Tumor Biology, Pathology, Novel Diagnostics

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OUTLINE

1. The 9th edition of TNM Classification for lung cancer

--PL04.03 Hisao Asamura and Katie Nishimura

2. Evaluation of Pathological Tumor and Nodal Responses Following Neoadjuvant Chemoimmunotherapy in NSCLC Patients

--OA15.03 Shujie Huang

3. Lung Immune Prognostic Index Predicts Outcomes from Upfront Chemotherapy + Immunotherapy ± Antiangiogenic in Advanced NSCLC

--OA15.05 M. Roulleaux Dugage

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IASLC
2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

The 9th edition of TNM Classification for lung cancer

Hisao Asamura[1] (Japan)
Katie Nishimura[2] (USA)

1. Chair, IASLC Staging and Prognostic Factors Committee (SPFC)
2. Cancer Research And Biostatistics (CRAB)

The IASLC Lung Cancer Staging Project 1990-





	6th edition	7th edition 1st Staging Project	8th edition 2nd Staging Project	9th edition 3rd Staging Project	10th edition 4th Staging Project
Chairperson	Clifton Mountain	Peter Goldstraw	Ramón Rami-Porta	Hisao Asamura	Valerie Rusch
Publication	2002	2010	2017	2024	2031
Period of diagnosis	1975-	1990 to 2000	1999 to 2010	2011 to 2019	
Total patients submitted	5,319	100,869	94,708	124,581	
Geographical origin					
-Europe	0	58,701 (58%)	46,560 (49%)	30,827 (25%)	
-North America	5,319 (100%)	21,130 (21%)	4,660 (5%)	19,608 (16%)	
-Asia/Australia	0	21,038 (21%)	43,298 (46%)	69,749 (56%)	
-South/Central America	0	0	190 (0.3%)	4,225 (3%)	
-Africa/Middle East	0	0	0	172 (0.1%)	
Patients included in analysis		81,495	77,154	87,339	
-NSCLC	5,253 (99%)	68,463 (84%)	70,967 (92%)	72,278 (83%)	
-SCLC		13,032 (16%)	6,189 (8%)	5,561 (7%)	
Treatment modalities					
-Surgery alone	mostly populated with surgical cases	41%	58%	47%	
-Radiotherapy + surgery		5%	2%	2%	
-Chemotherapy + surgery		4%	21%	13%	
-Chemotherapy alone		23%	9%	11%	
-Radiotherapy alone		11%	2%	3%	
-Chemotherapy + radiotherapy		12%	5%	6%	
-Trimodality		3%	4%	13%	
Type of data					
-Electronic data capture			3,905 (5%)	21,505 (25%)	
-Batch			73,251 (95%)	65,834 (75%)	

Add molecular and blood biomarkers?

IASLC 9th Edition, T-category:

No change

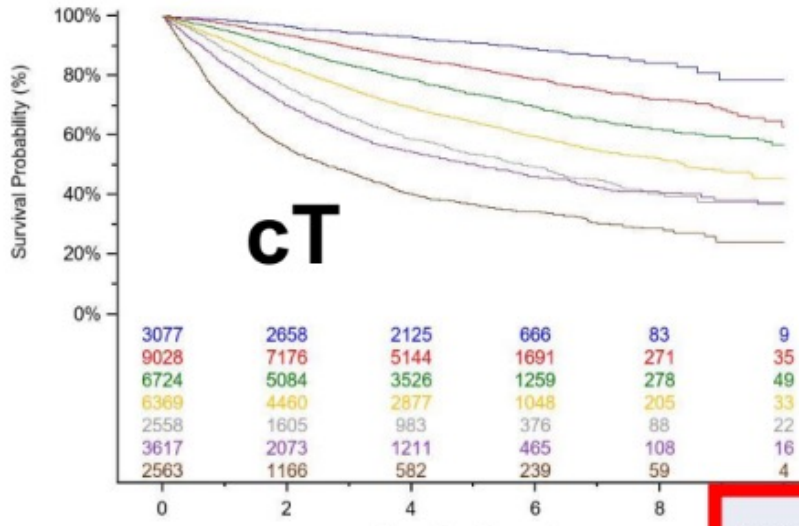
Proposed 9th Edition T-categories			9th Edition
TX		Primary tumor cannot be assessed	No changes
T0		No evidence of primary tumor	No changes
Tis		Carcinoma in situ Tis(AIS): adenocarcinoma Tis(SCIS): squamous cell carcinoma	No changes
T1		Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus). The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.	No changes
	T1mi	Minimally invasive adenocarcinoma	No changes
	T1a	Tumor 1 cm or less in greatest dimension	No changes
	T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension	No changes
	T1c	Tumor more than 2 cm but not more than 3 cm in greatest dimension	No changes
T2		Tumor more than 3 cm but not more than 5 cm; or tumor with any of the following features. T2 tumors with these features are classified T2a if 4 cm or less, or if size cannot be determined; and T2b if greater than 4 cm but not larger than 5 cm. • Involves main bronchus regardless of distance to the carina, but without involving the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung	No changes
	T2a	Tumor more than 3 cm but not more than 4 cm in greatest dimension	No changes
	T2b	Tumor more than 4 cm but not more than 5 cm in greatest dimension	No changes
T3		Tumor more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumours), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary	No changes
T4		Tumors more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary	No changes

IASLC 8th/9th Edition T-category

	cT
T1a vs T1b	<0.0001
T1b vs T1c	<0.0001
T1c vs T2a	<0.0001
T2a vs T2b	<0.0001
T2b vs T3	0.0002
T3 vs T4	<0.0001

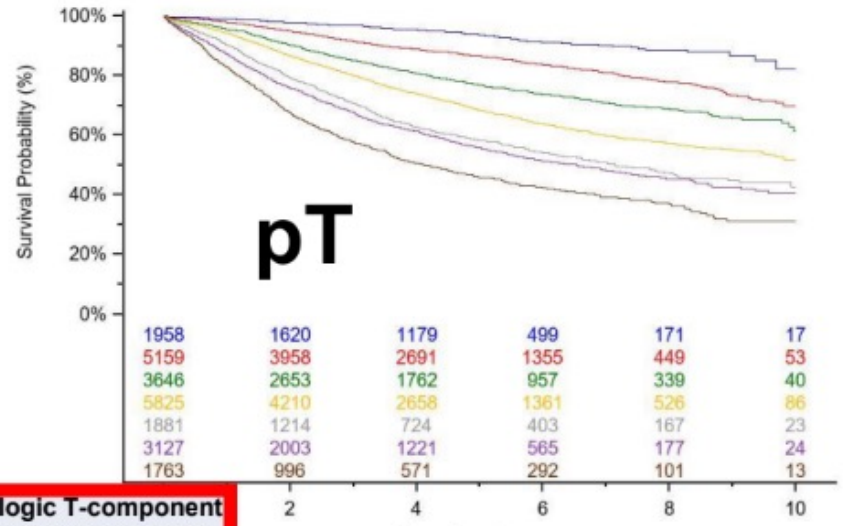
	pT
T1a vs T1b	<0.0001
T1b vs T1c	<0.0001
T1c vs T2a	<0.0001
T2a vs T2b	<0.0001
T2b vs T3	0.0337
T3 vs T4	<0.0001

8th Ed Staging Criteria in 9th Ed Dataset
Clinical Pre-Treatment T-Categories
M0, Any N, Any R



