.48
dose 3	0.15	3.69	0.58	0.16	22	26.91
dose 4	0.20	3.12	0.62	0.20	52	22.76

Overall: No Recommendation 0.0%
Mean patients 13.71
Mean DLTs 1.63
Mean last dose 3.66

13.5.2 Phase 2

The secondary endpoints of the phase 2 portion of this study are to assess safety and tolerability, progression free survival (PFS), overall survival (OS) and disease control rate based on RECIST 1.1. The proportion of toxicities by type and grade in the phase 2 study will be reported with exact binomial 95% confidence intervals. Standard life table methods will be used to analyze PFS and OS. We will report the one-year and median PFS and OS with 95% confidence intervals. The DCR is defined as the sum of CR, PR, and SD divided by the total number of patients in the phase 2 part of the study. The proportion of patients achieving disease control will be reported with exact 95% binomial confidence intervals. If a patient is allowed to stay on study for clinical benefit past progression, for the purposes of the analysis of PFS, the event will be dated at the first documentation of progression by RECIST 1.1 criteria.

13.6 Safety monitoring and early stopping rules for safety

Safety will be monitored after every patient in the phase 2 portion of the study, using the same definition of DLT as in the dose-escalation part of the study. The stopping rule for safety is based on the posterior probability that the adverse event (AE) rate is too high. Trial enrollment will be suspended for a safety evaluation if the AE rate convincingly exceeds 30%. This stopping rule will halt enrollment and trigger review of the data by the study team if the posterior probability of the AE rate exceeding 0.30 is 70% or higher. The prior probability for this toxicity monitoring rule will be a Beta distribution with parameters of 1 and 5, based on the assumption that there was one toxicity in the cohort of six patients treated at the MTD in the dose escalation. The stopping rule applies this prior distribution to the observed number of patients experiencing an AE and computes the resulting posterior probability that the rate is too high. If the posterior certainty that the rate is too high based on these assumptions is 70% or higher, the study should stop. The following table shows the resulting rules.

Study paused if:	3 AEs	4 AEs	5 AEs	6 AEs	7 AEs	8 AEs
And patients between:	3-4	5-7	8-10	11-13	14-16	17-19

Study paused if:	9 AEs	10 AEs	11 AEs	12 AEs	13 AEs	14 AEs
And patients between:	20-22	23-25	26-28	29-31	32-35	36-37

For example, the rule will call for stopping the study if 4 out of the first 5 patients experience AEs. The next table shows the percent of the time that the stopping rule will terminate the study under different hypothetical risks of AEs, along with the average sample size (based on 5000 simulations).

Risk of AE	0.10	0.20	0.25	0.30	0.35	0.40	0.45	0.50
% of Time Study Stops	0.7%	8.8%	20.3%	41.2%	62.1%	80.4%	93.2%	97.8%
Expected Sample Size	36.8	34.7	32.2	27.5	22.9	17.9	13.3	10.5

13.7 Analysis of Correlative Endpoints

13.7.1 Reverse Phase Protein Array (Integrated Biomarker)

Intensity of protein expression will be analyzed following standard data normalization for this type of array. Vistusertib is an ATP-competitive inhibitor of TORC1 and TORC2

complexes. The primary measure for assessing the PD effect of a drug on inhibition of TORC1 is decreased phosphorylation of 4EBP1 and S6. We will measure phosphorylated-4EBP1 (p4EBP1) and phosphorylated-S6 (primary measurement) as well as the ratio of p4EBP1 and pS6 to total (p4EBP1/4EBP1; pS6/S6) (secondary measurement) before and on treatment. Use of the ratio (phosphorylated to total) has been previously described in publications from the [redacted] group as another indicator of pathway activation status. In addition, it is expected that AZD2014 drug exposure sufficient to reduce p4EBP1 (and pS6) will result in reduced MCL-1 (due to decreased p4EBP1) and correlate with increased BAX, both of which may be associated with response. BAX and MCL-1 intensity will be measured pre- and on-treatment. Descriptive statistics and box plots with jittered data points will be used to visualize all raw data. The overall changes in p4EBP1, the ratio p4EBP1/4EBP1, pS6/S6, BAX, and MCL-1 will be assessed with paired t-tests. With at least 17 paired biopsies, we would be able to detect a one standard deviation change, assuming a correlation of 0.1, with 82% power and a two-sided alpha of 0.05. Exploratory correlative studies with pharmacodynamics (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics.

