BIOMARKERS OF IO RESPONSE

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ΟΓΚΟΛΟΓΙΚΟ ΚΕΝΤΡΟ
ΙΑΤΡΙΚΟ ΔΙΑΒΑΛΚΑΝΙΚΟ

Outline

1. Outcomes in NSCLC Patients Treated with First-Line Pembrolizumab and a PD-L1 TPS of 50-74% vs 75-100% or 50-89% vs 90-100%
2. Identification of Mismatch Repair Deficient Lung Adenocarcinomas Using Targeted Next-Generation Sequencing
3. Discrepancy of Tumor Neoantigen landscape Between Primary Lesions and Matched Metastases in Lung Cancer
4. Increased CD3+ T cells with a low FOXP3+/CD8+ T cell ratio can predict anti-PD-1 therapeutic response in non-small cell lung cancer patients
5. Prognostic value of complement activation in NSCLC and its association with PD-1 and PD-L1 expression

Outcomes in NSCLC Patients Treated with First-Line Pembrolizumab and a PD-L1 TPS of 50-74% vs 75-100% or 50-89% vs 90-100%

Elizabeth Jimenez Aguilar[1], Biagio Ricciuti[1], Justin F. Gainor[2], Mizuki Nishino[1], Sasha Kravets[1], Suzanne Dahlberg[1], Sara Khosrowjerdi[2], Christine A. Lydon[1], Anika Adeni[1], Safiya Subegdjo[1], Hira Rizvi[3], Matthew D. Hellmann[3], Mark M. Awad[1]

[1]Dana-Farber Cancer Institute, Boston, MA,
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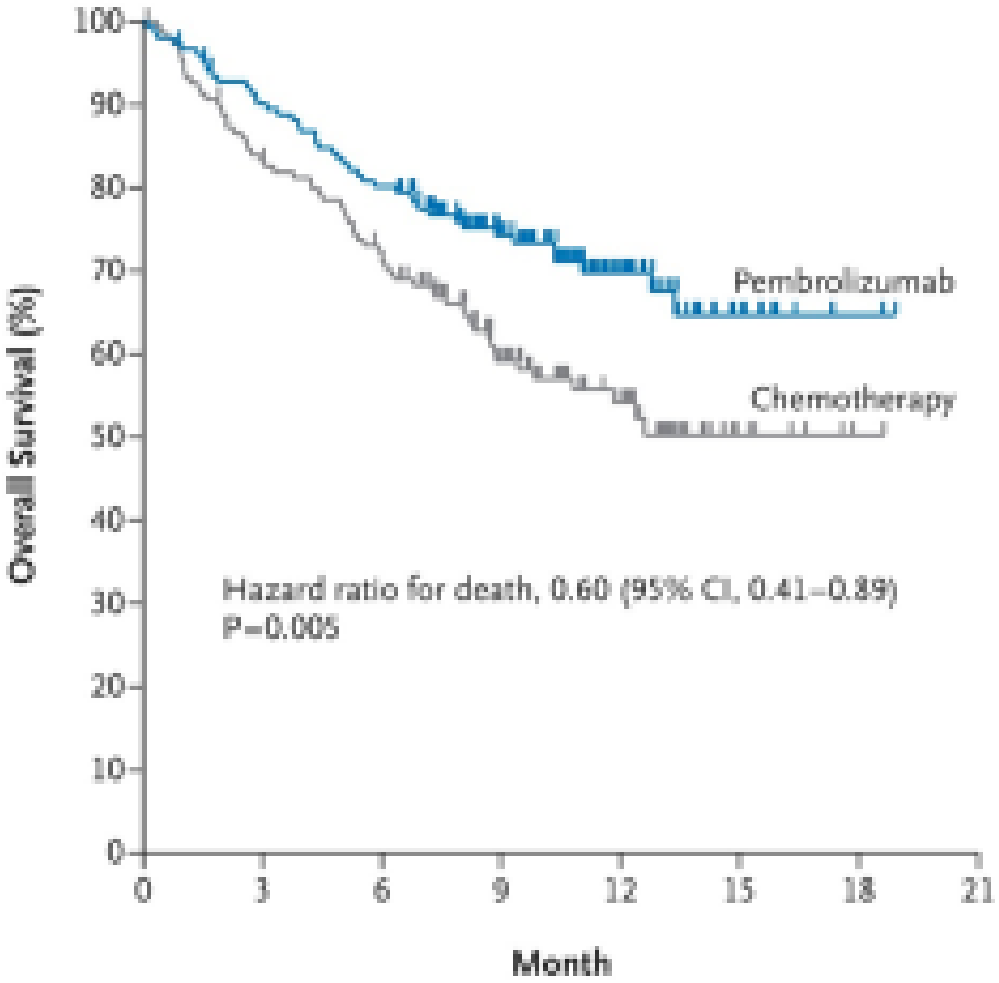
Background

KEYNOTE 024

Pembrolizumab for first-line NSCLCs with PD-L1 TPS ≥50%



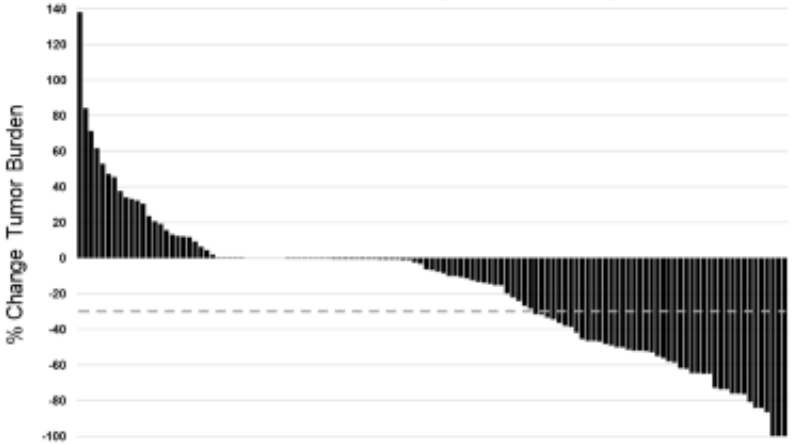
Reck M et al. *N Engl J Med* 2016;375:1823-1833.

Objective

In the first-line setting, are higher PD-L1 TPS cutoffs above 50% associated with improved clinical outcomes?

Entire Cohort

ORR = 37.4% (55 out of 147)



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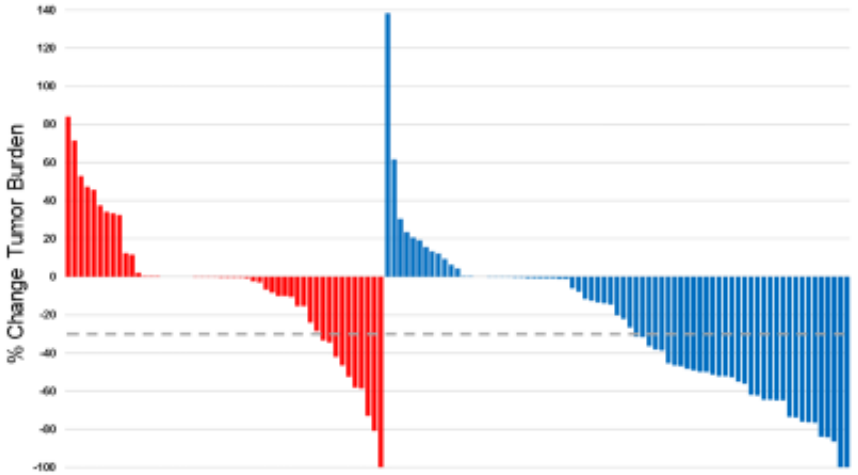
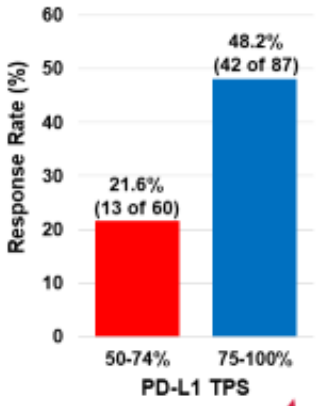
ORR: TPS 50-74% vs. TPS 75-100%



