STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-dinutuximab beta-101
Study Protocol Title:	An Open-Label, Multi-Center, Single-Arm, Phase 1 Study Evaluating the Safety and Pharmacokinetics of Dinutuximab Beta as Maintenance Therapy in Chinese Patients with High-Risk Neuroblastoma
Date:	6 July 2023
Version:	1.0

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
BLQ	below the limit of quantification
CV	coefficient of variation
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CTCAE	common terminology criteria for adverse events
ECG	electrocardiogram
EFS	event free survival
EOT	end of treatment
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PK	pharmacokinetic
QTcF	corrected QT interval by Fredericia
RA	retinoic acid
SAE	serious adverse event
SD	standard deviation
TEAE	treatment emergent adverse event
t_{max}	Time to maximum serum concentration
$t_{1/2}$	half-life

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-dinutuximab beta-101. The focus of this SAP is for the final analysis specified in the study protocol.

2. STUDY OVERVIEW

This is an open-label, multi-center, single-arm, Phase 1 study evaluating the safety and pharmacokinetics of dinutuximab beta as maintenance therapy in Chinese patients with high-risk neuroblastoma.

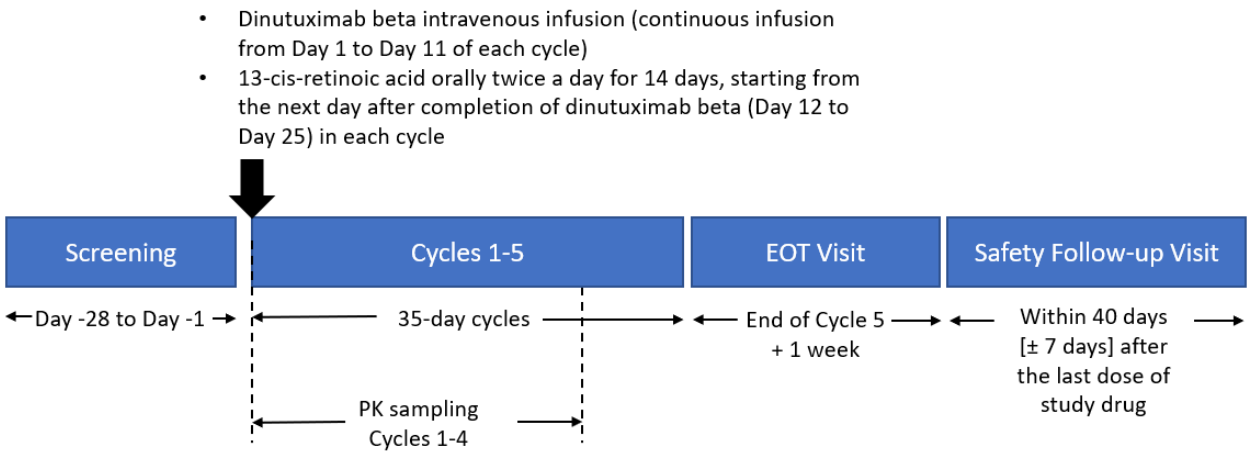
Potential patients will be screened for eligibility before study enrollment (screening period ≤ 28 days). The study will recruit approximately 8 patients who will be hospitalized (with a full resuscitation equipment) on Day 1 of each cycle and will receive continuous infusion of dinutuximab beta administered at a dose of 10 mg/m^2/day for 10 consecutive days in 35-day cycles (total dose 100 mg/m^2/cycle). Patients must be administered in a unit with a full resuscitation equipment. Patients will be discharged from the hospital at the investigator's discretion. Patients will continue to receive 13-cis-RA 160 mg/m²/day, divided approximately into 2 equal doses and given orally twice a day for 14 days after completion of dinutuximab beta infusion.

Patients may receive up to five 35-day cycles in the absence of relapse, disease progression or unacceptable toxicity.

Refer to Figure 1 for an overview of the study design and Appendix 1 for details on study assessments and procedures that will be carried out during the study.

The maximum duration of participation (Screening Visit to Safety Follow-up Visit) for individual patients will be approximately 35 weeks. Each patient will participate in the screening period (≤ 28 days), study intervention infusion period (≤ 25 weeks), and a post-infusion period (≤ 6 weeks). Additional clinical follow-up might be needed depending on findings during the study.

Figure 1: Study Schema



Abbreviations: EOT, end of treatment; PK, pharmacokinetic(s).

