Ivy Brain Tumor Center
AT THE BARROW NEUROLOGICAL INSTITUTE

Ribociclib and Everolimus

Protocol # IVY 2018-01

NCT# 03834740

A Phase 0 /I Study of Ribociclib (LEE011) in combination with Everolimus in Preoperative Rb-Intact Recurrent High-Grade Glioma Patients Scheduled for Resection to Evaluate Central Nervous System (CNS) Penetration

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List of abbreviations

ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under the curve
AUC_{0-12}	area under the curve over the first 12 hours
AUC_{0-24}	area under the curve over the first 24 hours
AUC_{0-t}	area under the curve over the period of time to X hours
BCRP	breast cancer resistance protein
BLRM	Bayesian logistic regression model
BNI	Barrow Neurological Institute
BSEP	bile salt export pump
CERT	Center for Education and Research on Therapeutics
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CrCL	creatinine clearance
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interactions
DHEA	dehydroepiandrosterone
DLT	dose-limiting toxicities
DS&E	Drug Safety and Epidemiology
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ERK	extracellular signal-regulated kinase
EIAED	enzyme inducing anti-epileptic drug
FIH	first in human
FMO3	flavin-containing monooxygenase 3
GBM	glioblastoma multiforme
GI	gastrointestinal
HED	human equivalent dose
hERG	human Ether-a-go-go Related Gene
IHC	immunohistochemistry
IUD	intrauterine device
IUS	intrauterine system

LFT	liver function test
MATE1	multidrug and toxin extrusion protein 1
MCL	mantle cell lymphoma
MEK	mitogen-activated protein kinase kinase
MTD	maximally tolerated dose
mTOR	mammalian target of rapamycin
Non-EIAED	non-enzyme inducing anti-epileptic drug
NSCLC	non-small cell lung cancer
OATP1B1	organic anion transporting polypeptide 1B1
OCT1	organic cation transporter 1
OCT2	organic cation transporter 2
OTC	over-the-counter
P-gp	P-glycoprotein
PD	pharmacodynamics
PG	pharmacogenetic
PIK3	phosphoinositide 3-kinase
pRB	retinoblastoma protein
PK	pharmacokinetic
PO	by mouth
PPIs	proton pump inhibitors
PXR	pregnane X-receptor
QD	daily
RDE	research development and extension
RP2D	recommended phase 2 dose
SAE	serious adverse event
SBP	systolic blood pressure
SUSARs	Suspected Unexpected Serious Adverse Reactions
$T_{1/2}$	terminal elimination half-life
T_{max}	time to reach maximal plasma concentrations
ULN	upper limit of normal

1 Background

1.1 Overview of glioblastoma pathogenesis, epidemiology and current treatment

1.1.1 Glioblastoma

Primary brain tumors are among the top 10 causes of cancer-related deaths in the United States, accounting for approximately 1.4% of all cancers and 2.4% of all cancer-related deaths. About 14 per 100,000 people in the United States are diagnosed with a primary brain tumor each year, and 6 to 8 per 100,000 are diagnosed with a primary malignant brain tumor. Glioblastoma Multiforme (GBM) is the most frequently reported malignant brain tumor histology (29.6%) in the National Cancer Database. The prognosis for patients who develop GBM is bleak, with average survival after diagnosis ranging from 12-16 months. Although conventional treatment with surgery, irradiation, and temozolomide postpones tumor progression and extends patients survival, these tumors universally recur and unrelentingly result in patient death. Nevertheless, the alkylating agent temozolomide remains the single most effective adjuvant chemotherapy available for GBM patients.

1.1.1.1 Targeted therapies in glioblastoma

Glioblastoma

Glioblastoma is a uniformly fatal extremely heterogeneous disease. Tumor heterogeneity translates into histological patterns, genetic alterations and gene expression profiles. The current treatment for glioblastoma is maximal surgical resection, followed by radiation therapy with concurrent and adjuvant temozolomide (the Stupp regimen). Recent genetic molecular advances have contributed to a better understanding of glioblastoma pathophysiology. A multitude of potentially clinically-relevant genetic molecular alterations have been identified as targets for further drug development. Currently, however, there is no FDA-approved targeted therapy with demonstrated efficacy.

1.1.2 Rb-Positive and mTOR-positive tumors

Defective Retinoblastoma (RB) and mTOR pathway regulation in Glioblastomas

The mitogenic PI3K/mTOR and retinoblastoma (Rb, 13q14) pathway are two key regulatory machineries controlling proliferation and cell cycle progression. These 2 pathways converge on cyclin-D and Cyclin-dependent kinases (CDK) 4/6 regulatory complex at the G1-S phase transition checkpoint. CDKN2A, located on 9p21 and deleted in many cancers, encodes the Inhibitor of CDK4 (INK4, p16) protein, a key inhibitor of the cell cycle via inhibiting CDK4 activity, and its homozygous deletion is associated with WHO grade III or IV gliomas. Primary GBM often displays loss of the INK4A/ARF tumor suppressor gene locus along with mutations/deletions for PTEN, which encodes key suppressor for mTOR signaling. Together, the RB pathway is altered in 79% whereas PI3K/mTOR pathway is altered in 56% in GBM patients. In GBM, although mutations and homozygotic deletions of the RB1 gene itself appear in only 11% of them. Instead, the RB pathway is preferentially altered at components that lead to RB inactivation by hyper-

phosphorylation, which leads to suppression of its cell cycle blocker function. Together, this allows testing combination therapy with cell cycle as well as mitogenic pathway inhibitors.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of Ribociclib

[redacted]

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacology

[redacted]

1.2.1.1.2 Non-clinical pharmacokinetics (PKs) and metabolism

[redacted]

[redacted]

1.2.1.1.3 Safety pharmacology and toxicology

[redacted]

[redacted]

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety and tolerability

[redacted]

A complete list of AEs, all grades and Grade 3/4 occurring in at least 10% of patients and suspected to be related to ribociclib are shown in Table 2.

Table 1 Serious adverse events with a suspected causal relationship with ribociclib single agent

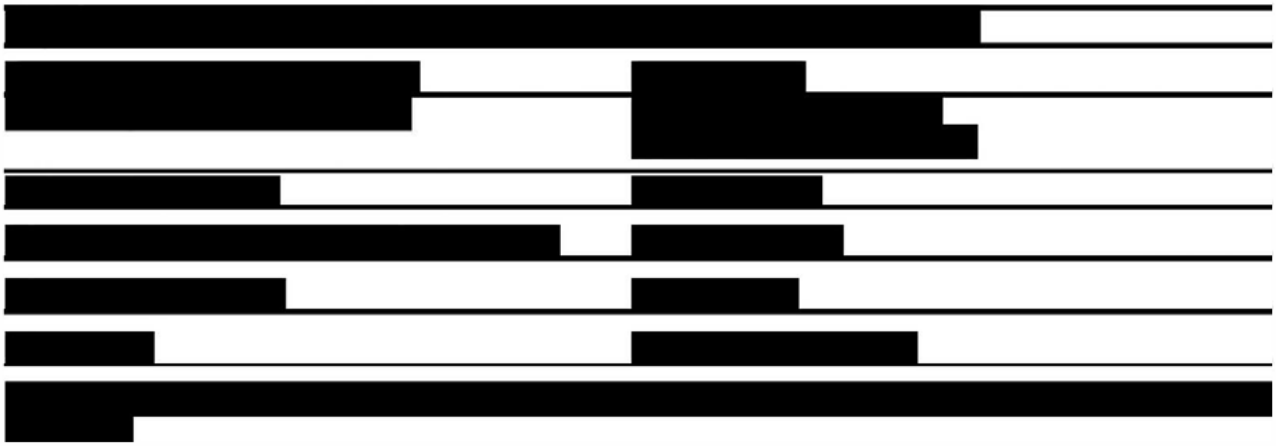
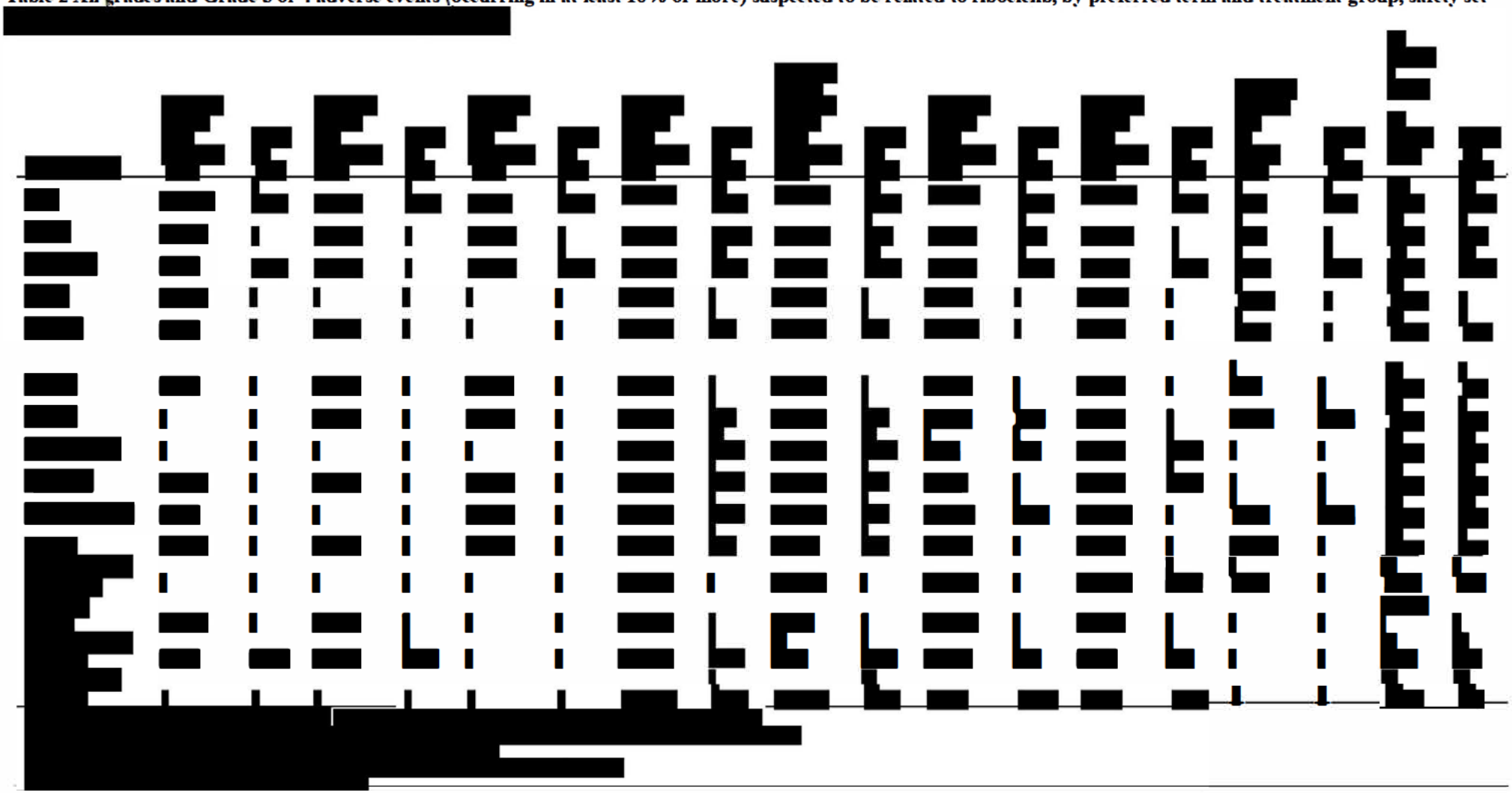


Table 2 All grades and Grade 3 or 4 adverse events (occurring in at least 10% or more) suspected to be related to ribociclib, by preferred term and treatment group, safety set



1.2.1.2.2 Clinical efficacy with ribociclib as single agent

[redacted]

[redacted]

1.2.1.2.3 Clinical efficacy with continuous dosing of ribociclib in combination

[redacted]

[redacted]

1.2.1.2.4 [redacted]

1.2.1.2.4.1 [redacted]

[redacted]

1.2.1.2.4.2 [redacted]

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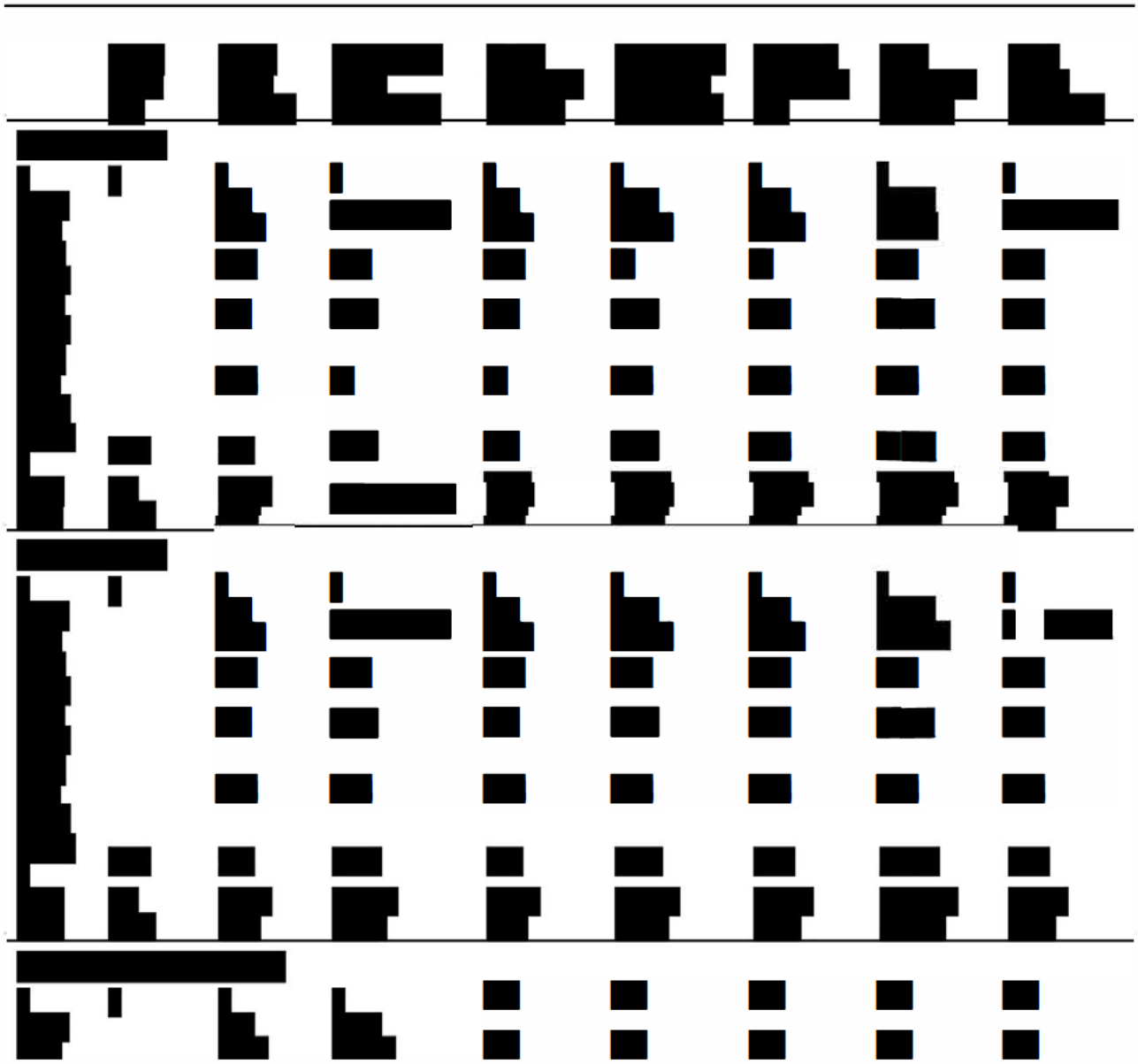

