15th CONGRESS on Lung CANCER

MADRID

23&24 November 2023

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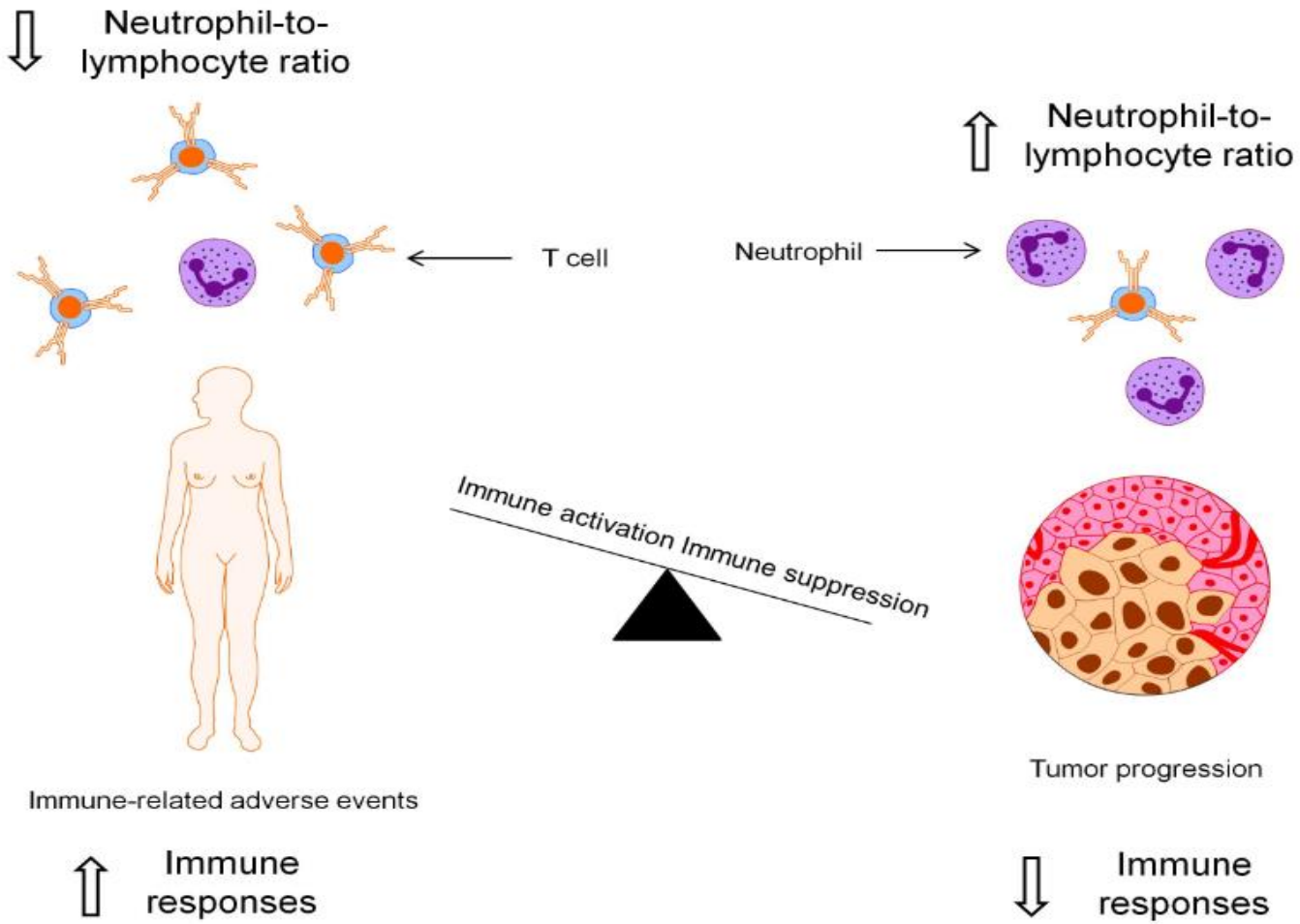
Fundación GECP lung cancer research

Neutrophil-to-lymphocyte ratio as a prognostic marker of immunotherapy outcome in advanced NSCLC

Daniel Parra Trujillo

Department of Medical Oncology. Hospital General Universitario de Alicante.

An elevated NLR seems to be related to tumour progression…



Lee PY, et al. Neutrophil-to-Lymphocyte Ratio Predicts Development of Immune-Related Adverse Events and Outcomes from Immune Checkpoint Blockade: A Case-Control Study. Cancers. 2021 Mar 15;13(6):1308.

