ECOG-ACRIN
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ECOG-ACRIN Operations Office – Boston
Frontier Science
900 Commonwealth Avenue Boston, MA 02215
(617) 632-3610 Fax: (617) 632-2990
Randomization: (617) 632-2022

Group Chair: Robert L. Comis, M.D. and Mitchell Schnall, M.D.
Group Statistician: Robert Gray, Ph.D. and Constantine Gatsonis, Ph.D.
Jean MacDonald, Director of Research Operations
Mary Steele, Director of Group Administration

July 31, 2014

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #9 to E2809, *Androgen Receptor Modulation Phase II, Randomized Study of MK-2206 - Bicalutamide Combination in Patients With Rising PSA at High-Risk of Progression After Primary Therapy.*

The following revisions to E2809 protocol have been made in this addendum:

	Section	**Change**
1.	Cover Page	Updated the version date.
2.	Section 6.1.4	Inserted into the first and second bullet points the phrase "confirmed on two consecutive additional determinations taken at least 4 weeks apart," to more clearly define undetectable PSA.

The following revisions to E2809 Informed Consent Document have been made in this addendum:

	Section	**Change**
1.	Cover Page	Updated the version date.
2.	"What side effects or risks can I expect from being in the study?"	Updated the risk section language to correspond with the condensed risk lists format.
3.	"What side effects or risks can I expect from being in the study?"	Inserted condensed risk list for Bicalutamide.

If you have any questions regarding this addendum, please contact hays.elizabeth@jimmy.harvard.edu or 617-632-3610.

We request review and approval of this addendum to E2809 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Protocol Development Manager

Enclosure

CC:

Anna C. Ferrari, M.D.	Carol Chami, R.N.
Ron Rodriguez, M.D.	Mary Vienneau
Michael Carducci, M.D.	Kerry Higgins
Glenn Liu, M.D.	Laura Gagnon
Yu-Hui Chen, M.P.H., M.S.	Mary Steele
James Corkery	Jean MacDonald
Tanya Mustacchio	Mary Bonds, MPH
Khemraj Hirani, MPharm, PhD, RPh, CPh, CCRP, MBA	Elizabeth Hays
	Lauren Lambert
Michelle Hobbs, PharmD	Adekunle A. Raji
Mark D. Walsh, PharmD, BCOP	Maddy Balois Oulette

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E2809

Androgen Receptor Modulation
Phase II, Randomized Study of MK-2206 - Bicalutamide Combination in Patients With Rising PSA at High-Risk of Progression After Primary Therapy

STUDY CHAIR: Anna C. Ferrari, M.D.
STUDY CO-CHAIR: Ron Rodriguez, M.D.
STUDY STATISTICIAN: Yu-Hui Chen, M.P.H., M.S.
Rev. 4/12 GU COMMITTEE CHAIR: Michael Carducci, M.D.
Rev. 4/12 PROSTATE SUB-COMMITTEE CHAIR: Glenn Liu, M.D.

Version Date: July 31, 2014
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Rev. 6/14

ACTIVATION DATE
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Addendum #6 – 6/13
Addendum #7 – 6/13
Update# 4 – 7/13
Addendum #8 – 6/14
Addendum #9 - 10/14

Rev. 3/11

NCI Supplied Agents:
MK-2206 (NSC 749607; IND 109493)

Commercial Agents:
Bicalutamide (Casodex)

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STUDY CHAIR

Anna C. Ferrari, M.D.
New York University Cancer Institute
160 East 34th St, 8th Floor
New York, NY 10016
Phone: 212-731-5389
Fax: 212-731-5545
Email: anna.ferrari@nyumc.org

Rev. 2/13

STUDY CO-CHAIR

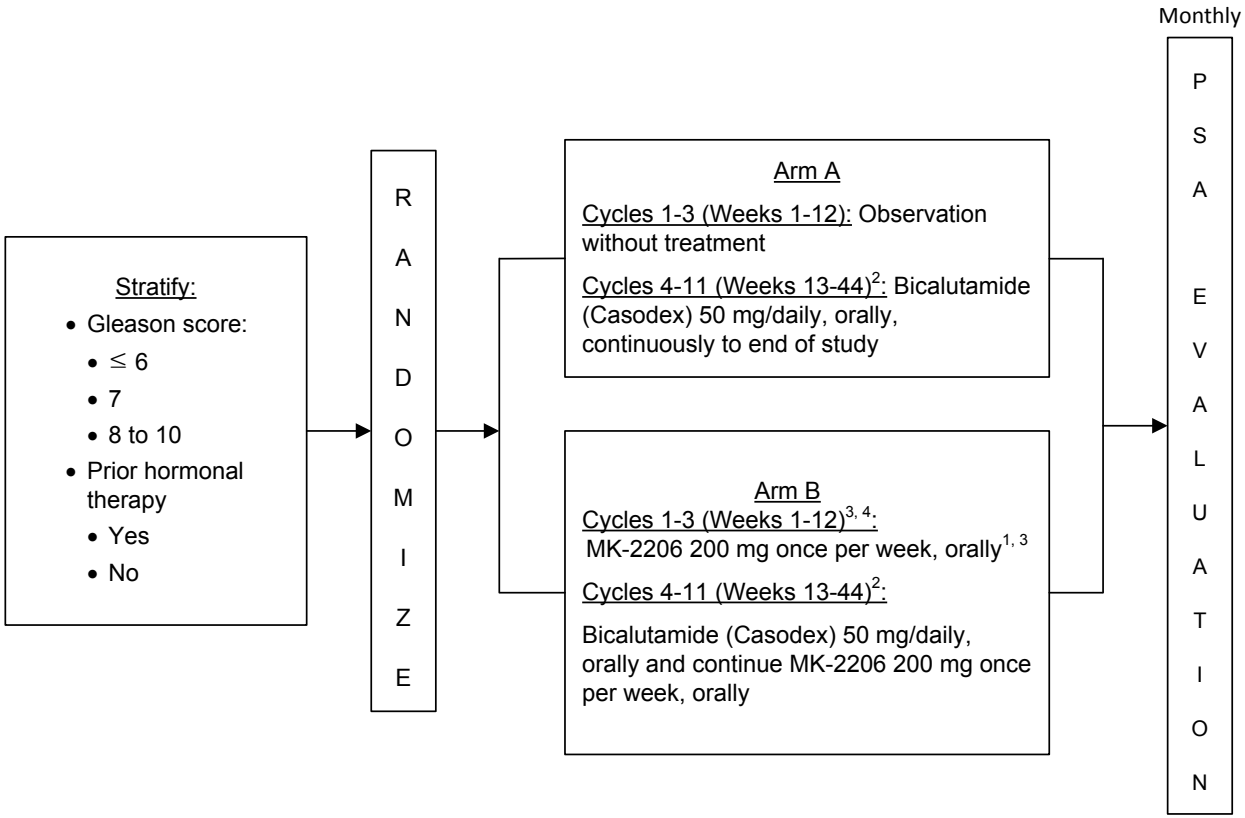
Ron Rodriguez, M.D.
University of Texas Health Science Center at San Antonio
Department of Urology
7703 Floyd Curl Drive, MC7845
San Antonio, TX 78229-3900
Phone: 210-567-5643
Fax: 210-567-6868
Email: rrodriguez@jhmi.edu

STUDY CHAIR LIAISON (SCL)

Rev. 4/12, 7/13

Samantha Davis
Clinical Trials Office of New York University Cancer Institute
1 Park Avenue, Mezzanine
New York, NY 10016
Phone: 212-263-4406
Fax: 212-263-4477
Email: samantha.davis2@nyumc.org

Schema



Accrual Goal = 104
Cycle Length = 28 days

1. MK-2206 should be taken at approximately the same time each week 2 hours before or after meals.
2. Patients on Arm A and Arm B who are responding at Cycle 11 (week 44) may continue on until Cycle 18 (week 72) at the investigator's discretion. (See Section 5.6).
3. Patients with PSA < 0.2 by the end of Cycle 3 (Week 12) will NOT receive bicalutamide until the PSA rises ≥ 0.2 ng/mL and the rise is confirmed on a second determination 2 weeks later.
4. Patients with a PSA rise of ≥ 50% above baseline may start bicalutamide early.

1. Introduction

1.1 Prostate Cancer

Around 25-30% of prostate cancer (PC) patients experience Prostate Specific Antigen (PSA) recurrence (~60,000 cases/year) after primary therapy (1,2), which precedes the development of clinical metastasis by months or years (3). Androgen deprivation therapy (ADT) is the only treatment modality currently available for recurrent PC. However, it is not curative (4) and exerts a selective pressure for survival and growth of preexisting androgen-independent clones (5) that drive castration resistant progression. In addition to negative impact in quality of life (QOL), ADT increases metabolic and cardiac morbidity that can compromise survival (6-8). Therefore, new treatment modalities to improve or substitute ADT are needed.

1.2 Androgen Receptor in Prostate Cancer

The evidence from human and experimental model systems indicates that the androgen receptor (AR) plays a pivotal role in supporting PC development (9-11) and progression in the androgen-dependent (AD) and androgen-independent (AI) stages of the disease (12-14).

AR is a member of the steroid receptor super family. Dihydrotestosterone (DHT) generated intracellularly by 5-alpha reductase from testosterone is the ligand with the highest affinity and specificity for the ligand binding domain (LBD) in the C-terminus of AR. Liganded AR is transferred to the nucleus where it binds to androgen-responsive elements (ARE) in the promoter of target genes and recruits co-activators and co-repressors to regulate their transcription. AR controls expression of a wide spectrum of genes involved in proliferation, differentiation, survival and metabolism (15).

AR over-expression and activation are among the most consistent findings in human tumor xenografts (16) and the dominant molecular pathway activated during emergence of castration resistant clones (17). AR over-expression is frequent in both localized (18) and metastatic tissues (19,20) of PC patients and has been linked to higher clinical stage and earlier relapses (16). Importantly, strategies to reduce AR levels of expression by either molecular silencing or by treatment with histone deacetylase inhibitors (HDACI) indicated that both, the androgen-dependent growth and the apoptosis response to biological and chemotherapeutic agents could be restored in androgen-independent LNCaP cells resistant to these treatments (21-24). Therefore, a clinical trial to test the effect of HDAC on restoration of hormone sensitivity is under way.

The regulation of AR transcriptional activation of downstream target genes can be initiated by ligand-dependent and ligand-independent mechanisms (25).

Ligand-dependent activation is the predominant pathway in normal and androgen-dependent PC cells. In the castrate environment it is sustained in part by over-expression and mutations of AR that exploit multiple mechanisms (26) including AR hypersensitivity to very low intracellular levels of androgens (27), and promiscuity for binding other steroid hormones such as estradiol and progesterone (28). In addition, PC cells develop mechanism to synthesize their own androgens by increasing the expression of genes that convert adrenal

androgens to testosterone (29) and by up-regulating steroidogenic enzymes that metabolize cholesterol to DHT (30,31). Therefore, the ligand-dependent pathway of AR activation remains active under castration-resistant conditions.

Non-steroidal anti-androgens are direct antagonist of AR. As such, bicalutamide regulates AR function by competing for agonists binding to the LBD, by decreasing AR phosphorylation by various growth factors (32) and by preventing recruitment to the ARE's of co-activators to initiate transcription of target genes (33-35). New generation anti-androgens such as MDV3100 also work by decreasing the nuclear localization of AR (34). In the clinic, anti-androgens have shown promising results in non-castrate and castration resistant PC patients (34,36-38).

Ligand-independent activation of AR stems from two different mechanisms: 1. Increased cross-talk of AR with intracellular second messengers of cell membrane growth factor receptors (GFR) and their ligands activated by autocrine and paracrine mechanisms that evolve during PC progression. These include among many others the epidermal growth factors/receptors (EGF/R, HER2), insulin-like growth factor/receptor (IGF/R) (39,40) and interleukin-6 (IL6) (35,41-43) which signal through networks of protein kinases (PKs) including PI3K/PTEN/AKT/mTor, Ras-Raf-MEK-ERK, Src/JAK /STAT. These relay downstream signals that directly or indirectly through their substrates phosphorylate and activate AR (44-47). 2. Androgen receptor splicing. A number of different AR splice variants (SV) were recently identified in castration resistant cell lines, in xenografts models (48) and tissues from PC patients (49,50). A common pattern of the SV is the loss of the LBD of AR with retention of the N terminus and 2 or 3 zinc fingers for DNA binding. The SV can translocate to the nucleus, bind to ARE's and regulate the expression of AR target and non target genes involved in diverse cellular functions. There is also evidence that SV can activate AKT-1 in PTEN positive PC cells and phosphorylate both AR wild type and SV's (50). Therefore, SV's are constitutively active and by lacking LBD are not inhibited by anti-androgens. Although the expression of the SV in PC cells is less abundant than wild type AR, it is thought that in the setting of castration they may hijack the wild type AR to regulate genes transcription (49,50). Thus, AR splicing provides yet another mechanism to escape androgen deprivation and support AI progression.

1.3 The PI3K/PTEN/AKT/mTor pathway

The PI3K/PTEN/AKT/mTor pathway is central to the transmission of growth regulatory signals from cell surface receptors. In brief, (51,52), upon activation of receptors by ligand binding, PI3K forms heterodimers comprised of a regulatory subunit (p85) and a catalytic subunit (p110) and serves as a docking site for AKT. The function of PI3K is tightly controlled and inactivated by the tumor suppressor PTEN, a dual specificity phosphatase whose expression is frequently lost in cancer (52,53). AKT is a serine-threonine kinase that once localized to the plasma membrane is phosphorylated and activated at threonine 308 by PDK-1 or at serine 473 by the mTor/Rictor complex. AKT is the central mediator of the PI3K activation cascade and affects multiple cellular functions that contribute to cancer: A. Stimulates protein synthesis and cell growth through the TSC 1/2 complex and its activation of the mTor/Raptor complex which affects glycolysis and angiogenesis by stabilizing insulin and Hif1alpha response to hypoxia (54); B. Induces proliferation by facilitating progression along the G1-S cell cycle

check point through inactivation of the cell cycle inhibitors p27 and p21 and by activating the forkhead box trancription factors (FOXO) and GSK3 which induces c-Myc and Cyclin D 1; C. Supports cell survival by limiting programmed cell death through inhibition of pro-apoptotic genes like Fas ligand, Bim and BAD and by promoting p53 degradation and deregulation of NFkB function. D. Deregulates glucose metabolism and insulin signaling by enhancing glucose uptake and glycogen synthesis in muscle and fat and by inhibiting of gluconeogenesis in the liver. mTor has two forms and complexes: the mTORC1-Raptor-mLST8 complex which controls protein synthesis and growth is Rapamycin sensitive. The mTORC2 Rictor -mLST8 complex, that phosphorylates AKT at Ser 473 and is Rapamycin insensitive. Therefore, Rapamycin analogues have clinical activity (55) that has been limited by the phosphorylation of AKT through the mTORC2-Rictor complex that results in induction of cyclin D1 and c-Myc through GSK3 (56) and also through activation of MAPK by a PI3K-dependent feedback loop (57).

The PI3K/PTEN/AKT/mTor pathway is frequently deregulated in prostate cancer and enhances AR activation. Multiple lines of evidence implicate decreased expression of PTEN and increased expression of PI3K, AKT and mTor in the development and progression of PC (58-60). Loss of PTEN expression through epigenetic silencing, deletions or mutations was observed in 15-63% of radical prostatectomies and correlated with high Gleason score, advanced stage and poor clinical outcome (59,61,62). It was also observed in 39-70% of castration resistant specimens (63,64). Amplfication of PI3K was detected in 39% of localized specimens and in 50% of castration resistant PC (65). Activation of AKT-1 has been detected primarily in cases with loss of PTEN (66). However, in a recent study of 400 radical prostatectomy specimens that quantified AKT-1 expression by fluorescence microscopy, expression of AKT-1 was detected in 81,75% and 73% had high levels of expression. Among those with high levels of AKT-1 there was a significant correlation with high Gleason scores, advanced stage, increased risk of biochemical recurrence and prostate specific mortality (67-69). Biologically, AKT activation has been shown to increase AR expression and activity in both normal and tumor epithelial cells (70), to accelerate androgen-independent progression (60) and development of resistance to hormone therapy (44). In the castrate environment, AKT phosphorylates the N-terminus and LBD of AR (71,72), decreases AR degradation (73) and sustains AR transcriptional activity and growth of PC cells at low androgen levels (74,75). It's been recently suggested that AKT activation can also provide an escape pathway to direct AR silencing (76). Activation of mTOR and/or Sk6 was also found to be increased in 12,5 and 26,5% respectively of intermediate-risk and 32 and 69% of high-risk localized PC specimens (77). In addition to the loss of PTEN and activation of AKT, androgens have been shown to activate mTor to promote PC cell proliferation through post-transcriptional increases in cyclin D (78). In the clinic, the response to Rapamycin or Temserolimus of castration resistant patients with PTEN deficiencies was modest (79,80) suggesting that release of mTORC-2 and PI3K provides a mechanism of escape and dual inhibitors or direct inhibition of AKT may be more effective.

It is apparent from the experimental and human data presented above that the PI3K/PTEN/AKT/mTor pathway in androgen-dependent and -independent PC cells supports a more stable and "hypersensitive" AR protein that facilitates the

recruitment of transcriptional co-activators to the ARE's and activation of growth and survival genes in the presence or absence of androgens (60,81-83).

In summary, there is a strong rationale for considering the AR as a therapeutic target in recurrent, non-castrate PC. Both experimental and human data suggest that PC cells have an "addiction" to AR activity. It is apparent that the AR facilitates the growth and survival of PC cells by responding to signals from androgens, other steroid hormones and multiple kinases whose activity becomes altered during PC progression. These molecules sustain AR levels and activation by increasing phosphorylation and protein stability or by serving as co-activators of transcription. In concert, they establish a vicious cycle that supports androgen-independent progression. Although activation of AR and its transcriptional activity by intracellular second messengers does not require ligand, ligand-binding facilitates the process and remains active throughout all stages of PC. Therefore, blocking the LBD remains crucial to block the androgen pathway of activation.

The availability of PK inhibitors, and effective anti-androgens provides the means to test novel therapeutic strategies aimed at the AR to control recurrent PC progression. Given the palliative nature and unfavorable toxicity profile of castration, a testosterone-sparing option with the potential to improve QOL and outcome is highly desirable for patients with rising PSA levels after primary therapy.

