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Pre-Operative Immuno-Modulatory SBRT (POIMS Trial): A Pilot Trial in Early Stage NSCLC

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THE UNIVERSITY OF KANSAS
CANCER CENTER

Investigator Initiated Trial

Pre-Operative Immuno-Modulatory SBRT (POIMS Trial): A pilot trial in early stage NSCLC

SPONSOR/INVESTIGATOR

Shalina Gupta-Burt, MD

Assistant Professor
Department of Radiation Oncology
University of Kansas School of Medicine
3901 Rainbow Blvd
Mail Station 4033
Kansas City KS 66160

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Agent: Stereotactic Body Radiation Therapy (SBRT)

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Funder: Varian

LIST OF COLLABORATORS

Co-Investigators:

Alykhan Nagji, MD, Assistant Professor, Cardiovascular & Thoracic Surgery, The University of Kansas Medical Center
Nirmal Veeramachaneni, MD, Assistant Professor, Cardiovascular & Thoracic Surgery, The University of Kansas Medical Center
Gregory Gan, MD, PhD, Assistant Professor, Radiation Oncology, The University of Kansas Medical Center
Shane Stecklein, MD,PhD, Assistant Professor, Radiation Oncology, The University of Kansas Medical Center
David Akhavan, MD, PhD, Assistant Professor, Radiation Oncology, The University of Kansas Medical Center

Rashna Madan MBBS, Professor, Department of Pathology and Laboratory Medicine, The University of Kansas Medical Center
Subhrajit Saha, PhD, Associate Professor, Radiation Oncology, The University of Kansas Medical Center
Habeeb Saleh, PhD, Chief, Medical Physics, Radiation Oncology, The University of Kansas Medical Center
Shahid Awan, PhD, Medical Physicist, Radiation Oncology, The University of Kansas Medical Center
Ying Cao, Statistician, Department of Radiation Oncology, The University of Kansas Medical Center

Steven Soper, PhD, Professor, Chemistry, Biomedical Engineering (Liquid Biopsy Core Facility) The University of Kansas
Malgorzata Witek, PhD, Associate Research Professor, Chemistry, Biomedical Engineering (Liquid Biopsy Core Facility) The University of Kansas
Andrew Godwin, PhD, Professor, Pathology & Laboratory Medicine, Director, Biospecimen Repository Core Facility [BRCF] and Director, Clinical Molecular Oncology Laboratory [CMOL]) The University of Kansas Medical Center
Amanda Schroder, Clinical Trials Coordinator, Radiation Oncology, The University of Kansas Medical Center
Michele Park, (Biospecimen Repository Core Facility [BRCF])
LaToya Berry, (Clinical Pharmacology Shared Resource [CPSR])

Participating Sites:

The University of Kansas Cancer Center

STATEMENT OF COMPLIANCE / PROTOCOL AGREEMENT

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Protocol Number	**IIT-2020-POIMS-Lung**
Protocol Title	**Pre-Operative Immuno-Modulatory SBRT (POIMS Trial): A pilot trial in early stage NSCLC**
Sponsor/Investigator	**Shalina Gupta-Burt, MD**

Signature of Principal Investigator Date

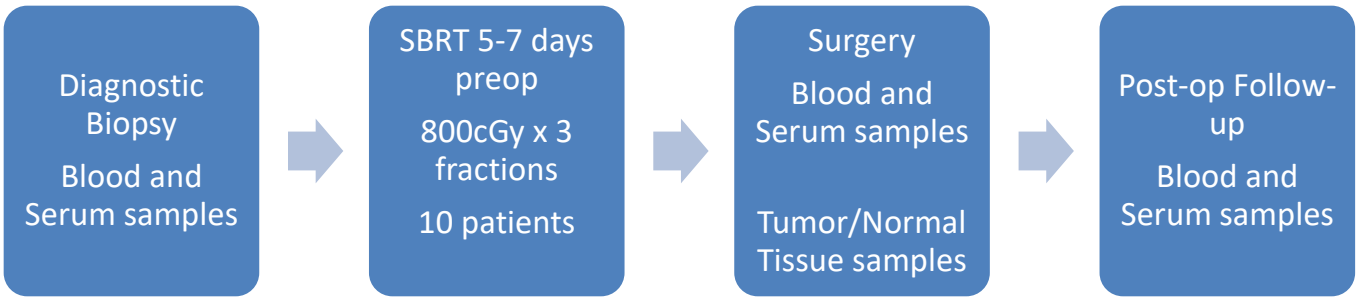
Printed Principal Investigator Name

Institution Name

TABLE OF CONTENTS

SCHEMATIC OF STUDY DESIGN

Pre-Operative Immuno-Modulatory SBRT (POIMS Trial) A pilot trial in early stage NSCLC



PROTOCOL SUMMARY

Title	Pre-Operative Immuno-Modulatory SBRT (POIMS Trial): A pilot trial in early stage NSCLC
Protocol Number	IIT-2020-POIMS-Lung
Phase	Pilot
Design	Single arm pilot trial
Study Duration	Approximately 5 years • Enrollment Period – approximately 18 months • Follow up period for adverse events to 36 months after surgery • Follow up period for post-operative surgical complication / wound healing events- 3-6 months after surgery • Follow-up period for disease outcome–36 months after surgery
Study Center	University of Kansas Cancer Center
Objectives	**Primary:** Assess the impact of non-ablative SBRT (800 cGy X 3 fractions) on immunomodulation in NSCLC tumor cells **Secondary:** Assess the impact of non-ablative SBRT (800 cGy X 3 fractions) prior to surgical resection on peri- and post-operative surgical complication rate, wound healing, and disease outcomes.
Number of Participants	10
Diagnosis and Main Inclusion Criteria	**Inclusion Criteria:** • Stage I-II NSCLC • Adequate diagnostic biopsy tissue to allow pre-SBRT tumor analysis • Candidate for oncologic surgery (lobectomy or sub lobar resection) for the lung cancer • Lesion located peripherally, ≥ 2 cm from bronchial margin, and 1 cm from visceral pleura, with location deemed acceptable by cardio-thoracic surgeon for resection. • Adequate pulmonary function test results **Exclusion Criteria:** • Prior history of lung/chest wall surgery • Prior chest radiation • Prior immunotherapy • History of autoimmune disease • Currently using immunosuppressive drugs
Study Product(s), Dose, Route, Regimen	SBRT 800 cGy x 3 fractions

Duration of Administration	Total: 4-5 days 1-2 days - consultation and simulation 3 treatment (study intervention) days Study intervention (SBRT) delivery will be scheduled for 3 consecutive days, but may be modified as needed by the treating radiation oncologist.
Interim Monitoring	The data safety monitoring committee (DSMC) of The University of Kansas Cancer Center is responsible for monitoring participant safety for this trial.
Statistical Methodology	We will summarize peri- and post- operative surgical complication rates as well as tumor control outcomes using descriptive statistics. Peri- and post- operative surgical complication rates will be quantified using the Clavien-Dindo classification of surgical complications [1,2.] Wound healing complication rates will be scaled as defined by the General Thoracic Surgery Database. [3]
Stopping Rules	If a participant experiences one or more of the following events, possibly related to study intervention, study will be suspended pending DSMC review to determine if study should continue. a. Wound healing delay beyond standard timeframe as deemed by study Cardio-Vascular (CV) surgeons b. Peri operative/post-operative surgical complications beyond acceptable institutional rates as determined by study CV surgeons c. Death from study intervention

1 INTRODUCTION

1.1 Background

Recent advances in immunotherapy has resulted in a new era for the treatment of NSCLC. Radiotherapy is commonly used in early stage, locally advanced and advanced stage of NSCLC treatment. More recently the utility of highly conformal, large fraction size radiation defined as SBRT has become standard of care for early stage and oligometastatic NSCLC. The interplay of XRT and immunotherapy, however, remains poorly defined in NSCLC.[4] The immunomodulatory potential of XRT has been long recognized but not yet well defined for clinical utility and integration into combined immunotherapy and XRT regimens. The phenotypic changes in tumor cell surface marker expression (e.g. PD-L1), tumor and surrounding normal tissue microenvironment, and serum/blood immune profile changes due to XRT have not been well elucidated in this patient population. This has been challenging in patients with NSCLC who receive radiation due the difficulty in obtaining post XRT tumor tissue.[5] Defining the independent effect of XRT, more specifically, SBRT on the immunoregulatory pathways is also complicated by the multitude of trials that combine various immunotherapy agents with XRT complicating the analysis. The impact of the immunomodulation by non-ablative lower dose SBRT prior to definitive surgery on immunoregulatory pathways needs to be defined.[6,7]