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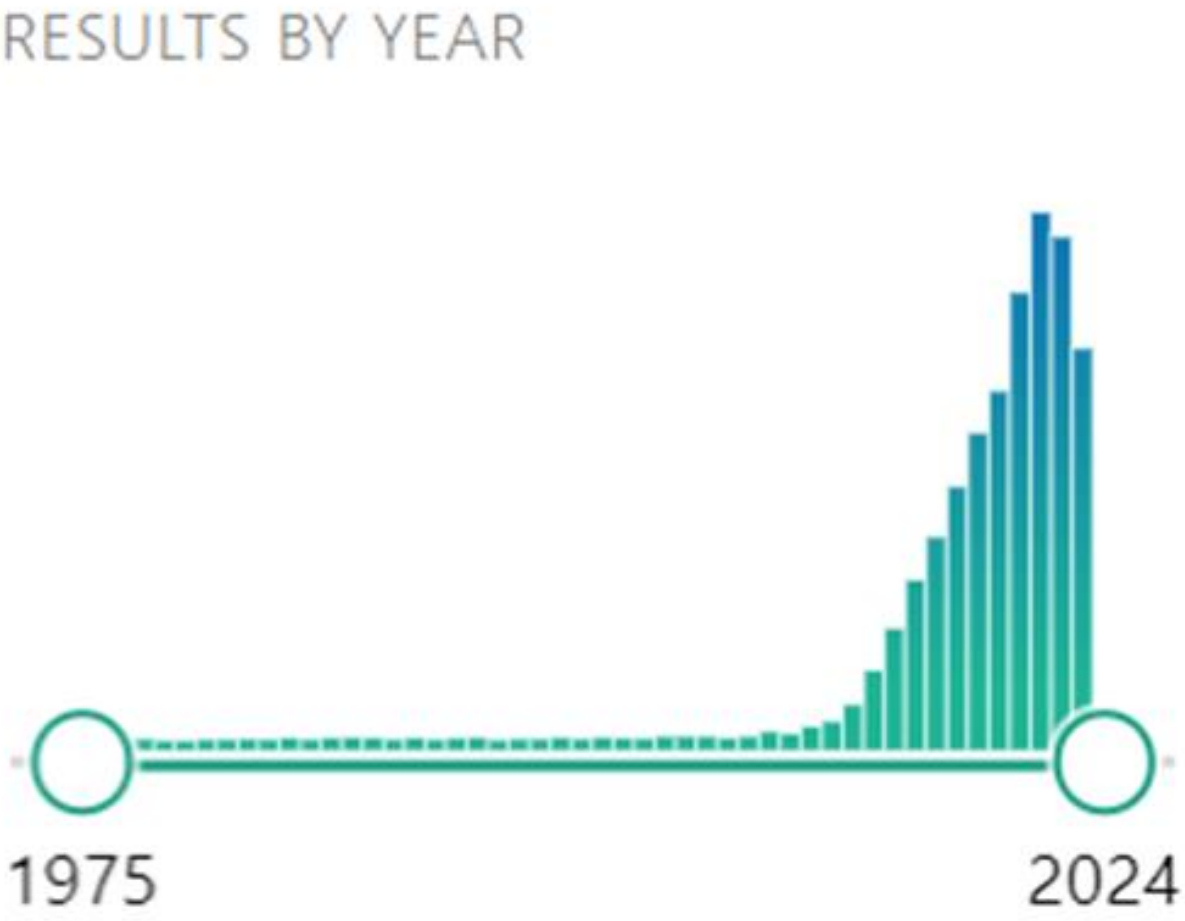

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Perspective

The Potential Role of Neutrophils in Promoting the Metastatic Phenotype of Tumors Releasing Interleukin-8

Vol. 10, 4895–4900, August 1, 2004

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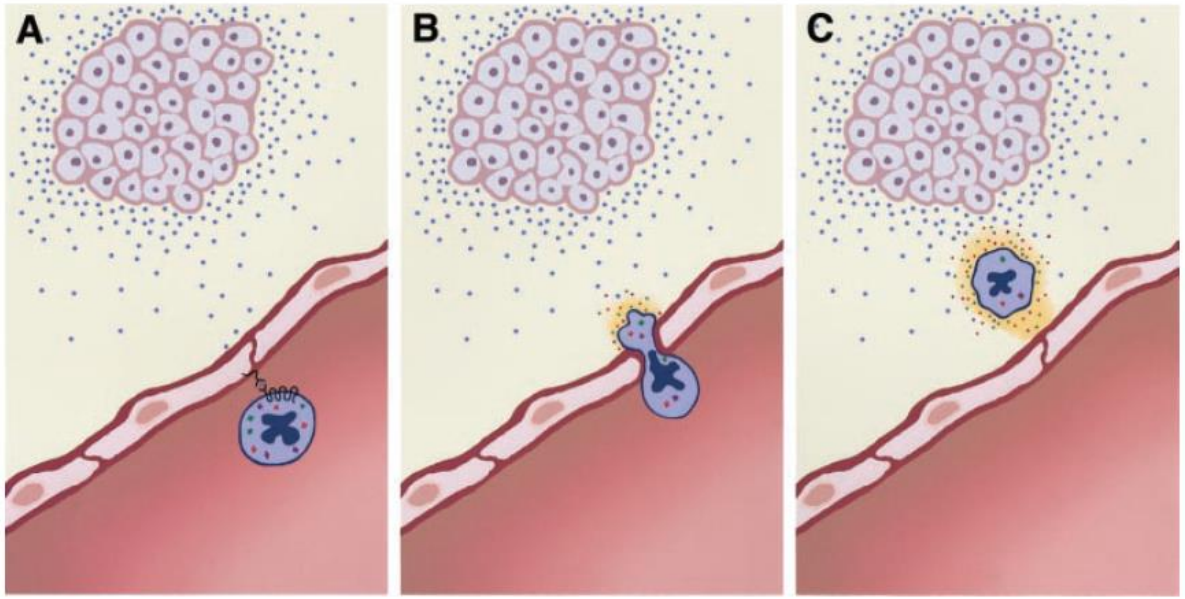
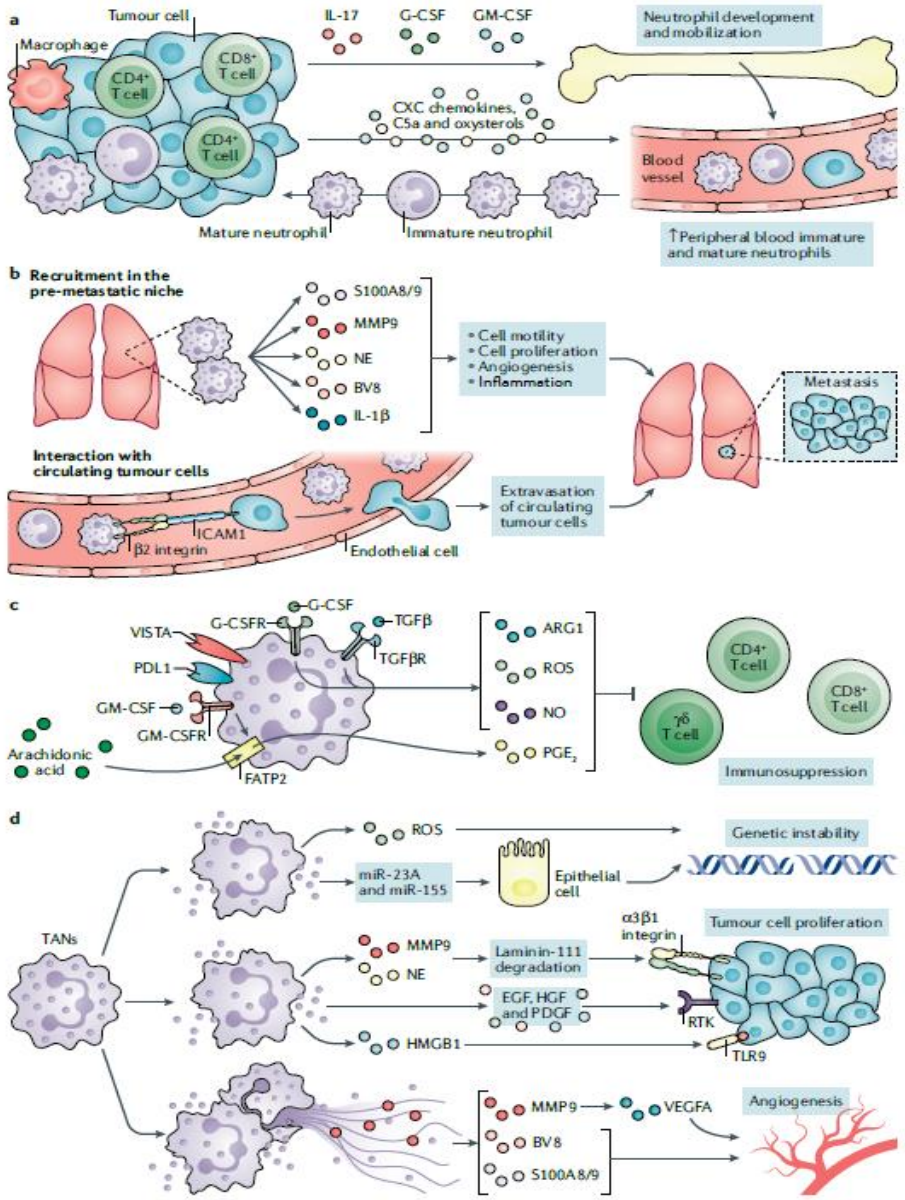


