

## SEX DIFFERENCES IN INCIDENCE OF IMMUNE RELATED ADVERSE EVENTS BY CHECKPOINT INHIBITORS IN CANCER – RESULTS FROM THE G-DEFINER TRIAL

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**Background:** Treatment with immune checkpoint inhibitors (ICIs) for cancer, including cutaneous melanoma (CM), may cause immune related adverse events (irAEs) of different severity grade. The mechanisms that drive the development of irAEs are multi-factorial but biological sex has been proposed to be one factor. Biological sex influence the innate and adaptive immune responses. This could lead to risk differences of irAEs between men and women. The Gender Difference in side effects of Immunotherapy: a possible clue to optimize cancer treatment (G-DEFINER) trial is a multicenter international observational trial aiming to investigate sex- and gender differences in irAEs caused by ICIs for melanoma and other cancers.

**Materials and Methods:** Patients with metastatic CM and other cancers treated with ICIs or combinations thereof were recruited between 1st of February 2019 until 28th of February 2023. Individual clinical, treatment, socioeconomic and Quality of Life data were recorded. Here we have described and analyzed differences in type, burden and incidence of irAEs.

**Results:** In total 250 patients were included in the analysis. Females had a significantly higher incidence of irAEs as compared to male. In the univariable analysis the HR was 1.31 (95% CI: 0.93-1.83; p=0.120) and the sHR increased to 1.44 (1.02-2.03; p=0.040) after adjustments for age, number of comorbidities, cancer type, tumor stage, ICI type, therapy setting, and chemotherapy administration. In patients treated with anti-CTLA4 and anti-PD-1, the irAE incidence was higher and the events occurred in the first 3 months, while in patients treated with PD-1/PD-L1 the events are continuously occurring during the time. Specifically, 74 melanoma patients were analyzed. At a median follow-up of 10.20 months, 45 patients developed  $\geq$ G2 irAEs corresponding to a 6-month incidence (95% confidence interval):

51.5% (40.8-65.0%), 12-month incidence 65.7% (54.7-78.9%) without any significant differences between F and M. GI and endocrine irAEs were most frequent. The irAE burden was found to be higher in CM patients than in patients of other tumor types (median: 6 vs 4; Kruskal-Wallis test  $p=0.0005$ ).

**Conclusion:** We found significantly higher incidence of irAEs in women than in men. We also found that patients treated with ICI because of CM had higher irAE burden than other patient groups. Further studies also within the G-DEFINER trial examining potential sex differences are of value in the long-term goal towards patient oriented treatment options and an overall patient centered health care.