16.1.9 DOCUMENTATION OF STATISTICAL METHODS AND INTERIM ANALYSIS PLAN

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-214
Study Protocol Title:	A Single-Arm, Multicenter, Open-Label, Phase 2 Study to Investigate the Efficacy and Safety of Tislelizumab (BGB A317) as Neo-Adjuvant Treatment in Patients With Early-Stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer
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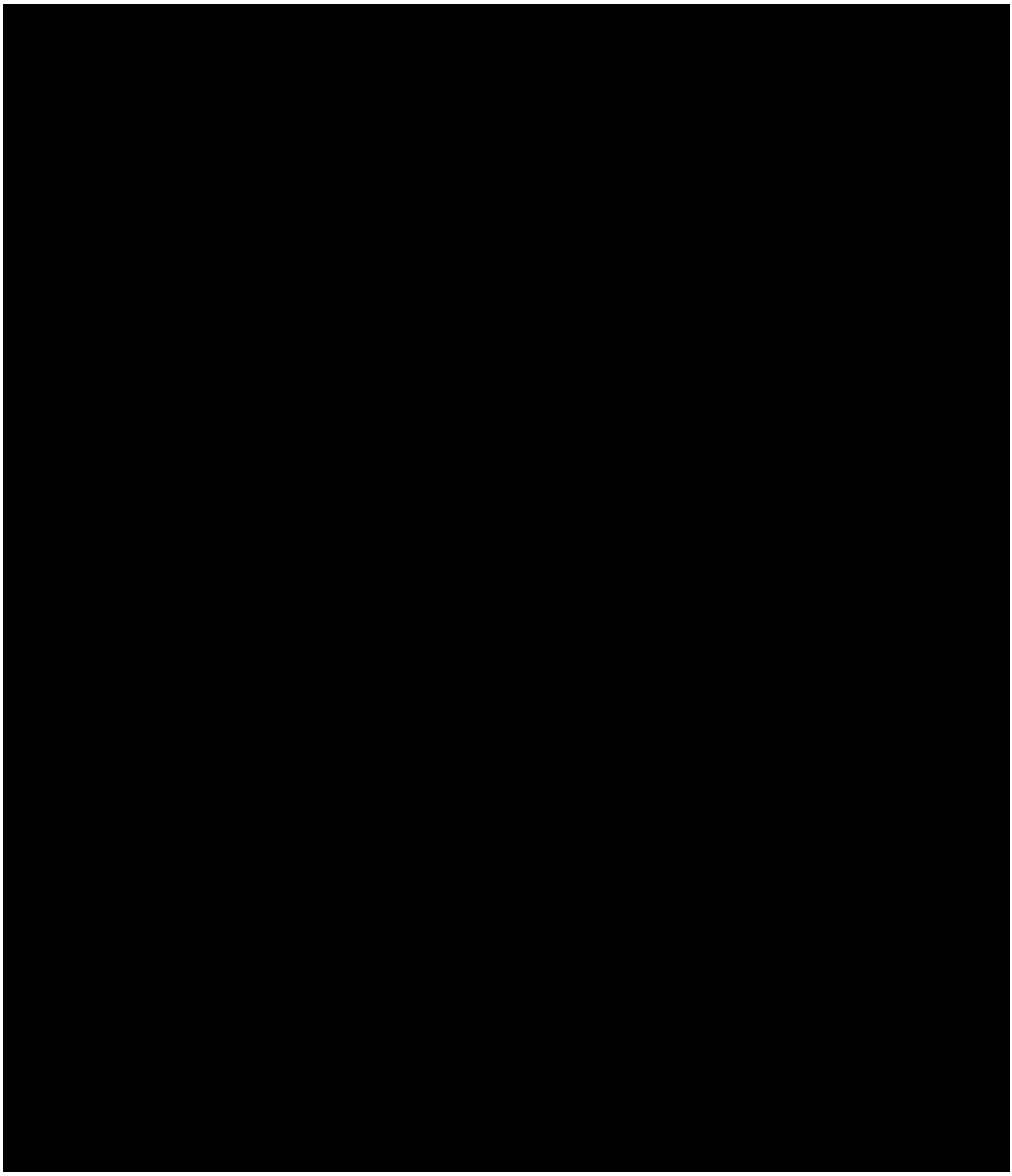

