THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

A Phase II Study of Ipilimumab PLUS Androgen Deprivation Therapy in Castrate Sensitive Prostate Carcinoma
2009-0378

Core Protocol Information

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Full Title:	A Phase II Study of Ipilimumab PLUS Androgen Deprivation Therapy in Castrate Sensitive Prostate Carcinoma
Protocol Phase:	Phase II
Version Status:	Activated -- Closed to new patient entry as of 10/11/2013
Version:	15
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Abstract

Objectives:

Primary Objectives:

- To estimate the rate of PSA </= 0.2ng/mL at 7 months in patients treated with androgen deprivation therapy (ADT) plus Ipilimumab.

Secondary Objectives:

- To profile *immunological changes* induced in patients with metastatic prostate carcinoma treated with intermittent ADT plus Ipilimumab.
- To assess the *time to testosterone recovery* (> 50ng/mL) in patients treated with intermittent ADT plus Ipilimumab.
- To assess the *time to PD off ADT*, after treatment with intermittent ADT plus Ipilimumab.
- To characterize ***safety*** and drug-related adverse events of ipilimumab combined with complete androgen ablation.
- To determine the *overall survival* of patients treated with intermittent ADT and ipilimumab.

Rationale: (Be as concise as possible)

Androgen ablation induces involution of prostate cancer at both primary and metastatic sites. Androgen

ablation also leads to an accumulation of mononuclear cells within the prostate, (which is associated with a better prognosis of the disease) and the development of new seroreactivities in patients with prostate cancer. These findings suggest that the induction of specific T cell responses might contribute to the anti-tumor effect of androgen ablation. Enhancing the host immune response against the tumor might lead to an improvement in the outcome of patients with metastatic prostate carcinoma.

T cell activation is a complex process that is initiated when an antigen is presented to the T cell receptor (TCR) followed by the interaction of additional T cell surface molecules with their respective ligands on the antigen presenting cell (APC). This second interaction can result in a positive or a negative costimulatory signal depending on which specific molecules are involved. CTLA-4 is a T-cell surface molecule that, on interaction with the B7 molecule of the APC, leads to the termination of the T-cell response. Blockage of CTLA-4 with the monoclonal antibody Ipilimumab has led to a remarkable enhancement of the immune response in experimental models of cancer and infection.

Durable responses and SD after treatment with ipilimumab have been observed in several malignancies, including melanoma, prostate and renal cell carcinoma.

Eligibility: (List All Criteria)

Inclusion:

1) Histologically or cytologically confirmed prostate carcinoma.

2) Evidence of metastatic disease on previous bone scan and/or CT scan and/or MRI.

3) Castrate-sensitive disease. Patients already on ADT are eligible as long as the time from initiation of LHRH analog or antagonist is not greater than 1 month AND the total exposure time to the LHRH analog or antagonist will not exceed 8 months (i.e. the effectiveness of current depot LHRH analog or antagonist does not extend beyond 8 months since its initiation).

4) Patients who have received prior hormonal therapy are allowed to participate as long as they have been off hormone ablation for 1.5 times as long as they were on it: e.g. 1) Patients who have received up to 4 months of hormonal ablation are eligible as long as they have been off hormonal ablation for >/= 6 months; 2) Patients who have received 1 year of hormonal ablation are eligible as long as they have been off hormone ablation for >/= 18 months; 3) Patients who have received up to 2 years of hormonal ablation are eligible as long as they have been off hormonal ablation for >/= 3 years have elapsed since its discontinuation.

5) ECOG performance status </= 1

6) Patients must have normal organ and marrow function as defined below: a) WBC >/= 3000/uL; b) ANC >/= 1500/uL; c) Platelets >/= 100 x 10^3/uL; d) Hemoglobin >/= 9 g/dL; e) Creatinine </= 2mg/dL; f) ALT </= 2.5 x ULN for patients without liver metastases. For patients with liver metastasis ALT </= 5 x ULN is allowed; g) Bilirubin </= 3 x ULN (except for patients with Gilbert's Syndrome, who must have a total bilirubin </= 3mg/dL)

7) Patients included in the study must be >/= 18 years old

8) Ability to understand and willingness to sign a written informed consent document.

