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Abstract #130

IgM-Rheumatoid Factor as a novel biomarker for a reduced survival in anti-PD-1 treated NSCLC patients through the decrease of CD137+ T-cells.

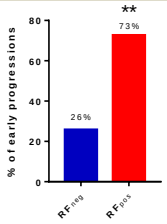
Alessio Ugolini[1], Ilaria Grazia Zizzari[1], Fulvia Ceccarelli[2], Andrea Botticelli[3], Tania Colasanti[2], Lidia Strigari[4], Aurelia Rughetti[1], Hassan Rahimi[1], Fabrizio Conti[2], Guido Valesini[2], Paolo Marchetti[3] and Marianna Nuti[1]

[1] Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy. [2] Arthritis Center, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy. [3] Oncology, Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy. [4] Medical Physics Unit, S. Orsola-Malpighi Hospital, Bologna, Italy.

ABSTRACT

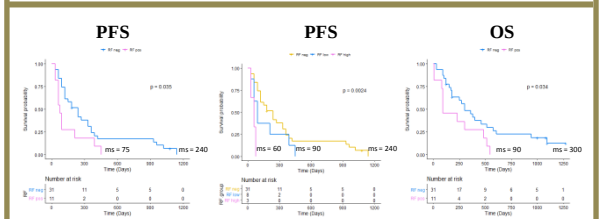
BACKGROUND. Despite anti-PD-1 targeting with Immune-Checkpoint Inhibitors (ICIs) has markedly improved the survival of Non-Small Cells Lung Cancer (NSCLC) patients, the onset of both primary and secondary resistances still occur in the majority of patients. The association between autoimmunity and cancer is an area of particular interest being the latter, as in the case of autoantibodies, an indication of a dysfunctional immune system. **METHODS.** We enrolled 42 patients with metastatic NSCLC before and during anti-PD-1 treatment, evaluating circulating levels of different autoantibodies and Peripheral Blood Mononuclear Cells (PBMCs) populations. **RESULTS.** The presence of IgM-Rheumatoid Factor (IgM-RF) in patients sera was strongly associated (OR, 7,66; 95% CI, 1.62 to 36.18; p=0.005) with the development of early progression. IgM-RF positivity resulted also as an important prognostic factor for a worse outcome in terms of both PFS (p=0.035) and OS (p=0.034), with a more marked reduction of PFS rate (p=0.002) identified when patients were further stratified based on IgM-RF titers. IgM-RF$^+$ patients showed a significant reduction (p=0.02) of the circulating tumor-specific CD137$^+$ T-cell population. To confirm the importance of this T-cell population in driving patients response, an higher percentage of CD137$^+$ T-cells at baseline correlated with a better outcome in terms of both PFS (p=0.006) and OS (p=0.002). Mechanistic experiments demonstrate that IgM-RF preferentially bound to naïve and central memory T-cells (p<0.0001) and a robust impairment (p=0.0001) of their migratory ability in response to CCL-19 was observed when exposed to IgM-RF. **CONCLUSIONS.** IgM-RF can be ascribed as a novel biomarker that is able to predict the development of early progression and, in addition, as a prognostic factor for a reduced PFS and OS in NSCLC patients in treatment with anti-PD-1 ICIs. The reduction of anti-tumor CD137$^+$ T-cells that was observed in IgM-RF$^+$ patients could make account for the reduced survival of the patients, since the frequency of this population in the blood of NSCLC patients resulted as an independent prognostic factor for a better outcome.

Fig. 1. IgM-RF and NSCLC patients outcome.



