

**A Phase II neoadjuvant study of Apalutamide, abiraterone acetate,
prednisone, degarelix and indomethacin in men with localized prostate cancer
pre-prostatectomy**

University of Washington / Seattle Cancer Care Alliance

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Janssen Scientific Affairs, LLC

Title: A Phase II neoadjuvant study of Apalutamide, abiraterone acetate, prednisone, degarelix and indomethacin in men with localized prostate cancer pre-prostatectomy

Objectives: To assess the pathologic effects of 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin in men with localized prostate cancer pre-prostatectomy.

Study Design: Open label, single-site, Phase II study designed to determine the pathologic effects that 3-months (12 weeks) of neoadjuvant therapy has on men with localized prostate cancer.

Primary Center: University of Washington/Seattle Cancer Care Alliance

Participating Institutions: 1 site in the United States.

Medication Support: Janssen Scientific Affairs, LLC

Timeline: This study is planned to complete enrollment in one year, with 2-years of additional follow up following accrual of the last subject.

Concept Rationale: For the majority of patients, prostate cancer is highly curable when caught at an early stage, with 10-year biochemical (i.e., PSA) progression free survival (PFS) and prostate cancer specific overall survival (OS) rates following radical prostatectomy (RP) reported at 68% and 97%, respectively.¹ Historically, those with higher risk localized disease have not had as favorable of outcomes, however. For instance, those with clinical stage T3 disease (i.e., tumor that extends beyond the prostatic capsule) the 10-year biochemical PFS rate has been reported to be 44% and the prostate cancer specific OS rate 85%.² Likewise, >50% of men classified as high risk per the D'Amico classification (PSA >20 ng/ml and/or biopsy Gleason score >7) have been reported to have a biochemical recurrence at 5-years post-RP.^{3,4} Given these relatively poor outcomes following RP in high risk patients, peri-operative (i.e., neoadjuvant or adjuvant) systemic therapy remains an attractive option to attenuate these high rates of relapse.

Neoadjuvant systemic therapy has been established as a standard in bladder, breast, as well as others cancers; however, pre-surgical neoadjuvant approaches have yet to be proven beneficial in prostate cancer.⁵⁻⁸ To date, there have been several randomized trials testing

neoadjuvant hormonal therapies (HT) (i.e., LHRH agonists and antiandrogens), as well as a number of single-arm trials testing chemo-hormonal and novel prostate cancer agents in the pre-surgical space.^{6,7} While most of the data thus far has shown that neoadjuvant treatment can lead to favorable pathologic outcomes (e.g. lower rates of capsular penetration and positive margins), none have shown that these approaches have any impact on long-term outcomes such as biochemical PFS or OS rates.⁹⁻¹³ Of note, while favorable pathologic outcomes post-neoadjuvant therapy have been described, rates of negative pathologic complete response (pCR) in these studies have only been documented in approximately 5% of patients.^{10,14-17} Given this historic lack of clinical efficacy, it seems likely that pre-surgical neoadjuvant therapies may only translate into improved clinical outcomes if a pCR rate substantially higher than 5% is achieved.

Over the past decade a number of new therapies have been proven effective in the treatment of castration-resistant prostate (CRPC) – a more advanced, HT-resistant and ultimately lethal form of prostate cancer.¹⁸ Theoretically, these agents may provide an opportunity to develop more effective neoadjuvant treatment strategies. One such agent, abiraterone acetate, is a potent CYP-17 inhibitor capable of suppressing testosterone from the castrate (i.e., <20 ng/dL) to undetectable range when combined with a GnRH agonist.^{19,20} A recent report by Taplin and colleagues found that 24 weeks of neoadjuvant GnRH agonist plus abiraterone acetate led to a pCR rate of 10%, with an additional 14% of patients achieving a near pCR (defined as ≤ 5 mm residual tumor).¹⁷ Our group has also reported on our efforts to more completely target AR-signaling in men pre-prostatectomy.²¹ In the “Total Androgen Pathway Suppression (TAPS) Study”, reported by Mostaghel, the GnRH agonist goserelin was combined with the following: 1) dutasteride (N=12), 2) bicalutamide and dutasteride (N=10) or 3) bicalutamide, dutasteride, and ketoconazole (N=13) for 3-months pre-prostatectomy. There were two (8.7%) pCR and nine (30.4%) near pCR (defined as ≤ 2 mm residual tumor) between cohort 2 (gosereline, bicalutamide and dutasteride) and cohort 3 (gosereline, bicalutamide, dutasteride, and ketoconazole).

It is notable that the rates of pCR achieved on both the Taplin and Mostaghel studies were comparable to those reported in older neoadjuvant HT trials, leaving the possibility that if a pre-surgical neoadjuvant HT strategy is going to ultimately prove beneficial, maximal inhibition of AR-signaling may be necessary. Fortunately, our toolbox of AR-directed drugs effective in

the CRPC setting continues to expand. In addition to abiraterone acetate, enzalutamide, a potent AR-antagonist, was also approved on the basis of Phase III data that it leads to improvements in OS.^{22,23} Recently, a newer AR-antagonist with several theoretical advantages over enzalutamide, apalutamide, has also entered Phase III clinical testing [clinicaltrials.gov: NCT01946204].

Another explanation for the lack of demonstrable long-term efficacy with neoadjuvant HTs is that these agents may not target more resistant cancer clones and/or emergent resistance pathways. A plausible mechanism by which resistance may develop in this context is via intratumoral steroidogenesis. Indeed, a number of steroidogenic enzymes have been shown to be upregulated in heavily pre-treated prostate cancer patients in comparison to primary prostatectomy samples.²⁴ Specifically, AKR1C3, which is capable of converting DHEA-S metabolites into the potent AR-ligands testosterone and dihydrotestosterone, is frequently found to be upregulated in clinical specimens and to correlate with stage of disease.²⁴⁻²⁶ In addition, cell culture and xenografts models of CRPC have implicated AKR1C3 in the emergence of resistance to both enzalutamide and abiraterone acetate.^{27,28} Importantly, in both the Mostaghel and Taplin trials, a significant residual amount of DHEA-S remained in circulation (~20 µg/dL) following combination GnRH agonist and CYP17 inhibitor therapy.^{17,21} In theory, this persistent serum DHEA-S may serve as a depot for intratumoral conversion to testosterone and DHT, with the final steps of conversion catalyzed by AKR1C3.²⁶

Taken in total, dual targeting of AKR1C3 and AR-signaling is likely to result in a more profound anti-tumor effect than previously reported in the literature. Indomethacin, a non-steroidal anti-inflammatory, has been shown to have the off target effect of inhibiting AKR1C3, and to inhibit prostate cancer cells in pre-clinical models.^{29,30} In addition, synergy between indomethacin and either abiraterone acetate or enzalutamide has been reported in otherwise resistant prostate cancer cell lines.^{27,28} Indomethacin has been FDA approved for decades, and has a long safety track record. Therefore, we propose a pre-surgical neoadjuvant trial testing 12-weeks of indomethacin combined with a regimen designed to completely ablate AR-signaling: abiraterone acetate, apalutamide and degarelix. *The hypothesis of this study is that 12-weeks of combination indomethacin, degarelix, apalutamide and abiraterone acetate will result in a robust anti-tumor effect manifested as a high pathologic complete response rate.*

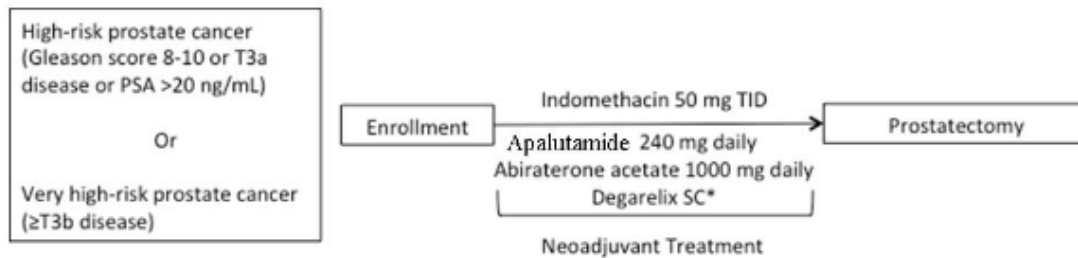
Treatment Plan: This is an open label, multi-site, Phase II neoadjuvant study in men with localized prostate cancer planning to undergo prostatectomy. This study will assess the pCR rate after 3-months (12 weeks) of neoadjuvant treatment with apalutamide, abiraterone acetate, degarelix and indomethacin as assessed on prostatectomy specimens.

All subjects must have localized, high or very-high risk (per NCCN criteria) prostate cancer and be willing to undergo prostatectomy as primary treatment. Subjects will be treated with neoadjuvant therapy for a total of 3-months (12 weeks) prior to prostatectomy. Therapy will consist of apalutamide, abiraterone acetate, degarelix and indomethacin. Abiraterone acetate, degarelix and indomethacin will be dosed at their respective FDA approved dose. These dosages are as follows: abiraterone acetate 1000 mg by mouth daily, indomethacin 50 mg by mouth three times daily (TID) and degarelix 240 mg subcutaneous (SC) injection on day 1 followed by two additional 80 mg SC injections every 4 weeks. All men will also be treated with prednisone 5 mg by mouth twice daily while on abiraterone acetate in order to blunt its associated mineralocorticoid side effects.* Apalutamide was recently approved by the FDA for use in men with non-metastatic castration resistant prostate cancer on the basis of Phase III data showing that it significantly prolonged the time to development of metastatic disease. Apalutamide is still under development as an investigational product for other types of prostate cancer. Apalutamide will be administered at the FDA approved dose for treating non-metastatic CRPC, 240 mg daily by mouth. The GnRH antagonist degarelix was chosen over other forms of HT (i.e., GnRH agonists) given that the neoadjuvant treatment period is relatively short at 12-weeks, and degarelix has been shown to result in more rapid castration and PSA suppression compared to the GnRH agonist leuprolide.³¹ Following 12-weeks of neoadjuvant treatment, patients will undergo prostatectomy. Lymph node dissection will be required for all patients with a $\geq 2\%$ estimated risk of nodal metastases per the Partin Nomogram.³² Patients should have clinical follow-up visits following prostatectomy per the standard practice of their treating urologist.

* Note: Because steroids can lead to hyperglycemia, subjects with a history of diabetes will be required to monitor their daily fasting blood glucose using a home glucometer. Fasting blood glucose values will be reviewed at scheduled follow up appointments. Patients will also be instructed to contact their provider if their fasting glucose is >150 mg/dL. Based on the daily fasting blood glucose levels, anti-hyperglycemic medications will be adjusted by the treating oncologist and/or the patient's primary care doctor or endocrinologist.

However, at a minimum, patients should be evaluated in clinic 28 days following their prostatectomy. Of note, the combination of apalutamide, abiraterone acetate and GnRH analogue therapy has been shown to have an acceptable safety profile when administered at these doses [see Investigator's Brochure].

Study scheme:



*Three doses of subcutaneous (SC) degarelix will be administered. Degarelix is administered every 4-weeks, with a 240 mg loading dose given for the first SC injection followed by 80 mg SC injections thereafter.

This study will be open to patients age ≥ 18 years who have a histologic diagnosis of prostatic adenocarcinoma and are planning to undergo prostatectomy as primary treatment of their prostate cancer. All patients must have high to very high-risk prostate cancer as defined per the NCCN criteria (i.e. high-risk = Gleason score 8-10 or T3a or PSA > 20 ng/mL; very high-risk = T3b-T4).

The primary endpoint will be the pathologic complete response (pCR) rate (i.e., no evidence of tumor) as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin. Secondary pathologic endpoints to be assessed from prostatectomy specimens following 3-months (12 weeks) of neoadjuvant therapy include: the negative margin rate, negative nodal metastases rate, near pCR (i.e., ≤ 5 mm of residual tumor) rate, the rate of pathologic T3 disease and apoptotic index (i.e. percentage of tumor cells undergoing apoptosis) as determined by cleaved caspase-3 immunohistochemistry. Other secondary endpoints will include: the proportion of men who receive adjuvant radiation therapy within 1-year of prostatectomy, the biochemical (i.e., PSA) progression free survival estimate two years after the last patient has accrued, the overall survival estimate two years after the last patient has accrued and safety (as assessed by CTCAE version 4.0).

In addition, excess tissue from prostatectomy specimens and plasma samples will be stored at -80°C . These biologic specimens will be used for additional correlative work. When possible, we also conduct exploratory biomarker studies on pre-treatment/archival biopsy specimens. Examples of studies to be conducted may include, but are not limited to: PTEN immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH, RNAseq analysis, serum drug/androgen levels and intraprostatic drug/androgen levels.

Study Population: Men with high (Gleason score 8-10 or T3a or PSA > 20 ng/mL) or very-high risk (T3b-T4) prostate cancer per the NCCN criteria who are willing to undergo radical prostatectomy as primary treatment for their prostate cancer.

Number of Patients: For this study we plan on enrolling 20 evaluable patients. Up to 22 patients will be enrolled if necessary in order to account for a potential 10% dropout rate.

Inclusion Criteria:

1. Willing and able to provide written informed consent.
2. Age ≥ 18 years
3. Eastern cooperative group (ECOG) performance status ≤ 2
4. Documented histologically confirmed adenocarcinoma of the prostate
5. Willing to undergo prostatectomy as primary treatment for localized prostate cancer
6. High risk prostate cancer (per NCCN criteria): Gleason score 8-10 or T3a or PSA > 20 ng/mL
or
Very-high risk prostate cancer (per NCCN criteria): T3b-T4
7. Serum testosterone ≥ 150 ng/dL
8. Able to swallow the study drugs whole
9. Willing to take abiraterone acetate on an empty stomach (no food should be consumed at least two hours before and for one hour after dosing).
10. Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months

following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

11. Medications known to lower the seizure threshold (see list under prohibited meds) must be discontinued or substituted at least 4 weeks prior to study entry.

