A Phase I/Ib Trial of the CDK4/6 Antagonist Ribociclib And The HDAC Inhibitor Belinostat In Patients With Metastatic Triple Negative Breast Cancer And Recurrent Ovarian Cancer With Response Prediction By Genomics (CHARGE)

IRB 130492

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450

Abbreviation or Term[1]	Definition/Explanation
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli Gratia (for example)
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HER	Human epidermal growth factor receptor
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase

Abbreviation or Term[1]	Definition/Explanation
LLQ	The lower limit of quantitation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	The maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once-daily
QTcF	QT interval corrected using Frederichia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TNBC	Triple-negative breast cancer
TSH	Thyroid-stimulating hormone
ULN	The upper limit of normal
ULQ	The upper limit of quantitation
UV	Ultraviolet

Abbreviation or Term[1]	Definition/Explanation
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in the protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

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Signature of Principal Investigator **Date**

_____

Principal Investigator Name (Print)

_____

Name of Institution

STUDY SUMMARY

Title	A Phase I/Ib Trial of the CDK4/6 Antagonist Ribociclib And The HDAC Inhibitor Belinostat In Patients With Metastatic Triple-Negative Breast Cancer And Recurrent Ovarian Cancer With Response Prediction By Genomics
Short Title	**CHARGE**
Protocol Identifiers (IRB – internal)	130492
IND number	148276
Phase	Phase I
Design	Open-Label
Study Duration	36 Months
Study Centers	This study will be conducted at the Huntsman Cancer Institute and the Inova Schar Cancer Institute.
Objectives	**Primary Objective:** To assess the MTD of ribociclib in combination with belinostat in women with metastatic triple-negative breast cancer or recurrent ovarian cancer. **Secondary Objectives:** To estimate the response rate and PFS in the overall study population. **Exploratory Objective:** To evaluate the accuracy of a gene expression biomarker. To assess efficacy within subgroups of the study population defined by RB1 mutation.
Number of Subjects	**Dose Escalation:** up to 24 **Dose Expansion:** 10
Diagnosis and Main Eligibility Criteria	**Dose escalation Population:** - People with incurable or metastatic breast cancer that is ER and PR ≤1% by local laboratory and HER2-negative (0 or 1+ by immunohistochemistry or 2+ and non-amplified by CAP/ASCO standard)

	OR - Women with platinum-resistant recurrent ovarian/primary peritoneal cancer **Dose expansion Population:** - People with incurable or metastatic breast cancer that is ER and PR ≤1% by local laboratory and HER2-negative (0 or 1+ by immunohistochemistry or 2+ and non-amplified by CAP/ASCO standard) **Inclusion Criteria:** • Measurable disease by RECIST 1.1. • Metastatic or unresectable and locally advanced and not amenable to treatment with curative intent. • Age ≥ 18 • ECOG performance status ≤ 2 • Willing to have biopsies of a metastatic lesion at two time points while on study **Exclusion Criteria:** • Previous use of CDK 4/6 or HDAC inhibitors • Major surgery, radiotherapy, chemotherapy, or investigational agents within four weeks of treatment day 1. • Use of valproic acid for any medical condition during the study or within 5 days of the first dose of belinostat • Congenital long QT syndrome • Patient is taking medication with a high risk of prolonging the QT interval or inducing Torsades de Pointes, if such treatment cannot be discontinued or switched to a different medication prior to starting the study drug. • Grade 2 ≥ Unresolved diarrhea

Study Product, Dose, Route, Regimen	Escalating doses of ribociclib PO and belinostat IV. See Table 1 for dose levels and Table 2/Figure 1 for the dose escalation plan.
Duration of administration	Subjects will receive combined treatment until intolerable toxicity or progression.
Reference therapy	None
Statistical Methodology	**Dose escalation:** This study will employ a 3+3 design modified to account for the fact that dose levels 1A and 1B are not strictly ordered. Dose level 1A represents an increase in the ribociclib dose, while 1B represents an increase in the belinostat dose. Descriptive statistics will be used to characterize toxicity profiles of each dosing regimen and percent of patients with potential DLT. **Dose Expansion:** The percent of patients with each adverse event with 95% confidence intervals will be reported. Response Rate, including partial and complete responses, and PFS will be reported for 16 patients treated at MTD identified in the Dose Escalation component. **Exploratory:** Cox regression will be used to determine if there is a significant relationship between the biomarker predictor and progression free survival.

SCHEMA

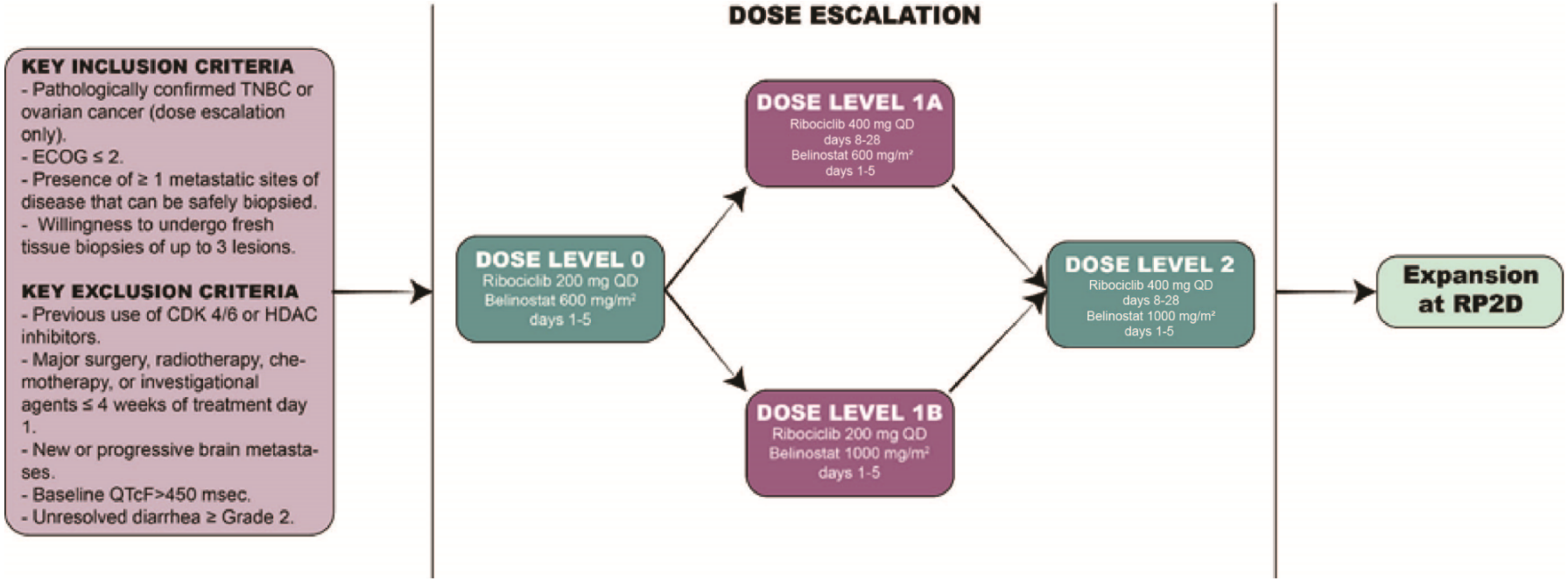

Figure 1 : Study Schema

1 OBJECTIVES

1.1 Primary Objective

To assess the maximum tolerated dose (MTD) of ribociclib and belinostat in combination.

Primary Endpoint: The incidence of DLTs during the defined DLT period.

1.2 Secondary Objectives

- To assess the safety of ribociclib and belinostat in combination.

  Secondary Endpoint: The frequency of adverse events (AEs) and serious adverse events (SAEs) characterized by type, severity (as defined by the NIH CTCAE, version 5.0), seriousness, duration, and relationship to study treatment.

- To assess the efficacy in the study population.

  Secondary Endpoints:

  - Progression-free survival (PFS) as defined as the time from study drug initiation to the time of documented disease progression (as assessed by RECIST 1.1) or death from any cause.
  - Objective response rate (the proportion of patients achieving PR or CR) as assessed by RECIST 1.1.

1.3 Exploratory Objectives

- To develop a multi-gene expression-based biomarker and evaluate its predictive accuracy.

  Exploratory Endpoint: Hazard ratio for the biomarker for predicting PFS.

- To explore how subclonal structure and phenotypic pathway activation varies in different sites of cancer.

  Exploratory Endpoint: Genomic pathway analysis output on biopsy samples.

- To assess efficacy within subgroups defined by RB1 mutation.

  Exploratory Endpoint: Objective response rate (PR and CR) and progression-free survival (PFS) will be analyzed within subgroups defined by RB1 mutation status.

2 BACKGROUND

2.1 Hypothesis

We hypothesize that ribociclib plus belinostat will be a well-tolerated and demonstrate activity in women with metastatic triple-negative breast or recurrent ovarian cancers.

2.2 Metastatic Triple Negative Breast Cancer

Triple-negative breast cancer (TNBC) refers to breast cancers that do not express the estrogen receptor (ER) or progesterone receptor (PR) and exhibit normal expression of the human epidermal growth factor receptor type (HER). TNBC is actually a heterogeneous group of diseases, and chemotherapy remains the only treatment for TNBC, with the exception of atezolizumab for first-line PD-L1 positive triple-negative, which improves PFS but does not seem to have the tail on the survival curve that immunotherapy has in some other diseases. The triple-negative phenotype is found in approximately 10-17% of all breast cancers and is associated with a poor prognosis. [1] Data suggest that the triple-negative phenotype is an independent predictor of distant metastasis and cause-specific survival. [2] In the metastatic setting, patients with TNBC have a median survival of approximately 13 months, with a median duration of response of 12 weeks for first-line treatment and 9 weeks for second-line. [3] Thus, there is an unmet clinical need for more effective treatments in this group of patients.

2.3 Recurrent Ovarian Cancer

Ovarian cancer/primary peritoneal cancer is the leading cause of death from gynecologic malignancies. [4] Although most women with advanced-stage ovarian cancer respond to first-line chemotherapy, more than 70% of patients die of recurrent disease within 5 years. [5] Therefore, new treatment paradigms for women diagnosed with epithelial ovarian cancer are needed.

2.4 CDK 4/6 and DAC inhibition in metastatic triple-negative breast cancer

Strikingly, there are no targeted therapies approved for metastatic TNBC cancer and new treatment strategies beyond cytotoxic chemotherapy are needed. This trial combines two targeted agents, a CDK inhibitor and a lysine deacetylase (DAC) inhibitor for use as the first targeted treatment for metastatic triple-negative breast cancer. This in itself would be a leap forward for women who currently endure sequential treatment with cytotoxic chemotherapies. However, we will also be using samples from this trial in NIH-funded research on clonal evolution and geographic heterogeneity in breast cancer.

Blockade of CDK4/6 and of lysine deacetylases (DAC) are both promising treatments for breast cancer. DAC inhibitors have been shown to have single-agent activity against triple-negative breast cancer in vivo, possibly through decreasing EMT, decreasing migration, and decreasing metastasis [6, 7] CDK4/6 inhibitor monotherapy causes cell cycle arrest and tumor regression in triple-negative breast cancer models. [8, 9] However, neither approach has been successfully translated into clinical use as a monotherapy.