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADI	actual dose intensity
AE	adverse event
ATC	Anatomical Therapeutic Chemical
CSCO	Chinese Society of Clinical Oncology
dMMR	mismatch repair deficient
EAS	Efficacy Analysis Set
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
IRR	infusion related reaction
IV	Intravenously
imAE	immune-mediated adverse event
IRR	infusion related reaction
MedDRA	Medical Dictionary for Regulatory Activities
MPR	major pathological response
MSI-H	microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NCI-CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
ORR	objective response rate
pCR	pathological complete response
PT	Preferred Term
Q3W	once every 3 weeks
R0	complete resection
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RDI	relative dose intensity
SAE	serious adverse event
SAS	safety analysis set
SAP	statistical analysis plan
SFD	study follow-up duration
SOC	System Organ Class
SRAE	surgery relevant adverse event

Abbreviation	Definition
TEAE	treatment-emergent adverse event
WHO DD	World Health Organization Drug Dictionary

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-A317-214: A Single-Arm, Multicenter, Open-Label, Phase 2 Study to Investigate the Efficacy and Safety of Tislelizumab (BGB A317) as Neo-Adjuvant Treatment in Patients With Early-Stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer. The focus of this SAP is for the planned primary analysis and final analysis specified in the study protocol. The analysis details for the biomarker analyses are not described within this SAP. These analyses may be planned and reported separately. This SAP is based on BGB-A317-214 Protocol Amendment 2.0 dated on 25 July 2022.

2. STUDY OVERVIEW

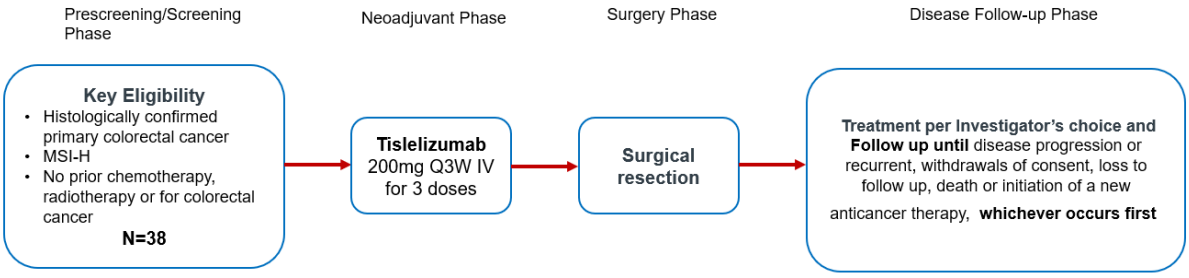
2.1. Study Design

This is an open-label, multicenter Phase 2 study designed to investigate the preliminary efficacy and safety of tislelizumab monotherapy as neo-adjuvant treatment in approximately 38 patients with early-stage (Stage II-III) MSI-H or dMMR colorectal cancer.

The study consists of a prescreening and/or screening phase, a treatment phase that includes a neo-adjuvant phase, surgery and disease follow-up phase.

The study schema is presented in Figure 1.

Figure 1. Study Schema



Abbreviations: MSI-H, microsatellite instability-high; IV, intravenously; N, number of patients; Q3W, once every 3 weeks.

Neo-adjuvant Phase:

During the neo-adjuvant phase, patients who are found to have disease progression at scheduled tumor assessments (before Cycle 3 and surgery) or at any time during neo-adjuvant treatment and are still deemed resectable and non-metastatic will proceed to receive surgery if amenable and will remain eligible for all on-study evaluations based on investigator's judgement.

Patients who discontinue neo-adjuvant treatment early because of urgent surgery (eg., because of intestinal obstruction, intestinal perforation, or intestinal bleeding), disease progression or intolerable AEs and do not proceed to a complete resection will proceed to receive other treatment

as determined by the investigator. Further in-clinic study procedures of these patients should be discussed with the medical monitor.

