Leucoselect Phytosome for Neoadjuvant Treatment of Early Stage Lung Cancer

NCT04515004

March 5, 2024

Human Protocol (Version 1.10)

General Information

***Please enter the full title of your study::**

Leucoselect Phytosome for Neoadjuvant Treatment of Early Stage Lung Cancer

***Please enter the Study Number you would like to use to reference the study:**

GSE-LP Pre-op for lung cancer
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

Add departments

and Specify Research Location:

Is Primary?	Department Name
◉	**VASDHS** - VASDHS

Assign key study personnel(KSP) access to the study

***Please add a Principal Investigator for the study:**

Mao, Jenny T., MD, FCCP

3.1 If applicable, please select the Research Staff personnel

A) Additional Investigators

Jih, Lily Jalu, MD
Co-Investigator

B) Research Support Staff

Collin, Lauren M.
Study Coordinator
Inouye, Kaili
Research Associate
Oliva, Diego, BS
Research Associate
Wei, Hongbing Heather
Technician

***Please add a Study Contact**

Collin, Lauren M.
Inouye, Kaili
Mao, Jenny T., MD, FCCP

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

VASDHS IRB
Human Subjects Protocol
v20190121

Section 1 - Preliminaries

Principal Investigator:

Jenny T. Mao, MD, FCCP

Protocol Title:

Leucoselect Phytosome for Neoadjuvant Treatment of Early Stage Lung Cancer

IRB Protocol Number:

H220087

Protocol Nickname:

GSE-LP Pre-op for lung cancer

Form Template Version:

v20150115

Date Prepared:

03/05/2024

Please be advised that this protocol application form has changed as a result of the 2018 Common Rule. There are new questions and sections, and you may be required to provide additional information to previous sections.

1a) Is this study considered human research?

- (●) Yes
- ( ) No
- ( ) I don't know

1b) Please select:

- (●) This is an application for a NEW human subject research protocol
- ( ) This is a revision of an existing protocol

Section 2 - Research Subjects

2a) What is the total planned number of VA-consented subjects?

Include the total number of subjects who will prospectively agree to participate in the study (e.g., documented consent, oral consent, or other).

100

2b) What is the total number of VA subjects who WILL NOT be consented?

Include the total number of subjects that will be included without consent (e.g., chart review). *Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still should enter the number of charts as your "planned subjects."*

0

Section 2.1 Consented Subject Groups

2.1) For each of the subject categories listed below, indicate whether or not these subject groups will participate in the study:

2.1a) Children under the age of 18
Note: If neonates or children will be involved in this study, certification by the Medical Center Director will be required. Only minimal risk research may be performed with children. Only non-invasive monitoring and/or prospective observational and retrospective record review studies that are minimal risk can be conducted in VA involving neonates.

○ Yes ◉ No

2.1b) Pregnant women

○ Yes ◉ No

2.1c) Individuals with cognitive/decisional impairment

○ Yes ◉ No

2.1d) Non-English-speaking individuals

○ Yes ◉ No

2.1e) Prisoners of War (explicitly targeting this group)

○ Yes ◉ No

2.1f) Non-Veterans (Note: Justification for inclusion of non-Veterans will be required)

○ Yes ◉ No

2.1g) Incarcerated individuals (Note: VA CRADO approval will be required)

○ Yes ◉ No

2.1h) VA employees - including VA paid, IPA, or WOC (Note: Union review and authorization may be required)

○ Yes ◉ No

2.1i) Students of the institution (e.g., resident trainees) or of the investigator

○ Yes ◉ No

2.1j) Patients with cancer (or high cancer risk) [explicitly targeting this group]

◉ Yes ○ No

Section 3 - Study Features (these items default to "No" for convenience)

3) This section consists of several Yes/No questions addressing protocol characteristics. Click on *Save and Continue*.

Section 3.1 Protocol Basics

Select all that apply

3.1a) The research **intends to change** the participant.

(•) Yes ( ) No

3.1b) **Interactions** with living participants to collect data or specimens with no intent to change them.

( ) Yes (•) No

3.1c) This is a study that **never** has any **subject contact and does not collect subject identifiers**

( ) Yes (•) No

3.1d) This is a **chart review** study involving retrospective or prospective medical records.

( ) Yes (•) No

3.1e) This is a **multi-site** study occurring in-part or in-full at other locations.

( ) Yes (•) No

3.1f) There is an **international** component to this research. *International research includes sending or receiving human derived data or specimens (identifiable, limited data set, coded, or deidentified) to or from an international source. International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator.*

( ) Yes (•) No

3.1g) This study includes **off-station activity** (not including VA-leased space or CBOC clinics) conducted under VASDHS IRB approval. *Note: this does not include research conducted by a collaborator at their home institution under their institutional approval.*

( ) Yes (•) No

3.1h) VA subjects will **participate** in part or in full **at other locations** (not including VA-leased space or clinics) under VASDHS IRB approval. *Note: if this study involves remote participation of subjects, please indicate "no" and describe their remote participation in section 9 of the application. This question is intended to understand whether participants must physically go to a non-VA location to participate in this VA research study.*

( ) Yes (•) No

Section 3.2 Specimen Use and Data Repository

Indicate whether or not each of the following applies to this protocol

3.2a) Involves specimens that are left over from pathological or diagnostic testing (**non-research specimens**)

(•) Yes ( ) No

3.2b) Involves **specimens collected for research** purposes **only**

(•) Yes ( ) No

3.2c) This study includes **specimen banking** (specimens are retained for use outside of the purposes of this protocol)

(•) Yes ( ) No

3.2d) The study involves **DNA** genotyping or other **genetic analysis**

(•) Yes ( ) No

Does this include whole genome sequencing?

( ) Yes (•) No

Will participants be informed of the results of any DNA testing?

○ Yes ◉ No

3.2e) Biological **specimens/material** will be sent outside of the VA.

○ Yes ◉ No

3.2f) A **data repository** is maintained (data are retained after completion of the protocol for other uses, IMPORTANT: see **?** before checking "yes")

◉ Yes ○ No

3.2g) **Data will be shared outside** of the VA (identifiable, coded, limited data set, or deidentified)

○ Yes ◉ No

Section 3.3 Treatment and Clinical Trials

Indicate whether or not each of the following applies to this protocol

3.3a) Includes a **treatment** component (a research treatment)

◉ Yes ○ No

3.3b) Study is a **clinical trial.** *Note: A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.*

◉ Yes ○ No

3.3c) Has a data safety monitoring board (**DSMB)** or data safety monitoring committee.

◉ Yes ○ No

3.3d) Has a **data safety monitoring plan** (but not a DSMB) (this is not the data security plan, it is a safety plan).

○ Yes ◉ No

Section 3.4 Drugs and Devices

Indicate whether or not each of the following applies to this protocol

3.4a) **Drugs** that require **FDA** action such as an Investigational New Drug (IND) approval or exemption or 510 (k) approval.

◉ Yes ○ No

3.4b) Other drugs, supplement, etc. that **do not require FDA** action for inclusion in the study.

○ Yes ◉ No

3.4c) Medical **devices requiring FDA** IDE approval or waiver

○ Yes ◉ No

3.4d) **Other** medical **devices**

○ Yes ◉ No

Section 3.5 Risk and Hazards

Indicate whether or not each of the following applies to this protocol

3.5a) Study places subjects at **greater than minimal risk** (do not include risks that are due to standard care)

(●) Yes ( ) No

3.5b) Human subjects are exposed to **radioisotopes** (do not include standard care).

( ) Yes (●) No

3.5c) Subjects have other **radiation exposure** (e.g., x-rays) (do not include standard clinical use).

( ) Yes (●) No

3.5d) Target population has psychiatric diagnosis, behavioral complaint, or chronic pain.

( ) Yes (●) No

Section 3.6 Clinical Facilities and Standard Care

Indicate whether or not each of the following applies to this protocol

3.6a) Study **uses VA clinical services** (e.g., adds required tests run in the VA lab for study purposes; research procedures concurrent with clinical care)

(●) Yes ( ) No

3.6b) Includes procedures or drugs that will be considered **part of standard care.**

(●) Yes ( ) No

3.6c) Involves **lab tests done for research** purposes.

(●) Yes ( ) No

Section 3.7 Subject Expenses and Compensation

Indicate whether or not each of the following applies to this protocol

3.7a) There may be expense or added **costs to the subject** or the subject's insurance.

( ) Yes (●) No

3.7b) This is a **qualifying cancer treatment trial** and subjects may be billed for study drugs or procedures.

( ) Yes (●) No

3.7c) This is a cancer treatment trial but **subjects will not be billed** for study drugs or procedures.

(●) Yes ( ) No

3.7d) Subjects will be **compensated** (either in cash or other means such as a gift certificate).

( ) Yes (●) No

Section 3.8 Subject Activities

Indicate whether or not each of the following applies to this protocol

3.8a) Involves **surveys or questionnaires** completed by subjects

(●) Yes ( ) No

3.8b) Includes the use of **recruitment materials** such as flyers, advertisements, or letters

(●) Yes ( ) No

3.8c) Involves facial **photographs** or audio or video **recordings** of **patients**

○ Yes ◉ No

Section 3.9 Sponsors and Collaboration

Indicate whether or not each of the following applies to this protocol

3.9a) This research is a funded research project **(commercial (industry) sponsor, NIH, VA, other).**

◉ Yes ○ No

3.9b) Other **commercial (industry) non-financial support** is provided (e.g., drugs or supplies).

◉ Yes ○ No

3.9d) The protocol has **Department of Defense** involvement (e.g., subjects or funding).

○ Yes ◉ No

3.9c) The PI or other study staff member has a financial interest or other **real or potential conflict** related to this study.

○ Yes ◉ No

3.9e) This study involves **collaborative** research activities (research conducted at other institutions under the authorities or approvals of the other institution/s). *Note: this may include other VA and/or non-VA institutions, but does not include off-site VA research.*

○ Yes ◉ No

Section 4 - Estimated Duration

4) What is the estimated duration of the entire study? (From IRB approval to IRB closure)

4.25 years

Section 5 - Lay Language Summary

5) Provide a summary or synopsis of the proposed study using non-technical language (not more than 1 paragraph)

Lung cancer is the leading cause of cancer death in the country, surpassing deaths caused by colorectal, prostate and breast cancers combined. Veterans are at higher risk of lung cancer due to the higher rate of smoking and environmental toxin exposures. The lack of effective therapy for lung cancer provides the impetus to search for alternative, safe, and effective treatment agents to improve treatment strategy against lung cancer, enhance the probability of a cure and reduce recurrence. Based on encouraging preclinical and clinical findings from an early phase I lung cancer prevention study, using a special formulation of a standardized grape seed extract with enhanced absorption called leucoselect phytosome (LP), the purpose of this new CSR&D Merit Review project is to evaluate the potential usefulness of LP for pre-surgical treatment of early stage lung cancer patients in a phase IIa clinical trial. Findings from this study may set the stage for larger, confirmatory trials in the near future.

Section 6 - Specific Aims

6) Provide a statement of specific aims and hypotheses that serve as the basis for this protocol. Emphasize those aspects that justify the use of human subjects.

