Negrar (VR) – 20 maggio 2022

Immunoterapia neoadiuvante: evidenze disponibili e prospettive future

Ponte naturale di Veja
Sant'Anna d'Alfaedo (VR)

Ettore D'Argento

UOC Oncologia Medica

CARCINOMA POLMONARE: QUALI NOVITÀ NEL 2022?

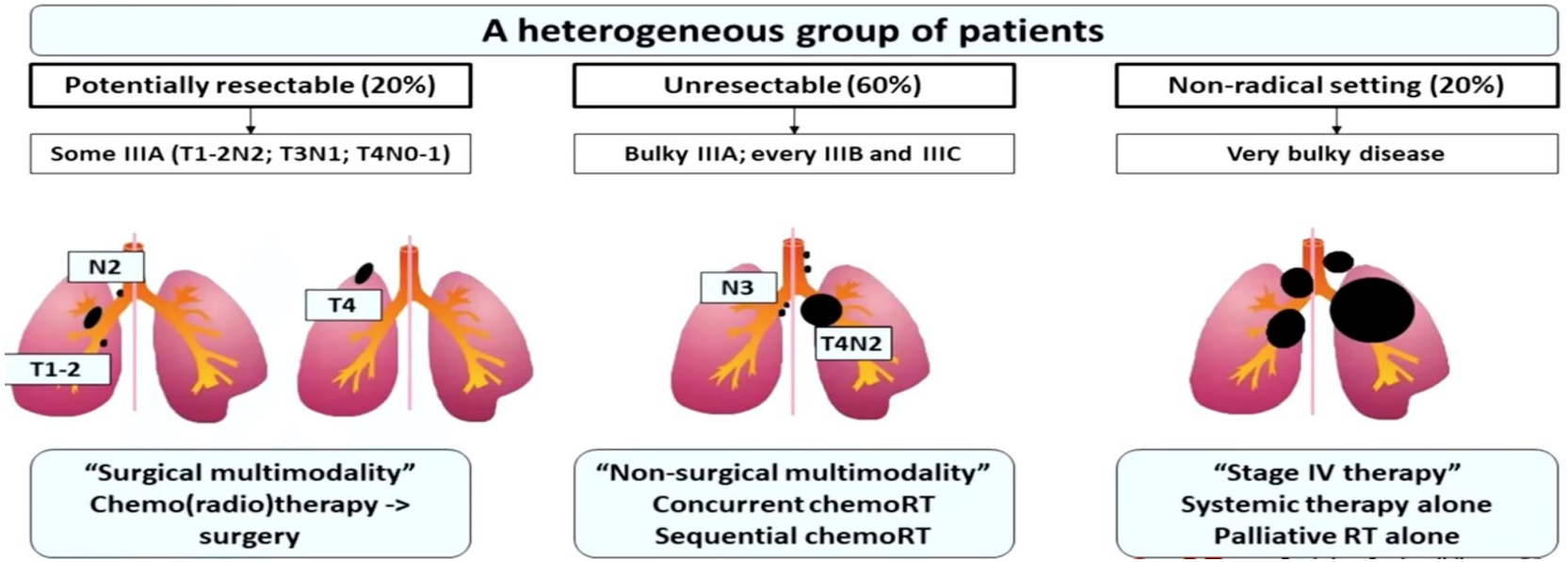
Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Comprehensive Cancer Center

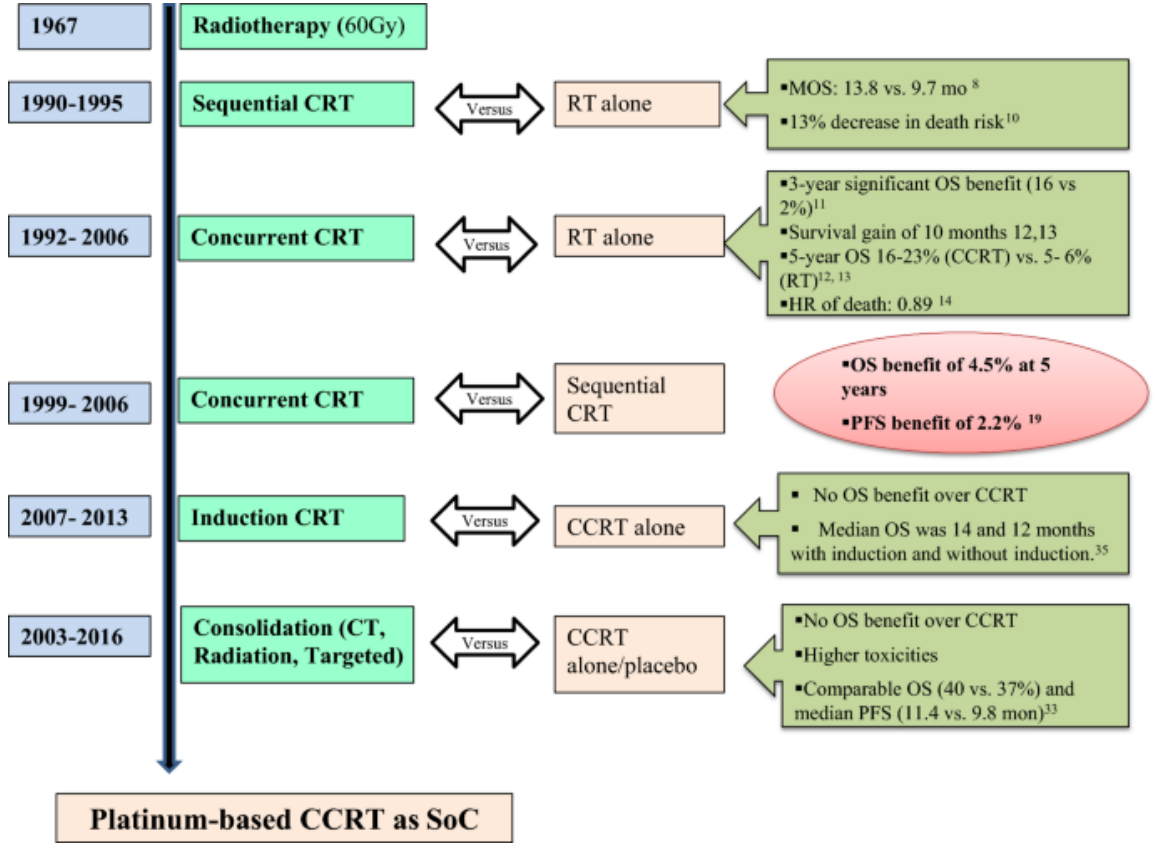
Roma, Ponte Sant'Angelo (Pons Aelius)

Roma 03/10/2021: incendio del Ponte di Ferro



- Therapeutically challenging subset
- Patients are treated for cure, but cure is elusive: 10%-30%
- Surgery and/or radiotherapy for local-regional control

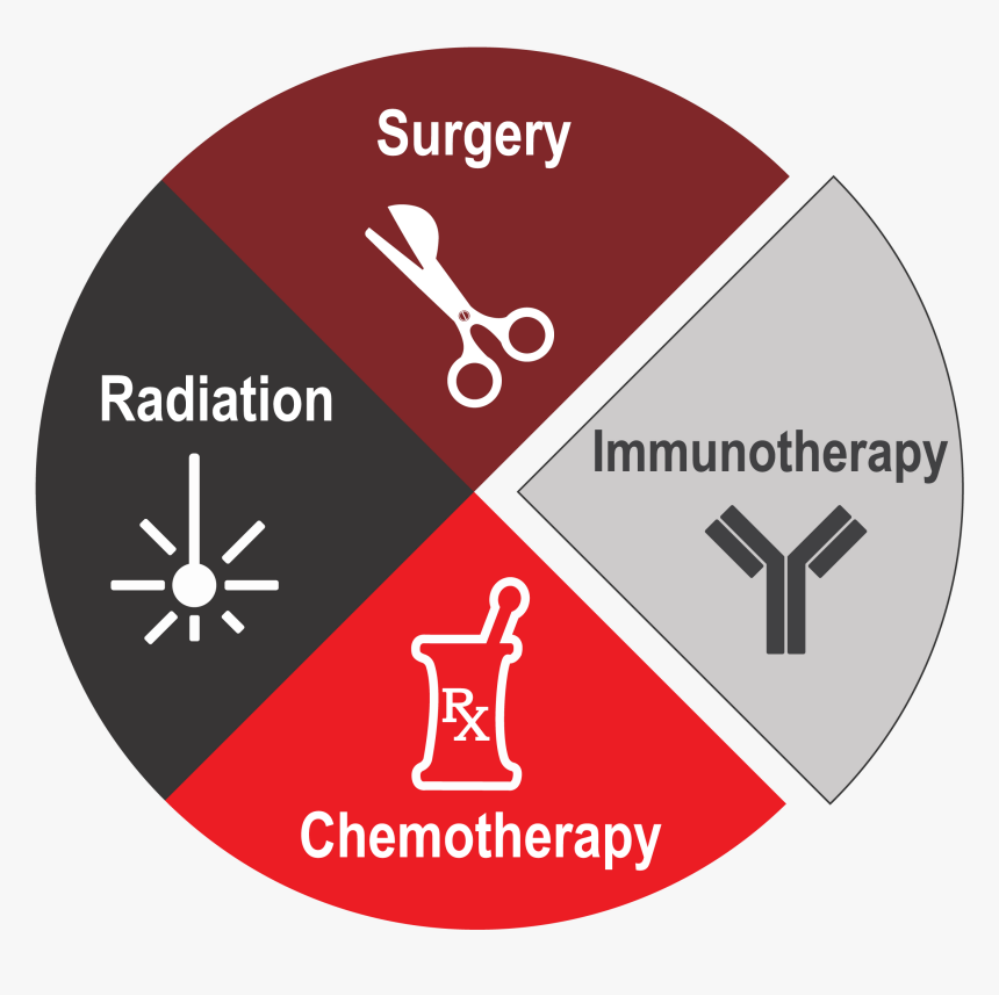
Chemotherapy ⟶ High risk of systemic relapse



Stage	Incidence, %	Treatment	Est. 5-Yr Survival, %
III	30-35	Combined modality therapy	15-25

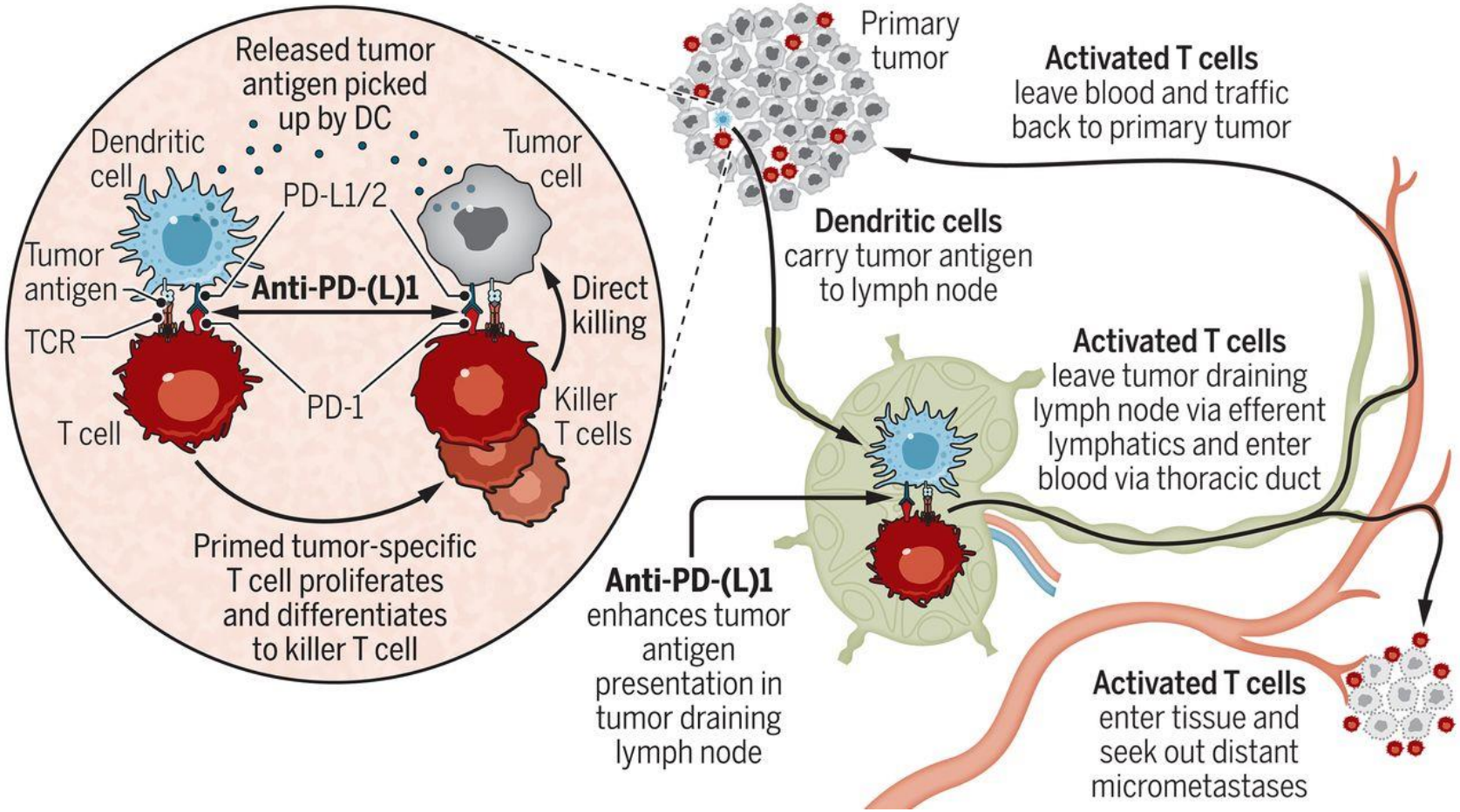
- **Immunotherapy is providing new hope and changing the management of stage III NSCLC**

Roma, Ponte Settimia Spizzichino

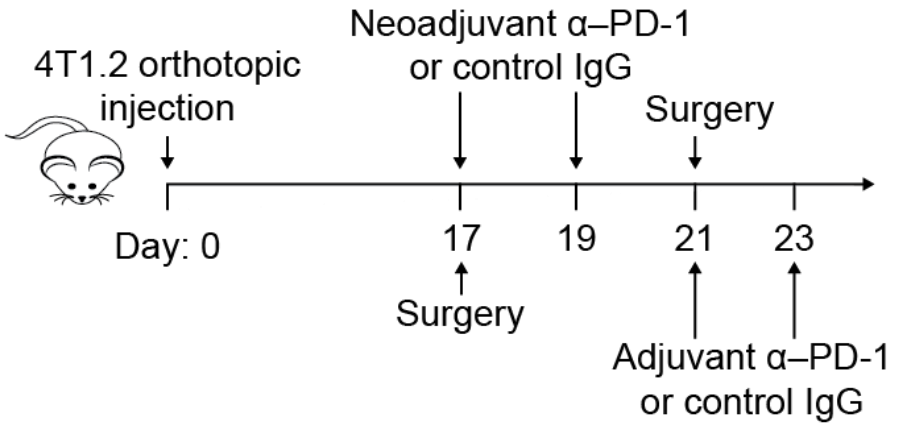


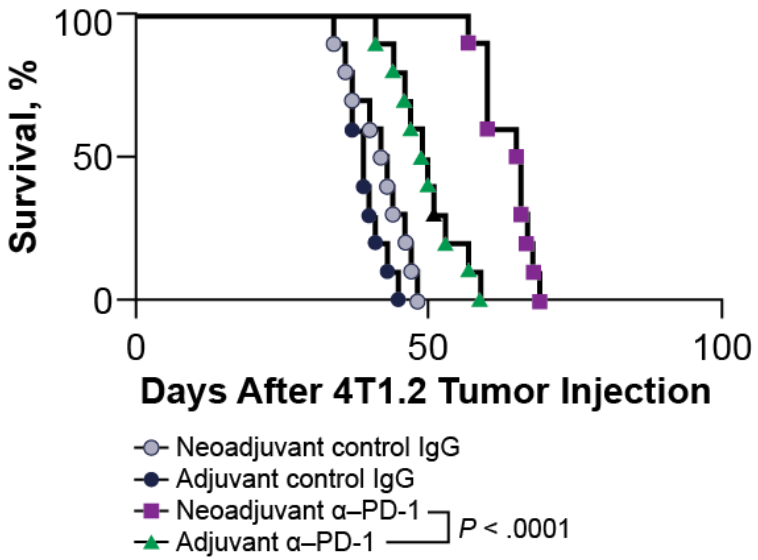
Roma, Isola Tiberina ed i suoi ponti

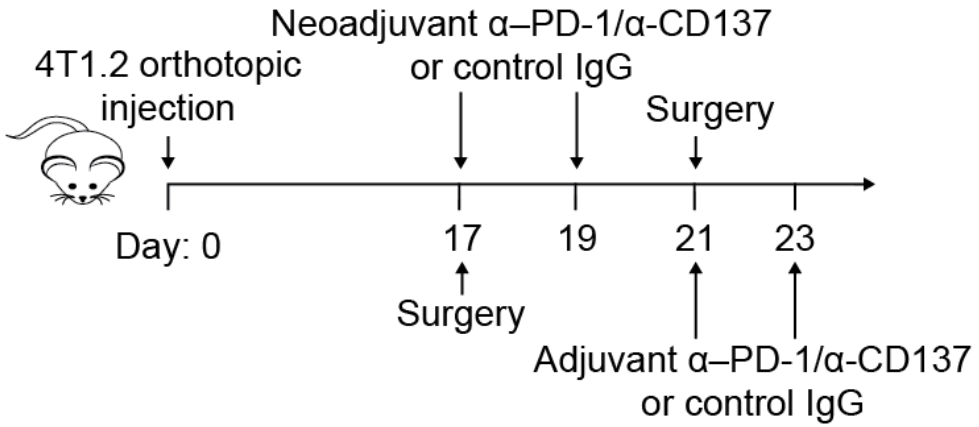
Enhancement of systemic antitumor T cell immunity after neoadjuvant PD-1 blockade

