MSI status plus Immunoscore to select metastatic colorectal cancer patients for immunotherapies

J. Galon[1], B. Mlecnik[1,2], F. Hermitte[3], F. Marliot[1,4], C. Bifulco[5], A. Lugli[6], I.D. Nagtegaal[7], A. Hartmann[8], M. van den Eynde[9], M. Roehrl[10], P. Ohashi[11], E. Zavadova[12], T. Torigoe[13], P.Patel[14], Y. Wang[15], Y. Kawakami[16], F.M. Marincola[17], P.A. Ascierto[18], B. Fox[19], F. Pagès[1,4]

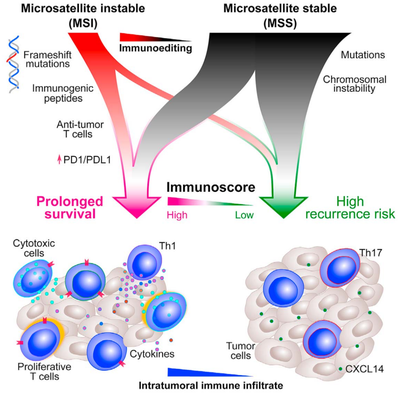
1- INSERM, Laboratory of Integrative Cancer Immunology, Sorbonne Université, Sorbonne Paris Cité, Université Paris Descartes, Université Paris Diderot; Centre de Recherche des Cordeliers, Paris, FR | 2 –Inovarion, Paris, FR | 3- R&D, HalioDx, Marseille, FR | 4- Laboratory of Immunology, AP-HP, Georges Pompidou European Hospital, Paris, FR | 5- Department of Pathology, Providence Portland Medical Center, Portland, OR, US | 6- Institute of Pathology, University of Bern, Bern, CH | 7- Pathology, Radboud University Medical Centre Nijmegen, Nijmegen, NL | 8- Department of Surgery, University Erlangen-Nürnberg, Erlangen, DE | 9- Department of Medical Oncology, Cliniques Universitaires St. Luc, Brussels, BE | 10- Department of Pathology, Memorial Sloan Kettering Cancer Center, New-York, AL, US | 11- Princess Margaret Cancer Centre, University Health Network, Toronto, ON, CA | 12- Pathology, General Faculty Hospital, VFN Charles University, Prague, CZ| 13- Department of Pathology, Sapporo Medical University School of Medicine, Sapporo, JP | 14- Cancer Biology, The Gujarat Cancer & Research Institute, Ahmedabad, IN | 15- Institute for Cancer Research, School of Basic Medical Science, Department of Pathology of the First Affiliated Hospital, Health Science Center of Xi'an Jiaotong University, Xian,CN | 16- Division of Cellular Signaling, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, JP | 17- Immune oncology discovery, AbbVie Inc., Redwood City, CA, US | 18- Melanoma, Cancer Immunotherapy and Innovative Therapy Unit, Istituto Nazionale Tumori - I.R.C.C.S - Fondazione Pascale, Napoli, IT | 19- Laboratory of Molecular and Tumor Immunology, Earle A. Chiles Research Institute at the Robert W. Franz Cancer Center, Portland, US.

Copies of this poster obtained through QR (Quick Response) are for personal use only and may not be reproduced without written permission of the authors

Introduction

Only a fraction of patients with metastatic disease respond to immune checkpoint inhibitors (ICI). Responders are more likely to be defective in mismatch repair genes (MSI+). MSI+ patients are over-represented in the group of tumors with high densities of CD8+ T-cells. Patients with high T-cell infiltration have a higher expression of PD-1 and PD-L1, and are more likely to respond to ICI.

These observations suggest that the response to ICI is strongly dependent on the presence of an established in situ adaptive immune reaction (*Mlecnik et al. Immunity 2016*).



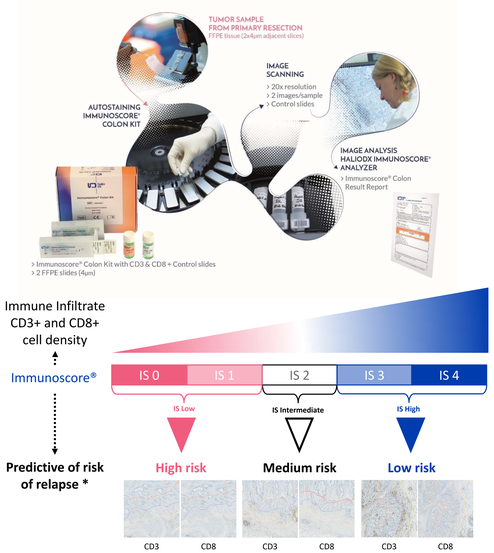
From *Mlecnik et al. Immunity 2016*

Eligibility of mCRC patients to ICI treatments

MSI colon cancer Stage IV patients are eligible to ICI. However this only concerns a minority of patients. Taking into account the evaluation of the *in situ* immune reaction in the primary tumor together with MSI status could clarify and extend the range of patients eligible to ICI.

The Immunoscore® test is a standardized tool measuring the host immune reaction (CD3+ and CD8+ cells) at the tumor site. Immunoscore classifies patients' tumors into 3 groups: Low (IS 0-1) associated with a high risk of relapse, Intermediate (IS 2), and High (IS 3-4) associated with a low risk of relapse.

