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TITLE: A Phase 1/2 Study of Darolutamide and Abemaciclib in High-risk Prostate Cancer.

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SCHEMA

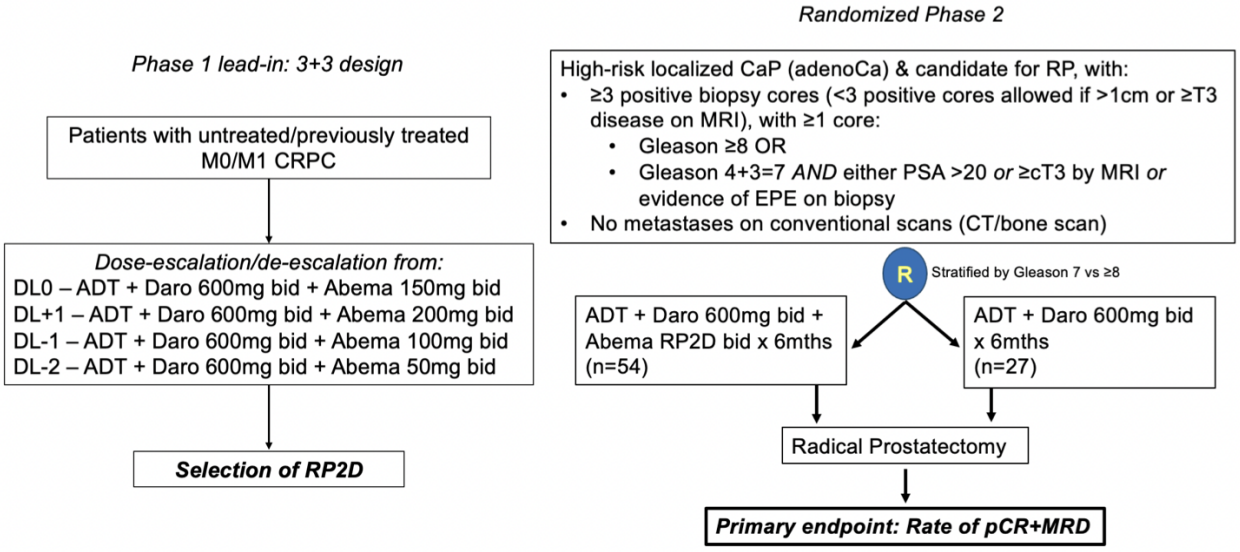

Phase 1 lead-in: 3+3 design
Patients with untreated/previously treated M0/M1 CRPC
Dose-escalation/de-escalation from:
DL0 – ADT + Daro 600mg bid + Abema 150mg bid
DL+1 – ADT + Daro 600mg bid + Abema 200mg bid
DL-1 – ADT + Daro 600mg bid + Abema 100mg bid
DL-2 – ADT + Daro 600mg bid + Abema 50mg bid
Selection of RP2D
Randomized Phase 2
High-risk localized CaP (adenoCa) & candidate for RP, with:
• ≥3 positive biopsy cores (<3 positive cores allowed if >1cm or ≥T3 disease on MRI), with ≥1 core:
• Gleason ≥8 OR
• Gleason 4+3=7 AND either PSA >20 or ≥cT3 by MRI or evidence of EPE on biopsy
• No metastases on conventional scans (CT/bone scan)
R
Stratified by Gleason 7 vs ≥8
ADT + Daro 600mg bid + Abema RP2D bid x 6mths (n=54)
ADT + Daro 600mg bid x 6mths (n=27)
Radical Prostatectomy
Primary endpoint: Rate of pCR+MRD

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1. OBJECTIVES

1.1 Study Design

This is a phase 1/2 trial to evaluate the safety and efficacy of abemaciclib in combination with darolutamide and androgen deprivation therapy (ADT) in patients with prostate cancer. The phase 1 trial will be a single-center study of darolutamide and abemaciclib in previously treated or untreated, metastatic or non-metastatic, castration-resistant prostate cancer (M0/M1 CRPC). This will be performed using a standard 3+3 design with the aim of establishing the recommended phase 2 dose (RP2D) of abemaciclib.

The phase 2 trial will be a multi-center, open label, prospective randomized study of neoadjuvant abemaciclib and darolutamide in addition to ADT (Arm 1) versus darolutamide and ADT (Arm 2) in patients with high-risk localized prostate cancer. Patients will be randomized 2:1 to Arm 1 and 2, respectively, and receive 6 months of neoadjuvant therapy prior to undergoing radical prostatectomy (RP). High-risk disease will be defined as Gleason ≥8, or Gleason 4+3=7 with PSA >20ng/dL and/or ≥T3 disease by MRI and/or evidence of extraprostatic extension (EPE) on biopsy. Randomization will be stratified by Gleason score 7 versus ≥8.

1.2 Primary Objectives

Phase 1:

- To assess the safety and tolerability of the combination of darolutamide and abemaciclib in untreated or previously treated M0/M1 CRPC, and to establish the RP2D of abemaciclib.

Phase 2:

- To determine whether the combination of neoadjuvant darolutamide, abemaciclib and ADT (with a GnRH agonist or antagonist) leads to a higher rate of pathologic response defined as achieving either a complete response (pCR) or minimal residual disease (MRD, defined as ≤5mm residual tumor) at RP compared to neoadjuvant darolutamide and ADT.

1.3 Secondary Objectives

Phase 1:

- To assess preliminary efficacy of darolutamide and abemaciclib, as determined by:
    a) Composite overall response rate (ORR) defined as the proportion of patients with PSA reduction by ≥50% or objective response per RECIST 1.1 (in patients with measurable disease at baseline); and
    b) Radiographic progression-free survival (rPFS) per RECIST 1.1 for soft tissue and PCWG3 for bone lesions.

Phase 2:

- To assess the safety and tolerability of darolutamide and abemaciclib as neoadjuvant therapy in men with high-risk prostate cancer.

- To assess the frequency of positive surgical margins, extracapsular extension, seminal vesicle invasion and lymph node positivity between both arms.
- To assess changes in PSA from baseline to RP (median nadir value, proportion of patients with PSA <0.2ng/ml, time to PSA nadir) in both arms.
- To determine the 3- and 5-year biochemical progression-free survival (bPFS) after RP among patients who achieve testosterone recovery (>200ngl/dl) in both arms.
- To evaluate the proportion free from further prostate cancer therapy, including adjuvant or salvage radiotherapy and/or ADT, at 2, 3 and 5-years post-RP in both arms.

1.4 Exploratory Objectives

Phase 1:

- To evaluate the pharmacokinetic profiles of darolutamide and abemaciclib when administered in combination.

Phase 2:

- To evaluate the pharmacokinetic profiles of darolutamide and abemaciclib when administered in combination in patients with localized prostate cancer.
- To assess changes in disease extent as measured by PSMA-PET before and after neoadjuvant therapy and explore associations between these and pathologic outcomes in both arms.
- To assess baseline cyclin D1 expression and Ki67 proliferation index by immunohistochemistry (IHC) and evaluate associations between these and pathologic outcomes in both arms.
- To assess changes in cyclin D1 expression and Ki67 proliferation index (by IHC) before, during and after neoadjuvant therapy in both arms, and evaluate associations between these and pathologic outcomes.
- To explore the association between baseline cell cycle dysregulation (as assessed by cyclin D amplification and/or CDKN2A/2B loss from OncoPanel) and pathologic outcomes in both arms.
- To evaluate the association between ERG, PTEN and Rb status (by OncoPanel and IHC) and pathologic outcomes in both arms.
- To evaluate associations between baseline and on-therapy changes in serum TK1 and pathologic outcomes in both arms.
- To assess changes in circulating tumor DNA (ctDNA) pre- and post-neoadjuvant therapy between treatment arms.
- To assess perioperative complications of RP in both arms.
- To explore the relationship between pharmacokinetic profiles of darolutamide and abemaciclib and safety and pathologic outcomes.

2. BACKGROUND

2.1 High-risk prostate cancer

Prostate cancer is the commonest cancer in men in the United States, with nearly 250,000 cases

expected in 2021.[1] The vast majority of men present with localized disease that is confined to the prostate and treatment is tailored according to how the disease is risk stratified. Risk stratification of localized prostate cancer uses features such as prostate specific antigen (PSA) level, clinical staging, biopsy Gleason grade and the proportion of biopsy cores positive for cancer, to assign men into low-, intermediate-, and high-risk groups.[2] High-risk disease is defined by Gleason ≥8 disease and/or PSA >20ng/ml and/or clinical T3 disease, and accounts for ~20% of patients with localized cancer, while low- and intermediate-risk disease account for ~30% and ~50% of cases respectively.[3]

Treatment options for localized prostate cancer include active surveillance (AS), radical prostatectomy (RP), and radiotherapy (RT) with concomitant androgen deprivation therapy (ADT), by means of testosterone suppression and first-generation anti-androgens such as bicalutamide. As is the preferred treatment option for most men with low-risk prostate cancer, whereas RP and RT with ADT are preferred for intermediate- and high-risk disease.[2] Randomized data from the randomized phase 3 PROTECT trial confirmed equivalence in 10-year oncologic outcomes between all 3 approaches for men with low- and intermediate-risk disease,[4] but there is limited data on optimal treatment for men with higher-risk disease. The addition of brachytherapy (BT) or BT boost to external beam RT has been to lower the risk of biochemical failure in three randomized trials, but none have demonstrated that it improves cancer-specific or overall survival.[5-7] A small Swedish randomized study also compared RP with RT and BT in men with T1b-T3a N0 prostate cancer, with no apparent difference in cancer-specific survival seen, although the trial was grossly underpowered and unable to complete accrual.[8] Amongst men with the highest-risk disease (Gleason 9-10), there is good quality retrospective data suggesting that RP followed by adjuvant RT and/or ADT and RT with BT provide similar oncologic outcomes,[9] with one study suggesting that the latter was associated with improved metastasis-free (MFS) and cancer-specific survival (CSS) compared to RP.[10]

Regardless of therapy choice, outcomes after definitive treatment of high-risk disease are guarded. The risk of biochemical recurrence (BCR) after RP for high-risk disease is around 50% at 5 years[11] and a substantial proportion of these men will subsequently die of prostate cancer.[12] Population-based data have also shown that men with high-risk disease are most likely to die from prostate cancer rather than any other causes;[13] furthermore, 66% of all deaths from prostate cancer at 10 years are in men with high-risk disease.[3] It is therefore evident that there is significant scope in improving outcomes and cure rates for men with high-risk prostate cancer.

2.1.1 Neoadjuvant therapy in high-risk prostate cancer

One approach to improving outcomes in high-risk disease is to utilize a multimodal approach to therapy. The underlying principle is that cancer is a systemic disease and therefore, local treatment alone is insufficient. This has been tested in various trials which have assessed whether the addition of ADT to RT can improve outcomes compared to RT alone, results of which have supported the argument that systemic therapy (with ADT) can augment the outcomes of local therapy (RT), particularly in intermediate- and high-risk disease.[14,15]

Neoadjuvant systemic therapy prior to RP has also been proposed as a means to improve outcomes for men with high-risk disease who are undergoing surgery. The potential benefits of

neoadjuvant therapy include downstaging of disease to potentially enable achievement of an R0 resection, controlling micrometastatic disease and permitting an in vivo pharmacodynamic assessment of response to therapy.[16] Neoadjuvant chemotherapy is routinely used prior to surgery in muscle-invasive bladder cancer[17,18] as well as breast cancer,[19] producing rates of pathologic complete response (pCR, i.e. absence of any residual cancer) in the order of 20-30%. Moreover, pathologic response at cystectomy or mastectomy has been shown to have significant prognostic impact on disease-free (DFS) and overall survival (OS) in these diseases.[20,21]

There has been evaluation of neoadjuvant therapy prior to RP in prostate cancer, with the earliest studies in the 1990s and early 2000s focusing on neoadjuvant testosterone suppression (with LHRH agonists) with or without first-generation anti-androgens such as flutamide or bicalutamide. Rates of pCR in these studies were generally 0-5%[22] and a meta-analysis of 10 studies showed that neoadjuvant ADT (with LHRH agonists +/- anti-androgen) led to a significant reduction in positive margin rates at RP compared to upfront RP (RR=0.49 [0.42-0.56]).[23] There was also a benefit seen with rates of organ confined disease (RR=1.63 [1.37-1.95]) with neoadjuvant therapy. However, no improvement in DFS (RR=1.04 [0.93-1.16]) or OS (RR=1.00 [0.97-1.04]) was seen with neoadjuvant ADT, although the number of studies with available data on these longer-term outcomes was small. It is also worth noting that these studies did not specifically enroll men with high-risk disease and as a consequence, most patients had low- or intermediate-risk disease, where the benefit of neoadjuvant therapy may be lower.

Correlative studies from early studies of neoadjuvant ADT have shown that LHRH agonists and first-generation anti-androgens do not appear to fully suppress intratumoral AR signaling,[24] while the addition of dutasteride (5-α-reductase inhibitor) and ketoconazole (an older CYPA17 inhibitor) to standard ADT led to greater suppression of intraprostatic androgen levels compared to standard ADT alone.[25] There has therefore been increasing interest in evaluating novel hormonal therapies that have been shown to demonstrate benefit in advanced prostate cancer, notably the CYPA17 inhibitor abiraterone and next-generation AR antagonists such as enzalutamide and apalutamide, in the neoadjuvant setting with the rationale being that more potent AR suppression can translate to superior pathologic (and long-term) outcomes.

Several phase 2 trials have evaluated 3-6 months of neoadjuvant abiraterone[26,27] and enzalutamide[28] alone prior to RP as well as combinations of abiraterone with either enzalutamide[29] or apalutamide.[30,31] These trials have generally enrolled men with unfavorable intermediate- or high-risk disease, and the rates of pCR observed have been in the order of 5-15%, with combination therapy not really being associated with higher pCR rates. Some trials have also assessed minimal residual disease (MRD) – defined as ≤5mm of residual tumor at RP – and the combined rates of pCR and MRD (pCR/MRD) in these trials have ranged from 15-30%, with the highest (30%) seen with neoadjuvant abiraterone and enzalutamide.[29] The prognostic impact of achievement of pCR/MRD was confirmed in a pooled analysis of a subset of patients treated on these studies,[32] with very few patients achieving pCR/MRD experiencing BCR after RP compared to a ~50% risk of BCR amongst men who did not achieve pCR/MRD.[33]

Given the safety, feasibility and relative success of neoadjuvant therapy with novel hormonal agents, a phase 3 randomized trial evaluating neoadjuvant and adjuvant ADT with or without apalutamide in men with high-risk prostate cancer is underway (PROTEUS, NCT03767244).[34] If

the trial meets its co-primary endpoints of higher pCR and metastasis-free survival (MFS) with addition of apalutamide, this may lead to widespread adoption of neoadjuvant therapy prior to RP in men with high-risk disease.

