

Phase I/II Trial of Ipilimumab (Immunotherapy) and Hypofractionated Stereotactic Radiation Therapy in Patients with Advanced Solid Malignancies

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1. Treatment Scheme

Notice: Treatment schedules shall have a standing window of allowance of +/- 3 days unless patient/logistical/medical reasons intervene. Any treatment day (radiation or ipilimumab administration) that falls on a weekend or holiday will be scheduled on the next business day. For treatment or dose modification questions, please contact Chad Tang, MD by pager (713-606-3929) or e-mail (ctang1@mdanderson.org), Aung Naing, MD by phone (713-792-2950) or e-mail (anaing@mdanderson.org), James Welsh, MD by phone (713-563-2447) or e-mail (jwelsh@mdanderson.org), or David Hong, MD by phone (713-563-5844) or e-mail (dshong@mdanderson.org). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

There will be five parallel treatment groups consisting of patients with metastatic disease from any primary. All treatment groups will receive ipilimumab (Yervoy™) at a dose of 3 mg/kg every 21 days for a total of 4 doses. Treatment assignment will be based on disease status at enrollment. In the event that a patient presents with both treatable liver and lung lesions, assignment will be based on provider preference. Administration of SBRT at 50 Gy in 4 fractions (treatment groups 1-4) versus SBRT in 60 Gy in 10 fractions (treatment group 5) will be based on meeting normal tissue dose constraints (section 6.3) and/or treating physician judgment. SBRT treatment is subject to dose de-escalation (see table below).

All patients who achieve systemic disease control (stable disease or partial response, based on ir-RC criteria) on post induction cycle 4 imaging will be given the option of receiving reinduction with an additional 4 cycles of ipilimumab at the maximum tolerated dose +/- radiation. Reinduction will be administered at least 8 weeks after the last cycle of ipilimumab. Optional radiation can be administered during reinduction. If administered, radiation will be sequenced with ipilimumab (concurrent vs. sequential) as was conducted during the initial induction. After the first round of reinduction, patients may receive additional reinduction if during their most recent post cycle 4 imaging disease control is observed without severe (grade >3) toxicity.

1. Patients with at least 1 liver metastasis treatable with SBRT at 50 Gy in 4 fractions will be assigned based on the investigators discretion to:

Treatment group 1) Concurrent (early) ipilimumab and SBRT: 50 Gy in 4 fractions to liver lesion(s).
Treatment group 2) Sequential (late) Ipilimumab x2→ SBRT→ Ipilimumab x2: 50 Gy in 4 fractions to liver lesion(s).
2. Patients with at least 1 lung metastasis treatable to SBRT at 50 Gy in 4 fractions will be assigned based on the investigators discretion to:

Treatment group 3) Concurrent (early) ipilimumab and SBRT: 50 Gy in 4 fractions to lung lesion(s).
Treatment group 4) Sequential (late) Ipilimumab x2→ SBRT→ Ipilimumab x2: 50 Gy in 4 fractions to lung lesion(s).
3. Patients with either 1 liver or lung metastasis not treatable with SBRT at 50 Gy in 4 fractions due to dose constraint violation, treating physician judgment of unacceptable normal tissue toxicity, or an adrenal metastasis will be assigned to:

Treatment group 5) Sequential (late) Ipilimumab x2→ SBRT→ Ipilimumab x2: 60 Gy in 10 fractions to target lesion(s).

Concurrent (early) SBRT and Ipilimumab (Treatment groups 1 and 3):

DAY 2-5: Stereotactic body radiation therapy (SBRT) directed at 1-4 targetable liver or lung lesion(s) or to a single adrenal lesion administered at the maximum tolerated dose (MTD). This will begin at 50 Gy/ 12.5 Gy daily for 4 days (treatment groups 1 and 3) and reduced as detailed in the table below. To minimize treatment breaks, patients should start radiation on a Monday.**DAY 1-21:** Ipilimumab (Yervoy™) therapy at 3 mg/kg will be given on day 1 as a 90 minute intravenous dose in an outpatient setting. Dose cycles will be repeated every 21 days: on days 22, 43, and 64 for a total of 4 cycles.

Sequential (late), Ipilimumab x2→ SBRT→Ipilimumab x2 (Treatment groups 2, 4 and 5):

DAY 30-33: SBRT directed at 1-4 targetable liver or lung lesion(s) administered at the MTD. To minimize treatment breaks, patients should start radiation on a Monday. For patients in group 5 SBRT will also start on day 30 and completed on day 41.

DAY 1-21: Ipilimumab (Yervoy™) therapy at 3 mg/kg will be given on day 1 as a 90 minute intravenous dose at 3mg/kg in an outpatient setting. Ipilimumab dose cycles will be repeated every 21 days: on days 1, 22, 43, and 64 for a total of 4 loading cycles.

Dose De-escalation

Dose Level	SBRT 50 Gy in 4 fractions (Treatment Groups 1-4)	SBRT 60 Gy in 10 fractions (Treatment Group 5)	Ipilimumab dose (Treatment Groups 1-5)
1	50 Gy in 12.5 Gy / fraction for 4 fractions	60 Gy in 6 Gy / fraction for 10 fractions	3mg/kg intravenous every 21 days
-1	37.5 Gy in 12.5 Gy / fraction for 3 fractions	48 Gy in 6 Gy / fraction for 8 fractions	3mg/kg intravenous every 21 days
-2	25 Gy in 12.5 Gy / fraction for 2 fractions	36 Gy in 6 Gy / fraction for 6 fractions	3mg/kg intravenous every 21 days

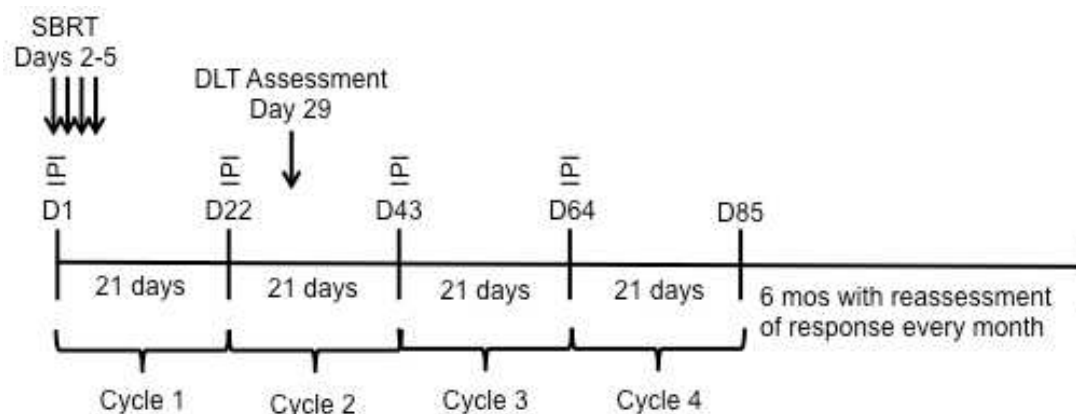


Diagram of Treatment Schedule for Concurrent (early) SBRT and Ipilimumab Dose De-Escalation Study (Treatment groups 1 and 3).

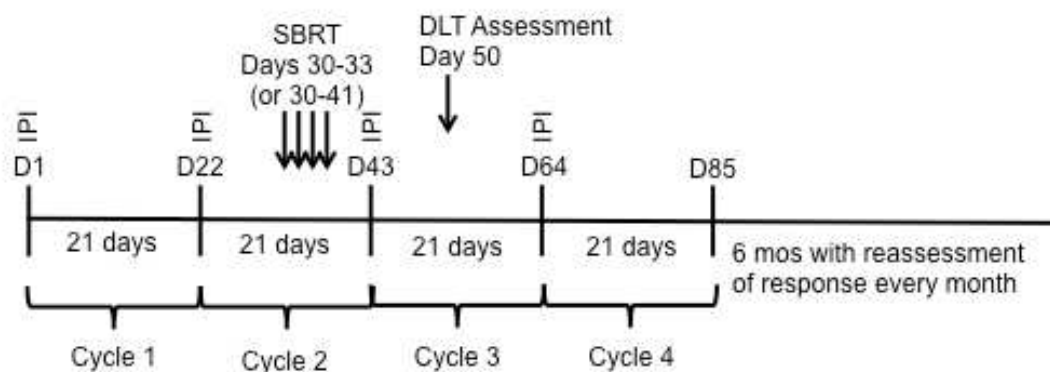


Diagram of Treatment Schedule for Sequential (late) (Ipilimumab x2 then SBRT followed by Ipilimumab x2) Dose De-Escalation Study (Treatment groups 2, 4 and 5).

Thyroid expansion cohort: An additional 20 patients with thyroid cancer (any histology) will be enrolled into a separate phase II analysis. Patients enrolled in this arm will be treated to a total dose of 50 Gy in 4 fractions, 60 Gy in 10 fractions, or 20 Gy in 5 fractions with stereotactic radiotherapy to a liver or lung lesion. Low dose radiation will be allowed on the other lesions (to help pull in the activated T cells). This will consist of a single dose of radiation on the last day of radiation in which the primary tumor is being treated. This low dose radiation will use a range of doses (from 200cGy-30cGy). The choice of radiation dose will be at the discretion of the treating radiation oncologist. This choice is based on the radiation target coverage with the goal of achieving >90% prescription dose coverage of the planning treatment volume while taking into account the dose tolerance of the adjacent organs. Dose constraints of adjacent organs is based on standard RTOG and institutional constraints. The choice of liver or lung lesion will be at the discretion of the treating radiation oncologist. Radiation sequencing with ipilimumab in this expansion arm will be sequential (as described above). A separate analysis will be conducted focusing on thyroid cancer patients, including those patients from this study in addition to thyroid cancer patients enrolled on the rest of this protocol.

2. Objectives

2.1. Primary Objectives

- a) To evaluate the safety and toxicity profile of intravenous ipilimumab (3mg/kg, Yervoy™) administered in combination with stereotactic body radiation therapy (SBRT) targeting 1-4 liver lesion(s) for patients with metastatic cancers.
- b) To evaluate the safety and toxicity profile of intravenous ipilimumab (3mg/kg, Yervoy™) administered in combination with stereotactic body radiation therapy (SBRT) targeting 1-4 lung lesion(s) for patients with metastatic cancer.
- c) To evaluate the safety and toxicity profile of intravenous ipilimumab (3mg/kg, Yervoy™) administered in combination with stereotactic body radiation therapy (SBRT) targeting 1 adrenal lesion for patients with metastatic cancer.
- d) To determine the Maximum Tolerated Dose (MTD) and Dose Limiting Toxicities (DLT) of ipilimumab (3mg/kg) and SBRT (adjustable dose) combination therapy.

2.2. Secondary Objectives

- a) To determine antitumor activity of ipilimumab therapy with SBRT treatment for 1-4 lung lesions in both the SBRT treated lesion and non-irradiate tumors.
- b) To determine antitumor activity of ipilimumab therapy with SBRT treatment for 1-4 liver lesions in both the SBRT treated lesion and non-irradiate tumors.
- c) To determine antitumor activity of ipilimumab therapy with SBRT treatment for 1 adrenal lesion in both the SBRT treated lesion and non-irradiate tumors.
- d) To evaluate treatment efficacy comparing different SBRT and ipilimumab treatment regimens (sequential vs. concurrent).
- e) To evaluate treatment efficacy comparing different SBRT treatment sites (liver vs. lung vs. adrenal).
- f) To evaluate treatment efficacy comparing different SBRT treatment sites (50 Gy in 4 fractions or 60 Gy in 6 fractions).
- g) To evaluate the potential predictive potential of tumor-associated and systemic immune biomarkers for therapy effectiveness and toxicity prediction.
- h) To determine the systemic antitumor activity of ipilimumab therapy with SBRT treatment in patients with thyroid cancer.
- i) To evaluate whether skeletal mass, neutrophil, neutrophil to lymphocyte ratio, and tumor bulk are correlated with clinical outcomes and adverse events.
- j) To evaluate whether tumor kinetics in combination with clinical correlates can help determine treatment response. The radiological response and clinical data will be analyzed using mathematical and statistical models to identify prognostic groups.

3. Background

Numerous clinical trials have demonstrated the ability of ipilimumab to induce long-lasting anti-tumor effects through the generation of anti-tumor immune memory (clinical trial results reviewed in (1)). However, such evidence also suggests that ipilimumab monotherapy is effective in a limited proportion of patients. As a result, there has been interest in combining ipilimumab with other therapies including

cytotoxic chemotherapy (dacarbazine) (2) and other checkpoint inhibitors (nivolumab) (3). In addition, recent interest has arisen in the combination of this drug with other treatment modalities, chief among which is radiation. Mounting preclinical evidence suggests that radiation induces a tumor antigen release that activates and primes systemic T-cells for anti-tumor immunity. One manifestation of this immunologic effect is termed the abscopal effect, which refers to systemic disease response outside of the radiation field to control limited local disease. Given that ipilimumab acts through the promotion of T-cell activity, numerous preclinical trials have demonstrated the abscopal effect with the combination of radiation and ipilimumab (4, 5). Exemplifying such a combination, Postow et al. reported marked unexpected systemic disease regression outside of a radiation field designed to palliate a paraspinal lesion in a patient with metastatic melanoma (6). This study and other like it (7) offers intriguing yet anecdotal clinical evidence of the effectiveness of this combination. As a result, numerous phase I/II trials have begun to systematically investigate this effect (8).

3.1. Ipilimumab

T-cell activation is a complex process 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 (9).

Yervoy™ (ipilimumab) monotherapy has been approved for use in the US (March, 2011), the EU (July, 2011) and Australia (July, 2011) for the treatment of patients with unresectable advanced melanoma. Thousands of subjects with several cancer types in 90 completed and ongoing studies, have been treated during its clinical development program, which is focused in melanoma, prostate cancer, lung cancer, and renal cell carcinoma. In melanoma, two Phase 3 studies (**MDX010-20** comparing ipilimumab 3mg/kg to a melanoma-specific vaccine gp100 in pretreated advanced melanoma (10) and **CA184024**, comparing ipilimumab 10mg/kg plus dacarbazine to dacarbazine alone in previously untreated advanced melanoma (2). In addition to one phase I study (Combination nivolumab, anti PD-1 antibody, with ipilimumab(3)) have demonstrated a survival benefit in patients treated with a combination of these two checkpoint inhibitors.

Over half of the patients treated with ipilimumab reported *immune-related adverse events* (irAE) defined as any AE associated with drug exposure and consistent with an immune-mediated event (thought to be a consequence of the intrinsic biological activity of ipilimumab). IrAEs predominantly involve the GI tract (manifested most often as diarrhea or colitis) and skin (pruritus and rash), and less commonly the liver (transaminase elevations), endocrine glands (manifested most often as hypophysitis/hypopituitarism), pulmonary system (cough and pneumonitis) and nervous system (motor neuropathy with or without sensory neuropathy). According to the Investigator's Brochure, most of these irAEs were clinically manageable and reversible with supportive care or corticosteroids.

