A Single Arm, Phase I/II Trial of Neoadjuvant Androgen Deprivation, Darolutamide, and Ipatasertib in Men with Localized, High Risk Prostate Cancer

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 20NOV2020

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, 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).

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

_____

Site Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

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SYNOPSIS

TITLE	A Single Arm, Phase I/II Trial of Neoadjuvant Androgen Deprivation, Darolutamide, and Ipatasertib in Men with Localized, High Risk Prostate Cancer
PHASE	Phase I/II
OBJECTIVES	Primary Objective: To estimate the efficacy of neoadjuvant androgen deprivation, darolutamide, and ipatasertib in men with previously untreated, localized, high-risk prostate cancer that is lacking PTEN, as measured by the pathological complete response or minimal residual disease Secondary Objectives: • To assess the toxicity profile of androgen deprivation, darolutamide, and ipatasertib in men with high risk, localized, hormone sensitive prostate cancer that is lacking PTEN • To measure 2 year biochemical recurrence-free survival (PSA ≤ 0.2 ng/mL) in men with high risk, localized, prostate cancer that is lacking PTEN • To measure rate of PSA_0 (undetectable PSA with testosterone recovery and no additional therapy) in men with high risk, localized, prostate cancer that is lacking PTEN Exploratory Objectives: • To measure rate of unfavorable pathology at prostatectomy in men with high risk, localized, hormone sensitive prostate cancer • To evaluate PI3K-AKT pathway activity in residual tumor • To evaluate proliferation of residual tumor, as measured by Ki67 • To investigate changes in resistance mechanisms (e.g. hormone receptor activity, neuroendocrine differentiation) between pre- and post-treatment tumors • To investigate changes in immunogenicity
STUDY DESIGN	This is a single arm phase I/II trial of androgen deprivation, darolutamide, and ipatasertib given for 6 cycles prior to radical prostatectomy in patients with non-metastatic, high risk disease with PTEN loss planning on undergoing radical prostatectomy. To ensure safety, there will be a Phase I de-escalation cohort in patients with castration-resistant prostate cancer. Evaluation for dose limiting toxicities will continue for 28 days, and blood samples will be drawn for pharmacokinetic (PK) studies.
KEY ELIGIBILITY CRITERIA	**For the Phase I de-escalation cohort** ***Key inclusion criteria:*** • Histologically confirmed prostate cancer • Evaluable disease, with PSA ≥ 1.0 ng/ml and/or visible prostate cancer on imaging • Male and ≥ 18 years of age • ECOG performance status of ≤ 2

	• Castration resistant prostate cancer, defined as biochemical, radiographic, and/or clinical progression despite castrate level of testosterone (<50 ng/dL) • Willing to undergo blood draws to measure PK levels **<u>For the Phase II neoadjuvant cohort</u>** ***Key Inclusion Criteria:*** • Histologically-confirmed diagnosis of localized, untreated prostate cancer with high-risk features. High-risk features is defined as: o Two or more cores from prostate biopsy that is/are grade group 4 (Gleason score 4+4=8) or higher, **<u>OR</u>** o Stage T3-4, M0, and at least 2 cores from prostate biopsy that are grade group 3 (Gleason score 4+3=7) or higher. • Sufficient archival tissue (at least 2 cores) available for targeted sequencing and immunohistochemistry. • Untreated disease and be eligible for (per PI discretion) and planning to undergo radical prostatectomy. • Measurable PSA • Adequate organ and bone marrow function within ≤ 14 days. • Male and ≥18 years of age. • ECOG performance status of ≤ 1. • CT or MRI of abdomen and pelvis and bone scan within ≤90 days of treatment. • Able to swallow pills • Must have 50% or more of tumor tissue evaluated be negative for PTEN expression by immunohistochemistry by Ventana SP218 immunohistochemistry assay on local review (screening evaluation) ***Key Exclusion Criteria:*** • Histology of small cell carcinoma prostate cancer. Adenocarcinoma with neuroendocrine features is allowed. • Prior treatment of prostate cancer with: second generation androgen receptor (AR) inhibitors, other investigational AR inhibitors or CYP17 enzyme inhibitor, radiation therapy, surgery, or chemotherapy. First generation antiandrogen (e.g. bicalutamide) for 28 days or fewer is allowed • Distant metastatic disease beyond N1 (regional) lymph nodes on conventional baseline imaging studies within ≤ 90 days. • Receipt of an investigational agent within ≤ 28 days; or herbal medications and marijuana products within ≤ 1 day. • Receipt of medications or agents that are likely to alter serum PSA levels within ≤ 42 days or 5 half-lives, whichever is shorter.

STATISTICAL CONSIDERATIONS	In this Simon MiniMax two-stage, single arm, phase I/II trial, we anticipate enrolling 17 evaluable PTEN-negative subjects in the Phase II neoadjuvant cohort. The therapy will be considered to be of little interest in the neoadjuvant setting if the exceptional response rate is <5% (similar to AR-targeted therapy alone) and considered active if the exceptional response rate is ≥30%. The study is designed with 90.5% power to detect the difference between the null hypothesis (5% or less response rate) and the alternative hypothesis (30%) with one-sided type I error of 0.05. In the first stage nine (9) patients will be recruited. If one (1) or more responses (pCR or MRD) are observed, another eight (8) evaluable patients will be recruited for a total of 17 evaluable patients. If 3 or more of 17 responses are observed, the study will be deemed a success. To account for 15% attrition, we plan to enroll 20 patients. ***The Phase I de-escalation cohort*** will consist of patients with metastatic or nonmetastatic castrate resistant prostate cancer, with the expected sample size of 6, ***assuming no more than 1 DLT in the first 6 patients.*** However, if dose reductions of ipatasertib are required, the sample size could be as large as 18.
TOTAL NUMBER OF SUBJECTS	N = 26-38 (Phase I de-escalation cohort = 6-18; Phase II neoadjuvant cohort = 20)
ESTIMATED ENROLLMENT PERIOD	12 months
ESTIMATED STUDY DURATION	42 months

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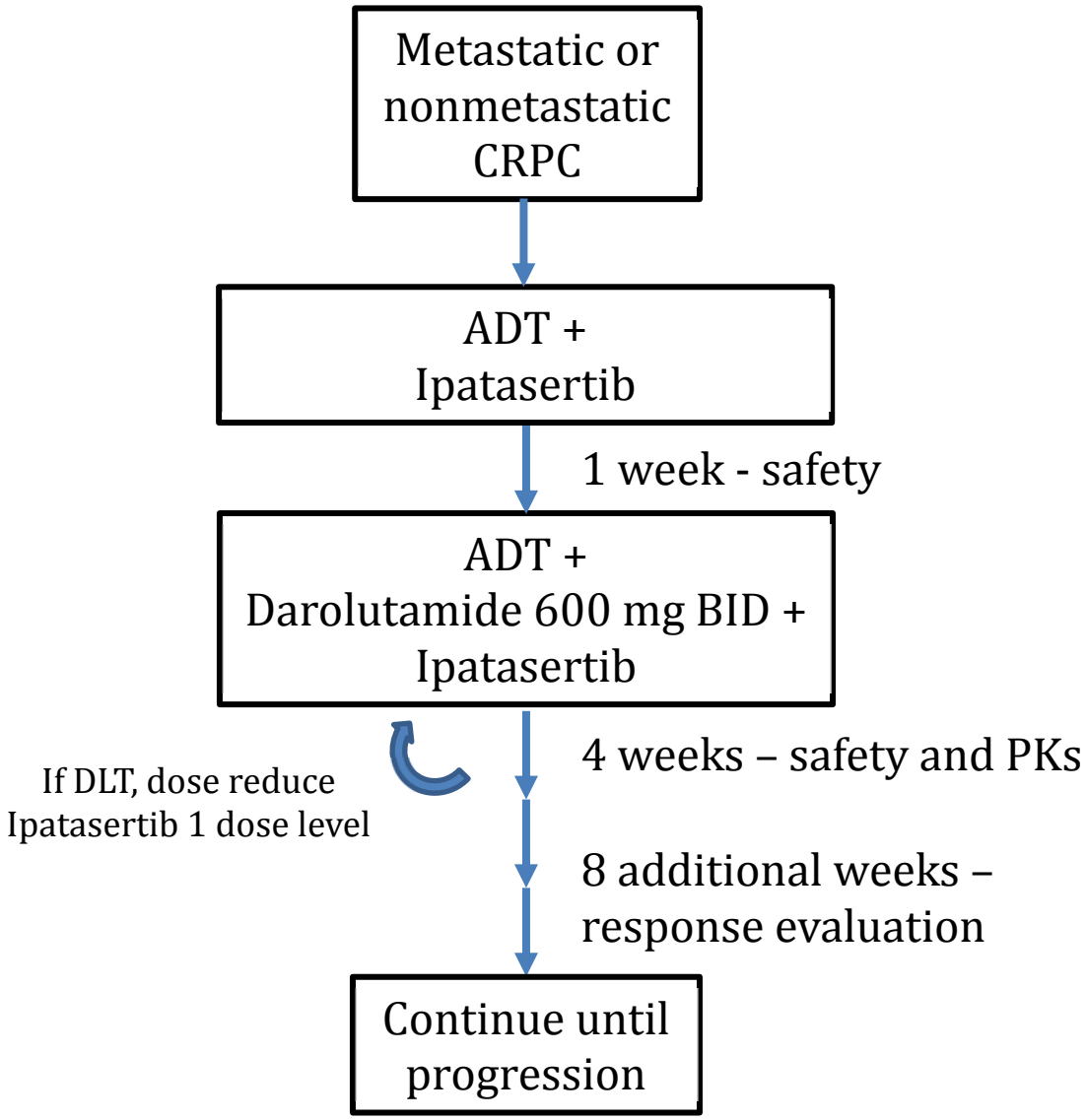
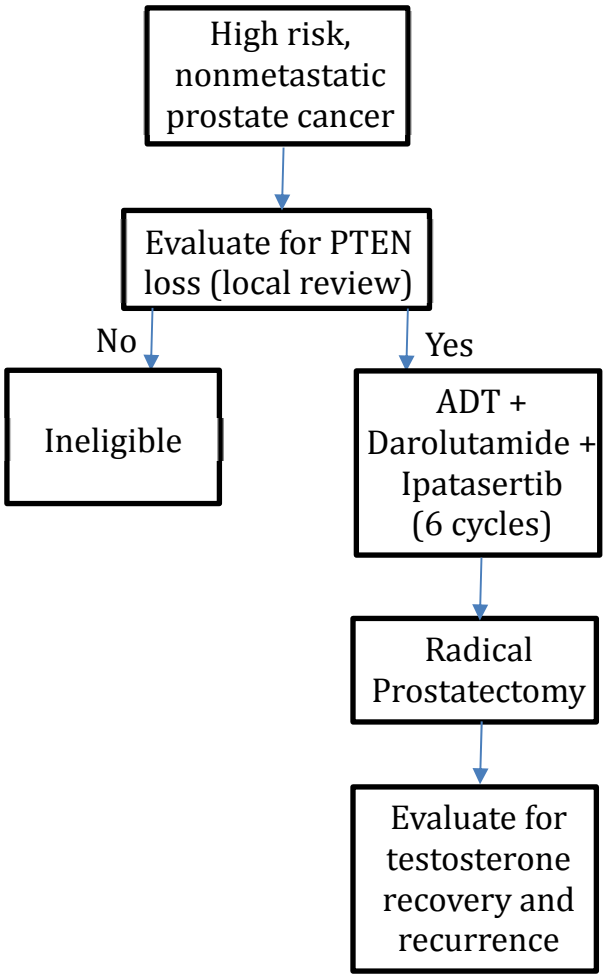
SCHEMA: PHASE I DE-ESCALATION COHORT



