Document Coversheet

Study Title: A Pilot Feasibility Study of Next Generation Sequencing-Based Stratification of Front Line Treatment of HighGrade Neuroendocrine Carcinoma

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	2/14/2023
NCT Number:	NCT04452292
IRB Number	59128
Coversheet created:	4/19/2023

PROTOCOL TYPE (VERSION 4)

Which IRB

◉ Medical ○ NonMedical

Protocol Process Type

○ Exemption
○ Expedited (Must be risk level 1)
◉ Full

IMPORTANT NOTE: You will not be able to change your selections for "Which IRB" and "Protocol Process Type" after saving this section. If you select the wrong IRB or Protocol Process Type, you may need to create a new application.

See below for guidance on these options, or refer to ORI's "Getting Started" page. Please contact the Office of Research Integrity (ORI) at 859-257-9428 with any questions prior to saving your selections.

Which IRB

The **Medical IRB** reviews research from the Colleges of:

- Dentistry
- Health Sciences
- Medicine
- Nursing
- Pharmacy and Health Sciences
- and Public Health.

The **Nonmedical IRB** reviews research from the Colleges of:

- Agriculture
- Arts and Sciences
- Business and Economics
- Communication and Information
- Design; Education
- Fine Arts
- Law
- and Social Work

Note: Studies that involve administration of drugs, testing safety or effectiveness of medical devices, or invasive medical procedures must be reviewed by the **Medical IRB** regardless of the college from which the application originates.

Which Protocol Process Type

Under federal regulations, the IRB can process an application to conduct research involving human subjects in one of three ways:

- by exemption certification
- by expedited review.
- by full review;

The investigator makes the preliminary determination of the type of review for which a study is eligible. Please refer to ORI's "Getting Started" page for more information about which activities are eligible for each type of review.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

PROJECT INFORMATION

0 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

MCC-20-MULTI-37: A Pilot Feasibility Study of generation sequencing-based stratification of front line treatment of high grade neuroendocrine carcinoma(Precision-Nec)

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

20-MULTI-37

Anticipated Ending Date of Research Project: 5/31/2032

Maximum number of human subjects (or records/specimens to be reviewed) 15

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? (•) Yes ( ) No

RISK LEVEL

0 unresolved comment(s)

Indicate which of the categories listed below accurately describes this protocol

- ○ (Risk Level 1) Not greater than minimal risk
- ◉ (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects
- ○ (Risk Level 3) Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ○ (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

Refer to UK's guidance document on assessing the research risk for additional information.

SUBJECT DEMOGRAPHICS **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 18 yrs to 99 yrs

Study Population:

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider these resources:
NIH Diversity Policy
FDA Diversity Guidance

Adult patients with histopathologically confirmed metastatic high-grade neuroendocrine carcinoma (excluding small cell carcinoma) of all types managed at the MCC will be considered potential candidates for this clinical trial. Specific criteria is listed below.

3.1.1 Histopathologically confirmed high-grade neuroendocrine carcinoma (i.e., large cell carcinoma, poorly differentiated neuroendocrine carcinoma, or mixed high grade neuroendocrine neoplasm) that is metastatic and/or not resectable.
3.1.2 Adequate tissue is available for genomic sequencing. Prior CLIA certified NGS report, if available, will also be acceptable for review by MCC's MTB.
3.1.3 Age 18 years or older
3.1.4 ECOG performance status = 2 (Appendix A)
3.1.5 Ability to understand and the willingness to sign a written informed consent document.
3.1.6 Patients may have received up to two cycles of chemotherapy prior to enrollment if deemed as an urgent clinical necessity or under visceral crisis; as determined by the treating physician, because these circumstances preclude the delay in treatment required for molecular profiling.
3.1.7 Adequate Bone Marrow Function
Absolute neutrophil count (ANC) = 1.5 × 109/L, Platelets = 100 × 109/L, Hemoglobin = 8 g/dL independent of transfusion = 14 days prior to screening.
3.1.8 Adequate Hepatic Function
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) = 3 × upper limit of normal (ULN); if liver metastases, then = 5 × ULN
Bilirubin = 1.5 × ULN; = 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome
3.1.9 Adequate Renal Function
Measured or calculated creatinine clearance (CrCL) = 60 mL/min. For calculated CrCL, the Cockcroft Gault formula or institutional standard formula can be used.

Exclusion Criteria
3.2.1 Patients with small cell carcinoma are excluded from the study
3.2.2 Patients with psychiatric illness or social situations that would limit compliance with study requirements.
3.2.3 Pregnant and nursing women, because of teratogenicity and toxicity risks.
3.2.4 Patients who have completed more than two cycles of chemotherapy for the current cancer diagnosis.
3.2.5 Patients with resectable cancer or eligible for curative therapy.
3.2.6 Patients with an actionable mutation for which Markey MTB or NCCN guidelines recommend up-front therapy with targeted agents (e.g., EGFR mutation, Alk Fusion, ROS1 mutation, etc.).

Attachments

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Census Regional Analyst Edition, Kentucky Race/Ethnic Table, Kentucky Population Data.
(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):

Participant Demographics

	Cisgender Man	Cisgender Woman	TGNB/TGE	Unknown/Not Reported
American Indian/Alaskan Native:				
Asian:				
Black/African American:				
Latinx:				
Native Hawaiian/Pacific Islander:				
White:	1			
American Arab/Middle Eastern/North African:				

Indigenous People Around the World:				
More than One Race:				
Unknown or Not Reported:				

If unknown, please explain why:

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☐ Non-English Speaking (translated long or short form)
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

Assessment of the potential recruitment of subjects with impaired consent capacity (or likelihood):

☐ Check this box if your study does NOT involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

Does this study focus on adult subjects with any conditions that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

INFORMED CONSENT/ASSENT PROCESS/WAIVER

0 unresolved comment(s)

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

Consent/Assent Tips:

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a “Reliance Consent Form” so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a PDF**.
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☑ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☐ Stamped Consent Doc(s) Not Needed

Attachments

Attach Type	File Name
Informed Consent/HIPAA Combined Form	MULTI-37 Consent-HIPAA vd 2-13-2023 CELAN PI CHANGE.pdf
InformedConsent-Highlighted/Tracked_Changes	MULTI-37 Consent-HIPAA vd 2-13-2023 TRACKED PI Change.pdf

Informed Consent Process:

Using active voice, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)
- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

Once a subject is referred for consideration in the study, the subject's history and status will be completely evaluated and treatment recommendations will then be discussed thoroughly with the subject. Any alternative forms of therapy will be presented as objectively as possible. The risks and hazards of the study drugs recommended will be explained to the subject. The Investigator shall seek consent only under circumstances that provide the subject sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The subject will be given as much time as needed to review the consent and ask any questions before making a decision. The subject will then receive a signed copy of the consent form.
Requests for information about the research or complaints will be addressed to the PI, research staff, Ombudsman or Office of Research Integrity as appropriate. All requests or complaints will be handled in a timely, courteous, and confidential manner following University policies.

