FOX CHASE CANCER CENTER
TEMPLE HEALTH

GU-079 Bicalutamide with or without metformin for biochemical recurrence in prostate cancer patients (BIMET-1)

Sponsored by Fox Chase Cancer Center

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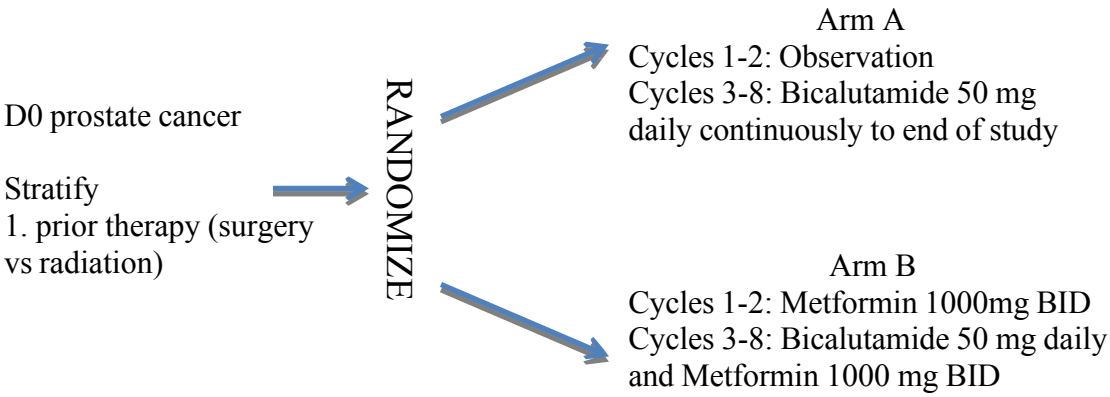
Schema



1 Cycle = 28 days = 4 weeks. Treatment will be administered on an outpatient basis

[x] Metformin starting dose is 500 mg BID, will be gradually increased to target dose of 1000mg BID (see dosing table below).

Treatment ARM A

Cycles 1 – 2: Observation without treatment

Cycles 3 – 8: Bicalutamide 50 mg daily, orally, continuously to the end of study (week 32).

Treatment ARM B

Cycles 1 - 2: In order to minimize gastrointestinal discomfort, metformin dosing will be ramped up over a period of 2 weeks. Metformin treatment will be started at 500 mg BID (Dose Level -2) and increased by an increment of 500 mg daily every week +/- 2 days provided no grade 2 or higher gastrointestinal toxicity is noted. If grade 2 or greater gastrointestinal toxicity occurs during the first 4 weeks of treatment, the subject will be evaluated every 2 weeks until resolution of toxicity to grade 0 or 1 and, then, the metformin dose will be increased to the next dose level. The target dose of metformin is 1000 mg BID. If patient cannot tolerate higher dose, metformin will continued at maximum tolerated dose as listed below.

Dose level	**Metformin dose**
Dose Level -2 (Week 1 +/- 2 days)	500 mg twice daily
Dose Level -1 (Week 2 +/- 2 days)	500 mg breakfast / 1000 mg at bedtime
Dose Level 0 (Week 3 and later)	1000 mg twice daily

Cycles 3 – 8: Continue metformin at maximum tolerated dose (up to 1000 mg BID). Start bicalutamide 50 mg/daily, orally, on a continuous basis to the end of study (week 32).

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1.0 INTRODUCTION

1.1 Biochemical recurrence of prostate cancer

Around 161,360 men will be diagnosed with prostate cancer in the United States in 2017 and an estimated 26,730 will die of the disease[1]. About 20 to 40% of patients undergoing radical prostatectomy (RP)[2] and 30 to 50% of patients undergoing radiation therapy (RT) at some time point will experience rising prostate specific antigen (PSA) following definitive therapy in the absence of visible metastases on imaging[3], a condition known as biochemical recurrence (BCR)[4]. The definition of BCR is dependent upon the type of local therapy. Biochemical recurrence after RP is defined by PSA level greater than 0.2 ng/mL measured 6 - 13 weeks after RP, followed by a confirmatory test showing a persistent PSA > 0.2 ng/mL [5]. Biochemical recurrence after RT is defined as a PSA rise of 2 ng/mL or more above the nadir, regardless of whether or not a patient receives androgen deprivation therapy (Phoenix definition)[6]. The Phoenix definition has shown improved accuracy over the ASTRO (American Society for Radiation Oncology) definition of biochemical failure (defined as three consecutive PSA rises following a nadir) in predicting clinical failures and has been widely used in clinical practice[7].

In this asymptomatic phase of the disease, the most effective management is still unknown since no intervention has been shown to prolong survival. Acceptable treatment options include: 1) salvage radiation therapy for BCR after prostatectomy; 2) salvage prostatectomy in selected cases after RT; 3) observation with close surveillance; 4) intermittent or continuous androgen deprivation therapy (ADT); or 5) enrollment in clinical trials.

Several retrospective studies demonstrated that early ADT has no significant effect on overall survival (OS) since it decreases prostate cancer-specific mortality (PCSM) but increases non-prostate cancer specific mortality[8-10]. Retrospective study by Garcia-Albeniz and colleagues presented at 2014 Annual ASCO Meeting used the CaPSURE registry to evaluate data from 2,012 patients with PSA-only relapse after radical prostatectomy or radiation therapy. Patients who underwent immediate ADT demonstrated no significant advantage in all-cause mortality (HR=0.94) or prostate cancer-specific mortality (HR=1.15). Estimated 5-year OS rates of 85.1% in the immediate ADT arm and 87.2% in the deferred ADT arm, and estimated 10-year OS was 71.6% in both arms, indicating that there may be no need for immediate ADT treatment in BCR patients[11].

Patients with BCR have a variable clinical course: some will have indolent course with no impact their OS; others may have a rapid progression to radiographically apparent metastasis with increased risk for dying from prostate cancer. Comparison of outcomes demonstrated that patients with BCR have a 88% 10-year OS rate in contrast to the 93% 10-year OS rate in men without BCR[12]. In a landmark study evaluating BCR following RP, the median time from BCR to clinical progression was noted to be 8 years and from metastasis to PCSM was 5 years[13], indicating that median OS from the diagnosis of BCR was around 13 years.

PSA doubling time (PSADT) after the prostate cancer treatment can also be used to provide some insight into prognosis. A study of 432 T1-3N0M0 prostate cancer patients who developed BCR following definitive three-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) from 1989 to 2005 demonstrated that PSADT remains a significant predictor of clinical failure and prostate cancer specific survival. Immediate use of ADT in patients with PSADT of <6 months was significantly associated with improved prostate cancer specific survival, although the survival benefit was less apparent in patients with longer PSADT[14].

Choueiri and colleagues reported a retrospective analysis of 3,071 men who underwent radical prostatectomy at Duke University (between 1988 and 2008). After a median follow-up of 7.4 years from the time of RP, 17.8 % men had had a BCR and 14.8 % had died of all causes. The median follow-up after PSA failure was 11.2 years. In men who experienced BCR, a PSA doubling time <6 months was associated with a significantly increased risk of overall death from any cause (HR = 1.55)[15].

D'Amico and colleagues have suggested that men who have a BCR with a PSADT > 15 months after RP are at minimal risk for prostate cancer metastasis or prostate cancer specific mortality, whereas those with a PSADT of 3 months or less are at very high risk. Another study of 8,669 patients with prostate cancer treated with RT (5,918 pts) or RP (2,751 pts) found that a PSADT < 3 months was also significantly associated with prostate cancer specific mortality[16].

A retrospective study of patients with BCR who were enrolled in four clinical trials at Johns Hopkins University of the non-hormonal agents: marimastat (a matrix metalloproteinase inhibitor), imatinib, ATN-224 (a copper/zinc-superoxide dismutase inhibitor) and lenalidomide demonstrated that changes in PSADT were prognostic for metastasis-free survival, which may suggest that the onset of metastasis may be delayed if an experimental agent is capable of significantly prolonging the PSADT[17].

In summary, the value of ADT is not clear in BCR population and no study has shown that therapeutic intervention in this setting may improve overall survival. Further research is needed to determine the optimal initiation point of ADT, and whether alternative therapies may delay the need for ADT and prolong survival in this patient population.

1.2 Androgen receptor role in prostate cancer

Several studies demonstrated that the androgen receptor (AR) plays a crucial role in pathogenesis of prostate cancer[18] and its progression in castration resistant disease[19]. AR is a member of the steroid receptor super family and controls expression of several genes involved in cell survival, differentiation, proliferation, and metabolism[20]. AR activation and overexpression are consistent findings in castration resistant clones, demonstrating the pivotal role of this molecular pathway[21]. The regulation of AR activation can be initiated by ligand-dependent and ligand-independent mechanisms [22].

Ligand-dependent activation is the predominant pathway in normal and castration sensitive prostate cancer cells. In the castrate environment it is sustained in part by overexpression and mutations of AR that exploit multiple mechanisms[23] including AR hypersensitivity to very low intracellular levels of androgens[24] and promiscuity for binding other steroid hormones (such as progesterone and estradiol) [25]. In addition, prostate cancer cells develop ligand independent mechanisms to synthesize their own androgens by increasing the expression of genes that convert adrenal androgens to testosterone[26]. Therefore, both pathways of AR activation remain activated in castration-resistant disease.

Antiandrogens regulate AR function by competing for agonists binding to the AR, by decreasing AR phosphorylation by various growth factors[27] and by preventing recruitment co-activators to initiate transcription of target downstream genes[28]. In the clinic, antiandrogens, such as bicalutamide, have been used in non-castrate and castration resistant prostate cancer patients[29]. There is a strong rationale for considering the AR as a therapeutic target in recurrent, non-castrate prostate cancer (BCR).

In the early 1990's, single agent bicalutamide (50 mg daily) was tested as monotherapy in metastatic prostate cancer patients with high PSA levels. By 3 months, 20% of patients had a PSA decline of 85%, and by 6 months, 40% of the patients reached a 90% decline. Those who achieved this response had longer OS; however, this was inferior to complete androgen blockade (castration). Single agent bicalutamide (50 mg daily) was also recently tested as one arm of ECOG 2809 study in patients with BCR and results are pending.

