Precision medicine for patients with identified actionable mutations at Wake Forest Baptist Comprehensive Cancer Center (WFBCCC): A pragmatic trial
WFBCCC # 04519

ClinicalTrials.gov: NCT04111107

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Confidential

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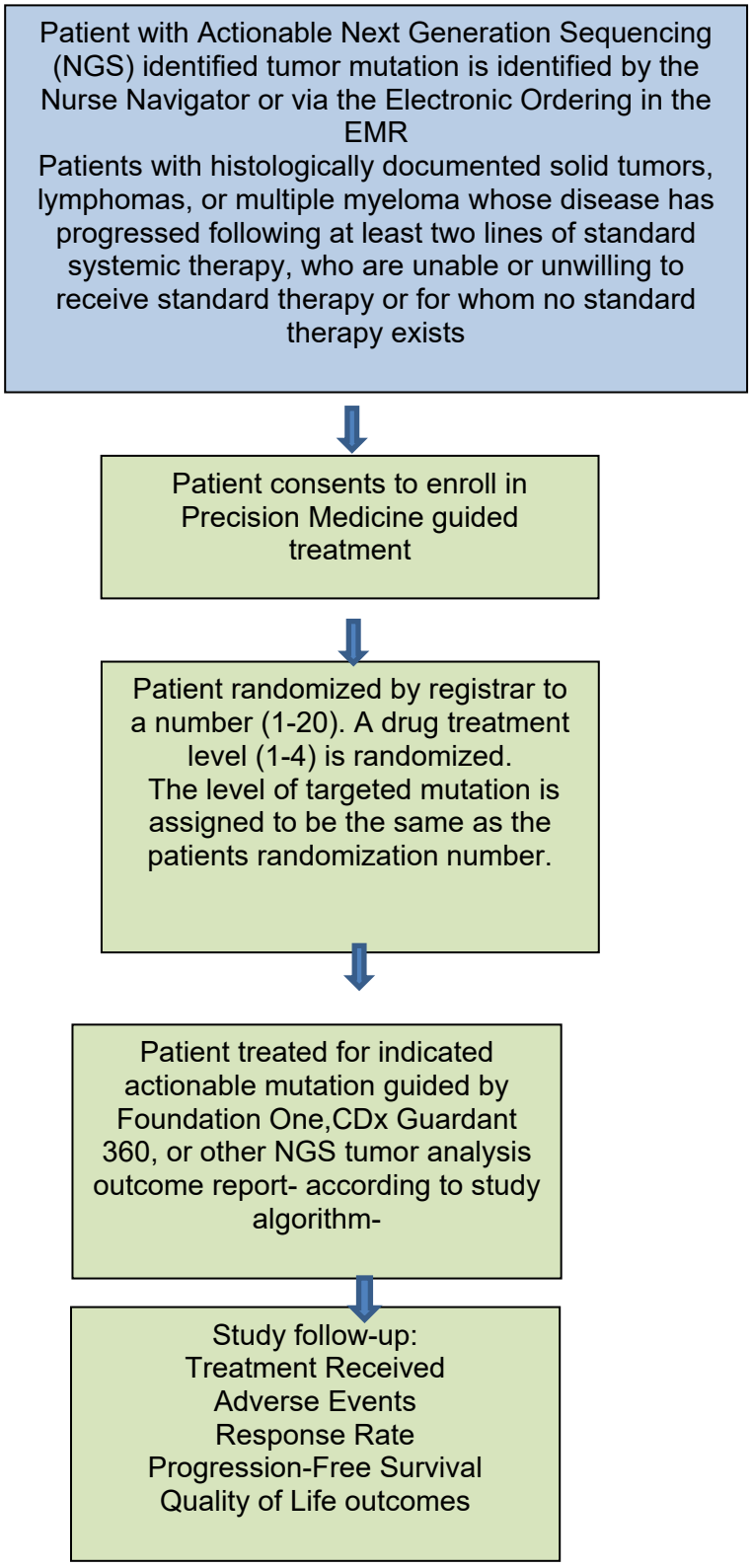

Patient with Actionable Next Generation Sequencing (NGS) identified tumor mutation is identified by the Nurse Navigator or via the Electronic Ordering in the EMR
Patients with histologically documented solid tumors, lymphomas, or multiple myeloma whose disease has progressed following at least two lines of standard systemic therapy, who are unable or unwilling to receive standard therapy or for whom no standard therapy exists
Patient consents to enroll in Precision Medicine guided treatment
Patient randomized by registrar to a number (1-20). A drug treatment level (1-4) is randomized.
The level of targeted mutation is assigned to be the same as the patients randomization number.
Patient treated for indicated actionable mutation guided by Foundation One,CDx Guardant 360, or other NGS tumor analysis outcome report- according to study algorithm-
Study follow-up:
Treatment Received
Adverse Events
Response Rate
Progression-Free Survival
Quality of Life outcomes

1.0 Introduction and Background

Precision medicine is a rapidly growing field with the potential to bypass ineffective treatments and target specific genetic mutations present in cancer cells. Although clinicians have access to increasing amounts of data regarding tumor genomics, it can be problematic to identify a primary driver mutation and the optimal treatment.(Paolillo, Londin, & Fortina, 2016). Due to this complexity many clinicians are uncomfortable interpreting genomic sequencing results from next generation sequencing assays ("NGS") [J. Clin Oncol 2014, 32, 1317-1323]. I A recent survey of providers at a major academic center revealed that more than half the providers were uncomfortable interpreting the information from a genomic test [Oncotarget 2017; 8; 27145-27154]. Various strategies have been used to facilitate the proper interpretation of genomic data including in-person and virtual molecular tumor boards but the limited experience and large numbers of permutations with multiple genetic mutations in a single tumor make the identification of one or more driver mutations in a particular patient largely a matter of an educated guess at best. This has the effect of discouraging the use of targeted therapies, that may provide benefit, in patients who have exhausted standard of care treatments. Frequently, physicians prescribe medications off-label in an effort to delay progression of disease. Off label prescribing involves prescribing a medication for an indication other than the condition for which there is FDA approval.Those physicians prescribing targeted therapies off label, based on NGS results face other challenges. These includelack of access to available drugs, costs of available drugs, and differing reimbursement policies among insurance companies, among others (Messner et al., 2016)

At Wake Forest Baptist Comprehensive Cancer Center ("WFBCCC"), solid tumors are most often analyzed using Foundation One CDx, an FDA approved NGS Cancer Profiling Test, while liquid samples are primarily analyzed using an assay from Guardant 360. Other NGS tests employed for tumor analysis include Caris Molecular Intelligence® Comprehensive Tumor Profiling. Results from the testing include any identified ,or actionable, genetic mutations and any known drugs with suspected or proven efficacy for treating these mutations. Off-label drug treatment options are included in the lab report. Additionally, any known drugs that lack efficacy for the tumor are outlined in the report. For many of the identified mutations, however, no off-label drug option is available.