Fig. 1 A schematic representation of a neutrophil responding to IL-8 ectopically released by a tumor with the consequent invasion and remodeling of the ECM. *A,* the neutrophil (represented as a *blue cell*) binds to the IL-8 molecules (*blue dots*) that were released by the tumor and tethered to the vascular endothelial cells. This interaction contributes to the activation of the neutrophil. *B,* the emigration of an "activated" neutrophil from the vascular compartment. During this process, the neutrophil gains access to the ECM (*light yellow area*) and releases vesicles of enzymes (*red, green,* and *purple dots*) that initiate ECM remodeling (the *darker yellow*). *C,* the neutrophil, responding to the IL-8 concentration gradient, migrates toward the tumor. Remodeling the ECM during this process thereby establishes an environment more favorable to the progression and metastasis of the tumor cells.

De Larco JE, Wuertz BRK, Furcht LT. The potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin Cancer Res. 2004 ;10(15):4895–900.



Jaillon S, Ponzetta A, Di Mitri D, Santoni A, Bonecchi R, Mantovani A. Neutrophil diversity and plasticity in tumour progression and therapy. Nat Rev Cancer 2020.

Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab

Stefan Diem[a,b,*,1], Sabine Schmid[a,1], Mirjam Krapf[c], Lukas Flatz[d,e,h], Diana Born[f],

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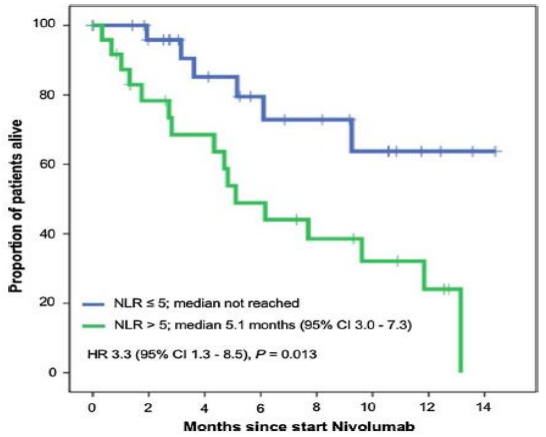

Fig. 3. Overall survival of NLR higher than median [=5] vs. equal or lower than median.

