Co-Principal Investigators:

W. Jeffrey Petty, MD
Section on Hematology and Oncology
Wake Forest Baptist Medical Center
Medical Center Boulevard
Winston-Salem, NC 27157
[redacted]

Jim Wudel, MD
Department of Surgical Sciences, Section on Cardiothoracic Surgery
Wake Forest Baptist Medical Center
Medical Center Boulevard
Winston-Salem, NC 27157
[redacted]

Karen M. Haas, PhD
Department of Microbiology and Immunology
Wake Forest Baptist Medical Center
575 N. Patterson Ave.
2E-024 Biotech Place
Winston-Salem, NC 27157
[redacted]

Frank Marini, PhD
Director, Center for Regenerative Imaging and Cell Imaging Shared Resource
Wake Forest Institute of Regenerative Medicine
Winston-Salem, NC 27101
[redacted]

Alexei Mikhailov, MD
Department of Pathology
Wake Forest Baptist Medical Center
Winston-Salem, NC 27101
[redacted]

Pierre Triozzi, MD
Section on Hematology and Oncology
Wake Forest Baptist Medical Center
[redacted]

Co-Investigator(s):

Thomas Lycan, DO
Hematology & Oncology
Wake Forest Baptist Medical Center
Medical Center Boulevard
Winston-Salem, NC 27157
[redacted]

Payal Gandhi, PA-C
Section on Hematology and Oncology
Wake Forest Baptist Medical Center
[redacted]

Jennifer Z. Miller, PharmD
Oncology Clinical Specialist
Pharmacy Department
Wake Forest Baptist Medical Center
[redacted]

Greg Hawkins, PhD
Center for Human Genomics
Wake Forest Baptist Medical Center
[redacted]

Biostatistician:

Beverly Levine, PhD
Biostatistics Core
Comprehensive Cancer Center
Wake Forest Baptist Medical Center
Medical Center Boulevard
Winston-Salem, NC 27157
[redacted]

Tissue Procurement Officer:

Elizabeth McWilliams
Wake Forest Baptist Medical Center
[redacted]

Research Nurse:

Sharon Averill
Comprehensive Cancer Center of Wake Forest
Baptist Medical Center
[redacted]

Study Coordinator: Jeffrey Kettler
Comprehensive Cancer Center of Wake Forest
Baptist Medical Center
[redacted]

Data Management: Amy Hughes
Comprehensive Cancer Center of Wake Forest
Baptist Medical Center
[redacted]

Regulatory Contact: Cindy Miller
Comprehensive Cancer Center of Wake Forest
Baptist Medical Center
[redacted]