Surgery:

Upon completion of neo-adjuvant therapy, patients will undergo surgical resection of their tumor. Surgical specimens will be assessed for pathological response. In addition, exploratory biomarker analysis of surgical specimens (primary tumor tissue and dissected lymph nodes) will be performed.

Before surgery, the investigator will reassess the patient to reconfirm disease resectability. The presurgical visit and associated assessments should occur within 14 days of surgery and in accordance with local institutional practice.

Disease Follow-up Phase:

Patients will continue adjuvant treatment and perform follow-up which will be determined by the investigator according to the stage of disease and benefit-risk assessment in accordance with the relevant clinical practice (eg. Colon and Rectal Cancer NCCN (National Comprehensive Cancer Network) guidelines, Chinese Society of Clinical Oncology (CSCO)guideline).

2.2. Study Assessments

Patients with the diagnosis of Stage II-III colorectal cancer and with unknown MSI and MMR status are required to provide blood and tumor tissues for central laboratory confirmation of MSI status during the prescreening period (defined as within 56 days prior to the first dose of the study drug). Patients with known MSI-H status by local laboratory must undergo central laboratory assessment of MSI-H during or after the screening period if tumor samples are obtainable.

Tumor imaging will be performed ≤ 28 days before first dose. During the study, tumor assessment will be performed after neo-adjuvant treatment and before surgery (9 weeks ± 7 days after first dose). After surgery, the post-surgery treatment and the follow up will determined by investigator. During this period tumor assessment will be performed every 12 weeks (± 14 days) for the first 3 years, and then every 24 weeks (± 28 days) for a total 5 years, and then once (± 28 days) each year thereafter based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Patients will continue with the scheduled tumor assessments until radiographic disease progression or recurrent per RECIST v1.1, withdrawal of consent, loss to follow-up, study termination by the sponsor, start of a new anticancer therapy (excluding adjuvant therapy), or death, whichever occurs first.

Patients will be evaluated for adverse events (AEs) and immune-mediated adverse events (imAEs) (all grades according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0)). Serious adverse events (SAEs) and any AEs that lead to treatment discontinuation will be followed and documented until the event is resolved, the investigators assess the event as stable, or the patient is lost to follow-up, whichever occurs first.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate major pathological response (MPR) rate in patients receiving tislelizumab as neo-adjuvant treatment.

3.2. Secondary Objective

- To evaluate pathological complete response (pCR) rate in patients receiving tislelizumab as neo-adjuvant treatment.
- To evaluate event free survival (EFS) in patients receiving tislelizumab as neo-adjuvant treatment
- To evaluate the safety and tolerability of neo-adjuvant treatment with tislelizumab in patients with early-stage (Stage II-III) MSI-H or dMMR colorectal cancer

3.3. Exploratory Objective

- To evaluate R0 resection rate in patients receiving tislelizumab as neo-adjuvant treatment
- To evaluate perioperative events (including but not limited to treatment related surgery delay, postoperative complication) in patients receiving tislelizumab as neo adjuvant treatment.

4. STUDY ENDPOINTS

4.1. Primary Endpoint(s)

- MPR rate is defined as the proportion of patients in the Efficacy Analysis Set (EAS) with $\leqslant$ 10% residual viable tumor in the resected primary tumor after completion of neo adjuvant therapy.

4.2. Secondary Endpoints

- The pCR rate is defined as the proportion of patients in the EAS with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neo-adjuvant therapy.
- EFS is defined as the time from first dose until any of the following events, whichever occurs first: progression of disease that precludes definitive surgery, local or distant recurrence, or death due to any cause in the Safety Analysis Set. The 2-year/3-year EFS rate is defined as the proportion of patients free from EFS events at 2 years and 3 years as estimated using the Kaplan-Meier method.
- Incidence and severity of TEAEs, including serious adverse events and imAEs, with severity determined according to NCI-CTCAE v5.0 in the safety analysis set (SAS).