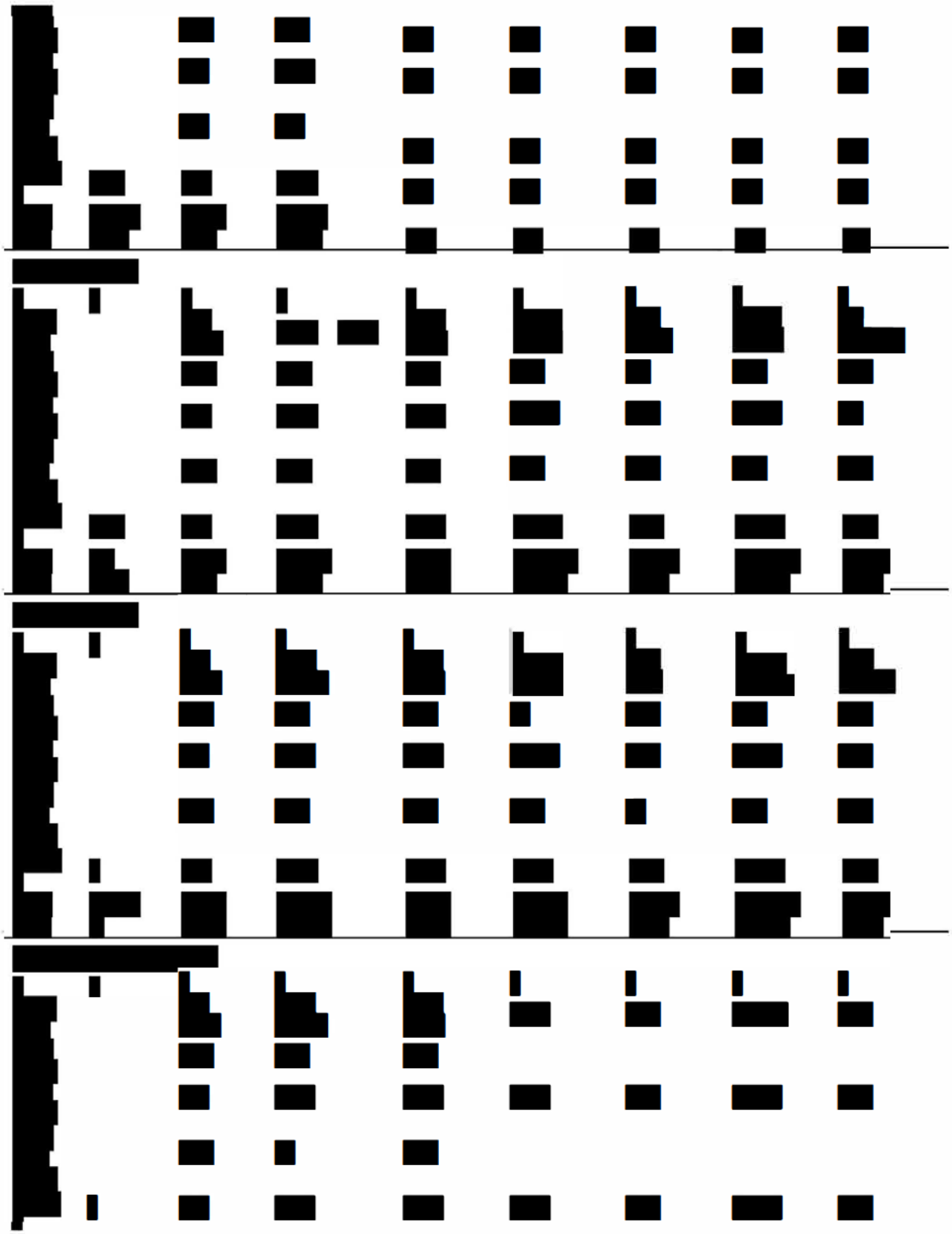

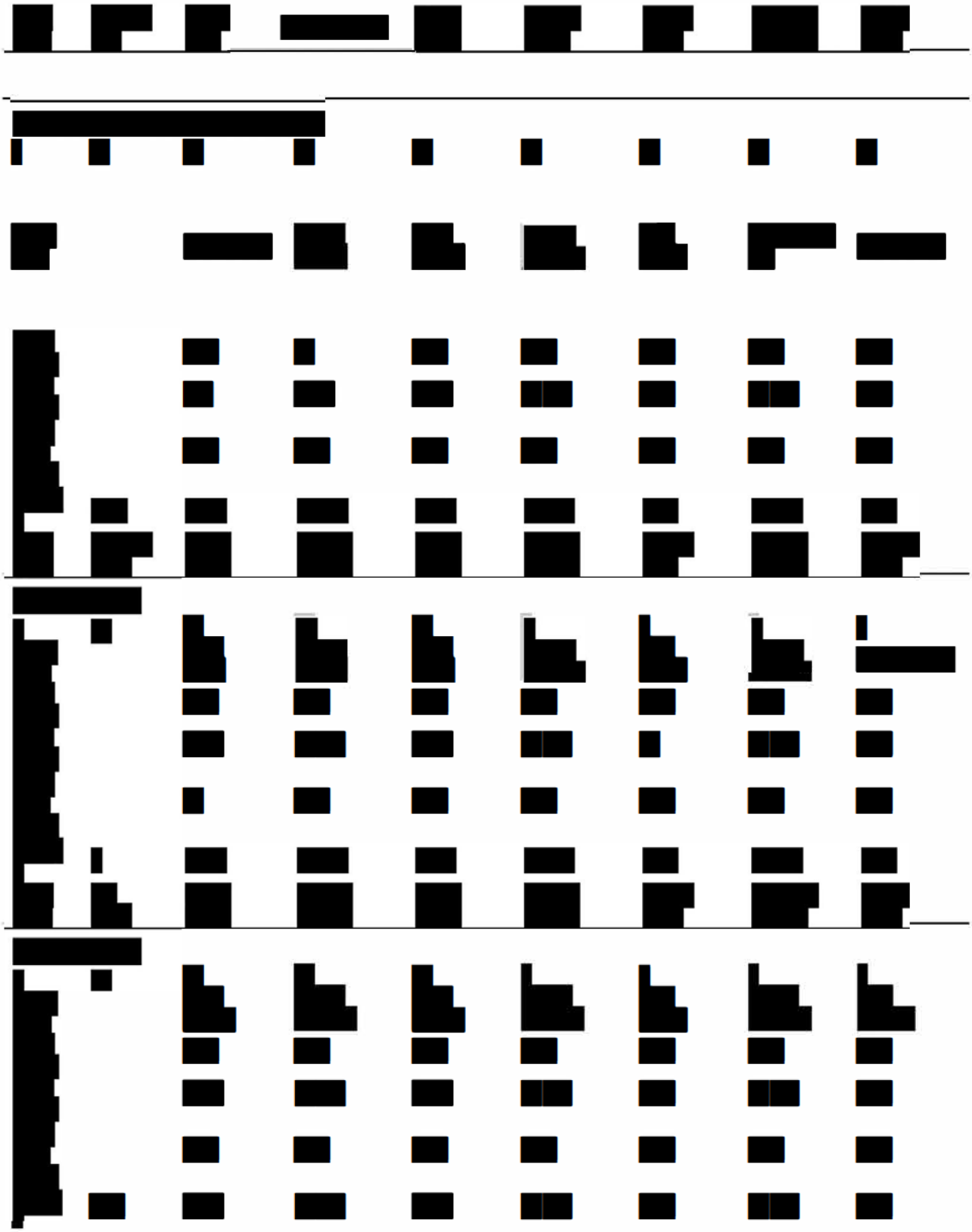

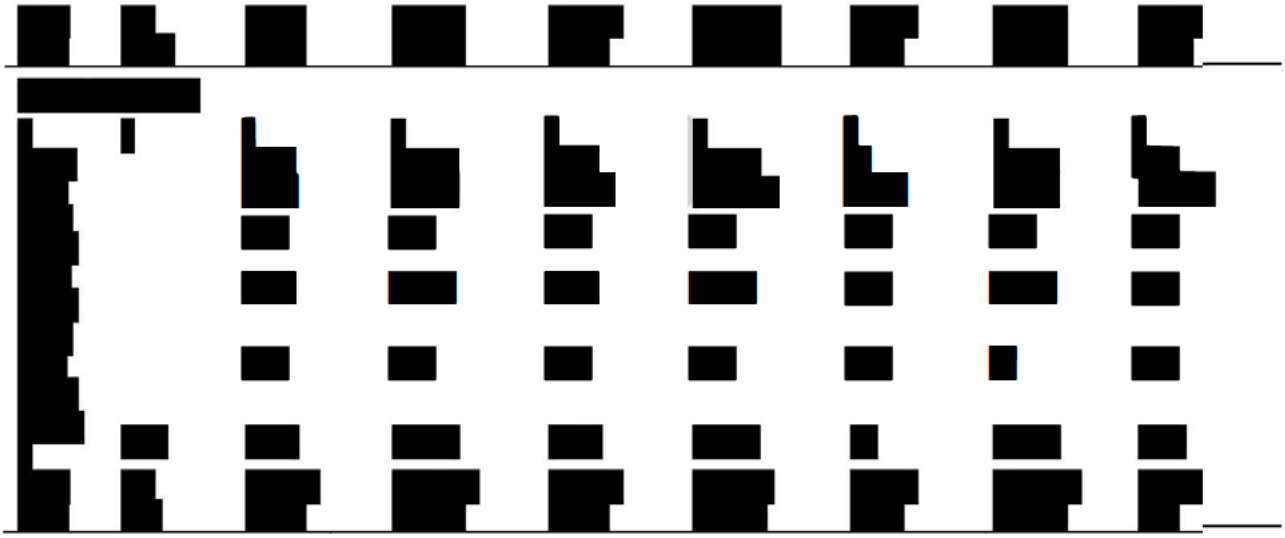

1.2.2 Overview of everolimus (RAD001/Afinitor)

Everolimus (RAD001; Afinitor®) is a derivative of rapamycin and has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets for cardiac and renal transplantation, and in the United States for the prevention of organ rejection of kidney transplantation. In July 2012, everolimus in combination with exemestane was approved for advanced breast cancer in the US, EU and other countries.

The following is a brief summary of the main characteristics of everolimus. More detailed information can be obtained from the everolimus Prescribing Information.

Everolimus is a selective mTOR inhibitor, specifically targeting the mTOR-raptor (regulatory-associated protein of mTOR, Raptor) signal transduction complex 1 (mTORC1). Everolimus potently inhibits proliferation of endothelial cells (Yu 1999, Lane et al. 2009) and has antiangiogenic activity in vivo (Guba et al. 2002, Tsutsumi et al. 2004, Mabuchi et al. 2007, Lane et al. 2009).

1.2.2.1 Nonclinical experience

Everolimus inhibits the proliferation of a wide range of human tumor cell lines in vitro at IC50s ranging from sub/low nM to µM. The antitumor efficacy of everolimus was compared to other compounds in a panel of six breast cancer xenograft models established after direct transplantation of patients' tumors onto nude mice [Report RD-2011-50492]. This panel included an ER + model, HBCx-3 (XTS-181), (Marangoni et al 2007). Everolimus given daily by oral gavage for 21 to 35 days at 20 mg/kg was well tolerated with no significant mean body weight loss. In all breast cancer models tested, tumor growth was significantly inhibited, and was particularly evident in the HBCx-3 (XTS-181) model with nine partial regressions in ten mice tested (-13.5% mean tumor volume regression, $p<0.001$).

All significant adverse events observed in toxicology studies with everolimus in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an

antiproliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

Based on data generated using human liver microsomes and microsomes from cells expressing single human cytochrome P450s enzymes, CYP3A4 was identified as the major enzyme involved in the microsomal biotransformation of everolimus. Everolimus inhibited competitively the metabolism of the CYP3A4 substrate cyclosporine with a Ki value of 2.3 µMol/L (2204 ng/mL) under *in vitro* conditions. Further details can be found in the everolimus Investigators Brochure.

1.2.2.2 Clinical experience

1.2.2.2.1 Everolimus pharmacokinetics

Everolimus is rapidly absorbed with a median t_{max} of one to two hours. The steady-state $AUC_{0-\tau}$ is dose-proportional over the dose range between 5 to 70 mg when given weekly and 5 and 10 mg when given daily. Steady-state was achieved within two weeks with the daily dosing regimen.

C_{max} is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. In healthy subjects, high fat meals reduced systemic exposure of a 10 mg dose of everolimus (as measured by AUC) by 22% and the peak plasma concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%. Food had no apparent effect on the post absorption phase concentration-time profile ([Study RAD001C2120]).

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus 10 mg/day [DMPK R303044]. Plasma protein binding is similar in healthy patients and in subjects with moderate hepatic impairment (approximately 74%, [Study RAD001A2303]).

The major and nearly exclusive enzyme responsible for the metabolism of everolimus in man was CYP3A4 (DMPK(US)1998/005; DMPK(CH) R99-2448), (Kuhn et al. 2001). Other CYP isoenzymes either do not metabolize everolimus or do so at very low rates. Everolimus is a moderate inhibitor of P-glycoprotein-like mediated efflux systems, although the compound has a high intrinsic permeability when P-glycoprotein is inhibited (Crowe 1998, Laplante et al. 2002, [DMPK(CH) 1997/417]). Following oral administration, everolimus is the main circulating component in human blood and contributes the majority of the overall pharmacologic activity (Study W107). Everolimus was also shown to increase exposure of exemestane: In [Study RAD001Y2301], average exemestane Cmin and C2h were 45% and 71% higher, respectively, when co-administered with everolimus.

No specific excretion studies have been undertaken in cancer patients; however, data available from the transplantation setting found the drug to be mainly eliminated through the feces.

1.2.2.2.2 Everolimus in combination with endocrine therapy in HR+ breast cancer

The combination of everolimus with hormonal therapy has been assessed in different disease settings in HR+ breast cancer and showed evidence of efficacy of everolimus in this patient population (Bachelot et al 2012; Baselga et al. 2009).

In newly diagnosed patients with ER+ breast cancer, a neoadjuvant randomized 270-patient Phase II study compared the combination of everolimus 10 mg QD and letrozole 2.5 mg QD to letrozole alone for 16 weeks of therapy prior to surgery. The overall response rate in the investigational everolimus + letrozole arm was higher than that with letrozole alone: 68% vs.59% based on palpation (p = 0.062) and 58% vs. 47% based on ultrasound (p = 0.021) respectively, meeting the predetermined endpoint for efficacy. Additionally, there was a greater antiproliferative response in the investigational arm, with a decrease of the Ki67 proliferation index to <1 in 57% of patients in the everolimus arm compared to 30% of patients in the placebo arm (p<0.01) (Baselga et al. 2009). A randomized Phase III, double-blind, placebo-controlled study (the BOLERO-2 Study) demonstrated very significant improvements in treatment of HR+ breast cancer that had recurred or progressed on letrozole or anastrozole. Response rate, progression-free survival (PFS), and clinical benefit rate were all significantly improved relative to exemestane monotherapy. The median PFS by local assessment was 7.8 months for everolimus + exemestane versus 3.2 months for exemestane (HR = 0.45; 95% CI: 0.38-0.54; p<.0001). Overall response rate (12.6% vs 1.7%; p<.0001) and clinical benefit rate (51.3% vs 26.4%; p<.0001) were superior in the everolimus + exemestane arm versus exemestane + placebo. Analyses by central assessment showed a median progression free survival of 11 months with everolimus versus 4.1 months with placebo (HR = 0.38; 95% CI: 0.31 – 0.48; p<.0001) confirming the results of the primary PFS analysis (Bachelot et al. 2012).

1.2.2.3 Safety profile of everolimus

The following AEs are considered to be class-effects of mTOR inhibitors: stomatitis/oral mucositis/ulcers, infections and infestations, rash and similar events, cytopenia, hemorrhages, non-infectious pneumonitis, hyperglycemia/new-onset diabetes mellitus, renal events, and thromboembolism. The more common metabolic side effects reported with mTOR inhibitors result from inhibitory effects on mTOR-regulated lipid and glucose pathways, while infections stem from the immunosuppressive properties of these agents. Virtually all of the side effects associated with mTOR inhibitors can be managed effectively with dose modification and/or supportive intervention.

The safety profile of everolimus observed in the Phase III BOLERO-2 study is consistent with prior experience in the oncology setting; events are predominantly low grade (grade 1 or 2). An increased risk of non-infectious pneumonitis, infection, and stomatitis in the everolimus plus exemestane arm relative to the control arm [exemestane + placebo] was observed, although each of these events can be effectively managed in this setting.

The most common adverse events (AEs) suspected to be related to treatment, with an incidence ≥10%, reported in association with everolimus plus exemestane therapy were consistent with what

was previously reported: stomatitis, rash, fatigue, decreased appetite, diarrhea, dysgeusia, nausea, pneumonitis, weight loss, anemia, epistaxis, hyperglycemia, thrombocytopenia, and pruritus. The most common grade 3-4 AEs suspected to be related to treatment with an incidence of ≥2% were: stomatitis, hyperglycemia, anemia, pneumonitis, fatigue, elevated alanine and aspartate transaminase concentrations, elevated γ-glutamyltransferase concentrations, dyspnea, neutropenia, and thrombocytopenia (Bachelot et al. 2012). No new safety concerns have emerged compared to previous experience with everolimus monotherapy or combination therapy.
Further details related to everolimus safety can be found in the [everolimus Investigator's Brochure] and package insert of the local supply of everolimus (if available) for more details.

1.2.3 Ribociclib in combination with everolimus

1.2.3.1 Synergy with everolimus and ribociclib (LEE011)

[redacted]

[redacted]

[redacted]

[redacted]

1.2.3.1.1 [redacted]

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[redacted]

2 Rationale

2.1 Study rationale and purpose

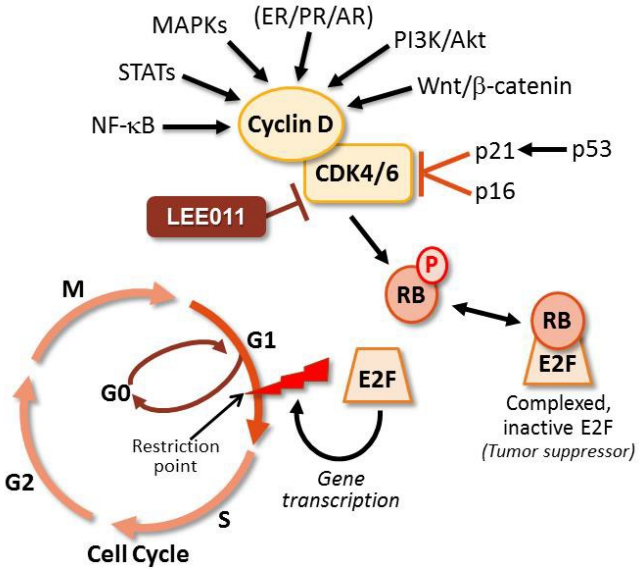
Primary brain tumors are among the top 10 causes of cancer-related deaths in the United States, accounting for approximately 1.4% of all cancers and 2.4% of all cancer-related deaths. About 14 per 100,000 people in the United States are diagnosed with a primary brain tumor each year, and 6 to 8 per 100,000 are diagnosed with a WHO grade III or IV primary brain tumor. Glioblastoma Multiforme (GBM, WHO Grade IV gliomas) is the most frequently reported malignant brain tumor histology (29.6%) in the National Cancer Database. The prognosis for patients who develop WHO Grade III or IV gliomas is bleak, with average survival after diagnosis ranging from 12-16 months. Although conventional treatment with surgery, irradiation, and temozolomide postpones tumor progression and extends patients survival, these tumors universally recur and unrelentingly result in patient death. Nevertheless, the alkylating agent temozolomide remains the only effective adjuvant chemotherapy available for high-grade glioma patients.

Aberrant mitogenic PI3K/mTOR signaling and cell cycle control are hallmarks of human cancers. In GBMs, activating mutations in PI3K/mTOR pathway including PIK3CA and mTOR as well as loss-of-function mutations/deletions in PTEN are found in approximately 56% of the patients. The pathway induces uncontrolled proliferation by activating D-type cyclins. Together D-type cyclins and cyclin-dependent kinases (CDK) 4/6 form complexes crucial for cell cycle progression, specifically the G1-S phase transition. These complexes phosphorylate Rb, a product of the retinoblastoma protein tumor suppressor gene. In its active form, hypophosphorylated pRb is bound to E2Fs inhibiting their transcriptional activity. Hyperphosphorylation of pRb renders it inactive and allows for the release of E2F transcription factors necessary for initiation of S-phase and cell cycle progression. An endogenous CDK4/6 inhibitor, p16INK4A, negatively regulates these processes and is frequently mutated in GBMs (~40%) (Verhaak et al., 2010). In recent years there have been numerous clinical trials in adults with cancer utilizing small molecule inhibitors targeting cell cycle regulatory genes such as CDKs. Ribociclib in particular has been approved recently by FDA to treat breast cancer patients. Combination therapy with ribociclib and everolimus is currently on-going in several solid cancers. However, combination therapy with CDK inhibitor and mTOR inhibitor have yet to be evaluated in adult high-grade glioma patients. Abundant preclinical evidence indicates that Rb-deficient cancer cells are resistant to CDK4/6 inhibition and ongoing trials with CDK4/6 inhibitors exclude patients with Rb-deficient tumors. Patients with Rb+ and mTOR+ will be selected in the trial to ensure maximal benefit from the combination therapy.

Previous LEE011X2106 Phase-1b clinical trial tested a combination of exemestane + everolimus +ribociclib in breast cancer patients. This combination appeared to be safe and demonstrated clinical activity at the RDE of ribociclib 300 mg (3weeks on/1 week off), everolimus 2.5 mg daily, and exemestane 25 mg daily. PK analysis indicated that ribociclib (200 mg-350 mg) increased exposure of everolimus (2.5 mg) due to CYP3A4 inhibition by ribociclib. At steady-state, everolimus exposure was largely within the exposures achieved with multiple doses of 5 and 10 mg of single agent everolimus. (Bardia et al. 2014). Thus, triplet combination of endocrine therapy with mTOR and CDK4/6 inhibition is feasible, permits lower dosing of everolimus with acceptable dose exposure levels, and shows encouraging signs of clinical activity, including in

patients with prior exposure to PI3K/AKT/mTOR or CDK4/6 inhibitors, suggesting that triplet therapy might overcome resistance to doublet therapy in a subset of patients. Therefore the combination therapy of ribociclib plus everolimus will be examined in this phase 0/I trial.