SCHEMA: PHASE II NEOADJUVANT COHORT



1. BACKGROUND AND RATIONALE

1.1 High risk localized prostate cancer

It is expected that 31,620 men will die from prostate cancer in the U.S. in 2019[1]. The majority of these men will have presented with intermediate or high-risk, localized cancer. While some will be cured, many (approximately 30%) will ultimately develop castration-resistant prostate cancer (CRPC) and succumb to the disease[2]. After diagnosis of localized disease, treatment options typically involve radical prostatectomy (RP) or radiation therapy (RT) in combination with androgen deprivation therapy (ADT). Following RP, 50% or more of patients with high-risk disease will experience a biochemical recurrence at 5 years, and approximately 20% will die of their disease within 10-15 years[3-5]. In a recent evaluation of patients with primary Gleason pattern 5 who underwent prostatectomy, patients had a median metastasis free survival (MFS) of 86.4 months[6]. PTEN is lost in approximately 20% of localized prostate cancers, making it one of the most common driver mutations[7-12]. Loss of PTEN expression is associated with increased Gleason score, tumor stage, risk of biochemical recurrence after prostatectomy, progression and death and risk of metastasis[13-19]. In the previously referenced study of prostate cancer patients with Gleason pattern 5 tumors, when there was PTEN loss (assessed by immunohistochemistry (IHC)), the median MFS was 33.9 months, with a hazard ratio of 4.56 on multivariable analysis[6]. As PTEN loss is associated with increased mortality and decreased response to therapy there is much interest in using targeted systemic therapy strategies in addition to prostatectomy to improve management of this lethal disease at a potentially curable disease state[20-23].

1.2 Neoadjuvant intensive androgen deprivation

While there is a proven benefit of using ADT concurrent with radiation therapy, the same benefit has not been found when ADT is given prior to radical prostatectomy in the neoadjuvant setting[24]. Recent strategies have employed more intensive androgen deprivation with newer hormonal agents, added in addition to standard androgen deprivation, such as abiraterone + prednisone and/or enzalutamide[25-26]. While rates of pathological complete response have remained low with these strategies (<10%), up to 24% of patients have had minimal residual disease (MRD). Moreover, patients who achieved MRD appeared to have better outcomes, as demonstrated by not having biochemical recurrence[27]. Unfortunately, in a recent summary of trials of neoadjuvant intensive androgen deprivation, of the patients with PTEN loss, 23 of 23 (100%) were nonresponders[28]. Other therapies beyond targeting the androgen receptor (AR) are needed to manage aggressive prostate cancers with PTEN loss.

1.3 The pan-AKT inhibitor Ipatasertib

Given the frequency of alterations of the PI3K-AKT pathway, whether through loss of function of the negative regulator PTEN or by activation of PI3K or AKT , inhibition of this pathway has long been of interest for management of diverse cancers[8]. Ipatasertib was developed as an inhibitor of all isoforms of AKT, which is downstream of PTEN and PI3K. A phase I trial demonstrated that it is tolerated well, and there is activity in patients with solid tumors[29]. Phase II trials have met their primary endpoint for patients with triple negative breast cancer (when given with paclitaxel) or with advanced prostate cancer (given with abiraterone + prednisone)[30-31]. These studies are the basis for two phase III trials that are on-going, in breast (IPATunity130, NCT03337724) and prostate cancer (IPATential150, NCT03072238), respectively.

1.4 Rationale

In addition to encouraging clinical results from late stage, castration resistant prostate cancer, the VanderWeele lab has demonstrated marked antitumor effects with ipatasertib and AR inhibition in preclinical studies (under review). These data include two independent patient-derived xenograft models of hormone sensitive prostate cancer that demonstrate almost complete inhibition of tumor growth (LuCaP 136) or marked tumor regression (LuCaP 147) when ipatasertib is combined with AR-targeted therapy. Interestingly, induction of glucocorticoid receptor is very common (88%) in residual tumor following neoadjuvant intensive androgen deprivation[28]. In preclinical models, sensitivity to ipatasertib is greatest in models where the glucocorticoid receptor is induced following AR-targeted therapy (under review). Together, these data suggest the neoadjuvant setting is a disease state where combined AKT- and AR-inhibition is particularly effective.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To estimate the efficacy of neoadjuvant androgen deprivation, darolutamide, and ipatasertib in men with previously untreated, localized, high-risk prostate cancer that is lacking PTEN, as measured by the pathological complete response or minimal residual disease

2.1.2 Secondary Objectives

- To assess the toxicity profile of androgen deprivation, darolutamide, and ipatasertib in men with high risk, localized, hormone sensitive prostate cancer that is lacking PTEN
- To measure 2 year biochemical recurrence-free survival (PSA $\leq$ 0.2 ng/mL) in men with high risk, localized, prostate cancer that is lacking PTEN
- To estimate rate of PSA_0 (undetectable PSA with testosterone recovery and no additional therapy) in men with high risk, localized, prostate cancer that is lacking PTEN

2.1.3 Exploratory/Correlative Objectives

- To measure rate of unfavorable pathology at prostatectomy in men with high risk, localized, hormone sensitive prostate cancer
- To evaluate PI3K-AKT pathway activity in residual tumor
- To evaluate proliferation of residual tumor, as measured by Ki67
- To investigate changes in resistance mechanisms (e.g. hormone receptor activity, neuroendocrine differentiation) between pre- and post-treatment tumors
- To investigate changes in immunogenicity

2.2 Endpoints

2.2.1 Primary Endpoint

- Combined rate of pathologic complete response (pCR) (defined as absence of pathologic disease on hematoxylin and eosin (H&E) stain (ypT0)), or with presence of minimal residual disease (<5 mm linearly)

2.2.2 Secondary Endpoints

- Grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
- Two year biochemical recurrence-free survival (PSA ≤ 0.2 ng/mL)
- Rate of PSA_0 (undetectable PSA on local institutions laboratory testing with testosterone recovery and no additional therapy)

3. ELIGIBILITY CRITERIA

Approximately 26-38 patients with prostate cancer will be enrolled in this study. This includes 6-18 patients in the Phase I de-escalation cohort with metastatic or nonmetastatic castration resistant prostate cancer, and 20 patients in the Phase II neoadjuvant cohort with high risk localized or locally advanced prostate cancer that is PTEN-null.

- For the Phase I de-escalation cohort, the patient must have castration resistant prostate cancer (metastatic or non-metastatic), as defined by PCWG3.
- For the Phase II neoadjuvant cohort, the patient must be a candidate for radical prostatectomy at the time of enrollment and be planning to undergo this procedure. The patient must have a histologically-confirmed diagnosis of localized, untreated prostate cancer with high risk features and must have sufficient archival tissue (at least 2 cores) available for targeted sequencing and immunohistochemistry. At least 50% of the tumor tissue evaluated must be negative for PTEN expression by immunohistochemistry on local review.

3.1 Eligibility Criteria for Phase I de-escalation cohort

3.1.1 Phase I Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Histologically confirmed prostate cancer
2. Male and ≥ 18 years of age
3. ECOG performance status of ≤ 2
4. Castration resistant prostate cancer, defined as biochemical, radiographic, and/or clinical progression despite castrate level of testosterone (<50 ng/dL). There is no restriction on prior therapies for CRPC.
5. Evaluable disease, with PSA ≥ 1.0 ng/ml and/or visible prostate cancer on imaging.
6. Serum testosterone < 50 ng/dL
7. Willing to undergo blood draws to measure PK levels
8. Able to swallow pills
9. Must have ability to understand and the willingness to sign a written informed consent prior to receiving a subject ID number.
10. Unless surgically sterile, sexually active patients must agree to use effective barrier method and refrain from sperm donation during the study treatment and for 3 months after the end of study treatment.
11. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study

12. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 14 days prior to registration.

System	Laboratory Value
Hematological	
Hemoglobin (Hgb)	≥ 9 g/dL
Absolute Neutrophil Count (ANC)	≥ 1,500/μL
Platelet count	≥ 100,000/μL
Renal	
Creatinine	≤ 2x upper limit of normal (ULN)
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN) or Gilbert's syndrome with normal direct bilirubin
Aspartate aminotransferase (AST)	≤ 2.5 × ULN
Alanine aminotransferase (ALT)	≤ 2.5 × ULN
Blood sugar	
HbA1C	≤ 7.5%
Fasting glucose	≤ 150 mg/dL

3.1.2 Phase I Exclusion criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Patients receiving systemic therapy for prostate cancer ≤ 21 days or 5 half-lives (whichever is shorter) prior to starting study drug are not eligible.
   NOTE: Patients must continue Androgen Deprivation Therapy, and patients can receive bone supportive therapy.
2. Histology of small cell carcinoma prostate cancer
3. Any active infection requiring IV antibiotics
4. Known additional malignancy that has a life-expectancy < 5 years.
5. Clinically significant acute infection requiring systemic antibacterial, antifungal, or antiviral therapy including:
   - **hepatitis B** (known positive HBV surface antigen (HBsAg) result),
   - **hepatitis C**, or
   - **human immunodeficiency virus** (positive HIV 1/2 antibodies).

   NOTES: Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects with HIV/AIDS with adequate antiviral therapy to control viral load would be allowed if they are stable and have been on treatment for ≥ 4 weeks prior to first dose of study drug(s). Subjects with viral hepatitis with controlled viral load would be allowed while on suppressive antiviral therapy.
6. History of type I or type II diabetes mellitus requiring insulin.
7. Any of the following within 6 months before registration: stroke, myocardial infarction, severe/unstable anginal pectoris, coronary/peripheral artery bypass graft, congestive heart failure New York Heart Association (NYHA) class III or IV.
8. Congenital long QT syndrome or QTcF > 480 milliseconds

9. Grade ≥ 2 uncontrolled or untreated hypercholesterolemia (>300 mg/dL) or hypertriglyceridemia (>300 mg/dL)
10. History of or active inflammatory bowel disease (IBD) or active bowel inflammation (diverticulitis)
11. Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
12. Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug
13. History of allergic reaction to darolutamide or ipatasertib.
14. Any condition that in the opinion of the investigator would impair the patients' ability to comply with study procedures.

3.2 Eligibility Criteria for Phase II Neoadjuvant Cohort

3.2.1 Phase II Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Histologically-confirmed diagnosis of localized, untreated prostate cancer with high-risk features. High-risk features is defined as:
   - Two or more cores from prostate biopsy that are grade group 4 (Gleason score 4+4=8) or higher,
     OR
   - Stage T3-4 (by clinical exam or MRI), M0, and at least 2 cores from prostate biopsy that are grade group 3 (Gleason score 4+3=7) or higher.

