Phase II Study of Autologous Lymphocyte Infusions After Radiation Therapy to Mitigate Radiation Induced Lymphopenia and Enhance Immune Reconstitution in Patients with Solid Tumor Malignancies

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Protocol Body

1.0 Objectives

The purpose of this study is to determine the safety and preliminary efficacy of un-manipulated autologous lymphocyte infusion (ALI) using the patient's own lymphocytes collected using apheresis, and infused after the completion of radiation/chemoradiation.

Primary Objective

To investigate the preliminary efficacy of autologous lymphocyte infusion (ALI) in improving the absolute lymphocyte counts in lung and esophageal cancer patients who had undergone chemo-radiation (CRT).

Secondary Objectives

1. To evaluate the feasibility and safety of ALI in patients who had undergone chemo-radiation.
2. To identify lymphocyte clonal populations in the tissue that are specific for tumor cells
3. To identify immune reconstitution in the peripheral blood shaped by ALI.
4. To conduct clonal analysis using T-cell receptor (TCR) sequencing from tumor and from peripheral blood.

2.0 Background

2.1 Background and Rationale

Lymphocytes transiting through or residing within tumors play a key role in protecting the host and sculpting emerging tumors in a dynamic interplay between recognizing tumor-associated antigens to eliminate tumor cells, while avoiding tumor evasion mechanisms that can lead to lymphocyte dysfunction. Several clinical studies have highlighted the positive prognostic value of both CD8+ tumor-infiltrating lymphocytes (TILs) and circulating lymphocytes in solid tumors. Ample evidence indicates that radiation-induced lymphopenia (RIL), caused by irradiation of circulating lymphocytes in the blood and primary and secondary lymphoid organs, which leads to immunosuppression, is a common, although often ignored, side effect of standard radiation therapy (RT). RIL is observed irrespective of the admisnistation of concurrent chemotherapy.[1] This toxicity results from the high radiosensitivity of lymphocytes (LD_{50} <2 Gy).[2,3] In the most sophisticated conventional photon therapy techniques (intensity-modulated radiation therapy [IMRT] and its newer form, volumetric modulated arc therapy [VMAT]), a large volume of tissue receives low and intermediate radiation doses, and lymphocytes residing in or trafficking through this low-dose "bath" can be severely affected. Most clinical series report an incidence of 30-90% of high grade RIL (grade 3 ≤500 cells/μL, grade 4 ≤200 cells/μL), meaning that for a significant portion of patients, the depth of lymphopenia reaches to below CD4 counts of <200, which is the functional definition of acquired immunodeficiency syndrome

(AIDS). It is remarkable that this is not a transient event that is only seen during RT, but is an effect that is persists for months to at least up to one year after completing RT, with only a partial recovery in lymphocyte counts.[4,5] It is also well known that high-grade RIL is associated with poorer overall survival,[6-11] disease recurrence,[12,13] distant metastasis,[14] and reduced pathologic complete response (pCR) rates.[15] These effects occur consistently in numerous tumor types, including gliomas, breast, pancreatic, lung, esophageal, hepatocellular malignancies, head and neck, cervical and bladder cancers.[11,16-23] This is particularly significant in lung cancers, since it is now standard therapy for patients to receive immune checkpoint inhibitors as part of routine cancer therapy. For locally advanced unresectable non-small cell lung cancer (NSCLC), patients receive a potentially curative regimen of 6 weeks of chemotherapy and radiotherapy, which is then followed by 1 year of durvalumab, an anti-PD-L1 agent shown to improve overall survival compared to placebo in the PACIFIC trial.[24] We do know that NSCLC patients who complete chemo-radiation therapy (CRT) have >50% incidence of grade 3 or greater RIL, which has a poor prognosis. Since no data is available on the extent of RIL on the PACIFIC trial, the relationship to the severity of RIL on the efficacy of durvalumab given during the consolidation phase is completely unknown.