SPECIFIC AIMS: This project will evaluate the feasibility of leucoselect phytosome (LP), a standardized grape seed procyanidin extract (GSE) complexed with soy phospholipids to enhance

bioavailability, for lung cancer treatment. We have found that oral LP significantly inhibited human lung cancer xenograft growth, reduced bronchial Ki-67 labeling index (a marker of proliferation), favorably modulated major eicosanoids pathways, and serum micro (mi)RNA miR-19a, -19b, and -106b in heavy current/former smokers. These findings are consistent with preclinical data demonstrating the multi-faceted, antineoplastic properties of GSE, via favorable modulations of 1) major eicosanoids pathways, such as inhibitions of cyclocoxygenase (COX)-2 /prostaglandin (PG)E2, induction of prostacyclin synthase (PTGIS)/PGI2 and increase production of 15(S)-hydroxy-eicosatetraenoic acid (15-HETE); 2) downregulation of miR-19a, -19b, with upregulations of their targets - tumor suppressors insulin-like growth factor II receptor (IGF-2R) and phosphatase and tensin homolog (PTEN), resulting in the reduction of the procarcinogenic phosphorylation of AKT (P-AKT); and down-regulation of miR-106b with upregulation of its target the tumor suppressor P21 WAF1/Cip1. While GSE is widely used as a health food supplement to promote cardiovascular health, clinical evidence of its efficacy against lung cancer is lacking. We therefore hypothesize that oral LP is safe, can favorably modulate anticancer mechanisms, and be useful against lung cancer. To test these hypotheses, a pilot clinical study will be conducted to determine the safety, feasibility, pharmacokinetics (PK) and pharmacodynamics (PD) of LP as a neoadjuvant agent for stage I & II resectable lung cancer. The mechanistic effects of LP will also be assessed systematically and correlated to functional significance.

Specific Aim #1: To determine the safety, feasibility and PK/PD of 2-3 weeks of oral LP as a neoadjuvant agent in stage I/II nonsmall cell lung cancer (NSCLC) patients. A single arm, phase IIa neoadjuvant NSCLC treatment study with 2-3 weeks of LP will be conducted in 30 newly diagnosed stage I/II resectable NSCLC patients. Subjects suspected of having lung cancer will be recruited from pulmonary clinics and screened. Subjects will consent to study participation and archive of specimens for research, including blood, urine, and from diagnostic procedures, such as bronchoscopy [bronchoalveolar lavage (BAL) fluid and cells, lesion biopsies and lymph node (LN) sampling] and/or transthoracic needle aspiration (TTNA) as clinically indicated, to be used as pre-treatment samples. Qualified subjects diagnosed with resectable stage I/II NSCLC will be enrolled and treated with 2-3 weeks of 4 capsules of LP until resection. At the time of resection, serial clinical specimens, including BAL, LN, lung tumor and adjacent lung tissue, blood and urine will be collected as post-treatment samples for assessing PK/bioavailability, PD and mechanisms of action when applicable. The safety of LP will be monitored weekly with the NCI common terminology criteria for adverse events Version 5.0 and adverse reaction questionnaires. Post-op phone follow up visits will occur at 3-4 weeks, 6 months and annually for up to 4 years. Time to progression, recurrence-free survival and overall survival will be assessed.

Specific Aim #2: To determine the antineoplastic and mechanistic effects of oral LP in stage I or II lung cancer patients. The mechanistic effects of GSE against lung cancer in a neoadjuvant setting will be assessed by comparing its bioactivity pre- and post-treatment when applicable, as measured by modulations of: 1) tumor pathological response, downstaging, Ki-67 labeling index, activated caspase 3 (apoptosis marker), COX-2, PTGIS, 15-LOX, PTEN, P-AKT, IGF2R; 2) markers of inflammation and antitumor immunity: PGE2, PGI2, 15-HETE, interleukin (IL)-6, IL-10, IL-12, C reactive protein (CRP) In plasma, tumors and/or BAL; 3) cancer-relevant, pathway specific gene expression profile in BAL cells and tumors; 4) epigenetic miRNA profile in BAL cells and tumors; 5) oncomirs:miR-19a, -19b, and -106b in serum and tumors.

Specific Aim #3: To validate the roles of miR-19a, -19b, and -106b in mediating the anti-neoplastic effects of GSE and the utility of their serum levels as surrogate endpoint biomarkers (SEBM) for therapeutic monitoring.

Section 7 - Background and Significance

7) Provide a succinct discussion of relevant background information to justify performing the proposed study.

Lung cancer is the leading cause of cancer death in the world and approximately 90% of cases are attributed to tobacco smoking. It is also a major cause of cancer-related death among Veterans, due to higher rate of smoking and exposures to various environmental toxins. Despite advancements in anti-cancer treatment, the 5-year survival for lung cancer remains dismal (1-3). The lack of effective therapy provides the impetus to search for alternative, safe and efficacious agents to improve management strategy against lung cancer, enhance the probability of a cure and reduce recurrence or second primary lung cancer. This Merit Review project will conduct a phase IIa trial to determine the feasibility of Leucoselect

phytosome (LP), a standardized grape seed procyanidin extract (GSE) complexed with soy phospholipid, as an anticancer agent for neoadjuvant treatment against early stage resectable lung cancer. The information gained from this study will determine the safety, feasibility, pharmacokinetics (PK) and pharmacodynamics (PD) of LP in nonsmall cell lung cancer (NSCLC) patients and help identify potential surrogate endpoint biomarkers (SEBM) for biomonitoring and as predictors of responsiveness in future confirmatory clinical trials.

Rationale for studying the utility of LP for systemic, neoadjuvant treatment of early stage lung cancer.

Current treatment standards. On March 4, 2022, the Food and Drug Administration (FDA) approved nivolumab (Opdivo) with platinum-doublet chemotherapy for adult patients with resectable (tumor ≥ 4 cm or node positive) NSCLC in the neoadjuvant setting. Based on finding from the study CHECKMATE-816 (NCT02998528), a randomized, open label trial in patients with resectable, histologically confirmed Stage IB (≥4 cm), II, or IIIA NSCLC (AJCC/UICC staging criteria) and measurable disease (RECIST v1. 1.). Patients were enrolled regardless of the tumor PD-L1 status. A total of 358 patients were randomized to receive either nivolumab plus platinum-doublet chemotherapy administered every 3 weeks for up to 3 cycles, or platinum-chemotherapy alone administered on the same schedule. The main efficacy outcome measures were event-free survival (EFS) and pathologic complete response (pCR) by blinded independent central review. Median EFS was 31.6 months (95% CI: 30.2, not reached) in the nivolumab plus chemotherapy arm and 20.8 months (95% CI: 14.0, 26.7) for those receiving chemotherapy alone. The hazard ratio was 0.63 (97.38% CI: 0.43, 0.91; p=0. 0052). The pCR rate was 24% (95% CI: 18.0, 31.0) in the nivolumab plus chemotherapy arm and 2.2% (95% CI: 0.6, 5.6) in the chemotherapy alone arm (39).

Dismal prognosis even in early stage diseases and the needs for innovative treatment strategy. According to the International Association for the Study of Lung Cancer Staging Project, the overall 5-year survival for stage IA NSCLC is 66%, stage IB is 56%, stage IIA is 43%, stage IIB is 35%, and stage IIIA is 23% (40). In other words, although early stage I/II NSCLC patients have better survival rate, approximately 50% of these patients will not survive beyond 5 years. Peri-operative platinum-based chemotherapy is associated with a survival rate that is only about 5.4% higher than that with surgery alone, with rates of grade 3 or higher toxic effects of more than 60% (41-43). Whereas new Immunochemotherapy should improve the survival rate, there may be patients who are unable or unwilling to undergo immunochemotherapy, and the therapy is not approved for stage IA -1B (T < 4 cm) patients. Innovative treatment strategies that are both safe and efficacious are clearly needed to improve such dismal outcomes even for early stage I/II diseases.

The balancing act of risks vs. benefits in lung cancer management. In recent years, the emergence of various targeted therapeutic agents has renewed

interests in evaluating their therapeutic potential in the neoadjuvant settings for resectable lung cancer, such as epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI) (44, 45), vascular endothelial growth factor (VEGF) antagonists (46), and immune check point inhibitors (ICI), including anti-programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1). While PD-1 blockade has demonstrated exciting pathologic responses in a small trial of neoadjuvant treatment of stage I to IIIA NSCLC (43), the long term efficacy and safety in such a setting remains to be seen, especially in view of the increased recognition that ICI can cause serious or fatal immune-related adverse events, including CV toxicities associated with high rate of fatality (myositis and pericarditis, heat block, vasculitis including temporal arteritis, etc.)(47). Furthermore, checkpoint inhibitor pneumonitis (CIP) has also been described recently, and development of CIP in NSCLC worsens survival in pts receiving immunotherapy (48). Whereas EGFR TKIs are also known to be associated with significant pulmonary toxicity, which prevented further evaluation of their potential for chemoprevention of primary, as well as second primary lung cancer. The search continues for the ideal agents and treatment modalities that will favorably balance the risk vs. benefit ratio. On the basis that natural agents such as GSE, may exert anti-cancer effects while promote general well-being and CV health, systematic exploration of its utility as an anticancer agent, either alone or as an adjunct to conventional therapy is clearly warranted.

Typically, patient treated with conventional neoadjuvant therapy are allowed a period of 4-6 weeks for recovery before surgery. Based on LP's potential, multifaceted antitumor properties and favorable safety profile, we hypothesize that using it in the neoadjuvant setting may result in better control of the primary tumor and eliminate systemic micrometastasis, thereby improve the rate of success in surgical resections and overall clinical outcomes, without causing delays in the definitive surgical resection.

In addition, the neoadjuvant approach provides a unique opportunity to study the *in vivo* effects of LP on the primary-tumor microenvironment and peripheral blood, providing valuable proof of concept evidence toward the utility of LP against lung cancer, as well as discovery of prospective biomarkers of response that may facilitate identification of patients who are most likely to benefit from such an approach.

This proposal will translate and validate preclinical findings, establish safety and feasibility, and set the stage for future confirmatory lung cancer treatment trials.

Section 9 - Design and Methods

9) Describe the research design and the procedures to be used to accomplish the specific aims of the project. Provide a precise description of the planned data collection (include what systems or databases will be used/accessed to gather data), analysis and interpretation. For chart review studies, include the timeframe of collection. Address sample size, inclusion of women and minorities. Define in clear terms exactly what will be done to the human subjects.

Population: Newly diagnosed stage I and II surgically resectable lung cancer patients.

Study Design: A single arm, Phase IIa study to evaluate the potential of Leucoselect phytosome, for preoperative, neoadjuvant treatment of stage I and II lung cancer.

General Study Overview. A single arm, phase IIa neoadjuvant pilot study of 2-3 weeks of oral LP prior to lung resection will be conducted in 30 newly diagnosed stage I and II NSCLC patients (pt). Pt. suspected of having lung cancer will be referred/recruited from pulmonary clinics and screened with history and physical examination (H&P), standardized respiratory/general health questionnaires that details subjects' demographic information, smoking behavior, occupation, medical conditions, and dietary history will be obtained using a food frequency self-assessment questionnaire. Routine blood tests (CBC; Chemistry panel; PT, PTT), pulmonary function tests (PFT), chest CT and/or PET/CT scans and 12-lead EKG will already be obtained as a part of clinical work up. Subjects will refrain from the ingestion of grapes/seed related products throughout the entire treatment period. Subjects will also consent to archive of specimens for research, including blood, urine, and from diagnostic procedures [bronchoscopic or transthoracic needle aspiration (TTNA)] specimens as clinically indicated; these biospecimens will serve as baseline, pre-treatment samples.

Subjects who are diagnosed with clinical, surgically resectable stage I or II lung cancer will be enrolled and treated with 4 capsules of LP (450 mg/cap, 127 mg of OPC/cap, Indena/Thorne Research) for approximately 2 weeks (+/- 7 days) until 4-7 days prior to surgical resection. Only subjects who meet entry criteria will be enrolled. Serum cotinine and exhaled carbon monoxide (CO) will be checked at screening to confirm smoking status. Former smokers are defined as having quit smoking for >12 months. Four to 7 days prior to scheduled surgery, subject will return to study clinic for follow up, with H&P, questionnaires, take the final dose of study drug, have serial clinical blood tests and collection of blood and urine for research. At the time of surgical resection, BAL fluid and cells, lung tumor and adjacent lung tissue, will be collected *as* post-treatment samples. Post-treatment samples will be compared with pre-treatment samples to assess PK /bioavailability, PD and mechanisms of action. The BAL performed at time of surgery is solely for research purposes. For subjects with NSCLC diagnosed only by TTNA, no pre-treatment BAL will be performed, unless an additional clinical bronchoscopy is indicated based on standard of care. Once enrolled for intervention, all subjects will be monitored with weekly phone follow up, preop H&P and blood tests. The safety and side effects of oral GSE will be monitored with the NCI common terminology criteria for adverse events Version 5.0 (CTCAE v5) and adverse reaction questionnaires. Post-op phone follow up will occur at 3-4 weeks, 6 months and annually for up to 4 years.