According to WFBCCC data, 9.4% of patients have five or fewer mutations identified in their cancer sample, 48.3% have 10 or fewer, 79.1% have 15 or fewer and 87.9% of patients who have NGS testing exhibit 20 or more genetic mutations in their cancer sample. For many of these mutations, however, no off-label drug is available.

The goal of the current pragmatic trial is to evaluate the impact of a simple method of selecting a treatment approach for identified mutations on subjects' progression free

survival (PFS) by assigning treatment in a balanced manner when no identified optimal off-label treatment is defined. The study also intends to collect information on barriers that providers encounter when prescribing treatment options using the NGS reports and to measure patients' quality of life before, after, and during treatment.

2.0 Objectives

2.1 Primary Objective

2.1.1 To estimate the progression-free ratio, as defined by the progression-free survival time on study treatment divided by the progression-free survival time on the last treatment received by patient, for an identified actionable mutation, who will be treated with an off-label treatment off label therapy based on a simplified selection methodology using the NGS results.

2.2 Secondary Objectives

2.2.1 To estimate patient response rate on off-label treatments for actionable mutations based on NGS results.

2.2.2 To estimate overall survival (OS) for patients treated with off-label treatments for actionable mutations based on NGS results.

2.2.3 To describe the safety of using off-label or other experimental treatments for patients with actionable mutations based on NGS results.

2.3 Exploratory Objectives

2.3.1 To describe health related quality of life in patients undergoing off-label treatment targeting genetic mutations, as measured by the PROMIS-29 Overall Health-Related Quality of Life, Including 4-Item Anxiety Subscale..

2.3.2 Using the Satisfaction with Medical Decision Scale, to describe patient satisfaction with decision to pursue off-label treatment.

2.3.3 To identify types of actionable mutations with available targeted treatment occurring in cancer patients.

2.3.4 To characterize the historical treatment regimens for these patients relative to the targetable mutation.

2.3.5 To describe patient clinical and demographic characteristics of those with actionable mutations based on NGS results.

2.3.6 To identify barriers to treatment based on NGS results.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Cancer patients at Wake Forest Baptist Comprehensive Cancer Center and its satellites who have next generation DNA sequencing results on their tumor biopsy or surgically resected tissue and/or blood samples and/or consent to the WFCCC Precision Oncology Registry to use their information for research.

3.1.2 Actionable mutation (defined as a mutation or gene amplification for which an off-label therapy is identified on the patient's NGS report for which NCCN guidelines do not recommend a specific treatment in the particular disease or for which there is no documentation in the patient's medical record of clinical data demonstrating lack of activity with the targeting of the specific mutation or amplification in the patient's specific disease) uncovered by the genomic sequencing of a tumor or those that have undergone liquid biopsy assay of their tumor genomic, performed by Wake Forest or another and who are medically able to receive targeted therapy based on those results.

3.1.3 Sequencing on a sample collected within 3 months prior to registration is strongly encouraged but must have been performed within the 12 months prior to registration.

3.1.4 Patients must have progressed through at least two lines of treatment, or are not candidates for or unwilling to receive any standard therapies. Patients who have received treatment on the present protocol who have progression of disease may be recruited to the trial for treatment using another targeted therapy provided that they fullfil the other criteria for participation in the trial. If a patient discontinues treatment on this protocol they can be considered for further participation in this trial provided they meet all of the eligibility criteria and are eligible for re-registration and re-consent.

3.1.5 ECOG of ≤ 3

3.1.6 Life expectancy of greater than *6 weeks*

3.1.7 The effects of the drugs used for cancer treatment on the developing human fetus are unknown. For this reason and because of the possibility that the agents are teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.2 Exclusion Criteria

3.2.1 Patients who have had or will receive chemotherapy or radiotherapy to major bone marrow bearing sites within 2 weeks prior to receiving treatment on the study.

3.2.2 Patients who have not recovered from toxicity of prior treatment if such toxicity will preclude treatment with the proposed targeted agent.

3.2.3 Patients may not be receiving any other investigational agents.

3.2.4 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.

3.2.5 Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with the targeted agent, breastfeeding should be discontinued if the mother is treated with the targeted agent.

3.3 Inclusion of Women and Minorities

3.3.1 Women and men of all races and ethnicity who meet the above-described eligibility criteria are eligible for this trial.

3.3.2 Based on WFBCCC population estimates, we expect approximately 50% of participants to be female, 13% Black or African American, and 6.5% of participants to be of Hispanic ethnicity. 3.0% of the remaining minority population will be comprised of individuals of other ethnicities. 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. However, the population will

change over time and these estimates may not reflect future ancestral distributions in the future.

4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the 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 A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form,
4. 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.

5. 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
- assign the patient a drug and dose
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 Progression free ratio, defined as the duration of time from start of treatment to the time of progression divided by the duration of time from the last treatment received pre-trial to the time of progression on that treatment. Those that die before progression or are lost to follow-up will be non-evaluable for the primary objective.

5.2 Secondary Outcomes

5.2.1 Overall survival (OS), defined as the duration of time from the start of treatment to date of death or date of last contact; those lost to follow-up will be censored.

5.2.2 Investigational Agent Safety To determine incidence of adverse events (AEs), serious adverse events (SAEs), and any laboratory abnormalities of each investigational agent tested.