Figure 3 Regulation of cell cycle checkpoint control



Mitogenic signals converge at the level of cyclin D1 upregulation and CDK4/6 association, localization, and kinase activity. CDK4/6 phosphorylates and inactivates retinoblastoma (RB) tumor suppressor proteins, leading to dissociation of E2F transcription factors and transcriptional regulation of genes important for G1/S transition and cell cycle progression through the restriction point (lightning bolt). Ribociclib is a highly specific inhibitor of CDK4/6 which blocks the cell cycle in the G1 phase. Figure adapted from (Lange and Yee 2011).

2.2 Rationale for the protocol design

Despite improvements in drug discovery tools, a novel agent today has only an 8% chance of becoming commercially available to patients, down from the historical success rate of 14% in 1985. Currently, conventional drug development requires up to 20 years from discovery to market, with recent costs ranging between $800 million and $1.8 billion. Unfortunately, it is estimated that 90% of all compounds developed in the laboratory fail during human trials and the current success rate for oncology agents is even lower. Specifically, only 5% of new investigational drugs applications submitted to the FDA for cancer therapies are ultimately successful and, for brain tumors, the rate of success has hovered closer to 1% during the last two decades. Importantly, 40% of exits from Phase I studies are currently due to undesirable pharmacokinetic characteristics that were not predicted from preclinical animal models.

Not unexpectedly, the rising costs associated with drug discovery have tilted the field towards industry. However, despite recent advances in cancer genomics, the FDA has reported a downturn in the submission of major drug and biologic product applications since 2000. Thus, although an improved molecular understanding of cancer has led to a wave of experimental targeted therapies, the challenge of efficiently interrogating these agents and identifying those with most promise

remains a significant impediment. Furthermore, even though targeted molecular pathways are often shared across several different cancer subtypes, market forces and the risk of CNS morbidity have left brain tumor patients as a comparatively low priority.

The efficiency and success of brain tumor targeted-therapy clinical trials are expected to be greatly improved with increased execution of Phase 0 clinical trials.

Phase 0 trials provide 'humanization' of preclinical models with validated pharmacodynamics assays and clinically-relevant methodologies for tissue analysis. For targeted cancer therapies, such as the proposed CDK4/6 and mTOR inhibitors, the Phase 0 trial enables rapid interrogation of biomarker assays for drug effect, as well as CNS penetration. Other established benefits include regulatory flexibility (through the FDA's exploratory IND mechanism), lower overall costs, more rapid demonstration of proof-of-concept, and endpoints that will streamline the design of subsequent Phase I/II/III trials. For this particular study, since a Phase I dose-escalation study has already been completed, a Phase I component will be added for patients with demonstrated pharmacokinetic and pharmacodynamic response.

The applicability of a Phase 0 study is most ideal in the situation of a targeted molecule, where there is availability of a validated biomarker for a well-understood target and evidence for linear drug kinetics. Here, we propose a set of Phase 0 clinical trials examining a novel targeted combination therapy, ribociclib+everolimus, which meets both these criteria.

2.3 Rationale for dose and regimen selection

[redacted]

The design of the Phase 0/2, open label study was chosen in order to establish the continuous dosing of ribociclib at 400 mg starting dose in combination with a fixed, dose of everolimus (2.5 mg) based on the CLEE011X2106 Phase I study. Based on the decreased levels of everolimus during the rest week of ribociclib and the improved safety data demonstrated with the continuous dosing of ribociclib in both the CLEE011X2101 study and CLEEX2108 study, it is believed that dosing ribociclib continuously with daily everolimus may lead to improved safety and efficacy. Because the exposure of ribociclib does not change when administered concurrently with everolimus, we believe that 400 mg of ribociclib will be safe to administer with 2.5 mg of everolimus daily. Each cycle in Phase 2 was determined to be 28 days. Patients will be assessed after each cycle for AEs and if the therapy is well tolerated. The pharmacokinetics and pharmacodynamics data from four

patients that have been treated with 400 mg of ribociclib and 2.5 mg of Everolimus we find that there is almost no detectable Everolimus in the brain/CSF and no PD effect for both Ribociclib and Everolimus. Based on these data and the fact that the MTD is not reached in CLEE011X2106 study with three combination drugs, we propose to increase both the doses of Ribociclib and Everolimus in our study to determine the MTD and the recommended Phase 2 dose (RP2D).

After dosing of ribociclib at 400mg and everolimus at 2.5mg in 6 patients, the data will be reviewed by the DSMB. If deemed safe to continue, dose escalation will be performed to evaluate brain penetration for both drugs. The dose escalation levels will be pre-determined with 6 patients in each level using a rolling-6 design and AEs will be closely monitored.

Due to persistent negative PK effects from everolimus, despite no adverse events limiting drug dosing, additional dose-levels will employ a single, high-dose administration of everolimus. Other combination drug studies have suggested 70mg weekly as a maximal-tolerated dose. As a lead-in to this combination dose in our study, a new dose level at 50mg once prior to surgery (in combination with 600mg ribociclib) will be introduced. This lead-in dose will give rise to 60mg at the next level and 70mg at the final level. Similarly, the phase 2 component of the study will reflect this new dosing regimen for patients with PK and PD effects from both drugs. Specifically, a lead-in regimen at 50mg q weekly in Phase 2 (in combination with ribociclib) will then be escalated towards 70mg weekly.

3 Objectives and endpoints

	Objective	Endpoint
Primary	• To determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) for study drug when administered in combination. • To identify recurrent high-grade glioma patients with positive PK and PD effects.	• MTD: highest dose of drug that did not cause a DLT in > 17% of participants • PK: total and unbound ribociclib and everolimus concentrations in non-enhancing and contrast-enhancing tumor tissue samples • PD: pRB-positive cells and pS6-positive cells
Secondary	• To explore safety and efficacy in recurrent high-grade glioma patients with demonstrated PK and PD effects and determine RP2D • To describe PK for Phase 2 patients	• Progression-free survival (PFS) • Overall survival (OS) • Drug-related toxicity • RP2D • Systemic PK profiles of ribociclib and everolimus when combined.
Exploratory	• To explore evidence for CDK4/6 and mTOR pathway activity in tumor tissue (as compared to	• Quantification of total and phosphorylated forms of Rb, FoxM1, S6, 4EBP, as well as cleaved Caspase-3 and MIB1. Expression of Cyclin D1,

	archival tissue) and mechanisms of resistance • Pharmacometabolomics: To explore the plasma metabolomic signature of the exposure of ribociclib and everolimus • To identify resistance mechanism and alternate pathways	Cyclin E1, PI3K/mTOR signaling components • Plasma metabolomic profiles (i.e., levels of ~250 metabolites) at the pretreatment and at predefined time points after the combination therapy. • Pharmacogenomics studies using RNA-seq and Whole Exome Sequencing to identify alterations in gene expression and mutational profile between pre-treatment and post-treatment tissues or plasma.

4 Protocol design

The proposed Phase 0 study for ribociclib and everolimus will investigate PK, PD, and PG endpoints for any recurrence Rb+ high-grade glioma patients.

The following criteria will be used to determine recurrent disease required for inclusion in the proposed study:

> For high-grade gliomas, the RANO criteria (published in 2010) will be utilized. This will be applicable for both Grade III and IV gliomas.

Enrollment in Phase 0 study occurs after the clinical decision is made for re-resection. This decision is based upon the radiographic criteria described above, in addition to clinical assessment and discussion of the risks/benefits for surgical resection. Therefore, patients enrolled in this study are not taken to the operating room due to study protocol.

4.1 Description of protocol design

4.1.1 Phase 0

In the proposed trial, patients will be administered ribociclib+everolimus prior to surgical resection of their tumor. Recurrent GBM patients will be randomized into one of the three time-interval cohorts for the first two dose levels.

In the lead-in dose escalation study, the first six subjects (lead-in) will receive ribociclib 400 mg and everolimus 2.5 mg orally-administered in 5 daily doses with the last dose. If one or less patient experiences DLT among the 6 patients, this regimen with ribociclib 400 mg and everolimus 2.5mg will be considered safe and we will continue with the dose escalation phase of the study up to Level 6.

Four dose escalation levels:
Level 0: ribociclib 400mg and everolimus 2.5
Level 1: ribociclib 600mg and everolimus 2.5mg
Level 2: ribociclib 600mg and everolimus 5mg
Level 3: ribociclib 600mg and everolimus 10mg
Level 4: ribociclib 600mg daily for 5 days and everolimus 50mg given once on Day 5.
Level 5: ribociclib 600mg daily for 5 days and everolimus 60mg given once on Day 5.
Level 6: ribociclib 600mg daily for 5 days and everolimus 70mg given once on Day 5.

Three to fourteen (3-14) patients will be enrolled into each level to observe AEs and DLTs. Detailed DLTs definition will be summarized in Table 9.

All patients will receive ribociclib and everolimus orally-administered in 5 daily doses.

Cohort 1: last ribociclib+everolimus dose 1 to 3 hours prior to craniotomy for tumor resection (n=8 patients)

Cohort 2: last ribociclib+everolimus dose 7 to 9 hours prior to craniotomy for tumor resection (n=8 patients)

Cohort 3: last ribociclib+everolimus dose 23 to 25 hours prior to craniotomy for tumor resection (n=8 patients)

In Dose Level 0 three to six patients will be enrolled into the time interval cohorts, sequentially whenever possible (e.g. cohort 1, cohort 2, cohort 3, cohort 1…), with at least 1 patient in each of the time intervals.

In Dose Level 1
Three to six patients will be enrolled into the time interval cohorts, sequentially whenever possible (e.g. cohort 1, cohort 2, cohort 3, cohort 1…), with at least one patient in time cohort 1 and two patients in cohort 2. If there are positive PK/PD results at the Maximum Tolerated Dose (MTD) or Optimal Biological Dose (OBD) dose level, the dose level will be expanded to 8 additional patients with 4 patients in each time cohort 1 and 3 (Sections 6.1.2 and 6.1.2.1).

In Dose Levels 2+, three to six patients will be enrolled into cohort 2. If there are positive PK/PD results at the Maximum Tolerated Dose (MTD) or Optimal Biological Dose (OBD) dose level, the dose level will be expanded to 8 additional patients with 4 patients in each time cohort 1 and 3 (Sections 6.1.2 and 6.1.2.1).

Dose Level	Time Interval	N=	Dose Expansion Cohort N=	Time Cohort Expansion N=
Level 0	Cohort 1	2	N/A	N/A
	Cohort 2	2		
	Cohort 3	2		
Level 1	Cohort 1	1	0	4
	Cohort 2	2	3	0
	Cohort 3	0	0	4
Level 2	Cohort 1	0	0	4
	Cohort 2	3	3	0
	Cohort 3	0	0	4
Level 3	Cohort 1	0	0	4
	Cohort 2	3	3	0
	Cohort 3	0	0	4
Level 4 - 6	Cohort 1	0	0	4
	Cohort 2	3	3	0
	Cohort 3	0	0	4

To assess the PK and PD endpoints listed above, blood, CSF and brain tumor tissue will be collected intraoperatively (enhancing and non-enhancing tumor tissue will be collected and analyzed separately).

Additionally, blood samples will be obtained on Day 4 in Dose Levels 1-3 (the day before the surgery for Cohorts 1 & 2; 2 days before surgery for Cohort 3) at pre-dosing (trough level), 0.5, 1, 2, 4, 7, and 24 hours post dose. (Note: 24 h sample is the pre-dosing (trough level) blood sample on Day 5).

Dose Level 4+ only: PK blood sampling will occur on Day 5: pre, 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose (Note: 24 h sample is the pre-dosing (trough level) blood sample on Day 6).

Dose Levels 0-3:

	PHASE 0 STUDY COHORT 1								
DAY 4 PRE-DOSE	Time 0	30 min	1 hour	2 hours	3 hours	4 hours	7 hours	24 hours ± 1 h	POSTOP-Phase 2
Blood	Ribociclib + everolimus	Blood	Blood	Blood		Blood	Blood	Blood	Ribociclib + everolimus
DAY 5 PRE-DOSE									
Blood			Blood* CSF* Tumor*						

	PHASE 0 STUDY COHORT 2								
DAY 4 PRE-DOSE	Time 0	30 min	1 hour	2 hours	4 hours	7 Hours	8-9 Hours	24 hours ± 1 h	POSTOP-Phase 2
Blood	Ribociclib + everolimus	Blood	Blood	Blood	Blood	Blood		Blood	Ribociclib + everolimus
DAY 5 PRE-DOSE									
Blood						Blood* CSF* Tumor*			

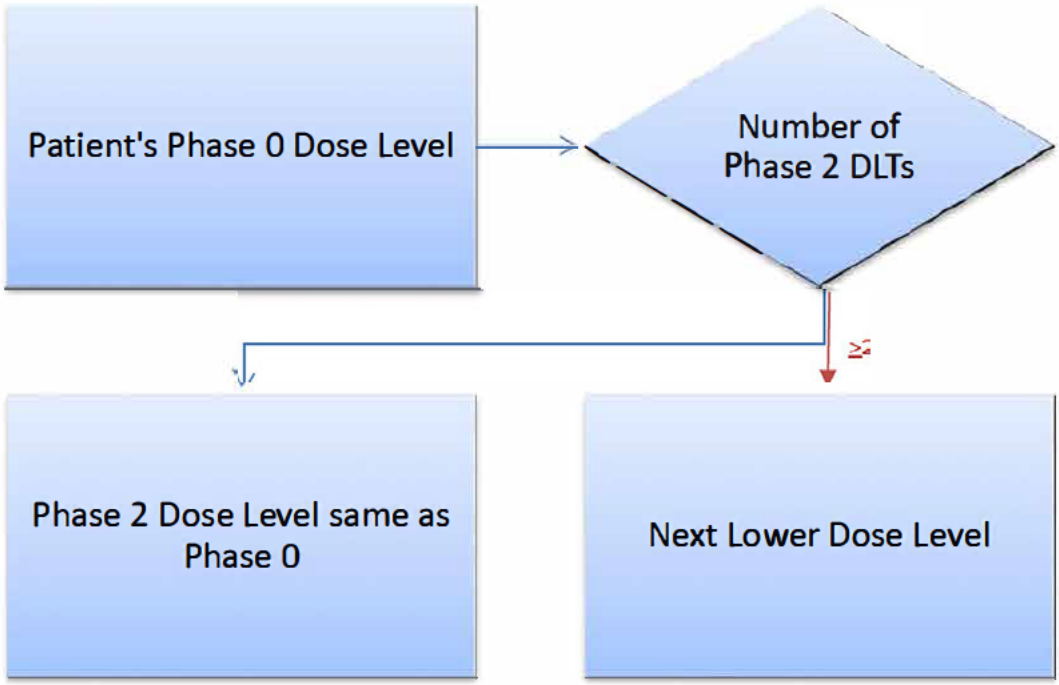
PHASE 0 STUDY COHORT 3								
DAY 4 PRE-DOSE	Time 0	30 min	1 hour	2 hours	4 hours	7 Hours	23 -25 hours	POSTOP-Phase 2
Blood	Ribociclib + everolimus	Blood	Blood	Blood	Blood	Blood	Blood	Ribociclib + everolimus

Phase 0 participants who do not proceed to Phase 2 will be contacted every 3 months by letter or phone for collection of survival data for up to 5 years. The start of follow up for long-term survival begins following completion of the Day 30 safety follow up call.

4.1.2 Phase 2 Dose expansion

Patients with tumors demonstrating favorable PK and PD will proceed to Phase 2 Dose Expansion. In Dose Levels 1-3, patients will continue treatment with the same treatment level as given in Phase 0, patients should take the treatment continuously in 28d cycles with 3 weeks on / 1 week off after surgery. In Dose Level 4+, patients should take everolimus in one dose weekly; ribociclib will be taken for 21 consecutive days followed by 1 rest week. The dose will be per Table 7. If more than one DLT is observed in 6 patients in the Phase 2 dose expansion, the enrollment will be stopped and the previous lower dose level will be considered the RP2D and will be given for the remaining patients enrolled. If more than one DLT is occurred with the Level 0, the study will be stopped due to toxicity. Typically DLTs are defined by 1 cycle of treatment, which is 28 days. Since Phase 0 treatment is given for only 5 days, Phase 0 dose escalation will only be determined by Phase 0 DLT rules unless determined otherwise by the DSMB. Patients will be treated until unacceptable toxicity is observed, or until disease progression as assessed by radiographic or clinical metrics. Preliminary rates of progression-free survival in patients with high-grade gliomas treated with ribociclib+everolimus will be measured through radiographic and clinical response metrics, specifically Response Assessment in Neuro-Oncology (RANO) criteria and investigator discretion. Phase 2 participants will return to the clinic to monitor safety per the schedule of events until treatment is ended and will then be contacted approximately every 3 months by letter or phone for collection of survival data. The start of follow up for long-term survival begins following completion of the Day 30 safety follow up call.. All Phase 0/2 participants will be followed for survival for up to 5 years.

Common Toxicity Criteria Adverse Event (CTC AE 4.03) will be utilized to review ribociclib+everolimus treatment effects in patients with brain tumors.



Trough steady-state blood samples will be obtained on days 1, 8, 15, and 22 of cycles 1 and 2 prior to the administration of ribociclib+everolimus on that day. Note: ribociclib+everolimus will be administered in the clinics on the clinic visit days to ensure the collection of trough level samples.

PHASE 2 STUDY				
	Cycle 1 (28 d)	Cycle 2 (28d)	Subsequent cycles (28d)	End of study
Day of cycle	D1, D8, D15, D22	D1, D8, D15, D22	N/A	N/A
Blood	Trough level*	Trough level*	N/A	N/A

* Trough blood sample is collected prior to the drug administration on that day. Ribociclib is administered in the clinics on the clinic visit days.

4.2 Timing of interim analyses and design adaptations

There will be no interim analysis in the study.

4.3 Definition of end of the Study

Study end will be defined by PK/PD/PG data collection using tissue derived from the last planned patient enrolled in the study.

4.4 Early Termination

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator if he/she violates the study plan or for administrative and/or other safety reasons. When a subject/ patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined.

Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g., personal reasons) will be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will be made by the investigator and study statistician. The replacement will generally receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced. Both the replacement and originally allocated number will be unique numbers.

5 Population

5.1 Patient population

Patients will be accrued at up to 3 sites.

The investigator or designee must ensure that only patients who meet **all** of the inclusion and **none** of the exclusion criteria are entered into this protocol.

Patients enrolled in this protocol are not permitted to participate in additional parallel investigational drug or device studies while on treatment.

Please note these are the minimum inclusion and exclusion criteria required for treatment on LEE011 + everolimus. Investigators should include disease and protocol specific eligibility criteria as applicable.