In another study, single agent bicalutamide at higher dose (150 mg daily) was compared to combined androgen suppression with orchiectomy or Zoladex (LHRH agonist) and flutamide (an antiandrogen) in patients with locally advanced prostate cancer. At 6.3 years follow-up there was no statistical difference between the two groups in time to progression or OS (56% mortality); however, there was a significant improvement in QOL in the bicalutamide arm due to improved emotional well-being, physical capacity and sexual interest[30].

In a smaller study 41 BCR patients were treated with high-dose (150 mg) bicalutamide and finasteride (5α-reductase inhibitor) but no androgen deprivation therapy. Thirty-four of 36 evaluable patients reached a PSA nadir that represented a decline of PSA by 95.5%. The median time to treatment failure was 21.3 months in more advanced patients with median PSA values at study entry of 19.1 ng/mL. At a follow up of 3.9 years, disease control was comparable to castration[31].

Monk et al[32] used a combination of finasteride and flutamide to treat 101 BCR patients with rising PSA between 1 and 10 ng/mL after primary therapy. Combined peripheral androgen blockade regimens achieved an undetectable (<0.2 ng/mL) PSA in 40 - 77% of patients depending on whether the PSA levels at study entry were above or below 10

ng/mL respectively and, achieved the nadir in 4 - 6 months. A ≥ 80% PSA decline was seen in 96% patients. The median time to PSA progression was 85 months. With a median follow-up of 10 years, the median survival time had not been reached, and the 5-year OS rate was 87%.

The existing data supports that in BCR patients starting hormone treatment achieving an undetectable PSA nadir (<0.2 ng/mL) may predict for a longer survival than those whose PSA remains detectable. Thus, an undetectable PSA nadir promises to be the most accurate measure of disease response and an important endpoint for clinical trials evaluating new approaches in hormone naïve patients. However, PSA declines ≥ 85% may also be considered to explore the activity of novel androgen-sparing combinations in a similar group and time frame.

1.3 Clinical Experience with Metformin

Metformin is a well-tolerated and inexpensive oral agent that is commonly used to treat diabetes mellitus and insulin resistance. It reduces serum glucose levels by inhibiting glycogenolysis and gluconeogenesis[33]. By inhibiting gluconeogenesis in the liver and increasing glucose uptake in skeletal muscle, metformin reduces glucose levels, increases insulin sensitivity and reduces hyperinsulinemia[34]. Metformin for the treatment of diabetes mellitus was approved in the 1970s in Europe and in 1995 in the United States. Its use in diabetes has shown to increase OS and prevent macrovascular complications better than other oral hypoglycemic drugs[35]. Metformin today has a wide variety of clinical indications: polycystic ovarian syndrome (PCOS), where insulin resistance is a key factor for the development of the metabolic disturbances. In this setting, it has a favorable effect on hyperlipidemia and hypertension[36]. It is also used in the management of the metabolic syndrome[37] and prevention of diabetes in high-risk population[38].

Its most potentially dangerous toxicity is lactic acidosis (3 cases per 100,000 patient years). Lactic acidosis is extremely rare if metformin use is restricted to individuals without any of predisposing conditions. Additional toxicities include: gastrointestinal (>1/10 - diarrhea, nausea, vomiting, abdominal bloating, flatulence, anorexia, metallic taste) which is usually transient when treatment is started and resolving spontaneously with continued treatment, rash (< 1/10,000), low vitamin B12 (9% after 6 months – it is suggested that vitamin B12 and/or hemoglobin levels be monitored at 6 - 12 months interval), hepatic dysfunction (<1/10,000), TSH elevations (< 1/10,000). Modest weight loss (up to five pounds) is common. Hypoglycemia does not normally occur when metformin is administered – extreme caloric restriction or excessive physical activity without adequate caloric intake may rarely lead to hypoglycemia.

1.4 Metformin and its role in cancer

Metformin has recently received increased attention for its potential anti-tumor effects that are thought to be independent of its hypoglycemic effects. The anti-tumor effect of metformin it is not completely understandable and has been attributed to several mechanisms:

activation of LKB1/AMPK pathway, inhibition of protein synthesis, induction of cell cycle arrest and/or apoptosis, reduction in circulating insulin levels, activation of the immune system and eradication of cancer stem cells.

The major link between metformin and cancer is believed to be the AMPK upstream kinase LKB1 (Fig. 1). Metformin activates LKB1 (tumor suppressor protein that is mutated in Peutz-Jeghers syndrome and inactivated in 30 – 50% NSCLC and other tumors[39]) and its downstream target AMPK, which, in turn, suppresses the activity of the mammalian target of rapamycin (mTOR), a signaling pathway with a central role in cancer cell growth and cancer pathogenesis. AMPK is a central cellular energy sensor whose activation leads to suppression of many of the processes highly dependent on ample cellular ATP supply, including gluconeogenesis, protein and fatty acid synthesis and cholesterol biosynthesis, while promoting catabolic processes such as fatty acid beta-oxidation and glycolysis[40].

Several studies demonstrated that activation of AMPK plays a prominent role in mediating the effects of metformin[41, 42]. Metformin decreases ATP synthesis and a rise in the cellular AMP:ATP ratio, effectively mimicking conditions of cellular energy stress[43]. While most research into metformin action has focused on insulin-responsive tissues, evidence suggests that cancer cells can initiate an AMPK-dependent energy stress response to metformin.

Another possible anticancer mechanism could be the decrease in circulating insulin levels since studies have demonstrated that type II diabetes and obesity are associated with an increased risk of cancer. Cancer cells express insulin as well as insulin-like growth factor receptors (IGF-R) and that, besides its metabolic effect, IGF-R promotes proliferation and metastasis[44]. Hyperinsulinemia may promote tumor growth by various indirect mechanisms too, such as proliferation of epithelial tissue, increasing bioavailability of steroid sex hormones and serum levels of insulin-like growth factors (IGF), as well as disrupting the homeostasis of adipokines, which are cytokines selectively secreted by adipose tissue and thought to be implicated in cancer pathogenesis. Anticancer effects of metformin have been demonstrated in a number of tumor model systems including the prostate, ovarian, breast, colorectal and endometrial carcinoma[45-47].

Although typically the antitumor effect of metformin has been attributed to its ability to activate the LKB1/AMPK/mTOR pathway or direct inhibition of insulin/IGF-mediated cellular proliferation, in reality the mechanism of action of this drug is much more complex. Intriguingly, there are some novel data to suggest metformin may specifically target cancer stem cells, which are hypothesized to be resistant to conventional therapies and be a major reason for recurrence following radiation or chemotherapy[48].

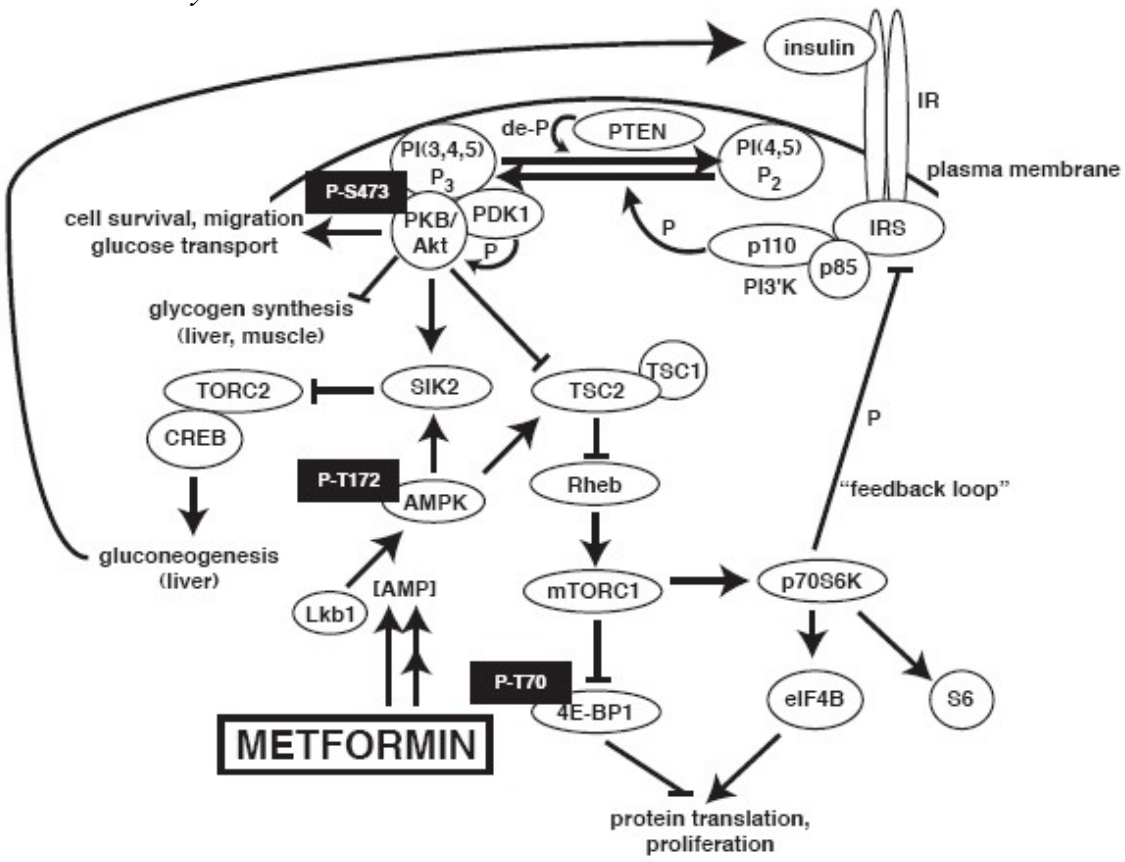
Interest in metformin as an anticancer agent began when endocrinologists noticed that diabetic patients taking metformin had a lower incidence of cancer. Evans et al. first described an association between metformin and decreased cancer incidence in 2005[49]. Several other retrospective studies showed that patients with diabetes taking metformin were less likely to

be diagnosed with cancer and that those who were diagnosed were less likely to die. Retrospective analysis of data from the ZODIAC trial, whose primary outcomes were diabetes-related complications, revealed that cancer related mortality was lower in patients taking metformin (HR 0.43; 95% CI 0.23 – 0.80)[50].

