IRB#: 07-022A (13)

Bicalutamide for the Treatment of Androgen Receptor Positive (AR(+)), Estrogen Receptor Negative, Progesterone Receptor Negative (ER(-)/PR(-)) Metastatic Breast Cancer Patients: A Phase II Feasibility Study

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Table of Contents

Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 07-022A (13)

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1.1 PROTOCOL ABSTRACT AND SUMMARY

1.2 Protocol Abstract

Estrogen receptor negative (ER(-)), progesterone receptor-negative (PR(-)) breast cancer represents approximately 25 – 30% of all breast cancers. Unlike estrogen receptor-positive (ER(+)) breast cancer, patients with ER(-)/PR(-) disease are not candidates for current anti-hormonal strategies. The biology of ER(-) disease is poorly understood and with the exception of trastuzumab for Her2/neu-positive tumors, targeted therapy options are limited. Genome-wide expression analysis has revealed a subset of ER(-)/PR(-) breast cancers that share a gene expression profile with hormone receptor-positive tumors[1]. Among these shared genes is the androgen receptor (AR**).** In-vitro studies of androgen blockade demonstrated a reduction in growth of ER(-)/PR(-)/AR(+) breast cancer cells. Clinical investigation of androgen blockade in breast cancer patients is therefore a rational therapeutic strategy.

The primary objective of this Phase II study is to evaluate the efficacy of bicalutamide (Casodex™, Astrazeneca), a well-tolerated anti-androgen used in prostate cancer, in women with ER(-)/PR(-)/AR(+) metastatic breast cancer. Efficacy will be measured by the response rate (RR), including those patients with a demonstrated complete response (CR), partial response (PR), or stable disease (SD) after 6 months from the first day of therapy. Secondary objectives include progression-free survival (PFS), safety and correlative studies. Correlative studies, including peripheral blood hormone levels and selected immunohistochemical markers, will further characterize the biology of this novel subtype of breast cancer. This is an important study for the field of breast cancer research because bicalutamide may allow a greater number of patients with breast cancer the option of treatment with hormonal therapy instead of, or in addition to, chemotherapy.

1.3 Protocol Summary

This is a multicenter, open-label, phase II study to evaluate the antitumor activity and safety of bicalutamide administered orally daily to patients with ER(-)/PR(-)/AR(+) metastatic breast cancer. Patients with measurable or non-measurable, metastatic breast cancer are eligible. Prior neo-adjuvant or adjuvant chemotherapy is permitted. There is no restriction on prior chemotherapy or hormonal therapy. Prior therapy with trastuzumab is allowed but may not be administered while on study.

Patients with metastatic, ER(-), PR(-) breast cancer may consent to androgen receptor testing while on breast cancer-directed treatment. If they are found to have AR(+) disease, they will be considered potentially eligible for treatment on study. At the time their treating physician determines they require a change in therapy, they may consent to participate in this study if they meet remaining eligibility criteria.

Eligible patients who have consented to trial participation will receive bicalutamide at a dose of 150mg PO daily. Up to two dose reductions of 50mg each will be allowed for grade 3 or 4 toxicity as specified by the protocol. The primary aim of the study is to evaluate the efficacy of

bicalutamide after 6 months of therapy. The study is a phase II design with a planned enrollment of 28 patients. If 4 or more patients demonstrate a response (defined as either a CR, PR or SD) after 6 months of therapy, bicalutamide will be considered a feasible and potentially promising therapy. Patients with progression of disease will be withdrawn from the study. Treatment may continue after 6 months in the absence of progression of disease or unacceptable toxicity.

Based on studies of bicalutamide in men with prostate cancer, an oral daily dose of 150 mg per day has been selected for this study. In men, the pharmacodynamic, pharmacokinetic, safety and efficacy data support this dose for monotherapy. Studies of doses up to 600 mg failed to show dose-related increases in adverse events. This study will not aim to provide extensive pharmacokinetic and pharmacodynamic data on different dose levels. It will not aim to recapitulate data from previous studies performed in men. Rather, this is a straightforward extrapolation of studies performed in men, to test this hormonal agent in women based on a rational biologic hypothesis. While there may be differences seen with its use in women, this study has been designed with a dose reduction schema and early stopping rules for toxicity. Additionally, correlative studies will include serum hormonal levels to further characterize differences seen in women.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

2.2 Primary Objective

The primary objective of this study is to:

- Evaluate the efficacy of treatment with bicalutamide at 6 months for patients with ER(-) /PR(-)/AR(+) metastatic breast cancer in terms of response (CR, PR) and SD.

2.3 Secondary Objectives

The secondary objectives of this study are to:

- Estimate the progression-free survival (PFS) at 6 months for patients with ER(-)/PR(-)/AR(+) metastatic breast cancer
- Evaluate the safety of bicalutamide for patients with ER(-)/PR(-)/AR(+) metastatic breast cancer.
- Perform correlative studies including:

  - Monitoring of changes in estradiol, total and free testosterone and sex-hormone binding globulin in response to androgen blockade in women with breast cancer
  - Immunohistochemical analysis of tissue including cytokeratins 5/6 and 17, SPDEF, ALCAM, ERBB2, FGFR4 and PSA
  - Collection and storage of AR+ paraffin embedded tissue samples from primary or metastatic site, if available. These samples will be used to further investigate the biology of AR+ breast cancer (ie, by building a tissue microarray).

3.1 BACKGROUND AND RATIONALE

Breast cancer remains one of the most common diseases affecting women with a lifetime risk of approximately 13% (or 1 in 7 women) [2]. It is estimated that in 2008 over 180,000 women will develop breast cancer and ~40,400 will die of their disease[3]. Approximately 70% of patients with breast cancer have tumors that express estrogen receptors or progesterone receptors, or both, and are candidates for hormonal therapy.

Estrogen receptor-negative, progesterone receptor-negative (ER(-)/PR(-)) breast cancer represents approximately 25 to 30% of all breast cancers and generally has a more aggressive clinical course than hormone receptor-positive disease. Therapeutic options for these patients are limited. Patients with ER(-)/PR(-) tumors gain little or no benefit from anti-estrogen therapy and targeted therapy is limited to trastuzumab in those patients with tumors that overexpress Her2/neu.

In addition to ER and PR, breast cancer cells express other nuclear hormone receptors. The androgen receptor (AR) is expressed in 60 to 80% of breast cancers and implicated in breast cancer biology[4]. Among postmenopausal women, high androgen levels are associated with an increased risk of developing breast cancer[5]. Furthermore, androgens can induce proliferation in breast tissue, and initiate tumor formation via the AR in animal models[6].

A recent analyses of gene expression profiles of primary breast cancers from investigators at MSKCC identified a subset of ER(-)/PR(-) tumors with a molecular signature that suggests an active hormonally regulated transcriptional program[1]. Gene expression signatures were used to develop a predictive model that can identify molecularly similar breast cancers in an independent human breast cancer data set and among breast cancer cell lines. A cell line with this signature demonstrated a proliferative response to androgen in an androgen receptor dependent manner that was inhibited by anti-androgens. This subset of breast cancers (ER(-) Class A) characterized by a hormonally related transcriptional program and proliferative response to androgen, suggests the potential for therapeutic strategies targeting the androgen signaling pathway. This trial is designed to test this hypothesis.

Admittedly, the mechanisms by which androgens contribute to increased risk of breast cancer are not well understood. In an older literature, androgens appeared to have a growth inhibitory effect in animal and cell-line experiments. However, this idea has not been supported in studies of human populations. Recent studies of CAG-repeat length in androgen receptor polymorphisms suggest that differing AR polymorphisms may modulate a woman's risk of breast cancer. It has been postulated that an association exists between AR CAG-repeat length and BRCA1-related breast cancer risk. Androgens may have both direct and indirect effects on breast tissue and ultimately breast cancer risk. As the mechanism by which androgens influence breast cancer risk remain unclear, we have designed this trial to test the hypothesis derived from our preclinical work that targeting androgen receptor signaling in the subset of ER(-) Class A tumors will be of benefit.

3.2 Studies of Bicalutamide in men with prostate cancer

Bicalutamide is an orally active, nonsteroidal anti-androgen that competitively inhibits the action of androgens by binding to cytosol androgen receptors in target tissues. Studies have demonstrated tolerability and efficacy of bicalutamide in men with locally advanced and metastatic prostate cancer.

Bicalutamide was initially evaluated in patients with prostate cancer at the 50 mg per day dose for use in combination with castration in combined androgen blockage (CAB) therapy. CAB therapy consists of an antiandrogen with either surgical castration or medical castration with a luteinizing hormone-releasing hormone analogue (LHRH-A).

Subsequently, studies evaluated bicalutamide at a dose of 50 mg per day (licensed for use in CAB) as monotherapy in patients with previously untreated, advanced prostate cancer. After bicalutamide 50 mg per day was shown to be inferior to castration in terms of survival, dose-finding phase II studies were performed to evaluate whether higher doses of bicalutamide would be more effective. Pharmacodynamic studies showed an increasing prostate specific antigen (PSA) response with increasing dose that reached a plateau at 150 – 200 mg per day, with the PSA response seen with 150 mg per day similar to that seen with castration. The use of bicalutamide in doses higher than 150 mg per day was not limited by safety concerns, as doses of up to 600 mg per day did not cause dose-related increases in adverse events[7].

A dose of bicalutamide 150 mg per day was selected for development as monotherapy based on pharmacodynamic results that showed the PSA response after 3 months of treatment at this dose level (>92% reduction) was comparable to that seen in patients who had undergone surgical castration. Bicalutamide 150 mg per day was subsequently evaluated against castration in two large randomized Phase III studies in men with M0 or M1 disease. Bicalutamide 150 mg per day demonstrated good tolerability in these studies[8]. 6% of bicalutamide-treated patients withdrew from treatment due to an adverse event. The reported side effect profile included gynecomastia and breast pain (35 – 40%), hot flashes (6-13%) and diarrhea (4-5%).