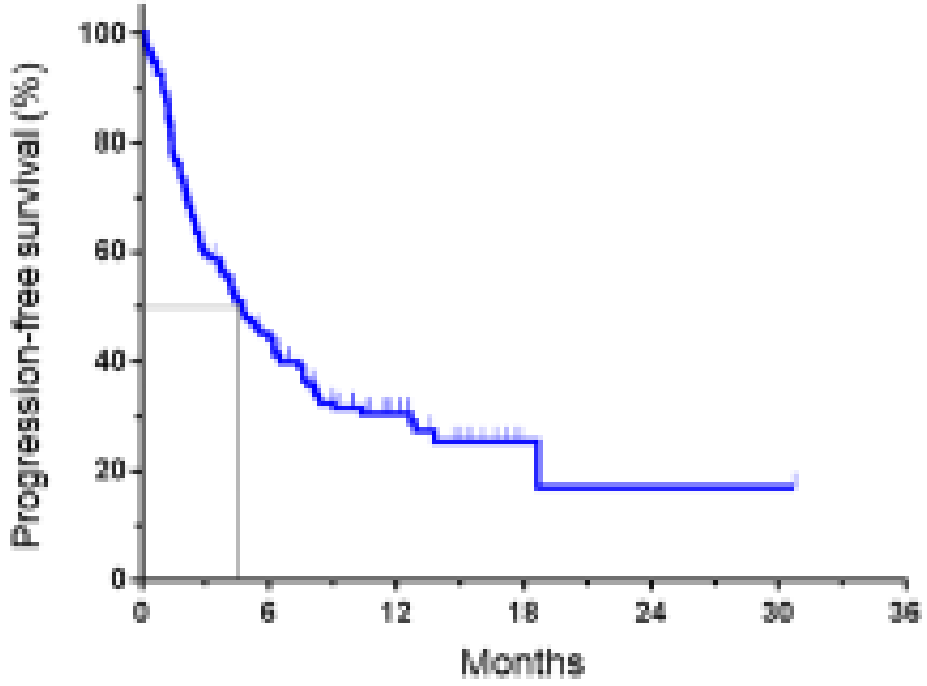
P = 0.001



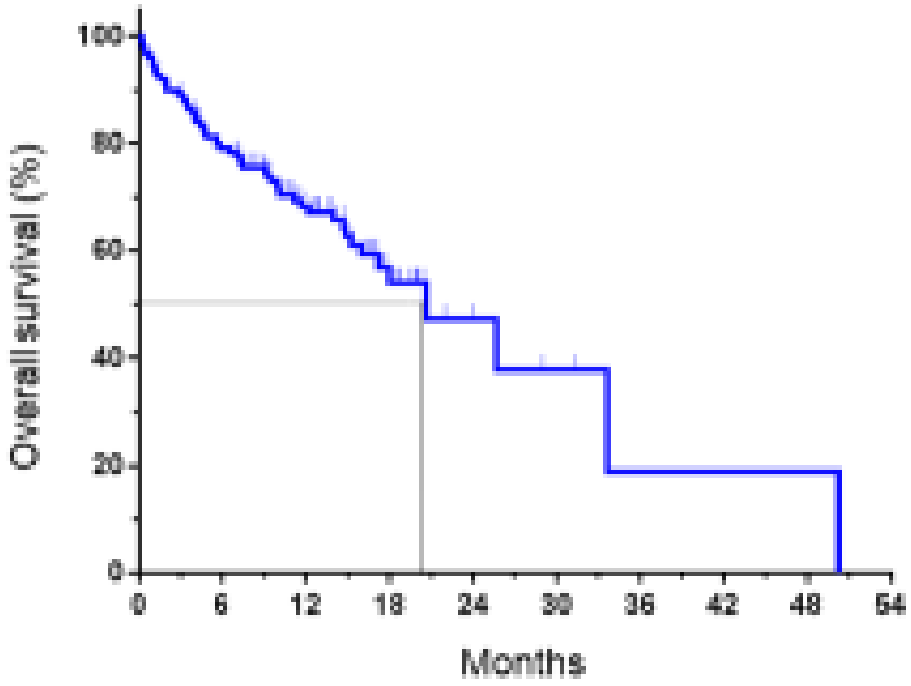
Mark M. Awad, Dana-Farber Cancer Institute, USA
WCLC 2018

Entire Cohort (N = 150)

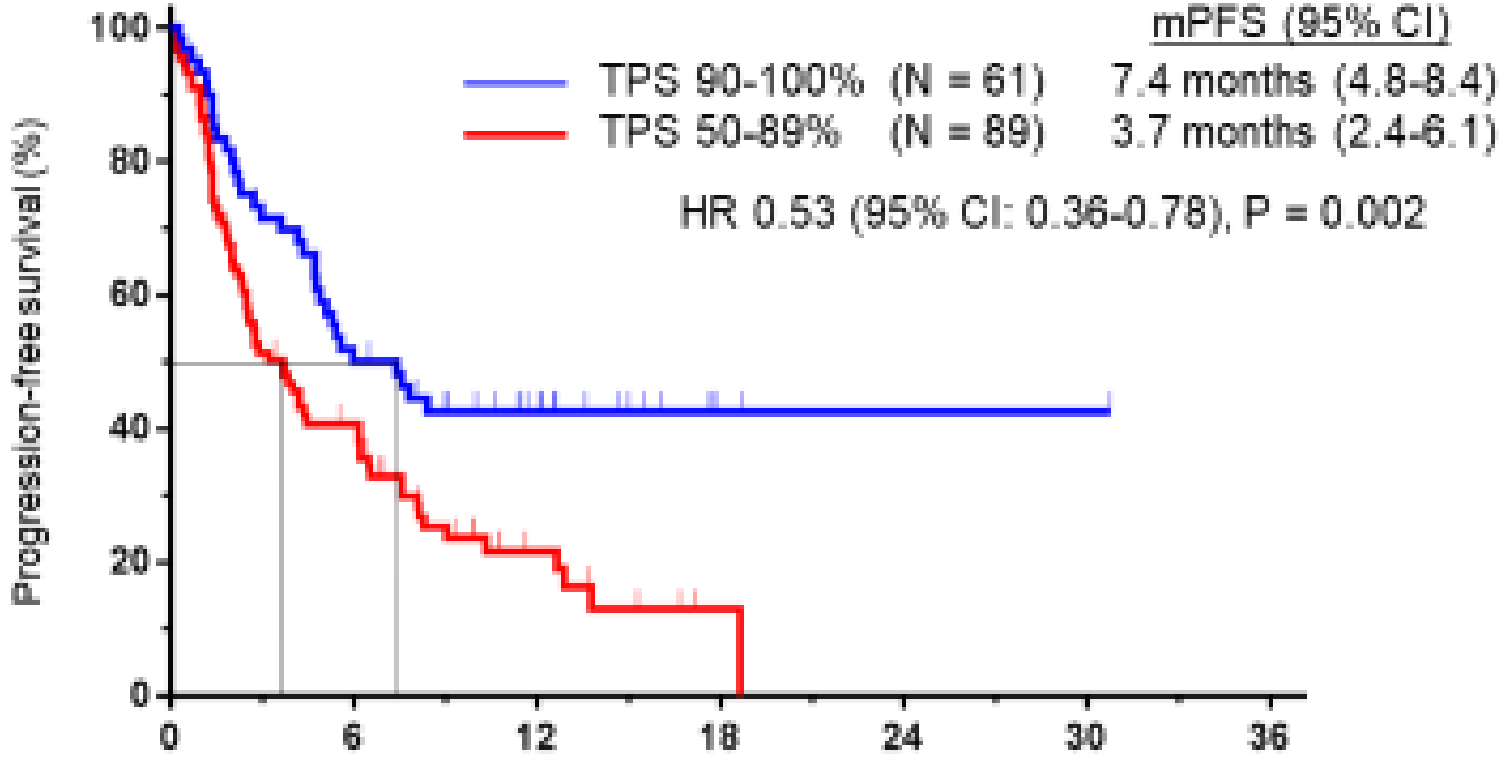
mPFS: 4.7 months [3.7-6.2]



mOS: 20.6 months [16.0-33.6]

