SUMMARY OF PROTOCOL CHANGES

For Protocol Amendment # to: **3 to 4**

UCCC Protocol #: **UCCC-HN-21-02**

Protocol Date: **12 September 2023**

#	Section	Change
1.	4.1 Inclusion	To ensure conformity with the eligibility criteria provided by the drug sponsor for this study the following additions, removals, and clarifications to the exclusion criteria have been made. 1. Added clarification details for subjects with Gilbert's syndrome to Inclusion Criteria #6. Creatinine clearance was also updated to >45 mL/min. 2. Updated the language for the contraception guidance for Inclusion Criteria #10. 3. Added inclusion criteria for #11 to include further details regarding the serum pregnancy tests at screening, with 72 hours of first dose, and throughout the study. 4. Provided further details for Inclusion Criteria #13 regarding condom use while engaging in any activity that allows for passage of ejaculate to another person during the study and 6 months following last dose. 5. Separated Inclusion Criteria # 13 into two separate criteria in #13 and #14. 6. Addition of inclusion criteria #15 "Participant must be willing and able to adhere to the lifestyle restrictions specified in this protocol." 7. Woman, man, female, male, she, he, her, him were updated to participant, they, them or their throughout the inclusion criteria.
2.	4.2 Exclusion	To ensure conformity with the eligibility criteria provided by the drug sponsor for this study the following additions, removals, and clarifications to the exclusion criteria have been made. 1. Updated Exclusion Criteria #7 to "clinically active infectious liver disease". 2. Exclusion Criteria #8 now includes significant genetic predisposition to or prior history of venous thromboembolic events. 3. The timepoint for Exclusion Criteria #'s 8 and 12 has been updated to enrollment. 4. Updated the language for Exclusion Criteria #9 to provide clarification regarding antimicrobial therapy and viral infections. 5. Removed requirement of prolonged steroids and other immune suppressive agents from Exclusion Criteria #10. 6. Removed Exclusion Criteria # 11 regarding concurrent malignancy to avoid contradicting Inclusion Criteria #9.
3.	9.8 Dosing Modifications for Other AE's	To ensure dosing modifications are consistent among all participants, guidelines were provided for all Grade 3 and Grade 4 AE's not already outlined in protocol.
4.	14. Adverse Events	To ensure compliance with the safety reporting mailbox change per sponsor, all email addresses and fax numbers have been updated.
5.	21. Appendix C	To ensure conformity with recommendations from the sponsor, this formula has been updated.

UCCC Protocol #: UCCC-HN-21-02

ClinicalTrials.gov Identifier: NCT05074940

Study Title: Phase II study to evaluate amivantamab in recurrent and metastatic adenoid cystic carcinoma

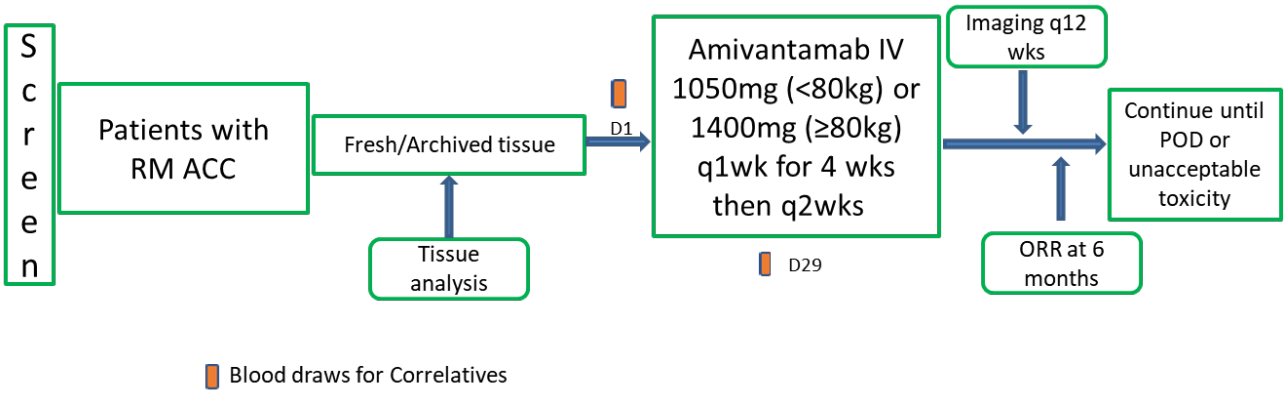
Principal Investigator:	Trisha Wise-Draper, MD, PhD University of Cincinnati Cancer Center wiseth@ucmail.uc.edu
Statistician:	Nusrat Harun, PhD Institution: CCHMC
Participating Sites & Site Principal Investigators:	Dana-Farber Cancer Institute; San Diego; University of Cincinnati; Washington University at St. Louis, University of Michigan
Financial Support	Janssen Scientific Affairs LLC (a pharmaceutical company of Johnson & Johnson)

IND #: 158,715 Exempt

IND Sponsor: Trisha Wise-Draper, MD, PhD

Protocol Type / Version # / Version Date: Original / Version 4/ 12 September 2023

1. SCHEMA



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2. OBJECTIVES

2.1. Primary Objectives

1. To determine the overall response rate (complete and partial response) in patients with recurrent and metastatic adenoid cystic carcinoma treated with amivantamab.

2.2. Secondary Objectives

1. To determine the progression free survival and overall survival in patients with recurrent and metastatic adenoid cystic carcinoma treated with amivantamab.

2. To determine safety and tolerability of amivantamab in patients with recurrent and metastatic adenoid cystic carcinoma.

2.3. Exploratory Objectives

1. To determine the molecular signatures of response and resistance to amivantamab with specific focus on EGFR, RAS and c-MET pathways.

2. To determine immune cell infiltration in biopsy samples and correlation with response.

3. To evaluate the effect of amivantamab on patient quality of life using standardized patient reported outcome surveys (FACT-HN).

3. BACKGROUND

3.1. Adenoid Cystic Carcinoma Background

Adenoid cystic carcinoma is a rare malignancy of salivary glands and other glandular tissue. It presents as a slow growing mass and is usually treated with surgery and adjuvant radiation. It is characterized by perineural invasion and a tendency for occult hematogenous dissemination at early stages of tumor development. [1] This leads to a high rate of local relapse and metastatic spread, which develops over several years. In one series, 62% of all patients experienced treatment failure and 38% developed distant metastases.[2] Recurrent and metastatic adenoid cystic carcinoma (R/M ACC) is incurable due to lack of effective systemic therapies. Therefore, despite being an indolent disease, the long-term outcomes remain poor with a 5- and 10-year overall survival of 76 and 48% respectively. The median OS after metastatic disease develops has been estimated to be around 3 years. The protracted course of the disease creates a higher prevalence of patients than would be suggested by incidence rates alone.

There is no standard of care systemic therapy for R/M ACC. [3] Genomic characterization has shown that about 40% of R/M ACC have mutations in various receptor tyrosine kinases, including EGFR, ERBB2, FGFR. [4] Several molecularly targeted therapies have been successfully investigated in R/M ACC. Multi-targeted receptor tyrosine kinase inhibitors (mTKI) like axitinib, lenvatinib, sorafenib have resulted in median PFS ranging from 6 to 17 months in several Phase II

studies and have become the mainstay of treatment. [5-9] A Phase II trial of lenvatinib in R/M ACC showed a 6-month PFS rate of 65.6% with a modest partial response of 15.6% and stable disease in 75% of the treated patients.[5] Cytotoxic chemotherapy regimens have consistently shown low response rates, most likely due to the slow growth kinetics.[10] EGFR inhibitors such as cetuximab achieved stable disease in most patients but did not lead to objective responses and are currently not used in R/M ACC. [11] Immunotherapy alone has not been successful, perhaps because ACC has a low tumor mutational burden and immune-excluded microenvironment. [12] The absence of standardized and effective treatment options highlights the need for conducting clinical trials with novel agents in R/M ACC.

3.2. Amivantamab Background

Amivantamab is a fully human EGFR-MET bispecific antibody with immune cell–directing activity that targets activating and resistant EGFR mutations and MET mutations and amplifications.[13] Amivantamab has the ability to inhibit aberrant EGFR and MET signaling through binding to the extracellular domains of these receptors, rather than targeting the kinase active site.[14] Amivantamab leads to degradation of EGFR and MET and also allows for targeting these cells for destruction by immune effector cells such as NK cells and macrophages. It has primarily been studied in patients with EGFR mutated non-small cell lung cancer. In the Phase I CRYSALIS trial, patients with advanced non-small cell lung cancer were treated with amivantamab monotherapy. The recommended Phase 2 dose was 1050 mg (1400 for patients >/=80kg) IV once weekly for the first cycle and biweekly thereafter. At the 1050 mg dose, 72% patients achieved concentrations above the EC90 based on preclinical models.[15] Adverse events in more than 20% were rash, infusion-related reactions, paronychia and constipation, hypoalbuminemia and dyspnea. The rate of grade 3 or higher AEs was 36% and serious AEs occurred in 30% patients. Serious adverse reactions in ≥ 2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death. [14]

3.3. Rationale

Pre-clinical studies have shown that approximately 53.2% ACC cases have strong c-MET expression. [16] EGFR is overexpressed in 70-90% of R/M ACC. [17] Additionally, proteogenomic analysis of ACC has revealed a distinct subtype which is characterized by overexpression of several receptor tyrosine kinases including EGFR, MET and AXL.[18] It has been hypothesized that TP63 overexpression drives AXL, EGFR and other RTKs and promotes oncogenesis. Increased MET expression has been associated with resistance to several targeted therapies in many solid tumor types, including resistance to EGFR inhibitors. It has been shown that combined inhibition of MET and EGFR decreases proliferation in ACC cell lines synergistically which is not seen with either agent alone.[19] Therefore, we hypothesize that amivantamab, a bispecific EGFR and MET inhibitor will be efficacious in ACC. We propose a Phase II study of amivantamab in patients with R/M ACC who are not eligible for curative intent therapy.

3.4. Correlative Studies Background

As mentioned above, EGFR and c-MET are highly expressed in ACC and amivantamab inhibits both proteins/pathways. Proteogenomic analysis of ACC has revealed two molecular subgroups: the ACC I group is characterized by Myc overexpression while the ACC II is characterized by upregulation of TP63 and other receptor tyrosine kinases including AXL, MET and EGFR. [18]. The RTKs (receptor tyrosine kinases) were overexpressed both at the RNA and protein level. ERBB family of proteins (total and phosphorylated EGFR, phospho-HER2), phospho-MET, phospho-MEK were significantly more abundant in ACCII. Therefore, we hypothesize that R/M ACC with upregulation of receptor tyrosine kinases and those in the ACCII subgroup will have increased response to amivantamab resulting in downregulation of Met and EGFR pathways (See Fig 1 below). We will analyze the expression of these RTKs as well as downstream RAS and other pathways that may mediate response or resistance in pre-treatment tissue specimens and compare to overall response.