2.2 Darolutamide

2.2.1 Mechanism of action

Darolutamide is a nonsteroidal AR antagonist that also inhibits testosterone-mediated nuclear localization of AR. It is comprised of a 1:1 mixture of two active diastereomers, (*S,R)*-darolutamide and (*S,S*)-darolutamide. For further information, please refer to the Investigator Brochure of darolutamide.

2.2.2 Summary of non-clinical and clinical studies

Darolutamide binds with high affinity and selectivity to AR with potent antagonism for human AR *in vitro*, and similar affinity and antagonism for AR are seen with both diastereomers and the major metabolite, keto-darolutamide. Pre-clinical studies have shown that darolutamide is a more potent AR inhibitor than bicalutamide while also retaining activity against AR variants (such as W742L or F877L) that are implicated in resistance to other AR antagonists.[35] It has also shown anti-tumor activity in VCaP xenograft mouse models in both intact and castrated mice. Furthermore, darolutamide has minimal central nervous system (CNS) penetration and low inhibitory activity against $GABA_A$ receptors and the 5-HT transporter.

Darolutamide has been evaluated in a range of clinical studies in men with advanced prostate cancer. In the phase 1/2 ARADEs study, darolutamide was evaluated at a range of doses in men with progression metastatic castration-resistant prostate cancer (M1 CRPC).[36] The maximum tolerated dose (MTD) was not achieved and no dose-limiting toxicities were observed. The phase 3 ARAMIS trial randomized men with M0 CRPC and a PSA doubling time of ≤10 months to continuation of ADT and either placebo or darolutamide 600mg bid. Treatment with darolutamide led to a significant benefit in terms of both MFS (median 40.4 months vs. 18.4 months, HR=0.41, $p<0.001$)[37] and overall survival (OS, 3-yr OS 83% vs. 77%, HR=0.69, $p=0.003$).[38] The results of this study led to FDA approval of the drug in men with M0 CRPC, and further evaluation of darolutamide along with radiotherapy in high-risk localized prostate cancer (DASL-HiCaP, NCT04136353) as well as with docetaxel in metastatic hormone-sensitive prostate cancer (ARASENS, NCT02799602) is ongoing.

2.2.3 Pharmacokinetics

Darolutamide is administered orally and has a bioavailability of 60-75%, with peak plasma concentrations seen 4 hours after administration. The volume of distribution of darolutamide is 119L, and the primary excretion of the drug is in urine (63%) and feces (32%). Steady-state levels of the drug are reached within 2-4 days and its half-life is 20 hours. Darolutamide is metabolized via oxidation (mainly by CYP3A4 and, to a lesser extent, by CYP1A1) and glucuronidation; keto-darolutamide is the only major metabolite in plasma.

There is no need for dose adjustment of darolutamide in patients with mild, moderate or severe renal impairment as well as patients with mild or moderate hepatic impairment. Darolutamide must be taken with food since this leads to a higher bioavailability.

Pooled pharmacokinetic analyses have suggested that strong CYP3A4 inducers such as rifampin may reduce darolutamide exposure and these are therefore not recommended to be co-administered with the drug. However, while darolutamide exposure may increase with co-administration of CYP3A4 inhibitors such as ketoconazole, the well-tolerated safety profile of darolutamide over the entire exposure range suggests that the increase in exposure is not regarded to be clinically significant, though close monitoring is recommended. Darolutamide also does not have clinically significant drug-drug interactions with other commonly administered medications, including substrates of CYP (eg. midazolam), BCRP and OAT transporter (eg. statins) and P-gp (eg. dabigatran), and sub-analysis from the ARAMIS study showed that the pharmacokinetic profile of darolutamide is unaffected by a range of commonly co-administered medications including statins, beta-blockers and anti-thrombotics.[39] However, since darolutamide does inhibit BCRP, concomitant use of BCRP substrates with darolutamide is suggested to be avoided where possible.

2.2.4 Safety

The pooled experience from phase 1-3 studies involving darolutamide suggest that it is very well-tolerated. No dose-limiting toxicities were seen in the phase 1 dose-escalation study, and the commonest adverse events (of any grade) were fatigue (31%), back pain (21%), arthralgia (15%), and constipation (14%), with most adverse events adjudicated to be related to prostate cancer. Adverse events related to darolutamide (adjudicated by the investigator) were seen in 35% of patients, most commonly fatigue (12%), hot flash (5%), decreased appetite (4%) and diarrhea (2%). 22% of patients had a grade 3 adverse event, most commonly fatigue (2%), back pain (2%) and arthralgia (2%), with only one grade 3 adverse event deemed to be related to darolutamide.

Safety data from the phase 3 ARAMIS study were consistent with the phase 1/2 study, with a similar rate of treatment-emergent adverse events (TEAEs) leading to treatment discontinuation in both arms (8.9% vs 8.7%). Overall, 83% of patients experienced at least one TEAE, with the most common TEAEs reported at a higher frequency with darolutamide being fatigue (12%), diarrhea (7%), hypertension (6%), extremity pain (6%), anemia (6%) and hot flush (5%). 25% of patients had at least one serious adverse event (SAE), with the most common being urinary retention (2%). Grade 5 TEAEs (i.e. leading to death) were seen in 4% of patients receiving darolutamide (and 3% in those receiving placebo), with only one grade 5 event (perforation of the small intestine) attributed to darolutamide.

2.3 Abemaciclib

2.3.1 Mechanism of action

Abemaciclib is a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor with particular selectivity for cyclin D1/CDK4 complex, and has a lower IC_{50} for CDK4 and CDK6 inhibition while also

having additional activity against CDK9.[40] For further information, please refer to the Investigator's Brochure.

2.3.2 Summary of non-clinical and clinical studies

Pre-clinical studies have shown that abemaciclib inhibits CDK4/6 to induce G1 cell cycle arrest in Rb-proficient tumors and the drug has demonstrated significant anti-tumor activity in multiple murine xenograft models of human cancers.[41] Abemaciclib has also shown single-agent activity against AR+ prostate cancer cells *in vitro* as well as against *in vivo* CRPC xenografts.[42]

Abemaciclib has been evaluated in a number of phase 1-3 studies against a range of solid tumors and has received regulatory approval in the treatment of advanced hormone receptor (HR)-positive HER2-negative breast cancer. In the phase 1 study, the MTD was identified as 200mg bid with the main dose-limiting toxicity being fatigue.[43] The MONARCH studies have evaluated abemaciclib in HR+ HER2- breast cancer and have led to FDA approval in the following patient populations:

- MONARCH 1 was a single-arm phase 2 study, which showed that abemaciclib 200mg bid led to an overall response rate (ORR) of 20% in women with advanced HR+ HER2- metastatic breast cancer who had previously received endocrine therapy and 1-2 lines of chemotherapy.[44]
- MONARCH 2 was a randomized phase 3 trial evaluating fulvestrant and either abemaciclib or placebo in women with advanced HR+ HER2- breast cancer that had progressed on first-line endocrine therapy. The addition of abemaciclib led to a significant improvement in ORR (48% vs. 23%), PFS (median 16 months vs. 9 months, HR=0.55, p<0.001) and OS (median 47 months vs. 37 months, HR=0.76, p=0.01).[45,46]
- MONARCH 3 was a randomized phase 3 trial evaluating an aromatase inhibitor (letrozole or anastrozole) with either abemaciclib 150mg bid or placebo in women with advanced HR+ HER2- breast cancer who had not received prior systemic therapy. ORR (59% vs. 44%) and PFS (median not reached vs. 15 months, HR=0.54, p<0.001) were both significantly greater in the abemaciclib arm.[47]

The use of abemaciclib as neoadjuvant and adjuvant therapy in localized HR+ HER2- breast cancer has also been tested in the phase 2 neoMONARCH and phase 3 monarchE studies, respectively.

- neoMONARCH showed that abemaciclib, either given alone or in combination with anastrozole, led to more potent cell cycle arrest after 2 weeks of therapy compared to anastrozole, while 4% of patients receiving abemaciclib and anastrozole had a pCR after 16 weeks of therapy.[48]
- In monarchE, a randomized study in women who had undergone surgery for localized breast cancer and were considered at high risk of recurrence (either ≥4 positive nodes, or 1-3 positive nodes and tumor size ≥5cm, grade 3 tumor or Ki67 ≥20%), the addition of 2 years of abemaciclib to endocrine therapy led to a significant improvement in the primary outcome of invasive disease-free survival (2-yr rate 92% vs. 89%, HR=0.75, p=0.01).[49]

Clinical evaluation of abemaciclib in prostate cancer is ongoing, with trials assessing its use:

- In patients with localized high-risk or locally advanced prostate cancer who are eligible

for definitive radiation therapy and androgen deprivation therapy (NCT02498983).
- In combination with abiraterone acetate plus prednisone in men with previously untreated mCRPC (CYCLONE 2, NCT03706365).
- In men with heavily treated (post novel hormonal agent and taxanes) mCRPC (CYCLONE 1, NCT04408924).
- In combination with atezolizumab in men with previously treated mCRPC (NCT04751929).

2.3.3 Pharmacokinetics

Abemaciclib is administered orally and has slow absorption, with a bioavailability of 45% and reaching maximal concentration around 4-6 hours after administration of multiple doses. It is highly bound to plasma proteins (albumin and alpha-1-acid glycoprotein), giving rise to a high volume of distribution (1300L), and it can penetrate the blood-brain barrier. It is primarily metabolized by oxidation via CYP3A4 and excreted in feces (81%), with minimal urinary excretion (3%), and has two major active metabolites (M2 and M20). Its half-life is 18.3 hours.

Given its clearance by CYP3A4, concomitant use of CYP3A4 inducers and moderate and strong CYP3A4 inhibitors with abemaciclib should be avoided. Pooled pharmacokinetic studies suggest that no dosage adjustment for abemaciclib is required for patients with mild or moderate hepatic impairment, but changing dosing to once daily is recommended for those with severe hepatic impairment. No dose adjustment is required for patients with mild or moderate renal impairment but there are no data for abemaciclib in patients with severe renal impairment or on dialysis. There is also no food effect with the drug, so abemaciclib may be taken with or without food.

2.3.4 Safety

The overall experience from phase 1-3 studies suggests that abemaciclib is relatively well-tolerated. In the phase 1 study, the most common adverse events were diarrhea (52%), nausea (30%), fatigue (21%), vomiting (18%) and neutropenia (16%), with the commonest grade 3 events being neutropenia (7%), fatigue (7%) and diarrhea (5%).[43] A similar safety profile has been observed in the MONARCH studies; in MONARCH-1, abemaciclib 200mg bid generally led to gastrointestinal and hematologic toxicities with diarrhea (20%), neutropenia (24%) and fatigue (13%) being the key grade 3 events observed in ≥10% of patients; there were 3 deaths, with 1 (from pneumonitis) deemed as possibly related to study drug, though subsequent autopsy showed lymphangitis carcinomatosis.[44] Results from MONARCH-2 and MONARCH-3 (where abemaciclib has generally been dosed at 150mg bid in conjunction with endocrine therapy) showed a similar incidence of grade 3 diarrhea (10-15%) and neutropenia (25-30%).[45,47] The rates of serious adverse events in MONARCH-2 and MONARCH-3 were 22% and 28% respectively, with diarrhea and lung infection being most common; 3 deaths in MONARCH-2 were felt to be treatment-related (sepsis, n=2; viral pneumonia, n=1) while 8 deaths in MONARCH-3 were due to a serious adverse event (most commonly lung infection, n=3).

In neoMONARCH, prophylactic loperamide was given for the first 28 days and then at the discretion of the treating physician; this seemed to reduce the incidence of grade 3 diarrhea (5%) but 44% of patients reported constipation, including grade 3 events in 2%. Other adverse events

included 9% of patients with grade 3 neutropenia and <1% of patients had grade 4 elevation in ALT or AST, or grade 4 leukopenia.[48] In monarchE, 46% of patients experienced at least one grade 3 or higher adverse event, most commonly neutropenia (19%) and diarrhea (8%); 2.7% of patients receiving abemaciclib developed interstitial lung disease. 14 patients (0.5%) receiving abemaciclib died within 30 days of starting study treatment (the same number as the placebo arm), with 11 deaths due to adverse events, including 2 (diarrhea and pneumonitis) considered possibly related to the study drug.[49]

2.4 Rationale for Dose Selection

In phase 1, the starting dose of darolutamide will be 600mg bid, which is the standard dose of the drug in M0 CRPC; darolutamide is not expected to have any drug-drug interactions and has minimal toxicity, and therefore the maximal dose will be used at outset. The starting dose of abemaciclib in phase 1 will be 150mg bid, which is the dose used in conjunction with endocrine therapy in breast cancer. The aim will be to escalate this to 200mg bid, which is the dose used as monotherapy in advanced breast cancer and also being evaluated in combination with abiraterone in mCRPC (NCT03706365).[50]

The recommended phase 2 dose (RP2D) of abemaciclib will be carried forward into the phase 2 part of the study. Phase 1 is being conducted in men with CRPC since we feel that the neoadjuvant (and potentially curative) setting is not appropriate for dose-finding studies.

2.5 Rationale for Combination of Darolutamide and Abemaciclib

While novel hormonal agents have shown superior efficacy in terms of pathologic outcomes at RP compared to traditional ADT, only a minority of patients (~15-30%) appear to derive benefit. Therefore, the use of darolutamide, a highly potent AR antagonist that has activity in prostate cancer models with high levels of AR or mutated AR variants that are resistant to other AR-directed therapies,[35,51,52] in the neoadjuvant setting may provide improved outcomes to those seen with abiraterone, enzalutamide and apalutamide.

The rationale for evaluating a CDK4/6 inhibitor with an AR antagonist is based on work showing that AR downstream signaling controls G1/S progression,[53] and that 10-20% of prostate cancers have genomic alterations that lead to dysregulation of the G1/S transition (eg. loss of CDKN1B/2A/2B or cyclin D amplification).[54] Furthermore, upregulation of cyclin D signaling[55] or alterations in cell cycle pathway genes[56] have been found to be an important mechanism of resistance to abiraterone and enzalutamide, while CDK4/6 inhibition has demonstrated anti-tumor activity in prostate cancer models expressing AR variants (such as F876L) that are associated with resistance to enzalutamide.[57] Further, abemaciclib has single-agent activity in AR+ prostate cancer cell lines and xenografts,[42] while combined AR inhibition and CDK4/6 inhibition with enzalutamide and palbociclib has been demonstrated to have pre-clinical evidence of efficacy and possible synergy.[58] Importantly, Rb loss – a theorized mediator of resistance to CDK4/6 inhibition – is infrequently observed in high-risk prostate cancers (1%).[54]

Taken together, these data highlight that the cyclin D-CDK4/6 complex and G1/S transition is a valid target in prostate cancer and demonstrate the potential of combining CDK4/6 inhibition

with AR inhibition to generate additive or synergistic activity. Therefore, the combination of darolutamide and abemaciclib would appear to have promise as neoadjuvant therapy in high-risk prostate cancer.