Participating Institution(s): WFBCCC

Version Date: 07/26/18

Amended: 05/18/21

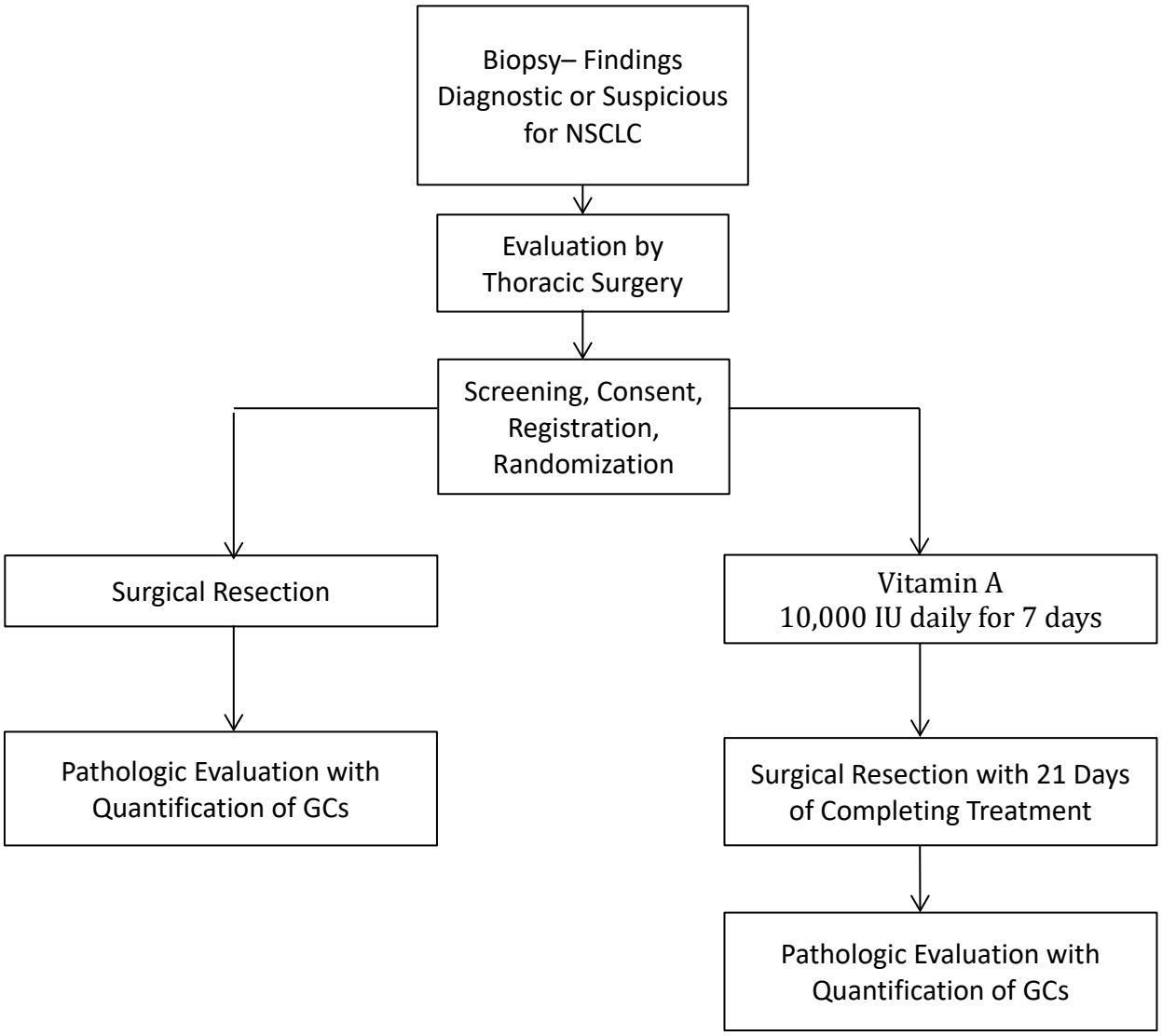
Confidential

Table of Contents

Schema 6
1.0 Introduction and Background 7
2.0 Objectives 9
2.1 Primary Objective 9
2.2 Secondary Objective(s) 9
2.3 Exploratory Objectives 9
3.0 Patient Selection 9
3.1 Inclusion Criteria 9
3.2 Exclusion Criteria 9
3.3 Inclusion of Women and Minorities 10
4.0 Registration Procedures 10
5.0 Study Outcomes and Study Measures 11
5.1 Primary Outcome 11
5.2 Secondary Outcomes 11
6.0 Treatment Plan 11
6.1 Study-Related Interventions 12
6.2 Treatment Administration 12
6.2.1 Dose Modifications 12
6.3 General Concomitant Medication and Supportive Care Guidelines 13
6.4 Duration of Therapy 13
6.5 Duration of Follow Up 13
7.0 Measurement of Effect 13
7.1.1 Methods for Pathologic Evaluation 13
7.1.2 Assessment for efficacy 13
8.0 Adverse Events List and Reporting Requirements 14
8.1 Adverse Event List for Vitamin A 14
8.2 Adverse Event Characteristics 14
8.4 STRC SAE Reporting Requirements 15
8.5 WFUHS IRB AE Reporting Requirements 15
9.0 Pharmaceutical Information 16
9.1 Pharmaceutical Accountability 16

9.2 Vitamin A 16
10.0 Data Management 17
11.0 Statistical Considerations 17
11.1 Power and Sample Size 17
11.2 Method of Randomization 17
11.3 Analysis of Primary Objective 17
11.5 Analysis of Exploratory Objective 18
11.6 Estimated Accrual Rate 18
11.7 Estimated Study Length 18
References 19
Appendix A – Protocol Registration Form 21
Appendix B – Subject Eligibility Checklist 22
Appendix C – Mandatory DSMC SAE Reporting Guidelines 24
Appendix D – Baseline Tobacco Use 31
Appendix E – Adverse Events Log 34
Appendix F – Outcomes Data Collection Form 35
Appendix G – Survival Form 36
Appendix H – Exploratory Outcomes Data Collection Form 37
Appendix I– Medical History 38
Appendix J – Vitals Form 39
Appendix K - Withdrawal of consent for the intervention and medical record use 41
Appendix L - Vitamin A Medication Log 42
Appendix M – Pre-Toxicity 43

Schema


Biopsy– Findings Diagnostic or Suspicious for NSCLC
Evaluation by Thoracic Surgery
Screening, Consent, Registration, Randomization
Surgical Resection
Pathologic Evaluation with Quantification of GCs
Vitamin A 10,000 IU daily for 7 days
Surgical Resection with 21 Days of Completing Treatment
Pathologic Evaluation with Quantification of GCs

1.0 Introduction and Background

Immunotherapy is rapidly replacing chemotherapy as the most effective treatment for non-small cell lung cancer. Immunotherapy resistance is complex and different factors may be responsible for individual patients with immunotherapy resistant lung cancers. Vitamin A deficiency is associated with increased risk of lung cancer, and this deficiency also has been associated with poor immune system function. Our proposed study seeks to improve immune system function in the neoadjuvant setting by treating patients with vitamin A prior to surgical resection for non-small cell lung cancer. The main endpoints of the study will be to evaluate the development of germinal centers in resected cancers and adjacent lymph nodes, histopathologic responses, and changes in immunologic biomarkers.

Vitamin A deficiency was first observed to reduce immune system function and increase risk of pulmonary infections in the early 1900s. This deficiency laterwas found to increase lung cancer risk in the 1960s. This observation gave rise to the concept of chemoprevention with the use of vitamin A or its derivatives proposed to reduce lung cancer risk [1]. Two chemically distinct but related classes of compounds were investigated for this purpose: retinoids and carotenoids. Retinoids are compounds that are highly similar to vitamin A (retinol). Retinoids have a single cyclic end group and a hydrophilic side chain. These compounds function by binding to retinoid receptors and altering transcription [2-7]. The molecular weights of retinoid compounds are similar to retinol (mw=286.5 g/mol). Carotenoids are much larger compounds (for beta carotene, mw = 536.9 g/mol) that contain multiple cyclic structures. These compounds do not directly interact with retinoic acid receptors. Certain carotenoids including beta carotene are prodrugs of vitamin A and can be converted to vitamin A through enzymatic cleavage in the intestine although the majority of beta-carotene enters the blood stream unchanged [8]. Carotenoids are felt to produce beneficial effects by serving as antioxidants in addition to functioning as pro-vitamins. Unfortunately, in the presence of tobacco carcinogens, beta-carotene undergoes eccentric cleavage leading to the formation of DNA damaging organic molecules, decreased retinoic acid concentrations in lung tissue [8, 9]. Unexpectedly, these drugs have also been shown to increase the development of epithelial pre-neoplasia [9].

Large clinical chemoprevention studies of retinoid or carotenoid supplementation have been negative with the indication of harm for beta-carotene supplementation in patients who continue to smoke [10-12]. The studies that examined beta-carotene and demonstrated increased risk of lung cancer for high risk populations included CARET and ATBC [11, 12]. Another study specifically examined the effects of the retinoid, retinyl palmitate, which will be used in the current study. In this study, called EUROSCAN, 2592 patients were randomized to receive retinyl palmitate or not and no change in cancer risk was observed for patients receiving retinyl palmitate in the entire population as well as the smoking and non-smoking cohorts [10]. Based on the concerns regarding beta-carotene and the lack of harm observed with retinyl palmitate in EUROSCAN, current practice guidelines recommend that patients who currently smoke should avoid high dose beta-carotene supplements but no such recommendations are made for avoiding vitamin A or retinyl palmitate which will be used in the current study [13].

The doses of retinyl palmitate used in prior chemoprevention studies have been much higher that what is currently recommended as a vitamin supplement. In the EURSOCAN study, patients received 300,000 IU of retinyl palmitate daily for the first year followed by 150,000 IU daily for the second year. To reduce risk of acute toxicity, a fifteen fold lower dose, 10,000 IU, was selected for this study. This dose is recommended for the prevention of vitamin A deficiency and is the upper limit of the current recommended daily intake.

While prior studies dampened enthusiasm in the retinoid chemoprevention field, the use of retinoids for lung cancer treatment has shown some promise particularly in combination with targeted agents. In a prior neoadjuvant study, the non-classical retinoid, bexarotene, demonstrated biological effects on cancer tissues even with a short, one week course of treatment [14]. Vitamin A itself and other classical retinoids are known to have beneficial effects on immune system function, and the effectiveness of vitamin A in combination with PD-1 drugs has not been adequately studied.

Vitamin A and other retinoids function by activating nuclear receptors including retinoic acid receptors (RARs) and retinoid X receptors (RXRs) [3, 6, 7]. Activation of these nuclear receptors leads to transcription of target genes and changes in cellular function. Several lines of evidence support an important role for vitamin A to support immune system function. Vitamin A deficiency increases risk of infections in experimental models. Also, vitamin A supplementation reduces mortality from infectious complications in populations with a high risk of deficiency. Furthermore, vitamin A supplementation has been shown to improve antibody titers in response to vaccination in clinical trials.

