STATISTICAL ANALYSIS PLAN

Product:	Tucatinib
Protocol Number:	SGNTUC-024
Protocol Version:	Amendment 05, 29-Apr-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
SAP Version:	1.0 29-Apr-2024
Sponsor:	Seagen, Inc.* 21823 30th Drive SE Bothell, WA 98021, USA

* Please note that as of 14 December 2023, Seagen Inc. became a part of Pfizer Inc.

APPROVAL SIGNATURES

The individuals signing below have reviewed and approve this statistical analysis plan.

PPD PhD
PPD
Seagen, Inc.

Date

PPD PhD
PPD
Seagen, Inc.

Date

PPD PharmD, BCOP
PPD
Seagen, Inc.

Date

PPD DO
PPD (or designate)
Seagen, Inc

Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADI	absolute dose intensity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{last}	area under the plasma concentration-time curve to the time of the last quantifiable concentration
BID	twice daily
BTC	biliary tract cancer
C_{max}	maximum observed concentration
C_{trough}	observed trough concentration in plasma
CAPOX	capecitabine, oxaliplatin
CDISC	clinical data interchange standards consortium
CI	confidence interval
cORR	confirmed objective response rate
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cutoff
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EOS	end of study
EOT	end of treatment
FOLFOX	leucovorin, fluorouracil, oxaliplatin
GFR	glomerular filtration rate
HER2	human epidermal growth factor receptor 2
IDI	intended dose intensity
INV	investigator
IRR	infusion-related reaction
IV	intravenous
KM	Kaplan-Meier
LLOQ	lower limit of quantification
LTEP	long-term extension phase
MedDRA	Medical Dictionary for Regulatory Affairs
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival

PK	pharmacokinetic
PO	orally
PR	partial response
PT	preferred term
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
SAE	serious adverse event
SD	stable disease
SMQ	standard MedDRA query
SMC	Safety Monitoring Committee
SOC	system organ class
T_{max}	time at which the maximum plasma concentration occurs
TEAE	treatment emergent adverse event
ULN	upper limit of normal

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGNTUC-024, entitled "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". Results of the proposed analyses will become the basis of the clinical study report (CSR) for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the final CSR. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the CSR.

2 STUDY OBJECTIVES AND ENDPOINTS

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 subjects 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 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

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	• Type, incidence, severity, seriousness, and relatedness of AEs, including DLTs, and laboratory abnormalities • Vital signs and other relevant safety variables

and FOLFOX in Japanese subjects	• 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 subjects	• 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 subjects 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 subjects 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 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) or 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

3 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 subjects with unresectable or metastatic HER2+ GI cancers.

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

Study Phase	Cohort	Tucatinib Dose PO BID	Treatment	Population(s)		Approximate Subjects per Cohort
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	≥3
	1B	300 mg				≥6

Study Phase	Cohort	Tucatinib Dose PO BID	Treatment	Population(s)		Approximate Subjects per Cohort
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+	• CRC	≥6
	1E	300 mg	Tucatinib, Trastuzumab, Pembrolizumab, mFOLFOX6	1L	• Gastric adenocarcinoma • Esophageal adenocarcinoma • GEJ adenocarcinoma	≥6
	1F		Tucatinib, Trastuzumab, Pembrolizumab, CAPOX			≥6
	1G		Tucatinib, Trastuzumab, Pembrolizumab			≥6
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

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. Subjects enrolled in these cohorts will receive tucatinib in combination with trastuzumab and FOLFOX chemotherapy. The recommended dose of tucatinib will be determined by evaluating the incidence of renal dose-limiting toxicities (DLTs) observed when tucatinib combined with trastuzumab and FOLFOX.

In Cohort 1A, subjects will receive tucatinib 150 mg twice daily (BID). If no renal in Cohort 1A, the SMC may recommend escalating to the 300 mg BID dose level for Cohort 1B. Alternate dose levels and/or regimens may be recommended by the SMC.