Preclinical evidence of antitumor activity of single PI3K/AKT/mTor inhibitors in PC models

Treatment of an androgen-dependent PC xenografts with a humanized IGF1R monoclonal antibody decreased AKT phosphorylation and induced extensive apoptosis that reached 60% tumor volume reduction. The effect was less pronounced in an androgen-independent derivative but became synergistic in combination with docetaxel (84). Treatment of androgen-dependent LNCaP cells and an androgen-independent derivative with MK-2206, the inhibitor of PKC, GSK3β and ribosomal protein S, reduced AR mRNA and protein levels, decreased tumor growth and induced apoptosis (85). Treatment of androgen-dependent and independent LNCaP cells with the MAPK inhibitor PD98059 and the mTor inhibitor Rapamycin did not affect AR levels but induced growth arrest without apoptosis (81,86,87).

Combinations of anti-androgen with PI3K/AKT/mTor or HDAC inhibitors

In vitro studies of androgen-dependent and -independent LNCaP cells showed the combination of bicalutamide with rapamycin was synergistic while the combination with an EGFR inhibitor (Iressa) was additive (88,89). The combination of bicalutamide with the HDAC inhibitors (SAHA and LBH589) was also synergistic and induced apoptosis that was more pronounced in androgen-independent LNCaP cells resistant to bicalutamide [24]. Treatment of androgen-independent LNCAP cells with the novel anti-androgen VN/124 in combination with an mTor inhibitor was also synergistic while the combination with the EGFR inhibitor (Gefitinib) was additive (90).

In vivo studies in a PTEN deficient xenografts model that is androgen-dependent, expresses AR and has an activated AKT/ mTor pathway showed that both casodex and castration had a similar effect on tumor volume reduction and

became additive in combination with rapamycin. While castration and casodex reduced AR levels and decreased proliferation they did not increase caspase activation and had no affect on mTor activation. In contrast, rapamycin inhibited S6RP but did not affect AR. The combination of casodex and rapamycin showed a pronounced decrease in proliferation markers (91). Unpublished data developed by Merck investigators with MK-2206 showed in the same PTEN knockout model that the growth inhibition in response to MK-2206 was more pronounced than casodex and the combination was strongly synergistic. Neither casodex or ADT affected phosphorylation of AKT.

In summary, the *in vivo* model confirms previous *in vitro* studies in androgen-dependent and independent LNCaP PC cells indicating that a combined approach to block the AR LBD with an antiandrogen and the ligand-independent pathway with inhibitors of AKT/mTor pathway has potential to enhance tumor responses. This approach might be most effective in patients with recurrent PC at high risk of progression since AR over-expression, loss of PTEN and AKT activation are frequent, and 2/3 of these patients are at increased risk of relapse and death form PC. Furthermore, AKT inhibitors may also serve to block the activity of AR splice variants that evade anti-androgen block.

1.4 Clinical Experience with Non-Castrating Peripheral Androgen Blockade Strategies

Peripheral androgen blockade strategies using monotherapy with a nonsteroidal anti-androgen or in combination with finasteride to block 5-alpha reductase and the conversion of testosterone to DHT were developed to avoid the side effects of androgen ablation and to improve QOL.

In the early 1990's, phase II and III trials with bicalutamide 50 mg was tested as monotherapy in metastatic D2 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 survival but was inferior to castration. This approach was never tested in rising PSA non-castrate patients (92-95). Instead, bicalutamide150 mg (96) was compared to combined androgen suppression with orchiectomy or LHRH agonist (Zoladex) and flutamide (Eulexin) in patients with locally advanced PC. At 6.3 years follow-up there was no statistical difference between the two groups in time to progression or overall survival (56% mortality). In the bicalutamide arm there was a significant improvement in QOL due to improved physical capacity, emotional well being and sexual interest (97). In a smaller study in more advanced patients with median PSA values at study entry of 19.1 ng/mL, the addition of finasteride after bicalutamide 150 mg induced a secondary PSA nadir suggesting PSA levels did not become undetectable and finasteride was needed to provide additional intracellular androgen blockade. At a follow up of 3.9 years, disease control was comparable to castration. However, undetectable PSA levels were not reported (98).

A more recent study by Picus, et al, (99) used a similar combination to treat 101 androgen-dependent non metastatic PC patients (D0) with rising PSA >1 and <10 ng/mL after primary therapy. From the median PSA at registration of 3.8 ng/mL, 97% (95/98) reached a PSA <1 ng/mL (>80% PSA decline) at a median of 3.2 months and 77% achieved an undetectable PSA (<0.2 ng/mL) at a median of 5.5 months that lasted several months (33 months). At 59 months, the median

time to progression (PSA>4 ng/mL or 50% above nadir) had not been reached with 47(46%) patients still on the same combination. There were 22 (33%) patients that experienced PSA failure and 15 patients responded to subsequent androgen deprivation. Eight patients died of unrelated causes and 22 went off therapy unrelated to progression. Toxicity was very low.

In a small phase II study of D2 patients with eulexin followed by the addition of finasteride (100), the median PSA decline on eulexin was 87% at a median of 9.1 weeks. After adding finasteride, the median PSA decline reached 94% at 16.5 weeks and 40% reached undetectable levels.

1.5 Nadir PSA Response to Castration and Outcome

In a retrospective analysis of 747 patients with biochemical recurrence and negative bone scan after surgery or radiation, a nadir PSA level <0.2 ng/mL at 8 months after hormonal therapy was, in multivariate analysis, an independent prognostic factor of PC-specific mortality compared to other known prognostic factors such as PSA doubling time (PSADT) <3 months, PSA level at the start of androgen deprivation and Gleason score 8-10. PSA nadir >0.2 accounted for 75% of the cancer deaths observed in the study (101). A retrospective analysis of 130 patients treated with androgen ablation for rising PSA also found that 31 (57%) of 54 (95% confidence interval 44% to 71%) patients with a rising PSA level alone and 28 (37%) of 76 (95% confidence interval 26% to 47%) with a rising PSA and clinical metastases achieved an undetectable PSA after androgen ablation (P = 0.02). The PSA level at the start of androgen ablation and the presence of metastases were the most significant predictive factors (102). The PSA nadir after neoadjuvant therapy was also a predictor of organ-confined disease and outcome (103). In metastatic D2 patients, the absolute PSA value after androgen deprivation was also a strong independent predictor of survival (104). In this study, at 7 months of initiation of androgen deprivation, patients who achieved a nadir PSA below 4 ng/ ml had less than half the risk of death than those that did not reach that nadir and those that achieved undetectable PSA levels had a quarter the risk than those that did not reach that nadir (p=<0.001 respectively). Therefore, a detectable PSA following castration reflects the surviving, prognostically relevant tumor cell population.

Conclusion: the existing retrospective data supports that in non-castrate patients starting androgen deprivation achieving an undetectable PSA nadir (<0.2 ng/mL) predicts for a longer survival than those whose PSA remains detectable. Thus, an undetectable PSA nadir promises to be the only accurate measure of disease response and an important endpoint for clinical trials evaluating new approaches in hormone naïve PC 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. Combined peripheral androgen blockade regimens induced 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 10ng/mL respectively and, achieved the nadir in 4-6 months. Based on this limited data, combined androgen-sparing regimens with high level of activity as proposed here can be expected to induce undetectable PSA by 8 months in 45% of patients whose PSA level at study entry is not restricted to <10 ng/mL and have a PSADT less than 12 months. In this group, only 20% may achieve a PSA nadir <0.2 with antiandrogen monotherapy.

1.6 Molecular Features and Response to Therapy

The experience with targeted therapy in solid tumors indicates that clinical responses are dependent on dominant molecular alterations of the target(s) as a result of their aberrant expression and/or mutations (105). Prostate cancer is a genetically complex and highly heterogeneous tumor with considerable variability in the level of AR expression and PK activation (106). We predict that the ability of the combination to down-regulate AR levels and PSA will be influenced by the genetic make up of the PC in each patient and account for differences in response across patients in the same therapeutic arm. Accurate prediction of the drug's effect requires a thorough knowledge of all the genes (and gene variants), microRNA's and proteins involved in the etiology of the disease and the drug's mode of action and metabolism. Therefore, analysis of primary tumor tissues will be important to determine the preexisting levels of expression and alterations of AR and relevant targets in the pathway of MK-2206 (i.e. PTEN, phopho AKT, GSK-3b, etc), and to establish their relation to clinical response. In addition, new markers and micro RNA's detected in serum of PC patients (107) have been correlated to the presence of PC in patients independent of PSA levels and need to be further explored in the setting of rising PSA. For these reasons we will request permission to retrieve and bank samples of the original tumor specimens for later molecular analysis.

1.7 Rationale and Hypothesis

Hypothesis: We postulate that a global strategy to modulate AR activation without testosterone deprivation can be implemented to successfully prevent the progression of androgen-dependent and preexisting androgen-independent clones in patients with recurrent PC at high-risk of progression. We propose utilizing combinations of agents to simultaneously block the AR LBD with antiandrogens and the cross-talk with activated PKs using specific inhibitors or agents that decrease the levels of AR expression. We predict that this combined approach will reduce expression and function of AR in PC and target tissues that will reduce PSA to undetectable levels. We expect a marked antitumor response with a prolonged period of remission or cure. By preserving testosterone, we expect patients to experience a better QOL compared to historical controls treated with androgen deprivation. Furthermore, in cases of progression, we predict that the recurrent tumor in a non-castrate environment will remain androgen-sensitive and responsive to androgen ablation. Finally, we predict that this prolonged hormone sensitive state will be associated with increased survival.

1.8 MK-2206

The PI3K/AKT pathway is downstream of the common growth factor tyrosine kinase receptors (TKR), including EGFR, HER2, IGFR, etc., and is a likely driver of tumor progression in most carcinomas (Altomare and Testa, 2005; Hennessy et al., 2005; Steelman et al., 2008). AKT protein kinase is activated in a substantial proportion of human solid tumors (breast, endometrial, ovarian, prostate, pancreatic, colon, gastric, and non-small cell lung cancer [NSCLC]). Upregulation of AKT can be caused by direct amplification/mutation of AKT, or by overexpression of TKRs, PI3K and RAS, and/or by inactivation of the tumor suppressor PTEN. Because of its key function in cell survival, AKT plays a pivotal role in rendering tumor cells insensitive or resistant to chemotherapy or targeted agents.

The rationale for the use of an AKT inhibitor in treatment of various malignancies is included in the following references (Staal, 1987; Shayesteh et al., 1999; Fry, 2001; Tanno et al., 2001; Testa and Bellacosa, 2001; Hu et al., 2002; Rahman et al., 2002; Min et al., 2003; Lee et al., 2004; St-Germain et al., 2004; Altomare and Testa, 2005; Hennessy et al., 2005; Kirkegaard et al., 2005; Nakanishi et al., 2005; Oki et al., 2005; Saal et al., 2005; Shoman et al., 2005; Vestey et al., 2005; Wolf and Slomovitz, 2005; Konecny et al., 2006; Kornblau et al., 2006; Nakayama et al., 2006; Oza, 2006; Uddin et al., 2006; Sosman et al., 2007; Cejka et al., 2008; Engelman et al., 2008; Han et al., 2008; Kinkade et al., 2008; Steelman et al., 2008; Kawauchi et al., 2009; Salvesen et al., 2009).

MK-2206 is the first allosteric inhibitor of AKT to enter clinical development (Investigator's Brochure, 2009). MK-2206 demonstrated AKT inhibition and antiproliferative activity as single agent and in combination with other agents in multiple human cancer cell lines, such as breast, ovarian, lung, and prostate. MK-2006 synergized antitumor effects of docetaxel, erlotinib, and carboplatin in vivo in various human tumor xenograft models.

Mechanism of Action

MK-2206 is a selective allosteric inhibitor of AKT (Investigator's Brochure, 2009). MK-2206 does not bind to the active site of AKT, and consequently does not compete with either ATP or peptide substrate for binding to AKT. It is equally potent against the two human AKT isoforms, AKT1 and AKT2, and ~5-fold less potent against AKT3.

Nonclinical Studies

In Vitro Activity Studies: In vitro single-agent activity of MK-2206

In an in vitro kinase assay with GSK3 alpha peptide as substrate, MK-2206 strongly inhibited kinase activity of the three human isoforms of AKT, AKT1, 2, and 3, with 50% inhibitory concentration (IC50) values of 8, 12, and 65 nM, respectively. MK-2206 exhibited no inhibition (IC50 > 50 micromol/L (mcM) against the (pleckstrin-homology domain)-deletion mutants of AKT, indicating that this domain is essential for binding MK-2206 to AKT. Apart from AKT, MK-2206 was tested at a single concentration of 1 mcM against a panel of ~250 proteins including kinases without demonstrating significant (≥50%) inhibition against any protein.

The antiproliferative potency of MK-2206 was evaluated against a panel of tumor cell lines using in vitro proliferation and viability assays. Among 52 cell lines, 18 cell lines were highly sensitive (IC50<1 mcM), 7 were moderately sensitive (IC50=1-5 mcM), and 27 cell lines were insensitive (IC50>5 mcM) to MK-2206. Highly sensitive cell lines included breast, ovarian, prostate, NSCLC, small cell lung cancer (SCLC), gastric, and endometrial cancer. At least one of the following genetic defects was represented in the majority of sensitive cell lines: PTEN mutation, PI3KCA mutation, AKT amplification, or genomic amplification of HER2 or MET. Nine of 27 cell lines that were insensitive to MK-2206 had either PTEN or PI3KCA mutation, or were deficient in PTEN protein. Among eight cell lines carrying RAS or BRAF activating mutation, six were insensitive to MK-2206.

MK-2206 activity in combination with other agents

In a proliferation/viability assay, various degrees of synergism between MK-2206 and lapatinib (a dual EGFR/HER2 inhibitor) were observed in eight breast cancer cell lines. MK-2206 and docetaxel demonstrated additive to synergistic antiproliferative activity against nine breast-cancer cell lines, however, the effects were dependent on agent sequence. Enhancement of antitumor activity occurred only when cells were treated first with docetaxel and then exposed to MK-2206. In contrast, co-administration of the two agents resulted in antagonism. Combination of MK-2206 with erlotinib produced various degrees of synergism in nine NSCLC cell lines, including A431 epidermoid cells overexpressing EGFR.

MK-2206 synergized antitumor activity of carboplatin, gemcitabine, doxorubicin, camptothecin, or 5-FU in ovarian, prostate and NSCLC cell lines. Antitumor activity of MK-2206/carboplatin, demonstrated in the ovarian cell line A2780, was accompanied with enhanced apoptosis (cleavage of caspases 3 and 7). However, the effect was dependent on the sequence of agent administration, as it occurred only when cells were exposed to carboplatin before or simultaneously with MK-2206. Enhancement of apoptosis did not occur when MK-2206 preceded carboplatin.

In Vivo Activity Studies

MK-2206 monotherapy administered as a single dose (10-240 mg/kg) to mice bearing human ovarian tumor (A2780) potently inhibited phosphorylation of AKT1/2 in blood as well as in tumor tissue. After a single dose of 30, 120, or 240 mg/kg of MK-2206, ≥80% inhibition of AKT1/2 was achieved in peripheral blood; inhibition persisted at this level for 6 and 24 hours at the 120- and 240-mg/kg dose, respectively. Pronounced inhibition (70-90%) of phosphorylation of AKT1/2 (pAKT1/2), lasting for at least 24 hours, was detected also in tumor tissue following the single 120- or 240- mg/kg dose. MK-2206 combinations with docetaxel, carboplatin, or erlotinib exhibited significantly more potent antitumor activity than each agent in monotherapy settings. For example, a combination of MK-2206 and docetaxel, administered for 4 weeks as one weekly intravenous (IV) dose of docetaxel (30 mg/kg) followed 24 hours later by MK-2206 (240 or 480 mg/kg) given orally (PO) once a week (QW), produced strong antitumor responses in the A2780 ovarian-cancer xenograft mouse model. MK-2206 monotherapy was ineffective at all doses. Although the combination was significantly more effective than docetaxel monotherapy, responses did not endure beyond the treatment period. Tumor regression was also observed in PC-3 prostate xenograft model following sequential treatment with docetaxel and MK-2206 (24 hours later). MK-2206 (120 mg/kg) was given three times per week (days 1, 3, 5) and docetaxel (5 mg/kg) once weekly on day 0. Inhibition of tumor growth was also enhanced when MK-2206 was combined with carboplatin and erlotinib in the NSCLC H460 and H292 xenograft models, respectively. Overall, the agents' combinations were well-tolerated at the effective dose levels, although transient 10-20%-weight loss was observed in some animals.

Pharmacokinetics

Pharmacokinetic (PK) parameters of MK-2206 in the rat, dog, and monkey are summarized in Table 1. Across the species, MK-2206 showed moderate plasma clearance (Cl) and high volume of distribution at steady state (Vdss) and

elimination half-life (t1/2) ranging from 4 hours in rats to >12 hours in dogs and monkeys.

Table 1. Summary of nonclinical pharmacokinetics for MK-2206

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IV Route					PO Route				
Specie	**Dose (mpk)**	**Cl (mL/min/kg)**	**Vd_{ss} (L/kg)**	**$t_{1/2}$ (h)**	**Dose (mpk)**	**AUC (mcM·h)**	**C_{max} (mcM)**	**t_{max} (h)**	**F (%)**
Rat	2	27.6	9	4.2	10	2.1	0.29	5	20
					100	35.2	2.76	2.7	35
Dog	0.5	7.7	8	12.5	2	8.89	0.38	4	83
Rhesus	0.5	10.8	11	14					

Cl: clearance; Vd_{ss}: volume of distribution at steady state; $t_{1/2}$: elimination half-life; AUC: the area under the time-concentration curve; C_{max}: maximum drug concentration in plasma; t_{max}: time needed to achieve C_{max}; F: oral availability; mcM: micromol/L; mpk: mg per kg; Vehicle: intravenous (IV): DMSO, oral route (PO): 0.5% methylcellulose (10 mpk), 30% Captisol (100 mpk), or 1% methylcellulose (3 mpk)

MK-2206 was significantly bound to plasma proteins (ranged from 96% to 88% in mice>rats>dogs>monkeys>humans) with moderate Cl in rats, but relatively low Cl in dogs and monkeys.

The oral availability of MK-2206 was acceptable in rats (20%-35%) and better in dogs (83%). Plasma Cl in rats occurred primarily by direct glucuronidation with < 3% of MK-2206 excreted in feces. In dogs, elimination occurred via multiple metabolic pathways including oxidation followed by glucuronidation, direct glucuronidation, and formation of a carbamoyl glucuronide. Relative to rats, a higher fraction (30%) of parent compound MK-2206 was excreted (urine, bile, and feces) in dogs. Significant intestinal secretion was observed in dogs. No metabolites of MK-2206 with biologic activity were noted.