Efficacy data from Phase I and II studies in melanoma suggest a trend of increasing durability and progression free survival (PFS) rates with increasing doses and duration of exposure to ipilimumab. However, preliminary data suggests that 10mg/kg of ipilimumab is associated with a higher frequency of SAEs and serious (Grade 3 or higher) irAEs than 3mg/kg of ipilimumab (2, 3, 10). It appears that an increased awareness and better management of these side effects has led to a decrease in their severity and an improvement in their control in recent trials. We propose to use ipilimumab at 3 mg/kg dose administered as 4 doses every 3 weeks and will implement a tight safety rule (see section 7.3) to stop the trial in case of excess toxicity.

It is important to note that because ipilimumab works indirectly through stimulation of the immune system by enhancing T-cell activation, its effect on tumor burden may take weeks to months to become apparent. The clinical activity of ipilimumab may manifest, not only as an early objective response, but also as stable disease (SD) with slow, continuous decline of tumor burden toward response and, in some cases, as a late objective response after initial tumor volume increase(11). For example, in one study (MDX010-19) the time to first response ranged from day 40 to day 441(10). Durable responses and SD after treatment with ipilimumab have been observed in several malignancies, including melanoma, prostate and renal cell carcinoma.

3.2. Stereotactic Body Radiation Therapy

The development of precise radiation beam-shaping along with improved algorithms/computing power for target tracking and radiation dosimetry, and new techniques to minimize setup variations has facilitated the implementation of stereotactic body radiation therapy (SBRT). This modality allows for highly conformal treatment with markedly increased radiation doses (>10 Gy per dose). SBRT has been shown to achieve high levels of tumor control with relatively large total doses given over a small number of fractions. This process, termed hypofractionation, results in the delivery of high biological effective dose (BED) while sparing normal tissue toxicities.

In the setting of numerous prospective single arm trials, SBRT has shown efficacy in the control various metastatic disease sites. Herfrath et al reported on a phase I/II clinical trial that achieved local tumor control rates of 81% 18 months following SBRT (14-26 Gy total dose) with no major side effects(12). More contemporary trials have reported even better rates of local control with higher SBRT doses. Rusthoven et al. reported local control rates of 92% at 2 years following SBRT (36-60 Gy)(13). Similar results have been reported in the control of pulmonary metastases, with prospective trials reporting 96% local control in 1-3 pulmonary lesions 2 years following SBRT treatment (48-60 Gy)(14).

In addition to palliation of metastatic disease, SBRT has demonstrated efficacy in the definitive management of early stage I NSCLC. Although the standard of care has been surgical resection, a significant portion of the population is unable to tolerate surgery due to medical comorbidities or refusal due to personal preference. The predominant non-surgical intervention is SBRT in these cases. In a multi-institutional retrospective series, Onishi reported low rates (14.5%) of local progression 2 years following 18-75 Gy definitive SBRT for stage I NSCLC(15). Furthermore, greater control was shown with higher doses. Patients receiving BED ≥ 100 Gy achieved lower rates of local failure (8.1%) and better 3-year overall survival (88.4%) compared with those receiving BED <100 Gy (local failure: 26.4% and overall survival: 69.4%, both $p < 0.05$).

In addition to achieving high rates of local control, radiation therapy has also been shown to promote a potent immunogenic release of tumor antigen and local cytokine release, priming the adaptive immune system towards tumor control(5). Nowhere is this more evident than with SBRT. Complementary to the ability of SBRT to achieve local control, preclinical studies have demonstrated that such high BEDs promote tumor-antigen release, achieving T-cell priming in a manner superior to that seen with conventional fractionation(16, 17). Such immune education has been shown to promote distal disease control (also known as the abscopal effect) both in pre-clinical models and in clinical cases. Clinical descriptions of this phenomenon has been predominately through limited and often sporadic case reports where unexpected and pronounced distal tumor regression is observed outside of SBRT radiation fields (18, 19).

3.3. Rationale and Scientific Impact

Encouraged by mounting evidence, a number of early phase I trials have begun to prospectively investigate the pairing of immune stimulants with radiation to achieve ever more instances of the abscopal effect. Brody et al. reported on 15 patients with advanced stage low-grade lymphomas.

Objective responses in non-irradiated sites were observed in 6 patients following 4 Gy radiation coupled with the injection of a C-G enriched synthetic oligodeoxynucleotide, an established toll-like receptor agonist meant to produce immunostimulation (20). Similar results were observed applying this strategy to treat cutaneous lymphomas(21). Furthermore, Seung et al. treated 11 metastatic melanoma and renal cell carcinoma patients with 60 Gy SBRT given in 3 fractions followed by adjuvant systemic IL-2 administration (22). In this study, complete metabolic resolution in non-irradiated sites was observed in 6 patients with partial responses in 2 others. Assessment of responders found that they exhibited significantly greater frequencies of proliferating CD4+ T-cells expressing an early activated phenotype, providing further evidence of an immune-mediated phenomenon (22).

Focus has increasingly shifted towards combining radiation with the new emerging class of checkpoint inhibitors, chief among these has been as ipilimumab, which has recently been approved for melanoma. In murine models featuring relatively immunogenic tumors, anti-CTLA-4 monoclonal antibodies have been shown to induce immune-mediated regression and specific T-cell memory (23). However, additional immune conditioning in the form of vaccinations or chemotherapy were required to induce anti-tumor immunity in poorly immunogenic tumors (24, 25), a finding corroborated by clinical studies which show a relatively low proportion of patients achieving lasting clinical responses (26). To this end, radiation when coupled with anti-CTLA-4 monoclonal antibody was found to induce a potent immune response in non-immunogenic tumor that were previously unresponsive to anti-CTLA-4 monotherapy(4). A number of preclinical studies conducted by Dr. Demaria's group and others have provided evidence that radiation induced antigen release is a potent immune adjuvant that when combined with anti-CTLA-4 therapy results in profound immune-mediated systemic disease control outside of the radiation field (4, 27).

At least two clinical cases of systemic disease regression have been reported following the combination of ipilimumab with SBRT. Postow et al. reported on a patient with metastatic melanoma who was previously enrolled on a trial with ipilimumab. While receiving maintenance ipilimumab therapy, the patient was treated with SBRT to 28.5 Gy in 3 fractions to palliate a symptomatic paraspinal mass (6). Following 1 month after SBRT, metastatic foci in the right hilum and spleen showed marked regression. A similar report by Hiniker et al. detailed another patient with metastatic melanoma who received SBRT to 54 Gy in 3 fractions to two out of five metastatic liver lesions (7). Follow up imaging noted metabolic resolution of all liver lesions in addition to a left axillary lesion well outside of the radiation field. In light of these pre-clinical and clinical studies, we are optimistic that our study, combining CTLA-4 blockade (ipilimumab) with SBRT, will result in increased anti-tumor responses in both locally irradiated and systemic non-irradiated disease sites.

This phase I/II clinical trial is designed to test the effectiveness of SBRT targeting 1-4 lung or liver lesions concurrent with or followed by systemic ipilimumab in patients with metastatic disease. For all arms of this trial, ipilimumab will be administered at 3 mg/kg every 21 days for 4 cycles. First, a limited dose de-escalation scheme will be implemented to identify the maximum tolerated dose (MTD) for SBRT treatment. Within this dose de-escalation scheme, the first cohort will receive 50 Gy in 12.5 Gy fractions or 60 Gy in 6 Gy fractions with subsequent dose reduction for high rates of MTD. Two different radiation and ipilimumab administration schemes will be tested in parallel: concurrent SBRT and ipilimumab and sequential ipilimumab x2 followed SBRT followed another 2 cycles of ipilimumab. The rationale for adding in SBRT after two cycles of ipilimumab is based on the fundamental observation that ipilimumab can take a few cycles of treatment to induce an immune response. This is supported by the work of Jedd Wolchok which demonstrated that lymphocyte infiltration can take weeks to happen which is one of the fundamental reasons that the standard RECIST criteria are not adequate for assessing responses to checkpoint inhibitors and as such he and others have proved the development of irRC to better assess the delayed immunologic responses seen with ipilimumab.

Based on this work and others we feel that having an arm that giving 2 cycles of ipilimumab prior to SBRT provides a rational way of combining with radiation.

Our hypotheses are as follows: 1) SBRT targeting a limited number of liver or lung metastasis in conjunction with ipilimumab will result in improved local and systemic disease control; 2) that the responsible mechanism of action is through the SBRT mediated release of immunogenic tumor antigens that promotes systemic immune-mediated tumor response that is further potentiated by systemic ipilimumab therapy.

4. Eligibility Criteria

To be eligible for this trial, patients must meet all of the following criteria.

4.1. Inclusion Criteria

1. Patients must have histological confirmation of metastatic cancer with at least one metastatic or primary lesion in the liver, lung, or adrenal gland.
2. Patients who have completed previous systemic therapies 5 drug half-lives or 4-weeks prior to enrollment on study, whichever is shorter. Note: patients with anaplastic thyroid will be waived from this inclusion criteria given the rapid trajectory of their disease.
3. All patients must have at least one metastatic or primary lesion within the lung or liver located in an anatomical location amenable to SBRT treatment with 50 Gy in 4 fractions, or if not, with either a lung, liver, or adrenal lesion treatable to 60 Gy in 10 fractions.
4. Repeat radiation in fields previously radiated will be allowed at the discretion of the treating physician.
5. Age \geq 18 years
6. ECOG performance status \leq 2 (Karnofsky $>$ 60%).
7. Patients must have normal organ and marrow function as defined below:
 - Total bilirubin \leq 2.0 mg/dL. (Does NOT apply to patients with Gilbert's Syndrome)
 - AST(SGOT)/ALT(SGPT) $<$ 2.5 X institutional upper limit of normal (patients with liver involvement will be allowed \leq 5.0 X institutional upper normal limit)
 - WBC \square 2500/uL, ANC \square 1000/uL
 - Platelets \square 75K
 - Hemoglobin \square 9g/dL
 - Creatinine \square 2.0 x ULN
8. Patients must be willing and able to review, understand, and provide written consent before starting therapy.
9. Patients with brain metastasis will be included as long as they *are free of neurologic symptoms related to metastatic brain lesions and who do not require or receive systemic corticosteroid therapy in the 14 days prior to beginning ipilimumab therapy*
10. Patients that have previously progressed on immunotherapy such as ipilimumab will be eligible.

4.2. Exclusion Criteria

1. Serious autoimmune disease at the discretion of the treating attending: Patients with a history of active serious 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. Active diverticulitis, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis or other known risk factors for bowel perforation.
3. 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.
4. 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.
5. Known active HIV, Hepatitis B, or Hepatitis C that has not been documented to be cured.
6. Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to one month prior to or after any dose of ipilimumab).
7. Concomitant therapy with any of the following: IL-2, interferon or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigational therapies; or chronic use of systemic corticosteroids while receiving ipilimumab (as long as steroid replacement is significantly greater than what is required for physiologic replacement, i.e. in hypothyroidism).
8. Pregnant women are excluded from this study. Women of child-bearing potential and men must agree to use contraception prior to study entry and for the duration of study participation. Acceptable forms of birth control include: Birth control pills plus a barrier method, such as a condom or diaphragm, Intrauterine devices (IUD) plus a barrier method, Implantable or injectable birth control (such as NorplantR or epo-ProveraR) started at least 3 months before joining the study, plus a barrier method, or Double-barrier method, such as a condom when used in combination with a diaphragm. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician.
9. History of or current immunodeficiency disease or prior treatment compromising immune function at the discretion of the treating physician.
10. Prior allogeneic stem cell transplantation;

4.3. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. The patient population screened for this study adheres to the referral patterns reported at M.D. Anderson Cancer Center.

5. Ipilimumab Information

5.1. Ipilimumab (Yervoy™): manufactured by Bristol-Myers Squibb Co (BMY).

5.1.1. *Physical/Chemical Properties:*

Ipilimumab is an IgG1 monoclonal antibody. It is a soluble protein consisting of 4 polypeptide chains, 2 identical heavy chains consisting of 467 amino acids and 2 identical light chains consisting of 235 amino acids. It has a projected relative mass (Mr) of 145,424 dalton (d) based on the amino acid sequence.

5.1.2. *Mechanism of Action:*

Ipilimumab is a human immunoglobulin G (IgG1) κ anti-CTLA-4 monoclonal antibody (mAb) that binds to CTLA-4 antigen expressed on the plasma membrane of T cells and blocks the interaction of CTLA-4 with its natural ligands, B7.1 (CD80) and B7.2 (CD86). *In vitro* studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, and does not show any binding to human B7.1, B7.2 negative cell lines, demonstrating by immunohistochemistry that ipilimumab is specific and non-cross reactive in non-human primate tissues.

5.1.3. Pharmacology:

Ipilimumab is a human immunoglobulin G (IgG1) κ anti-CTLA-4 monoclonal antibody (mAb). *In vitro* studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without non-specific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys.

Ipilimumab was originally produced and purified from a hybridoma clone. Subsequently, a transfectoma (CHO cell) has been generated that is capable of producing more ipilimumab on a per cell basis than the hybridoma. Material from the transfectoma will be utilized in this and future ipilimumab clinical studies. Biochemical, immunologic and *in vivo* preclinical primate assessments demonstrated similarity between hybridoma and transfectoma-derived ipilimumab.

5.1.4. Pre-clinical Toxicology

Complete information on the pre-clinical toxicology studies can be found in the ipilimumab Investigator Brochure (IB). Non-clinical toxicity assessments included *in-vitro* evaluation for the potential of ipilimumab to mediate complement-dependent cellular cytotoxicity (CDCC) or antibody-dependent cellular cytotoxicity (ADCC), and toxicology assessments in cynomolgus monkeys alone and in the presence of vaccines.

The *in vitro* studies demonstrated that ipilimumab did not mediate CDCC of PHA- or (CD)3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 μ g/mL. These data are consistent with the requirement of high levels of antigen expression on the surface of target cells for efficient ADCC or CDCC. Since ipilimumab is a human IgG1, an isotype generally capable of mediating CDCC and ADCC, the lack of these activities is likely due to a very low expression of CTLA-4 on activated T cells. Therefore, these data suggest that ipilimumab treatment would not result in depletion of activated T cells *in vivo*. Indeed, no depletion of T cells or T cell subsets were noted in toxicology studies in cynomolgus monkeys.

