Protocol Title

Phase II Trial of Everolimus or Everolimus plus Paclitaxel as First-line Therapy in Cisplatin-ineligible Participants with Advanced Urothelial Carcinoma: Hoosier Oncology Group GU10-147

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Trial Supported by
Novartis

Investigational New Drug (IND) Application #: Exempt

Version Date: 10JAN2014

PROTOCOL SIGNATURE PAGE

Phase II Trial of Everolimus as First-line Therapy in Cisplatin-ineligible Participants with Advanced Urothelial Carcinoma: Hoosier Oncology Group GU10-147

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Hoosier Oncology Group and keep a record for your files.

_____ _____
Signature of Investigator Date

_____
Investigator Name (printed)

_____
Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

_____ ❑ Not Submitting to IRB
Expected IRB Approval Date

PLEASE COMPLETE AND EMAIL TO HOOSIER ONCOLOGY GROUP

STUDY SYNOPSIS

TITLE	Phase II Trial of Everolimus as First-line Therapy in Cisplatin-ineligible Participants with Advanced Urothelial Carcinoma: Hoosier Oncology Group GU10-147
STUDY PHASE	Phase II
OBJECTIVES	Primary Objective: To evaluate clinical benefit rate (complete response, partial response, and stable disease) at 4 months from initiation of treatment. Secondary Objective: To determine the: • Safety of everolimus and everolimus plus paclitaxel in this participant population. • Progression-free survival. • Survival at 1-year from the initiation of treatment.
STUDY DESIGN	Participants will be enrolled into one of two parallel cohorts: : **Cohort 1 (single agent everolimus)** • Calculated creatinine clearance (Cockroft-Gault) < 60 ml/min **AND** Karnofsky performance status 60-70%. **Cohort 2 (everolimus plus paclitaxel)** • If participants have a calculated creatinine clearance (Cockroft-Gault) < 60 ml/min then their Karnofsky performance status must to be >70%. **OR** • If participants have a Karnofsky performance status of 60-70% then their calculated creatinine clearance (Cockroft-Gault) must be ≥ 60ml/min. Participants in cohort 1 will take everolimus 10 mg PO daily (continuously, without scheduled treatment interruptions). The cycle length will last 28 days. Everolimus will be dispensed on Day 1 of each cycle by the study center personnel on an outparticipant basis. Participants will be provided with an adequate supply of everolimus for self administration at home. Participants in Cohort 2 will take everolimus 10 mg daily continuously as described above for Cohort 1 participants. Participants in cohort 2 will also receive paclitaxel 80 mg/m2 IV as a 1 hour infusion on days 1, 8, and 15, of a 28-day cycle.
TOTAL NUMBER OF PARTICIPANTS FOR ACCRUAL	A total of 68 participants will be enrolled in this study.

ELIGIBILITY CRITERIA	• Written informed consent and HIPAA authorization for release of personal health information.
	• Age ≥ 18 years at the time of consent.
	• Must be ineligible for cisplatin, based on the following, within 30 days prior to registration for protocol therapy:
	Cohort 1 (single agent everolimus)
	  • Calculated creatinine clearance (Cockroft-Gault) < 60 ml/min AND
	  • Karnofsky performance status 60-70%
	Cohort 2 (everolimus plus paclitaxel)
	  • Calculated creatinine clearance (Cockroft-Gault) < 60 ml/min OR
	  • Karnofsky performance status 60-70%
	• Histological or cytological proof of transitional cell carcinoma (TCC) of the bladder, urethra, ureter, or renal pelvis (urothelial carcinoma). Histology may be mixed, but still requires a component of TCC.
	• Measurable disease according to RECIST and obtained by imaging within 30 days prior to registration for protocol therapy.
	
	NOTE: If the participant has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation.
	• Women of childbearing potential (WOCBP) and males of childbearing potential and their sexual partner(s) who are WOCBP must be willing to use a highly effective method of contraception from the time consent is signed until 8 weeks after treatment discontinuation. Examples of highly effective contraception methods include a combination of any two of the following:
	  o Use of oral, injected or implanted hormonal methods of contraception
	  o Placement of an intrauterine device (IUD) or intrauterine system (IUS)
	  o Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
	  o Total abstinence
	  o Male/female sterilization
	
	• WOCBP must have a negative pregnancy test within 7 days prior to prior to registration for protocol therapy.
	
	NOTE: Females are considered not of child bearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal (defined as amenorrhea for at least 12 consecutive months).
	• Females must not be breastfeeding.
	• No prior chemotherapy for metastatic disease. Prior chemotherapy

	in the neoadjuvant/adjuvant setting is allowed if completed at least 12 months prior to registration for protocol therapy. • No active CNS metastases or leptomeningeal metastases. Participants with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis. **NOTE:** A participant with prior brain metastasis may be considered if they have completed their treatment for brain metastasis, no longer require corticosteroids, and are asymptomatic. • No prior malignancy is allowed except for adequately treated basal cell or adequately treated squamous cell skin cancer, in situ cervical cancer, Gleason ≤ grade 7 prostate cancers (treated definitively with no evidence of PSA progression). Patients with other localized malignancies, definitively treated, and estimated at low risk of recurrence (<30%) based on available risk prediction tools, are eligible if approved by the sponsor investigator. • No treatment with any anticancer therapy or investigational agent within 30 days prior to registration for protocol therapy. • No known hypersensitivity to any protocol treatment. • No prior treatment with mTOR inhibitor (sirolimus, temsirolimus, everolimus). • No history of immunization with attenuated live vaccines within one week prior to registration for protocol therapy or during study period. • No history of any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as: o Symptomatic congestive heart failure of New York heart Association Class III or IV. (Please refer to the SPM). o Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease. o Severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or 0_2 saturation that is 88% or less at rest on room air. o Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN. o Active (acute or chronic) or uncontrolled severe infections. o Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis. o A known history of HIV seropositivity. o Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small

	bowel resection). o An active, bleeding diathesis. • No history of major surgery (defined as requiring general anesthesia) or significant traumatic injury within 30 days prior to registration for protocol therapy. **NOTE:** Must have recovered from the side effects of any major surgery. • Prior radiation therapy is allowed to < 25% of the bone marrow [see bone marrow radiation chart in the study procedure manual (SPM)]. **NOTE:** No radiation therapy within 30 days prior to registration for protocol therapy. **Laboratory values must be obtained within 7 days prior to registration for protocol therapy.** • Absolute neutrophil count (ANC) $\geq$ 1.5 K/mm^3 • Hemoglobin (Hgb) $\geq$ 9 g/dL • Platelets $\geq$ 100 K/mm^3 • Calculated creatinine clearance of < 60 using the Cockcroft-Gault formula: Males: $\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$ Females: Estimated creatinine clearance for males × 0.85 • Bilirubin $\leq$ 1.5 x ULN • Aminotransferases (AST and ALT) $\leq$ 2.5 x ULN (unless liver metastases, then $\leq$ 5 × ULN) • INR $\leq$ 1.5 (Anticoagulants are allowed if target INR $\leq$ 1.5 on a stable dose of warfarin or on a stable dose of Low molecular weight (LMW) heparin for at least 2 weeks prior to registration for protocol therapy). • Fasting serum cholesterol $\leq$300 mg/dL OR $\leq$7.75 mmol/L • Fasting triglycerides $\leq$ 2.5 x ULN. • Random serum glucose $\leq$ 1.5 x ULN **NOTE:** If random serum glucose is > 1.5 x ULN then a fasting serum glucose must be performed and must be $\leq$ 1.5 x ULN.
STATISTICAL CONSIDERATIONS	**Sample Size Considerations** This study will involve two parallel cohorts. **The study is not designed for statistical comparisons of the cohorts.** Each cohort will employ a separate Simon's 2-stage MinMax design.

	For cohort 1 (single agent everolimus), the sample size is based on the assumption that a clinical benefit rate of ≤ 10% is not worthy of further evaluation while a clinical benefit rate of ≥ 30% warrants additional testing. In the first stage, more than 1 participant with an objective response or stable disease (at 4 months) out of 15 evaluable participants is needed. In the second stage, an additional 10 evaluable participants will be required and more than 5 participants with an objective response or stable disease (at 4 months) are needed to consider the treatment successful with alpha = 0.05 and 80% power. The probability of early termination is 55% when the clinical benefit rate is ≤ 10%. For cohort 2 (single agent everolimus plus paclitaxel), the sample size is based on the assumption that a clinical benefit rate of ≤ 25% is not worthy of further evaluation while a clinical benefit rate of ≥ 45% warrants additional testing. In the first stage, more than 4 participants with an objective response or stable disease (at 4 months) out of 17 evaluable participants are needed. In the second stage, an additional 19 evaluable participants (for a total of 36 evaluable participants) will be required and more than 13 participants with an objective response or stable disease (at 4 months) are needed to consider the treatment successful with alpha = 0.05 and 80% power. The probability of early termination is 57% when the clinical benefit rate is ≤ 25%. For both cohorts, the primary endpoint is clinical benefit rate which includes response (defined as partial and complete response) and stable disease (at 4 months). It will be reported with 95% confidence intervals (CI). Survival which is part of the secondary endpoints will be calculated from the date of initiation of treatment to the death or last date of contact. Survival at 1 year will be estimated from a Kaplan-Meier analysis. Progression-free survival will be calculated from the date of initiation of therapy until progressive disease or death due to any cause. If the participant did not progress nor die, the participant will be censored on the date of the last disease assessment performed. Progression-free survival will be analyzed using the method of Kaplan and Meier. Toxicities will be graded according to the NCI Common Toxicity Criteria (version 4.0). Participants enrolled in this study will be carefully monitored during the entire treatment phase and will be followed as is appropriate, with safety evaluations. All participants receiving at least 1 dose of the study regimen will be included in the safety analysis. Incidence and type of grades 3 and 4 adverse events, including serious adverse events, will be tabulated and summarized using descriptive statistics. The participant is evaluable for efficacy if the participant receives at least one dose of treatment and at least one post-baseline disease evaluation. Dosage adjustments or interruptions will be based on treatment-related toxicity. Early discontinuation of treatment (<2 cycles) secondary to toxicity will be considered a treatment failure. Assume 10% of the cohorts are nonevaluable or dropout, we plan to accrue 68 (28+40) participants. Accrual rate of 2-4 participants per month is anticipated, and thus the trial accrual time will be approximately 17-34

	months. Potential biomarkers will be assessed by repeating the analysis of each clinical outcome with the level of each individual marker included as factor or covariate as appropriate. Markers with a continuous, rather than a discrete, measurement will also be evaluated as a discrete factor by dividing participants into low and high expression classes at the point of the distribution that maximizes the association between the marker and each clinical outcome. Significance of this association will be evaluated using a test for maximal chi-square values. Archival tissue samples will be submitted to a CLIA-certified lab for transcriptional profiling. The Co-Expression Extrapolation algorithm will be utilized to generate scores for sensitivity to paclitaxel and/or everolimus. The scores will be correlated with clinical outcomes. The correlation will be explored using Kendall's tau statistic. Baseline comorbidity scores will be calculated using the Charlson index and correlated with adverse events and clinical outcomes, which also be quantified using Kendall's tau statistic