The corresponding pharmacokinetic data for the relationship between *(R)*-bicalutamide (the active enantiomer) steady-state concentration (Css) and dosage shows a departure in linearity at doses >50 mg/day and a clear plateau for doses > 300mg/day[9]. Pharmacokinetics are unaffected by age, body-weight, renal impairment and mild-to-moderate hepatic impairment. Bicalutamide does not demonstrate any clinically relevant interaction with other drugs.

A dose of bicalutamide 150 mg/day was selected for the ongoing bicalutamide ('Casodex') Early Prostate Cancer (EPC) Program. This program was designed to evaluate whether the addition of bicalutamide 150 mg to standard care can reduce the risk of disease progression, as well as improve overall survival in patients with localized or locally advanced prostate cancer. Consisting of three randomized, double-blind, placebo-controlled trials, it is the largest prostate cancer study to date. Following standard care, 8113 men with localized or locally advanced prostate cancer were randomized to receive oral bicalutamide 150 mg once daily or oral placebo. At a median follow-up of 7.4 years, the data suggest that adjuvant hormonal therapy for patients

at low risk of disease progression (ie localized disease) is currently not appropriate. For patients with locally advanced disease, however, the addition of bicalutamide to standard care significantly increases PFS and shows a trend towards improved OS[10].

For safety and tolerability, the most common adverse events reported with bicalutamide were breast pain (73.6%) and gynecomastia (68.8%). Symptoms were reported as mild to moderate in over 90% of cases. Symptoms typically developed within the first 6 to 9 months of treatment. Other adverse events were infrequent and included impotence (9.3% with bicalutamide and 6.5% with standard care alone), decreased libido (3.6% and 1.2%, respectively), hotflushes (9.2% and 5.4% respectively), and abnormal liver function tests (3.1% and 1.7%, respectively). Withdrawal rates from the study due to adverse events were 29.3% with bicalutamide and 10.0% with standard care alone. Withdrawal rates secondary to breast pain and/or gynecomastia were 16.8% and 0.7% respectively. In the bicalutamide group, fewer patients died from prostate cancer than those receiving standard care alone (6.4% vs 7.5%). Deaths from heart failure and gastrointestinal carcinoma were higher in the bicalutamide group, though there were no consistent patterns to suggest that these were due to drug toxicity.

The most common adverse events and causes of death, as number (%) of patients[10]

Variable	Bicalutamide 150 mg + standard care N=4022	Standard care alone N=4031
Adverse Event		
Breast pain	2962 (73.6%)	308 (7.6%)
Gynecomastia	2766 (68.8%)	334 (8.3%)
Pharyngitis	448 (11.1%)	470 (11.7%)
Asthenia	442 (11.0%)	315 (7.8%)
Back pain	420 (10.4%)	490 (12.2%)
Rash	404 (10.0%)	337 (8.4%)
Constipation	380 (9.4%)	314 (7.8%)
Impotence	375 (9.3%)	263 (6.5%)
Hot flushes	370 (9.2%)	216 (5.4%)
Arthralgia	355 (8.8%)	405 (10.0%)
Cause of death		
Prostate cancer	257 (6.4%)	302 (7.5%)
Myocardial infarction	81 (2.0%)	76 (1.9%)
Cause unknown	68 (1.7%)	63 (1.6%)
Gastrointestinal carcinoma	54 (1.3%)	38 (0.9%)
Heart failure	49 (1.2%)	25 (0.6%)
Cerebrovascular accident	47 (1.2%)	45 (1.1%)
Lung carcinoma	44 (1.1%)	47 (1.2%)
Heart arrest	37 (0.9%)	33 (0.8%)
Pneumonia	34 (0.8%)	45 (1.1%)

The most common side effects of gynecomastia and breast pain reflect the pharmacology of bicalutamide. Gynecomastia, the proliferation of the glandular component of the male breast, occurs because of an increase in the ratio of estrogen to androgen. Bicalutamide treatment causes gynecomastia because of blockade of androgenic activity and the increase in peripheral aromatization of androgens to estrogens. The reported rates of gynecomastia and breast pain were lower in trials of bicalutamide in metastatic patients than in the EPC study of patients with localized or locally advanced disease. The toxicity profile of bicalutamide 50 mg in combination with an LHRH analogue (as included in the AstraZeneca package insert) is included in Appendix A.

3.3 Studies of Bicalutamide in Women

In two small studies bicalutamide has been given at a dose of 25 mg per day to women with polycystic ovary disease and for treatment of hirsuitism[11,12]. To date, there have been no studies of bicalutamide as an anti-cancer therapy in women, or using doses above 25 mg per day.

3.4 Rationale for bicalutamide study dose selection

Though bicalutamide has not been well tested in women, the extensive studies of this drug in men with prostate cancer demonstrating good tolerability provide support for its use in women. The selection of a dose of 150 mg per day is based on pharmacokinetic, pharmacodynamic and safety data from studies performed in men with prostate cancer. Notably, studies of doses above 150 mg (up to 600 mg) failed to show dose-limiting toxicity. The dose of 150 mg reflects an optimal steady-state concentration and PSA-lowering effect in men with prostate cancer.

Because there may be differences seen with the use of bicalutamide in women, this study has been designed with a dose reduction schema for toxicity. Correlative studies include a panel of serum hormonal studies that will provide information on differences seen in the hormonal/metabolic pathways in women. The goal of this study is to test the hypothesis that androgen blockade in women with ER(-)/PR(-)/AR(+) breast cancer (ER(-) Class A) is an effective hormonal treatment. This study will not perform pharmacokinetic and pharmacodynamic studies.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a multicenter, open-label, one-stage, phase II study to evaluate the antitumor activity and safety of bicalutamide administered orally daily to patients with ER(-)/PR(-)/AR(+) metastatic breast cancer. Patients with non-measurable or measurable, metastatic breast cancer are eligible. Prior neo-adjuvant or adjuvant chemotherapy is permitted. Prior therapy with trastuzumab is necessary for patients with Her-2/neu positive disease (3+ IHC or FISH > 2.0). There is no limitation on prior treatment with chemotherapy or hormonal therapies.

After signing the protocol consent form for androgen receptor testing, the patient's tumor will be evaluated for androgen receptor status using a commercially available immunohistochemical analysis. Androgen receptor testing may occur on primary breast tumor or tissue from biopsy of a metastatic site. Participating centers may send unstained slides to MSKCC for ER, PR and AR testing. Participating sites may instead choose to perform androgen receptor testing themselves however, estrogen receptor, progesterone receptor and androgen receptor status will be centrally confirmed at Memorial Sloan-Kettering Cancer Center by the Department of Pathology for tumors which test ER(-)/PR(-)/AR(+) locally. If this patient meets the remaining eligibility criteria for study participation, they may later consent to treatment on study. Patients with ER(-)/PR(-)/AR(+) breast cancer on local testing may begin bicalutamide if otherwise eligible while confirmation of receptor status at MSKCC takes place. If the patient's tumor is AR(-) at MSKCC, or if either estrogen or progesterone receptors are positive at MSKCC, the patient may continue on treatment with bicalutamide if the tumor tested ER(-), PR(-), AR(+) locally.

The primary aim of the study is to evaluate the efficacy of bicalutamide in terms of response (CR+PR) and SD at 6 months. The study has a projected enrollment of 28 patients. If 4 or more patients demonstrate a response (defined as a CR, PR or SD by RECIST criteria) after 6 months of treatment, bicalutamide will be considered a feasible and promising therapy.

4.3 Intervention

Patients will receive bicalutamide at a dose of 150mg PO daily. Patients will be seen monthly for an assessment by a care provider familiar with the protocol. Clinical assessment and serum studies will be performed per protocol (See Time and Events Schedule, Section 10) . Patients may be seen before their scheduled monthly follow-up if they are experiencing any adverse effects or symptoms that may be consistent with progression of disease. Patients will undergo a radiologic extent of disease evaluation (EOD) every 3 months. An EOD may be performed earlier than a 3 month interval if progression of disease is suspected. Response will be evaluated using RECIST criteria as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

If a patient experiences unacceptable toxicity at the initial dose level, up to two dose reductions of 50mg each will be permitted. Dose reduction of bicalutamide from the initial dose of 150mg PO daily to100mg PO daily will occur for an individual patient if that patient experiences unacceptable toxicity. A second dose reduction of 50mg is acceptable. Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3. Treatment may be delayed no more than 2 weeks to allow recovery from acute toxicity. In the event of a treatment delay exceeding 2 weeks, the patient will be withdrawn from the study.

A patient will be withdrawn from the study in the following situations:

- For an unacceptable toxicity, defined as a Grade 3 or 4 non-hematologic toxicity after 2 (50 mg) dose reductions (see Section 11.2.5); or
- For unacceptable toxicity that fails to resolve after a maximum treatment delay of 2 weeks; or
- Progression of disease

Treatment with bicalutamide will continue until one or more of the criteria for withdrawal from study are met. After 6 months of treatment, patients will be considered responders if they achieve a CR, PR or SD by RECIST criteria. At the investigator's discretion, and in the absence of disease progression by RECIST criteria, treatment with bicalutamide may continue beyond 6 months. Study drug is provided by AstraZeneca.

4.4 Correlative Studies

As a secondary objective, correlative studies will be performed to further elucidate the biology of this potentially novel subtype of ER(-)/PR(-)/AR(+) (ER(-) Class A) breast cancer and to measure the effect of androgen blockade on peripheral hormonal levels.

In patients with prostate cancer, the use of bicalutamide leads to increased testosterone and estrogen levels. Little data is available for women treated with androgen blockade, but changes in hormonal levels are anticipated. A serum hormone panel will be drawn at baseline, after one month and at the end of study . This serum hormonal panel will include: estradiol, total and free testosterone, and sex-hormone binding globulin.