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)

Subjects will be closely followed for unacceptable toxicities for either 21-days (for subjects enrolled in Cohorts 1C, 1F, or 1G) or 28 days (for subjects 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.

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 subjects with HER2+ GI malignancies enrolled from Japan.

Subjects in Cohort 1D will be carefully monitored through the first 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. A minimum of 3 subjects 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 subjects have enrolled and completed 28 days of study treatment. If the overall safety in the first 3 subjects enrolled is deemed acceptable, no further enrollment will take place.

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 further evaluate the safety and tolerability of the treatment regimens to be evaluated in Phase 2.

Efficacy Assessment

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. 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. Subjects that discontinue study treatment for reasons other than documented progressive disease per RECIST will continue to have disease approximately every 9 weeks until radiographic disease progression. After the occurrence of documented disease progression, subjects will be followed for survival approximately every 12 weeks until death, withdrawal of consent, study closure.

Safety Assessment

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.

A detailed study assessment schedule can be found in the protocol.

Long Term Extension Phase (LTEP)

As of protocol amendment 5, long term follow-up has been terminated. Subjects on treatment who transition to the LTEP will have efficacy and safety assessments performed per institutional standard of care, with the exception of pregnancy tests which will continue on a scheduled basis. A schedule of study assessments during the LTEP can be found in the protocol. Following implementation of Amendment 5 and entry of remaining on-treatment subjects into the LTEP, data will no longer be collected in eCRFs. Only pregnancies, SAEs, and AESIs will be reported to the sponsor during the LTEP, utilizing the Pregnancy Report Form and SAE form. No additional analyses specific to LTEP are planned.

4 ANALYSIS SETS

4.1 All Screened Subjects Set

The All Screened Subjects Set will include all subjects who has signed the informed consent.

4.2 All Enrolled Subjects Set

The All Enrolled Subjects Set will include all subjects who are enrolled in the study.

4.3 DLT-evaluable Analysis Set

The DLT-Evaluable Analysis Set for Cohort 1A and 1B includes all subjects 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.

The DLT-Evaluable Analysis Set for Cohort 1C includes all subjects 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 1D includes all subjects 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 DLT-Evaluable Analysis Set for Cohort 1E includes all subjects 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 subjects 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 subjects 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.

4.4 Full Analysis Set

The Full Analysis Set will include all subjects 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.

4.5 Safety Analysis Set

The safety analysis set will include all subjects who are enrolled in the study and receive any amount of study treatment. The safety analysis set will be used for all safety analyses. For this study, the safety analysis set is the same as full analysis set.

4.6 Response Evaluable Set

Response evaluable 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 or discontinued due to clinical progression, toxicity or death. The Response Evaluable set will be used for the analysis of cORR and DOR.

4.7 Pharmacokinetics (PK) Analysis Set

The pharmacokinetic analysis set will include all subjects in the safety set from whom at least one PK assessment was reported. The PK analysis set will be used for PK analysis.

5 STATISTICAL CONSIDERATIONS

5.1 General Principles

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be used to summarize continuous variables. Frequencies and percentages will be used to

summarize categorical variables. The median survival time will be estimated using the Kaplan-Meier method; the associated confidence interval (CI) will be calculated based on the complementary log-log transformation (Collett 1994). The two-sided exact CI using the Clopper-Pearson method will be calculated for the response rates where applicable (e.g., cORR) (Clopper 1934).

Unless otherwise specified, all statistical tests will be performed using a two-sided alpha of 0.1. Confidence intervals will be calculated at a two-sided 90% level.

Any analysis not described in this plan will be considered exploratory, and will be documented in the CSR as a post hoc analysis or a change to the planned analysis.

All statistical tables, listings, and figures will be produced using SAS, version 9.3 or more recent. Other statistical software, if used, will be described in the CSR.

5.2 Determination of Sample Size

Approximately 6 DLT-evaluable subjects may be treated in each phase 1b dose escalation cohort (i.e., Cohort 1A and 1B) 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 subjects in order to have at least 3 DLT-evaluable subjects, and approximately 8 subjects in Cohort 1B in order to have at least 6 DLT-evaluable subjects in the case a renal DLT is observed in the first 3 DLT-evaluable subjects.