2.6 Correlative Studies Background

Correlative studies are planned on imaging, tissue and blood from patients treated in phase 2.

2.6.1 Imaging biomarkers

Prostate-specific membrane antigen (PSMA) is a prostate specific transmembrane protein that is highly specific for prostate adenocarcinoma compared to benign prostate.[59] Radionuclides such as ^{68}Ga-PSMA gozetotide or ^{18}F-DCFPyL can bind PSMA and be imaged via PET, thereby aiding in staging and monitoring of prostate cancer. Indeed, both agents have received FDA approval in the initial staging of high-risk prostate cancer on the basis of single-arm phase 2/3 studies that have shown excellent predictive ability of PSMA-PET in identifying pathologic node positive disease in high-risk prostate cancer patients undergoing RP.[60,61] Furthermore, the proPSMA study showed that ^{68}Ga-PSMA-PET had superior diagnostic accuracy to conventional imaging (CT/bone scan) in staging patients with high-risk prostate cancer.[62]

All patients in phase 2 will receive a ^{68}Ga-PSMA-PET at baseline as standard-of-care, and patients treated at Dana-Farber Cancer Institute (DFCI, predicted n=40) will undergo a research-only ^{68}Ga-PSMA-PET at completion of neoadjuvant therapy prior to RP. This will enable assessment of changes in disease extent and metabolic activity as measured by PSMA-PET pre- and post-neoadjuvant therapy, and correlation of these molecular changes ("molecular response") with pathologic response. Furthermore, changes in metabolic activity (SUV_{max}) in the primary tumor pre- and post-therapy will be determined and correlated with pathologic outcomes. These studies will provide excellent insights into the impact of systemic therapy on disease extent, as measured by PSMA-PET, and provide the first data on PSMA-PET in the neoadjuvant setting.

2.6.2 Tissue-based biomarkers

Tissue-based biomarkers will be evaluated on biopsy specimens as well as RP specimens, as indicated below. Optional on-treatment biopsies during neoadjuvant therapy will also be performed in patients treated at DFCI who will additionally consent to our institutional prostate tissue banking protocol (DFCI 01-045).

2.6.2.1 Targeted DNA sequencing

OncoPanel is a massively parallel next-generation sequencing (NGS) platform at DFCI for genomic profiling of tumor tissue.[63] OncoPanel testing is done at the Center for Advanced Molecular Diagnostics, a CLIA-certified laboratory in the Department of Pathology at Brigham and Women's Hospital. OncoPanel version 3 interrogates 447 genes known to be involved in cancer biology and will be performed on tumor from biopsy specimens (i.e. pre-treatment). Associations between aberrations in cell-cycle pathway genes (eg. amplification of CCND1, loss

of CDKN2A/2B, Rb loss) and pathologic response to neoadjuvant therapy will be explored. While there are pre-clinical data suggesting that these genomic alterations may be associated with resistance to CDK4/6 inhibition,[64] these have generally not been corroborated in clinical trials of breast cancer patients receiving CDK4/6 inhibitors.[65] We will also evaluate the associations between pathologic response and mutational inactivation or loss of PTEN as well as TMPRSS2-ERG fusion, since there are pre-clinical data suggesting that prostate cancer cells that are PTEN mutated and harboring TMPRSS2-ERG fusion may be resistant to CDK4/6 inhibition.[58] Furthermore, correlative work from the neoadjuvant abiraterone and enzalutamide trial showed that ERG-positive and PTEN-loss cancers had notably lower rates of pCR/MRD with neoadjuvant therapy.[29]

2.6.2.2 Immunohistochemistry (IHC)

IHC will be performed to assess for cyclin D, ERG, PTEN and Ki67 expression on biopsy and RP specimens. We will evaluate changes in cyclin D and Ki67 expression between biopsy and RP and explore associations in these changes and pathologic response to patients receiving neoadjuvant darolutamide and abemaciclib. Ki67 expression in particular may act as a pharmacodynamic marker of CDK4/6 inhibition and we will assess rates of complete cell cycle arrest (CCCA, Ki67 ≤2.7%) after neoadjuvant therapy, as has previously been performed in neoadjuvant CDK4/6 inhibitor trials in breast cancer.[48,66] Expression of these markers have not previously been systematically assessed in high-risk localized prostate cancer and therefore, these studies will provide insights into baseline levels of Ki67 expression in high-risk prostate cancer and whether reduction in Ki67 expression correlates with response to CDK4/6 inhibition.

We will also evaluate PTEN and ERG expression by IHC (in addition to NGS, as described above) to (a) assess correlation between IHC expression and NGS, and (b) explore associations between PTEN and ERG status (by IHC) and response to neoadjuvant therapy.

2.6.3 Blood-based biomarkers

2.6.3.1 Circulating cell-free DNA (cfDNA)

Detection of cfDNA offers the ability of assessing an individual patient's tumor burden over time as well as in response to therapy. While changes in cfDNA have been associated with outcomes in advanced prostate cancer,[67] evaluation of cfDNA during and after neoadjuvant therapy has not been performed to date and may offer prognostic or predictive ability. Furthermore, the laboratory of Dr Matthew Freedman has pioneered a technique called cfMeDIP-seq that is capable of detecting tumor DNA at very low levels, which is pertinent for earlier stage cancers.[68,69] We will therefore utilize this technique to see explore changes in cfDNA during neoadjuvant therapy and assess whether global (eg. absolute changes or appearance/disappearance) or specific (eg. in certain alterations) changes in cfDNA correlate with pathologic outcomes.

2.6.3.2 Serum thymidine kinase 1 (TK1)

TK1 is an enzyme required for DNA synthesis and expressed in all cells during normal cell

division through E2F-dependent transcription. Given their higher replicative capacity, tumors can secrete pathologic levels of TK1, which can be detected in serum. Since TK1 is linked to G1-S cell cycle progression, serum TK1 levels have been proposed as a pharmacodynamic biomarker for CDK4/6 inhibition.[70] Preliminary data from breast cancer have highlighted the potential prognostic role for changes in TK1 during therapy with CDK4/6 inhibitors.[71,72] We will aim to explore whether baseline TK1 levels and dynamic changes in TK1 activity are associated with pathologic outcomes to neoadjuvant therapy.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria for Phase 1

3.1.1 Provision of signed informed consent prior to any study specific procedures, or have a legally authorized representative sign on the participant's behalf.

3.1.2 Ability to swallow oral medications and comply with study procedures and requirements.

3.1.3 Males ≥18 years

3.1.4 Histologically or cytologically confirmed adenocarcinoma of the prostate without histologic variants (including neuroendocrine differentiation, small cell, sarcomatoid, ductal adenocarcinoma, squamous or transitional cell carcinoma) comprising >50% of the sample as determined by academic medical center pathology review; men without histologic confirmation are eligible provided there is unequivocal evidence of prostate cancer (eg. very high PSA) in the view of the treating physician.

3.1.5 M0 or M1 (by CT/MRI and bone scans) CRPC with evidence of progression at study entry demonstrated during continuous androgen deprivation therapy (LHRH/GnRH agonists/antagonists/post orchiectomy) and castrate level of serum testosterone (≤50 ng/dl). Progression is defined as one or more of the following:

- Sequence of at least 2 rising PSA values at a minimum of 1-week intervals with the last result being at least 1.0 ng/mL if confirmed PSA rise is the only indication of progression. Patients who received an anti-androgen (flutamide, bicalutamide or nilutamide) must have PSA progression ≥4 weeks after the last dose.

- Radiographic progression per RECIST 1.1 for soft tissue and/or per PCWG3 for bone (i.e., appearance of ≥2 new bone lesions), with or without PSA progression.

3.1.6 Serum testosterone level must be ≤50 ng/dL (1.73 nmol/L) at the screening visit. Participants who have not undergone bilateral orchiectomy are required to continue LHRH/GnRH agonists/antagonists) throughout the study. Use of relugolix is permitted.

3.1.7 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.8 Participants must have adequate organ and marrow function as below:

System	***Laboratory Value***
Hematologic	
ANC	$\geq 1.5\times10^9$/L
Platelets	$\geq 100\times10^9$/L
Hemoglobin	≥9g/dL (≥90g/L) independent of transfusions
Hepatic	
Total bilirubin	≤1.5 × ULN OR <2 × ULN if known or suspected Gilbert's syndrome
ALT and AST	≤3 × ULN OR ≤5 × ULN if liver metastases present
Renal	
eGFR	≥30 mL/min/1.73 m^2 (based on Cockcroft-Gault formula [Appendix D] OR 24 hour urine collection

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; eGFR = estimated glomerular filtration rate; ULN = upper limit of normal.

3.1.9 The effects of darolutamide and abemaciclib on the developing human fetus are unknown. Participants and their partners must agree to use an effective contraception method (hormonal or barrier method of birth control, or abstinence) during the study and for 3 weeks after the last dose of study treatment (darolutamide and/or abemaciclib) if engaged in sex with a woman of childbearing potential, and participants must not donate sperm during this period. Should a woman become pregnant or suspect she is pregnant while her partner is participating in this study, she should inform her treating physician immediately.

3.2 Exclusion Criteria for Phase 1

3.2.1 Participants who have had chemotherapy or radiotherapy within 4 weeks prior to planned cycle 1 day 1 of study treatment.

3.2.2 Participants who have received anti-neoplastic intervention or experimental anti-neoplastic therapy within 14 days of planned cycle 1 day 1 of study therapy.

3.2.3 Participants who are receiving any other investigational agents.

3.2.4 Participants who have previously received darolutamide, abemaciclib or another CDK4/6 inhibitor.

3.2.5 Participants who have not recovered from adverse events due to prior anti-cancer therapy (i.e. have residual toxicities ≥Grade 2) with the exception of alopecia.

3.2.6 Any of the following within 6 months before planned cycle 1 day 1 of study therapy:
- Stroke
- Myocardial infarction
- Severe/unstable angina pectoris
- Coronary/peripheral artery bypass graft
- Congestive heart failure New York Heart Association (NYHA) Class III or IV.

3.2.7 Known or suspected contraindications, hypersensitivity or allergy to darolutamide or abemaciclib or to any of their excipients.

3.2.8 Participants with hepatitis C, hepatitis B or human immunodeficiency (HIV) who are on anti-viral therapy that has the potential to interact with darolutamide or abemaciclib.

3.2.9 Participants with untreated brain metastases. Participants with *treated brain metastases* are eligible if follow-up brain imaging at least 4 weeks after central nervous system (CNS)-directed therapy shows no evidence of progression and ongoing corticosteroids are not required. Participants with *new or progressive brain metastases* (active brain metastases) or *leptomeningeal disease* are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

3.2.10 Participants treated with drugs known to be strong inhibitors and/or inducers of cytochrome P450 3A4 (CYP3A4) and the treatment cannot be discontinued or switched to a different medication at least 5 half-lives prior to starting study drug.

NOTE: precaution is warranted with concomitant use of agents with a narrow therapeutic index that are substrates of P-gp, BCRP and OCT1.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the participant is considering a new over-the-counter medicine or herbal product.

3.2.11 The participant has serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).

3.2.12 Concurrent active malignancy whose natural history or treatment has the potential to interfere with safety or efficacy assessment of the investigational regimen. Patients with non-melanomatous skin cancer, superficial bladder cancer, cancer not needing active therapy for at least 2 years, cancer for which the treating investigator deems the subject to

be in remission, or any prior malignancy that was treated with curative intent (no evidence of disease for at least 3 years) are permitted to enroll.

3.3 Inclusion Criteria for Phase 2

3.3.1 Provision of signed informed consent prior to any study specific procedures, or have a legally authorized representative sign on the participant's behalf.

3.3.2 Ability to swallow oral medications and comply with study procedures and requirements.

3.3.3 Males ≥18 years.

3.3.4 Histologically confirmed adenocarcinoma of the prostate without histologic variants (including neuroendocrine differentiation, small cell, sarcomatoid, ductal adenocarcinoma, squamous or transitional cell carcinoma) comprising >50% of the sample as determined by academic medical center pathology review.

3.3.5 ≥3 biopsy cores (either systematic or targeted, or a combination) involved with prostate cancer. Prostate biopsy must have been performed within 6 months of screening. <3 biopsy cores with cancer are allowed if the patient has >1cm of tumor or ≥cT3 disease on MRI prostate.

3.3.6 Participants must have at least 1 biopsy core with either:

- Gleason ≥8 OR
- Gleason 4+3=7 AND at least one of the following:
  - PSA >20ng/dL
  - ≥cT3 disease by MRI
  - Evidence of EPE on biopsy

3.3.7 No evidence of distant metastatic disease as determined by radionuclide bone scan and CT/MRI, and/or PSMA-PET. cN1 disease (with pelvic nodes ≤2cm) on CT or PSMA-PET is permitted. If PSMA-PET does not show evidence of distant metastatic disease, CT/MRI and bone scan is not required. Either PSMA-PET or CT/MRI abdomen and bone scan (along with MRI prostate) is required before C1D1.

NOTE: participants with evidence of M1 disease on PSMA-PET imaging at baseline are eligible (and their participation is encouraged), provided that all avid non-regional nodes are <1.5cm in short axis, all visceral lesions are <1cm and all soft tissue component to bone lesions are <1cm (i.e. considered non-measurable by conventional imaging). All participants treated at DFCI must undergo PSMA-PET at baseline or within 21 days of C1D1 (per institutional practice) and will also undergo a research-only PSMA-PET after completion of therapy and prior to RP.

3.3.8 Participants must be candidates for RP and be considered surgically resectable by a Urologist.

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

3.3.10 Participants must have adequate organ and marrow function as defined below:

System	***Laboratory Value***
Hematologic	
ANC	≥1.5×10^9/L
Platelets	≥100×10^9/L
Hemoglobin	≥9g/dL (≥90g/L) independent of transfusions
Hepatic	
Total bilirubin	≤1.5 × ULN <2 × ULN if known or suspected Gilbert's syndrome
ALT and AST	≤3 × ULN
Renal	
eGFR	≥30 mL/min/1.73 m^2 (based on Cockcroft-Gault formula [Appendix D] OR 24 hour urine collection

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; eGFR = estimated glomerular filtration rate; ULN = upper limit of normal.