Principle of the Immunoscore test



* Based on the international Immunoscore® SITC study results (2681 CC patients samples) *Pagès et al. The Lancet 2018.*

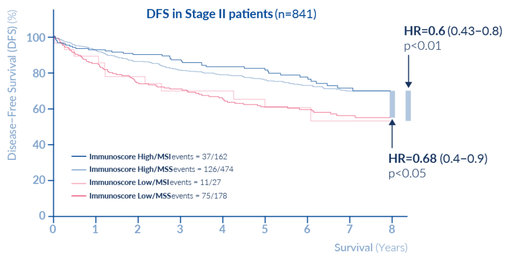
Background & Rationale

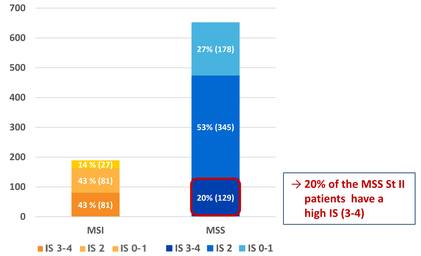
In the Immunoscore International validation study (*Pagès et al. The Lancet 2018*), a subgroup analysis on the Stage II patients with available MSS/MSI status (n=841) showed that up to 20% of the MSS patients (n=129/652) had a High Immunoscore (IS 3-4).

Unanswered question: what is the IS High proportion among patients who experienced a relapse?

- We investigated the IS distribution of primary tumors of UICC-TNM Stage I-III patients who experienced metachronous metastases in this international cohort;
- MSI status was assessed with the molecular new Bethesda panel and by IHC.

Background: Observed distribution among Stage II cases with MSS / MSI available status

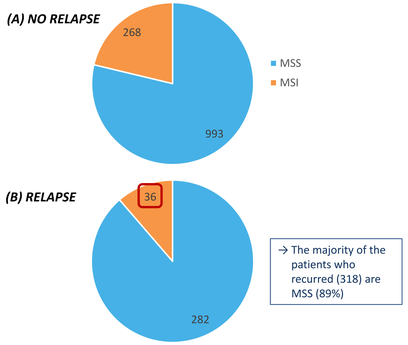




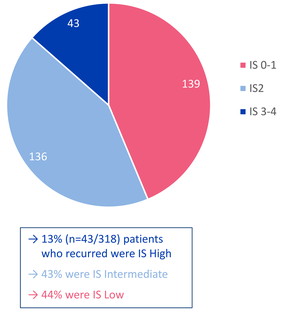
Results: Immunoscore® versus MSI/MSS status in Stage I-II-III patients

In the Immunoscore international validation study (*Pagès et al. The Lancet 2018*), we recorded **1579 UICC-TNM Stage I/II/III patients** with available MSI status and IS. **318 patients (20%) experienced a relapse**. Among those patients, 36 patients (11 %) were MSI+ whereas the vast majority of them (**89 %; 282 patients**) were **MSS**.

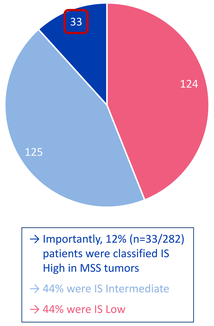
Distribution of MSI / MSS among 1579 Stage I-II-III patients with relapse (A) or without relapse (B)



IS distribution among the 318 patients who recurred



IS distribution among the 282 MSS patients who recurred



Conclusions

- ✓ In our series of 318 Stage I-II-III CC patients who relapsed, combining MSI+ status (n=36 patients) with IS high (n=33 patients) to select patients for ICI extends from 11% to 22 % the patients eligible to such immunotherapy.
- ✓ The proportion of metastatic colon cancer patients eligible for ICI could be refined and extended by the characterization of their primary tumor immune infiltrate based on the Immunoscore status, as suggested by *Le et al Cancer Immunol Res 2017*.
- ✓ Interventional trials are now needed to validate the predictive value of Immunoscore.
- ✓ Immunoscore could also be helpful in identifying the highly infiltrated tumors in the early-stage settings, in order to select the MSS patients who could benefit from ICI.

References

- *Pagès F, Mlecnik B, Marliot F et al.* International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. **Lancet. 2018; 391 (10135)**
- *Mlecnik B, Bindea G, Angell HK et al.* Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability. **Immunity.2016;15;44(3)**
- *Sinicrope F, Shi Q, Hermitte F et al.* Association of immune markers and Immunoscore with survival of Stage III colon carcinoma (CC) patients (pts) treated with adjuvant FOLFOX: NCCTG N047 (Alliance). **J Clin Oncol. 2017; 35:15s (suppl; abstr 3579)**
- *Sinicrope F, Shi Q, Hermitte F et al.* Immunoscore to provide prognostic information in low- (T1-3N1) and high-risk (T4 or N2) subsets of Stage III colon carcinoma patients treated with adjuvant FOLFOX in a phase III trial (NCCTG N0147; Alliance). **J Clin Oncol. 2018; 36:4s (suppl; abstr 614)**