	Deaths / N	Median in Years	5-Year Estimate
T1A	271 / 3077	NR	91% (90, 92)
T1B	1435 / 9028	NR	83% (82, 83)
T1C	1595 / 6724	NR	74% (73, 75)
T2A	2029 / 6369	8 (8, 9)	64% (63, 66)
T2B	1041 / 2558	6 (5, 6)	54% (51, 56)
T3	1573 / 3617	5 (5, 6)	50% (48, 52)
T4	1411 / 2563	3 (2, 3)	37% (35, 39)

8th Ed Staging Criteria in 9th Ed Dataset
Pathologic Post-Surgical T-Categories
M0, Any N, Any R



	Deaths / N	Median in Years	5-Year Estimate
T1A	120 / 1958	NR	94% (93, 95)
T1B	653 / 5159	NR	87% (86, 88)
T1C	746 / 3646	NR	77% (75, 79)
T2A	1659 / 5825	NR	68% (67, 70)
T2B	695 / 1881	7 (7, 8)	58% (56, 61)
T3	1252 / 3127	7 (6, 7)	56% (54, 58)
T4	859 / 1763	4 (4, 5)	46% (43, 49)

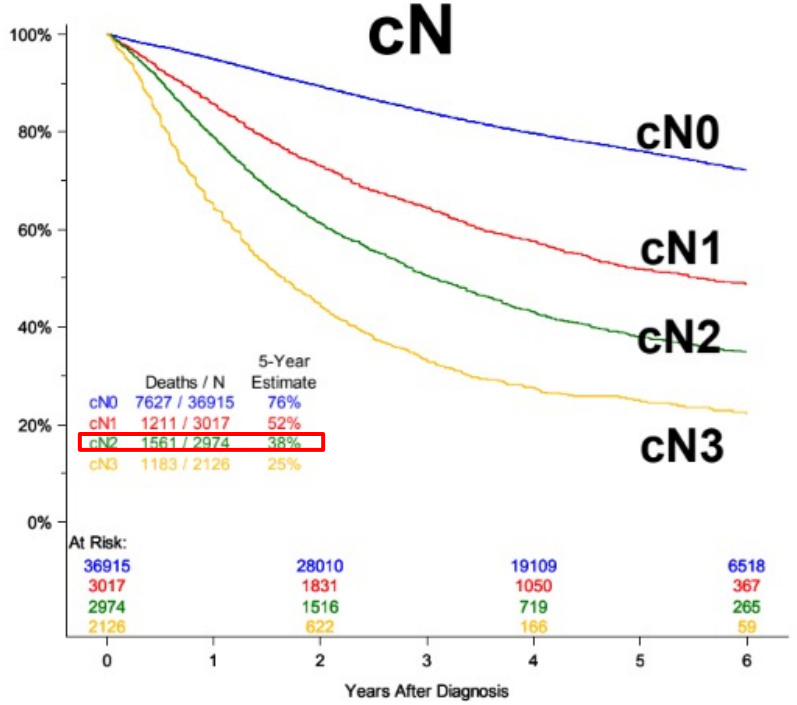
9th Ed Adjusted HR	Clinical T-component n=33,523; R^2=36.3488		Pathologic T-component n=23,196; R^2=34.6729	
	HR (95% CI)	P-value	HR (95% CI)	P-value
T1b (vs T1a)	1.79 (1.58-2.04)	<.0001	1.97 (1.62-2.39)	<.0001
T1c (vs T1b)	1.54 (1.43-1.65)	<.0001	1.63 (1.46-1.81)	<.0001
T2a (vs T1c)	1.36 (1.27-1.45)	<.0001	1.40 (1.29-1.53)	<.0001
T2b (vs T2a)	1.35 (1.25-1.45)	<.0001	1.30 (1.18-1.42)	<.0001
T3 (vs T2b)	1.10 (1.02-1.19)	0.0157	1.13 (1.03-1.24)	0.0107
T4 (vs T3)	1.52 (1.41-1.63)	<.0001	1.33 (1.22-1.45)	<.0001

IASLC 9th Edition, N-category:
Split N2 into N2a and N2b

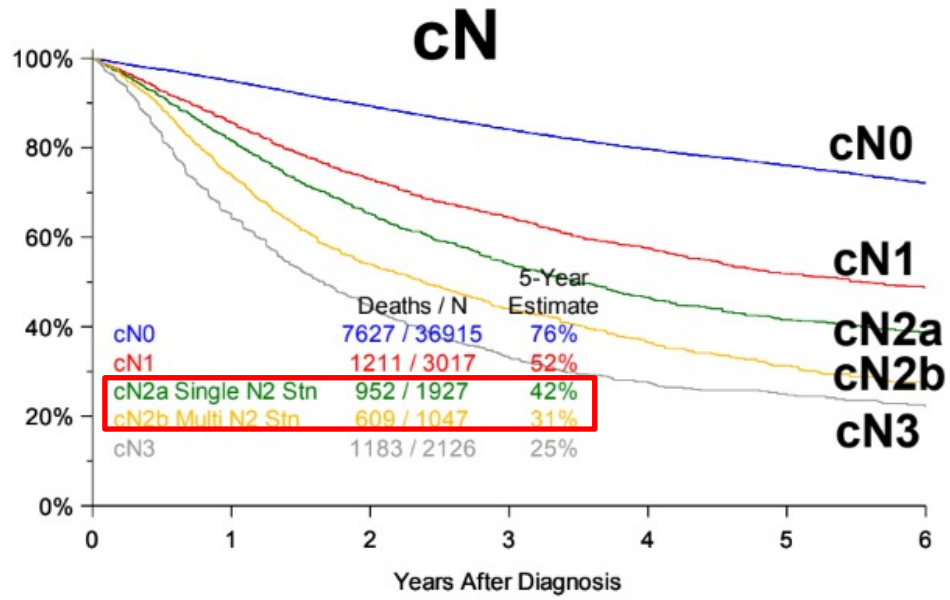
Proposed 9th Edition N-categories		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral h nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal ly
	N2a	Single N2 station involvement
	N2b	Multiple N2 station involvement
N3		Metastasis in contralateral mediastinal, contralateral hil or supraclavicular lymph node(s)

IASLC 8th vs 9th Edition N-category - Clinical

8th Edition Clinical N-category



9th Edition Clinical N-category



	cN (44,309 patients)	
9th Ed Adjusted HR	HR (95% CI)	P-value
N1 vs N0	1.96 (1.84, 2.08)	<0.0001
N2a vs N1	1.42 (1.28, 1.56)	<0.0001
N2b vs N2a	1.27 (1.13, 1.43)	<0.0001
N3 vs N2b	1.51 (1.35, 1.70)	<0.0001