   NOTE: Pathology confirmation of malignancy must be performed by the participating site (i.e. reports should be issued by the participating site; if a subject's pathology report was not issued by the participating site, archival tissue should be requested by the participating site for internal pathology review.)
2. Sufficient archival tissue (at least 2 cores) available for targeted sequencing and immunohistochemistry to evaluate for PTEN loss using the Ventana SP218 immunohistochemistry assay at the local institution.
   - The tumor evaluated for PTEN expression should be selected based on containing both high grade and high volume of tumor content. The slide evaluated for PTEN expression should be saved for confirmatory central review. Eligibility is based on local review.
3. Measurable PSA
4. Must have PTEN loss per local institution evaluation, defined as 50% or more of tumor tissue being negative for PTEN expression on Ventana SP218 immunohistochemistry assay.
5. Disease must be untreated and subject must be eligible for (per PI discretion) and planning to undergo radical prostatectomy.
6. Male and ≥18 years of age.
7. ECOG performance status of ≤ 1 within 14 days prior to signing consent.
8. CT or MRI of abdomen and pelvis and bone scan within ≤90 days prior to starting study drug.
9. Able to swallow pills

10. Must have ability to understand and the willingness to sign a written informed consent prior to starting study drug.
11. Sexually active patients, unless surgically sterile, must agree to use effective barrier method and refrain from sperm donation during the study treatment and for 3 months after the end of study treatment.
12. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study
13. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 14 days prior to registration.

System	Laboratory Value
Hematological	
Hemoglobin (Hgb)	≥ 9 g/dL
Absolute Neutrophil Count (ANC)	≥ 1,500/μL
Platelet count	≥ 100,000/μL
Renal	
Creatinine	≤ 2x upper limit of normal (ULN)
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN) or. Gilbert's syndrome with normal direct bilirubin
Aspartate aminotransferase (AST)	≤ 2.5 × ULN
Alanine aminotransferase (ALT)	≤ 2.5 × ULN
Blood sugar	
HbA1C	≤ 7.5%
Fasting glucose	≤ 150 mg/dL

3.2.2 Phase II Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Histology of small cell carcinoma prostate cancer. Adenocarcinoma with neuroendocrine features is allowed.
2. Active infection requiring IV antibiotics
3. Distant metastatic disease beyond N1 (regional) lymph nodes on conventional baseline imaging studies within 90 days prior to signing consent.
4. Known additional malignancy that has a life-expectancy < 10 years.
5. Clinically significant acute infection requiring systemic antibacterial, antifungal, or antiviral therapy including:
   a. **tuberculosis** (clinical evaluation that includes clinical history, physical examination, and radiographic findings, and TB testing in line with local practice),
   b. **hepatitis B** (known positive HBV surface antigen (HBsAg) result),
   c. **hepatitis C**, or
   d. **human immunodeficiency virus** (positive HIV 1/2 antibodies).

   NOTES: Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects with HIV/AIDS with adequate antiviral therapy to control viral load would be allowed

if they are stable and have been on treatment for ≥ 4 weeks prior to first dose of study drug(s). Subjects with viral hepatitis with controlled viral load would be allowed while on suppressive antiviral therapy. Testing not required.

6. Prior treatment of prostate cancer with: second generation androgen receptor (AR) inhibitors, other investigational AR inhibitors or CYP17 enzyme inhibitor, radiation therapy, surgery, or chemotherapy. First generation antiandrogen (e.g. bicalutamide) for 28 days or fewer is allowed.
7. Receipt of an investigational agent within ≤ 28 days prior to registration; or herbal medications and marijuana products within ≤ 1 day prior to registration.
8. Receipt of medications (e.g. finasteride, dutasteride) or agents that are likely to alter serum PSA levels within ≤ 42 days or 5 half-lives prior to registration, whichever is shorter.
9. History of type I or type II diabetes mellitus requiring insulin.
10. Any of the following within 6 months before registration: stroke, myocardial infarction, severe/unstable anginal pectoris, coronary/peripheral artery bypass graft, congestive heart failure New York Heart Association (NYHA) class III or IV.
11. Congenital long QT syndrome or QTcF > 480 milliseconds
12. Grade ≥ 2 uncontrolled or untreated hypercholesterolemia (>300 mg/dL) or hypertriglyceridemia (>300 mg/dL)
13. History of or active IBD or active bowel inflammation (diverticulitis)
14. Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
15. Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug
16. History of allergic reaction to darolutamide or ipatasertib.
17. Any condition that in the opinion of the investigator would impair the patients' ability to comply with study procedures.

4. SUBJECT REGISTRATION

All subjects must be registered through Big Ten Cancer Research Consortium (Big Ten CRC) Administrative Headquarters'(AHQ) electronic data capture (EDC) system. A subject is considered registered when an 'On Study' date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within **10 business days** of registration.

5. TREATMENT PLAN

The proposed trial is a single arm, Phase I/II trial looking for an efficacy signal in the Phase II neoadjuvant setting in patients with PTEN-null tumors. The active therapy is a combination of androgen deprivation therapy, darolutamide, and ipatasertib. Patients will be treated for 6 cycles prior to prostatectomy, since pCR+MRD rate is higher with 6 months of ADT + abiraterone (24%) than 3 months (4%)[24]. Since the combination has not been evaluated before, a Phase I de-escalation cohort in

patients with castration resistant prostate cancer will be performed to evaluate safety and drug-drug interaction.

5.1 Phase I de-escalation cohort

The Phase I de-escalation cohort will enroll 6 patients to assess the safety of ipatasertib and darolutamide. Ipatasertib has already been evaluated in combination with the AR pathway inhibitors, including phase II[30] and phase III trials with abiraterone (NCT03072238) where 400 mg was found to be safe. Therefore, patients in dose level 1 will receive the expected final dose of darolutamide 600 mg BID and ipatasertib 400 mg daily. Treatment will begin with ipatasertib alone for 7 days (cycle 0). Darolutamide will be added at standard dose starting with cycle 1. Subjects will complete an oral drug diary to document compliance with self-administration of darolutamide and ipatasertib.

	Ipatasertib (once daily)	**Darolutamide** (twice daily)	**ADT**
Cycle 0 Days 1-7 (7 day cycle)	Monotherapy	--	As per site standards
Cycle 1 Day 1	AM dose with PKs	No AM dose. PM dose taken after ipatasertib monotherapy PKs	As per site standards
Cycle 1 Day 2+	✓	✓	As per site standards

Evaluation for dose limiting toxicities will continue for 28 days after the addition of darolutamide (cycle 2 day 1), and blood samples will be drawn for pharmacokinetic (PK) studies. If one or fewer patients experience a DLT, the trial will advance to the Phase II neoadjuvant cohort. If two or more patients experience a DLT at dose level 1, the dose will be reduced to dose level -1 for already enrolled patients and another 6 patients will be enrolled to evaluate darolutamide 600 mg BID and ipatasertib 300 mg daily. If at least two patients experience a DLT at dose level -1 before all six of the planned patients are enrolled the dose of ipatasertib will immediately be reduced to dose level -2 for already enrolled patients and another 6 patients will be enrolled to evaluate darolutamide 600 mg BID and ipatasertib 200 mg daily. The study will be terminated if there are 2 or more DLTs at dose level -2 and will not proceed to phase II.

Dose Level	**Ipatasertib**	**Darolutamide**	**ADT per institutional standards**
-2	200 mg daily	600 mg BID	As per site standards
-1	300 mg daily	600 mg BID	As per site standards
1 (start)	400 mg daily	600 mg BID	As per site standards

PK evaluations will continue through Cycle 3 Day 1. Enrollment in the Phase II neoadjuvant cohort can proceed before PK studies are complete.

Patients will have response evaluated at Cycle 4 Day 1 (+/- evaluation window), including PSA response and radiographic response per modified PCWG3. If there is progression on bone scan alone, patients

should have confirmatory bone scan at least 6 weeks later. Patients in the Phase I cohort will continue on therapy until the time of progression or unacceptable treatment-related toxicity. Response evaluation should continue every 12 weeks (+/- 4 weeks) for two years, and then every 16 weeks (+/- 8 weeks). Treatment of bone metastases can sometimes result in a "flare", with the appearance of progression in the setting of clinical response. If radiologic imaging shows progressive disease (PD) and the patient does not have clinical progression, tumor assessment may be repeated by the site ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. If repeat imaging confirms PD, patients will be discontinued from study therapy.

5.1.1 Definition of Dose Limiting Toxicities (DLTs)

A DLT is defined as an event not clearly due to the underlying disease or extraneous causes, that occurs within the first 28 days of treatment with combination of ipatasertib and darolutamide and meets any of the criteria included in the table below. The DLT observation period will end after Cycle 1 has been completed and study drugs have been restarted in Cycle 2. NCI CTCAE version 5 will be used for all grading.

Toxicity	DLT Criteria
Hematology	Common terminology criteria for adverse events (CTCAE) grade 3 neutropenia (neutrophil count decreased) for > 7 days (complete blood count plus differential must be measured every 3 days until neutrophil recovery to grade 2 or better)
	CTCAE grade 3 thrombocytopenia (platelet count decreased) for > 7 consecutive days or with grade > 1 bleeding or requirement for platelet transfusion
	CTCAE grade 4 thrombocytopenia
	Febrile neutropenia (absolute neutrophil count < 1 $x10^9$/l, fever > 38.3°C)
Hepatobiliary	Total bilirubin ≥ 2.0 x ULN to ≤ 3 x ULN for > 7 consecutive days
	CTCAE grade 3 or 4 total bilirubin (blood bilirubin increased)
	CTCAE grade 3 or grade 4 AST or ALT increased
	Hy's Law (one of the following): • ALT or AST >8×ULN • ALT or AST >5×ULN for more than 2 weeks • ALT or AST >3×ULN and total bilirubin >2×ULN or INR >1.5 • ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
Non-hematologic	Any nonhematologic AE ≥ grade 3, with the exceptions of grade 3 nausea, vomiting, diarrhea, electrolyte abnormality, constipation, fever, fatigue, or rash in which there has been suboptimal prophylaxis or management and that resolves to grade ≤ 2 within 72 hours
Drug delay	Delay in administration of a study drug ≥ 14 days due to toxicity

5.2 Phase II Neoadjuvant cohort

The single arm, two stage Phase II neoadjuvant portion of the trial will examine the recommended dose of ipatasertib with darolutamide in the neoadjuvant setting, selected for patients with loss of PTEN by IHC. If after 9 evaluable patients there are no patients with exceptional response (defined as pCR or MRD), accrual will halt due to lack of efficacy. Accrual will not pause while the 9th patient is on therapy; additional patients may accrue prior to pathologic evaluation of the 9th radical prostatectomy. Patients in the Phase II neoadjuvant cohort will continue on therapy for 6 cycles.

5.3 Ipatasertib, Darolutamide and ADT Administration

Androgen deprivation therapy (ADT) will be determined by the treating physician or designee and obtained as per institutional standards.

Drug	Dose	Route	Schedule	Cycle Length
ADT (per site standards)	As per site standards	As per site standards	As per site standards	As per site standards
Ipatasertib	Phase I cohort-determined dose	oral	Daily	28 days
Darolutamide	600 mg	oral	BID	
• Diaries will be provided to record self-administration of oral study drugs. • Darolutamide should be taken with food • Each dose of ipatasertib should be taken with a minimum of 3 ounces (90 mL) of fluid. Ipatasertib may be taken with or without food. If a dose is missed (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up. • The AM dose of ipatasertib and darolutamide can be taken together.				