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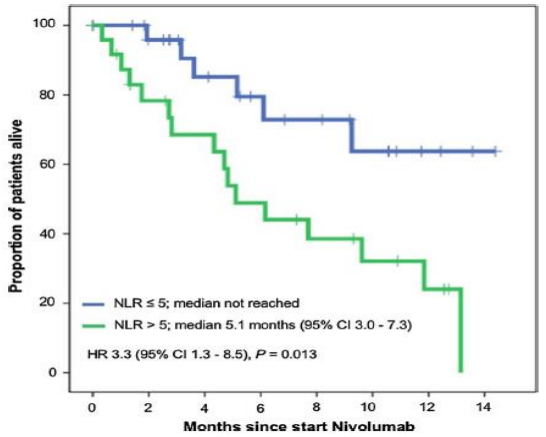

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Systematic Review

Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Prognostic Markers for Advanced Non-Small-Cell Lung Cancer Treated with Immunotherapy: A Systematic Review and Meta-Analysis

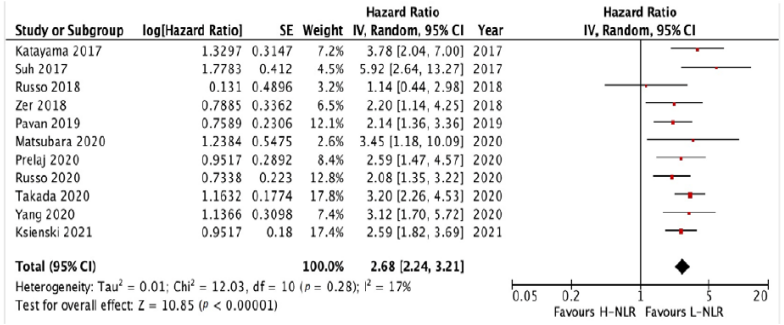

Figure 3. Forest plot H-NLR versus L-NLR to OS in patients treated with immunotherapy. Red dots represent study weights; the bivalve represent the overall effect.

Platini H, , et al. NLR and PLR ratio as prognostic markers for advanced non-small-cell lung cancer treated with immunotherapy: A systematic review and meta-analysis. Medicina (Kaunas);58(8):1069.

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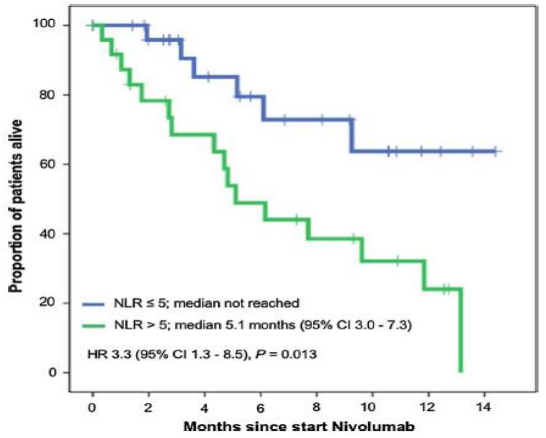

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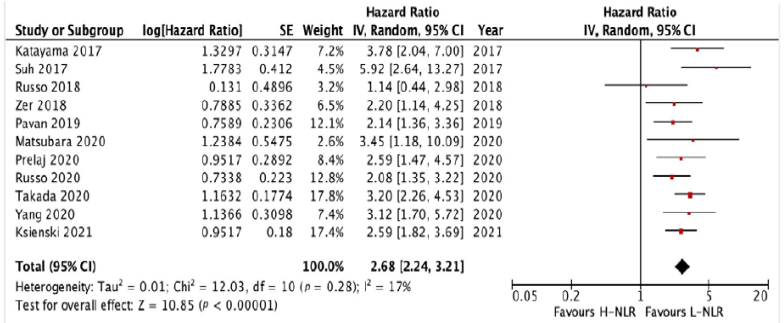

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BMJ Open

Association of the neutrophil to lymphocyte ratio and clinical outcomes in patients with lung cancer receiving immunotherapy: a meta-analysis

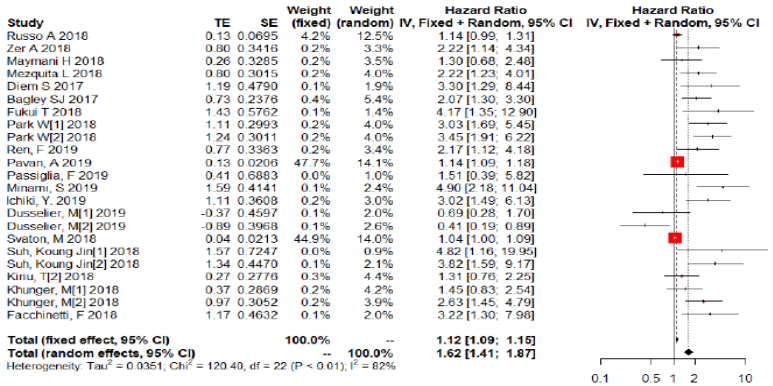


Figure 2 Forest plot of the association between the neutrophil to lymphocyte ratio and overall survival in patients with lung cancer receiving immunotherapy.

Jin J, Yang L, Liu D et al. Association of the NLR and clinical outcomes in patients with lung cancer receiving immunotherapy: a meta-analysis. BMJ Open. 2020;10(6):e035031.

Study objective:

- Analysis of the correlation between pre-treatment neutrophil-to-lymphocyte ratio (NLR), Disease Control Rate (DCR) and Duration Of Response (DOR) in advanced NSCLC treated with immunotherapy.

- Assess a global correlation and a specific one in the CT-IT and IT group.

- Stratify the NLR with prognostic/predictive factors (age, histology, ECOG-PS, steroid and antibiotic use, smoking status, PD-L1…).

Secondary objectives:

- Analysis between NLR, Objective Response Rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS).

- Construct a ROC defining cut-off point to refine the analysis.

*All patients were treated in Hospital General Universitario de Alicante, Spain.

Patient selection. Retrospective analysis.

- Patients **diagnosed** with **NSCLC in a metastatic stage or who have relapsed after a curative treatment.**

- First line treatment with **inmmunotherapy or chemo-immunotherapy between January 2020 and January 2023**.

- **Blood cell counts** used to measure NLR were performed whithin a **month prior to the start of the treatment**.

- A **minimum** of **4 months** was required in order **to assess response.**

Baseline characteristics

Age: range from 31 to 89 yo. Median 64.5 yo.

Sex: 55.5% men. 44.4% women.