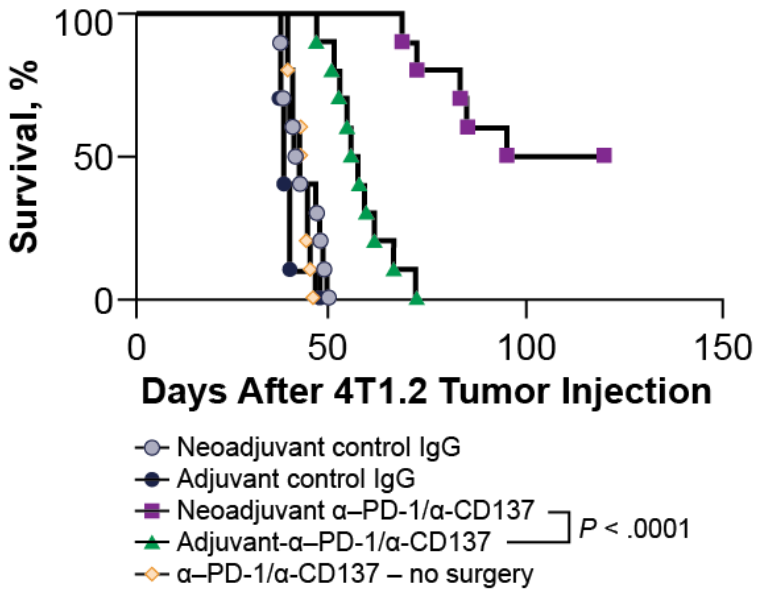


Neoadjuvant Anti–PD-1 + Anti-CD137 is Better Than Adjuvant (At Least in Mice)



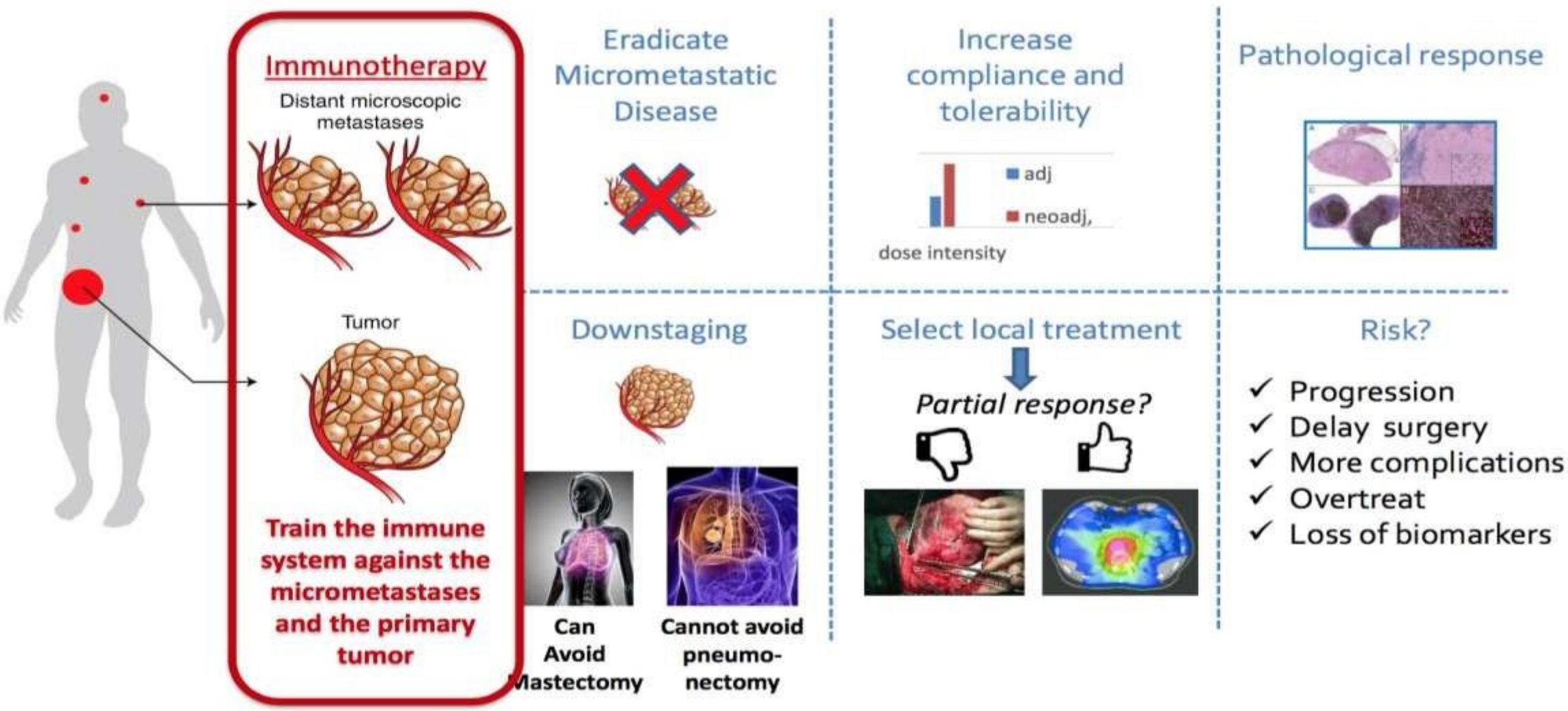






Liu J et al. Cancer Discov. 2016;6:1382-1399.

Theoretical benefit for induction Treatment



Neoadjuvant ICI or ICI Plus Chemotherapy in Patients With Resectable and Operable Stage I–III Lung Cancers Phase II Trials

Trial	Author(s)	Agent(s)	MPR, % (95% CI)	pCR, % (95% CI)
Johns Hopkins University/Memorial Sloan Kettering Cancer Center (21 patients)	Forde et al[10]	Nivolumab	43 (21 to 66)	14 (4 to 34)
LCMC3; Lung Cancer Mutation Consortium (82 patients)	Kwiatkowski et al[12]	Atezolizumab	18 (11 to 28)	5 (2 to 12)
NEOSTAR; MD Anderson Cancer Center (44 patients)	Cascone et al[13]	Nivolumab ± ipilimumab	25 (14 to 40)	18 (9 to 32)
NADIM; Spanish Lung Cancer Group (30 patients)	Provencio-Pulla et al[14]	Nivolumab + paclitaxel/ carboplatin	80 (64 to 91)	75 (4 to 76)
Columbia University New York/MGH (30 patients)	Shu et al[11]	Atezolizumab + paclitaxel/ carboplatin	57 (36 to 76)	33 (18 to 52)
Duke/Dartmouth/Mayo Clinic (25 patients)	Ready et al[15]	Pembrolizumab	28 (12 to 49)	8 (1 to 26)

The NEW ENGLAND JOURNAL of MEDICINE

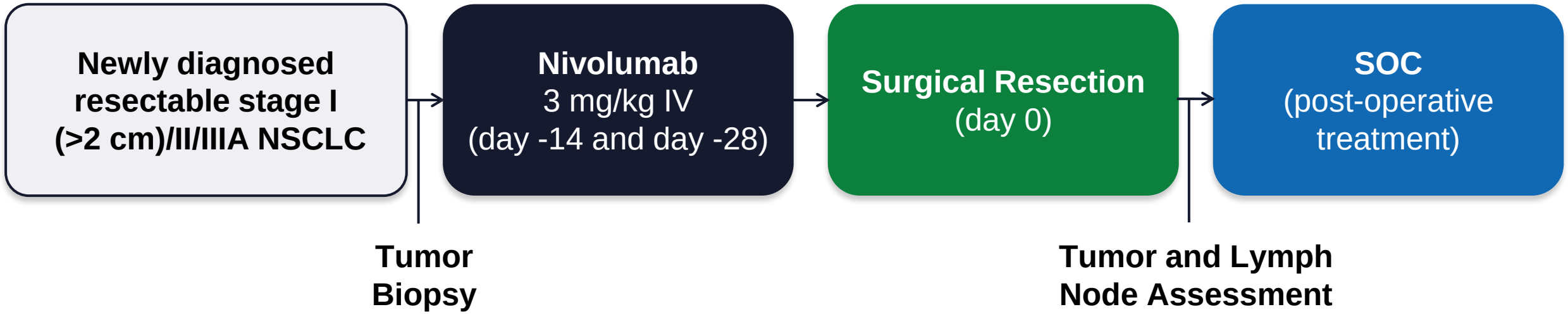
ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

Roma, Ponte Milvio

Neoadjuvant Nivolumab Schema

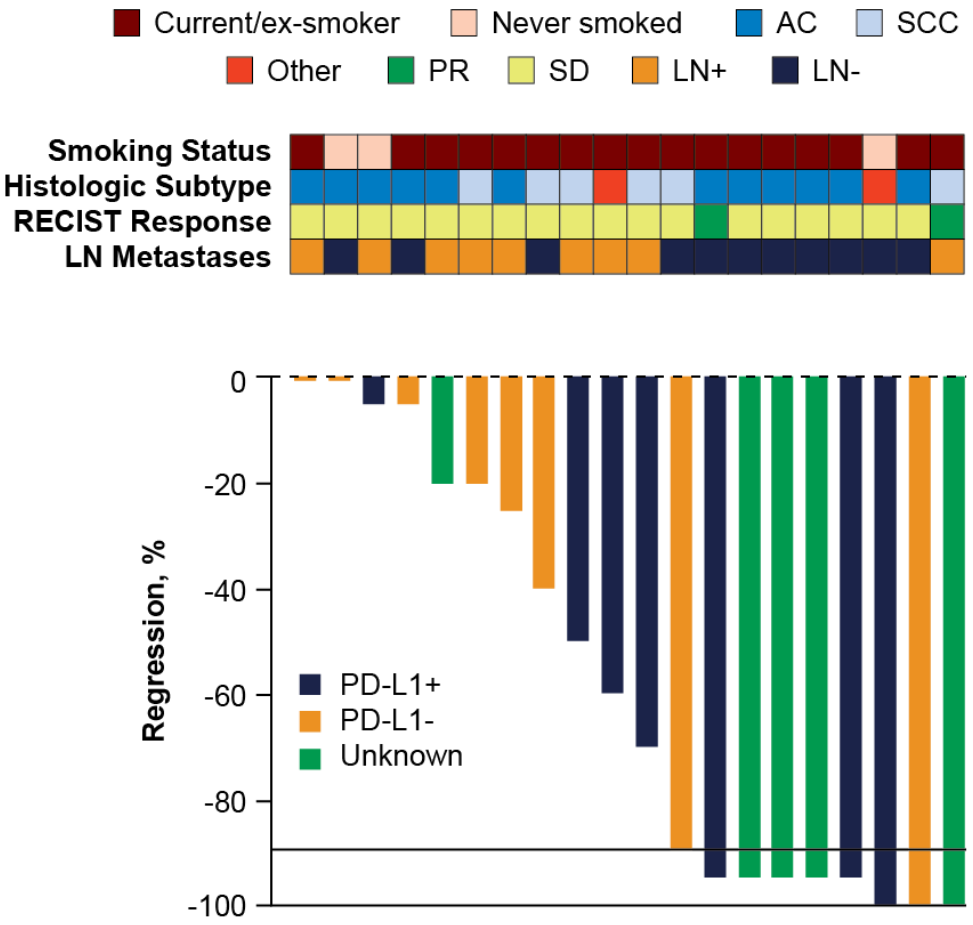


- **Primary endpoints:** Safety and feasibility
- **Also evaluated:** Tumor pathological response; expression of PD-L1; mutational burden; and mutation-associated, neoantigen-specific T-cell responses

1. Forde PM et al. N Engl J Med. 2018;378:1976-1986.

Pathological Assessment of Response to Neoadjuvant Nivolumab

% of Pathological Regression According to Subgroup



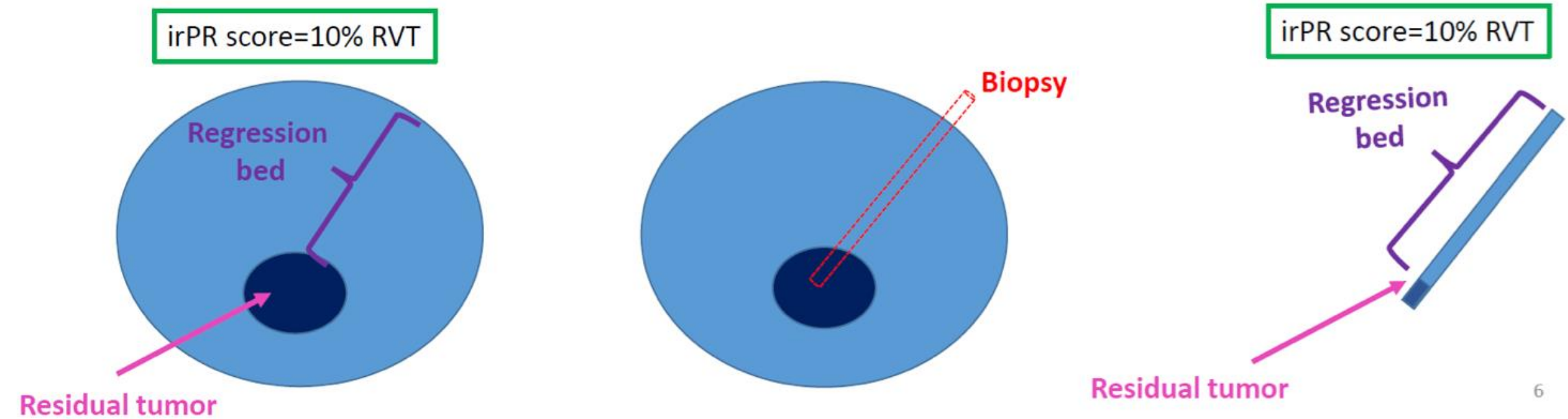
- Major pathological response occurred in 9/20 resected tumors (45%; 95% CI, 23-68)

Treatment related adverse events in 23%
No treatment-related surgical delays

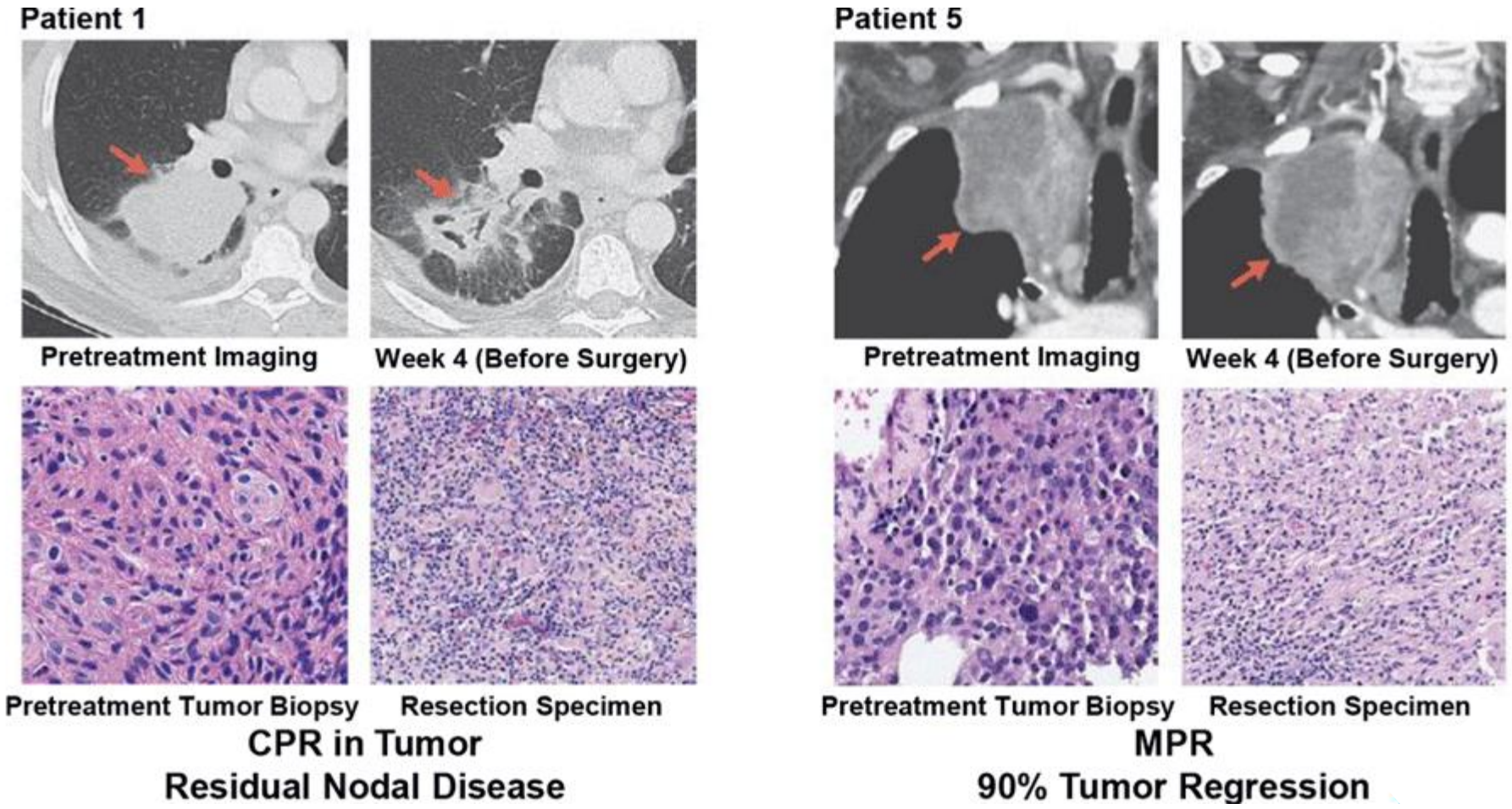
Forde PM et al. N Engl J Med. 2018;378:1976-1986.

