Neoadjuvante und adjuvante Therapie des NSCLC mit Immun Checkpoint Inhibitoren

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Declaration of Interest

Consultancies Speaker's Honoraria:

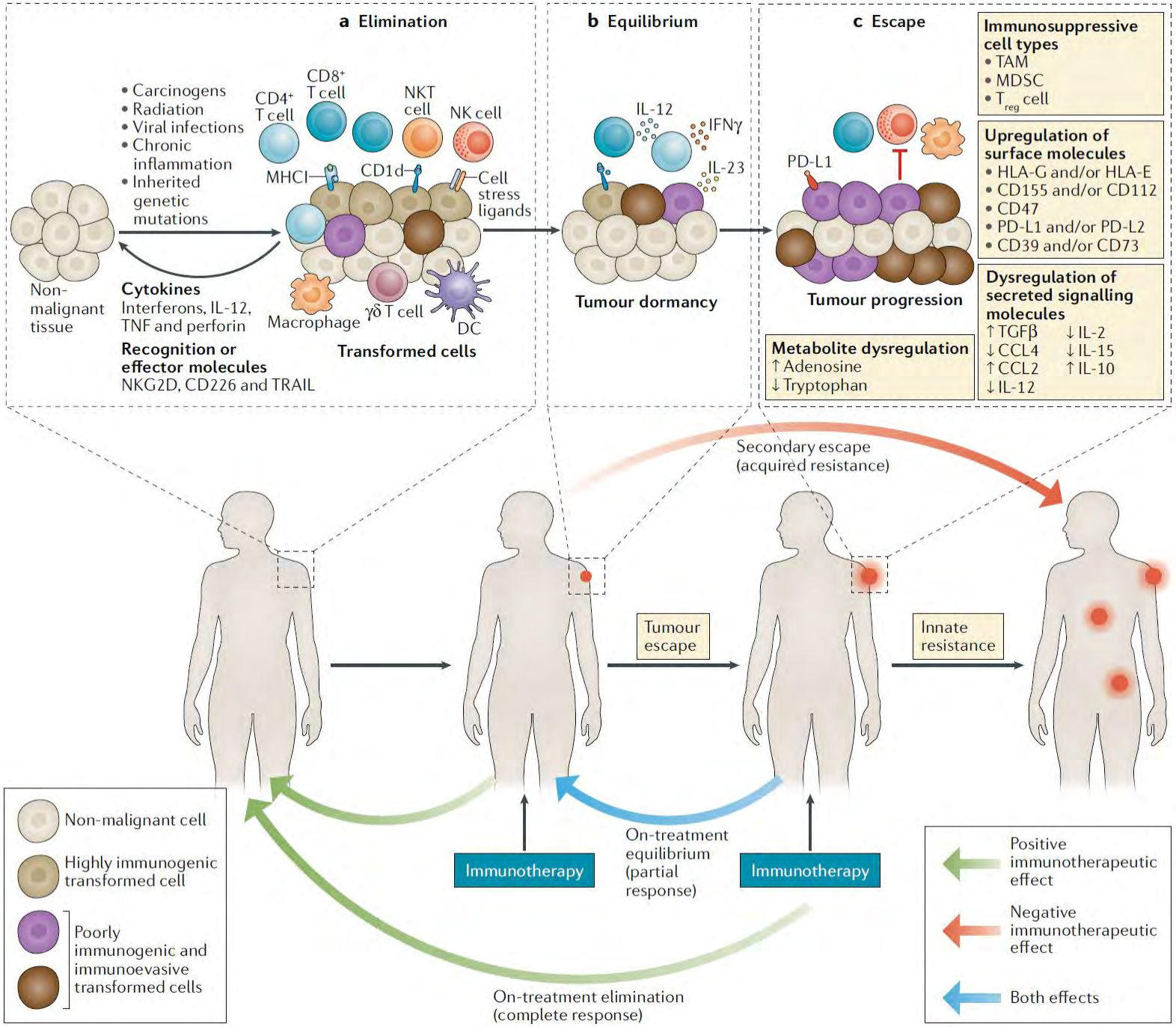
Roche, Novartis, BMS, MSD, Imugene, Ariad, Pfizer, Merrimack, Merck KGaA, Fibrogen, AstraZeneca, Tesaro, Gilead. Eli Lilly, Athenex

Krebs als immunologische Erkrankung

Krebs beinhaltet immer ein Versagen des Immunsytems. Mögliche Epitope werden toleriert.

Entwicklung und Progredienz sind von immunologischer Evolution begleitet.

Die häufigsten Mutationen und Translokationen sind nicht immunogen.



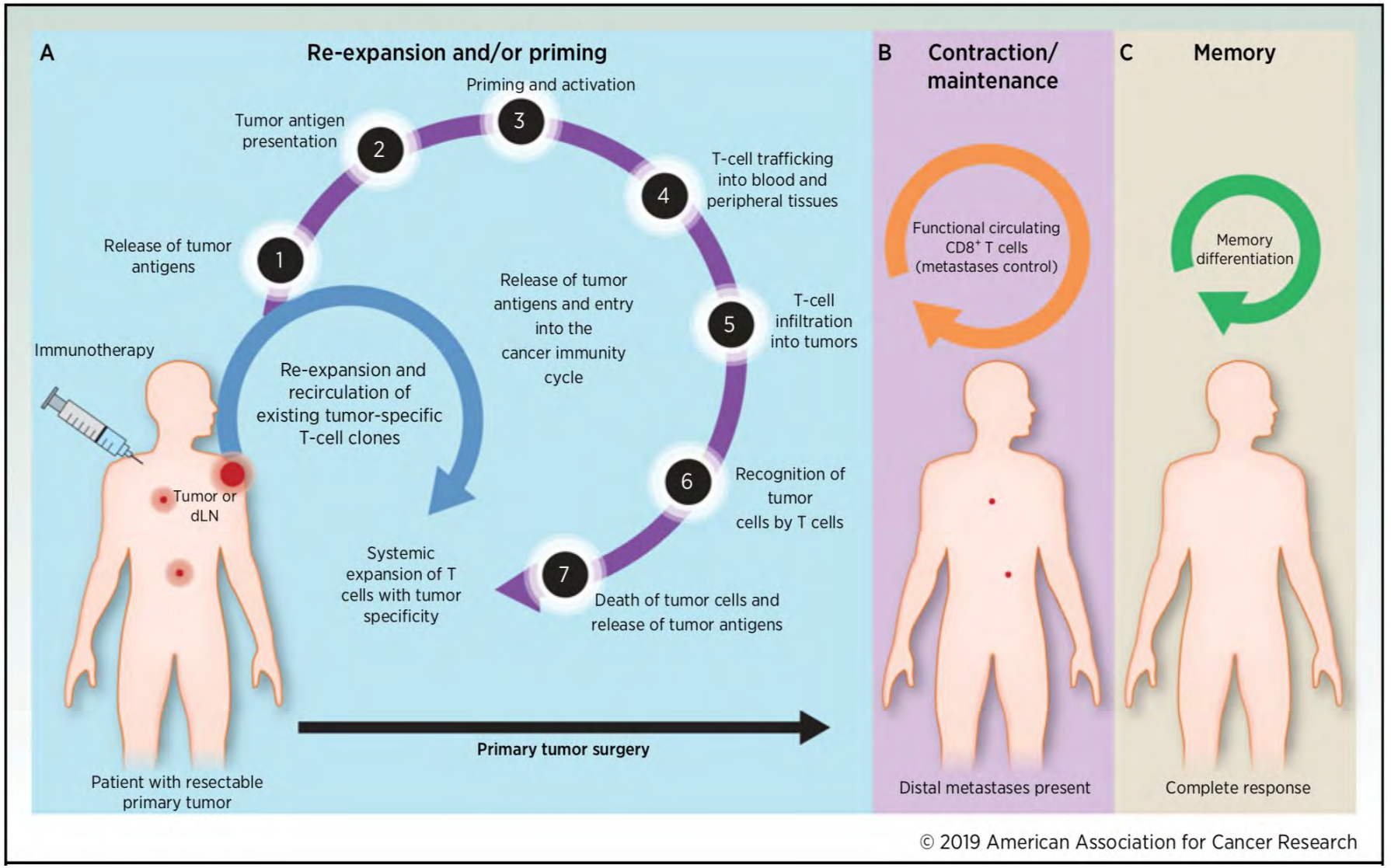
O'Donnell et al., Nat Rev Clin Oncol 2019

