Neoadjuvant Lung Cancer Immunotherapy

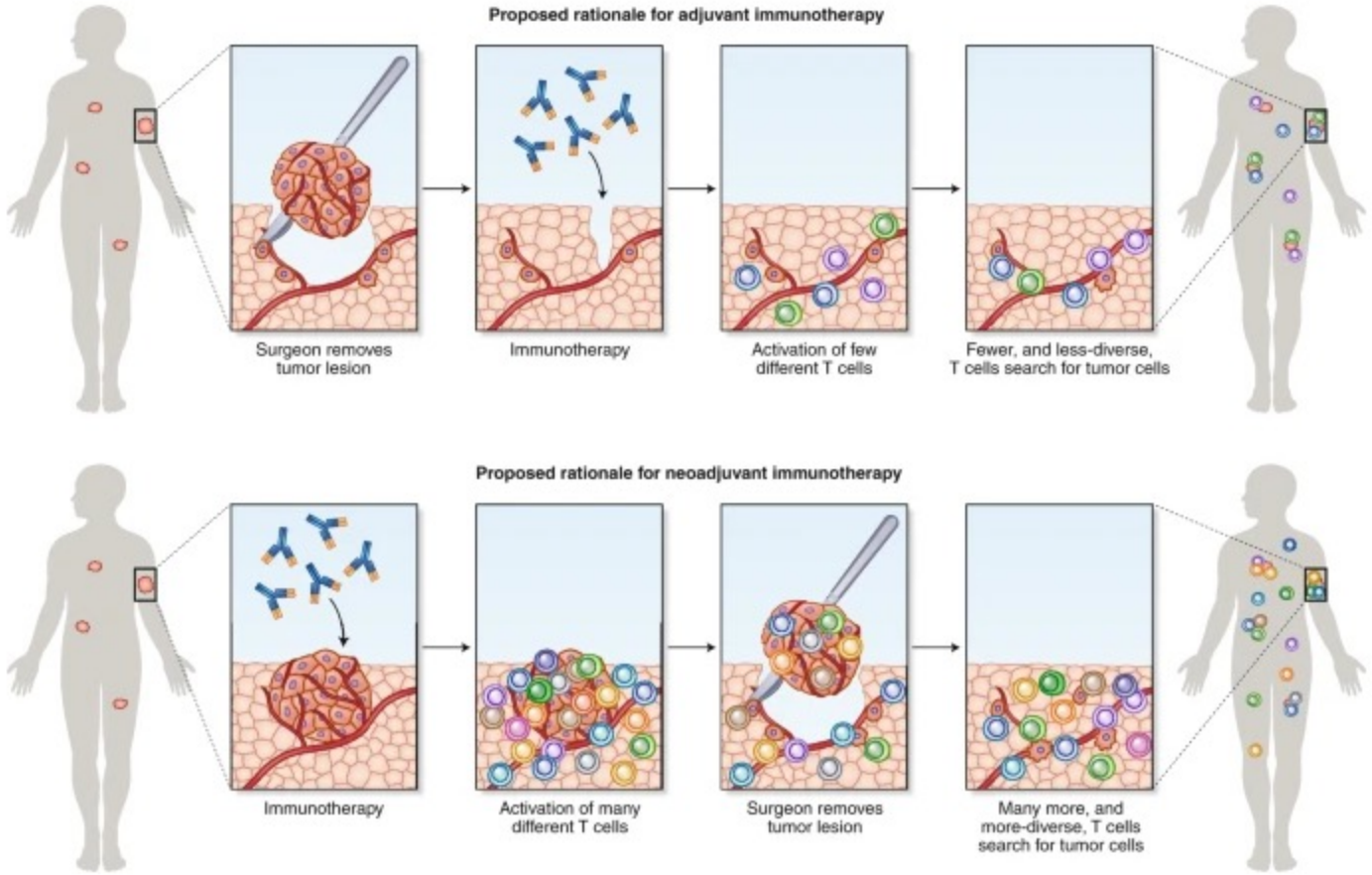
Luis E. Raez MD FACP FCCP
Chief Scientific Officer & Medical Director
Memorial Cancer Institute/Memorial Health Care System
Research Professor at the I-Health Institute
Florida Atlantic University (FAU)
Past-President Florida Society of Clinical Oncology (FLASCO)

Memorial Cancer Institute

CANCER CENTER of EXCELLENCE Florida HEALTH

FAU I-HEALTH Florida Atlantic University

Fig. 1: Neoadjuvant and adjuvant approaches to immunotherapy.

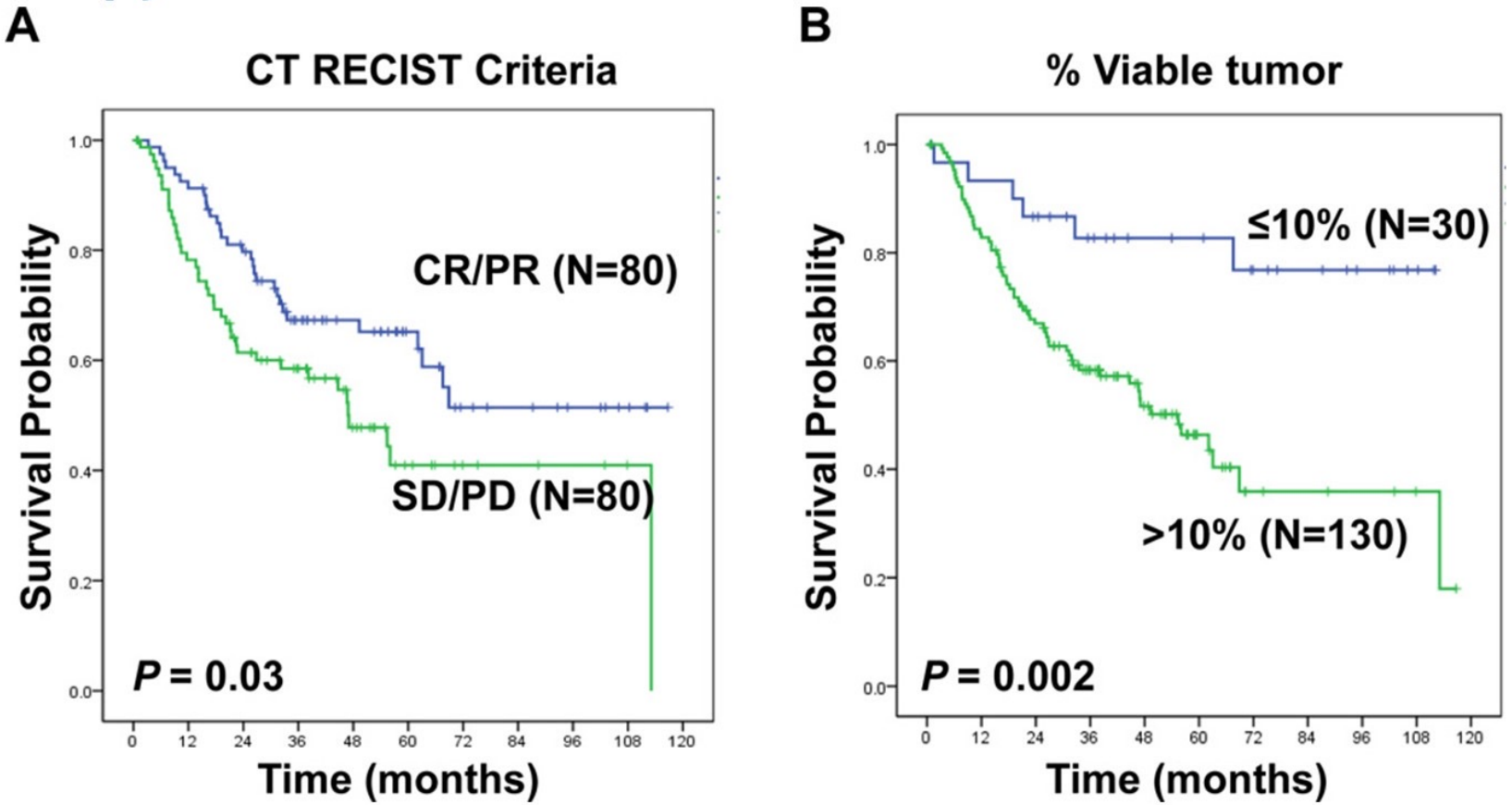


In adjuvant approaches, shown above, immunotherapy (as indicated by the antibodies) is given after surgery, which results in the activation of T cells directed to different antigens, as indicated by the different colors. In neoadjuvant approaches, therapy is given before surgery, which results in the raising of a more diverse T cell response.