The Simon two-stage design for the primary objective requires that there is one response for the study to continue to the second stage. If the study is a success, four or more responses will have been observed at the final analysis. If all of the responders have biopsies, the sample size for comparisons between responders and non-responders would be 4 responders and 13 non-responders. In this case, assuming conservatively 4 per group, if the coefficient of variation in the pre and post treatment changes is 80% or less, there would be 81% power to detect fold changes of 3.2 with one-sided 0.10 alpha level t-tests. First priority will be given to comparisons between responders and non-responders. If the number of responders with paired biopsies is lower than expected, Cuzick non-parametric tests for trend will be used to assess pre minus post changes across categories of progressive disease, stable disease and response (64).

Data from biopsies taken at baseline will be used to provide estimates of the intra-patient standard deviations for p4EBP1, pS6, BAX, and MCL-1 as measured with RPPA. Because repeated samples of tumor biopsies are not possible, the inter-patient variability will be used as a conservative estimate since this will always be greater than the intra-patient variability.

As suggested for phase 0 testing (65), a statistically significant (at the 0.10 significance level) response at the patient level will be defined as post treatment changes that are 1.8 times this baseline standard deviation. Summaries of the proportions of these responses with 90% confidence intervals will be provided. If there are a reasonable number of responses, logistic regression models or Fisher's exact tests may be used to assess if patients with protein marker responses also have an increased probability of achieving an OR.

13.8 Reporting and Exclusions

13.8.1 Evaluation of Toxicity

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

13.8.2 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).

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. Subanalyses 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 subanalyses 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.

REFERENCES

1. Wei W, Clarke CJ, Somers GR, Cresswell KS, Loveland KA, Trapani JA, et al. Expression of IFI 16 in epithelial cells and lymphoid tissues. Histochemistry and cell biology. 2003;119:45-54.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11-30.
3. Kalemkerian GP, Akerley W, Bogner P, Borghaei H, Chow LQ, Downey RJ, et al. Small cell lung cancer. J Natl Compr Canc Netw. 2013;11:78-98.
4. Oze I, Hotta K, Kiura K, Ochi N, Takigawa N, Fujiwara Y, et al. Twenty-seven years of phase III trials for patients with extensive disease small-cell lung cancer: disappointing results. PloS one. 2009;4:e7835.
5. Ikegaki N, Katsumata M, Minna J, Tsujimoto Y. Expression of bcl-2 in small cell lung carcinoma cells. Cancer Res. 1994;54:6-8.
6. Jiang SX, Sato Y, Kuwao S, Kameya T. Expression of bcl-2 oncogene protein is prevalent in small cell lung carcinomas. J Pathol. 1995;177:135-8.
7. Oltersdorf T, Elmore SW, Shoemaker AR, Armstrong RC, Augeri DJ, Belli BA, et al. An inhibitor of Bcl-2 family proteins induces regression of solid tumours. Nature. 2005;435:677-81.
8. Hann CL, Daniel VC, Sugar EA, Dobromilskaya I, Murphy SC, Cope L, et al. Therapeutic efficacy of ABT-737, a selective inhibitor of BCL-2, in small cell lung cancer. Cancer Res. 2008;68:2321-8.
9. Gandhi L, Camidge DR, Ribeiro de Oliveira M, Bonomi P, Gandara D, Khaira D, et al. Phase I study of Navitoclax (ABT-263), a novel Bcl-2 family inhibitor, in patients with small-cell lung cancer and other solid tumors. J Clin Oncol. 2011;29:909-16.
10. Rudin CM, Hann CL, Garon EB, Ribeiro de Oliveira M, Bonomi PD, Camidge DR, et al. Phase II study of single-agent navitoclax (ABT-263) and biomarker correlates in patients with relapsed small cell lung cancer. Clin Cancer Res. 2012;18:3163-9.
11. Mason KD, Carpinelli MR, Fletcher JI, Collinge JE, Hilton AA, Ellis S, et al. Programmed anuclear cell death delimits platelet life span. Cell. 2007;128:1173-86.
12. Ackler S, Mitten MJ, Foster K, Oleksijew A, Refici M, Tahir SK, et al. The Bcl-2 inhibitor ABT-263 enhances the response of multiple chemotherapeutic regimens in hematologic tumors in vivo. Cancer Chemother Pharmacol. 2010;66:869-80.
13. Jin L, Tabe Y, Kojima K, Shikami M, Benito J, Ruvolo V, et al. PI3K inhibitor GDC-0941 enhances apoptotic effects of BH-3 mimetic ABT-737 in AML cells in the hypoxic bone marrow microenvironment. Journal of molecular medicine. 2013;91:1383-97.
14. Vaillant F, Merino D, Lee L, Breslin K, Pal B, Ritchie ME, et al. Targeting BCL-2 with the BH3 mimetic ABT-199 in estrogen receptor-positive breast cancer. Cancer Cell. 2013;24:120-9.
15. Gardner EE, Connis N, Poirier JT, Cope L, Dobromilskaya I, Gallia GL, et al. Rapamycin Rescues ABT-737 Efficacy in Small Cell Lung Cancer. Cancer Res. 2014;74:2846-56.
16. Faber AC, Farago AF, Costa C, Dastur A, Gomez-Caraballo M, Robbins R, et al. Assessment of ABT-263 activity across a cancer cell line collection leads to a potent combination therapy for small-cell lung cancer. Proc Natl Acad Sci U S A. 2015.
17. van Delft MF, Wei AH, Mason KD, Vandenberg CJ, Chen L, Czabotar PE, et al. The BH3 mimetic ABT-737 targets selective Bcl-2 proteins and efficiently induces apoptosis via Bak/Bax if Mcl-1 is neutralized. Cancer Cell. 2006;10:389-99.

