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Radical RADiotherapy and Immunotherapy for metastatic CAncer of the Lung (RRADICAL)

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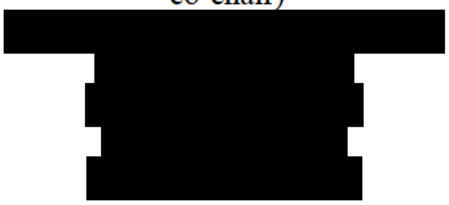

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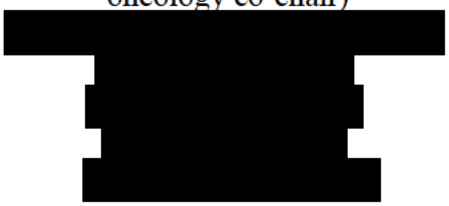

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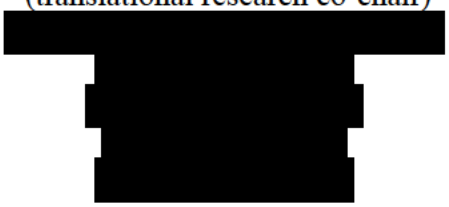

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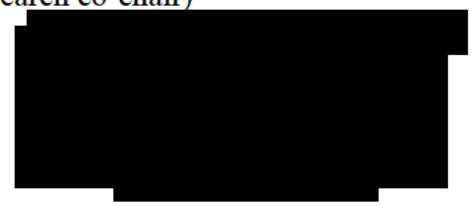

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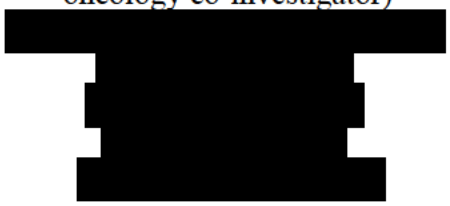

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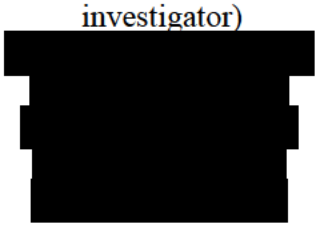

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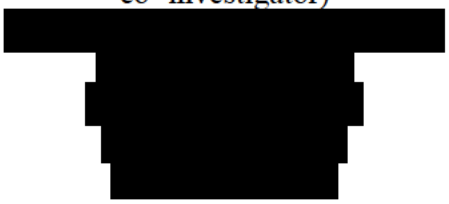

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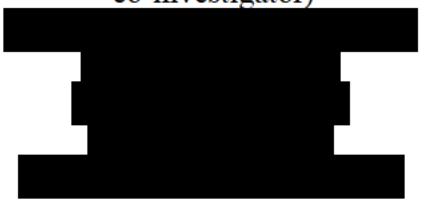

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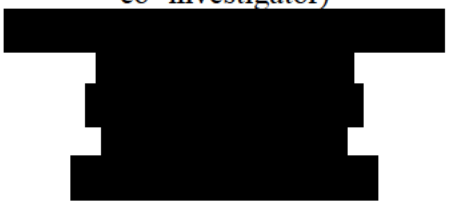

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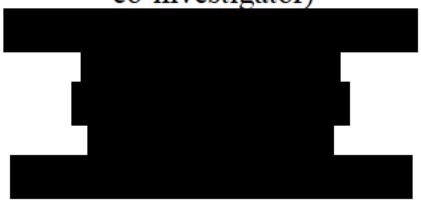

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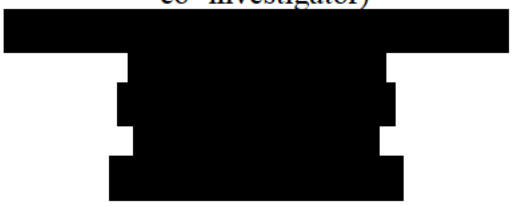

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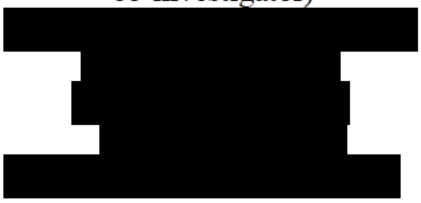

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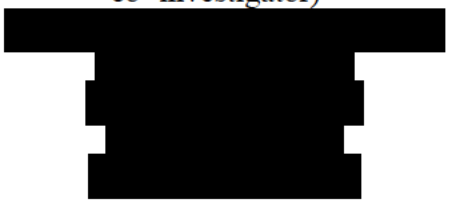

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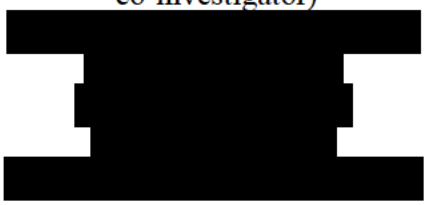

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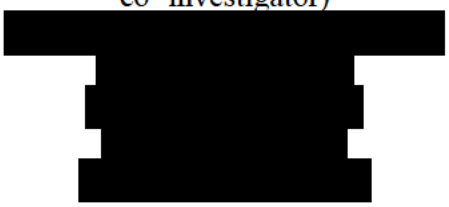

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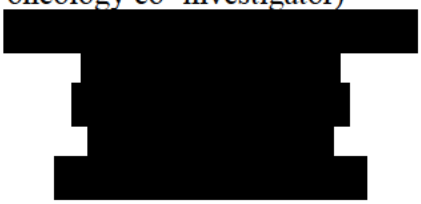

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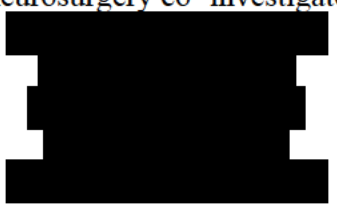

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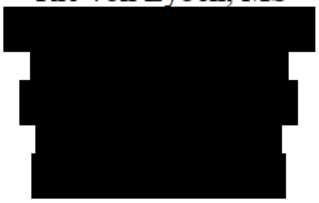

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For Protocol Amendment 1.5 of : LUN0088, Radical RADiotherapy and Immunotherapy for metastatic CAncer of the Lung (RRADICAL)

Protocol version: 1.5
Protocol Version Date: Aug 4, 2021

Section	Change
Global	The protocol version date is updated in the document footer. Formatting
Study Personnel	Removed: Sukhmani Padda, Gordon Li, Iris Gibbs; Peter Maxim, Edward Graves, Omid Tehrani, Patrick Swift, Samantha Wong Ngan Kim Huynh Nguyen, Manpreet Bedi. Added: Eleanor Brown, Katy Barnick
Front Page	Added IRB, Oncore, and NCT # for this study
Section 9	Updated footnote 11 to state starting at 108-week follow-up, the history & physical exam, ECOG PS, and imaging studies will all be optional.
Section 12	Changed statistical assumptions and planned sample size

TABLE OF CONTENTS

PROTOCOL SYNOPSIS 6
SCHEMA 10
1. OBJECTIVES 12
1.1. Primary Objective 12
1.2. Secondary Objectives 12
1.3. Exploratory Objectives 12
2. BACKGROUND 12
2.1 Introduction 12
2.2 Trial Design 13
2.3 Previous Studies 14
2.4 Translational Research 15
2.5 Study Design 15
3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES 16
3.1 Inclusion Criteria 16
3.2 Exclusion Criteria 16
3.3 Informed Consent Process 16
3.4 Randomization Procedures 17
3.5 Study Timeline 17
4. TREATMENT PLAN 17
4.1 Pre-treatment tests 17
4.2 Drug therapy 17
4.3 Radiation Therapy 18
4.4 General Concomitant Medication and Supportive Care Guidelines 21
4.5 Criteria for Removal from Study 21
4.6 Alternatives 21
5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION 21
5.1 Investigational Agent/Device/Procedure 21
5.2 Study agent #1: nivolumab (Opdivo) 21
5.3 Study agent #2: pembrolizumab (Keytruda) 22
5.4 Study agent #3: atezolizumab (Tecentriq) 22
6. DOSE MODIFICATIONS 22
7. ADVERSE EVENTS AND REPORTING PROCEDURES 22
7.1 Potential Adverse Events 22