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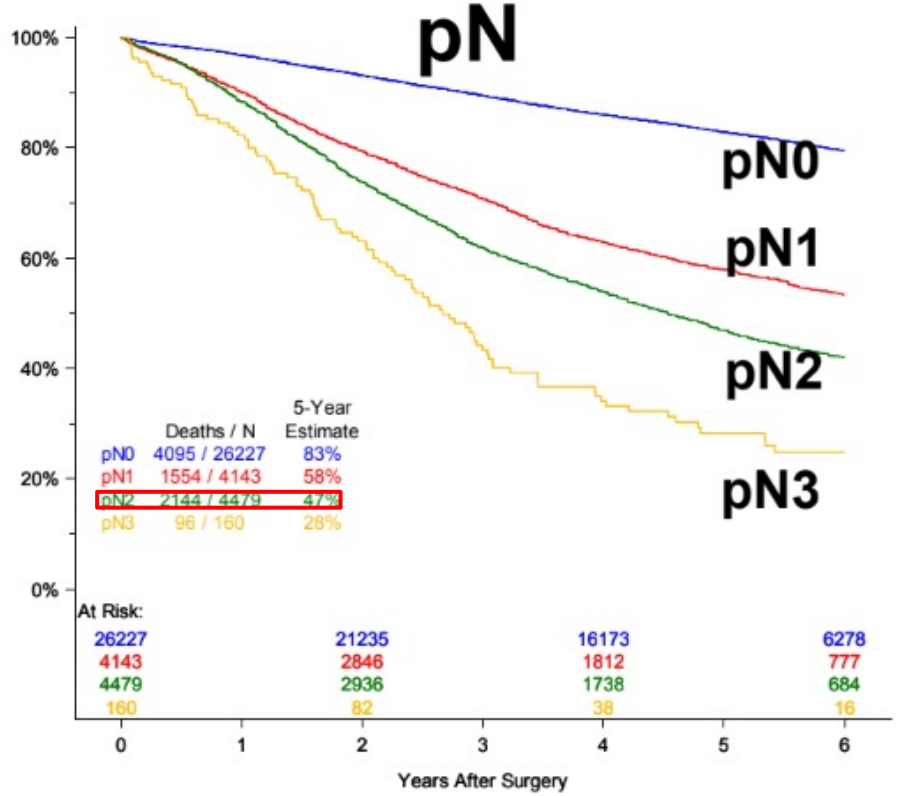
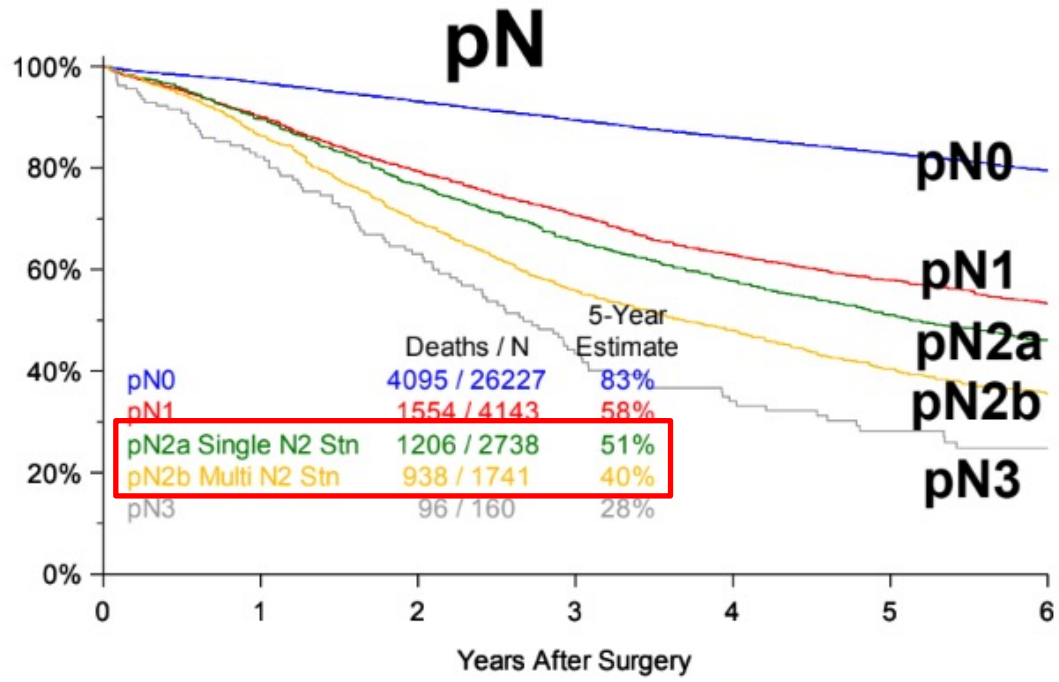
IASLC 8th vs 9th Edition N-category - Pathologic

8th Edition Pathologic N-category



9th Edition Pathologic N-category



9th Ed Adjusted HR	pN (34,379 patients) HR (95% CI)	P-value
N1 vs N0	2.40 (2.26, 2.55)	<0.0001
N2a vs N1	1.45 (1.31, 1.60)	<0.0001
N2b vs N2a	1.46 (1.32, 1.62)	<0.0001
N3 vs N2b	1.62 (1.29, 2.03)	<0.0001

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IASLC 9th Edition, M-category:
Divide M1c into two subcategories

Proposed 9th Edition M-categories		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumor nodule(s) in a pleural or pericardial effusion. to tumor. In a few patients, how (pericardial) fluid are negative Where these elements and clin tumor, the effusion should be e
	M1b	**Single** extrathoracic metastasi (non-regional) node
	M1c1	**Multiple** extrathoracic metasta
	M1c2	**Multiple** extrathoracic metasta

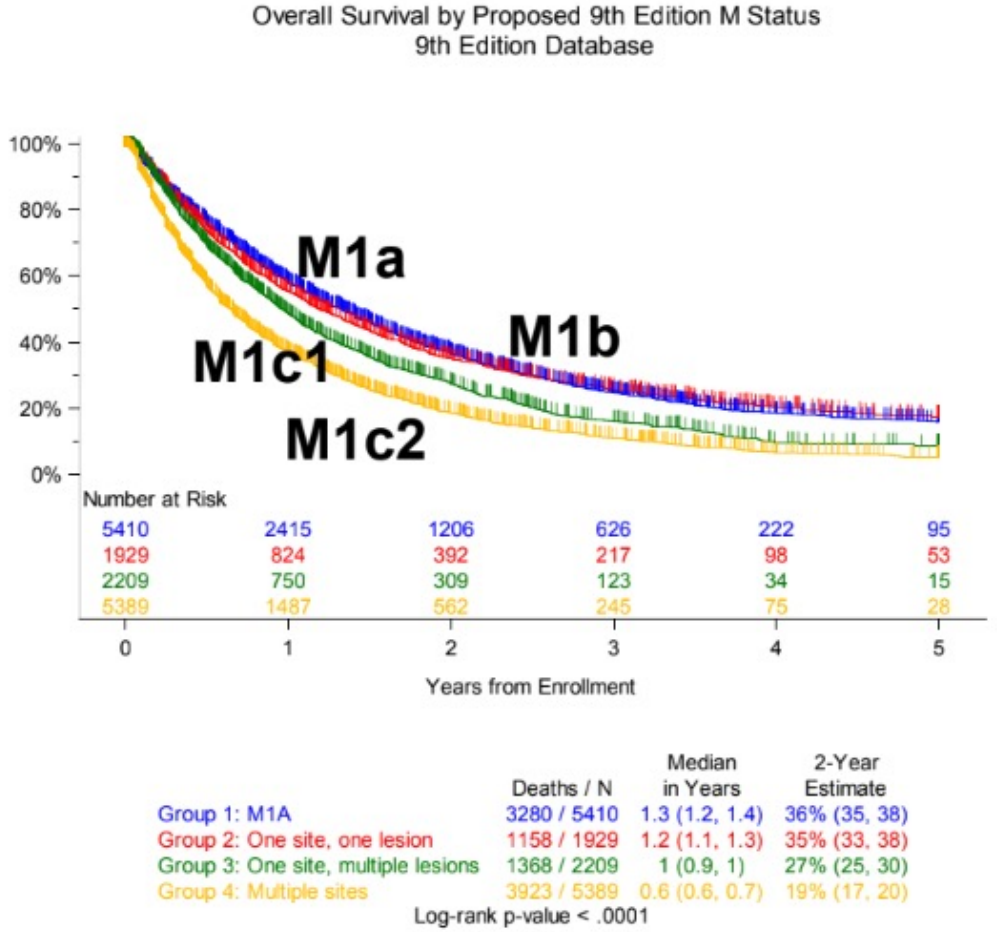
IASLC 8th vs 9th Edition M-category – Clinical: Divide M1c into two Subcategories