5.2.3 To measure response rate of treatment based on a simplified selection methodology using the NGS results.

5.3 Planned EHR Data Collection

The following data points will be collected. The NGS data will consist of the clinical NGS data report, sequence variant reports (example: VCF or variant call files), binary DNA sequence alignment data (BAM files or SAM files), and any quality control reports supporting the validity of the clinical NGS data. The accompanying clinical data will be extracted from the clinical records (through manual and automated processes) and will include demographic information, diagnoses, and medical treatments in addition to information regarding the relationship of NGS to treatment decisions.

- Age, gender, ethnicity, race, insurance type and coverage
- Marital status
- Occupation
- Educational level
- Military service
- Family medical history
- Patient's medical history
    - Previous cancer diagnoses and treatments
    - Previous or current conditions
    - Current prescription medications
- Treating physician and physician ordering tumor DNA sequencing
- Extent of financial assistance provided if applicable
- Vendor used for tumor DNA sequencing

- Previous and current tobacco and alcohol use information if available
- The date of DNA sequencing results and date of results discussion
- If NGS data revealed somatic mutations warranting further investigation by Genetic Counseling, the type of mutation present and the referral date to Genetic Counseling
- Type of treatment plan toward mutation of interest if applicable/known
- Response and progression-free survival for last known treatment
- Progression-free and overall survival times for new targeted therapy
- Response to new targeted therapy

6.0 Treatment Plan

Patients with actionable tumor mutations who have failed at least two lines of standard of care therapy or are unable or unwilling to receive standard therapy and consent to participate will be included. Patients will be treated according to the following algorithm:

1) Next Gen Sequencing report obtained as Standard of Care, preferably within the t 3 months but necessarily within 12 months prior to of enrollment date will be used . If more than one report exists in this time period, the most recent report will be used.
2) Patients will be stratified according to whether their NGS assay reports mutation frequency or not.
3) If the assay reports mutation frequency and more than one molecular abnormality is identified as actionable the first mutation selected for treatment will be the mutation with the reported highest frequency, with subsequentl selections being in order of frequency from highest to lowest.
    a. If two or more actionable mutations are reported to have the same frequency then, of these, the mutation selected for protocol treatment shall be chosen via randomization, as described in 4b-4d below..
    b. If both mutations and amplifications are reported, mutations shall be selected before amplifications.
    c. If two or more amplifications are reported, they shall be selected in the order of greatest to least amplification.
    d. If two or more amplifications are reported to have the same degree of amplification, of these theamplification selected for protocol treatment shall be chosen via randomization table as in 4b-4d below.
4) If the assay does not report mutation frequency the initial actionable mutation selected will be randomly assigned (in a manner to balance the likelihood of a mutation being selected) as follows:
    a. If there is a single actionable mutation that mutation will be selected
    b. If there are 2-5 actionable mutations patient will be randomly assigned a number from 1-5 and the first mutation selected will be the mutation corresponding to the randomly assigned number. If the randomly assigned number is greater than the

number of actionable mutations, the last listed actionable mutation will be selected.

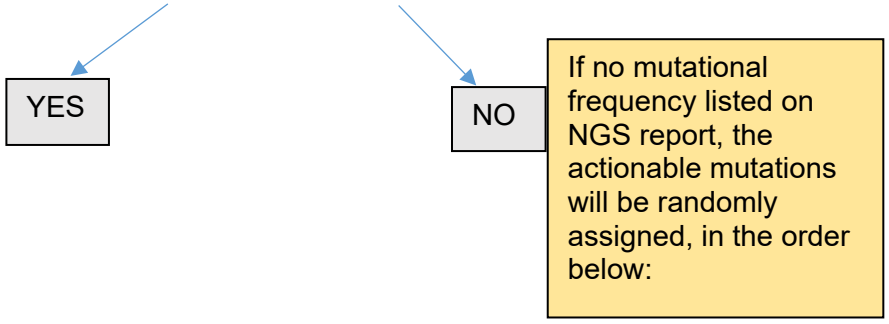
c. If there are 6-10 actionable mutations patient will be randomly assigned a number from 1-10 and the first mutation selected will be the mutation corresponding to the randomly assigned number. If the randomly assigned number is greater than the number of actionable mutations, the last listed actionable mutation will be selected.
d. If there are 11-15 actionable mutations patient will be randomly assigned a number from 1-15 and the first mutation selected will be the mutation corresponding to the randomly assigned number. If the randomly assigned number is greater than the number of actionable mutations, the last listed actionable mutation will be selected.
e. If there are greater than 15 actionable mutations patient will be randomly assigned a number from 1-20 and the first mutation selected will be the mutation corresponding to the randomly assigned number. If the randomly assigned number is greater than the number of actionable mutations, the last listed actionable mutation will be selected.
f. If mutations and amplifications of different genes are reported, each shall be counted as an actionable mutation.

5) Noting that 87.9% of our patients have 20 or fewer mutations identified, of which many are not actionable, it is anticipated that in almost all patients, the probably of an actionable mutation being selected will be balanced
6) Patients will be randomly assigned a second “Treatment Number” from 1-6. 1-6 because it is rare for there to be more than 6 drug options for the treatment of an actionable mutation.This will be used to select the first chosen drug for treatment of a actionable mutation.

7) Once an actionable mutation is selected, if more than one drug is listed as a possible treatment, the drug(s) corresponding to the patient’s Treatment Number listed in the tumor analysis report for the selected mutation will be selected as treatment. Patients must have adequate organ and marrow function to permit administration of the study drug as specified in the drug packaging label. If the subject has a medical contraindication to the selected drug (according to the drug label) or the selected drug(s)cannot be obtained for the patient, the study team will select the next drug(s) presented by the tumor sequencing report. If necessary, this process will be repeated until a suitable drug is selected, returning to the top of the list of the drugs listed for the selected mutation if necessary. If the list of drugs proposed for the selected actionable mutation is exhausted, then the next listed actionable mutation will be selected and the process repeated, if necessary returning to the top of the list of actionable mutations if the first selected mutation is not at the top of the list on the report. Documentation for why particular drugs were not selected, if applicable, will be obtained for alternative

Patient has NGS performed as prescribed by their doctor and/or is entered in the Precision Medicine RegistryCCCWFU 04218 IRB00054757
and has failed at least Is the Mutational Frequency listed on the NGS Report? receive standard therapy

therapies in order to evaluate some of the potential barriers to treatment using the NGS method.