4.3. Exploratory Endpoints

- Complete resection (R0) rate – defined as the proportion of patients with R0 resection.
- To evaluate perioperative events (including but not limited to treatment-related surgery delay, postoperative complication) in patients receiving tislelizumab as neo adjuvant treatment.

5. SAMPLE SIZE CONSIDERATIONS

Sample size is based on clinical considerations. Thirty evaluable patients (who received neo-adjuvant treatment followed by surgery) will be enrolled and will provide a reasonably robust estimate and precision (95% CI) of the primary endpoint MPR rate. Table 1 summarizes the 95% CI of MPR rate under different assumptions of MPR estimate. With a 20% drop out rate, a total of 38 patients will be enrolled in this study.

Table 1 95% CI of MPR rate under different assumptions of MPR estimate

MPR estimate	95% CI
MPR=30%	(14.7%, 49.4%)
MPR=40%	(22.7%, 59.4%)
MPR=50%	(31.3%, 68.7%)
MPR=60%	(40.6%, 77.3%)

6. STATISTICAL METHODS

6.1. Analysis Sets

The Efficacy Analysis Set (EAS) includes all enrolled patients who receive neoadjuvant treatment followed by surgery. This will be the primary analysis set for the efficacy analyses.

The Safety Analysis Set (SAS) includes all enrolled patients who receive ≥ 1 dose of study drug; it will be the analysis set for the safety analyses, baseline characteristics and efficacy analysis of EFS.

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 drug

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks) for 3 cycles before surgery.

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.

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

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

- Number (%) of patients with surgery not performed and reason
- Number (%) of patients with surgery performed
- Number (%) of patients with surgery delayed and reason
- Time from first dose of tislelizumab to surgery (weeks)
- Approach of surgery
- Type of surgery
- Number of lymph node dissected

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
- Weight (kg)
- BMI (kg/m^2)
- Eastern Cooperative Oncology Group (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 Colorectal Cancer includes the following characteristics.

- Disease stage at study entry (stage II and stage III)
- TNM staging at study entry (T1/T2/T3/T4/N0/N1/N2/M0/M1)

- Time from initial diagnosis to time of first dose date
- Site of primary location
- Histopathologic type at study entry
- Histologic grade at study entry
- Presence of a clinical history of Lynch syndrome (Yes, No or unknown)
- Known KRAS, NRAS, BRAF, HER-2, BRCA1/2, NTRK Status
- Central MSI status
- Local MSI status
- Local MMR status

6.4.5. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 or higher. 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. Concomitant Procedure/Surgery

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

The number (percentage) of patients reporting concomitant procedure/surgery, and primary reason for procedure/surgery will be summarized in the safety analysis set.

6.4.7. Prior and Concomitant Medications

Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that 1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) started on or after the date of the first dose of study drug 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 or higher. 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.

6.4.8. Systemically Administered Corticosteroids/Immunosuppressants During the Study

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.

6.5. Efficacy Analysis

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

6.5.1. Primary Efficacy Endpoints

The primary efficacy endpoint is MPR rate defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor after completion of neo-adjuvant therapy. The MPR rate will be summarized descriptively, and Clopper Pearson 95% CI will be calculated to evaluate the precision of MPR estimate. The percentage of residual viable tumor in the resected primary tumor will be summarized by category (0, ≤ 10, ≤ 25, ≤ 50, >50).

The primary analysis of MPR rate will be performed in Efficacy Analysis Set. Two sensitivity analyses of MPR rate will be performed. One is based on Safety Analysis Set, and those patients who are not performing surgery after completion of neo-adjuvant therapy will be treated as non-MPR. The other sensitivity analysis will be performed on patients with central MSI-H status. The analysis of MPR rate will occur after all the patients in the Efficacy Analysis Set have been assessed for pathological response.

6.5.2. Secondary Efficacy Endpoints

pCR rate

The 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 neo-adjuvant therapy. The pCR rate will be summarized descriptively, and a Clopper-Pearson 95% CI will also be calculated.