Immun Checkpoint Inhibitoren bei NSCLC: Themen

1. Neoadjuvante Therapie
2. Adjuvant Therapie

nicht inkludiert: nicht resektables NSCLC

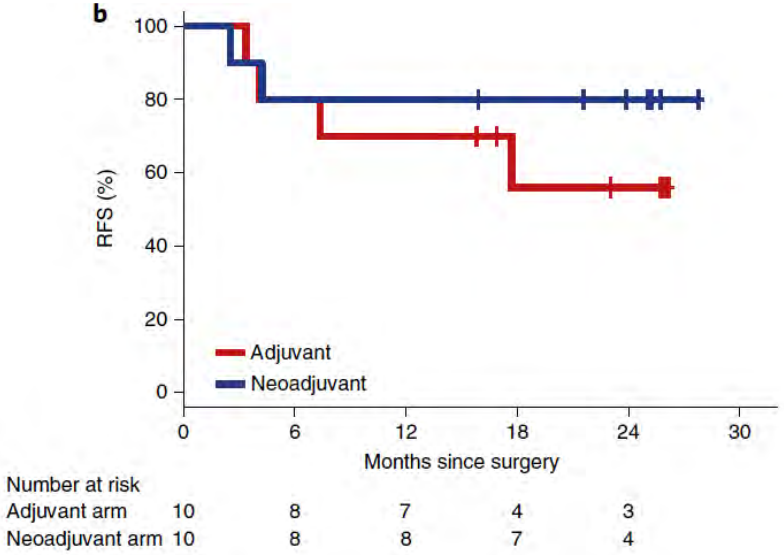
Neoadjuvante Immunotherapie und Tumor-spezifische T-Zell-Antwort

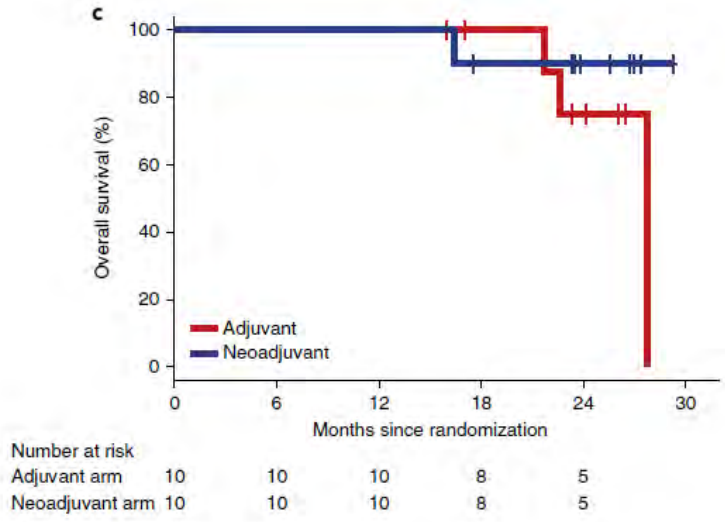


J.S. O'Donnell et al., Clin. Cancer Res. 2019; DOI: 10.1158/1078-0432.CCR-18-2641

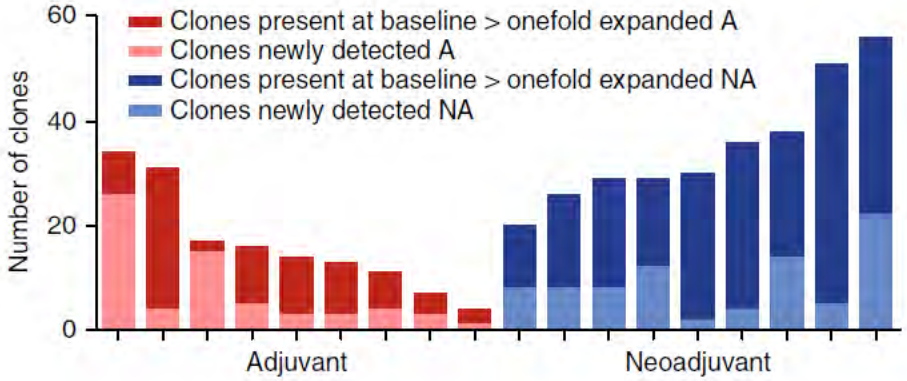
Neoadjuvant versus adjuvant: Malignes Melanom

Stadium III Melanom:
anti-CTLA4+PD-1 Therapie:

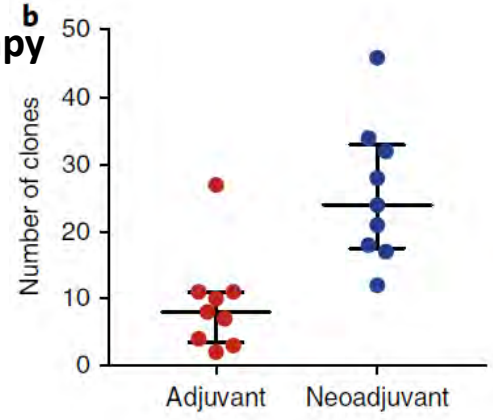




TIL clones proliferated to periphery



Top 100 tumor-resident T-cell clones at baseline expanding >1fold in peripheral blood during therapy



Neoadjuvante PD-1/CTLA4 Inhibition resultiert in einer intensiven T-Zell-Aktivierung und einer präferentiellen Proliferation von Tumor-residenten T_{ex} Zellklonen in Kombination mit der Entstehung neuer T-Zellklonen.

Blank et al. Nat. Med. 2018

Auswirkungen neoadjuvanter Chemotherapie auf immunkompetente Zellen bei NSCLC

Zunahme von

- **zytotoxen T Zellen**
- **Memory T Zellen**
- **B Zell Infiltration**
- **Änderung des T-Zell-Repertoires**

P.O. Gaudreau et al., J. Toracic Oncol. 16: 127-139, 2021;
A. Reuben et al., Nat. Commun. 11: 603, 2020

Biomarkers for ICPIs:
From the “Inflammatory” Status to Antigeneicity of “Self”

- PD-L1
- Lung Immune Prognostic Index (Neutrophil to Lymphocyte Ratio and LDH)
- IFN-gamma Genotype
- Leukemia Inhibitory Factor (LIF)

- Tumour Mutation Burden
- Microsatellite Instability („high“ vs. „low“)
- High Neoantigen Expression