MK-2206 was also metabolized by oxidation in human liver microsomes, primarily via the 3A4 isoenzyme of the P450 cytochrome (CYP) enzyme complex. MK-2206 was neither a potent inhibitor nor inducer of human CYPs, although at clinically relevant concentrations, it appeared to slightly induce CYP3A4. Transport experiments in the P-glycoprotein (P-gp)-transfected cell lines (L-MDR1) suggested that MK-2206 could be a P-gp substrate. In addition, MK-2206 demonstrated weak inhibition of vectorial transport of digoxin in L-MDR1 cells (IC_{50} of 13.4 mcM).

Toxicology

In the 10-day tolerability studies, dose-limiting toxicities (DLTs) were observed at the dose of ≥200 mg/kg/day and ≥15 mg/kg/day in rats and dogs, respectively. In a 4-week safety study in dogs, MK-2206 was administered at 2.5, 5, or 10 mg/kg PO every-other-day (QOD) followed by a 2-week recovery period. The 10-mg/kg dose was poorly tolerated as manifested by severe body-weight loss and other physical and histomorphological signs of toxicity, which required cessation of dosing by the end of the second week of treatment. The 5-mg/kg dose was tolerated and although treatment-related toxicities occurred, they were transient. As no significant toxicities were observed in dogs at the 2.5-mg/kg dose, this dose was defined as NOAEL (no observed adverse effect level). Exposure at this level characterized by the maximum plasma concentration

(C_{max}) and the area under the time-concentration curve (AUC_{0-48h}) corresponded to 0.37 mcM and 8.52 mcM·h, respectively. A potential safety concern associated with MK-2206 therapy is prolongation of the QT-corrected (QTc) interval, which seemed to be dose-dependent. While QTc-prolongation was persistent in dogs at the 10-mg/kg dose, it declined and returned to baseline between 24 to 72 hours post-dosing at 5 and 2.5 mg/kg. No cardiovascular changes were observed at the 1-mg/kg dose of MK-2206 (C_{max} of 0.092 mcM and AUC_{0-24h} of 1.6 mcM) within 48 hours following dosing in dogs.

A tissue distribution study demonstrated that [^{14}C]MK-2206 was widely distributed in Sprague Dawley (albino) and Long Evans (pigmented) rats except for the central nervous system. The majority of the radioactivity went into the muscle, liver and skin shortly after dosing. In Sprague Dawley and Long Evans rats, the radioactivity in most tissues was comparable. It declined in parallel to that in blood and became negligible 3 days post-dose. However, the radioactivity was more sustained at higher levels in the skin and the uveal tract of the eye in Long Evans than in Sprague Dawley rats. The concentration (ng equivalent [^{14}C]MK-2206/g tissue) in the skin and the uveal tract of Long Evans rats was 37- and 84-fold higher than that in the respective tissues of Sprague Dawley rats 24 hours post-dose.

An additional safety concern involves MK-2206-induced hyperglycemia and hyperinsulinemia. MK-2206 induced hyperglycemia in all preclinical species tested. In the most sensitive species, the dog, the glucose level was elevated by 24%-35%, when MK-2206 was administered at 5 mg/kg QOD for 4 weeks (AUC_{0-48} of 19.6 mcM·h and C_{max} of 0.73 mcM). Such exposure is expected to correspond with human exposures achievable at the upper MK-2206 dosing range.

Results from genetic toxicology assays demonstrated that MK-2206 was neither genotoxic nor mutagenic.

Clinical Development of MK-2206

Preliminary clinical PK/pharmacodynamic and safety experience is derived from a Merck-sponsored phase 1 study in healthy volunteers (HVs) and company phase 1 studies in patients with advanced solid tumors.

Projections derived from preclinical PK and metabolism studies in dogs suggested that the target exposure corresponding to a plasma concentration of ≥100 nM MK-2206 over 8 hours and AUC_{0-48h} of ~2 mcM·h in humans could be attained by MK-2206 dosed at 30-70 mg QOD on a 28-day cycle schedule. Clinical PK/pharmacodynamic data confirmed that the MK-2206 dose of 60 mg QOD conferred substantial and lasting inhibition of AKT as measured in tumor biopsies from cancer patients. The 60-mg QOD dose level is being currently investigated as the maximum tolerated dose (MTD) in the expanded cohort of patients.

Based on preclinical and clinical experience from Merck-sponsored studies, PK modeling and simulation analysis suggests potential benefit of a less frequent dosing schedule (*i.e.*, QW). It is potentially feasible to administer MK-2206 at higher dose levels on a less frequent dosing schedule to maximize significant or peak target inhibition. This approach may also alleviate DLTs (*e.g.*, skin rash) associated with accumulated exposure to MK-2206. Dose escalation on a QW

schedule is currently being evaluated at the MK-2206 doses ranging from 90-300 mg.

Clinical Pharmacokinetics

The clinical PK for MK-2206 was evaluated in HVs receiving a single dose (0.25-100 mg) and in cancer patients given either a 30-, 45-, 60-, 75-, or 90-mg dose on the QOD schedule or 90-, 135-, 200-, 250-, or 300-mg dose on the QW schedule.

Although Day 1 $AUC_{0\text{-}48h}$ and C_{max} values achieved at ≤90 mg in cancer patients overlapped with the ranges observed in HVs, overall, MK-2206 exposures in cancer patients trended on average somewhat higher than those observed in HVs. In all cohorts evaluated at ≤200 mg QW, exposures after the first and last dose in Cycle 1 were below the dog NOAEL $AUC_{0\text{-}48h}$ and C_{max} values of 8.52 mcM•h and 365 nM, respectively. The mean first dose MK-2206 $AUC_{0\text{-}48h}$ and C_{max} were 1.77 mM•h and 62.2 nM, respectively, for 60 mg QOD, and 14.8 mM•h and 466 nM, respectively, for 300 mg QW. The dog NOAEL exposures were exceeded in humans following the first dose of 300 mg QW.

The variability in $AUC_{0\text{-}48h}$ and C_{max} following the first dose, where it could be assessed, was low to moderate across all dose levels, with the coefficient of variation (CV) values ranging from approximately 10%–60%. There does not appear to be a substantial or consistent departure from dose proportionality for either $AUC_{0\text{-}48hr}$ or C_{max} following the first dose up to the 300-mg dose level, except for an apparent plateau in exposures observed at 200 mg (n=3). Dose proportionality could not be reliably assessed beyond 135 mg (n=4) due to limited numbers of patients at each dose level.

T_{max} and apparent terminal $t_{1/2}$ values from cancer patients were generally within the ranges observed in HVs. Median T_{max} values ranged from 4–10 hours across all dose regimens, and harmonic mean apparent terminal half-life ($t_{1/2}$) values ranged from approximately 60–80 hours, with the exception of the 90mg QOD cohort. At 90 mg QOD, apparent terminal $t_{1/2}$ was assessable in one patient and was approximately 50 hours.

Clinical Efficacy/Pharmacodynamics

Preliminary pharmacodynamic results in cancer patients indicate that phosphorylation of AKT in whole blood is substantially inhibited at all dose levels evaluated on the QOD and QW schedule. Additionally, preliminary results indicate that substantial pAKT inhibition was demonstrated in tumor tissue at 60 mg QOD. As there is a causal relationship between the development of hyperglycemia/hyperinsulinemia and mechanism of AKT inhibition, such events could potentially implicate pharmacodynamic activity of MK-2206. In cancer patients, reversible grade 1/2 hyperglycemia was observed across all dose levels in a total of 59 patients. Hyperinsulinemia occurred in 26 patients who received MK-2206 60 mg QOD. From a preliminary analysis, these adverse events (AEs) do not appear to be dose-dependent. Neither hyperglycemia nor hyperinsulinemia was observed at any single dose in HVs.

Thus far, no formal efficacy studies have been performed with MK-2206; however, in patients with advanced solid tumors, early indications of antitumor activity included substantial decreases in CA125 in some patients with ovarian cancer and PSA stabilization in some prostate cancer patients. Minor RECIST

responses, *e.g.*, <30% decreases in tumor size, have also been observed in a patient with melanoma (16%), a patient with pancreatic cancer (23%), and in a patient with neuroendocrine tumor (20%). No partial responses, *e.g.*, confirmed >30% decreases in tumor size, have been observed.

Clinical Toxicology

Preclinical efficacy and safety studies and preliminary safety data from the clinical studies support the use of MK-2206 via the oral route, both as monotherapy and in combination with other anticancer agents.

Overall, MK-2206 has been generally well-tolerated when administered as a single PO dose (0.25-100 mg) to HVs, or to cancer patients as the 30-60 mg PO dose on the QOD schedule and the 90-200 mg PO dose on the QW schedule. Mild-to-moderate skin rash was observed in 21 of 42 patients (50.0%) and severe skin rash was observed in 5 of 42 patients (11.9%) at the dose of 60 mg QOD. Skin rash resolved following the 1- to 2- week therapy break. The higher doses evaluated in oncology patients (*i.e.,* 75 and 90 mg QOD and 300 mg QW) were not tolerated and resulted in DLT of grade 3/grade 4 skin rash.

Mild to moderate mucositis and conjunctivitis were associated with rash. The supportive-care measures included hydration, topical steroid preparations, oral corticosteroids, oral antihistamines, and oral antibiotics. Other common AEs included nausea, fatigue, vomiting, and diarrhea. These AEs were mild to moderate and in most cases were resolved by the standard supportive care and did not require therapy modifications. Hyperglycemia and hyperinsulinemia, both expected mechanism-based AEs, were observed in approximately 76% and 57% of patients, respectively, receiving MK-2206 on the QOD schedule. Episodes were generally mild, transient, and did not require therapeutic intervention. Importantly, administration of insulin may not counteract MK-2206-induced hyperglycemia due to mechanism-based insulin resistance. In this case, hydration and oral antihyperglycemic agents can be used as the supportive-care measures. Grade 3 hyperglycemia occurred in 1 patient who received 60 mg QOD and required treatment with PO antihyperglycemic medication. Grade 4 hyperglycemia was reported in one patient who received MK-2206 45 mg QOD in combination with erlotinib. In addition to supportive care measures, blood glucose management included administration of insulin and PO antihyperglycemic medication.

Grade 1/grade 2 prolongation of QTc-interval was observed in 14 out of 64 patients (21.9%) with available 12-lead ECG data. Prolongations ≥30 msec but <60 msec occurred in 4 of these patients. Grade 3 QTc prolongation was reported in one patient who received 135 mg QW. Episodes of QTc interval prolongation were in general isolated with no apparent dependency on dose or exposure levels, and were not considered clinically significant by investigators and were not reported as adverse experiences. Eleven patients experienced sinus bradycardia (<50 bpm) during Holter or ECG monitoring. These events were asymptomatic and were not clinically significant. While a causal relationship between these events and administration of MK-2206 is uncertain, similar side effects were seen preclinically in conscious dogs. Consequently, patients with a history or current evidence of heart disease should be excluded from enrollment on MK-2206 trials. Standard 12-lead ECG measurements should be performed at the protocol-specified time-points.

Developmental/Reproductive Toxicity

Developmental and reproductive toxicity studies of MK-2206 have not been performed thus far. MK-2206 was not tested in pregnant or breast-feeding women. Women of child-bearing potential and men participating in clinical studies of MK-2206 must use appropriate contraception, including abstinence and double-barrier methods, throughout MK-2206 therapy. In preclinical mutagenicity studies, MK-2206 was neither genotoxic or mutagenic.

Drug Interactions

No clinical drug interaction studies have been performed with MK-2206. Oxidative metabolism of MK-2206 in human liver microsomes was catalyzed primarily by CYP3A4. MK-2206 was not an inhibitor of the major CYPs. MK-2206 was shown to be a P-gp substrate.

MK-2206 Dose selection:

The 200 mg PO on the QW schedule of MK-2206 was chosen to be used in combination with bicalutamide for the following reasons:

- the 200 mg dose reached a mean Cmax of 170 nM (after the first dose) and a Cmax of ~225 nM (SS). The PK targetof 60 nM was achieved with a C12 hours in 99.9% and C24 hours in 92.8 % of the patients. The mean coverage above target PK was 133 hours out of 168 hours.
- Preliminary pharmacodynamic results in cancer patients indicate that phosphorylation of AKT in whole blood is substantially inhibited at all dose levels evaluated on the QOD and QW schedule.
- The QW has been generally well-tolerated. Severe skin rash was observed in 16.7% compared 11.9% at the dose of 60 mg QOD. Hyperglycemia was not observed.
- Although too early, PSA stabilization was observed in CRPC patients at the 90 and 200 mg QW.

1.9 Selection Criteria

The criteria to select patients with biochemical recurrence (D0) as the only manifestation of disease progression after definitive local therapy was based on parameters identified to be best predictors of outcome in long term studies of this group of patients. D0 patients at high-risk of progression and PC-related death included those with a PSA doubling time (PSADT) of < 12 months or a time to PSA rise of < 3 years from surgery or a Gleason score 8-10. However, in practical terms, it is generally accepted that the PSADT is the best marker and tends to occur in those with a high Gleason score (108-113). In these cases, the potential benefits would likely outweigh the side effects of investigational agents and the benefits of a successful intervention should be more readily apparent since they have a shorter time to progression. We also considered the fact that there are spontaneous fluctuations in PSA levels in non-castrate patients and that these could affect the evaluation of PSA change in response to novel therapeutic interventions. Therefore, from weeks 1-12 weeks of the study we will measure PSA changes as a result of spontaneous fluctuations in the control arm A and under the effect of the MK-2206 alone in arm B. A 12 week period is safe and adequate to measure sequential PSA levels and will increase our ability to detect smaller, nonrandom effects of MK-2206 on serum PSA. If treatment with

MK-2206 does not translate into a PSA decline beyond spontaneous fluctuations it does not exclude the potential synergy with bicalutamide. Therefore, unless there is clear evidence of disease progression, patients on both arms will proceed to the second phase of the treatment. In the setting of normal androgen levels, MK-2206 alone is unlikely to induce PSA declines to the extent expected with bicalutamide. We may be able to assess this difference by the PSA response observed from weeks 13-44 in patients treated with bicalutamide in arm A.

To have a real-time assessment of the PSA response to antiandrogen monotherapy in patients with a PSADT<12 months and to evaluate the potential added benefit of MK-2206, we will measure sequential PSA levels for a period of 32 weeks, weeks 13-44, the effect of bicalutamide in patients randomized to arm A and the potential benefit of adding MK-2206 to bicalutamide in patients randomized to arm B. We chose 8 months of antiandrogen monotherapy or combined therapy as a cut point to asses response, because it was the duration of treatment required to achieve maximum PSA response to castration and to have prognostic implications (101,102). Thus, if the combination is more active than single agent, more patients treated in arm B should reach undetectable PSA.

This study design, using bicalutamide as a backbone, may serve to sequentially evaluate the activity of various targeted agents/combinations in the Rising PSA non-castrate patient population

In summary, during the initial 3 months on study, we will determine the effect of MK-2206 on PSA compared to spontaneous variations. In the subsequent 8 months of study, we will evaluate the effect on PSA decline of MK-2206-bicalutamide compared with bicalutamide alone, by the proportion of patients that achieve an undetectable PSA (<0.2 ng/mL) in both arms. We estimate 20% of patients in the control group will reach undetectable PSA and this will increase to 45% in the MK-2206-bicalutamide group.

1.10 Gender and Ethnicity

Study entry is open to male patients of all ethnic backgrounds. In recent ECOG Phase II trials, approximately 11% of patients were non-Caucasian. Given the limited size of the patient population to be accrued on these regimens, there will be limited power to determine differences in toxicity or efficacy between racial groups. However, we will describe any apparent differences observed in toxicity or efficacy.

2. Objectives

2.1 Primary

2.1.1 To compare the two regimens on the proportion of patients with undetectable PSA level (< 0.2 ng/mL) at 44 weeks.

2.2 Secondary

2.2.1 To assess the proportion of patients with PSA decline ≥ 85% at 44 weeks on the combination therapy arm compared to that of bicalutamide monotherapy arm.

2.2.2 To assess the distribution of best PSA response in each study arm.

2.2.3 To assess the time to PSA progression in each arm of the study.

2.2.4 To assess the time to PSA nadir in each arm of the study.

2.2.5 To assess the duration of PSA response in each arm of the study.

2.2.6 To characterize the PSA slope pre-study, during treatment, and off treatment.

2.2.7 To evaluate the safety and tolerability of MK-2206 in this patient population.

2.2.8 To determine whether Gleason score has any effect on PSA response to treatment.

2.2.9 To determine whether prior hormonal therapy has any effect on PSA response to treatment.

2.3 Laboratory Studies Objectives

Samples of the primary tumor specimen will be retrieved for banking and future analysis of the molecular profile of the primary PC tissues with emphasis on the AR and Akt upstream and downstream signaling pathways.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F) _____

NOTE: All questions regarding eligibility should be directed to the Study Chair or Study Chair Liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Patient must be at least 18 years of age.

_____ 3.1.2 Patient must have histologically confirmed diagnosis of prostate cancer.

_____ 3.1.3 Patient must have had previous treatment with definitive surgery or radiation therapy or cryoablation.

_____ 3.1.4 Patient may have prior salvage therapy (surgery, radiation or other local ablative procedures) within 4 weeks prior to randomization if the intent was for cure. Prophylactic radiotherapy to prevent gynecomastia within 4 weeks prior to randomization is allowed.

_____ 3.1.5 Patient must have no evidence of metastatic disease on physical exam, CT abdomen/pelvis (or MRI), chest x-ray (or CT chest) and bone scan within 8 weeks prior to randomization.

Study:_____ Date:_____

_____ 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.

Date prior neoadjuvant and/or adjuvant therapy stopped:_____

_____ 3.1.7 Patient may not have had therapy modulating testosterone levels (such as luteinizing-hormone, releasing-hormone agonists/antagonists and antiandrogens) within 1 year prior to randomization, *unless* it was in the neoadjuvant and/or adjuvant setting.

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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.

Serum total testosterone level: _____ Date of test:_____

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_____ 3.1.9 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 ≥ 0.4 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 (PSA1) measured at any time point since the threshold was reached.

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The PSADT must be <12 months; requires two consecutive PSA rises (PSA2 and PSA3) above the PSA1; PSA2 and PSA3 must be obtained within 6 months of study entry. All baseline PSAs should be obtained, preferably, at the same reference lab.

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_____ 3.1.10 **PSADT calculation needs 3 PSA values:**

PSA1:_____ Date:_____ is any PSA value that is equal or greater than the threshold PSA (0.4 ng/mL for radical prostatectomy or 2 ng/mL above the nadir for primary radiation therapy) indicating biochemical relapse.