The primary analysis of pCR rate will be performed in Efficacy Analysis Set. Sensitivity analyses of pCR rate will be performed in the Safety Analysis Set as well as on patients with central MSI-H status. The analysis of pCR rate will occur at the same time of the analysis of MPR rate.

EFS

EFS is defined as the time from the time of first dose until any of the following events, whichever occurs first: progression of disease that precludes definitive surgery (surgery with R0 outcome), local or distant recurrence, or death due to any cause. The 2-year/3-year EFS rate is defined as the proportion of patients free from EFS events at 2 years and 3 years after the first dose.

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.

Details of EFS derivation rules are listed as below:

- Subjects who do not undergo surgery for reason with progressive disease (as assessed radiologically per RECIST 1.1 or clinical progression) and subjects who had progressive disease during neoadjuvant treatment phase, but went to surgery and ended up with positive margins (R1/R2) at their last surgery will be considered to have an EFS event and classified as progression of disease that precludes definitive surgery.

- Subjects who did not undergo surgery for reason other than progressive disease and have progressive disease per RECIST 1.1 after pre-surgical tumor assessment will be considered to have an EFS event.
- Subjects who had local or distant recurrence after surgery will be considered to have an EFS event.
- Subjects who died without progression of disease precluding definitive surgery or local/distant recurrence will be considered to have an EFS event.

The following censoring rules will be applied for the primary definition of EFS:

- Subjects who did not report progression/recurrence of disease or death will be censored on the date of their last adequate radiologic assessment. Secondary primary malignancy tumor discovered other than colorectal cancer during the study will not be considered as progression/recurrence of disease.
- Subjects who had progressive disease during neoadjuvant treatment phase, but went to surgery and had clear margins (R0), will not be considered to have an EFS event.
- Subjects who did not have any on study tumor assessments and did not die will be censored on the date of first dose.
- Subjects who received subsequent anti-cancer therapy (excluding adjuvant therapy) will be censored at the date of the last adequate tumor assessment on or prior to the date of initiation of the subsequent anti-cancer therapy.
- Subjects missed more than 1 tumor assessment before progression of disease that precludes definitive surgery, local or distant recurrence or death, its EFS will be censored at the date of last adequate disease assessment before the missing tumor assessments.

The primary analysis of EFS is based on Safety Analysis Set. Sensitivity analyses of EFS will be performed in Efficacy Analysis Set as well as on patients with central MSI-H status. The censoring rules for the analysis of EFS are presented in Table 2. Kaplan Meier methodology will be used to estimate median, Q1, and Q3 of EFS, and the event-free rates at 24 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.

The primary analysis of EFS will be performed after a minimal of 12 months after the first dose of the last patient.

Table 2 Censoring Rules for Event-free Survival Per RECIST Version 1.1

	Derivation rules	Outcome
Progression of disease precluding definitive	Date of radiographic progression or date of last presurgical tumor	Event

surgery (surgery with R0 outcome)	assessment +1 if no radiographic progression	
Local/distant recurrence	Date of recurrence	Event
Death without progression of disease precluding definitive surgery or local/distant recurrence	Date of death	Event
No surgery with reason other than progressive disease, and progression after pre-surgical visit	Date of radiographic progression after pre-surgical visit	Event
New anticancer therapy (excluding adjuvant therapy) started	Last adequate radiological assessment before the new anticancer therapy	Censored
No progression of disease that precludes definitive surgery, local or distant recurrence, 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
Progression of disease 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
No baseline or any post-baseline tumor assessments without death within the first 2 consecutive tumor assessments after first dose	First dose date	Censored

6.5.3. Exploratory Efficacy Endpoints

R0 Resection Rate

R0 resection rate defined as the proportion of patients with R0 resection, will be summarized in the Efficacy Evaluable Analysis Set. Tumor stage ypTNM after surgery will also be summarized.

