Non-Interventional Study (NIS) Protocol

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Title:	Demographic, clinical characteristics, and treatment outcomes associated with dedifferentiated liposarcoma patients in China
Brief lay title:	Real-world study of dedifferentiated liposarcoma patients in China
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Medicinal product:	Not applicable
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorization holder(s):	Not applicable
Joint PASS:	No
Research question and objectives:	This study will characterize patients with dedifferentiated liposarcoma (DDLPS) in China, including an understanding of demographic, and clinical characteristics as well as treatment patterns and clinical outcomes associated with the current real-world treatment.
Country(-ies) of study:	China
Author:	[redacted]

Marketing authorisation holder(s):	Not applicable
In case of PASS, add: **MAH contact person:**	Not applicable
In case of PASS, add:	Not applicable
In case of PASS, add:	Not applicable
Date:	31 May 2023

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2. LIST OF ABBREVIATIONS

1L	First line
2L	Second line
3L	Third line
AE	Adverse Event
BI	Boehringer Ingelheim
CDC	Center for Disease Control and Prevention Center
CI	Confidence Interval
CSCO	Chinese Society of Clinical Oncology
CTN	Clinical Trial Notification
DDLPS	Dedifferentiated liposarcoma
ECOG	Eastern Cooperative Oncology Group
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HCRU	Healthcare resource utilization
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
KM	Kaplan-Meier
LOT	Line of therapy
MAH	Marketing Authorization Holder
MDM2	Mouse double minute 2 homolog
NATDSS	National Anti-Tumor Drug Surveillance System
NCC	National Cancer Center
NCCN	National Comprehensive Cancer Network
NIS	Non-Interventional Study
NIS-DMRP	Non-interventional Study-Data Management and Review Plan
OS	Overall survival
PASS	Post-Authorization Safety Study
QC	Quality control
SD	Standard deviation
SEAP	Statistical and Epidemiological Analysis Plan
SEER	Surveillance, Epidemiology, and End Results
SOP	Standard operating procedure
TP53	Tumor protein 53

3. RESPONSIBLE PARTIES

BI NIS [redacted]
[redacted] investigator: [redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Not applicable			
Name of active ingredient: Not applicable			
Protocol date: 31 May 2023	**Study number:** 1403.0024	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	Demographic, clinical characteristics, and treatment outcomes associated with dedifferentiated liposarcoma patients in China		
Rationale and background:	Liposarcoma is a malignancy of fat tissue and is one of the most commonly occurring types of soft tissue sarcoma, a heterogeneous group of rare malignancies with over 150 different histological subtypes. In 2020, the World Health Organization, reclassified liposarcomas into the following distinct categories: atypical lipomatous tumor/well-differentiated liposarcoma; myxoid liposarcoma; pleomorphic liposarcoma; myxoid pleomorphic liposarcoma; and dedifferentiated liposarcoma (DDLPS), which represents 15-20% of all liposarcoma cases [R23-1182]. DDLPS is characterized by amplification of the mouse double minute 2 homolog (MDM2) gene. MDM2 is a negative regulator of tumor protein 53 (TP53) [P20-03237]. There are few published epidemiological studies of DDLPS with quite limited incidence and prevalence data. The mainstay of first line (1L) therapy for advanced DDLPS remains an anthracycline-based regimen despite its moderate efficacy in this setting (objective response rate <15%; median progression-free survival: 2 to 4 months; median overall survival (OS, from initiation of 1L treatment to death or end of study): 8 to 12 months) [R21-0720]. Notably, the natural history, patient journey and treatment outcomes of this rare disease is poorly understood in Chinese patients. Boehringer Ingelheim (BI) is currently developing BI 907828, an orally available MDM2-p53 antagonist, for treatment of DDLPS. On 22 August 2022, BI China received Clinical Trial Notification (CTN) for MDM2 DDLPS indication from China authority. In the CTN, China authority recommended BI to collect Chinese DDLPS patients' survival and other related clinical data in the real-world, to provide support for future analysis during New Drug Application. Therefore, we conduct this study to investigate the patient characteristics, current treatment patterns and outcomes in Chinese DDLPS patients.		

Research question and objectives:	Primary objective: • To describe the overall survival (OS) of Chinese unresectable locally advanced or metastatic DDLPS patients Secondary objectives: • To describe the treatment patterns of Chinese DDLPS patients Exploratory objective: • To describe demographic, clinical characteristics and treatment outcomes of Chinese DDLPS patients • To describe the direct medical cost and healthcare resource utilization of Chinese DDLPS patients
Study design:	This will be a non-interventional/observational study of Chinese DDLPS patients using existing data curated by [redacted]. No Boehringer Ingelheim (BI) product will be studied, and no new interventions or procedures will be collected. The proposed study period will be January 1, 2013 through December 31, 2022. Eligible patients will be identified from January 1, 2013 to December 31, 2021 (one year before end of study period). Patients will be followed from index date until death, end of study period, or loss to follow-up, whichever occurs first.
Population:	Inclusion criteria: • Patient has two or more documented clinical visits in the National Anti-Tumor Drug Surveillance System (NATDSS) network on or after January 1, 2013. • Patient has a confirmed diagnosis of DDLPS during his/her lifetime. • At least 18 years old at the date of initial diagnosis No exclusion criteria are applied. Eligible population will be divided into two groups: • Cohort 1 will include unresectable locally advanced or metastatic DDLPS patients who received at least one line of systemic antineoplastic treatment by the end of cohort identification period (index date = start date of 1L treatment). • Cohort 2 will include patients with DDLPS who have not initiated 1L systemic antineoplastic treatment by the end of cohort identification period (index date = date of initial DDLPS diagnosis during cohort identification period). Patients initiated 1L treatment afterwards or patients received adjuvant and/or neoadjuvant therapy only through follow-up will be included in Cohort 2.
Variables:	This analysis is descriptive, in that there is no *a priori* hypothesis being assessed. Thus, there are no pre-specified exposures or covariates that will be used as the basis for comparison a priori. The primary outcome is OS. Secondary outcomes include survival after initial diagnosis, and treatment patterns. Exploratory outcomes may include patient demographics, clinical characteristics, duration of treatment, time to next treatment by lines, healthcare resource utilization and direct medical cost, etc.