Exclusion Criteria:

1. Prior local therapy to treat prostate cancer (e.g. radical prostatectomy, radiation therapy, brachytherapy)
2. Prior use of apalutamide, abiraterone acetate or degarelix
3. Prior or ongoing systemic therapy for prostate cancer including, but not limited to:
 - a. Hormonal therapy (e.g., leuprolide, goserelin, triptorelin, degarelix)
 - b. CYP-17 inhibitors (e.g., ketoconazole)
 - c. Antiandrogens (e.g., bicalutamide, nilutamide)
 - d. Second generation antiandrogens (e.g., enzalutamide, apalutamide)
 - e. Immunotherapy (e.g., sipuleucel-T, ipilimumab)
 - f. Chemotherapy (e.g., docetaxel, cabazitaxel)
4. Evidence of serious and/or unstable pre-existing medical, psychiatric or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study
5. Any psychological, familial, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule.
6. Abnormal bone marrow function (absolute neutrophil count [ANC] $<1500/\text{mm}^3$, platelet count $<100,000/\text{mm}^3$, hemoglobin <9 g/dL)
7. Abnormal liver function (total bilirubin >1.5 x upper limit of normal [ULN]; AST or ALT ≥ 2.5 x ULN)
Note: In subjects with Gilbert's syndrome, if total bilirubin is $>1.5 \times$ ULN, measure direct and indirect bilirubin and if direct bilirubin is $\leq 1.5 \times$ ULN, subject may be eligible
8. Abnormal kidney function (GFR <45 mL/min)
9. Serum albumin <3 g/dL

10. Serum potassium <3.5 mmol/L
11. Seizure or known condition that may pre-dispose to seizure (e.g. prior stroke within 1 year to randomization, brain arteriovenous malformation, Schwannoma, meningioma, or other benign CNS or meningeal disease which may require treatment with surgery or radiation therapy)
12. Severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to randomization
13. History of stroke within the last 5-years
14. History of gastrointestinal (GI) bleed requiring transfusion
15. History of peptic ulcer disease requiring treatment within the last 5-years
16. History of asthma that is NSAID-induced or with asthma that is classified as ‘mild-persistent’ or worse (based on symptoms occurring more than 2 days per week)
17. Uncontrolled hypertension
18. Gastrointestinal disorder affecting absorption
19. Active infection (e.g., human immunodeficiency virus [HIV] or viral hepatitis)
20. Any chronic medical condition requiring a higher dose of corticosteroid than 10 mg prednisone/prednisolone once daily
21. Any condition that in the opinion of the investigator, would preclude participation in this study
22. Child Pugh Class B & C
23. Pre-existing viral hepatitis

Primary Endpoints:

The rate of pCR (i.e., no evidence of residual tumor) as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.

Secondary Endpoints:

1. The negative margin rate as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
2. The rate of near pCR (i.e. ≤ 5 mm of residual tumor) as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
3. The rate of pathologic T3 disease as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
4. The rate of nodal metastases as assessed on surgical lymph node specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
5. Apoptotic index (i.e., percentage of tumor cells undergoing apoptosis) as determined by cleaved caspase-3 immunohistochemistry following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
6. The proportion of men who receive adjuvant radiation therapy within 1-year of prostatectomy.
7. The biochemical (i.e., PSA) progression free survival estimate two years after the last patient has accrued (i.e., confirmed PSA post-radical prostatectomy ≥ 0.2 ng/mL).
8. The overall survival estimate two years after the last patient has accrued.
9. Safety as assessed by the incidence and severity of adverse events and serious adverse events graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
10. Exploratory biomarker Assessment. Examples of these may include, but are not limited to: assessment for genomic PTEN loss via fluorescence in situ hybridization (FISH), PTEN immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH, RNAseq analysis, serum drug/androgen levels and intraprostatic drug/androgen levels.

Statistical Considerations: This is an open-label, multi-site Phase II trial testing 3-months (12-weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin. The primary endpoint will be the pCR rate as assessed from prostatectomy specimens. Prior neoadjuvant hormonal therapy trials have documented pCR rates on the order of 5%, while still failing to show improvements in biochemical PFS or OS.^{10,11,14} Therefore, we would consider a pCR rate of $\leq 5\%$ to be insufficient evidence of activity to warrant further study in this patient population. The minimum level of activity we would require to consider further study with the proposed regimen would be a pCR rate of $\geq 25\%$. Therefore, based on an exact binomial test, if we observe ≥ 3 pCR out of a total sample size of 20, we would have 91% power at a one-sided alpha of 7.5% to detect a difference between $H_0 = 5\%$ and a $H_1 = 25\%$.³³

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1. Introduction

1.1. Overview and Rationale

For the majority of patients, prostate cancer is highly curable when caught at an early stage, with 10-year biochemical (i.e., PSA) progression free survival (PFS) and prostate cancer specific overall survival (OS) rates following radical prostatectomy (RP) reported at 68% and 97%, respectively.¹ Historically, those with higher risk localized disease have not had as favorable of outcomes, however. For instance, those with clinical stage T3 disease (i.e. tumor that extends beyond the prostatic capsule) the 10-year biochemical PFS rate has been reported to be 44% and the prostate cancer specific OS rate 85%.² Likewise, >50% of men classified as high risk per the D'Amico classification (PSA >20 ng/ml and/or biopsy Gleason score >7) have been reported to have a biochemical recurrence at 5-years post-RP.^{3,4} Given these relatively poor outcomes following RP in high risk patients, peri-operative (i.e., neoadjuvant or adjuvant) systemic therapy remains an attractive option to attenuate these high rates of relapse.

Neoadjuvant systemic therapy has been established as a standard in bladder, breast, as well as others cancers; however, pre-surgical neoadjuvant approaches have yet to be proven beneficial in prostate cancer.⁵⁻⁸ To date, there have been several randomized trials testing neoadjuvant hormonal therapies (HT) (i.e., LHRH agonists and antiandrogens), as well as a number of single-arm trials testing chemo-hormonal and novel prostate cancer agents in the pre-surgical space.^{6,7} While most of the data thus far has shown that neoadjuvant treatment can lead to favorable pathologic outcomes (e.g., lower rates of capsular penetration and positive margins), none have shown that these approaches have any impact on long-term outcomes such as biochemical PFS or OS rates.⁹⁻¹³ Of note, while favorable pathologic outcomes post-neoadjuvant therapy have been described, rates of negative pathologic complete response (pCR) in these studies have only been documented in approximately 5% of patients.^{10,14-17} Given this historic lack of clinical efficacy, it seems likely that pre-surgical neoadjuvant therapies may only translate into improved clinical outcomes if a pCR rate substantially higher than 5% is achieved.

Over the past decade a number of new therapies have been proven effective in the treatment of castration-resistant prostate (CRPC) – a more advanced, HT-resistant and

ultimately lethal form of prostate cancer.¹⁸ Theoretically, these agents may provide an opportunity to develop more effective neoadjuvant treatment strategies. One such agent, abiraterone acetate, is a potent CYP-17 inhibitor capable of suppressing testosterone from the castrate (i.e. <20 ng/dL) to undetectable range when combined with a GnRH agonist.^{19,20} A recent report by Taplin and colleagues found that 24 weeks of neoadjuvant GnRH agonist plus abiraterone acetate led to a pCR rate of 10%, with an additional 14% of patients achieving a near pCR (defined as ≤ 5 mm residual tumor).¹⁷ Our group has also reported on our efforts to more completely target AR-signaling in men pre-prostatectomy.²¹ In the “Total Androgen Pathway Suppression (TAPS) Study,” reported by Mostaghel, the GnRH agonist goserelin was combined with the following: 1) dutasteride (N=12), 2) bicalutamide and dutasteride (N=10) or 3) bicalutamide, dutasteride, and ketoconazole (N=13) for 3-months pre-prostatectomy. There were two (8.7%) pCR and nine (30.4%) near pCR (defined as ≤ 2 mm residual tumor) between cohort 2 (gosereline, bicalutamide and dutasteride) and cohort 3 (gosereline, bicalutamide, dutasteride, and ketoconazole).

It is notable that the rates of pCR achieved on both the Taplin and Mostaghel studies were comparable to those reported in older neoadjuvant HT trials, leaving the possibility that if a pre-surgical neoadjuvant HT strategy is going to ultimately prove beneficial, maximal inhibition of AR-signaling may be necessary. Fortunately, our toolbox of AR-directed drugs effective in the CRPC setting continues to expand. In addition to abiraterone acetate, enzalutamide, a potent AR-antagonist, was also approved on the basis of Phase III data that it leads to improvements in OS.^{22,23} Recently, a newer AR-antagonist with several theoretical advantages over enzalutamide, apalutamide, has also entered Phase III clinical testing [clinicaltrials.gov: NCT01946204].

Another explanation for the lack of demonstrable long-term efficacy with neoadjuvant HTs is that these agents may not target more resistant cancer clones and/or emergent resistance pathways. A plausible mechanism by which resistance may develop in this context is via intratumoral steroidogenesis. Indeed, a number of steroidogenic enzymes have been shown to be upregulated in heavily pre-treated prostate cancer patients in comparison to primary prostatectomy samples.²⁴ Specifically, AKR1C3, which is capable of converting DHEA-S metabolites into the potent AR-ligands testosterone and dihydrotestosterone, is

frequently found to be upregulated in clinical specimens and to correlate with stage of disease.²⁴⁻²⁶ In addition, cell culture and xenografts models of CRPC have implicated AKR1C3 in the emergence of resistance to both enzalutamide and abiraterone acetate.^{27,28} Importantly, in both the Mostaghel and Taplin trials, a significant residual amount of DHEA-S remained in circulation (~20 µg/dL) following combination GnRH agonist and CYP17 inhibitor therapy.^{17,21} In theory, this persistent serum DHEA-S may serve as a depot for intratumoral conversion to testosterone and DHT, with the final steps of conversion catalyzed by AKR1C3.²⁶

Taken in total, dual targeting of AKR1C3 and AR-signaling is likely to result in a more profound anti-tumor effect than previously reported in the literature. Indomethacin, a non-steroidal anti-inflammatory, has been shown to have the off target effect of inhibiting AKR1C3, and to inhibit prostate cancer cells in pre-clinical models.^{29,30} In addition, synergy between indomethacin and either abiraterone or enzalutamide has been reported in otherwise resistant prostate cancer cell lines.^{27,28} Indomethacin has been FDA approved for decades, and has a long safety track record. Therefore, we propose a pre-surgical neoadjuvant trial testing 12-weeks of indomethacin combined with a regimen designed to completely ablate AR-signaling: abiraterone acetate, apalutamide and degarelix. *The hypothesis of this study is that 12-weeks of combination indomethacin, degarelix, apalutamide and abiraterone acetate will result in a robust anti-tumor effect manifested as a high pathologic complete response rate.*

1.2. Androgen/Androgen Receptor Directed Therapies

The initial management of advanced prostate cancer, as well as higher risk localized prostate cancer being treated with radiation therapy, typically involves targeting the androgen/androgen receptor (AR) signaling axis through lowering serum testosterone levels to the castrate range (i.e. testosterone <20-50 ng/dL).^{18,34} This is accomplished either through surgical castration or now more commonly medical castration with a GnRH agonist/antagonist [i.e., hormonal therapy (HT)]. Hormonal therapy is initially highly effective in those with metastatic prostate cancer, leading to objective responses in >85% of individuals.³⁵ Unfortunately, after a variable period of symptom relief, androgen ablation invariably ceases to suppress prostate cancer growth and patients eventually succumb to their

disease. This disease state defined by progression in spite of androgen ablation has been termed castrate resistant prostate cancer (CRPC) (Figure 1).³⁶

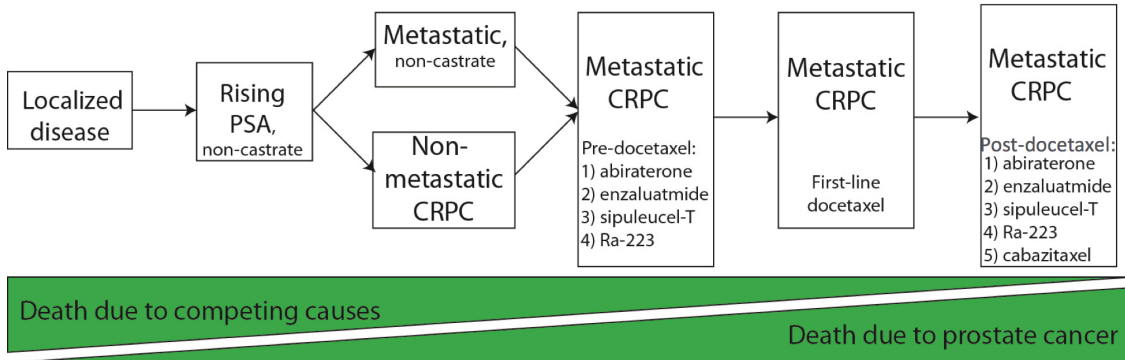


Figure 1: Prostate cancer clinical states model (adapted from Scher *et al*, 2000).

Recently it has come to light that CRPC is still largely dependent on androgen/AR axis signaling. This realization has led to the development of multiple newer AR directed therapies. Mechanistically these agents primarily work either through ligand depletion (e.g., abiraterone acetate) or through interference with AR trafficking and signaling (e.g., enzalutamide, apalutamide).¹⁸ The current standard treatment of CRPC entails the continuation of hormonal therapy with the sequential administration of a number of secondary androgen-directed agents (e.g., abiraterone acetate, enzalutamide), immunotherapeutics (e.g., sipuleucel-t), radiopharmaceuticals (e.g., radium-223) and/or chemotherapeutics (e.g., docetaxel, cabazitaxel) (Figure 1).^{18-20,22,23,37-39}

1.2.1. Abiraterone Acetate

Developed through rational design based on a parent pregnenolone structure, abiraterone acetate functions through inhibition of cytochrome P450-17 (CYP-17), a key family of enzymes involved in gonadal, adrenal and intratumoral androgen synthesis.⁴⁰⁻⁴³ When given in conjunction with a GnRH analogue, it has the ability to rapidly drive castrate level testosterone (i.e. <20-50 ng/dL) to undetectable.^{44,45} Unlike ketoconazole, another CYP-17 inhibitor used in the CRPC setting, abiraterone acetate is highly specific for the CYP-17 family of enzymes, making it generally better tolerated than ketoconazole.^{42,46,47} It can lead to mineralocorticoid excess, however, through a compensatory elevation in

adrenocorticotrophic hormone (ACTH) that occurs in response to depressed cortisol levels. When prednisone is co-administered with abiraterone acetate, mineralocorticoid associated side effects (e.g., fluid retention, hypokalemia and hypertension) are mostly prevented, although these are observed more frequently in those receiving abiraterone acetate compared to placebo.^{19,20,48} Abiraterone acetate is currently FDA approved for the treatment of CRPC in patients who are either pre- or post-docetaxel. In addition, abiraterone acetate was more recently FDA approved for the treatment of metastatic high-risk castration-sensitive prostate cancer on the basis of Phase III data demonstrating a robust overall survival advantage in this population.⁴⁹

1.2.1.1. Abiraterone Acetate Clinical Trial Experience

Two dose escalation Phase I studies were completed utilizing abiraterone acetate.^{44,50} Neither study documented dose-limiting toxicities, however, side effects of note included: hypertension (12-29%), hypokalemia (24-48%) and peripheral edema (5-24%). This side effect profile was felt most likely to be a result of mineralocorticoid excess secondary to a compensatory elevation in ACTH occurring in the context of partially blocking adrenal steroid synthesis. These side effects were managed with eplerenone, beta-blockers, diuretics and/or corticosteroids. Furthermore, these studies provided preliminary evidence for abiraterone acetate's efficacy in men with chemotherapy naïve CRPC.