Doane and colleagues describe a panel of IHC markers that identifies ER(-) class A breast cancers. A combination of ER, PR, SPDEF and ALCAM was estimated to predict ER(-)/PR(-) samples as ER(-) Class A with a sensitivity approaching 100% (95% CI 69 -100%) and a specificity of 94% (95% CI 79-99%)[1]. Other genes that are overexpressed in ER(-) Class A will also be evaluated for their protein expression with IHC including Her2/neu and FGFR4. Her2/neu has been previously shown to stabilize AR protein levels and optimize binding of AR to promoters of androgen-regulated genes in prostate cancer cells[14]. FGFR4 is overexpressed in ER(-) Class A tumors, and previous research has demonstrated molecular 'cross-talk' between FGFR4 and Her2/neu leading to activation of the mTOR translational pathway and subsequent cyclin D1 activation[15]. This convergence of data suggests that further investigation into the role of FGFR4, Her2/neu and AR in ER(-) Class A breast cancers is warranted.

The ER(-) Class A subtype was noted by Doane and colleagues to be distinct from the 'basal subtype' previously identified by Perou and colleagues[16]. The basal subtype generally corresponds to a proportion of ER(-) breast cancers. Cytokeratins 5/6 and 17 are expressed in the basal subtype but not in the ER(-) Class A subtype. Correlative studies of CK 5/6 and 17 will be performed to further explore these previously noted differences in expression patterns between the ER(-) Class A and a basal subtypes.

Paraffin embedded tissue from primary tumor or metastatic sites which have tested AR+, will be requested from patients. Specimens will be collected, if available and at stored for the purpose of future correlative studies on the biology of AR+ breast cancer (ie, creation of tissue microarray of ER(-)/PR(-)/AR(+) breast cancer).

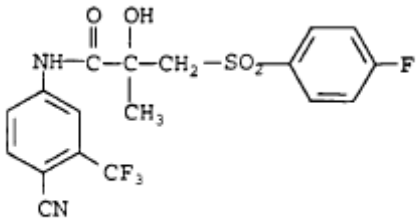
Based on the preclinical data demonstrating a response to androgen blockade in a subset of ER(-) /PR(-)/AR(+) breast cancer, further study of androgen blockade is warranted. A feasibility study to evaluate the efficacy of bicalutamide in women with ER(-)/PR(-)/AR(+) breast cancer is therefore rational, and a logical next step. This is an important study for the field of breast cancer research because bicalutamide may allow a greater number of patients with breast cancer the option of treatment with hormonal therapy instead of, or in addition to, chemotherapy.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

CASODEX® (bicalutamide)

Drug Composition:

CASODEX® (bicalutamide) Tablets for oral administration contain 50 mg of bicalutamide, a non-steroidal antiandrogen with no other known endocrine activity. The chemical name is propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-,(+-). The structural and empirical formulas are:



$C_{18}H_{14}N_2O_4F_4S$

Bicalutamide has a molecular weight of 430.37. The pKa' is approximately 12. Bicalutamide is a fine white to off-white powder which is practically insoluble in water at 37°C (5 mg per 1000 mL), slightly soluble in chloroform and absolute ethanol, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran.

CASODEX is a racemate with its antiandrogenic activity being almost exclusively exhibited by the R-enantiomer of bicalutamide; the S-enantiomer is essentially inactive.

The inactive ingredients of CASODEX Tablets are lactose, magnesium stearate, methylhydroxypropylcellulose, polyethylene glycol, polyvidone, sodium starch glycollate, and titanium dioxide.

Drug is supplied as 50 mg Tablets by AstraZeneca:
(NDC 0310-0705) White, film-coated tablets (identified on one side with "CDX50" and on the reverse with the "CASODEX logo") are supplied in unit dose blisters of 30 tablets per carton (0310-0705-39), bottles of 30 tablets (0310-0705-30) and bottles of 100 tablets (0310-0705-10).

Store at controlled room temperature, 20°-25°C (68°-77°F).

Pharmacokinetics:

Bicalutamide has good oral absorption (though the absolute oral bioavailability is not known). Taking the drug with food has no significant effect on absorption. Both the parent drug and its metabolites have renal and hepatic clearance. Renal impairment has no significant effect on clearance. Patients with severe hepatic disease have increased plasma half-life of a metabolite of bicalutamide. *In-vitro* protein binding studies have shown that bicalutamide can displace coumarin anticoagulants from binding sites. Patients already on coumarin anticoagulants should have closely monitored Prothrombin times while taking bicalutamide. In men, the mean half-life of the drug is 5.8 days (standard deviation 2.29).

Contraindications:

Bicalutamide is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the tablet's components. It is contraindicated for use in pregnant women.

Toxicity:

Bicalutamide has not been tested in women at the intended doses for this study. Toxicities that have been reported in men with prostate cancer are listed above, in section 3.1 (with further details in Appendix A).

The anticipated toxicities of bicalutamide in women at doses of 50 – 150 mg include (listed in order of most likely to least likely to occur):

- Breast pain/tenderness
- Hot flashes
- Diarrhea
- Abnormal Hepatic Function
- Anemia
- Constipation
- Nausea
- Abdominal pain

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

A patient will be eligible for androgen receptor expression testing if the following criteria are met:

- Pathologically confirmed adenocarcinoma of the breast which is ER(-) and PR(-).
- Non-measurable or Measurable, metastatic disease

A patient will be eligible for participation in the therapeutic trial if the following criteria are met:

- Androgen receptor expression testing confirms that the patient's tumor is ER(-)/PR(-) /AR(+). ER, PR and AR are considered positive if greater than 10% of cell nuclei are immunoreactive. Receptor testing may be performed on either primary tumor specimen or tissue from a metastatic site.
- Prior neo-adjuvant or adjuvant chemotherapy is allowed. Any number of chemotherapy regimens are allowed for metastatic disease. There is no restriction on prior treatment with hormonal agents.
- Prior treatment with trastuzumab must have been given if patient has Her2/neu positive disease (defined as IHC=3+ or FISH amplified).
- At least 2 weeks since prior cytotoxic chemotherapy. Patients should have recovered from all acute effects of such therapy.
- Absence of active brain metastatic disease or leptomeningeal disease. If patient has a history of brain metastases, lesions must be stable for at least 3 months (as documented by either head CT or brain MRI).
- At least 4 weeks from major surgery with full recovery
- ECOG performance status 0-1
- Age 18 years or greater
- Laboratory parameters as follows:

    - ANC $\geq 1.5 \times 10^9$ cells/L
    - Platelets $\geq 100 \times 10^9$ cells/L
    - Hgb $\geq$ 9g/dL

    - AST (SGOT), ALT (SGPT) $\leq$ 2.5 x upper limit of normal range (ULN); total bilirubin $\leq$ 1.5 x ULN; alkaline phosphatase $\leq$ 2.5 x ULN (unless bone metastases are present in the absence of liver metastases), creatinine $\leq$ 1.5 mg/dL

- If female of childbearing potential, pregnancy test is negative

- If fertile, the patient agrees to use an effective method to avoid pregnancy for the duration of the study
- Informed consent has been obtained

6.3 Subject Exclusion Criteria

A patient will not be eligible for treatment on this study if any of the following criteria apply:

- Concurrent chemotherapy, hormonal therapy or biologic therapy is being administered to treat breast cancer.
- Serious intercurrent medical or psychiatric illness, including serious active infection.

- History of other malignancy within the last five years, which could affect the diagnosis or assessment of breast cancer (except non-melanomatous skin carcinoma).
- Patients who have received an investigational drug within the previous 3 weeks.
- Patient is currently enrolled in another clinical study in which investigational therapies are administered. In addition, a patient may not enroll in such clinical trials while participating in this study.

7.1 RECRUITMENT PLAN

Patients will be recruited for enrollment on this trial primarily through referrals from their primary oncologists. Efforts will be made to enroll women from a diversity of ethnic and socio-economic backgrounds. There will be no payments made to participants or physicians for participation in this study. Prior to enrollment on the study, the physician will discuss the study protocol in detail with the patient, including possible toxicities. An informed consent will be reviewed by the physician with the patient.

Androgen Receptor Testing:
If a patient wishes to undergo androgen receptor testing on the protocol, an informed consent will be signed prior to reviewing pathologic specimens for AR status. Androgen receptor testing may be performed using the Dako antibody, catalog number M3562, Animal/Clone AR441 (antibody dilution of 1:300 with citrate buffer pretreatment). The pathology specimen submitted for AR testing can be from either the primary or the metastatic site.

Dr. Dilip Giri and team at MSKCC Department of Pathology will verify the invasive breast cancer is AR positive. Fewer than 10 unstained slides or a tumor block will be accepted if that is all that is available. I

7.2 For participating sites sending pathology specimens to MSKCC for AR testing

Participating sites must send unstained slides to MSKCC for AR testing. All specimens submitted to MSKCC for AR testing must have previously tested ER(-)/PR(-) locally. ER, PR and AR are considered positive if greater than 10% of cell nuclei are immunoreactive. Dr. Dilip Giri and team at MSKCC Department of Pathology will verify the invasive breast cancer is AR positive. If the patient is AR (+), the MSKCC Department of Pathology will verify the specimen is ER(-)/PR(-).If the patient is AR (-), the patient is ineligible and the study staff will take steps to register the patient as ineligible.

Pathology specimens may be requested from either the primary or the metastatic site. Sites must request 10 unstained slides to send to MSKCC. Fewer than 10 unstained slides or a tumor block will be accepted if that is all that is available. Specimen submissions are to be shipped with an accompanying pathology report and the tumor tissue shipment form provided by the 07-022 MSKCC research staff using the MSKCC issued patient ID. The MSKCC study staff must be notified of all shipments. Shipments cannot be accepted on weekends. All shipments should be directed to the address listed on the tissue sample shipment form.This tissue will also be used for

correlative studies as discussed in section 10.0

8.1 PRETREATMENT EVALUATION

Baseline evaluations will be performed for ER(-)/PR(-)/AR(+) patients to determine study eligibility. Patients who have received any chemotherapy must have a washout period of 2 weeks before the first dose of study drug is administered. The investigator will document the designated washout period in the patient's source documentation.