Pre-operative vs. Postoperative IO: General considerations

- **Both have the disadvantage that you are treating a lot of people who may be cured by surgery alone with expensive drugs for a long time**
  - No robust biomarkers for relapse or benefit from IO
- **Postoperative:**
  - No delay or potential interference with the most effective regimen (surgery)
  - Longest experience, more accurate staging
  - Patients/surgeons don't like to delay surgery
- **Preoperative:**
  - Ability to assess antitumor efficacy of the intervention, – may not need postoperative IO if pCR
  - Early systemic therapy
  - Intact nodal drainage and tumor might be a benefit for immunity/IO therapy
  - Access to pre- and post biospecimens for research

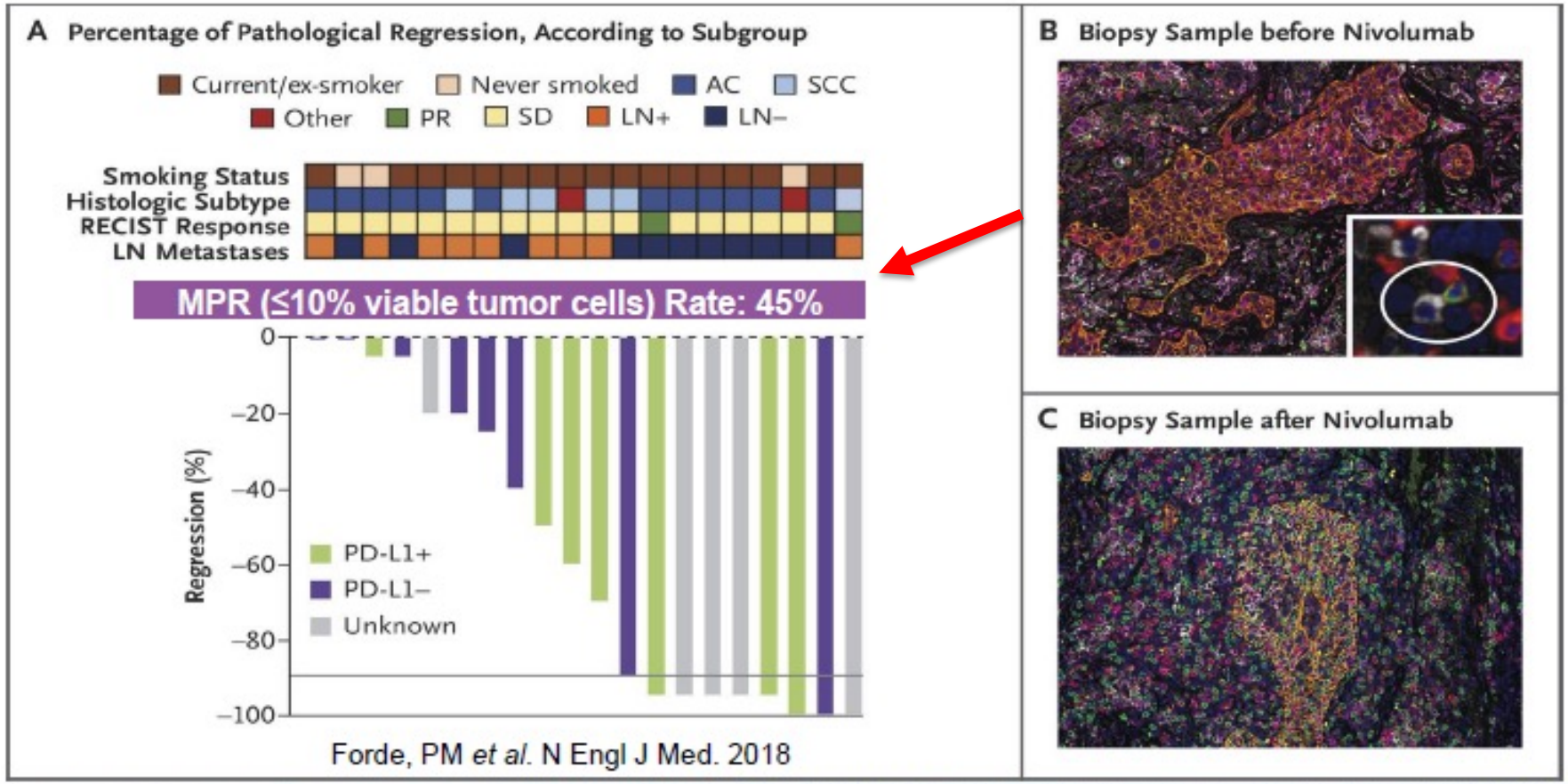
CT RECIST vs. MPR and prediction of OS after neoadjuvant chemotherapy in resectable NSCLC



41% discordance rate between CT RECIST response and histopathologic response.