- **Microenvironment**
- **Lymphocyte Infiltration („hot“ vs. „cold“)**

- Microbiome

- Response to Neoadjuvant ICPI-Based Treatment

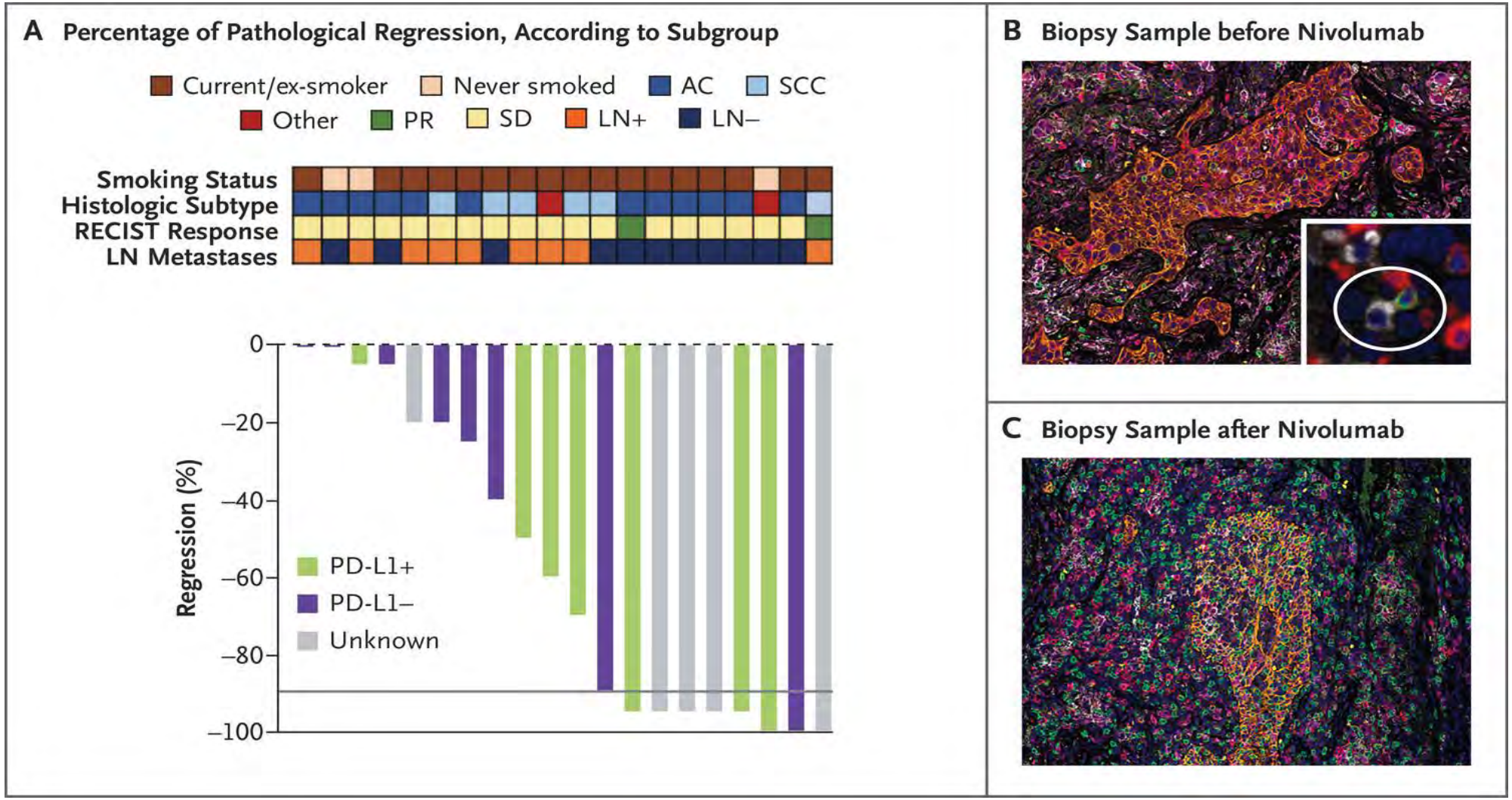
Optionen neoadjuvanter Therapie mit Immun Checkpoint Inhibitoren bei NSCLC

- **Monotherapie**
- **Kombinierte Immuntherapie**
- **Immune Checkpoint Inhibitor Therapie plus Chemotherapie**
- **Immune Checkpoint Inhibitor Therapie plus Multimodalität**

Phase II Studien neoadjuvanter Immune Checkpoint Inhibitor Therapie

1. Monotherapie with Nivolumab

Effekt neoadjuvanter Blockade von PD-1 mit Nivolumab: Pathologie.



PM Forde et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1716078

Phase II Studien neoadjuvanter Immune Checkpoint Inhibitor Therapie

2. Poly-Immuntherapie with Nivolumab plus Ipilimumab

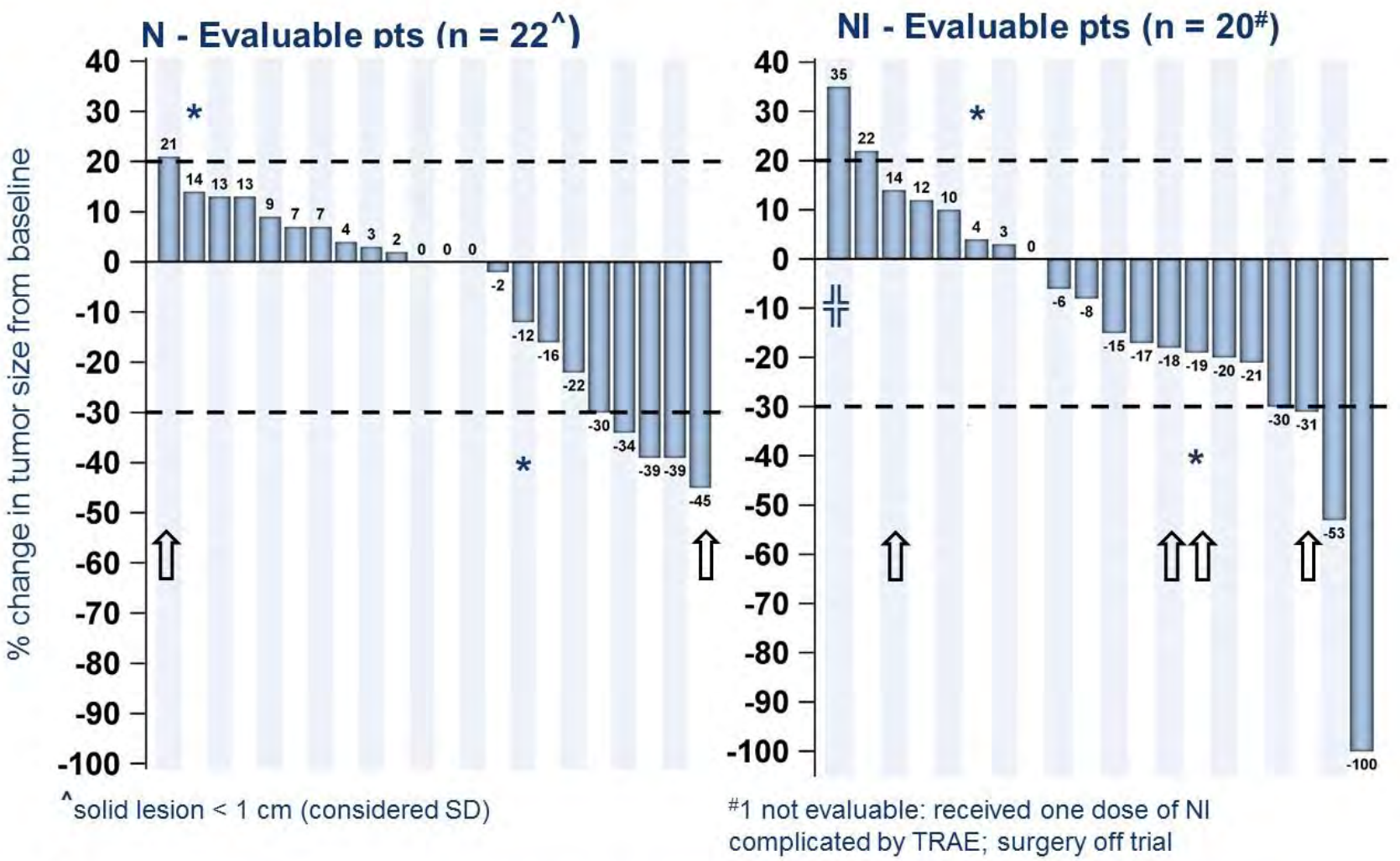
Radiographic responses (RECIST)

Response (RECIST)	Overall n = 44	N n = 23	NI n = 21
	n (%)	n (%)	n (%)
CR	**1 (2%)**	**0 (0%)**	**1 (5%)**
PR	**8 (18%)**	**5 (22%)**	**3 (14%)**
SD	28 (64%)	15 (65%)	13 (62%)
PD	6 (14%)	3 (13%)	3 (14%)
Not evaluable	1 (2%)	0 (0%)	1 (5%)#

received one dose NI complicated by TRAE

ORR (CR+PR): 20% (9/44)

ORR by Arm:
N: 22% (5/23)
NI: 19% (4/21)



^solid lesion < 1 cm (considered SD)

#1 not evaluable: received one dose of NI complicated by TRAE; surgery off trial

⇧ no surgery on trial * Overall PD due to new lesions; ╬ SD with cavitation, wall thickness increase/inflammation

Phase II NEOSTAR Trial: Finale Analyse

Major Pathological Response (mPR) als primärer Endpunkt (n=44)