5.4 Concomitant Medications

5.4.1 Allowed Concomitant Medications

All treatments the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Patients are recommended to use the following therapies during the study:

- Prophylaxis use of loperamide is recommended in the first cycle, and as clinically indicated in subsequent cycles to prevent diarrhea. Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines provided in Section 6.2.1.1. Patients should be educated/reminded to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated and per institutional practice.

5.4.2 Cautionary Concomitant Medications

Ipatasertib Cautionary Therapy

In vitro data suggest that ipatasertib is metabolized by CYP3A and may be a time-dependent inhibitor of CYP3A4. A clinical drug–drug interaction study with midazolam (a sensitive CYP3A substrate) showed a 2.2-fold increase in midazolam exposures in presence of steady-state Ipatasertib dosed at 600 mg QD. Therefore, sensitive CYP3A substrates with narrow therapeutic window should be avoided. Given that ipatasertib is primarily metabolized by CYP3A, there is a high potential for drug–drug interactions of ipatasertib with any medication that strongly inhibits or induces CYP3A. Data from a clinical study showed that ipatasertib exposures were reduced by approximately 50% when co-administered with

enzalutamide, a strong CYP3A inducer. Strong CYP3A inhibitors are expected to increase ipatasertib exposures significantly.
Therefore, the following drugs should be avoided or used with caution.

- Strong CYP3A4/5 inhibitors, such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and/or grapefruit juice
- Strong CYP3A4/5 inducers, such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- CYP3A4/5 substrates with a narrow therapeutic index, such as, but not limited to, alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine
- Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 7 days after the last dose of these drugs.
- Patients are permitted to take moderate inhibitors of CYP3A4 with caution.

Patients should be closely monitored. Refer to the following information for further guidance on CYP450–drug interactions and a list of common substrates, inhibitors, and inducers:

Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (U.S. Food and Drug Administration [FDA]):
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

The above lists of medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment.

Darolutamide Cautionary Therapy

- Combined P-gp and Strong or Moderate CYP3A4 Inducer
  Concomitant use of darolutamide with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease darolutamide activity. Avoid concomitant use of darolutamide with combined P-gp and strong or moderate CYP3A4 inducers.
- Combined P-gp and Strong CYP3A4 Inhibitors
  Concomitant use of darolutamide with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure which may increase the risk of darolutamide adverse reactions. Monitor patients more frequently for darolutamide adverse reactions and modify darolutamide dosage as needed.

Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

5.4.3 Prohibited Concomitant Medications

Prohibited Therapy

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy) is prohibited for various time periods prior to starting study treatment. See Section 3, Eligibility Criteria.
- Chronic use of a strong CYP3A4/5 inhibitor or inducer, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible after enrollment.

Prohibited Food

Use of the following foods are prohibited as described below:

- Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study treatment period and for 10 days after the last dose of study treatment.
- Consumption of St. John's wort, a potent CYP3A4 enzyme inducer, is prohibited for up to 14 days prior to and during the study treatment period, and for 10 days after the last dose of study treatment.

5.5 Supportive Care

Diarrhea is a common adverse event associated with ipatasertib treatment. To improve diarrhea management and patient experiences, loperamide (2 mg once a day) will be administered daily as prophylaxis for diarrhea in the first cycle if allowed by local guidance. If side effects of loperamide are not tolerated, doses may be reduced at any time. Investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgments.

If diarrhea occurs, it should be managed per guidelines in Section 6.2.1.1; upon resolution or when study treatment is restarted, loperamide prophylaxis should be considered to resume and continue based on clinical judgments (if allowed by local guidance).

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events.

Subjects 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 Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

Risks associated with ipatasertib

Hyperglycemia, including cases of Grade 3 or Grade 4 hyperglycemia, has been reported in patients receiving ipatasertib as monotherapy or ipatasertib in combination with other anticancer drugs or hormonal therapy. Hyperglycemia of any grade, regardless of causality, was reported in 35.3% of patients who received ipatasertib as a single agent in the Phase I Study PAM4743g, with Grade 3 hyperglycemia occurring in 1 patient (2.0%). In the GO27983 study, hyperglycemia of any grade, regardless of causality, was reported in 22.6%, 9.1%, and 7.4% of patients in the ipatasertib 400 mg, 200 mg, and placebo arms, respectively. Grade 3 hyperglycemia occurred in 10.7%, 2.3%, and 2.5% of patients in the 400 mg, 200 mg, and placebo arms, respectively. One patient (1.2%) in the ipatasertib

400 mg arm experienced Grade 4 hyperglycemia. There were no other instances of Grade 4 or higher hyperglycemia events in any arm. In the GO29227 study, hyperglycemia of any grade, regardless of causality, was reported in 9.5% and 3.3% of patients in the ipatasertib 400 mg and placebo arms, respectively. There were no reports of Grade ≥3 hyperglycemia.

GI toxicities such as nausea, vomiting, diarrhea, and stomatitis/oral mucositis have been commonly observed in patients receiving ipatasertib as monotherapy or in combination with other anticancer drugs.GI toxicities of any grade, regardless of causality, were commonly reported in patients who received ipatasertib as a single agent in the Phase I Study PAM4743g, including nausea (78.4%), diarrhea (72.5%), vomiting (58.8%), and stomatitis or mucosal inflammation (7.8%). In this study, the reported Grade 3 GI toxicities included diarrhea (7.8%), and nausea (2.0%). In the GO27983 study, GI toxicities, irrespective of grade or causality (presented by proportion of patients affected in the ipatasertib 400 mg, ipatasertib 200 mg, and placebo arms, respectively), included diarrhea (77.4%, 48.9%, and 24.7%), nausea (53.6%, 35.2%, and 24.7%), vomiting (32.1%, 27.3%, and 14.8%), and oral mucositis (6.0%, 3.4%, and 1.2%). The only Grade 3 GI AEs that affected ≥ 2 patients, irrespective of causality, were diarrhea (13.1%, 2.3%, and 1.2%) and nausea (2.4%, 0%, and 0%). There were no Grade 4 or 5 events in this category in this study. In the GO29227 study, GI toxicities of any grade, regardless of causality, reported in the ipatasertib 400 mg and placebo arms, respectively, included diarrhea (92.1% and 20.0%), nausea (52.4% and 33.3%), vomiting (27.0% and 23.3%), and oral mucositis (23.8% and 15.0%). Grade 3 diarrhea occurred in 22.2% of the ipatasertib 400 mg arm and 0% of the placebo arm. Grade 3 vomiting was reported in 3.2% and 0% of the ipatasertib 400 mg and placebo arms, respectively. With regard to Grade 3 nausea and Grade 3 oral mucositis, there was 1 patient in each arm (1.6% and 1.7% in the ipatasertib 400 mg and placebo arms, respectively). There were no Grade 4 or Grade 5 diarrhea, nausea, vomiting, or oral mucositis events in any arm.

Rash, primarily manifested as maculo-papular type with or without pruritus, has been commonly reported in patients receiving treatment with ipatasertib. Rash-related events of any grade, regardless of causality, were reported in 15.7% of patients who received ipatasertib as a single agent in the Phase I Study PAM4743g; Grade 3 rash (toxic skin eruption as reported term) was reported in 1 patient (2.0%). In the GO27983 study, irrespective of grade or causality, the proportion of patients experiencing a rash-related event was 23.8%, 9.1%, and 6.2% in the ipatasertib 400 mg, ipatasertib 200 mg, and placebo arms, respectively. Of patients in the ipatasertib 400 mg, 200 mg, and placebo arms, 9.5%, 2.3%, and 0%, experienced Grade 3 rash, respectively. One patient (1.2%) in the ipatasertib 400 mg arm experienced a Grade 4 event. There were no other instances of Grade ≥4 events in this study. In the GO29227 study, rash of any grade, regardless of causality, was reported in 30.2% and 30.0% of the ipatasertib 400 mg and placebo arms, respectively. There was 1 patient with Grade 3 rash in each arm (1.6% and 1.7% in the ipatasertib 400 mg and placebo arms, respectively). There were no cases of Grade 4 or Grade 5 rash events in any arm. Cases of Grade 3 rash requiring dose interruption and treatment with topical or systemic corticosteroids have also been observed from other ongoing ipatasertib studies.

Erythema multiforme: In the blinded Study CO39303, erythema multiforme of any grade regardless of causality was reported in 6 (0.5%) patients. Grade 3 erythema multiforme was reported in 5 of these 6 patients. In the blinded Study CO40016, one Grade 3 event of erythema multiforme was reported. An analysis of the first 4 cases of erythema multiforme reported, with a cut off date of 7 June 2018, found that the frequency of reported events of erythema multiforme is 4 out of 1051 patients (0.38%) and is a higher frequency than the reported global incidence rate of 1.2-6 per million. Published literature

suggests a possible causal association between PI3K inhibitors and erythema multiforme. The first dose latencies ranged from 9-16 days for these four cases, which is consistent with the literature describing drug-induced erythema multiforme. On 1 June 2018 an independent Data Monitoring Committee conducted a review of the totality of the safety data (unblinded), including skin toxicity-related events and details of the four erythema multiforme cases (from Study CO39303), and concluded that Study CO39303 be continued with no modifications to the conduct. Further evaluation and assessment will occur after Studies CO39303 and CO40016 are unblinded.

Fatigue or asthenia of any grade, regardless of causality, has been observed in 62.7% of patients receiving ipatasertib as a single agent in the Phase I Study PAM4743g, with 5 (9.8%) cases of Grade 3 asthenia/fatigue reported. In the GO27983 study, asthenia/fatigue of any grade, irrespective of causality, was reported in 48.8%, 45.5%, and 43.2% of patients in the ipatasertib 400 mg, 200 mg, and placebo arms, respectively. Grade 3 asthenia/fatigue occurred in 9.5%, 5.7%, and 3.7% of patients, respectively, as above. There were no cases of Grade 4 or Grade 5 asthenia/fatigue events in any arm. In the GO29227 study, asthenia/fatigue of any grade, regardless of causality, was reported in 49.2% and 43.3% of the ipatasertib 400 mg and placebo arms, respectively. Grade 3 asthenia/fatigue was reported in 6.3% and 6.7% of the ipatasertib 400 mg and placebo arms, respectively. There were no cases of Grade 4 or Grade 5 asthenia/fatigue events in any arm.

Refer to the Ipatasertib Investigator's Brochure for further information regarding the nonclinical and clinical safety evaluation of ipatasertib as a single agent and in combination with chemotherapy.

6.1 Dose Delays/Dose Modifications

Unless otherwise noted in the dose modification tables below, treatment may be delayed ≤ 28 days from the expected day of the next treatment for any reason. If treatment is delayed ≤ 28 days subjects will proceed with the next cycle of treatment at the dose level recommended according to the tables below. Held or missed doses are not to be made up and will not alter the duration of total therapy prior to prostatectomy.

6.2 Darolutamide Dose Modifications

The darolutamide dose may be adjusted as necessary, using discretion based on clinical judgment and per local guidance. If a patient experiences a greater than or equal to Grade 3 toxicity or an intolerable adverse reaction, withhold dosing or reduce to 300 mg twice daily until symptoms improve. Then the treatment may be resumed at a dose of 600 mg twice daily. Dose reduction below 300 mg twice daily is not recommended.

