IDENTIFIERS: NCT03115801

UNIQUE PROTOCOL ID: 1606017369

BRIEF TITLE: A Phase II Randomized Trial of Immunotherapy Plus Radiotherapy in Metastatic Genitourinary Cancers

VERSION DATE: 05SEP2019

VERSION #: 4.1

IRB APPROVAL: 20OCT2020

Document History

Amendment number	Version number	Version Date
Amendment 4	**4.1**	**09.05.2019**
Amendment 3	4.0	07.12.2017
Amendment 2	3.0	06.21.2017
Amendment 1	2.0	12.15.2016
Initial Protocol	1.0	10.27.2016

TITLE: A Phase II randomized controlled trial of PD-1/PDL-1 axis blockade versus PD-1/PDL-1 axis blockade plus radiotherapy in metastatic genitourinary (renal/urothelial) malignancies

IRB Protocol #: 1606017369
Version Date: 09.05.2019
Version number: 4.1

Principal Investigator:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Biostatistician:

[redacted]

Study Coordinator:

Sharanya Chandrasekhar
525 East 68th street
Box 169
New York, NY 10065
212-746-7277
shc2043@med.cornell.edu

Data Coordinator:

[redacted]

Participating Centers:

1. Stich Radiation Oncology – 525 East 68th Street, Box 169, New York, NY 10065
2. Lower Manhattan Cancer Center – 21 West Broadway, New York, NY 10007

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

All abbreviations used throughout the protocol must be defined

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBAF	Human Research Billing Analysis Form
ICF	Informed Consent Form
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAP	Unanticipated Problem
WCM	Weill Cornell Medical College
ANC	Absolute Neutrophil Count
BID	Twice a Day
CAT (or CT scan)	Computed Axial Tomography
CBC	Complete Blood Count
CR	Complete Response
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECOG PS	Eastern Cooperative Oncology Group Performance Status
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
irRC	Immune related response criteria
MRI	Magnetic Resonance Imaging
PD	Progressive Disease
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response
QD	Once Daily
QoL	Quality Of Life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SPD	Sum of the products diameters
SD	Stable Disease
TNM Staging	Tumor, Node and Metastasis Staging
TA	Tumor assessment
BOR	Best overall response

Document history:

Amendment number	Version number	Version Date
Amendment 4	**4.1**	**09.05.2019**
Amendment 3	4.0	07.12.2017
Amendment 2	3.0	06.21.2017
Amendment 1	2.0	12.15.2016
Initial Protocol	1.0	10.27.2016

Summary of changes: Amendment 4.1 dated 09.05.2019

Changes to the DSMB monitoring plan based on DSMB's recommendations.

Summary of changes : Amendment 4 dated 07.20.2017

1. Adding Pembrolizumab (Keytruda) for Urothelial Cancer patients.
2. Removing MRI brain from screening procedures for the patients in the Urothelial Cancer cohort.
    a. Rationale for removing MRI brain from Urothelial Cohort :
        -

Summary of changes: Amendment 2 dated 03.08.2017

1. Removing Dr. Encouse Golden from the protocol and adding Dr. Himanshu Nagar as the Principal investigator on the study. Dr. Encouse Golden will be leaving the institution as of June 2017.
2. Optional research biopsies

Summary of changes: Amendment 1 dated 12.15.2016

1. Adding new FDA approved modified dose for nivolumab – flat dose of 240mg.
2. Administrative changes
3. Changes to calendars for both nivolumab and atezolizumab (administrative changes)
4. Inclusion criteria - At least 2 weeks since last radiation therapy.

1

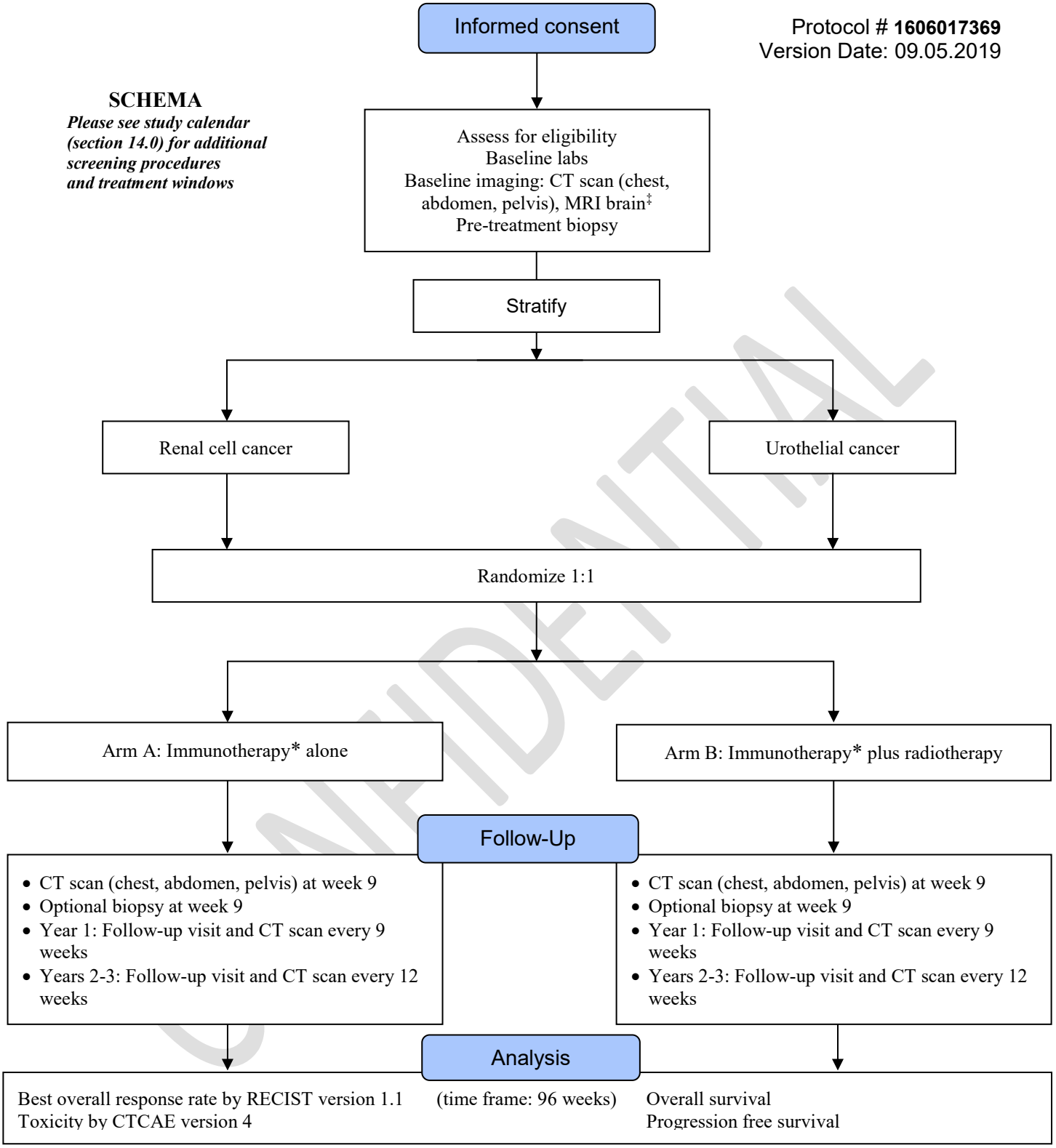
Protocol Summary

Full Title:	Phase II randomized trial of PD-1/PDL-1 axis blockade versus PD-1/PDL-1 axis blockade plus radiotherapy in metastatic genitourinary (renal/urothelial) malignancies
Short Title:	*Immunotherapy Plus Radiotherapy in Genitourinary Malignancies*
Clinical Phase:	*Phase II*
Principal Investigator:	*Dr. Himanshu Nagar. M.D. .*
Sample Size:	*N = 112*
Accrual Ceiling:	*129*
Study Population:	Eligible patients have metastatic renal cell carcinoma/urothelial carcinoma with at least 2 measurable sites of disease.
Accrual Period:	We expect to accrue up to 112 patients over three years and at an accrual rate of approximately 40 patients per year.
Study Design:	Eligible patients have metastatic renal cell carcinoma/urothelial carcinoma with at least 2 measurable sites of disease. All eligible patients will be randomly assigned to immunotherapy (Nivolumab/Atezolizumab/Pembrolizumab) versus immunotherapy (Nivolumab/Atezolizumab/ Pembrolizumab) plus radiotherapy, 10 Gy x3 (conformally or by IMRT/IGRT to maximally spare normal tissue), to one of their measurable lesions. For patients assigned to the immunotherapy plus radiotherapy arm, immunotherapy treatment starts with the first radiotherapy fraction. Nivolumab will be given every 2 weeks for patients with metastatic renal cell cancer and Atezolizumab (flat dose 1200mg) or Pembrolizumab (flat dose 200mg) will be given every 3 weeks for patients with metastatic urothelial cancer. Patients will be re-imaged at 9 week (year 1) or 12 week (years 2-3) intervals and evaluated for response (defined as an objective response of measurable metastatic sites outside the radiation field). This response will be evaluated with CT scans in non-irradiated measurable metastatic sites per RECIST version 1.1. Patients will continue to receive their respective immunotherapies for up to three years or until disease progression or until a dose limiting toxicity is reached.

Study Duration:	*Participants will have approximately up to 25-35/yr visits and a follow-up for up to 3 years.*
Study Agent/ Intervention:	Patients with metastatic renal cell carcinoma will receive Nivolumab intravenously at a flat dose of 240mg every two weeks. Infusions will be given over 60 minutes (not bolus or IV push). Patients will continue to receive infusions every two weeks for up to three years or until disease progression or until a dose limiting toxicity is reached. Patients with metastatic urothelial cancer will receive Atezolizumab intravenously at 1200mg every three weeks or Pembrolizumab at a flat dose of 200mg every three weeks (Physician's discretion). Patients will continue to receive infusions every two or three weeks for up to three years or until disease progression or until a dose limiting toxicity is reached. Patients randomized to the radiotherapy arm will receive radiation every other day. A dose of 10 Gy x3 days will be administered.
Primary Objectives:	The primary aim is to estimate the difference in best overall response (BOR; time frame: 96 weeks) rates using RECIST version 1.1, in patients with metastatic renal cell/urothelial carcinoma when treated with immunotherapy alone and immunotherapy plus radiotherapy (to a single metastatic site).
Secondary Objectives:	The secondary aims are: 1) to estimate the median progression free survival and the median overall survival for patients treated with immunotherapy and immunotherapy plus radiotherapy, and 2) to assess the toxicity (per CTCAE version 4.0) of patients treated with immunotherapy and immunotherapy plus radiotherapy.
Exploratory (Correlatives) Objectives:	Exploratory analyses will include: 1) examination of an association between clinical responses and anti-tumor immune responses (cellular and humoral responses) and 2) comparison of T cell subsets within tumors and in the peripheral blood at baseline versus at the time of response evaluation.
Endpoints:	The primary endpoint will be BOR (time frame: 96 weeks) rates as evaluated using RECIST version 1.1. Other end points include progression free-survival and overall survival.

SCHEMA

Please see study calendar (section 14.0) for additional screening procedures and treatment windows



- *Renal cell cancer patients – Nivolumab (flat dose of 240mg) q2 weeks up to 3 years. Immune labs to be drawn prior to infusion on Days1, 29 and 57.
- *Urothelial cancer patients – Nivolumab (flat dose of 240mg) q2 weeks up to 3 years or Atezolizumab (1200mg) q3 weeks up to 3 years or Pembrolizumab (flat dose of 200mg) every 3 weeks up to 3 years. Immune labs to be drawn prior to infusion on Days1, 43 and 64.
- Radiation (10 Gy x3 fractions) will be delivered on days 1, 3 and 5.
- ‡ MRI brain for patients in the RENAL Cancer cohort only.

Table of Contents

1.0 Study Objective

1.3 *1.1 Primary Objectives*

The primary objective of this study is to estimate, in patients with metastatic renal cell/urothelial carcinoma, the best overall response (BOR; time from: 96 weeks) rates of immunotherapy alone and of immunotherapy plus radiotherapy (to a single metastatic site) and to estimate the difference in BOR rates between these two treatment groups.

1.3.1.1 1.2 Secondary Objectives

The secondary objectives are to estimate the progression free survival and overall survival for patients treated with immunotherapy and immunotherapy plus radiotherapy and to assess the toxicities related to these two treatment groups.

1.3.1.2 1.3 Exploratory Objectives

The following exploratory analyses will be performed: 1.) The examination of an association between clinical responses and anti-tumor immune responses; 2.) The comparison of changes in T cell subsets within tumors and in the peripheral blood at baseline versus at response evaluation.

1.4 2.0 Background

2.1 Disease

Combining radiotherapy with immunotherapy presents potential therapeutic advantages. Because of its localized nature, radiotherapy is devoid of most systemic effects, including interference with systemic immunotherapy, commonly encountered with chemotherapy. However, a radiotherapy-focused intervention on the tumor may selectively subvert its micro-environment and, in combination with the optimal immune intervention, ideally render the cancer an *in situ* vaccine.

