Fresolimumab and Stereotactic Ablative Radiotherapy in Early Stage Non-Small Cell Lung Cancer

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Original Date: 10 July 2015
Version Date: 7 August 2015
Version Date: 30 September 2015
Version Date: 6 October 2015
Version Date: 26 June 2017
Version Date: 22 November 2017
Version Date: 1 February 2019
Version Date: 19 June 2019
Version Date: 24 June 2019
Current Version Date: 30 June 2022

Activation Date (OnCore):
SRC approval Date: 8 August 2015
SRC approval Date: 1 February 2019

For Protocol Amendment of : LUN0071, Fresolimumab and Stereotactic Ablative Radiotherapy in Early Stage Non-Small Cell Lung Cancer (FRESO)

Protocol Version Date: 26 March 2022

Section	Change
Global	The protocol version date is updated in the document footer. Genzyme replaced with Sanofi Genzyme
Page 1, 2	Updated personnel and version table
Page 8, 38	Accrual will occur over 60 months
Page 9, 17	Study duration updated
Page 9, 11, 17, 18, 33	Added SABR windows (-1/+5 days)
Section 4.2.3, page 20	Added follow up details
Section 11.3, page 37	Added "Case report forms will be developed using REDCap database system and will be maintained by the Clinical Research Coordinator assigned to this study"
Page 7, 9, 10, 11, 14, 35, 36, 39	Clarified that the primary endpoint is the severity of pulmonary fibrosis.
Page 7, 9, 11, 15, 35, 39	Clarified evaluation of severity vs. pattern.
Page 35	Added that scores will be assigned by consensus by at least two radiologists or radiation oncologists dedicated to the study.
Page 35	Added that in the phase 2 component of the study, the severity score of fibrosis in study subjects will be compared to historical controls. Historical controls will consist of patients previously treated with the same dose of SABR (50 Gy in four fractions) at Stanford in the absence of fresolimumab.
Page 35, 39	Added that patients who are lost to follow up and who do not have a scan within +/-6 months of the 12-month time point will be excluded from analysis.
Page 35, 39	Added that patients who develop inflammatory lung conditions unrelated to radiotherapy (i.e. pneumonia, ARDS, drug-induced pneumonitis, etc.) will be excluded from the final endpoint analysis if the area of unrelated inflammation impedes scoring of fibrosis severity of the irradiated lesion.
Page 39	Added that our institutional experience revealed the presence of moderate-to-severe late radiation induced fibrosis in approximately 75% of SABR patients at 1 year.
Page 39	Added that patients who are lost to follow up and who do not have a scan within +/-6 months of the 12-month time point will be excluded from analysis. Patients who develop inflammatory lung conditions unrelated to radiotherapy (i.e. pneumonia, ARDS, drug-induced pneumonitis, etc.) will be excluded from the final endpoint analysis if the area of unrelated inflammation

	impedes scoring of fibrosis severity of the irradiated lesion
Page 39	**Added that our institutional experience revealed the presence of moderate-to-severe late radiation induced fibrosis in ~75% of patients treated with SABR (50 Gy in 4 fractions) at 1 year.**

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PROTOCOL SYNOPSIS

Title of Study: Fresolimumab and Stereotactic Ablative Radiotherapy in Early Stage Non-Small Cell Lung cancer

Study Phase: 1-2

Study Center(s): Stanford University Hospital

Indication:

Stereotactic ablative radiotherapy (SABR) has emerged as an effective and safe treatment modality for early stage non-small cell lung cancer (NSCLC). However, most patients develop significant fibrosis of lung tissue in the target region, which inhibits local lung function and complicates early diagnosis of possible tumor recurrence. Additionally, the main pattern of failure after SABR for early stage NSCLC is regional/distant recurrence. Thus, there is an unmet need for therapeutic strategies that can reduce post-treatment fibrosis and decrease regional/distant recurrence.

Phase 1:

Primary Objective*:*

Evaluate the safe dose of fresolimumab in combination with SABR in patients

Secondary Objectives*:*

- Evaluate potential adverse events in patients receiving fresolimumab plus SABR
- Evaluate post-treatment changes in pulmonary function
- Evaluate recurrence rates and progression-free survival (PFS)
- Assess pharmacokinetics (PK) of fresolimumab in combination with SABR (optional for patient)
- Evaluate the rate and severity of radiation-induced pulmonary fibrosis after SABR plus fresolimumab

Phase 2:

Primary Objective*:*

Evaluate the rate of moderate-to-severe radiation-induced pulmonary fibrosis after SABR plus fresolimumab

Secondary Objectives*:*

- Evaluate the pattern of radiation-induced pulmonary fibrosis after SABR plus fresolimumab
- Evaluate potential adverse events in patients receiving fresolimumab plus SABR
- Evaluate post-treatment changes in pulmonary function
- Evaluate recurrence rates and progression-free survival (PFS)

Hypothesis:

We hypothesize that inhibition of TGFβ using fresolimumab will reduce the development of radiation-induced pulmonary fibrosis after SABR for early stage NSCLC.

Phase 1 will help determine a safe and tolerable dose of fresolimumab in combination with SABR in patients with early stage NSCLC. After the dose has been determined, we will then proceed to a single-arm, phase 2 study, in which patients will receive fresolimumab at the dose determined from Phase 1 in addition to SABR.

Study Design:

We propose a prospective, phase 1-2 clinical trial to evaluate the evaluate the safety and efficacy of combining fresolimumab with SABR in the treatment of early stage NSCLC.

Phase 1 will help determine a safe and tolerable dose of fresolimumab in combination with SABR in patients with early stage NSCLC. After the dose has been determined, we will then proceed to a single-arm, phase 2 study, in which patients will receive fresolimumab at the dose determined from Phase 1 in addition to SABR.

Comprehensive Safety Review

The rate of NSCLC recurrence will be continuously evaluated for the 1st 10 subjects through 6 months follow-up. In the event that there are ≥ 3 NSCLC recurrences in the first 10 subjects, enrollment will be paused, and a comprehensive safety review will be conducted, which will include the Stanford Cancer Institute Data Safety Monitoring Committee (DSMC). If, after review, the DSMC recommends proceeding with the study, the report of the safety review will be submitted to the IND, and FDA's concurrence will be sought before proceeding with enrollment.

Similarly, development of new malignancies will be monitored for the first 10 patients through the 6 month follow-up time point [except keratoacanthomas / squamous cell carcinomas (SCC) of the skin]. Keratoacanthomas and SCC are not included because these are known events that regress after discontinuation of fresolimumab therapy, per the Investigator's Brochure. These lesions will be referred to a dermatologic oncologist or dermatologist for evaluation, treatment, and monitoring, but will not be tabulated towards the criteria for enrollment pause. New malignancies are expected to be rare, and if more than 2 subjects develop new malignancies, enrollment would be similarly paused for a comprehensive safety review as above.

Primary and Secondary Endpoint(s):

Phase 1:

Primary Endpoint

Dose limiting toxicities (DLTs) of fresolimumab when combined with SABR

Secondary Endpoint

- Score the pattern of late radiation induced fibrosis at 12 months after SABR with and without fresolimumab
- Evaluate pattern and severity of acute radiation-induced fibrosis in the first 6 months after SABR
- Score potential adverse events (AEs) of fresolimumab combined with SABR using CTCAE v4
- Measure post-treatment changes in pulmonary function using pulmonary function test parameters at enrollment, 6-month, and 12-month follow-up
- Evaluate recurrence and progression-free survival at 12 months
- Measure blood pharmacokinetics (PK) of fresolimumab in combination with SABR (optional for patient)

Exploratory Endpoint:

- Assess extent of radiation-induced lung toxicity by quantitative imaging analysis of CT volumes and FDG uptake parameters

Phase 2

Primary Endpoint

Evaluate the presence of late moderate-to-severe radiation-induced fibrosis up to 12 months after SABR with fresolimumab

Secondary Endpoint

- Score the pattern of late radiation induced fibrosis at 12 months after SABR with and without fresolimumab
- Evaluate pattern and severity of acute radiation-induced fibrosis in the first 6 months after SABR
- Score potential adverse events (AEs) of fresolimumab combined with SABR using CTCAE v4
- Measure post-treatment changes in pulmonary function using pulmonary function test parameters at enrollment, 6-month, and 12-month follow-up
- Evaluate recurrence and progression-free survival at 12 months

Exploratory Endpoint:

- Assess extent of radiation-induced lung toxicity by quantitative imaging analysis of CT volumes and FDG uptake parameters

Number of Patients: 55 to 60

In 2014, ~80 lung SABR procedures were performed at Stanford Hospital. It is estimated that 2 to 3 patients can reasonably be expected to accrue per month. Accrual will occur over 60 months.

Inclusion Criteria:

1. Newly diagnosed, histologically-proven T1-T2bN0M0 (Stage IA-IIA) NSCLC, with maximum tumor diameter ≤ 5 cm under consideration for stereotactic ablative body radiotherapy (SABR) as definitive primary treatment
2. Patient judged to be inoperable or at high surgical risk by a board-qualified thoracic cancer surgeon who has evaluated the subject within the prior 12 weeks, or the patient's case has been discussed at a multidisciplinary tumor board with a thoracic cancer surgeon in attendance, or a patient who refuses surgery or declines to be evaluated for surgery
3. ECOG PS 0 to 2
4. Age greater than or equal to 18 years old and able to give informed consent
5. Men or women of child-bearing potential must agree to use an acceptable method of birth control (hormonal or barrier method of birth control; abstinence) to avoid pregnancy for at least 90 days after last study treatment (radiation or fresolimumab)

Exclusion Criteria:

1. Significant anemia (hemoglobin < 9.0 g/dL) or neutropenia (ANC < 1000/mm^3)
2. Prior history of multifocal adenocarcinoma in situ (ie, classic or pure bronchioloalveolar carcinoma)
3. Prior history of keratoacanthoma (well-differentiated squamous cell skin cancer variant, often centrally ulcerated). History of basal cell cancer is allowed.
4. Pre-malignant skin lesion(s) noted on prescreening skin exam, except for actinic (solar) keratosis
5. Prior radiotherapy overlapping with high dose region of planned SABR course
6. Prior history of head and neck; oral; or bladder cancer
7. Prior receipt of systemic treatment (chemotherapy, targeted therapy, or immunotherapy) for the lesion under consideration of treatment

8. Uncontrolled, inter-current or recent illness that in the investigator's opinion precludes participation in the study, including those undergoing therapy for a separate invasive malignancy
9. Contraindication to receiving radiotherapy
10. Known allergy to components of fresolimumab
11. Pregnant or breastfeeding. All women of child-bearing potential (last menstrual period within the previous 12 months and not surgically sterile) will be tested for pregnancy at pre-entry.

