41 - CD39 affect the prognostic role of NLR via N2 neutrophils in metastatic melanoma patients treated with immunotherapy

Domenico Mallardo[1], Mario Fordellone[2], Andrew White[3], Margaret Ottaviano[1], Francesca Sparano[1], Michael Bailey[3], Arianna Facchini[1], Sufey Ong[3], Piera Maiolino[1], Corrado Caracò[1], Sarah Church[3], Ernesta Cavalcanti[1], Sarah Warren[3], Alfredo Budillon[1], Alessandra Cesano[3], Ester Simeone[1], Paolo Chiodini[2], Paolo Antonio Ascierto[1]

1-I.N.T. IRCCS Fondazione "G. Pascale" Napoli; 2-Medical Statistics Unit, Universitiy of Campania "Luigi Vanvitelli", 81100 Naples, Italy; 3-NanoString Technologies Inc, Seattle, Washington, USA.

Background: The immune checkpoint inhibitors (ICIs) revolutionized cancer therapeutic landscape and substantially improved the survival of patients (pts) with advanced malignancies. Several predictive biomarkers are under evaluation, in order to identify patients who can benefit from ICI. Recently, elevated NLR, calculated from absolute neutrophil count and white cell count, were found to be independent predictors of reduced survival and increased risk of progression in melanoma patients receiving ICI. The purpose of this study is to retrospectively investigate relationship of NLR with inflammation-immune mediators.

Methods: Gene profiling analysis was performed from 78 basal PBMCs of metastatic melanoma pts treated in first line with anti-PD1 using NanoString IO360 panel. Patient's characteristics are listed in table1. To identify the best genes signature the Sparse Partial Least Squares Discriminant Analysis (sPLS-DA) was applied.

Results: Overall, 78 patients were included in the analysis. Pts with high NLR at baseline (ratio >5.57) had a poorer PFS (HR=7.27, 95% CI = 3.57-14.8; p < 0.0001) and OS (HR=3.98; 95% CI = 2.0-7.9) than the pts with low NLR. Brain metastases were present in a higher proportion of pts with high NLR compared to those with low NLR (p=0.01). In the trascriptomic analysis, NLR was associated with SH2D1A, CD3, ZAP70, CD45RA genes, while a high NLR with CCNA1, LDHA, IL18R1, CD39, PTEN, MYD88 and MMP9 genes (ROC curve, AUC=0.97, p<0001). The signatures are also associated to response. In addition, CD39 expression is higher in NLR high and is associate with increase of N2 neutrophils. NLR increase on treatment is also associated to worse outcome and a specific genetic signature.

Conclusions: NLR high is related with immunosuppressive, inflammatory and tumor related genes; in particular with N2 neutrophils associate to adenosine pathway activation. This could explain the prognostic role of NLR. Further investigations are needed to get additional information.