A phase 3 randomized trial comparing nivolumab (3mg/kg) with everolimus in patients with renal cell carcinoma demonstrated an improvement in overall survival with nivolumab, whereby the median overall survival was 25 months versus 19.6 months, respectively. Additionally, the BOR was greater with nivolumab versus everolimus (25% versus 5%, median time to response 3.5 months versus 3.7 months).[3] Similarly, in a phase II trial for patients with metastatic urothelial cancer treated with atezolizumab, atezolizumab demonstrated an objective response rate of 15% compared to a 10% historical response rate with conventional chemotherapy.[4]

The promising data on the effect of PD1/PDL1 blockade in renal cell and urothelial carcinoma render this an optimal clinical setting to test this regimen with radiotherapy in order to assess the role of radiotherapy in inducing abscopal responses. **Thus, we are proposing a PHASE II prospective randomized trial that compares PD1/PDL1 blockade alone to PD1/PDL1 blockade plus radiotherapy in patients with metastatic renal cell or urothelial cancer.**

2.2 Investigational Agents

Nivolumab (Opdivo®)

Nivolumab is a fully human IgG4 PD-1 immune checkpoint-inhibiting antibody that selectively blocks the interaction between PD-1, which is expressed on activated T cells, and PD-1 ligand 1 (PD-L1) or 2 (PD-L2), which are expressed on both immune and tumor cells. The interaction between PD-1 and PD-L1 or PD-L2 normally results in inhibition of cellular immune responses.

Atezolizumab (Tecentriq™)

Atezolizumab is an engineered humanized monoclonal IgG1 antibody that binds selectively to PD-L1 and prevents its interaction with PD-1 and B7-1, while sparing the interaction between PD-L2 with PD-1.

Pembrolizumab (Keytruda™)

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

2.3 Therapeutic Rationale

An attractive area of research supports the use of immune manipulations to recover patients' initial antitumor immunity. It is a strategy that has the advantages of being both natural and potentially long-lasting.[5] We propose combining radiotherapy with immunotherapy directed to a metastatic site to establish a "hub" for *in situ* immunization against an irradiated tumor, to enhance "tumor rejection" at additional metastatic sites. The use of radiotherapy has been explored as a viable approach to establish an individualized vaccine. In a "proof of principle" clinical trial, we previously showed that radiotherapy in combination with GM-CSF, a dendritic cell recruiter and activator, in patients with metastatic solid tumors was safe and effective at establishing abscopal responses in 27% of treated patients. We found that those who achieved an abscopal response not only possessed a better immune system (as demonstrated by a lower neutrophil to lymphocyte ratio) at baseline but also demonstrated a longer median survival.[6] Additionally, we recently completed the accrual of a phase II clinical trial for patients with metastatic non-small cell lung cancer treated with ipilimumab, a CTLA4 inhibitor and T-cell activator, plus radiotherapy to a metastatic site. We were able to achieve responses (either partial or complete per RECIST version 1.1) in 18% of treated patients (~30% of treated patients had an abscopal response), whereby CTLA-4 blockade alone historically achieved response rates of only ~5.[7,8] An example of a patient with a complete response to treatment is shown (Figure 1). The patient was treated to one liver metastasis, 6Gy x5, while receiving CTLA-4 blockade. The posttreatment PET/CT (completed on January 2013) demonstrated a complete response to therapy ~4 months after the initiation of

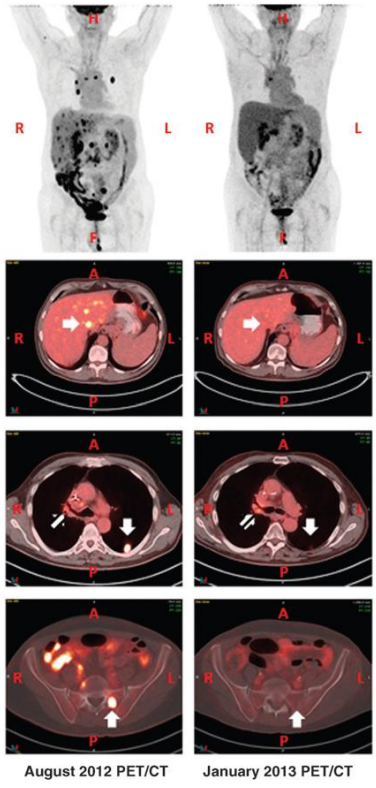


Figure 1

treatment. The patient remains alive >3 years post treatment.[9,10]

1.4.1.1.1 2.3.1 PD1/PDL1 and T-Cell Activation

The mechanistic rationale for the use of immunotherapy with anti-programmed death 1 (PD-1) receptor and anti-programmed death ligand 1 (PD-L1) antibodies are displayed (Figure 2).[11] Antigen-presenting cells take up tumor associated-antigens released from cancer cells and present them to T cells. Cancer cells can also present antigens to activated T cells for their subsequent T-cell mediated elimination. Upon T cell activation, PD-1 receptors are expressed on T cells and inhibit immune responses through engagement of PD-L1 and PD-L2 on antigen presenting cells and PD-L1 on cancer cells. The immune modulation mediated by this pathway ensures protection of tissue from collateral damage during an inflammatory response. Tumor cells use this regulatory mechanism to evade tumor-directed T-cell responses by upregulating the PD-1 ligands, B7-H1 and B7-DC. Therefore, monoclonal antibody (mAb)-mediated blockade of the PD-1/PD-L1/PD-L2 pathway can enhance antitumor immunity. Thus, the advances in the understanding of the mechanisms that regulate T cell activation have allowed the rational design of new immunotherapeutic strategies against tumors, including renal cell and urothelial carcinoma.

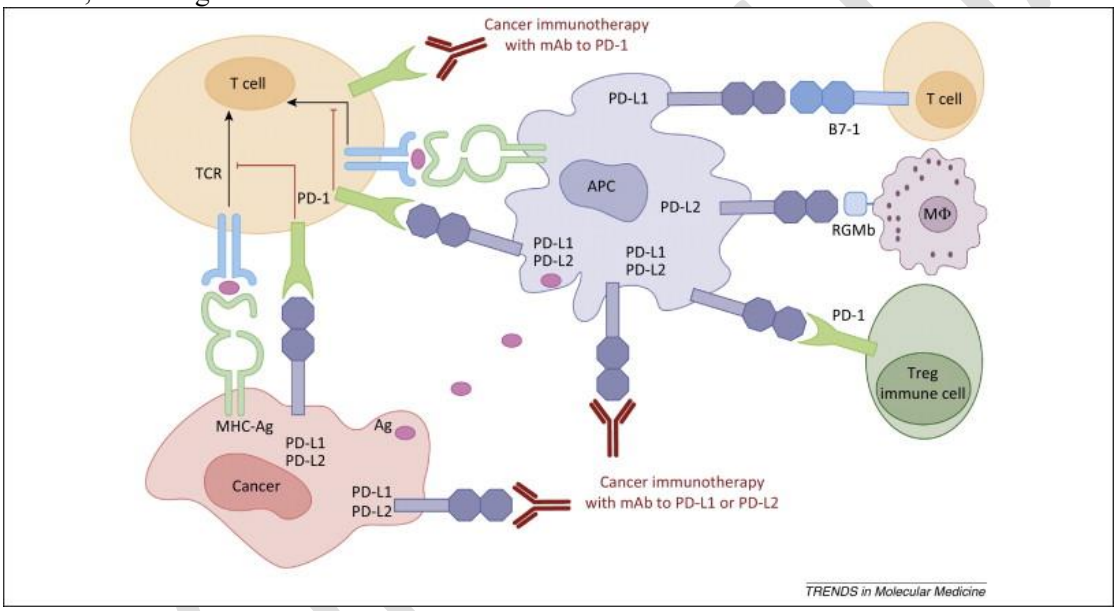


Figure 2[11]

1.4.1.1.2 2.3.2 PD1/PDL1 axis blockade

The identification of multiple tumor-associated antigens in recent years has provided many potential good targets for vaccination. The ability of cytolytic T cells to eradicate cancers has been unequivocally demonstrated in experimental models.[12] Clinical trials have also provided evidence that treating cancer successfully via immune manipulation is efficacious.[13,14] However, significant clinical responses of patients with well-established/vascularized tumors are difficult to achieve with current immunotherapeutic strategies. Immune tolerance is a major therapeutic obstacle that occurs when a tumor becomes clinically apparent and upon tumor progression. The PD1/PDL1 axis is a key component in the maintenance of immune tolerance. Although the PD1/PDL1 axis is required for normal lymphoid homeostasis, in conditions of suboptimal antigen-presenting cell function, such as in tumor-bearing hosts, the transient blockade of the PD1/PDL1 axis reignites effective anti-tumor immunity.[15-17] However, the efficacy of PD1/PDL1 axis blockade as a

single treatment modality remains limited to intrinsically immunogenic tumors, where exhausted T cells prevail. For poorly immunogenic tumors, like most human cancers, additional immunomodulatory signals may be necessary to recruit/produce additional antigen specific effector T cells to achieve clinically meaningful responses.[18] Results from recent clinical trials show that T cell manipulation is a potent strategy to induce active antitumor immunity, however the importance of integration of this modality with additional immunotherapeutic approaches is becoming more evident.[19]

Interestingly, radiotherapy can lead to an adaptive upregulation of tumor cell PD-L1 expression, dependent on CD8+ T cell production of IFNγ, thereby limiting the efficacy of a radiation-induced anticancer immune response. Thus, tumor cell expression of PD-L1 may act as a biomarker for local antitumor response, suggesting that local radiotherapy may be sufficient to prime CD8+ T-cell responses, but unable to generate durable anticancer immunity. However, antibodies targeting the PD-1/PD-L1 axis given concurrently with radiotherapy may be capable to overcome this type of immune tolerance, while bolstering treatment response and extending survival.[20]

1.4.1.1.3 2.3.3 Radiotherapy-induced immunogenic cell death

Radiotherapy has been shown to have immunogenic properties. Three hallmarks of tumor cell death responsible for the establishment of adaptive antitumor immunity leading to tumor rejection have been thoroughly elucidated (Figure 3).[1] Calreticulin cell-surface translocation (a dendritic cell "eat me signal") accelerates the uptake of tumor associated antigen (needed for dendritic cell cross-presentation to helper and

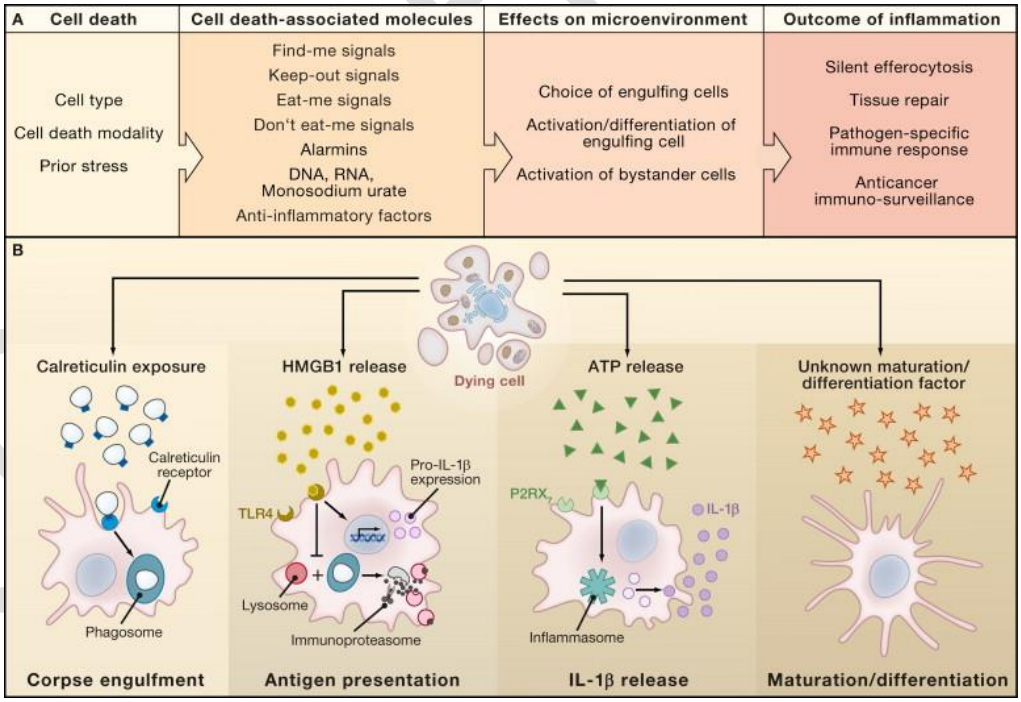


Figure 3[1]

effector T cells), while the release of danger associated molecular patterns (DAMPs, such as HMGB1 and ATP) into the peri-tumoral milieu lead to dendritic cell activation via the P2RX7 and TLR4 receptors. We previously showed that radiotherapy fosters immunogenic cell death in tumor cells in a dose-dependent manner (Figure 4).[2] Thus, radiation is capable of acting locally to inflame a tumor and promote cross-

priming of effector T cells with the capacity to circulate in the blood and promote tumor rejection in non-irradited tumors. In addition to immunogenic cell death, radiotherapy has been shown to increase cell surface expression of MHC class I molecules and increase antigen presentation, thereby improving cytotoxic T cell recognition of irradiated tumor cells.[21]

1.4.1.1.4 2.3.4 Abscopal effect of radiotherapy

Originally described by R.H. Mole in 1953, the abscopal effect of radiotherapy is a remote effect of ionizing radiation on tumors outside of the radiation field.[22] The phenomenon was termed the abscopal effect, from the Latin *ab* (position away from) and *scopus* (mark or target). Other investigators, over the years, have reported findings consistent with the abscopal effect, which was considered to be the result of recovered anti-tumor immunity after radiotherapy.[23-25] The absocapl effect of radiotherapy is rare and its mechanism remains unexplained, although a variety of biologic events have been proposed [26] including the involvement of the immune system.[26-28]

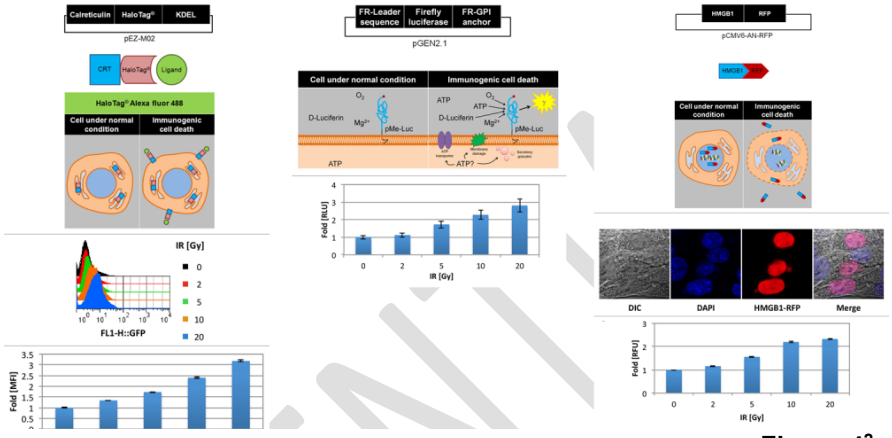


Figure 4[2]

1.4.1.1.5 2.3.5 Immunotherapy plus radiotherapy: preclinical studies

In addition to inciting immunogenic cell death, ionizing radiation has been shown to alter the tumor milieu by enhancing trafficking of immune cells, inducing inflammatory cytokines and co-stimulatory molecules, and promoting cross-priming (reviewed in ref [29]). We have applied the term "abscopal" (ab-scopus, away from the target, originally introduced by Mole et al.[22]) to define a systemic effect elicited by radiotherapy in the presence of immunotherapy.[28]

We have shown that local radiotherapy in combination with immune checkpoint blockade (to break immune tolerance of established primary tumors) can be used in place of vaccination with autologous tumor cells to promote effector T-cell mediated anti-tumor responses in poorly immunogenic 4T1 mouse mammary carcinoma.[30,31] The elicited immune response was effective against spontaneous lung metastases as well as the primary tumor. Regressing primary tumors demonstrated an increased infiltration of effector T cells and an expanded pool of circulating tumor-specific memory effector T cells was observed. These results demonstrate that radiotherapy to the primary tumor may induce a therapeutically effective anti-tumor response in combination with immune checkpoint blockade, suggesting that radiotherapy may provide antigenic stimulation similar to vaccination with irradiated autologous tumor cells.