New concept

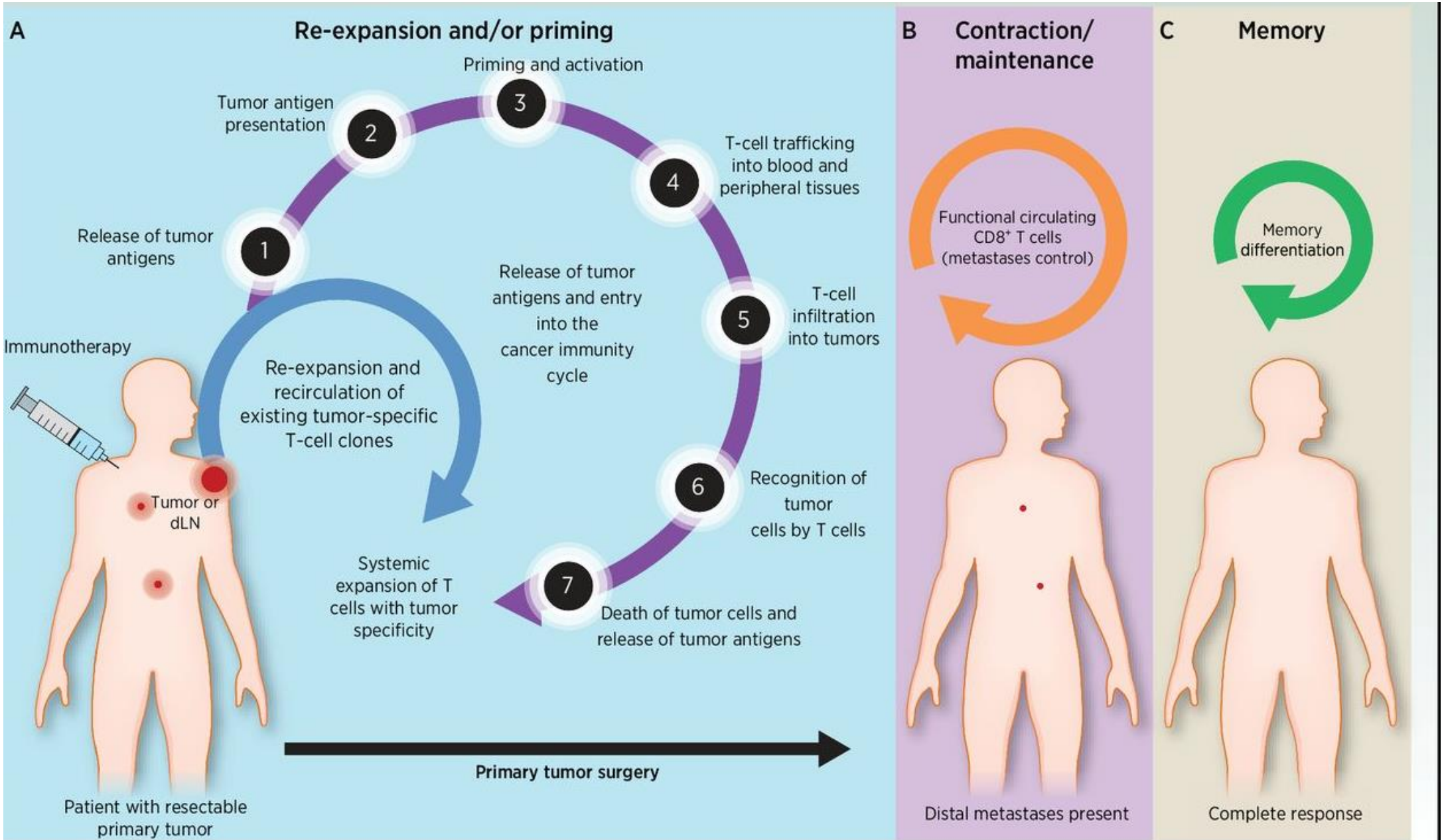
MPR_{bx} = Major pathologic response (MPR, ≤10% residual viable tumor) assessed on biopsy, rather than definitive surgical resection



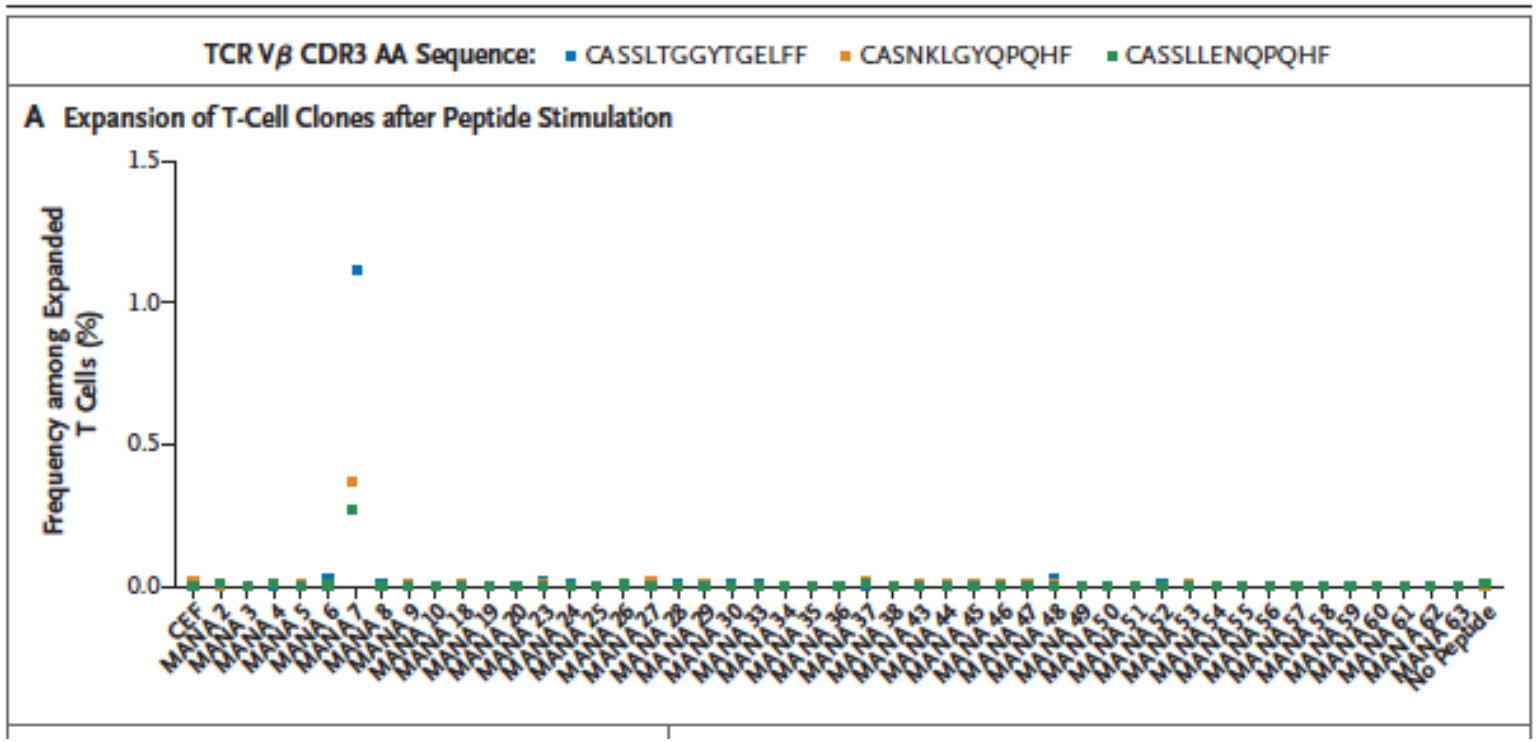
Radiographic response is not predictive

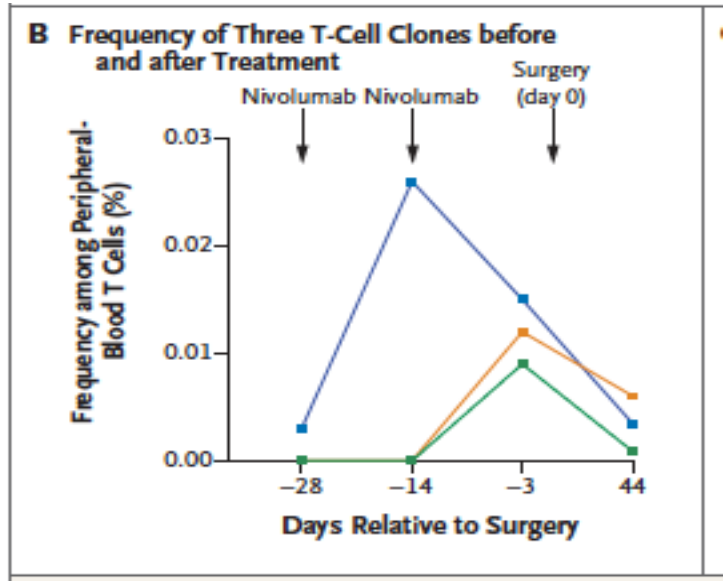


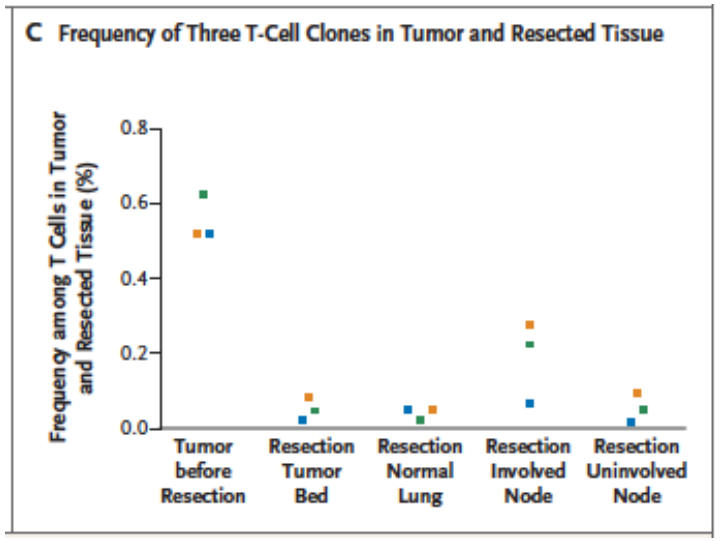
1. Forde PM et al. N Engl J Med. 2018;378:1976-1986.


A
Re-expansion and/or priming
B
Contraction/
maintenance
C
Memory
Priming and activation
Tumor antigen
presentation
T-cell trafficking
into blood and
peripheral tissues
Release of tumor
antigens
Release of tumor
antigens and entry
into the
cancer immunity
cycle
T-cell
infiltration
into tumors
Immunotherapy
Re-expansion and
recirculation of
existing tumor-specific
T-cell clones
Tumor or
dLN
Recognition of
tumor
cells by T cells
Systemic
expansion of T
cells with tumor
specificity
Death of tumor cells and
release of tumor antigens
Primary tumor surgery
Functional circulating
CD8+ T cells
(metastases control)
Memory
differentiation
Patient with resectable
primary tumor
Distal metastases present
Complete response

Identification of Mutation-Associated, Neoantigen-Specific T Cells after Neoadjuvant Treatment with Nivolumab







1. Forde PM et al. N Engl J Med. 2018;378:1976-1986.

IASLC | 2020 World Conference on Lung Cancer Singapore

wclc2020.IASLC.com | #WCLC20

CONQUERING THORACIC CANCERS WORLDWIDE

Surgical and Clinical Outcomes With Neoadjuvant Atezolizumab in Resectable Stage IB-IIIB NSCLC: LCMC3 Trial Primary Analysis

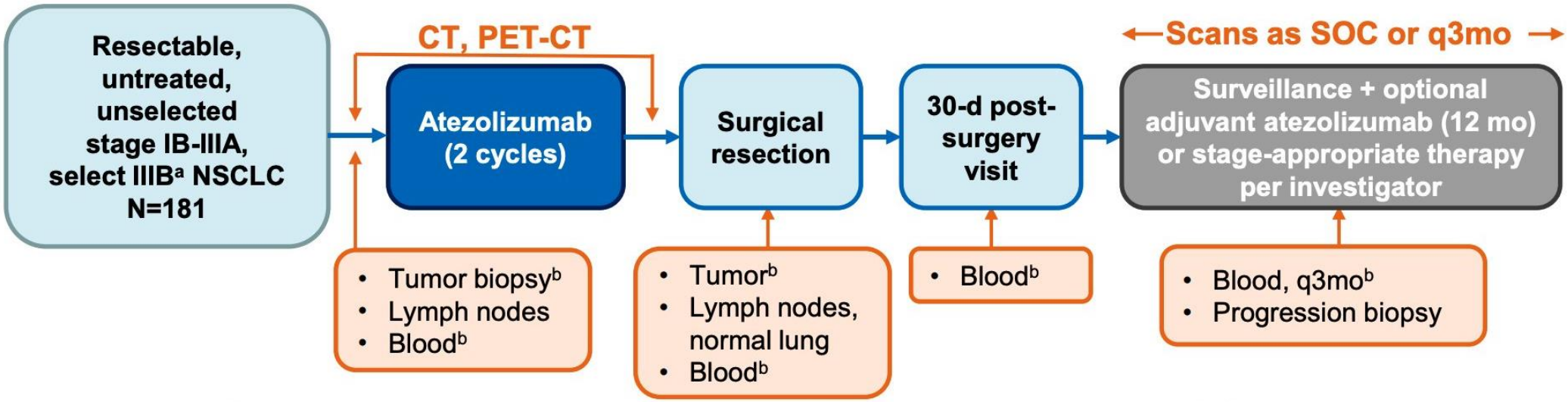
Jay M. Lee,[1] Jamie Chaft,[2] Alan Nicholas,[3] G. Alexander Patterson,[4] Saiama N. Waqar,[4] Eric M. Toloza,[5] Eric Haura,[5] Dan J. Raz,[6] Karen L. Reckamp,[7] Robert E. Merritt,[8] Dwight Owen,[8] David J. Finley,[9] Ciaran J. McNamee,[10] Justin D. Blasberg,[11] Edward B. Garon,[1] John D. Mitchell,[12] Robert C. Doebele,[12] Frank Baciewicz,[13] Misako Nagasaka,[14] Harvey I. Pass,[15] Katja Schulze,[3] See Phan,[3] Ann Johnson,[3] Paul A. Bunn,[12] Bruce E. Johnson,[16] Mark G. Kris,[2] David J. Kwiatkowski,[10] Ignacio I. Wistuba,[17] David P. Carbone,[8] Valerie W. Rusch[2]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Genentech, Inc, South San Francisco, CA, USA; [4]Washington University School of Medicine, St Louis, MO, USA; [5]Moffitt Cancer Center, Tampa, FL, USA; [6]City of Hope Comprehensive Cancer Center Los Angeles, CA, USA; [7]Cedars Sinai (previously City of Hope Comprehensive Cancer Center), Los Angeles, CA, USA; [8]The Ohio State University Wexner Medical Center, Columbus, OH, USA; [9]Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; [10]Brigham and Women's Hospital, Boston, MA, USA; [11]Yale School of Medicine, New Haven, CT, USA; [12]University of Colorado Cancer Center, Aurora, CO, USA; [13]Wayne State University, Detroit, MI, USA; [14]Karmanos Cancer Institute, Detroit, MI, USA; [15]New York University, New York, NY, USA; [16]Dana-Farber Cancer Institute, Boston, MA, USA; [17]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Presented by Dr Jay M. Lee LCMC3: Neoadjuvant Atezolizumab in Resectable NSCLC JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT

Roma, Ponte Flaminio

LCMC3 study design



Primary endpoint:

- Major pathologic response (≤10% viable tumor cells)

Secondary endpoints:

- Pathologic response by PD-L1
- Radiographic response by
  - PD-L1, TMB, neoantigen, gene expression profiling

Exploratory endpoints:

- DFS, OS
- Biomarkers
  - ctDNA, TCRseq, flow cytometry, IF, IHC, NGS

Safety:

- Adverse events

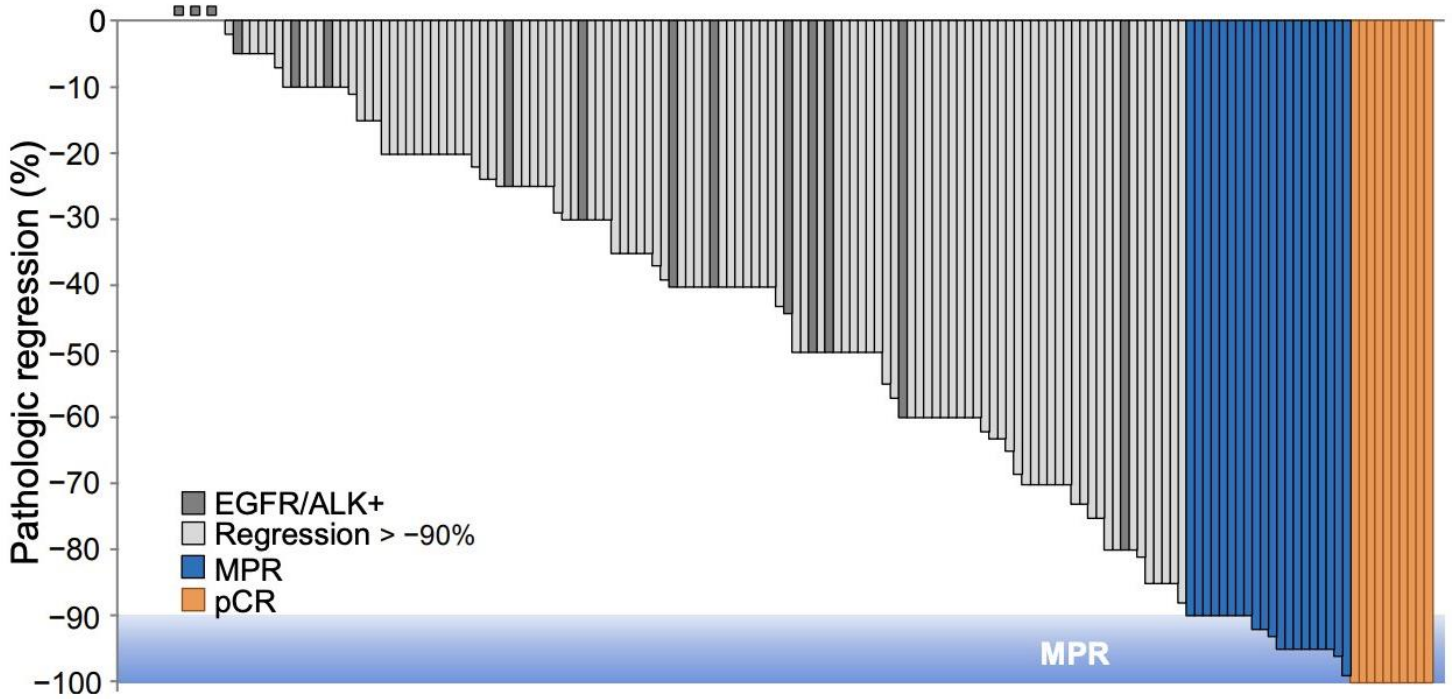
NCT02927301

ctDNA, circulating tumor DNA; DFS, disease-free survival; IF, immunofluorescence; NGS, next-generation sequencing; PET-CT, positron emission tomography–computed tomography; q3mo, every 3 months. SOC, standard of care; TCRseq, T-cell receptor sequencing; TMB, tumor mutational burden.