WN William et al J Thorac Oncol. 2013 Feb; 8(2): 222-228

Neoadjuvant nivolumab is feasible, safe and active in operable NSCLC

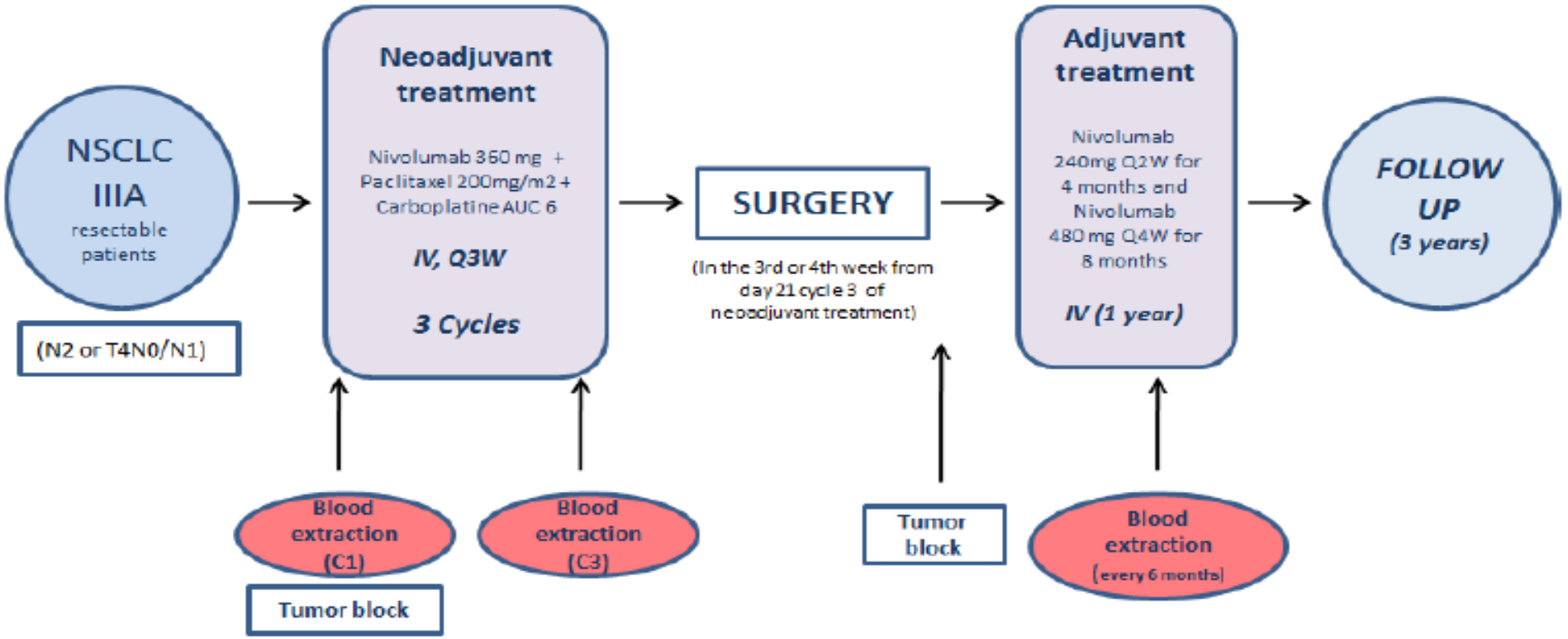


Forde, PM *et al.* N Engl J Med. 2018

Neoadjuvant Chemo-Immunotherapy
NADIM: Study Design & Endpoints

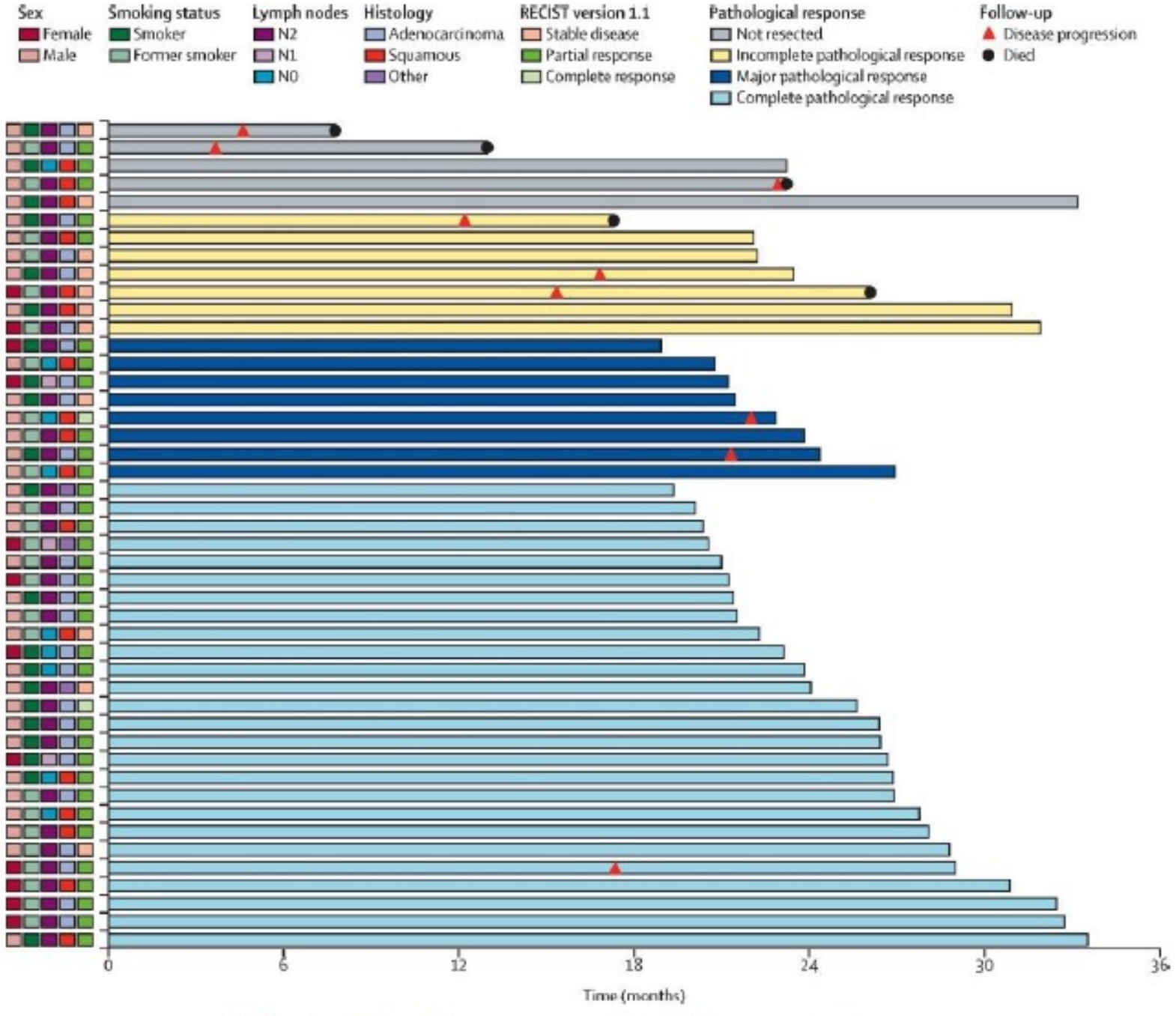
Primary Endpoint:
PFS at 24 months

Secondary Endpoints:
Down-staging rate, complete resection rate, ORR, safety, TTP, OS at 3 years



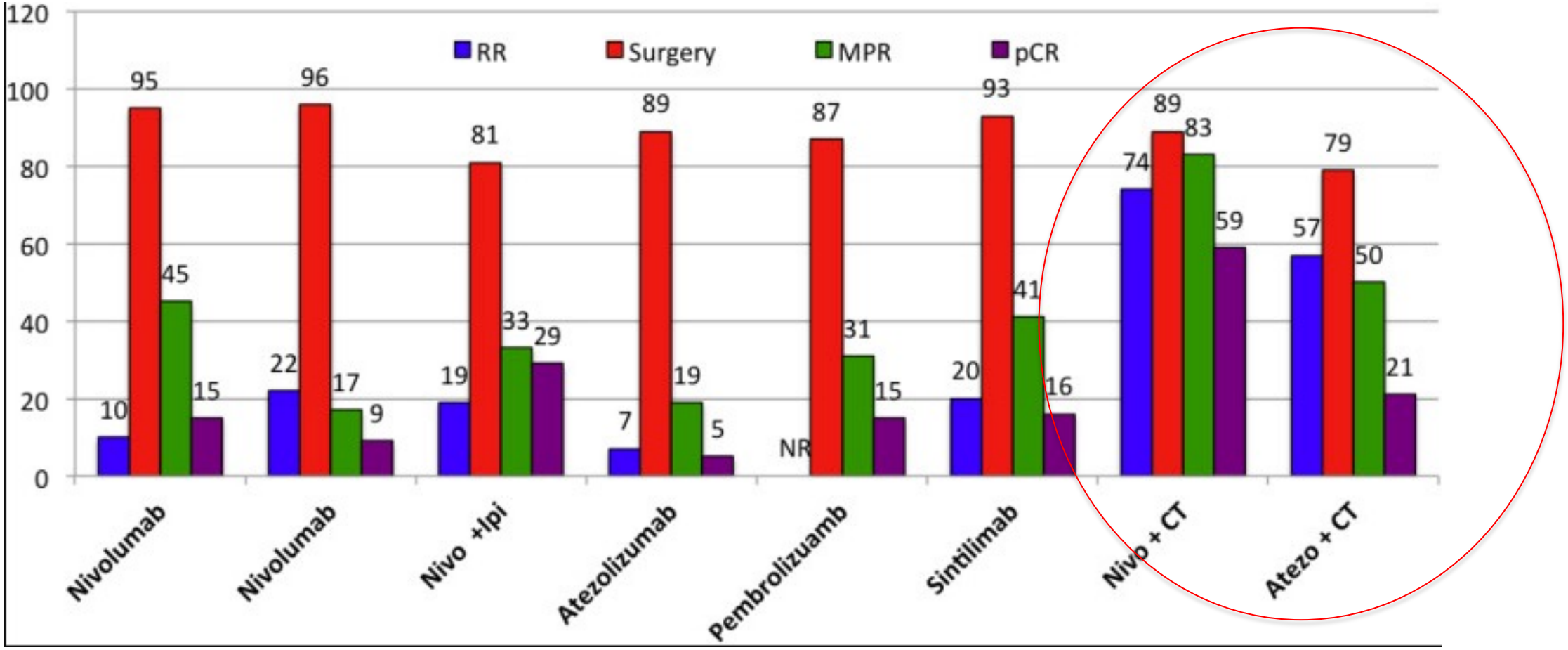
Key Results - NADIM

- 46 patients with clinical stage IIIA enrolled, 74% N2 including 54% multi-station N2
- 30% of pts had ≥G3 toxicity, no delays to surgery due to toxicity
- ORR 76% 41 of 46 patients underwent R0 resection*. 37/46 (80%) downstaged at resection.
- 24 month PFS – 77% (59.9-87.7)
- 74% (34/46) had MPR and **57% (26/46) pts had pCR**



*2 pts elected not to have surgery, 3 pts had progressive disease

Efficacy of neoadjuvant immune checkpoint inhibitors (ICIs) with or without chemotherapy (CT)



CheckMate 816 study design[a]

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG performance status 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
Stage (IB-II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex

N = 358

R 1:1

Primary analysis population

NIVO 360 mg Q3W + chemo[d] Q3W (3 cycles)

Chemo[e] Q3W (3 cycles)

NIVO 3 mg/kg Q2W (3 cycles) + IPI 1 mg/kg (cycle 1 only)[f]

FDA approved 3/2022

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT[g] → Follow-up

Primary endpoints
- pCR by BIPR
- EFS by BICR

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

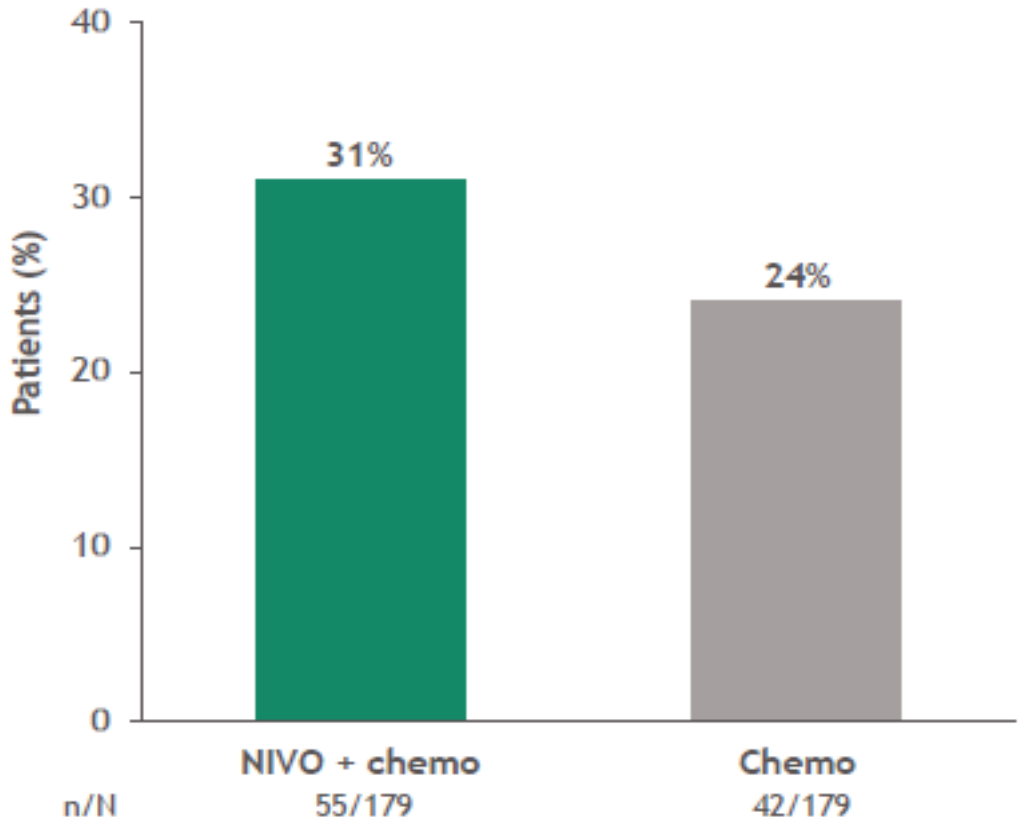
Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