No mortality or signs of toxicity were observed in three independent 14-day intravenous toxicology studies in cynomolgus monkeys at multiple doses up to 30 mg/kg/dose. Furthermore, ipilimumab was evaluated in sub chronic and chronic toxicology studies in cynomolgus monkeys with and without hepatitis B (HepB) and melanoma vaccine. Ipilimumab was well tolerated alone or in combination in all studies. There were no significant changes in clinical signs, body weight values, clinical pathology values or T-cell activation markers. In addition, there were no significant histopathology changes in the stomach or colon.

5.1.5. Pharmacokinetics of Ipilimumab in Patients

Pharmacokinetic (PK) profiles for ipilimumab have been analyzed. The primary objective of Protocol MDX-010-015 was to determine the safety and PK profile of single and multiple doses of ipilimumab derived from a transfectoma or hybridoma cell line. This study is still ongoing and data is

preliminary. Mean plasma concentrations of ipilimumab administered at dosages of 2.8 mg/kg (transfectoma-derived drug product), 3 mg/kg (hybridoma-derived drug product), 5 mg/kg and 7.5 mg/kg (transfectoma) appear to be dose-proportional over time. Preliminary PK analyses reveal that the volume variables were approximately that of plasma volume (range of mean apparent volume of distribution at steady state [V_{ss}] across cohorts 2.8, 3, 5, 7.5, 10, 15 and 20 mg/kg was 57.3 to 82.6 mL/kg), indicating drug distribution was mostly limited to the intravascular space. The clearance (Cl) was low (range 0.11 to 0.29 mL/h/kg) and reflective of the half-life (range 297 to 414 h). Mean residence time (MRT) was long (range 435 to 538 h), consistent with the long terminal disposition phase of ipilimumab. In general, there was moderate variability in the PK parameters among patients, with coefficient of variation (CV) of 11% to 48% in AUC (0-21d), 20% to 59% in Cl and 17% to 46% in ss. Future clinical studies, including this study, will utilize the transfectoma derived product.

5.1.6. Clinical Safety

The safety profile of ipilimumab has been consistent across trials with a) the majority of adverse events being inflammatory in nature and consistent with the proposed mechanism of action of ipilimumab (immune-related adverse events, IRAEs), b) the same types of such immune-mediated events in the GI tract, skin, liver, and endocrine system being reported and c) most of these events being manageable with immune suppressive therapies. Overall, nearly all subjects in clinical studies with ipilimumab reported AEs of any grade and most reported at least 1 AE that was considered treatment related.

1. Details of Drug-Related Aes and SAEs:

Drug-related adverse events (Aes) have been reported in studies with ipilimumab as monotherapy as well as in combination studies with vaccines, cytokines, chemotherapy, and other checkpoint inhibitors.

The AE profile of ipilimumab is relatively well characterized with drug-related Aes mostly being immune-related adverse events (IRAEs), which are considered to be associated with the mechanism of action of ipilimumab. The most common IRAEs are colitis and diarrhea, rash, pruritus, deficiencies of endocrine organs (pituitary, adrenal, or thyroid), hepatitis, or uveitis. Rare complications (all <1%) are ocular inflammation, arthritis/arthralgias, autoimmune meningitis, autoimmune nephritis, pure red cell aplasia, polymyositis, infusion reaction, myasthenia gravis, and bowel perforations resulting from underlying severe colitis, which have required surgical intervention.

Drug-related Grade 3 or 4 serious Aes (SAEs) consist mostly of immune-related SAEs and include: rash/desquamation, pruritus, uveitis, speech impairment, abdominal pain, diarrhea/colitis, nausea/vomiting, transaminase elevation, adrenal insufficiency, and panhypopituitarism. Please refer to the most recent version of Investigator's Brochure (IB) for the latest update on SAEs.

5.1.7. Immune-Related Adverse Events (IRAEs):

Many of the adverse events considered related to ipilimumab appear to be immune in nature and presumably a consequence of the intrinsic biological activity of ipilimumab. An immune-related adverse event (IRAE) is defined as any adverse event associated with drug exposure and consistent with an immune-mediated phenomenon. Disease progression, infections and other etiologic causes are ruled out or deemed unlikely as contributing to the event. Supportive data, such as autoimmune serology tests or biopsies, are helpful but not necessary to deem an event an IRAE. Events of unclear etiology which were plausibly "immune mediated" have been conservatively categorized as IRAEs even if serologic or histopathology data are absent. These IRAEs likely reflect

a loss of tolerance to some self antigens or an unchecked immune response to gut or skin flora. Some breakthrough of immunity may be inseparably linked to the clinical antitumor activity of ipilimumab.

Pooled analysis of phase II and III trials of ipilimumab in patients with advanced melanoma showed the following: Of 622 subjects treated with 3mg/kg ipilimumab, 56.8-61.3% reported any IRAEs, 6.3-13% reported Grade 3/4 IRAEs and 0.8-1.1% reported Grade 5 IRAEs. Of 325 patients treated with 10mg/kg ipilimumab, 84.3% reported any drug related AE, and 30.5% reported Grade 3/4 IRAEs (IB v 16).

- 1. Immune-related gastrointestinal events:** GI IRAEs occurred in 28.2-31.1% (Grade 3/4 4.5-7.6%, Grade 5 0-0.9%) of subjects treated with 3mg/kg of ipilimumab and in 36.3% (Grade 3/4: 11.7%; Grade 5: 0%) of subjects treated with 10mg/kg of ipilimumab. The clinical presentation of GI IRAEs included diarrhea, increase in the frequency of bowel movements, abdominal pain or hematochezia, with or without fever. Among approximately 10,000 subjects in the BMS internal safety database, 0.5% (51/10,000) reported colitis that was unresponsive to medical management and necessitated colectomy, or had bowel wall perforations associated with ipilimumab-induced colitis. Fourteen of the 51 subjects died of bowel wall perforation complications. Patients should be carefully monitored for GI symptoms that may be indicative of immune-related colitis, diarrhea or GI perforation. Diarrhea or colitis occurring after initiation of ipilimumab therapy should be evaluated to exclude infectious or alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic infiltration. GI IRAEs should be monitored until resolution.
- 2. Inflammatory hepatotoxicities:** Hepatic IRAEs were reported in 2.1-3.8% (Grade 3/4: 0-2.3%; Grade 5: 0-0.8%) subjects treated with 3mg/kg of ipilimumab and in 8% (Grade 3/4: 6.8%, Grade 5: 0%) of patients treated with 10mg/kg of ipilimumab. Hepatic IRAEs were mostly clinically silent and manifested as transaminase or bilirubin laboratory abnormalities. Fatal hepatic failure has been reported in clinical trials of ipilimumab. Serum transaminase and bilirubin levels must be evaluated before each dose of ipilimumab as early laboratory changes may be indicative of emerging immune-related hepatitis. Evaluations to exclude other causes of hepatic injury, such as infections, disease progression or medications should be undertaken, Liver function abnormalities should be monitored until resolution. Liver biopsies from subjects who had IR hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).
- 3. Endocrine toxicities:** Endocrine IRAEs were reported in 3.4-7.6% (Grade 3/4: 0.9-3.8%, Grade 5: 0%) of subjects receiving 3mg/kg of ipilimumab and in 6.2% (Grade 3/4: 2.5%; Grade 5: 0%) of subjects receiving 10mg/kg of ipilimumab. Ipilimumab can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, and adrenal insufficiency and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease. The most common presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, electrolyte disturbances and hypotension. Adrenal crisis as a cause of the patient's symptoms should be excluded. Based on the available data with known outcome, most of the subjects symptomatically improved with hormone replacement therapy. It is possible that long-term hormone replacement therapy will be required for subjects developing hypophysitis/hypopituitarism after treatment with ipilimumab.
- 4. Dermatologic toxicities:** Skin IRAEs were reported in 38.9-42.3% (Grade 3/4 0.8-2.4%, Grade 5 0) of subjects receiving 3mg/kg of ipilimumab and in 51.4% (Grade 3/4: 2.5%; Grade 5:0%) of subjects receiving 10mg/kg of ipilimumab. Skin IRAEs presented mostly as a rash and/or pruritus. Some subjects reported vitiligo associated with ipilimumab administration. Fatal toxic epidermal necrolysis has been reported in clinical trials of ipilimumab.

- 5. Neurological toxicities:** Neurological irAEs were reported in 0-0.5% (Grade 3/4: 0-0.3%, Grade 5: 0-0.3%) of subjects receiving 3mg/kg of ipilimumab and in 0.3% (Grade 3/4: 0%; Grade 5: 0%) of subjects receiving 10mg/kg of ipilimumab. Neurological manifestations included muscle weakness and sensory neuropathy. Among approximately 10,000 subjects treated in the ipilimumab program as of 24-Jun-2011, 11 (0.1%) cases of Guillain-Barre syndrome and 5 (0.05%) cases of myasthenia gravis considered related to study drug were reported, and 2 of the Guillain-Barre syndromes had a fatal outcome. Patients may present with muscle weakness. Sensory neuropathy may also occur. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 days should be evaluated and non-inflammatory causes such as disease progression, infections, metabolic syndromes and medications should be excluded.
- 6. Other toxicities:** Other irAEs were reported in 2.3-3.8% (Grade 3/4: 0.8-1.5%, Grade 5: 0-0.3%) of subjects receiving 3mg/kg of ipilimumab and in 5.2% (Grade 3/4: 2.2%; Grade 5: 0.6%) of subjects receiving 10mg/kg of ipilimumab. Ocular inflammation, manifested as Grade 2 or Grade 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects (<1%) and occasionally occurred in the absence of clinically apparent GI symptoms. Other presumed irAEs reported include, but were not limited to, arthrititis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, noninfective myocarditis, polymyositis, and myasthenia gravis, of which were individually reported for <1% of subjects.

5.1.8. Onset and Resolution of irAEs:

The median time to onset of Grade 3-5 irAEs in MDX010-20 and Phase 2 studies was 7 to 9 weeks. The time to onset of irAEs was comparable between the 3- and 10-mg/kg doses. With the recommended treatment guidelines, the median times to resolution of Grades 3-4 irAEs was 4 to 8 weeks. The time to resolution of irAEs was comparable between the 3 and 10-mg/kg doses.

5.1.9. Ipilimumab Dose-dependent Safety Profile

In MDX010-20, immune-related adverse events (irAEs) occurred in 60% of subjects treated with ipilimumab (**3mg/kg**) and \geq Grade 3 events occurred in 12-16%. Treatment related Aes leading to discontinuation of therapy were reported in 9.9% of the ipilimumab monotherapy arm vs 3.0% of the gp100 monotherapy arm. The most common (>1%) treatment related Aes leading to discontinuation in the ipilimumab monotherapy arm were colitis (2.3%), diarrhea (1.5%), and uveitis (1.5%). In a pooled 3mg/kg group from the Phase 2 studies, 8.1% of subjects reported treatment-related Aes leading to discontinuation. The most common were hypopituitarism (2.7%), colitis (1.8%), and decreased appetite (1.8%). In MDX010-20, treatment-related deaths (defined as a treatment-related AE with an outcome of death, reported at any time during the study) were reported in 4 subjects (3.1%) in the ipilimumab monotherapy group, 8 subjects (2.1%) in the ipilimumab plus gp100 group and 2 (1.5%) subjects in the gp100 monotherapy group.

In CA184024, any irAEs occurred in 76% of subjects treated with ipilimumab (**10mg/kg**) + DTIC, Grade 3 events were reported in 31.6% and Grade 4 events in 10.1%. Treatment-related SAEs were reported for 47% and 6.8% in the ipilimumab plus DTIC and DTIC monotherapy groups respectively. The most common events in the ipilimumab plus DTIC group were increased ALT and AST (19% each). Other SAEs reported in \geq 5% of subjects in the ipilimumab plus DTIC group included diarrhea (6.5%) and pyrexia (5.7%). There were no treatment-related Aes with an outcome of death in the ipilimumab plus DTIC group and 1 (0.4%) in the DTIC group (GI hemorrhage). In a pooled analysis of 325 patients receiving 10mg/kg ipilimumab therapy, Aes (any grade) were

reported in 96.9%, Grade 3-4 Aes in 37.5%, related Aes in 84.3%, Grade 3-4 related Aes in 30.5%, SAEs in 51.7%, related SAEs in 29.2%.

In **CA184022**, 3 dose levels of ipilimumab were studied, including 0.3 (n=72) vs 3 (n=71) vs 10mg/kg (n=71). Overall irAEs were reported in 64.8% and 70.4% of patients treated at 3mg/kg and 10mg/kg respectively, Grade 3-4 irAEs were reported in 7% and 25.4% respectively, GI irAEs in 32.4% and 39.4% respectively, Grade 3-4 GI irAEs in 2.8% and 15.5% respectively, hepatic grade 3-4 irAEs in 0% and 2.8% respectively, endocrine Grade 3-4 irAEs in 2.8% and 1.4% respectively and skin Grade 3-4 irAEs in 1.4% and 4.2% respectively.

In summary, the safety profile of ipilimumab 10mg/kg remains consistent with the low-dose safety profile in that most of the treatment-related SAEs are characteristic of immune-related toxicity, and most of the IRAEs are reported in the GI, hepatic and endocrine systems. However, the frequency of IRAEs, particularly of high grade events, is higher with 10mg/kg of ipilimumab at multiple doses compared with the IRAE frequency reported for lower doses.

5.1.10. Drug Related Deaths:

Based on the data available in the BMS internal safety database as of 24-June-2011, study-drug related deaths based on the investigator's assessment were reported in 82 subjects. Therefore, the reported rate of treatment-related deaths from the program-wide studies was approximately 0.8% (82/10,000). While a causal role of ipilimumab in these 82 deaths could not be ruled out, confounding factors could be identified in most of these cases.

5.1.11. Clinical Efficacy:

Ipilimumab prolonged survival in subjects with pre-treated and previously untreated advanced melanoma, based on results from 2 large, multinational, double-blind, Phase 3 studies (MDX010-20 and CA184024), supported by data from Phase 2 studies.

In prostate cancer, ipilimumab is being evaluated in Phase 1 and 2 studies, as well as in a randomized Phase 3 trial. Although sample sizes were small, response as measured by $\geq 50\%$ decline in PSA have been reported. Responses were durable, ranging between 2 and 24 months.

5.1.12. Association between safety (IRAEs) and efficacy (OS):

Results from MDX010-20 suggested a tendency for improved OS in subjects with any IRAEs. In CA184024, analyses using the Cox proportional hazards model were conducted to assess the association of IRAEs and OS. Overall, the results showed a significant improvement in OS in subjects with Grade 3/4 IRAEs (any Grade 3/4: HR 0.23 [95% CI: 0.10, 0.54]; liver Grade 3/4: HR 0.25 [95% CI: 0.10, 0.65])(28). These results should be interpreted with caution, as the analysis was not adjusted for other prognostic factors.