18. Meuwissen R, Linn SC, Linnoila RI, Zevenhoven J, Mooi WJ, Berns A. Induction of small cell lung cancer by somatic inactivation of both Trp53 and Rb1 in a conditional mouse model. Cancer Cell. 2003;4:181-9.
19. McFadden DG, Papagiannakopoulos T, Taylor-Weiner A, Stewart C, Carter SL, Cibulskis K, et al. Genetic and clonal dissection of murine small cell lung carcinoma progression by genome sequencing. Cell. 2014;156:1298-311.
20. Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. Nat Rev Cancer. 2002;2:647-56.
21. Borner C. The Bcl-2 protein family: sensors and checkpoints for life-or-death decisions. Molecular immunology. 2003;39:615-47.
22. Cory S, Huang DC, Adams JM. The Bcl-2 family: roles in cell survival and oncogenesis. Oncogene. 2003;22:8590-607.
23. Willis S, Day CL, Hinds MG, Huang DC. The Bcl-2-regulated apoptotic pathway. Journal of cell science. 2003;116:4053-6.
24. Lindsten T, Ross AJ, King A, Zong WX, Rathmell JC, Shiels HA, et al. The combined functions of proapoptotic Bcl-2 family members bak and bax are essential for normal development of multiple tissues. Molecular cell. 2000;6:1389-99.
25. Wei MC, Zong WX, Cheng EH, Lindsten T, Panoutsakopoulou V, Ross AJ, et al. Proapoptotic BAX and BAK: a requisite gateway to mitochondrial dysfunction and death. Science. 2001;292:727-30.
26. Degenhardt K, Sundararajan R, Lindsten T, Thompson C, White E. Bax and Bak independently promote cytochrome C release from mitochondria. J Biol Chem. 2002;277:14127-34.
27. Adams JM, Cory S. Life-or-death decisions by the Bcl-2 protein family. Trends in biochemical sciences. 2001;26:61-6.
28. Yang E, Korsmeyer SJ. Molecular thanatopsis: a discourse on the BCL2 family and cell death. Blood. 1996;88:386-401.
29. Fadeel B, Zhivotovsky B, Orrenius S. All along the watchtower: on the regulation of apoptosis regulators. FASEB J. 1999;13:1647-57.
30. Tsujimoto Y, Shimizu S. Bcl-2 family: life-or-death switch. FEBS letters. 2000;466:6-10.
31. Korsmeyer SJ. BCL-2 gene family and the regulation of programmed cell death. Cancer Res. 1999;59:1693s-700s.
32. Lock R, Carol H, Houghton PJ, Morton CL, Kolb EA, Gorlick R, et al. Initial testing (stage 1) of the BH3 mimetic ABT-263 by the pediatric preclinical testing program. Pediatric blood & cancer. 2008;50:1181-9.
33. Schoenwaelder SM, Jarman KE, Gardiner EE, Hua M, Qiao J, White MJ, et al. Bcl-xL-inhibitory BH3 mimetics can induce a transient thrombocytopathy that undermines the hemostatic function of platelets. Blood. 2011;118:1663-74.
34. Wilson WH, O'Connor OA, Czuczman MS, LaCasce AS, Gerecitano JF, Leonard JP, et al. Navitoclax, a targeted high-affinity inhibitor of BCL-2, in lymphoid malignancies: a phase 1 dose-escalation study of safety, pharmacokinetics, pharmacodynamics, and antitumour activity. The lancet oncology. 2010;11:1149-59.
35. Roberts AW, Seymour JF, Brown JR, Wierda WG, Kipps TJ, Khaw SL, et al. Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease. J Clin Oncol. 2012;30:488-96.
36. Merino D, Khaw SL, Glaser SP, Anderson DJ, Belmont LD, Wong C, et al. Bcl-2, Bcl-x(L),