The mechanisms through which vitamin A promotes immune system function are complex and involve both B-cell and T-cell mediated effects. The focus of the current study will be to examine changes in B-cell function although T-cell subsets will also be examined. In published studies from preclinical models, retinoid treatment of B-cells has been shown to increase cellular proliferation, improve antibody diversification through somatic hypermutation, and increase immunoglobulin production. In addition, animal models have shown that retinoid treatment increases formation of germinal centers which are critical for B-cell maturation.

Given the opportunities to improve patient outcomes by improving immunologic function, investigation of vitamin A supplementation in patients with lung cancer is an exciting opportunity to investigate an immunologic active treatment with minimal toxicities. Vitamin A treatment side effects can occur following prolonged exposure to very high doses but are extremely uncommon with shorter courses of treatment. Changes in cellular function, however, are quite rapid with target gene expression changes occurring within 24 hours. Increases in germinal center (GC) formation triggered by retinoids are seen in animal models following 6 days of retinoid treatment with measurements performed on day 10 (4 days after completing retinoid treatment) [15]. For this study we will examine a 7-day period of treatment with vitamin A in a window-of -opportunity neoadjuvant setting.

In our study, we will examine clinical outcomes including pathologic response and overall survival. The rational for induction of GC formation improving outcomes arises from an early study of resected lung cancers found that primary lung cancers with GC

formation have lower risk of nodal metastases [16]. Although underpowered for statistical comparison, the risk of relapse and overall survival appeared improved in tumors with GCs in this study as well. These findings suggest that inducing GC formation with vitamin A could lead to improved survival for early stage lung cancer patients.

2.0 Objectives

2.1 Primary Objective

2.1.1 To compare the percentage of resected cancers containing germinal centers (GCs) in patients who receive neoadjuvant vitamin A to controls.

2.2 Secondary Objective(s)

2.2.1 To compare the abundance of GCs in adjacent lymph nodes in patients who receive neoadjuvant vitamin A to controls.

2.2.2 To compare histopathologic responses based on tumor necrosis in lung cancer patients who receive neoadjuvant vitamin A to controls.

2.2.3 To compare overall survival of patients who receive neoadjuvant vitamin A to controls.

2.3 Exploratory Objectives

2.3.1 To describe immunophenotypic changes of monocytes including myeloid derived suppressor cells (MDSCs) in pre- and post-treatment blood samples.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Patient must be $\geq$ 18 years of age

3.1.2 Patients must have either biopsy proven or radiographically suspected non-small cell lung cancer.

3.1.3 Patients must have disease in the chest that is felt to be surgically resectable.

3.1.4 ECOG performance status of 0-2.

3.1.5 Ability to understand and the willingness to sign an IRB-approved informed consent document

3.2 Exclusion Criteria

3.2.1 Patients < 18 years of age

3.2.2 Women who are pregnant or breast feeding.

3.2.3 Patients may not be receiving any other investigational agents for the treatment of NSCLC.

3.2.4 Patients may not be taking the following medications: high dose vitamin A supplement (multivitamin supplements prohibited only if vitamin A content is greater than 3,500 IU), bexarotene, alitretinoin, tretinoin, adapalene, isotretinoin, acetretin, doxycycline, minocycline, or demeclocycline,

3.2.5 Uncontrolled intercurrent illness including, but not limited to, pancreatitis, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Hypervitaminosis A – toxic effects of ingesting too much vitamin A

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study.

The study consent form will also be provided in Spanish for Spanish-speaking participants. Based on CCCWFU population estimates, we expect approximately 40% of participants to be women. Translating this to our sample size estimate of 180, we plan to enroll at least 48 women. Similarly, we expect approximately 5% of study participants to be Hispanic/Latino (N=6). We plan to enroll at least 15% Black or African American (N=18), no American Indian/Alaska Natives, 5% Asian (N=6). Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be linked to a study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix B)
2. Complete the Protocol Registration Form (Appendix A)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.
   Contact Information:

Protocol Registrar PHONE (336) 713-6767
Protocol Registrar FAX (336) 713-6772
Protocol Registrar E-MAIL (registra@wakehealth.edu)

*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study
- assign the patient to treatment arm

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 Presence/absence of germinal centers (GCs) in resected cancer tissues from patients who receive neoadjuvant vitamin A and controls.

5.2 Secondary Outcomes

5.2.1 Measurement of GCs per unit area in adjacent lymph nodes will be assessed using semi-quantitative designation (high, moderate, low, or absent) in patients who receive neoadjuvant vitamin A and controls.

5.2.2 Pathologic response will be defined by tumor necrosis which will be dichotomized as present or absent in patients who receive neoadjuvant vitamin A and controls.

5.2.3 Overall survival of patients receiving neoadjuvant Vitamin A and in controls.

5.3 Exploratory Outcomes

5.3.1 Immunophenotypic changes among monocytes including quantification of MDSCs in pre- and post-treatment blood and tissue samples. Peripheral blood samples at 2 time points (before treatment, and after treatment. Treatment Plan

5.3 Study-Related Interventions

	Pre-Study[a]	After completion of Vitamin A	Post-Operative
Informed consent	X		
Demographics	X		
Medical history	X		
Concurrent meds	X		
Physical exam	X		
Vital signs	X	X	
Performance Status	X		
B-HCG[d]	X		
Adverse event evaluation		X	X
Research Blood Draw[e]	X	X	
GC Measurement			X

a: Pre-study requirements listed in table must be completed **within** 28 days prior to registration. The research blood draw should be collected **prior** to starting Vitamin A.
b: Additional monitoring interventions may be done per the treating physician depending on which treatment is being given post-assignment.
c: Alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, SGOT[AST], SGPT[ALT]
d: Serum pregnancy test (women of childbearing potential).
e: This procedure is only applicable for patients who chose to participate in the research blood draw

5.4 Treatment Administration

Patients who are randomized to receive Vitamin A may start no later than 3 months from the time of registration in a time frame that allows them to have surgery with 10 days of completing treatment Vitamin A treatment. Vitamin A will be administered at 10,000 IU orally for 7 consecutive days. Surgery may occur on the day that the last Vitamin A dose is taken. If surgery is delayed more than 21 days from completing Vitamin A, the patient will be considered non-evaluable and will be replaced.

6.2.1 Dose Modifications

No dose modifications will be performed. Patients who have unacceptable side effects or withdraw consent prior to undergoing surgical resection will discontinue treatment, considered non-evaluable, and will be replaced.