Based on the current clinical experience with the use of corticosteroids for the management of treatment-emergent IRAEs, corticosteroids do not adversely affect the antitumor response in subjects with objective responses and concomitant serious IRAEs(29).

5.1.13. Formulation

Ipilimumab injection, 50mg/vial (5mg/mL) is formulated as a clear, colorless, sterile, non-pyrogenic, single-use, isotonic aqueous solution which may contain particles. It is supplied in 10-cc Type I flint glass vials stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5mg/mL at a pH of about 7.

Each 50mg vial contains: 52.5mg Ipilimumab drug substance, 61.32mg sodium chloride USP, 33.10mg TRIS-hydrochloride, 0.4126mg diethylenetriamine pentacetic acid, 105mg mannitol USP, 1.05mg polysorbate 80 (plant-derived) 10.5mL water for injection USP qs to.

Table 1: Ipilimumab Drug Information

Unit	Route	Appearance
Ipilimumab 5mg/ml, 10 mg or 40 mg vial	IV Infusion	Clear, colorless sterile solution in a single-use 10 ml or 40 mL vial

5.1.14. Packaging and Labeling

Ipilimumab available at a concentration of 5 mg/mL in single use vials containing 10 ml (NDC 0003-2327-11) or 40 mL (NDC 0003-2328-22) solution.

5.1.15. Storage, Handling and Dispensing of Ipilimumab

1. Storage

Ipilimumab should be stored in a secure area according to local regulations.

The Investigator should ensure that the ipilimumab is stored in accordance with the environmental conditions (temperature, light and humidity) as determined by BMS and defined in the Investigator Brochure or SmPC/reference label.

Ipilimumab must be stored at a temperature $\leq 2^{\circ}\text{C}$ and $\leq 8^{\circ}\text{C}$. Do not freeze. Protect from light.

2. Handling and Disposal

As with all, injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.

If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water.

After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

3. Dispensing

It is the responsibility of the Investigator to ensure that ipilimumab is only dispensed to study subjects. The ipilimumab must be dispensed only from official study sites by authorized personnel according to local regulations.

4. Destruction of Ipilimumab:

If ipilimumab is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

5. Preparation of Ipilimumab

Ipilimumab injections will be prepared per the Package Insert.

Do not draw into each vial more than once. Any partial vials should be safely discarded and should not be stored for reuse.

Ipilimumab is administered as an IV infusion only.

6. Administration

Ipilimumab will be administered as an IV infusion at doses of 3 mg/kg dose over 90 (+/-10) minutes with a 10 cc normal saline flush at the end.

Dose Calculations

Total dose should be calculated as follows:

Subject body weight in kg x 3 mg = total dose, mg Total infusion volume should be calculated as follows:

Total dose in mg ÷ 5 mg/mL = infusion volume, mL

Rate of infusion should be calculated as follows:

Infusion volume in mL ÷ 90 minutes = rate of infusion, mL/min

For example, a patient weighing 114 kg (250 lb) planned to receive 3 mg/kg of the study drug would be administered 342 mg of ipilimumab (114 kg x 3 mg/kg = 342 mg) with an infusion volume of 68.4 mL (342 mg ÷ 5 mg/mL = 68.4 mL) at a rate of approximately 0.8 mL/min (68.4 mL ÷ 90 minutes) in 90 minutes.

15.1.16 Withholding Dose Due to Toxicities Likely Attributable to Ipilimumab

Doses may "withheld" for a 21 days after which time the decision must be made by the principle investigator whether to withhold for an additional study (see criteria below), withdraw the patient from the study, or to continue with the next cycle: *Example: it may be necessary to withhold (maximum 21 days) an ipilimumab dose for the following adverse event(s) considered related to ipilimumab:*

Any Grade 2 non-skin related adverse event except for laboratory abnormalities

Any ≥ Grade 3 laboratory abnormality.

It is necessary to withhold (maximum 21 days) ipilimumab dosing for the following adverse events:

Any ≥ Grade 3 skin-related adverse event regardless of causality;

Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, warrants withholding the dose of study medication.

A dose withholding longer than 21 days after the scheduled dose will lead to permanent discontinuation.

Criteria to Resume Ipilimumab therapy addressed:

When the adverse event(s) resolve(s) to Grade 1 or baseline value, and for endocrinopathies which are controlled with chronic therapy:

Restart dosing at the next scheduled time point per protocol.

If the adverse event has not resolved in the protocol-specified dosing window (ie, 3 weeks from last dose ± 2 days), the next scheduled dose will be withheld.

15.1.17 Drug ordering:

Please see Appendix A for information on provisions for ordering ipilimumab from BMS
It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time.
It is imperative that only product designated for this protocol be used for this study.

6. Radiation Information

6.1. Dosimetry

All patients will receive stereotactic body radiation therapy (SBRT) for a total dose of 50 Gy with 12.5 Gy/fraction in 4 fractions or 60 Gy in 10 fractions prescribed to the planning target volume (PTV). Dose de-escalation will be achieved through sequential SBRT dose reduction by 1 (from the 50 Gy group) or 2 (from the 60 Gy group) fractions for high rates of DLTs. It is required that the prescribed isodose line should cover 100% of the internal gross tumor volume (IGTV) in all cases. It is recommended that prescribed isodose line cover more than 95% of the PTV if normal tissue dose is within threshold (as defined in 6.5). In the event that normal tissue dose is considered unacceptably high when treated with 50 Gy in 4 fractions, then patients can be alternatively treated with 60 Gy in 10 fractions. For central lung lesion close to critical structures, compromised PTV coverage is allowed in order to meet normal tissue dose constraints. In this case, treating physician should make clinical judgments regarding optimal target coverage and normal tissues sparing.

There is no or little aperture margin recommended. The external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, which typically ranges from 70-95%. However, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. Heterogeneity correction should be applied for planning.

6.2. Radiation Technique

Patients will be evaluated for regularity of breathing, responsiveness to feedback guidance, breath-hold capability. Based on this evaluation, a treatment delivery technique will be selected among the following:

1. Breath-hold (with or without feedback guidance).
2. Gated treatment.
3. Free-breathing (with or without feedback guidance).
4. Abdominal compression.
5. A combination of the above techniques.

A CT scan obtained using the same method of respiratory management as intended for treatment will be required for treatment planning purposes. This includes 4-dimensional CT (4DCT) for free-breathing, gated or abdominal compression techniques or repeated breath-hold CTs for breath hold techniques. Feedback guidance, including visual and/or audio techniques, will be used for all patients who would both benefit from and respond to training with such devices.

4DCT is a fast CT scan that capable of imaging tumor position during the entire breath cycle. A CT scan is obtained with the patient in each couch position for a whole breath cycle (usually lasting 5 to 6 seconds in each position) followed by repositioning to the next couch position. Following a scan, the computer resorts all images and reconstructs the tumor positions for an entire breath cycle, i.e., a movie file is

created which captures organ movement throughout the breath cycle. Radiotherapy will be designed based on the path of organ motion captured by 4DCT.

6.3. Target Volumes

1. Gross Target Volume (GTV): Gross tumor as observed on a non-contrast CT should be delineated on lung (for lung tumors) or abdominal (for liver or adrenal tumors) windows from either 4DCT or repeated breath-hold CTs (see IGTV below).

2. Internal Gross Target Volume (IGTV): IGTV is the volume containing the GTV throughout its motion during respiration or positional variability during repeated breath holds. The motion during free breathing (with or without abdominal compression) will be determined from 4DCT, the variability of tumor location during breath hold will be determined by repeated breath hold CTs obtained on the same day. One method to combine the data from the multiple CT datasets is to create a maximal intensity projection (MIP) that is used as an aid to contour the IGTV. All CT datasets will be transferred to the treatment planning system for reference.

3. Clinical Target Volume (CTV) + Planning Target Volume (PTV): GTV plus 5-10 mm margin (based on physician discretion). Due to tight PTV margin, CTV margin is not recommended to be edited except when normal tissue toxicity is concerning based on treating physician's judgment. The prescribed dose of radiation (either 50 Gy or 60 Gy) will be dosed to the PTV, we recommend 95% coverage if possible.

6.4. Daily treatment Setup:

The appropriate immobilization will be chosen for each patient. Most patients will be immobilized with arms up using a commercially available vacuum immobilization bag that extends from the patient's head to their pelvis combined with a wing board.

On-board imaging: Daily on-board imaging such as CT on-rails, cone beam CT, or 4-D cone beam CT will be conducted prior to each radiation fraction. Position adjustment and target coverage confirmation will be performed daily based on imaging study. The setup uncertainty will be kept to less than a 3 mm (2 s) variation. This value is based on the uncertainties of the couch readouts added in quadrature with $\frac{1}{2}$ the voxel size of the CT. Adjustment of patient position is needed if target coverage is judged by the treating physician to be inadequate and/or critical normal tissues toxicity is concerning. Repeated on-board CT after position adjustment is recommended if more than 5 mm shift is conducted.

6.5. Dose Volume Constraints

Maximum doses allowed in radiation planning are as outlined below. In the event that a treatment plan cannot reasonably meet dose constraints for 50 Gy in 4 fractions (or the corresponding dose de-escalation), then a separate plan will be generated for 60 Gy in 10 fractions. In the event that the subsequent treatment plan cannot reasonably meet dose constraints for 60 Gy in 10 fractions (or the corresponding dose de-escalation), then this patient is ineligible for this study, pending treating physician judgement.

50 Gy in 4 fractions dose constraints:

- Spinal Cord: 25 Gy \leq 1 cc
- Lung: V20 \leq 20%, V10 < 30%, V5 < 40%
- Esophagus: 40 Gy \leq 1 cc, 36 Gy \leq 10 cc
- Trachea: 40 Gy \leq 1 cc, 36 Gy \leq 10 cc
- Main bronchus and bronchial tree: 48 Gy \leq 1 cc, 40 Gy \leq 10 cc
- Heart: 48 Gy \leq 1 cc, 40 Gy \leq 10 cc

- Brachial plexus: 40 Gy \leq 1 cc, 35 Gy \leq 10 cc
- Major vessels: 48 Gy \leq 1 cc, 40 Gy \leq 10 cc
- Skin (defined as outer 0.5 cm of body surface): 40 Gy \leq 1 cc, 35 Gy \leq 10 cc
- Kidney: 8.4Gy to 200cc

60 Gy in 10 fractions dose constraints:

- Spinal Cord: 40 Gy \leq 1 cc
- Lung: V20 \leq 20%, V10 < 30%, V5 < 50%
- Esophagus: 60 Gy \leq 1 cc, 40 Gy \leq 10 cc
- Trachea: 70 Gy \leq 1 cc, 60 Gy \leq 10 cc
- Main bronchus: 70 Gy \leq 1 cc, 60 Gy \leq 10 cc
- Heart: 70 Gy \leq 5 cc, 50 Gy \leq 10 cc
- Brachial plexus: 50 Gy \leq 1 cc, 40 Gy \leq 10 cc
- Major vessels: 70 Gy \leq 5 cc, 60 Gy \leq 10 cc
- Skin (defined as outer 0.5 cm of body surface): 60 Gy \leq 1 cc, 50 Gy \leq 10 cc
- Kidney: V50 \leq 33%

For patients who have received previous radiotherapy, the attending radiation oncologist is required to evaluate the previous treatment plan, particularly the dose delivered to critical structures and make a clinical judgment based on BED, previous radiation therapy, and current SBRT doses using above dose volume constraints as a guide.

7. Treatment Plan

Notice: Treatment schedules shall have a standing window of allowance of +/- 3 days unless patient/logistical/medical reasons intervene. Any treatment day that falls on a weekend or holiday will be scheduled on the next business day. Patients will undergo a therapy wash out period of 5 drug half-lives or 4-weeks whichever is shorter.

Any treatment day (radiation or ipilimumab administration) that falls on a weekend or holiday will be scheduled on the next business day. For treatment or dose modification questions, please contact Chad Tang, MD by pager (713-606-3929) or e-mail (ctang1@mdanderson.org), Aung Naing, MD by phone (713-792-2950) or e-mail (anaing@mdanderson.org), James Welsh, MD by phone (713-563-2447) or e-mail (jwelsh@mdanderson.org), or David Hong, MD by phone (713-563-5844) or e-mail (dshong@mdanderson.org). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

7.1. Agent Administration and SBRT Dose and De-Escalation

Following enrollment, patients will be categorized into 1 of 5 treatment groups (listed below). All treatment groups will receive ipilimumab (Yervoy™) at a dose of 3 mg/kg every 21 days for a total of 4 doses. In the event that patients meet criteria for multiple groups (i.e. exhibit treatable liver, lung, and adrenal metastasis), patient will be assigned to one group based treating physician preference guided by SBRT dosimetric considerations. Assignment may include evaluation of competing treatment plans with attention to normal tissue toxicities.

In the event that a treatment plan cannot reasonably meet dose constraints for 50 Gy in 4 fractions, then a separate plan will be generated for 60 Gy in 10 fractions. In the event that the subsequent treatment plan cannot reasonably meet dose constraints for 60 Gy in 10 fractions, then this patient is ineligible for this study.

1. Patients with at least 1 liver metastasis treatable with SBRT at 50 Gy in 4 fractions will be assigned based on the investigators discretion to:

Treatment group 1) Concurrent ipilimumab and SBRT: 50 Gy in 4 fractions to 1-4 liver lesion(s).

Treatment group 2) Sequential Ipilimumab x2→ SBRT→ Ipilimumab x2:

2. Patients with at least 1 lung metastasis treatable to SBRT at 50 Gy in 4 fractions will be assigned based on the investigators discretion to:

Treatment group 3) Concurrent ipilimumab and SBRT: 50 Gy in 4 fractions to 1-4 lung lesion(s).

Treatment group 4) Sequential Ipilimumab x2→ SBRT→ Ipilimumab x2:

3. Patients with either 1 liver or lung metastasis not treatable to SBRT at 50 Gy in 4 fractions or an adrenal metastasis will be assigned to:

Treatment group 5) Sequential Ipilimumab x2→ SBRT→ Ipilimumab x2 SBRT will be 60 Gy in 10 fractions to 1-4 lung, liver, or adrenal lesion (s).