3.3.11 The effects of darolutamide and abemaciclib on the developing human fetus are unknown. Participants and their partners must agree to use an effective contraception method (hormonal or barrier method of birth control, or abstinence) during the study and for 3 weeks after the last dose of study treatment (darolutamide and/or abemaciclib) if engaged in sex with a woman of childbearing potential, and participants must not donate sperm during this period. Should a woman become pregnant or suspect she is pregnant while her partner is participating in this study, she should inform her treating physician immediately.

3.4 Exclusion Criteria for Phase 2

3.4.1 Prior radiotherapy, bilateral orchiectomy, investigational therapy or systemic therapy (including LHRH/GnRH agonists/antagonists, anti-androgens, CYP17 inhibitors, AR antagonists) for prostate cancer. LHRH/GnRH agonists/antagonists are permitted if begun within 4 weeks of day 1; up to 4 weeks of bicalutamide is permitted if it is stopped 2 weeks prior to day 1. Prior therapy with 5-α-reductase inhibitors is allowed but must be stopped 2 weeks prior to day 1.

3.4.2 Hypogonadism or severe androgen deficiency as defined by screening serum testosterone < 200ng/dL. Patients who have a low screening testosterone due to prior ADT (per 3.4.1) will still be allowed to enroll on study if they do not have a known history of hypogonadism or severe androgen deficiency.

3.4.3 Major surgery or radiotherapy within 4 weeks of start of treatment.

3.4.4 Any of the following within 6 months before randomization:
- Stroke
- Myocardial infarction
- Severe/unstable angina pectoris
- Coronary/peripheral artery bypass graft
- Congestive heart failure New York Heart Association (NYHA) Class III or IV.

3.4.5 Known or suspected contraindications, hypersensitivity or allergy to darolutamide or abemaciclib or to any of their excipients.

3.4.6 Participants with hepatitis C, hepatitis B or human immunodeficiency (HIV) who are on anti-viral therapy that has the potential to interact with darolutamide or abemaciclib.

3.4.7 Patient treated with drugs known to be moderate or strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) and the treatment cannot be discontinued or switched to a different medication at least 5 half-lives prior to starting study drug.

NOTE: precaution is warranted with concomitant use of agents with a narrow therapeutic index that are substrates of CYP3A4, P-gp, BCRP and OCT1.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the participant is considering a new over-the-counter medicine or herbal product.

3.4.8 The participant has serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min] or history of renal transplant, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).

3.4.9 Concurrent active malignancy whose natural history or treatment has the potential to interfere with safety or efficacy assessment of the investigational regimen. Patients with non-melanomatous skin cancer, superficial bladder cancer, cancer not needing active therapy for at least 2 years, cancer for which the treating investigator deems the subject to be in remission, or any prior malignancy that was treated with curative intent (no evidence of disease for at least 3 years) are permitted to enroll.

3.5 Inclusion of Women and Minorities

Males of all races and ethnic groups are eligible for this trial. Females are not included as they do not develop prostate cancer.

4. REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed regarding registration in CTMS. Phase I will not involve randomizing participants, while phase II will, and therefore registration procedures for each phase will differ slightly as noted below. For Phase 1 participants, the treating investigator and DFCI regulatory team will review subject eligibility. Once the participant is confirmed eligible, they will be assigned the current dose level for Abemaciclib and be registered in CTMS prior to beginning protocol therapy.

For Phase II, the treating investigator and DFCI regulatory team will review subject eligibility. For external sites, subject eligibility will be reviewed by the PCCTC, sponsor PI and DFCI regulatory team. Once the subject is confirmed eligible, the PCCTC will send a registration confirmation to the site coordinator and PI. The study coordinator or data manager at each site will be directed to enter the participant in Medidata RAVE and randomize the participant to study treatment. Sites will confirm with the PCCTC and DFCI the treatment arm that the participant was randomized to in order to complete registration procedures.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Dana-Farber Cancer Institute via the PCCTC.

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Sponsor-Investigator. If the participant does not receive protocol therapy following registration, the participant must be taken

off study, which will be updated in the CTMS (OnCore) with an appropriate date and reason entered via regular data reports provided to DF/HCC by the PCCTC.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site e-mailed to the PCCTC Project Manager:

- Signed and dated DFCI eligibility checklist (signed by MD)
- Signed participant consent form (subject initials on all pages of consent)
- HIPAA authorization form
- External site subject registration form/eligibility checklist
- Copies of:
    - Pathology report.
    - Radiology reports, including radionuclide bone scan, CT and MRI scans.
    - Concomitant medication list.
    - Progress note or equivalent documentation of consent visit.
    - Progress note or equivalent documentation of medical and oncologic history.
    - Screening labs
        - Complete blood count with differential
        - Electrolytes
        - Liver function tests
        - PSA
        - Testosterone
    - Screening visit note with vital signs, height, weight and ECOG performance status.

Participating sites will enroll subjects to Phase II only, which will require participants to be randomized in Medidata RAVE. Once the PCCTC Project Manager reviews the documents specified above and confirms eligibility, The PCCTC Project Manager will notify the DF/HCC Project Manager, who will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The PCCTC Project Manager will e-mail the site confirming patient eligibility, and if applicable the dose treatment level, to the participating site. Sites will be directed to access Medidata RAVE to enter and randomize the participant to the Phase II portion of the study. Sites will confirm with the PCCTC and DFCI the treatment arm that the participant was randomized to in order to complete registration procedures.

5. TREATMENT PLAN

5.1 Treatment Regimen

Darolutamide and abemaciclib will be administered orally twice daily on days 1 through 28 of a 28-day cycle. There is no required length of time between Darolutamide and Abemaciclib dosing. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.

<u>Phase 1</u>

In Phase 1, a standard 3+3 dose escalation scheme with 4 dose levels of abemaciclib (50mg, 100mg, 150mg and 200mg bid) and a constant dose of darolutamide (600mg bid) will apply, as described in the Tables below. The dose will be escalated either until an MTD is identified or the maximum planned dose is achieved. MTD is defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in cycle 1. If only three patients are treated at the MTD, an additional three patients will be added for a total of six patients at the MTD.

Patients will continue on therapy until progression per PCWG3 criteria,[73] or withdrawal for other reasons stated in section 5.6.

Dose Escalation Schedule		
Dose Level	**Dose**	
	Darolutamide	**Abemaciclib**
Level +1	600mg bid	200mg bid
Level 0 – Starting Dose	600mg bid	150mg bid
Level -1	600mg bid	100mg bid
Level -2	600mg bid	50mg bid

Dose Level -2					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Darolutamide	Take doses approximately 12 hours apart with food.	2 × 300mg tablets	Orally	BID	28 days (4 weeks)
Abemaciclib	Take doses approximately 12 hours apart with or without food.	1 × 50mg tablets	Orally	BID	

Dose Level -1					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Darolutamide	Take doses approximately 12 hours apart with food.	2 × 300mg tablets	Orally	BID	28 days (4 weeks)
Abemaciclib	Take doses approximately 12	2 × 50mg tablets	Orally	BID	

	hours apart with or without food.				

Dose Level 0					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Darolutamide	Take doses approximately 12 hours apart with food.	2 × 300mg tablets	Orally	BID	28 days (4 weeks)
Abemaciclib	Take doses approximately 12 hours apart with or without food.	3 × 50mg tablets	Orally	BID	

Dose Level +1					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Darolutamide	Take doses approximately 12 hours apart with food.	2 × 300mg tablets	Orally	BID	28 days (4 weeks)
Abemaciclib	Take doses approximately 12 hours apart with or without food.	4 × 50mg tablets	Orally	BID	

Phase 2

In phase 2, eligible patients will be randomized 2:1 to receive 6 cycles of neoadjuvant treatment with either:

- ADT (GnRH agonist or antagonist), darolutamide and abemaciclib (Arm 1)
- ADT (GnRH agonist or antagonist) and darolutamide (Arm 2)

Randomization will be stratified by Gleason score (7 vs. ≥8). 28 days will constitute 1 cycle of therapy and patients will undergo RP after 6 cycles. The dose of abemaciclib in phase 2 will be RP2D from the phase 1 study. The choice of agent for ADT (leuprolide, goserelin or degarelix) will be at the discretion of the treating physician.

Regimen Description – Arm 1					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**

Darolutamide	Take doses approximately 12 hours apart with food.	2 × 300mg tablets	Orally	BID	28 days (4 weeks)
Abemaciclib	Take doses approximately 12 hours apart with or without food.	*TBD* × 50mg tablets (based on RP2D)	Orally	BID	

Regimen Description – Arm 2					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Darolutamide	Take doses approximately 12 hours apart with food.	2 × 300mg tablets	Orally	BID	28 days (4 weeks)

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

For cycle 1, day 1, the patient's laboratory and clinical parameters must meet those outlined in the eligibility criteria (sections 3.1 and 3.3 for phase 1 and 2 respectively).

5.2.2 Subsequent Cycles

For subsequent cycles, please refer to Section 6 for dose delay/modifications.

5.3 Agent Administration

5.3.1 Darolutamide

Darolutamide will be supplied as tablets for oral administration. The tablets should be stored at room temperature according to the range provided on the product label and not crushed, chewed or dissolved. Investigators should instruct patients to store the tablets in the original package and in a location inaccessible to children.

Darolutamide must be taken with food. Doses must be administered at least 12 hours apart on Days 1 through 28 of a 28-day cycle, for a total of 56 doses per cycle. During all cycles, Darolutamide should be taken at approximately the same times each day. If a dose is missed (e.g., missed morning dose and did not re-dose within appropriate time) it should not be taken if it is less than 8 hours until the next dose. If the subject vomits a dose, that dose should be omitted and the next dose taken at the usual scheduled time. All doses given, missed, and

vomited, should be recorded.

5.3.2 Abemaciclib

Abemaciclib will be supplied as tablets for oral administration. The tablets should be stored at room temperature according to the range provided on the product label and not crushed, chewed or dissolved. Investigators should instruct patients to store the tablets in the original package and in a location inaccessible to children.

Abemaciclib will be taken orally every 12 (± 2) hours on Days 1 through 28 of a 28-day cycle, for a total of 56 doses per cycle. During all cycles, abemaciclib should be taken at approximately the same times each day. If a patient vomits a dose, that dose should be omitted and the next dose taken at the usual scheduled time; if a patient misses a dose the dose should be taken as soon as possible on the same day and then twice daily dose administration should resume (with at least 6 hours separating doses).

5.4 Definition of Dose-Limiting Toxicity (DLT)

For patients treated in phase 1, DLT will be defined as any abemaciclib or darolutamide-related toxicity resulting in discontinuation or dose reduction per the guidelines in Section 6.1 to 6.2 within the first 28 days of treatment, for which there is no clear alternative explanation (i.e. disease related). To be evaluable for DLTs, at least 75% of doses of both drugs need to be taken by the participant (please also see Statistical Analysis Plan).

DLTs will be defined as any of the following events not clearly due to the underlying disease or extraneous causes:

- Any death
- Dose delay of >14 days for the study drug(s) due to an adverse event
- Non-hematologic toxicity:
    - Grade 3 or higher
    - Hy's Law cases (AST or ALT >3 x upper limit of normal (ULN) AND total bilirubin >2 x ULN AND ALP <2 x ULN AND no other reason for liver injury)
    - AST or ALT >8 x ULN or AST or ALT > 5 x ULN for ≥14 days regardless of the absence of presence of hepatic metastases
- Hematologic toxicity:
    - Grade 4 that persists for more than 7 days
    - Grade 3 or higher thrombocytopenia with clinically significant bleeding
    - Febrile neutropenia

The DLT definition may exclude:

- Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
- Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis

- Grade 3 fatigue for less than 1 week

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

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

Number of Participants with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 participants at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the RP2D. At least 6 participants must be entered at the RP2D.

5.5 General Concomitant Medication and Supportive Care Guidelines

Supportive care medications are allowed at any time on trial. Specifically, the following agents are permitted:

- Anticoagulation with LMWH, warfarin or subcutaneous or oral Factor Xa inhibitor for prophylactic or therapeutic uses.
- Antiemetics;
- Antidiarrheal therapy (see Section 6.2.5) and topical treatments for stomatitis;
- Antiallergic measures such as corticosteroids and antihistamines.
- Bisphosphonates. Subjects being treated with bisphosphonates when they enter the study may continue the medication as long as the dose is stable. Subjects may also initiate bisphosphonate therapy while on protocol therapy if it is thought to be medically necessary. The reason for bisphosphonates initiation during after study enrollment must be clearly specified;

- Non-live vaccines are allowed including toxoid and recombinant vaccines.
- Painkillers;
- Packed red blood cells;
- Concurrent metformin is allowable;

The following agents are not permitted:

- Any other therapy administered for the treatment of prostate cancer, either approved or experimental, is prohibited. This includes but is not limited to hormonal therapy (other than concurrent administration of a GnRH/ LHRH agonist/antagonist), 5-α-reductase inhibitors, chemotherapy, immunotherapy, herbal therapy, or other alternative systemic therapy targeting prostate cancer. Any investigational medical device is prohibited.
    - Local anti-cancer therapies can be considered in case of progression or clinical indication, including radiotherapy, thermal ablation and surgery.
    - Limited data are available with darolutamide, abemaciclib and radiotherapy. Thus, caution should be exercised with co-administering study drugs with radiotherapy. The sponsor must be contacted in these situations to ensure adequate risks related to the procedure and concomitant study treatment. In this situation where a target lesion is treated by such procedure, the participant may continue the study but may not be evaluable for response. However, the patient might remain evaluable for progression after discussion with the study sponsor.
- Live vaccines.
- Prophylactic myeloid growth factor administration is not permitted for the prevention of neutropenia, but is only permitted if clinically indicated in response to a clinically significant episode of neutropenia.

5.6 CYP3A modulators

See Sections 6.1.1 and 6.2.8 for information regarding use of CYP3A modulators with darolutamide and abemaciclib respectively.

The PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agents.

5.7 Discontinuation from Study Treatment

Phase 1

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression by PCWG3 criteria,[73] including clinical progression. Patients should not be discontinued from study therapy for PSA progression alone. PCWG3 criteria allow treatment beyond radiographic progression if the treating physician feels that the patient is continuing to derive clinical benefit from therapy, and the patient will continue until felt to be “no longer clinically benefiting” (NLCB).

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated by DFCI in OnCore in accordance with REGIST-OP-1.

Phase 2

Treatment on study will be for 6 cycles (1 cycle = 28 +/- 3 days) of neoadjuvant therapy. In the absence of treatment delays due to adverse events, treatment may continue for the duration of the study until one of the following criteria:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated by DFCI in OnCore in accordance with REGIST-OP-1.