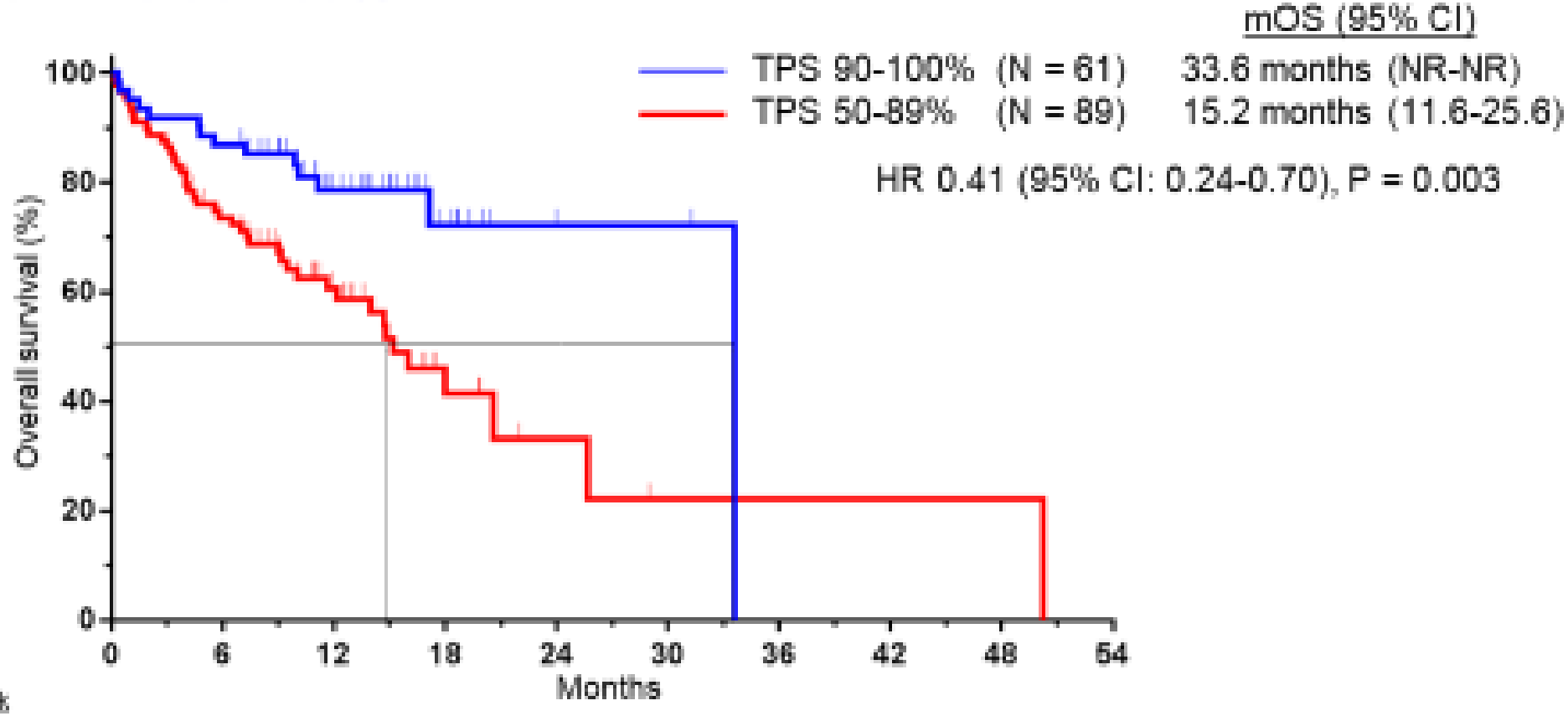


PFS: TPS 50-89% vs. TPS 90-100%



No. at risk							
TPS 90-100%	61	28	15	2	1	1	0
TPS 50-89%	89	32	8	1	0	0	0

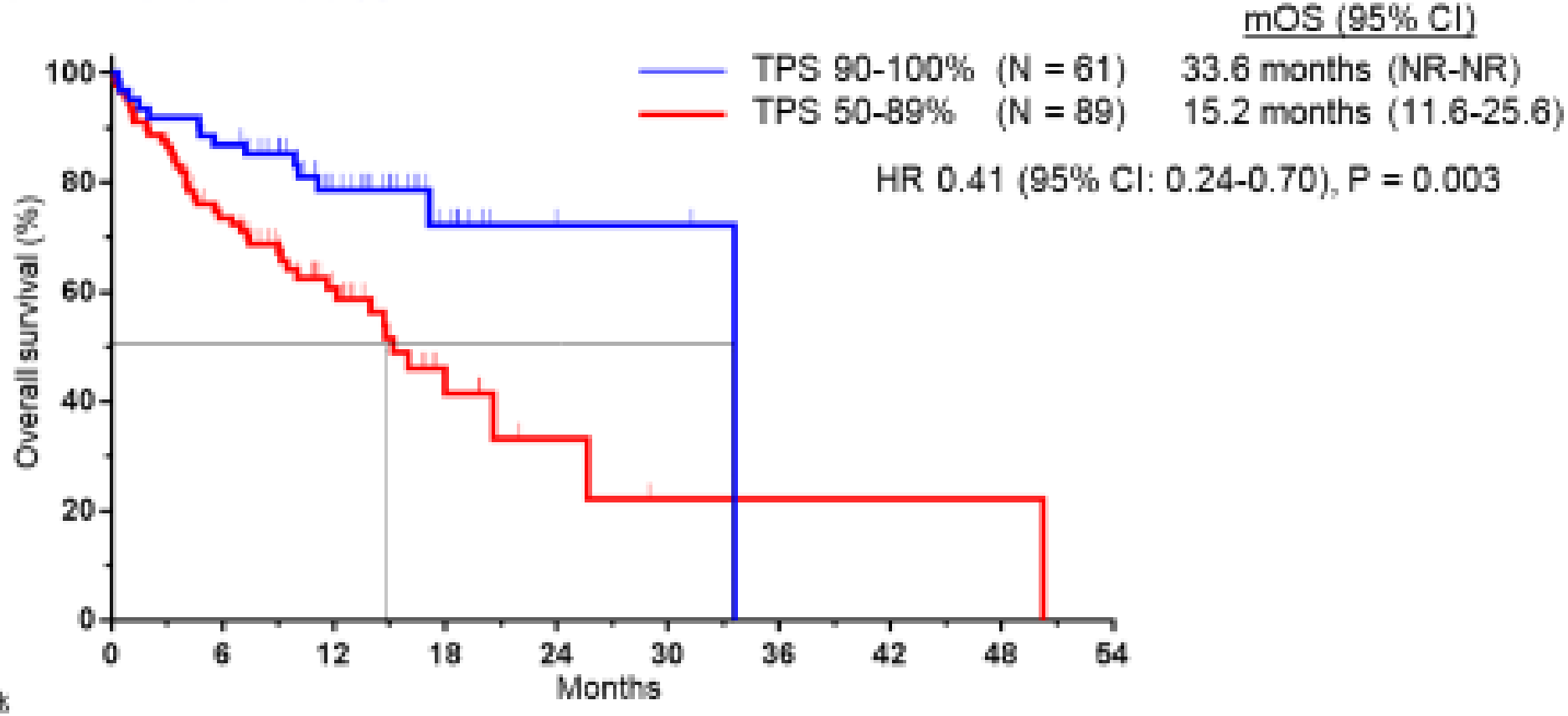
OS: TPS 50-89% vs. TPS 90-100%



No. at risk

TPS 90-100%	61	53	29	10	2	2	0	0	0	0
TPS 50-89%	89	61	31	7	3	1	1	1	1	0

OS: TPS 50-89% vs. TPS 90-100%



No. at risk

TPS 90-100%	61	53	29	10	2	2	0	0	0	0
TPS 50-89%	89	61	31	7	3	1	1	1	1	0

Conclusion

- PD-L1 is a continuous biomarker predictive of immunotherapy benefit in NSCLC at TPS levels above 50%
- Outcomes in PD-L1 TPS subgroups (≥75%, ≥90%) should be analyzed in completed first-line immunotherapy trials (eg KEYNOTE 024, CheckMate 026)
- Randomized prospective trials of pembrolizumab +/- a second agent should ensure balance between PD-L1 subgroups
- The ideal PD-L1 TPS cutoff for using pembrolizumab monotherapy over pembrolizumab + platinum doublet chemotherapy remains unclear