Cell culture and animal data have demonstrated that cytotoxic doses of XRT may not elicit a clinically meaningful alteration in the immune profile. In contrast, several cell culture and animal model studies have indicated that fractionated low dose XRT may provide a more immunomodulatory effect.[8,9,10] In addition, there is a lack of consensus regarding the superiority of single fraction versus multi-fraction SBRT yielding greater immunomodulation.[11,12] Studies using an animal model have concluded a fractionated regimen induces a greater abscopal effect than single dose radiation. Furthermore, they showed a regimen of 800 cGy X 3 fractions yielded the most significant changes in the immune profile compared to 2000 cGy X 1 or 600 cGy X 5.[13] Clinical trials combining radiation with a multitude of immunotherapeutic agents are difficult to interpret due to variations in the trial design, including the specification of the irradiated site, dose/fractionation regimens, scheduling and sequencing differences, selection of the immunotherapeutic agent, and vast disparity in patient/disease selection criteria. The in vivo phenotypic changes in tumor cell surface marker expression, tumor and normal tissue microenvironment and gene expression profiles, serum/blood immune profile changes, and circulating tumor cell immunophenotypic and gene expression alterations of non-ablative low dose radiation fractionated SBRT in patients with early stage NSCLC has not been elucidated. Based on published literature, we believe that this proposed trial, using non-ablative SBRT prior to surgery, will be safe. Recent work from the Netherlands reported the results of a systemic review of seven retrospective case series on salvage surgery after local recurrence in patients who had definitive treatment with SBRT. They noted acceptable morbidity and mortality in appropriately selected patients.[14] A recent prospective trial of ablative SBRT performed 10 weeks before surgery noted no perioperative mortality and reported Grade 3 or 4 toxicity in 7 of 40 patients.[15]

1.2 Rationale

The current proposal is structured as a pilot trial to evaluate the impact of non-ablative SBRT (800 cGy X 3 fractions) as an immunomodulatory mechanism in patients with early stage NSCLC who are surgical candidates. Tumor, normal tissue and blood specimens will be analyzed for immunomodulatory changes including phenotypic changes in tumor cell surface marker expression, tumor and normal tissue microenvironment and gene expression profiles, serum/blood immune profile changes, and circulating tumor cell immunophenotypic and gene expression alterations.

Published literature showed that cytotoxic doses of XRT may not elicit a clinically meaningful alteration in the immune profile. Further, studies using an animal model have concluded a fractionated regimen induces a greater abscopal effect than single dose radiation. Furthermore, they showed a regimen of 800 cGy X 3 fractions yielded the most significant changes in the immune profile compared to 2000 cGy X 1 or 600 cGy X 5.[16]

The immune response within the tumor milieu is a complex dynamic process with an interplay among lymphocyte subsets, antigen presenting cells/dendritic cells, macrophages, and tumor cells. The interactions between the various components is orchestrated by a variety of extracellular and intracellular signaling pathways involving ligand and cell surface expression, cytokine release, and activation or inhibition of a variety of T cell subsets. In order to comprehensively define the immunomodulatory effect of three fractions of 800 cGy on the primary tumor, we will analyze the following: tumor cell surface phenotype, tumor microenvironment immune profile and gene expression profile, T cell repertoire changes in tumor tissue and peripheral blood, and circulating tumor cell phenotype and gene expression profiles. Each of these components has been shown to be impacted by radiation in either a cell culture or animal model systems. By characterizing, quantitating and defining these changes related to three fractions of 800 cGy, it will directly provide important insights to inform rational uses of XRT and immunotherapy in the future.

1.3 Risk/Benefit Assessment

1.3.1 KNOWN POTENTIAL RISKS

Immediate Risks	Wound healing problems, increase in peri-operative bleeding, bronchopleural fistula, prolonged air leak, conversion to open procedure, and/or infection.
Other Risks	Inconvenience to participant due to additional study-related visits (in addition to standard of care visits): 1 screening/enrollment visit, 1 simulation visit and 3 SBRT treatments.

1.3.2 KNOWN POTENTIAL BENEFITS

Long-Range Potential Benefits	Improved disease free survival

1.3.3 Assessment of Potential Risks and Benefits

Rationale for necessity of exposing participants to risks	Potential for improved disease free survival Improve understanding of radiation-mediated immuno modulation of cancer cells in the tumor microenvironment
Justification why benefits outweigh risks	This study can lead to an improvement in cancer control and will improve our understanding of radiation-related cancer biology. The delivered radiation dose (800 x 3) is known to be safe and well-tolerated, and in fact is significantly below the most common SBRT dose regimen used for NSCLC (1800-2000 x 3). Therefore, the investigators believe the risks to the patients are minimized.

Therefore, the potential benefit of this study is judged to outweigh risk and the risk/benefit ratio is in favor of benefit.

1.4 Measures to Minimize Bias: Randomization and Blinding

This study is not randomized or blinded. Consecutive participants will be enrolled to avoid bias.

2 HYPOTHESIS

Primary: Non-ablative SBRT (800 cGy X 3 fractions) given 5-7 days preoperatively in selected patients with stage I-II NSCLC will result in alterations in the tumor immunoprofile, tumor microenvironment, gene expression profiles and peripheral blood immune repertoire.

Secondary: This regimen will be well tolerated, associated with minimal toxicity, and will not impact on wound healing.

It should be noted that this is designed as a pilot trial, so statistical analysis will be descriptive and formal hypothesis-testing will not be performed

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

Assess the impact of non-ablative SBRT (800 cGy X 3 fractions) on immunomodulation in NSCLC tumor cells through analysis of targeted cell surface, tumor immune microenvironment, gene expression profile, radiation mediated changes in T-cell repertoire in tumor issue and peripheral blood and circulating tumor cell surface expression.

3.2 Secondary Objectives

- Assess the impact of non-ablative SBRT (800 cGy X 3 fractions) prior to surgical resection on peri- and post-operative complication rate, and wound healing.
    - Surgical complications wil be assessed using the Clavien-Dindo Classification system. The Clavien-Dindo classification system has been validated and established as an "objective, reproducible" grading classification.[17]
    - This classification system uses a grading based on the extent of intervention needed to manage a specific complication. See appendices C and D for examples.
    - Wound healing will be assessed and charted by the study cardio-vascular (CV) surgeons using the General Thoracic Surgery Database with particular references to pages 246-248. See Appendix E.
- Describe loco-regional control, metastasis-free survival, disease-free and overall survival in patients treated on this trial with pre-operative SBRT followed by surgery

3.3 Primary Endpoints

What is being measured	Measurement time frame	Measurement Tool
The impact of non-ablative SBRT on Immunomodulation in tumor cells Pre and post study intervention biopsy tissue comparison of immunomodulatory parameters including but not limited to PDL1, PDL2, HCA2, IDO, HC10, B2m, Calreticulin, MHC-1, Fas, ICAM	From time of consent and collection of archival tumor tissue to time of surgery with collection of post-study intervention tumor tissue.	Techniques anticipated include but are not limited to: Immunohistochemistry, Targeted Nanostring (PanCancer ImmunoOncology 360; PanCancer Progression Panel), CTC Isolation, Tumor tissue and peripheral blood T-cell repertoire

3.4 Secondary Endpoints

What is being measured	Measurement time frame	Measurement Tool
The impact of pre-surgical non-ablative SBRT on peri- and post-operative surgical complication rate	From Day of post-SBRT surgery through 6 month **(± 2 months)** post-operative follow up visit	Medical Record Review Clavien-Dindo Classification system
The impact of pre-surgical non-ablative SBRT on wound healing	From Day of post-SBRT surgery through 6 month **(± 2 months)** post-operative follow up visit	Medical record review General Thoracic Surgery Database.
Loco-regional control, metastasis-free survival, disease free and overall survival	From Day of enrollment through 36 month follow up visit	Medical record review

4 STUDY DESIGN

4.1 Overall Design

This is a single arm pilot study. Participants with medically operable NSCLC will receive SBRT 800 cGy X 3 fractions delivered 5-7 days prior to planned surgery.

4.2 Justification for Dose

Published literature shows that cytotoxic doses of XRT (e.g. 1800-2000 cGy x3) may not elicit a clinically meaningful alteration in the immune profile. In addition, studies using an animal model have concluded a fractionated regimen induces a greater abscopal effect than single dose radiation. Furthermore, these studies showed a regimen of 800 cGy X 3 fractions yielded the most significant changes in the immune profile compared to 2000 cGy X 1 or 600 cGy X 5.[18]

Based on these prior data, we chose 800 cGy x 3 for this trial.

4.3 End of Study Definition

End of study is defined as the time of completion of 36 month follow-up after enrollment of all patients still eligible for follow-up (excluding death and drop-out prior to 36 months).

5 PARTICIPANT SELECTION

Patients with Stage 1-2 Non-Small Stage Lung Cancer and who are candidates for oncological surgical resection may be eligible for this trial if they meet all entry criteria.