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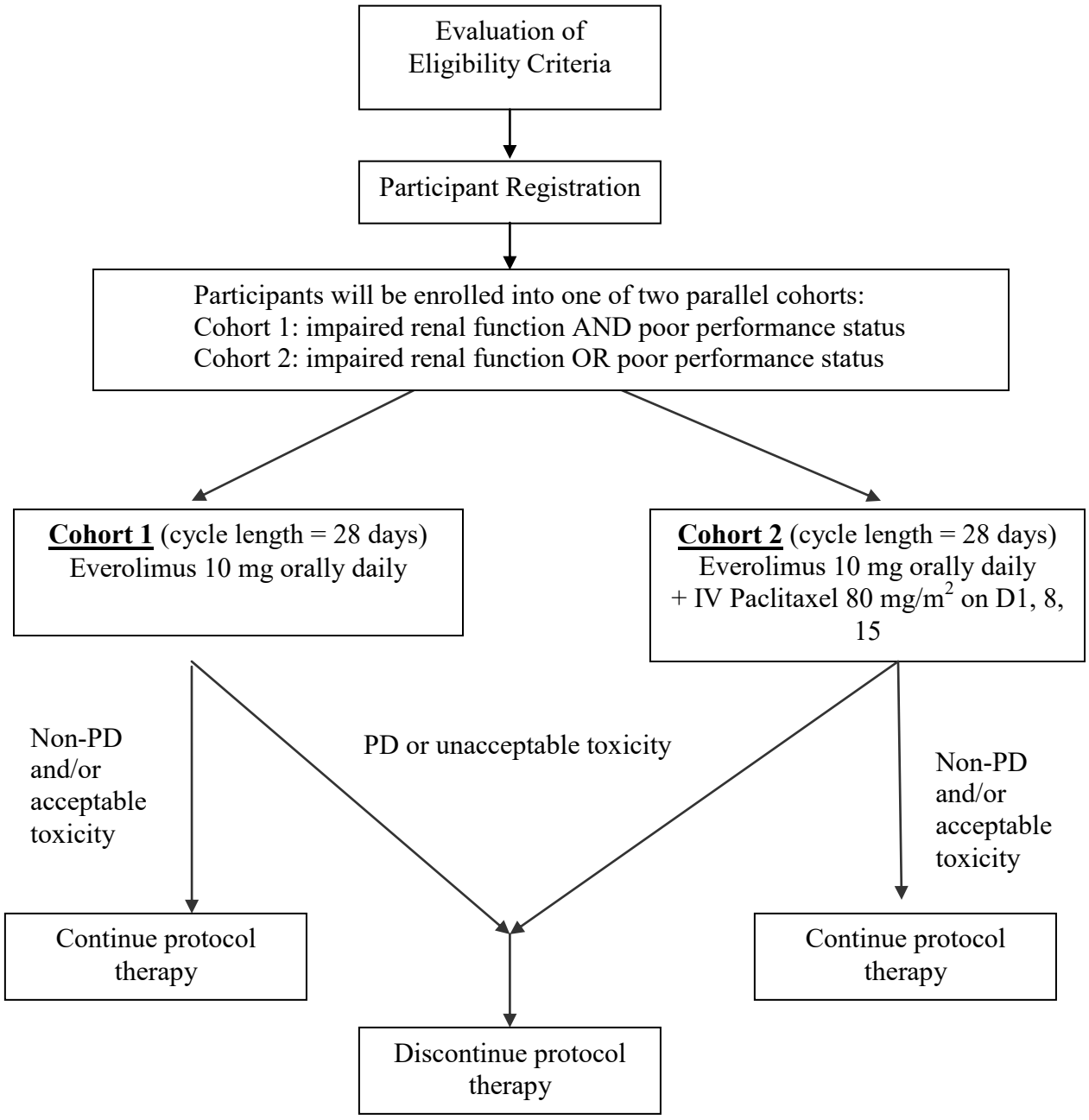
SCHEMA

Phase II Trial of Everolimus or Everolimus plus Paclitaxel as First-line Therapy in Cisplatin-ineligible Participants with Advanced Urothelial Carcinoma: Hoosier Oncology Group GU10-147



The cycle length = 28 days.
Restaging evaluations will be performed after every 2 cycles.

1 BACKGROUND & RATIONALE

Transitional cell carcinoma (TCC) of the urinary bladder is the second most common genitourinary malignancy. Each year in the United States, more than 60,000 participants will develop TCC and over 12,000 will die of their disease [1]. While TCC is a chemosensitive neoplasm, current therapeutic approaches are inadequate. Response durations are short and the median survival of participants with metastatic disease is slightly over 1 year [2]. These findings highlight the need for novel approaches to the treatment of metastatic TCC.

A large proportion of participants with TCC are ineligible for cisplatin-based therapy.

Cisplatin-based combination chemotherapy is considered the standard of care for participants with metastatic TCC. However, a large proportion of participants are ineligible for such treatment based on renal function or disease/functional status. In a retrospective study of 512 participants with pathologic stage ≥ T3 and/or node positive TCC being considered for adjuvant chemotherapy, approximately 40% were ineligible for cisplatin-containing therapy based on a calculated creatinine clearance of < 60 ml/min – in participants over 60 years old, 63% were ineligible [3]. The median age of diagnosis of advanced bladder cancer is 70, and the proportion of 'cisplatin-ineligible' participants is expectedly higher in the metastatic disease population. There is no standard treatment for cisplatin-ineligible participants with advanced urothelial carcinoma.

A recently reported randomized phase II study explored gemcitabine plus carboplatin versus methotrexate, vinblastine, plus carboplatin in cisplatin-ineligible participants with metastatic TCC. Cisplatin-ineligibility in this study was defined as a World Health Organization Performance Status of 2 and/or a creatinine clearance of < 60 ml/min [4]. Notably, this trial demonstrated that the severe acute toxicity rate was approximately 25% in participants with both impaired renal function and that these participants were the least likely to experience a response to treatment. The study of "new drugs with alternative mechanisms of action" in this participant population was recommended by the authors.

"Targeted" therapies as first-line treatment for cisplatin-ineligible participants.

Bellmunt et al explored the activity of sunitinib as a first-line treatment in participants with advanced urothelial carcinoma who were ineligible for cisplatin therapy [5]. Preliminary results indicated that of the 16 participants evaluable for efficacy, there were 2 partial responses, and 8 participants achieved stable disease lasting greater than 3 months for a clinical benefit rate of 64%. Notably, the median time to progression of 6 months compared favorably to chemotherapy in this population. This study demonstrates the feasibility of exploring "targeted" agents as first-line therapy in cisplatin-ineligible participants.

Rationale for mTOR inhibition in urothelial carcinoma

<u>Multiple lines of evidence support targeting mTOR in participants with urothelial carcinoma:</u>

1. PTEN mutations are present in approximately 30% of participants with urothelial carcinoma.
2. The PI3Kinase pathway is a key mediator of urothelial carcinoma invasion and prognosis [6-7].

3. mTOR pathway markers, including pS-6 and p-4E BP1, are overexpressed in the majority of participants with invasive urothelial carcinomas [8].
4. Inactivation of p53 and PTEN promotes tumorigenesis in human bladder cells and is correlated with poor survival in human tumors. The synergistic effects of p53 and PTEN deletion are mediated by deregulation of mTOR signaling [9].

Clinical experience with everolimus

Everolimus is an oral inhibitor of mTOR which has shown activity in a variety of hematologic malignancies and solid tumors. A randomized phase III trial of everolimus versus placebo in participants with renal carcinoma that had previously progressed on sunitinib, sorafenib, or both demonstrated an improvement in progression free survival with everolimus relative to placebo (4 vs. 19 months, $P < 0.001$)[10]. Everolimus was well tolerated with stomatitis, rash, and fatigue as the most common adverse events. This study led to the approval of everolimus by the US Food and Drug Administration for the treatment of renal carcinoma. Several ongoing studies are exploring mTOR inhibitors in a variety of tumor types.

Combination therapy with everolimus and paclitaxel

Paclitaxel is among the most active single agents in the treatment of urothelial carcinoma [11]. Furthermore, paclitaxel has demonstrated safety in the treatment of cisplatin-ineligible participants with metastatic urothelial carcinoma [12]. Preclinical data suggest that the PI3 kinase/Akt/mTOR signalling pathways may be associated with resistance to taxanes. Inhibition of mTOR has been shown to counteract Akt-mediated resistance to drugs inhibiting tubulin and to restore apoptosis in cancer cells [13-14]. In vivo combinations of everolimus and paclitaxel have demonstrated additive and synergistic effects in tumor models. The combination of paclitaxel plus everolimus has shown safety in a phase I trial, without apparent pharmacokinetic drug interactions [15]. A phase Ib/II study (study J2101) has explored weekly paclitaxel in combination with trastuzumab and everolimus in participants with metastatic breast cancer [16]. Trastuzumab (2mg/kg on day 1, 8, 15 and 22) and paclitaxel (80mg/m2 on day 1, 8 and 15) were administered in combination with 3 schedules of everolimus (5mg daily, 10mg daily, and 30mg weekly) in 4-week cycles. In this study, the 10mg daily was felt to demonstrate the most promising preliminary efficacy results. In addition, a pharmacodynamic model, supported by a clinical tumor pharmacodynamic study showed that the 10mg daily dosage achieved more profound and sustained suppression of mTOR activity than could be achieved with weekly dosing. Therefore, the 10mg daily dose of everolimus in combination with weekly paclitaxel and trastuzumab was selected for further development.

Given the safety and activity of weekly paclitaxel in cisplatin-ineligible participants with metastatic urothelial carcinoma, the preclinical evidence of synergy combining paclitaxel plus everolimus, and the safety of combination therapy in phase I testing, the combination of paclitaxel plus everolimus warrants evaluation in cisplatin-ineligible participants with advanced urothelial carcinoma.

Rationale for the current study

Several lines of evidence support the current study:

1. A large proportion of participants with advanced urothelial carcinoma are ineligible for cisplatin-based chemotherapy. There is no standard treatment for this participant population.

Furthermore, combination cytotoxic chemotherapy regimens are poorly tolerated by many of these participants 4.
2. Preclinical studies support targeting PI3K/AKT/mTOR signaling in urothelial carcinoma.
3. Everolimus is a well tolerated orally bioavailable inhibitor of mTOR with activity in multiple tumor types.
4. Prelinical studies have demonstrated synergistic antitumor activity when combining everolimus and paclitaxel supporting evaluation of this combination in cisplatin-ineligible participants with advanced urothelial carcinoma.