Noto and colleagues reported meta-analysis with 11,117 (5.3%) cases of incident cancer at any site reported among 210,892 patients in 10 studies (2 RCTs, 6 cohort studies, 2 case-control studies). The risks of cancer among metformin users were significantly lower than those among non-metformin users: the pooled RRs (95% CI) were 0.66 (0.49–0.88) for cancer mortality, 0.67 (0.53–0.85) for all-cancer incidence, 0.68 (0.53–0.88) for colorectal cancer (n = 6), 0.20 (0.07–0.59) for hepatocellular cancer (n = 4), 0.67 (0.45–0.99) for lung cancer (n = 3)[51].

Figure 1

Simplified schematic of the molecular mechanism of metformin action. Phospho-specific antibody epitopes relevant to key molecular markers are highlighted within the black boxes. An additional marker, stathmin 1 (STMN 1), is a surrogate marker for the signaling throughput via the PI3K/PTEN signaling pathway that can be monitored by immunohistochemistry.



1.5 Metformin and prostate cancer

Several preclinical studies have demonstrated an effect of metformin on inhibiting growth of multiple cancer cell lines including prostate and breast. Ben Sahra and colleagues showed that metformin caused 50% decrease in cell viability in human prostate cancer cell lines (DU145, PC-3 and LNCaP) compared with only a modest 20% decrease in a normal prostate cell line (P69), suggesting that metformin may specifically target the prostate cancer cells[45]. Metformin was also reported to activate AMPK and to cause growth inhibition in prostate and colon cancer cells[52].

Study published by Demir et al. suggested that mechanism for the anti-tumor activity of metformin in prostate cancer cell lines is independent of its anti-diabetic effects[53]. Metformin disrupted the AR translational MID1 regulator complex leading to release of the associated AR mRNA and subsequently to down-regulation of AR protein in AR positive cell lines. Metformin reduced levels of cyclin D in prostate cancer cells in vitro and in vivo and blocked cell cycle in G(0)/G(1) phase. Interestingly, this effect was independent of AMKP, and it was only observed in malignant cells and not normal prostate cells[54].

Colquhoun and colleagues randomized LNCaP prostate cancer xenografts on a high-carbohydrate, high-fat (HC-HF) diet into four treatment groups; control (n=16, vehicle only), metformin alone (n=8), bicalutamide alone (n=9) or combined metformin and bicalutamide (n=8). Metformin was dissolved in cell culture medium and was administered at a dose of 50 mg/kg. Bicalutamide was dissolved in DMSO and was also administered at a dose of 100 μg/kg. Both drugs were administered on days 12, 14, 16, 19, 21 and 23 by intraperitoneal injection. Treatment with metformin and/or bicalutamide was well tolerated. Study revealed no significant difference in tumor volume in mice treated with metformin when compared with untreated control mice ($P = 0.15$). Conversely, mice treated with bicalutamide had significantly smaller tumors than untreated control mice ($P = 0.02$), and mice treated with a combination of metformin and bicalutamide had highly significantly smaller tumors than untreated mice ($P < 0.0004$). Serum PSA was significantly elevated in all treatment groups at the experiment termination, compared with levels obtained before treatment (P=0.001).Treatment with metformin did not reduce PSA levels significantly (P=0.97), whereas treatment with bicalutamide or the combination of metformin + bicalutamide significantly reduced PSA levels (34.0 and 19.0 ng/ml, respectively, P=0.002). The serum PSA level for the combination treatment regimen was significantly lower than that for either monotherapy ($P = 0.002$)[55].

In a population-based case–control study of 1001 patients with prostate cancer and 942 controls, metformin use was associated with a 44% risk reduction in prostate cancer incidence in Caucasians[56]. Spratt and colleagues from at Memorial Sloan-Kettering Cancer Center studied 2901 consecutive patients (157 diabetic patients on metformin, 162 diabetic

patients not on metformin, and 2582 non-diabetic patients) with localized prostate cancer treated with external-beam radiation therapy from 1992 to 2008. With a median follow-up of 8.7 years, the 10-yr actuarial rates for metformin, diabetic non-metformin, and nondiabetic patients for prostate cancer specific mortality were 2.7%, 21.9%, and 8.2% (log-rank $p \leq 0.001$)[57]. Surprisingly, metformin strongly decreased the clinically defined transformation to CRPC which at the end may improve prostate cancer specific mortality[57].

Margel et al[58] reported that duration of metformin treatment among diabetic men after a diagnosis of prostate cancer was associated with decreased prostate cancer–specific and all-cause mortality. This population-based observational cohort study included 3,837 men who were identified from several Ontario health care databases from 1997 to 2008. Eligible patients had to be at least 66 years of age and have been diagnosed with diabetes followed by a diagnosis of prostate cancer. By the end of follow-up in 2009 (median, 4.64 years), 1,343 men had died (35%), including 291 (7.6%) from prostate cancer. Prostate cancer–specific mortality was decreased by 24% for each additional 6 months of metformin use after diagnosis; use of other antidiabetic medications did not significantly decrease prostate cancer–specific mortality.

Metformin as a single agent has shown modest therapeutic activity in patients with castration-resistant prostate cancer (CRPC). A single arm Phase II study enrolled 42 patients with chemotherapy naïve mCRPC treated with metformin 1000 mg twice daily until disease progression (defined as PSA increase 25% above baseline, progression of measurable disease or bone lesions, clinical progression, and start of palliative radiotherapy or death at week 12). 36% of patients were progression-free at 12 weeks, 9.1% were progression-free at 24 weeks, and in two patients had ≥ 50% PSA decline. In 23 patients (52.3%) a prolongation of PSADT was observed. Additionally, insulin sensitivity markers improved by 26% in the first 12 weeks of treatment. This study demonstrated that treatment with metformin is safe in non-diabetic patients[59].

Joshua et al. reported the results of the study of 24 men (median age 64, median PSA 6 ng/mL) with confirmed prostate cancer that were given 500 mg of metformin three times a day before the surgery (neoadjuvant treatment). Median duration of drug treatment was 41 days (range 18 - 81). No grade 3 adverse events were reported, all patients underwent subsequent radical prostatectomy with no adverse events related to metformin. Significant pre-and postoperative changes were noted in serum IGF1 ($p=0.02$), fasting glucose ($p=0.03$), BMI ($p<0.01$). PSA reduction was not statistically significant ($p=0.08$). In addition, metformin reduced Ki67 proliferation index by 29%, compared to the baseline biopsy[60].

Despite exciting in vitro and preclinical evidence of metformin's antineoplastic activity, the clinical evidence has been confusing. Although metformin does not appear to be associated with a reduced prostate cancer risk or with a reduced risk for recurrence after surgery[61]; there is strong suggestion that metformin may reduce risk of castration resistant disease development and death from prostate cancer by 25% to 45%[62, 63] .

1.6 Obesity and prostate cancer

Two-thirds of the adult male population in the US is overweight or obese[64] and excess bodyweight deregulates several pathways such insulin levels, free insulin growth factor 1 (IGF-1), adiponectin, and sex hormones that could potentially affect prostate cancer outcomes. Several studies have demonstrated association between obesity and the incidence of prostate and other cancers[65]. It has been postulated that increased insulin resistance and adipokines may play an important role [66]. Circulating levels of adiponectin and leptin in obese patients may also be important in prostate cancer pathogenesis[67]. Adiponectin levels (inhibitory adipokine) are reduced in obese patients, while leptin levels are increased, which at the end may promote prostate cancer growth[68]. This theory is supported by evidence showing that hyperinsulinemia upregulates insulin receptors in PCa cells and increases tumor growth[69]. Hyperinsulinemia and metabolic syndrome may play a role in carcinogenesis and be negatively associated with prostate cancer prognosis[70]. Increased insulin level decreases sex hormone-binding globulins, and causing an increase in free unbound androgens which at the end may lead to worse prognosis[71]. In prostate cancer patients treated with RP, obesity was associated with higher-grade tumors, a trend toward increased risk of positive surgical margins, and higher biochemical failure rates[72]. In diabetic patients, obesity is associated with higher risk of high-risk prostate cancer, which is independent of the lower risk for prostate cancer in diabetic patients[73]. The lower risk for prostate cancer in diabetic patients is possibly explained by lower levels of testosterone in these patients[74]. Another retrospective study showed that the presence of metabolic syndrome was associated with a shorter median time to progression (16 vs 36 months) and median OS (36.5 vs. 46.7 months) in prostate cancer patients receiving ADT[75] .

Cao and Ma recently reported a meta-analysis of six post-diagnosis survival studies on 18,203 patients with 932 deaths and found that 5 kg/m(2) increase in BMI was associated with 20% higher prostate cancer-specific mortality. The sixteen studies followed 26,479 prostate cancer patients after their primary treatment, a 5 kg/m(2) increase in BMI was significantly associated with 21% increased risk of BCR (RR: 1.21, 95% CI: 1.11-1.31 P < 0.01). This study demonstrated that elevated BMI is associated with increased risk of biochemical recurrence and prostate cancer-specific mortality[76]. Unanswered question is does weight loss reduce the risk of recurrence, the development of metastases, and death from prostate in men with the disease?

1.7 Rationale and Hypothesis

Obesity and metabolic syndrome are prevalent among prostate cancer patients. Hyperinsulinemia is associated with a shorter median time to progression and median OS in patient with biochemical recurrence. Early ADT is frequently used in this patient population, with no proven benefit, which may increase mortality and morbidity.

Metformin is an inexpensive and safe drug that may have anticancer activity through

both insulin-dependent and insulin-independent mechanisms, which involve activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), inhibiting mTOR signaling pathway[77]. Recent evidence suggests activation of AMPK leads to down regulation of AR[78] and inhibits xenograft growth of several PCa cell lines[54]. Metformin should work better in early, castrate sensitive prostate cancer since in castration resistant disease AR signaling is increased (through amplification, mutations, and intracellular androgen stimulation) which may hamper metformin's ability to inhibit cancer growth.