PSA2:_____ Date:_____must be higher than PSA1, obtained at least 2 weeks after PSA1 and within 6 months or less from randomization

PSA3:_____ Date:_____must be higher than PSA2 and obtained at least 2 weeks after PSA2

Baseline PSA _____Date:_____must have reached a minimum of 2 ng/mL but be no greater than 50ng/mL and equal or higher than PSA3. PSA3 may be used as baseline PSA if obtained within 1 week of randomization

_____ 3.1.11 Patient's PSA doubling time (PSADT) must be less than 12 months, calculated using the following formula:

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

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 Patient must have an ECOG Performance Status of 0 or 1.

_____ 3.1.13 Patient must have adequate end-organ function as evident by the following lab values obtained within 4 weeks prior to randomization:

3.1.13.1 Granulocytes ≥ 1500/mm^3

3.1.13.2 Granulocytes: _____ Date of test: _____

3.1.13.3 Platelet count ≥ 100,000/mm^3

3.1.13.4 Platelet count: _____ Date of test: _____

3.1.13.5 Serum creatinine within normal institutional limits or creatinine clearance ≥ 50 ml/min for patients with creatinine levels above institutional normal.

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Creatinine: _____ ULN: _____

Creatinine Clearance: _____ Date of test: _____

3.1.13.6 Serum total bilirubin ≤ 1.5 times the upper limit of normal (ULN), and alkaline phosphatase (ALP) ≤ 2.5 × ULN

Serum total bilirubin:_____

ULN:_____ Date of test:_____

Alkaline phosphatase:_____

ULN:_____ Date of test:_____

3.1.13.7 SGOT (AST) and SGPT (ALT) < 2.5 x institutional upper limit of normal.

SGOT (AST): _____

ULN:_____ Date of test: _____

SGPT (ALT): _____

ULN:_____ Date of test: _____

_____ 3.1.14 HIV-positive patients are excluded from this study because of possible pharmacokinetic interactions with MK-2206.

_____ 3.1.15 Patient cannot receive concurrent therapeutic administration of anticoagulant therapy. Low dosage aspirin ≤ 325 mg per day is allowed

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_____ 3.1.16 Patients with impaired cardiac function including any one of the following will be excluded from entry on study:

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- Baseline QTc > 450 msec (male) (Patients with QTc 450-480 msec will be allowed to participate in this trial if they do not have any of the other cardiac conditions mentioned in this section). A list of medications that may cause QTc interval prolongation are listed in Appendix VII, and should be avoided by patients entering on trial.
- Patients with congenital long QT syndrome
- History of sustained ventricular tachycardia
- Any history of ventricular fibrillation or torsades de pointes
- Concomitant use of drugs with a risk of causing torsades de pointes
- Bracardia defined as heart rate < 50 beats per minute. Patients with a pacemaker and heart rate ≥ 50 beats per minute are eligible.
- Myocardial infarction or unstable angina within 6 months of study entry
- Congestive heart failure (NY Heart Association class III or IV)
- Right bundle branch block and left anterior hemi-block (bifasicular block)

_____ 3.1.17 Patient must not have GI tract disease resulting in an inability to take oral medication, malabsorption syndrome, a requirement for IV alimentation, prior surgical procedures affecting absorption, uncontrolled inflammatory GI disease (e.g., Crohn's, ulcerative colitis).

_____ 3.1.18 Patient may not be receiving any other investigational agents or receiving concurrent anticancer therapy (chemotherapy, immunotherapy, radiation therapy, surgery for cancer, or experimental medications) at time of randomization.

_____ 3.1.19 Patient may not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to MK-2206 or bicalutamide.

_____ 3.1.20 Patient must not have any uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

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_____ 3.1.21 Patients with diabetes or at risk for hyperglycemia MUST not be excluded from trials with MK-2206, but the hyperglycemia should be well controlled before the patient enters the trial. Please follow Section 5.4.4 for glucose monitoring during study for this patient population.

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_____ 3.1.22 Patients receiving any medications or substances that are inhibitors or inducers of CYP 450 3A4 are ineligible. Lists including medications and substances known or with the potential to interact with the CYP 450 3A4 isoenzymes are provided in Appendix VI.

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_____ 3.1.23 Patient must NOT have 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 has been adequately treated and patient has been continuously disease free for ≥ 2 years.

Date of last evidence disease:_____

_____ 3.1.24 The effect of the study medications on the developing human fetus are unknown. For this reason, patient must agree to use barrier contraception during and for 3 months after discontinuation of study treatment. If patient impregnates a woman while on treatment or within 3 months of discontinuing treatment, he should inform his treating physician immediately.

_____ 3.1.25 Patients must discontinue use of enzyme-inducing anti-epileptic drugs (EIAEDs) ≥ 14 days prior to study enrollment. The investigator may prescribe non-EIAEDs. Patients who must begin EIAED therapy while on study will be allowed to remain.

_____ 3.1.26 Patients must not be taking cytochrome P450 enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine or phenobarbital), St John's Wort, ketoconazole, dexamethasone, the dysrhythmic drugs (terfenadine, quinidine, procainamide, sotalol, probucol, bepridil, indapamide or flecainide), haloperidol, risperidone, rifampin, grapefruit, or grapefruit juice within two weeks of randomization and during the course of therapy (Appendix VI has a list of additional medications which have the potential for interaction.)

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_____ 3.1.27 Patients may have received targeted agents (angiogenesis inhibitors, EGFR inhibitors, mTOR inhibitors, PI3K inhibitors, etc.), however patients must have discontinued treatment with the targeted agent(s) at least 4 weeks prior to enrollment. If the patient stopped targeted agent(s) due to unresolved or persistent grade 3 or 4 toxicity, patient cannot be enrolled onto the study regardless of the length of time since discontinuation of treatment with targeted agent(s).

_____ _____

Physician Signature **Date**

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Randomization Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

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Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for E2809 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Submitting Regulatory Documents

Before an ECOG-ACRIN Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. **A. CTSU IRB Certification Form.**
   Or
   B. OMB # No. 0990-0263 (replaces form 310)
   Or
   C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**
- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

4. **Investigator's Statement**

The Investigator's Statement documents that the Investigator has read this protocol, received IRB approval and will obtain informed consent in writing for patients who meet the eligibility criteria.

NOTE: This form only needs to be submitted by the Principal Investigator, not for each sub-investigator.

Before submission, confirm the following on the Investigator's Statement:

- **All fields are complete**
- **The statement is signed by the Principal Investigator**

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The CTSU encourages you to link to the following CTSU RSS webpage so that more information on RSS2.0 as well as the submission forms can be accessed. Log into http://www.ctsu.org and click on the Regulatory tab to access the RSS webpage. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com**.**

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Patients must not start protocol treatment prior to randomization.

Treatment should start within seven working days after randomization.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.

- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Protocol Number

4.2 Investigator Identification

- 4.2.1 Institution and affiliate name (Institution CTEP ID)
- 4.2.2 Investigator's name (NCI number)
- 4.2.3 Cooperative Group Credit
- 4.2.4 Credit Investigator
- 4.2.5 Protocol specific contact information

4.3 Patient Identification

- 4.3.1 Patient's initials (first and last)
- 4.3.2 Patient's Hospital ID and/or Social Security number
- 4.3.3 Patient demographics
  - 4.3.3.1 Gender
  - 4.3.3.2 Birth date
  - 4.3.3.3 Race
  - 4.3.3.4 Ethnicity
  - 4.3.3.5 Nine-digit ZIP code
  - 4.3.3.6 Method of payment
  - 4.3.3.7 Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1. An eligibility checklist has been appended to the protocol. A confirmation of

randomization will be forwarded by the ECOG-ACRIN Operations Office – Boston.

4.5 Stratification Factors

4.5.1 Gleason Score

- ≤ 6
- 7
- 8 to 10

4.5.2 Prior Hormonal Therapy

- Yes
- No

4.6 Additional Requirements

4.6.1 Patients must provide a signed and dated, written informed consent form.

4.6.2 Specimens are to be submitted for laboratory research studies as outlined in Section 10.

NOTE: All specimens submitted are to be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. See Section 10.

4.7 Investigator Drug Brochure and Safety Alerts

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MK-2206 is an INVESTIGATIONAL AGENT (NSC 749607; IND 109493). A copy of the Investigator's Drug Brochure (IDB) can be requested from the PMB (See Section 8.1.1). The IDB provides relevant and current scientific information about the investigational product. The IDB should be submitted to your IRB/EC according to GCP regulations. The IDB and any correspondence to the Institutional Review Board (IRB)/Ethics Committee (EC) should be kept in the E2809 regulatory files.

Should any SAE report on this study qualify as a safety alert report requiring expedited reporting, the SAE report will be sent by the sponsors to regulatory authorities globally (including the FDA) and ECOG-ACRIN. ECOG-ACRIN, following regulatory review, will disseminate these safety alert reports to all ECOG-ACRIN investigators in the bimonthly group mailings. These reports should be forwarded to your IRB/EC within 90 days of receipt for review. Reporting instructions are provided with each safety alert. These safety alerts and any correspondence to your IRB/EC should be maintained in your E2809 study files.

4.8 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E2809 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

5. Treatment Plan

5.1 Administration Schedule

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

NOTE: Reported adverse events and potential risks for both MK-2206 and Bicalutamide are described in Sections 5.3, and 8.2.10. Appropriate dose modifications for MK-2206 are described in Section 5.4. No investigational or commercial agents or therapies, other than those described below, may be administered with the intent to treat the patient's malignancy while on study. There are no dose modifications for bicalutamide.

NOTE: Patients will be asked to complete a Patient Medication Calendar (Appendix IV) at home to keep a record of pills taken each day as well as omissions, side-effects, other medications, etc. Pill counts will also be made by a study monitor at each follow-up.

5.1.1 Treatment ARM A

Cycles 1-3 (Weeks 1-12): observation without treatment

NOTE: Patients with a PSA rise of ≥ 50 % above baseline may start bicalutamide early (See Section 5.6.1.1).

Cycles 4-11 (Weeks 13-44): bicalutamide (Casodex) 50 mg/daily, orally, continuously to the end of study.

NOTE: If by the end of Cycle 11 (week 44) patient achieved a PSA decline of ≥ 50% in the absence of toxicity or progression, patient may continue on bicalutamide to the completion of Cycle 18 (week 72). If criteria was not met, patient must come off-treatment after completion of Cycle 11 (week 44). (See Sections 5.6.1.2 and 5.6.1.3).

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5.1.2 Treatment ARM B

NOTE: To prevent phototoxicity patients should avoid exposure to the sun and wear protective clothing while on MK-2206.

Cycles 1-3 (Weeks 1-12): MK-2206 200 mg once per week, orally. Should be taken at approximately the same time each week 2 hours before or two hours after a meal.

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ECG monitoring prior to and during MK2206 administration

On day 1 of cycle 1, the patient will take the medication in the clinic.

- Prior to drug administration obtain ONE ECG
- If QTc is ≤ 480 msec administer MK2206. Repeat ONE ECG within 4 to 10 hours after the treatment.
- If QTc remains ≤ 480 msec one ECG will be performed once, at random, on day 1 of any subsequent treatment cycle.

If the pre-treatment or post-treatment QTc value is greater than 480 and less than 515 msec

a. Measure serum phosphorous, potassium, magnesium, troponin, and calcium, and the patient must receive supplements to correct any low values.

b. After correction of imbalances obtain three ECG's at least 5 minutes apart, so as to obtain an average pre-treatment QTc reading.

c. Notify CTEP. Any final decisions concerning any dose modification/interruptions or patient discontinuing study drug permanently should be based on QTc calculations.

d. If treatment is given, the drug must be taken in the office followed by three ECG's at least 5 minutes apart within 4 to 10 hours after MK2206 administration to obtain a post-treatment average.

e. A weekly ECG prior to dosing must be obtained at either the clinic or the local cardiologist to measure QTc.

f. If QTc remains abnormal refer to a specialist if clinically indicated.

g. At the end of the cycle QTc status should be re-evaluated.
   - if the QTc is less or equal than 480 msec monitor ECG only randomly.
   - if the QTc value is greater than 480 and less than 515 msec further discussion regarding continuation of the patient on the same dose and in the study should be initiated between the investigator and CTEP.

In general, there will be dose reductions for:

- Multiple QTc equal or greater than 480 and less than 515 msec
- Repeat dosing delays due to prolonged QTc intervals

If QTc ≥ 515 msec MK2206 will be discontinued

All cardiac events should be treated as per the local standard of care and referred to a specialist by the investigator if clinically indicated.

NOTE: Patients with a PSA rise of ≥ 50 % above baseline may start bicalutamide early (See Section 5.6.2.1).

Cycles 4-11 (Weeks 13-44): Continue MK-2206 200 mg once per week, orally. Start bicalutamide (Casodex) 50 mg/daily, orally, on a continuous basis.

NOTE: Patients on MK2206 alone that reach a PSA < 0.2 ng/mL by week 12 will NOT receive bicalutamide until the PSA rises to ≥ 0.2 ng/mL and is confirmed on a second determination 2 weeks later. Only after confirmation is obtained will bicalutamide be added to the patient's treatment regimen to be continued through the end of Cycle11 (Week 44).

NOTE: If by the end of Cycle 11, patient achieved a PSA decline of ≥ 50% in the absence of toxicity or progression, patient may continue on the combination of bicalutamide and MK-2206 to the completion of Cycle 18. If criteria was not met, patient must come off-treatment after completion of Cycle 11. (See Section 5.6.2.3).

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5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E2809 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.2.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study arm includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration:* When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event:* The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at http://ctep.cancer.gov.

Step 2: Grade the event using the NCI CTCAE version 4.0.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

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Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is **NOT** listed in:

- **Arm A** – the drug package insert or protocol
- **Arm B** – the current NCI Specific Protocol Exceptions to Expedited Reporting (SPEER) for MK-2206

NOTE: The NCI SPEER for MK-2206 is included in Section 5.3 of the protocol.

- **FOR THIS PROTOCOL**, events listed in the **SPEER** for MK-2206 should be considered EXPECTED if the grade being reported is the same or lower than the grade noted in the parentheses next to the AE in the SPEER. Events listed in the SPEER column should be considered UNEXPECTED if the grade being reported exceeds the grade noted in parentheses next to the AE in the SPEER.
- The SPEER is presented in the last column of the CAEPR and identified with ***bold*** and ***italicized*** text.

Step 5: Review the ”Additional instructions, requirements, and exceptions for protocol E2809” table in section 5.2.6 and footnote b in Section 5.2.7 for protocol and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

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5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)for Arm A and B
- the FDA (800-332-0178) for Arm A
- the NCI (301-897-7497) for Arm B

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617-632-2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) for Arm A and the NCI (301-230-0159) for Arm B in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 When to Report an Event in an Expedited Manner

Some adverse events require 24-hour notification (refer to Section 5.2.6). Please complete a 24-Hour Notification Report via the NCI CTEP-AERS website (http://ctep.cancer.gov) within 24 hours of learning of the event. The full CTEP-AERS report must be completed and submitted via CTEP-AERS within 5 calendar days.

If the CTEP-AERS system is down, a 24-hour notification call must be made to ECOG-ACRIN (617-632-3610) and to NCI (301-897-7497). Once the system is restored, a 24-hour Notification Report must be entered into the CTEP-AERS system by the original submitter of the report at the site.

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Sections 5.2.6 and 5.2.7.

NOTE: Adverse events that meet the reporting requirements in Sections 5.2.6 or 5.2.7 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Sections 5.2.6 or 5.2.7 must be

reported on an expedited adverse event report form (using CTEP-AERS).

5.2.5 Other Recipients of Adverse Event Reports

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.6 Expedited Reporting for Investigational Agents

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of Investigational Agent [MK-2206] in this Study (Arm B) OR Within 30 Days of the Last Dose of Any Protocol Treatment.

Attribution	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see additional information below under section entitled "Additional instructions, requirements, and exceptions for protocol E2809"

March 2005

NOTE: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines:
  - **24 Hours; 5 calendar days** – The investigator must initially report the AE via CTEP-AERS within <u>24 hours</u> of learning of the event followed by a complete CTEP-AERS report within <u>5 calendar days</u> of the initial 24-hour report.

- **10 calendar days** – A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates **hospitalization* (or prolongation of existing hospitalization)** must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in **persistent or significant disability/incapacity, congenital anomaly, or birth defect** must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- Hospitalizations are defined as lasting 24 hours or longer and these events must be reported via CTEP-AERS.

Additional instructions, requirements and exceptions for protocol E2809

1. Additional Instructions:

- With respect to determining the specific day by which the event must be reported, the day the reporter learns of the adverse event constitutes "Day 0"
- For grade 2 and 3 unexpected events, CTEP-AERS reporting is only required if the event is related to the investigational agent(s); it is not required if the event is related only to the commercial agent(s) included in the protocol treatment.

  NOTE: For grade 3 unexpected events with hospitalization lasting ≥ 24 hours (or prolonged hospitalization), an CTEP-AERS report is required even if the event is unrelated to the investigational agent(s).
- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

2. ECOG-ACRIN and Protocol Specific expedited reporting requirements:

The adverse events listed below also require expedited reporting for this trial:

ECOG-ACRIN specific expedited reporting requirements:

- **Hospitalizations:** Any grade 1 or 2 adverse event with precipitates a hospitalization lasting > 24 hours (or prolongs hospitalization) must be reported via CTEP-AERS within 10 calendar days of learning of the event regardless of the attribution and designation as expected or unexpected.

5.2.7 Expedited Reporting for Commercial Agents

Commercial reporting requirements are provided below. The commercial agent used in arm A of this study Bicalutamide.

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arm A

Attribution	Grade 4		Grade 5[a]		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment regardless of attribution.

NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

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5.2.8 Reporting Second Primary Cancers

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN:

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office – Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215

  2. Submit a copy of the pathology report to ECOG-ACRIN confirming the diagnosis.

3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN

- **A <u>secondary</u> malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office – Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215

  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

  3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.

  4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-2206 (NSC 749607)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 193 patients. Below is the CAEPR for MK-2206.

NOTE: FOR THIS PROTOCOL, events listed in the SPEER column should be considered EXPECTED if the grade being reported is the same or lower than the grade noted in the parentheses next to the AE in the SPEER. Events listed in the SPEER column should be considered UNEXPECTED if the grade being reported exceeds the grade noted in parentheses next to the AE in the SPEER.