Exclusion:

1) Autoimmune disease: Patients with a history of inflammatory bowel disease (including Crohn's disease and ulcerative colitis) and autoimmune disorders such as rheumatoid arthritis, systemic progressive sclerosis [scleroderma], Systemic Lupus Erythematosus or autoimmune vasculitis [e.g.,

Wegener's Granulomatosis] are excluded from this study.

2) Any underlying medical or psychiatric condition, which in the opinion of the Investigator, will make the administration of study drug hazardous or obscure the interpretation of AEs: e.g. a condition associated with frequent diarrhea or chronic skin conditions, recent surgery or colonic biopsy from which the patient has not recovered, or partial endocrine organ deficiencies.

3) Patients with known brain metastases.

4) Patients with small cell carcinoma of the prostate.

5) History of other malignancies, other than nonmelanoma skin cancer or Ta or T1 (low grade) bladder carcinomas, unless in complete remission and off therapy for that disease for at least 5 years.

6) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, history of congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

7) Known HIV, Hepatitis B, or Hepatitis C.

8) Untreated symptomatic spinal cord compressions.

9) Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to one month prior to or after any dose of ipilimumab).

10) Concomitant therapy with any of the following: IL-2, interferon or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids (used in the management of cancer or non-cancer-related illnesses).

11) Previous participation in another ipilimumab clinical trial or prior treatment with a CD137 agonist or CTLA-4 inhibitor or agonist.

12) History of acute diverticulitis, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis or other known risk factors for bowel perforation.

13) Patients who do not agree to practice appropriate birth control methods while on therapy.

14) Concurrent use of 5-alpha reductase inhibitors (finasteride or dutasteride).

Is there an age limit? Yes

Why? Provide scientific justification:
Prostate cancer does not occur in patients under the age of 18.

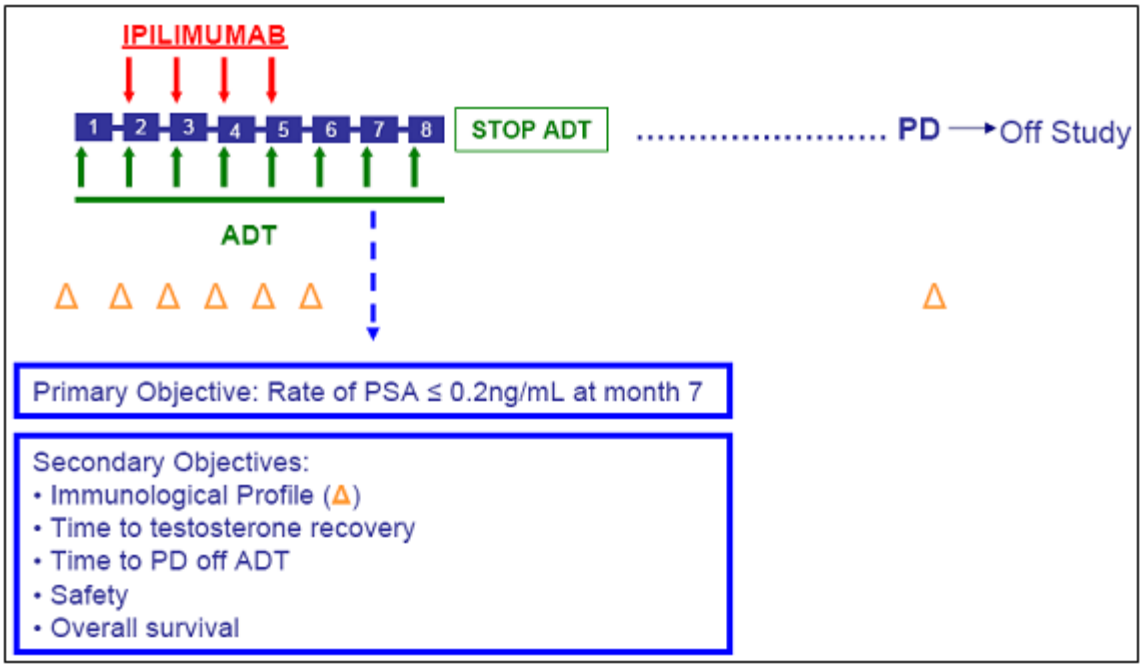
Disease Group:

Prostate

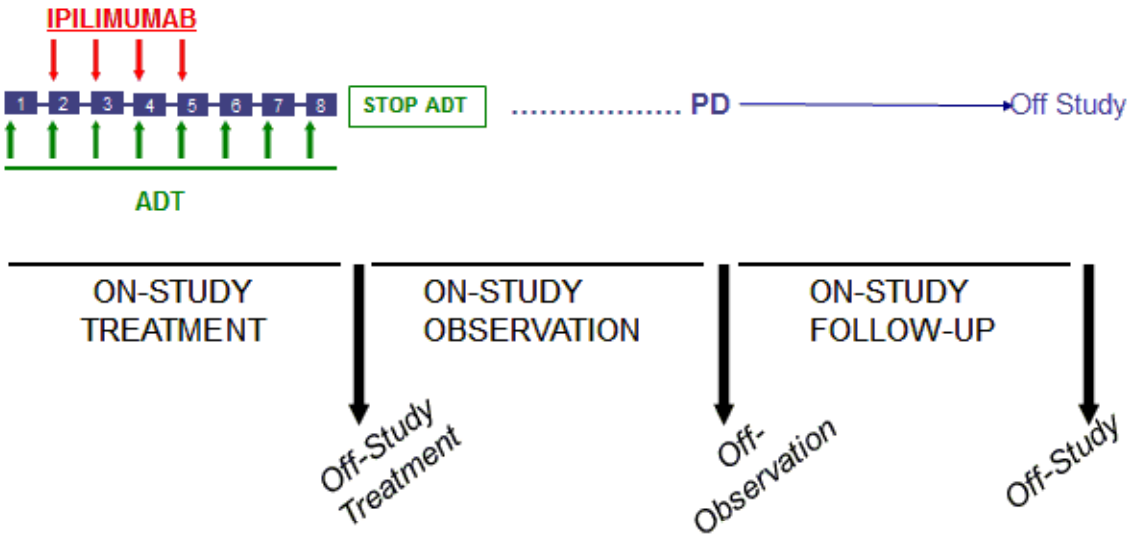
Treatment Agents/Devices/Interventions:

Degarelix, Goserelin Acetate, Ipilimumab, Leuprolide Acetate

Proposed Treatment/Study Plan:



Schema: Study Phases



	Pre-study Evaluation	On-Study Evaluation[h]	Prior to each Dose of Ipi and every 4 weeks for 6 months after last dose of ipi	Every 12 weeks beginning 6 months after last dose of Ipi	Disease Progression (+/- 14 days of the time the patient enters on study follow-up)	Long-ter up (every after progressi months dose
Physical Exam (interim history pertaining to current medications and treatment related toxicities)	X[b]	X	X	X	X	
CT Abd/Pelvis (preferred) or MRI Abd/Pelvis[k]	X[a]				X	
Chest X-ray[k]	X[a,d]				X[d]	
Bone Scan[k]	X[a]				X	
Complete Medical History	X[b]					
Electrocardiogram	X[b]					
Height	X[c]					
Weight	X[c]					
PS (ECOG)	X[c]					
BP, Pulse, Temperature	X[c]					
Concurrent Medications	X[c]	X	X	X	X	
Baseline Toxicity Evaluation	X[c]					
CBC with diff. and plt.	X[c]	X	X	X[j]	X	
Serum Chemistry[e]	X[c]	X	X	X	X	
Urine N-telopeptides (NTX)	X[c]	X	X	X[j]		

PSA Assessment	X[c,f]	X	X	X	X	
Serum Testosterone Levels	X[c,g]	X	X	X	X	
Autoimmune Panel	X[c]					
ACTH	X[c]	X	X	X	X	
Cortisol	X[c]	X	X	X	X	
TSH	X[c]	X	X	X	X	
Free T4	X[c]	X	X	X	X	
Amylase	X[c]	X	X	X	X	
Lipase	X[c]	X	X	X	X	
SPEP and anti-TPO titer	X[c]	X	X	X	X	
Adverse Events[i]			X	X	X	
Correlative Studies[l]		X	X	X	X	
Survival						X