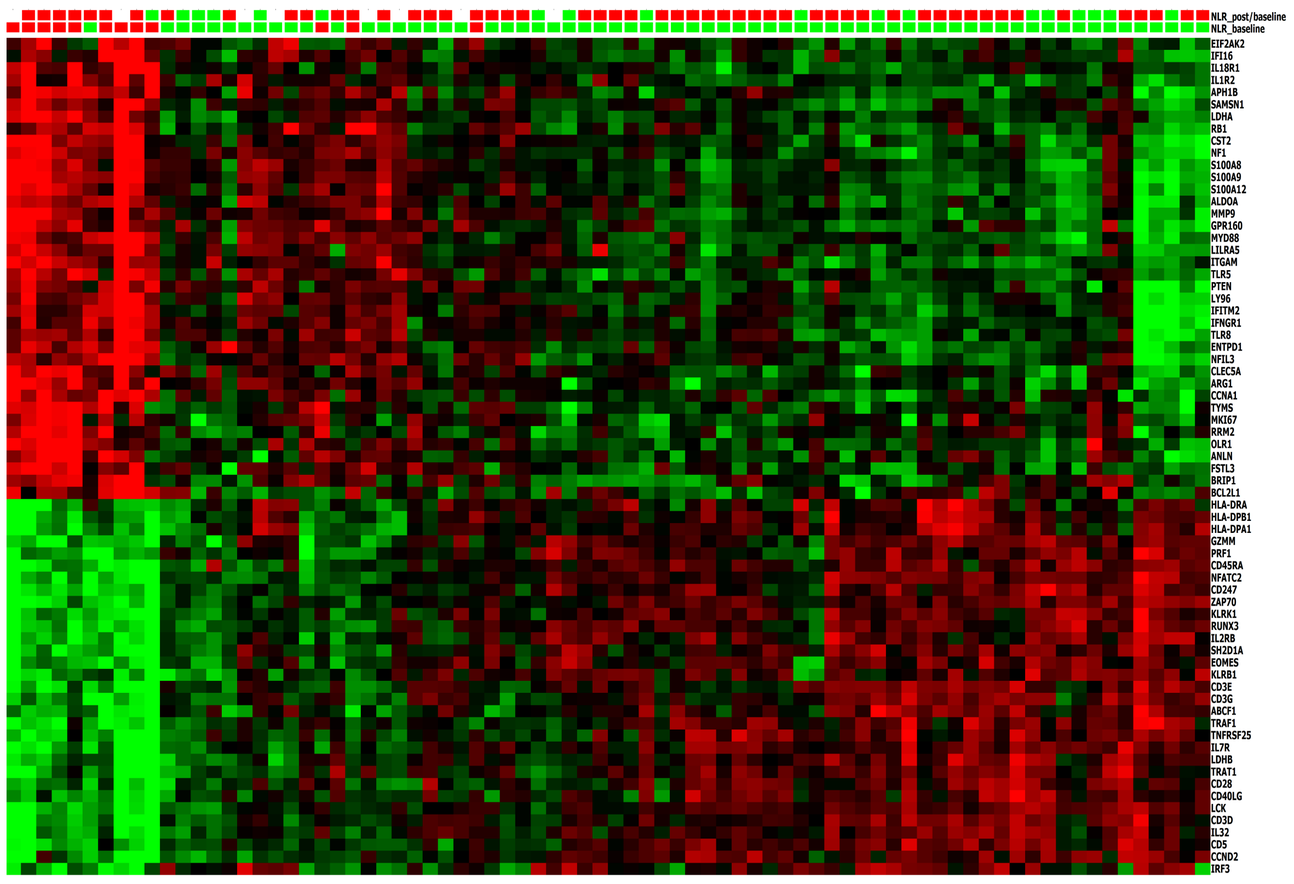

Figure 5. Transcriptomic analysis of PBMC obtained at baseline, according to NLR

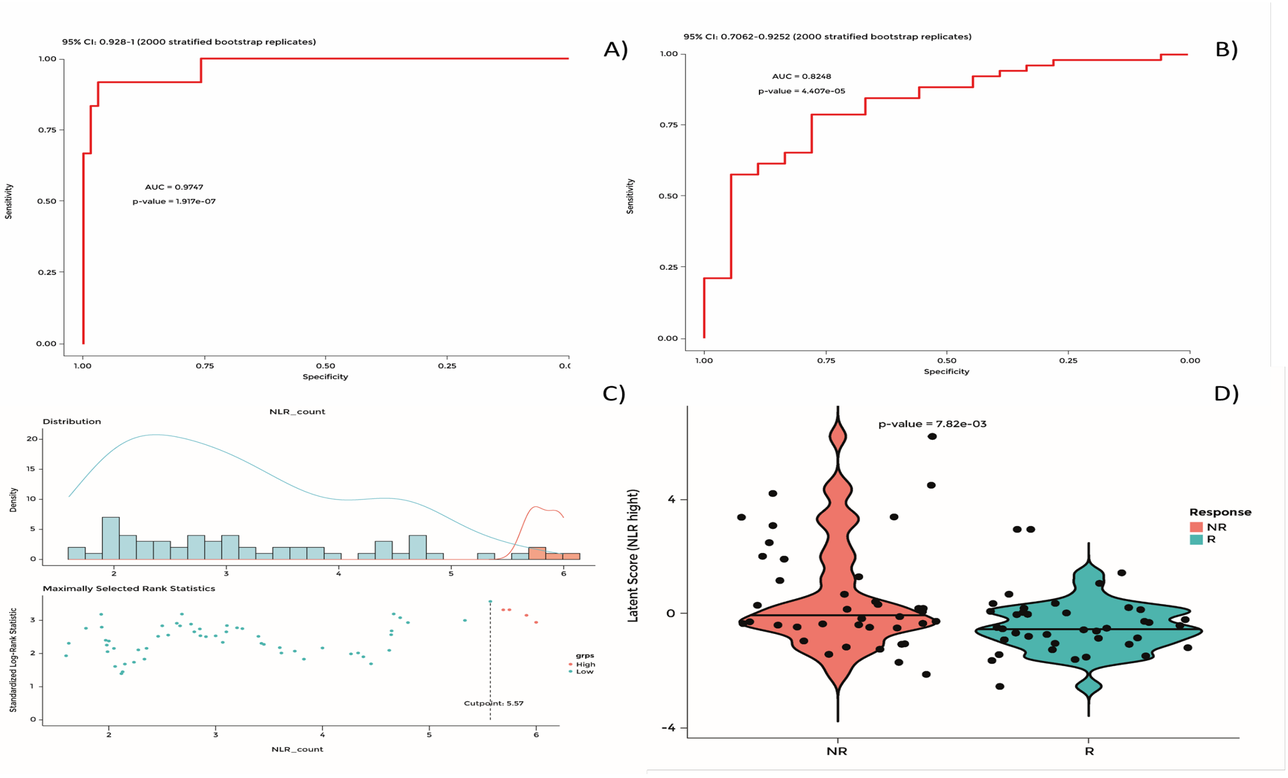

Figure 1. Accuracy of gene selection, through latent score, for baseline NLR (A) and for high $NLR_{post}/NLR_{baseline}$(B); Identification of the optimal cut-point to define the subgroups of low and high NLR (C); NLR according to response to treatment, at 3 months (D);