Cohorts 1C, 1E, 1F, and 1G may enroll approximately 8 subjects in each cohort to ensure at least 6 subjects in each cohort complete the appropriate DLT period (21 days for Cohorts 1C, 1F and 1G; 28 days for Cohort 1E).

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

Phase 2 Tumor Specific Expansion

Two tumor specific expansion cohorts may be enrolled in Phase 2. Cohort 2A may enroll up to 40 subjects in subjects with unresectable or metastatic HER2+ gastric, esophageal, and GEJ adenocarcinoma being treated in the first-line setting. Cohort 2B may enroll up to 20 subjects with unresectable or metastatic CRC being treated in the first-line or greater setting.

For a sample size of 40 subjects, 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 subjects, 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%)

5.3 Randomization and Blinding

This is an open-label study. No randomization will be utilized. Blinding will not be performed.

5.4 Data Transformations and Derivations

The following data conventions will be used for the tables, listings, and figures.

Age: Reported age in years will be used

Study treatment: tucatinib, trastuzumab, FOLFOX, CAPOX, Pembrolizumab. In this study, subjects are considered to be on study treatment if they are receiving any of the study drugs (tucatinib, trastuzumab, FOLFOX, CAPOX, and Pembrolizumab).

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

Study Day: For subjects received treatment, study day starts on the date of the first dose (date - date of the first dose + 1) for dates on or after the first dose date. For dates prior to the first dose date, study day is calculated as (date - date of the first dose). The first dose date is the earliest date of administration of any study treatment.

Other time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date–Start Date+1) (in days) unless otherwise specified in the planned analysis section.

The following unit conversion will be implemented unless otherwise specified:

$$\text{Months} = \text{Days}/30.4375$$

$$\text{Years} = \text{Days}/365.25$$

Response assessment date: At each response assessment time point, scans to evaluate tumor lesions can be performed on multiple dates.

- The date of response for CR or PR will be recorded as the date of the last radiographic evaluation included in the series for that assessment.
- The date of response for non-CR/non-PD or SD will be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.
- The date of progression (PD) will be recorded as the earliest date that PD has been documented, i.e., the earliest of the following:
    - Date of target lesion assessment when the target lesion response is PD,

- Date of non-target lesion assessment when the lesion status is unequivocal progression,
- Date of documenting new lesion.

In the cases where a PD occurs due to the fact that an equivocal new lesion was continuously present and later confirmed to be an unequivocal new lesion, the PD date should be backdated to the date when the equivocal new lesion was first identified. The tumor response on the date when the equivocal new lesion was first identified will be changed to PD. If an equivocal new lesion was later absent or confirmed to be a benign lesion, then this new lesion is not considered to define a PD. In cases where PD occurs on a date after an equivocal new lesion is identified, but the progression is not due to a change of the equivocal new lesion to an unequivocal lesion, but from progression of other lesions, the PD date will not be backdated, but will be the date when definitive PD is recorded.

5.5 Handling of Dropouts and Missing Data

Except for the scenarios covered in this section, missing data will not be imputed.

Missing AE dates will be imputed for the purpose of calculating duration of events (Appendix A).

Missing start and end date of subsequent cancer-related therapy and prior treatment date will be imputed for the purpose of deriving the time-to-event endpoints, and other applicable analysis as applicable (Appendix C).

Missing end date of tucatinib administration will be imputed for the purpose of deriving cumulative dose of tucatinib (Appendix D).

Missing date of death will be imputed for deriving time-to-event endpoints (Appendix E).

Unless otherwise specified, lab values which are recorded or provided as being less than the lower limit of quantification (LLOQ), will be included in figures and summaries as LLOQ.

PK values which are recorded as being less than the lower limit of quantification (LLOQ), will be included in figures and summaries as LLOQ/2.

5.6 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough subjects to warrant an analysis by center.