Data sources:	[redacted] will develop a custom, curated dataset for this study based on longitudinal electronic medical records data from the National Anti-Tumor Drug Surveillance System (NATDSS), the largest cancer registry database in China. This database, established in 2018 by China National Cancer Center (NCC), covers over 1400 hospitals across 31 provinces and over 10 million cancer patients in China. This multicenter hospital-based database consists of data of 1509 variables from 7 aspects including drug, patient basic information, inpatient, outpatient, medical technology, treatment and follow up. NATDSS is linked with National Mortality Database from Chinese Center for Disease Control and Prevention Center (China CDC) to obtain patients' death information.
Study size:	The patient sample will be a convenience population of all eligible patients in the database who met inclusion and exclusion criteria during the study period; no priori power analyses were conducted.
Data analysis:	This study will be descriptive in nature. Continuous variables will be summarized using mean, standard deviation (SD), median and range. Categorical measures will be summarized using frequencies and percentages. OS will be estimated by the Kaplan-Meier (KM) method to obtain median estimates with two-sided 95% confidence intervals (CIs). OS may be assessed by line of therapy (LOT) and type of treatment received in each LOT, pending feasibility. Subgroup analyses will be conducted in both Cohort 1 and 2: • Unresectable locally advanced DDLPS patients • Metastatic DDLPS patients • Brightline-1-like cohort including patients who received doxorubicin monotherapy or doxorubicin-based regimens as 1L treatment. • Real-world Brightline-1 cohort including patients matching the inclusion and exclusion criteria in Brightline-1 trial • Additional subgroups pending feasibility, which may include age, sex, and year of diagnosis. Sensitivity analyses will be conducted: • to only include patients in areas covered by the National Mortality Database and with higher completeness on survival data • to only include patients before COVID-19 emergence (cohort identification period: January 1, 2013 – December 31, 2019) to assess the possible impact of COVID-19 pandemic on treatment patterns and outcomes
Milestones:	1) Protocol approval: May 2023 2) Start of analysis: Dec 2023 3) End of analysis: Feb 2024 4) Final report of study results: Apr 2024

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	*October 2023*
Start of data collection	*December 2023*
End of data analysis	*February 2024*
Final report of study results:	*April 2024*

7. RATIONALE AND BACKGROUND

Liposarcoma is a malignancy of fat tissue and is one of the most commonly occurring types of soft tissue sarcoma, a heterogeneous group of rare malignancies with over 150 different histological subtypes. Liposarcomas have several forms based on clinical presentation, severity, genetic abnormality, and preferred treatment regimens [R23-1186] [R22-3794]. In 2020, the World Health Organization, reclassified liposarcomas into the following distinct categories: atypical lipomatous tumor/well-differentiated liposarcoma; myxoid liposarcoma; pleomorphic liposarcoma; myxoid pleomorphic liposarcoma; and dedifferentiated liposarcoma (DDLPS), which represents 15-20% of all liposarcoma cases [R23-1182].

DDLPS is characterized by amplification of the mouse double minute 2 homolog (MDM2) gene. MDM2 is a negative regulator of tumor protein 53 (TP53) [P20-03237]. There are few published epidemiological studies of DDLPS with quite limited incidence and prevalence data. According to an internal BI analysis of Surveillance, Epidemiology, and End Results (SEER) registry-21, the age-adjusted incidence rate of DDLPS is 0.18 per 10,000 person-years. Incidence is higher in men than women (0.26 per 10,000 py vs 0.11 per 10,000 py) (data on file).

DDLPS is typically a high-grade tumor that metastasizes in more than 20% of cases (lungs, liver, bone, skin, or brain). The mainstay of first line (1L) therapy for advanced DDLPS remains an anthracycline-based regimen despite its moderate efficacy in this setting (objective response rate <15%; median progression-free survival: 2 to 4 months; median overall survival (OS, from initiation of 1L treatment to death or end of study): 8 to 12 months) [R21-0720]. Notably, the natural history, patient journey and treatment outcomes of this rare disease is poorly understood in Chinese patients.

Boehringer Ingelheim (BI) is currently developing BI 907828, an orally available MDM2-p53 antagonist, for treatment of DDLPS. On 22 August 2022, BI China received Clinical Trial Notification (CTN) for MDM2 DDLPS indication from China authority. In the CTN, China authority recommended BI to collect Chinese DDLPS patients' survival and other related clinical data in the real-world, to provide support for future analysis during New Drug Application. Therefore, we conduct this study to investigate the patient characteristics, current treatment patterns and outcomes in Chinese DDLPS patients.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective:
To describe the overall survival of Chinese unresectable locally advanced or metastatic DDLPS patients

Secondary objectives:
To describe the treatment patterns of Chinese DDLPS patients

Exploratory objective:
To describe demographic, clinical characteristics and treatment outcomes of Chinese DDLPS patientsTo describe the direct medical cost and healthcare resource utilization of Chinese DDLPS patients

9. RESEARCH METHODS

9.1. STUDY DESIGN

This will be a non-interventional/observational study of Chinese DDLPS patients using existing data curated by [redacted]. No Boehringer Ingelheim (BI) product will be studied, and no new interventions or procedures will be performed.
The primary outcome is overall survival (OS). Secondary outcomes include survival after initial diagnosis, and treatment patterns. Exploratory outcomes may include patient demographics, clinical characteristics, duration of treatment, time to next treatment by lines, healthcare resource utilization and direct medical cost, etc. None of the outcomes reflect safety issues.

9.2. SETTING

9.2.1. Study sites

This is a non-interventional study based on existing data. Details of data source are described in Section 9.9.4.

9.2.2. Study population

Inclusion criteria:
- Patient has two or more documented clinical visits in the National Anti-Tumor Drug Surveillance System (NATDSS) network on or after January 1, 2013.
- Patient has a confirmed diagnosis of DDLPS during his/her lifetime.
- At least 18 years old at the date of initial diagnosis

No exclusion criteria are applied.