7.2 Adverse Event Reporting 22
8. CORRELATIVE/SPECIAL STUDIES 23
9. STUDY CALENDAR 23
10. MEASUREMENTS 25
10.1 Primary Outcome 25
10.2 Secondary outcome #1 26
10.3 Secondary outcome #2 27
10.4 Secondary outcome #3 27
10.5 Secondary outcome #4 28
10.6 Secondary outcome #5 29
11. REGULATORY CONSIDERATIONS 30
11.1 Institutional Review of Protocol 30
11.2 Data and Safety Monitoring Plan 30
11.3 Data Management Plan 30
12. STATISTICAL CONSIDERATIONS 31
12.1 Primary and Secondary Endpoints 31
12.2 Analysis Plan 31
12.3 Sample Size Justification 33
12.4 Patient Accrual 33
12.5 Interim Analyses 34
13. REFERENCES 35
APPENDICES 38
II. Subject Information: 38
IV. Inclusion/Exclusion Criteria 38
Statement of Eligibility 39
Protocol Pre-review Checklist 40

PROTOCOL SYNOPSIS

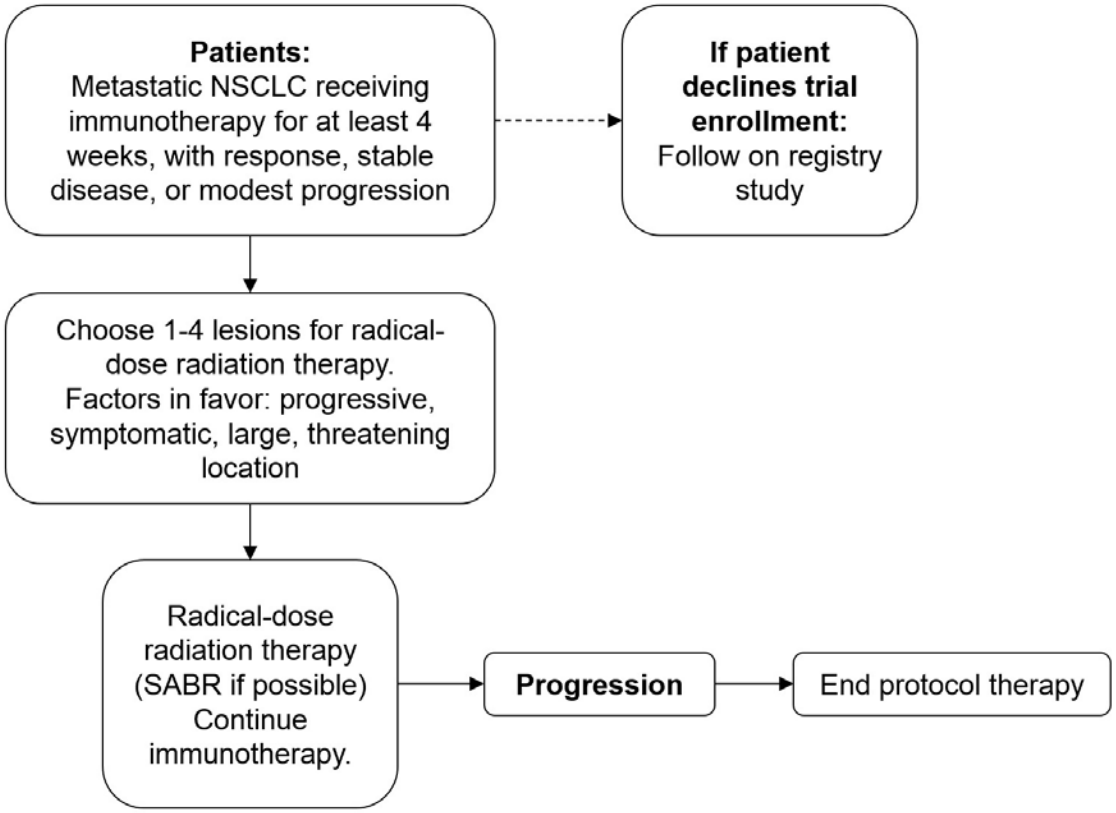
TITLE	Radical RADiotherapy and Immunotherapy for metastatic CAncer of the Lung (RRADICAL)
STUDY PHASE	2
INDICATION	Most patients with metastatic non-small cell lung cancer (NSCLC) now receive immunotherapy with anti-PD-1/anti-PD-L1 agents (currently approved agents: nivolumab, pembrolizumab, and atezolizumab), but only 20% of patients have an objective response to this therapy. We hope to improve the proportion of lung cancer patients who benefit from immunotherapy through the addition of radical-dose (RT) for cytoreduction and immune system priming. In this phase II trial, patients who have been started on immunotherapy and have not had marked progression will receive radical-dose RT, preferably stereotactic ablative radiation therapy (SABR), to the highest risk lesions (generally progressive or bulky masses). We hypothesize that eliminating as much tumor bulk as possible with radiotherapy will prolong or even induce the efficacy of immunotherapy. The goal is to prolong duration of benefit from immunotherapy through cytoreduction and immune system priming. We will evaluate whether progression-free survival is improved compared to historical controls who received immunotherapy without radiation therapy. **Inclusion Criteria:** 1. Has stage IV non-small cell lung cancer, or initially stage I-III disease with distant metastatic recurrence 2. Age ≥ 18 3. Has been receiving anti-PD-1 or anti-PD-L1 immunotherapy for at least four weeks (refer to section 4.2.1) 4. Has had restaging imaging after initiation of immunotherapy, at least 4 weeks after pre-immunotherapy baseline imaging. CT or PET/CT of at least chest/upper abdomen must be performed within 4 weeks prior to registration. For patients with history of brain metastases, brain MRI or CT is required within 4 weeks of registration; for other patients brain MRI or CT is required within 12 weeks of registration. Diagnostic PET/CT performed as part of radiation simulation can be used as the restaging imaging.

	5. Most recent imaging shows measurable disease as defined by RECIST 1.1 6. Evaluation by a Stanford medical oncologist must show: a. The patient is expected to continue on immunotherapy for at least three more months b. Imaging must show response, stable disease, or modest progression c. If there is modest progression, the patient must be clinically stable in terms of performance status and overall disease-related symptoms 7. Has at least one extracranial tumor safely treatable with radical-dose radiation therapy and that has not been previously treated with radiation 8. ECOG performance status 0-2 9. Has the ability to understand and the willingness to sign a written informed consent document. **Exclusion Criteria:** 1. Untreated brain metastases, if not planned to be treated in this course of radiation therapy 2. Pregnancy or women of childbearing potential not willing/able to use contraception during protocol treatment
INVESTIGATIONAL PRODUCT OR PROCEDURE	Addition of radical-dose radiation therapy to standard-of-care anti-PD-1/anti-PD-L1 immunotherapy
PRIMARY OBJECTIVE(S)	• Determine if progression-free survival at 24 weeks with this treatment combination is improved compared to historical controls who received immunotherapy without radiation therapy (see section 12.2)
SECONDARY OBJECTIVE(S)	• Assess acute (0-6 months) and late (>6 months) grade 3-5 toxicity • Assess overall survival • Correlate circulating tumor DNA (ratio of post-RT to pre-RT level) with radiographic response • Correlate immune markers in peripheral blood with radiographic response • Assess dose-limiting toxicity
TREATMENT SUMMARY	This trial's target population is NSCLC patients who have recently started immunotherapy, and have either response, stable disease, or modest progression on follow-up imaging. Patients with substantial progression are excluded because they are unlikely to benefit from immunotherapy even with the addition of RT. The eligible patients are at high risk for progressing within the next few months if they stay on immunotherapy. In this single-arm phase II trial (with an additional prospective registry control group), patients will remain on immunotherapy, with the addition of radical-dose radiation therapy to up to four lesions.

	The hypothesis is that radiation therapy will achieve cytoreduction and immune system priming, and thereby delay disease progression and benefit patients. As much of the overall disease bulk will be targeted as is considered safe, in order to achieve maximal cytoreduction. Stereotactic ablative radiation therapy (SABR) will be given whenever possible because of its higher expected effectiveness and reduced acute toxicity compared to conventional radiation therapy. This study will test whether the addition of RT improves disease control compared to patients not receiving RT. The primary endpoint is progression-free survival 24 weeks after study entry (PFS24), which will be compared to historical controls treated with immunotherapy without the addition of RT (see section 12.2). If we are able to demonstrate that RT delays progression with acceptable rate of toxicity, the RT+immunotherapy combination strategy could be tested in a randomized phase III trial. Patients who are eligible but decline to enroll on the therapeutic arm of the study, or are ineligible only due to enrollment in a different trial, will be offered enrollment on a separate registry arm, where they will receive standard of care immunotherapy without the addition of radiation, and will be followed for progression and other clinical endpoints. This will serve as an internal check on the historical controls' PFS24 estimate. **Intervention and Mode of Delivery:** Patients will continue on the same anti-PD-1 or anti-PD-L1 immunotherapy that they were previously receiving. Systemic treatment on protocol will continue until RECIST progression or unacceptable toxicity. Upon study entry, radical-dose radiation therapy will be given to 1-4 extracranial lesions. The lesions to be treated are at the discretion of the treating radiation oncologist. Factors in favor of selecting a lesion include large size, progression on most recent imaging, causing symptoms, and being in a threatening location (further growth is likely to cause symptoms). A conglomerate of masses or closely spaced masses can be considered to be one lesion. Treatment of brain metastases is not part of protocol therapy. Brain metastases, if present, will be treated as per standard of care, generally with radiation therapy.
SAMPLE SIZE	At least 43 patients in interventional arm, plus approximately 30 patients in companion registry study.