5.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned, and no alpha adjustment is needed for this study.

5.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for efficacy endpoints including cORR, DOR and PFS. Subgroups may include but are not limited to the following:

- Treatment Regimens
  - Tucatinib (150 mg BID), Trastuzumb and FOLFOX

- Tucatinib (300 mg BID), Trastuzumb and FOLFOX
- Tucatinib (300 mg BID), Trastuzumb, FOLFOX and Pembrolizumab
- Tucatinib (300 mg BID), Trastuzumb, CAPOX and Pembrolizumab

Within each treatment regimen, subgroups may also be summarized per disease type (i.e., CRC, BTC and GEA).

Time-to-event subgroup analysis may not be performed if the number of subjects in the subgroup is not sufficiently large (e.g., <5).

5.9 Covariates

Covariates are not considered for adjustment in the analyses.

5.10 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 subjects in Cohort 1A have been followed for at least 2 cycles. The SMC will undertake similar analyses when the first 6 DLT-evaluable subjects 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, subjects will be evaluated after 3 DLT-evaluable subjects complete 2 cycles of treatment. For Cohort 1E, subjects will be evaluated after 6 DLT-evaluable subjects complete 2 cycles of treatment. For Cohort 1F and 1G, subjects will be evaluated after 6 DLT-evaluable subjects 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 subjects 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.

6 PLANNED ANALYSES

6.1 Disposition

An accounting of study subjects by disposition will be tabulated by cohort and total using the All Enrolled Subjects Set. The number of subjects in each analysis set will be summarized by cohort and total. The number of subjects enrolled in each country and at each site will be summarized by cohort and total.

The number and percentage of subjects who signed informed consent, and number of screen failures, the percentage relative to the total number of subjects screened will be summarized using All Screened Subjects Set. The reasons for screen failure will also be described, if applicable.

Reasons for discontinuation of treatment and study will be summarized using the Full Analysis set. Follow up time and subsequent treatment information will be summarized.

6.2 Demographic and Baseline Characteristics

Analysis set: Full Analysis Set

Demographics and baseline characteristics, including age, gender, ethnicity, race, baseline weight, and ECOG score will be listed and summarized; summaries will be presented for each cohort and total. Disease specific characteristics, including previous cancer-related treatments will be listed and summarized for each cohort and the total.

6.3 Protocol Deviations

Analysis set: Full Analysis Set

Important protocol deviations are those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the subject's rights, safety, or welfare. Important protocol deviations also include exemptions to the selected study inclusion/exclusion criteria. Important protocol deviations will be summarized by category and cohort. A list of subjects with important protocol deviations will be presented.

6.4 Treatment Administration

Analysis set: Safety Analysis Set

Exposure will be summarized by cohort using counts and percentages for categorical variables and summary statistics (mean, median, standard deviation, and range) for continuous variables. The following information will be summarized by cohort separately for tucatinib, trastuzumab, oxaliplatin, fluorouracil, leucovorin, capecitabine and pembrolizumab:

- total number of treatment cycles per subject,
- duration of treatment (months),
- dose modification by type (dose reduced, drug interrupted, dose hold, drug withdrawn) and by reason,
- dose holds due to AE,
- duration of dose holds due to AE,
- absolute dose intensity (ADI) and relative dose intensity (RDI) for tucatinib only.

Duration of treatment is defined, per study drug, as the time from first dose date to the earliest of following dates:

- exposure end date:
  - for tucatinib, the last dose date;
  - for trastuzumab, the last dose date + 20 if dosing schedule is Q3W; the last dose date + 13 if dosing schedule is Q2W, the last dose + 6 if dosing schedule is Q1W;
  - for FOLFOX, date of last dose + 13 for oxaliplatin, fluorouracil, leucovorin;
  - for CAPOX, date of last dose + 20 for oxaliplatin; date of last dose + 7 for capecitabine;

- for pembrolizumab, date of last dose + 41;
- date of death,
- end of study date,
- analysis data cutoff (DCO) date.