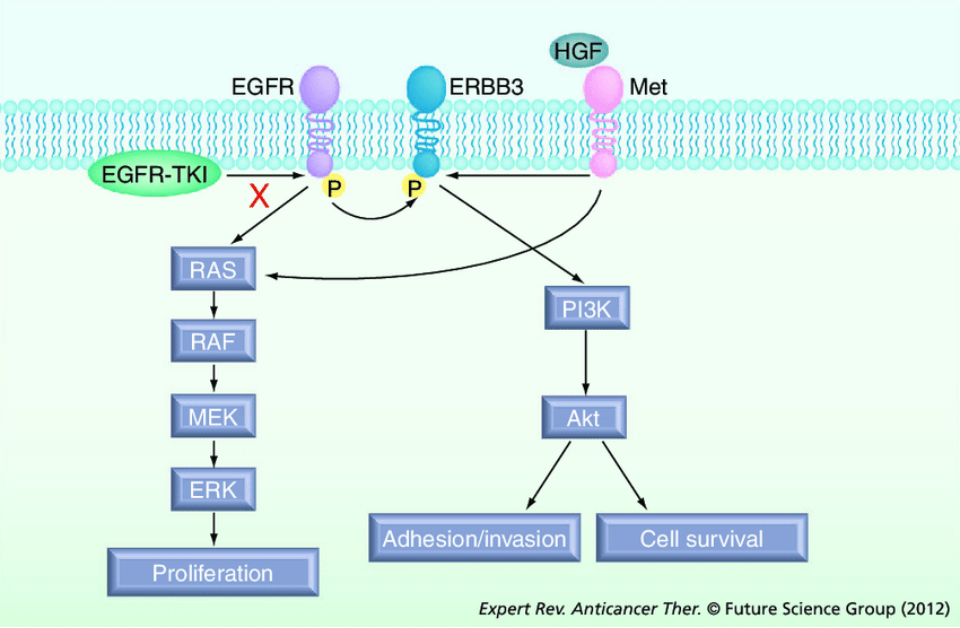

Fig. 1 Targeting the Met pathway in lung cancer April 2012 Expert Review of Anti-infective Therapy 12(4):519-28.

Amivantamab has been shown to induce cell-mediated cytotoxicity in NSCLC patient derived cells co-cultured with peripheral blood mononuclear cells (PBMCs), increase IFN-gamma production and increase macrophages and NK cell recruitment in the tumor. Therefore, we hypothesize that similar effects will occur in ACC upon treatment with amivantamab. Using patient PBMCs treated with amivantamab, we will analyze them for immune activation and function by co-culturing with available established ACC lines and measuring cytotoxicity. We will also analyze pre-treatment tissue for baseline immune cell infiltration to compare to overall response.

4. PATIENT SELECTION: ELIGIBILITY

4.1. Inclusion Criteria

1. Pathologically or cytologically confirmed adenoid cystic carcinoma. Non-salivary gland primary sites are allowed.

2. Recurrent and/or metastatic disease not amenable to other curative intent therapy. Patients must have had evidence of progressive disease by RECIST v1.1 within 6 months of study enrollment.

3. Presence of measurable disease as defined by RECIST v1.1

4. Age ≥18 years.

5. ECOG performance status ≤1 (Karnofsky ≥70%, see Appendix A).

6. Patients must have adequate organ and marrow function as defined below:

Hemoglobin	≥ 9 g/dL
Absolute neutrophil count	≥1,500/mcL
Platelets	≥75,0000/mcL
Total bilirubin	≤1.5 x institutional upper limit of normal (ULN); subjects with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits
AST(SGOT)/ALT(SGPT)	≤3 × institutional ULN, ≤5 x institutional ULN for those with liver metastases
Creatinine OR Calculated or measured creatinine clearance	< 1.5 institutional ULN
	>45 mL/min/1.73 m^2

7. Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression in the last 4 weeks.

8. Patients with **new or progressive brain metastases** (active brain metastases) or **leptomeningeal disease** are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

9. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

10. Before enrollment, a participant must be (as defined in Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information) either of the following:
    a. Not of childbearing potential
    b. Of child-bearing potential and practicing true abstinence during the entire period of the study, including up to 6 months after the last dose of study treatment is given
    c. Of childbearing potential and practicing 2 methods of contraception, including 1 highly effective user independent method and a second method (examples of highly effective methods of contraception are located **in Appendix 2:** Contraceptive Guidance and Collection of Pregnancy Information).

    Subjects must agree to continue contraception throughout the study and continuing through 6 months after the last dose of study drug.

    Note: If the childbearing potential changes after start of the study (e.g., participant who is not heterosexually active becomes active, premenarchal participant experiences menarche) the participant must begin a highly effective method of birth control, as described above.

11. A participant of childbearing potential must have a negative serum (b-human chorionic gonadotropin [b-hCG]) at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.

12. A participant must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 6 months after receiving the last dose of study drug.

13. A participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for 6 months after receiving the last dose of study treatment. A participant who is sexually active with a partner of childbearing potential must agree to use a condom with spermicidal foam/gel/film/cream/suppository and his partner must also be practicing a highly effective method of contraception (i.e., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device [IUD] or intrauterine system [IUS]). If the subject is vasectomized, they must still use a condom (with or without spermicide) for prevention of passage of exposure through ejaculation, but their partner is not required to use contraception.

14. The subject must also not donate sperm during the study and for 6 months after receiving the last dose of study drug.

15. Ability to understand and the willingness to sign a written informed consent document.

16. Participant must be willing and able to adhere to the lifestyle restrictions specified in this protocol.

4.2. Exclusion Criteria

1. History of allergy or intolerance to study drug components.

2. Prior use of amivantamab.

3. Patients who have had chemotherapy or immunotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study. Palliative radiotherapy is allowed and does not require washout as long as it does not include a target lesion.

4. Positive hepatitis B (hepatitis B virus [HBV]) surface antigen (HBsAg)
   Note: Subjects with a prior history of HBV demonstrated by positive hepatitis B core antibody are eligible if they have at Screening 1) a negative HBsAg and 2) a HBV DNA (viral load) below the lower limit of quantification, per local testing. Subjects with a positive HBsAg due to recent vaccination are eligible if HBV DNA (viral load) is below the lower limit of quantification, per local testing.

5. Positive hepatitis C antibody (anti-HCV).
   Note: Subjects with a prior history of HCV, who have completed antiviral treatment and have subsequently documented HCV RNA below the lower limit of quantification per local testing are eligible.

6. Participant is positive for human immunodeficiency virus (HIV), with 1 or more of the following:
   1. Receiving ART that may interfere with study treatment (consult sponsor for review of medication prior to enrollment)
   2. CD4 count <350 at screening
   3. AIDS-defining opportunistic infection within 6 months of start of screening
   4. Not agreeing to start ART and be on ART>4 weeks plus having HIV viral load <400 copies/mL at end of 4-week period (to ensure ART is tolerated and HIV controlled).

   Note: Known human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

7. Other clinically active infectious liver disease.

8. Participant has active cardiovascular disease including, but not limited to:
   - A medical history of deep vein thrombosis or pulmonary embolism within 1 month prior to enrollment or any of the following within 6 months prior to enrollment: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated thrombus (clots), or incidental or asymptomatic pulmonary embolism are not exclusionary.

- Participant has a significant genetic predisposition to venous thromboembolic (VTE) events such as Factor V Leiden.
- Participant has a prior history of VTE and is not on appropriate therapeutic anticoagulation as per NCCN or local guidelines.
- Uncontrolled (persistent) hypertension: systolic blood pressure >160 mm Hg; diastolic blood pressure >100 mm Hg.
- Congestive heart failure (CHF), defined as New York Heart Association (NYHA) class III-IV or hospitalization for CHF (any NYHA class; refer **to Appendix 3**: New York Heart Association Criteria) within 6 months of starting drug.

9. Subject has uncontrolled illness, including but not limited to:
   - Uncontrolled diabetes
   - Ongoing or active infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week prior to starting study treatment] or diagnosed or suspected viral infection).
   - Active bleeding diathesis
   - Impaired oxygenation requiring continuous oxygen supplementation (e.g., due to medical condition requiring chronic continuous oxygen therapy).
   - Psychiatric illness/social situation that would limit compliance with study requirements.
   - Any ophthalmologic condition that is clinically unstable

10. Active or past medical history of Interstitial lung disease (ILD)/pneumonitis, including drug-induced or radiation ILD/ pneumonitis.

11. Participant had major surgery excluding placement of vascular access or tumor biopsy or had significant traumatic injury within 4 weeks before enrollment, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study. Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

12. Immune-mediated rash from checkpoint inhibitors that has not resolved prior to enrollment.

13. Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1) with the exception of alopecia or Grade 2 neuropathy.

14. Patients who are receiving any other investigational agents. Patients who have received other investigational agents previously who are no longer receiving these investigational agents may be eligible at the discretion of the PI. A 30 day washout from last dose of previous anticancer drug is required.

15. Pregnant women are excluded from this study. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with breastfeeding should be discontinued if the mother is treated with amivantamab.

16. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions, and requirements.

4.3. Inclusion of Women and Minorities

Women and minorities will be included.

5. REGISTRATION PROCEDURES

5.1. Assignment of Screening and Subject Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to eligibility being confirmed. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. The screening number will become the subject's study number once they are confirmed to be eligible (registered).

Any subject who is re-screened will be provided with a new screening number for each instance for which they are being screened. The screening number will be their study number as well once they are confirmed to be eligible and registered to treatment.

5.2. Screen Failures & Re-Screening

Patients who are screen-failures may be re-screened at a later time to determine if they could meet eligibility criteria as long as they have not yet started treatment. The cost of re-screening tests will not be covered by the study. Any patient undergoing such re-screening must undergo informed consent and be provided with a new screening number for each instance for which they are being re-screened. Results from assessments performed during the prior screening period are acceptable in lieu of a repeat screening tests if these prior tests are still within the protocol specified time frames. All screen-failures must be recorded in the study EDC, REDCap [21,22].

5.3. Patient Screening

All subjects must provide informed consent prior to the initiation of study procedures, including screening. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment. These screening labs and ECOG may happen on C1D1 so long as they occur prior to treatment, these may be used for both screening and C1D1.
- For women of reproductive potential, a serum pregnancy test will be performed within 7 days prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria as long as they have not yet started treatment; however, the cost of re-screening tests will not be covered by the study. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

5.4. Patient Registration

To determine if a patient meets eligibility criteria, the following documents should be compiled by research team and provided to the University of Cincinnati PI and UC Project Manager/Monitor as soon after the subject has consented as possible:

- Study informed consent form signed and dated by the patient.
- Source documents verifying every inclusion and exclusion criteria for the patient.

Upon receipt, the UC PI or qualified designee will confirm subject eligibility. This is required for all patients enrolled at both the University of Cincinnati and at sub-sites to ensure consistency and compliance with the protocol. Eligibility must be confirmed by the UC PI prior to the initiation of any study procedures. Once eligibility is confirmed, a research team member may then proceed to register the subject to enrolled status within the study EDC REDCap[21,22].

5.5. General Guidelines

Following registration, patients should begin protocol treatment as soon as possible. Issues that would cause significant treatment delays should be discussed with the Principal Investigator.

6. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

6.1. Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Lab
1	Genomic Mutational Analysis	Whole Exome Sequencing and Next Generation Sequencing	Integrated Genomic analysis to determine any mutations in EGFR, RAS or c-MET pathways	M	Baseline only	FFPE Slides	15 slides	Caris Life Sciences
2	Pathway Expression Analysis	Whole Transcriptome Sequencing	Integrated RNA expression analysis of EGFR and c-MET pathways	O	Baseline only	FFPE slides	10 slides	Caris Life Sciences

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Lab
3	Protein Expression	Immunohisto-chemistry	Exploratory EGFR, PD-L1, MET (SP 44 assay) as well as Myc and TP63 expression to identify ACC I and II groups etc. protein expression	O	Baseline only	FFPE slides	10 slides	Caris Life Sciences & TWD Lab.
4	Characterization of peripheral blood immune activation	Flow Cytometry	Exploratory For Immune Cell Quantitation and Activation	O	Baseline, Day 29	PBMCs isolated from Whole Blood	4 EDTA tubes (40 mls) per time point	TWD Lab & UCCC CTO Transl. Lab.
5	Cytokine analysis	ELISA and/or Luminex/ CodePlex analysis via IsoLight technology	Exploratory To detect cytokine expression	O	Baseline, Day 29	Plasma isolated from blood and serum from red -top serum tubes	Plasma will be isolated from the whole blood collected for PBMC isolation in EDTA tubes. In addition, serum will be isolated from red -top SST tubes.	TWD Lab & UCCC CTO Transl. Lab.
6	PBMC Cytotoxicity	PBMC cytotoxicity assays	Exploratory To determine if amivantamab increases cytotoxicity	O	Baseline, Day 29	PBMCs isolated from whole blood	4 EDTA tubes (40 mls) per time point to be combined with #4	TWD Lab

Specimen Collection Schedule

Specimen Type	Baseline (After Eligibility confirmed but Pre-treatment)	Day 29
Archival biopsy tissue (35 unstained slides or block)	X	

Peripheral Blood (45mLs in four 10mL EDTA tubes and one 5mL serum tube)	X	X[1]

*If the baseline sample is not collected, then D29 should not be collected.

6.2. Integrated Correlative Studies

Please consult the study lab manual for more details on the analysis to be performed and collection and shipping procedures. All samples will be labeled with a unique number: UCCC-HN-21-02-xx-yy where xx is the assigned subsite number and yy is the patient number. Patient identifiers will not be included on the samples and link between identifiers and unique number will be kept in secure database at each institution. All samples will be stored in the CTO laboratory and kept until all analyses are considered complete on study at which time they will be anonymized and retained for potential future research. Any patient who withdraws may request destruction of remaining samples that have not yet been analyzed; destruction will be performed per the standard operating procedures of the respective laboratories with which samples may be stored

6.3. Tissue – Genomic Mutation Analysis

Collection of Specimen(s):

- Tumor block ideally or 15 FFPE slides will be collected at baseline prior to treatment; Archival is acceptable for pre-treatment. Selected blocks should exhibit 50mm^2 with 20% tumor content for downstream analysis. Blocks should be identified by a pathologist and if specifications do not meet threshold requested, discussed with study PI.

Handling of Specimens(s):

- Normal operating procedures.

Shipping of Specimen(s):

- Ship per standard operating procedures; ideally these blocks are sent per SOC to Caris Life Sciences directly. If not institution SOC, notify UCCC CTO Translational Lab by email at ctolabuccc@ucmail.uc.edu, ***the day of shipping the sample***. Tissue will be stored in the UCCC CTO Translational laboratory. Laboratory staff is responsible for bulk shipment of tissue to Caris Life Sciences laboratory if not sent directly from site. If the tissue has already been characterized by another standard test (Tempus, Foundation One, Inhouse platform etc.) and at minimum includes below mutation analysis and results are able to be provided, these results can be used in lieu of sending this tissue.

Site(s) Performing Correlative Study:

- Caris Life Sciences.

Analysis:

- Genomic analysis to determine any mutations in EGFR, RAS or c-MET pathways using Whole Exome Sequencing and Next Generation Sequencing.

6.4. Tissue – Pathway Expression Analysis

Collection of Specimen(s):

- Tumor block ideally or 10 FFPE slides will be collected at baseline prior to treatment; Archival is acceptable for pre-treatment. Selected blocks should exhibit 50mm^2 with 20%

tumor content for downstream analysis. Blocks should be identified by a pathologist and if specifications do not meet threshold requested, discussed with study PI.

Handling of Specimens(s):

- Normal operating procedures.

Shipping of Specimen(s):

- Ship per standard operating procedures; ideally these blocks are sent per SOC to Caris Life Sciences directly. If not institution SOC, notify UCCC CTO Translational Lab by email at ctolabuccc@ucmail.uc.edu, ***the day of shipping the sample***. Tissue will be stored in the UCCC CTO Translational laboratory. Laboratory staff is responsible for bulk shipment of tissue to Caris Life Sciences laboratory if not sent directly from site. If the tissue has already been characterized by another standard test (Tempus, Foundation One, Inhouse platform etc.) and at minimum includes below pathway analysis and results are able to be provided, these results can be used in lieu of sending this tissue.

Site(s) Performing Correlative Study:

- Caris Life Sciences.

Analysis:

- RNA expression analysis of EGFR and c-MET pathways using Whole Transcriptome Sequencing.

6.5. Exploratory/Ancillary Correlative Studies

Please consult the study lab manual for more details on the analysis to be performed and collection and shipping procedures.

6.6. Tissue – Protein Expression

Collection of Specimen(s):

- Tumor block (or at least 10 FFPE slides) will be collected at baseline prior to treatment; Archival is acceptable for pre-treatment.

Handling of Specimens(s):

- Normal operating procedures.

Shipping of Specimen(s):

- Ship per standard operating procedures; Notify UCCC CTO Translational Lab by email at ctolabuccc@ucmail.uc.edu, ***the day of shipping the sample***. Tissue will be stored in the UCCC CTO Translational laboratory. Laboratory staff is responsible for bulk shipment of tissue to Caris Life Sciences laboratory or to TWD Laboratory.

Site(s) Performing Correlative Study:

- Caris Life Sciences and Trisha Wise-Draper (TWD) Laboratory

Analysis:

- EGFR, PD-L1 as well as Myc and TP63 expression to identify ACC I and II groups etc. protein expression.

6.7. Peripheral Blood - Immune Cell Characterization and Cytotoxicity

Collection of Specimen(s):

- 4 EDTA 10ml tubes will be collected at baseline (pre-treatment) and at Day 29.

Handling of Specimens(s):

- Normal operating procedures; do not shake or freeze tubes; Label each tube as follows:
    - Clinical trial study number (HN2102)
    - Subject's (ID) (site number, patient ID example: HN02-01)
    - Date the tube was drawn (example: 2/2/2018)
    - Time of blood draw (example: 15:00)
    - Study time-point (example: Day 1)

Site(s) Performing Correlative Study:

- UCCC CTO Translational Laboratory and Wise-Draper Laboratory
- Isolation of PBMCs to be performed either at subsite or after delivery to UCCC CTO laboratory on-site depending on agreement with primary site.

Shipping of Specimen(s):

- Isolated PBMCs will be stored in liquid nitrogen at site and batch shipped according to standard operating procedures if isolated at subsites. Otherwise, whole blood should be shipped overnight after collection. Please refer to laboratory manual for more details.
- Place sample in absorbent pack and 95kPa biohazard specimen transport bag along with sample requisition form.
- If shipping frozen PBMCs, place biohazard specimen bag containing frozen PBMCs into a frozen shipping box and cover with approximately 3lbs of dry ice. Otherwise, ship whole blood at ambient temperature.
- Follow IATA shipping instructions and standards by properly labeling all shipping boxes to prevent delays.
- Attach provided FedEx Airbill to the shipping box.
- Ship per standard operating procedures; Notify UCCC CTO Translational Lab by email at ctolabuccc@ucmail.uc.edu, ***the day of shipping the sample.***
- Samples to be shipped Monday-Thursday only via FedEx Priority Overnight.

6.8. Peripheral Blood - Cytokine Analysis

Collection of Specimen(s):

- Plasma will be isolated from whole blood prior to isolation of PBMCs for phenotypic analysis. Additionally, one 5mL red-top serum tube will be collected and serum will be isolated. Tubes will be collected at baseline (after eligibility but pre-treatment), Day 29 as previously stated.

Handling of Specimens(s):

- Do not shake or freeze tubes; Label each tube as follows:
    - Clinical trial study number (HN21-02)
    - Subject's (ID) (site number, patient ID example: HN02-01)
    - Date the tube was drawn (example: 2/2/2018)
    - Time of blood draw (example: 15:00)
    - Study time-point (example: Day 1)

Site(s) Performing Correlative Study:

- University of Cincinnati Translational Laboratory, Wise-Draper Laboratory.
- Separation of plasma to be performed either at subsite during PBMC isolation or after delivery to UCCC CTO laboratory below. Serum separation to be performed at collection site.

Shipping of Specimen(s):

- Isolated plasma and serum will be stored at site in a -80 degree freezer and batch shipped according to standard operating procedures.
- Place sample in absorbent pack and 95kPa biohazard specimen transport bag along with sample requisition form.
- Place biohazard specimen bag containing frozen plasma and serum into a frozen shipping box and cover with approximately 3lbs of dry ice. If plasma separation to occur at UCCC, whole blood to be shipped at ambient temperature.
- Follow IATA shipping instructions and standards by properly labeling all shipping boxes to prevent delays.
- Attach provided FedEx Airbill to the shipping box. Ship per standard operating procedures; Notify UCCC CTO Translational Lab by email at ctolabuccc@ucmail.uc.edu ***the day of shipping the sample***.
- Samples to be shipped Monday-Thursday only via FedEx Priority Overnight.

7. TREATMENT PLAN

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. The Dosing Tables are provided below. **Table 1** is to be referred to for the first dose of Amivantamab, which will be split over two days (Cycle 1, Day 1 and Day 2). **Table 2** is to be referred to for all doses other than the first split dose (Cycle 1, Days 1 and 2).

The dispensing tables are provided to be used as guides for doses that may be either chosen during study conduct or predetermined for the clinical study. Actual doses may be determined during study conduct and communicated appropriately to the Pharmacy. Doses not provided on the existing table require a revision to the IPPI.

Either 3 mL (150 mg/vial) or 7 mL vial (350mg/vial) can be used for preparation of doses. Certain studies will utilize 7 mL vials only, in such cases 3 mL vials will not be supplied, please refer to study protocol.

7.1. Dispensing Table 1 – Use for Administration of First Dose: Split Dosing for Cycle 1, Day 1 and Day 2

Total Planned Dose (mg)	Cycle 1 Day	Split Dose (mg)	Amivantamab Vials per Bag		Volume of Amivantamab added to 250 mL IV Bag (mL)	Volume of D5W or NS Removed from 250 mL IV Bag (mL)	Total Infusion Volume* (mL)
			3mL vial (150mg/vial)	7mL vial (350mg/vial)			
1050	Day 1	350	3	1	7	7	250
	Day 2	700	5	2	14	14	250
1400	Day 1	350	3	1	7	7	250
	Day 2	1050	7	3	21	21	250

* Manufacturer's potential overfill in the IV bag will NOT be removed and therefore total infusion volume may be slightly greater than 250 mL. It is important to infuse the entire IV bag containing the IP dose.