Refer to the darolutamide Investigator's Brochure or package insert for further guidance.

6.3 Ipatasertib Dose Levels for Dose Reductions

Dose level	**Dose of Ipatasertib**		
Starting Dose	400 mg daily	300 mg daily	200 mg daily
Dose level (-1)	300 mg daily	200 mg daily	Remove from study drugs

Dose level (-2)	200 mg daily	Remove from study drugs	--
Dose level (-3)	Remove from study drugs	--	--

If a dose level below that included in the above table is required the subject will be removed from protocol mandated treatment and will be followed up per protocol and proceed to prostatectomy.

6.3.1 Adverse Event Management Guidelines

6.3.1.1 Diarrhea Management Guidelines

Specific guidelines for managing diarrhea to improve safety and tolerability are provided below. In this study, all patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance.

Treatment modifications for diarrhea (any grade), when it occurs, should be instituted as early as possible. Guidelines for treatment of diarrhea following the prophylactic dose of loperamide (where allowed) includes use of loperamide 2 mg every 4 hours or after each loose, watery stool, up to the maximum total dose of 16 mg/day or per institutional guidelines and standard of care, including, but not limited to, additional therapy with Lomotil® (diphenoxylate and atropine), codeine, or octreotide. Duration of diarrhea may be minimized by taking ipatasertib with food, avoiding lactose-containing foods, and hydrating with 8–10 glasses per day (~12 oz/glass) of electrolyte-containing clear liquid, such as broth or low-calorie drinks.

For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib, gastroenterologists should be consulted to rule out the risk of colitis and infection (e.g., obtaining CT images or a stool culture for infectious workup [*Clostridium difficile*, enteric bacteria, cytomegalovirus]). Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed.

Dose of darolutamide should be maintained as tolerated. Dose reductions of ipatasertib will be reduced by 100 mg (i.e., 400 to 300 mg, or 300 mg to 200 mg). If Grade ≥ 2 diarrhea persists following dose reductions of ipatasertib to 200 mg daily and with maximum treatment for diarrhea, ipatasertib should be discontinued.

Severity of Diarrhea	Management Guideline
Prevention	• All patients are recommended to receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle, if allowed by local investigator. Loperamide dose adjustment may be made per investigator discretion. • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated.

Severity of Diarrhea	Management Guideline
Grade 1 Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	• Continue study drugs at the current dose level. • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8−10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance.
Grade 2 Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline	• Rule out infectious etiology. • Manage with loperamide as early as possible 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8−10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better. • Reduce ipatasertib by one (or one additional) dose level for recurrent Grade 2 diarrhea. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.
Grade 3 Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level when treatment is restarted. • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.

Severity of Diarrhea	Management Guideline
Grade 4 Life-threatening consequences; urgent intervention indicated	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Permanently discontinue ipatasertib.
ADL = activities of daily living; BID = twice a day; QD = once a day.	

6.3.1.2 Fasting Hyperglycemia

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours. Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined below and are intended to provide guidance for fasting glucose measurements assessed in the clinic. Decisions regarding study treatment should be made on fasting levels drawn in the clinic whenever possible.

Home glucose measurements may be used to trigger contact between patient and investigative site team and may lead to an unscheduled clinic visit to assess fasting glucose. Guidance for when to call the investigator/site staff (or designated endocrinologist, if applicable) should be provided to patients for hypoglycemia (e.g., glucose value under 70 mg/dL) and hyperglycemia (e.g., glucose value over 300 mg/dL). Alternative thresholds may be selected as clinically indicated per investigator discretion or institutional guidance and noted in the source documents. For any patients performing home glucose monitoring, the blood glucose log should be reviewed at each clinic visit (and source data retained), entry of results into the patient's eCRF will be limited to values which result in intervention.

In the event of ipatasertib interruption, anti-diabetic medications may need to be held or reduced (per investigator judgement) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Severity of Fasting Hyperglycemia	Management Guideline
Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L)	• Monitor fasting glucose per protocol • Consider initiating home glucose monitoring
Fasting glucose value >160 to 250 mg/dL (> 8.9–13.9 mmol/L)	• Interruption of ipatasertib until fasting hyperglycemia resolves to <160 mg/dL or better. • Initiate home glucose monitoring • Start oral anti-diabetic medications (e.g., metformin). • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level. • If the patient previously has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication.
Glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L)	• Interrupt ipatasertib dosing until fasting hyperglycemia resolves to <160 mg/dL or better. • Initiate home glucose monitoring • Treat hyperglycemia as medically appropriate. Start (or increase

	dose of) oral anti-diabetic medications (e.g., metformin). • Ipatasertib should be reduced by one dose level when treatment is restarted. • If hyperglycemia w/ a glucose value between 250-500 mg/dL recurs, permanently discontinue ipatasertib.
Glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences	• Interrupt ipatasertib dosing until resolution to Grade 1 or better. • Treat hyperglycemia as medically appropriate. • Initiate home glucose monitoring • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Permanently discontinue ipatasertib.

6.3.1.3 Neutropenia and/or Thrombocytopenia

Addition of hematopoietic growth factors is allowed. If a dose delay is required as a result of neutropenia at any grade, patients should receive prophylactic granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor per institutional standards. Patients should be counseled as to the risk of fever and infection and to the importance of contacting their treating physician or designee immediately if these conditions occur so that they can be promptly and appropriately managed. Dosage modification guidelines for neutropenia and/or thrombocytopenia attributable to ipatasertib are outlined below.

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Grade 2	• Ipatasertib may be continued at the original dose.
Grade 3	• Ipatasertib should be held until recovery to Grade 1. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. o First episode: resume the original dose. o Recurrent episode: Ipatasertib should be reduced by one dose level when treatment is restarted. If patient has had recurrent Grade 3 neutropenia episodes on study, permanently discontinue ipatasertib. • Following a treatment hold of up to 4 weeks, if recovery to Grade 1 or better neutropenia does not occur, discontinue ipatasertib.
Febrile neutropenia and Grade 4 neutropenia	• Permanently discontinue ipatasertib treatment.

6.3.1.4 Nausea and/or Vomiting

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other anti-emetics (i.e., prochlorperazine or metoclopramide per institutional guidelines).

Severity of Nausea and /or Vomiting	Management Guideline
Grade 1	• Provide supportive care as needed.
Grade 2	• Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron.
Grade ≥ 3	• Interrupt ipatasertib until nausea or vomiting resolves to Grade 2 or better. • Provide maximum supportive care per local guidelines, with a minimum of two anti-emetics, including ondansetron. • If Grade ≥ 3 nausea or vomiting recurs, ipatasertib should be reduced by one dose level when treatment is restarted.

6.3.1.5 Rash

Ipatasertib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity attributable to study treatment are shown in below.

Severity of Rash	Management Guideline
Grade 1	• Continue study drugs. • Consider topical corticosteroids.
Grade 2	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids.
Grade 3	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If the skin toxicity resolves to Grade 1 or better or is no longer clinically significant within 28 days, following completion of the steroid taper, ipatasertib may be resumed at one dose level below the previous dose. • If recovery of the skin toxicity to Grade 1 or better does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib.

Severity of Rash	Management Guideline
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. Ipatasertib should be permanently discontinued.

6.3.1.6 Pneumonitis

Pneumonitis is not known to be causally related to any of the study drugs; however, it has been observed with other drugs treating pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function.

Severity of Pneumonitis	Management Guideline
Grade 1	• Continue study drugs. • Perform CT scan and PFTs. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment until improvement to Grade 1 or better. Consider resuming ipatasertib at same dose level or one dose level below per investigator's assessment. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • For recurrent Grade 2 pneumonitis, discontinue ipatasertib. • Discontinue ipatasertib if recovery to Grade 1 or better is not evident within 28 days.
Grade 3	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib until improvement to Grade 1 or better. Resume ipatasertib at one dose level below previous dose per investigator's assessment. If recovery to Grade 1 or better is not evident within 28 days, discontinue study treatments. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • For recurrent non-infectious Grade 3 pneumonitis events, ipatasertib should be permanently discontinued.
Grade 4	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Permanently discontinue ipatasertib. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

6.3.1.7 Mucositis

Mouthwash such as magic mouth wash (if inaccessible, warm salt or bicarbonate water) should be used as supportive care per institution guidelines. Brushing teeth after meals, keeping lips moisturized with

non-Vaseline® products, and avoiding alcohol, spicy food, and smoking have all been shown to reduce pain and infection related to mucositis. Ranitidine or omeprazole may be helpful if patients have epigastric pain.

Severity of Mucositis	Management Guidelines
Grade 1 or 2	• Manage with maximum supportive care. • If Grade ≥ 2 mucositis recurs in subsequent 4 week cycles, despite maximal supportive care, the dose of ipatasertib should be reduced by one dose level.
Grade ≥ 3	• Hold ipatasertib until recovery to Grade 1 or better. If the mucositis resolves to Grade 1 or better during the current cycle, the dose of ipatasertib should be reduced by one dose level. • If recovery of mucositis to Grade 1 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue ipatasertib.

6.3.1.8 Other Non-Hematologic Toxicities

- If other Grade ≥ 3 non hematologic toxicities not described above develop in patients, treatment with ipatasertib may be held, depending on the attribution of the toxicity, at the discretion of the investigator. During this time, treatment may continue with the other non-attributable treatment agent (darolutamide). Grade ≥ 3 non-hematologic toxicity should be monitored at least weekly.
- If the toxicity resolves to Grade 1 or better within 2 weeks, treatment may resume with the attributable agent.
- If the toxicity resolves to Grade 1 or better in 2–4 weeks, the dose of the attributable drug should be reduced by one level.
- Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes > 4 weeks, treatment may resume with the attributable agent with dose reduction, or the attributable agent may be permanently discontinued, at the discretion of the investigator.
- For Grade ≥ 3 toxicities associated primarily with laboratory abnormalities only (e.g., elevation of ALT, AST, lipase, or amylase, or decreases in phosphorus without clinical or other evidence of pancreatitis or other hepatic dysfunction), study treatment may continue without interruption and/or dose reduction at the discretion of the investigator per institutional practice. However, study treatment should be discontinued if the increase in ALT or ALT meets the criteria for "Hy's law":
    - ALT or AST >8xULN
    - ALT or AST >5xULN for more than 2 weeks
    - ALT or AST >3xULN and TBL >2xULN or INR >1.5
    - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

6.4 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in section 6.2.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances

outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Subject has received 6 cycles of study drugs (in the Phase II neoadjuvant cohort)
- Documented radiographic progression (Phase I or Phase II)
- The treating physician/designee thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- If protocol therapy is interrupted for ≥ 28 days from the expected day of the next treatment.

If ipatasertib is permanently discontinued due to toxicity, darolutamide may continue per protocol. If darolutamide is permanently discontinued due to toxicity, ipatasertib should also be discontinued and the patient should proceed to prostatectomy (Phase II).