Cumulative dose is defined as the sum of the actual dose amount that a subject received across all cycles.

Intended Dose Intensity (IDI) is defined as the intended dose of drug per unit of time, i.e., 300 mg/day for tucatinib for Cohort 1A subjects and 600 mg/day for tucatinib for all other cohorts subjects.

Absolute Dose Intensity (ADI) is defined as the actual dose (mg/kg) per unit of time that the patient received over the entire treatment period, i.e., cumulative dose / (exposure end date – first dose date + 1) for tucatinib.

Relative Dose Intensity (RDI) = ADI/IDI × 100%.

6.5 Efficacy Analyses

The analysis for efficacy endpoints, including cORR and DOR will be conducted using the Response Evaluable Set, and PFS, will be conducted using the full analysis set, unless otherwise specified. OS analysis will not be performed due to limited utility in doing an analysis of OS, given small sample size of cohorts and termination of survival follow-up in protocol amendment 5. Subjects will be analyzed per treatment regimen and disease type.

6.5.1 Confirmed objective response rate (cORR) by Investigator Assessment

Confirmed objective response rate (cORR) per investigator assessment is defined as the proportion of subjects achieving a best overall response of a confirmed CR or a confirmed PR per RECIST 1.1 by investigator assessment. Only tumor assessments before first documented PD and subsequent cancer-related therapies will be considered. For a response to be considered as confirmed, the subsequent response needs to be at least 4 weeks after the initial response. Subjects with unconfirmed CR or PR $\geq$ 5 weeks after the date of randomization will be considered to have SD as their best overall response on the date of the corresponding unconfirmed CR and PR. A subject will have a best overall response of SD if there is at least one SD assessment (including the unconfirmed CR/PR) $\geq$ 5 weeks after the first dose date and the subject does not qualify for confirmed CR or confirmed PR.

The analysis of cORR by investigator will be conducted for subjects in the response evaluable set with measurable disease at baseline per investigator assessment.

6.5.2 Progression Free Survival (PFS) by Investigator Assessment

Progression-free survival (PFS) is defined as the time from first dose date to the first documented disease progression (as assessed by investigator per RECIST 1.1) or to death due to any cause, whichever occurs first.

Specifically,

PFS = Date of first documented PD or death or censoring − first dose date + 1.

PFS is defined based on the table below:

Table 1: PFS Event and Censoring Rules

Scenario	Event/Censor Date	Outcome
No post-baseline tumor assessments	Date of first dose date	Censored
No documented disease progression or death	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD	Censored
Subsequent cancer-related therapy (systemic, radiation, surgery, or other) started before PD or death observed	Date of last CR, PR, SD, or non-CR/non-PD on or prior to date of subsequent cancer-related therapy	Censored
Progressive disease (PD)	Date of PD	Event
Death without PD	Date of death	Event
Death or progression right after two or more consecutively missed tumor assessments	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD prior to the missed visits	Censored

Kaplan-Meier curves and estimates of the median PFS time will be provided with the two-sided 90% confidence intervals (CI) using the complementary log-log transformation method . KM estimates of the 25th and 75th percentiles of PFS time and the observed minimum and maximum PFS time will also be reported. In addition, estimated probability of PFS will be reported at every 3 months until the time of the last PFS event.

6.5.3 Duration of Response (DOR)

Duration of response is defined as the time from the date of the first objective response (confirmed CR or confirmed PR) to the date of the first documented PD per RECIST 1.1 or death due to any cause, whichever occurs first. The same derivation of PD date and censoring rules as for PFS analysis will apply for DOR.

Duration of response will only be calculated for the subgroup of subjects achieving a confirmed CR or confirmed PR. Kaplan-Meier curves and estimates of median DOR will be provided with the two-sided 90% CI using the complementary log-log transformation method. Estimated probability of progression-free survival will be reported at every 3 months until the time of the last event.

The analysis of DOR will be based on investigator assessment.

6.6 Safety Analyses

Analysis sets: Safety Analysis Set

All safety endpoints will be analyzed using the safety analysis set.