Legend

a = Within 42 days of study entry +/- 3 days

b = Within 28 days of study entry +/- 3 days

c = Within 14 days of study entry +/- 1 day

d = If lung metastases are evident on chest x-ray, CT of the chest should be obtained as well

e = Must include: creatinine, BUN, sodium, chloride, CO2, potassium, calcium, magnesium, phosphorus, glucose, albumin, total protein, total bilirubin, SGOT [AST], SGPT (ALT), alkaline phosphatase, bone alkaline phosphatase (ALP) and LDH

f = for patients registered after initial androgen ablation, PSA must have been assessed within 3 weeks prior to androgen ablation initiation and that will be considered as baseline

g = for patients registered after initiation of androgen ablation serum testosterone levels are preferable within 3 weeks prior to initiation of androgen ablation, though lack of this information will be acceptable for these patients

h = On study tests/visits that must occur within a defined time frame shall have a standing window of allowance that is equal to +/- 2 days for any laboratory testing

i = Adverse events will be monitored using the NCI CTCAE Version 3.0

j = Bone alkaline phosphatase and urine N-telopeptides (NTX) at Week 25 (month 7)

k = Restaging scans or other disease assessment diagnostics during study are at the discretion of study collaborator or the principal investigator and shall be performed if disease progression is suspected

l = 90mL of peripheral blood will be collected and may be banked for future research related to immunologic response

Table 2. Regimen Description.				
Agent	**Dose**	**Route**	**Schedule**	**Duration**
1. LHRH Analogue (one of the following) or Antagonist				
Leuprolide	7.5mg*	IM	Once a month*	8 months
Goserelin	3.6mg*	SC	Once a month*	8 months
Degarelix	80mg	SC	Once a month	8 months
2. Ipilimumab				
	10mg/kg	IV over 90 min**	Once every 4 weeks x 4	

* Leuprolide 22.5mg or Goserelin 10.8mg every 3 months can be used for ADT as long as the total duration of ADT does not exceed 8 months. For example, a 3-month depot formulation can be used for the first six months, followed by two 1-month depot formulations, to complete 8 months of ADT.
** Ipilimumab administration will be allowed a standing window for completion of the infusion +/- 10 minutes of targeted time.

Statistical Considerations:

This is a single arm phase II trial to evaluate the rate of PSA $\leq$ 0.2ng/mL in patients treated with ADT plus Ipilimumab. The primary endpoint is the proportion of patients achieving a PSA $\leq$ 0.2ng/mL at month 7.

The trial was originally designed to use a Simon's optimal two-stage design to stop the trial if 7 or less among the first 16 patients achieved a PSA $\leq$ 0.2ng/mL at month 7. However, since then ipilimumab has been approved by the FDA for use in melanoma patients and there are data showing that the full effect of immunotherapies can take many months (possibly longer than 7) to become evident. On the other hand, the accrual rate for this trial has been faster than we originally expected. Since its activation on 06/17/2011, we have already enrolled 9 patients. Given the fast accrual rate and the desirability of a longer wait time and of data from the secondary endpoints to reliably assess efficacy, we now propose to change the study to a single-stage design for efficacy endpoint. Based on new safety data obtained since the trial was first designed, the safety monitoring plan has also been changed as described below. We will perform a final analysis on the primary and secondary efficacy endpoints when the study is complete.

Let S be the event of achieving PSA $\leq$ 0.2ng/mL at month 7. It is assumed that ADT plus Ipilimumab will have a target rate of 60% for S. A rate of 40% or lower is considered a failure and the combination therapy will be rejected under this circumstance. With a sample size of 48 patients, we will have an 80% power to detect such a 20% difference using a Chi-squared test and with a two-sided type I error rate of 0.05. The sample size was computed using nQuery Advisor 7.0.

Safety Monitoring and Rules:
The PI will meet with the research nurse and data coordinator regularly to monitor toxicity events. Toxicity reports will be generated monthly and reviewed by the PI and the statistician. If at any time during the study,one of the following criteria is met, then accrual will be suspended until the PI has reviewed the events and determined the appropriate course of action, which could include a protocol amendment to decrease the dose of ipilimumab.