7.2. Dispensing Table 2 – Use for Administration of Full Dose in Single Bag

Total Planned Dose (mg)	Amivantamab Vials per Bag		Volume of Amivantamab added to 250 mL IV Bag (mL)	Volume of D5W or NS Removed from 250 mL IV Bag (mL)	Total Infusion Volume* (mL)
	3mL vial (150mg/vial)	7mL vial (350mg/vial)			
1050	7	3	21	21	250
1400	10	4	28	28	250

* Manufacturer's potential overfill in the IV bag will NOT be removed and therefore total infusion volume may be slightly greater than 250 mL. It is important to infuse the entire IV bag containing the IP dose.

As a mitigation against the risk of IRRs, the initial dose of amivantamab (Cycle 1, Days 1 and 2), **is administered as a split dose over 2 days (e.g., Cycle 1 Day 1 [350mg] and Cycle 1 Day 2 [remainder of dose]).** During this initial dose, interruption of the infusion should be considered even with mild symptoms to prevent more severe manifestations of IRR.

7.3. Administration rate - Table 3 – Use for Administration of 1050 mg Dose

Q2W 1050 mg Dose Level			
Daily Dose (in 250 mL IV bag)		**Rate (mL/hr)***	**Estimated Duration (hr:min)****
Cycle 1 Day 1 : 350 mg			Total: 4:00
	Step 1	50	2:00
	Step 2	75	2:00
Cycle 1 Day 2 : 700 mg			Total: 4:00
	Step 1	50	2:00
	Step 2	75	2:00
Cycle 1 Day 8: 1050 mg		85	3:00
All subsequent doses: 1050 mg		125	2:00

***Duration time and infusion rate (mL/hr) can remain the same even with a dose reduction for phase 1 studies.**
****Infusion times are the planned, approximate infusion times. The infusion rate should not be adjusted to meet a time duration listed in this table. Administer entire volume of the prepared dose in the IV bag.**

7.4. Administration rate - Table **4** – Use for Administration of 1400 mg Dose

Q2W 1400 mg Dose Level			
Daily Dose (in 250 mL IV bag)		**Rate (mL/hr)***	**Estimated Duration (hr:min)****
Cycle 1 Day 1: 350 mg			Total: 4:00
	Step 1	50	2:00
	Step 2	75	2:00
Cycle 1 Day 2 : 1050 mg			Total: 5:41
	Step 1	33	2:00
	Step 2	50	3:41
Cycle 1 Day 8: 1400 mg		65	4:00
Cycle 1 Day 15: 1400 mg		85	3:00
All subsequent doses: 1400 mg		125	2:00

***Duration time and infusion rate (mL/hr) can remain the same even with a dose reduction for phase 1 studies.**
****Infusion times are the planned, approximate infusion times. The infusion rate should not be adjusted to meet a time duration listed in this table. Administer entire volume of the prepared dose in the IV bag.**

8. DOSING DELAYS/DOSE MODIFICATIONS

When dose modification is required, modification should occur as listed below. Any dose/dosage adjustment should be overseen by medically qualified study-site personnel (principal or sub-investigator unless an immediate safety risk appears to be present).

If a participant experiences a toxicity requiring dose reduction after withholding study treatment and resolution, then the dose of amivantamab should be preferentially reduced, as outlined in the table below.

8.1. Dose modifications for amivantamab monotherapy

Dose Level	**<80 kg**	**≥80 kg**
Dose level 1	1050 mg	1400 mg
Dose level -1	700 mg	1050 mg
Dose level -2	350 mg	700 mg

See section “Guidelines for the Prevention, Monitoring, and Management of Amivantamab (JNJ-61186372) Rash Related Adverse Events” for discussion of events necessitating dose reductions.

9. TOXICITY MANAGEMENT GUIDELINES/SAFETY MONITORING

9.1. Guidelines for Monitoring and Management of Amivantamab (JNJ-61186372) Infusion-Related Reactions

Infusion reactions have been commonly observed during treatment with amivantamab predominantly with the first exposure on Cycle 1 Day 1, and typically within the first 90 minutes of the infusion.. The majority of IRRs are Grade 1 or 2 (Section 2.2). Refer to Summary of Data and Guidance for Investigators in the current version of the Investigator’s Brochure. The

guidelines described here relate to the safe administration of amivantamab during initial dosing.

During the amivantamab infusions, subjects should be clinically monitored at regular intervals as specified in the study calendar (including an assessment prior to the start of infusion). The monitoring should include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation measurements. Subjects must remain at the infusion center for monitoring for at least 1 hour after the end of the first dose of amivantamab (Cycle 1 Day 1), after which time, vital signs should be obtained.

Particularly with the initial dose (Cycle 1, Days 1 and 2), participants should be educated on 1) the likelihood of experiencing an IRR with the initial dose, 2) the symptoms to anticipate (which include chills, dyspnea, chest discomfort, fever, flushing, among others), 3) that they should alert nursing staff if they experience these symptoms, and 4) that the experience of an IRR will not preclude further therapy with amivantamab.

Participants must be monitored closely for early signs and symptoms indicative of an acute IRR. Even with mild symptoms, the study treatment infusion should be interrupted immediately, as described in the tables below, to prevent more serious grade IRRs from occurring.

Trained clinical personnel should be prepared to intervene in the event of IRRs. Resources necessary for resuscitation (ie, agents such as epinephrine, aerosolized bronchodilator, IV antihistamines, IV corticosteroids; medical equipment such as oxygen, airway management equipment including suction, and a defibrillator) must be readily available.

9.2. Pre-Infusion Medications for Amivantamab

Required pre-infusion medications (a corticosteroid, an antihistamine, and an antipyretic) must be administered as described in Table 1. Optional pre-infusion medications may also be administered as outlined in Table 1.

Table 1: Pre-Infusion Medications

Required Pre-Infusion Medications[a, b, d, e]				
Medication	**Dose**	**Route of Administration**	**Recommended Dosing Window Prior to Study Drug Administration**	**Cycle/Day**
Glucocorticoid	Dexamethasone (10 mg) or Methylprednisolone (40 mg)	IV or Oral	45 to 60 minutes	C1D1, C1D2[c]
Antihistamine	Diphenhydramine (25 to 50 mg) or equivalent	IV or	15 to 30 minutes	All
		Oral	30 to 60 minutes	
Antipyretic	Paracetamol (acetaminophen 650 to 1,000 mg) or equivalent	IV or	15 to 30 minutes	All
		Oral	30 to 60 minutes	
Optional Pre-Infusion Medications[a, f]				

Medication	Dose	Route of Administration	Recommended Dosing Window Prior to Study Drug Administration	Cycle/Day
Glucocorticoid[c]	Dexamethasone (10 mg) Methylprednisolone (40 mg)	IV or	45 to 60 minutes	C1D8 and beyond
		Oral	60 to 90 minutes	
H_2 -antagonist	Ranitidine (50 mg) or equivalent	IV	15 to 30 minutes	Any
Antiemetic	Ondansetron (16 mg) or equivalent	IV	15 to 30 minutes	Any
	Ondansetron (8 mg) or equivalent	Oral	15 to 30 minutes	

IV=intravenous.

a. If a medication noted in this table is not locally available, a similar medication and dose may be substituted and administered per local guidelines.
b. Participants for whom required medications are contraindicated should explore alternative medications with their study physician. If alternative medications are not suitable for the intent above, participants are not required to take the corresponding medication.
c. Beginning with Cycle 1 Day 8, optional pre-dose steroids may be administered if clinically indicated for participants who experienced an infusion-related reaction on Cycle 1 Day 1 or Cycle 1 Day 2.
d. The recommended dose of dexamethasone to be administered is 10 mg and should not be lower than 9. 8 mg.
e. Required Pre-Infusion glucocorticoid, antihistamine, and antipyretic may be administered IV or oral route.
f. Optional Pre-Infusion glucocorticoid may be administered by IV push or oral route.

9.3. Post-Infusion Medications for Amivantamab

Post-infusion medications listed in Table 2 may be prescribed and continued for up to 48 hours after the infusion if clinically indicated. The administration of post-infusion medications and use of supportive care measures should be instituted as clinically necessary at the discretion of the investigator.

Post-Infusion Medications

Optional post-infusion medications may be prescribed and continued for up to 48 hours after any infusion if clinically indicated, at the discretion of the investigator (Table 2).

Table 2: Post-Infusion Medications

Optional Post Infusion Medications[a]				
Medication	**Dose**	**Route of Administration**	**Administration Instructions**	**Cycle/Day**
Glucocorticoid	Dexamethasone (10 mg) or comparable corticosteroid	IV or Oral	As clinically indicated	Any
Antihistamine	Diphenhydramine (25 to 50 mg) or equivalent	IV or Oral	As clinically indicated	Any
Antipyretic	Paracetamol (acetaminophen) (650 to 1,000 mg)	IV or Oral	As clinically indicated	Any

Post-Infusion Medications

Optional post-infusion medications may be prescribed and continued for up to 48 hours after any infusion if clinically indicated, at the discretion of the investigator (Table 2).

Table 2: Post-Infusion Medications

Optional Post Infusion Medications[a]				
Medication	**Dose**	**Route of Administration**	**Administration Instructions**	**Cycle/Day**
Opiates	Meperidine (25 to 100 mg)	IV or Oral	As clinically indicated	Any
Antiemetic	Ondansetron (8 to 16 mg) or equivalent, long or short acting agents	IV	As clinically indicated	Any
	Ondansetron (8 mg) or equivalent, long or short acting agents	Oral		

IV=intravenous.

a. Optional medications can be used prophylactically as clinically indicated. If a medication noted in this table is not locally available, a similar medication and dose may be substituted and administered per local guidelines.

9.4. Treatment of Infusion-Related Reactions

Subjects who experience early symptoms of IRRs, manifesting as, but not limited to, chills, nausea, dyspnea, flushing, chest discomfort, vomiting, or any other symptoms during the time of the infusion, should have their infusions interrupted, if indicated, and the symptoms managed according to the recommendations provided in Table 3 below. With the initial dose of amivantamab (Cycle 1, Days 1 and 2), interruption of the infusion should be considered even with mild symptoms to prevent more severe manifestations of IRR. All NCI CTCAE Grade 3 or 4 infusion-related reactions should be reported within 24 hours to the Sponsor-Investigator.

Table 3: Management of Infusion-Related Reactions

Toxicity Grade*	**Treatment / Intervention**	**Premedication at subsequent dosing**
Grade 1 Mild reaction	Monitor subject as medically indicated until recovery from symptoms. If occurring with initial dose (i.e., Cycle 1 Day 1 or 2), consider early infusion interruption to prevent more severe symptoms. If infusion is interrupted, please follow the guidance for Grade 2 interruptions.	Antihistamine, antipyretic, and glucocorticoid., as per Table 1.
Grade 2 Mild to moderate reaction; therapy or infusion interrupted but responds promptly to symptomatic treatment	**Interrupt infusion** If clinically indicated, start IV fluids; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol (acetaminophen) 650 to 1000 mg; consider corticosteroids and bronchodilator therapy; H1 and H2 antagonist, antiemetic and; supplemental oxygen; monitor subject closely until recovery from symptoms **First interruption for infusion-related reaction: Restart infusion at 50% of the rate at the time of interruption**: if no further evidence of infusion-related reaction after 30 minutes, the rate may be increased to	Antihistamine, antipyretic, and glucocorticoid., as per Table 1. Consider meperidine if subject experiences chills and rigors.