Objective response rate and radiographic down-staging

Objective response rate

Patients, n (%)	NIVO + chemo (n = 179)	Chemo (n = 179)
ORR[a]	96 (54)[b]	67 (37)[b]
Best overall response		
Complete response	1 (1)	3 (2)
Partial response	95 (53)	64 (36)
Stable disease	70 (39)	88 (49)
Progressive disease	8 (4)	11 (6)
Not evaluable	1 (1)	1 (1)
Not reported	4 (2)	12 (7)

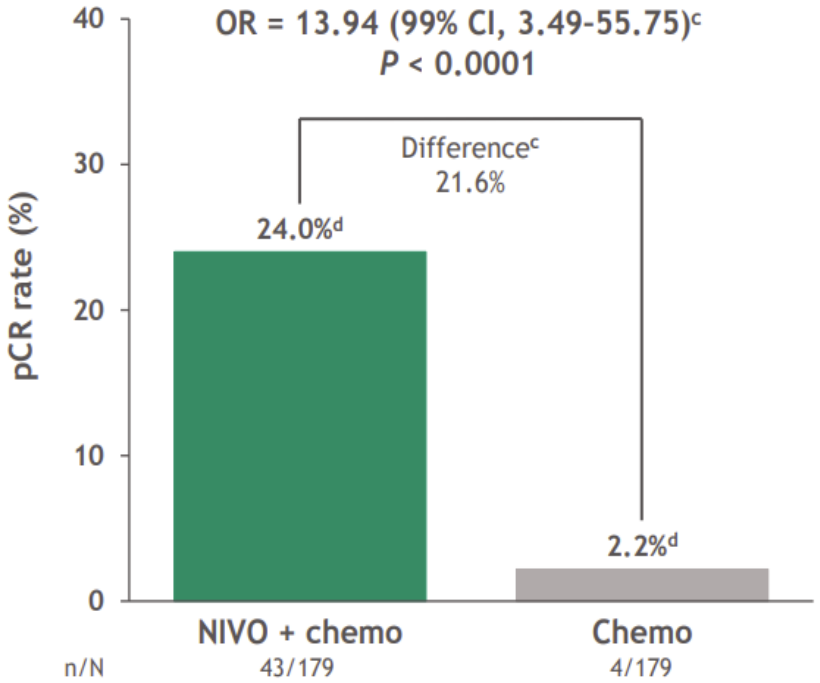
Patients with radiographic down-staging[c]



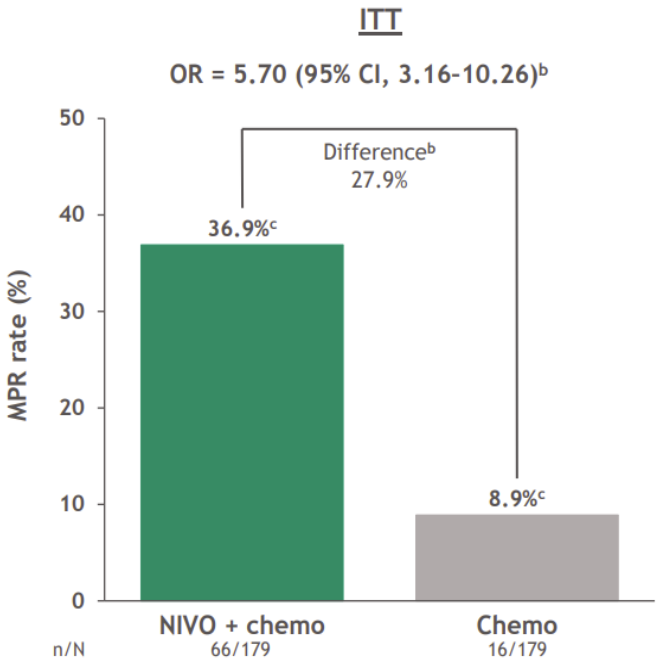
[a]Objective response rate was up to the presurgical scan; [b]ORR rates 95% CI: NIVO + chemo, 46-61; chemo, 30-45; [c]Decrease in stage from baseline to presurgical scan.

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

Primary endpoint: ITT (ypT0N0)[b]