C.2). Outcome measures.

The **primary (**1^0**) end point** is safety and feasibility (defined as delay in the planned surgery of *>14* days that is possibly related to study medication).

The **secondary** (2^0) **endpoints** will include:

1. Modulation of tumor Ki-67 (proliferation).
2. Histopathology: pathological response of resected tumor, LN, downstaging.
3. Modulations of tumor activated caspase 3 (apoptosis), COX-2, PTGIS, 15-LOX, PTEN, P-AKT, IGF2R.
4. PK: GSP/metabolites in pre- & post- treatment plasma, tumor and lung tissue.
5. The effects on markers of inflammation and immunity: PGE_2, PGI_2, 15-HETE, IL-6, IL-10, IL-12, CRP.
6. Modulation of cancer-relevant, pathway specific gene expression profile in BAL cells and tumor.
7. Epigenetic changes (miRNA profile) in BAL cells and tumor.
8. Changes of miR-19a, -19b, and -106b in serum and tumor.

- The antineoplastic mechanisms of action by GSE will be determined by comparing the above SEBM obtained before and after LP treatment when applicable. Each patient will serve as his/her own control.
- Levels of GSE/metabolites in plasma, BAL fluid, tumor/lung tissue and urine will be correlated to above SEBM.
- Respiratory, general health and quality of life questionnaires - (SF 36), will be used to assess the other potential clinical benefits of GSE.
- Time to progression, recurrence-free survival and overall survival will be determined at each post-op follow up visit and compare to historical controls matched by stage, cell type and adjuvant therapy.
- Potential impact of primary tumor somatic mutations and immune checkpoint expressions including PD-L1 on the responsiveness to LP treatment will be assessed. Our pathology department routinely profiles EGFR, ALK, c-MET, ROS1, BRAF mutations and PD-L1 expression in lung tumors.

It is expected that stage IB ($T \geq 4$ cm) - II patients will receive adjuvant therapy (chemotherapy, with or without radiation when applicable). The impact of LP neoadjuvant treatment on those participants who are treated with subsequent adjuvant therapy will also be assessed.

C.3). LP dose selection & treatment duration: The dose is based on experiences from our phase I lung cancer chemoprevention trial, showing that 4 capsules of LP is well tolerated in heavy active or ex-smokers with significant, favorable modulations of a variety of SEBM. The 2-3 weeks treatment duration is based on typical time lag from diagnosis to resection without undue delays, as well as preclinical findings, that such a treatment duration should allow detections of changes in various SEBM.

C.3.1). LP bioactivity quality assurance: With each new batch of LP, prior to dispensing, proliferative bioactivity assay will be conducted first by treatment lung neoplastic cells with LP *in vitro* as previously described (8, 34).

C.3.2). Table 1. Summary of outcome measures and follow up schedule:

Study Day	0	1	7	14-21	18-28	39-52	225	405	770	1135	1500
Visit #	**1(S)**	**2**	**3(P)**	**4**	**5**	**6(P)**	**7(P)**	**8(P)**	**9 (P)**	**10 (P)**	**11(P)**
History & Physical exam	x	x	x	x	x	x	x	x	x	x	x
Serum Chemistry	x			x							
CBC, PT, PTT	x			x							
Blood samples	x	x		x							
Serum cotinine	x										
EKG	x										
PFT	x										
Chest CT, PET/CT	x										
Bronchoscopy	x				x						
Urine	x	x		x							
Carbon Monoxide	x										
Pregnancy test*	x										
Surgical samples					x						
Questionnaires	x		x	x	x	x	x	x	x	x	x

P = phone interview. S = screening. *When applicable.

P = phone interview. S = screening. *When applicable.

C.4). Patient recruitment: Pts. will be recruited from Pulmonary & Thoracic surgery clinics. Since 2014, a weekly multidisciplinary thoracic conference, attended by pulmonologists, thoracic surgeons, and Interventional Radiologists, has been conducted to discuss management approaches for all patients at the VASDHS who have been found to have suspicious lung lesions.

Inclusion criteria:

Initial screening:

1) Age over 21.

2) Lesions suspicious for lung cancer.

3) Competent to provide consent.

4) Clinically relevant CBC values within normal limits (WNL).

5) liver function test WNL.

6) Normal Creatinine clearance as measured by the Cockcroft-Gault equation.

7) ECOG Performance status: 0-1.

Enrollment for treatment with LP:

- Histologically proven and surgically resectable clinical IA and IB (T2a < 4 cm) stage NSCLC.
- Histologically proven and surgically resectable clinical I and II stage NSCLC unable or unwilling to receive standard neoadjuvant immunochemotherapy.

Exclusion criteria:

1) Inability to provide informed consent (e.g. cognitive impairment, severe psychiatric disorders).

2) Hypersensitivity to grapes or related products.

3) Advance respiratory disease (Predicted post resection FEV_1 < 0.8 liters based on pre-resection PFT obtained at screening, resting hypoxemia, to ensure pts have adequate reserve to undergo diagnostic procedures and surgical resection).

4) Unstable angina.

5) Other concurrent malignancy, excluding non-melanoma type skin cancer. Have had cancer before (unless there is a 5 year cancer free period) except for, non-melanomatous skin cancer, localized prostate cancer, carcinoma in situ (CIS) of the cervix, or superficial bladder cancer, with last treatment greater than 6 months prior to registration onto this study.

6) Have had a solid organ or bone marrow transplant.

7) Pregnancy.

8) Breast feeding.

9) Systemic corticoid steroid therapy of > 10 mg prednisone equivalent daily.

10) Coagulopathy (PT-INR > 1.2, PTT > 40 seconds) or history of bleeding /clotting problems.

11) Concurrent use of Grapes or related products.

12) Unwilling to refrain from drinking more than 1 glass of wine a day.

13) Pts receiving medications known to be modulators of cytochrome P450 3A4 if alternative medication cannot be provided.

14) Currently taking other investigational agents.

15) Pts with concurrent medical conditions that may interfere with completion of tests, therapy, or the follow up schedule.

C.5). Compliance monitoring Pt adherence will be monitored by:

1) Drug calendar for self-recording of drug-taking.

2) Pill counts at follow up visits.

3) Plasma, lung tumor/tissue, and urine GSE /metabolites levels.

C.6). Toxicity monitoring

Toxicity will be monitored with serial adverse reaction questionnaires and the NCI CTCAE v5 will be used to define grades (severity) of toxicity. All adverse events will be evaluated by the investigator.

C.7). Treatment modification and discontinuation according to level of toxicity

- For any Grade 1 toxicity, there will be no dose modification.
- For Grade 2 toxicity, the investigator will withhold the treatment until values return to Grade 1 or less, then restart the drug and the dose will be reduced by 25%.
- If a Grade 3 toxicity occurs, treatment will be withheld until the toxicity Grade reaches ≤ 1, and the dose will be reduced by 50%. Tests will be repeated to confirm values within 72 hours.
- Any Grade 4 toxicity will result in removal of the patient from active treatment. These patients will be closely monitored and treated as indicated by the clinical situation until the toxic effects resolve.
- The development of Grade 4 toxicity in any 2 subjects, thought to be possibly related to the study drugs, will result in termination of the study.

C.8). Adverse Event Stopping Rule Enrollment will be held if there is at least a 90% probability that fewer than 90% of patients can continue to surgery without

treatment-related delays. if one patient experiences a treatment-related death, accrual to the study will be suspended.

C.9). Safety monitoring rule: After treatment of an initial cohort of 10 patients, a designated physician committee will review safety data on all adverse events compiled into incidence table. The decision to halt the trial because of undue risk to patient receiving drug will be considered if indicated.

C.10). Clinical specimens collection, processing and distribution. Clinical specimens for biomarker analysis will be procured at baseline and post treatment, and distributed in batches to Drs. Mao's and Jih's laboratories for specialized assays and analyses of paired samples to minimize inter-assay variabilities when applicable (see summary table below).

Total mRNA will be isolated using miRNeasy miniprep kits (Qiagen) to allow assays of mRNA and/or miRNA expression. Each bronchial biopsy and $1x10^6$ BAL cells usually yield 6-9 mg of Total RNA. Total protein will be collected from a portion of the BAL cells or lung tumors and tissues by homogenizing in Laemmli buffer when applicable. Samples will be stored at $–80^0$C until analysis.

Mechanisms or associations	Marker	Specimen source	Lab doing assays
Bioavailability and PK	GSE and metabolites	plasma, BAL fluid & cell extract, Tumor, Urine.	Mao
Cellular proliferation	Ki-67	Tumor (Bronch., TTNA, and resected).	Jih
Histopathology	Pathologic response, staging.	Tumor (Bronch., TTNA, and resected), LN	Jih
Apoptosis	Activated Caspase 3 (ASP175)	Tumor (Bronch., TTNA, and resected).	Jih
Tumor suppressor or promotor	PTEN, IGF2R; P-AKT	Tumor (Bronch., TTNA, and resected).	Jih
Markers of inflammation and immune function	PGE_2, COX-2, PGI_2, PTGIS, 15-HETE, IL-6, IL-10, IL-12. CRP.	BAL fluid, plasma, Lung tumor and tissue.	Mao

GEP	Cancer-specific pathway array	BAL cell, tumor (bronch, TTNA, or resection).	Mao
Epigenetic profile Oncomirs	miRNA array MiR-19a, -b, and -106b	BAL cell, tumor (bronch, TTNA, or resection), serum	Mao
Others to be defined in the future			

C.11). Analysis of GSE and metabolites in plasma, BAL fluid and cells, tumor and urine samples Samples will be stored at -80^{0}C until analyzed. Cells will be homogenized and extracted, GSE and metabolites in various samples will be measured with LC-UV-MS as previously described (8, 34).

C.12). Pathological Assessments. Primary lung tumor and lymph-node surgical specimens will be staged according to the criteria of the American Joint Committee on Cancer (7th edition) for evaluating tumor size, affected lymph nodes, and metastases. Primary tumors and lymph nodes will be assessed for the percentage of residual viable tumor that will be identified on routine hematoxylin and eosin (H & E) staining. VASDHS Pathology Department performs routine molecular profiles of lung tumors for EGFR, ALK, c-MET, ROS1, BRAF mutations and PD-L1 expression.

- Tumors and lymph nodes with no more than 10% viable tumor cells will be considered to have had a major pathological response (43, 54).
- Tumors and lymph nodes will be representatively sampled with one section per centermeter diameter of the specimen, examined by light microscopy for histologic diagnosis and the extent of treatment effects, including necrosis, fibrosis and inflammation.
- The treatment effects will be semi-quantitatively estimated in 10% increments.

C.13). Assessments of tumor Ki-67 LI, activated caspase 3, PTEN, IGF2R, P-AKT. Immunohistochemistry (IHC) will be performed on Paraffin-embedded 4 m sections from bronchial or TTNA biopsies and resected tumors and the staining scores will be determined as previously described (8, 19). Histopathology and IHC scoring will be assessed in a blinded fashion.

C.14). Effects on COX-2/PGE_2 PTGIS/PGI_2, and 15-LOX/15-HETE axis. PGI_2, 15-HETE and PGE_2, levels in biospecimens will be measured using specific enzyme immunoassay (Cayman Chemical Co).