Version 2.1, March 22, 2013[1]

Adverse Events with Possible Relationship to MK-2206 (CTCAE 4.0 Term) [n= 193]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
	Sinus bradycardia		***Sinus bradycardia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		

INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Creatinine increased		
	Electrocardiogram QT corrected interval prolonged		***Electrocardiogram QT corrected interval prolonged (Gr 2)***
	Hemoglobin increased		
	Investigations - Other (eosinophilia)		***Investigations - Other (eosinophilia) (Gr 2)***
	Investigations - Other (insulin c-peptide increased)		
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hypokalemia		
	Hyponatremia		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache		***Headache (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on MK-2206 trials but with the relationship to MK-2206 still undetermined:

CARDIAC DISORDERS - Atrioventricular block complete; Palpitations

EAR AND LABYRINTH DISORDERS - Vertigo

ENDOCRINE DISORDERS - Hypothyroidism

EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blepharitis); Eye disorders - Other (eye swelling); Eye disorders - Other (foreign body sensation in eyes); Eye disorders - Other (iritis); Eye disorders - Other (mydriasis); Eye disorders - Other (visual acuity reduced); Eye pain; Floaters; Keratitis; Photophobia; Retinal detachment; Uveitis

GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Cheilitis; Dry mouth; Dyspepsia; Dysphagia; Gastritis; Lip pain; Oral pain; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Flu like symptoms; General disorders and administration site conditions - Other (throat tightness); Injection site reaction; Irritability; Localized edema; Non-cardiac chest pain; Pain

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (herpetic vesicular rash [due to herpes zoster infection]); Infections and infestations - Other (oral herpes); Nail infection; Paronychia; Rhinitis infective; Sepsis; Skin infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Aspartate aminotransferase increased; Blood bilirubin increased; INR increased; Investigations - Other (blood LDH increased); Investigations - Other (hyperinsulinemia); Investigations - Other (glucose urine present); Lipase increased; Serum amylase increased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Generalized muscle weakness; Myalgia; Neck pain; Pain in extremity

NERVOUS SYSTEM DISORDERS - Akathisia; Dizziness; Lethargy; Presyncope; Reversible posterior leukoencephalopathy syndrome; Seizure

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Renal and urinary disorders - Other (renal tubular necrosis); Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Gynecomastia; Reproductive system and breast disorders - Other (genital hemorrhage); Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchial obstruction; Cough; Dyspnea; Hypoxia; Pneumonitis; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Sore throat

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (skin discoloration); Skin and subcutaneous tissue disorders - Other (skin irritation); Urticaria

VASCULAR DISORDERS - Hematoma; Hypertension; Hypotension; Thromboembolic event

NOTE: MK-2206 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.4 Dose Modifications

All toxicities should be graded according to the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE).

The CTEP Version 4.0 of the CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

Dose reductions 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 to 2 (or within 1 grade of starting values of pre-existing laboratory abnormalities) from a treatment-related toxicity within 42 days (leading to treatment delay of > 42 days).

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Dose modifications are not necessary for Grade 1 or 2 toxicities, except changes in ECG (follow section 5.4.3 ECG monitoring) and grade 2 or greater drug included papulo-macular rash (follow section 5.4.5 instructions).

No dose level modifications of bicalutamide are allowed.

5.4.1 Dose Levels

Arm A:

Dose Level	Bicalutamide
0	(Cycle 4 +)* 50 mg/daily
-1	No dose modifications
-2	No dose modifications

*Patients with a PSA rise of > 50% above baseline may start bicalutamide early.

5.4.2 Arm B:

Dose Level	Bicalutamide	MK-2206
0	(Cycle 4 +)* 50 mg/daily	(All cycles) 200 mg once per week
-1	No dose modifications	135 mg once per week
-2	No dose modifications	90 mg once per week

*Patients with a PSA rise of > 50% above baseline may start bicalutamide early.

NOTE: Patients requiring a dose reduction below the -2 dose level must be taken off study.

5.4.3 Suggested Dose Modifications

There will be no dose reductions for bicalutamide. In case of CTCAE Grade 3 or 4 transaminase elevations **both** bicalutamide and MK-2206 will be stopped until the event resolves to ≤ Grade 1.

In all cases of toxicity that cannot be attributed to MK-2206 alone, **both** drugs will be stopped until the event resolves to ≤ Grade 1. Treatment will be restarted with full dose of bicalutamide and MK-2206 should be reduced according to the guidelines provided.

For toxicities that are attributed to MK-2206 **alone**, follow the chart below regarding MK-2206 dose modification, but bicalutamide will continue at its normal dosage.

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For Grade 3-4 toxicities at least possibly related to study medication		
Toxicities	**Occurrence**	**Suggested MK-2206 Dose Modifications**
Bone marrow suppression ANC <0.5 ng/μL for > 7 days ANC <1.0 ng/μL with fever (temperature of ≥100.5° F /38.5°C) Platelet count <25 ng/μL	1st occurrence	1. Interrupt MK-2206 until recovery to ≤ Grade 1 2. Treatment according to the findings 3. Restart with reduced dose 4. Increase to 200 mg once per week if toxicity is maintained at ≤ Grade 1 within 28 days 5. Discontinue from study therapy if the event has not resolved to ≤ Grade 1 within 42 days or event occurs during therapy at the 135 mg once per week reduced dose.
Liver Toxicity CTCAE Grade 3/4 transaminase elevations Other CTCAE Grade 3 or 4 non-hematologic toxicities	2nd occurrence	1. Interrupt MK-2206 until recovery to ≤ Grade 1 2. Treatment according to the findings 3. Restart with reduced dose 4. Increase to 200 mg once per week if toxicity is maintained at ≤ Grade 1 within 28 days 5. Discontinue from study therapy if the event has not resolved to ≤ Grade 1 within 42 days or event occurs during therapy at the 90 mg once per week reduced dose.
	3rd occurrence	Discontinue from study treatment.

Abbreviations: ANC (absolute neutrophil count)

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ECG monitoring prior to and during MK2206 administration

On day 1 of cycle 1, the patient will take the medication in the clinic.

- Prior to drug administration obtain ONE ECG.
- If QTc is ≤ 480 msec administer MK2206. Repeat ONE ECG within 4 to 10 hours after the treatment.
- If QTc remains ≤ 480 msec one ECG will be performed once, at random, on day 1 of any subsequent treatment cycle.

If the pre-treatment or post-treatment QTc value is greater than 480 and less than 515 msec

a. Measure serum phosphorous, potassium, magnesium, troponin, and calcium, and the patient must receive supplements to correct any low values.

b. After correction of imbalances obtain three ECG's at least 5 minutes apart, so as to obtain an average pre-treatment QTc reading.

c. Notify CTEP. Any final decisions concerning any dose modification/interruptions or patient discontinuing study drug permanently should be based on QTc calculations.

d. If treatment is given, the drug must be taken in the office followed by three ECG's at least 5 minutes apart within 4 to 10 hours after MK2206 administration to obtain a post-treatment average.

e. A weekly ECG prior to dosing must be obtained at either the clinic or the local cardiologist to measure QTc.

f. If QTc remains abnormal refer to a specialist if clinically indicated.

g. At the end of the cycle QTc status should be re-evaluated.
   - if the QTc is less or equal than 480 msec monitor ECG only randomly.
   - if the QTc value is greater than 480 and less than 515 msec further discussion regarding continuation of the patient on the same dose and in the study should be initiated between the investigator and CTEP.

In general, there will be dose reductions for:

- Multiple QTc equal or greater than 480 and less than 515 msec
- Repeat dosing delays due to prolonged QTc intervals

If QTc ≥ 515 msec MK2206 will be discontinued

All cardiac events should be treated as per the local standard of care and referred to a specialist by the investigator if clinically indicated.

5.4.4 Hyperglycemia

Grade 3 hyperglycemic events (>250 mg/dL) should lead to consultation with an endocrinologist or other specialist. If glucose levels do no return to grade 1 or lower within one week of appropriate therapy, patients should be considered to have a DLT (dose modification, etc.).

Appropriate therapy will usually involve oral antihyperglycemic agents, since the inhibition of glucose transport into the cell by AKT/mTOR inhibitors may render insulin ineffective. The goal of therapy is to keep fasting glucose <150 mg/dL, random blood glucose levels <180 mg/dL, and Hemoglobin A1c <8%. Glucose monitoring should be performed weekly, during the first cycle of therapy, and on day 1 of subsequent cycles, prior to drug administration. Hemoglobin A1c

monitoring, for patients requiring treatment of hyperglycemia, should be performed with each cycle of MK-2206 therapy.

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5.4.5 Drug induced maculo-papular rash treatment guide

In case of grade 2 or greater drug induced papulo-macular rash, use the following precautions:

1. Interrupt MK2206.

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2. Use antihistamines such as Fexofenadine or Loratidine that are not CYP3A4 inducers/inhibitors and if needed use anti-pruritic medications that are non steroidal such as topical 2% clindamycin and non CYP3A4 inducers/inhibitors antibiotics.

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3. If rash does not decrease to grade 1 or less within 2 weeks, corticosteroids such as 1% hydrocortisone in a lotion base may be used after consultation with Study Chair.

4. If rash resolves to grade 1 or less within 42 days, restart MK2206 at 135mg once per week. If grade 2 or higher rash recurs at the 135 mg dose, patient should come off study. If rash persists at grade 1 or less during 28 days, the dose may be increased back to 200mg once per week or maintained at 135mg once per week at the discretion of the principal investigator.

If the rash recurs again after increasing the dose back to MK2206 200mg dose follow steps 1- 3 and if the rash decreases to grade 1 or less for 28 days re-introduce the MK2206 at 90mg once per week. If tolerated at the 90 mg for 28 days may increase MK2206 back to 200mg once per week or left at 90mg once per week at the discretion of the principal investigator.

5. Patient should be taken off study for a second recurrence of rash at a reduced dose level (either 135mg or 90mg) or a third recurrence at 200mg dose of MK2206.

5.5 Supportive Care

Patients are allowed to receive full supportive care therapies concomitantly during the study. At each visit, appropriate documentation of all forms of premedication, supportive care, and concomitant medications must be recorded on the CRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day follow-up visit.

NOTE: If the patient has an AE that falls after week 45 they must have a return visit for evaluation or communicate by phone within 30 days and provide documentation describing the event.

5.6 Duration of Therapy

5.6.1 Arm A

5.6.1.1 Cycles 1-3 (Weeks 1-12)

- Patients with a PSA rise of ≥ 50% above baseline or nadir (whichever is lowest) and a rise of at least 5 ng/mL, confirmed by a repeat PSA at least 2 weeks

later, may be started on bicalutamide before the end of Cycle 3 (week 12) at the discretion of the treating physician.

- Patients with a PSA rise of < 50% above baseline or nadir, stable PSA, or declining PSA, will continue observation until the end of Cycle 3 (week 12).
- Patients with PSA < 0.2 ng/mL by the end of Cycle 3 (week 12) will NOT receive bicalutamide until the PSA rises to ≥ 0.2 ng/mL and the rise is confirmed on a second determination 2 weeks later.

5.6.1.2 Cycles 4-11 (Weeks 13-44)

- Patients with a PSA rise of ≥ 50% above baseline or nadir (whichever is lowest) and a rise of at least 5 ng/mL, confirmed by a repeat PSA at least 2 weeks later, will be considered failures and removed from study.
- Patients with a PSA rise of < 50% above baseline or nadir, stable PSA, or declining PSA, will continue on bicalutamide to the end of study.

5.6.1.3 End of Study

- Patients on Arm A will not be eligible to receive MK-2206.
- Patients who achieve a reduction in PSA by ≥ 50% may continue receiving bicalutamide up to the completion of Cycle 18 (week 72) in the absence of toxicity, progression or other reason for needing to go off study.

5.6.2 Arm B

5.6.2.1 Cycles 1-3 (Weeks 1-12)

- Patients with a PSA rise of ≥ 50% above baseline or nadir (whichever is lowest) and a rise of at least 5 ng/mL, confirmed by a repeat PSA at least 2 weeks later, may be started on bicalutamide before the end of Cycle 3 (week 12) at the discretion of the treating physician.
- Patients with a PSA rise of < 50% above baseline or nadir, stable PSA, or declining PSA, will continue MK-2206 until the end of Cycle 3 (week 12).
- Patients with PSA < 0.2 ng/mL by the end of Cycle 3 (Week 12) will NOT receive bicalutamide until the PSA rises to ≥ 0.2 ng/mL and the rise is confirmed on a second determination 2 weeks later.

5.6.2.2 Cycles 4-11 (Weeks 13-44)

- Patients receiving the combination therapy who experience a PSA rise of ≥ 50% above baseline or nadir (whichever is lowest) and a rise of at least 5 ng/mL, confirmed by a repeat PSA at least 2 weeks later, will be considered failures and removed from study.
- Patients with a PSA rise of < 50% above baseline or nadir, stable PSA, or declining PSA, will continue therapy to the end of study.
- Patients on MK2206 alone between weeks 13-44 who experience a PSA rise to ≥ 0.2 ng/mL, and the rise is confirmed on a second determination 2 weeks later, will receive bicalutamide to the end of week 44.

5.6.2.3 End of Study

- Patients who achieve a reduction in PSA by ≥ 50% may continue receiving the combination therapy up to the completion of Cycle 18 (week 72), in the absence of toxicity, progression, or other reason for needing to go off study.

5.7 Discontinuation of Therapy

Patients will receive protocol therapy unless:

5.7.1 Progression of Disease

- PSA Progression

OR

- Clinical progression

5.7.2 Unacceptable toxicity – type and grade must be documented on the E2809 Adverse Event Form. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.7.3 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E2809 Forms Packet.

5.7.4 Patient withdraws consent.

5.8 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until clinical metastatic progression and for survival for 10 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Biochemical Response

6.1.1 Complete Response

Complete biochemical response will be a PSA <0.2 ng/mL (confirmed on two consecutive additional determinations taken at least 4 weeks apart).

6.1.2 Partial Response

A reduction in PSA ≥ 50% from baseline without evidence of progression (confirmed on two consecutive additional determinations taken at least 4 weeks apart).

6.1.3 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.

6.1.4 Progressive Disease

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- For patient who achieved a ≥ 50% decline in PSA (confirmed on two consecutive additional determinations taken at least 4 weeks apart), 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.

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- For patients with an undetectable PSA nadir (< 0.2 ng/mL confirmed on two consecutive additional determinations taken at least 4 weeks apart), 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.
- 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.

6.2 Clinical Progression

The appearance of new lesions on examination or radiographs (CXR, CT scan, MRI scan, or bone scan), or development of symptoms consistent with metastatic disease (i.e. bone pain) with or without a concurrent increase in serum PSA from baseline.

6.3 Survival

Survival will be measured from the date of randomization.

6.4 Time to PSA Progression

Time to PSA progression is defined as time from registration to first confirmed rise in PSA (or development of clinical progression) meeting progressive criteria

after starting bicalutamide treatment. The 50% rise of PSA from baseline during the first 12 weeks which triggers the early treatment with bicalutamide is not considered a PSA progression.

6.5 Time to PSA Nadir

Time to PSA nadir is defined as the time from registration 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.

6.6 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.

6.7 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.

6.8 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. Study Parameters

7.1 Therapeutic Parameters

1. Prestudy scans and x-rays must be done within **8 weeks** prior to randomization.
2. Prestudy CBC (with differential and platelet count) should be done within **4 weeks** prior to randomization.
3. All required prestudy chemistries, as outlined in Section 3.1.13, should be done within **4 weeks** prior to randomization.

	Pre-Study	Cycle 1 Day 1	Day 1 of Each Cycle (Cycles 2-6)	Day 1 of Cycle 7 (Week 25)	Day 1 of each cycle (cycles 8-11)	Day after Cycle 11 finished (Day 1 of Week 45)	Day 1 of Each Cycle (Cycles 13-18)[6]	End of Treatment[6]	Follow-up[7]
Medical history, height	X								
Concurrent meds	X	X	X	X	X	X	X	X	
Physical exam, vitals[1], weight	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	
CBC w/diff, plts[2]	X	X	X	X	X	X	X	X	X
Serum chemistries[3]	X	X	X	X	X	X	X	X	
Total testosterone	X					X		X	
PSA	X	X	X	X	X	X	X	X	X[5]
Rev. 4/12 Radiologic evaluation	X[4]			X[4]		X[4]	X[10]	X	
ECG	X	X[11] (Arm B)	As indicated						
AE Evaluation		X	X	X	X	X	X	X	X[8]
Tumor tissue	X[9]								

1. Blood pressure, pulse
2. Rev. 4/12 CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be obtained within 4 days of day 1 of treatment cycle.
3. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium. There is a +/- 7 day leeway for scheduled tests while on study (leeway does not apply to tests/labs required at baseline to determine patient eligibility). For patients with known diabetes: Glucose monitoring should be performed weekly, during the first cycle of therapy, and on day 1 of subsequent cycles, prior to drug administration. Hemoglobin A1c monitoring, for patients requiring treatment of hyperglycemia, should be performed with each cycle of MK-2206 therapy. Rev. 6/13
4. Rev. 4/12 CXR, CT abdomen/pelvis (or MRI), **and** bone scan required at baseline, day 1 cycle 7 and end of cycle 11. There is a +/- 7 day leeway for

scheduled tests while on study (leeway does not apply to test/labs required at baseline to determine patient eligibility).

5. After going off treatment, patients will be evaluated for PSA levels monthly for the first 6 months and then every 3 months until PSA progression.
6. For those patients who continue study treatment after Cycle 11.
7. Follow-up for study purposes will be every 3 months until 2 years, every 6 months 2-5 years and every year up to 10 years.
8. Until documentation of progression (serological or clinical).
9. Submit for patients who consent to allow tissue to be submitted for use in research. See Section 10.

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10. If the patient remains on study after the end of study (Cycle 11), repeat at the end of cycle 18 or sooner if clinically indicated. There is a +/- 7 day leeway for scheduled tests while on study (leeway does not apply to tests/labs required at baseline to determine patient eligibility).

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11. **ECG Monitoring prior to and during MK2206 administration**

On day 1 of cycle 1, the patient will take the medication in the clinic.

- Prior to drug administration obtain ONE ECG
- If QTc is ≤ 480 msec administer MK2206. Repeat ONE ECG within 4 to 10 hours after the treatment.
- If QTc remains ≤ 480 msec one ECG will be performed once, at random, on day 1 of any subsequent treatment cycle.