Table 2: Independent Cohorts

Metastatic or primary lesion amenable to SBRT treatment

	Liver lesion treatable with 50 Gy / 4 Fc (n=40)	Lung lesion treatable with 50 Gy / 4 Fc (n=40)	Liver/lung lesion not treatable with 50 Gy/ 4 Fc or adrenal lesion (n=20)
Treatment Sequence	Concurrent: SBRT (50 Gy/ 4 Fc) + Ipilimumab (n=40)	Treatment Group 1 (n=20)	Treatment Group 3 (n=20)
	Sequential: SBRT (50 Gy/ 4 Fc) + Ipilimumab (n=40)	Treatment Group 2 (n=20)	Treatment Group 4 (n=20)
	Sequential: SBRT (60 Gy/ 10 Fc) + Ipilimumab (n=20)	Treatment Group 5 (n=20)	

All studies will be conducted with the following treatment scheme: Patients will be simulated up to 3 weeks prior to the anticipated SBRT start date. The first SBRT fraction will optimally be administered on a Monday. Within the three cohorts (treatment groups 1 and 3) receiving concurrent SBRT and ipilimumab, ipilimumab administration will begin the day prior to the first SBRT fraction. Among patients receiving sequential SBRT and ipilimumab (treatment groups 2, 4, and 5), ipilimumab administration will occur on approximately the fourth day (day 8) following radiation completion.

Prior to starting each ipilimumab treatment cycle, patients will arrive at the Clinical Center for Targeted Therapy and undergo safety assessments, while H&N and thoracic patient may receive their Ipilimumab in the thoracic clinic. In all arms, safety will be assessed by physical examination, observing and

questioning patients regarding adverse experiences, and monitoring clinical chemistry and hematology. Disease progression will be based upon the irRC Criteria. All patients will be evaluated upon their first receipt of ipilimumab.

7.1.1. 3+3 Dose De-Escalation of SBRT

For treatment groups 1-4 (as outlined in 7.1) studies will be initiated with two 3 patients cohorts for each treatment group. Dose de-escalations will occur independently in each cohort. The first 3 patients within each group will be treated with SBRT at a dose of 50 Gy given in four 12.5 Gy fractions. In the event that 0-1 DLTs are observed, 3 additional patients will be treated at the current radiation dose. Assessing this group of 6 patients, If <2 DLTs are observed in this group then 14 additional patients will be enrolled in the respective treatment group. In the event that 2 or more toxicities are observed within the 6 patients, the SBRT dose will be successively reduced by one 12.5 Gy fraction. Long term toxicities will be evaluated every three months for a duration of one year after the last cycle of ipilimumab. If patients are unable to arrive for in person appointments, it is acceptable to call for assessment. All Grade 3 or greater events will be reviewed by both the radiation Oncology PI and the Phase I co-PI to discuss attribution. If long term grade 3 or greater toxicity occurs in great then 33% our recommended phase II dose would be reduced from 50Gy to 37.5Gy and further evaluation of the dose will occur with at least a total of 6 more patients. A similar scheme will be conducted for treatment group 5 (as outlined in 7.1). Studies will be initiated with two 3 patient cohorts. The first 3 patients will be treated with SBRT at a dose of 60 Gy given in ten 6 Gy fractions. If 0-1 DLTs are observed, 3 additional patients will be treated at the current radiation dose. If <2 DLTs are observed in this group then 14 additional patients will be enrolled in the respective treatment group. In the event that 2 or more toxicities are observed within the 6 patients, the SBRT dose will be successively reduced by two 6 Gy fraction.

DLTs will be assessed at one week after two cycle of Ipilimumab for groups 1,3 (day 29 \pm 7) and one week after cycle three for groups 2,4,and 5 (day 50 \pm 7). After cycle 4 of ipilimumab treatment, patients will be assessed for AEs and restaged. Repeat staging and toxicity assessment with occur every 1-3 months thereafter for the first six months and at least bimonthly thereafter.

Table 3: Dose De-escalation

Dose Level	SBRT 50 Gy in 4 fractions (Treatment Groups 1-4)	SBRT 60 Gy in 10 fractions (Treatment Group 5)	Ipilimumab dose (Treatment Groups 1-5)
1	50 Gy in 12.5 Gy / fraction for 4 fractions	60 Gy in 6 Gy / fraction for 10 fractions	3mg/kg intravenous every 21 days
-1	37.5 Gy in 12.5 Gy / fraction for 3 fractions	48 Gy in 6 Gy / fraction for 8 fractions	3mg/kg intravenous every 21 days
-2	25 Gy in 12.5 Gy / fraction for 2 fractions	36 Gy in 6 Gy / fraction for 6 fractions	3mg/kg intravenous every 21 days

Table 4: Regimen Description

Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
Ipilimumab (Yervoy)	None	Mix in 100 mL of 0.9% Normal Saline	IV 90 minute	Day 1 (\pm 3)	21 days (3 weeks; \pm 3 days)

Ipilimumab (Yervoy)

Ipilimumab will be administered as a single 90 minute (+/- 15 minutes) intravenous infusion on the first day of each cycle (± 3). The calculated dose will be diluted in 100 mL of 0.9% Normal Saline.

Ipilimumab will be conducted for 4 x 21 day (± 3 days) cycles.

7.1.2. Ipilimumab Reinduction

Patients who achieve disease control on ipilimumab will be eligible for re-induction with ipilimumab +/- radiation therapy. Patients will be eligible for reinduction if they achieved disease control (either SD or PR as scored by ir-RC criteria) on their first post cycle 4 imaging and did not exhibit severe (Grade >3 toxicity) during therapy. Patients with PD on post cycle 2 imaging are eligible for reinduction as long as SD or PR is observed on the first post cycle 4 imaging. The decision to initiate reinduction will be based on both the treating physician and patients' preferences.

Ipilimumab reinduction will consist of 4 cycles of ipilimumab administered at the maximum tolerated dose given every 3 weeks. Radiation may be given during reinduction, but is not required. Pending the treating radiation oncologist judgment, additional radiation therapy to a previously non-irradiated lesion can be administered during re-induction. Timing of radiation during reinduction will parallel treatment timing during induction. Specifically, patients treated in Treatment Groups 1 and 3 (concurrent arms) will initiate radiation 1 day after the first dose of ipilimumab reinduction, while those treated in Treatment Groups 2,4,and 5 (sequential arms) will initiate radiation approximately 8 days after the second dose of ipilimumab reinduction. Timing of radiation during reinduction will be at the discretion of treating Radiation Oncologist.

The target lesion for radiation will be chosen by the treating radiation oncologist. The target lesion must not have been previously irradiated. The target lesion does not have to be within the same organ that was initially treated during induction (e.g. patients who received initial lung lesion irradiation can have liver or a bone lesion irradiated during re-induction). Radiation dose and fraction will be either at the initial induction dose (50 Gy in 4 fractions or 60 Gy in 10 fractions) or at a lower palliation dose (30 Gy in 10 fractions) or low dose radiation ranging from 200cGy-30cGy in 4 or 10 fractions,at the discretion of the treating radiation oncologist.

Ipilimumab reinduction will occur 8 weeks after the last cycle of ipilimumab induction or later. After the 4th cycle of reinduction, system imaging (CT, MRI, Ultrasound, or x-ray) to assess the global disease burden will be conducted. If disease control is once again observed (SD or PR by ir-RC, compared to the original pretreatment baseline imaging) without severe (Grade >3) toxicity then patients will be eligible for a second round of reinduction therapy to given in the same manner as the first round of reinduction. Patients may continue to have additional rounds of reinduction therapy until PD is observed at their post cycle 4 imaging or severe toxicity (Grade >3) occurs.

7.2. Definition of Dose-Limiting Toxicity and Maximum Tolerated Dose:**7.2.1. Dose Limiting Toxicity (DLT):****DLT is defined as any:**

- DLTs are defined as any adverse event(s) considered related to the combination of ipilimumab and radiation as described below:

-

- Any \geq Grade 3 bronchospasm or other hypersensitivity reaction;
 - Any other \geq Grade 3 non-skin related adverse event with the exception of laboratory abnormalities;
 - Any Grade 4 laboratory abnormalities, except AST, ALT, or total bilirubin;
 - AST or ALT $> 8 \times$ ULN,
 - Total bilirubin $> 5 \times$ ULN;
 - Any other Grade 4 adverse event;
 1. Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing;
 2. Any motor neurologic toxicity \geq Grade 3 regardless of causality;
 3. Any \geq Grade 3 treatment-related sensory neurologic toxicity.
 4. Combination related toxicity that prevents administration of ipilimumab for > 21 days from the scheduled dose
-
- The time frame for DLT assessment will be within 29 days (± 7 days) of therapy initiation in the concurrent arm and 50 (± 7 days) days of therapy initiation in the sequential arm.
 - Any clinically \geq grade 3 non-hematologic toxicity as defined in the NCI CTC v4.0, expected and believed to be related to the combination of study drug and radiation (except nausea and vomiting, diarrhea and electrolyte imbalances responsive to appropriate regimens, alopecia or fatigue lasting less than 7 days).
 - Any grade 4 neutropenia (with or without fever and/or sepsis) or thrombocytopenia (with or without bleeding) lasting at least 1 week or longer (as defined by the NCI-CTC v4.0).
 - Any of the Grade 4 hematologic adverse events for > 5 days.
 - Any \geq grade 3 nausea or vomiting lasting > 5 days despite anti-emetics regimens or \geq grade 3 diarrhea refractory to anti-diarrhea medications.
 - Grade 3 fatigue lasting more than 7 days.
 - Any other grade 3 non-hematologic toxicity including symptoms/signs of vascular leak or cytokine release syndrome; or any severe or life-threatening complication or abnormality not defined in the NCI-CTCAE v4.0 that is attributable to the therapy.

The Maximum Tolerated Dose (MTD) is defined:

- The highest dose level with less than 2 patients with DLT out of at least six patients in the cohort. Management and dose modifications associated with adverse events are outlined in the below table. The MTD will be determined independently and in parallel for each of the 4 cohorts (section 7.1).

Table 5: Dose De-Escalation and Maximum Tolerated Dose Scheme

Number of Patients with DLT* at a Given Dose Level (assessed independent for each of the 4 cohorts)	De-Escalation Decision Rule
0 out of 3	Enter 3 more patients at this dose level

≥ 2	Dose de-escalation will occur. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be entered at the next lowest dose level, as per table 3.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, then this is the maximum tolerated dose (MTD). If 1 or more of this group suffer DLT, then dose de-escalation will occur. Three additional patients will be entered at the next lowest dose level.
MTD: The highest dose at which no more than 1 of 6 evaluable patients has had a DLT. Six patients should be treated before the dose is declared the MTD.	

**The time window for DLT evaluation in the dose de-escalation phase is 29 days in the concurrent SBRT and ipilimumab group and 50 days in the sequential SBRT and ipilimumab group (Approximately 1 week after initiation of ipilimumab cycle 2)*

All patients will be treated at the highest current dose level. All enrolled participants will be considered in the DLT analysis. ***If at any time more than or equal to one third (33%) of the participants at a dose level experience DLT, the MTD will be reassessed and the next lowest dose level for the combination therapy will be considered the MTD.***

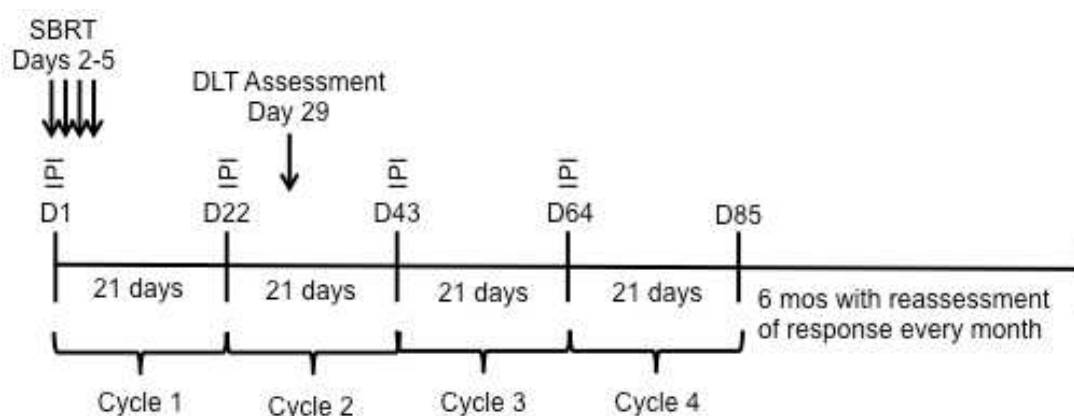


Figure 1: Diagram of Treatment Schedule for Concurrent SBRT and Ipilimumab Dose De-Escalation Study (Treatment groups 1 and 3).

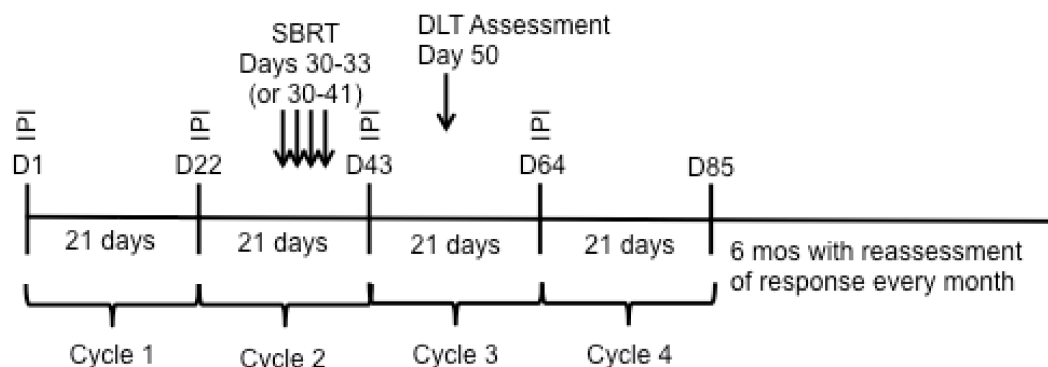


Figure 2: Diagram of Treatment Schedule for Sequential SBRT and Ipilimumab Dose De-Escalation Study (Treatment groups 2, 4, and 5).

7.3. Duration of Therapy and Criteria for Treatment Delay

7.3.1. Duration of Therapy:

In the absence of withholding treatment cycles due to adverse events, study treatment will be continued for the full 4 ipilimumab cycles.

7.3.2. Criteria for Treatment Delay:

Patients will delay treatment with ipilimumab if they experience at least one of the following adverse events considered by the Investigator to be “possibly”, “probably” or “certainly” related to ipilimumab and SBRT treatment:

- Any Grade 3 non-skin related adverse event (excluding alopecia, and Grade 3 nausea, vomiting, and diarrhea for which adequate supportive therapy has been instituted)
- Any Grade 3 skin-related adverse event (including irAEs)
- Any of the Grade 4 hematologic adverse events for >5 days
- Grade 3 fatigue only if ≥ 7 days
- SBRT scheduling conflicts or machine maintenance issues

7.3.3. Criteria for Restart of Treatment:

Patients requiring delay or cessation of ipilimumab based on the judgment of the attending physician can be restarted as long as:

- The adverse event is not listed in 7.2.1, and:
- If the adverse event has resolved to \leq Grade 1 severity or returns to baseline within 4 weeks (28 days) of dose administration, ipilimumab will be restarted ≥ 4 weeks from the last dose administration, to complete dosing regimen outlined above.
- If the adverse event has not resolved to \leq Grade 1 severity or returned to baseline in the protocol-specified dosing window (3 weeks), the next scheduled dose will be omitted and remaining doses of ipilimumab administered if approved by the Principal Investigator.
- Treatment delays for reasons other than adverse events (e.g. for scheduling conflicts or SBRT machine maintenance issues) are allowed as long as all four 3 week cycle ipilimumab doses are given within 8 months. In this scenario, all 4 doses should be administered separated by a minimum interval of 3 weeks.