STATISTICAL CONSIDERATIONS	**Definition of primary outcome/endpoint:** Progression-free survival at 24 weeks (PFS24) is proportion of patients without RECIST 1.1 disease progression or death 24 weeks from date of study entry. **Definition of secondary outcomes/endpoints:** • Acute toxicity is defined as toxicity that occurs 0-6 months after first day of radiation therapy. Late toxicity is toxicity that occurs >6 months after first day of radiation therapy. Toxicity is measured with CTCAE v4. • Overall survival is defined as time from study entry to death • For the ctDNA and immune marker endpoints, best radiographic response is defined using RECIST 1.1 criteria • Dose-limiting toxicity is defined as any grade 3-5 toxicity related to study radiation therapy, except certain expected toxicities. **Analytic plan for primary objective:** Progression will be evaluated by follow up CT, PET/CT, and brain MRI imaging and clinic visits **Analytic plan for secondary objectives:** • Potential adverse events will be monitored by treating physicians at each follow up visit, and scored using CTCAE v4 with type and grade • Patients will be followed for progression and death through clinic visits, scans, and chart reviews • For the ctDNA and immune marker endpoints, change in biomarker level from before to after radiation will be correlated with best radiographic response • For the dose-limiting toxicity endpoint, a single interim analysis will be performed and observed rate will be compared to acceptable rate. **Sample size justification:** The null hypothesis is that PFS24 for the study population will be the same as a similar population treated with immunotherapy alone without addition of radiation therapy (see section 12.2). PFS24 with nivolumab in unselected patients is 30-40%. We assume that PFS24 in our patient population would be 35%. The alternate hypothesis is that the study patients' PFS24 is improved over historical controls, at 52%. The exact binomial test will be used to test this hypothesis. PFS will be measured from the date of study entry. Based on historical data, for the study population we estimate that 24 week progression-free survival (PFS24) after continuing immunotherapy alone (without radiation therapy) is 35%. The alternate hypothesis is that their PFS24 is 52%. With one-sided alpha of 0.1 and at least 80% power, 39 patients are required. Assuming 10% dropout/unevaluable patients, total enrollment will be at least 43 patients.

SCHEMA



Primary outcome: Progression-free survival at 24 weeks compared to historical controls

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
CBC	Complete blood count
CMP	Complete metabolic panel
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECOG PS	Eastern Cooperative Oncology Group performance status
FDG-PET	Fluorodeoxyglucose positron emission tomography
GTV	Gross tumor volume
NSCLC	Non-small cell lung cancer
OS	Overall Survival
PD-1	Programmed death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free Survival
PTV	Planning target volume
RECIST	Response evaluation criteria in solid tumors
SABR	Stereotactic ablative radiotherapy
RT	Radiation therapy
PFS24	Progression-free survival 24 weeks after study entry

1. OBJECTIVES

1.1. Primary Objective

- Determine if progression-free survival at 24 weeks with this treatment combination is improved compared to historical controls who received immunotherapy without radiation therapy

1.2. Secondary Objectives

- Assess acute (0-6 months) and late (>6 months) grade 3-5 toxicity
- Assess overall survival
- Correlate circulating tumor DNA (ratio of post-RT to pre-RT level) with radiographic response
- Correlate immune markers in peripheral blood with radiographic response
- Assess dose-limiting toxicity

1.3. Exploratory Objectives

- Analyze progression-free survival with immune-related response criteria
- Measure time to discontinuation of study immunotherapy agent
- Assess patterns of progression

2. BACKGROUND

2.1 Introduction

Of the 221,000 patients diagnosed with lung cancer each year in the US, around 60% present with metastatic incurable disease. Conventionally, radiation therapy (RT) has played a purely palliative role in these patients with metastatic disease, with no routine role for higher dose, advanced RT used to assist with overall disease control.

Cancer immunotherapy harnesses the body's immune system to recognize and attack cancer cells. Recently, three immunotherapeutic agents (nivolumab, pembrolizumab, and atezolizumab) have been approved by the FDA for use in metastatic non-small cell lung cancer (NSCLC) that has progressed on first-line chemotherapy [Brahmer, Borghaei, Garon, Rittmeyer], with more anticipated soon. The development of these anti-programmed death 1 (anti-PD-1)/ anti-programmed death-ligand 1 (anti-PD-L1) agents represent an important advance in the treatment of NSCLC. The clinical benefit of the new agents is noteworthy. In a recent trial of squamous cell lung cancer, nivolumab improved 1-year overall survival from 24% to 42% when compared to docetaxel [Brahmer]. The large majority of metastatic NSCLC patients will be treated with immunotherapy at some point in their disease course. However, only 20% of these patients have an objective response to anti-PD-1/anti-PD-L1 treatment and median overall survival after starting this treatment is less than one year. This indicates a need for new treatment approaches, especially in patients who do not have a good radiographic response to immunotherapy.

Local external beam radiation therapy can also act to stimulate the immune system, through mechanisms such as exposure of tumor-specific antigens to T cells [Gandhi]. Preclinical data in a mouse model of melanoma have shown a synergistic antitumor effect of radiation therapy and immunotherapy with anti-PD-1/anti-PD-L1 therapy [Twyman-Saint Victor]. The added tumor shrinkage from radiation therapy is seen even at tumor sites not exposed to radiation, known as

the abscopal effect. There are emerging data that patients with reduced disease bulk have higher response rates to anti-PD-1/anti-PD-L1 therapy, which provides a second rationale for adding radiation therapy to immunotherapy [Lee].

2.2 Trial Design

This trial's target population is NSCLC patients who have recently started immunotherapy, and have either response, stable disease, or modest progression on follow-up imaging. Patients with substantial progression are excluded because they are unlikely to benefit from immunotherapy even with the addition of RT. The eligible patients are at high risk for progressing within the next few months if they stay on immunotherapy. In this single-arm phase II trial (with an additional prospective registry control group), patients will remain on immunotherapy, with the addition of radical-dose radiation therapy to up to four sites of disease. The hypothesis is that radiation therapy will achieve cytoreduction and immune system priming, and thereby delay disease progression and benefit patients. As much of the overall disease bulk will be targeted as is considered safe, in order to achieve maximal cytoreduction. Stereotactic ablative radiation therapy (SABR) will be given whenever possible because of its higher expected effectiveness and reduced acute toxicity compared to conventional radiation therapy.

This trial differs from other recently opened trials of combination of RT and immunotherapy. Most other trials are attempting to demonstrate response in non-target lesions after radiation (abscopal effect). Based on recent experience combining RT with immunotherapy we are skeptical that a majority of patients will exhibit this dramatic response to RT. Instead, **we hypothesize that eliminating as much tumor bulk as possible with radiotherapy will prolong or even induce the efficacy of immunotherapy.**

This study will test whether the addition of RT improves disease control compared to patients not receiving RT. The primary endpoint is progression-free survival 24 weeks after study entry (PFS24), which will be compared to historical controls treated with immunotherapy without the addition of RT. If we are able to demonstrate that RT delays progression with acceptable rate of toxicity, the RT+immunotherapy combination strategy could be tested in a randomized phase III trial.

Patients who are eligible but decline to enroll on the therapeutic arm of the study, or are ineligible only due to enrollment in a different trial, will be offered enrollment on a separate registry arm, where they will receive standard of care immunotherapy without the addition of radiation, and will be followed for progression and other clinical endpoints. This will serve as an internal check on the historical controls' PFS24 estimate.

We expect that the large majority of patients enrolling on this study will be receiving immunotherapy as second-line or later therapy. This informs the historical control PFS24 estimate. There are several ongoing trials studying the best way to give anti-PD-1/anti-PD-L1 immunotherapy for NSCLC (first-line versus later line of therapy; whether PD-L1 biomarker testing is needed and what PD-L1 level/test is most helpful). For instance, a randomized trial recently suggested that first-line pembrolizumab improves outcomes compared to platinum-based chemotherapy, and showed improved PFS24 compared to immunotherapy used as a later line of therapy [Reck]. We will record line of therapy for patients entering the study, in order to make sure the trial patients' outcomes are compared to an appropriate historical control patient

population.

