14 Reporting of Serious Adverse Events, Adverse Events of Clinical Interests and Pregnancy

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

14.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

ADR: An **Adverse Drug Reaction of an investigational medicinal product** is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction.
  Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

AECI: The following **Adverse Events of Clinical Interest** should be reported as a SAE **in an expedited way on a SAE form**:

The following adverse events are considered as Adverse events of clinical interest.

- Grade 3-4 peripheral neuropathy
- Progressive multifocal leukoencenphalopathy (PML)
- Grade 3-4 pulmonary AEs
- Grade 3-4 Cardiac AEs
- Secondary malignancies

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the timeframes specified by national legislations.

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

New primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

14.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital

- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

14.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v5.0 https://www.eortc.be/services/doc/ctc/.

14.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	Description
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.
The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

14.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following reference documents:

- For Brentuximab vedotin: Investigator's brochure (IB)
- For Adriamycin: Summary of Product Characteristics (SmPC)
- For Cyclophosphamide: Summary of Product Characteristics (SmPC).
- For Dacarbazine: Summary of Product Characteristics (SmPC).
- For Dexamethasone: Summary of Product Characteristics (SmPC).
- For Etoposide: Summary of Product Characteristics (SmPC).
- For Vinblastine: Summary of Product Characteristics (SmPC).
- For Radiotherapy: Safety information related to radiotherapy is compared to known complications of radiotherapy (depending or area irradiated). Anticipated adverse events related to radiotherapy are described in section 7.2.2.2)

14.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) and Adverse Events of Clinical Interest (AECIs) occurring from the time a subject is registered until 5 years after last protocol treatment administration and to any SAE that occurs outside of the SAE detection period (after the 6 months detection period), if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

Registration till 30 days after last protocol treatment administration:	All SAEs/AECIs
Any time after the 30 days period after the last protocol treatment administration (especially for bv):	Only SARs

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE/AECI data must be collected on the study-specific SAE form.

All SAEs/AECIs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE forms must be sent to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027 or Email: Pharmacovigilance@eortc.org

To enable the Sponsor to comply with regulatory reporting requirements, all initial reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the SAE causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).

14.7 Reporting responsibilities for EORTC

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at the Pharmaceutical Company.

- The EORTC Pharmacovigilance Unit will report all SAEs in English (including pregnancies and suspected pregnancies) to Takeda Pharmaceuticals (or designee) regardless of expectedness or causality within 24 hours of the Sponsor's awareness of the event(s) from the first dose until 30 days after the last dose of BrAVD or BrECADD, as per any Agreements. Any SAE that occurs at any time during the study or after completion of brentuximab vedotin treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Takeda Pharmacovigilance (or designee) per any agreement. All new cases of primary malignancy must be reported to Takeda Pharmacovigilance (or designee) per any agreement.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the Newsletter and which will be accessible to all participating investigators.

The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs/unexpected events to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all participating investigators whenever applicable.

14.8 Adverse Events of Clinical Interest

The following adverse events of clinical interest should be reported on a SAE-form by following the procedure described in the paragraph 14.6:

- Grade 3-4 peripheral neuropathy
- Progressive multifocal leukoencenphalopathy (PML)
- Grade 3-4 pulmonary AEs
- Grade 3-4 Cardiac AEs
- Secondary malignancies

14.9 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or until 6 months after last protocol treatment administration must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax/Email, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter

14.10 Products complaints or medication errors (including overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda Pharmacovigilance or designee (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate CRF form. Individuals who identify a potential medication error situation should immediately contact Takeda and report the event.

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed.

For Product Complaints or Medication Errors: E-mail: Cco.smbx.dk-ComplaintDK@takeda.com

15 Quality assurance

15.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

15.2 On-site quality control

The EORTC Headquarters or delegates will perform on-site quality control visits.

The first visit in a participating site will be performed within 3 months after the first patient's registration at this site. Frequency and number of subsequent visits will depend on site's accrual and quality observed during the first visit.

Overall, the frequency of site visits will be around one visit a year per recruiting site.

The aim of these site visits will be:

- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of data reported on the case report forms with the source data
- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled

7.2 Evaluation of safety

7.2.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

The collection period will start from registration. All adverse events must be followed until resolution or stabilization.

7.2.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page https://www.eortc.be/services/doc/ctc/

Planned safety analysis and tabulations are described in the statistics section.

7.2.2.1 Chemotherapy regimens

- Cardiac dysfunction
- Fertility
- Secondary malignancy

7.2.2.2 Expected side effects of radiotherapy

Any observations regarding radiation reactions will be recorded according to Criteria for Adverse Events version 5.0 (CTCAE) (see Appendix E).

7.2.2.2.1 Acute toxicity

Acute toxicity is defined as toxicity within 90 days after end of radiotherapy. Most frequently expected acute toxicity (highly depending on the area irradiated):

- Dysphagia
- Nausea
- Abdominal discomfort and other lower GI symptoms
- Bone marrow toxicity
- Radiation pneumonitis
- Skin reaction

7.2.2.2.2 Late toxicity

Late toxicity is defined as toxicity after 90 days after end of radiotherapy. Most relevant RT-related late toxicities

- Second malignancies
- Cardiovascular diseases (coronary heart disease, valvular disease, heart failure, conduction abnormalities)
- Hypothyroidism (in case of RT of the neck)
- Muscular atrophy
- Pulmonary fibrosis
- Functional asplenia (in case of RT of the spleen).

Risks of second malignancies and cardiovascular diseases have been shown to be dose and volume related.

7.2.3 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter 14, Reporting Serious Adverse Events)

7.2.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as unrelated). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

7.2.5 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.