There are several lines of evidence demonstrating that inhibiting DAC increases the sensitivity of breast cancer to CDK4/6 inhibition. Recently, we showed that inhibitors of cell cycle progression, including CDKN1A, CDKN1C, CDKN2B, and CDKN2D, are increased by DAC inhibition in breast cancer cell lines, including triple-negative cell lines. [10] Others have shown cell cycle arrest by DAC inhibitors due to increases in p21 or decreases in CDK2 and cyclin A. [11-13] We also see an increase in RB1 expression in breast cancer cell

lines. In the TCGA breast cancer analysis, RB1 was frequently down-regulated but not mutated or lost in triple-negative breast cancer. [14] Therefore, we hypothesized that DAC inhibition would increase the sensitivity of breast cancer to CDK4/6 inhibition. We first tested this hypothesis in a small panel of cell lines. We showed and published that all showed synergy between a CDK4/6 inhibitor (PD-0322991) and DAC inhibitors. [10] Since then, we have tested the combination of the DAC inhibitor vorinostat and the CDK4/6 inhibitor PD-322991 in a larger panel of cell lines and have shown at least additivity in most triple-negative cell lines. Indeed, it seems that those cancers least sensitive to CDK4/6 inhibition may benefit the most from co-treatment with a DAC inhibitor.

Recently, we investigated ribociclib and belinostat in six triple-negative breast cancer cell lines. All 6 cell lines showed growth inhibition with belinostat and panobinostat. Synergy was seen in four of the six cell lines at multiple doses.

We have also recently completed an analysis on a window of opportunity trial of the DAC inhibitor high-dose valproic acid, in breast cancer.[15] In that study, women were treated with valproic acid for one week before definitive therapy began. Fifty percent of women with triple-negative breast cancers had a significant decrease in Ki-67 with one week of valproic acid, providing proof of principle biologic activity of DAC inhibition in triple-negative breast cancer. (By contrast, no HER2 positive tumor had a decrease in Ki-67 with valproic acid treatment.)

Given the genomic similarities between serous ovarian cancer and triple-negative breast cancer seen in the TCGA and pan-cancer analyses [16], we have chosen to include ovarian cancers in the dose-escalation component to increase accrual rate but not in the dose-expansion.

2.5 Ribociclib and Belinostat in Combination

Ribociclib and belinostat are anticancer agents that would be expected to be clinically usable in combination. Direct physical interactions between the two drugs are unlikely. Belinostat has no effect on CYP3A4, the main metabolizing enzyme for ribociclib, so ribociclib pharmacokinetics should not be affected. Although ribociclib can inhibit CYP3A4, which partially metabolizes belinostat, belinostat is primarily metabolized by hepatic UGT1A1. Although both drugs can cause myelosuppression, the toxicity profile is different. At the recommended phase 2 doses, belinostat is most likely to cause thrombocytopenia, while ribociclib is most likely to cause leucopenia.

2.6 Justification for starting doses

2.6.1 Ribociclib dosing justification

The 200mg continuous daily dosing of ribociclib has been used as a standard for combination trials involving ribociclib. Based on pharmacokinetic modeling [17] 200mg daily of ribociclib is predicted to have a Cmax of 61ng/ml and AUC of 4814 h*ng/ml on day 1, increasing ~ 3 times by the end of the first cycles, which puts it in the expected therapeutic concentration of 0.5 microM in the serum. Pharmacodynamically, at doses of 140-260mg, Ki-67 in tumors was decreased ~30-

50%. The dose of 200mg is FDA-approved as the second allowable dose reduction for on-label use of ribociclib. Thus, 200mg continuous dosing is at the low end of the potential therapeutic dosing of ribociclib.

For example, the TRINITI trial was a phase I/II trial of the combination of exemestane, everolimus, and ribociclib. (NCT02732119) The starting dose for ribociclib was 200mg daily continuous dosing, and the recommended phase 2 dose of ribociclib was 300mg daily continuous dosing. The rate of grade 3 neutropenia was less than 10% with no grade 3 thrombocytopenia. In a phase 1b/II trial of ribociclib with trastuzumab, a continuous dose of 400mg daily was tested.[18] 400mg continuous dosing was considered safe and tolerable. QTc prolongation was rare. These trials demonstrate that 200mg continuous dosing, which theoretically reduces the risk of tumor escape and resistance during the week off, is safe.

Therefore, 200mg continuous dosing balances the need to first test the combination in a dose of ribociclib that minimizes the risks of neutropenia and QTc prolongation while not using doses that would be clearly subtherapeutic.

2.6.2 Belinostat dosing justification

The dose of 600mg/m2 has been used as the starting dose for combination trials with belinostat. For example, Belinostat 600-1000mg/m2 was combined with either carboplatin or paclitaxel monotherapy.[19] No DLTs were observed with these combinations despite the myelosuppressive potential of these chemotherapies. The dose of 600mg/m2 has also been used as a dose level in a phase 1 trial of belinostat combined with azacytidine with only 1 instance of grade ¾ hematologic toxicity in the 6 patients at that level.[20] Indeed, when belinostat 1000mg/m2 was combined with carboplatin and paclitaxel, the rate of grade3/4 neutropenia was 17% and of thrombocytopenia was 12%.

Pharmacokinetic and pharmacodynamics studies demonstrate that belinostat concentrations vary linearly with dose in the 600-1000mg/m2 range and that levels of 1 micron are sufficient to maximally increase histone acetylation levels peripherally. These levels can be achieved with a 600mg/m2 dose.[21, 22]

Therefore, 600mg/m2 is potentially a therapeutic dose but allows for testing at a dose that has been safely combined with cytotoxic chemotherapy.

2.7 Predictive Genomic Biomarkers

Neither CDK4/6 inhibition nor DAC inhibition have a well-defined predictive biomarker to determine which cancers will respond and which will not. Because of the complex genomic effects of inhibition of the 11 DACs and the multiple targets of DACs, including histones, p53, etc, it is unlikely that a single gene or protein alteration will predict sensitivity. We have published a method for predicting sensitivity to targeted drugs using genome-wide gene expression analysis. [23] After demonstrating proof of principle by accurately predicting sensitivity to vemurafenib, we developed a genomic biomarker for the DAC inhibitor valproic acid. We then validated that this biomarker predicted sensitivity in vitro

and in vivo. In the window of opportunity discussed above, our genomic signature had an AUC of 0.66 for predicting decreased Ki-67 with one week of treatment with valproic acid. We will develop a similar multi-gene gene expression based biomarker for the combination of ribociclib and belinostat.

2.8 Heterogeneity and Rationale for Biopsies

In addition to developing a multi-gene biomarker for this specific combination, the exploratory studies will investigate subclonal heterogeneity across different metastatic sites and through time. Tumor subclonal heterogeneity reflects a state in which cancer cells within the same tumor are fundamentally different from each other. The use of modern sequencing technologies to analyze heterogeneity in patient tumors has confirmed hypotheses formed decades ago regarding different subclonal cell populations within a tumor, namely that cancers undergo stepwise evolution giving rise to heterogeneous competing subclones. [24-26]. However, evidence suggests that as tumors progress, their genetic evolution converges on similar biological characteristics, i.e. phenotypes.

Studies of tumor heterogeneity using modern –omic technologies indicate tumor cells are indeed extremely diverse, spatially and temporally. Tumor diversity through space is a phenomenon that has been well-studied by research groups comparing mutations identified in multiple regions sampled from primary tumors or by comparing primary tumor mutations to those identified in metastases. [27-29] Studies of spatial heterogeneity have also shed light on the biology of metastasis.

Recently, technological improvements have allowed for the study of tumor heterogeneity at the single-cell level. Thus, rather than disentangling bulk level events by computationally assigning them to specific subclones, co-occurrence of mutations can also be identified in single cells to better map evolutionary and mutational trajectory [30]. An early single-cell study utilized flow sorting of single cell nuclei followed by whole genome amplification to identify copy number differences between single triple negative breast cancer (TNBC) cells [31]. However, these single cell genomes were sequenced at a relatively low depth of 6X compared to what is now possible. Nevertheless, this low-depth data was sensitive enough to identify which subclone from the primary tumor seeded the liver metastasis in the patient studied. Similarly, Wang and colleagues (2014) performed whole genome and whole exome sequencing on single cells from one TNBC and one ER+ patient breast tumor, finding that copy number variation was largely similar in all cells studied and thus likely occurs early in cancer initiation, whereas private mutations were more likely to be point mutations than copy number variations. Further, the study found the TNBC cancer had a mutation rate approximately 13 times that of the ER+ cancer. More recently, Li and colleagues (2017) demonstrated that nearly twice the number of somatic mutations could be detected by single cell exome sequencing of 20 tumor cells from a patient with RCC than by exome sequencing of bulk tumor tissue, and identified LOC440040 and LOC440563 as potential novel driver genes of RCC stem cells. Thus, study of the tumor genome and/or exome at the single cell level demonstrates utility in identifying and establishing order of mutational events. Our recent studies are using depths of 20-60X, which allow greater refinement of subclonal structure and functional genomics.

It is important to note that while studying heterogeneity allows for the identification of subclones present in a tumor, phenotypic plasticity can occur due to non-genetic factors. Isogenic cancer cells may demonstrate differing phenotypes due to various causes such as stochastic events occurring during transcription and translation or differing interactions with heterogeneous normal cells in the microenvironment [32]. Despite the pervasive notion that nonsynonymous changes in genotype lead directly to production of a novel phenotype, it has been hypothesized rather that changes in genotype lead to differing frequencies of phenotypes already present in the population [33]. Indeed, the link from tumor cell genotype to output phenotype has yet to be fully elucidated, and microenvironmental impacts on this process have yet to be disentangled. Therefore, the output of heterogeneity at all -omic levels, cellular phenotype, is an important level of data for impacting treatment decision making.

To accompany this protocol, we have a funded NIH grant through the Cancer Systems Biology Consortium for the exploratory studies of the biopsies obtained before and during treatment on this study. Our studies will illuminate the landscape of ovarian and breast. We will profile the phylogeny, subclone seeding, and genetic evolution of tumor subclones across multiple metastases within a single patient using biopsies from multiple sites (up to 3) prior to treatment when accessible. In some patients, in which individual clones co-occur in multiple metastatic sites, we will determine if the presence of polyclones is due to polyclonal seeding and cooperation, or by monoclonal seeding plus evolution due to similar environmental factors[34]. Demonstrating that polyclonal seeding involves non-random associations of clones would provide evidence in favor of a clonal cooperation model—implying that a tumor achieves the hallmarks of cancer as a collective, through cooperative interaction of tumor subclones, rather than via a single cell evolving all attributes. This study will provide a unique dataset of biopsy samples that combined with our novel computational algorithms and deep single-cell –omic analyses will allow us to identify generalizable and interpretable phenotypes that can be therapeutically targeted in resistant cancer, regardless of the outcome of this trial.

All biopsies will be by image or palpation guided core biopsy. As discussed below, biopsies with risks of greater than 1.5% will not be performed. Biopsies at baseline and C2D15 are mandatory. However, biopsy results are not needed before proceeding with the trial, so all patients who undergo the biopsy will be able to enroll in the trial. We have followed the recommendations put forth in the ASCO framework for research biopsies.[35] Biopsies will be used for key correlative analyses that are part of planned analyses funded through an NIH U54 grant as part of the Cancer Systems Biology Consortium. As such, these analyses would all be classified as potential or expected utility. Thus, per the ASCO framework, mandatory biopsies that are low risk (<0.5% risk) or moderate risk (0.5-1.5%) risk are acceptable. Preference will be given to low-risk biopsies, such as needle biopsies of breast masses, superficial lymph nodes, and subcutaneous masses. When low-risk targets are not available, moderate risk targets, such as peripheral liver masses, pleural masses, will be chosen. We will not perform high-risk biopsies, such as lung biopsies in which lung tissue needs to be traversed.

2.9 Rationale for Populations

For the dose escalation, women with triple-negative breast cancer and women with recurrent ovarian cancer will be allowed, given the genomic similarities seen between these two cancers in TCGA analyses. This allows a balance between maximizing accrual and focusing on signals of activity and toxicity in the population of interest. For the dose-expansion, only women with triple-negative breast cancer will be allowed so that we can detect any signal of response in this population that would warrant larger studies.