5.2 Inclusion criteria

Patients eligible for inclusion in this early treatment protocol have to meet **all** of the following criteria:

1. Prior resection of histologically-diagnosed WHO Grade III or IV glioma.
    A. Glioma patients who have progressed on or following standard (Stupp regimen) therapy, which included maximal surgical resection, temozolomide, and fractionated radiotherapy.
2. Recurrence must be confirmed by diagnostic biopsy with local pathology review or contrast-enhanced MRI.
3. Subjects must have measurable disease preoperatively, defined as at least 1 contrast-enhancing lesion, with 2 perpendicular measurements of at least 1 cm, as per RANO criteria.
4. For gliomas, archival tissue must demonstrate: (a) RB positivity (≥20%) on immunohistochemistry OR no RB mutations on next-generation sequencing (NGS), (b)

Chromosomal loss of CDKN2A/B/C OR CDK4/6 or CCND1/2 amplification on array CGH, (c) mTOR+: PTEN loss OR PIK3C2B or AKT3 amplification on aCGH OR mutations for PIK3CA or PIK3R1, or mTOR or PTEN mutations using rhAMP analysis or pS6 positivity on immunohistochemistry (≥10% for pS6). If mutations within the mTOR/PI3K pathways cannot be accurately detected due to poor tissue quality the enrollment criteria will be determined using RB and pS6 positivity.

5. Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (Appendix 1).
6. Patients ≥ 18 years of age.
7. Ability to understand and the willingness to sign a written informed consent document (personally or by the legally authorized representative, if applicable).
8. Patient has voluntarily agreed to participate by giving written informed consent (personally or via legally-authorized representative(s), and assent if applicable).

(Written informed consent for the protocol must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.)

9. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other procedures.
10. Confirmed negative serum pregnancy test (β-hCG) before starting study treatment or patient has had a hysterectomy.
11. Patient has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by the local laboratory for eligibility):

The following laboratory criteria have been met:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (recommended)
- Hemoglobin (Hgb) ≥ 9.0 g/dL (Participants may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator.)
- Platelets ≥ 100 x 10^9/L (at the time of surgery)
- Potassium, total calcium (corrected for serum albumin), magnesium, sodium, and phosphorus within normal limits for the institution or corrected to within normal limits with supplements before first dose of study medication
- 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)
- Serum creatinine < 1.5 mg/dL
- Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min
- In the absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN.
- Serum total bilirubin ≤ULN, or ≤ 3.0 x ULN in patients with well-documented Gilbert's syndrome
- Serum cholesterol ≤ 300 mg/dL or ≤ 7.75 mmol/L AND triclycerides ≤ 2.5 x ULN (**NOTE**: in case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.)

12. QTcF interval at screening < 450 msec [using Fridericia's correction (formula = $QT/(RR)^{0.33}$)]

13. Resting heart rate 50-90 bpm (may be repeated up to 2x)
14. Must be able to swallow ribociclib and everolimus capsules/tablets
15. If patient is receiving tamoxifen or toremifene, a washout period of 5 half-lives prior to enrollment is required

5.3 Exclusion criteria

Patients eligible must not meet **any** of the following criteria:

1. Archival tissue is not available for research use or there is not a sufficient quantity available to confirm eligibility.
2. Archival tumor is not Rb-positive status and mTOR-positive status.
3. Patient has not received prior radiotherapy.
4. Co-morbid condition(s) that, at the opinion of the investigator, prevent safe surgical treatment.
5. Active infection or fever > 38.5°C that in the opinion of the investigator would be a safety risk to the patient.
6. Active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, and active and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA).
7. Known severely impaired lung function (spirometry and DLCO 50% or less of normal and O2 saturation 88% or less at rest on room air).
8. Active, bleeding diathesis.
9. Patients with known hypersensitivity to any of the excipients of ribociclib or mTOR inhibitors (sirolimus or everolimus), including peanut, soy and lactose.
10. Patients with a clinically significant hypersensitivity to everolimus or to other rapamycin derivatives.
11. Prior therapy with ribociclib or any CDK4/6 inhibitor (e.g. palbociclib, abemaciclib), or with everolimus. Prior therapy is defined as a therapeutic dosing.
12. Patient who has received radiotherapy ≤4 weeks or limited field radiation for palliation ≤2 weeks prior to starting study drug, and who has not recovered to grade 1 or better from related side effects of such therapy (exceptions include alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion) and/or in whom ≥25% of the bone marrow (Ellis, 1961) was irradiated.
13. Patient has a concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
14. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
15. Patient has a known history of HIV infection (seropositivity; testing not mandatory).
16. Patients who have received live attenuated vaccines within 1 week of start of everolimus and during the study. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

17. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.)
18. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy as indicated by the medical history. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary.
19. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, including any of the following:
    - History of acute coronary syndromes (including myocardial infarction, unstable angina pectoris, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening .
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV).
    - Documented cardiomyopathy.
    - Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) at screening.
    - 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).
    - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
        - Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication.
        - Inability to determine the QT interval on screening (QTcF, using Fridericia's correction).
    - Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening (may be repeated up to 2x).
20. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug (see Appendix 2 for details):

    • Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pomelos/pummelos, star-fruit, pomegranates or pomegranate juice and Seville oranges.

    • That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.

• Herbal preparations/medications, dietary supplements known as strong inhibitors or inducers of CYP3A4 or those with a known risk of QT prolongation. (Does not include Ca, Mg, Vit D or KCl supplements).

• Known strong inhibitors or inducers of P-gp.

21. Patients taking ACE inhibitors.
22. Patient is currently receiving warfarin or other coumarin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed.
23. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer.
24. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects (tumor biopsy is not considered as major surgery).
25. Patient has not recovered from all toxicities related to prior anticancer therapies to NCI-CTCAE version 4.03 Grade ≤2 (Exception to this criterion: patients with grade 1 taxane-induced neuropathy, any grade of alopecia, amenorrhea or other toxicities not considered a safety risk for the patient as per investigator's discretion, are allowed to enter the study.).
26. Patient with a Child-Pugh score B or C.
27. Patient has a history of non-compliance to medical regimen or inability to grant consent.
28. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
29. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unwilling to use** highly effective methods of contraception during dosing and for 3 months after the last dose of study treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. 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) or tubal ligation at least six 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 sterilization (at least 6 months prior to screening) with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate. For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception.
    - In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
    - Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

30. Sexually active males unwilling to use a condom during intercourse while taking drug and for 21 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

6 Treatment

6.1 Protocol treatment

For this protocol, the term "treatment" refers to ribociclib+everolimus.

Table 6 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dosage Form and Strength	Frequency and/or Regimen
Phase 0		(5 day regimen)	
Ribociclib (LEE011)	Tablet for oral use	200mg tablets 2.5mg tablet	Once daily
Everolimus	Tablet for oral use		Once daily or Twice daily*
Phase 2 (optional)		(28 day cycle)	
Ribociclib (LEE011)	Tablet for oral use	200mg tablets 2.5mg tablet	Once daily for 3 weeks, 1 week off
Everolimus	Tablet for oral use		Once daily* or Twice daily** for 3 weeks, 1 week off

*Dose Level 4+: everolimus is taken once on Day 5 in Phase 0. In Phase 2, everolimus dose will be given weekly on Days 1, 8, 15, 22 of each cycle.

**Dose Level 3: everolimus is taken twice daily in Phase 2.

6.1.1 Phase 0 & 2 Dose Escalation Schedule

Table 7 Dose Escalation Schedule

Dose Level	Phase 0 Dose of Study Drug[a]	Minimum Number of Patients	Phase 2 Dose of Study Drug[a]
0	ribociclib 400mg and everolimus 2.5mg	6	ribociclib 400mg and everolimus 2.5mg
1	ribociclib 600mg and everolimus 2.5mg	3	ribociclib 600mg and everolimus 2.5mg

Dose Level	Phase 0 Dose of Study Drug[a]	Minimum Number of Patients	Phase 2 Dose of Study Drug[a]
2	ribociclib 600mg and everolimus 5mg	3	ribociclib 600mg and everolimus 5mg
3	ribociclib 600mg and everolimus 10mg[b]	3	ribociclib 600mg and everolimus 10mg[c]
4	ribociclib 600mg, qd and everolimus 50mg once[d]	3	ribociclib 600mg daily and everolimus 50mg once weekly[e]
5	ribociclib 600mg, qd and everolimus 60mg once[d]	3	Cycle 1: ribociclib 600mg, qd and everolimus 50mg once weekly[e] Cycle 2+: 600 mg, qd and everolimus 60mg once weekly[f]
6	ribociclib 600mg, qd and everolimus 70mg once[d]	3	Cycle 1: ribociclib 600mg, qd and everolimus 50mg once weekly[e] Cycle 2: 600 mg, qd and everolimus 60mg once weekly[f] Cycle 3+: 600 mg, qd and everolimus 60mg once weekly[f]

a. The Phase 0 dose given to the patient will be the RP2D. If more than one DLT is observed in 6 patients in Phase 2, the regimen at that given level will be considered as the maximal administered dose and the next lower dose level will be the MTD/RP2D for subsequent patients enrolled into Phase 2

b. In Phase 0, the everolimus dose will be given in one dose (10mg, qd).

c. In Phase 2, dose will be given in two doses (5mg, bid)

d. In Phase 0, the everolimus dose will be given in one dose on Day 5 only; ribociclib dose will be given daily for 5 days.

e. In Phase 2, everolimus dose will be given once weekly on Days 1, 8, 15, 22 of each cycle with ribociclib administered daily for 21 consecutive days and 1 rest week.

f. If the dose is well tolerated in Cycle 1, the dose may be escalated based on investigator discretion.

6.1.2 Phase 0 Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)

Dose escalation will proceed according to the following scheme for Phase 0:

Table 8 Phase 0 Dose Escalation Schedule - DLT and MTD

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

0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose and the lower dose level demonstrated positive PK/PD results (OBD).
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose (RP2D). If Dose Level 3 is reached, ≤1 out of 6 have experienced DLTs and the dose level has demonstrated positive PK/PD results, the time cohort will be expanded.

If one patient develops a DLT out of three, then the cohort will be expanded to include a total of 6 patients. If greater than or equal to two patients develop DLT, then that dose level will be considered the maximum administered dose (MAD) and further dose escalation will be terminated. A total of 6 patients will be treated at the next lower dose. The maximum tolerated dose (MTD) will be the dose at which no more than 1 patient develops DLT when at least 6 patients have been treated.

At the time of dose escalation, a written report will be submitted to the DSMB Chair (or qualified alternate) describing the cohorts, dose levels, adverse events, safety reports and any DLTs observed. The DSMB Chair will review the report and provide a written authorization to proceed or request more information within 2 business days. Approval for the dose escalation must be obtained prior to implementation.

6.1.2.1 Optimal Biological Dose (OBD)

If positive tumor PK and PD effects are observed in patients treated at a specific dose, but no DLT is observed, dose escalation will continue as planned in order to demonstrate whether an increase in biological effect can be observed with increasing dosage or if such effect is maximized (ie, the OBD is attained). If the OBD has been achieved with <2 DLTs out of 6 patients, the OBD cohort will be expanded to an additional 8 patients to assure safety and to evaluate time course of PK and PD effects at 2 time cohorts (i.e., 2 ± 1 h and 24 ± 1 h), with 4 patients in each time cohorts, following the administration of the final dose on Day 5.

6.1.3 Dose Limiting Toxicity for Phase 0 or Phase 2

Dose limiting toxicity (DLT) will be defined as adverse event(s) which is/are attributable to the study treatment and unrelated to disease, disease progression, inter-current illness, or concomitant medications during the first 5 days in Phase 0 or in the first cycle (28 days) of Phase 2. The

maximum tolerated dose of ribociclib+everolimus will be that dose at which fewer than one-third of patients experience a dose limiting toxicity within each Phase. If multiple toxicities are seen, the presence of dose limiting toxicity should be based on the most severe toxicity experienced.

Table 9 DLT Criteria

TOXICITY	DLT CRITERIA
Hematology	CTCAE grade 4 neutropenia for more than 7 consecutive days
	CTCAE grade 4 thrombocytopenia
	CTCAE grade 3 thrombocytopenia with bleeding
	Grade 4 granulocytopenia lasting ≥ 5 days without hematopoeitic growth factor support
	Febrile neutropenia (decrease in neutrophils associated with fever ≥ 38.5°C, ANC < 1.0 x 10^9/L)
Gastro-intestinal	≥ CTCAE grade 3 vomiting or nausea ≥ 48 hrs despite optimal anti-emetic therapy
	≥ CTCAE grade 3 diarrhea ≥ 48 hrs despite optimal anti-diarrhea treatment
Hepato-biliary	CTCAE grade 2 bilirubin for more than 7 consecutive days
	≥ CTCAE grade 3 total bilirubin
	≥ CTCAE grade 2 ALT with a ≥ grade 2 bilirubin elevation of any duration in the absence of liver metastases
	≥ CTCAE grade 3 ALT for more than 4 consecutive days
	CTCAE grade 4 ALT or AST
	CTCAE grade 4 serum alkaline phosphatase > 7 consecutive days
Cardiac	Cardiac toxicity ≥ CTCAE grade 3
	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin ≥ CTCAE grade 3
ECG QT Interval	QTcF interval ≥ 501 ms on at least two separate ECGs
Renal	≥ CTCAE grade ≥ 3 serum creatinine
Stomatitis	CTCAE Grade 4
Non-infectious pneumonitis	CTCAE Grade 4
Metabolic events (hyperglyciemia, dyslipidemia)	CTCAE Grade 4
Non-hematologic events	Inability to receive the subsequent planned dose due to toxicity
	Inability to begin the next cycle of treatment (at full dose) within 2 weeks of the scheduled dose due to unresolved toxicity
	Grade ≥ 2 non-hematological toxicity that persists beyond the first 42 days that in the judgment of the Principal Investigator is dose-limiting
	Certain Grade 2 toxicity (e.g. renal neurological, cardiovascular, gastrointestinal) which in the judgment of the Principal Investigator is dose-limiting
	≥ CTCAE grade 3, except for the exclusions noted below:
Exceptions to DLT criteria	< 5 days of CTCAE grade 3 fatigue
	Untreated nausea or vomiting, or alopecia
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting or diarrhea will be based on institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

6.1.4 Dosing regimen

6.1.4.1 Ribociclib + Everolimus

The Barrow Neurological Institute / St. Joseph's Hospital and Medical Center will purchase commercially available supplies of ribociclib (Kisqali®) and everolimus (Afinitor®). Ribociclib+everolimus will be administered orally once daily on a 5-day dosing schedule during Phase 0 and a 28-day dosing schedule (3 weeks on, 1 week off) during Phase 2. The investigator must instruct the patient to take the treatment exactly as prescribed.

- Patients should take ribociclib+everolimus once daily at approximately the same time each day with a large glass of water (~ 250 ml) at the same time each day, in the morning, afternoon, or evening. The dose taken on the day of surgery will vary depending upon the planned time of the resection (see Section 4.1).
- Patients can take ribociclib+everolimus without regard to meals; however, dietary habits around the time of dosing should be as consistent as possible throughout the study.
- Patients should be instructed to swallow the ribociclib 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.
- Patients must avoid consumption of grapefruit, grapefruit hybrids, pomelos/pummelos, star-fruit, pomegranates or Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medication, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
- No herbal or dietary supplements known as strong inhibitors or inducers of CYP3A4 or those with a known risk of QT prolongation are permitted, due to potential interactions with ribociclib and everolimus; multivitamins are allowed.
- In Phase 2, Dose Levels 0-2, patients will take ribociclib+everolimus for 21 consecutive days followed by 1 rest week.
- In Phase 2, Dose Level 3, patients should take everolimus in two 5mg doses, approximately 12 hours apart (BID) for a total of 10mg. In Phase 0, the dose is 10mg given in one dose per day (qd).
- In Phase 2, Dose Level 4+, patients should take everolimus in one dose weekly. Ribociclib will be taken for 21 consecutive days followed by 1 rest week.

6.1.4.2 Additional Dosing Guidelines for Pharmacokinetic Sampling / ECG / Chemistry panel / Lipid Panel Collection

On days with PK, ECG sampling, chemistry panel and/or lipid panel sampling, the following additional guidelines should be followed:

- On a day when PK blood collection is scheduled at the clinic, patients must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days, patients may take the study treatment at home.
- On a day of chemistry panel and/or lipid panel sampling, patients should be fasting from food and drink for at least 8 hours overnight; however, it will not be considered a deviation if the patient is not fasting. Water is allowed during all fasting periods; however, coffee, tea and juice are not permitted during the fasting period. Patients must also take study treatment in the clinic under the supervision of the Investigator or designee. On all other days, patients may take the study treatment at home.
- Pre-dose samples should be drawn prior to dosing. The sampling time of the PK samples and the dosing time must be precisely recorded in the CRF. Furthermore, the dosing date and time the study medication was taken on the day before the PK assessment must be precisely recorded in the CRF.
- Post-dose PK samples should be collected after dosing of the study treatment and precisely recorded in the CRF.
- If a pre-dose PK sample should be obtained, then the sample should be collected after the ECG and before dosing of the study treatment when possible; or allow approximately 30 minutes after the sample is drawn before obtaining the ECG.

6.1.5 Guidelines for continuation of treatment beyond tumor resection (Optional Phase 2)

Patients with positive PK and PD responses will be provided the option of continuing on therapy until tumor progression. PK data evaluates the drug concentration in enhancing and non-enhancing region of the tumor. PD analysis evaluates the biomarker response after 5-day treatment and compares this with archival tissue. If both are positive the patients will be enrolled into Phase 2 portion of the trial with the same dose level taken during Phase 0 (unless there is more than one DLT observed in Phase 2, see Section 4.1.2). If the PD data is not conclusive due to treatment effect or limited tissue samples from the surgery, the PK data would be the primary guidance on deciding phase 2 enrollment.

Some anticipated risks and safety considerations of the ribococlib+everolimus combination will be closely monitored. Preclinical and Phase I clinical data available from ongoing studies with ribociclib and everolimus separately suggest few overlapping toxicities for the proposed

combinations. Special attention will be paid to blood counts (cytopenias), mucositis, liver function test abnormalities and QTc prolongation. Clinical data from the [CLEE011X2101] study do not show marked accumulation in ribociclib with time, suggesting that it does not substantially inhibit its own metabolism or clearance. Everolimus and ribociclib are *in vitro* inhibitors and substrates of CYP3A4, and the latter is also a time-dependent CYP3A4 inactivator. The available preclinical and clinical data therefore suggest the possibility of a drug interaction, specifically one that may increase exposure to everolimus. Based on simulation using Simcyp software (Simcyp Version 12, release 1), the projected increase in the AUCleac 0-6h of everolimus was 3.5-fold following the starting daily dose of 200 mg ribociclib co-administered with 2.5 mg of everolimus for 14 days. No significant effect on ribociclib metabolism was predicted when co-administered with everolimus. Appropriate eligibility criteria, dose modification guidelines and stopping rules are included in this protocol.

6.1.6 Treatment duration

All Phase 0 patients will receive a 5-day regimen as described above. Patients with Rb+ mTOR+ tumors will be provided the option of continuing on therapy until tumor progression. In Phase 2 continuation therapy, patients will receive RP2D daily schedule (28 day cycle).

6.2 Dose modification post-tumor resection (Phase 2)

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patients to continue the ribociclib+everolimus treatment. See Table 10 for dose reductions. Any changes in ribociclib+everolimus administration must be recorded.