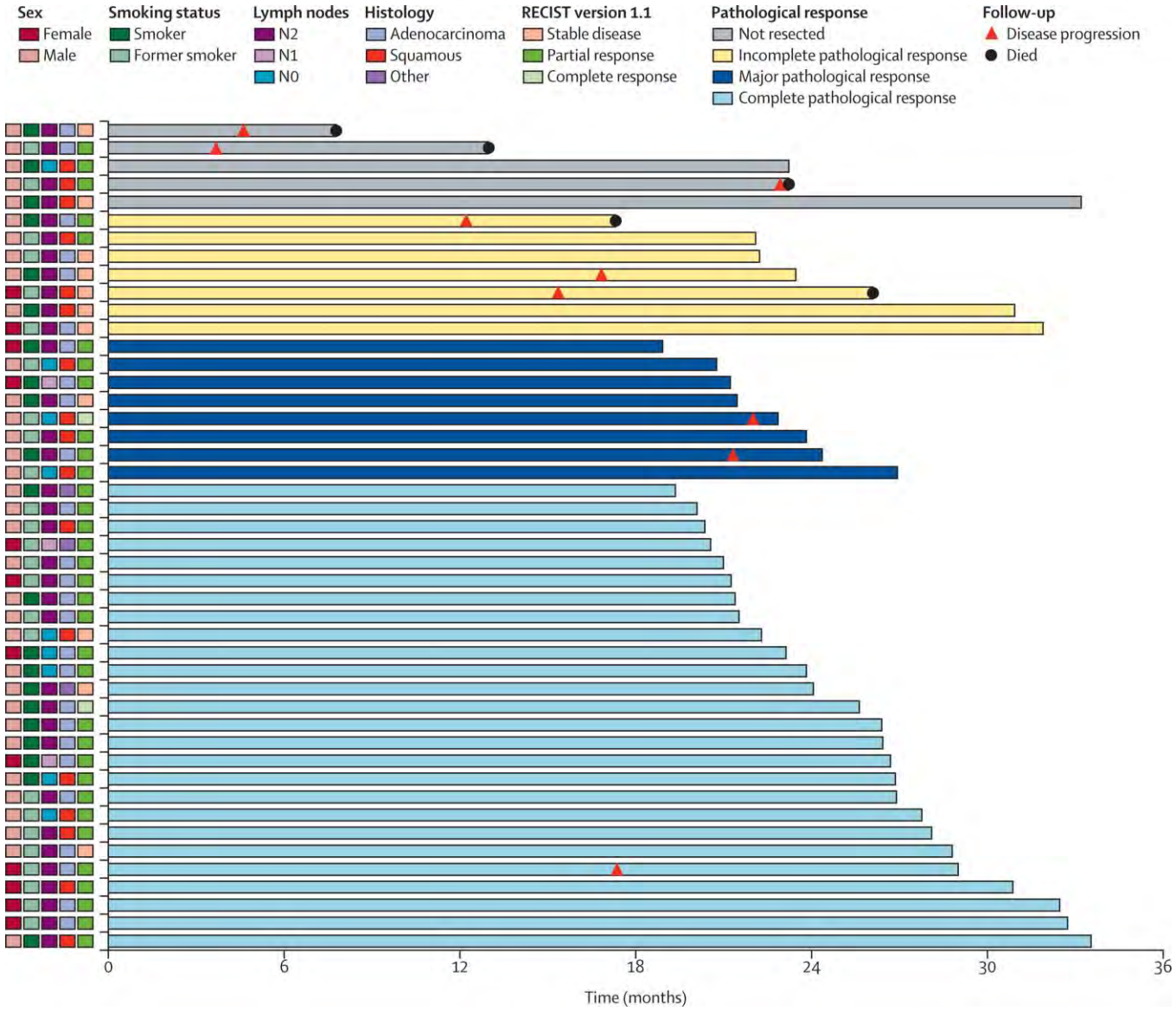
	Nivo+Ipi	Nivo
mPR	38%	22%
pCR	38%	10%
Viable Tumour	9%	50%