Eligible population will be divided into two groups:

- Cohort 1 will include unresectable locally advanced or metastatic DDLPS patients who received at least one line of systemic antineoplastic treatment by the end of cohort identification period (index date = start date of 1L treatment).
- Cohort 2 will include patients with DDLPS who have not initiated 1L systemic antineoplastic treatment by the end of cohort identification period (index date = date of initial DDLPS diagnosis during cohort identification period). Patients initiated 1L treatment afterwards or patients received adjuvant and/or neoadjuvant therapy only through follow-up will be included in Cohort 2.

In both cohorts, 1L therapy will be defined as the initial set of drugs used after unresectable locally advanced or metastatic diagnosis. Metastatic patients will be defined as those with metastatic diagnosis or presence of metastatic sites; unresectable locally advanced patients will be defined as those with advanced diagnosis and without subsequent surgical resection.

9.2.3. Study visits

Definitions of relevant time periods are detailed below.

Study period: January 1, 2013 – December 31, 2022

Baseline period: All available data prior to index date

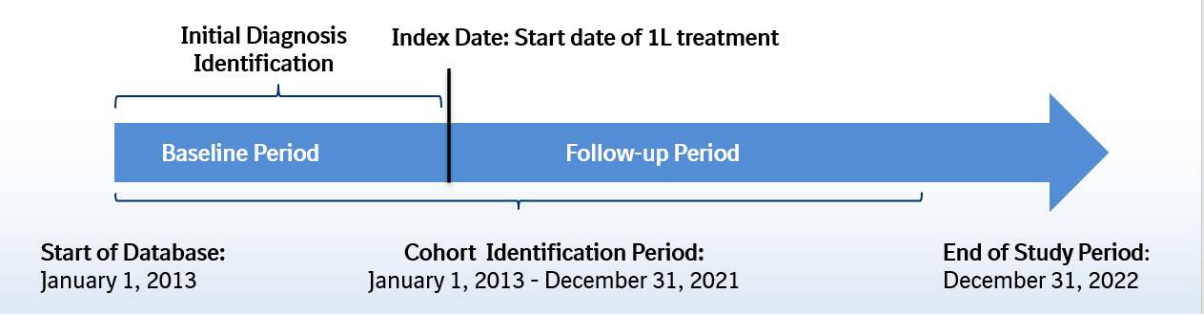
Cohort identification period: January 1, 2013 – December 31, 2021 (one year before end of study period)

Index date: The index date for Cohort 1 will set to the date of initiation of 1L treatment; the index date for Cohort 2 will be the date of initial DDLPS diagnosis during cohort identification period.

Follow-up period: From index date until date of death, if available, or the date of censoring if there is no record of death, whichever occurs first. For survival and treatment patterns, the date of censoring will be the last activity date, defined as the date of the last visit of any type prior to the end of the study period.

Figure 1 illustrates the time periods for the study timelines.

(a). Cohort 1



(b). Cohort 2

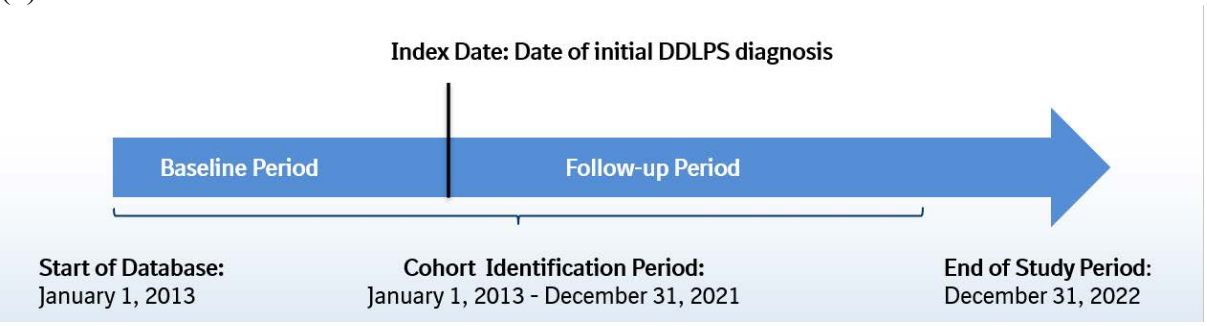


Figure 1. Overall study period

9.2.4. Study discontinuation

Not applicable.

9.3. VARIABLES

The analysis will be descriptive only, and there are no *a priori* hypotheses. There will be no prespecified exposures or covariates to be used as the basis for formal statistical testing and for *a priori* comparison of groups.

9.3.1. Outcomes

9.3.1.1. Primary outcomes

OS

- **Outcome type:** Primary
- **Outcome name:** OS
- **Time frame:** Time from index date until the earliest record of death or end of the study period
- **Population:** Cohort 1

OS as an event for each patient in Cohort 1 will be defined as the date of death minus the index date or the start day of each LOT. For patients with no record of death, OS will be censored at the last activity date before the end of the study period.

9.3.1.2. Secondary outcomes

Survival after initial diagnosis

- **Outcome type**: Secondary
- **Outcome name**: Survival after initial diagnosis
- **Time frame**: Time from initial diagnosis until the earliest record of death or end of the study period
- **Population**: Cohort 1, Cohort 2

Survival after initial diagnosis for each patient will be defined as the date of death minus the date of initial diagnosis. For patients with no record of death, survival after initial diagnosis will be censored at the last activity date before the end of the study period.

