STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-213
Study Protocol Title:	A Phase 2, Multicenter, Open-label, 2-Cohort Study to Investigate the Efficacy and Safety of PET Guided Neoadjuvant Treatment With Tislelizumab (BGB-A317) Plus Chemotherapy/Chemoradiotherapy in Patients With Resectable Esophageal Squamous Cell Carcinoma
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BGB-A317	Tislelizumab
cCRT	concurrent chemoradiotherapy
CL	clearance
CR	complete response
CT	computed tomography
DCR	disease control rate
DFS	disease-free survival
DOR	duration of response
EC	esophageal carcinoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
ESCC	esophageal squamous cell carcinoma
eCRF	electronic case report form
EDC	electronic data capture (system)
EFS	event-free survival
FcγR	fragment crystallizable region (typically, of immunoglobulin G)
FDG	Fluorodeoxyglucose
GEJ	gastroesophageal junction
HBV	hepatitis B virus
HCC	hepatocellular cancer
HCV	hepatitis C virus
IB	investigator's brochure
ICC	investigator chosen chemotherapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product

Abbreviation	Definition
IV	Intravenous
Ig	immunoglobulin
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion related reaction
MedDRA	Medical Dictionary for Regulatory Activities
MPR	major pathological response
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PD-L2	programmed cell death protein ligand-2
PET-CT	positron emission tomography-computed tomography
PK	pharmacokinetic(s)
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
ULN	upper limit of normal
Vc	central volume

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB-A317-213: A Phase 2, multicenter, open-label, 2-cohort study to investigate the efficacy and safety of PET guided neoadjuvant treatment with Tislelizumab (BGB-A317) plus chemotherapy/chemoradiotherapy in patients with resectable esophageal squamous cell carcinoma. This SAP is based on BGB-A317-213 Protocol Amendment 1.0 dated on 22 July 2022.

2. STUDY OVERVIEW

2.1. Study Design

This is a Phase 2, multicenter, open-label, 2-cohort study to investigate the efficacy and safety of PET guided neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy in resectable esophageal squamous cell carcinoma (ESCC).

The study consists of a screening phase, treatment phase (includes induction phase, neoadjuvant phase, and surgery phase), safety follow-up phase, and survival/disease follow-up phase.

In induction phase, after completing all screening activities, eligible patients will receive one cycle induction therapy of chemotherapy doublet (cisplatin and paclitaxel).

In neoadjuvant phase, all patients will be grouped into one of two cohorts based on the change of PET SUVmax (15-21 days after the last dose of induction therapy):

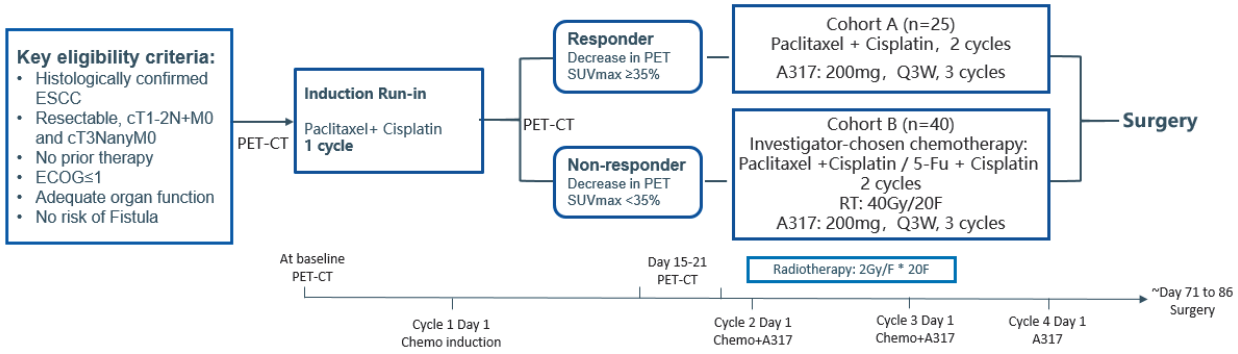
- Cohort A (Responder: decrease in PET SUVmax ≥ 35%):
  - Tislelizumab 3 cycles + chemotherapy doublet (cisplatin and paclitaxel) 2 cycles
- Cohort B (Non-Responder: decrease in PET SUVmax < 35%):
  - Tislelizumab 3 cycles + chemotherapy doublet 2 cycles + radiotherapy (40Gy/20F)

    Note: Chemotherapy doublets (Paclitaxel + Cisplatin/5-Fu + Cisplatin (Investigator-chosen))

In the surgery phase, upon completion of neoadjuvant therapy, patients will undergo surgical resection of tumor after reassessment to reconfirm disease resectability. Surgical specimens will be assessed for pathological response (pCR and MPR). The surgical procedure should be performed within 4-6 weeks from the last administered dose of chemotherapy treatment in cohort A or the last dose of chemoradiotherapy treatment in Cohort B.

The study schema is in Figure 1.

Figure 1. Study Schema



Abbreviations: A317, Tislelizumab; PET-CT, Positron Emission Tomography-Computed Tomography; Chemo, Chemotherapy; RT, Radiotherapy; 5-Fu, 5-fluorouracil; ESCC, esophageal squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; N, number of patients; Q3W, once every 3 weeks.

2.2. Study Assessments

Tumor Assessment:

Patients who undergo surgical resection of tumor and surgical specimens will be assessed for pathological response (pCR and MPR).

Tumor imaging will be performed within 28 days before first dose of study drug. Patient will undergo 2 times of PET-CT (including neck, chest, and abdomen), the first is at screening and the second is from 15 to 21 days after induction therapy, for evaluating SUVmax and to determine the subsequent treatment cohort. Patient will undergo computed tomography (CT) scans or magnetic resonance imaging (MRI) of the neck, chest, and abdomen before surgery to re-confirm the resectability.