7.3.4. Criteria for Permanent Discontinuation of Ipilimumab

- Patients will continued to be monitored with visits or phone calls (if patient is unable to arrive) as discussed in section 9.1.3 but will no longer receive further treatment with ipilimumab if:
- They suffer any of the following adverse events with at least a possible, probable or definite attribution to Ipilimumab:
 5. *Adverse event(s) considered related to ipilimumab as described below:*
 - Any \geq Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment;
 - Any \geq Grade 3 bronchospasm or other hypersensitivity reaction;
 - Any other \geq Grade 3 non-skin related adverse event with the exception of laboratory abnormalities;
 - Any Grade 4 laboratory abnormalities, except AST, ALT, or total bilirubin;
 - AST or ALT $> 8 \times$ ULN,
 - Total bilirubin $> 5 \times$ ULN;
 - Any other Grade 4 adverse event;
 - Drug related toxicity that prevents administration of ipilimumab for > 21 days from the scheduled dose
 6. Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing;
 7. Subject experiences an allergic/infusion reaction while receiving study drug at a slower infusion rate due to a prior allergic/infusion reaction;
 8. Any motor neurologic toxicity \geq Grade 3 regardless of causality;
 9. Any \geq Grade 3 treatment-related sensory neurologic toxicity.
 10. Drug related toxicity that prevents administration of ipilimumab for > 21 days from the scheduled dose
- 1. *Exceptions to Permanent Discontinuation of ipilimumab dosing:*
 - Hospitalization for \leq Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up;

7.3.5 Criteria for Removal from Study

Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

- The development of unacceptable toxicity
- Pregnancy,
- Any other situation where, in the opinion of the treating physician, continued treatment per protocol, would not be in the best interest of the patient.
- The patient withdraws consent (subject's decision to withdraw for any reason).
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Patient refusal or non-compliance with SBRT
- Study completion

7.4. Immune Related Adverse Events (IRAEs): Definition, Monitoring and Treatment

Blocking CTLA-4 function may permit the emergence of auto-reactive T cells and resultant clinical

autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypopituitarism were drug-related, presumptive autoimmune events, now termed IRAEs, noted in previous ipilimumab studies.

For the purposes of this study, an IRAE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an IRAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected IRAEs must be documented on an AE or SAE form.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic IRAE (e.g., systemic lupus erythematosus-like diseases) or organ specific IRAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an IRAE is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It has been reported that systemic corticosteroid therapy does not seem to have an attenuating effect on ipilimumab activity (29). However, administration of a prophylactic corticosteroid, budesonide, did not impart any clinical benefit in patients treated with ipilimumab (30). If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as Grade ≥ 3 diarrhea requires corticosteroid treatment.

7.5. Radiation Related Adverse Events: Definition, Monitoring and Treatment

Acute radiation reactions including esophagitis, pneumonitis, gastritis, soft tissue toxicity and other adverse events will be evaluated during the period of treatment and during subsequent visits. The adverse events will be graded according to National Cancer Institute (NCI) CTCAE v4.0.

Toxicity following SBRT treatment for liver and lung lesions appears to elicit minimal toxicity. With regard to liver SBRT, the actuarial rate of any Grade ≥ 3 toxicities have been reported to be 2% with only one instance of grade 3 soft tissue toxicity(13). Toxicity rates in patients receiving lung SBRT have been reported to 7.9% which included 1 instance of grade 3 dyspnea, chest wall fraction and skin reaction. Dosimetric considerations are important as centrally located lung lesions have been associated with significantly higher incidence of grade ≥ 3 toxicities (17%) compared with peripheral lesions (46%)(31).

7.6. Infusion Reactions and Fever Associated with Ipilimumab

7.6.1. Infusion Reactions

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypo- or hypertension, bronchospasm or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient.

The following treatment guidelines are suggested:

Severe infusion reactions require the immediate interruption of ipilimumab and permanent discontinuation from further treatment.

Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. In each case of an infusion reaction, the investigator should institute treatment measures according to the best available medical practice and institutional norms.

The following treatment guidelines are suggested:

CTCAE Grade 1 Allergic reaction/hypersensitivity (transient flushing or rash, drug fever < 38°C)

Treatment: Decrease the ipilimumab infusion rate by 50% and monitor closely for any worsening.

CTCAE Grade 1 or Grade 2 Allergic reaction/hypersensitivity manifesting only as delayed drug fever (starting after the completion of ipilimumab infusion)

Treatment: Maintain ipilimumab dose and infusion rate for future infusions. Consideration could be given to administration of acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) prior to the subsequent ipilimumab infusion, if not otherwise contraindicated in subjects. Dose and schedule of these agents is entirely at the investigator's discretion.

CTCAE Grade 2 Allergic reaction/hypersensitivity (Rash, flushing urticaria, dyspnea, drug fever $\geq 38^\circ\text{C}$)

Treatment: Interrupt ipilimumab infusion. Administer bronchodilators, oxygen, etc as medically indicated. Resume infusion at 50% of previous rate once infusion reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening.

CTCAE Grade 3 or Grade 4 Allergic Reaction/Hypersensitivity: A CTCAE Grade 3 hypersensitivity reaction (symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema; hypotension) or a Grade 4 hypersensitivity reaction (anaphylaxis).

Treatment: Stop ipilimumab infusion immediately and disconnect infusion tubing from the subject. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated. Contact the PI and document as a serious adverse event. No further ipilimumab treatment to be administered.

Once an ipilimumab infusion rate has been decreased due to an infusion reaction, it should remain decreased for all subsequent infusions. If the subject has a second allergic/infusion reaction at the slower infusion rate, then the infusion should be stopped and the subject should be discontinued from ipilimumab. If a subject experiences a Grade 3 or 4 allergic/infusion reaction at any time, the subject should be discontinued from ipilimumab.

7.7. Treatment of Ipilimumab Related Isolated Drug Fever

In the event of isolated drug fever, the Investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology.

If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (Investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion should be administered. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following pre-medication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the Investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

7.8. Concomitant, Prohibited and Restricted Therapies During the Study

7.8.1. Concomitant Therapies

- All patients should have antiemetic medications available once discharged from the clinic. Oral antiemetic medications should be prescribed and administered as needed, and adjusted during the cycle at the discretion of the treating investigator.
- If patients experience nausea and vomiting despite the premedication, the patient may take PRN antiemetics per treating physician's discretion.
- All patients may have emollient or lubricating creams to be placed on the corresponding SBRT field for symptomatic skin irritation after SBRT treatment completion at the discretion of the treating investigator.

Radiation outside of the SBRT treatment fields will also be allowed based on the treating physician discretion.

7.8.2. Prohibited Therapies

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease for up to one month pre and post dosing with ipilimumab.

Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving ipilimumab treatments, other than palliative (pain controlling) radiation therapy (RT) in situations that are not clearly indicative for PD.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational);
- Any other investigational agents;
- Any other (non-CA184024 related) CTLA-4 inhibitors or agonists;
- CD137 agonists;
- Immunosuppressive agents;
- Chronic systemic corticosteroids while receiving ipilimumab (as long as steroid replacement is significantly greater than what is required for physiologic replacement, i.e. in hypothyroidism);
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug).

8. Criteria for Evaluation

8.1. Evaluations at Baseline

Notice: On-study tests/visits that must occur within a defined time frame shall have a standing window of allowance that is equal to +/- 3 days for any laboratory testing unless patient/logistical/medical reasons intervene. Overlapping baseline tests can be combined with tests required for cycle 1 of ipilimumab administration as long as these baseline tests occur within 3 days before cycle 1.

8.1.1. Four weeks prior to study initiation

The following appropriate imaging studies for tumor assessment should be obtained within 4 weeks prior to study initiation to provide diagnosis and measurement of target lesions.

- CT scans of the chest, abdomen and/or pelvis (contrast-enhanced preferred); or
- MRI of the abdomen or pelvis; or
- PET/CT scan (preferred)

The following imaging modalities are to be used in the event that above imaging modalities cannot be

obtained

- Ultrasound (US) (special circumstances only, as described below in 9.4); or
Chest radiograph (least preferred)

8.1.2. *Within 3 weeks prior to radiation initiation.*

- CT simulation for purposes of SBRT planning (as described in 6.2).

8.1.3. *Within 2 weeks prior to study initiation.*

The following studies should be obtained within 14 days prior to study initiation. All abnormal and normal results must be noted in the case report forms (CRF).

- Medical history to include determination of tumor-related symptoms.
- ECG
- Physical examination to include height, weight, vital signs, and performance status.
- CBC with differential and platelet count.
- Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT or SGPT, total bilirubin, alkaline phosphatase, and uric acid.
- Routine urinalysis.
- Serum pregnancy test for females of childbearing potential within 7 days of registration.
- Initial optional tumor biopsy from the lesion targeted for SBRT radiation and/or other metastatic lesion for additional tumor marker studies
- Initial optional tumor mutation biomarker panel (MD Anderson 46 gene panel) from a prior biopsy or from the optional tumor biopsy sample
- Initial optional serum biomarkers will be obtained. All patients enrolled in the phase II expansion portion of this study must consent to protocol PA13-0291 and agree to at least two blood draws (1 during the 2 weeks prior to study initiation and 1 during the last cycle of ipilimumab) unless deemed unsafe by the treating physician.

8.1.4. *Monitoring following study completion.*

Patients will return monthly for up to 6 months following completion of the last cycle of ipilimumab and every 2 months thereafter with the following evaluation: CBC with differential and platelet count, serum chemistries, laboratory evaluation, and body imaging to assess for toxicity and disease response.

8.2. Evaluations During Study

8.2.1. *Before each Ipilimumab administration*

Every patient needs to be evaluated by the treating physician before each ipilimumab administration with the following laboratory tests. Overlapping baseline tests can be combined with tests required for cycle 1 of ipilimumab administration as long as these baseline tests occur within 3 days before cycle 1:

- CBC with differential/platelets
- Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT (AST) or SGPT (AGT), total bilirubin, alkaline phosphatase and uric acid.
- TSH measurement
- Patient weight for dose calculation purposes

8.2.2 *DLT assessment (Concurrent arms: 1 week after 2nd dose of ipilimumab, sequential arms: 1 week after 3rd dose of ipilimumab)*

- Physical examination to include height, weight and vital signs.
- Physical examination, interim history pertaining to any change from baseline, current medications and treatment-related toxicities. Adverse events will be monitored using the NCI CTCAE Version 4.0.
- Laboratory testing CBC with differential/platelets
- Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT (AST) or SGPT (AGT), total bilirubin, alkaline phosphatase and uric acid.

8.2.3. Every 1-3 months for the first 6 months from completion of last cycle of ipilimumab and every 2-4 months thereafter

- Physical examination to include height, weight and vital signs.
- Physical examination, interim history pertaining to any change from baseline, current medications and treatment-related toxicities. Adverse events will be monitored using the NCI CTCAE Version 4.0.
- Laboratory testing CBC with differential/platelets
- Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT (AST) or SGPT (AGT), total bilirubin, alkaline phosphatase and uric acid.
- All appointments after the last cycle of ipilimumab will allow a window of ± 1 months.
- Radiation oncology follow up appointments will be at the discretion of the treating radiation oncologist. We recommend follow up at 3 and 6 months after the completion of the last cycle of ipilimumab followed by appointments as per standard of care.

8.2.4. At the end of every 2nd study cycle and every 2-3 months from completion of last cycle of ipilimumab induction and re-induction (in patients who receive re-induction)

- Imaging studies: Response assessment during and post treatment should be performed using the same modality as the pretreatment assessment whenever feasible, and all lesions assessed pretreatment must be included in the post-treatment evaluation:
 - CT scans of the chest, abdomen and/or pelvis (preferred); or
 - MRI of abdomen and pelvis; or
 - PET/CT (preferred)
 - All appointments after the last cycle of ipilimumab will allow a window of ± 1 months.

8.2.5. Tumor biopsies and serum biomarker evaluation (optional)

Patients with accessible tumor who consent for biopsies per protocol will undergo a baseline biopsy of a non-irradiated lesion. Similarly, patients who consent for optional serum studies will undergo baseline blood draw for evaluation. Optional biomarker studies will be under protocol PA13-0291. A tentative calendar is shown in Sections 12.1 and 12.2.

8.3. Measurement of Effect

1. Response and progression will be evaluated in this study using guidelines proposed by the Immune Related Response Criteria (irRC) (11). Patients with measurable disease will also be assessed using standard RECIST v 1.1 and World Health Organization (WHO) treatment response criteria after both induction and re-induction.
2. The best achieved objective response via ir-RC criteria (as described below) will consider all imaging conducted after the fourth cycle of ipilimumab during initial induction. If in the event that patient receives re-induction, imaging will be obtained after the 2nd and 4th cycle of re-induction and every 2-3 months thereafter. All imaging obtained during and after re-induction will be considered when obtaining the best achieved objective response.

irRC: Measurable Disease Prior to Therapy (day <1)

Index lesions: Up to 15 index lesions per patient (5 per organ, up to 10 visceral and 5 cutaneous) with minimum size 5 x 5 mm will be accurately measured in two dimensions (two largest perpendicular diameters) on CT or MRI scan (slice thickness no greater than 5 mm) prior to therapy initiation. Lesions measured with calipers by clinical exam may be conducted on lesions no smaller than 10 mm in the smallest dimension. Lesions that cannot be accurately measured with calipers should be recorded as non-measurable.

SBRT-treated index lesions: Defined as all index liver, lung, or adrenal lesions treated by SBRT as part of this protocol.