Intervention and Mode of Delivery:

Phase 1 component:

Fresolimumab will be administered intravenously (IV) at a dose of 3 mg/kg on Days 1, 15, and 36 and SABR will be administered at 12.5 Gy/fraction in 4 fractions between Days 8 and 12 to a total of 5 patients who will be evaluated for safety, and additional patients will be enrolled if specific AE's are observed. A dose reduction may be implemented if excessive toxicity is observed.

Phase 2 component:

Fresolimumab will be administered IV at the dose selected in the preceding Phase 1 component (3 mg/Kg) on Days 1, 15 (+ 6 days), and 36 (+/- 6 days) and SABR (-1/+5 days) will be administered at 12.5 Gy/fraction in 4 fractions between Days 8 and 12.

Duration of Intervention and Evaluation: The study duration will be approximately 6 years (5 years for accrual and 1 year for follow-up)

Statistical Methods:

Definition of primary outcome/endpoint:

Phase 1:

DLT is defined as CTCAE grade 3 or higher radiation pneumonitis or bronchopulmonary hemorrhage

Phase 2:

Presence of radiation-induced pulmonary fibrosis is defined as presence of a moderate-to-severe level of fibrosis in each patient by 12 months

Definition of secondary outcomes/endpoints:

Phase 1:

- Potential adverse events is defined by CTCAE v4
- Post-treatment changes in pulmonary function will be evaluated by changes in pulmonary function test at enrollment, 6-month, and 12-month follow-up
- Recurrence is defined as presence of local, regional, and/or distant recurrence by 12 month
- Progression-free survival is time from time from study enrollment until the first documented date of disease progression.
- Extent of radiation-induced lung toxicity is morphological changes on CT and PET after treatment
- Presence of radiation induced pulmonary fibrosis is defined as presence of a moderate-to-severe level of fibrosis in each patient by 12 months
- Severity of radiation induced pulmonary fibrosis is degree of fibrosis after SABR

Phase 2:

- Severity of radiation induced pulmonary fibrosis is degree of fibrosis after SABR
- See Phase 1 definitions for the rest of the objectives

Analytic plan for primary objective:

Phase 1:
A safe dose of fresolimumab is reached when ≤10% of the patients receiving fresolimumab plus SABR develops DLTs, defined as CTCAE v4 grade 3 or higher radiation pneumonitis and bronchopulmonary hemorrhage.

Phase 2:
Rate of radiation-induced pulmonary fibrosis is defined as percentage of patients with a moderate-to-severe level of fibrosis. Presence of fibrosis will be determined by CT imaging after treatment.

Analytic plan for secondary objectives:

Phase 1:

- Potential adverse events will be monitored by treating physicians at each follow-up visit, and scored using CTCAE v4 with type and grade
- Post-treatment changes in pulmonary function will be evaluated by changes in pulmonary function test (PFT) at enrollment, 6-month, and 12-month follow-up
- Recurrence rates will be evaluated by follow-up CT imaging studies up to 1 year
- Progression-free survival will be evaluated by following the above imaging results at each follow-up visit up to 1 year
- Pharmacokinetics (PK) of fresolimumab will be determined by measurement of drug level in blood samples. Blood sample will be collected once before fresolimumab administration and again within 1-4 hours post administration.
- Rate of radiation induced pulmonary fibrosis is defined as percentage of patients with a moderate-to-severe level of fibrosis. Presence of fibrosis will be determined by CT imaging after treatment.
- Pattern of radiation-induced pulmonary fibrosis will be scored using the "Late Radiation Fibrosis Score" developed by Dahele, *et al.* [2]

Phase 2:
Please see Phase 1 definitions for the objectives

Sample size justification:

Phase 1:
Post-SABR pneumonitis is expected to occur in ≤ 10% of patients with stage I disease. Based on this percentage, we propose to start out with a cohort of 5 patients at the pre-selected dose of 3mg/kg of fresolimumab. If one patient develops DLT, then 5 more patients will be enrolled at the same dose to make a total of 10 patients. If no more patients experience DLT, then the total percentage of patients experiencing DLT is 10% and is considered acceptable for toxicity.

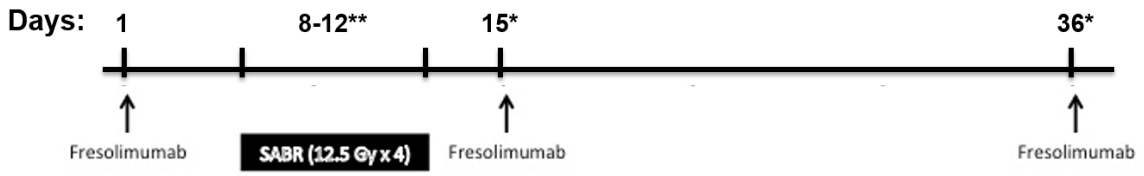
Phase 2:
A sample of size 50 was chosen in order to have 80% power to detect a decrease in the incidence of post SABR moderate-to-severe fibrosis from 75% to 60% with a one sided significance level of 10%.

Funding, Regulatory, and Feasibility Issues:
This study is sponsored by Varian, Inc. and Sanofi Genzyme, Inc. The fresolimumab used in this study will be provided by Sanofi Genzyme, Inc. Sanofi Genzyme has committed to providing the medication.

Patient Acceptability/Ethics and Consent Issues: SABR is the definitive treatments for patients with stage I NSCLC who are unable or unwilling to undergo surgical resection. This study involves adding fresolimumab to the above standard treatment. The treatment is limited to three IV administrations of the medication, at the dose that is anticipated to be tolerable based on prior clinical trials. We also structure the follow-up visits of the study to match those that would be needed following SABR treatment. We believe with the above study design, we can increase patient acceptance and tolerability of the trial.
Sponsor Information This study is sponsored by Varian, Inc., and Sanofi Genzyme, Inc. The fresolimumab used in this study will be provided by Sanofi Genzyme, Inc.

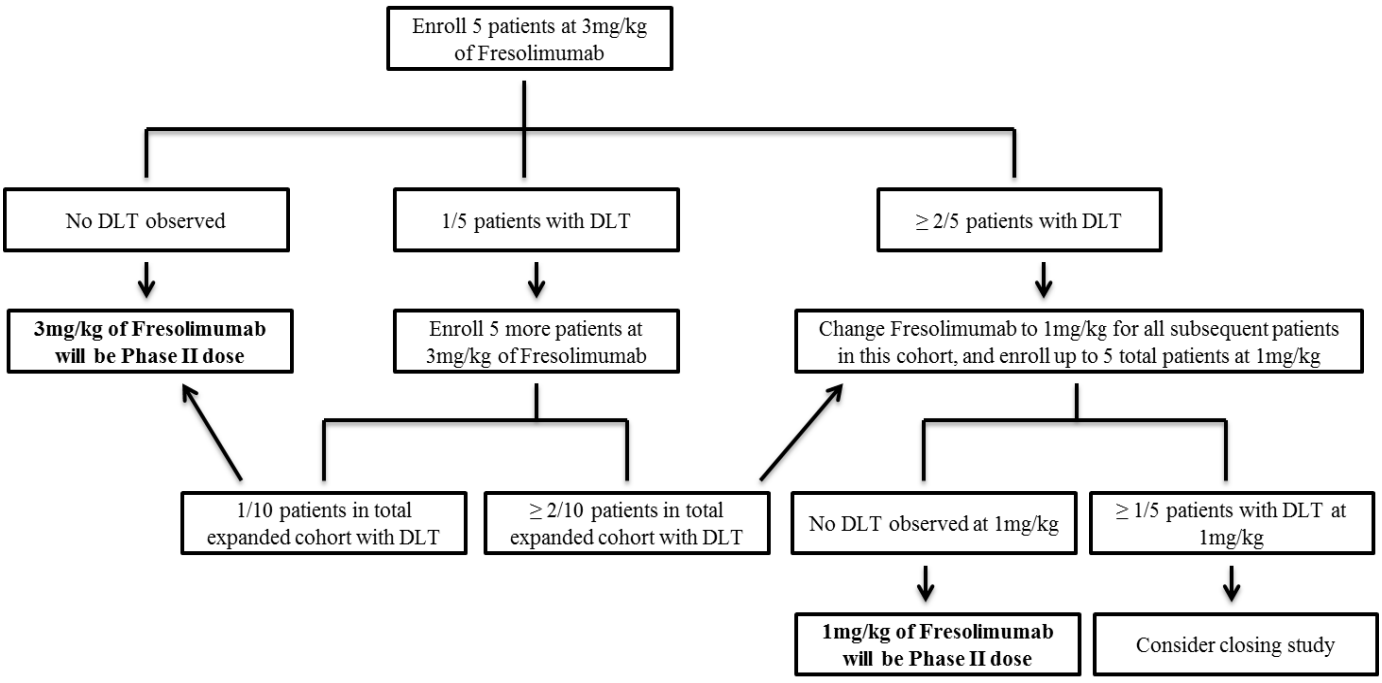
Study Schema

Phase 1-2 Treatment Administration Schema:



** -1/+5 days to allow for weekends and holidays and unforeseen circumstances
* +/- 6 days to allow for weekends and holidays and unforeseen circumstances

Phase 1 Schema:



Phase 2:

Fresolimumab will be administered IV at the dose determined from Phase 1 on Days 1, 15 (+ 6 days), and 36 (+/- 6 days), with SABR (-1/+5 days) being administered at 12.5 Gy/fraction in 4 fractions between Days 8 and 12.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ANC	Absolute neutrophil count
BED	Biologically equivalent dose
CBC	Complete blood count
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTV	Clinical target volume
DLCO	Diffusing capacity of the lung for carbon monoxide
DM	Distant metastasis
DNA	Deoxyribonucleic acid
DNF	Distant nodal failure
DMF	Distant metastatic failure
ECOG PS	Eastern Cooperative Oncology Group performance status
EDTA	Ethylenediaminetetraacetic acid
EMT	Epithelial mesenchymal transformation
FDG-PET	Fluorodeoxyglucose positron emission tomography
FEV-1	Forced expiratory volume in 1 second
FFF	Flattening free filter mode
FNA	Fine needle aspirate
GTV	Gross tumor volume
HNF	Hilar node failure
IDN	Identification number
ILF	Involved lobe failure
ITV	internal target volume
LC	Local Control
MF	Marginal failure
MNF	Ipsilateral mediastinal nodal failure (MNF)
NLF	Non-primary lobe failure
NSCLC	Non-small cell lung cancer
OS	Overall Survival
PFT	Pulmonary function test
PTF	Primary tumor failure
PTV	Planning target volume
QOL	Quality of life
RECIST	Response evaluation criteria in solid tumors
RC	Regional control
RPM	Revolutions per minute
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiation therapy
XRT	External beam radiation therapy