5.8 Duration of Follow Up

Phase 1

An end of treatment and safety assessment should be performed 30-42 days after the last dose of study treatment to include any adverse events occurring within 30 days after the last dose of study treatment. In the event subjects cannot be seen for the end treatment safety assessment at the site of enrollment due to the ongoing COVID-19 situation or other extenuating

circumstances, safety assessments may be conducted at alternate locations if these assessments are deemed of adequate quality by the treating investigator.

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Participants who stop study treatment prior to the time recommended in the protocol will continue to be followed according to the protocol. Participants will be requested to allow their ongoing health status to be periodically reviewed (approximately every 6 months) via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries. Follow-up will include survival status and disease status – i.e., following participants for radiographic progression if study treatment was discontinued prior to progression. Follow up will continue every 6 months until 5 years after discontinuing treatment.

Phase 2

Participants will be followed every 3 months (+/- 28 days) for the first year after RP, every 4 months (+/- 28 days) in year 2, every 6 months (+/- 28 days) in year 3, after which follow-up will occur every year (+/- 28 days) until 5 years after RP. Long-term follow-up assessments in years 4 and 5 may take place locally and information collected via review of medical records. Whenever long-term follow-up PSA blood draws are done at the research clinic conducting the study, the research team should collect ctDNA samples. In the event subjects cannot be seen for the long-term follow-up assessments at the site of enrollment due to the ongoing COVID-19 situation or other extenuating circumstances, assessments may be conducted at alternate locations if these assessments are deemed of adequate quality by the treating investigator.

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol. If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries.

5.9 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Guidelines for dose modification for toxicity are provided below. The final dose reduction or delay for each subject may be determined by the investigator and sponsor. However, these guidelines provide the minimum dose reduction or delay criteria. Study treatment may be suspended for a maximum of 28 days to allow a patient sufficient time for recovery from study treatment-related toxicity. If a patient does not recover from the toxicity within 28 days from the time of last treatment, the patient should be considered for permanent discontinuation from study treatment. In exceptional circumstances, a delay >28 days is permitted upon agreement between the investigator and the principal investigator, Dr. Praful Ravi, if the treating physician feels it is in the patient's best interests. If the patient must hold treatment for >28 days due to a health issue unrelated to trial therapy, such as COVID-19 infection, resumption of treatment on study may be permitted but must be approved on a case-by-case basis by the principal investigator. If the treating investigator feels that it is unsafe to resume one of the study drugs and the patient is felt to be clinically benefiting, patients in phase 1 may continue on monotherapy of the other agent; if such a scenario occurs in phase 2, patients must discontinue from the trial and proceed to RP.

6.1 Dose Modifications for Toxicity Attributed to Darolutamide

There are two dose levels for darolutamide (600mg bid and 300mg bid), which apply to patients in both phase 1 and phase 2:

Dose Level	Darolutamide dose
0	600mg po bid
-1	300mg po bid

Suggested guidelines for management of toxicities attributed to darolutamide are as following:

AE Severity	Management for Darolutamide
≤ Grade 2	No change in dose.
Grade 3	Hold until ≤ Grade 2. Resume at same dose level.
Grade 4	Hold until ≤ Grade 2. Resume at one dose level lower, if indicated.*

*Participants who experience ≥ grade 2 toxicity at dose level -1 should be withdrawn from the study.

No dose adjustment of darolutamide is required for patients with renal impairment. Dose adjustment for hepatic impairment should follow the guidelines above.

6.1.1 Guidance for concomitant therapy

This applies to patients in Arm 2 of phase 2 only (i.e. ADT and darolutamide alone):

CYP3A4 inducers: avoid concomitant use of strong CYP3A4 inducers.

CYP3A4 inhibitors: no significant toxicity from darolutamide is expected but concomitant use of strong CYP3A4 inhibitors should be done with caution.

6.2 Dose Modifications for Toxicity Attributed to Abemaciclib

In phase 1, dose levels for abemaciclib should follow the (de)escalation outlined in Section 5.1.

In phase 2, dose levels for abemaciclib will be as below, with the RP2D ascribed as dose level 0. The dose decreases for abemaciclib will be in 50mg increments. If the RP2D is 200mg bid, there will be 4 dose levels (to enable reduction to 50mg bid); if the RP2D is 150mg bid, there will only be 3 dose levels (to enable reduction to 50mg bid).

Dose Level	Abemaciclib dose
0	RP2D po bid
-1	(RP2D – 50mg) po bid
-2	(RP2D – 100mg) po bid
-3*	(RP2D – 150mg) po bid

* only if RP2D is 200mg

6.2.1 Guidance for hematologic toxicity

Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib. Patients should be monitored closely for signs of infection, anemia, and bleeding. Complete blood counts should be monitored every 2 weeks for the first 2 months on abemaciclib and then monthly thereafter.

Growth factors should not be administered to enable a patient to satisfy study inclusion criteria. Granulocyte colony stimulating factor (G-CSF) or similar agents are not permitted as primary prophylaxis. Blood cell growth factors are only to be used in a manner consistent with American Society of Clinical Oncology (ASCO) guidelines. Dosing of abemaciclib must be suspended if the administration of growth factors is required and must not be restarted within 48 hours of the last dose of growth factors having been administered. When restarted, the dose of abemaciclib must be reduced by 1 dose level if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

Fever or infection in the presence of severe neutropenia should be managed promptly with

broad- spectrum antibacterial therapy, including coverage for enteric (gram-negative and anaerobic) bacteria. If neutropenic fever persists for 5 days despite broad-spectrum antibacterial therapy, empiric antifungal therapy should be initiated. Anemia and thrombocytopenia should be treated supportively and if necessary with red cell or platelet transfusions.

Hematologic Toxicity	**Abemaciclib Dose Adjustments and Delays**
Grade 1 or Grade 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Recurrent Grade 3, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose level.
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for hematologic toxicity

6.2.2 Guidance for non-hematologic toxicities (except diarrhea, ALT/AST increase, and ILD/pneumonitis)

Nonhematologic Toxicity (excluding diarrhea, ALT/AST increased, and interstitial lung disease /pneumonitis)	**Abemaciclib Dose Adjustments and Delays**
Grade 1 or Grade 2	No dose modification is required
Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3 or Grade 4	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose level.

6.2.3 Management of diarrhea

When abemaciclib is initiated, the patient should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses ofclear liquids per day).
- Site personnel should assess response within 24 hours.

- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to either baseline or Grade1, study drug should be suspended until diarrhea is resolved to baseline or Grade 1.
- When abemaciclib recommences, dosing should be adjusted as outlined in the table below

The following is recommended in management of diarrhea:

Diarrhea	Abemaciclib Dose Adjustments and Delays
Grade 1	No dose modification is required.
Grade 2 that does not resolve within 24 hours to ≤Grade 1	Suspend dose until toxicity resolves to ≤Grade 1. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures, or Grade 3, or Grade 4, or requires hospitalization	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose level.

In severe cases of diarrhea, measuring neutrophil counts and body temperature and proactively managing diarrhea with antidiarrheal agents is recommended. In addition, patients with ≥ grade 3 diarrhea should be reviewed by a treating physician once per week until the diarrhea has resolved to ≤ grade 1.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibacterial therapy should be initiated, including coverage for enteric (gram-negative and anaerobic) bacteria. If neutropenic fever persists for 5 days despite broad-spectrum antibacterial therapy, empiric antifungal therapy should be initiated. If diarrhea persists after antibiotic treatment, testing for *Clostridium difficile* is indicated as antibiotic therapy might precipitate *C. difficile* infection.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given IV fluid (IV hydration) and electrolyte replacement. In these patients, electrolytes and renal function should be monitored regularly during the period of IV hydration.

For reference, the CTCAE version 5 table for diarrhea is provided below:

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Abbreviation: ADL = activities of daily living

6.2.4 Guidance for management of hepatic toxicity

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation have been considered as adverse drug reactions with the use of abemaciclib. Hepatic monitoring should depend on the severity and persistence of the observed laboratory test abnormalities.

Liver function tests including ALT should be monitored prior to the start of therapy, at least every 2 weeks for the first 2 months, then monthly. These tests may be ordered locally, and performed within 3 business days for each timepoint.

Increased ALT or AST	Abemaciclib Dose Adjustments and Delays
Grade 1 or Grade 2	No dose modification is required
Persistent or recurrent Grade 2, or Grade 3	Suspend dose until toxicity resolves to baseline or Grade 1 Resume at next lower dose
≥Grade 2 with total bilirubin >2×ULN, in the absence of cholestasis, or Grade 4	Discontinue abemaciclib

For reference, the CTCAE version 5 table for ALT/AST increased is provided below:

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
>ULN through 3.0 x ULN if baseline was normal; 1.5 through 3.0 x baseline if baseline was abnormal	>3.0 through 5.0 x ULN if baseline was normal; >3.0 through 5.0 x baseline if baseline was abnormal	>5.0 through 20.0 x ULN if baseline was normal; >5.0 through 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Death

Abbreviation: ULN = upper limit of normal.

Liver testing, including ALT, AST, ALP, total and direct bilirubin, GGT, and creatine kinase (CK), should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of …	*develops the following elevations:*
ALT or AST <1.5x ULN	ALT or AST ≥5x ULN or ALT or AST ≥3x ULN concurrent with TBL ≥2x ULN
ALT or AST ≥1.5x ULN	ALT or AST ≥3x baseline or ALT or AST ≥2x baseline concurrent with TBL ≥2x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), and history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking, and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time-international normalized ratio; serological tests for viral hepatitis A, B, C, E, and autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial evaluation results, further testing should be considered, in consultation with the Lilly designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol (below). Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, and/or a liver biopsy.

For patients who experienced hepatotoxicity and resumed treatment, AST, ALT, and bilirubin should be monitored every week for the first month, every 2 weeks for the following 2 months, and monthly thereafter.

Table: Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs – Red Blood Cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs – White Blood Cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen Protein Adducts
Platelets	Alkaline Phosphatase Isoenzymes

Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl Alcohol (EtOH)
Prothrombin Time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (Quantitative)
Hepatitis A Virus (HAV) Testing:	Immunoglobulin IgG (Quantitative)
HAV Total Antibody	Immunoglobulin IgM (Quantitative)
HAV IgM Antibody	Phosphatidylethanol (Peth)
Hepatis B Virus (HBV) Testing:	**Urine Chemistry**
Hepatitis B surface antigen (HbsAg)	Drug Screen
Hepatitis B surface antibody (Anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (Anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [d]	Anti-actin antibody [b]
Hepatis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody
HCV RNA [d]	EBV DNA [d]
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA [d]
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [d]	HSV (Type 1 and 2) DNA [d]
Microbiology [c]	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

[a] This is not required if Anti-Actin Antibody is tested.

[b] This is not required if Anti-smooth muscle antibody (ASMA) is tested.

[c] Assayed by Investigator-designated local laboratory ONLY; no Central Testing available.

[d] Reflex/confirmation dependent on regulatory requirements and/or testing availability

6.2.5 Guidance for interstitial lung disease/pneumonitis

Interstitial lung disease/pneumonitis has been identified as an adverse drug reaction for

abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the Investigator's Brochure.

Ask your participants to report any new or worsening pulmonary symptoms such as dyspnea, cough, and fever and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high-resolution CT, bronchoalveolar lavage, and biopsy as clinically indicated. Refer to the below guidance on dose adjustments of abemaciclib for participants with ILD/pneumonitis. Discontinue abemaciclib in cases of severe (Grade 3 or Grade 4) ILD/pneumonitis.

Interstitial Lung Disease/Pneumonitis	Abemaciclib Dose Adjustments and Delays
Grade 1 or Grade 2	No dose modification is required.
Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Suspend dose until toxicity resolves to baseline or Grade ≤1. Resume at next lower dose level.
Grade 3 or Grade 4	Discontinue abemaciclib

6.2.6 Guidance for monitoring renal function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

Dose adjustments (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. Other measures of renal function such as cystatin C GFR should be used as an alternative to either creatinine or creatinine calculations of GFR.

If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for nonhematological toxicities (Section 6.2.2) if considered related to abemaciclib.

6.2.7 Guidance for venous thromboembolic events

In breast cancer, venous thromboembolic event (VTE) has been identified as an adverse drug reaction for abemaciclib in combination with endocrine therapy (ET). In the randomized Phase 3 studies in breast cancer participants who received abemaciclib in combination with ET, a greater number of participants experienced VTEs in the abemaciclib plus ET arms than in the placebo

plus ET arm or ET alone arm. The majority of participants who experienced VTEs were treated with anticoagulants.

In studies with single-agent abemaciclib use in the metastatic breast cancer population or other tumor types, including non-small cell lung cancer, no increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. Monitor participants for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate.

Dose modifications and management of abemaciclib should follow the protocol guidance for nonhematological toxicities in Section 6.2.2.

6.2.8 Guidance for concomitant therapy

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites. The following applies to all patients treated in Phase 1 as well as in Arm 1 of Phase 2:

CYP3A inducers: Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A inhibitors: Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with co-administered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. Avoid grapefruit or grapefruit juice. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the dose of abemaciclib by 50mg at the start of CYP3A inhibitor treatment. That is, for patients receiving 200, or 150, or 100mg twice daily when the CYP3A inhibitor treatment is indicated, reduce the abemaciclib dose to 150, 100, or 50mg twice daily, respectively. Irrespective of the patient's current abemaciclib dose, in the case of the very strong inhibitor ketoconazole (non-topical administration routes only), reduce the abemaciclib dose to 50mg twice daily. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

6.2.9 Guidance for use of radiotherapy with abemaciclib

Limited data are available with abemaciclib and radiotherapy or alternate dosing schedules (e.g. induction phase). Thus, caution should be exercised with co-administering abemaciclib with radiotherapy.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential Aes (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in**

addition to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List for Darolutamide

Frequent adverse events reported in >10% of patients treated with darolutamide include fatigue (27%), back pain (22%), arthralgia (17%), pain (17%), nausea (16%), constipation (14%), diarrhea (14%) and decreased appetite (13%).

Grade 3 or higher adverse events reported in >2% of patients treated with darolutamide include anemia (2%), back pain (2%), elevated blood alkaline phosphatase (2%) and general physical health deterioration (2%).

7.1.2 Adverse Event List for Abemaciclib

Frequent adverse events reported in >20% of patients treated with single-agent abemaciclib include diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (46%), abdominal pain (39%), vomiting (35%), headaches (21%), creatinine increased (99%), white blood cell decreased (91%), neutrophil count decreased (88%), anemia (69%), platelet count decreased (41%), ALT increased (30%), AST increased (26%), hypokalemia (26%) and hyponatremia (21%).