6.3 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

6.4 Duration of Therapy

Treatment will continue for 7 days. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), specifically if Grade 3 or 4 toxicity is observed
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.5 Duration of Follow Up

Patients will be followed for a minimum of 30 days after the last study drug is administered for adverse events monitoring. Patients will be followed for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be followed until death for monitoring survival study endpoints.

7.0 Measurement of Effect

7.1.1 Methods for Pathologic Evaluation

Standard pathologic evaluation will be performed following surgical resection. This evaluation includes measurement of lymph node involvement as well as assessment of histopathologic changes such as necrosis within the tumor. This will be classified as present or absent for the purposes of statistical comparison.

7.1.2 Assessment for efficacy

Germinal center formation has been observed in 35% of lung cancers with the majority of these occurring at the tumor margin. In the clinical

laboratory and the laboratory of Dr. Marini, IHC will be performed to assess the microenvironment components using an IHC panel. GCs will be assessed as being present or absent and the density GCs at within lymph nodes will be estimated using standard digital microscopy and automated methods under the supervision of Dr. Marini and Dr. Mikhailov. If necessary, manual assessment of GC density within lymph nodes will be performed and graded as high, moderate, low, or absen8.0

Adverse Events List and Reporting Requirements

8.1 Adverse Event List for Vitamin A

Check with your doctor immediately if any of the following side effects occur while taking vitamin A:

- Bleeding from gums or sore mouth
- bulging soft spot on head (in babies)
- confusion or unusual excitement
- diarrhea
- dizziness or drowsiness
- double vision
- headache (severe)
- irritability (severe)
- peeling of skin, especially on lips and palms
- vomiting (severe)

Check with your doctor as soon as possible if any of the following side effects occur while taking vitamin A:

- Bone or joint pain
- convulsions (seizures)
- drying or cracking of skin or lips
- dry mouth
- fever
- general feeling of discomfort or illness or weakness
- headache
- increased sensitivity of skin to sunlight
- increase in frequency of urination, especially at night, or in amount of urine
- irritability
- loss of appetite
- loss of hair
- stomach pain
- unusual tiredness
- vomiting
- yellow-orange patches on soles of feet, palms of hands, or skin around nose and lips

8.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

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

8.4 DSMC SAE Reporting Requirements

The Data Safety and Monitoring Committee (DSMC) is responsible for reviewing SAEs for CCCWFU Institutional studies as outlined in Appendix C. DSMC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All CCCWFU Clinical Research Management (CRM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

8.5 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

9.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the commercial agent administered in this study can be found in Section 8.0.

9.1 Pharmaceutical Accountability

All drugs used in this protocol are commercially available.

9.2 Vitamin A

Product Description: Vitamin A is provided as retinyl palmitate in 10,000 IU capsules from Major Pharmaceuticals.

Storage:
Vitamin A stock bottles will be purchased and stored in the investigational pharmacy. Temperature conditions will be monitored per standard practice. Unopened vials of Vitamin A are stable until the expiration date indicated on the package when stored at controlled room temperature.

Route of Administration: Oral
Drug Accountability: Patients will be asked to record the time and date of medication self-administration with form attached in Appendix.

Disposal: Dispose through the Institutional waste stream and guidelines.

10.0 Data Management

Informed consent document	EPIC
Protocol registration form (Appendix A)	WISER/OnCore
Baseline Tobacco Use (Appendix D)	WISER/OnCore
Adverse Events Log (Appendix E)	WISER/OnCore
Outcomes Data Collection (Appendix F)	WISER/OnCore
Survival Form (Appendix G)	WISER/OnCore

11.0 Statistical Considerations

11.1 Power and Sample Size

Roughly 35% of lung cancers express germinal centers (GC) with the majority of GCs being detected at the tumor margin. Given our target sample size of n=90 patients per arm, we will have 80% power, using a one-tailed alpha of 0.05, to detect an increase to 53% expressing GCs in the treatment arm, given the expected “background” 35% in the standard-of-care arm. Given the current surgical volume, it is estimated that we will enroll 90 patients per year, so that total accrual will last approximately 2 years.

11.2 Method of Randomization

Patients will be randomized in a 1:1 ratio to receive the vitamin A treatment intervention or standard of care. Patients will be stratified for randomization based on pre-operative stage (stage 1, 2, or 3).

11.3 Analysis of Primary Objective

11.3.1 The outcome for our primary objective is dichotomous—GCs present/absent. Following basic bivariate analysis in contingency tables of presence/absence by treatment arm we will model presence/absence of GCs in a logistic regression model as a function of treatment arm, stage, and age at diagnosis. We will first examine the statistical interaction term between stage and treatment arm, and if it is significant, we will present findings stratified by stage. If it is not significant, we will remove the interaction term from the final model and include stage as a simple covariate only.

11.4 Analysis of secondary objectives

11.4.1 Number of GCs per unit area in lymph nodes will be quantified ordinally only, in mutually exclusive ordered groups of high, moderate, low, or absent. We will examine association between treatment arm and rank order of number of GCs in contingency table analysis using methods that incorporate the ordinal ranking of one of the variables. We will also model the outcome of rank order of number of GCs as a function of treatment arm, age, and stage using ordinal logistic regression. As above we will first examine whether there is a significant

interaction between stage and treatment arm with respect to the outcome, and if so will present findings stratified by stage.

11.4.2 Presence/absence of necrosis will be analyzed in a similar manner as the dichotomous outcome of presence/absence of GCs, described above under 11.3.1.

11.4.3 Overall survival will be estimated in treatment and control groups using standard Kaplan-Meier life table analyses and will also be evaluated in the multivariable setting using Cox proportional hazards modeling, where covariates of age and stage will be included. As described above we will first examine whether the statistical interaction between stage and treatment arm is significant.

11.5 Analysis of Exploratory Objective

Analyses of changes in lymphocytes will be exploratory in nature. Changes in T regulatory cell concentrations and MDSCs will be assessed in each arm (Dr. Triozzi). These measures will be compared longitudinally between groups using a mixed models approach with subjects being considered as random effects and time and treatment and time by treatment interaction considered as fixed effects. For these analyses the baseline (pre-treatment) assessment of each outcome will be included as a covariate in the mixed model.

11.6 Estimated Accrual Rate

90 patients per year.

11.7 Estimated Study Length

Approximately 2 years of accrual plus 6 months for follow-up on last patient and data analysis for a total of 2.5 years.

References

1. Sporn MB, Dunlop NM, Newton DL, Smith JM. Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). Fed Proc 1976; 35:1332-8..

2. Dragnev KH, I Pitha-Rowe, Y Ma, WJ Petty, D Sekula, B Murphy, M Rendi, N Suh, MB Sporn, SJ Freemantle, and E Dmitrovsky. Specific chemopreventive agents trigger proteasomal degradation of G1 cyclins: Implications for combination therapy. Clin Cancer Res 2004; 10:2570-7.