2.10 Risk/Benefit Assessment

Potential Risks: Patients undergoing treatment with ribociclib and belinostat may suffer side effects from this treatment. Patients will undergo the physical risks of additional blood draws, mandatory biopsies, and tests. These risks are not significantly increased compared to patients who participate in other research trials or those that are treated with investigational drugs.

Protection against Risks: Potential risks may arise due to treatment with an investigational drug. However, participants will be carefully monitored by the co-investigator physicians participating in this trial. Standard adverse event criteria and reporting mechanisms will be followed.

Potential Benefits: Treatment with ribociclib and belinostat may reduce tumor size and sites of metastasis providing symptom improvement and prolonged progression free survival in patients that do not have curable breast or ovarian cancers. Because the anticipated benefits to participants are substantial, the risks to subjects are reasonable in relation to the anticipated benefits.

3 DRUG INFORMATION

3.1 Ribociclib

Refer to the most recent Package Insert for detailed background information on Ribociclib. The following are extracted from the Package Insert.

3.1.1 Pharmacology

Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb). In vitro, ribociclib decreased pRb phosphorylation leading to arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer cell lines. In vivo, treatment with single agent ribociclib in a rat xenograft model with human tumor cells led to decreased tumor volumes, which correlated with inhibition of pRb phosphorylation.

3.1.2 Physical and Chemical Properties

Ribociclib is a kinase inhibitor. The chemical name of ribociclib succinate is: Butanedioic acid—7-cyclopentyl-N,N-dimethyl-2-([5-(piperazin-1-yl)pyridin-2-yl]amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (1/1). Ribociclib succinate is a light yellow to yellowish brown crystalline powder. The molecular formula for ribociclib succinate is C23H30N8O·C4H6O4 and the molecular weight is 552.64 g/mol (Free base: 434.55 g/mol).

3.1.3 Pharmaceutical Properties and Formulation

Ribociclib film-coated tablets are supplied for oral use and contain 200 mg of ribociclib free base (equivalent to 254.40 mg ribociclib succinate). The tablets also contain colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide red, lecithin (soya), polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide, and xanthan gum as inactive ingredients.

Tablets are light greyish violet, round, curved with beveled edge, debossed with “RIC” on one side and “NVR” on the other side; available in:

Store at 20º C to 25°C (68º F to 77°F). Store in the original package

3.1.4 Pharmacokinetics

Ribociclib exhibited over-proportional increases in exposure (peak plasma concentrations (Cmax) and area under the time concentration curve (AUC) across the dose range of 50 mg to 1200 mg following both single dose and repeated doses.

Following repeated 600 mg once daily administration, steady-state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range: 0.972 to 6.40).

Absorption

The time to reach Cmax (Tmax) following ribociclib administration was between 1 and 4 hours.

Food Effect: Compared to the fasted state, oral administration of a single 600 mg dose of ribociclib film-coated tablet with a high-fat, high-calorie meal (approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein) had no effect on the rate and extent of absorption of ribociclib (Cmax GMR: 1.00; 90% CI: 0.898, 1.11; AUCinf GMR: 1.06; 90% CI: 1.01, 1.12).

Distribution

Binding of ribociclib to human plasma proteins in vitro was approximately 70% and independent of concentration (10 to10,000 ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean in vivo blood-to plasma ratio of 1.04.

The apparent volume of distribution at steady-state (Vss/F) was 1090 L based on population PK analysis.

Metabolism

In vitro and in vivo studies indicated ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of radio-labeled ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation (dealkylation, C and/or N-oxygenation, oxidation (-2H)) and combinations thereof. Phase II conjugates of ribociclib Phase I metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation, and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma (44%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9%, 9%, and 8% of total radioactivity, and 22%, 20%, and 18% of ribociclib exposure. Clinical activity (pharmacological and safety) of ribociclib was due primarily to the parent drug, with negligible contribution from circulating metabolites. Ribociclib was extensively metabolized with unchanged drug accounting for 17% and 12% in feces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 14% and 4% of the administered dose in feces and urine, respectively. Numerous other metabolites were detected in both feces and urine in minor amounts (≤ 3% of the administered dose).

Elimination

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 L/hr (66% CV) at steady-state at 600 mg in patients with advanced cancer. The geometric mean apparent plasma terminal half-life ($T_{1/2}$) of ribociclib ranged from 29.7 to 54.7 hours and geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy subjects. Ribociclib is eliminated mainly via feces, with a small contribution of the renal route. In 6 healthy male subjects, following a single oral dose of radio-labeled ribociclib, 92% of the total administered radioactive dose was recovered within 22 days; feces was the major route of excretion (69%), with 23% of the dose recovered in urine.

3.1.5 Clinical Safety

QT Interval Prolongation

Ribociclib has been shown to prolong the QT interval in a concentration-dependent manner. Based on the observed QT prolongation during treatment, Ribociclib may require dose interruption, reduction, or discontinuation. Across MONALEESA-2, MONALEESA-7, and MONALEESA-3 in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 14 out of 1054 patients (1%) had a > 500 ms post-baseline QTcF value, and 59 out of 1054 patients (6%) had a > 60 ms increase from baseline in QTcF intervals.

These ECG changes occurred within the first four weeks of treatment and were reversible with dose interruption. There were no reported cases of Torsades de Pointes. In MONALEESA-2, on the ribociclib plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3

Assess ECG prior to initiation of treatment. Initiate treatment with ribociclib only in patients with QTcF values less than 450 msec. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting ribociclib therapy.

Avoid the use of ribociclib in patients who already have or who are at significant risk of developing QTcF prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias
- electrolyte abnormalities

Avoid using ribociclib with drugs known to prolong QTcF interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

<u>Hepatobiliary Toxicity</u>

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, increases in transaminases were observed. Across all studies, Grade 3 or 4 increases in ALT (10% vs. 2%) and AST (7% vs. 2%) were reported in the ribociclib and placebo arms, respectively.

Among the patients who had Grade ≥ 3 ALT/AST elevation, the median time-to-onset was 85 days for the ribociclib plus aromatase inhibitor or fulvestrant treatment group. The median time to resolution to Grade ≤ 2 was 22 days in the ribiciclib plus aromatase inhibitor or fulvestrant treatment group. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of ribociclib. No cases occurred in MONALEESA-7.

Perform LFTs before initiating therapy with ribociclib. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.Based on the severity of the transaminase elevations, ribociclib may require dose interruption, reduction, or discontinuation.

Recommendations for patients who have elevated AST/ALT Grade ≥ 3 at baseline have not been established.

Neutropenia

In MONALEESA-2, MONALEESA-7, and MONALEESA-3, neutropenia was the most frequently reported adverse reaction (74%), and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 58% of patients

receiving ribociclib plus an aromatase inhibitor or fulvestrant. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade ≥ 2 neutropenia was 16 days. The median time to resolution of Grade ≥ 3 (to normalization or Grade < 3) was 12 days in the ribociclib plus aromatase inhibitor or fulvestrant treatment group. Febrile neutropenia was reported in 1% of patients receiving ribociclib plus an aromatase inhibitor or fulvestrant. Treatment discontinuation due to neutropenia was 0.8%.

Perform CBC before initiating therapy with ribociclib. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

Based on the severity of the neutropenia, ribociclib may require dose interruption, reduction or discontinuation

Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, ribociclib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ribociclib to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with ribociclib and for at least 3 weeks after the last dose.

3.2 Belinostat

Refer to the most recent Package Insert for detailed background information on Belinostat. The following are extracted from the Package Insert.

3.2.1 Pharmacology

Belinostat is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. In vitro, belinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Belinostat shows preferential cytotoxicity towards tumor cells compared to normal cells. Belinostat inhibited the enzymatic activity of histone deacetylases at nanomolar concentrations (<250nM).

3.2.2 Physical and Chemical Properties

Belinostat is a histone deacetylase inhibitor with a sulfonamide-hydroxamide structure. The chemical name of belinostat is (2E)-N-hydroxy-3-[3-

(phenylsulfamoyl)phenyl]prop-2-enamide. The molecular formula is C15 H14 N2O4S and the molecular weight is 318.35 g/mol.

3.2.3 Pharmaceutical Properties and Formulation

Belinostat is a white to off-white powder. It is slightly soluble in distilled water (0.14 mg/mL) and polyethylene glycol 400 (about 1.5 mg/mL), and is freely soluble in ethanol (> 200 mg/mL). The pKa values are 7.87 and 8.71 by potentiometry and 7.86 and 8.59 by UV.

Belinostat for injection is supplied as a sterile lyophilized yellow powder containing 500 mg belinostat as the active ingredient. Each vial also contains 1000 mg L-Arginine, USP as an inactive ingredient. The drug product is supplied in a single-use 30 mL clear glass vial with a coated stopper and aluminum crimp seal with "flip-off" cap. Belinostat is intended for intravenous administration after reconstitution with 9 mL Sterile Water for injection, and the reconstituted solution is further diluted with 250 mL of sterile 0.9% Sodium Chloride injection prior to infusion.

3.2.4 Pharmacokinetics

The pharmacokinetic characteristics of belinostat were analyzed from pooled data from phase 1/2 clinical studies that used doses of belinostat ranging from 150 to 1200 mg/m2. The total mean plasma clearance and elimination half-life were 1240 mL/min and 1.1 hours, respectively. The total clearance approximates average hepatic blood flow (1500 mL/min), suggesting high hepatic extraction (clearance being flow dependent).

Distribution

The mean belinostat volume of distribution approaches total body water, indicating that belinostat has limited body tissue distribution. In vitro plasma studies have shown that between 92.9% and 95.8% of belinostat is bound to protein in an equilibrium dialysis assay, and was independent of belinostat plasma concentrations from 500 to 25,000 ng/mL.

Metabolism

Belinostat is primarily metabolized by hepatic UGT1A1. Strong UGT1A1 inhibitors are expected to increase exposure to belinostat. Belinostat also undergoes hepatic metabolism by CYP2A6, CYP2C9, and CYP3A4 enzymes to form belinostat amide and belinostat acid. The enzymes responsible for the formation of methyl belinostat and 3-(anilinosulfonyl)-benzenecarboxylic acid, (3-ASBA) are not known.

Excretion

Belinostat is eliminated predominantly through metabolism with less than 2% of the dose recovered unchanged in urine. All major human metabolites (methyl belinostat, belinostat amide, belinostat acid, belinostat glucuronide, and 3-ASBA) are generally excreted in urine within the first 24 hours after dose administration. Metabolites 3-

ASBA and belinostat glucuronide represented the highest fractions of the belinostat dose excreted in urine (4.61% and 30.5%, respectively).

Drug-Drug Interactions

In vitro studies showed belinostat and its metabolites (including belinostat glucuronide, belinostat amide, methyl belinostat) inhibited metabolic activities of CYP2C8 and CYP2C9. Other metabolites (3-ASBA and belinostat acid) inhibited CYP2C8.

In cancer patients, co-administration of Belinostat (1,000 mg/m2) and warfarin (5 mg), a known CYP2C9 substrate, did not increase the AUC or Cmax of either R- or S-warfarin.

Belinostat is likely a glycoprotein (P-gp) substrate but is unlikely to inhibit P-gp.

3.2.5 Clinical Safety

Hematologic Toxicity

Belinostat can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and/or anemia; monitor blood counts weekly during treatment, and modify dosage as necessary.

Infections

Serious and sometimes fatal infections, including pneumonia and sepsis, have occurred with belinostat. Do not administer belinostat to patients with an active infection. Patients with a history of extensive or intensive chemotherapy may be at higher risk of life threatening infections

Hepatotoxicity

Belinostat can cause fatal hepatotoxicity and liver function test abnormalities. Monitor liver function tests before treatment and before the start of each cycle. Interrupt or adjust dosage until recovery, or permanently discontinue belinostat based on the severity of the hepatic toxicity.

Tumor Lysis Syndrome

Tumor lysis syndrome has occurred in belinostat-treated patients in the clinical trial of patients with relapsed or refractory PTCL. Monitor patients with advanced stage disease and/or high tumor burden and take appropriate precautions.