1. OBJECTIVES

Phase 1:

***Primary Objective**:*

Evaluate the safe dose of fresolimumab in combination with SABR in patients

***Secondary Objectives**:*

- Evaluate potential adverse events in patients receiving fresolimumab plus SABR
- Evaluate post-treatment changes in pulmonary function
- Evaluate recurrence rates and progression-free survival
- Assess pharmacokinetics (PK) of fresolimumab in combination with SABR (optional for patient)
- Evaluate the rate and severity of radiation-induced pulmonary fibrosis after SABR plus fresolimumab

Phase 2:

Primary Objective:

Evaluate the rate of radiation-induced moderate-to-severe pulmonary fibrosis after SABR plus fresolimumab

Secondary Objectives:

- Evaluate the pattern of radiation induced pulmonary fibrosis after SABR plus fresolimumab
- Evaluate potential adverse events in patients receiving fresolimumab plus SABR
- Evaluate post-treatment changes in pulmonary function
- Evaluate recurrence rates and progression-free survival

2. BACKGROUND

2.1 Study Disease

Lung cancer is the leading cause of cancer mortality worldwide, accounting for over 1.3 million deaths each year, largely because it is most often diagnosed at advanced stages [1]. However, early stage non-small cell lung cancer (NSCLC) is often surgically curable with the appropriate resection, preferably lobectomy [2]. Unfortunately, a significant fraction of patients with early stage NSCLC cannot tolerate surgery owing to medical comorbidities.

2.2 Study Agent/Device/Procedure

Stereotactic Ablative Radiotherapy

In non-operable NSCLC patients, stereotactic ablative radiotherapy (SABR), also called stereotactic body radiation therapy (SBRT), has recently emerged as an important treatment option [3, 4]. A landmark prospective phase 2 clinical trial conducted by the Radiation Therapy Oncology Group, RTOG 0236, found that SABR resulted in outstanding local control (LC) and overall survival (OS) rates of 98% and 56% at 3 years in a cohort of strictly medically inoperable patients with peripherally located stage I NSCLC [5]. While extremely well tolerated, SABR almost always produces a significant fibrotic reaction in the targeted region of the lung. These fibrotic reactions result in loss of function of the affected lung tissue and significantly complicate detection of post-SABR recurrences.

Transforming growth factor-beta

Transforming growth factor-beta (TGFβ) is a pleiotropic cytokine expressed as three isoforms; TGFβ1, TGFβ2, and TGFβ3 and belongs to a superfamily of ligands comprised of more than 30 proteins such as bone morphogenetic proteins, activins, and inhibin. TGFβ isoforms are involved in a number of normal biologic and physiologic processes such as cell proliferation, cell differentiation, cell motility, apoptosis, angiogenesis, and extracellular matrix production [6]. In normal non-cancerous cells TGFβ limits the growth of epithelial, endothelial, neuronal, and

hematopoietic cells through induction of anti-proliferative and apoptotic responses but in cancer TGFβ has been shown to have growth promoting and prometastatic effects [7, 8].

TGFβ has been implicated in the growth, progression, and metastasis of cancer and is known to be a key mediator in epithelial homeostasis; controlling key events such as the differentiation, proliferation, growth and senescence of cells. Typically, TGFβ suppresses the proliferation of cells and clear senesced cells through the induction of apoptosis [7, 8]. These antiproliferative effects are primarily mediated by mobilization of cyclin-dependent kinase inhibitors and suppression of c-Myc and in the absence of promitogenic gene mutations or other mitogenic stimuli, disruption of TGFβ signaling does not induce cell proliferation. However, work of numerous investigators has revealed that mutations in TGFβ receptors or its signal transduction pathways, which abrogate the cytostatic activity of the growth factor in epithelial and hematopoietic cells, play a key role in tumor progression of many types of cancer [9].
In addition, TGFβ has additional direct effects on tumor promotion by inducing epithelial-mesenchymal transformation (EMT), a morphologic and functional change for cancer cells. Cancer cells which have undergone EMT are much more motile and invasive which leads to increased metastasis [10, 11].

In animal models, TGFβ has been implicated as a key regulator promoting the development of radiation-induced lung fibrosis. In rodents, expression of TGFβ is induced after pulmonary irradiation and inhibition of TGFβ via monoclonal antibodies or small molecule inhibitors results in dramatically decreased development of fibrosis. For example, in a study designed to determine if TGFβ neutralization ameliorates radiation-induced fibrosis in the lung, Fischer 344 rats were administered a single dose of 1D11 after receiving 5 fractionated doses of radiation. Results demonstrated that a single dose of anti-TGFβ antibody significantly reduces inflammation, TGFβ activation and expression, and radiation-induced fibrosis [12]. Additionally, TGFβ inhibition has been show to radiosensitize various types of cancer cells. For example, in studies involving syngeneic murine breast cancer and glioblastoma models TGFβ neutralization using a anti-TGFβ monoclonal antibody resulted in tumor growth delay [13, 14]. This suggests inhibition of TGFβ may be of therapeutic value in combination with radiotherapy.

Description of Fresolimumab

Fresolimumab is a fully human IgG4 kappa monoclonal antibody generated using recombinant technology in collaboration between Sanofi Genzyme Corporation and Cambridge Antibody Technology (Cambridge, UK). Fresolimumab is capable of neutralizing all mammalian isoforms of TGFβ (ie, β1, β2, and β3). Fresolimumab is a high-affinity antibody with dissociation constants (Kd) of 1.8 nM, 2.8 nM, and 1.4 nM for TGFβ1; TGFβ 2, and TGFβ 3, respectively. Fresolimumab has entered clinical trials, including a recently completed multi-institutional phase 1 trial (NCI-06-C-0200) in patients with advanced malignant melanoma and renal cell cancer. It is also being evaluated as an anti-fibrotic agent in patients with fibrotic conditions.

Previous clinical experience with Fresolimumab in Cancer Patients

A first in human, single-dose multi-institutional phase 1 study of Fresolimumab was carried out in patients with idiopathic pulmonary fibrosis (clinicaltrials.gov: NCT00125385). No drug-related serious adverse events (SAEs) were reported. A single dose phase 1 trial of fresolimumab in patients with treatment resistant focal segmental glomerulosclerosis (clinical trials.gov: NCT00464321) has also been completed.

A phase 1 multi-institution, dose-escalation trial of Fresolimumab in subjects with metastatic malignant melanoma and renal cell cancer was the lead institution was recently completed (NCI-06-C-0200). This protocol represented the first study of Fresolimumab in patients with cancer and the first to involve repeated doses of the antibody. Cohorts of patients with advanced malignant melanoma and renal cell cancer that had failed at least 1 prior therapy were treated with intravenous Fresolimumab administered at 0.1, 0.3, 1, 3, 10 or 15 mg/kg in a 3 + 3 dose-escalation design. If no dose-limiting toxicity occurred within 28 days of the first dose (Day 0), 3 additional doses were administered 2 weeks apart (Days 28, 42 and 56). Patients achieving at least stable disease or better by RECIST criteria were eligible to receive Extended Treatment consisting of 4 doses of Fresolimumab at the highest dose level determined to be safe at the time every 2 weeks for up to 2 additional courses. Twenty-two patients (21 with melanoma and one renal cell cancer patient) were treated in the initial dose-escalation component of the study and an additional 7 patients (all with malignant melanoma) were treated in a safety cohort expansion at the highest dose of 15 mg/kg. No dose-limiting toxicities were observed and the highest dose level of Fresolimumab, 15 mg/kg, was determined to be safe.

Evidence of clinical benefit (SD or better) was seen in 7 of 29 (24%) total patients enrolled in the study: PR (N = 1), SD (N = 3) and MR (N = 3). Two of these 7 patients were determined to have met SD criteria per protocol but did not receive Extended Therapy. In the phase 1 study, for SD responses follow-up measurements had to meet the SD criteria at least once at a minimum interval of not less than 8 weeks. The remaining 5 responses were observed in subjects receiving Fresolimumab at starting doses of 1 mg/kg or less. Of these, 3 patients had mixed responses with shrinkage of metastases in the liver and at other sites, and one patient with skin disease achieved a PR with >89% reduction of target lesions lasting about one year.

2.3 Rationale

Based on the clinical and preclinical data described above, we propose a prospective phase 1-2 clinical trial that will test the hypothesis that TGFβ inhibition using fresolimumab will reduce the development of pulmonary fibrosis after SABR for early stage NSCLC. Thousands of patients per year with early stage NSCLC are treated with SABR and all would benefit from the knowledge gained from this. If successful, the addition of fresolimumab to SABR could increase the ease and speed with which local recurrence can be diagnosed, increasing the chance that additional local therapy could be used for salvage. Additionally, proving that TGFβ inhibition can reduce or prevent radiation-induced fibrosis would serve as a proof-of-principle for applying this approach in other caner types where fibrosis is a significant side effect (eg, head and neck cancer, breast cancer, etc).

2.4 Study Design

Phase 1 component:

Fresolimumab will be on Days 1, 15, and 36 and SABR will be administered at 12.5 Gy/fraction in 4 fractions between Days 8 and 12 to a total of 5 patients who will be evaluated for safety, and additional patients will be enrolled if specific AE's are observed. A dose reduction may be implemented if excessive toxicity is observed.

Blood would be collected for pharmacokinetic studies (only Phase 1). This is a single-arm, open-label study

Phase 2 component:

Up to a total of 60 patients, including the Phase 1 portion. Fresolimumab will be administered IV at the dose selected in the preceding Phase 1 (3 mg/Kg) component on Days 1, 15 (+ 6 days), and 36 (+/- 6 days) and SABR (-1/+5 days) will be administered at 12.5 Gy/fraction in 4 fractions between Days 8 and 12.