Bicalutamide is a non-steroidal antiandrogen, which functions by blocking the AR. It exerts its effect predominantly through induction of a G1/S phase arrest of the cell cycle[79]. Published preclinical data suggest the additive anticancer effects of combining metformin and bicalutamide in the prostate cancer patients with metabolic syndrome and possible synergistic activity with antiandrogens: in AR-positive cells, this effect appeared to be mediated by reducing proliferation rates by modulating the AR, whereas in AR-negative cells the combination treatment appeared to promote apoptosis.

HYPOTHESIS*:*

Metformin will enhance the antitumor effects of the antiandrogen bicalutamide in the setting of preserved testosterone, effectively delaying onset of metastases while preserving quality of life in overweight and obese men with castrate naïve non-metastatic prostate cancer with biochemical recurrence.

2.0 OBJECTIVES

2.1 Primary endpoint:

The proportion of patients with undetectable PSA (< 0.2 ng/mL) at 32 weeks with metformin plus bicalutamide compared to bicalutamide monotherapy.

2.2 Secondary endpoints:

- The proportion of patients with PSA decline > 85% at 32 weeks with metformin plus bicalutamide compared to bicalutamide monotherapy.
- The time to PSA progression with metformin plus bicalutamide compared to bicalutamide monotherapy.
- To evaluate the time to onset of radiographic evidence of metastatic disease (rPFS) with metformin plus bicalutamide compared to bicalutamide monotherapy.
- To characterize the PSADT changes pre-study, during treatment, and off treatment.
- To evaluate the safety and tolerability of metformin in this patient population.
- To evaluate QOL with metformin plus bicalutamide compared to bicalutamide monotherapy.
- To evaluate the time to next therapy (i.e. antiandrogen or GnRH antagonist/agonist).

2.3 Exploratory endpoints:

- Immunogenicity of bicalutamide +/- metformin by flow cytometric analysis of T-cell frequency, activation status, cytokine profiles, antibody levels and analysis of sCD27 and sCD40L
- Evaluate circulating PSA levels and correlations with immunogenicity and/ or efficacy

3.0 PATIENTS SELECTION

3.1 Inclusion Criteria

3.1.1 Ability to understand and the willingness to sign a written informed consent.

3.1.2 Male 18 years or older.

3.1.3 Histologically or cytologically confirmed diagnosis of prostate cancer.

3.1.4 Patient must have had previous treatment with definitive surgery or radiation therapy or cryoablation.

3.1.5 Patient may have prior salvage therapy (surgery, radiation or other local ablative procedures) within 6 months prior to randomization if the intent was for cure. Prophylactic radiotherapy to prevent gynecomastia within 4 weeks prior to randomization is allowed.

3.1.6 Patient may have had prior neoadjuvant and/or adjuvant therapy (chemotherapy, vaccines or experimental agents) within 4 weeks prior to randomization, if the PSA rise and PSADT were documented after the testosterone level was > 150 ng/dL.

3.1.7 Patients may have had therapy modulating testosterone levels (such as luteinizing-hormone, releasing-hormone agonists/antagonists and antiandrogens) in the past as long as the testosterone level is > 150 ng/dL within 4 weeks of trial entry. Agents such as 5 alpha reductase inhibitors, ketoconazole, abiraterone, systemic steroids, or herbal supplements known to decrease PSA levels including any dose of Megestrol acetate, Finasteride (e.g., Saw Palmetto and PC-SPES, African pygeum extract, lycopene, alanine, glutamic acid and glycine, beta-sitosterol, lycopene, nettle root extract, quercitin, Belizian Man Vine extract, mulra puama extract and epimedium extract Campesterol, Beta- sitosterol, Stigmasterol, Sitostanol and Brassicasterol) are not permitted at any time during the period that the PSA values are being collected.

3.1.8 Patient must have hormone-sensitive prostate cancer as evident by a serum total testosterone level > 150 ng/dL within 12 weeks prior to randomization.

3.1.9 PSA must be < 30 ng/mL at study entry.

3.1.10 Patient must have evidence of biochemical failure after primary therapy and

subsequent progression. Biochemical failure is declared when the PSA reaches a threshold value after primary treatment and it differs for radical prostatectomy or radiation therapy.

- For radical prostatectomy the threshold for this study is PSA ≥ 0.2 ng/mL
- For radiation therapy the threshold is a PSA rise of 2 ng/mL above the nadir PSA achieved post radiation with or without hormone therapy (2006 RTGO-ASTRO Consensus definition).
- PSA progression requires a PSA rise above the threshold measured at any time point since the threshold was reached.

3.1.11 PSA doubling time between 3 and 12 months. PSA calculation requires at least two consecutive PSA rises (PSA2 and PSA3) above the threshold PSA (at least 3 PSA values); PSA2 and PSA3 must be obtained within 12 months of study entry. All baseline PSAs should be obtained at the same reference lab. Patient's PSA doubling time must be calculated using the following formula (http://www.mskcc.org/nomograms/prostate/psa-doubling-time):

$$\text{PSADT in days} = \frac{0.693\ (t)}{\ln (PSA3) - \ln (PSA2)}$$

Where t = the number of days between PSA3 and PSA2

ln = the natural log

PSADT in months = PSADT in days divided by 30.4375

3.1.12 ECOG performance status 0 to 2.

3.1.13 Ability to swallow the study drugs.

3.1.14 Subjects must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1,000/mL
- Hemoglobin ≥ 10 g/dL
- Platelets ≥ 100,000/mL
- Total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT) ≤ 1.5 X institutional ULN
- Creatinine clearance ≥ 60 mL/min/1.73 m2
- Hgb A1c ≤ 6.5%

3.2 Exclusion Criteria

3.2.1 Evidence of metastatic disease on imaging studies (CT, x-ray, and/or bone scan).

3.2.2 Diagnosis of diabetes mellitus defined as:

- Fasting blood glucose > 126 mg/dl or,
- Random blood glucose > 200 mg/dl
- Hemoglobin A1C > 6.5%

3.2.3 Need for treatment with any conventional modality for prostate cancer (surgery, radiation therapy, and hormonal therapy).

3.2.4 Treatment with any investigational drug 30 days prior to randomization.

3.2.5 Radiation therapy within prior 6 months (prophylactic radiotherapy to prevent gynecomastia within 4 weeks prior to randomization is allowed).

3.2.6 Known hypersensitivity to metformin.

3.2.7 Prior history of lactic acidosis.

3.2.8 Any history of myocardial infarction in the past 12 months.

3.2.9 Subjects who consume more than 3 alcoholic beverages per day.

3.2.10 Subjects with serious intercurrent illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or other nonmalignant medical or psychiatric illness that is uncontrolled or whose control may be jeopardized by the complications of this therapy or may limit compliance with the study requirements (at the discretion of the investigator).

3.2.11 Patient with previous or concurrent malignancy. Exceptions are made for patients who meet any of the following conditions: Basal cell or squamous cell carcinoma of the skin or prior malignancy that has been adequately treated and patient has been continuously disease free for $\geq$ 2 years.

3.2.12 Subjects currently treated with metformin and/or bicalutamide or who have been treated with metformin and/or bicalutamide in the past 6 months.

3.2.13 Subjects who have taken 5a-reductase inhibitors (finasteride or dutasteride), saw palmetto, or PC-SPES within the last 6 weeks are ineligible. Subjects will be eligible for the study after the wash out period of 6 weeks.

4.0 PROTOCOL MANAGEMENT

4.1 Registration and Randomization Procedures

Participants may be registered from 8:00 am to 4:00 pm EST excluding holidays by emailing the Investigator-Sponsored Research Unit (ISRU) at: **FCCC.MONITOR@fccc.edu.** Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist

Following registration, participants must begin protocol treatment within 7 calendar days of registration. Issues that would cause treatment delays must be discussed with the Sponsor-Investigator. If a registered participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled. For additional registration questions, please email **FCCC.MONITOR@fccc.edu** or call **(215) 728-5544.**

The FCCC ISRU will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to the initiation of treatment.

Exceptions to the current registration policies will not be permitted.

5.0 TREATMENT PLAN

5.1 Informed Consent and Consent for Tissue Collection

Prior to study entry, all patients must sign inform consent. All patients will be presented with the option to donate a biopsy specimen for research purposes, and consent for this will be documented separately within the informed consent.

5.2 Baseline Disease Assessment

Imaging will be performed as described in the Study Calendar (Section 6.0).

5.3 Study Treatment

Upon initiation of treatment, both agents will be administered orally at the assigned doses and schedules. One cycle = 28 days = 4 weeks. Treatment will be administered on an outpatient basis.

5.3.1 Treatment ARM A

Cycles 1 – 2: Observation without treatment
Cycles 3 – 8: Bicalutamide 50 mg daily, orally, continuously to the end of study (week 32).

5.3.2 Treatment ARM B

Cycles 1 - 2: In order to minimize gastrointestinal discomfort, metformin dosing will be ramped up over a period of 2 weeks. Metformin treatment will

be started at 500 mg BID (Dose Level -2) and increased by an increment of 500 mg daily every week +/- 2 days provided no grade 2 or higher gastrointestinal toxicity is noted. If grade 2 or greater gastrointestinal toxicity occurs during the first 4 weeks of treatment, the subject will be evaluated every 2 weeks until resolution of toxicity to grade 0 or 1 and, then, the metformin dose will be increased to the next dose level. The target dose of metformin is 1000 mg BID. If patient cannot tolerate higher dose, metformin will continued at maximum tolerated dose as listed below.

Dose level	**Metformin dose**
Dose Level -2 (Week 1 +/- 2 days)	500 mg twice daily
Dose Level -1 (Week 2 +/- 2 days)	500 mg breakfast / 1000 mg at bedtime
Dose Level 0 (Week 3 and later)	1000 mg twice daily

Cycles 3 – 8: Continue metformin at maximum tolerated dose (up to 1000 mg BID). Start bicalutamide 50 mg/daily, orally, on a continuous basis to the end of study (week 32).

5.4 Guideline for Study Medication Administration

5.4.1 Pill Diary

A blank pill diary (Appendix I) will be provided to the patient by the study coordinator at cycle 1 and at each subsequent visit, and a completed pill diary should be returned by the patient at Day 1 of cycle 2 and each subsequent cycle.