Gastrointestinal Toxicity

Nausea, vomiting and diarrhea occur with belinostat and may require the use of antiemetic and antidiarrheal medications.

Embryo-fetal Toxicity

Belinostat can cause fetal harm when administered to a pregnant woman. Belinostat may cause teratogenicity and/or embryo-fetal lethality because it is genotoxic and targets actively dividing cells. Women of childbearing potential should be advised to avoid pregnancy while receiving Belinostat. If this drug is used during pregnancy, or if

the patient becomes pregnant while taking this drug, the patient should be apprised of potential hazard to the fetus

4 STUDY DESIGN

4.1 Description

This is an open-label, multi-center, phase I study designed to assess the maximum tolerated dose of ribociclib and belinostat in combination. The trial will open with a modified 3+3 dose escalation followed by an expansion cohort at the identified Recommended Phase 2 Dose (RP2D). Dose escalation will be open to the enrollment of patients diagnosed with triple-negative breast cancer or ovarian cancer. However, dose expansion will only be open to the enrollment of patients diagnosed with triple-negative breast cancer.

4.2 Dose Limiting Toxicity

The dose limiting toxicity (DLT) evaluation period for this study will be defined as the first cycle of treatment (from cycle one day one dosing to cycle two day 1). Patients will be assessed over this period for the occurrence of adverse events, per CTCAE v5.0.

For the purpose of dose finding, any of the following AEs occurring within the defined DLT period which are attributable (possibly, probably, or definitely related) to any or all agents in the combination will be classified as a DLT:

- Hematologic:
  - Grade 3 Thrombocytopenia with clinically significant bleeding
  - Grade 4-5 Thrombocytopenia
  - Grade ≥ 3 Febrile Neutropenia
  - Grade 4-5 Neutropenia lasting >7 days
- Non-Hematologic:
  - Any grade ≥ 4 toxicity
  - Any grade 3 toxicity lasting >48 hours despite maximal medical therapy except for clinically non-significant laboratory abnormalities.
  - Grade ≥ 3 ECG QTcF interval prolongation

Patients who experience a dose limiting toxicity during the DLT defined period will be discontinued from study therapy.

Patients who take less than 50% of the ribociclib or belinostat doses in the first cycle or discontinue study therapy for reasons other than toxicity will be considered non-evaluable for the DLT evaluation and will be replaced.

4.3 Dose Escalation

This study will employ a 3+3 design modified to account for the fact that dose levels 1A and 1B are not strictly ordered. Dose level 1A represents an increase in the ribociclib dose, while 1B represents an increase in the belinostat dose.

Table 1: Dose levels for Dose Escalation

	Ribociclib	Belinostat*
Dose Level 0 (starting dose)	200mg QD	600mg/m^2 daily for 5 days*
Dose Level 1A	400mg QD on Days 8-28	600mg/m^2 daily for 5 days*
Dose Level 1B	200mg QD	1000mg/m^2 daily for 5 days*
Dose Level 2	400mg QD on Days 8-28	1000mg/m^2 daily for 5 days*

*Starting on Day 1 of each cycle. Administration on 5 consecutive days is preferred. Administration within 7 days allowed as needed to accommodate holidays and infusion schedules.

Subjects will be accrued in groups of three subjects. All subjects must complete the DLT evaluation period prior to opening to the enrollment of the next three subjects. Escalation will continue until DLT stopping rules are met or the highest defined dose level is reached.

Enrollment will begin at Dose Level 0. If the dose level is deemed safe per the dose escalation rules (Table 2), Dose Levels 1A and 1B will open to enrollment simultaneously. If slots are available on both Dose Level 1A and Dose Level 1B when a subject enrolls, slots on Dose Level 1A will be prioritized above slots on Dose Level 1B. If Dose Levels 1A and 1B are deemed tolerable but Dose Level 2 is not, then the recommended dose for dose expansion will be Dose Level 1A. Escalation to Dose Level 2 will require that both Dose Levels 1A and 1B are deemed tolerable, i.e, not above MTD.

Table 2: 3+3 Dose Escalation Design

Number of patients with DLT at a given dose level	Escalation or De-escalation Rules
0 out of 3	• Enroll 3 patients at the next higher dose level; or • If at the highest defined dose level, enroll 3 more patients at the same dose level. o If 0 out of 6 patients experience a DLT, enroll 3 patients at the next higher dose level or if at the highest defined dose, this will be considered the RP2D.
1 out of 3	Enter 3 more patients at this dose level (total of 6 patients)

	• If only 1 out of 6 patients experience a DLT, enroll 3 patients at the next higher dose level or if at the highest defined dose, this will be considered the RP2D. • If ≥ 2 out of 6 patients experience a DLT, this dose level exceeds the MTD and is declared the maximally administered dose (MAD). Enroll 3 patients at the next lower dose level (if available). o If at Dose Level 2, de-escalate to Dose Level 1A.
≥ 2 of 3	This dose level exceeds the MTD and is declared the maximally administered dose (MAD). Enroll 3 patients at the next lower dose level (if available)
In order for a dose level to be declared the RP2D, 6 patients must complete the DLT evaluation period at that dose level with ≤ 1 DLT observed.	

DSMC review and approval from the primary medical monitor is required prior to all dose escalations and cohort expansions.

4.4 Number of Patients

This study will enroll up to 34 patients. Between 3 and 24 patients will be enrolled to the dose escalation cohort. An additional 10 patients will be enrolled to the dose expansion cohort.

4.5 Number of Study Centers

This study will be conducted at the Huntsman Cancer Institute and one additional site.

4.6 Study Duration

The estimated duration for accrual is 18 months and the duration of patient participation is approximately 36 months.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with the enrolling investigator's signature in the patient research chart.

Patient No. _____

Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

For dose escalation cohorts only:

5.1.1 _____ Pathologically confirmed breast cancer with the following features:

_____Measurable disease by RECIST 1.1;

_____ER and PR ≤ 1% by immunohistochemistry;

_____Her-2/neu negative (0 or 1+ by immunohistochemistry OR not-amplified by CAP/ASCO standards);

_____Metastatic or unresectable and locally advanced and not amenable to treatment with curative intent, in the opinion of the enrolling investigator.

OR

_____ Platinum-resistant (defined as progression within 12 months of last platinum therapy administration), pathologically confirmed serous ovarian cancer that is recurrent and unresectable, in the opinion of the enrolling investigator.

For dose expansion cohort only:

5.1.2 _____ Pathologically confirmed breast cancer with the following features:

_____ Measurable disease by RECIST 1.1;

_____ER and PR ≤ 1% by immunohistochemistry;

_____Her-2/neu negative (0 or 1+ by immunohistochemistry OR not-amplified by CAP/ASCO standards);

_____Metastatic or unresectable and locally advanced and not amenable to treatment with curative intent, in the opinion of the enrolling investigator.

For all patients:

5.1.3 _____ Age ≥ 18.

5.1.4 _____ ECOG performance Status ≤ 2.

5.1.5 _____ Able to swallow pills.

5.1.6 _____ Adequate organ function as defined as:

- Hematologic:
  - Absolute Neutrophil Count > 1,500/mcL
  - Platelets > 100,000/mm3
  - Hemoglobin > 9g/dL
- Hepatic:
  - Serum bilirubin levels ≤1.5 mg/dL. Higher levels are acceptable if these can be attributed to active hemolysis or ineffective erythropoiesis. Bilirubin above 1.5mg/dL due to Gilbert's is still excluded.
  - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 2.5 X upper limit of normal.
    - AST(SGOT)/ALT(SGPT) ≤ 5 × institutional ULN for patients with liver metastasis.
  - Alkaline phosphatase < 2.5 X upper limit of normal, unless bone metastasis is present in the absence of liver metastasis
- Renal:
  - Serum creatinine levels ≤1.5 mg/dL
  - Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of study medication:
    - Potassium
    - Magnesium
    - Total Calcium (corrected for serum albumin)
- Coagulation
  - INR ≤1.5 (unless the patient is receiving anticoagulants and the INR is within the therapeutic range of intended use for that anticoagulant within 7 days prior to the first dose of study drug)

5.1.7 _____ Presence of ≥ 1 metastatic sites of disease that can be safely accessed for core needle biopsy and patient willingness to undergo fresh tissue biopsies of up to 3 lesions. (Safely accessible means risk of mortality or major morbidity < 1.5%, such as core needle biopsy of breast, superficial lymph node, subcutaneous nodule, peripheral liver nodule, pleural nodule, omental nodule, etc. or per investigator discretion)

5.1.8 _____ Negative serum or urine pregnancy test at screening for women of childbearing potential.

5.1.9 _____ Agrees to continue use of approved birth control for at least 6 months after receiving the last dose of study drugs. See section 7.3 for list of approved birth control methods.

5.1.10 _____ Able to provide informed consent and have signed an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Previous use of CDK 4/6 or HDAC inhibitors for cancer treatment

5.2.2 _____ Major surgery, radiotherapy, anticancer therapy, or investigational agents ≤ 4 weeks of treatment day 1 or ≤5 half-lives, whichever is shorter.

5.2.3 _____ Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease unless determined by the treating physician that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

5.2.4 _____ Medical condition that in the opinion of the enrolling investigator would require the use of valproic acid within ≤ 5 days of the first dose of belinostat or while on study.

5.2.5 _____ Active infection requiring systemic therapy.

5.2.6 _____ History of allergy or hypersensitivity to belinostat, ribociclib, or their binders.

5.2.7 _____ Uncontrolled arrhythmia, congestive heart failure or angina. Patients who have had a myocardial infarction, symptomatic pericarditis, or cardiac surgery should be at least 6 months from the event and free of active symptoms

5.2.8 _____ Known left ventricular ejection fraction < 50%. (Echocardiogram is not required for study entry)

5.2.9 _____ Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)

5.2.10 _____ Congenital long QT syndrome.

5.2.11 _____Baseline QTcF>450 msec. The heart rate on the qualifying ECG must be between 50 and 90 BPM.

5.2.12 _____ Concurrent use of medication known to inhibit UGT1A1. Patients currently taking these medications must have discontinued ≥7 days prior to treatment day 1.

5.2.13 _____ Concurrent use of herbal supplements, unless approved by the prinicipal investigator. Patients currently taking herbal supplements must have discontinued ≥ 7 days prior to treatment day 1.

5.2.14 _____ Concurrent use of medication with a known risk of inducing Torsades de Pointes (on the known risk list of crediblemeds.org) that cannot be discontinued or switched to a different medication ≥ 7 days prior to starting the study drug.

5.2.15 _____ Unresolved diarrhea ≥ Grade 2, per CTCAE v5.0.

5.2.16 _____ Use of any of the following substances ≤ 7 days prior to the start of the treatment:

- Known strong and moderate inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pomelos, star-fruit, and Seville oranges.
- Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5. Examples include certain benzodiazepines such as alprazolam and anti-seizure medications such as carbamazepine. Ultimately determination of drugs with a narrow therapeutic window is left to the discretion of the principal investigator.

5.2.17 _____ Patient is currently receiving warfarin or other coumarin derived anti-coagulant, for treatment, prophylaxis or otherwise.

Note: Therapy with heparin, low molecular weight heparin (LMWH), an oral factor Xa inhibitor, an oral direct thrombin inhibitor, or fondaparinux is allowed**.**

5.2.18 _____ Impaired GI function that may alter absorption of medicines, such as uncontrolled inflammatory bowel disease, uncontrolled vomiting, or major stomach or small bowel resection.

5.2.19 _____ Pregnant or breast feeding

5.2.20 _____ Women of child-bearing potential defined as all women physiologically capable of becoming pregnant or men whose female partner is of child-bearing potential, unless they are using highly effective methods of contraception during the study treatment and for 6 months after stopping the treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male partner sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient and the success of the vasectomy must be medically confirmed as per local practice.
- Placement of an intrauterine device (IUD).
- Use of hormonal contraception plus a barrier contraceptive.