5.1 Inclusion Criteria

PARTICIPANT MRN		**PARTICIPANT INITIALS**
Verified	**Criteria**	
	5.1.1	Ability of participant OR Legally Authorized Representative (LAR) to understand this study, and participant or LAR willingness to sign a written informed consent
	5.1.2	Males and females age ≥ 18 years
	5.1.3	ECOG Performance Status 0 - 1 (*Appendix A.*)
	5.1.4	Women of childbearing potential must have a negative serum pregnancy test 48 hours prior to initiating study intervention.
	5.1.5	Histological confirmation of Stage I or II NSCLC
	5.1.6	Candidate for oncologic surgery (lobectomy or sub lobar resection)

PARTICIPANT MRN		PARTICIPANT INITIALS		
Verified	**Criteria**			
	5.1.7	Adequate diagnostic biopsy tissue to allow for pre-SBRT tumor analysis		
	5.1.7	Lesion must be located peripherally, ≥ 2 cm from bronchial margin and 1 cm from visceral pleura with location deemed acceptable by cardiothoracic surgeon for resection.		
	5.1.8	Pulmonary function: Baseline PFTs including adequate FEV1 deemed by cardiothoracic surgeon to be acceptable for oncologic surgery, with a predicted post-operative FEV1 of 40% or greater and DLCO of 40% or greater.		
Adequate organ function, defined as follows:			**Result**	**Date**
		White blood cell (WBC) count ≥ 3.0 ×10^3 cells/mm^3		
		Hemoglobin ≥10 g/dL		
		Absolute Neutrophil Count ≥ 1.5 K/UL		
		Platelets ≥ 150 K/UL		
		Serum creatinine clearance > 50 mL/min		
		Total bilirubin ≤ 2.0 x ULN		
		Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN		
		Women of child-bearing potential and men with partners of child-bearing potential must agree to practice sexual abstinence or to use the forms of contraception listed in Child-Bearing Potential/Pregnancy section for the duration of study participation and for **6 months** following completion of therapy.		

5.2 Exclusion Criteria

Participants meeting any of the exclusion criteria listed below at screening will be excluded from study participation.

PARTICIPANT MRN	**PARTICIPANT INITIALS**

No	**Criteria**	
	5.2.1	Simultaneously enrolled in any therapeutic clinical trial
	5.2.2	Diagnosed with a psychiatric illness or is in a social situation that would limit compliance with study requirements
	5.2.3	Is pregnant or breastfeeding
	5.2.4	Prior history of lung/chest wall surgery
	5.2.5	Prior history of radiation treatment to the chest
	5.2.6	History of autoimmune disease
	5.2.7	Current use of immunosuppressive drugs
	5.2.8	Prior history of immunotherapy
	5.2.9	Prior history of metastatic cancer or concurrent active secondary malignancy

Eligibility Confirmed	**Print Name**	**Signature**	**Date**
Clinical Research Coordinator			
Double Check			
Treating Physician			

Once eligibility has been confirmed, use the link below to register your participant.
Please allow up to 24 business hours for the registration process.

6 CHILD-BEARING POTENTIAL / PREGNANCY

Because the effect of the study intervention is considered possibly teratogenic and has potential risks to the fetus, pregnant females will not be included in the study. However, no female of childbearing potential will be excluded from the study.

An effective form of contraception of the woman's choice will be required during study participation. Participants should not get pregnant, breastfeed, donate sperm or father a child while participating in this study and for **6 months** after the last dose of the study medication.

Women of childbearing potential and male participants must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. If a woman becomes pregnant or suspects she is pregnant while participating in this study or if her male partner is a participant in this study, the treating physician should be informed immediately.

Child-bearing potential is defined as any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has either not undergone a hysterectomy or bilateral oophorectomy or has not been naturally postmenopausal for at least 12 consecutive months.

Participants must agree to use one of the following acceptable forms of birth control.

- Sexual Abstinence
- One barrier method (cervical cap with spermicide plus make condom; diaphragm with spermicide plus male condom) PLUS hormonal method (oral contraceptives, implants, or injections) or an intrauterine device (e.g., Copper-T).

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she should inform her treating physician immediately.

If the partner of a man becomes pregnant or suspects she is pregnant while he is participating in this study, he should inform his treating physician immediately.

Men of child-bearing potential must not father a child or donate sperm while receiving investigational product and for **6 months** after their last study intervention.

6.1 Screen Failures

Patients who screen fail cannot be re-screened at a later date.

Screen failures will be offered standard of care treatment per institutional guidelines and physician discretion. They will not be counted towards enrollment and will not be included in analysis of the data.

6.2 Participant Replacement

Participants will not be replaced once they have successfully completed surgery.

7 PARTICIPANT REGISTRATION PROCEDURES

7.1 General Guidelines

Eligible participants will be registered through The University of Kansas Cancer Center Clinical Research Office central registration process and registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before initiating study intervention will be considered ineligible and study intervention will be denied.

Issues that would cause study intervention delays should be discussed with the Sponsor/Investigator. If a participant does not receive protocol therapy following registration, notify The University of Kansas Cancer Center Clinical Site Management team via email at ***KUCC-CTO-IIT@kumc.edu*** and update participant's status in the CRIS system.

7.2 Registration Process

The University of Kansas Cancer Center participant registration is accessible for registration Monday through Friday, 8:00 AM to 5:00 PM Central Time. Please allow up to 24 hours for completion of registration.

The registration procedures are as follows:

1. Obtain written informed consent prior to the performance of any study related procedures or assessments. Tests required at screening and performed as part of customary care prior to signing consent, are allowed IF those tests were performed within the timeframe listed in Participant Selection section.
2. Complete appropriate baseline demographic information in CRIS. Print, complete and obtain appropriate signatures for the inclusion/exclusion criteria to document eligibility. Maintain completed documents in participant's research record. Participants must meet all eligibility criteria to be eligible for registration.
3. Use the hyperlink at the bottom of the eligibility criteria or in the CRIS system, complete information and submit to initiate the registration process.
4. Email confirmation of registration will be sent to the person initiating the registration. Registration confirmation should be maintained as part of the participant's research record.

8 STUDY INTERVENTION PLAN

8.1 Radiation Treatment Regimen

Study Intervention	Dose	Schedule	Cycle Length
SBRT	800 cGy x 3 fractions	Daily	5-7 days prior to planned surgery

RADIATION THERAPY

Modalities:
Stereotactic Body Radiation Therapy has now been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic Radiology and Oncology.[19,20]

This protocol will follow that guideline.

Dose Fractionation
Patients will receive 2400 cGy in 3 fractions of 800 cGy/fraction to the prescription line at the edge of the PTV (see section below with title *Prescription Dose Constraints for Treatment Planning* for more prescription details). Treatment delivery will be scheduled for 3 consecutive days, but may be modified as needed by the treating radiation oncologist.

A minimum of 18 hours between fractions is required.

Technical Factors

- **Physical Factors**
  Only photon (x-ray) beams produced by linear accelerators, with photon energies of 6-15 MV will be allowed.

- **Dose Verification at Treatment**
  Patient specific QA will be performed for each patient prior to first fraction. Additionally, in-vivo dosimeter measurements (e.g., TLD/NanoDots/Mosfet) may be obtained for surface dose verification for accessible beams as per institutional preference.

Localization, Simulation, and Immobilization

- **Patient Positioning**
  Patients will be positioned in a reproducible position. A variety of immobilization systems may be used.

- **Inhibition of Effects of Internal Organ Motion**
  Special considerations must be made to account for the effect of internal organ motion (e.g., breathing) on target positioning and reproducibility. Acceptable maneuvers include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques.

Localization.

- IGRT will be required with CBCT images obtained prior to each fraction and verified by treating physician prior to treatment delivery.

Treatment Planning/Target Volumes

- Computed tomography will be the primary image platform for targeting and treatment planning. The target lesion will be outlined by the treating physician and will be designated as the gross tumor volume (GTV), which will also be designated the clinical target volume (CTV)(i.e. GTV=CTV). 4DCT data sets will be used to generate internal tumor volume (ITV). The PTV will include the ITV plus an additional 0.5 cm margin uniformly applied to the ITV. Per physician discretion, these volumes can be adjusted based on each patient's clinical situation and anatomy.

Dosimetry

- Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, noncoplanar beams are preferable. For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity corrections.

Prescription Dose Constraints for Treatment Planning

The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose. Dose homogeneity within the GTV of +/- 5% is highly recommended.

Organs At Risk (OAR) visible in the planning CT will be contoured. Dose constraints are defined below.