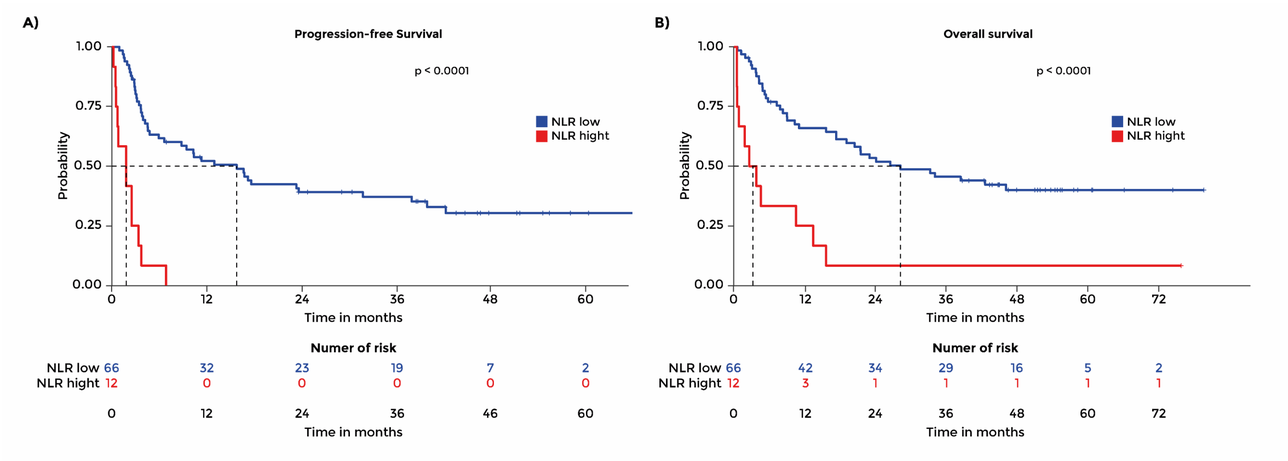

Figure 2. PFS (A) and OS (B) in patients with high or low baseline NLR. PFS: median follow-up was 54.7 months in patients with low NLR, and was not available for those with high NLR. OS: median follow-up was 51.8 months in patients with low NLR, and 75.7 months for those with high NLR.