5.4.2 Bicalutamide

Bicalutamide will be self-administered by the patient once daily. It may be taken with or without food. The tablet should be taken at approximately the same time every day. Bicalutamide and metformin may be taken together.

5.4.3 Metformin

Metformin will be taken at the assigned dose twice daily. Metformin is administered orally, with food. Bicalutamide and metformin may be taken together.

5.4.4 Missed doses

Patients who forget to take their scheduled dose of study drug should be instructed not to make up the missed dose. Missed doses of study drug should be recorded in the patient's study record.

5.5 Dose Modifications

All toxicities should be graded according to the Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). Dose modifications will be based on the highest grade since the prior dose and will be performed as outlined below depending on the type and severity of the toxicity encountered, provided that the criteria have not been met for subject withdrawal from study. Patients will be withdrawn from the study if they fail to recover to CTCAE grade 0-2 (or within 1 grade of starting values of pre-existing laboratory abnormalities) from a treatment related toxicity within 4 weeks. Treatment may be delayed no more than 4 consecutive weeks to allow recovery from toxicity or the patient will be removed from the study. Dose modifications are not necessary for Grade 1 or 2 toxicities. The reason for dose modification, delay, and missed doses must be detailed in the source document. Dose re- escalation will not be allowed during this study.

5.5.1. Dose Modifications for Metformin

The major toxic effects of metformin which limit dose are gastrointestinal (nausea, abdominal bloating, diarrhea). During the ramp-up period, subjects experiencing gastrointestinal symptoms should be encouraged to take tablets with food. If no improvement, subjects should try taking study medication every other day for two weeks, once per day for two weeks and then twice per day thereafter. Subjects not tolerating study medication after this approach may go off study treatment but Investigators are urged to re-challenge willing subjects 4 weeks later. Dose adjustments, for reasons of toxicity, will be as in the tables below. (Please note that none of the recommended dose adjustments require splitting of study medication pills. Pills are not to be split or crushed, prior to taking, for any reason.) Breaks of up to 4 weeks consecutively or 8 weeks overall are allowed to ascertain the cause of the adverse events.

Gastrointestinal Toxicity **Toxicity / Adverse Event**	**Grade**	**Investigator Action**
Gastrointestinal Toxicity of any type	Grade 1	Patient should be encouraged to remain on full dose. If patient is unwilling, stop study treatment for one week. For subjects who were unwilling to remain on full dose, after one week without study drug, follow the ramp-up procedure. If Grade 1 symptoms persist or recur during the ramp-up or at full dose and the patient is unwilling to continue, follow instructions for Grade 2 toxicity.
Nausea Distension/Bloating Diarrhea Gastrointestinal - Other	Grade 2 (or higher)	Reduce to 500 mg BID for one week. If symptoms resolve or are Grade 1 only, after one week, resume full dose (1000 mg BID). If symptoms persist or recur at Grade 2 or higher, stop study treatment for 4 weeks, then resume study treatment as follows: Re-start study drug according to original ramp-up schedule. If toxicity persists or recurs, the study drug should be adjusted to the maximum dose that is tolerated with Grade 1 toxicity or lower. A second attempt to increase to full dose should be made 4 weeks later and if the full dose is not tolerated at that time, the maximum tolerated dose should be used for the remainder of the study.

Hepatic dysfunction* (bilirubin > ULN except for Gilbert's Disease)	Grade 1 (or greater)	Hold study drug for up to 4 weeks. If bilirubin returns to normal within that time frame, begin 500 mg BID for 4 weeks, then 1000 mg BID.
Hepatic dysfunction* AST or ALT=1.8- 3.0 X ULN		Repeat AST & ALT in 2 weeks. If either AST or ALT > 1.8 X ULN, continue at discretion of Investigator, monitoring AST & ALT every two weeks until both < 1.8 X ULN – then resume annual testing. If Investigator decides to stop medication, resume once AST &ALT < 1.8 X ULN, starting with 500 mg BID for 4 weeks, then increasing to 2 tablets per day with annual AST & ALT assessments
Hepatic dysfunction* AST or ALT > 3.0 X ULN		Hold study drug. Repeat LFTs in 2 weeks. If AST and ALT < 1.8 ULN, resume medication. Resumption involves 500 mg BID for 4 weeks, then increase to 1000mg BID per day with resumption of protocol specified monitoring if both AST and ALT remain at < 1.8 x ULN. If repeat AST and ALT are 1.8-3.0 x ULN, follow steps as described in section above. If AST and/or ALT > 3.0 x ULN, initiate workup for liver disease. If AST or ALT=1.8-3.0 resume medication at the discretion of the investigator.
Renal dysfunction Creatinine > 115 µmol/L 1.3 mg/dL		Hold study drug for up to 4 weeks. After resolution of event, use ramp-up schedule.
Clinical diagnosis of congestive heart failure	> Grade 3	Hold study drug for up to 4 weeks. Re-start may be considered if underlying condition (e.g. acute MI) has resolved. If Metformin is started after CHF, the ramp-up schedule should be used. Do not re-start if symptoms persist or ongoing treatment of CHF is required.
Acidosis (Lactate > 5.0 mM) (pH < 7.3)	Grade 3	Stop study drug and do not re-start. Report as a serious adverse event.
Anemia Hgb < 110 or MCV > 105	> Grade 1	Perform CBC and serum B12 level. Initiate anemia workup if cause of anemia not apparent. Continue at full dose. (Treatment is not held for anemia regardless of toxicity grade.)
Skin Reactions Major – generalized urticaria, bullous rashes, exfoliative dermatitis	Generalized	Stop study drug and do not re-start

Stevens Johnson Syndrome Localized	Localized	Hold study drug for up to 4 weeks if possibly, probably or definitely related to study drug. When rash clears, 500 mg BID per day for 4 weeks, then 1000 mg BID per day – if rash recurs, and is thought to be possibly, probably or definitely related to study medication, discontinue study medication.
Hospitalization for any reason		Hold study drug for up to 4 weeks. The Investigator is to determine when it is safe to re-start. The drug should be re-started using a schedule (if the hospitalization resulted in discontinuation of the drug for 2 weeks or longer. If the discontinuation of the drug was less than 2 weeks, the drug should be re-started at full dose without a ramp-up.

* Be alert to signs of acidosis; protocol specific biochemistry should be checked annually. If subject develops malaise, nausea, dark urine, jaundice or right upper quadrant pain, study medication should be stopped until biochemistry is performed. Medication should be resumed according to the algorithms above (if first biochemistry results are normal, resume immediately at full dose)

Other Situations

Diagnostic Imaging:
If the subject is scheduled for any CT scans requiring intravenous contrast material, metformin should not be taken for 24 hours prior to the investigation or for 48 hours after the procedure. (This does not include contrast used for MRI or nuclear medicine scans, including MUGA). Study medication will then be resumed at full dose (without ramp-up) provided there is no concern about renal function. If there is concern about renal function, creatinine should be checked prior to resumption of study medication.

***General Anesthetic**:*
If general anesthetic is required for surgery, study drug should not be taken on the morning of surgery or for 48 hours after anesthetic and surgery. Study medication will then be resumed at full dose (without ramp-up) provided there is no concern about renal function. The drug is restarted at full dose if the duration of interruption was less than 2 weeks. If the duration of drug interruption was more than 2 weeks, it should be restarted using a 4 week ramp-up schedule (one caplet per day for 4 weeks, then two caplets per day). If there is concern about renal function, creatinine should be checked prior to resumption of study medication.

Any Situation Considered Medically Necessary:
Study medication may be held in any situation which the Investigator considers it medically necessary, for up to 4 weeks.

5.5.2. Dose Modifications for Bicalutamide
Not allowed. In case of CTCAE grade 3 or 4 transaminase elevation, bicalutamide will be stopped until the event resolved to Grade 1 or less.

5.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 8 cycles (32 weeks) or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.7 Medication Compliance

At each study visit, patients should be instructed on the proper dosing regimen. Any missed doses should be documented in the patient's study record. Patient should be instructed not to make up any missed doses.

5.8 Concomitant Medications and Treatments

All concomitant medications received within 28 days before the first dose of study medication and 30 days after the last dose of study medication will be recorded in the patient study records, including all prescription, over-the-counter, herbal supplements, and intravenous medications and fluids. Any changes to the concomitant medication regimes should be recorded throughout the study.

5.9 Duration of Follow-up

All patients will be followed for response during 32 weeks, and followed for survival, adverse events, and disease status every 12 months (+/- 2 months) for up to 5 years from end of treatment. Any patients who experience adverse events should be followed until one of the following occurs:
Resolution of the adverse event to ≤ Grade 1 or baseline severity.
Determination that the adverse event is stable and will not resolve.
Initiation of another anti-cancer treatment.

6.1 STUDY PROCEDURES

6.1 Schedule of Assessments

A Cycle is defined as 4 weeks. Patients will be evaluated according to the schedule in Table 1.

Table 1. Schedule of assessments

		Treatment cycles[2]									
Assessment	Screening[1]	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Off Treatment[7]	Follow Up[9]
Informed consent	x										
Tissue collection consent	x										
Demographics	x										
Medical history	x										
Concomitant Medications	x		x	x	x	x	x	x	x	x	
Review of Systems	x		x	x	x	x	x	x	x	x	
Physical exam[2]	x		x	x	x	x	x	x	x	x	
Vital signs[3]	x		x	x	x	x	x	x	x	x	
Adverse event recording			x	x	x	x	x	x	x	x	X
Height	x										
Weight	x	x	x	x	x	x	x	x	x	x	
ECOG PS	x		x	x	x	x	x	x	x	x	
CBC with differential[6]	x			x						x	
Serum Chemistry[4,6]	x		x	x	x	x	X	x	x	x	
Fasting Lipids[5,6]	x			x						x	
PSA[6]	x	x	x	x	x	x	X	x	x	x	
Testosterone[6]	x	x	x	x	x	x	X	x	x	x	
HgbA1c	x			x						x	
Vitamin B12	x									x	
CT CAP with IV contrast[8]	x										
Bone scan*	x										
Research blood	x			x						x	
Research blood, optional	X			X						X	
FACT – P, version 4	x									x	
Survival & disease status9											X

1. Physical examinations, blood tests must be performed within 2 weeks of treatment.
2. Evaluation is scheduled Day 1 of each cycle **+/-** 2 days to allow for logistical issues.
3. Vital signs include temperature, pulse, respiratory rate, and blood pressure
4. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, phosphorous, magnesium, total protein, SGOT, SGPT, sodium

5. Cholesterol, LDL, HDL, Triglycerides.
6. All Labs (CBC, chemistries, fasting lipids, PSA, and testosterone) may be drawn up to 3 days prior to day 1 if site is unable to obtain results on day of treatment.
7. Off treatment evaluation should be scheduled at week 33 +/- 2 days to allow for logistical issues.
8. At physician discretion, a Chest x-ray can be done in place of a Chest CT at screening. Repeated bone or CT scans can be ordered during treatment if clinically indicated.
9. Follow up by telephone will occur once annually for 5 years, starting a year after the off-treatment visit +/- 2 months.

