

Initial project duration – 32 months – starting from the 2 March 2019, extended to 28 February 2023 due to COVID-related extension of 12 months

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## Clinical Oncology, Biology, Biostatistics, Bioinformatics

### Overview

In patients who are suffering from cancer, the increasing use of immunotherapeutic treatments is associated with immune-related adverse events (irAEs), which are caused by non-specific activation of the immune system. Sex influences a patient's adaptive immunity, and may influence the type of irAE, as well the frequency and severity of these events. Together with genetic and biological differences, the roots of irAE inequalities between female and male patients could also be linked to psycho-social and behavioural determinants.

The G-DEFINER study examines the interdependent dimensions of gender and explores psychosocial and behavioural determinants, such as: marital status, ethnicity, employment status, level of education, living arrangement, income, smoking, alcohol consumption, levels of physical activity, obesity and dietary habits. Further the G-DEFINER study also aims to determine how distress and health status can play a role in irAE events. Lastly the study is collecting biological biospecimens from patients in order to study gene-expression, genetic variations and the patient's microbiome as predictors of irAEs.

### Progress to date

The G-DEFINER Consortium has delivered the clinical study protocol, the case report forms (CRFs), and the Standard Operating Procedures (SOPs). Further the study leads have established a standard set of irAEs that will be recorded. The G-DEFINER consortium has developed an online portal which enables G-DEFINER members to register all the clinical data related to the patient's disease, treatment, and outcomes, together with the gender-related data. The portal and the relevant data is required to achieve the Project results. All these documents provide a framework which enables us to record data to progress the study.

G-DEFINER is a prospective clinical study which recruits patients who are undergoing immunotherapy treatment. Besides the clinical, psychosocial and behavioural data being collected, the study protocol also allows us to obtain biospecimens (blood and stool samples) from patients prior to treatment, during treatment and if a patient develops serious irAEs. The biospecimens are being collected and stored and the extracted DNA and RNA will be used to perform gene-expression, SNP analysis and microbiota analyses to identify the features associated with irAEs development. The results of a preliminary analysis including data on the first 106 patients was presented at the ESMO Congress 2021. At October 2021 a total of 145 patients have been recruited.

### Impact of COVID-19

The recruitment of patient is critical to the success of the G-DEFINER project. The pandemic directly impacted the G-Definer group with members of the team contracting the illness and dealing with the impact of the condition physically and mentally. The impact of COVID on the treatment of patients with cancer has also directly affected patient enrolment. As a result the COVID pandemic significantly delayed all the clinical activities related to G-DEFINER.

### Team members

	Woman	Man	Other
<b>Gender balance in the whole consortium</b>	17 (68%)	8 (32%)	0 (0%)
<b>Presence of women as lead researchers/PIs</b>	3 (75%)	1 (25%)	0 (0%)
<b>Gender Experts in the team</b>	1 (100%)	0 (0%)	0 (0%)
<b>Subsequent team members trained</b>	1 (100%)	0 (0%)	0 (0%)

## **Contribution to the achievement of UN Sustainable Development Goals (SDGs)**

One of the goals of the new global Sustainable Development is to ensure there is equitable and universal access to health care and social protection. It is well known that response to therapies or the occurrence of adverse events differs depending on a patient's gender. Some physiological parameters are different in men and women and affect the absorption and elimination of drugs, and can impact their mechanism of action. Despite these differences, all medical practice today codified by Evidence Based Medicine and by Guidelines is based on evidence obtained from large trials conducted mainly on male patients. Thus, biomedical knowledge and practices are not gender neutral and hence equitable.

The G-DEFINER project falls under the umbrella of “gender medicine” (which, according to the WHO indication, is defined as the study of the influence of biological (defined by sex) and socio-economic and cultural (defined by gender) differences on the state of health and disease of each person), and can contribute to the achievement of equitable medical treatment.

The results of the G-DEFINER study can contribute to understanding the mechanisms associated with the differences in the incidence of immune-related adverse events in female and male cancer patients treated with immunotherapeutic agents. The results we generate could identify personalised immunotherapy treatments for patients for instance adjusting the dosage of drugs according to the individual risk of developing immune related adverse events.

## **Differences/inequalities between women and men highlighted by the project**

G-DEFINER aims is to compare the incidence of immune-related adverse events in female and male cancer patients treated with immunotherapy agents. Further we aim study the clinical and biological factors associated to the development of immune-related adverse events. We anticipate that G-DEFINER will identify outcome differences based on gender, but not any differences in respect to treatment administration.

Our initial analysis supports our hypothesis where there is a prevalence of men recruited to the clinical study. However this finding is related to the tumour type, as the majority of patients recruited are those presenting with lung or head and neck tumours.

## **Positive impact of the project on gender equality/scientific evidence on gender in the field**

G-DEFINER is expected to impact on scientific knowledge and on sex and gender inequalities in the field of oncology, by highlighting whether sex and gender differences exist in the occurrence of immune-related adverse events. This, in turn, will have a positive impact on management of patients who will undergo treatment with immunotherapeutic agents. Thus improving clinical practice and decision making in relation to the individualised treatment where consideration is given to anticipated toxicity profiles.

## **Socio-economic impact; involvement of policy makers/civil society**

Towards completion of our project we will engage with pharmaceutical companies and stakeholders to discuss how future clinical trials can utilise our results. The Project has attracted interest from WECAN (<https://wecanadvocate.eu/>), an informal network of leaders of cancer patient umbrella organisations active in Europe, which has invited the project PI to present G-DEFINER at “WECAN Science 2020” (WECAN Academy, Bruxelles, January 25th 2020).