3. Dragnev KH, WJ Petty, and E Dmitrovsky. Retinoid targets in cancer therapy and prevention. Cancer Biol Ther 2003; 2:S150-6.

4. Petty WJ, KH Dragnev, and E Dmitrovsky. Cyclin D1 as a target for chemoprevention. Lung Cancer 2003; 41:S155-61.

5. Pitha-Rowe I, WJ Petty, Q Feng, PH Koza-Taylor, DA DiMattia, L Pinder, KH Dragnev, N Memoli, VA Memoli, T Turi, J Beebe, S Kitareewan, and E Dmitrovsky. Expression profiling uncovers UBE1L as a target for lung cancer chemoprevention. Cancer Research 2004; 64:8109-8115.

6. Dragnev KH, WJ Petty, JR Rigas, and E Dmitrovsky. Non-classical retinoids and lung carcinogenesis. Clin Lung Cancer. 2005; 6:237-44.

7. Petty WJ, N Li, A Biddle, Y Ma, R Bounds, NB Desai, KH Dragnev, S Freemantle, and E Dmitrovsky. A novel RARβ isoform and retinoid resistance in lung carcinogenesis. J Natl Cancer Inst 2005; 97:1645-51.

8. Novotny JA, Harrison DJ, Pawlosky R, Flanagan VP, Harrison EH, Kurilich AC. Beta-carotene conversion to vitamin A decreases as the dietary dose increases in humans. J Nutr. 2010; 140:915-8.

9. Wang XD, Liu C, Bronson RT, Smith DE, Krinsky NI, Russell M. Retinoid signaling and activator protein-1 expression in ferrets given beta-carotene supplements and exposed to tobacco smoke. J Natl Cancer Inst 1999; 91:60-6.

10. van Zandwijk N, Dalesio O, Pastorino U, de Vries N, van Tinteren H. EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer. For the EUropean Organization for Research and Treatment of Cancer Head and Neck and Lung Cancer Cooperative Groups. J Natl Cancer Inst 2000; 92:977-86.

11. Goodman GE, Thornquist MD, Balmes J, Cullen MR, Meyskens FL Jr, Omenn GS, Valanis B, Williams JH Jr. The Beta-Carotene and Retinol Efficacy Trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. J Natl Cancer Inst 2004; 96:1743-50.

12. Albanes D, Heinonen OP, Huttunen JK, Taylor PR, Virtamo J, Edwards BK, Haapakoski J, Rautalahti M, Hartman AM, Palmgren J, et al. Effects of alpha-tocopherol and beta-

carotene supplements on cancer incidence in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. Am J Clin Nutr 1995; 62:1427S-1430S.

13. Lillenbaum R. (2018). Lung cancer chemoprevention. In T. Post (Ed.) UpToDate. Waltham, Mass.: UpToDate. Retrieved from www.uptodate.com

14. Dragnev KH, WJ Petty, S Shah, WC Nugent, LD Lewis, CC Black, V Memoli, JR Rigas, and E Dmitrovsky. A proof-of-principle clinical trial of bexarotene in non-small cell lung cancer. Clin Cancer Res 2007; 13:1794-1800.

15. Yifan Ma and A. Catharine Ross. Toll-Like Receptor 3 Ligand and Retinoic Acid Enhance Germinal Center Formation and Increase the Tetanus Toxoid Vaccine Response. Clinical and Vaccine Immunology 2009; 16:1476–1484.

16. Elizabeth B. Gottlin, Rex C. Bentley, Michael J. Campa, David S. Pisetsky, James E. Herndon II, and Edward F. Patz, Jr. The Association of Intratumoral Germinal Centers with Early-Stage Non-small Cell Lung Cancer. Journal of Thoracic Oncology 2011; 6:1687-1690.

Appendix A – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic

☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

Performance Status: ___ ☐ ECOG

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by WISER): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix B – Subject Eligibility Checklist

IRB Protocol No. ___ ___ ___ ___ ___ ___ ___ ___	**CCCWFU Protocol No.62218**
Study Title: A Pilot Study of Neoadjuvant Vitamin A for Resectable Non-Small Cell Lung Cancer	
Principal Investigator: W. Jeffrey Petty, MD	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm ***
Patient must be ≥18 years of age			
Patients must have biopsy proven or radiographically suspected non-small cell lung cancer.	☐	☐	
Patients must have disease in the chest that is felt to be surgically resectable.	☐	☐	
ECOG performance status of 0-2	☐	☐	
Ability to understand and the willingness to sign an IRB-approved informed consent document			
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm ***
Patients <18 years of age			
Women who are pregnant or breast feeding.	☐	☐	
Patients may not be receiving any other investigational agents for the treatment of NSCLC	☐	☐	
Patients may not bne taking the following medications: high dose vitamin A supplement (multivitamin supplements prohibited only if vitamin A content is greater than 3,500 IU), bexarotene, alitretinoin, tretinoin, adapalene, isotretinoin, acetretin, doxycycline, minocycline or demeclocycline	☐	☐	
Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements	☐	☐	
Hypervitaminosis A – toxic effects of ingeting too much vitamin A	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

WISER Assigned PID: _____

Signature of research professional confirming eligibility:_____
Date: ___ ___/___ ___/___ ___

Signature of Treating Physician: _____

Date: ___ ___/___ ___/___ ___

Signature of Principal Investigator**: _____
Date: ___ ___/___ ___/___ ___

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix C – Mandatory DSMC SAE Reporting Guidelines

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	**Date: 02/11/2021**

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites. There are three types of trials that are included in this category:
    a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
    b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
    c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients

enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization ≥ 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Definitely”. Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***

13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the STRC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

Glenn Lesser, MD – Hematology Oncology [redacted]
Mercedes Porosnicu, MD-- Hematology Oncology [redacted]
Ryan Hughes, MD – Radiation Oncology [redacted]
Michael Goodman, MD -- Hematology Oncology [redacted]
Daniel Reed, MD -- Hematology Oncology [redacted]
Mary Beth Seegars, MD -- Hematology Oncology [redacted]

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the

table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment shouldbe considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