Rationale for treatment options:
There is no standard treatment for cisplatin-ineligible participants with metastatic bladder cancer and many participants in this subset tolerate combination chemotherapy poorly. Furthermore, a recent randomized phase II study of combination chemotherapy regimens in this participant population revealed that participants with both a poor performance status and impaired renal function had a high rate of severe acute toxicity with combination chemotherapy and were least likely to respond to therapy. Therefore, in the current study, participants with either poor performance status or impaired renal function will be assigned to treatment with paclitaxel plus everolimus while participants with both poor performance status and impaired renal function will be assigned to treatment with single-agent everolimus.

2 OBJECTIVES

2.1 Primary Objective:

To evaluate clinical benefit rate (complete response, partial response, and stable disease) at 4 months from initiation of treatment.

2.2 Secondary Objectives:

To determine the:

- Safety of everolimus and everolimus plus paclitaxel in this participant population.
- Progression-free survival.
- Survival at 1-year from the initiation of treatment.

2.3 Exploratory Objectives:

- To correlate mTOR pathway markers in archived tumor samples with clinical benefit rate.
- To correlate gene expression models derived from archived tumor samples using the Co-Expression Extrapolation Algorithm with clinical benefit rate.
- To correlate baseline Charlson comorbidity score with adverse events and clinical outcomes.

3 ELIGIBILITY CRITERIA

3.1 Written informed consent and HIPAA authorization for release of personal health information.

3.2 Age $\geq$ 18 years at the time of consent.

3.3 Must be ineligible for cisplatin, based on the following, within 30 days prior to registration for protocol therapy:

Cohort 1 (single agent everolimus)

- Calculated creatinine clearance (Cockroft-Gault) < 60 ml/min **AND**
  Karnofsky performance status 60-70%.

Cohort 2 (everolimus plus paclitaxel)

- If participants have a calculated creatinine clearance (Cockroft-Gault) < 60 ml/min then their
  Karnofsky performance status must to be >70%.
  OR
- If participants have a Karnofsky performance status of 60-70% then their calculated creatinine clearance (Cockroft-Gault) must be ≥ 60ml/min.

NOTE: Calculated creatinine clearance using the Cockcroft-Gault formula:

$$\text{Males: } \frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Females: Estimated creatinine clearance for males × 0.85

3.4 Histological or cytological proof of transitional cell carcinoma (TCC) of the bladder, urethra, ureter, or renal pelvis (urothelial carcinoma). Histology may be mixed, but still requires a component of TCC.

3.5 Measurable disease according to RECIST and obtained by imaging within 30 days prior to registration for protocol therapy.

NOTE: If the participant has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation.

3.6 Women of childbearing potential (WOCBP) and males of childbearing potential and their sexual partner(s) who are WOCBP must be willing to use a highly effective method of contraception from the time consent is signed until 8 weeks after treatment discontinuation. Highly effective contraception methods include a combination of any two of the following:

a. Use of oral, injected or implanted hormonal methods of contraception
b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
d. Total abstinence
e. Male/female sterilization

3.7 WOCBP potential must have a negative pregnancy test within 7 days prior to prior to registration for protocol therapy.

NOTE: Women are considered not of child bearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal (defined as amenorrhea for at least 12 consecutive months).

3.8 Females must not be breastfeeding.

3.9 No prior chemotherapy for metastatic disease. Prior chemotherapy in the neoadjuvant/adjuvant setting is allowed if completed at least 12 months prior to registration for protocol therapy.

3.10 No active CNS metastases or leptomeningeal metastases. Participants with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis.

NOTE: A participant with prior brain metastasis may be considered if they have completed their treatment for brain metastasis, no longer require corticosteroids, and are asymptomatic.

3.11 No prior malignancy is allowed except for adequately treated basal cell or adequately treated squamous cell skin cancer, in situ cervical cancer, Gleason ≤ grade 7 prostate cancers (treated definitively with no evidence of PSA progression). Patients with other localized malignancies, definitively treated, and estimated at low risk of recurrence (<30%) based on available risk prediction tools, are eligible if approved by the sponsor investigator.

3.12 No treatment with any anticancer therapy or investigational agent within 30 days prior to registration for protocol therapy.

3.13 No known hypersensitivity to any protocol treatment.

3.14 No prior treatment with mTOR inhibitor (sirolimus, temsirolimus, everolimus).

3.15 No history of immunization with attenuated live vaccines within one week prior to registration for protocol therapy or during study period.

3.16 No history of any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

- Symptomatic congestive heart failure of New York heart Association Class III or IV. (Please refer to the SPM).
- Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease.

- Severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or 0_2 saturation that is 88% or less at rest on room air.
- Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN.
- Active (acute or chronic) or uncontrolled severe infections.
- Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis.
- A known history of HIV seropositivity.
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).
- An active, bleeding diathesis.

3.17 No history of major surgery (defined as requiring general anesthesia) or significant traumatic injury within 30 days prior to registration for protocol therapy.

NOTE: Must have recovered from the side effects of any major surgery.

3.18 Prior radiation therapy is allowed to < 25% of the bone marrow [see bone marrow radiation chart in the study procedure manual (SPM)].

NOTE: No radiation therapy within 30 days prior to registration for protocol therapy.

Laboratory values must be obtained within 7 days prior to registration for protocol therapy.

3.19 Absolute neutrophil count (ANC) $\geq$ 1.5 K/mm^3

3.20 Hemoglobin (Hgb) $\geq$ 9 g/dL

3.21 Platelets $\geq$ 100 K/mm^3

3.22 Bilirubin $\leq$ 1.5 x ULN

3.23 Aminotransferases (AST and ALT) $\leq$ 2.5 x ULN (unless liver metastases, then $\leq$ 5 $\times$ ULN)

3.24 INR $\leq$ 1.5 (Anticoagulants are allowed if target INR $\leq$ 1.5 on a stable dose of warfarin or on a stable dose of Low molecular weight (LMW) heparin for at least 2 weeks prior to registration for protocol therapy).

3.25 Fasting serum cholesterol $\leq$300 mg/dL OR $\leq$7.75 mmol/L

3.26 Fasting triglycerides $\leq$ 2.5 x ULN.

3.27 Random serum glucose ≤ 1.5 x ULN
Note: If random serum glucose is > 1.5 x ULN then a fasting serum glucose must be performed and must be ≤ 1.5 x ULN.

4 PARTICIPANT REGISTRATION

All participants must be registered through Hoosier Oncology Group's electronic data capture (EDC) system.

Detailed guidelines for participant registration and electronic case report form (eCRF) completion can be found in the Study Procedures Manual (SPM) associated with this protocol.

Participants must be registered prior to starting protocol therapy and begin therapy within 5 business days of registration.

4.1 Randomization

There will be no randomization in this protocol.

4.2 Blinding

The study treatment is not blinded to the participant or the investigator.

5 TREATMENT PLAN

5.1 Treatment Plan

Participants will be enrolled into one of two parallel cohorts based on the following:

Cohort 1 (single agent everolimus)
- Calculated creatinine clearance (Cockroft-Gault) < 60 ml/min AND
- Karnofsky performance status 60-70%

Cohort 2 (everolimus plus paclitaxel)
- Calculated creatinine clearance (Cockroft-Gault) < 60 ml/min OR
- Karnofsky performance status 60-70%

Participants in cohort 1 will take everolimus 10 mg PO daily (continuously, without scheduled treatment interruptions). The cycle length will last 28 days. Everolimus will be dispensed on Day 1 of each cycle by the study center personnel on an outparticipant basis. Participants will be provided with an adequate supply of everolimus for self administration at home. All dosages prescribed and dispensed to the participant and all dose changes during the study will be recorded.

Participants are to bring their unused everolimus to the clinic on Day 1 of each cycle, and a new supply of everolimus will be dispensed on Day 1 of each cycle. Compliance should be verified by the investigator's staff by counting the number of tablets consumed between visits.

The participant will continue to take everolimus until disease progression (by RECIST criteria), unacceptable toxicity, death or discontinuation for any other reason (i.e. withdrawal of consent, administrative reasons). The participant will be asked to return all unused everolimus at the end-of-treatment visit.

Participants in Cohort 2 will take everolimus 10 mg daily continuously as described above for Cohort 1 participants. Participants in cohort 2 will also receive paclitaxel 80 mg/m2 IV as a 1 hour infusion on days 1, 8, and 15, of a 28-day cycle.

5.1.1 Pre-medication

There will be no standard pre-medications prior to administration of everolimus.

All participants in cohort 2 should receive premedication with corticosteroids, antihistamines and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Pre-medications for paclitaxel administration should be used per institutional guidelines.

5.1.2 Drug Administration

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for Everolimus will be described on the medication label. Everolimus is supplied by Novartis. Everolimus is formulated as tablets for oral administration of 2.5mg, 5mg, and 10mg strength. Tablets are blister-packed under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

The extent of absorption of everolimus through topical exposure is not known. Therefore, caregivers are advised to avoid contact with suspensions of Afinitor Tablets. Wash hands thoroughly before and after preparation of either suspension.

Participants will be instructed to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed. Patients will be instructed to take 10 mg tablets of everolimus orally with a glass of water, once daily at the same time each day. Everolimus may be taken with or without food; however, any dietary habits around the time of intake should be as consistent as possible throughout the study. The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. For patients unable to swallow tablets, the tablet(s) should be dispersed completely in a glass of water

(containing approximately 30 mL) by gently stirring until the tablet(s) is fully disintegrated (approximately 7 minutes), immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered. If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice. Everolimus should not be taken with grapefruit, star fruit, Seville oranges or juices containing those ingredients.

Table 1: Drug administration

Cohort	Drug	Dose	Frequency of administration	Length of the cycle
1	Everolimus	10 mg PO	Daily	28 days
2	Everolimus + Paclitaxel	10 mg PO + 80 mg/m^2 IV	Daily + Days 1, 8 and 15	28 days

NOTE: * IV Paclitaxel may be given ± 3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in participant's chart and case report forms.

NOTE: Drug dose may be recalculated only if participant's weight changes by > 10% during the course of the study.

5.1.3 Missed doses

Missed doses of either Everolimus or Paclitaxel will not be made up on subsequent days. Patients that meet criteria to proceed with treatment will resume with the next scheduled treatment.

5.2 Supportive Care

Administration of other chemotherapy or immunotherapy, or hormonal therapy (with the exception of contraceptives and replacement steroids), or experimental medications during the study is not allowed. Participants cannot receive radiation therapy while on study. Supportive care may be administered at the discretion of the treating Physician. Granulocyte colony stimulating factors may be used at the direction of the Treating Physician but should not be used prophylactically during cycle #1 or in lieu of a recommended dose reduction.

5.3 Concomitant Medications

Participants should be instructed not to take any additional medications (over-the-counter or other products including nutritional supplements) during the study without prior consultation with/approval from the treating physician.

Everolimus is metabolized primarily by the cytochrome P450 isoenzyme, CYP3A4, to produce its primary active metabolite. Drugs or substances known to be inhibitors, inducers or substrates of the isoenzyme CYP3A4 should be avoided unless use of the drug is essential and no substitute is available (strong inhibitors should not be used). Refer to Table 2 below for concomitant treatments to avoid. For a complete list of drugs which are substrates for CYP3A4, please refer to this website: **http://medicine.iupui.edu/flockhart/clinlist.htm**.

A strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance. A moderate inhibitor is one that causes a > 2-fold increase in plasma AUG valued or 50-80% decrease in clearance. A weak inhibitor is one that causes a > 1.25-fold increase in plasma AUC values or 20-50% decrease in clearance. (Distinction is not always categorical as interaction can vary according to conditions).

Table 2: Clinically relevant drug interaction: substrates, inducers, and inhibitors of isoenzyme CYP3A4

Substrates (competitive inhibition)	
Antibiotics1: clarithromycin* erythromycin telithromycin* Anti-arrhythmics: quinidine Benzodiazepines: alprazolam diazepam midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Protease Inhibitors: indinavir* ritonavir* saquinavir* Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine	Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors2: cerivastatin lovastatin simvastatin Miscellaneous: aripiprazole aprepitant buspirone gleevec* haloperidol methadone pimozide quinine sildenafil tamoxifen trazodone vincristine
Inducers	
Carbamazepine Dexamethasone	Primidone Progesterone

Ethosuximide Glucocorticoids Griseofulvin Nafcillin Nevirapine Oxcarbazepine Phenobarbital Phenylbutazone Phenytoin*	Rifabutin* Rifampicin* Rifapentin Roxfecoxib St John's Wort Sulfadimidine Sulfinpyrazone Troglitazone
Inhibitors	
Primidone Progesterone Rifabutin* Rifampicin* Rifapentin Roxfecoxib St John's Wort Sulfadimidine Sulfinpyrazone Troglitazone Cannabinoids Cimetidine Cisapride Clarithromycin Clotrimazole Cyclosporine Danazol Delaviridine Dexamethasone Diethyldithiocarbamate Diltiazem Dirithromycin Disulfiram Entacapone (high dose) Erythromycin Ethinyl estradiol Fluconazole Ketoconazole* Mibefradil Nefazodone* Nelfinavir* Norfloxacin Norfluoxetine	Fluoxetine Fluvoxamine* Gestodene Grapefruit juice Indinavir Isoniazid Itraconazole* Omeprazole Oxiconazole Paroxetine Posaconazole* Propoxyphene Quinidine Quinine Quinupristin and dalfopristin Ranitidine Ritonavir* Saquinavir* Sertindole Sertraline Sevilla orange Telithromcyin* Troglitazone Troleandomycin Valproic acid Verapamil Voriconazole* Zafirlukast Zileuton
Based on: Ingelman-Sunderberg, 2004 Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan; 369(1):89-104 and [http://www.medicine.iupui.edu/flockhart/clinlist.htm as of February 15, 2007] * Asterisk denotes strong inhibition/ induction. These strong inhibitors are not allowed during the study. [1]Macrolide antibiotics: Azithromycin is not a CYP3A4 substrate. It may therefore be employed where antibiotic therapy with a macrolide is desirable in a participant being treated with everolimus [2]Statins: Atorvastatin OR Pravastatin may be co-administered with everolimus, since a PK interaction study has shown that there is no relevant PK interaction.	

Strong inhibitors should not be co-administered with everolimus. Drugs or substances known to be inhibitors, inducers or substrates of the isoenzyme CYP3A4 should be avoided unless use of the drug is essential and no substitute is available.

The following concomitant treatments are not allowed during the study:

- Co-administration with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, ritonavir), and strong inducers (e.g., rifampin, rifabutin).
- Seville oranges, grapefruit, star fruit and their juices affect cytochrome P450 and PgP activity.

- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate inducers (e.g., carbamazepine, phenobarbital, and phenytoin) should also be avoided if possible or otherwise subject to caution (e.g., increased frequency of safety monitoring). If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus by approximately 50%. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the Everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.

Everolimus may affect the response to vaccinations making the response to the vaccination, less effective. Live vaccines (BCG, varicella, Zoster, typhoid, small pox, rubella, rotavirus, measles and mumps) should be avoided while a participant is treated with everolimus.

6 DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be used to grade adverse events.

Participants enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 7.

Participants will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Participants discontinued from the treatment phase of the study for any reason will be evaluated at least 30 days after the last dose of study drug.

6.1 Treatment-Limiting Adverse Event

A treatment-limiting adverse event is any adverse event related to protocol therapy experienced during the study resulting in treatment termination.

6.2 Dose Modifications

For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted. The guidelines set forth in this section should be followed. If treatment is interrupted due to toxicity, Everolimus should not be resumed until recovery to baseline or ≤ Grade 1, then reintroduce Everolimus at the initial dose or lower dose level depending on toxicity type and grade. **The maximum allowed time of interruption of Everolimus is 4 weeks.**

Patients enrolled in Cohort 2 who are unable to tolerate paclitaxel, may continue on protocol and receive Everolimus alone. In that instance, the schedule of events will be as per the schedule outlined for Cohort 1.

Table 3: Dose reduction for Everolimus

Dose Level	Dose and Schedule
0 (starting dose)	10 mg po daily
Decrease 1 dose level	5 mg po daily
Decrease 2 dose levels	5 mg po every other day
Note: If a participant has already decreased 2 dose levels, no further dose reduction is permitted. Participants requiring a third dose reduction must discontinue everolimus.	

Table 4: Dose reduction for Paclitaxel

Dose Level	Dose and Schedule
0 (starting dose)	80 mg/m2
Decrease 1 dose level	60 mg/m2
Note: If a participant has already decreased 1 dose level, no further dose reduction is permitted. Participants requiring an additional dose reduction will be required to discontinue paclitaxel.	

Table 5: Dosing guidelines for hematologic toxicities

AE	Grade	Required Dose Reduction
Thrombocytopenia	Grade 2 (platelets < 75-50 x 10^9/L)	**Everolimus:** No action. **Paclitaxel:** Hold until improvement to ≥ 75 x10^9/L. Reintroduce at the same dose level.
	Grade 3 (platelets < 50-25 x 10^9/L)	**Everolimus:** Hold until improvement to grade ≤ 1. If resolution occurs ≤ 7 days, reintroduce at the dose level prior to interruption. If resolution occurs > 7 days, or event occurs within 4 weeks, reintroduce at one dose lower if available. **Paclitaxel:** Hold until improvement to ≥ 75 x10^9/L. Reintroduce at the same dose level. If significant bleeding is associated, reintroduce at the next lowest dose level.
	Grade 4 (platelets < 25 x 10^9/L)	**Everolimus:** Hold until improvement to grade ≤ 1. Reintroduce at the next lowest dose level if available. **Paclitaxel:** Hold until improvement to ≥ 75 x10^9/L. Reintroduce at the next lowest dose level.
Neutropenia or anemia	Grade 3 (neutrophil <1-0.5 x10^9/L)	**Everolimus:** Hold until improvement to grade ≤ 1 or baseline value If AE resolution occurs ≤ 7 days, reintroduce at the same dose level. If AE occurs > 7 days, or event occurs within 4 weeks, reintroduce at the next lowest dose level if available. **Paclitaxel:** Hold until improvement to ≥ 1.5 x10^9/L. If improvement occurs ≤ 7 days, reintroduce paclitaxel at the same dose level. If improvement occurs ≥ 7 days, or event recurs within the same cycle, reintroduce at the next lowest dose level.
	Grade 4 (neutrophil < 0.5 x10^9/L)	**Everolimus:** Hold until improvement to grade ≤ 1 or baseline value. Reintroduce at the next lowest dose level if available.* **Paclitaxel:** Hold until improvement to grade ≤ 1 or baseline value. Reintroduce at the next lowest dose level if available.
Febrile neutropenia		**Everolimus:** Hold until improvement to grade ≤ 1 (or baseline value) and no fever. Reintroduce at the next lowest dose level if available.* If febrile neutropenia recurs, discontinue. **Paclitaxel:** Hold until improvement to neutrophils to grade ≤ 1 and no fever. Reintroduce at the next lowest dose level.

Recurrence of grade 3 toxicity after dose reduction		**Everolimus:** Reduce dose to the next lower dose level, if available. The lowest possible dose level of Everolimus is 5 mg every other day (2.5 mg daily). Below this level Everolimus must be discontinued. **Paclitaxel:** Reduce dose to the next lower dose level, if available.
*** Recurrence of grade 4 toxicity (including febrile neutropenia) after dose reduction**		**Everolimus/Paclitaxel:** Permanently discontinue treatment.
Toxicity requiring interruption for > 4 weeks	Any	**Everolimus/Paclitaxel:** Permanently discontinue treatment.

Table 6: Dosing guidelines for non-hematologic toxicities

AE	Grade	Required Dose Reduction	Recommended Management
Non-infection Pneumonitis			Please refer to Section 6.3.5
Reactivation of HBV or HCV flare			Please refer to Section 6.3.6
AST or ALT elevation	Grade 1 (> ULN – 3.0 x ULN) Grade 2 (> 3.0 – 5.0 x ULN)	**Everolimus:** Maintain current dose level **Paclitaxel:** Maintain current dose level	Medical management at investigator's discretion
AST or ALT elevation	Grade 3 (> 5.0 – 20.0 x ULN)*	**Everolimus:** Interrupt Everolimus administration until resolution to grade ≤ 1 (or ≤ grade 2 if baseline values were within range of grade 2). If resolution occurs ≤ 7 days, Everolimus should be restarted at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 4 weeks, hold Everolimus until recovery to grade ≤ 1 or baseline value and reintroduce Everolimus at one dose level lower, if available. **Paclitaxel:** Hold Paclitaxel until symptoms improve to grade ≤ 1 or baseline value. Reintroduce at the next lowest dose level if available.	
AST or ALT elevation	Grade 4 (>20.0 x ULN)*	**Everolimus:** Interrupt Everolimus administration until resolution to grade ≤ 1 (or ≤ grade 2 if baseline values were within range	

		of grade 2). If resolution occurs ≤ 7 days, Everolimus should be restarted at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 4 weeks, hold Everolimus until recovery to grade ≤ 1 or baseline value and reintroduce Everolimus at one dose level lower, if available. **Paclitaxel:** Hold Paclitaxel until symptoms improve to grade ≤ 1 or baseline value. Reintroduce at the next lowest dose level if available.	
Neurotoxicity	≥ 2	**Everolimus:** If intolerable to participant, hold until improvement to grade ≤ 1. Reintroduce Everolimus at the same dose level. **Paclitaxel:** Hold until improvement to grade ≤ 1. Reintroduce at the next lowest dose level.	Medical management at investigator's discretion
Stomatitis	2*/3	*For intolerable grade 2 AE **Everolimus:** Hold until improvement to grade ≤ 1or baseline value. If resolution occurs within ≤ 7 days, Everolimus should be reintroduced at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 4 weeks, hold Everolimus until recovery to grade ≤ 1 or baseline value and reintroduce Everolimus at next lowest dose level if available. **Paclitaxel:** No action.	Please refer to section 6.3.2.3 Medical management at investigator's discretion and as per protocol suggestions Patients will be withdrawn from study if they fail to recover to grade ≤ 1 or baseline within 4 weeks.
	Recurrence of intolerable grade 2 or grade 3 event after dose reduction	**Everolimus:** Reduce dose to next lower dose level, if available. The lowest possible dose level of Everolimus is 2.5 mg daily. Below this level, Everolimus must be discontinued. If toxicity recurs at Grade 3, consider discontinuation	
	4	**Everolimus:** Discontinue treatment. **Paclitaxel:** No action.	
Other toxicities (except specific	3	**Everolimus:** Hold until improvement to grade	Medical management at investigator's discretion