T. Cascone et al., Nature Med. doi: 10.1038/s41591-020-01224-2, 2021

Phase II Studien neoadjuvanter Immune Checkpoint Inhibitor Therapie

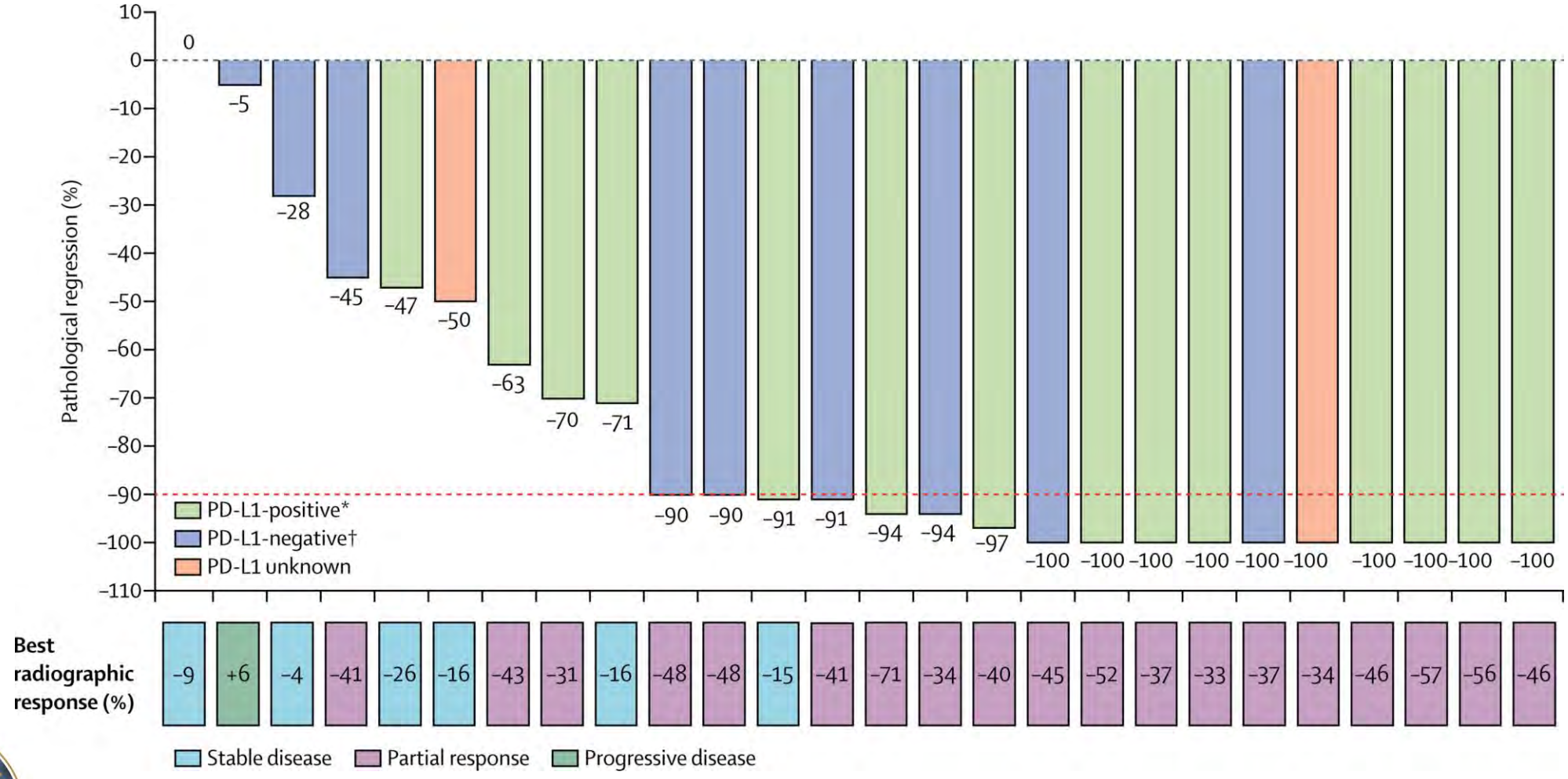
3. **Kombinierte Immuno-Chemotherapie**

Neoadjuvantes Nivolumab (PD-1 – Inhibitor) plus Chemotherapie



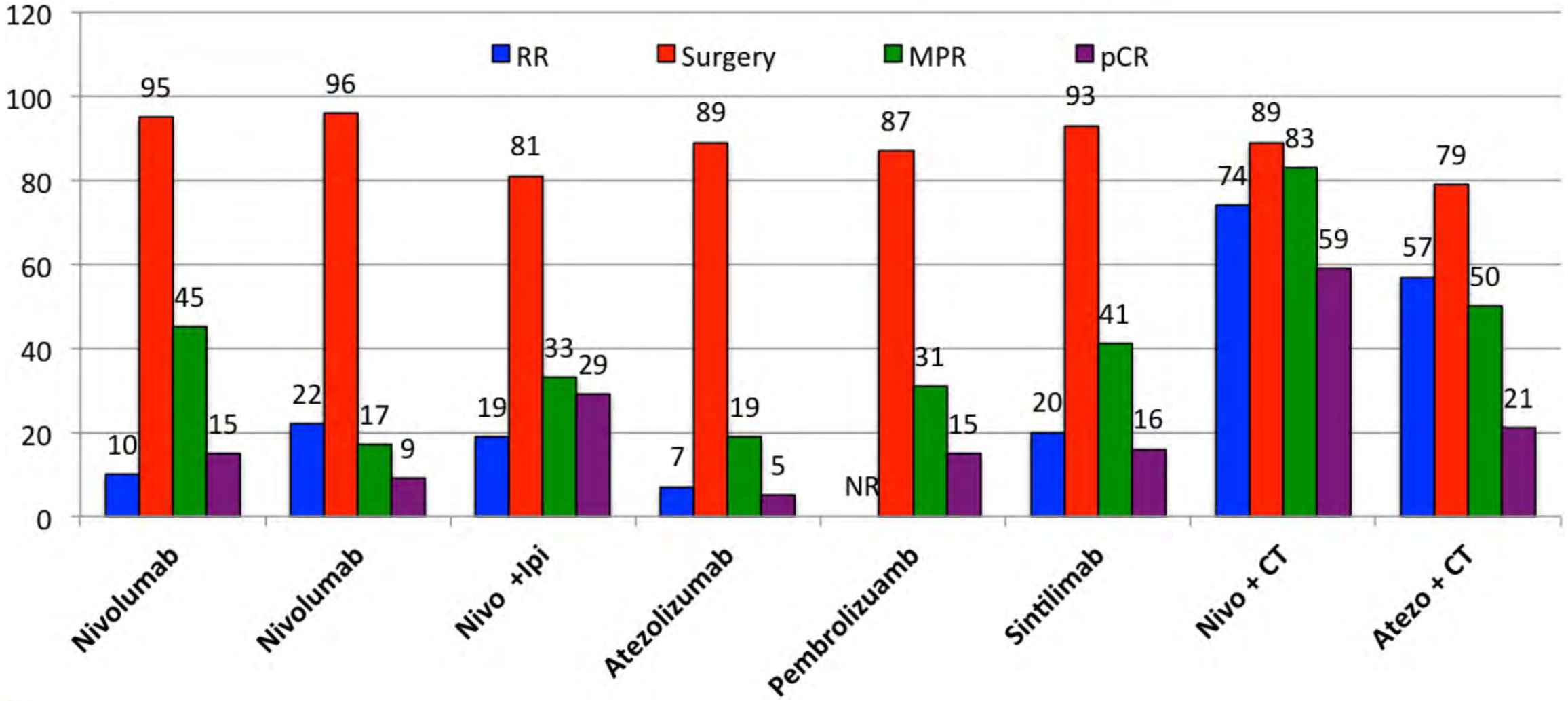
M. Provencio et al., Lancet Oncol. DOI: 10.1016/S1470-2045(20)30453-8

Neoadjuvantes Atezolizumab (PD-L1 – Inhibitor) und Chemotherapie: Ergebnisse von Pathologie und Radiologie



Catherine A Shu et al., Lancet Oncol. DOI: 10.1016/S1470-2045(20)30140-6

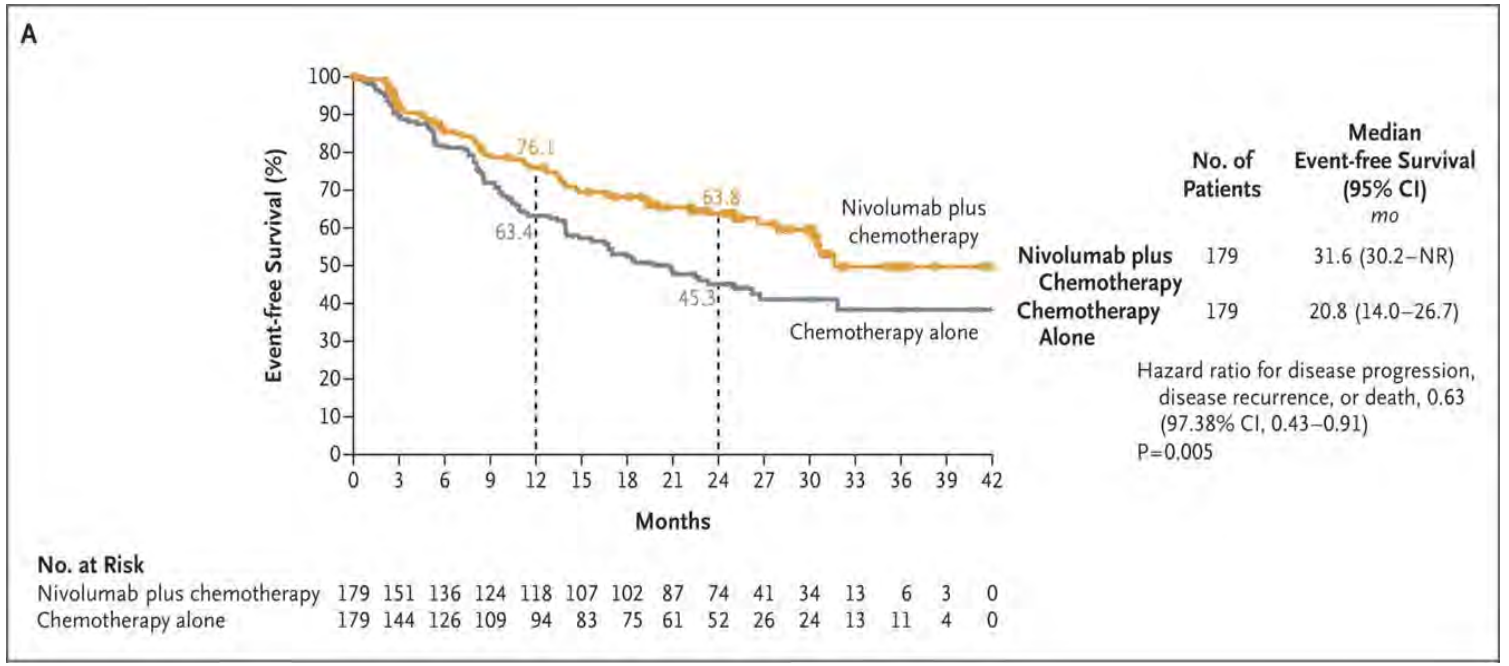
Efficacy of Neoadjuvant Immune Checkpoint Inhibitor-Based Treatment of NSCLC