Dose Constraints

1. **Modification as defined in the chart below** of the Dose Constraints as defined by RTOG 9501 Arm 2 12 Gy X 4 is the basis of dose limitations of the organs at risk to be used this protocol**.**[21]

2. **The risk of end-organ damage as defined in the table is anticipated to be less than 1%.**

Organ at Risk	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)**	**Endpoint (≥ Grade 3)**
Spinal Cord	<0.35 cc <1.2 cc	10.4 Gy (5.2 Gy/fx) 6.8 Gy (3.4 Gy/fx)	13 Gy (6.5 Gy/fx)	Myelitis
Esophagus	<5 cc	9.4 Gy (4.7 Gy/fx)	15 Gy (7.5/fx)	Stenosis/fistula
Brachial Plexus	<3 cc	11.8 Gy (5.9 Gy/fx)	13.6 Gy(6.8Gy/fx)	Neuropathy
Heart/Pericardium	<15 cc	14 Gy (7 Gy/fx)	17 Gy (8.5 Gy/fx)	Pericarditis
Great vessels	<10 cc	21.5 Gy (10.75 Gy/fx)	24.5 Gy (12.25 Gy/fx)	Aneurysm
Trachea and Large Bronchus	<4 cc	7.8 Gy (3.9 Gy/fx)	17.4 Gy (8.7 Gy/fx)	Stenosis/fistula
Rib	<1 cc	16 Gy (8 Gy/fx)	20 Gy (10Gy/fx)	Pain or fracture
Skin	<10 cc	16.6 Gy (8.3 Gy/fx)	18 Gy (9 Gy)	Ulceration
Stomach	<10 cc	8.8 Gy (4.4 Gyfx)	18.6 Gy (6.8 Gy)	Ulceration/fistula
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥ Grade 3)**
Lung (Right & Left)	1500 cc	5.8 Gy (2.9 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	6.2 Gy (3.1 Cy//fx		Pneumonitis

Quality assurance

Patient safety will be ensured with effective treatment delivery with a robust quality assurance protocol as defined below.

- Prior to treatment each patient will be discussed by quality assurance team as defined by a study investigator, treating radiation oncologist, study physicist and dosimetrist.

- The treating radiation oncologist will confirm prior to the first fraction delivery that the radiation treatment plans must meet target dose levels for dose homogeneity..

- Prior to plan approval, the organ at risk dose volume histogram must be verified by the treating radiation oncologist and physicist. Dose constraints as defined shall not be exceeded.

- Image-guided radiation treatment (I GRT/SBRT) with cone beam CT will be used to verify patient positioning prior to each treatment. And will require approval by the treating radiation oncologist prior to treatment delivery.

Possible side effects of SBRT as listed below.

The likelihood of the defined organ risk/toxicity is anticipated to be less than 1%, as the dose constraints defined in this protocol are well below the RTOG-0915 defined dose constraints for SBRT of the lung.

Organ at Risk	**Possible Side Effect**	**Volume**	**Volume Max (Gy)** **Dose threshold as defined for end organ damage in RTOG 0915**
Spinal Cord	Myelitis	< 0.35 cc < 1.2 cc	20.8 Gy (5.2 Gy/fx) 13.6 Gy (3.4 Gy/fx)
Esophagus	Stenosis/fistula	< 5 cc	18.8 Gy (4.7 Gy/fx)
Brachial Plexus	Neuropathy	< 3 cc	23.6 Gy (5.9 Gy/fx)
Heart/Pericardium	Pericarditis	< 15 cc	28 Gy (7 Gy/fx)
Great vessels	Aneurysm	< 10 cc	43 Gy (10.75 Gy/fx)
Trachea and Large Bronchus	Stenosis/fistula	< 4 cc	15.6 Gy (3.9 Gy/fx)
Rib	Pain or fracture	< 1 cc	32 Gy (8 Gy/fx)
Skin	Ulceration	< 10 cc	33.2 Gy (8.3 Gy/fx)
Stomach	Ulceration/fistula	< 10 cc	17.6 Gy (4.4 Gy/fx)
Parallel Tissue	**Possible Side Effect**	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**
Lung (Right & Left)	Basic Lung Function	1500 cc	11.6 Gy (2.9 Gy/fx)
Lung (Right & Left)	Pneumonitis	1000 cc	12.4 Gy (3.1 Gy/fx)

Surgery

- Surgery will occur 5 to 7 days post completion of the last fractionation of radiation treatment. Surgery will consist of a lobectomy or sub lobar resection. The technique will be at the discretion of the study cardiothoracic surgeon, and may employ either an open approach, video assisted thoracoscopic or robotic-assisted approach. Surgical sampling of the at risk hilar and mediastinal nodes may be performed at the time of resection but is not a requirement of the study.
- In the event adjuvant systemic therapy is elected, follow up studies as defined in this protocol may be modified as clinical necessity requires. Participants will be continued for secondary objectives and will be reported using descriptive statistical analysis.

Pathology Processing

- After resection, the tumor will be oriented by the surgeon and submitted to the pathology lab. In the pathology lab it will undergo gross examination in a standard manner. The specimen will be submitted for microscopic examination. Samples for translational research use will be processed and transferred to the appropriate laboratory as defined in the study laboratory manual.

8.2 Sample Procurement

8.2.1 Pre-SBRT Biopsy Sample

Pre-SBRT biopsy samples will be obtained at time of diagnostic biopsy and will consist of a minimum of two core biopsies.

- **Required collection of archival tumor biopsy tissue (either from initial diagnosis of lung cancer done prior to any study intervention or from any subsequent biopsy), for translational studies.**
  A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report prior to study enrollment. If only 10 to 14 slides are available, the specimen may still be used, after Principal Investigator confirmation has been obtained.

- **Required fresh tumor biopsy for translational studies**.
  If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, if participant consents, then fresh tumor tissue can be obtained from a biopsy performed after screening.

  If participant does not consent, they cannot participate in this study.

  Refer to Lab Manual for additional information on tumor specimens collected at screening.

8.2.2 Surgical Sample

Post-assessment by pathologist and verification that adequate tissue has been obtained for clinical use, the remainder of the tumor tissue will be processed for translational studies as defined in study laboratory manual.

9 STUDY PROCEDURES AND SCHEDULE

9.1 Screening/Enrollment/Baseline

SCREENING VISIT

- Informed Consent
- Cancer history
- Demographics - including date of birth, gender, race, and zip code
- Review participant eligibility criteria to ensure participant qualification for study entry
- Physical exam to include vital signs, weight and height at baseline – which helps in the evaluation for surgical candidacy
- Baseline medical history to aid in assessment of possible adverse events
- ECOG Performance Status
- Pulmonary function test
- CBC with differential (± 3 Days)
- CMP (Serum chemistries) (± 3 Days) Serum chemistries to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, total bilirubin, magnesium, lactate dehydrogenase (LDH), phosphate
- Urinalysis(± 3 Days)

- Urine pregnancy test (women only) (± 7 Days)
- Imaging (Chest) – CT preferred.
    - IV and oral contrast will be used for all imaging unless contraindicated. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used. If CT contraindicated – MRI will be allowed (IV contrast will be used unless contraindicated). The same type of imaging used at screening must continue to be used throughout the study. Studies will be evaluated using RECIST Version 1.1.[22]

- **Required collection of archival tumor biopsy tissue (either from initial diagnosis of lung cancer done prior to any study intervention or from any subsequent biopsy), for translational studies.**
    A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report prior to study enrollment. If only 10 to 14 slides are available, the specimen may still be used, after Principal Investigator confirmation has been obtained.

- **Required fresh tumor biopsy for translational studies**.
  If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, if participant consents, then fresh tumor tissue can be obtained from a biopsy performed after screening.

  If participant does not consent, they cannot participate in this study.

  Refer to Lab Manual for additional information on tumor specimens collected at screening.

At any time after enrollment and before surgery
Pre-operative anesthesia clinic clearance for surgery is required and *may* include

- EKG
- Stress Test
- Cardiac Clearance

9.1.1 Procedures During Study Intervention

Day 0 - Simulation

- Radiation Simulation
- Adverse event assessment

Day 1 – Prior to 1st fraction

- Blood collection for translational studies

Day 1 – 1st Fraction

- Radiation – Fraction 1
- Adverse event assessment

Day 2 – 2nd Fraction

- Radiation – Fraction 2
- Adverse event assessment

Day 3 – 3rd Fraction

- Radiation – Fraction 3
- Adverse event assessment

NOTE: There is a 5-7 day rest period after radiation and before surgery.