Our long-term objectives are to counteract the effects of severe RIL in order to improve therapy response and cancer outcomes. *Our central hypotheses is that RIL affects not only the quantity, but, more importantly, the quality of lymphocytes, which can be restored through ALI.* The rationale of the current project, which lay the groundwork to achieve our long-term objectives, is to determine if immune reconstitution using ALI can restore the lymphocytes needed for tumor immunity reconstitution.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Histologically or cytologically documented NSCLC or esophageal cancers
3.1.2 Stage II-IVA disease where definitive chemoradiation is the standard of care
3.1.3 Age ≥ 18

3.2 Exclusion Criteria

3.2.1 Prior radiotherapy to the chest
3.2.2 Life expectancy<6 months
3.2.3 Any systemic therapy, aside from standard of care immunotherapy, that is planned to be administered prior to 6 weeks after ALI.
3.2.4 Pregnancy

The informed consent process will begin at recognition of potential subject eligibility and consent will be obtained per institutional practices before study therapy is initiated. Patients will be assessed by the medical team for decision-making capacity. This means the ability to understand and appreciate the nature and consequences of a decision regarding medical treatment and the ability to reach an informed decision in the matter. Signing the informed consent does not mean the patient is

eligible.

This protocol will follow the SOP 04_Informed Consent Process. SOP 04 has been read by the research staff and investigators.

4.0 Evaluation During Study

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule and occasional missed required research samples. Missed samples for correlative studies will not constitute protocol deviations.

4.1 Pre-Apheresis Patient Evaluations

Studies listed below will be done prior to start treatment only if these were not done before study entry either as part of diagnostic or routine workup.

4.2 Within 30 days of study enrollment

- History and Physical examination
- CBC with diff, chemistry (Na, K, chloride, CO2, BUN, creatinine, glucose, calcium, magnesium, phosphorus), Hepatic function panel (ALT, AST, bilirubin, albumin, total protein, prealbumin), LDH,
- Chest X-ray. If CT/PET or CT scans of neck or chest have been done, a chest x-ray is not necessary.
- Urine analysis
- Pregnancy test (urine)

4.3 Evaluation prior to apheresis and prior to ALI

- Complete History and Physical Examination: To include performance status assessment, recent weight loss, and respiratory examination.
- Laboratory tests to include complete blood count (CBC) with differential and comprehensive metabolic panel. Donor infectious disease panel only prior to Apheresis.
- Research Labs: 5 to 20 mL of peripheral blood for studying immune reconstitution.
- Urine analysis

4.4 Evaluations weeks 3 (+/- 14 days) and week 6 (+/- 14 days) after cell infusion

a. Physical examination including weight and vital signs.
b. CBC w/diff and platelets, chemistry panel.

c. AE assessment.
d. Research Labs: 5 to 20 mL of peripheral blood for studying immune reconstitution.

Table 1. Table of Evaluations

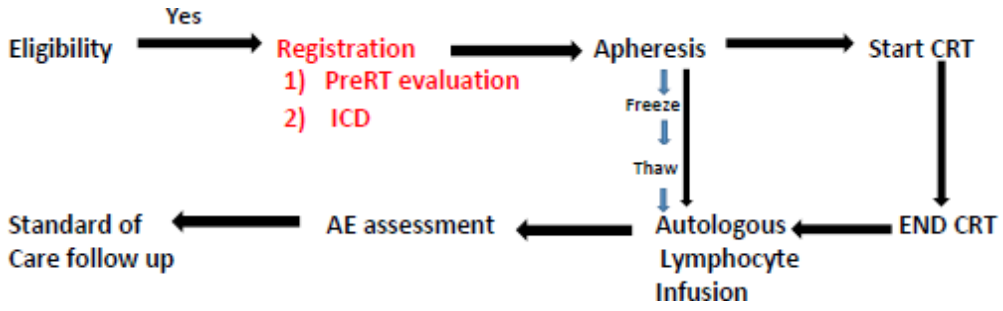
	Pre-apheresis	Day 0	Day 3	Week 3	Week 6
History & Physical	x	x		x	x
CBC; *Chem, Hepatic functional, and; LDH;	x	x		x	x
Donor infectious disease panel	x				
**Research Labs: immune reconstitution, phenotype, function (optional)	x	x		x	x
Pregnancy Test	x				
Urinalysis	x	x			
AE assessment		x	x	x	x

-Time frame windows: Pre-assessment is done within 30 days of starting standard of care lymphodepleting chemotherapy/XRT, as part of the standard of care for treatment of the aforementioned malignancies. **Day 0 indicates day of ALI infusion (+/- 3 days); Day 3 (+/- 3 days); weeks 3 and 6** (+/- 14 days) indicate 3 and 6 weeks after ALI.