Description of treatment patterns

- **Outcome type**: Secondary
- **Outcome name**: Treatment patterns
- **Time frame**: Treatment patterns are assessed at the index date and during follow-up
- **Population**: Cohort 1, Cohort 2

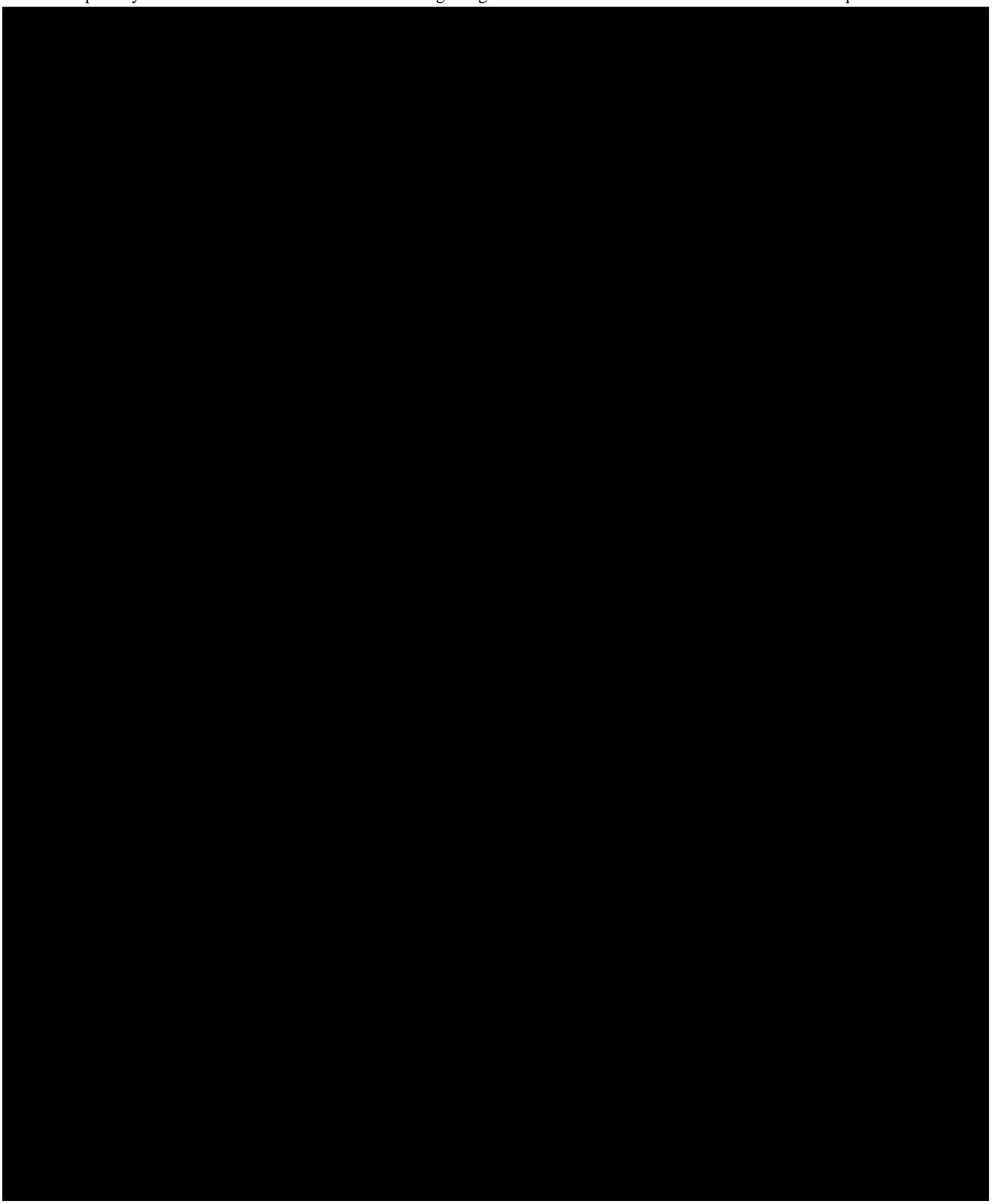
The following variables of interest will be assessed to describe treatment patterns defined by LOT and regimens.