M1c1 = Multiple extrathoracic lesions in a single organ system,

M1c2 = Multiple extrathoracic lesions in multiple organ systems

M1a, M1b remain as previously defined.

	cM (14,937 patients)	
9th Ed Adjusted HR	HR (95% CI)	P-value
M1b vs M1a	1.06 (0.99, 1.13)	0.1101
M1c1 vs M1b	1.27 (1.17, 1.37)	<0.0001
M1c2 vs M1b	1.39 (1.31, 1.48)	<0.0001



8th Ed Categories

8th Ed TNM Categories					
T/M	Label	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 Inv	IIB	IIIA	IIIB	IIIC
	T3 Sat	IIB	IIIA	IIIB	IIIC
T4	T4 > 7	IIIA	IIIA	IIIB	IIIC
	T4 Inv	IIIA	IIIA	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIC
M1	M1a Contr Nod	IVA	IVA	IVA	IVA
	M1a Pleur	IVA	IVA	IVA	IVA
	M1b Single Lesion	IVA	IVA	IVA	IVA
	M1c Multiple Lesions	IVB	IVB	IVB	IVB

Proposed 9th Ed TNM Categories

Proposed 9th Ed TNM Categories						
T/M	Label	N0	N1	N2		N3
9th				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
		IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3		IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Satellite nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral nodules	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Contralateral nodules	IVA	IVA	IVA	IVA	IVA
	M1a Pleural, pericardial effusion	IVA	IVA	IVA	IVA	IVA
	M1b Single Extrathoracic Lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. Lesions, Single Organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. Lesions, Mult. Organ systems	IVB	IVB	IVB	IVB	IVB

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Evaluation of combined pathological responses in primary tumor and lymph nodes following neoadjuvant chemoimmunotherapy in non-small cell lung cancer

Shujie Huang

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China

Objective

To depict the pathological combined tumor-nodal response in NSCLC patients after neoadjuvant chemoimmunotherapy as well as the underlying clinical significance

Methods

Time of enrollment: March 2019 ~ April 2022

Sample size: 81 patients

Inclusion: patients aged ≥ 18 with histologically confirmed cT1-4N+M0 NSCLC treated with neoadjuvant chemoimmunotherapy followed by surgery

Exclusion: epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) sensitive mutation

Histological evaluation:

- ypT(MPR): ≤ 10% residual tumor in the primary tumor bed
- ypT(PCR): none of the viable tumor in the primary tumor bed
- ypN0: no evidence of viable tumor in the examined lymph nodes
- ypT(PCR) + ypN0 = combined good-responder group, the rest of the patients were considered as poor-responders

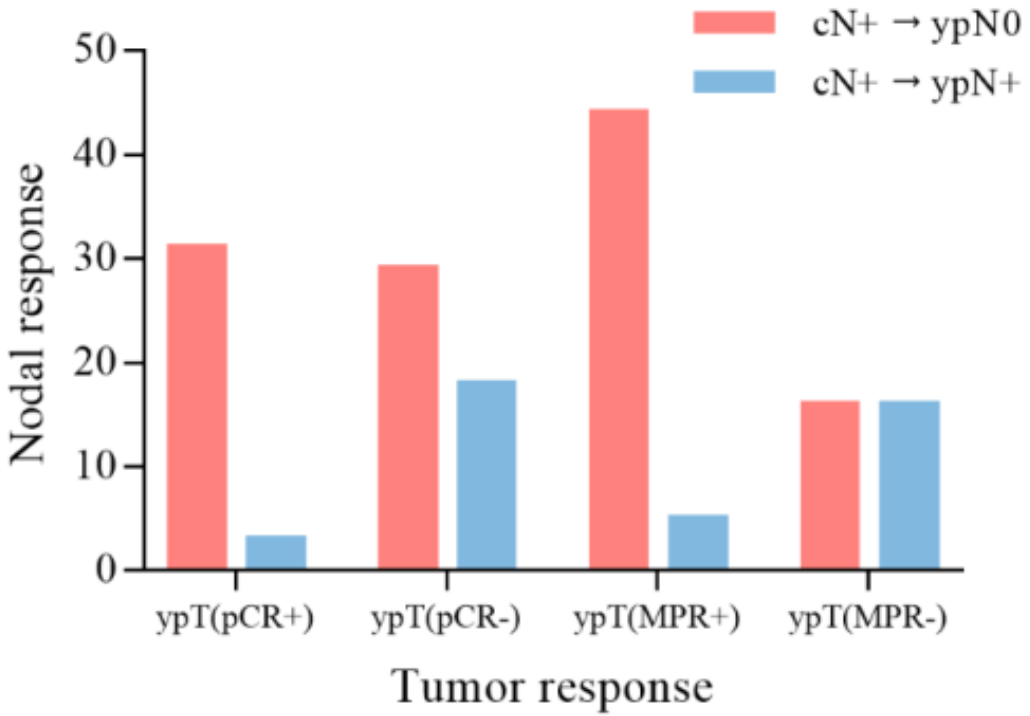
- **Outcome evaluation:**
  - Event-free survival defined as as the time from diagnosis to any progression or recurrence of disease after surgery, or death from any cause.

Clinicopathological characteristics

Characteristics	Total (n=81)
Age (median, IQR)	63 (55-67)
Sex	
Male	71 (87.7%)
Female	10 (12.3%)
Histology	
Adenocarcinoma	21 (25.9%)
Squamous cell carcinoma	50 (61.7%)
Others	10 (12.3%)
Clinical TNM stage	
IIB	10 (12.3%)
IIIA	41 (50.6%)
IIIB	28 (34.6%)
IIIC	2 (2.5%)
Clinical tumor stage	
T1	14 (17.3%)
T2	29 (35.8%)
T3	25 (30.9%)
T4	13 (16.0%)
Clinical nodal stage	
cN1	24 (29.6%)
cN2	49 (60.5%)
cN3	8 (9.9%)

Characteristics	Total (n=81)
Tumor response	
ypT(pCR)	34 (42.0%)
ypT(MPR)	49 (60.5%)
Nodal response	
ypN0	60 (74.1%)
Nodal downstage	66 (81.5%)
Neoadjuvant pathological stage	
0	30 (37.0%)
I	24 (29.7%)
II	15 (18.5%)
III	12 (14.8%)
Combined pathological response	
ypT(pCR+) / ypN0 (combined well responder)	30 (37.0%)
ypT(pCR+) / ypN+	2 (2.5%)
ypT(pCR-) / ypN0	30 (37.0%)
ypT(pCR-) / ypN+	19 (23.5%)
Lymphovascular invasion	
Yes	2 (2.5%)
No	79 (97.5%)
Perineural invasion	
Yes	2 (2.5%)
No	79 (97.5%)
R0	
Yes	76 (93.8%)
No	5 (6.2%)