Outline

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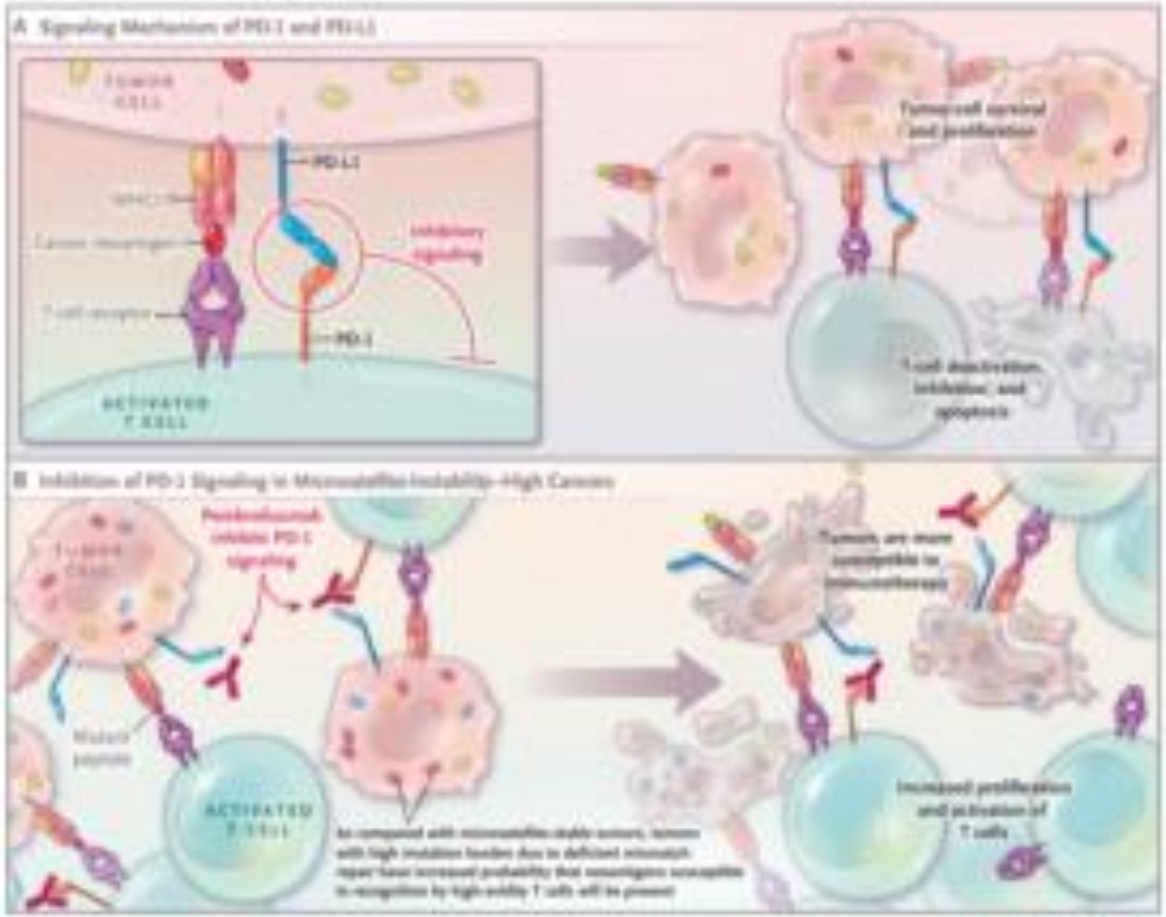
Background

Pembrolizumab obtained the first FDA approval agnostic of cancer site for MSI-H



Pembrolizumab Response Rate by Tumor Type.[A]

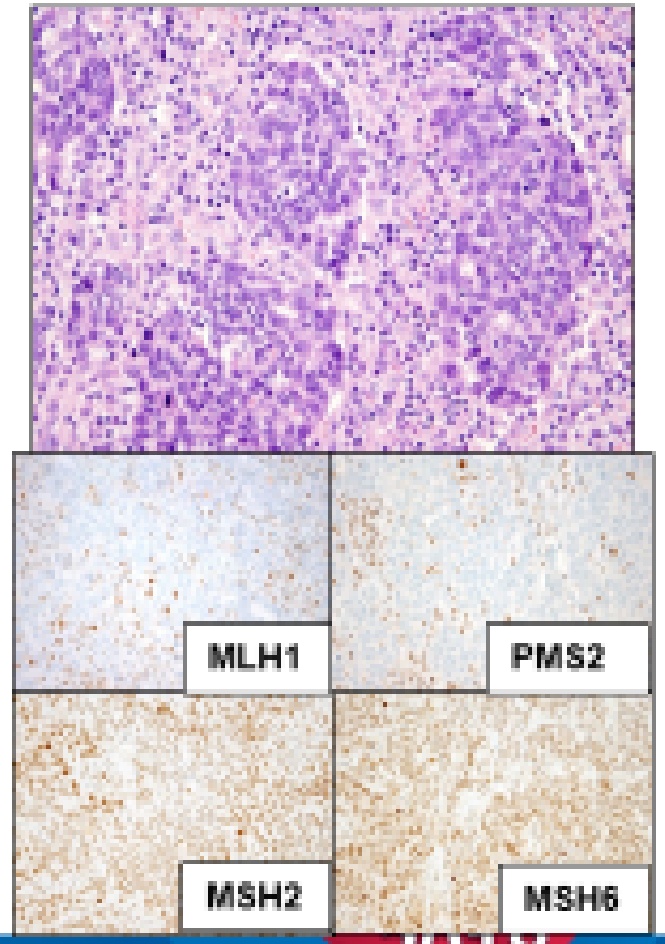
Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

Lemery et al. N Engl J Med, 2017

RESULTS I: MMR-D/MSI NSCLC

- Three (3) lung tumors (all adenocarcinoma) showed a MSI/MMR-D signature, and were confirmed by orthogonal methods for a prevalence of 0.1% of all lung tumors and 0.2% of non-squamous NSCLC.

Case	TMB/Mb (%ile)	HP indel/Mb	MMR IHC	MMR Gene Mutation	MLH1 Promoter Methylation
1	42.5 (99)	7.08	MLH1/PMS2 loss	MLH1 p.Q328*	ND
2	42.6 (99)	9.88	MLH1/PMS2 loss	MLH1 p.E324*	ND
3	42.6 (99)	8.36	MLH1/PMS2 loss	ND	Y



Discussion

Study strengths

- Large and well characterize cohort (2242)
- Squamous and non-squamous histology
- Large targeted NGS panel
- Correlation with TMB and PD-L1
- All cases were confirmed (PCR/IHC)