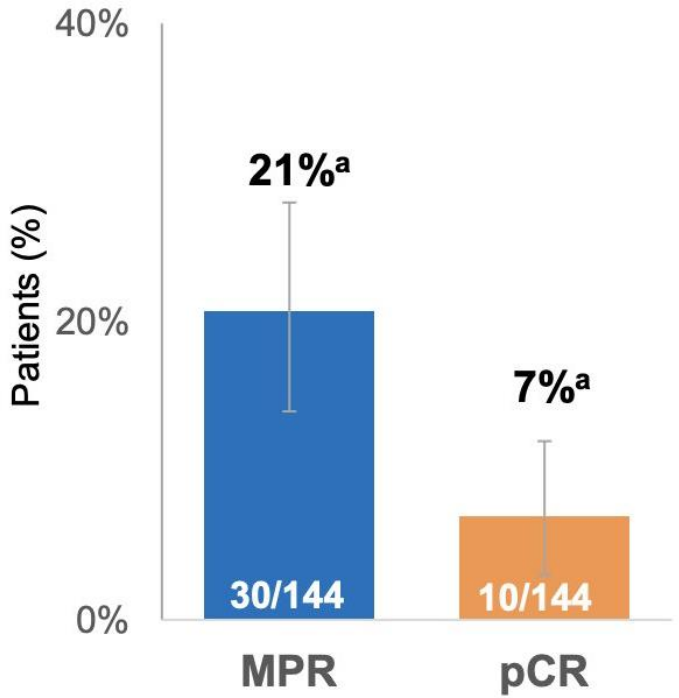
[a] T4 due to mediastinal organ invasion were excluded. [b] Mandatory

Primary endpoint: major pathologic response in surgery population

Pathologic response in surgery population (n=159)



Major pathologic response in primary efficacy population (n=144)



Pathologic regression defined as % viable tumor cells – 100%.
MPR, major pathologic response; pCR, pathologic complete response.
[a] Error bars indicate 95% CI.

Conclusions

- The primary endpoint of MPR was met, with an observed MPR of 21%
  - pCR rate was 7%
- Neoadjuvant atezolizumab monotherapy was well tolerated, with no new safety signals
- Following neoadjuvant atezolizumab, resection was performed:
  - with low perioperative morbidity and mortality
  - usually within the narrow protocol window (88%)
  - within short time frame from completion of atezolizumab
  - with high R0 resection rates (92%)
- This study provides additional clinical evidence for the ongoing placebo-controlled Phase III IMpower030 study of atezolizumab combined with platinum-based chemotherapy[1]

1. NCT03456063.

ARTICLES
https://doi.org/10.1038/s41591-020-01224-2
nature medicine
Check for updates

Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial

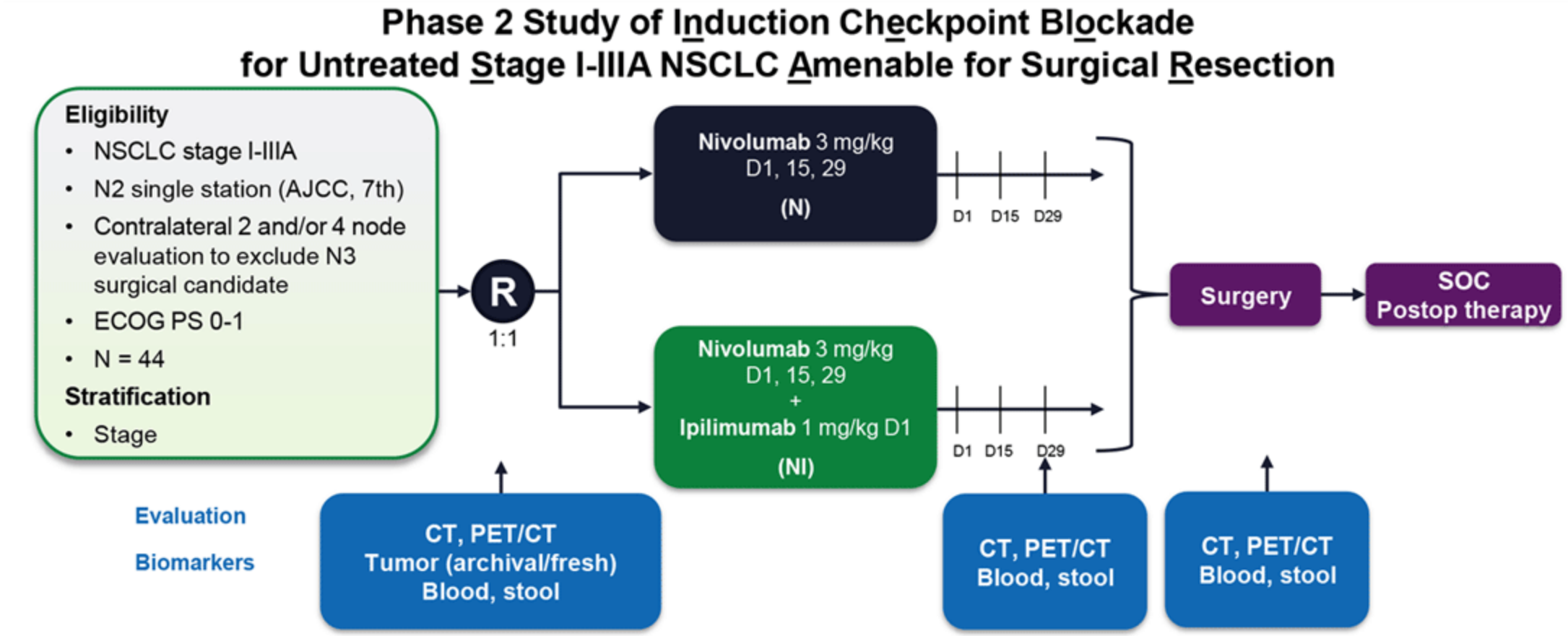
Tina Cascone[1✉], William N. William Jr[1,15], Annikka Weissferdt[2,3], Cheuk H. Leung[4], Heather Y. Lin[4], Apar Pataer[3], Myrna C. B. Godoy[5], Brett W. Carter[5], Lorenzo Federico[6], Alexandre Reuben[1], Md Abdul Wadud Khan[7], Hitoshi Dejima[8,16], Alejandro Francisco-Cruz[8], Edwin R. Parra[8], Luisa M. Solis[8], Junya Fujimoto[8], Hai T. Tran[1], Neda Kalhor[2], Frank V. Fossella[1], Frank E. Mott[1], Anne S. Tsao[1], George Blumenschein Jr[1], Xiuning Le[1], Jianjun Zhang[1], Ferdinandos Skoulidis[1], Jonathan M. Kurie[1], Mehmet Altan[1], Charles Lu[1], Bonnie S. Glisson[1], Lauren Averett Byers[1], Yasir Y. Elamin[1], Reza J. Mehran[3], David C. Rice[3], Garrett L. Walsh[3], Wayne L. Hofstetter[3], Jack A. Roth[3], Mara B. Antonoff[3], Humam Kadara[8], Cara Haymaker[8], Chantale Bernatchez[6,8], Nadim J. Ajami[9], Robert R. Jenq[9,10,11], Padmanee Sharma[12,13], James P. Allison[13], Andrew Futreal[9], Jennifer A. Wargo[7], Ignacio I. Wistuba[1,8], Stephen G. Swisher[3], J. Jack Lee[4], Don L. Gibbons[1], Ara A. Vaporciyan[3], John V. Heymach[1,14,17] and Boris Sepesi[3,17]

Ipilimumab improves clinical outcomes when combined with nivolumab in metastatic non-small cell lung cancer (NSCLC), but

Roma, Ponte Cestio

Roma, Ponte Fabricio

NEOSTAR: study design



- **Primary endpoint:** ≤10% viable tumor (MPR)

1. Cascone T et al. ASCO 2019. Abstract 8504.

NEOSTAR primary endpoint: MPR rate

Percentage viable tumor	Total (*n* = 44) *n* (%)	Nivo (*n* = 23) *n* (%)	Nivo + Ipi (*n* = 21) *n* (%)	□ value
MPR (≤10% viable tumor)[a+b]	13 (29%)	5 (22%) (95% CI: 7–44%)	8 (38%) (95% CI: 18–62%)	0.235
0% viable tumor (pCR)[a]	8 (18%)	2 (9%) (95% CI: 1–28%)	6 (29%) (95% CI: 11–52%)	0.126
1–10% viable tumor[b]	5 (11%)	3 (13%)	2 (10%)	
11–50% viable tumor	10 (23%)	6 (26%)	4 (19%)	
51–100% viable tumor	14 (32%)	10 (43%)	4 (19%)	
ǂNo surgery on trial	7 (16%)	2 (9%)	5 (23%)	

Articles

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

Mariano Provencio, Ernest Nadal, Amelia Insa, María Rosario García-Campelo, Joaquín Casal-Rubio, Manuel Dómine, Margarita Majem, Delvys Rodríguez-Abreu, Alex Martínez-Martí, Javier De Castro Carpeño, Manuel Cobo, Guillermo López Vivanco, Edel Del Barco, Reyes Bernabé Caro, Nuria Viñolas, Isidoro Barneto Aranda, Santiago Viteri, Eva Pereira, Ana Royuela, Marta Casarrubios, Clara Salas Antón, Edwin R Parra, Ignacio Wistuba, Virginia Calvo, Raquel Laza-Briviesca, Atocha Romero, Bartomeu Massuti, Alberto Cruz-Bermúdez

Summary

Background Non-small-cell lung cancer (NSCLC) is terminal in most patients with locally advanced stage disease.

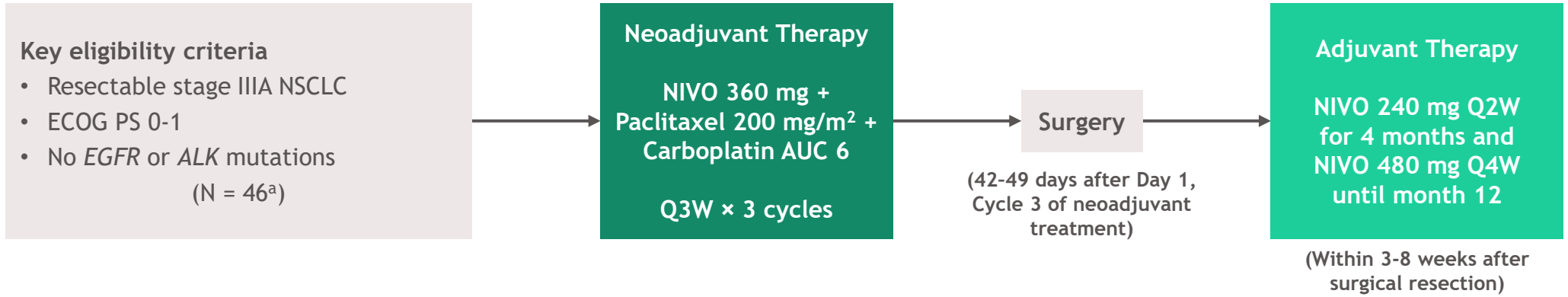
Lancet Oncol 2020

Roma, Ponte Sisto

Roma, Ponte Principe Amedeo di Savoia Aosta

NADIM (NCT03081689): study design

- NADIM was a phase 2, open-label study that assessed neoadjuvant NIVO in combination with chemotherapy in resectable stage IIIA NSCLC
- Patients received the combination prior to surgical resection, followed by adjuvant NIVO therapy



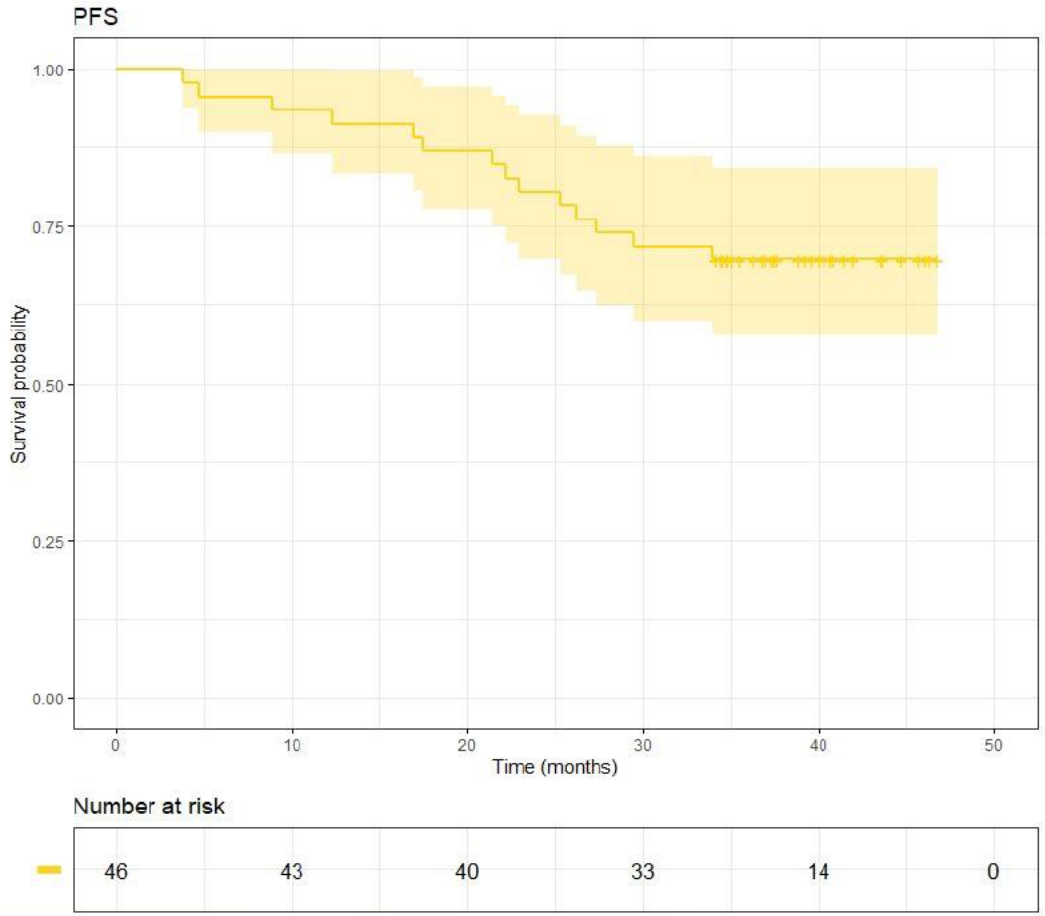
Primary endpoint:
- PFS at 24 months

Secondary endpoints:
- OS at 3 years
- Pathologic and imaging response
- Downstaging rate
- Complete resection rate
- PD rate at 3 years
- Surgical outcome
- Safety

Exploratory endpoint:
- ctDNA as a biomarker

[a]Modified ITT population, which included all patients who received neoadjuvant treatment. Per-protocol population (n = 37) included all patients who had tumor resection and received ≥ 1 cycle of adjuvant treatment.
AUC, area under the curve; ctDNA, circulating tumor DNA; NIVO, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status.
Provencio M et al. *Lancet Oncol*. 2020;21:1413–1422.