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the alteration.

SECTION 2.

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

e) If the research involves using or accessing identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

- Private information/specimens are “identifiable” if the investigator may ascertain the identity of the subject or if identifiers are associated with the information (e.g., medical records). This could be any of the 18 HIPAA identifiers including dates of service.
- If not using identifiable private information or identifiable biospecimens, insert N/A below.

☐ Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

*If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the **Cover Letter Template** as a guide. There is an English and a Spanish version.*

○ **Option 1**

Describe how your study meets these criteria:

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

○ **Option 2**

Describe how your study meets these criteria:

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

○ **Option 3**

Describe how your study meets these criteria:

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

Pro Tips:

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section or under the Additional Information section to include supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

Neuroendocrine tumors vary widely in both disease site and grade, ranging from low grade, relatively benign carcinoid tumors to aggressive and rapidly fatal high-grade neuroendocrine carcinomas. High grade neuroendocrine carcinomas (HG-NECs) can originate anywhere in the body, and are highly aggressive, with dismal 5-year overall survival rates. The lung and gastrointestinal tract (small bowel, colon, rectum or pancreas) form the majority of these HG-NECs sites. HG-NECs are classified into three subtypes based on histopathology, specifically, as small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma (LCNEC) or poorly differentiated neuroendocrine carcinoma.

There is a lack of consensus for upfront systemic regimens for HG-NECs and as such, treatment is often per physician preference. Most often, HG-NECs are treated with platinum-based chemotherapeutic regimens, with marked heterogeneity in response. It is well established that small cell neuroendocrine carcinomas are characterized by a co-mutation for TP53 and RB1, and are exceptionally platinum-sensitive. However less is known about LCNECs.

Large-Cell Neuroendocrine Carcinoma
LCNEC was first introduced in 1991 by Travis et. al [5] as a new type of lung cancer. The 2015 World Health Organization Classification categorized LCNEC under neuroendocrine tumors, along with typical carcinoma, atypical carcinoma and the more undifferentiated tumor represented by small cell lung cancer. Prior to 2015, LCNEC was classified under a general category of large cell carcinoma, however as pathologists studied this entity in detail, it was evident that LCNEC has a distinct clinicopathological identity [6-8]. Histopathologically, these tumors are characterized by high mitotic rate (more than 10 mitosis per high power field), extensive necrosis, and neuroendocrine features, specifically the presence of chromogranin A, neuron specific enolase and synaptophysin.

LCNEC is a rare and aggressive disease with a paucity of data regarding disease progression. Precise incidence and prevalence is unknown. From 2003-2012, the Dutch Cancer Registry reported 952 histologically confirmed new cases of pulmonary LCNECs. Among these cases, 383 patients presented with advanced disease, primarily metastases to liver, bone or brain. The prognosis is poor with overall 5-year survival for metastatic disease less than 5% , which is similar to small cell lung cancer (SCLC), although some studies suggest that the prognosis for early stage LCNEC might be slightly better and similar to non-small cell lung cancer (NSCLC).

Molecular Profiling of HG-NECs
Molecular profiling of small-cell neuroendocrine carcinomas is well established and validated, indicating universally expressed co-mutation for TP53 and RB1 [2]. Recently there have been attempts to define genomic profiles of LCNEC. The development of a 241-gene panel on pulmonary tumors, next generation sequencing allows LCNECs to be further defined.
Based on specific genetic signatures, Rekhtman and colleagues sub-classified 45 LCNECs into two major cohorts:
small cell-like (TP53/RB1 co-mutated; n=18) and
non-small cell-like (n=25),
as well as one minor cohort (carcinoid-like n=2).
Similarly, molecular profiling of gastrointestinal high-grade neuroendocrine carcinomas (GI-NECs) indicate that they can also be dichotomously categorized by the presence or absence of co-mutations for TP53 and RB1.

Treatment regimens for small cell neuroendocrine carcinoma are well established, based on clinical trials conducted in SCLC. In contrast, current guidelines regarding optimal treatment for large-cell and poorly differentiated neuroendocrine carcinomas are nonexistent, driven by the paucity of data on these rare and highly fatal tumors. Additionally, the WHO recently defined a new subtype of high-grade neuroendocrine carcinoma, mixed neuroendocrine neoplasm (MINEN), which features characteristics found in large-cell carcinomas and in other tumor types, including adenocarcinomas for example.

To date, there are no prospective randomized clinical trials examining front line therapies for metastatic HG-NECs, based on mutational profiles. Given the gap in evidence-based information for treatment and the emerging more refined classification of these tumors, we propose to utilize recent genomic profiles of high-grade large cell neuroendocrine carcinomas to guide and inform clinicians of optimal treatments.

We hypothesize that upfront genetic profiling of HG-NEC can segregate these tumors into NGS-based groups that will impact

treatment decisions (feasibility study) and ultimately, improve overall treatment response and outcomes.

Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

Primary Objective
To study the feasibility of upfront next generation sequencing (NGS) directed treatment in high grade neuroendocrine carcinomas (excluding small cell carcinoma). Feasibility is defined as being able to sequence the patient within 2 months of initial medical oncology visit and more than 50% of patients are assigned to molecularly defined cohorts (TP53 and RB1 co-mutated vs. non-co-mutated).