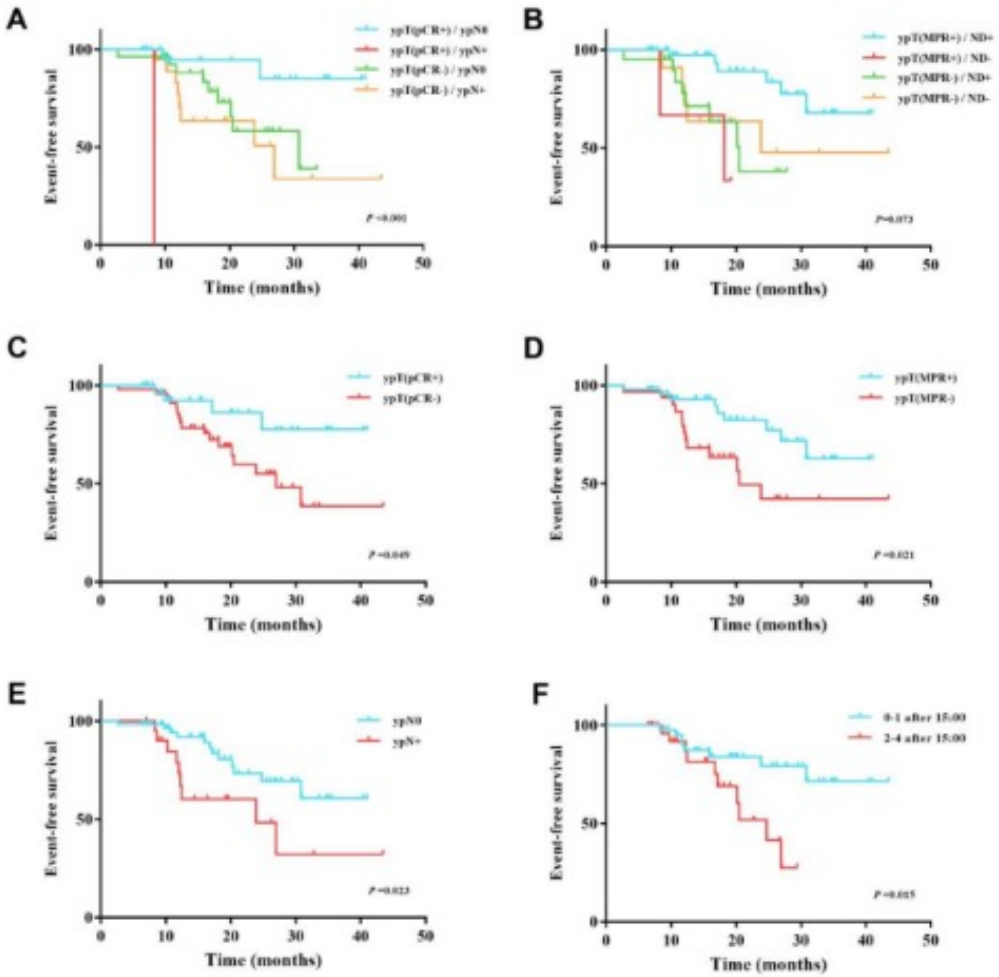
Results



- 34 (42.0%) patients achieved pCR, 60 (74.1%) patients achieved ypN0
- In patients with ypT(PCR+) and ypT(mPR+) status, the nodal responses were better
- In patients with ypT(PCR+) and ypT(mPR+) status, poor nodal responses still can be observed
- In patients with ypT(PCR-) and ypT(mPR-) status, complete nodal response can be achieved, but 38% of ypT(PCR-) cohort and 50% ypT(mPR-) cohort remained nodal-positive

Results

- Significantly better EFS was observed in ypT(pCR+)/ypN0 cohort than that in other cohorts
- Better EFS in patients with ypT(pCR+/mPR+) than ypT(pCR-/mPR-)
- Better EFS in patients with complete nodal response (ypN0) than ypN+
- Receiving immune checkpoint inhibitor infusions after 15:00 more than once was significantly associated with worse EFS



Conclusion and Take home message

- A significant but not absolute correlation was observed between a good tumor response and a good nodal response in NSCLC patients after neoadjuvant chemoimmunotherapy, but an inconsistent response was also found.
- Neoadjuvant chemoimmunotherapy led to a better response in metastatic LNs, which indicates a better prognosis.
- The combination of tumor and nodal response is significantly associated with prognosis and combined good tumor-nodal response can be used as a reliable prognosis predictor.

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Abstract N# 2496, OA15-Pathological Biomarkers for Immunotherapy

Lung Immune Prognostic Index (LIPI) predicts outcomes from upfront chemotherapy + immunotherapy +/- antiangiogenic in advanced NSCLC

Matthieu Roulleaux Dugage[1,2], Teresa Gorria[3], Adrien Rochand[1], Louis-Marie Garcin[1], Stéphane Oudard[1], Víctor Albarrán-Artahona[3], Juan Carlos Laguna[3], Irene Nalda[3], Francisco Javier Muñoz-Carrillo[3], Laia Aguilar[4], Aina Arcocha[3], Lorena Lupinacci[6], Cristina Teixidó[4], Benjamin Besse[5], Laura Mezquita[3,4,7]*, Edouard Auclin[1]*

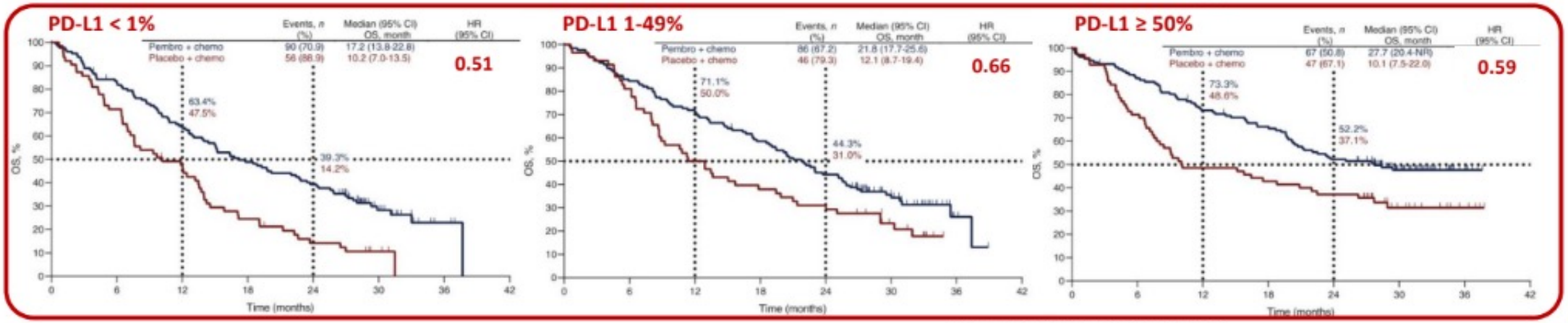
[1] *Medical Oncology Department, Hôpital Européen Georges Pompidou, Paris, France;* [2] *Laboratoire d'Immunomonitoring en Oncologie, Gustave Roussy, Villejuif, France;* [3] *Medical Oncology Department, Hospital Clinic of Barcelona, Spain;* [4] *Laboratory of Translational Genomics and targeted therapies in Solid Tumors, IDIBAPS, Barcelona, Spain;* [5] *Paris-Saclay University, Cancer Medicine Department, Gustave Roussy, Villejuif, France;* [6] *Department of Medicine, Hospital Italiano, Buenos Aires, Argentina;* [7] *Department of Medicine, University of Barcelona, Barcelona, Spain;* ***contributed equally***

Introduction: aNSCLC in the era of combination therapies

	Chemotherapy (CT)	Chemo-immunotherapy (CT+IT) +/- antiangiogenics (AA)
ORR (%)	20-41%	47-64%
mPFS - months	4.9-6.8	6.3-9.0
mOS - months	10.6-14.7	17.5-22.0

Nishio, JTO 2021 – Gandhi, NEJM 2018 - Socinski , NEJM 2018 – West, Lancet Oncol 2019 – Paz-Ares, NEJM 2018 – Jotte, JTO 2020