Non-SBRT-treated index lesions: Defined as all index lesions not treated by SBRT as part of this protocol.

irRC: Index and non-Index Lesions:

For the irRC, index and measurable new lesions are taken into account (in contrast to conventional WHO treatment response criteria, which do not require the measurement of new lesions, nor are new lesion measurements included in the assessment of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions ($\geq 5 \times 5$ mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 new visceral lesions) are added together to provide the total tumor burden. In addition to a global irRC which will encompass all lesions under the previous definition, the irRC of lesions included within the SBRT PTV and outside the SBRT PTV will also be assessed as follows:

1. **Global irRC:** irRC that factors all lesions including both index and non-index as outlined in 9.5.
2. **In-Field irRC:** irRC in which only index within the SBRT PTV will be considered and any non-index lesions arising inside the SBRT PTV
3. **Out-Field irRC:** irRC in which only index lesions outside the SBRT PTV will be considered and any non-index lesions arising outside the SBRT PTV

8.4. Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or physical calipers. All baseline evaluation studies should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment. 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, cross sectional imaging is preferable.

Multidetector CT, PET/CT and MRI. These techniques should be performed with contiguous slices of 5 mm or less in thickness. This applies to tumors of the neck, chest, abdomen and pelvis. Head and neck tumors and those of extremities may require specific imaging protocols or evaluation with ultrasound. 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. These will not be used to assess response on this study.

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) if clinically indicated.

8.5. Response Criteria

8.5.1. Immune Related Response Criteria (irRC)

Evaluation of Target Lesions

Response in new patients will be conducted using the Immune Related Response Criteria (irRC), as described by (11). “For irRC, only index and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions ($\geq 5 \times 5$ mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden.”

For the purposes of this study, 3 separate tumor burdens will be calculated for each patient and used to define 3 separate irRCs as discussed in 9.3. All criteria will be considered separately for all 3 irRCs: global, in-field, and out-field.

$$\text{Global Tumor Burden} = \text{SPD}(\text{all index lesions}) + \text{SPD}(\text{new, measurable lesions})$$

$$\text{In-Field Tumor Burden} = \text{SPD}(\text{all index lesions targeted by SBRT in this protocol}) + \text{SPD}(\text{new, measurable lesions inside the SBRT PTV})$$

$$\text{Out-Field Tumor Burden} = \text{SPD}(\text{all index lesions NOT targeted by SBRT in this protocol}) + \text{SPD}(\text{new, measurable lesions outside the SBRT PTV})$$

Complete Response (irCR): irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

Partial Response (irPR): irPR, decrease in tumor burden $\geq 50\%$ relative to baseline confirmed by a consecutive assessment at least 4 wk after first documentation.

Progressive Disease (irPD): irPD, increase in tumor burden $\geq 25\%$ relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

- If a patient is classified as having irPD at a post-baseline tumor assessment, then confirmation of irPD by a second scan in the absence of rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden $\geq 25\%$ compared with the nadir at two consecutive time points at least 4 wk apart. It is recommended that this be done at the discretion of the investigator because follow-up with observation alone may not be appropriate for patients with a rapid decline in performance status.

Stable Disease (irSD): irSD, not meeting criteria for irCR or irPR, in absence of irPD. In contrast to other response criteria, this criteria does not require repeat confirmation.

The following two tables are adapted from (11) and describe irRC criteria and compare/contrast irRC criteria with standard WHO criteria.

Table 2. Derivation of irRC overall responses

Measurable response Index and new, measurable lesions (tumor burden),* %	Nonmeasurable response		Overall response
	Non-index lesions	New, nonmeasurable lesions	Using irRC
$\downarrow 100$	Absent	Absent	irCR [†]
$\downarrow 100$	Stable	Any	irPR [†]
$\downarrow 100$	Unequivocal progression	Any	irPR [†]
$\downarrow \geq 50$	Absent/Stable	Any	irPR [†]
$\downarrow \geq 50$	Unequivocal progression	Any	irPR [†]
$\downarrow < 50$ to $< 25\uparrow$	Absent/Stable	Any	irSD
$\downarrow < 50$ to $< 25\uparrow$	Unequivocal progression	Any	irSD
$\geq 25\uparrow$	Any	Any	irPD [†]

*Decreases assessed relative to baseline, including measurable lesions only ($> 5 \times 5$ mm).
[†]Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., $\geq 5 \times 5$ mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., $< 5 \times 5$ mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	$\geq 50\%$ decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	$\geq 50\%$ decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

8.5.2 Parallel evaluation using ViSion

Radiologists at the MD Anderson Cancer Center have developed a multimedia structured reporting system, called ViSion, which will be used to capture the key images and metrics recorded by a radiologist during tumor response assessment. The captured images are tagged with metadata by a radiologist to identify the anatomical location and radiological observation/diagnosis of each finding. The ViSion system provides the ability to link related image findings from serial examinations for display in unique disease timelines. Target and non-target lesions may be designated by a radiologist from which the calculation and display of irRC is automated. The radiologist's actual image analysis is performed using a standard FDA-cleared picture archiving and communications system (PACS) display with electronic calipers – ViSion only captures the key images and measurements for subsequent storage, analysis and display. An example of a ViSion report with disease timelines and a RECIST graph is illustrated below.

Patient:
MRN: 100001
Gender: Male
DOB: 1948-01-01

ViSion Report

Send notification Report state: [View](#) List View Homunculus View

There are 8 findings available Show details / Hide details









Key Images	Side	Anatomy	Pathology	Priority	Metric	Target	Audio/Video
Chest							
	Right	Lung	Metastasis	Important	20 mm	1	
	Right	Lung	Metastasis	Important	12 mm	2	
		Anterior mediastinal lymph node (6)	Metastasis	Important			
	Left	Axillary lymph node	Metastasis	Important			

Figure 1. A ViSion report contains key images tagged with metadata and disease metrics.



Figure 2. Related image findings are linked and displayed in a disease timeline.

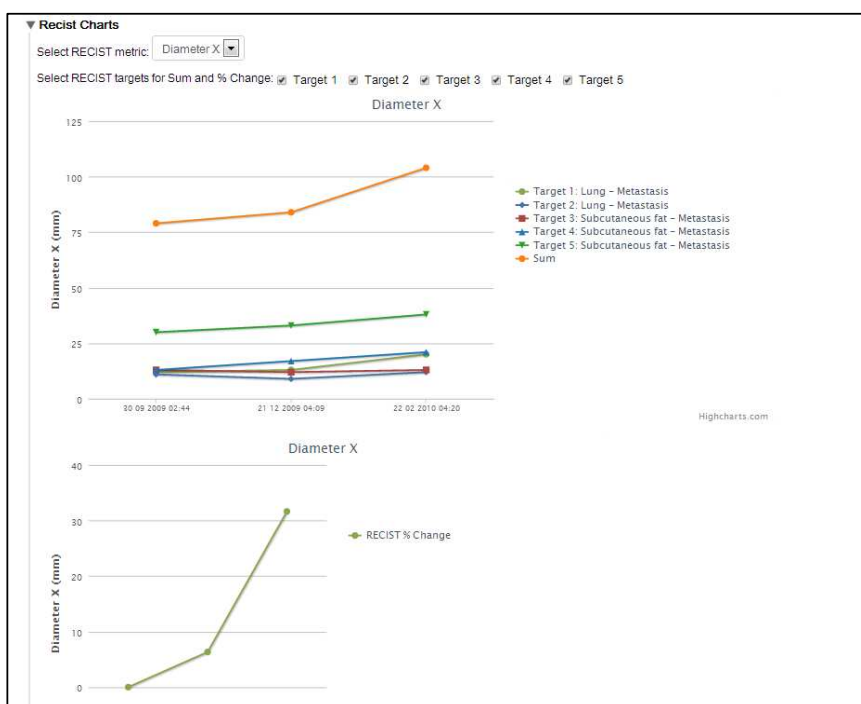


Figure 3. ViSion aggregates data from designated target lesions to produce a RECIST graph.

8.6 Systemic Biomarkers

The objective of this portion of the study is to correlate systemic serum markers, obtainable by peripheral

venous access to patient responses and observed toxicities. Voluntary participation in this portion of the protocol is optional for all study participants.

Systemic lymphocyte counts obtained from routine CBC with differential will be analyzed and associated with clinical outcomes and toxicities from the lab draws obtained throughout this protocol.

Tumor-specific antigens that can elicit cellular and humoral immunity, are expressed on cancer cells and can be identified for development of immunotherapy in these patients. Patient serum will be analyzed to assess candidate tumor-associated antigens or genes that elicit cellular and humoral immune responses in patients with solid tumors. This analysis will correlate antigen-expression and immune responses with patient data such as tumor type, treatment response, and clinical outcome of patients who have received ipilimumab and SBRT.

This study will be done in collaboration with Dr. Padmanee Sharma, MD/PhD, and Dr. James Allison, PhD and covered by the immunotherapy platform supported by MD Anderson Laboratory Protocol PA13-0291. All samples will be collected using procedures characterized in this protocol and all patients will be consented for procedures done under this optional protocol separately. Specifically, this study will allow for the collection of blood, to be drawn at the time of routine blood-draw, for biomarker analysis. We defer to protocol PA13-0291 for details regarding this portion of the protocol. Blood for biomarker analysis can be collected before drug initiation, at the end of every ipilimumab cycle (± 1 week), and during follow up visits (± 1 week). See study calendars for tentative schedules (Sections 12.1 and 12.2).

All patients within the dose-escalation arm must consent for this portion of the study and at a minimum have blood draws collected within 2 weeks prior to study initiation and during the last cycle of ipilimumab administration, prior to therapy completion unless deemed unsafe by the treating physician.

8.7. Biopsies

The objective of this portion of the study is to correlate histologic/immunohistologic analyses of biopsy samples to patient responses and observed toxicities. Voluntary participation in this portion of the protocol is optional for all study participants. All patients will have the option of tumor assessment on the initial tumor sample via a standard mutation biomarker panel (MD Anderson 46 gene panel). Assessment can be conducted from any prior biopsy or from the optional tumor biopsy sample.

This study will be done in collaboration with Dr. Padmanee Sharma, MD/PhD, Dr. James Allison, PhD, and covered by the immunotherapy platform supported by MD Anderson Laboratory Protocol PA13-0291. All samples will be collected using procedures characterized in this protocol and all patients will be consented for procedures done under this optional protocol separately. Specifically, biopsies will optimally be obtained from both the lesion targeted for SBRT and at non-irradiated disease site. The method for biopsy depends on lesion location and may include, palpation and biopsy, biopsy under ultrasound guidance, biopsy under bronchoscopic guidance, or biopsy under CT guidance. Judgment of biopsy safety is under the discretion of the treating physician. We defer to protocol PA13-0291 for details regarding this portion of the protocol. Biopsies can be obtained 1-2 weeks prior to therapy initialization and at the end of ipilimumab cycle 4 (± 1 week). See study calendars for tentative schedules (Sections 12.1 and 12.2).

9. Adverse Event Reporting

9.1. Serious Adverse Event Reporting (SAE) (Appendix B)

A serious adverse event is – any adverse drug or radiation experience occurring at any dose that results in any of the following outcomes:

4. Death
5. A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
6. Inpatient hospitalization or prolongation of existing hospitalization
7. A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
8. A congenital anomaly/birth defect.

NOTE: Immune-mediated adverse reactions are expected and well described in the package insert for ipilimumab. Hospitalizations required for intravenous administration of high dose steroids will be considered adverse events and will not be considered SAEs. If the adverse event has not improved within 7 days of intravenous high dose steroids, it will be deemed serious and reported in an expedited manner to the appropriate groups.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigators or the IND Sponsor, Investigational New Drug (IND) Office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events with possible, probable, or definite attribution to the study drug must have a written report faxed within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

The MDACC Internal Adverse Event Reporting Form will be used for reporting to the Sponsor (Safety Project Manager IND Office).

Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IRB and the Sponsor (Safety Project Manager IND Office). This may include the development of a secondary malignancy.

9.2. Reporting of Adverse Events

This study uses FDA approved agents with known toxicity profiles. Therefore, Grade 1 and 2 toxicities (related or unrelated) will not be collected or documented as these are not considered clinically significant in this patient population and/or they are expected for these study agents. Grade 3 and 4 toxicities that are felt to be treatment related and unexpected (per package insert) will be documented. Unless otherwise documented in the electronic medical record as clinically significant and study drug related, all lab abnormalities will be assumed to be related to the patient's other co-morbid conditions, prior therapies, other concomitant therapies/medications, or underlying cancer. Adverse Events will be documented according to the Recommended Adverse Event Recording Guidelines for Phase I protocol.

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

All Serious Adverse Events must be reported to BMS Worldwide Safety

- All SAEs, whether related or unrelated to ipilimumab and all pregnancies must be reported to BMS (by the investigator or designee) within 24 hours.
- All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Fax Number: 609-818-3804

10. Statistical Considerations

Data Collection

All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database at the University of Texas M D Anderson Cancer Center at Houston.

Data Protection and Confidentiality

All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database (CORE) at the University of Texas M D Anderson Cancer Center at Houston. All protocol participants must be registered in the CORE. The date in the current informed consent document is displayed to ensure only the most current IRB approved version is used. Consent date, registration date, off study date, and evaluability data are required for all registrants.

The principal investigator agrees to keep all information and results concerning the study confidential. The confidentiality obligation applies to all personnel involved with this clinical trial. The Investigator must ensure that each participant's anonymity will be maintained in accordance with applicable laws. The principal investigator should keep a separate log of ID numbers, names and addresses. Documents that contain the names associated with these ID numbers (e.g., written consent/assent forms), should be maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the IRB.

The Principal Investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including re-analysis in

combination with results of other studies), for regulatory submission purposes and for applicable reporting (if any).

Under this protocol, we will collaborate with Dr. Vivek Verma at the University of Nebraska under an IRB approved, legally executed Material Transfer Agreement. All data sent to Dr. Verma will be de-identified with no names, dates, or medical record numbers. The de-identified data will be sent in an Excel spreadsheet via MDACC encrypted email and will be used to perform toxicity analysis. Patient identification information will be removed from all documents. The data will be coded by anonymous study numbers using a key kept separate from the database that only the principal investigator will have access to. Data will be stored on a password and firewall protected computer.

10.1. Data Set Descriptions

This study will utilize a standard 3+3 design and dose de-escalation will proceed according to the following scheme. De-escalation will occur independently and in parallel for each of the 5 treatment groups (section 7.1):

1. Patients with at least 1 liver metastasis treatable with SBRT at 50 Gy in 4 fractions will be assigned based on the investigators discretion to:
 - Treatment group 1)** Concurrent (early) ipilimumab and SBRT: 50 Gy in 4 fractions to 1-4 liver lesion(s).
 - Treatment group 2)** Sequential (late) ipilimumab and SBRT: 50 Gy in 4 fractions to 1-4 liver lesion(s).
2. Patients with at least 1 lung metastasis treatable to SBRT at 50 Gy in 4 fractions will be assigned based on the investigators discretion to:
 - Treatment group 3)** Concurrent (early) ipilimumab and SBRT: 50 Gy in 4 fractions to 1-4 lung lesion(s).
 - Treatment group 4)** Sequential (late) ipilimumab and SBRT: 50 Gy in 4 fractions to 1-4 lung lesion(s).
3. Patients with either 1 liver or lung metastasis not treatable to SBRT at 50 Gy in 4 fractions or an adrenal metastasis will be assigned to:
 - Treatment group 5)** Sequential (late) ipilimumab and SBRT: 60 Gy in 10 fractions to 1-4 lung, liver, or adrenal lesion (s).