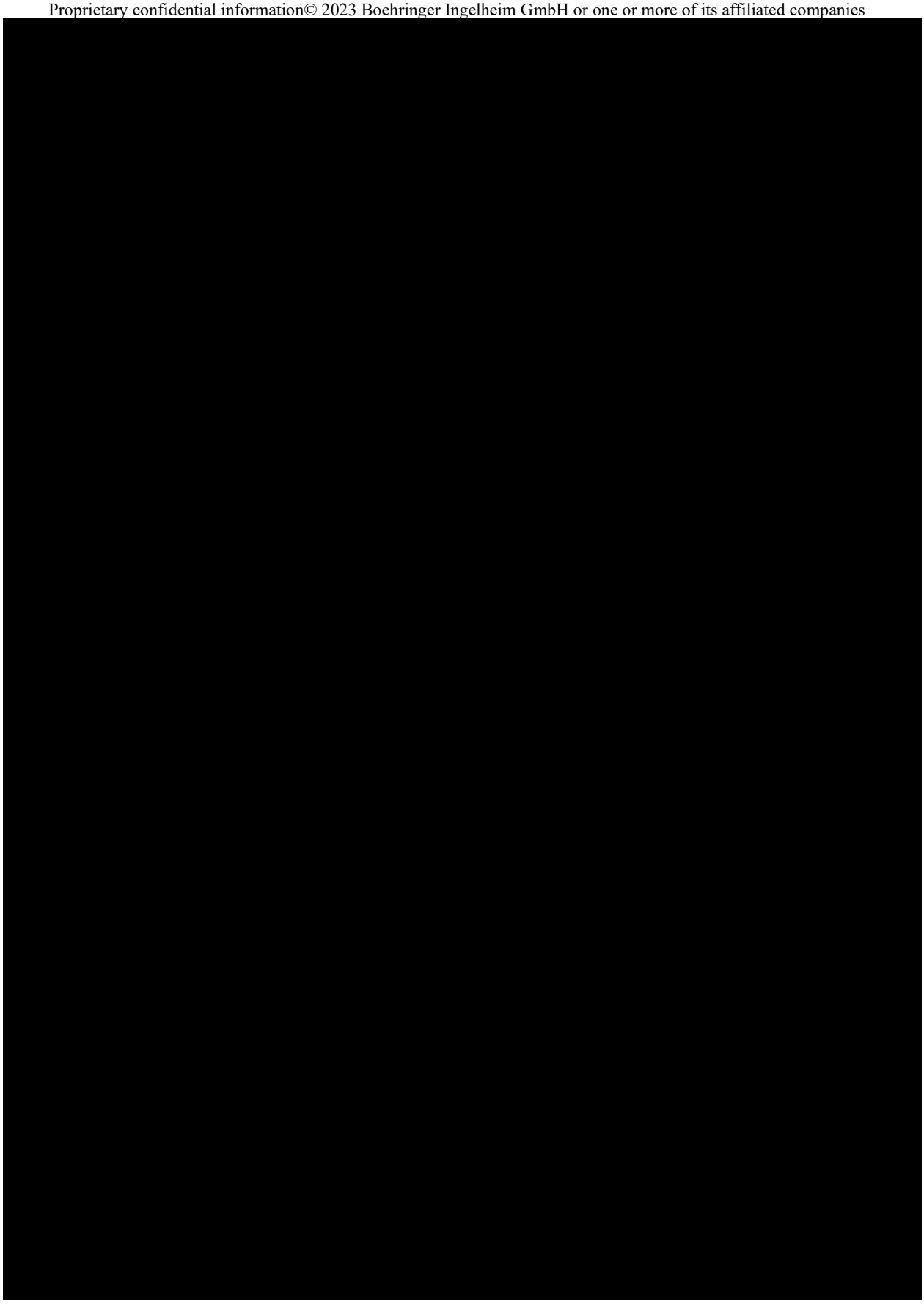
Treatment patterns by LOT and regimens

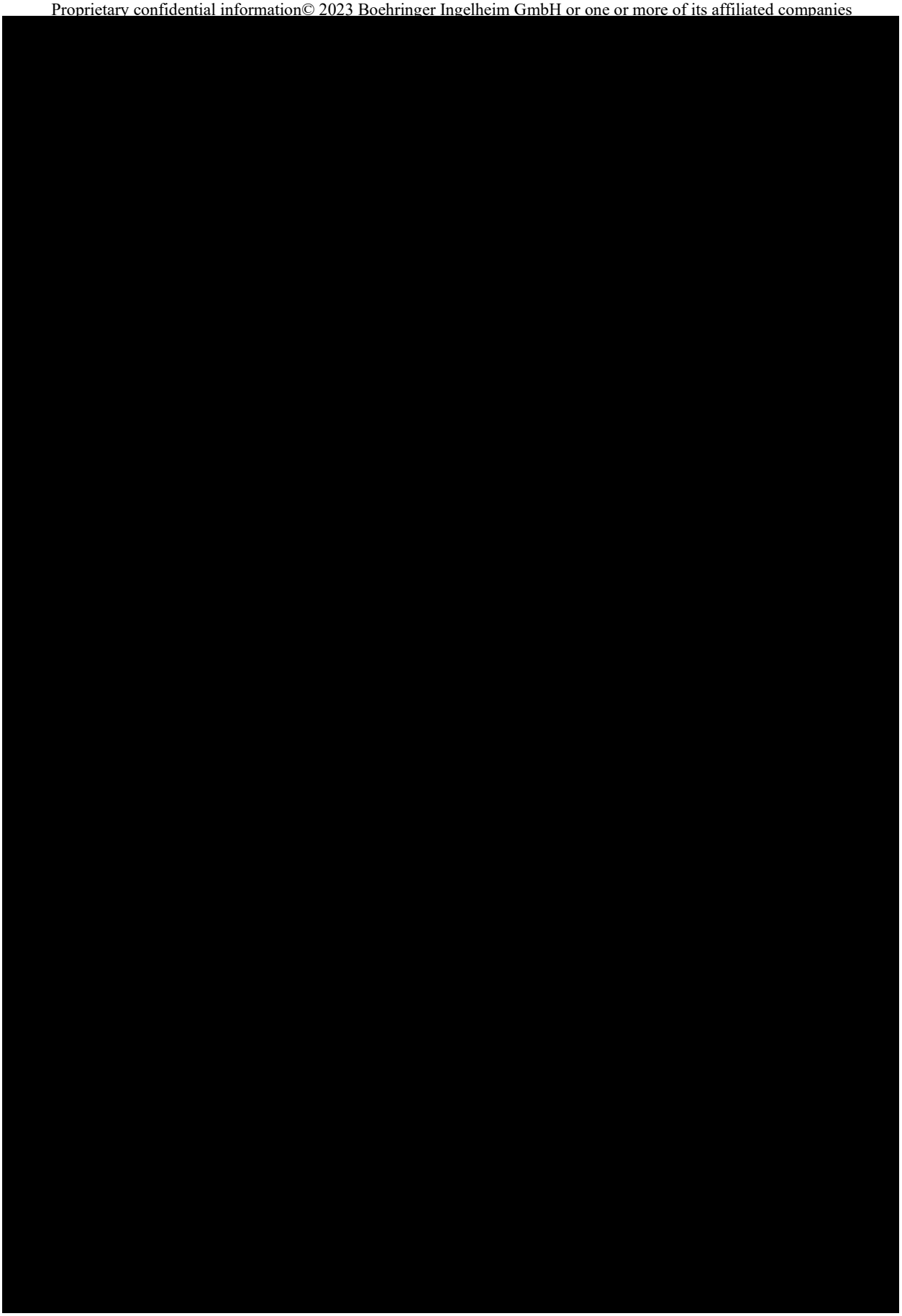
Variable	Definition	Timing
1L Treatment Type	Regimen name from LOT data for treatments with line number = 1, 2 and 3. Treatment types will be classified as follows, specific treatments and categories may change upon examination of the data: NCCN/CSCO preferred • Doxorubicin • Epirubicin • Liposomal doxorubicin • AD (doxorubicin, dacarbazine) • AIM (doxorubicin, ifosfamide, mesna) • Ifosfamide, epirubicin, mesna • Larotrectinib (NTRK fusion pos sarcomas only) • Entrectinib (NTRK fusion pos sarcomas only) • Pazopanib • Eribulin • Trabectedin Other • AD LMS only (doxorubicin, dacarbazine) • Gemcitabine and docetaxel	Any time after index date
2L Treatment Type		
3L Treatment Type		