Secondary Objectives:
To evaluate progression-free survival on front-line chemotherapy.
To evaluate the objective response rate.

Exploratory Objective: To identify prevalence of potentially targetable mutations in high grade neuroendocrine carcinoma

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

This is a single-arm, pilot trial in patients with metastatic high grade large cell neuroendocrine carcinoma (HG-LCNEC) to study the feasibility of upfront NGS directed treatment in high grade neuroendocrine carcinomas. Tumor samples will receive next generation sequencing (NGS) profiling to classify the tumor as one of three subtypes: small cell-like, non-small cell-like or non-typeable. Non-typeable cases will not be eligible for participation in this study, neither is small cell neuroendocrine carcinoma (HG-SCNEC). The systemic therapy regimen will be determined based on the NGS profile of the tumor.

Feasibility is defined as being able to sequence the patient within 2 months of initial medical oncology visit and being able to assign into molecularly-defined cohorts (TP53 and RB1 co-mutated vs non-co-mutated).

Secondary outcomes include ORR and progression-free survival (PFS). Radiological response will be assessed via RECIST Version 1.1 criteria (Appendix B) based on standard-of-care CT scans completed at q2 monthly intervals during treatment and q3 month during observation. PFS is defined from date of on study to the date of disease progression or death or date of last follow-up whichever occurs first. PFS will be assessed via standard-of-care CT scans (q2 month intervals during active treatment and q3 months during observation) as graded by RECIST Version 1.1 criteria for up to three years post-study enrollment.

All patients who received anticancer therapy will be included in the toxicity and safety analysis. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific AE, the incidence of AE causing withdrawal from the study and incidence of SAE. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be evaluated.

Subjects receive treatment on the recommended regimens for as long as the treating oncologist feels they are benefiting from the treatment, and the patient wishes to continue. Subjects will be followed until disease progression.

Attachments

Attach Type	File Name
StudyDesign	Attachment_Treatment plan schema.pdf

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?

- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

Subjects will be identified by referral from community oncologist and primary care physicians, as well as internal referrals from physicians at the University of Kentucky's multidisciplinary cancer program. Subjects will initially be evaluated by treating oncologist, and will be offered initial information about the clinical trial if appropriate. Agreeable subjects will then be invited to participate in an informed consent process as described below. The study will be posted on the web-site of the Markey Cancer Center in the general information list and listed in the Markey Cancer Center quarterly: Clinical Research Newsletter. The study is also currently posted at ClinicalTrials.gov.
We do not plan to do any advertisments.

Attachments

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

Prior to any study-required tests, subjects must provide written informed consent to participate in this study. It is now standard of care to send tumor tissue for molecular testing so subjects may begin standard of care (SOC) treatment while waiting for results from this test. Patients can receive up to two cycles of Standard of Care (SOC) chemotherapy while NGS results are being obtained before the patient can be presented at Markey Molecular Tumor Board (MTB). Based on the results, subjects may then be changed to a different, FDA-approved treatment which matches the molecular patterns. All study visits, labs, tests and procedures are SOC and would be done if the subject were not on study.

Screening shall include: complete history; physical examination and evaluation of ECOG (Eastern Cooperative Oncology Group) Performance Status; histopathological confirmed diagnosis of high grade neuroendocrine carcinoma; CBC; serum chemistries and baseline computerized tomographic (CT) scan (within 6 weeks of starting treatment) for RECIST 1.1 evaluation. Baseline lab tests and radio-graphic studies should be completed within 6 weeks prior to registration/initiation of treatment. All of these are standard of care for metastatic carcinoma of HG-NEC type.

The case will be reviewed at MTB once the NGS report is ready, patient meets inclusion criteria and has consented to participate in the study. The MTB will provide a written review of the molecular sequencing of the subject, and the study statistician will review and assign subjects to cohorts, in consultation with the PI. Subjects will be assigned to the current FDA-approved, NCCN-recommended treatment regimen based on their molecular profile and will continue treatment for as long as the risk-benefit profile remains favorable, the study remains active, and they wish to continue.

All the procedures to be carried out are illustrated in the attached study calendar. All the tests/procedures are standard of care for this patient population.

Attachments

Attach Type	File Name
ResearchProcedures	Study Calander.pdf

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

This study has no data collection instruments.

Attachments

Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

Research staff of the Markey Cancer Center Clinical Research Organization with oncology research related experience, ranging from one to fifteen years, will assist the PI in the conduct of the study. All subjects will have study medication dispensed in the Markey

Cancer Center's closely monitored clinic area, with on-site pharmacy and medical support, certified oncology nurses and ready access to emergency care. The University's social

Additional Key Personnel for this study are identified on the MCC-CRO Global KP (MCCCRO Master SP List). This allows for cross-coverage of studies managed by the MCC-CRO.

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

Tumor tissue collected will be left-over from SOC biopsies. Risks of blood draw include soreness, bruising, pain, infection, possible fainting, bleeding.
Risks of having genetic testing for this study relate to accidental breach of confidence and would include emotional, social, or financial consequences. In some cases, it could be used to make it harder for the subject to get or keep a job or health insurance. Genetic information could be used in ways that could cause the subject or their family distress. We will take every precaution to protect our subjects' information.
HG-NEC is an aggressive cancer with poor prognosis. At the time of this study, overall 5-year survival for metastatic disease is less than 5 percent. Currently, there is no standard front-line treatment. Physician mainly treat with platinum based chemotherapy with markedly uneven results. The treatment plan matched specifically to the subjects' molecular profile should be more effective than the usual treatment approach. As all therapies recommended will be the current FDA-approved treatments for that molecular pattern, we feel the risk-benefit ratio is acceptable.

Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

Subjects can get the usual treatment for this type of cancer without being on study. They can participate in another study, if one is available. They can receive only palliative care or refuse all treatment.