6.2.1 General guidelines for dose modifications

- For grade 1 and tolerable grade 2 treatment-related toxicities, with the exception of pneumonitis, patients may continue at the current dose of ribociclib+everolimus treatment.
- For intolerable grade 2 treatment-related toxicities as those that are irreversible (e.g., neurotoxicities, ocular toxicities, or cardiac toxicities) or prolonged grade 2 toxicities (i.e., those lasting longer than 14 days), or any grade 3 toxicities, with the exception of pneumonitis, dosing should be interrupted until resolution to grade 1 or lower followed by resumption of a new 28 days regimen. Dosing reductions could also be considered after grade 3 toxicities (Table 11).
- For any grade 4 toxicity, dosing should be interrupted and the patients should be followed until the toxicity resolution to baseline levels, grade 1, or become stable. Following recovery from grade 4 events, **no additional ribociclib+everolimus treatment** should be given to the patient except for neutropenia and thrombocytopenia (details in Table 11).

More detailed ribociclib and everolimus dose modification guidelines are described in Section 6.2.2 respectively for selected toxicities. Any variance from these guidelines in view of patient safety must first be discussed with the Sponsor unless there is an urgent need for action.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria version 4.03.

Patients whose treatment is interrupted or permanently discontinued due to an AE must be followed until resolution or stabilization of the event. Patients with more than 1 interruption should be discontinued from ribociclib treatment.

6.2.2 Dose modification and dose delay of ribociclib+everolimus

Guidelines for dose, modifications, interruptions and re-initiation of ribociclib+everolimus treatment are described in Table 11. The following are the dose modification levels in Table 10.

Table 10 Dose Modification Levels

Ribociclib	
Dose	**Number of tablets & strength**
200 mg (qd)*	1 x 200 mg tablet
400 mg (qd)	2 x 200 mg tablet
600 mg (qd)	3 x 200 mg tablet

* One dose de-escalation will be allowed below dose level 0 if needed as a dose modification.

Everolimus	
Dose	**Number of tablets & strength**
2.5 mg **every other day (qod)***	1 x 2.5 mg tablet
2.5 mg daily (qd)	1 x 2.5 mg tablet
5 mg daily (qd)	2x 2.5 mg tablet
10 mg (qd)	4x 2.5 mg tablet

Everolimus- for Dose Levels 4-6 and possible dose reductions	
Dose	**Number of tablets & strength**
25 mg (1/weekly) – 50% of dose level 4	2 x 10 mg tablet and 2 x 2.5mg tablet
30 mg (1/weekly) - 50% of dose level 5	3 x 10 mg tablet
35 mg (1/weekly) - 50% of dose level 6	3 x 10 mg tablet and 2 x 2.5mg tablet
40 mg (1/weekly) – 1 dose reduction from dose level 4	4 x 10 mg tablet
50 mg (1/weekly) – 1 dose reduction from dose level 5	5 x 10 mg tablet
60 mg (1/weekly) – 1 dose reduction from dose level 6	6 x 10 mg tablet
70 mg (1/weekly)	7 x 10 mg tablet

6.2.3 Follow-up for toxicities

An unscheduled visit should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments.

Ongoing SAEs at the final safety evaluation visit or the end of study treatment visit (whichever is later) should be followed until they improve becoming non-serious events, stabilize, or return to baseline levels. Refer to Section 8.2 for SAE.

Table 11 Criteria for post-tumor resection interruption and re-initiation of ribociclib+everolimus treatment

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
HEMATOLOGICAL		
Anemia		
Grade 1 (Hemoglobin (Hgb) <LLN -10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L)	Continue regimen	Continue regimen
Grade 2 (Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L)	Continue regimen	Continue regimen
Grade 3 (Hgb <8.0 g/dL; <4.9 mmol/L;	Dose interruption until recovery to grade ≤ 1. Re-initiate ribociclib at the same dose.	Dose interruption until recovery to grade ≤ 1. Re-initiate everolimus at the same dose.
Grade 4 (transfusion indicated Life-threatening)	Discontinue ribociclib	Discontinue everolimus
Neutropenia (ANC)		
Grade 1 (ANC < LLN - 1.5 x 10^9/L)	Continue regimen	Continue regimen
Grade 2 (ANC < 1.5 and ≥ 1.0 x 10^9/L)	Continue regimen	Continue regimen
Grade 3 (ANC < 1.0 and ≥ 0.5 x 10^9/L)	Dose interruption until recovery to ≥1.0x10^9/L (≤grade 2). Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3, temporary dose interruption until recovery to ≥1.0x10^9/L (≤grade 2). If resolved in ≤7 days, then maintain dose level. If resolved in >7 days, then reduce ribociclib dose to the next lower dose level.	Dose interruption until recovery to grade ≤2. Re-initiate everolimus at the same dose level. If ribociclib is interrupted/ discontinued, everolimus should also be interrupted/discontinued. Resume everolimus at <u>same</u> dose level if ribociclib is resumed at either the same or lower dose.
Grade 4 (ANC < 0.5 x 10^9/L)	Dose interruption until recovery to ≥1.0x10^9/L. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4, discontinue ribociclib+everolimus	Dose interruption until recovery to grade ≤2. Re-initiate everolimus at the next lower dose level. If toxicity recurs at grade 4, discontinue ribociclib+everolimus
Febrile neutropenia Grade 3 (ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C (101°F) or a sustained temperature of ≥ 38 °C (100.4°F) for more than one hour)	Dose interruption until improvement of ANC ≥1.0x10^9/L (≤Grade 2) and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib +everolimus.	Dose interruption until improvement of ANC ≥1.0x10^9/L (≤Grade 2) and no fever. Re-initiate everolimus at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib +everolimus.
Febrile neutropenia Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment.	Discontinue treatment.

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
Thrombocytopenia		
Grade 1 (PLT < LLN - 75 x 10^9/L)	Continue regimen	Continue regimen
Grade 2 (PLT < 75 and ≥ 50 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose.	Dose interruption until recovery to grade ≤1. Re-initiate everolimus at the same dose.
Grade 3 (PLT < 50 and ≥ 25 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3, temporary dose interruption until recovery to grade ≤1 and reduce ribociclib to the next lower dose level.	Dose interruption until recovery to grade ≤1. Re-initiate everolimus at the next lower dose level. If toxicity recurs at grade 3, temporary dose interruption until recovery to grade ≤1 and reduce everolimus to the next lower dose level.
Grade 4 (PLT < 25 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib	Dose interruption until recovery to grade ≤1. Re-initiate everolimus at the next lower dose level. If toxicity recurs at grade 4: discontinue everolimus

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)		
Total Bilirubin without ALT/AST increase above baseline value** (for patients with Gilbert Syndrome these dose modifications apply to changes in direct (conjugated) bilirubin only)		
Grade 1 (> ULN and ≤ 1.5 x ULN)	Maintain dose level with liver function test (LFTs)*** monitored as per protocol Confirm at 48-72 hours later	Continue regimen
Grade 2 (> 1.5 and ≤ 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤21 days, then maintain dose level. If resolved to ≤ grade 1 in >21-28 days or toxicity recurs, then reduce 1 dose level. Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption. If toxicity recurs after 1 dose reduction, or recovery to < grade 1 in > 28 days, discontinue ribocicilb+everolimus.	If ribociclib is interrupted/ discontinued, everolimus should also be interrupted/discontinued. Resume everolimus at same dose level if ribociclib is resumed at either the same or lower dose. If toxicity recurs after 1 dose reduction, or recovery to ≤ grade 1 in > 28 days, discontinue ribocicilb+everolimus.
Grade 3 (> 3.0 and ≤ 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Dose interruption of ribociclib, until resolved to ≤ grade 1, then lower 1 dose level of ribocidlib Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If resolved to ≤ grade 1 in > 28 days or toxicity recurs, discontinue ribociclib+everolimus	If ribociclib is interrupted/ discontinued, everolimus should also be interrupted/discontinued. Resume everolimus at same dose level if ribociclib is resumed at lower dose level. If toxicity recurs after 1 dose reduction, or recovery to ≤ grade 1 in > 28 days, discontinue ribocicilb+everolimus.
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from ribociclib+everolimus	
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of liver metastases, evidence of obstruction, such as elevated ALP and GGT typical of gallbladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, other pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.		

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
AST or ALT		
AST or ALT without bilirubin elevation >2 x ULN		
Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 to 72 hours later)	Maintain dose level with LFTs*** monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1.	Continue regimen
Increase from baseline grade 0 or 1 to Grade 2 (> 3.0 and ≤ 5.0 x ULN)	Dose interruption of ribociclib: If resolved to ≤ baseline value in ≤ then 21 days, then maintain dose level If resolved to ≤ baseline value in > then 21 days or toxicity recurs, then reduce 1 dose level of ribociclib. Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption. If toxicity recurs after 1 dose reduction or recovery to ≤ baseline value is >28 days, discontinue ribocicilb+everolimus t.	If ribociclib is interrupted/ discontinued, everolimus should also be interrupted/discontinued. Resume everolimus at same dose level If toxicity recurs after 1 dose reduction, or recovery to ≤ grade 1 in > 28 days, discontinue ribocicilb+everolimus.
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of ribociclib until resolved ≤ baseline value then reduce 1 dose level of ribociclib. Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption. If toxicity recurs after 1 dose reduction or recovery to ≤ baseline value is >28 days ribocicilb+everolimus.	If ribociclib is interrupted/ discontinued, everolimus should also be interrupted/discontinued. Resume everolimus at same dose level if ribociclib is resumed at either the same or lower dose. If toxicity recurs after 1 dose reduction, or recovery to ≤ grade 1 in > 28 days, discontinue ribocicilb+everolimus.
Increase from baseline grade 2 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of ribociclib until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after 1 dose reduction or recovery to ≤ baseline grade is > 28 days, discontinue ribociclib+everolimus.	If ribociclib is interrupted/ discontinued, everolimus should also be interrupted/discontinued. Resume everolimus at same dose level if ribociclib is resumed at either the same or lower dose. If toxicity recurs after 1 dose reduction, or recovery to ≤ grade 1 in > 28 days, discontinue ribocicilb+everolimus.
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Discontinue study treatment.	Discontinue study treatment.
AST or ALT and concurrent Total Bilirubin		
For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT >3.0 x ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis Or	Discontinue study treatment.	Discontinue study treatment.

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
For patient with elevated AST or ALT or total bilirubin at baseline: baseline: [AST or ALT >2 x baseline AND >3.0x ULN] OR [AST or ALT 8.0 x ULN]- whichever is lower- combined with [total bilirubin > 2 x baseline AND >2.0 x ULN]		
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.		

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
QTcF Prolongation		
For all grades	Check the quality of the ECG and the QT value and repeat if needed. Perform analysis of serum electrolytes (K+, Ca++, Phos Mg++). If outside of normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. Check compliance with correct dose and administration of ribociclib. (Consider collecting a time matched PK sample: record date/time of last study drug dose.)	N/A
Grade 1 (QTc 450-480 ms)	Perform steps 1-4 as directed in "For All Grades." Continue regimen.	Continue regimen.
Grade 2 (QTc 481-500 ms)	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Perform a repeat ECG one hour after the first QTcF of ≥481 ms. • If QTcF <481 ms, restart ribociclib at the same dose. No dose adjustment required for first occurrence. • If QTcF remains ≥481 ms, repeat ECG as clinically indicated until the QTcF returns to <481 ms. Ribociclib should be reduced by 1 dose level • If QTcF ≥481 ms recurs, ribociclib should again be reduced by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who has therapy interrupted due to QTcF ≥481 ms.	If ribociclib is interrupted/ discontinued, everolimus should also be interrupted/discontinued. Resume everolimus at same dose level if ribociclib is resumed at same or lower dose level.

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
Grade 3 (QTc ≥501 ms on at least two separate ECGs	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Perform a repeat ECG within one hour of the first QTcF of ≥501 ms. • If QTcF remains ≥501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms. • If QTcF returns to <481 ms, ribociclib should be reduced by 1 dose level (please refer to the dosing schedule table). • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. Repeat ECGs 7 days and 14 days after dose resumption for any patient who has therapy interrupted due to QTcF ≥501 ms. If QTcF of ≥501 ms recurs, discontinue ribociclib	If ribociclib is interrupted/ discontinued, everolimus should also be interrupted/discontinued. Resume everolimus at same dose level if ribociclib is resumed at lower dose level.
Grade 4 (QT/QTc ≥501 or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia, unexplained syncope	Discontinue ribociclib+everolimus. Perform steps 1-4 as directed in "For All Grades." Obtain local cardiologist consultation (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.	

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
Stomatitis		
Grade 1 Minimal symptoms; normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouthwash several times per day	
Grade 2 Symptomatic but can eat and swallow modified diet	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at same or lower dose level.	Interrupt everolimus until recovery to Grade ≤ 1. Reinitiate everolimus at same dose. If recurs at Grade 2, interrupt dose until recover to Grade ≤ 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. Manage with topical analgesic mouth treatments.
Grade 3 Symptomatic and unable to adequately eat or hydrate orally	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at lower dose level.	Dose interruption of everolimus until recovery to Grade < 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
Grade 4 Symptoms associated with life-threatening consequences	Discontinue ribociclib+everolimus	Discontinue everolimus and treat with appropriate medical therapy
Non-infectious pneumonitis		
Grade 1 Asymptomatic, radiographic findings only	No dose adjustment required. Initiate appropriate monitoring.	
Grade 2 Symptomatic but not interfering with Activities of Daily Living (ADL)	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at same or lower dose.	Consider dose interruption of everolimus. Rule out infection and consider treatment with corticosteroids until symptoms improve to Grade < 1 Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. Discontinue everolimus if failure to recover within 4 weeks.
Grade 3 Symptomatic, interfering with ADL; Oxygen indicated	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at same or lower dose.	Dose interruption of everolimus until symptoms improve to Grade < 1 Rule out infection and consider treatment with corticosteroids Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. If toxicity recurs at Grade 3, consider discontinuation

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
Grade 4 Life-threatening, ventilator support indicated	Discontinue ribociclib+everolimus	Discontinue everolimus, rule out infection, and consider treatment with corticosteroids.
Metabolic Events (hyperglycemia, dyslipidemia)		
Grade 1	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at same or lower dose.	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
Grade 2	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at same or lower dose.	If toxicity is tolerable, no dose adjustment required. Manage with appropriate medical therapy and monitor.
Grade 3	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at lower dose.	Dose interruption of everolimus until recovery to Grade < 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. Manage with appropriate medical therapy and monitor.
Grade 4	Discontinue ribociclib+everolimus	Discontinue everolimus and treat with appropriate medical therapy
All other adverse reactions Non-hematologic (excluding metabolic events)		
Grade 1	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at same or lower dose.	If toxicity is tolerable, no dose adjustment required Initiate appropriate medical therapy and monitor.
Grade 2	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at same or lower dose.	If toxicity is tolerable, no dose adjustment required Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, interrupt dose until recovery to Grade ≤ 1. Re-initiate everolimus at same dose level. If the same toxicity recurs at grade 2, interrupt everolimus until recovery to grade ≤ 1 and re-initiate treatment at lower dose level (50% of previous dose).

Worst toxicity (CTCAE 4.03 Grade)*	Regimen Modifications for Ribociclib Management Recommendations	Regimen Modifications for Everolimus Management Recommendations
Grade 3	If everolimus is interrupted/ discontinued, ribociclib should also be interrupted/discontinued. Resume ribociclib at same dose level if everolimus is resumed at lower dose.	Dose interruption until recovery to grade ≤ 1. Initiate appropriate medical therapy and monitor. Re-initiate everolimus at the next lower dose level (50% of previous dose). If toxicity recurs at grade 3, discontinue treatment study.
Grade 4	Discontinue ribociclib+everolimus	Discontinue everolimus and treat with appropriate medical therapy.
Severity Description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms * Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All dose modifications should be based on the worst preceding toxicity. ** If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then continue treatment at the discretion of the Investigator. ***LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase and GGT. If dose reduction is required, the suggested dose is approximately 50% lower than the previously administered dose.		

Ribociclib dose adjustment and management recommendation for ILD/pneumonitis (CTCAE v4.03)

Grade	Dose Adjustment and Management Recommendations
1 (asymptomatic)	No dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated.
2 (symptomatic)	Interrupt ribociclib dose until recovery to Grade ≤1, then resume ribociclib at the next lower dose level*.
3 and 4 (severe)	Discontinue ribociclib

* An individualized benefit-risk assessment should be performed before resuming ribociclib

6.2.3.1 Guidelines for the follow-up of laboratory hematologic abnormalities

In case of any occurrence of febrile neutropenia, neutropenia ≥ grade 3, or thrombocytopenia ≥ grade 3, hematology tests must be performed weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 2. Subsequent monitoring must be performed every 3 weeks. (See Table 12)

6.2.3.2 Guidelines for the follow-up of laboratory liver abnormalities

In patients with any clinically relevant laboratory liver abnormality, as defined below, hepatic toxicity monitoring must include **ALL** of the following liver function tests (LFTs): albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), indirect bilirubin, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), creatine kinase, prothrombin time (PT) or INR and GGT. Note: for patients with Gilbert Syndrome, total and direct bilirubin must be monitored, but intensified monitoring applies to changes in direct bilirubin only. (See Table 12) In case of any occurrence of ALT/AST/total bilirubin increase to grade 2 the LFTs must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Thereafter monitoring must be continued every 2 weeks (or more frequently if clinically indicated) for two additional cycles (e.g. 6 weeks). If there is no recurrence of ≥ grade 2 ALT/AST/total bilirubin elevations during this period, subsequent monitoring must be performed every 3 weeks.

In case of any occurrence of ALT/ AST/ bilirubin increase to grade 3 or 4, LFTs must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Thereafter monitoring must be continued every 2 weeks (or more frequently if clinically indicated) for four additional cycles (e.g. 12 weeks). If there is no recurrence of ≥ grade 2 ALT/AST/total bilirubin elevations during this period, subsequent monitoring must be performed every 3 weeks.

Patients who discontinue ribociclib+everolimus treatment due to liver toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 3 weeks). (See Table 12)

6.2.3.3 Guidelines for the follow-up of laboratory renal abnormalities

In case of any occurrence of serum creatinine results of grade 2 or greater, tests must be performed weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Subsequent monitoring must be performed every 3 weeks.

In case of any occurrence of serum creatinine ≥ grade 3, tests must be performed twice weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Subsequent monitoring must be performed every 3 weeks. (See Table 12)

6.2.3.4 Guidelines for the treatment of study drug induced diarrhea

Mild to moderate diarrhea has been observed frequently in patients treated with ribociclib. Patients should be monitored for diarrhea and given appropriate supportive care with diagnostic or therapeutic intervention, including interruption of therapy with ribociclib as appropriate. If a patient has experienced ribociclib-related diarrhea, and it is considered

sufficiently severe to warrant the use of prophylactic anti-diarrhea therapy, then prophylaxis may be instituted in that patient with subsequent treatment.

6.2.3.5 Guidelines for the treatment of study drug induced nausea and vomiting

Preclinical studies have identified vomiting as an AE of ribociclib administration in dogs. Nausea and vomiting are the most common non-hematologic adverse reactions observed with ribociclib; the majority of cases are mild to moderate. Hence, prophylactic treatment with anti-emetics is not required when starting therapy with ribociclib. However, all patients should be carefully monitored for the development of nausea and/or emesis, and if they occur, treatment with anti-emetics may be instituted. If a patient has experienced ribociclib-related nausea and/or vomiting, and it is considered sufficiently severe to warrant the use of prophylactic anti-emetic therapy, then prophylactic therapy may be used in that patient with subsequent treatment.