1.4.1.1.6 2.3.6 Harnessing the pro-immunogenic effects of radiation in cancer treatment: a new paradigm

Experimental work done in two syngeneic mouse models (Lewis lung tumors and mammary carcinomas)

testing radiotherapy with FLT-3 ligand (a growth factor for dendritic cells) demonstrated the induction of an immune response that reduced tumor growth outside the field of radiation [28,32]. The findings inspired a clinical trial testing the combination of subcutaneously injected GM-CSF (a growth factor and activator of dendritic cells) with radiotherapy to a metastatic site in patients with solid tumors. GM-CSF increased the percentage of dendritic cells and their maturation, facilitating cross-presentation of newly released antigens after cell death at the site of radiotherapy. With a standard radiation fractionation of 3.5 Gy x10 fractions, abscopal responses were detected in 27% of the patients accrued to the trial.[6] Those who achieved an abscopal response from therapy presented with a better pretreatment immune system (as demonstrated by a baseline neutrophil to lymphocyte ratio <4) and subsequently demonstrated an improved overall survival (Figure 5).

Abscopal responses were also detected among 15 patients with low-grade B-cell lymphoma treated by low-dose radiotherapy to a single tumor site that was injected with a synthetic oligodeoxynucleotide (also referred to as CpG) that targets TLR9, express on the surface of dendritic cells. These compounds can activate both lymphoma B-cells as well as nearby antigen-presenting cells, particularly plasmacytoid dendritic cells, as previously demonstrated in a murine lymphoma model.[33]

Another combination strategy to overcome immune-tolerance consists of the blockade of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a negative regulator of T cell activation. Prolonged survival and some cures occurred in a syngeneic model of poorly immunogenic mammary carcinoma, a process requiring CD8+T cells [30]. Postow et al.[34] recently reported a clinical case report with the same combination. A melanoma patient with disease progression while receiving ipilimumab, a monoclonal antibody that targets CTLA-4, was treated with hypo-fractionated radiotherapy to a pleural-based paraspinal metastasis. Several other pre–existing metastases in the spleen and in the right lung hilum (outside the radiation field) completely regressed and remained controlled for an additional eight months. Importantly, immuno-monitoring of several markers, including antibody response to NY-ESO-1 mirrored the clinical course. Seromic analysis detected 10 antigenic targets with enhanced antibody responses after radiotherapy. A similar effect was previously reported in a study of radiation with a recombinant cancer vaccine to prostate cancer.[35] These results, although still anecdotal, support the concept that local radiotherapy and immunotherapy can synergize to produce a therapeutically effective anti-tumor immune-response.

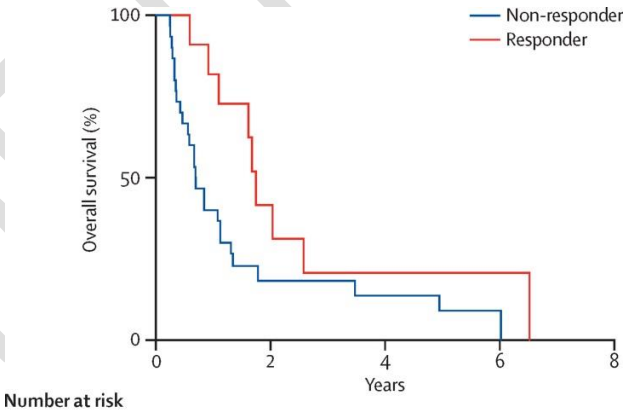


Figure 5

Combining radiotherapy with immunotherapy is promising and presents advantages. Because of its localized nature, radiotherapy is devoid of most systemic effects commonly encountered with chemotherapy, thereby limiting interference with a systemic immunotherapy. Moreover, a radiotherapy-focused intervention on the tumor may selectively subvert its micro-environment and in combination with the optimal immune intervention, may ideally render the cancer a personalized *in situ* vaccine.

We recently presented our results of a phase II clinical trial of radiotherapy with CTLA-4 blockade in lung cancer patients, whereby 18% of treated patients achieved a partial or complete response by RECIST version 1.1 (30% of treated patients achieved an abscopal response). Similar to our trial of radiotherapy in

combination with GM-CSF for metastatic solid tumors, patients who achieved stable disease or a complete/partial response subsequently demonstrated an improved median survival compared to those who had disease progression upon completion of their treatment.[6]

Finally, the promising data on the effect of PD1/PDL1 axis blockade in renal cell and urothelial cancers render this clinical setting optimal to test the approach with radiotherapy to assess the role of radiotherapy in improving treatment responses per RECIST version 1.1, while inducing abscopal effects (a surrogate for radiotherapy induced antitumor immunity) for the purpose of improving overall survival. **Thus, we are proposing a Phase II prospective randomized trial that compares PD1/PDL1 axis blockade alone to PD1/PDL1 axis blockade and radiotherapy in patients with metastatic renal cell and urothelial cancers.**

1.5 3.0 Summary of investigational program [Nivolumab]

1.5.1.1 3.1 Clinical Pharmacology

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. Nivolumab injection for intravenous infusion is supplied in single-dose vials. Each mL of nivolumab solution contains Nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

1.5.1.1.1.1.1 3.1.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Combined Nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased antitumor activity.

1.5.1.2 3.2 Non-Clinical Toxicology

1.5.1.2.1.1 3.2.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

1.5.1.2.1.2 3.2.1.1 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis–infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

1.5.1.3 3.3 Clinical Safety

Nivolumab monotherapy (OPDIVO™) is approved for the treatment of unresectable or metastatic melanoma in multiple countries including Japan, the US, and the EU. Nivolumab is also approved for the treatment of metastatic NSCLC and Renal Cell Carcinoma in the US.

Qualitative and qualitative information received as of 29-Apr-2015 has been consistent with the established safety profile as observed in clinical trials. No new safety concerns were identified based on the global post marketing reports.

1.5.1.4 3.4 Clinical Studies

[Renal Cell Carcinoma]

Trial 6 was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after one or two prior anti-angiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. This trial excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

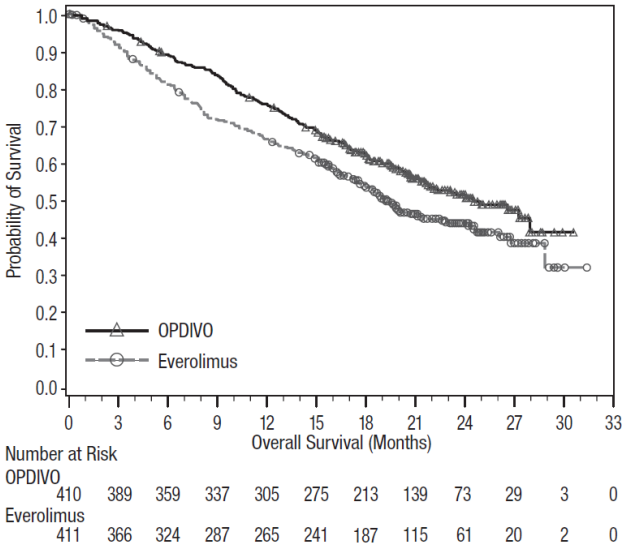
Patients were stratified by region, Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group and the number of prior anti-angiogenic therapies. Patients were randomized to nivolumab (n=410) administered intravenously at 3 mg/kg every 2 weeks or everolimus (n=411) administered orally 10 mg daily. The median age was 62 years (range: 18 to 88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and white (88%) and 34% and 66% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. The majority of patients (77%) were treated with one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 34% favorable, 47% intermediate, and 19% poor. The first tumor assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. The major efficacy outcome measure was overall survival (OS). The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with everolimus at the pre-specified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table and Figure). OS benefit was observed regardless of PD-L1 expression level.

Other endpoints include confirmed objective response rates, which are also presented Table 18.

Table 18: Efficacy Results - Trial 6

	OPDIVO (n=410)	Everolimus (n=411)
Overall Survival		
Events (%)	183 (45)	215 (52)
Median survival in months (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (95% CI)	0.73[a] (0.60, 0.89)	
p-value	0.0018[b]	
Confirmed Objective Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median duration of response in months (95% CI)	23.0 (12.0, NE)	13.7 (8.3, 21.9)
Median time to onset of confirmed response in months (min, max)	3.0 (1.4, 13.0)	3.7 (1.5, 11.2)

[a] Hazard ratio is obtained from a Cox proportional hazards model stratified by MSKCC risk group, number of prior anti-angiogenic therapies, and region with treatment as the sole covariate.
[b] p-value is obtained from a two-sided log-rank test stratified by MSKCC risk group, number of prior anti-angiogenic therapies, and region. The corresponding O'Brien-Fleming efficacy boundary significance level is 0.0148.



1.5.1.5 3.5 How Supplied/Storage And Handling - nivolumab

Carton Contents	NDC
40 mg/4 mL single-dose vial	0003-3772-11
100 mg/10 mL single-dose vial	0003-3774-12

Store nivolumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake.

1.5.1.6 3.6 Drug Related SAEs: Nivolumab

1.5.1.6.1 3.6.1 Immune-mediated Pneumonitis

Immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with nivolumab treatment. Across clinical trial experience in patients receiving nivolumab, fatal immune-mediated pneumonitis occurred in 0.2% (5/2166) of patients. All five fatal cases occurred in a dose-finding study with nivolumab doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

In Renal Cell Carcinoma patients, pneumonitis, including interstitial lung disease, occurred in 5% (21/406) of patients receiving nivolumab. Immune mediated pneumonitis occurred in 4.4% (18/406) of patients receiving nivolumab (one with Grade 4, four with Grade 3, twelve with Grade 2, and one with Grade 1). The median time to onset was 3.82 months (range: 2 days to 22.3 months). The median duration was 1.3 months (range: 0.3 to 9.8 months).

1.5.1.6.2 3.6.2 Immune-Mediated Colitis

Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, can occur with nivolumab treatment. Monitor patients for signs and symptoms of colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. When administered as a single agent, withhold nivolumab for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue nivolumab for life-threatening (Grade 4) or for recurrent colitis upon restarting nivolumab.

In patients with RCC, diarrhea or colitis occurred in 25% (100/406) of patients receiving nivolumab and 32% (126/397) of patients receiving everolimus. Immune-mediated diarrhea or colitis occurred in 3.2% (13/406) of patients receiving nivolumab (five patients with Grade 3, seven with Grade 2, and one with Grade 1). The median time to onset was 4.8 months (range: 2 days to 15.6 months). The median duration was 1.3 months (range: 0.2 to 3.9 months).

1.5.1.6.3 3.6.3 Immune-Mediated Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology, can occur with nivolumab treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold nivolumab for moderate (Grade 2) and permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis

In Renal cell carcinoma patients, there was an increased incidence of liver test abnormalities compared to baseline with increases in AST (33% vs. 39%), alkaline phosphatase (32% vs. 32%), ALT (22% vs. 31%), and total bilirubin (9% vs. 3.5%) in the nivolumab and Everolimus arms, respectively. Immune-mediated hepatitis requiring systemic immunosuppression occurred in 1.5% (6/406) of patients receiving nivolumab (five with Grade 3 and one with Grade 2). The median time to onset was 3.7 months (range: 14 days to 5.3 months). The median duration was 1.8 months (range: 0.9 to 16.3 months).

1.5.1.6.4 3.6.4 Immune mediated Endocrinopathies

1.5.1.6.5 3.6.4.1 Hypophysitis

Hypophysitis can occur with nivolumab treatment. Monitor patients for signs and symptoms of hypophysitis. Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater hypophysitis. Withhold nivolumab for moderate (Grade 2) or severe (Grade 3) and permanently discontinue nivolumab for life-threatening (Grade 4) hypophysitis

1.5.1.6.6 In RCC, hypophysitis occurred in 0.5% (2/406) of patients receiving nivolumab. The time to onset for the Grade 3 event was 9.2 months and for the Grade 1 event was 3.2 months.