The following must be completed within 28 days of initiation of study drug:

- Medical history including history of prior therapy
- Medication list (include medications taken within 30 days of baseline visit)
- Physical exam, height and weight.

- Vital signs

- ECOG performance status.
- CBC with differential and platelet count, comprehensive blood panel (including chemistries and liver function tests), tumor markers (Ca15-3 & CEA, or CA 27.29)

- Estradiol, total testosterone, free testosterone, sex-hormone binding globulin,
- Serum pregnancy test (for women of childbearing-potential) will be conducted within 72h of first study drug administration (negative results required for study drug administration).

- CT scan of chest, abdomen and pelvis
- Bone scan or PET scan

9.1 TREATMENT/INTERVENTION PLAN

9.2 Agent Administration

Treatment will be administered on an outpatient basis. Bicalutamide is administered orally at 150 mg (three 50mg tablets) on a continuous daily schedule. A cycle length consists of 4 weeks of therapy. Please refer to the Time and Events Calendar (Section 10) for a detailed description of required tests. Radiographic tumor assessment will take place every 3 cycles.

Expected adverse events for bicalutamide are described in Section 5.0. Appropriate dose modifications for bicalutamide are described in Section 4.2 and Section 11.2. Two 50mg dose reductions are permitted per protocol. A treatment delay of up to 2 weeks is permitted. Therapy will continue until disease progression or unacceptable toxicity.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Day 0 and every 4 weeks (+/- 5 days), the following clinical and laboratory assessments must be done prior to continuation of treatment with bicalutamide:

- History and physical examination, including:
  - Vital signs
  - ECOG performance status
  - Weight
  - Concomitant medications
- Laboratory assessments, including: (screening labs can be used as Day 0 labs)
  - CBC with differential and platelet count
  - Comprehensive metabolic panel (Na, K, Cl, CO2, BUN, Creatinine, Ca, Glucose, Total Protein, Albumin, Alkaline Phosphatase, Total Bilirubin, AST and ALT)
- Adverse Event Evaluation (toxicity assessment using the NCI CTC version 3)
- Blood for correlative study of hormonal levels including estradiol, total testosterone, free testosterone, and sex-hormone binding globulin will be performed at baseline, after Cycle #1 and at the end of study. (See further description below)

Every 12 weeks (+/- two weeks), tumor assessments will be performed. Patients with measurable disease will be evaluated for complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) using RECIST criteria, using the same modality of imaging performed at baseline. Patients with non-measurable disease will be evaluated for either stable disease or progressive disease. Responders and stable disease patients will continue on study unless they develop unacceptable toxicity. Progressive disease or unacceptable toxicity (after a maximum of two dose reductions) will be the criteria for treatment failure and discontinuation from the study.

Response assessment will include:

- Radiologic scans of disease sites (e.g. CT scan of chest, abdomen and pelvis and PET or bone scan if there are bone lesions identified on pre-study bone imaging)
- Measurement of all target lesions that are followed by physical examination
- Patients achieving a CR or PR must have confirmation of response at least 4 weeks following the initial response determination.

- End-of-Study (EOS) Evaluation: At the time patients are removed from study, laboratory and clinical evaluations to assess adverse events (AEs) will be performed. Serum hormone panel including estradiol, free and total testosterone and serum hormone binding globulin will be collected. Radiologic studies for antitumor response will be repeated if they have not been performed within the previous 28 days.
- Adverse Event Resolution Follow-up: Any AE that started anytime beginning from the

time the patient has registered, and up to 30 days after the last dose of bicalutamide, must be followed until the AE has resolved or stabilized.

Correlative study methods:
All correlative studies will be performed for the purpose of exploratory analysis. Correlative study will include immunohistochemical (IHC) analysis of proteins representing the ER(-) Class A and Basal subtypes, including ALCAM, SPDEF and CK 5/6. IHC analysis will be performed using preexisting formalin fixed paraffin embedded biopsy or excision tissue from cancer sites. An exploratory analysis will be performed to correlate IHC expression profile and response to bicalutamide. In addition, the effect of bicalutamide administration on serum hormone level will be investigated. Estradiol, free and total testosterone and serum hormone binding globulin will be measured at baseline, after cycle #1 and at the end of study to describe changes in these circulating hormones in response to androgen blockade in women.

Paraffin embedded tissue from primary tumor or metastatic site which has tested AR+ will be requested from participating patients. These tumor blocks, if available, will be collected and stored for the purpose of future correlative studies to understand the biology of AR+ breast cancer.

Time and Events Schedule

Study Parameter	Prestudy	Every cycle[a]	Every 3 cycles	Study Termination (EOS)	AE resolution
Informed consent[b]	X				
History	X				
Concomitant medications	X	X		X	
Physical examination	X	X		X	X
Vital signs	X	X		X	X
Height and body weight	X	X[c]		X[c]	
ECOG performance status	X	X		X	X
Adverse Event Evaluation		X		X	
Disease Status					
Tumor assessment (clinical) Tumor assessment with CT scan	X	X[d]	X[e]	X	
Tumor assessment with PET or Bone scan[g]	X		X	X	
Toxicity assessment (by patient and by physician)		X		X	
CBC with differential and platelet count	X	X		X	
Comprehensive blood panel (including chemistries and liver function tests) [h]	X	X		X	X
Tumor Markers (Ca 15-3 & CEA, or CA 27-29)	X	X		X	
Estradiol, total testosterone, free testosterone, sex-hormone binding globulin *Only after Cycle #1.	X	X*		X	
Pregnancy test	X[f]				

[a] one cycle is equal to 4 weeks

[b] after study consent form has been signed, pathological testing of tumor for androgen receptor (AR) status will be performed. If patient's tumor is AR+ then they will be eligible to participate in the therapeutic study. If AR- they will not be permitted to participate in study.

[c] body weight only

[d] by physical exam

[e] confirm response 28 days

[f] females of childbearing potential only, within 72 hours of drug initiation

[g] bone scan or PET must be repeated if bone disease is known from baseline scans. If patient does not have bone disease, follow-up bone or PET scans are at the discretion of the treating physician. If PET/CT scans are being performed and can monitor for bone lesions, then no further bone scans are necessary.

* after Cycle 1

[h] Comprehensive blood panel may include the following: Na, K, Cl, CO2, BUN, Creatinine, Ca, Glucose, Total Protein, Albumin, Alkaline Phosphatase, Total Bilirubin, AST and ALT

11.1 TOXICITIES/SIDE EFFECTS

These adverse event management guidelines are intended to ensure the safety of each patient while attempting to characterize the safety and tolerability of the test products. In agreeing to the provisions of this protocol, the investigator accepts all legal responsibilities for prompt notification of SAEs to the SAE manager in the Office of Clinical Research and to AstraZeneca as per section 11.4.

Adverse events occurring during the study will be graded according to the NCI CTCAE Scale Version 3.0 (see http://ctep.cancer.gov/forms/CTCAEv3.pdf) where applicable. Adverse events that are not included on the toxicity scale will be designated as Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening, and Grade 5 = death.

The investigator should evaluate all adverse events and should make an immediate effort to determine their etiology. Adverse events that are determined not to be possibly, probably, or definitely related to study drug may not require further evaluation but will need to be recorded on the CRFs. Study medication may be interrupted for an adverse event at the discretion of the investigator. Patients requiring toxicity management should be assessed and evaluated at least weekly as indicated by the severity of the event.

11.2 Definitions

The definitions of adverse events (AEs) and serious adverse events (SAEs) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

11.2.1 Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (*eg,* nausea, chest pain), signs (*eg,* tachycardia, enlarged liver) or the abnormal results of an investigation (*eg,* laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. In cancer clinical trials, many AEs are in fact related to progression of the patient's underlying malignancy.

An adverse event includes:

- An exacerbation of a pre-existing illness;
- An increase in frequency or intensity of a pre-existing episodic event or condition;
- A condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study;
- Continuously persistent disease or symptoms that were present at baseline and worsen following the start of the study.

An adverse event does not include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, or transfusion); however, the condition that leads to the procedure is an adverse event (Procedures that occur during the trial should be recorded on the Concurrent Procedure CRF);
- Pre-existing diseases, conditions or laboratory abnormalities present or detected at the start of the study that do not worsen;
- Hospitalizations or procedures that are done for elective purposes not related to an untoward medical occurrence (eg, hospitalizations for cosmetic or elective surgery or social/convenience admissions);
- The disease being studied or signs/symptoms associated with the disease unless more severe than expected for the patient's condition;
- Overdose of study drug without any clinical signs or symptoms.

11.2.2 Serious adverse event

A serious adverse event is an AE occurring during any study phase (*eg,* run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

- results in death
- is immediately life-threatening (defined as an immediate risk of death from the event as it occurred)
- requires in-patient hospitalization or prolongation of existing hospitalization (Exception: hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an adverse event. NOTE: Complications that occur during hospitalization are adverse events and if a complication prolongs hospitalization, then the event is serious)
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.
- Is a Grade 4 laboratory abnormality.

The causality of SAEs (their relationship to study treatment) will be assessed by the investigator(s).

11.3 Dosing Delays/Dose Modifications

Dose reductions are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.

Dose reductions for toxicity should be made according to guidelines, which follow. A maximum of two 50mg (bicalutamide) dose reductions will be allowed per patient.

11.3.1 Gastrointestinal Toxicity

If ≥ grade 3 diarrhea occurs, that is not controlled with anti-diarrheal agents (eg. loperamide), bicalutamide should be withheld until resolution to ≤ grade 1, then reinstituted at the next lower dose level.