KEYNOTE-189 : PD-L1 is not a reliable biomarker for chemoimmunotherapy



Rodriguez-Abreu, Ann Oncol 2021

Introduction: LIPI is a simple, low-cost and validated biomarker

Tumor burden
Tumor glycolysis
Immune suppression

LDH
plasmatic levels

Neutrophils :
Immune suppression
NETosis, ROS production

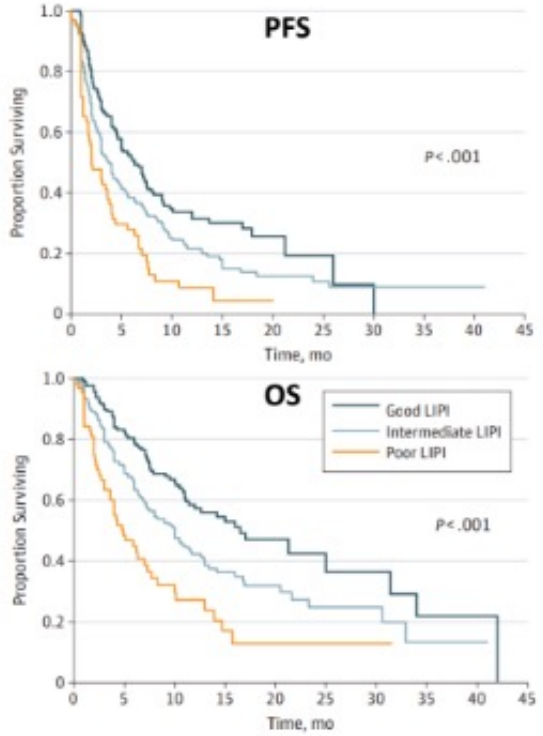
dNLR
$\frac{neutrophils}{leucocytes - neutrophils}$

Lung Immune Prognostic Index (LIPI)

LIPI good :
dNLR<3 + LDH<ULN

LIPI intermediate :
dNLR≥3 or LDH≥ULN

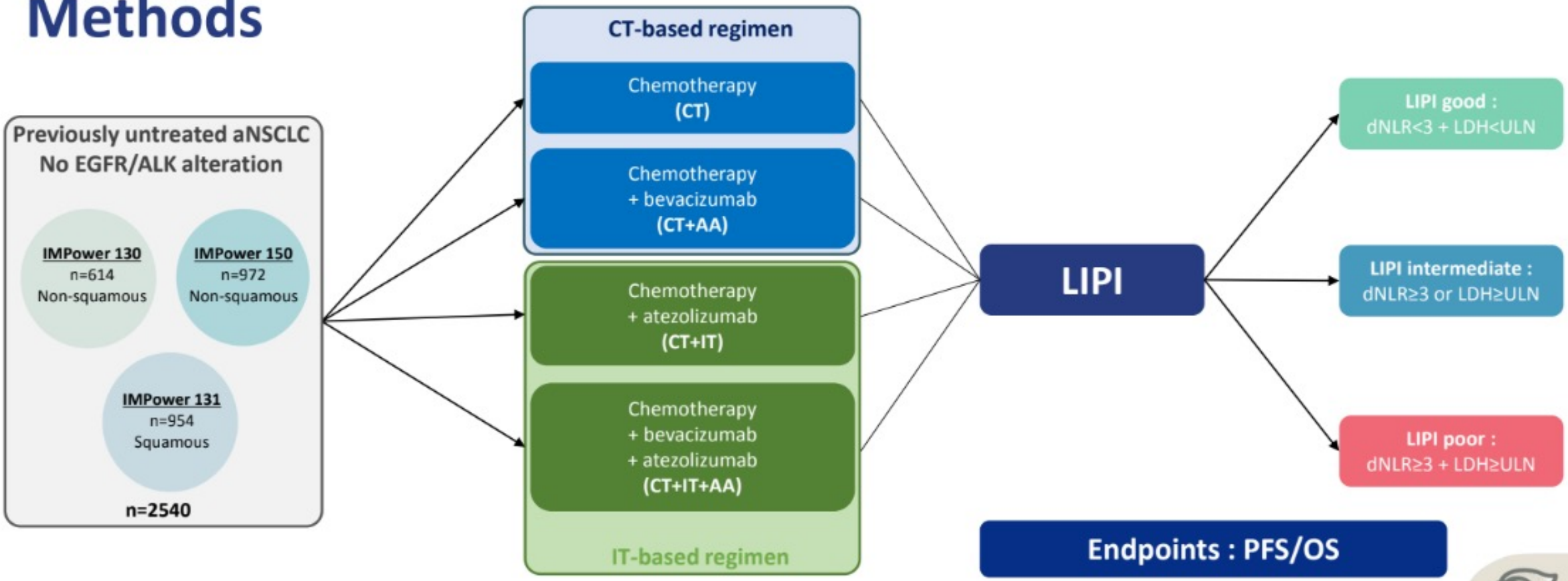
LIPI poor :
dNLR≥3 + LDH≥ULN



Miholjcic, EJC 2023
Hendrick, Nat Rev Immunol 2022
Mequita, JAMA Oncol 2018

Objective : Validation of the independent prognostic value of LIPI and to explore its predictive role in 1st line combination therapies in aNSCLC

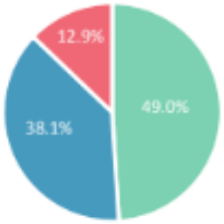
Methods


Previously untreated aNSCLC
No EGFR/ALK alteration
IMPower 130
n=614
Non-squamous
IMPower 150
n=972
Non-squamous
IMPower 131
n=954
Squamous
n=2540
CT-based regimen
Chemotherapy
(CT)
Chemotherapy
+ bevacizumab
(CT+AA)
Chemotherapy
+ atezolizumab
(CT+IT)
Chemotherapy
+ bevacizumab
+ atezolizumab
(CT+IT+AA)
IT-based regimen
LIPI
LIPI good :
dNLR<3 + LDH<ULN
LIPI intermediate :
dNLR≥3 or LDH≥ULN
LIPI poor :
dNLR≥3 + LDH≥ULN
Endpoints : PFS/OS

Results

		LIPI good n=1235 - 48.6%	LIPI intermediate n=1037 - 40.8%	LIPI poor n=268 - 10.6%	p-value
Treatment	CT	250 (20.2%)	218 (21%)	61 (22.8%)	0.90
	CT+AA	152 (12.3%)	134 (12.9%)	29 (10.8%)	
	CT+IT	669 (54.2%)	555 (53.5%)	140 (52.2%)	
	CT+IT+AA	164 (13.3%)	130 (12.5%)	38 (14.2%)	
Histology	Squamous	460 (37.2%)	404 (39%)	89 (33.2%)	0.21
Age	≤65	668 (54.1%)	579 (55.8%)	146 (54.5%)	0.70
	>65	567 (45.9%)	458 (44.2%)	122 (45.5%)	
Sex	Female	366 (29.6%)	332 (32%)	88 (32.8%)	0.37
Smoking status	Current	308 (24.9%)	291 (28.1%)	62 (23.1%)	0.26
	Previous	779 (63.1%)	636 (61.3%)	178 (66.4%)	
	Never	148 (12%)	110 (10.6%)	27 (10.1%)	
ECOG PS	0	532 (43.3%)	388 (37.5%)	73 (27.3%)	<0.001
	1	**696 (56.6%)**	**647 (62.5%)**	**194 (72.7%)**	
	2	1 (0.1%)	0 (0%)	0 (0%)	
KRAS	Mutated	87 (35.7%)	71 (33.8%)	22 (36.1%)	0.90
	Unknown	991	827	207	
Number of metastatic sites - median (min-max)		**2 (0-6)**	**2 (1-7)**	**2 (0-8)**	<0.001
Albumin (g/L) – median (min-max)		**40 (15-51)**	**38.2 (15-51)**	**36 (10-50)**	<0.001
PD-L1 TPS	<1%	825 (66.8%)	677 (65.3%)	187 (69.8%)	0.68
	1-49%	257 (20.8%)	231 (22.3%)	50 (18.6%)	
	≥50%	153 (12.4%)	129 (12.4%)	31 (11.6%)	