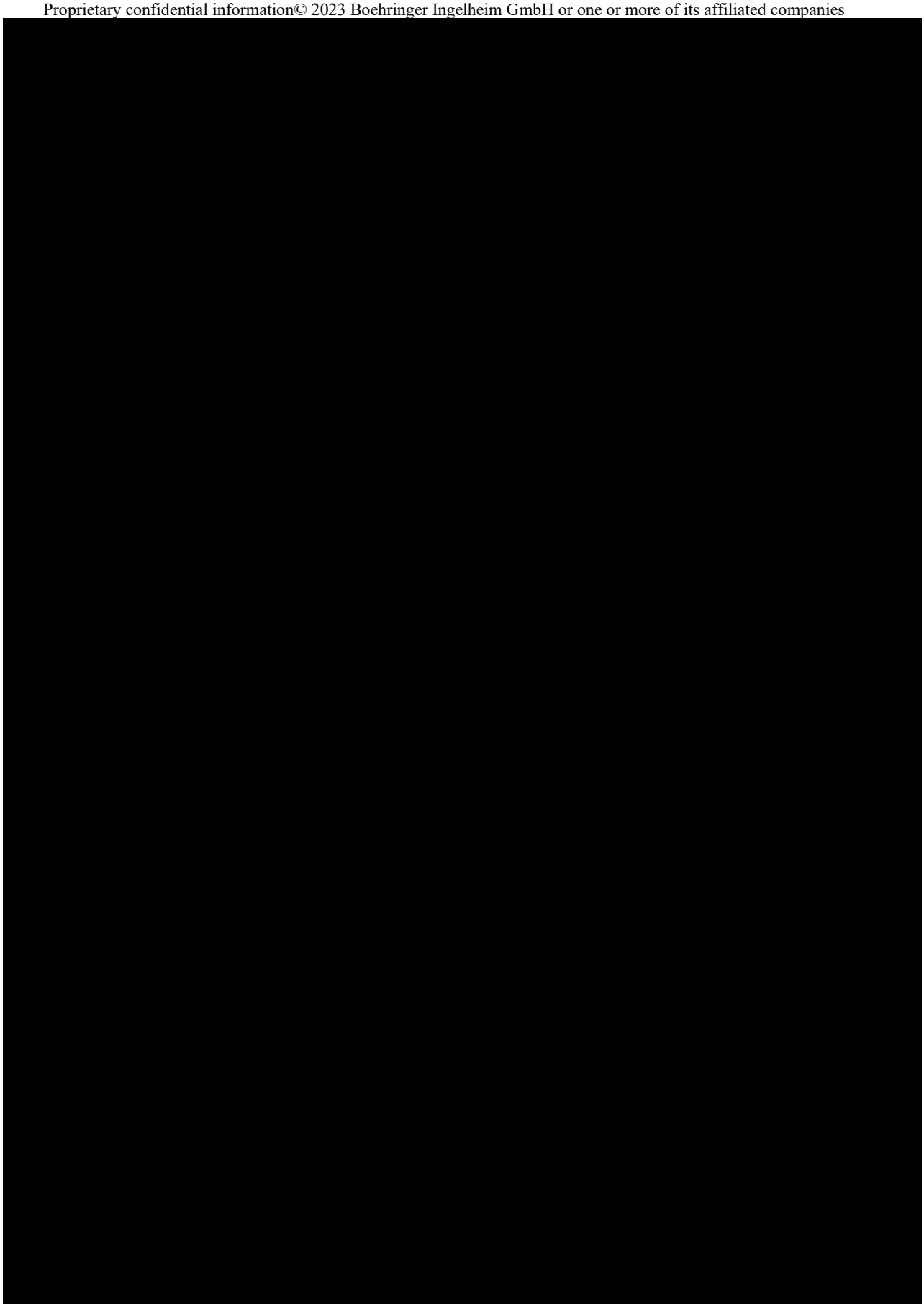
Variable	Definition	Timing
	• Gemcitabine • Gemcitabine and vinorelbine • Gemcitabine and dacarbazine • Dacarbazine • Ifosfamide • Temozolomide • Vinorelbine • Regorafenib • MAID (mesna, doxorubicin, ifosfamide, dacarbazine) • Pembrolizumab • durvalumab • Other	
Total number of treatment lines	From LOT data, for all lines after index date, categorical variable defined as total of treatment lines reported.	Any time after index date
Concurrent steroid therapy	Any record of a drug classified as a corticosteroid.	Anytime from the start to end of 1L, 2L, or 3L
Concurrent immunosuppressant therapy	Any record of a drug classified as an immunosuppressant therapy.	Anytime from the start to end of 1L, 2L, or 3L
Concurrent hormone replacement therapy	Any record of a drug classified as a hormone replacement therapy.	Anytime from the start to end of 1L, 2L, or 3L

Abbreviations: 1L = first line; 2L = second line; 3L = third line; CSCO = Chinese Society of Clinical Oncology; LOT = line of therapy; NCCN = National Comprehensive Cancer Network









9.4. DATA SOURCES

[redacted] will develop a custom, curated dataset for this study based on longitudinal electronic medical records data from the National Anti-Tumor Drug Surveillance System (NATDSS), the largest cancer registry database in China. This database, established in 2018 by China National Cancer Center (NCC), covers over 1400 hospitals across 31 provinces and over 10 million cancer patients in China. This multicenter hospital-based database consists of data of 1509 variables from 7 aspects including drug, patient basic information, inpatient, outpatient, medical technology, treatment and follow up. NATDSS is linked with National Mortality Database from Chinese Center for Disease Control and Prevention Center (China CDC) to obtain patients' death information [R23-1183].

9.5. STUDY SIZE

The patient sample was a convenience population of all eligible patients in the [redacted] database who met inclusion and exclusion criteria during the study period; no priori power analyses were conducted.