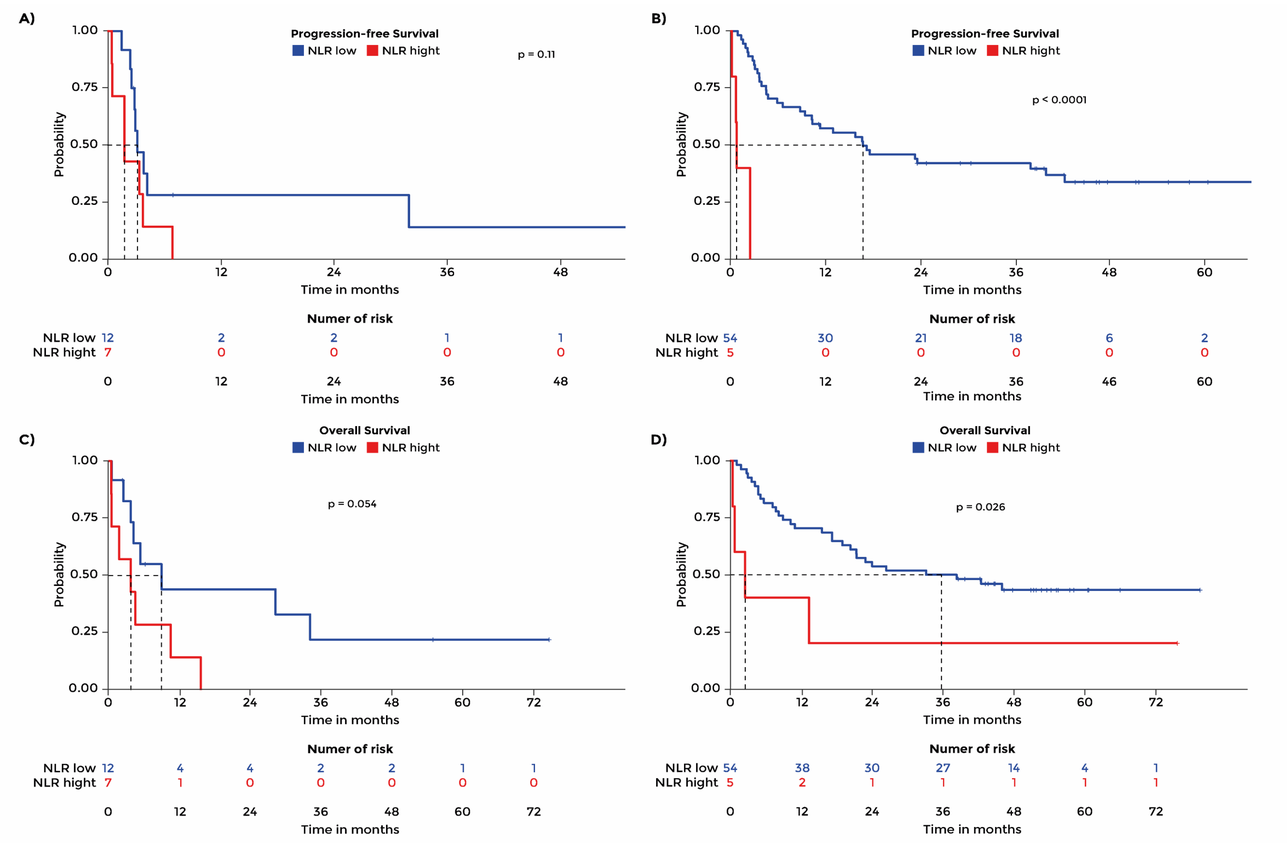

Figure 3. PFS in patients with brain metastases (A) and without brain metastases (B); OS in patients with brain metastases (C) and without brain metastases (D), according to high or low baseline NLR