This is a single-arm, open-label study conducted under IND 125981 (Sponsor-Investigator/ IND Holder: Maximilian Diehn, MD, PhD).

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion & Exclusion Criteria

Inclusion Criteria:

1. Newly diagnosed, histologically-proven T1-T2bN0M0 (Stage IA-IIA) NSCLC, with maximum tumor diameter ≤ 5 cm under consideration for stereotactic ablative body radiotherapy (SABR) as definitive primary treatment
2. Patient judged to be inoperable or at high surgical risk by a board-qualified thoracic cancer surgeon who has evaluated the subject within the prior 12 weeks, or the patient's case has been discussed at a multidisciplinary tumor board with a thoracic cancer surgeon in attendance, or a patient who refuses surgery or declines to be evaluated for surgery within 12 weeks
3. ECOG PS 0 to 2
4. Age greater than or equal to 18 years old and able to give informed consent
5. Men or women of child-bearing potential must agree to use an acceptable method of birth control (hormonal or barrier method of birth control; abstinence) to avoid pregnancy for at least 90 days after last study treatment (radiation or fresolimumab)

Exclusion Criteria:

1. Significant anemia (hemoglobin below 9.0 g/dL) or neutropenia (ANC < 1000/mm^3)
2. Prior history of multifocal adenocarcinoma in situ (ie, classic or pure bronchioloalveolar carcinoma)
3. Prior history of keratoacanthoma (well-differentiated squamous cell skin cancer variant, often centrally ulcerated). History of basal cell cancer is allowed.
4. Pre-malignant skin lesion(s) noted on prescreening skin exam, except for actinic (solar) keratosis
5. Prior radiotherapy overlapping with high dose region of planned SABR course
6. Prior history of head and neck; oral; or bladder cancer
7. Prior receipt of systemic treatment (chemotherapy, targeted therapy, or immunotherapy) for the lesion under consideration of treatment
8. Uncontrolled, inter-current or recent illness that in the investigator's opinion precludes participation in the study, including those undergoing therapy for a separate invasive malignancy
9. Contraindication to receiving radiotherapy

10. Known allergy to components of fresolimumab
11. Pregnant or breastfeeding. All women of child-bearing potential (last menstrual period within the previous 12 months and not surgically sterile) will be tested for pregnancy at pre-entry.

3.2 Informed Consent Process

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

3.3 Randomization Procedures

Phase 1: Single-arm, non-randomized
Phase 2: Single-arm, non-randomized

3.4 Study Timeline

Estimated study length: 6 years consisting of 5 year(s) accrual + 1 year follow-up

Primary Completion (for CT.gov):
The study is expected to reach primary completion approximately 72 months from the time the study opens to accrual

Study Completion:
The study is expected to reach study completion approximately 72 months from the time the study opens to accrual. Phase 1 is expected to be completed in approximately 18 months, and phase 2 in approximately 36 months

4. TREATMENT PLAN

4.1. Pre-treatment tests

The following will be completed prior to treatment (for specifics see study calendar):

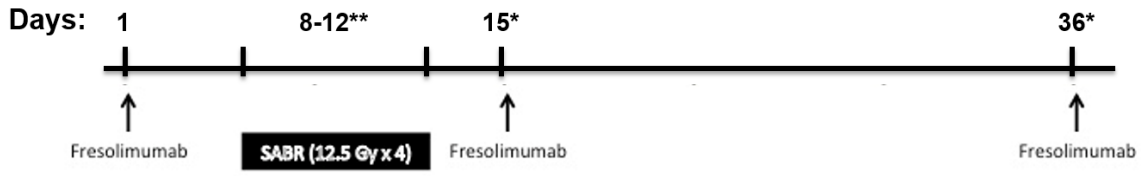
a) Medical history and clinical examination, including a full skin exam by the investigators.
b) Laboratory testing
c) Baseline imaging- Acceptable to use simulation scans.
d) Signed informed consent document.

4.2. Drug Therapy

4.2.1 Fresolimumab Administration

Fresolimumab will be administered IV at a dose of 3 mg/kg on Days 1, 15, and 36, with SABR (-1/+5 days) being administered at 12.5 Gy/fraction in 4 fractions between Days 8 and 12.

Administration Schema:



** -1/+5 days to allow for weekends and holidays and unforeseen circumstances
* +/- 6 days to allow for weekends and holidays and unforeseen circumstances

Phase 1 (see study Schema, pg 9):
We will enroll 5 patients at 3 mg/kg of fresolimumab.

Dose limiting toxicity (DLT) is defined as the following grade 3; 4; or 5 CTCAE v4 events determined to be of possibly; probably; of definite relationship to treatment; occurring after 1st dose of fresolimumab and up to 30 days after the last dose of fresolimumab:

1) Radiation pneumonitis, or
2) Bronchopulmonary hemorrhage

Of the 5 patients, if none experience DLT, then 3 mg/kg will be the dose for the Phase 2 component.

If one patient experiences DLT, an additional 5 patients will be enrolled at 3 mg/kg. If no more patients experiences DLT, then 3 mg/kg will be the dose for the Phase 2 component. If 2 or more patients experience DLT in the total expanded cohort (or 2 or more patients in the initial cohort experience DLT), then the investigational dose of fresolimumab will be changed to 1 mg/kg. If 2 or more patients in the initial cohort experience DLT before all 5 patients have been enrolled, the remaining patients will receive the lower dose of 1 mg/kg.

At the lower dose (1 mg/kg), 5 more patients will be enrolled. If no more patients experience grade 3 or higher toxicity, then 1 mg/kg will be the dose for the Phase 2 component.

If one or more patients of 5 experience DLT at the reduced dose, the investigators will consider closing the study.

Phase 2:

Fresolimumab will be administered IV at the dose determined from Phase 1 on Days 1, 15 (+ 6 days), and 36 (+/- 6 days), with SABR (-1/+5 days) being administered at 12.5 Gy/fraction in 4 fractions between Days 8 and 12.

4.2.2 General Concomitant Medication and Supportive Care Guidelines
In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records. Patients must be instructed not to take additional medications including over-the-counter products and herbal/alternative medications during the study without prior consultation with the investigator.

Permitted treatments during the study include, but are not limited to the following:

- Pain medication to allow the patient to be as comfortable as possible
- Nutritional support or appetite stimulants (eg, megestrol)
- Oxygen therapy and blood products or transfusions

The following concomitant treatments are not allowed during the study:

- Concurrent use of other investigational drugs is not permitted.

- The administration of other antineoplastic therapy (eg, chemotherapy, hormone therapy, immunotherapy, targeted therapy, and monoclonal antibodies) is not permitted.

4.2.3 Duration of Therapy

Patients will be seen on Days 1, 15, and 36 when they receive fresolimumab, and will be seen in follow-up at 3rd; 6th; 9th and 12th month from end of SABR completion (+/- 2 weeks). History and physical exam, ECOG PS, toxicity evaluation, CT Thorax (Chest) imaging, and labs will be evaluated at each of these visits. Skin exams will be conducted at the 3rd month from end of SABR completion. PFTs will be completed at 6th and 12th month. PET/CT imaging will be evaluated at 6th month. The duration of the treatment phase of the study will be through the 1st follow-up visit, approximately 90 days after the SABR is completed.

4.2.4 Duration of Follow-Up

The follow-up portion of the study will begin approximately 90 days after SABR is completed through 12 months from enrollment. Further follow-up information is on the study calendar.

4.2.5 Criteria for Removal from Study

Patients who develop the following conditions during the course of treatment will discontinue further planned study treatments (fresolimumab or SABR). Long-term follow-up visits will still be performed as feasible unless patient completely withdraws consent (treatment and follow up).

- Disease progression by RECIST or death
- Unacceptable toxicity (Section 7.12)
- Pregnancy
- Patient request for no further treatment
- Noncompliance
- Lost to follow-up
- Inability of subject to comply with study requirements
- Any general or specific changes in the patient's condition that render further treatment unacceptable in the judgment of the investigator

4.2.6 Alternatives

Alternative treatments include surgical resection, SABR alone, or no therapy.

4.2.7 Compensation

Patients will not be paid for their participation in the study.

4.3. Procedures: SABR Administration and Radiation Treatment Planning

4.3.1. Fiducials

We may implant peri-tumoral metallic fiducial markers for image-guided tumor localization as needed, generally for lower lobe locations where the magnitude of tumor motion tends to be greatest. The fiducials will be used as surrogates for targeting the daily tumor position during treatment. The fiducials will be placed directly into the tumor and/or periphery under CT guidance. Fiducials may be implanted prior to enrollment as this is a standard of care procedure for any patient receiving SABR for lung tumors.

4.3.2. Simulation

During radiotherapy simulation, customized immobilization devices will be formed for each patient, and 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.

4.3.3. Treatment planning

The treating physicians will contour the gross tumor volume (GTV) on axial CT slices using lung windows for visualizing tumor/lung interfaces and mediastinal windows for tumor/soft tissue

interfaces, with the aid of fused PET. No explicit expansion for microscopic extension will be added to form the clinical target volume (CTV), ie, CTV = GTV. Breathing-induced tumor motion will be assessed using the 4-D CT data and managed by respiratory gating, dynamic tumor tracking, or motion-inclusive technique, and the internal target volume (ITV) will be designed accordingly. A 0.5 cm setup margin will be added to the ITV to form the final planning target volume (PTV).

Treatment will be delivered using 6 or 10 MV photons using a linear accelerator with daily kilovoltage (kV) X-ray portal imaging and/or daily cone-beam CT for anatomy-based matching.

4.3.4. Dosimetry

Treatment can be planned using forward or inverse planning. In the case of the former, three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. For forward planned 3D conformal RT, when static beams are used, typically ≥ 10 (at least 7) non-opposing, non-coplanar beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. Alternatively, dynamic conformal arcs (coplanar or non-coplanar) may be used. In order to obtain acceptable coverage, field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (ie, no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). For inverse planning, volumetric modulated arc therapy or fixed beam IMRT will be performed. In all cases, the treatment isocenter will be adjusted based on pre-treatment imaging.

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity corrections with algorithms that accurately model buildup and lateral electron scatter (eg, Monte Carlo, AAA, Acuros XB, superposition-convolution). Simple pencil beam algorithms are not acceptable.