If the pre-treatment or post-treatment QTc value is greater than 480 and less than 515 msec

a. Measure serum phosphorous, potassium, magnesium, troponin, and calcium, and the patient must receive supplements to correct any low values.
b. After correction of imbalances obtain three ECG's at least 5 minutes apart, so as to obtain an average pre-treatment QTc reading.
c. Notify CTEP. Any final decisions concerning any dose modification/interruptions or patient discontinuing study drug permanently should be based on QTc calculations.
d. If treatment is given, the drug must be taken in the office followed by three ECG's at least 5 minutes apart within 4 to 10 hours after MK2206 administration to obtain a post-treatment average.
e. A weekly ECG prior to dosing must be obtained at either the clinic or the local cardiologist to measure QTc.
f. If QTc remains abnormal refer to a specialist if clinically indicated.
g. At the end of the cycle QTc status should be re-evaluated.
    - if the QTc is less or equal than 480 msec monitor ECG only randomly.
    - if the QTc value is greater than 480 and less than 515 msec further discussion regarding continuation of the patient on the same dose and in the study should be initiated between the investigator and CTEP.

In general, there will be dose reductions for:

- Multiple QTc equal or greater than 480 and less than 515 msec
- Repeat dosing delays due to prolonged QTc intervals

If QTc ≥ 515 msec MK2206 will be discontinued

All cardiac events should be treated as per the local standard of care and referred to a specialist by the investigator if clinically indicated.

8. Drug Formulation and Procurement

8.1 MK-2206

8.1.1 Availability

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NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Drug Ordering: Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application at https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account from https://eapps-ctep.nci.nih.gov/iam/ and the maintenance of an "active" account status and a "current" password.

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For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Inventory Records: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.

8.1.2 Other Names

Chemical Name or Amino Acid Sequence: 8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl-1,2,4-triazolo[3,4-*f*]-1,6-naphthyridin-3(2*H*)-one mono-hydrochloride salt

Molecular Formula: $C_{25}H_{22}N_5OCl$ **M.W.:** 443.93

Approximate Solubility: Soluble in water (7.54 mg/mL; pH = 6.) but less soluble in acetonitrile (1.4 mg/mL) and ethanol (2 mg/mL). Its mono-hydrochloride salt is slightly hygroscopic (absorbs 1.9 wt% water up to 95% relative humidity).

8.1.3 Classification

Akt inhibitor

8.1.4 Mode of Action

The PI3K-Akt pathway is activated downstream of EGFR, HER2, IGF1R, and cMet, and is a suspected driver of tumor progression in most cancers. Overexpression or activating mutations in receptors tyrosine kinases, PI3K and Ras, inactivation of the tumor suppressor PTEN, or amplification or mutation of Akt can activate Akt protein kinase in most carcinomas. It is believed that Akt inhibitors that target the pathway downstream of the most common mutations have broader utility and provide less resistance in the clinic.

8.1.5 Storage and Stability

Storage: Store intact bottles at room temperature, not to exceed 30^0C.

Stability: Shelf life studies of MK-2206 are ongoing.

8.1.6 Dose Specifics

MK-2206 200 mg per week, orally. MK-2206 should be taken 2 hours before or 2 hours after food.

8.1.7 How Supplied

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MK-2206 tablets are supplied by Merck and distributed by the DCTD, NCI. The 5-mg, 25-mg, and 200-mg tablets are film coated, packaged in HDPE bottles. The 5 mg and 25 mg bottles contain 10 and 20 tablets, respectively. When inventory allows, the 5 mg and 25 mg bottles also contain 30 tablets each. The 200-mg bottles contain 5 tablets each. The pharmaceutical collaborator does not have stability data to support repackaging MK-2206 tablets in any container other than what is provided.

The white film (Opadry® 20A18273) coating consists of hydroxypropyl cellulose, hydroxypropyl methylcellulose and titanium dioxide.

Inactive ingredients consist of microcrystalline cellulose (Avicel PH102®), calcium phosphate dibasic anhydrous (ATAB®), croscarmellose sodium, and magnesium stearate.

8.1.8 Route of Administration

Orally (2 hours before or after food).

8.1.9 Availability

MK-2206 is an investigational agent (IND). MK-2206 tablets are supplied by Merck and distributed by the DCTD, NCI.

Initial Drug Orders for Each Patient

8.1.10 Potential Drug Interactions

MK-2206 is not a CYP3A4 inducer at clinically relevant concentrations. MK-2206 is a substrate for P-glycoprotein (P-gp) mediated transport.

8.1.11 Side Effects

Please refer to the CAEPR (Section 5.3).

8.1.12 Nursing/Patient Implications

1. MK-2206 should be taken 2 hours before or after food.
2. If a patient vomits within 30 minutes of taking a dose of MK-2206, the dose should be replaced that day at the discretion of the investigator.
3. A Patient Medication Calendar (Appendix IV) will be provided to the patient by the study coordinator at baseline and each subsequent visit, and a completed medication calendar should be returned by the patient at Day 1 of each cycle.

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4. **ECG monitoring prior to and during MK2206 administration**

   On day 1 of cycle 1, the patient will take the medication in the clinic.

   - Prior to drug administration obtain ONE ECG.
   - If QTc is ≤ 480 msec administer MK2206. Repeat ONE ECG within 4 to 10 hours after the treatment.
   - If QTc remains ≤ 480 msec one ECG will be performed once, at random, on day 1 of any subsequent treatment cycle.

<u>If the pre-treatment or post-treatment QTc value is greater than 480 and less than 515 msec</u>

a. Measure serum phosphorous, potassium, magnesium, troponin, and calcium, and the patient must receive supplements to correct any low values.
b. After correction of imbalances obtain three ECG's at least 5 minutes apart, so as to obtain an average pre-treatment QTc reading.
c. <u>Notify CTEP</u>. Any final decisions concerning any dose modification/interruptions or patient discontinuing study drug permanently should be based on QTc calculations.
d. If treatment is given, the drug must be taken in the office followed by three ECG's at least 5 minutes apart within 4 to 10 hours after MK2206 administration to obtain a post-treatment average.
e. A weekly ECG prior to dosing must be obtained at either the clinic or the local cardiologist to measure QTc.
f. If QTc remains abnormal refer to a specialist if clinically indicated.
g. At the end of the cycle QTc status should be re-evaluated.
   - if the QTc is less or equal than 480 msec monitor ECG only randomly.
   - if the QTc value is greater than 480 and less than 515 msec further discussion regarding continuation of the patient on the same dose and in the study should be initiated between the investigator and CTEP.

<u>In general, there will be dose reductions for:</u>

- Multiple QTc equal or greater than 480 and less than 515 msec
- Repeat dosing delays due to prolonged QTc intervals

If QTc ≥ 515 msec MK2206 will be discontinued

All cardiac events should be treated as per the local standard of care and referred to a specialist by the investigator if clinically indicated.

5. If a patient suffers from hyperglycemia it must be monitored closely.

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

8.2.1 Avaliability

Bicalutamide is commercially available

8.2.2 Other Names

Casodex®, a commercially available agent.

8.2.3 Chemical Name

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

8.2.4 Molecular Formula

$C_{18}H_{14}N_2O_4F_4S$

8.2.5 Mode of Action

Competitive inhibitor of androgen binding to cytosolic androgen receptors.

8.2.6 How Supplied

White, film-covered oral tablet containing 50 mg of bicalutamide. It is manufactured by AstraZeneca Pharmaceuticals in 50 mg tablets for oral administration and will not be provided by the study.

8.2.7 Storage

Controlled room temperature, 20-25°C.

8.2.8 Dose Specifics

50 mg/daily orally beginning Cycle 4 (week 13), continuously to the end of study (please see Section 5.1.1). The tablet should be taken at approximately the same time every day.

8.2.9 Route of Administration

Oral, may be taken with or without food.

8.2.10 Side Effects

The most serious side-effect that has been associated with bicalutamide administration 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 according to the table in Section 7.1. Other common side-effects of bicalutamide overlap those of leuprolide acetate, including hot flashes, generalized pain, asthenia, constipation, diarrhea, nocturia, testicular atrophy, and gynecomastia.

9. Statistical Considerations

9.1 Study Design/Primary Endpoints

The primary objective of this study is to compare the proportion of patients with undetectable PSA level (<0.2 ng/mL) at 44 weeks from study entry between two regimens (combination therapy-Arm B vs. bicalutamide monotherapy-Arm A). Patients randomized to Arm A will be observed for 12 weeks followed by a 32-week bicalutamide treatment, while patients randomized to Arm B will be treated with MK-2206 for 12 weeks followed by a 32-week combination therapy with bicalutamide and MK-2206. The primary comparison will be an intention to treat analysis of all randomized patients. Although patients will be stratified based on Gleason score and prior hormonal therapy, no subgroup analyses are planned.

We propose to equally randomize 52 patients to each arm, and a total of 104 patients will be accrued to the study. The primary endpoint of this study is the proportion of patients with undetectable PSA level at 44 weeks from study entry. Patients who withdraw from the study prior to treatment completion will be considered non-responders. Based on preliminary data, we expect that 20% of patients will achieve undetectable PSA level at 44 weeks with bicalutamide monotherapy. With this design, we will have approximately 90% power with one-sided alpha of 0.10 to detect a 25% absolute improvement in proportion of patients with undetectable PSA level at 44 weeks from 20% on Arm A to 45% on Arm B using Fisher's exact test. Although it is unlikely to observe a large imbalance in dropout rates between two arms, the study will still have about 80% power to detect such an improvement with a 0% dropout rate in Arm A and a 10% dropout rate in Arm B assuming the response rates are 45% and 20% on Arms B and A for patients with treatment completion, and 0% for those who withdraw before the end of treatment.

9.2 Secondary Endpoints

Our secondary objectives include comparison of the proportion of patients that achieve a
≥ 85% PSA decline at 44 weeks between the two arms, and evaluation of PSA response, time to PSA progression, time to PSA nadir, duration of PSA response, as well as PSA slope pre-treatment, during treatment, and off treatment. In addition, this study will evaluate whether Gleason score, and prior hormonal therapy have any effect on PSA response to treatment.

Exact binomial confidence intervals will be used to describe the proportion of patients with ≥85% PSA decline at 44 weeks and the distribution of best PSA response (defined in Section 6.1). Patients who withdraw from the study prior to treatment completion will be considered non-responders for the analysis regarding 85% PSA decline at 44 weeks. Given 52 patients per arm, there will be 88% power to test the proportion of patients with ≥85% PSA decline of 75% in the combination arm vs. 50% in bicalutamide monotherapy arm based on a 0.10 level one-sided Fisher's exact test.

Duration of PSA response is defined as time from PSA response to PSA progression. Time to PSA progression, time to PSA nadir from registration, and duration of PSA response will be estimated on each arm and characterized using the method of Kaplan and Meier. Because patients with PSA rise greater than or

equal to 50% above baseline confirmed on a second measurement at least 2 weeks later will be allowed to proceed to take bicalutamide before the end of 12 weeks, the analysis of time to PSA nadir will be restricted to patients who do not start bicalutamide treatment early. Additionally, the percentage of patients who start bicaltamide treatment early in both arms will be reported.

PSA slope will be assessed by multiple PSA values for four phases, prior to registration, from registration to starting bicalutamide treatment, from starting bicalutamide treatment until PSA nadir, and within a year after going off treatment; all values are required to be obtained from the same laboratory. Linear regression will be used to calculate PSA slope using natural log-transformed PSA values on the time of PSA measurements for each patient. This endpoint is exploratory and the analysis is descriptive in nature.

As for the relationship between Gleason score, prior hormonal therapy and PSA response, we will fit a logistic regression to determine whether Gleason score and prior hormonal therapy have any effect on PSA response to treatment.

Another important objective is to evaluate the safety and tolerability of MK-2206 in this patient population. All patients who receive treatment, regardless of eligibility, will be evaluated for toxicity. The 90% confidence interval for the true probability of observing a toxicity of Grade 4 or higher on a given arm will be no wider than 25%. The probability of observing one or more toxicities on a given arm with a true rate of 5% is 93%.

9.3 Accrual

We propose to equally randomize 52 patients to each arm, and a total of 104 patients will be accrued to the study. According to previous ECOG studies with similar patient population, accrual is expected to be 6-8 patients per month and completed within 15 months.

9.4 Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

9.5 Gender and Ethnicity

Based on previous data from E5803, the anticipated accrual in subgroups defined by gender and race for the present study is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	3	3
Not Hispanic or Latino	0	101	101
Ethnic Category: Total of all subjects	0	104	104
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	0	11	11
Native Hawaiian or other Pacific Islander	0	0	0
White	0	93	93
Racial Category: Total of all subjects	0	104	104

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Correlative Studies

Tissue specimens are requested for research. The research projects are currently undefined. Specimens are to be submitted only from patients who have answered "Yes" to "**My specimens may be kept for use in future research to learn about, prevent, treat, or cure cancer.**"

10.1 Sample Submissions

Samples must be labeled with the protocol number, ECOG-ACRIN patient sequence number, date AND time of collection, and sample type (Plasma, urine, etc.).

Questions about sample collection or submission are to be directed to the ECOG-ACRIN Pathology Coordinating Office-Reference Laboratory (PCORL), 312- 503-3384.

10.1.1 Sample Preparations

Ship Ambient → To PCORL

A. Tissue Specimens

When a patient is randomized to receive protocol therapy, the submitting pathologist and clinical research associate should refer to Appendix II (Pathology Submission Guidelines).

Required materials

i. Forms:

- Pathology Material Submission Form (#638 v04.2), Parts A & B completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
- Copy of the surgical and pathology reports.
- Reports of immunologic studies, if performed

ii. Biological Material Submission:

- Tumor tissue block: preferably from the prostatectomy specimen. If not available, submit block from the original biopsy
- Normal tissue block

NOTE: If a block is unavailable for submission, contact the ECOG-ACRIN PCORL to discuss alternative requirements.

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10.1.2 Shipping Guidelines

All submissions are to be logged into and tracked via the ECOG-ACRIN Sample Tracking System (STS).

Tissue blocks and the related reports and forms are to be submitted at ambient temperature within 1 month of patient registration.

Ship to the ECOG-ACRIN PCORL:

ECOG-ACRIN Pathology Coordinating Office-Reference Laboratory

Robert H. Lurie Comprehensive Cancer Center
of Northwestern University Medical School

Olson Pavilion - Room 8421

710 North Fairbanks Court

Chicago, IL 60611

Tel: (312) 503-3384

FAX: (312) 503-3385

A shipping manifest generated from the STS is to be submitted with the samples.

10.1.3 Central Receiving Laboratories: Sample Processing and Routing

Samples will be processed to maximize utilization of the specimens for research. E.g., processing of blocks will include, but not be limited to, the generation of tissue microarrays (TMAs) and the extraction of DNA and RNA.

10.2 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

Study Specific Notes

If STS is unavailable at time of shipment, specimens are to be submitted with the appropriate documentation outlined above and notify the PCORL (312-503-3384) of the shipment. Retro actively enter all specimen collection and shipping information when STS is available.

10.3 Banking

The specimens collected for this study will be forwarded and retained at the ECOG-ACRIN Pathology Coordinating Office-References Laboratory (PCORL) for possible use in ECOG-ACRIN approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.4 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used for any approved laboratory research studies will be submitted electronically to the ECOG-ACRIN Operations Office – Boston on a monthly basis.

11. Records to Be Kept

Please refer to the **E2809** Forms Packet for the forms submission schedule and copies of all forms. The E2809 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office – Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study is being conducted under an IND. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston by electronic means.

11.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study is being conducted under an IND. All records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

1. Han M, Partin A, Pound C, Epstein J, Walsh P. Long term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy: the 15-year Johns Hopkins experience. Urologic Clinics of North America. 2001 August 1, 2001;28:555-65.
2. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol. 2004 Sep;172(3):910-4.
3. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Death in Patients With Recurrent Prostate Cancer After Radical Prostatectomy: Prostate-Specific Antigen Doubling Time Subgroups and Their Associated Contributions to All-Cause Mortality. JCO. 2007 May 1 1765-71.
4. Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, DiPaola RS, et al. Survival Following Primary Androgen Deprivation Therapy Among Men With Localized Prostate Cancer. . JAMA. 2008 July 9;300(17):173 - 81.

5. Isaacs JT, Coffey DS. Adaptation versus selection as the mechanism responsible for the relapse of prostatic cancer to androgen ablation therapy as studied in the dunning R-3327-H adenocarcinoma. Cancer research. 1981;41:5070-5.

6. Smith M. Osteoporosis during androgen deprivation therapy for prostate cancer. Urology. 2002;60(3 (Suppl 1)):79-85.

7. Alibhai S.M.H, Duong-Hua M, Sutradhar R, Fleshner NE, Warde P, Cheung AM, et al. Impact of Androgen Deprivation on Cardiovascular Disease and Diabetes. Journal of Clinical Oncology. 2009 July 20;27(21):3452-8.

8. Estefaniu J, Bae K, Shipley W, Hanks G, Pilepich MV, Sandler H, et al. Cardiovascular mortality after androgen deprivation therapy for localized prostate cancer:RTOG85-31 Joournal of Clinical Oncology. 2009;27(1):92-9.

9. Uzgare AR, Isaacs JT. Enhanced redundancy in Akt and mitogen-activated protein kinase-induced survival of malignant versus normal prostate epithelial cells. Cancer research. 2004 Sep 1;64(17):6190-9.

10. Uzgare AR, Kaplan PJ, Greenberg NM. Differential expression and/or activation of P38MAPK, erk1/2, and jnk during the initiation and progression of prostate cancer. The Prostate. 2003 May 1;55(2):128-39.

11. Yeh S, Lin, H-K., Kang, H-Y., Thin, TH., Lin, M-F., Chang, Ch. From Her2/Neu signals cascade to androgen receptor and its coactivators: A novel pathway by induction of androgen target genes through MAP kinase in prostate cancer cells. Proc Natl Acad Sci. 1999;96:5458-63.

12. Tomlins SA, Mehra R, Rhodes DR, Cao X, Wang L, Dhanasekaran SM, et al. Integrative molecular concept modeling of prostate cancer progression. Nat Genet. 2007 Jan;39(1):41-51.

13. Shah RB, Mehra R, Chinnaiyan AM, Shen R, Ghosh D, Zhou M, et al. Androgen-independent prostate cancer is a heterogeneous group of diseases: lessons from a rapid autopsy program. Cancer research. 2004 Dec 15;64(24):9209-16.

14. Wang Q, Li W, Zhang Y, Yuan X, Xu K, Yu J, et al. Androgen receptor regulates a distinct transcription program in androgen-independent prostate cancer. Cell. 2009 Jul 23;138(2):245-56.

15. Heinlein CA, C C. Androgen Receptor in prostate cancer. Endocr Rev. 2004;25:276-308.

16. Henshall SM, Quinn DI, Lee CS, Head DR, Golovsky D, Brenner PC, et al. Altered expression of androgen receptor in the malignant epithelium and adjacent stroma is associated with early relapse in prostate cancer. Cancer research. 2001 Jan 15;61(2):423-7.