Table 3: Management of Infusion-Related Reactions

Toxicity Grade*	Treatment / Intervention	Premedication at subsequent dosing
	100% of the infusion rate at the time of interruption; monitor subject closely. Infusion rate escalation may resume after an additional 30 minutes per the IPPI schedule, after the infusion has been administered for at least 30 minutes at 100% of the infusion rate used at the time of dose interruption. **Second interruption for infusion-related reaction:** Stop and consider discontinuation of further study drug treatment at that visit; administer diphenhydramine 50 mg IV or equivalent, and monitor subject until resolution of symptoms. The amount of study drug infused must be recorded in the CRF. If continuing administration after the second interruption, restart infusion at 50% of the rate at the time of the second interruption. If no further evidence of infusion-related reaction after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor subject closely. Infusion rate escalation may resume after an additional 30 minutes per the IPPI schedule, . after the infusion has been administered for at least 30 minutes at 100% of the infusion rate used at the time of dose interruption.	
Grade 3 or 4 Severe reaction Grade 3: prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: life-threatening; pressor or ventilator support indicated	Stop infusion Start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed (other drugs as appropriate). Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids), as appropriate.	Based on severity of symptoms, consider permanent discontinuation of study drug. Discussion with Sponsor-Investigator required before continuing with subsequent dosing. Grade 4: Do not rechallenge

*Per NCI CTCAE Version 5.0

9.5. Guidelines for the Prevention, Monitoring, and Management of Amivantamab (JNJ-61186372) Rash Related Adverse Events

The prevention and management of EGFR inhibitor-induced rash-related AEs can be conducted in accordance with local institutional guidelines or the following Protocol recommendations.

General considerations in rash management

- Instruct subjects to avoid unnecessary exposure to sunlight.
- Employ a proactive approach (i.e., prophylactic treatment; see below for recommendations).
- Consider consultation with a dermatologist, especially for severe rash, atypical appearance, or distribution, or lack of improvement within 2 weeks of treatment.
- If subject develops rash, follow steps outlined under "Reactive management."

Prophylactic treatment

The exact prophylactic regimen should be based on the investigator's experience; however, the following regimen is suggested:

- Broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15.
- Thick, alcohol-free emollient cream (e.g., glycerin and cetomacrogol cream) on dry areas of the body.
- Topical agents can be applied on a daily basis starting on Day 1 of study treatment, and more often as needed.

Reactive management

It is strongly recommended that subjects who develop rash/skin toxicities receive evaluations for management on the specific side effect.

- Start topical corticosteroids (e.g., hydrocortisone 2.5% cream).
- Offer topical clindamycin (1% gel) or systemic antibiotics (doxycycline 100 mg bid or minocycline 100 mg bid).
- For pruritic lesions, the use of cool compresses and oral antihistamine agents may be helpful.
- For fissuring, the use of Monsel's solution (ferric subsulfate solution), silver nitrate, or zinc oxide cream is advised.
- For desquamation, thick emollients and mild soap are recommended.
- For paronychia, antiseptic soaks and local potent corticosteroids in addition to oral antibiotics are recommended and, if no improvement is seen, a dermatology or surgery consultation is recommended.
- For infected lesions, bacterial and fungal culturing followed by the appropriate culture driven systemic or topical antibiotics is indicated.

Consider the following algorithm described in Table 4 below in a stepwise manner:

Table 4: Suggested Algorithm for Management of Rash in Subjects Receiving Amivantamab Monotherapy

Step	Rash grading[a]	Management of Rash	Amivantamab Dose Adjustment[b,c]
1	1	Initiate prophylactic regimen if not already	Continue current dose.

		started and add reactive therapies as above. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 2	 Reassess after 2 weeks; if rash does not improve, proceed to Step 2.
2	2	Initiate prophylactic regimen if not already started, including topical corticosteroids and systemic antibiotics as above.[d] Reassess after 2 weeks; if rash does not improve, proceed to Step 3.	Consider reducing dose by one dose level. Reassess after 2 weeks; if rash does not improve, proceed to Step 3.
3	3 or intolerable Grade 2	Initiate prophylactic regimen if not already started, moderate strength topical corticosteroids and systemic antibiotics as above plus prednisone (0.5 mg/kg) for 7 days. Consider low doses of isotretinoin (20-30 mg/day). Consider obtaining dermatology consultation and manage rash per dermatologist's recommendation.	Temporarily interrupt treatment until rash improves ≤ Grade 2, then follow steps outlined for the appropriate grading. Reassess after 2 weeks; if rash worsens or does not improve, permanently discontinue treatment.
4	4	Initiate reactive management as above. Start moderate strength topical corticosteroids[d] and systemic antibiotics as above, plus systemic prednisone (0.5 mg/kg) for 7 days. Consider low doses of acitretin or isotretinoin (20-30 mg/day). Reassess after 2 weeks. Consider dermatology consultation and manage rash per recommendation.	Permanently discontinue amivantamab for Grade 4 events.
	Severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN)	Consult dermatologist and manage rash per recommendation.	Permanently discontinue amivantamab.

[a] Grading per NCI CTCAE (Version 5)

[b] If drug must be withheld due to toxicity for 2 consecutive doses, then study drug cannot be restarted without prior permission from the sponsor investigator as medical monitor. Subjects considered by the investigator and sponsor to be benefiting from treatment may be continued, potentially at a lower dose upon satisfactory resolution of the toxicity.

[c] Resolution defined as: ≤Grade 1 non-hematologic toxicity or back to baseline

[d] For example, hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream

Table 5: Guidance for Withholding Doses for Toxicities Based on Grade

Grade[a]	Action[b]	Dose Modification After Resolution of Toxicity[c]
1	None	Continue both agents at current dose level; consider supportive care according to local standards as appropriate

2	None, or consider either withholding dose or dose reduce	If withheld <28 days, restart study treatment at current dose level or consider dose reduction.
3 or 4	Withhold amivantamab	After consultation with the Medical Monitor, may restart study treatment at current dose level or consider dose reduction of study treatment

a. Per National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0.
b. For all toxicities, consider supportive care according to protocol as appropriate.
c. Resolution defined as: ≤Grade 1 or back to baseline status for the participant (except for rash, oral mucositis, or paronychia which should recover to ≤Grade 2 or baseline).

9.6. Guidelines for the Prevention, Monitoring, and Management of Pulmonary Toxicity

Patients with metastases to the lung (NSCLC) are at risk of multiple adverse events affecting pulmonary function, including disease progression, pulmonary embolus, infectious pneumonias, and more rarely, drug related ILD/pneumonitis. Patient respiratory status should be assessed at every visit; any clinically significant change in respiratory status should prompt immediate investigation into the etiology in accordance with local practice/guidelines to institute appropriate treatments and to rule out early ILD/pneumonitis. If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pulmonary adverse event is observed, including ILD/pneumonitis, study treatments should be withheld, and appropriate treatment management should be promptly initiated.

The following evaluations are recommended in order to exclude alternative etiologies such as lymphangitic carcinomatosis, pulmonary embolism, infection, allergy, and cardiogenic edema:

- Detailed focused history reviewing respiratory status and exercise tolerance.
- Focused physical exam including full assessment of vital signs (with pulse oximetry).
- Unscheduled radiological assessment, including chest x-ray or computerized tomography (CT) scan (high-resolution CT is preferred).
- Infectious evaluation, including blood and sputum cultures, atypical pneumonia panels, and SARS-CoV-2 testing, if indicated
- Hematology and other laboratory tests, including serum albumin levels
- Referral to pulmonologist for evaluation, including bronchoscopy with biopsy, cell counts, and cultures as feasible
- Evaluation of cardiac function, if indicated

Where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered, and study treatment permanently discontinued. For symptomatic patients with pneumonitis (Grade 2 and above), treatment with steroids should be initiated per local guidelines, in addition to withholding of study treatment. Confirmation of ILD/pneumonitis of any grade should prompt discontinuation of all study treatment and should be reported as a serious adverse event. In the absence of a diagnosis of ILD/pneumonitis, study treatment may be restarted.

9.7. Dose Modifications for All Other Adverse Events

Table 6: Dose Modification Recommendations for All Other Adverse Events felt to be Related to Study Drug.

Other Adverse Reactions [See Adverse Reactions (14)]	Grade	Dose modification
	Grade 3	• Withhold Amivantamab until recovery to ≤ Grade 1 or baseline. • Resume at reduced dose if recovery occurs within 1 week. • Resume at reduced dose if recovery occurs after 1 week but within 4 weeks. • Permanently discontinue if recover does not occur within 4 weeks.
	Grade 4	• Withhold Amivantamab until recovery to ≤ Grade 1 or baseline. • Resume at reduced dose if recovery occurs within 4 weeks. • Permanently discontinue if recover does not occur within 4 weeks.

9.8. General Concomitant Medication and Therapies

Prohibited Medications and Therapies
The following concomitant medications and therapies are prohibited during the study. The Sponsor-Investigator must be notified in advance, or as soon as possible thereafter, of any instances in which prohibited therapies were administered.

- Any chemotherapy, anti-cancer therapy (other than study treatment[s]), or experimental therapy
- Radiotherapy to tumor lesions being assessed for tumor response prior to radiographic progression.

Subjects, who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management other than specified as allowed, should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

Restricted Concomitant Medications
The following concomitant medications and therapies are restricted during the study and should be avoided, when possible, or used with caution.

- Avoid co-administration of medicines that prolong QT interval. If there are no other alternative medications that can be used, limit treatment duration when possible.
- Due to the potential for hypomagnesemia associated with EGFR inhibitors, concomitant medications that may decrease serum magnesium should be avoided if possible.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

10. DURATION OF TREATMENT, FOLLOW-UP & WITHDRAWALS

10.1. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
- Termination of the study by University of Cincinnati PI
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the study EDC (REDCAP) and within study source documentation.

10.2. Safety 30-day Post Treatment Visit

The mandatory Safety Follow-Up Visit should be conducted approximately **30 days** after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur **within 30 days** of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

10.3. Duration of Follow-Up

Patients will be followed after completion or removal from active treatment; or confirmed progression or who start a new anti-cancer therapy or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Subjects in the follow-up phase and should be contacted by telephone or seen in clinic **every 12 weeks +/- 2 weeks** to assess for survival status until death, withdrawal of consent, lost to follow-up or at the end of the study, whichever occurs first. Patients will be followed **up to 5 years.**

10.4. Lost to Follow-Up

Patients who have begun or completed active treatment who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up."

In the absence of a clear withdrawal of consent, study teams should make every attempt to contact subjects during the follow-up phase to determine the patient's status following the UCCC CTO's workflows or institution specific requirements. A patient will be considered to be "lost to follow-up" per the UCCC CTO's workflows and policies or institution-specific requirements.

In the event that the subject has withdrawn consent to the collection of any follow-up data, the survival status of the patient can be obtained instead from publicly available death registries or other publicly available (e.g., obituaries) where it is possible to do so under applicable local laws to obtain a current survival status.

10.5. Withdrawal of Consent

Patients are free to withdraw from the study at any time. A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AEs. The PI and/or treating physician will continue to follow up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow up (e.g., contact for survival status, and data collection in follow-up) and/or
- Only active treatment.

The withdrawal of consent must be documented in REDCap and in source documentation.

