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Title page

An open-label, multicenter rollover study to provide continued treatment with anetumab ravtansine for participants with solid tumors who were enrolled in previous Bayer-sponsored studies

Anetumab ravtansine rollover study

Bayer study drug	BAY 94-9343/Anetumab ravtansine		
Study purpose:	Safety, enable participants still benefiting to continue treatment		
Clinical study phase:	2	**Date:**	07 JUN 2022
Study No.:	20322	**Version:**	2
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

ADC	Antibody-drug conjugate
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BAY 94-9343	Anetumab ravtansine
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ENR	Enrolled analysis set
ICF	Informed consent form
IRR	Infusion-related reaction
KM	Kaplan-Meier
LKAD	Last Known Alive Date
MedDRA	Medical Dictionary for Regulatory Activities
MSLN	Mesothelin
N/A	Not Applicable
NCI	National Cancer Institute
OS	Overall Survival
PT	Preferred Term
RBC	Red Blood Cell
ROS	Rollover study
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

Anetumab ravtansine (BAY 94-9343) is an antibody-drug conjugate (ADC) directed at mesothelin (MSLN) antigens that are expressed in a variety of malignancies and conjugated to a synthetic cytotoxic anticancer agent, maytansine derivative (DM4, BAY 1006640). The purpose of this study is to collect long-term safety information on anetumab ravtansine and to enable participants who received an anetumab ravtansine-containing treatment in any Bayer-sponsored anetumab ravtansine parent study to continue to receive study treatment and/or follow-up at the time of parent study closure.

This statistical analysis plan (SAP) is based on procedures and objectives as described in the clinical study protocol amendment 2, dated 18 JUN 2019.

2. Study Objectives

The primary purpose of this study is to assess the long-term safety of continued anetumab ravtansine treatment in patients who were treated with anetumab ravtansine in a parent study.

Objectives	Endpoints
Primary	
• Safety	• Incidence of TEAEs • Incidence of TESAEs • Incidence of drug-related TEAEs and TESAEs
Secondary	
• Survival	• Overall survival (OS)
Tertiary/Exploratory	
• Tumor response	• Investigator-determined tumor assessment

3. Study Design

This is an open-label rollover study (ROS) to enable participants who received anetumab ravtansine in any applicable Bayer-sponsored anetumab ravtansine parent study to continue treatment or follow-up (per current epoch of parent study) at the time of parent study closure.

Participants who discontinue treatment in this study will continue to receive survival follow-up in a long-term follow-up phase. All tumor assessments are at the investigator's discretion and per investigator criteria. Clinic visits occur only during treatment and at the end of treatment safety follow-up visit 30 (+5) days after last treatment. This study has no active follow-up phase other than the safety follow-up visit.

4. General Statistical Considerations

4.1 General Principles

Summary tables will be generated by overall and participant data listings will be generated separately for each parent study. Parent studies include Phase 1 studies 15051, 15834, 17631, 18327, and 18329, and Phase 2 study 15743.

The statistical evaluation will be performed using the SAS software package release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Data will be analyzed using descriptive statistical methods:

Unless otherwise specified, the following statistics will be presented: For continuous and ordinal data, the number of participants with data available and missing data, mean, standard deviation,

minimum, interquartile range, median, and maximum. For categorical variables, the number of participants and percentage in each category will be generated.

If a subgroup has fewer than 8 participants, summary statistics will not be produced, and the results for the subgroup may be reported entirely with listings.

4.2 Handling of Dropouts

Patients enrolled but not treated in this study will not be included in safety or efficacy summaries. All data available will be reported in safety listings.

4.3 Handling of Missing Data

All missing or partial data will be presented in the participant data listing as they are recorded on the Case Report Form (CRF). Missing data will not be imputed for analyses.

4.4 Interim Analyses and Data Monitoring

No interim analyses are planned. Safety will be monitored on an ongoing basis using clinical data only.