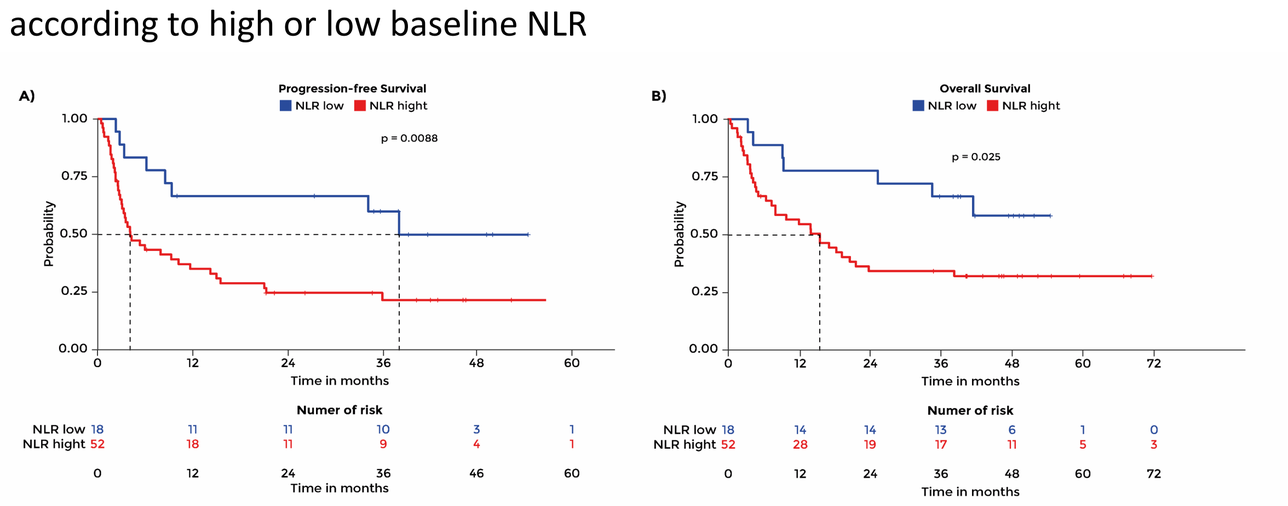

Figure 4. PFS (A) and OS (B) according to rising or consistent NLR after 3 months of treatment.

Characteristics	n=78, n (%)
Age (years), median (range)	61 (27–91)
Gender:	
• Female	41 (53)
• Male	37 (47)
Melanoma AJCC VII stage:	
• Stage IV	74 (94)
• Stage IIIC	4 (5)
• Stage IIIB	1 (1)
brain metastases at baseline	18 (23)
BRAF status:	
• Wild-type	59 (76)
• Mutation	16 (21)
• NA	3 (3)

Gene	Rho, p-value
Positively associated with NLR	
CD39 (ENTPD1)	0.663, <0.0001
PTEN	0.034, <0.0001
MYD88	0.662, <0.0001
MMP9	0.749, <0.0001
Negatively associated with NLR	
HLA-DRA	-0.473, <0.0001
HLA-DPB1	-0.547, <0.0001
HLA-DPA1	-0.558, <0.0001
CD5	-0.557, <0.0001
CD28	-0.578, <0.0001
NFATC2	-0.660, <0.0001
CD247	-0.610, <0.0001
ZAP70	-0.723, <0.0001
IL2RB	-0.499, <0.0001
CD3E	-0.532, <0.0001
CD3G	-0.558, <0.0001
IL7R	-0.620, <0.0001
TRAT1	-0.515, <0.0001
CD40LG	-0.537, <0.0001
CD3D	-0.525, <0.0001
IL32	-0.511, <0.0001

Presenter: Domenico Mallardo
dome.mallardo@gmail.com
Corresponding: Paolo Antonio Ascierto
paolo.ascierto@gmail.com

sitc 2023 San Diego Nov. 1–5

sitc Society for Immunotherapy of Cancer

ISTITUTO NAZIONALE TUMORI IRCCS – Fondazione Pascale