6.2 Screening

All patients must undergo pre-treatment evaluations. Pre-treatment evaluations will be used to determine the patient's study eligibility and will include a history and physical (including height and weight), ECOG performance status score, vital sign measurements, CBC with differential and platelet counts, and serum chemistry profiles. Imaging studies for baseline tumor assessment will be performed within 6 weeks of the initiation of therapy. Patients must sign an informed consent form prior to undergoing protocol-specific evaluations (prior imaging studies are allowed in order to decrease radiation exposure) and receiving treatment. Patients may be re-screened if they previously failed the pre-treatment evaluation. Rescreening must occur 3 months or more from last screening and a maximum of 2 re-screenings are allowed.

6.3 Treatment Evaluations

Patients will be examined by the treating physician or designee on day 1 of each cycle prior to treatment. This examination will include a physical exam, toxicity assessment, concomitant medication review, and performance status. The physical exam must not occur more than 14 days prior to day 1 treatment. Chemistries, PSA, testosterone will be performed every 4 weeks, prior to each cycle. All required labs (such as CBC, chemistries, lipids, PSA, testosterone, etc) may be drawn up to 3 days prior to day 1 if site is unable to obtain results on day of treatment.

6.4 End of Study and Follow up

Patients will have an evaluation and physical examination when they are taken off study treatment or complete study treatment (week 33). The reason for ending study treatment must be described in the source document and in OnCore. This evaluation will include a physical examination (including weight and vital signs), ECOG performance status score, CBC with differential and platelet counts, serum chemistry profiles, PSA, testosterone, HgbA1c, fasting lipids, research blood collection and toxicity assessment. Patients will be contacted every 12 months (+/- 2 months) to collect survival information, disease status, and the presence of persistent AEs for the next 5 years.

7.0 MEASUREMENT OF EFFECT

7.1 Definitions of Biochemical Response and Progression

7.1.1 Complete Response: PSA <0.2 ng/mL confirmed on two consecutive

additional determinations taken at least 4 weeks apart.

7.1.2 ***Partial Response:*** A reduction in PSA ≥ 50% from baseline without evidence of clinical or radiographic progression confirmed on two consecutive additional determinations taken at least 4 weeks apart.

7.1.3 ***Stable Disease:*** Patients who do not meet the criteria for response (CR or PR) or serological progression for at least 3 months (90 days) will be categorized as having stable disease.

7.1.4 ***Progressive Disease:***

1) For patient who achieved a ≥ 50% decline in PSA, progression is defined as an increase in PSA value by 50% above baseline or nadir (whichever is lowest), confirmed by a second PSA rise at least two weeks later. The PSA rise must be at least 5 ng/mL. Changes in PSA below 5 ng/mL will not be considered assessable for progression.

2) For patients with an undetectable PSA nadir (< 0.2 ng/mL), progression is defined as a PSA rise to the detectable range (detectable PSA is ≥ 0.2 ng/mL) confirmed by a second PSA rise at least 2 weeks later.

3) For patients whose PSA has not decreased by 50%, progression is defined as an increase in PSA value ≥ 50% of baseline (on trial) or nadir PSA, whichever is lowest, confirmed by a repeat PSA at least 2 weeks later. The PSA must have risen by at least 5 ng/mL.

7.2 Radiographic Progression

The appearance of new lesions on examination or radiographs (CXR, CT scan, MRI scan, or bone scan) with or without a concurrent increase in serum PSA from baseline.

7.3 Survival

Survival will be measured from the date of randomization.

7.4 Time to PSA Progression

Time to PSA progression is defined as time from randomization to first confirmed rise in PSA (or development of clinical progression) meeting progressive criteria after starting bicalutamide treatment.

7.5 Time to PSA Nadir

Time to PSA nadir is defined as the time from randomization to the date that PSA nadir is documented. PSA nadir is defined as the lowest PSA value achieved after registration or baseline PSA, whichever is lowest.

7.6 PSA Slope

The change in PSA will be graphically depicted and a PSA slope calculated. The change in PSA slope (and PSADT) pre-study, during-study, and off-study will be determined to see if the treatments have any disease modifying effects, especially in those patients experiencing stable disease. This end-point is exploratory, but may help to interpret PSA response.

7.7 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration.

7.8 Duration of Response

The period measured from the time that PSA criteria are met for complete or partial response (whichever status is recorded first) until the first date that progressive disease is documented.

7.9 Quality of life (QOL)

Quality of life will be assessed during the screening visit and after the study completion using The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. It is a relevant, worldwide tool used for assessing the health-related quality of life in men with prostate cancer.

8.0 TISSUE COLLECTION AND CORRELATIVE STUDIES

8.1 Pathology Review

There will be no central pathology review for this study. Patient must have diagnosis of prostate cancer histologically confirmed at the participating institution.

8.2 Tissue Collection

The collection of a representative block of the diagnostic tumor tissue (if available) is an important part of this trial; however, the participation of subjects is optional. Blocks will be carefully banked as part of the Fox Chase tissue/tumor bank. Tumor blocks will be the preferred material to collect, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumor block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by

courier on request.

The tissue may be used by researchers now or in the future to better understand the nature of prostate cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial the surgical/ histology number and/or patient initials. Material issued to

researchers will be anonymized and only identified by a coded number. Diagnostic pathology reports are received as part of the supporting documentation required for this trial. Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the subject. All subjects on whom a diagnostic tumor block is collected will be aware of this retrieval and will have given their consent.

8.2.1 Use of Tumor Blocks

As part of the embedded correlative science for the protocol, the following research is planned using archival tissue samples collected and banked at the time of study entry:

a) Insulin Receptor (IR)

We plan to quantify IR expression by IHC and correlate results with clinical outcomes.

b) LKB1

We plan to quantify LBK1 expression by IHC and correlate results with clinical outcomes. LKB1 expression is key to the ability of metformin to affect AMPK activity within tumors and to suppress the growth-promoting outputs of this signaling pathway (i.e. mTOR-regulated protein translation). LKB1 expression is essential for direct (insulin independent) effects of metformin.

c) Phosphoantibody Markers of Activation of Key Signaling Pathways

Expression of IR and LKB1 will be indicative of the capacity of tumor cells to respond to indirect (insulin and IR mediated) and direct (insulin independent, LKB1 mediated) effects of metformin respectively, however, the expression of these factors cannot distinguish whether the pathways underling these responses are actually activated. Multiple other genetic factors may alter pathway activation. As a result, activation markers of these pathways [PI3K (STMN1), PKB/Akt (P-PKB/Akt,) mTOR (P-4E-BP1) and IRS-1 (P-IRS-1)] will be evaluated as predictors of metformin benefit. If one or more of these biomarkers are activated at prostate cancer diagnosis, it is predicted that metformin benefit is possible. If none of these pathways is activated, it is predicted that metformin benefit will not be seen, regardless of IR and/or

LKB1 expression.

8.3 Use of Blood Samples

Correlative studies will be an integrated component of the clinical trial. Investigations of fasting glucose and insulin levels at baseline, 9 weeks post randomization and at the end of study treatment will be mandatory and will explore the indirect insulin-mediated effect of metformin on protocol defined outcomes. Other measurement will include, but not limited to IGF1 level Inhibition of the downstream targets of the mTOR pathway: 4E-BPI and p70S6K1, IGF-1/IGFBP-3 (observed on peripheral blood mononuclear cells (PBMCs).

a) **Genomic/Gene Expression Profile Predictive of Metformin Benefit** Large-scale genomic studies over the past two decades have identified numerous recurrent genetic events in prostate cancer. More recent studies are focusing on building a comprehensive, genome-wide understanding of various types of prostate cancer. We plan to use such analyses to search for a genomic/gene expression profile predictive of metformin benefit. In the case of observed metformin benefit, we will perform comprehensive genomic/gene expression analysis of peripheral blood and available tumor material. Considering rapid technical advances in the genomic analysis arena, at the time of analysis, we will choose the most appropriate methodology to delineate the genetic/gene expression predictors of metformin benefit.

b) **Blood Collection and Analysis** Investigation of a core group of blood variables (at baseline, 9 weeks after enrolment and at the end of treatment) and tumor related factors (at diagnosis) will be examined as predictors of metformin benefit in this trial is outlined below. We will also collect additional samples that will allow us to examine a broader array of both prognostic and predictive factors in future work. The blood collection for fasting glucose and insulin is a mandatory part of the baseline, 9 weeks and end of treatment measurements.

   After an overnight fast of at least 12 hours, participants will provide the following blood specimens: 1 tube for immediate glucose analysis (performed according to established institutional practice), light green topped tubes (containing lithium heparin - for plasma), red topped tubes (for serum) and lavender topped tube (for DNA). *Lavender topped tubes for DNA should be collected even for patients who consent to blood banking but refuse genetic testing. DNA may be used to study gene expression without fitting the definition of genetic testing.* The green topped tubes will be centrifuged within half an hour of collection and the plasma collected frozen immediately in 1 ml aliquots at -80°C. The red topped tubes will sit for 30 minutes at room temperature and then be centrifuged and the collected serum frozen immediately in 1 ml aliquots at -80°C. Lavender topped tubes (whole blood in EDTA) will be collected and frozen at -80°C in 1 ml aliquots for subsequent thawing and DNA extraction. Specimens will be stored at

participating centers immediately after collection and then shipped to a central laboratory, frozen on dry ice, in batches of 10 sets or more (1 set = entire blood collection at one patient visit), for subsequent storage and ultimate analysis. Our plan to collect lymphocytes for DNA at both baseline and at the end of study (week 33) will provide the necessary sample to evaluate not only germline DNA but also potential changes in DNA methylation as a result of the metformin intervention.