1.5.1.6.7 3.6.4.2 Adrenal Insufficiency

Adrenal insufficiency can occur with nivolumab treatment. Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold nivolumab for moderate (Grade 2) and permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency.

In RCC patients, adrenal insufficiency occurred in 2.0% (8/406) of patients receiving nivolumab (three with Grade 3, four with Grade 2, and one with Grade 1). The median time to onset was 5.8 months (range: 22 days to 20.9 months).

1.5.1.6.8 3.6.4.3 Hypothyroidism and Hyperthyroidism

Thyroid disorders can occur with nivolumab treatment. Monitor thyroid function prior to and periodically during treatment. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of nivolumab for hypothyroidism or hyperthyroidism.

In RCC, thyroid disease occurred in 11% (43/406) of patients on nivolumab, including one Grade 3 event, and in 12/397 (3.0%) patients on everolimus. Hypothyroidism/ thyroiditis occurred in 8% (33/406) of patients receiving nivolumab (two patients with Grade 3, 17 patients with Grade 2, and 14 patients with Grade 1). The median time to onset was 4.6 months (range: 15 days to 13.6 months).

1.5.1.6.9 3.6.4.4 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus can occur with nivolumab treatment. Monitor for hyperglycemia. Administer insulin for type 1 diabetes and withhold nivolumab in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue nivolumab for life-threatening (Grade 4) hyperglycemia.

In RCC, hyperglycemic adverse events occurred in 9% (37/406) of patients. Diabetes mellitus or diabetic ketoacidosis occurred in 1.5% (6/406) of patients receiving nivolumab (three patients with Grade 3, two patients with Grade 2, and one patient with Grade 1).

The median time to onset was 7.8 months (range: 2.3 to 21.8 months).

1.5.1.6.10 3.6.5 Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology, can occur with nivolumab treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Withhold nivolumab for moderate (Grade 2) or severe (Grade 3) increased serum creatinine and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue nivolumab. Permanently discontinue nivolumab and administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine.

In RCC, renal injury occurred in 7% (27/406) of patients on nivolumab and 3.0% (12/397) of patients on everolimus, rather than laboratory creatinine. Immune-mediated nephritis and renal dysfunction occurred in 3.2% (13/406) of patients receiving nivolumab (one with Grade 5, one with Grade 4, five with Grade 3, and six with Grade 2). The median time to onset was 5.4 months (range: 1.1 to 12.3 months). Median duration was 1.4 months (range: 0.1 to 18 months).

1.5.1.6.11 3.6.6 Immune-Mediated Rash

Immune-mediated rash can occur with nivolumab treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of nivolumab. Monitor patients for rash. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold nivolumab for severe (Grade 3) rash and permanently discontinue nivolumab for life-threatening (Grade 4) rash.

In RCC, rash occurred in 28% (112/406) of patients on nivolumab and 36% (143/397) of patients on everolimus. Immune-mediated rash, defined as a rash treated with systemic or topical corticosteroids, occurred in 7% (30/406) of patients receiving nivolumab (four with Grade 3, seven with Grade 2, and nineteen with Grade 1). The median time to onset was 3.2 months (range: 2 days to 25.8 months). Median duration was 2.6 months (range: 0.3 to 9.4 months).

1.5.1.6.12 3.6.7 Immune-Mediated Encephalitis

Immune-mediated encephalitis can occur with nivolumab treatment. Withhold nivolumab in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI and lumbar puncture. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue nivolumab for immune-mediated encephalitis

1.5.1.6.13 3.6.8 Other immune-mediated adverse reactions

Other clinically significant immune-mediated adverse reactions can occur with nivolumab. Immune-mediated adverse reactions may occur after discontinuation of nivolumab therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting nivolumab after completion of corticosteroid taper based on the severity of the event.

1.5.1.6.14 3.6.9 Infusion Reactions

Severe infusion reactions have been reported in less than 1.0% of patients in clinical trials of nivolumab. Discontinue nivolumab in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

1.5.1.6.15 3.6.10 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, nivolumab can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a nivolumab-containing regimen and for at least 5 months after the last dose of nivolumab

1.5.1.6.16 3.6.11 Drug Related Deaths

Based on reports from the safety data base the rate of death on treatment or within 30 days of the last dose of study drug was 4.7%. Serious adverse reactions occurred in 47% of patients receiving nivolumab. The most frequent serious adverse reactions reported in at least 2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia.

The most common adverse reactions (reported in at least 20% of patients) were asthenic conditions, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia.

1.6 4.0 Summary of investigational program [Atezolizumab]

Atezolizumab is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma. Atezolizumab is an Fc-engineered, humanized, monoclonal antibody that binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors. Atezolizumab is a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

Atezolizumab injection for intravenous infusion is a sterile, preservative-free, and colorless to slightly yellow solution in single-dose vials. Each mL of Atezolizumab contains 60 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), sucrose (821.6 mg), polysorbate 20 (8 mg), pH 5.8.

1.6.1.1 4.1 Clinical Pharmacology

1.6.1.1.1 4.1.1 Mechanism of Action

PD-L1 may be expressed on tumor cells and/or tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment.

Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production. Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

1.6.1.2 4.2 Non-clinical toxicology

1.6.1.2.1 4.2.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of atezolizumab for carcinogenicity or genotoxicity. Animal fertility studies have not been conducted with atezolizumab; however, an assessment of the male and female reproductive organs was included in a 26-week, repeat-dose toxicity study in cynomolgus monkeys. Weekly administration of atezolizumab to female monkeys at the highest dose tested caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries. This effect occurred at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible. There was no effect on the male monkey reproductive organs.

1.6.1.2.2 4.2.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

1.6.1.3 4.3 Clinical Studies

Urothelial Carcinoma

Atezolizumab was investigated in Study 1, a multicenter, open-label, two-cohort trial that included patients with locally advanced or metastatic urothelial carcinoma. In Cohort 2 of Study 1, 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with atezolizumab. This study excluded patients who had: a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, or administration of systemic immunostimulatory agents or systemic immunosuppressive medications. Patients received an intravenous infusion of 1200 mg of atezolizumab every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed objective response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DoR).

In this cohort, the median age was 66 years, 78% were male, 91% patients were Caucasian. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had visceral metastases. Sixty-two percent of patients had an ECOG score of 1 and 35% of patients had a baseline creatinine clearance of < 60 mL/min. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty one percent of patients had received ≥ 2 prior systemic regimens in the metastatic setting. Seventy-three percent of patients received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens.

Tumor specimens were evaluated prospectively using the Ventana PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 310 patients, 32% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [ICs] covering ≥ 5% of the tumor area). The remaining, 68% of patients, were classified as having PD-L1 expression of <5% (PD-L1 stained tumor infiltrating ICs covering < 5% of the tumor area).

Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 3.
The median follow-up time for this cohort was 14.4 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

1.6.1.4 4.4 How Supplied/Storage and Handling - Atezolizumab

Atezolizumab injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion supplied as a carton containing one 1200 mg/20 mL single-dose vial (NDC 50242-917-01).

Storage: Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.

Do not freeze. Do not shake.

1.6.1.5 4.5 Drug Related SAEs: Atezolizumab

1.6.1.5.1 4.5.1 Immune-Related Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving Atezolizumab. Across clinical trials, 2.6% (51/1978) of patients developed pneumonitis. Fatal pneumonitis occurred in two patients. In 523 patients with urothelial carcinoma who received Atezolizumab, pneumonitis occurred in 6 (1.1%) patients. Of these patients, there was one patient with fatal pneumonitis, one patient with Grade 3, three patients with Grade 2, and one patient with Grade 1 pneumonitis. Atezolizumab was held in all cases and five patients were treated with corticosteroids.

The median time to onset was 2.6 months (range: 15 days to 4.2 months). The median duration was 15 days (range: 6 days to 3.1+ months).

Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer steroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Withhold Atezolizumab until resolution for Grade 2 pneumonitis. Permanently discontinue Atezolizumab for Grade 3 or 4 pneumonitis.

1.6.1.5.2 4.5.2 Immune-Related Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving Atezolizumab. Liver test abnormalities occurred in patients who received Atezolizumab. Across clinical trials (n=1978), Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.3%), and total bilirubin (1.6%). In patients with urothelial carcinoma (n=523) Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.5%), and total bilirubin (2.1%). Immune-mediated hepatitis occurred in 1.3% of patients. Of these cases, one patient died from hepatitis, five patients had Grade 3, and one patient had Grade 2 hepatitis. The median time to onset was 1.1 months (range: 0.4 to 7.7 months).

Monitor patients for signs and symptoms of hepatitis. Monitor AST, ALT, and bilirubin prior to and periodically during treatment with Atezolizumab. Administer corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin, followed by corticosteroid taper. Withhold Atezolizumab for Grade 2 and permanently discontinue Atezolizumab for Grade 3 or 4 immune mediated Hepatitis.

1.6.1.5.3 4.5.3 Immune-Related Colitis

Immune-mediated colitis or diarrhea, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving Atezolizumab. Across clinical trials, colitis or diarrhea occurred in 19.7% (389/1978) of all patients and in 18.7% (98/523) of patients with urothelial carcinoma. Ten patients (1.9%) developed Grade 3 or 4 diarrhea. Four patients (0.8%) had immune-mediated colitis or diarrhea with a median time to onset of 1.7 months (range: 1.1 to 3.1 months).

Monitor patients for signs and symptoms of diarrhea or colitis. Withhold treatment with Atezolizumab for Grade 2 diarrhea or colitis. If symptoms persist for longer than 5 days or recur, administer 1–2 mg/kg prednisone or equivalent per day. Withhold treatment with Atezolizumab for Grade 3 diarrhea or colitis. Treat with IV methylprednisolone 1–2 mg/kg per day and convert to oral steroids once the patient has improved. For both Grade 2 and Grade 3 diarrhea or colitis, when symptoms improve to Grade 0 or Grade 1, taper steroids over ≥ 1 month. Resume treatment with Atezolizumab if the event improves to Grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone per day. Permanently discontinue Atezolizumab for Grade 4 diarrhea or colitis.

1.6.1.5.4 4.5.4 Immune-Related Endocrinopathies

Immune-related thyroid disorders, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus, including diabetic ketoacidosis, have occurred in patients receiving Atezolizumab. Monitor patients for clinical signs and symptoms of endocrinopathies.

1.6.1.5.4.1 4.5.4.1 Hypophysitis

Hypophysitis occurred in 0.2% (1/523) of patients with urothelial cancer receiving Atezolizumab. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids and hormone replacement as clinically indicated. Withhold Atezolizumab for Grade 2 or Grade 3 and permanently discontinue for Grade 4 hypophysitis.

1.6.1.5.4.2 4.5.4.2 Thyroid Disorders

Thyroid function was assessed routinely only at baseline and the end of the study. Across clinical trials, hypothyroidism occurred in 3.9% (77/1978) of patients and in 2.5% (13/523) of patients with urothelial carcinoma. One patient had Grade 3 and twelve patients had Grade 1–2 hypothyroidism. The median time to first onset was 5.4 months (range: 21 days to 11.3 months).

Hyperthyroidism occurred in 1.0% (20/1978) of patients across clinical trials and in 0.6% (3/523) of patients with urothelial carcinoma. The median time to onset was 3.2 months (range: 1.4 to 5.8 months). TSH was decreased and below the patient's baseline in 3.8% (5/131) of patients with a follow-up measurement.

Monitor thyroid function prior to and periodically during treatment with Atezolizumab. Asymptomatic patients with abnormal thyroid function tests can receive Atezolizumab. For symptomatic hypothyroidism, withhold Atezolizumab and initiate thyroid hormone replacement as needed. Manage isolated hypothyroidism with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, withhold Atezolizumab and initiate an anti-thyroid drug as needed. Resume treatment with Atezolizumab when symptoms of hypothyroidism or hyperthyroidism are controlled and thyroid function is improving.

1.6.1.5.4.3 4.5.4.3 Adrenal Insufficiency

Adrenal insufficiency occurred in 0.4% (7/1978) of patients across clinical trials, including two patients with Grade 3, four patients with Grade 2, and one patient with Grade 1. Adrenal insufficiency resolved in two patients.

For symptomatic adrenal insufficiency, withhold Atezolizumab and administer methylprednisolone 1–2 mg/kg per day IV followed by oral prednisone 1–2 mg/kg per day or equivalent once symptoms improve. Start steroid taper when symptoms improve to ≤ Grade 1 and taper steroids over ≥ 1 month. Resume treatment with Atezolizumab if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone per day and the patient is stable on replacement therapy, if required.

1.6.1.5.4.4 4.5.4.4 Diabetes Mellitus

New onset diabetes with ketoacidosis has occurred in patients receiving Atezolizumab. Diabetes mellitus without an alternative etiology occurred in one (0.2%) patient with urothelial carcinoma. Initiate treatment with insulin for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycemia (fasting glucose >250–500 mg/dL), withhold Atezolizumab. Resume treatment with Atezolizumab when metabolic control is achieved on insulin replacement therapy.

1.6.1.5.5 4.5.5 Other Immune-Related Adverse Reactions

Other immune-related adverse reactions including meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré, ocular inflammatory toxicity, and pancreatitis, including increases in serum amylase and lipase levels, have occurred in ≤ 1.0% of patients treated with Atezolizumab.

4.5.5.1 Meningitis / Encephalitis

Monitor patients for clinical signs and symptoms of meningitis or encephalitis. Permanently discontinue Atezolizumab for any grade of meningitis or encephalitis. Treat with IV steroids (1– 2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or equivalent) once the patient has improved. When symptoms improve to ≤ Grade 1, taper steroids over ≥ 1 month.