RESULTS: PFS



ITT population:

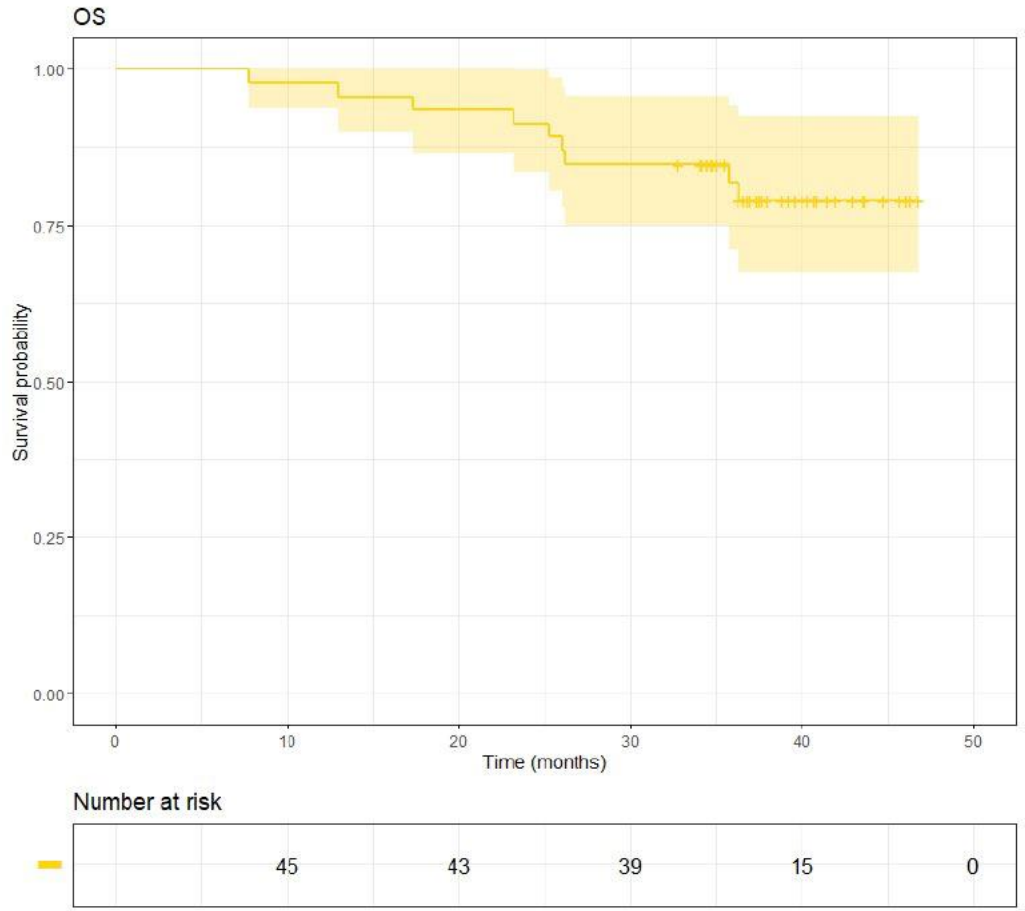
- **PFS 69.6%** (95%CI: 54.1-80.7%) **at 36 and 42 months.**

PP population:

- **PFS 81.1%** (95%CI: 64.4-90.5%) **at 36 and 42 months.**

The median PFS for patients who had progressive disease was 21.4 months (95% CI: 8.8–26.2 months)

RESULTS: OS



ITT population:

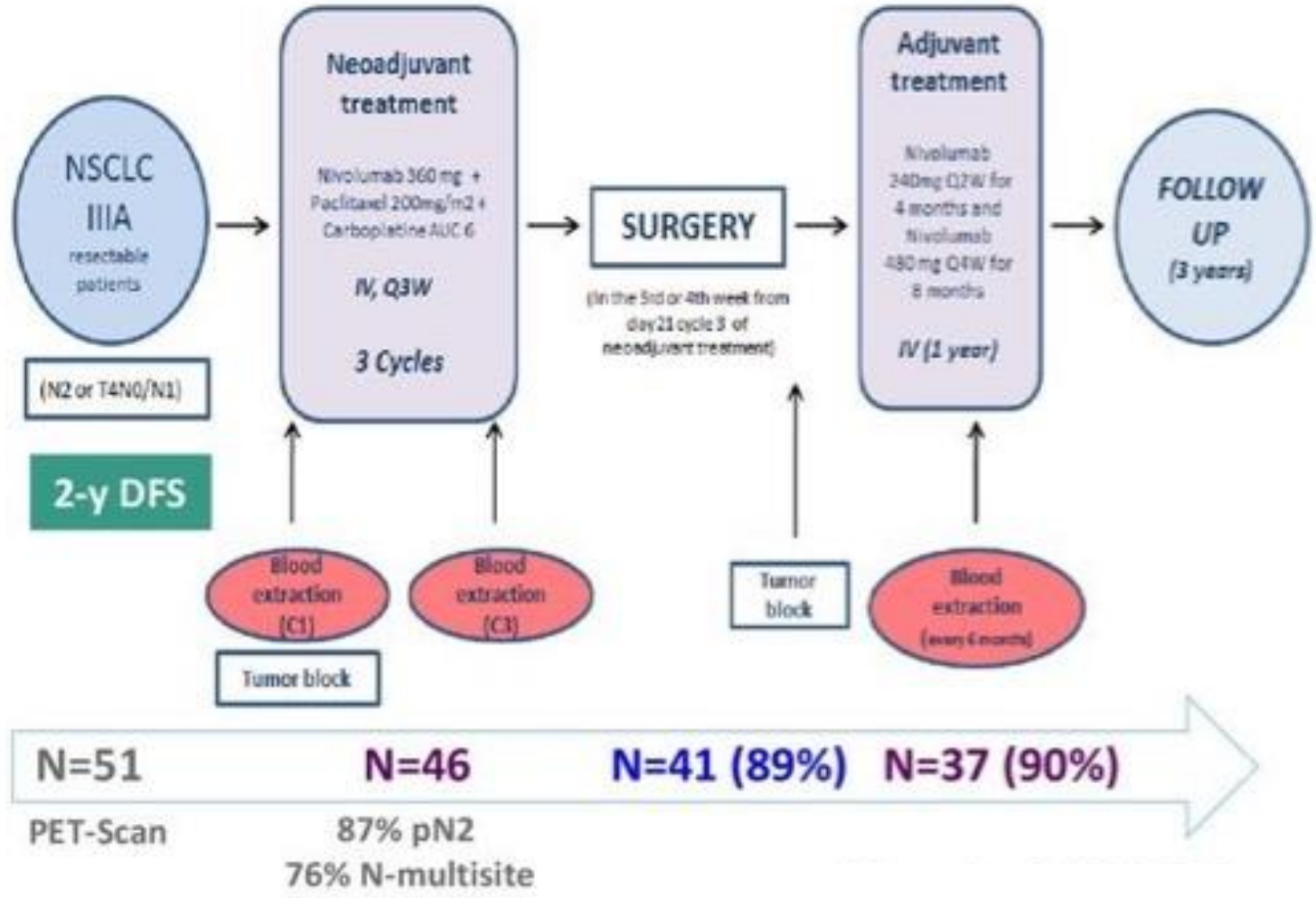
- **OS 81.9%** (95% CI: 66.8-90.6%) **at 36 months.**
- **OS 78.9%** (95%CI: 63.1-88.6%) **at 42 months.**

PP population:

- **OS 91.0%** (95%CI: 74.2-97.0%) **at 36 months.**
- **OS 87.3%** (95%CI: 69.3-95.1%) **at 42 months.**

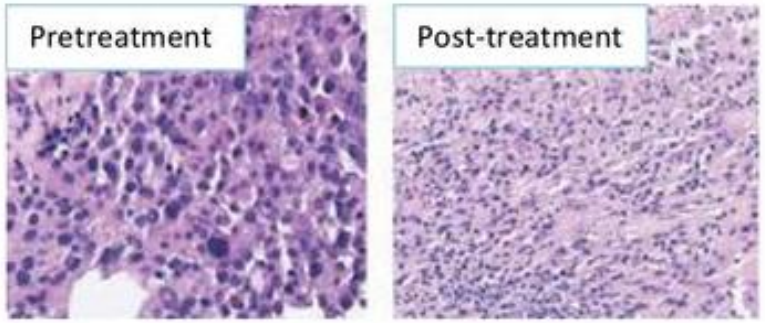
NADIM

Chemo-Immunotherapy for Stage IIIA Resectable NSCLC: Phase 2 Study



MPR (≤ 10% viable cells): 83%

pCR: 59%



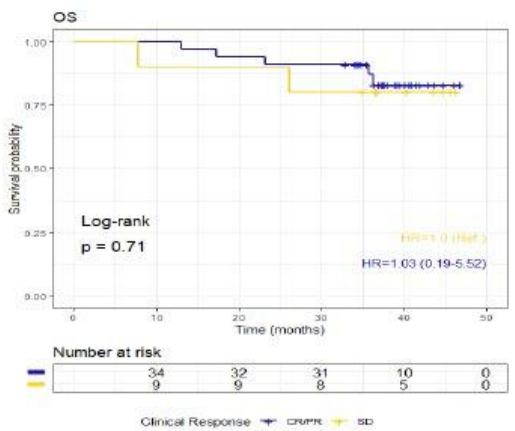
Survival surrogate	*HR (PFS)*	*95% CI*	*P*	*Adjusted PFS C-statistic*	*95% CI*	*HR (OS)*	*95% CI*	*P*	*Adjusted OS C-statistic*	*95% CI*
Clinical respone (CR+PR vs SD)	0.93	0.24-3.56	0.921	0.61	0.45-0.78	1.03	0.19-5.52	0.974	0.68	0.44-0.93
Pathological response (Complete vs Major+Incomplete)	0.25	0.06-1.00	**0.05**	0.68	0.52-0.84	--	--	--	0.83	0.75-0.91
ctDNA Clearance	0.3	0.08-1.11	**0.072**	0.62	0.43-0.81	0.05	0.00-0.68	**0.024**	0.79	0.55-1.03

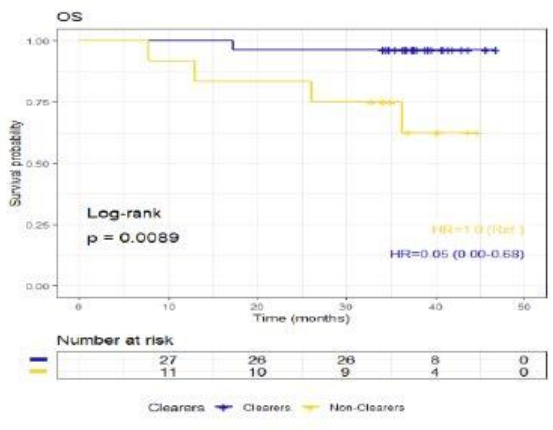
MOLECULAR RESPONSE

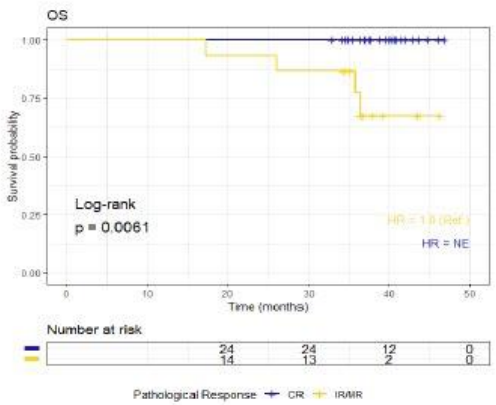
Clearers

Non-clearers

ctDNA clearance (i.e lack of detectable ctDNA at the end of neoadjuvant tx), **significantly predicted long-term survival.**



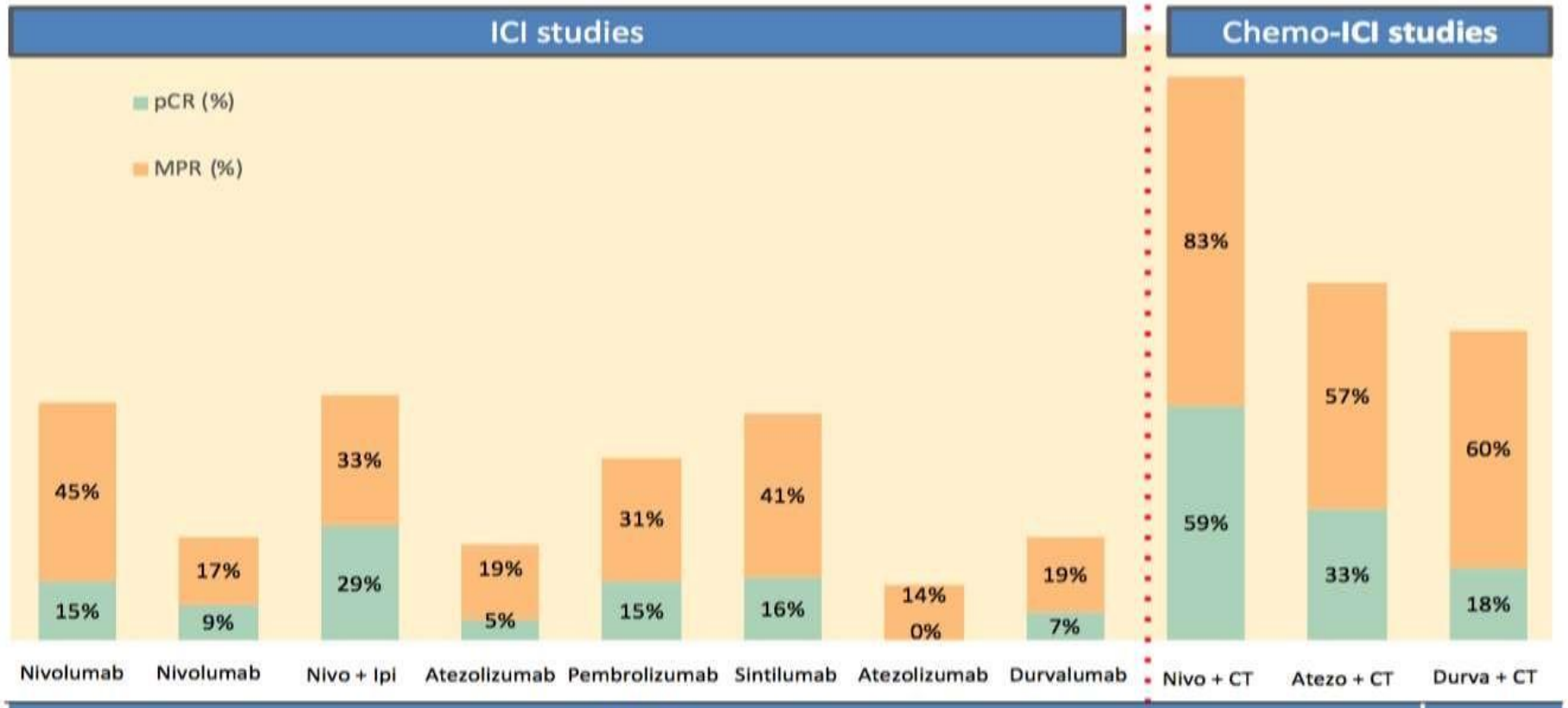




TAKE HOME MESSAGE

- NADIM showed **positive results in terms of survival**, **OS rate** at 36 months of **81.9% in the ITT** population rising to **91.0% in the PP** population with a 94% data maturity.
- **PFS** at 36 months **was 69.6% and 81.1% in the ITT and PP** population, respectively. Survival time was almost three times that reported in historical series, in which the 3-year OS did not exceed 30%.
- The addition of neoadjuvant nivolumab to chemotherapy did **not worse the safety profile**.
- In an exploratory analysis, **clinical responses** based on CT-scans and according to RECIST v1.1 criteria **did not predict survival** outcomes. However, in the multivariate analysis, pathological complete response **(pCR) or undetectable ctDNA levels after neoadjuvant** treatment significantly **predicted long-term survival**.

Neadjuvant Immunotherapy or Chemo-immunotherapy?