6.5 Protocol Discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS: PHASE I DE-ESCALATION COHORT

Cycle = 28 days	Screen		Phase I De-escalation Cohort[2] (±3 days)					Safety follow up[2]
	-90 days	-14 days[1]	Cycle 0 Day 1 (7 day cycle)	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2-4 Day 1	Cycle 7+ Q3 cycles[2] (±4 wks)	30 days post Tx[3]
REQUIRED ASSESSMENTS								
Medical history, smoking history, trial awareness[5]	X							
Diagnosis and Staging[6]	X							
Physical exam, Vital signs, ECOG Performance status[7]		X	X	X	X	X	X	X
AEs & concomitant medications		X	X	X	X	X	X	X
ECG	X							
LABORATORY ASSESSMENTS[8]								
Complete Blood Cell Count with diff (CBC)		X	X	X	X	X	X	X
Comprehensive Metabolic Profile (CMP)[9]		X	X	X	X	X	X	X
HgA1C; LDH		X						X
Fasting glucose (if not part of CMP)		X	X	X	X	X	X	
Testosterone		X						X
Prostate specific antigen		X	X	X	X	X	X	X
Antibody studies for Hepatitis B, C and HIV	X							
DISEASE ASSESSMENT								
CT or MRI of chest, abdomen and pelvis	X					pre-C4	X[10]	
Bone scan	X					pre-C4	X[10]	
TREATMENT EXPOSURE								
Ipatasertib (once daily, continuous)			X	X	X	X	X	
Darolutamide (twice daily, continuous)				X[12]	X	X	X	
Androgen deprivation therapy (per standard of care)			SOC	SOC	SOC	SOC	SOC	
CORRELATIVE STUDIES (SPECIMEN COLLECTION)								
Blood for somatic baseline			X					
Archival tissue slides, if available[11]	X							
Pharmacokinetic studies[12]				X[12]	X	C3		
Research blood/plasma collection			X	X		C2, C4		X
BANKING SAMPLES (SPECIMEN COLLECTION)								
Whole Blood and Unstained Slides (if available)[13]				X				
Serum and Plasma				X				X

Key to Footnotes: Phase I De-escalation Cohort

[1]If screening (baseline) labs were performed within 7 days of C1D1 of treatment, these do not need to be repeated.

[2]Visits should occur every 28 days. A window of 3 days will be applied to all treatment study visits; for safety follow-up visit a 7-day window will apply. Subjects will be seen every cycle through cycle 4 day 1, then may be seen every 12 weeks ± 4 weeks (every 2-4 cycles) until documented disease progression or discontinue therapy.

[3]A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment.

[4]Subjects without documented disease progression will be followed for disease progression every 6 months for 2 years.

[5]Medical history to include: smoking history, trial awareness question, prior ICH and genetic testing of tumor tissue.

[6]Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging.

a. Staging may be captured from initial diagnosis.
b. Repeat abdominal imaging to confirm stage must be performed within 90 days of trial initiation.
c. Staging will be based on the 8th edition of the AJCC Cancer Staging Manual.

[7]Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status

[8]Laboratory assessment will be performed prior to treatment initiation as noted and every cycle thereafter at clinic visits during treatment periods.

[9]CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

[10]After Cycle 4, disease assessments will be performed every 12 weeks (+/- 4 weeks) for two years, and then every 16 weeks (+/- 8 weeks).

[11]Fixed paraffin-embedded blocks/slides will be requested by the investigator enrolling the patient. Request should be placed when the patient is being screened and slides should be shipped by C1D1 of treatment. If available, slides are required for central confirmation of PTEN analysis and other biomarker research. See CLM for collection, labeling, and shipping instructions.

[12]Plasma will be collected on Cycle 1 Day 1 for Ipatasertib monotherapy PKs (pre-dose, +1h, +2h, +3h, +5h). Subjects will begin Darolutimide in the evening of C1D1 *AFTER* drawing samples for PKs on Ipatasertib. Additonal samples will be collected on Cycle 1 Day 15 and Cycle 3 Day 1 (pre-dose, +1h, +2h, +3h, +5h on each day) to evaluate PKs for combination therapy.

[13]Submission of unstained slides for banking from an archived FFPE tumor block (if available). See CLM for collection, labeling, and shipping instructions.

STUDY CALENDAR & EVALUATIONS: PHASE II NEOADJUVANT COHORT

	Screen		Phase II Neoadjuvant Cohort [2] (±3 days)				Surgery[3]	Safety follow up[2]	Long-term Follow up[5]
			Cycles 1-2		Cycles 3-6	Cycle 6			
Cycle = 28 days	-90 days	-14 days[1]	Day 1	Days 8, 15	Day 1	Day 29	(±14d)	30 days (±7d) post[4]	Q 6 months (±30 days)
REQUIRED ASSESSMENTS									
Medical history, smoking history, trial awareness[6]	X								
Diagnosis and Staging[7]	X								
Physical exam, Vital signs, ECOG Performance status[8]		X	X		X	X		X	
AEs & concomitant medications		X	X		X	X		X	
Immunohistochemistry for PTEN[11]	X								
ECG	X								
LABORATORY ASSESSMENTS[9]									
Complete Blood Cell Count with diff (CBC)		X	X		X	X		X	
Comprehensive Metabolic Profile (CMP)[10]		X	X		X	X		X	
HgA1C		X				X		X	
Fasting glucose		X	X	X	X	X		X	
Testosterone; Prostate specific antigen		X	X		X	X		X	X
DISEASE ASSESSMENT									
CT or MRI of abdomen and pelvis	X								
Bone scan	X								
TREATMENT EXPOSURE									
Ipatasertib (once daily, continuous)			X	X	X				
Darolutamide (twice daily, continuous)			X	X	X				
Androgen deprivation therapy (per standard of care)			SOC	SOC	SOC				
CORRELATIVE STUDIES (SPECIMEN COLLECTION)									
Whole blood for somatic baseline			Pre-C1						
Archival biopsy slides[12]	X								
Research blood/plasma collection[14]			Pre-C1,C2			X			
Prostatectomy specimen							X		
BANKING SAMPLES (SPECIMEN COLLECTION)									
Whole Blood			Cycle 1						
Unstained Slides (if available)			Cycle 1				X		
Serum and Plasma			Cycle 1					X	
FOLLOW-UP									
Survival status, evidence of biochemical progression									X

Key to Footnotes: Phase II Neoadjuvant Cohort

[1]If screening (baseline) labs were performed within 7 days of C1D1 of treatment, these do not need to be repeated.

[2]Visits should occur every 28 days. A window of 3 days will be applied to all treatment study visits; for safety follow-up visit a 7-day window will apply.

[3]Prostatectomy will occur within 28 days (±14 days) of end of the sixth cycle.

[4]A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment.

[5]Subjects without documented disease progression will be followed for disease progression every 6 months for 2 years.

[6]Medical history to include smoking history, trial awareness question prior IHC and genetic testing of tumor tissue.

[7]Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging.

d. Staging may be captured from initial diagnosis.
e. Repeat abdominal imaging to confirm stage must be performed within 90 days of trial initiation.
f. Staging will be based on the 8th edition of the AJCC Cancer Staging Manual.

[8]Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status

[9]Laboratory assessment will be performed prior to treatment initiation as noted and every cycle therafter at clinic visits during treatment periods. Following the conclusion of treatment, testosterone and PSA assessment will be continued with each visit during long term follow up at the interval noted above.

[10]CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

[11]Immunohistochemistry for PTEN expression will be performed and evaluated by the enrolling institution for each patient and retrospectively undergo central review.

[12] Fixed paraffin-embedded blocks/slides will be requested by the investigator enrolling the patient. Request should be placed when the patient is being screened and slides should be shipped by C1D1 of treatment. Slides are requested for central confirmation of PTEN analysis and other biomarker research. See CLM for collection, labeling, and shipping instructions.

[13]Submission of unstained slides for banking from an archived FFPE tumor block (if available). See CLM for collection, labeling, and shipping instructions.

[14]Blood collected for biomarker evaluation (e.g. Immunogenicity and ctDNA).

7.1 Safety Follow-up Evaluations

A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

7.2 Long Term Follow-up Evaluations

Subjects in the Phase I cohort will not have any long term follow-up evaluations.

All subjects in the Phase II neoadjuvant cohort will be followed every 6 months for two years following prostatectomy or until documented biochemical recurrence. If a subject does not undergo prostatectomy and does not have documented disease progression, he will be followed for disease progression every 6 months for 2 years. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. In cases of disease recurrence the choice of followup therapy will be as per the treating physician. However, adjuvant or salvage therapy should not start until after PSA and testosterone level results are obtained at least four weeks after surgery.

8. BIOSPECIMEN STUDIES AND PROCEDURES

The current study will collect pre-treatment and post-treatment archival tissue from diagnostic biopsy and radical prostatectomy, respectively, for use in exploratory studies. We hypothesize that co-inhibition of AR and AKT will cause an exceptional pathologic response in patients with prostate cancer with PTEN loss, but other pathways may contribute to resistance to this strategy. These include persistent activation of hormone receptors or the PI3K pathway despite inhibition, or differentiation toward neuroendocrine phenotype. In addition, PI3K pathway inhibition may release repression of immune pathways. Exploratory objectives of this study include evaluation for PI3K-AKT pathway activity and effects on other drivers of proliferation and survival (e.g. androgen receptor (AR), glucocorticoid receptor (GR), proliferation (using Ki-67) and change in neuroendocrine marker expression among others). See Correlative Laboratory Manual for detailed collection, processing, and shipping instructions.

8.1 Source and Timing of Biospecimen Collections

8.1.1 Phase I de-escalation cohort

Tissue – For the Phase I cohort, the most recent archival tissue available will be requested. This is mandatory if available, but patients may enroll if archival tissue is not available. If and when funding becomes available, these studies will include immunohistochemical (IHC) analysis (such as evaluation of expression of hormone receptors, markers of proliferation, neuroendocrine markers, and immune markers), as well as extraction and evaluation of DNA and RNA for genetic analysis.

Blood for Pharmacokinetics –

Plasma will be collected Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 3 Day 1 (pre-dose, +1h, +2h, +3h, +5h on each day) to evaluate PKs. Plasma will be collected on Cycle 1 Day 1 for Ipatasertib monotherapy PKs (pre-dose, +1h, +2h, +3h, +5h). Subjects will begin Darolutimide in the evening

AFTER drawing samples for PKs on Ipatasertib. Additonal samples will be collected on Cycle 1 Day 15 and Cycle 3 Day 1 (pre-dose, +1h, +2h, +3h, +5h on each day) to evaluate PKs for combination therapy.

Blood/plasma for immunogenicity studies and ctDNA - Blood will be collected Cycle 0 Day 1, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, and at safety follow up. Analysis to be performed upon receipt of funding.

Blood for somatic baseline - Whole blood will be collected prior to C1D1 treatment for somatic baseline comparison.

8.1.2 Phase II Neoadjuvant cohort

Prostate biopsy - Archival tissue must be available to evaluate for PTEN loss locally using the Ventana SP218 immunohistochemistry assay. Central review to confirm PTEN loss will be performed retrospectively. If and when funding becomes available, additional studies may include immunohistochemical (IHC) analysis (such as evaluation of expression of hormone receptors, markers of proliferation, and neuroendocrine markers), as well as extraction and evaluation of DNA and RNA for genetic analysis.

Prostatectomy specimen - Once the prostatectomy specimen has been evaluated for clinical purposes, tissue is required for central review and correlative studies. If there is more than minimal residual disease on a single block, a block representative of the residual disease is requested to be used for exploratory studies, as well as a corresponding H&E slide. If and when funding becomes available, these studies will include immunohistochemical (IHC) analysis (such as evaluation of expression of hormone receptors, markers of proliferation, neuroendocrine markers, and immune markers), as well as extraction and evaluation of DNA and RNA for genetic analysis. If there is a pathological complete response (pCR) or minimal residual disease (MRD) by local review, slides from **each block** are requested for central review.