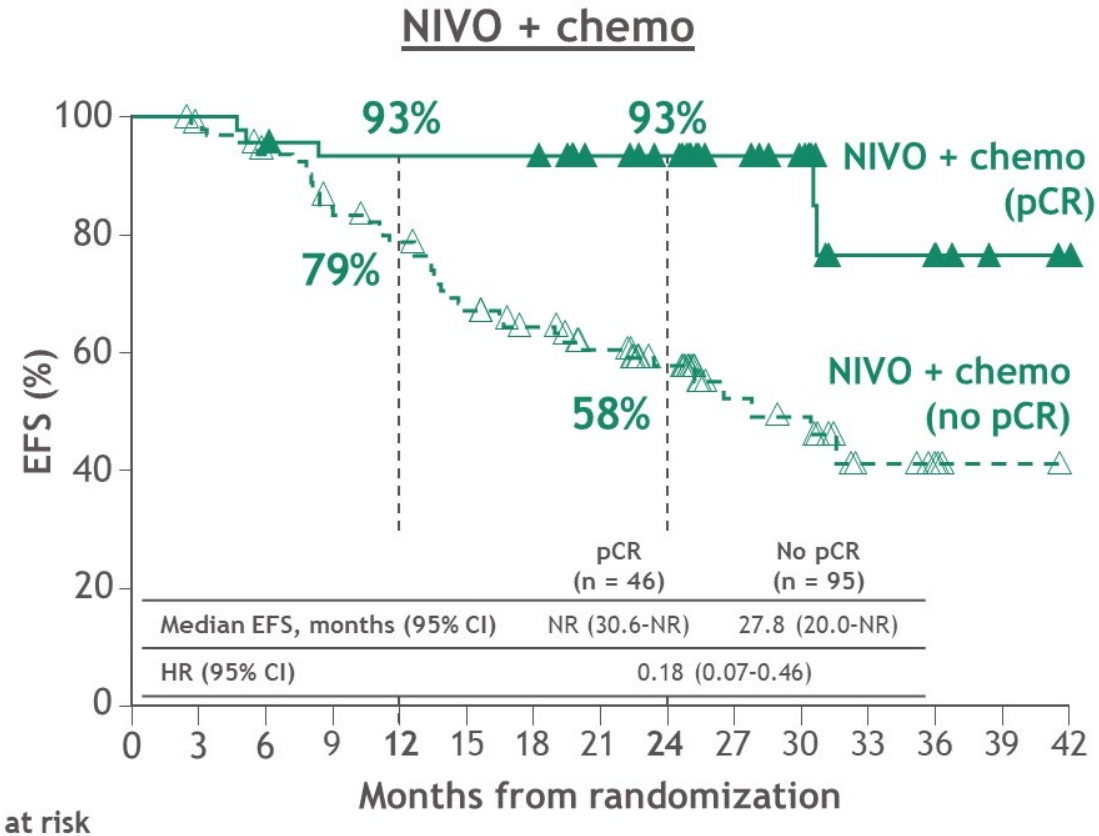


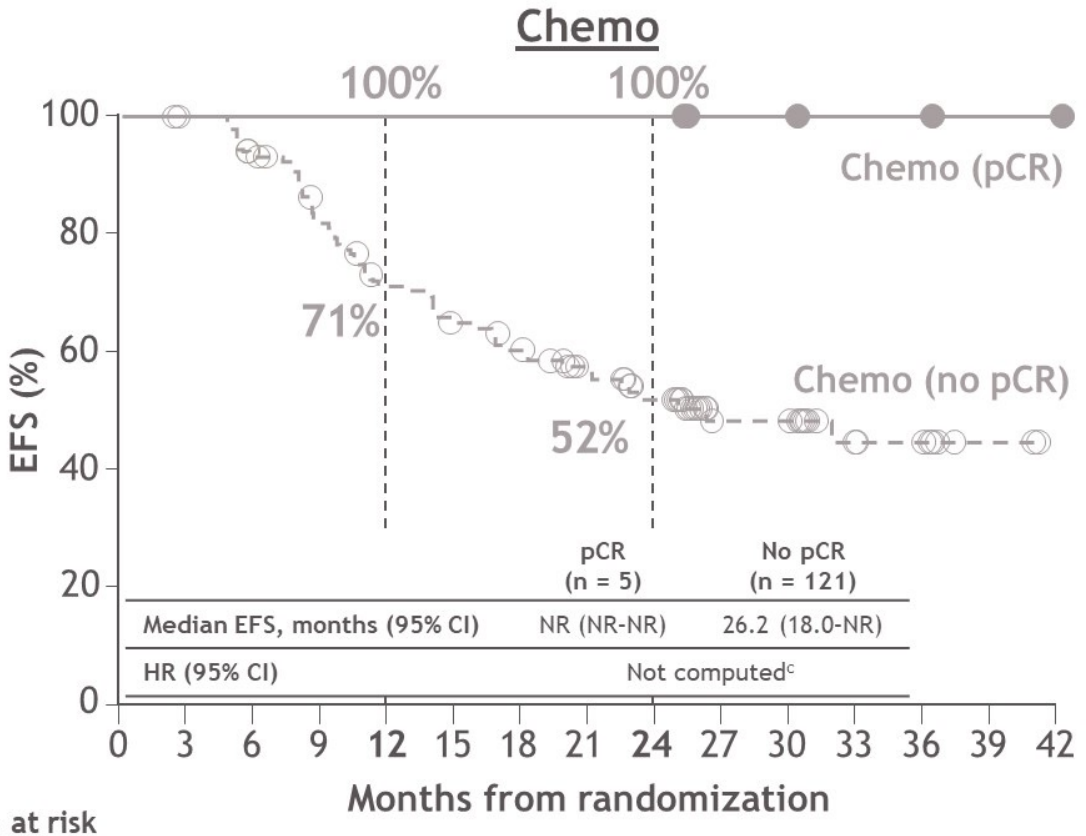
MPR[a] rate with neoadjuvant NIVO + chemo vs chemo



[a]Per BIPR; MPR: ≤ 10% residual viable tumor cells in both the primary tumor (lung) and sampled lymph nodes; [b]Calculated by stratified Cochran-Mantel-Haenszel method; [c]MPR rates 95% CI: NIVO + chemo, 29.8-44.4; chemo, 5.2-14.1.

EFS by pCR status[a] (primary tumor) in the path-evaluable patient population





No. at risk

pCR	46	46	43	42	42	42	42	37	34	20	15	7	4	2	0
No pCR	95	92	84	74	68	57	52	45	35	18	16	6	2	1	0

No. at risk

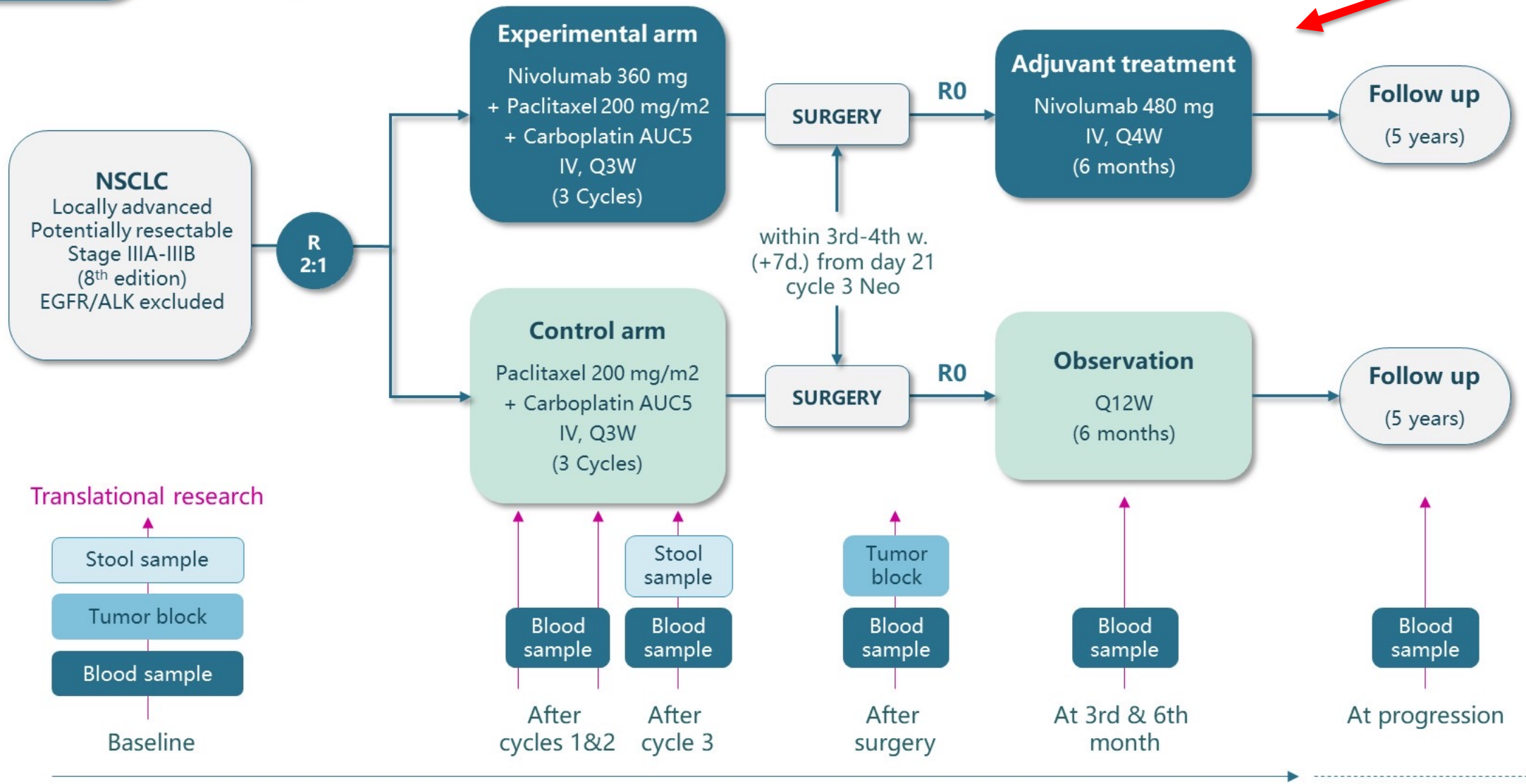
pCR	5	5	5	5	5	5	5	5	5	3	2	2	2	1	0
No pCR	121	119	108	93	79	71	64	53	44	21	20	10	8	2	0

- EFS was also improved in patients with MPR[b] in the primary tumor compared with those without; HR (95% CI) was 0.26 (0.14-0.50) for NIVO + chemo and 0.48 (0.22-1.05) for chemo, respectively

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

[a]pCR: 0% RVT cells in the primary tumor in the path-evaluable patient population (patients who underwent surgery and had pathologically evaluable samples); [b]MPR: ≤ 10% RVT cells in the primary tumor in the path-evaluable patient population; [c]HR was not computed for the chemo arm due to only 5 patients having a pCR.

NADIM II Study design

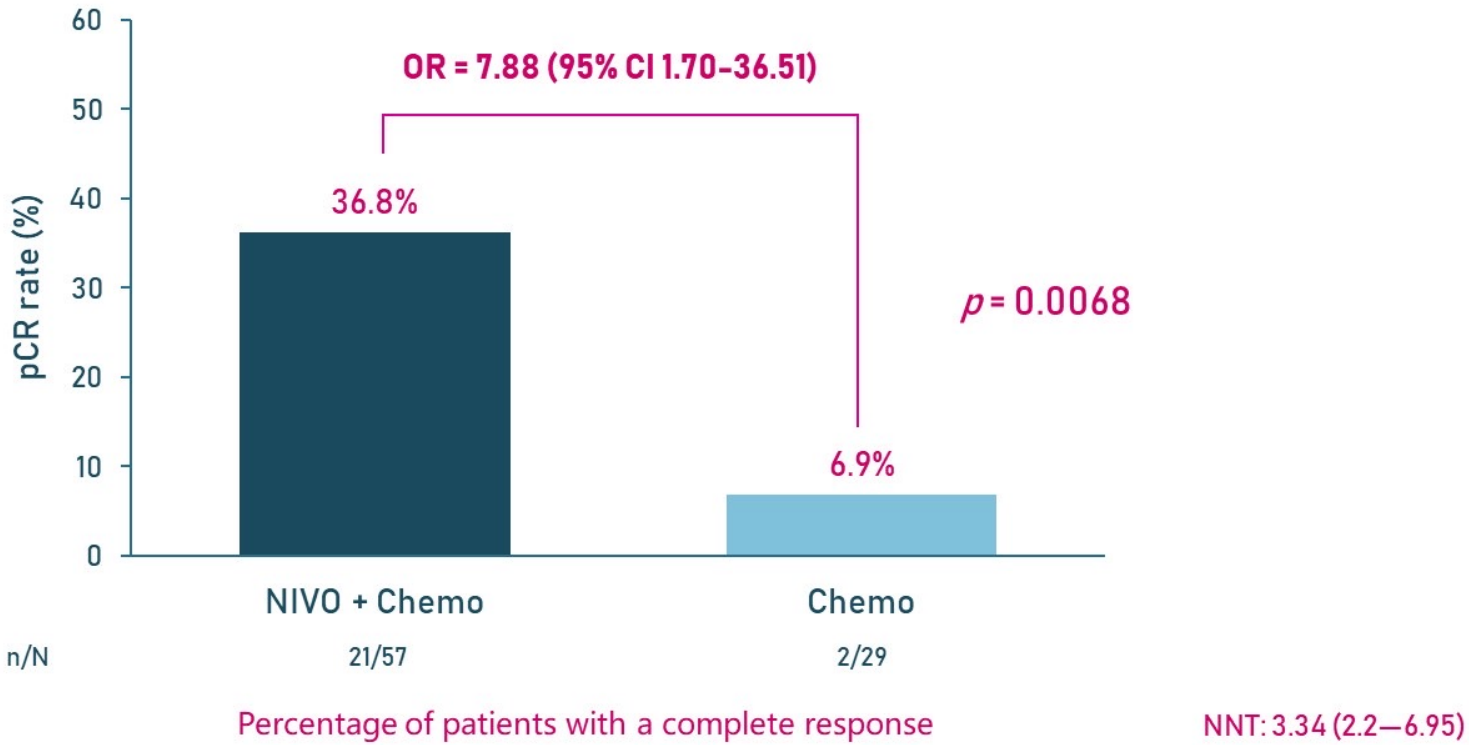


NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

Primary endpoint - pCR

pCR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population[b]