Grade 3 adverse events reported in >5% of patients treated with single-agent abemaciclib include diarrhea (20%), fatigue (13%), white blood cell decreased (28%), neutrophil count decreased (27%) and hypokalemia (5%).

7.1.3 Adverse Event List for 68Ga gozetotide

The safety of ^{68}Ga gozetotide was evaluated in 960 patients, each receiving one dose of ^{68}Ga gozetotide. The average injected activity was 188.7 ± 40.7 MBq (5.1 ± 1.1 mCi). No serious adverse reactions were attributed to ^{68}Ga gozetotide. The most commonly reported adverse reactions were nausea, diarrhea, and dizziness, occurring at a rate of < 1%.

7.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For expedited reporting purposes only: Aes for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided. Other Aes for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-

heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

Attribution of the AE:
Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Adverse Event Reporting

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Sponsor-Investigator.

Investigators **must** report to the Sponsor-Investigator any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.1 Adverse Event Reporting Guidelines

All participating sites will report Aes to the PCCTC per DF/HCC requirements, and the IRB of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.

Attribution	DF/HCC Reportable Adverse Events (Aes)				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for Aes occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.					

7.3.2 Site Responsibilities

Sites are responsible for reporting Aes to the PCCTC per Section 7.3.1 and all SAEs to the PCCTC within 24 hours or 1 business day.

PCCTC:
Prostate Cancer Clinical Trials Consortium
Email: pcctc@mskcc.org

The PCCTC will report expedited Aes and all SAEs to DFCI.

7.4 Reporting to Eli Lilly

To comply with applicable laws, regulations and standards regarding Investigator's and Institution's obligations, as the sponsor of the Study, DFCI will collect and report adverse events to regulatory authorities, IRBs, Ethics Committees or other third parties. In addition to the obligations set forth below, Investigator and Institution agree DFCI will provide Lilly with a copy of all information DFCI submits to regulators related to any adverse events for 43bemaciclib that occur during the Study that DFCI have not otherwise provided Lilly;

DFCI will notify Lilly, sub-investigators, and the IRB of any problems involving risk to Study participants and report new safety information to IRBs in accordance with applicable requirements.

DFCI will notify Lilly within fifteen (15) business days of DFCI receiving notification of any "serious" adverse event experienced by a patient participating in the Study and receiving abemaciclib. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the participant and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. Investigator and Institution further agree to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with abemaciclib.

The PCCTC, on behalf of participating sites and the Sponsor-Investigator will report SAEs to Lilly.

7.5 Reporting to Bayer

All serious Aes (SAEs) must be reported to Bayer within 24 hours of the Principal Investigator's awareness and must include the following minimum information:

1. The name and contact information of the reporter
2. The name of the study drug(s)
3. A description of the reported SAE
4. A patient identified by one or more of the following:
    a. Patient initials
    b. Patient number
    c. Knowledge that a patient who experienced the adverse event exists
    d. Age
    e. Sex
5. An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug.

Additional data which would aid the review and causality assessment of the case include but are not limited to: the date of onset, the severity, the time from administration of study drug(s) to

start of the event, the duration and outcome of the event, any possible etiology for the event, the final diagnosis or syndrome, if known, and action(s) taken, if any.

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death.
b. Is life-threatening.

The term 'life-threatening' in the definition refers to an event in which the patient 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours.
- The admission is pre-planned.
  (i.e. elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE.
  (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect.
f. Is another medically important serious event as judged by the investigator.

The PCCTC, on behalf of participating sites and the Sponsor-Investigator will report SAEs to Bayer.

7.6 Reporting to Telix

Telix must be notified of any SAEs related to ^{68}Ga gozetotide in patients undergoing the second (research) ^{68}Ga-PSMA-PET scan once the Investigator or other study site personnel are aware of the event.

The completed and signed SAE report form should be sent within 24 hours to Telix via the email address: pharmacovigilance@telixpharma.com.

This report should provide a detailed description of the SAE. Any other relevant documents such as pseudonymized copies of hospital records may also be attached, if available.

All reports of death, both toxic death and death as a result of progression of disease, should be reported to Telix immediately. A detailed description of the cause of death should be provided. Autopsy reports, if available, should also be sent to Telix as soon as they become available. Any

additional information which becomes known to the Investigator should be provided as a follow-up.

Following are the steps which should be followed for reporting of SAEs by Investigators:

1) Capture and assess all Aes that occur at the site as required and in accordance with the protocol.
2) Notify Telix immediately, and at the latest within 24 hours of becoming aware of the initial SAE.
3) Obtain and maintain in subject's files pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
4) Complete and submit to Telix further follow-up information until the SAE has resolved or a decision for no further follow up has been taken.

DFCI will report SAEs to Telix and the PCCTC.

7.7 Reporting to the Food and Drug Administration (FDA)

The Sponsor will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.8 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.9 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the PI on the toxicity case report forms. **Aes reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL AND IMAGING AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1 Darolutamide

8.1.1 Description

Darolutamide is an oral AR antagonist that is a 1:1 mixture of 2 diastereomers (*S,R*)-darolutamide and (*S,S*)-darolutamide. Its chemical formula is $C_{19}H_{19}ClN_6O_2$ and its

molecular mass is 398.85g/mol.

8.1.2 Form

Darolutamide is provided as a blue film-coated immediate-release tablet.

8.1.3 Storage and Stability

Darolutamide tablets are packaged in high-density polyethylene (HDPE) white opaque plastic bottle. The bottle cannot be stored above 30°C.

8.1.4 Compatibility

N/A

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability

Darolutamide 300mg tablets will be provided by Bayer in 120 count bottles.

8.1.7 Preparation

N/A

8.1.8 Administration

Darolutamide must be taken with food. Doses must be administered at least 12 hours apart. If a dose is missed (e.g., missed morning dose and did not re-dose within appropriate time) it should not be taken if it is less than 8 hours until the next dose. If the subject vomits a dose, that dose should be omitted and the next dose taken at the usual scheduled time. All doses given, missed, and vomited, should be recorded.

8.1.9 Ordering

Bayer will supply darolutamide and ordering will take place through Bayer. The study team will complete the Drug Request Form, which is kept as a separate document.

8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug

Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 Destruction and Return

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to Bayer. Destruction will be documented in the Drug Accountability Record Form.

8.2 Abemaciclib

8.2.1 Description

Abemaciclib is an oral inhibitor of CDK4 and CDK6. Its chemical formula is $C_{27}H_{32}F_2N_8$ and its molecular weight is 506.60.

8.2.2 Form

Abemaciclib is provided as 50mg tablets.

8.2.3 Storage and Stability

Abemaciclib needs to be stored in the original package. Abemaciclib needs to be kept at room temperature. The drug products are stable when stored according to the instructions on the label.

8.2.4 Compatibility

N/A

8.2.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.6 Availability

Abemaciclib 50mg tablets will be provided by Lilly in 60 count bottles.

8.2.7 Preparation

N/A

8.2.8 Administration

Abemaciclib may be taken with or without food. Tablets should not be crushed, chewed or dissolved. Doses must be administered orally twice daily with a minimum of 6 hours between doses, at approximately the same time every day. If a participant misses a dose at the scheduled time for nonmedical reasons, the dose should be taken as soon as possible on the same day and then twice-daily administration should be resumed (with at least 6 hours separating doses). If a participant vomits after taking a dose, then the dose should not be retaken and the next dose should be taken at the usual scheduled time. All doses given, missed, and vomited, should be recorded.

8.2.9 Ordering

Lilly will supply abemaciclib and ordering will take place through Lilly. The study team will complete the Drug Request Form, which is kept as a separate document.

8.2.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.2.11 Destruction and Return

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to Lilly. Destruction will be documented in the Drug Accountability Record Form.

8.3 LHRH/GnRH agonist or antagonist

8.3.1 Description

Leuprolide and goserelin are GnRH agonists, and degarelix and relugolix are GnRH antagonists.

8.3.2 Form

Leuprolide is a sterile solution administered as an intramuscular injection while goserelin and degarelix are administered as a subcutaneous injections. Relugolix is taken orally.

8.3.3 Storage and Stability

They will be stored at the site specific pharmacy.

8.3.4 Compatibility

We do not anticipate any excess toxicity with the combination of GnRH agonist/antagonist with darolutamide and abemaciclib.

8.3.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.3.6 Availability

These are commercially available and will be ordered by the institution's pharmacy.

8.3.7 Preparation

N/A

8.3.8 Administration

These will be administered according to their label as intramuscular or subcutaneous injections at their recommended doses. Leuprolide may be administered at a dose of 7.5mg every 4 weeks or as 22.5mg given every 12 weeks per treating investigator discretion. Dosing of goserelin is 3.6mg every 4 weeks. Dosing of degarelix is 240mg loading followed 4 weeks later by maintenance doses of 80mg, to be given every 4 weeks. Relugolix is given as 360mg loading dose on day 1 and 120mg daily thereafter.

8.3.9 Accountability

As degarelix, leuprolide, goserelin and relugolix will come from commercial sources, no drug accountability logs will be kept.

8.4 ^{68}Ga Gozetotide

8.4.1 Description

^{68}Ga Gozetotide is the imaging agent for PSMA PET and is commercially available. Refer to the package insert for further information.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

Neither the phase 1 or phase 2 studies require any biomarker selection. However, we will assess the utility of genomic, IHC and serum biomarkers as exploratory objectives in phase 2, as outlined in section 2.6.

9.2 Laboratory Correlative Studies

Please refer to the Laboratory Manual for instructions on sample collection and processing.

9.3 Pharmacokinetic Studies

The plasma pharmacokinetics of darolutamide and abemaciclib will be defined for the first dose of both drugs and again when steady state conditions have been achieved after at least 7 days of uninterrupted dosing during cycle 1 to assess whether or not the pharmacokinetic behavior of either drugs is altered by their concurrent administration. Pharmacokinetic sampling will be performed in all patients enrolled in the Phase I dose escalation part of the clinical trial and in an additional 12 patients treated with the RP2D of the combination regimen during the Phase II part.

The sampling schedule has been devised to accommodate treatment on an outpatient basis. Patients should be instructed to take the doses of the two drugs at the same times every day during cycle 1 until the final pharmacokinetic sample has been collected. The morning doses should be taken together at a time will allow the patient to arrive at the clinical to obtain a sample before dosing and to remain for an additional 8 hours. The second daily doses should be taken 12.0 ± 0.25 hours after the morning dose. It is important for the patient to consume a full meal before arriving at the clinic each morning when pharmacokinetic samples are to be collected and before taking the second daily dose. It is also very important that the patient is aware that the morning doses of the two drugs on days 2, 7, and 8 must not be taken before arriving at the clinic and the predose pharmacokinetic sample has been collected.

The first set of samples will be obtained on day 1 of cycle 1 shortly before taking the first dose of both drugs and at 1.0, 2.0, 4.0, 6.0 and 8.0 hours after dosing. The patient will return to the clinic on the following day for collection of a single sample 24.0 hours after taking the day 1 morning dose and prior to taking the day 2 morning dose. The second set of samples may be obtained any day following day 7 of cycle 1 according to the same schedule (just before taking the morning dose of both drugs, at 1.0, 2.0, 4.0, 6.0 and 8.0 hours after dosing, and on the next day 24.0 hours after taking the morning dose on the prior day and prior to taking their next morning dose. There is an allowable window of (+/-) 10 minutes for collection times for the 1, 2, 4, 6 and 8 hours post-dose samples and (+/-) 60 minutes for the 24 hours post-dose sample; however they should be collected as close to the hour as possible.

Please refer to the Laboratory Manual for specimen collection and preparation details, as well as details of shipment.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 4 weeks (28 days) prior to start of protocol

therapy. Scans must be done ≤4 weeks prior to the start of therapy. If the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

10.1 Phase 1

	Baseline (within 28 days of C1D1)	C1 (± 3 days)		C2 (± 3 days)		C≥3 D1 (± 3 days)	End of treatment[d]	Follow-up[d]	EDC Timepoints
		D1	D15	D1	D15				
Darolutamide[A]		A	A	A	A	A			Days 1-28 of each cycle
Abemaciclib[B]		B	B	B	B	B			Days 1-28 of each cycle
ADT[C]		C				C			Every 1 or 3 months
Informed consent	X								N/A
Demographics	X								Baseline
Medical history	X								Baseline
Concurrent medications		X ----------X							Baseline, Day 1 of each cycle, End of treatment, Follow-up
Physical exam	X	X	X	X	X	X	X		Baseline, Days 1 and 15 for first 2 cycles, Day 1 of subsequent cycles, End of treatment
Vital signs	X	X	X	X	X	X	X		Baseline, Days 1 and 15 for first 2 cycles, Day 1 of subsequent cycles, End of treatment
Height	X								Baseline
Weight	X	X	X	X	X	X	X		Baseline, Days 1 and 15 for first 2 cycles, Day 1 of subsequent cycles, End of treatment
ECOG PS	X	X	X	X	X	X	X		Baseline, Days 1 and 15 for first 2 cycles, Day 1 of subsequent cycles, End of treatment
CBC w/diff, PLTs	X	X	X	X	X	X	X		Baseline, Days 1 and 15 for first 2 cycles, Day 1 of subsequent cycles, End of treatment
Serum chemistry[a]	X	X	X	X	X	X	X		Baseline, Days 1 and 15 for first 2 cycles, Day 1 of subsequent cycles, End of treatment
PSA	X	X		X		X	X		Baseline, Day 1 of each cycle, End of treatment
Testosterone	X	X		X		X	X		Baseline, Day 1 of each cycle, End of treatment
Pharmacokinetics[b]		X	X						C1D1 and C1D15
ECG – only if clinically indicated	X								Baseline – only if clinically indicated
Adverse event evaluation		X ----------X							All visits
Radiologic evaluation[c]	X	Every 12 weeks on treatment							Baseline, C4D1 and every 3 cycles thereafter. If a Radiologic Evaluation is performed during any other Cycle, it must be captured in the CRF.
Survival & Disease Status		X ----------X							All visits

A: Darolutamide bid, cycle length = 28 days; B: Abemaciclib bid, cycle length = 28 days; C: leuprolide, goserelin, degarelix or relugolix per investigator discretion

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium; cystatin C may be checked if

clinically indicated to evaluate increase in serum creatinine
b: Samples obtained prior to dose and at 1, 2, 4, 6, 8 and 24hrs after dosing. Allowable window of +/- 10 minutes for collection of 1, 2, 4, 6 and 8hrs post-dose samples and +/- 60 minutes for the 24hrs post-dose sample. All patients in phase 1 will have pharmacokinetic sampling. See Section 9.3.
c: Cross-sectional imaging of Chest, Abdomen and Pelvis as well as bone scintigraphy
d: An end of treatment and safety assessment should be performed 30-42 days after the last dose of study treatment to include any adverse events occurring within 30 days after the last dose of study treatment. Survival follow-up will be approximately every 6 months until 5 years after discontinuing treatment via review of routine care visits and include review of disease status – i.e., progression events.