11.3.2 Breast Pain/Tenderness

If ≥ grade 3 breast pain occurs, that is not controlled with non-opioid pain medications (NSAIDs, Tylenol), bicalutamide should be withheld until resolution to ≤ to grade 1, then reinstituted at the next lower dose level. If ≥ grade 3 breast pain occurs at a reduced dose level, and is not controlled with non-opioid pain medications, bicalutamide should be withheld until resolution to ≤ grade 1, then reinstituted at the next lower dose level. If, after 2 dose reductions (to 50mg PO daily), ≥ grade 3 breast pain persists, opioid pain medicine is encouraged. If symptoms persist, patient may be referred to a radiation oncologist (if no breast irradiation previously administered, and at discretion of treating radiation oncologist) for breast irradiation to palliate symptoms. If none of these interventions successfully alleviates symptoms, and if ≥ grade 3 breast pain persists, then patient will be discontinued from study. Toxicity will be reported, and patient will be evaluated as unable to tolerate bicalutamide. If ≤ grade 2 breast pain persists, patient may elect to stop treatment on study, or to continue. If patient chooses to discontinue study treatment, toxicity will be noted; however, this will not constitute unacceptable toxicity for purposes of adverse event reporting.

11.3.3 Hot flashes

If ≥ grade 3 hot flashes occur, bicalutamide may be reduced to the next lower dose level, at the discretion of the treating physician. Pharmacologic intervention with low-dose SSRI (or an alternative oral therapy that has been demonstrated to have beneficial effect for treatment of hot flashes greater than that reported for placebo eg. clonidine, buproprion) may be administered. If ≥ grade 3 hot flashes persist at lower dose level, a second dose reduction may be instituted. If ≥ Grade 3 hot flashes persist at lowest treatment dose (50mg), patient will be taken off study, and adverse effect will be reported as intolerable toxicity. If ≤ grade 2 hot flashes persist at lowest treatment dose (50mg), patient may be taken off study at discretion of treating physician. Toxicity will be reported; however, it will not constitute unacceptable toxicity for purposes of adverse event reporting.

11.3.4 Abnormal Hepatic Function

Bicalutamide should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from bicalutamide may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications. A maximum of 2 weeks will be permitted for liver enzymes to return to within normal range for the institution.

If transaminases (ALT/AST) are elevated > 2.5x normal levels, treatment should be withheld until levels fall to ≤ 2.5 x normal levels. If total bilirubin is elevated > 1.5 x normal level, treatment should be withheld until level falls to ≤ 1.5 x normal levels. If alkaline phosphatase is elevated > 2.5 x normal value, treatment should be withheld until levels fall to ≤ 2.5 x normal level (unless bone metastases are present in the absence of liver metastases). A dose reduction should then be administered following resolution of any or all of these liver enzyme abnormalities.

If transaminases are subsequently elevated > 2.5 x normal; or, if total bilirubin is elevated > 1.5 x normal value, or if alkaline phosphatase is elevated > 2.5 x normal value (unless bone metastases are present in the absence of liver metastases), treatment will again be withheld until AST/ALT decrease to ≤ 2.5 x normal, total bilirubin decreases to ≤ 1.5 x normal value and alkaline phosphatase decreases to ≤ 2.5 x normal value. A second dose reduction should then be administered.

If, after 2 dose reductions, AST, ALT, total bilirubin and/or alkaline phosphatase remain elevated, patient should be taken off study, and laboratory abnormalities should be reported as an unacceptable toxicity.

11.3.5 Other toxicities

If toxicities are ≤ grade 2, manage symptomatically if possible and retreat without dose reduction.

If toxicities are ≥ grade 3, except for anemia, treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level.

For any grade 3 or 4 toxicity not mentioned above, treatment should be withheld until the patient recovers completely or to grade 1 toxicity. The treatment should then be resumed at the next dose level. For grade 1 or 2 toxicities, no dose reduction should be made.

A maximum of two weeks will be permitted for resolution of grade 3 or 4 toxicities. If toxicity has not resolved by the end of two weeks, patient will be taken off study.

Dose Modification Table

Dose Level (starting dose)	Bicalutamide (mg)
0	150
-1	100
-2	50

11.3 Concomitant Treatment/ Medications for Symptom Relief

Irradiation is permitted during the study for treatment of symptomatic breast pain, as outlined above, if it is deemed feasible and appropriate care. Administration of other chemotherapy, immunotherapy, biologic therapy or anti-tumor hormonal therapy during the study is not allowed. Supportive care, including but not limited to antiemetic medications, may be administered at the discretion of the investigator. Concurrent treatment with bisphosphonates is allowed. All concomitant treatments, including blood and blood products, must be reported on the case report form. Granulocyte stimulating factor and/or erythropoietin may be administered at the discretion of the investigator, consistent with institution guidelines.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Efficacy, defined as the response rate (CR, PR or SD by RECIST criteria) is the primary endpoint of this trial, and patients with measurable disease will be assessed by standard criteria. Patients with non-measurable disease will be evaluated for SD or progressive disease only. For the purposes of this study, patients should be evaluated radiographically every 12 weeks. In addition to a baseline scan, confirmatory CT scan will also be obtained at least 4 weeks following initial documentation of an objective response.

A radiologist will review all of the scans with non-measurable and measurable sites of disease (e.g. CT scans). Target lesions will be identified prospectively, and recorded on a data collection form. These lesions will be followed over the duration of the study as discussed below. The use of a designated study radiologist and data collection forms should ensure quality assurance and verification of tumor response. At participating sites, staff radiologists may evaluate study scans and the principal investigator will calculate response for prespecified target lesions.

12.2 Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (uni dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques (CT, MRI, x-ray) or as >10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target Lesions: All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target Lesions: All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout followup.

12.3 Guidelines for Evaluation of Measurable Disease

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

Tumor lesions that are situated in a previously irradiated area are considered measurable if there is clear disease progression following radiation therapy. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US): When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

Tumor Markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

12.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non-target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level Incomplete Response/
Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Evaluation of Best Overall Response

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

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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." Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.
Non-measurable disease: Patients with non-measurable disease (ie, bone only disease) will be evaluated only as either stable disease or progressive disease.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study if any of the following conditions apply:

- intercurrent illness which would in the judgment of the investigator effect assessments of clinical status to a significant degree or require discontinuation of drug;
- unacceptable toxicity;
- progressive disease;
- request by the patient to withdraw;
- patient non-compliance with protocol;
- irradiation of an indicator lesion during the trial;
- if at the discretion of the investigator continued treatment would be harmful or ineffective.

14.0 BIOSTATISTICS

This is a multicenter, open-label, phase II study to evaluate the efficacy of bicalutamide administered orally daily to patients with ER(-)/PR(-)/AR(+) metastatic breast cancer. The primary endpoint of this trial is the response rate (RR), defined as the total number of patients who demonstrate a complete response (CR), partial response (PR) or stable disease (SD) (after 6 months from the first day of treatment) divided by the total number of patients treated. Upon

completion of the study, the RR will be estimated via the observed response rate and an exact confidence interval will be constructed. The response rate for patients with only measurable disease will be reported separately as the number of patients who demonstrate a CR, PR or SD >6months divided by the number of patients with measurable disease treated with bicalutamide. For this trial, a target response rate of 20% or higher is considered promising. A target response rate below 5% is considered unacceptable.

This study is designed as a single-stage, phase II which requires a total of 28 patients. If 4 or more patients have a CR, PR or SD after 6 months from the first day of treatment, bicalutamide will be considered feasible and will merit further clinical study. With 28 patients, this design discriminates between true response rates of $\leq 5\%$ and $\geq 20\%$ at a Type I error of 5% and a Type II error of 16%.

Secondary objectives of this study include estimating median progression-free survival at 6 months and describing the rate of selected non-hematologic and hematologic toxicities. Progression-free survival will be estimated by the Kaplan-Meier method. Selected toxicities will be described by frequency and grade, by cycle and overall cycles, with the maximum grade over all cycles used as the summary measure per patient. The safety endpoint will also be measured as the percentage of patients who are able to tolerate daily treatment with bicalutamide after a maximum of 2 (50mg) dose reductions from the starting dose of 150mg, for 6 months from the first day of treatment.

Data analysis plan:
Upon completion of the study, response rate will be estimated via the observed response rate and an exact confidence interval will be constructed. Categorical variables (such as toxicities, responses) will be summarized by counts, percentages or contingency tables and confidence intervals. Continuous variables and changes in continuous variables will be summarized by means, medians and standard deviations. For the correlative studies, analysis is exploratory in nature and hypothesis generating. The relationship between immunohistochemical expression and response will be explored using graphical methods. Similarly, changes in hormone levels over time during treatment with bicalutamide will be described.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

15.2 For Participating Centers:

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC).

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to fax registration/eligibility documents to the 07-022 Research Staff at MSKCC 646-227-2482.

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and HIPAA Authorization form (Research Authorization)
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.
The data collected for this study will be entered into the Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

16.1.1 Data Management Requirements for Participating Sites

Data
Standardized Case Report Forms (CRFs) and directions for use and sign off requirements have been generated for this study. Blank case report forms will be sent to the study staff at each participating site for use. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. Relevant source documentation to be submitted throughout the study includes:

For Step 1:

- Pathology report confirming ER/PR/AR status.

For Step 2:

- Baseline measures to assess pre–protocol disease status
  - Medical history
  - Physical examination, including height and weight measurement
  - ECOG performance status
  - Vital signs
  - Prior medication evaluation
  - Laboratory tests (CBC, comprehensive panel, tumor markers)
  - Bone scan or PET Scan
  - CT Chest/Abdomen/Pelvis
  - Pathologic confirmation of breast cancer and hormone receptor status
- Laboratory records
- Treatment records
- Toxicities/adverse events not previously submitted with SAE Reports
- Response designation

16.1.2 Data and Source Documentation Submission for Participating Sites

Participating sites should fax CRFs and source documentation to MSKCC to the contact provided below. Submissions should include a cover page listing all CRFs enclosed per participant.