Table 12 Follow-up evaluations for selected toxicities

Toxicity	Follow-up evaluation*
Investigations (hematologic)	Febrile neutropenia, neutropenia or thrombocytopenia ≥ CTCAE Grade 3 Test weekly (or more frequently) until ≤ Grade 2 Subsequent monitoring must be performed every 3 weeks
Investigations (hepatic)	Total ALT/AST/total bilirubin Grade 2: Test weekly (or more frequently) until ≤ Grade 1 Thereafter, continue to test every 2 weeks (or more frequently) for 2 cycles (6 weeks). If no recurrence of ≥ Grade 2 event, continue monitoring every cycle (3 weeks) Total ALT/AST/total bilirubin ≥ Grade 3: Test weekly (or more frequently) until ≤ Grade 1 Thereafter, continue to test every 2 weeks (or more frequently) for 4 cycles (12 weeks). If no recurrence of ≥ grade 2 event, continue monitoring every cycle (3 weeks) Discontinuation due to liver toxicity: Test weekly (or more frequently) until ≤ Grade 1 or stabilization
Investigations (renal)	Serum creatinine Grade 2: Test weekly (or more frequently) until Grade 1 Thereafter, test every cycle (3 weeks) Serum creatinine ≥ Grade 3: Test twice weekly (or more frequently) until ≤ Grade 1 Thereafter, test every cycle (3 weeks)
Investigations (Metabolic)	Hyperglycemia ≥ Grade 3 Test weekly (or more frequently) until Grade 1

*Note: this table refers only to the evaluation schedule to monitor selected toxicities. Refer to Table 11 Criteria for post-tumor resection interruption and re-initiation of ribociclib+everolimus treatment

6.3 Concomitant medications

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g., anti-emetics, anti-diarrheal agents) is permitted, except when specifically prohibited. Anesthesia may use medications that would otherwise be prohibited when deemed clinically necessary, but if possible should be avoided.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the ribociclib+everolimus treatment. All medications, including herbal/natural medications (excluding ribociclib treatment and prior antineoplastic treatments and blood

transfusions), surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose of administration of ribociclib treatment through 30 days after the last dose of treatment will be recorded. Medications include not only physician prescribed medications, but also all over-the counter (OTC) medications, herbal medications (prohibited, see Section 6.3.3), food or vitamin supplements, and blood transfusions.

For up to date information on prohibited medications please refer to the following websites:

- Medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes (please refer to http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm)
- Strong inhibitors or strong inducers of CYP3A4/5 (please refer to http://medicine.iupui.edu/flockhart/table.htm or http://www.druginteractioninfo.org)
- Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5, CYP2C8 and/or CYP2C9 (please refer to http://medicine.iupui.edu/flockhart/table.htm or http://www.druginteractioninfo.org)

6.3.1 Permitted concomitant therapy

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, herbal medicines, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

If patients take concomitant medications chronically, any change in dose schedule of concomitant medication throughout the study period should be clearly documented.

6.3.1.1 Palliative radiotherapy

In Phase 2 Palliative radiation is permitted. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow.

If palliative radiotherapy is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.

No dose modification of study treatment is needed during palliative radiotherapy.

Refer to the ribociclib Investigators Brochure and other drug package insert and Appendix 2 for information on possible interactions with other drugs.

6.3.1.2 Use of antiemetic medications

Ribociclib has low to minimal emetogenic potential according to a definition of antineoplastic agent emetogenicity (Grunberg et al, 2010). Antiemetic therapy can be used according to clinical guidelines for antineoplastic medications with low to minimal emetogenic potential for treatment and/or prevention of nausea and vomiting as a result of study treatment (NCCN Clinical Practice Guidelines in Oncology. Antiemesis, 2016; Roila F et al, 2016).

Potential drug interaction between ribociclib/placebo and antiemetic medications should always be taken into consideration. Example of prohibited antiemetic medication is intravenously administered ondansetron that in combination with ribociclib may precipitate TdP. Refer to Sections 6.3.1, 6.3.2 and 6.3.3 for list of medications that are prohibited or allowed to be used with ribociclib+everolimus.

If a clinical decision to use ondansetron is made in order to treat the patient, this will be recorded in the concomitant medications but will not be recorded as a deviation. Efforts to not utilize ondansetron should be made.

6.3.2 Permitted concomitant therapy requiring caution and/or action with ribociclib

Medications to be used with caution during ribociclib and everolimus in this study are listed below (see Appendix 2). This list is not comprehensive and is only meant to be used as a guide. These medications should be excluded from patient use if possible. If they must be given, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time.

- Moderate inhibitors or inducers of CYP3A4/5 (may increase or decrease ribociclib exposure, respectively)
- Moderate P-gp inhibitors and inducers
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index (ribociclib may increase exposure to these medications)
- Strong inhibitors of BSEP (based on in vitro data co-administration with ribociclib may lead to intrahepatic cholestasis)
- Medications that carry a possible risk for QT prolongation (may precipitate QT prolongation and TdP)
- Sensitive substrates of the renal transporters, MATE1, OCT2 and BCRP (has a potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements)

6.3.2.1 Hematopoietic growth factors

Prophylactic use of WBC growth factors with ribociclib is not recommended.

6.3.2.2 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially increasing the risk of reducing ribociclib drug exposure to subtherapeutic levels. Systemic corticosteroid treatment should not be given during the study, except for:

- Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);
- A short duration (< 5 days) of systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease, or as an antiemetic);

- Patients may be given dexamethasone alcohol-free mouthwash when starting everolimus treatment prophylactically for stomatitis;
- As determined by the investigator for clinical treatment.

Corticosteroid usage for CNS-related symptoms must be recorded, but are allowed.

6.3.2.3 Drugs that are metabolized by CYP450 enzymes

In vitro drug metabolism studies show that the metabolism of ribociclib is mediated by P450 enzymes CYP1A2, CYP2E1, and CYP3A4. Ribociclib is a time-dependent CYP3A4/5 inhibitor. Clinical studies have not yet been performed to confirm the potential effect of ribociclib on substrate drugs metabolized by these enzymes in patients.

Concomitant treatment of ribociclib with weak inhibitors or inducers of CYP3A4/5 is permitted. Caution is advised when ribociclib is co-administered with drugs that are moderate inhibitors or inducers of CYP3A4/5 (Appendix 2). Duration of concomitant treatment should be kept as short as possible, or completely avoided whenever possible. Patients receiving such medications must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require dose titration or adjustment. Note that co-administration of ribociclib with strong inducers of CYP3A4/5 is prohibited (Section 6.3.3.4).

Concomitant treatment of ribociclib with medications known to be metabolized by CYP1A2 and CYP2E1is allowed with caution (Appendix 2), except for drugs which have narrow therapeutic index/sensitive substrates for these CYP isoforms (Section 6.3.3.5 and Appendix 2).

6.3.2.4 Gastric protection agents

The use of gastric protection agents including antacids, H2-antagonists, and proton pump inhibitors (PPIs; Appendix 2) is allowed.

6.3.3 Prohibited concomitant therapy with ribociclib and everolimus

Patient must be able to stop receiving any of the following medications 7 days prior to starting study drug:

- Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pomelos/pummelos, star-fruit, pomegranates or pomegranate juice and Seville oranges.
- That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
- Strong P-gp inhibitors and inducers.
- Herbal preparations/medications, dietary supplements known as strong inhibitors or inducers of CYP3A4 or those with a known risk of QT prolongation.
- Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication are exclusionary to participation.

6.3.3.1 Other anticancer therapy

Anticancer therapy (chemotherapy, targeted therapy, biologic therapy, or radiation therapy (except palliative radiotherapy as described in Section 6.3.1.1), and anti-cancer surgery) other than the ribociclib treatment must not be given to patients while they are enrolled in the treatment trial (i.e.: during the initial 5-day regimen). If such agents are required then the patient must be permanently discontinued from the treatment portion of the study.

6.3.3.2 Hematopoietic growth factors

Hematopoietic growth factors may be used according to ASCO guidelines. **(http://jco.ascopubs.org/content/early/2015/07/08/JCO.2015.62.3488.full)**

6.3.3.3 Other investigational therapies

Other investigational therapies must not be used while the patient is on the study.

6.3.3.4 Strong CYP3A inhibitors and inducers

In vitro metabolism studies suggest that oxidative metabolism of ribociclib is predominantly mediated by CYP3A4/5.

Strong inhibitors or inducers of CYP3A4/5 are prohibited, with the exception of phenytoin and carbamazepine. Patients receiving other concomitant medications known to strongly inhibit and/or induce CYP3A4/5 that are deemed medically necessary should be excluded from the study. Refer to Appendix 2 for a list of these medications. Please note that this list may not be comprehensive. Patients should stop using medications at least 7 days prior to first dose of treatment.

6.3.3.5 Medications that are CYP2C8, CYP2C9 and CYP3A4/5 substrates with narrow therapeutic index

Ribociclib is a potent inhibitor of drugs metabolized by the cytochromes CYP2C8, CYP2C9 and CYP3A4/5 *in vitro*. Because of the potential risk for drug-drug interactions, using concomitant medications known to be metabolized by these enzymes and that have a low therapeutic index is not permitted in the study. Refer to Appendix 2 for a list of these medications. Please note that this list may not be comprehensive. Patients should stop using medications at least 7 days prior to first dose of treatment.

6.3.3.6 Herbal medications

Herbal preparations/medications are not allowed throughout the study, as a potential drug-drug interaction is always possible. These herbal medications include, but are not limited to: Cannabis Oil, St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

Patients should stop using herbal medications at least 7 days prior to first dose of treatment.

6.3.3.7 Medications that may prolong the QT interval or have a known risk of inducing Torsades de Pointes

There is preclinical and clinical evidence that ribociclib can induce QTc prolongation. [redacted] While events of QTc prolongation have been observed at the dose of 600 mg qd, none of these events have been clinically significant or associated with other cardiac abnormalities. QT changes become evident in the first cycle by Day 8 and later (once steady-state is reached), are associated with the maximum drug levels between 1 and 8 h post-dose, and remain stable or improve in subsequent cycles. All ribociclib protocols have strict eligibility criteria related to baseline cardiac status particularly related to arrhythmias and baseline increase in QT interval. Local ECG monitoring for changes in the QT interval are conducted at various time points. Criteria for stopping ribociclib treatment are provided if the QTcF is > 500 ms. Clear restarting guidelines are provided in all protocols.

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. In the case of a QTcF >500 ms, the ECG should be repeated and assessed by a physician to confirm the value. The mean value of three ECG collected at 2 min intervals should be used. Treatment with ribociclib should only be resumed once the reason for the QT prolongation (electrolyte abnormality, concomitant treatment etc.) has been identified and corrected, and the QTcF has returned below 500 ms.

The co-administration of medications that may increase the risk of QTc prolongation are prohibited in clinical trials with ribociclib. These include medications that may increase the exposure of ribociclib (e.g., strong CYP3A4 inhibitors; see 6.3.3.4) and medications that have a strong risk for QT prolongation. Medications that have a mild to moderate risk for QT prolongation should be used with caution. In case of QT prolongation, review of concomitant medication usage should be performed. A list associated with QT prolongation and Torsades de Pointes is available online at www.qtdrugs.org.

6.4 Patient numbering, treatment assignment

6.4.1 Patient numbering

After the patient has signed the consent form, a unique screening (baseline) number will be assigned. This number is a 4-digit number starting with 0001. Once assigned, a baseline number cannot be reused for another patient.

6.4.2 Treatment assignment

Patient assignment to one of the three time-escalation cohorts in Phase 0 will rotate with 1 patient being placed into cohort 1, then 1 patient into cohort 2, and then 1 patient into cohort 3 and so on, whenever possible. Flexibility of assignment into the time cohorts within a dose level will be allowed, per Sponsor discretion, to assist with the scheduling of patients at the investigative site. For each dose level, three to six patients will be enrolled into the time interval cohorts, sequentially whenever possible (e.g. cohort 1, cohort 2, cohort 3, cohort 1…), with at least 1 patient in each of the time intervals. See Section 4.1.1.

6.4.3 Treatment blinding

This study is open-label; therefore, the patient, the investigator's site personnel and Sponsor-Investigator are not blinded to treatment. Drug identity (name, strength) is included in the label text; disclosure envelopes are not provided.

6.5 Study drug preparation and dispensation

6.5.1 Study drug packaging and labeling

Clinical supplies will be obtained commercially by the Sponsor-Investigator and/or site investigator(s).

6.5.2 Drug supply and storage

Ribociclib/everolimus must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the product label(s).

6.5.3 Study drug compliance and accountability

Clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received, the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel if directly handling tablets or capsules that are returned (i.e., when counting returns). At the end of the study, all clinical supplies including partial and empty containers must be destroyed per institutional policies.

6.5.3.1 Study drug compliance

During Phase 0 of the trial, patients will receive 5 consecutive doses of ribociclib+everolimus and their compliance measure will be assessed by the study research nurse and principal investigator at each patient visit and information provided by the patient and/or caregiver. The same will apply when patients enroll in the Phase 2 continuation trial where patients receive 21 consecutive daily doses (3 weeks on / 1 week off).

6.5.3.2 Study drug accountability

The study research nurse and principal investigator will maintain study drug accountability for the duration of the proposed study. Records of study medication used, dosages administered, and intervals between visits and the completion of the study should be captured in the Drug Accountability Form.

6.5.3.3 Handling of other study treatment

Clinical supplies should be kept in a secured location; storage conditions: according to the product label(s). The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the institution or third party, as appropriate, if permitted by local regulations, policies and authorized by IBTC.

7 Visit schedule and assessments

7.1 Protocol flow and visit schedule

Table 13 lists all of the assessments and indicates when they are performed. Each post-surgical Phase 2 treatment cycle in patients is 28 days (the 28 days cycle length is fixed regardless of whether the dose of ribociclib+everolimus is withheld). All visits are to be scheduled according to the appropriate number of calendar days from Cycle 1 Day 1 of ribociclib+everolimus drug administration post-surgery. A visit window of ±1 in Cycle 1 Days 8, 15, 22 and ±3 days in Cycle 2 onward is allowed. PK sampling on Day 4/5 post-dose will have ±5 min window for 0.5hr and 1 hour samples and ±15min window for remaining samples (2, 4, 7h).

Note: If treatment with ribociclib+everolimus is withheld at any time during the post-surgical phase (Phase 2), all study visits, and safety assessments should continue according to the appropriate number of calendar days from Cycle 1 Day 1 as per the schedule of assessments.

Surveillance imaging will adhere to current clinical standards, which include MR imaging at a minimum of every 3 months for Grade III/IV recurrent gliomas.

Table 13 Visit evaluation schedule

	PHASE 0						PHASE 2					Survival Follow Up Call/Letter
	Screening/ Baseline	Enrollment	At Home	Pre-surgical assess-ment	Craniotomy for resection tumor resection	Phase 0 Follow - Up	Cycle 1 (28d)	Cycle 2 (28d)	Subsequent cycles (28d)	End of study treat-ment (EoT)	Safety Follow-up (phone)	
Visit Number	1	2	n/a	3	4	5	6-9	10-13	14, 15,...	Last		
Day of cycle	-28 to-1	Day 1	Day 2 & 3	Day 4	Cohort 1&2 Day 5 or Cohort 3 Day 6	Post-Operative Visit	Day of Cycle	Day of Cycle	Day of Cycle	Last	30 days after last dose	~every 3 months after safety phone call
Obtain Informed Consent	X											
Collect archival tissue	X											
Patient history												
Inclusion/exclusion criteria	X	Day 1 pre										
Diagnosis and extent of cancer	X											
Demography	X											
Relevant medical history/current medical conditions	X											
Prior antineoplastic therapy (meds, surgery, radiation)	X											
Prior/concomitant medications	X	Continuous									X	
Surgical and Medical Procedures	X	X		X	X	Continuous						
Phone Call / Letter												~Q3 months[13]
Safety assessments												
MRI of brain	X[1]					X (post-op)	MR imaging minimum every 3 months			last MRI obtained		
Response Assessment (RANO)	X[1]					X (post-op)	minimum every 3 months			X		
Physical examination	X[2]					X	1	1	1	X		
Performance status (ECOG)	X	X				X	1	1	1	X		
Height	X[2]											
Weight	X[2]					X	1	1	1	X		
ECG (12-Lead)	X[2]	X[2,4]		X[4]	X[4]	X	15[5]	1,15[5]	1[5,6]	X		

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	PHASE 0						PHASE 2					Survival Follow Up Call/Letter
	Screening/ Baseline	Enrollment	At Home	Pre-surgical assess-ment	Craniotomy for resection tumor resection	Phase 0 Follow - Up	Cycle 1 (28d)	Cycle 2 (28d)	Subsequent cycles (28d)	End of study treat-ment (EoT)	Safety Follow-up (phone)	
Visit Number	1	2	n/a	3	4	5	6-9	10-13	14, 15,...	Last		
Day of cycle	-28 to-1	Day 1	Day 2 & 3	Day 4	Cohort 1&2 Day 5 or Cohort 3 Day 6	Post-Operative Visit	Day of Cycle	Day of Cycle	Day of Cycle	Last	30 days after last dose	~every 3 months after safety phone call
Vital signs	X[2]					X	1, 15	1, 15	1	X		
Adverse events	Continuous—first study drug administration up to 30 days after last dose of study treatment										X	
Laboratory assessments												
Hematology (CBC w/Diff)	X			X[7]		X	15	1, 15	1	X		
Chemistry (CMP, Mg+, Phos)	X[2]			X[7]		X	15	1, 15	1	X		
eGFR[3]	X[2]			X[7]								
Coagulation (PT/INR, PTT)	X[2]			X[7]								
Lipid panel	X[2]								1[8]			
Urinalysis (dipstick) with microscopic analysis	X[2]						15	1	1			
Pregnancy test (serum HCG) if applicable	X[2]											
Pregnancy test (urine) if applicable						X	1	1	1	X		
Study Drug												
Drug administration		X[9]	X[9]	X[9]	X[9]		Daily Days 1-28 day cycle[10]					
Review of Home Dosing Diary and Symptom Diary				X			1	1	1	X		
PK & Biomarker sample collections												
PK Blood Sampling		X		X[11]	X[11]		1,8,15,22[10]	1,8,15,22[10]				
Collection of PK CSF					X							
Collection of PK/PD Tumor tissue					X					X[12]		
Biomarker blood collection	X[2]											

1 The most recent MRI scan available should be utilized.

	PHASE 0						PHASE 2					Survival Follow Up Call/Letter
	Screening/ Baseline	Enrollment	At Home	Pre-surgical assess-ment	Craniotomy for resection tumor resection	Phase 0 Follow - Up	Cycle 1 (28d)	Cycle 2 (28d)	Subsequent cycles (28d)	End of study treat-ment (EoT)	Safety Follow-up (phone)	
Visit Number	1	2	n/a	3	4	5	6-9	10-13	14, 15,...	Last		
Day of cycle	-28 to-1	Day 1	Day 2 & 3	Day 4	Cohort 1&2 Day 5 or Cohort 3 Day 6	Post-Operative Visit	Day of Cycle	Day of Cycle	Day of Cycle	Last	30 days after last dose	~every 3 months after safety phone call

2	Screening assessment may be completed at Day 1 predose, if completed at screening, does not need to be repeated at Day 1 pre-dose except for ECG and ECOG. Results must be available to confirm eligibility prior to dosing.
3	Estimated glomerular filtration rate (eGFR)
4	ECG Day 1 Pre-dose, Day 1: 2-4 hrs post-dose, and pre-surgical assessment (can be completed on Day 4 *or* Day 5 (Cohort 1&2) / Day 6 (Cohort 3)).
5	ECG Pre-dose and 2-4 hours post dose on C1D15, C2D15, C3D1, C6D1; C9D1; and every 3rd cycle…
6	ECG Pre-dose C2D1, C4D1, C5D1; C7D1, C8D1, C10D1, C11D1; and every 1st and 2nd cycle…
7	Performed at pre-surgical assessment as per SOC on Day 4 (can be completed on Day 5 (Cohort 1&2) or Day 6 (Cohort 3)).
8	Lipid panel performed every 4th cycle D1
9	Study drugs are administered in the clinics on D1, D4 and D5. Patients may take medications at home on D2 and D3
10	Trough blood sample is collected prior to the drug administration on that day. Study drugs are administered in the clinics on the clinic visit days 1, 8, 15, 22.
11	Blood samples will be obtained on Day 4 (the day before the surgery for Cohorts 1 & 2; 2 days before surgery for Cohort 3) at pre-dosing (trough level), 0.5, 1, 2, 4, 7 hours post dose (±5 min window for 0.5hr and 1hr; ±15min window for 2, 4, 7hr samples). A pre-dosing (trough level) blood sample will also be obtained on Day 5 and a sample will be collected intra-operatively. In Dose Level 4+ only, PK blood sampling will occur at the same timepoints (pre, 0.5, 1, 2, 4, 6, 8 and 24) but will be obtained on Day 5 (the day of surgery); the 24 hour sample will be obtained on Day 6.
12	Only Patients that have a recurrence and undergo an additional surgery for tumor resection
13	The start of follow up for long-term survival begins following completion of the Day 30 safety follow up call. Subjects will continue to be followed until death or withdrawal of consent for the collection and reporting of data or lost to follow-up for up to 5 years. Public records may be used to collect survival data, i.e., obituary notices and public database searches for survival information.