Blood/plasma for immunogenicity studies and ctDNA - Blood will be collected Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 6 Day 1. Analysis to be performed upon receipt of funding.

Blood for somatic baseline - Whole blood will be collected prior to C1D1 treatment for somatic baseline comparison.

8.2 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples that were collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN), as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

8.3 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples for future unspecified Big Ten Cancer Research Consortium studies. HCRN will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived pre-treatment formalin fixed paraffin embedded prostate tumor tissue sample and also from the prostatectomy sample, when applicable.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.4 Confidentiality of Biospecimens

Samples will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Phase II Neoadjuvant cohort

9.1.1 Pathological response

Response for the Phase II neoadjuvant cohort will be evaluated at the time of prostatectomy. Those with pathological complete response (absence of pathologic disease on hematoxylin and eosin (H&E) stain (defined as ypT0)), or with presence of minimal residual disease (<5 mm linearly), will be considered to be responders. Those with more than minimal residual disease will be considered to have no response.

9.1.2 Biochemical recurrence

Relapse or recurrence will be determined by detectable PSA (≥ 0.1 ng/mL) on scheduled bloodwork confirmed with a rising PSA at least one week later, the appearance of metastatic disease on imaging, or biopsy-proven relapse. For biochemical recurrence, the date of recurrence will be dated back to the initial detectable PSA.

9.1.3 PSA_0

PSA_0 is defined as recovery of testosterone to non-castrate level (>50 ng/dL) and undetectable PSA (reported as ≤ 0.1 ng/mL or undetectable).

9.2 Phase I De-escalation Cohort

Response will be evaluated in the Phase I Cohort at 12 weeks, using PCWG3 criteria. No additional timepoints for response evaluation are mandated, with the exception of those with bone-only progression requiring confirmation scan. For those without progression and continuing on therapy, tumor evaluation should occur at least annually. Patients will continue to be followed until the time of progression or end of treatment, whichever comes first. The timing (date) and cause (radiographic progression, clinical progression, PSA progression, toxicity) of end of treatment will be recorded. It is recommended that treatment continue until radiographic progression, but physician/designee discretion is allowed.

9.3 Prostate Cancer Working Group 3 (PCWG3) response criteria

This study makes use of a modified version of the PCWG3 response criteria for the Phase I cohort, which consists of the following three distinct evaluations, with separate evaluation for measurable disease (modified RECIST 1.1), bone metastases (2+2 rule), or PSA response. Please see below for details.

9.4 Measurable disease

Measurable disease is defined as the presence of at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.4.1 Malignant Lymph Nodes

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

9.5 Non-measurable Lesions

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

9.6 Target Lesions

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

9.7 Non-target Lesions

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

9.8 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.9 Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

9.10 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects 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 objective progression even after discontinuation of treatment.

9.11 Imaging biomarkers: Bone

Record changes on bone scan as improved or stable (no new lesions) or worse (new lesions). Changes in intensity of uptake do not constitute progression or regression. For progression to occur, at least two new lesions must appear on first post-treatment scan, with at least two additional lesions on the next scan at least 6 weeks later (2+2 rule). If at least two additional lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first scan, when the first two new lesions were documented. For all scans after the 12 week scan, at least two new lesions indicates progression. Date of progression is the date of the scan that first documents the second lesion.

9.12 Blood-based marker: PSA

Record the percent change from baseline at 12 weeks, and separately, the maximal change at any time. PSA at twelve weeks will be used to determine response. PSA decrease of 50% or more will be counted as PSA response. PSA increase of 25% or more will be counted as PSA progression.

10. DRUG INFORMATION

10.1 Ipatasertib

Ipatasertib is an AKT inhibitor that acts by binding to the adenosine triphosphate (ATP)-binding pocket of the activated isoforms of AKT.

Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

10.1.1 Supplier/How Supplied

The Ipatasertib Drug Product will be supplied by Genentech, Inc. at no charge to subjects participating in this clinical trial as 100- and 200-mg tablets.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation

Ipatasertib is provided as oral tablets.

10.1.3 Storage and Stability

Ipatasertib should be stored at room temperature.

10.1.4 Handling and Disposal

Ipatasertib should be handled in accordance with good practice rules and local guidelines for oral anticancer drugs.

After final drug reconciliation, unused ipatasertib should be disposed at the site following procedures for the disposal of anticancer drugs.

10.1.5 Dispensing

Ipatasertib must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Ipatasertib should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.6 Adverse Events

Adverse events associated with ipatasertib use include diarrhea, nausea, vomiting, alopecia, neuropathy, fatigue, rash and decreased neutrophil count. Please refer to the IB for the comprehensive list of adverse events associated with ipatasertib use.

10.2 Darolutamide

Darolutamide is an androgen receptor inhibitor that competitively inhibits androgen binding, nuclear translocation and androgen receptor mediated transcription.

Please refer to the latest version of the prescribing information that can be found at *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*, and/or on the manufacturer's website.

10.2.1 Supplier/How Supplied

Darolutamide will be supplied by Bayer at no charge to subjects participating in this clinical trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.2.2 Preparation

Darolutamide is provided as oral tablets.

10.2.3 Storage and Stability

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

10.2.4 Handling and Disposal

Darolutamide should be handled in accordance with good practice rules and local guidelines for oral anticancer drugs.

After final drug reconciliation, unused darolutamide should be disposed at the site following procedures for the disposal of anticancer drugs.

10.2.5 Dispensing

Darolutamide must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Darolutamide should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.2.6 Adverse Events

Adverse events associated with darolutamide include fatigue, pain in an extremity, rash, ischemic heart disease and heart failure. Please refer to the package insert for darolutamide for the comprehensive list of adverse events associated with darolutamide use.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if tthey induce clinical signs or symptoms or require treatment or further diagnostic tests.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. NOTE: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject 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 for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- 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 subject 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.

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s).

To ensure consistency of AE and SAE causality assessments, site investigators should apply the following general guideline:

Yes
There is a plausible temporal relationship between the onset of the AE and administration of ipatasertib, and the AE cannot be readily explained by the subject's clinical state, inter-current illness, or concomitant therapies; and/or the AE follows a known pattern of response to ipatasertib; and/or the AE abates or resolves upon discontinuation of atezolizumab or dose reduction and, if applicable, reappears upon re- challenge.

No
Evidence exists that the AE has an etiology other than the ipatasertib (e.g., preexisting medical condition, underlying disease, inter-current illness, or concomitant medication); and/or the AE has no plausible temporal relationship to ipatasertib administration (e.g., cancer diagnosed 2 days after first dose of Ipatasertib).

Expected adverse events are those adverse events that are listed or characterized in the current Investigator Brochure (IB).

Unexpected adverse events are those not listed in the current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the package insert or IB.

11.1.5 AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product. AESIs shall be forwarded to Genentech as described in the Genentech Safety Data Exchange Agreement (SDEA).

The Ipatasertib Events of Special Interest are:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- Suspected transmission of an infectious agent by the study drug, as defined below
  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Grade ≥ 3 fasting hyperglycemia
- Grade ≥ 3 hepatotoxicity
- Grade ≥ 3 ALT/AST elevations
- Grade ≥ 2 colitis/enterocolitis
- Grade ≥ 3 diarrhea
- Grade ≥ 3 rash
- Grade ≥ 2 pneumonitis

11.1.6 Selected Adverse Events

Additional data including grade, timing and required interventions will be collected for the following selected adverse events:

- Diarrhea
- Asthenia (fatigue)
- Nausea
- Neutropenia (neutrophil count decreased, febrile neutropenia)
- Rash (e.g., maculopapular, erythema, urticarial, dermatitis, rash popular, skin exfoliation, toxic skin eruption)
- Erythema multiforme
- Vomiting
- Oral mucositis (stomatitis, mucosal inflammation, mouth inflammation, mouth ulceration)
- Hyperlipidemia (hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, blood cholesterol increased, blood triglycerides increased)
- Hepatotoxicity (ALT, AST increased)
- Hyperglycemia (blood glucose increased)

- Pneumonitis (interstitial lung diseases)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Reporting of Pregnancy

- Pregnancy will be reported from time of first study drug until 30 days after discontinuation of study drug(s).
- Pregnancy will be reported to Big Ten CRC AHQ **within 1 business day** of discovery of the event.
- Pregnancy will be reported using the Big Ten CRC Pregnancy Reporting Form (see Documents/Info tab of the EDC).

The initial pregnancy notification and pregnancy follow-up will be recorded on the Big Ten CRC Pregnancy Reporting Form. The form will include an assessment of the possible relationship to the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy will be reported on the SAE Submission Form.

The site will submit the completed Pregnancy Reporting Form to Big Ten CRC AHQ within **24 hours** of discovery of the event. The form will be sent electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the event as per local requirements.

11.2.3 Serious Adverse Events (SAEs)

11.2.3.1 Site Requirements for Reporting SAEs to Big Ten CRC Administrative Headquarters

- SAEs will be reported from time of study drug administration until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form and entered in the SAE tab in the EDC system**.**
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

For SAEs and AESIs assessed as at least possibly related to the study drug(s) or assessed as unknown relation, the site will submit the completed SAE Submission Form (see Documents/Info tab in the EDC) to Big Ten CRC AHQ within **1 business day** of discovery of the event. The form will be sent electronically to Big Ten CRC AHQ at safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the SAE as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved, sites must electronically submit a follow up SAE Submission Form within a reasonable timeframe to Big Ten CRC AHQ at safety@hoosiercancer.org.

SAEs assessed as unreleated to study drug will entered in to the EDC within 30 days of awareness of the event.

11.2.3.2 Big Ten CRC AHQ Requirements for Reporting SAEs or Pregnancies to Genentech

Upon receipt of an SAE Submission Form or Pregnancy Reporting Form from the site, Big Ten CRC AHQ will report to Genentech **within 1 calendar day**, as described in the Genentech Safety Data Exchange Agreement (SDEA). Follow-up information will be provided to Genentech as it is received from a site.

Genentech Contact:
Email: usds_aereporting-d@gene.com.

SAEs assessed as unrelated to study drug will be reported to Genentech on a monthly basis.

11.2.3.3 Big Ten CRC AHQ Requirements for Reporting SAEs or Pregnancies to Bayer

Upon receipt of an SAE Submission Form or Pregnancy Reporting Form from the site, Big Ten CRC AHQ will report to Bayer within **24 hours** of receipt of the SAE Reporting Form/ Pregnancy Reporting Form from a site. Follow-up information will be provided to Bayer HealthCare Oncology as it is received from a site.

SAE Reports will be sent to the email address provided below. By sending to this e-mail address, the Bayer Pharmacovigilance group and the Bayer clinical operations project manager will receive copies of the reports. This process will be tested and established before the first patient is enrolled in the trial.

Bayer Safety Contacts:
Fax: 973-709-2185
For e-mail transmission of individual SAE reports: DrugSafety.GPV.US@bayer.com

SAEs assessed as unrelated to study drug will be reported to Bayer on a monthly basis.