4.5.5.2 Motor and Sensory Neuropathy

Monitor patients for symptoms of motor and sensory neuropathy. Permanently discontinue Atezolizumab for any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Institute medical intervention as appropriate. Consider initiation of systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone.

4.5.5.3 Pancreatitis

Symptomatic pancreatitis without an alternative etiology occurred in 0.1% (2/1978) of patients across clinical trials. Monitor patients for signs and symptoms of acute pancreatitis. Withhold Atezolizumab for ≥ Grade 3 serum amylase or lipase levels (> 2.0 ULN), or Grade 2 or 3 pancreatitis. Treat with 1−2 mg/kg IV methylprednisolone or equivalent per day. Once symptoms improve, follow with 1−2 mg/kg of oral prednisone or equivalent per day. Resume treatment with Atezolizumab if serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Permanently discontinue Atezolizumab for Grade 4 or any grade of recurrent pancreatitis.

Severe infections, including sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal hemorrhage occurred in patients receiving Atezolizumab. Across clinical trials, infections occurred in 38.4% (759/1978) of patients. In 523 patients with urothelial carcinoma who received Atezolizumab, infection occurred in 197 (37.7%) patients. Grade 3 or 4 infection occurred in 60 (11.5%) patients, while three patients died due to infections. Urinary tract infections were the most common cause of Grade 3 or higher infection, occurring in 37 (7.1%). Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold Atezolizumab for ≥ Grade 3 infection.

1.6.1.5.6 4.5.6 Infusion-Related Reactions

Severe infusion reactions have occurred in patients in clinical trials of Atezolizumab. Infusion related reactions occurred in 1.3% (25/1978) of patients across clinical trials and in 1.7% (9/523) of patients with urothelial carcinoma. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue Atezolizumab in patients with Grade 3 or 4 infusion reactions.

4.5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, Atezolizumab can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Atezolizumab and for at least 5 months after the last dose.

1.6.1.5.7 4.5.8 Drug related deaths

No information currently available.

1.7 Summary of investigational program

1.8 5.0 Overall Risk/Benefit Assessment

Nivolumab, Atezolizumab and Pembrolizumab have demonstrated durable tumor regressions and upon use as single agents have generally been well tolerated in the majority of patients. Drug-related immune-mediated phenomena have been observed in about half of the patients, predominately involving the lung, GI

tract, endocrine glands, or skin. Serious drug related pneumonitis (defined as those meeting the SAE definition) occurred in approximately 1-2% of subjects. Treatment related pneumonitis causing death occurred in ~0.2% of patients. The rate of SAEs is less than would be expected with high dose IL-2 or combination chemotherapy regimens. Meanwhile, the expected response rate for PD1/PDL1 checkpoint blockade is in the 15 - 20% range. In addition, preliminary data suggest that duration of response with PD1/PDL1 checkpoint blockade may be more durable than responses with combination chemotherapy.

The overall risk benefit ratio for patients entering this protocol is therefore at least comparable to, and possibly better than alternative options.

1.9 6.0 Study Rationale

1.9.1.1 6.1 Combining radiotherapy and PD1/PDL1 blockade

The availability of Nivolumab and Atezolizumab and the Phase I/ II experience with the antibody, make them compelling to translate the preclinical findings of abscopal effects in poorly immunogenic syngeneic murine tumors. Moreover, modern image guided radiotherapy has the advantage of enabling conformal and precise delivery of large radiation doses to a selected volume, with both the advantage of convenience to the patient (only five visits) and possibly, the induction of a more favorable inflammatory response.

1.9.1.2 6.2 Study Design

The specific aims are:

1. To explore the induction of immune-mediated tumor responses outside the radiation field (abscopal effect) after immunotherapy and radiotherapy in metastatic renal cell and urothelial cancers, by estimating and comparing the best overall response (time frame: 96 weeks) rates in patients treated with immunotherapy alone or in combination with radiation.
2. To assess progression free survival (PFS), Overall survival (OS) and safety.
3. To compare the induction of effector T cell responses in patients with metastatic renal cell and urothelial cancer treated with either immunotherapy alone or in combination with radiation.

Eligible patients with metastatic renal cell and urothelial cancers must have at least two separate measurable sites of disease. Extent of metastatic disease is recorded by CT scanning or MRI. There are two cohorts of patients; patients with renal cell carcinoma and patients with urothelial cancers. Patients will be stratified into one of two cohorts (based on tumor type, renal cell carcinoma [cohort 1] or urothelial carcinoma [cohort 2]) and subsequently randomized to either immunotherapy without radiation (Arm A) or immunotherapy with radiation (Arm B).

In Arm A:
1. Patient with Renal Cell carcinoma will receive Nivolumab alone Days* 1, 15, 29, 43 and 57.
2. Patients with Urothelial cancer will receive either Nivolumab on Days* 1, 15, 29 43 and 57, or Atezolizumab or Pembrolizumab on Days* 1, 22, 43 and 64.

(* - infusions will have a ± 3 days window to accommodate inevitable scheduling changes and holidays)

In Arm B:

1. Radiation is given to one lesion, 30 Gy in 3 fractions of 10 Gy each, over a one week interval (with a minimum of 36hrs between each fraction), conformally or by intensity modulated radiation treatment to maximally spare normal tissue On the day of radiation (Day 1) immunotherapy is administered and repeated on the scheduled days. Patients will receive radiation on Day 1 and immunotherapy will be given ± 24hr from Day 1.
2. Patient with Renal Cell carcinoma will receive Nivolumab alone Days* 1, 15, 29, 43 and 57.
3. Patients with Urothelial cancer will receive either Nivolumab alone on Days* 1, 15, 29,43 and 57 or Atezolizumab or Pembrolizuab on Days* 1, 22, 43 and 64.

(* - infusions will have a ± 3 days window to accommodate inevitable scheduling changes and holidays)

Patients on both treatment arms will undergo re-imaging on Day 63 (±7days), (Renal cell carcinoma patients should have received 5 doses; Urothelial Cancer patients should have received 3-4 doses) and every 9 weeks (± 7 days) for one year and every 12 weeks(±7 days) thereafter.

1.10 7.0 Correlative studies

1.10.1.1 7.1 Evaluation of the cellular immune responses

The development of immune responses to multiple tumor associated antigens has been suggested to play a crucial role in determining the therapeutic efficacy of immunotherapy.[36] It has been suggested that the mutational load may predict for responses to PD1/PDL1 axis blockade and may be responsible the expression of neoepitopes necessary for the development of antitumor immunity. These immune analyses are considered exploratory and ancillary to the primary goals of the trial. The most comprehensive analysis will be based on testing the T cell and B cell response to renal cell and urothelial cancer associated tumor antigens. The advantage of this approach is the inclusion of all antigens expressed by tumors including unknown as well as cryptic epitopes.

1.10.1.2 7.2 Immune monitoring

Serial blood samples collected at baseline, and at selected time points during and post treatment will be processed to collect plasma/serum and peripheral blood mononuclear cells (PBMCs) which be used to evaluate humor and cellular immunity induced by PD1/PDL1 axis blockade alone vs. PD1/PDL1 axis blockade and radiotherapy.

Immune monitoring labs will be collected before each infusion on the following days.

Nivolumab patients will have immune monitoring samples on Days 1(±24hrs), 29 (±3days), and 57(±3days)

Atezolizumab patients will have immune monitoring samples on Days 1(±24hrs), 43(±3days) and 64 (±3days).

Pembrolizumab patients will have immune monitoring samples on Days 1 (±24hrs), 43(±3days) and 64 (±3days).

1.10.1.3 7.3 Determine the repertoire of humoral responses induced by immunotherapy and radiation

We will use seromics technology to evaluate the repertoire of antibody responses. Seromics is an antibody profiling method utilizing protein microarrays with the capacity to detect >8000 antigens induced by a vaccine. Assays will be performed as described previously.[37] Plasma/serum collected at the various time points will be plated onto ProtoArrays (v4.0; Invitrogen) and incubated with fluorescent antibodies. Arrays will be scanned at 10uM resolution using microarray scanner (Axon 4200AL with GenePix Pro Software; Molecular Devices) to detect fluorescence. We will look specifically at antibodies to neoepitopes, differentiation and cancer-testis antigens, in addition to p53, survivin etc.

1.10.1.4 7.4 Determine the induction and the quality of the T cell responses in patients

For initial screening for CD4+ and CD8+ T cell responses to PD1/PDL1 axis blockade vs. PD1/PDL1 axis blockade plus radiotherapy, we will analyze PBMCs directly ex vivo and after in vitro stimulation. For ex vivo analysis, PBMCs will be stimulated with peptide pools to differentiation and cancer testis antigens and discovered neoepitopes for 6 hours and evaluated by intracellular cytokine staining. Staining for cytokines will be performed using a panel of antibodies to IL-2, IFNγ, TNF, and IL4. For in vitro stimulation, PBMCs will be first stimulated with overlapping peptide pools 20 days and then evaluated by intracellular cytokine staining, similar to the ex vivo analysis.

For an in-depth analysis of CD4+ and CD8+ T cell responses to treatment, we will use flow based assays including Cytometry either by multicolor-flow or by Time-of-Flight (CYTOF) at a single-cell level as described previously.[38] Cells are labeled using antibodies with metal-labeled isotopes and analyzed by a high throughput mass spectrometry to quantify 36 or more parameters at a better resolution than can be seen using flow cytometry. We will simultaneously analyze differentiate various T cell subsets (naïve, memory, central memory, terminal effector), phenotype (e.g. PD-1, CTLA-4 for exhausted phenotypes; foxp3 for Treg) cytokine secretion (IL-2, IFNγ, TNF, MIP1 alpha and IL4), antigen specificity (tetramer staining), and proliferative potential (CFSE).

1.10.1.5 7.5 Tissue biopsies

Pre- and post-treatment tumor biopsies of both irradiated tumors and non-irradiated tumors will be taken when possible and analyzed for lymphocyte infiltration, character of lymphocyte infiltration (CD4 and CD8 T cell subsets, TH1 vs TH2 profiles (by T-bet vs, GATA-3 staining), T regulatory cells (foxp3+), PD-1 or CTLA-4 expressing T cells, and DC subsets), NKG2d levels, and MHC class I levels using standard immunohistochemistry techniques.[39] In addition we will evaluate the tumor cells for MI count and expression of PD-1 ligands e.g. PD-L1/L2. Baseline tumor tissue will also be examined for cancer testis antigen expression (NY-ESO-1, MAGEA3, PRAME etc) and gene expression.

1.10.1.6 7.6 Endpoint analyses for immune responses analyses

The main immunological end-point will be the induction or boosting of treatment induced T cells (CD4+ and CD8+) and B cells for defined antigen approaches. In addition, the magnitude and duration of T and B cell responses will be examined. Treatment-induced responses will be calculated as the difference between the pre-treatment measurement and the measurement at the different time points at which blood was collected (time of evaluation) in the same patient. The percentage of patients with the induction of treatment-induced T and B cell responses will be reported.

1.11 8.0 Subject Selection Criteria

1.11.1.1 8.1 Inclusion Criteria

1. Ability to understand and the willingness to sign a written informed consent document;
2. Any prior therapy is permitted except prior therapy with PD1/PDL1 inhibitor.
3. Histologic diagnosis of metastatic renal cell carcinoma or urothelial cancer;
4. Patients must have at least 2 distinct measurable metastatic sites at least 1 cm or larger in their largest diameter per RECIST 1.1
5. Patients must have adequate organ and marrow function as defined by initial laboratory tests:
   - WBC ≥ 2000/uL
   - ANC ≥ 1000/uL
   - Platelets ≥ 50 x 10^3/uL
   - Hemoglobin ≥ 10.0 g/dL
   - Creatinine ≤ 3.0 x ULN
   - AST/ALT ≤ 2.5 x ULN
   - Bilirubin ≤ 3.0 x ULN, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL);
6. At least 2 weeks since last chemotherapy and 4 weeks since last immunotherapy treatment.
7. At least 2 weeks since last radiation therapy.
8. Performance status ECOG 0-1
9. Men and women, ages > 18 years of age.
10. Life expectancy > 3 months
11. Stable brain metastases for at least 4 weeks and not steroid dependent
12. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the study in such a manner that the risk of pregnancy is minimized. Should a woman become pregnant or suspect she is pregnant while she is enrolled in this study, she should inform her treating physician immediately.
    WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL]. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

    WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study medication.

1.11.1.2 8.2 Exclusion Criteria

1. Patients having no lesions outside the field of radiation thus nullifying the ability to measure an abscopal effect;

2. Any other malignancy from which the patient has been disease-free for less than 5 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix;
3. Autoimmune/auto inflammatory disease: Patients with a history of inflammatory bowel disease are excluded from this study as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], Systemic Lupus Erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis];
4. 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, such as a condition associated with frequent diarrhea;
5. Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to one month prior to or after any dose of PD-1/PDL-1 blocking antibody).
6. A history of prior treatment with PD-1/PDL-1blocking antibody;
7. Patients who have had immunotherapy within 4 weeks prior to entering the study.
8. Concomitant therapy with any of the following: IL-2, interferon or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids;
9. Patients undergoing therapy with other investigational agents or other chemotherapy agents;
10. Women who:
    a) are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for at least 8 weeks after cessation of study drug, or
    b) have a positive pregnancy test at baseline, or
    c) are pregnant or breastfeeding
11. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious) illness

9.0 Study Therapy [Nivolumab]

9.1 Nivolumab

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Patients with Renal cell carcinoma will receive Nivolumab intravenously at a flat dose of 240mg every two weeks. Infusions will be given over 60 minutes (<u>not</u> bolus or IV push).

In Arm A:
Patient with Renal Cell carcinoma will receive nivolumab alone Days* 1, 15, 29, 43 and 57.
(* - infusions will have a ± 3 days window to accommodate inevitable scheduling changes and holidays)

In Arm B:
Radiation is given to one lesion, 30 Gy in 3 fractions of 10 Gy each, over one week interval (with a minimum of 36 hours between each fraction), conformally or by intensity modulated radiation treatment to maximally spare normal tissue.