17. Chen CD, Welsbie DS, Tran C, Baek SH, Chen R, Vessella R, et al. Molecular determinants of resistance to antiandrogen therapy. Nat Med. 2004 Jan;10(1):33-9.

18. Hendriksen PJ, Dits NF, Kokame K, Veldhoven A, van Weerden WM, Bangma CH, et al. Evolution of the androgen receptor pathway during progression of prostate cancer. Cancer research. 2006 May 15;66(10):5012-20.

19. Hobisch A, Culig Z, Radmayr C, Bartsch G, Klocker H, Hittmair A. Distant metastases from prostatic carcinoma express androgen receptor protein. Cancer research. 1995;55(14):3068-72.

20. Leversha MA, Han J, Asgari Z, Danila DC, Lin O, Gonzalez-Espinoza R, et al. Fluorescence In situ Hybridization Analysis of Circulating Tumor Cells in Metastatic Prostate Cancer. Clin Cancer Res. 2009 Mar 15;15(6):2091-7.

21. Eder IE, Haag P, Basik M, Mousses S, Bektic J, Bartsch G, et al. Gene expression changes following androgen receptor elimination in LNCaP prostate cancer cells. Mol Carcinog. 2003 Aug;37(4):181-91.

22. Zegarra-Moro OL, Schmidt LJ, Huang H, Tindall DJ. Disruption of androgen receptor function inhibits proliferation of androgen-refractory prostate cancer cells. Cancer research. 2002 Feb 15;62(4):1008-13.

23. Liao X, Tang S, Thrasher JB, Griebling TL, Li B. Small-interfering RNA-induced androgen receptor silencing leads to apoptotic cell death in prostate cancer. Mol Cancer Ther. 2005 Apr;4(4):505-15.

24. Liu XM, Gomez-Pinillos A, Liu XJ, Johnson EM, AC F. Induction of bicalutamide sensitivity in prostate cancer cells by an epigenetic Pura-mediated decrease in androgen receptor levels. The Prostate. 2009.

25. Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. Nat Rev Cancer. 2001 Oct;1(1):34-45.

26. Steinkamp MP, O'Mahony OA, Brogley M, Rehman H, Lapensee EW, Dhanasekaran S, et al. Treatment-dependent androgen receptor mutations in prostate cancer exploit multiple mechanisms to evade therapy. Cancer research. 2009 May 15;69(10):4434-42.

27. Culig Z, Hobisch, A, Bartsch, G, Klocker, H. Androgen receptor-an uodate of mechanisms of action in prostate cancer. Urol Res. 2000;28:211-9.

28. Gregory C, He B, Johnson R, Ford O, Mohler J, French F, et al. A mechanism for androgen receptor-mediated prostate cancer recurrence after androgen deprivation therapy. Cancer research. 2001;61(11):4315-9.

29. Stanbrough M, Bubley GJ, Ross K, Golub TR, Rubin MA, Penning TM, et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. Cancer research. 2006 Mar 1;66(5):2815-25.

30. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer research. 2008 Jun 1;68(11):4447-54.

31. Locke JA, Guns ES, Lubik AA, Adomat HH, Hendy SC, Wood CA, et al. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. Cancer research. 2008 Aug 1;68(15):6407-15.

32. Culig Z, Hobisch A, Cronauer MV, Radmayr C, Trapman J, Hittmair A, et al. Androgen receptor activation in prostatic tumor cell lines by insulin-like growth factor-I, keratinocyte growth factor, and epidermal growth factor. Cancer research. 1994;54:5474-8.

33. Masiello D, Cheng S, Bubley G, Lu M, Balk S. Bicalutamide functions as an androgen receptor antagonist by assembly of a transcriptionally inactive receptor. The Journal of biological chemistry. 2002;277(29):26321-6.

34. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science (New York, NY. 2009 May 8;324(5928):787-90.

35. Huang ZQ, Li J, Wong J. AR possesses an intrinsic hormone-independent transcriptional activity. Mol Endocrinol. 2002 May;16(5):924-37.

36. See W, Iversen P, Wirth M, et.al. Immediate treatment with bicalutamide 150 mg as adjuvant therapy significantly reduces the risk of psa progression in early prostate cancer. Eur Urol. 2003 July 29, 2003;44(5):512-8.

37. Scher H, Libertz C, Kelly W, al e. Bicalutamide for advanced prostate cancer: The natural versus treated history of disease. J Clin Oncol. 1997;15:2928-38.

38. Small EJ, Vogelzang NJ. Second-line hormonal therapy for advanced prostate cancer: A shifting paradigm. J Clin Oncol. 1997;15:382-8.

39. Kulik g, Klippel A, Weber MJ. Antiapoptotic signaling by the insulin-like-growth factor I receptor, phophatidylinositol 3-kinase and Akt. Mol Cell Biol. 1997;17:1595-606.

40. Hallawel GO, Turner G, Davies D, Poulson R, Brewster S, Macauley V. Expression of type 1 Insulin-like growth factor receptor is up regulated in primary prostate cancer and commony persists in metastatic disease. Can Res. 2002 May 15;62:2942-50.

41. Culig Z, Hobisch A, Cronauer MV, Bartsch G, Klocker H. Activation of androgen receptor mediated transcription by insulin-like growth factor-I prostatic tumour cell lines. JCB Suppl 18D. 1994:460A.

42. Calvo B, Levine A, Marcos M, Collins Q, Iacocca M, Caskey L, et al. Human epidermal receptor-2 expression in prostate cancer. Clin Cancer Res. 2003;9(3):1087-97.

43. Lee L.F., Louie M.C., Desai S.J., Yang J., Chen H.W., Evans C.P., et al. Interleukin-6 confers androgen-independent growth and migration of LNCaP. Oncogene. 2005;23:2197-205.

44. Mousses S, Wagner U, Chen Y, Kim J, Bubendorf L, Bittmer M, et al. Failure of hormone therapy in prostate cancer involves systemic restoration of androgen responsive genes and activation of rapamycin sensitive signaling. Oncogene. 2001;20:6718-23.

45. Di Lorenzo G, Tortora G, D'Armiento F, De Rosa G, Staibano S, Autorino R, et al. Expression of epidermal growth factor receptor correlates with disease relapse and progression to androgen-independence in human prostate cancer. Clin Cancer Res. 2002;8(11):3438-44.

46. Gregory CW, Whang YE, McCall W, Fei X, Liu Y, Ponguta LA, et al. Heregulin-induced activation of HER2 and HER3 increases androgen receptor transactivation and CWR-R1 human recurrent prostate cancer cell growth. Clin Cancer Res. 2005 Mar 1;11(5):1704-12.

47. Kousteni S, Bellido T, Plotkin LI, O'Brien CA, Bodenner DL, Han L, et al. Nongenotropic, sex-nonspecific signaling through the estrogen or androgen receptors: dissociation from transcriptional activity. Cell. 2001 Mar 9;104(5):719-30.

48. Dehm SM, Schmidt LJ, Heemers HV, Vessella RL, Tindall DJ. Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. Cancer research. 2008 Jul 1;68(13):5469-77.

49. Hu R, Dunn TA, Wei S, Isharwal S, Veltri RW, Humphreys E, et al. Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer. Cancer research. 2009 Jan 1;69(1):16-22.

50. Guo Z, Yang X, Sun F, Jiang R, Linn DE, Chen H, et al. A novel androgen receptor splice variant is up-regulated during prostate cancer progression and promotes androgen depletion-resistant growth. Cancer research. 2009 Mar 15;69(6):2305-13.

51. Cantley LC. The phosphoinositide 3-kinase pathway. Science (New York, NY. 2002 May 31;296(5573):1655-7.

52. Steelman LS, Stadelman KM, Chappell WH, Horn S, Basecke J, Cervello M, et al. Akt as a therapeutic target in cancer. Expert Opin Ther Targets. 2008 Sep;12(9):1139-65.

53. Dahia P. PTEN a unique tumor suppressor gene. Endoc RealatCancer. 2000;7:115-29.

54. Majumder PK, Febbo PG, Bikoff R, Berger R, Xue Q, McMahon LM, et al. mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways. Nat Med. 2004 Jun;10(6):594-601.

55. Sun SY, Rosenberg LM, Wang X, Zhou Z, Yue P, Fu H, et al. Activation of Akt and eIF4E survival pathways by rapamycin-mediated mammalian target of rapamycin inhibition. Cancer research. 2005 Aug 15;65(16):7052-8.

56. Gera JF, Mellinghoff IK, Shi Y, Rettig MB, Tran C, Hsu JH, et al. AKT activity determines sensitivity to mammalian target of rapamycin (mTOR) inhibitors by regulating cyclin D1 and c-myc expression. The Journal of biological chemistry. 2004 Jan 23;279(4):2737-46.

57. Carracedo A, Ma L, Teruya-Feldstein J, Rojo F, Salmena L, Alimonti A, et al. Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. J Clin Invest. 2008 Sep;118(9):3065-74.

58. Majumder PK, Yeh JJ, George DJ, Febbo PG, Kum J, Xue Q, et al. Prostate intraepithelial neoplasia induced by prostate restricted Akt activation: the MPAKT model. Proceedings of the National Academy of Sciences of the United States of America. 2003 Jun 24;100(13):7841-6.

59. Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science (New York, NY. 1997 Mar 28;275(5308):1943-7.

60. Mulholland DJ, Dedhar S, Wu H, Nelson CC. PTEN and GSK3beta: key regulators of progression to androgen-independent prostate cancer. Oncogene. 2006 Jan 19;25(3):329-37.

61. Yoshimoto M, cunha IW, Coudry RA, al. e. FISH analysis of 107 prostate cancers shows that PTEN genomic deletion is associated with poor clincal outcome Br J Cancer. 2007;97:678-85.

62. McMenamin ME, Soung P, Perera S, Kaplna I, Loda M, WR S. Loss od PTEN expression in paraffin embedded primary prostate cancer correlates with high Gleason score and advanced stage. Cancer research. 1999;59:4291-6.

63. Suzuki H, Freije D, Nusskern DR, Okami K, Cairns P, Sidransky D, et al. Interfocal heterogeneity of PTEN/MMAC1 gene alterations in multiple metastatic prostate cancer tissues. Cancer research. 1998 Jan 15;58(2):204-9.

64. Bertram J, Peacock JW, Fazli L, al. e. Loss of PTEN is associatyed with progression to androgen independence. The Prostate. 2005;66:895-902.

65. Edwards J, Krishna NS, Witton CJ, Bartlett JM. Gene amplifications associated with the development of hormone-resistant prostate cancer. Clin Cancer Res. 2003 Nov 1;9(14):5271-81.

66. Stern D. More than a marker...phosphorylated Akt in prostate carcinoma. Clin Cancer Res. 2004;10:6407-10.

67. Malik S, Brattain M, Ghosh P, Troyer D, Prihoda T, Bedolla R, et al. Immunohistochemical demonstration of phospho-Akt in high Gleason grade prostate cancer. Clin Cancer Res. 2002;8(4):1168-71.

68. Ayala G, Thompson T, Yang G, Frolov A, Li R, Scardino P, et al. High levels of phosphorylated form of Akt-1 in prostate cancer and non-neoplastic prostate tissues are strong predictors of biochemical recurrence. Clin Cancer Res. 2004 Oct 1;10(19):6572-8.

69. Li R, Dai H, Wheeler TM, Sayeeduddin M, Scardino PT, Frolov A, et al. Prognostic value of Akt-1 in human prostate cancer: a computerized quantitative assessment with quantum dot technology. Clin Cancer Res. 2009 May 15;15(10):3568-73.

70. Manin M, Baron S, Goossens K, Beaudoin C, Jean C, Veyssiere G, et al. Androgen receptor expression is regulated by the phosphoinositide 3-kinase/Akt pathway in normal and tumoral epithelial cells. Biochem J. 2002 Sep 15;366(Pt 3):729-36.

71. Wen Y, Hu M, Makino K, Spohn B, Bartholomeusz G, Yan D, et al. HER-2/neu promotes androgen-independent survival and growth of prostate cancer cells through the Akt pathway. Cancer research. 2000;60(24):6841-5.

72. Nan B, Snabboon T, Unni E, Yuan X-J, Whang Y, Marcelli M. The PTEN tumor suppressor is a negative modulator of androgen receptor transcriptional activity. J Mol Endocrinol. 2003;31(1):169-83.

73. Ellerby LM, Hackam AS, Propp SS, Ellerby HM, Rabizadeh S, Cashman NR, et al. Kennedy's disease: caspase cleavage of the androgen receptor is a crucial event in cytotoxicity. J Neurochem. 1999 Jan;72(1):185-95.

74. Sharma M, Chuang W, Sun Z. Phosphatidylinositol 3-kinase/Akt stimulates androgen pathway through GSK3beta inhibition and nuclear beta-catenin accumulation. The Journal of biological chemistry. 2002;277(34):30935-41.

75. Graff JR, Konicek BW, McNulty AM, Wang Z, Houck K, Allen S, et al. Increased AKT activity contributes to prostate cancer progression by dramatically accelerating prostate tumor growth and diminishing p27Kip1 expression. The Journal of biological chemistry. 2000 Aug 11;275(32):24500-5.

76. Cohen MB, Rokhlin OW. Mechanisms of prostate cancer cell survival after inhibition of AR expression. J Cell Biochem. 2009 Feb 15;106(3):363-71.

77. Garcia JA, A. M. Reuther, A. J. Stephenson, R. Dreicer, E. Klein, C. Magi-Galluzzi. mTOR pathway in prostate cancer: Immunohistochemical expression on tissue microarrays. . Genitourinary Cancers Symposium, Abs#32 2008;Genitourinary Cancers Symposium, Abs#32

78. Xu Y, Chen SY, Ross KN, Balk SP. Androgens induce prostate cancer cell proliferation through mammalian target of rapamycin activation and post-transcriptional increases in cyclin D proteins. Cancer research. 2006 Aug 1;66(15):7783-92.

79. Thomas G, Speicher L, Reiter R, al. e. Demonstration that temsirolimus preferentially inhibits the mTOR pathway in the tumors of prostate cancer patients with PTEN deficiences AACR-NCI-EORTC International Conference. 2005.

80. Amato R.J, Jac J, Mohammed T, S S. Pilot study of rapamycin in patients with castration resistant prostate cancer. Clin Genitourin Cancer 2008:97-102.

81. Craft N, Shostak, Y., Carey, M., Sawyers, C.L. A mechanism for hormone-independent prostate cancer through the modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase. Nature Medicine. 1999;5(3):280-5.

82. Heinlein CA, C C. Androgen receptor coregulators: an overview. Endocr Rev. 2002;23(2):175-200.

83. Craft N, C. S. Mechanistic concepts in androgen-dependence of prostate cancer Cancer and metastasis review. 1999;5:421-7.

84. Wu JD, Haugk K, Coleman I, Woodke L, Vessella R, Nelson P, et al. Combined In vivo Effect of A12, a Type 1 Insulin-Like Growth Factor Receptor Antibody, and Docetaxel against Prostate Cancer Tumors. Clin Cancer Res. 2006 Oct 15;12(20):6153-60.

85. Lewis JE KB, McNulty AM, Parsons S, Lynch RL, Graff JR Enzastaurin (LY317615.HCl) reduces Androgen Receptor (AR) expression in hormone-dependent and independent prostate cancers. Proc AACR. 2007 January, 2007.

86. Zelivianski S, Spellman M, M K, Kakitelashvilli V, Zhou XW, Lugo E, et al. ERK ihibitor PD98059 enhances docetaxel-induced apoptosis of androgen-independent human prostate cancer cells. . Int J of Can. 2003;107:478-85.

87. Ghosh PM, Malik SN, Bedolla RG, Wang Y, Mikhailova M, Prihoda TJ, et al. Signal transduction pathways in androgen-dependent and -independent prostate cancer cell proliferation. Endocr Relat Cancer. 2005 March 1, 2005;12(1):119-34.

88. Ferrari AC, Wang L, Liu X. Androgen receptor (AR) modulation strategies for recurrent prostate cancer (PC) without androgen suppression. 2006 ASCO Annual Meeting Proceedings Part I 2006; Atlanta, GA; 2006. p. Abstract #4657.

89. Festuccia C, Gravina GL, Angelucci A, Millimaggi D, Muzi P, Vicentini C, et al. Additive antitumor effects of the epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib (Iressa), and the nonsteroidal antiandrogen, bicalutamide (Casodex), in prostate cancer cells in vitro. International journal of cancer. 2005 Jul 1;115(4):630-40.

90. Schayowitz A, Sabnis G, Njar VC, Brodie AM. Synergistic effect of a novel antiandrogen, VN/124-1, and signal transduction inhibitors in prostate cancer progression to hormone independence in vitro. Mol Cancer Ther. 2008 Jan;7(1):121-32.

91. Zhang W, Zhu J, Efferson CL, Ware C, Tammam J, Angagaw M, et al. Inhibition of tumor growth progression by antiandrogens and mTOR inhibitor in a Pten-deficient mouse model of prostate cancer. Cancer research. 2009 Sep 15;69(18):7466-72.

92. Soloway MS, Schellhammer PF, Smith JAJ, Chodak GW, Vogelzang NJ, Kennealey GT. Bicalutamide in the treatment of advaned prostatic carcinoma: a phase II noncomparative multicenter trial evaluating safety, efficacy and long-term endocrine effects of monotherapy. J Urol. 1995;154:2110-4.

93. Kaisary AV, Tyrrell CJ, Beacock C, Lunglmayr G, Debruyne F. A randomised comparison of monotherapy with Casodex 50 mg daily and castration in the treatment of metastatic prostate carcinoma. Casodex Study Group. Eur Urol. 1995;28(3):215-22.

94. Iversen P, Tveter K, Varenhorst E. Randomised study of Casodex 50 mg monotherapy vs orchidectomy in the treatment of metastatic prostate cancer. The Scandinavian Casodex Cooperative Group. Scand J Urol Nephrol. 1996;30:93-8.

95. Kolvenbag GJ, Blackledge GR, Gotting-Smith K. Bicalutamide (Casodex) in the treatment of prostate cancer: history of clinical development. The Prostate. 1998 Jan 1;34(1):61-72.

96. Backledge G. High-dose bicalutamide monotherapy for the treatment of prostate cancer. Urology. 1996;47(Suppl.1A):44-7.

97. Iversen P, Tryyell C, Kaisary A, Anderson J, van Poppel E, Tammela T, et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. Journal of Urology. 2000;164:1579-82.

98. Tay M-H, Kaufman D, Regan M, Leibowitz S, George D, Febbo D, et al. Finasteride and bicalutamide as primary hormonal therapy in patients with advanced adenocarcinoma of the prostate Annals of Oncology. 2004;15:974-8.