*Chem Panel – CBC with diff, chemistry (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium, magnesium, phosphorus), Hepatic functional panel (ALT AST, bilirubin, , albumin, total protein, prealbumin),
**Research labs would be a part of LAB99-062 and/or LAB09-0307, if patient consents.

5.0 Trial Procedures

Trial Schematic:



5.1 Radiation therapy will be administered as per standard of care for the management of locally advanced stage II-IVA NSCLC or esophageal cancers. There are no specific guidelines for the delivery of radiation, as long as it is considered definitive management of the disease using chemoradiation therapy.

5.2 All patients will be treated with standard of care concurrent chemotherapy with radiotherapy according to the discretion of the treating medical oncologist.

Consolidation immunotherapy is typically recommended after completing chemoradiation for 1 year, but that will also be to the recommendation and discretion of the medical oncologist.

5.3 SOC Autologous lymphocyte collection

Autologous lymphocyte collection will be standard of care. Patients will sign a separate Apheresis consent.

5.4 Autologous Lymphocyte Infusion

Within three days of completing the last dose of radiation therapy, the patient will have an appointment scheduled in the Apheresis Unit for the infusion of unmanipulated cryopreserved cells. Patients will be pre medicated with acetaminophen (325-650 mg PO) and diphenhydramine (12.5-25 mg PO or IV) prior to infusion. Cells will be infused without a leukoreduction filter at a rate determined by cell volume.

5.5 Translational study

Since major secondary objectives include the assessment of lymphocyte clonality, patients are encouraged to co-enroll to MD Anderson protocol LAB99-062, an IRB-approved protocol that consents patients being treated with cellular therapy for blood draws at specified time points.

6.0 Post-treatment

6.1 Day 3 (+/- 3 days)

a. AE assessment

6.2 Week 3 (+/- 14 days) and week 6 (+/- 14 days) after cell infusion

a. Physical examination including weight and vital signs.
b. CBC w/diff and platelets, chemistry panel.
c. Research Labs: 5 to 20 mL of peripheral blood for studying immune reconstitution.

7.0 Criteria for Removal/replace from the Study

a. Patient withdrawal of the informed consent/authorization or refusal to continue on study
b. Inability to collect cell dose or receive cell infusion
c. Death
d. Since the primary variable of absolute lymphocyte counts (ALC) will be measured at baseline before CRT starts and at week 6 (+/-14 days) post-CRT, patients will be replaced if the above events occur and result in missed measures of ALC at one of the two time points.
e. Difficult venous access requiring central access for apheresis (assessed by Thoracic

center).

8.0 Radiation Therapy

8.1 Radiation therapy will be administered as per standard of care for the management of locally advanced stage II-IVA NSCLC or esophageal cancer. There are no specific guidelines for the delivery of radiation, as long as it is considered definitive management of the disease using chemoradiation therapy. Patients will sign a separate consent for radiation.

9.0 Study Design/Statistical Considerations

Standard of care has shown that autologous lymphocytes and stem cell products using apheresis of patients own blood products are feasible and safe. In this study, our primary objective is to investigate the preliminary efficacy of autologous lymphocyte infusion (ALI) in improving the lymphocyte counts in lung and esophageal cancer patients after chemo-radiation therapy. This is an open-label Phase II one-arm study.