4.3.5. Prescription dose constraints

For all subjects, the decision of whether a treatment plan is acceptable will be made on a case-by-case basis by the treating radiation oncologist. Successful treatment planning will require accomplishment of all of the following criteria:

1. ***Prescription dose****:* The prescription dose will be 50 Gray (Gy) in four 12.5 Gy fractions.
2. ***Maximum dose***: The treatment plan should be created such that 100% corresponds to the prescription dose. The maximum dose for the plan must be at least 110% and no more than 140% and this point must be located within the PTV and ideally within the GTV. A maximum dose of 120 to 130% of the prescription dose centered in the GTV would be typical.
3. ***Planning Target Volume Coverage***: 95% of the target volume (PTV) must be conformally covered by the prescription isodose surface (PTV V100%RX ≥ 95%) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (PTV V90%RX > 99%).
4. ***High Dose Spillage***: The cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should be no more than 15% of the PTV volume. The ratio of the volume receiving greater than or equal to the prescription dose to the PTV volume should ideally be < 1.2 (see table below). These will not be required to be met in treating small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3.5 cm results in the inability to meet a conformality ratio of 1.2.

5. ***Intermediate Dose Spillage***: The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:
   a. *Location*: The maximum total dose over all fractions in Gy to any point 2 cm or greater away from the PTV in any direction must be no greater than is given by the table below.
   b. *Volume*: The ratio of the volume of 50% of the prescription dose isodose to the volume of the PTV must be no greater than is given in the table below.

PTV (cc)	Rx isodose vol / PTV		50% Rx isodose vol / PTV		Maximum dose (% of Rx) @ 2 cm from PTV	
	Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor
1.8	< 1.2	< 1.5	< 5.9	< 7.5	< 50.0	< 57.0
3.8	< 1.2	< 1.5	< 5.5	< 6.5	< 50.0	< 57.0
7.4	< 1.2	< 1.5	< 5.1	< 6.0	< 50.0	< 58.0
13.2	< 1.2	< 1.5	< 4.7	< 5.8	< 50.0	< 58.0
22	< 1.2	< 1.5	< 4.5	< 5.5	< 54.0	< 63.0
34	< 1.2	< 1.5	< 4.3	< 5.3	< 58.0	< 68.0
50	< 1.2	< 1.5	< 4.0	< 5.0	< 62.0	< 77.0
70	< 1.2	< 1.5	< 3.5	< 4.8	< 66.0	< 86.0
95	< 1.2	< 1.5	< 3.3	< 4.4	< 70.0	< 89.0
126	< 1.2	< 1.5	< 3.1	< 4.0	< 73.0	< 91.0
163	< 1.2	< 1.5	< 2.9	< 3.7	< 77.0	< 94.0

Note: Use interpolation if volume of PTV falls between table entries

4.3.6. Prescription dose constraint tables

The following tables list dose constraints to critical structures based on the number of fractions prescribed. Exceeding these dose limits by more than 5% constitutes an unacceptable protocol deviation.

Critical structures with <u>absolute</u> volume and <u>absolute</u> point dose limits: Exceeding any of these limits constitutes a major protocol violation.

Critical structure	**Volume dose limits (4 fractions)**		**Maximum Point dose limit (< 0.035 mL)**
	Dose	**Volume**	**Dose**
Spinal cord	20.8 Gy 13.6 Gy	< 0.35 mL < 1.2 mL	26 Gy
Brachial plexus	23.6 Gy	< 3 mL	27.2 Gy
Skin	33.2 Gy	< 10 mL	36 Gy
Lungs-GTV	12.4 Gy 11.6 Gy 20 Gy	< 1000 mL < 1500 mL < 10% (require < 15%)	NA
Stomach	17.6 Gy	< 10 mL	27.2 Gy
Small bowel*	17.6 Gy 12 Gy	< 5 cc < 10 cc	27.2 Gy

***** Avoid circumferential radiation

Critical structures with <u>relative</u> volume and <u>absolute</u> point dose limits: The volume dose limits are suggested limits for these structures. Exceeding these limits is not a protocol violation. The recommended maximum point dose limits are also suggested limits that may not

be met. However, exceeding any of the required maximum point dose limits constitutes a major violation. Critical structure maximum doses may exceed the prescription dose as described below only when the PTV abuts or overlaps the structure.

Critical structure	Volume dose limits (4 fractions)		Maximum point dose limit (<0.035 mL)	
	Dose	Volume	Recommended	Required
Esophagus*	18.8 Gy	< 5 mL	30 Gy	105% of PTV prescription dose
Heart/pericardium	28 Gy	< 15 mL	30 Gy	105% of PTV prescription dose
Great vessels*	43 Gy	< 10 mL	49 Gy	105% of PTV prescription dose
Trachea and ipsilateral bronchus*	15.6 Gy	< 4 mL	34.8 Gy	105% of PTV prescription dose
Chest wall#	33.6 Gy	< 10cc (< 30cc required)	NA	105% of PTV prescription dose
Liver	19.2 Gy	< 700 mL	NA	105% of PTV prescription dose

* Avoid circumferential radiation

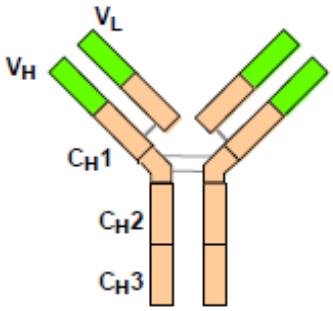
Chest wall limits (including "required" maximum point dose limit) may be exceeded for an otherwise excellent plan. This will not be considered a violation.

5. INVESTIGATIONAL AGENT INFORMATION: Fresolimumab

5.1 Description/Mechanism of Action

Fresolimumab is an engineered human IgG4 kappa monoclonal antibody capable of neutralizing all mammalian isoforms of TGFβ (ie, TGFβ1; TGFβ2; and TGFβ3). Fresolimumab is a high-affinity antibody.

The structural formula for fresolimumab is depicted below:



5.2 Pharmacokinetics

The pharmacokinetics of fresolimumab have been characterized in patients with advanced malignant melanoma and RCC, IPF, and FSGS in Phase 1 trials following single and multiple IV doses ranging from 0.1 mg/kg to 15 mg/kg. Toxicology studies at doses of 0.1 to 50 mg/kg have been conducted in non-human primates and generally have had exposures 10-fold lower than the exposure levels seen with the corresponding dose in humans.

Dose-normalized values of Cmax were approximately similar among dose groups, regardless of patient disease. Fresolimumab clearance showed no obvious dose-dependent trend, suggesting that the target antigen was not saturated in the studied dose range. The overall terminal elimination half-life is approximately 2 to 3 weeks.

Serum concentrations of fresolimumab from the phase 1 studies were pooled and analyzed using a non-linear mixed-effects modeling procedure. The PK of fresolimumab was best described using a 2-compartment open model with first-order elimination from the central compartment. The evaluation of covariate effects showed an effect of weight as the most important covariate using a full allometric model. Over the range of body weights of 50 to 100 kg, the typical value of clearance changed by no more than 30%. There was no difference in the PK behavior of fresolimumab based on patient disease. No other covariates were identified as being predictive of PK variability.

5.3 How Supplied/Storage

Fresolimumab is supplied as a sterile lyophilized powder intended to be reconstituted with 5.1 mL of sterile Water for Injection (sWFI). The composition of the lyophilized powder is listed below:

Component	Amount (mg) per 50 mg Vial	Function
Fresolimumab	53	Active Ingredient
Mannitol, USP/EP	159	Stabilizer
Sucrose, NF	53	Stabilizer
Polysorbate 80, NF	0.53	Stabilizer
Sodium phosphate, dibasic heptahydrate, USP	46.6	Buffer
Sodium phosphate, monobasic monohydrate, USP	12.7	Buffer
Sodium chloride, USP	7.7	Buffer
Nitrogen, NF		Inert Gas
Approximate weight of lyophilized cake	**334 mg**	

USP: United States Pharmacopeia; EP: European Pharmacopeia; NF: National Formulary

Prior to administration, lyophilized fresolimumab will be reconstituted with 5.1 mL (50 mg vial) of sWFI to result in a protein concentration of approximately 10 mg/mL in a 50 mM sodium phosphate buffer at pH 7.1, containing 25 mM sodium chloride, 3% mannitol, 1% sucrose, and 0.01% polysorbate 80. Filter needles must not be used to remove reconstituted drug product from the vial. However, due to the nature of proteins and their ability to precipitate, the use of a 0.22 µm low protein binding inline filter is required when administering this product (diluted as a solution for infusion). The composition of reconstituted fresolimumab is listed below:

Component	Concentration (mg/mL)
Fresolimumab	10
Mannitol	30
Sucrose	10
Polysorbate 80	0.1
Sodium phosphate, dibasic heptahydrate	8.8
Sodium phosphate, monobasic monohydrate	2.3
Sodium chloride	1.5

The lyophilized product is stored in clear glass vials of 5 mL capacity (nominal), which meet the USP standard for Type I glass, closed by a siliconized butyl rubber stopper.

Fresolimumab vials must be stored at 2 to 8°C or 35.6 to 46.4°F until preparation for infusion. Reconstituted fresolimumab is stable for up to 24 hours after reconstitution with sWFI at either room temperature or under refrigeration (between 2 to 8°C or 35.6 to 46.4°F). Although stable for up to 24 hours under these conditions, fresolimumab in sWFI should be used immediately. Reconstituted fresolimumab in sWFI that is further diluted in dextrose 5% in water at a concentration of 0.3 mg/mL to 7 mg/mL is stable for up to 24 hours at room temperature.

Infusion bag should be administered over 30 mins using an intravenous infusion pump (through inline 0.22 micron low protein binding filter). Fresolimumab should not be infused in the same intravenous line with other products.

5.4 Manufacture

To produce the antibody in sufficient quantities for clinical use, a mammalian cell line (derived from a murine myeloma) was constructed using the human deoxyribonucleic acid sequences for the anti-TGFβ antibody, selected by phage display technology, and the human IgG4 constant domains. This cell line enables manufacture of the human protein in large-scale fermenters. The protein is purified, filled into glass vials, and lyophilized.