J. Remon et al., JTO 15: 914-947, 2020

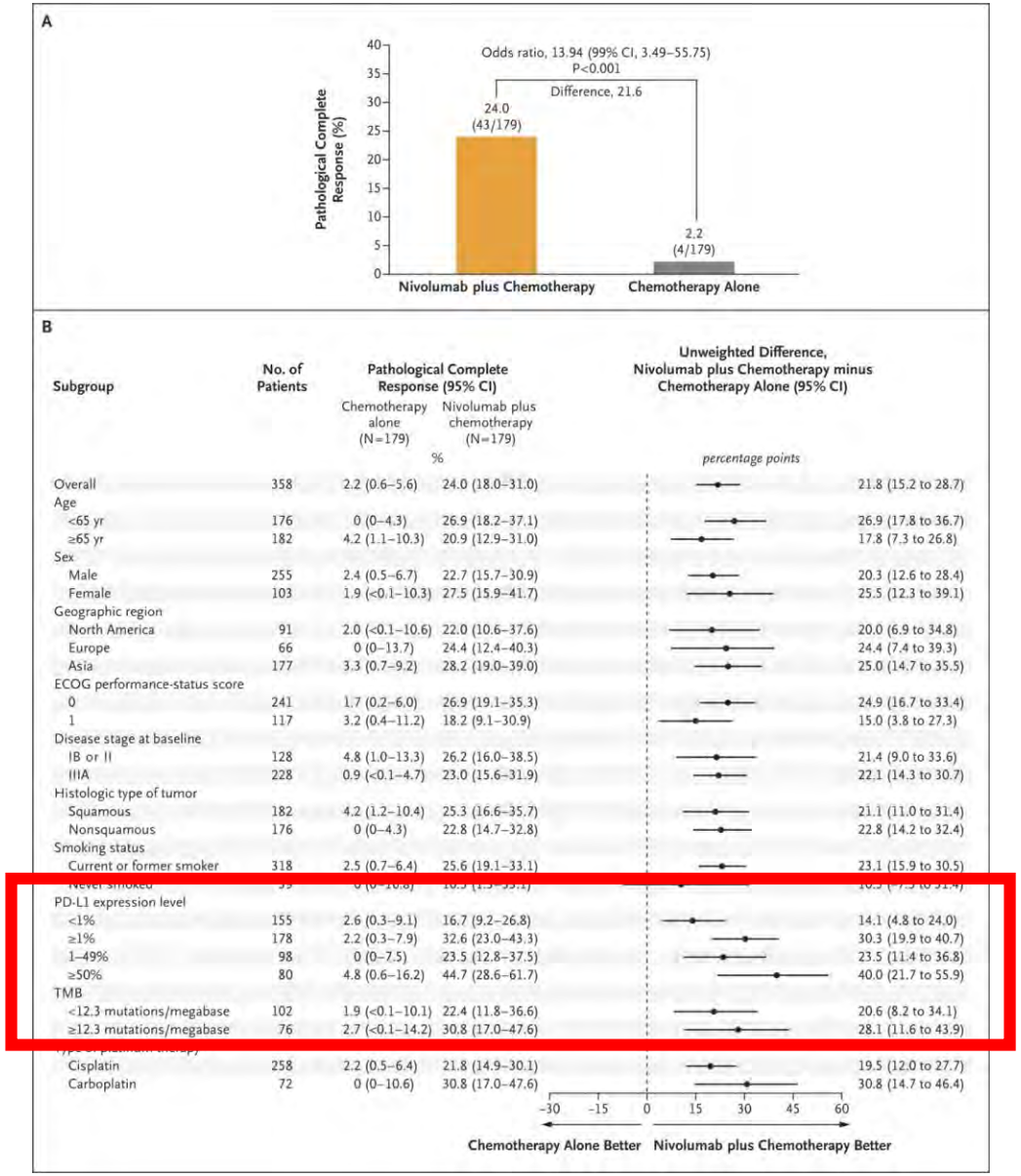
Phase III Studien: Immunotherapie vs. Chemotherapie

Checkmate 816: 358 PatientInnen, Stage IB-IIIA Disease: Medianes EFS



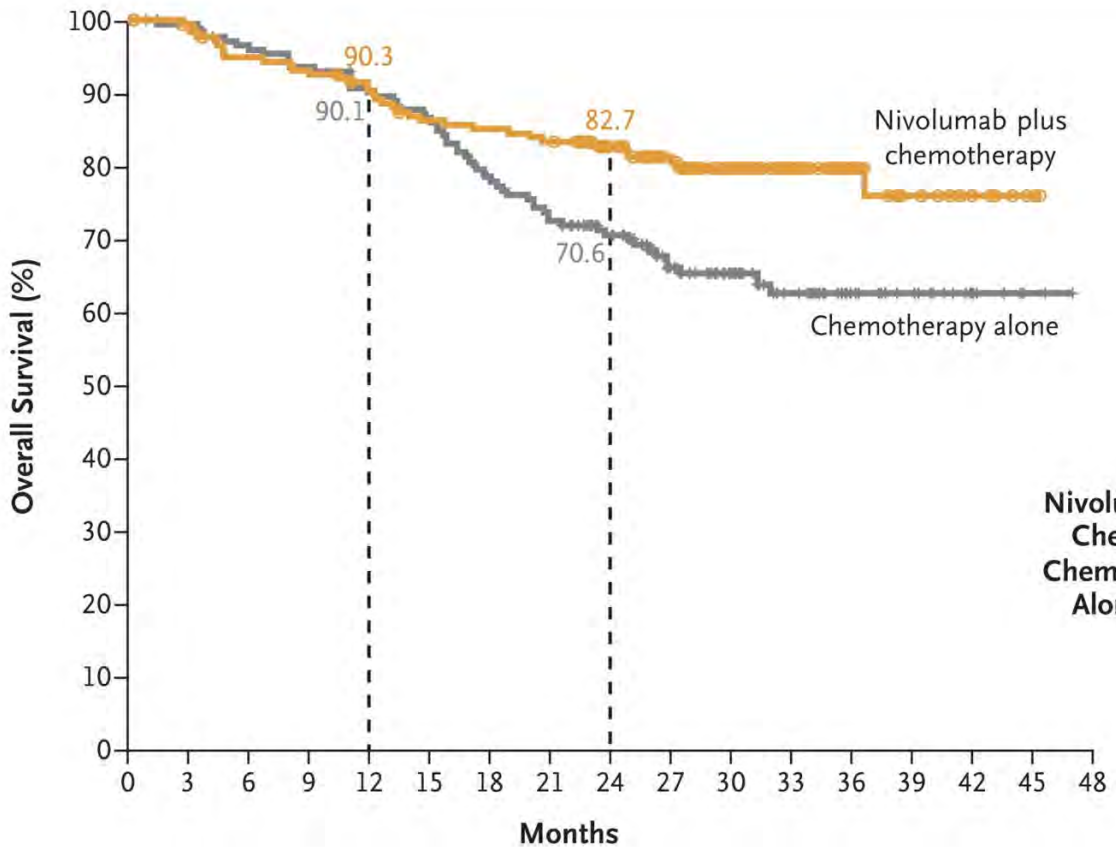
N. Girard et al., AACR Annual Meeting 2022, P. Forde et al.: N. Engl. J. Med. 386: 1973, 2022