QPCR for COX-2, PTGIS, 15-LOX-1, 15-LOX-2 mRNA expressions in BAL cells, using primers/reagents/protocol from SA Biosicence, and IHC for protein levels in tumor tissues as previously described (28).

C.15). IL-6, -10, -12, and CRP levels: will be measured using specific ELISA as previously described (19, 21).

C.16). Human Cancer PathwayFinder GEP and MiRNA qPCR Arrays.A Human Cancer PathwayFinder qPCR array (designed to rapidly assess the status of 7 biological pathways frequently altered during malignant transformation and tumorigenesis, include genes involved in: **1)** Cell Cycle Control & DNA Damage Repair. **2)** Apoptosis and Cell Senescence. **3)** Signal Transduction Molecules and Transcription Factors. **4)** Adhesion. **5)** Angiogenesis. **6)** Invasion and Metastasis. **7)** Epithelial Mesenchymal Transition, and a Human Cancer PathwatFinder miRNA 384HC qPCR array (MIHS-3102Z) from SA bioscience, Qiagen, will be used to assess the effects of GSE on pathway specific, cancer-relevant gene, as well as miRNA expression in BAL cells and tumor according to the manufacturer's instructions. QPCR will be performed using the Biorad MyiQ cycler.

C.17). Measurement of serum MiR-19a, -19b, and -106b. Total RNA in pre- and post-treatment serum will be isolated using the miRNA serum/plasma kit and spiked with a synthetic Syn-cel-mir-39 miRNA mimic, converted into cDNA, and miR-specific qPCR will be performed as previously described (11).

C.18). Measurement of time to progression, overall survival and recurrence free-survival. Time to progression and overall survival will be determined from the start of neoadjuvant therapy, and recurrence-free survival will be determined from the date of surgery.

C.19). Statistical considerations.

C.19.1). Sample size determination. The samples size is based on the fact that a typical cancer phase IIa study might include fewer than 30 patients to estimate a response rate (55), as well as our prior lung cancer chemoprevention study assessing the effects of LP on modulating relevant SEBM, in which 8 subjects was sufficient to show statistically significant changes of a variety of biomarkers of interests *[(11)]*. For example, our data indicates that the bronchial Ki-67 score is reduced 55% (13.8 +/- 3.5 (SE) reduced to 6.25 +/- 1.36(SE). The common SD= 2.66* 8 = 7.5 and with a moderate pre-post correlation of 0.7, the SD of the difference for a paired t-test is 5.8. The corresponding effect size is a large 1.3. Our sample size of 30 patients is adequate to detect 50% of this reduction with more than 90% power

and alpha=0.05. If there were a 20% loss at follow up, the 24 remaining patients is still adequate for 85% power.

Another important SEBM is pathologic response rate. Using data from the recent PD-1 inhibitor study by Forde et al, in which a 45% major pathological response rate was observed in a sample size of 20, assuming LP will lead to half of that response rate, our sample size of 30 is adequate to detect such a response rate with 80% power and alpha=0.05.

In addition, our preclinical studies also showed large effect sizes (up to 4) for expression alterations between control and GSE/LP treatments. The sample sizes of 10 will have minimally detectable effect sizes (with 80% power) of 0.66, assuming a paired t-test with a 0.05 two-sided significance level for comparing mean levels of the study outcomes between time points (ex. Pre- & post-treatment), This suggests that these studies should have sufficient power to detect effects even smaller than those observed in the preliminary data.

C.19.2). Statistical analysis: The 1^0 endpoint is safety and feasibility.

Feasibility is defined as delay in the planned surgery of > 14 days that is possibly related to study medication; treatment would not be feasible if there is at least a 90% probability that fewer than 90% of patients can continue to surgery without treatment-related delays, and treatment will not be safe if the probability was 70% or more that the risk of grade 3 toxic effect was more than 25%.

For 2^0 endpoints, each patient will serve as his/her own control for pre- and post-treatment comparisons. Comparisons will be made using mixed effects models for quantitative outcomes followed (when appropriate) by paired student's *t* test to compare pre- and post- 2-3 weeks treatment, or through logistic regression analysis when the scale is categorical or ordinal.

Comparisons of the 2^0 endpoints such as Ki-67 LI, pathological response, downstaging (e.g. decrease from pretreatment FNA pathologically positive N1 stage to post-treatment N0 pathological stage), caspase 3, GEP, miRNA profile, and serum miRNA, etc. will take place between baseline and post 2-3 weeks treatment and between sample types. Mixed effects models with fixed effects for time and sample type and a random effect for subject will be used. The modified PK data will be correlated to treatment effects on the various 2^0 endpoints. Additionally, these 2^0 endpoints will be correlated to each

other using the framework of the mixed models. These models will be considered both cross-sectionally (e.g. correlation of various endpoints at each time point) and longitudinally (correlation of the changes between the various 2^0 endpoints). Subgroup analysis will also control for underlying somatic tumor mutations, pt's clinical characteristics, including lung cancer stage, cell type, smoking status, etc.

Analyses of time to progression, overall survival and recurrence free-survival. Patients who did not experience these events of interest will be censored at the time of the last available follow-up. All time-to-event outcomes will be estimated using Kaplan-Meier methods. Comparisons will be made with historical control matched by stage of disease, cell type and adjuvant therapy.

Analyses of qPCR GEP and miRNA arrays. Data for both types of arrays will be analyzed using SA bioscience's qPCR array software package, which automatically performs all C_t based fold-change calculations from raw threshold cycle (C_t) data (C_t >35 is considered a negative call). We will use multiple testing corrected t-tests (pre vs post treatment comparison) or linear regression models (correlation with biomarkers). These corrections will be made using the *multtest* package in R to compute the false discovery rate (FDR) (56) for sets of significant genes, followed by multivariate analyses on the array data using weighted gene coexpression network analysis (WGCNA)(57). The GEP profile will then be correlated with the miRNA profile to identify specific miRNA likely to be involved in the alteration of specific gene expression using the MirMiner package (58).

C.19.3). Anticipated results, alternative and future plans. We anticipate that LP will be well tolerated and favorably modulate the various endpoints, such as decrease in Ki-67 LI, COX-2/PGE_2, miR-19a /b, -106b, and P-AKT; significant pathologic response and downstaging; increase in PTGIS/PGI_2, 15-HETE, PTEN, and IGF2R, etc.

The qPCR arrays will yield important clues to help further characterization of anti-neoplastic mechanisms, such as focused proteomics assays on archived samples, using the Luminex multiplex system, and metabolomics assays to further validate the functional significance of GEP in response to GSE. The modified PK/bioavailability study will define physiologic relevant levels of GSE/metabolites in reference to bioactivity.

Because LP may potentially reduce adverse effects from and enhance efficacy of adjuvant chemo and/or radiation therapy, subgroup analysis will be performed on patients who receive adjuvant therapy based on standard of practice.

With favorable preliminary findings from interim analysis, we may amend the study protocol to continue LP in the participants as an adjunct to chemotherapy and/or radiation, and as a chemopreventive agent for second primary lung cancer.

An interim analysis will take place after 10 subjects are enrolled in aim 1. In the event significant bioactivity is inconsistently observed, "the dose will be escalated to 5 capsules a day for the next 10 subjects as tolerated, with a second interim analysis to determine if escalation to 6 capsules for the remaining 10 subjects is warranted." Significant findings in Ki-67 LI, pathologic response, downstaging and/or a combination of 2^0 endpoints without significant toxicity will support moving onto phase IIb studies.

Broad-ranging assays and analyses are described to demonstrate a wide range of possible outcomes, but assays will be prioritized in the event sample availabilities become limiting. For example, Ki-67 in tumors, pathologic response and staging, serum miR-19a, 19b, and -106b will be prioritized over other markers.

Section 9.1 Clinical Procedures

9.1) Differentiate research procedures (or any procedures done for research purposes only) from clinical procedures (procedures that are done as part of standard care).

(Note: this differentiation should be clear in the consent form as well)

Pt. suspected of having lung cancer will be referred/recruited from clinics and screened with history and physical examination (H&P), standardized respiratory/general health questionnaires that details subjects' demographic information, smoking behavior, occupation, medical conditions, and dietary history will be obtained using a food frequency self-assessment questionnaire. Routine blood tests (CBC; Chemistry panel; PT, PTT), pulmonary function tests (PFT), chest CT and/or PET/CT scans and 12-lead EKG will already be obtained as a part of clinical work up. Serum cotinine and exhaled carbon monoxide (CO) will be checked at screening to confirm smoking status. Subjects will refrain from the ingestion of grapes/seed related products throughout the entire treatment period. Subjects will also consent to archive of specimens for research, including blood, urine, and from diagnostic procedures [bronchoscopic or transthoracic needle aspiration (TTNA)] specimens as clinically indicated; these biospecimens will serve as baseline, pre-treatment samples.

Subjects who are diagnosed with clinical, surgically resectable stage I or II lung cancer will be enrolled and treated with 4 capsules of LP (450 mg/cap, 127 mg of OPC/cap, Indena/Thorne Research) for approximately 2 weeks (+/- 7 days) until 4-7 days prior to surgical resection. Only subjects who meet entry criteria will be enrolled. Four to 7 days prior to scheduled surgery, subject will return to study clinic for follow up, with H&P, questionnaires, serial clinical blood tests and collection of blood and urine for research. At the time of surgical resection, BAL fluid and cells, lung tumor and adjacent lung tissue, will be collected as post treatment samples. Post-treatment samples will be compared with pre-treatment samples to assess PK/bioavailability, PD

and mechanisms of action.

The BAL performed at time of surgery is solely for research purposes. For subjects with NSCLC diagnosed only by TTNA, no pre-treatment BAL will be performed, unless an additional clinical bronchoscopy is to be performed based on standard of care.

Once enrolled for intervention, all subjects will be monitored with weekly phone follow up, preop H&P and blood tests. The safety and side effects of oral GSE will be monitored with the NCI common terminology criteria for adverse events Version 5.0 (CTCAE v5) and adverse reaction questionnaires. Post-op phone follow up will occur at 3-4 weeks, 6 months and annually for up to 4 years.

Section 9.2 IND Drugs

9.2) For each drug requiring an IND, provide the drug name, dose, and route of administration

Drug name: Leucoselect phytosome.
Dose: 450 mg/capsule, 4 capsules
Route of Administration: Once a day by mouth.

9.2b) Enter the IND Number:

119762

9.2c) Identify who/what entity holds the IND and the status of the IND

Jenny T. Mao, M.D. holds the IND including the new study amendment for the current study. A study amendment for change of institution from NMVAHCS to VASDHS is being filed.

9.2d) Identify the storage and security of the drug. For example, at the VASDHS, state "The investigational drug will be stored in the Research Pharmacy in accordance with 119-SOPP-10/151-SOPP-38." Also, identify whether the drug is a controlled substance.

The investigational drug will be stored in the Research Pharmacy in accordance with 119-SOPP-10 /151-SOPP-38.
The study drug is not a controlled substance.

Section 9.5 Data Banking

9.5) Provide details about the data repository for example,

- **Identify what information will be retained.**
- **Whether participation in the repository will be optional or required.**
- **Whether or not identifiers are included with the banked data, *Note: If banking is optional and identifiable information will be retained, then the combined consent/HIPAA form may not be used. Please use the single consent and HIPAA form 10-0493.***
- **Provide future use examples.**
- **Indicate how the study will comply with VHA Handbook 1200.12.**

identifiers are included with the banked data. The key code that links to subject identifiers be retained. Only Dr. Mao and study coordinators will have access to the key.

Anonymized (de-identified) case report forms will be retained. Information include general demographics (age, gender, ethnicity), general medical and family history, social and occupational history, laboratory testing (CBC, chemistry panel, PT/PTT, serum cotinine), diagnostic testing results (imaging, cell and tissue sampling), follow up visits, study drug compliance data (drug calendar), adverse events reporting, etc.