Smoking status: 93.3% smokers (59.5% active and 40.5% former smokers).
Median pack-years: 48.

ECOG-PS: 74.4% were PS1.

Histology: adenocarcinoma 67.8%, SCC 20%.

NGS in 75.6% of patients.

Driver mutations: 14.3% KRAS G12C, 5.2% EGFR mut.

Stage IV at diagnosis: 75.6%.

		n	%
Sex	Men	50	55.5
	Women	40	44.4
Smoking history	**Smokers**	84	93.3
	Active	50	59.5
	Former	34	40.5
	Never	6	6.7
PS	0	13	14.4
	1	67	74.4
	2	9	10
	3	1	1.1
	4	0	0
Histology	Adenocarcinoma	61	67.8
	Squamous	20	22.2
	NOS	6	6.7
	Neuroendocrine	2	2.2
	Large-cell	1	1.1
Mutation deteccion method	NGS	68	75.6
	PCR	8	8.9
	None	14	15.6
Type of mutation	No mutation	58	75.3
	KRAS	11	14.3
	EGFR	4	5.2
	MET	1	1.1
	HER2	1	1.1
	BRCA2	2	2.2
Stage at diagnosis	**I-IIIC**	22	24.4
	IV	68	75.6
	IVA	35	38.9
	IVB	33	36.7

CT-IT schemes

- KN 189: CDDP/CBDCA + pemetrexed + pembrolizumab
- KN 407: CBDCA + paclitaxel + pembrolizumab
- ABCP: atezolizumab + bevacizumab + CBDCA + paclitaxel

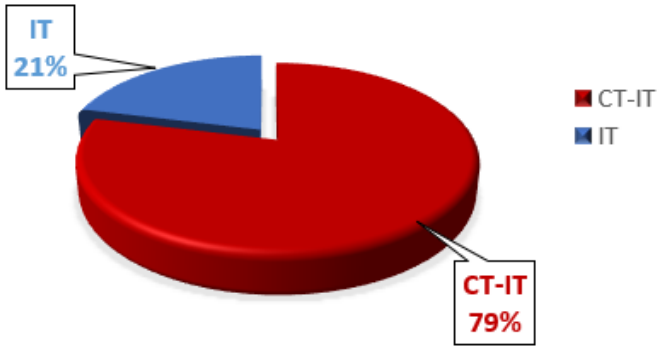
Immunotherapy

- KN 024: pembrolizumab monotherapy

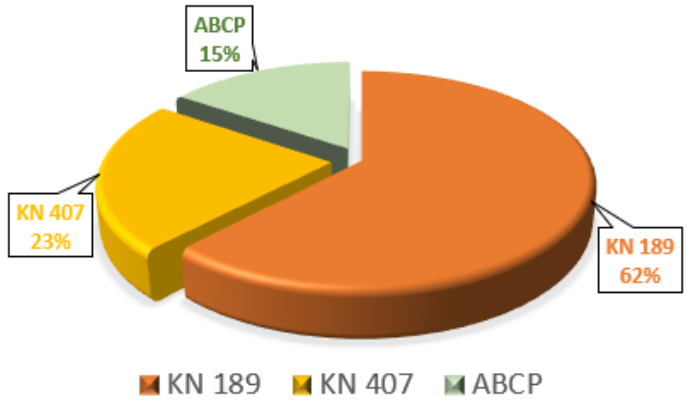
Median NLR

All patients: 3.7.
Response or stable dis: 3.7
Progressive disease: 4.3.

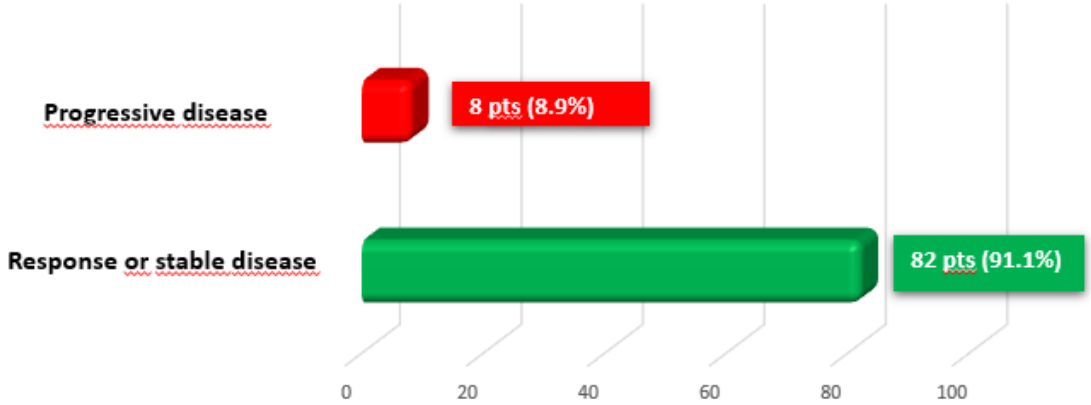
TYPE OF TREATMENT



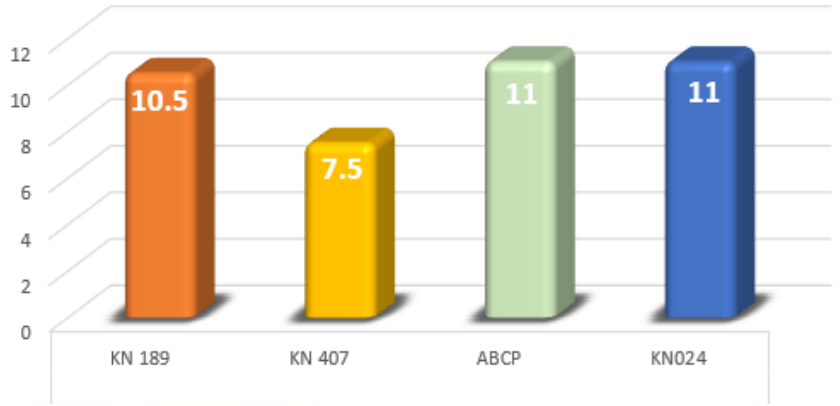
CT-IT REGIMENS



Disease Control Rate (DCR)



Duration of response (months)



Results (1). NLR and Disease Control Rate

NLR cut-off point: ≤ 5 or > 5.