Day of Surgery (Occurs during days 8-10)

- ECOG
- CBC with Differential (± 3 Days)
- CMP (Serum Chemistries) (± 3 Days)
- Physical exam
- Adverse event assessment
- Peri-operative surgical complication assessment
- Blood collection for translational studies BEFORE surgery
- Surgical specimen collection

9.1.2 Follow-Up Visits

POST OPERATIVE FOLLOW UP

24 Hours post-op

- Physical exam
- Adverse event assessment
- Post-operative surgical complication assessment
- CBC with Differential (± 3 Days)
- Basic Metabolic Panel (BMP) (± 3 Days)
- Post-operative chest x-ray (within 24 hours of surgery)

Day of Discharge (post-op)

- Physical exam
- Adverse event assessment
- Post-operative surgical complication assessment
- Wound healing assessment
- Blood collection for translational studies

- **1-3 weeks post-op** Physical exam
- Adverse event assessment
- Post-operative surgical complication assessment
- Wound healing assessment
- Chest X-Ray (CXR)

6 Months (post-op) (± 2 months)

- Imaging (Chest) – CT preferred.
    - IV and oral contrast will be used for all imaging unless contraindicated. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used. If CT contraindicated – MRI will be allowed (IV contrast will be used unless contraindicated). The same type of imaging used at screening must continue to be used throughout the study. Studies will be evaluated using RECIST Version 1.1.
- Physical exam
- Adverse event assessment
- Post-operative surgical complication assessment
- Wound healing assessment
- Check pregnancy status

Every 6 months (± 2 months) after initial 6-month follow up
Last study follow up at month 36 after enrollment

- Imaging (Chest) – CT preferred.
    - IV AND oral contrast will be used for all imaging unless contraindicated. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used. If CT contraindicated. The same type of imaging used at screening must continue to be used throughout the study. Studies will be evaluated using RECIST Version 1.1
- Physical exam
- Adverse event assessment

9.2 Lost to Follow Up

Institution policy will be followed for participants considered lost to follow up.

9.3 SCHEDULE OF EVENTS TABLE

Screening Period	Screening & Baseline	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Days 8 – 10**	**Post-Operative Follow Up**				
		Simu-lation	1st Fraction	2nd Fraction	3rd Fraction	Surgery	24 Hours	Day of Discharge	1-3weeks	6 months	Every 6 months after surgery (Last follow up at 36 months)
Simulation		X									
SBRT			X	X	X						
Informed Consent	X										
Cancer History	X										
Demographics	X										
Inclusion/Exclusion	X										
Physical Exam	X					X	X	X	X	X	X
ECOG Performance Status (PS)	X					X					
Pre-Op Anesthesia Clearance	To be completed before surgery										
PFT	X										
Adverse Event Assessment	X (Med Hx Review)	X	X	X	X	X	X	X	X	X	X
Peri- / Post-Operative Surgical Complication Assessment						X	X	X	X	X	
Wound Healing Assessment								X	X	X	
CBC with Diff	X					X Before Surgery	X				
CMP (Serum Chemistries)	X					X Before Surgery					
BMP							X				
Urinalysis	X										
Pregnancy (URINE) Test	X										

Screening Period	Screening & Baseline	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Days 8 – 10**	**Post-Operative Follow Up**				
		Simu-lation	1st Fraction	2nd Fraction	3rd Fraction	Surgery	24 Hours	Day of Discharge	1-3weeks	6 months	Every 6 months after surgery (Last follow up at 36 months)
Pregnancy Status Check										X	
CT Imaging of chest	X									X	X
Chest X-Ray							X		X		
Blood Collection for Translational Studies	X		X Before SBRT			X Before Surgery		X			
Tumor Tissue Collection	X (Archival)					X (Surgical Specimen)					

9.4 Supportive Care Guidelines

Therapies required for standard supporting care following surgery is acceptable.

9.4.1 Prohibited or Restricted Concomitant Medications

We strongly encourage physicians to avoid use of immunosuppressive medications up to 1 month following surgery as this can affect surgical wound healing and may alter the immune microenvironment.

9.4.2 Diet

No dietary modifications required in this study.

9.5 Participant Discontinuation/Withdrawal from the Study

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Participants may be withdrawn from the study intervention if any of the following occur:

- Intercurrent illness that prevents further administration of study intervention.
- Unacceptable adverse event(s).
- Participant decides to withdraw from the protocol therapy.
- General or specific changes in the participant's condition render the participant unacceptable for further study intervention in the judgment of the treating investigator.
- Major violation of the study protocol (i.e., unable to adhere to study schedule) that in the opinion of the treating investigator, puts the participant at undue risk.
- Discontinuation of the study by The University of Kansas Cancer Center.
- Confirmed pregnancy.
- Completed follow up as per protocol
- Lost to follow-up.
- Death

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the electronic case report form (eCRF). Alternative care options will be discussed with the participant. Safety monitoring and follow-up assessments should continue as appropriate according to the study schedule, unless the participant has withdrawn consent for study participation. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in CRIS.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Sponsor/Investigator.

10 TRANSLATIONAL STUDIES

1. Targeted Cell Surface Analysis

Radiation can alter the cell surface expression of many immunomodulatory proteins. Upregulation of PDL1 and PDL2 has been demonstrated in multiple cell lines. Altered expression of MHC 1 on tumor cells has also been reported. Changes in the composition of the immune regulatory cells within the tumor micro-environment in response to changes in tumor cell phenotype has also been demonstrated. Utilizing paired pre-XRT (biopsy) and post XRT (surgical specimen) tumor tissues and normal tissue samples from the resection sample, we will use immunohistochemistry to assess cell surface markers and immune parameters. Tumor panels will include PDL1, PDL2, HCA2, IDO, HC10, B2m, Calreticulin, MHC-1, Fas, ICAM. T-cell panels will include CD3, CD8, FoxP3, TBet, Ki67, GranzymeB; and CD3, CD8, PD1, 1263 Tim3, Lag3, GranzymeB.

2. Tumor Immune Microenvironment

Using the "biopsy-XRT-resection" approach, we will be able to gain insight into the composition of the tumor immune microenvironment before SBRT and understand how SBRT influences the microenvironment and expression of immunotherapy targets. Prior rodent studies have delineated how radiation dose and fractionation can alter the STING pathway.[23],[24],[25] The consequence of this is recruitment and activation of dendritic cells which can prime CD8+ T cells and mediate a systemic cytotoxic tumor response.[26] Similarly, other groups have utilized murine models to delineate how radiation can increase the CD8/CD4 ratio and broaden the T-cell repertoire Ko et al IJROBP 2019).[27] We propose to examine changes in the tumor immune microenvironment focusing on transcriptomic changes as well as functional changes in the T-cell receptor repertoire.

3. Gene Expression Profile

We will use the NanoString nCounter® PanCancer ImmunoOncology (IO) 360™ Gene Expression Panel to perform quantitative highly multiplexed gene expression profiling. Total DNA and RNA will be collected from FFPE-embedded biopsy (pre-radiotherapy) and surgical (post-radiotherapy) specimens using the AllPrep DNA/RNA FFPE Kit (Qiagen). DNA will be cryopreserved for future translational genomic studies. RNA will be analyzed on the nCounter® PanCancer IO 360™ Gene Expression Panel using the instrumentation in the Clinical Molecular Oncology Laboratory (CMOL) overseen by Dr. Andrew Godwin at KU Cancer Center. This platform quantifies expression levels for 770 transcripts, including 40 housekeeping genes for automated normalization, and provides a quantitative measure of immune-related biological signatures, pathways, and processes, extrapolated relative levels of immune cell subtypes, and expression of immunotherapy targets within each sample. Paired analysis between pre-radiotherapy and post-radiotherapy samples will enable us to detect radiotherapy induced changes in the tumor immune microenvironment and expression of immunotherapy targets.

These studies will provide critical insight into the potential of radiotherapy as an immunogenic adjunct in NSCLC and identify novel therapeutic approaches to combine radiotherapy with immunotherapy.

4. Radiation-Mediated Changes in T-cell Repertoire in Tumor Tissue

We will use the AmpliSeq™ for Illumina® Direct FFPE DNA to develop a highly multiplexed targeted resequencing panel followed by DNA sequencing in order to measure T cell diversity and clonal expansion by sequencing T cell receptor (TCR) beta chain rearrangements. Paired pre-RT core needle biopsy and post-RT resected tumors will be compared for unique immune cell receptor transcripts that

have infiltrated tumor tissue after radiation treatment. This project will lay the groundwork for future work to identify radiation treatment regimens that may be augmented with immune-therapeutics.

5. Radiation-Mediated Changes in T-cell Repertoire in Peripheral Blood

We will process peripheral blood T cells in order to measure T cell diversity and clonal expansion by sequencing TCR beta chain rearrangements. We will simultaneously evaluate T cell profile by flow cytometry, assessing for markers of T cell exhaustion.