The specific 1-4 lesions to be treated with RT will be decided by the treating radiation oncologist, using criteria specified in section 4.3.1. The criteria are intended to cause more threatening lesions to be treated with RT, so that even if a systemic effect of RT is not observed, the RT will provide some benefit from local palliation.

2.3 Previous Studies

Radical-dose RT in metastatic NSCLC

A randomized trial recently reported in abstract form provides support for radiation therapy as a means to improve survival in stage IV NSCLC [Gomez 2016]. 49 patients with newly diagnosed oligometastatic NSCLC (3 or fewer metastases) were randomized to standard systemic therapy, or local treatment to all sites of disease with radiation therapy or surgery, followed by standard systemic therapy. Median progression-free survival was dramatically improved in the local therapy arm, at 14.4 months vs. 3.9 months (p=0.01). The overall survival endpoint is not mature.

Efficacy of RT and immunotherapy

In mouse studies using a variety of tumor types, the addition of RT to anti-PD-1/anti-PD-L1 therapy has been shown to improve tumor control at both irradiated and non-irradiated sites [Sharabi, Park, Twyman-Saint Victor]. The combination of RT and immunotherapy seems to be most effective when the radiation dose per fraction is high, similar to clinical treatments with hypofractionated approaches like SABR [Gandhi]. This is one rationale for the use of hypofractionated, radical-dose radiation therapy (2 weeks or fewer, higher biologically effective dose than standard palliative RT) in the current trial.

Safety of RT and immunotherapy

The safety of anti-PD-1/anti-PD-L1 immunotherapy and radical-dose radiation therapy to multiple lesions has been demonstrated separately and in combination. Multiple phase II-III studies of nivolumab, pembrolizumab, and atezolizumab showed acceptable toxicity rates for NSCLC patients [Brahmer, Borghaei, Garon, Rittmeyer]. Radical-dose radiation therapy to multiple disease sites with SABR has also been shown to be safe. In a prospective study of 121 patients receiving SABR to 1-5 metastases in a variety of locations, grade 3-5 toxicity rate was very low at 1% [Milano]. Another similar study also showed severe toxicity rate under 10%, with grade 3-5 complications from 8/113 metastases treated (7% rate) [Salama]. Because of the pattern of metastatic spread of NSCLC, many treated lesions in the current trial will be in the chest. Simultaneous treatment to multiple lesions in the thorax has been shown to be safe, with 5/63 (8%) of patients experiencing grade 3+ acute/late toxicity [Owen].

Several recent prospective studies support the safety of the combination of anti-PD-1/anti-PD-L1immunotherapy with radiation therapy as is used in the current protocol. A phase 1 study evaluated safety of REGN2810, an anti-PD-1 antibody [Papadopoulos 2016]. 34 of the patients received high dose radiation therapy (9 Gy x 3 fractions or 6 Gy x 5 fractions) concurrently with REGN2810. There were no dose-limiting toxicites. In a second study, 11 patients received palliative radiation therapy followed by the anti-PD-1 antibody pembrolizumab [Segal]. There were no grade 3+ drug-related adverse events and the combination was considered to be safe.

Retrospective data also support the safety of the approach taken in this trial. One report described safe treatment of 12 lesions with radiation therapy in seven patients receiving pembrolizumab [Das]. Unpublished data also show that around 50 patients in nivolumab clinical trials also received RT while on nivolumab, and did not have any serious adverse events [personal communication from Dr. Corey Langer, University of Pennsylvania].

2.4 Translational Research

Translational research correlative studies will be performed. The goal of these is to identify biomarkers of a good response to the combination of RT and immunotherapy, to improve patient selection for this treatment strategy in the future.

The first study will involve measuring the level of pre-RT circulating tumor DNA (ctDNA) and change in ctDNA level after radiation therapy [Newman]. Blood will be collected pre- and post-radiation therapy. Also, whenever possible, tumor tissue will be collected, consisting of a punch from a paraffin embedded tissue block or several unstained slides. Samples will be sent to the Diehn lab at Stanford for processing and analysis.

The goal of the ctDNA correlative study is to identify a biomarker of early response to radiation treatment. The significance of change in ctDNA level after radiation therapy has not been well studied, especially in patients with metastatic disease. We hypothesize that patients with greater post-radiation therapy reduction in ctDNA level will later be found to have better radiographic response. This could be due to cancer cell death both in the radiation treated lesion and non-irradiated lesions (from immune potentiation). If it is found that patients with greater ctDNA change have more benefit from radiation therapy, this biomarker could be useful. For instance, one lesion could be treated with radiation and change in ctDNA level measured. If a large change was seen, additional lesions could be irradiated to attempt to trigger an abscopal response.

The second study will involve markers of immune response in peripheral blood. Immune cell subtypes such as activated T cells and myeloid-derived suppressor cells have been shown in preclinical studies to be associated with the increased immune response from the addition of RT to checkpoint blockade immunotherapy [Deng]. Flow cytometry has been able to detect these changes after RT in several preclinical studies [Deng, Sharabi]. Peripheral blood flow cytometry will be performed before and after RT, including with sensitive mass spectrometry methods partially developed at Stanford [Lin, Chang]. We will perform exploratory analysis to see if pre-RT levels of various cell subsets, or relative change after RT, predicts for longer progression-free survival. In patients who have pre-RT research biopsy performed as part of a fiducial placement procedure, immune markers will also be examined for the tumor tissue.

2.5 Study Design

For clinicaltrials.gov documentation:

The primary purpose of the protocol is **treatment**.
The interventional model is **parallel.**
There are **two** interventional arms.
The study is **open**. No masking is used.
The study is **not randomized**.
The primary outcome is **efficacy**.

The FDA has approved nivolumab, pembrolizumab, and atezolizumab for the treatment setting used in this trial, so no Investigational New Drug application is required.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Inclusion Criteria

1. Has stage IV non-small cell lung cancer, or initially stage I-III disease with distant metastatic recurrence
2. Age ≥ 18
3. Has been receiving anti-PD-1 or anti-PD-L1 immunotherapy for at least four weeks (refer to section 4.2.1)
4. Has had restaging imaging after initiation of immunotherapy, at least 4 weeks after pre-immunotherapy baseline imaging. CT or PET/CT of at least chest/upper abdomen must be performed within 4 weeks prior to registration. For patients with history of brain metastases, brain MRI or CT is required within 4 weeks of registration; for other patients brain MRI or CT is required within 12 weeks of registration. Diagnostic PET/CT performed as part of radiation simulation can be used as the restaging imaging.
5. Most recent imaging shows measurable disease as defined by RECIST 1.1
6. Evaluation by a Stanford medical oncologist must show:
    a. The patient is expected to continue on immunotherapy for at least three more months
    b. Imaging must show response, stable disease, or modest progression
    c. If there is modest progression, the patient must be clinically stable in terms of performance status and overall disease-related symptoms
7. Has at least one extracranial tumor safely treatable with radical-dose radiation therapy and that has not been previously treated with radiation
8. ECOG performance status 0-2
9. Has the ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

1. Untreated brain metastases, if not planned to be treated in this course of radiation therapy
2. Pregnancy or women of childbearing potential not willing/able to use contraception during protocol treatment

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

Remote consenting may be conducted.

3.4 Randomization Procedures

N/A

3.5 Study Timeline

Primary Completion:
We estimate the primary completion date will be Feb. 25, 2022.

Study Completion:
We estimate the study completion date will be Feb. 25, 2023.

4. TREATMENT PLAN

4.1 Pre-treatment tests

- History and physical
- Laboratory testing: CBC with differential and complete metabolic panel. Pregnancy test or documentation of adequate contraception for women of childbearing potential.

4.2 Drug therapy

4.2.1 Immunotherapy administration

Patients will continue on the same anti-PD-1 or anti-PD-L1 immunotherapy that they were previously receiving. Currently available anti-PD-1/anti-PD-L1drugs include nivolumab, generally dosed every 2 weeks or every 4 weeks, pembrolizumab, generally dosed every 3 weeks, and atezolizumab, generally dosed every 3 weeks. It is acceptable to give cytotoxic chemotherapy along with immunotherapy, but no chemotherapy can be given from 7 days before first day of protocol radiation therapy to 7 days after last day of protocol radiation therapy. For chemotherapy/immunotherapy combinations, only standard of care regimens are allowed. Currently the allowed combinations are carboplatin/pemetrexed/pembrolizumab and pemetrexed/pembrolizumab [Langer].

Laboratory monitoring for patients on immunotherapy will be performed as per standard of care. For labs required at study entry (CBC w/ diff and CMP), the medical or radiation oncologist will review and initial with date on any abnormal laboratory value/report.

As systemic therapy will be given as per standard of care, it is acceptable for immunotherapy to be given by a physician outside of Stanford ie. local oncologist, however, a Stanford physician will need to evaluate the subject at protocol specified follow up time points. Additionally, study visits may be conducted via video (i.e., MyHealth video, telehealth, telemedicine) or phone.