Objective response rate (ORR) by Investigators

The ORR is defined as the percentage of patients who have a complete response or partial response before surgery (or at pre-surgical tumor assessment if a subject has no 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. Participants who received new anti-cancer therapy before the pre-surgery tumor assessment will be counted as non-responders. The ORR will be summarized with descriptive statistics and the corresponding two-sided 95% CIs calculated from Clopper Pearson exact method will be also presented. The analysis of ORR is based on Safety Analysis Set

Perioperative events

Evaluation of perioperative events (including but not limited to treatment-related surgery delay, postoperative complication) in patients receiving tislelizumab as neo adjuvant treatment are described in Section 6.6.2.5

6.5.4. Subgroup Analysis

To determine if the treatment effect is consistent across various subgroups, MPR and pCR rate and their 95% CIs will be estimated and plotted within each category of the following subgroups:

- Location of primary tumour (left side colon vs right side colon vs rectum)
- Clinical T stage (T3/T4)
- Clinical N stage (N0/N1/N2)
- TNM stage (stage II vs stage III)
- Central MSI-H status (MSI-H, not MSI-H, and Unknown)

6.5.5. Post-Treatment Subsequent Anti-Cancer Therapy

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

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

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

The analysis above for post-treatment subsequent anticancer adjuvant therapy will be repeated for post-treatment subsequent anti-cancer non-adjuvant 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 except adjuvant 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 dose of study drug.

Tumor response per RECIST or event driven endpoints have not been commonly used for the efficacy evaluation of TCM. EFS 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 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 electrocardiogram (ECG) findings.

6.6.1. Extent of Exposure

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

- Duration of exposure (months): 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.
- 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 (mg): is defined as the cumulative dose of the study drug during the treatment period of the study.
- Actual dose intensity (ADI) (mg/cycle) 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 number (percentage) of patients requiring dose modification, including dose interruptions and dose delay 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 dose of study drug 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 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)
    - Treatment-related TEAEs by PT
- Serious TEAEs
    - Serious TEAEs by SOC and PT
    - Serious TEAEs by PT
    - Treatment-related serious TEAEs by SOC and PT
    - Treatment-related serious TEAEs by PT
- TEAEs of Grade 3 or Higher
    - TEAEs of Grade 3 or Higher by SOC and PT
    - TEAEs of Grade 3 or Higher by PT

  - Treatment-related TEAEs of Grade 3 or Higher by SOC and PT
  - Treatment-related TEAEs of Grade 3 or Higher by PT
- TEAEs leading to death
  - TEAEs leading to death by SOC and PT
  - TEAEs leading to death by PT
  - Treatment-related TEAEs leading to death by SOC and PT
  - Treatment-related TEAEs leading to death by PT
- TEAEs leading to treatment discontinuation by SOC and PT
  - Treatment-related TEAEs leading to treatment discontinuation by SOC and PT
- TEAEs leading to treatment modification by SOC and PT
  - Treatment-related TEAEs leading to treatment modification 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 tislelizumab, 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 and Worst Grade (Grade ≥3 and All Grades)
- imAEs by category and maximum severity
- 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
- Summary of imAEs Treated with Systemic Corticosteroids by Category
- Summary of imAEs Treated with Hormone therapy
- 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, including those occurred during the study treatment period and those reported during the disease 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 will be summarized for surgery related safety analysis on efficacy evaluable analysis set. An 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 SRAEs, 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 3.

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 (eg, 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 3 Clinical Laboratory Assessment

Serum Chemistry	Hematology	Coagulation

Alanine aminotransferase Aspartate aminotransferase Total bilirubin Direct bilirubin Blood urea nitrogen or urea Creatinine Glucose Alkaline phosphatase Lactate dehydrogenase Potassium Sodium Corrected calcium Total protein Albumin Creatine kinase /CK-MB	CBC including RBC Hemoglobin Platelet counts WBC count with differential	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio
Thyroid Function		
TSH Free T3 Free T4		

Abbreviations: CBC, complete blood count; CK-MB, creatine kinase cardiac isoenzyme; pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WBC, white blood cells.

6.6.4. 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

6.6.5. 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 4 summarizes the major changes in the planned analyses from the statistical section of the study protocol, including the timing, rational and descriptions of the changes. The changes are all made before database lock and not based on any comparative data.