Anonymized case report forms" means de-identified but still retaining the subject's study ID rather than stripped of all linking identifiers.

Participation in the repository is required.

The study will comply with VHA Handbook 1200.12 using a SOP for management of data bank.

The data bank and biorepository will be deposited upon completion of this study and no future use (outside of the original protocol) would be permitted until the repository is established.

Section 9.6 Specimens

9.6) Identify the biological materials, procedures for obtaining material, and the sources of the specimens. ***Effective 12/01/2019: Specify whether research or clinical staff (from which service) will be collecting the specimens and describe "hand-off" procedures to ensure that release of the specimens has been authorized by Pathology and Laboratory Medicine Service (PALMS).***

Specimen types: Plasma, serum, BAL fluid & cell extract, Urine. Tumor (from Bronch., TTNA, and resected).

Clinical specimens for biomarker analysis will be procured at baseline and post treatment, and distributed in batches to Drs. Mao's and Jih's laboratories for specialized assays and analyses of paired samples to minimize inter-assay variabilities when applicable.

See attachment General Specimen Processing Plan, Summary table for research specimen collection.

For research samples requiring pathology processing, samples will be collected in containers pre-labelled with study ID, subject study ID, date of sample procurement, type of sample. Biopsies and tissues will be sent to surgical pathology lab for processing, sectioning and staining along with study specific histopathology form.

When specimen are ready for pick up, pathology will contact Mao lab staff, the hand off will be documented on the ORAM histopathology form with signature and date by persons releasing and receiving the samples.

Section 9.7 Specimen Banking

9.7a) Select the specimen banking method(s):

9.7a1) Specimens will be banked at the **local VA facility.**

(•) Yes ( ) No

9.7a2) Specimens will be banked at **another VA** facility.

( ) Yes (•) No

9.7a3) Specimens banked at a non-VA location.

( ) Yes (•) No

9.7b) Provide the details about the specimen repository/bank -

- **What specimens are banked, where will they be stored?**
- **How specimens will be labeled, etc. Also include whether any data will be retained with or linked to the specimens (specify if identifiable information will be retained). .**
- **Will banking be optional or mandatory?** ***Note: If banking is optional and identifiable information will be retained with the specimens, then the combined consent/HIPAA form may not be used. Please use the single consent and HIPAA form 10-0493.***
- **Who will have acess to and management of the specimens?**

Blood, Urine, BAL fluid & cells, Tumor from diagnostic bronchoscopy or TTNA and/or bx, tumor and adjacent lung tissue will be banked and stored in Dr. Mao's Lab in bldg 1, Rm 6051 and/or

6052.

samples will be aliquoted or placed into prelabeled tubes or containers with study ID, subject study ID, date of sample procurement, type of sample, quantity, aliquot #.

Data will be retained with a potential link to the specimens. The key to study code and identifiable information will be retained by Dr Mao and study coordinator mainly for Quality assurance. Data from data repository will be linked to the specimen, by specific study ID#.

Banking will be mandatory.

Only Dr. Mao and designated study coordinator/staff will have access to and manage the specimens.

A data and specimen banking SOP will be established in accordance to the management procedures required in 1200.12

Section 9.8 Questionnaires & Surveys

9.8) Provide the name and a reference for questionnaires/surveys that are standard or identify them here and attach a copy of the questionnaire/survey. ***Questionnaires or surveys that are not clinical standard references must be uploaded. Reference the help link for additional information related to surveys administered to VA personnel and approved platforms for web-based surveys.***

1. Dietary Frequency Questionnaires

FOOD/ALCOHOL USE
(Collected Once)

ALCOHOL USE

For servings definitions, please use National Center of Health Statistics (CDC) Standard for ounce
1 drink = 1 serving = wine = 5 oz = 1 glass
liquor = 1.5 oz = 1 shot
beer = 12 oz = 1 can

Lifetime: Have you ever consumed alcohol on a regular basis? _____ No _____ Yes
(Regular basis if defined as at least once a month)
IF NO Skip to NEXT SECTION.

When did you first begin consuming any type of alcohol such as beer, wine coolers, liquor, etc.
_____
Y Y Y Y

Current: During the past year have you consumed alcohol on a regular basis? _____ No _____ Yes

If NO, when did you stop consuming any type of alcohol? _____
Y Y Y Y

If YES, currently:

FREQUENCY:
_____ Daily/Everyday _____ Some of the time (1-2 days)
_____ Monthly _____ Unknown
_____ Never _____ Weekly
_____ Refused to answer question _____ Yearly

ALCOHOL TYPE # OF SERVINGS FREQUENCY
Beer (serving = 12 oz can/bottle)
Wine (serving = 5 oz glass)
Liquor/shots (1.5 oz shot)

FOOD/ALCOHOL USE
(Collected Once)

FOOD HABITS

Of the following, what type of foods do you normally eat?

For servings definitions, please use National Center of Health Statistics (CDC) Standard for ounce
1 serving = 1 medium fruit (e.g. apple, orange, banana, pear)
½ cup cut-up fruit
½ cup raw or cooked vegetables
¼ cup dried fruit (e.g. raisins, apricots, mango)
1 cup raw leafy vegetables
½ cup cooked or canned peas or beans

FREQUENCY:
_____ Daily/Everyday _____ Some of the time (1-2 days)
_____ Monthly _____ Unknown
_____ Never _____ Weekly
_____ Refused to answer question _____ Yearly

FOOD TYPE # OF SERVINGS FREQUENCY
Fruit juices
Fruit, not counting juice
Green salad
Non-fried potatoes
Carrots
Other vegetables

2. Pre-registration form see attachment.

3. The 36-item Short Form Survey (SF-36).

Section 9.9 Data Safety Monitoring Board or Plan

9.9) Provide a Data Safety Monitoring Plan (DSMP) or the details of a Data Safety Monitoring Board; if a written plan is available, attach a copy of the plan to the submission form.

DATA SAFETY AND MONITORING PLAN
I. Monitoring the progress of trials and the safety of participants
Data and safety monitoring for this study will be provided by the Clinical Science Research & Development (CSR&D) centralized Data Monitoring Committee (DMC). The DMC is provided by CSR&D to ensure independent oversight of the safety and integrity of the project. The DMC is an independent multidisciplinary group, whose members have collectively – through research, education, training, experience, and expertise – the requisite knowledge pertinent to the subject areas to be reviewed. Membership details are available on the CSRD website. The DMC will provide an ongoing independent evaluation of this study focused on safety and feasibility, including participant accrual and retention, adverse events monitoring, and data analyses. Meetings will be held three times per year at which recommendations will be made to the Director of CSR&D for endorsement. These recommendations will range from approval to continue (unconditionally or with conditions to be addressed) to probation or possibly termination, if there are problems with enrollment or safety concerns.

The PI and study coordinator will review and report all unanticipated problems, adverse events, protocol compliance, etc., as they occur; The report will address the outcomes of the event or problems and in case of a serious adverse event or death, comment on the association of the event to participation in the study. Reports for events determined by the investigator that are related to or possibly related to participation or reports of events resulting in death will be promptly forwarded to the DMC. Serious Adverse Events (SAE) shall be reported as they occur (reported within 24 h on working days of discovery). The DMC will determine whether further action is necessary, depending on the nature of the adverse events, whether it is related to the

study and whether the frequency and gravity of the situation warrants intervention in accordance to the protocol safety monitoring provision. For example, the DMC could determine that no action is required and the report is filed for an expected SAE. Alternatively, the DMC and IRB could require further explanation or clarification from the investigator of the mechanism(s) in place to prevent or to minimize future occurrences, or ask for protocol modification or suspension, for unexpected SAE.

II. Plans for assuring compliance with requirements regarding the reporting of adverse events (AE's). The PI will assure that all adverse event be reported to the IRB, the FDA, and the DMC in accordance to established VASDHS IRB policy and procedures (within 5 working days) and federal regulations. The PI will also notify the FDA of any adverse event associated with the use of a test drug that is "both serious and unexpected". Toxicities or adverse consequences of interventions will be summarized as part of the progress reports in the non-competitive renewal applications.

III. Plans to assure that any action resulting in a temporary or permanent suspension of a CSR&D funded clinical trial is reported to the DMC and grant program director responsible for the grant. The PI will be responsible to assure that any action taken either by the FDA, IRB, or the investigators to temporarily or permanently suspend the clinical trial, is reported to the DMC and program director responsible for the grant.

VI. Plans for assuring data accuracy and protocol compliance. Data will be verified and protocol compliance checks will be performed by a data manager and the principal investigator.

Section 9.10 Laboratory Tests

9.10) For each research laboratory test (not lab tests used as part of standard care), identify the test and indicate if the test results will or will not be used clinically for diagnosis, treatment, or prevention of disease. ***Please note, only results from properly accredited laboratories can be used for diagnosis, treatment, and prevention of disease.***

serum cotinine and exhaled carbon monoxide- to determine smoking status. will not be used for diagnosis, treatment and prevention of disease.

Pregnancy test to determine eligibility for woman of reproductive age.

Section 10 - Human Subjects

10) Describe the characteristics of the proposed subject population. Include age, gender, ethnicity, and health status as appropriate. ***Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still describe the characteristics related to the subjects whose charts you will review.***

- **Provide inclusion and exclusion criteria as appropriate. Provide a statement how non pregnancy is confirmed if pregnancy is an exclusion criteria.**
- **For multisite studies, provide the total number of subjects from all sites and include description of the local site's role as a coordinating center if applicable.**
- **Indicate the number of VA participants to be studied.**
- **Indicate the estimated number of consented subjects that will fail the screening process, if any.**

Inclusion criteria:

A. Initial screening:
1) Age over 21.
2) Lesions suspicious for lung cancer.
3) Competent to provide consent.
4) Clinically relevant CBC values within normal limits (WNL).
5) liver function test WNL.
6) Normal Creatinine clearance as measured by the Cockcroft-Gault equation.

7) ECOG Performance status: 0-1.

B. Enrollment for treatment with LP:
• Histologically proven and surgically resectable clinical IA and IB (T2a < 4 cm) stage NSCLC.
• Histologically proven and surgically resectable clinical I and II stage NSCLC unable or unwilling to receive standard neoadjuvant immunochemotherapy.

Exclusion criteria:
1) Inability to provide informed consent (e.g. cognitive impairment, severe psychiatric disorders).
2) Hypersensitivity to grapes or related products.
3) Advance respiratory disease (Predicted post resection FEV1 < 0.8 liters based on pre-resection PFT obtained at screening, resting hypoxemia, to ensure pts have adequate reserve to undergo diagnostic procedures and surgical resection).
4) Unstable angina.
5) Other concurrent malignancy, excluding non-melanoma type skin cancer. Have had cancer before (unless there is a 5-year cancer free period) except for, non-melanomatous skin cancer, localized prostate cancer, carcinoma in situ (CIS) of the cervix, or superficial bladder cancer, with last treatment greater than 6 months prior to registration onto this study.
6) Have had a solid organ or bone marrow transplant.
7) Pregnancy.
8) Breast feeding.
9) Systemic corticoid steroid therapy of > 10 mg prednisone equivalent daily.
10) Coagulopathy (PT-INR > 1.2, PTT > 40 seconds) or history of bleeding/clotting problems.
11) Concurrent use of Grapes or related products.
12) Unwilling to refrain from drinking more than 1 glass of wine a day.
13) Pts receiving medications known to be modulators of cytochrome P450 3A4 if alternative medication cannot be provided.
14) Currently taking other investigational agents.
15) Pts with concurrent medical conditions that may interfere with completion of tests, therapy, or the follow up schedule.

A pregnancy test will be performed for woman of reproductive age.

Number of patients to enroll for intervention:30.
Number of patients to consent:100.