A subsequent Phase II study evaluated abiraterone acetate in men with CRPC post-docetaxel treatment.⁵¹ This study incorporated prednisone 5 mg twice daily into the treatment regimen in an effort to mitigate the aforementioned mineralocorticoid associated side effects. At a dose of 1000 mg daily, abiraterone acetate was found to produce PSA declines of at least 50% in 22/58 (36%) men. Partial responses by Response Evaluation Criteria in Solid Tumors (RECIST) criteria were seen in 4/22 (18%) patients with evaluable tumors. Importantly, no significant hypertension or hypokalemia was noted – likely due to the co-administration of prednisone.

Proof of principle that further androgen suppression is effective in controlling CRPC was provided for in the landmark Phase III COU-AA-301 trial. In that study it was demonstrated that abiraterone acetate, when given to men with CRPC previously treated with docetaxel, resulted in a significant reduction in the risk of death compared to placebo (HR 0.65, 95% CI, 0.54-0.77; $P < 0.001$).¹⁹ Subsequently the COU-AA-302 trial demonstrated similar efficacy in men with CRPC pre-docetaxel (HR 0.79, 95% CI, 0.66-0.96; $P < .0151$).²⁰ These two trials demonstrated a higher incidence of mineralocorticoid associated side effects in spite of the co-administration of prednisone. Hypokalemia, peripheral edema and hypertension occurred at approximate rates of 17%, 28-31% and 10-22% in the abiraterone acetate cohorts respectively. Other adverse events observed were generally low grade. Of note there did appear to be higher rates of fatigue, arthralgias, aminotransferase abnormalities and non-fatal cardiac events with abiraterone acetate. Overall, abiraterone acetate was felt to be generally well tolerated, however. A summary of the adverse events observed in these two Phase III trials are listed in Table 1. Ultimately, on the basis of the COU-AA-301 and COU-AA-302 trials abiraterone acetate was approved in the post- and pre-docetaxel setting respectively.

More recently, the Phase III LATITUDE study testing abiraterone acetate in men with metastatic castration-sensitive prostate cancer was completed.⁴⁹ This study showed a robust overall survival advantage in men with at least two of the three following high-risk factors: a Gleason score of 8 or more, at least three bone lesions, and the presence of measurable visceral metastasis. The median overall survival was significantly longer in the abiraterone acetate group than in the placebo group (not reached vs. 34.7 months) (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76; $P < 0.001$). Adverse events on the LATITUDE study were consistent with those observed in COU-AA-301 and COU-AA-302 (Table 2).

COU-AA-301

COU-AA-302

Adverse Event	COU-AA-301				COU-AA-302			
	Abiraterone acetate + Prednisone (n=791)		Placebo + Prednisone (n=394)		Abiraterone acetate + Prednisone (n=542)		Placebo + Prednisone (n=540)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Anemia	23	7.5	26	7.4	-	-	-	-
Thrombocytopenia	4	1.4	3	0.5	-	-	-	-
Neutropenia	1	0.1	0.3	0.3	-	-	-	-
Febrile neutropenia	0	0	0	0	-	-	-	-
Diarrhea	18	0.6	53	1.3	22		18	
Fatigue	44	8.3	169	9.9	39		34	
Asthenia	13	2.3	52	2	-	-	-	-
Back pain	30	5.9	129	9.6	32		32	
Nausea	30	1.6	124	2.5	-	-	-	-
Vomiting	21	1.8	97	2.8	-	-	-	-
Hematuria	8	1.4	31	2.3	-	-	-	-
Abdominal pain	12	2	44	1.5	-	-	-	-
Pain in arm or leg	17	2.4	79	5	17		16	
Dyspnea	13	1.3	46	2.3	-	-	-	-
Constipation	26	1	120	1	23		19	
Pyrexia	9	0.4	35	1.3	-	-	-	-
Arthralgia	27	4.2	89	4.1	28		24	
Urinary tract infection	12	2.1	28	0.5	-	-	-	-
Pain	2	0.6	19	1.8	-	-	-	-
Bone pain	25	5.6	110	7.4	20		19	
Fluid retention or edema	31	2.3	88	1	28	0.7	24	2
Hypokalemia	17	3.8	33	0.8	17	2	13	2
Cardiac disorder*	13	4.1	42	2.3	19	6	16	3

Liver-function test abnormalities or									
Hepatotoxicity	10	3.4	32	3	4.2	8	9.8	3	
Hypertension	10	1.3	31	0.3	-	-	-	-	
Hot flush	-	-	-	-	22		18		
Muscle spasm	-	-	-	-	14		20		
Cough	-	-	-	-	17		14		

Table 1: Adverse events observed on the COU-AA-301 [de Bono *et al*, 2011] and COU-AA-302 [Ryan *et al*, 2013] trials.

*Cardiac disorders included: ischemic heart disease, myocardial infarction, supraventricular tacharrhythmias, ventricular tachyarrhythmias, cardiac failure and possible arrhythmia-related tests, signs and symptoms

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
	All Grades ¹ %	Grade 3-4 %	All Grades %	Grade 3-4 %
General disorders				
Fatigue	39	2.2	34	1.7
Edema ²	25	0.4	21	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort ³	30	2.0	25	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23	0.4	19	0.6
Diarrhea	22	0.9	18	0.9
Dyspepsia	11	0.0	5.0	0.2
Vascular disorders				
Hot flush	22	0.2	18	0.0
Hypertension	22	3.9	13	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17	0.0	14	0.2
Dyspnea	12	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	14	0.2	11	0.0
Injury, poisoning and procedural complications				
Contusion	13	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	13	0.0	8.0	0.0
Nasopharyngitis	11	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

¹ Adverse events graded according to CTCAE version 3.0.

² Includes terms Edema peripheral, Pitting edema, and Generalized edema.

³ Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness.

Table 2: Adverse events observed on the LATITUDE trial [Fizazi, et al. 2017].

Abiraterone acetate plus the GnRH agonist leuprolide have also been tested in the neoadjuvant setting. Taplin and colleagues recently reported on the results of a randomized Phase II study.¹⁷ In that trial men were randomized between 24 weeks of neoadjuvant GnRH agonist plus 12 weeks of abiraterone acetate (N=28) and 24 weeks of both neoadjuvant GnRH plus abiraterone acetate (N=30). That trial demonstrated a negative margin rate of 90% and pCR rate of 10% in the cohort receiving 24 weeks of both leuprolide and abiraterone acetate, with an additional 14% of patients achieving a near pCR (defined as ≤ 5 mm residual tumor). The cohort

receiving 24 weeks of GnRH agonist and 12 weeks of abiraterone acetate achieved a negative margin rate of 81%, a pCR rate of 4% and a near pCR rate of 0%.

Differences in pathologic outcomes between cohorts were not statistically significant; although, the trial was not powered to detect these differences.

1.2.2. Apalutamide

Apalutamide works through competitive AR inhibition and unlike the older anti-androgens (e.g., bicalutamide, nilutamide), is a pure AR antagonist. It additionally has the ability to prevent AR nuclear translocation and DNA binding to nuclear response elements.⁵² It is generally felt to function similarly to enzalutamide, another AR targeted therapy approved for men with mCRPC pre- and post-docetaxel. In docetaxel pre-treated patients enzalutamide was shown to result in a 37% reduced risk of death compared to placebo (HR 0.63, 95% CI, 0.53-0.75; P<0.001), and in docetaxel naïve patients it led to a 29% reduction in the risk of death compared to placebo (HR 0.71, 95% CI, 0.60 to 0.84; P<0.001).^{53,54} Preclinical work comparing apalutamide to enzalutamide, however, demonstrated that apalutamide may have several theoretical advantages over enzalutamide.⁵⁵ Namely, in mouse models apalutamide was able to achieve a maximal therapeutic effect at 30 mg/kg/day compared to 100 mg/kg/day of enzalutamide (Figure 2). apalutamide is also able to achieve equivalent intra-tumoral concentrations at a lower plasma steady state concentration compared to enzalutamide. Finally, while high-dose apalutamide (i.e., 3-fold higher than the Phase II dose of 240 mg/day based on dose per m² body surface area and standard species conversion factors) has resulted in tremors and seizures in dogs, apalutamide is less effective than enzalutamide at crossing the blood-brain barrier. This may result in decreased CNS toxicities in those treated with apalutamide compared to enzalutamide. For instance, while enzalutamide has been implicated in causing seizures in a minority of patients, possibly through off target inhibition of GABA-A, no seizure have occurred in subjects treated on the Phase I/II studies of apalutamide (see apalutamide Investigator's Brochure).^{53,56}

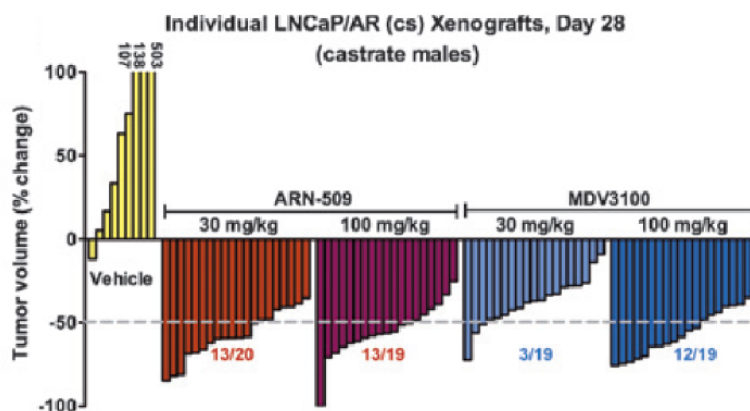


Figure 2: Apalutamide comparative efficacy to enzalutamide (MDV-3100) in mouse xenograft models. Apalutamide is able to achieve maximal therapeutic effect at 30 mg/kg/day compared to 100 mg/kg/day of enzalutamide.

1.2.2.1. Apalutamide Clinical Trial Experience

The first in human Phase I/II study of apalutamide is currently ongoing [Clinicaltrials.gov, NCT01171898]. This study is evaluating men with mCRPC. Results from the Phase I portion of this study (N=30) demonstrated that apalutamide is generally safe and well tolerated. At the maximum tested dose of 300 mg daily by mouth only 1/4 subjects experienced a grade 3 adverse event (AE) (abdominal pain). The other three individuals receiving a dose of 300 mg daily did not experience dose-limiting toxicities (DLT) (see Apalutamide Investigator's Brochure). Common grade 1-2 AEs observed in the Phase I study included: fatigue (47%), nausea (30%), abdominal pain (20%), arthralgias (13%), diarrhea (17%), dyspnea (13%) and peripheral sensory neuropathy (13%). Five patients experienced serious adverse events and one patient discontinued the study due to an adverse event (atrial fibrillation) deemed unrelated to study treatment. PSA declines $\geq 50\%$ were observed in 12 (55%) patients. ^{18}F -16 β -fluoro-5 α -dihydrotestosterone (FDHT) PET evaluation demonstrated AR blockade at four weeks across multiple doses. Given promising activity observed across all doses in conjunction with no appreciable difference in FDHT-PET uptake at 240 mg compared to 300 mg of apalutamide, a dose of 240 mg has been selected for Phase II testing.^{52,53}

The Phase II portion of this study is ongoing and will evaluate three expansion cohorts with a total enrollment of 97 patients (see Apalutamide Investigator's Brochure).⁵³ The primary endpoint of the Phase II study is PSA response at 12 weeks according to Prostate Cancer Working Group 2 (PCWG2) Criteria.⁵⁷ All cohorts will consist of men who are chemotherapy naïve and have CRPC. Specific cohorts are: 1) non-metastatic CRPC, 2) mCRPC pre-abiraterone acetate and 3) mCRPC post-abiraterone acetate. Preliminary results for the non-metastatic CRPC cohort, mCRPC pre-abiraterone acetate cohort and the mCRPC post-abiraterone acetate cohort demonstrated $\geq 50\%$ PSA declines at 12-weeks in 89%, 88% and 22% of subjects, respectively (see Apalutamide Investigator's Brochure).⁵⁸ As of 31 March 2017, the most common drug-related treatment-related adverse events (TEAEs) across Cohorts 1, 2, and 3 respectively were fatigue, diarrhea, and nausea. Most AEs across the cohorts were Grade 1 or 2. Grade 3 AEs in >1 subject included hypertension and hyponatremia, malignant melanoma, and fatigue in Cohort 1; anemia in Cohort 2; and back pain in Cohort 3. Grade 4 TEAEs included abdominal adhesions, duodenal ulcer, anemia, and glioblastoma multiforme in Cohort 1; dehydration, asthenia, and confusional state in Cohort 2; no Grade 4 TEAEs were reported in Cohort 3. The most common TEAE leading to discontinuation was fatigue. Serious adverse events were reported in 32 (33%) subjects. No SAEs in Phase 2 were assessed as drug-related. No new deaths or seizures were reported for this Phase 2 portion of the study. Hypothyroidism or increased blood thyroid stimulating hormone (TSH) was reported as an TEAE in in all 3 cohorts. Most TEAEs of rash or pruritus were Grade 1 or 2 in severity, were treated topically, and none were reported as serious. Over the Phase 2 duration of the study, the TEAE of fracture was reported in Cohorts 1 and 2, and none of the events were considered related to study drug or led to discontinuation of study drug. Falls were only reported in Cohort 1, none of the TEAEs of fall were reported as serious, and none led to discontinuation of study drug. Refer to the apalutamide Investigator's Brochure for additional details on AEs.

Apalutamide was recently approved by the FDA for use in men with non-metastatic CRPC on the basis of Phase III data showing that it significantly prolonged the time to development of metastatic disease⁵⁹. In the pivotal Phase III study, patients with a PSA doubling time ≤ 10 months were randomized 2:1 between apalutamide or placebo. Men in the apalutamide group had a median metastasis-free survival of 40.5 months vs. 16.2 months in the placebo group (HR = 0.28; 95% CI 0.23 to 0.35; $P < 0.001$).⁵⁹ The following adverse events were considered to be related to apalutamide and occurred at a higher rate in the apalutamide group than in the placebo group: fatigue (30.4% vs. 21.1%), rash (23.8% vs. 5.5%), falls (15.6% vs. 9.0%), fracture (11.7% vs. 6.5%), hypothyroidism (8.1% vs. 2.0%), and seizure (0.2% vs. 0%). Several additional studies evaluating apalutamide are ongoing, including a Phase I trial evaluating it in combination with abiraterone acetate in a mCRPC population [clinicaltrials.gov, NCT01792687].