AEs above and hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section 6.3.4)		≤ 1 or baseline value. If resolution occurs within ≤ 7 days, Everolimus should b reintroduced at the dose level prior to interruption. If resolution takes > 7 days, or if AE recurs within 4 weeks, hold Everolimus until recovery to grade ≤ 1 or baseline value and reintroduce Everolimus at the next lowest dose level if available. **Paclitaxel:** Hold Paclitaxel until symptoms improve to grade ≤ 1 or baseline value. Reintroduce at the next lowest dose level if available.	and as per protocol suggestions Patients will be withdrawn from study if they fail to recover to grade ≤ 1 or baseline within 4 weeks.
Any other non-hematologic toxicity	4	**Everolimus:** Hold until improvement to grade ≤ 1 or baseline value. Reintroduce at the next lowest dose level if available. **Paclitaxel:** Hold Paclitaxel until symptoms improve to grade ≤ 1 or baseline value. Reintroduce at the next lowest dose level if available.	
Any non-hematologic toxicity recurrence after dose reduction	4	**Everolimus/Paclitaxel:** Permanently discontinue treatment.	Medical management at investigator's discretion
Clinical liver failure (asterixis or encephalopathy/coma)	3 / 4	**Everolimus/Paclitaxel:** Permanently discontinue treatment.	Medical management at investigator's discretion
Any non-hematologic toxicity requiring interruption for > 4 weeks		**Everolimus/Paclitaxel:** Permanently discontinue treatment.	Medical management at investigator's discretion
* Should HCV flare be confirmed, the guidelines for flare must take precedence (see Section 6.3.6)			

6.3 Management of Specific Everolimus related toxicities

Overall, safety data available from completed, controlled and uncontrolled studies indicate that Everolimus is generally well tolerated at weekly or daily dose schedules. The safety profile is characterized by manageable adverse events (AEs). These AEs are generally reversible and non-cumulative.

Adverse events most frequently observed with Everolimus are stomatitis, rash, diarrhea, fatigue, infections, asthenia, nausea, peripheral edema, decreased appetite, headache, dysgeusia, epistaxis, mucosal inflammation, pneumonitis, weight decreased, vomiting, pruritus, cough, dyspnea, dry skin, nail disorder, and pyrexia. Overall, the most frequently observed laboratory abnormalities include decreased hematology parameters including hemoglobin, lymphocytes, platelets, and neutrophils (or collectively as pancytopenia);

increased clinical chemistry parameters including cholesterol, triglycerides, glucose, aspartate transaminases,creatinine, alanine transaminases, and bilirubin; and decreased clinical chemistry parameters including phosphate and potassium. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2).

6.3.1 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking Everolimus Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally have had a fatal outcome.

Physicians and patients should be aware of the increased risk of infection with Everolimus Treat pre-existing infections prior to starting treatment with Everolimus. While taking Everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Everolimus.

If a diagnosis of invasive systemic fungal infection is made, discontinue Everolimus and treat with appropriate antifungal therapy.

6.3.2 Management of skin toxicity

For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

6.3.2.1 Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

6.3.2.2 Renal Failure Events

Cases of renal failure (including acute renal failure), some with fatal outcome, occurred in patients treated with everolimus. Renal function of patients should be monitored

particularly where patients have additional risk factors that may further impair renal function.

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking everolimus. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

6.3.2.3 Management of stomatitis/oral mucositis/mouth ulcers

Adverse Drug Reaction	**Severity**	**Everolimus Dose Adjustment and Management Recommendations**
Stomatitis	Grade 1 (Minimal symptoms, normal diet)	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 (Symptomatic but can eat and swallow modified diet)	Temporary dose interruption until recovery to grade ≤1. Re-initiate study drug at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate study drug at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine,butyl aminobenzoate, tetracaine hydrocholoride, menthol or phenol)with or without topical corticosteroids (i.e. triamcinolone oral paste)*.
	Grade 3 (Symptomatic and unable to adequately eat or hydrate orally)	Temporary dose interruption until recovery to grade ≤1. Re-initiate study drug at lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine,butyl aminobenzoate, tetracaine hydrocholoride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*
	Grade 4 (Symptoms associated with life-threatening consequences)	Discontinue study drug and treat with appropriate medical therapy.

* using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa e.g. gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to Everolimus should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with Everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (Grade 1), no dose adjustment required. Manage with **non-alcoholic mouth wash or salt water (0.9%) mouth wash** several times a day until resolution.

2. For more severe toxicity (Grade 2 in which case participants have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case participants cannot maintain adequate oral alimentation), the suggested treatments are **topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol)** with or without **topical corticosteroids,** such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

4. Antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all participants due to their strong inhibition of Everolimus metabolism, thereby leading to higher Everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

6.3.3 Management of diarrhea

Appearance of grade 1-2 diarrhea attributed to study drug toxicity may be treated with loperamide, initiated at the earliest onset (for example 4 mg orally followed by 2 mg orally every 2 hours until resolution of diarrhea).

6.3.4 Management of hyperlipidemia and hyperglycemia

Adverse Drug Reaction	**Severity**	**Everolimus Dose Adjustment and Management Recommendations**
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate study drug at lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue study drug and treat with appropriate medical therapy.

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (> 300 mg/dL or 7.75 mmol/L) or Grade 2 hypertriglyceridemia (>2.5 x ULN) should be treated with a 3-

hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death.

Participants should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors. The risk versus benefit of using this therapy should be determined for individual participants based on their risk of cardiovascular complications of hyperlipidemia.

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking everolimus. Monitoring of blood cholesterol and triglycerides prior to the start of everolimus therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Hyperglycemia has been observed in participants receiving everolimus therapy. Monitoring of fasting serum glucose is recommended prior to the start of Everolimus and periodically thereafter. More frequent monitoring is recommended when everolimus is co-administered with other drugs that may induce hyperglycemia. Optimal glucose control should be achieved before starting a participant on everolimus and glucose should be monitored during everolimus therapy.

6.3.5 Management of non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

- A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.

If non-infectious pneumonitis develops, the guidelines in the Table below should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 7: Management of non-infectious pneumonitis

Worst grade pneumonitis	Required investigations	Management	Everolimus dose adjustment
Grade 1 (Asymptomatic, radiographic findings only)	CT scans with lung windows. Repeat at least every 3 cycles until return to within normal limits.	No specific therapy is required.	Administer 100% of everolimus dose. Initiate appropriate monitoring.
Grade 2 (Symptomatic, not interfering with Activities of Daily Living)	CT scan with lung windows. Consider pulmonary function testing including: spirometry, DLCO and room air 0_2 saturation at rest. Consider bronchoscopy*. Repeat each subsequent cycle until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of Everolimus until recovery to Grade ≤ 1. Re-initiate Everolimus at one dose level lower. Participants will be withdrawn from study if they fail to recover to ≤ Grade 1 within 4 weeks. Everolimus dose cannot be escalated.
Grade 3 (Symptomatic, Interfering with Activities of Daily Living. O_2 indicated	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO and room air 0_2 saturation at rest. Repeat each subsequent cycle until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy is recommended*.	Prescribe corticosteroids if infectious etiology is ruled out. Taper as medically indicated.	Rule out infection and hold treatment until recovery to Grade ≤ 1. Consider re-initiating Everolimus at one dose level lower (approximately 50% lower than the dose previously administered depending on individual clinical circumstances). Discontinue Everolimus if failure to recover within ≤ 4 weeks. If toxicity recurs at Grade 3, consider discontinuation
Grade 4 (Life-threatening, ventlatory support indicated)	CT scan with lung windows and required pulmonary function testing, if possible, including: spirometry, DLCO and room air O_2 saturation at rest. Repeat each subsequent cycle until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible*.	Consider corticosteroids if infectious etiology is ruled out. Taper as medically indicated.	Rule out infection and discontinue treatment.
*If bronchoscopy is performed, a biopsy and/or bronchiolar lavage (BAL) should be performed.			

6.3.6 Management of Hepatitis reactivation/ flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo 2004). Sporadic cases of Hepatitis B reactivation have also been seen in this setting with Everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality (Loomba 2008). A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

6.3.6.1 Monitoring and prophylactic treatment for hepatitis B reactivation

Details of monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing.

Table 8: Action to be taken based on screening hepatitis B results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBs Ab	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBc Ab	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of study drug Monitor HBV-DNA approximately every 4-8 weeks		No prophylaxis Monitor HBV-DNA approximately every 3-4 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug. For HBV reactivation definition and management guidelines, see Table 9.

Table 9: Guidelines for management of hepatitis B reactivation

HBV reactivation (with or without clinical signs and symptoms)*	
For participants with baseline results: Positive HBV-DNA **OR** positive HBsAg --- **reactivation is defined as:** [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value **OR** new appearance of measurable HBV-DNA]	**Treat**: Start a second antiviral medication AND Interrupt study drug administration until resolution: • ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days** study drug should be re-started at one dose lower, if available. (see Table 3 & 4 – Study drug dose reductions) If the participant is already receiving the lowest dose of study drug according to the protocol, the participant should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. **If resolution occurs > 28 days** Participants should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.
For participants with baseline results: Negative HBV-DNA **and** HBsAg **AND** [Positive HBs Ab (with no prior history of vaccination against HBV), **OR** positive HBc Ab] --- **reactivation is defined as:** New appearance of measurable HBV-DNA	**Treat** : Start first antiviral medication AND **Interrupt** study drug administration until resolution: • ≤ undetectable (negative) HBV-DNA levels **If resolution occurs within ≤ 28 days** study drug should be re-started at one dose lower, if available. (see Table 3 & 4 – Study drug dose reductions) If the participant is already receiving the lowest dose of study drug according to the protocol, the participant should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. **If resolution occurs > 28 days** Participants should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

* All reactivations of HBV are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.

6.3.6.2 Monitoring for hepatitis C flare

The following two categories of participants should be monitored every 4–8 weeks for HCV reactivation:

- Participants with detectable HCV RNA-PCR test at screening.
- Participants known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered 'cured')

For definitions of HCV flare and actions to be taken in the event of a flare, please refer to Table 10.

Table 10: Guidelines for management of hepatitis C flare*

Baseline results	HCV flare definition*	HCV flare management
Detectable HCV-RNA	> 2 $\log_{10}$ IU/mL increase in HCV-RNA **AND** ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA **AND** ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus

* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 4.0 – Metabolic/Laboratory- Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).

6.3.7 Management of anemia

Investigator should manage anemia as medically indicated per institutional guidelines.