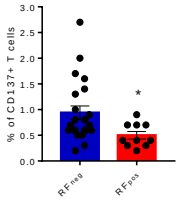
Clinical Subgroup	OR (95% CI)	P value
Overall	7.66 (1.62-36.18)	0.005
Age - yr		
< 68	51.67 (1.61-1657)	0.0008
> 68	2.28 (0.41-12.73)	0.3
Sex		
Male	5.6 (1.00-31.32)	0.04
Female	11.57 (0.51-358.6)	0.04
Histologic diagnosis		
Squamous-cell carcinoma	9 (0.75-107.4)	0.05
Non Squamous-cell carcinoma	6.67 (0.80-54.96)	0.06
Sites of metastasis at beginning of ICI treatment		
≤ 2	6.5 (1.09-38.65)	0.03
>2	11.67 (0.46-295.2)	0.05
ICIs line of treatment		
First line	25 (0.34-1832)	0.04
> First line	5.25 (1.05-26.2)	0.03
ECOG Performance status score		
< 2	9.2 (1.69-49.86)	0.005
2	1	1
Smoking Status		
Non Smokers	15 (0.18-1236)	0.08
Smokers	6.12 (1.26-29.7)	0.01

Left. Percentage of early progressions in NSCLC patients divided in RF_{pos} vs Rf_{neg} subgroups. **Right.** Odd ratios for development of early progression in pre-assigned clinical subgroups. **p<0.01.

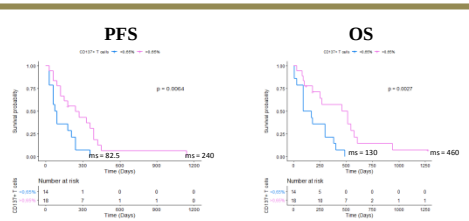


Kaplan-Meier representation of PFS (**left** and **middle**) and OS (**right**) after the anti-PD-1 treatment among the NSCLC patients divided into RF_{pos} vs RF_{neg} (**left** and **right**) and RF_{neg} vs RF_{low} vs RF_{high} subgroups (**middle**); ms = median survival.

Fig. 2. CD137$^+$ T-cells and NSCLC patients outcome.

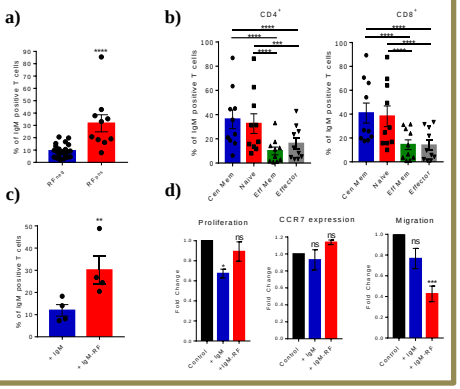


Percentage of CD137$^+$ T-cells at baseline in NSCLC patients divided in RF_{pos} vs Rf_{neg} subgroups. p<0.05.



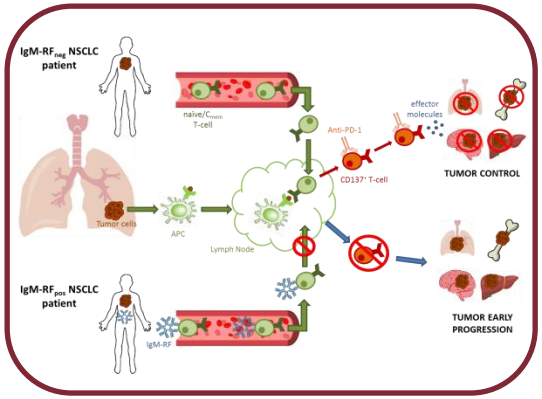
Kaplan-Meier representation of PFS (**left**) and OS (**right**) after the anti-PD-1 treatment among the NSCLC patients based on the percentage of CD137$^+$ T-cells at baseline; ms = median survival.

Fig. 3. IgM-RF impairs naïve and C_{Mem} T-cells migration.



a). Percentage of IgM$^+$ T-cells at baseline in NSCLC patients divided in RF_{pos} vs Rf_{neg} subgroups. **b).** Percentage of IgM-positive T-cells after the T-cells and anti-IgM staining on PBMCs isolated from NSCLC patients at baseline, divided into RF_{pos} and RF_{neg} groups. **c).** Percentage of IgM-positive T-cells *in vitro*. **d).** Fold change compared to the experiment control (untreated sample) of the percentages of proliferated (left), CCR7 positive (middle) and migrated (right) T-cells of untreated, control IgM or IgM-RF treated T-cells.
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

SUMMARY



Correspondence: marianna.nuti@uniroma1.it ; alessiougolini217@gmail.com
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