Disease follow-up tumor assessment will be performed by computed tomography (CT) scans or magnetic resonance imaging (MRI) every 3 months after study treatment discontinuation (including chemotherapy, radiotherapy, tislelizumab and surgery) for the first 2 years, every 6 months in Years 3 based on RECIST v1.1. The allowed time window for disease follow-up assessments is 2 weeks in Years 1 to 2, and ± 4 weeks in Year 3. Tumor assessments should continue per protocol until disease progression (precluding definitive surgery), local or distant recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first.

Response will be assessed by the investigator using RECIST v1.1

Safety Assessment:

All adverse events (AEs) and serious adverse events (SAEs) (all severity grades, per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0) will be recorded during the study (AE from the time of the first dose and SAEs from the time of signing the informed consent) and for up to 30 days after the last study treatment (including chemotherapy, radiotherapy, tislelizumab and surgery) or until the initiation of another anticancer therapy, whichever occurs first.

At the EOT/Safety Follow-up Visit, ongoing AEs will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until death, withdrawal of consent, or loss to follow up, whichever occurs first.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the pathological complete response (pCR) in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.

3.2. Secondary Objective

- To evaluate the disease-free survival (DFS) of neoadjuvant treatment with tislelizumab plus chemotherapy/ chemoradiotherapy after R0 resection.
- To evaluate the Event-free survival (EFS) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy.
- To evaluate the R0 resection rate in patients receiving tislelizumab plus chemotherapy/ chemoradiotherapy as neoadjuvant treatment.
- To evaluate objective response rate (ORR) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy before surgery as assessed by the investigator.
- To evaluate the safety of tislelizumab combined with chemotherapy/chemoradiotherapy as neoadjuvant treatment.

3.3. Exploratory Objective

- To evaluate overall survival (OS) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy.
- To evaluate the potential association of biomarkers with clinical efficacy in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.
- To evaluate the major pathological response (MPR) rate in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.

4. STUDY ENDPOINTS

4.1. Primary Endpoint(s)

- pCR rate, defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes (ypT0N0) after completion of neoadjuvant therapy in an Efficacy Evaluable Analysis Set.

4.2. Secondary Endpoints

- 1-year/3-year Disease-Free Survival (DFS) rate, defined as the proportion of patients free from disease events at 1st year and 3rd year after the first date of no disease (R0 resection as surgery outcome) in an Efficacy Evaluable Analysis Set. DFS is defined as the time from the first date of no disease to local or distant recurrence or death due to any cause, whichever occurs first. DFS rate will be analyzed only for patients who undergo R0 resection.
- 1-year/3-year Event-Free Survival (EFS) rate, defined as the proportion of patients free from EFS events at 1st year and 3rd year after the first dose in a Safety Analysis Set. EFS is defined as time from first dose date to any of the following events which occurs first: progression of disease that precludes definitive surgery, local or distant recurrence, or death due to any cause.
- R0 resection rate, defined as the proportion of patients with R0 resection in an Efficacy Evaluable Analysis Set.
- Objective response rate (ORR), defined as the proportion of patients who had complete response or partial response before surgery as assessed by the investigator per RECIST v1.1 in all patients with measurable disease at baseline in the Safety Analysis Set.
- The incidence and severity of treatment-emergent adverse events (TEAEs) is determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) .

4.3. Exploratory Endpoints

- 1-year/3-year OS rate, defined as the proportion of patients alive at 1st year and 3rd year after first dose in the Safety Analysis Set.
- To evaluate the potential association of biomarkers (including PD-L1 and gene expression profile) with clinical efficacy (including but not limited to pCR, MPR, DFS, EFS, R0 resection, ORR, OS and ORR).
- MPR rate, defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy in an Efficacy Evaluable Analysis Set.

5. SAMPLE SIZE CONSIDERATIONS

Approximately 65 patients are expected to be enrolled in this study, considering about 10% patients not receiving surgery. It is assumed that 25 patients will be categorized into cohort A and 40 patients will be categorized into cohort B according to their PET SUVmax decrease. The actual number of patients in each cohort will be based on the actual ratio of responder versus non-responder and may vary from this assumption.

The pCR rate of responders was reported about 21.9% - 31.8% in historical studies (Büschenfelde et al. 2011; Ilson et al. 2012; Greally et al. 2019). The pCR rate in cohort A is assumed to be 37%. Assuming there are 23 evaluable patients in cohort A, it will provide the probability of 66.2% to

observe 8 pCRs out of 23 evaluable patients with point of estimate of pCR rate = 34.7% greater than the historical pCR rate in cohort A.

The pCR rate of non-responders was reported about 4% - 13.6% in historical studies (Büschenfelde et al. 2011; Ilson et al. 2012; Greally et al. 2019). **Error! Reference source not found.Error! Reference source not found.**The pCR rate in cohort B is assumed to be 22%. Assuming there are 35 evaluable patients in cohort B, it will provide a probability of 91.0% to observe 5 pCRs out of 35 evaluable patients with point of estimate of pCR rate = 14.3% greater than the historical pCR rate in cohort B. **Error! Reference source not found.Error! Reference source not found.**

Table 1 presents the estimates of the 95% CI around the observed pCR in cohort A for several potential outcomes using the sample sizes of 23 evaluable patients using the Clopper-Pearson method.

Table 2 presents the estimates of the 95% CI around the observed pCR in cohort B for several potential outcomes using the sample sizes of 35 evaluable patients using the Clopper-Pearson method.