	Forde et al.	NEOSTAR		LCMC3	MK3475-223	Li et al.	PRINCEPS	IONESCO	NADIM	COLUMBIA	SAKK 16/14
N	22	23	21	101	15	40	30	50	46	14	67
Stage	I-IIIA	I-IIIA		IB-IIIA	I-II	IB-IIIA	I-IIIA	IB-IIIA	IIIA	IB-IIIA	IIIA (N2)
Surgery	95%	96%	81%	89%	87%	93%	100%	92%	90%	79%	82%
RR	10%	22%	19%	7%	NR	20%	7%	9%	74	57%	58%

Benitez et al. Clin Cancer Res 2020

AACR American Association for Cancer Research ANNUAL MEETING 2022 New Orleans
APRIL 8-13, 2022 • #AACR22

Nivolumab + platinum-doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (IB-IIIA) non-small cell lung cancer: event-free survival results from the phase 3 CheckMate 816 trial

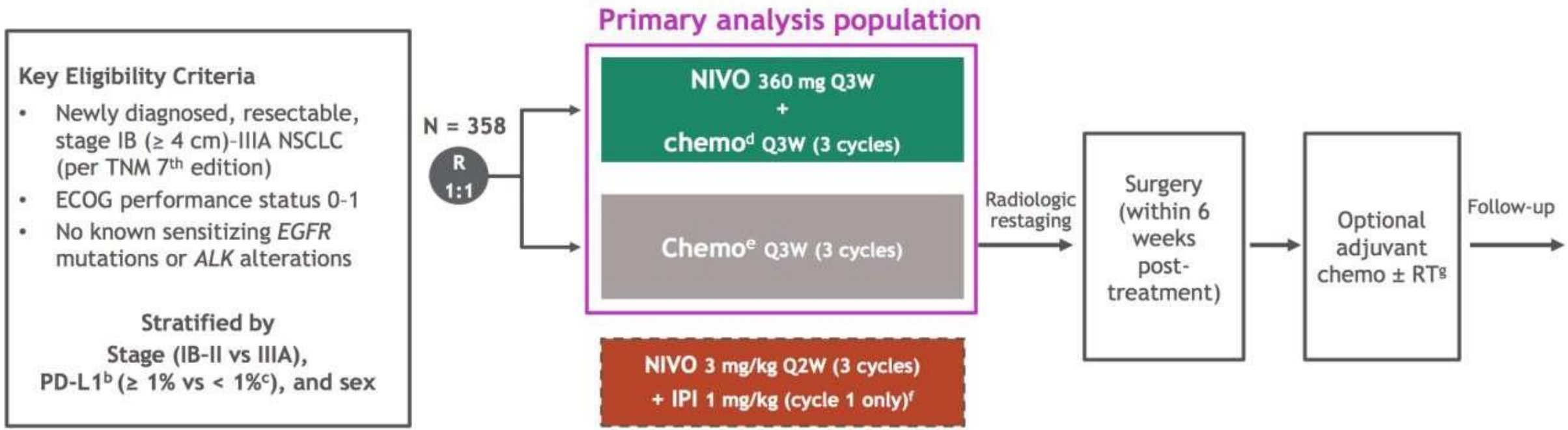
Nicolas Girard,[1] Jonathan Spicer,[2] Mariano Provencio,[3] Shun Lu,[4] Stephen Broderick,[5] Mark M. Awad,[6] Tetsuya Mitsudomi,[7] Keith Kerr,[8] Julie Brahmer,[5] Scott J. Swanson,[6] Enriqueta Felip,[9] Changli Wang,[10] Gene B. Saylors,[11] Ke-Neng Chen,[12] Fumihiro Tanaka,[13] Moishe Liberman,[14] Cecile Dorange,[15] Javed Mahmood,[15] Junliang Cai,[15] Patrick M. Forde[5]

[1]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; [2]McGill University Health Center, Montreal, Québec, Canada; [3]Hospital Universitario Puerta de Hierro, Madrid, Spain; [4]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China; [5]Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [8]Aberdeen Royal Infirmary, Aberdeen, UK; [9]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [10]Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [11]Charleston Oncology, Charleston, SC, USA; [12]Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China; [13]University of Occupational and Environmental Health, Kitakyushu, Japan; [14]University of Montreal, Centre de Recherche du CHUM, Montreal, Quebec, Canada; [15]Bristol Myers Squibb, Princeton, NJ, USA

Presentation Number CT012

Roma, Ponte della Musica – Armando Trovajoli

CheckMate 816 study design[a]



Primary endpoints
- pCR by BIPR
- EFS by BICR

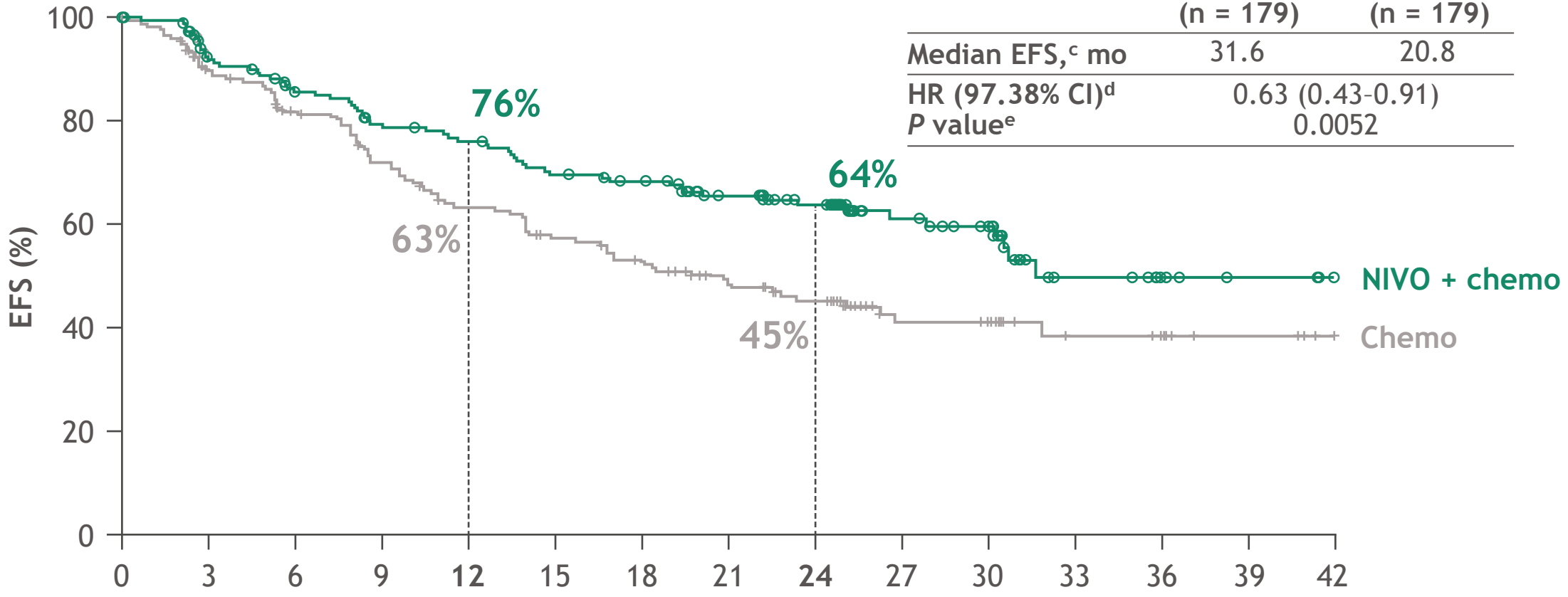
Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

Forde et al , AACR 2021

Primary endpoint: EFS[a,b] with neoadjuvant NIVO + chemo vs chemo

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS,[c] mo	31.6	20.8
HR (97.38% CI)[d]	0.63 (0.43–0.91)	
P value[e]	0.0052	



No. at risk

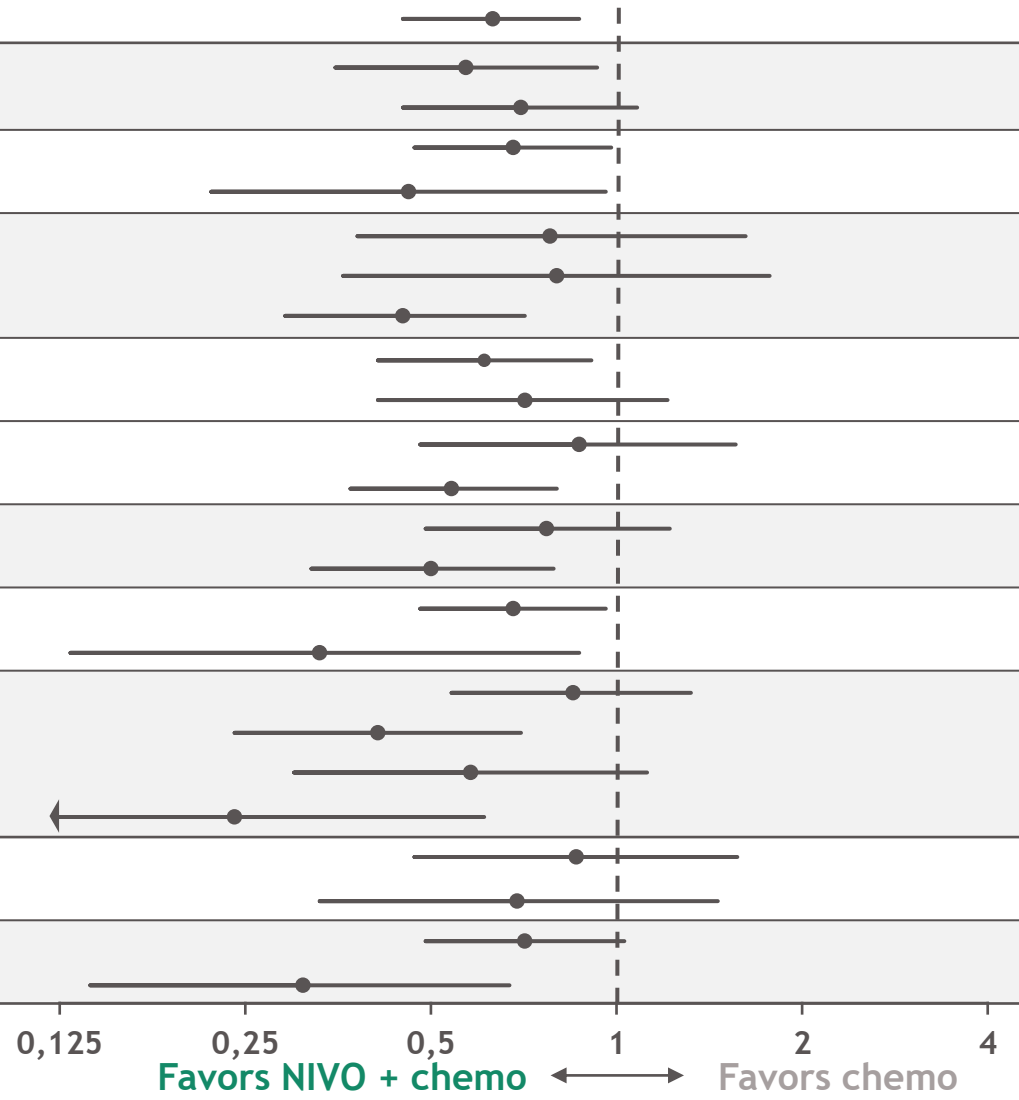
NIVO + chemo	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemo	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]Per BICR; [b]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy; [c]95% CI = 30.2–NR (NIVO + chemo) and 14.0–26.7 (chemo); [d]95% CI = 0.45-0.87; [e]The significance boundary at this interim analysis was 0.0262.

EFS subgroup analysis

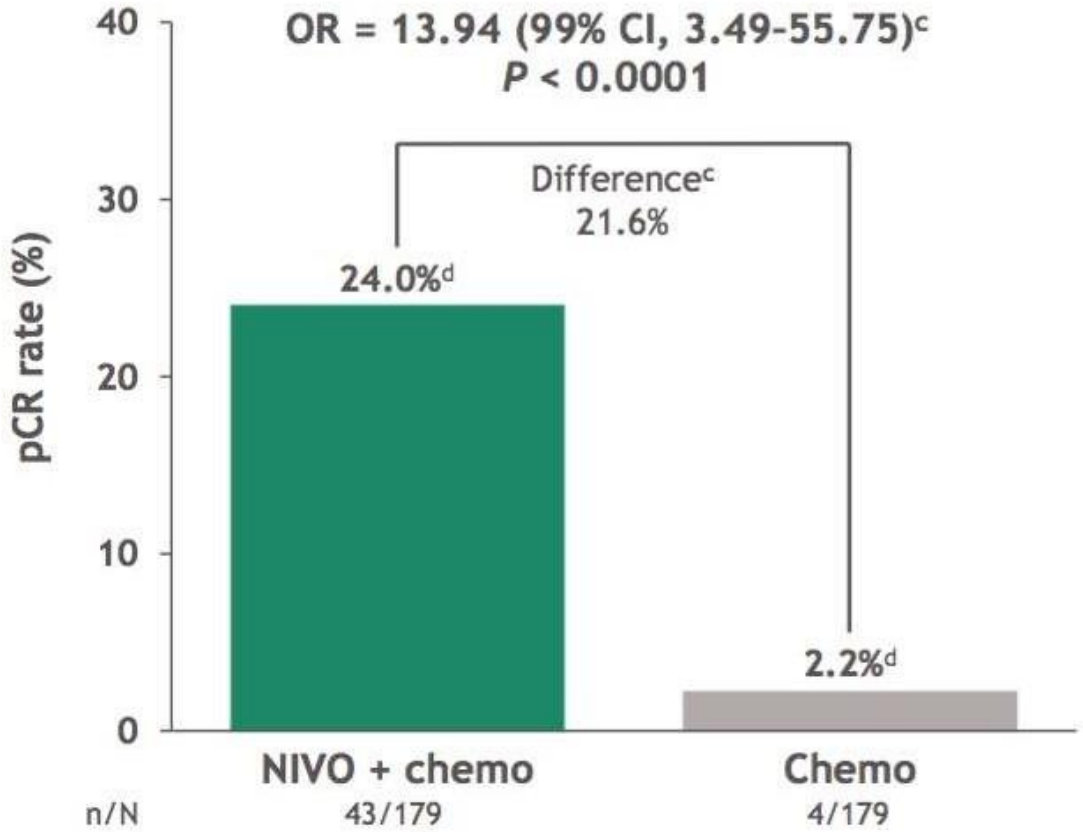
	Median EFS[a], mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	32	21		0.63
< 65 years (n = 176)	NR	21		0.57
≥ 65 years (n = 182)	30	18		0.70
Male (n = 255)	31	17		0.68
Female (n = 103)	NR	32		0.46
North America (n = 91)	NR	NR		0.78
Europe (n = 66)	32	21		0.80
Asia (n = 177)	NR	16		0.45
ECOG PS 0 (n = 241)	NR	23		0.61
ECOG PS 1 (n = 117)	30	14		0.71
Stage IB-II (n = 127)	NR	NR		0.87
Stage IIIA (n = 228)	32	16		0.54
Squamous (n = 182)	31	23		0.77
Non-squamous (n = 176)	NR	20		0.50
Current/former smoker (n = 318)	32	22		0.68
Never smoker (n = 39)	NR	10		0.33
PD-L1 < 1% (n = 155)	25	18		0.85
PD-L1 ≥ 1% (n = 178)	NR	21		0.41
PD-L1 1-49% (n = 98)	NR	27		0.58
PD-L1 ≥ 50% (n = 80)	NR	20		0.24
TMB < 12.3 mut/Mb (n = 102)	30	27		0.86
TMB ≥ 12.3 mut/Mb (n = 76)	NR	22		0.69
Cisplatin (n = 258)	NR	21		0.71
Carboplatin (n = 72)	NR	11		0.31



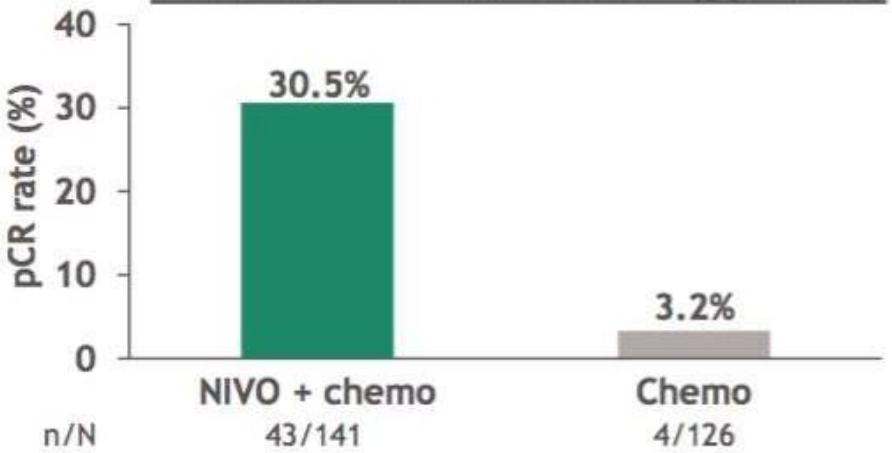
[a]Per BICR.

Primary endpoint: pCR[a] rate with neoadjuvant NIVO + chemo vs chemo

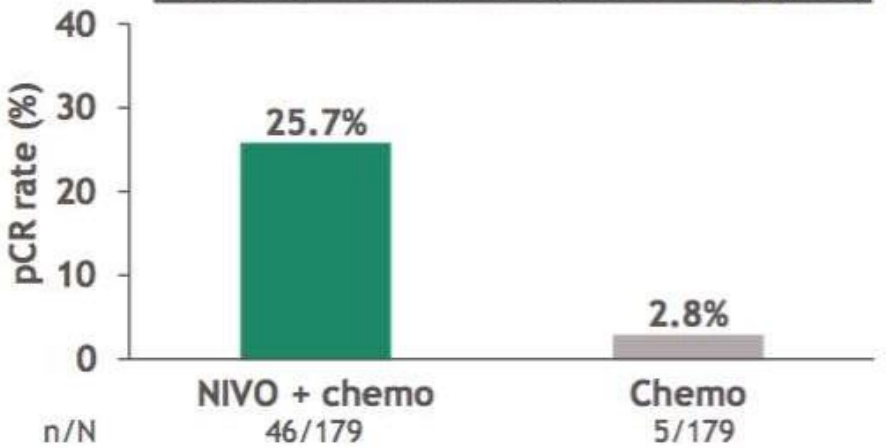
Primary endpoint: ITT (ypT0N0)[b]



Patients with resection[e] (ypT0N0)



Primary tumor only in ITT (ypT0)



- pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

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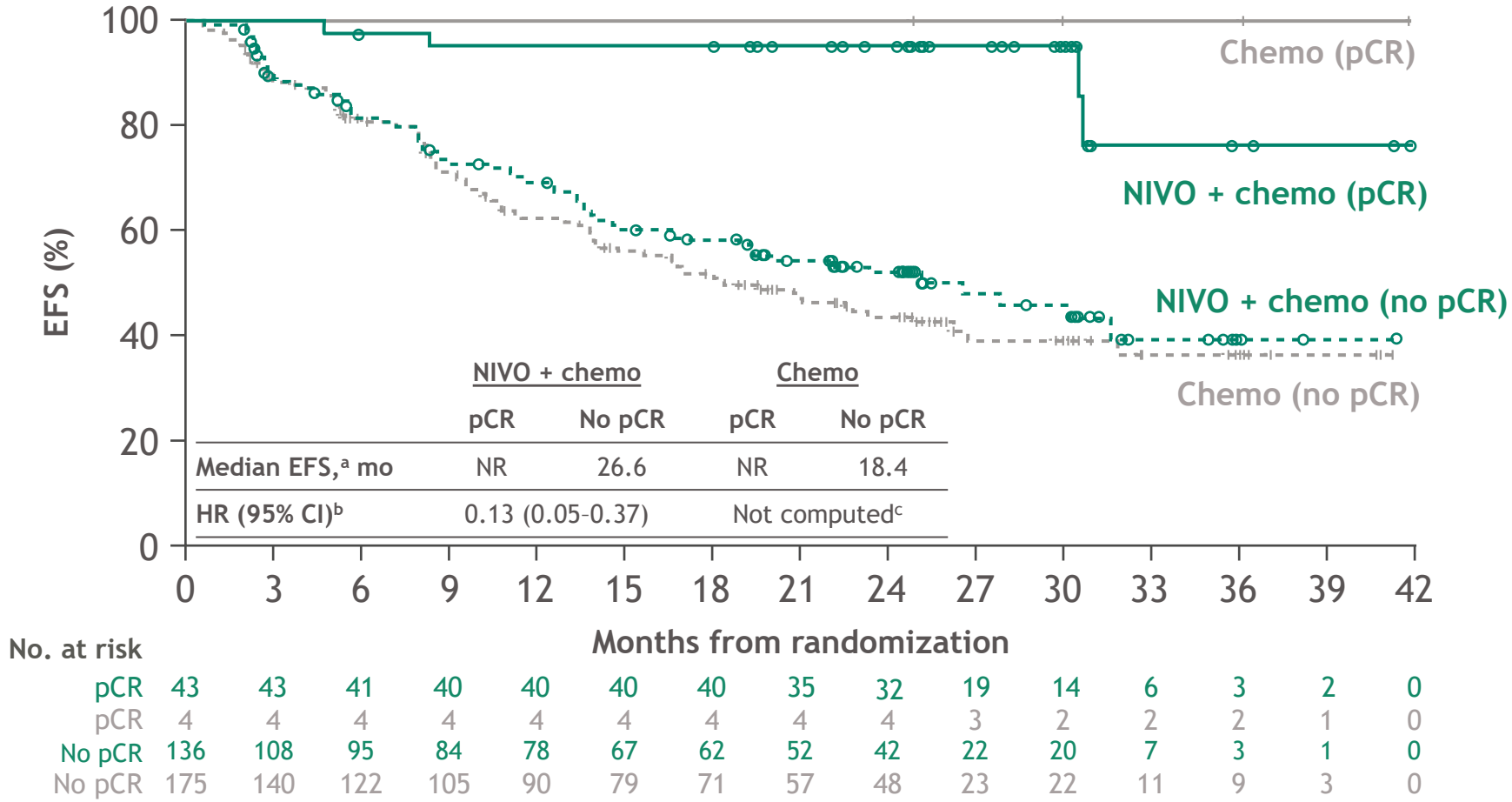
pCR subgroup analysis

	pCR[a] rate, %		Unweighted pCR difference, % (95% CI)	Unweighted pCR difference, %
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	24	2		22
< 65 years (n = 176)	27	0		27
≥ 65 years (n = 182)	21	4		17
Male (n = 255)	23	2		20
Female (n = 103)	28	2		26
North America (n = 91)	22	2		20
Europe (n = 66)	24	0		24
Asia (n = 177)	28	3		25
Stage IB-II (n = 128)	**26**	**5**		**21**
Stage IIIA (n = 228)	**23**	**1**		**22**
Squamous (n = 182)	**25**	**4**		**21**
Non-squamous (n = 176)	**23**	**0**		**23**
Current/former smoker (n = 318)	26	2		23
Never smoker (n = 39)	10	0		10
PD-L1 < 1% (n = 155)	**17**	**3**		**14**
PD-L1 ≥ 1% (n = 178)	**33**	**2**		**30**
PD-L1 1-49% (n = 98)	24	0		24
PD-L1 ≥ 50% (n = 80)	45	5		40
TMB < 12.3 mut/Mb (n = 102)	22	2		21
TMB ≥ 12.3 mut/Mb (n = 76)	31	3		28
Cisplatin (n = 258)	22	2		20
Carboplatin (n = 72)	31	0		31

[a]Per BIPR in ITT.

Exploratory analysis: EFS by pCR status



	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median EFS,[a] mo	NR	26.6	NR	18.4
HR (95% CI)[b]	0.13 (0.05–0.37)		Not computed[c]	

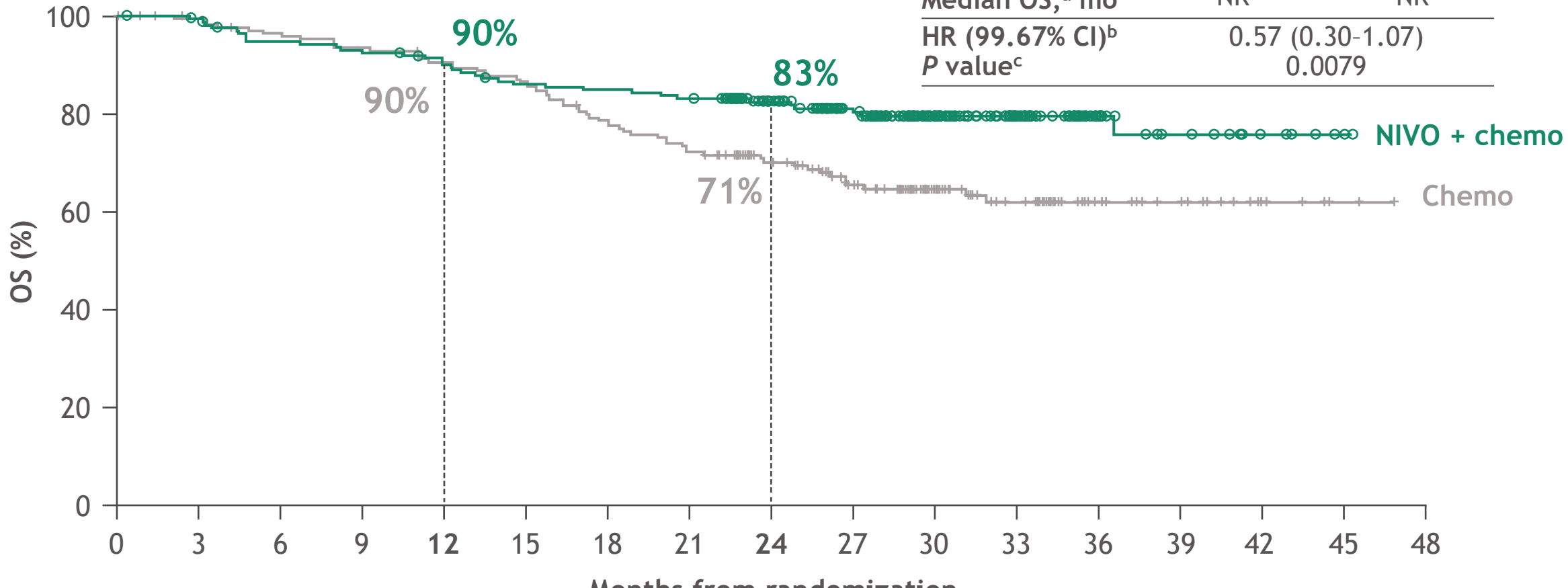
- pCR rates were significantly improved with NIVO + chemo vs chemo (24.0% vs 2.2%)
- In patients without pCR, HR (95% CI) for NIVO + chemo vs chemo was 0.84 (0.61–1.17)

Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]95% CI = 30.6–NR (NIVO + chemo, pCR), 16.6–NR (NIVO + chemo, no pCR) and NR–NR (chemo, pCR), 13.9–26.2 (chemo, no pCR); [b]In the pooled patient population (NIVO + chemo and chemo arms combined), EFS HR (95% CI) was 0.11 (0.04–0.29) for patients with pCR vs those without pCR; [c]HR was not computed for the chemo arm due to only 4 patients having a pCR.

Overall survival: interim analysis

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR
HR (99.67% CI)[b]	0.57 (0.30–1.07)	
P value[c]	0.0079	



No. at risk																	
NIVO + chemo	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemo	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]95% CI = NR-NR (NIVO + chemo) and NR-NR (chemo); [b]95% CI = 0.38-0.87; [c]Significance boundary for OS (0.0033) was not met at this interim analysis.

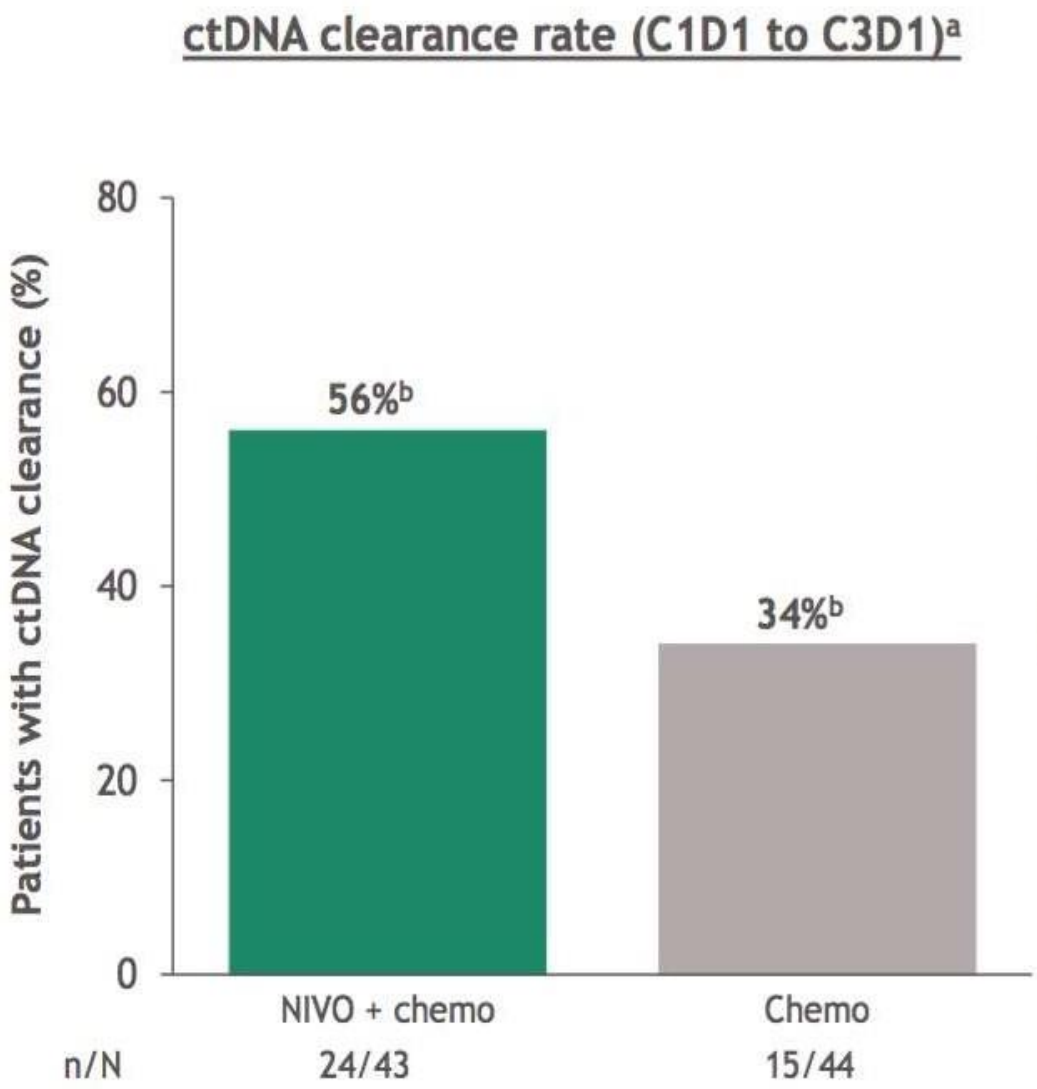
Adverse events[a] summary

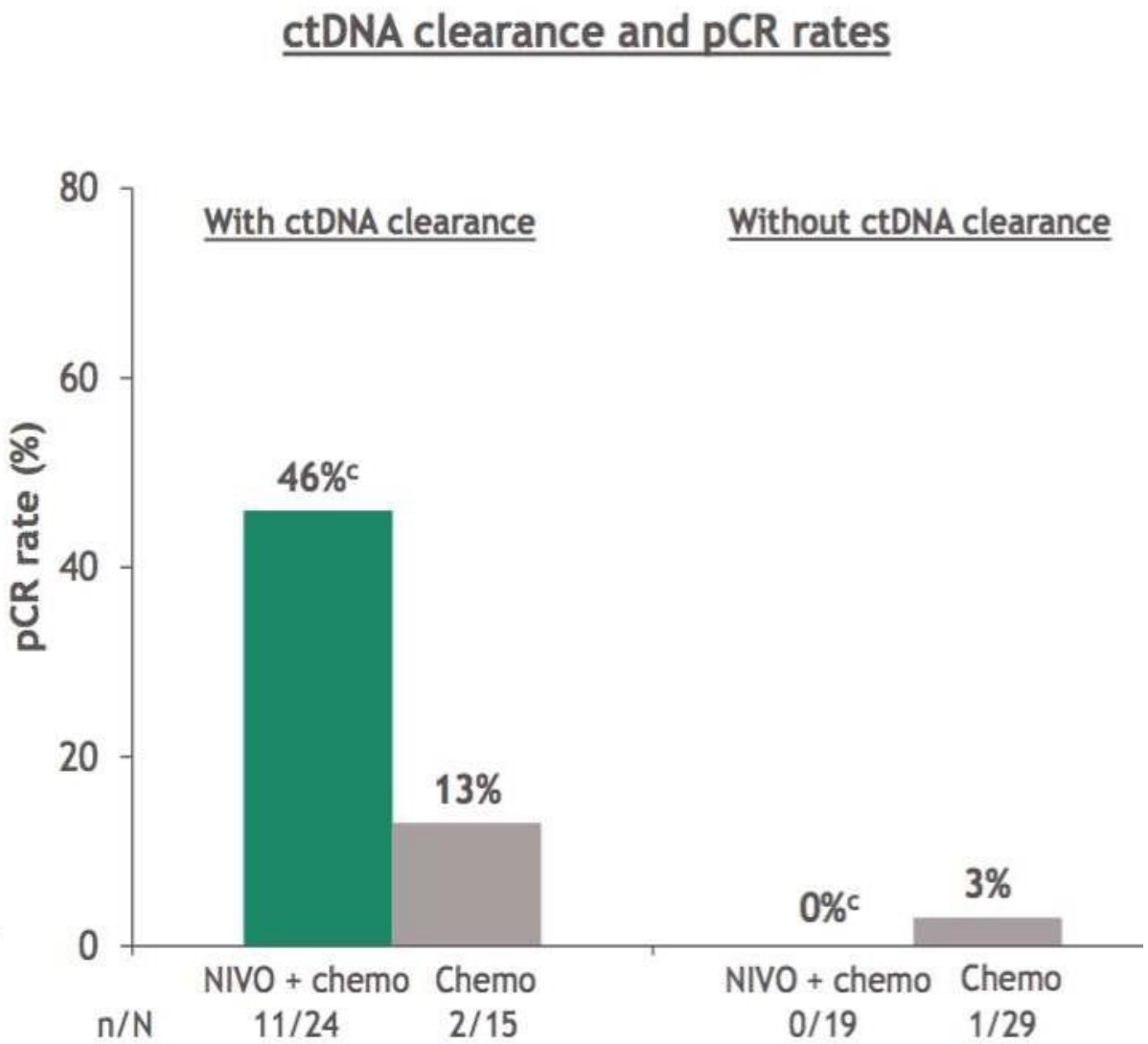
Patients (%)	NIVO + chemo (n = 176)		Chemo (n = 176)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All AEs	93	41	97	44
TRAEs	82	34	89	37
All AEs leading to discontinuation	10	6	11	4
TRAEs leading to discontinuation	10	6	10	3
All SAEs	17	11	14	10
Treatment-related SAEs	12	8	10	8
Surgery-related AEs[b,c]	42	11	47	15
Treatment-related deaths[d]	0		2	

- Grade 5 surgery-related AEs[e] were reported in 2 patients in the NIVO + chemo arm and were deemed unrelated to study drug per investigator (1 each due to pulmonary embolism and aortic rupture)

[a]Includes events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose as per CTCAE Version 4.0; MedDRA Version 24.0; [b]Includes events reported up to 90 days after definitive surgery; [c]Denominator based on patients with definitive surgery (n = 149 in the NIVO + chemo group, n = 135 in the chemo group); [d]Treatment-related deaths (not limited to 30 days window after last neoadjuvant dose) in the chemotherapy arm were due to pancytopenia, diarrhea, acute kidney injury (all in 1 patient), enterocolitis, and pneumonia; [e]Grade 5 AEs are defined as events that led to death within 24 hours of AE onset.