Back to Top

Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies

FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

Specimens from subjects (either archival or fresh tumor tissue) are reviewed for NGS status for participation in the study.
Medical/Clinical information pertaining to the protocol is included in the subjects' medical records. Copies are also kept in subjects' protocol charts. This ensures timely record review, and allows for collection of data points required to meet primary and secondary objectives of the study.
Confidentiality of medical information is discussed at length in the informed consent. Subjects are made aware of what data will be collected, where it is stored and who has access to the information. Study data may be published or shared with other researchers, but the identity and medical history of each study participant will remain strictly confidential. Representatives of University of Kentucky, Markey Cancer Center, the Food and Drug Administration (FDA), the Kentucky Cancer Registry, and the Institutional Review Board (IRB) may review the study data and medical records relating to this research study.

During the study, information will be collected to assess compliance with the study requirements. These records will be used by the Markey Cancer Center in connection with complying with their obligations relating to this study. The records will not be used for any other purposes or disclosed to any other party without the subject's permission. All records will be coded with an identification number to protect their identity. Data will be stored in a secured area for at least six years or two years after the study is completed, whichever occurs first. All data stored is on site at Markey Cancer Center Clinical Research Organization in locked facilities, and with limited access to records by designated research staff. All research records will be held for a minimum of six years following completion of the study.
Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety will be assessed by physical examinations, ECGs, clinical chemistry and hematology tests and monitoring of adverse events. Adverse events that occur between the signing of the informed consent through 30 days following the last dose of study drug will be recorded. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.

UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Do you confirm that you will retain all IRB-related records for a minimum of 6 years after study closure?
◉ Yes ○ No

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

Subjects will not receive any payment for participating in this study.

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is "standard" – and thus not covered by the sponsor/study – unless you tell them.

All tests, visits, and procedures are standard of care for this patient population and will be billed to the subject's insurance. All drugs recommended will be FDA-approved for the tumor markers and the drugs will be charged to the subject's insurance.

Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

The Principal Investigator has primary responsibility for monitoring the safe conduct of this study. Additionally, the Markey Cancer Center Data Safety and Monitoring Committee outlines oversight and monitoring of all cancer clinical trials. The Committee is responsible for reviewing data to identify patient safety and protocol compliance issues. The Markey Protocol Review Committee (PRC) assigns studies a DSMC review timeline based on the phase, origination of the study and known safety issues.

The members of the MCC DSMC consist of Medical Oncologists, a Pharmacist, a Nurse Manager, a Certified Clinical Research Professional and a Reporter. These members were selected based on their experience, reputation for objectivity, and knowledge of

clinical trial methodology. The DSMC reviews the protocol to assure the following: progress of the trial and safety of participants; compliance with requirements for the reporting of adverse events; any actions resulting in a temporary or permanent suspension by the sponsor; and data accuracy and protocol compliance. The DSMC, the Protocol Review Committee (PRC), the responsible disease-specific Clinical Care and Research Team (CCART) and/or the UK IRB are empowered to immediately suspend accrual to any study under its purview for failure to comply with AE/SAE reporting requirements, poor study enrollment, protocol violations or issues related to patient safety.

Back to Top

Future Use and Sharing of Research Data

If the results of this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

Your information or samples collected for this study will NOT be used or shared for future research studies, even if we remove the identifiable information like your name, medical record number, and/or date of birth.

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the "Additional Information/Materials" section. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?
○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?
○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?
○ Yes ○ No

If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

HIPAA

0 unresolved comment(s)

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

☐ HIPAA De-identification Certification Form
☐ HIPAA Waiver of Authorization

Attachments

STUDY DRUG INFORMATION

0 unresolved comment(s)

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?

○ Yes ◉ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☐ Investigational Drug Service (IDS) UK Hospital

Other Location:

Is the study being conducted under a valid Investigational New Drug (IND) application?

○ Yes ○ No

If Yes, list IND #(s) and complete the following:

IND Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access SOP.

Complete and attach the required Study Drug Form picking "Study Drug Form" for the document type. Any

applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.) should be attached using "Other Drug Documentation" for the document type.

Attachments

STUDY DEVICE INFORMATION

0 unresolved comment(s)

A DEVICE may be a:

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer “no” above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE), Humanitarian Device Exemption (HDE) or Compassionate Use?

○ Yes ○ No

If Yes, complete the following:
IDE or HDE #(s)

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment IDE or Compassionate Use under the Food and Drug Administration (FDA) Expanded Access program.

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor’s authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Medical Device SOP.

Does the intended use of any research device being tested (not clinically observed) in this study meet the regulatory definition of Significant Risk (SR) device?

- Yes. Device(s) as used in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- No. All devices, as used in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Complete and attach the required Study Device Form, picking the "Study Device Form" for the document type. Any applicable device documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.) should be attached using "Other Device Documentation" for the document type.

Attachments

RESEARCH SITES

0 unresolved comment(s)

To complete this section, ensure the responses are accurate then click "SAVE".

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☑ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☑ UK Healthcare Good Samaritan Hospital
- ☑ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky, at sites that are geographically separate from UK, or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page), including:

- A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.
- Supportive documentation, including letters of support, can be attached below.
- NOTE: If the non-UK sites or non-UK personnel are engaged in the research, there are additional federal and university requirements which need to be completed for their participation. For instance, the other site(s) may need to complete their own IRB review, or a cooperative review arrangement may need to be established with non-UK

sites.
- Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

List all other non-UK owned/operated locations where the research will be conducted:

Describe the role of any non-UK site(s) or non-UK personnel who will be participating in your research.

Attachments

B) Is this a multi-site study for which **you are the lead investigator or UK is the lead site**? ○ Yes ◉ No

If YES, describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites:

C) If your research involves collaboration with any sites and/or personnel outside the University of Kentucky, then it is considered multisite research and IRB reliance issues will need to be addressed. This may include national multi-center trials as well local studies involving sites/personnel external to UK. If you would like to request that the University of Kentucky IRB (UK IRB) serve as the lead IRB for your study, or if you would like the UK IRB to defer review to another IRB, please contact the IRBReliance@uky.edu.