Table 5: Dose De-Escalation and Maximum Tolerated Dose Scheme

Number of Patients with DLT* at a Given Dose Level (assessed independent for each of the 4 cohorts)	De-Escalation Decision Rule
0 out of 3	Enter 3 more patients at this dose level

≥ 2	Dose de-escalation will occur. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be entered at the next lowest radiation dose level, as per table 2.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, then this is the maximum tolerated dose (MTD). If 1 or more of this group suffer DLT, then dose de-escalation will occur. Three additional patients will be entered at the next lowest dose level.
MTD: The highest dose at which no more than 1 of 6 evaluable patients has had a DLT. Six patients should be treated before the dose is declared the MTD.	

**The time window for DLT evaluation in the dose de-escalation phase is 29 days in the concurrent SBRT and ipilimumab group and 50 days in the sequential SBRT and ipilimumab group (Approximately 1 week after initiation of ipilimumab cycle 2)*

Dose De-escalation

Dose Level	SBRT 50 Gy in 4 fractions (Treatment Groups 1-4)	SBRT 60 Gy in 10 fractions (Treatment Group 5)	Ipilimumab dose (Treatment Groups 1-5)
1	50 Gy in 12.5 Gy / fraction for 4 fractions	60 Gy in 6 Gy / fraction for 10 fractions	3mg/kg intravenous every 21 days
-1	37.5 Gy in 12.5 Gy / fraction for 3 fractions	48 Gy in 6 Gy / fraction for 8 fractions	3mg/kg intravenous every 21 days
-2	25 Gy in 12.5 Gy / fraction for 2 fractions	36 Gy in 6 Gy / fraction for 6 fractions	3mg/kg intravenous every 21 days

Additional subjects will generally be accrued in multiples of three, or until DLT is observed in $\geq 33\%$ of subjects treated. This may be done concurrent with the higher dose cohort.

Once the MTD is determined for a specific cohort, an additional 14 patient expansion cohort (20 patients total for each cohort) will be enrolled in in that cohort at the MTD dose to further define this dose and help determine biological endpoints. Should DLTs occur in more than 33% of patients enrolled into this expanded cohort, dosing at that level will be stopped. The next lower dose level will be considered the MTD. A review of all DLTs observed will be conducted, and the need to lower the dose will be based on the discussion and agreement between the IRB and the Investigator.

All patients who receive any ipilimumab will be considered evaluable for response and will be included in the efficacy data set.

10.1.1. Safety Evaluation

The incidence of clinical and laboratory adverse events will be reported and graded according to the NCI-CTCAE version 4.0 (available at <http://ctep.cancer.gov/reporting/ctc.html>). Adverse events will be reported in frequency tables overall, by intensity, and by relationship. Laboratory values will be reported in shift tables and with summary statistics.

10.1.2. Efficacy Evaluation

Information on the anti-tumor activity of ipilimumab and SBRT combination therapy will be collected in throughout this study. Tumor response will be determined using the Immune Related Response Criteria (irRC) as described in section 8.3. Efficacy evaluations using radiologic assessments will be performed every 2 cycles of study treatment and monthly thereafter. The same radiologic procedures used to define measurable or non-measurable disease at baseline must be used throughout the study.

10.2. Analysis

10.2.1. Statistical Analysis

Descriptive statistics will be computed for all relevant outcomes, including tumor response, and biomarker response. Descriptive analysis will include a global assessment of patient outcomes among all cohorts. Cohort analysis will be conducted between cohorts (**Table 2**). All patients receiving at least 1 treatment with ipilimumab at the MTD will be included in the analysis.

Demographics, safety, and treatment efficacy will be compared in two separate analyses:

1. Among different treatment regimes: treatment groups 1, 3 vs. treatment groups 2, 4, and 5.
2. Among different SBRT targets: treatment groups 1 and 2 vs. treatment groups 3 and 4.

Table 2: Independent Cohorts

Metastatic or primary lesion amenable to SBRT treatment

		Liver lesion treatable with 50 Gy / 4 Fc (n=40)	Lung lesion treatable with 50 Gy / 4 Fc (n=40)	Liver/lung lesion not treatable with 50 Gy/ 4 Fc or adrenal lesion (n=20)
Treatment Sequence	Concurrent: SBRT (50 Gy/ 4 Fc) + Ipilimumab (n=40)	Treatment Group 1 (n=20)	Treatment Group 3 (n=20)	
	Sequential: SBRT (50 Gy/ 4 Fc) + Ipilimumab (n=40)	Treatment Group 2 (n=20)	Treatment Group 4 (n=20)	

Sequential: SBRT (60 Gy/ 10 Fc) + Ipilimumab (n=20)	Treatment Group 5 (n=20)
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10.2.2. Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated by dose/cohort. Summary statistics for age, body weight, height, and Body Mass Index (BMI) will be tabulated by dose/cohort. Comparisons by Chi-Squared or Fisher Exact Test will be conducted to assess for baseline differences between cohorts.

10.2.3. Safety Analyses

All recorded adverse events will be recorded per MDACC guidelines using CTCAE Version 4.0. Frequency of grade ≥ 3 adverse events will be compared via Chi-Squared or Fisher Exact Test.

10.2.4. Efficacy Analyses

Treatment success will be defined as CR or PR assessed using irRC (e.g. the best response obtained by a patient). Measurements from all imaging, including those obtained during and after re-induction ipilimumab, will be considered in this analysis. Patients will be continuously evaluated for disease response via imaging until they are removed from the study. For secondary objectives a), b), and c), success probabilities will be estimated for each target separately (liver, lung, adrenal) along with appropriate 95% confidence intervals. Efficacy comparisons between groups will be assessed with regard to the irRC outcomes (out of field (primary endpoint) while global, in-field irRC will be used for hypothesis generating) using Pearson chi-squared or Fisher exact tests. For secondary objective d) cohorts 2, 4, and 5 (sequential) will be compared with cohorts 1 and 3 (concurrent). For secondary objective e) comparisons will be performed between cohorts 1 and 2 (liver), 3 and 4 (lung), and 5 (adrenal).

1. **Global irRC:** irRC that factors all lesions both index and non-index as outlined in 8.3.
2. **In-Field irRC:** irRC in which only SBRT-treated lesions will be considered and non-index lesions arising inside the SBRT PTV
3. **Out-Field irRC:** irRC in which only non SBRT-treated lesions will be considered and non-index lesions arising outside the SBRT PTV

For secondary objective d), the two groups being compared will have at least 60 and 40 patients respectively. With these sample sizes, we would have 80% power using a two-sided 5% alpha to detect a response rate of 46% as statistically different from a response rate of 20%, 58% as different from 30%, 68% as statistically different from 40% and 77% as statistically different from 50%.

To increase statistical power, we will also combine the patients into a single dataset and fit a logistic regression model with response (CR+PR) as the outcome and SBRT dose, order (sequential or concurrent), target (liver, lung, adrenal) among other factors (including but not limited to: number of metastatic disease sites, number of prior treatments, primary cancer histology, age, pre-treatment KPS and Royal Marsden Score) as the predictors.

Time-to-event analyses will be conducted via Kaplan-Meier analysis, with comparisons via the log-rank test made with regards **overall survival**, with analysis beginning at receipt of the first SBRT fraction. At the discretion of the investigators, multivariate Cox regression will be done to adjust for (among other

factors): number of metastatic disease sites, number of prior treatments, primary cancer histology, age, pre-treatment KPS and Royal Marsden Score.

10.2.5. Sample Size/Accrual Rate

The maximum planned number of patients will be 100, with 20 patients being treated in each of the 5 arms. It is estimated that approximately 3 patients per month into each treatment group will be accrued and an approximate 4 week interval will be allowed between dose levels.

10.2.6. Treatment Group Stratification

In the event that a patient presents with both a liver and a lung lesion that are both amenable to stereotactic radiation, the treatment of either the liver or lung site will be at the discretion of the treating physician. Otherwise patients will be stratified in a 1:1 ratio between receiving concurrent or sequential SBRT and ipilimumab.

10.2.7. Thyroid Patient Expansion

An additional 20 patients with thyroid cancer (any histology) will be enrolled into a separate phase II expansion arm. A separate analysis (analyzed as described above) will be conducted with these 20 patients in addition to all other patients enrolled on this study with thyroid cancer.

11. References

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12. Study Calendars

12.1. Dose De-Escalation Study Calendar: Sequential Ipilimumab x2→SBRT→ Ipilimumab x2

Assessment Tool (Study related visit range \pm 2 days)	Baseline ³	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Follow Up Period Every 1-3 months (every 2- 4 months after) \pm 1 month ^{10,11}		
		Week			Week			Week			Week					
		1	2	3	1	2	3	1	2	3	1	2	3			
SBRT						X ⁴										
Ipilimumab		X ⁶			X				X				X			
DLT Assessment									X ⁸							
History & Physical Exam (including weight measurement)¹	X	X			X				X	X			X			X
CBC & differential¹	X	X			X				X	X			X			X
ECG	X ⁷															
Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium Albumin, alkaline phosphatase, total bilirubin, SGOT (AST), SGPT[ALT], TSH¹	X	X			X				X	X			X			X
Urinalysis¹	X															
Serum pregnancy test (women of childbearing potential)¹	X															
irRC imaging and tumor assessment	X ²							X					X			X
Biomarker studies (optional)	X ⁵				X ⁵			X ₅				X ₅			X ⁵	X ⁵
Biopsies (optional)	X ⁹														X	

- Physical exams and lab tests measurements will be given a window of \pm 3 days unless patient/logistical/medical reasons intervene. Every patient requires physician evaluation within 7 days before start of study and \pm 3 days before each subsequent ipilimumab administration.
- Initial tumor assessment should occur within 4-weeks before start of study.
- Baseline visit within 2 weeks prior to initiation of therapy. Overlapping baseline tests can be combined with tests required for cycle 1 of ipilimumab administration as long as these baseline tests occur within 3 days before cycle 1.
- SBRT will be given on days 30-33 of treatment protocol for 50Gy in 4 fraction, Patients receiving 60Gy in 10 fractions will receive radiation on days 30-41, ipilimumab will be started on day 1
- Per protocol PA13-0291, for all patients within the expansion arms, serum biomarker measurements will be taken at baseline (2 weeks prior to therapy initiation) and during the last cycle of ipilimumab administration. Additional draws may be obtained during follow up and cycles 1-4 of ipilimumab administration.
- First ipilimumab treatment will begin on day 1 (\pm 3) and start a 21 day/cycle combination therapy.
- A baseline ECG will be recorded within 1-2-weeks (\pm 3 days) prior to therapy initiation
- (\pm 7 days) DLT assessment will include both evaluate by the phase I research nurse with optional input from the radiation oncology research nurses.
- Optional biopsies will be obtained prior to the first cycle of ipilimumab and at the end of the last cycle per the discretion of the treating physician.

10. Follow up appointments after last cycle of ipilimumab will occur in the Clinical Center for Targeted Therapy. Radiation oncology follow up visits will occur on the discretion of the treating radiation oncologist, we recommend at 3 and 6 months.
11. Patients will be offered 4 cycles of reinduction ipilimumab +/- radiation if disease control (SD or PR) is observed at the first imaging after cycle 4 of ipilimumab. Reinduction can occur 8 weeks or later after the last cycle of ipilimumab induction. Patients can be offered repeat reinduction if disease control is observed and severe (grade >3 toxicity) is not observed.

12.2. Dose De-Escalation Study Calendar: Concurrent Ipilimumab and SBRT

Assessment Tool (Study related visit range \pm 2 days)	Baseline ³	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Follow Up Period Every 1-3 months (every 2-4 months after) +1 month ^{10,11}
					Week			Week			Week			
		1	2	3	1	2	3	1	2	3	1	2	3	
SBRT		X ⁴												
Ipilimumab		X ⁶			X			X			X			
DLT Assessment						X ⁸								
History & Physical Exam (including weight measurement) ¹	X	X			X	X		X			X			X
CBC & differential ¹	X	X			X	X		X			X			X
ECG ⁷	X ⁷													
Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium Albumin, alkaline phosphatase, total bilirubin, SGOT (AST), SGPT[ALT], TSH ¹	X	X			X			X			X			X
						X								
Urinalysis ¹	X													X
Serum pregnancy test (women of childbearing potential) ¹	X													
irRC imaging and tumor assessment	X ²						X					X		X
Biomarker studies (optional)	X ⁵			X ⁵			X ⁵			X ⁵		X ⁵		X ⁵
Biopsies (optional) ⁹	X												X	

- Physical exams and lab tests measurements will be given a window of \pm 3 days unless patient/logistical/medical reasons intervene. Every patient requires physician evaluation within 7 days before start of study and \pm 3 days before each subsequent ipilimumab administration.
- Initial tumor assessment should occur within 4-weeks before start of study.
- Baseline visit within 2 weeks prior to initiation of therapy. Overlapping baseline tests can be combined with tests required for cycle 1 of ipilimumab administration as long as these baseline tests occur within 3 days before cycle 1.
- SBRT will be given on days 2-5 of treatment protocol.
- Per protocol PA13-0291, for all patients within the expansion arms, serum biomarker measurements will be taken at baseline (2 weeks prior to therapy initiation) and during the last cycle of ipilimumab administration. Additional draws may be obtained during follow up and cycles 1-4 of ipilimumab administration.
- First ipilimumab treatment will begin on day 1 (\pm 3) and start a 21 day/cycle combination therapy.
- A baseline ECG will be recorded within 1-2-weeks (\pm 3 days) prior to therapy initiation

8. (\pm 7 days) DLT assessment will include both evaluate by the phase I research nurse with optional input from the radiation oncology research nurses.
9. Optional biopsies will be obtained prior to the first cycle of ipilimumab and at the end of the last cycle per the discretion of the treating physician.
10. Follow up appointments after last cycle of ipilimumab will occur in the Clinical Center for Targeted Therapy. Radiation oncology follow up visits will occur on the discretion of the treating radiation oncologist, we recommend at 3 and 6 months.
 11. Patients will be offered 4 cycles of reinduction ipilimumab +/- radiation if disease control (SD or PR) is observed at the first imaging after cycle 4 of ipilimumab. Reinduction can occur 8 weeks or later after the last cycle of ipilimumab induction. Patients can be offered repeat reinduction if disease control is observed and severe (grade >3 toxicity) is not observed.
- 12.