7.1.1 List of Efficacy/Pharmacokinetic/Pharmacodynamics and Pharmacometabolomics Measurements

7.1.1.1 Pharmacokinetic (PK) Measurements

Sample collection and processing: All patients will donate approximately a total of nine 6 mL blood samples (approximately 48ml of blood) the day before the surgery and during the surgery as noted in Table 13. If intravenous vein (IV) blood collection utilized, the approximate total volume of blood will be 58mL of blood. See the Ivy Brain Tumor Center Laboratory Manual for details regarding collection, processing, packaging and shipment.

PK sample analysis: The total and unbound concentrations of ribociclib and its active metabolite, LEQ803, in plasma, CSF, and tumor tissues (including contrast-enhancing and non-enhancing regions) will be determined by a validated LC-MS/MS method as described previously by us (Bao X, J Pharmaceutical and Biomedical Analysis, 2019). The total and unbound concentrations of everolimus in whole blood, CSF, and tumor tissues (including contrast-enhancing and non-enhancing regions) will be determined by a validated LC-MS/MS method. All analyses will be performed at the KCI Pharmacology Core Laboratory.

7.1.1.2 Pharmacometabolomics

Rationale: Novel metabolomics technologies allow high-throughput assessment of a large number of endogenous metabolites, which provide powerful tools for mapping biochemical pathways implicated in disease and in response to drug treatment. Pharmacometabolomics is an emerging field that applies metabolomics to define metabolic signature of drug exposure, thereby enabling identification of biochemical pathways implicated in drug efficacy and adverse drug reactions. By defining metabolite profiles both at baseline (prior to) and post drug exposure, pharmacometabolomics has the potential to provide early insights into mechanism of drug action and molecular basis for variation in drug response.

The plasma metabolic signatures of ribociclib plus everolimus exposure in patients will be defined using a LC-MS/MS based targeted metabolomics platform, which has been established in the Karmanos Cancer Institute Pharmacology Core (Bao X, J Clin Pharm, 2019).

We will identify the plasma metabolites that are significantly altered by ribociclib and everolimus exposure, which may provide insights into the mechanism of drug action. In addition, we will explore the associations between the metabolite changes and PK/PD parameters, toxicity, or clinical response. This may help identify potential metabolic biomarkers for the early prediction of clinical outcome.

Pharmacometabolomic samples: No extra sample collection is required for pharmacometabolomic study. Metabolomic profiling will be performed using the plasma PK samples collected at pretreatment and following the combination therapy at 2, 7, and 24 h.

LC-MS/MS based targeted metabolomics: Metabolites in plasma samples will be quantitatively profiled using a LC-MS/MS based targeted metabolomics platform in the Karmanos Cancer

Institute Pharmacology Core, as described previously (Bao X, J Clin Pharm, 2019). This platform can quantitatively measure about ~250 metabolites that are involved in major human metabolic pathways. All LC-MS/MS analyses were performed on an AB SCIEX QTRAP 6500 LC-MS/MS system. Analyst® 1.6 software was used for system control and data acquisition and MultiQuant 3.0 software was used for data processing and quantitation.

Metabolomic data analysis: Metabolomics data analyses were performed using the MetaboAnalyst web-based statistical package (http://www.metaboanalyst.ca/). Features (i.e., Metabolites) with >50% missing values were removed from the analysis, and the remaining missing values were replaced by the minimum value of a feature. To meet the normality assumption, individual metabolite concentrations were log-transformed and then auto-scaled (mean-centered and divided by the standard deviation of each metabolite). A one-way analysis of variance (ANOVA), if significant, followed by Fisher's LSD post-hoc analysis was performed to identify significantly changed metabolites among groups. The study of metabolic signature of the drug exposure in patients was intended to be hypothesis-generating and thus a false discovery rate (FDR) adjusted p-value < 0.2 along with unadjusted p-value < 0.05 was used to identify plasma metabolites significantly changed. A heat map was used to visualize metabolic signatures of ribociclib plus everolimus exposure, with significantly changed metabolites ranked in ascending order according to the FDR adjusted p-values from the ANOVA test.

7.1.1.3 Pharmacodynamic (PD) Measurements

See the Ivy Brain Tumor Center Laboratory Manual for details regarding collection, processing, packaging and shipment.

Identification of a positive PD effect (as defined by a significantly >30% decrease in the percentage of phospho-RB+ cells as well as phospho-S6+ cells) will be based upon comparative analysis of archival and post-treatment tumor tissue. Tumor tissues will be analyzed for pRB and total RB by immunohistochemistry (IHC). IHC analysis will be used to identify the status of pRB, RB, pFOXM1, FOXM1, pS6, S6, p-4EBP, cleaved caspase 3 and MIB-1 (ki67) in archival versus ribociclib+everolimus treated GBM tissue samples. For immunohistochemistry, the staining will be quantified using Aperio Brightfield Toolbox Software available at Barrow Neurological Institute. In addition, western blotting will be performed for pRB (S780), total RB, cleaved caspase 3 and MIB-1 on frozen treated tumor tissue and analyzed using the LiCOR Odyssey Imaging system. For comparison, treatment naïve tumor tissue with similar pathology from the Biobank will be used. The normalized average staining and/or luminescence for banked treatment naïve tumor will be used as a baseline to determine the pharmacodynamics of CDK4/CDK6 inhibition in the treated tumor tissues.

7.1.1.4 Biomarker Evaluation in Blood Samples

See the Ivy Brain Tumor Center Laboratory Manual for details regarding collection, processing, packaging and shipment. Pre-treatment blood sample will be collected for biomarker evaluation and baseline analysis. The tests include genetic sequencing to obtain status of the germline

mutations, liquid biopsy for tumor DNA or tumor secreted extra-cellular vesicles to identify biomarkers that will help predict drug efficacy.

7.1.1.5 Biomarker Evaluation in Tumor Samples

It has been shown that mTOR inhibition sometimes leads to paradoxical activation of upstream PI3K pathway activation. To assess this, protein from FFPE slides from pre- and post-treatment samples will be extracted and be analyzed by nanostring nCounter analysis system for their cancer panel examination. This cancer panel includes key components in the PI3K/mTOR signaling pathway, cell cycle pathway, MAPK as well as apoptosis pathways. The system also allows simultaneous comparison with protein and mRNA expression. This would allow comparison with surgical tissue with archival tissue.

Additional downstream target genes for E2F1 and mTOR pathways will be analyzed. Whole exome sequencing and RNAseq will be performed (Novogene). RNA and DNA will be extracted from matched archival and treated tissues (i.e.: pre- and post-treatment) for all patients, with blood samples as germline normal controls. RNA-sequencing and Exome sequencing will be performed to analyze differences in expression, mutations and copy number variations in genes before and after treatment. In addition, quantitative RT-PCR analysis will be performed for downstream genetic targets of E2F1 involved in cell cycle (CCNA1, CCNE1, CCNB1, CDK2, and CDK1), DNA replication (MCM2, MCM3, MCM5, MCM7, CDT1 and CDC6) and mitosis (CDC20, PLK1, MAD2 and CCNB1) to assess the effect of CDK4/6 inhibition. Since mTORC1 increases HIF1α and phosphorylated STAT3 protein levels, we will also assess expression levels of HIF1α and STAT3 target genes (VEGFa, MYC, CCND1 and BIRC5).

In addition, gliomas can be sub-classified by IHC as mesenchymal, proneural, or classical signatures based on the sequencing analysis and comparison to the TCGA database.

See the Ivy Brain Tumor Center Laboratory Manual for details regarding collection, processing, packaging and shipment.

7.1.1.6 Patient Derived Xenografts (PDX)

Participant-related tissue, cells and fluids from outpatient and inpatient sources will be collected by St. Joseph's Hospital and Medical Center (SJHMC); tissue will be processed, and stored by the IBTC team according to standard collection, processing, and storage procedures and with Institution Biosafety Committee (IBC) approval. The IBTC team will prepare all tissue samples according to approved protocols and/or standard procedures (also called Working Instructions, WIs) for storage, development into cell lines, creation of Patient-derived xenografts (PDXs) and/or preparation for histochemistry, as needed. Only SJHMC will be asked to collect tissue and provide to the IBTC. If a patient does not qualify for the treatment portion of the trial, the patient's intra-operative tissue may be collected if the patient has signed the informed consent and agrees to the tissue collection.

See the Ivy Brain Tumor Center Laboratory Manual for details regarding collection, processing, packaging and shipment.

7.1.1.7 Requirements for Historical and Post-treatment Tissue Samples

See the Ivy Brain Tumor Center Laboratory Manual for details regarding collection, processing, packaging and shipment.

7.1.1.7.1 Historical/Archival Tissue Samples

Pretreatment archival tissue samples will be requested to evaluate for PD and biomarkers to determine study eligibility after obtaining informed consent. Archival tissue will be requested from pathology lab.

Request will be for approximately 3-10-micron sections of archival tissue FFPE blocks which contain > 3 mm x 3 mm portions of viable tumor, on 10 unstained slides, a representative H & E slide from this tissue, and 12 scrolls of 20-micron thickness of the pathology core tissue for (2 scrolls per 2 ml tube), if there is adequate tissue available. Adjustments to the request may be made based on the available tissue. If adjustments are necessary, the decision should be made in conjunction with the nursing team, pathology lab and research lab.

7.1.1.7.2 Intraoperative Tissue Samples

Post-treatment surgical tissue should be placed in formalin until taken to hospital histology lab where it will be prepared as a FFPE block (see Appendix 3 for tissue fixation protocol) and then made into approximately 3-10-micron sections of 20 unstained slides plus one H & E slide and 12 scrolls of 20-micron thickness of the pathology core tissue for (2 scrolls per 2 ml tube), if there is adequate tissue available. In addition, one tumor sample (dimensions, 0.5 cm^3) will be collected from patients and divided into two equal portions.

The H&E slide will be examined by neuropathologist to confirm the presence of viable tumor in the resected tissue before proceeding with PD analysis.

7.1.1.8 Response Assessment in neuro-oncology criteria (RANO)

In Phase 0, RANO criteria will be used to confirm recurrence. In Phase 2, only those patients who have received at least one cycle of therapy and obtained an MRI in Phase 2 will be considered evaluable. Patients who have disease progression prior to the end of Cycle 1 will not be considered evaluable. The Phase 2 baseline MRI will be the first MRI taken post-operatively. Subsequent MRIs will be compared to the Phase 2 baseline.

MRI scans will be evaluated using the Criteria for response assessment incorporating MRI and clinical factors (Chukwueke, 2018)

7.1.1.8.1 Phase 2 Evaluation of Target Lesions

Complete Response (CR)

Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have achieved CR; the best response possible is SD.

Partial Response (PR)

Requires all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of scan evaluation.

Stable Disease (SD)

Requires all of the following: Does not qualify for CR, PR or progression; stable nonenhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Progressive Disease (PD)

Defined by any of the following: ≥25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response on stable or increasing doses of corticosteroids†; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy† not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

7.1.1.8.2 Evaluation of Non-Target Lesions

Complete Response (CR)

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

Incomplete Response/Stable Disease (SD)

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

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

7.1.1.8.3 Evaluation Response

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the date of surgery to time of progression.

7.1.1.9 Information to be collected at screening

Data to be collected on patient characteristics at screening include:

- Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Relevant medical history
- Diagnosis and extent of disease, including:
    - Date of diagnosis
    - Site of active disease
    - Prior antineoplastic therapies (medications, radiation, surgeries)
    - Prior and Concomitant
    - Medications, surgical and medical procedures
    - MRI

Note: All other medications taken within 28 days before the first dose of study treatment is administered must be recorded and updated on a continual basis if there is new change to the medication.

Patients will have the following performed at screening:

- Physical examination*
- Laboratory testing*:
    - Chemistry, (comprehensive metabolic panel, magnesium, phosphorus)
    - Hematology (CBC w/differential)
    - Coagulation (PT/INR, aPTT)
    - Lipid panel
    - Urinalysis
    - Serum pregnancy test (if applicable)
- Estimated glomerular filtration rate (eGFR)
- ECOG Performance Status
- 12-lead ECG
- Weight*
- Height*
- Vital signs*
- RANO assessment (see section 5.2)

*Assessments may be done at Day 1 predose as part of screening to determine eligibility. Results must be available prior to dosing to allow eligibility review by the investigator.

If assessments are available in the medical record at the investigator's site or from the patient's referring physician and are completed within the screening window, these may be utilized for eligibility review. All lab tests per protocol must be present.

7.1.1.10 Information to be collected on screening failures

A patient who signs an informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure.

7.1.1.11 Treatment period

Following completion of screening procedures and verifying patient eligibility, study treatment should start as soon as possible.

Patients who discontinue study treatment should be scheduled for a visit as soon as possible and within approximately 7 days after the last dose of study treatment, at which time all of the assessments listed for the EOT visit will be performed.

7.1.1.11.1 Day 1 Enrollment

The following assessments will be performed on Day 1:

- Review of surgical and medical procedures
- ECOG
- 12-lead ECG
- Collection of AEs and Concomitant medication(s)
- Screening assessments not previously collected as noted in section 7.1.1.9
- Day 1 pre-dose PK sample
- Day 1 pre-dose biomarker blood sample
- Confirm eligibility prior to study drug administration
- In clinic/hospital study drug administration
- Provide the patient the following for home dosing on Days 2 and 3
    - Instructions for study medication
    - Dosing Diary
    - Symptom Diary
    - Study drug

7.1.1.11.2 Day 2 and 3

Phase 0 patients will record study drug administration in the Dosing Diary and record symptoms in the Symptom Diary.

7.1.1.11.3 Day 4

The following assessments will be performed on Day 4:

- Review of medical and surgical procedures
- Collection of AEs and Concomitant medication(s)
- Review of home dosing diary and symptom diary

- 12-lead ECG
- Trough PK Sample (Dose Levels 0-3)
- Laboratory testing (may also be performed as a pre-surgical assessment on Day 5 or Day 6):
    - Chemistry, (comprehensive metabolic panel, magnesium, phosphorus)
    - Hematology (CBC w/differential)
    - Coagulation (PT/INR, aPTT)
    - eGFR
- In clinic/hospital study drug administration
- PK blood sampling: 0.5, 1, 2, 4, 7 hours post-dose (Dose Levels 0-3)
    - *In Dose Level 4+ only, PK blood sampling will occur on Day 5 instead of Day 4.*

7.1.1.11.4 Day 5

- Review of medical and surgical procedures
- Collection of AEs and Concomitant medication(s)
- 12-Lead ECG (if not collected on Day 4)
- In clinic/hospital study drug administration
- Craniotomy (Day 5 for Cohort 1 & 2; Day 6 for Cohort 3)
    - PK Collection of blood, CSF and tumor
    - Biomarker tumor collection
- Dose Level 1-3: Day 5 trough/24hrs post-dose
- Dose Level 4+ only: PK blood sampling: pre, 0.5, 1, 2, 4, 6, 8 and 24 hours (Day 6) post-dose

7.1.1.11.5 Follow-up / EOT visit

Phase 0 patients will have a follow up visit 7-14 days after surgery (routine post-operative visit). All Phase 2 patients should be scheduled for an EOT visit within 7 (±3) days following discontinuation of study treatment.

The following assessments will be performed at the EOT visit:

- Physical exam
- ECOG performance status
- Weight
- Vital signs
- Laboratory blood collections
    - CMP, magnesium, phosphorus
    - Hematology (CBC w/differential)
    - Urine pregnancy test (if applicable)
- 12-lead ECG
- Collection of AEs and Concomitant medication(s)
- MRI (last standard of care MRI completed)

Patients who have had a recurrence and who undergo an additional surgical procedure, may have tissue obtained and sent to the lab per Section 7.1.1.5.

7.1.1.11.6 Safety Follow Up

All Phase 0 and Phase 2 patients will have a safety follow-up phone call 30 days after last dose (±7) days following discontinuation of study treatment.

The following assessments will be performed at the safety follow-up phone call:

- Collection of AEs and Concomitant medication(s)

7.1.1.12 End of Phase Disposition

At a minimum, all patients who discontinue ribociclib+everolimus treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days ± 7 days following the last dose of treatment.

7.1.1.13 Criteria for patient withdrawal

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator if he/she violates the study plan or for administrative and/or other safety reasons. When a subject/ patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.

Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g., personal reasons) will be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will be made by the investigator and study statistician. The replacement will generally receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced. Both the replacement and originally allocated number will be unique numbers.

Patient death will be considered as a withdrawal from the study. Patients may also be withdrawn (the physician may decide to remove the patient from any further study activity) if any of the following occur:

- Adverse event(s) (see Section 8.1)
- Drug discontinuation if their surgery is delayed by 4 or more weeks due to drug toxicity
- Disease progression
- Major protocol deviation
- Technical problems
- Physician decision
- Non-compliance with study treatment.
- Death
- Completed

Patients must be withdrawn if any of the following occur:

- Lost to follow-up
- Subject/guardian decision
- Study terminated by sponsor
- Pregnancy (Pregnancy will be followed for outcome)

7.1.1.14 Replacement policy

Patients who do not receive a minimum of 5 daily doses or who vomit within 4 hours of any dose will be replaced upon Sponsor-Investigator discretion.