RESEARCH ATTRIBUTES

0 unresolved comment(s)

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

	For additional requirements and information:
☐ Academic Degree/Required Research	• Cancer Research (MCC PRMC) • Certificate of Confidentiality (look up "Confidentiality/Privacy...") • CCTS (Center for Clinical and Translational Science)
☐ Alcohol/Drug/Substance Abuse Research	• Clinical Research (look up "What is the definition of....)
☐ Biological Specimen Bank Creation (for sharing)	• Clinical Trial
☑ Cancer Research	• Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...")
☐ CCTS-Center for Clinical & Translational Science	• Collection of Biological Specimens (look up "Specimen/Tissue Collection...")
☐ Certificate of Confidentiality	• Community-Based Participatory Research (look up "Community-Engaged...")
☑ Clinical Research	• Data & Safety Monitoring Board (DSMB) *For Medical IRB: Service Request Form for CCTS DSMB
☐ Clinical Trial - Phase 1	
☑ Clinical Trial	
☐ Collection of Biological Specimens for internal banking and use (not sharing)	
☐ Community-Based Participatory Research	
☐ Deception	• Data & Safety Monitoring Plan • Deception* *For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Educational/Student Records (e.g., GPA, test scores)	
☐ Emergency Use (Single Patient)	• Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF) • Genetic Research (look up "Specimen/Tissue Collection...") • Gene Transfer • HIV/AIDS Research (look up "Reportable Diseases/Conditions") • Screening for Reportable Diseases [E2.0000] (PDF) • International Research (look up "International & Non-English Speaking") • NIH Genomic Data Sharing (GDS) Policy (PDF) • Planned Emergency Research Involving Waiver of Informed Consent* *For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process" • Use, storage and disposal of radioactive material and radiation producing devices
☐ Gene Transfer	
☐ Genetic Research	
☐ GWAS (Genome-Wide Association Study) or NIH Genomic Data Sharing (GDS)	
☐ Human Cells, Tissues, and Cellular and Tissue Based Products	
☐ Individual Expanded Access or Compassionate Use	
☐ International Research	
☐ Planned Emergency Research Involving Exception from Informed Consent	
☐ Recombinant DNA	
☐ Registry or data repository creation	
☐ Stem Cell Research	
☐ Suicide Ideation or Behavior Research	
☐ Survey Research	
☐ Transplants	
☐ Use, storage and disposal of radioactive material and radiation producing devices	
☐ Vaccine Trials	

FUNDING/SUPPORT

0 unresolved comment(s)

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☐ Not applicable

Check All That Apply

- ☐ Grant application pending
- ☐ (HHS) Dept. of Health & Human Services
  - ☐ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☑ Internal Grant Program w/ proposal
- ☐ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☐ Pharmaceutical Company
- ☐ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Other:

Click applicable listing(s) for additional requirements and information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

KL2 Career Development Grant and Markey Cancer Center

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application using the "Add Related Grants" button.
If required by your funding agency, upload your grant using the "Grant/Contract Attachments" button.

Add Related Grants

Grant/Contract Attachments

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP and DoD Summary for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

Assurance/Certification Attachments

OTHER REVIEW COMMITTEES

0 unresolved comment(s)

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

◉ Yes ○ No

☐ Institutional Biosafety Committee
☐ Radiation Safety Committee
☐ Radioactive Drug Research Committee
☑ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
☐ Graduate Medical Education Committee (GME)
☐ Office of Medical Education (OME)

Additional Information

- Institutional Biosafety Committee (IBC) - Attach required IBC materials
- Radiation Safety Committee (RSC) - For applicability, see instructions and attach form
- Radioactive Drug Research Committee (RDRC)
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)** - Attach MCC PRMC materials, if any, per instructions.
- Office of Medical Education (OME)
- Graduate Medical Education Committee (GME)

Attachments

**** If your study involves cancer research, be sure to select "Cancer Research" in the "Research Attributes" section.** ORI will send your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRMC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

ADDITIONAL INFORMATION/MATERIALS

0 unresolved comment(s)

Do you want specific information inserted into your approval letter? ◉ Yes ○ No

Approval Letter Details:

If you wish to have specific language included in your approval letter (e.g., serial #, internal tracking identifier, etc…), type that language in the box below exactly as it should appear in the letter. The text you enter will automatically appear at the top of all approval letters, identical to how you typed it, until you update it. Don't include instructions or questions to ORI staff as those will appear in your approval letter. **If these details need to be changed for any reason, you are responsible for updating the content of this field.**

MR Changing PI to Kunos, Updating Consents vd 2/13/2023

Additional Materials:

If you have other materials you would like to include for the IRB's consideration, check all that apply and attach the corresponding documents using the Attachments button below.

- ☑ Detailed protocol
- ☐ Dept. of Health & Human Services (DHHS) approved protocol (such as NIH sponsored Cooperative Group Clinical Trial)
- ☐ Other Documents

Protocol/Other Attachments

Attach Type	File Name
Protocol	MCC-20-MULTI-37. Amendment 1. 25NOV2020.pdf

NOTE: Instructions for Dept. of Health & Human Services (DHHS)-approved protocol]

If you have password protected documents, that feature should be disabled prior to uploading to ensure access for IRB review.

To view the materials currently attached to your application, click “All Attachments” on the left menu bar.

6. STUDY DESIGN AND STATISTICAL CONSIDERATIONS

6.1 Study Design and Endpoints

This is a single-arm, pilot trial in patients with metastatic high grade large cell neuroendocrine carcinoma (HG-LCNEC) to study the feasibility of upfront NGS directed treatment in high grade neuroendocrine carcinomas. Tumor samples will receive next generation sequencing (NGS) profiling to classify the tumor as: small cell-like or non-small cell-like. Non-typeable cases will not be eligible for participation in this study, neither is small cell neuroendocrine carcinoma (HG-SCNEC). The systemic therapy regimen will be determined based on the NGS profile of the tumor.

Feasibility is defined as being able to sequence the patient within 2 months of initial medical oncology visit and being able to assign into molecularly-defined cohorts (TP53 and RB1 co-mutated vs non-co-mutated).

Secondary outcomes include ORR and progression-free survival (PFS). Radiological response will be assessed via RECIST Version 1.1 criteria (Appendix B) based on standard-of-care CT scans completed at q2 monthly intervals during treatment and q3 month during observation. PFS is defined from date of on study to the date of disease progression or death or date of last follow-up whichever occurs first. PFS will be assessed via standard-of-care CT scans (q2 month intervals during active treatment and q3 months during observation) as graded by RECIST Version 1.1 criteria for up to one year post-study enrollment.