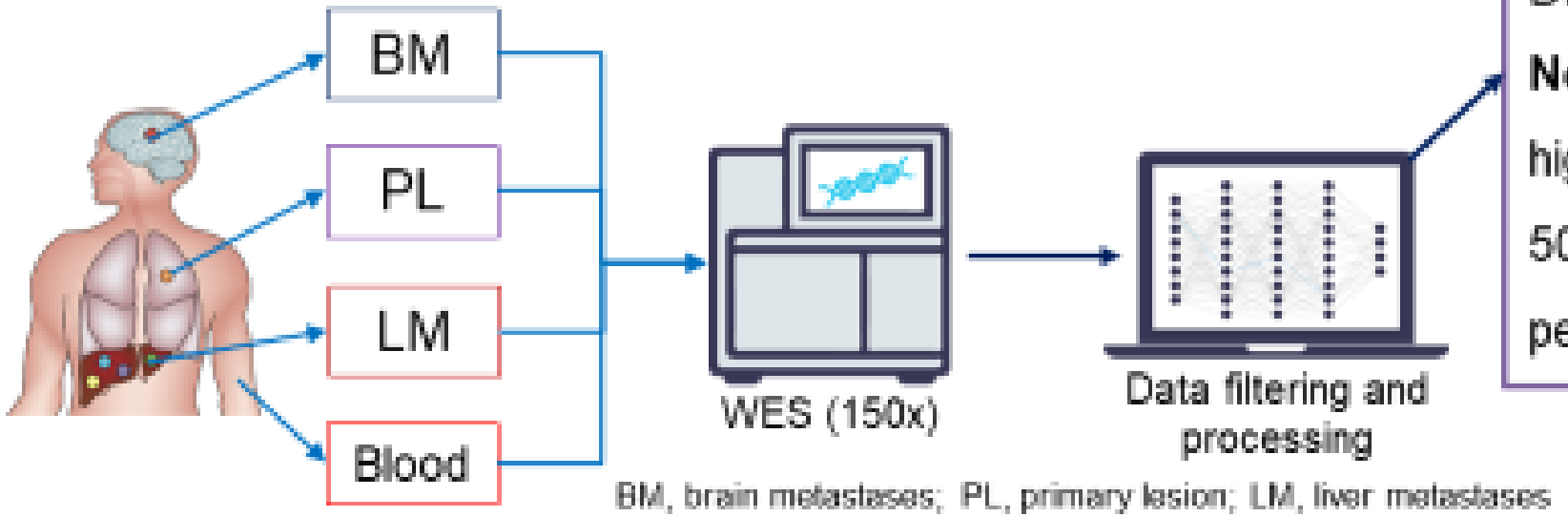
Study limitations

- Restrospective nature of the study
- MSI is a rare feature among NSCLC
- Difficult to extract conclusions (3 cases)
- Other biomarkers are lacking (immune microenvironment, neoantigens characterization…)

PURPOSE

- To compare the **tumor neoantigen landscape** between primary lesions and matched metastases in lung cancer

STUDY DESIGN

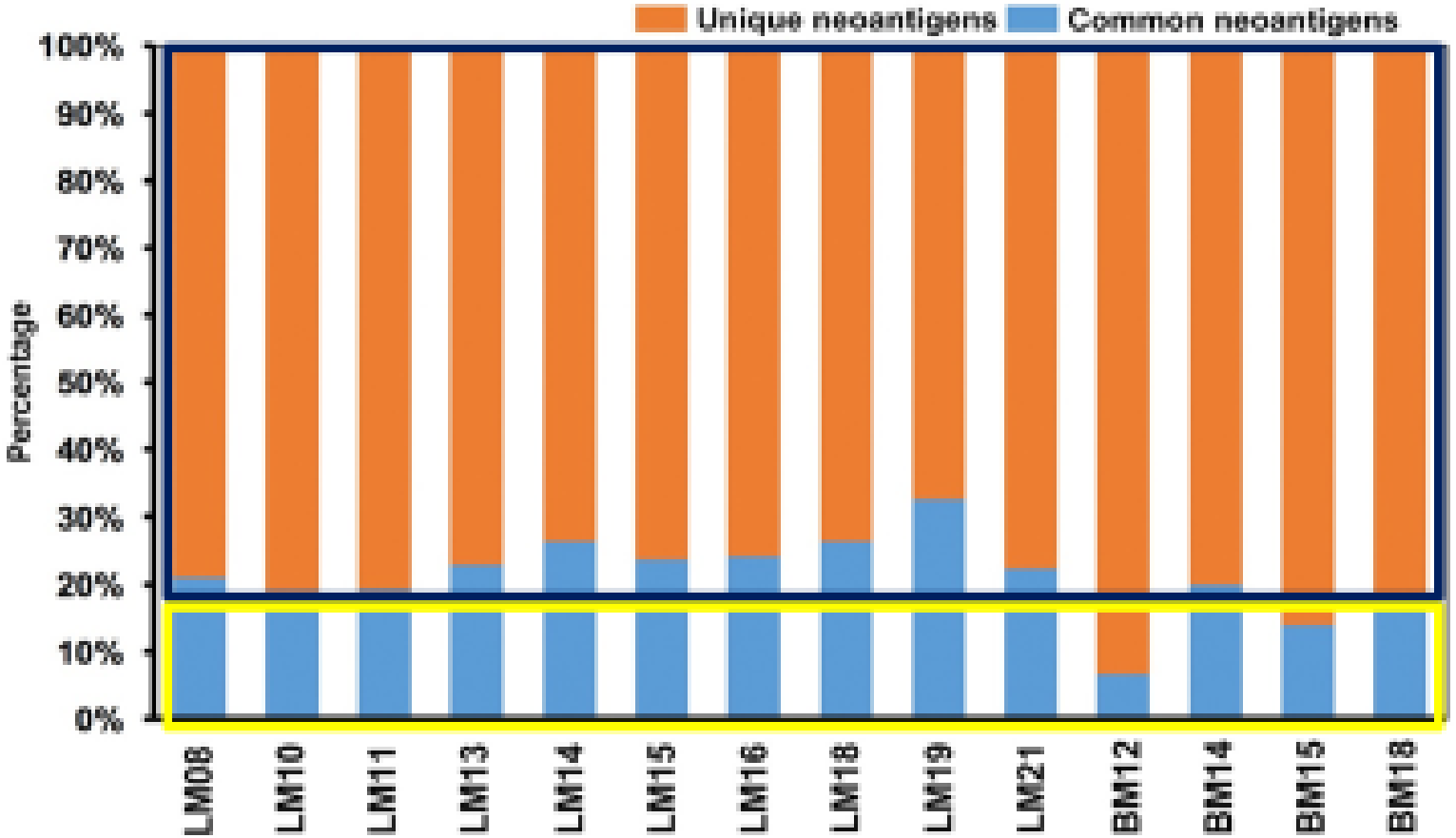


Variants selection: tumor specific, AF≥0.05, DP≥10, mutation reads≥3

Neoantigen prediction: high affinity to HLA (IC_{50}< 500nM), fold change > 10, peptide length 9-10

BM, brain metastases; PL, primary lesion; LM, liver metastases

RESULTS

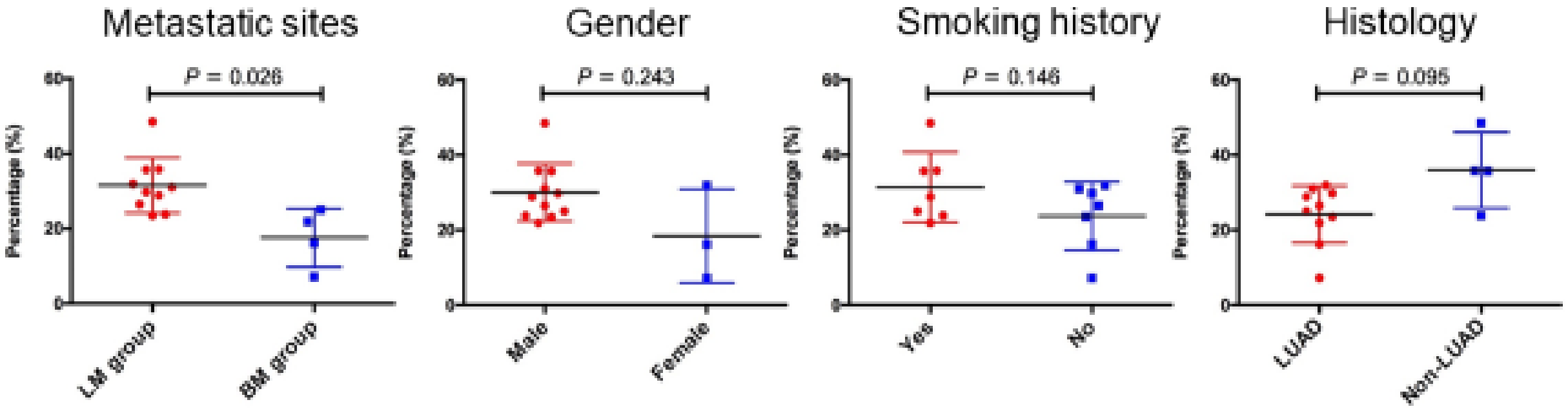


More than 80% of neoantigens are unique, which may not be suitable for vaccination therapy

Potential targets for following vaccination therapy

RESULTS

- Pts with LM had significantly higher **rate of common neoantigens** than those with BM, while gender, smoking and histology had no impact on it



TAKE HOME MESSAGES

Single-cell RNA sequencing is feasible within patient biopsy samples obtained during treatment with targeted therapies

A greater fraction of cytotoxic T cells was seen during response to treatment with targeted therapies, compared to disease progression

Macrophage subpopulations can be identified with gene expression patterns favoring either pro- or anti-inflammatory effect

MMR-D/MSI is very rare in lung carcinoma (0.1%), where it appears to arise as somatic event and is enriched in adenocarcinoma.