If there is RECIST 1.1 disease progression or unacceptable toxicity, the patient will be considered to be off of protocol therapy and will not be required to be seen at protocol specified follow up time points. After progression, it will be the decision of the treating medical oncologist whether to continue immunotherapy, switch to another therapy, or discontinue active therapy.

The treating medical oncologist may also decide to stop immunotherapy for other reasons such as an excellent sustained radiographic response to treatment. In this case, the patient should continue on the protocol follow-up schedule.

4.2.2 Modality Review

For patients receiving immunotherapy at an outside facility, immunotherapy quality assurance review will be performed by one of the Medical Oncologist study investigators. This will include verifying that correct medication dosing and dose schedule are being used.

4.2.3 Anticipated Adverse Events

Adverse events from immunotherapy:

The adverse events from nivolumab, pembrolizumab, and atezolizumab are outlined in the package inserts. The most common adverse reactions are fatigue, musculoskeletal pain, decreased appetite, cough, and constipation. Other serious adverse events reported included pneumonitis, immune-mediated colitis, hepatitis, endocrinopathies, nephritis, rash, and encephalitis.

Management of pneumonitis:

Pneumonitis is of particular concern in patients with lung cancer who have recently received radiation therapy. Immune mediated pneumonitis can mimic infection, radiation pneumonitis, or lymphangitic spread of disease. If the patient is believed to have moderate immune-mediated pneumonitis, immunotherapy should be held until pneumonitis resolves. Steroids should be initiated. If a patient is believed to have severe/life-threatening immune-mediated pneumonitis, steroids should be initiated, and pulmonary consultation should be sought. Immunotherapy should be permanently discontinued. If pneumonitis is thought to be due to radiation therapy rather than immunotherapy, the medication can be continued.

4.3 Radiation Therapy

4.3.1 Radiation therapy overview

Radical-dose radiation therapy will be given to 1-4 extracranial lesions. Radiation therapy must be given at Stanford. The lesions to be treated are at the discretion of the treating radiation oncologist. Factors in favor of selecting a lesion include large size, progression on most recent imaging, causing symptoms, and being in a threatening location (further growth is likely to cause symptoms). A conglomerate of masses or

closely spaced masses can be considered to be one lesion.

Treatment of brain metastases is not part of protocol therapy. Brain metastases, if present, will be treated as per standard of care, generally with radiation therapy.

It is acceptable to treat the 1-4 lesions concurrently or sequentially, as long as total planned course of treatment is 10 daily sessions or less. Radiation therapy should be completed in around two weeks, though it is acceptable to extend this if necessary, for instance due to department holidays or linear accelerator downtime. Ideally, radiation therapy will start on the day of an immunotherapy infusion. However, this will not always be possible for logistical reasons. If a RT session falls on the day of an infusion, the two treatments can be given in either order.

If a lesion has previously been treated with external beam radiation therapy, it is not eligible to be treated on this study. However, it is acceptable for a radiation field to about a prior field.

4.3.2 Radiation dose

Either stereotactic or conventional image-guided radiation therapy can be used. SABR is preferred when feasible. Four radiation therapy schedules are allowed. The treating physician will choose between ablative and non- ablative dosing based on lesion location and size. Lesions abutting critical normal structures should have non-ablative dosing. Examples of these structures include spinal cord, small bowel, brachial plexus, large vessels/airways, and esophagus.

Dose schedules:

Ablative:
50 Gy in 5 fractions, or 50 Gy in 10 fractions
Non-ablative:
27 Gy in 3 fractions, or 40 Gy in 10 fractions

4.3.3 Simulation

When possible, the simulation CT will be used as the baseline study for response assessment. Therefore, the simulation CT borders should generally be extended to include all known areas of extracranial disease. During radiotherapy simulation, customized immobilization devices will be formed for each patient. For targets in thorax or upper abdomen, 4-dimensional CT (4 D CT) will be acquired in the treatment position.
Acquisition of a PET CT in the treatment position is encouraged but not required.

4.3.4 Treatment planning

The treating physician will contour the GTV. No explicit expansion for microscopic extension will be added to form the clinical target volume (CTV), i.e., CTV = GTV. The only exception is tumors in the spine, which will have a custom CTV margin

added as per International Spine Radiosurgery Consortium guidelines, because of the high risk of failure when GTV alone is treated [Cox 2012]. For treatments in the chest and upper abdomen, breathing induced tumor motion will be assessed using the 4DCT data and managed by deep inspiration breath hold, respiratory gating, dynamic tumor tracking, or motion inclusive technique, and the internal target volume (ITV) will be designed accordingly. Up to a 7mm setup margin will be added to the ITV (or GTV for treatments outside of the chest/upper abdomen) to form the final planning target volume (PTV). It is acceptable to reduce the PTV margin in the vicinity of critical normal structures such as spinal cord, bowel, or esophagus.

The treatment plan will be generally be normalized such that at least 95% of each PTV is covered by the prescription dose. It is acceptable to cover less than 95% of the PTV with prescription dose in cases of PTV overlap with critical normal structures. An inhomogeneous dose distribution (i.e., maximum point dose ~120-150% of prescription dose) is acceptable as long as the hot spot is centered in the GTV and normal tissue constraints are met.

Treatment will be delivered using 6-15 MV photons using a linear accelerator with daily kilovoltage (kV) X-ray imaging and/or daily cone beam CT for anatomy based matching. Intensity modulated radiation therapy (IMRT), particularly volumetric modulated arc therapy (VMAT), is highly encouraged. 3D conformal therapy can also be used. If 3D conformal therapy is used, it may be necessary to treat two sets of fields daily: one set that covers the full tumor, and another that covers only the part of the tumor not overlapping critical normal structures. For example, for a tumor abutting the spinal cord, the periphery of the tumor could receive a dose of 30 Gy in 10 fractions while the central part of the tumor receives a total of 40 Gy in 10 fractions using a separate set of fields that avoid the spinal cord.

Highly conformal treatment will be given. The ratio of the volume receiving greater than or equal to the prescription dose to the PTV volume should ideally be < 1.2.

4.3.5 Critical structures

Because of the variety of fractionation schedules and disease sites within the body to be treated, absolute normal tissue dose requirements are not specified in this protocol. Stanford institutional guidelines on normal tissue doses exist for each disease site and will be used.

Dose constraints will be based on the individual radiation plans for the 1-4 treated lesions. A plan sum should also be generated if multiple lesions are treated, to make sure that additive organ doses are not excessive.

When a small part of a critical structure overlaps the PTV, it is acceptable for the dose to 0.03 mL of the critical structure to be up to 110% of prescription dose within the overlap region.

4.3.6 R.T. Quality Assurance Review

Every radiation plan will be prospectively reviewed by the protocol investigators.

4.3.7 Radiation therapy adverse events

Potential radiation therapy adverse events depend on the treated location. We expect that most treated lesions will be in the thorax. Therefore, acute toxicity could include esophagitis causing pain with swallowing, fatigue, skin reaction, or cough. Subacute/late toxicity could include radiation pneumonitis, lung fibrosis, chest wall fracture/rib pain, hemoptysis, large airway necrosis, heart failure, pericarditis, esophageal stricture.

Symptomatic radiation pneumonitis should be treated with inhaled or oral steroids. Severe cases should be treated with high dose oral steroids for at least a one month taper.

For treatment of extra-thoracic disease sites, acute toxicity could include skin reaction, fatigue, nausea, vomiting, dysphagia, and mucositis. Subacute/late toxicity could include skin changes/alopecia, brachial plexopathy, stroke, myelitis, bowel obstruction/perforation/fistula, spinal compression fracture, other bone fracture, radiation-induced river disease, kidney failure, change in bowel/bladder habits, sexual dysfunction.

4.4 General Concomitant Medication and Supportive Care Guidelines

Guidelines for use of medications for treatment toxicity are listed in sections 4.2.3 and 4.3.7. Other supportive care, such as management of pain, will be as per standard Stanford Cancer Center clinical practices.

4.5 Criteria for Removal from Study

Patients will be removed from the treatment plan and switched to usual care at time of:

1. Unacceptable toxicity
2. Progression of disease
3. Patient withdrawal of consent

4.6 Alternatives

Patients are allowed to withdraw consent for study treatment at any time, and would be switched back to standard of care treatment with systemic therapy and/or radiation therapy.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

No investigational agents or devices will be used in this study. The study tests a combination of two standard of care treatments: anti-PD-1/anti-PD-L1immunotherapy (current approved agents are nivolumab, pembrolizumab, or atezolizumab); and conformal image-guided radiation therapy.