5.2.21 _____ Known HIV infection with a detectable viral load within 6 months of the anticipated start of treatment.

Note: Patients on effective anti-retroviral therapy with an undetectable viral load within 6 months of the anticipated start of treatment are eligible for this trial.

5.2.22 _____ Known chronic hepatitis B virus (HBV) or hepatitis C virus infection with a detectable viral load.

Note: Patients with an undetectable HBV viral load on appropriate suppressive therapy are eligible. Patients with an undetectable HCV viral load are eligible.

5.2.23 _____ Malignancy other than breast carcinoma or ovarian cancer (dose escalation) anticipated to need systemic treatment within 1 year in the opinion of the enrolling investigator.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

5.3 Recruitment Strategies

Potential patients will be identified by Investigators in the setting of their outpatient clinics.

6 TREATMENT PLAN

6.1 Administration Schedule

Ribociclib and belinostat will be given at escalating doses and on multiple administration schedules throughout the dose escalation component of the study. See Table 1 for detail on dose levels and administration schedules.

The MTD identified in the dose escalation component will be used to define the dose and administration schedule used in the dose expansion.

Ribociclib will be taken at home. If the patient vomits on the same day as ribociclib administration, no additional doses of ribociclib should be taken that day. The next planned dose should be taken at the next due administration time. Missed doses beyond 6 hours after the regular scheduled administration time must be skipped, and should not be replaced on a subsequent day.

Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of study medication:

- Sodium
- Potassium
- Magnesium
- Total Calcium (corrected for serum albumin)

6.2 Ribociclib

6.2.1 How Supplied, Stored, Packaged and Labeled

Ribociclib film-coated capsules/tablets are supplied for oral use and contain 200 mg of ribociclib free base (equivalent to 254.40 mg ribociclib succinate). Tablets are light greyish violet, round, curved with beveled edge, debossed with “RIC” on one side and “NVR” on the other side.

Refer to the clinical labels for the current shelf-life, in-use period, and storage conditions. Store in the original package.

6.2.2 Preparation and Administration

Investigational study medication will be prepared and dispensed by properly trained and delegated individuals.

Ribociclib will be taken orally with or without food every 24 hours (± 6 hours).

Patients should be instructed to swallow the ribociclib capsules/tablets whole and not to chew, crush or open them.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.

6.2.3 Accountability and Compliance

Patients will be required to return all unused ribociclib tablets at the end of every cycle. The number of tablets returned by the patient will be counted, documented, and recorded by site personnel and reconciled with the patient's dosing diary to support the accountability process. Study site personnel must make reasonable efforts to obtain study drug packaging and any unused tablets from patients who do not routinely return them at study site visits.

Patients will be instructed to record drug compliance on the CHARGE drug diary (see appendix 0). A member of the study team will review patient drug compliance at the end of treatment for each cycle and provide patient re-education as required.

Excess or unused study drug should be returned to the investigative site, for accounting and disposal in accordance with Institutional SOPs.

6.3 Belinostat

6.3.1 How Supplied, Stored, Packaged and Labeled

Belinostat for injection is supplied as a sterile lyophilized yellow powder containing 500 mg belinostat as the active ingredient. Each vial also contains 1000 mg L-Arginine, USP as an inactive ingredient. The drug product is supplied in a single-use 30 mL clear glass vial with a coated stopper and aluminum crimp seal with "flip-off" cap. Belinostat is a white to off-white powder.

6.3.2 Preparation and Administration

Belinostat is intended for intravenous administration after reconstitution with 9 mL Sterile Water for injection, and the reconstituted solution is further diluted with 250 mL of sterile 0.9% Sodium Chloride injection prior to infusion.

Reconstitution and Infusion Instructions

a) Aseptically reconstitute each vial of belinostat by adding 9 mL of Sterile Water for injection, USP, into the belinostat vial with a suitable syringe to achieve a concentration of 50 mg of belinostat per mL. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted product may be stored for up to 12 hours at ambient temperature (15-25°C; 59-77°F).

b) Aseptically withdraw the volume needed for the required dosage (based on the 50 mg/mL concentration and the patient's BSA [m2]) and transfer to an infusion bag containing 250 mL of 0.9 % Sodium Chloride injection. The infusion bag with drug solution may be stored at ambient room temperature (15- 25°C; 59-77°F) for up to 36 hours including infusion time.

c) Visually inspect the solution for particulate matter. Do not use if cloudiness or particulates are observed.

d) Connect the infusion bag containing drug solution to an infusion set with a 0.22 μm in-line filter for administration.

e) Infuse intravenously over 30 to 45 minutes. If infusion site pain or other symptoms potentially attributable to the infusion occur, the infusion time may be extended by an additional 15 minutes.

Exercise care in the handling and preparation of solutions prepared with belinostat.

6.4 Concomitant Medications and Therapies

6.4.1 Prohibited Therapy

Due to the potential for interaction with either or both of the study drugs, the following medications will be prohibited:

- Anti-cancer systemic chemotherapy or biological therapy.
- Other investigational agents.
- Warfarin or other Coumadin derived anticoagulants
- Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5. Examples include certain benzodiazepines such as alprazolam and anti-seizure medications such as carbamazepine. Ultimately determination of drugs with a narrow therapeutic window is left to the discretion of the principal investigator.
- Known strong and moderate inducers or inhibitors of CYP3A4/5 and including grapefruit, grapefruit hybrids, pomelos, star-fruit, and Seville oranges.
    - Because it is minimally absorbed from the GI tract, loperamide for the management of diarrhea is allowed
- Any non-conventional alternative or herbal medicines. St. John's Wort, grapefruit, grapefruit hybrids, pomelos, star-fruit, and Seville oranges are prohibited.
    - *Conventional multivitamins, vitamins, and supplements may be permitted if deemed clinically necessary by the principal investigator.*
- Known strong inhibitors of UGT1A1
- Medications with a *known-risk* of inducing Torsades de Pointes (TdP) (refer to crediblemeds.org to identify medications with a known risk for TdP)
- Live vaccines

The following medications must be **used with caution** until study treatment has been permanently discontinued:

- Medications with a *possible risk* of Torsades de Pointes (TdP) (refer to crediblemeds.org to identify medications with a possible risk for TdP) should be used with caution on study treatment
    - *In circumstances of prolonged QTcF on study treatment, it is recommended that medications with possible risks of TdP be discontinued, if clinically possible*
- Medications that are known CYP3A4/5 substrates should be used with caution as concentrations of these medicines may be increased by ribociclib (a known moderate CYP3A4 inhibitor)
- Strong inhibitors of BSEP (based on in vitro data co-administration with ribociclib may lead to intrahepatic cholestasis)
- Sensitive substrates of MATE1, OCT2, and BCRP (ribociclib has the potential to increase exposure to substrates of these transporters, although no animal or clinical data are available)

6.5 Duration of Therapy

Subjects will receive combined treatment until intolerable toxicity or confirmed disease progression.

All subjects will be followed for 30 days after the last dose of study medication for adverse events.

6.5.1 Criteria for discontinuation of treatment ("off treatment")

Patients may withdraw from treatment or the study overall at any time at their own request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in Dose Modification Section and the Dose Limiting Toxicity Section, the following will result in treatment discontinuation:

- Disease progression
- Unacceptable Toxicity
- Subject withdraws from the study treatment and/or study procedures.
- Non-compliance
- Pregnancy
- Study terminated by investigator sponsor
- Subject is lost to follow-up.
- Death.

6.5.2 Criteria for discontinuation of study ("off study")

Subjects will be taken off study for the following:

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol. Noncompliance will be defined by the investigator
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Participant withdraws consent to all study participation.
- Initiation of subsequent anticancer therapy.
- Death.
- Screen failure.

7 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting.

7.1 Dose Modifications and Guidelines for Adverse Event Management

7.1.1 Dose Modifications

Doses may not be lowered below dose level 0 for either drug (see Table 1). If ribociclib is discontinued, then belinostat must also be discontinued. If belinostat is discontinued, ribociclib may be continued at the investigator's discretion.

If doses are delayed for more than 6 weeks for any reason, then the subject will be taken off study. If ribociclib is interrupted, it may be restarted once the reason for interruption has resolved. If belinostat is interrupted and all 5 infusions cannot be completed within 7 days, belinostat will be resumed at the start of the subsequent cycle. Belinostat may be restarted once the criteria for resuming belinostat in Table 3 have been met.

Note: Patients who experience a dose limiting toxicity during the DLT defined period will be discontinued from study therapy. See Section 4.2 for details.

7.1.2 Guidelines for Management of Adverse Events

Table 3: Guidelines for Adverse Event Management

Event	CTCAE.v5.0 Grade	Ribociclib Modification	Belinostat Modification
Neutrophil Count Decreased	Grade 3*	Dose interruption until ANC >1000/mcL. Resume at same dose level. If grade 3 toxicity recurs, then dose interruption until ANC > 1000/mcL and then reduce ribociclib by one dose level.	Dose interruption until ANC > 1000/ mcL. Resume at the same dose. If grade 3 toxicity recurs, then dose interruption until ANC > 1000/mcL and then reduce belinostat by one dose level
	Grade 4*	Dose interruption until ANC > 1000/mcL. Reduce ribociclib by one dose level.	Dose interruption until ANC > 1000/mcL. Reduce belinostat by one dose level.
Platelet Count Decreased	Grade 3*	Dose interruption until Platelets>50,000/mcL. Resume at same dose level. If grade 3 toxicity recurs, then dose interruption until Platelets > 50/mcL and then reduce ribociclib by one dose level.	Dose interruption until platelets count > 50,000/mcL. Reduce belinostat by one dose level
	Grade 4*	Dose interruption until Platelets>50,000/mcL. Reduce ribociclib by one dose level.	Dose interruption until platelets count > 50,000/mcL. Reduce belinostat by one dose level

Febrile Neutropenia	Grade 3*	Dose interruption until ANC > 1000/mcL. Reduce ribociclib by one dose level.	Dose interruption until ANC > 1000/mcL. Reduce belinostat by one dose level.
AST and/or ALT elevation without bilirubin increase above 2 x ULN	Grade 2	Dose interruption until grade ≤1. Reduce ribociclib by one dose level. Repeat LFTs twice a week after dose resumption.	No adjustment
	Grade 3*	Dose interruption until grade ≤1. Reduce ribociclib by one dose level. Repeat LFTs twice a week after dose resumption.	Dose interruption until grade ≤1. Reduce belinostat by one dose level.
	Grade 4*	Discontinue ribociclib	Discontinue belinostat
AST and/or ALT elevation with bilirubin increase above 2 x ULN in the absence of biliary obstruction	Grade 1-4*	Discontinue ribociclib	Discontinue belinostat
Total bilirubin without ALT/AST increase above baseline values	Grade 1	Monitor LFTs every 2 weeks	Monitor LFTs every 2 weeks
	Grade 2	Dose interruption until grade ≤1. Reduce ribociclib by one dose level Repeat LFTs twice a week after dose resumption.	Dose interruption until grade ≤1. Reduce belinostat by one dose level Repeat LFTs twice a week after dose resumption.
	Grade 3*	Dose interruption until grade ≤1. Reduce ribociclib by one dose level	Dose interruption until grade ≤1. Reduce belinostat by one dose level

		Repeat LFTs twice a week after dose resumption.	Repeat LFTs twice a week after dose resumption.
	Grade 4*	Discontinue ribociclib	Discontinue belinostat
Electrocardiogram QT corrected interval prolonged	Grade 2	1st Occurrence at current dose level: Dose interruption until QTcF < Grade 2 on repeat ECG. Analysis of serum potassium, calcium, phosphorus, and magnesium should be performed. If values are below lower limit of normal, adequate corrective measures should be taken. Any corrected lab values should be re-checked prior to resuming dosing. Resume at same dose level. 2nd Occurrence at current dose level: Dose interruption until QTcF < Grade 2 on repeat ECG and then reduce ribociclib by one dose level.	Dose interruption until QTcF < Grade 2 on repeat ECG. Analysis of serum potassium, calcium, phosphorus, and magnesium should be performed and if values are below lower limit of normal, adequate corrective measures should be taken. Any corrected lab values should be re-checked prior to resuming dosing. Resume at same dose level.