Table 1: Estimates of 95% CI Using Clopper-Pearson After Enrollment of 23 Patients in Cohort A

Number of pCR Among 23 Patients	Observed pCR	95% CI of Observed pCR
7	30.4%	13.2% – 52.9%
8	34.7%	16.4% – 57.3%
9	39.1%	19.7% – 61.5%

Table 2: Estimates of 95% CI Using Clopper-Pearson After Enrollment of 35 Patients in Cohort B

Number of pCR Among 35 Patients	Observed pCR	95% CI of Observed pCR
4	11.4%	3.2% – 26.7%
5	14.3%	4.8% – 30.3%
6	17.1%	6.6% – 33.6%
7	20.0%	8.4% – 36.9%

6. STATISTICAL METHODS

6.1. Analysis Sets

The Efficacy Evaluable Analysis Set includes all patients who receive neoadjuvant treatment followed by surgery.

The Safety Analysis Set includes all enrolled patients who receive at least 1 dose of any component of study drugs; it will be the primary analysis set for the safety analyses.

6.2. Multiplicity Adjustment

Since no formal hypothesis is tested in this study, multiplicity adjustment is not needed.

6.3. Data Analysis General Considerations

6.3.1. Definitions and Computations

Study drugs

Study drugs include tislelizumab, chemotherapy doublet and radiotherapy.

Study day

Study day will be calculated in reference to the date of the first dose of study drug for both safety analysis and efficacy analysis. For assessments conducted on or after the date of first dose of study drug, the study day will be calculated as (assessment date – date of first dose of study drug + 1). For assessments conducted before the date of first dose of study drug, study day is calculated as (assessment date – date of first dose of study drug). There is no study day 0. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix 1.

Baseline value

Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the first dose of study drug.

Study Follow-up Duration

Study follow-up duration (SFD) is defined as the duration from the first dose date to the study discontinuation date (e.g., death, consent withdrawal, lost to follow-up) or to cutoff date if a patient is still ongoing.

All calculations and analyses will be conducted using SAS® Version 9.4 or higher.

6.3.2. Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 decimal place.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 decimal place.

- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25.
- For laboratory results collected in numerical range, if lab results ≥ x then set as x; if < x, then x/2.
- For by-visit observed data analysis, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.3.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for the handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix 1. By-visit endpoints will be analyzed using observed data unless otherwise specified. For observed data analysis, missing data will not be imputed, and only the observed records will be included.

6.4. Patient Characteristics

6.4.1. Patient Disposition

The number (percentage) of patients who signed informed consent, enrolled in the study, screen failures, screened previously, and reason for screen failure will be summarized in all patients by cohort.

The number (percentage) of patients treated, discontinued from the study, discontinued from the treatment (all treatments), reasons for discontinued from the study, reasons for discontinued from the treatment, and the duration of study follow-up will be summarized in the safety analysis set by cohort.

The reasons for patients discontinued from tislelizumab, chemotherapy or radiotherapy will be summarized separately in safety analysis set.

The following information of surgery will be summarized by cohort in safety analysis set:

- Number (%) of patients not receiving surgery and reason
- Number (%) of patients with delayed surgery and reason
- Number (%) of patients received surgery
- Intent of surgery (curable, palliative)
- Name of surgery (McKeown Esophagectomy, Ivor Lewis Esophagectomy, Transhiatal Esophagectomy)
- Inclusion type (Traditional Open Surgery, Minimally Invasive Surgery, Robotic Assisted Surgery)

- Lymph node dissection type (Two-field, Three-field)
- Duration of Surgery

Patient data listings of patient disposition will be provided.

6.4.2. Protocol Deviations

Protocol deviation criteria will be established together with its category/term of important and non-important. Patients with important protocol deviations will be identified and documented before the database lock. Important protocol deviations will be summarized for all patients in the safety analysis set. They will also be listed by each category. Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per patient.

6.4.3. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics in the safety analysis set, including the following variables:

- Age (continuously and by categories [< 65 or ≥ 65 years])
- Sex
- Race
- Ethnicity
- Weight (kg)
- BMI (kg/m^2)
- ECOG performance status

6.4.4. Disease History

The number (percentage) of patients reporting a history of disease and characteristics, as recorded on the eCRF, will be summarized in the safety analysis set.

Disease history of ESCC includes the following characteristics.

- Disease stage at study entry
- TNM staging at initial diagnosis
- Patients with metastatic disease at study entry
- Time from initial diagnosis to time of first dose date
- Site of primary location of esophageal cancer
- Histology type
- PD-L1 score status
- Histologic grade

6.4.5. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by System Organ Class and Preferred Term for the Safety Analysis Set.

Patient data listings of medical history will be provided.

6.4.6. Prior and Concomitant Medications

Prior medications are defined as medications that stopped before the first dose of study drugs. Concomitant medications are defined as medications that 1) started before the first dose of study drugs and were continuing at the time of the first dose of study drugs, or 2) started on or after the date of the first dose of study drugs up to 30 days after the patient's last dose.

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes Version B3 March 1, 2022. They will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred name in the safety analysis set.

6.4.7. Systemically Administered Corticosteroids/Immunosuppressants During the Study

Systemic corticosteroid/immunosuppressant received between the first dose of study drug and up to 90 days after last dose will be summarized. The number (percentage) of patients with at least one systemically administered corticosteroids/immunosuppressive drugs during the study will be summarized by ATC medication class and WHO DD preferred name in the safety analysis set.

6.4.8. Concomitant Procedure/Surgery

Concomitant procedure or surgery is defined as procedure or surgery that performed on or after the date of the first dose of study drugs up to 30 days after the patient's last study treatment.

The number (percentage) of patients reporting concomitant procedure/surgery, type or name of procedure/surgery and treatment intent will be summarized in the safety analysis set.

6.4.9. PET-CT Procedures

The number (percentage) of patients performed PET-CT scan (baseline and after induction therapy), reason for PET scan not performed, SUVmax in primary tumor and number (percentage) of patients with SUVmax decrease ≥ 35% will be summarized in the safety analysis set.

