TITLE PAGE

Protocol Number:	C4251005/SGNTUC-024
Version:	Amendment 06, 06-Nov-2024
Protocol Title:	A phase 1b/2 dose escalation and expansion study of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy or pembrolizumab-containing combinations for HER2+ gastrointestinal cancers
Investigational Product:	Tucatinib
Brief Title:	Tucatinib plus trastuzumab and oxaliplatin-based chemotherapy or pembrolizumab-containing combinations for HER2+ gastrointestinal cancers
Phase:	1b/2
IND Number:	134840
Sponsor:	Seagen Inc., a wholly owned subsidiary of Pfizer 21823 30th Drive SE Bothell, WA 98021, USA
SAE Email or Fax:	See email or fax number specified on the SAE report form.

DOCUMENT HISTORY

Version	Date
Original	13-Apr-2020
Amendment 1	05-Aug-2020
Amendment 2	02-Dec-2020
Amendment 2.1	01-Mar-2021
Amendment 3.0	16-Sep-2021
Amendment 3.1	27-Sep-2021
Amendment 4.0	21-Dec-2021
Amendment 5.0	29-Mar-2024
Amendment 6.0	06-Nov-2024

1. PROTOCOL AMENDMENT SUMMARY OF CHANGES (SOC) TABLE

Amendment 06 (06-NOV-2024)

Overall Rationale for the Amendment: The primary purpose of this amendment is to align with Pfizer required safety reporting requirements and to incorporate other Pfizer specific text, requirements, and formatting across the document.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
New section providing details about reporting lack of efficacy.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 9.5.1.5 Lack of Efficacy
Non-Substantial Modifications		
Adjusted text to align with Pfizer management of overdose guidelines. Added text: Overdose is reportable to Pfizer Safety only when associated with an SAE.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 7.12.1 Tucatinib (Subsection of Management of Overdose); Section 7.12.2 Pembrolizumab (Subsection of Management of Overdose)
Added reference to Appendix G for more details on recording and reporting AEs and SAEs Added text on considerations in determining to record a test result, medical condition, or other incident on AE eCRF. Added	To support Study transition to Pfizer Pharmacovigilance processes and systems	Section 9.5.1 Adverse Events Section 9.5.1.1 Definitions, in the Adverse Event subsection

Description of Change	Brief Rationale	Section # and Name
new bullets of text about events NOT meeting the AE definition. To the SAE definitions table, added text with additional details for the terms "Hospitalization" and "Disabling/incapacitating Added text with details if the investigator does not know if the study intervention caused the event or not Added text referencing sections with information on procedures for AESIs being reported as AEs or SAEs and to indicate the SAE should be reported to Pfizer Safety using Pfizer SAE Submission Assistant (PSSA). Removed overdose of tucatinib or pembrolizumab from AESIs.		Section 9.5.1.1 Definitions, under table in the "Serious Adverse Events" subsection Section 9.5.1.2 Adverse Events of Special Interest
Referenced additional details on recording AEs.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 9.5.1.3 Procedures for Eliciting and Recording Adverse Events, under subsection "Recording Serious Adverse Events"
Added content providing definitions and guidance on environmental exposure, exposure during pregnancy, exposure during breastfeeding, and occupational exposure.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 9.5.1.4 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure (including Section 9.5.1.4.1 Environmental Exposure, Section 9.5.1.4.2 Exposure During Pregnancy, Section 9.5.1.4.3 Exposure During Breastfeeding, and Section 9.5.1.4.4 Occupational Exposure)
Updated section to add required Pfizer protocol template language about safety reporting after the participant has completed study participation or if a participant has started a new anticancer therapy.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 9.5.1.7 Reporting Periods for Adverse Events and Serious Adverse Events
Updated section to add required Pfizer protocol template language and remove redundant text due to this update.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 9.5.1.8 Serious Adverse Events Require Immediate Reporting

Description of Change	Brief Rationale	Section # and Name
Update section with additional required Pfizer protocol template language about SUSARs or other specific safety information.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 9.5.1.9 Sponsor Safety Reporting to Regulatory Authorities
Updated section with additional Pfizer protocol template language about pregnancy testing.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 9.5.5 Pregnancy Testing
Removed redundant text about AESIs being reported since serious AESIs will be reported as SAEs. Only SAEs and pregnancies will be reported using the PSSA during the LTEP portion of the study..	Consistency with updates made in other sections for safety reporting needed as study transitions to Pfizer Pharmacovigilance processes and systems	Section 5.1.8 Long-Term Extension Phase; Section 8.1 Schedule of Events; Section 10.2 Data Management Procedures;
Added text to align with Pfizer protocol template about sample destruction in the event of participant withdrawal and to indicate if the participant withdraws from the study and also withdraws consent for collection of future information, no further evaluations will be performed, and no additional data will be collected except for publicly available information in accordance with local law. The sponsor may retain and continue to use any data collected before such withdrawal of consent.	To align with Pfizer's Protocol Template	Section 6.4.2 Participant Withdrawal from Study
Added this section to provide details about withdrawal of consent.	To align with Pfizer's Protocol Template	Section 6.4.3 Withdrawal of Consent
Added Pfizer required text including language about preparation, handling, storage, and accountability applicable to all study interventions,	To align with Pfizer's Protocol Template	Section 7.1 Preparation, Handling, Storage, and Accountability
Added Section for Single Reference Safety Documents (SRSD) information	To align with Pfizer's Protocol Template	Section 7.2 Single Reference Safety Document
Added these sections to provide information to clinical trial staff members about preparation and dispensing tucatinib, FOLFOX or CAPOX chemotherapy agents, or pembrolizumab.	To align with Pfizer's Protocol Template	Section 7.4.6 Preparation and Dispensing (for tucatinib) Section 7.5.5 Preparation and Dispensing (for FOLFOX) Section 7.6.5 Preparation and Dispensing (for CAPOX)

Description of Change	Brief Rationale	Section # and Name
		Section 7.8.6 Preparation and Dispensing (for pembrolizumab)
Placed text about preparation under new heading Section 7.7.6 (see below).	To consolidate preparation text into preparation and dispensing section of document	Section 7.7.3 Dose and Administration (for trastuzumab)
Relocated placement of storage related text.	To consolidate storage text into storage section of document	Section 7.7.4 Storage and Handling (for trastuzumab)
Added a header and made minor text adjustments.	To align with Pfizer's Protocol Template	Section 7.7.6 Preparation and Dispensing (for trastuzumab)
Relocated text about preparation of pembrolizumab infusion and administration of infusion solution to Section 7.8.6.	To consolidate text about preparation into one section to align with Pfizer's Protocol Template.	Section 7.8.3 Dose and Administration (for pembrolizumab)
Added text about treatment of immune-related AEs based on severity.	To align with Pfizer's Protocol Template	Section 7.9.5.1 Immune-Related Events and Dose Modifications (Withhold, Treat, Discontinue) subsection "Treatment of Immune-related Adverse Events"
Added text about supportive care for hypersensitivity reactions and to indicate participants should be closely observed while receiving study intervention infusions and monitored for clinical signs of a systemic reaction.	To align with Pfizer's Protocol Template	Section 7.9.7 Allergic/Hypersensitivity Reactions
Added level 3 heading to this section	Administrative	Section 7.9.8 Anaphylaxis
Removed "and AESIs" from first bullet	Only pregnancies and SAEs will be reported during the LTEP	Section 8.6 Long-term Extension Phase – Beginning of each Cycle and End of Treatment
Adjusted location of this section heading so that it encompassed pregnancy test bullet points previously in follow-up section.	Move section header to more appropriate location.	Section 8.9 End of Study
Update section with additional required Pfizer protocol template language about modifications allowed for the SAP and that major modifications must be reflected in a protocol amendment.	To align with Pfizer's Protocol Template	Section 11.3 Statistical and Analytical Plans
Content update to use Pfizer template text – original text that is redundant (impacts several subsections) was removed. Section title was updated from "Informed Consent, Ethical Review, and Regulatory	To support Study transition to Pfizer processes and to align with required Pfizer protocol template language.	Section 12 Regulatory, Ethical, and Study Oversight Considerations includes subsection 12.2 through 12.11

Description of Change	Brief Rationale	Section # and Name
Considerations" to "Regulatory, Ethical, and Study Oversight Considerations."		
Removal of Investigator's agreement and the investigator's signature.	The investigator's agreement and signature are personal identifiable information.	Former Appendix G
Change Title of Appendix to Procedures for Recording and Reporting AEs and SAEs and added preferred Pfizer text not captured in body of document to include additional details relevant for safety reporting.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Updated Appendix G
Added an Appendix "heading" to house the summary of changes tables for all prior amendments	Administrative update	Appendix H Summary of Changes for Prior Amendments
Added Pfizer study identifier; Added statement indicating Seagen Inc. is a wholly owned subsidiary of Pfizer in appropriate locations	To align with the Pfizer protocol template and to provide Pfizer study identifier.	Title Page; Synopsis; Footers throughout
Removed Medical Monitor and Study Director's name and contact information	The medical monitor's name and contact information is personal identifiable information	Title page
Update confidentiality statement	To align with Pfizer's Protocol Template	Title page
Moved Document History from end of document to page immediately following the Title Page	To align with Pfizer's Protocol Template	Document History Page (this was formerly Appendix H at end of the document; but was moved to page immediately following Title page)
Replaced "package insert" with "product label" or "local product labeling."	Provide more informational terminology of product labeling or product label.	Throughout document
Administrative updates including, but not limited to: updating "subject" to "participant," updating "study drug" to "study intervention," and other minor editorial modifications. Updates to section numbering or appendix labels were made to meet Pfizer requirements.	Administrative updates to align with Pfizer document format and requirements and/or minor clarifications.	Throughout document

2. PROTOCOL SYNOPSIS

Protocol Number	**Product Name**
C4251005; SGNTUC-024	Tucatinib
Version	**Sponsor**
Amendment 06	Seagen Inc., a wholly owned subsidiary of Pfizer 21823 30th Drive SE Bothell, WA 98021, USA
Phase	
1b/2	

Protocol Title

A phase 1b/2 dose escalation and expansion study of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy or pembrolizumab-containing combinations for HER2+ gastrointestinal cancers.

Study Objectives

Phase 1b Tucatinib Dose Escalation with Trastuzumab and FOLFOX (Cohort 1A and Cohort 1B)

Primary Objective	Corresponding Primary Endpoint
• To determine the recommended dose of tucatinib when combined with trastuzumab and oxaliplatin-based chemotherapy in participants with human epidermal growth factor receptor 2 positive (HER2+) gastrointestinal (GI) cancers	• Incidence of renal dose-limiting toxicities (DLTs)
Secondary Objectives	**Corresponding Secondary Endpoints**
• To evaluate the safety and tolerability of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities • Vital signs and other relevant safety variables
• To evaluate the combination of tucatinib, trastuzumab, and oxaliplatin-based chemotherapy for potential nephrotoxicity	• Change in glomerular filtration rate (GFR), as estimated using serum cystatin C, from baseline through 2 cycles of combination therapy
• To evaluate the pharmacokinetics (PK) of tucatinib	• PK parameters of tucatinib (including but not limited to AUC_{last}, C_{max}, C_{trough}, and T_{max})
• To evaluate the PK of oxaliplatin in the presence and absence of tucatinib	• PK parameters of oxaliplatin (including but not limited to AUC_{last}, C_{max}, T_{max})
Exploratory Objectives	**Corresponding Exploratory Endpoints**
• To evaluate the antitumor activity of tucatinib in combination with trastuzumab, and oxaliplatin-based chemotherapy	• Objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment (INV)
• To explore correlations between tissue and blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in tissue and blood

Phase 1b Safety Evaluation of Tucatinib in Combination with Trastuzumab + CAPOX (Cohort 1C), or in Combination with Trastuzumab and Pembrolizumab-Containing Combinations (Cohorts 1E, 1F, and 1G)

Primary Objectives	Corresponding Primary Endpoints
• To evaluate the safety and tolerability of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers	• Type, incidence, severity, seriousness, and relatedness of AEs, including DLTs, and laboratory abnormalities • Vital signs and other relevant safety variables
Secondary Objectives	**Corresponding Secondary Endpoints**
• To evaluate the antitumor activity of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers as measured by objective response rate (ORR) according to RECIST v1.1 per INV	• ORR according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers as measured by duration of response (DOR) according to RECIST v1.1 per INV	• DOR (confirmed CR or PR) according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers as measured by progression-free survival (PFS) according to RECIST v1.1 per INV	• PFS according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers as measured by overall survival (OS)	• OS
• To evaluate the PK of tucatinib	• PK parameters of tucatinib (including but not limited to C_{trough})
Exploratory Objective	**Corresponding Exploratory Endpoint**
• To explore correlations between tissue and blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in tissue and blood

Phase 1b Japan Safety Evaluation of Tucatinib in Combination with Trastuzumab and FOLFOX (Cohort 1D)

Primary Objective	Corresponding Endpoints
• To assess the safety and tolerability of tucatinib in combination with trastuzumab and FOLFOX in Japanese participants	• Type, incidence, severity, seriousness, and relatedness of AEs, including DLTs, and laboratory abnormalities • Vital signs and other relevant safety variables • Frequency of dose holds, dose reductions, and discontinuations of tucatinib, trastuzumab, and components of FOLFOX
Exploratory Objective	Corresponding Endpoints
• To assess the PK of tucatinib when administered in combination with trastuzumab and FOLFOX in Japanese participants	• PK parameters of tucatinib (including but not limited to AUC_{last}, C_{max}, C_{trough}, and T_{max})

Phase 2 Tumor Specific Expansion

Primary Objectives	Corresponding Endpoints
• Cohort 2A: To evaluate the safety and tolerability of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy (FOLFOX or CAPOX) as first-line (1L) therapy in participants with unresectable or metastatic HER2+ gastric, esophageal, or gastroesophageal junction (GEJ) adenocarcinoma • Cohort 2B: To evaluate the safety and tolerability of tucatinib combined with trastuzumab and FOLFOX in participants with unresectable or metastatic HER2+ colorectal adenocarcinoma (CRC)	• Type, incidence, severity, seriousness, and relatedness of AEs, including DLTs, and laboratory abnormalities • Vital signs and other relevant safety variables
Secondary Objectives	Corresponding Endpoints
• To evaluate the anti-tumor activity of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy (FOLFOX or CAPOX) as 1L therapy for HER2+ gastric, esophageal, or GEJ adenocarcinoma as measured by confirmed objective response rate (cORR), according to RECIST v1.1 per INV	• cORR (confirmed complete response [CR] or partial response [PR]) according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy as 1L therapy for HER2+ gastric, esophageal, or GEJ adenocarcinoma as measured by DOR according to RECIST v1.1 per INV	• DOR (confirmed CR or PR) according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with pembrolizumab, trastuzumab, and	• PFS according to RECIST v1.1 per INV

oxaliplatin-based chemotherapy as 1L therapy for HER2+ gastric, esophageal, or GEJ adenocarcinoma as measured by PFS according to RECIST v1.1 per INV	
• To evaluate the anti-tumor activity of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy as 1L therapy for HER2+ gastric, esophageal, or GEJ adenocarcinoma as measured by OS	• OS
Exploratory Objectives	Corresponding Endpoints
• To evaluate the anti-tumor activity of tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy (FOLFOX) as 1L+ therapy for HER2+ CRC as measured by cORR, according to RECIST v1.1 per INV	• cORR (CR or PR) according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for HER2+ CRC as measured by DOR according to RECIST v1.1 per INV	• DOR (confirmed CR or PR) according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for HER2+ CRC as measured by PFS according to RECIST v1.1 per INV	• PFS according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for HER2+ CRC as measured by OS	• OS
• To evaluate the PK of tucatinib given with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy as 1L therapy for unresectable or metastatic HER2+ gastric, esophageal, or GEJ adenocarcinoma (Cohort 2A) and to evaluate the PK of tucatinib given with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for metastatic HER2+ CRC (Cohort 2B)	• PK parameter of tucatinib (C_{trough})
• To explore correlations between tissue and blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in tissue and blood

Study Population

This study will enroll participants with unresectable or metastatic human epidermal growth factor receptor 2 (HER2+) esophageal adenocarcinoma, GEJ adenocarcinoma, gastric adenocarcinoma, CRC, cholangiocarcinoma, or gallbladder carcinoma. A table summarizing the study population to be enrolled in each cohort is included under Study Design.

Inclusion Criteria

1. Participants must have an unresectable or metastatic solid malignancy that is histologically or cytologically confirmed to be one of the tumor types listed below:

Cohorts 1A, 1B, 1C, and 1D

- Colorectal adenocarcinoma (CRC)
- Gastric adenocarcinoma
- GEJ adenocarcinoma
- Esophageal adenocarcinoma
- Cholangiocarcinoma
- Gallbladder carcinoma

Cohorts 1E, 1F, 1G, and 2A

- Gastric adenocarcinoma
- GEJ adenocarcinoma
- Esophageal adenocarcinoma

Cohort 2B

- CRC

2. Participants must be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment for all cohorts, with the exception of Cohort 1G. Participants in Cohorts 1A, 1B, 1C, or 2B can be receiving an oxaliplatin-based regimen during the screening period:
    - For Cohorts 1A and 1B: up to 2 consecutive cycles of leucovorin, fluorouracil, oxaliplatin (FOLFOX) (≤85 mg/m^2 oxaliplatin per 2-week cycle) may have been received during the screening period prior to Cycle 1 Day 1 of study treatment.
    - For Cohorts 1C: up to 2 consecutive cycles of FOLFOX (≤85 mg/m^2 oxaliplatin per 2-week cycle) or one cycle of CAPOX (≤130 mg/m^2 oxaliplatin per 3-week cycle) may have been received during the screening period prior to Cycle 1 Day 1 of study treatment.
    - For Cohorts 1A, 1B, 1C: if participant has received oxaliplatin in prior cycles at higher doses than those listed above, there must be a minimum of 28 days off treatment prior to Cycle 1 Day 1 of treatment in this study.
    - For Cohort 2B prior to enrollment (Cycle 1 Day 1):
        - Participants may have received up to 1 cycle of FOLFOX (≤85 mg/m^2 oxaliplatin per 2-week cycle) during the screening period prior to Cycle 1 Day 1 but may not have received prior oxaliplatin for metastatic disease
        - Oxaliplatin received in an adjuvant setting is permitted if >6 months prior to Cycle 1 Day 1
        - At least 21 days must have elapsed from prior systemic anticancer therapy (including hormonal and biologic therapy but excluding 1 cycle of FOLFOX), non-central nervous system radiation, and treatment with other experimental agents
3. HER2+ disease, as determined by historic or local laboratory testing based on one of the following:
    - For CRC, cholangiocarcinoma, and gallbladder carcinoma:

- HER2 amplification or overexpression from fresh or archival tumor tissue utilizing one of the following tests processed in a Clinical Laboratory Improvement Amendments (CLIA)- or International Organization for Standardization (ISO)-accredited laboratory:
  - HER2 overexpression (3+ immunohistochemistry [IHC])
  - HER2 (ERBB2) amplification by in situ hybridization assay (fluorescence in situ hybridization [FISH] or chromogenic in situ hybridization (CISH) signal ratio ≥2.0 or gene copy number >6)
  - HER2 (ERBB2) amplification by next generation sequencing (NGS) assay
- HER2 amplification in a CLIA certified or ISO accredited blood-based NGS assay

- For Gastric, GEJ, and esophageal adenocarcinoma: HER2 overexpression/amplification by IHC and ISH (IHC3+ or IHC2+/ISH+) from a tumor tissue sample, processed in a CLIA- or ISO-accredited laboratory and evaluated following ASCO/CAP guidelines for HER2 testing in gastroesophageal adenocarcinoma.

4. Phase 1b cohorts: measurable or non-measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as determined by the investigator

   Phase 2 cohorts: measurable disease according to RECIST v1.1 as determined by the investigator
5. Age 18 years or older at time of consent or ≥ the age of majority per regional requirements
6. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1
7. Life expectancy ≥3 months, in the opinion of the investigator
8. Adequate hepatic function, as defined by:
   - Total bilirubin ≤1.5× upper limit of normal (ULN), except for participants with known Gilbert's disease, who may enroll if the conjugated bilirubin is ≤1.5× ULN
   - Transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) ≤2.5× ULN (≤5× ULN if liver metastases are present)
9. Adequate baseline hematologic parameters as defined by:
   - Absolute neutrophil count (ANC) ≥1.5×10³/µL
   - Platelet count ≥100×10³/µL; participants with stable platelet count from 75–100×10³/µL may be included with approval from the medical monitor
   - Hemoglobin ≥8 g/dL. Participants on a stable dose of erythropoietin (≥ approximately 3 months) are eligible.
   - In participants transfused before study entry, transfusion must be ≥14 days prior to start of therapy to establish adequate hematologic parameters independent from transfusion support

10. Estimated glomerular filtration rate (GFR):
    - Cohorts 1A, 1B: ≥90 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) equation.
        - Participants with estimated GFR ≥60 to <90 mL/min/1.73 m² may be enrolled in Cohort 1B with medical monitor approval.
    - Cohorts 1C, 1D, 1E, 1F, 2A, and 2B: ≥60 mL/min/1.73 m² using the MDRD equation.
11. International normalized ratio (INR) and partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) ≤1.5× ULN, unless on medication known to alter INR and PTT/aPTT (Note: warfarin and other coumarin derivatives are prohibited for participants receiving CAPOX.)
12. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan documented within 4 weeks prior to enrollment
13. Participants of childbearing potential under the following conditions:
    a. Must have a negative serum/plasma or urine pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 24 hours before the first dose of study intervention. Participants with false positive results and documented verification that the participant is not pregnant are eligible for participation
    b. Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study treatment
    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 7 months after the final dose of study treatment
    d. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study treatment
14. Participants who can father children, under the following conditions:
    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 7 months after the final dose of study treatment
    b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study treatment
    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use one of 2 contraception options starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study treatment

15. Participant must provide signed informed consent that has been approved by an institutional review board/independent ethics committee (IRB/IEC) prior to initiation of any study related tests or procedures that are not part of standard-of-care for the participant's disease
16. Participant must be willing and able to comply with study procedures, laboratory tests, and other requirements of the study. Participants with a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study are not eligible.
17. For participants with prior central nervous system (CNS)-directed radiation therapy, at least 7 days must have elapsed from prior stereotactic radiosurgery (SRS) and at least 21 days must have elapsed from prior whole brain radiation therapy (WBRT). Participants must have recovered from all radiation-related toxicities and not require corticosteroids. For non-CNS-directed radiation therapy, participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
18. Participants in the phase 2 1L+ CRC expansion (Cohort 2B) must have a rat sarcoma virus (RAS) wild-type genotype in primary or metastatic tumor tissue, based on expanded RAS historic or local testing including KRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146), and NRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)
19. Participants must be willing and able to adhere to antidiarrheal prophylaxis, if required.

Exclusion Criteria

1. History of known hypersensitivity to planned study treatment:
    a. All cohorts: trastuzumab or compounds chemically or biologically similar to tucatinib
    b. All cohorts except for Cohort 1G: oxaliplatin, fluoropyrimidines, or leucovorin
    c. For Cohorts 1E, 1F, 1G or 2A: severe hypersensitivity (≥ Grade 3) to pembrolizumab

    Participants who have had Grade 1 or 2 infusion-related reactions to oxaliplatin, pembrolizumab, and/or trastuzumab that were successfully managed may enroll. Participants with known allergy to any of the excipients in the study treatment(s) may enroll unless severe hypersensitivity (≥ Grade 3) to excipients has occurred. Participants with known hypersensitivity or allergy to required concomitant medications are excluded.
2. Participants in Cohorts 1A, 1B, 1C, and 2B: Treatment with oxaliplatin in excess of the limitations specified in inclusion criterion 2
3. Major surgery <28 days prior to Cycle 1, Day 1
4. Participants in the Phase 1b cohorts with known active CNS metastasis (irradiated or resected lesions are permitted, provided the lesions are fully treated and inactive,

participant is asymptomatic, and no steroids have been administered for at least 30 days). Participants in Cohorts 2A and 2B with known active CNS lesions may be included but must not have any of the following:

a Any untreated brain lesions >2.0 cm in size, unless approved by the medical monitor

b Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to participant (eg, brain stem lesions). Participants who undergo local treatment for such lesions identified by screening brain magnetic resonance imaging (MRI) may still be eligible for the study

c Known or suspected leptomeningeal disease as documented by the investigator

d Have poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain lesions notwithstanding CNS-directed therapy

5. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
   - Alopecia
   - Clinically insignificant electrolyte abnormalities
   - Hemoglobin <8 g/dL
6. Clinically significant cardiopulmonary disease such as:
   - Ventricular arrhythmia requiring therapy
   - Symptomatic hypertension or uncontrolled asymptomatic hypertension ≥150/≥90 mmHg despite standard medical management, as determined by the investigator
   - Any history of symptomatic congestive heart failure (CHF), left ventricular systolic dysfunction, or decrease in ejection fraction
   - Severe dyspnea at rest (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0 Grade 3 or above) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy, except when therapy is needed for obstructive sleep apnea
7. Known myocardial infarction or unstable angina within 6 months prior to enrollment

8. Known to be positive for hepatitis C infection (positive by polymerase chain reaction [PCR]). Participants who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of at least 12 weeks.

   Known to be positive for hepatitis B (HBV) by surface antigen (HBsAg) expression. Participants who are positive for either hepatitis B surface antibody (HBsAB) or antibodies to the hepatitis B core antigen (HBcAB) should be screened using PCR measurement of hepatitis B DNA levels. Participants with hepatitis B DNA levels by PCR that require nucleoside analogue therapy are not eligible for the trial. The latest local guidelines should be followed regarding the monitoring of hepatitis B DNA levels by PCR for participants on study treatment.

9. Presence of known chronic liver disease
10. Known dihydropyrimidine dehydrogenase deficiency (for all cohorts except for Cohort 1G)
11. Participants known to be positive for human immunodeficiency virus (HIV) are excluded if they meet any of the following criteria:
    - CD4+ T-cell count of <350 cells/μL
    - Detectable HIV viral load
    - History of an opportunistic infection within the past 12 months
    - On stable antiretroviral therapy for <4 weeks

    Note: No testing for HIV is required unless mandated by a local health authority.
12. Participants who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 7 months following the last dose of study treatment
13. Unable to swallow pills or requires enteral feeding or parenteral nutrition
14. Have used a strong Cytochrome (CYP) P450 2C8 inhibitor within 5 half-lives of the inhibitor or have used a strong CYP2C8 or CYP3A4 inducer within 5 days prior to enrollment
15. Other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
16. Has an active infection requiring systemic therapy.
17. Require therapy with warfarin or other coumarin derivatives if receiving CAPOX (Cohorts 1C, 1F, 2A) as part of this study (non-coumarin anticoagulants are allowed)
18. Currently participating in another interventional trial
19. Participants enrolled in Cohorts 1E, 1F, 1G, and 2A who have unresectable or metastatic, gastric, esophageal, and GEJ adenocarcinoma cannot have had previous chemotherapy for metastatic/unresectable disease; adjuvant or neoadjuvant chemotherapy, or biologic therapy is permitted if more than 6 months have elapsed between the end of therapy and first recurrence

20. Participants enrolled in Cohort 2A and Cohort 2B cannot have received prior anti-HER2 therapies
21. Have received a live vaccine <30 days of enrollment
22. Has ongoing ≥ Grade 2 diarrhea of any etiology at screening
23. Participants in Cohorts 1E, 1F, 1G: Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (Note: The repeat imaging should be performed during study screening.), clinically stable and without requirement of steroid treatment for at least 30 days before the first dose of study intervention.
24. Participants in Cohorts 1E, 1F, 1G, 2A: Has received prior therapy with an anti-programmed cell death 1 (PD-1), anti-programmed cell death ligand 1 (PD-L1), or anti-programmed cell death ligand 2 (PD-L2) agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], OX 40, CD137), and was discontinued from that treatment due to a Grade 3 or higher immune-related adverse event (irAE).
25. Participants in Cohorts 1E, 1F, 1G, 2A: Has had an allogeneic tissue/solid organ transplant.
26. Participants in Cohorts 1E, 1F, 1G, 2A: Has a diagnosis of immunodeficiency (excluding HIV) or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
27. Participants in Cohorts 1E, 1F, 1G, 2A: Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
28. Participants in Cohorts 1E, 1F, 1G, 2A: Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
29. Participants in Cohorts 1E, 1F, 1G, 2A: Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.
30. Participants in Cohorts 1E, 1F, 1G, 2A: Has received radiation therapy to the lung that is >30 Gy within 6 months of the first dose of trial treatment.

Number of Planned Participants

Approximately 40 participants will be enrolled and treated in the study.

Study Design

This is a phase 1b/2, dose escalation and expansion study of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy (FOLFOX or CAPOX), or pembrolizumab-containing combinations for participants with unresectable or metastatic HER2+ GI cancers. Participants with gastric, esophageal, or GEJ adenocarcinoma, cholangiocarcinoma, gallbladder carcinoma, or CRC will be included in phase 1b. During the phase 2 portion of the study, expansion cohorts in participants with unresectable or metastatic HER2+ esophageal, GEJ, and gastric adenocarcinoma and unresectable or metastatic HER2+ CRC may be enrolled to further characterize safety and obtain preliminary evidence of antitumor activity.

Summary of cohorts, treatments, populations, and number of participants

Study Phase	Cohort	Tucatinib Dose PO BID	Treatment	Population(s)		Approximate Participants per Cohort[b]
Phase 1b Tucatinib Dose Escalation with Trastuzumab and FOLFOX	1A	150 mg	Tucatinib, Trastuzumab, mFOLFOX6 or mFOLFOX7	1L+	• Cholangiocarcinoma • Gallbladder cancer • Gastric adenocarcinoma • Esophageal adenocarcinoma • GEJ adenocarcinoma • CRC	≥3
	1B	300 mg				≥6
Phase 1b Safety Evaluation of Tucatinib with Trastuzumab and CAPOX (Cohort 1C) or with Trastuzumab and Pembrolizumab-Containing Combinations (Cohorts 1E, 1F, 1G)	1C	300 mg	Tucatinib, Trastuzumab, CAPOX	1L+		≥6[a]
	1E	300 mg	Tucatinib, Trastuzumab, Pembrolizumab, mFOLFOX6	1L	• Gastric adenocarcinoma • Esophageal adenocarcinoma • GEJ adenocarcinoma	≥6[a]
	1F		Tucatinib, Trastuzumab, Pembrolizumab, CAPOX			≥6[a]
	1G		Tucatinib, Trastuzumab, Pembrolizumab			≥6[a]
Phase 1b Tucatinib Japan Safety Evaluation in Combination with Trastuzumab and FOLFOX	1D	300 mg	Tucatinib, Trastuzumab, mFOLFOX6	1L+	• Cholangiocarcinoma • Gallbladder cancer • Gastric adenocarcinoma • Esophageal adenocarcinoma • GEJ adenocarcinoma • CRC	≥3
Phase 2 Tumor Specific Expansion	2A	300 mg	Tucatinib, Pembrolizumab, Trastuzumab,	1L	• Gastric adenocarcinoma • Esophageal adenocarcinoma	up to 40

Study Phase	Cohort	Tucatinib Dose PO BID	Treatment	Population(s)		Approximate Participants per Cohort[b]
			mFOLFOX6 or CAPOX		• GEJ adenocarcinoma	
	2B		Tucatinib, Trastuzumab, mFOLFOX6	1L+	• CRC	up to 20

BID=twice daily; CRC=colorectal adenocarcinoma; GEJ=gastroesophageal junction; PO=oral; 1L=first-line
a Enrollment may remain open until at least 3 participants are enrolled in Japan
b No additional enrollment will occur for any cohort as of Amendment 5.

In the current study (C4251005), as of 17 November 2021, 11 participants have been enrolled in the tucatinib 300 mg PO BID dose cohort (Cohort 1B) and 8 participants have completed the DLT period and are evaluable for DLTs. No DLTs were observed in these participants, and the plasma and ultrafiltrate pharmacokinetics profile and the mean urinary platinum output profile of oxaliplatin were similar when participants received oxaliplatin alone compared to when oxaliplatin was received in combination with tucatinib (150 or 300 mg PO BID), suggesting that tucatinib did not impact the renal disposition of oxaliplatin. Preliminary data indicate all DLT evaluable participants who have received tucatinib (300 mg), trastuzumab, and FOLFOX experienced diarrhea, including 3 participants with gastroesophageal adenocarcinoma who experienced Grade 3 diarrhea events. The remaining 5 participants experienced either Grade 1 diarrhea (n=3) or Grade 2 diarrhea (n=2). No Grade 4 or fatal diarrhea events were observed. The median time to the first event of diarrhea (any grade) was 8 days after the first dose of tucatinib. In the three participants with Grade 3 events, diarrhea was noted after non-adherence to the recommended antidiarrheal management strategy; however, all events resolved to ≤ Grade 1 diarrhea with a management strategy of dose modification and antidiarrheal treatment with loperamide. No AESIs (nephrotoxicity or hepatotoxicity) have been reported.

Based on the Grade 3 diarrhea events observed in Cohort 1B, antidiarrheal prophylaxis will be required for all participants enrolled in Cohorts 1D, 1E, and for all participants in Cohort 2A who are treated with tucatinib + trastuzumab + pembrolizumab + mFOLFOX6. As of 12-Dec-2023, antidiarrheal prophylaxis is also required in Cohort 2B. Beginning on Cycle 1 Day 1, loperamide will be administered at a dose of 4 mg three times daily for 14 days (Days 1-14), followed by 4 mg twice daily on Days 15-42 for all participants enrolled in Cohorts 1D, 1E, and 2B. The first dose of loperamide must be administered concomitantly with the first dose of tucatinib. The dosing of loperamide should be titrated for a goal of 1-2 stools per day throughout Days 1-42 and afterwards, as necessary. The dose of loperamide can be modified, or loperamide can be held at any point during the study as per investigator discretion if participant has constipation or <1 stool per day. Following this initial 42-day period, participants may continue on antidiarrheal prophylaxis at a dose of 2 to 4 mg as needed, not to exceed 16 mg per day.

Antidiarrheal prophylaxis, as described above, will not be required for participants enrolled in Cohorts 1C, 1F, and 1G or for participants in Cohort 2A who are treated with tucatinib + trastuzumab + pembrolizumab + CAPOX, unless recommended by the SMC and required by the Sponsor based on a review of the data from these cohorts during the course of the study.

Participants must be instructed on the optimal use of antidiarrheals for symptomatic control of treatment-associated diarrhea.

The SMC will review safety data after 3 participants in each cohort are treated without antidiarrheal prophylaxis.

- If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in ≤1 participant, treatment without antidiarrheal prophylaxis is continued and evaluated in 3 more participants in the cohort.
    - If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in ≤1 of 6 participants, antidiarrheal prophylaxis will not be required in the cohort.
    - If Grade 3 or higher diarrhea events are observed in ≥2 of 6 participants, antidiarrheal prophylaxis will be required in the cohort.
- If Grade 3 or higher diarrhea events without optimal use of antidiarrheals are observed in 2 or more participants, antidiarrheal prophylaxis will be required in the cohort.

Phase 1b Tucatinib Dose Escalation with Trastuzumab and FOLFOX (Cohorts 1A and 1B)

The dose escalation portion of the study will determine the recommended dose of tucatinib to be administered with oxaliplatin-based chemotherapy.

Dose Escalation Process

Dose escalation will use a 3+3 design. Approximately 5 participants may be enrolled and treated at the 150 mg twice daily (BID) dose level to ensure there are at least 3 dose-limiting toxicity (DLT)-evaluable participants for safety monitoring committee (SMC) review (Cohort 1A). If no renal DLTs are observed at the 150 mg BID dose level (Cohort 1A), the SMC may recommend escalating to the 300 mg BID dose level for Cohort 1B. Approximately 8 participants will be enrolled in Cohort 1B to ensure at least 6 DLT and pharmacokinetic (PK) evaluable participants.

A renal DLT is defined as a sustained increase in serum cystatin C >1.5× baseline that is not related to pre-renal or post-renal etiologies (including disease progression, dehydration and intercurrent illness), and occurs during the period of treatment with tucatinib in combination with trastuzumab and FOLFOX, between the first dose of tucatinib and the end of Cycle 3. If 1 renal DLT is observed at the initial 150 mg BID dose level (Cohort 1A), an additional 3 participants (for a total of 6 evaluable participants) will be treated at this dose level, and the SMC will evaluate dose escalation to 200 or 250 mg BID if no further renal DLTs are observed.

If 1 renal DLT is observed in the first 3 participants at the intermediate dose, an additional 3 participants (for a total of 6 evaluable participants) will be treated at this dose level, and the SMC will evaluate dose escalation if no further DLTs are observed. If ≥2 renal DLTs are observed in the first 3 (or 6) participants treated at the initial 150 mg BID tucatinib dose level (Cohort 1A), alternative dose levels and/or regimens <150 mg BID may be considered by the SMC. If ≥2 renal DLTs are observed in the 6 participants of the escalated tucatinib dosing

cohort (Cohort 1B) (or ≥33% of participants if more than 6 DLT-evaluable participants are enrolled in a cohort), the SMC will consider appropriate dose modification.

If ≤1 renal DLTs are observed in each of the 6 DLT-evaluable participants treated at the 300 mg BID dose level (Cohort 1B), this will be declared the recommended phase 2 dose of tucatinib with oxaliplatin.

In addition to evaluating renal DLTs, the SMC will review the totality of the safety data and may recommend expanding enrollment to either cohort with continued monitoring for safety by the SMC or may recommend evaluation of alternative dosing.

After the recommended phase 2 dose of tucatinib has been identified, an additional 10 participants may be enrolled in either cohort to further characterize the safety profile of the combination and to evaluate management of potential adverse events (AEs).

Trastuzumab and FOLFOX – Cohort 1A

Participants should be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment prior to enrollment and may have received up to 2 consecutive cycles of FOLFOX (≤85 mg/m^2 oxaliplatin per 2-week cycle) during the screening period prior to Cycle 1 Day 1 of study treatment. If participants have received oxaliplatin in prior cycles at doses higher than 85 mg/m^2, there must be a minimum of 28 days from the last dose of the previous regimen prior to Cycle 1 Day 1 of treatment in this study. Concurrent treatment with anti-vascular endothelial growth factor (anti-VEGF) antibodies is prohibited while on trial. There is no upper limit for the number of prior lines of therapy received, and prior exposure to oxaliplatin is allowed, provided the participant had not experienced Grade ≥3 hypersensitivity due to oxaliplatin.

Enrolled participants will be treated with FOLFOX, trastuzumab, and tucatinib given in 14-day cycles. After enrolling on study, participants in Cohort 1A will receive 7 days of FOLFOX and trastuzumab without tucatinib. The starting dose of tucatinib for Cohort 1A is 150 mg orally (PO) twice daily (BID), and the first dose will be administered on Cycle 1 Day 8 and continuously thereafter until the participant comes off study. Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure.

Trastuzumab and FOLFOX - Cohort 1B

Participants should be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment prior to enrollment and may have received up to 2 consecutive cycles of FOLFOX (≤85 mg/m^2 oxaliplatin per 2-week cycle) during the screening period prior to Cycle 1 Day 1 of study treatment. If participants have received oxaliplatin in prior cycles at doses higher than 85 mg/m^2, there must be a minimum of 28 days from the last dose of the previous regimen prior to Cycle 1 Day 1 of treatment in this study. Concurrent treatment with anti-VEGF antibodies is prohibited while on trial. There is no upper limit for the number of prior lines of therapy received, and prior exposure to oxaliplatin is allowed, provided the participant had not experienced Grade ≥3 hypersensitivity due to oxaliplatin.

Enrolled participants will be treated with FOLFOX, trastuzumab, and tucatinib given in 14-day cycles. After enrolling on study, participants in Cohort 1B will receive 7 days of FOLFOX and trastuzumab without tucatinib. The first dose of tucatinib (300 mg PO BID or

an intermediate dose as recommended by the safety monitoring committee [SMC]) will be administered on Cycle 1 Day 8 and continuously thereafter until the participant comes off study. Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure.

Phase 1b Safety Evaluation of Tucatinib with Trastuzumab and CAPOX (Cohort 1C) or with Trastuzumab and Pembrolizumab-Containing Combinations (Cohorts 1E, 1F, 1G)

After the recommended phase 2 dose of tucatinib with oxaliplatin-based chemotherapy has been identified, additional cohorts may be opened to further evaluate the safety and tolerability of tucatinib combined with the following regimens:

- Trastuzumab + CAPOX (Cohort 1C)
- Pembrolizumab + Trastuzumab + mFOLFOX6 (Cohort 1E)
- Pembrolizumab + Trastuzumab + CAPOX (Cohort 1F)
- Pembrolizumab + Trastuzumab (Cohort 1G)

Participants will be closely followed for unacceptable toxicities for either 21-days (for participants enrolled in Cohorts 1C, 1F, or 1G) or 28 days (for participants enrolled in Cohort 1E) after the first dose of study intervention (ie, the DLT evaluation period) for the occurrence of specific AEs that are deemed to be dose-limiting. If 3 or more DLTs are observed in a cohort, enrollment to that cohort may be delayed to further examine safety data and consider study design changes as recommended by the SMC.

Trastuzumab and CAPOX – Cohort 1C

Participants in Cohort 1C should be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment prior to enrollment. Eligible participants may have received oxaliplatin-based chemotherapy (1 cycle of CAPOX at a dose of $\leq$130 mg/m^2 per 3-week cycle or 2 consecutive cycles of FOLFOX at a dose of $\leq$85 mg/m^2 per 2-week cycle) during the screening period prior to Cycle 1 Day 1. Concurrent treatment with anti-VEGF antibodies is prohibited while on trial. There is no upper limit for the number of prior lines of therapy received, and prior exposure to oxaliplatin is allowed, provided the participant had not experienced Grade $\geq$3 hypersensitivity due to oxaliplatin.

Enrolled participants will be treated with CAPOX, trastuzumab, and tucatinib given in 21-day cycles. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) may be administered on Cycle 1 Day 1. Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure.

Antidiarrheal prophylaxis will not be required for participants enrolled in Cohort 1C, unless recommended by the SMC and required by the Sponsor based on a review of the data from this cohort during the course of the study. Participants should be instructed on the optimal use of antidiarrheals for symptomatic diarrhea.

Approximately 8 participants may be enrolled to Cohort 1C to ensure that 6 participants complete 1 cycle of tucatinib+trastuzumab+CAPOX. If 8 participants are enrolled,

enrollment may remain open to ensure at least 3 to 6 participants from Japan are enrolled in this cohort.

Once at least 3 participants have completed 1 cycle of tucatinib+trastuzumab+CAPOX, a comprehensive review of the safety profile by the SMC will occur. Based on the totality of the safety data, the SMC may declare the combination safe and tolerable, or may recommend expanding enrollment to the cohort with continued monitoring for safety by the SMC or may recommend evaluation of alternative dosing.

Pembrolizumab, Trastuzumab, mFOLFOX6 (Cohort 1E)

Cohort 1E will evaluate the safety and tolerability of tucatinib combined with pembrolizumab, trastuzumab and mFOLFOX6 in participants with unresectable or metastatic HER2+ gastric, esophageal, or GEJ adenocarcinoma who have not previously received treatment in the first-line (1L) setting. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) will be administered on Cycle 1 Day 1.

Enrolled participants will be treated with mFOLFOX6 and tucatinib given in 14-day cycles. Trastuzumab will be given in 21-day cycles. Pembrolizumab will be given in 42-day cycles. Antidiarrheal prophylaxis will also be administered for the first 42 days of study treatment and as needed thereafter. Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure. Approximately 8 participants may be enrolled to ensure that 6 participants complete 28 days of study treatment. If 8 participants are enrolled, enrollment may remain open to ensure at least 3 to 6 participants from Japan are enrolled in this cohort.

Once at least 6 participants have completed 28 days of study treatment, a comprehensive review of the safety profile by the SMC will occur. Based on the totality of the safety data, the SMC may declare the combination safe and tolerable, or may recommend expanding enrollment to the cohort with continued monitoring for safety by the SMC or may recommend evaluation of alternative dosing.

Pembrolizumab, Trastuzumab, CAPOX (Cohort 1F)

Cohort 1F will evaluate the safety and tolerability of tucatinib combined with pembrolizumab, trastuzumab, and CAPOX in participants with unresectable or metastatic HER2+ gastric, esophageal, or GEJ adenocarcinoma who have not previously received treatment in the 1L setting. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) will be administered on Cycle 1 Day 1.

Enrolled participants will be treated with CAPOX, trastuzumab, and tucatinib given in 21-day cycles. Pembrolizumab will be given in 42-day cycles. Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure.

Antidiarrheal prophylaxis will not be required for participants enrolled in Cohort 1F, unless recommended by the SMC and required by the Sponsor based on a review of the data from this cohort during the course of the study. Participants should be instructed on the optimal use of antidiarrheals for symptomatic diarrhea.