7.2 Assessment types

7.2.1 PK, PD, and pharmacometabolomics assessments

As described above.

7.2.2 Safety and tolerability assessments

Adverse experiences will be graded and recorded throughout the study according to NCI-CTCAE, version 4.03. Toxicities will be characterized in terms including duration, intensity, and time to onset. Safety endpoints will include all types of adverse experiences, in addition to laboratory safety assessments, ECOG performance scale status, and vital signs.

Safety evaluation will include the following and may also be performed at any time based on the clinical judgment of the Investigator.

Screening: vital signs, physical examination (including height/weight), ECOG, tumor evaluation, ECG

Post-Treatment: vital signs, physical examination, ECOG

Laboratory safety tests (e.g., INR/PT, aPTT, complete blood count, and serum chemistries) will be obtained and assessed per routine preoperative and/or postoperative neurosurgical protocols.

7.2.2.1 Physical examination

Physical examinations will include an examination as per standard of care. The exam may include a review of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a neurologic evaluation. The physical exam should be completed by appropriately licensed personnel as per institutional guidelines or as delegated by the Investigator.

7.2.2.2 Vital signs

Vital signs include body temperature, blood pressure, pulse, and pulse oximetry measurements. Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for five minutes.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening only.

7.2.2.4 Performance status

ECOG performance status will be assessed as per the assessment schedule (refer to Table 13). Assessment of ECOG performance status will be performed within the time windows described above of the scheduled assessment, even if study treatment is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated. (See Appendix 1). ECOG should be completed by a physician, nurse or other appropriately licensed personnel as delegated by the Investigator.

7.2.2.5 Laboratory evaluations

The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1).

Table 14 Clinical laboratory parameters collection plan

Test Name	Test Category
Hematology	Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils [% or absolute])
Blood Chemistry	Albumin, ALT, AST, calcium, corrected calcium, creatinine, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, potassium, sodium, fasting glucose, alkaline phosphatase, magnesium, phosphorus
Lipid Panel	HDL, LDL, triglycerides, cholesterol
Urinalysis	Macroscopic panel (dipstick) (bilirubin, blood, glucose, ketones, WBC, pH, protein, specific gravity) Reflexive Microscopic panel (RBC, WBC, casts)
Pregnancy test	At screening visit, serum pregnancy test At subsequent cycles, urinary pregnancy test.
Coagulation	International normalized ration (INR) and pro-thrombin time (PT) or Quick Test; activated partial thromboplastin time (PTT)

7.2.2.5.1 Hematology

Hematology assessments of the parameters listed in Table 15 will be tested as per the schedule of assessments (Table 13).

7.2.2.5.2 Clinical chemistry

Blood chemistry assessments of the parameters listed in Table 15 will be tested as per the schedule of assessments (Table 13).

7.2.2.5.3 Coagulation

International normalized ration (INR), prothrombin time (PT) and active partial thromboplastin time (aPPT) or Quick Test will be measured per the schedule of assessments (Table 13).

7.2.2.5.4 Urinalysis

Dipstick measurements will be performed as per Table 15 and according to the schedule of assessments (Table 13). Any significant findings on dipstick will be followed up with microscopic evaluation as per Table 15.

7.2.2.5.5 Pregnancy and assessments of fertility

During screening, a serum pregnancy test will be completed as per routine preoperative neurosurgical protocol prior to starting study treatment.

Women who are determined to be of child bearing potential before the study will only be tested at screening. When non-child bearing potential status is determined during the study, pregnancy testing will not be completed. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If a positive pregnancy test is performed in between study visits, the patients must immediately notify the investigator.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Adverse Events that are not serious will be captured following first administration of study drug.

Abnormal laboratory values or test results occurring after study drug administration are adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Information about all AEs is collected.

Except for screening failures, adverse events that begin or worsen after the first study drug administration should be recorded. Conditions that were already present at the time of informed consent should be recorded as part of medical history. Adverse event monitoring should be

continued for at least 30 days following the last dose of ribociclib+everolimus treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the study.

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

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and Ongoing at End of study)
3. Its relationship to the ribociclib and/or everolimus treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the ribociclib+everolimus treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented, should not be reported as a serious adverse event.

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. Events that are clearly related to surgical complications experienced as a result of the craniotomy and not related to study participation or the test article(s) should not be recorded as AEs. If there is any indication that the event may be related to study participation or the test article, the event should be recorded as an adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in ribociclib and/or everolimus treatment), should be recorded. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest (AESI)

Based upon the currently available information from the pre-clinical studies, mechanism of action, pharmacological class effect, and clinical data for ribociclib and everolimus, defined AESIs to date are: Hepatotoxicity, QT prolongation and Interstitial Lung Disease, and Pneumonitis.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- 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
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Hospitalization due solely to progression of the underlying cancer
- Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs.
- Events that are clearly related to surgical complications experienced as a result of the craniotomy and not related to study participation or the test article(s) should not be recorded as AEs. If there is any indication that the event may be related to study participation or the test article, the event should be recorded as an adverse event.

- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the first study drug administration and until at least 30 days after the patient has stopped treatment must be reported to Ivy Brain Tumor Center (IBTC) within 24 hours of learning of its occurrence.

Any SAE experienced after this 30 days period should only be reported if the investigator suspects a causal relationship to the treatment. Recurrent episodes, complications, or progression of the initial SAE 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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and send the completed, signed form safety@ivybraintumorcenter.org within 24 hours of learning of its occurrence.

The original copy of the SAE Report Form must be kept at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original 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, 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 treatment, IBTC may need to report the event in a MedWatch report to the FDA.

8.3 Emergency unblinding of treatment assignment

N/A

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to IBTC immediately (within 24 hours) of learning of its occurrence. Patients who become pregnant during the trial must be withdrawn. The pregnancy will be followed up from the estimated date of delivery plus 3 months 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.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 3 months after treatment has been stopped.

If a pregnancy occurs while on ribociclib treatment, the newborn will be followed for at least 3 months.

8.5 Warnings and precautions

No evidence available at the time of the approval of this protocol indicated that special warnings or precautions were appropriate, [redacted] or Product Label. [redacted] his information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

Patients will have blood drawn for clinical labs, PK and PD through direct venipuncture, whenever possible. Venipuncture may cause some pain, bleeding or bruising where the needle entered the patient's body. Some patients may have an intravenous (IV) catheter placed or a midline catheter for blood collection, as determined needed by the investigator. Placing an IV may cause some pain, and bleeding or bruising at the spot where the needle entered the patient's body. There may also be a risk of irritation of the vein (phlebitis), infection, blood clot, leakage or infiltration and/or nerve or tendon injury during insertion. Care will be taken to avoid these problems. The longer an IV catheter is left in place, the more common it is for redness or infection to develop. This information will be included in the patient informed consent and discussed with the patient as needed.

8.6 Data and Safety Monitoring Board

A group of experts will be assembled to assess the progress, safety data and, if needed critical efficacy endpoints of the study as part of a Data and Safety Monitoring Board. Safety and toxicity will be assessed throughout the study duration, including preoperative and peri-operative time periods. The DSMB charter will be documented in a separate document. Study stopping rules are, if two or more patients have a ≥ 4 week delay to surgery due to ribociclib or everolimus related toxicity, the study will be stopped. Also see Table 8 for additional stopping rules. Based on its

review, the DSMB will provide recommendations regarding study modification, continuation or termination.

8.6.1 Dose Escalations

At the time of dose escalation, a written report will be submitted to the DSMB Chair (or qualified alternate) describing the cohorts, dose levels, adverse events, safety reports and any DLTs observed. The DSMC Chair will review the report and provide a written authorization to proceed or request more information within 2 business days. Approval for the dose escalation must be obtained prior to implementation.

9 Data collection and management

9.1 Site monitoring

The Ivy Brain Tumor Center (IBTC) will be the monitoring entity for this study. A monitor from IBTC will audit study-related activities to ensure the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations and Good Clinical Practice (GCP).

9.2 Data confidentiality, collection, management, and quality control

All databases will be kept on a password-protected, HIPAA-compliant computer system, REDCap Cloud. REDCap is a secure web application with authentication and data logging. Only authorized study personnel will have access to the study data. Individually-identifiable health information will be protected by assignment of patient identifiers and password-protection of the key. Only the Investigators and the Research will have access to this database. All biological specimens will be de-identified and assigned the corresponding patient code from which they are derived.

9.3 Analysis sets

9.3.1 Full Analysis Set

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics division of the Ivy Brain Tumor Center (IBTC).

9.4 Patient demographics/other baseline characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of patients screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the Full Analysis Set (if any) will be summarized.

9.5 Primary objective

	Objective	Endpoint
Primary	• To determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) for study drug when administered in combination. • To identify recurrent high-grade glioma patients with positive PK and PD effects.	• MTD: highest dose of drug that did not cause a DLT in > 17% of participants • PK: total and unbound ribociclib and everolimus drug concentrations in non-enhancing and contrast-enhancing tumor tissue samples • PD: pRB-positive cells and pS6-positive cells

9.6 Secondary and exploratory objectives

	Objective	Endpoint
Secondary	• To explore safety and efficacy in recurrent high-grade glioma patients with demonstrated PK and PD effects and determine RP2D • To describe PK for Phase 2 patients	• Progression-free survival (PFS): rate measured from time of surgery to date of recurrence • Overall survival (OS): Median Overall Survival (OS) from time of surgery to date of death from any cause • Drug-related toxicity • RP2D • Systemic PK profiles of ribociclib and everolimus when combined.
Exploratory	• To explore evidence for CDK4/6 and mTOR pathway activity in tumor tissue (as compared to archival tissue) and mechanisms of resistance • Pharmacometabolomics: To explore the plasma metabolomic signature of the exposure of ribociclib and everolimus	• Quantification of total and phosphorylated forms of Rb, FoxM1, S6, 4EBP, as well as cleaved Caspase-3 and MIB1. Expression of Cyclin D1, Cyclin E1, PI3K/mTOR signaling components • Plasma metabolomic profiles (i.e., levels of ~250 metabolites) at the pretreatment and at predefined time points after the combination therapy. • Pharmacogenomics studies using RNA-seq and Whole Exome Sequencing to identify alterations in gene expression and mutational profile between pre-

	• To identify resistance mechanism and alternate pathways	treatment and post-treatment tissues and plasma.

9.6.1 Statistical hypothesis, model, and method of analysis

If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended. Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in results for the study. Post hoc exploratory analyses will be clearly identified. No separate Statistical Analysis Plan (SAP) will be issued for this study.

9.6.2 Safety objectives

Safety measurements are described in 7.2.2.

9.6.3 Adverse Events (AEs)

Adverse events (AEs) are described in 8.1.

9.7 Statistical Methods

All continuous variables (e.g., drug concentrations in plasma and high-grade glioma tissue, and any continuous PD biomarkers, and their pre/post treatment change) will be summarized with standard descriptive statistics (N, median, mean, standard deviation, minimum, maximum, and the 80% confidence interval [CI] for the mean). The 80% confidence level is appropriate for a Phase 0 study with small sample sizes.

These continuous variables will be summarized by time interval and overall. Statistical graphics (e.g., boxplots and scatterplots) will be used as appropriate. The pre/post treatment changes (as % change variables) will also be displayed as waterfall plots. All categorical variables (e.g., PD parameters such as scoring of Rb phosphorylation staining intensity: 0, 1, 2, or 3) will be summarized as frequency distributions. If dichotomized (e.g., score 2 or higher), those proportions will be described by point estimates and 80% CIs using the Wilson's method. These categorical variables will be summarized by time interval, and overall. The pre/post treatment changes in categorical variables (whether dichotomized or not) will be displayed as 2-way frequency distributions (i.e., contingency tables).

9.7.1 Objectives, endpoints, analysis, and sample size justification

The primary objective of Phase 0 dose escalation and expansion studies is to determine the MTD and to identify patients with positive PK and PD effects and the key secondary objective is to explore the clinical effect of everolimus plus ribociclib in recurrent GBM patients. The exploratory objectives are to explore pharmacometabolomics (PM) markers, mechanisms of resistance, and to examine evidence for CDK4/6 and mTOR pathway activity described in the

previous section. The primary endpoints are MTD as well as PK and PD effects, which are for the Phase 0 component, and the progression-free survival (PFS) is a key secondary endpoint, which are for the Phase 2 dose expansion component. Other endpoints for the secondary objective are RP2D, overall survival (OS) and drug-related toxicity. In particular, the positive PK effect will be defined as unbound ribociclib and everolimus drug concentrations in non-enhancing tumor tissue > *in vitro* IC50 of each agent. The positive PD effect will be defined as >30% decrease in pRB-positive cells and >30% decrease in pS6-positive cells. The PFS will be defined as the time duration from the date of surgery to disease progression or death from any cause and the OS the time duration from date of surgery to death from any cause. A Kaplan-Meier (KM) curve will be used to summarize the distributions of survival outcomes (PFS and OS) and the median PFS/OS and their associated 95% confidence interval (CI) will be estimated using KM estimates.

This study will be prospectively conducted as an open-label, multi-institution study (up to 3 sites) with four dose escalation and three time-escalation cohorts in the Phase 0 component and exploratory efficacy study in the dose expansion component. Patient assigned to one of the four dose escalation levels in Phase 0 will be assigned to one of three time-escalation cohorts in turn with 1 patient being placed into cohort 1, then 1 patient into cohort 2, and then 1 patient into cohort 3 and so on. Approximately 8 subjects in each cohort will be enrolled.

The required sample size will be from 6 (when Level 0 becomes MTD) to 32 patients (if dose Levels 1-5 are expanded to 6 and the time cohort is expanded to 8 additional patients). The expected sample size for the Phase 2 dose expansion study will be at most 3 to 12 patients under the assumption that at most 50% of Phase 0 dose escalation patients will have PK/PD responses. Considering the drop-out rate of 20%, the total required sample size will be approximately 30 patients.

Table 15 Target Accrual

Phase 0 Study	Cohort 1 Target Accrual	Cohort 2 Target Accrual	Cohort 3 Target Accrual
High-grade Glioma	3-11	3-20	3-11

The Phase 2 dose expansion study will be considered an exploratory study and no formal statistical comparison will be carried out. Thus, in this case, its outcome will be summarized with descriptive statistics (N, median, mean, standard deviation, minimum, maximum, and the 80% confidence interval [CI] for the mean).

9.7.2 Statistical considerations for accrual

Glioma patients will be accrued at up to 3 sites. We estimate that, in the 12 months after opening the proposed Phase 0 study, 190 recurrent WHO Grade III and IV patients will be study eligible and 30-40% of those readily enrolled. That yields an estimated BNI accrual rate of 57-76 patients/year and thus we anticipate complete study accrual within 12 months. For the Phase 2 dose expansion study, we estimate that approximately 50% of Phase 0 study patients will enroll.

10 Ethical considerations and administrative procedures

10.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

The initial informed consent form and any subsequent revised written informed consent form, and written information must receive the IRB/IEC's approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

10.3 Discontinuation of the study

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator if he/she violates the study plan or for administrative and/or other safety reasons. When a subject/ patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section

Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g., personal reasons) will be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will be made by the investigator and study statistician. The replacement will generally receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced. Both the replacement and originally allocated number will be unique numbers.

10.4 Publication of the study and results

10.4.1 Communication and Publication of Clinical Trial Results

Communication and publication of study results will be coordinated by Ivy Brain Tumor Center (IBTC).

10.5 Study documentation, record keeping and retention of documents

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable

regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

10.6 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to IBTC. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

10.7 Audits and inspections

Source data/documents must be available to inspections by IBTC or designee or Health Authorities.

10.8 Financial disclosures

N/A

11 Protocol adherence

11.1 Amendments to the protocol

All protocol amendments will be reviewed and approved by the IBTC, as well as each investigative site's IRB.

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13 Appendices

Appendix 1: ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	Descriptions
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

Appendix 2: List of prohibited concomitant medications and concomitant medications requiring caution

Table 16 Prohibited medications that are strong inducers or inhibitors of CYP3A, or CYP3A substrates with narrow therapeutic index

Category	Drug Name
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir,ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycinvoriconazole
Strong CYP3A4/5 inducers	Apalutamide, carbamazepine[3], enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin[3], rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[2,3]
CYP3A4/5 substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, lomitapide[5], lovastatin, nicardipine, nisoldipine, pimozide, quinidine, simvastatin, sirolimus, tacrolimus
Medications with a known risk for QT prolongation[4]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin,bepridil chloroquine, cocaine chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, levomethadyl, mesoridazine methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terlipressin, terodiline, terfenadine, thioridazine, vandetanib
Herbal preparations/ medications or dietary supplements	Herbal preparations/medications or dietary supplements known as strong inducers or inhibitors of CYP3A4/5 or those with a known risk of QT prolongation are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh, and ginseng. Patients should stop using these herbal medications or dietary supplements 7 days prior to first dose of study drug.
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, hormonal therapy, including but not limited to all SERMS [including raloxifene], biologic or radiation therapy [except for palliative radiotherapy as outlined in the protocol], and surgery) other than the study treatments must not be given while the patient is on the study medication. If such agents are required, then the patient must discontinue the study drug.

Category	Drug Name
[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes) or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood. [2] Herbal product [3] P-gp inducer [4] The list provided is as of December 2019.Check https www.crediblemeds.org/healthcare-providers/drug-list for the most updated list. [5] Drug has warning for risk of hepatotoxicity.As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at qtdrugs.org. Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University “Clinically Relevant” Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.	

Table 17 List of medications to be used with caution during study drug treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Aprepitant, amprenavir, asafoetida resin (Ferula asafoetida) cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein,lopinavir[5], modafinil, nafcillin, telotristat
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, aprepitant, atorvastatin, avanafil, bosutinib,brotizolam, budesonide, buspirone, cannabinoids[6], cannabidiol[6], cobimetinib, darifenacin, dasatininb, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, , levomethadyl (LAAM), lomitapide, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, simvastatin, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
BSEP inhibitors	Alectinib, atorvastatin, bromocriptine, candesartan, clobetasol, clofaziminie, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone,pioglitazone, reserpine,rifamycin, simeprevir, telmisartan,timcodar, troglitazone, velpatasvir
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine , asenapine, , atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib,clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine(retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, nicardipine, nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, osimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, tipiracil/trifluridine, tizanidine, tolterodine, toremifene,trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OCT1/2 substrates[4]	Amantadine, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxyplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium,, and zidovudine
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.

[2] The list provided is as of January 2018. Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

[3] MATE1 and MATE2 share considerable substrate specificity.

[4] OCT1 and OCT2 share considerable substrate specificity.

[5] Lopinavir and atazanavir is prohibited when combined with ritonavir (see Table 17)

[6] Based data that, exposure of cannabidiol (CBD), tetrahydrocannabinol (THC), 11-hydroxy THC, increased by ~2-3 folds when co-administered with ketoconazole (CYP3A4 inhibitor); Stott et al, Springerplus. 2013; 2: 236

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University “Clinically Relevant” Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.