6.5. Efficacy Analysis

No formal hypothesis testing is planned for efficacy analysis. All efficacy analyses will be performed descriptively by cohorts.

6.5.1. Primary Efficacy Endpoints

pCR rate is the primary endpoint of the study. pCR rate is defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy followed by surgery as assessed by the investigator.

The pCR rate in Cohort A (Responder: decrease in PET SUVmax ≥ 35%) and Cohort B (Non-Responder: decrease in PET SUVmax<35%) will be summarized. Clopper-Pearson 95% confidence interval (CI) of pCR in Cohorts A and B will be calculated. These analyses will be performed in the Efficacy Evaluable Analysis Set as the primary analysis. A sensitivity analysis of the pCR rate will also be performed in the Safety Analysis Set, and those patients who have not received surgery will be treated as non-pCR. The analysis of pCR rate will occur after all the patients in the Efficacy Evaluable Analysis Set have been assessed for pathological response.

6.5.2. Secondary Efficacy Endpoints

1-year/3-year Disease-Free Survival (DFS) Rate

The 1-year/3-year Disease-Free Survival (DFS) rate is defined as the proportion of patients free from disease events at 1st year and 3rd year after the first date of no disease (R0 resection as surgery outcome). DFS is defined as the time from the first date of no disease to local or distant recurrence or death due to any cause, whichever occurs first.

The analysis of DFS is based on Efficacy Evaluable Analysis Set with patients who undergo R0 resection. The censoring rules for the analysis of DFS are presented in Table 3. DFS will be summarized by cohorts. Kaplan Meier methodology will be used to estimate median, Q1, and Q3 of DFS, and the event-free rates at 12 and 36 months. 95% CIs for median and other quantiles of DFS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley, 1982). And 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926). Kaplan-Meier curves will be constructed to provide a visual description of the DFS change with time.

Table 3: Censoring Rules for Disease-free Survival Per RECIST Version 1.1

	Derivation rules	Primary Outcome	Sensitivity Analysis 1	Sensitivity Analysis 2
Local or distant recurrence documented between scheduled visits	Date of recurrence	Event	Event	Event
Death before local/distant recurrence	Date of death	Event	Event	Event
New anticancer therapy started	Last adequate radiological assessment	Censored	Event at local or distant	Censored

	before the new anticancer therapy		recurrence or death	
No local or distant recurrence documented, or death documented at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored	Censored	Censored
local or distant recurrence, or death documented after > 1 consecutive missed tumor assessments	Date of last adequate radiologic assessment before missed tumor assessments	Censored	Censored	Event at local or distant recurrence or death
No post-surgery tumor assessments, died after 26 weeks from the first date of no disease	First date of no disease	Censored	Censored	Event

1-year/3-year Event-Free Survival (EFS) Rate

The 1-year/3-year Event-Free Survival (EFS) rate is defined as the proportion of patients free from EFS events including progression of disease that precludes definitive surgery, local or distant recurrence, or death due to any cause at the 1st year and 3rd year after the first dose date.

Progression of disease that precludes definitive surgery is defined as radiographic progression per RECIST 1.1 as assessed by the investigator that precludes surgery for both curative intent and R0 outcome (i.e., definitive surgery). Local recurrence is defined as recurrence in the area of the anastomosis or regional lymph node diagnosed by radiological examination and/or histopathological confirmation after definitive surgery. Distant recurrence is defined as extra-regional lymph node metastasis, distant organ metastasis, or pleural or peritoneal dissemination diagnosed by radiological examination and/or histopathological confirmation after definitive surgery.

The analysis of EFS is based on Safety Analysis Set. The censoring rules for the analysis of EFS are presented in Table 4. Kaplan Meier methodology will be used to estimate median, Q1, and Q3 of PFS, and the event-free rates at 12 and 36 months. 95% CIs for median and other quantiles of EFS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). And 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926). Kaplan-Meier curves will be constructed to provide a visual description of the EFS change with time.

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Table 4: Censoring Rules for Event-free Survival Per RECIST Version 1.1

	Derivation rules	Primary Outcome	Sensitivity Analysis 1	Sensitivity Analysis 2	Sensitivity Analysis 3
Progression of disease precluding definitive surgery, or Local or distant recurrence documented between scheduled visits	Date of progression or recurrence	Event	Event	Event	Event
Death before progression of disease precluding definitive surgery or local/distant recurrence	Date of death	Event	Event	Event	Event
New anticancer therapy started	Last adequate radiological assessment before the new anticancer therapy	Censored	Event at PD that precludes definitive surgery, local or distant recurrence or death	Censored	Censored
No PD that precludes definitive surgery, local or distant recurrence documented, or death documented at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored	Censored	Censored	Censored
PD that precludes definitive surgery, local or distant recurrence, or death documented after ≥ 2 consecutive missed tumor assessments	Date of last adequate radiologic assessment before missed tumor assessments	Censored	Censored	Event at PD that precludes definitive surgery, local or distant recurrence or death	Censored

No baseline or any post-baseline tumor assessments, died after 26 weeks	First dose date	Censored	Censored	Censored	Censored
No surgery or surgery with R1/2 outcome with no PD precluding definitive surgery	If PD before actual or planned surgery date [a], censor on first PD date before actual or planned surgery date. If no PD before actual or planned surgery date, censor on date of last adequate radiologic assessment prior to actual or planned surgery date or on date of data cut-off or withdrawal from study, whichever is earlier	N/A	N/A	N/A	Censored

[a] Planned surgery date is defined as the last administered dose of chemotherapy treatment (the last dose of chemoradiotherapy in Cohort B) regardless the last dose of Tislelizumab plus 6 weeks.