Section 11 - Recruitment

11) Describe, step-by-step, the plans for recruitment of subjects (or selection of subjects as in record review). This description must include how, when, and where potential subjects are approached as well as procedures for identifying potential participants (through medical records, physician referral, third-party sources, etc.). Include how selection is equitable. Indicate if vulnerability to coercion may be present and if so plans to ensure voluntary participation.

Since 2017, The clinical lung cancer screening program has been in place, is currently following 2540 patients with ongoing enrollment. A Lung cancer clinic has been recently established where all patients with suspicious lung lesions are referred to and followed. Potentially eligible patients with lung lesions suspicious for lung cancer will also be identified at the weekly Thoracic conference and referred for screening.

Pts will be recruited from Pulmonary and Thoracic Surgery clinics. Potential participants will be identified from clinic and referred to study coordinator to contact and consent.

The provider will first discuss the findings, opportunity to participate in the trial and then ask for the patients' permission to allow study personnel to speak with or contact them through phone or letter if interested.

Study flyer may be handed out at this time.

A two-tier screening process will be used to identify eligible patients. The first tier is to screen and exclude individuals with significant exclusion criteria. Those passing the screen will undergo standard clinical diagnostic procedures and consent to archive of various biologic specimens. Those patients who are confirmed to have stage I and II resectable lung cancer will be enrolled to receive ~2-3 weeks of LP treatment until prior to surgical resection.

Section 11.1 Recruitment Materials

11.1) Identify all recruitment materials (flyers, advertisements, letters, etc.) that will be used; include the web address for any web-based advertisements. The text of all communications with prospective participants must be reviewed and approved by the IRB before it can be used. You will be reminded to attach copies of recruitment materials to the initial submission packet. ***Note: Posting of flyers with pull tabs is not permitted within VASDHS (including the VMRF building). However, you may request to advertise on the e-boards (located at the elevators and throughout the facility) or on the VASDHS Research Opportunities web-page.***

Study flyer will be used.

Section 12 - Informed Consent

12) Indicate whether or not each category of consent is involved in this study:

12a) Will the study team obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without (or prior to) obtaining informed consent of the prospective subject or the prospective subject's LAR?

(•) Yes ( ) No

Check one or both of the below boxes if they apply to this study:

Information will be obtained through oral or written communication with the prospective subject or the subject's Legally Authorized Representative (LAR) and this is not a FDA regulated study.

( ) Yes (•) No

Identifiable information or biospecimens will be obtained by accessing records or stored identifiable biospecimens and this is not an FDA regulated study.

( ) Yes (•) No

Since both boxes were checked "no", a request for an informed consent waiver is needed.

12b) **Signed** informed consent

(•) Yes ( ) No

12c) Waiver of documented consent (e.g., **oral** consent) for all or part of the study.

( ) Yes (•) No

12d) Request for a **waiver** of consent for all or some study activities.

(•) Yes ( ) No

12e) Alteration of **other required elements** of consent.

( ) Yes (•) No

12f) **Child** assent to participate (Director approval will be required)

( ) Yes (•) No

12g) Will any language **other than English** be used by those obtaining consent and understood by the prospective participant or the legally authorized representative?

( ) Yes (•) No

12h) **Decisional Capacity Assessment** to determine if participants have the capacity to consent for themselves.

(•) Yes ( ) No

12i) **Surrogate** consent (legally authorized representative)

○ Yes ◉ No

Section 12.1 Informed Consent Process

12.1a) Will consent be obtained before any study procedures are performed (including screening procedures except screening procedures with Consent and/or HIPAA waiver when required)?

◉ Yes ○ No

12.1b) Will the information being communicated to the participant or legally authorized representative during the consent process include exculpatory language through which the participant or legally authorized representative is made to waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the VA or its agents from liability for negligence.

○ Yes ◉ No

12.1c) A master list of all VA subjects consented (written or not) under this protocol will be maintained.

◉ Agree ○ Disagree

12.1d) Identify the circumstances under which consent will be obtained including where the process will take place; any waiting period between describing the research and obtaining consent including sufficient time for the prospective participant to consider participation, and any steps taken to minimize the possibility of coercion or undue influence.

Potential subjects identified in clinic will first be asked if they may be interested in participating in the research study. If they are interested, an informed consent from will be either provided to them directly or mailed to them. A separate screening visit will be arranged, during which time the study candidate will provide written consent to participating in the study and then formally undergo screening procedures. This two tiered process will provide necessary time for potential participants to review the consent form and ask questions prior to deciding to undergo formal screening, thereby minimizing the possibility of coercion or undue influence.

Section 12.4 Waiver of Informed Consent

12.4a) Is it practicable to conduct the research without the waiver or alteration of consent?

○ Yes ◉ No

12.4b) Does the research examine public benefit or service programs and is subject to state or local government approval?

○ Yes ◉ No

12.4c) Will the research involve greater than minimal risk?

○ Yes ◉ No

12.4d) Will waiving or altering informed consent adversely affect the subjects' rights and welfare?

○ Yes ◉ No

12.4e) Is it appropriate to provide pertinent information to subjects later BUT this information will NOT be provided?

○ Yes ◉ No

12.4f) Identify to what aspects of the study you are requesting a waiver of consent (i.e., full study or specific aspects). Describe the waiver or alteration needed and why it can be granted (include why the research is not practical without the waiver or alteration and how the waiver enables conducting the study).

Waiver of informed consent or alteration of consent elements may be allowed if the IRB documents these findings and approves waiver or alteration.

Waiver of consent will be needed to allow more focused screening of potential subjects. Potential patients will be identified at Thoracic tumor board conference or referred by patient's Patient's Pulmonary or thoracic surgery providers.

Medical records in CPRS will be reviewed to help better identify potential candidates within the VASDHS to participate in the study.

Patient's pulmonary or thoracic surgery providers will inform patients meeting available entry criteria about the study and that they will be contacted by the study coordinator. The study coordinator will then provide thorough explanation of the study, mail or deliver the informed consent form to the patient, then schedule the screening visit.

12.4g) Explain why the research could not practicably conducted without using identifiable information.

This study focuses on patients with suspicious lesions for lung cancer and enroll exclusively early stage lung cancer for neoadjuvant treatment.
Identification of potential candidates cannot be performed without reviewing patient's medical records. In addition, review of entry criteria will help exclude those who may be at undue risk for invasive procedures who are not surgical candidates (e.g. resting hypoxemia, other concurrent malignancy, ischemic heart disease, etc.).

Section 12.6 Decisional Capacity Assessment

12.6a) Describe the method(s) for determination of decisional capacity: (see ? for guidance) ***Please note that documentation of the assessement is required.***

Criteria for Decision-Making Capacity
(1) An individual is presumed to have decision-making capacity unless any one or more of the following apply:
(a) It has been documented by a qualified practitioner, in the individual's medical record in a signed and dated progress note that the individual lacks capacity to make the decision to participate in the proposed study. NOTE: The qualified practitioner may be a member of the research team.
(b) The individual has been ruled incompetent by a court of law.
(2) If there is any question as to whether or not a potential adult subject has decision-making capacity, and there is no documentation
in the medical record that the individual lacks decision-making capacity, and the individual has not been ruled incompetent by a court of
law, the investigator must consult with a qualified practitioner (who may be a member of the research team) about the individual's
decision-making capacity before proceeding with the informed consent process.

12.6b) If subjects with limited decisional capacity will be enrolled, describe methods for obtaining subject assent or why they are not indicated:

N/A

12.6c) If subjects with limited decisional capacity will be enrolled, describe procedures for respecting subject dissent and any additional safeguards or why these features are not needed:

N/A

12.6d) If subjects with limited decisional capacity will be enrolled, describe the risk and, if greater than minimal, the relation to potential benefits:

N/A

12.6e) If subjects with limited decisional capacity will be enrolled, describe the justification for the inclusion of any incompetent persons or persons with impaired decision-making capacity:

N/A

Section 12.9 HIPAA Authorization

For each category below, indicate whether or not this study involves the indicated process:

12.9a) **Signed** HIPAA Authorization. ***New Template is available in the ? Help section***

(•) Yes ( ) No

12.9b) HIPAA waiver to cover the entire study

( ) Yes (•) No

12.9c) HIPAA waiver for recruitment, screening, and/or for a portion of the study.

(•) Yes ( ) No

12.9d) HIPAA Authorization or waiver is **not required** for some or all of the study subjects (e.g. no health data).

( ) Yes (•) No

Section 12.10 HIPAA Waivers and Alterations

12.10a) Describe the purpose/nature of the HIPAA waiver or alteration and list specifically, what identifiers and health information are being requested under the waiver/alteration and identify whether the waiver is for access, use, and/or collection of this information.

HIPPA waiver will be used for prescreening of candidates referred from clinic. Potential patients will be identified at Thoracic conference or referred by patient's pulmonary or thoracic surgery providers.
Medical records in CPRS will be reviewed to help better identify potential candidates likley to meet entry criteria within the VASDHS to participate in the study.

Patient's pulmonary or thoracic surgery providers will inform patients meeting available entry criteria about the study and that they will be contacted by the study coordinator. No forms of coercion, pressure or other tactics will be employed on any potential candidate for this study.

The study coordinator will provide thorough explanation of the study, mail or deliver the informed consent form for the patient, then schedule the screening visit.

Identification of the patient's name and SSN would allow the study coordinator to open CPRS and review potential candidate's medical record to assess for inclusion/exclusion criteria.

12.10b) The proposed access, use, and/or disclosure of PHI involves no more than a minimal risk to the

privacy of individuals.

◉ Agree ○ Disagree

12.10c) The plan to protect the identifiers from improper use and disclosure is adequate.

◉ Agree ○ Disagree

Describe the plan

Patient confidentiality will be maintained by assigning each subject a study identification number. In so far as possible, study staff will know either the identity of the subject or their data as recorded by identification number, but not both. The Clinical Coordinator and Patient Director, who are experienced in confidentiality, will need to know both the identity and the data. Forms will be designed so that identifying information can be removed from the collected data immediately following completion of the interview or tests. The confidentiality measures will be explained to the subject at the appropriate time, as part of the informed consent and before the collection of any data from him/her. In addition, scrupulous care will be used in handling data when the subject is present, to reassure the subject that similar care is used throughout the study. Study notebooks will be maintained in a dedicated and secure environment and the computer containing subject data will be located in the Clinical Coordinator's office and password protected.

12.10d) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

◉ Agree ○ Disagree

12.10d2) Describe the plan:

Identifiers and source documents will be destroyed at the earliest opportunity according to VHA R&D policy.

12.10e) By signing this protocol for submission, the PI is providing written assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by the Privacy Rule. 38 U.S.C. 7332 Information: If the waiver of HIPAA authorization is for the use of 38 USC 7332 information (applicable to drug abuse, alcohol abuse, HIV infection, and sickle cell anemia records), by signing this protocol for submission the PI is providing written assurance that the purpose of the data is to conduct scientific research and that no personnel involved may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner. (Ref: 38 U.S.C. 7332(b)(2)(B))

◉ Agree ○ Disagree

12.10f) The research could not practicably be conducted without the waiver or alteration.

◉ Agree ○ Disagree

12.10f2) Describe how the waiver/alteration enables the research to be conducted

This study focuses on patients with suspicious lesions for lung cancer and enroll exclusively early stage lung cancer for neoadjuvant treatment.
Identification of potential candidates cannot be performed without reviewing patient's medical records. In addition, review of entry criteria will help exclude those who may be at undue risk for invasive procedures who are not surgical candiates (e.g. resting hypoxemia, other concurrent malignancy, ischemic heart disease, etc.).
Due to the nature of the study, prescreening of potential study participants for eligibility criteria will help focus research and recruitment efforts and eliminate time wasted on contacting subjects who clearly do not qualify and minimize potential anxiety and confusion from such encounters.

12.10g) The research could not practicably be conducted without access to and use of the PHI.