Approximately 8 participants will be enrolled to ensure that 6 participants complete 21 days of study treatment. If 8 participants are enrolled, enrollment may remain open to ensure at least 3 to 6 participants from Japan are enrolled in this cohort.

Once at least 6 participants have completed 21 days of study treatment, a comprehensive review of the safety profile by the SMC will occur. Based on the totality of the safety data, the SMC may declare the combination safe and tolerable, or may recommend expanding enrollment to the cohort with continued monitoring for safety by the SMC or may recommend evaluation of alternative dosing.

Trastuzumab, Pembrolizumab (Cohort 1G)

Cohort 1G will evaluate the safety and tolerability of tucatinib combined with pembrolizumab and trastuzumab in participants with unresectable or metastatic HER2+ gastric, esophageal, or GEJ adenocarcinoma who have not previously received treatment in the 1L setting. This cohort may be opened based on SMC review of the safety from Cohorts 1A, 1B, 1C, 1E, and/or 1F. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) will be administered on Cycle 1 Day 1.

Enrolled participants will be treated with trastuzumab and tucatinib given in 21-day cycles. Pembrolizumab will be given in 42-day cycles. Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure.

Antidiarrheal prophylaxis will not be required for participants enrolled in Cohort 1G, unless recommended by the SMC and required by the Sponsor based on a review of the data from this cohort during the course of the study. Participants should be instructed on the optimal use of antidiarrheals for symptomatic diarrhea.

Approximately 8 participants will be enrolled to ensure that 6 participants complete 21 days of study treatment. If 8 participants are enrolled, enrollment may remain open to ensure at least 3 to 6 participants from Japan are enrolled in this cohort.

Once at least 6 participants have completed 21 days of study treatment and are evaluable for safety, a comprehensive review of the safety profile by the SMC will occur. Based on the totality of the safety data, the SMC may declare the combination safe and tolerable, or may recommend expanding enrollment to the cohort with continued monitoring for safety by the SMC or may recommend evaluation of alternative dosing.

Phase 1b Japan Safety Evaluation of Tucatinib in Combination with Trastuzumab and FOLFOX (Cohort 1D)

After the recommended dose of tucatinib with oxaliplatin-based chemotherapy has been identified, Cohort 1D may be opened to evaluate the safety and tolerability of tucatinib combined with trastuzumab, and mFOLFOX6 in participants with HER2+ GI malignancies enrolled from Japan. Participants should be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment prior to enrollment. Concurrent treatment with anti-VEGF antibodies is prohibited while on trial. There is no upper limit for the number of prior lines of therapy received, and prior exposure to oxaliplatin is allowed, provided the participant had not experienced Grade ≥3 hypersensitivity due to oxaliplatin.

Enrolled participants will be treated with mFOLFOX6 and tucatinib given in 14-day cycles; trastuzumab will be given every 21 days. The first dose of tucatinib (300 mg PO BID) or an

intermediate dose as recommended by the SMC) will be administered on Cycle 1 Day 1 and continuously thereafter until the participant comes off study. Antidiarrheal prophylaxis will also be administered for the first 42 days of study treatment and as needed thereafter. Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure.

Participants in Cohort 1D will be carefully monitored through the 28-days of treatment and evaluated for AEs that are unexpected based on the known safety profile of each individual agent and of the combination of tucatinib, trastuzumab, and mFOLFOX6. Investigators must ensure that participants do not have other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures required per the protocol (such as compliance with additional study visits, laboratory assessments, oral medications, and close outpatient monitoring). During the first cycle, the participant may be hospitalized for a minimum of 15 days with discharge permitted if a participant has no ongoing ≥ Grade 3 AEs and is otherwise considered appropriate for discharge by the investigator based on history (which includes assessment of any new or ongoing AEs and concomitant medication use), physical exam (including vital signs), and laboratory evaluations (including complete blood count, blood chemistry, renal function tests, and liver enzyme tests). For participants undergoing outpatient follow-up, the investigator must ensure that the participant will be followed closely in the outpatient setting by methods they determine to be appropriate to assure the participant's safety, and participants should be instructed to contact the investigator immediately in the event they experience an AE. In case of emergency, adequate means of communication between the site and the participant should be ensured by the investigator regardless of time of day or in the event of a holiday.

A minimum of 3 participants will be enrolled and receive tucatinib, trastuzumab, and mFOLFOX6. The global medical monitor, Japanese investigators, study statistician, and other study team members will conduct an evaluation of overall safety after 3 participants have enrolled and completed 28 days of study treatment. If the overall safety in the first 3 participants enrolled is deemed acceptable, no further enrollment will take place. If one DLT is observed, an additional 3 participants will be enrolled. If a DLT is reported for 1/6 participants, treatment is considered to be tolerated; if 2/6 DLTs are observed, the investigators and sponsor will evaluate the totality of the safety data and determine if the regimen is safe and tolerable. If 3 or more DLTs are observed, enrollment to the cohort may be delayed to further examine safety data and consider study design changes. Ad hoc meetings with the global medical monitor, Japanese investigators, study statistician, and other study team members may be called to review safety data as needed.

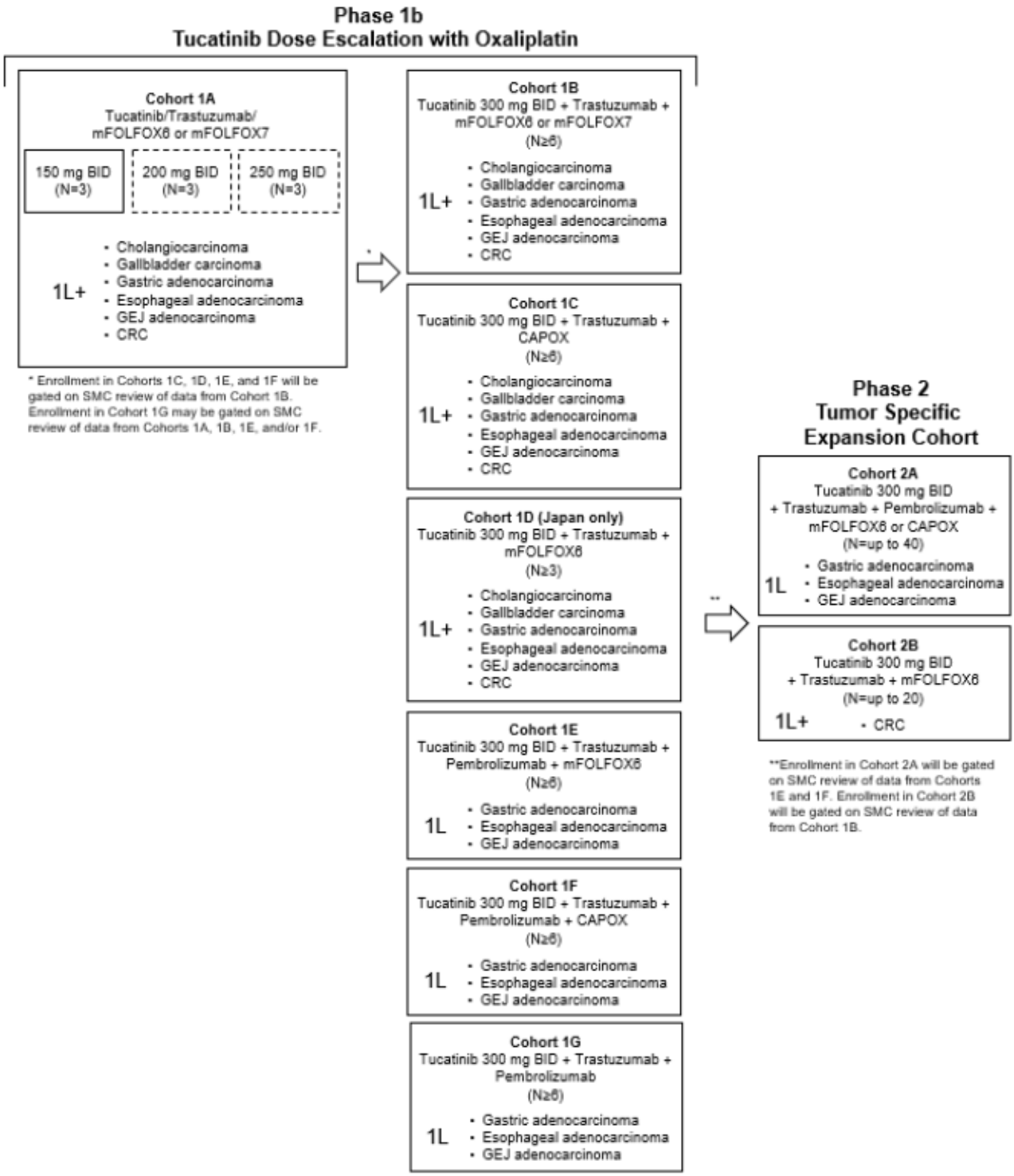
Phase 2 Tumor-Specific Expansion Cohorts (Cohorts 2A and 2B)

Tumor specific expansion cohorts may be enrolled following the completion of the phase 1b portion of the study to determine the safety and tolerability of the treatment regimens to be evaluated in Phase 2.

A 1L HER2+ gastric, esophageal or GEJ adenocarcinoma expansion cohort for tucatinib in combination with pembrolizumab, trastuzumab, and mFOLFOX6 or CAPOX (Cohort 2A) may be opened and enroll approximately 40 participants. Enrollment will be gated on SMC review of data from Cohorts 1E and 1F. Antidiarrheal prophylaxis will also be administered

for the first 42 days of study treatment for participants who are treated with mFOLFOX6 and as needed thereafter. Participants in Cohort 2A treated with CAPOX will not require antidiarrheal prophylaxis, unless recommended by the SMC and required by the Sponsor based on a review of the data from Cohort 1C and/or Cohort 1F. Participants in Cohort 2A should be instructed on the optimal use of antidiarrheals for symptomatic diarrhea.

A 1L+ HER2+ CRC expansion cohort for tucatinib in combination with trastuzumab and mFOLFOX6 (Cohort 2B) may also be enrolled with approximately 20 participants. Enrollment will be gated on SMC review of data from Cohort 1B (including DLT frequency and PK data). As of 12-Dec-2023, 5 participants were enrolled and treated in Cohort 2B. Tucatinib-related Grade 3 diarrhea was reported in 2 of 5 participants during the first 42-days of study treatment. Based on this finding, loperamide prophylaxis is now required for Cohort 2B.



Investigational Product, Dose, and Mode of Administration (All Cohorts)

For the phase 1b tucatinib dose escalation with oxaliplatin (Cohorts 1A and 1B), tucatinib will be administered 150 mg or 300 mg PO BID from Cycle 1 Day 8 onwards. Intermediate dose levels of tucatinib (200 or 250 mg PO BID) may be evaluated per SMC recommendation based on the incidence of renal DLTs observed in Cohort 1A or 1B. For Phase 1b Cohorts 1D, 1E, and 1G and the Phase 2 cohorts, tucatinib will be administered from Cycle 1 Day 1 onwards. For Cohorts 1C and 1F, the first dose of tucatinib will be administered on Cycle 1 Day 1.

For the phase 2 expansion cohorts (Cohorts 2A and 2B), tucatinib 300 mg PO BID (or recommended phase 2 dose) will be administered starting on Cycle 1 Day 1.

Trastuzumab dosing schedule:

- For Cohorts 1A and 1B, a 6 mg/kg loading dose will be administered intravenously (IV) on Cycle 1 Day 1, followed by a dose of 4 mg/kg IV every 2 weeks starting on Cycle 2 Day 1.
- For all other cohorts (Cohorts 1C, 1D, 1E, 1F, 1G, 2A, 2B), an 8 mg/kg loading dose will be administered IV on Cycle 1 Day 1, followed by a dose of 6 mg/kg IV every 3 weeks thereafter.

FOLFOX dosing schedules (Cohorts 1A, 1B, 1D, 1E, 2A, 2B):

Participants enrolled in Cohorts 1A or 1B receiving FOLFOX on study may be dosed using either the mFOLFOX6 or mFOLFOX7 regimen per investigator preference but should remain on the same FOLFOX regimen throughout study participation. Participants enrolled in Cohorts 1D, 1E, 2A, and 2B will receive mFOLFOX6.

- mFOLFOX6: oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2 (IV Bolus after leucovorin), and fluorouracil 2400 mg/m^2 (continuous infusion over 46 hours) will be administered IV every 2 weeks starting from Cycle 1 Day 1 onwards.

OR

- mFOLFOX7: oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and fluorouracil 2400 mg/m^2 (continuous infusion over 46 hours) will be administered IV every 2 weeks starting from Cycle 1 Day 1 onwards.

CAPOX dosing schedule (Cohorts 1C, 1F, and 2A): oxaliplatin 130 mg/m^2 will be administered IV every 3 weeks starting from Cycle 1 Day 1 onwards, and capecitabine 1000 mg/mg^2 is taken PO BID (Days 1-14 of each 21-day cycle).

Pembrolizumab dosing schedules (Cohorts 1E, 1F, 1G, and 2A): 400 mg administered IV every 42 days.

Duration of Treatment

Study treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, death, or study closure. Pembrolizumab will be given for a maximum of 18 doses (Cohorts 1E, 1F, 1G, 2A); study treatment will continue in these cohorts until unacceptable toxicity, disease progression, withdrawal of consent, death, or study closure.

Participants still receiving clinical benefit and remaining on study treatment as of Amendment 5 may continue receiving study intervention during the LTEP. Participants may remain in LTEP until unacceptable toxicity, disease progression, withdrawal of consent, death, or study closure.

Efficacy Assessments

Disease response will be assessed by the investigator according to RECIST v1.1. Treatment decisions will be made based upon local assessment of radiologic scans. Radiographic disease assessments will evaluate all known sites of disease, preferably using high quality spiral contrast computed tomography (CT), and covering, at a minimum, the chest, abdomen, and pelvis. Positron emission tomography-CT scans (if high quality CT scan is included) and/or MRI scans may also be used as appropriate, as well as additional imaging of any other known sites of disease (eg, nuclear bone scan imaging for bone lesions). For each participant, the same imaging modality as used at screening/baseline should be used throughout the study. Images may be collected by an independent central review (ICR) facility for possible future analysis. Disease assessments will be done at screening/baseline and every 8 weeks for the first 24 weeks in Cohorts 1A and 1B and then every 12 weeks thereafter and every 6 weeks for the first 24 weeks in Cohorts 1C, 1D, 1E, 1F, 1G, 2A, and 2B and then every 9 weeks thereafter, irrespective of dose interruptions.

During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

Pharmacokinetic Assessments

Blood (oxaliplatin and tucatinib) and urine (oxaliplatin) samples for PK assessments will be collected at protocol-defined time points. Plasma concentrations of tucatinib will be analyzed using validated mass spectrometry methods. Concentrations of total platinum in plasma, free platinum in plasma ultrafiltrates, and platinum in urine will be determined using validated methods. Remaining PK samples will be archived and may be used for the analysis of administered compounds or related species with exploratory, non-validated assays.

PK parameters will be calculated using standard non-compartmental methods. PK parameters to be estimated include, but are not limited to, area under the plasma concentration-time curve to the time of the last quantifiable concentration (AUC_{last}), maximum observed concentration (C_{max}), observed trough concentration in plasma (C_{trough}; tucatinib only), and time of C_{max} (T_{max}).

Following implementation of Amendment 5, no PK samples will be collected at EOT.

Biomarker Assessments

Biomarker assessments will be performed in peripheral blood and tumor tissue as outlined in this section. HER2 status for eligibility will be determined by historic/local NGS, IHC, FISH, or cell-free DNA-based NGS. Exploratory, predictive, and prognostic biomarkers associated with response, resistance, or safety observations may be monitored before and during treatment with tucatinib. Pharmacodynamic assessments will include disease burden monitoring and changes to target expression. Correlative studies will be conducted to gain a better understanding of target-response relationship, predictive/prognostic biomarkers,

mechanism of action, resistance mechanisms, and pharmacodynamics. Assays may include IHC, in situ hybridization, and tissue or blood-based NGS of RNA or DNA.

Following implementation of Amendment 5, no blood samples for biomarker assessments will be drawn at EOT.

Safety Assessments

Safety assessments will include the surveillance and recording of AEs, including serious AEs, physical examination findings, vital signs, electrocardiograms, concomitant medications, pregnancy testing, and laboratory tests. Assessment of cardiac ejection fraction will be performed using MUGA scan or ECHO. During the LTEP, all safety assessments other than pregnancy testing will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue to be performed as outlined in the schedule of events for participants of childbearing potential. During the LTEP, only information related to pregnancies, SAEs, and AESIs will be reported to the Sponsor.

Statistical Methods

Safety and efficacy will be assessed using descriptive statistics, including the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables. Confirmed objective response rate (cORR) per investigator is defined as the proportion of participants with confirmed complete response (CR) or partial response (PR), according to RECIST v1.1. The 2-sided 90% exact confidence interval (CI) using Clopper-Pearson method will be calculated for the response rates.

<u>Phase 1b Tucatinib Dose Escalation with FOLFOX (Cohorts 1A and 1B)</u>

The tucatinib dose escalation will follow a 3+3 scheme. Approximately 6 DLT-evaluable participants may be treated in each phase 1b dose escalation cohort in order to identify the recommended phase 2 dose of tucatinib in combination with trastuzumab and oxaliplatin-based regimens.

The DLT-Evaluable Analysis Set includes all participants in Cohort 1A or 1B who meet one of the following criteria: (1) had a renal DLT or (2) had taken at least 75% of planned oxaliplatin and tucatinib doses per cycle and have been followed for at least 2 cycles of study treatment (through the end of Cycle 3 for FOLFOX regimens), inclusive of dose delays.

Cohort 1A may enroll approximately 5 participants in order to have at least 3 DLT-evaluable participants, and approximately 8 participants in Cohort 1B in order to have at least 6 DLT-evaluable participants in the case that a renal DLT is observed in the first 3 DLT-evaluable participants.

<u>Phase 1b Safety Evaluation of Tucatinib with Trastuzumab and CAPOX (Cohort 1C) or with Trastuzumab and Pembrolizumab-Containing Regimens (Cohorts 1E, 1F, 1G)</u>

Cohorts 1C, 1E, 1F, and 1G may enroll approximately 8 participants in each cohort to ensure at least 6 participants in each cohort complete the appropriate DLT period (21-days for Cohorts 1C, 1F and 1G; 28-days for Cohort 1E). Enrollment may remain open to ensure at least 3 participants from Japan are enrolled into each cohort.

The DLT-Evaluable Analysis Set for Cohort 1C includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned capecitabine, oxaliplatin, trastuzumab, and tucatinib for the first 21 days of study treatment and have been followed for at 21 days of study treatment.

The DLT-Evaluable Analysis Set for Cohort 1E includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned fluorouracil, oxaliplatin, pembrolizumab, trastuzumab, and tucatinib for the first 28 days of study treatment and have been followed for at 28 days of study treatment.

The DLT-Evaluable Analysis Set for Cohort 1F includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned capecitabine, oxaliplatin, pembrolizumab, trastuzumab, and tucatinib for the first 21 days of study treatment and have been followed for at 21 days of study treatment.

The DLT-Evaluable Analysis Set for Cohort 1G includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned pembrolizumab, trastuzumab, and tucatinib for the first 21 days of study treatment and have been followed for at 21 days of study treatment.

Phase 1b Tucatinib Japan Safety Evaluation in Combination with Trastuzumab and FOLFOX (Cohort 1D)

Cohort 1D (Japan-specific cohort) will enroll a minimum of 3 participants to receive tucatinib, trastuzumab, and mFOLFOX6. The DLT-evaluable analysis set in Cohort 1D includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned fluorouracil, oxaliplatin, trastuzumab, and tucatinib doses and have been followed for at least 28 days.

Phase 2 Tumor Specific Expansion

Tumor specific expansion cohorts may be enrolled. For example, a 1L gastric, esophageal, and GEJ adenocarcinoma expansion cohort (Cohort 2A) may enroll up to 40 participants, and a 1L+ CRC expansion cohort (Cohort 2B) may enroll up to 20 participants.

For a sample size of 40 participants in Cohort 2A, assuming cORR is between 60% and 80%, the 2-sided 90% exact CIs are summarized below:

Confirmed ORR	90% Exact CIs (N=40)
60%	(46%, 73%)
70%	(56%, 82%)
80%	(67%, 90%)

For a sample size of 20 participants in Cohort 2B, assuming confirmed ORR is between 55% and 65%, the 2-sided 90% exact CI are summarized below:

Confirmed ORR	90% Exact CIs (N=20)
55%	(35%, 74%)
60%	(39%, 78%)
65%	(44%, 82%)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
1L	first line
5-FU	5-fluorouracil
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	area under the plasma concentration-time curve to the time of the last quantifiable concentration
β-hCG	beta human chorionic gonadotropin
BAP	biomarker analysis plan
BICR	blinded independent central review
BID	twice daily
BUN	blood urea nitrogen
C_{max}	maximum observed concentration
C_{trough}	observed trough concentration in plasma
CAPOX	capecitabine and oxaliplatin
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CISH	chromogenic in situ hybridization
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
cORR	confirmed objective response rate
CR	complete response
CRC	colorectal adenocarcinoma
CSR	clinical study report
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome

Term	Definition
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
EC	exclusion criterion
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
Enrollment	Cycle 1 Day 1
EOI	end of infusion
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin embedded
FISH	fluorescence in situ hybridization
FOLFOX	leucovorin, fluorouracil, oxaliplatin
FT3	free triiodothyronine
FT4	free thyroxine
GEC	gastroesophageal cancer
GEJ	gastroesophageal junction
GFR	glomerular filtration rate
GI	gastrointestinal
Gy	gray
HbcAB	hepatitis B core antigen
HbsAB	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen expression
HBV	hepatitis B
HER2	human epidermal growth factor receptor 2

Term	Definition
HIV	human immunodeficiency virus
IC	inclusion criterion
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICR	independent central review
IEC	independent ethics committee
IFN-γ	interferon- γ
Ig	immunoglobulin
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
INV	investigator assessment
IO	Immuno-oncology
irAE	Immune-related adverse event
IRB	institutional review board
IRR	infusion-related reaction
ISO	international organization for standardization
IV	intravenous(ly)
LTEP	long-term extension phase
LVEF	left ventricular ejection fraction
MATE1	multidrug and toxin extrusion protein 1
MATE2-K	multidrug and toxin extrusion protein 2K
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease [study]
mFOLFOX	modified FOLFOX
MRI	magnetic resonance imaging
MSI	microsatellite instability-high/deficient mismatch repair
MQI	medically qualified individual
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not estimable
NGS	next generation sequencing
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer (

Term	Definition
OCT2	organic cation transporter 2
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1
PD-L1/2	programmed cell death ligand 1/2
PET	positron emission tomography
PFS	progression-free survival
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PKCθ	protein kinase C-theta
PLT	platelet
PO	orally
PR	partial response
PSSA	Pfizer SAE submission assistant
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
RAS	rat sarcoma virus
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SJS	Stevens-Johnson Syndrome
SMC	Safety Monitoring Committee
SOE	schedule of events
SRS	stereotactic radiosurgery
SRSD	single reference safety document
T3	triiodothyronine
TEN	toxic epidermal necrolysis
T1DM	Type 1 diabetes mellitus
T_{max}	time at which the maximum plasma concentration (C_{max}) occurs
ULN	upper limit of normal

Term	Definition
UPC	Urine Protein/Creatinine
US	United States
VEGF	vascular endothelial growth factor
WBC	white blood cell
WBRT	whole brain radiation therapy

3. INTRODUCTION

3.1. HER2 in Cancer

Encoded by the ERBB2 gene, human epidermal growth factor receptor 2 (HER2) is part of a family of 4 related receptor tyrosine kinases, which include HER1 (also known as epidermal growth factor receptor [EGFR]), HER2, HER3, and HER4. HER1-4 are single-pass transmembrane glycoprotein receptors containing an extracellular ligand binding region and an intracellular signaling domain. HER2 has no known ligand, but it is the preferred dimerization partner for the other HER family receptors. When overexpressed in tumors, HER2 forms ligand-independent homodimeric complexes that autophosphorylate. HER2 homo- or heterodimerization results in the activation of multiple signaling cascades, including the Ras/Raf/MEK/MAPK, PI3K/AKT, Src, and STAT pathways. These signaling pathways lead to cell proliferation, inhibition of apoptosis, and metastasis (Riese 1998; Olayioye 2000; Yarden 2001; Schlessinger 2002; Holbro 2004; Hynes 2005).

HER2 is a validated target in multiple solid tumors, with anti-HER2 biologics and small molecule drugs approved for patients with HER2+ breast and gastric cancers. Amplification of the HER2-gene or overexpression of its protein occurs in approximately 15% to 20% of breast cancers (Haque 2012; American Cancer Society (ACS) 2018) and 6% to 30% of gastric and esophageal cancers (Kelly 2016). Recently, interest has grown in HER2-targeting strategies for patients with refractory metastatic colorectal carcinoma, where overexpression of HER2 has been found to occur in approximately 3% to 5% of patients (Valtorta 2015; Takegawa 2017). HER2 can also be overexpressed in other gastrointestinal (GI) cancers, such as cholangiocarcinoma and gallbladder carcinoma, where studies suggest ERBB2 amplification ranges from 1% to 6% (Weinberg 2019; Albrecht 2020).

3.2. Tucatinib

Tucatinib (previously known as ONT-380 and ARRAY-380 and marketed as TUKYSA®) is an oral, potent, HER2-specific tyrosine kinase inhibitor that is being developed by Seagen, a wholly owned subsidiary of Pfizer (Bothell, WA). Unlike other small molecule inhibitors of HER2, including lapatinib, neratinib, and afatinib, all of which are dual-inhibitors of both EGFR and HER2, tucatinib selectively inhibits HER2. This enables tucatinib to provide potent inhibition of HER2 while minimizing many of the EGFR-related side effects including severe skin rash and GI toxicity.

A complete summary of the clinical and nonclinical data relevant to tucatinib and its study in human participants is provided in the Investigator's Brochure.

3.3. Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients

across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/prescribing information for detailed pharmaceutical/therapeutic background of pembrolizumab.

3.4. Study Rationale

5-fluorouracil, an inhibitor of nucleic acid synthesis, has been used for years for treatment of GI cancers, both as a single agent and in combination with other chemotherapeutic agents, including oxaliplatin (a platinum analog that blocks DNA replication) and leucovorin (a folate analog). The combination of oxaliplatin, fluorouracil, and leucovorin (FOLFOX) has been found to be a safe and effective and is used as the standard-of-care treatment for gastroesophageal, colorectal, biliary tract, and gallbladder cancers. Additionally, the combination of capecitabine, a prodrug of fluorouracil, and oxaliplatin (CAPOX) has been found to be safe and effective for the treatment of gastric, esophageal, and gastroesophageal junction (GEJ) adenocarcinoma, metastatic colorectal adenocarcinoma (CRC), and biliary tract cancer. FOLFOX and CAPOX regimens are viewed as clinically interchangeable in treatment guidelines and are used with different frequencies based primarily on geographic location and local treatment preference (Loree 2014; Janjigian 2020).

Trastuzumab is a humanized anti-HER2 antibody that binds to subdomain IV of the HER2 extracellular domain and exerts its antitumor effects by blocking HER2-cleavage, stimulating antibody-dependent, cell-mediated cytotoxicity and inhibiting ligand independent, HER2-mediated mitogenic signaling (Arteaga 2011). Trastuzumab is approved for treatment of patients with metastatic HER2+ gastric or GEJ adenocarcinomas. While the prognostic value of HER2 status in gastroesophageal cancer (GEC) is not clear, patients with HER2 positive (HER2+) advanced stage disease may benefit from the addition of trastuzumab (a HER2-directed monoclonal antibody) to chemotherapy as first-line (1L) therapy (Bang 2010). Trastuzumab in combination with a second HER2 inhibitor (either pertuzumab or lapatinib) is a recommended treatment option in the United States for advanced or metastatic colon cancer that is HER2-amplified and rat sarcoma virus (*RAS*) and *BRAF* wild-type (Benson 2021).

The addition of tucatinib and trastuzumab to oxaliplatin-based chemotherapy (FOLFOX or CAPOX) is being evaluated in this study based on preclinical and clinical data demonstrating superior activity of dual targeted inhibition of HER2 with tucatinib and trastuzumab compared with either single agent alone.

A randomized, double-blind, placebo-controlled, active-comparator global clinical trial (ONT-380-206; HER2CLIMB) has been conducted to evaluate tucatinib (300 mg twice daily [BID]) in combination with trastuzumab and capecitabine compared to trastuzumab and capecitabine alone in 612 participants with locally advanced unresectable or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab, and T-DM1 (Murthy 2020). The addition of tucatinib to the combination resulted in a comparable safety profile to trastuzumab and capecitabine alone. The primary endpoint for Study ONT-380-206, progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 based on blinded independent central review (BICR), was met. With a median PFS follow-up of 10.4 months, the primary analysis of PFS per BICR demonstrated

treatment on the tucatinib arm was superior to the control arm and resulted in a 46% reduction in the risk of disease progression or death (stratified hazard ratio=0.54 [95% confidence interval {CI}: 0.42, 0.71], P<0.00001). The median PFS was 7.8 months (95% CI: 7.5, 9.6) and 5.6 months (95% CI: 4.2, 7.1) for the tucatinib and control arms, respectively. Overall survival (OS) was significantly prolonged on the tucatinib arm versus the control arm, with a 34% reduction in the risk of death (hazard ratio=0.66 [95% CI: 0.50, 0.88]; P=0.0048). The median OS was 21.9 months (95% CI: 18.3, 31.0) and 17.4 months (95% CI: 13.6, 19.9) for the tucatinib and control arms, respectively.

In addition to results seen in the HER2CLIMB trial, the combination of tucatinib (300 mg BID) and trastuzumab has shown promising activity in HER2+ metastatic CRC, based on initial results reported from the single-arm, phase 2 trial, C4251002 (SGNTUC-017, MOUNTAINEER) (Strickler 2019). In this study, participants with HER2+, RAS-wildtype metastatic CRC who had been previously treated with fluorouracil, oxaliplatin, irinotecan and an anti-vascular endothelial growth factor (VEGF) antibody received tucatinib (300 mg BID) in combination with trastuzumab (8 mg/kg IV followed by 6 mg/kg every 3 weeks [Q3W]). The primary endpoint was objective response rate (ORR). Interim data from the initial 26 participants was presented at the European Society for Medical Oncology 2019 Congress. The investigators reported an ORR of 52.2% (12 of 23 participants; 95% CI: 30.6, 73.2) that consisted of 12 partial responses (PRs) in 23 evaluable participants, 11 of which were confirmed at a second assessment time point (Strickler 2019). Additionally, the median duration of response (DOR) was 10.4 months (6.0–not estimable [NE]), with a median PFS of 8.1 months (3.8–NE) and a median OS of 18.7 months (12.3–NE).

The primary objective of the phase 1b tucatinib dose escalation with oxaliplatin portion of this study is to determine the recommended dose of tucatinib when combined with trastuzumab and oxaliplatin-based chemotherapy in participants with HER2+ GI cancers. In addition, the potential for nephrotoxicity of oxaliplatin when used in combination with tucatinib will be evaluated. Tucatinib inhibits the multidrug and toxin extrusion proteins 1 and 2-K (MATE1/MATE2-K) and organic cation transporter 2 (OCT2). These transporters actively secrete creatinine from the blood to the urine through renal tubular cells. Inhibition of these transporters results in an increase in serum creatinine, which does not reflect a change in glomerular function. In the HER2CLIMB trial, 13.9% of participants randomized to the tucatinib arm had elevations in serum creatinine after the first cycle of treatment with tucatinib. The mean increase in creatinine was approximately 30%, remained stable while on therapy, and returned to baseline upon treatment discontinuation. A dedicated pharmacology study (SGNTUC-020) was conducted and demonstrated that tucatinib had no effects on renal function as assessed by iohexol, and elevations of serum creatinine are a result of tucatinib inhibition of kidney transporters responsible for the renal secretion of creatinine (OCT2/MATE1).

Oxaliplatin is also a substrate for MATE1/2-K and OCT2 transporters and is actively transported through the proximal renal tubular epithelial cell. The relative importance of this active transport in the metabolism of oxaliplatin is unknown. Due to this uncertainty, and the theoretical risk of oxaliplatin accumulation in the kidney and resultant nephrotoxicity, a lower starting dose of tucatinib (150 mg BID) has been chosen for the phase 1b Cohort 1A for this trial. In addition to standard methods for evaluating renal toxicity, non-creatinine measures of glomerular function (cystatin C) will be closely monitored in order to detect

reduced glomerular function that may be associated with oxaliplatin-induced nephrotoxicity. The pharmacokinetics (PK) of oxaliplatin in the blood and urine will be examined as well in order to accurately characterize the disposition of oxaliplatin in the presence of tucatinib.

Preclinical and clinical evidence support combining pembrolizumab with trastuzumab and cytotoxic chemotherapy to treat HER2+ cancers. The combination can induce durable clinical responses in a subset of patients with trastuzumab-refractory HER2+ metastatic breast cancer (Loi 2019). Although the mechanistic basis for synergy between anti-HER2 and antiPD-1-based therapies has not been definitively established, possible contributors have been identified. Analysis of tumor samples from patients treated with trastuzumab shows upregulation of PD-1 and enhanced gene expression signatures of immune infiltration (Varadan 2016), which could increase the efficacy of pembrolizumab. Similarly, trastuzumab increases PD-L1 expression in a mouse model of breast cancer (Chaganty 2018). In addition, administration of trastuzumab with pembrolizumab can augment HER2-specific T-cell responses, promote T cell and dendritic cell trafficking, and induce expansion of peripheral memory T cells (Taylor 2007; Park 2010; Mortenson 2013).

The results of an interim analysis of pembrolizumab or placebo plus trastuzumab and chemotherapy in participants with HER2+ metastatic gastric or GEJ cancer showed a significant improvement in ORR for participants in the experimental arm, while the incidence of AEs was similar between arms with no safety concerns observed (Janjigian 2021). The confirmed ORR (95% CI) was 74.4% (66.2-81.6) for pembrolizumab + SOC vs 51.9% (43.0-60.7) for placebo + SOC (difference, 22.7 percentage points [95% CI, 11.2-33.7], P = 0.00006).

The effects of tucatinib on tumor growth kinetics, as well as tucatinib anti-tumor efficacy in combination with trastuzumab and PD-1 checkpoint blockade, were evaluated using HER2+ murine cancer models (trastuzumab-sensitive H2N113 and trastuzumab-resistant fo5) (Li 2021). An anti-tumor immune response may be an important component of the efficacy of tucatinib. This is supported by in vitro data demonstrating tucatinib stimulated human peripheral T cells and in vivo data showing favorable effects on the tumor immune microenvironment mediated by tucatinib treatment. These changes were associated with improved efficacy when tucatinib was combined with PD-1 inhibition or trastuzumab in the setting of trastuzumab resistance. These findings suggest that the combination of tucatinib and PD-1 inhibition is a rational combination that warrants investigation in the clinical setting. To determine whether pembrolizumab can be safely combined with trastuzumab and tucatinib, combination treatment regimens with and without chemotherapy will be evaluated in Phase 1b.

The phase 2 portion of this study may include tumor-specific expansion cohorts as 1L therapy for participants with gastric, esophageal, and GEJ adenocarcinoma (Cohort 2A) and as 1L+ therapy for participants with CRC (Cohort 2B). The primary objective of the phase 2 portion of the study will be to evaluate the safety and tolerability of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy as 1L therapy for participants with gastric, esophageal and GEJ adenocarcinoma (Cohort 2A) and tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for participants with CRC (Cohort 2B). Secondary objectives will include evaluation of the anti-tumor activity of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-

based chemotherapy as 1L therapy in participants with HER2+ 1L gastric, esophageal, and GEJ adenocarcinoma (Cohort 2A). Exploratory objectives include evaluation of the anti-tumor activity of tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy in HER2+ 1L+ CRC (Cohort 2B) and to evaluate the PK of tucatinib given with trastuzumab and oxaliplatin-based chemotherapy (with or without pembrolizumab) (Cohorts 2A, 2B).

4. OBJECTIVES

This study will evaluate the safety and tolerability, efficacy, and PK of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy (FOLFOX or CAPOX) or with pembrolizumab-containing combinations in participants with unresectable or metastatic HER2+ GI cancers. Specific objectives and corresponding endpoints for the study are summarized below (Table 1, Table 2, Table 3, Table 4).

4.1. Phase 1b Tucatinib Dose Escalation with Trastuzumab and FOLFOX (Cohort 1A and Cohort 1B)

Table 1. Objectives and Corresponding Endpoints

Primary Objective	Corresponding Primary Endpoint
• To determine the recommended dose of tucatinib when combined with trastuzumab and oxaliplatin-based chemotherapy in participants with human epidermal growth factor receptor 2 positive (HER2+) GI cancers	• Incidence of renal dose-limiting toxicities (DLTs)
Secondary Objectives	**Corresponding Secondary Endpoints**
• To evaluate the safety and tolerability of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities • Vital signs and other relevant safety variables
• To evaluate the combination of tucatinib, trastuzumab, and oxaliplatin-based chemotherapy for potential nephrotoxicity	• Change in glomerular filtration rate (GFR), as estimated using serum cystatin C, from baseline through 2 cycles of combination therapy
• To evaluate the pharmacokinetics (PK) of tucatinib	• PK parameters of tucatinib (including but not limited to AUC_{last}, C_{max}, C_{trough}, and T_{max})
• To evaluate the PK of oxaliplatin in the presence and absence of tucatinib	• PK parameters of oxaliplatin (including but not limited to AUC_{last}, C_{max}, T_{max})
Exploratory Objectives	**Corresponding Exploratory Endpoints**
• To evaluate the antitumor activity of tucatinib in combination with trastuzumab, and oxaliplatin-based chemotherapy	• Objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment (INV)
• To explore correlations between tissue and blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in tissue and blood

4.2. Phase 1b Safety Evaluation of Tucatinib in Combination with Trastuzumab + CAPOX (Cohort 1C), or in Combination with Trastuzumab and Pembrolizumab-Containing Combinations (Cohorts 1E, 1F, and 1G)

Table 2. Objectives and Corresponding Endpoints

Primary Objectives	Corresponding Primary Endpoints
• To evaluate the safety and tolerability of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs), including DLTs, and laboratory abnormalities • Vital signs and other relevant safety variables
Secondary Objectives	**Corresponding Secondary Endpoints**
• To evaluate the antitumor activity of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers as measured by objective response rate (ORR) according to RECIST v1.1 per INV	• ORR according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers as measured by duration of response (DOR) according to RECIST v1.1 per INV	• DOR (confirmed CR or PR) according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers as measured by progression-free survival (PFS) according to RECIST v1.1 per INV	• PFS according to RECIST v1.1 per INV •
• To evaluate the anti-tumor activity of tucatinib in combination with trastuzumab and CAPOX or tucatinib in combination with trastuzumab and pembrolizumab-containing combinations in HER2+ GI cancers as measured by overall survival (OS)	• OS
• To evaluate the PK of tucatinib	• PK parameters of tucatinib (including but not limited to C_{trough})
Exploratory Objective	**Corresponding Exploratory Endpoint**
• To explore correlations between tissue and blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in tissue and blood

4.3. Phase 1b Japan Safety Evaluation of Tucatinib in Combination with Trastuzumab and mFOLFOX6 (Cohort 1D)

Table 3. Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To assess the safety and tolerability of tucatinib in combination with trastuzumab and FOLFOX in Japanese participants	• Type, incidence, severity, seriousness, and relatedness of AEs, including DLTs, and laboratory abnormalities • Vital signs and other relevant safety variables • Frequency of dose holds, dose reductions, and discontinuations of tucatinib, trastuzumab, and components of FOLFOX
Exploratory Objective	Corresponding Endpoint
• To assess the PK of tucatinib when administered in combination with trastuzumab and FOLFOX in Japanese participants	• PK parameters of tucatinib (including but not limited to AUC_{last}, C_{max}, C_{trough}, and T_{max})

4.4. Phase 2 Tumor-Specific Expansion

Table 4. Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• Cohort 2A: To evaluate the safety and tolerability of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy (FOLFOX or CAPOX) as first-line (1L) therapy in participants with unresectable or metastatic HER2+ gastric, esophageal, or gastroesophageal junction (GEJ) adenocarcinoma • Cohort 2B: To evaluate the safety and tolerability of tucatinib combined with trastuzumab and FOLFOX in participants with unresectable or metastatic HER2+ colorectal adenocarcinoma (CRC)	• Type, incidence, severity, seriousness, and relatedness of AEs, including DLTs, and laboratory abnormalities • Vital signs and other relevant safety variables
Secondary Objectives	Corresponding Endpoints
• To evaluate the anti-tumor activity of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy (FOLFOX or CAPOX) as 1L therapy for HER2+ gastric, esophageal, or GEJ adenocarcinoma as measured by confirmed objective response rate (cORR), according to RECIST v1.1 per INV	• cORR (confirmed complete response [CR] or partial response [PR]) according to RECIST v1.1 per INV

Table 4. Objectives and Corresponding Endpoints

• To evaluate the anti-tumor activity of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy as 1L therapy for HER2+ gastric, esophageal, or GEJ adenocarcinoma as measured by DOR according to RECIST v1.1 per INV	• DOR (confirmed CR or PR) according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy as 1L therapy for HER2+ gastric, esophageal, or GEJ adenocarcinoma as measured by PFS according to RECIST v1.1 per INV	• PFS according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy as 1L therapy for HER2+ gastric, esophageal, or GEJ adenocarcinoma as measured by OS	• OS
Exploratory Objectives	Corresponding Endpoints
• To evaluate the anti-tumor activity of tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy (FOLFOX) as 1L+ therapy for HER2+ CRC as measured by cORR, according to RECIST v1.1 per INV	• cORR (CR or PR) according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for HER2+ CRC as measured by DOR according to RECIST v1.1 per INV	• DOR (confirmed CR or PR) according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for HER2+ CRC as measured by PFS according to RECIST v1.1 per INV	• PFS according to RECIST v1.1 per INV
• To evaluate the anti-tumor activity of tucatinib combined with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for HER2+ CRC as measured by OS	• OS
• To evaluate the PK of tucatinib given with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy as 1L therapy for unresectable or metastatic HER2+ gastric, esophageal, or GEJ adenocarcinoma (Cohort 2A) and to evaluate the PK of tucatinib given with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for metastatic HER2+ CRC (Cohort 2B)	• PK parameter of tucatinib (C_{trough})
• To explore correlations between tissue and blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in tissue and blood

5. INVESTIGATIONAL PLAN

5.1. Summary of Study Design

This is a phase 1b/2 dose escalation and expansion study of tucatinib in combination with trastuzumab, and oxaliplatin-based chemotherapy (FOLFOX or CAPOX) or pembrolizumab-containing combinations for participants with unresectable or metastatic HER2+ GI cancers. Approximately 40 participants will be enrolled across approximately 25 clinical sites.

Participants are eligible if they have one of the following cancers:

- CRC
- Gastric adenocarcinoma
- Esophageal adenocarcinoma
- GEJ adenocarcinoma
- Cholangiocarcinoma
- Gallbladder carcinoma

Table 5. Summary of Cohorts, Treatments, Populations, and Number of Participants

Study Phase	Cohort	Tucatinib Dose PO BID	Treatment	Population(s)		Approximate Participants per Cohort[b]
Phase 1b Tucatinib Dose Escalation with Trastuzumab and FOLFOX	1A	150 mg	Tucatinib, Trastuzumab, mFOLFOX6 or mFOLFOX7	1L+	• Cholangiocarcinoma • Gallbladder cancer • Gastric adenocarcinoma • Esophageal adenocarcinoma • GEJ adenocarcinoma • CRC	≥3
	1B	300 mg				≥6
Phase 1b Safety Evaluation of Tucatinib with Trastuzumab and CAPOX (Cohort 1C) or with Trastuzumab and Pembrolizumab-Containing Combinations (Cohorts 1E, 1F, 1G)	1C	300 mg	Tucatinib, Trastuzumab, CAPOX	1L+		≥6[a]
	1E	300 mg	Tucatinib, Trastuzumab, Pembrolizumab, mFOLFOX6	1L	• Gastric adenocarcinoma • Esophageal adenocarcinoma • GEJ adenocarcinoma	≥6[a]
	1F		Tucatinib, Trastuzumab, Pembrolizumab, CAPOX			≥6[a]
	1G		Tucatinib, Trastuzumab, Pembrolizumab			≥6[a]

Table 5. Summary of Cohorts, Treatments, Populations, and Number of Participants

Study Phase	Cohort	Tucatinib Dose PO BID	Treatment	Population(s)		Approximate Participants per Cohort[b]
Phase 1b Tucatinib Japan Safety Evaluation in Combination with Trastuzumab and FOLFOX	1D	300 mg	Tucatinib, Trastuzumab, mFOLFOX6	1L+	• Cholangiocarcinoma • Gallbladder cancer • Gastric adenocarcinoma • Esophageal adenocarcinoma • GEJ adenocarcinoma • CRC	≥3
Phase 2 Tumor Specific Expansion	2A	300 mg	Tucatinib, Pembrolizumab, Trastuzumab, mFOLFOX6 or CAPOX	1L	• Gastric adenocarcinoma • Esophageal adenocarcinoma • GEJ adenocarcinoma	up to 40
	2B		Tucatinib, Trastuzumab, mFOLFOX6	1L+	• CRC	up to 20

BID = twice daily; CRC = colorectal adenocarcinoma; GEJ = gastroesophageal junction; PO = oral; 1L = first-line

a Enrollment may remain open until at least 3 participants are enrolled in Japan

b No additional enrollment will occur for any cohort as of Amendment 5.