6. Tumor Tissue and Circulating Tumor Cell Analysis

Circulating tumor cells (CTCs) have been widely used for diagnostic purposes as well as a biomarker to screen for treatment failure. Furthermore, CTCs have been shown to prognosticate both lung and head/neck squamous cell carcinoma patient disease-free survival and contribute to both loco-regional and distant metastasis.[28,29,30,31] In our model system, we have previously demonstrated that radiotherapy can induce accelerated tumor repopulation in vivo and this is likely regulated by epithelial-to-mesenchymal transition (EMT).[32,33] Predictably, generation of "mesenchymal" CTCs require EMT and those CTCs with persistent EMT pathway activation have been correlated as a poor patient prognostic outcome particularly in head and neck cancer. [34,35] In addition, EMT gene expression in CTC's from lung cancer patients who undergo curative surgical resection have been shown to be a poor prognostic feature.[36] Furthermore, PD-L1 expression (and other immunomodulatory proteins) are known to be upregulated in pre-clinical models[37,38] following radiotherapy and immune cell surface proteins (i.e. PD-L1) has been shown to be expressed in CTCs.[39]

We propose to examine CTC before and after SBRT. Both mesenchymal and nonmesenchymal (epithelial) expressing CTCs will be isolated from whole blood using specialized nanofabricated cell isolation chips (KU Lawrence collaboration, Sopek, Witek) designed for harvesting CTCs and demonstrate a 10-100x higher cell capture rate compared with commercial vendors.[40] Endpoints include mesenchymal and epithelial CTC cell enumeration before and after SBRT; examination of PD-L1 cell surface expression in CTCs; as well as targeted transcriptomic analysis of collected CTCs using a modified Nanostring nCounter® PanCancer Progression Panel customized with supplemental user-defined genes focusing on p38-MAPK pathway.

We hypothesize from this work that following SBRT there will be a higher proportion of mesenchymal CTCs over epithelial CTCs and these results will be confirmed using targeted transcriptomic analysis. We also anticipate that patients receiving SBRT will have upregulation of PDL1 cell surface expression and will be confirmed by immunofluorescence. We also hypothesize that genes in the p38-MAPK pathway will be upregulated following SBRT and promising genes candidates will be confirmed by immunohistochemistry looking at tumor tissue before and after SBRT. The goal of this work will be to: 1) explore the effect of SBRT on mesenchymal CTC generation; 2) examine the gene expression profile of CTCs with a focus on EMT; and 3) identify promising novel targets within the MAPK pathway that are up-regulated following SBRT that maybe relevant and targetable for metastasis.

11 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

Although pregnancy is not always serious by regulatory definition, for the purposes of this protocol, this is considered to be an SAE and follow the SAE reporting timeline.

Refer to Appendix B for additional Adverse Event/Serious Adverse Event information.

11.1 Adverse Event Monitoring

Baseline adverse events are recorded and graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[41]. Additional serious adverse event and adverse event monitoring begins after initiation of study intervention and ends 36 months following surgery (i.e.; end of study).

11.2 Adverse Event Reporting

Information for adverse events, whether reported by the participant, directly observed or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported in the CRIS system within 5 days of being reported.

All adverse events experienced by participants will be collected. Medical conditions are collected as baseline adverse events and evaluated as above. Additional adverse event monitoring begins after initiation of study intervention and ends 36 months following surgery.

Participants who experience an ongoing adverse event related to study intervention beyond 36 months will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the Sponsor/Investigator.

Study participants should also be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

11.3 Serious Adverse Event Reporting

SAEs regardless of expectedness or relationship will be reported to The University of Kansas Cancer Center IIT Regulatory Department within 24 hours of notification as follows:

- Enter into CRIS
- Submit a complete FDA 3500A MedWatch form and all supporting documents to The University of Kansas Cancer Center IIT Regulatory department at ***KUCC-CTO-IIT@kumc.edu.***

Follow-up source documentation is required within 5 days.
Local policy will be followed for reporting SAEs to the IRB.

11.3.1 Pregnancy Reporting

If a woman becomes pregnant or suspects that she is pregnant while participating in this study she must inform the investigator immediately. Reporting requirements are the same as for an SAE in above. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male participant becomes pregnant during the male participants participation, he must inform the investigator immediately. Reporting requirements are the same as for an SAE above. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

12 STATISTICAL CONSIDERATIONS

12.1 Description of Statistical Methods

We will summarize peri- and post- operative surgical complication rates as well as tumor control outcomes using descriptive statistics.

Peri- and post- operative surgical complication rates will be quantified using the Clavien-Dindo classification of surgical complications.

Wound healing complication rates will be scaled as defined by the General Thoracic Surgery Database with particular references to pages 246-248.

12.2 Study Stopping Rules

If a participant experiences one or more of the following events, possibly related to study intervention, study will be suspended pending data safety monitoring committee (DSMC) review to determine if study should continue:

a. Wound healing delay beyond standard timeframe as deemed by study Cardio-Vascular (CV) surgeons
b. Peri operative/post-operative surgical complications beyond acceptable institutional rates as determined by study CV surgeons
c. Death from study intervention

13 REGULATORY REQUIREMENTS AND DATA REPORTING

13.1 Institutional Review Board/Ethics Committee Approval

Before trial initiation this protocol and informed consent form will be submitted for review and approval by the IRB of record for the clinical site. Any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by the IRB. In accordance with FDA 21 CFR 56 of the Code of Federal Regulations the Investigator will forward the Sponsor/Investigator a copy of the IRB approval letter for the initial approval, amendments, informed consent and any informed consent updates.

The Investigator will be responsible for providing the Sponsor/Investigator a list of IRB members including profession and affiliation or a United States Department of Health and Human Services General Assurance number and expiration date. If neither of these is available, the IRB Chairperson must submit a statement indicating the members of the board responsible for the review meet the FDA and other appropriate regulatory requirements.

Sub-sites will not be activated until the Sponsor/Investigator has received documentation of IRB approval.

13.2 Investigators Protocol Agreement

The Investigator must sign the Protocol Agreement before the study is activated. The original will be forwarded to the Sponsor/Investigator and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed when a protocol amendment is issued.

13.3 Remaining Samples

Any samples remaining after the trial specified analyses is completed will be stored by the Sponsor/Investigator at The University of Kansas Cancer Center if the participant consented for use of their remaining samples for future research purposes. This includes the original specimen collected from the participant (blood, tumor tissue) as well as derivatives created from the original specimen (DNA, RNA, blocks or slides).

If a participant has not consented for their remaining samples to be used for future research purposes remaining samples and derivatives will be destroyed and documented in accordance with The University of Kansas Cancer Center policy.

13.4 Confidentiality

The Investigator and any other personnel involved in the trial shall not disclose or use for any purposes other than for the performance of this trial any data, records or other information disclosed to the Investigator or other trial personnel. Such information shall remain the confidential and proprietary property of the Sponsor/Investigator and shall be disclosed only to the Investigator or other designated trial personnel.

Participant confidentiality will be ensured by using assigned site-specific participant ID numbers throughout the trial.

13.5 Publication

The Sponsor/Investigator holds the primary responsibility for publication.

Data
Funder and its co-development collaborator may use the data generated under the Research Agreement for all purposes, subject to Institutions right to publish.

Publication
The University of Kansas Cancer Center Sponsor/Investigator shall publish the results of the approved study, subject to reasonable delay to allow for filing of patent applications on any inventions (as applicable). Sponsor/Investigator will provide the funder with the opportunity to review and comment on any publications, prior to submission.

13.6 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the FDA Modernization Act (FDAMA) and the FDA Amendments Act (FDAA) the Sponsor/Investigator of the trial is solely responsible for determining if the trial and results meet the requirement for submission to the Clinical Trials Data Bank, *http://www.clinicilaatrials.gov*. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial location and trial site contact information.

13.7 Required Site Documentation

Before the study is initiated at any site the following documentation must be provided to The University of Kansas Cancer Center IIT Regulatory Department.

- A copy of the official IRB approval letter for protocol and informed consent.
- A copy of the IRB-approved consent form.
- CVs and medical licensure for the Principal Investigator and all Sub-Investigators who will be involved with conduct of the study.
- Appropriately completed and signed Form FDA 1572 with appropriate documentation.
- COP and CLIA Laboratory certification numbers and institution laboratory normal values.
- Executed clinical research contract.

13.8 Data Management

Web-based eCRFs will be used to collect participant data. All eCRFs and resulting data will be developed and maintained in a manner consistent with currently available regulations and guidance pertinent to the use of computerized systems in clinical trials. All users of the eCRF system will be trained prior to the use of the system.

A Risk-Based Monitoring (RBM) approach will be used focusing on critical variables and triggered events and ensuring the eCRF accurately reflects data recorded in source documents.

13.9 Data Monitoring

Data monitoring procedures will be carried out by The University of Kansas Cancer Center Clinical Trials Office (CTO) Clinical Site Managers for all participating sites and will be performed on a regular basis to comply with Good Clinical Practice.

The study will be monitored at appropriate intervals, no less than those assigned per The University of Kansas Cancer Center Protocol Review and Monitoring Committee (PRMC) risk level designation, to assure compliance to GCP and to assess the data quality and study integrity.

Interim monitoring visits (IMV) will occur at regular intervals following enrollment/registration of the first study participant with the frequency and duration of each visit depending on recruitment status and participant enrollment/registration.

Review of the case report forms, cross-reference with source documents, review of trial related regulatory documents and logs will be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the trial is conducted according to protocol design and regulatory requirements.

The monitor will complete a follow-up letter and provide to the Sponsor/Investigator. The letter will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to ensure compliance. The site will be expected to submit any Corrective and Preventative Action Plan (CAPA) in writing to the Sponsor/Investigator. A copy of the monitoring forms, follow up letter and CAPA will be kept in the site monitor's trial file and will be followed up at the next monitoring session.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data.