Whole study population (n = 90)

		NLR groups		Total
		NLR < 5	NLR >5	
Disease Control Rate	Response or stable dis.	91,9%	89,3%	91,1%
	Proggresive disease	8,1%	10,7%	8,9%
Total		100,0%	100,0%	100,0%

	Valor	gl	p value
Chi-cuadrado de Pearson	,167[a]	1	,683

CT-IT population (n = 71)

		NLR groups		Total
		NLR < 5	NLR > 5	
Disease Control Rate	Response or stable dis.	94,0%	90,5%	93,0%
	Progressive disease	6,0%	9,5%	7,0%
Total		100,0%	100,0%	100,0%

	Valor	gl	p value
Chi-cuadrado de Pearson	,281[a]	1	,596

IT population (n = 19)

		NLR groups		Total
		NLR ≤ 5	NLR > 5	
Disease Control Rate	Response or stable dis.	83,3%	85,7%	84,2%
	Proggresive disease	16,7%	14,3%	15,8%
Total		100,0%	100,0%	100,0%

	Valor	gl	p value
Chi-cuadrado de Pearson	,019[a]	1	,891

Results (2). NLR and Duration Of Response.

DOR: from 0 to 56 months. Median 10.5 months.

NLR cut-off point: ≤ 5 or > 5.

Whole study population (n = 90)

	NLR groups	N	Median DOR
Duration of response	NLR ≤ 5	62	11,00
	NLR > 5	28	9,00
	Total	90	

	DOR
U de Mann-Whitney	855,000
p value	,910

CT-IT population (n = 71)

	NLR groups	N	Median DOR
Duration of response	NLR ≤ 5	50	10,50
	NLR > 5	21	9,00
	Total	71	

	DOR
U de Mann-Whitney	509,500
p value	,845

IT population (n = 19)

	NLR groups	N	Median DOR
Duration of response	NLR ≤ 5	12	14,00
	NLR > 5	7	9,00
	Total	19	

	DOR
U de Mann-Whitney	35,500
p value	,582

Subgroup analysis (1). NLR and DCR.

Age ≥70 (n = 27)		NLR groups	
		NLR ≤ 5	NLR > 5
DCR	Response or stable dis.	94,4%	66,7%
	Progressive disease	5,6%	33,3%

	Value	p value
Chi-cuadrado	3,668[a]	,055

PD-L1 < 1% (n = 43)		NLR groups	
		NLR ≤ 5	NLR > 5
DCR	Response or stable dis.	94,3%	75,0%
	Progressive disease	5,7%	25,0%

	value	p value
Chi-cuadrado	2,871[a]	,090

ADC (n = 61)		NLR groups	
		NLR ≤ 5	NLR > 5
DCR	Response or stable dis.	91,0%	100,0%
	Progressive disease	8,9%	0,0%

P value = 0.217

Age <70 (n = 63)		NLR groups	
		NLR ≤ 5	NLR > 5
DCR	Response or stable dis.	90,9%	100,0%
	Progressive disease	1,1%	0,0%

P value = 0.174

PD-L1 ≥1% (n = 45)		NLR groups	
		NLR ≤ 5	NLR > 5
DCR	Response or stable dis.	88,0%	95,0%
	Progressive disease	12,0%	5,0%

P value = 0.412

SCC (n = 20)		NLR groups	
		NLR ≤ 5	NLR > 5
DCR	Response or stable dis.	93,3%	80,0%
	Progressive disease	6,7%	20,0%

P value = 0.389

Subgroup analysis (2). NLR and DOR.

Age ≥70 (n= 27)	NLR groups	
	NLR ≤ 5	NLR > 5
n	18	9
Median DOR	9.5	9
Mann-Whitney	60.5	
p value	0.29	

PD-L1 < 1% (n = 43)	NLR groups	
	NLR ≤ 5	NLR > 5
n	35	8
Median DOR	11	6
Mann-Whitney	81.5	
p value	0.067	

ADC (n = 61)	NLR groups	
	NLR ≤ 5	NLR > 5
n	45	16
Median DOR	11	9.5
Mann-Whitney	345	
p value	0.805	

Age <70 (n= 63)	NLR groups	
	NLR ≤ 5	NLR > 5
n	44	19
Median DOR	11	12
Mann-Whitney	378	
p value	0,55	

PD-L1 ≥1% (n = 45)	NLR groups	
	NLR ≤ 5	NLR > 5
n	25	20
Median DOR	11	12.5
Mann-Whitney	232	
p value	0.68	

SCC (n = 20)	NLR groups	
	NLR ≤ 5	NLR > 5
n	15	5
Median DOR	9	9
Mann-Whitney	32	
p value	0.63	

Impact of immunosenescence and inflammaging on the effects of immune checkpoint inhibitors

Chuandong Hou [a,b], Zining Wang [a,b], Xuechun Lu [b,*]