A preliminary feasibility check will be conducted to assess potential eligible sample size as below.

Criteria
Patients with at least one diagnosis of DDLPS
Patients aged 18 years old or above at initial diagnosis
Patients have two or more documented clinical visits between January 1, 2013 and December 31, 2022

We estimated the precision we can expect from the estimates of a median OS for different potential sample sizes. It is assumed that the enrollment rates follow uniform distribution in the study period and that the survival time follows exponential distribution with median OS=8, 10, and 12 months. The censor rate is approximately 20% with type I of right censoring. The 95% CI of median OS is shown in the below table under different scenarios.

N (Sample Size)	Median Overall Survival from start of 1L, Months	95% CI of Median Overall Survival
1500	8	(7.419, 8.625)
1000	8	(7.287, 8.764)
500	8	(7.011, 9.095)
300	8	(6.732, 9.435)
1500	10	(9.262, 10.784)
1000	10	(9.100, 10.972)
500	10	(8.754, 11.378)
300	10	(8.408, 11.814)
1500	12	(11.110, 12.948)
1000	12	(10.916, 13.175)
500	12	(10.491, 13.677)
300	12	(10.073, 14.198)

9.6. DATA MANAGEMENT

The data management plan is summarized below. Full details of the data management plan are documented in a separate Non-interventional Study-Data Management and Review Plan (NIS-DMRP).

For this study, BI will not have access to the original data. Data will be managed by [redacted]. Source code of data management and data analyses data will be stored for at least 15 years at [redacted].

9.7. DATA ANALYSIS

The statistical analysis plan for the study is summarized below. Full details of the statistical analysis will be documented in the Statistical and Epidemiological Analysis Plan (SEAP), which will be finalized before the end of data collection.

This study will be descriptive in nature.

It is anticipated that sample sizes for variables may vary due to unknown or missing data in the database. The number of patients with missing data for each variable will be summarized and reported. With the exception of the imputation of partial missing date values, no other imputation of missing values will be undertaken; however, the impact of missing data on interpretation of findings will be acknowledged and discussed in the final study report.

For all analyses, data for patients will be censored when lost to follow-up (i.e., still alive as of their last visit prior to end of study period).

9.7.1. Analysis of primary objectives

OS will be estimated by the Kaplan-Meier (KM) method to obtain median estimates with 95% CIs and interquartile ranges (IQRs) for Cohort 1, calculated using the log-log transformation. OS will be examined from each appropriate index date. Estimates at appropriate timepoints (dependent on the data) of the probability of remaining event free will be presented, together with a survival plot for OS. OS may be assessed by LOT and type of treatment received in each LOT, pending feasibility.

9.7.2. Analysis of secondary objectives

Survival after initial diagnosis will be estimated by the KM method to obtain median estimates with 95% CIs and interquartile ranges (IQRs) for Cohort 1 and Cohort 2.

Treatment patterns for Cohort 1 and Cohort 2 will be tabulated (See Section 9.3.1.2 for variable definitions). Continuous variables will be summarized using mean, standard deviation (SD), median, and interquartile range (IQR). Categorical variables will be summarized using counts (n) and proportions (%). The number of missing values will be reported for each variable, and percentages for categorical variables will be based on non-missing values.

9.7.3. Analysis of exploratory objectives

Patient demographic, clinical characteristics and treatment outcomes will be reported for Cohort 1 and Cohort 2 (See Section 9.3.1.3 for variable definitions). If multiple records for a variable exist during the baseline period, the record closest to index will be chosen. The number of missing values will be reported for each variable, and percentages for categorical variables will be based on non-missing values. Time from diagnosis to 1L treatment, time to next treatment and duration of treatment by LOT will be estimated using KM methods to obtain median estimates with 95% CIs and IQRs.

HCRU including number of visits and days of hospitalization will be summarized as counts (n) and proportions (%). Direct medical cost will be summarized using mean, median and IQR.

9.7.4. Subgroup analysis

The above analyses may be performed in additional subgroups for Cohort 1 and Cohort 2, pending sample size and feasibility. These include:

- Unresectable locally advanced DDLPS patients
- Metastatic DDLPS patients
- Brightline-1-like cohort including patients who received doxorubicin monotherapy or doxorubicin-based regimens as 1L treatment
- Real-world Brightline-1 cohort including patients matching the inclusion and exclusion criteria in Brightline-1 trial
- Additional subgroups, which may include age, sex, and year of initial diagnosis.

9.7.5. Sensitivity analyses

Sensitivity analyses will be conducted:

- to only include patients in areas covered by the mortality surveillance system and with higher completeness on survival data.
- to only include patients before COVID-19 emergence (cohort identification period: January 1, 2013 – December 31, 2019) to assess the possible impact of COVID-19 pandemic on treatment patterns and outcomes.

9.7.6. Safety Analysis

Not applicable.

9.8. QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the NIS-DMRP.

The study will strictly follow key elements of the Guideline for Good Pharmacoepidemiology Practices (GPP) and other relevant standard operating procedures (SOPs). The study report will be reviewed, approved and archived per BI SOP.

One Data Analyst from [redacted] will build measures (variables) for cohort inclusion and outcomes. Whenever possible, validated algorithms will be used for variables, to minimize misclassification and information bias. All measures created, cohorts developed, statistical analyses implemented, and tables output will undergo quality control review performed by at least one additional Analyst from [redacted]. Quality controls include checks for the validity and logical content of codes and checks for missing values and variables. In order to control for potential inconsistencies and errors, all variables will be tabulated. The distribution of each variable will be examined.

The NIS Lead will verify that the Data Analyst has followed methodology specified in the protocol, as well as any relevant programming SOPs and good programming practices. Documentation of key programming decisions should be evident within the program. The investigator or NIS Lead will verify that any assumptions made by the data analyst are consistent with expectations.

9.9. LIMITATIONS OF THE RESEARCH METHODS

There are several limitations of this study. Firstly, CDC mortality surveillance data may only capture 80% of the total deaths, which may result in over-estimate of the survival outcomes. We attempt to conduct sensitivity analyses in area with higher completeness on survival data. Still, results should be interpreted with caution.