R0 Resection Rate

R0 resection rate defined as the proportion of patients with R0 resection, will be summarized by cohorts in the Efficacy Evaluable Analysis Set.

ORR by Investigators

The ORR is defined as the percentage of patients with measurable disease at baseline who have a complete response or partial response before surgery as assessed by investigators per RECIST v1.1. Patients with no post-baseline response assessment (for any reason) before surgery will be considered as non-responders. The ORR will be summarized with descriptive statistics by cohorts and the corresponding two-sided 95% CIs calculated from Clopper Pearson exact method will be also presented. The primary analysis of ORR is based on Safety Analysis Set with measurable disease at baseline.

A sensitivity analysis of the ORR will also be performed in the Safety Analysis Set regardless of whether patients have measurable disease at baseline.

6.5.3. Exploratory Efficacy Endpoints

Overall Survival

1-year/3-year OS rate is defined as the proportion of patients alive at 1st year and 3rd year after first dose. OS is defined as the time from first dose date to the documented death date for patients who died prior to or on the clinical cutoff date. For patients who are alive by the clinical cutoff date,

OS will be censored at the last known alive date. The last known alive date will be defined as either the clinical data cutoff date for patients who are still on treatment, or last available date showing patients alive or cut-off date whichever comes first for other alive patients.

Every effort should be made to ensure complete death dates. In the rare case, if day of death date is missing, death date is imputed as the max (last available date showing patients alive + 1, first day of month of death date).

The distribution of OS, including median, Q1, and Q3, and event-free rates at 12 and 36 months, will be estimated using the Kaplan-Meier method by cohorts in Safety Analysis Set. 95% CIs for median, Q1, and Q3 of OS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). The 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926). Kaplan-Meier survival probabilities over time will be plotted.

MPR Rate

MPR rate is defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy. MPR rate and its Clopper-Pearson 95% confidence interval (CI) will be summarized by cohorts in the Efficacy Evaluable Analysis Set.

6.5.4. Subgroup Analysis

To determine if the treatment effect is consistent across PD-L1 subgroups, all the efficacy endpoints including pCR rate, MPR rate, ORR, EFS, DFS and OS will be summarized by baseline PD-L1 status (TAP < 10%, ≥ 10%, and Unknown) using the sample approach in the primary analysis set. Kaplan-Meier plot of DFS, EFS and OS by baseline PD-L1 status will also be provided.

6.5.5. Post-Treatment Subsequent Anti-Cancer Therapy

Post treatment anti-cancer therapy is defined as the anti-cancer therapy started after the last dose of study drug(s).

A summary of number and percentage of patients who received any subsequent systemic anticancer therapy, radiotherapy, procedures or surgery will be provided by cohort based on safety analysis set. Time to first post-treatment anti-cancer therapy, time to first post-treatment immunotherapy, post-treatment anti-cancer therapy duration will be summarized with descriptive statistics by cohorts based on safety analysis set.

The number (percentage) of patients who received any subsequent systemic anticancer therapy will be summarized by cohort and by ATC medication class and WHO DD preferred name in the safety analysis set.

The analysis above for post-treatment subsequent anticancer therapy will be repeated for post treatment adjuvant anti-cancer therapy.

Separate flags of start date of new anti-cancer therapy for efficacy and safety analyses are derived individually.

- As for efficacy analysis, start date of new anti-cancer therapy will be the earliest date of prohibited anti-cancer therapy taken during treatment, date of the post-treatment systemic anti-

cancer therapy and date of other anti-cancer therapy such as post-treatment surgery and radiotherapy as deemed appropriate.

- The start date of new anti-cancer therapy in defining TEAE for safety analysis is always the first date of new systemic anti-cancer therapy taken after the last study treatment.

Tumor response per RECIST or event driven endpoints have not been commonly used for the efficacy evaluation of TCM. ORR, PFS or OS benefit of Chinese herbal medicines or Chinese patent medicines has not yet been established. Therefore, TCM will not be considered as new anti-cancer therapy in the efficacy and safety analysis.

Patient data listings of post-treatment anti-cancer therapy, procedure, radiotherapy, or surgery will be provided.

6.6. Safety Analysis

All safety analyses will be performed by cohorts in Safety Analysis Set. Safety and tolerability will be assessed, where applicable, by incidence, severity, and change from baseline values for all relevant parameters including AEs, laboratory values, vital signs, and ECG findings.

6.6.1. Extent of Exposure

The following measures of the extent of exposure will be summarized:

Duration of exposure (months).

- For tislelizumab and paclitaxel, duration of exposure (months) is defined as (last date of exposure - first dose date + 1) / 30.4375. For treatment ongoing patients, use cutoff date as the 'last date of exposure'; for patients discontinued from treatment, 'last date of exposure' is defined as the earliest date of cutoff date, death date and last dose date + 20.
- For cisplatin, duration of exposure (months) is defined as (last date of exposure – first date of exposure + 1) / 30.4375. For treatment ongoing patients, use cutoff date as the 'last date of exposure'; for patients discontinued from treatment, 'last date of exposure' is defined as the earliest date of cutoff date, death date and last dose date + 20 or 18. Apply 18 for cisplatin if it is given in 3 divided doses on Days 1, 2, and 3 depending on local guidelines. Apply 20 for cisplatin if it is given on Day 1 or 2, given every 21 days.
- For 5-FU which is given on days 1 to 4 of each 21-day cycle, duration of exposure (months) is defined as (last date of exposure - first dose date + 1) / 30.4375. For treatment ongoing patients, use cutoff date as the 'last date of exposure'; for patients discontinued from treatment, 'last date of exposure' is defined as the earliest date of cutoff date, death date and last dose date + 17.

Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study drug is administered.