ctDNA clearance and association with pathological response





Forde et al , AACR 2021

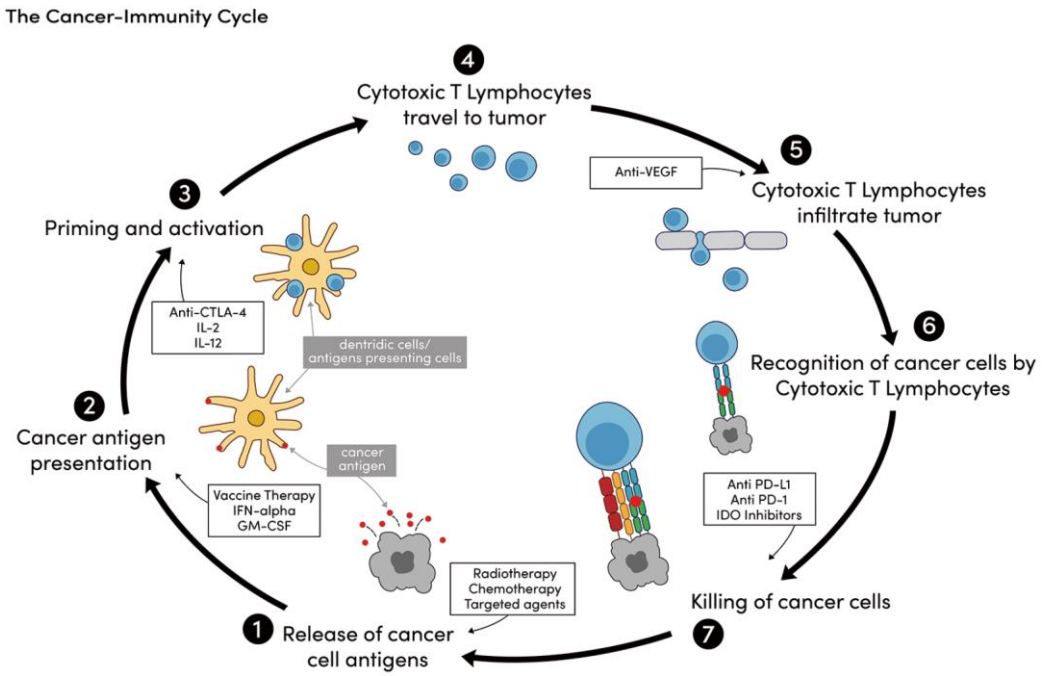
The NEW ENGLAND JOURNAL of MEDICINE

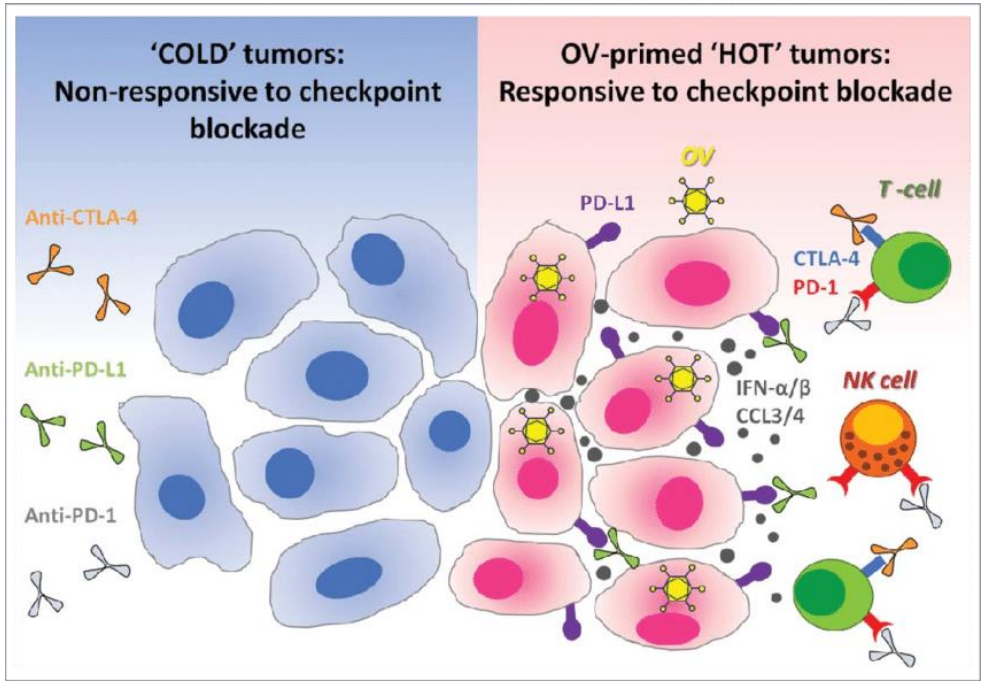
ORIGINAL ARTICLE

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

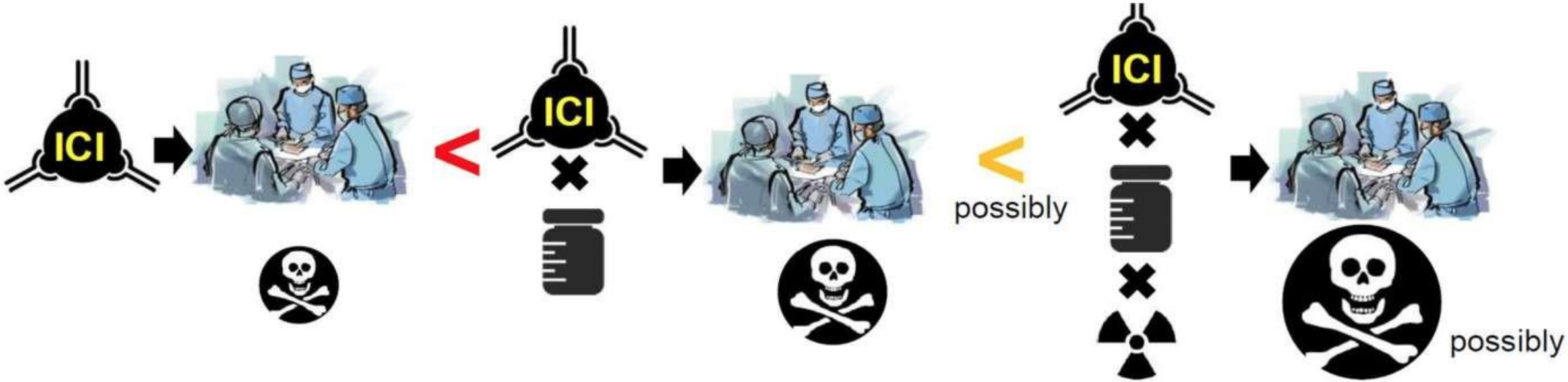
Neoadjuvant Immunotherapy and CTRT



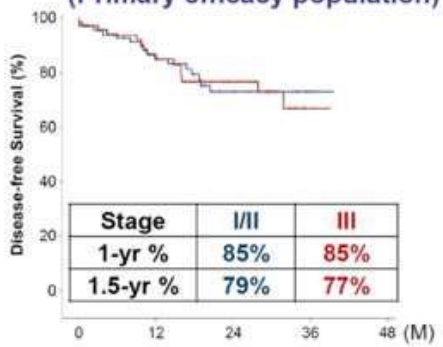


Chemoradiotherapy with ICI							
Hong et al.[17]	I/II	Single-arm cohort study	11	0/0/100	Durvalumab	Two cycles 1500 mg IV Q4W	pCR
Radiotherapy with ICI							
Altorki et al.[28]	II	Randomized two-arm study	30	37/16/47	Durvalumab	Two cycles 1120 mg IV Q3W	MPR
			30	26/33/40	Durvalumab + SBRT		

Neoadjuvant IO: *what do we know so far?*



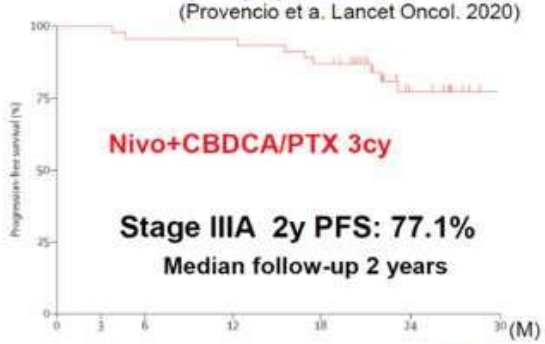
DFS (LCMC3)
(Primary efficacy population)



Stage	I/II	III
1-yr %	85%	85%
1.5-yr %	79%	77%

Neoadjuvant TRAEs (G3 ≤) : **6%**

PFS (NADIM)
(ITT population)
(Provencio et a. Lancet Oncol. 2020)



Nivo+CBDCA/PTX 3cy

Stage IIIA 2y PFS: 77.1%
Median follow-up 2 years

Neoadjuvant TRAEs (G3 ≤) : **30%**

When should single ICI be used?

- Early stage? Stage III but for stage I/II?
- Poor PS, comorbidities, elderly, platinum unfit?

Modified by Toyooka S, WCLC 2020

Select the right patient for efficacy (*biomarkers*)

Tumor cells

PDL- 1 expression

TMB

Specific mutated gene pathways

- INF-γ
- KRAS
- STK11

Tumor microenvironment

PDL- 1 expression

- Immune cells with specific phenotypes

- CD8+, CD4+ T-cells, FOXP3 T-cells
- TAMs, myeloid cells

Diversity of TCR repertoires:

- TILs, TCR clonality

Circulating factors

ct-DNA

Cytokines

Inflammatory factors

Soluble proteins

Pheripheral blood cells:

- CD8+, CD 4+ T-cells, FOXP3 T-cells

Host-related markers

Gender

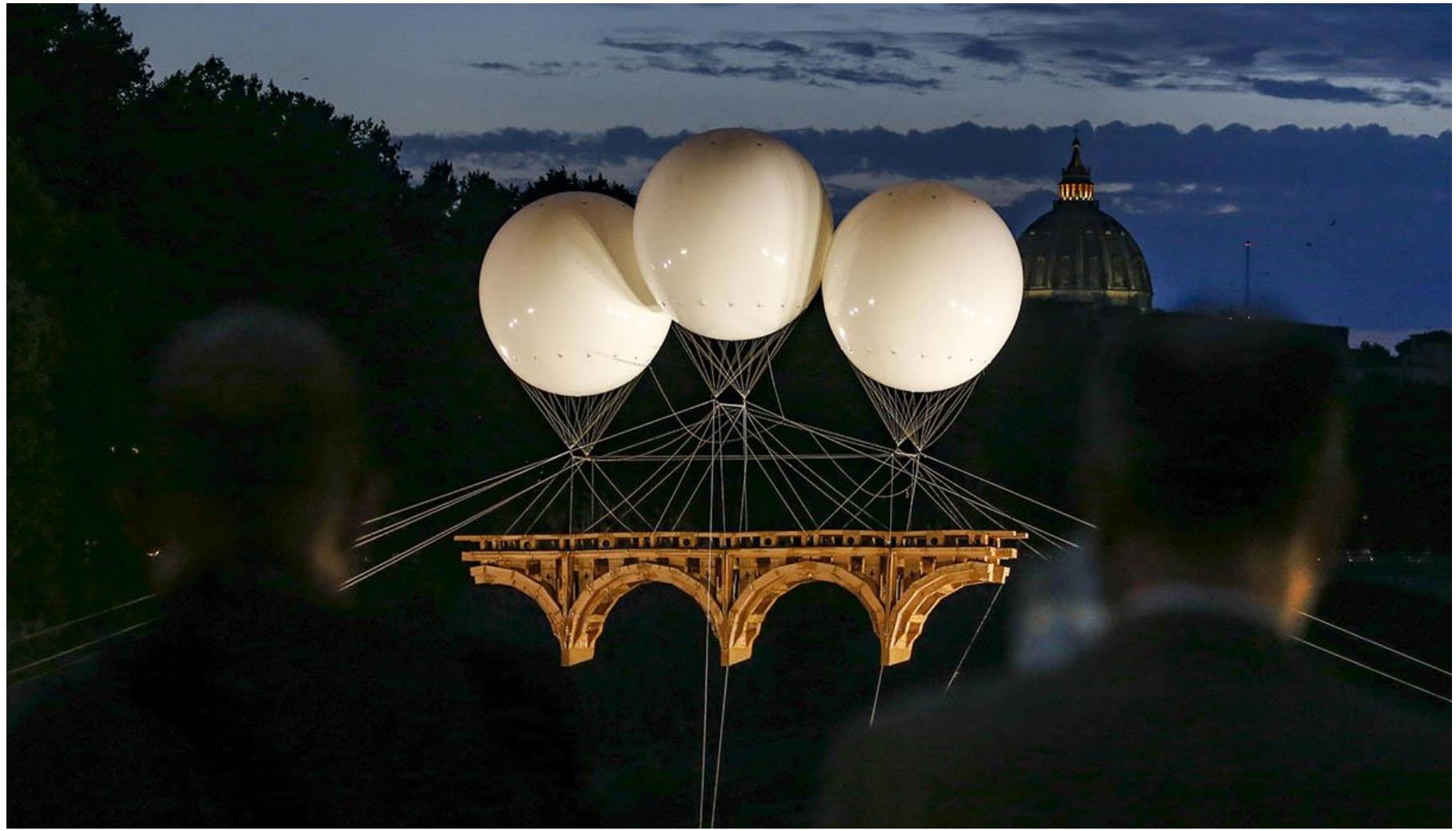
Age

Intestinal microbiota

Specific mutations

Microbiome

Epigenetics



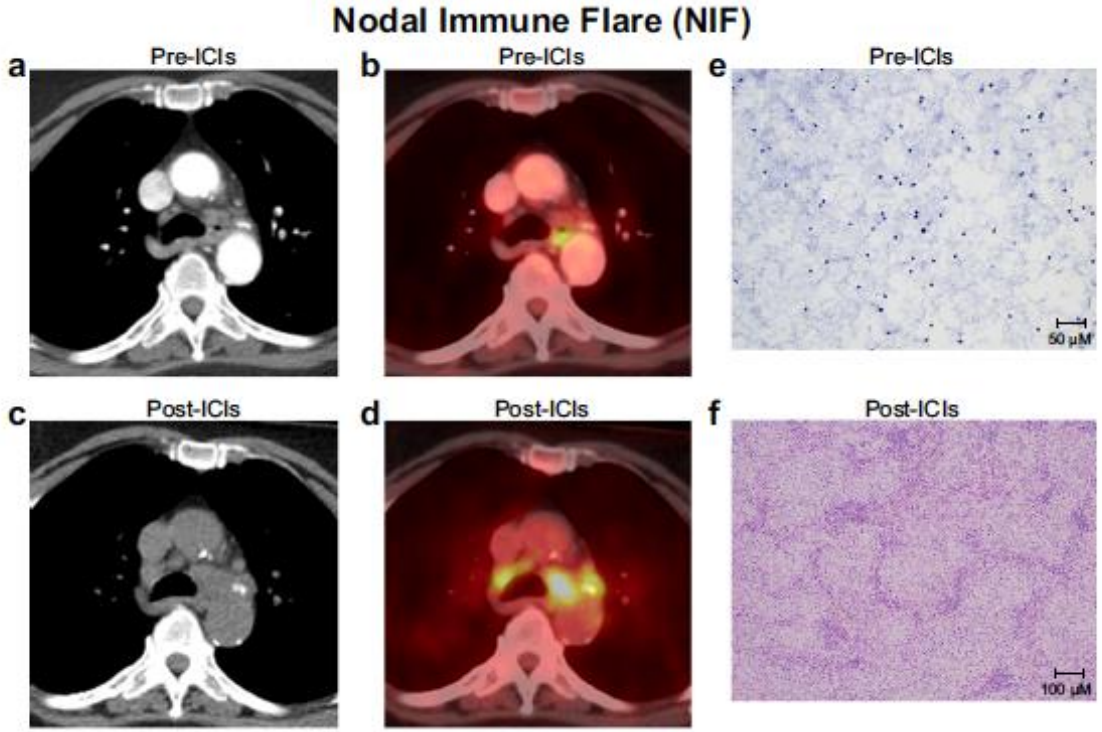
nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-25188-0 OPEN

Nodal immune flare mimics nodal disease progression following neoadjuvant immune checkpoint inhibitors in non-small cell lung cancer

Tina Cascone[1✉], Annikka Weissferdt[2,3], Myrna C. B. Godoy[4], William N. William Jr.[1,5], Cheuk H. Leung[6], Heather Y. Lin[6], Sreyashi Basu[7], Shalini S. Yadav[7], Apar Pataer[3], Kyle G. Mitchell[3], Md Abdul Wadud Khan[8], Yushu Shi[6,9], Cara Haymaker[10], Luisa M. Solis[10], Edwin R. Parra[10], Humam Kadara[10], Ignacio I. Wistuba[1,10], Padmanee Sharma[7,11], James P. Allison[7,12], Nadim J. Ajami[13], Jennifer A. Wargo[8], Robert R. Jenq[13,14], Don L. Gibbons[1], J. Jack Lee[6], Stephen G. Swisher[3], Ara A. Vaporciyan[3], John V. Heymach[1,15✉] & Boris Sepesi[3,15]



«NIF is associated with an inflamed nodal immune microenvironment and with fecal abundance of genera belonging to the family Coriobacteriaceae of phylum Actinobacteria, but not with tumor responses or treatment-related toxicity. Our findings suggest that this apparent radiological cancer progression in lymph nodes may occur due to an inflammatory response after neoadjuvant immunotherapy, and such cases should be evaluated by pathological examination to distinguish NIF from true nodal progression and to ensure appropriate clinical treatment planning ….»

Surgery delay summary[a]

	All stages		Stage IB/II		Stage IIIA	
	NIVO + chemo (n = 149)	Chemo (n = 135)	NIVO + chemo (n = 55)	Chemo (n = 52)	NIVO + chemo (n = 94)	Chemo (n = 83)
Patients with delayed surgery,[b,c] n (%)	31 (21)	24 (18)	9 (16)	13 (25)	22 (23)	11 (13)
AE	6 (4)	9 (7)	2 (4)	7 (13)	4 (4)	2 (2)
Length of delay in surgery, weeks						
Median (IQR)	2.0 (0.6-3.0)	2.4 (1.0-3.7)	2.1 (0.9-2.9)	2.1 (1.3-3.6)	1.9 (0.6-3.0)	2.6 (0.6-4.9)
Of patients with delayed surgery, proportion n (%) with delay of[d]						
≤ 2 weeks	17 (55)	11 (46)	4 (44)	6 (46)	13 (59)	5 (46)
> 2 and ≤ 4 weeks	8 (26)	8 (33)	4 (44)	5 (38)	4 (18)	3 (27)
> 4 and ≤ 6 weeks	3 (10)	2 (8)	0	0	3 (14)	2 (18)
> 6 weeks	3 (10)	3 (12)	1 (11)	2 (15)	2 (9)	1 (9)

- Median (IQR) time from last neoadjuvant dose to definitive surgery was 5.3 (4.6-6.0) weeks with NIVO + chemo and 5.0 (4.6-5.9) weeks with chemo for all patients with definitive surgery

Grazie per l’attenzione!