In the current study (C4251005; SGNTUC-024), as of 17 November 2021, 11 participants have been enrolled in the tucatinib 300 mg PO BID dose cohort (Cohort 1B) and 8 participants have completed the DLT period and are evaluable for DLTs. No DLTs were observed in these participants, and the plasma and ultrafiltrate pharmacokinetics profile and the mean urinary output profile of oxaliplatin were similar when participants received oxaliplatin alone compared to when oxaliplatin was received in combinations with tucatinib (150 or 300 mg PO BID), suggesting that tucatinib did not impact the renal disposition of oxaliplatin. Preliminary data indicate all DLT evaluable participants who have received tucatinib (300 mg), trastuzumab, and FOLFOX experienced diarrhea, including 3 participants with gastroesophageal adenocarcinoma who have experienced Grade 3 diarrhea events. The remaining 5 participants experienced either Grade 1 diarrhea (n=3) or Grade 2 diarrhea (n=2). No Grade 4 or fatal diarrhea events were observed. The median time to the first event of diarrhea (any grade) was 8 days after initiation of tucatinib. In the three participants with Grade 3 events, diarrhea was noted after non-adherence to the recommended antidiarrheal management strategy; however, all events resolved to ≤Grade 1 diarrhea with a management strategy of dose modification (as per Section 7.9.10) and antidiarrheal treatment with

loperamide. No adverse events of special interest (AESIs; nephrotoxicity or hepatotoxicity) have been reported.

Based on the Grade 3 diarrhea events observed in Cohort 1B, antidiarrheal prophylaxis will be required for all participants enrolled in Cohorts 1D, 1E, and for all participants in Cohort 2A who are treated with tucatinib + trastuzumab + pembrolizumab + mFOLFOX6. As of 12-Dec-2023, 5 participants were enrolled and treated in Cohort 2B. Tucatinib-related Grade 3 diarrhea was reported in 2 of 5 participants during the first 42-days of study treatment. Based on this finding, loperamide prophylaxis is now required for Cohort 2B. Beginning on Cycle 1 Day 1, loperamide will be administered at a dose of 4 mg three times daily for 14 days (Days 1-14), followed by 4 mg twice daily on Days 15-42 (see also Section 7.11.2). The first dose of loperamide must be administered concomitantly with the first dose of tucatinib. The dosing of loperamide should be titrated such that participants have 1-2 stools per day throughout Days 1-42 and afterwards, as necessary. The dose of loperamide can modified, or loperamide can be held at any point during the study as per investigator discretion if participant has constipation or <1 stool per day. Following this initial 42-day period, participants may continue on antidiarrheal prophylaxis at a dose of 2 to 4 mg as needed, not to exceed 16 mg per day.

Antidiarrheal prophylaxis, as described above, will not be required for participants enrolled in Cohorts 1C, 1F, and 1G, or for participants in Cohort 2A who are treated with tucatinib + trastuzumab + pembrolizumab + CAPOX, unless recommended by the SMC and required by the Sponsor based on a review of the data from these cohorts during the course of the study. Should antidiarrheal prophylaxis be required, the dose and schedule of loperamide as described above will be followed (see also Section 7.11.2). Participants must be instructed on the optimal use of antidiarrheals for symptomatic control of treatment-associated diarrhea as described in Section 7.9.9.

5.1.1. Phase 1b Tucatinib Dose Escalation With Trastuzumab and FOLFOX (Cohort 1A and 1B)

The dose escalation portion of the study will determine the recommended dose of tucatinib to be administered with oxaliplatin-based chemotherapy.

5.1.1.1. Trastuzumab and FOLFOX – Cohort 1A

For the tucatinib dose escalation utilizing FOLFOX (Cohorts 1A and 1B) (Figure 1), participants should be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment prior to enrollment and may have received up to 2 consecutive cycles of FOLFOX (≤85 mg/m^2 oxaliplatin per 2-week cycle) during the screening period prior to Cycle 1 Day 1 of study treatment. If participants have received oxaliplatin in prior cycles at doses higher than 85 mg/m^2, there must be a minimum of 28 days from the last dose of the previous regimen prior to Cycle 1 Day 1 of treatment in this study. Concurrent treatment with anti-VEGF antibodies is prohibited while on trial. There is no upper limit for the number of prior lines of therapy received, and prior exposure to oxaliplatin is allowed, provided the participant had not experienced Grade ≥3 hypersensitivity due to oxaliplatin.

Enrolled participants will be treated with FOLFOX, trastuzumab, and tucatinib given in 14-day cycles. After enrolling on study, participants in Cohort 1A will receive 7 days of FOLFOX and trastuzumab without tucatinib. The starting dose of tucatinib for Cohort 1A is

150 mg orally (PO) BID and the first dose will be administered on Cycle 1 Day 8 and continuously thereafter until the participant comes off study. Participants should receive prophylaxis for chemotherapy induced nausea and vomiting as per the investigator's institutional standards. Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure.

5.1.1.2. Trastuzumab and FOLFOX - Cohort 1B

Participants in Cohort 1B should be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment prior to enrollment and may have received up to 2 consecutive cycles of FOLFOX (≤85 mg/m^2 oxaliplatin per 2-week cycle) during the screening period prior to Cycle 1 Day 1 of study treatment. If participants have received oxaliplatin in prior cycles at doses higher than 85 mg/m^2, there must be a minimum of 28 days from the last dose of the previous regimen prior to Cycle 1 Day 1 of treatment in this study. Concurrent treatment with anti-VEGF antibodies is prohibited while on trial. There is no upper limit for the number of prior lines of therapy received, and prior exposure to oxaliplatin is allowed, provided the participant had not experienced Grade ≥3 hypersensitivity due to oxaliplatin.

Enrolled participants will be treated with FOLFOX, trastuzumab, and tucatinib given in 14-day cycles. After enrolling on study, participants in Cohort 1B will receive 7 days of FOLFOX and trastuzumab without tucatinib. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the safety monitoring committee [SMC]) will be administered on Cycle 1 Day 8 and continuously thereafter until the participant comes off study. Participants should receive prophylaxis for chemotherapy induced nausea and vomiting as per the investigator's institutional standards. Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure.

5.1.1.3. Dose-escalation Process

Dose-escalation will use a 3+3 design to determine a safe dose of tucatinib combined with oxaliplatin by assessing renal DLTs (See Section 5.1.5). A renal DLT is defined as a sustained increase in serum cystatin C >1.5× baseline that is not related to pre-renal or post-renal etiologies (including disease progression, dehydration and intercurrent illness) and occurs during the period of treatment with tucatinib in combination with trastuzumab and FOLFOX between the first dose of tucatinib and the end of Cycle 3.

Approximately 5 participants may be enrolled and treated with tucatinib at the 150 mg BID dose level to ensure there are at least 3 DLT-evaluable participants for the SMC review (Figure 1; Cohort 1A). Once the 3 participants are evaluable for renal DLT (Section 5.1.5), enrollment will be paused, and the SMC will undertake a safety evaluation.

- If no renal DLTs are observed at the 150 mg BID dose level, the SMC may recommend escalating to the 300 mg BID dose level, with approximately 8 participants being enrolled in Cohort 1B treated at this dose to ensure at least 6 DLT and PK-evaluable participants in Cohort 1B.

- If ≤1 renal DLTs are observed in 6 DLT-evaluable participants treated at the 300 mg BID dose level in Cohort 1B, this will be declared the recommended phase 2 dose of tucatinib with oxaliplatin-based chemotherapy.
- If 1 renal DLT is observed at the 150 mg BID dose level in Cohort 1A, an additional 3 participants (for a total of 6 evaluable participants) will be treated at this dose level. Once 6 participants are evaluable for renal DLTs, enrollment will be paused, and the SMC will undertake a safety evaluation.
    - If 1 renal DLT is observed in the 6 participants treated at 150 mg BID in Cohort 1A, the SMC may recommend escalation to the 200 mg BID or 250 mg BID dose level. The SMC may also recommend an alternative dose level/schedule as warranted by the cumulative safety data.

    – If 1 renal DLT is observed in the first 3 participants at an intermediate dose, an additional 3 participants (for a total of 6 evaluable participants) will be treated at this dose level and the SMC will evaluate dose escalation if no further DLTs are observed.

    – If the dose escalation has proceeded from 150 mg to 200 mg or 250 mg, and ≥2 renal DLTs are observed in up to 6 evaluable participants treated at this level, then the SMC may recommend dose de-escalation to the 150 mg or 200 mg dose level, respectively.
- If ≥2 renal DLTs are observed in the first 3 or 6 participants treated at the 150 mg BID dose level in Cohort 1A, alternative dose levels and/or regimens <150 mg BID may be considered by the SMC.
- If ≥2 renal DLTs are observed in the 6 DLT-evaluable participants treated at the 300 mg dose level (Cohort 1B) (or ≥33% of participants if more than 6 participants are enrolled in a cohort), dose levels of 250 and/or 200 mg may be explored, or an alternative dose level/schedule as recommended by the SMC.

In addition to renal DLTs, the SMC will take into consideration other adverse events (AEs) when making the determination to escalate, de-escalate, or declare the recommended dose level. The criteria for these additional AEs to be considered are provided in Section 5.1.7.1. Additional safety experiences in later cycles will also be considered when confirming the recommended dose. Based on the totality of the safety data, the SMC may recommend expanding enrollment to either cohort with continued monitoring for safety by the SMC, evaluation of alternative dosing, or supportive care measures for the management of AEs.

Dose modifications are described in Section 7.9.

5.1.2. Phase 1b Safety Evaluation with Trastuzumab and CAPOX (Cohort 1C) or with Trastuzumab and Pembrolizumab-Containing Combinations (Cohorts 1E, 1F, 1G)

After the recommended dose of tucatinib with oxaliplatin-based chemotherapy has been identified, additional cohorts may be opened to further evaluate the safety and tolerability of tucatinib combined with the following regimens:

- Trastuzumab + CAPOX (Cohort 1C)
- Pembrolizumab + Trastuzumab + FOLFOX (Cohort 1E)

- Pembrolizumab + Trastuzumab + CAPOX (Cohort 1F)
- Pembrolizumab + Trastuzumab (Cohort 1G)

Participants will be closely followed for unacceptable toxicities for either 21-days (for participants enrolled in Cohorts 1C, 1F, or 1G) or 28 days (for participants enrolled in Cohort 1E) after the first dose of study intervention (ie, the DLT evaluation period) for the occurrence of specific AEs that are deemed to be dose-limiting. If 3 or more DLTs are observed in a cohort, enrollment to that cohort may be delayed to further examine safety data and consider study design changes as recommended by the SMC.

5.1.2.1. Trastuzumab and CAPOX (Cohort 1C)

Participants in Cohort 1C (Figure 1) should be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment prior to enrollment. Eligible participants may have received oxaliplatin-based chemotherapy (1 cycle of CAPOX at a dose of $\leq$130 mg/m^2 per 3-week cycle or 2 consecutive cycles of FOLFOX at a dose of $\leq$85 mg/m^2 per 2-week cycle) during the screening period prior to Cycle 1 Day 1. Concurrent treatment with anti-VEGF antibodies is prohibited while on trial. There is no upper limit for the number of prior lines of therapy received, and prior exposure to oxaliplatin is allowed, provided the participant had not experienced Grade $\geq$3 hypersensitivity due to oxaliplatin.

Enrolled participants will be treated with CAPOX, trastuzumab, and tucatinib given in 21-day cycles. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) will be administered on Cycle 1 Day 1. Participants should receive prophylaxis for chemotherapy induced nausea and vomiting as per the investigator's institutional standards. Participants must be instructed on the optimal use of antidiarrheals for symptomatic control of treatment-associated diarrhea as described in Section 7.9.9.

Antidiarrheal prophylaxis will not be required for participants enrolled in Cohort 1C, unless recommended by the SMC and required by the Sponsor based on a review of the data from this cohort.

The SMC will review safety data after 3 participants in this cohort are treated without antidiarrheal prophylaxis.

- If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in $\leq$1 participant, treatment without antidiarrheal prophylaxis is continued and evaluated in 3 more participants in this cohort.
    - If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in $\leq$1 of 6 participants, antidiarrheal prophylaxis will not be required in this cohort.
    - If Grade 3 or higher diarrhea events are observed in $\geq$2 of 6 participants, antidiarrheal prophylaxis will be required in this cohort.
- If Grade 3 or higher diarrhea events without optimal use of antidiarrheals are observed in 2 or more participants, antidiarrheal prophylaxis will be required in this cohort.

Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure.

Approximately 8 participants will be enrolled to ensure that 6 participants complete 1 cycle of tucatinib + trastuzumab + CAPOX. If 8 participants are enrolled, enrollment may remain open to ensure at least 3 to 6 participants from Japan are enrolled in this cohort.

Once at least 6 participants have completed 1 cycle and are evaluable for safety, the SMC will evaluate whether the combination is safe and tolerable. The SMC will review the totality of the safety data, with a focus on DLTs described in Section 5.1.7.2. Additional safety experiences in later cycles will also be considered. The SMC may also recommend expanding enrollment to the cohort with continued monitoring for safety or evaluation of alternative dosing.

5.1.2.2. Pembrolizumab, Trastuzumab, FOLFOX (Cohort 1E)

Cohort 1E will evaluate the safety and tolerability of tucatinib combined with pembrolizumab, trastuzumab, and modified FOLFOX (mFOLFOX6) in participants with unresectable or metastatic HER2+ gastric, esophageal, or GEJ adenocarcinoma who have not previously received treatment for metastatic/unresectable disease in the 1L setting. Participants in Cohort 1E should be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment prior to enrollment. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) will be administered on Cycle 1 Day 1).

Enrolled participants will be treated with mFOLFOX6 and tucatinib given in 14-day cycles. Trastuzumab will be given in 21-day cycles. Pembrolizumab will be given in 42-day cycles. Antidiarrheal prophylaxis will also be administered for the first 42 days of study treatment and as needed thereafter (see Section 7.11.2).

Approximately 8 participants may be enrolled to ensure that 6 participants complete 28 days of study treatment. If 8 participants are enrolled, enrollment may remain open to ensure at least 3 to 6 participants from Japan are enrolled in this cohort.

Once at least 6 participants have completed 2 cycles of tucatinib + pembrolizumab + trastuzumab + FOLFOX, the SMC will evaluate whether the combination is safe and tolerable. The SMC will review the totality of the safety data, with a focus on the DLTs described in Section 5.1.6. Additional safety experiences in later cycles will also be considered. The SMC may also recommend expanding enrollment to the cohort with continued monitoring for safety or evaluation of alternative dosing.

5.1.2.3. Pembrolizumab, Trastuzumab, CAPOX (Cohort 1F)

Cohort 1F will evaluate the safety and tolerability of tucatinib combined with pembrolizumab, trastuzumab, and CAPOX in participants with unresectable or metastatic HER2+ gastric, esophageal, or GEJ adenocarcinoma who have not previously received treatment for metastatic/unresectable disease in the 1L setting. Participants in Cohort 1F should be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment prior to enrollment. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) will be administered on Cycle 1 Day 1.

Enrolled participants will be treated with CAPOX, trastuzumab, and tucatinib given in 21-day cycles. Pembrolizumab will be given in 42-day cycles. Participants must be instructed on

the optimal use of antidiarrheals for symptomatic control of treatment-associated diarrhea as described in Section 7.9.9.

Antidiarrheal prophylaxis will not be required for participants enrolled in Cohort 1F, unless recommended by the SMC and required by the Sponsor based on a review of the data from this cohort.

The SMC will review safety data after 3 participants in this cohort are treated without antidiarrheal prophylaxis.

- If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in ≤1 participant, treatment without antidiarrheal prophylaxis is continued and evaluated in 3 more participants in this cohort.
    - If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in ≤1 of 6 participants, antidiarrheal prophylaxis will not be required in this cohort.
    - If Grade 3 or higher diarrhea events are observed in ≥2 of 6 participants, antidiarrheal prophylaxis will be required in this cohort.
- If Grade 3 or higher diarrhea events without optimal use of antidiarrheals are observed in 2 or more participants, antidiarrheal prophylaxis will be required in this cohort.

Approximately 8 participants will be enrolled to ensure that 6 participants complete 21 days of study treatment. If 8 participants are enrolled, enrollment may remain open to ensure at least 3 to 6 participants from Japan are enrolled in this cohort.

Once at least 6 participants have completed 21 days of study treatment, a comprehensive review of the safety profile by the SMC will occur. Based on the totality of the safety data, the SMC may declare the combination safe and tolerable, or may recommend expanding enrollment to the cohort with continued monitoring for safety by the SMC, or may recommend evaluation of alternative dosing

5.1.2.4. Trastuzumab, Pembrolizumab (Cohort 1G)

Cohort 1G will evaluate the safety and tolerability of tucatinib combined with pembrolizumab and trastuzumab in participants with unresectable or metastatic HER2+ gastric, esophageal, or GEJ adenocarcinoma who have not previously received treatment for metastatic/unresectable disease in the 1L setting. This cohort may be opened based on SMC review of the safety results from Cohorts 1A, 1B, 1C, 1E, and/or 1F. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) will be administered on Cycle 1 Day 1.

Enrolled participants will be treated with trastuzumab and tucatinib given in 21-day cycles. Pembrolizumab will be given in 42-day cycles. Participants must be instructed on the optimal use of antidiarrheals for symptomatic control of treatment-associated diarrhea as described in Section 7.9.9.

Antidiarrheal prophylaxis will not be required for participants enrolled in Cohort 1G, unless recommended by the SMC and required by the Sponsor based on a review of the data from this cohort.

The SMC will review safety data after 3 participants in this cohort are treated without antidiarrheal prophylaxis.

- If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in ≤1 participant, treatment without antidiarrheal prophylaxis is continued and evaluated in 3 more participants in this cohort.
    - If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in ≤1 of 6 participants, antidiarrheal prophylaxis will not be required in this cohort.
    - If Grade 3 or higher diarrhea events are observed in ≥2 of 6 participants, antidiarrheal prophylaxis will be required in this cohort.
- If Grade 3 or higher diarrhea events without optimal use of antidiarrheals are observed in 2 or more participants, antidiarrheal prophylaxis will be required in this cohort.

Approximately 8 participants will be enrolled to ensure that 6 participants complete 21 days of study treatment. If 8 participants are enrolled, enrollment may remain open to ensure at least 3 to 6 participants from Japan are enrolled in this cohort.

Once at least 6 participants have completed 21 days of study treatment and are evaluable for safety, a comprehensive review of the safety profile by the SMC will occur. Based on the totality of the safety data, the SMC may declare the combination safe and tolerable, or may recommend expanding enrollment to the cohort with continued monitoring for safety by the SMC or may recommend evaluation of alternative dosing.

5.1.3. Phase 1b Tucatinib Japan Safety Evaluation in Combination with Trastuzumab and FOLFOX (Cohort 1D)

After the recommended dose of tucatinib with oxaliplatin-based chemotherapy has been identified, Cohort 1D will evaluate the safety and tolerability of tucatinib combined with trastuzumab and mFOLFOX6 in Japanese participants with HER2+ GI malignancies.

A minimum of 3 participants will be enrolled and receive tucatinib (at the recommended dose determined in phase 1b dose escalation) trastuzumab, and mFOLFOX6. Enrolled participants will be treated with mFOLFOX6 and tucatinib given in 14-day cycles; trastuzumab will be given every 21 days. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) will be administered on Cycle 1 Day 1 and continuously thereafter until the participant comes off study. Antidiarrheal prophylaxis will also be administered for the first 42 days of study treatment and as needed thereafter (see Section 7.11.2). Participants will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, death, or study closure. Dose modifications due to AEs will be permitted and guidelines regarding the resumption or discontinuation of study treatment will be followed per Section 7.9. Data from participants who are not DLT-evaluable will be included in the safety evaluation.

Participants in the Japan-specific cohort will be carefully monitored through the first cycle of treatment and evaluated for AEs that are unexpected based on the known safety profile of each individual agent and of the combination of tucatinib, trastuzumab, and oxaliplatin-based chemotherapy. Investigators must ensure that participants do not have other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or

compliance with study procedures required per the protocol (such as compliance with additional study visits, laboratory assessments, oral medications, and close outpatient monitoring). During the first cycle, the participant may be hospitalized for a minimum of 15 days with discharge permitted if a participant has no ongoing ≥ Grade 3 AEs and is otherwise considered appropriate for discharge by the investigator based on history (which includes assessment of any new or ongoing AEs and concomitant medication use), physical exam (including vital signs), and laboratory evaluations (including complete blood count [CBC], blood chemistry, renal function tests, and liver enzyme tests). For participants undergoing outpatient follow-up, the investigator must ensure that the participant will be followed closely in the outpatient setting by methods they determine to be appropriate to assure the participant's safety, and participants should be instructed to contact the investigator immediately in the event they experience an AE. In case of emergency, adequate means of communication between the site and the participant should be ensured by the investigator regardless of time of day or in the event of a holiday.

The global medical monitor, Japanese investigators, study statistician, and other study team members will conduct an evaluation of overall safety after 3 participants have enrolled and completed 28 days of study treatment. If the overall safety in the first 3 participants enrolled is deemed acceptable, no further enrollment will take place. If one DLT is observed, an additional 3 participants will be enrolled. If a DLT is reported for 1/6 participants, treatment is considered to be tolerated; if 2/6 DLTs are observed, the investigators and sponsor will evaluate the totality of the safety data and determine if the regimen is safe and tolerable. If 3 or more DLTs are observed, enrollment to the cohort may be delayed to further examine safety data and consider study design changes. Ad hoc meetings with the global medical monitor, Japanese investigators, study statistician, and other study team members may be called to review safety data as needed.

5.1.4. Phase 2 Tumor Specific Expansion Cohorts

Tumor specific expansion cohorts (Figure 1) may be enrolled following the completion of phase 1b, to determine safety and tolerability of the specific regimens to be evaluated in the Phase 2 cohorts.

5.1.4.1. Phase 2 Tumor Specific Expansion Cohort 2A

A 1L HER2+ gastric, esophageal or GEJ adenocarcinoma expansion cohort for tucatinib in combination with pembrolizumab, trastuzumab, and mFOLFOX6 or CAPOX (Cohort 2A) may be enrolled with approximately 40 participants. Enrollment will be gated on SMC review of data from Cohorts 1E and 1F. Antidiarrheal prophylaxis will also be administered for the first 42 days of study treatment for participants who are treated with mFOLFOX6. Participants in Cohort 2A treated with CAPOX will not require antidiarrheal prophylaxis unless recommended by the SMC and required by the Sponsor based on a review of the data from Cohort 1C and/or Cohort 1F. Antidiarrheal prophylaxis, if required, will be followed as described in Section 7.11.2.

The primary objective for Cohort 2A will be evaluation of the safety and tolerability of tucatinib combined with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy. Secondary objectives will include evaluation of the anti-tumor activity of tucatinib given in combination with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy.

Exploratory objectives will include evaluation of the PK of tucatinib given in combination with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy.

5.1.4.2. Phase 2 Tumor Specific Expansion Cohort 2B

A 1L+ HER2+ CRC tumor specific expansion cohort for tucatinib in combination with trastuzumab and mFOLFOX6 (Cohort 2B) may also be enrolled with approximately 20 participants. Enrollment will be gated on SMC review of data from Cohort 1B (including DLT frequency and PK data). The primary objective for Cohort 2B will be evaluation of the safety and tolerability of tucatinib given in combination with trastuzumab and oxaliplatin-based chemotherapy. Exploratory objectives will include evaluation of anti-tumor activity and the PK of tucatinib given in combination with trastuzumab and oxaliplatin-based chemotherapy.

Participants must be instructed on the optimal use of antidiarrheals for symptomatic control of treatment-associated diarrhea as described in Section 7.9.9.

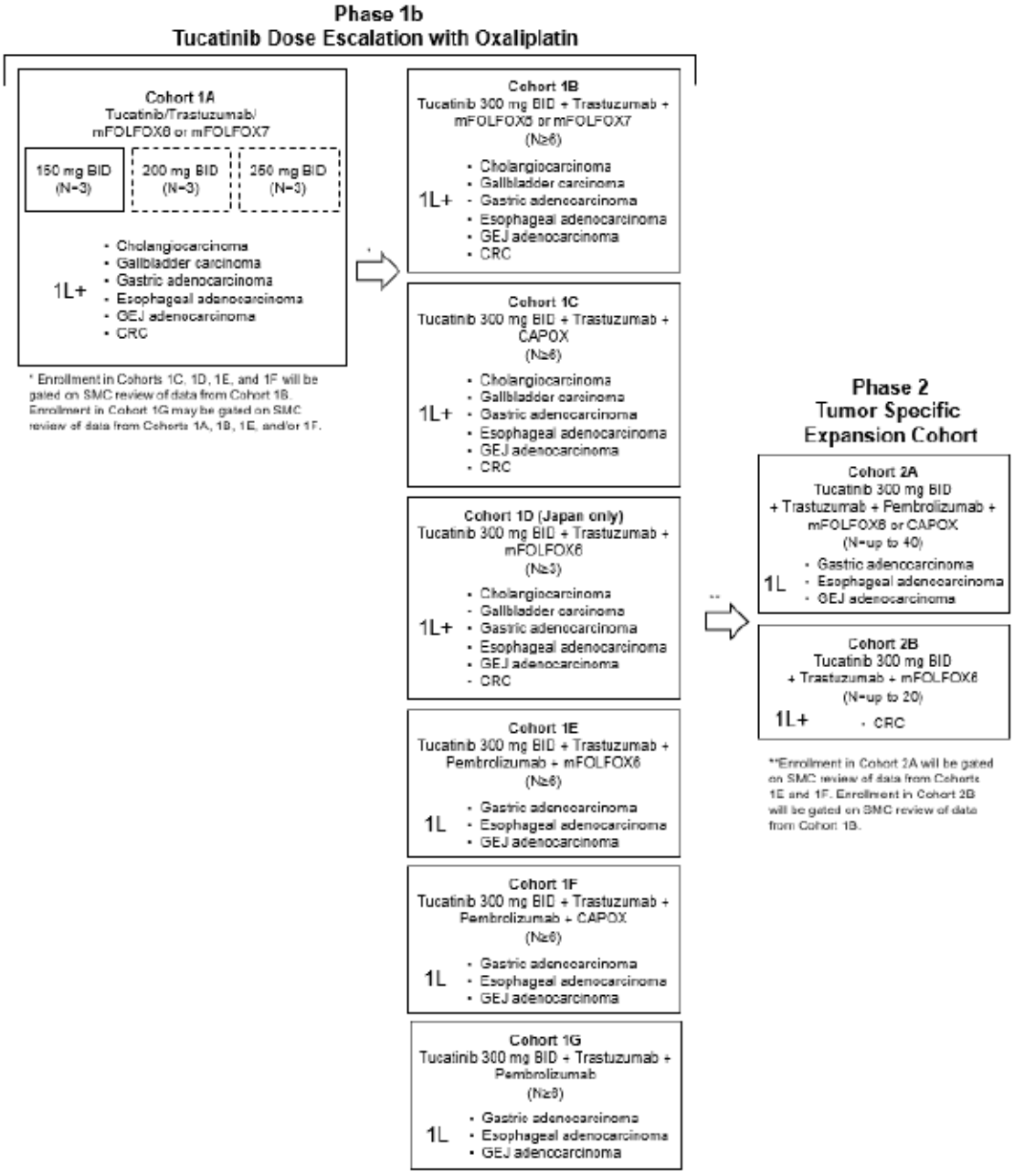
The SMC will review safety data after 3 participants in Cohort 2B are treated without antidiarrheal prophylaxis.

- If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in ≤1 participant, treatment without antidiarrheal prophylaxis is continued and evaluated in 3 more participants in this cohort.
    - If Grade 3 or higher treatment-related diarrhea events without optimal use of antidiarrheals are observed in ≤1 of 6 participants, antidiarrheal prophylaxis will not be required in this cohort.
    - If Grade 3 or higher diarrhea events are observed in ≥2 of 6 participants, antidiarrheal prophylaxis will be required in this cohort.
- If Grade 3 or higher diarrhea events without optimal use of antidiarrheals are observed in 2 or more participants, antidiarrheal prophylaxis will be required in this cohort.

As of 12-Dec-2023, 5 participants were enrolled and treated in Cohort 2B. Tucatinib-related Grade 3 diarrhea was reported in 2 of 5 participants during the first 42-days of study treatment. Based on this finding, loperamide prophylaxis is now required for Cohort 2B. Antidiarrheal prophylaxis will be followed as described in Section 7.11.2.

A study schema is provided in Figure 1. See Appendix A for a schedule of events.

Figure 1: Study design



5.1.5. Renal Dose-limiting Toxicity for Phase 1b Dose Escalation (Cohort 1A, 1B)

A renal DLT is defined as an increase in serum cystatin C >1.5× baseline that is not related to pre-renal or post-renal etiologies (including disease progression, dehydration and intercurrent illness), and occurs during the period of treatment with tucatinib in combination with trastuzumab and FOLFOX between the first dose of tucatinib and the end of Cycle 3.

Increases of serum cystatin C for which there is an alternative clinical explanation (eg, clearly related to an intercurrent illness or disease progression) will not be considered renal DLTs. The relationship of an increase in serum cystatin C to study treatment will be determined by the investigator. In the event that it is not clear if the laboratory abnormality

meets the criteria for a renal DLT, the study medical monitor should be contacted, and the SMC consulted as needed.

Participants in Cohorts 1A and 1B will be considered DLT-evaluable if they have met one of the following criteria: (1) had a renal DLT or (2) had taken at least 75% of planned oxaliplatin, and tucatinib doses per cycle and been followed for at least 2 cycles of study treatment (through the end of Cycle 3 of FOLFOX), inclusive of dose delays. Participants that are determined not to be DLT-evaluable will be replaced.

The starting dose level of tucatinib will be 150 mg PO BID in Cohort 1A. This dose will be initiated on Cycle 1 Day 8, which will allow assessment of oxaliplatin PK in the absence of tucatinib and will be given continuously with each subsequent 14-day cycle of treatment until unacceptable toxicity, disease progression, withdrawal of consent, death, or study closure. Participants enrolled on Cohort 1B will be treated with tucatinib (300 mg PO BID or intermediate dose) starting on Cycle 1 Day 8. The SMC will be responsible for monitoring the safety of participants at regular intervals (see Section 5.1.7). Tucatinib dose in Cohorts 1B will be based on recommendations from the SMC after evaluation of the Cohort 1A data. The tucatinib dose to be used in all subsequent oxaliplatin-containing cohorts of the study (Cohorts 1C-1F and 2A-2B) will be determined by the SMC after review of the Cohort 1B data (FOLFOX).

5.1.6. Dose-limiting Toxicities for Phase 1b Safety Evaluation of Tucatinib with Trastuzumab + CAPOX (Cohort 1C), Tucatinib with Trastuzumab + Pembrolizumab-Containing Combinations (Cohorts 1E, 1F, 1G), and Japan Safety Evaluation with Tucatinib with Trastuzumab + FOLFOX (Cohort 1D)

For participants enrolled in Cohorts 1C, 1D, 1E, 1F, and 1G, DLTs will be AEs or laboratory abnormalities that occur during the defined DLT period for each cohort (21 days for Cohorts 1C, 1F, and 1G; 28 days for Cohorts 1D and 1E). DLTs will be AEs or laboratory abnormalities that are considered to be related to tucatinib or tucatinib in combination with chemotherapy (mFOLFOX6/CAPOX) and/or trastuzumab and/or pembrolizumab. DLT is defined as any of the following:

Hepatic

- Any instance of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >3× upper limit of normal (ULN) AND total bilirubin >2× ULN that is NOT thought to be due to disease progression or other medical illness

Non-hematologic

- Any clinically significant, non-hematologic treatment-related AE ≥ Grade 3, with the following exceptions:
  - Grade 3 fatigue ≤7 days
  - Grade 3 diarrhea, nausea, or vomiting without optimal use of anti-emetics or antidiarrheals
  - Grade 3 rash without maximal use of corticosteroids or anti-infectives

Hematologic:

- ≥ Grade 3 febrile neutropenia
- Absolute neutrophil count (ANC) decreased Grade 4 for >7 days
- Thrombocytopenia Grade 4, or Grade 3 associated with significant bleeding
- Grade 4 anemia

AEs or laboratory abnormalities that are attributed only to trastuzumab and/or chemotherapy (mFOLFOX6/CAPOX) and/or pembrolizumab alone will not be considered DLTs. Events for which there is an alternative clinical explanation (eg, clearly related to an intercurrent illness or disease progression), will not be considered DLTs.

Participants will be considered evaluable for DLT if they received at least 75% of the planned administrations of each study intervention and were followed during the DLT period, or if they experienced a DLT during the DLT period.

Participants who experience a DLT may continue on study treatment if treatment discontinuation is not required by protocol dose modification criteria (Section 7.9) and the investigator believes it to be in the participant's interest.

5.1.7. Safety Monitoring Committee

5.1.7.1. Phase 1b Tucatinib Dose Escalation with Trastuzumab and FOLFOX (Cohorts 1A, 1B)

The SMC will be responsible for monitoring the safety of participants at regular intervals and will meet after all participants in Cohort 1A are DLT-evaluable and again after all participants in Cohort 1B are DLT-evaluable. In particular, the SMC will evaluate renal DLTs, overall safety data, and PK data (if available) at each evaluation of a dose level during the phase 1b dose escalation portion of the study. The SMC will look at the cumulative data including deaths, discontinuations, dose reductions, AEs, and serious adverse events (SAEs), and PK data on a regular basis.

In addition to renal DLTs (Section 5.1.5), the SMC will take into consideration other AEs when making the determination to escalate, de-escalate, or declare the recommended dose level in dose escalation. The AEs must be determined to be related to tucatinib, tucatinib in combination with FOLFOX and/or trastuzumab and not attributed to FOLFOX and/or trastuzumab alone.

Hepatic

- Any instance of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >3× upper limit of normal (ULN) AND total bilirubin >2× ULN that is NOT thought to be due to disease progression or other medical illness

Non-hematologic

- Any clinically significant, non-hematologic treatment-related AE ≥ Grade 3, with the following exceptions:
  - Grade 3 fatigue ≤7 days

- Grade 3 diarrhea, nausea, or vomiting without optimal use of anti-emetics or antidiarrheals
- Grade 3 rash without maximal use of corticosteroids or anti-infectives

Hematologic:

- ≥ Grade 3 febrile neutropenia
- Absolute neutrophil count (ANC) decreased Grade 4 for >7 days
- Thrombocytopenia Grade 4, or Grade 3 associated with significant bleeding
- Grade 4 anemia

The SMC will make recommendations to the sponsor regarding the conduct of the study, including changes to dose levels/administration schedule, expansion of cohorts to enroll additional participants, and make recommendations concerning study continuation as planned, protocol amendment, or early discontinuation of the study for excessive toxicity. The sponsor will provide a copy of each SMC recommendation to the investigators.

Further details are documented in the study SMC charter.

5.1.7.2. Phase 1b Safety Evaluation of Tucatinib with Trastuzumab and CAPOX or with Trastuzumab and Pembrolizumab-Containing Combinations (Cohorts 1C, 1E, 1F, 1G)

Should participants enroll to Cohorts 1C, 1E, 1F, or 1G, the SMC will be responsible for monitoring the safety of participants in these cohorts at regular intervals. In particular, the SMC will evaluate DLTs as described in Section 5.1.7 and other safety data; PK data may also be evaluated, if available.

The SMC will make recommendations to the sponsor regarding the conduct of the study, including changes to dose levels/administration schedule, expansion of cohorts to enroll additional participants, and make recommendations concerning study continuation as planned, protocol amendment, or early discontinuation of the study for excessive toxicity. The sponsor will provide a copy of each SMC recommendation to the investigators.

Further details are documented in the study SMC charter.

5.1.7.3. Phase 2 Tumor-Specific Expansion (Cohorts 2A, 2B)

The SMC will be responsible for monitoring the safety of participants at regular intervals, in particular, the SMC will evaluate AEs, SAEs, treatment modifications, laboratory abnormalities, and deaths and may make recommendations to the sponsor regarding the conduct of the study.

5.1.8. Long-term Extension Phase

No additional enrollment to any cohort will occur as of Amendment 5.

Participants still on study treatment who have not met a protocol defined reason for end of treatment may continue into the LTEP. Participants who have experienced progressive disease, ended study treatment, or are in long term follow-up will not proceed to the LTEP. During the LTEP, only information related to pregnancies and SAEs will be reported to the Sponsor. All safety and efficacy assessments will be performed per institutional guidelines

and investigator-determined usual and customary clinical care, with the exception of pregnancy testing which will continue as outlined in the schedule of events for participants of childbearing potential. Participants enrolled in the LTEP may remain on study treatment until unacceptable toxicity, disease progression, withdrawal of consent, death, or study closure.

5.1.9. End of Study

The study will end when the last LTEP participant has had their last visit/contact. Participants in long-term follow-up will have a last visit/contact upon implementation of Amendment 5. Pembrolizumab will be given for a maximum of 18 doses (Cohorts 1E, 1F, 1G, 2A); study treatment will continue in these cohorts until unacceptable toxicity, disease progression, withdrawal of consent, death, or study closure. In addition, the sponsor may terminate the study at any time (see Section 12.1).

5.2. Discussion and Rationale for Study Design

This phase 1b/2 study is designed to determine the recommended dose of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy. Specifically, the theoretical potential for oxaliplatin induced nephrotoxicity as a result of multidrug and toxin extrusion (MATE) protein inhibition will be assessed. The study will be conducted using a standard 3+3 design and include 2 tucatinib dose levels. Intermediate dose levels or alternate dosing schedules may be explored based upon SMC recommendations. Once the initial dose of tucatinib (150 mg) is deemed safe by the SMC, an escalation cohort (Cohort 1B) with up to 8 participants (to ensure 6 DLT-evaluable and PK evaluable participants) will be enrolled with a tucatinib dose of 300 mg (or intermediate dose) in combination with trastuzumab and FOLFOX. FOLFOX is established as safe and effective for the treatment of GI cancers. Additionally, the study may assess the safety, tolerability, and efficacy of tucatinib in combination with trastuzumab and CAPOX or pembrolizumab-containing combinations.

In addition to the primary endpoint of safety and tolerability, secondary endpoints will assess the PK of tucatinib and oxaliplatin when used in combination. A preliminary analysis of efficacy in the phase 1b portion of the study, based on ORR, may be performed. Efficacy analyses are planned during the phase 2 portion of the study.

5.2.1. Method of Assigning Participants to Treatment Groups

This is an open-label, dose escalation and expansion study. Following informed consent and screening assessments, eligible participants with HER2+ GI malignancies will be assigned to currently enrolling cohorts. When disease specific cohorts are opened, participants will be enrolled on the basis of the participants' disease type.

5.2.2. Rationale for Selection of Doses

In vitro studies using transfected MDCKII cells showed that tucatinib similarly inhibited OCT2 and MATE1-mediated transport of creatinine and oxaliplatin. The initial dose level of tucatinib was chosen based on PK modeling that showed that the 150 mg dose level resulted in minimal MATE inhibition, as assessed by serum creatinine. Therefore, if a drug-drug interaction (DDI) truly exists, this dose level should have minimal impact on the disposition of oxaliplatin.

Results from a clinical drug interaction study (SGNTUC-020) in healthy volunteers with metformin (a substrate of MATE 1/2-K) showed that co-administration of tucatinib (multiple

doses, 300 mg BID) with metformin increased the metformin plasma exposure by 48% and caused a transient increase in serum creatinine level without any effect on kidney function. Measures of renal function including actual glomerular filtration rate (GFR) as assessed by iohexol and urine albumin levels were not affected by tucatinib. Thus, observed serum creatinine increase in clinical studies with tucatinib is due to inhibition of tubular secretion of creatinine via OCT2 and MATE1.

A clear dose-response relationship was observed in another healthy volunteer study (SGNTUC-015), where change in serum creatinine from baseline increased as tucatinib dose increased (50, 150, and 300 mg BID). Median serum creatinine maximum concentrations remained below ULN (NCI CTCAE v5.0 criteria) in participants receiving multiple doses of 150 mg BID tucatinib; thus, the change in serum creatinine in the presence of 150 mg BID was considered safe as it was due to transport inhibition and did not represent kidney injury.

Although the extent of oxaliplatin clearance due to tubular secretion via OCT2 and/or MATE1/2-K transport is not well characterized, the similarity of creatinine and oxaliplatin OCT2/MATE1/MATE2-K in vitro inhibition by tucatinib and the known dose-response of serum creatinine changes in the presence of tucatinib in healthy volunteers were used to infer that oxaliplatin disposition at the proximal tubule level might similarly be tucatinib dose-dependent.

Despite this theoretical risk, several MATE transporter inhibitors have been co-administered with oxaliplatin in the clinic without exhibiting apparent signs of acute kidney injury. In vitro inhibition data for both ondansetron and imatinib displayed potential for in vivo interaction with MATE (OCT2 to a much lesser extent) transporter substrates based on criteria as described in the 2020 in vitro interaction studies guidance (In Vitro Drug Interaction Studies-Cytochrome (CYP) P450 Enzyme- and Transporter-Mediated Drug Interactions; Guidance for Industry, 2020). Ondansetron is an anti-emetic that is recommended for prevention of chemotherapy induced nausea and vomiting. As FOLFOX is considered a moderately emetogenic regimen, ondansetron is frequently given prophylactically and as a treatment for nausea and vomiting associated with this regimen. It is also included as part of the American Society for Clinical Oncology and National Comprehensive Cancer Network guidelines as a recommended medication in this setting. Despite the potential for in vivo interaction based on MATE transporter inhibition, there are no recommended dose modifications for ondansetron when used in combination with oxaliplatin.

Imatinib, a second MATE transporter inhibitor, has been administered in combination with FOLFOX for patients with pancreatic cancer and metastatic CRC (Starling 2012; Hoehler 2013; Michael 2013). In these studies, with a total of 86 participants, there were no reports of renal toxicities. The most common DLTs reported were febrile neutropenia and Grade 3/4 neutropenia. Imatinib has also been administered in combination with 130 mg/m^2 oxaliplatin (such as is used in CAPOX) for patients with metastatic CRC with no reports of renal toxicities (Hoehler 2013).

As tucatinib in vitro data exhibited similar MATE/OCT2 inhibition propensity as ondansetron and imatinib, the clinical experience with ondansetron and imatinib in combination with oxaliplatin suggests a relatively low risk for dose escalating directly to 300 mg tucatinib BID (the therapeutic dose level) if no renal DLTs are observed with oxaliplatin in combination with 150 mg BID tucatinib.

FOLFOX regimens were chosen as they are well-tolerated and commonly utilized in the standard-of-care treatment for GI malignancies. Additionally, these regimens use a lower overall dose of oxaliplatin as compared to other FOLFOX regimens. The mFOLFOX6 regimen (14-day cycle) consists of oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2 (IV bolus), then fluorouracil 2400 mg/m^2 (IV administration over 46 hours). The mFOLFOX7 (14-day cycle) regimen consists of oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and fluorouracil 2400 mg/m^2 (IV administration over 46 hours). Participants receiving FOLFOX in Cohorts 1A and 1B may be dosed using either the mFOLFOX6 or mFOLFOX7 regimen per investigator preference but must remain on the same FOLFOX regimen throughout study participation. Participants enrolled in Cohorts 1D, 1E, 2A, and 2B will be treated with mFOLFOX6.

Trastuzumab is approved for treatment of HER2-overexpressing metastatic gastric or GEJ adenocarcinoma. In Cohorts 1A and 1B utilizing FOLFOX, trastuzumab will be given at a loading dose of 6 mg/kg in Cycle 1 followed by 4 mg/kg in subsequent cycles. The biweekly trastuzumab schedule has been evaluated in various phase 2 studies and been found to be safe and tolerable (Orlando 2014; Qiu 2014; Mondaca 2019).