1.3. Indomethacin and AKR1C3 Inhibition

Indomethacin is a non-steroidal anti-inflammatory that has been approved for the treatment of mild to moderate acute pain in adults for several decades. Pre-clinical work has shown that it has the off target effect of inhibiting AKR1C3, a steroidogenic enzyme responsible for converting androgenic substrates downstream of DHEA-S into the potent androgens testosterone and dihydrotestosterone (DHT) (Figure 3).^{26,30} Our group has shown that following neoadjuvant treatment with a CYP-17 inhibitor (i.e., abiraterone acetate or ketoconazole) plus GnRH analogue, persistent DHEA-S (~ 20 $\mu\text{g/dL}$) is present in circulation. It has been hypothesized that this persistent DHEA-S may serve as an intratumoral depot for conversion to testosterone and DHT via AKR1C3 – potentially driving resistance.^{17,21,26}

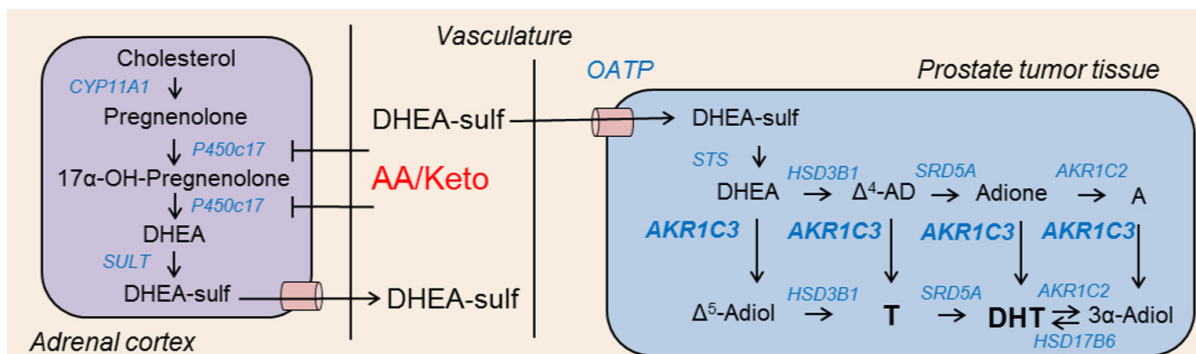


Figure 3: following CYP-17 inhibition with abiraterone acetate (AA) or ketoconazole (Keto), DHEA-S serum concentrations remain high (~20 µg/dL) and may serve as a precursor for intracrine production of testosterone and DHT. Resistance to CYP-17 inhibition may proceed via intratumoral AKR1C3 over expression coupled with the DHEA-S depot.²⁶

In support of its viability as a drug target, AKR1C3 is also frequently found to be upregulated in clinical specimens and to correlate with stage of disease.²⁴⁻²⁶ In addition, cell culture and xenografts models of CRPC have implicated AKR1C3 in the emergence of resistance to both enzalutamide and abiraterone acetate.^{27,28} Importantly, indomethacin has been shown to inhibit enzalutamide resistant cell lines (*in vitro* and *in vivo*) and to result in synergistic cell death when used in combination with enzalutamide.²⁷ Given that chronic COX inhibition has been associated with deleterious side effects, indomethacin analogues that specifically inhibit AKR1C3 are under development.³⁰ However, it is anticipated that a short course of indomethacin, as outlined in this protocol, should be well tolerated and offer a cost effective means to inhibit steroidogenesis within the tumor microenvironment.

1.4. Exploratory Biomarkers

We plan to incorporate a number of exploratory biomarkers into this study design. In the event that this trial fails to meet its primary endpoint, these correlatives will provide valuable insights into potential mechanisms of resistance to combinatorial AR-signaling suppression. Given our rapidly evolving understanding of prostate cancer pathobiology, genetics and epigenetics, it is impossible to prospectively define all the relevant biomarkers for the patient population enrolled on this study. So as to not miss an opportunity to assess a yet to be described biomarker; we will plan to store prostatectomy specimens and plasma samples at

-80°C for future biomarker work. When possible, we also conduct exploratory biomarker studies on pre-treatment/archival biopsy specimens. Key biomarkers and exploratory analyses we plan to conduct are described below.

1.4.2. PTEN

PTEN is a tumor suppressor gene implicated in the tumorigenesis and progression of prostate cancer.⁶⁰⁻⁶³ It plays an important role in the modulation of phosphatidylinositol-3-kinase (PI3K) signaling, most likely through preventing the activation of the protein kinase Akt.⁶⁴ Loss or inactivation of PTEN can in turn lead to the upregulation of PI3K/AKT signaling as well as downstream mTOR signaling.⁶⁵ Genomic PTEN loss as determined through Fluorescence in situ hybridization (FISH) as well as lost PTEN expression as determined by immunohistochemistry (IHC) have been associated with adverse pathological markers as well as increased risk of recurrence following prostatectomy.⁶⁶⁻⁷⁰

1.4.3. MYC

MYC is an onco-protein that functions as a transcription factor, regulating cell proliferation, metabolism, protein synthesis, mitochondrial function and stem cell renewal.⁷¹ Like PTEN, its expression has been associated with prostate cancer initiation and progression.⁷¹⁻⁷³ Indeed, MYC has been shown to be able to transform benign prostate cancer cells in a single step and its overexpression has been documented at the earliest stages of transformation in prostatic intraepithelial neoplasia samples.^{72,74} The region on chromosome 8q24 that encompasses the MYC locus is often altered (e.g. amplified, deleted) in more advanced disease.^{71,75-77} Interestingly, while alterations in chromosome 8q24 have been documented in more advanced cases of prostate cancer, MYC protein expression seems to be higher in Gleason 3 disease compared to Gleason 4-5 disease.⁷¹

1.4.4. ERG

Gene fusions between the androgen receptor regulated TMPRSS2 gene and members of the ETS family of nuclear transcription factors (primarily ERG) are frequently

recognized in prostate cancer specimens.⁷⁸ Furthermore, these gene fusions may synergize with PTEN loss, leading to more aggressive prostate cancer behavior.^{66,79}

1.4.5. KI-67

KI-67 (Ki67) is a nuclear protein complex that is present during all active phases of the cell cycle, but absent during the G0 phase, making it a marker of cellular proliferation.⁸⁰ In men with localized prostate cancer, Ki67 has been found to independently associate with the risk of developing progressive disease following both radiation therapy and radical prostatectomy.^{66,81}

1.4.6. RNAseq

In order to explore signaling pathways that may be implicated in the emergences of resistance to AR-directed therapy, we will perform RNAseq on tumor samples. Micro and macrodissection methods (as described in the lab manual) will be used to obtain samples that are enriched for cancer cells.

1.4.7. Intraprostatic and Serum Drug/Androgen Levels

Heterogeneity in intraprostatic drug and androgen levels has been documented in prostate surgical specimens in men treated with neoadjuvant AR-directed therapies.^{17,21}

Furthermore, prior studies have correlated intraprostatic abiraterone acetate levels with intraprostatic androgen levels and complete response rates following neoadjuvant therapy.¹⁷

2. Study Objective:

2.1. Primary Objective:

The rate of pCR (i.e. no evidence of residual tumor) as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.

2.2. Secondary Objectives:

1. To determine the negative margin rate as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
2. To determine the rate of near pCR (i.e., ≤ 5 mm of residual tumor) as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
3. To determine the rate of pathologic T3 disease as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
4. To determine the rate of nodal metastases as assessed on surgical lymph node specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
5. To determine the apoptotic index (i.e. percentage of tumor cells undergoing apoptosis) as determined by cleaved caspase-3 immunohistochemistry following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin.
6. To determine the proportion of men who receive adjuvant radiation therapy within 1-year of prostatectomy.
7. To determine the biochemical (i.e., PSA) progression free survival estimate two years after the last patient has accrued (i.e., confirmed PSA post-radical prostatectomy ≥ 0.2 ng/mL).
8. To determine the overall survival estimate two years after the last patient has accrued.
9. Safety as assessed by the incidence and severity of adverse events and serious adverse events graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
10. Exploratory biomarker Assessment. Examples of these may include, but are not limited to: PTEN immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH, RNAseq analysis, serum drug/androgen levels and intraprostatic drug/androgen levels.

3. Patient Population

For this study we plan on enrolling 20 evaluable patients. Up to 22 patients will be enrolled if necessary in order to account for a potential 10% dropout rate.

3.1. Inclusion Criteria:

1. Willing and able to provide written informed consent.
2. Age \geq 18 years
3. Eastern cooperative group (ECOG) performance status \leq 2
4. Documented histologically confirmed adenocarcinoma of the prostate
5. Willing to undergo prostatectomy as primary treatment for localized prostate cancer
6. High risk prostate cancer (per NCCN criteria): Gleason score 8-10 or T3a or PSA $>$ 20 ng/mL
or
Very-high risk prostate cancer (per NCCN criteria): T3b-T4
7. Serum testosterone \geq 150 ng/dL
8. Able to swallow the study drugs whole
9. Willing to take abiraterone acetate on an empty stomach (no food should be consumed at least two hours before and for one hour after dosing).
10. Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.
11. Medications known to lower the seizure threshold (see list under prohibited meds) must be discontinued or substituted at least 4 weeks prior to study entry.

3.2. Exclusion Criteria:

1. Prior local therapy to treat prostate cancer (e.g., radical prostatectomy, radiation therapy, brachytherapy)
2. Prior use of apalutamide, abiraterone acetate or degarelix
3. Prior or ongoing systemic therapy for prostate cancer including, but not limited to:
 - a. Hormonal therapy (e.g., leuprolide, goserelin, triptorelin, degarelix)
 - b. CYP-17 inhibitors (e.g., ketoconazole)
 - c. Antiandrogens (e.g., bicalutamide, nilutamide)
 - d. Second generation antiandrogens (e.g., enzalutamide, apalutamide)
 - e. Immunotherapy (e.g., sipuleucel-T, ipilimumab)
 - f. Chemotherapy (e.g., docetaxel, cabazitaxel)
4. Evidence of serious and/or unstable pre-existing medical, psychiatric or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study
5. Any psychological, familial, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule.
6. Abnormal bone marrow function [absolute neutrophil count (ANC) $<1500/\text{mm}^3$, platelet count $<100,000/\text{mm}^3$, hemoglobin $<9 \text{ g/dL}$]
7. Abnormal liver function (total bilirubin $>1.5 \times$ upper limit of normal [ULN]; AST or ALT $\geq 2.5 \times$ ULN)
Note: In subjects with Gilbert's syndrome, if total bilirubin is $>1.5 \times$ ULN, measure direct and indirect bilirubin and if direct bilirubin is $\leq 1.5 \times$ ULN, subject may be eligible
8. Abnormal kidney function (GFR $<45 \text{ mL/min}$)
9. Serum albumin $<3 \text{ g/dL}$
10. Serum potassium $<3.5 \text{ mmol/L}$
11. Seizure or known condition that may pre-dispose to seizure (e.g. prior stroke within 1 year to randomization, brain arteriovenous malformation,

Schwannoma, meningioma, or other benign CNS or meningeal disease which may require treatment with surgery or radiation therapy)

12. Severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to randomization
13. History of stroke within the last 5-years
14. History of gastrointestinal (GI) bleed requiring transfusion
15. History of peptic ulcer disease requiring treatment within the last 5-years
16. History of asthma that is NSAID-induced or with asthma that is classified as ‘mild-persistent’ or worse (based on symptoms occurring more than 2 days per week)
17. Uncontrolled hypertension
18. Gastrointestinal disorder affecting absorption
19. Active infection (eg, human immunodeficiency virus [HIV] or viral hepatitis)
20. Any chronic medical condition requiring a higher dose of corticosteroid than 10 mg prednisone/prednisolone once daily
21. Any condition that in the opinion of the investigator, would preclude participation in this study
22. Child Pugh Class B & C
23. Pre-existing viral hepatitis

3.3. Inclusion of Women and Minorities

This study is focused on prostate cancer; therefore the treatment cohort is only applicable to men. Men from all ethnic and race groups are eligible for this study.

4. Treatment Plan

4.1. Study Design

This is an open label, multi-site, Phase II neoadjuvant study in men with localized prostate cancer planning to undergo prostatectomy. This study will assess the pCR rate after 3-months (12 weeks) of neoadjuvant treatment with apalutamide, abiraterone acetate, degarelix and indomethacin as assessed on prostatectomy specimens.

All subjects must have localized, high or very-high risk (per NCCN criteria) prostate cancer and be willing to undergo prostatectomy as primary treatment. Subjects will be treated with neoadjuvant therapy for a total of 3-months (12 weeks) prior to prostatectomy. Therapy will consist of apalutamide, abiraterone acetate, degarelix and indomethacin (Figure 4). Abiraterone acetate, degarelix and indomethacin will be dosed at its respective FDA approved dose. These dosages are as follows: abiraterone acetate 1000 mg (four 250mg tablets) by mouth daily, indomethacin 50 mg by mouth three times daily (TID) and degarelix 240 mg subcutaneous (SC) injection on day 1 followed by two additional 80 mg SC injections every 4 weeks. All men will also be treated with prednisone 5 mg by mouth twice daily while on abiraterone acetate in order to blunt its associated mineralocorticoid side effects.[†] Apalutamide was recently approved by the FDA for use in men with non-metastatic castration resistant prostate cancer on the basis of Phase III data showing that it significantly prolonged the time to development of metastatic disease. Apalutamide is still under development as an investigational product for other types of prostate cancer. Apalutamide will be administered at the FDA approved dose for treating non-metastatic CRPC, 240 mg daily by mouth. The GnRH antagonist degarelix was chosen over other forms of HT (i.e., GnRH agonists) given that the neoadjuvant treatment period is relatively short at 12-weeks, and degarelix has been shown to result in more rapid castration and PSA suppression compared to the GnRH agonist leuprolide.³¹ Following 12-weeks of neoadjuvant treatment, patients will undergo prostatectomy. Lymph node dissection will be required for all patients

[†] Note: Because steroids can lead to hyperglycemia, subjects with a history of diabetes will be required to monitor their daily fasting blood glucose using a home glucometer. Fasting blood glucose values will be reviewed at scheduled follow up appointments. Patients will also be instructed to contact their provider if their fasting glucose is >150 mg/dL. Based on the daily fasting blood glucose levels, anti-hyperglycemic medications will be adjusted by the treating oncologist and/or the patient's primary care doctor or endocrinologist.

with a $\geq 2\%$ estimated risk of nodal metastases per the Partin Nomogram.³² Patients should have clinical follow-up visits following prostatectomy per the standard practice of their treating urologist. However, at a minimum, patients should be evaluated in clinic 28 days following their prostatectomy. Of note, the combination of apalutamide, abiraterone acetate and GnRH analogue therapy has been shown to have an acceptable safety profile when administered at these doses [see Investigator’s Brochure].

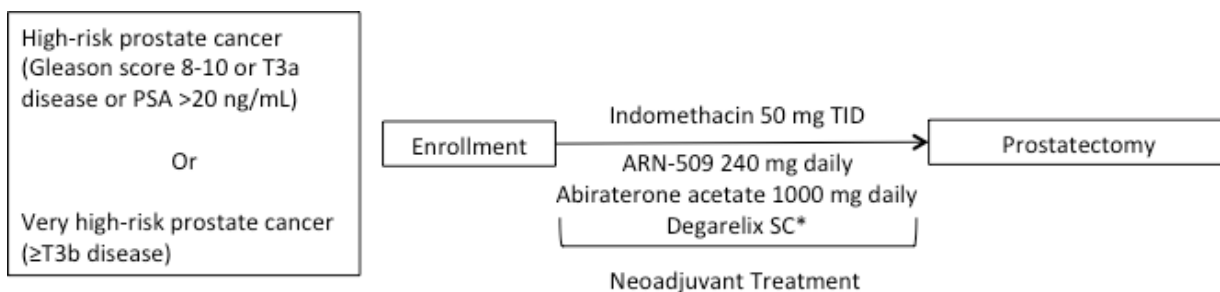


Figure 4: Study scheme.