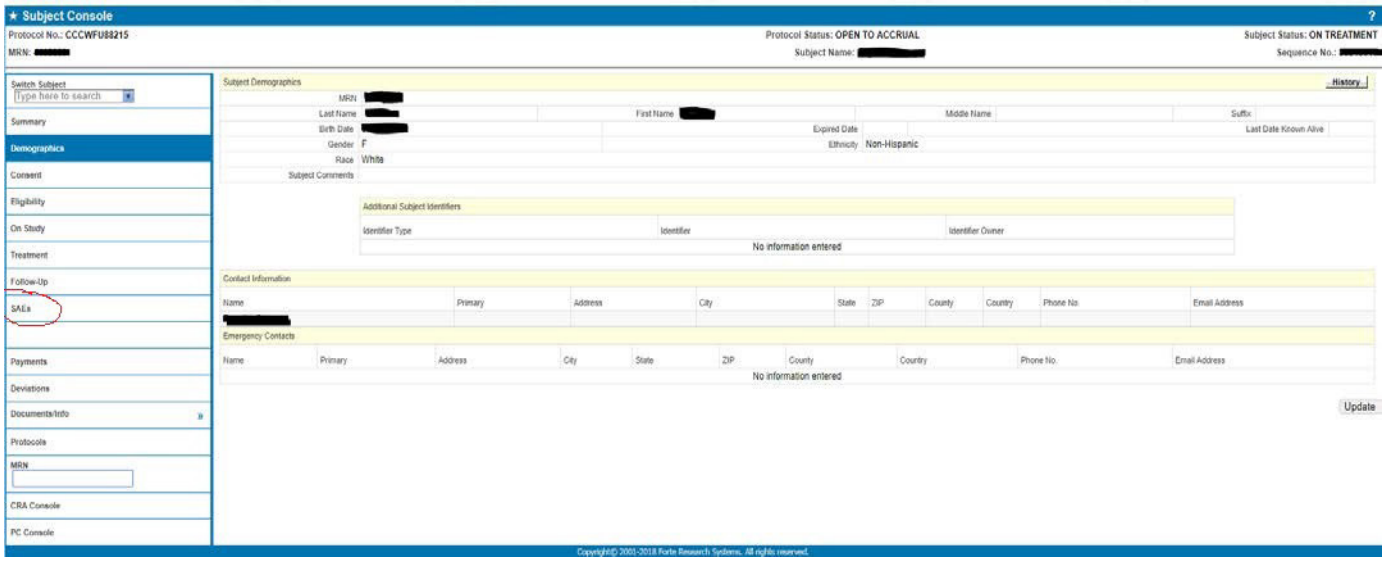
Acronyms

AE – Adverse Event
DSMC-Data and Safety Monitoring Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

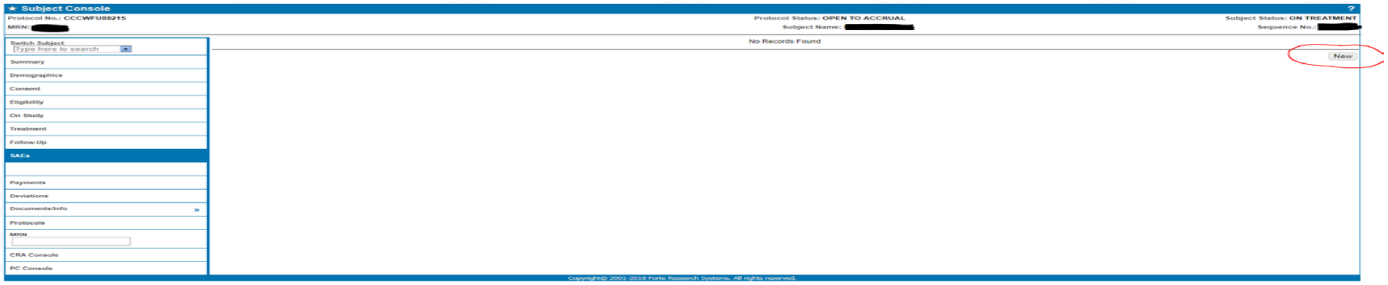
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

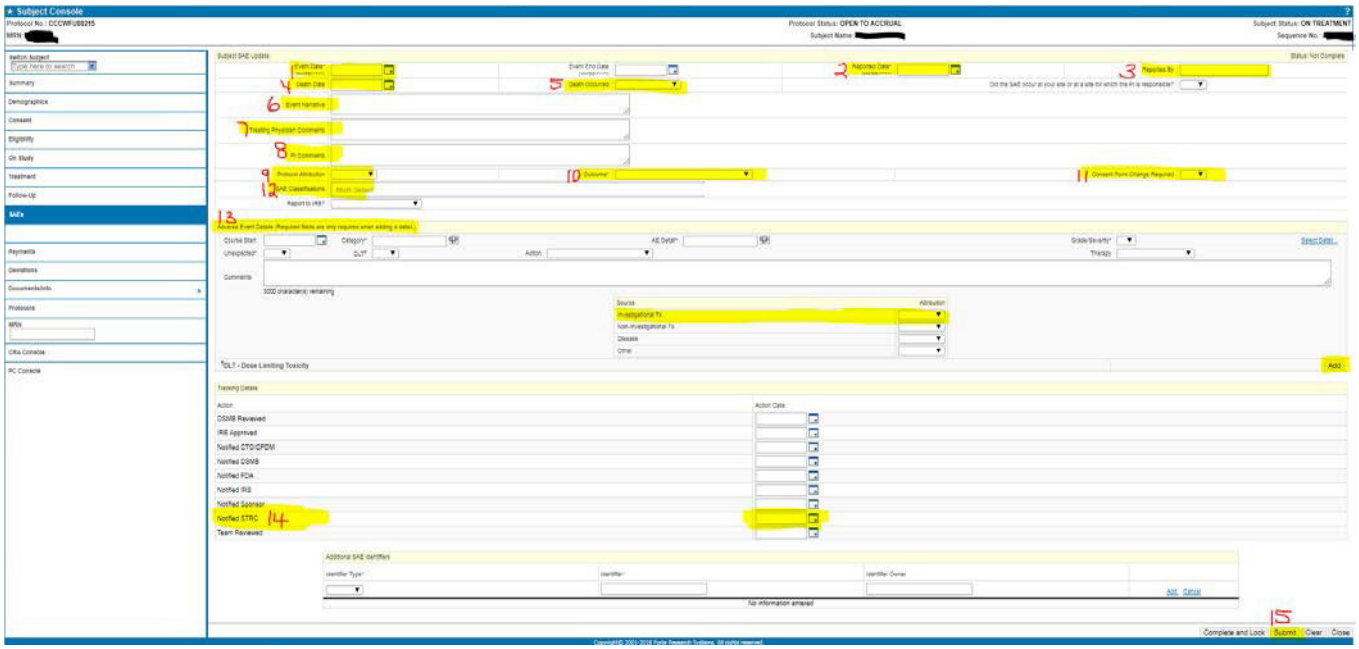
Screen Shot 1:



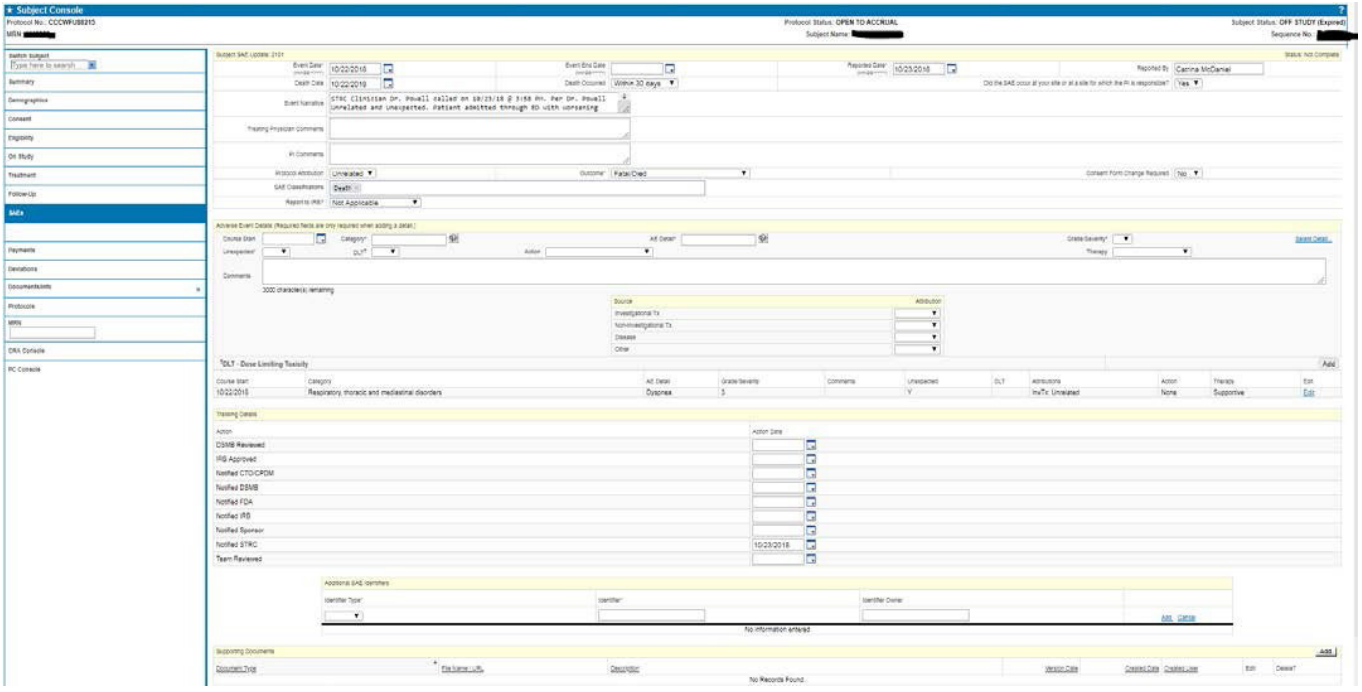
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



Appendix D – Baseline Tobacco Use

CASE REPORT STUDY FORM FOR PATIENT TOBACCO USE
TO BE USED AT BASELINE

Study Number: 6 2 2 1 8 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: W. Jeffrey Petty, M.D. Date: ___ ___/___ ___/___ ___

Research Personnel Filling out form_____

CANCER PATIENT TOBACCO USE QUESTIONNAIRE (C-TUQ)

Please answer the following questions. This information is confidential and will not be shared with your medical providers.

Section 1. Basic Tobacco Use Information

1. Have you smoked at least 100 cigarettes (5 packs=100 cigarettes) in your entire life?

☐ Yes
☐ No **Go to Section 2 (page 2).**
☐ Don't know/Not sure **Go to Section 2 (page 2).**

2. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.

_____ Years *If you smoked less than one year, write "1."*

3. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day?

A pack usually has 20 cigarettes in it.

_____ Number of cigarettes per day

4. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.

☐ I smoked a cigarette today (at least one puff).
☐ 1-7 days. Number of days since last cigarette: _____

☐ Less than 1 month. Number of weeks since last cigarette: _____
☐ Less than 1 year. Number of months since last cigarette: _____
☐ More than 1 year. Number of years since last cigarette: _____
☐ Don't know/Don't remember

5. In the past 30 days, have you smoked any cigarettes, even one or two puffs?

☐ Yes
☐ No → Go to Question 7.

6. In the past 30 days, have you been trying to quit (or trying to stay off) smoking cigarettes?

☐ Yes
☐ No

Section 2. Use of Other Products

7. Which of the following products have you ever used regularly?

Check all that apply.

☐ Cigarettes
☐ E-cigarettes or other electronic nicotine delivery system
☐ Traditional cigars, cigarillos or filtered cigars
☐ Pipes
☐ Hookah
☐ Clove cigarettes or kreteks
☐ Bidis
☐ Smokeless tobacco, like dip, chew, or snuff
☐ Snus
☐ Paan with tobacco, gutka, zarda, khaini
☐ None
☐ Other, *Please specify*: _____

8. In the past 30 days, which of the following products have you used?

Check all that apply.

☐ Cigarettes
☐ E-cigarettes or other electronic nicotine delivery system
☐ Traditional cigars, cigarillos or filtered cigars

☐ Pipes
☐ Hookah
☐ Clove cigarettes or kreteks
☐ Bidis
☐ Smokeless tobacco, like dip, chew, or snuff
☐ Snus
☐ Paan with tobacco, gutka, zarda, khaini
☐ None
☐ Other, Please specify: _____

Section 3. Second-Hand Smoke Exposure

9. Are you currently living with a smoker?

☐ Yes
☐ No

10. In the past 30 days, have you…

	Yes	No
a. Lived in a place where other people smoked cigarettes indoors?	☐	☐
b. Worked in a place where other people smoked cigarettes indoors?	☐	☐

11. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors?

☐ Yes →In total, for about how many years? ____ *If less than 1, write "1."*
☐ No

12. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors?

☐ Yes →In total, for about how many years? ____ *If less than 1, write "1."*
☐ No

Thank you for completing this questionnaire.

Appendix E – Adverse Events Log

Patient: _____ MRN: _____

PID: _____ Cycle/Start Date: _____

ADVERSE EVENT CTC Term Version 5.0	LAB VALUE	GRADE:	START/STOP DATE:	ATTRIBUTION: 1=Definite 2=Probable 3=Possible 4=Unlikely 5=Unrelated	EXPECTED: N=No Y=Yes	ACTION TAKEN: No=None DR=Dose reduced RI=Regimen interrupted TD=Therapy discontinued INTR=Interrupted then reduced	SAE: N=No Y=Yes

Principal Investigator Signature/Date: _____

Appendix F – Outcomes Data Collection Form

Instructions: Use this form to collect data related to necrosis and number of germinal centers.