On the day of radiation (Day 1) immunotherapy is administered and repeated on the scheduled days.
Patients will receive radiation on Day 1 and immunotherapy will be given ± 24hr from Day 1.

Patients on both treatment arms will undergo re-imaging on Day 63 (±7 days) (after the first 5 doses of Nivolumab) and every 9 (±7 days) weeks for one year and every 12 weeks (±7 days) thereafter.
The first dose will be administered on Day 1(± 24hrs) and repeated on Days 15, 22, 43 and 57.
Radiation will be delivered every other day (with a minimum of 36 hours between the fractions) preferably starting on a Monday. A dose of 10 Gy x 3 days will be tested.

9.2 Preparation and Administration of Nivolumab

Dose Calculations
For Advanced Renal cell carcinoma: Nivolumab is given every 2 weeks. The recommended dose of nivolumab is a flat dose of 240mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

9.2.1 Preparation

1. Withdraw the required volume of nivolumab and transfer into an intravenous container.

2. Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.

- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.

9.2.2 Storage of Infusion

The product does not contain a preservative. After preparation, store the nivolumab infusion either:

- At room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

9.2.3 Administration

Administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not co-administer other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

9.3 Dose Modifications

Recommendations for nivolumab modifications are provided in Table 1. There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue nivolumab in patients with severe or life-threatening infusion reactions. Please refer to Table below for Recommended Dose Modifications.

Adverse Reaction	Severity*	Dose Modifications
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose[a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue

Rash	Grade 3 rash	Withhold dose[a]
	Grade 4 rash	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

[a] Resume treatment when adverse reaction returns to Grade 0 or1.
* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

10.0 Study Therapy [Atezolizumab]

10.1 Atezolizumb

Atezolizumab is an Fc-engineered, humanized, monoclonal antibody that binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors. Atezolizumab is a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

In Arm A:
Patients with Urothelial cancer will receive either Nivolumab on Days* 1, 15, 29, 43 and 57 or Atezolizumab or Pembrolizumab on Days* 1, 22, 43, 64
(* - infusions will have a ± 3 days window to accommodate inevitable scheduling changes and holidays)

In Arm B:
Radiation is given to one lesion, 30 Gy in 3 fractions of 10 Gy each, over one week interval (with a minimum of 36 hours between each fraction), conformally or by intensity modulated radiation treatment to maximally spare normal tissue.

On the day of radiation (Day 1) immunotherapy is administered and repeated on the scheduled days.
Patients will receive radiation on Day 1 and immunotherapy will be given ± 24hr from Day 1.

Patients on both treatment arms will undergo re-imaging on Day 63 (±7 days) (after completing 5(after completing 4 doses of Atezolizumab) and every 9weeks (±7 days) for one year and every 12 weeks (±7 days) thereafter.

The first dose will be administered on Day 1(± 24hrs) and repeated on Days 15, 22, 43 and 64.
Radiation will be delivered every other day (with a minimum of 36 hours between each fraction), starting on Day 1. A dose of 10 Gy x 3 days will be tested.

Dose Calculations

Injection: 1200 mg/20 mL (60 mg/mL) colorless to slightly yellow solution in a single-dose vial.

For Advanced Urothelial Cancer: Atezolizumab is given every 3 weeks.
The recommended dose of Atezolizumab is 1200mg administered (flat dose) as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer Atezolizumab as an intravenous push or bolus.

10.2 Preparation and Administration of Atezolizumab

Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration whenever solution and container permit. Atezolizumab is a colorless to slightly yellow solution. Discard the vial if the solution is cloudy, discolored, or visible particles are observed.

Do not shake the vial.

Prepare the solution for infusion as follows:
- Withdraw 20 mL of Atezolizumab from the vial.
- Dilute into a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with 0.9% Sodium Chloride Injection only.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used or empty vials of Atezolizumab.

10.2.1 Storage of Infusion

This product does not contain a preservative.

Administer immediately once prepared. If diluted Atezolizumab infusion solution is not used immediately, it can be stored either:
- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration for infusion.
- Under refrigeration at 2°C–8°C (36°F–46°F) for no more than 24 hours.

Do not freeze.
Do not shake.

10.2.2 Administration

Administer the initial infusion over 60 minutes through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not co-administer other drugs through the same intravenous line.

10.3 Dose Modifications

No dose reductions of Atezolizumab are recommended.

Withhold/Permanently Discontinue Atezolizumab for any of the following:

Adverse Reaction	Severity*	Dose Modifications
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently Discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Colitis or Diarrhea	Grade 2 or Grade 3	Withhold dose[a]
	Grade 4	Permanently discontinue
Symptomatic Hypophysitis, Adrenal Insufficiency, Hypothyroidism, Hyperthyroidism	Grade 2	Withhold dose[a]
	Grade 4 Hypophysitis	Permanently discontinue
Hyperglycemia	Grade 3 or Grade 4	Withhold dose[a]
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose[a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Ocular inflammatory toxicity	Grade 2	Withhold dose[a]
	Grade 3 or 4	Permanently discontinue
Infection	Grade 3 and above	Withhold dose[a]
Pancreatitis	Grade 2 and above	Withhold dose[a]
Recurrent Pancreatitis	Grade 4 or any grade of recurrence	Permanently discontinue
Increase in amylase or lipase > 2.0 times ULN	Grade 3 and above	Withhold dose[a]
Infusion-related reactions	Grade 2 and above	Withhold dose[a]
	Grade 3 or 4	Permanently discontinue
Rash	Grade 3 rash	Withhold dose[a]
	Grade 4 rash	Permanently discontinue
Myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis	All grades	Permanently discontinue

a Resume treatment when adverse reaction returns to Grade 0 or1.
* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

11.0 Radiation Therapy Guidelines

11.1 Planning

After a lesion to be treated with radiotherapy is identified, the site is imaged at the time of CT simulation. Contrast Media may be used during the CT simulation, as deemed necessary by the treating physician. CT scan thickness should be <0.5 cm through the tumor bed region. These images will be used in treatment planning in accordance with the dose specific constraints per the Task Group 101of the American Association of Physicists in Medicine.

The clinical tumor volume (CTV) is defined as the lesion of interest with the expected motion changes. The planning target volume (PTV) is the CTV + a 0.5-1 cm margin for setup error.

Respiratory gating may be used during the CT simulation to delineate in internal target volume (ITV) for chest and abdominal lesions that are subject to motion during the respiratory cycle. In this setting, a 0.5-1cm margin for setup error will be added to the ITV to establish the PTV.

Treatment Planning: 3D-Conformal or Intensity Modulated Radiation Therapy (IMRT) treatment planning is allowed. This includes "field-in-field" beams as well as the use of dynamic multi-leaf collimator (MLC) derived using inverse planning or electronic compensator techniques. Field arrangements and technique should be chosen that satisfy the PTV_eval and normal tissue dose constraints (TG101) using Dose-Volume Histogram (DVH) analysis by carefully selecting the gantry and table angle combinations that do not enter or exit through other organs of the body, the dose can be confined to the traditional treatment volumes. Non-coplanar beam arrangements are encouraged, but not required. Dose calculations with tissue inhomogeneity correction must be used. Beams entering lesions that will be monitored for abscopal responses will be avoided.

11.2 Treatment

Radiotherapy is delivered by external beam with a linear accelerator. The PTV is treated with radiation every other day (with a minimum of 36 hours between each fraction)starting on Day 1. A dose of 30 Gy in 3 fractions of 10 Gy each is delivered to an isodose surface encompassing the PTV.

The prescription dose is the dose delivered to a reference point within the CTV. The PTV receives a minimum of 90% of the prescription dose.

Treatment Machine: A linear accelerator with > 4 MV x-rays is required.

Immobilization Technique: Patients will be immobilized with a vac-loc or alpha cradle that is indexed to the treatment table.

Target Positioning Verification: Digitally acquired radiographic images will be used to verify the position of the target with respect to the treatment machine's isocenter using digitally reconstructed radiographs (DRRs) or orthogonals (for IMRT) on the first day. Both kV and MV images may be used to verify setup.

Target Localization: Cone-beam CT (CBCT) images will be acquired prior to treatment for each fraction. By using image guided radiation treatment (IGRT) to image the tumor bed in "real-time", the operator may automatically align the tumor bed with the treatment machine on each day of treatment.

11.3Treatment modifications for Radiation Adverse Events

Dosing delay: except for radiation-associated mucositis and skin toxicity, the patient should have resolution or return to baseline of all grade 3-4 toxicities prior to the start of the next immunotherapy treatment.

12.0 Immunological Studies

12.1 Assessment of Baseline Immune Function

Baseline cellular/humoral immune function to tumor or defined antigens will be determined for each patient from peripheral blood obtained before the administration of investigational agents (radiation and PD-1/PDl-1). For patients with accessible tumor four punch biopsies measuring approximately 4-6mm of radiated and non-radiated tumor will be obtained to prepare tumor RNA.

12.2 On Study Evaluations

As summarized in the Study Calendar, patients are evaluated pre-treatment for definition of metastatic sites on with either CT scans or MRI. At least two measurable metastatic sites are identified. Non irradiated lesions will be followed and reported for responses per RECIST.

12.3 Off Study Criteria

- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicity
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Authorized Physicians must notify the data manager and Principle Investigator when a patient is taken off study.

13.0 Prohibited and Restricted therapies during the Study

13.1 Prohibited Therapies

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease unless indicated as a component of the protocol regimen (including those for common medical conditions) for up to one month pre and post dosing with nivolumab or atezolizumab. Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving nivolumab/atezolizumab treatments.

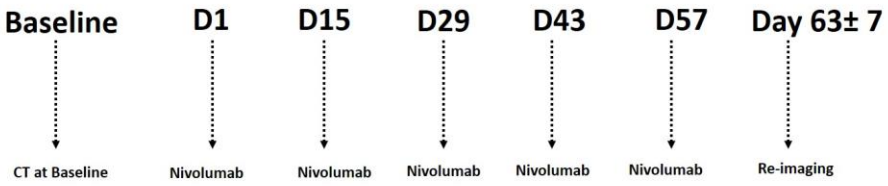
Patients may not use any of the following therapies during the study:
- Any non-study anti-cancer agent (investigational or non-investigational);
- Any other investigational agents; Any other PD-1 or PDL-1 inhibitors;
- Immunosuppressive agents;
- Chronic systemic corticosteroids;

- 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).

14.0 Study Calendar

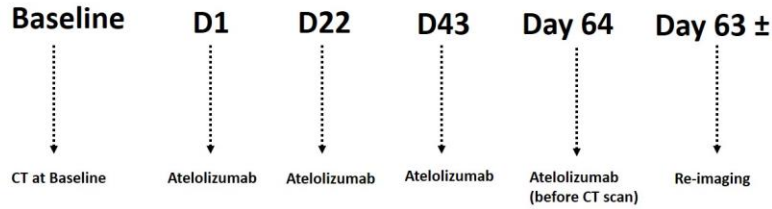
Arm A – Immunotherapy Alone

Renal Cell Carcinoma patients



Cohort 1

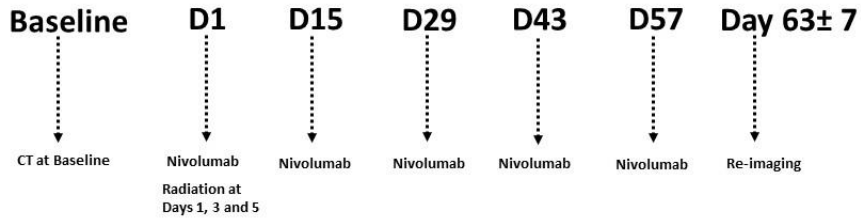
Urothelial Cancer patients



*Infusions will have a ± 3 day window to accommodate scheduling changes and holidays.

Arm B – Immunotherapy and Radiation

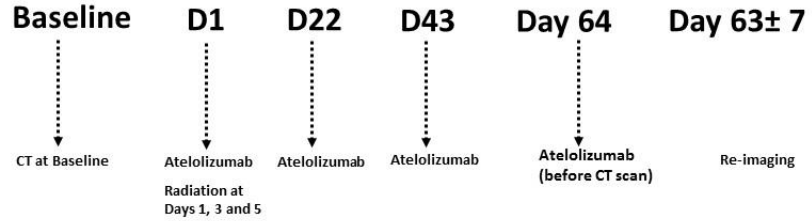
Renal Cell Carcinoma patients



Cohort 1

Arm B – Immunotherapy and Radiation

Urothelial Cancer patients



Cohort 2

*Infusions will have a ± 3 day window to accommodate scheduling changes and holidays.