10.2 Phase 2

	Baseline (within 28 days of C1D1)	**C1 (±3 days)**		**C2 (± 3 days)**		**C3-C6 D1 (± 3 days)**	**Pre-RP (≤2 weeks before RP)**	**RP**	**Post-RP (4-8 weeks after RP)**	**Follow-up[I] (± 28 days)**	**EDC Timepoints**
		D1	**D15**	**D1**	**D15**						
Darolutamide[A]		A	A	A	A	A					Days 1-28 of each cycle
Abemaciclib[B]		B	B	B	B	B					Days 1-28 of each cycle
ADT[a]		X	X	X	X	X					C1D1 and C4D1[a]
Informed consent	X										N/A
Demographics	X										Baseline
Medical history	X										Baseline
Concurrent medications		X ----------X									All visits
Physical exam	X	X	X	X	X	X	X		X	X	Baseline, All visits except RP
Vital signs	X	X	X	X	X	X	X		X	X	Baseline, All visits
Height	X										Baseline
Weight	X	X	X	X	X	X	X		X	X	Baseline, All visits except RP
ECOG PS	X	X	X	X	X	X	X		X	X	Baseline, All visits except RP
CBC w/diff, PLTs	X	X	X	X	X	X	X		X	X	Baseline, Days 1 and 15 for first 2 cycles, Day 1 of C3-6, Pre-RP, Post-RP, Follow-up
Serum chemistry[b]	X	X	X	X	X	X	X		X	X	Baseline, Days 1 and 15 for first 2 cycles, Day 1 of C3-6, Pre-RP, Post-RP, Follow-up
Coagulation factors[c]	X						X				Baseline, Pre-RP
PSA	X	X		X		X	X		X	X	Baseline, Day 1 of every cycle, Pre-RP, Post-RP Follow-up
Testosterone	X	X					X		X	X	Baseline, C1D1, Pre-RP, Post-RP, Follow-up
Pharmacokinetics[d]		X	X								C1D1 and C1D15
Prostatectomy[e]								X			RP
ECG – only if clinically indicated	X										Baseline – only if clinically indicated
Adverse event evaluation		X ----------X									All visits
Radiologic evaluation[f,g]	X						X				Baseline and Pre-RP. If a Radiologic Evaluation is performed during any other time, it must be captured in the CRF.
Diagnostic biopsy[h]	X										Baseline
Research biopsy[i]				X		X					C2D1, C3D1 and C4D1[i]
Blood for germline DNA[J]		X									C1D1
Research sample[k]		X		X		X	X		X		Day 1 of every cycle, Pre-RP, Post-RP
Survival		X ----------X									All visits

A: Darolutamide bid, cycle length = 28 days; B: Abemaciclib bid, cycle length = 28 days
a: Either leuprolide, goserelin, degarelix or relugolix per investigator discretion. Participants who have started ADT within four weeks of cycle 1/day 1 are eligible to enroll.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium; cystatin C may be checked if clinically indicated to evaluate increase in serum creatinine
c: PT, APTT, INR
d: Samples obtained prior to dose and at 1, 2, 4, 6, 8 and 24hrs after dosing. The first 12 patients enrolled in phase 2 at DFCI will have pharmacokinetic sampling. See section 9.3.
e: Tissue will be requested for central pathology review. Pathology report from local pathologist will be requested
f: Radiologic evaluation must include MRI prostate as well as either PSMA-PET and/or CT/MRI abdomen, bone scan (and CT chest, if clinically indicated) at baseline. Patients undergoing PSMA-PET need not necessarily undergo conventional imaging provided they otherwise meet inclusion criteria, but either PSMA-PET or conventional imaging (or both) are needed at baseline.
g: PSMA-PET may be performed up to 21 days after C1D1 (if conventional imaging has already been performed at baseline), and is required in patients treated at DFCI. A research-only PSMA-PET is required pre-RP in patients treated at DFCI.
h: Tissue from the diagnostic biopsy will be requested (tissue blocks wherever possible; if not possible, 15 unstained slides from each positive core sample for a total of 45 to be sent to the central analytical laboratory. See the Lab Manual for processing instructions. Pathology report (including the assessment of the local pathologist regarding Gleason score) from diagnostic biopsy must accompany registration materials.
i: Optional research biopsies will be performed in patients treated at DFCI who additionally consent to 01-045; up to 15 patients may undergo optional biopsies prior to C2D1 (n=5), C3D1 (n=5) and C4D1 (n=5)
j: Pre-study genomic DNA sample can be drawn any time between and including baseline and C1D1.
k: Blood for cfDNA and serum TK1; see Laboratory Manual for processing instructions
l: Every 3 months in year 1 after RP, every 4 months in year 2, every 6 months in year 3 and annually thereafter until year 5 is suggested

11. MEASUREMENT OF EFFECT

11.1 Phase 1

In Phase 1, the primary objective is safety and tolerability of the combination of darolutamide and abemaciclib. Nevertheless, evidence of efficacy of the combination will be measured via the following criteria where patients have measurable disease.

11.1.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 12 weeks. Since efficacy is only a secondary objective, a confirmatory scan is not required.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. Response and progression of osseous lesions by bone scintigraphy will be per PCWG3 criteria.[73]

11.1.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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.

Non-measurable disease. 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, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

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

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

11.1.1.3 Methods for Evaluation of Disease

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

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

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

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

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

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

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

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the

study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

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

Tumor markers. Refer to section 11.1.2.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.1.4 Response Criteria

11.1.1.4.1 Evaluation of Target Lesions

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

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.

11.1.1.4.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.1.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.1.4.4 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not	No	PR	

	evaluated			
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

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

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

11.1.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

11.1.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from the start of treatment to death due to any cause, or censored at date last known alive.

Radiographic progression-free Survival (rPFS): rPFS is defined as the time from protocol treatment initiation to the earlier of progression by PCWG3 criteria[73] or death due to any cause. PCWG3 progression is defined as when it is felt by the treating physician that the patient is "no longer clinically benefiting" (NLCB) from therapy. Generally, this is understood as radiographic or clinical/symptomatic progression (i.e. not PSA progression alone), but PCWG3 criteria allow treatment beyond radiographic progression if the treating physician feels that the patient is continuing to derive clinical benefit from therapy (compared to other available treatments or no treatment). Participants alive without disease progression are censored at date of last disease evaluation.

11.1.2 PSA response and progression

Evaluable for PSA response
Only those patients with PSA ≥1.0ng/mL at baseline and have received at least one cycle of therapy will be evaluable for PSA response.

Biochemical (PSA) Response[74]
The laboratory will utilize a consistent method to check serum PSA at baseline, on treatment as per the study calendar, and at study termination.
A PSA response will be defined as any PSA decline ≥50% from baseline during trial therapy.

PSA Progression-Free Survival (PSA-PFS)
PSA Progression-Free Survival is defined as the time from protocol treatment initiation to the first PSA failure (two consecutive increases in PSA of ≥25% and ≥2 ng/mL above nadir, as per PCWG3)[73] or death, or it is censored at date of last PSA test for participants alive without PSA progression.

Duration of PSA response
The duration of PSA response is measured from the time of PSA response till the PSA progression, or it is censored at date of last PSA test.

11.2 Phase 2

In Phase 2, the primary objective is to assess pathologic response to neoadjuvant therapy with secondary objectives being to evaluate longer-term biochemical and metastatic endpoints.

11.2.1 Pathologic response

This is defined as achieving either pCR or MRD at RP. pCR is defined as the absence of

morphologically identifiable carcinoma in the RP specimen. MRD will be defined as residual tumor in the RP specimen measuring ≤5 mm.[29] If the tumor is multifocal, the size of the largest focus will be used to determine the size of the residual tumor. RP specimens will initially be evaluated by the site pathologist using standard methods. Prostate biopsy specimens will be evaluated by central pathology review at completion of the study.

11.2.2 Biochemical progression-free survival (bPFS)

bPFS will be defined as the duration between date of RP and the date of first evidence of any of the following:

- PSA ≥0.1ng/ml confirmed at the next measurement.[75]
- Any evidence of metastatic disease seen on CT, MRI or bone scan.
- Local recurrence as demonstrated by CT or MRI scan.
- Treatment with postoperative radiotherapy for a rising PSA or any cancer-directed systemic therapy or radiotherapy initiated >6months after RP.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The PCCTC will collect, manage, and perform quality checks on the data for this study. Data collected during this study will be entered into a secure database managed by the PCCTC and data from the database will be provided to ODQ by the PCCTC as needed for data safety monitoring. Standardized eCRFs and CRF Completion Guidelines will be created by the PCCTC for the collection of study data. Access and training for Medidata Rave EDC will be made available to participating sites upon local regulatory approval.

12.1.2 Responsibility for Data Submission

The participating site investigator is responsible for ensuring eCRFs are completed accurately and in a timely manner in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

For the Phase I portion in defining the Recommended Phase II Dose (RP2D), the trial will be reporting to the Data Safety Monitoring Committee (DSMC). Once the RP2D is established and the Phase II portion is ready to accrue, the trial will be transitioned to the Data Safety Monitoring

Board (DSMB) for continued safety and statistical efficacy assessment.

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team.

The DSMC generally reviews each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported across all sites; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The Board is chaired by a medical oncologist from outside of DF/HCC and its membership composed of internal and external institutional representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Sponsor-Investigator, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; all adverse events and serious adverse events reported across all sites by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

In addition to review by DSMC, the PCCTC will conduct regularly scheduled monitoring visits.

Reports will be generated by the PCCTC to monitor subject accruals and the completeness of data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Principal Investigator for discussion and action.

The monitoring visit will include a review of source documentation to evaluate:

- Regulatory/IRB compliance (review of current protocol and amendments, Informed consent documents and procedures, annual continuing review reports, AEs/SAEs)
- Protocol defined treatment compliance
- Subject records
    - A signed and dated informed consent form for each subject

- Adherence to eligibility criteria
- Source Data Verification for identified subjects

Monitoring findings will be reviewed and disseminated to the site investigators and staff.

The PCCTC may also perform site audits. If a site is notified of an external audit relating to this study, the site should notify the PCCTC immediately. The PCCTC and/or Monitors assigned to this study will provide site support during audits (quality control and/or regulatory agency) including review and assisting sites with responses to audit findings.

12.3 Multi-Center Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor-Investigator, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a multi-center phase 1/2 study of darolutamide and abemaciclib in prostate cancer.

13.1.1 Phase 1
In phase 1, men with previously treated or untreated M0 or M1 CRPC will be enrolled in a standard 3+3 dose escalation design with a starting dose of darolutamide 600mg bid and abemaciclib 150mg bid. We will monitor for DLTs during the first cycle of therapy and (de)escalate per Sections 5.1 and 5.4. MTD is defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in cycle 1. If only three patients are treated at the MTD, an additional three patients will be added for a total of six patients at the MTD. The RP2D will be determined after an MTD is identified or the maximum planned dose is achieved.

<u>Primary endpoint</u>
- RP2D of darolutamide and abemaciclib administered in combination.

<u>Secondary endpoints</u>
- Overall response rate (ORR: PSA reduction by ≥50% or radiographic response per RECIST 1.1) of darolutamide and abemaciclib in men with M0/M1 CRPC.
- rPFS (as defined in Section 11.1.1.6) of darolutamide and abemaciclib in men with M0/M1 CRPC.
- Pharmacokinetic profiles of darolutamide and abemaciclib when administered in combination in CRPC.

<u>Exploratory endpoint</u>
- Pharmacokinetic profiles of darolutamide and abemaciclib when administered in combination

in CRPC.

13.1.2 Phase 2

In phase 2, men with newly-diagnosed high-risk prostate cancer will be randomized 2:1 to receive 6 months of neoadjuvant therapy with leuprolide, darolutamide and abemaciclib (Arm 1) or leuprolide and darolutamide (Arm 2).

Primary endpoint
- Rate of pCR/MRD (as defined in Section 11.2.1) in Arm 1 and Arm 2.

Secondary endpoints
- Change in PSA from baseline to RP (median nadir value, proportion of patients with PSA <0.2ng/ml, time to PSA nadir) in Arm 1 and Arm 2.
- Rate of 3- and 5-year bPFS (as defined in Section 11.2.2) after RP among patients who achieve testosterone recovery (>200ngl/dl) in Arm 1 and Arm 2.
- Proportion free from further prostate cancer therapy, including adjuvant or salvage radiotherapy and/or ADT, at 2, 3 and 5-years post-RP in Arm 1 and Arm 2.

Exploratory endpoints
- Biomarkers of response and resistance to neoadjuvant therapy with darolutamide and/or abemaciclib.
- Imaging biomarkers as measured by PSMA-PET and relationship with systemic therapy and pathologic outcomes.
- Pharmacokinetic profiles of darolutamide and abemaciclib when administered in combination in localized prostate cancer.

13.2 Sample Size, Accrual Rate and Study Duration

13.2.1 Phase 1

The phase 1 part of the trial employs the standard 3+3 design to define the RP2D of abemaciclib in combination of darolutamide in patients with M0/M1 CRPC. With 2 planned dose levels for abemaciclib (150mg and 200mg), a total of 6-12 patients are anticipated.

With anticipated accrual of 4-5 patients a month, we anticipate that accrual for phase 1 will be completed in ~2 months, with determination of the RP2D made ~1 month after the last patient is accrued. Patients in phase 1 will remain on study drugs under routine clinical follow-up until development of progression or unacceptable toxicity.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino		+	2	=	2
Not Hispanic or Latino		+	7	=	7

Ethnic Category: Total of all subjects	0	+	9	=	9
Racial Category					
American Indian or Alaskan Native		+	0	=	0
Asian		+	1	=	1
Black or African American		+	1	=	1
Native Hawaiian or other Pacific Islander		+	0	=	0
White		+	7	=	7
Racial Category: Total of all subjects	0	+	9	=	9

13.2.2 Phase 2

The primary endpoint in phase 2 will be the proportion of patients achieving pCR or MRD in the phase 2 component of the study, in line with other neoadjuvant trials. We hypothesize that the rate of pCR/MRD with neoadjuvant ADT and darolutamide (Arm 2) will be 15%, based on the neoadjuvant enzalutamide data.[28] In order to obtain a large enough signal of benefit to merit further study of darolutamide and abemaciclib, we propose that the addition of abemaciclib (Arm 1) will increase pCR/MRD rate to 40%. The planned sample size is 81 patients in Phase 2 (randomized 2:1), which will provide 81% power to distinguish a pCR/MRD rate of 40% in Arm 1 (n=54) from a rate of 15% in Arm 2 (n=27), using a Fisher's exact test for binomial proportion (one-sided α=0.1).