FAX: 646-227-2482 to the attention of Protocol 07-022 Research Staff

16.1.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSKCC according to chart 16.0.3.1:

Data and Source Submission Requirements and Timelines for Therapeutic Studies

	Baseline	*Visit 1*	*Visit 2*	*Visit 3*	*Visit 4*	*SAE*	*Off Study*
SUBMISSION SCHEDULE							
Source Documentation	Within 24 hours (see section 15.1.1)	within 14 days of the end of cycle				Within 3 days of event (see section 17.2.1); updates to be submitted as available	Within 14 days of visit
CRFs	Within 7 days of visit						
Required Forms							
Demographics/Disease Form[1]	X						
Patient Disease	X						
Concomitant Medications Form	X	X	X	X	X		X
Diagnostic Test Form	X						
Physical Exam Form	X	X	X	X	X		X
Pathology Form	X						
Treatment Form		X	X	X	X		X
Laboratory Form	X	X	X	X	X		X
Treatment Modification Form		X	X	X	X		
Past Treatment Form	X						
Comorbidity	X						
Lesion/EOD Form					X[1]		X
Toxicity Form	X	X	X	X	X	X	X
Serious Adverse Event Form						X	
Hospitalization Form						X	
Protocol Outcome				X			X
Patient Status Form							X

[1] For step 1 ineligible patients, this is the only form required.

16.1.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Quality Assurance for Participating Sites

Each site participating in the accrual of participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected participant records can be audited on-site at participating sites or (2) source documents for selected participants will be sent to MSKCC for audit. Audits will usually be determined by participant accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of MSKCC PI.

Audits will be conducted at least once shortly after initiation of participant recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial. The number of participants audited will be determined by available time and the complexity of the protocol.

The audit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Required specimen submission
- Pharmacy review, if applicable
- Case Report Form submissions to MSKCC: timelines and accuracy

A wrap-up session will be conducted at the participating site and preliminary findings will be discussed with the participating site PI and research team. The preliminary results will be sent to the MSKCC PI.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant by participant case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the participating site must be sent to the MSKCC IRB/PB, CRQA and maintained in the department's protocol regulatory binder.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites participant's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the participating sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC promptly upon request.

16.1.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (*e.g.*, protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control. Additionally, two institutional committees are responsible for monitoring the activities of our clinical trials programs. The committees, *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board. Patients treated collaborating institutions will also be included in these reviews.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (*e.g.*, NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed, and the monitoring procedures will be established at the time of protocol activation.

16.2 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

16.2.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non-expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non-expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue or makes the eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.2.2 Additional IRB Correspondence

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations
A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.2.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.
After study closure, the participating site will maintain all source documents, study related documents and CRFs for 3 years.

16.3 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments maybe withheld (if applicable), until the outstanding issues have been resolved.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative options for treatment will be reviewed, including chemotherapy or hormonal therapy, as appropriate. Financial costs and burdens of the trial will be reviewed, including a detailed discussion of the tests that will be the financial responsibility of the study, and the tests which will be the financial responsibility of the patient.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE

- The intervention
- Detailed text that includes the following
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

17.2.1 Physician Reporting of Adverse Events

Patients in the treatment population will be followed for the development of AEs from study drug initiation through the end of study or 30 days after the end of treatment, whichever is longer. AEs and SAEs that develop during this period are followed until resolution or stabilization (resolved with sequelae). Only patients with clear documentation that no study drug was administered may be excluded from the treated population.

The safety/tolerability will be evaluated for treatment-emergent adverse events and serious adverse events, laboratory abnormalities, physical examinations, vital signs and patients experiencing dose modifications, dose interruptions, and/or premature discontinuation of study drug.

The investigator or designee must completely and promptly record each adverse event in the source documentation and in the appropriate CRF, regardless of relationship to study drug as determined by the investigator. The Principal Investigator must assess AE/SAE causality for any patients treated at his/her site and for any patients treated under the direct care of his/her sub-investigators. The investigator should attempt, if possible, to establish a diagnosis based on the patient's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the investigator should report the diagnosis, not the symptoms, as the adverse event.

Clinically significant laboratory abnormalities present at the Baseline visit will be recorded as pre-treatment signs and symptoms. Clinical Chemistry liver and renal function will be summarized using the NCI CTCAE for alkaline phosphatase, AST, ALT, total bilirubin, and creatinine. The number and percentage of patients that have each NCI CTCAE grade will be summarized using the most severe grade for the first cycle of therapy and for anytime during the study. The incidence of patients with clinically significant chemistry values (NCI CTCAE toxicity Grades of 3 or 4) that occurred after the first dose of study drug will be presented. Data for patients with clinically significant values will also be listed.

AEs and SAEs should be reported on the appropriate Case Report Forms. In addition, all SAEs must be reported promptly to AstraZeneca after the investigator recognizes/classifies the event as a SAE. The specific reporting time frame depends on the type of SAE. For life-threatening or fatal events, the investigator must report initial information on the SAE no later than the next business day, preferably by fax or alternatively by phone or email; at a minimum, a description of the event and the investigator's judgment of causality must be provided at the time of the

initial report. If a SAE is reported by phone or by e-mail, the investigator must fax a completed SAE report form to AstraZeneca within 24 hours. For an event that is not life-threatening or fatal, the investigator must fax a completed SAE report form within 2 business days after he/she recognizes/classifies the event as a SAE.

SAE reports should be faxed to AstraZeneca at: 1-866-984-7229.

"Lack of efficacy" (progressive disease) is not considered an adverse event. The signs and symptoms or clinical sequelae resulting from lack of efficacy should be reported if they fulfill the adverse event of SAE definitions.

17.2.2 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within 3 calendar days of learning of the event.
- Participating sites should notify the MSKCC PI of any grade 5 event immediately.
- Participating sites should use the SAE Report Template **(*appendix C*)** to report SAEs to MSKCC.

SAE contact information for the Coordinating Center is listed below:

FAX: 646-227-2482 to the attention of Dr. Traina/07-022 Research Staff at MSKCC

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.1 and to AstraZeneca as described in 17.2.1.
- The MSKCC PI is responsible for informing all participating sites about unexpected SAEs and fatalities within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.2.3 Safety Reports

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

17.2.4 Additional Investigator Responsibilities for Follow-up of Serious Adverse Events

The investigator and supporting personnel responsible for patient care should institute any supplemental investigations of SAEs based on their clinical judgment of likely causative factors. This may include extra clinical laboratory tests, physical examinations or consulting an appropriate specialist. Astrazeneca may also request the investigator to conduct supplemental assessments. The results of any additional assessments conducted must be reported to Astrazeneca. If a patient dies during participation in the study and an autopsy is performed, a copy of the report must be submitted to Astrazeneca. If during the follow-up period for an SAE a patient dies due to another event unrelated to the SAE being followed, the event causing the death will be reported as a separate SAE.

17.2.5 Sponsor Notification of Post-Study Serious Adverse Events

The investigator should notify AstraZeneca of any death or SAE occurring after a patient has withdrawn from the study, when such death or SAE may reasonably be related to medication used in the study. However, investigators are not obligated to actively seek adverse events in former study participants.

Adverse events will be recorded on the case report forms by the investigator using verbatim terms that best describe the event. Grading of severity will be based upon the NCI CTCAE version 3.0. All adverse events will be coded to a MedDRA term by the sponsor. All MedDRA terms will then be mapped into the appropriate NCI CTCAE version 3.0 term.

Adverse events will be analyzed in terms of treatment-emergent AEs defined to be any AEs that begin or worsen in intensity after study drug initiation through 30 days after the last dose of study drug.

The incidence of all adverse events (all AEs regardless of causality) and all treatment related adverse events (those AEs thought to be possibly, probably or definitely related to study drug) will be summarized by NCI CTCAE version 3.0 term and maximum grade. The incidence of Serious Adverse Events (SAEs) and AEs that lead to discontinuation of study drug will also be summarized. Listings of patients that discontinued study drug due to an adverse vent, patients with SAEs and deaths will be presented. Patients with SAEs will be described by narrative.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.
Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

18.1 For Participating Sites

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCES

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20.0 APPENDICES

Appendix A – Bicalutamide (drug insert information provided by AstraZeneca)

DRUG INFORMATION

CASODEX®
(bicalutamide)
TABLETS

CLINICAL PHARMACOLOGY

Mechanism of Action

CASODEX is a non-steroidal antiandrogen. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue.

In clinical trials with CASODEX as a single agent for prostate cancer, rises in serum testosterone and estradiol have been noted.

Pharmacokinetics

Absorption:
Bicalutamide is well-absorbed following oral administration, although the absolute bioavailability is unknown. Co-administration of bicalutamide with food has no clinically significant effect on rate or extent of absorption.

Distribution:
Bicalutamide is highly protein-bound (96%). See Drug-Drug Interactions below.

Metabolism/Elimination:
Bicalutamide undergoes stereospecific metabolism. The S (inactive) isomer is metabolized primarily by glucuronidation. The R (active) isomer also undergoes glucuronidation but is predominantly oxidized to an inactive metabolite followed by glucuronidation. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S-enantiomer is rapidly cleared relative to the R-enantiomer, with the R-enantiomer accounting for about 99% of total steady-state plasma levels.

Special Populations:

Geriatric:
In two studies in patients given 50 or 150 mg daily, no significant relationship between age and steady-state levels of total bicalutamide or the active R-enantiomer has been shown.

Hepatic Insufficiency:
No clinically significant difference in the pharmacokinetics of either enantiomer of bicalutamide was noted in patients with mild-to-moderate hepatic disease as compared to healthy controls. However, the half-life of the R-enantiomer was increased approximately 76% (5.9 and 10.4 days for normal and impaired patients, respectively) in patients with severe liver disease (n=4).

Renal Insufficiency:
Renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of total bicalutamide or the active R-enantiomer.

Women, Pediatrics:
Bicalutamide has not been extensively studied in women or pediatric subjects.