All reasonable care is taken during production to maintain product quality and integrity. The purification process (including 3 chromatography columns with different mechanisms for removal of contaminants, a low pH virus inactivation step and a virus retentive nano-filtration step) provides for the clearance of process-derived impurities and potential microbiological contaminants resulting in low impurity levels. Virus clearance studies have shown that the process is capable of clearing enveloped and nonenveloped viruses (murine leukemia virus and minute virus of mice). Purified drug substance, formulated bulk drug, and finished drug product fresolimumab are tested for identity, purity, potency, and stability against a set of release specifications that ensure that the product is suitable for parenteral use in the clinic.

5.5 Adverse Reactions

Clinical experience with fresolimumab is limited. Experience in the Phase 1 single-dose IPF study, the Phase 1 single-dose FSGS study, and the Phase 1 multiple-dose oncology study have demonstrated that fresolimumab is well tolerated at single doses up to 8 mg/kg in patients with IPF, at single doses up to 4 mg/kg in patients with FSGS, and at multiple doses up to 15

mg/kg in patients with advanced melanoma or renal cell carcinoma (RCC). No dose limiting toxicities or acute infusion-associated events suggestive of cytokine release or hypersensitivity have been reported, although infusion reaction could still occur.

5.6 Contraindication

There are no established contraindications to fresolimumab.

6. DOSE MODIFICATIONS

There will be no adjustments in radiation dose. In the event a patient develops DLT prior to completion of SABR, efforts will be made to finish the remaining dose of radiation once the patient recovers adequately.

Regarding fresolimumab, dose will be either administered on a given day or withheld. If a patient develops dose limiting toxicity that has not resolved by Day 15 and/or 36, fresolimumab dose will be skipped for that dose number.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

7.1.1. Radiation

The most common adverse events associated with SABR treatment are esophagitis, pneumonitis, and pulmonary fibrosis. The complete list of known adverse events associated with SABR treatment is as follows:

- Cardiac Disorders
  - Pericardial effusion
  - Pericarditis
  - Restrictive cardiomyopathy
- Gastrointestinal Disorders
  - Dysphagia
  - Esophagitis
  - Esophageal fistula
  - Esophageal obstruction
  - Esophageal perforation
  - Esophageal stenosis
  - Esophageal ulcer
  - Esophageal hemorrhage
- Injury, Poisoning, and Procedural Complications
  - Fracture (to be limited to rib fractures only)
- Nervous System Disorders
  - Brachial plexopathy
  - Recurrent laryngeal nerve palsy
  - Myelitis
- Respiratory, Thoracic, and Mediastinal Disorders
  - Atelectasis
  - Bronchopulmonary hemorrhage
  - Mediastinal hemorrhage
  - Pleural hemorrhage
  - Tracheal hemorrhage
  - Bronchial fistula
  - Pulmonary fistula
  - Bronchopleural fistula
  - Tracheal fistula

- Hypoxia
- Bronchial obstruction
- Tracheal obstruction
- Pleural effusion
- Pneumonitis
- Pulmonary fibrosis

• Skin and Subcutaneous Disorders
- Skin ulceration (thorax only)

7.1.2 Fresolimumab

Clinical experience with fresolimumab is limited. Most common adverse reactions reported from previous studies include fatigue, peripheral edema, nasopharyngitis, pustular rash, headache, bronchitis, diarrhea, and dyspnea.

7.1.2.1 Skin

Based on the clinical experience to date, the main epithelial adverse reaction to fresolimumab appears to be adverse events involving the skin, most notably keratoacanthoma and squamous cell carcinoma. The development of these lesions appears to be related to both dose and duration of exposure. Because of this potential risk, skin exams, evaluating for treatment emergent lesions such as KA and drug reactions should be performed in all patients receiving fresolimumab. Patients who develop concerning treatment-emergent skin lesions should be referred to a dermatologic oncologist or dermatologist for evaluation within 2 weeks of reported symptoms.

7.1.2.2 Acceleration of Neoplasia

Available literature suggests neutralization of TGFβ does not cause de novo malignancies. In advanced cancers, TGFβ neutralization may ameliorate cancer progression; however, in certain settings such as in the presence of premalignant lesions, it is possible that neutralization of TGFβ may contribute to premalignant/malignant transformation. Long-term studies to investigate any carcinogenic or mutagenic effects of fresolimumab have not been conducted. Patients receiving fresolimumab should be carefully monitored for the development of malignancies.

7.1.2.3 Bleeding and Anemia

Across the clinical studies, the majority of bleeding adverse events reported have been mild, self-limited events of gum bleeding without associated gingival lesions and nose bleeding without discrete nasal lesions. Anemia in the absence of bleeding was seen in some patients in all of the phase 1 studies, but in the majority of cases was considered unrelated to study drug and could be explained by underlying diseases.

Patients should be carefully monitored for the development of anemia and bleeding while receiving fresolimumab.

7.1.2.4 Mouth Sores

A small number of patients treated with fresolimumab have experienced mouth or gum sores. Most of the sores were mild in nature. Patients should be examined for mouth sores while taking fresolimumab.

7.1.2.5 Immune Modulation

No evidence of significant immune dysregulation has been seen in clinical studies to date. Herpes Zoster, transient vitiligo, and hypopigmentation of the skin and/or hair have been reported before.

7.1.2.6 Reproductive Function

The effects of fresolimumab on male and female reproductive function and/or fetal growth and development have not been investigated in formal toxicity studies. Fresolimumab is an antibody and is expected to be able to cross the placenta and enter the fetal circulation during pregnancy. The effects of fresolimumab in this situation are unknown. Pregnant or lactating women are excluded from clinical studies of fresolimumab. Women who become pregnant or start lactating during the study will be discontinued from study treatment. Sexually-active men or sexually active women of childbearing potential (last menstrual period within the previous 12 months and not surgically sterile) must use contraception or abstinence when being treated with fresolimumab.

7.1.2.7 Overdose

Animal studies have not clearly identified any acute dose related toxic effects. In the event of fresolimumab overdose, the administration should be immediately discontinued and appropriate precautions should be taken.

7.2 Definition of an Adverse Event

In the event of an adverse event the first concern will be for the safety of the subject.

An adverse event is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

If disease progression is noted during a protocol-specified reevaluation of the status of a patient's cancer, and the progression is manifested solely by results of tumor markers and/or radiologic imaging, that occurrence of progressive disease will NOT be recorded as an adverse experience. Progression of disease is not considered an adverse experience unless it results in hospitalization or death.

7.3 Reporting Adverse Events

Adverse events will be graded according to CTCAE v4. 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 AEs will be collected from signing of informed consent through 30 days after last study treatment. Prior to Day 1, only Serious Adverse Events (SAEs, see below) deemed related to study procedures need to be collected. All SAEs will be tracked until resolution, or until 30 after the last dose of the study treatment.

Each occurrence of a given adverse event will be recorded. Use of steroid as treatment for adverse event will be recorded. Only the most severe grade over the course of a given episode will be recorded.

Laboratory events defined as worsening of the laboratory value by one CTCAE v4 (Common Terminology Criteria for Adverse Events, version 4) grade or more from baseline value that meet the regulatory criteria for a serious adverse event (SAE) will be reported.

Note: All deaths due to any cause must be reported immediately (within 24 hours) to Sanofi Genzyme.

7.4 Definition of a Serious Adverse Event

A serious adverse experience is any event which is fatal, life threatening, disabling, or incapacitating or results in hospitalization, prolongs a hospital stay or is associated with congenital abnormality. In addition, any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious adverse event. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

***Life threatening definition*:**

An adverse event is life threatening if the patient was at immediate risk of death from the event as it occurred (ie, it does not include a reaction that if it had occurred in a more serious form might have caused death). For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis could be fatal.

Disability/incapacitating definition:

An adverse experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

Hospitalization definition:

An adverse event that results in emergency department admission greater than 24 hours or requires general in-patient hospitalization. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

7.5 Immediate Reporting of Serious Adverse Events

Attribution of Adverse Events:

Code	Attribution	Definition
1	Unrelated	The Adverse Event is clearly not related to the investigational agent(s)
2	Unlikely	The Adverse Event is doubtfully related to the investigational agent(s)
3	Possible	The Adverse Event may be related to the investigational agent(s)
4	Probable	The Adverse Event is likely related to the investigational agent(s)
5	Definite	The Adverse Event is clearly related to the investigational agent(s)

All subjects/patients with serious adverse experiences must be followed up for outcome.

All adverse events are serious and unexpected suspected adverse reactions, ie, serious and unexpected adverse events that are possibly, probably, or definitely related to the study drug fresolimumab, will be reported to the FDA via IND Safety Report [21CFR§312.32] within 14 calendar days, or within 7 calendar days if the event is an unexpected fatal or life-threatening suspected adverse reaction.

Any serious adverse experience, including death due to any cause, pregnancy, which occurs to any subject/patient treated on study or within 30 days following cessation of treatment, whether or not related to the investigational product, must be reported to Sanofi Genzyme and the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) within 2 working days.

Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is

brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately.

In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

The above should be reported to Stanford DSMC using the study specific case report form (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.

Attribution of SAE to study drug should follow the standard attribution and grading system as specified by CTEP (http://ctep.cancer.gov/reporting/adeers.html, see table below).

7.6 Special Considerations

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse or transmission of an infectious agent via a medicinal product.

Serious adverse events occurring after a patient is discontinued from the study will NOT be reported unless the investigator feels that the event may have been caused by the study drug or a protocol procedure. Study-specific clinical outcomes of death because of disease progression are exempt from serious adverse event reporting, unless the investigator deems them related to use of the study drug. Hospitalization for study drug administration is not a serious adverse event.

In general, serious adverse events assessed as clearly being due to disease progression and not due to study drug(s) should be excluded from adverse event reporting. However, in cases where the specificity or severity of an event is not consistent with the risk information, the event should be reported.

7.7 Definition of Reportable Information

In addition to the above events, the following information should be reported to Sanofi Genzyme and the Stanford DSMC:

1. New information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency.
2. Complaints that are unresolved by the research team, or that indicate increased or unexpected risks.
3. Unanticipated adverse device effect. New information about the effect on health or safety.

7.8 Definition of an Unanticipated Problem

Unanticipated problems involving risks to participants or others (UPs) are events (including internal or external events, death, life-threatening experiences, injuries, breaches of confidentiality, or other problems) that occur any time during or after the research study, which in the opinion of the PD are:

1. Unexpected - not in the consent form, protocol, package insert, or label; or unexpected in its frequency, severity, or specificity, AND

2. Related to the research procedures – caused by, or probably caused by research activity, or, if a device is involved, probably caused by, or associated with the device, AND
3. Harmful – caused harm to participants or others, or placed them at increased risk of harm (including physical, psychological, economic, or social harm).

