Immunoprofiling of Mismatch Repair-deficient (MMRd) Endometrial Cancer (EC) patients: Immune Checkpoint Inhibitor (ICI) – Responders (R) versus Non-Responders (NR)

Juan Francisco Grau Béjar[1,2], Elisa Yaniz Galende[1], Catherine Genestie[4], Jean-Yves Scoazec[4,5], Elodie Edmond[5], Audrey Le Formal[1], Felix Blanc-Durand[1,3], Judith Michels[3], Maria Kfoury[3], Philippe Morice[3], Patricia Pautier[3], Emeline Colomba[3], Alexandra Leary[1,3]

1.Gynecological Cancer Translational Research Laboratory, INSERM U981, Institut Gustave Roussy, Villejuif, France; 2.Gynecological Cancer Program, Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. 3.Gynecological Cancer Unit, Institut Gustave Roussy; 4..Pathology Department, Institut Gustave Roussy; 5.Experimental and Translational Pathology Platform (PETRA), AMMICa Inserm US23/UAR CNRS 3655, Gustave Roussy Cancer Campus.

Background & Objectives

- MMRd status is a robust predictive biomarker for ICI in EC, however half of MMRd EC pts do not respond (*Oaknin et al, 2020; Makker et al, 2022; O'Malley et al, 2022*)
- We aim to describe the immune tumor microenvironment (iTME) of Responders (R) versus Non-Responders (NR) MMRd EC pts to identify new predictive biomarkers for ICI beyond MMR or TMB status

Methods

- Clinical data and outcomes of metastatic MMRd EC patients, treated with ICI at Gustave Roussy Institute (2016-2021), were retrospectively collected
- Pts were classified as ICI-R (CR, PR, or SD ≥12 months) and NR (PD or SD <12 months).
- Immunofluorescence (IF) and Immunohistochemistry (IHC) panels were performed for CK, CD3, CD4, CD8, CD20,CD57, FOXP3 and CD23 (quantified by number of + cells or semi-quantitative scoring).
- Non-parametric statistical tests were performed.

Results

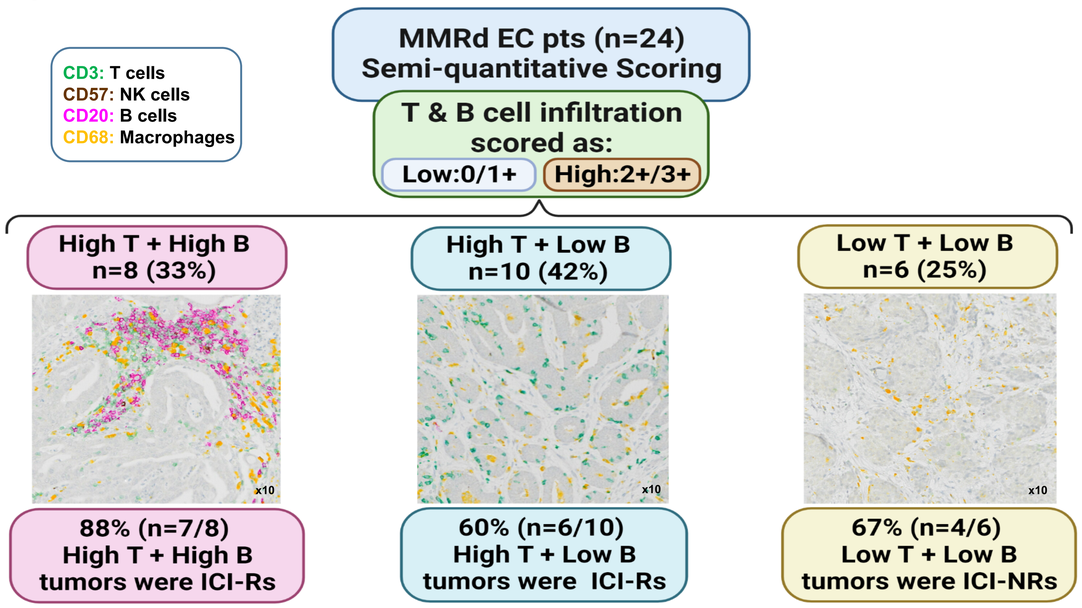
Table 1. Study Population (n=24). Clinicopathological features.