Checkmate 816:pCR



N. Girard et al., AACR Annual Meeting 2022, P. Forde et al.: N. Engl. J. Med. 386: 1973, 2022

Checkmate 816: Medianes Overall Survival



	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008

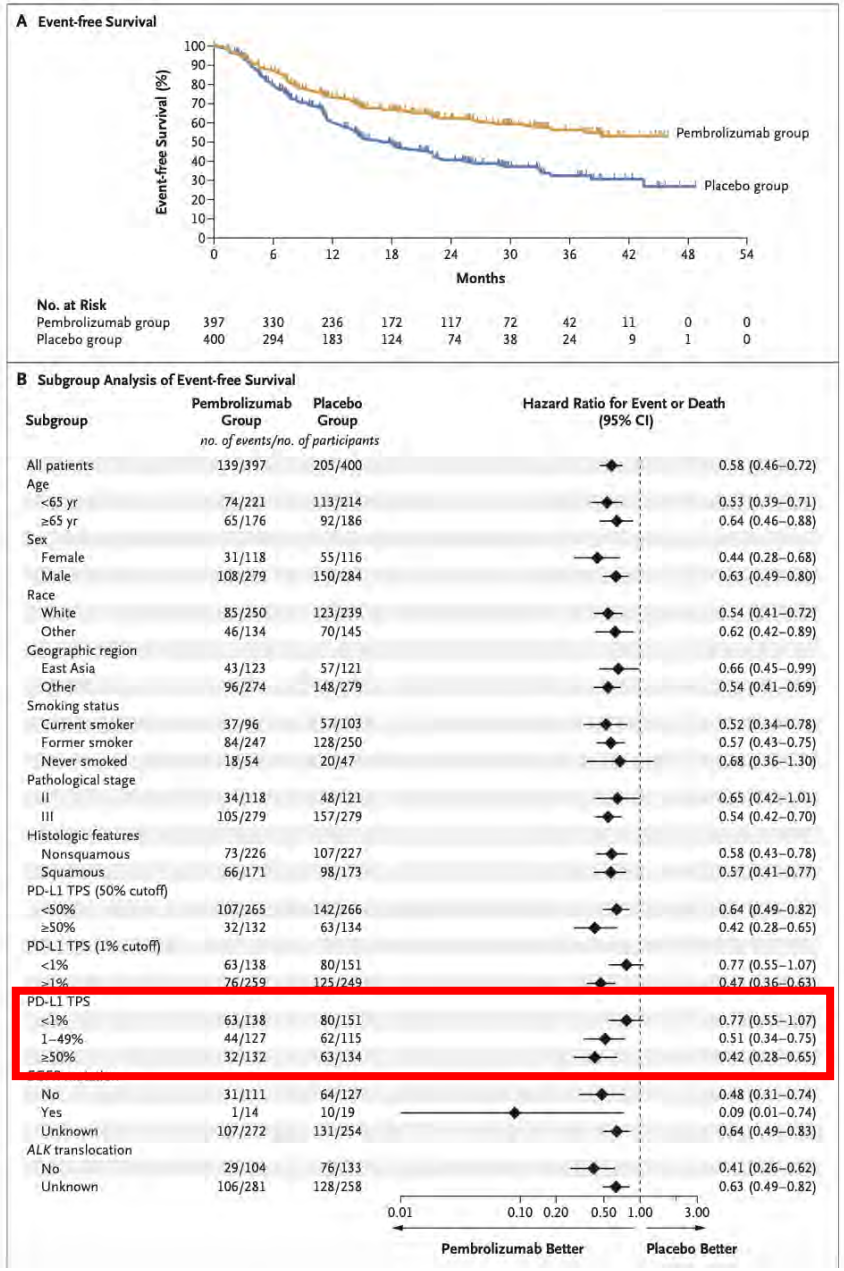
No. at Risk

Nivolumab plus chemotherapy	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemotherapy alone	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

N. Girard et al., AACR Annual Meeting 2022, P. Forde et al.: N. Engl. J. Med. 386: 1973, 2022

Phase III Studie: Neoadjuavnte Chemo-Immunotherapie gefolgt von adjuvanter Immuntherapie

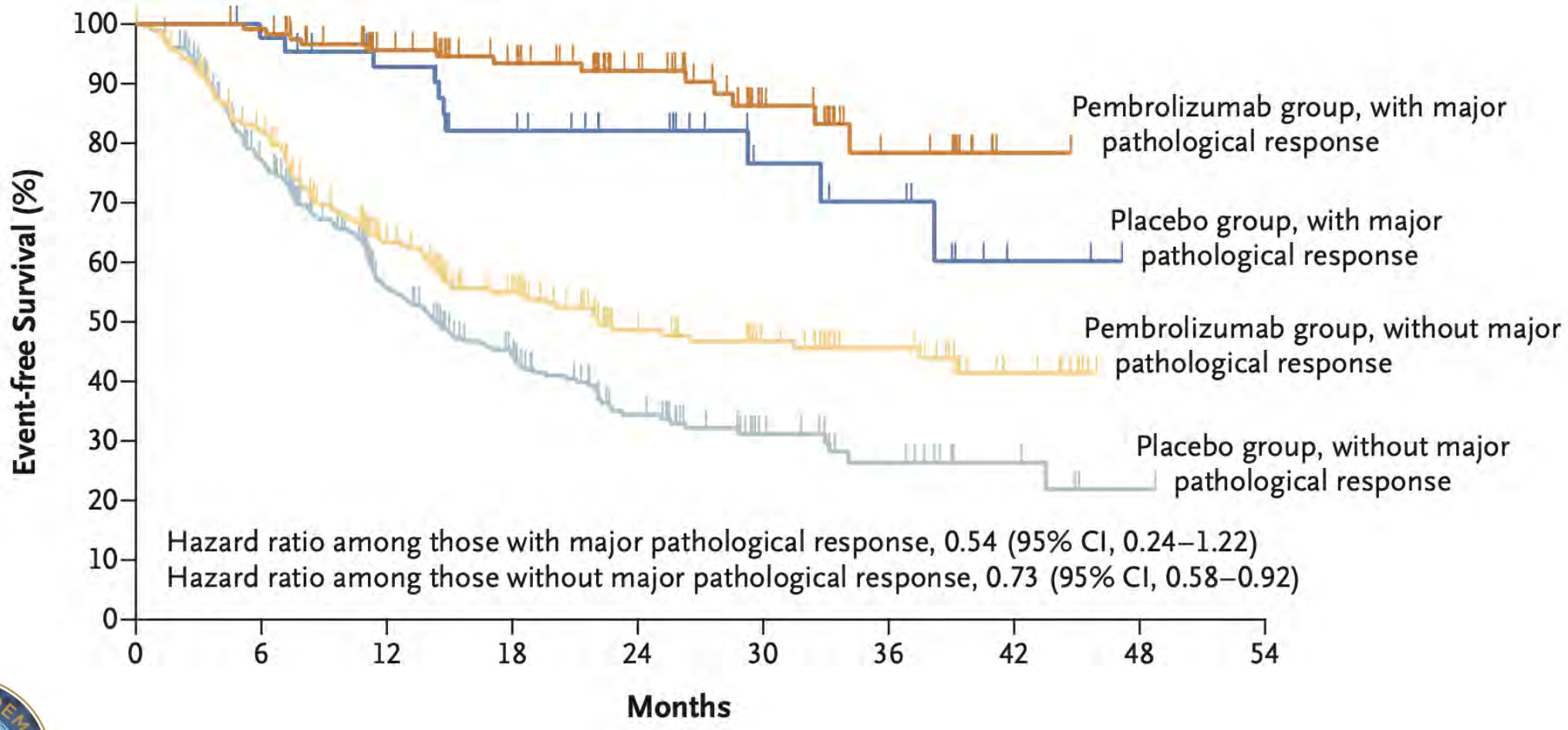
Event Free Survival nach perioperativem* Pembrolizumab plus Chemotherapie



***4 neoadjuvante Zyklen von Pembrolizumab plus Platin-hältiger Chemotherapie gefolgt von Operation gefolgt von 13 Zyklen Pembrolizumab**

H. Wakelee et al., ASCO 2023 and NEJM 2023

Event Free Survival mit perioperativem Pembolizumab plus Chemotherapie in Abhängigkeit von der Major Pathological Response



H. Wakelee et al., ASCO 2023 and NEJM 2023

The NEW ENGLAND JOURNAL of MEDICINE

Checkmate 77T: Neoadjuvantes Nivolumab plus Chemotherapie gefolgt von Operation gefolgt von adjuvantem Nivolumab