- $\geq$ 40% of subjects treated on the ipilimumab arm develop a $\geq$ Grade 3 toxicity thought to be related to the ipilimumab.
- $\geq$ 10% of subjects experience an ipilimumab related $\geq$ Grade 3 toxicity that cannot be alleviated or controlled by appropriate care and/or steroid and/or infliximab therapy within 14 days of the initiation of such therapy

- Any 2 ipilimumab related deaths unless also attributed to progression have occurred

Endpoint Definitions and Analysis Plan

For the primary analysis, the proportion of patients achieving PSA $\leq$ 0.2ng/mL at 7 months will be estimated in the ITT population, along with the exact 95% confidence interval. Kaplan-Meier methods will be used to analyze the time-to-event outcomes, including:

1. Time to testosterone recovery: Defined as the time between day 224 of the protocol and the date at which serum testosterone returns to > 50ng/mL. As per Section 5.1, the effect of ADT should not last beyond 8 months, i.e. beyond day 224. Patients who have not achieved testosterone recovery (ie, returns to > 50ng/mL) at the last follow-up time will be treated as censoring.
2. Time to PD off ADT: defined as the time between day 224 of the protocol and the date of the first PSA measurement that is $\geq$20% above the nadir, as long as the rise is confirmed by a two additional PSA measurements separated by at least one week as described in Section 7.2. Patients who have not experienced PSA progression at the last follow-up time will be treated as censoring.
3. Overall survival: defined as the time between the date of registration and the date of death. Patients who have not died at the last follow-up time will be treated as censoring.

Note: For patients who experience SAEs prior to 7 months, treatment will be discontinued. However, these patients will continue to be followed-up for the efficacy assessment. They will be counted as successes for PSA response if they achieve a PSA level less than or equal to 0.2ng/ml at 7 months.

Where Will Participants Be Enrolled:

Only at MDACC

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Estimated Accrual:

Total Accrual at MDACC:	48
Estimated monthly accrual at MDACC:	1-2

Accrual Comments:

Do you expect your target population to include non-english speaking participants? No

Location of Treatment:

This protocol is performed on an Outpatient basis.

Length of Stay: What is the length & frequency of hospitalization?

n/a

Return Visits: How often must participants come to MDACC?

Patients will return every 4 weeks for follow-up and treatment with ipilimumab for the first 32 weeks on study. Patients will return every 4 weeks for 6 months after last dose of Ipilimumab and every 12 weeks thereafter.

Home Care: Specify what, if any, treatment may be given at home.

n/a

Name of Person at MDACC Responsible for Data Management: Mary Storms

Prior protocol at M. D. Anderson:

Has the Principal Investigator ever had a clinical or behavioral protocol at MDACC that accrued patients? Yes

Data Monitoring Committee:

Is treatment assignment randomized? No

Is this a blinded or double-blinded study? No

Does this protocol have a schedule for interim and final analysis? No

Radiation Safety:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	No
Is the radioactive compound (or drug) FDA approved and/or commercially available?	No

Investigational New Drugs:

Does this protocol require an IND? Yes
Please list the IND holder and provide the IND number:

IND Holder: MDACC
IND Number: 106,207

Investigational Device:

Is the Investigational Device approved by the FDA? N/A

Is the Investigational Device being used in the manner approved by the FDA? N/A

Has the Investigational Device been modified in a manner not approved by the FDA? N/A

Name of Device:

Manufacturer:

What is the FDA Status of the Investigational Device?

Is the study being conducted under an Investigational Device Exemption (IDE)?

IDE Holder:

IDE Number:

Risk Assessment:
Please answer the following questions regarding the Investigational Device.

Intended as an implant?	No
Purported or represented to be for use supporting or sustaining human life?	No
For use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health?	No

You may attach sponsor documentation of the risk assessment:

Will participant be charged for the Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor or Supporter? Yes

Sponsor or Supporter: Bristol-Myers Squibb
Type(s) of Support: Funds
Agent

Monitored by Sponsor or Sponsor Represenative (CRO)? No

Is this Protocol listed on any Federal Grant or Foundation Funding Application? No

Biosafety:

Does this study involve the use of Recombinant DNA Technology?	No
Does this study involve the use of organisms that are infectious to humans?	No
Does this study involve stem cells?	No

Technology Commercialization:

Does this study include any agents or devices manufactured or produced at MD Anderson Cancer Center?	No

Laboratory Tests:

Where will laboratory tests be performed on patient materials? (Please select all that apply)
Division of Pathology & Laboratory Medicine CLIA Certified Laboratory

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study?	No