7.9 Reporting of Pregnancy

If a patient or their partner inadvertently becomes pregnant while on treatment with fresolimumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Sanofi Genzyme without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study, the pregnancy must be reported to Sanofi Genzyme. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Sanofi Genzyme.

7.10 Definition of an Overdose for This Protocol

Overdose is defined as any dose more than 25% above the prescribed dose described in the study protocol.

7.11 Reporting of Overdose to Sanofi Genzyme

If an adverse experience(s) is associated with ("results from") the overdose of test drug, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 24 hours to Sanofi Genzyme.

7.12 Stopping Rules

Crude rates of grade 3 or higher radiation pneumonitis or bronchopulmonary hemorrhage will be evaluated after 25 patients have finished treatment and completed 6 months of follow up. If a crude rate of >20% is observed, the study will be suspended to evaluate the likelihood of these toxicities being caused by the combination treatment and to decide whether to allow accrual of another test cohort. If a crude rate of ≤ 20% is observed, the study will proceed to primary completion.

All outcome data (toxicity and efficacy) will be reviewed every 6 months by the Principal Investigators and key Co-Investigators. This study will be monitored by the Stanford DSMC. All potential adverse events will be reported to the thoracic disease management group and the DSMC. The study will terminate when the target accrual is met and all data are analyzed.

Comprehensive Safety Review

The rate of NSCLC recurrence will be continuously evaluated for the 1st 10 subjects through 6 months follow-up. In the event that there are ≥ 3 NSCLC recurrences in the first 10 subjects, enrollment will be paused, and a comprehensive safety review will be conducted, which will include the Stanford Cancer Institute Data Safety Monitoring Committee (DSMC). If,

after review, the DSMC recommends proceeding with the study, the report of the safety review will be submitted to the IND, and FDA's concurrence will be sought before proceeding with enrollment.

Similarly, development of new malignancies will be monitored for the first 10 patients through the 6 month follow-up time point [except keratoacanthomas / squamous cell carcinomas (SCC) of the skin]. Keratoacanthomas and SCC are not included because these are known events that regress after discontinuation of fresolimumab therapy, per the Investigator's Brochure. These lesions will be referred to a dermatologic oncologist or dermatologist for evaluation, treatment, and monitoring, but will not be tabulated towards the criteria for enrollment pause. New malignancies are expected to be rare, and if more than 2 subjects develop new malignancies, enrollment would be similarly paused for a comprehensive safety review as above.

7.13 Confidentiality

Study data will be maintained in protected patient binders. Only research personnel listed on this protocol will have access to this information. Only the patients unique IDN will be used. Specimens will be stored under the patient's IDN.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetic Analyses

Serum samples will be collected before and within 4 hours post each dose of fresolimumab for PK studies. Instructions for collection are as follows:

Group Name(s)	Container(s)	Collection Instructions
SM/ GC1008 Pre-infusion PK	1- 5mL gold top serum separation tube 1- 7mL clear cryovial	One 5mL gold top serum separation tube. Collect 5mL blood into the Serum Separator tube. Fill tube completely**. It is important to thoroughly mix the blood with the clotting activation agent by inverting the tube not less than five times**. Allow blood to clot for 30 minutes (tube standing upright). Use pipette provided to transfer all of the serum into the appropriately labeled tubes. Freeze immediately at -70ºC until shipment. **Keep all samples frozen until ready to ship**. Ship frozen to Covance CLS Day of Collection
SM/ GC1008 Post-infusion PK	1- 5mL gold top serum separation tube per timepoint 1- 7mL clear cryovial per timepoint	One 5mL gold top serum separation tube. Collect 5mL blood into the Serum Separator tube. Fill tube completely**. It is important to thoroughly mix the blood with the clotting activation agent by inverting the tube not less than five times**. Allow blood to clot for 30 minutes (tube standing upright). Use pipette provided to transfer all of the serum into the appropriately labeled tube. Freeze immediately at -70ºC until shipment. **Keep all samples frozen until ready to ship**. Ship frozen to Covance CLS Day of Collection

8.2 Coding of specimens for privacy protection

At the time of enrollment 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

Parameters	Pre-Entry[6]	Day 1	Day 8-12[4]	Day 15[7]	Day 36 [8]	3 month [9,10]	6 month[10]	9 month[10]	12 month [10]
History & Physical Exam	X	X		X	X	X	X	X	X
Complete skin exam [1]	X					X			
ECOG PS	X	X		X	X	X	X	X	X
Labs [2]	X	X		X	X	X	X	X	X
CT Thorax (Chest)	X[11]					X	X	X	X
PET/CT	X[11]						X		
Toxicity evaluation		X		X	X	X	X	X	X
PFT [3]	X						X		X
SABR [4]			X						
Fresolimumab [5]		X		X	X				

1 To be performed by the investigators. Suspect lesions will be referred for further evaluation to a dermatologic oncologist or dermatologist as appropriate

2 Includes CBC with differential and complete metabolic panel. Also urine or serum pregnancy test required for women of childbearing potential at pre-entry only

3 Including DLCO, FEV1, and FVC

4 12.5 Gy/fraction in 4 fractions between Days 8 to 12. Minus 1 to + up to 5 days to allow for weekends and holidays and unforeseen circumstances.

5 3 mg/kg IV (or other determined dose from Phase 1) given on days 1, 15, and 36

6 All pre-entry assessment should be obtained within 4 weeks of enrollment

7 3 days after completion of SABR, + up to 6 more days to allow for weekends and holidays and unforeseen circumstances

8 Target 21 days after dose 2 of fresolimumab. +/- 6 days to allow for weekends and holidays and unforeseen circumstances

9 Needs to be at least 90 days after completion of SABR for safety analysis

10 +/- 2 weeks to allow for weekends and holidays and unforeseen circumstances. Date counted from completion of SABR.

11 Acceptable to use non-diagnostic simulation planning scans for baseline imaging

10. MEASUREMENT OF ENDPOINT

10.1 Scoring of post-SABR radiologic changes

The extent of SABR-induced radiologic changes will be scored at each follow-up scan. Scoring of radiologic changes will be performed by at least two radiologists or radiation oncologists dedicated to the study, who will be blinded to the treatments the patients receive. Scores will be assigned by consensus.

Assessment of fibrosis will be performed based on three previously-published scales by Dahele, *et al*. [15] In the phase 2 component of the study, the severity score of fibrosis in study subjects will be compared to historical controls. Historical controls will consist of patients previously-treated with the same dose of SABR (50 Gy in four fractions) at Stanford in the absence of fresolimumab.

Late Radiation Fibrosis Score (Pattern):

Late CT changes will be defined as occurring at 12 months after enrollment and will consist of:

1) "Modified conventional pattern" of fibrosis characterized by consolidation, volume loss, and bronchiectasis with or without GGO,
2) Mass-like fibrosis characterized by a well-circumscribed focal consolidation limited to the tumor region but which is larger than the original tumor,
3) "Scar-like fibrosis" consisting of a linear opacity in the tumor region with associated volume loss, or
4) "No evidence of increasing density" including stable or regressing mass at the location of the treated tumor with no or minimal GGO or only normal appearing lung tissue.

Acute Radiation Fibrosis Score (Pattern):

The categories of acute findings (occurring in the first 6 months after enrollment) will be:

1) Diffuse consolidation,
2) Patchy consolidation,
3) Diffuse ground-glass opacities (GGOs),
4) Patchy GGO, or
5) No evidence of increasing density. The term "diffuse" will apply to abnormalities that are at least 5 cm in maximum diameter and which contain more than 50% abnormal lung. Abnormalities not meeting these criteria will be termed "patchy".

Severity Score:

We will assign an overall severity score of radiographic fibrosis at 6 and 12 months after enrollment using the categories:

1) "Severe" (much more extensive than usually seen after SABR),
2) "Moderate" (changes that are commonly seen after SABR),
3) "Mild"/"minor" (unusually slight changes compared to what is normally observed after SABR), or
4) "None."

"Presence of moderate-to-severe fibrosis" at 12 months will be defined as severity fibrosis scores 1 or 2 (ie, "Severe" or "Moderate") . This will serve as the primary endpoint for Phase 2.

Pattern and severity of fibrosis at 6 months and pattern of fibrosis at 12 months will be evaluated as secondary endpoints for both Phase 1 and 2 of the study.

Patients who are lost to follow-up and who do not have a scan within +/-6 months of the 12-month time point will be excluded from analysis. Patients who develop inflammatory lung conditions unrelated to radiotherapy (i.e. pneumonia, ARDS, drug-induced pneumonitis, etc.)

will be excluded from the final endpoint analysis if the area of unrelated inflammation impedes scoring of fibrosis severity of the irradiated lesion.

Quantitative image analyses:
Finally, we will explore quantitative image analysis metrics for evaluating radiation fibrosis. This will include analyses such as contouring the region of fibrosis and quantifying its volume relative to the total lung volume and/or the original dose distribution. Similarly, FDG-uptake metrics will be examined on the follow-up PET/CT.

10.2 Additional Secondary Endpoints

Patients will be evaluated for anti-tumor effect by follow-up imaging (lung protocol CT and/or PET-CT imaging) as outlined above. Lung protocol CT scans (biphasic imaging, 1.25 mm cuts) and/or FDG PET-CT scans will be obtained at all follow-up intervals as described in the treatment calendar. All subsequent scans (post-treatment) will be compared to the same pretreatment CT or PET/CT that was used in conjunction with radiation treatment planning.

Patients will be evaluated for objective response at the follow-up intervals specified above.

Response to SBRT will be assessed and reported according to RECIST Version 1.1 criteria.
Evaluation of Target Lesions (Primary Tumor)

> **Complete Response (CR)**: Disappearance of target lesion.
> **Partial Response (PR)** : t least a 30% decrease in the diameter of target lesion, taking as reference the baseline diameter.
> **Progressive Disease (PD)** : At least a 20% increase in the diameter of the target lesion, taking as reference the smallest diameter on study (this includes the baseline diameter if that is the smallest on study). In addition to the relative increase of 20%, the diameter must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
> **Stable Disease (SD)** : Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest diameter while on study.