IMpower130



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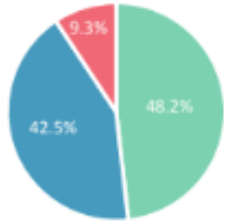

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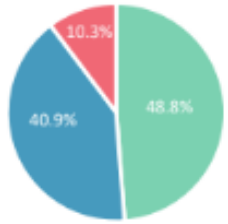
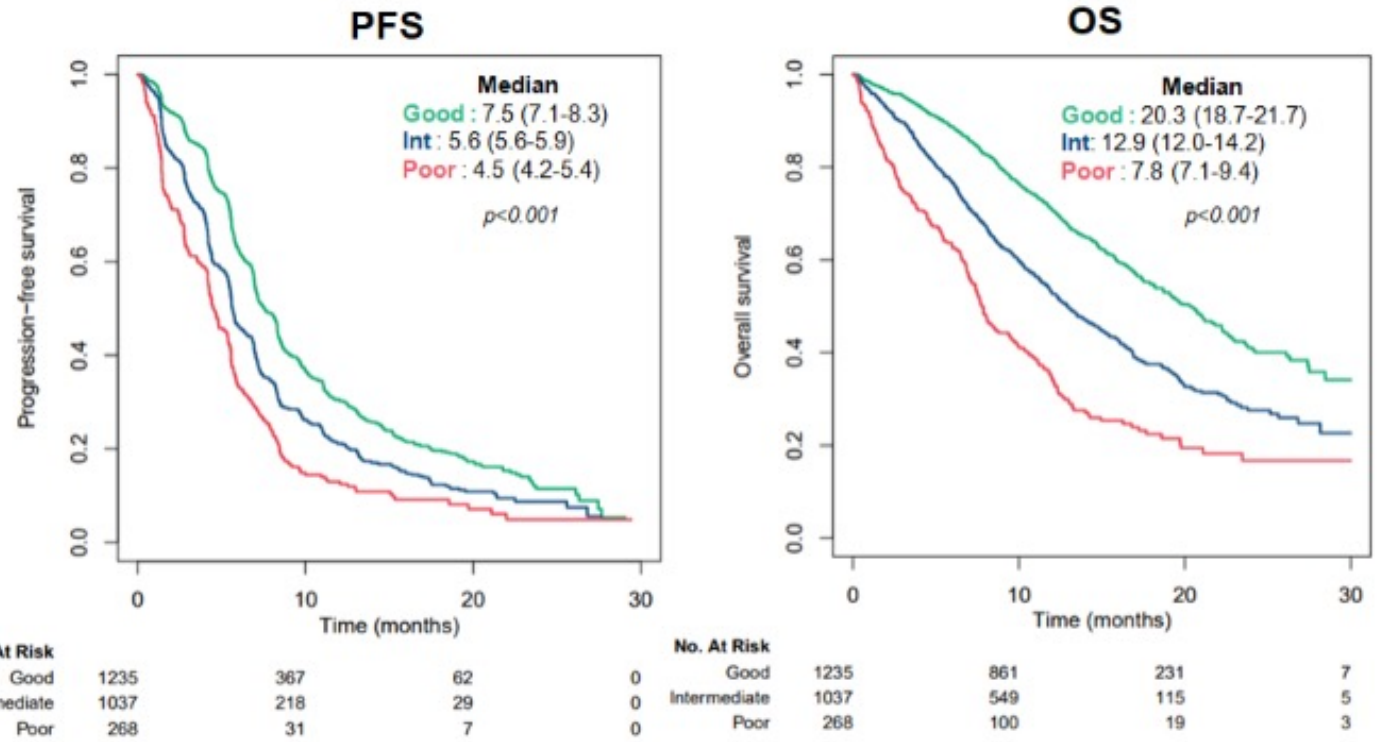


LIPI is a strong independent prognostic factor in first-line aNSCLC



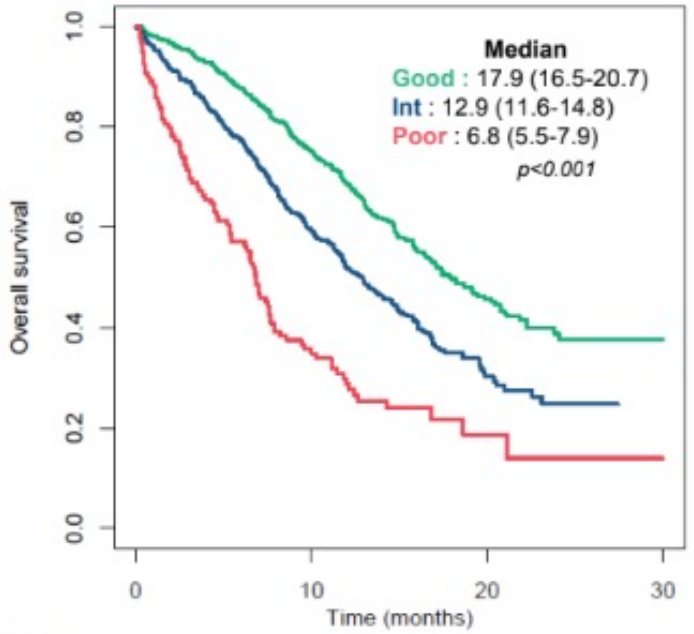
MULTIVARIATE ANALYSIS*			
Treatment	LIPI	HR for OS (95% CI) vs. LIPI good	p-value
CT	Intermediate	1.63 (1.28-2.08)	<0.001
	Poor	2.07 (1.47-2.92)	<0.001
CT+AA	Intermediate	1.78 (1.25-2.54)	0.001
	Poor	3.26 (1.92-5.52)	<0.001
CT+IT	Intermediate	1.59 (1.36-1.86)	*<0.001*
	Poor	2.64 (2.1-3.32)	*<0.001*
CT+IT+AA	Intermediate	2 (1.35-2.95)	<0.001
	Poor	5.53 (3.32-9.21)	<0.001

age, smoking status, PD-L1, number of metastatic sites, brain or **liver involvement and **performance status***