14 DSMC OVERSIGHT

The NCI-approved Data Safety and Monitoring Committee (DSMC) of The University of Kansas Cancer Center will monitor every participant receiving study intervention on this protocol for safety, conduct and scientific progress of research protocols, and the validity and integrity of the data for clinical trials. This protocol will adhere to the policies of the currently approved University of Kansas Cancer Center Data and Safety Monitoring Plan which is in accordance with NCI and The University of Kansas Cancer Center -IRB policy and guidelines. The committee is led by a senior practicing oncologist and consists of The University of Kansas Cancer Center faculty and staff with expertise in oncology, research, pharmacy, research nursing and data management. The University of Kansas Cancer Center DSMC has the authority to require amendments, suspend, or terminate any research activities that fall within its jurisdiction, and can institute other appropriate actions as needed to protect participant safety.

The DSMC is an autonomous committee. However, its actions are communicated to other committees engaged in oversight of clinical research at The University of Kansas Cancer Center. The PI is responsible for forwarding all DSMC letters, including those recommending continuation of the study, to the IRB and PRMC. DSMC recommendations for modifications to the trial are forwarded to the Deputy Director of The University of Kansas Cancer Center. The PI is notified of this recommendation and is expected to alert all collaborating investigators about the DSMC action. At this time the PI may appeal the Committee's decision to the Deputy Director of The University of Kansas Cancer Center or their designee. The Deputy Director of The University of Kansas Cancer Center or their designee will notify the PI if he/she concurs with the DSMC's recommendation, including suspension or closure.

14.1 Serious Adverse Events

Serious adverse events that require expedited reporting will be reviewed by the DSMC Chair or designee who will determine if immediate action is required. If determined to be necessary by the DSMC, all participating sites will be notified of the event and any resulting action within one working day of this determination.

14.2 Review of Serious Adverse Event Rates

Once per month, serious adverse event rates will be monitored by the DSMC Coordinator. If any study site has had 2 or more of the same SAE reported within one month, or more than 6 of the same SAE in 6 months, the DSMC will review summaries of SAEs, and discuss events in detail with the PI. The DSMC chair or designee determines whether further action is required. The Sponsor/Investigator, in collaboration with the DSMC Coordinator ensure that collaborating investigators and IRBs for all participating sites are notified of any resulting action.

14.3 Study Safety and Progress

An overall assessment of toxicities as described in the protocol is reviewed at DSMC meetings. This review enables DSMC committee members to assess whether significant risks are occurring that would warrant study suspension/closure or protocol amendment.

14.4 The University of Kansas Cancer Center Quality Assurance Auditing

The study will be audited by The University of Kansas Cancer Center Quality Assurance Department at appropriate intervals, no less than those assigned per The University of Kansas Cancer Center Protocol Review and Monitoring Committee (PRMC) risk level designation, to assure compliance to GCP and Good Documentation Practices (GCP).

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Collection and Management Responsibilities

Electronic case report forms (eCRFs) will be completed for each participant enrolled and registered on this study. All CRFs will be customized per this study, in order to emphasize completeness and accuracy. The investigatory and trained study staff will enter and edit the data via a secure network with secure identification and password requirements. A complete electronic audit trail will be maintained.

Source documents serve as the evidence of the existence of the participant and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed by the Sponsor/Investigator or assigned Clinical Site Manager.

Data captured in the eCRF is to be transcribed from source documents and must be consistent with any discrepancies explained and document. The medical chart and any other clinical worksheets, procedural reports, etc. will be the source documentation of data captured into the study database.

15.2 Protocol Deviations

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. All deviations will be entered into the CRIS system must be reported to the DSMC. All deviations will be reported to the IRB per local reporting policy.

15.3 Study Closure

Upon study closure, the Sponsor/Investigator and/or Institution will be required to certify that all safety reporting obligations were met.

15.4 Study Records Retention

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, ECG, signed ICFs, participant diaries and pathology reports. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

16 APPENDICES

Appendix A: ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Appendix B: Reportable Events

Adverse Event (AE) Definition

Adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study intervention and that does not necessarily have a causal relationship to this intervention. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom or disease temporally associated with the use of study intervention, whether or not considered related to the study intervention.

Progression of the cancer under study or events which are unequivocally due to disease progression should not be reported as an AE during the study unless the treating investigator considers it to be study intervention related.

Serious Adverse Event (SAE) Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or causes prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect
- Is an important medical event defined as a medical event or multiple medical events that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgement may jeopardize the participant or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study intervention.

Although pregnancy is not always serious by regulatory definition, for the purposes of this protocol, this event is considered to be an SAE and follow the SAE reporting timeline.

Any component of the study endpoints that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis is reported an SAE.)

NOTE: The following hospitalizations are not considered SAE's:

- An Emergency room or other hospital department visit <24 hours that does not result in admission. Unless considered an important medical or life-threatening event)
- Elective surgery planned prior to signing consent.
- Admissions as per protocol for a planned medical/surgical procedure.
- Routine health assessment requiring admission for baseline/trending of health status. (e.g., routine colonoscopy)

- Medical /surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention. (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAE.

Unanticipated Problem

An Unanticipated Problem is any incident, experience or outcome involving risk to participants or others in any human participant research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given the research procedures described in the IRB-approved protocol and informed consent document and the characteristics of the population being studied.
- Related or possibly related to participation in such research (i.e., there is a reasonable possibility the incident, experience or outcome may have been caused by the procedures involved in such research).
- Suggests that the research placed participants or others at a greater risk of harm (including physical, psychological, economic or social harm) that was previously known or recognized.

Suspected Adverse Reaction

A Suspected Adverse Reaction (SAR) is any AE for which there is a reasonable possibility that it was caused by the study intervention.

Reasonable possibility means there is evidence to suggest a causal relationship between the study intervention and the AE. Examples of reasonable possibility are:

- A single occurrence of an event that is uncommon and know to be strongly associated with study intervention exposure.
- One or more occurrences of an event that is not commonly associated with study intervention exposure but is otherwise uncommon in the population exposed to the study intervention.
- An aggregate analysis of specific events observed in a clinical trial that indicates that those events occur more frequently in the study intervention group than in a concurrent or historical control group.

Expectedness and Attribution

Both AE's and SAE's are evaluated with regard to expectedness and attribution.

Expectedness

Expected events are those that have previously been identified as resulting from administration of the agent. For the purposes of this study an event is considered expected when it appears in the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

An event is unexpected when it varies in nature, intensity or frequency from information provided in the Investigator's Brochure, the package inserts or when it is not included in the informed consent document as a potential risk.

Attribution

Attribution is the relationship between an event and the study intervention. Attribution is assigned as follows:

- Definite – The event is clearly related to the study intervention
- Probable – The event is likely related to the study intervention
- Possible – The event may be related to the study intervention
- Unlikely – The AE is doubtfully related to the study intervention
- Unrelated – The AE is clearly NOT related to the study intervention

Adverse Event Monitoring

Baseline adverse events are recorded and graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Additional serious adverse event and adverse event monitoring begins after initiation of study intervention and ends 36 months following surgery or until the start of a new anti-cancer therapy whichever is earlier.

Adverse event data collection and reporting are a part of every clinical trial and are done to ensure the safety of participants enrolled in the studies as well as those who will enroll in future studies using similar agents.

Adverse events should be evaluated to determine

- Start and end dates
- Severity or grade
- Seriousness
- Relationship to study intervention
- Action taken (i.e., dose held, dose reduced, medical intervention)
- Outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Participants experiencing an adverse event, regardless of its relationship to study intervention will be monitored until:

- Adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline.
- Clinically significant abnormal laboratory values have returned to baseline.
- The treating investigator has determined there is a satisfactory explanation other than the study intervention for the changes observed.
- Death

The following laboratory abnormalities should be documented and reported as adverse events.

- Meets the definition of an SAE.
- Requires medical intervention (i.e., dose modification and/or other intervention such as supportive medication administration, supplementation, physical therapy, diet change, fluid

Appendix C: Clavien-Dindo Classification for Surgical Complications

The Clavien-Dindo Classification of Surgical Complications

Full Scale			Contracted Form	
Grades	Definition		Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.		**Grade I:**	Same as for Full Scale
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.			
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.		**Grade II:**	Same as for Full Scale
Grade III:	Requiring surgical, endoscopic or radiological intervention		**Grade III:**	Grades IIIa & IIIb
Grade III-a:	intervention not under general anesthesia			
Grade III-b:	intervention under general anesthesia			
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management		**Grade IV:**	Grades IVa & IVb
Grade IV-a:	single organ dysfunction (including dialysis)			
Grade IV-b:	multi organ dysfunction			
Grade V:	Death of a patient		**Grade V:**	Same as for Full Scale
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.			