If NGS report lists the mutational frequency, targeted mutation will be the highest frequency mutation

If no mutational frequency listed on NGS report, the actionable mutations will be assigned, in the manner below (based on their presentation in the NGS report):

If single actionable mutation is identified	2-5 actionable mutations	6-10 actionable mutations	11-15 actionable mutations	>-15 actionable mutations
Single Actionable Mutation will be targeted	Patient randomly assigned number from (1-5). Mutations assigned a number chronologically, starting with first presented mutation, #1. The mutation number that is the same as the randomly assigned patient number will be targeted. For example, for patient randomized to the number 5, the 5th mutation will be targeted.	Patient randomly assigned number from (1-10). Mutations assigned a number chronologically , starting with first presented mutation,#1. The mutation number that is the same as the randomized patient number will be targeted. For example, for patient randomized to number 7, the 7th mutation will be targeted. *If randomly assigned number is greater than number of actionable mutations, the last listed actionable mutation will be selected.*	Patient randomly assigned number from (1-15). Mutations assigned a number chronologically starting with the first mutation,#1. The mutation number that is the same as the randomized patient number will be targeted. For example, for patient randomized to number 15, the 15th mutation will be targeted. *If randomly assigned number is greater than number of actionable mutations, the last listed actionable mutation will be selected.*	Patient randomly assigned number from (1-20). Mutations listed on the report will be assigned a number starting with the first mutation,#1. The mutation number that is the same as the randomized patient number will be targeted. For example, for patient randomized to number 19, the 19th mutation will be targeted. *If randomly assigned number is greater than number of actionable mutations, the last listed actionable mutation will be selected.*

All Patients will be randomly assigned a second “Treatment Medication Number” from 1-6. (it is rare for more than 6 drug options for the treatment of an actionable mutation.)

If more than one drug is listed as possible treatment, the drug corresponding to the patient’s Treatment Number (listed in the tumor analysis report for the selected mutation) will be selected as treatment. If drug is contraindicated or unattainable for the patient,-the next drug on the list will be selected.

Study-Related Activities

	Pre-Study [a]	Cycle 2, Day 1	Day 1; every even cycle (after cycle 2)	End of Treatment ±7 days	Follow up for Safety (30+ days after last treatment) required only if pt has treatment related AEs at end of treatment visit
Informed Consent	X				
Demographics	X				
Medical History	X				
Concurrent Meds	X				
Physical Exam	X	X	X	X	X
Vital Signs	X	X	X	X	X
Performance Status	X	X	X	X	X
Bone Marrow Biopsy [h]	X	X	X	X	
Imaging[d]	X	X	X[f]	X	
CBC w/diff, platelets [e]	X	X	X	X	X
Serum Chemistry[b]	X	X	X	X	X
B-HCG[c]	X				
Dose Adjustment Form		X	X		
Adverse Event Evaluation		X	X	X	X
Survival Status/Telephone Follow up [g]					X
PROMIS 29	X	X		X	
Satisfaction with Medical Decision Scale	X	X		X	
Patient Reported Outcome-Demographics/Health Literacy	X				

[a] Pre-study requirements listed in table must be completed **within** 30 days prior to registration. Imaging demonstrating disease progression should be completed within 60 days of registration. Imaging should be repeated if the scan occurred more than 30 days prior to treatment initiation..

[b] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

[c] Serum pregnancy test within 10 days of Pre-study visit (women of childbearing potential only).

[d] Imaging will be performed as part of SOC for solid tumors every other cycle, however due to patients on different drug treatment regimen, this may occur at 6 weeks ±2 weeks,, 8 weeks ± 2 weeksor 12 weeks ± 2 weeks. Not required for leukemias. As clinically indicated in Multiple myeloma.

[e] Labs will be performed in accordance with the recommendations of the prescribing instructions for the drug that is utilized

[f] If treatment is discontinued for reasons other than progression, imaging will be performed on the same schedule as was utilized while patient was receiving treatment until progression.

[g] Survival and information related to cancer treatment received after the study and disease status is monitored bimonthly via telephone contact or EMR review after treatment termination. Medical record review will be performed to coincide with the bimonthly telephone call to obtain information regarding evidence and of relapse (as documented on CT, PET, biopsy, etc).

[h] If clinically indicated bone marrow biopsy will be repeated to evaluate response to therapy.

6.1 Treatment Administration

6.1.1 Treatment will be administered on an *inpatient or outpatient* basis based on the type of medication selected. The physician will administer the drug as directed in theFDA approved label.

6.1.2 If the drug is approved with different doses or schedules for different cancers, it will be administered according to the indication for the organ system matching that of the patient (if available). If not available, the drug will be administered at a dose as as indicated by the organ system most closely related to the patients primary disease. The cycling will be determined as directed in Section 6.2.1.

6.1.3 Reported adverse events and potential risks are described in the label and will be communicated to the patient at the time of drug selection.

Appropriate dose modifications for the drugs are described in the FDA label and made at the treating physician's discretion.

6.1.4 Investigational agent

The investigational agent in this protocol will be an FDA approved targeted therapy that target specific mutations in specific disease.
Supportive care regimens will vary depending on the type of drug that will be administered at the treating physician's discretion.

6.2 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 in the medical record.

6.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for the number of cycles indicated on the FDA label, or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- 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.

6.4 Duration of Follow Up

Patients will be followed for adverse events a minimum of 30 days after date of last study drug iadministration, unless otherwise specified in this section of the protocol. Follow-up for serious adverse events and mortality after the last study drug dose is administered will take place during the routine clinic visits that the patient will have during the 30-day follow-up window (Also referenced in Appendix D). If no visit occurs during this window, a phone call confirmation should be made to the patient to determine vital status and whether any adverse events and in particular, Grade 4 unexpected adverse events occurred during that window of time and recorded on Appendix F.

If a patient is removed from the study, patients will be followed for 30 days after removal from study for adverse events. 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.

6.5 Criteria for Removal from Study

Patient refusal to continue on study or unable/unwilling to comply with study procedures.

7.0 Dosing Delays/Dose Modifications

As this protocol will use multiple chemotherapeutic agents Dosing delays and modifications will be made as indicated in the FDA label of the drug unless indicated differently by the treating physician.

8.0 Measurement of Effect

The response criteria will vary based on the type of cancer being treated. A cache of response forms is in Appendix (TBD).