We anticipate accrual of ~8-9 patients per month over 3-4 sites in phase 2. Accrual for Phase 2 will complete in ~10 months and the last RP will therefore be performed ~18 months after phase 2 opens. Patients in phase 2 will then enter routine clinical follow-up.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino		+	9	=	9
Not Hispanic or Latino		+	72	=	72
Ethnic Category: Total of all subjects	0	+	81	=	81
Racial Category					
American Indian or Alaskan Native		+	2	=	2
Asian		+	5	=	5
Black or African American		+	8	=	8
Native Hawaiian or other Pacific Islander		+	1	=	1
White		+	65	=	65
Racial Category: Total of all subjects	0	+	81	=	81

13.3 Stratification Factors

There will be no stratification factors in phase 1. In phase 2, randomization will be stratified by Gleason score (7 vs. ≥8). No interim monitoring or efficacy determination is planned.

13.4 Analysis of Primary Endpoints

In phase 1, DLTs are defined using criteria in section 5.4 and assessed by the investigator, based on toxicity grade (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), clinical significance, and possible relationship to either study drug. DLTs are defined for the combination treatment at each dose level. The MTD for the study drug combination is defined as the maximum dose combination at which <33% of patients experience a DLT during Cycle 1 (the DLT-evaluation period). If a DLT is observed in 1 of 3 patients, then 3 additional patients will be enrolled at that same dose level. Dose escalation will continue to a dose of abemaciclib 200mg bid, which is the maximal dose levels. If DLTs are seen in 0-1 of 6 patients at dose level +1 (darolutamide 600mg bid and abemaciclib 200mg bid), then this will be the RP2D; otherwise the maximally tolerated dose (MTD) will be the RP2D.

In phase 2, the number and percent of patients achieving pCR or MRD will be summarized by treatment arm. The difference in response rate (Arm 1 – Arm 2) will be provided with one-sided 90% exact binomial CI. The primary comparison between Arm 1 and Arm 2 will be conducted using the Fisher's exact test for binomial proportion, with one-sided *P* value of ≤0.1 considered statistically significant. The Cochran-Mantel- Haenszel test accounting for the stratification factor at randomization will be performed as a sensitivity analysis.

In phase 2, the primary outcome will be based on a central pathology review after patients complete 6 months of neoadjuvant therapy and radical prostatectomy (approximately 7~8 months after enrollment). Therefore, interim analysis is not planned, considering the trial sample size, accrual duration, and timing of outcome assessment.

13.5 Analysis of Secondary Endpoints

In phase 1, ORR will be analyzed amongst all patients who received protocol treatment and summarized with two-sided 80% exact binomial CI. Kaplan-Meier methodology will estimate the distribution of rPFS.

Secondary efficacy endpoints in phase 2 include pathological parameters from RP and PSA kinetics prior to RP (nadir value, achieving nadir PSA < 0.2 ng/mL, and time to PSA nadir). These data will be summarized with descriptive statistics (median, range, and proportions) by each arm. The rate of bPFS or proportion free from further prostate cancer therapy will be estimated from the Kaplan Meier methodology by each arm. For toxicity reporting, all adverse events and laboratory test results will be graded and analyzed using CTCAE version 5.

For pharmacokinetic analyses in phase 1 and phase 2, parameters and variables will be calculated according to standard equations. The geometric mean and percent coefficient of variation will be calculated for each parameter and compared to historical data from prior clinical trials of each drug given as a single agent.

13.6 Analysis of Exploratory Endpoints

For the correlative parameters from the phase 2 of the trial, biomarkers will be quantified using the appropriate methods for each assay and used as discrete or continuous variables to evaluate association with clinical outcomes. Ki67 expression by immunohistochemistry will be measured as % of positive staining from pre-treatment biopsy specimens and in cases with residual disease on RP. The quantitative change (percent or fold change) in Ki67 scores before and after treatment will be calculated and correlated with pathological outcomes in those with residual tumors. ERG, PTEN and RB1 status by immunohistochemistry will be measured in cases with residual disease on RP, calculated as intensity (e.g. WT/reduced/complete loss, weak/moderate/strong) and % of positive staining (0,1-10%,10-50%,>50%). Genomic analysis of the diagnostic biopsies includes cyclin D1 amplification, CKDN2A/2B loss, and RB1 loss, and the estimated prevalence of these biomarkers ranges from 5% to 20% in this cohort.

For the PSMA-PET sub-study, PET-based parameters before and after neoadjuvant therapy will be summarized as mean (STD), median (range, IQR) or frequency as appropriate. With 40 paired datasets, there is 87% power to detect a 0.5σ mean change in SUV_{max} in the primary prostate tumor pre- and post-treatment using Wilcoxon signed rank test (two-sided α=0.05). The percent change in SUV_{max} from baseline will be compared between pathological response groups. If 30% of patients achieve pathological response (pCR/MRD, 12 out of 40), there is 80% power to detect a 1σ mean difference in SUV_{max} between responders and non-responders (Wilcoxon rank sum test, two-sided α=0.05).

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

Evaluation of toxicity will be done in the safety population, which will include all patients who received at least one dose of study treatment. Patients will be analyzed in the treatment group according to the dose of study treatments they actually received.

13.7.2 Evaluation of the Primary Efficacy Endpoint

In Phase 2, all patients who complete 6 cycles of neoadjuvant therapy and undergo RP will be evaluable for the primary efficacy endpoint of pCR/MRD.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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APPENDIX B: DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLAN

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INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1.Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Policies and Operations.

GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1.Coordinating Center (Prostate Cancer Clinical Trials Consortium (PCCTC))

The PCCTC is the entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines).

The general responsibilities of the PCCTC may include but are not limited to:

- *Assist in protocol development.*
- *Review registration materials for eligibility*
- *Distribute protocol and informed consent document updates to External Sites as needed.*
- *Oversee the data collection process from External Sites.*
- *Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by External Sites and provide to the DF/HCC Sponsor for timely review and submission to the IRB of record, as necessary.*
- *Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the reporting requirements for the IRB of record to all External Sites.*
- *Provide External Sites with information regarding DF/HCC requirements that they will be expected to comply with.*
- *Carry out plan to monitor External Sites either by on-site or remote monitoring.*
- *Maintain Regulatory documents of all External Sites which includes but is not limited to the following: local IRB approvals/notifications from all External Sites, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites*
- *Conduct regular communications with all External Sites (conference calls, emails, etc) and maintain documentation all relevant communications.*

2.2.External Site

An External Site is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site may include but are not limited to:

- *Document the delegation of research specific activities to study personnel.*
- *Commit to the accrual of participants to the protocol.*
- *Submit protocol and/or amendments to their IRB of record. For studies under a single IRB, the Coordinating Center will facilitate any study-wide submissions.*
- *Maintain regulatory files as per ICH GCP and federal requirements.*
- *Provide the Coordinating Center with regulatory documents or source documents as requested.*
- *Participate in protocol training prior to enrolling participants and throughout the trial as required.*
- *Update Coordinating Center with research staff changes on a timely basis.*
- *Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.*
- *Submit Serious Adverse Event (SAE) reports to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC and protocol requirements.*
- *Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable.*
- *Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.*
- *Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.*
- *Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.*
- *Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.*

DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1. Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the PCCTC. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- ***Protocol revisions:*** *External Sites will receive written notification of protocol revisions from the PCCTC. All protocol revisions should be IRB approved and implemented within a timely manner from receipt of the notification.*

- ***Protocol closures and temporary holds:*** *External Sites will receive notification of protocol closures and temporary holds from the PCCTC. Closures and holds will be effective immediately. In addition, the PCCTC will update the External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.*

3.2. Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites must send their version of the informed consent document to the PCCTC for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the PCCTC for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, the approved consent form must also be submitted to the PCCTC after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.3. IRB Re-Approval

Verification of IRB re-approval for the External Sites is required in order to continue research activities. There is no grace period for continuing approvals.

The PCCTC will not register participants if a re-approval letter is not received for the External Site on or before the anniversary of the previous approval date.

3.4. DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the PCCTC should be de-identified. It is recommended that the assigned protocol case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5. Participant Registration and Randomization

To register a participant, the following documents should be completed by the External Site and faxed or e-mailed to the PCCTC (pcctc@mskcc.org). Source documents should be redacted to remove PHI and each page labelled with the assigned protocol case number and participant initials.

- Copy of required laboratory tests including:
  - Histological or cytological confirmation of prostate adenocarcinoma or documentation of unequivacol evidence of prostate cancer (eg. very high PSA) in the view of the treating physician
  - Complete blood count with differential
  - Serum chemistry panel
  - Liver Function Tests
  - Coagulation factors
  - eGFR
  - Testosterone and two most recent PSA values
- *Demographics (Race, ethnicity and DOB)*
- *Screening visits physician note with vital signs, weight, height, ECOG performance status, physical examination and medical history*
- *For Phase 1: Documentation of M0 or M1 CRPC with evidence of progression during continuous androgen deprivation therapy and castrate level of testosterone (see protocol for definition of progression)*
- *For Phase 2: Documentation of Gleason score*
- *Screening ECG*
- *Imaging reports for disease status:*
  - *Phase 1:*
    - *CT/MRI chest, abdomen, pelvis*
    - *Bone scan*
  - *Phase 2:*
    - *MRI Prostate*
    - *CT/MRI abdomen and Bone scan -OR- PSMA PET*
    - *CT chest (if clinically indicated)*
- *Signed informed consent document (Informed consent should include initials for patient on every page)*
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The PCCTC will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the PCCTC will:

- *Review all source documents and the eligibility form to confirm subject meets eligibility. All source documents will be sent to the sponsor PI and regulatory coordinator at DFCI for review.*
- *DFCI will register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).*
- *Upon receiving confirmation of registration from DFCI, the PCCTC will inform the External Site and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.*

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, sex, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. External Sites should submit all de-identified subsequent communication and documents to the PCCTC, using this case number to identify the subject.

Registration can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.6. Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from the PCCTC. The DF/HCC Sponsor and IRB of record must be notified of any violations to this policy.

3.7. Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, sex, race and ethnicity. Once eligibility has been established and the subject successfully registered, the subject is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8. Data Management

Standardized eCRFs and CRF Completion Guidelines will be created by the PCCTC for the collection of study data. Access and training for PCCTC Medidata Rave EDC will be made available to participating sites upon local regulatory approval.

Data entry should be done with 14 calendar days from being collected. Queries should be answered (response entered into the EDC within 14 calendar days of being issued).

If study forms are not submitted on schedule, the External Sites will periodically receive a Missing Form Report from the PCCTC noting the missing forms.

3.9. Protocol Reporting Requirements

3.9.1. Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor and to the IRB of record.

Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g., enrollment of a subject who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2. Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the PCCTC in a timely manner. The PCCTC will provide training for the requirements for the reporting of violations.

3.9.3. Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4. MONITORING: QUALITY CONTROL

The PCCTC, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1. Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents or have source documents available for review electronically, to the PCCTC for monitoring. External Sites may also be subject to on-site monitoring conducted by the PCCTC.

The PCCTC will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

External Sites will be required to participate in monthly Coordinating Center initiated teleconferences.

Remote Monitoring:External Sites will be required to forward de-identified copies of participants' medical record and source documents to the PCCTC to aid in source data verification. Alternatively, external sites may also give access to subject EMR for remote monitoring by PCCTC.

and/or

On-Site Monitoring:Source documentation verification (SDV) will be conducted on-site by having access to participants' complete medical record and source documents

4.2. Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor and/or PCCTC may increase the monitoring activities at External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.3. Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The following minimum accrual requirements are recommended:
Phase I: 2 per site/annually
Phase II-III: 3 per site/annually.

5. AUDITING: QUALITY ASSURANCE

5.1. DF/HCC Internal Audits

All External Sites are subject to audit by the PCCTC or DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

5.2. Audit Notifications

It is the External Site's responsibility to notify the PCCTC of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the PCCTC, within 12 weeks after the audit date.

5.3. Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The PCCTC must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the IRB as applicable.

5.4. External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.

APPENDIX C: COCKCROFT-GAULT FORMULA

Female: $Cr_{Cl}=[(140–age) \times weight / (72 \times S_{Cr})] \times 0.85$
Male: $Cr_{Cl} = (140–age) \times weight / (72 \times S_{Cr})$

Abbreviations/ Units
Cr_{Cl} (creatinine clearance) = mL/minute
Age = years
Weight = kg
S_{Cr} (serum creatinine) = mg/dL

APPENDIX D: ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core antibody
AST	Aspartate aminotransferase
BID	Twice daily
bPFS	biochemical progression free survival
CLIA	Clinical Laboratory Improvement Amendments
CrCl	Creatinine Clearance
CRF	Case report form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
cfDNA	circulating cell-free DNA
CTMS	Clinical Trials Management System
CYP3A4	Cytochrome P450 3A4
DF/HCC	Dana-Farber/Harvard Cancer Center
DF/PCC	Dana-Farber/Partners CancerCare
dL	Deciliter
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
ECE	Extracapsular extension
ECOG	Eastern Cooperative Oncology Group
EU	European Union
eGFR	estimatedGlomerular filtration rate
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
HBsAg	HBV surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hr	Hour
IHC	Immunohistochemistry
IND	Investigational New Drug
IgG4	Immunoglobulin G4
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional Review board
IV	Intravenous
kg	Kilogram
LDH	Lactase dehydrogenase
LFT	Liver function test
LHRH	Luteinizing hormone-releasing hormone
LLN	Lower limit of normal

LN	Lymph node
mcl	Microliter
mCRPC	Metastatic castration resistant prostate cancer
mg	Milligram
mHSPC	Metastatic hormone sensitive prostate cancer
min	Minute
mL	Milliliter
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N/A	Not applicable
NCI	National Cancer Institute
ODQ	Office of Data Quality
OHRS	Office for Human Research Studies
ORR	Objective response rate
OS	Overall survival
PCR	Partial complete response
PCCTC	Prostate Cancer Clinical Trials Consortium
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetics
PSA	Prostate specific androgen
PSMA	Prostate specific membrane antigen
PT	Prothrombin Time
PTT	Partial thromboplastin time
RBC	Red blood cell
RP	Radical Prostatectomy
RP2D	Recommended Phase 2 Dose
rPFS	radiographic progression free survival
SAE	Serious adverse event
SC	Subcutaneous
SCCHN	Squamous cell carcinoma of the head and neck
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
ULN	Upper limit of normal
US	United States
USPI	United State Product Insert
V_{ss}	Volume of distribution at steady state
WBC	White blood cell
wnl	Within normal limits