Adverse events will be coded by standard preferred terms (PT) and system organ classifications (SOC) using Medical Dictionary for Regulatory Activities (MedDRA, version 26.0 or higher).

Laboratory values will be graded using the National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE, version 5.0).

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug, Global-B3 Mar2023 or higher).

6.6.1 Adverse Events

Adverse events will be summarized by MedDRA preferred term (PT) in descending frequency of occurrence in the total column unless otherwise specified. For incidence reporting, if a subject reports more than one AE that was coded to the same SOC or PT, the subject will be counted only once for that specific SOC or PT. For summaries by severity, only the worst grade for an AE will be counted for a subject.

Treatment-emergent adverse event (TEAE) is defined as a newly occurring or worsening AE after the first dose of study treatment through 30 days after the last dose of study treatment, or through 90 days after the last dose of study treatment for SAE in cohorts utilizing Pembrolizumab.

Treatment-related AE is defined as AE assessed by the investigator as 'related' to any study treatment.

Summaries of TEAEs by cohort will include (but may not limit to):

- all TEAEs
- TEAE by PT
- grade 3 or higher TEAEs by PT
- serious TEAEs by PT
- TEAEs leading to dose hold by PT
- TEAE leading to dose reduction by PT
- TEAE leading to drug interruption by PT
- TEAEs leading to death by PT
- TEAE leading to drug discontinuation by PT
- treatment-related TEAEs by PT
- grade 3 or higher treatment-related TEAE by PT
- treatment-related serious TEAEs by PT
- treatment-related TEAE leading to death by PT
- TEAEs by SOC and PT
- Serious TEAE by SOC and PT
- TEAEs by SOC, PT and maximum severity. At each SOC or PT, multiple occurrences of events within a subject are counted only once at the highest severity.

All TEAEs, grade 3 or higher TEAEs, serious TEAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to death will be listed.

6.6.2 Adverse Events of Special Interest and Other Adverse Events

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. The incidence of AESI will be summarized by PT or lab values and listings will also be produced.

The AESIs to be summarized are described in Protocol Section 7.5.1.1 and are as the following:

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 subjects with documented Gilbert's syndrome
    - AST or ALT elevations >20 ×ULN
    - Bilirubin elevations >10.0 ×ULN
2. Increase of serum cystatin C >1.5× baseline
3. ≥ Grade 3 diarrhea
4. An overdose of tucatinib or pembrolizumab, as defined in Protocol Section 5.10

In addition, treatment-emergent AESI leading to dose modifications and study treatment discontinuation will be summarized. For selected AESI, time to first onset or resolution will be analyzed as appropriate. Time to first onset of a specific AESI will be calculated as time from the first dose of study drug to the start of first treatment-emergent event that meets the respective search criteria. Resolution is defined as event outcome of 'recovered/resolved' or 'recovered/resolved with sequelae'. For events with an outcome of 'recovered/resolved' or 'recovered/resolved with sequelae', time to resolution will be calculated as time from the event start date to end date. Time to first onset will be summarized at the subject level. Time to resolution will be summarized at the event level.

In addition to the protocol defined AESIs, the incidence of treatment emergent adverse events for additional risks will be summarized by PT or lab values and listings will also be produced. The TEAEs for the following additional risks to be summarized are:

- Hepatotoxicity: Drug related hepatic disorders - comprehensive search SMQ (Narrow)
- Diarrhea: Preferred term of Diarrhoea

6.6.3 Dose-limiting Toxicity

The observed number and proportion of subjects experiencing a renal DLT for Cohort 1A and 1B and DLT for Cohort 1C, 1D, 1E, 1F, 1G will be reported by cohort.

6.6.4 Clinical Laboratory Results

Clinical laboratory results collected during the study are specified in the protocol section of 7.5.3, including serum chemistry and hematology samples. The collection schedules are specified in Appendix A in the study protocol.