In addition to blood samples collection listed above additional blood samples will be collected at the NCI site for immune assessments in some patients (exploratory): 6 (10mL) green top sodium heparin tubes for PBMC and 2 (8mL) SST tubes for serum samples) at baseline, week 9 and week 32 (end of study). Immune assessments will be performed at the Laboratory of Tumor Immunology and Biology at the NCI's Center for Cancer Research (CCR) and will include flow cytometry-based and serum assays. Samples will be analyzed in batches after enrolling all patients in order to ensure best laboratory practices and quality data. From samples acquired the following assays will be performed:

1 Analyses of PBMCs: PBMCs separated by Ficoll-Hypaque density gradient centrifugation, will be analyzed for changes in standard immune cell types (CD4 and CD8 T cells, natural killer [NK] cells, regulatory T cells [Tregs], myeloid-derived suppressor cells [MDSCs], and dendritic cells) as well as 123 immune cell subsets, as described elsewhere (Lepone et al 2016)[80].

2 Analyses of soluble factors: Sera will be analyzed pre- and post-therapy for the following soluble factors: sCD27 and sCD40 ligand.

3 Additional assays: Blood samples may be used for additional research studies, which may include phenotypic and functional analysis of immune-cell subsets (such as CD4 and CD8 T cells, NK cells, Tregs, and MDSC), T cell clonality, circulating tumor cells, RNA and proteomic analyses, and analyses of cytokines (such as IFN-γ, IL-10, IL-12, IL-2, IL-4, etc.), chemokines, antibodies, tumor-associated antigens, and/or other markers.

c) Insulin (plasma)

Our core analyses will explore the indirect, insulin mediated, effect of metformin as a predictor of invasive disease free survival (primarily), overall survival and prostate cancer free interval, including an evaluation of both baseline fasting insulin (primarily), change in insulin over 9 weeks (secondarily) and at the end of treatment. This primary focus on insulin reflects the recognition that insulin at diagnosis is a prognostic factor in prostate cancer, and it reflects the major impact metformin has on insulin levels; our hypothesis is that higher insulin

level at baseline will predict metformin benefit in the overall study population. Additionally, in exploratory analyses we will examine the relationship between changes in insulin level during the first 6 months of metformin administration.

d) Glucose (plasma)

We plan to examine whether baseline glucose predicts metformin benefit independent of insulin or whether glucose modifies effects of insulin as a predictor of metformin benefit. We will also investigate Homeostasis Model Assessment (HOMA), an empirically derived estimate of insulin sensitivity calculated from a single measure of fasting insulin and glucose that correlates well with the gold standard frequently sampled intravenous glucose tolerance test, as a predictor of metformin benefit, focusing on whether it provides additional prediction beyond insulin alone

Research Blood Samples Taken at Baseline and Again at 9 weeks and at End of Study Treatment	One Tube (7 ml) (1.4 teaspoons)	Light Green Top Tubes (3 x 4.5 ml) (2.7 teaspoons)	Red Top Tube (2 x 6 ml) (2.4 teaspoons)	Lavender Top Tube (1 x 6 ml) (1.2 teaspoons)
	Sera for Fasting Glucose *(done locally according to institution's procedures & mandatory)*	Insulin *(done centrally & mandatory)* Plasma for storage for future research *(optional)*	Serum for storage for future research *(optional)*	DNA extraction *(done centrally & optional)* *Lavender topped tubes for DNA should be collected even for patients who consent to blood banking but refuse genetic testing. DNA may be used to study gene expression without fitting the definition of genetic testing.*

Research Blood Samples Taken at Baseline and Again at 9 weeks and at End of Study Treatment	Green Top Sodium Heparin tubes (6 x 10 ml)	SST tubes (2 x 8 ml)

	PBMC for immune assessments *(done at the NCI & mandatory)*	Serum samples for soluble factor analyses *(done at the NCI & mandatory)*

TOTAL VOLUME DRAWN = 114.7 ML

9.0 BACKGROUND THERAPEUTIC INFORMATION

9.1 Metformin (Please refer to the package insert for more comprehensive information.)

9.1.1 Availiability: Metformin is commercially available

9.1.2 Other Names: Glucophage; Glumetza; 1,1-Dimethylbiguanide; Metiguanide; Diabex; Dimethylbiguanide; Metforminum; Diabetosan; Fluamine: a commercially available agent.

9.1.3 Chemical Name: 3-(diaminomethylidene)-1,1-dimethylguanidine

9.1.4 Molecular Formula: C4H11N5
Metformin HCl is a white crystalline powder soluble in water and 95% ethyl alcohol. It is practically insoluble in ether and in chloroform. Melting Point: 218-220o C

9.1.5 Mode of Action:
Metformin HCl is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the diabetic animal and only when there is insulin secretion. Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effects on the pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that metformin might potentiate the effect of insulin or reduce hepatic gluconeogenesis. Metformin absorption is relatively slow and may extend over about 6 hours. The drug is excreted in urine at high renal clearance rate of about 450 mL/min. The initial elimination of metformin is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5 % of the absorbed dose is slow

with a halflife between 9 and 17 hours. Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady-state ranges about 1 to 2 mcg/mL. Certain drugs may potentiate the effect of metformin HCl, particularly sulfonylurea type of drugs in the treatment of diabetes. The simultaneous administration of these two types of drugs could produce a hypoglycemic reaction, especially if they are given in patients already receiving other drugs which, themselves, can potentiate the effect of sulfonylureas. These drugs can be: long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propanolol. In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to sulfonylureas, which are extensively bound to serum proteins.

Human Toxicity

In man, no adverse effect has been reported on liver or kidney function, the hematopoietic system or on the blood vessels. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases / 1000 patient/years with approximately 0.015 fatal cases / 1000 patient/years). The consecutive administration of both phenformin and metformin to the same patient has allowed for the demonstration of a fundamental difference between these two biguanides in relation to lactacidemia. In some instances, patients developed hyperlactacidemia with phenformin when the same patients were presenting normal lactic acid levels while being treated with metformin. In other instances, hyperlactacidemia observed during a treatment with phenformin did regress when metformin was substituted for phenformin. Metformin may increase lactacidemia but to a degree that is clinically less significant than the elevation seen after phenformin.

Teratology

Teratological studies were carried out in albino rats divided in three groups: No abnormalities were found, even when high doses were administered. The number of animals was the same in each group. Death rate in the three groups of treated animals and controls was approximately the same. However, the number of living animals in each group treated was slightly lower than in the control group. Also, the frequency of litters exceeding 10 live animals was slightly higher in the control group. A loss of weight at the time of weaning has been observed when compared to the control group. Nevertheless, on a statistical basis, differences were shown to be non-significant. There is no difference between the groups of treated animals and the control group regarding the number of stillborn. The number of deaths after birth was slightly higher in metformin treated groups than in the control group, but the

comparison of average death rates is not significant ($p > 0.05$).

9.1.6 How Supplied: It will not be provided by the study (Commercial supply)

9.1.7 Storage: Store at room temperature (15° to 30°C) in well-closed containers

9.1.8 Dose Specifics: 1000 mg twice daily orally, continuously to the end of study (for details of dose escalation please see Section 5.4.3). The tablets should be taken at approximately the same time every day.

9.1.9 Route of Administration: Metformin is administered orally, with food

9.1.10 Side Effects: Please refer to protocol section heading "Clinical Experience with Metformin" for a summary of adverse effects.

9.1.11 Dose Adjustments
Please see section **5.5.1.**

9.1.12 Concomitant Therapy

Permitted
Subjects may receive bisphosphonates, at the discretion of their treating physician, before during or after randomization and study treatment with metformin.

Not permitted
Sulfonylureas, thiazolidenediones or insulin for any reason unless these drugs become necessary to treat a new diagnosis of diabetes mellitus while on study therapy in which case the patient will discontinue study treatment. Subjects should avoid excessive alcohol intake (i.e. less than 3 alcoholic beverages on any given day). Androgen deprivation therapy is not permitted.

9.2 Bicalutamide (Please refer to the package insert for more comprehensive information.)

9.2.1 Availiability: Bicalutamide is commercially available

9.2.2 Other Names: Casodex®, a commercially available agent.

9.2.3 Chemical Name: Propanamide, N-[4-cyano-3-(trifluromethyl)phenyl]-3-[4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-,(+/-)

9.2.4 Molecular Formula: C18H14N2O4F4S

9.2.5 Mode of Action: Competitive inhibitor of androgen binding to cytosolic androgen receptors.

9.2.6 How Supplied: White, film-covered oral tablet containing 50 mg of bicalutamide. It will not be provided by the study (Commercial supply)

9.2.7 Storage: Controlled room temperature, 20-25°C.

9.2.8 Dose Specifics: 50 mg/daily orally beginning Cycle 3 (week 13), continuously to the end of study (please see Section XXX). The tablet should be taken at approximately the same time every day.

9.2.9 Route of Administration: Oral, may be taken with or without food.

9.2.10 Side Effects:

The most serious side effect that has been associated with bicalutamide is severe liver injury, which has been reported in approximately 1% of patients in controlled clinical trials. Hepatotoxicity typically occurs within the first three to four months of continuous treatment. It is not known whether the regimen used in this trial can cause liver injury. Transaminase levels will be drawn every 4 weeks. Other common side- effects of bicalutamide overlap those of leuprolide acetate, including hot flashes, generalized pain, asthenia, constipation, diarrhea, nocturia, testicular atrophy, and gynecomastia.

10.0 ADVERSE EVENTS

10.1 Definition of Adverse Experience

10.1.1 Adverse Events (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*.

10.1.2 Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

10.1.3 Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity

tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

10.1.4 Attribution/Relationship to study drug

- Definite – clearly related
- Probable – likely related
- Possible – may be related
- Unlikely – doubtfully related
- Unrelated – clearly not related

10.1.5 Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or

2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event.