Total dose received per patient is defined as the cumulative dose of the study drug during the treatment period of the study. The dose unit is mg for tislelizumab and mg/m2 for the Chemotherapy doublets.

Actual dose intensity (ADI) (mg/cycle) for tislelizumab is defined as the 21* total cumulative dose (mg) received by a patient / (last dose date prior to cut off date + 21 – first dose date).

Relative dose intensity (RDI) is defined as the actual dose intensity divided by the planned dose intensity *100. The planned dose intensity is 200 (mg/cycle) for tislelizumab.

The derivation of ADI, planned dose and RDI for Chemotherapy are show in Table 5: Derivation of ADI, Planned Dose and RDI for ChemotherapyTable 5.

Table 5: Derivation of ADI, Planned Dose and RDI for Chemotherapy

	ADI (mg/m^2/cycle)	Planned dose per cycle	RDI
Paclitaxel	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA*} \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	135 mg/m^2	$\frac{ADI}{135}$
Cisplatin**	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA*} \times 21}{\max(\frac{date\ of\ last\ dose\ up\ to\ cutoff + 21\ or\ 19 - first\ dose\ date}{21}, number\ of\ cycles\ in\ last\ dosing\ CRF\ page)}$	80 mg/m^2	$\frac{ADI}{80}$
5-FU (4 continuous doses Q3W)	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA*}}{\max(\frac{date\ of\ last\ dose\ up\ to\ cutoff + 18 - first\ dose\ date}{21}, number\ of\ cycles\ in\ last\ dosing\ CRF\ page)}$	800 * 5 mg/m^2	$\frac{ADI}{4000}$

*Body Surface Area (BSA) is defined as sqrt(height(cm)*weight(kg)/3600) or sqrt(height(cm)*weight (lb)/3131). Baseline weight is used to derive BSA at each visit unless weight change for one visit is at least 10% greater compared to baseline weight.

** Cisplatin: Apply 19 if it is given in 3 divided doses on Days 1, 2, and 3 depending on local guidelines, apply 21 if it is given on Day 1 or 2, given every 21 days.

The number (percentage) of patients requiring dose modifications, dose interruptions and dose delay will be summarized for each study drug.

Extent of exposure to radiotherapy including duration of exposure, number of fractions received, cumulative dose, radiotherapy completion status, patients with dose modification will be summarized.

Patient data listings will be provided for all dosing records, and for the above calculated summary statistics.

6.6.2. Adverse Events

AEs will be graded by the investigators using NCI-CTCAE Version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. AEs will be coded to the MedDRA (Version 25.0 or higher) lowest

level term closest to the verbatim term, along with the linked MedDRA Preferred Term (PT) and primary System Organ Class (SOC).

6.6.2.1 Treatment Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an AE that had onset or increase in severity level date on or after the date of the first dose of study drug up to 30 days after the last treatment (any component of combination treatment or surgery, whichever is last) or the initiation of subsequent anticancer therapy, whichever comes first. Treatment-related TEAEs include those events considered by the investigator to be related to study drug or with a missing assessment of the causal relationship. Summary tables will generally focus on those TEAEs and treatment related TEAEs.

An AE overview table, including the number and percentage of patients with TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with Grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to dose modification, treatment-related TEAEs, treatment-related version of any of the above categories, infusion-related reactions will be provided.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC, PT, and the worst grade. A patient will be counted only once by the highest severity grade within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. Summaries of the number (%) of patients with the below types of TEAE will be generated:

- All TEAEs
    - TEAEs by SOC, PT and Worst Grade (≥Grade 3 and All Grades)
    - TEAEs by PT
    - Treatment-related TEAEs by SOC, PT and Worst Grade (≥ Grade 3 and All Grades)
    - Tislelizumab related TEAEs by SOC, PT and Worst Grade (≥ Grade 3 and All Grades)
    - Chemotherapy related TEAEs by SOC, PT and Worst Grade (≥ Grade 3 and All Grades)
    - Radiotherapy related TEAEs by SOC, PT and Worst Grade (≥ Grade 3 and All Grades)
    - Treatment-related TEAEs by PT
    - Tislelizumab related TEAEs by PT
    - Chemotherapy related TEAEs by PT
    - Radiotherapy related TEAEs by PT
- Serious TEAEs
    - Serious TEAEs by SOC and PT
    - Treatment-related serious TEAEs by SOC and PT
    - Tislelizumab related serious TEAEs by SOC and PT

- Chemotherapy related serious TEAEs by SOC and PT
- Radiotherapy related serious TEAEs by SOC and PT
- Serious TEAEs by PT

- TEAEs of Grade 3 or Higher
  - TEAEs of Grade 3 or Higher by SOC and PT
  - Treatment-related TEAEs of Grade 3 or Higher by SOC and PT
  - Tislelizumab related TEAEs of Grade 3 or Higher by SOC and PT
  - Chemotherapy related TEAEs of Grade 3 or Higher by SOC and PT
  - Radiotherapy related TEAEs of Grade 3 or Higher by SOC and PT
- TEAEs leading to death
  - TEAEs leading to death by SOC and PT
  - Treatment-related TEAEs leading to death by SOC and PT
  - Tislelizumab-related TEAEs leading to death by SOC and PT
  - Chemotherapy related TEAEs leading to death by SOC and PT
  - Radiotherapy related TEAEs leading to death by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT
  - TEAEs leading to any treatment discontinuation by SOC and PT
  - TEAEs leading to discontinuation of Tislelizumab by SOC and PT
  - TEAEs leading to discontinuation of Chemotherapy by SOC and PT
  - TEAEs leading to discontinuation of Radiotherapy by SOC and PT
- TEAEs leading to treatment modification by SOC and PT
  - TEAEs leading to any modification by SOC and PT
  - TEAEs leading to dose modification of tislelizumab by SOC and PT
  - TEAEs leading to dose modification of Chemotherapy by SOC and PT
  - TEAEs leading to dose modification of Radiotherapy by SOC and PT
- TEAE leading to cancellation of surgery by SOC, PT and Worst Grade (≥ Grade 3 and All Grades).
- TEAE leading to surgery delay by SOC, PT and Worst Grade (≥ Grade 3 and All Grades).