◉ Agree ○ Disagree

12.10g2) Describe why it would be impracticable to conduct this research without the PHI described 12.10a. (v3 /8/18)

Potential subjects must have lung lesions suspicious for lung cancer, which will require chart review.

Section 13 - Alternatives to Participation

13) Describe the alternatives to participation in this research study (see ? for guidance)

Neoadjuvant treatment of early stage nonsmall cell lung cancer is not recommended for stage IA and 1B (T2a < 4 cm) patients.

For stage IB (T greater than or equal to 4 cm) and II disease, neoadjuvant immunochemotherapy has been recently approved by the FDA. Patients will be informed of recommendation for standard immunochemotherapy by their providers and the option of participating in this research study only if they are unable or unwilling to receive immunochemotherapy.

The alternatives is to not participate in this research.

Section 14 - Potential Risks

14) Describe any potential or known risks or discomforts and assess their likelihood and seriousness (see ? for guidance)

All substances and study procedures may involve risks that are currently unknown or unforeseeable. LP is commercially available as a health food supplement. The amount used in the study is based on prior clinical trials and is usually well tolerated. (Indena, http:/www. phytosomes.info/public/leucoselect phytosome.asp). LP has not been studied before in lung cancer patients, therefore the risk for subjects with resectable lung cancer is not known. There exists a small chance of other discomforts or risks (including long-term) from the supplement that are unknown. One of the risks of participating in this study is the possibility that LP may not demonstrate significant anti-neoplastic effects against lung cancer.

Supplement. In general, the supplement is well tolerated with few side effects. Side effects from GSE consumption may include, regardless of causality, a dry, itchy scalp, dizziness, headaches, high blood pressure, hives, indigestion, and nausea. While speculative and not proven clinically, some inconsistent information on the internet suggests that GSE may have blood thinning effects.

Procedures. Physical examinations, blood pressure measurements, and questionnaires present practically no risk. The PFT, radiographic imaging, bronchoscopy or TTNA, and surgeries are all a part of clinical management. There are no additional risks beyond the risks intrinsic to these clinical procedures. Additional sampling in the lung abnormality or lymph nodes at the time of the initial diagnostic procedure may be required to obtain enough cells and tissue for both clinical diagnosis and research.

Risks of bronchoscopy/BAL performed solely for purposes of research sample collection include a very small chance of transient hypoxia, fever, rarely pneumothorax or toxicity of topical anesthetic.

One set of blood samples will be obtained at baseline then prior to surgery, beyond the usual clinical management. The risks of simple venipuncture (inserting a needle into a vein to obtain blood samples) include: mild stinging when the needle is inserted, fainting, infection, bruising, and formation of a blood clot, pain, and/or bleeding at the site of the needle puncture.

Section 15 - Risk Management

15) Describe the procedures for protecting against or minimizing any potential risks/discomforts, and the adequacy of resources for conducting the study and resources participants may need as a consequence of the research. When applicable, include detail of the following safety measures: (a) The type of safety information to be collected, including AEs; (b) Frequency of safety data collection; (c) Frequency or periodicity of review of cumulative safety data; (d) Statistical tests for analyzing the safety data to determine if harm is occurring; and (e) Conditions that trigger an immediate suspension of the research. See ? for further requirements.

The study protocol has been specifically designed in order to reduce risk associated with every aspect of this study. General methods of risk reduction include the development and implementation of confidentiality procedures, screening mechanisms to identify subjects with increase risk and exclude them form participation, performance of tests only by highly trained and qualified personnel, and careful monitoring for adverse events so that they may be immediately identified, addressed, and the consequences reduced.
1) Minimizing risk associated with subject identification:
Patient confidentiality will be maintained by assigning each subject a study identification number. In so far as possible, study staff will know either the identity of the subject or their data as recorded by identification number, but not both. The Clinical Coordinator and Patient Director, who are experienced in confidentiality, will need to know both the identity and the data. Forms will be designed so that identifying information can be removed from the collected data immediately following completion of the interview or tests. The confidentiality measures will be explained to the subject at the appropriate time, as part of the informed consent and before the collection of any data from him/her. In addition, scrupulous care will be used in handling data when the subject is present, to reassure the subject that similar care is used throughout the study. Study notebooks will be maintained in a dedicated and secure environment and the computer containing subject data will be located in the Clinical Coordinator's office and password protected.
2) Minimizing risk associated with the administration of treatment drugs:
Patients will be screened for concomitant medications. Those with conflicting medications will either be offered alternative medications, or will be excluded from the study. Women of child bearing potential will be asked to take proper birth control measures. Patients will also be monitored closely for signs of toxicity as identified by frequent interviews, physical exams and blood tests. Preset toxicity values have been identified and a protocol for dose modification, withdrawal from the study, or active intervention with treatment has been established. Follow up with complete history and physical and blood tests (CBC, chemistry panel, PT, PTT, lipid panel) will be performed.

3) Minimizing risks associated with testing performed as part of the research protocol:
Technicians appropriately trained and skilled in venipuncture will perform the procedure to minimize risk and discomfort. All clinical diagnostic and treatment procedures will be performed in testing facilities, procedure units and operating room that are equipped, staffed, supervised, and accredited by the VASDHS hospital according to nationally-established guidelines and regulations.

Section 17 - Potential Benefits

17) Discuss benefits that may be gained by the subject as well as potential benefits to society in general (see ? for guidance)

Participation has a favorable risk/benefit ratio as patients may benefit from anti-neoplastic effects of LP treatment. Furthermore, patients may benefit from prevention of subsequent lung cancer or recurrence or other type of cancer. It is also possible that patients may not derive any benefit.

Section 18 - Risk/Benefit Analysis

18) Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS
Participation has a favorable risk/benefit ratio as patients may benefit from anti-neoplastic effects of LP treatment. Furthermore, patients may benefit from prevention of subsequent lung cancer or recurrence or other type of cancer. It is also possible that patients may not derive any

benefit.

IMPORTANCE OF THE KNOWLEDGE TO BE GAINED
Other potential benefits may include a better understanding of lung cancer and carcinogenesis and improved management strategy for lung cancer. The information gained will also help plan the direction and conduct of future clinical trials.

Section 21 - Responsibilities and Qualifications

Here are the identified study staff members

Jenny T. Mao, MD, FCCP

Lily Jalu Jih, MD, Lauren M. Collin, Diego Oliva, BS, Kaili Inouye, Hongbing Heather Wei

21) For each staff member listed above, describe their role and qualifications. Also indicate which of the study staff are authorized to obtain consent, when applicable to the study.

Jenny T. Mao, M.D. (Principal Investigator. Dr. Mao has recently transferred to the VA San Diego Healthcare System (VASDHS) as an 8/8th staff physician and Professor of Medicine in the Division of Pulmonary, Critical care and Sleep Medicine at the University of California San Diego (UCSD). Previously, she developed and directed the LIFE-Lung (fluorescence) bronchoscopy and Lung cancer chemoprevention program at the University of California, Los Angeles (UCLA). She has extensive expertise in molecular, tumor and respiratory cell biology, as well as investigator-initiated, NIH-sponsored clinical trials. In recent years she has focused her research on investigating health food supplements, including grape seed procyanidin extract (GSE), for their anti-neoplastic properties. She has expertise in translational and basic science research design, protocol development, biologic monitoring, and the supervision of both basic and clinical research staff. To advance the preclinical findings from her lab with GSE, and a standardized GSE with enhanced bioavailability, leucoselect phytosome (LP), as well as clinical findings from her phase I lung cancer chemoprevention trial with LP, she has developed this pilot proposal to evaluate the feasibility of GSE/LP for lung cancer treatment. During the entire project, Dr. Mao will interact closely with her research team and oversee all aspects of the study, from development of experimental designs and methods, preparation of forms and documents and obtain regulatory approvals in accordance with the applicable institution policies, to implementation of the study protocol, obtain informed consent from the participants, appropriate allocation of biologic specimens for various functional and biomarker studies, and modification of the study protocol should the need arises. She will conduct regular meetings with her research team to review progress, be directly involved in decision making, maintaining communications and interactions among various personnel/team members and obtaining appropriate consultation if necessary. The principal investigator will also be responsible for data analysis and interpretation, preparation of manuscripts and presentations of the findings of the study.

Lily Jih, M.D. (Co-investigator). Dr. Jih is Chief of the Pathology and Laboratory Medicine at the Clinical and Pathology Services at the VA San Diego Healthcare System (VASDHS) and an Associate Professor of Pathology at UCSD. She has extensive experience in tissue acquisition and performing histological and immunohistochemical interpretations of various tissue samples, both for human subjects and animal models. Dr. Jih will assist Dr. Mao in sample procurement, processing and archiving, as well as performing and interpreting histopathology and immunohistochemistry for Ki-67, and other biomarkers of interests, on tumor samples, in addition to evaluating the pathologic responses of primary tumors, lymph nodes, and the pathological staging per AJCC standards. She will also assist Dr. Mao on preparation of manuscripts for publication. No salary is requested.

Diego Olivia, B.S. (Staff research associate). Mr. Olivia is experienced in cell molecular biology techniques and conduct of clinical study including human subject recruitment, informed consent, etc. He has been hired and trained by Dr. Mao to support clinical study activities, perform sample collection and processing, help support the management of the biorepository, perform cell based assays, EIA, ELISA, qPCR assays, etc.

Kaili Inuoye M.S. Staff research associate. Ms. Inuoye is experienced in general cell and molecular biology techniques, as well as preclinical murine models. She also has a micro MBA on laboratory management. She will support and coordinate clinical study activities, including human subject recruitment, informed consent, etc., perform sample collection and processing, help support the management of the biorepository, perform cell based assays, EIA, ELISA, qPCR assays, etc.

Hongbing Heather Wei. M.S. Staff research associate. Ms. Wei has extensive experiences with cell /molecular biology techniques and laboratory management. She will support processing and archiving of biologic samples for Dr. Mao's clinical study, management of the biorepository, perform cell based assays, EIA, ELISA, qPCR assays, etc.

Section 22 - Bibliography

22) List relevant articles that the IRB can use to provide necessary background for the protocol. Do not include an extensive NIH-grant-style bibliography. (Up to 5 recommended, but use more if needed to support the protocol or citations above.)

Mao JT, Roth MD, Fishbein MC, Aberle DR, Zhang ZF, Rao JY, Tashkin DP, Goodglick L, Holmes EC, Cameron RB, Dubinett SM, Elashoff R, Szabo E, Elashoff D. Lung cancer chemoprevention with celecoxib in former smokers. Cancer Prev Res (Phila). 2011. 4(7):984-93.

Mao JT, Xue B, Smoake J, Lu QY, Park H, Henning SM, Burns W, Bernabei A, Elashoff D, Serio KJ, Massie L. MicroRNA-19a/b mediates grape seed procyanidin extract-induced anti-neoplastic effects against lung cancer. J Nutr Biochem. 2016. Aug;34:118-25.

Mao JT, Smoake J, Park HK, Lu QY, Xue B. Grape Seed Procyanidin Extract Mediates Antineoplastic Effects against Lung Cancer via Modulations of Prostacyclin and 15-HETE Eicosanoid Pathways. Cancer Prev Res (Phila). 2016 Dec;9(12):925-932.

Mao JT, Lu QY, Xue B, Neis P, Zamora FD, Lundmark L, Qualls C, Massie L. A Pilot Study of a Grape Seed Procyanidin Extract for Lung Cancer Chemoprevention. Cancer Prev Res (Phila). 2019 Aug;12(8):557-566.

Mao JT, Xue B, Fan S, Neis P, Qualls C, Massie L, Fiehn O. Leucoselect Phytosome Modulates Serum Eicosapentaenoic Acid, Docosahexaenoic Acid, and Prostaglandin E3 in a Phase I Lung Cancer Chemoprevention Study. Cancer Prev Res (Phila). 2021 Jun;14(6):619-626.