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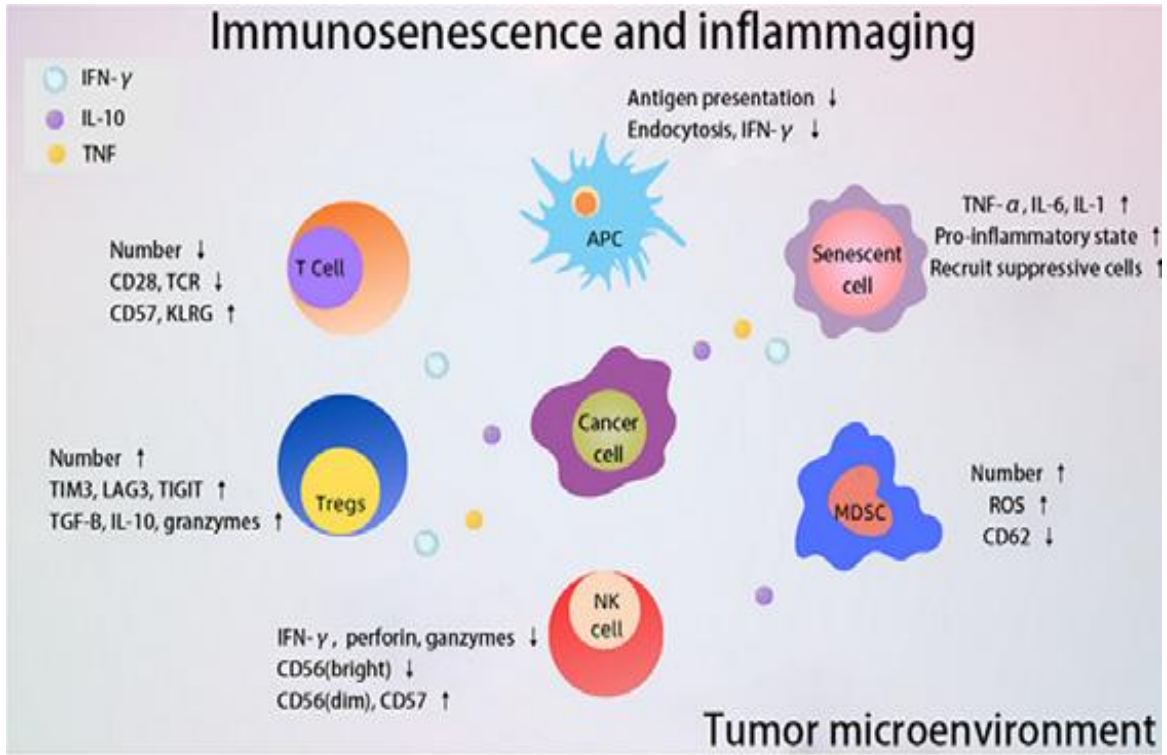

Rodriguez JE, et al. Immunosenescence, inflammaging, and cancer immunotherapy efficacy. Expert Rev Anticancer Ther 2022 ; 22(9):915–26.

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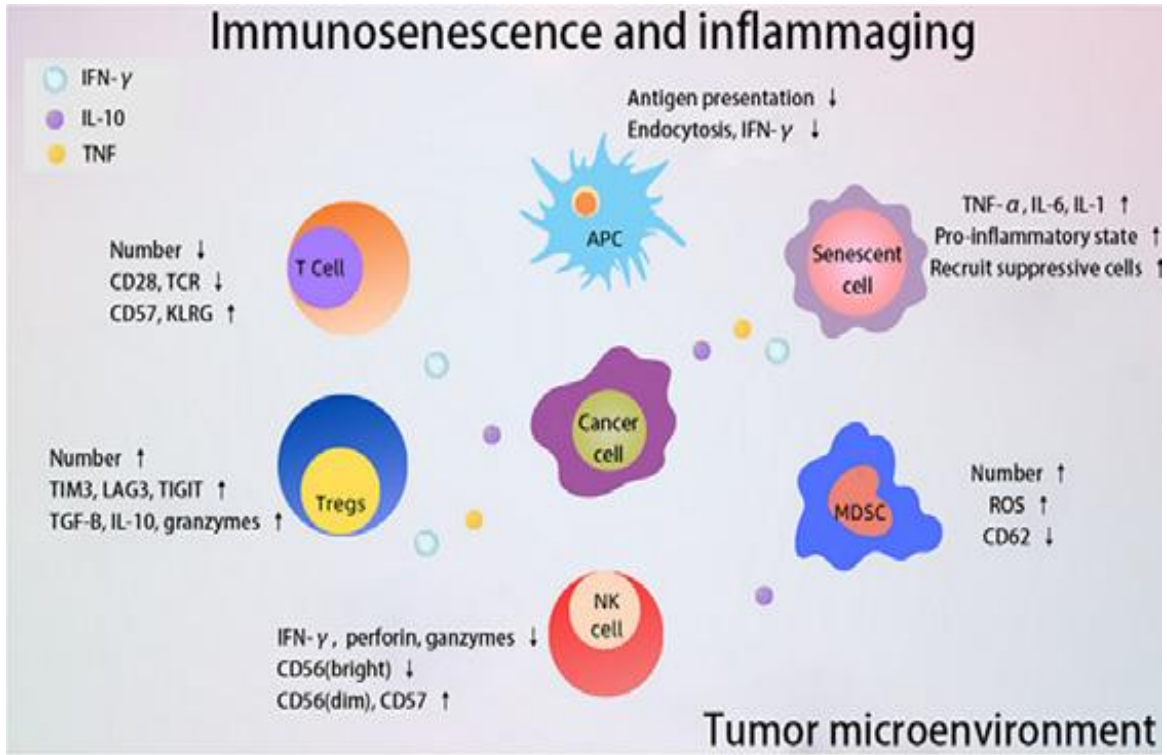