5.2 Study agent #1: nivolumab (Opdivo)

Nivolumab is a monoclonal antibody that blocks the interaction between PD-1 and its ligands,

PD-L1 and PD-L2. This releases PD-1 pathway mediated inhibition of the immune response, including the anti-tumor immune response. It is FDA approved for treatment of metastatic NSCLC with progression on platinum-based chemotherapy or EGFR/ALK targeted therapy. For details of pharmacokinetics and toxicity data, please see the most updated package insert.

5.3 Study agent #2: pembrolizumab (Keytruda)

Pembrolizumab is a monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This releases PD-1 pathway mediated inhibition of the immune response, including the anti-tumor immune response. It is FDA approved for treatment of metastatic NSCLC in patients whose tumors have ≥50% PD-L1 expression, or have ≥1% PD-L1 expression and progressed on prior therapy. For details of pharmacokinetics and toxicity data, please see the most updated package insert.

5.4 Study agent #3: atezolizumab (Tecentriq)

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases inhibition of the immune response, including the anti- tumor immune response. It is FDA approved for treatment of metastatic NSCLC with progression on platinum-based chemotherapy or EGFR/ALK targeted therapy. For details of pharmacokinetics and toxicity data, please see the most updated package insert.

6. DOSE MODIFICATIONS

Typically, patients who experience toxicity from anti-PD-1/anti-PD-L1immunotherapy do not have dose reduction. Instead, immunotherapy is continued at current dose or discontinued per the judgement of the treating medical oncologist. Since immunotherapy administration on this study is per standard of care, the decision on termination of the immunotherapy agent will be made by the treating medical oncologist.

If a patient is experiencing unacceptable toxicity from radiation therapy while radiation therapy is ongoing, radiation therapy will be discontinued.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

See sections 4.2.3 and 4.3.7.

7.2 Adverse Event Reporting

Adverse events will be graded according to CTCAE v4.03. Baseline and follow up toxicities will be evaluated and documented either by the medical or radiation oncologist. At each follow-up study visit, required Adverse Events and any other grade 3-5 Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) occurring less than 6 months after the conclusion of study RT (unless patient has entered long-term follow-up phase due to disease progression/unacceptable toxicity) will be reported and tracked until resolution.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Analysis of plasma and core biopsy specimens for biomarker development

8.1.1 *Collection of specimens*

For patients who consent to the optional blood testing component, peripheral blood specimens will be drawn before and after radiation therapy, and optionally at follow-up visits. The first specimen will be drawn on the first day of RT (before RT), or up to 14 days before that. The second specimen will be drawn on the last day of RT (after RT), or up to 14 days after that. Also, if a patient has pre-radiation CT-guided biopsy or fiducial placement for routine clinical purposes, research cores may be obtained during that procedure. Collection of specimens is optional. Patients will elect whether they want to participate in this portion of the study on the consent form. This correlative study will be performed at Stanford University.

8.1.2 *Handling of specimens*

a) For each blood collection, up to 50 ml will be drawn (purple/violet tubes, EDTA preserved). EDTA tubes must be stored as soon as possible between 1-6°C until processed. The samples are viable for up to 24 hours after collection if stored at proper temperature

b) After collection, blood will be centrifuged at low RPM. The plasma will be removed and centrifuged at high RPM, then stored at -80°C. ctDNA analysis will be performed on this specimen in collaborator's labs at Stanford University. The remaining cellular material will then be stored at -80°C for later immune marker analysis.

c) Core biopsy specimens: The core biopsy samples will be brought immediately to the pathology department for processing.

De-identified specimens may be saved for future research. If additional correlative work is proposed pending scientific advances, this may require the cooperation of other laboratories.

8.1.3 *Coding of specimens for privacy protection*

At the time of registration each patient will be given a specific confidential identification number (IDN). Specimens will be stored under the patient's IDN. The information can be shared with other investigators listed on this protocol. Study data will be maintained in password protected computer files (protected online database). Only research personnel will have access to this information.

9. STUDY CALENDAR

This study calendar is for patients enrolled in the interventional arm who will receive radiation therapy on study. For patients in the separate registry arm, clinic visits,

laboratory draws, and scans will be per standard of care and are not mandated to be on a specific schedule. For interventional arm patients, after disease progression or unacceptable toxicity, the patient enters the long-term follow-up period and visit/imaging schedule will be at the discretion of the treating medical oncologist and not mandated by the study.

All treatment and evaluation items in the study calendar are part of standard medical care, except for the peripheral blood biomarker lab draw which is a research procedure. Also, if a patient has pre-radiation CT-guided biopsy or fiducial placement for routine clinical purposes, research cores may be obtained during that procedure.

Action	**Pre Entry[1]**	**Pre-RT**	**Day 1 of RT**	**Last day of RT**	**8 weeks after sim[2]**	**16 weeks after sim[2]**	**24 weeks after sim[2]**	**36 weeks after sim[3]**	**48 weeks after sim[3]**	**Every 12 weeks until disease progression or unacceptable toxicity[3]**	**After disease progression or un-acceptable toxicity**
History & Physical Exam	X				X	X	X	X	X	X[11]	
ECOG PS	X				X	X	X	X	X	X[11]	
Labs											
CBC/diff.	X[9]										
CMP	X[9]										
CT Thorax (Chest), or PET/CT	X				X	X	X	X	X	X[11]	
Brain MRI or CT, if known brain metastases	X				X	X	X	X	X	X[11]	
Vital status evaluation					X	X	X	X	X	X	X[10]
Study consent		X[12]									
Toxicity evaluation		X			X	X	X	X	X	X[11]	
Fiducial placement (as clinically indicated)		X									
Research cores during fiducial placement (optional)		X									
Radiation therapy			X	X							
Lesion measure-ments				X[4]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	

Peripheral blood biomarkers (if consented for this portion of study)			X[6]	X[7]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	

Sim=simulation

[1] Within 4 weeks prior to enrollment

[2] +/- 2 weeks

[3] +/- 4 weeks

[4] After the last day of RT or up to 4 weeks following the completion of RT: For each radiation treated lesion, document diameter on sim CT, location and radiation dose.

[5] Document size of each radiation treated lesion. Also document RECIST response compared to radiation SIM CT. For follow-up time points starting with 108 weeks: if imaging studies were not performed, lesion measurements are not required.

[6] Blood drawn before first fraction of RT or any time up to 14 days before first fraction.

[7] Blood drawn after last fraction of RT or any time up to 14 days after last fraction.

[8] Optional

[9] Labs collected prior to study and prior to each cycle of immunotherapy at the discretion of the treating medical oncologist.

[10]After disease progression/unacceptable toxicity, vital status will be recorded every 6-12 months by chart review and/or telephone calls.

[11]Adverse events will be recorded until the 96-week follow-up visit. Starting with the 108-week follow-up visit, adverse events will not be recorded, and the history & physical exam, ECOG PS, and imaging studies will all be optional.

[12] Within 60 days prior to first dose of study radiation therapy

10. MEASUREMENTS

10.1 Primary Outcome

Title: Progression-free survival at 24 weeks (PFS24)
Time frame: 24 weeks after study entry
Safety issue: no

10.1.1 Relevant Subset

Patients who enroll on the interventional arm and receive radiation therapy on protocol will be analyzed.

Patients who meet eligibility criteria but choose not to enroll on protocol treatment will be offered the option of participating in a registry arm. These patients will receive standard of care treatment and follow-up (including imaging), not dictated by the protocol. They will be followed for endpoints including radiographic progression, discontinuation of immunotherapy, and death.

10.1.2 Measurement Definition

Progression-free survival at 24 weeks (PFS24) is proportion of patients without RECIST 1.1 disease progression or death 24 weeks from date of study entry.

10.1.3 Measurement Methods

The baseline imaging study on the interventional arm will be the radiation simulation CT when possible. If not all known lesions are visible on the simulation CT, the most recent prior diagnostic CT or PET/CT can be used instead. Progression will be evaluated by follow up CT, PET/CT, and brain MRI imaging and clinic visits. Progression compared to simulation CT will be defined as per the RECIST 1.1 criteria.

10.1.4 Measurement Time Points

Patients on the interventional arm will undergo CT scans to cover all known sites of disease at 8 week intervals (±2 weeks) for the first 24 weeks, and then at 12 week intervals (±4 weeks). PET-CT is an acceptable alternative. Patients with known brain metastases will have brain MRI or CT at 3-4 month intervals (up to 6 month intervals acceptable if last treatment for brain metastases is 1 year or more prior to the scan). After disease progression or unacceptable toxicity, imaging schedule will be at the discretion of the treating medical oncologist.

10.1.5 Response Review

There are no plans for response review by an independent third party.