Drug-Drug Interactions:
There is no evidence that bicalutamide induces hepatic enzymes. *In vitro* protein-binding studies have shown that bicalutamide can displace coumarin anticoagulants from binding sites. Prothrombin times should be closely monitored in patients already receiving coumarin anticoagulants who are started on CASODEX.

Pharmacokinetics of the active enantiomer of CASODEX in normal males and patients with prostate cancer are presented in Table 1.

Table 1

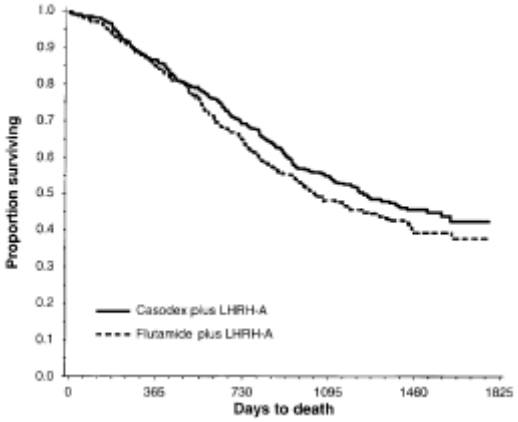
Parameter	Mean	Standard Deviation
Normal Males (n=30)		
Apparent Oral Clearance (L/hr)	0.320	0.103
Single Dose Peak Concentration (µg/mL)	0.768	0.178
Single Dose Time to Peak Concentration (hours)	31.3	14.6
Half-life (days)	5.8	2.29
Patients with Prostate Cancer (n=40)		
C_{ss} (µg/mL)	8.939	3.504

C_{ss}=Mean Steady-State Concentration

Clinical Studies:
In a multicenter, double-blind, controlled clinical trial, 813 patients with previously untreated advanced prostate cancer were randomized to receive CASODEX 50 mg once daily (404 patients) or flutamide 250 mg (409 patients) three times a day, each in combination with LHRH analogues (either goserelin acetate implant or leuprolide acetate depot).

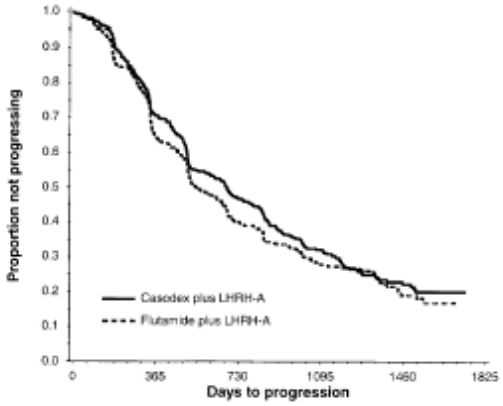
In an analysis conducted after a median follow-up of 160 weeks was reached, 213 (52.7%) patients treated with CASODEX-LHRH analogue therapy and 235 (57.5%) patients treated with flutamide-LHRH analogue therapy had died. There was no significant difference in survival between treatment groups (see Figure 1). The hazard ratio for time to death (survival) was 0.87 (95% confidence interval 0.72 to 1.05).

Figure 1 - The Kaplan-Meier probability of death for both antiandrogen treatment groups.



There was no significant difference in time to objective tumor progression between treatment groups (see Figure 2). Objective tumor progression was defined as the appearance of any bone metastases or the worsening of any existing bone metastases on bone scan attributable to metastatic disease, or an increase by 25% or more of any existing measurable extraskeletal metastases. The hazard ratio for time to progression of CASODEX plus LHRH analogue to that of flutamide plus LHRH analogue was 0.93 (95% confidence interval, 0.79 to 1.10).

Figure 2 - Kaplan-Meier curve for time to progression for both antiandrogen treatment groups



Quality of life was assessed with self-administered patient questionnaires on pain, social functioning, emotional well-being, vitality, activity limitation, bed disability, overall health, physical capacity, general symptoms, and treatment related symptoms. Assessment of the Quality of Life questionnaires did not indicate consistent significant differences between the two treatment groups.

INDICATIONS AND USAGE
CASODEX is indicated for use in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of Stage D2 metastatic carcinoma of the prostate.

CONTRAINDICATIONS
CASODEX is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the tablet's components.

CASODEX has no proven indication for women. Further, CASODEX should not be used by women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. CASODEX may cause fetal harm when administered to pregnant women. The male offspring of rats receiving doses of 10 mg/kg/day (plasma drug concentrations in rats equal to approximately 2/3 human therapeutic concentrations*) and above were observed to have reduced anogenital distance and hypospadias in reproductive toxicology studies. These pharmacological effects have been observed with other antiandrogens. No other teratogenic effects were observed in rabbits receiving doses up to 200 mg/kg/day (approximately 1/3 human therapeutic concentrations*) or rats receiving doses up to 250 mg/kg/day (approximately 2 times human therapeutic concentrations*).

*Based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient.

WARNINGS
Hepatitis:
Rare cases of death or hospitalization due to severe liver injury have been reported postmarketing in association with the use of CASODEX. Hepatotoxicity in these reports generally occurred within the first three to four months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in approximately 1% of CASODEX patients in controlled clinical trials.

Serum transaminase levels should be measured prior to starting treatment with CASODEX, at regular intervals for the first four months of treatment, and periodically thereafter. If clinical symptoms or signs suggestive of liver dysfunction occur (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness), the serum transaminases, in particular the serum ALT, should be measured immediately. If at any time a patient has jaundice, or their ALT rises above two times the upper limit of normal, CASODEX should be immediately discontinued with close follow-up of liver function.

PRECAUTIONS

General:

1. CASODEX should be used with caution in patients with moderate-to-severe hepatic impairment. CASODEX is extensively metabolized by the liver. Limited data in subjects with severe hepatic impairment suggest that excretion of CASODEX may be delayed and could lead to further accumulation. Periodic liver function tests should be considered for hepatic-impaired patients on long-term therapy (See WARNINGS).

2. In clinical trials with CASODEX as a single agent for prostate cancer, gynecomastia and breast pain have been reported in up to 38% and 39% of patients, respectively.

Drug Interactions:

In vitro studies have shown CASODEX can displace coumarin anticoagulants, such as warfarin, from their protein-binding sites. It is recommended that if CASODEX is started in patients already receiving coumarin anticoagulants, prothrombin times should be closely monitored and adjustment of the anticoagulant dose may be necessary (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Two-year oral carcinogenicity studies were conducted in both male and female rats and mice at doses of 5, 15 or 75 mg/kg/day of bicalutamide. A variety of tumor target organ effects were identified and were attributed to the antiandrogenicity of bicalutamide, namely, testicular benign interstitial (Leydig) cell tumors in male rats at all dose levels (the steady-state plasma concentration with the 5 mg/kg/day dose is approximately 2/3 human therapeutic concentrations*) and uterine adenocarcinoma in female rats at 75 mg/kg/day (approximately 1 1/2 times the human therapeutic concentrations*). There is no evidence of Leydig cell hyperplasia in patients; uterine tumors are not relevant to the indicated patient population. A small increase in the incidence of hepatocellular carcinoma in male mice given 75 mg/kg/day of bicalutamide (approximately 4 times human therapeutic concentrations*) and an increased incidence of benign thyroid follicular cell adenomas in rats given 5 mg/kg/day (approximately 2/3 human therapeutic concentrations*) and above were recorded. These neoplastic changes were progressions of non-neoplastic changes related to hepatic enzyme induction observed in animal toxicity studies. Enzyme induction has not been observed following bicalutamide administration in man. There were no tumorigenic effects suggestive of genotoxic carcinogenesis.

A comprehensive battery of both *in vitro* and *in vivo* genotoxicity tests (yeast gene conversion, Ames, *E. coli*, CHO/HGPRT, human lymphocyte cytogenetic, mouse micronucleus, and rat bone marrow cytogenetic tests) has demonstrated that CASODEX does not have genotoxic activity.

Administration of CASODEX may lead to inhibition of spermatogenesis. The long-term effects of CASODEX on male fertility have not been studied.

In male rats dosed at 250 mg/kg/day (approximately 2 times human therapeutic concentrations*), the precoital interval and time to successful mating were increased in the first pairing but no effects on fertility following successful mating were seen. These effects were reversed by 7 weeks after the end of an 11-week period of dosing.

No effects on female rats dosed at 10, 50 and 250 mg/kg/day (approximately 2/3, 1 and 2 times human therapeutic concentrations, respectively*) or their female offspring were observed. Administration of bicalutamide to pregnant females resulted in feminization of the male offspring leading to hypospadias at all dose levels. Affected male offspring were also impotent.
*Based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient.

Pregnancy:

Pregnancy Category X:
(See CONTRAINDICATIONS)

Nursing Mothers:

CASODEX is not indicated for use in women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CASODEX is administered to a nursing woman.

Pediatric Use:
Safety and effectiveness of CASODEX in pediatric patients have not been established.

ADVERSE REACTIONS
In patients with advanced prostate cancer treated with CASODEX in combination with an LHRH analogue, the most frequent adverse experience was hot flashes (53%).
In the multicenter, double-blind, controlled clinical trial comparing CASODEX 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analogue, the following adverse experiences with an incidence of 5% or greater, regardless of causality, have been reported.