When a subject is discontinued/withdraws to active treatment prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation or withdrawal, should be followed in accordance with the safety requirements outlined in Section 14.

11. OTHER RESEARCH ACTIVITY SPECIFICATIONS

The Study Calendar summarizes the trial procedures to be performed at each visit.

11.1. Medical History

A medical history for each subject will be obtained by the Investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

Medical history must be graded per CTCAE v.5 to facilitate the identification of grade changes from baseline. Subjects will be asked about their medical conditions at each study visit (e.g., any new admissions or changes in existing conditions) and new medical history, if any, will be recorded throughout the study.

11.2. Prior and Concomitant Medications

Prior Medications
The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirements, and record prior medication taken by the subject within 28 days before starting the trial (time of consent). Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

Concomitant Medications
The Investigator or qualified designee will record medication, if any, taken by the subject during the trial.

11.3. Adverse Events

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Study Calendar or more frequently if clinically indicated.
Please refer to Section 14 for detailed information regarding the assessment and recording and reporting of AEs.

11.4. Full Physical Exam

The Investigator or qualified designee will perform a full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Full physical exam requires assessment of major organ sites (Constitutional, Head and Neck, Cardiovascular, Pulmonary, Abdominal, Musculoskeletal, Lymph, Neurological, and Skin).

11.5. Directed Physical Exam

Except for at screening, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

11.6. Vital Signs

The Investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, and at treatment discontinuation as specified in the Study Calendar. Vital signs should include: temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only. Vitals will be collected on C1D1 and C1D2 prior to dosing and 30 minutes (+/- 5 minutes) into infusion. On C1D1, vital signs will be obtained one hour after dosing (temperature, pulse, respiratory rate and blood pressure).

11.7. Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess ECOG status **(see Appendix A)** at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Study Calendar.

11.8. Tumor Imaging and Assessment of Disease

Only the Investigator or qualified designee (MD only) may determine the assessment of disease recurrence.

Patients will undergo imaging CT (with contrast unless contraindicated) of the target areas or MRI as clinically indicated **every 12 weeks (+/- 2 weeks).** If patient has a PR or CR, confirmation scans are required at least 4 weeks after scan in which response was first observed. Patients should be consistent with imaging type throughout the course of the study (e.g., baseline is a CT then all other imaging should be CT) unless clinically indicated.

11.9. Laboratory Safety Evaluations (Hematology and Chemistry)

Laboratory tests for hematology, chemistry, and others are specified in Table 5 and should be performed at the timepoints specified in the study calendar.

Table 7. Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Albumin	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Urine pregnancy test (β-hCG) †

Hematology	Chemistry	Other
Platelet count	Alanine aminotransferase (ALT)	
WBC (total and differential)	Aspartate aminotransferase (AST)	
Red Blood Cell Count	CO_2 or bicarbonate	
Absolute Neutrophil Count	Calcium	
Absolute Lymphocyte Count	Chloride	
Absolute Eosinophil Count	Glucose	
	Phosphorus	
	Potassium	
	Sodium	
	Creatinine	
	Magnesium	
	Total Bilirubin	
	Direct Bilirubin (If total bilirubin is elevated above the upper limit of normal)	
	Total protein	
	Blood Urea Nitrogen	
† Done on all women of child-bearing potential		

12. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 14.

12.1. Amivantamab Pharmaceutical Information

See the Investigator's Brochure for more information.

Amivantamab is a fully human IgG1-based bispecific Ab directed against the EGF and MET receptors, produced by cultivation of recombinant Chinese hamster ovary (CHO) cells followed by isolation, chromatographic purification, and formulation.

Amivantamab is produced in a CHO mammalian cell expression system, and has a structure typical of monoclonal antibodies (mAbs), consisting of 2 heavy chains (HC) and 2 light chains (LC), joined by disulfide bridges. CHO cells were genetically altered to produce the 2 parental low -fucose Abs CNTO 4005 (anti-EGFR mAb derived from zalutumumab, with the same variable region sequence) and CNTO 9541 (anti-MET mAb) separately in cell culture medium. The drug substance is manufactured from CNTO 4005 and CNTO 9541 parents using controlled antigen binding fragment (Fab) arm exchange (FAE) redox process, followed by purification and formulation steps.

Amivantamab has a molecular mass of 148,209 Da for the G0/G0 glycoform, and isoelectric points ranging from 8.40 to 9.10. The absorptivity constant for amivantamab at 280 nm was determined to be 1.40 (mg/mL)-1cm-1.

12.2. Preparation of Amivantamab

IMPORTANT INFORMATION ABOUT AMIVANTAMAB

- Amivantamab is sterile and does not contain a preservative; therefore IP preparation and administration must be performed using aseptic technique.. It is recommended that the IP preparation is performed under a laminar flow hood or biosafety cabinet. IP vials containing liquid solution must be processed immediately and cannot be used to prepare supplies for additional doses.Liquid IP at cold storage (refrigerated)
- Liquid at cold storage must be stored at 5°C ± 3°C (2°C to 8°C) and protected from light during storage. Do not shake the product.
- SHOULD NOT BE FROZEN
- All vials are for single use only.

- Ensure that amivantamab vials remain in the original cartons until study drug preparation takes place. Vials may be removed from their shipping boxes.
- IP preparation and administration can occur under ambient temperature & light conditions. Ambient temperature encompasses Japan room temperature.
- All used vials of the IP are kept until study drug accountability has been performed according to site policies.
- Potentially hazardous materials such as used vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of amivantamab with other agents.
- Do not mix amivantamab with other agents in the IV bag/container and do not infuse amivantamab concomitantly in the same intravenous administration set with other agents.
- Administration sets and catheters must be adequately primed/flushed with 5.0% Dextrose (glucose) solution (sterile, pyrogen free) (D5W) before and after administration of amivantamab to ensure that IP does not come in contact with other drug solutions.
- Study drug must be administered within 10 hours from first vial puncture for each prepared dose.

12.2.1. Administration Materials

Description of materials required for preparation of the study IP are noted in the table below. The indicated ancillary supplies must be utilized. Ancillary supplies as noted in the table are source locally by the site/pharmacy. If site is unable to provide supplies, contact Sponsor/SM. Approval must be obtained from the Sponsor prior to use of any non-listed ancillary supply.

The site is responsible for maintaining an inventory log of ancillary supplies used in this trial, including catalog number, lot numbers (if available), and expiry (if applicable).

Table 8. Preparation and Administration of Amivantamab

Materials Required for Preparation and Administration of Amivantamab			
Category	**Description**	**Quantity for Unit Operation**	**Provided by**
Investigational	Drug Product Amivantamab 50 mg /mL	As needed	**Sponsor**

Product	injectable solution provided as 3 mL/vial OR 7ml/vial		
Diluent	250 mL 0.9% normal saline solution(NS) or 5.0% Dextrose (glucose) solution (sterile, pyrogen free) (D5W); IV bags made of polypropylene (PP), polyethylene (PE) , polyolefin (PO) and polyvinylchloride (PVC)	1 (unless study supplies are used for flushing)	**Site***
Ancillary Supplies	IV Administration Set made of polyvinylchloride (PVC) or polybutadiene (PBD), polypropylene (PP), polyethylene (PE) and polyurethane (PU) and with 0.2 µm polyether sulfone (PES) filter	1	**Site***
	Extension set made with polyvinylchloride (PVC) polypropylene (PP), polyethylene (PE) polyurethane (PU) and polybutadiene (PBD) and 0.2 µm PES filter	1, if needed	**Site***
	Sterile Syringes made of polypropylenen (PP)/polystyrene (PS), Polycarbonate (PC)	As needed	**Site**
	18 to 23 G Needles	As needed	**Site**

* Provided by Site unless required materials of construction are unavailable, then Provided by Sponsor

12.3. Closed System Drug Transfer Device

Any commercially available CSTD may be used in the preparation of the IP provided the guidelines for preparation and administration are followed:

- For transfer volumes ≥ 1 mL: a new syringe and CSTD must be used for each step to avoid over dilution. (For e.g., If a syringe and CSTD is used for the in-vial dilution, you cannot use the same syringe and the CSTD for withdrawal of the dose)
- The holdup volumes of the CSTD components (vial spike and syringe adapter) must be considered when drawing up the dose as this will impact the number of IP vials required to prepare the dose.

12.4. Availability

Amivantamab is an investigational agent being supplied to investigators by Janssen Biotech.

12.5. Agent Ordering

Sites will receive instructions on agent ordering at the time of study activation from the University of Cincinnati as provided by Janssen Scientific Affairs.

12.6. Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received using institutional Drug Accountability Record (DARF) or other methods of recording. Store and maintain separate Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

12.7. Investigator Brochure Availability

The current versions of the IBs will be accessible to site investigators and research staff throughout the duration of this study.

13. STATISTICAL CONSIDERATIONS

13.1. Study Design/Endpoints

The study will be an open-label phase II single arm trial. 18 patients with R/M ACC will be included. Patients will receive amivantamab at 1050mg weekly for the first cycle and biweekly thereafter (1400mg for patients ≥80kg). Response will be measured using RECIST criteria and overall response rate will be defined as patients who have complete or partial response as their best response. Progression free survival will be measured as time of treatment allocation to confirmed progressive disease or death. Toxicity will be graded according to the CTCAE v5 and patients who have received any amount of study drug will be evaluable for toxicity.

An interim safety analysis will be conducted when 50% of patients have been enrolled. At that time an assessment will also be completed to determine the rate of ACC I vs II (determined by p63 staining) of subjects enrolled.

The primary analysis would be to determine the best ORR of patients with R/M ACC treated with amivantamab.

13.2. Sample Size/Accrual Rate

The proposed sample size will be 18 subjects with an accrual rate of 18 patients per year.

Statistical power calculation:

The one-sided exact 90% confidence interval (CI) to observe an ORR (complete or partial response) of 27.8% with 18 patients would be (14.2%, 100%) requiring 5 responses. The table below shows the lower bound for the one-sided 90% CI for various number of responses with a sample of 18:

Responses	ORR	One-sided 90% CI Lower Bound
4	22.2	10.1
5	27.8	14.2

6	33.3	18.5

If ≥ 2 responses occur or ≥20% of those with ACC type II have a confirmed response at interim analysis, or 5 responses upon completion of the 18 patient enrollment, then further investigation will be warranted and an amendment to enroll additional patients will be considered to confirm activity.

13.3. Stratification Factors

None.

13.4. Analysis of Primary Efficacy Endpoints

The primary endpoint analysis of ORR will be conducted when all patients have been evaluated. ORR will be reported as a proportion with 90% exact binomial confidence interval. Progression free survival will be measured as time of treatment allocation to confirmed progressive disease or death and overall survival will be measured as time of treatment allocation to death. Descriptive statistics will be used to summarize patient characteristics. Responses will be summarized as frequencies and percentages and all confidence intervals will be reported at alpha level of 0.10. PFS and OS rates will be estimated using the Kaplan-Meier (KM) method. Median PFS and OS along with 90% confidence intervals will be reported with KM curves. Toxicities will be summarized as the number and percentage of patients with each type of toxicity.

13.5. Evaluation of Secondary Toxicity Endpoints

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

13.6. Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific (see Section 16 Measurement of Effect).

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been

identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc.*). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The corresponding confidence intervals should also be provided.