Patient data listings of all AEs, treatment-emergent or otherwise will be provided.

6.6.2.2 Immune-Mediated Adverse Event

Immune-mediated adverse events are of special interest and summarized by category within a pre-defined list. The identification of immune-mediated adverse events is described in immune-mediated adverse event charter. All imAE up to 90 days from the last dose of any treatment, regardless of whether the patient starts a new anticancer therapy, will be summarized. If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE.

An overall summary table and separate summaries of the following incidence of immune-mediated adverse events will be provided:

- imAEs by category and PT
- imAEs by category and maximum severity
- imAEs by PT
- imAEs by category, PT and Worst Grade (Grade ≥3 and All Grades)
- Serious imAEs by category and PT
- imAEs leading to discontinuation of tislelizumab by category and PT
- imAEs leading to dose modification of tislelizumab by category and PT
- imAEs leading to death by category and PT
- Summary of imAEs Treated with Immunosuppressants by Category
- Glossary of imAEs
- Summary of imAEs Treated with Systemic Corticosteroids by Category
- imAEs Outcome, Time to Onset, and Duration by Category

Patient data listings of imAEs will be provided.

6.6.2.3 Infusion-related Adverse Event

For infusion related reaction (IRR)s, a summary of incidence by SOC, PT and Worst Grade (≥ Grade 3 and All Grades) will be provided. Summaries of IRRs of grade ≥ 3 or higher will also be provided by SOC and PT.

6.6.2.4 Death

All deaths and causes of death will be summarized by cohorts, including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

Patient data listings of deaths will be provided.

6.6.2.5 Surgery Relevant Safety

Surgery relevant adverse events (SRAE) is defined as adverse events collected in the CRF, from the date of surgery up to 30 days after surgery, which will be summarized for surgery related safety analysis on efficacy evaluable analysis set. A SRAE overview table, including the number and percentage of patients with SRAE, Serious SRAE, SRAE with grade 3 or above, SRAEs that led to death, treatment-related SRAEs, treatment-related version of any of the above categories, surgery-related SRAE s, surgery-related version of any of the above categories will be provided. Incidence of these SRAEs by SOC, PT and Worst Grade (≥ Grade 3 and All Grades), Serious SRAE by SOC and PT, SRAE leading to death by SOC and PT will be summarized.

6.6.3. Laboratory Values

Laboratory safety tests will be evaluated for selected parameters described in Table 6.

Laboratories parameters (e.g., hematology, chemistry, and coagulation) are graded in NCI-CTCAE Version 5.0 will be summarized by shifts from baseline NCI-CTCAE grades to maximum post-baseline grades. In the summary of laboratory abnormalities worsened by ≥ 2 Grades (e.g., hematology and chemistry), parameters with NCI-CTCAE grading in both high and low directions will be summarized separately. The summary tables will report laboratory assessments up to 30 days of the last dose date.

Laboratory parameters for potential Hy's Law for liver injury and abnormal thyroid function will also be summarized.

Table 6: Clinical Laboratory Assessment

Serum Chemistry	Hematology	Thyroid Function
Alanine aminotransferase	Hemoglobin	Free triiodothyronine
Aspartate aminotransferase	WBC count	Free thyroxine
Total bilirubin	Platelet counts	Thyroid stimulating hormone
Direct bilirubin	Neutrophil count	
Potassium		
Sodium		
Creatinine		
Glucose		
Creatine Kinase (CK) [a]		
CK-MB [a]		

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme; WBC, white blood cell.

a. All patients will have creatine kinase and CK-MB testing at screening, and to be repeated at all scheduled visits if CK-MB fractionation is not available, assess troponin I and/or troponin T instead.

6.6.4. Vital Signs

The number and percentage of patients satisfying the following conditions of systolic blood pressure at any time post-baseline will be summarized:

- 140 mmHg to 159 mmHg, 160 mmHg to 179 mmHg, or ≥ 180 mmHg
- > 0, > 20, > 40, or > 60 mmHg maximum increase from baseline

The number and percentage of patients satisfying the following conditions of diastolic blood pressure at any time post-baseline will be summarized:

- 90 mmHg to 99 mmHg, 100 mmHg to 109 mmHg, or ≥ 110 mmHg
- > 0, > 10, > 20, or > 30 mmHg maximum increase from baseline

6.6.5. Electrocardiograms (ECG)

The number and percentage of patients satisfying the following QTcF conditions at any time post-baseline will be summarized:

- > 450, > 480, or > 500 msec
- > 30 or > 60 msec maximum increase from baseline

6.6.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

A shift table from baseline to worst post-baseline in ECOG Performance Status will be summarized.

6.7. Pharmacokinetic Analysis

No pharmacokinetic analysis is planned.

6.8. Immunogenicity Analysis

No immunogenicity analysis is planned.

7. INTERIM ANALYSIS

No interim analysis is planned.

8. CHANGES IN THE PLANNED ANALYSIS

Table 7: Statistical Analysis Plan Changes

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
1.0	This version	Protocol Amendment 1.0	To clarify the definition of the efficacy evaluable analysis set.	Delete “This will be the primary analysis set for the efficacy analyses.” from the definition of efficacy evaluable analysis set in the protocol.
1.0	This version	Protocol Amendment 1.0	To clarify the definition of the safety analysis set.	Delete “Patients will be analyzed according to the actual treatment regimen received.” from the definition of safety analysis set in the protocol.