(OHRP Guidance on reviewing unanticipated problems 2007)

10.2 Recording and Reporting Responsibilities

10.2.1 Investigative site recording responsibilities:

1. Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

2. All AEs and SAEs will be recorded in the "AE case report forms" (CRF)

and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.

3. All reportable SAEs will be recorded on the FDA MedWatch form 3500a. After submitting the initial report it may be necessary to submit follow up reports to the Sponsor should the event require further investigation.

10.2.2 Investigative site reporting responsibilities:
1. The investigator/ site is responsible to report all SAEs which occur on or after the first day of treatment to the sponsor within 24 hours of becoming aware of the event. All subsequent SAEs must be reported for up to 30 days after the last treatment.
2. Each investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent by email to SAE.FCCC@fccc.edu.
3. If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the OCR, draft revisions will be made in track changes and submitted to the OCR for consideration. Any consent revisions must receive OCR approval **prior** to submission to the IRB.
4. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the Study Monitor for confirmation with the Sponsor-Investigator.
5. If the results of an investigator or OCR investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.
6. Copies of all related correspondence and reporting documents must be submitted to the ISRU and will be maintained in the trial master file.

The participating site should report events to:

Investigator-Sponsored Research Unit
Office of Clinical Research
Fox Chase Cancer Center
SAE.FCCC@fccc.edu

10.2.3 Sponsor Reporting Responsibilities:
1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.
i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents,

such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

ii. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

iii. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

2. If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the OCR for each site's IRB of record along with the report of the adverse event.

3. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at OCR.

4. SAEs that are related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions are as directed by FDA guidelines (http://www.fda.gov/medwatch/index.html). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.

Food and Drug Administration:
Telephone 1-800-FDA-1088
Fax 1-800-FDA-0178
http://www.fda.gov/medwatch/report.htm

Mandatory Drug Reporting:
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852
Office of Post-Marketing Drug Risk Assessment (HFD 730)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(301) 827-3169 for any further questions regarding where to send drug mandatory reporting forms

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample size

We will test the hypothesis that only 20% of patients on either arm of the study will have undetectable PSA at 32 weeks, versus the alternative that 40% of arm B patients will. An initial cohort of 39 patients and, if continued, a second cohort of 27 patients will be randomized 2:1 to arms B and A respectively.

After stratification for prior therapy we will randomize, 2:1, nominally 13 patients to arm A and 26 patients to arm B. Because of post stratification randomization, the exact numbers in the two arms may vary slightly from 13 and 26, but the total patient number in the the initial cohort will be exactly 39 and the final sample number be exactly 66. Our intent is to compare the proportions of patients with undetectable PSA at 32 weeks. This is most simply described by the difference (E1/26) – (C1/13), where C1 and E1 are the numbers of undetectable PSAs in arms A and B respectively. The cut point for continuation of the trial past the first cohort requires that
(E1/26) – (C1/13) > -2/13 = -0.1538462…. To avoid confusion due to round off of such fractions, we identify the decision boundary by 13 E1 – 26 C1 > -52, exactly equivalent the first expression, and obtained by multiplying all terms by 13*26.

If 13 E1 – 26 C1 exceeds -52 AND E1 is at least 6 then we will randomize an additional 9 patients to arm A and 18 patients to arm B. Otherwise the study will be terminated and the null hypothesis accepted. Letting C2 and E2 be the numbers of undetectable PSAs in the second cohort, we will finally reject the null hypothesis if 22(E1 + E2) – 44(C1 + C2) is at least 88 and E1 + E2 is at least 14. The initial cohort will consist of 39 and the final cohort of 27 patients for a total of 66 patients. If the true null is 20% undetectable PSAs type I error will be 3.24% and power will be 80.3%. In this case the chance of early stopping under the null will be 60% but will be 3.23% if the true arm B fraction of undetectable PSAs is 40%.

If the null (arm A) fraction undetectable PSAs is 25% type I error increases to 10.9% and power increases to 83.3% if the arm B fraction undetectable is 45% (20% higher). If the null fraction is 30% type I error increases to 19.7% and power to 83.2% (arm B 50%, 20% higher).

The above discussion is based on the exact 2:1 split in the combined strata. This may not occur so the table below describes the decision boundaries for all possible outcomes of the split. In all cases study power is at least 80% and type I error is less than 5%. Type I error when the null fraction is 30% is always under 20%. To use the table we compute nc1 E1 – ne1 C1 where nc1 and ne1 are the actual numbers of arm A and arm B respectively in the initial cohort of 39. If this number, nc1 E1 – ne1 C1 > -a1, and E1 > m1 in the table, then the trial may be continued past the initial cohort. Otherwise it is terminated and the null hypothesis accepted. If the second cohort is recruited, then nc2(E1+E2) – ne2(C1+C2) must be computed. nc2 and ne2 are the total numbers of patients in arms A and B respectively. If nc2(E1+E2) – ne2(C1+C2) is at least r and E1+E2 is at least m2 in the table, then the null hypothesis will be rejected. The table is indexed by nc1 and nc2 only. This is so because nc1+ne1 = 39 invariably as does nc2+ne2 = 66. For example, suppose nc1 = 13 hence ne1 = 26. Then if E1 = 7 and C1 = 4, E1 > m1 = 6 and 13 E1 – 26 C1 = 13 * 7 – 26 * 4 = 91 – 104
= -13, and -13 > -52, so the second cohort would be recruited. Finally, suppose nc2 = 22 hence ne2 = 44 and suppose E2 = 9 and C2 = 2. Then E1+E2 = 9+7=16 > m2=14 and
22(E1+E2) – 44(C1+C2) = 22*16 – 44*6 = 352-264 =88 which is at least r = 88. In this case the null hypothesis would be rejected.

		decision boundaries				
nc1	nc2	a1	m1	r	m2	
12	21	-42	6	72	14	
12	22	-42	6	88	14	
12	23	-42	6	88	13	
13	21	-52	6	72	14	
13	22	-52	6	88	14	(this row used in example above)
13	23	-52	6	88	13	
14	21	-68	6	72	14	
14	22	-68	6	88	14	
14	23	-68	6	88	13	

11.2 Toxicity assessment

A DLT rate of 20% will be considered excessive for arm B. A rate of 5% is expected and acceptable. If 5 of the initial cohort in arm B experience DLT, the study will be halted for reassessment of dose. If 7 of arm B patients experience DLT the regimen will be considered too toxic. This set of rules has at least 80% chance of declaring arm B too toxic when the true DLT rate is 20%. This chance under the null is about 1%. The chance of halting the trial early is over 57% for a 20% DLT rate and less than 1% if this rate is only 5%.

11.3 Secondary assessments

We will test the hypothesis that the fraction of arm A and arm B patients with at least 85% reduction in PSA at 32 weeks will be the same. We will sort the 66 patients 32 week PSAs into groups above or below their grand median 32 week PSA. We will then submit the doubly dichotomized data to Fisher's exact test. The test will distinguish an odds ratio of 3.19 from one of 1.0 with 80% power and at most 10% type I error.

We will characterize the time to PSA progression and the time to onset of metastatic disease using the method of Kaplan and Meier. We will compare arms A and B for each of these end points with log-rank tests. Patients will be followed for PSA progression and for onset of metastatic disease for at least 60 months.

11.4 Definition of Populations for Analyses

All Treated Subjects: all subjects who are treated with bicalutamide (arm A) or bicalutamide and metformin (Arm B). All Randomized Subjects: all subjects who received treatment.

11.5 Safety Analyses

Safety analyses will be conducted on treated patients. All adverse events will be summarized 1) without regard to causal relationship and 2) by causal relationship to study drugs, based on the Investigator's opinion. Worst toxicity grades per subject will be tabulated for selected adverse events and laboratory measurements. Any serious adverse event or

adverse event resulting in premature and permanent discontinuation of any study drug will be described in detail. Adverse events and other symptoms will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

12.0 DATA SAFETY MONITORING PLAN

12.1 Monitoring Plan

FCCC ISRU will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the ISRU will collect and report data to the study Sponsor-Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the ISRU and Sponsor-Investigator as applicable.

12.2 Data Safety Monitoring Board

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least every 6 months by the Fox Chase Cancer Center Data Safety Monitoring Board (FCCC DSMB). In this capacity the FCCC DSMB will serve as an advisory committee to the Sponsor-Investigator. The FCCC DSMB will review those aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Sponsor-Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Sponsor-Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

13.0 Administrative

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

13.1 Data Reporting

The FCCC Study Monitor will request case report forms to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit.

The ISRU is responsible for compiling and submitting data to the Sponsor-Investigator and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Data and Safety Monitoring Board.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location.

The ISRU is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, study specific Serious Adverse Events.

13.2 Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and the OCR and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases the Study Monitor must be notified of any plans to move records to an offsite location prior to doing so.

13.3 Study Agents

Any study agent supplied through the OCR from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

13.4 Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

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APPENDIX I

Diary for_____dosing.
(Name of Study Drug)

Study Participant's Initials_____Sequence #_____Cycle #_____

Instructions

Please complete this diary when taking your_____. Your prescribed dose is_____.

_____should be taken orally_____day for_____days. You should take your dose at approximately the same time every day.

_____should be taken with / without (choose one or edit) food.
If you miss a dose, record this in your diary. Doses should not be doubled to make up for missed doses. If you vomit after taking a dose, record this in your diary. Do not take an additional dose to make up for this dose.

Bring your empty container or unused pills back to the hospital at the end of each cycle of treatment. There are certain medications that are prohibited while you are on this study. Please let your physician or protocol nurse know about all medications you are taking, and check with them before beginning any new medications.

If you have any questions, please contact your protocol coordinator_____at

_____.

Study Participant's Initials_____Sequence #_____Cycle #_____

Study Drug Name_____

Day	Date	Time	Dose	Reason, if dose not taken
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				

20				

21				
22				
23				
24				
25				
26				
27				
28				

Date_____Study Participant Signature_____

Study Participant's Initials_____Sequence #_____Cycle #_____

SECTION TO BE COMPLETED BY CLINICAL RESEARCH COORDINATOR

Total # of pills dispensed_____Date _____

Total # of pills returned_____Date_____

CRC Signature_____Date_____

APPENDIX II

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					

GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Patient Name _____

Signature _____

Date _____