Table 4 Statistical Analysis Plan Changes

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
1.0	This version	Protocol V2.0	To be consistent with FDA guidance	Change EFS definition from "time from first dose until any of the following events, whichever occurs first: radiographic disease progression according to RECIST v1.1, local or distant recurrence, or death due to any cause" in the protocol to "time from first dose until any of the following events, whichever occurs first: progression of disease that precludes definitive surgery, local or distant recurrence, or death due to any cause." in the SAP
1.0	This version	Protocol V2.0	For exploratory purpose	Add ORR exploratory analysis in the SAP

9. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

Greenwood M. The Natural Duration of Cancer. Reports on Public health and medical subjects. 1926;33:1-26.

ICH. Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials: E9(R1). 2019.

Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Washington, DC, USA, November 27, 2017.

CTCAE V5.0, November 27, 2017. *Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.* Washington, DC, USA: Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

Eisenhauer EA, T. P. B. J. S. L. S. D. F. R. e. a., 2009. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*, pp. 45:228-47.

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-surgical - 12wk - 24wk - 36wk - 48wk - 60wk - 72wk - 84wk - 96wk - 108wk - 120wk - 132wk - 144wk - 156wk - 180wk - 204wk - 228wk - 252wk-…) for this study with TA as every 12 weeks for the first 3 years (156 wks) after surgery, then every 24 weeks for a total of 5 years (260 wks), and then once each year thereafter.
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 5 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 weeks TA window) < earliest of PD/recurrence/death date, then censor EFS at the –LPTADT
    b. Otherwise, EFS event at the earliest of PD/recurrence/death date

Table 5 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 Week 44 for an unscheduled visit, it will be mapped to Week 48 TA since it is within the Threshold for Week 48. Assuming it is SD and the subsequent TA of the patient is PD after Week 74, PFS will be censored at LPTADT (Week 44); had the PD occurred prior to Week 74, it would be counted as an EFS event.

Table 5 Example of scheduled tumor assessments with time window

Months	Scheduled time lower limit	Scheduled month	Scheduled time upper limit	Threshold
Baseline		Baseline		First dose date
Pre-surgery		Pre-surgery		Surgery date (Week 0)
Every 12 weeks for the first 3 years after surgery	Week 12 - 2 weeks	Week 12	Week 12 + 2 weeks	Week 18
	Week 24 - 2 weeks	Week 24	Week 24 + 2 weeks	Week 30
	Week 36 - 2 weeks	Week 36	Week 36 + 2 weeks	Week 42
	Week 48 - 2 weeks	Week 48	Week 48 + 2 weeks	Week 54
	Week 60 - 2 weeks	Week 60	Week 60 + 2 weeks	Week 66
	Week 72 - 2 weeks	Week 72	Week 72 + 2 weeks	Week 78
	Week 84 - 2 weeks	Week 84	Week 84 + 2 weeks	Week 90
	Week 96 - 2 weeks	Week 96	Week 96 + 2 weeks	Week 102
	Week 108 - 2 weeks	Week 108	Week 108 + 2 weeks	Week 114
	Week 120 - 2 weeks	Week 120	Week 120+ 2 weeks	Week 126

	Week 132 - 2 weeks	Week 132	Week 132 + 2 weeks	Week 138
	Week 144 - 2 weeks	Week 144	Week 144 + 2 weeks	Week 150
	Week 156 - 2 weeks	Week 156	Week 156 + 2 weeks	Week 168
Every 24 weeks for a total of 5 years after surgery	Week 180 - 4 weeks	Week 180	Week 180 + 4 weeks	Week 192
	Week 204 - 4 weeks	Week 204	Week 204 + 4 weeks	Week 216
	Week 228 - 4 weeks	Week 228	Week 228 + 4 weeks	Week 240
	Week 252 - 4 weeks	Week 252	Week 252 + 4 weeks	Week 264
once each year thereafter	Week 304 - 4 weeks	Week 304	Week 304 + 4 weeks	Week 278
	…	…	…	…