*Three doses of subcutaneous (SC) degarelix will be administered. Degarelix is administered every 4-weeks, with a 240 mg loading dose given for the first SC injection followed by 80 mg SC injections thereafter.

This study will be open to patients age ≥ 18 years who have a histologic diagnosis of prostatic adenocarcinoma and are planning to undergo prostatectomy as primary treatment of their prostate cancer. All patients must have high to very high-risk prostate cancer as defined per the NCCN criteria (i.e., high-risk = Gleason score 8-10 or T3a or PSA > 20 ng/mL; very high-risk = T3b-T4).

The primary endpoint will be the pathologic complete response (pCR) rate (i.e., no evidence of tumor) as assessed on prostatectomy specimens following 3-months (12 weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin. Secondary pathologic endpoints to be assessed from prostatectomy specimens following 3-months (12 weeks) of neoadjuvant therapy include: the negative margin rate, negative nodal metastases rate, near pCR (i.e., ≤ 5 mm of residual tumor) rate, the rate of pathologic T3 disease and apoptotic index (i.e. percentage of tumor cells undergoing apoptosis) as determined by cleaved caspase-3 immunohistochemistry. Other secondary endpoints will include: the proportion of men who receive adjuvant radiation therapy within 1-year of prostatectomy, the biochemical (i.e., PSA) progression free survival estimate two years after the last patient has

accrued, the overall survival estimate two years after the last patient has accrued and safety (as assessed by CTCAE version 4.0).

In addition, excess tissue from prostatectomy specimens and plasma samples will be stored at -80°C. These biologic specimens will be used for additional correlative work. When possible, we also conduct exploratory biomarker studies on pre-treatment/archival biopsy specimens. Examples of studies to be conducted may include, but are not limited to: PTEN immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH, RNAseq analysis, serum drug/androgen levels and intraprostatic drug/androgen levels.

4.2. Dose Adjustment, Delays and Treatment Discontinuation

4.2.1. Adverse Events Attributed to a Study Drug

For the purpose of determining how to dose adjust a study drug, an AE will be considered attributed to a given study drug if it is felt that the AE was probably or definitely related to that study drug (see Section 9.6: Evaluating Adverse Events). Please refer to Section 8: Pharmaceutical Information for guidelines on how to dose adjust/delay treatment with each study drug. Note that for AEs that are attributed to a study drug, treatment should be permanently discontinued for recurrent Grade 3 toxicity, Grade 3 toxicity lasting longer than 5 days, or any Grade toxicity that has not resolved to Grade 1 or less within 2 weeks.

4.2.2. Adverse Events Not Attributed to a Study Drug

If a Grade 1 or 2 AE occurs that is not attributed to one of the study drugs, that patient may continue on treatment without dose adjustment/delays. If a Grade ≥ 3 AE occurs that is not attributed to a study drug, all drugs should be held until that AE returns to Grade 2 or lower (prednisone may be continued). If a Grade ≥ 3 AE persists for more than two weeks, that patient should be removed from the study. The algorithm for managing toxicities that are not attributed to a study drug is provided below:

Toxicity	Action Required
Grade 1 or 2	No change

≥Grade 3	Hold all drugs except prednisone until return to Grade 1 or 2, resume at full dose*
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*Note: Treatment will be permanently discontinued for Grade 3 toxicity lasting longer than 2 weeks. Prednisone should be tapered if study drugs are permanently discontinued.

4.3. Removal of Patients from Study

A patient may be removed from the study for a variety of reasons, including:

1. Worsening symptoms that can be attributed to prostate cancer
2. Unacceptable adverse event(s)
 - Patients develop urinary outlet obstruction requiring urinary catheterization and/or surgical intervention
 - Patients who develop grade 3 or higher liver function abnormalities:
 - Bilirubin ≥ 3 times institutional upper limit of normal (ULN)
 - AST (SGOT) or ALT (SGPT) ≥ 5 times ULN
 - Patients with AST/ALT elevation >3 times ULN with bilirubin elevation >2 times ULN
 - Patients develop decreased renal function with serum creatinine ≥ 2.5 times baseline level
 - Patients develop hypersensitivity or anaphylactoid reactions to abiraterone acetate, apalutamide, indomethacin or degarelix.
3. Intercurrent illness that prevents further participation
4. Experiencing a treatment delay of longer than 2 weeks; however, if the patient is receiving clinical benefit, treatment may be delayed for longer than 2 weeks and then resumed at the discretion of the Investigator.
5. Patient refuses further treatment through the study and/or withdraws consent to participate

6. Patient is noncompliant with respect to taking drugs, keeping appointments, or having tests required for the evaluation of drug safety and efficacy
7. General or specific changes in the patient's condition that render the patient unacceptable for further treatment in this study in the judgment of the investigator.

Under no circumstance will care of a withdrawn patient be adversely affected by a decision to withdraw or be withdrawn from the study.

5.0 Treatment Assessment and Evaluation

All required treatment and end of study procedures and assessments must be done within 7 days (+/-) of the specified study visit date unless otherwise noted. Screening study procedures and assessments must be done 30 days prior to enrollment. The results of tests and/or procedures conducted as per standard of care purposes may be used for research purposes if conducted within the protocol-defined window. Long-term follow-up procedures and assessments should occur within 30 days (+/-) from the specified study visit date.

5.1. Screening (performed within 30 days of enrollment)

1. Comprehensive medical history and physical exam, including height and weight, medications, ECOG performance status assessment, blood pressure and heart rate.
2. CBC (Complete blood count) with differential and platelet count.
3. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO₂).
4. Serum testosterone.
5. TSH (thyroid stimulating hormone).
Note: Free T3 and T4 should be checked if TSH is abnormal.
6. Electrocardiogram (EKG).

5.2. Neoadjuvant Treatment (Days 1 to 57)

1. Comprehensive medical history and physical exam, including weight, medications, ECOG performance status assessment, blood pressure and heart rate (Days 1, 29 and 57).
2. Serum PSA (Days 1, 29 and 57).
3. CBC (Days 1, 29 and 57).
4. CMP (Days 1, 15, 29, 43, 57 and 71).
5. TSH (Days 1, 29 and 57).
Note: Free T3 and T4 should be checked if TSH is abnormal.
6. Androgen panel (Day 1).

5.3. Exploratory biomarker collection: blood samples and pre-treatment prostate biopsy specimens. (Day 1) Surgery (Day 85)

1. Nursing assessment.
2. Prostatectomy specimen pathologic assessment.
3. CBC.
4. CMP.
5. Serum PSA.
6. Androgen panel.
7. Exploratory biomarker collection: blood samples and post-treatment prostatectomy specimens..

5.4.Follow Up

1. Comprehensive medical history and physical exam, including weight, medications, ECOG performance status assessment, blood pressure and heart rate (Day 113).
2. Serum PSA (Days 113, 450 and 815).
3. Telephone, mail or email follow up (Days 450 and 815) (see Appendix C).

6. Study Calendar

	Screening Day -30 to -1	Neoadjuvant Treatment						Surgery Day 85 ^g (+/-7 days)	Follow Up		
		Day 1 ^a (+/-7 days)	Day 15 (+/-7 days)	Day 29 (+/-7 days)	Day 43 (+/-7 days)	Day 57 (+/-7 days)	Day 71 (+/-7 days)		Day 113 (+/-7 days)	Day 450 (+/-30 days)	Day 815 (+/-30 days)
Informed Consent	x										
History and Physical ^b	x	x		x		x		x	x		
Telephone, mail or email follow up ^c										x	x
Study drug dispensation		x		x		x					
Unused study drug collection				x		x		x			
Degarelix injection		x		x		x					
Prostatectomy								x			
Prostatectomy specimen pathologic assessment								x			
CBC ^d	x	x		x		x		x			
CMP ^d	x	x	x	x	x	x	x	x			
TSH ^d	x	x		x		x					
Serum PSA		x		x		x		x	x	x	x
Serum Testosterone	x										
Androgen panel ^e		x						x			
EKG	x										
Exploratory biomarkers ^f		x						x			

a. Screening visit labs and assessments may be used for this visit if they occurred ≤8 days prior to Day 1.

b. History and physical assessment will include ECOG performance status and toxicity assessments. Visits will also document medications, blood pressure, and heart rate. Note that for the Day 85 visit, a nursing assessment will suffice for the History and Physical.

c. The purpose of long term follow up is to determine if a prostate cancer relapse has occurred, if adjuvant radiation therapy has been given or if the patient has expired.

d. CBC = Complete blood count with platelets and differential; CMP = Comprehensive metabolic panel (Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2); TSH = Thyroid stimulating hormone (note: must check T3 and T4 if TSH is abnormal)
 Note that the Day 15, 43 and 71 CMP check can be done at an outside lab.

e. Androgen panel = dihydrotestosterone, (DHT), testosterone and dehydroepiandrosterone (DHEA-S) serum levels

f. See sections 1.4 and 7.1 for a description of exploratory biomarkers. These will be performed on tissue and/or plasma sample. Samples collected at these time points will be stored for future correlative work.

g. These assessments may occur up to 7 days prior to prostatectomy.

7. Study Assessments

7.1. Pathologic Assessment

Prostatectomy specimens will be submitted in their entirety. Pathologic CR is defined as no evidence of cancer on fully submitted prostatectomy specimens using standard surgical pathology assessments (i.e. H&E assessment will be used for the purpose of defining pathologic CR per protocol). For complete details on handling of prostatectomy specimens, please refer to the lab manual.

7.2. Exploratory Biomarkers

This study will incorporate a number of additional exploratory biomarkers. Given our rapidly evolving understanding of prostate cancer pathobiology, genetics and epigenetics, it is impossible to prospectively define all the relevant biomarkers for the patient population enrolled on this study. So as to not miss an opportunity to assess the utility of yet to be described biomarkers in the context of combinatorial AR-pathway suppression; we will plan to store prostatectomy specimens and plasma samples at -80°C for future analyses. These samples will be stored for up to 5 years.

Prostate tissue will be obtained post-treatment with apalutamide, abiraterone acetate, indomethacin and degarelix, and other biospecimens (e.g., plasma) will be obtained pre- and post-treatment. When possible, we will also obtain pre-treatment/archival prostate biopsy specimens for these exploratory studies. All biopsy material will be Formalin-Fixed Paraffin Embedded (FFPE) and IHC and FISH assays will be performed on these FFPE samples in Lawrence True's laboratory at University of Washington. RNAseq will be performed in Peter Nelson's laboratory at Fred Hutchinson Cancer Research Center and will be performed on tumor samples that have been processed as described in the lab manual. Liquid chromatography/mass spectrometry (LC/MS) assessment of intraprostatic drug and androgen levels will be determined in Dr. Mostaghel's laboratory at the Fred Hutchinson Cancer Research Center. Admittedly, given that we may not be able to obtain adequate tumor tissue to assess all of these biomarkers, we will prioritize assessing them in the order that they are described below. Samples will not be labeled with identifiable patient information, and instead will have a

coded study ID unique to each enrolled subject. The study PI (Dr. Michael T. Schweizer) and his designees will have access to these samples. Samples will be stored in the GU Cancer Research Lab at the University of Washington Medical Center or in Peter Nelson's lab at the Fred Hutchinson Cancer Research Center.

PTEN: PTEN protein expression will be determined via IHC using a rabbit monoclonal anti-PTEN antibody (clone D4.3, #9188, Cell Signaling Technologies). PTEN IHC and FISH assays will be conducted similar to the methods previously described by Lotan and colleagues.⁶⁸

MYC: Alterations in chromosome 8q24, the region that encompasses the MYC locus, will be assessed via FISH. FISH hybridization will be done with the multicolor probes (ProVysion, Vysis, Inc., Downers Grove, IL) to detect and quantify chromosome 8 centromere probe [chromosome enumeration probe 8 (CEP8)] and with two locus-specific probes, the lipoprotein lipase (LPL; 8p21.3) and the c-MYC8q24 probe. MYC/chromosome 8q24 FISH assays will be conducted similar to the methods previously described by Jenkins and colleagues.⁷⁶

ERG: Given that ERG protein expression has been shown to be an excellent surrogate of TMPRSS2-ERG fusion status, we will plan to assess ERG expression using IHC.⁸²⁻⁸⁴ ERG IHC will be done using an anti-ERG mouse monoclonal antibody (clone 9FY; Biocare, Concord, CA). ERG IHC assays will be conducted similar to the methods described by Chaux and colleagues.⁸²

KI-67: Ki67 will be assessed via IHC using an anti-Ki67 mouse monoclonal (clone 7B11; Zymed Laboratories, South San Francisco, Calif). The mouse PowerVision+ kit (Leica Microsystems, Buffalo Grove, Ill) will be used for these assays. Ki67 IHC assays will be conducted using standard lab practices and in accordance with the mouse PowerVision[®] kit instructions.

RNAseq: After RNA extraction, total RNA (~200 ng) will be quality controlled using the Agilent bioanalyzer, to ensure that specimens have RIN scores > 7.0. Strand-specific sequencing libraries will be prepared using the TruSeq Stranded Total RNA library kit (Illumina). If 200 ng of total RNA are not available, then we will use a high-sensitivity, strand-agnostic workflow, using the Ovation RNA-seq System v2.0 kit (NuGen)

according to manufacturer's protocols with some modifications, which we have validated with Total RNA input amounts as low as 500 picograms to have high correlation ($R^2 > 0.85$) with the high input workflow in terms of gene-level expression measures. Barcoded libraries will be quality-controlled using the Kappa PCR kit and pooled in equimolar ratios for subsequent cluster generation and sequencing on an Illumina HiSeq 2000 or 2500 instrument to yield ~50,000,000 paired end 100x100 bp tags for each sample. Paired-end reads will then be mapped to the human genome (build hg19, NCBIv.38) and isoform specific gene expression measures will be derived using the RSEM package, which uses an expectation maximization algorithm to derive the abundance of each gene isoform after taking into account the read mapping uncertainty with a statistical model.⁸⁵ This analysis will yield information on the relative abundance, with 95% Confidence Interval, of all known gene isoforms annotated in RefSeq, Ensembl, and UCSC gene annotations. Differential expression between groups will be determined using the RSEM output with the EBseq pipeline.⁸⁶ The unaligned reads after RSEM analysis may contain information on splice junctions of novel transcriptional isoforms and fusion genes. Using these unaligned reads, the relative abundance of novel splice junctions in each sample, independent of existing known exon annotation, will be estimated using the SpliceMap package.⁸⁷ To identify fusion transcripts, we will use TopHat-Fusion with all reads as well as specifically those reads that were not aligned by RSEM.⁸⁸ Since it can be used independent of gene annotation, TopHat-Fusion can also provide redundant information to SpliceMap on novel splice variant junctions. Completely novel RNA species will be identified as peaks of expressed sequence tags (ESTs) using Bowtie to align sub-segments of each read, followed by peak calling using MACS, SICER, and GCLS, and DEseq analysis of detected peaks to identify differential expression of novel transcript peaks between samples when present in at least one sample.⁸⁹⁻⁹² Aligned RNA-seq data will be output as .bam files and coverage tracks (wig and tdf format) and visualized using IGV and the UCSC Genome browser.⁹³⁻⁹⁵ This suite of analytical approaches will therefore allow us to identify and visualize known genes and isoforms, novel splice junctions, and fusion genes present in expressed transcripts.