Section 23 - Sponsors and Collaborators

23) Clarify any industry financial or other support (e.g., NIH funds the study or Company X provides the assay kits). Identify non-VA Research collaborators and their role in this protocol, including whether or not they have access to subjects or identified data.

Study is funded by VA Clinical Science R&D Merit Review Award CX002028.

In the submission form, upload a copy of the grant, subaward, CRADA, etc. as appliable to the study.

Section 25 - Impact on Clinical Services

25a) Which VA Clinical Services participate in the performance of the project? (NOTE: All clinical trials and any use of clinical services will require project review and approval by the Office of Research Agreements Management (ORAM) to assure availability of those clinical resources. Prior discussion with the appropriate clinical service chief is strongly encouraged)

Check all that apply

- [x] Pharmacy
- [x] Laboratory
- [ ] Cardiology
- [ ] Radiology
- [ ] Nursing
- [x] Pathology
- [ ] Nuclear Medicine
- [ ] MAS (Charts)

☐ Other (list below)

25b) Describe the specific impact or service that will be provided for this protocol.

Research Pharmacy will be responsible for inventorying, storing and dispensing the study medication.

Pathology will be responsible for processing of clinical specimens and provision of portion of samples for assessment of outcome measures when applicable.

Laboratory (Mao research lab) will be responsible for some specimen collection, processing, archiving, distribution and tracking of research samples, as well as assaying of specific biomarkers, when applicable.

To minimize venipuncture, research blood draw will be piggybacked with standard of care blood draw when applicable.

Blood and urine specimens collected for clinical care will only be collected by Blood Draw Lab personnel to maintain quality control over correct specimen labeling, processing, and transport to the Clinical Laboratory.

Pathology (Dr. Jih) and study team is in agreement that the BAL samples will be aliquoted in the procedure unit, one for clinical use, one for research. All samples will be accessioned at pathology, then the portion of BAL samples for research will be sent to Mao research lab.

Section 27 - Privacy, Confidentiality, and Information Security

27a) Provide a brief description of how participant privacy and confidentiality will be protected in this study. Describe the circumstance under which it may be possible for a research team member to identify subjects and any related protections or assurances to prohibit or avoid identification. Describe how the number of people with access to identifiers for research purposes is limited in order to protect a participant's privacy.

Patient confidentiality will be maintained by assigning each subject a study identification number. In so far as possible, study staff will know either the identity of the subject or their data as recorded by identification number, but not both. The Clinical Coordinator and Patient Director, who are experienced in confidentiality, will need to know both the identity and the data. Forms will be designed so that identifying information can be removed from the collected data immediately following completion of the interview or tests. The confidentiality measures will be explained to the subject at the appropriate time, as part of the informed consent and before the collection of any data from him/her. In addition, scrupulous care will be used in handling data when the subject is present, to reassure the subject that similar care is used throughout the study. Study notebooks will be maintained in a dedicated and secure environment and the computer containing subject data will be located in the Clinical Coordinator's office and password protected.

27.b) Entry of a CPRS Research Informed Consent Note is required when subjects will be admitted as inpatients or treated as an outpatients for research *and* the study involves research medical care or may affect medical care.

- ***If a Research consent Note is required, then a Research Progress Note should also be entered for each procedure or intervention.***
- ***Scanning the Consent and HIPAA Authorization into CPRS is not required. Linking the Consent to the Research Informed Consent Note may be permitted and can be useful for trials involving the Research Pharmacy or when research will be performed in conjunction with clinical procedures.***
- ***For Non-Veterans, if Research Informed Consent Notes are entered, then the NOPP Acknowledgment must be scanned into the record. Otherwise a copy of the signed NOPP must be retained with the Investigator's research records and a copy sent to the Privacy Officer; see the ? Help for more information.***

27.b1) Is entry of CPRS notes required based on the above criteria?

- ○ CPRS notes are needed for ALL subjects
- ◉ CPRS notes are needed for SOME subjects
- ○ CPRS notes are NOT needed for any subjects

Identify for which group or groups CPRS records will be entered and to which groups this requirement does not apply.

Patient who meet entry criteria and are enrolled to received study medication will require entry of a CPRS research informed consent note.

Those patients who are consented to participate but do not qualify based on entry criteria (e.g. no diagnosis of early stage lung cancer) will not be enrolled and entry of CPRS Research Informed Consent note will not be required.

27c) Select the VA Sensitive Information (VASI) use category

- ○ This study does not collect or use any VASI
- ○ This study uses but does not save, collect, copy, or record VASI
- ◉ This study does collect or record VASI

Section 27.1 VA Sensitive Information (VASI)

27.1a) For each type of VASI, indicate all that apply:

Indicate which of the following will be collected/recorded:

- ☑ Protected Health Information (PHI)
- ☑ Names
- ☐ Device identifiers and serial numbers
- ☑ E-mail addresses
- ☐ Medical record numbers
- ☐ URLs (Universal Resource Locator)
- ☑ All elements of dates (except year) or any age over 89
- ☐ Health plan beneficiary numbers
- ☐ IP Addresses (Internet Protocol)
- ☑ Telephone numbers
- ☐ Account numbers
- ☐ Biometric Identifiers including finger and voice print
- ☐ Fax numbers
- ☐ Certificate or license numbers
- ☐ Full face photographic images and comparable images
- ☐ All geographic subdivisions smaller than a state
- ☐ Vehicle ID and serial numbers including license plate numbers
- ☑ Social security numbers or scrambled SSNs (describe below)
- ☐ Other unique identifying number, characteristic, or code (describe below)

27.1a1) Describe why SSN are needed for this study

The first letter of last name and last 4 of SSN is typically required to access patient record CPRS. Occasionally full SSN maybe required when there are patients with same first letter in their last name and same last 4 of SSN.

27.1b) Consent Forms and/or HIPAA Authorization

(●) Yes ( ) No

27.1c) Images with personal identifiers are used for this study (x-rays, MRI images with patient names, record numbers, dates, etc.)?

(●) Yes ( ) No

27.1c1) Identify where images will be stored (e.g., in the medical record, with study hardcopy records, with study electronic VASI records).

Pertinent diagnostic images (x ray, PET and/or CT, MRI, bronchoscopy), will be stored in the medical record, with study hardcopy records, with study electronic VASI records

27.1d) Photos with faces or audio video recordings are used for this study.

( ) Yes (●) No

27.1e) Biological specimens with identifiers are used for this study.

(●) Yes ( ) No

Section 27.2 Data Collection, Tools, and Resources

27.2a) Will any specially obtained software be used?

( ) Yes (●) No

27.2b) Will any mobile devices (laptop, tablet, portable hard-drive, etc.) be used in support of this study?

(●) Yes ( ) No

27.2b1) Provide details of the device/s. Indicate whether the device is FIPS 140-2 encryption validated and confirm that the device is listed in the VA EIL. Provide details regarding the nature of the data that will be stored or transmitted on the device and confirm whether a copy of all data will be stored on the VA network.

There will be 3 USB drives used to store coded study data, specifically lab assay data run in the PI's lab. The 3 devices are identical in make and model and adhere to the FIPS 140-2 encryption requirements -- Apricorn 64GB Aegis Secure Key 3z USB 3.1 Flash Drive 64 GB USB 3.1. The USBs will be listed under the PI's EIL once purchased. A copy of the data stored on these devices will be in the PI's R drive (R:\Mao_J) as well so that there is a backup of the data.

27.2c) Does the study require use of an electronic data capture system?

○ Yes ◉ No

27.2d) Will any other web-based applications be used (e.g., for recruitment, completing online questionnaires, or processing data)?

○ Yes ◉ No

27.2e) Will coded data that excludes personal identifiers be used? Coded data excludes *all* HIPAA identifiers (per VHA Handbook 1605.1 Appendix B), including dates

◉ Yes ○ No

27.2e1) Identify where the code key is stored and in what format (electronic, paper).

The code key will be stored in protected, study specific folder on on the secured VA Network R Drive (R:\Mao_J). Only approved staff have access to the PI's R drive.

Section 27.3 Data Sharing and Transportation

27.3a) Does this study involve collecting, sharing or transporting any type of data outside of the local VA?

○ Yes ◉ No

Section 27.4 Research Record Storage and Retention

For each type of record, indicate whether it is collected for this study

27.4a) Hardcopy records/data (includes paper, pictures, film, etc.)

◉ Yes ○ No

27.4a1) Identify precisely where hardcopy data will be stored to include physical site, building, and room number, etc. For each location identify whether VASI or non-sensitive information is stored at that location. For VASI, identify how the data is secured.

Hard copy records/data, including source documents, case report form (CRF)s, informed consent forms (ICF)s, etc. will be kept in study specific folders in locked cabinets and behind locked research study room in building 1, room 6051. Only the Principle Investigator and study coordinator(s) will have access to the filing cabinet.

27.4a2) Are all of the above locations at VA?

◉ Yes ○ No

27.4b) Electronic study records (includes computer files, removable disk files, digital files, etc.).

(●) Yes ( ) No

27.4b1) Identify precisely where ***non-sensitive*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

A study specific, password protected electronic folder will be housed in the Research folder within the R drive (R:\Mao_J).

Subfolders will be created for regulatory items, biorepository, study data and Biomarker assays.

The three USBs with coded study data will be stored securely in the PI's locked research spaces -- Rooms 6051, 6052, 6049, where only authorized lab personnel are permitted to enter.

27.4b2) Identify precisely where ***VASI*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

If no VASI is collected or recorded for this study, simply indicate that the "Study does not collect or record VASI".

A study specific access program has been developed and will be housed in the study specific, password protected electronic folder within the Research folder inthe R drive (R:\Mao_J).

27.4b3) Are any of the locations described in 27.4b outside of the VA Secure Network? *Note: this includes storage on a computer local hard drive.*

( ) Yes (●) No

27.4c) Record Retention - VHA requires compliance with Records Control Schedule (RCS-10) for retention of electronic and hard copy records. Following study closure, these temporary records must be retained for six years and then destroyed. Longer retention may be permitted if required by other Federal regulations or requirements. Will RCS-10 requirements be followed (i.e., 6-year retention)?

(●) I will adhere to VHA Records Control Schedule-10 requirements
( ) I request an exception to RCS-10 requirements

Section 27.5 Additional Privacy or Information Security Details

Provide any other privacy or information security details here.

n/a

Section 27.6 Attestations

In the event of real or suspected breach of security, the Information Security Officer, Privacy Officer, VA Police (if appropriate), and the individual's supervisor will be notified within one hour of learning of the event.

(●) Agree ( ) Disagree

Study staff will be up to date on any required VHA Privacy Policy and Information Security training or they will not be allowed access to VA Sensitive Information.

◉ Agree ○ Disagree	
Access to research sensitive information, if any, will be removed when study personnel are no longer part of the research team.	
◉ Agree ○ Disagree	
At least one copy of all study records (whether sensitive or non-sensitive) will be retained under VA control and only destroyed in compliance with the approved Records Control Schedule	
◉ Agree ○ Disagree	
The VA retains ownership of the research data. Should the investigator leave the VA, custody of the research records will be assigned to another investigator and the Research Service notified in writing, or custody of the research records will be transferred to the Research Service.	
◉ Agree ○ Disagree	

Section 28 - Protocol Association to New or Existing Project	
28) Is this a new R&D Project? Before you go on to complete the *Initial Review Submission Form* (which is used for attachments), please address the association of this Protocol to an R&D Committee Project. This Protocol may represent a new R&D Project, or it may be an additional Protocol under an existing R&D Project (such as when a single grant supports multiple Protocols). Will this Protocol be submitted to the R&D Committee as a new Project?	
◉ Yes ○ No	

The Protocol Application is now complete for a Protocol that will also be a new R&D Committee Project.

Next you will go on to the Initial Review Submission Form which is used to package up the Protocol Application and any needed attachments and submit them to the IRB.

Click on *Save and Continue*