All patients will be closely monitored for AEs throughout the study and for 40 days after the last dose of study drug.

PK analysis will be performed for dinutuximab beta.

Tumor assessments or monitoring will be performed by the investigators at Screening Visit, end of treatment Cycle 3, and end of treatment Visit per their clinical practice. International Neuroblastoma Response Criteria (INRC) (Brodeur et al 1993) is recommended as a reference for response evaluation in patients evaluable for tumor assessment. Patients who, at the time of progression, have an ongoing AE that leads to treatment discontinuation and who have completed the scheduled Safety Follow-up Visit will be followed up until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a new anticancer therapy, end of study, whichever comes first.

Patients who have discontinued study drug(s) will return to the site for an End-of-Treatment (EOT) Visit. After the EOT Visit, patients will have scheduled follow-up visits for safety.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To assess the safety and tolerability of ≤5 treatment cycles of dinutuximab beta in combination with 13-cis-retinoic acid (RA) as maintenance therapy in Chinese patients with high-risk neuroblastoma.
- To characterize the pharmacokinetics (PK) of dinutuximab beta in Chinese patients.

3.2. Secondary Objective

There is no secondary endpoint.

3.3. Exploratory Objective

- To explore the preliminary anti-tumor activity and event free survival rate (EFS), of ≤5 treatment cycles of dinutuximab beta in combination with 13-cis-RA as maintenance therapy in Chinese patients with high risk neuroblastoma, if applicable

4. STUDY ENDPOINTS

4.1. Primary Endpoint(s)

- Adverse events (AEs) characterized by type, frequency, severity (as graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0), timing, seriousness, and relationship to study drug(s); and other safety assessments.
- PK parameters of dinutuximab beta, including but not limited to area under the concentration-time curve (AUC), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), time to C_{max} (t_{max}), and half-life ($t_{1/2}$), if data permits.

4.2. Secondary Endpoints

There is no secondary endpoint.

4.3. Exploratory Endpoints

- EFS is defined as the time from initiating study drug(s) to disease progression, death from any cause, relapse, secondary malignancy as assessed by investigators, including EFS rate at 6 months as measured by Kaplan-Meier method

5. SAMPLE SIZE CONSIDERATIONS

The study plans to enroll 8 patients as recommended for PK studies by Center of Drug Evaluation (CDE) technical guidance on clinical pharmacokinetic study of chemical drugs (CDE of National Medical Products Administration (NMPA) 2005). Therefore, a sample size of 8 patients is proposed in this single-arm PK study.

6. STATISTICAL METHODS

6.1. Analysis Sets

The Safety Analysis Set includes all patients who received any dose of any study drug. The safety analysis set is used for all primary safety and efficacy analyses

The PK analysis set includes patients who have at least one available post-baseline PK data in Safety Analysis Set. The PK analysis set will be used for PK 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 include dinutuximab beta and 13-cis-RA therapy.

Study day will be calculated in reference to the date of the first dose of study drug. For assessments conducted on or after the first dose, the study day will be calculated as assessment date – the first dose date + 1). For assessments conducted before the first dose, study day is calculated as (assessment date –the first dose date). 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.

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

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

6.3.2. Conventions

No formal hypothesis will be tested in this study. Data will be mainly analyzed descriptively. Confidence intervals will be constructed to describe the precision of the point estimates of interest.

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.
- Duration of image-based event will be based on the actual date the radiograph was obtained rather than the associated visit date.
- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, 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 are provided in Appendix 2.

By-visit endpoints will be analyzed using observed data unless otherwise specified.

6.4. Patient Characteristics

6.4.1. Patient Disposition

The number (percentage) of patients treated, discontinued from the study, reasons for discontinued from the study, and the duration of study follow-up will be summarized in the safety analysis set. The patients who discontinued treatment and the primary reason for the end of treatment will be summarized among patients who were treated.

The following patient disposition information will be summarized separately for dinutuximab and 13-cis-RA when appropriate:

- Number of patients treated
- Number (%) of treated patients who discontinued from treatment
- Reason(s) for treatment discontinuation
- Number (%) of treated patients who discontinued from study
- Reason(s) for study discontinuation

6.4.2. Protocol Deviations

Important protocol deviation criteria will be established, and patients with important protocol deviations will be identified and documented. Important protocol deviations will be listed.

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
- Sex
- Height
- Weight
- BMI

- 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. A listing of disease history will be provided.