Study Number: ___ ___ ___ ___ ___	PID: ___ ___ ___ ___ ___ ___ ___ ___
Investigator: W. Jeffrey Petty, M.D.	Date: ___ ___/___ ___/___ ___

1. Necrosis: ☐ Present ☐ Not Present

2. Germinal centers in tumor: ☐ Present ☐ Not Present
   a. Location:
      i. Intratumoral_____(Y/N)
      ii. At margins_____(Y/N)

3. Density of germinal centers in lymph nodes:
   ☐ High ☐ Moderate ☐ Low ☐ Not Present

Appendix G – Survival Form

WISER PID: __ __ __ __ __ __ __ __ **Date Completed:** __ __ / __ __ / __ __

PI: _____ **Study Number:** 6 2 2 1 8

Date of 6 Month Follow Up:___ ___ / ___ ___ / ___ ___

Name of person completing form _____

Follow Up:

☐ Phone Call to patient

☐ Phone call with family member who verified patient is alive

☐ Patient completed office visit follow up

☐ Patient completed office visit at another facility

Comments:

_____

_____

Is this subject still living? Yes ☐ No ☐ Unknown ☐

If the subject has expired, list date of death: ___ ___ / ___ ___ / ___ ___

Appendix H – Exploratory Outcomes Data Collection Form

Instructions: Use this form to collect data related to the exploratory aims.

Study Number: 6 2 2 1 8 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: W. Jeffrey Petty, M.D. Date: ___ ___/___ ___/___ ___

1. Lymphocyte count: _____
2. T regulatory cell concentration: _____
3. MDSC: _____

Appendix I– Medical History

Study Number: 6 2 2 1 8 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: W. Jeffrey Petty, M.D. Date: ___ ___/___ ___/___ ___

Instructions: Fill this form out to capture Medical History

1. Medical Comorbidities
   - ☐ Acute Myocardial Infarction
   - ☐ History of Myocardial Infarction
   - ☐ Congestive Heart Failure
   - ☐ Peripheral Vascular Disease
   - ☐ Cerebrovascular Disease
   - ☐ Chronic Obstructive Pulmonary Disease (COPD)
   - ☐ Dementia
   - ☐ Paralysis (Hemiplegia or Paraplegia)
   - ☐ Diabetes
   - ☐ Diabetes with Complications
   - ☐ Renal Disease
   - ☐ Mild Liver Disease
   - ☐ Moderate/Severe Liver Disease
   - ☐ Peptic Ulcer Disease
   - ☐ Rheumatologic Disease
   - ☐ AIDS

   (Additional)

   _____

   _____

2. Concurrent medications

a. List all prescription and over-the-counter medications. For PRN, circle “yes” or “no.”

Medication Name	Is it PRN?	Medication Name	Is it PRN?
1.	yes no	11.	yes no
2.	yes no	12.	yes no
3.	yes no	13.	yes no
4.	yes no	14.	yes no
5.	yes no	15.	yes no
6.	yes no	16.	yes no
7.	yes no	17.	yes no
8.	yes no	18.	yes no
9.	yes no	19.	yes no
10.	yes no	20.	yes no

Appendix J – Vitals Form

Study Number: _6__ _2__ _2__ _1__ _8__ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: W. Jeffrey Petty, M.D.__ Date: ___ ___/___ ___/___ ___

Instructions: Fill this form out at the baseline/pre-study visit, and after completion of Vitamin A

Study Visit:

- ☐ Pre-study
- ☐ After completion of Vitamin A
- ☐ Post Operative

1. **Height (inches):** ___ ___
2. **Weight (lbs):** ___ ___ ___
3. **BSA:** (Calculated using Mosteller's equation)
4. **BMI:** (Calculated)
5. **Temperature (ºF):** ___ ___ ___.___
   a. Route: _____
6. **Blood Pressure**
   a. Systolic (mmHg): ___ ___ ___
   b. Diastolic (mmHg): ___ ___ ___
7. **Heart Rate (beats per minute):** ___ ___ ___
8. **Pulse Ox:** ___ ___%
9. **Respiratory Rate (breaths per minute):** ___ ___
10. **ECOG Status:**

☐ 0: Fully active, able to carry on all pre-disease performance without restriction.

☐ 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

☐ 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

☐ 3: Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.

☐ 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

☐ 5: Dead

Vitals Form – page 2

11. **Allergies**

Appendix K - Withdrawal of consent for the intervention and medical record use

Study Number: ___ ___ ___ ___ ___ PID: ___ ___ ___ ___ ___ ___ ___ ___

PI: _____ Date (mm/dd/yyyy): ___ ___/___ ___/___ ___ ___ ___

Instructions:

- I withdraw consent for further study intervention/treatment. ☐Yes ☐No Initials: _____
- I withdraw from further research activities (surveys, questionnaires, research assessments and other non-invasive research activities). ☐Yes ☐No Initials: _____
- I withdraw my consent to allow the further collection of research-related information from my medical record to be used in this research project. ☐Yes ☐No Initials: _____

Specimen collection/use withdrawal (no research specimen collection, skip section)
I withdraw my consent for any use of my specimen for this current research.

☐Yes ☐ No Initials: _____

I withdraw my consent for any use of my specimen for future research. ☐Yes ☐No Initials: _____

I acknowledge that any data or deidentified materials that have already been created from my specimen may still be used for research. Initials: _____

Patient signature: _____ Date (mm/dd/yy): ___ ___/___ ___/___ ___

Investigator signature: _____ Date(mm/dd/yy): ___ ___/___ ___/___ ___

Comments:
_____
_____
_____
_____
_____
_____

Appendix L - Vitamin A Medication Log

Patient Name: _____ Study ID: 62218-____ ____ ____ ____

Number of Pills Given: _____ Pill Bottle(s) returned: Circle Yes or No

Total Daily Dose: 10,000 IU Number of Pills Returned: _____

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT

SPECIAL INSTRUCTIONS

1. Take Vitamin A capsule by mouth for 7 consecutive days.
2. Log the date and time dose is taken each day.
3. If a dose is missed, please note the reason under comments.
4. Remember to bring any unused medication back at the next visit.

Day	Medication	Date	Time		Number of Pills Taken	Comments
Example	*Vitamin A*	*01/01/2019*	*9:00*	*AM*	*1*	
1	Vitamin A					
2	Vitamin A					
3	Vitamin A					
4	Vitamin A					
5	Vitamin A					
6	Vitamin A					
7	Vitamin A					

Patient Signature: _____ Date: _____

Study Team Signature: _____ Date: _____

Comments:

_____

_____

Appendix M – Pre-Toxicity

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed:** __ __ / __ __ / __ __
PI: _W. Jeffery Petty, MD________________ **Study Number:** _62218

Evaluation Date	**Onset Date**	**Toxicity Code**	**Grade** (1-5) per CTC	**Lab value**	**UOM**	**Lower Limit Normal**	**Upper Limit Normal**	**Related to Disease** N=No Y=Yes	**Symptom Description**	**Comments**
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
	CTCAE Version 5 - https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf									
	Version 1/10/18									