11.2.3.4 Sponsor-Investigator Responsibilities

Big Ten CRC AHQ will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.2.3.5 Big Ten CRC AHQ Responsibilities for Reporting SAEs to FDA

Big Ten CRC AHQ has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. Big Ten CRC AHQ will cross-reference this submission to Genentech and Bayer's parent IND at the time of submission. Additionally, Big Ten CRC AHQ will submit a copy of these documents to Genentech and Bayer at the time of submission to FDA.

Big Ten CRC AHQ will be responsible for all communication with the FDA in accordance with 21CFR312 which includes but is not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, Big Ten CRC AHQ will submit a copy of these reports to Genentech and Bayer at the time of submission to FDA.

11.2.3.6 IND Safety Reports Unrelated to this Trial

Genentech Inc. and Bayer will provide Big Ten CRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. Big Ten CRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. Big Ten CRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from Big Ten CRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Study Design

This is a phaseI/ II single armed study. Patients and caregivers will not be blinded as there is only one treatment arm.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

- Combined rate of pathologic complete response (pCR) (defined as absence of pathologic disease on hematoxylin and eosin (H&E) stain (ypT0)), or with presence of minimal residual disease (<5 mm linearly)

12.2.2 Definition of Secondary Endpoints

- Grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
- Two year biochemical recurrence-free survival (defined as PSA $\leq$ 0.2 ng/mL)
- Rate of PSA_0 (undetectable PSA on local institutions laboratory testing with testosterone recovery and no additional therapy)

12.3 Sample Size and Accrual

In this Simon MiniMax two-stage, single arm, phase I/II trial, we anticipate enrolling 17 evaluable PTEN-negative subjects in the primary analysis (phase II) cohort. The therapy will be considered to be of little interest in the neoadjuvant setting if the exceptional response rate is <5% (similar to AR-targeted therapy alone) and considered active if the exceptional response rate is ≥30%. The study is designed with 90.5% power to detect the difference between the null hypothesis (5% or less response rate) and the alternative hypothesis (30%) with one-sided type I error of 0.05. In the first stage nine (9) patients will be recruited. If one (1) or more responses (pCR or MRD) are observed, another eight (8) evaluable patients will be recruited for a total of 17 evaluable patients. If 3 or more of 17 responses are observed, the study will be deemed a success. To account for 15% attrition, we plan to enroll 20 patients.

The Phase I de-escalation cohort will consist of patients with metastatic or nonmetastatic castrate resistant prostate cancer, with the expected sample size of 6, ***assuming no more than 1 DLT in the first 6 patients.*** However, if dose reductions of ipatasertib are required, the sample size could be as large as 18.

12.4 Assessment of Safety

Any subject that receives at least one dose of treatment on this protocol will be evaluated for toxicity. Drug toxicity will be defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

12.5 Assessment of Efficacy

Efficacy will be determined at the time of prostatectomy, 6 months after drug initiation, by the rate of response. Response is defined by the combined rate of pathologic complete response (pCR) and minimal residual disease (MRD), as defined by residual tumor <5 mm in cross section.

12.6 Data Analysis Plans

Success rates and corresponding confidence intervals will be computed for primary, secondary and exploratory variables. Descriptive statistics, such as mean, median, SD, min and max, will be provided for continuous variables, and contingency tables will be provided for pairs discrete variables. Kaplan-Meier methodology will be used to estimate BCR-free survival. Two year biochemical recurrence-free survival and rate of PSA_0 (undetectable PSA with testosterone recovery and no additional therapy) will be computed. Data will be analyzed by the study statistician using ***R*** and ***Stata*** software.

12.6.1 Analysis Plans for Primary Objective

The primary endpoint is ***the response rate***. This is the combined rate of pathologic complete response (pCR) and minimal residual disease (MRD), as defined by residual tumor <5 mm in cross section. Point estimator and 95% confidence interval will be provided.

12.6.2 Analysis Plans for Secondary Objectives

For secondary endpoints, descriptive statistics will be given for rates of toxicity and rates of PSA_0. Kaplan-Meier methodology will be used to estimate BCR-free survival, with 95% confidence envelope around the survival curve.

12.6.3 Analysis Plans for Exploratory Objectives

For exploratory endpoints descriptive statistics will be used to evaluate the mean, median, SD and the range of observed values.

12.7 Interim Analysis/Criteria for Stopping Study

12.7.1 Phase I (De-escalation Cohort)

The study will be terminated if there are 2 or more DLTs at dose level -2 (darolutamide 600 mg BID and ipatasertib 200 mg daily) and will not proceed to Phase II.

12.7.2 Phase II (Neoadjuvant Cohort)

In the Phase II neoadjuvant cohort, if after 9 evaluable patients there are no patients with exceptional response (defined as pCR or MRD), accrual will halt due to lack of efficacy. Accrual will not pause while the 9th patient is on therapy, so additional patients may accrue prior to pathologic evaluation of the 9th radical prostatectomy.

For the Phase II neoadjuvant cohort, an additional ***early stopping rule for safety*** will also be followed throughout the duration of the study. If, at any time, 2 or more patients experience a delay in time to prostatectomy of >28 days after the final dose of ipatasertib (i.e., a delay of > 1 week beyond the allowed timeline of 7-21 days) ***due to an ipatasertib-related AE***, the study and all study treatment will be stopped. An ipatasertib-related AE is defined as an AE that is possibly, probably, or definitely related to ipatasertib. Should the study stop early, discussion of reopening the study using modified ipatasertib treatment regimens may be considered after discussion between the PI and Genentech, and after approval by the DSMC.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

BTCRC AHQ oversight activities include**:**

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution DSMC and attend DSMC reviews:
  - during the Phase I portion of the study, monthly to present safety summary reports
  - during the Phase II neoadjuvant portion of the study, as applicable: following any reports of protocol deviations that meet IRB expedited reporting requirements, continued non-compliance or SAEs; and overall study data delinquency that exceeds 10% incomplete forms or sites with data delinquency that are not responding sufficiently to the BTCRC AHQ data delinquency escalation process
  - throughout the study, semi-annual comprehensive DSMC review

- During the Phase I portion of the study there will be weekly safety calls with all participating institutions. During the neoadjuvant portion of the study there will be monthly calls with all participating institutions

13.2 Robert H. Lurie Comprehensive Cancer Center's Data Safety Monitoring Committee

BTCRC AHQ will provide the following for the Robert H. Lurie Comprehensive Cancer Center's DSMC to review:

- Adverse event/ serious adverse event summary report
- Monitoring reports
- Audit results if applicable
- Study accrual patterns
- Data delinquency
- Protocol deviations
- Annual report, prior to submission to the FDA (if the study is under an IND).

The Robert H. Lurie Comprehensive Cancer Center's DSMC will conduct a comprehensive study review semi-annually, based on the date the study was originally opened with NU. Ad hoc reviews may be performed as necessary to ensure patient safety and data integrity. Documentation of DSMC reviews will be provided to sponsor-investigator and BTCRC AHQ. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with BTCRC AHQ to address the DSMC's concerns.

Link to the Robert H. Lurie Comprehensive Cancer Center's Data and Safety Monitoring Plan: https://www.cancer.northwestern.edu/docs/research/data-safety-monitoring-plan.pdf

13.3 DSMC Review of Safety Data

The Sponsor Investigator and the study team will review all available safety data prior to making dose de-escalation decisions. Once a decision has been reached, the official decision and the supporting safety data will be submitted to the NU DSMC. Treatment of additional subjects may not proceed until the DSMC approves the dosing decision for the next stage. This process will also apply during any interim analyses.

13.4 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

The level of risk attributed to this study requires high-intensity monitoring, as outlined in the DSMP. This study will be monitored in accordance with the study phase and risk level with oversight from the NU Data and Safety Monitoring Committee. For cause visits may occur as necessary. The database will be monitored regularly in house and if significant discrepancies arise, an onsite monitoring visit will be scheduled. Monitoring will be conducted by adequately qualified HCRN employees. During onsite monitoring visits, source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available

for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by Big Ten CRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Bayer or Genentech Inc or their designee as well as inspection by appropriate regulatory agencies.

13.5 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to Big Ten CRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

Big Ten CRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through a web-based clinical research platform compliant with Good Clinical Practices and Federal Rules and Regulations. Big Ten CRC AHQ personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/Big Ten CRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, drug diaries, and detailed records of drug disposition. All source documents are to remain in the subject's file

and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until Big Ten CRC AHQ confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Big Ten CRC AHQ, Bayer, Genentech Inc, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects's identity will remain confidential.

14.5 Publication Policy

All potential publications and/or data for potential publications (e.g., manuscripts, abstracts, posters, clinicaltrials.gov releases, etc.) must be approved in accordance with the Data Safety Monitoring Committee (DSMC) Data Release Policies and Processes. The investigator is expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigator must send a copy of the draft communication materials (e.g., abstract, poster, manuscript, etc.) to the study's biostatistician and assigned Quality Assurance Manager (QAM) [CROqualityassurance@northwestern.edu] to confirm that the DSMC-approved data and statistical analyses are used appropriately.

Link to the DSMC Data Release Policies and Processes:
https://www.cancer.northwestern.edu/docs/research/publication-policies.pdf

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to Big Ten CRC AHQ before he or she can enroll subjects into the study.

The site 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 subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

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

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16. TABLE OF ABBREVIATIONS

Abbreviation	Definition
IND	Investigational new drug
PSA	Prostate specific antigen
PTEN	Phosphatase and tensin homolog
PK	Pharmacokinetic
PCWG3	Prostate Cancer Working Group 3
ECOG	Eastern Cooperative Oncology Group
CRPC	Castration resistant prostate cancer
ADT	Androgen deprivation therapy
DLT	Dose limiting toxicity
RP	Radical prostatectomy
RT	Radiation therapy
MFS	Metastasis free survival
IHC	Immunohistochemistry
MRD	Minimal residual disease
AR	Androgen receptor
PI3K	Phosphoinositide 3-Kinase
AKT	Protein kinase B
pCR	Pathologic complete response
H&E	Hematoxylin and eosin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Hgb	Hemoglobin
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
HgA1c	Hemoglobin A1C
HBV	Hepatitis B

HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HCV	Hepatitis C virus
NYHA	New York Heart Association
IBD	Inflammatory bowel disease
CYP3A	Cytochrome P450 3A
PI	Primary investigator
ULN	Upper limit of normal
Big Ten CRC	Big Ten Cancer Research Consortium
AHQ	Administrated headquarters
EDC	Electronic data capture
BID	Twice per day
mg	Milligram
qday	Once per day
ADL	Activities of daily living
PFTs	Pulmonary function tests
eCRF	Electronic case report form
AE	Adverse event
CBC	Complete blood count with differential
CMP	Complete metabolic profile
TNM	Tumor Node Metastasis
AJCC	American Joint Committee on Cancer
FFPE	Formalin fixed paraffin embedded
CLM	Correlative Laboratory Manual
ctDNA	Circulating tumor DNA
GR	Glucocorticoid receptor
PR	Partial response
PD	Progressive disease
SD	Stable disease
ATP	Adenosine triphosphate
IB	Investigator's brochure
SAE	Serious adverse event
AESI	Adverse event of special interest
SDEA	Safety data exchange agreement
IRB	Investigational Review Board
DSMC	Data and Safety Monitoring Committee
NU	Northwestern University

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