and Bcl-w are not equivalent targets of ABT-737 and navitoclax (ABT-263) in lymphoid and leukemic cells. Blood. 2012;119:5807-16.
37. Chiarini F, Evangelisti C, McCubrey JA, Martelli AM. Current treatment strategies for inhibiting mTOR in cancer. Trends in pharmacological sciences. 2015;36:124-35.
38. Xu K, Liu P, Wei W. mTOR signaling in tumorigenesis. Biochimica et biophysica acta. 2014;1846:638-54.
39. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015;15:7-24.
40. Martini M, De Santis MC, Braccini L, Gulluni F, Hirsch E. PI3K/AKT signaling pathway and cancer: an updated review. Annals of medicine. 2014;46:372-83.
41. Guichard SM, Curwen J, Bihani T, D'Cruz CM, Yates JW, Grondine M, et al. AZD2014, an Inhibitor of mTORC1 and mTORC2, Is Highly Effective in ER+ Breast Cancer When Administered Using Intermittent or Continuous Schedules. Mol Cancer Ther. 2015;14:2508-18.
42. Hamilton E, Patel M, Cluck W, Weiser A, Pant S, Fields Jones S, et al. A phase I study of continuous (Con) and intermittent (Int) AZD2014 plus fulvestrant (F) in patients (pts) with estrogen receptor (ER+) metastatic breast cancer (BC). J Clin Oncol. 2016;34:#563.
43. Kaefer A, Yang J, Noertersheuser P, Mensing S, Humerickhouse R, Awni W, et al. Mechanism-based pharmacokinetic/pharmacodynamic meta-analysis of navitoclax (ABT-263) induced thrombocytopenia. Cancer Chemother Pharmacol. 2014;74:593-602.
44. Yang J, Pradhan RS, Rosen LS, Graham AM, Holen KD, Xiong H. Effect of rifampin on the pharmacokinetics, safety and tolerability of navitoclax (ABT-263), a dual inhibitor of Bcl-2 and Bcl-XL , in patients with cancer. Journal of clinical pharmacy and therapeutics. 2014;39:680-4.
45. Vogler M. Targeting BCL2-Proteins for the Treatment of Solid Tumours. Advances in medicine. 2014;2014:943648.
46. Salem AH, Yang J, Graham A, Patnaik A, Holen K, Pradhan R, et al. Effect of co-administration of ketoconazole, a strong CYP3A inhibitor, on the pharmacokinetics, safety and tolerability of navitoclax, a first-in-class oral Bcl-2 family inhibitor, in cancer patients. Anticancer Res. 2014;34:2001-6.
47. Pike KG, Malagu K, Hummersone MG, Menear KA, Duggan HM, Gomez S, et al. Optimization of potent and selective dual mTORC1 and mTORC2 inhibitors: the discovery of AZD8055 and AZD2014. Bioorganic & medicinal chemistry letters. 2013;23:1212-6.
48. Leary RJ, Kinde I, Diehl F, Schmidt K, Clouser C, Duncan C, et al. Development of personalized tumor biomarkers using massively parallel sequencing. Science translational medicine. 2010;2:20ra14.
49. Sausen M, Leary RJ, Jones S, Wu J, Reynolds CP, Liu X, et al. Integrated genomic analyses identify ARID1A and ARID1B alterations in the childhood cancer neuroblastoma. Nat Genet. 2013;45:12-7.
50. Jones S, Anagnostou V, Lytle K, Parpart-Li S, Nesselbush M, Riley DR, et al. Personalized genomic analyses for cancer mutation discovery and interpretation. Science translational medicine. 2015;7:283ra53.
51. Leary RJ, Sausen M, Kinde I, Papadopoulos N, Carpten JD, Craig D, et al. Detection of chromosomal alterations in the circulation of cancer patients with whole-genome sequencing. Science translational medicine. 2012;4:162ra54.
52. Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, et al. Detection of