Sample size justification
Absolute Lymphocyte counts (ALC) will be measured at baseline before CRT starts and at week 6 (+/-14 days) post-CRT. The primary outcome is the change between the two measures, i.e., absolute lymphocyte counts at week 6 (+/- 14 days) minus baseline ALC, referred as ALC change. Recently, we reviewed 755 patients with stage I-III esophageal carcinoma who received concurrent CRT with or without surgery in 2004–2015 [1]. The means of the absolute lymphocyte counts were 1,570 cells/μL (SD=610) and 980 cells/μL (SD=600) at based line and at the first follow-up visit post-CRT, respectively. We incorporate this clinical evidence in our sample size justification.

Assume the mean of the ALC change is -590 cells/μL for historically treated patients without ALI. Using one-sided one sample t-test, a sample size of 20 patients will provide 80% power at the 0.1 significance level (alpha) to detect a difference of ALC change between ALI treated and historical patients of 290 cells/μL, with an estimated standard deviation of the ALC change of 600 (PASS version 13).

Analysis Populations
Efficacy evaluable population - Patients who undergo ALI and have complete measures of ALC at baseline before CRT starts and at week 6 (+/-14 days) post-CRT.

Safety population - All patients who undergo ALI will be included in the analysis for safety. We plan to enroll 20 patients.

Statistical Analysis Plan
Demographic/clinical characteristics **and safety** data will be summarized using descriptive statistics such as frequencies and percentages, means, standard deviations, medians and ranges.

The number of patients who fail to complete the planned ALI treatment (i.e., inability to collect cell dose or receive cell infusion), will be counted and used as the summary of feasibility for this study. We will evaluate the feasibility of this study for future research and, it will be considered as feasible if less than 5 patients fail planned ALI treatment, while it will be stopped if 10 or more patients fail the planned ALI treatment during any time of the trial. The primary outcome of ALC will be summarized by means and standard deviations along with box-and-whisker plots. One-sided one sample t-test will be used to compare ALC change between this study and historical data. The lymphocyte reconstitution rate (achieving ALC ≥ 1.00 K/uL) at 42 days will be estimated along with the 95% confidence intervals. If numbers permit, box-and-whisker plots will be used to explore possible associations between covariate of interest and ALC measured at different time points. Regression models will be also applied to explore possible associations between immune reconstitution rate, ALC and covariates of interests. Additional analyses may be further performed if deemed appropriate. If the trial is stopped early due to feasibility, data will be summarized as planned, while no comparison will be made to historical data.

Toxicity Monitoring.
Toxicity will be defined as adverse events related to cell infusion within 42 days of ALI.

AEs related to the ALI:
1. These expected events will be monitored at approximately 30 minutes and 60 minutes post infusion: Fever, Chills, Decrease in blood pressure, Rash, Shortness of breath. These events will not be considered as adverse events, and will not be used for toxicity monitoring.
2. Unexpected Toxicities within 42 days of the study cell infusion:
    - Grades 3-5 allergic reactions related to the ALI
    - Grade 3-5 organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) not pre-existing or due to the underlying malignancy or due to chemoradiation therapy
    - Treatment-related death

The unexpected toxicities will be considered as adverse events, and will be used for toxicity monitoring.

The method of Thall, Simon and Estey (1995) will be used for toxicity monitoring for this study. Denote the probability of toxicity by PT. We assume a priori, PT ~ beta (0.2, 1.8). We will stop the arm if Pr(PT> 0.1 | data)>0.80. That is, we will stop the arm for new patient enrollment if at any time during the study, we determine that there is more than 80% chance that the toxicity rate is more than 10%. This toxicity stopping rule will be applied starting from the **10th** patient. Stopping boundaries corresponding to this stopping rule are presented in Table 2. The operating characteristics are summarized in Table 3. These boundaries and characteristics are generated using the in-house R Shiny application available at: http://qctrlshiny/postprobtoxicity/.