MMR-D/MSI lung adenocarcinomas are poorly differentiated and are associated with a moderate/brisk lymphoid infiltrates, as has been seen in other tumor types.

MMR-D/MSI may coexist with other relatively uncommon driver alterations in lung adencarcinoma, including those not traditionally associated with response to immune checkpoint blockade.

Tumor neoantigen burden was similar between primary lesions and metastases in lung cancer

Pts with LM had higher rate of common neoantigens than those with BM

For each case, there was a large percentage of different neoantigens between primary lesion and matched metastasis

Whether this discrepancy could affect the efficacy of personalized vaccine therapy for patients with multiple metastases

Ignacio Gil-Bazo, Clínica Universidad de Navarra, Spain (igbazo@unav.es)

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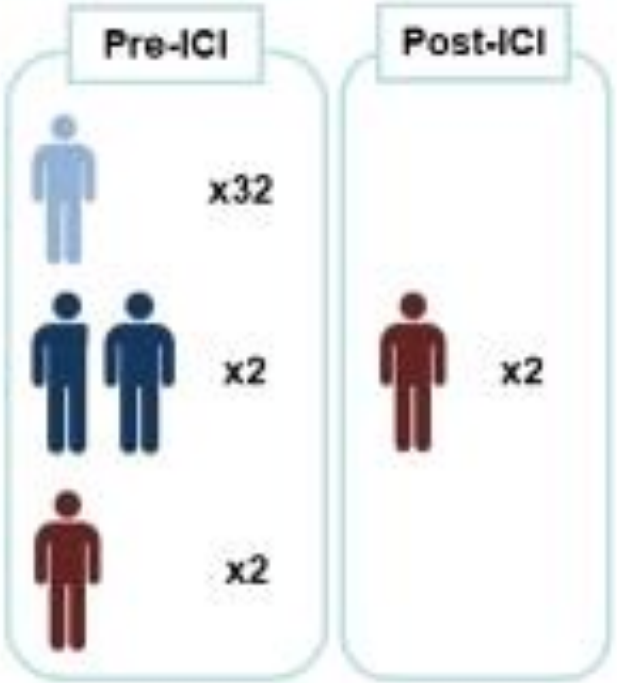
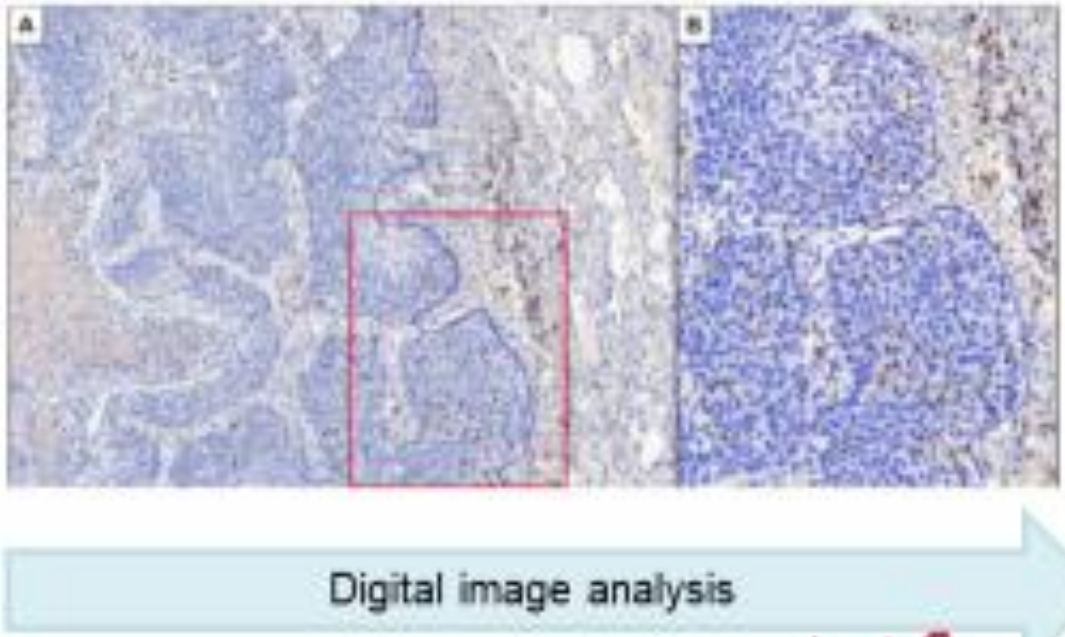
Increased CD3+ T cells with a low FOXP3+/CD8+ T cell ratio can predict anti-PD-1 therapeutic response in non-small cell lung cancer patients

*Hyojin Kim[1], Hyun Jung Kwon[1], Yeon Bi Han[1], Soo Young Park[1], Eun Sun Kim[1], Se Hyun Kim[2], Yu Jung Kim[2], Jong Seok Lee[2], Jin-Haeng Chung[*1]*

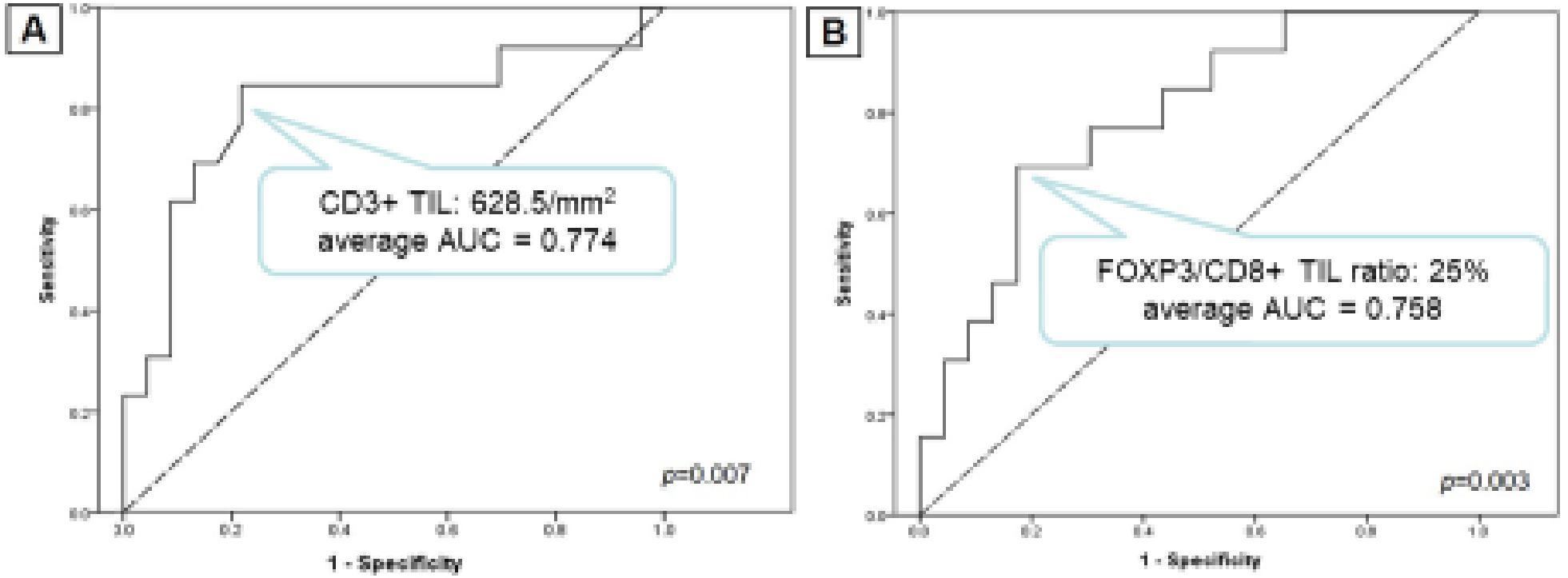
Department of [1]Pathology; and [2]Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