In Cohorts 1C, 1D, 1E, 1F, 1G, 2A, and 2B, trastuzumab will be given as a loading dose of 8 mg/kg in Cycle 1 followed by 6 mg/kg in subsequent cycles (21-day cycles). This is the approved dosing schedule of trastuzumab in the treatment of HER2+ breast cancer and metastatic gastric or gastroesophageal junction adenocarcinoma.

In Cohort 1C, 1F and 2A, the CAPOX regimen (21-day cycle) was chosen as a chemotherapy backbone because it is well-tolerated and utilized in the treatment of metastatic CRC, esophageal, gastric, and GEJ adenocarcinoma (Hoehler 2013). The CAPOX regimen consists of 1000 mg/m^2 capecitabine (PO BID for 14 days) and oxaliplatin 130 mg/m^2 (IV, Day 1) given over a 21-day cycle. The addition of trastuzumab to CAPOX has been shown to be safe and tolerable (Rivera 2019).

Pembrolizumab is approved for the treatment of multiple GI malignancies, including microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR) CRC, esophageal adenocarcinoma, and HER2+ gastric or GEJ adenocarcinoma. The current approved dosing regimens of pembrolizumab for IV administration are 200 mg IV Q3W and 400 mg IV Q6W for adults. The planned dose of pembrolizumab in Cohorts 1E, 1F, 1G and 2A is 400 mg every 6 weeks. The 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate (Lala 2018). Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation analyses, given the following rationale:

Pharmacokinetic simulations demonstrating that in terms of pembrolizumab exposures:

- C_{avg} (or area under the concentration-time curve [AUC]) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
- Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.

- Maximum observed concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- Exposure-response for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and non-small cell lung cancer (NSCLC) show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

The results of an interim analysis of pembrolizumab or placebo plus trastuzumab and chemotherapy in participants with HER2+ metastatic gastric or GEJ cancer showed a significant improvement in ORR for participants in the experimental arm, while the incidence of AEs was similar between arms with no safety concerns observed (Janjigian 2021). The cORR (95% CI) was 74.4% (66.2-81.6) for pembrolizumab + SOC vs 51.9% (43.0-60.7) for placebo + SOC (difference, 22.7 percentage points [95% CI, 11.2-33.7], P = 0.00006. Based on the results of this study, accelerated approval was granted in the US for pembrolizumab plus trastuzumab and chemotherapy in the treatment of 1L HER2+ GEC. These results serve as the basis for evaluating tucatinib with pembrolizumab-containing regimens in Cohorts 1E, 1F, 1G, and 2A.

5.2.3. Blinding and Unblinding

This is an open-label study.

6. STUDY POPULATION

This study will enroll participants with unresectable or metastatic HER2+ gastric adenocarcinoma, esophageal adenocarcinoma, GEJ adenocarcinoma, CRC, cholangiocarcinoma, and gallbladder carcinoma.

Participants must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are participant to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

6.1. Inclusion Criteria

1. Participants must have an unresectable or metastatic solid malignancy that is histologically or cytologically confirmed to be one of the tumor types listed below:

   Cohorts 1A, 1B, 1C, and 1D

   - CRC
   - Gastric adenocarcinoma
   - GEJ adenocarcinoma
   - Esophageal adenocarcinoma
   - Cholangiocarcinoma
   - Gallbladder carcinoma

   Cohorts 1E, 1F, 1G, and 2A

- Gastric adenocarcinoma
- GEJ adenocarcinoma
- Esophageal adenocarcinoma

Cohort 2B

- CRC

2. Participants must be candidates to receive an oxaliplatin-based regimen as part of their standard-of-care treatment for all cohorts, with the exception of Cohort 1G. Participants in Cohorts 1A, 1B, 1C, or 2B can be receiving an oxaliplatin-based regimen during the screening period:
   - For Cohorts 1A and 1B: up to 2 consecutive cycles of FOLFOX (≤85 mg/m^2 oxaliplatin per 2-week cycle) may have been received during the screening period prior to Cycle 1 Day 1 of study treatment.
   - For Cohorts 1C: up to 2 consecutive cycles of FOLFOX (≤85 mg/m^2 oxaliplatin per 2-week cycle) or one cycle of CAPOX (≤130 mg/m^2 oxaliplatin per 3-week cycle) may have been received during the screening period prior to Cycle 1 Day 1 of study treatment.
   - For Cohorts 1A, 1B, 1C: if participant has received oxaliplatin in prior cycles at higher doses than those listed above, there must be a minimum of 28 days off treatment prior to Cycle 1 Day 1 of treatment in this study.
   - For Cohort 2B prior to enrollment (Cycle 1 Day 1):
     - Participants may have received up to 1 cycle of FOLFOX (≤85 mg/m^2 oxaliplatin per 2-week cycle) during the screening period prior to Cycle 1 Day 1 but may not have received prior oxaliplatin for metastatic disease
     - Oxaliplatin received in an adjuvant setting is permitted if >6 months prior to Cycle 1 Day 1
     - At least 21 days must have elapsed from prior systemic anticancer therapy (including hormonal and biologic therapy but excluding 1 cycle of FOLFOX), non-central nervous system radiation, and treatment with other experimental agents
3. HER2+ disease, as determined by historic or local laboratory testing based on one of the following:
   - For CRC, cholangiocarcinoma, and gallbladder carcinoma:
     - HER2 amplification or overexpression from fresh or archival tumor tissue utilizing one of the following tests processed in a Clinical Laboratory Improvement Amendments (CLIA)- or International Organization for Standardization (ISO)-accredited laboratory:
       - HER2 overexpression (3+ immunohistochemistry [IHC])

- HER2 (ERBB2) amplification by in situ hybridization assay (fluorescence in situ hybridization [FISH] or chromogenic in situ hybridization signal ratio ≥2.0 or gene copy number >6)
- HER2 (ERBB2) amplification by next generation sequencing (NGS) assay

  - HER2 amplification in a CLIA certified or ISO accredited blood-based NGS assay

- For Gastric, GEJ, and esophageal adenocarcinomas: HER2 overexpression/amplification by IHC and ISH (IHC3+ or IHC2+/ISH+) assay of a tumor tissue sample, processed in a CLIA- or ISO-accredited laboratory and evaluated following ASCO/CAP 2016 guidelines for HER2 testing in gastroesophageal adenocarcinoma.

4. Phase 1b cohorts: measurable or non-measurable disease according to RECIST v1.1 as determined by the investigator

   Phase 2 cohorts: measurable disease according to RECIST v1.1 as determined by the investigator

5. Age 18 years or older at time of consent or ≥ the age of majority per regional requirements
6. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix B)
7. Life expectancy ≥3 months, in the opinion of the investigator
8. Adequate hepatic function, as defined by:
   - Total bilirubin ≤1.5× ULN, except for participants with known Gilbert's disease, who may enroll if the conjugated bilirubin is ≤1.5× ULN
   - Transaminases (AST and ALT) ≤2.5× ULN (≤5× ULN if liver metastases are present)
9. Adequate baseline hematologic parameters as defined by:
   - ANC ≥1.5×10³/µL
   - Platelet count ≥100×10³/µL; participants with stable platelet count from 75–100×10³/µL may be included with approval from the medical monitor
   - Hemoglobin ≥8 g/dL. Participants on a stable dose of erythropoietin (≥ approximately 3 months) are eligible.
   - In participants transfused before study entry, transfusion must be ≥14 days prior to start of therapy to establish adequate hematologic parameters independent from transfusion support
10. Estimated GFR:
    - Cohorts 1A, 1B: ≥90 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) equation.

- Participants with estimated GFR ≥60 to <90 mL/min/1.73 m² may be enrolled in Cohort 1B with medical monitor approval.

- Cohorts 1C, 1D, 1E, 1F, 2A, and 2B: ≥60 mL/min/1.73 m² using the MDRD equation.

11. International normalized ratio (INR) and partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) ≤1.5× ULN, unless on medication known to alter INR and PTT/aPTT (Note: warfarin and other coumarin derivatives are prohibited for participants receiving CAPOX.)
12. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan documented within 4 weeks prior to enrollment.
13. Participants of childbearing potential, as defined in Section 6.3, under the following conditions:
    a Must have a negative serum/plasma or urine pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 24 hours before the first dose of study intervention. Participants with false positive results and documented verification that the participant is not pregnant are eligible for participation
    b Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study treatment
    c Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 7 months after the final dose of study treatment
    d If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix C) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study treatment.
14. Participants who can father children, under the following conditions:
    a Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 7 months after the final dose of study treatment
    b If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix C) starting at time of informed consent and continuing throughout the study and for at least7 months after the final dose of study treatment
    c If sexually active with a person who is pregnant or breastfeeding, must consistently use one of 2 contraception options (as defined in Appendix C) starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study treatment

15. Participant must provide signed informed consent that has been approved by an institutional review board/independent ethics committee (IRB/IEC) prior to initiation of any study related tests or procedures that are not part of standard-of-care for the participant's disease.
16. Participant must be willing and able to comply with study procedures, laboratory tests, and other requirements of the study. Participants with a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study are not eligible.
17. For participants with prior central nervous system (CNS)-directed radiation therapy, at least 7 days must have elapsed from prior stereotactic radiosurgery (SRS) and at least 21 days must have elapsed from prior whole brain radiation therapy (WBRT). Participants must have recovered from all radiation-related toxicities and not require corticosteroids. For non- CNS disease, participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
18. Participants in the phase 2 1L+ CRC expansion (Cohort 2B) must have a RAS wild-type genotype in primary or metastatic tumor tissue, based on expanded RAS historic or local testing including KRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146), and NRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146).
19. Participants must be willing and able to adhere to antidiarrheal prophylaxis, if required.

6.2. Exclusion Criteria

1. History of known hypersensitivity to planned study treatment:
   a All cohorts: trastuzumab or compounds chemically or biologically similar to tucatinib
   b All cohorts except for Cohort 1G: oxaliplatin, fluoropyrimidines, or leucovorin
   c For Cohorts 1E, 1F, 1G or 2A: severe hypersensitivity (≥Grade 3) to pembrolizumab

   Participants who have had Grade 1 or 2 infusion-related reactions (IRRs) to oxaliplatin, pembrolizumab, and/or trastuzumab that were successfully managed may enroll. Participants with known allergy to any of the excipients in the study treatment(s) may enroll, unless severe hypersensitivity (≥Grade 3) to excipients has occurred. Participants with known hypersensitivity or allergy to required concomitant medications are excluded.
2. Participants in Cohorts 1A, 1B, 1C, and 2B: Treatment with oxaliplatin in excess of the limitations specified in inclusion criterion 2
3. Major surgery <28 days prior to Cycle 1, Day 1

4. Participants in the Phase 1b cohorts with known active CNS metastasis (irradiated or resected lesions are permitted, provided the lesions are fully treated and inactive, participant is asymptomatic, and no steroids have been administered for at least 30 days). Participants in Cohorts 2A and 2B with known active CNS lesions may be included but must not have any of the following:
    a Any untreated brain lesions >2.0 cm in size, unless approved by the medical monitor
    b Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to participant (eg, brain stem lesions). Participants who undergo local treatment for such lesions identified by screening brain magnetic resonance imaging (MRI) may still be eligible for the study
    c Known or suspected leptomeningeal disease as documented by the investigator
    d Have poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain lesions notwithstanding CNS-directed therapy
5. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    - Alopecia
    - Clinically insignificant electrolyte abnormalities
    - Hemoglobin <8 g/dL
6. Clinically significant cardiopulmonary disease such as:
    - Ventricular arrhythmia requiring therapy
    - Symptomatic hypertension or uncontrolled asymptomatic hypertension ≥150/≥90 mmHg despite standard medical management, as determined by the investigator
    - Any history of symptomatic congestive heart failure (CHF), left ventricular systolic dysfunction, or decrease in ejection fraction
    - Severe dyspnea at rest (NCI CTCAE v5.0 Grade 3 or above) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy, except when therapy is needed for obstructive sleep apnea
7. Known myocardial infarction or unstable angina within 6 months prior to enrollment
8. Known to be positive for hepatitis C infection (positive by polymerase chain reaction [PCR]). Participants who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of at least 12 weeks.

    Known to be positive for hepatitis B (HBV) by surface antigen (hBsAg) expression. Participants who are positive for either hepatitis B surface antibody (hBsAB) or antibodies to the hepatitis B core antigen (hBcAB) should be screened using PCR measurement of hepatitis B DNA levels. Participants with hepatitis B DNA levels by

PCR that require nucleoside analogue therapy are not eligible for the trial. The latest local guidelines should be followed regarding the monitoring of hepatitis B DNA levels by PCR for participants on study treatment.

9. Presence of known chronic liver disease
10. Known dihydropyrimidine dehydrogenase deficiency (for all cohorts except for Cohort 1G)
11. Participants known to be positive for human immunodeficiency virus (HIV) are excluded if they meet any of the following criteria:
    - CD4+ T-cell count of <350 cells/μL
    - Detectable HIV viral load
    - History of an opportunistic infection within the past 12 months
    - On stable antiretroviral therapy for <4 weeks

    Note: No testing for HIV is required unless mandated by a local health authority.
12. Participants who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 7 months following the last dose of study treatment
13. Unable to swallow pills or requires enteral feeding or parenteral nutrition
14. Have used a strong CYP P450 2C8 inhibitor within 5 half-lives of the inhibitor or have used a strong CYP2C8 or CYP3A4 inducer within 5 days prior to enrollment
15. Other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
16. Has an active infection requiring systemic therapy.
17. Require therapy with warfarin or other coumarin derivatives if receiving CAPOX (Cohorts 1C, 1F, 2A) as part of this study (non-coumarin anticoagulants are allowed)
18. Currently participating in another interventional trial
19. Participants enrolled in Cohorts 1E, 1F, 1G, and 2A who have unresectable or metastatic, gastric, esophageal, and GEJ adenocarcinoma cannot have had previous chemotherapy for metastatic/unresectable disease; adjuvant or neoadjuvant chemotherapy, or biologic therapy is permitted if more than 6 months have elapsed between the end of therapy and first recurrence
20. Participants enrolled in Cohort 2A and Cohort 2B cannot have received prior anti-HER2 therapies
21. Have received a live vaccine <30 days of enrollment
22. Has ongoing ≥ Grade 2 diarrhea of any etiology at screening
23. Participants in Cohorts 1E, 1F, 1G: Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (Note: The repeat imaging should

be performed during study screening.), clinically stable and without requirement of steroid treatment for at least 30 days before the first dose of study intervention.

24. Participants in Cohorts 1E, 1F, 1G, 2A: Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137), and was discontinued from that treatment due to a Grade 3 or higher immune-related adverse event (irAE).
25. Participants in Cohorts 1E, 1F, 1G, 2A: Has had an allogeneic tissue/solid organ transplant.
26. Participants in Cohorts 1E, 1F, 1G, 2A: Has a diagnosis of immunodeficiency (excluding HIV) or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
27. Participants in Cohorts 1E, 1F, 1G, 2A: Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
28. Participants in Cohorts 1E, 1F, 1G, 2A: Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
29. Participants in Cohorts 1E, 1F, 1G, 2A: Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
30. Participants in Cohorts 1E, 1F, 1G, 2A: Has received radiation therapy to the lung that is >30 gray (Gy) within 6 months of the first dose of trial treatment.

6.3. Childbearing Potential

A person of childbearing potential is anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person over age 45 in the absence of other biological, physiological, or pharmacological causes.

A person who can father children is anyone born male who has testes and who has not undergone surgical sterilization (eg, vasectomy followed by a clinical test proving that the procedure was effective).

6.4. Removal of Participants from Therapy or Assessment

Pfizer or their designee must be notified if a participant is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the participant's medical records and electronic case report form (eCRF).

6.4.1. Discontinuation of Study Treatment

A participant's study treatment may be discontinued for any of the following reasons:

- Progressive disease (according to RECIST v1.1), as assessed by investigator
- Clinical disease progression
- AE
- Pregnancy or begins to breastfeed while on study
- Investigator decision
- Participant decision, non-AE
  Note: Ensure that participants who decide to stop treatment **because of an AE** are not included in this rationale.
- Study termination by sponsor
- Non-compliance with study requirements
- Other, non-AE

Participants who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

6.4.2. Participant Withdrawal from Study

A participant may withdraw from the study at any time at their own request. Reasons for permanent discontinuation of study intervention may include the following:

- Participant withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent for collection of future information, no further evaluations will be performed, and no additional data will be collected except for publicly available information as appropriately directed in accordance with local law. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.4.3. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention or withdraw consent will transition to end of study. Participants should notify the investigator in writing of the decision to withdraw consent from future follow up, whenever possible.

The withdrawal of consent should be explained in detail in the medical records by the investigator.

7. TREATMENTS

7.1. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.
3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.
4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the pharmacy instructions/IP Manual. Temperature excursions should be reported only for centrally sourced study interventions.
5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention. See the pharmacy instructions/IP Manual for storage conditions of the study intervention.
6. Study interventions should be stored in their original containers.
7. The investigator, institution, head of the medical institution, (where applicable) or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All centrally sourced study interventions will be accounted for using a study intervention accountability form/record. All unused tucatinib study intervention that is taken home by the participant, must be returned to the investigator

by the participant. **Returned tucatinib study intervention must not be redispensed to the participants.**

8. Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy instructions/IP Manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

7.2. Single Reference Safety Documents

Single reference safety documents (SRSD) for each of the study interventions are summarized in Table 6.

Table 6. Single Reference Safety Documents for Study Interventions

Study Intervention	SRSD
Tucatinib	Investigator's brochure
Leucovorin or Levoleucovorin	Leucovorin: UK SmPC **or** Levoleucovorin: French SmPC
Oxaliplatin	Irish SmPC
5-Fluorouracil	Irish SmPC
Capecitabine	EU SmPC
Trastuzumab	EU SmPC
Pembrolizumab	Investigator's brochure
Loperamide	Lithuanian SmPC

7.3. Treatments Administered

7.3.1. Tucatinib, Trastuzumab, and FOLFOX (Cohorts 1A, 1B, 1D, 2B)

As shown in Table 5, participants in the study will receive combination therapy of tucatinib with trastuzumab and mFOLFOX6 (Table 7) or mFOLFOX7 in 14-day cycles (Table 8). In Cohorts 1A and 1B, FOLFOX may be administered using either the mFOLFOX6 or mFOLFOX7 regimen but should remain consistent throughout study participation. In Cohorts 1D and 2B, participants will receive mFOLFOX6. In Cohorts 1A and 1B, participants will receive trastuzumab and FOLFOX starting on Cycle 1 Day 1, while the first dose of tucatinib will be administered on Cycle 1 Day 8. In Cohorts 1D and 2B, tucatinib, trastuzumab and FOLFOX will be administered starting on Cycle 1 Day 1. The starting dose of tucatinib in Cohort 1A is 150 mg PO BID in 14-day cycles. The starting dose of tucatinib in Cohort 1B is 300 mg PO BID or an alternative dose level as recommended by the SMC.

The dose of tucatinib in Cohorts 1D and 2B will be determined by SMC review of data from Cohort 1A and 1B.

Table 7. Tucatinib and mFOLFOX6 Administered in 14-day Cycles With Trastuzumab (Cohorts 1A, 1B, 1D, 2B)

Drug	Dose/Route	Administration	Days
Tucatinib	150-300 mg[a] PO	BID	Daily
Oxaliplatin	85 mg/m^2 IV	Administer over 2 h	Day 1
Leucovorin[b]	400 mg/m^2 IV	Administer over 2 h concurrent with oxaliplatin	Day 1
Fluorouracil	400 mg/m^2 IV	Bolus	Day 1
Fluorouracil	2400 mg/m^2 IV	Administer over 46 h	Day 1
Trastuzumab Q2W: Cohorts 1A and 1B	6 mg/kg IV (loading dose)	Administer over 90 min	Day 1 (Cycle 1 only)
	4 mg/kg IV	Administer over 30 min	Day 1 of every subsequent cycle
Trastuzumab Q3W: Cohorts 1D and 2B	8 mg/kg IV (loading dose)	Administer over 90 min	Day 1 (Cycle 1 only)
	6 mg/kg IV	Administer over 30 min	Day 1 of every subsequent cycle

a Dose to be based on the RP2D from dose escalation
b Levoleucovorin (200 mg/m^2) can be substituted based on investigator preference in cases of supply shortages. Levoleucovorin is dosed at 1-half the usual dose of racemic d,l-leucovorin.

Table 8. Tucatinib, mFOLFOX7, and Trastuzumab Administered in 14-day Cycles (Cohorts 1A and 1B Only)

Drug	Dose/Route	Administration	Days
Tucatinib	150-300 mg[a] PO	BID	Daily starting from Cycle 1 Day 8
Oxaliplatin	85 mg/m^2 IV	Administer over 2 h	Day 1
Leucovorin[b]	200 mg/m^2 IV	Administer over 2 h concurrent with oxaliplatin	Day 1
Fluorouracil	2400 mg/m^2 IV	Administer over 46 h	Day 1
Trastuzumab	6 mg/kg IV (loading dose)	Administer over 90 min	Day 1 (Cycle 1 only)
Trastuzumab	4 mg/kg IV	Administer over 30 min	Day 1 of every subsequent cycle

a Dose to be based on the RP2D from dose escalation

Table 8. Tucatinib, mFOLFOX7, and Trastuzumab Administered in 14-day Cycles (Cohorts 1A and 1B Only)

Drug	Dose/Route	Administration	Days

b Levoleucovorin (100 mg/m^2) can be substituted based on investigator preference in cases of supply shortages. Levoleucovorin is dosed at 1-half the usual dose of racemic d,l-leucovorin.

7.3.2. Tucatinib, Trastuzumab, and CAPOX (Cohort 1C)

Participants in Cohort 1C will receive combination therapy of tucatinib with trastuzumab and CAPOX in 21-day cycles (Table 9). The first dose of tucatinib will be administered on Cycle 1 Day 1. The dose of tucatinib will be determined by SMC review of data from Cohort 1A and 1B.

Table 9. Tucatinib, CAPOX, and Trastuzumab Administered in 21-day Cycles (Cohort 1C)

Drug	Dose/Route	Administration	Days
Tucatinib	300 mg[a] PO	BID	Daily starting from Cycle 1 Day 1
Oxaliplatin	130 mg/m^2 IV	Administer over 2 h	Day 1
Capecitabine[b]	1000 mg/m^2, PO	BID	Cycle 1: Evening of Day 1 to morning of Day 15 Cycle 2 and each subsequent cycle: Day 1 - Day 14
Trastuzumab	8 mg/kg IV (loading dose)	Administer over 90 min	Day 1 (Cycle 1 only)
Trastuzumab	6 mg/kg IV	Administer over 30 min	Day 1 of every subsequent cycle

a Dose to be based on what the RP2D from dose escalation
b Starting dose of capecitabine may be reduced per investigator preference or institutional standards upon approval by medical monitor but will not be lower than 850 mg/m^2 PO BID.

7.3.3. Tucatinib, Trastuzumab, FOLFOX, and Pembrolizumab (Cohorts 1E, 2A)

Participants in Cohorts 1E and 2A will receive combination therapy with tucatinib and mFOLFOX6 (Table 10) in 14-day cycles. Trastuzumab will be given in 21-day cycles, and pembrolizumab in 42-day cycles. The first dose of tucatinib will be administered on Cycle 1 Day 1. The dose of tucatinib will be determined by SMC review of data from Cohort 1A and 1B.

Table 10. Tucatinib and mFOLFOX6 Administered in 14-day Cycles With Trastuzumab (Q3W) and Pembrolizumab (Q6W) (Cohorts 1E, 2A)

Drug	Dose/Route	Administration	Days
Tucatinib	300 mg[a] PO	BID	Daily
Oxaliplatin	85 mg/m^2 IV	Administer over 2 h	Day 1
Leucovorin[b]	400 mg/m^2 IV	Administer over 2 h concurrent with oxaliplatin	Day 1
Fluorouracil	400 mg/m^2 IV	Bolus	Day 1
Fluorouracil	2400 mg/m^2 IV	Administer over 46 h	Day 1
Trastuzumab	8 mg/kg IV (loading dose)	Administer over 90 min	Day 1 (Cycle 1 only)
Trastuzumab	6 mg/kg IV	Administer over 30 min	Q3W after loading dose
Pembrolizumab	400 mg IV	Administer over 30 min	Cycle 1: Day 1, then Q6W

a Dose to be based on the RP2D from dose escalation
b Levoleucovorin (200 mg/m^2) can be substituted based on investigator preference in cases of supply shortages. Levoleucovorin is dosed at 1-half the usual dose of racemic d,l-leucovorin.

7.3.4. Tucatinib, Trastuzumab, CAPOX, and Pembrolizumab (Cohorts 1F, 2A)

Participants in Cohort 1F and 2A will receive combination therapy with tucatinib, trastuzumab, and CAPOX in 21-day cycles (Table 11). Pembrolizumab will be given in 42-day cycles. The first dose of tucatinib will be administered on Cycle 1 Day 1 in Cohort 1F. The first dose of tucatinib in Cohort 2A will be administered on Cycle 1 Day 1.

Table 11. Tucatinib, CAPOX, and trastuzumab, and administered in 21-day cycles with Pembrolizumab (Q6W) (Cohorts 1F, 2A)

Drug	Dose/Route	Administration	Days
Tucatinib	300 mg[a] PO	BID	Daily
Oxaliplatin	130 mg/m^2 IV	Administer over 2 h	Day 1
Capecitabine[b]	1000 mg/m^2, PO	BID	Cycle 1: Evening of Day 1 to morning of Day 15 Cycle 2 and each subsequent cycle: Day 1 - Day 14
Trastuzumab	8 mg/kg IV (loading dose)	Administer over 90 min	Day 1 (Cycle 1 only)
Trastuzumab	6 mg/kg IV	Administer over 30 min	Day 1 of every subsequent cycle
Pembrolizumab	400 mg IV	Administer over 30 min	Cycle 1 Day 1, then Q6W

a Dose to be based on the RP2D from dose escalation
b Starting dose of capecitabine may be reduced per investigator preference or institutional standards upon approval by medical monitor but will not be lower than 850 mg/m^2 PO BID.

7.3.5. Tucatinib, Trastuzumab, and Pembrolizumab (Cohort 1G)

Participants in Cohort 1G will receive combination therapy with tucatinib and trastuzumab in 21-day cycles (Table 12). Pembrolizumab will be given in 42-day cycles. The first dose of tucatinib will be administered on Cycle 1 Day 1.

Table 12. Tucatinib, trastuzumab administered in 21-day cycles and pembrolizumab (Cohort 1G)

Drug	Dose/Route	Administration	Days
Tucatinib	300 mg[a] PO	BID	Daily
Trastuzumab	8 mg/kg IV (loading dose)	Administer over 90 min	Day 1 (Cycle 1 only)
Trastuzumab	6 mg/kg IV	Administer over 30 min	Day 1 of every subsequent cycle
Pembrolizumab	400 mg IV	Administer over 30 min	Cycle 1 Day 1, then Q6W

a Dose to be based on the RP2D from dose escalation

7.4. Investigational Product (Tucatinib)

Detailed information describing the preparation, administration, and storage of tucatinib is located in the Pharmacy Instructions/IP Manual.

Study personnel should instruct participants on tucatinib administration techniques and drug diary prior to the first dose of tucatinib and ensure that the participant understands these instructions before granting treatment independence.

7.4.1. Description

Tucatinib drug product is supplied as both a coated yellow oval-shaped tablet in a 150 mg dosage strength and a coated yellow round convex tablet in a 50 mg dosage strength. The tablets are manufactured from a drug product [redacted] of tucatinib in [redacted] copolymer, which is then combined with the pharmaceutical excipients (microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, and magnesium stearate), and compressed into tablets.

7.4.2. Method of Procurement

The investigational study intervention (tucatinib) will be provided by the sponsor.

7.4.3. Dose and Administration

The investigational study intervention (tucatinib) will be administered PO BID. Participants will be instructed by the pharmacist or investigator as to the specific number of tablets required for each dose. At each visit during study treatment, participants will be supplied with the appropriate number of tablets for the number of doses to be taken prior to the next scheduled visit.

Participants will be instructed to take tucatinib tablets twice each day (once in the morning, and once in the evening) approximately 8 to 12 hours between doses in the same calendar day. It is recommended that if a participant misses a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the participant should not take the missed dose but should wait and take the next regularly scheduled dose. Tablets may be taken with or without food. Tablets must be swallowed whole and may not be crushed, chewed or dissolved in liquid. On the day of dosing, the individual unit dose of the tucatinib tablet may be exposed to ambient temperature for up to 6 hours prior to dose.

Complete dosing instructions will be provided to the pharmacist prior to the initiation of the study. Complete dosing instructions will also be provided to study participants and will include the minimum times between doses, dosing in relation to meals, and instructions for missed doses. Participants will be instructed to take their morning dose of tucatinib in the clinic at the start of the oxaliplatin infusion on days when samples will be collected for PK analysis (Section 9.3). Participant compliance with investigational study intervention dosing instructions will be assessed with the use of participant diaries and study intervention accountability.

Dose modifications of tucatinib are described in Section 7.9.

7.4.4. Storage and Handling

Tablets of tucatinib are packaged in round, high-density polyethylene bottles containing a desiccant, with an induction sealed liner and child-resistant plastic closure cap. Bottles of tucatinib tablets are to be stored under refrigeration at 2–8°C in a secure, access-limited location.

The tablets are coated with a non-hazardous film to prevent any exposure to the active pharmaceutical ingredient during routine handling. Avoid breaking or crushing tablets. In the event the tablets are broken or crushed, wash hands and exposed skin thoroughly with soap and water.

Refer to the Pharmacy Instructions/IP Manual for more information.

7.4.5. Packaging and Labeling

Each bottle of investigational study intervention will be labeled in compliance with applicable regulatory requirements.

7.4.6. Preparation and Dispensing

A qualified staff member will dispense the tucatinib study intervention via the IRT system in the bottles provided, in quantities appropriate according to the SOE. The participant should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

7.4.7. Study Intervention Accountability

Tucatinib used during the course of the study should be handled according to the Pharmacy Instructions/IP Manual. Tucatinib tablets are to be tracked and documented from the time of receipt at the site, through participant dosing, and until the sponsor approves of the final return or destruction. All supplies, including partially used or empty bottles, should be tracked.

The sponsor or designee will conduct drug accountability monitoring during the course of the study according to the Study Operations Manual. All used and unused bottles of tucatinib should be handled according to the sponsor's instructions and disposed according to the Pharmacy Instructions/IP manual.

7.5. FOLFOX Regimen (Cohorts 1A, 1B, 1D, 1E, 2A, and 2B)

7.5.1. Description

Oxaliplatin is a platinum analog that blocks DNA replication. It is indicated for treatment of advanced gastric cancer and CRC. Fluorouracil is an inhibitor of nucleic acid synthesis that is indicated for treatment of advanced carcinoma of the colon, rectum, breast, stomach, and pancreas. Leucovorin, also known as folinic acid, is a derivative of folic acid indicated for treatment of advanced gastric cancer and CRC in combination with fluorouracil. FOLFOX will be administered in this study using either the mFOLFOX6 or mFOLFOX7 regimen in Cohorts 1A and 1B; only mFOLFOX6 will be used in Cohorts 1D, 1E, 2A, and 2B.

7.5.2. Method of Procurement

Details regarding sourcing of FOLFOX chemotherapy agents may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

7.5.3. Dose and Administration

For preparation and complete prescribing information for FOLFOX chemotherapy agents, please refer to the most current local product labeling.

Administration of FOLFOX will commence on Day 1 of each treatment cycle and will be administered every 2 weeks as described in Table 7 and Table 8. Oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 (FOLFOX6) or 200 mg/m^2 (FOLFOX7) will be administered IV over 120 min (±15 min). For mFOLFOX6, after completion of the leucovorin and oxaliplatin infusions, fluorouracil 400 mg/m^2 (IV bolus), then fluorouracil 2400 mg/m^2 will be administered IV over 46 hours (±1 hour). For mFOLFOX7, after completion of the leucovorin and oxaliplatin infusions, fluorouracil 2400 mg/m^2 will be administered IV over 46 hours. For body weight changes, doses should be recalculated according to institutional standard of care.

7.5.4. Storage and Handling

FOLFOX chemotherapy agents should be stored in accordance with manufacturer, supplier, and institutional procedures.

7.5.5. Preparation and Dispensing

For preparation and complete prescribing information for FOLFOX chemotherapy agents, please refer to the most current local product labeling.

Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of the FOLFOX chemotherapy agents.

7.6. CAPOX Regimen (Cohorts 1C, 1F, and 2A)

7.6.1. Description

CAPOX consists of capecitabine and oxaliplatin. Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Oxaliplatin is a platinum analog that blocks DNA replication.

7.6.2. Method of Procurement

Details regarding sourcing of CAPOX chemotherapy agents may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

7.6.3. Dose and Administration

Capecitabine will be given at 1000 mg/m^2 PO BID from the evening of Day 1 until the morning of Day 15 (Cycle 1) and PO BID Day 1-Day 14 for all subsequent cycles. The starting dose of capecitabine may be reduced per investigator preference or institutional standards upon approval by the medical monitor but will not be lower than 850 mg/m^2 PO BID. As capecitabine is an oral drug available in fixed doses, the dose administered may not

exactly match the calculated dose. Determination of the rounding of capecitabine doses for administration should be made according to local institutional practices, with documentation of both the calculated and administered dose.

Oxaliplatin will be given at 130 mg/m^2 IV on Day 1 of each 21-day cycle.

7.6.4. Storage and Handling

Capecitabine and oxaliplatin should be handled and stored according to the local product labeling.

7.6.5. Preparation and Dispensing

For preparation and complete prescribing information for CAPOX chemotherapy agents, please refer to the most current local product labeling.

Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of the CAPOX chemotherapy agents.

7.7. Trastuzumab

7.7.1. Description

Trastuzumab is a humanized Ig-1 kappa monoclonal antibody that binds to the extracellular domain of HER2; it mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells that over express HER2 protein.

7.7.2. Method of Procurement

Details regarding sourcing of trastuzumab may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

7.7.3. Dose and Administration

In Cohorts 1A and 1B, trastuzumab will be given as a loading dose of 6 mg/kg IV (over 90 min) followed by 4 mg/kg (over 30 min) every 2 weeks (Table 7, Table 8). In all other cohorts, trastuzumab will be given as a loading dose of 8 mg/kg IV (over 90 min) followed by 6 mg/kg (over 30 min) Q3W (Table 7, Table 8, Table 9, Table 10, Table 11 and Table 12). For body weight changes, doses should be recalculated according to institutional standard of care. Trastuzumab infusion rates may be adjusted per institutional guidelines. If dosing of trastuzumab has been held for >4 weeks, the IV loading dose should be given per approved dosing instructions.

7.7.4. Storage and Handling

Refrigeration should be set at 2–8°C for storage of vials containing trastuzumab. Follow the local product labeling for more information. Trastuzumab should be stored according to the local product labeling.

7.7.5. Packaging and Labeling

Each vial of trastuzumab provided by the sponsor will be labeled in compliance with applicable regulatory requirements.

7.7.6. Preparation and Dispensing

Single-dose vial (150 mg/vial) as a lyophilized sterile powder for reconstitution is commercially available and should be prepared and administered per instructions in the trastuzumab local product labeling. Trastuzumab will be administered IV under the direction of the investigator (subcutaneous administration is not allowed on study).

Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

7.7.7. Study Treatment Accountability

Trastuzumab used during the course of the study should be handled according to its local product labeling. Sponsor-supplied trastuzumab vials are to be tracked and documented from the time of receipt at the site, through participant dosing, and until the sponsor approves of the final return or destruction. All supplies, including partially used or empty vials, should be tracked.

The sponsor or designee will conduct drug accountability monitoring during the course of the study. All used and unused vials of trastuzumab should be handled according to the sponsor's instructions.

7.8. Pembrolizumab (Cohorts 1E, 1F, 1G, and 2A)

7.8.1. Description

Pembrolizumab is a potent and highly selective humanized monoclonal antibody of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and PD-L1 and PD-L2.

7.8.2. Method of Procurement

Details regarding sourcing of pembrolizumab may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

7.8.3. Dose and Administration

Pembrolizumab will be administered using IV infusion on Day 1 of each 6-week treatment cycle after all procedures and assessments have been completed.

Pembrolizumab will be administered as a dose of 400 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes (-5 min/+10 min).

The pembrolizumab infusion should be administered first, followed by trastuzumab, oxaliplatin, and capecitabine.

7.8.4. Storage and Handling

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

7.8.5. Packaging and Labeling

Refer to the Pharmacy Binder for information regarding packaging and labeling.

7.8.6. Preparation and Dispensing

Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

7.8.7. Study Treatment Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study treatments in accordance with the protocol and any applicable laws and regulations

7.9. Dose Modifications

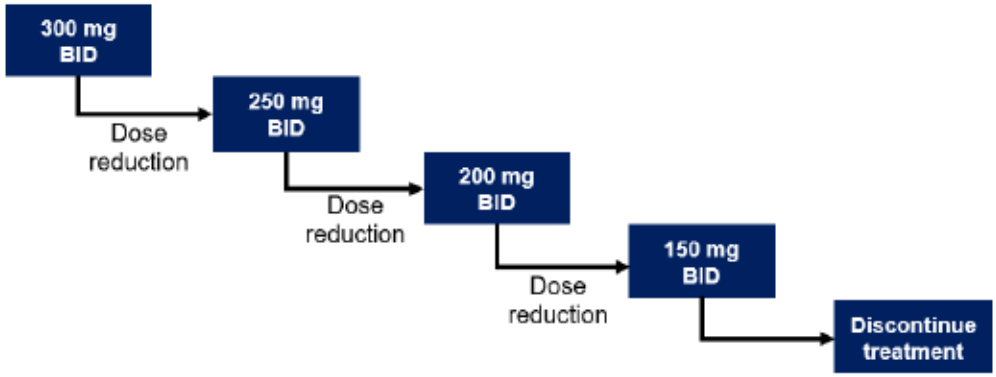
7.9.1. Tucatinib Dose Modifications

Dose modifications of tucatinib will be made on a per-participant basis. Dose reductions will be made in increments of 50 mg (Figure 2). Dose reductions to below 150 mg BID are not allowed unless alternative dose levels are recommended by the SMC. Participants who, in the

opinion of the investigator, would require a dose reduction to <150 mg BID should discontinue study treatment.

The dose of tucatinib should not be re-escalated after a dose reduction is made. Tucatinib should be discontinued if a delay greater than 6 weeks is required due to treatment-related toxicity unless a longer delay is approved by the study medical monitor.

Figure 2: Tucatinib Dose Reduction Schedule for AEs Based on Starting Dose



General dose modification guidelines for tucatinib are provided in Table 13. Information on dose modifications due to renal toxicity are discussed in Section 9.5.3.1.

Table 13. Tucatinib Dose Modifications for AEs[a]

Adverse Reactions, Severity[b]	Tucatinib Dose Modification
Hepatotoxicity (regardless of relationship to tucatinib)	
ALT or AST >3× to ≤5× ULN	No dose adjustment required
Bilirubin >1.5× to ≤3× ULN	Hold tucatinib until recovery to ≤1.5× ULN. Then resume tucatinib at the same dose level
ALT or AST >5× to ≤20× ULN	Hold tucatinib until recovery to ≤3× ULN or until return to pretreatment level in participants with known liver metastasis. Then resume tucatinib at the next lower dose level
Bilirubin >3× to ≤10× ULN	Hold tucatinib until recovery to ≤1.5× ULN. Then resume tucatinib at the next lower dose level
ALT or AST >20× ULN OR Bilirubin >10× ULN	Permanently discontinue tucatinib
ALT or AST >3× ULN AND Bilirubin >2× ULN	Permanently discontinue tucatinib
Diarrhea related to tucatinib (as assessed by the investigator)	
Grade 3 WITHOUT antidiarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to ≤ Grade 1 or pretreatment level. Then resume tucatinib at the same dose level.

Table 13. Tucatinib Dose Modifications for AEs[a]

Adverse Reactions, Severity[b]	Tucatinib Dose Modification
Grade 3 WITH antidiarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to ≤ Grade 1 or pretreatment level. Then resume tucatinib at the next lower dose level.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue tucatinib treatment.
Nausea and vomiting related to tucatinib	
Grade 3 nausea or vomiting WITHOUT optimal use of anti-emetics	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 nausea or vomiting WITH optimal use of anti-emetics	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.
Grade 4 nausea or vomiting regardless of use of anti-emetics	Permanently discontinue tucatinib treatment.
Rash related to tucatinib	
Grade 3 rash WITHOUT optimal use of topical corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 rash WITH optimal use of topical corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.
Grade 4 rash regardless of use of topical corticosteroids or anti-infectives	Permanently discontinue tucatinib treatment.
Other adverse reactions that are related to tucatinib	
Grade 3 AEs other than Grade 3 fatigue lasting ≤3 days, alopecia[c], nausea, vomiting, diarrhea, rash, correctable electrolyte abnormalities which return to ≤ Grade 1 within 7 days	Hold tucatinib until recovery to ≤ Grade 1 or pretreatment level. Then resume tucatinib at the next lower dose level.
Grade 4	Permanently discontinue tucatinib.

a AE severity graded using the NCI CTCAE v5.0.
b If the AE in question does not recover to the grade required for restarting study medication as outlined in the table, the participant may need to discontinue the drug completely. Participants requiring a hold of tucatinib for > 6 weeks must discontinue study treatment unless a longer delay is approved by the medical monitor.
c No dose modifications are required for alopecia

7.9.2. FOLFOX Dose Modifications

Doses of fluorouracil, oxaliplatin, and leucovorin may be adjusted depending on an individual participant's tolerance. Table 14 presents recommended dose reduction levels for oxaliplatin (non-neurological toxicity) and fluorouracil. Table 15 presents dose modification guidelines for AEs attributed to FOLFOX. Table 16 presents dose modification guidelines for oxaliplatin-associated neurological toxicity attributed to FOLFOX. Dose reductions or treatment interruptions/discontinuation for reasons other than those described below may be made by the investigator per institutional practice and if deemed in the best interest of participant safety. Whenever possible, these decisions should first be discussed with the

medical monitor. During the LTEP, investigators may choose to follow institutional standard of care for FOLFOX dose modifications.

Table 14. Oxaliplatin (Non-neurological Toxicity) and Fluorouracil Dose Reduction Levels for FOLFOX

	Starting Dose	Dose Level - 1	Dose Level - 2
Oxaliplatin (FOLFOX)	85 mg/m^2	65 mg/m^2	50 mg/m^2
Fluorouracil - mFOLFOX6 Bolus Infusion - mFOLFOX7 Infusion	 400 mg/m^2 2400 mg/m^2 2400 mg/m^2	 320 mg/m^2 1900 mg/m^2 2000 mg/m^2	 260 mg/m^2 1500 mg/m^2 1600 mg/m^2

Table 15. Dose Modifications for AEs Attributed to FOLFOX

Toxicity CTCAE Grade (v5.0)	Subsequent Cycles Based on Interval Toxicity	Prior to Each Treatment Cycle
Neutropenia[a] (ANC) • Grade 1 • Grade 2 • Grade 3 • Grade 4	• Maintain dose level • Maintain dose level • Decrease both 5-FU and oxaliplatin 1 dose level • Decrease both 5-FU and oxaliplatin 1 dose level	• If ANC <1.5×10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity • If ANC <1.5×10^9/L after 4 weeks, discontinue therapy
Thrombocytopenia[a] • Grade 1 • Grade 2 • Grade 3 • Grade 4	• Maintain dose level • Maintain dose level • Decrease both 5-FU and oxaliplatin 1 dose level • Decrease both 5-FU and oxaliplatin 1 dose level	• If PLT <75×10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity • If PLT <75×10^9/L after 4 weeks, discontinue therapy
Febrile neutropenia	Decrease both 5-FU and oxaliplatin 1 dose level	
Diarrhea[b] • Grade 1 • Grade 2 • Grade 3 • Grade 4	• Maintain dose level • Maintain dose level • Decrease both 5-FU and oxaliplatin 1 dose level • Decrease both 5-FU and oxaliplatin 1 dose level	If Grade ≥2 diarrhea at start of cycle, hold and check weekly then treat based on interval toxicity
Other nonhematologic toxicities[c]	Dose modifications for other nonhematologic AEs related to therapy that are observed at the start of subsequent course and at the time of retreatment are based on CTCAE v5.0 and follow the same criteria as diarrhea above.	
Leucovorin (or levoleucovorin) dose modifications may be made at the investigator's discretion and per institutional standards.		

Table 15. Dose Modifications for AEs Attributed to FOLFOX

Toxicity CTCAE Grade (v5.0)	Subsequent Cycles Based on Interval Toxicity	Prior to Each Treatment Cycle

a Laboratory values from Day 1 of each cycle should be used to determine dose modifications to FOLFOX for neutropenia and thrombocytopenia

b mFOLFOX6 may cause severe diarrhea; discontinuation of the 5-FU bolus dose may be considered prior to modification of tucatinib dosing (refer to Section 7.9.10).

c For other nonhematologic toxicities, the next cycle of therapy may be started despite the occurrence of a Grade 2 AE, if consistent with local standards.