circulating tumor DNA in early- and late-stage human malignancies. Science translational medicine. 2014;6:224ra24.
53. Sausen M, Phallen J, Adleff V, Jones S, Leary RJ, Barrett MT, et al. Clinical implications of genomic alterations in the tumour and circulation of pancreatic cancer patients. Nature communications. 2015;6:7686.
54. Diaz LA, Jr., Sausen M, Fisher GA, Velculescu VE. Insights into therapeutic resistance from whole-genome analyses of circulating tumor DNA. Oncotarget. 2013;4:1856-7.
55. 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.
56. Socinski MA, Smit EF, Lorigan P, Konduri K, Reck M, Szczesna A, et al. Phase III study of pemetrexed plus carboplatin (PC) versus etoposide plus carboplatin (EC) in chemonaive patients (pts) with extensive-stage disease small cell lung cancer (ED-SCLC): Interim results. Journal of Clinical Oncology. 2008.
57. Hotchkiss RS, Swanson PE, Knudson CM, Chang KC, Cobb JP, Osborne DF, et al. Overexpression of Bcl-2 in transgenic mice decreases apoptosis and improves survival in sepsis. J Immunol. 1999;162:4148-56.
58. 2013 UFDG. Guidance for Industry: Bioanalytical Method Validation. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM). Draft Guidance, Septmeber 2013. U.S. Food and Drug Administration. 2013.
59. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.
60. Rustin GJ. Can we now agree to use the same definition to measure response according to CA-125? J Clin Oncol. 2004;22:4035-6.
61. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol. 1999;17:3461-7.
62. Sonpavde G, Fleming MT, Hutson TE, Galsky MD. Trial design for metastatic castration-resistant prostate cancer. J Clin Oncol. 2008;26:3647-8; author reply 8-9.
63. Vergote I, Rustin GJ, Eisenhauer EA, Kristensen GB, Pujade-Lauraine E, Parmar MK, et al. Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup. J Natl Cancer Inst. 2000;92:1534-5.
64. Cuzick J. A Wilcoxon-type test for trend. Statistics in medicine. 1985;4:87-90.
65. Rubinstein LV, Steinberg SM, Kummar S, Kinders R, Parchment RE, Murgo AJ, et al. The statistics of phase 0 trials. Statistics in medicine. 2010;29:1072-6.

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. PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

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

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

Navitoclax and vistusertib interact with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4 and 3A5. Navitoclax and vistusertib are metabolized by these enzymes and may be affected by other drugs that strongly inhibit or induce CYP3A4 and 3A5.
- Navitoclax is also a moderate inhibitor of CYP2C8 and a strong inhibitor of CYP2C9 and may prevent other drugs that need these enzymes to be processed further in the liver.
- Vistusertib is a substrate of the drug transport proteins P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).
- Vistusertib induces CYP3A4 in test tubes but it is not known if this will happen in patients. Concomitant treatment with vistusertib may increase the exposure to specific substrates of the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K. Substrates of these drug cannot be given until after the appropriate wash-out period (a minimum of 5 x reported elimination half-life) before the first dose of vistusertib.

<u>TO THE PATIENT:</u> Take this paper with you to your medical appointments and keep the attached information card in your wallet.

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

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

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

Navitoclax and vistusertib must be used very carefully with other medicines that use certain **liver enzymes to be effective**. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP3A4/5 and substrate of CYP2C8 and CYP2C9."**

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.

Aspirin and ibuprofen are not allowed while taking navitoclax. Be careful! Over-the-counter drugs used for multi-symptoms such as for cough and cold contain aspirin or ibuprofen.

Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drugs **navitoclax and vistusertib.** This clinical trial is sponsored by the NCI. **Navitoclax and vistusertib** may interact with drugs that are ***processed by your liver***. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Navitoclax and vistusertib interact with ***specific liver enzymes called CYP3A4 and CYP3A5***, and must be used very carefully with other medicines that interact with ***these enzymes.***

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***"strong inducers/inhibitors of CYP3A4 and substrate of CYP2C8 and CYP2C9"***
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

APPENDIX C. DRUG DIARY FOR NAVITOCLAX LEAD-IN DOSING

Subject ID: _____ Subject Initials: _____ Lead-in Start Date: _____

Instructions:

- Use this diary to record each dose of navitoclax that you take – write in the date, the number of tablets and the time taken as well as any comments
- The Lead-in Dose is **150 mg once a day** for 7 days. You will take **two (2)** of the 25 mg tablets and **one (1)** of the 100 mg tablets.
- Navitoclax should be taken whole with food. Do not split, crush or chew the tablets.
- Navitoclax should be taken at approximately the same time each day.
- If you miss a dose of navitoclax (not taken within 8 hours of scheduled time), skip the dose and resume taking navitoclax at the next scheduled time; do not "double up" doses to make up a missed dose.
- If you vomit after taking navitoclax, do not retake the dose. Mark the vomited dose in the diary. Resume taking navitoclax at the next scheduled time.
- Use the comments section to record any side effects or anything else you would like to tell the doctor/research nurse.
- **Please bring the empty bottle or any leftover tablets and this diary to your next clinic visit.**

Lead-in Day	Date	# of 25 mg tablets	# of 100 mg tablets	Time	Comments (such as side effects, symptoms, other medications)
1					
2					
3					
4					
5					
6					
7					

Completed by: _____ Date: _____
Signature of Participant

FOR STUDY STAFF USE		
Date Dispensed: _____	# of 25 mg tablets _____	# of 100 mg tablets _____
Date Returned: _____	# of 25 mg tablets _____	# of 100 mg tablets _____
Discrepancy/Comments:		
Reviewed By: _____ Signature of Study Staff		Date: _____

APPENDIX D. DRUG ADMINISTRATION DIARY FOR NAVITOCLAX AND VISTUSERTIB

Subject ID: _____ Subject Initials: _____ Dose Level: __1___

Cycle #: ___ Cycle Start Date: _____

Instructions:

- Use this diary to record each dose of navitoclax and vistusertib that you take – write in the date, the number of tablets and the time taken as well as any comments

- Your **navitoclax** dose is: 150 mg **once a day**
  - Take two (2) 25 mg tablets and one (1) 100 mg tablets.
  - Navitoclax should be taken with food and swallowed whole. Do not split, crush or chew the tablets.
  - If you miss a dose of navitoclax (not taken within 8 hours of scheduled time), skip the dose and resume taking navitoclax at the next scheduled time; do not "double up" doses to make up a missed dose.
  - If you vomit after taking navitoclax, do not retake the dose. Mark the vomited dose in the diary. Resume taking navitoclax at the next scheduled time.

- Your **vistusertib** dose is _____ mg **twice a day, approximately 12 hours apart**
  - Take _____ 10 mg tablets and one (1) 25 mg tablets at each dose.
  - Vistusertib can be taken with or without food.
    - If you do take with food, do not eat overly sugary or fatty foods.
    - Avoid taking with grapefruit juice.
  - If you miss a scheduled vistusertib dose, you may take it up to 2 hours after the regular dose time. If it is more than 2 hours after the scheduled dose time, the missed dose should not be taken. Take the next dose at the regularly scheduled time; do not "double up" doses to make up a missed dose.
  - If you need to take a vistusertib dose earlier for whatever reason, you can take the dose up to 2 hours earlier then the scheduled dose time. You should make every effort to take the tablets on time.
  - If vomiting occurs within 30 minutes after taking vistusertib, or later if the tablet(s) can be identified in the vomit content, you can re-take a new tablet(s). Mark the vomited dose in the diary.

- Whenever possible, all doses should be taken at approximately the same time each day.

- Use the comments section to record any side effects or anything else you would like to tell the doctor/research nurse.

- **Please bring the empty bottle or any leftover tablets and this diary to your next clinic visit.**

Subject ID: **Subject Initials:** **Dose Level:** **Cycle #:** **Cycle Start Date:**

Day	Date	Navitoclax Tablets			Vistusertib Tablets						Comments (such as side effects, symptoms, other medications)
					AM			PM			
		Time	# of 25 mg	# of 100 mg	Time	# of 10 mg	# of 25 mg	Time	# of 10 mg	# of 25 mg	
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											

Completed by: _____ Date: _____
Signature of Participant

FOR STUDY STAFF USE			
Date Dispensed:_____	Navitoclax	# of 25 mg tablets _____	# of 100 mg tablets _____
	Vistusertib	# of 10 mg tablets _____	# of 25 mg tablets _____
Date Returned: _____	Navitoclax	# of 25 mg tablets _____	# of 100 mg tablets _____
	Vistusertib	# of 10 mg tablets	# of 25 mg tablets
Discrepancy/Comments:			
Reviewed By: _____ Signature of Study Staff			Date: _____