10.2 Secondary outcome #1

Title: Acute (0-6 months) and late (>6 months) grade 3-5 toxicity
Time frame: 0-4 years after study entry
Safety issue: yes

10.2.1 Relevant Subset

Patients who enroll on the interventional arm and receive radiation therapy on protocol will be analyzed.

10.2.2 Measurement Definition

Acute toxicity is defined as toxicity that occurs 0-6 months after first day of radiation therapy. Late toxicity is toxicity that occurs >6 months after first day of radiation therapy. Toxicity is measured with CTCAE v4.

10.2.3 Measurement Methods

Toxicity will be assessed at follow-up clinic visits. Also, patients will be followed for hospitalization and other medical events.

10.2.4 Measurement Time Points

Follow-up clinic visits at 8 week intervals (±2 weeks) for the first 24 weeks, and then at 12 week intervals (±4 weeks) until disease progression.

If there is RECIST 1.1 disease progression or unacceptable toxicity, the patient will be considered to be off of protocol therapy and will not be required to be seen at protocol specified follow up time points. The patient will then be followed for survival outcomes collected during standard of care visits, with study data collection typically occurring every 6-12 months. If the patient is lost to follow-up and not seen at Stanford, phone calls will be performed to check for survival status annually.

10.2.5 Response Review

There are no plans for response review by an independent third party.

10.3 Secondary outcome #2

Title: Overall survival
Time frame: 0-4 years after study entry
Safety issue: no

10.3.1 Relevant Subset

Patients who enroll on the interventional arm and receive radiation therapy on protocol will be included in this analysis. Patients who enroll on the registry arm will also be analyzed as a separate arm.

10.3.2 Measurement

Definition Time from study

entry to death.

10.3.3 Measurement Methods

The electronic medical record will be monitored for patient deaths.

10.3.4 Measurement Time Points

There is no specific time point for this measurement.

10.3.5 Response Review

There are no plans for response review by an independent third party.

10.4 Secondary outcome #3

Title: Correlation of circulating tumor DNA (ratio of post-RT to pre-RT level) with

radiographic response
Time frame: 0 to approximately 1 year after study entry
Safety issue: no

10.4.1 Relevant Subset

Patients who enroll on the interventional arm, receive radiation therapy on protocol, and have pre- and post-RT research blood draws will be included in this analysis.

10.4.2 Measurement Definition

- ctDNA measured as percentage of total circulating free DNA
- Radiographic tumor assessments using RECIST 1.1 criteria, using radiation simulation CT as baseline scan. Best response after RT will be recorded.

10.4.3 Measurement Methods

ctDNA levels will be measured using CAncer Personalized Profiling by deep Sequencing (CAPP-Seq).

10.4.4 Measurement Time Points

- ctDNA specimens (also see section 8.1.1): The first specimen will be drawn on the first day of RT (before RT), or up to 14 days earlier. The second specimen will be drawn on the last day of RT (after RT), or up to 14 days later.
- Radiographic response: Each post-RT restaging imaging study will be scored for RECIST 1.1 response, until best response is achieved.

10.4.5 Response Review

There are no plans for response review by an independent third party.

10.5 Secondary outcome #4

Title: Correlation of immune markers in peripheral blood with radiographic response
Time frame: 0 to approximately 1 year after study entry
Safety issue: no

10.5.1 Relevant Subset

Patients who enroll on the interventional arm, receive radiation therapy on protocol, and have pre- and post-RT research blood draws will be included in this analysis.

10.5.2 Measurement Definition

- Immune markers including frequency of myeloid-derived suppressor cells and antigen- specific CD8+ T cells
- Radiographic tumor assessments using RECIST 1.1 criteria, using radiation simulation CT as baseline scan. Best response after RT will be recorded.

Measurement Methods

Immune markers will be measured using flow cytometry performed by the Human Immune Monitoring Core at Stanford.

10.5.3 Measurement Time Points

- Peripheral blood flow cytometry specimens (also see section 8.1.1): The first specimen will be drawn on the first day of RT (before RT), or up to 14 days earlier. The second specimen will be drawn on the last day of RT (after RT), or up to 14 days after.
- Radiographic response: Each post-RT restaging imaging study will be scored for RECIST 1.1 response, until best response is achieved.

10.5.4 Response Review

There are no plans for response review by an independent third party.

10.6 Secondary outcome #5

Title: Dose-limiting toxicity (DLT)
Time frame: 0-4 years after study entry
Safety issue: yes

10.6.1 Relevant Subset

Patients who enroll on the interventional arm and receive at least one dose of radiation therapy on protocol will be analyzed.

10.6.2 Measurement Definition

Any grade 3-5 toxicity related to study radiation therapy, except the following:
- grade 4 radiation dermatitis or mucositis that reduces to grade 2 or lower within 1 month after completion of study radiation therapy
- grade 3 radiation dermatitis, mucositis, pain, dysphagia, diarrhea, fatigue, anorexia, weight loss, esophagitis, endocrine disorder

10.6.3 Measurement Methods

Toxicity will be assessed at follow-up clinic visits. Also, patients will be followed for hospitalization and other medical events.

10.6.4 Measurement Time Points

Follow-up clinic visits at 8 week intervals (±2 weeks) for the first 24 weeks, and then at 12 week intervals (±4 weeks) until disease progression or unacceptable toxicity.

10.6.5 Response Review

There are no plans for response review by an independent third party.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

While study accrual is ongoing, the study team will provide the DSMC with a yearly report that lists a summary of the frequency and severity of grade 3-5 adverse events observed so far.

The DSMC will also review results of the single interim safety analysis (see section 12.2), and based on this review will provide a determination of whether patient accrual should continue.

11.3 Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using REDCap database system and will be maintained by the Clinical Research Coordinator assigned to this study.

The study team will hold monthly meetings. Topics for discussion will include screening of candidates, eligibility, accrual progress, data entry completeness, adverse event grading and attribution, and serious adverse events.

12. STATISTICAL CONSIDERATIONS

12.1 Primary and Secondary Endpoints

Primary endpoint

Determine if progression-free survival at 24 weeks (PFS24, measured from study entry) with this treatment combination is improved compared to historical controls who received immunotherapy without radiation therapy

Secondary endpoints

- Acute (0-6 months) and late (>6 months) grade 3-5 toxicity (CTCAE v4)
- Overall survival
- Correlation of circulating tumor DNA (ratio of post-RT to pre-RT level) with radiographic response
- Correlation of immune markers in peripheral blood with radiographic response
- Dose-limiting toxicity

Exploratory endpoints

- Progression-free survival with immune-related response criteria
- Time to discontinuation of study immunotherapy agent
- Patterns of response and progression, including abscopal responses

12.2 Analysis Plan

12.2.1 Primary endpoint

For the primary endpoint, the null hypothesis is that progression-free survival at 24 weeks from study entry (PFS24) for the radiation-treated study population will be the same as a similar population treated with immunotherapy alone without addition of radiation therapy. Most patients in our study will be treated with immunotherapy as 2nd or later line of therapy. PFS24 with 2nd line nivolumab in unselected NSCLC patients is 30% for adenocarcinoma subtype and 40% for squamous cell subtype [Brahmer 2015, Borghaei 2015]. As almost all metastatic NSCLC patients treated at Stanford have adenocarcinoma, but we are excluding patients with the worst prognosis (those with rapid progression on immunotherapy), we assume a baseline PFS24 of 35%. Also, the current trial is enrolling a broader group of patients than those treated on the phase III nivolumab studies; for instance, we allow ECOG performance status of 0-2 as opposed to 0-1 on those studies. This would be expected to result in a lower PFS24.

The alternate hypothesis is that the study patients' PFS24 is improved over the 35%

historical control rate, at 52%. The exact binomial test will be used to test this hypothesis. PFS will be measured from the date of study entry. The alternate hypothesis PFS24 was initially set at 50% when the study was started, but was adjusted to 52% after several studies showed a greater than 15% improvement in PFS24 with the addition of radiotherapy to immunotherapy [Theelen, Welsh]. One phase 2 trial showed a PFS24 of approximately 52% with immunotherapy plus radiotherapy, versus 35% with immunotherapy alone, exactly matching our revised values [Theelen, Fig. 2].

All patients who undergo protocol radiation therapy will be analyzed ("per-protocol" analysis). Patients who enroll on the study but do not receive any protocol treatment will be excluded from analysis. Since patients with a variety of responses to immunotherapy are allowed on study, we will perform an exploratory analysis testing whether pre-RT radiographic response to immunotherapy influences post-RT PFS.

PFS24 and other survival endpoints will also be calculated for the registry arm patients. For both interventional arm and registry arm, start date for these endpoints will be date of study entry. The registry arm PFS24 will serve as an internal check on the historical controls' PFS24 estimate, but there is no plan to formally compare the interventional arm and registry arm PFS24 due to lack of statistical power for this comparison.