13.7. Exploratory Endpoints

All subjects will be evaluated for the following exploratory endpoints:

1. Frequency of mutations and expression levels of EGFR, RAS and c-MET as well as downstream signaling proteins.
2. Percent of immune cell infiltration in tumor sections.
3. FACT-HN Scores.

14. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

14.1. Listing of Known Risks of Amivantamab

Please refer to the FDA package insert for RYBREVANT (amivantamab) injection, for intravenous use (Initial U.S. Approval: 2021) and Investigator's Brochure for a complete listing of known adverse events.

14.2. Janssen Safety Contact Information and Reporting Timeframes

Contact details for required reporting to the provider of the study drug, Janssen, are listed below; and within each of the respective sections that follow, the respective reporting timeframes are noted. Please ensure that the University of Cincinnati Sponsor-Investigator and study monitor are included on all correspondence to Janssen.

- SAE/Pregnancy Notifications: GMS_AE_Inbo@its.jnj.com CC: AHe5@ITS.JNJ.com) & PCifuen1@ITS.JNJ.com
- Product Quality Complaints (PQC): DL-DPYIE-Globalcontacts-NIS@its.jnj.com CC: AHe5@ITS.JNJ.com) & PCifuen1@ITS.JNJ.com & TBhatt3@ITS.JNJ.com
- Phone: contact the study assigned Janssen Trial Manager – the University of Cincinnati will provide sites with the most current contact information.
- Fax: 1-215-293-9955

14.3. Adverse Events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug/intervention and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The severity (grade) of an adverse event may be determined by a study coordinator using the

CTCAE Version 5.

The causal relationship (attribution) to study drug/device/intervention is determined by a study physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

1. Unrelated – The AE is clearly NOT related to the study intervention
2. Unlikely – The AE is doubtfully related to the study intervention
3. Possible – The AE may be related to the study intervention
4. Probable – The AE is likely related to the study intervention
5. Definite – The AE is clearly related to the study intervention

The expectedness of the occurrence of an adverse event is determined by a study physician and should be used to help determine whether prompt reporting requirements to regulatory authorities (IRB, FDA etc…) are required (such as when the AE is an SAE).

1. Expected – An adverse event is expected if it is described as an anticipated risk in the package insert, or Investigator Brochure (IB) and described within this protocol as a known adverse event.
2. Unexpected – If an adverse event is not described within the package insert or IB, or within this protocol or consent form as an expected risk to subjects then the AE will be considered to be unexpected.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

14.4. Adverse Events of Clinical Importance

Adverse events of special interest/clinical importance are events that the study drug provider Janssen is actively monitoring as a result of a previously identified signal (even if non-serious) AEs or laboratory findings that would require **24-hour reporting to the principal investigator/Sponsor-Investigator** regardless of causality or seriousness include the following:

<u>Amivantamab:</u>

- Infusion related reaction (IRR) (grade 3 or higher)
- Interstitial Lung Disease/Pneumonitis (regardless of grade)
- Hepatic events consisting of the following
    - Any potential or confirmed Hy's law case (consistent with the FDA Guidance on Drug Induced Liver Injury)
    - Following lab criteria:
        - ALT or AST >5x ULN for 2 weeks or ALT or AST >8x ULN
        - ALT or AST ≥3x ULN if associated with the appearance or worsening of symptoms of liver injury, hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia
        - Persistent elevation of ALT or AST≥3x ULN for ≥4 weeks. The Sponsor-

Investigator should be consulted for subjects with baseline ALT and/or AST near 3x ULN.

In case of any amendments to the above list, Janssen will notify the University of Cincinnati Sponsor-Investigator who will inform sub-sites and ensure that these changes are updated in the protocol as soon as practical.

All sites must, within 3 business days of becoming aware of the event(s) of clinical importance, report all AECI to Janssen using the Janssen AE form. If batch/lot number is available, it must be reported. If batch/lot number is not available, it must be documented that it is not available. All AECI will be collected in REDCap.

- AECI Notifications: GMS_AE_Inbo@its.jnj.com CC: AHe5@ITS.JNJ.com) & PCifuen1@ITS.JNJ.com
- Fax: 1-215-293-9955

14.5. Serious Adverse events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

1. Results in Death
2. Is Life Threatening
3. Requires inpatient or prolonged hospitalization. For reports of hospitalization, it is the sign, symptom or diagnosis which led to hospitalization that is the serious event for which details must be provideD
4. Results in persistent or significant disability or incapacity
5. Results in a congenital abnormality or birth defects
6. Any suspected transmission of any infectious agent via administration of a medicinal product.
7. Is considered to be a serious/significant medical condition in the opinion of the PI. Any untoward medical occurrence that is considered medically significant. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not result in death, be life-threatening or require hospitalization but may be considered a serious adverse drug experience when, based on appropriate medical judgement, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the bulleted list above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse or malignancy.

The following are NOT considered to be SAEs for the purposes of this protocol:

1. Surgery or procedure planned before entry into a study. [Note: Hospitalizations that were planned before the signing of ICF and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]
2. Admissions per protocol for planned medical/surgical procedures.

3. Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
4. Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
5. Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

14.6. Serious Adverse Events Collection & Reporting

All Serious Adverse Events (SAEs) that occur after consent and within **30 days** after the subject's end of active treatment or before initiation of a new anti-cancer therapy must be collected and should be reported to the University of Cincinnati sponsor-investigator using the Janssen adverse event form within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE. SAEs should be reported on the Janssen Scientific Affairs TV-FRM-09760 form that will be provided at the time of study activation from the University of Cincinnati as provided by Janssen Scientific Affairs

SAEs considered by the Investigator to be related to study intervention will be reported regardless of the timeframe from last dose of protocol therapy. SAEs must be followed to resolution or stabilization.

The study team will report SAEs to their institutional IRB and FDA according to their respective prompt reporting timeframes. All sites must within 3 business days of becoming aware of the event(s) report all SAEs to Janssen. If batch/lot number is available, it must be reported. If batch/lot number is not available, it must be documented that it is not available.

- SAE/Pregnancy Notifications: GMS_AE_Inbo@its.jnj.com CC: AHe5@ITS.JNJ.com) & PCifuen1@ITS.JNJ.com
- Fax: 1-215-293-9955

A Representative or designee for Janssen will provide the University of Cincinnati Sponsor-Investigator with a list of the Study's SAEs (previously received by Janssen from the study sites) on a quarterly basis. The Sponsor-Investigator will confirm to Janssen that all applicable SAEs related to the study drug have been reported to Janssen.

14.7. Adverse Event Collection and Reporting

The collection of AE information should begin at the time of consent. All adverse events regardless of attribution should be collected continuously during the treatment period and for a minimum of **30 days** following the last dose of study treatment.

Concomitant illnesses/conditions that existed before entry into the study are to be documented as medical history and graded at baseline, but will not be considered AEs unless the illness/condition worsens in severity per CTCAE or becomes more frequent in occurrence after initiating protocol

therapy.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented but not reported as an SAE. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All AEs must be collected and recorded following ICH-GCP, and institutional specific practices and entered into the study EDC, REDCAP. A listing of all adverse events will be provided annually and in final study report by the University of Cincinnati Sponsor-Investigator to Janssen.

14.8. Follow-Up of Adverse Events

All AEs experienced by a subject, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

14.9. Adverse Event Grading

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

14.10. Special Situations

The following special situations must be reported to Janssen with or without an associated serious adverse event (SAE):

- Drug exposure during pregnancy (paternal, maternal)
- Suspected transmission of any infectious agent via administration of a Janssen Product(s) under study.

The following special situations must be reported to Janssen when associated with a serious adverse event (SAE):

- Overdose of Janssen Product(s) under study
- Exposure to Janssen Product(s) under study from breastfeeding
- Suspected abuse/misuse of Janssen product(s) under study
- Inadvertent or accidental exposure to Janssen Product(s) under study
- Any failure of expected pharmacological action (i.e., lack of effect) of Janssen Product(s) under study
- Medication error (includes potential, intercepted or actual) involving a Janssen product (with or without patient exposure to the Janssen Product(s) under study, e.g., name confusion)
- Unexpected therapeutic or clinical benefit from use of Janssen Product(s) under study

If no SAE is associated with the special situation, the special situation should be recorded in the study record and in REDCap and sent annually to Janssen. These safety events may not meet the definition of an adverse event; however, for reporting purposes, **they are deemed to be adverse events. If an SAE is associated with the special situation,** then it should be reported within 3 business days of becoming aware of the special situation to:

- GMS_AE_Inbo@its.jnj.com
  - CC: Andy He (AHe5@ITS.JNJ.com) & Paul Cifuentes (Pcifuen1@ITS.JNJ.com)

NOTE: Please note the underscores (_) in the email name this is critical to highlight as if its missing then the SAE will fail to transmit.

14.11. Product Quality Complaints

A PQC may have an impact on the safety and efficacy of the study drug and should be reported Within 3 business days of becoming aware of the event(s) to:

- Product Quality Complaints (PQC): DL-DPYIE-Globalcontacts-NIS@its.jnj.com
  - CC: Andy He (Ahe5@ITS.JNJ.com) & Paul Cifuentes (Pcifuen1@ITS.JNJ.com) & Tarak Bhatt (Tbhatt3@ITS.JNJ.com)

Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the drug provider Janssen, and are mandated by regulatory agencies worldwide. Janssen has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected, when available, for all PQC reports, including reports of failure of expected pharmacological action (i.e., lack of effect) of the study drug. A sample of the suspected study drug shall be maintained for further investigation if requested by Janssen.

Any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or delivery system is considered a PQC. Not all PQCs involve a patient.

Examples of PQC include but are not limited to:

- Mislabeling or misbranding
- Information concerning microbial contamination, including a suspected transmission of any infectious agent by a product
- Any significant chemical, physical, or other changes that indicate deterioration in the distributed product
- Any foreign matter reported to be in the product
- Mixed product, e.g., two drugs are mixed-up in the packaging process
- Incorrect tablet sequence (e.g., oral contraceptive tablets)
- Insecure closure with serious medical consequences, e.g., cytotoxics, child-resistant containers, potent drugs
- Suspected counterfeit or tampered product
- Adverse Device Effects including any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation, installation, operation, or any malfunction of a medical device or combination product. This also includes any event that is a result of a use error or intentional misuse and dosing device malfunctions (e.g. auto-injector button not working, needle detaching from syringe, etc.)
- Physical defect (e.g. abnormal product odour, broken or crushed tablets, etc.)

14.12. "Extraordinary" correspondence

Correspondence with a regulatory authority or ethics committee regarding a safety issue that may impact the safety or benefit-risk balance of the study drug, and/or may impact patients or public health. Examples include:

- Safety issues relating to a quality defect
- Major safety issues identified with changes in the nature, severity or frequency of known serious adverse reactions which are medically significant or the detection of new risk factors for the development of a known adverse reaction or a new serious adverse reaction.
- Major safety issues identified in the context of ongoing or newly completed post-marketing studies e.g. an unexpected increased rate of fatal or life-threatening adverse events.

Provide notice to the University of Cincinnati Sponsor Investigator and to Janssen and provide copies of such extraordinary correspondence **within 24 hours** of such report or correspondence being sent to applicable health authority.