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APPENDIX 1. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

In general, missing or partial dates will not be imputed at the data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

1.1 Prior/Concomitant Medications/Procedures

When the start date or end date of a medication/therapy/procedure is partially missing, the date will be imputed to determine whether the medication/therapy/procedure is prior or concomitant. The following rules will be applied to impute partial dates for medications.

If start date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed start date > death date, then set to death date

If end date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

1.2 Adverse Events

The imputation rule for the safety analysis will be used to address the issues with partial dates. When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment-emergent by default. The following rules will be applied to impute partial dates for adverse events:

If year of the start date is missing or start date is completely missing, do not impute. Impute AE end date first if both AE start date and end date are partially missing.

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

If year of the end date is missing or end date is completely missing, do not impute.

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date

- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month
- If the imputed AE start date is after AE end date (maybe imputed), then update AE start date with AE end date as final imputed AE start date
- If the imputed start date > death date, then set to death date

1.3 Disease History and Prior Therapy (Drug, Surgery/Procedure, Radiotherapy)

For prior therapy, impute end date first.

If end date of a prior therapy is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > first dose date, then set to first dose date -1

If start date of a prior therapy is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed start date > end date, then set to end date

The following rules will be applied to impute partial dates such as initial diagnosis date, initial BCLC staging date, relapse date, therapy date (start/end date), or surgery date etc.

If date of a disease history is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed date > first dose date, then set to first dose date – 1

If diagnosis date of metastatic disease/locally advanced is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed date > first dose date, then set to first dose date – 1
- If the imputed date < (imputed) date of initial diagnosis date, then set to initial diagnosis date.

If the date of response to prior therapy is partially missing, impute as follows:

- If both month and day are missing, then set to January 01

- If only day is missing, then set to the first of the month
- If the imputed date > first dose date, then set to first dose date – 1

If the imputed date < the start date of prior therapy, then set to the start date of prior therapy +1.

1.4 Subsequent Anti-Cancer Therapy

If start date of subsequent anti-cancer therapy is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed start date > min (death date, data cutoff date, study discontinuation date, start date of the next subsequent therapy), then set it as min (death date, data cutoff date, study discontinuation date, start date of the next subsequent therapy)

If stop date of is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed stop date > min (death date, data cutoff date, study discontinuation date, start date of the next subsequent therapy), then set it as min (death date, data cutoff date, study discontinuation date, start date of the next subsequent therapy)
- The (imputed) stop date must be after or equal to the (imputed) start date

If year of the start date/stop date is missing, do not impute.

APPENDIX 2. RULES FOR IDENTIFYING MISSING TUMOR ASSESSMENTS

Identifying two missing tumor assessments

1) Input scheduled TA visit list
    a. Pre-surgery (After neoadjuvant treatment), (3mo-6mo-9mo-12mo-15mo-18mo-21mo-24mo-30mo-36-mo) after surgery or last treatment for this study with TA as every 3 months for the first 2 years (24 months), then every 6 months during Year 3.
2) Identify last evaluable TA before PD or death (--LPTADT) and map it to the closest scheduled visit (--LPTADT_WK).
    a. In the event of unscheduled TA, choose the closest scheduled visit number as –LPTADT_WK. It can be achieved programmatically by following the classification rule (e.g., defining thresholds) depicted in Table 8 below. (The team can consider mapping all tumor visits if the scheduled visits are uncleaned or questionable)
    b. Otherwise, assign the scheduled visit number (assuming it is coded correctly) to --LPTADT_WK
3) Find the 2nd TA visit after LPTADT_WK according to the list in step 1 (-LPTADT_WK_2)
    a. If LPTADT_WK_2+2wk (assuming 2-week TA window) < earliest of PD/death date, then censor PFS at the –LPTADT
    b. Otherwise, EFS event at the earliest of PD/death date

Table 8 shows how to assign unscheduled TA to a schedule visit. The threshold column is defined as the mid-point between current and next visit (except for baseline); it is the upper limit for LPTADT to be mapped to the prior scheduled assessment (step 2a above). For example, if LPTADT is Month 13 for an unscheduled visit, it will be mapped to Month 12 TA since it is within the threshold for Month 12. Assuming it is SD and the subsequent TA of the patient is local recurrence after Month 18 + 2 weeks, EFS will be censored at LPTADT (Month 13); had the local recurrence occurred prior to Month 18 + 2 weeks, it would be counted as an EFS event.

Table 8: Example of Scheduled Tumor Assessments with Time Window

Months	Scheduled time lower limit	Scheduled month	Scheduled time upper limit	Threshold
Surgery Date [a]		Surgery Date [a]		
Every 3 months for the first 2 years	Month 3 - 2 weeks	Month 3	Month 3 + 2 weeks	Month 4.5
	Month 6 - 2 weeks	Month 6	Month 6 + 2 weeks	Month 7.5
	Month 9 - 2 weeks	Month 9	Month 9 + 2 weeks	Month 10.5
	Month 12 - 2 weeks	Month 12	Month 12 + 2 weeks	Month 13.5
	Month 15 - 2 weeks	Month 15	Month 15 + 2 weeks	Month 16.5
	Month 18 - 2 weeks	Month 18	Month 18 + 2 weeks	Month 19.5
	Month 21 - 2 weeks	Month 21	Month 21 + 2 weeks	Month 22.5
	Month 24 - 2 weeks	Month 24	Month 24 + 2 weeks	Month 27
Every 6 months during year 3	Month 30 - 4 weeks	Month 30	Month 30 + 4 weeks	Month 33
	Month 36 - 4 weeks	Month 36	Month 36 + 4 weeks	

[a] For patients who don't undergo surgery, use treatment discontinuation date.