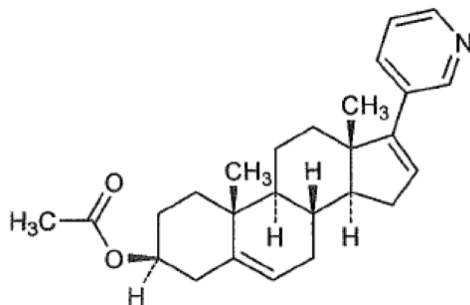
Intraprostatic and Serum Drug/Androgen Levels: Abiraterone acetate and apalutamide drug levels will be determined in serum, and benign fresh frozen prostate specimens using LC/MS. An Agilent 1290 UPLC, AB Sciex 550 LC/MS system will be used along with a Phenomenex Kinetex column to do the quantification according to standard lab procedure developed in Dr. Mostaghel's laboratory. Similarly, intraprostatic androgens (i.e., DHT and testosterone) will be quantified with LC/MS according to standard lab methods developed in the Mostaghel laboratory.

7.3. Safety

Safety will be evaluated based on the incidence, severity, duration, causality, seriousness, and type of adverse events (AEs), and changes in the patient's physical examination, vital signs, and clinical laboratory results. Investigators will use the NCI CTCAE version 4.0 (published 14 June 2010) to assess the severity of AEs and toxicities (see Appendix A). For safety considerations specific to the study drugs, see section 8 of the protocol.

8. Pharmaceutical Information

8.1. Drug Name: Abiraterone acetate [Adapted from FDA prescribing information, refer to this document for more detail.]



- **Chemical Name:** (3 β) 17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate
- **Molecular Formula:** C₂₆H₃₃NO₂ **Molecular Weight:** 391.55 g/mol
- **Description:** Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. The 250 mg tablets are oval-shaped tablets debossed with AA250 on one side. Its molecular formula is C₂₆H₃₃NO₂ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19. Inactive ingredients in the tablets are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

8.1.1. Clinical Pharmacology

Abiraterone acetate is administered in 250 mg tablets, with the FDA approved dose being 1000 mg (4 tablets) by mouth daily. Following administration abiraterone acetate is hydrolyzed *in vivo* to abiraterone, a 17 α -hydroxylase/C17,20-lyase (CYP17) inhibitor. Following ingestion the time to maximum plasma concentration of abiraterone acetate is 2 hours. At a dose of 1000 mg daily abiraterone acetate achieves a steady-state C_{max} of 226 +/- 178 ng/mL (mean +/- SD) and an area under the curve (AUC) of 1173 +/- 690 ng.hr/mL (mean +/- SD). Systemic exposure of abiraterone acetate is increased when administered with food, with an approximate 7- and 5-fold increase in the C_{max} and AUC

respectively when given with a low-fat meal. When given with a fatty meal, the C_{max} and AUC increased 17- and 10-fold respectively. Given this variation, no food should be consumed at least 2 hours before and one hour after taking abiraterone acetate.

Abiraterone acetate sulphate and N-oxide abiraterone acetate sulphate are the two main circulating inactive metabolites. CYP3A4 is involved in the formation of N-oxide abiraterone acetate sulphate and SULT2A1 is involved in the formation of N-oxide abiraterone acetate sulphate and Abiraterone acetate sulphate. Abiraterone acetate is highly bound (>99%) to human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution is (mean +/- SD) 19669 +/- 13358 L. The mean (+/- SD) terminal half-life of abiraterone acetate in plasma is 12 +/- 5 hours. It is predominately excreted in feces (88%), with the major compounds present in feces being unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of administered dose respectively).

8.1.2. Safety/Precautions

- **Mineralocorticoid excess:** Use abiraterone acetate with caution in patients with a history of cardiovascular disease. The safety of abiraterone acetate in patients with LVEF < 50% or NYHA Class III or IV heart failure in Study 1 or LVEF < 50 % or NYHA Class II to IV heart failure in Study 2 was not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly.
- **Adrenocortical insufficiency:** Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.
- **Hepatotoxicity:** Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue abiraterone acetate dosing as recommended.

- **Food effect:** abiraterone acetate must be taken on an empty stomach. Exposure (area under the curve) of abiraterone acetate increases up to 10 fold when abiraterone acetate is taken with meals.
- **Unforeseeable risks to embryo or fetus:** Patients should be informed that abiraterone acetate may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone acetate or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with abiraterone acetate.

8.1.3. Information for Patients

- Patients should be informed that abiraterone acetate and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients should be informed that abiraterone acetate must not be taken with food and that no food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. Patients should be informed that taking abiraterone acetate with food causes increased exposure and this may result in adverse reactions.
- Patients should be apprised of the common side effects associated with abiraterone acetate, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Patients should be instructed to report any perceived adverse events (including the aforementioned).

8.1.4. Laboratory tests

- Liver function tests (e.g. AST/ALT, bilirubin) should be monitored periodically while on abiraterone acetate.
- Electrolytes (e.g., sodium, potassium) should be monitored periodically while on abiraterone acetate.

8.1.5. Drug Interactions

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. As such, drugs metabolized by this route can exhibit increased plasma concentrations when co-administered with abiraterone acetate. Drugs with narrow therapeutic indices (e.g., thioridazine) that are metabolized via CYP2D6 should be avoided.

Based on *in vitro* data, abiraterone acetate is a CYP3A4 substrate. Strong CYP3A4 inhibitors or inducers on pharmacokinetics of abiraterone acetate have not been evaluated *in vivo*; however, caution should be taken when strong CYP3A4 inhibitors/inducers are being co-administered.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index (e.g., paclitaxel) if used concomitantly with abiraterone acetate.

8.1.6. Adverse Reactions

The most common adverse reactions ($\geq 10\%$) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities ($> 20\%$) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia. Additional adverse events observed in the Phase III trials can be found in Table 1.

8.1.7. Dose Modifications for LFT Abnormalities Attributed to Abiraterone Acetate When Given in Combination with Apalutamide

Dose modifications are provided as guidance and should not replace the investigator’s own clinical judgment.

Toxicity	Dose of abiraterone acetate	Dose of apalutamide	Dose of prednisone
Grade 1	No change	No change	No change
Grade 2	Hold until return to Grade 1 or baseline, resume after discussion and agreement with medical monitor*	No change	No change
≥Grade 3	Discontinue	Discontinue	Taper off

*Note: Treatment will be permanently discontinued for Grade 3 toxicity lasting longer than 5 days, or any grade toxicity that has not resolved to Grade 1 or less within 2 weeks

8.1.8. Dose Modifications for Hypokalemia Attributed to Abiraterone Acetate When Given in Combination with Apalutamide

Dose modifications are provided as guidance and should not replace the investigator’s own clinical judgment.

Toxicity	Dose of abiraterone acetate	Dose of Apalutamide	Dose of prednisone
Grade 1 or 2	Initiate oral potassium supplementation, titrate to ≥3.5 to ≤5.0 mmol/L, maintenance at ≥4.0 mmol/L recommended*	No change	No change
≥Grade 3	Hold and initiate IV potassium and cardiac monitoring, resume only after discussion and approval by the medical monitor*	No change	No change
Recurrence ≥Grade 3, or Grade 4	Discontinue	Discontinue	Taper off

*Note: Treatment will be permanently discontinued for Grade 3 toxicity lasting longer than 5 days, or any grade toxicity that has not resolved to Grade 1 or less within 2 weeks. Subjects will be allowed to resume/continue treatment if serum potassium level is maintained ≥ 3.5 to ≤ 5.0 mmol/L with oral potassium supplementation.

8.1.9. Dose Modifications for Hypertension and Edema/Fluid Retention Attributed to Abiraterone Acetate When Given in Combination with Apalutamide

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

Toxicity	Dose of abiraterone acetate	Dose of Apalutamide	Dose of prednisone
Grade 1	No change	No change	No change
Grade 2	Hold until return to Grade 1 or baseline, resume at full dose*	No change	No change
\geq Grade 3	Hold until Grade 1 or baseline, resume at full dose*	No change	No change
Recurrence \geq Grade 3, or Grade 4	Discontinue	Discontinue	Taper off

*Note: Treatment will be permanently discontinued for Grade 3 toxicity lasting longer than 5 days, or any grade toxicity that has not resolved to Grade 1 or less within 2 weeks.

8.1.10. Administration, Supply and Storage

Abiraterone acetate is marketed but not approved for the indication under study.

8.1.10.1. Administration

Abiraterone acetate is available in tablets and should only be taken orally. The current FDA approved dose of 1000 mg daily, or four 250 mg tablets by mouth daily, will be administered. A 28-day supply will be provided at the beginning of each month of the trial. Abiraterone acetate must be taken with prednisone 5 mg by mouth twice daily to prevent symptoms of mineralocorticoid excess and must be taken on an empty stomach (i.e. no food 2 hours prior and 1 hour after ingestion).

8.1.10.2. Supply

Abiraterone acetate is available in 250 mg tablets.

8.1.10.3. Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F)

8.2. Apalutamide[Adapted from the Apalutamide Investigator’s Brochure; refer to this document for more detail]

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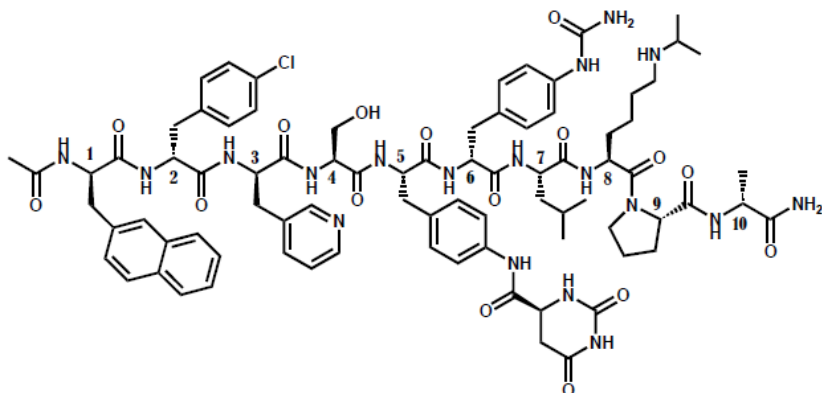
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8.3. Drug Name: Degarelix [Adapted from FDA prescribing information, refer to this document for more detail]



- **Chemical Name:** D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-Dphenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[[[(4S)-hexahydro-2,6-dioxo-4pyrimidinyl]carbonyl]amino]-L phenylalanyl-4-[(aminocarbonyl)amino]-D-phenylalanyl-L leucyl-N6-(1methylethyl)-L-lysyl-L-prolyl
- **Molecular Formula:** C₈₂H₁₀₃N₁₈O₁₆Cl
- **Molecular Weight:** 1632.3 Da
- **Description:** Degarelix (as the acetate) is formulated as a sterile lyophilized powder for injection. Degarelix is a synthetic linear decapeptide amide containing seven unnatural amino acids, five of which are D-amino acids. The acetate salt of degarelix is a white to off-white amorphous powder of low density as obtained after lyophilization. Firmagon (the trade name of degarelix) delivers degarelix acetate, equivalent to 120 mg of degarelix for the starting dose, and 80 mg of degarelix for the maintenance dose. The 80 mg vial contains 200 mg mannitol and the 120 mg vial contains 150 mg mannitol.

8.3.1. Clinical Pharmacology

Degarelix forms a depot upon subcutaneous administration, from which it is released to the circulation. Following administration of degarelix 240 mg at a product concentration of 40 mg/mL, the mean C_{max} was 26.2 ng/mL (coefficient of variation, CV 83%) and the mean AUC was 1054 ng·day/mL (CV 35%). Typically C_{max} occurred within 2 days after subcutaneous administration. In prostate cancer patients at a product concentration of 40 mg/mL, the pharmacokinetics of degarelix were linear over a dose range of 120 to

240 mg. The pharmacokinetic behavior of the drug is strongly influenced by its concentration in the injection solution.

The distribution volume of degarelix after intravenous (> 1 L/kg) or subcutaneous administration (> 1000 L) indicates that degarelix is distributed throughout total body water. *In vitro* plasma protein binding of degarelix is estimated to be approximately 90%.

Degarelix is subject to peptide hydrolysis during the passage of the hepato-biliary system and is mainly excreted as peptide fragments in the feces. No quantitatively significant metabolites were detected in plasma samples after subcutaneous administration. *In vitro* studies have shown that degarelix is not a substrate, inducer or inhibitor of the CYP450 or p-glycoprotein transporter systems.

Following subcutaneous administration of 240 mg degarelix at a concentration of 40 mg/mL to prostate cancer patients, it is eliminated in a biphasic fashion, with a median terminal half-life of approximately 53 days. The long half-life after subcutaneous administration is a consequence of a very slow release of degarelix from the depot formed at the injection site(s). Approximately 20-30% of a given dose of degarelix was renally excreted, suggesting that approximately 70-80% is excreted via the hepato-biliary system in humans. Following subcutaneous administration of degarelix to prostate cancer patients the clearance is approximately 9 L/hr.

8.3.2. Safety/Precautions

- **Hypersensitivity reactions:** Hypersensitivity reactions, including anaphylaxis, urticaria and angioedema, have been reported post-marketing with degarelix. In case of a serious hypersensitivity reaction, discontinue degarelix immediately if the injection has not been completed, and manage as clinically indicated. Patients with a known history of serious hypersensitivity reactions to degarelix should not be re-challenged with degarelix.
- **Effect on QT/QTc interval:** Long-term androgen deprivation therapy prolongs the QT interval. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA

(e.g. quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications.

In the randomized, active-controlled trial comparing degarelix to leuprolide, periodic electrocardiograms were performed. Seven patients, three (<1%) in the pooled degarelix group and four (2%) patients in the leuprolide 7.5 mg group, had a QTcF \geq 500 msec. From baseline to end of study the median change for degarelix was 12.3 msec and for leuprolide was 16.7 msec.

- **Laboratory testing:** Therapy with degarelix results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after degarelix may be affected. The therapeutic effect of degarelix should be monitored by measuring serum concentrations of prostate-specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.

8.3.3. Information for Patients

- Patients should be informed of the possible side effects of androgen deprivation therapy, including hot flashes, flushing of the skin, increased weight, decreased sex drive, and difficulties with erectile function. Possible side effects related to therapy with degarelix include redness, swelling, and itching at the injection site; these are usually mild, self-limiting, and decrease within three days.