4.5 Data Rules

Duration in months will be calculated as (end date – start date + 1) / 30.4375.

4.6 Validity Review Meeting

At the Validity Review Meeting, participants will be assigned to the relevant analysis sets based on the rules described in Section 5.

5. Analysis Sets

For purposes of statistical analysis, the following analysis sets were defined in the protocol:

Analysis set	Description
Enrolled (ENR)	All participants who signed the informed consent form (ICF)
Safety (SAF)	All participants who take at least 1 dose of study intervention within this rollover study

The enrolled analysis set will be used for study disposition and enrollment, and for listings of safety events. The safety analysis set (SAF) will be used for efficacy and safety summaries.

6. Statistical Methodology

6.1 Population characteristics

Where summarized, population characteristics will be summarized by overall on the SAF.

6.1.1 Disposition

The number of participants in each analysis set will be presented on the enrolled analysis set. The number and percentage of SAF participants who enroll, initiate treatment, discontinue treatment, receive safety follow-up, receive long-term follow-up, and discontinue long-term follow-up will be tabulated, along with reasons for discontinuation. Listings of all discontinued subjects including reasons for discontinuation will be provided by parent study.

6.1.2 Demographic and Baseline Characteristics

Data listings for all enrolled participants will contain the minimal information collected in this study, including parent study, age at entry into the study, weight, age group, sex, and race. Summary statistics will be reported for the SAF. Summary statistics and a listing of cancer type will be produced.

6.1.3 Concomitant Medication

Concomitant medications are non-study medications used between the first date of treatment and 30 days following the last study treatment in this study.

Concomitant medications will be coded using the most recent World Health Organization Drug Dictionary (WHO-DD) version at the time the study ends and the Anatomical Therapeutic Chemical (ATC) classification system.

Concomitant medication will be reported in the safety analysis set. Listings will be provided by parent study.

6.2 Efficacy

6.2.1 Overall Survival

Overall survival is defined in the SAF as the time from first treatment in this study until death from any cause. Participants without reported death as of the cut-off date for this study will be censored at their last known alive date. Overall survival data will be listed by overall. Last known alive date will be based on dates of actual participant contact including date of last visit or telephone contact of any kind, last assessment, and last laboratory sample collection date. Censoring rules are described in Table 6-1. Details on last known alive date will be described in programming specifications.

Table 6-1 Censoring for Overall Survival

Situation	End Date	Censored	Reason for Censoring
Death between first treatment date and the date of analysis / database cut-off date (i.e. there is a death date and this date is before or on the date of analysis / database cut-off date)	Date of Death	No	N/A
Alive at the date of analysis / database cut-off date (i.e. there is a clear assessment that the participant was alive this day, e.g. from information collected on or after the date of analysis / database cut-off date)	Last known alive date (LKAD) prior to database cut-off	Yes	No Death
No information of survival status as of the data cut-off date used for an analysis database (e.g., lost to follow-up)	Last known alive date (LKAD) prior to database cut-off	Yes	No Death and no survival status
Lost to follow-up with no contact information at all after the first treatment date	Date of randomization	Yes	Lost to follow-up after randomization date
If month and/or year are missing for death date	The nearest prior time point: Last known alive date (LKAD) prior to database cut-off	Yes	Missing month and/or year for death date

OS will be summarized using Kaplan-Meier estimates [1]. Medians and 95% Brookmeyer-Crowley confidence intervals [2] with complementary log-log transformation [3] will be reported. The number of participants at risk, number of events, and number of censored participants per month will also be reported.

6.2.2 Disease Progression

Investigator-determined disease progression will be collected as an exploratory endpoint at the end of treatment and presented in data listings for the enrolled analysis set. Clinical assessment and radiologically confirmed outcomes recorded on the CRF per the standard of care at the site. Progression (clinical or radiological) and date of procedure (date on which radiological procedures were performed or date of clinical assessment) will be listed.

6.3 Safety

Unless otherwise specified, safety analyses will be performed on the SAF. Data will be presented by overall and listings by parent study.