8.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1.(Eisenhauer et al., 2009) Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. For diseases where RECIST is not employed, response will be measured in accordance with the measurement instrument used for

that specific disease. The specific measrurement Criteria being used will be recorded prior to treatment

8.1.1 Definitions

- **Evaluable for toxicity:**

All patients will be evaluable for toxicity from the time of their first treatment with the study treatment of interest.

- **Evaluable for objective response:**

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

- **Evaluable Non-Target Disease Response**.

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

- **Measurable disease / measurable lesions**

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

- **Malignant lymph nodes**.

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

- **Non-measurable disease / non-measurable lesions**:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- **Target lesions**

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions**

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.1.2 Methods for Evaluation of Measurable Disease

- **Method(s) for obtaining measurements:**
  All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

  The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

  Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- **Time frame for obtaining measurements**
  Patients will under imaging every two cycles of therapy ± 10 days until progression. In the event that patient discontinues treatment for reasons other than progression, imaging shall continue until progression on the same schedule employed while the patient was receiving treatment

- **Use of imaging techniques (e.g., x-ray, CT, MRI, PET) for measuring disease**
  Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

  Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice

thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body
scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, the CT portion of the PET-CT may be used for RECIST measurements at baseline Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

- **How tumor markers will be measured and assessed, if applicable**
  Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

- **Use of cytology or histology for assessment, if applicable**
  Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

8.1.3 Response Criteria

- **Definition of complete response (CR)** for target and non-target lesions, as appropriate
  - Target Lesions:
    - Disappearance of all target lesions and normalization of tumor marker level. **Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm** (the sum may not be "0" if there are target nodes)
    - Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
  - Non-target lesions:
    - Disappearance of all non-target lesions and normalization of tumor marker level. **All lymph nodes must be non-pathological in size (< 10 mm short axis)**

- **Definition of partial response (PR)** for target and non-target lesions, as appropriate
  - Target lesions:
    - At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
  - Non-target lesions

- **Non-CR/Non-PD:** Persistence of 1 or more **non-target lesion(s)**and/or maintenance of tumor marker level above the normal limits

- **Definition of progressive disease (PD)** for target and non-target lesions, as appropriate
  - Target Lesions:
    - > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) **and minimum 5 mm increase over the nadir**
    - When sum becomes very small, increases within measurement error (2-3 mm) can lead to 20% increase
    - (Note: the appearance of one or more new lesions is also considered progressions)

  - Non-target lesions:
    - *Unequivocal progression* of existing non-target lesions. The appearance of one or more new lesions.
    - *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase
    - Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

- **Definition of stable disease (SD)** for target and non-target lesions, as appropriate
  - Target lesions:
    - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

- **Definition and evaluation of best overall response**, if applicable
  The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Best Overall Response Table When Confirmation of CR or PR is required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	BEST overall response
CR	CR	CR
CR	PR	SD, PD, OR PR
CR	SD	SD provided minimum criteria for SD duration are met. Otherwise PD
CR	PD	SD provided minimum criteria for SD duration are met. Otherwise PD

CR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration are met. Otherwise PD
PR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
NE	NE	NE

Overall Response Table for Patients with Measurable Disease

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
CR	NE	No	PR	
PR	Non-PD or NE	No	PR	
SD	Non-PD or NE	No	SD	documented at least once ≥4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Overall Response Table for Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.1.4 Survival Outcomes

Progression-Free Survival is defined as the duration of time from the start of treatment to the time of progression, death, or date of last contact; those lost to follow-up will be censored.

Progression-Free Ratio is defined as the duration of time from start of treatment to the time of progression divided by the duration of time from the last treatment received pre-trial to the time of progression on that treatment. Those that die before progression or are lost to follow-up will be non-evaluable for the primary objective.(Cirkel et al., 2016)

Overall Survival is defined as the duration of time from the start of treatment to date of death or date of last contact; those lost to follow-up will be censored.

8.1.5 Response Review

All radiologic reads will be performed by radiologists with expertise in the evaluation of tumor size by RECIST or particular response criteria used for evaluation of response in the particular tumor type.

8.2 Antitumor Effect

When part of standard of care, specific tumor markers may be measured and if measured will be recorded but tumor response for solid tumors will be based in RECIST criteria.

8.3 Hematologic Tumors

Antitumor Effect for Hematologic measures will be evaluated using existing standard Hematologic Response Criteria and will be defined prior to the intiation of therapy.

8.4 Neuro-oncology Tumors

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Antitumor effect for Neuro-oncology tumors will be evaluated using the RANO Criteria {Wen, 2010 #8}.

8.5 Patient Reported Outcomes

Baseline patient health literacy will be measured using a three item Health Literacy Scale. Quality of Life will be evaluated using the PROMIS-29 with the 4 point Anxiety Subscale. To measure patient’s satisfaction with their decision to pursue next generation sequencing and subsequent therapy, the 5 item Satisfaction with Medical Decision Scale, will be used.

9.0 Adverse Events List and Reporting Requirements

Adverse Events for Off-Label Therapies

The adverse events associated with the targeted or off-label therapeutic agents will vary. These will be outlined to the patient by the treating physician. As per WFCCC standard of care, patients will be provided with a document that explains the adverse events associated with the medication prescribed.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems deviations or changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

9.1 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' 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.

9.2 DSMC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. All Adverse Events that occur during protocol intervention 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 SAE consol in WISER.

All WFBCCC Clinical Protocol and Data Management (CPDM) 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.

9.3 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.

10.0 Pharmaceutical Information

10.1 Pharmaceutical Accountability

The targeted off-label chemotherapeutic or immunotherapy agents are commercially available. Their description, use, preparation, administration, storage and stability parameters are outlined in the package insert. Disposal of remaining portions of the agents should be done per the Wake Forest Waste Stream.