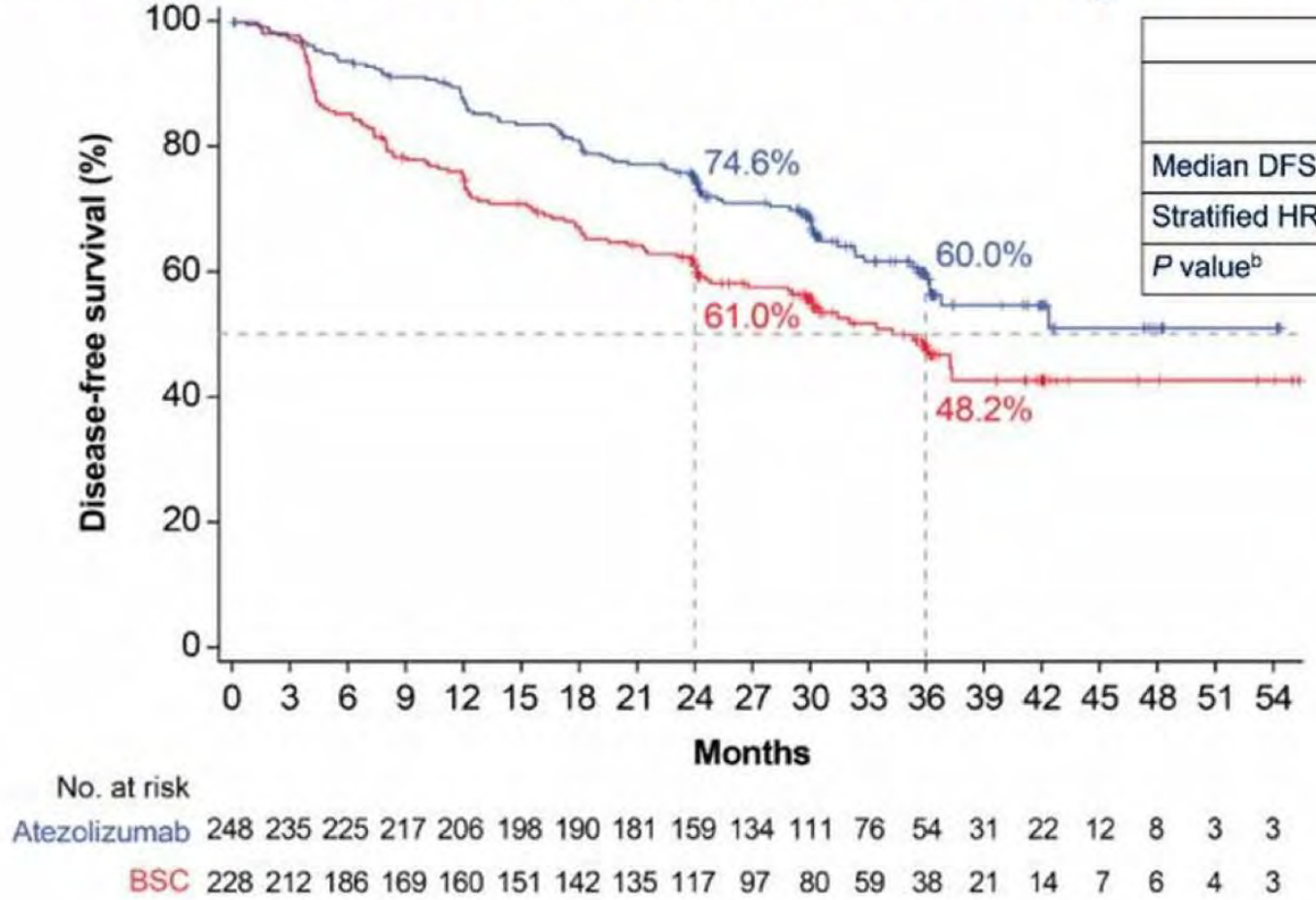
	Nivo+Chemo/Nivo (n=229)	Chemo/Placebo (n=232)
Median EFS	NR (28.9-NR)	18.4 (13.6-28.1)
HR		0.58 (0.42-0.81)
P Value		0.00025
Subgroups:		
PD-L1 <1%	29.0	19.8
PD-L1 1-49%	30.2	28.1
PD-L1 >50%	NR	8.0

T. Cascone et al., ESMO 2023, LBA 1

Studienergebnisse adjuvanter Immune Checkpoint Inhibitor Therapie nach adjuvanter Chemotherapie bei NSCLC

- **IMpower 010**
- **PEARLS / KEYNOTE 091**

Atezolizumab following surgery and chemotherapy reduced the risk of disease recurrence or death by 34% in people with stage II-IIIA NSCLC whose tumors express ≥1% PD-L1[a]

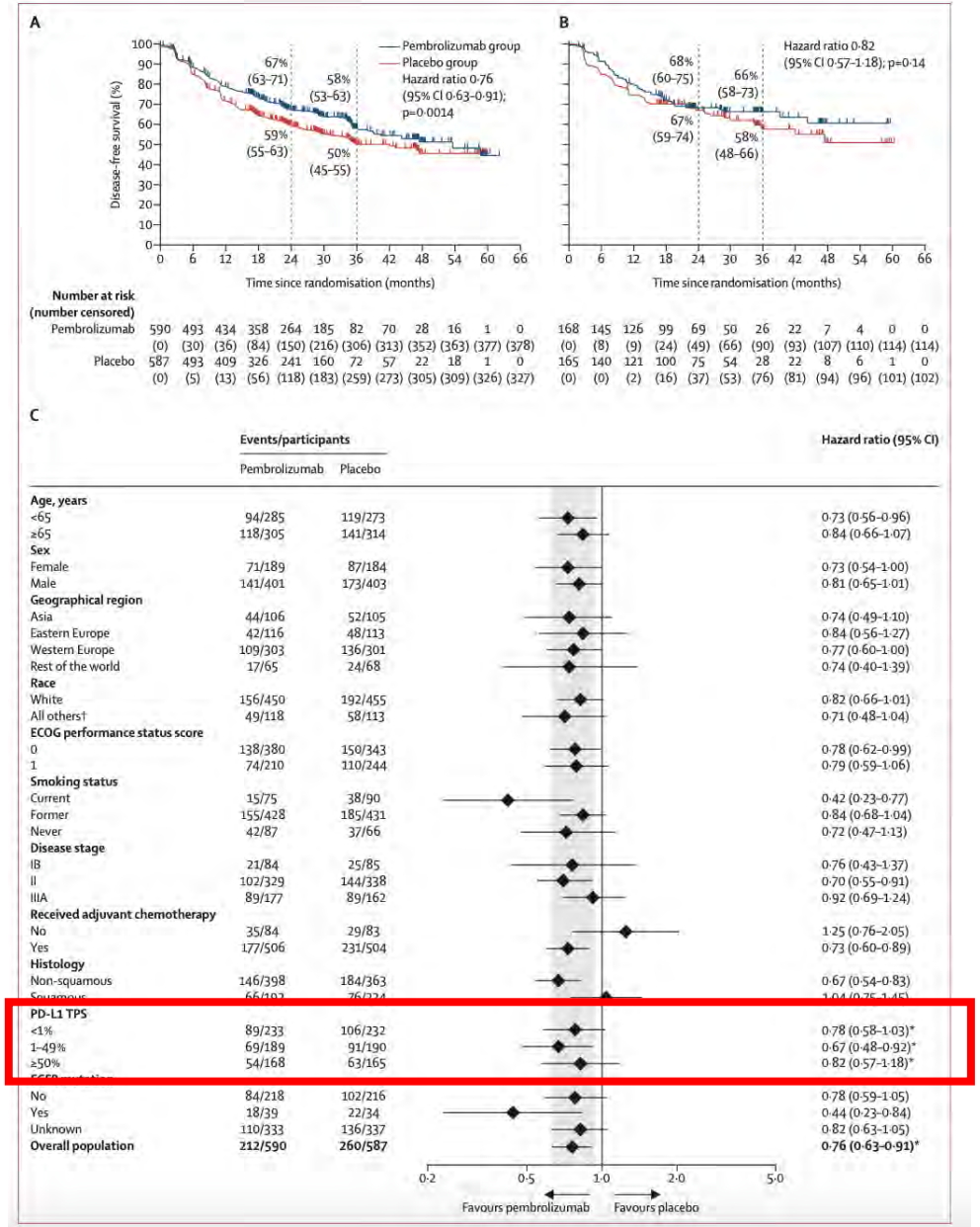


	PD-L1 TC ≥1% stage II-IIIA	
	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

[a] H. Wakelee et al., Proc. Soc. Am. Clin. Oncol. 8500, 2021

Studienergebnisse adjuvanter Immune Checkpoint Inhibitor Therapie nach adjuvanter Chemotherapie bei NSCLC: PEARLS/Keynote 091



Mary O'Brien et al., Lancet 2022

Neoadjuvante und adjuvante Therapie von NSCLC mit Immune Checkpoint Inhibitoren

State of the Art in perioperativer (= neoadjuvanter und adjuvanter) interdisziplinärer Therapie des NSCLC unabhängig von PD-L1 Expression