12.2.2 Secondary endpoints

Interim safety analysis

A patient on this study had fatal radiation pneumonitis that was likely related to study radiation therapy. Also, since study activation, several retrospective studies have shown higher than previously expected rates of radiation pneumonitis in patients treated with radiation therapy combined with anti-PD-1/anti-PD-L1 immunotherapy [Tian, Shaverdian]. This raised concern for a potentially high rate of radiation pneumonitis or other severe toxicities among patients in this study. After its August 2020 annual review of the study, the DSMC requested to review aggregate toxicity data.

It was decided in collaboration with the DSMC to immediately conduct a single interim safety analysis to help make a decision about whether to complete enrollment. At the time of this decision, 42 patients had enrolled and received protocol treatment. The procedures for the interim analysis of these 42 patients are described here.

We define dose-limiting toxicities (DLT) in section 10.6. In general, DLT is defined as any grade 3-5 toxicity related to study radiation therapy, except for certain expected toxicities. We wished to exclude a rate of DLTs that is much higher than that seen in prior studies of high-dose hypofractionated lung radiation alone. Analyzable patients for the interim safety analysis will be eligible patients who enrolled in the treatment arm and received at least one dose of study radiation therapy.

In the RTOG 0915 study of SBRT for peripheral lung cancers, the rate of protocol-

specified AEs (generally, grade 3-5 AEs attributed to radiation) was 11.9% (10/84) [Videtic]. In the RTOG 0813 study of SBRT radiation for central lung cancers, the rate of dose-limiting toxicity was 5.6% (5/89); the rate of grade 3-5 toxicity was 22% (20/92) [Bezjak]. Note that in RTOG 0813 DLTs were only counted if they occurred in the first year after treatment, whereas the rate of grade 3-5 toxicity also includes AEs that occurred later.

Based on these published rates of AEs with radiation alone (without concurrent immunotherapy as in the current study, which could raise the risk of AEs), we will consider an acceptable true rate of DLTs from the protocol radiotherapy to be 20% or less, while a DLT rate of >35% would be unacceptable.

If observed DLT rate is 19.0% (8/42) or less, 95% confidence interval for DLT rate would be 10.0-33.3% or less, and we would recommend to the DSMC that study enrollment be continued.

If observed DLT rate is 33.3% (14/42) or more, 95% confidence interval for DLT rate would be 21.0-48.4% or more, the true DLT rate is very likely to be >20% and we would recommend to the DSMC that study enrollment be stopped.

If observed DLT rate is in between these values (9 to 13 out of 42), it is consistent with a range of true DLT rates that includes both safe and unsafe rates. In this case, we will ask the DSMC to make a decision about whether to continue or stop enrollment.

Other secondary endpoints

Adverse events will be tabulated by organ system and severity. Proportions of patients with adverse events will be estimated with 95% confidence intervals.

Plasma biomarkers (e.g. cell free DNA level) will be summarized using medians and interquartile ranges; changes in biomarkers will be assessed using the Wilcoxon signed rank test. Correlation of biomarkers with radiographic response will be evaluated using a Wilcoxon rank sum test on patients with and without the event of interest. If feasible, these analyses will be supplemented by more formal analyses with the Cox model.

12.3 Sample Size Justification

The null hypothesis is that PFS24 for the interventional arm population will be the same as a similar population treated with immunotherapy alone without addition of radiation therapy. A null hypothesis PFS24 of 35% is assumed (see section 12.2). The alternate hypothesis is that the study patients' PFS24 is improved over historical controls, at 52%. The exact binomial test will be used to test this hypothesis. With one-sided alpha of 0.1 and at least 80% power, 39 evaluable patients are required. Assuming 10% dropout/unevaluable patients, total enrollment will be at least 43 patients.

12.4 Patient Accrual

[This section was not edited after the revised sample size was determined, but is left in place for historical documentation purposes.]

We anticipate that this study will take 2.5 years to accrue with another 6 months required for follow up. We estimate that an additional 30 patients will enroll on the companion registry study.

The yearly accrual estimate of 22 patients on the interventional arm is based on the monthly number of patients starting anti-PD-1/anti-PD-L1immunotherapy at Stanford Cancer Center (data from Stanford Cancer Institute Research Database). Around 75 patients started these drugs over a 7 month period in 2016 (yearly rate of ~130 patients). We estimate that 70% of patients starting these drugs have stage IV NSCLC. Assuming that 50% of those patients are eligible for this study, and 65% agree to go on the interventional arm, yearly accrual would be 30 patients, a comfortable margin above our required 22 patient yearly accrual. Of the 35% of patients who do not agree to enroll in the interventional arm, if 75% of these patients agree to enroll on the registry arm, then total registry arm enrollment will meet the target of 30. Assuming 10% of these patients are lost to follow-up/unevaluable, 27 patients on the registry arm will be available for analysis.

12.5 Interim Analyses

There will be a single interim analysis for safety after at least 42 patients have received protocol treatment; see section 12.2.

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APPENDICES

APPENDIX A: Participant Eligibility Checklist

Protocol Title:	Radical RADiotherapy and Immunotherapy for metastatic CAncer of the Lung (RRADICAL)
Protocol Number:	IRB 40088
Principal Investigator:	Michael Gensheimer, MD

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☒ IRB Approved ☒ Contract signed ☒

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	Yes	No	Window	Last day to Register	Supporting Documentation*
1. Has stage IV non-small cell lung cancer, or initially stage I-III disease with distant metastatic recurrence	☐	☐			
2. Age ≥ 18	☐	☐			
3. Has been receiving anti-PD-1 or anti-PD-L1 immunotherapy for at least four weeks (refer to section 4.2.1)	☐	☐			
4. Has had restaging imaging after initiation of immunotherapy, at least 4 weeks after pre-immunotherapy baseline imaging. CT or PET/CT of at least chest/upper abdomen must be performed within 4 weeks prior to registration. For patients with history of brain metastases, brain MRI or CT is required within 4 weeks of registration; for other patients brain MRI or CT is required within 12 weeks of registration. Diagnostic PET/CT performed as part of radiation simulation can be used as the restaging imaging.	☐	☐			
5. Most recent imaging shows measurable disease as defined by RECIST 1.1	☐	☐			
6. Evaluation by a Stanford medical oncologist must show: a. The patient is expected to continue on immunotherapy for at least three more months b. Imaging must show response, stable disease, or modest progression	☐ ☐	☐ ☐			

c. If there is modest progression, the patient must be clinically stable in terms of performance status and overall disease-related symptoms	☐	☐			
7. Has at least one extracranial tumor safely treatable with radical-dose radiation therapy and that has not been previously treated with radiation	☐	☐			
8. ECOG performance status 0-2	☐	☐			
9. Has the ability to understand and the willingness to sign a written informed consent document.	☐	☐			
Exclusion Criteria (From IRB approved protocol)					
1. Untreated brain metastases, if not planned to be treated in this course of radiation therapy	☐	☐			
2. Pregnancy or women of childbearing potential not willing/able to use contraception during protocol treatment	☐	☐			

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

Statement of Eligibility

By signing this form of this trial I verify that this subject is[☐ **eligible** / ☐ **Ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

APPENDIX B**: Protocol Pre-review Checklist**

The protocols will be pre-reviewed prior to the assignment of an SRC meeting date in order to ensure that protocols contain all the required elements and information in the appropriate format. This Checklist is intended to be helpful in the protocol writing process.
Appendix B is not part of the protocol. Please delete it after completing the protocol.

Protocol Pre-review Checklist

No	Description	Yes	No
1	Protocol is in the appropriate template for either Interventional or Non-interventional study		
2	Title page includes names and addresses of Principal Investigator, Co-investigators, Biostatistician and Coordinator as appropriate		
3	Sponsor information is included if appropriate		
4	Title page includes protocol version and date		
5	Protocol document has page numbers		
6	Schema is legible		
7	List of Abbreviations is relevant to this protocol		
8	Table of contents is complete		
9	Instructions in the template are deleted		
10	Section titles are appropriately designated and numbered		
11	All the sections in the template are complete		
12	Study calendar is complete		
13	Protocol contains adequate background/rationale information		
14	Objectives and measurements of outcome are clearly stated		
15	The sections on objectives, eligibility, outcome measurements, statistics and study calendar are consistent		
16	Monitoring plan refers to Stanford DSMC		
17	Statistical section is appropriate for this study		
18	Appropriate references are included		
19	Protocol includes eligibility checklist		
20	Protocol includes questionnaires as needed		
21	Protocol includes CRF statement		
22	Protocol document is well organized		

Note: Some of the requirements are applicable to only **Interventional** studies as specified in the template.