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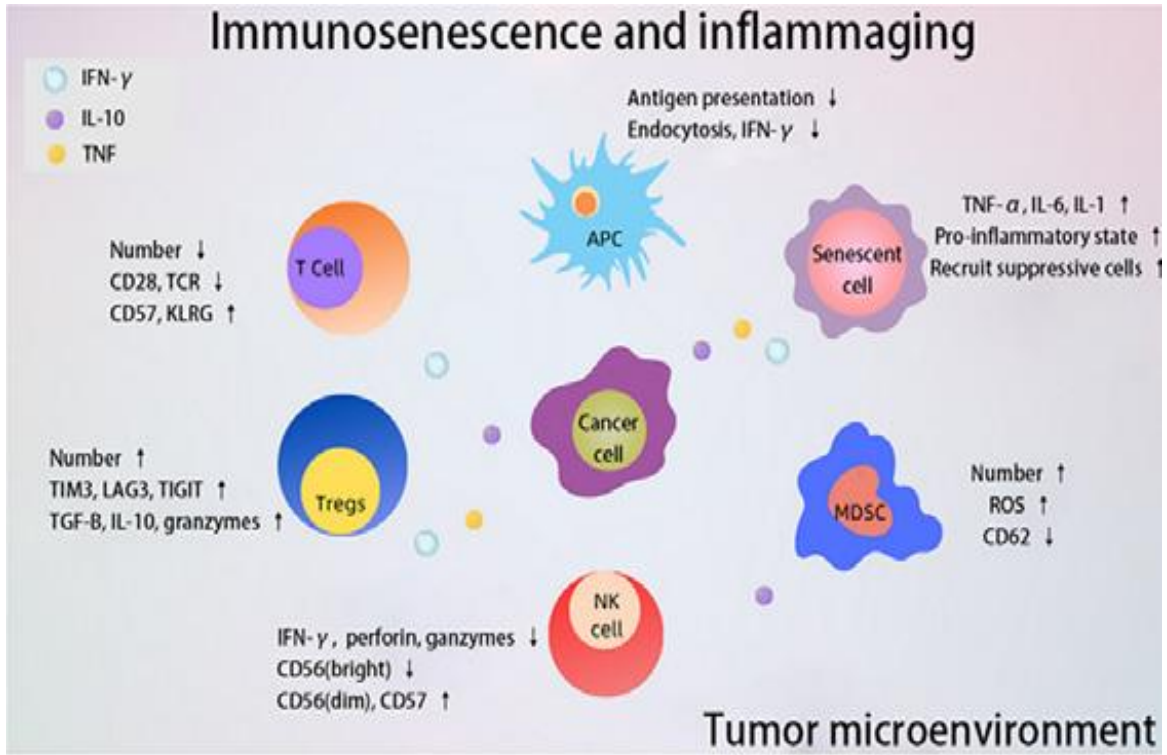

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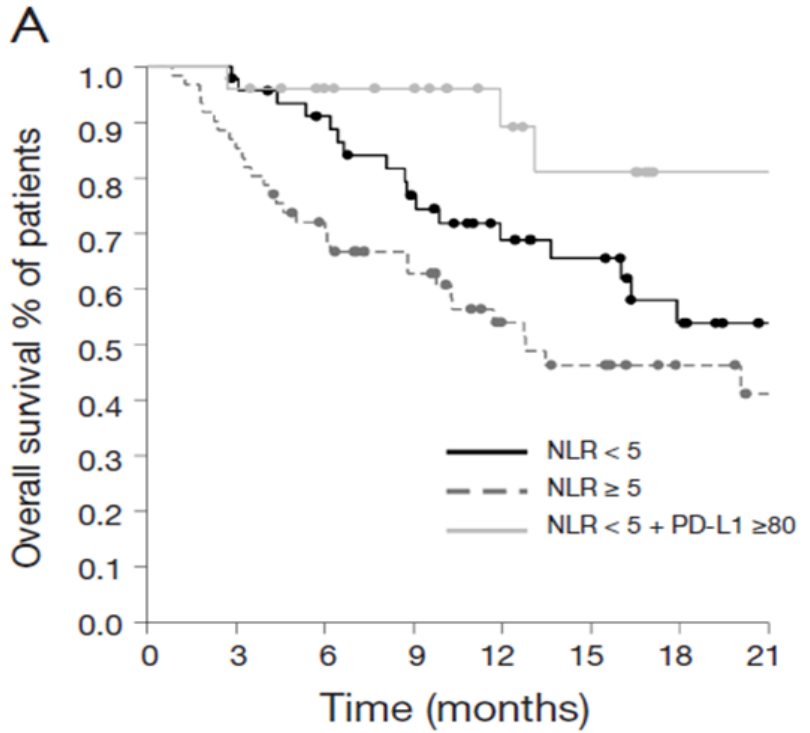

	2-year OS, %	95% CI	P value	HR (p-value) [95% CI]
NLR >5, NLR <5	41.2	38.1–44.6	0.006	
NLR <5 + PD-L1 ≥80%	53.9	49.4–58.8		
	81.0	72.9–89.5		0.20 (0.007) [0.06–0.64]

Banna GL et al. Neutrophil-to-lymphocyte ratio in combination with PD-L1 or lactate dehydrogenase as biomarkers for high PD-L1 non-small cell lung cancer treated with first-line pembrolizumab. Transl Lung Cancer Res;9(4):1533–42.

Conclusions

No association between NLR, DCR and DOR was found in a retrospective analysis of our study population with a cut-off point of 5.

In the **subgroup analysis**, **a trend for statistical significance was observed in those patients who are ≥70 yo. and PD-L1 negative**.

An **univariate analysis** was made to carry out the **first exploratory analysis**. A multivariate analysis will be made in a second stage.

Next step will be performing an analysis of the **correlation between NLR and ORR according RECIST criteria, PFS and OS** including additional factors (PS, smoking status, gender, steroids and antibiotics use).

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