Failure will be documented by biopsy when possible and otherwise will be defined as radiologic progression on CT and/or PET/CT that leads to a change in management, including institution of systemic or local anti-cancer therapy. Failures will be categorized as follows:

Type of Recurrence	Description (after SABR treatment effects have subsided)
Local Failure	
Primary tumor failure (PTF)	Appearance of residual tumor located within the extent of the primary targeted tumor.
Marginal failure (MF)	Appearance of tumor ≤ 2 cm in any direction of the primary tumor or structures immediately adjacent to the primary tumor (lung/chest wall, mediastinum/diaphragm/spine).
Involved lobe failure (ILF)	Appearance of tumor > 2 cm in any direction of the primary tumor.
Regional Failure	
Non-primary lobe failure (NLF)	Appearance of tumor within another ipsilateral (non-primary) lobe.

Type of Recurrence	Description (after SABR treatment effects have subsided)
Hilar node failure (HNF)	Appearance of tumor in ipsilateral hilar lymph nodes.
Ipsilateral mediastinal nodal failure (MNF)	Appearance of tumor in ipsilateral mediastinal and/or subcarinal lymph nodes.
Distant Failure	
Distant nodal failure (DNF)	Appearance of tumor in ipsilateral supraclavicular or contralateral lymph nodes.
Distant metastatic failure (DMF)	Appearance of tumor deposits characteristic of NSCLC metastasis (chest wall other than incision sites or immediately adjacent to primary, mediastinal structures/diaphragm, malignant pleural effusion/pericardial effusion), contralateral lung and/or other distant sites.

Potential adverse events will be monitored by treating physicians at each follow-up visit, and scored using CTCAE v4 with type and grade.

Post-treatment changes in pulmonary function will be evaluated by changes in pulmonary function test at enrollment, 6-month, and 12-month follow-up.

Recurrence rate is determined by time from study enrollment to first documented date of recurrence.

Progression-free survival (PFS) is time from time from study enrollment until the first documented date of disease progression.

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 (eg, 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.

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. CRFs will be kept in a locked cabinet, only accessible to the research team.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

Rie von Eyben (Biostatistician at Stanford University) is the statistician for this study.

12.1.1 Randomization

This is a non-randomized study.

12.2 Interim analyses

A review of the safety data will be completed every 6 months at the weekly Thoracic Radiation Oncology Team Meetings.

12.3 Descriptive Statistics and Exploratory Data Analysis

See section 12.4.2.

12.4 Primary and Secondary Endpoints

Phase 1:

Primary Endpoint

- Dose limiting toxicities (DLTs) of fresolimumab when combined with SABR

Secondary Endpoint

- Score the pattern of late radiation induced fibrosis at 12 months after SABR with and without fresolimumab
- Evaluate severity and pattern of acute radiation-induced fibrosis in the first 6 months after SABR
- Score potential adverse events (AEs) of fresolimumab combined with SABR using CTCAE v4
- Measure post-treatment changes in pulmonary function using pulmonary function test parameters at enrollment, 6-month, and 12-month follow-up
- Evaluate recurrence and progression-free survival at 12 months
- Measure blood pharmacokinetics (PK) of fresolimumab in combination with SABR (optional for patient)

Exploratory Endpoint:

- Assess extent of radiation-induced lung toxicity by quantitative imaging analysis of CT volumes and FDG uptake parameters

Phase 2

Primary Endpoint

Evaluate the presence of late moderate-to-severe radiation-induced fibrosis up to 12 months after SABR with fresolimumab

Secondary Endpoint

- Score the pattern of late radiation induced fibrosis at 12 months after SABR with and without fresolimumab
- Evaluate severity and pattern of acute radiation-induced fibrosis in the first 6 months after SABR
- Score potential adverse events (AEs) of fresolimumab combined with SABR using CTCAE v4
- Measure post-treatment changes in pulmonary function using pulmonary function test parameters at enrollment, 6-month, and 12-month follow-up
- Evaluate recurrence and progression-free survival at 12 months

Exploratory Endpoint:

- Assess extent of radiation-induced lung toxicity by quantitative imaging analysis of CT volumes and FDG uptake parameters

12.4.1 Analysis Population

Analysis will be carried out in all patients who complete protocol procedures. Patients who are lost to follow-up and who do not have a scan within +/-6 months of the 12-month time point will be excluded from analysis. Patients who develop inflammatory lung conditions unrelated to radiotherapy (i.e. pneumonia, ARDS, drug-induced pneumonitis, etc.) will be excluded from the final endpoint analysis if the area of unrelated inflammation impedes scoring of fibrosis severity of the irradiated lesion.

12.4.2. Analysis Plan

Approximately 60% of SABR patients develop acute radiologic changes in the lung at 3 months [16]. Late radiologic changes, reflecting fibrosis, are more frequent in SABR patients at 1 year [15]. Our institutional experience revealed the presence of moderate-to-severe late radiation induced fibrosis in ~75% of patients treated with SABR (50 Gy in 4 fractions) via VMAT technique at 1 year.

Primary analysis: The outcome of moderate-to-severe radiologic fibrosis rate will be tested in evaluable patients in a one-sample one-sided test of proportion comparing the observed rate, which is expected to be at most 58%, to the historically observed rate of ~75%. The observed rate and the 95% confidence interval calculated using the exact method will be reported.

Secondary analysis: Local control at 12 months will be estimated along with a one-sided lower 95% confidence bound to allow an informal assessment of the null hypothesis that the proportion is larger than 80%. Patients with distant progression before local failure will be censored one day after the last imaging study; patients who die before local control will be censored at the time of death. These definitions are used for comparability. Cumulative incidence estimates for local failure and other failure type will also be presented.

Time to event data (local control, PFS, time to progression) will be evaluated using Kaplan-Meier estimates with 95% confidence intervals at multiples of 12 months based on Greenwood's formula with a log transform. Confidence intervals for median times to event, if relevant, will be constructed using the method of Brookmeyer and Crowley.

Proportions (eg, proportion of patients with grade 4 or higher toxicity) will be estimated along with 95% exact confidence intervals. Patient clinical and demographic characteristics will be reported with the appropriate summary statistic (mean, range, proportion, etc.) Adverse events will be tabulated by organ system and severity.

12.5 Sample Size

12.5.1 Accrual Estimates

Number of Patients: 55 to 60

In 2014, ~80 lung SABR procedures were performed at Stanford Hospital. It is estimated that 2 to 3 patients can reasonably be expected to accrue per month. Accrual will occur over 60 months.

12.5.2 Sample Size Justification

Phase 1:

Post-SABR pneumonitis grade 3 or greater is expected to occur in ≤ 10% of patients with stage I disease. Based on this percentage, we propose to start out with a cohort of 5 patients at the pre-selected dose of 3 mg/kg of fresolimumab. If one patient develops DLT, then 5 more patients will be enrolled at the same dose to make a total of 10 patients. If no more patients

experience DLT, then the total percentage of patients experiencing DLT is 10% and is considered acceptable for toxicity.

Phase 2:
A sample of size 50 was chosen in order to have 80% power to detect a decrease in the incidence of post-SABR moderate-to-severe fibrosis from 75% to 60% with a one-sided significance level of 10%.

13. INVESTIGATOR RESOURCES

13.1 Qualifications

The study staff will include, but is not limited to, the Principal Investigators, Co-Investigators, research coordinators, research nurses, and any residents or fellows working with the physicians. Also, laboratory personnel in the Principal Investigators' laboratory will be involved in analyzing the plasma and tumor specimens collected from patients.

All study staff have completed the required training specific for their responsibilities in this study. Furthermore, each member of the research team from each institution will be given a thorough explanation of the protocol and their responsibilities, including helping with scheduling, procedures, follow-up, data entry, or analysis. All research investigators will be required to complete proper training through their institutional review boards.

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APPENDIX A: **Participant Eligibility Checklist**

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

Protocol Title:	**Fresolimumab and Stereotactic Ablative Radiotherapy in Early Stage Non-Small Cell Lung Cancer**
Protocol Number:	**IRB-34863 / LUN0071**
Principal Investigator:	**Max Diehn, MD, PhD**

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**	**Supporting Documentation**
1. Newly diagnosed, histologically proven T1-T2bN0M0 (Stage IA-IIA) NSCLC, with maximum tumor diameter ≤ 5 cm under consideration for stereotactic ablative body radiotherapy (SABR) as definitive primary treatment.	☐	☐	
2. Patient judged to be inoperable or at high surgical risk by a board-qualified thoracic cancer surgeon who has evaluated the subject within the prior 12 weeks, or the patient's case has been discussed at a multidisciplinary tumor board with a thoracic cancer surgeon in attendance, or a patient who refuses surgery or declines to be evaluated for surgery	☐	☐	
3. ECOG PS 0-2	☐	☐	
4. Age greater than or equal to 18 years old and able to give informed consent.	☐	☐	
5. Men or women of child-bearing potential must agree to use an acceptable method of birth control (hormonal or barrier method of birth control; abstinence) to avoid pregnancy for at least 90 days after last study treatment (radiation or fresolimumab)	☐	☐	
Exclusion Criteria (From IRB-approved protocol)			
1. Significant anemia (hemoglobin below 9.0 g/dL) or neutropenia (ANC < 1000/mm^3)	☐	☐	
2. Prior history of multifocal adenocarcinoma in situ (ie, classic or pure bronchioloalveolar carcinoma)	☐	☐	
3. Prior history of keratoacanthoma (well-differentiated	☐	☐	

squamous cell skin cancer variant, often centrally ulcerated). History of basal cell cancer is allowed.			
4. Pre-malignant skin lesion(s) noted on prescreening skin exam, except for actinic (solar) keratosis	☐	☐	
5. Prior radiotherapy overlapping with high dose region of planned SABR course	☐	☐	
6. Prior history of head and neck; oral; or bladder cancer	☐	☐	
7. Prior receipt of systemic treatment (chemotherapy, targeted therapy, or immunotherapy) for the lesion under consideration of treatment	☐	☐	
8. Uncontrolled, inter-current or recent illness that in the investigator's opinion precludes participation in the study, including those undergoing therapy for a separate invasive malignancy	☐	☐	
9. Contraindication to receiving radiotherapy	☐	☐	
10. Known allergy to components of fresolimumab	☐	☐	
11. Pregnant or breastfeeding. All women of child-bearing potential (last menstrual period within the previous 12 months and not surgically sterile) will be tested for pregnancy at pre-entry.	☐	☐	

*****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.

IV. 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:	