11.0 Data Management

Informed consent document	EPIC
Patient Demographics and clinical data	WISER/OnCore, REDCap
Current Medications List	WISER/OnCore
NGS Result	NGS Database
Patient Withdrawal Form	WISER/OnCore
Adverse Events Log	WISER/OnCore
Vitals	WISER/OnCore
30 day Treatment Follow-up Form	WISER/OnCore
Evaluation of Best Overall Response	WISER/OnCore
Off-Study Form	WISER/OnCore
Study Medication Form	REDCap
PROMIS 29	REDCap
Satisfaction with Medical Decision Scale	REDCap
Patient Reported Outcome-Demographics	REDCap
Telephone Follow up Form	REDCap
Health Literacy Questionnaire	REDCap

12.0 Confidentiality and Privacy

One risk inherent in this project is the loss of confidentiality. Confidentiality will be protected by collecting only information needed to assess operational outcomes and maintaining all study information in a secure manner. Data will be collected on an identifiable level. Following data collection, the data will be kept indefinitely. Data access will be limited to registry staff (Investigators, CPDM staff, and patient navigators). Data and records will be kept password protected, in OnCore (WISER), REDCap and the NGS database. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the collection of this data. The data could be used for a research study. Data will only be given to the research study by the registry staff upon an IRB approval. The Registry staff will serve as honest brokers of the data. All data provided for research will be completely deidentified.

13.0 Data Safety and Monitoring

The principal investigator will be responsible for the overall monitoring of the data of participants.

14.0 Statistical Considerations

14.1 Introduction

It should be noted that the primary analyses for this protocol are examining whether the process of using next generation sequencing methods to identify a potential treatment for patients who have failed previous ttherapies have any clinically beneficial effects. The goal is not to evaluate a particular treatment per se, but rather an approach to assign a treatment to patients using next generation sequencing methods.

14.2 Analysis of Primary Objective

The primary objective of this non-randomized, single-arm pragmatic trial is to estimate the progression-free ratio as defined by the duration of time from start of treatment to the time of progression divided by the duration of time from the last treatment received pre-trial to the time of progression on that treatment. Those that die before progression or are lost to follow-up will be non-evaluable for the primary objective. The median progression-free ratio will be estimated with the range and a two-sided Wilcoxon Signed Rank test will be calculated to see if the PFS ratio is different from 1.0.

14.3 Analysis of Secondary and Exploratory Objectives

Response rate will be estimated for all patients with corresponding 95% confidence intervals. Progression-free survival and overall survival times will be displayed using Kaplan-Meier curves with median survival times and confidence intervals. Adverse events will be summarized in incidence tables by type and grade severity for all patients and presented by type of treatment received. For exploratory objectives, the frequency of types of actionable mutations and previous treatment history will be summarized and demographic characteristics presented. Logistic models will be constructed for each type of mutation (yes/no) to preliminarially explore associations with clinical and demographic characteristics. For quality of life and patient satisfaction outcomes, changes over time will be assessed using a repeated measures ANOVA, with any between time associations utilizing Tukey adjustment for post-hoc comparisons. Transformations and/or non-parametric approaches will be considered for any outcomes violating parametric assumptions.

14.4 Power and Sample Size

This trial is powered to detect differences in the progression-free ratio for those with actionable mutations identified by NGS results and then treated with a targeted therapy. A hypothesized PFS ratio larger than 1.3 would suggest that the targeted therapy is doing better than the previous treatment received (not targeted), and we assume a null hypothesis PFS ratio of 1.0 (no difference). Using pilot data seen in Von Hoff et al, we assume a conservative standard deviation of 1.71. With 269 evaluable participants, we have 80% power to detect differences in PFS ratio from 1.0 to 1.3, assuming a two-sided Wilcoxon test with level of significance equal to 0.05. This does assume the actual underlying distribution is normal, but powers for a non-parametric Wilcoxon test. ("PASS 16 Power Analysis and Sample Size Software," 2018)As those that die before progression or are lost to follow-up will be non-evaluable for the primary objective, we conservatively allow for 20% non-evaluable. Therefore, we plan to recruit 337 total patients in this trial.

14.5 Estimated Accrual Rate

The WFCCC Precision Oncology Registry plans to accrue approximately 50 participants per month. We anticipate approximately 20-30% of those will have an actionable mutation identified from NGS that can be treated with a targeted therapy, i.e. 10-15 a month.

14.6 Estimated Study Length

Given anticipated accrual rates of 10-15 per month, it should take around 2– 3 years to enroll 337 patients.

References

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Appendix A-Eligibility Checklist

IRB Protocol No.	WFBCCC Protocol No.04519
Precision medicine for patients with identified actionable mutations at Wake Forest Baptist Comprehensive Cancer Center (WFBCCC): A pragmatic trial	
Principal Investigator: Stefan C. Grant, MD	

Inclusion Criteria (as outlined in study protocol)	Criteria is met	Criteria is NOT met	Source Used to Confirm * (Please document dates and lab results)
Cancer patients at Wake Forest Baptist Comprehensive Cancer Center and its satellites who have next generation DNA sequencing results on their tumor biopsy or surgically resected tissue and/or blood samples and /or consent to the WFCCC Precision Oncology Registry to use their information for research.	☐	☐	
Actionable mutation (defined as a mutation or amplification for which an off-label therapy is identified on the patient's NGS report for which NCCN guidelines do not recommend a specific treatment in the particular disease or for which there is no documentation in the patient's medical record of clinical data demonstrating lack of activity with the targeting of the specific mutation in the patient's specific disease) uncovered by the genomic sequencing of a tumor or those that have undergone liquid biopsy assay of their tumor genomic, performed by Wake Forest or another and who are medically able to receive targeted therapy based on those results	☐	☐	
Sequencing on a sample collected within 3 months prior to registration is strongly encouraged but must have been performed within the 12 months prior to registration.	☐	☐	
Patients must have progressed through at least two lines of treatment, or are not candidates for or unwilling to receive any standard therapies. Patients who have received treatment on the present protocol who have progression of disease may be recruited to the trial for treatment using another targeted therapy provided that they fullfill the other criteria for participation in the trial. If a patient discontinues treatment on this protocol they can be considered for further participation in this trial provided they meet all of the eligibility criteria and are eligible for re-registration and re-consent.	☐	☐	
ECOG of ≤ 3	☐	☐	

Life expectancy of greater than 6 weeks	☐	☐	
The effects of the drugs used for cancer treatment on the developing human fetus are unknown. For this reason, and because of the possibility that the agents are teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Patients who have had or will have chemotherapy or radiotherapy to major bone bearing sites within 2 weeks prior to receiving treatment on the study	☐	☐	
Patients who have not recovered from toxicity of prior treatment if such toxicity will preclude treatment with the proposed targeted agent.	☐	☐	
Patients may not be receiving any other investigational agents	☐	☐	
	☐	☐	
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.	☐	☐	
Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with the targeted agent, breastfeeding should be discontinued if the mother is treated with the targeted agent.	☐	☐	

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

OnCore 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 B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

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

ZIPCODE: ___ ___ ___ ___ ___

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 OnCore): ___ ___ ___ ___ ___ ___ ___ ___

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

Compete the eligibility checklist in WISER and then give the completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-713-6772 or registra@wakehealth.edu, respectively.