Table 16. Dose Modification for Oxaliplatin-associated Neurotoxicity Attributed to FOLFOX

Paresthesia and Peripheral Sensory Neuropathy (Grade[a])	Duration of Neurotoxicity		
	1–7 Days	>7 Days	Persistent (Not Resolved Between Cycles)
Paresthesias/dysesthesias of short duration that resolve and do not interfere with function (Grade 1)	No Change	No Change	No Change
Paresthesias/dysesthesias interfering with instrumental activities of daily living (Grade 2)	No Change	No Change	FOLFOX: Decrease oxaliplatin to 65 mg/m^2
Paresthesias/dysesthesias with pain or with functional impairment that interfere with self-care activities of daily living (Grade 3)	1st time: FOLFOX: Decrease oxaliplatin to 65 mg/m^2 2nd time: FOLFOX: Decrease oxaliplatin to 40 mg/m^2	STOP	STOP
Persistent paresthesias/dysesthesias that are life-threatening (Grade 4)	STOP	STOP	STOP
Pharyngo-laryngeal dysesthesias	No Change	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours

a AE severity graded using the NCI CTCAE v5.0.

A new cycle of FOLFOX will be repeated every 2 weeks but may not be administered if the ANC $<1.5\times10^9$/L, platelets $<75.0\times10^9$/L, white blood cells $<3.0\times10^9$/L, or diarrhea have not recovered to $\leq$ Grade 1. Up to a 4-week delay is allowed in the initiation of a new cycle of treatment for resolution of toxicities. A treatment delay of 1 component of the FOLFOX regimen (ie, fluorouracil/leucovorin, or oxaliplatin) results in a similar delay of the other component to allow both therapies to be given together on Day 1 of each 2-week cycle.

Trastuzumab, tucatinib and pembrolizumab (as applicable) may be continued during periods of FOLFOX treatment delay.

In the event that oxaliplatin administration is discontinued for any reason prior to disease progression, fluorouracil/leucovorin, trastuzumab, and tucatinib therapy may be continued until disease progression. In the event that FOLFOX chemotherapy administration is discontinued for any reason prior to disease progression, trastuzumab and tucatinib therapy may be continued until disease progression.

At the discretion of the PI, participants enrolled in Cohort 1A at a tucatinib dose below that recommended by the SMC for subsequent cohorts may increase to the higher tucatinib dose at any time following SMC approval.

If FOLFOX chemotherapy interruptions are ≤6 weeks from the previous cycle and the participant has recovered from toxicities as specified above, and the participant's disease has not progressed, FOLFOX should be restarted at doses according to the tables above. If the FOLFOX chemotherapy interruption is >6 weeks, but the participant has recovered from toxicity and the participant's disease has not progressed, then the participant may continue FOLFOX therapy after consultation with and approval by the sponsor's medical monitor.

7.9.3. CAPOX Dose Modifications

Doses of oxaliplatin and capecitabine may be adjusted depending on an individual participant's tolerance. Table 17 presents recommended dose reduction levels for oxaliplatin (non-neurological toxicity) and capecitabine. Table 18 presents dose modification guidelines for AEs attributed to CAPOX, and Table 19 presents dose modification guidelines for oxaliplatin-associated neurological toxicity attributed to CAPOX. Dose reductions or treatment interruptions/discontinuation for reasons other than those described below may be made by the investigator per institutional practice and if deemed in the best interest of participant safety. Whenever possible, these decisions should first be discussed with the medical monitor.

Capecitabine must be held for any participant who experiences a Grade 2 or greater AE considered related to capecitabine or to the combination of tucatinib and capecitabine and/or trastuzumab (as determined by the investigator). Held doses of capecitabine should not be made up within each cycle.

During the LTEP, investigators may choose to follow institutional standard of care for CAPOX dose modifications.

Capecitabine dose should not be re-escalated after a dose reduction is made.

In the event that oxaliplatin administration is discontinued for any reason prior to disease progression, capecitabine, trastuzumab, tucatinib, and pembrolizumab (as applicable) therapy may be continued until disease progression. In the event that CAPOX chemotherapy administration is discontinued for any reason prior to disease progression, trastuzumab and tucatinib therapy may be continued until disease progression.

Table 17. Oxaliplatin (Non-neurological Toxicity) and Capecitabine Dose Reduction Levels for CAPOX

	Starting Dose	Dose Level – 1	Dose Level – 2
Oxaliplatin (CAPOX)	130 mg/m^2	100 mg/m^2	85 mg/m^2
Capecitabine[a]	1000 mg/m^2	750 mg/m^2	500 mg/m^2

a Starting dose of capecitabine may be reduced per investigator preference or institutional standards upon approval by medical monitor but will not be lower than 850 mg/m^2 PO BID. For participants with starting doses of capecitabine <1000 mg/m^2, dose reductions of capecitabine should be 25% of the starting dose for dose level 1 and 50% of the starting dose for dose level 2.

Table 18. Dose Modifications for AEs attributed to CAPOX

CAPOX Drug(s)	Toxicity CTCAE Grade (v5.0)	Subsequent Cycles Based on Interval Toxicity	Prior to Each Treatment Cycle
Oxaliplatin	Neutropenia (ANC)[a] • Grade 1 • Grade 2 • Grade 3 • Grade 4	 • Maintain dose level • Maintain dose level • Decrease oxaliplatin 1 dose level • Decrease oxaliplatin 1 dose level	• If ANC <1.5×10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity • If ANC <1.5×10^9/L after 4 weeks, discontinue therapy
	Thrombocytopenia[a] • Grade 1 • Grade 2 • Grade 3 • Grade 4	 • Maintain dose level • Maintain dose level • Decrease oxaliplatin 1 dose level • Decrease oxaliplatin 1 dose level	• If PLT <75×10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity • If PLT <75×10^9/L after 4 weeks, discontinue therapy
	Leukopenia • Grade 1 • Grade 2 • Grade 3 • Grade 4	 • Maintain dose level • Maintain dose level • Decrease oxaliplatin 1 dose level • Decrease oxaliplatin 1 dose level	• If WBC <3.0×10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity • If WBC <3.0×10^9/L after 4 weeks, discontinue therapy
	Diarrhea • Grade 1 • Grade 2 • Grade 3 • Grade 4	 • Maintain dose level • Maintain dose level • Decrease oxaliplatin 1 dose level • Decrease oxaliplatin 1 dose level	• If Grade ≥2 diarrhea at start of cycle, hold and check weekly then treat based on interval toxicity
	Other nonhematologic toxicities	Oxaliplatin dose modifications for other nonhematologic AEs related to CAPOX that are observed at the start of subsequent course and at the time of retreatment are based on CTCAE v5.0 and follow the same criteria as diarrhea above.	
Oxaliplatin and Capecitabine	Febrile neutropenia	Decrease oxaliplatin 1 dose level and capecitabine to 75% of starting dose	• If ANC <1.5×10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity • If ANC <1.5×10^9/L after 4 weeks, discontinue therapy • If Grade ≥3 sepsis occurs, discontinue capecitabine and oxaliplatin

Table 18. Dose Modifications for AEs attributed to CAPOX

CAPOX Drug(s)	Toxicity CTCAE Grade (v5.0)	Subsequent Cycles Based on Interval Toxicity	Prior to Each Treatment Cycle
Capecitabine	Hand and Foot Syndrome		• If Grade ≥2 hand-foot syndrome occurs, administration of capecitabine should be immediately interrupted until the event resolves or decreases in intensity to Grade ≤1
	• Grade 1	• Maintain dose level	
	• Grade 2	• 1st time: Maintain dose level • 2nd time: Decrease capecitabine to 75% of starting dose • 3rd time: Decrease capecitabine to 50% of starting dose • 4th time: Discontinue capecitabine permanently	
	• Grade 3	• 1st time: Decrease capecitabine to 75% of starting dose • 2nd time: Decrease capecitabine to 50% of starting dose • 3rd time: Discontinue capecitabine permanently	
Capecitabine (Continued)	Stomatitis		• If Grade ≥2 stomatitis occurs, administration of capecitabine should be immediately interrupted until the event resolves or decreases in intensity to Grade ≤1
	• Grade 1	• Maintain dose level	
	• Grade 2	• 1st time: Maintain dose level • 2nd time: Decrease capecitabine to 75% of starting dose • 3rd time: Decrease capecitabine to 50% of starting dose • 4th time: Discontinue capecitabine permanently	
	• Grade 3	• 1st time: Decrease capecitabine to 75% of starting dose • 2nd time: Decrease capecitabine to 50% of starting dose • 3rd time: Discontinue capecitabine permanently	
	• Grade 4	• Discontinue capecitabine permanently	
	Cardiotoxicity[b]		• If Grade ≥2 cardiotoxicity is attributable to capecitabine, permanently discontinue therapy
	• Grade 1 • Grade 2	• Maintain dose level • Discontinue capecitabine permanently	

Table 18. Dose Modifications for AEs attributed to CAPOX

CAPOX Drug(s)	Toxicity CTCAE Grade (v5.0)	Subsequent Cycles Based on Interval Toxicity	Prior to Each Treatment Cycle
Capecitabine (Continued)	**Other Adverse Events Related to Capecitabine**		
	Toxicity CTCAE Grade (v5.0)	**During a Course of Therapy**	**Dose Adjustment for Next Treatment (% of Starting Dose)[c]**
	Grade 1	Maintain dose level	Maintain dose level
	Grade 2[d] 1st appearance 2nd appearance 3rd appearance 4th appearance	 Interrupt until resolved to Grade ≤ 1 Interrupt until resolved to Grade ≤ 1 Interrupt until resolved to Grade ≤ 1 Discontinue permanently	 100% 75% 50% NA
	Grade 3 1st appearance 2nd appearance 3rd appearance	 Interrupt until resolved to Grade ≤ 1 Interrupt until resolved to Grade ≤ 1 Discontinue permanently	 75% 50% NA
	Grade 4 1st appearance	 Discontinue permanently	 NA

NA = not applicable

a Laboratory values from Day 1 of each cycle should be used to determine dose modifications to CAPOX for neutropenia and thrombocytopenia

b Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy (XELODA product labeling, Genentech, Inc., Feb 2019)

c Dose modification table is based upon capecitabine product labeling; dose rounding should be performed per institutional guidelines

d In certain instances of asymptomatic or mildly symptomatic Grade 2 laboratory abnormalities (for example, anemia), investigators may choose to maintain capecitabine dose level and/or to resume capecitabine prior to resolution to Grade 1. This should be done only when the risk to patient from capecitabine dose interruption and/or reduction outweighs the risk to the patient from the AE, and when the action is consistent with usual and customary clinical practice.

Table 19. Dose Modification for Oxaliplatin-associated Neurotoxicity Attributed to CAPOX[a]

Paresthesia and Peripheral Sensory Neuropathy (Grade[b])	Duration of Neurotoxicity[a]		
	1–7 Days	>7 Days	Persistent (Not Resolved Between Cycles)
Paresthesias/dysesthesias of short duration that resolve and do not interfere with function (Grade 1)	No Change	No Change	No Change
Paresthesias/dysesthesias interfering with instrumental	No Change	No Change	CAPOX: Decrease oxaliplatin to 100 mg/m^2

Table 19. Dose Modification for Oxaliplatin-associated Neurotoxicity Attributed to CAPOX[a]

Paresthesia and Peripheral Sensory Neuropathy (Grade[b])	Duration of Neurotoxicity[a]		
	1–7 Days	>7 Days	Persistent (Not Resolved Between Cycles)
activities of daily living (Grade 2)			
Paresthesias/dysesthesias with pain or with functional impairment that interfere with self-care activities of daily living ADL (Grade 3)	1st time: CAPOX: Decrease oxaliplatin to 100 mg/m^2 2nd time: CAPOX: Decrease oxaliplatin to 65 mg/m^2	STOP	STOP
Persistent paresthesias/dysesthesias that are life-threatening (Grade 4)	STOP	STOP	STOP
Pharyngo-laryngeal dysesthesias	No Change	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours

a Neurotoxicity attributed to capecitabine should be managed following the guidelines for other adverse events related to capecitabine listed in Table 18.
b AE severity graded using the NCI CTCAE v5.0.

7.9.4. Trastuzumab Dose Modifications

In the event of Grade ≥3 trastuzumab-related AEs other than IRRs (Section 7.9.6), hold trastuzumab until the AE resolved to Grade ≤1 or pretreatment levels and initiate or intensify applicable medical therapy, as appropriate. Resume trastuzumab at the same dose; the trastuzumab dose may not be reduced. If dosing of trastuzumab is held for >4 weeks and the medical monitor has agreed to restart trastuzumab, the IV loading dose of 6 mg/kg for Cohorts 1A and 1B or 8 mg/kg for all other cohorts should be given per approved dosing instructions. Trastuzumab may also be given on a weekly basis at 2 mg/kg IV once weekly, in order to resynchronize administration to Day 1 of each cycle after discussion with the medical monitor. Trastuzumab should be discontinued if a delay greater than 6 weeks is required due to treatment-related toxicity, unless a longer delay is approved by the study medical monitor. In the event that trastuzumab is discontinued for any reason prior to disease progression, tucatinib, CAPOX, or FOLFOX therapy may be continued until disease progression. Trastuzumab dose modification guidelines for left ventricular dysfunction and cardiomyopathy are presented in Section 7.9.4.1 for IRR in Section 7.9.6 and for hypersensitivity reaction in Section 7.9.7.

7.9.4.1. Dose Modifications for Left Ventricular Dysfunction

Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab can also cause asymptomatic decline in LVEF.

Trastuzumab dose modification guidelines for left ventricular dysfunction, regardless of relationship to study intervention, are provided in Table 20.

Table 20. Trastuzumab Dose Modification Guidelines for Left Ventricular Dysfunction

LVEF at Assessment	Action
Symptomatic CHF	Discontinue trastuzumab
LVEF ≥50%	Continue treatment with trastuzumab
LVEF 45% to <50% with <10 percentage points decrease from baseline	Continue treatment with trastuzumab
LVEF <45% or 45% to <50% with ≥10 percentage points decrease from baseline	Hold trastuzumab, repeat LVEF in 3-4 weeks
• Repeat LVEF at 3-4 weeks:	
o LVEF ≥50%	Resume treatment with trastuzumab
o LVEF 45% to 49%	
– <10 percentage points decrease from baseline	Resume treatment with trastuzumab
– ≥10 percentage points decrease from baseline	Discontinue trastuzumab
o LVEF <45%	Discontinue trastuzumab

CHF = Congestive Heart Failure; LVEF = Left Ventricular Ejection Fraction

7.9.5. Pembrolizumab Dose Modifications

7.9.5.1. Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs (irAEs) Associated with Pembrolizumab Combination Treatment

AEs associated with pembrolizumab combination exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab combination administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose reductions of pembrolizumab are not allowed.

Attribution of Toxicity:

When study treatments are administered in combination, attribution of an AE to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to combinations, pembrolizumab must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for irAEs.

In these cases where the toxicity is attributed to combinations, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

Holding Study Treatments:

When study treatments are administered in combination and if the AE is considered immune-related, pembrolizumab should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from combination therapy.

Restarting Study Treatments:

Participants may restart pembrolizumab combination treatments as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for irAEs, combination treatment may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab are provided in Table 21.

Treatment of Immune-related Adverse Events

For immunotherapeutic agents, treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade version 5.0). In general, Grade 1 or 2 irAEs are treated symptomatically, and persistent Grade 2, Grade 3, or Grade 4 irAEs are managed with moderate to high corticosteroids.

Table 21. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab combination treatments must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab combination treatments have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus)

	Recurrent Grade 3 or Grade 4	Permanently discontinue	equivalent) followed by taper	• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT Elevation or Increased Bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and	

	Grade 3 or 4	Withhold or permanently discontinue[d]	initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

a AST/ALT: >3.0 to 5.0× ULN if baseline normal; >3.0 to 5.0× baseline if baseline abnormal; bilirubin:>1.5 to 3.0× ULN if baseline normal; >1.5 to 3.0× baseline if baseline abnormal.
b AST/ALT: >5.0 to 20.0× ULN, if baseline normal; >5.0 to 20.0× baseline, if baseline abnormal; bilirubin:>3.0 to 10.0× ULN if baseline normal; >3.0 to 10.0× baseline if baseline abnormal.
c AST/ALT: >20.0× ULN, if baseline normal; >20.0× baseline, if baseline abnormal; bilirubin: >10.0× ULN if baseline normal; >10.0× baseline if baseline abnormal.
d The decision to withhold or permanently discontinue pembrolizumab combination treatment is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab combination treatment may be resumed.
e Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).
AE(s)=adverse event(s); ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.
Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

7.9.5.2. Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab combination treatment may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab combination treatment-associated infusion reactions are provided in Table 22.

Table 22. Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Stop Infusion Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg PO (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg,	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors	No subsequent dosing

Table 22. Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	• Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	

CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs.
Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov

7.9.5.3. Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab combination treatment may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 42 days of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

7.9.6. Infusion-related Reactions

Symptoms of IRR occurring after administration of trastuzumab, oxaliplatin, leucovorin, or fluorouracil include fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. In severe cases, symptoms have included bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, usually reported during or immediately following the initial infusion. However, the onset and clinical course are variable, including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

Interrupt infusion in all participants experiencing dyspnea or clinically significant hypotension, and administer supportive therapy (which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen). Any IRR related to study treatment with any IV administered agent should be managed according to the prescribing information and/or institutional standard of care for the causative agent. Participants should be evaluated and

carefully monitored until complete resolution of signs and symptoms. In subsequent infusions, premedicate participants with antihistamines and/or corticosteroids.

Discontinue the causative agent(s) in participants with Grade 3-4 infusion reactions.

7.9.7. Allergic/Hypersensitivity Reactions

Allergic/hypersensitivity reactions are characterized by adverse local or general responses from exposure to an allergen (NCI CTCAE v5.0). For purposes of this study, allergic/hypersensitivity reactions are differentiated from IRRs by being defined as occurring >24 hours after infusion of study treatment. Allergic/hypersensitivity reactions may manifest in the same manner as IRRs, ie, a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension.

Supportive Care for Hypersensitivity Reactions Types 1 and 3:
Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex mediated Type 3 hypersensitivity reactions are similar to the AEs of Type 1 reactions but are likely to be delayed from the time of infusion and may include symptoms such as rash, urticaria, polyarthritis, myalgia, polysynovitis, fever, and, if severe, glomerulonephritis.

All participants should be closely observed while receiving study intervention infusions and monitoring for clinical signs of a systemic reaction will continue thereafter for clinical signs of allergic reactions/hypersensitivity.

In the case of a hypersensitivity reaction, the participant will be treated symptomatically with supportive care, further monitoring, and treatment with antihistamines and/or corticosteroids. Study infusions may be stopped and the participant will be followed until the end of the study.

7.9.8. Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalized or systemic allergic/hypersensitivity reaction. Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death. (NCI CTCAE v5.0; Rosello 2017).

If anaphylaxis occurs, administration of the causative agent (s) should be immediately and permanently discontinued.

7.9.9. Management of Diarrhea

Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. If an alternate cause of diarrhea is suspected and/or identified, treat accordingly.

For participants who are receiving primary antidiarrheal prophylaxis, please refer to Section 7.11.2 for dosing guidance. Antidiarrheal prophylaxis should be held in situations where use is contraindicated (eg, immune mediated colitis/diarrhea, bacterial enterocolitis), until resolution of the contraindication.

In participants receiving antidiarrheals for symptomatic control of treatment-associated diarrhea:

- **Early Detection:** Instruct participants to report diarrhea on the first symptom/sign of diarrhea.
- **Early Intervention:**
    - For participants who are not receiving prophylaxis, provide participants with prescription for loperamide (or other instructions for obtaining loperamide) and instruct them to start treatment as soon as first unformed stool occurs. The recommended dose of loperamide is 4 mg at first unformed stool, followed by 2 mg every 2 to 4 hours until diarrhea free (maximum 16 mg/day).
    - In participants who have persistent Grade 1 diarrhea despite loperamide (including participants receiving antidiarrheal prophylaxis), consider treatment with Lomotil (diphenoxylate hydrochloride and atropine sulfate) 2.5 mg/0.025 mg every 6 to 8 hours
    - Instruct participants to call site if diarrhea persists >48 hours or there is an increase of ≥7 stools per day over baseline (Grade 3 Diarrhea per CTCAE v5.0), or with other warning signs such as fever, bloody stools, or severe abdominal pain.
    - Instruct participants to maintain oral hydration. Intervention with IV fluids and electrolyte replacement should be considered as clinically indicated.
    - Instruct participants to seek medical attention if unable to maintain oral hydration due to diarrhea or with other warning signs as noted above. If diarrhea is severe (ie, requiring IV rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics should be prescribed. In participants with severe diarrhea, or any diarrhea associated with severe nausea or vomiting, hospitalization should be considered for IV hydration and correction of electrolyte imbalances.

7.9.10. Dose Modifications for Diarrhea

Tucatinib should be modified before chemotherapy or pembrolizumab (where applicable), except in instances where participants are receiving mFOLFOX6, where discontinuation of the fluorouracil bolus dose may first be considered. See Table 13 for dose modification guidelines of tucatinib for diarrhea. Dose modifications for chemotherapy should also be considered where appropriate (see Table 15 and Table 18). For participants receiving treatment with pembrolizumab, interruption of pembrolizumab should be considered if no improvement in the participant's condition is achieved after initiation of supportive care measures and dose modifications to tucatinib and/or chemotherapy (where appropriate). Diagnostic work-up for irAEs (ie, colitis) should be also initiated (see Table 21). When diarrhea is under control, treatment with tucatinib, pembrolizumab, and chemotherapy may be reinstated when applicable. Use of prophylactic antidiarrheals may also be considered where clinically indicated.

7.10. Required Premedication and Postmedication

Premedication and postmedication should be administered in accordance with local product labeling and per institutional standard of care.

7.11. Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent through the safety reporting period.

7.11.1. Potential Concomitant Drug Interactions

7.11.1.1. Tucatinib

Tucatinib is cleared predominantly by CYP2C8 and to a lesser extent by CYP3A4. Strong CYP2C8 inhibitors and strong CYP2C8 or CYP3A4 inducers are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib treatment.

Tucatinib exhibits inhibition of human CYP3A enzymes, and therefore has the potential to interact with other medications that are substrates of CYP3A. Use of sensitive CYP3A substrates should be avoided 1 week prior to enrollment and during study treatment. Consider using an alternate medication that is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Treatment with tucatinib is associated with mild increases in serum creatinine that were reversible upon treatment discontinuation. A dedicated DDI study demonstrated no impact on renal function.

7.11.1.2. Trastuzumab

Please refer to the local product labeling for trastuzumab potential drug interactions.

In PK studies, trastuzumab (a monoclonal antibody) did not alter the plasma concentrations of small molecules such as paclitaxel, docetaxel, or doxorubicin. It is therefore very unlikely that trastuzumab would have an effect on the PK of tucatinib. There was no DDI between tucatinib and trastuzumab observed in Study ONT-380-005, a combination study of tucatinib with capecitabine and trastuzumab.

7.11.1.3. FOLFOX

Please refer to the local product labeling for FOLFOX potential drug interactions.

7.11.1.4. CAPOX

Please refer to the local product labeling for CAPOX potential drug interactions.

7.11.1.5. Pembrolizumab

As pembrolizumab is an IgG4 antibody that is administered parenterally and cleared by catabolism, food and DDI are not anticipated to affect exposure. No dedicated DDI studies have therefore been performed. As systemic corticosteroids may be used to treat immune mediated ARs concomitant with pembrolizumab, the potential for a PK DDI with pembrolizumab was, however, assessed. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Similarly, the potential of DDI between pembrolizumab and chemotherapy agents as well as other small molecules is expected to be low.

No effect of coadministered pemetrexed and carboplatin, epacadostat, or axitinib on pembrolizumab PK was observed.

7.11.2. Required Concomitant Therapy

All participants enrolled in Cohorts 1D, 1E, and 2B, and all participants enrolled in Cohort 2A who are treated with tucatinib + trastuzumab + pembrolizumab + mFOLFOX6 must also receive primary prophylaxis with antidiarrheal medication beginning concomitantly with the first dose of tucatinib on Cycle 1 Day 1, as follows: loperamide 4 mg three times daily (Days 1 to 14) for the first 14 days followed by 4 mg twice daily (Day 15 through Day 42). Following this initial 42-day period, participants may continue on antidiarrheal prophylaxis at a dose of 2 to 4 mg as needed, not to exceed 16 mg per day (see Section 7.9.9). The Investigator must ensure that all participants who are scheduled to receive tucatinib have an adequate supply of loperamide prior to Cycle 1 Day 1 of treatment.

- The first dose of loperamide must be administered concomitantly with the first dose of tucatinib. The dosing of loperamide should be titrated such that participants have 1-2 stools per day throughout Days 1-42 and afterwards, as necessary. The dose of loperamide can be modified, or loperamide can be held at any point during the study as per investigator discretion if participant has constipation or <1 stool per day.
- Antidiarrheal prophylaxis should be held in situations where use is contraindicated (eg, immune mediated colitis/diarrhea, bacterial enterocolitis), until resolution of the contraindication.
- If tucatinib is discontinued during the first 42 days of treatment, antidiarrheal prophylaxis is no longer required, but should be used as needed (see Section 7.9.9).
- The Investigator must ensure that all participants who are scheduled to receive tucatinib have an adequate supply of loperamide prior to Cycle 1 Day 1 of treatment. Details regarding sourcing of loperamide may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.
- The Investigator must review the Patient Instructions for the prophylaxis and management of diarrhea with the participant prior to treatment on Cycle 1 Day 1.
- The Investigator must ensure that all participants have received and agreed to use a diary to record the number of stools and the amount of loperamide and/or other antidiarrheals used and must review the results of the diary with patients during each visit in the first 6 weeks of study treatment. Investigators should review the data in order to accurately record diarrhea AEs and the grades for the events that occur during the first 6 weeks of study treatment (Days 1-42).

Antidiarrheal prophylaxis will not be required for participants enrolled in Cohorts 1C, 1F, 1G, or for participants in Cohort 2A who are treated with tucatinib + trastuzumab + pembrolizumab + CAPOX, unless recommended by the SMC and required by the Sponsor based on a review of the data from these cohorts during the course of the study. Should antidiarrheal prophylaxis be required, the dose and schedule of loperamide as described above will be followed. Participants must be instructed on the optimal use of antidiarrheals for symptomatic control of treatment-associated diarrhea as described in Section 7.9.9.

7.11.3. Allowed Concomitant Therapy

Participants may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria. However, efforts should be made to maintain stable doses of concomitant medications during the course of study treatment. All blood products and concomitant medications received from Day 1 (predose) through the safety reporting period are to be recorded in the medical records.

- During study treatment, participants may receive supportive care, including bisphosphonates, hematologic and anti-infectious support, pain management, antacids, laxatives, and treatment of other newly diagnosed or concurrent medical conditions
- Antidiarrheals are required for Cohorts 1D, 1E, 2B, and all participants enrolled in Cohort 2A who are treated with tucatinib + trastuzumab + pembrolizumab + mFOLFOX6 (see Section 7.11.2). For other cohorts, prophylactic use of antidiarrheals is permitted at the discretion of the investigator. Symptomatic treatment of diarrhea should follow recommendations as described in Section 7.9.9. Prophylactic and symptomatic treatment of nausea and vomiting may be used per standard-of-care
- Thoracentesis or paracentesis may be performed, if needed for comfort, following consultation with the medical monitor
- If surgical intervention or localized radiation become indicated (either for palliation or down-staging of previously unresectable tumor), these interventions should be avoided if clinically feasible until after the second response assessment and the medical monitor should be consulted prior to the intervention occurring
- Blood products and growth factors should be utilized as clinically indicated and following institutional policies and recommendations
- Routine prophylaxis with vaccines is permitted, if vaccines used do not contain live micro-organisms
- Systemic glucocorticoids are permitted only for the following purposes:
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - As needed for the prevention of emesis
    - Premedication for IV contrast allergies
    - Short-term oral or IV use in doses >10 mg/day prednisone equivalent for COPD exacerbations
    - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- In addition, the following glucocorticoid use is allowed:
    - For topical use or ocular use
    - Intraarticular joint use

- For inhalation in the management of asthma or chronic obstructive pulmonary disease

7.11.4. Concomitant Therapies to be Used with Caution

Participants on anti-coagulant treatment should be closely monitored during study treatment.

Sensitive substrates of CYP3A (Appendix F); tucatinib exhibits inhibition of human CYP3A enzymes, and therefore has the potential to interact with other medications that are substrates of CYP3A. Therefore, concomitant use of tucatinib with sensitive CYP3A substrates should be avoided 1 week prior to the first dose of tucatinib and while on study treatment. Consider using an alternate medication that is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Concomitant use of tucatinib with digoxin, a P-glycoprotein (P-gp) substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dosage adjustment recommendations due to drug interactions.

7.11.5. Prohibited Concomitant Therapy

The following therapies are prohibited during the study (unless otherwise noted):

- Investigational drugs and devices
- Anticancer therapy, including but not limited to chemotherapy, hormonal therapy, and anti-VEGF antibodies
- Immunotherapy not specified in this protocol; if the investigator determines participant requires treatment with the aforementioned therapy for any reason, pembrolizumab must be discontinued.
- Radiation therapy, except for palliative radiotherapy at focal non-central nervous system sites that are not considered target lesions according to RECIST v1.1, which may be given after consultation with the medical monitor. Radiation therapy directed at target lesions according to RECIST v1.1 requires prior approval by the medical monitor. Tucatinib, CAPOX, and FOLFOX must be held 7 days prior to and 7 days post radiation therapy.
- Live or live attenuated vaccines within 30 days before the first dose of study intervention, while participating in the study, and for at least 3 months after last dose of chemotherapy. if the investigator determines participant requires treatment with the aforementioned therapy for any reason, pembrolizumab must be discontinued. Note: Killed vaccines are allowed.
- Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of study treatment (see Appendix D)

- Strong inhibitors or inducers of CYP2C8 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib treatment (Appendix E). Moderate inhibitors of CYP2C8 should be used with caution.
- Warfarin therapy, or therapy with other coumarin derivatives is not permitted on the study for any participant receiving CAPOX (Cohorts 1C, 1F, and 2A).
- Participants may not receive immunosuppressive medications during the study. If the investigator determines participant requires treatment with the aforementioned therapy for any reason, pembrolizumab must be discontinued.

7.12. Management of Overdose

7.12.1. Tucatinib

In the event of an overdose of tucatinib, defined as any dose greater than the prescribed dose, study personnel should:

- Care for and medically stabilize the participant until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of tucatinib.
- Notify the medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of tucatinib administered, participant weight) and AEs, if any.

Overdose events (with or without associated AEs) are to be captured on the AE eCRF.

Overdose is reportable to Pfizer Safety only when associated with an SAE.

7.12.2. Pembrolizumab

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Overdose is reportable to Pfizer Safety only when associated with an SAE.

7.12.3. Trastuzumab, Oxaliplatin, Capecitabine, Leucovorin, and Fluorouracil

Refer to the local product labeling for overdose information for trastuzumab, oxaliplatin, capecitabine, leucovorin, and fluorouracil.

7.13. Treatment Compliance

Study treatment administration will be performed by study site staff and documented in source documents and the eCRF.

Study-drug compliance will be assessed on a participant-by-participant basis using participant diaries. The pharmacist or designee will record the number of tucatinib tablets dispensed to each individual participant, and the number of tablets returned to the clinic at the end of each cycle.

Data regarding the administration and dose of trastuzumab, pembrolizumab, oxaliplatin, leucovorin, capecitabine, and fluorouracil will also be collected by the site after each cycle. Dose

modifications and interruptions of any study treatment will be documented in the source documents and the eCRF.

Following implementation of Amendment 5 and entry of remaining on-treatment participants into the LTEP, treatment administration data will no longer be collected in eCRFs. Please refer to Section 10.2 for further detail on LTEP data collection requirements.

8. STUDY ACTIVITIES

8.1. Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 9.5.1.7). Any study protocol-related AE (defined in Section 9.5.1.1) as well as any concomitant medications given for treatment of the AE should be recorded from the time of informed consent.

Clinical laboratory assessments (serum/plasma chemistry panel, coagulation panel, serum cystatin C, CBC with differential [manual differential if clinically indicated, see Section 9.5.3], urinalysis [including urine protein and creatinine, with microscopy if clinically indicated], physical exam, vital signs, weight, and performance status) may be performed within 1 day prior to administration of study treatment. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

Participants still receiving clinical benefit and remaining on study treatment as of Amendment 5 may continue receiving study intervention during the LTEP. During this phase of the study, only information related to pregnancies and SAEs will be reported to the Sponsor. All safety and efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care, with the exception of pregnancy testing which will continue as outlined in the schedule of events for participants of childbearing potential.

A schedule of events is provided in Appendix A. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 9.

8.2. Screening Visit (Days –28 to –1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (including assessment of diarrhea and antidiarrheal usage)
- Hepatitis B and C screening
- Radiological disease assessment (computed tomography [CT], positron emission tomography [PET]-CT, and/or MRI)
- Concomitant medications and AEs
- Electrocardiogram (ECG)
- ECHO/MUGA
- Blood sample for biomarker analysis

- Collection of most recently available tissue, if available. For participants enrolled in Cohorts 2A and 2B, collection of most recently available tissue is required.
- Thyroid function tests for Cohorts 1E, 1F, 1G, and 2A

8.2.1. Baseline Visit (Day –7 to Day –1)*

- Inclusion/exclusion criteria
- Vital signs, weight, height
- Physical exam
- ECOG Performance status
- Confirmation of last blood transfusion
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Coagulation panel
- Urinalysis
- Urine protein/creatinine ratio
- Concomitant medications and AEs
- Pregnancy test for participants of childbearing potential within 24 hours of treatment
- Radiological disease assessment (CT, PET-CT, and/or MRI) for participants receiving oxaliplatin during screening period

* Baseline visit should be scheduled to ensure that determination of estimated GFR can occur within 7 days of enrollment.

8.3. FOLFOX Treatment Period (14-day cycles) Phase 1b Tucatinib Dose Escalation (Cohorts 1A and 1B), Japan-specific Cohort 1D, Pembrolizumab Cohort 1E, and Phase 2 Tumor Specific Expansion Cohorts (Cohorts 2A and 2B)

8.3.1. Cycle 1 Day 1 – FOLFOX

- Vital signs, including weight*
- Physical exam*
- ECOG Performance status*
- Confirmation of last blood transfusion
- CBC with differential*
- Serum/plasma chemistry panel*
- Serum cystatin C*(If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)

- Urinalysis*
- Urine protein/creatinine ratio
- Blood samples for oxaliplatin PK (predose and postdose; Cohorts 1A and 1B only, see Table 23)
- Blood samples for tucatinib PK (predose and postdose for Cohort 1D only, see Table 25)
- Urine samples for oxaliplatin PK (predose and postdose; Cohorts 1A and 1B only, see Table 24)
- Pregnancy test for participants of childbearing potential, to be done within 24 hours of treatment
- Concomitant medications and AEs (including assessment of diarrhea events and antidiarrheal usage)
- Ensure participant has adequate supply of loperamide prior to Cycle 1 Day 1 and administer 1st dose of loperamide concomitantly with the first dose of tucatinib (not applicable to Cohort 1A and Cohort 1B).
- Administer oxaliplatin, leucovorin, fluorouracil Q2W
- Administer trastuzumab and continue Q2W in Cohorts 1A and 1B
- Administer trastuzumab and continue Q3W in Cohorts 1D, 1E, 2A, and 2B
- Administer pembrolizumab and continue Q6W in Cohorts 1E and 2A

Cohorts 1D, 1E, 2A, and 2B:

- Tucatinib dispensation and administration (Participant will self-administer the remainder of tucatinib doses during the treatment cycle and document in the diary.)
- Administration of first dose of loperamide concomitant with first dose of tucatinib (Participant will self-administer the remainder of loperamide doses during the treatment cycle and document in the diary.)

Note: For participants enrolled in Cohorts 1D, 1E, and 2B, and for participants enrolled in Cohort 2A who receive mFOLFOX6, beginning with the first dose of tucatinib, loperamide should be taken as follows: 4 mg three times daily (Days 1 to 14) during Cycle 1 followed by 4 mg twice daily (Day 15 through Day 42). The first dose of loperamide must be administered concomitantly with the first dose of tucatinib. The dosing of loperamide should be titrated such that participants have 1-2 stools per day throughout Days 1-42 and afterwards, as necessary. The dose of loperamide can be modified, or loperamide can be held at any point during the study as per investigator discretion if participant has constipation or <1 stool per day. Use of antidiarrheals will be collected. Following this initial 42-day period, participants may continue on antidiarrheal prophylaxis at a dose of 2 to 4 mg as needed, not to exceed 16 mg per day (see Section 7.11.2 for more details).

* Predose assessments do not need to be repeated if performed within 1 day prior to dose administration

8.3.2. Cycle 1 Day 3 (±1 d) – FOLFOX (Cohorts 1A and 1B only)

- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Concomitant medications and AEs

8.3.3. Cycle 1 Day 8 (±1 d) – FOLFOX (Cohorts 1A, 1B, 1D, 1E, 2A and 2B)

- Vital signs, including weight
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Concomitant medications and AEs (including assessment of diarrhea events)
- Assess antidiarrheal medication usage (not applicable to Cohorts 1A and 1B)

Tucatinib phase 1b dose escalation cohorts utilizing FOLFOX only (Cohorts 1A and 1B):

- Tucatinib dispensation and administration. (Participant will self-administer the remainder of doses during the treatment cycle and document in the diary.)

8.3.4. Cycle 2 and Cycle 3 Day 1 (±1 d) – FOLFOX (Cohorts 1A, 1B, 1D, 1E, 2A, and 2B)

- Vital signs, including weight
- Physical exam
- ECOG Performance status
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Urinalysis
- Urine protein/creatinine ratio
- Pregnancy test for participants of childbearing potential, to be done within 24 hours of treatment
- Concomitant medications and AEs (including assessment of diarrhea events)
- Documentation of concomitant medications, including assessment of antidiarrheal medication usage from previous cycle (not applicable to Cohorts 1A and 1B). Use of all antidiarrheals is to be documented in the participant's diary.

Note: For participants enrolled in Cohorts 1D,1E, 2B, and for participants enrolled in Cohort 2A who receive mFOLFOX6, beginning with the first dose of tucatinib, loperamide should be taken as follows: 4 mg three times daily (Days 1 to 14) during Cycle 1 followed by 4 mg twice daily

(Day 15 through Day 42). The first dose of loperamide must be administered concomitantly with the first dose of tucatinib. The dosing of loperamide should be titrated such that participants have 1-2 stools per day throughout Days 1-42 and afterwards, as necessary. The dose of loperamide can be modified, or loperamide can be held at any point during the study as per investigator discretion if participant has constipation or <1 stool day. Use of antidiarrheals will be collected. Following this initial 42-day period, participants may continue on antidiarrheal prophylaxis at a dose of 2 to 4 mg as needed, not to exceed 16 mg per day (see Section 7.11.2 for more details).

- Administer oxaliplatin, leucovorin, fluorouracil Q2W
- Administer trastuzumab Q2W in Cohorts 1A and 1B
- Administer trastuzumab Q3W in Cohorts 1D, 1E, 2A, and 2B
- Administer pembrolizumab Q6W in Cohorts 1E and 2A
- Tucatinib dispensation and administration. (Participant will self-administer the remainder of tucatinib doses during the treatment cycle and document in the diary.)
- Blood samples for tucatinib PK (predose and postdose in Cycle 2 only for Cohorts 1A and 1B only; predose only in Cycle 3; see Table 23; predose only in Cycles 2 and 3 for Cohorts 1D, 1E, 2A, and 2B; see Table 25 and Table 26)
- Blood samples for oxaliplatin PK (predose and postdose, Cycle 2 only, Cohorts 1A and 1B only; see Table 23)
- Urine samples for oxaliplatin PK (predose and postdose, Cycle 2 only; Cohorts 1A and 1B only, see Table 24)

8.3.5. Cycle 2 and Cycle 3 Day 3 (±1 d) – FOLFOX (Cohorts 1A and 1B only)

- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- AEs

8.3.6. Cycle 2 and Cycle 3 Day 8 (±1 d) – FOLFOX (Cohorts 1A, 1B, 1D, 1E, 2A and 2B)

- Vital signs, including weight (not applicable to Cohorts 2A and 2B)
- CBC with differential (not applicable to Cohorts 2A and 2B)
- Serum/plasma chemistry panel (not applicable to Cohorts 2A and 2B)
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected) (not applicable to Cohorts 2A and 2B)
- Coagulation panel (not applicable to Cohorts 2A and 2B)
- Urinalysis (not applicable to Cohorts 2A and 2B)
- Urine protein/creatinine ratio (not applicable to Cohorts 2A and 2B)
- Concomitant medications and AEs (including assessment of diarrhea events)

- Assess antidiarrheal medication usage (not applicable to Cohorts 1A and 1B)

8.3.7. Cycle 4 (and All Subsequent Cycles) Day 1 (±1 d) – FOLFOX

- Vital signs, including weight
- Physical exam
- ECOG Performance status
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Urinalysis
- Urine protein/creatinine ratio
- Pregnancy test for participants of childbearing potential, to be done within 24 hours of treatment
- AEs (including assessment of diarrhea events)
- Assess antidiarrheal medication usage (not applicable to Cohorts 1A and 1B). Use of all antidiarrheals is to be documented in the participant's diary.
- Documentation of concomitant medications, including assessment of antidiarrheal medication usage from previous cycle; Use of all antidiarrheals is to be documented in the participant's diary (not applicable to Cohorts 1A and 1B).
- Administer oxaliplatin, leucovorin, fluorouracil Q2W
- Administer trastuzumab Q2W in Cohorts 1A and 1B
- Administer trastuzumab Q3W in Cohorts 1D, 1E, 2A, and 2B
- Administer pembrolizumab Q6W in Cohorts 1E and 2A
- Tucatinib dispensation and administration. (Participant will self-administer the remainder of doses during the treatment cycle and document in the diary.)
- Blood samples for tucatinib PK through Cycle 6, only predose (Cohorts 1A, 1B, 1D, 1E, 2A, and 2B; see Table 23, Table 25, and Table 26)

8.3.8. Every 6 Weeks* or 8 Weeks† (±7 d) – FOLFOX

- Radiological disease assessment (CT, PET-CT, and/or MRI)
- Thyroid function tests for Cohorts 1E and 2A Q6W

* Scans occur every 6 weeks for Cohorts 1D, 1E, 2A, and 2B for the first 24 weeks, then every 9 weeks

† Scans occur every 8 weeks for phase 1b cohorts utilizing FOLFOX (Cohorts 1A and 1B) for the first 24 weeks, then every 12 weeks

8.3.9. Every 12 Weeks (±7 d) – FOLFOX

- ECHO or MUGA scan

8.4. CAPOX Treatment Periods (21-day cycles) – Phase 1b CAPOX Cohort (Cohort 1C), Phase 1b Pembrolizumab (Cohort 1F), and Phase 2 Tumor-Specific Expansion Cohort (Cohort 2A)

Note: For participants enrolled in Cohorts 1C and 1F and participants enrolled in Cohort 2A who are treated with CAPOX, antidiarrheal prophylaxis is not required, unless recommended by the SMC and required by the Sponsor based on a review of the data during the course of the study. Should antidiarrheal prophylaxis with loperamide be required, the dose and scheduled will be as follows: beginning with the first dose of tucatinib: 4 mg three times daily (Days 1 to 14) during Cycle 1 followed by 4 mg twice daily (Day 15 through Day 42). The dosing of loperamide should be titrated such that participants have 1-2 stools per day throughout Days 1-42 and afterwards, as necessary. The dose of loperamide can be modified, or loperamide can be held at any point during the study as per investigator discretion if participant has constipation or <1 stool per day. Following this initial 42-day period, participants may continue on antidiarrheal prophylaxis at a dose of 2 to 4 mg as needed, not to exceed 16 mg per day (see Section 7.11.2 for more details)

8.4.1. Cycle 1 Day 1 – CAPOX

- Vital signs, including weight*
- Physical exam*
- ECOG Performance status*
- Confirmation of last blood transfusion
- CBC with differential*
- Serum/plasma chemistry panel*
- Serum cystatin C* (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Urinalysis*
- Urine protein/creatinine ratio
- Pregnancy test for participants of childbearing potential, to be done within 24 hours of treatment
- Concomitant medications and AEs (including assessment of diarrhea events)
- Assess antidiarrheal medication usage. Use of all antidiarrheals is to be documented in the participant's diary.
- Ensure participants have loperamide to use as needed for symptomatic diarrhea, as described in Section 7.9.9. If needed, participants will self-administer loperamide during the treatment cycle and document in the diary.
- Administer oxaliplatin

- Administer capecitabine† (Participant will self-administer the remainder of doses during the treatment cycle and document in the diary.)
- Administer trastuzumab and continue Q3W
- Administer pembrolizumab and continue Q6W (Cohort 1F and 2A)
- Tucatinib dispensation and administration. (Participant will self-administer the remainder of doses during the treatment cycle and document in the diary.)