Side effects that have been reported in **men** taking **bicalutamide with an LHRH analogue** on clinical trial **(regardless of causality)** are listed in the following table:

Toxicity (by system)	>5% Frequency (with % frequency, regardless of toxicity)	>/= 2% and < 5% Frequency (listed in order of decreasing frequency in each system, regardless of causality)
Abnormal Laboratory Values		AST, ALT, bilirubin, BUN and creatinine, decreased hemoglobin and white blood cell count
Constitutional/general	Pain (general) (35%) Back Pain (25%) Asthenia (22%) Pelvic Pain (21%) Infection (18%) Abdominal Pain (11%) Chest Pain (8%) Headache (7%) Flu Syndrome (7%)	Fever Chills Neoplasm Neck Pain Sepsis Hernia Cyst Cataract
Cardiovascular	Hot Flashes (53%) Hypertension (8%)	Angina Pectoris Congestive Heart Failure Myocardial Infarct Coronary Artery Disorder Syncope
Dermatologic	Rash (9%) Sweating (6%)	Dry Skin Alopecia Pruritis Herpes Zoster Skin Carcinoma Skin Disorder
Gastrointestinal	Constipation (22%) Nausea (15%) Diarrhea (12%) Increased Liver Enzymes (7%) Dyspepsia (7%) Flatulence (6%) Anorexia (6%) Vomiting (6%)	Melena Rectal Hemorrhage Dry Mouth Dysphagia Gastrointestinal Disorder Periodontal Abscess Gastrointestinal Carcinoma
Hematologic	Anemia (11%)	
Metabolic and Nutritional	Peripheral edema (13%) Weight loss (7%) Hyperglycemia (6%) Increased Alkaline Phosphatase (5%) Weight Gain (5%)	Edema BUN increased Creatinine increased Dehydration Gout Hypercholesteremia
Musculoskeletal	Bone Pain (9%) Myasthenia (7%) Arthritis (5%) Pathological Fracture (4%)	Myalgia Leg Cramps
Neurologic	Dizziness (10%) Parasthesia (8%) Insomnia (7%) Anxiety (5%) Depression (4%)	Hypertonia Confusion Somnolence Libido decreased Neuropathy Nervousness

Respiratory	Dyspnea (13%) Cough increased (8%) Pharyngitis (8%) Bronchitis (6%) Pneumonia (4%) Rhinitis (4%)	Lung disorder Asthma Epistaxis Sinusitis
Urogenital	Nocturia (12%) Hematuria (12%) Urinary Tract Infection (9%) Gynecomastia (9%) Impotence (7%) Breast Pain (6%) Urinary Frequency (6%) Urinary Retention (5%) Urinary Impairment (5%) Urinary Incontinence (4%)	Dysuria Urinary Urgency Hydronephrosis Urinary Tract Disorder

The most common side effects reported by men taking bicalutamide with an LHRH analogue include hot flashes (53%), breast tenderness (39%) and gynecomastia (38%).

Rare cases of death or hospitalization due to severe liver injury have been reported in association with the use of bicalutamide. Hepatotoxicity in these reports generally occurred within the first three to four months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in approximately 1% of patients taking bicalutamide on a clinical trial. If clinical symptoms or signs suggestive of liver dysfunction occur (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness), the serum transaminases should be measured immediately.

Other adverse experiences (greater than or equal to 2%, but less than 5%) reported in the CASODEX-LHRH analogue treatment group are listed below by body system and are in order of decreasing frequency within each body system regardless of causality.

Body as a Whole: Neoplasm; Neck pain; Fever; Chills; Sepsis; Hernia; Cyst

Cardiovascular: Angina pectoris; Congestive heart failure; Myocardial infarct; Heart arrest; Coronary artery disorder; Syncope

Digestive: Melena; Rectal hemorrhage; Dry mouth; Dysphagia; Gastrointestinal disorder; Periodontal abscess; Gastrointestinal carcinoma

Metabolic and Nutritional: Edema; Bun increased; Creatinine increased; Dehydration; Gout; Hypercholesteremia

Musculoskeletal: Myalgia; Leg cramps

Nervous: Hypertonia; Confusion; Somnolence; Libido decreased; Neuropathy; Nervousness

Respiratory: Lung disorder; Asthma; Epistaxis; Sinusitis

Skin and Appendages: Dry skin; Alopecia; Pruritus; Herpes zoster; Skin carcinoma; Skin disorder

Special Senses: Cataract specified

Urogenital: Dysuria; Urinary urgency; Hydronephrosis; Urinary tract disorder

Abnormal Laboratory Test Values: Laboratory abnormalities including elevated AST, ALT, bilirubin, BUN, and creatinine and decreased hemoglobin and white cell count have been reported in both CASODEX-LHRH analogue treated and flutamide-LHRH analogue treated patients.

Postmarketing Experience: Rare cases of interstitial pneumonitis and pulmonary fibrosis have been reported with CASODEX.

OVERDOSAGE
Long-term clinical trials have been conducted with dosages up to 200 mg of CASODEX daily and these dosages have been well tolerated. A single dose of CASODEX that results in symptoms of an overdose considered to be life-threatening has not been established. There is no specific antidote; treatment of an overdose should be symptomatic. In the management of an overdose with CASODEX, vomiting may be induced if the patient is alert. It should be remembered that, in this patient population, multiple drugs may have been taken. Dialysis is not likely to be helpful since CASODEX is highly protein bound and is extensively metabolized. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

DOSAGE AND ADMINISTRATION
The recommended dose for CASODEX therapy in combination with an LHRH analogue is one 50 mg tablet once daily (morning or evening), with or without food. It is recommended that CASODEX be taken at the same time each day. Treatment with CASODEX should be started at the same time as treatment with an LHRH analogue.

Dosage Adjustment in Renal Impairment:
No dosage adjustment is necessary for patients with renal impairment (see CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

Dosage Adjustment in Hepatic Impairment:
No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. Although there is a 76% (5.9 and 10.4 days for normal and impaired patients, respectively) increase in the half-life of the active enantiomer of bicalutamide in patients with severe liver impairment (n=4), no dosage adjustment is necessary (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment, PRECAUTIONS and WARNINGS sections).

Appendix B: Bicalutamide medication diary

Patient Name: _____
MRN: _____

Cycle	Day	Was study drug taken (circle Y or N)	Date study drug taken	Time study drug taken	AM/PM	# of 50 mg tablets taken	If no study drug taken, please explain reason for missing dose
	1	Yes No					
	2	Yes No					
	3	Yes No					
	4	Yes No					
	5	Yes No					
	6	Yes No					
	7	Yes No					
	8	Yes No					
	9	Yes No					
	10	Yes No					
	11	Yes No					
	12	Yes No					
	13	Yes No					
	14	Yes No					
	15	Yes No					
	16	Yes No					
	17	Yes No					
	18	Yes No					
	19	Yes No					
	20	Yes No					
	21	Yes No					
	22	Yes No					
	23	Yes No					
	24	Yes No					
	25	Yes No					
	26	Yes No					
	27	Yes No					
	28	Yes No					

MD/RN Signature:

Date:

Appendix C: SAE Reporting Form for Multicenter Studies

FOR MSKCC USE ONLY

MSKCC IRB PROTOCOL # -

__ __ __

SERIOUS ADVERSE EVENT REPORT FORM FOR NON-MSKCC SITES

Protocol Title: _____

_____

Participating Site Name: _____

Date of Report: __ __ / __ __ / __ __ __ __
m m d d y y y y

Check one:

☐ **Initial Report**

☐ **Follow-up Report** → **Date of original Report** __ __ / __ __ / __ __ __ __
m m d d y y y y

PARTICIPANT INFORMATION

Participant Initials: ____ ____ ____

Participant ID: _____

Treatment Start Date: __ __ / __ __ / __ __ __ __
m m d d y y y y

Last Protocol Treatment Date: __ __ / __ __ / __ __ __ __
m m d d y y y y

Participant Status: (check one)

☐ **Alive**

☐ **Deceased**

PROTOCOL INFORMATION

Type of Protocol Therapy (circle one):

☐ **Multiple**	☐ **Radiation**	☐ **Transplant**
☐ **Drug**	☐ **Nutrition**	☐ **Alternative Med**
☐ **Surgery**	☐ **Non-Treatment**	☐ **Adoptive Cell**

Radiation Therapy
Type**: N/A or** _____

Surgery Procedure
Type**: N/A or** _____

Drug Therapy Agents**: N/A or**

1. _____ **2.** _____

3. _____ **4.** _____

CONCOMINANT MEDICATIONS

(IF ADMINISTERED WHILE ADMITTED OR POTENTIALLY RELATED TO THE SAE)

Generic Name	Start Date mm/dd/yyyy	End Date mm/dd/yyyy

SAE INFORMATION

SAE Start Date mm/dd/yyyy	Event	Grade[1]	SAE End Date mm/dd/yyyy	Relationship[2]	Expected[3]	Severity[4]	Intervention[5]

[1] Grades **per CTCAE v.3.0 =** 1- **Mild,** 2-**Moderate,** 3-**Severe,** 4-**Life Threatening or Disabling,** 5-**Death**

[2] Relationship **=** 1-**Unrelated,** 2-**Unlikely,** 3-**Possible,** 4-**Probable,** 5-**Definite,** 6-**Likely,** 9-**Unknown**

[3] Expected**=** Y-**Yes,** N-**No,** U-**Unknown,** N/E-**Not Evaluable**

[4] Severity**=** 1-**Life Threatening,** 2-**Disabling,** 3-**Hospitalized,** 4-**Congential Anomaly,** 5-**Secondary Cancer,**
6-**Overdose,** 7-**Serious (other),** 8-**Not Serious**

[5] Intervention**=** 1-**None,** 2-**Interrupted,** 3-**Reduced,** 4-**Discontinued,** 5-**Med Given,** 6-**Not Applicable,** 7-**Surgery,** 8-**Hospitalized,** 9-**Unknown,** 10-**Other,** 11-**Transfusion,** 12-**Dose Not Escalated,** 13-**Pain Meds Lowered,**14-**Interrupted/Meds Given,** 15-**Interrupted/Reduced**

SAE HEMATOLOGIC INFORMATION

Lab Test	**Lab Date** mm/dd/yyyy	**Lab Value**	**Baseline Value**	**Baseline Date** mm/dd/yyyy	**Recovery Value**	**Recovery Date** mm/dd/yyyy

NON HEMATOLOGIC/UNEXPECTED REACTION DETAIL

Brief description of event, including relevant findings:

Complications and sequelae (including death):

Patient's past medical history related to this event:

REPORTING INFORMATION

SAE Reported By: _____

Participating Site PI Name (print):_____

Participating Site PI Signature:_____

Date: m m / d d / y y y y