Materials and methods





Results


A
CD3+ TIL: 628.5/mm²
average AUC = 0.774
p=0.007
Sensitivity
1 - Specificity
B
FOXP3/CD8+ TIL ratio: 25%
average AUC = 0.758
p=0.003
Sensitivity
1 - Specificity

Take Home Message

- ✓ A high number of CD3+ T cells and a low FOXP3+/CD8+ T cell ratio were identified as independent factors predicting the response to PD-1 blockade in NSCLC
- ✓ Properly sampled biopsy tissue can be useful in evaluating tumor infiltrating lymphocyte status.

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UNIVERSITY OF NAVARRA

Universidad de Navarra

Prognostic value of complement activation in NSCLC and its association with PD-1 and PD-L1 expression

Daniel Ajona, Maria José Pajares, Javier Freire, Javier Gomez-Roman, Elena Martinez-Terroba, Sergio Ortiz-Espinosa, Ana Lledo, Elisabeth Arenas-Lazaro, Jackeline Agorreta, Fernando Lecanda, **Luis M. Montuenga**, Ruben Pio

Program in Solid Tumors
CIMA-University of Navarra
Pamplona, Spain

19th World Conference on Lung Cancer
September, 2018
Toronto, Canada

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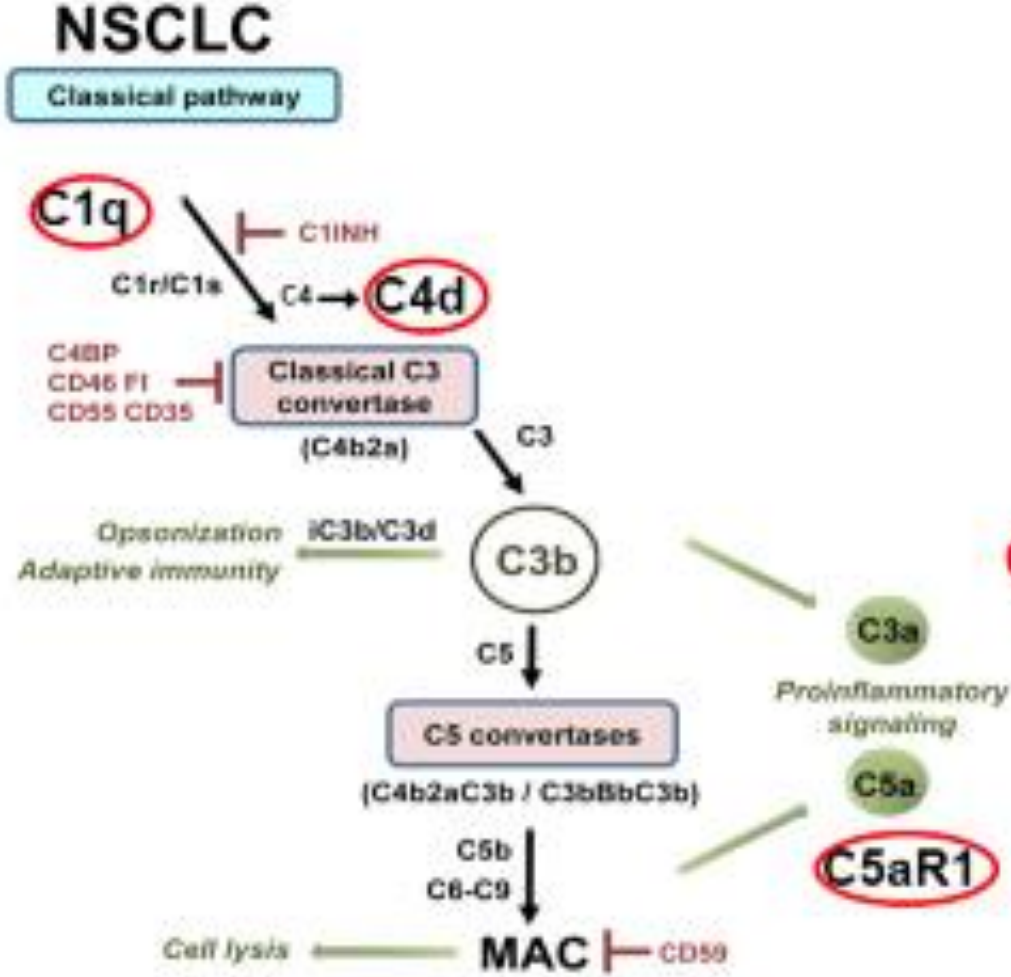
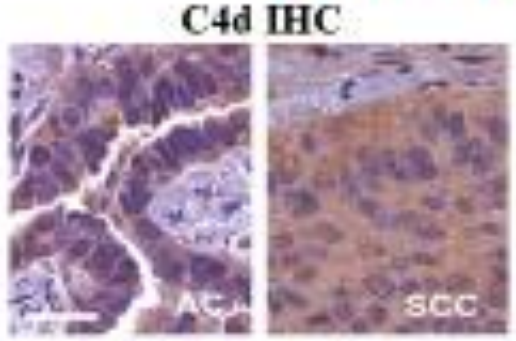
IdiSNA

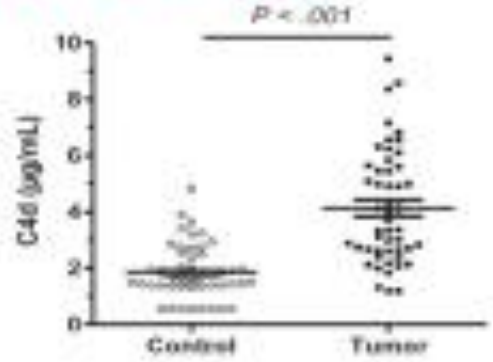
BACKGROUND

The complement system



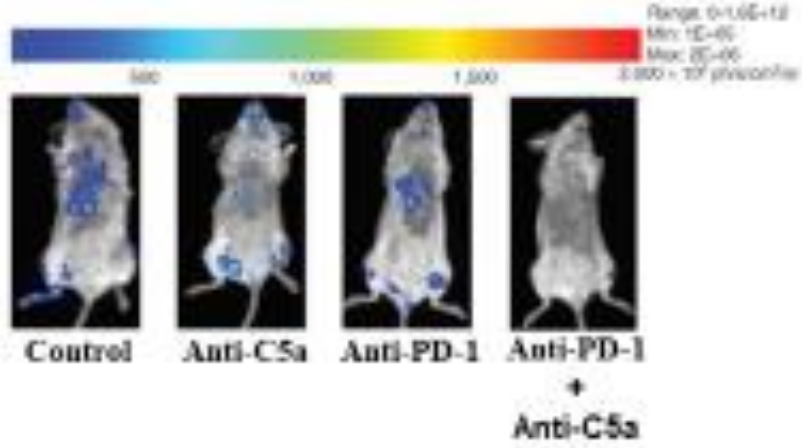
NSCLC cells activate the classical pathway of complement

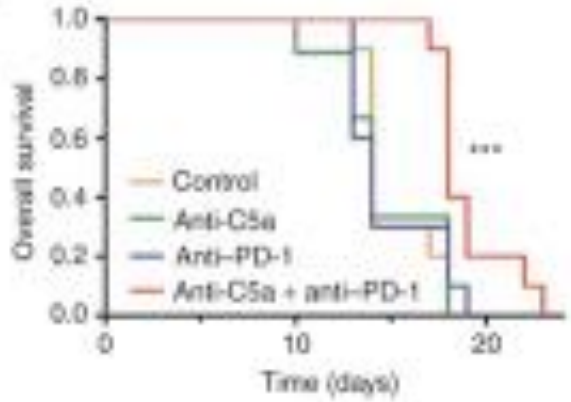




Ajona D et al. JNCI, 2013

Combined PD-1/C5a blockade synergistically protects against lung cancer progression