6.4.5. Prior Anticancer Therapies

Prior systemic therapies, prior anti-cancer radiotherapy, and prior stem cell transplantation will be summarized in the safety analysis set. The variables include number of patients with any prior anti-cancer therapy, number of prior regimens, and best overall response for prior systemic therapies, and transplantation type, number of transplantations for prior stem cell transplantation. The therapies with the same sequence/regimen number are counted as one prior therapy.

6.4.6. Prior and Concomitant Medications

Prior medications are defined as medications that started and 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, before the last dose of any study medication and continue up to 40 days after the patient's last dose (as of the Safety Follow-up Visit).

Prior and concomitant medications will be coded using the version B3 202203 or higher of World Health Organization Drug Dictionary (WHO DD) drug codes. 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. A listing of prior and concomitant medications will be provided.

6.4.7. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 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 in the safety analysis set. A listing of medical history will be provided.

6.5. Efficacy Analysis

6.5.1. Efficacy Endpoint(s)

The analysis of event free survival (EFS) is based on the safety analysis set. EFS is defined as the time from initiating study drug(s) to disease progression, death from any cause, relapse, secondary malignancy as assessed by investigators. The distribution of EFS, including median, Q1 and Q3, and event-free rates at the 6th month, will be estimated using the Kaplan-Meier

method for each treatment group. Ninety-five percent CIs for median and Q1 and Q3 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).

The censoring rules for the primary analysis of EFS are presented in Table 1.

Table 1: Handling of Intercurrent Events and Missing Values of Event Free Survival

	Derivation rules	**Outcome**
No event at the time of data cut-off or withdrawal from study or lost to follow up	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
Intercurrent events		
Discontinuation of the treatment	Tumor assessment data collected after discontinuation of study treatment will be used for analysis (treatment policy strategy)	No impact
New anticancer therapy started prior to EFS events.	Last adequate disease assessment before the new anticancer therapy (hypothetical strategy)	Censored
Missing values not related to intercurrent events		
Patients' withdrawal from the study or lost to follow-up	Last adequate disease assessment prior to patient withdrawal from the study (hypothetical strategy)	Censored
No baseline or post-baseline disease assessments without death	Date of the first dose	Censored
disease assessments with death	Date of death	Event

6.6. Safety Analyses

All safety analyses will be performed based on the 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, ECG findings. Summaries will be separated for dinutuximab and 13-cis-RA only for extent of exposure and related treatment emergent adverse events (TEAEs, as defined in Section 6.6.2).

6.6.1. Extent of Exposure

The following measures of the extent of exposure will be summarized separately for dinutuximab and 13-cis-RA:

- Duration of exposure (days): calculated as following:
  - For dinutuximab: earlier of (last dose date + 24 days, data cutoff date) + 1 - first dose date

  - For 13cis-RA: earlier of (last dose date + 21 days, data cutoff date) + 1 - first dose date
- Number of treatment cycles received: defined as the number of the last treatment cycles in which at least one dose of the study drug is administered.

- Total dose received per patient (mg/m^2 and mg): defined as the cumulative dose of the study drug during the treatment period of the study, with and without BSA adjustment.
- Actual dose intensity per cycle (mg/m^2/cycle): defined as the total dose received by a patient divided by the number of treatment cycles received.
- Relative dose intensity per cycle (%): defined as the total dose received divided by protocol specified planned total dose for 5 cycles.
- Dose reduction
  - Number of dose reductions and reasons
  - Number of dose-reduced cycles
- Dose interruption
  - Number of dose reductions and reasons
  - Number of dose-interrupted cycles
- Dose delay and reason

6.6.2. Adverse Events

AEs will be graded by investigators using CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (Version 25.1 or higher) lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

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 through 40 days after the last dose (permanent discontinuation of study drug) or the initiation of new anti-cancer therapy, whichever is earlier. Summary tables will generally focus on those AEs that were treatment-emergent (TE). All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

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 reduction, TEAEs that led to dose interruption, TEAEs that led to dose delay, treatment-related TEAEs grade 3 or

above. Treatment-related AEs include those events considered by the investigator to be related to study drug or with a missing assessment of the causal relationship.

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. The number (percentage) of patients with treatment-emergent SAEs, treatment-related TEAEs, TEAEs with grade 3 or above, treatment-related SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose modifications, and infusion-related reactions will be summarized by SOC and PT. TEAEs with grade 3 or above will also be summarized by PT in descending order.