6.3.1 Primary Safety Outcomes

The primary safety outcomes include incidence of TEAEs and TESAE, as well as drug-related TEAEs and TESAEs. Their analysis is described in Section 6.3.3 below.

6.3.2 Study Drug Exposure

Exposure to anetumab ravtansine will be summarized in the SAF, including number of cycles and duration of treatment during the rollover study. Exposure to combination therapies that continue from the parent study will be presented in data listings only.

Duration of treatment is defined as (last dose date-first dose date) +1.

6.3.3 Adverse Events

Treatment-emergent AEs (TEAEs)

In this study, treatment-emergent adverse events are defined as adverse events starting or worsening during the treatment period. The treatment period extends from the first date of treatment in this study until the safety follow-up (30 days after the last administration of study treatment).

Coding and grading of TEAEs

TEAEs will be coded using the latest MedDRA version, and toxicity will be graded using NCI-CTCAE v5.0. Corneal epitheliopathy events (classified as corneal disorders) will be graded according to the Bayer Grading System.

Study drug-related AEs

AEs will be reported as study drug-related if they are documented by the investigator as related to any study drug.

AEs of Special Interest (AESIs)

Adverse events of special interest include any corneal epitheliopathy and infusion-related reactions (IRRs).

Reporting of TEAEs

The incidence of TEAEs and TESAEs, as well as drug-related TEAEs and TESAEs will be summarized in descriptive summary tables (number and percentage of participants) by latest MedDRA version SOC and prefered term (PT) and by worst grade for the following:

- Overview of TEAEs
- TEAEs
- TEAEs in descending order of frequency by Preferred Term (PT)
- Study drug-related TEAEs
- Study drug-related TEAEs in descending order of frequency by PT
- TESAEs
- TESAEs in descending order of frequency by PT
- Study drug-related TESAEs
- Study drug-related TESAEs in descending order of frequency by PT
- TE(S)AEs leading to permanent discontinuation
- TE(S)AEs leading to dose interruption

- TE(S)AEs leading to dose reduction
- Overview AEs of special interest

All AEs, TEAEs, TESAEs, and TEAEs leading to discontinuation of study drug will be presented in separate listings. Listings will be provided in all enrolled participants. AEs of special interest will be included in summary tables of AEs and will be presented in data listings.

A summary of deaths during the treatment period and following 30 days after treatment end in this study will be reported for the safety set. A listing of all deaths at any time during the study will be provided in all enrolled participants.

6.3.4 Laboratory assessments

The following laboratory parameters will be summarized in all treated participants:

- Hematology: platelet count, red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count (WBC) with differential
- Clinical chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine
- Serum pregnancy test results will be reported through listings

The clinically relevant laboratory parameter changes occurring during the study were to be reported as adverse events (Section 8.2.3 of the clinical study protocol).

For purposes of the safety analysis, only numerical laboratory values (no clinical assessments) will be used for providing severity ranges for the laboratory data. Ranges are described in Bayer internal documentation [4]. Laboratory toxicities assigned by the investigator or reported as AEs will be documented in the AE CRFs and reported in AE tables and listings; these toxicities may include clinical assessments. The incidence of laboratory toxicities will be summarized in frequency tables.

For laboratory assessments with normal ranges, low/normal/high status will be reported in listings as applicable.

6.3.5 Other Safety Measures

In addition, all laboratory assessments, vital signs, and ophthalmologic examination results will be presented in data listings. Listings will be reported in all enrolled participants.

7. Document history and changes in the planned statistical analysis

SAP version 1.0, dated 23 MAY 2019.

8. References

1. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 53:457-81 (1958)
2. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 38:29-41 (1982).

3. Collett, D. *Modelling Survival Data in Medical Research: Third Edition*. CRC Press. (2015) p. 29.
4. Handling Laboratory Findings in Bayer Oncology Clinical Trials (Internal) 15 FEB 2019