* Predose assessments do not need to be repeated if performed within 1 day prior to dose administration

† Capecitabine is administered BID beginning the evening of Day 1 to the morning of Day 15 of Cycle 1.

8.4.2. Cycle 1 Day 8 (±1 d) – CAPOX

- Vital signs, including weight
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Concomitant medications and AEs (including assessment of diarrhea events)
- Assess antidiarrheal medication usage. Use of all antidiarrheals is to be documented in the participant's diary.

8.4.3. Cycle 2 Day 1 (±1 d) – CAPOX

- Vital signs, including weight
- Physical exam
- ECOG Performance status
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Urinalysis
- Urine protein/creatinine ratio
- Pregnancy test for participants of childbearing potential, to be done within 24 hours of treatment
- AEs (including assessment of diarrhea events)
- Documentation of concomitant medications, including assessment of antidiarrheal medication usage from previous cycle. Use of all antidiarrheals is to be documented in the participant's diary.

- Ensure participants have loperamide to use as needed for symptomatic diarrhea, as described in Section 7.9.9.
- Administer oxaliplatin
- Administer capecitabine†
- Administer trastuzumab and continue Q3W
- Tucatinib dispensation and administration. (Participant will self-administer the remainder of doses during the treatment cycle and document in the diary.)
- Blood samples for tucatinib PK (predose; see Table 26)

†Capecitabine is administered BID Day 1 through Day 14 of Cycle 2.

8.4.4. Cycle 2 Day 8 (±1 d) – CAPOX

- Vital signs, including weight (not applicable to Cohort 2A)
- CBC with differential (not applicable to Cohort 2A)
- Serum/plasma chemistry panel (not applicable to Cohort 2A)
- Blood for serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected) (not applicable to Cohort 2A)
- Coagulation panel (not applicable to Cohort 2A)
- Urinalysis (not applicable to Cohort 2A)
- Urine protein/creatinine ratio (not applicable to Cohort 2A)
- Concomitant medications and AEs (including assessment of diarrhea events)
- Assess antidiarrheal medication usage

8.4.5. Cycle 3 (and All Subsequent Cycles) Day 1 (±1 d) – CAPOX

- Vital signs, including weight
- Physical exam
- ECOG Performance status
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Urinalysis
- Urine protein/creatinine ratio
- Pregnancy test for participants of childbearing potential, to be done within 24 hours of treatment
- AEs (including assessment of diarrhea events)

- Documentation of concomitant medications, including assessment of antidiarrheal medication usage from previous cycle. Use of all antidiarrheals is to be documented in the participant's diary.
- Administer oxaliplatin
- Administer capecitabine†
- Administer trastuzumab Q3W
- Administer pembrolizumab Q6W
- Tucatinib dispensation and administration. (Participant will self-administer the remainder of doses during the treatment cycle and document in the diary.)
- Blood samples for tucatinib PK (through Cycle 6), only predose (see Table 26)

†Capecitabine is administered BID Day 1-Day 14 of each cycle.

8.4.6. Every 6 Weeks (±7 d) CAPOX up to 24 Weeks and Every 9 Weeks Thereafter

- Radiological disease assessment (CT, PET-CT, and/or MRI)
- Thyroid function tests Q6W for Cohorts 1F and 2A

8.4.7. Every 12 Weeks (±7 d) - CAPOX

- ECHO or MUGA scan

8.5. Pembrolizumab (Chemotherapy-free) Treatment Periods (21-day cycles) – Pembrolizumab Cohort 1G

Note: For participants enrolled in Cohort 1G, antidiarrheal prophylaxis is not required, unless recommended by the SMC and required by the Sponsor based on a review of the data during the course of the study. Should antidiarrheal prophylaxis with loperamide will be required, the dose and schedule will be as follows: beginning with the first dose of tucatinib: 4 mg three times daily (Days 1 to 14) during Cycle 1 followed by 4 mg twice daily (Day 15 through Day 42). The dosing of loperamide should be titrated such that participants have 1-2 stools per day throughout Days 1-42 and afterwards, as necessary. The dose of loperamide can be modified, or loperamide can be held at any point during the study as per investigator discretion if participant has constipation or <1 stool per day. Following this initial 42-day period, participants may continue on antidiarrheal prophylaxis at a dose of 2 to 4 mg as needed, not to exceed 16 mg per day (see Section 7.11.2 for more details)

8.5.1. Cycle 1 Day 1

- Vital signs, including weight*
- Physical exam*
- ECOG Performance status*
- Confirmation of last blood transfusion
- CBC with differential*
- Serum/plasma chemistry panel*

- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Urinalysis*
- Urine protein/creatinine ratio
- Pregnancy test for participants of childbearing potential, to be done within 24 hours of treatment
- Concomitant medications and AEs
- Ensure participants have loperamide to use as needed for symptomatic diarrhea as described in Section 7.9.9.
- Administer trastuzumab and continue Q3W
- Administer pembrolizumab and continue Q6W
- Tucatinib dispensation and administration. (Participant will self-administer the remainder of doses during the treatment cycle and document in the diary.)

* Predose assessments do not need to be repeated if performed within 1 day prior to dose administration

8.5.2. Cycle 1 Day 8 (±1 d)

- Vital signs, including weight
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Concomitant medications and AEs (including assessment of diarrhea events)
- Assess usage of antidiarrheal medication

8.5.3. Cycle 2 Day 1 (±1 d)

- Vital signs, including weight
- Physical exam
- ECOG Performance status
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Urinalysis
- Urine protein/creatinine ratio
- Pregnancy test for participants of childbearing potential, to be done within 24 hours of treatment

- AEs (including assessment of diarrhea events)
- Documentation of concomitant medications, including assessment of antidiarrheal medication usage from previous cycle. Use of all antidiarrheals is to be documented in the participant's diary.
- Ensure participants have loperamide to use as needed for symptomatic diarrhea as described in Section 7.9.9.
- Administer trastuzumab and continue Q3W
- Tucatinib dispensation and administration. (Participant will self-administer the remainder of doses during the treatment cycle and document in the diary.)
- Blood samples for tucatinib PK (predose, see Table 26)

8.5.4. Cycle 2 Day 8 (±1 d)

- Vital signs, including weight
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Coagulation panel
- Urinalysis
- Urine protein/creatinine ratio
- Concomitant medications and AEs (including assessment of diarrhea events)
- Assess usage of antidiarrheal medication
- Ensure participants have loperamide to use as needed for symptomatic diarrhea as described in Section 7.9.9.

8.5.5. Cycle 3 (and All Subsequent Cycles) Day 1 (±1 d)

- Vital signs, including weight
- Physical exam
- ECOG Performance status
- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Urinalysis
- Urine protein/creatinine ratio
- Pregnancy test for participants of childbearing potential, to be done within 24 hours of treatment

- AEs (including assessment of diarrhea events)
- Documentation of concomitant medications, including assessment of antidiarrheal medication usage from previous cycle. Use of all antidiarrheals is to be documented in the participant's diary.
- Ensure participants have loperamide to use as needed for symptomatic diarrhea as described in Section 7.9.9.
- Administer trastuzumab Q3W
- Administer pembrolizumab Q6W
- Tucatinib dispensation and administration. (Participant will self-administer the remainder of doses during the treatment cycle and document in the diary.)
- Blood samples for tucatinib PK (through Cycle 6), only predose (Table 26)

8.5.6. Every 6 Weeks (±7 d) up to 24 Weeks and Every 9 Weeks Thereafter

- Radiological disease assessment (CT, PET-CT, and/or MRI)
- Thyroid function tests Q6W

8.5.7. Every 12 Weeks (±7 d)

- ECHO or MUGA scan

8.6. Long-term Extension Phase – Beginning of each Cycle and End of Treatment

Participants still receiving clinical benefit and remaining on study treatment as of Amendment 5 may continue receiving study interventions during the LTEP.

- Only information related to pregnancies and SAEs (Section 9.5.1.1 and Section 9.5.1.4.2) will be reported to the Sponsor
- All safety and efficacy assessments will be performed per usual and customary clinical practice, with the exception of pregnancy testing
- Pregnancy testing will continue to be performed as outlined in the schedule of events in participants of childbearing potential

8.7. End of Treatment Visit (30 to 37 Days After Last Dose of Study Treatment)

End of Treatment (EOT) visits should occur 30 to 37 days after the last dose of study treatment unless delayed due to an AE. Participants are considered to be receiving study treatment until all study treatments (oxaliplatin, capecitabine, fluorouracil, leucovorin, trastuzumab, pembrolizumab, and tucatinib) are discontinued, or if any new anticancer treatment is given. Note: The time to EOT visit may be longer than 37 days, but in no case should it be <30 days. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the participant will be contacted 30 to 37 days following the last treatment to assess for AEs.

- Vital signs, including weight
- Physical exam
- ECOG Performance status

- CBC with differential
- Serum/plasma chemistry panel
- Serum cystatin C (If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected)
- Coagulation panel
- Urinalysis
- Urine protein/creatinine ratio
- ECG
- ECHO or MUGA scan
- Pregnancy test for participants of childbearing potential
- AEs (including assessment of diarrhea events)
- Documentation of concomitant medications, including assessment of antidiarrheal medication usage from previous cycle. Use of all antidiarrheals is to be documented in the participant's diary.
- Radiological disease assessment (CT, PET-CT, and/or MRI)
- Blood sample for biomarker analysis (will not be collected after implementation of Amendment 5)
- Blood samples for tucatinib PK (Cohort 1D only, see Table 25; will not be collected after implementation of Amendment 5)

8.8. Follow-up (Every 9 or 12 Weeks ±14 Days)

As of Amendment 5, long term follow-up will be discontinued. Participants in long term follow-up as of Amendment 5 will transition to end of study.

Participants who discontinue study treatment will remain on study for follow-up (assessment of anticancer therapy and survival) until withdrawal of consent from the study, death, or administrative study closure whichever occurs first.

Participants that discontinue study treatment for reasons other than documented progressive disease per RECIST will continue to have disease assessments (CT, PET-CT, and/or MRI scans) approximately every 9 weeks (± 14 days) until radiographic disease progression (see Appendix A).

After the occurrence of documented disease progression, participants will be followed for survival approximately every 12 weeks (± 14 days) until death, withdrawal of consent, study closure.

8.9. End of Study

The date the participant met criteria for study discontinuation and the reason for study discontinuation will be recorded.

For participants of childbearing potential:

- Confirm with the participant that monthly pregnancy tests have been performed and have been negative
- Remind participant that monthly pregnancy tests will be performed for 7 months after the last dose of study treatment

9. STUDY ASSESSMENTS

9.1. Screening/Baseline Assessments

Screening/Baseline assessments will be conducted to establish study baseline status and determine study eligibility. Only participants who sign an informed consent and meet all inclusion and exclusion criteria specified in Section 6 will be enrolled in this study.

Participant medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

A physical exam, height, vital signs, weight, disease assessment (CT, PET-CT, or MRI scan) for baseline response efficacy assessment, CBC with differential, urinalysis, ECHO/MUGA, hepatitis B and C screening, serum/plasma chemistry panel, serum cystatin C, coagulation tests, ECOG performance status, ECG, blood sample for biomarker analysis, collection of most recently available tissue, urine protein/creatinine ratio, confirmation of last blood transfusion, review of AEs and concomitant medications, and serum/plasma pregnancy test (for females of childbearing potential) are required for all participants at screening and/or baseline as described in Section 8.2 and Appendix A.

9.2. Response/Efficacy Assessments

The determination of antitumor activity will be based on confirmed objective response assessments as defined by RECIST v1.1 (Eisenhauer 2009). Disease response will be assessed by the investigator. Treatment decisions will be made based upon local assessment of radiologic scans. Radiographic disease assessments will evaluate all known sites of disease, preferably using high quality spiral contrast CT, and covering, at a minimum, the chest, abdomen, and pelvis. PET-CT scans (if high quality CT scan is included) and/or MRI scans may also be used as appropriate, as well as additional imaging of any other known sites of disease (eg, nuclear bone scan imaging for bone lesions). For each participant, the same imaging modality as used at screening/baseline should be used throughout the study. Disease assessments will be performed at protocol-specified time points outlined in Section 8 and Appendix A.

Participants' clinical data must be available for eCRF source verification. Images may be collected by an independent central review facility for possible future analysis. Copies of tumor images must be made available for review by the Sponsor (or its designee) upon request.

During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

9.3. Pharmacokinetic Assessments

Blood (oxaliplatin and tucatinib) and urine (oxaliplatin) samples for PK assessments will be collected at protocol-defined time points (Table 23, Table 24, Table 25, and Table 26). Plasma concentrations of tucatinib will be analyzed using validated mass spectrometry methods. Concentrations of total platinum in plasma, free platinum in plasma ultrafiltrates, and platinum in

urine will be determined using validated methods. Remaining PK samples will be archived and may be used for the analysis of administered compounds or related species with exploratory, non-validated assays.

PK parameters will be calculated using standard non-compartmental methods. PK parameters to be estimated for Cohorts 1A, 1B, and 1D include but are not limited to area under the plasma concentration-time curve to the time of the last quantifiable concentration (AUC_{last}), maximum observed concentration (C_{max}), observed trough concentration in plasma (C_{trough}; tucatinib only), and time of C_{max} (T_{max}). For the other cohorts, PK parameters include, but are not limited to, observed trough concentration in plasma (C_{trough}; tucatinib only).

Following implementation of Amendment 5, no PK samples will be collected at EOT.

Table 23. Plasma Pharmacokinetic Sample Collection in FOLFOX Phase 1b Cohorts (Cohorts 1A, 1B)

Study Day	Time	Relative Time	Oxaliplatin[a]	Tucatinib
Cycle 1 Day 1	Predose (within 24 h)	Start of oxaliplatin infusion (2 h), first dose	X	-
	1 h intra-dose (±15 min)		X	-
	EOI (within 15 min)		X	-
Cycle 1 Day 1	1 h (±15 min)	End of oxaliplatin infusion (2 h), first dose	X	-
	2 h (±15 min)		X	-
	4 h (±15 min)		X	-
	6 h (±30 min)		X	-
Cycle 2 Day 1	Predose (within 2 h)	Start of oxaliplatin infusion (2 h), second dose[b]	X	X
	1 h intra-dose (±15 min)		X	X
	EOI (within 15 min)		X	X
Cycle 2 Day 1	1 h (±15 min)	End of oxaliplatin infusion (2 h), second dose	X	X
	2 h (±15 min)		X	X
	4 h (±15 min)		X	X
	6 h (±30 min)		X	X
Cycles 3-6 Day 1	Predose (within 2 hours)	Prior to time of AM tucatinib administration[b]		X

a Blood samples for oxaliplatin PK (predose and postdose) (Cohort 1A and 1B only)
b Participants should be instructed to take their morning dose of tucatinib in the clinic at the start of the oxaliplatin infusion.

Table 24. Urine Pharmacokinetic Sample Collection in FOLFOX Phase 1b Cohorts (Cohorts 1A, 1B)[a]

Study Day	Collection Window Start Time[a]	Collection Window End Time[a]	Relative Time	Oxaliplatin in Urine
Cycles 1 and 2 Day 1	Start of oxaliplatin infusion (within 15 min)	EOI (within 30 min)	Start of oxaliplatin infusion (2 h), first dose	X
Cycles 1 and 2 Day 1	EOI (within 30 min)	2 hours (±30 min)	End of oxaliplatin infusion (2 h), first dose	X
	2 hours (±30 min)	6 hours (±1 hour)		X
	6 hours (±1 hour)	24 hours (±2 hours)		X

a 24-hour urine sampling (START of oxaliplatin infusion to EOI, EOI to 2 hours post-EOI, 2 to 6 hours post-EOI, 6 to 24 hours post-EOI) will be performed from start of oxaliplatin infusion on D1 of Cycles 1-2. The postdose continuous urine collection will be taken at the end of each collection period (EOI, 2, 6, and 24 hours post-EOI) and the next collection time period will begin. Participants should be encouraged to stay hydrated to facilitate urine collection for PK analysis.

Table 25. Plasma Pharmacokinetic Sample Collection Timepoints: Japan-specific Cohort (1D)

Cycle	Cycle Day	Time	Window	Relative Time	Tucatinib PK
1	1	Predose	Within 24 hrs	Time of first tucatinib administration	X
		1 hr post-dose	± 5 min		X
		2 hrs post-dose	± 5 min		X
		3 hrs post-dose	± 15 min		X
		4 hrs post-dose	± 15 min		X
		6 hrs post-dose	± 15 min		X
		8 hrs post-dose	± 15 min		X
		10 hrs post-dose	± 30 min		X
		12 hrs post-dose	± 15 min	Prior to second tucatinib Day 1 administration	X
2-6	1	Predose	Within 2 hrs	Prior to time of AM tucatinib administration	X
EOT			30 to 37 days		X

Table 26. Plasma Pharmacokinetic Sample Collection for Cohorts 1C, 1E, 1F, 1G, 2A, 2B

Study Day	Time	Relative Time	Tucatinib
Cycles 2-6 Day 1	Predose (within 2 h)	Prior to time of AM tucatinib administration	X

9.4. Biomarker Assessments

Participants eligible for enrollment will have HER2 status determined by historic/local IHC, FISH, NGS, or cell-free DNA in samples prior to screening. When available, archival or fresh tumor blocks are to be collected at screening. Blood samples for biomarker assay will be drawn at screening and at EOT.

Biomarker assessments may include an exploratory assessment of mutations as potential biomarkers of response. Additional analyses including but not limited to IHC and NGS may be performed to interrogate biomarkers that are associated with tumor growth, survival, and resistance to targeted therapeutics. This assessment may enable the correlation of additional biomarkers with treatment outcome and may ultimately guide or refine patient selection strategies to better match tucatinib regimens with tumor phenotype/genotype in the future.

Refer to the Central Laboratory Manual for information on collection, processing, storage, and shipment of samples.

Following implementation of Amendment 5, no blood samples for biomarker assessments will be drawn at EOT.

9.5. Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests. Assessment of cardiac ejection fraction will be performed using MUGA scan or ECHO.

During the LTEP, all safety and efficacy assessments other than pregnancy testing will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue to be performed as outlined in the schedule of events. Following implementation of Amendment 5, only information related to pregnancies (defined in Section 9.5.1.4.2), and SAEs and AESIs (defined in Section 9.5.1.1) will be reported to the Sponsor.

Safety will be monitored over the course of the study by an SMC as described in Section 5.1.7.

9.5.1. Adverse Events

See Appendix G for additional details on recording and reporting AEs and SAEs.

9.5.1.1. Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a participant or clinical investigational participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events eCRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 that increase in CTCAE grade should be recorded.
- Medical conditions present or ongoing predose on study Day 1 that worsen in severity, increase in frequency, become related to study treatment, or worsen in any other way but do not meet the threshold for increase in CTCAE grade should be recorded.
- All AEs (regardless of relationship to study treatment should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 9.5.1.7). Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- In general, an abnormal laboratory value (eg, hematology, clinical chemistry, or urinalysis) should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, requires additional diagnostic testing or medical/surgical intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record "anemia" rather than "low hemoglobin").

  During the LTEP, SAEs will be reported to the Sponsor solely on the SAE form following the same reporting guidelines as outlined in Section 9.5.1.3, and will not be recorded within the eCRF.
- New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the participant at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the participant's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a participant exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the participant and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 9.5.1.6 for the definition of potential DILI).

If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and report such an assessment in the dedicated section of the Pfizer SAE submission assistant (PSSA) and in accordance with the SAE reporting requirements.

Adverse Event Severity

AE severity should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (tucatinib, trastuzumab, leucovorin, fluorouracil, capecitabine, oxaliplatin) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

9.5.1.2. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) are defined by the sponsor as a potential safety issue identified as a result of ongoing safety monitoring of their products. As such, surveillance for the AESIs MUST be undertaken at each treatment evaluation. Development of one of these AESIs (≥ Grade 1 unless otherwise noted) MUST be reported in terms of NCI CTCAE v5.0 grade and attribution.

All AESIs must be reported as an AE or SAE following the procedures described in Section 9.5.1.3, Section 9.5.1.7, and Section 9.5.1.8. In addition, an AESI that is also an SAE must be reported using the PSSA (Section 9.5.1.8). During the LTEP, only serious AESIs will be reported via PSSA..

AESIs for this study are:

1. Hepatotoxicity:
   - AST or ALT elevations that are >3× ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin >2× ULN, except in participants with documented Gilbert's syndrome
   - AST or ALT elevations >20 ×ULN
   - Bilirubin elevations >10.0 ×ULN

Measurement of conjugated and unconjugated bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology. The sponsor will subsequently determine whether the elevations are associated with other possible causes of aminotransferase elevation and hyperbilirubinemia, such as viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

2. Increase of serum cystatin C >1.5× baseline
3. ≥ Grade 3 diarrhea

9.5.1.3. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during participant questioning, discovered during physical examination, laboratory testing, and/or other means by recording them on the eCRF and/or SAE form, as appropriate. Diaries may be used for recording the number of stools per day to aid with accurately documenting and grading diarrhea AEs.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events eCRF (See Table 27 for more details):

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Important exceptions for this study are adverse reactions associated with the infusion of study treatment. Record each sign or symptom as an individual AE in addition to the IRR term. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

The SAE should be reported to Pfizer Safety using the PSSA (see Appendix G for more details). However, during the LTEP, SAEs will be reported to the Sponsor via PSSA following the same reporting guidelines as outlined below and will not be recorded within the eCRF.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and eCRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

9.5.1.4. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Refer to Appendix G for guidance on reporting/recording environmental exposure, exposure during pregnancy (EDP), exposure during breastfeeding (EDB), and occupational exposures.

9.5.1.4.1. Environmental Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness. Refer to Appendix G for guidance on reporting/recording environmental exposure.

9.5.1.4.2. Exposure During Pregnancy

An EDP occurs if:

- A participant is found to be pregnant while receiving or after discontinuing study intervention.
- A participant who is receiving or has discontinued study intervention inseminates a partner.
- A nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

- A family member or healthcare provider reports that they are pregnant after exposure to study intervention, for example, by ingestion or skin contact.

- A family member or healthcare provider who has been exposed to the study intervention, for example, by ingestion or skin contact and then inseminates their partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy). Refer to Appendix G for guidance on reporting/recording EDP.

- If EDP occurs in a participant or a participant's partner after the start of study intervention and until 7 months after the last dose of the last study intervention, the investigator must report this information to Pfizer Safety on the PSSA and an EDP supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 7 months after the last dose of the last study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety via PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs

when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to their partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to their partner.

9.5.1.4.3. Exposure During Breastfeeding

An EDB occurs if:

- A participant is found to be breastfeeding while receiving or after discontinuing study intervention (until 7 months after the last dose of the last study intervention).

- A nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a family member or healthcare provider who reports breastfeeding after having been exposed to study intervention, for example, by ingestion or skin contact. Refer to Appendix G for guidance on reporting/recording EDB.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed PSSA is maintained in the investigator site file.

9.5.1.4.4. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the PSSA regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA must be maintained in the investigator site file.

9.5.1.5. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. **Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety only if associated with an SAE.**

9.5.1.6. Potential Drug-induced Liver Injury

Hy's Law can be used to estimate severity and the likelihood that a study treatment may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential drug-induced liver injury (DILI) in the clinical setting(s) being studied. However, finding 1 Hy's

Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

Definition

Briefly, potential Hy's Law cases include the following 3 components:

- Aminotransferase (ALT and/or AST) elevation >3× ULN

AND

- Total bilirubin >2× ULN, without initial findings of cholestasis (ie, elevated serum alkaline phosphatase),

AND

- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Reporting Requirements

Any potential Hy's Law case should be handled as an SAE and reported promptly to the Sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3× ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study treatment.

Left Ventricular Ejection Fraction Decreased

For asymptomatic declines in LVEF leading to a change in study treatment or discontinuation of study treatment, the term "ejection fraction decreased" should be used, and severity Grades 2 to 4 used to report asymptomatic LVEF decrease.

For symptomatic congestive heart failure (CHF), the term "heart failure" should be used, and severity Grades 2 to 5 used to report symptomatic CHF.

9.5.1.7. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs is from study Day 1 (predose) through 30 days after the last study treatment. However, all study protocol-related AEs are to be recorded from the time of informed consent. For Cohorts 1A, 1B, 1C, 1D, and 2B, the safety reporting period for all SAEs is from study Day 1 (predose) through 30 days after the last study treatment. For Cohorts 1E, 1F, 1G, and 2A, all AEs meeting serious criteria, from the time of treatment allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the

investigator. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using PSSA.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the participant dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started. SAEs occurring during the safety reporting period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting.

9.5.1.8. Serious Adverse Events Require Immediate Reporting

All SAEs occurring in a participant during the safety reporting period are reported to Pfizer Safety on the PSSA immediately upon awareness and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Participant number
- Date of event onset
- Description of the event
- Study treatment, if known
- Investigator causality assessment

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

9.5.1.9. Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 9.5.1.8). The sponsor will report all SAEs, including suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities as required per local legislation or regulatory reporting requirements. An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

9.5.2. Vital Signs

Vital signs measures are to include heart rate, blood pressure, temperature, and respiratory rate.

9.5.3. Clinical Laboratory Tests

Samples will be drawn for central and local labs. Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions. The following laboratory assessments will be performed to evaluate safety at scheduled time points (see Appendix A) during the course of the study:

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, and total bilirubin.
- The CBC with differential is to include the following tests: white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit.
- A coagulation panel is to include the following tests: INR, prothrombin time, and PTT/aPTT.
- Cystatin C in serum (central laboratory test).
- The estimated GFR should be calculated using the MDRD equation, with serum creatinine reported in mg/dL.

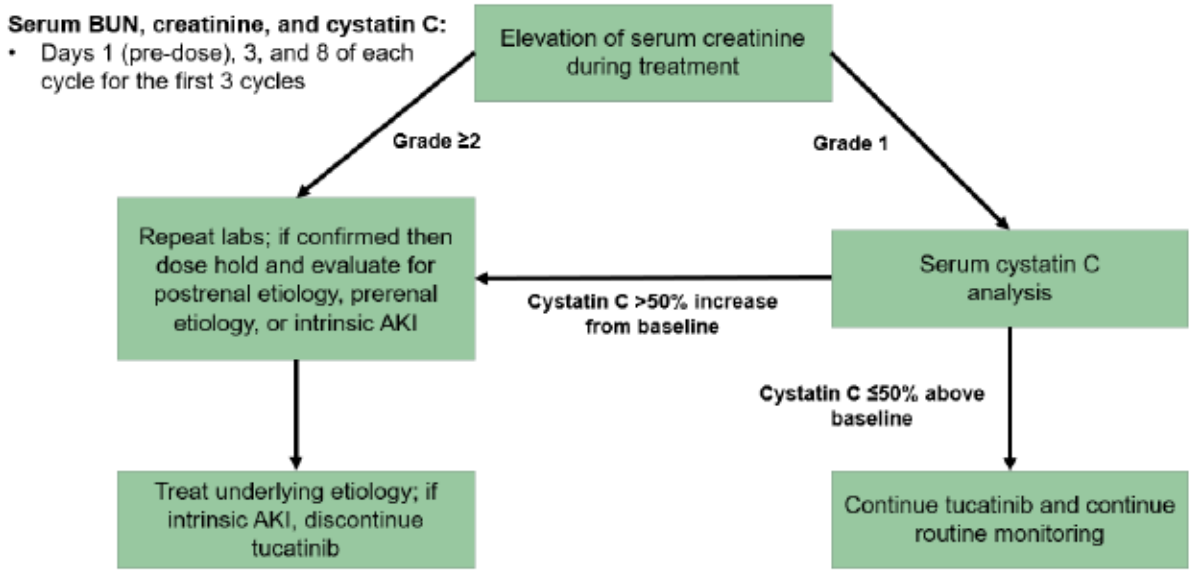
  GFR (mL/min/1.73 m^2) = $175 \times (\text{serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$
- Urinalysis
  - Standard urinalysis (with microscopy if clinically indicated)
  - Urine protein and urine creatinine for urine protein/creatinine ratio
  - 24-hour urine collection required in cycles when urine protein/creatinine ratio >2.0
- A serum/plasma or urine β-hCG pregnancy test for participants of childbearing potential
- Thyroid function tests (triiodothyronine [T3] or free triiodothyronine [FT3], free thyroxine [FT4], thyroid stimulating hormone [TSH])

During the LTEP, all safety assessments other than pregnancy testing will be performed per institutional guidelines and investigator-determined usual and customary care. Pregnancy testing will continue to be performed as outlined in the schedule of events in participants of childbearing potential.

9.5.3.1. Monitoring for Renal Toxicity

Dose holds or discontinuation of tucatinib may be required in the case of renal function changes. The algorithm for assessment and treatment of renal function abnormalities is detailed in Figure 3.

Figure 3: Decision Tree for Changes in Renal Function



Serum BUN, creatinine, and cystatin C will be drawn at the same time for each time point when renal function is being assessed. It is expected that the BUN and creatinine results will be available prior to the cystatin C, so initial treatment decisions will be made using these results.

Evaluation of the etiology of abnormal creatinine or cystatin C values may include additional bloodwork, urinalysis, imaging (ultrasound or CT), and/or consult with nephrology. Tucatinib must be discontinued in participants with confirmed cystatin C increases >50% from baseline, that are not due to pre or post renal etiologies or for which there is no alternative clinical explanation (eg, clearly related to an intercurrent illness or disease progression). Isolated proteinuria is not indicative of tubular injury and should not necessarily lead to discontinuation of tucatinib.

9.5.4. Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. For adult participants only, measurements of height obtained within the prior 12 months may be utilized.

9.5.5. Pregnancy Testing

For participants of childbearing potential, a serum/plasma or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at the times listed in the SOEs (Appendix A). A negative pregnancy result is required before the participant may receive study treatment. Pregnancy tests may also be repeated as requested per institutional review board/independent ethics committee (IRB/IEC) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. Pregnancy tests will be performed once a month for 7 months after the last dose of study treatment. Participants will do monthly home pregnancy tests during the follow-up period and report interim monthly results at long-term follow-up visits.

During the LTEP, pregnancy testing will continue to be performed as outlined above and in the schedule of events for participants of childbearing potential. Pregnancy reporting should continue and will be collected by the Sponsor.

9.5.6. Cardiac Function

9.5.6.1. MUGA or ECHO

Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation, and at EOT (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. ECHO/MUGA assessments should also be undertaken every 6 months for at least 2 years following trastuzumab discontinuation. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.

In the LTEP, cardiac function assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

9.5.6.2. Electrocardiogram

ECGs will be performed at baseline, at the EOT visit, and as clinically indicated. To correct for heart rate, QT intervals should be calculated using the Fridericia formula.

In the LTEP, ECG assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

9.6. Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Response will be assessed according to RECIST v1.1, which is the gold standard for evaluating anticancer therapies. The intervals of evaluation in this protocol are considered appropriate for disease management.

PK assessments are also common in clinical studies to help characterize dose -exposure -response relationships.

10. DATA QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Site Training and Monitoring Procedures

A study manual with instructions for study compliance and eCRF completion will be provided. Prior to the enrollment of participants at the site, Pfizer or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration, and withdrawal processes
- Current Investigator's Brochure/ local product labeling
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines

- The eCRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing, and record keeping
- Participant coding and randomization (if applicable)
- Study samples/specimen collection, handling, and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Pfizer representative will typically review regulatory documentation, eCRFs, source documentation, and investigational product storage, preparation, and accountability. The eCRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents until the final database lock occurs. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study participants and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Pfizer or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

10.2. Data Management Procedures

Pfizer will provide CRF Completion Guidelines for eCRF data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

Following implementation of Amendment 5 and entry of remaining on-treatment participants into the LTEP, data will no longer be collected in eCRFs. Only pregnancies and SAEs will be reported to the Sponsor during the LTEP, utilizing the Pregnancy Report Form and SAE form (for both SAEs and AESIs). Please see Section 9.5.1.3 and 9.5.1.4.2 for further detail on pregnancy, SAE, and AESI reporting requirements.

10.3. Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect participant confidentiality are to be employed during monitoring. The eCRFs and related source documents will typically be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this

study and other medical records as required to confirm that the information collected is correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

10.4. Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- eCRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.
- During the LTEP, eCRFs will not be collected.

10.5. Quality Assurance Procedures

The Research and Development Quality group of Pfizer or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Pfizer as part of the written record.

10.6. Data Handling and Record Keeping

10.6.1. Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. Data reported on the eCRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to an eCRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

10.6.2. Investigator Record Retention

The investigator shall retain study treatment disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Pfizer, whichever is longer. The investigator must contact Pfizer prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Pfizer.

11. DATA ANALYSIS METHODS

11.1. Determination of Sample Size

The tucatinib dose escalation will follow a 3+3 scheme. Approximately 6 DLT-evaluable participants may be treated in each phase 1b dose escalation cohort in order to identify the recommended phase 2 dose of tucatinib in combination with trastuzumab and oxaliplatin-based regimens.

Cohort 1A may enroll approximately 5 participants in order to have at least 3 DLT-evaluable participants, and approximately 8 participants in Cohort 1B in order to have at least 6 DLT-evaluable participants in the case a renal DLT is observed in the first 3 DLT-evaluable participants.

Cohorts 1C, 1E, 1F, and 1G may enroll approximately 8 participants in each cohort to ensure at least 6 participants in each cohort complete the appropriate DLT period (21 days for Cohorts 1C, 1F and 1G; 28 days for Cohort 1E). Enrollment may remain open to ensure at least 3 participants from Japan are enrolled into each cohort.

Cohort 1D (Japan-specific cohort) will enroll a minimum of 3 participants to receive tucatinib, trastuzumab, and mFOLFOX6.

Phase 2 Tumor Specific Expansion

Tumor specific expansion cohorts may be enrolled. For example, a 1L gastric, esophageal, and GEJ adenocarcinoma expansion cohort (Cohort 2A) may enroll up to 40 participants, and a 1L+ CRC expansion cohort (Cohort 2B) may enroll up to 20 participants.

For a sample size of 40 participants, assuming confirmed ORR is between 60% and 80%, the 2-sided 90% exact CIs are summarized below:

Confirmed ORR	90% Exact CI. (N=40)
60%	(46%, 73%)
70%	(56%, 82%)
80%	(67%, 90%)

For a sample size of 20 participants, assuming confirmed ORR is between 55% and 65%, the 2-sided 90% exact CI are summarized below:

Confirmed ORR	90% Exact CI. (N=20)
55%	(35%, 74%)
60%	(39%, 78%)
65%	(44%, 82%)

11.2. Study Endpoint Definitions

11.2.1. Objective Response Rate

Confirmed ORR per investigator is defined as the proportion of participants with confirmed CR or PR, according to RECIST v1.1. Only response assessments before first documented progressive disease or new anticancer therapies will be considered.

11.2.2. Duration of Response

DOR is defined as the time from first documentation of objective response of confirmed CR or confirmed PR to the first documentation of disease progression according to RECIST v1.1 or death from any cause, whichever occurs first. Only participants with an objective response will be included in the analysis of DOR. DOR per ICR may be evaluated in selected cohorts.

11.2.3. Progression-free Survival

PFS is defined as the time from the date of treatment initiation to the date of disease progression according to RECIST version 1.1 or death from any cause, whichever occurs first. Participants without documentation of progression or death at the time of analysis will be censored at the date of the last disease assessment with an overall response of CR, PR, stable disease, or non-CR/non-progressive disease. If there is no radiographic post-baseline tumor assessment, PFS will be censored at the date of treatment initiation. PFS per ICR may be evaluated in selected cohorts.

Detailed methodology, including handling rules for missing assessments and censoring approaches for the analysis of PFS, is provided in the statistical analysis plan (SAP).

11.2.4. Overall Survival

OS is defined as the time from treatment initiation to death due to any cause. For a participant who is not known to have died by the end of study follow-up, observation of OS is censored on the date the participant was last known to be alive (ie, the date of last contact). Participants lacking data beyond the day of treatment initiation will have their survival time censored on the date of treatment initiation (ie, OS duration of 1 day).

11.3. Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (eg, adding baseline assessments to define a subgroup). The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment. The SAP will be finalized prior to final database lock.

11.3.1. General Considerations

In general, descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables.

The exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates where applicable.

11.3.1.1. Randomization and Blinding

Blinding will not be performed.

11.3.1.2. Adjustments for Covariates

No adjustment for covariates is planned in the analyses.

11.3.1.3. Handling of Dropouts and Missing Data

No imputation will be conducted for missing data unless otherwise specified in the SAP.

11.3.1.4. Multicenter Studies

This study will be conducted at multiple study centers; however, it is not anticipated that any center will accrue enough participants to warrant an analysis by center.

11.3.1.5. Multiple Comparisons and Multiplicity

No multiple comparisons are planned, and no alpha adjustment is needed because no formal statistical testing will be performed in this study.

11.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (eg, Start Date and End Date) will be calculated as (End Date – Start Date +1 [in days]) unless otherwise specified in the planned analysis section.

Unless otherwise specified in the analysis plan, baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of study treatment.

11.3.1.7. Analysis Sets

Phase 1b Tucatinib Dose Escalation with FOLFOX (Cohorts 1A and 1B)

The **DLT-Evaluable Analysis set** includes all participants in Cohort 1A or 1B who meet one of the following criteria: (1) had a renal DLT or (2) had taken at least 75% of planned oxaliplatin and tucatinib doses per cycle and have been followed for at least 2 cycles of study treatment (through the end of Cycle 3 for FOLFOX regimens), inclusive of dose.

Phase 1b Safety Evaluation of Tucatinib with Trastuzumab and CAPOX (Cohort 1C) or with Trastuzumab and Pembrolizumab-Containing Regimens (Cohorts 1E, 1F, 1G)

The **DLT-Evaluable Analysis Set** for Cohort 1C includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned capecitabine, oxaliplatin, trastuzumab, and tucatinib for the first 21-days of study treatment and have been followed for at 21 days of study treatment.

The **DLT-Evaluable Analysis Set** for Cohort 1E includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned fluorouracil, oxaliplatin, pembrolizumab, trastuzumab, and tucatinib for the first 28 days of study treatment and have been followed for at 28 days of study treatment.

The **DLT-Evaluable Analysis Set** for Cohort 1F includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned capecitabine, oxaliplatin, pembrolizumab, trastuzumab, and tucatinib for the first 21 days of study treatment and have been followed for at 21 days of study treatment.

The **DLT-Evaluable Analysis Set** for Cohort 1G includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned pembrolizumab, trastuzumab, and tucatinib for the first 21 days of study treatment and have been followed for at 21 days of study treatment.

Phase 1b Tucatinib Japan Safety Evaluation in Combination with Trastuzumab and FOLFOX (Cohort 1D)

The **DLT-evaluable analysis set** in Cohort 1D includes all participants who meet one of the following criteria: (1) had a DLT or (2) had taken at least 75% of planned fluorouracil, oxaliplatin, trastuzumab, and tucatinib doses and have been followed for at least 28 days.

The **Full Analysis Set** will include all participants who are enrolled in the study and receive any amount of study treatment. The **Full Analysis Set** will be used for the analysis of PFS.

The **Safety Analysis Set** will include all participants who receive any amount of study treatment. The safety analysis set will be used for all safety analyses.

The **PK Analysis Set** will include all participants in the safety set from whom at least 1 PK assessment was reported. The PK analysis set will be used for PK analysis.

The **Response Evaluable Analysis Set** will include all participants who meet all following criteria: (1) had measurable disease at baseline, (2) received any amount of study treatment, and (3) had at least one post-baseline disease assessment of discontinued due to clinical progression, toxicity, or death.

Additional analysis sets of participants may be defined in the SAP.

11.3.1.8. Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

11.3.1.9. Timing of Analyses

Safety analysis during the phase 1b portion of the study will be undertaken by the SMC when the first 3 DLT-evaluable participants in Cohort 1A have been followed for at least 2 cycles. The SMC will undertake similar analyses when the first 6 DLT-evaluable participants in Cohort 1B have been followed for at least 2 cycles. Once the dose escalation phase is completed, the SMC will evaluate the safety of study regimen throughout the phase 2.

For Cohort 1D, participants will be evaluated after 3 participants complete 2 cycles of treatment. For Cohort 1E, participants will be evaluated after 6 participants complete 2 cycles of treatment. For Cohort 1F and 1G, participants will be evaluated after 6 participants complete 1 cycle of treatment.

The final analysis of the primary endpoint and secondary endpoints will be conducted separately for each phase 2 cohort (Cohort 2A and Cohort 2B) when all treated participants have been followed for at least 8 months (or all responders have been followed for a minimum of 6 months after their initial response, whichever comes first), have discontinued from the study or had 30 days safety follow-up after progressive disease, whichever comes first, or following study termination by the sponsor.

Safety in Japanese participants will be evaluated after 1 cycle of treatment as described in Section 5.1.3.

11.3.2. Participant Disposition

An accounting of study participants by disposition will be tabulated and the number of participants in each analysis set will be summarized. Participants who discontinue study treatment and participants who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

11.3.3. Participant Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the SAP.

11.3.4. Treatment Compliance

The dose administered at each cycle for each treatment agent will be assessed and dose intensity will be summarized. Details will be provided in the SAP.

11.3.5. Efficacy Analyses

The ORR will be summarized using the response evaluable set. The 2-sided 90% exact Clopper Pearson CI for the confirmed ORR will be provided (Clopper 1934).

11.3.6. Pharmacokinetic Analyses

Individual tucatinib plasma and oxaliplatin plasma (total and free platinum) and urine (platinum) concentrations at each sampling time will be listed and summarized with descriptive statistics.

The PK parameter for tucatinib and oxaliplatin to be calculated (if possible) may include but is not limited to C_{trough}.

Additional exploratory PK analyses may be conducted, including exploratory analyses investigating the relationship between tucatinib and oxaliplatin exposure, efficacy and safety endpoints. These analyses will be described in a separate analysis plan.

11.3.7. Biomarker Analyses

Relationships of biomarker parameters (eg, baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK parameters may be explored. Relationships and associated data that are determined to be of interest will be summarized. Details will be described separately in the SAP or Biomarker Analysis Plan (BAP).

11.3.8. Safety Analyses

11.3.8.1. Extent of Exposure

Duration of treatment will be summarized and listed.

Duration of treatment, number of cycles, total dose, dose intensity and dose modifications will be summarized. Details will be provided in the SAP.

11.3.8.2. Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will be defined as treatment emergent if they are newly occurring or worsen following study treatment.

AEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA), preferred term, severity, and relationship to study treatment. In the event of multiple occurrences of the same AE with the same preferred term in 1 participant, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AEs leading to premature discontinuation of study treatment will be summarized and listed in the same manner. AESIs will be separately summarized and listed.

11.3.8.3. Dose-limiting Toxicity

The observed number and proportion of participants experiencing a renal DLT will be reported by dose levels.

11.3.8.4. Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

11.3.8.5. Clinical Laboratory Results

Laboratory values (eg, chemistry, hematology, and urinalysis) may be presented graphically by visit. Summary statistics may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE v5.0 and flagged when values are outside the normal reference range.

11.3.8.6. Glomerular Filtration Rate

Change in GFR (as estimated using serum cystatin C) from baseline through 2 cycles of combination therapy will be summarized.

11.3.8.7. Other Safety Analyses

The frequency and percentage of participants with post-baseline clinically significant vital signs will be summarized. Abnormal physical examination findings may be collected as AEs. ECOG performance status will be listed.

Cardiac ejection fraction data and change from baseline will be summarized.

11.3.9. Interim Analyses

No formal interim analyses are planned.

12. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

12.1. Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study participant) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling participants who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

12.2. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European MDR 2017/745 for clinical device research, and all other applicable local regulations.

12.2.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

12.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct their personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current IRB/EC version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

12.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in electronic and/or paper form and will be secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

12.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the

protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

12.6. Data Quality Assurance

All participant data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

Guidance on completion of eCRFs will be provided in the CRF Completion Guidelines document.

The investigator must ensure that the eCRFs are securely stored at the study site in electronic form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the Clinical Monitoring Plan, Centralized Monitoring Plan, and Data Management Plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the

retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

12.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A Source Document Identification Log (or equivalent) should be maintained with the Investigator Site File on site. Definition of what constitutes a source document and its origin can be found in the Source Document Locator or equivalent, which is maintained by the site.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source record) that supports the information entered on the eCRF.

The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH GCP guidelines, and all applicable regulatory requirements.