8.3.4. Drug Interactions

No drug-drug interaction studies have been conducted with degarelix. Degarelix is not a substrate for the human CYP450 system. Degarelix is not an inducer or inhibitor of the CYP450 system *in vitro*. Therefore, clinically significant CYP450 pharmacokinetic drug-drug interactions are unlikely.

8.3.5. Adverse Reactions

A total of 1325 patients with prostate cancer received degarelix either as a monthly treatment (60-160 mg) or as a single dose (up to 320 mg). A total of 1032 patients (78%) were treated for at least 6 months and 853 patients (64%) were treated for one year or more. The most commonly observed adverse reactions during degarelix

therapy included injection site reactions (e.g., pain, erythema, swelling or induration), hot flashes, increased weight, fatigue, and increases in serum levels of transaminases and gamma-glutamyltransferase (GGT). The majority of the adverse reactions were Grade 1 or 2, with Grade 3/4 adverse reaction incidences of 1% or less.

Degarelix was studied in an active-controlled trial (N = 610) in which patients with prostate cancer were randomized to receive degarelix (subcutaneous) or leuprolide (intramuscular) monthly for 12 months. Adverse reactions reported in 5% of patients or more are shown in Table 2.

	Degarelix 240/160 mg (subcutaneous) N = 202	Degarelix 240/80 mg (subcutaneous) N = 207	Degarelix 7.5 mg (intramuscular) N = 201
Percentage of subjects with adverse events	83%	79%	78%
<i>Body as a whole</i>			
Injection site adverse events	44%	35%	<1%
Weight increase	11%	9%	12%
Fatigue	6%	3%	6%
Chills	4%	5%	0%
<i>Cardiovascular system</i>			
Hot flash	26%	26%	21%
Hypertension	7%	6%	4%
<i>Musculoskeletal system</i>			
Back pain	6%	6%	8%
Arthralgia	4%	5%	9%
<i>Urogenital system</i>			
Urinary tract infection	2%	5%	9%
<i>Digestive system</i>			
Increases in Transaminases and GGT	10%	10%	5%
Constipation	3%	5%	5%

Table 2: Adverse reactions reported in $\geq 5\%$ of patients treated with degarelix in a randomized controlled trial.

8.3.6. Dose Modifications for Toxicities Attributed to Degarelix

No dose modifications are allowed for degarelix. If a Grade 2 or higher AE persists at the time a subsequent dose of degarelix is due, the drug should be discontinued.

8.3.7. Administration, Supply and Storage

Degarelix is marketed but not approved for the indication under study.

8.3.7.1. Administration

Degarelix is administered as a subcutaneous injection in the abdominal region. As with other drugs administered by subcutaneous injection, the injection site should vary periodically. Injections should be given in areas of the abdomen that will not be exposed to pressure, e.g., not close to waistband or belt nor close to the ribs.

Degarelix is available as:

- NDC 55566-8401-2, Starting dose – One carton contains: Two vials each with 120 mg powder for injection Two prefilled syringes containing 3 mL of sterile water for injection, USP Two vial adapters Two administration needles
- NDC 55566-8301-2, Maintenance dose – One carton contains: One vial with 80 mg powder for injection One prefilled syringe containing 4.2 mL of sterile water for injection, USP One vial adapter One administration needle

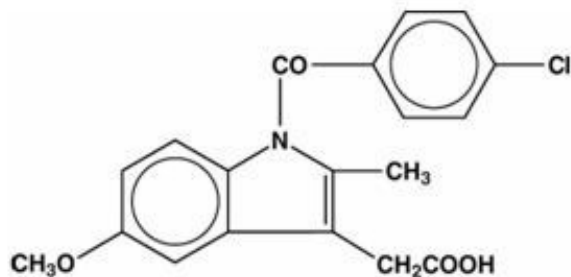
8.3.7.2. Supply

Degarelix is supplied as a powder to be reconstituted with Sterile Water for Injection, USP (WFI). The instruction for reconstitution needs to be carefully followed. Administration of other concentrations is not recommended. Refer to the FDA package insert for details regarding how to properly reconstitute degarelix.

8.3.7.3. Storage

Store degarelix at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

8.4. Drug Name: Indomethacin [Adapted from FDA prescribing information, refer to this document for more detail]



- **Chemical Name:** 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid
- **Molecular Formula:** C₁₉H₁₆ClNO₄
- **Molecular Weight:** 357.79 Da
- **Description:** Indomethacin is commonly available as capsules for oral administration that contain either 25 mg or 50 mg of indomethacin. Indocin[®], the brand of indomethacin manufacture by Merck, is formulated with the following inactive ingredients: colloidal silicon dioxide, FD&C Blue 1, FD&C Red 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide.

8.4.1. Clinical Pharmacology

Following single oral doses of indomethacin 25 mg or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL, respectively at about 2 hours. Orally administered indomethacin is virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours.

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean half-life of indomethacin is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 or 50 mg t.i.d., the steady-state plasma concentrations of indomethacin are an average 1.4 times those following the first dose.

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60 percent of an oral dosage is recovered in urine as drug and metabolites (26 percent as

indomethacin and its glucuronide), and 33 percent is recovered in feces (1.5 percent as indomethacin). About 99% of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta.

8.4.2. Safety/Precautions

8.4.2.1. Warnings

- **Cardiovascular Thrombotic Events:** Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see GI warnings).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10- 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke.

- **Hypertension:** NSAIDs, including indomethacin, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including indomethacin, should be used with caution in

patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

- **Congestive Heart Failure and Edema:** Fluid retention and edema have been observed in some patients taking NSAIDs. Indomethacin should be used with caution in patients with fluid retention or heart failure.

In a study of patients with severe heart failure and hyponatremia, indomethacin was associated with significant deterioration of circulatory hemodynamics, presumably due to inhibition of prostaglandin dependent compensatory mechanisms.

- **Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation:** NSAIDs, including indomethacin, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Rarely, in patients taking indomethacin, intestinal ulceration has been associated with stenosis and obstruction. Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal pain in ulcerative colitis patients or the development of ulcerative colitis and regional ileitis have been reported to occur rarely.

NSAIDs should be prescribed with extreme caution in those with prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a

greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

- **Renal Effects:** Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate over renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, patients with volume depletion, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of indomethacin, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

- **Anaphylactic/Anaphylactoid Reactions:** As with other NSAIDs, anaphylactic/anaphylactoid reactions may occur in patients without known prior exposure to indomethacin. Indomethacin should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Emergency help should be sought in cases where an anaphylactic/anaphylactoid reaction occurs.
- **Skin Reactions:** NSAIDs, including indomethacin, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.
- **Ocular Effects:** Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with indomethacin. The prescribing physician should be alert to the possible association between the changes noted and indomethacin. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients where therapy is prolonged.
- **Central Nervous System Effects:** Indomethacin may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. If severe CNS adverse reactions develop, indomethacin should be discontinued.

Indomethacin may cause drowsiness; therefore, patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with indomethacin.

8.4.2.2. Precautions

- **Hepatic Effects:** Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including indomethacin. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with indomethacin. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), indomethacin should be discontinued.

- **Hematological Effects:** Anemia is sometimes seen in patients receiving NSAIDs, including indomethacin. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including indomethacin, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving indomethacin who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

- **Preexisting Asthma:** Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including

bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, indomethacin should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

8.4.3. Information for Patients

Patients should be informed of the following information before initiating therapy with indomethacin:

- Indomethacin, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up.
- Indomethacin, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up.
- Indomethacin, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
- Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

- Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
- Patients should be informed of the signs of an anaphylactic/anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help.

8.4.4. Drug Interactions

- **ACE-Inhibitors and Angiotensin II Antagonists:** Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors and angiotensin II antagonists. Indomethacin can reduce the antihypertensive effects of captopril and losartan. These interactions should be given consideration in patients taking NSAIDs concomitantly with ACE- inhibitors or angiotensin II antagonists. In some patients with compromised renal function, the co- administration of an NSAID and an ACE- inhibitor or an angiotensin II antagonist may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible.
- **Aspirin:** When indomethacin is administered with aspirin, its protein binding is reduced, although the clearance of free indomethacin is not altered. The clinical significance of this interaction is not known.

The use of indomethacin in conjunction with aspirin or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indomethacin and aspirin does not produce any greater therapeutic effect than the use of indomethacin alone. In a clinical study of the combined use of indomethacin and aspirin, the incidence of gastrointestinal side effects was significantly increased with combined therapy.

In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood levels approximately 20%.

- **Beta-adrenoceptor blocking agents:** Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by non-steroidal anti- inflammatory drugs including

indomethacin has been reported. Therefore, when using these blocking agents to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained.

- **Cyclosporine:** Administration of non-steroidal anti-inflammatory drugs concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporine, and renal function should be carefully monitored.
- **Diiflunisal:** In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, diflunisal and indomethacin should not be used concomitantly.
- **Digoxin:** Indomethacin given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when indomethacin and digoxin are used concomitantly, serum digoxin levels should be closely monitored.
- **Diuretics:** In some patients, the administration of indomethacin can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. This response has been attributed to inhibition of renal prostaglandin synthesis.

Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together.

Indomethacin and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of indomethacin and

potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by indomethacin.

During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.^[1]

- **Lithium:** Indomethacin 50 mg t.i.d. produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when NSAIDs and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Read circulars for lithium preparations before use of such concomitant therapy.) In addition, the frequency of monitoring serum lithium concentration should be increased at the outset of such combination drug treatment.
- **Methotrexate:** NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.
- **NSAIDs:** The concomitant use of indomethacin with other NSAIDs is not recommended due to the increased possibility of gastrointestinal toxicity, with little or no increase in efficacy.
- **Oral anticoagulants:** Clinical studies have shown that indomethacin does not influence the hypoprothrombinemia produced by anticoagulants. However, when any additional drug, including indomethacin, is added to the treatment of patients on anticoagulant therapy, the patients should be observed for alterations of the prothrombin time. In post-marketing experience, bleeding has been reported in patients on concomitant treatment with anticoagulants and indomethacin. Caution should be exercised when indomethacin and anticoagulants are administered concomitantly. The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than

users of either drug alone.

- **Probenecid:** When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in small increments.

Drug/Laboratory Test Interactions: False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

8.4.5. Adverse Reactions

Headaches (12% to 16%) and vomiting ($\leq 12\%$) are the most frequently reported adverse reactions on indomethacin. Less frequent adverse reactions, include: presyncope ($\leq 3\%$), syncope ($\leq 2\%$), dizziness (3% to 9%), depression ($< 3\%$), drowsiness ($< 3\%$), fatigue ($< 3\%$), malaise ($< 3\%$), vertigo ($< 3\%$), pruritus (1% to 4%), hyperhidrosis (2%), skin rash (1% to 2%), hot flash (2%), epigastric pain (3% to 9%), heartburn (3% to 9%), nausea (3% to 9%), dyspepsia (2% to 9%), constipation ($\leq 6\%$), diarrhea ($\leq 3\%$), abdominal pain ($< 3\%$), decreased appetite ($\geq 2\%$), rectal irritation (suppository), tenesmus (suppository), tinnitus ($< 3\%$) and swelling (3%). For additional information on adverse reactions associated with indomethacin, please refer to the FDA prescribing information.

8.4.6. Dose Modifications for Toxicities Attributed to Indomethacin

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

Toxicity	Dose of Indomethacin
Grade 1	No change
Grade 2	Hold until return to Grade 1 or baseline, resume after discussion and agreement with medical monitor*

≥Grade 3 or higher	Hold until Grade 1 or baseline, resume at 25 mg three times daily*,**
Recurrence ≥Grade 3	Discontinue

*Note: Treatment will be permanently discontinued for Grade 3 toxicity lasting longer than 5 days, or any grade toxicity that has not resolved to Grade 1 or less within 2 weeks.

**Note: if a dose reduction is required, the patient will be provided with a supply of indomethacin 25 mg capsules.

8.4.7. Administration, Supply and Storage

Indomethacin is marketed, but not approved for the indication under study.

8.4.7.1. Administration

Indomethacin (Indocin®) will come in 50 mg capsules. The dose being tested in this study is 50 mg, or one capsule, by mouth three times daily. A 28-day supply will be provided at the beginning of each month of the trial.

8.4.7.2. Supply

Indomethacin (Indocin®) 50 mg capsules (opaque blue and white capsules, coded INDOCIN and MSD 50) will be packaged in 100 cc high-density polyethylene (HDPE) bottles with child-resistant closures (CRC). A 28-day supply will be provided at the beginning of each month of the trial.

8.4.7.3. Storage

Store at room temperature, between 59 and 86 °F (15 and 30 °C). Store away from heat, moisture, and light.

9. Data Monitoring and Adverse Event Reporting Requirements

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

Additionally, scheduled meetings will take place weekly and will include the protocol Principal Investigator (Michael Schweizer, MD), research nurse, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol.

During these meetings the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives. If

≥3 out of the first 10 subjects enrolled are removed from the study due to a safety issue, the trial will terminate prematurely. Depending on the number of patients removed from the study due to safety issues, study accrual may have to be put on hold until the 10th subject has completed the treatment period (i.e., through Day 85). For example, if 2 subjects were removed for safety reasons prior to accruing the 10th subject, accrual would not continue until the 10th subject completes the treatment period. Safety issues will be continually monitored and safety oversight will be provided through the weekly meetings between the PI and relevant staff.

9.1. Management of Safety Data

As the Sponsor-Investigator / Principal Investigator of the Study, Dr. Michael T. Schweizer shall be solely responsible for complying with required timelines, any safety-reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations.

This Study has been designated as an interventional study. As such, all adverse events regardless of causality and special situations excluding those from subjects not exposed to apalutamide, abiraterone, degarelix and/or indomethacin (hereafter referred to as Study Drugs) and product quality complaints with or without an adverse event as described in this clinical protocol, and pregnancies of partners, will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug. Note, adverse event collection is not expected to occur at the time of long-term telephone follow up (i.e., Days 450 and 815).

The following list of adverse events are expected and clearly related to prostatectomy and associated procedures. These will not be collected or reported at the Day 113 visit.

- Post-operative pain
- Constipation

- Hematuria
- Nausea
- Vomiting
- Bleeding
- Anemia
- Bladder leak

For the purposes of this study, the Janssen medicinal products are:

Abiraterone Acetate

Apalutamide

9.2. Definitions

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

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9.6. Evaluating Adverse Events

The grade and severity of the event will be determined using the DCT/NCI Common Terminology Criteria, CTCAE v.4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. Study staff must use one of the CTCAE criteria to define the event. Adverse events not included in the CTCAE v.4.0 should be reported and graded under the “Other” adverse event within the appropriate category and grade 1 to 5 according to the general grade definitions, mild, moderate, severe, life-threatening, fatal or disabling, as provided in the CTCAE.