All patients who received anticancer therapy will be included in the toxicity and safety analysis. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific AE, the incidence of AE causing withdrawal from the study and incidence of SAE. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be evaluated.

Listings of AEs by patients will include the following information: time to onset, the duration of each AE, the severity of each AE, the relationship of the AE to study therapy, whether it was a serious AE (or not), and whether the AE caused withdrawal. Toxicities will be graded according to Common Toxicity Criteria (CTCAE) v5.

6.2 Sample Size/Accrual Rate

We plan to enroll 15 patients on this pilot trial to study the feasibility of upfront NGS directed treatment in high grade neuroendocrine carcinomas and evaluate the ORR and progression-free survival.

Feasibility is defined as being able to sequence the patient within 2 months of initial medical oncology visit and being able to assign into molecularly defined cohorts (TP53 and RB1 co-mutated vs non co-mutated). If more than 50% patients are not able to sequence within 2 months

of initial medical oncology visit or more than 50% patients are not able to assign into molecularly defined cohorts, the study will be deemed not feasible. No stopping rule is planned to stop enrollment based on feasibility. With 15 patients, the probability of unfeasible of the study is calculated with true unfeasibility probability p from 0.2 to 0.8 (Table 1). From this calculation we see if the true unfeasibility rate <0.5, the probability to declaim the trial unfeasible is low and if the true unfeasibility rate >0.5, the probability to declaim the trial unfeasible is high.

Table 1: Probability of unfeasibility for this pilot study

True prob. of unfeasible	**p=0.2**	**p=0.3**	**p=0.4**	**p=0.5**	**p=0.6**	**p=0.7**	**p=0.8**
Prob. of unfeasible	0.0042	0.050	0.213	0.50	0.787	0.950	0.996

The expected accrual rate is about 8 patients per year and accrual duration is approximately 2 years, with an additional 1 year follow-up after the last patient is enrolled on the study for observation of disease progression. Thus, the total study duration is about 3 years.

All patients who completed at least 2-cycle treatments will be evaluable for the ORR objective. Patients who fail to complete 2-cycles of the treatment due to toxicity or withdrawal from study will be excluded from the ORR evaluation. All patients enrolled on the study will be evaluable for the PFS.

6.3 Study Cohorts

Patients with large cell, HG-NEC will be enrolled into one of two cohorts, small cell-like or non-small cell-like cohorts, based on the next generation sequencing panel performed on the tumor sample. It is expected to enroll 6 patients for small cell-like subtype (40%) and 9 patients for non-small cell-like subtype (60%).

6.4 Analysis of Primary and Secondary Endpoints

Percentage of patients who are able to sequence within 2 months of initial medical oncology visit will be estimated and percentage of patients who are able to assign into molecularly defined cohorts will be estimated for assessment of feasibility of the study. The ORR will be estimated with a standard error (SE). All patients will be followed until disease progression, death or end of study, whichever occurs first, for evaluation of PFS. The PFS will be estimated using Kaplan-Meier method for the entire cohort. Summary statistics will be provided for the analysis of potentially targetable mutations in high grade neuroendocrine carcinoma.

KEY INFORMATION FOR MCC-20-MULTI-37: A Pilot Feasibility Study of Next Generation Sequencing-based stratification of front-line treatment of high-grade Neuroendocrine Carcinoma (Precision-NEC)

We are asking you to choose whether or not to volunteer for a research study about using molecular analysis to guide treatment planning for patients with high-grade neuroendocrine cancer (HG-NEC). We are asking you to take part in this research because you have HG-NEC that has spread to other places in your body and your cancer cannot be cured by surgery. The purpose of this study is to use results of molecular analysis of your tumor tissue to inform treatment planning for your disease.

This top sheet provides Key Information to help you decide whether to participate. More detailed information is provided after this page. Ask the research team questions. If you have questions later, contact information for Dr. Charles Kunos, MD, the researcher (i.e., Investigator) in charge of this study, can be found below.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

HG-NEC is an aggressive cancer and currently, there is no standard front-line treatment. The usual approach involves treatment with platinum-based chemotherapy. For some patients this works well but for many others it does not. Among patients who get the usual approach, about 5 out of 100 are free of cancer after 5 years.

One of the ways doctors are trying to find better treatments is by looking at the cancer on a molecular level. We know that many drugs are effective only against cancers with certain tumor mutations. We also know that some of the tumor mutation patterns in HG-NEC seem very similar to patterns of other cancer types. There are treatments that work against those mutation patterns approved by the FDA for other cancer types. In this study, we will test the match of your tumor tissue's mutation patterns to the mutation patterns found in other cancer types. We will then recommend the FDA-approved treatment for you based on your tumor mutations profile. We hope this molecularly-guided plan for treatment will be more effective against your cancer (high-grade neuroendocrine cancer) than just the usual approach using platinum-based chemotherapy.

Of course, getting the tumor analysis done and reviewing treatment options takes time. By doing this feasibility study, we hope to find out if we can complete molecular analysis (sequencing) and begin your treatment in a timely manner. Additionally, we want to learn how effective this approach will be. Your participation in this research study will last about 3 years.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

The treatment plan matched specifically for you should be more effective than the usual treatment approach you might otherwise receive, *however*, there may be no added benefit to you at all. For a complete description of benefits, refer to the **Detailed Consent**, found on the following pages.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

Next generation molecular sequencing is now standard of care for all patients with HG-NEC and you can get treatment for your cancer without being on this study. For a complete description of risks, refer to the **Detailed Consent** and/or **Appendix**.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer to be in this study.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study contact Charles Kunos, MD of the University of Kentucky Department of Radiation Medicine at 859-562-0210

If you have any concerns or questions about your rights as a volunteer in this research, contact staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

DETAILED CONSENT:

ARE THERE REASONS WHY YOU WOULD NOT QUALIFY FOR THIS STUDY?

You cannot be in this study if you are under 18 years of age or if you are pregnant or nursing an infant.