Both observed value and changes from baseline will be summarized with descriptive statistics for each scheduled visit by cohort. Shift from baseline to maximum post-baseline NCI CTCAE grade will be summarized for each lab test by cohort. Post baseline period is defined as from the date of the first dose of study treatment to the date of last dose + 30 days.

Treatment-emergent laboratory abnormalities will also be summarized.

Laboratory results and NCI CTCAE grades for hematology and serum chemistry will be presented in data listings. Normal ranges will be documented, and out-of-range values will be flagged. A separate listing of laboratory results with CTCAE grade 3 or higher will be presented.

Change in GFR (as estimated using serum cystatin C) from baseline will be summarized for Cohort 1A and 1B and per visit. Box plots of cystatin C will also be presented for Cohort 1A and 1B subjects. GFR (as estimated using serum cystatin C) and serum cystatin C for Cohort 1A and 1B will be listed.

6.6.4.1 Incidence of Liver Abnormalities

The incidence of potential drug-induced liver abnormalities will be summarized by cohort. In addition to the laboratory abnormalities defined for AESI in Section 6.6.2, the followings will also be summarized:

- (AST and/or ALT) > 3 × ULN + Total Bilirubin > 2 × ULN + Alkaline Phosphatase < 1.5 × ULN
- (AST and/or ALT) > 3 × ULN
- (AST and/or ALT) 5 × ULN
- (AST and/or ALT) 10 × ULN

6.6.5 Concomitant Medications

Concomitant medications will be summarized by the WHO Drug ATC class and preferred name. The number and percentage of subjects who take concomitant medications will be tabulated. Multiple occurrences of the same medication within a subject will be summarized only once. Concomitant medications will also be listed by subject.

6.6.6 Vital Signs

Vital signs (heart rate, blood pressure, temperature, and respiratory rate) will be listed by subject and visit for each cohort. Clinically significant vital signs are defined as: heart rate >100 bpm; temperature >38.0 degrees C (100.4 F), respiratory rate >20 breaths per min. Blood pressure will be summarized for subjects with systolic blood pressure >=120 mmHg or diastolic blood pressure >=80 mmHg, as well as for subjects with systolic blood pressure >=140 mmHg or diastolic blood pressure >=90 mmHg.

6.6.7 Deaths

The number of total deaths, deaths that occur within 30 days of last study treatment, and deaths that occur more than 30 days after last study treatment as well as the relationship to disease will be summarized in cohorts without using Pembrolizumab. The number of total deaths, deaths that occur within 30 days of last study treatment, deaths that occur more than 30 days but within 90 days of last study treatment, and death that occur more than 90 days after last study treatment, as well as the relationship to disease will be summarized in cohorts utilizing Pembrolizumab. In addition, cause of death will be identified by descending MedDRA preferred term (unless otherwise specified) and summarized. Death information will be listed by subject.

6.7 Pharmacokinetic Analyses

Analysis sets: PK Analysis Set

The analyses described in this section will be produced for the pharmacokinetics analysis set.

Tucatinib and oxaliplatin concentrations will be summarized with descriptive statistics at each PK sampling time point. PK parameters of tucatinib and oxaliplatin will be determined by noncompartmental analysis and summarized with descriptive statistics. Additional PK analyses may be performed.

For the calculation of summary statistics, <LLOQ results are imputed to LLOQ/2 value. The summary statistics for a timepoint will not be calculated if more than 50% of the results are <LLOQ.

The analyses described in this section will be produced for the pharmacokinetics analysis set.

6.8 Mechanism of Action Biomarkers

The analyses for biomarkers related to drug mechanism(s) of action will be defined in a separate Biomarker Analysis Plan and may be included in a separate report.

7 INTERIM ANALYSIS

No formal interim analyses are planned.

8 CHANGES FROM PLANNED ANALYSES

8.1 Changes from the Protocol

OS analysis will not be performed due to limited utility in doing an analysis of OS, given small sample size of cohorts and termination of survival follow-up in protocol amendment 5.

8.2 Changes from the Original SAP

Not Applicable.

9 REFERENCES

Collett D (1991). Statistical inference for binary data. Modelling Binary Data. London, Chapman and Hall: 23-26.