Patient data listings of SAEs, fatal AEs will be provided.

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

6.6.3. Laboratory Values

Laboratory safety tests will be evaluated for selected parameters described in Table 2.

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be summarized by visit.

Laboratory parameters ALT, AST, total bilirubin, hemoglobin, platelet counts, WBC count, neutrophil and lymphocyte that are graded in NCI CTCAE Version 5.0 will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately.

Patient data listings of all laboratory data collected will be provided.

Table 2: Laboratory Tests

Clinical chemistry	Hematology	Coagulation	Urinalysis
Alanine aminotransferase Aspartate aminotransferase Total bilirubin Potassium Sodium Total calcium Creatinine	Hemoglobin Platelet count White blood cell count Lymphocyte count Neutrophil count Basophils	Prothrombin time Activated partial thromboplastin time International normalized ratio	Glucose Protein Blood Ketones

Clinical chemistry	Hematology	Coagulation	Urinalysis
Chloride C-reactive protein Gamma-glutamyl transferase			

6.6.4. Vital Signs

Descriptive statistics for vital sign parameters systolic and diastolic blood pressure (BP), pulse rate, temperature, and weight and changes from baseline will be presented by visit.

6.6.5. Electrocardiograms (ECG)

Actual value and change from baseline for the QT interval, heart rate and corrected QT interval by Fredericia (QTcF) will be summarized. The average of the readings for the visit will be used for the summary.

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

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

6.7. Pharmacokinetic Analyses

Actual dose and blood draw times will be used to calculate the PK parameters. Parameters will be listed individually and summarized using descriptive statistics.

The following PK parameters will be calculated as appropriate for the data collected. Other PK parameters may be calculated if supported by the data.

- C_{max}: Maximum serum concentration
- t_{max}: Time to maximum serum concentration
- C_{min}: Minimum serum concentration
- $t_{1/2}$: Half-life
- AUC_{0-t}: Area under the serum concentration-time curve from zero to the last measurable concentration
- $AUC_{0-\infty}$: Area under the serum concentration-time curve from zero to infinity

Calculation and presentation of PK parameters will be based on the Work Instruction: Best Practice Guidance: Non-Compartmental Pharmacokinetic Data Analysis for Clinical Studies. Version 1.0, Document Number VV-QDOC-13140.

6.7.1. Reporting of Pharmacokinetic Concentrations for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous concentrations, exclusions and any special treatment for descriptive statistics and plots. The concentration and time data will be listed individually and summarized using descriptive statistics.

The following conventions will be used for reporting descriptive statistics for concentration data.

- PK concentrations should be reported in listings at the same level of precision as that in the source data.
- If a concentration at a given time point is below the assay quantification limit (BLQ), the concentration shall be reported as the term "BLQ" with the lower limit of quantitation (LLOQ) defined in the footnotes. BLQ values shall be treated as zero for computation of descriptive statistics. BLQ values will not be included for calculations of geometric mean and geometric coefficient of variation (CV%).
- If the calculated mean concentration is BLQ, the mean value shall be reported in outputs (such as tables) as BLQ and SD and geometric CV% shall be reported as ND (not determined). Minimum, median, and maximum may be reported.

6.7.2. Plots of Pharmacokinetic concentrations

Concentration versus time data will be plotted individually and summarized graphically using arithmetic mean (+SD) plots by treatment group, respectively in linear and log-linear scale. Arithmetic mean concentrations that are BLQ shall be set to zero for plotting on both linear scale but not shown in log-linear scale.

6.7.3. Reporting of PK parameters for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous PK parameters, exclusions and any special treatment for descriptive statistics.

- All the PK parameters should have at least the following summary statistics: sample size (n), mean, standard deviation (SD), coefficient of variance (CV%), median, minimum, maximum, geometric mean, geometric CV%.
- For in-text tables, Geometric mean (geometric CV%) will be the default method of reporting PK parameters. t_{max} should be presented as median, range (minimum, maximum), when presenting the summary statistics. $t_{1/2}$ should be presented as geometric mean, range (minimum, maximum).
- For any parameters that $n \leq 2$, SD should not be presented.
- The units for all PK parameters will be provided.

- It is recognized that the number of decimals in reported concentrations, for example: "9632.94401 ng/mL" or "9.963294401 ug/mL" are highly improbable and will be queried (since bioanalytical assays generally do not have this level of precision). Usually the first-in-human dose escalation trial will provide the numerical range of PK parameters eg. AUC range from 10 to 10,000 ng.hr/mL and C_{max} range from 1 to 1000 ng/mL.