Appendix C - Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?
☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** ☐ **No** ☐
If yes, please provide what is currently indicated in the EMR:
Ethnicity: _____ Race: _____

Additional comments: _____
_____
_____

Appendix D – DSMC Notification SOP

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	**Date: 03/12/2021**

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 DSMC 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 6-9527 / 6-7972 / Pager 336-806-8397

Mercedes Porosnicu, MD-- Hematology Oncology 6-7980 / 6-0230 / Pager 336-806-9150
Ryan Hughes, MD – Radiation Oncology 3-3600 / Pager 336-806-9865
Michael Goodman, MD -- Hematology Oncology 6-7970 / Pager 336-806-7283
Daniel Reed, MD -- Hematology Oncology 3-3841 / Pager 336-806-0637
Mary Beth Seegars, MD -- Hematology Oncology 6-4815 / Pager 336-806-9948

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.

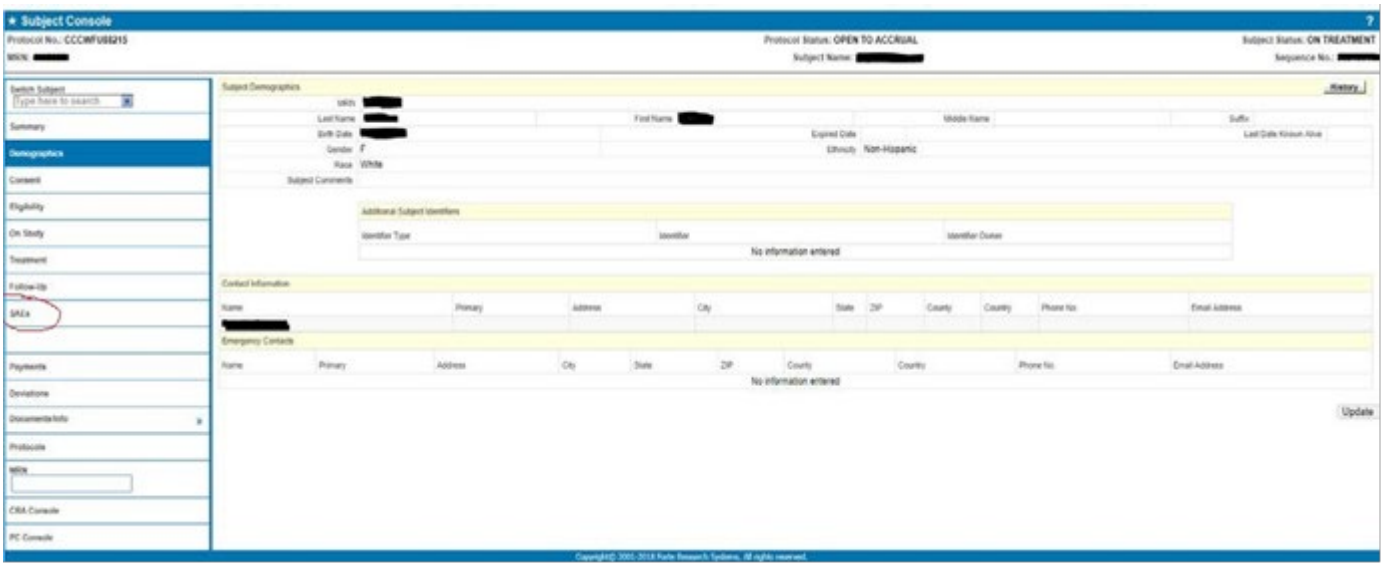
Acronyms

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:

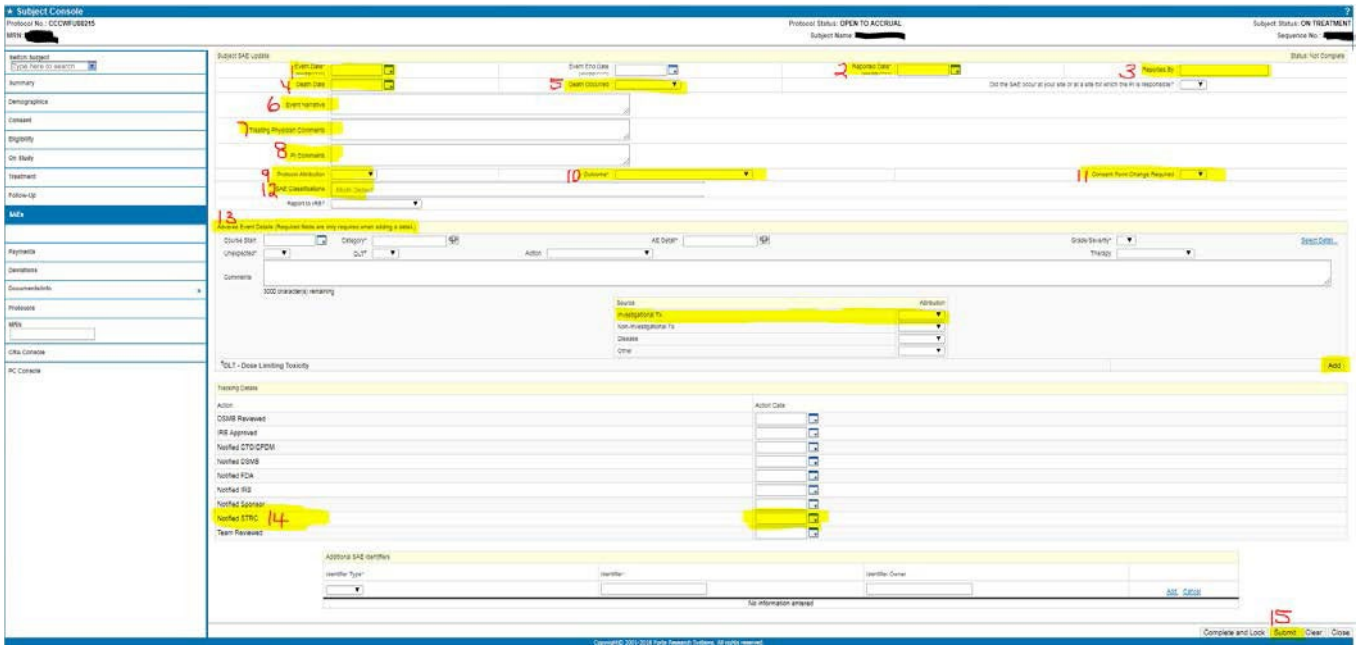
The following screen shots come from the SAE Console within the Subject Console in WISER.