Percentage of patients with a complete response

NNT: 3.34 (2.2—6.95)

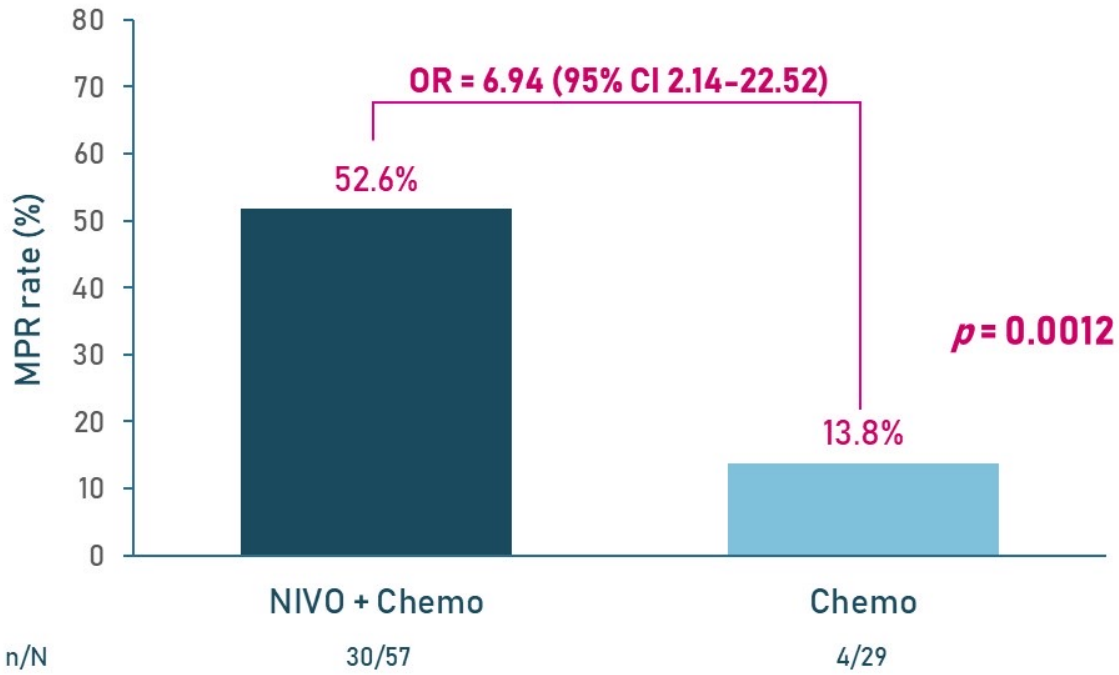
[a]pCR was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders

Chemo, chemotherapy; ITT, intention-to-treat; Nivo, nivolumab; pCR, pathological complete response; RR, risk ratio

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

Secondary endpoints - MPR

MPR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population [b]



Percentage of patients with a complete response or a major response

NNT: 2.57 (1.76–4.81)

[a]MPR was defined as ≤10% residual viable tumor cells in both the primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders

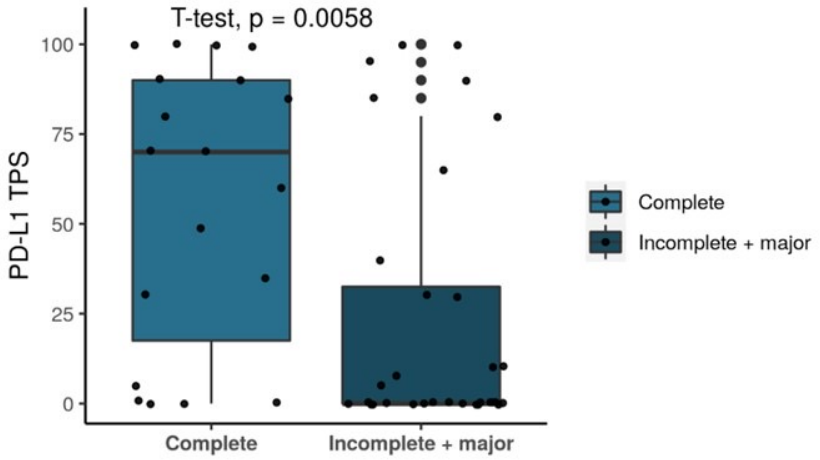
Chemo, chemotherapy; ITT, intention-to-treat; MPR, major pathological response; Nivo, nivolumab; RR, risk ratio

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

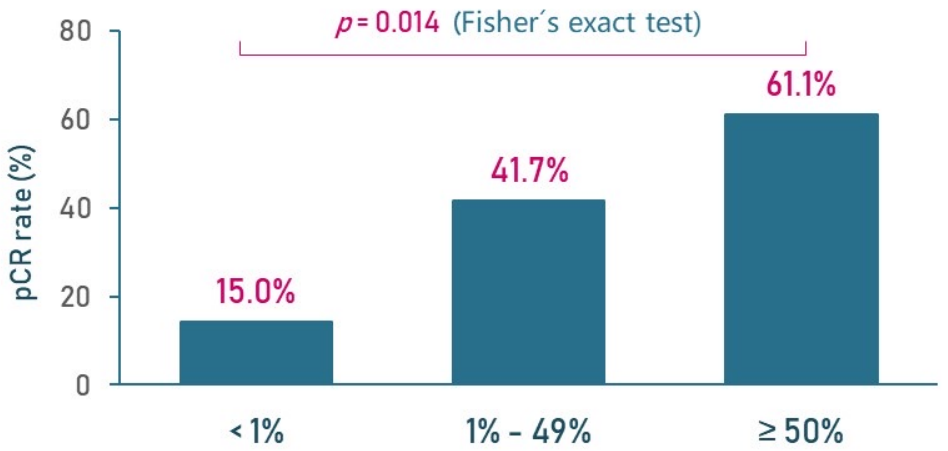
Secondary endpoints – Predictive biomarkers

Predictive biomarkers of response (pCR)[a] to neoadjuvant NIVO + CT (ITT population)[b]

- Patients who achieved pCR had higher PD-L1 expression than patients who did not
- pCR rate raised across increasing categories of PD-L1 TPS
- Predictive value of PD-L1 TPS for pCR was AUC 0.728 (95% CI 0.58-0.87; $p = 0.001$)
- **OR** for pCR in the PD-L1 positive group (**≥1%**): **16.0 (**95% CI 1.86-137.61; ***p* = 0.007)**