WHERE WILL THE STUDY TAKE PLACE AND WHAT IS THE TOTAL AMOUNT OF TIME INVOLVED?

The research procedures will be conducted at UK Medical Center. You will need to come to the clinic every 4 weeks while you are getting treatment. You will get treatment as long as the treatment helps you and you want to continue. You will come to clinic for another visit 30 days after you finish treatment. Each of these visits will take about 2 hours. You will be in the study for about 3 years.

WHAT WILL YOU BE ASKED TO DO?

If you decide to take part in this study, while you are receiving the commonly-used, platinum-based chemotherapy, your tumor tissue will be sent to a laboratory for molecular sequencing. Those results will be analyzed by the Markey Cancer Center Molecular Tumor Board and results will be provided to your oncologist. Based on your cancer's molecular profile you may then be changed to a different FDA-approved treatment regimen that best matches the patterns of your tumor's mutations.

You will get the FDA-approved treatment for your cancer based on your tumor's molecular profile. While on treatment, you will come to the clinic every 4 weeks. At each visit you will meet with your doctor and the research team and have a physical exam and laboratory tests (e.g., blood tests). You will get a CT scan every 2 months during study treatment. This study will collect information about how you are responding to the treatment.

You will take the recommended treatment until your disease gets worse or the side effects become too severe.

After you finish your study treatment, your doctor will continue to follow your progress every 3 months through clinic visits. During the follow-up period, you will get CT scan every 3 months for at least one year. Additionally, your research team will monitor you for potential side effects and worsening of your condition in conjunction with your oncologist until the study is completed.

There are no additional tests or procedures for this study. You will have the same tests and visits on this study as you would have if you were not on study. For a list of all tests and procedures for this study, see the **Appendix: Study Visits/Procedures.**

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Physical:

You will not receive any investigational treatment on this study.

There is no additional physical risk from collecting leftover tumor tissue from a procedure that is being done as part of your clinical care.

Risks of blood collection:

Risks associated with blood sampling are generally slight, but may include soreness, bruising, pain, infection, possible fainting, bleeding.

Risk of having genetic testing:

Even without your name or identifiers, genetic information is unique to you making it possible for someone to trace it back to you. The results of genetic research apply to both you and your family members. In some cases, it could be used to make it harder for you to get or keep a job or health insurance. Genetic information could be used in ways that could cause you or your family distress. There is a federal law called the Genetic Information Non- discrimination Act (GINA). Generally, GINA makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you or treat you differently based on your genetic information. Be aware that GINA does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not prohibit discrimination on the basis of an already known genetic disease.

Unknown Risks

In addition to the risks listed above, you may experience a previously unknown risk or side effect. Tell the study doctor or study staff right away if you have any problems or ill effects from participating in this study. The

information in this form tells you what is known about the research study at the time this consent is first signed. If any new information is discovered during the research study that may affect whether you want to continue to take part, you will be informed in a timely manner.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

We do not know if you will get any benefit from taking part in this study. However, if you take part in this study, information learned may help others with your condition.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to take part in the study, there are other choices.

- You may choose to have cancer treatment without being on study. At UK, our standard treatment would be platinum-based chemotherapy with carboplatin and etoposide.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

WHAT WILL IT COST YOU TO PARTICIPATE?

You and/or your insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that you would normally receive for any conditions you may have. These are costs that are considered medically necessary and will be part of the care you receive, even if you do not take part in this study.

The University of Kentucky may not be allowed to bill your insurance company, Medicare, or Medicaid for the medical procedures done strictly for research. These costs will be paid by the Markey Cancer Center. The research-related tests/procedures for this study are: review by the Molecular Tumor Board and some of the laboratory tests.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

When we write about or share the results from the study, we will write about the combined information. We will keep your name and other identifying information private. We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, and what that information is. Your information will be stored in a password-protected database and any physical files (scans, slides or paper records) will be stored in locked file cabinets located behind locked doors.

You should know that in some cases we may have to show your information to other people. For example, the law may require us to share your information with:

- a court or agencies, if you have a reportable disease/condition;
- authorities, if you report information about a child being abused; or if you pose a danger to yourself or someone else.

To ensure the study Is conducted properly, officials of the National Cancer Institute, the Kentucky Cancer Registry and/or the University of Kentucky may look at or copy pertinent portions of records that identify you.

CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can choose to leave the study at any time. You will not be treated differently if you decide to stop taking part in the study.

If you choose to leave the study early, data collected until that point will remain in the study database and may not be removed.

The investigators (researchers overseeing this trial) may need to remove you from the study. You may be removed if:

- you are not able to follow the directions,
- we find that your participation in the study is more risk than benefit to you, or
- the agency paying for the study chooses to stop this study early for a number of scientific reasons.

ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may not take part in this study if you are currently involved in another research study. It is important to let your study doctor know if you are in another research study. You should discuss this with your study doctor before you agree to participate in another research study while you are in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is due to the study, you should call Dr. Charles Kunos, MD at (859) 562-0210immediately. If you need to call on the weekend or after normal business hours, please call the UK paging operator at (859) 323-5321 and ask them to page the oncologist on-call. The oncologist will contact Charles Kunos, MD if necessary. Charles Kunos, MD or your treating oncologist will determine what type of treatment, if any, is best for you at that time.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.

Medical costs related to your care and treatment because of study-related harm **will be your responsibility**. These costs may be paid by your insurer if you are insured by a health insurance company (you should ask your insurer if you have any questions regarding your insurer's willingness to pay under these circumstances). If you have any questions regarding Medicare/Medicaid coverage, you should contact Medicare by calling 1-800-Medicare (1-800-633-4227) or Medicaid 1-800-635-2570.

A co-payment/deductible may be needed by your insurer or Medicare/Medicaid even if your insurer or Medicare/ Medicaid has agreed to pay the costs. The amount of this co-payment/deductible may be costly.

You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

You will not receive any rewards or payment for taking part in the study.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

We will tell you if we learn new information that could change your mind about staying in the study. We may ask you to sign a new consent form if the information is provided to you after you have joined the study.

WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESEARCH TESTS?