12.8. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be reidentified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), and participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

12.9. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;

- Inadequate recruitment of participants by the investigator;

- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The

investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

12.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. When appliable, editorial or technical support provided by a third party and paid for by Pfizer, or provided by a Pfizer employee, may be a reportable transfer of value under the Sunshine Act for US licensed physicians or other healthcare professionals. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

12.11. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent, which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

12.12. Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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Appendix A. Schedule of Events: Phase 1b and Phase 2 Cohorts Utilizing FOLFOX

		Screening/ Baseline		Treatment Period (14-day cycles)									EOT	Follow -up[FF]	LTEP
		D–28 to D–1	D–7 to D–1[A]	Cycle 1			Cycles 2–3			Cycle >3	Every 6[D] or 8[E] Weeks[F]	Every 12 Weeks[F]	30 days post last dose	Every 9 or 12 weeks	-
				D1	D3[B]	D8	D1	D3[B]	D8[C]	D1					
Visit window (days)					±1	±1	±1	±1	±1	±1	±7	±7	+7	±14	±1[GG]
Screening/ Baseline	Informed consent[G]	X													
	Inclusion/exclusion criteria	X	X												
	Medical history (including assessment of diarrhea and antidiarrheal usage)	X													
	Height		X												
	Serology for hepatitis B and C	X													
	Tumor specimen collection if available[H]	X													
Safety assessments	Vital signs, including weight[I]		X	X		X	X		X[C]	X			X		X[CC]
	Physical exam[J]		X	X			X			X			X		X[CC]
	ECOG performance status[J]		X	X			X			X			X		X[CC]
	Confirmation of last blood transfusion		X	X											X[CC]
	CBC with differential[J]		X	X		X	X		X[C]	X			X		X[CC]
	Serum/plasma chemistry panel and serum cystatin C[J]		X[K]	X[K]	X[K]	X[K]	X[K]	X[K]	X[C,K]	X[K]			X[K]		X[CC]

		Screening/ Baseline		Treatment Period (14-day cycles)									EOT	Follow -up[FF]	LTEP
		D–28 to D–1	D–7 to D–1[A]	Cycle 1			Cycles 2–3			Cycle >3	Every 6[D] or 8[E] Weeks[F]	Every 12 Weeks[F]	30 days post last dose	Every 9 or 12 weeks	-
				D1	D3[B]	D8	D1	D3[B]	D8[C]	D1					
	Coagulation panel[J]		X						X[C]				X		X[CC]
	Urinalysis, with microscopy if clinically indicated[J]		X	X			X		X[C]	X			X		X[CC]
	Urine Protein/Creatinine (UPC) Ratio[J]		X	X			X		X[C]	X			X		X[CC]
	ECG	X											X		X[CC]
	Echocardiogram or MUGA scan[L]	X										X	X		X[CC]
	Thyroid function test[M]	X									X				X[CC]
	Serum/plasma or urine β-hCG pregnancy test (for females of childbearing potential)[N]		X[N]	X			X			X			X[O]	X[O]	X[N,O]
	Adverse events and concomitant medications[P] (including diarrhea AEs and Antidiarrheal Usage)	Collected throughout study reporting period from screening to EOT visit[P]													X[BB, CC]
Participant Diary	Issue Participant Diaries			Issue participant appropriate visit diary and ensure site required fields are completed; Participant diaries should be reviewed at each visit.											
Study Treatment	Oxaliplatin[Q]			X			X			X					X
	Leucovorin[Q]			X			X			X					X
	Fluorouracil[Q]			X			X			X					X
	Trastuzumab[R]			Cohorts 1A and 1B: Trastuzumab is administered Q2W All other Cohorts: Trastuzumab is administered Q3W											X

		Screening/ Baseline		Treatment Period (14-day cycles)									EOT	Follow -up[FF]	LTEP
		D–28 to D–1	D–7 to D–1[A]	Cycle 1			Cycles 2–3			Cycle >3	Every 6[D] or 8[E] Weeks[F]	Every 12 Weeks[F]	30 days post last dose	Every 9 or 12 weeks	-
				D1	D3[B]	D8	D1	D3[B]	D8[C]	D1					
	Pembrolizumab[S]			Pembrolizumab is administered Q6W											X
	Tucatinib					BID from Cycle 1 Day 8 for Cohorts 1A and 1B[T]									X
				BID from Cycle 1 Day 1 for Cohorts 1D, 1E, 2A, and 2B[T]											X
Disease	CT scan, PET-CT, and/or MRI assessments[U]	X	X[V]								X		X	X[U]	X[CC]
	Survival and anticancer therapy													X	
PK/PD (Pharmaco-kinetics/ Pharmaco-dynamics)	Blood samples for oxaliplatin PK (predose and postdose)[W]			X			X[X]								
	Urine samples for oxaliplatin PK (predose and postdose)[Y]			X			X[X]								
	Blood samples for tucatinib PK (predose and postdose)[Z]			X			X[AA]			X[AA]			X[DD]		
	Blood sample for biomarker assay	X											X[EE]		

A. Baseline visit should be scheduled to ensure that determination of estimated GFR can occur within 7 days of enrollment.
B. Cohorts 1A and 1B only.
C. Phase 1b cohorts must complete all assessments; phase 2 cohorts only need to complete the assessments for AEs and antidiarrheal usage.
D. For Cohorts 1D, 1E, 2A, and 2B utilizing FOLFOX, scans will be obtained every 6 weeks.
E. For the tucatinib phase 1b dose escalation cohorts utilizing FOLFOX (Cohorts 1A and 1B) scans will be obtained every 8 weeks.
F. Scheduling determined by Cycle 1 Day 1 (enrollment).
G. All participants must sign informed consent for the study before Screening/Baseline procedures are conducted.

H. Most recently collected tissue, if available. For participants enrolled in Cohorts 2A and 2B, collection of most recently available tissue is required.
I. Vital signs to be collected are systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate.
J. Assessment to be done predose on days when study treatment(s) are administered. Predose labs can be done within 1 day prior to study visit. Confirm lab results prior to administering study treatment dosing.
K. Serum cystatin C (after the Phase 2 dose has been identified, if no renal DLTs have been observed during dose escalation, cystatin C will not be collected).
L. Cardiac ejection fraction assessed by transthoracic ECHO will be performed at screening, every 12 weeks until treatment discontinuation irrespective of dose delays or interruption, and at the EOT visit. ECHO is the preferred modality for assessment of LVEF. If clinically indicated, MUGA scan may be used in place of ECHO. The same method for LVEF assessment should be employed at each assessment. An ECHO or MUGA is not required at EOT if one has been performed in the previous 12 weeks (excluding the Screening/Baseline assessment). ECHO/MUGA assessments should also be undertaken every 6 months for at least 2 years following trastuzumab discontinuation.
M. Thyroid function tests Q6W in Cohorts 1E, 2A.
N. Participants of childbearing potential only; pregnancy test must be performed within 24 hours prior to study treatment dosing on Day 1 of each cycle. Confirm negative pregnancy test prior to continuing study treatment dosing.
O. After last dose of study treatment, pregnancy tests will be performed once a month for 7 months.
P. SAEs and AESIs will be followed until resolution of acute events. Treatment-related SAEs occurring after the EOT visit will be followed until resolution of acute events. Concomitant medications and concomitant procedures will be collected, including antidiarrheal medication usage (not applicable to Cohorts 1A and 1B). Antidiarrheals should be administered to participants enrolled in Cohorts 1D and 1E and participants enrolled in Cohort 2A who receive tucatinib + trastuzumab + pembrolizumab + mFOLFOX6 as described in Section 7.11.2. Antidiarrheal prophylaxis, if required, will be followed as described in Section 7.11.2.
Q. **mFOLFOX6:** Oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 will be administered IV over 120 min (±15 minutes) then fluorouracil 400 mg/m^2 (IV bolus), then fluorouracil 2400 mg/m^2 will be administered IV over 46 hours (±1 hour); **mFOLFOX7:** Oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2 will be administered IV over 120 min (±15 minutes) then fluorouracil 2400 mg/m^2 will be administered IV over 46 hours (±1 hour).
R. Trastuzumab Q2W in Cohorts 1A and 1B and Q3W in other cohorts.
S. Pembrolizumab Q6W Cohorts 1E and 2A for a maximum of 18 doses.
T. Participants are to be instructed to bring their morning dose of tucatinib on Day 1 of Cycles ≥2 to ensure correct timing of the PK sampling for Cohorts 1A and 1B, and on Day 1 of Cycle 2-6 for Cohorts 2A and 2B.
U. At minimum, disease assessments, preferably using CT scans, must include the chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease such as bone imaging. Scans should be performed at screening, during study treatment, and at the EOT visit. During study treatment, scans should be performed every 8 weeks ±7 days (based on Cycle 1 Day 1) for the first 24 weeks and then every 12 weeks ±7 days thereafter in Cohorts 1A and 1B. In Cohorts 1D, 1E, 2A, and 2B, scans should be performed every 6 weeks ±7 days for the first 24 weeks and then every 9 weeks ±7 days thereafter. If cycles are delayed for any reason or there is an interim unscheduled assessment, scans should continue to be performed according to the original schedule. Participants who discontinue study treatment for reasons other than documented progressive disease per RECIST will continue to have disease assessments (CT, PET-CT, and/or MRI scans) approximately every 9 weeks (± 14 days) until radiographic disease progression. After the occurrence of documented disease progression, participants will be followed approximately every 12 weeks (± 14 days) until death, withdrawal of consent, study closure. Disease should be evaluated using the same imaging modality as at screening/baseline. If bone imaging is collected, any RECIST-appropriate imaging modality may be used.
V. Disease assessment will be repeated only for those participants receiving oxaliplatin during the screening period.
W. Oxaliplatin plasma PK samples will be collected in Cycles 1 and 2 for Cohorts 1A and 1B only.
X. Cycle 2 only.

Y. Participants should be encouraged to stay hydrated to facilitate urine collection for PK analysis. Urine samples for oxaliplatin PK are collected only for phase 1b Cohorts 1A and 1B.
Z. Tucatinib PK samples will be collected from Cycle 2 to Cycle 6 for Cohorts 1A and 1B (Table 23), Cycles 1-6 and EOT for Cohort 1D (Table 25), and Cycles 2-6 for Cohorts 1C, 1E, 1F, 1G, and phase 2 cohorts according to Table 26.
AA. Predose only in Cycle ≥3 through Cycle 6.
BB. Only SAEs, AESIs, and pregnancy captured by the Sponsor.
CC. During the LTEP, safety and efficacy assessments that include determination of disease progression will be performed per institutional guidelines and investigator-determined usual and customary clinical care.
DD. Following implementation of Amendment 5, no PK samples will be collected at EOT.
EE. Following implementation of Amendment 5, no blood samples for biomarker assessments will be drawn at EOT.
FF. As of Amendment 5, long term follow-up will be discontinued. Participants discontinuing study treatment will only be followed through the conclusion of the safety reporting period. Participants in long term follow-up as of Amendment 5 will transition to end of study.
GG. The ±1 day visit window is only applicable to drug administration and pregnancy testing during the LTEP

Schedule of Events: Phase 1b and Phase 2 Cohorts Utilizing CAPOX and Pembrolizumab Cohort 1G

		Screening/ Baseline		Treatment Period (21-day cycles)							EOT	Follow-up[W]	LTEP
		D–28 to D–1	D–7 to D–1[A]	Cycle 1		Cycle 2		Cycle >2	Every 6 Weeks[C]	Every 12 Weeks[C]	30 days post last dose	Every 9 or 12 Weeks	-
				D1	D8[B]	D1	D8[B]	D1					
Visit window (days)					±1	±1	±1	±1	±7	±7	+7	±14	±1[X]
Screening/ Baseline	Informed consent[D]	X											
	Inclusion/exclusion criteria	X	X										
	Medical history (including assessment of diarrhea and antidiarrheal usage)	X											
	Height		X										
	Serology for hepatitis B and C	X											

		Screening/ Baseline		Treatment Period (21-day cycles)							EOT	Follow-up[W]	LTEP
		D–28 to D–1	D–7 to D–1[A]	Cycle 1		Cycle 2		Cycle >2	Every 6 Weeks[C]	Every 12 Weeks[C]	30 days post last dose	Every 9 or 12 Weeks	-
				D1	D8[B]	D1	D8[B]	D1					
	Tumor specimen collection if available	X											
Safety assessments	Vital signs, including weight[E, F]		X	X	X	X	X[B]	X			X		X[U]
	Physical exam[F]		X	X		X		X			X		X[U]
	ECOG performance status[F]		X	X		X		X			X		X[U]
	Confirmation of last blood transfusion		X	X									X[U]
	CBC with differential[F]		X	X	X	X	X[B]	X			X		X[U]
	Serum/plasma chemistry panel and serum cystatin C[F]		X[G]	X[G]	X[G]	X[G]	X[B, G]	X[G]			X[G]		X[U]
	Coagulation panel[F]		X				X[B]				X		X[U]
	Urinalysis, with microscopy if clinically indicated[F]		X	X		X	X[B]	X			X		X[U]
	Urine Protein/Creatinine (UPC) Ratio[F]		X	X		X	X[B]	X			X		X[U]
	ECG	X									X		X[U]
	Echocardiogram or MUGA scan[H]	X								X	X		X[U]
	Thyroid function test[I]	X							X				X[U]
	Serum/plasma or urine β-hCG pregnancy test for		X[J]	X		X		X			X[K]	X[K]	X[J,K]

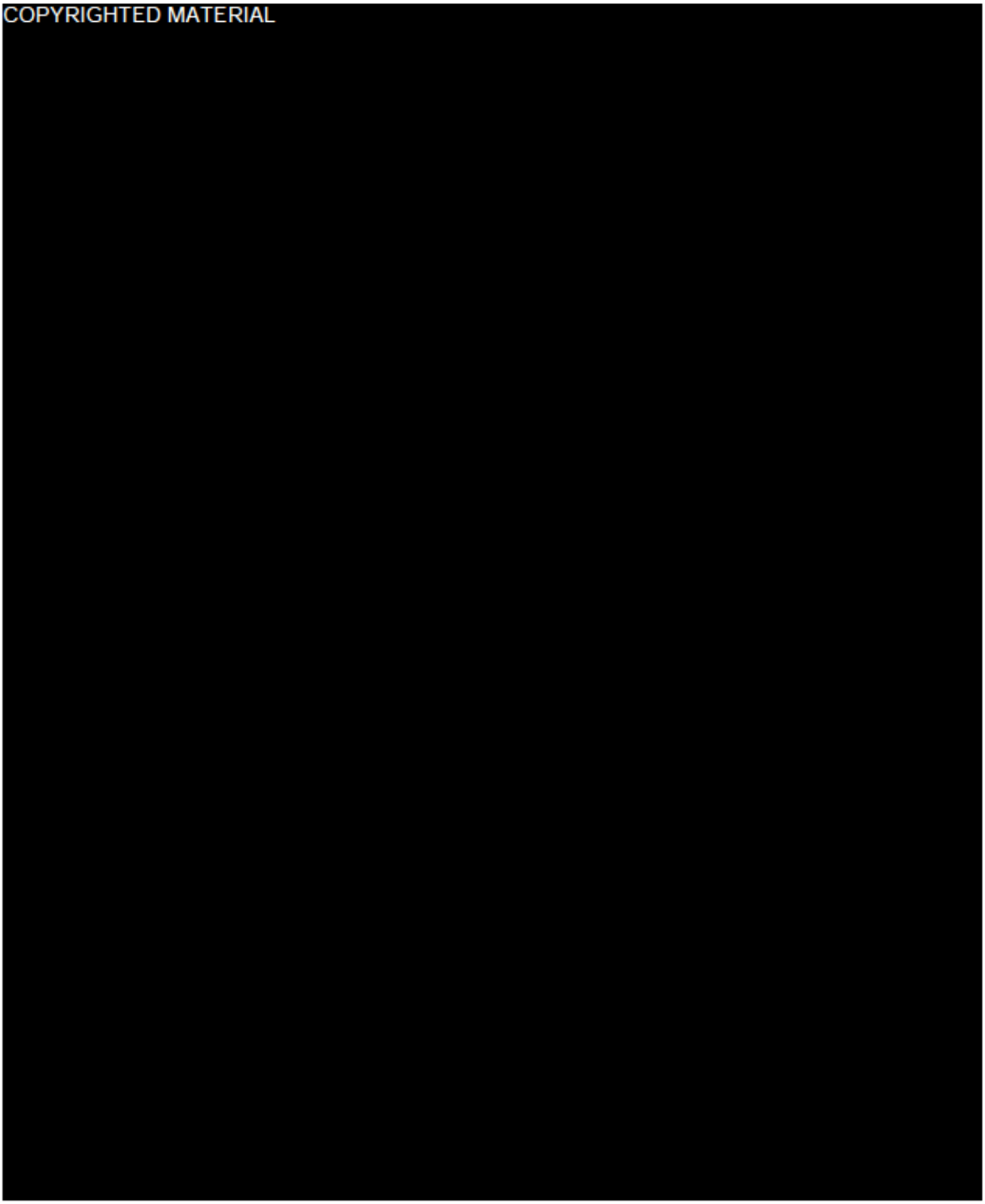
		Screening/ Baseline		Treatment Period (21-day cycles)							EOT	Follow-up[W]	LTEP
		D–28 to D–1	D–7 to D–1[A]	Cycle 1		Cycle 2		Cycle >2	Every 6 Weeks[C]	Every 12 Weeks[C]	30 days post last dose	Every 9 or 12 Weeks	-
				D1	D8[B]	D1	D8[B]	D1					
	females of childbearing potential[J]												
	Adverse events and concomitant medications (including diarrhea AEs and Antidiarrheal Usage)	Collected throughout study reporting period from screening to EOT visit[L]											X[T, U]
Participant Diary	Issue Participant Diaries			Issue participant appropriate visit diary and ensure site required fields are completed; Participant diaries should be reviewed at each visit.									
Study Treatment	Oxaliplatin[M]			X		X		X					X
	Capecitabine[M]			X		X		X					X
	Trastuzumab[N]			X		X		X					X
	Pembrolizumab[O]			Pembrolizumab is administered Q6W									X
	Tucatinib			BID from Cycle 1 Day 1[P]									X
Disease	CT scan, PET-CT, and/or MRI assessments[Q]	X	X[R]						X		X	X[Q]	X[U]
	Survival and anticancer therapy											X	
PK/PD (Pharmaco-kinetics/ Pharmaco-dynamics)	Blood samples for tucatinib PK (predose)[S]					X[S]		X[S]					
	Blood sample for biomarker assay	X									X[V]		

A. Baseline visit should be scheduled to ensure that determination of estimated GFR can occur within 7 days of enrollment.
B. For Cycle 1 Day 8, all cohorts must complete all assessments. For Cycle 2 Day 8, Phase 1b cohorts must complete all assessments but Phase 2 cohorts only need to complete the assessments for AEs and antidiarrheal usage.
C. Scheduling determined by Cycle 1 Day 1 (enrollment).
D. All participants must sign informed consent for the study before Screening/Baseline procedures are conducted.

E. Vital signs to be collected are systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate.
F. Assessment to be done predose on days when study treatment(s) are administered. Predose labs can be done within 1 day prior to study visit. Confirm lab results prior to administering study treatment dosing.
G. Serum cystatin C (after the Phase 2 dose has been identified, if no renal DLTs have been observed during dose escalation, cystatin C will not be collected).
H. Cardiac ejection fraction assessed by transthoracic ECHO will be performed at screening, every 12 weeks until treatment discontinuation irrespective of dose delays or interruption, and at the EOT visit. ECHO is the preferred modality for assessment of LVEF. If clinically indicated, MUGA scan may be used in place of ECHO. The same method for LVEF assessment should be employed at each assessment. An ECHO or MUGA is not required at EOT if one has been performed in the previous 12 weeks (excluding the Screening/Baseline assessment). ECHO/MUGA assessments should also be undertaken every 6 months for at least 2 years following trastuzumab discontinuation.
I. Thyroid function tests Q6W in Cohorts 1F, 1G, and 2A.
J. Participants of childbearing potential only; pregnancy test must be performed within 24 hours prior to study treatment dosing on Day 1 of each cycle. Confirm negative pregnancy test prior to continuing study treatment dosing.
K. After the last dose of study treatment, pregnancy tests will be performed once a month for 7 months.
L. SAEs and AESIs will be followed until resolution of acute events. Treatment-related SAEs occurring after the EOT visit will be followed until resolution of acute events. Concomitant medications and concomitant procedures will be collected, including antidiarrheal medication usage. Mandatory antidiarrheal prophylaxis will not be required for participants enrolled in Cohorts 1C, 1F, 1G, or for participants in Cohort 2A who are treated with tucatinib + trastuzumab + pembrolizumab + CAPOX, unless recommended by the SMC and required by the Sponsor based on a review of the data from these cohorts. Antidiarrheal prophylaxis, if required, will be followed as described in Section 7.11.2.
M. Oxaliplatin 130 mg/m^2 will be administered IV over 120 min (±15 minutes). Capecitabine 1000 mg/m^2 will be administered PO BID beginning the evening of Day 1 to morning of Day 15 (Cycle 1) and PO BID Day 1-Day 14 for all subsequent cycles.
N. Trastuzumab Q3W.
O. Pembrolizumab Q6W Cohorts 1F, 1G, and 2A for a maximum of 18 doses.
P. The first dose of tucatinib (300 mg PO BID or an intermediate dose as recommended by the SMC) may be administered on Cycle 1 Day 1. Participants are to be instructed to bring their morning dose of tucatinib on Day 1 of Cycles ≥2 to ensure correct timing of the PK sampling for Cohorts 1C and 1F and on Day 1 of Cycle 2-6 for Cohort 2A.
Q. At minimum, disease assessments, preferably using CT scans, must include the chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease such as bone imaging. Scans should be performed at screening, during study treatment, and at the EOT visit. During study treatment, scans should be performed every 6 weeks ±7 days (based on Cycle 1 Day 1) for the first 24 weeks then every 9 weeks ±7 days until the occurrence of documented disease progression. If cycles are delayed for any reason or there is an interim unscheduled assessment, scans should continue to be performed according to the original schedule Participants who discontinue study treatment for reasons other than documented progressive disease per RECIST will continue to have disease assessments (CT, PET-CT, and/or MRI scans) approximately every 9 weeks (± 14 days) until radiographic disease progression. After the occurrence of documented disease progression, participants will be followed approximately every 12 weeks (± 14 days) until death, withdrawal of consent, study closure. Disease should be evaluated using the same imaging modality as at screening/baseline. If bone imaging is collected, any RECIST-appropriate imaging modality may be used.
R. Disease assessment will be repeated only for those participants receiving oxaliplatin during the screening period.
S. Tucatinib predose PK samples will be collected from Cycle 2 to Cycle 6 for Cohorts 1C, 1E, 1F, 1G, and 2A according to Table 26.
T. Only SAEs, AESIs, and pregnancy captured by the Sponsor.
U. During the LTEP, safety and efficacy assessments that include determination of disease progression will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

V. Following implementation of Amendment 5, no blood samples for biomarker assessments will be drawn at EOT.
W. As of Amendment 5, long term follow-up will be discontinued. Participants discontinuing study treatment will only be followed through the conclusion of the safety reporting period. Participants in long term follow-up as of Amendment 5 will transition to end of study.
X. The ±1 day visit window is only applicable to drug administration and pregnancy testing during the LTEP

Appendix B. Performance Status Scales Conversion



Appendix C. Guidance On Contraception

For the purposes of this guidance, complete abstinence, if consistent with the participant's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 7 months after the final dose of study treatment; see Section 6.1).

Acceptable methods for highly effective birth control (preventing conception)

Participants who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods:
• Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
• Intrauterine device with failure rate <1%
• Tubal ligation
• Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
• Barrier method/s (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)

a A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

Acceptable methods for preventing secondary exposure to seminal fluid

Participants born male and who are sexually active with a pregnant or breastfeeding person, must use the contraceptives in Option 1 or 2:
• Option 1: Male condom (with or without spermicide) and cervical cap
• Option 2: Male condom (with or without spermicide) and diaphragm

Unacceptable methods of contraception

• Periodic abstinence
• No method
• Withdrawal
• Rhythm
• Spermicide only
• Progestin-only pills
• Concomitant use of female and male condoms

Appendix D. CYP3A Inducers and Their Elimination Half-lives

CYP3A4 inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Drug[a, b]	Elimination Half-life [c] (hours)
Strong Inducers	
Barbiturates	Variable
Carbamazepine	25–65 hours (single dose), 12–17 hours (repeat dose)
Phenytoin	7–42 hours
Rifampin	3–4 hours (single dose), 2–3 hours (repeat dose)
St. John's Wort	9–43 hours[d]

Note: Any additional CYP3A4 inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency)

b EMA. "Guideline on the investigation of drug interactions" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

c Drug product labeling

d (Kerb 1996)

Appendix E. CYP2C8 inhibitors/inducers and Their elimination Half-lives

CYP2C8 inhibitors and inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Drug[a, b]	Elimination Half-life[c]
Strong inhibitors	
Gemfibrozil	1–2 hours
Moderate inhibitors	
Clopidogrel	6 hours
Deferasirox	8-16 hours
Teriflunomide	18-19 days
Moderate inducer	
Rifampin	3–5 hours

Note: Any additional CYP2C8 inhibitors/inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency)

b EMA. "Guideline on the investigation of drug interactions" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

c Drug product labeling

Appendix F. Examples of Clinical Substrates for CYP3A-mediated Metabolism

Sensitive (AUC increase ≥5-fold with strong index inhibitor)	Moderate Sensitive (AUC increase 2- to 5-fold with strong index inhibitor)
alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[c], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[d], midazolam, naloxegol, nisoldipine, saquinavir[c], simvastatin[d], sirolimus, tacrolimus, tipranavir[c], triazolam, vardenafil	alprazolam, aprepitant, atorvastatin[a], colchicine, eliglustat[b], pimozide, rilpivirine, rivaroxaban, tadalafil
budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[c], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2- to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.

This table is prepared to provide examples of clinical substrates and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (Hachad 2010).

a Listed based on pharmacogenetic studies.

b Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.

c Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.

d Acid form is an OATP1B1 substrate.

Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

Appendix G. Procedures for Recording and Reporting AEs and SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for reporting SAEs via PSSA to Pfizer Safety throughout the safety reporting period. These requirements are delineated for exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

Table 27. Reporting SAEs via PSSA

Safety Event	Reported via PSSA to Pfizer Safety Within 24 Hours of Awareness
SAE	All
Nonserious AE	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE) **
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB)	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety via PSSA.
**EDB is reported to Pfizer Safety via PSSA, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety via PSSA.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Report Form.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

SAE Reporting to Pfizer Safety Via Electronic Data Collection Tool (DCT)

SAE Reporting to Pfizer Safety via an electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (PSSA).
- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the backup method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

Appendix H. Summary of Changes for Prior Global Amendments

Section(s)	Change	Rationale
Synopsis	Remove "as applicable" from estimated GFR inclusion criterion	There is not a situation where it will not be applicable.
Synopsis	Links to appendices within the body of the protocol were removed.	Administrative change (internal links to appendices or external links to other documents should not be included in the synopsis).
Section 4.1	Remove "as applicable" from estimated GFR inclusion criterion	There is not a situation where it will not be applicable.
Section 5.4.2	Added text to indicate that FDA approved biosimilars of trastuzumab are allowed.	Clarification
Section 5.5.3	Removed "Herceptin" since trastuzumab biosimilars will be allowed	Update
Section 5.5.1	Text was added to Table 3: After Hepatotoxicity heading added "(regardless of relationship to tucatinib)"; after Diarrhea heading added "related to tucatinib (as assessed by the investigator)" In the "Other adverse reactions that are related to tucatinib" update tucatinib dose modification text to indicate for Grade 3 AEs hold tucatinib until recovery to ≤ Grade 1 or pretreatment level.	This table has been updated to be consistent with all tucatinib clinical trials in gastrointestinal indications. Dose modifications due to hepatotoxicity are intended to be regardless of causality, and this was not specified in the trial. Dose modifications for other adverse events are only required if the event is assessed as being related to tucatinib. This is now clearly stated in the table. Other adverse reaction dose modification text was clarified because subjects with Grade 2 anemia and Grade 1 or higher clinically insignificant electrolyte abnormalities are allowed to enroll so recovery to pretreatment level would be acceptable in these cases.
Section 5.5.4	Added text about IRRs related to study treatment.	Clarification
Section 5.7.3	Added text to clarify CYP3A substrates should be avoided 1 week prior to the first dose of tucatinib and while on study treatment.	Clarification

Section(s)	Change	Rationale
Section 6.5	Text added to indicate patients discontinuing study for reasons other than documented progressive disease should continue scans until disease progression, death, withdrawal of consent, or study closure	Clarification
Section 7.2	Added "confirmed" to "…objective response assessments" to be consistent with 9.2.1	Clarification
Section 7.5.3	Remove "as applicable" from estimated GFR bullet	For consistency with estimated GFR inclusion criterion update
Section 7.5.3.1	Updated Figure 3	Clarification
Appendix A	Footnote F text was replaced with the following text (shown in underline): Cardiac ejection fraction assessed by transthoracic ECHO will be performed at screening, every 12 weeks until treatment discontinuation irrespective of dose delays or interruption, and at the EOT visit. ECHO is the preferred modality for assessment of LVEF. If clinically indicated, MUGA scan may be used in place of ECHO. The same method for LVEF assessment should be employed at each assessment. An ECHO or MUGA is not required at EOT if one has been performed in the previous 12 weeks (excluding the Screening/Baseline assessment). The following text (shown in strikethrough) was removed from Footnote F: ~~Echocardiogram or MUGA scan will be assessed during treatment and at EOT only. Scheduling is determined by date of most recent screening or on treatment echocardiogram/MUGA. Not required at EOT visit if an echocardiogram or MUGA scan was done within the previous 12 weeks (excluding the Screening/Baseline assessment)~~.	Clarification
Appendix A	The row for CT scan, PET-CT, and/or MRI assessment was updated with an X in the Follow-up column.	Imaging for patients who come off trial due to non-radiographic progressive disease will be required to continue scanning until progressive disease. This is addressed in the current footnote

Section(s)	Change	Rationale
		K but was missing from the Schedule of Events table.
Throughout protocol	Minor corrections, updates, formatting, and changes	Administrative changes

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Cover page	Updated name and contact information for medical monitor Updated title to indicate study will include expansion cohorts	Provide updated medical contact information
Synopsis, Study Objectives	Updated study objectives to include tabular summary of Phase 1b Tucatinib Dose Escalation with Oxaliplatin-based Chemotherapy objectives and endpoints Added tabular summary for the added Phase 2 Tumor Specific Expansion objectives and endpoints	Consistency with study design changes
Synopsis, Inclusion criterion (IC) 2 Section 4.1, IC 2	Added text about permitted oxaliplatin doses prior to Cycle 1 Day 1 in the phase 1b portion of the study for Cohorts 1A, 1B, and 1C and for phase 2 Cohort 2B	Inclusion criterion update
Synopsis, IC3 Section 4.1, IC3	For CRC, cholangiocarcinoma, and gallbladder carcinoma added text International Organization for Standardization text For Gastric, GEJ, and esophageal adenocarcinomas added text about Conformité Européenne (CE)-marked HER2 IHC tests	Consistency with other tucatinib protocols
Synopsis, IC 4 Section 4.1, IC 4	Added clarifying text about requirement for measurable or non-measurable disease for the various cohorts in phase 1b and phase 2 cohorts	Cohort specific clarifications
Synopsis, IC 10 Section 4.1, IC 10	Added clarifying text about estimated glomerular filtration rate for phase 1b Cohort 1A and phase 2 cohorts	Cohort specific clarifications
Synopsis, IC 11 Section 4.1, IC 11	Added note about prohibitions of warfarin and other coumarin derivatives for subjects receiving CAPOX	Safety related clarification
Synopsis, IC 15 Section 4.1, IC 15	Adjusted text about signed informed consent to indicate approval by IRB/IEC	Consistency with other tucatinib protocols

Section(s)	Change	Rationale
Synopsis, IC 17 Section 4.1, IC 17	Added new IC about stereotactic radiosurgery and whole brain radiation therapy	Radiation related inclusion criterion
Synopsis, IC 18 Section4.1, IC 18	Added new IC about RAS mutation status for subjects in the phase 2 1L+ CRC tumor specific expansion cohort	Cohort specific clarification
Synopsis, Exclusion Criterion (EC) 1 Section 4.2, EC 1	Changed "fluorouracil" to broader term "fluoropyrimidines" and added "known hypersensitivity" in place of "allergic reactions"	Consistency with other tucatinib protocols
Synopsis, EC 2 Section 4.2, EC 2	Adjusted text about permissible oxaliplatin treatments to refer back to details in IC 2	Simplification of existing EC text and consistency with IC2
Synopsis, EC 3 Section 4.2, EC 3	Adjusted text about surgeries from "…<28 days prior to enrollment" to "….<28 days prior to Cycle 1, Day 1	Clarification of timing
Synopsis, EC 4 Section 4.2, EC 4	Added text about CNS lesion status	Consistency with study design updates and other tucatinib protocols
Synopsis, EC 5 Section 4.2, EC 5	Added hemoglobin ≥8 g/dL as an exception	Consistency with other protocol sections
Synopsis, EC 11 Section 4.2, EC 11	Updated text about exclusion of subjects with human immunodeficiency virus (HIV)	Consistency with current HIV guidances and other tucatinib protocols
Synopsis, EC 17 Section 4.2, EC 17	Added EC as follows: Require therapy with warfarin or other coumarin derivatives if receiving CAPOX as part of this study (non-coumarin anticoagulants are allowed)	New EC addition for cohorts utilizing CAPOX and for consistency with capecitabine label recommendations
Synopsis, EC 18 Section 4.2, EC 18	Added EC as follows: Currently participating in another interventional trial	New EC addition

Section(s)	Change	Rationale
Synopsis, EC 19 Section 4.2, EC 19	Added EC as follows: Subjects enrolled in Cohort 2A (1L gastric, esophageal, and GEJ adenocarcinoma) cannot have had previous chemotherapy for metastatic/unresectable disease; adjuvant or neo-adjuvant chemotherapy or biologic therapy is permitted if more than 12 months have elapsed between the end of therapy and first recurrence	New EC addition
Synopsis, EC 20 Section 4.2, EC 20	Added EC as follows: Subjects enrolled in Cohorts 2A and 2B expansion cohorts cannot have received prior anti-HER2 therapies	New EC addition for expansion cohorts specifying no prior anti-HER2 therapies
Synopsis, Number of Planned Subjects	Adjusted approximate number of subjects planned to be enrolled from "15 to 30" to "65"	Consistency with study design updates and addition of new cohorts
Synopsis, Study Design Sections 3.1, 3.1.1, and 3.1.2	Updated lead-in text slightly to reflect study design changes Added tabular summary of the cohorts, treatments, populations, and number of subjects Adjusted text to include sections for phase 1b Cohorts 1A, 1B, and 1C in the study Added section about new phase 2 expansion portion of the study Added study design graphic with revised study design	Consistency with study design updates and addition of new cohorts
Synopsis, Investigational Product, Dose, and Mode of Administration (All Cohorts)	Adjusted text to reflect changes and updates needed to be consistent with revised study design	Consistency with study design updates and addition of new cohorts
Synopsis, Efficacy Assessments	Adjusted text about image collection for future analysis Adjusted text about disease assessment	Consistency with study design updates and addition of new cohorts
Synopsis, Biomarker Assessments	Minor updates to biomarker text	Clarifications
Synopsis, Statistical Methods	Adjusted text throughout this section to be consistent with revised study design Added sample size/cORR estimates for the tumor specific expansion cohorts	Consistency with study design updates and addition of new cohorts

Section(s)	Change	Rationale
Section 1.3	Added rationale for including CAPOX in this study Updated text to be consistent with new study design Updated text to indicate both FOLFOX and CAPOX will be used Added text about phase 2 portion of the study	Consistency with study design updates and addition of information about new cohorts
Section 2	Adjusted text to reflect phase 1b/2 design and addition of CAPOX Updated Table 1 (objectives and corresponding endpoints) to be consistent with revised study design and revised study objectives for phase 1b Added Table 2 (objectives and corresponding endpoints) phase 2 tumor specific expansion objectives and corresponding endpoints	Consistency with study design updates and addition of new cohorts
Section 3.1	Updated text to be consistent with study design revisions Added tabular summary of the cohorts, treatments, populations, and number of subjects	Consistency with study design updates
Section 3.1.1 (This includes the subsections 3.1.1.1 through 3.1.1.4)	Updated text to include sections for each of the phase 1b cohorts Adjusted dose-escalation process language to be consistent with revised study design Adjusted toxicity text to reflect revisions to study design	Consistency with study design updates
Section 3.1.2	Added text about the phase 2 cohorts Added revised study design graphic (Figure 1)	Consistency with study design updates
Section 3.1.3	Adjusted renal dose-limiting toxicity language to be consistent with revised study design	Consistency with study design updates
Section 3.1.4	Adjusted text in safety monitoring committee section to be consistent with revised study design.	Consistency with study design updates and addition of new cohorts
Section 3.1.5	Added End of Study section	Consistency with other tucatinib protocols
Section 3.2	Adjusted text in Discussion and Rationale for Study Design to be consistent with revised study design	Consistency with study design updates and addition of new cohorts
Section 3.2.1	Updated text to reflect changes in study design	Consistency with study design updates

Section(s)	Change	Rationale
Section3.2.2	Adjusted Rationale for Selection of Doses section to include information about CAPOX Other minor text adjustments based on study design updates	Consistency with study design updates and addition of new cohorts.
Section 4.4.1	Added non-compliance with study requirements as a reason for possible discontinuation of study treatment	Study specific clarification
Section 5.1.1	Adjusted text to reflect revisions to study design Added table for mFOLFOX6 regimen	Consistency with study design updates and addition of new cohorts.
Section 5.1.2	Added text and table about treatment with tucatinib, trastuzumab, and CAPOX	Consistency with study design updates and addition of new cohorts.
Section 5.3.1	Added text about use of mFOLFOX6 or mFOLFOX7 regimens	Clarification about use of FOLFOX regimens
Section 5.3.3	Added text about mFOLFOX6 regimen	Consistency with study updates
Section 5.4 (includes Sections 5.4.1 through 5.4.4)	Added text about CAPOX regimen including description (5.4.1), method of procurement (5.4.2), dose, preparation, and administration (5.4.3), and storage and handling (5.4.4)	Addition of CAPOX regimen related information
Section 5.6.1	Adjusted text to be consistent with new study design, adjusted Table 7 on tucatinib dose modifications for adverse events to include information about nausea and vomiting, and rash, adjusted text about other adverse reactions related to tucatinib, added footnotes, as appropriate	Consistency with dose modifications in other tucatinib protocols
Section 5.6.2	Added text to indicate investigators can escalate tucatinib dose for subjects enrolled in Cohort 1A following SMC approval of higher tucatinib doses in subsequent cohorts Adjusted content in tables in this section to reflect changes to study designs	Clarification for Cohort 1A dose escalations and consistency with study updates
Section 5.6.3	Added text and tabular content (Table 11) about capecitabine dose modifications	Updates related to addition of capecitabine as a component of CAPOX and revised study design
Section 5.6.4	Added text about continuing treatment in the event trastuzumab is discontinued	Clarification about other study drugs in the event trastuzumab is discontinued

Section(s)	Change	Rationale
Section 5.6.4.1	Adjusted Table 12 content about trastuzumab dose modification guidelines for left ventricular ejection fraction (LVEF)/left ventricular dysfunction	Consistency with other tucatinib protocols and most recent dose modifications guidelines
Section 5.8.1.1	Deleted text that is repeated in Section 5.8.4	Removal of repeated text
Section 5.8.1.4	Added text about CAPOX drug interactions	Update related to addition of CAPOX
Section 5.8.4	Updates to cytochrome (CYP) P450 text Added text about warfarin/coumarin derivatives	Consistency with current CYP recommendations and consistency with con medication exclusions for capecitabine/CAPOX
Section5.9	Added text about capturing overdoses events on the AE eCRF and within the safety database	Consistency with other tucatinib protocols
Section 6.3.1	Updated Cycle 1 Day 1 to include info about tucatinib administration for cohorts utilizing FOLFOX Added urine protein/creatinine ratio bullet point (this was also added to Sections 6.3.4, 6.3.6, and 6.3.7)	Consistency with study design updates
Section 6.3.3	Updated text to clarify tucatinib administration in the tucatinib dose escalation utilizing FOLFOX	Consistency with study design updates
Section 6.3.4 Section 6.3.7	Added text about tucatinib dispensation and administration	Clarification
Section 6.3.8	Updated text about radiological disease assessment for phase 1b and phase 2 cohorts utilizing FOLFOX to indicate 6 weeks for phase 2 cohorts and 8 weeks for phase 1b cohorts	Clarification related to study design updates
Section 6.4 (includes subsections 6.4.1 through 6.4.9)	Added study activities information for phase 1b tucatinib dose escalation utilizing CAPOX (Cohort 1C) and phase 2 tumor expansion cohort utilizing CAPOX (Cohort 2A)	Updates to be consistent with study design updates
Section 6.5	Added capecitabine to end of treatment text	Update to be consistent with study design update adding in capecitabine as a component of CAPOX
Section 7.1	Added “most recently available” to archival tissue to be supplied.	Provide flexibility in the event most recent samples have been depleted or are unavailable.