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.

Dindo D., Demartines N., Clavien P.A.; Ann Surg. 2004; 244: 931-937

Appendix D: Examples of Grading Using Clavien-Dindo Classification

Grades	Organ System	Examples
Grade I	Cardiac	Atrial fibrillation converting after correction of K^+-level
	Respiratory	Atelectasis requiring physiotherapy
	Neurological	Transient confusion not requiring therapy
	Gastrointestinal	Noninfectious diarrhea
	Renal	Transient elevation of serum creatinine
	Other	Wound infection treated by opening of the wound at the bedside
Grade II	Cardiac	Tachyarrhythmia requiring β-receptor antagonists for heart rate control
	Respiratory	Pneumonia treated with antibiotics on the ward
	Neurological	TIA requiring treatment with anticoagulants
	Gastrointestinal	Infectious diarrhea requiring antibiotics
	Renal	Urinary tract infection requiring antibiotics
	Other	Same as for I but followed by treatment with antibiotics because of additional phlegmonous infection
Grade IIIa	Cardiac	Bradyarrhythmia requiring pacemaker implantation in local anesthesia
	Neurological	See grade IV
	Gastrointestinal	Biloma after liver resection requiring percutaneous drainage
	Renal	Stenosis of the ureter after kidney transplantation treated by stenting
	Other	Closure of dehiscent noninfected wound in the OR under local anesthesia
Grade IIIb	Cardiac	Cardiac temponade after thoracic surgery requiring fenestration
	Respiratory	Bronchopleural fistulas after thoracic surgery requiring surgical closure
	Neurological	See grade IV
	Gastrointestinal	Anastomotic leakage after descendorectostomy requiring relaparotomy
	Renal	Stenosis of the ureter after kidney transplantation treated by surgery
	Other	Wound infection leading to eventration of small bowel
Grade IVa	Cardiac	Heart failure leading to low-output syndrome
	Respiratory	Lung failure requiring intubation
	Neurological	Ischemic stroke/brain hemorrhage
	Gastrointestinal	Necrotizing pancreatitis
	Renal	Renal insufficiency requiring dialysis
Grade IVb	Cardiac	Same as for IVa but in combination with renal failure
	Respiratory	Same as for IVa but in combination with renal failure
	Gastrointestinal	Same as for IVa but in combination with hemodynamic instability
	Neurological	Ischemic stroke/brain hemorrhage with respiratory failure
	Renal	Same as for IVa but in combination with hemodynamic instability
Suffix "d"	Cardiac	Cardiac insufficiency after myocardial infarction (IVa–d)
	Respiratory	Dyspnea after pneumonectomy for severe bleeding after chest tube placement (IIIb–d)
	Gastrointestinal	Residual fecal incontinence after abscess following descendorectostomy with surgical evacuation. (IIIb–d)
	Neurological	Stroke with sensorimotor hemisyndrome (IVa–d)
	Renal	Residual renal insufficiency after sepsis with multiorgan dysfunction (IVb–d)
	Other	Hoarseness after thyroid surgery (I–d)

TIA, transient ischemic attack; OR, operating room.

Appendix E: Wound Healing Assessment - GTSD Training Manual- Pages 246-248

General Thoracic Surgery Database

V2.41 Training Manual

September 4, 2020

Diagnosis of empyema should be confirmed by thoracentesis or drain placement: frank pus or cloudy fluid may be aspirated from the pleural space. The fluid typically has leukocytosis, low pH (<7.2), low glucose (<60 mg/dl) high LDH, elevated protein and may contain infectious organisms.

Every empyema is an organ space infection. It is not necessary to capture both empyema and SSI. Capture empyema as it is more specific than SSI.

ParentLongName: Postoperative Events Occurred
ParentShortName: POEvents
ParentValue: = "Yes"
ParentHarvestCodes: 1

Harvest Codes:

Code:	Value:
1	Yes
2	No

SeqNo: 3740
Long Name: Surgical Site Infection
Short Name: SurgSiteInfect
Definition: Indicate the extent of surgical site infection if one was present within 30 days of surgery.

Intent/Clarification:

Surgical Site Infection (SSI)

Superficial incisional SSI
Must meet the following criteria:
Date of event for infection occurs within 30 days after any NHSN operative procedure (where day 1 = the procedure date) AND involves only skin and subcutaneous tissue of the incision AND patient has at least *one* of the following:

a. purulent drainage from the superficial incision.
b. organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST).
c. superficial incision that is deliberately opened by a surgeon, attending physician** or other designee and culture or non-culture based testing is not performed. AND patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat.
d. diagnosis of a superficial incisional SSI by the surgeon or attending physician** or other designee.

There are two specific types of superficial incisional SSIs:

1. Superficial Incisional Primary (SIP) – a superficial incisional SSI that is identified in the primary incision in a patient that has had an operation with one or more incisions (for example, C-section incision or chest incision for CBGB)
2. Superficial Incisional Secondary (SIS) – a superficial incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (for example, donor site incision for CBGB)

246 | Page

General Thoracic Surgery Database
V2.41 Training Manual
September 4, 2020

An infected burn wound is classified as BURN and is not an SSI.

Deep incisional SSI
Must meet the following criteria:
The date of event for infection occurs within 30 days after the NHSN operative procedure (where day 1 = the procedure date) AND involves deep soft tissues of the incision (for example, fascial and muscle layers) AND patient has at least *one* of the following:

a. purulent drainage from the deep incision.
b. a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, attending physician** or other designee AND organism is identified by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST) or culture or non-culture based microbiologic testing method is not performed AND patient has at least *one* of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture or non-culture based test that has a negative finding does not meet this criterion.
c. an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

There are two specific types of deep incisional SSIs:

1. Deep Incisional Primary (DIP) – a deep incisional SSI that is identified in a primary incision in a patient that has had an operation with one or more incisions (for example, C-section incision or chest incision for CBGB)
2. Deep Incisional Secondary (DIS) – a deep incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (for example, donor site incision for CBGB)

Organ/Space SSI
Must meet the following criteria:
Date of event for infection occurs within 30 days after operative procedure (where day 1 = the procedure date) AND infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure AND patient has at least *one* of the following:

1. purulent drainage from a drain that is placed into the organ/space(for example, closed suction drainage system, open drain, T-tube drain, CT guided drainage)
2. organisms are identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST).
3. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection. AND meets at least *one* criterion for a specific organ/space infection of Mediastinitis (see below).

MED-Mediastinitis
Mediastinitis must meet at least *one* of the following criteria:

1. Patient has organism(s) identified from mediastinal tissue or fluid by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment, for example, not Active Surveillance Culture/Testing (ASC/AST)
2. Patient has evidence of mediastinitis on gross anatomic or histopathologic exam.
3. Patient has at least *one* of the following signs or symptoms: fever (>38.0°C), chest pain*, or sternal instability*

And at least *one* of the following:

247 | Page

- purulent drainage from mediastinal area
- mediastinal widening on imaging test

Patient ≤1 year of age has at least *one* of the following signs or symptoms: fever (>38.0°C), hypothermia (<36.0°C), apnea*, bradycardia*, or sternal instability* **And at least *one* of the following:**

- purulent drainage from mediastinal area
- mediastinal widening on imaging test

* *With no other recognized cause*

The mediastinal space is the area under the sternum and in front of the vertebral column, containing the heart and its large vessels, trachea, esophagus, thymus, lymph nodes, and other structures and tissues. It is divided into anterior, middle, posterior, and superior regions.

Report mediastinitis (MED) following cardiac surgery that is accompanied by osteomyelitis as SSI-MED rather than SSI-BONE.

CDC, Surgical Site Infection (SSI) Event, January 2018,
https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf

ParentLongName: Postoperative Events Occurred
ParentShortName: POEvents
ParentValue: = "Yes"
ParentHarvestCodes: 1

Harvest Codes:

Code:	Value:
1	None
2	Superficial
3	Deep
4	Organ space

SeqNo: 3750
Long Name: Sepsis
Short Name: Sepsis
Definition: Indicate whether the patient experienced sepsis (septicemia) requiring positive blood cultures in the postoperative period.

Intent/Clarification: Sepsis is defined as evidence of serious infection accompanied by a deleterious systemic response. In the time period of the first 48 postoperative or post procedural hours, the diagnosis of sepsis requires the presence of a Systemic Inflammatory Response Syndrome (SIRS) resulting from a proven infection (such as bacteremia, fungemia or urinary tract infection). In the time period after the first 48 postoperative or post procedural hours, sepsis may be diagnosed by the presence of a SIRS resulting from suspected or proven infection. During the first 48 hours, a SIRS may result from the stress associated with surgery and/or cardiopulmonary bypass. Thus, the clinical criteria for sepsis during this time period should be more stringent. A systemic inflammatory response syndrome (SIRS) is present when at least two of the following criteria are

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