Table 2. Early stopping boundaries for toxicity monitoring

# of patients	Stop the arm if there are this many patients with unexpected toxicities:
10	3-10
15	3-15
20	Always stop

Table 3. Operating characteristics for toxicity monitoring

True toxicity rate	Prob(stop early)	Average sample size
0.05	0.037	19.8
0.10	0.183	18.7
0.15	0.390	17.2
0.20	0.601	15.4
0.30	0.872	12.5

10.0 Protocol Monitoring

The PI Gheath Al-Atrash and Co-Chair Steven Lin are monitoring the day-to-day implementation and performance of this study, i.e., good clinical practice.

Data Monitoring Committee:

This study will be monitored by MD Anderson's Data Safety Monitoring Committee.

11.0 Adverse Events (AE) Assessment, Collection and Reporting Requirements

Definitions
Active Treatment
For the purpose of this study, the investigational component of the treatment plan is the infusion of autologous lymphocytes.

Active treatment period
From the infusion of the autologous lymphocytes up to 3 days after the infusion.

Follow-up period
Is defined from 3 days from the autologous lymphocyte infusion until 42 days post infusion.

Definition of adverse events
An Adverse Event is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study therapy.

Serious adverse events must be followed until clinical recovery and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event. Additionally, any serious adverse events occurring after the 30 day time period that are related to the study treatment must be reported to the IRB. Hospitalizations for treatment of disease, or related to complications from treatment administered prior to the infusion of cells will not be captured.

Data Collection
Collection of adverse events (AEs) will begin at the time of apheresis to start of radiation and from ALI through week 6 and will reflect the onset and resolution date and maximum grade. If a patient is taken off study while an event is still ongoing, this will be followed until resolution unless another therapy is initiated. Additionally, patients may be on multiple concurrent medications that are not necessarily related to the ALI. These medications are considered standard of care and have no scientific contributions to the protocol, therefore concurrent medications will not be captured.

Assessment of Adverse Events Severity
All grades of AEs related to ALI will be collected. Adverse events unrelated to the ALI will not be collected. Events not included in the CTCAE 5.0 will be scored as follows:

General grading:
Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
Grade 4: Life Threatening: discomfort that represents immediate risk of death

Causality Assessment
The investigational component of the treatment plan of this study is the infusion of cells after chemoradiation therapy. Therefore, events known to be caused by the cell infusion and its direct consequences will be assessed as <u>definitely related</u> when assessing the causality. When the relationship of the adverse event cannot be rule out between the cells and the chemoradiation therapy, the event will be scored as <u>probably or possible related</u>. Events known to be related to

drugs used as chemotherapy as well as to drugs used as supportive treatment will be scored as unrelated to the cell infusion.
The principal investigator will be the final arbiter in determining the causality assessment.

Abnormal Laboratory Findings
For the purpose of this study, abnormal laboratory findings considered associated to the original disease as well as isolated changes in laboratory parameters such as electrolyte magnesium and metabolic imbalances, uric acid changes, elevations of GPT, GOT, LDH, alkaline phosphatase, and CBC would not be considered adverse events and will not be collected in the database.

Serious Adverse Event Reporting (SAE)
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

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

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

12.0 Data Security/Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigator, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency, as applicable.

All research activities will be conducted in as private a setting as possible.

Access to Study Records
Study records may be accessed by IRB approved study personnel, or authorized inspectors. The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the

Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Methods of Storage of Study Records

All data collected from MD Anderson Cancer Center (MDACC) sources will be maintained on a password protected server compliant with HIPAA. Study staff will have role based restricted access to directories and files on the server, according to project responsibilities. Only those with data entry permissions can add records. The PI or a delegate will review the conditions under which data will be released to recipient- investigators. Each application for use will need IRB approval and consents, if appropriate. The level of identifiability will determine the process for review and approval as well as the way information is shared.

Any study data or records maintained in paper documents will be stored in the offices of the PI or other delegated study staff, in a locked cabinet or other comparable controlled environment, and will be accessible only to authorized study team members or authorized inspectors.

Duration of Study Record Storage

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Sharing of Study Records

There are no plans to share study data with entities external to MD Anderson Cancer Center, aside from authorized inspectors as applicable (i.e. authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product). If data will be shared, IRB approval will be sought, and applicable inter-institutional agreements executed, prior to data sharing.

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