Generally, tests done for research purposes are not meant to provide clinical information. We will not provide you with individual research results.

There is a slight possibility that during a research project, an investigator could discover something that could affect the health of you or your family. If this occurs, the finding will be reviewed by Markey's Molecular Tumor Board to determine if it is in your best interest to contact you.

Do you give permission for us to contact you about research results or incidental findings that are determined to be important to you/your family's health? (Incidental findings are unforeseen findings discovered during the course of the research that may affect you or your family's health).

☐ Yes ☐ No _____Initials

You may also withdraw your consent to be contacted with information about research results or incidental findings by sending a written request to Charles Kunos, MD Telephone: (859) 562-0210 at University of Kentucky c/o Markey Cancer Center Clinical Research Organization / CC 140 Pavilion H / 800 Rose Street / Lexington, KY 40536-0293.

WHAT ELSE DO YOU NEED TO KNOW?

If you volunteer to take part in this study, you will be one of about 15 people to do so.

The Markey Cancer Center is providing financial support and/or material for this study.

A description of this clinical trial will be available on ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WILL YOUR INFORMATION (OR SPECIMEN SAMPLES) BE USED FOR FUTURE RESEARCH?

Your information or samples collected for this study will NOT be used or shared for future research studies, even if we remove the identifiable information like your name, medical record number, and/or date of birth.

This Space Intentionally Blank

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections describe how researchers may use your health information.

Your health information that may be accessed, used and/or released includes:

- Demographic Information (your name, address, telephone number, email address, health insurance number, social security number; your birth month and year, gender, ethnic and racial background)
- History and diagnosis of your disease
- Specific information about treatments you have received
- Past and present medical records pertaining to your health condition
- Information about other medical conditions that may affect your treatment
- Medical data, including physical examinations, laboratory test results, tumor measurements, CT scans, MRIs, X-rays, photographs of radiation therapy target areas, and pathology results related to your disease
- Information on side effects (adverse events) you may experience, and how these were treated
- Long-term information about your general health status and the status of your disease

The Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity;
- Law enforcement agencies, when required by law;
- University of Kentucky representatives;
- UK Hospital, UK Markey Cancer Center;
- U.S. Food and Drug Administration (FDA);
- National Cancer Institute (NCI) and Kentucky Cancer Registry;
- National Institutes of Health (NIH);

If you become pregnant anytime during the study or within 90 days after stopping study treatment, you must inform the study doctor.

The researchers agree to only share your health information with the people listed in this document.

Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this consent form. If you decide not to sign this form, it will not affect your:

- Current or future healthcare at the University of Kentucky;
- Current or future payments to the University of Kentucky;
- Ability to enroll in any health plans (if applicable); or
- Eligibility for benefits (if applicable).

After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:

Send a written letter to:

Charles Kunos at University of Kentucky c/o Markey Cancer Center Clinical Research Organization /

CC 140 Pavilion H / 800 Rose Street / Lexington, KY 40536-0293.

- to inform him of your decision.
- Researchers may use and release your health information **already** collected for this research study.

- Your protected health information may still be used and released should you have a bad reaction (adverse event).

You will not be allowed to review the information collected for this research study until after the study is completed. When the study is over, you may have the right to access the information.

The use and sharing of your information has no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Monday-Friday at (859) 323-1184.

This Space Intentionally Blank

Appendix: Study Visits and Procedures

	Pre-Screening	Baseline Visit	Week 4					Off-Treatment	30-day follow-up after the last dose *	** Ongoing Follow-up (up to 1-yr post-enrollment)	Off Study
			C 1 D 1	4 *	8 *	12 *	16 *				
CLIA-certified NGS ordered	X										
Informed Consent	X										
Demographics	X										
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	
Medical History	X										
Record drug administration	X	X	X	X	X	X	X	X			
Physical Exam, with vital signs, weight	X	X	X	X	X	X	X	X	X	X	
Height	X										
Adverse Event Evaluation	X	X	X	X	X	X	X	X	X	X	
CBC w/ diff [1]	X	X	X	X	X	X	X		X	X	
CMP [2]	X	X	X		X		X		X	X	
B-hCG (in WCBP)	X										
Imaging (CT C/A/P)	X				X		X			X[3]	
Assessment of disease progression					X		X			X	
Record date of progression for PFS			Record the date of progression on the study form.								
Survival Status											X

LEGEND for the STUDY CALENDAR:

* data and samples may be collected ±1 week from this timeframe.
** After the 16-week visit, Q4 weeks 1-year post study enrollment (i.e., the end of study observation period) or death, whichever occurs first.

1. CBC w/diff: White Blood Cell count (WBC), Hematocrit (HCT), Platelet count, and Absolute Neutrophil Count (ANC). This panel will be run and assessed in timeframes per standard of care for the specific disease site of the neuroendocrine tumor.

2. Serum Chemistry Panel (CMP) includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, AST/SGOT, ALT/SGPT, alkaline phosphatase, total bilirubin. This panel will be run and assessed in timeframes per standard of care for the specific disease site of the neuroendocrine tumor.

3. Imaging: Every 2 months during therapy to assess disease progression, and thereafter per standard of care (currently every 3 months) up to 1-year post-study enrollment. There is a three-week window for imaging after Week 16, to allow for flexibility in patient scheduling and to avoid protocol deviations.

4. Assessments to be made generally at the end of the week, with a one-week study visit window to allow for flexibility in patient scheduling. Study visit windows can flex up to 3 weeks, to avoid protocol deviations.

5. For pregnancy testing in women of child-bearing potential: serum or urine tests are acceptable, and will be assessed in timeframes per standard of care for the specific disease site of the neuroendocrine tumor.

INFORMED CONSENT : SIGNATURES

This consent includes the following:

- **Key Information Page**
- **Detailed Consent**
- **Appendix: Study tests and procedures**

You will receive a copy of this consent form after it has been signed.

_____ _____ **Signature of research participant** **Date** _____ **Printed name of research participant**
_____ _____ **Printed name of [authorized] person obtaining informed consent and HIPAA authorization)** **Date** _____ **Signature of Principal Investigator or Sub/Co-Investigator**