Pathological response

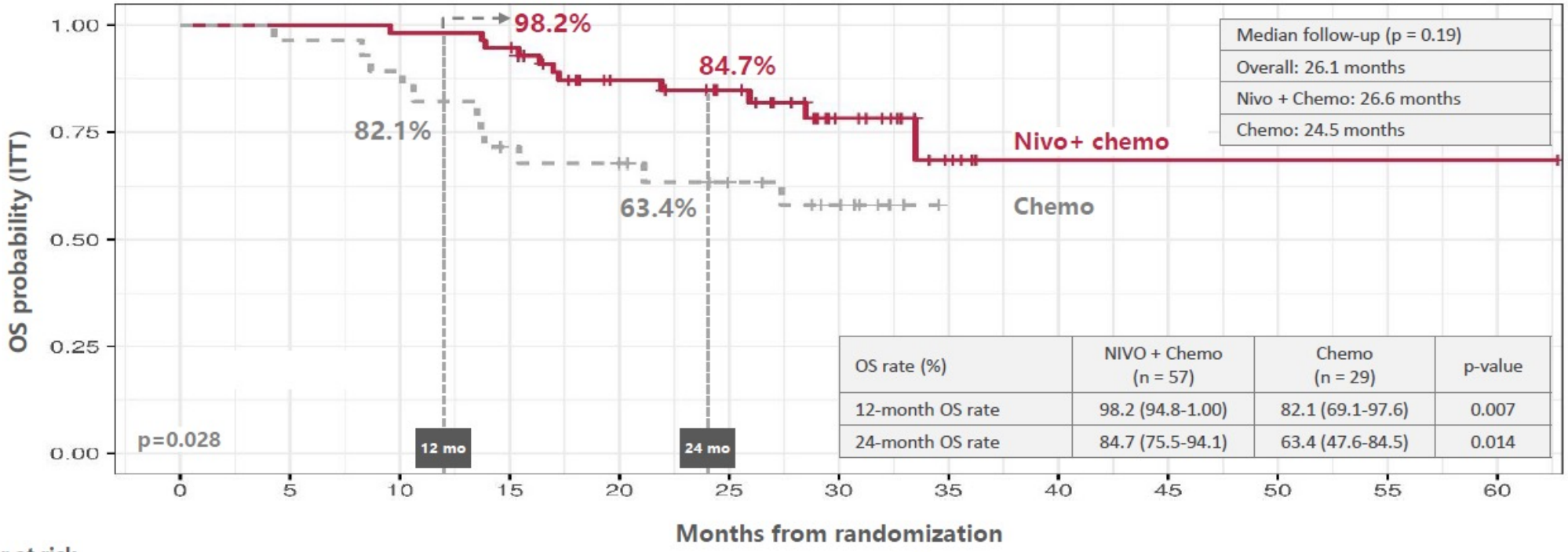


PD-L1 Tumor Proportion Score

[a]pCR was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders
IQR, interquartile range; ITT, intention-to-treat; pCR, pathological complete response; TPS, tumor proportion score, RR, risk ratio; PD-L1 positive group defined as ≥1% TPS.

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

SECONDARY ENDPOINTS – Overall survival



Median follow-up (p = 0.19)
Overall: 26.1 months
Nivo + Chemo: 26.6 months
Chemo: 24.5 months

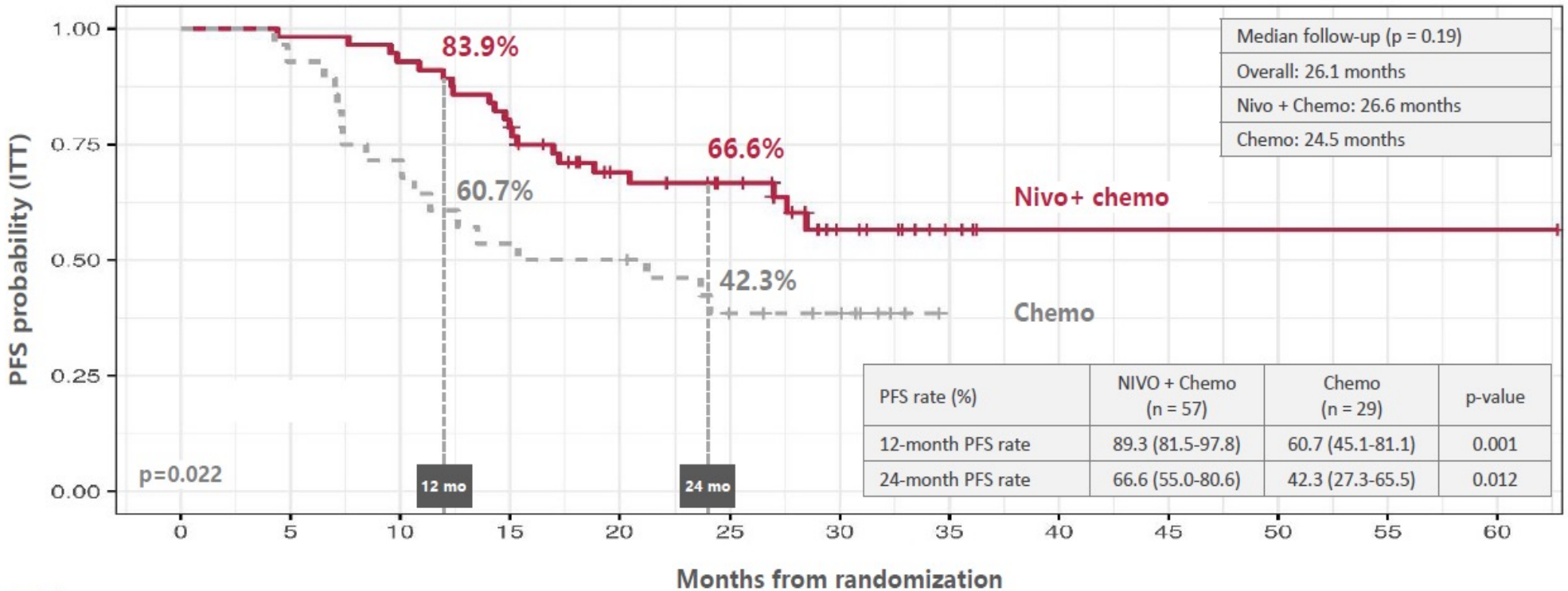
OS rate (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)	p-value
12-month OS rate	98.2 (94.8-1.00)	82.1 (69.1-97.6)	0.007
24-month OS rate	84.7 (75.5-94.1)	63.4 (47.6-84.5)	0.014

Number at risk

Nivo + chemo	56	56	55	53	37	31	15	5	1	1	1	1	1
Chemo	28	27	25	19	17	13	9	0	0	0	0	0	0

Overall survival was defined as the time from randomization to death. OS was censored on the last date a participant was known to be alive

SECONDARY ENDPOINTS – Progression-free survival



Median follow-up (p = 0.19)
Overall: 26.1 months
Nivo + Chemo: 26.6 months
Chemo: 24.5 months

PFS rate (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)	p-value
12-month PFS rate	89.3 (81.5-97.8)	60.7 (45.1-81.1)	0.001
24-month PFS rate	66.6 (55.0-80.6)	42.3 (27.3-65.5)	0.012

Number at risk													
Nivo + chemo	56	55	52	44	30	24	11	4	1	1	1	1	1
Chemo	28	26	20	15	14	9	7	0	0	0	0	0	0

Progression-free survival was defined as the time from randomization to any of the following events: progression of disease, recurrence disease, or death due to any cause. Progression/recurrence will have determined by RECIST 1.1

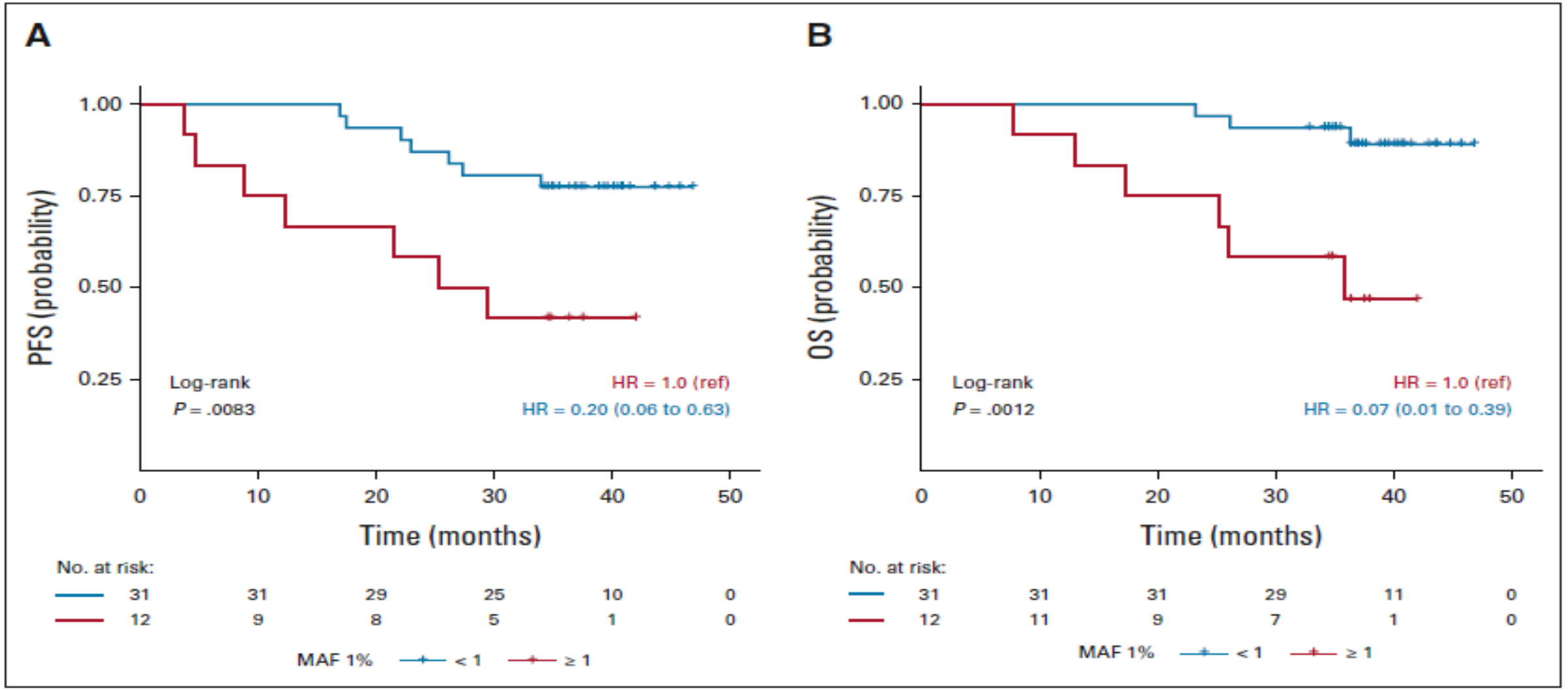


FIG 2. Kaplan-Meier curves for (A) PFS and (B) OS by ctDNA levels at baseline, using a cutoff of < 1% MAF. ctDNA, circulating tumor DNA; HR, hazard ratio; MAF, mutant allele fraction; OS, overall survival; PFS, progression-free survival; ref, reference category.