  In this scenario, for reporting PK parameters such as AUC and $C_{max,}$ the following guidance is provided for rounding:

  – If the numerical value is below 100 then one decimal place may be used eg, 0.1 or 99.9.

  – For values ranging from >100, whole numbers should be used eg, 100 or 9999.

  – If > 10,000 the clinical pharmacologist may decide on changing units eg, from μg/ml to mg/ml.

  – For reporting times eg, for t_{max} or $t_{1/2}$, if <1 hr use 2 decimals; time up to 24 hr should be reported to one decimal place eg., 23.5 hr, time >24 hr should be rounded to nearest whole number eg, 105 hr.

7. INTERIM ANALYSES

No interim analysis is planned.

8. CHANGES IN THE PLANNED ANALYSIS

Table 3: Statistical Analysis Plan Changes

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
1.0	06 July, 2023	Protocol Amendment 1.0	No or very few important protocol deviations are expected.	Remove summary of important deviations.

9. REFERENCES

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Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, De Bernardi B, Evans AE, Favrot M, Hedborg F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol. 1993 Aug;11(8):1466-77.

APPENDIX 1. SCHEDULE OF ASSESSMENT

	Screening (Day −28 to Day −1)	**Cycles 1 to 5**																	**EOT/early termination [b]**	**Safety follow-up [c]**
Visit day		Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11[a]	Day 12	Day 15	Day 22	Day 25	Day 29	Day 35	-7 to 7 days or 0 to 7 days	+ 40 days
Visit window		± 3																		**± 7**
Informed consent	X																			
Inclusion/exclusion criteria	X																			
Demography	X																			
Medical history	X																			
Oxygen saturation on room air	X	X																		X
Pregnancy test in WOCBP[d]	X	X																		
HBsAg/HCV-Ab[e]	X																			
Ophthalmologic examination	X																		X	X
Height/weight	X	X																		
Physical examinations [f]	X	X----------X																	X	X
Vital signs	X	X----------X																	X	X
Performance status	X	X----------X																	X	X
ECHO or MUGA scan	X	As clinically indicated																	X	X
12-Lead ECG [g]	X	X										X							X	X
Chest X-Ray [h]		X	As clinically indicated																	
Complete blood count (including differential count)/biochemistry [i, j]	X	X							X			X		X	X		X		X	X
Urinalysis [i, j]	X	X																	X	X
Coagulation [i, j]	X	X																	X	X

Dinutuximab beta infusion [k]		X----------Continuous infusion----------X																	
13-cis-RA												X----------X							
PK sampling in Cycle 1[l]		X		X					X			X		X^m	X^m		X		
PK sampling in Cycle 2-4[l]		X										X							
Tumor assessments [n]	X																	X	
Adverse events	X----------X																		
Concomitant medications [o]	X----------X																		

Abbreviations: AE, adverse event; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; EOT, end of treatment; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; INRC, international neuroblastoma response criteria; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; PK, pharmacokinetic(s); QTcF, QT interval corrected for heart rate using Fridericia's formula; WOCBP, woman of childbearing potential; ^{123}I, iodone-123.

[a] Day 1 evaluations must be done before the start of the dinutuximab beta infusion. Day 11 evaluations must be done just before the end of the dinutuximab beta infusion.

[b] The EOT Visit is conducted within ± 1 week of the end of Cycle 5. For early termination, the EOT Visit is conducted ≤ 7 days after the investigator determines that the patient must permanently discontinue the study drug or the patient decides to withdraw from the study before the end of Cycle 5.

[c] Safety Follow-up Visit: within 40 days [± 7 days] after last dose of study drug; initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever comes first.

[d] Pregnancy test in WOCBP is described in Appendix 4 of the protocol.

[e] If HCV-Ab positive, HCV-RNA test will be required for eligibility check.

[f] Physical examinations is presented in Section 8.2.2 of the protocol.

[g] At each timepoint, 3 consecutive 12-lead ECGs should be performed approximately 2 minutes apart to determine the mean QTcF interval.

[h] Chest X-ray should be performed within 7 days before the start of dinutuximab beta infusion in each cycle. It can be skipped if chest MRI or CT scan has been performed already before administration per investigator's discretion.

[i] If clinical chemistry, hematology, coagulation and urinalysis at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration (Section 8.2.5 of the protocol).