LIPI can be combined with PD-L1 expression for IT-based regimen

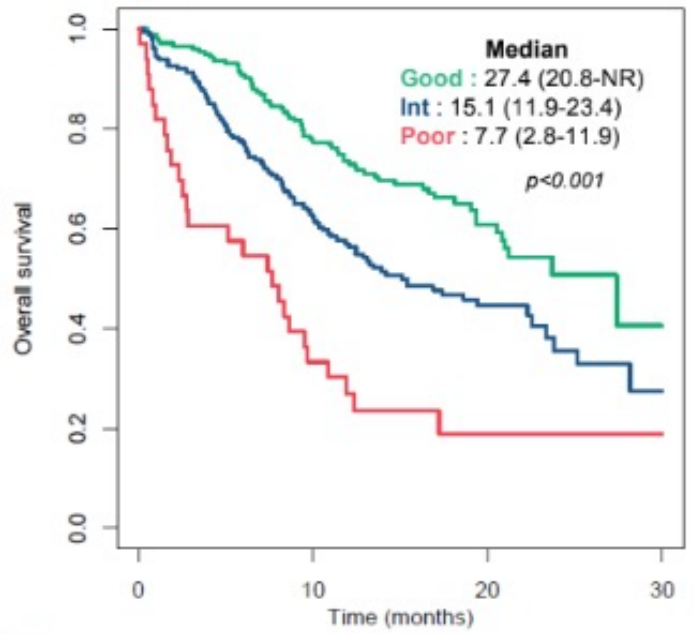
OS

PD-L1 <1%



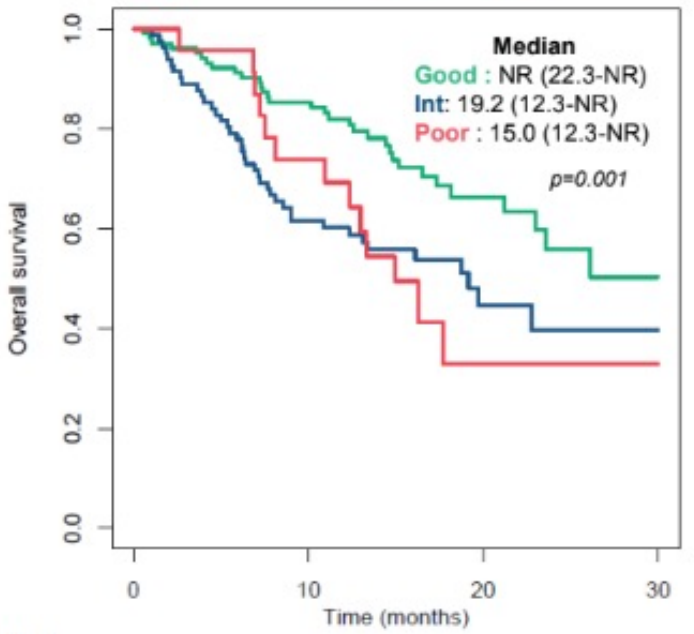
No. At Risk				
Good	549	377	85	1
Intermediate	438	229	38	0
Poor	120	38	4	1

PD-L1 1-49%



No. At Risk				
Good	179	127	42	1
Intermediate	165	95	35	3
Poor	35	11	4	1

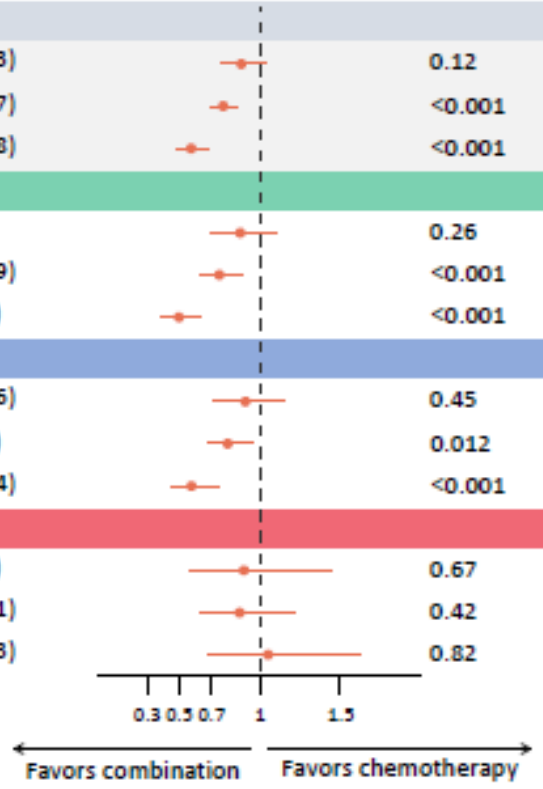
PD-L1 ≥ 50%

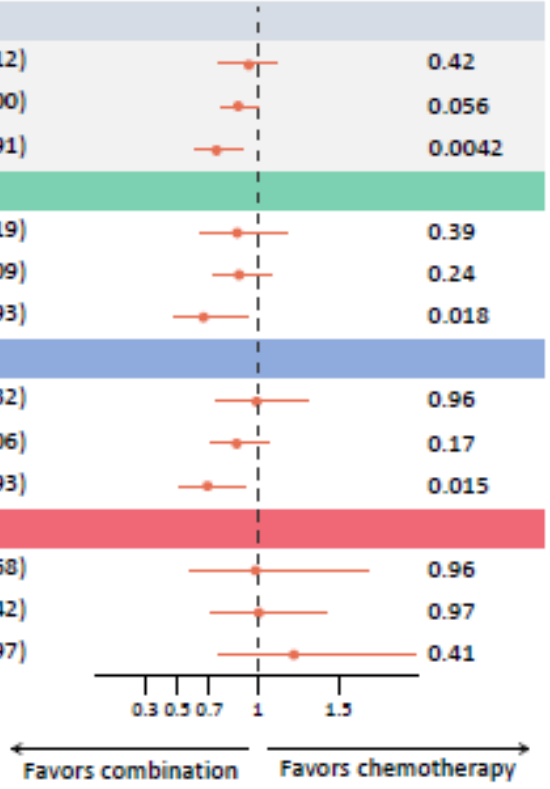


No. At Risk				
Good	105	80	25	3
Intermediate	82	45	13	1
Poor	23	16	3	1

LIPI is correlated with benefit from CT-IT combinations vs. CT

Group	Treatment	n	Progression-free survival		Overall survival	
		Combo/CT	HR for PFS (95%CI)	p-value	HR for OS (95%CI)	p-value
Overall						
	CT+AA	315/529	0.88 (0.76-1.03)	0.12	0.92 (0.76-1.12)	0.42
	CT+IT	1364/529	0.77 (0.69-0.87)	<0.001	0.88 (0.77-1.00)	0.056
	CT+IT+AA	332/529	0.48 (0.49-0.68)	<0.001	0.74 (0.61-0.91)	0.0042
LIPI Good						
	CT+AA	152/250	0.88 (0.7-1.1)	0.26	0.87 (0.64-1.19)	0.39
	CT+IT	669/250	0.75 (0.63-0.89)	<0.001	0.88 (0.72-1.09)	0.24
	CT+IT+AA	164/250	0.5 (0.39-0.64)	<0.001	0.67 (0.47-0.93)	0.018
LIPI Intermediate						
	CT+AA	134/218	0.91 (0.72-1.16)	0.45	0.99 (0.75-1.32)	0.96
	CT+IT	555/218	0.8 (0.67-0.95)	0.012	0.87 (0.71-1.06)	0.17
	CT+IT+AA	130/218	0.58 (0.45-0.74)	<0.001	0.69 (0.51-0.93)	0.015
LIPI Poor						
	CT+AA	29/61	0.9 (0.56-1.45)	0.67	0.99 (0.58-1.68)	0.96
	CT+IT	140/61	0.88 (0.64-1.21)	0.42	1.01 (0.71-1.42)	0.97
	CT+IT+AA	38/61	1.05 (0.68-1.63)	0.82	1.22 (0.76-1.97)	0.41





Take-home messages

- This is the first validation of LIPI as a **strong independent prognostic factor** in first-line aNSCLC **regardless treatment regimen in prospective setting** of clinical trials
- LIPI provides **additional information to PD-L1** and should be considered in IT clinical trials as **stratification factor**

- LIPI **good**/**intermediate** patients yield greater benefit from **CT+IT+AA**

- **LIPI poor** population was consistently associated with:
  - **Poor PFS/OS outcomes**
  - **No benefit of IT**-containing regimen compared to chemotherapy
  - Innovative approaches are needed

- Prospective studies should confirm the additional predictive value for guiding treatment selection