Title	SOP 04–AE registration
Document type	SOP
Version N.	3.1
Date	February 20th 2020

	NAME	DATE
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REVIEWED BY	Site PIs	
APPROVED BY	Site PIs	
PURPOSE: To outline the process for adverse events registration in the G-DEFINER study.		

Abbreviations

Acronym	Description
AE	Adverse event
CI	Clinical investigator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data Capture Forms
DCU- SVUH	Dublin City University, Dublin -St Vincent's University Hospital, Ireland
DM	Data Manager
eCRF	Electronic Case Report Form
G-DEFINER	Gender Difference in sidEeFfects of ImmuNotherapy: a possible clue to optimize cancErtReatment
GDPR	General Data Protection Regulation
ICI	Immune Checkpoint Inhibitors
IEC	Institutional Ethics Committee
INT	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
irAE	Immune-related adverse event
Onk-Pat KI	Dept of Oncology-Pathology, Karolinska University Hospital, Sweden
OUH	Oslo University Hospital – The Radium Hospital, Norway
PI	Principal investigator
SAE	Serious adverse event
SOP	Standard Operating Procedure

Related documents:

Document type	Title
Protocol	Protocol-G Definer-ENG
FORM	CRF 03 - Immune Related Adverse Event Log

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1. Scope and applicability

The purpose of this Standard Operating Procedure (SOP) is to outline the procedures for assessing and registering the immune-related adverse events (irAEs), which are the main outcomes of the G-DEFINER study. This SOP does not describe the procedure for irAEs management.
In general, all the adverse events even unrelated with ICI treatment must be assessed, registered and managed according to the local laws and regulations, procedures and protocols in use.

2. Glossary/definitions

Adverse event
Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Immune-related adverse event
Unique set of adverse effects that may occur during treatment with ICI.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

3. Responsibilities

This SOP applies to all members of the clinical research team of the G-DEFINER study involved in patients management.

4. Procedure

4.1 Instructions to participants

- At the beginning of the study the participants enrolled in the G-DEFINER study must be instructed to contact the reference oncologist if they experience any untoward event, even outside the scheduled oncologic visits.

4.2 irAE causality assessment

- Before registering the irAE, perform a clinical assessment of whether the adverse event is likely to be related to the ICI.
- Clinical judgment should be used to determine the causal relationship, using all information available and considering all relevant factors, including medical history, confounding factors such as concomitant diseases, concomitant treatments, lack of efficacy, worsening of conditions, pattern of reaction, temporal relationship, de-challenge or re-challenge.
- Arguments that may suggest a reasonable causal relationship could be:
    - The event is consistent with what is known about irAEs.
    - The event is known to be caused by or attributed to ICI.
    - A plausible time to onset of the event relative to the time of ICI exposure.
    - Evidence that the event is reproducible when ICI is re-introduced.

4.3irAE to record

- All types of irAEsmust be recorded where possible.
- irAEs should be reported until the study end. These will only be the irAEs found in records as patient will not be contacted as per the PIL section 5 'no additional data will be requested directly from you'.

4.4irAE assessment

- During oncologic visit.
    - The PI/CI or delegated study team member will conduct a review of all adverse events since the last visit and subsequently grade and assign causality. This process will be captured in the patients medical file.
    - There will be a review of results of clinical measurements, laboratory investigations and any other relevant investigations to determine if an irAE has occurred.
    - Refer to paragraph 4.2 for irAE causality assessment.
- Outside oncologic visits.
  Should the study participant contact the reference oncologist at occurrence of any untoward event, the CI should assess irAEs by:
    - Review of all reported information from the study participant and relevant sources to determine if an irAE has occurred.
    - Schedule of an oncologic visit to perform any relevant investigations such as clinical measurements, laboratory investigations or others as deemed necessary to determine if an irAE has occurred. Study samples may also be taken at this visit as per SOP 3 if applicable
    - Refer to paragraph 4.2 for irAE causality assessment.

4.5irAE reporting

- Data collection. . The "CRF 03 - Immune Related Adverse Event Log" may be used to capture irAEs, start/stop date, grade, frequency, treatment required, casualty and action taken with the study medication.
- Electronic registration. The irAE data must be later registered in the study database. The database is structured so as to facilitate the registration of all needed information (e.g.it includes the list of irAEs).

4.5.1ICI treatment ongoing

- Register whether ICI treatment is ongoing or not at theirAE occurrence.
- If ICI is not ongoing, the interruption cause must be specified, together with the date of of last infusion..

4.5.2 irAE type

- A list of the commonly observed irAEs is reported the protocol "ANNEX 04 - irAE List -0.1-30.05.2019"
- Additional events can be added to the list (under heading "other").

4.5.3 irAE grade assessment

The clinical grade of irAEs must be assessed by using the CTCAE Guidelines grading system version 5.0.

- **Grade 1 (mild)** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Grade 2 (moderate)** minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL);
- **Grade 3 (severe)** severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling limiting self care ADL;
- **Grade 4 (life threatening)** life threatening consequences; urgent intervention indicated;
- **Grade 5 (fatal)** Death (loss of life) as a result of an adverse event.

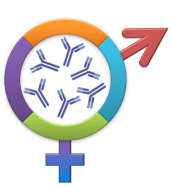
Usually, the following hospitalizations are not considered SAE:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reasons)
- Admission for administration of subsequent anti-cancer therapy in the absence of any other AE.

4.5.4 Other information

Additional information to be captured and entered on eCRF AE log:

- Start/stop date or ongoing
- CTCAE v5.0 grade
- frequency
- Causalty
- Treatment required
- Action taken

Title	  SOP 04–AE registration
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5. Dissemination

The SOP will be disseminated according to the G-DEFINER "SOP 01 - Development, Approval and Review documents", and the PI at each site will ensure implementation of the SOP.

6. References

- Directive 2001/20/EC & 2005/28/EC.
  DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001. Official Journal of the European Communities.http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf
- ICH/GCP Guidelines (http://www.ich.org/)
- GDPR EU 2016/679
- Good Clinical Practice (GCP)

7. Document history

Version No.	Date	Reviewer	Details of changes
0.1	May 28th 2019	RM	First draft
1.0	July 17th 2019	RM	First revision
2.0	August 16th 2019	Naoise Kelly	Substantial revision
3.0	October 7th 2019	RM	Accepted version 2.0 with modifications
3.1	February 20th 2020	RM	Sections modified: 4.3 (speciied that the irAEs after the study end will only be the irAEs found in records as patient will not be contacted as per the PIL section 5 'no additional data will be requested directly from you) 4.5 and 4.5.4 .