15.0 Study Procedures and Observations - Nivolumab Alone and Nivolumab plus Radiation

Procedure	**Screening Visit (- 28 days)**	**Day 1[h]**	**Day 3[h]**	**Day 5[h]**	**Day 15[h]**	**Day 29[h]**	**Day 43[h]**	**Day 57[h]**	**Day 63 (+/-7days)**	F/U **Q 9wks (±7days) for first year[k]**	**Follow up Q12 weeks (±7days) after 1st year[k] years 2 and 3**
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Medical History	X										
Pregnancy Test	X	X[a]				X[a]	X[a]	X[a]	X[a]		
Physical Examination Complete	X										
Physical Examination Limited		X				X	X	X	X	X	X
Vital Signs	X	X				X	X	X	X	X	X
Adverse Events Assessment	X	X				X	X	X	X	X	X
Serum Chemistry[b]	X	X				X	X	X	X	X	X
Hematology[b]	X	X				X	X	X	X	X	X
Urinalysis	X	X				X	X	X		X	X
CT (Chest,Abdomen,Pelvis)[i]	X								X	X[d]	Q 12 W
MRI Brain[i]	X										
Nivolumab infusion[j] - ARM A		**X**			**X**	**X**	**X**	**X**			
Radiation Therapy[e] - ARM B		**X**	**X**	**X**							
Endocrine Panels[c]	X				X	X	X	X			
Genomic Bloods/T-cell collection		X[f]				X[f]		X[f]			
Tumor biopsies	X[g]								X[g]		

a. Before each infusion.
b. SOC labs (COMP, CBC w/diff,)
c. TSH, T3, T4
d. Scans day 63 ± 7.
e. Radiation is given to one, randomly selected lesion 30 Gy in 3 fractions of 10 Gy each (ARM B only)
f. to be collected PRIOR to infusion on days 1, 29 and 57.
g. Optional biopsy done at Day 63 (±7 days).
h. infusions will have a ± 3 day window.
i. prior scans will be valid until the screening period of 28 days
j. infusions will be ±24hrs from Day 1 of radiation. k. Patients will come off-study if they have disease progression. Patients will be followed for 30 days from the day they come off-study.

1.12 16.0 Study Procedures and Observations - Atezolizumab Alone and Atezolizumab plus Radiation

Procedure	**Screening Visit (- 28 days)**	**Day 1[h]**	**Day 3[h]**	**Day 5[h]**	**Day 22[h]**	**Day 43[h]**	**Day 64[h]**	**Day 63 (+/-7days)**	F/U**Q 9wks (±7days)** for first year[k]	**Follow up Q12 weeks (±7days) after 1st year[k], years 2 and 3**
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Medical History	X									
Pregnancy Test	X	X[a]			X[a]	X[a]	X[a]	X[a]		
Physical Examination Complete	X									
Physical Examination Limited		X			X	X	X	X	X	X
Vital Signs	X	X			X	X	X	X	X	X
Adverse Events Assessment	X	X			X	X	X	X	X	X
Serum Chemistry[b]	X	X			X	X	X	X	X	X
Hematology[b]	X	X			X	X	X	X	X	X
Urinalysis	X	X			X	X			X	X
CT imaging (Chest, Abdomen,Pelvis)	X							X	X[d]	Q 12 W
MRI Brain	X									
Atezolizumab/Pembrolizumabinfusion[j] - ARM A		**X**			**X**	**X**	**X**			
Radiation Therapy[e] - ARM B		**X**	**X**	**X**						
Endocrine Panels[c]	X				X	X				
Genomic Bloods/T-cell collection		X[f]				X[f]	X[f]			
Tumor biopsies	X[g]							X[g]		

a. Before each infusion.
b. SOC labs (COMP, CBC w/diff,)
c. TSH, T3, T4
d. Scans day 63 ± 7.
e. Radiation is given to one, randomly selected lesion 30Gy in 3 fractions of 10 Gy each (ARM B only)
f. to be collected PRIOR to infusion on days 1,43 and 64.
g. Optional biopsy done at Day 63(±7 days).
h. infusions will have a ± 3 day window.
i. prior scans will be valid until the screening period of 28 days,
j. infusions will be ±24hrs from Day 1 of radiation. k. Patients will come off-study if they have disease progression. Patients will be followed for 30 days from the day they come off-study.

17.0 Procedures by Visit

17.1 Study completion or early discontinuation Visit

At the time of study early withdrawal, the reason for early withdrawal and any new or continuing AEs should be documented.

17.2 Study Drug Discontinuation

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable toxicity,
- Patient decides to withdraw from the study (patients will be followed up to 30 days from the withdrawn date. If patient withdraws consent, patient will not be followed and no data will be collected), or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
- Physician's discretion, or
- Patient non-compliance

17.3 Details of Procedures

17.3.1 Study Materials

Both Nivolumab and Atezolizumab are FDA approved therapy for metastatic renal and urothelial cancers (respectively) and will be covered by the patients' insurance.

The radiotherapy component of this study is a standard procedure and will be routinely billed to providers.

17.3.2 Safety Assessments

All patients who receive at least one dose of Immunotherapy will be considered evaluable for safety parameters. Additionally, any occurrence of a SAE from time of consent up to and including follow-up visits will be reported. Refer to safety reporting section 6.2

Safety will be evaluated for all treated patients using the NCI CTCAE version 4.03 (http://ctep.cancer.gov). Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations and clinical laboratory tests.

1.12.1.1 17.4 Criteria for Evaluation

1.12.1.1.1 17.4.1 Safety Evaluation

This protocol will be monitored by the WCM Data Safety Monitoring Committee which oversees the safety of all WCM investigator initiated clinical trials. The trial will be monitored for all adverse events, laboratory abnormalities, and serious adverse events at least once every 12 months. In addition, serious adverse events are monitored for all studies on a monthly basis.

1.12.1.1.2 17.4.2 Efficacy Evaluation

For the purposes of this study, patients should be re-evaluated for response every 9 weeks, in year 1, every 12 weeks in years 2 and 3. Confirmatory scans may also be obtained 4 weeks following initial documentation of objective response or progressive disease.

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Patients will be followed for scans every 9 weeks for the first year or until disease progression and every 12 weeks after the first year or until disease progression.

Measurable and non-measurable lesions:

- Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
- Malignant lymph nodes: pathologically enlarged and measurable lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathologic lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Irradiated lesions, bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease:

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

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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

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

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity. Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

1.13 18.0 Response Criteria

1.13.1.1 18.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm).
(Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

1.13.1.2 18.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

1.13.1.3 18.3 Evaluation of Overall Response Criteria

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

1.14 19.0 Response According to Revised Response Evaluation Criteria in Solid Tumors Version 1.1

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when confirmation is Required
CR	**CR**	**No**	**CR**	**≥ 4 weeks confirmation**
CR	**Non-CR/Non-PD**	**No**	**PR**	**≥ 4 weeks confirmation**
CR	**Not Evaluated**	**No**	**PR**	
PR	**Non-CR/Non-PD/Not Evaluated**	**No**	**PR**	
SD	**Non-CR/Non-PD/Not Evaluated**	**No**	**SD**	**Documented at least once ≥ 4 weeks confirmation from baseline**
PD	**Any**	**Yes or No**	**PD**	**No prior SD, PR or CR.**
Any	**PD**	**Yes or No**	**PD**	
Any	**Any**	**Yes**	**PD**	

CR = Complete response; PD = Progressive Disease; PR=Partial response; SD =Stable disease.

1.15 20.0 Response Endpoints

PD1/PDL1 blockade is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to become evident. Some patients may have objective volume increases of tumor lesions or other disease parameters (based on study indication, i.e., hematologic malignancies) within 12 weeks following start of PD1/PDL1 blockade dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter

increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Therefore, patients with tumor volume increase detected or lack of laboratory parameter response documentation prior to week 12 but without rapid clinical deterioration should continue to be treated with PD1/PDL1 blockade and clinically observed with a stringent imaging schedule to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity or immunotherapy and more likely capture its true potential to induce clinical responses.

Radiotherapy in the dose and fractionation proposed in this study is a standard palliation dose for metastatic lesions. It is expected that approximately 50% of the irradiated lesions will achieve an objective response (PR+CR). To enable a comparison of response between the two arms, the irradiated lesion will be excluded from RECIST response measurements (both at baseline, before RT, and at subsequent assessments).

1.16 21.0 Adverse Event Reporting

1.16.1.1 21.1 Collection of Safety Information

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

1.16.1.2 21.2 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

1.16.1.3 21.3 Adverse Event Characteristics and Related Attributions

CTCAE Version 4.0 will be used for tracking the Adverse Events in this study.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Attribution of the AE:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

1.16.1.4 21.4 Recording of Adverse Events

All adverse events will be recorded on a patient specific AE log. The AE log will be maintained by the research staff and kept in the patient's research chart.

1.16.1.5 21.5 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

1.16.1.6 21.6 Definition of SAE

A ***serious AE*** **or reaction** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the patient or subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization, (refer to note for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above)

NOTE:
Pregnancy: Incidence of pregnancy is not considered a SAE; pregnancy must, however, be reported immediately to the investigator. Overdose: An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. Hospitalizations (exceptions): Criteria for hospitalizations not reported as SAEs include admissions for:

- Planned as per protocol medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status documentation (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state (planned prior to entry into study trial; appropriate documentation required)
- Admission encountered for other life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

1.16.1.7 21.7 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

Following the subject's written consent to participate in the study, all SAEs should be collected and reported, including those thought to be associated with clinical trial procedures. SAE terminology and severity grading will be based on (*i.e. CTCAEv4*).

The following categories and definitions of causal relationship to study drug should be used for all clinical studies:

- Certain: There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of study drug (dechallenge), and recurs with rechallenge when clinically feasible.
- Probable: There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is reasonable causal relationship between the study drug and the AE. Dechallenge information is lacking or unclear.
- Not likely: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE.
- Not related: There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.
- Adverse events classified as "serious" require expeditious handling and reporting to WCM to comply with regulatory requirements.
- All SAEs whether related or unrelated to the ipilimumab, must be immediately reported to WCM (by the investigator or designee) within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.
- Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed by WCM. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.
- An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, WCM considers an overdose, regardless of adverse outcome, as an important medical event.
- AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of immunotherapy, or those experiencing AEs that are present at the end of their participation in the study; such subjects should receive post-treatment follow-up as appropriate.
- All SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify WCM of any SAE that may occur after this time period which they believe to be certainly, probably, or possibly related to immunotherapy.

1.16.1.8 21.8 Pregnancy

Sexually active women of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

Before enrolling women of childbearing potential (WOCBP) in this clinical trial, Investigators must review the guideline about study participation for WOCBP which can be found in the GCP Manual for Investigators. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a **negative** pregnancy test within 72 hours **prior** to receiving immunotherapy. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive nivolumab or atezolizumab and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If following initiation of study treatment, it is subsequently discovered that a trial subject is pregnant or may have been pregnant at the time of immunotherapy exposure, including during at least 6 half-lives after product administration, the immunotherapy will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Exceptions to immunotherapy discontinuation may be considered for life-threatening conditions only after consultation with the Principal Investigator or as otherwise specified in this protocol. Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks.

1.17 22.0 Registration Procedures

1.17.1.1 22.1 Patient Registration

Patients will be centrally registered with the Office of Billing Compliance. To register a patient, submit the following documents via the JIRA Registration Process:

- Legible copy of the HRBAF
- First and last page of signed informed consent form

Registration must be completed within 24 hours of the signing of informed consent.

1.17.1.2 22.2 Administrative Section

1.17.1.2.1 22.2.1 Compliance with the Protocol and Protocol Revisions

The study will be conducted as described in the final approved protocol. Documentation of approval signed by the chairperson or designee of the IRB(s) will be sent to the WCM protocol manager.

All revisions (protocol amendments, administrative letters, and changes to the informed consent) will be submitted to the WCM protocol manager. The Investigator will not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

1.17.1.2.2 22.2.2 Informed Consent

The Investigator will ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and will include all elements required by the Code of Federal Regulations 21 Part 50.25 and the local IRB. .

1.17.1.2.3 22.2.3 Records and Reports

Adequate and accurate case histories designed to record all observations and other data pertinent to the investigation (e.g. case report form) will be prepared and maintained on each individual treated with Ipilimumab. The investigator will retain, in a confidential manner, the data pertinent to the study.

1.17.1.2.4 22.2.4 Records Retention

The Investigator will retain source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. case report form) for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Documentation of such transfer will be provided to WCM.

1.18 23.0 Laboratory Correlative Studies

Serial blood samples for immune monitoring, Genomics and T-cell response will be collected at baseline, and at selected time points as outlined in section (6.2) and Appendix 1.

1.19 24.0 Storage of Samples

All blood and tissue samples will be stored in a -80°C locked freezer in the WCM core lab indefinitely for research purposes only. These specimens will not be linked to any clinical data and will be de-identified in the clinical research database REDCap. Only the Principal investigator and data manager will have access to the master list with the patient name and an identification number. This master list will be secured in a locked cabinet in the WCM radiation oncology department. Only the investigators listed on this protocol will have access to these samples.

1.20 25.0 Confidentiality

The medical, hospital and research records associated with this study are considered confidential. Members of the treating team and designated study assistants will have access to the records as required to administer treatment and comply with the protocol. Neither the name nor any other identifying information for an individual will be used for reporting or publication regarding this study. All laboratory and baseline data will be de-identified and transferred via secure links at WCM. Patient records will be made available for inspection to auditing agencies to satisfy regulatory requirements.

1.21 26.0 Research Conflict of Interest

There are no research conflicts associated with this study.

1.22 27.0 Data and Safety Monitoring Plan (DSMP)

The WCM Data and Safety Monitoring Board (DSMB) will review the IRB approved protocol, informed consent documents, the data and safety monitoring plan and any stopping guidelines prior to study initiation. During the course of the study, the DSMB will review cumulative study data annually to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. The WCM DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCM DSMB to address.

The study PI will submit all written DSMB recommendations to the IRB upon receipt.

The WCM Data and Safety Monitoring Committee (DSMC) is the central monitoring board for this study. The WCM Cancer Institute Data and Safety Monitoring Committee (DSMC) is the local monitoring board for WCM patients.

1.22.1.1 27.1 Monitoring Plan

This study will be conducted in accordance with the guidelines in the 2001 NCI approved data Safety and Monitoring plan for the WCM Cancer Institute and with the WCM approved data Safety and Monitoring plan for the WCM Cancer Institute. Monitoring will occur on a semi-annual basis from the date the first patient is enrolled. Reports to the Data Safety and Monitoring Committee will include the following information: accruals, targets, responses, adverse events and evidence of reporting to appropriate review committees. The WCM Data and Safety Monitoring Board (DSMB) will review the IRB approved protocol, the data and safety monitoring plan and any stopping guidelines during protocol initiation. The WCM DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCM DSMB to address. The study team will meet on a monthly basis to review AE data and a copy of the report will be sent to the study statistician. As per the DSMB review dated 30AUG2019, a final study report once available will be submitted to the DSMB for their final review.