Screen Shot 1:

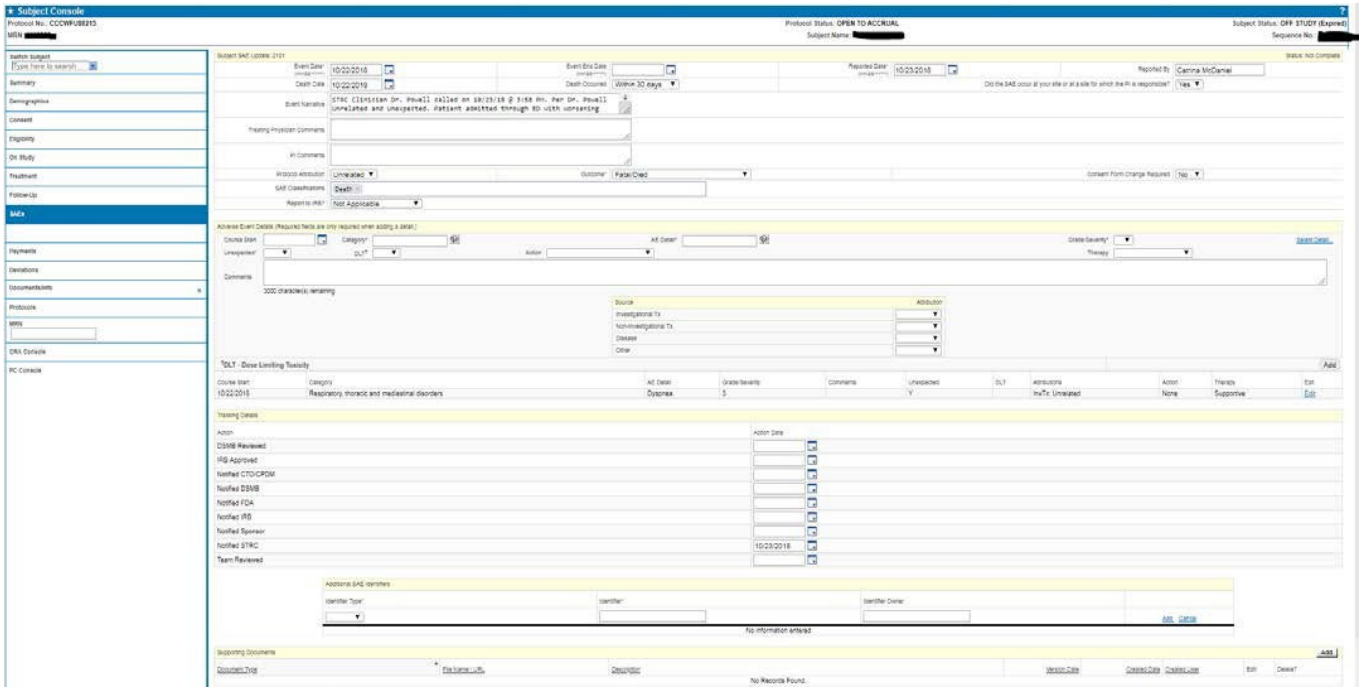


Screen Shot 2:

Screen Shot 3:



Screen Shot 4:


Subject Console
Protocol No.: CCCWFU88213
Protocol Status: OPEN TO ACCRUAL
Subject Status: OFF STUDY (Expired)
Subject Name
Sequence No.
Switch Subject
Summary
Demographics
Consent
Eligibility
On Study
Treatment
Follow-Up
AdEx
Payments
Deviations
Documents/Alerts
Protocols
MRN
DNA Console
PC Console
Event Date* 10/22/2015
Death Date 10/22/2015
Reported Date* 10/23/2015
Reported By Carrina McDaniel
Death Occurred Within 30 days
Did the SAE occur at your site or at a site for which the PI is responsible? Yes
Event Narrative STRC Clinician Dr. Powell called on 10/23/15 @ 3:58 PM. Per Dr. Powell Unrelated and unexpected. Patient admitted through ED with worsening
Treating Physician Comments
PI Comments
Protocol Attribution Unrelated
Outcome* Fatal/Died
Consent Form Change Required No
SAE Classifications Death
Report to IRB? Not Applicable
Course Start
Category*
AE Detail*
Grade/Severity*
Unexpected*
DLT*
Action
Therapy
Comments
2000 character(s) remaining
Source
Attribution
Investigational Tx
Non-Investigational Tx
Disease
Other
DLT - Dose Limiting Toxicity
Add
Course Start
Category
AE Detail
Grade/Severity
Comments
Unexpected
DLT
Attributions
Action
Therapy
Edit
10/22/2015
Respiratory, thoracic and mediastinal disorders
Dyspnea
3
Y
Inv/Tx: Unrelated
None
Supportive
Edit
Tracking Details
Action
Action Date
DSMB Reviewed
IRB Approved
Notified CTO/CPDM
Notified DSMB
Notified FDA
Notified IRB
Notified Sponsor
Notified STRC
10/23/2015
Team Reviewed
Additional SAE Identifiers
Identifier Type*
Identifier*
Identifier Owner
Add Cancel
No information entered
Supporting Documents
Add
Document Type
File Name - URL
Description
Version Date
Created Date
Created User
Edit
Delete?
No Records Found