	Grade 3*	Dose interruption until QTcF < Grade 2 on repeat ECG. Reduce ribociclib by 1 dose level. Analysis of serum potassium, calcium, phosphorus, and magnesium should be performed and if values are below lower limit of normal, adequate corrective measures should be taken. Any corrected lab values should be re-checked prior to resuming dosing. ECG should be repeated weekly for two weeks after dose resumption for any patient who had therapy interrupted due to Grade 3 QT prolongation.	Dose interruption until QTcF < Grade 2 on repeat ECG. In case of QT prolongation, analysis of serum potassium, calcium, phosphorus, and magnesium should be performed and if values are below lower limit of normal, adequate corrective measures should be taken. Any corrected lab values should be re-checked prior to resuming dosing. Reduce belinostat by 1 dose level.
	Grade 4*	Discontinue ribociclib	Discontinue belinostat
Diarrhea	Grade 1-2	Initiate loperamide Analysis of serum potassium, calcium, phosphorus, and magnesium, should be performed and if values are below lower limit of normal, adequate corrective measures should be taken.	Initiate loperamide Analysis of serum potassium, calcium, phosphorus, and magnesium, should be performed and if values are below lower limit of normal, adequate corrective measures should be taken.
	Grade 3*	Dose interruption until grade ≤ 1 for 24 hours. Analysis of serum potassium, calcium, phosphorus, and magnesium, should be	Dose interruption until grade ≤ 1 for 24 hours. Analysis of serum potassium, calcium, phosphorus, and

		performed and if values are below lower limit of normal, adequate corrective measures should be taken. Reduce ribociclib by 1 dose level	magnesium, should be performed and if values are below lower limit of normal, adequate corrective measures should be taken. Reduce belinostat by 1 dose level
	Grade 4*	Dose interruption until grade ≤ 1 for 24 hours. Analysis of serum potassium, calcium, phosphorus, and magnesium should be performed and if values are below lower limit of normal, adequate corrective measures should be taken. Reduce ribociclib by 1 dose level	Dose interruption until grade ≤ 1 for 24 hours. Analysis of serum potassium, calcium, phosphorus, and magnesium should be performed and if values are below lower limit of normal, adequate corrective measures should be taken. Reduce belinostat by 1 dose level
ILD/pneumonitis	Grade 1 (asymptomatic)	Monitor as clinically appropriate	No change
	Grade 2 (symptomatic)	Dose interruption until grade ≤1. Reduce ribociclib by 1 dose	No change
	Grade 3-4*	Discontinue ribociclib	No change
Other AEs	Grade ≥ 3*	Dose interruption until recovery to grade 1 or baseline. If possibly related to ribociclib, reduce ribociclib dose by 1 dose level.	Dose interruption until recovery to grade 1 or baseline. If possibly related to belinostat, reduce belinostat dose by 1 dose level.
*AE may be classified as a DLT. Refer to Section 4.2 for details.			

7.2 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study. The use of granulocyte-colony stimulating factors is not permitted during study participation except to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

7.3 Contraception

Women of child-bearing potential must use appropriate methods of birth control from the start of study therapy until 6 months after the last dose of study medication. Appropriate forms of birth control include oral or implanted contraceptives, intrauterine device (IUD), diaphragm with spermicide, cervical cap, abstinence from heterosexual intercourse, use of a condom by the sexual partner, sterile sexual partner, and also based on the judgment of the investigator.

Male subjects with partners of childbearing potential will be advised to use an effective form of contraception from the start of study therapy until three months after the last dose of study therapy.

8 SCHEDULE OF EVENTS

The Schedule of Events table provides an overview of the protocol visits and procedures. Refer to the Study Procedures section of the protocol for detailed information on each assessment required for compliance with the protocol. The Investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Events table in order to conduct evaluations or assessments required to protect the wellbeing of the patient. This Schedule of Events will be followed for the entire study.

Table 4: Schedule of Events

1 cycle = 28 days	**Screening** [1]	**Cycle 1**				**Cycle 2**				**Cycle 3+ (Odd)**	**Cycle 4+ (Even)**	**EOT Visit**[2]	**Safety Visit** [3]	**Follow-up**
Day of the cycle Window (days)		**1**	**8** [4] (± 3)	**15** (± 3)	**22** (± 3)	**1** (± 3)	**8** [4] (± 3)	**15** (± 3)	**22** (± 3)	**1** (± 7)	**1** (± 7)			
Informed Consent	X													
Medical History	X													
Concomitant Medication History	X													
Eligibility Review	X													
Vitals [5]	X	X	X	X		X	X	X		X	X	X		
Physical Exam with ECOG Performance Status	X	X				X				X	X	X		
Complete Blood Count (CBC) with Differential[6]	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry [7]	X	X		X		X		X		X	X	X		
Pregnancy Test (Serum/Urine) [8]	X													
12 Lead ECG [9]	X	X	X	X		X	X	X				X		
Disease Assessment [10]	X									X				
Fresh Tissue Biopsy [11]	X							X				X		
Blood for germline control[12]	X													
Belinostat Administration[13]		X				X				X	X			
Ribociclib Dispensation[14]		X				X				X	X			
Adverse Events and Concomitant Medications Review	X	X										X	X	
Progression Status Review [15]														X

[1] All Pre-study/Screening procedures should be completed within 28 days of study enrollment - with the exception of laboratory tests which need to be completed within 2 weeks prior to study enrollment.

[2] To be conducted when the decision to discontinue treatment in made.

[3] Patients should come to clinic or be contacted by phone or email 30 days (+7 days) after their last dose of study therapy to follow up on any ongoing or new adverse events.

[4] Day 8 assessments are only required for patients in dose escalation.

[5] Vitals include weight, blood pressure, pulse, respiratory rate, O_2 saturation and temperature. Vitals will be completed prior to study drug administration at each visit. Height is only required at screening. Weight (kg) will be recorded at Screening, Day 1 of all cycles, and at the end of study treatment. BSA (m2) will be used to calculate belinostat dosing using screening height and weight recorded. BSA must be recalculated for weight changes ≥ 10%. Height from screening or another day may be used when recalculating belinostat dose.

[6] Blood counts will be monitored weekly for the first two cycles. If cytopenias requiring dose interruptions/reductions are not encountered during the first two cycles, blood counts may be checked on day one of every cycle. If a dose reduction for hematologic toxicity is needed, CBC should be checked weekly the following cycle. All safety laboratory assessments may be performed up to 3 days prior to the scheduled clinic visit and must be reviewed by the treating investigator prior to Day 1 study drug administration.

[7] Chemistry includes magnesium, phosphorus, and a CMP (Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Total Potassium, Protein, Sodium, and Urea Nitrogen). All safety laboratory assessments may be performed up to 3 days prior to the scheduled clinic visit and must be reviewed by the treating investigator prior to Day 1 study drug administration.

[8] Pregnancy test (serum or urine; if urine is positive it must be confirmed with serum test) must be obtained at screening for all women of childbearing potential and as clinically indicated while on treatment.

[9] In the event that the QTcF is prolonged (≥ Grade 2), the ECG should be repeated in triplicate with readings two minutes apart. Dose modifications section should be consulted if the mean QTcF is > 480 ms. On ribociclib dispensation days (i.e. C1D1 and C2D1 for dose levels 0 and 1B, C1D8 and C2D8 for dose levels 1A and 2), an ECG must be completed pre-ribociclib dose and 1 to 8 hours post-ribociclib dose. On all other days of ribociclib treatment, the ECG must be obtained between 1 hour and 8 hours post-ribociclib dose.

[10] Disease assessments should be conducted every 8 weeks, 7 days prior to the beginning of the next cycle to allow for timely result review for the treating investigator. Use of contrast according to institutional practice is recommended but not required. MRI of chest, abdomen, and pelvis may be substituted for CT, if determined to be clinically indicated by treating investigator. The same imaging modality should be used consistently for each patient.

[11] Fresh tissue biopsy at baseline and C2D15 are required. Baseline biopsies of all safely accessible tumors (metastases or primary) up to a maximum of 3 sites should be performed. Baseline biopsy to be performed ≤ 14 days before cycle 1 day 1 and C2D15 biopsy to be performed on C2D15 (±3 days). EOT biopsy is recommended but optional. The C2D15 biopsy and EOT biopsy can be a single site but should be one of the sites biopsied at baseline. Biopsies must be performed as core needle biopsies. Acceptable sites include breast, superficial lymph node such as axilla, cervical, or inguinal, subcutaneous nodules, peripheral liver, pleura, omentum, or similar risk areas.)

[12] Blood should be collected at the time of biopsy (+/-7 days).

[13] Belinostat administration on 5 consecutive days is preferred. However, administration within 7 days is allowed as needed to accommodate holidays, infusion schedules, or other unforeseen circumstances.

[14] Ribociclib should be dispensed on day 8 of cycles 1-2 for dose levels 1A and 2 in the dose escalation phase.
[15] For patients who discontinue treatment for any reason other than progression, follow up phone call or medical record review will be performed every three months after the EOT visit for 2 years or until disease progression or initiation of an alternative anti-cancer therapy.

10 STUDY PROCEDURES

10.1 Screening

For screening procedures see the Schedule of Events and the Assessments Section. Screening activities may only begin after a subject has signed consent. All screening activities must take place within 28 days prior to cycle one day one, unless otherwise noted.

10.2 Treatment Period

Once a subject has completed screening, has been found to be eligible, and has been registered, treatment procedures may begin. See the Schedule of Events and the Assessments Section for treatment period procedures.

10.3 End of Treatment

Upon discontinuation of study treatment an End of Treatment visit will occur. The end of treatment visit should occur when the decision to discontinue treatment is made. If this visit overlaps with a regularly scheduled visit, only the procedures listed in the calendar for the EOT visit will be performed. For End of Treatment procedures see the Schedule of Events and the Assessments Section.

10.4 Safety Visit

If possible, all patients should return to clinic 30 days (+7 days) after their last dose of study medication for adverse event assessment. If a patient is not willing or unable to return to clinic for this visit, the study team should make every effort to contact the patient by phone or email for adverse event collection.

10.5 Follow-Up

Patients that discontinue study treatment for any reason other than disease progression, must be followed until disease progression or initiation of a different anti-cancer therapy every 3 months via medical record review, email, or telephone call for 2 years.

11 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

11.1 Physical Examinations and Vital Signs

Patients will have physical examinations to include major body systems, vital signs, assessment of ECOG performance status (see Appendix 0), weight and height (height will be measured at screening only) at the time points described in the Schedule of Events. If necessary to facilitate scheduling, physical exam may occur two business days prior to study treatment, including Cycle 1 Day 1.

Vital signs, to include blood pressure, pulse rate, respiratory rate, O_2 saturation, and temperature will be also recorded at the time points described in the Schedule of Events. Vital signs should be taken prior to administration of any investigational products at the visit.

11.2 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Events and Adverse Events Section. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner. Should the treating investigator feel that the adverse event is attributed to study therapy, then dose modification guidelines in the Section 7.1 will be followed.

11.3 12-Lead Electrocardiograms

All patients require a single 12-lead ECG measurement according to the Schedule of Events. The parameters to be recorded are QT, QTc, PR, and QRS. A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. If the QTcF is prolonged (≥ Grade 2) then a triplicate ECG should be conducted with two minutes between readings. If the mean QTcF prolongation is ≥ Grade 2, follow dose modification guidelines in Section 7.1. On C1D1 and C2D1, an ECG must be completed pre-ribociclib dose and 1 to 8 hours post-ribociclib dose. On all other days of ribociclib administration when an ECG is indicated by the study calendar, an ECG will be obtained between 1 hour and 8 hours post-ribociclib dose.