7 STUDY CALENDAR & EVALUATIONS

Study Day	Pre-study		Cycles (1 cycle = 28 days)			End of treatment visit	Follow up[12]
	-30 days	-7 days	Day 1[5]	Day 8	Day 15	30 days (± 7) after last treatment	
REQUIRED ASSESSMENTS							
Medical history	X						
Height	X						
Physical examination	X		X			X	
Vital signs, weight	X		X			X	
Karnofsky performance status	X		X			X	
Charlson comorbidty score	X						
Calculated Creatinine Clearance (Cokcroft-Gault)	X	X	X			X	
PTT and INR		X					
Blood Chemistries[1]		X	X			X	
Cohort 2: Creatinine				X	X		
Cohort 1: WBC, Hgb, Plts		X	X			X	
Cohort 2: WBC, Hgb, Plts		X	X	X	X	X	
Fasting serum glucose		X					
Lipid profile (fasting)		X	X[2]			X	
Hepatitis B and C testing	X[3]						
Urine pregnancy		X					
Adverse event and concomitant medication assessment	X		X			X	
DISEASE ASSESSMENT							
CT chest , abdomen, pelvis	X		X[4]				X
Bone scan	X[5]		X[5]				
CT scan or Brain MRI	X[6]						
TREATMENT							
Everolimus[7]			X	X	X		
Cohort 2 only: Paclitaxel			X	X	X		
CORRELATIVE STUDIES							
Archived tumor block submission[8]			X				
Tumor slide submission[9]			X				
Optional whole blood[10]			X				
Optional plasma and serum [11]			X			X	
FOLLOW-UP							
Disease progression and survival							X

See Next Page for Study Calendar & Evaluations Footnotes.

Study Calendar & Evaluations Footnotes:

1. Comprehensive metabolic panel (sodium, potassium, BUN, creatinine, AST, ALT, Alk.phos, total bilirubin, magnesium, calcium, and phosphorus) on day 1 of each cycle.
2. A lipid panel should be checked every other month after baseline.
3. Please refer to section 6.3.6 for testing parameters.
4. Participants will undergo repeat cross-sectional imaging (CT scan of the chest, abdomen, and pelvis) after every 2 cycles until disease progression.
5. Bone scan should be done at baseline only if clinically indicated (elevated alkaline phosphatase, bone pain), and repeated every 2 cycles if clinically indicated
6. Participants with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis.
7. Participants will receive Everolimus 10 mg PO daily continuously (in the absence of a dose delay or dose reduction for toxicity).
8. Submission of an archived paraffin embedded tumor block for COXEN analysis. If the previous biopsy is not available, a discussion needs to take place with the Sponsor Investigator ,participants will not need to undergo a new biopsy. See SPM for collection and shipping instructions.
9. Submission of unstained tumor slides for Immunohistochemical staining and for banking for future use from the participant‘s previous biopsy are requested. If the previous biopsy is not available, a discussion needs to take place with the Sponsor Investigator, participants will not need to undergo a new biopsy. See SPM for collection and shipping instructions.
10. Optional whole blood for banking for future use is requested at Cycle 1 Day 1, pretreatment. See SPM for collection and shipping instructions.
11. Optional serum and plasma are requested at Cycle 1 Day 1 (pretreatment), Cycle 2 Day1 (pretreatment) and at time of progression. See SPM for collection, processing and shipping instructions.
12. All participants who receive study drug will be followed for disease progression and survival every three months for 2 years from registration for protocol therapy, every 6 months for years 3 - 5, and annually thereafter. For survival outcomes, telephone communication is acceptable after participants have been followed and treatment related toxicities have resolved or returned to baseline and/or participants have initiated a subsequent therapy.

7.1 Baseline/Screening

7.1.1 Within 30 days prior to registration for protocol therapy:

- Complete medical history
- Complete physical examination (including vital signs, height, body weight)
- Karnofsky Performance Status
- Charlson comorbidity score (see Appendix A)
- Calculated creatinine clearance (Cockroft-Gault equation)
- Adverse event and concomitant medication assessment
- CT scan or brain MRI to exclude brain metastasis, only in participants with neurological symptoms.
- Radiological assessment of tumors with a CT scan of the chest, abdomen, and pelvis
- Bone scan, if clinically indicated (elevated alkaline phosphatase, bone pain)
- Hepatitis B testing -
  The following three categories of participants should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab:

  1. All participants who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain Portugal, and Greece. [http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/hepatitis-b.aspx#849]
  2. Participants with any of the following risk factors:
     - known or suspected past hepatitis B infection,
     - blood transfusion(s) prior to 1990,
     - current or prior IV drug users,
     - current or prior dialysis,
     - household contact with hepatitis B infected participant(s),
     - current or prior high-risk sexual activity,
     - body piercing or tattoos,
     - mother known to have hepatitis B
     - history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.
  3. Additional participants at the discretion of the investigator

  NOTE: The management guidelines, in Section 6.3.6.1, are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.
- Hepatitis C testing -
  Participants with any of the following risk factors for hepatitis C should be tested using quantitative RNA-PCR
  - known or suspected past hepatitis C infection (including participants with past interferon 'curative' treatment),
  - blood transfusions prior to 1990,
  - current or prior IV drug users,
  - current or prior dialysis,
  - Immediate household contact of hepatitis C infected participant(s),

- current or prior high-risk sexual activity,
- body piercing or tattoos,
- At the discretion of the investigator, additional participants may also be tested for hepatitis C.

NOTE: The management guidelines, in Section 6.3.6.2, are provided according to the results of the baseline assessment of hepatitis C viral load.

7.1.2 Within 7 days of registration for protocol therapy:

- Complete blood count (CBC) with differential and platelet count
- Comprehensive metabolic panel (sodium, potassium, BUN, creatinine, AST, ALT, Alk.phos, total bilirubin, magnesium, calcium, and phosphorus)
- Lipid profile (fasting)
- Calculated creatinine clearance (Cockroft-Gault equation)
- PTT and INR
- Fasting serum glucose
- Urine pregnancy test for women of childbearing potential

7.1.3 Pregnancy and assessment of fertility:

Women of childbearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant), and males of childbearing potential and their sexual partner(s) who are WOCBP must use highly effective contraception during the study and for 8 weeks after stopping treatment. Highly effective contraception is defined as either:

- 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]
- 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 partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject].
- Use of a combination of any two of the following (a+b or a+c or b+c):
  - Use of oral, injected, implanted or other hormonal methods of contraception
  - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- In case of use of oral contraception, women should have been stable on the oral agent before taking study treatment.

Sexually active males must use a condom during intercourse while taking the drug and for 8 weeks after stopping treatment and should not father a child in this period.

A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

Female partners of male patients must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.

7.2 On Treatment

7.2.1 Day 1 of each cycle (within 3 days prior):
NOTE: Cycle 1 Day 1 testing need not be repeated if completed within 7 days of starting protocol therapy.

- Physical examination, including vital signs and body weight
- Karnofsky Performance Status
- CBC with differential and platelet count
- Comprehensive metabolic panel (sodium, potassium, BUN, creatinine, AST, ALT, Alk.phos, total bilirubin, magnesium, calcium, and phosphorus)
- Calculated creatinine clearance (Cockroft-Gault equation).
- Lipid profile (fasting)
- Adverse event and concomitant medication assessment
- Everolimus administration – cohort 1
- Everolimus and Paclitaxel administration – cohort 2. CBC and creatinine will be performed prior to each dose of paclitaxel.

7.2.2 Correlative sample submissions:

- Submission of an archived paraffin embedded tumor block for COXEN analysis. If the previous biopsy is not available, a discussion needs to take place with the Sponsor Investigator, participants will not need to undergo a new biopsy. See SPM for collection and shipping instructions.
- Submission of unstained tumor slides for Immunohistochemical staining and for banking for future use from the participant‘s previous biopsy are requested. If the previous biopsy is not available, a discussion needs to take place with the Sponsor Investigator, participants will not need to undergo a new biopsy. See SPM for collection and shipping instructions.
- Optional whole blood for banking for future use is requested at Cycle 1 Day 1, pretreatment. See SPM for collection and shipping instructions.
- Optional serum and plasma are requested at Cycle 1 Day 1 (pretreatment), Cycle 2 Day1 (pretreatment) and at time of progression. See SPM for collection, processing and shipping instructions.

7.2.3 Radiological Assessments:

Participants will undergo repeat cross-sectional imaging (CT scan of the chest, abdomen, and pelvis) after every 2 cycles (eg, after cycle 2, after cycle 4) until disease progression. Bone scans will be repeated at these intervals if clinically indicated.

7.3 Treatment Discontinuation

A participant will be discontinued from the treatment under the following circumstances:

- If there is evidence of progressive disease by RECIST criteria.
- If the attending physician thinks a change of therapy would be in the best interest of the participant.
- If the participant requests discontinuation.
- If the drug(s) exhibit(s) unacceptable adverse event.
- If a participant becomes pregnant.
- Treatment interruption for greater than 4 weeks due to treatment related adverse event or any other reasons.
- Participants can stop participating at any time. However, if they decide to stop participating in the study, participants will continue to be followed for disease progression and survival as indicated in the schedule of events table (if haven't withdrawn consent).

7.4 End of Treatment Evaluations: 30 days (±7 days) post last therapy

This is a single assessment that will be performed when participant goes off treatment because of 1) progressive disease or 2) toxicity, or 3) in cases of physician decision or where 4) participant withdraws consent. Participants who withdraw consent should be encouraged to have the end of treatment evaluations done.

All participants, including those who discontinue protocol therapy early, should be evaluated approximately 30 days after their last dose according to the end of treatment evaluations. Every effort should be made to complete these assessments as close to 30 days after the last dose as possible.

The following evaluations will be performed following the last treatment:

- Physical examination, including vital signs and body weight
- Karnofsky Performance Status
- CBC with differential and platelet count
- Comprehensive metabolic panel (sodium, potassium, BUN, creatinine, AST, ALT, Alk.phos, total bilitubin, magnesium, calcium, and phosphorus) prior to dosing on day 1 of each cycle.
- Lipid profile (fasting)
- Calculated creatinine clearance (Cockroft-Gault equation)

- Adverse event and concomitant medication assessment
- Radiological assessments of tumors with a CT scan of the chest, abdomen, and pelvis, if not done within the last 6 weeks.
- Bone scan, if clinically indicated, and not done within the last 6 weeks.

7.5 Follow-Up

All participants who receive study drug will be followed for disease progression and survival every 3 months for 2 years from registration for protocol therapy, every 6 months for years 3 - 5, and annually thereafter. For survival outcomes, telephone communication is acceptable after participants have been followed and treatment related toxicities have resolved or returned to baseline and/or participants have initiated a subsequent therapy.

8 CRITERIA FOR DISEASE EVALUATION

8.1 Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST)

8.1.1 Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

8.1.2 Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter (LD) >20 mm using conventional techniques or >10 mm with spiral CT scan.