[j] The test for clinical chemistry, hematology, coagulation, and urinalysis, excluding PK sampling, will be performed within 72 hours before study drug administration on Day 1 of each cycle. All laboratory tests with values considered clinically abnormal during participation in the study or within 40 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor (Section 8.2.5 of the protocol).

[k] The recommended dose of dinutuximab beta depends on the patient's body surface area (BSA) and the actual dose is calculated on every Day 1 of Cycle 1 to 5 (BSA = SQRT [weight (kg) x height (cm)/ 3600]).

[l] PK sampling time refers to Table 4.

[m] PK sampling on Day 15 and Day 22 in Cycle 1 is optional.

[n] Tumor assessments will be performed by the investigators at Screening Visit, end of treatment Cycle 3 and end of treatment Visit per their clinical practice. The INRC (Brodeur et al 1993) is recommended as a reference for response evaluation in patients evaluable for response. Tumor assessments may include MRI and/or CT scan and/or ^{123}I-MIBG scan and/or ^{18}F-FDG-PET and/or bone marrow assessment.

[o] Concomitant medications will be defined as medications that started before the first dose of study drug(s) and were continuing at the time of the first dose of study drug(s), or started on or after the date of the first dose of study drug(s) up to 40 days after the patient's last dose (as of the Safety Follow-up Visit) in Section 10.1.5 of the protocol.

X: evaluations must be regularly repeated during the timepoints indicated according to routine medical care to ensure safe treatment of the patient.

Table 4: Dinutuximab Beta PK Sampling Schedule

Cycle	**Cycle 1 (35 days per cycle)**							**Cycle 2, 3, and 4**	
Time	D1 Predose	D3	D8	D11	D15[a]	D22[a]	D29	D1 Predose	D11
Window Allowed	-30 mins[b]	± 1 h[c]	± 1 h[c]	-5 mins[d]				-30 mins[b]	-5 mins[d]
PK Serum Sample	X	X	X	X	X	X	X	X	X

Abbreviation: PK, pharmacokinetic(s).
[a] PK sampling on Day 15 and Day 22 in Cycle 1 is optional. That adjustment needs to be aligned with pharmacologists. PK sampling on Day 29 in Cycle 1 is required even if the infusion time will be delayed or extended.
[b] 30 minutes before starting infusion.
[c] Infusion starting time ± 1 hour.
[d] 5 minutes before the end of infusion, even if the infusion time will extend to the next days.

APPENDIX 2. 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. **Prior/Concomitant Medications/Procedures**

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

If the start date of medication 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 end date of medication 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 start date or end date of medication is completely missing, do not impute. If the imputed of a medication end date > last known alive date or end of study date, then set to the last known alive date or end of study date, whichever occurs first.

2. **Adverse Events**

The imputation rule for the safety analyses 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 the start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then the imputed day and month will be January 01 or the first dosing date if they have the same year, whichever is later.
- If only day is missing, then the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later
- If the start date is completely missing, the imputed day will be the first dosing date as long as AE end date is not before the first dosing date.

If the end date of an AE 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 end date is completely missing, do not impute.

If the imputed AE end date > last known alive date or end of study date, then set to the last known alive date or end of study date, whichever occurs first.

3. **Deaths**

In case complete death dates are not recorded, impute as follows:

- If both month and day are missing, then the imputed month and day will be 01Jan or the last date of a patient known to be alive + 1, whichever is later.
- If only day is missing, the death will be assumed to be on the first day of the month or the last date of a patient known to be alive +1, whichever is later.

4. **Subsequent Anti-cancer Therapies**

If the start date of a subsequent anti-cancer therapy is incomplete or missing, impute as follows:

- If both month and day are missing, then the imputed month and day will be 01Jan or the last day of the month for the last adequate disease assessment if they have the same year.
- If only day is missing, then the imputed day will be the first day of the month.

5. **Diagnosis**

If a diagnosis date 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 a diagnosis date is completely missing, do not impute.

6. **Prior Therapy/Response to Prior Therapy**

If a prior therapy or response to prior therapy date is partially missing, impute as follows:

- If only day is missing, then set to the 15th of the month or the first study drug dose date, whichever is earlier. An imputed start date can be no later than the end date and vice versa.
- If month and day are missing, then set to be June 15th or the first study drug dose date, whichever is earlier. An imputed start date can be no later than the end date and vice versa.

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