11.4 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the Study Calendar and when clinically indicated. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit, including Cycle 1 Day 1. Safety laboratory analyses will be performed by the local laboratory for each study center. Safety laboratory analyses on Day 22 of Cycles 1-2 may be completed at an outside laboratory facility. All safety laboratory assessments must be reviewed by the treating investigator prior to study drug administration on Day 1 of each cycle. When applicable, results from the pregnancy test must also be available for review prior to dosing.

Table 5: Laboratory Assessments

Laboratory Assessments

CBC with Platelet Count and Differential (Hematology)	• White Blood Cell Count • Hemoglobin • Platelets • Absolute Neutrophil Count • Absolute Lymphocytes

Chemistry	• Complete Metabolic Panel
	  ○ Sodium
	  ○ Potassium
	  ○ Chloride
	  ○ Carbon Dioxide
	  ○ Alkaline Phosphatase
	  ○ Aspartate Aminotransferase
	  ○ Alanine Aminotransferase
	  ○ Urea Nitrogen
	  ○ Glucose
	  ○ Creatinine
	  ○ Calcium
	  ○ Protein
	  ○ Albumin
	  ○ Bilirubin
	  ○ Anion Gap
	• Magnesium
	• Phosphorus

Pregnancy	Beta-hCG Qualitative Urine or Serum

11.5 Disease Assessment

The decision for body areas to be scanned will depend on the disease under study and the extent of disease. Tumor assessments must include all known or suspected disease sites. The minimum recommended body areas to be scanned are chest, abdomen, and pelvis. Antitumor activity will be assessed through radiological tumor assessments conducted at baseline (within 28 days prior to cycle one day one), then every 8 weeks (±7 days) from cycle one day one until disease progression or initiation of subsequent anti-cancer therapy. After 6 cycles, imaging frequency can be decreased to every 12 weeks. In addition, radiological tumor assessments will be conducted whenever disease progression is suspected (eg, symptomatic deterioration) or when clinically indicated. The schedule of tumor assessments should be fixed according to the calendar, starting with cycle one day one, regardless of treatment schedule or treatment delays or interruptions due to toxicity.

Brain CT or MRI scans are required at baseline for all patients with stable brain lesions and for those for whom Central Nervous System (CNS) involvement is suspected. If stable brain metastases are present at baseline, brain imaging should be repeated at each tumor assessment. Otherwise, brain imaging will be conducted post-baseline only when clinically indicated.

The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

11.6 Fresh Tissue Biopsy

All sites safely accessible in the judgment of the investigator should be biopsied, up to a maximum of 3. Biopsies are required at screening (≤14 days prior to cycle one day one) and at cycle two day 15 (± 3 days). An optional biopsy will also be offered to all patients at the time of treatment discontinuation (+ 7 days of the end of treatment visit). The biopsies at cycle two day 15 and end of treatment can be from a single site but should be one of the sites biopsied at baseline. Biopsies must be performed as core needle biopsies. Acceptable sites include breast, superficial lymph node such as axilla, cervical, or inguinal, subcutaneous nodules, peripheral liver, pleura, omentum, or similar risk areas.) Refer to the laboratory manual for specimen processing detail.

12 CRITERIA FOR EVALUATION AND ENDPOINT

12.1 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained in the sitting position.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the flow chart.

PFS and response rate are a secondary objectives for this trial. Disease assessments will be measured by CT scans and evaluated using on RECIST v1.1 criteria. The following definitions and criteria should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor responses.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter (LD) ≥ 10 mm using CT, MRI, or caliper measurements or ≥20 mm with x-ray. A lymph node must be ≥15 mm in short axis when assessed by CT scan

Non-measurable lesions - all other lesions including small lesions (LD < 10 mm with CT, MRI, or caliper measurements or <20 mm with x-ray).

Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of two lesions per organ and five 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).
- A sum of the LD for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.2 Response Criteria:

Table 6: Evaluation of target lesions

	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions (Must persist for a minimum of four weeks)
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD (Must persist for a minimum of four weeks)
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Table 7: Evaluation of Non-target Lesions

	Evaluation of non-target lesions
Complete Response (CR)	Disappearance of all non-target lesions

Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

12.2.1 Evaluation of Best Overall Response

The best overall response is the best response observed until progression/recurrence and is determined as indicated in the table below:

Table 8: Evaluation of Best Overall Response

Target Lesions	**Non-Target Lesions**	**Evaluation of New Lesions**	**Best Overall Response**
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Efficacy will be evaluated by progression-free survival and the objective response rate.

12.2.2 Progression Free Survival

PFS is a secondary endpoint on this study. It is determined from the time of enrollment until disease progression or death (any cause). Patient data will be censored as detailed in Table 9.

Table 9: PFS Censoring Criteria

Situation	**Date of Progression or Censoring**	**Outcome**
Incomplete or no baseline tumor assessments	Date of registration	Censored

Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment.	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
New anticancer treatment started without disease progression	Date of last progression assessment with documented non-progression before start of new treatment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with documented non-progression	Censored

12.3 Stopping Rules

Refer to section 4.2 for the definition and evaluation of Dose Limiting Toxicities.

During the dose-escalation cohort, the trial will be stopped if the dose level 0 is found to exceed the MTD per the rules in section 4.3, table 3. During the dose-expansion cohort, we will review the toxicity every 3 subjects using a Bayesian approach. The criteria for termination during dose expansion is greater 95% Bayesian posterior probability that the true proportion of subjects with DLT in the first cycle is greater than 20%. A "non-informative" uniform prior distribution for DLT is used. The table below gives the minimum number of DLTs to stop the study for excess toxicity.

Table 10: Dose Expansion Stopping Rules

Number of Subjects (including patients in the dose-escalation)	Minimum number of DLTS needed to terminate
6	3

7	4
8	4
9	**4**
10	5
11	5
12	**5**
13	5
14	6
15	**6**

13 STATISTICAL CONSIDERATIONS

13.1 Statistical Plan

Primary Objective and Endpoints

The primary objective is to assess the safety and tolerability of Ribociclib + Belinostat in the study population and to access the MTD. The rate of dose-limiting toxicities (DLTs) is the primary endpoint.

The dose-escalation cohort will be conducted using a 3+3 design modified to account for the fact that Dose Level 1A and 1B are not strictly ordered. Dose Level 1A represents an increase in the ribociclib dose from dose level 0 while 1B represents an increase in the belinostat dose from dose level 0. The complete dose escalation scheme is described in Section 4.

Table 11: Probability of Escalation to Dose Level 2

Lower True level 1 DLT Probability = 0%											
HigherTrue Level 1 DLT Probability	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Probability of Escalation	1	0.906	0.709	0.492	0.311	0.172	0.083	0.031	0.009	0.001	0
Lower True level 1 DLT Probability = 10%											
HigherTrue Level 1 DLT Probability	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	
Probability of Escalation	0.82	0.642	0.45	0.283	0.156	0.076	0.03	0.008	0.001	0	

Lower True level 1 DLT Probability = 20%									
HigherTrue Level 1 DLT Probability	20%	30%	40%	50%	60%	70%	80%	90%	100%
Probability of Escalation	0.505	0.349	0.219	0.124	0.059	0.023	0.006	0.001	0

Lower True level 1 DLT Probability = 30%								
HigherTrue Level 1 DLT Probability	30%	40%	50%	60%	70%	80%	90%	100%
Probability of Escalation	0.247	0.152	0.086	0.041	0.016	0.004	0.001	0

Lower True level 1 DLT Probability = 40%							
HigherTrue Level 1 DLT Probability	40%	50%	60%	70%	80%	90%	100%
Probability of Escalation	0.096	0.053	0.025	0.01	0.003	0	0

Lower True level 1 DLT Probability = 50%						
HigherTrue Level 1 DLT Probability	50%	60%	70%	80%	90%	100%
Probability of Escalation	0.03	0.014	0.005	0.001	0	0

Lower True level 1 DLT Probability = 60%					
HigherTrue Level 1 DLT Probability	60%	70%	80%	90%	100%
Probability of Escalation	0.007	0.003	0.001	0	0

Lower True level 1 DLT Probability = 70%				
HigherTrue Level 1 DLT Probability	70%	80%	90%	100%
Probability of Escalation	0.001	0	0	0

Lower True level 1 DLT Probability = 80%

HigherTrue Level 1 DLT Probability	80%	90%	100%
Probability of Escalation	0	0	0

For the dose-expansion cohort, analyses will be combined with the 6 patients at the MTD, for a total of 16 patients at MTD. These 16 patients give 80% power to detect any adverse event that occurs with a frequency of at least 10%.

Secondary Objective and Endpoints

A secondary endpoint is safety as summarized by the frequency of adverse events. All subjects who receive any study treatment will be included in the final summaries and listings of safety data. Detailed information collected for each AE will include a description of the event, duration, severity, relatedness to study drugs, action taken, and clinical outcome. Severity of the AEs will be graded according to the CTCAE version 5.0. The statistical analysis of the safety data will be descriptive and tabular in nature.

The other secondary objectives are to assess the response rate (PR and CR) and estimate PFS in the study population and subgroups defined by RB1 mutation status. PFS will be estimated using Kaplan-Meier methods. The proportion of subjects in each response category will be reported along with a 95% exact binomial confidence interval computed using the Clopper-Pearson method.

For triple-negative breast cancer, there are no options other than chemotherapy or atezolizumab, so for efficacy, we will focus on estimating the objective response rate and PFS at various timepoints. We will report the ORR and its 95% exact binomial confidence interval (Clopper-Pearson). The table below gives the confidence intervals based on the number of responses seen in 16 patients:

Table 12: Confidence Intervals Based on Observed Response

Count	count as percentage	lower bound on percent	upper bound on percent	half interval size
0	0	0.00	20.59	10.30
1	6	0.16	30.23	15.04
2	13	1.55	38.35	18.40
3	19	4.05	45.65	20.80
4	25	7.27	52.38	22.56
5	31	11.02	58.66	23.82
6	38	15.20	64.57	24.68
7	44	19.75	70.12	25.18
8	50	24.65	75.35	25.35
9	56	29.88	80.25	25.18
10	63	35.43	84.80	24.68
11	69	41.34	88.98	23.82
12	75	47.62	92.73	22.56

13	81	54.35	95.95	20.80
14	88	61.65	98.45	18.40
15	94	69.77	99.84	15.04
16	100	79.41	100.00	10.30

Exploratory Objective and Endpoints

- To develop a multi-gene expression based biomarker and evaluate its predictive accuracy.

  Biopsy tissue will be processed for single cell RNA and DNA sequencing. Sequencing patterns will be analyzed in multiple ways as specified in our U54 grant from the Cancer Systems Biology Consortium. These analyses will be correlated with response and survival to identify possible predictors of benefit.

- To explore how subclonal structure and phenotypic pathway activation varies in different sites of the cancer.

  The aims of our U54 grant from the Cancer Systems Biology Consortium include determining the variability of subclonal structure of tumors across space and time. The single cell sequencing data from each biopsy will be used to reconstruct the genomic and phenotypic subclones present at each site.

- To assess efficacy within subgroups defined by RB1 mutation.

  Because RB1 mutation has been proposed as a resistance marker for CDK4/6 inhibitors, we will compare response rate and PFS between patients with and without RB1 mutations. This analysis will be primarily descriptive as the presence of RB1 mutation is expected to be low with potentially only 1 or 2 people having the mutation.

13.2 Population for analyses

13.2.1 Evaluable for primary endpoint

Patients who have received one belinostat infusion and taken 50% of the required ribociclib during the DLT period will be considered evaluable for the MTD. Patients who do not meet the defined level of compliance will be replaced.