	ICI-Responders n=15	ICI Non-Responders n=9
Age (mean;years)	61	59
Histology (Endometrioid/others*)	73%/27%	89%/11%
Histopathologic grade (1-2/3)	80%/20%	78%/22%
Lynch syndrome (LS)/ Sporadic EC	27%/73%	11%/89%
Prior lines for advanced/recurrent disease (median;range)	1 (0-2)	1 (1-2)

*Serous, clear cell and mixed carcinoma;

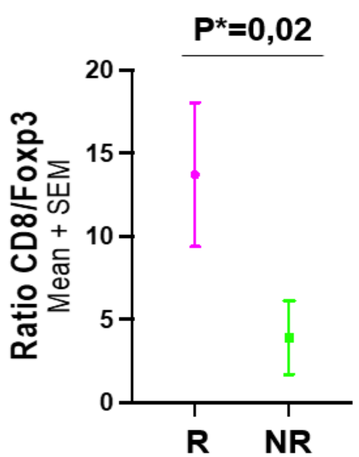
Acknowledgments:
This study has been funded by the Comprehensive Program of Cancer Immunotherapy & Immunology I (CAIMI-I) supported by the BBVA Foundation (grant 89/2017) and the Program Parrainage pour la Recherche contre les Cancers Gynécologiques- IGR.

Figure A. Immune profiles of MMRd EC



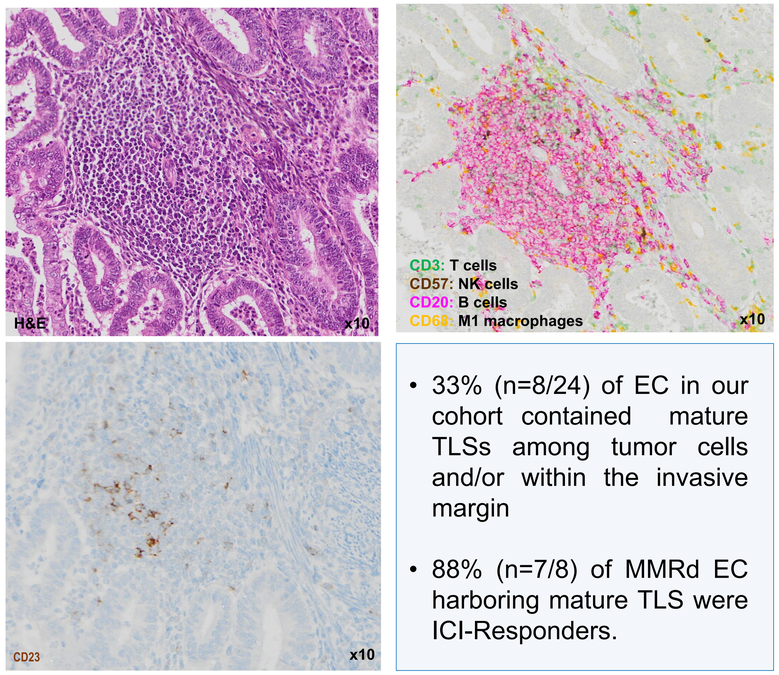
- As expected, 75% of MMRd EC demonstrated high intratumoral T cell infiltration.
- High T cell infiltration alone may be not sufficient to predict response to ICI, as a proportion of High T cell infiltrated EC are Non-Responders.
- Combined T and B cell infiltration was most associated with response to ICI in MMRd EC

Figure C. Lymphocyte subpopulations analysis



- Automated image analysis confirmed that T or B cell infiltration separately did not predict response (data not shown)
- However, the ratio of effector to suppressor T cells (CD8+/FOXP3+) significantly predicted response to ICI in MMRd EC

Figure B. Tertiary Lymphoid Structures (TLS) analysis. Mature TLSs (mTLS) were defined by the presence of CD23+ follicular dendritic cells. **View of H&E, Multiplexed Chromogenic and CD23 IHC panels**



- 33% (n=8/24) of EC in our cohort contained mature TLSs among tumor cells and/or within the invasive margin
- 88% (n=7/8) of MMRd EC harboring mature TLS were ICI-Responders.

Conclusions

- **Lynch Syndrome was associated with response to ICI: 80% (n=4/5) of LS pts were ICI-Responders.**
- **T cell infiltration is frequent in MMRd EC but may be not sufficient on its own to predict response to ICI.**
- **<u>Immunological features</u> strongly associated with <u>response to ICI in MMRd EC</u> were:**
  - **Combined High T and B cells infiltration,**
  - **The presence of mature TLS, and**
  - **High CD8/Foxp3 Ratio**

Contact: Juanfrancisco.GRAU-BEJAR@gustaveroussy.fr

FPN:550P

The authors have no COIs to declare regarding the present study