- GMS_AE_Inbo@its.jnj.com
    - CC: Andy He (Ahe5@ITS.JNJ.com) & Paul Cifuentes (Pcifuen1@ITS.JNJ.com)

NOTE: Please note the underscores (_) in the email name this is critical to highlight as if its missing then the SAE will fail to transmit.

14.13. Pregnancy

Reports of drug exposure during pregnancy, or Abnormal Pregnancy Outcomes (e.g. spontaneous

abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) must be reported by sites to the University of Cincinnati sponsor-investigator and to Janssen **within 3 business days of their knowledge of the event using the Janssen adverse event form**. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects exposed to the study drug will be reported by the Investigator **within 3 business days of their knowledge of the event** using the Serious Adverse Event Form.

- SAE/Pregnancy Notifications: GMS_AE_Inbo@its.jnj.com
    - CC: Andy He (Ahe5@ITS.JNJ.com) & Paul Cifuentes (Pcifuen1@ITS.JNJ.com)

NOTE: Please note the underscores (_) in the email name this is critical to highlight as if its missing then the SAE will fail to transmit.

If a subject becomes pregnant during the study, in addition to reporting the pregnancy within 3 business days to the UC Sponsor-Investigator and Janssen, a determination regarding study drug discontinuation and subject discontinuation must be made by the investigator in alignment with the protocol inclusion/exclusion criteria and in consultation with the reference safety information.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented in REDCap using the adverse event forms. Any pregnancy occurring in a patient or patient's partner from the time of consent to 6 months after the last dose of study drug must be reported and then followed for outcomes. Newborn infants should be followed until 30 days old.

An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported as an AE. Hospitalization associated with normal delivery of a healthy newborn should not be considered an SAE.

14.14. Contraception/Birth Control

Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation. See Appendix E. Effective birth control is considered to be:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral route, Intravaginal route or Transdermal route
2. Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral, Injectable, or Implantable
3. Intrauterine device
4. Intrauterine hormone-releasing system
5. Bilateral tubal occlusion
6. Vasectomized partner
7. Sexual abstinence

14.15. Breast Feeding

Participants must not breast-feed while receiving protocol therapy and for 6 months following the last dose of protocol therapy.

14.16. Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine AE reporting mechanisms outlined within this protocol.

14.17. Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

15. STUDY CALENDAR

Study Milestones	Screening	Cycle 1	Cycles 2+	30-Day Safety	Long term follow-up
Time point	-28 Days	Weeks 1-4	Q4 Weeks	30 Days Post End of Treatment	Q12 weeks Post End of Treatment up to 5 Years
Windows		+/-1 Days	+/-3 Days	+/- 7 Days	+/- 2 Weeks
Amivantamab		X[D]	X[D]		
Informed consent	X				
Demographics	X				
Medical history	X				
Con meds	X	X	X	X	
Adverse events [F]	X[E]	X	X	X[E]	
Full Physical exam	X				
Directed PE if clinically indicated		X	X		
Vital signs [F]	X	X[G]	X	X	
Height [F]	X				
Weight [F]	X	X	X		
Performance status	X	X	X		
CBC w/diff, plts [F]	X	X	X		
Serum chemistry [F]	X	X	X		
Imaging (CT with contrast)	X		X[C]		
Pregnancy test	X				
Follow-up data & survival status				X	X
Correlative Tissue	X[B]				
Correlative Blood	X[A]	X[A]			
FACT-HN survey[H]	X	X[H]	X[H]	X	

A. Correlative blood samples must be collected after eligibility is confirmed but prior to treatment at baseline. Correlative blood collection also occurs at Cycle 1 Day 29 +/- 1 week. Refer to Section 6 for correlative collection methods & amounts. If the baseline sample is not collected, then Cycle 1 Day 29 should not be collected.
B. Correlative tissue must be requested during screening and provided to the UCCC CTO Lab as soon as possible after eligibility is confirmed. Refer to Section 6 for correlative collection methods & amounts.
C. Imaging starting on C3D1 is to be done every 12 weeks while on active treatment with a +/- 2-week window. No required imaging in follow-up or at EOT.
D. Amivantamab weekly during Cycle 1. Then Amivantamab every 2 weeks starting Cycle 2 Day 1. Cycles are every 4 weeks.
E. Adverse events to be collected from the time of consent and for 30 days from dose of last study drug. Serious Adverse Events are to be collected from the time of consent and for 30 days from dose of last study drug.
F. AEs and Vital signs (vitals collected prior to administration of each dose of trial treatment) to be completed every visit. Labs to be completed with each infusion. Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height is to be collected only at screening.

G. Subjects must remain at the infusion center for monitoring for at least 1 hour after the end of the first dose of amivantamab (Cycle 1 Day 1). After one hour, vital signs will be obtained (temperature, pulse, respiratory rate and blood pressure). Vitals should also be collected Cycle 1 Day 1 and Cycle 1 Day 2 prior to dosing and 30 minutes (+/- 5 minutes) into infusion.
H. FACT-HN surveys to be completed at 4 timepoints: Screening, Cycle 2 Day 1, Cycle 7 Day 1 and End of Treatment. The screening FACT-HN may be completed at the Cycle 1 Day 1 visit instead only if it was unable to be completed during the screening period.

16. MEASUREMENT OF EFFECT

16.1. Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

16.2. Definitions

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

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

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

16.3. Disease Parameters

Measurable Disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable but only if there was clear progression after irradiation occurred.

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

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

16.4. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

imaged but are assessable by clinical exam.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-Ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

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

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

Tumor Markers. Tumor markers alone cannot be used to assess response and will not be used on this protocol.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

16.5. Response Criteria

16.5.1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also

considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

16.5.2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

16.5.3. Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**

PD	Any	Yes or No	PD	
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

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

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

16.6. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

16.7. Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

16.8. Response Review

Independent radiologist(s) at University of Cincinnati will review all scans directly or in collaboration with study sites as a central review at the completion of the study to confirm response measurements and accurate assessment.

For trials where the response rate is the primary endpoint, all responses should be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach. This study will utilize such an approach by having a H&N Radiologist at the University of Cincinnati act in this capacity as an independent reviewer (or such independent radiologist at a collaborating institution if needed).

17. STUDY OVERSIGHT, DATA REPORTING & REGULATORY

17.1. Study Oversight

This protocol is monitored at several levels, as described in this section. The UC Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events. The UC Principal Investigator has access to the data at all times through the study EDC, REDCap.

This study will also be reviewed in accordance with the UCCC CTO's SOPs, policies and guidance which may include periodic routine or for cause internal auditing. The study team must adhere to the current policies, SOPs, guidance and workflows of the UCCC CTO in the conduct of this protocol or institution specific policies, SOPs and guidance.

All study investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via REDCap and timely reporting of adverse events. This includes timely review of data collected on electronic CRFs submitted via REDCap as well as review of any source documentation collected locally.

This study will also be reviewed in accordance with the enrolling institution's data safety monitoring plan.

17.2. Data Reporting

Data collection and storage at the University of Cincinnati will be managed by the University of Cincinnati Cancer Center, Clinical Trials Office (UCCC CTO). The UCCC CTO will maintain storage of all clinical data in accordance with federal guidelines and ICH-GCP. Data will be entered into the secure study EDC, REDCap and into the CTO CTMS as applicable. All hardcopies of data will be securely maintained (in a locked room or cabinet) and will only be accessible to members of the study team or UCCC CTO personnel.

Study data collected at sub-sites should be stored securely per local policies and be made accessible to UC as required.

17.3. Data Safety Monitoring Board

Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients. Immediately after the study is approved and before the first patient is enrolled, investigators will meet, develop and finalize all measurements/variables for the study. Each patient, once enrolled, will be provided a unique ID for the study. Personal information, such as name, SSN, address, phone number and DOB, will be de-identified whenever possible from study records. Confidentiality will be maintained during the phases of the trial including preparation of interim results, review, and response to internal auditing or DSMB or IRB recommendations.

Exceptions may be made under circumstances where there are serious adverse events or when it is deemed appropriate for patient safety.

Study progress will be monitored regularly by the UCCC Data Safety Monitoring Board (DSMB). DSMB oversight begins at the enrollment of the first subject and formal reviews commence typically every 6 months from the date of first subject enrollment. Review frequency may increase as the DSMB deems necessary.

Membership consists of persons independent of, and without any conflicts of interest with, this trial. The DSMB includes experts in the fields of relevant clinical expertise (oncology) and biostatistics.

It is the responsibility of the UC Investigator to ensure that the DSMB is apprised of all new safety information relevant to the study. Study progress & safety information will be prepared by the DSMB Coordinator with input from the UC PI as to the current status of the trial. This compiled information presented to the DSMB will include: a narrative summary from the UC PI as to trial progress and identification of any trends of significance or explanation of any SAEs or other safety related events; the accrual rate with projected completion date for the accrual phase; exclusion rates and reasons when relevant; pretreatment characteristics of patients accrued when relevant; and, the frequency and severity of adverse events.

The DSMB will function in an advisory capacity and recommendations/requests from the

DSMB will be reviewed by the UC investigator and promptly addressed.

The study data from participating sub-sites will be reviewed remotely via the study EDC REDCap and in person by the Study Monitor as per the Clinical Monitoring Plan (Plan kept on file with UCCC CTO office).

17.4. Incidental/Secondary Findings Disclosure Procedure

Any incidental germline and/or somatic mutations identified will be shared with the treating investigator. In most cases, these data will be readily available through the Caris Life Sciences Investigator Portal. If not readily available, the PI will share the report with the subsite. The treatment investigator will use institution SOPs to determine if genetic counseling is advised and/or to discuss findings with patient.

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19. APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

20. APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

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21. APPENDIX C Cockcroft-Gault Formula for Estimated Creatinine Clearance

Cockcroft-Gault Formula for Estimated Creatinine Clearance for Adults

$$eCrCl = \frac{(140\text{-Age}) \times \text{Mass (Kilograms)} \times [0.85 \text{ if female}]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

OR

$$eCrCl = \frac{(140\text{-Age}) \times \text{Mass (Kilograms)} \times \text{Constant}}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where Constant = 1.23 for men and 1.04 for women

Reference: http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/

22. APPENDIX D NEW YORK HEART ASSOCIATION CRITERIA

The following table presents the New York Heart Association classification of cardiac disease:

Class	Functional Capacity – Patient Assessment	Objective Assessment
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).	Class A - No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).	Class B - Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.	Class C - Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.	Class D - Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Classification of Functional Capacity and Objective Assessment. Available at http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-HeartFailure_UCM_306328_Article.jsp Accessed 15 June 2021.

23. Appendix E QOLs

FACT-HN (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4

GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4

GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

24. Appendix F Contraceptive Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 14.14. Pregnancy information will be collected and reported as noted in Sections 14.10 and 14.13.

Definitions

Patient of Childbearing Potential (POCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Patient Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.

- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in patients not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  If there is a question about menopausal status in patients on HRT, the patient will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.

- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (e.g., a premenarchal patient experiences menarche) or the risk of pregnancy changes (e.g., a patient who is not heterosexually active becomes active), a patient must begin 2 methods of contraception, including 1 highly effective method, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by patients should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy During the Study

Participants who become pregnant during the study will be withdrawn from the study treatment and followed for safety.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the patient of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** Failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] o oral o injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study treatment.
c) Male condom and female condom should not be used together (due to risk of failure with friction).