13.2.2 Evaluable for safety

Patients who have received one dose of each medication will be included in the safety data set.

13.2.3 Evaluable for response

Patients who have received one dose of each study medication will be considered evaluable for all efficacy analysis.

14 REGISTRATION GUIDELINES

Subjects must meet all of the eligibility requirements before registration. Study-related screening procedures can only begin once the subject has signed the consent form. Subjects must not begin protocol treatment prior to registration.

Treatment should start as soon as logistically possible after registration.

To register eligible subjects on study, complete a Clinical Trials Office Subject Registration Form and submit to CTORegistrations@hci.utah.edu.

For sites outside of Huntsman Cancer Institute, submit registration forms to MultisiteRegistrations@hci.utah.edu

15 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.

16 SPECIAL INSTRUCTIONS

16.1 Correlative Science

16.1.1 Tissue Collection

Fresh tissue biopsies will be performed at the time points indicated in the Schedule of Events. Up to four cores will be collected at each biopsy according to institutional standards. These tissues will be used to establish a biomarker panel predictive of treatment efficacy which will be validated in future clinical trials.

Testing may include, but is not limited to:

- Multiomics platforms
- Immunohistochemistry
- Flow cytometry

Specimen collection and processing instructions can be found in the lab manual.

16.1.2 Blood Collection

Up to 10 mLs of blood will be collected at the time points indicated on the Schedule of Events. These samples will be used to establish a germline control.

Testing may include, but is not limited to:

- Genome analysis

Specimen collection and processing instructions can be found in the lab manual.

17 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Human Subject Protections

The study will be conducted in accordance with the appropriate FDA, IRB, ICH GCP and other federal and local regulatory requirements, as applicable. Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version. All patients must be at least 18 years of age to participate.

17.2 Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other applicable patient-facing documents. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information.

The investigator or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

17.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a Phase I study classified as high risk per the NCI-approved DSM plan.

Each high-risk study will be assigned a physician member of the DSMC as medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all

serious adverse events (SAEs). Specific notifications will also be issued when a dose-limiting toxicity is encountered and when the MTD dose is defined. Approval of the medical monitor is required for all dose escalations. All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly.

Each high-risk study will also be assigned a dedicated research compliance officer who will monitor the trial. High-risk studies will be monitored by RCO personnel after the first patient is enrolled and every three months thereafter during active enrollment. The RCO monitor will review the study status and summarize enrollment, toxicities, SAEs, dose escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments which increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. High-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then quarterly thereafter.

An initial audit of high-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of high-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

17.4 Adverse Events and Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

17.4.1 Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Collection of adverse events will begin from the time of consent and end 30 days after the last dose of study drug (or until a new cancer treatment is initiated).

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade based on CTCAE v.5.0 (grade 1-5)
- Its relationship to the study drug(s) (definite, probable, possible, unlikely, not related)
- Its duration (start and end dates or if continuing at final exam)
- Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 8 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about ribociclib and belinostat are described in the Drug Information (section 3) and the current product insert for ribociclib and belinostat. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

17.4.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug

- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Collection of serious adverse events will begin after signature of the treatment ICF and end 90 days after the last dose of study treatment or upon initiation of a new cancer treatment.

Any death from any cause while a patient is receiving treatment on this protocol or up to 90 days after the last dose of protocol treatment must be reported. Any death which occurs more than 90 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

17.5 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, Novartis, and Acrotech Pharmaceuticals, according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to HCI-RCO@utah.edu as soon as possible, but no later than 1 working day of first knowledge or notification of event.

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study. The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

The HCI DSMC will notify all participating sites of all unexpected and related SAEs via the Research Compliance Office (RCO). The RCO will also notify all investigators at remote clinical sites participating in a multisite trial of any other safety updates, including external safety reports, manufacturer's reports, and updates to the investigator's brochure.

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FDA Notifications:

- Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:
- Serious
- Unexpected
- Definitely, Probably or Possibly Related to the investigational drug

- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.
- The Regulatory Coordinator will submit the report as an amendment to the IND application.
- All other adverse events and safety information not requiring expedited reporting that occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.

IRB Notification:

Events meeting the University of Utah IRB reporting requirements (http://www.research.utah.edu/irb/) will be submitted through the IRB's electronic reporting system within 10 working days.

Novartis Notifications:

The principal investigator has the obligation to report all serious adverse events to the FDA (if applicable), IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E)

Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment, complete the SAE Report Form in English, and send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) or provided by e-mail to clinicalsafetyop.phuseh@novartis.com within 24 hours.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the

blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries

Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be reported by the investigator to the Novartis Oncology Drug Safety and Epidemiology Department (DS&E) by fax **(fax: 877-778-9739)**. Pregnancy follow-up should include an assessment of the possible relationship to the investigational product of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

<u>Acrotech Notifications:</u>

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the investigator must report the event to the Acrotech Biopharma Drug Safety group, Licensing authority and ethics committee. Sponsor with investigator shall send SAE report after due analysis to licensing authority, ethics committee and head of the institute where the trial is being conducted within 14 calendar days A follow up report shall be sent to sponsor, Licensing authority, and head of the institute where the trial is conducted within 14 days of the occurrence of a serious adverse event which shall include outcome and treatment provided. If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE. All SAE shall be notified to all participating investigators in the study.

The study center must transmit the SAE form to the Acrotech Biopharma Drug Safety group at the e-mail address: drugsafety@acrotechbiopharma.com, Licensing Authority and Ethics committee which accorded approval at your site. Even if an initial report is made aware by the site personnel telephonically (SAE phone number +1-732-839-9400) to the sponsor

representative, an SAE form completed with all available details must still be faxed within 24 hours of knowledge of the event at the study center.

Supplemental information shall be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission, and emergency room notes, treatments administered for the events, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The investigator is expected to take all therapeutic measures necessary for the resolution of the SAE. Any medications or procedures necessary for the treatment of the SAE must be recorded on the appropriate pages of the patient's SAE form. All SAEs are to be followed up by the study staff until resolution or until the SAE is deemed stable. The Sponsor may contact the study center to solicit additional information or follow up on the event.

In the case of an SAE, the investigator at each site must complete, sign and date the appropriate SAE form pages, check that the data are consistent, and send a copy (within 24 hours) to drugsafety@acrotechbiopharma.com

The information must include at least the following

- Name, address, and telephone number of the reporting Investigator.
- Study drug and Protocol Number.
- Patient identification number, initials, sex, and date of birth.
- Description of the SAE, measures taken, and outcome.
- Preliminary classification of causal relationship by the Investigator.

17.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or within 30 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

17.7 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

17.8 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

17.9 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

17.10 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

17.11 Record Keeping

Per 21 CFR 312.57, the Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified. If for any reason the Investigator at another participating institution is no longer able to retain study records, the HCI Investigator Sponsor should be notified before any destruction so that the records can be transferred to an acceptable designee. Once retention requirements have been met, the participating site Investigator must get HCI Investigator Sponsor approval before the destruction of any records.

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Appendix 1: ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hour
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649–655.

Appendix 2: Ribociclib Dosing Diary

Subject Number: _____ Date: _____

Take ribociclib _____ mg [_____ tablet(s)] once daily (± 6 hours) with or without food. If you vomit on the same day as ribociclib administration, do not take any additional doses of ribociclib. Take the next planned dose at your regularly scheduled time. Missed doses beyond 6 hours after the regular scheduled administration time must be skipped and should not be replaced.

Date	Time	Number of tablets taken	Notes

Patient Signature

Date

Appendix 3: Strong CYP3A4 Inducers and Inhibitors

Strong CYP3A4 Inducers	Strong CYP3A4 Inhibitors	
Apalutamide	Atazanavir	Ketoconazole
Carbamazepine	Boceprevir	Loperamide
Enzalutamide	Clarithromycin	Lopinavir
Fosphenytoin	Cobicistat	Methimazole
Lumacaftor	Conivaptan	Midostaurin
Midostaurin	Curcumin	Naloxone
Mitotane	Danazol	Nefazodone
Pentobarbital	Danoprevir	Nelfinavir
Phenobarbital	Darunavir	Nilotinib
Phenytoin	Delavirdine	Posaconazole
Primidone	Diltiazem	Ritonavir
Rifabutin	Ditiocarb	Saquinavir
Rifampicin	Econazole	Stiripentol
Rifamycin	Efavirenz	Telaprevir
Rifaximin	Elvitegravir	Telithromycin
Rimexolone	Ergotamine	Terfenadine
St. John's Wort	Grapefruit juice	Tipranavir
	Idelalisib	Troleandomycin
	Indinavir	Voriconazole
	Itraconazole	

Appendix 4: Moderate CYP3A4 Inducers and Inhibitors

Moderate CYP3A4 Inducers	Moderate CYP3A4 Inhibitors	
Avasimibe	Abiraterone	Isavuconazonium
Bexarotene	Aprepitant	Isoniazid
Bosentan	Barnidipine	Isradipine
Dabrafenib	Benidipine	Linagliptin
Dexamethasone	Ciprofloxacin	Lovastatin
Echinacea	Clindamycin	Luliconazole
Efavirenz	Clozapine	Miconazole
Etravirine	Crizotinib	Milnacipran
Modafinil	Cyclosporine	Netupitant
Nafcillin	Danazol	Nicardipine
	Desvenlafaxine	Nilvadipine
	Dronedarone	Primaquine
	Erythromycin	Seproxetine
	Fluconazole	Simeprevir
	Fluvoxamine	Tioconazole
	Fosamprenavir	Venetoclax
	Fosnetupitant	Verapamil
	Fusidic acid	Voriconazole
	Haloperidol	Zimelidine
	Indalpine	Ziprasidone
	Isavuconazole	

Appendix 5: UGT1A1 Inhibitors

UGT1A1 Inhibitors	
Adenine	Pazopanib
Amitriptyline	Pexidartinib
Atazanavir	Pibrentasvir
Dacomitinib	Probenecid
Dasabuvir	Propofol
Deferasirox	Regorafenib
Eltrombopag	Rucaparib
Enasidenib	Silibinin
Erlotinib	Sodium aurothiomalate
Ertugliflozin	Sorafenib
Flunitrazepam	Ubrogepant
Flurbiprofen	Valproic acid
Fostamatinib	
Gemfibrozil	
Glecaprevir	
Indinavir	
Indomethacin	
Ketoconazole	
Nilotinib	
Ombitasvir	
Paritaprevir	

Appendix 6: Medications with a Known Risk for Torsades de Pointes

Generic Name	Brand Names (Partial List)
Amiodarone	Cordarone, Pacerone, Nexterone
Anagrelide	Agrylin, Xagrid
Arsenic trioxide	Trisenox
Azithromycin	Zithromax, Zmax
Bepridil	Vascor
Chloroquine	Aralen
Chlorpromazine	Thorazine, Largactil, Megaphen
Cilostazol	Pletal
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin
Citalopram	Celexa, Cipramil
Clarithromycin	Biaxin, Prevpac
Cocaine	Cocaine
Disopyramide	Norpace
Dofetilide	Tikosyn
Donepezil	Aricept
Dronedarone	Multaq
Droperidol	Inapsine, Droleptan, Dridol, Xomolix
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine
Fluconazole	Diflucan, Trican
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol
Hydroxychloroquine	Plaquenil, Quineprox
Ibutilide	Corvert
Levofloxacin	Levaquin, Tavanic
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon
Moxifloxacin	Avelox, Avalox, Avelon
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax
Oxaliplatin	Eloxatin
Papaverine HCl (Intra-coronary)	

Pentamidine	Pentam
Pimozide	Orap
Procainamide	Pronestyl, Procan
Propofol	Diprivan, Propoven
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora
Sevoflurane	Ultane, Sojourn
Sotalol	Betapace, Sotalex, Sotacor
Thioridazine	Mellaril, Novoridazine, Thioril
Vandetanib	Caprelsa