Collett D (1994). Interval-censored survival data. Modelling survival data in medical research. Boca Raton, Fla., Chapman & Hall/CRC: 237-251.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-47.

Haybittle, JL (1971). Repeated assessments of results in clinical trials of cancer treatment. Br. J. Radiol. 44 (526): 793–797.

10 APPENDICES

Appendix A: Imputation of Partial Missing Adverse Event Dates

For an AE with a partial start or end date, if it can be determined that the event occurred prior to the date of first dose of study treatment, the partial date will not be imputed. Otherwise, the partial date will be imputed using the rules described below. AE start dates should be imputed before imputation of AE condition end date in all cases.

Incomplete AE Start Date:

AE day only is missing.

- If the month/year is the same as the month/year of first dose of any study treatment, then AE start date will be imputed as the first dose date of any study treatment.
- If the month/year is after the month/year of first dose of any study treatment, then AE start date will be imputed as the first day of the month.

AE day and month are missing.

If the year is the same as the year of first dose of any study treatment, then AE start date will be imputed as the first dose date of any study treatment.
If the year is after the year of first dose of any study treatment, then AE start date will be imputed as January 1st.

AE day, month and year are missing.

AE start date will be imputed as the first dose date of any study treatment.

If AE condition end date is known with a full date, and the imputed start date is after the end date, the start date will be set to the AE end date.

Incomplete AE End Date:

If AE outcome is "not recovered/resolved", "unknown", or blank, then AE condition end date will not be imputed.

If AE outcome is "recovering/resolving", "recovered/resolved", "recovered/resolved with sequelae", or "fatal", then apply the following:

AE day only is missing.

AE condition end date will be imputed as the minimum of (death date, DCO date or data extraction date sans DCO, last day of the AE end date month/year, EOS date).

AE day and month are missing.

- If the year is equal to the year of the last dose date, then AE end date will be imputed as the minimum of (last dose date + 30, death date, DCO date or data extraction date sans DCO, December 31st of the end date year, EOS date).
- If the year is not equal to the year of the last dose date, then AE end date will be imputed as the minimum of (death date, DCO date or data extraction date sans DCO, December 31st of the end date year, EOS date).

AE day, month and year are missing.

AE end date will not be imputed.

Within a single record, if the imputed end date is before the start date, then the imputed end date will be set to the start date.

Example

AE Number 4: Condition/Event NAUSEA
First dose date 02APR2012

Prior to imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	UNAPR2012	2	recovering/resolving
2	UNAPR2012	04MAY2012	1	recovered/resolved

Post imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	**30**APR2012	2	recovering/resolving
2	**02**APR2012	04MAY2012	1	recovered/resolved

Appendix B: Definition of the Term "Treatment-Emergent" with Respect to AE Classification

Treatment-emergent adverse event (TEAE) is defined as a newly occurring or worsening AE after the first dose of study treatment through 30 days after the last dose of study treatment, or through 90 days after the last dose of study treatment for SAE in cohorts utilizing Pembrolizumab.

Appendix C: Imputation of Partial Missing Start and End Date of Prior Systemic Therapy and Subsequent Cancer-Related Therapy

Partial missing date will be imputed when both month and year are present and only day is missing.

- Prior therapy start date: first day of the month
- Prior therapy end date: the earlier of
  - Last day of the month and year
  - First dose date of study drug
- Subsequent therapy start date: the later of
  - First day of the month and year
  - First dose date of study drug
- Subsequent therapy end date: the earlier of
  - Last day of the month
  - Study end date

Appendix D: Imputation of Partial Missing Death Dates

Death dates are imputed if only the day is missing.

The imputation of partial missing death date depends on the last-known-alive date derived from eCRF.

If the last-known-alive date is in the same month and year of the partial missing death date, then the partial missing death date is imputed as the last known alive date

If the last-known-alive date is not in the same month and year of the partial missing death date, then the partial missing death date is imputed as day 15 of the month and year.