8.1.3 Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

8.1.4 Baseline documentation of "Target" and "Non-Target" lesions - all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their LD. The baseline sum LD will be used as reference by which to characterize the objective tumor. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

8.2 Response Criteria for Target Lesions

Table 11:

Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target

	lesions, taking as reference the baseline sum LD
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

8.3 Response Criteria for Non-Target Lesions

Table 12:

Response	**Evaluation of Non-Target Lesions**
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
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[(1)]

Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or the Sponsor Investigator).

8.4 Evaluation of best overall response

The objective response rate is the proportion of all participants with confirmed PR or CR according to RECIST, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

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

Table 13: Evaluation of best overall response

Target Lesions	**Non-Target lesion**	**New Lesion**	**Overall Response**
CR	CR	No	CR
CR	Incomplete Response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "**symptomatic deterioration**". Every effort should be made to document the Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST)

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

8.5 Definitions for Response Evaluation

8.5.1 First Documentation of Response **-** The time between initiation of therapy and first documentation of PR or CR.

8.5.2 Confirmation of Response - To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

8.6 Endpoint Definitions

8.6.1 Progression Free Survival (PFS) - The length of time during and after treatment in, which a participant is living with a disease that does not get worse. It is the time between the initiation of therapy and documented date of progression or death.

8.6.2 Clinical Benefit rate - It is the percentage of participants with documentation of complete response, partial response or stable disease after initiation of treatment.

8.7 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease.

8.7.1 CT and MRI

CT and MRI are the best currently available and most reproducible methods for measuring target lesions. Conventional CT and MRI should be performed with contiguous cuts of 10mm or less in slice thickness. Spiral CT should be performed by use of a 5mm contiguous reconstruction algorithm. This specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities require specific procedures.

8.7.2 Chest X-Ray

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung (CT is preferable).

8.7.3 Clinical Examination

Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

8.7.4 Cytology and Histology

Cytologic and histologic techniques can be used to differentiate between complete and partial responses in rare cases (e.g. after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

9 BIOLOGICAL CORRELATIVES

Please refer to the Study Procedures Manual (SMP) for collection, processing and shipping of correlative samples.

mTOR pathway markers by IHC

mTOR pathway markers, including pS-6 and p-4E BP1, are over expressed in the majority of participants with invasive urothelial carcinomas 8. Archived tumor specimens will be evaluated for PTEN, p-S6, p-4E BP1 by IHC and results will be correlated with clinical outcomes.

Fifteen (15) unstained positively charged slides will be collected from the participant's previous biopsy to bank for future use. The participant will not need to undergo a new biopsy if the previous biopsy is not available. See SPM for collection and shipping instructions.

CoExpression Extrapolation (COXEN)

In recent years, the expanding use of gene array technologies has offered promise for a personalized therapeutic approach. For urothelial carcinoma, the coexpression extrapolation (COXEN) algorithm is an example of the power of gene arrays to predict optimal drug therapy for an individual participant17. Through sophisticated informatics and biostatistical methodologies, COXEN leverages the existing public National Cancer Institute (NCI) Developmental Therapeutics Program drug sensitivity NCI-60 cell line data with Affymetrix® gene expression profiles and clinicopathologic human data from

participants with tumors not contained in the NCI-60 cell lines (i.e urothelial carcinoma) to produce a COXEN score predictive of response to existing drugs.

Formalin-fixed paraffin embedded bladder cancer specimens will be sent to the laboratory of Dr. Dan Theodorescu for mRNA profiling (see SPM) and data analysis for generation of a COXEN score for everolimus and paclitaxel sensitivity. The COXEN score will be generated as previously described 17.

Blood biomarkers

Optional blood banking for future blood biomarker studies: whole blood is requested at baseline; serum and plasma are requested at baseline, Cycle 2 Day1 and at progression. See SPM for collection, processing and shipping instructions.

10 CTM INFORMATION & ADVERSE EVENTS MANAGEMENT

10.1 Drug Name: Everolimus (RAD-001)

10.1.1 Classification - Mammalian target of rapamycin (mTOR) inhibitor

10.1.2 Action - Everolimus has antiproliferative and antiangiogenic properties. Reduces protein synthesis and cell proliferation by binding to the FK binding protein-12 (FKBP-12), an intracellular protein, to form a complex that inhibits activation of mTOR (mammalian target of rapamycin) serine-threonine kinase activity. Also reduces angiogenesis by inhibiting vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF-1) expression.

10.1.3 Availability - Study drug will be provided by Novartis via Hoosier Oncology Group.

10.1.4 Storage - Store everolimus tablets at 25° C (77°F); excursions permitted between 15°–30°C (59**°–86°F). Store in the original container, protect from light and moisture.**

10.1.5 Administration - Everolimus will be taken at a dose of 10 mg, once daily at the same time every day, either with or without food. Everolimus tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. For patients unable to swallow tablets, the tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring until the tablet(s) is fully disintegrated (approximately 7 minutes), immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered. If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

10.1.6 Side Effects -

Very Common: ≥ 10%

- Infections
- Thrombocytopenia
- Neutropenia
- Anemia
- Decreased appetite
- Hyperglycemia
- Hypercholesterolemia
- Dysgeusia
- Headaches
- Pneumonitis
- Epistaxis
- Cough
- Dyspnea
- Nausea and vomiting
- Diarrhea
- Mouth sores
- Rash and pruritis
- Decreased weight
- Fatigue
- Asthenia
- Peripheral edema

Common: 1% to 9%

- Leukopenia, neutropenia, lymphopenia
- Abdominal pain
- Hypertriglyceridemia
- Hyperlipidemia
- Hypophosphatemia
- Hypokalemia
- Diabetes mellitus
- Difficulty swallowing
- Hand-foot syndrome, a condition of redness and painful blisters can occur on hands and feet.
- Skin or nail changes (acne, redness, dryness or irritation)
- Increased blood pressure
- Hemorrhage
- Fever
- Arthralagia
- Inflammation of the lining of the digestive system and other mucous membranes
- A participant with hepatitis B or hepatitis C who takes everolimus could be susceptible to the virus becoming more active

- Dehydration
- Insomnia
- Dry mouth
- Oral pain
- Renal failure
- Dyspepsia
- Alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased

Uncommon to Rare: < 1%

- Loss of taste sensation
- Secondary amenorrhea (delayed menstruation), menstrual irregularities
- Cardiac failure
- Deep vein thrombosis
- Hemoptysis
- Acute renal failure
- Proteinuria
- Increased daytime urination
- Pulmonary embolism
- Pancytopenia, pure red cell aplasia
- Non-cardiac chest pain
- Impaired wound healing
- Respiratory failure
- Hypersensitivity - anaphylaxis, dyspnea, flushing, chest pain

NOTE: Participants should not receive live vaccines and have close contact with people who have received live vaccines within 7 days of starting everolimus (Afinitor®) and while on this study without consultation with the study doctor. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella (Chicken Pox), and typhoid vaccines.

10.2 Drug Name: Paclitaxel

10.2.1 Classification - Taxane

10.2.2 Action - Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

10.2.3 Availability - Paclitaxel is commercially available and will not be provided by Hoosier Oncology Group.

10.2.4 Storage - Unopened vials of TAXOL (paclitaxel) Injection are stable until the date indicated on the package when stored between 20°–25° C (68°–77° F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the reaching room temperature with quality under these circumstances. precipitate is noted, the vial should recommended are stable at ambient conditions for up to 27 hours.

10.2.5 Administration - Paclitaxel will be administered intravenously over 1 hour.

10.2.6 Side Effects -

Common: > 10%

- Cardiovascular: Flushing (28%), ECG abnormal (14% to 23%), edema (21%), hypotension (4% to 12%)
- Dermatologic: Alopecia (87%), rash (12%)
- Gastrointestinal: Nausea/vomiting (52%), diarrhea (38%), mucositis (17% to 35%; grades 3/4: up to 3%), stomatitis (15%; most common at doses >390 mg/m2), abdominal pain (with intraperitoneal paclitaxel)
- Hematologic: Neutropenia (78% to 98%; grade 4: 14% to 75%; onset 8-10 days, median nadir 11 days, recovery 15-21 days), leukopenia (90%; grade 4: 17%), anemia (47% to 90%; grades 3/4: 2% to 16%), thrombocytopenia (4% to 20%; grades 3/4: 1% to 7%), bleeding (14%)
- Hepatic: Alkaline phosphatase increased (22%), AST increased (19%)
- Local: Injection site reaction (erythema, tenderness, skin discoloration, swelling: 13%)
- Neuromuscular & skeletal: Peripheral neuropathy (42% to 70%; grades 3/4: up to 7%), arthralgia/myalgia (60%), weakness (17%)
- Renal: Creatinine increased (observed in KS participants only: 18% to 34%; severe: 5% to 7%)
- Miscellaneous: Hypersensitivity reaction (31% to 45%; grades 3/4: up to 2%), infection (15% to 30%)

Less Common: 1% - 10%

- Cardiovascular: Bradycardia (3%), tachycardia (2%), hypertension (1%), rhythm abnormalities (1%), syncope (1%), venous thrombosis (1%)
- Dermatologic: Nail changes (2%)
- Hematologic: Febrile neutropenia (2%)
- Hepatic: Bilirubin increased (7%)
- Respiratory: Dyspnea (2%)

Rare: < 1%
(Limited to important or life-threatening): Anaphylaxis, ataxia, atrial fibrillation, AV block, back pain, cardiac conduction abnormalities, cellulitis, CHF, chills, conjunctivitis, dehydration,

enterocolitis, extravasation recall, hepatic encephalopathy, hepatic necrosis, induration, intestinal obstruction, intestinal perforation, interstitial pneumonia, ischemic colitis, lacrimation increased, maculopapular rash, malaise, MI, necrotic changes and ulceration following extravasation, neuroencephalopathy, neutropenic enterocolitis, ototoxicity (tinnitus and hearing loss), pancreatitis, paralytic ileus, phlebitis, pruritus, pulmonary embolism, pulmonary fibrosis, radiation recall, radiation pneumonitis, pruritus, renal insufficiency, seizure, skin exfoliation, skin fibrosis, skin necrosis, Stevens-Johnson syndrome, supraventricular tachycardia, toxic epidermal necrolysis, ventricular tachycardia (asymptomatic), visual disturbances (scintillating scotomata)

11 ADVERSE EVENTS

11.1 Definitions of Adverse Events

11.1.1 Adverse Event (AE) - Any untoward medical occurrence in a participant or clinical trial subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

11.1.2 Serious Adverse Event (SAE) - A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

Events **NOT** considered to be SAEs are hospitalization for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
- treatment on an emergency outpatient basis for an event not fulfilling any of the

definitions of a SAE given above and not resulting in hospital admission
- respite care in the absence of any deterioration in the patient's general condition
- hospital admission solely for administration of study drug or chemotherapy

11.1.3 Unexpected Adverse Event - An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's Brochure or package insert.

11.2 Adverse Event (AE) Assessment and Reporting

Adverse events (AEs) will be recorded from the time of consent and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. AEs that begin or worsen after consent should be recorded in the AE eCRF. Conditions that were already present at that time of consent should be recorded in the medical history. AEs (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 AE.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical exam, lab test, or other assessments. As far as possible, each AE should be evaluated to determine:
- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates or if continuing at the safety follow-up visit)
- Its relationship to the study treatment (Reasonable possibility that AE is related: see Table 14 below)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, hospitalized, unknown, not applicable)
- Whether medication or therapy was given (no concomitant mediation/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
- Whether it is serious, where a SAE is defined as in the section above.