The event will be determined to be expected or unexpected

The determination of whether an AE is expected is based on agent-specific adverse event information provided in Section 7 and 8 Pharmaceutical Information. Unexpected AEs are those not listed in the agent-specific adverse event information provided in Section 7 and 8 Pharmaceutical Information.

The event will be evaluated for relationship to the medical treatment or procedure. The Investigator should document his/her opinion of the relationship of the event to study medication as follows:

- *Unrelated*- The adverse event is clearly not related to the investigational agent(s).
- *Unlikely*- The adverse event is doubtfully related to the investigational agent(s).
- *Possible*-The adverse event may be related to the investigational agent(s).
- *Probable*-The adverse event is most likely related to the investigational agent(s).
- *Definite*- The adverse event is clearly related to the investigational agent(s).

Based on this information, a decision will be made whether an adverse event should be reported as an expedited report (Serious Adverse Event, section 3.0) in addition to the routinely reported clinical data. All expedited adverse event reports that meet reporting criteria per institutional requirements should be submitted to the Institutional Review Board (IRB) and to the FDA. Additionally, all SAEs should be submitted to Janssen Scientific Affairs, LLC within 24 hours of becoming aware of event and via secure e-mail.

9.6.1. Documenting Adverse Events

Each individual sign or symptom must be documented separately. Worksheets must be signed and dated by person conducting evaluation to be used as source documentation. The attribution of all adverse events must be verified by an investigator. Evaluation of laboratory toxicities may be documented directly on a printed laboratory report or CRF provided it is signed by the investigator. However, if an action was conducted due to this abnormality (e.g. RBC transfusion due to low Hgb) this would be recorded on the AE form also.

Recording should be done in a concise manner using standard, acceptable medical terms.

The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

- A. Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
- B. Surgery or procedure planned prior to entry into the Study.

If, in the Sponsor Investigator's judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

9.6.2. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs’ request.

9.6.3. Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Scientific Affairs will provide to the Principal Investigator a listing of all SAEs reported to the Janssen Scientific Affairs. The Principal Investigator will review this listing and provide any discrepancies to Janssen Scientific Affairs.

Upon request, the Principal Investigator shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

9.7. IRB Reporting

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9.8. Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB before implementation. Changes to the protocol or informed consent will be reviewed and approved by Janssen Scientific Affairs, LLC prior to submitting to the IRB for approval.

9.9. Informed consent

Written informed consent will be obtained by a study investigator or study research nurse working on this study. An explanation of the nature of study, its purpose,

procedures involved, expected duration, potential risks and benefits will be provided to each participant by the investigator or the research nurse. Each participant will be informed that participation in the study is voluntary and that he may withdraw from the study at any time, and that withdrawal of consent will not affect his subsequent medical treatment. Participants will be allowed time needed to make an informed decision. Participants will be encouraged to ask questions about the study and the consent before signing the consent form. Original signed consent forms will be filed in each patient's research chart, while each patient will receive a copy of the consent document. No patient will enter the study before his informed consent has been obtained.

10. Statistical Methods

This is an open-label, multi-site Phase II trial testing 3-months (12-weeks) of neoadjuvant apalutamide, abiraterone acetate, degarelix and indomethacin. The primary endpoint will be the pCR rate as assessed from prostatectomy specimens. Prior neoadjuvant hormonal therapy trials have documented pCR rates on the order of 5%, while still failing to show improvements in biochemical PFS or OS.^{10,11,14} Therefore, we would consider a pCR rate of $\leq 5\%$ to be insufficient evidence of activity to warrant further study in this patient population. The minimum level of activity we would require to consider further study with the proposed regimen would be a pCR rate of $\geq 25\%$. Therefore, based on an exact binomial test, if we observe ≥ 3 pCR out of a total sample size of 20, we would have 91% power at a one-sided alpha of 7.5% to detect a difference between $H_0 = 5\%$ and a $H_1 = 25\%$.³³

10.1. Data Analysis

The primary objective of this trial is to determine the pCR rate as determined from prostatectomy specimens following neoadjuvant treatment with 3-months (12-weeks) of apalutamide, abiraterone acetate, indomethacin and degarelix in men with high to very-high risk prostate cancer (per NCCN guideline). We will use a 1-sample chi-square test to compare the proportion with a pCR to the null hypothesis value of 5%. The 95% confidence interval (CI) of the primary endpoint estimate will be computed.

Secondary pathologic endpoints to be assessed from prostatectomy specimens following 3-months (12 weeks) of neoadjuvant therapy include: the negative margin rate, negative nodal metastases rate, near pCR (i.e. ≤ 5 mm of residual tumor) rate, the rate of pathologic T3 disease and apoptotic index (i.e. percentage of tumor cells undergoing apoptosis) as determined by cleaved caspase-3 immunohistochemistry. Other secondary endpoints will include: the proportion of men who receive adjuvant radiation therapy within 1-year of prostatectomy, the biochemical (i.e. PSA) progression free survival estimate two years after the last patient has accrued, the overall survival estimate two years after the last patient has accrued and safety (as assessed by CTCAE version 4.0). In addition, prostatectomy specimens and plasma samples will be stored at -80°C . These biologic specimens will be used for additional correlative work. Examples of studies to be conducted

may include, but are not limited to: assessment for genomic PTEN loss via fluorescence in situ hybridization (FISH), PTEN immunohistochemistry (IHC), assessment for alteration in MYC/chromosome 8q24 via FISH, RNAseq analysis, intraprostatic drug/androgen levels and serum drug/androgen levels.

The proportions of men who achieve pCR and near pCR, exhibit pathologic T3 disease, have no evidence for nodal metastases, and the proportion who receive adjuvant radiation therapy within the first year post-prostatectomy, and the proportions with specific adverse event grades will be computed along with their 95% CI. In addition, the PSA PFS and overall survival at 2 years after the last enrollment will be estimated using Kaplan-Meier methods and 95% CI will be estimated using Greenwood's formula.⁹⁶ PSA progression (i.e. biochemical failure) will be defined per the American Urological Association (AUA) guidelines (i.e. confirmed PSA post-radical prostatectomy ≥ 0.2 ng/mL).

We will characterize toxicity as percentage by type and grade. Changes in exploratory biomarkers pre- and post-treatment will be assessed using paired t-test or signed-rank test for continuous variables, or McNemar chi-square tests for categorical variables. In addition, baseline exploratory biomarker levels/values, as well as changes in these levels/values pre-/post-treatment will be correlated with the primary endpoint and secondary endpoints using chi-square tests and logistic regression, or (for PFS and OS) using proportional hazards models, Kaplan-Meier methods and log-rank tests.

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Appendix A
NCI COMMON TOXICITY CRITERIA, VERSION 4.0

Version 4.0 of the NCI CTC, dated 14 June 2010, may be viewed and/or downloaded by accessing the following website:

[Http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

**Appendix B
 Prohibited Concomitant Medications**

Generic Name	Brand Name*
aminophylline	Aminocont; Aminomal; Diaphyllin; Filotempo; Neophyllin; Norphyl; Phyllocontin; Syntophyllin; Tefamin; Truphylline; Xing You Shan;
aminophylline in combination	Asmeton; Cha Xin Na Min; Emergent-Ez; Fufang Dan An Pian; Ke Zhi
amitriptyline	Amirol; Amitrip; Amixide; Deprelia; Diapatol; Elatrol; cElatrolet; Elavil; Endep; Enovil; Emitrip; Klotriptyl; Laroxyl; Levate; Limbitrol; Limbitryl; Mutabase; Mutabon; Nobritol; Novo-Triptyn; Peritriptyl; Redomex; Saroten; Sarotex; Sedans; Syneudon; Teperin; Triptizol; Triptyl; Tryptizol
amitriptyline in combination	PMS-Levazine
bupropion	Aplenzin; Buproban; Contrave; Elontril; Forfivo; Fortivo XL; Le Fu Ting; Prexaton; Quomem; Voxra; Wellbutrin; Wellbutrin XL; Wellbutrin SR; Yue Ting; Zyban
chlorpromazine	Aminazin; Chlorazin; Hibernol; Klorproman; Largactil; Megaphen; Ormazine; Plegomazin; Solidon; Taroctyl; Thorazine; Vegetamin; Wintermin; Zuledin Note: in Ireland also called "Clonazine" – very easy to confuse with clozapine.
clozapine	Azaleptin; Clopine; Closastene; Clozaril; CloZAPine; Denzapine; Elcrit; Fazacio ODT; Klozapol; Lanolept; Leponex; Lozapine; Nemea; Ozapim; Synthron, Versacloz; Zaponex
desipramine	Deprexan; Norpramin; Nortimil; Pertofrane
doxepin	Adapin; Anten; Aponal; Deptran; Gilex; Li Ke Ning; Quitaxon; Silenor; Sinepin; Sinequan; Zonalon
imipramine	Impril; Melipramin; Mipralin; Norfranil; Novo-Pramine; Persamine; Pertofram; Pryleugan; Talendep; Tofranil; Tolerade
lithium	Arthriselect; Camcolit; Carbolith; Carbolithium; Eskolith; Hypnorex; Li-Liquid; Licarbium; Limas; Liskonum; Litarex; Lithane; Lithicarb; Lithioderm; Lithionit; Lithobid; Liticarb; Litiomal; Lito; Maniprex; Neurolepsin; Plenur; Priadel; Quilonorm; Quilonum; Saniquiet; Sedalit; Teralithe
lithium in combination	Boripharm No 23; Emser Salz; Girheulit HOM; Helidonium-Plus; Heweurat N; rheuma-loges; Rhus Toxicodendron Compose; Rhus-Plus; Ricinus Compose
maprotiline	Cronmolin; Deprilept; Ludiomil; Mapromil; Melodil; Neuomil; Psymion
meperidine/pethidine	Alodan ; Atropine and Demerol; Centralgine ; Demerol ; Dolantin ; Dolantina; Dolantine ; Dolargan; Dolcontral; Dolestine ; Dolosal ; Dolsin; Fada; Hospira; Liba; Mepergan ; Meprozone; Mialgin; Opystan; Pethidine ; Petigan Miro ; Psyquil compositum

meperidine/pethidine in combination	Pamergan P100
mesoridazine	Serentil, Mesorin
mirtazapine	Arintapin; Avanza; Axit; Combar; Esprital; Mi Er Ning; Miro; Mirta TAD; Mirtabene; Mirtachem; Mirtadepi; Mirtagamma; Mirtalan; MirtaLich; Mirtamylan; Mirtaron; Mirtaz; Mirtazelon; Mirtazon; Mirtazonal; Mirtel; Mirtin; Mirtor; Mirzaten; Norset; Noxibel; Paidisheng; Psidep; Remergil; Remergon; Remeron; Remirta; Rexer; Yarocen; Zispin
olanzapine	Anzorin, Arenbil; Arkolamyl; Atyzyo; Bloonis; Clingoza; Egolanza; Lansyn; Lanzek; Lazapix; Nolian; Nykob; Olafid; Olanzaran; Olanzep; Olanzin; Olanzine; Olapin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Oulan Ning; Ozilormar; Parnassan; Ranofren; Sanza; Stygapon; Synza; Ximin; Zalasta; Zamil; Zappa; Zapris; Zerpi; Zolafren; Zolaxa; Zonapir; Zopridoxin; Zylap; Zypadhera; Zypine; Zyprexa; Zyprexa Relprew; Zydis
olanzapine in combination	Symbyax
risperidone	Aleptan; Apo-Risperid; Arketin; Calmapride; Diaforin; Doresol; Hunperdal; Jing Ping; Ke Tong; Leptinorm; Lergitec; Orizon; Ozidal; Perdox; Ranperidon; Resdone; Ridal; Ridonex; Rileptid; Ripedon; Risepro; Rispa; Rispaksole; Rispefar; Rispemylan; Rispen; Rispera; Risperanne; Risperdal; Risperdalconsta; Risperdaloro; Risperigamma; Risperon; Rispolept; Rispolux; Rispond; Rispons; Risset; Rixadone; Rorendo; Ryspolit; Si Li Shu; Sizodon; Speridan; Suo Le; Torendo; Zhuo Fei; Zhuo Fu; Ziperid; Zoridal
theophylline	Aerolate; Afonilum; Aminomal; An Fei Lin; Apnecut; Apo-Theo; Asmalix; Asmalon; Bi Chuan; Bronchoparat; Bronchoretard; Cylmin; Diffumal; Elixifilin; Elixophyllin; Etipramid; Euphyllin; Euphyllina; Euphylline; Euphyllong; Frivent; Gan Fei Lin; Nuelin; Protheo; Pulmophylline; Quelesu; ratio-Theo-Bronc; Respicur; Retafyllin; Shi Er Ping; Slo-Bid; Slo-Phyllin; Telbans; Teotard; Terdan; Teromol; Theo-24; Theo-Dur; Theo; Theochron; Theodur; Theofol; Theolair; Theoplus; Theospirex; Theostat ; Theotard; Theotrim; Theovent; Tromphyllin; Unicon; Unicontin; Unifyl; Uniphyl; Uniphyllin Continus; Uniphyllin; UniXan; Xanthium; Xi Fu Li; Yan Er
theophylline in combination	Antong; Baladex; Bi Chuan; Binfolipase; Broncho-Euphyllin; Broncomar; Do-Do ChestEze; Elixophyllin-GG; Elixophyllin-KI; Insanovin; Marax ; Neoasma; Theofol Comp; Theophedrinum-N; Xu Hong; Yi Xi Qing
thioridazine	Detril; Elperil; Melleril; Ridazin; Ridazine; Thiodazine; Thioril; Sonapa
ziprasidone	Geodon; Li Fu Jun An; Pramaxima; Si Bei Ge; Ypsila; Zeldox; Zipwell; Zypsila; Zypsilan

**** Note: this document is intended as an aid in identifying prohibited meds, but due to the global scope of the Apalutamide studies may not be all inclusive.**

Appendix C Follow-up Letter Template

Dear Mr. [insert subject name],

I am writing to follow up with you regarding the clinical trial you participated in around the time of your prostate surgery. In this trial you received apalutamide, abiraterone acetate, prednisone and indomethacin, which were pills taken every day for 3 months. You also received monthly injection of degarelix during this time period.

As part of this study, we are seeking to determine if you have received any additional treatment for your prostate cancer and if your cancer has relapsed. We kindly ask that you answer the following questions to the best of your ability and respond either by phone, postal mail or email (contact information is below).

Questions:

1. What was your most recent PSA? On what date was this test done?
2. Have you had any imaging tests to determine if your prostate cancer has spread anywhere? These could include CT scans, bone scans, or other similar tests.

If yes, please indicate the type of scan(s), date the scan was performed and if the scan revealed signs of cancer.

3. Since your prostate surgery, have you received any additional treatment for prostate cancer? These could include radiation therapy or hormone therapies (also known as androgen deprivation therapy).

If yes, please indicate the type of treatment(s) and on what date each treatment was started and stopped.

Sincerely,

[Insert study coordinator's name, address, email and phone number]