99. Picus J, Halabi E, Small E, Hussain A, Phillips G, Kaplan N, et al. Efficacy of peripheral androgen blockade on prostate cancer. Results of CALGB 9782. . Proc Am Soc Clin Onc 2006:234s.

100. Brufsky A, Fontaine-Rothe P, Berlane K, Rieker P, Jiroutek M, Kaplan I, et al. Finasteride and flutamide as potency-sparing androgen-ablative therapy for advanced adenocarcinoma of the prostate. Urology. 1997;49(6):913-20.

101. Stewart AJ, Scher HI, Chen MH, McLeod DG, Carroll PR, Moul JW, et al. Prostate-specific antigen nadir and cancer-specific mortality following hormonal therapy for prostate-specific antigen failure. J Clin Oncol. 2005 Sep 20;23(27):6556-60.

102. Beekman K, Morris M, Slovin S, Heller G, Wilton A, Bianco F, Jr., et al. Androgen deprivation for minimal metastatic disease: threshold for achieving undetectable prostate-specific antigen. Urology. 2005 May;65(5):947-52.

103. Hachiya T, Minei S, Kobayashi K, Ishida H, K O. Prediction of organ-confined disease by prostate-specific antigen nadir after neoadjuvant therapy. Int J Urol. 2000;7(11):393-401.

104. Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol. 2006 Aug 20;24(24):3984-90.

105. Baselga J. Targeting tyrosine kinases in cancer: the second wave. Science (New York, NY. 2006 May 26;312(5777):1175-8.

106. Varambally S, Yu J, Laxman B, Rhodes DR, Mehra R, Tomlins SA, et al. Integrative genomic and proteomic analysis of prostate cancer reveals signatures of metastatic progression. Cancer Cell. 2005 Nov;8(5):393-406.

107. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proceedings of the National Academy of Sciences of the United States of America. 2008 Jul 29;105(30):10513-8.

108. Scher HI, M. E, D'Amico AV, Halabi S, Small EJ, Morris M, et al. Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations formthe prostate-specific antigen working group. J Clin Oncol. 2004;22(3):537-56.

109. D'Amico AV, Cote K, Laffredo M, A. R, Schultz D. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. J Clin Onc. 2002;23(23):4567-73.

110. D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. J Urol. 2004 Dec;172(5 Pt 2):S42-6; discussion S6-7.

111. Kim-Sing C, Pickles T. Intervention after PSA failure: Examination of intervention time and subsequent outcomes from a prospective patient database. International Journal of Radiation Oncology*Biology*Physics. 2004;60(2):463.

112. Hanlon AL, Horwitz EM, Hanks GE, Pollack A. Short-term androgen deprivation and PSA doubling time: their association and relationship to disease progression after radiation therapy for prostate cancer. International Journal of Radiation Oncology*Biology*Physics. 2004;58(1):43.

113. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Risk of Prostate Cancer-Specific Mortality Following Biochemical Recurrence After Radical Prostatectomy. JAMA. 2005 July 27, 2005;294(4):433-9.

Androgen Receptor Modulation
Phase II, Randomized Study of MK-2206 - Bicalutamide Combination in Patients With Rising PSA at High-Risk of Progression After Primary Therapy

Version Date: December 28, 2012

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #5]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum #5 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

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Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E2809
4. Pathology Submission Form (#638 v04.2)

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Pathology Coordinating Office:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- Pathology Material Submission Form (#638 v04.2)

Instructions:

1. Place the Patient ID label provided by the ECOG-ACRIN Operations Office – Boston in Part A of the Pathology Material Submission Form.

   If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:

   - Patient's name (last, first)
   - Protocol number
   - Protocol case number (the patient's ECOG-ACRIN sequence number; for intergroup studies, include both the ECOG-ACRIN and other group's sequence numbers)
   - Patient's hospital number
   - Institution
   - Affiliate (if appropriate)
2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material and the Pathology Material Submission Form, to the appropriate pathologist.
3. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed Pathology Material Submission Form (#638 v04.2) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.
4. Keep a copy of the Pathology Material Submission Form (#638 v04.2) for your records. (The original should be sent to the PCO.)
5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Pathology Coordinating Office. (See appropriate List of Required Material.)

Pathology specimens submitted WILL NOT be processed by the Pathology Coordinating Office until all necessary items are received.

Mail pathology materials to:

ECOG-ACRIN Pathology Coordinating Office
Robert H. Lurie Comprehensive Cancer Center
of Northwestern University Medical School
Olson Pavilion - Room 8421
710 North Fairbanks Court
Chicago, IL 60611

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact

the Pathology Coordinator at the ECOG-ACRIN Pathology Coordinating Office by telephone (312) 503-3384 or by fax (312) 503-3385.

List of Required Material

E2809: Androgen Receptor Modulation Phase II, Randomized Study of MK-2206 - Bicalutamide Combination in Patients With Rising PSA at High-Risk of Progression After Primary Therapy

Pre-Treatment

1. Pathology Material Submission Form (#638 v04.2) – Parts A & B completed. *[or appropriate pathology submission form]*
2. Institutional pathology report **(must be included with EVERY pathology submission)**.
3. Institutional surgical report
4. Biological materials.
    - One Tumor tissue block: preferably from the prostatectomy specimen. If not available, submit block from the original biopsy.
    - One normal tissue or block.

NOTE: If a block is unavailable for submission, contact the ECOG-ACRIN PCO to discuss submission requirements.

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for E2809: **Androgen Receptor Modulation** Phase II, Randomized Study of Patients With Rising PSA at High-Risk of Progression After Primary Therapy to Assess the Clinical and Molecular Efficacy of the MK-2206 - Bicalutamide Combination to Suppress the Androgen Receptor Without Testosterone Ablation

The patient named on the attached Pathology Material Submission Form (# 638v 04.2) has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for laboratory studies.

Please complete PART B of the Submission Form. Keep a copy for your records and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Pathology Coordinating Office.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned upon written request for purposes of patient management only.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

If you have any questions regarding this request, please contact the Pathology Coordinating Office at (312) 503-3384 or FAX (312) 503-3385.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

Form No. 638 v04.2 **ECOG DIAGNOSTIC PATHOLOGY MATERIAL SUBMISSION FORM**

Instructions: **This form is a required part of pathology submission.** Please complete and submit along with all pathology material and corresponding pathology reports requested by the protocol. See list of required materials as specified in EACH protocol.

ECOG PCO-RL IS FULLY- COMPLIANT WITH DHHS, HIPAA, AND OHRP REGULATIONS

Tel. 312-503-3384
Fax 312-503-3385

PART A: To Be Completed By Data Manager/CRA

DO NOT USE INITIALS – Submit Patient's FULL Name
(The Patient has authorized the use of PHI.)

Date sample sent to ECOG _____/_____/_____ (M,D,Y)
Data Manager_____
Address _____
_____
Telephone No. ( ) _____
Fax No. ( ) _____
Email address _____

Patient's Name:
Last_____ First _____
ECOG Prot. No. _____ ECOG Patient Seq. No. _____
Participating Group Prot. No. _____ Participating Group Patient ID No._____
Group _____ Institution_____ PI_____
Step No. _____ Affiliate _____
ECOG Parent Prot. No. _____ Seq. No._____

PART B: TO BE COMPLETED BY DATA MANAGER/CRA AND SUBMITTING PATHOLOGIST

	Status* (See Below)	Date Specimen Collected (M/D/Y)	Disease Site	Number of Slides/Vials	Specimen ID Numbers	Type of Stain	PCO-RL Use Only: PCO ID Numbers
Complete for Slides/Vials		/ /					
		/ /					
	Status* (See Below)	**Date Specimen Collected (M/D/Y)**	**Disease Site**	**Number of Blocks/Punch**	**Specimen ID Numbers**	**Fixative**	**PCO ID Numbers**
Complete for Blocks/Punch		/ /					
		/ /					

***Status:** Please identify the clinical status of the sample.
List ***all*** that apply:

1. Original diagnostic material
2. AML/MDS diagnosis
3. Pre-protocol treatment biopsy/tissue
4. Post-protocol treatment biopsy/tissue
5. Post-surgery biopsy/tissue
6. Relapse/recurrence
7. Remission/response
8. Other, specify: _____

Submitting Pathologist _____
Telephone No. ( ) _____
Address _____
_____

Did the patient consent to participate in the storage of samples for future research? Yes No

MATERIAL RETURN (All materials will be retained by the ECOG PCO unless return is requested here.)

Does the submitting institution's policy require the return of any submitted material (blocks, H&E slides, etc.)? Yes No

If so, please indicate which materials must be returned _____

All materials will be returned to the **submitting pathologist** unless an alternate address is indicated here_____

If materials were not able to be submitted for this protocol and its correlative studies, please circle the reason for non-submission. Attach a formal letter referencing regulations, policy, and/or other explanation. If possible, include a copy of the policy.

Federal/State Regulations ____ Hospital/Institutional Policy _____ Insufficient Tissue _____ Other_____ (Specify) _____

Pathologist or Investigator's Signature _____

(PCO-RL Use Only)
PV _____

PART C: ECOG PATHOLOGY COORDINATING OFFICE USE ONLY

Date Sample Received at PCO ____/____/____ Date Sent to Reviewer ____/____/____ Date Sent to PI/Central Lab ____/____/_____

Site Compliance %_____ Name of Reviewer _____ PI/Central Lab _____

PCO Comments: _____ Staff Init. _____

Investigator: Keep a copy for your files and submit original form to the destination specified in protocol. 2/05

Androgen Receptor Modulation
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Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. Your physician and research staff will maintain very close contact with you. This is important so as to allow your physician to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Androgen Receptor Modulation
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Appendix IV

Patient Medication Calendar (Pill Diary)

Patient Name: _____

ECOG-ACRIN Patient Sequence Number: _____

Patient's Treatment Arm (e.g., "A"): _____

Patient's Initials: _____

Protocol Number: **E2809**

Cycle # _____

Start Day of Week: _____

Start Date (e.g., 01/01/09) for first dose of this cycle: _____

NOTE: A cycle is 28 days (4 weeks)

Directions for Arm A:

1. Unless your doctor decides to begin bicalutamide early, for the first three cycles of the study, you will not take any study medication and you are not responsible for submitting a patient pill diary.
2. Unless your doctor decides to begin bicalutamide early, starting with Cycle 4, for each cycle, take 1 Bicalutamide tablet (50 mg) orally once daily continuously through Cycle 11.
3. After Cycle 11, your doctor may advise you to stop and come off-treatment **or** continue on treatment through Cycle 18.
4. For each Cycle that you end up taking bicalutamide you should complete an **ARM A** Patient Medication Calendar (Pill Diary) appropriately based on the days you actually took medication during the cycle.
5. If a dose is forgotten do not take it at a later time. Skip that dose and note in the calendar that the dose was missed.

Directions for Arm B:

1. For cycles 1-3, take 200 mg of MK-2206 by mouth each week. You should take the medication at about the same time 2 hours before or after meals. Your doctor may also decide to start bicalutamide early.
2. Unless started early, starting with Cycle 4, you will take 1 Bicalutamide tablet (50 mg) orally every day ***in addition*** to continuing the weekly MK-2206 treatment. You will continue this combined therapy through Cycle 11.
3. After Cycle 11, your doctor may advise you to stop and come off-treatment **or** continue on the combined treatment through Cycle 18.
4. For each Cycle that you end up taking either MK-2206 or the combination of MK-2206 and bicalutamide you should complete an **ARM B** Patient Medication Calendar (Pill Diary) appropriately based on the days you actually took medication during the cycle.

5. If a dose is forgotten do not take it at a later time. Skip that dose and note in the calendar that the dose was missed.

Note the number of pills you take each day. If you develop any side effects, please record side effects, the date, and anything you would like to tell the doctor in the comments section of your calendar.

Bring your bottles and any unused pills along with your completed calendar/diary to your next appointment.

Signature of Patient: _____ Date: _____

E2809 Patient Medication Calendar (Diary) – ARM A

Patient ID: _____ **Cycle #**: _____

Cycle Day	Day of Week	Date	Bicalutamide (Casodex®) (50 mg)	Comments
Example:	*Mon.*	*1/2/10*	*1 tablet/time taken*	*Side effects/other medication taken*
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
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21				
22				
23				
24				
25				
26				
27				
28				

E2809 Patient Medication Calendar (Diary) – ARM B

Patient ID: _____ **Cycle #**: _____

Cycle Day	Day of Week	Date	MK-2206 (5 mg)	MK-2206 (25 mg)	MK-2206 (200 mg)	Bicalutamide (Casodex®) (50 mg)	Comments
Ex:	*Mon.*	*1/2/10*	*# tablet/time taken*			*1 tablet/time taken*	*Side effects/other medication taken*
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
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Appendix V

Cooperative Research and Development Agreement (CRADA)

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborators (http://ctep.cancer.gov/industry/ipo.html) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data”):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Suite 7111
   Bethesda, Maryland 20892
   FAX 301-402-1584
   Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator=s confidential/ proprietary information.

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Appendix VI

List of CYP3A4 Inhibitors and Inducers

CYP3A4 Inhibitors

Rev. 2/13

Amiodarone	Diclofenac	Lomustine	Primaquine
Aprepitant	Diethyl-dithiocarbamate	Methadone	Propoxyphene
Atazanavir	Dihydroergotamine	Methimazole	Quinidine
Azithromycin	Diltiazem	Methoxsalen	Quinine
Bupropion	Diphenhydramine	Metoclopramide	Quinupristin
Cerivastatin	Disulfiram	Metronidazole	Ranitidine
Chloramphenicol	Doxycycline	Mibefradil	Ranolazine
Chlorpromazine	Efavirenz	Miconazole	Ritonavir
Chlorpheniramine	Enoxacin	Mifepristone	Saquinavir
Chlorzoxazone	Entacapone	Modafinil	Sertraline
Cimetidine	Ergotamine	Nefazodone	
Ciprofloxacin	Erythromycin	Nelfinavir	Star fruit
Clarithromycin	Ethinyl estradiol	Nevirapine	Sulconazole
Clemastine	Fluconazole	Nicardipine	Telithromycin
Clofazimine	Fluoroquinolones	Nifedipine	Tetracycline
Clotrimazole	Fluoxetine	Nizatidine	Thiotepa
Cocaine	Fluvastatin	Norfloxacin	Ticlopidine
Conivaptan	Fluvoxamine	Omeprazole	Topiramate
Cyclophosphamide	Fosamprenavir	Orphenadrine	Tranylcypromine
Cyclosporine	Furafilline	Paroxetine	Trimetropin
Danazol	Gestodene		Troleandomycin
Dasatinib (1)	Grapefruit juice (2)	Perphenazine	Valproic acid
Delavirdine	Haloperidol	Phencyclidine	Venlafaxine
Dexmedetomidine	Hydralazine	Pilocarpine	Verapamil
	Hydroxyzine		Voriconazole
	Interferon		Zafirlukast
	Itraconazole		
	Imatinib		
	Indinavir		
	Isoniazid		
	Itraconazole		
	Ketoconazole		

CYP3A4 Inducers

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Aminoglutethimide	Modafinil	Phenytoin	Rifapentine
Barbiturates	Nafcillin	Primidone	Secobarbital
β-naphthoflavone	Nevirapine	Rifabutin	St. John's wort (3)
Carbamazepine	Oxcarbazepine	Rifampin	Troglitazone
Dexamethasone	Pentobarbital		
Efavirenz	Phenobarbital		
Ethanol			
Fosphenytoin			
Glucocorticoids			

When MK-2206 is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of MK-2206 is the potential outcome. The co-administration of 'inducers' would potentially lower plasma MK-2206 concentrations.

NOTE: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

Only major substrates and effective inducers are listed.
Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

(1) Investigator's Brochure: MK-2206. Merck. January 2009.
(2) Malhotra et al. (2001). Clin Pharmacol Ther. 69:14-23.
(3) Mathijssen et al. (2002). J Natl Cancer Inst. 94:1247-1249.
Frye et al. (2004). Clin Pharmacol Ther. 76:323-329.

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Appendix VII
Medications That May Cause QTc Prolongation

The following table presents a list of drugs that may prolong the QTc. These drugs are prohibited during the study. MK-2206 may be administered after a 5 half-life washout period elapses following the use of these drugs. Washout period is based on roughly 5 half-lives and rounded to a convenient interval.

Compound	Compound Half Life	Possible Washout Period - Hours	Possible Washout Period - Days
Alfuzocin	~10 hours		7
Amantadine	17 +/- 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hr (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$=7-10 hour)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 +/- 7 hours		7
Cisapride	6 – 12 hour, up to 20 hour	60	
Clarithromycin	Non linear PK3-4 hr (250mg Q12) 5-7 hr (500mg Q12)	36	
Cloroquine	6 to 60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hr	48	
Dolesetron	8.1 hr		
Domperidone	7-8 hr	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	
Erythromycin	* Each salt form has different Half life*		
Felbamate	20-23 hr		5
Flecainide	20 hr (12-27)		5
Foscarnet	87.5+/-41.8 hours *distribution and release from bone*		20
Fosphenytoin	12-29 hr		6
Gatifloxacin	7-14 hr	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hr		3
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 +/-5 hr		5
Ibutilide	6 hours (2-12) * variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isradipine	8 hours (multiple metabolites)	48	

Levofloxacin	6-8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20
Lithium	24 hour (10-50)		7
Compound	**Compound Half Life**	**Possible Washout Period - Hours**	**Possible Washout Period - Days**
Mesoridazine	24-48 hours (animal study)		10
Methadone	15-30 hours		7
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	48	
Moxifloxacin	12 +/-1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2 hour post IV infusion	12	
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4+/-1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3-4 hour for PA and NAPA (active metabolite)	24	
Protiptyline*	> 24 hours, wide interpatient variability		
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3-4 hours in children	36	
Quinine	4-5 hours		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ =21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant		7
Tamoxifen	5-7 days (biphasic)		30
Telithromycin	2-3 hr	24	
Thioridazine	20-40 hours (Phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenifil	4 to 5 hours		
Venlaflaxine	5 +/-2 hours for parent comp. 11+-2 hours for OVD (active metabolite)	60	
Voriconizole	6 hours; dose dependent		
Ziprasidone	7 hr	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	18	

*Weakly associated with Torsades de Pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in patients without other risk factors (*e.g.*, concomitant QT prolonging drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).

References:

1. Physician's Desk Reference 2002
2. Facts and Comparisons (update to June 2005)
3. The Pharmacological Basis of Therapeutics 9th Edition, 1996

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Appendix VIII

Performance Status Criteria

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