Section(s)	Change	Rationale
Section 7.2	Added text: "Images will be collected by an ICR facility for possible future analysis."	Clarification about image collection
Section 7.3	Updated Table 13 and Table 14 titles to reflect applicable cohorts Added Table 15 for PK related goals for phase 2 tumor specific expansion cohorts	Updates to be consistent with study design updates
Section 7,.4	Minor updates to biomarker text Added the following statement: Refer to the Central Laboratory Manual for information on collection, processing, storage, and shipment of samples.	Clarifications
Section 7.5.1.2	Added text (at end of the section) about Left Ventricular Ejection Fraction Decreased	Consistency with other tucatinib protocols
Section 7.5.1.5	Added text about reporting to regulatory authorities	Consistency with other tucatinib protocols
Section 7.5.3	Added clarification about Cystatin C being a central lab test	Clarification
Section 7.5.3.1	Updated the decision tree for changes in renal function graphic so that Cystatin C <50% above baseline to Cystatin C ≤50% above baseline Added text about isolated proteinuria	Previous graphic left out the possibility of an exactly 50% increase from baseline Additional guidance about proteinuria
Section 7.5.6.1	Added text about continuing ECHO/MUGA assessments every 6 months for at least 2 years following trastuzumab discontinuation	Additional guidance for trastuzumab to be consistent with other tucatinib protocols and safety recommendations
Section 9	Removed Overview of study outcome measurements table	Consistency with other tucatinib protocols
Section 9.1	Updated sample size determination text to be consistent with revised study design Added sample size/cORR estimates for the tumor specific expansion cohorts	Update to be consistent with study design updates and synopsis updates
Section 9.2	Added definitions of duration of response, progression-free survival, and overall survival	Updated due to study design updates that included these endpoints

Section(s)	Change	Rationale
Section 9.3(includes subsections 9.3.1 through 9.3.9)	Minor text updates for clarification Updates to definition of analysis sets to be consistent with study design updates Updates to timing of analysis	Consistency with other tucatinib protocols Consistency with updates in other sections of the protocol and updates to study design Consistency with updates to study design
Section 10	Added text about European guidelines.	Consistency with other tucatinib protocols
Appendix A	Original FOLFOX schedule of events (SOE) was updated including: Indicated 14-day cycles in the "Treatment Period" column heading Addition of line item for urine protein/creatinine ratio Update to footnote E to indicate 24 hours urine required if urine/protein creatinine ratio is >2.0. Update to footnote F to include text about continuing ECHO/MUGA assessments every 6 months for 2 years following trastuzumab discontinuation. Update to footnote I about mFOLFOX6 and mFOLFOX7 regimens Update to footnote J about tucatinib doses. Adjusted text in footnote K about imaging for subjects who discontinue study treatment Updates to CT scan, PET-CT, and/or MRI assessment frequency was added via addition of footnotes P and Q Clarifications to line item about tucatinib study treatment to include info on Cohorts 2A and 2B Updates to PK sampling were made via footnotes R and S and addition to footnote N Added footnote K to the sampling for CT scan, PET-CT, and/or MRI assessments on the X in the "follow-up" column Removed "after disease progression" text from the Follow-up column A new SOE for cohorts receiving CAPOX was added	Updates to be consistent with study design updates

Section(s)	Change	Rationale
Appendix E	Updated CYP information to match current CYP guidelines	Consistency with current CYP related text and other tucatinib protocols
Appendix F	Removed statement about OATP1B1 that was no longer relevant	Administrative update
Throughout document	Minor corrections, updates, formatting, and changes Update to indicate local labs may be performed on plasma or serum	Administrative changes Clarification based on site feedback

Summary of Changes in Amendment 2.1

Section(s)	Change	Rationale
5.6.2	• Updated heading for Section 5.6.2 from "mFOLFOX7 Dose Modifications" to "FOLFOX Dose Modifications." • Updated text in Section 5.6.2 to more clearly refer to tabular content in the section. • Minor clarifications to titles of Tables 8, 9 and 10 and minor clarifications to content of Tables 8 and 10	• Update to more accurately reflect section content • Updates for clarity. • Minor updates for clarity

Section(s)	Change	Rationale
5.6.3	• Updated text to be consistent with changes described in tables (see below for more details). • Added Table 11 containing oxaliplatin (non-neurological toxicity) and capecitabine dose reduction levels • Table on dose modification for clinical adverse events considered related to capecitabine was updated to adding dose modification information about hematologic and nonhematologic AEs for oxaliplatin and capecitabine. (Note this was originally Table 11 but is now Table 12) • Addition of Table 13 containing dose modification information for oxaliplatin associated neurotoxicity attributed to CAPOX.	• Updates for consistency with added section content • Addition of omitted dose reduction level guidance for non-neurological toxicity • Addition of dose modification guidance for oxaliplatin and capecitabine as part of the CAPOX regimen • Additional omitted dose modification guidance for oxaliplatin associated neurotoxicity attributed to CAPOX.
Throughout document	• Updated table numbering throughout document to accommodate the table additions described in Section 5.6.3	• Administrative change

Summary of Changes in Amendment 3.0

Section(s)	Change	Rationale
Cover page/ Synopsis	Changed the title to reflect the addition of pembrolizumab	Clarification
List of Abbreviations and Definitions of Terms	Updated abbreviation list	Consistency with updates throughout protocol
Synopsis / Objectives / Section 2.1	Changed heading to reflect dose-escalation Phase 1A / 1B cohorts	Clarification of dose-escalation cohorts
Synopsis / Objectives / Section 2.2	Identified sub-section for Phase 1b Cohorts 1C, 1E, 1F, and 1G Updated objectives to reflect tucatinib/trastuzumab/pembrolizumab treatment arms Added "including DLTs" to primary endpoint. Defined PK endpoint for tucatinib as including but not limited to C_{trough}	To identify objectives for Phase 1b Cohorts 1C, 1E, 1F, and 1G; Cohorts 1E, 1F, and 1G are new cohorts to which pembrolizumab has been added.
Synopsis / Objectives / Section 2.3	Added Japan-specific study (Cohort 1D) to Phase 1b	To identify the objectives for the Japan-specific cohort
Synopsis / Objectives / Section 2.4	Clarified objectives for 2A with addition of pembrolizumab. Added "including DLTs" to primary endpoint Moved PK analysis to exploratory	To add pembrolizumab to the treatment regimen for Cohort 2A PK data will not be a secondary objective of the Phase 2 portion of the study.
Synopsis / Section 4.1 Inclusion Criteria: #1	Identified cohorts and associated indications	Clarification
Synopsis / Section 4.1 Inclusion Criteria: #2	Clarified cohorts and which can be receiving an oxaliplatin-based regimen during the screening period	Clarification
Synopsis / Section 4.1 Inclusion Criteria: #3	Updates to details of HER2 testing procedures for gastric, GEJ, and esophageal adenocarcinoma	Clarification
Synopsis / Section 4.1 Inclusion Criteria #5	Adjusted text to include age of majority in the geographic region	Flexibility across geographic regions to be consistent with geographic variations in age of legal consent
Synopsis / Section 4.1 Inclusion Criteria: #9	Added that subjects can be on a stable dose of erythropoietin	Clarification

Section(s)	Change	Rationale
Synopsis / Section 4.1 Inclusion Criteria: #10	Adjusted text to reflect inclusion of additional cohorts	Clarification
Synopsis / Section 4.1 Inclusion Criteria: #13	Changed negative pregnancy testing to within 24 hours of first dose from within 7 days of enrollment.	Consistency with inclusion criterion used in Seagen and Merck protocols that include pembrolizumab rts
Synopsis / Section 4.1 Inclusion Criteria: #16	Added that subjects with a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study are not eligible.	Clarification
Synopsis / Section 4.1 Inclusion Criteria: #17	Added that subjects who have received CNS-directed radiotherapy must have recovered from all radiation-related toxicities and not require corticosteroids. Also, a 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.	To align with pembrolizumab inclusion criteria
Synopsis / Section 4.2 Exclusion Criteria: #1	Clarified cohorts and hypersensitivity exclusion criteria	To add exclusion criteria for subjects with hypersensitivity to treatment
Synopsis / Section 4.2 Exclusion Criteria: #2	Clarified exclusion criteria for exceeding limits of oxaliplatin-based regimen as part of their standard-of-care treatment	Clarification for new cohorts
Synopsis / Section 4.2 Exclusion Criteria: #4	Clarified that subjects in Cohorts 2A and 2B with known active CNS lesions may be included under specified criteria.	Clarification of criteria for inclusion of subjects with known active CNS lesions in Cohorts 2A and 2B
Synopsis / Section 4.2 Exclusion Criteria: #8	Indicated that subjects who are positive for either hepatitis B surface antibody (HBsAB) or antibodies to the hepatitis B core antigen (HBcAB) should be screened using PCR measurement of hepatitis B DNA levels.	To provide clarity with regard to hepatitis B testing
Synopsis / Section 4.2 Exclusion Criteria: #11	Clarified that HIV testing is not required unless mandated by the local health authority	To provide flexibility in wording because some countries do not allow HIV testing
Synopsis / Section 4.2 Exclusion Criteria: #16	Adjusted EC wording to indicate subjects cannot have active infection requiring systemic therapy	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab
Synopsis / Section 4.2 Exclusion Criteria: #18	Identified cohorts receiving CAPOX	Clarification

Section(s)	Change	Rationale
Synopsis / Section 4.2 Exclusion Criteria: #19	For Cohorts 1E, 1F, 1G, 2A who have unresectable or metastatic, gastric, esophageal, and GEJ adenocarcinoma) cannot have had previous chemotherapy for metastatic/unresectable disease; adjuvant or neoadjuvant chemotherapy, or biologic therapy is permitted if more than 12 months have elapsed between the end of therapy and first recurrence	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab cohorts
Synopsis / Section 4.2 Exclusion Criteria: #21	Added live vaccine exclusion criterion	Consistency with other tucatinib protocols
Synopsis / Section 4.2 Exclusion Criteria: #22	Added ongoing ≥ Grade 2 diarrhea of any etiology at screening	To rule out subjects with potential susceptibility to treatment reactions
Synopsis / Section 4.2 Exclusion Criteria: #23	Subjects in Cohorts 1E, 1F, 1G, 2A: added known active CNS metastases and/or carcinomatous meningitis for pembrolizumab cohorts	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab cohorts
Synopsis / Section 4.2 Exclusion Criteria: #24	For Cohorts 1E, 1F, 1G, 2A, added prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab cohorts
Synopsis / Section 4.2 Exclusion Criteria: #25	For Cohorts 1E, 1F, 1G, 2A, added allogeneic tissue/solid organ transplant	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab cohorts
Synopsis / Section 4.2 Exclusion Criteria: #26	For Cohorts 1E, 1F, 1G, 2A, added for a diagnosis of immunodeficiency (excluding HIV) or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab cohorts
Synopsis / Section 4.2 Exclusion Criteria: #27	For Cohorts 1E, 1F, 1G, 2A, added known additional malignancy that is progressing or has required active treatment within the past 3 years	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab cohorts
Synopsis / Section 4.2 Exclusion Criteria: #28	For Cohorts 1E, 1F, 1G, 2A, added an active autoimmune disease that has required systemic treatment in past 2 years	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab cohorts
Synopsis / Section 4.2 Exclusion Criteria: #29	For Cohorts 1E, 1F, 1G, 2A, added a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab cohorts

Section(s)	Change	Rationale
Synopsis / Section 4.2 Exclusion Criteria: #30	Subjects in Cohorts 1E, 1F, 1G, 2A: added received radiation therapy to the lung that is >30 Gy within 6 months of the first dose of trial treatment.	To provide consistency with exclusion criteria used in other Seagen and Merck protocols that include pembrolizumab cohorts
Synopsis / Number of Planned Subjects / Section 3.1	Updated the total number of subjects enrolled in the global study	Updated the sample size to account for the additional patient populations
Synopsis / Study Design / Section 3.1	Updated study design table to describe cohorts 1A, 1B, 1C, 1D, 1E, 1F, and 1G and associated patient populations; Cohort 1C moved from dose escalation to safety evaluation cohorts, which include tucatinib/trastuzumab/pembrolizumab Cohorts 1E, 1F, 1G. Deleted "Subjects with gastric and GEJ adenocarcinoma should also be receiving trastuzumab as part of their standard-of-care regimen." Added to the dose escalation process that the SMC will review the totality of the safety data. Updated DLT criteria for Cohort 1D.	Updated to add tucatinib/trastuzumab/pembrolizumab cohorts; defined Cohorts 1C as safety evaluation cohort; defined Japan-specific Cohort 1D
Synopsis / Section 3.1.1 / Section 3.1.1.1 / Section 3.1.1.2 / Section 3.1.1.3	Described the dose-escalation Cohorts in Phase 1b	Updated to describe dose-escalation gating rules
Synopsis / Section 3.1.2 / Section 3.1.2.1 / Section 3.1.2.2 / Section 3.1.2.3 / Section 3.1.2.4	Described the cohorts comprising the safety evaluation portion of Phase 1b; moved Cohort 1C from Dose Escalation to Safety Evaluation; added tucatinib/trastuzumab /pembrolizumab regimens 1E, 1F, and 1G	To clarify the new study design
Section 3.1.3.	Provided design for Japan-specific study as Phase 1b	To define the Japan-specific study as Phase 1b.
Synopsis / Section 3.1.4	Defined Cohort 2A as including tucatinib/trastuzumab/pembrolizumab. Added criteria for SMC review. Added that exploratory objectives will include evaluation of the PK of tucatinib given in combination with trastuzumab and oxaliplatin-based chemotherapy and updated study design figure.	To describe the composition of the expansion cohorts and update text and study figure to be consistent with changes made to study.

Section(s)	Change	Rationale
Synopsis / Investigational Product, Dose, and Mode of Administration (All Cohorts)	Identified cohorts associated with chemotherapy regimens; added tucatinib/trastuzumab/pembrolizumab treatment; changed administration of the first dose of tucatinib from Day 8 to Day 1	Added treatment regimens associated with the tucatinib/trastuzumab/pembrolizumab cohorts
Synopsis / Duration of Treatment Section 3.1.8	Indicated that pembrolizumab will be given for a maximum of 18 doses	To align with pembrolizumab dosing guidance
Synopsis / Efficacy Assessments	Updated to add tucatinib/trastuzumab/pembrolizumab cohorts; added imaging assessments to be every 6 weeks for first 24 weeks and every 9 weeks thereafter.	Added timing of efficacy assessments for post-dose-escalation cohorts
Synopsis / Statistical Methods / Section 9.1.	Defined evaluable analysis sets for various cohorts	To define analysis data set
Section 1.3.	Referenced background information for pembrolizumab	To characterize the therapeutic profile of pembrolizumab
Section 1.4	Adjusted text about HER2 prognostic value and the combination of HER2 targeting agents given with trastuzumab	Clarification
Section 1.4.	Added rationale for pembrolizumab cohorts, including interim results from the KEYNOTE-811	To provide the rationale for the pembrolizumab cohorts
Section 3.1.5	Specified that renal DLT applies to the dose-escalation cohorts (1A and 1B)	To specify that renal DLT parameters apply only to the dose escalation cohorts (1A and 1B)
Section 3.1.6.	Defined DLT criteria for Safety Evaluation cohorts	To define dose-limiting criteria for Cohorts 1C, 1D, 1E, 1F, and 1G
Section 3.1.7.1.	Updated role of SMC in reviewing for dose-escalation Cohorts 1A and 1B	To describe role of SMC in reviewing safety data for Cohorts 1A and 1B
Section 3.1.7.2	Defined role of SMC in reviewing for tucatinib/trastuzumab/pembrolizumab Cohorts 1C, 1E, 1F, 1G	To describe role of SMC in reviewing safety data for Cohorts 1C, 1E, 1F, and 1G
Section 3.1.7.3.	Added section for SMC review of safety for Phase 2 cohorts	To describe role of SMC in reviewing safety data for Cohorts 2A and 2B
Section 3.2.	Added rationale for including tucatinib/trastuzumab/pembrolizumab cohorts	To provide basis for addition of tucatinib/trastuzumab/pembrolizumab to Phase 1b.
Section 3.2.2	Added the rationale for the pembrolizumab dose, including interim results from the KEYNOTE-811	To provide the dose justification for pembrolizumab
Section 5.1.1	Defined treatments for FOLFOX cohorts; differentiated trastuzumab Q2W and Q3W regimens	Clarification

Section(s)	Change	Rationale
Section 5.1.2	Defined treatments for CAPOX cohorts	Clarification
Section 5.1.3	Added treatment regimen for pembrolizumab and FOLFOX	To provide treatment regimen of FOLFOX and pembrolizumab
Section 5.1.4	Added treatment regimen for pembrolizumab and CAPOX	To provide treatment regimen of CAPOX and pembrolizumab
Section 5.1.5	Added treatment regimen for tucatinib/trastuzumab/ pembrolizumab without chemotherapy	To provide treatment regimen of tucatinib/trastuzumab/ pembrolizumab without chemotherapy
Section 5.2	Added that study personnel should instruct subjects on tucatinib administration techniques	To ensure subjects receive instructions for tucatinib administration
Section 5.3	Identified cohorts receiving the FOLFOX regimen	Clarification
Section 5.3.1	Added gastric cancer to oncology indications that use oxaliplatin	Correction of omission
Section 5.3.2	Indicated sourcing for FOLFOX may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.	To clarify sourcing for FOLFOX
Section 5.4	Identified cohorts receiving the CAPOX regimen	Clarification
Section 5.4.2	Indicated sourcing for CAPOX may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.	To clarify sourcing for CAPOX
Section 5.4.3	Added that the starting dose of capecitabine may be reduced per investigator preference or institutional standards upon approval by the medical monitor, but will not be lower than 850 mg/m^2 PO BID	To provide dosing instructions for capecitabine
Section 5.5.2	Indicated sourcing for trastuzumab may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.	To clarify sourcing of trastuzumab
Section 5.5.3	Added Q2W and Q3W regimens for trastuzumab	To clarify regimens of trastuzumab based on treatment regimens for Cohorts 1A and 1B (Q2W) vs Cohorts 1C, 1D, 1E, 1F, 1G, 2A, and 2B
Section 5.5.6	Study Drug Accountability was changed to Study Treatment Accountability	Consistency with changes throughout protocol to clearly indicate distinctions between study drug and study treatment

Section(s)	Change	Rationale
Section 5.6 / Section 5.6.1 / Section 5.6.2 / Section 5.6.3 / Section 5.6.4 / Section 5.6.5 / Section 5.6.6	Provided pembrolizumab administration information	To provide the instructions for administration of pembrolizumab
Section 5.7.2 / Section 5.7.3	Added that dose reductions or treatment interruptions/discontinuation may be made by the investigator per institutional practice and if deemed in the best interest of subject safety.	To provide investigator discretion for monitoring of subject safety
Section 5.7.4	Removed 6 mg/kg from the instructions about restarting trastuzumab and indicated investigators should use the loading dose based on the regimen	FOLFOX and CAPOX use different loading doses so 6 mg/kg does not apply to both
Section 5.7.4.1	Changed percentage decrease to percentage points decrease	Clarification
Section 5.7.5 / Section 5.7.5.1	Provided dose modification guidelines for pembrolizumab immune-related events	To describe the guidelines for the management of immune-related AEs associated with pembrolizumab
Section 5.7.5.2	Added dose modification guidelines for pembrolizumab	To provide guidelines in the event of adverse reactions to pembrolizumab
Section 5.7.2	Added a footnote to neutropenia/thrombocytopenia to indicate that the labs from D1 of each cycle should be used to determine dose modifications for FOLFOX; deleted dose adjustments for leukopenia	To clarify dose modification guidelines with regard to neutropenia/thrombocytopenia for FOLFOX
Section 5.7.5.3	Provided criteria for dose interruption of pembrolizumab	Provided dose guidelines for interruption of pembrolizumab
Section 5.7.6	Moved to after pembrolizumab dose modification guidelines	To correct organization
Section 5.7.7	Moved to after pembrolizumab dose modification guidelines	To correct organization
Section 5.7.8	Added dose modification guidelines for diarrhea	To provide guidelines for management of diarrhea associated with treatment
Section 5.9.1.5	Added that DDI are not expected with pembrolizumab	Clarified potential for drug-drug interactions with pembrolizumab
Section 5.9.2	Clarified glucocorticoid use	To clarify concomitant use of glucocorticoids
Section 5.9.4	Add instructions with regard to recording of concomitant treatment and discontinuation (including instructions on immunotherapy not specified in this protocol and live or live attenuated vaccines)	To provide for the recording of concomitant treatment and to clarify the criteria for discontinuation of treatment in the event of use of prohibited medications

Section(s)	Change	Rationale
Section 5.10 / Section 5.10.2	Provided information with regard to overdose of pembrolizumab	To define an overdose of pembrolizumab and treatment instructions
Section 5.10.3	Provided overdose information for trastuzumab, oxaliplatin, capecitabine, leucovorin, and fluorouracil	To provide information on overdose
Throughout Section 6	Adjusted text from "Blood for cystatin C" to "Serum cystatin C" and minor text changes	Consistency with schedule of events and text in remainder of protocol which refers to serum cystatin Clarifications, as needed, for existing text
Section 6.2	Removed bullet for vital signs, weight, height Added bullet about thyroid function tests for selected cohorts	Consistency with schedule of events
Section 6.3	Added Japan-specific (1D) cohort and tucatinib/trastuzumab/pembrolizumab Cohort 1E	To add study procedures for Japan-specific cohort and FOLFOX/ tucatinib/trastuzumab/pembrolizumab cohort
Section 6.3.1 / Section 6.3.4 / Section 6.3.7 / Section 6.4.1 / Section 6.4.4 /Section 6.4.7	Pregnancy test for subjects of childbearing potential to be done within 24 hours of treatment Specified blood samples for oxaliplatin PK in Cohorts 1A and 1B only Specified trastuzumab Q2W in Cohorts 1A and 1B and Q3W in Cohorts 1D, 1E, 2A, and 2B	Consistency with schedule of events
Section 6.3.1	Added pembrolizumab administration and updated information for trastuzumab administration	To add administration of pembrolizumab to Cycle 1 procedures for the FOLFOX combination regimen To clarify Q2W and Q3W trastuzumab dosing

Section(s)	Change	Rationale
Section 6.3.1 Section 6.3.2 Section 6.3.3 Section 6.3.4 Section 6.3.5 Section 6.3.6 Section 6.3.7 Section 6.4.1 Section 6.4.2 Section 6.4.3 Section 6.4.5 Section 6.5.3 Section 6.6	Added for cystatin C, "If after the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation, cystatin C will not be collected"	To qualify guidelines for cystatin C testing in the event the Phase 2 dose has been identified and no renal DLTs have been seen during dose escalation
Section 6.3.8 / Appendix A Schedule of Events	Clarified imaging assessments to be every 6 weeks for 24 weeks and every 9 weeks thereafter for post-dose escalation cohorts (1B, 1C, 1D, 1E, 1F, 1G, 2A, and 2B Added information about thyroid function tests for cohorts 1E and 2A	To clarify imaging schedule for post-dose escalation cohorts To provide guidance for frequency of thyroid function tests
Section 6.4.1	Added administration of pembrolizumab to Cycle 1 procedures for the CAPOX combination regimen	To add administration of pembrolizumab to Cycle 1 procedures for the CAPOX combination regimen
Section 6.4.1, 6.4.3	Deleted blood samples for oxaliplatin PK	Potential drug-drug interactions will be evaluated during the dose-escalation phase (Cohorts 1A and 1B)
Section 6.4.6	Clarified imaging assessments to be every 6 weeks for 24 weeks and every 9 weeks thereafter Added information about thyroid function tests for cohorts 1F and 2A)	To clarify imaging schedule for Cohorts 1C, 1F, and 2A To provide guidance for frequency of thyroid function tests
Section 6.5 Section 6.5.1 Section 6.5.2 Section 6.5.3 Section 6.5.4 Section 6.5.5 Section 6.5.6 Section 6.5.7	Added treatment procedures for tucatinib/trastuzumab/pembrolizumab regimen (Cohort 1G)	To list treatment procedures by time point for tucatinib/trastuzumab/pembrolizumab treatment arm
Section 6.6	Updated content to be consistent with updates in body of protocol	Consistency

Section(s)	Change	Rationale
Section 6.7	Added follow-up imaging every 9 weeks until disease progression and every 12 weeks until death, withdrawal of consent, study closure.	To provide timing of follow-up imaging assessments
Section 7.1	Adjusted text as shown: Only subjects who sign an informed consent and meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study. Added text: "…confirmation of last blood transfusion, review of adverse events and concomitant medications,…"	Consistency with SOE
Section 7.3. Section 9.3.6	Updated PK parameters for cohorts	To define the PK parameters for new cohorts
Section 7.4	Provided instructions for collecting tissue for biomarker status	To provide the procedure for collecting tissue samples for biomarker analysis
Section 7.5.1.1	Defined NCI CTAE Adjusted text in second bullet under Hepatotoxicity from: Grade 4 AST, ALT, or bilirubin from grade to elevations – new text is: • AST or ALT elevations >20 x ULN • Bilirubin elevations >10.0 x ULN	Consistency with other tucatinib protocols
Section 7.5.1.1	Added an overdose of tucatinib or pembrolizumab and ≥ Grade 3 diarrhea as AESI	To update definition of AESIs
Section 7.5.1.3	Added serious AE reporting during and for 90 days after the end of treatment for Cohorts 1E, 1F, 1G, and 2A	To define the reporting period for serious AEs
Section 7.5.3	Added thyroid tests	To align with pembrolizumab testing requirements
Section 7.5.5	Minor adjustments to the text around pregnancy testing to be more well defined and more consistent with the schedule of events line item for pregnancy testing.	Clarifications to be consistent with SOE content
Section 9.3.1.7	Defined DLT-evaluable analysis sets for various cohorts	To define evaluable analysis sets for new cohorts
Section 9.3.1.9	Added timing of evaluation of various cohorts.	To provide the timing of the analyses for the new cohorts
Appendix A, Schedule of Events for Phase 1b and	Moved Height assessment from D-28 to D-1 cell to D-7 to D-1 cell	Updates to be consistent with changes made to the body of the protocol, existing content in the

Section(s)	Change	Rationale
Phase 2 Cohorts Utilizing FOLFOX	Deleted assessment of vital signs, including weight from D-28 to D-1 cell Adjusted footnote text on pregnancy testing and added a new footnote in the EOT and Follow-up column for the pregnancy test assessment row of the schedule of events. Added footnote B for Day 3, Cohorts 1A and 1B only Added footnote C for Day 8, Phase 1b cohorts only Updated footnote D for Cohorts 1D, 1E, 2A, and 2B utilizing FOLFOX: scans will be obtained every 6 weeks. Added footnote H, For Phase 1b cohorts, most recently collected tissue, if available. For subjects enrolled in Cohorts 2A and 2B, collection of most recently available tissue is required Updated footnote K: cystatin C will not be collected if no renal DLTs have been observed during dose escalation. Added footnote R, trastuzumab Q2W in Cohorts 1A and 1B and Q3W in other cohorts Added footnote S, pembrolizumab to be given for a maximum of 18 doses Updated footnote U on timing of scans Reordered several footnotes to be more sequentially alphabetically ordered.	protocol, and for consistency with other tucatinib protocols.
Appendix A, Schedule of Events for Phase 1b and Phase 2 Cohorts Utilizing CAPOX and Pembrolizumab Cohort 1G	Moved Height assessment from D-28 to D-1 cell to D-7 to D-1 cell Deleted assessment of vital signs, including weight from D-28 to D-1 cell	Updates to be consistent with changes made to the body of the protocol, existing content in the protocol, and for consistency with other tucatinib protocols.

Section(s)	Change	Rationale
	Adjusted footnote text on pregnancy testing and added a new footnote in the EOT and Follow-up column for the pregnancy test assessment row of the schedule of events. Updated footnote G, cystatin C will not be collected if no renal DLTs have been observed during dose escalation. Added footnote N, trastuzumab Q3W Added footnote O, pembrolizumab to be given for a maximum of 18 doses Deleted PK sampling for oxaliplatin Updated footnote T for tucatinib PK sampling through Cycle 6 Updated footnote Q on timing of scans Reordered several footnotes to be more sequentially alphabetically ordered.	
Appendix A: Schedule of Events	Added pembrolizumab administration to both SOEs	To include timing of pembrolizumab administration
Throughout document	Defined CRC as colorectal adenocarcinoma	Clarification
Throughout document	Changed "…the first dose of study treatment" to "enrollment (Cycle 1 Day 1) And, where appropriate throughout protocol, parenthetically indicated interchangeability of Cycle 1 Day 1 (enrollment) or enrollment (Cycle 1 Day 1)	Consistency with text in entire protocol and to clearly indicate enrollment and Cycle 1 Day 1 are interchangeable
Throughout document	Changed "…study drug(s)…" to "….study treatment(s)"	Clarification. Tucatinib is considered to be the investigational study drug. But all drugs being used are consider part of the study treatment.
Throughout document	Minor corrections (clerical and/or for clarity, adjusting run-on sentences, and formatting related) and minor adjustments to text to be consistent with changes described above	Administrative changes and consistency

Summary of Changes in Amendment 3.1

Section(s)	Change	Rationale
Synopsis and Section 2.2 (Table 2)	Moved ORR objective and endpoint from exploratory to secondary.	ORR must be a secondary objective/endpoint for these cohorts since DOR, OS, and PFS are also secondary endpoints.
Synopsis, Exclusion Criterion (EC) 23 and Section 4.2 EC 23	Removed Cohort 2A from EC 23.	Consistency with EC 4. For Phase 2 cohorts subjects with active CNS metastases are allowed if they meet certain criteria.
Section 5.7.2, Table 14	Removed extra row	Empty row was not needed
Throughout protocol	Updated footers and dates, as appropriate	Administrative

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
Synopsis, Inclusion Criteria (IC) 19 and Section 4.1 IC 19	Added inclusion criterion indicating subjects must be willing and able to adhere to antidiarrheal prophylaxis.	Antidiarrheals must be taken if required.
Synopsis, Exclusion Criteria (EC) 1 and Section 4.2, EC 1	Added text indicating subjects should not have allergy or hypersensitivity to any required concomitant medications.	Ensure subjects do not have allergy or hypersensitivity to loperamide
Synopsis, Study Design and Section 3.1, Section 3.1.2.1 through Section 3.2.1.4, and Section 3.1.3 and Section 3.1.4	Added text indicating antidiarrheal prophylaxis required for all subjects in Cohorts 1D and 1E and for subjects in Cohort 2A who receive tucatinib + trastuzumab + pembrolizumab + FOLFOX. Provided information on loperamide dosage and summary of preliminary data from the ongoing study (SGNTUC-024). In sections about details of each cohort – added text about the antidiarrheal prophylaxis approach as appropriate for each cohort (ie, if require or not, when subject will be expected to use antidiarrheal, titration of loperamide doses, etc) Provided summary of how SMC review of safety data will be done for cohorts where subjects are not required to receive mandatory antidiarrheal prophylaxis.	Based on preliminary data from Cohorts 1A and 1B and SMC recommendations. antidiarrheals will be given prophylactically for Cohorts 1D and 1E and for subjects in Cohorts 2A who receive who receive tucatinib + trastuzumab + pembrolizumab + FOLFOX as specified. Also provided guidance on approach for antidiarrheal prophylaxis for subjects in other cohorts.
Synopsis, Study Design, Figure and Section 3.1.4.2, Figure 1	Updated Cohort 1C to be N≥6	Consistency with updates to body of protocol
Synopsis, Statistical Methods and Section 9.1	The phrase "up to" has been replaced with "approximately," and the phrase "at least" has been added in relationship to DLT evaluable subjects. Updated to indicate Cohort 1C will enroll approximately 8 subjects to have 6 subjects that complete the DLT period.	Minor adjustments to language for clarity. Consistency with updates to the body of the protocol.
Section 3.1.4	Separated text about Cohort 2A into Section 3.1.4.1 and Cohort 2B into Section 3.1.4.2	For clarity
Section 5.1.1 and Section 5.1.3	Where applicable, updated table footnotes to include levoleucovorin dose information.	Clarification about levoleucovorin dose that can be substituted in cases of supply shortages (for the mFOLFOX6 and mFOLFOX7 regimens).

Section(s)	Change	Rationale
Section 5.7.2 and Section 5.7.3	Added text indicating pembrolizumab may be continued during periods of FOLFOX delay in subjects receiving FOLFOX or during periods of oxaliplatin treatment delay in subjects receiving CAPOX.	Other study treatments may be continued in the event of FOLFOX or oxaliplatin (as part of CAPOX) treatment delay.
Section 5.7.8	Added section with text for management of diarrhea. Included text about antidiarrheal prophylaxis, when antidiarrheal prophylaxis is contraindicated and text about early detection and early intervention approaches, and instructions that should be provided by the investigator. Addition of this section moved subsequent sections up by one level (the old 5.7.8 became 5.7.9, etc).	To provide details on antidiarrheal usage prophylactically (Cohorts 1D and 1E and for subjects in Cohort 2A who receive tucatinib + trastuzumab + pembrolizumab + FOLFOX) and for other cohorts in the event of symptomatic diarrhea events.
Section 5.9.2	Added Section to indicate loperamide is a required concomitant medication for subjects enrolled in Cohorts 1D and 1E and for subjects in cohort 2A who receive tucatinib + trastuzumab + pembrolizumab + FOLFOX; included details about administration of loperamide.	Based on preliminary data from Cohorts 1A and 1B and SMC recommendations. antidiarrheals will be given prophylactically, as specified, to reduce risk of possible diarrhea adverse events.
Section 5.9.3	Updated text related to antidiarrheals in allowed concomitant medication therapy to be consistent with other updates in the current amendment.	Consistency between this section and other sections that have been updated within current amendment.
Section 6.2 through Section 6.6 and subsections therein.	Adjusted bullets and added text as needed to provide details for the approach for the mandatory antidiarrheal prophylaxis in Cohorts 1D and 1E and for subjects in cohort 2A who receive tucatinib + trastuzumab + pembrolizumab + FOLFOX, for treatment of symptomatic diarrhea in other cohorts, provided guidance on usage of subject diaries, and for assessing diarrhea events, as appropriate, in each section/cohort.	Consistency within protocol based on updates related to requirement for antidiarrheal prophylaxis.
Section 7.3	Updated relative time column in Table 22 to indicated "Prior to time of AM tucatinib administration" for PK samples for Cycles 3-6 Day 1. Updated text in "Time" column for cycle 2-6 in Table 24 to indicate time of tucatinib PK is predose. Updated "Relative Time" column in Table 24 and Table 25 to indicate "Prior to time of AM tucatinib administration"	Clarification to be consistent with rest of protocol and schedule of events

Section(s)	Change	Rationale
Section 7.5.1.2	Change pregnancy reporting from with 48 hours to within 24 hours of becoming aware of a pregnancy. Added text that "Diaries may be used for recording number of stools per day to aid with accurately documenting and grading diarrhea AEs."	Consistency with current pregnancy reporting guidelines. Provide information about diaries.
Appendix A, Schedule of Events for Phase 1b and Phase 2 Cohorts Utilizing FOLFOX	Removed footnote that was on Day 8 that stated "Phase 1b cohorts only". But kept footnote "C" on Cycle 2-3 Day 8 and clarified text to indicate assessments that applied to each of the Phase 1b and Phase 2 cohorts utilizing FOLFOX.	Consistency with updates made in this amendment.
	On the AE and concomitant medications Row, added parenthetical text about diarrhea AEs and antidiarrheal usage.	To clearly indicate diarrhea AEs and antidiarrheal usage should be captured.
	Added row for "Issue Subject Diaries" with appropriate issue and collection/review information.	Consistency with updates to Section 8
	Adjusted how dosing for trastuzumab (Q2W or Q3W) and pembrolizumab (Q6W) is presented.	Clarification to indicate trastuzumab dosing is Q2W for Cohorts 1A and 1B and Q3W for all other cohorts, and that pembrolizumab dosing is Q6W.
	Update footnote P with text about concomitant medicines and antidiarrheals.	Consistent with updates to Section 7.1.1.2
	Updated footnote Z to include information about sampling times for Cohort 1E and to provide clarifications about sampling times for Cohort 1D.	Correction of typographical omission and consistency with tables cited.
Appendix A, Schedule of Events for Phase 1b and Phase 2 Cohorts Utilizing CAPOX and Pembrolizumab Cohort 1G	Updated footnote B to indicate which assessments apply to which cohorts on Cycle 1 Day 8 and Cycle 2 Day 8.	Consistency with updates to the body of the protocol.
	On the AE and concomitant medications Row, added parenthetical text about diarrhea AEs and antidiarrheal usage.	To clearly indicate diarrhea AEs and antidiarrheal usage should be captured.
	Added row for Subject Diaries with appropriate issue and collection/review information.	Consistency with updates to Section 8.
	Adjusted how dosing for pembrolizumab (Q6W) is presented.	Dosing is Q6W for pembrolizumab.

Section(s)	Change	Rationale
	Removed "postdose" from parenthetical text on row for "Blood samples for tucatinib PK"	Consistency with the protocol body
	Update footnote L with text about concomitant medicines to indicate to refer to section 5.9.2.	Consistent with updates to Section 7.1.1.2
	Updated footnote S to include Cohorts 1E, and 1G, and incorporated predose instruction previously included in footnote T. Removed footnote T since it was no longer needed	Consolidation of related information previously contained in 2 footnotes into 1 footnote.
Throughout document	Minor editorial and formatting updates; updated footers and dates, as appropriate	Administrative

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Cover page	Added PPD as Study Director and updated email address contact for PPD Medical Monitor.	Provision of Study Director contact information and updated Medical Monitor email address.
Cover page	Indicated that Seagen Inc. has been acquired by Pfizer Inc.	Seagen is part of Pfizer as of 14 Dec 2023
Synopsis, Study Objectives; Section 2.4	To evaluate the PK of tucatinib given with pembrolizumab, trastuzumab, and oxaliplatin-based chemotherapy as 1L therapy for unresectable or metastatic HER2+ gastric, esophageal, or GEJ adenocarcinoma (Cohort 2A) ~~or~~ and to evaluate the PK of tucatinib given with trastuzumab and oxaliplatin-based chemotherapy as 1L+ therapy for metastatic HER2+ CRC (Cohort 2B)	Addition of text to more clearly indicate PK is also evaluated for Cohort 2B
Synopsis, Number of Planned Subjects; Section 3.1	Edited text to reflect altered enrollment projection from approximately 120 to approximately 40 subjects.	Provide updated enrollment projection upon implementation of Amendment 5
Synopsis, Study Design; Section 3.1, Section 3.1.8	Added footnote b to table in synopsis and Section 3.1 summarizing cohorts, treatments, populations, and number of subjects to indicate that no additional enrollment will occur for any cohort as of Amendment 5. This text was also included in Section 3.1.8	No additional enrollment will occur as of Amendment 5 due to sponsor decision
Synopsis, Study Design	Specification of loperamide prophylaxis regimen for Cohorts 1D, 1E, and 2B	Clearly indicate which cohorts require loperamide prophylaxis
Synopsis, Study Design; Synopsis, Phase 2 Tumor-Specific Expansion Cohorts (Cohorts 2A and 2B); Section 3.1; Section 3.1.4.2; Section 5.9.2; Section 5.9.3; Section 6.3.1; Section 6.3.4	Edited text to indicate that loperamide prophylaxis is now required for Cohort 2B	Based on review of Cohort 2B data as of 12-Dec-2023, text was updated to indicate loperamide prophylaxis is now mandatory for Cohort 2B
Synopsis, Duration of Treatment; Section 6.1	Added language describing that subjects still receiving clinical benefit and remaining on study treatment as of Amendment 5, may continue to receive study drug during the LTEP	Specify potential for continued study drug in subjects receiving clinical benefit as of Amendment 5

Section(s)	Change	Rationale
Synopsis, Efficacy Assessments; Section 7.2	Added text: "During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care"	Clarify collection of efficacy assessments during the LTEP
Synopsis, Pharmacokinetic Assessments	Clarified that no PK assessments will be performed following implementation of Amendment 5	Specify that PK samples will not be collected at EOT following implementation of Amendment 5
Synopsis, Biomarker Assessments	Clarified that no blood samples for biomarker assessments will be drawn at EOT following implementation of Amendment 5	Addition of guidance about blood samples at EOT following implementation of Amendment 5
Synopsis, Safety Assessments; Section 6.1; Section 7.5	Provided guidance for safety assessments, including pregnancy testing, and reporting during the LTEP.	Clarify safety assessments to be collected during LTEP
Section 3.1.8 (new section)	Addition of Section 3.1.8 Long-term Extension Phase to describe LTEP design	Provide details about addition of an LTEP to the study that are consistent with LTEP related updates throughout the document
Section 3.1.9	Clarification of End of Study after implementation of LTEP	Update end of study text for consistency with addition of the LTEP
Section 5.3.3; Section 5.5.3; Section 5.6.3	Removed recommendation to recalculate doses if there is a >10% change in baseline body weight Edited text to indicate that for body weight changes, doses of trastuzumab and FOLFOX should be recalculated according to institutional standard of care	Clarify dose recalculation requirements during the LTEP
Section 5.7.2	Added text "During the LTEP, investigators may choose to follow institutional standard of care for FOLFOX dose modifications"	Clearly indicate investigators may follow institutional SOC
Section 5.7.2, Table 14	Added footnote b to Table 14 to provide more information about management of diarrhea related to mFOLFOX6	5-FU bolus may be discontinued in event of severe diarrhea with mFOLFOX6
Section 5.7.2, Table 14	Added footnote c to Table 14 to provide more information about management of other nonhematologic toxicities	Guidance about next cycle of therapy during Grade 2 nonhematological toxicities
Section 5.7.3	Clarified that "During the LTEP, investigators may choose to follow institutional standard of care for CAPOX dose modifications"	Clearly indicate investigators may follow institutional SOC

Section(s)	Change	Rationale
Section 5.7.3, Table 17	Added footnote a to Table 17 to clarify determination of dose modifications to CAPOX for neutropenia and thrombocytopenia. This has shifted all subsequent footnotes	Provide guidance related to CAPOX dose modifications
Section 5.11	Identified that treatment administration data will no longer be collected in eCRFs after LTEP implementation and referenced Section 8.2 for LTEP data collection requirements	Update data collection guidance after LTEP implementation
Section 6.3.1	Corrected text to clearly indicate when blood samples for tucatinib PK are collected, for consistency across protocol	Update to ensure consistency across protocol
Section 6.6 (new section)	Added the following content: Subjects still receiving clinical benefit and remaining on study treatment as of Amendment 5 may continue receiving study drugs during the LTEP. • Only information related to pregnancies, SAEs, and AESIs (Section 9.5.1.1) will be reported to the Sponsor • All safety and efficacy assessments will be performed per usual and customary practice, with the exception of pregnancy testing • Pregnancy testing will continue to be performed as outlined in the schedule of events in subjects of child-bearing potential	Specify safety information, assessments, and pregnancy testing to be collected during the LTEP
Section 6.7	Clarified that blood samples for biomarker analysis and tucatinib PK will not be collected after implementation of Amendment 5	Update to ensure consistency across protocol
Section 6.8	Added text to indicate that as of Amendment 5, long-term follow up will be discontinued and that subjects in long term follow-up as of Amendment 5 will transition to end of study	Consistency with updates made across the protocol during this amendment
Section 7.3	Clarified that no PK assessments will be performed following implementation of Amendment 5 Adjusted Table 22 footnote order	Specify that PK samples will not be collected at EOT following implementation of Amendment 5 Administrative update

Section(s)	Change	Rationale
Section 7.4	Clarified that no blood samples for biomarker assessments will be drawn at EOT following implementation of Amendment 5	Addition of guidance about blood samples at EOT following implementation of Amendment 5
Section 7.5.1.1, Adverse Event	Identified that SAEs should be reported to the Sponsor solely on the SAE form, following the reporting guidelines in Section 7.5.1.2 and will not be recorded within the eCRF	Clarification of data collection during LTEP
Section 7.5.1.1, Adverse Events of Special Interest	Added the following text: "During the LTEP, AESIs will be reported to the sponsor using an SAE form only and will not be recorded within the eCRF."	Clarification of data collection during LTEP
Section 7.5.1.2, Recording Serious Adverse Events	Added the following text: "However, during the LTEP, SAEs will be reported to the Sponsor solely on the SAE form following the same reporting guidelines as outlined below, and will not be recorded within the eCRF."	Guidance on recording SAEs during the LTEP
Section 7.5.1.2, Collection of Data on the eCRF	Added text to clarify pregnancy data collection during the LTEP	Guidance for data collection of pregnancies that occur during the LTEP
Section 7.5.3	Clarified that local laboratory testing will be performed per institutional guidelines and investigator-determined usual and customary care, except for pregnancy testing (which will continue to be collected as outlined in the schedule of events).	Consistency with updates made in the body of the document
Section 7.5.5	Added the following text: "During the LTEP, pregnancy testing will continue to be performed as outlined above in the schedule of events for subjects of child-bearing potential. Pregnancy reporting should continue and will be collected by the Sponsor using the Pregnancy Report Form. Please see Section 7.5.1.2 for further details on pregnancy reporting requirements."	Provided guidance for pregnancy testing and reporting during the LTEP
Section 7.5.6.1 and Section 7.5.6.2	Clarified cardiac function and ECG assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care during the LTEP.	Provide updated guidance regarding ECG assessments during the LTEP

Section(s)	Change	Rationale
Section 8.1	Clarified that eCRFs will be reviewed for completeness, adherence to provided guidelines, and accuracy compared to source documents until the final database lock occurs	Clarify eCRF review period
Section 8.2	Added text to indicate data collection needed during LTEP	Guidance for data collection during LTEP
Section 8.4	Added text to indicate eCRFs will not be collected during LTEP	eCRFs will not be collected in the LTEP
Section 9.3.1.7	Edited text as follows: The Full Analysis Set will be used for the analysis of ~~efficacy endpoints.~~ PFS. Added the following text: "The Response Evaluable Analysis Set will include all subjects who meet all following criteria: (1) had measurable disease at baseline, (2) received any amount of study treatment, and (3) had at least one post-baseline disease assessment of discontinued due to clinical progression, toxicity, or death."	Ensure subjects evaluated for ORR have measurable disease at baseline per RECIST v1.1 and are eligible to achieve an objective response.
Section 9.3.5	Edited text as follows: The ORR will be summarized using the ~~full analysis~~ response evaluable set.	Ensure subjects evaluated for ORR have measurable disease at baseline per RECIST v1.1 and are eligible to achieve an objective response.
Appendix A: Schedule of Events: Phase 1b and Phase 2 Cohorts Utilizing FOLFOX	Added column for assessments needed during the LTEP to SOE tables. Footnotes BB, CC, DD, EE, FF, and GG were added to ensure guidance about assessments, as of Amendment 5 and during the LTEP, is clearly described in the FOLFOX related SOE table. Updated footnote P to reflect that loperamide prophylaxis is now required for Cohort 2B. Updated footnotes J to remove "24 hour urine is required if urine protein/creatinine ratio is >2.0" Updated footnote N to reflect pregnancy testing requirements during the LTEP	Column added to indicate timing of assessments to be done during the LTEP. Clear descriptions for AE collection, blood biomarker sampling, and other safety and efficacy assessments during the LTEP. Update to ensure consistency across protocol Removed text intended only for cohorts 1A/1B that was inadvertently not removed in a previous amendment. Provided guidance for pregnancy testing and reporting during the LTEP

Section(s)	Change	Rationale
	Updated footnote Z	To ensure consistency with updates made in the body of the document.
Appendix A: Schedule of Events - Phase 1b and Phase 2 Cohorts Utilizing CAPOX and Pembrolizumab Cohort 1G	Added column for assessments needed during the LTEP to SOE tables.	Column added to indicate timing of assessments to be done during the LTEP.
	Updated footnote F to remove "24 hour urine is required if urine protein/creatinine ratio is >2.0"	Removed text intended only for cohorts 1A/1B that was inadvertently not removed in a previous amendment.
	Added footnotes T, U, V, W, and X to ensure guidance about assessments, as of Amendment 5 and during the LTEP, is clearly described in the CAPOX and Pembrolizumab related SOE table.	Clear descriptions for AE collection, blood biomarker sampling, and other safety and efficacy assessments during the LTEP
	Updated footnote K to reflect pregnancy testing requirements during the LTEP	Provided guidance for pregnancy testing and reporting during the LTEP
Throughout document	Correction of typographical errors, formatting errors, and minor administrative corrections	Administrative updates