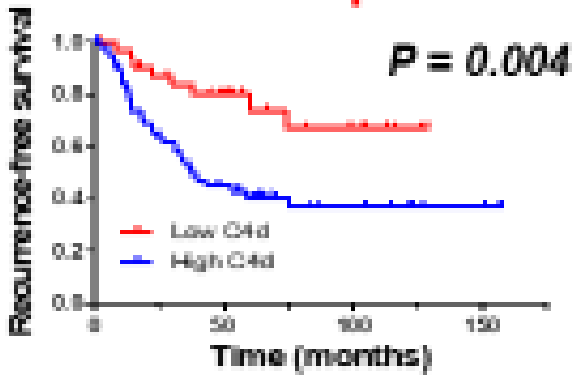


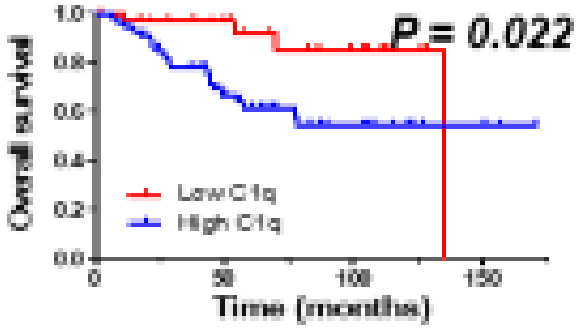


Ajona D et al. Cancer Discovery, 2017

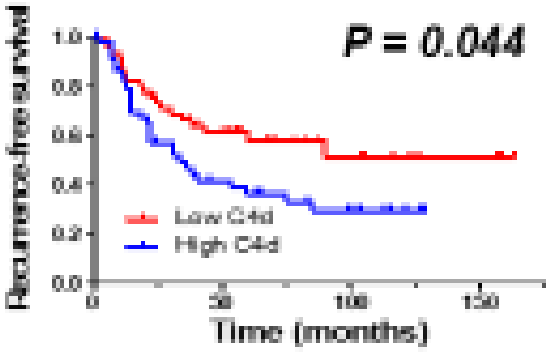
Complement activation predicts poor prognosis in NSCLC patients

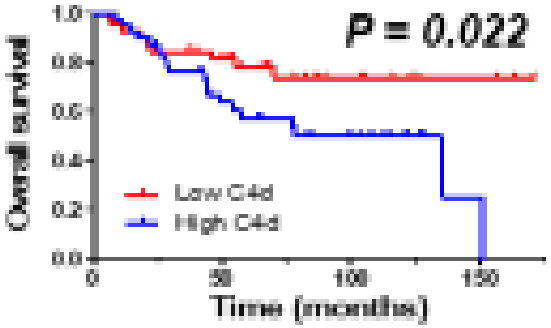
C1q



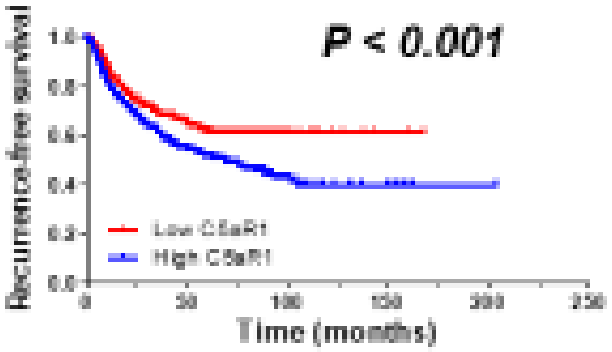


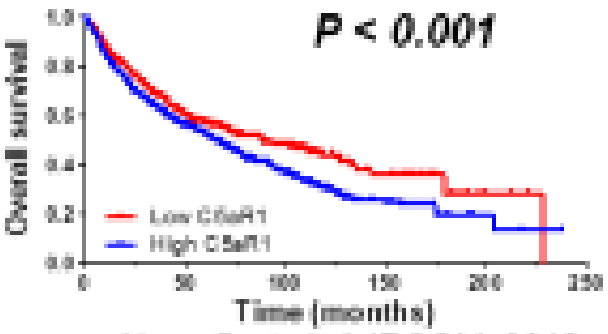
C4d





C5aR1



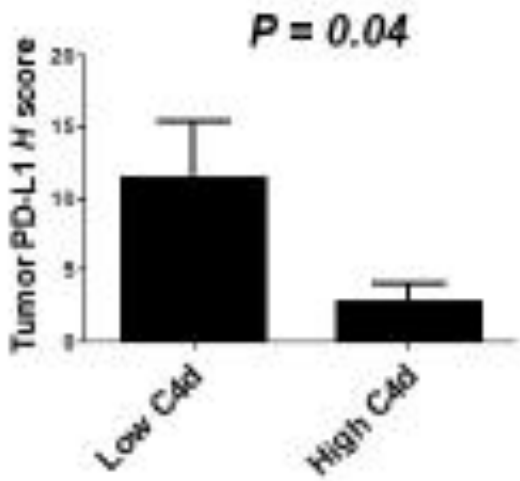


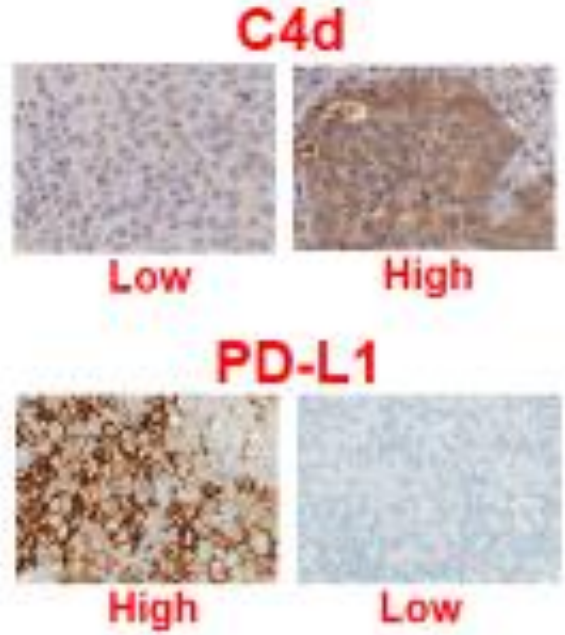
Ajona D et al. AJRCCM, 2018

Univariate and multivariate Cox regression analyses

	RFS				OS			
	Crude HR (95% CI)	P	Adjusted HR (95% CI)*	Adjusted P	Crude HR (95% CI)	P	Adjusted HR (95% CI)*	Adjusted P
C4d	1.808 (1.006-3.24)	0.047	1.531 (2.741-0.846)	0.439	2.465 (1.108-5.485)	0.027	2.818 (1.055-7.546)	0.039
C1q	2.982 (1.372-6.598)	0.006	5.079 (1.315-7.215)	0.01	5.07 (1.051-8.985)	0.04	2.883 (1.075-6.707)	0.035
C5aR1	2.067 (1.109-3.856)	0.022	2.239 (1.158-4.327)	0.017	2.384 (0.98-5.802)	0.055	3.098 (0.982-9.775)	0.054

C4d is associated with low levels of PD-L1 in NSCLC cells





- Prognostic value of PD-1 and PD-L1

	MARKER	TUMOR CELLS	TILs
Disease-free survival	PD-1	n.s	n.s
	PD-L1	n.s	**
Overall survival	PD-1	n.s	n.s
	PD-L1	n.s	n.s

Conclusions

- Complement activity predicts poor prognosis in primary NSCLC.

- C4d, a marker of complement activation, is associated with low levels of PD-L1 on tumor cells.

- Hypothesis: complement activation may modulate and predict response to PD-1/PD-L1 immune checkpoint-based immunotherapies.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THANK YOU