All AEs should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an AE is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the

interventions required to treat it, and the outcome. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

Information about common side effects already known about the investigational drug can be found in the Investigators' Brochure. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

11.3 Serious Adverse Event (SAE) Reporting

11.3.1 Study Center (Site) Requirements for Reporting SAEs

Investigators and other site personnel must report any SAEs occurring during the course of the study **within 1 business day** of discovery of the event. This includes events both related and unrelated to the investigational product.

The definition of "related" being that there is a reasonable possibility the drug caused the adverse experience.

Table 14: The relationship of the adverse event to the study drug

Unrelated	The Adverse Event is *clearly not related* to the investigational agent(s)
Unlikely	The Adverse Event is *doubtfully related* to the investigational agent(s)
Possible	The Adverse Event *may be related* to the investigational agent(s)
Probable	The Adverse Event is *likely related* to the investigational agent(s)
Definite	The Adverse Event is *clearly related* to the investigational agent(s)

The completed SAE Report Form (see SPM) must be faxed to Hoosier Oncology Group within 1 business day of discovery of the event. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information will be faxed to Hoosier Oncology Group, 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, whether the blind was broken or not (if applicable), and whether the participant continued or withdrew from study participation.

11.3.2 Death and Immediately Life-Threatening Events

Any death and immediately life-threatening event from any cause while a participant is receiving trial treatment on this protocol or up to 30 days after the last dose of trial treatment, or any death and immediately life-threatening event occurring more than 30 days after trial treatment has ended but which is felt to be treatment related must be reported within one business day of discovery of the event. All deaths must be reported primarily for the purposes of SAE reporting; however, deaths due unequivocally to progression are not SAEs.

Your local IRB should be notified and their reporting procedure followed. The completed SAE Reporting Form should be faxed to Hoosier Oncology Group **within 1 business day of discovery of the event**.

11.3.3 HOG Requirements for Reporting SAEs to FDA and Novartis

The Sponsor Investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology (DS&E) Department.

Hoosier Oncology Group has been designated to manage the SAE reporting requirements for the FDA and Novartis on behalf of Matthew D Galsky, MD, Sponsor Investigator, and will be responsible for all communication with the FDA and Novartis.

All events reported to the FDA are to be filed utilizing the Form FDA 3500A (MedWatch Form) per federal guidelines.

To ensure participant safety, every SAE, regardless of suspected causality, occurring;

- after the participant has provided informed consent and at least 30 days after the participant has stopped study treatment/participation
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the participant has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a participant (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the participant has stopped study treatment

All SAEs must be reported to Novartis Pharmaceuticals DS&E Dept. (**fax: 877-778-9739**) **within 1 business day** of Hoosier Oncology Group learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported **within 5 business days**.

Any SAEs experienced after this 30 days period should only be reported to Novartis DS&E Dept. if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within **1 business day** 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. The end date of the first event must be provided. The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this 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, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report Form in English, and send the completed, signed form by fax to Hoosier Oncology Group within **1 business day** of discovery of the event**. Hoosier Oncology Group will** forward the corresponding SAE Report Form to Novartis DS&E Dept. **within 1 business day** of receipt of the SAE Reporting Form.

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

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the comparator drug company by the investigator.

11.4 IND Safety Reports Unrelated to This Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be reviewed by the Sponsor Investigator and will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

11.5 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure participant safety each pregnancy must also be reported to Novartis DS&E Dept. within **1 business day** of learning of its occurrence. The pregnancy should be followed up to

determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The newborn will be followed for at least 12 months.

12 STATISTICAL CONSIDERATIONS

This study will involve two parallel cohorts. **The study is not designed for statistical comparisons of the cohorts.** Each cohort will employ a separate Simon's 2-stage MinMax design.

For cohort 1 (single agent everolimus), the sample size is based on the assumption that a clinical benefit rate of ≤ 10% is not worthy of further evaluation while a clinical benefit rate of ≥ 30% warrants additional testing. In the first stage, more than 1 participant with an objective response or stable disease (at 4 months) out of 15 evaluable participants is needed. In the second stage, an additional 10 evaluable participants will be required and more than 5 participants with an objective response or stable disease (at 4 months) are needed to consider the treatment successful with alpha = 0.05 and 80% power. The probability of early termination is 55% when the clinical benefit rate is ≤ 10%.

For cohort 2 (single agent everolimus plus paclitaxel), the sample size is based on the assumption that a clinical benefit rate of ≤ 25% is not worthy of further evaluation while a clinical benefit rate of ≥ 45% warrants additional testing. In the first stage, more than 4 participants with an objective response or stable disease (at 4 months) out of 17 evaluable participants are needed. In the second stage, an additional 19 evaluable participants (for a total of 36 evaluable participants) will be required and more than 13 participants with an objective response or stable disease (at 4 months) are needed to consider the treatment successful with alpha = 0.05 and 80% power. The probability of early termination is 57% when the clinical benefit rate is ≤ 25%.

For both cohorts, the primary endpoint is clinical benefit rate which includes response (defined as partial and complete response) and stable disease (at 4 months). It will be reported with 95% confidence intervals (CI).

Survival which is part of the secondary endpoints will be calculated from the date of initiation of treatment to the death or last date of contact. Survival at 1 year will be estimated from a Kaplan-Meier analysis. Progression-free survival will be calculated from the date of initiation of therapy until progressive disease or death due to any cause. If the participant did not progress nor die, the participant will be censored on the date of the last disease assessment performed. Progression-free survival will be analyzed using the method of Kaplan and Meier. Toxicities will be graded according to the NCI Common Toxicity Criteria (version 4.0). Participants enrolled in this study will be carefully monitored during the entire treatment phase and will be followed as is appropriate, with safety evaluations. All participants receiving at least 1 dose of the study regimen will be included in the safety analysis. Incidence and type of grades 3 and 4 adverse events, including serious adverse events, will be tabulated and summarized using descriptive statistics.

The participant is evaluable for efficacy if the participant receives at least one dose of treatment and at least one post-baseline disease evaluation.

Dosage adjustments or interruptions will be based on treatment-related toxicity. Early discontinuation of treatment (<2 cycles) secondary to toxicity will be considered a treatment failure.

Assume 10% of the cohorts are nonevaluable or dropout, we plan to accrue 68 (28+40) participants. Accrual rate of 2-4 participants per month is anticipated, and thus the trial accrual time will be approximately 17-34 months.

Potential biomarkers (mTOR pathway markers, including pS-6 and p-4E BP1 in archival tissue using immunohistochemistry) will be assessed by repeating the analysis of each clinical outcome with the level of each individual marker included as factor or covariate as appropriate. Markers with a continuous, rather than a discrete, measurement will also be evaluated as a discrete factor by dividing participants into low and high expression classes at the point of the distribution that maximizes the association between the marker and each clinical outcome. Significance of this association will be evaluated using a test for maximal chi-square values. For binary outcomes, chi-square test will be used while for time-to-event outcomes, log-rank test will be used.

Archival tissue samples will be submitted to a CLIA-certified lab for transcriptional profiling. The Co-Expression Extrapolation algorithm will be utilized to generate scores for sensitivity to paclitaxel and/or everolimus. The scores will be correlated with clinical outcomes. The correlation will be explored using Kendall's tau statistic.
Baseline comorbidity scores will be calculated using the Charlson index and correlated with adverse events and clinical outcomes, which also be quantified using Kendall's tau statistic

13 TRIAL MANAGEMENT

13.1 Quality Controls and Quality Assurance

13.1.1 Study Monitoring

Monitoring visits to the trial sites will be made periodically during the trial, to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The investigator/institution guarantee access to source documents by HOG or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by Novartis or its designee as well as inspection by appropriate regulatory agencies.

It is important for the investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

13.1.2 Data and Safety Monitoring Plan

HOG data safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the Sponsor Investigator of recommended action
- Notification of sites coordinated by the HOG of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

13.1.3 Data/Safety Monitoring and Reporting Guidelines

The HOG will compile data summary reports for this trial and submit these reports monthly to the Sponsor Investigator. The HOG will submit data summary reports a minimum of twice a year to a Data Safety Monitoring Committee (DSMC) for review.

13.2 Data Handling and Record Keeping

13.2.1 Case Report Forms

An electronic case report form (eCRF) is required and must be completed for each included participant. The completed dataset is the sole property of HOG and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from HOG.

13.2.2 Record Retention

To enable evaluations and/or audits from Health Authorities/HOG, the investigator agrees to keep records, including the identity of all participating participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all eCRF's, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRF's will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

13.3 Changes to the Protocol

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment. All protocol amendments must be reviewed by the Sponsor Investigator, Hoosier Oncology Group, and Novartis before implementation.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by Hoosier Oncology Group. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study site. Local requirements must be followed. A copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

a) Increases in drug dose or duration of exposure to subjects,
b) Significant changes in the study design (e.g. addition or deletion of a control group)
c) Increases in the number of invasive procedures,
d) Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

a) changes in the staff used to monitor trials
b) minor changes in the packaging or labeling of study drug.

If a protocol amendment requires a change to the written Informed Consent Form, then the IRB must be notified. Approval of the revised written Informed Consent Form by the IRB is required before the revised form is used.

The principal investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

Novartis' willingness to supply study drug is predicated upon the review of the protocol. Hoosier Oncology Group agrees to provide written notice to Novartis of any modifications to the protocol or informed consent.

13.4 Ethics

13.4.1 Ethics Review

The final study protocol, including the final version of the written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB. The investigator must submit written approval to the HOG office before he or she can enroll any participant into the study.

The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. Novartis will provide this information to the Sponsor Investigator. These reports will be reviewed by the Sponsor Investigator and those considered unexpected and possibly related to protocol therapy plus all deaths within 30 days of discontinuing treatment will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

13.4.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

13.4.3 Written Informed Consent

The investigator will ensure the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Participants must also be notified they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

The participant's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed written Informed Consent Form. A copy of the signed written Informed Consent Form must be given to the participant.

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15 APPENDIX A

Charlson Comorbidity Index

Comorbidity	Relative Weight Assignment
Metastatic solid tumor	6
AIDS	6
Moderate to severe liver disease	3
Hemiplegia	2
Moderate to severe renal failure	2
Diabetes with end organ damage	2
Neoplasia	2
Leukemia/lymphoma	2
Myocardial infarct	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic obstructive pulmonary disease	1
Connective tissue disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1

From Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis, 40(5): 373-383

Instructions:

The total score is obtained by adding the relative weight of each co-morbidity.