1.22.1.2 27.2 Stopping Rules

Treatment will be held if patients experience hematological or non-hematological toxicities while on therapy. Patients will be monitored until resolution of the adverse event to grade 0 or baseline. Based on PI's discretion, patients will resume or be withdrawn from study. In addition, the study will also follow the dose modification

tables, 9.6 and 10.4 for nivolumab and atezolizumab for holding therapy or to permanently withdraw patients from study. Adverse events will be recorded based on CTCAE v4.03.

1.23 28.0 Data Management

Data will be entered into the REDCap database and maintained at WCM by trained Radiation Oncology data manager Christina Castro.

The system provides audit trails that track creation and modification of records that include user ID and timestamp. Once entered, the data is subjected to validation procedures that are executed either immediately or upon saving the eCRF page or during the batch validation process. Validation failures that are identified before the page is saved can be corrected immediately. Validation failures during saving of the eCRF page and during batch validation processes will generate a discrepancy. Depending on the database account privileges, the data managers may be able to correct a discrepancy or if not, route it to the project data manager at WCM who can take appropriate action to correct the problem. Data clarification forms can also be printed out when necessary to be sent to the project data manager. Once the discrepancy is closed, by marking "resolved" or "irresolvable", the data is marked clean and an audit trail is generated by the system.

All key end points will be source verified by a second person and errors will be corrected. Once the data is verified and all discrepancies are closed, the data can be locked/frozen. Locking and freezing can be done at different granular levels and will follow institutional SOPs and any specific requirements for the project.

Security measures that will be taken in order to protect patient data will include firewall technology and database level security which will be achieved by assigning roles and privileges to different levels of users and by requiring that the users authenticate themselves using user ID and password. Additional security for data transfer between remote clients and servers will be achieved by using digital certificates/SSL. All data will be backed-up to tape periodically according to the Institutional SOPs. All data will be stored for at least 5 years following the termination of this study.

1.24 29.0 Statistical Considerations

112 patients will be randomly assigned in a 1:1 ratio to treatment with immunotherapy (Nivolumab or Atezolizumab) or to treatment with immunotherapy (Nivolumab or Atezolizumab) plus radiotherapy in this phase II trial. With 56 patients per group, if the expected response rate (PR or CR) is 20% with immunotherapy alone, we can detect a response rate of 40% for immunotherapy plus radiotherapy with a 1-sided alpha of 20% and a power of 90%.

Forty patients per year will be randomized to the trial over ~ 3 years of accrual, assuming an accrual rate of approximately 20 patients per year for each cohort (see study calendar).

1.24.1.1 29.1 Statistical analysis

Both arms will run in parallel but will be analyzed separately. When the target accrual is met for a cohort, it will be closed to accrual even though other cohorts may still be accruing. Analyses will be done separately for each arm. Analyses will be similar for the two arms.

The primary objective of this study is the comparison of best overall response rates between each arm after start of treatment. Fisher's Exact test will be used to estimate 95% confidence intervals for the difference and to perform a one-sided test with an alpha level of 20%. Response rates for each arm will also be estimated at this level. With 56 patients treated under each modality, if the true responses are 20% and 40% in the immunotherapy alone and immunotherapy and radiation arms, respectively, we have a 90% probability of detecting a difference between modalities. Secondary objectives include time to disease progression and mortality. Median times for these events will be estimated with 95% confidence intervals. Graphical summaries will include Kaplan-Meier curves and log-rank tests which will be used to detect differences between treatments. Median survival and progression times will be estimated if sufficient events are observed. Cox proportional hazards regression will be used to account for baseline characteristics. Stratified exploratory analyses by type of cancer (renal cancer cell carcinoma or urothelial carcinoma) will also be performed.

Toxicities will be summarized per arm and prepared using Chi-square or Fisher's Exact tests, where appropriate.

Patient and disease characteristics will be summarized and compared at randomization between the two treatment arms using descriptive statistics and graphical displays. Although randomization will remove systematic biases we will test for differences in arms using Chi-square or Fisher's exact methods for categorical variables and t-tests or Kruskal-Wallis tests (with appropriate transformations of data if necessary for continuous variables). Differences in RECIST outcomes within each patient comparing non-irradiated and irradiated lesions will be summarized. Similar techniques will be used for exploratory analyses of the following:

1. Distribution of changes in T cells from baseline to response evaluation.
2. Association between abscopal responses and T cell changes from baseline. Changes from baseline in immune responses will be summarized over the time course of the study and post treatment using descriptive statistics and graphical displays. The patterns of changes in immune parameters will be examined using exploratory statistical approaches to assess the relationship of changes in individual parameters to clinical outcomes. Mixed effects regression models and general estimating equations will be used to compare the patterns of change in immune response over time in the two treatment groups.

Changes from pretreatment to follow up levels of immunologic parameters and other parameters described above in irradiated tumors (and non-irradiated tumors) will be compared between the two treatment groups using descriptive statistics and graphical displays.

All patients will be followed for progression-free survival and overall survival. Kaplan-Meier curves for progression-free survival and overall survival will be provided to summarize the results.

1.24.1.2 29.2 Interim Analyses

A futility analysis will be conducted after 50% of the total 18-week RECIST responses (estimated median time to response ~14 weeks) for final analysis have occurred (i.e., N/2 of N). No accrual suspension is required to conduct the futility analysis. If at this point the relative risk of no response in the immunotherapy arm over the immunotherapy plus radiation arm is 1.0 or less, the study will be stopped for futility.

Appendix 1: Laboratory Correlative Manual

At Baseline: Pre- treatment biopsy*

For renal cell carcinoma patients -:Six 10 mL lavender top (EDTA) tubes— WCM Core
At days 1, 29 and 57 One red top (serum) tube—serum to be processed and frozen by WCM Core.
(Total research blood draw this day 70 mL)

For urothelial cancer patients -: Six 10 mL lavender top (EDTA) tubes— WCM Core
At days 1, 43 and 64 One red top (serum) tube—serum to be processed and frozen by WCM Core.
(Total research blood draw this day 70 mL)

At day 63: Optional Biopsy* at Day 63 (± 7days)

*Tissue Biopsies: 1 formalin fixed-processed and embedded. Block delivered to Dr. Demaria.

References

1 Zitvogel, L., Kepp, O. & Kroemer, G. Decoding cell death signals in inflammation and immunity. *Cell* **140**, 798-804, doi:10.1016/j.cell.2010.02.015 (2010).
2 Golden, E. B. *et al.* Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death. *Oncoimmunology* **3**, e28518, doi:10.4161/onci.28518 (2014).
3 Motzer, R. J. *et al.* Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *The New England journal of medicine* **373**, 1803-1813, doi:10.1056/NEJMoa1510665 (2015).
4 Rosenberg, J. E. *et al.* Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* **387**, 1909-1920, doi:10.1016/S0140-6736(16)00561-4 (2016).
5 Bishop, M. R. *et al.* Allogeneic lymphocytes induce tumor regression of advanced metastatic breast cancer. *J Clin Oncol* **22**, 3886-3892 (2004).
6 Golden, E. B. *et al.* Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. *The Lancet. Oncology* **16**, 795-803, doi:10.1016/S1470-2045(15)00054-6 (2015).
7 Golden, E. B., Chachoua, A., Fenton-Kerimian, M., Demaria, S. & Formenti, S. C. Abscopal Responses in Metastatic Non-Small Cell Lung Cancer Patients Treated on a Phase 2 Study of Combined Radiation Therapy and Ipilimumab: Evidence for the In Situ Vaccination Hypothesis of Radiation. *International journal of radiation oncology, biology, physics* **93**, S66-S67 (2015).
8 Zatloukal, P. *et al.* Randomized phase II clinical trial comparing tremelimumab with best supportive care following first-line platinum-based therapy in patients with advanced non-small cell lung cancer. *J Clin Oncol* **27** (2009).
9 Golden, E. B., Demaria, S., Schiff, P. B., Chachoua, A. & Formenti, S. C. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. *Cancer immunology research* **1**, 365-372, doi:10.1158/2326-6066.CIR-13-0115 (2013).
10 Demaria, S., Golden, E. B. & Formenti, S. C. Role of Local Radiation Therapy in Cancer Immunotherapy. *JAMA oncology*, doi:10.1001/jamaoncol.2015.2756 (2015).
11 Ohaegbulam, K. C., Assal, A., Lazar-Molnar, E., Yao, Y. & Zang, X. Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. *Trends Mol Med* **21**, 24-33, doi:10.1016/j.molmed.2014.10.009 (2015).
12 Melief, C. J. Tumor eradication by adoptive transfer of cytotoxic T lymphocytes. *Adv Cancer Res* **58**, 143-175 (1992).
13 Rosenberg, S. A. Progress in human tumour immunology and immunotherapy. *Nature* **411**, 380-384 (2001).
14 Antonia, S., Mule, J. J. & Weber, J. S. Current developments of immunotherapy in the clinic. *Curr Opin Immunol* **16**, 130-136 (2004).
15 Iwai, Y. *et al.* Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci U S A* **99**, 12293-12297, doi:10.1073/pnas.192461099 (2002).
16 Topalian, S. L. *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *The New England journal of medicine* **366**, 2443-2454, doi:10.1056/NEJMoa1200690 (2012).
17 Brahmer, J. R. *et al.* Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *The New England journal of medicine* **366**, 2455-2465, doi:10.1056/NEJMoa1200694 (2012).
18 Larkin, J. *et al.* Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *The New England journal of medicine* **373**, 23-34, doi:10.1056/NEJMoa1504030 (2015).
19 Drake, C. G. Combination immunotherapy approaches. *Ann Oncol* **23 Suppl 8**, viii41-46, doi:10.1093/annonc/mds262 (2012).
20 Dovedi, S. J. *et al.* Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-

L1 blockade. *Cancer research* **74**, 5458-5468, doi:10.1158/0008-5472.CAN-14-1258 (2014).

21 Reits, E. A. *et al.* Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *The Journal of experimental medicine* **203**, 1259-1271, doi:10.1084/jem.20052494 (2006).

22 Mole, R. H. Whole body irradiation; radiobiology or medicine? *Br J Radiol* **26**, 234-241 (1953).

23 Kingsley, D. P. An interesting case of possible abscopal effect in malignant melanoma. *Br J Radiol* **48**, 863-866 (1975).

24 Ehlers, G. & Fridman, M. Abscopal effect of radiation in papillary adenocarcinoma. *Br J Radiol* **46**, 220-222 (1973).

25 Ohba, K. *et al.* Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis. *Gut* **43**, 575-577 (1998).

26 Nikitina, E. Y. & Gabrilovich, D. I. Combination of gamma-irradiation and dendritic cell administration induces a potent antitumor response in tumor-bearing mice: approach to treatment of advanced stage cancer. *Int J Cancer* **94**, 825-833 (2001).

27 Ganss, R., Ryschich, E., Klar, E., Arnold, B. & Hammerling, G. J. Combination of T-cell therapy and trigger of inflammation induces remodeling of the vasculature and tumor eradication. *Cancer Res* **62**, 1462-1470 (2002).

28 Demaria, S. *et al.* Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *International journal of radiation oncology, biology, physics* **58**, 862-870, doi:10.1016/j.ijrobp.2003.09.012 (2004).

29 Demaria, S., Bhardwaj, N., McBride, W. H. & Formenti, S. C. Combining radiotherapy and immunotherapy: a revived partnership. *Int J Radiat Oncol Biol Phys* **63**, 655-666 (2005).

30 Demaria, S. *et al.* Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res* **11**, 728-734 (2005).

31 Dewan, M. Z. *et al.* Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* **15**, 5379-5388, doi:10.1158/1078-0432.CCR-09-0265 (2009).

32 Chakravarty, P. K. *et al.* Flt3-ligand administration after radiation therapy prolongs survival in a murine model of metastatic lung cancer. *Cancer research* **59**, 6028-6032 (1999).

33 Brody, J. D. *et al.* In situ vaccination with a TLR9 agonist induces systemic lymphoma regression: a phase I/II study. *J Clin Oncol* **28**, 4324-4332, doi:10.1200/JCO.2010.28.9793 (2010).

34 Postow, M. A. *et al.* Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* **366**, 925-931, doi:10.1056/NEJMoa1112824 (2012).

35 Gulley, J. L. *et al.* Combining a recombinant cancer vaccine with standard definitive radiotherapy in patients with localized prostate cancer. *Clin Cancer Res* **11**, 3353-3362, doi:10.1158/1078-0432.CCR-04-2062 (2005).

36 Lurquin, C. *et al.* Contrasting frequencies of antitumor and anti-vaccine T cells in metastases of a melanoma patient vaccinated with a MAGE tumor antigen. *The Journal of experimental medicine* **201**, 249-257, doi:10.1084/jem.20041378 (2005).

37 Gnjatic, S. *et al.* Seromic profiling of ovarian and pancreatic cancer. *Proc Natl Acad Sci U S A* **107**, 5088-5093, doi:10.1073/pnas.0914213107 (2010).

38 Newell, E. W., Sigal, N., Bendall, S. C., Nolan, G. P. & Davis, M. M. Cytometry by time-of-flight shows combinatorial cytokine expression and virus-specific cell niches within a continuum of CD8+ T cell phenotypes. *Immunity* **36**, 142-152, doi:10.1016/j.immuni.2012.01.002 (2012).

39 Bogunovic, D. *et al.* Immune profile and mitotic index of metastatic melanoma lesions enhance clinical staging in predicting patient survival. *Proc Natl Acad Sci U S A* **106**, 20429-20434, doi:10.1073/pnas.0905139106 (2009).