Secondly, the study could be subjected to missing clinical information that is not routinely recorded by clinicians, variations in the reporting, and selection biases arise from the use of diagnostic and therapeutic codes. Under-reporting of comorbidities and of treatment received outside the oncology clinic setting may result in misclassification of treatments and outcomes.

Additionally, as this study population includes patients from tertiary or oncology hospitals in China, study results might not be generalizable to entire Chinese DDLPS patients. As oncology care remain only possible or most optimally delivered though face-to-face, patients' access to oncological services is possibly limited during COVID-19 pandemic impacts, consequently resulting in less patient diagnosis and hospital visits.

9.10. OTHER ASPECTS

9.10.1. Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence of this study.

9.10.2. Study records

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for GPP, and the relevant BI SOPs.

10.1. STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/ IEC according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Ethical approval will be obtained prior to start of data collection. The finalized protocol will be submitted to an IRB in China for review and approval.

10.2. STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Only anonymized data will be used in the study. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable based on secondary use of data without any potential that any employee of BI or agent working on behalf of BI will access individually identifiable patient data.

Based on current guidelines from the International Society for Pharmacoepidemiology and the EMA, non-interventional studies such as the one described in this study protocol, conducted using electronic claims and/or health care records, do not require expedited reporting of suspected adverse events/reactions. Specifically, as stated in section VI.C.1.2.1 of *Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products*, for non-interventional study designs, which are based on use of secondary data, reporting of adverse reactions is not required. In addition, this study does not involve BI product and no safety outcomes are included in the study. No BI employees will have access to the original data. As such, with no individual medical record review, the safety reporting is not applicable.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

At this time, this study is planned to help inform the asset program and may be used to supplement regulatory submissions. However, it is not conducted solely for regulatory approval.

13. REFERENCES

13.1. PUBLISHED REFERENCES

P20-03237 Cornillie J, Wozniak A, Li H, Gebreyohannes YK, Wellens J, Hompes D, Debiec-Rychter M, Sciot R, Schöffski P. Anti-tumor activity of the MDM2-TP53 inhibitor BI-907828 in dedifferentiated liposarcoma patient-derived xenograft models harboring MDM2 amplification. Clin Transl Oncol. 2020 Apr;22(4):546-554. doi: 10.1007/s12094-019-02158-z. Epub 2019 Jun 14. PMID: 31201607.

R22-3794 Dei Tos AP (August 2000). "Liposarcoma: new entities and evolving concepts". Ann Diagn Pathol. 4 (4): 252–66.

R23-1186 Nie L, Chen X, Gong J, Zhang M, Xu M, Chen N, Zhou Q (December 2020). "Synchronous Renal Dedifferentiated Liposarcoma and Retroperitoneal Well-Differentiated Liposarcoma: A Case Report With Literature Review". International Journal of Surgical Pathology. 29 (6): 667–671.

R23-1182 Porrino J, Al-Dasuqi K, Irshaid L, Wang A, Kani K, Haims A, Maloney E (June 2021). "Update of pediatric soft tissue tumors with review of conventional MRI appearance-part 1: tumor-like lesions, adipocytic tumors, fibroblastic and myofibroblastic tumors, and perivascular tumors". Skeletal Radiology. 51 (3): 477–504

R21-0720 Savina M, Cesne A le, Blay JY, et al. Patterns of care and outcomes of patients with METAstatic soft tissue SARComa in a real-life setting: the METASARC observational study. BMC Med 2017; 15; 78

R23-1183 Hongmei Zeng, Yunning Liu, Lijun Wang, Peng Yin, Baohua Wang, Ruiying Fu, Xianhui Ran, Rongshou Zheng, Siwei Zhang, Jiangmei Liu, Jinling You, Kexin Sun, Shaoming Wang, Li Li, Ru Chen, Wenqiang Wei, Maigeng Zhou, Jing Wu, Jie He. National Cancer Data Linkage Platform of China: Design, Methods, and Application[J]. China CDC Weekly, 2022, 4(13): 271-275. doi: 10.46234/ccdcw2022.068

R14-4775 Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11):1130-1139.

13.2. UNPUBLISHED REFERENCES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Demographic, clinical characteristics, and treatment outcomes associated with dedifferentiated liposarcoma patients in China

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2,9.7.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.1, 9.3

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	9.3.1

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				9.2
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.3.1

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.4

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				9.3
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	
9.1.3 Covariates and other characteristics?	☒	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				9.4
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2, 9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Annex 1

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date:

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Charlson Comorbidity Index		
Condition	**ICD-9**	**ICD-10**
Myocardial infarction	410.x, 412.x	I21.x, I22.x, I25.2
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 47.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9

Cerebrovascular disease	362.34, 430.x–438.x	G45.x, G46.x, H34.0, I60.x–I69.x
Dementia	290.x, 294.1, 331.2	F01.x–F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Rheumatic disease	446.5, 710.0–710.4, 714.0–714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	531.x–534.x	K25.x–K28.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complication	250.0–250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9
Diabetes with chronic complication	250.4–250.7	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7
Hemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0–344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Any malignancy	140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.xx, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x
Moderate or severe liver disease	456.0–456.2, 572.2–572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumor	197.x–198.x	C78.xx, C79.xx, C7B.xx
AIDS/HIV	042.x–044.x	B20.x

Abbreviations: AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	**Local NIS**
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Local Medical Director	X (if local study)		X
Local Head MAcc / HEOR Director	X (if local study)		X
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs / Market Access*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X
Local Head MA/Clinical Development			X (does not apply to NISed without chart abstraction)

** After review by Global TM for function*

Study Title: Demographic, clinical characteristics, and treatment outcomes associated with dedifferentiated liposarcoma patients in China

Study Number: 1403.0024

Protocol Version: 1.0

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.
Note: Please insert respective signatories with regard to the SOP.

Position: _____ Name/Date: < /dd mmm yyyy> Signature: _____

Position: _____ Name/Date: < / dd mmm yyyy> Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____