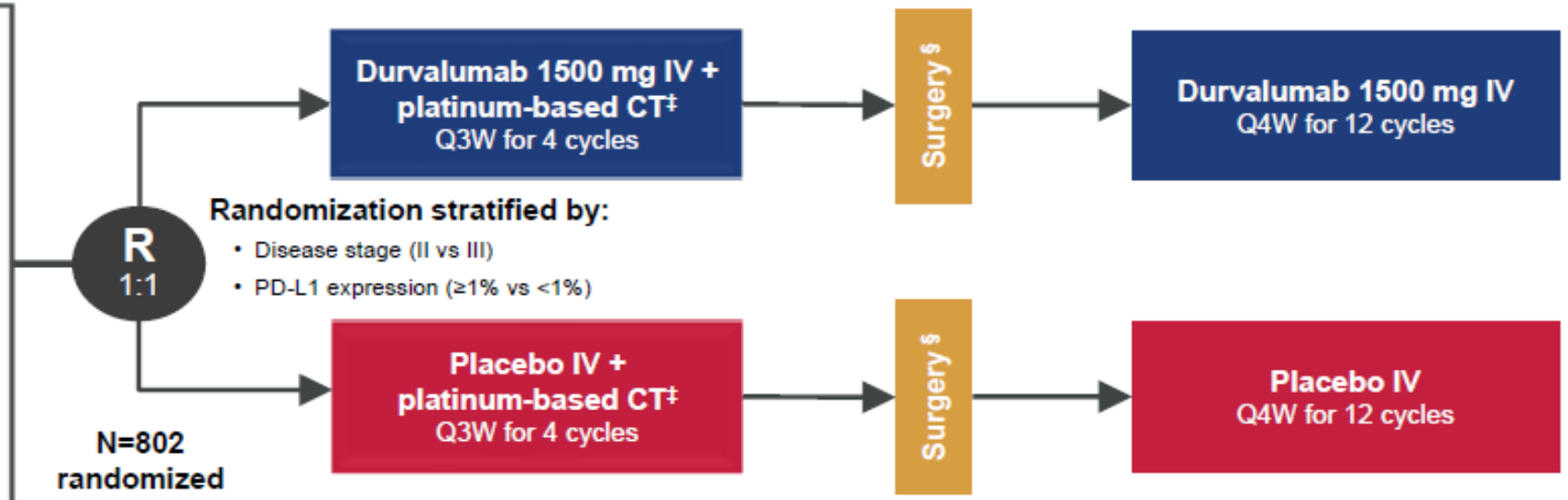
Provencio M. JCO 2022 40:25, 2924-2933

AEGEAN: a phase 3, global, randomized, double-blind, placebo-controlled study

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Study population

- Treatment-naïve
- ECOG PS 0 or 1
- Resectable NSCLC* (stage IIA–IIIB[N2]; AJCC 8th ed)
- Lobectomy, sleeve resection, or bilobectomy as planned surgery*
- Confirmed PD-L1 status†
- No documented *EGFR/ALK* aberrations*



Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented *EGFR/ALK* aberrations¶

Primary:

- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

Key secondary:

- MPR by central lab (per IASLC 2020[1])
- DFS using BICR (per RECIST v1.1)
- OS

*The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations. †Ventana SP263 immunohistochemistry assay. ‡Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment). §Post-operative radiotherapy (PORT) was permitted where indicated per local guidance. ¶All efficacy analyses reported in this presentation were performed on the mITT population, which includes all randomized patients who did not have documented *EGFR/ALK* aberrations. AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; DFS, disease-free survival; EFS, event-free survival; mITT, modified intent-to-treat; MPR, major pathologic response; pCR, pathologic complete response.

[1]Travis WD, et al. *J Thorac Oncol* 2020;15:709-40.

Baseline characteristics and planned treatment (mITT)

- Baseline characteristics were largely balanced between the study arms
- The planned neoadjuvant CT doublet regimen was carboplatin-based for >70% of patients

TNM classification†		D arm (N=366)	PBO arm (N=374)
Primary tumor, %	T1	12.0	11.5
	T2	26.5	28.9
	T3	35.0	34.5
	T4	26.5	25.1
Regional lymph nodes, %	N0	30.1	27.3
	N1	20.5	23.3
	N2	49.5	49.5

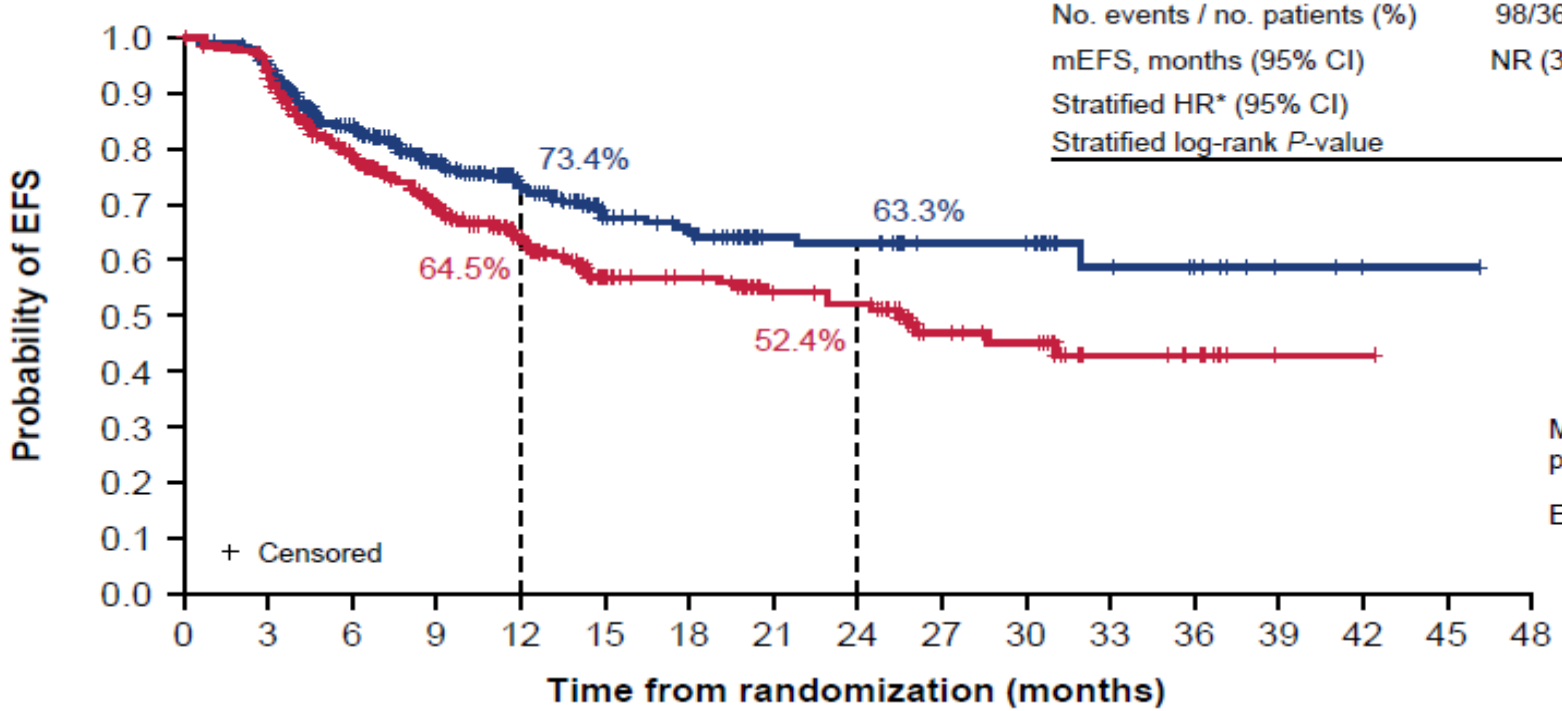
Characteristics*		D arm (N=366)	PBO arm (N=374)
Age	Median (range), years	65.0 (30–88)	65.0 (39–85)
	≥75 years, %	12.0	9.6
Sex, %	Male	68.9	74.3
	Female	31.1	25.7
ECOG PS, %	0	68.6	68.2
	1	31.4	31.8
Race‡, %	Asian	39.1	43.9
	White	56.3	51.1
	Other	4.6	5.1
Region, %	Asia	38.8	43.6
	Europe	38.5	37.4
	North America	11.7	11.5
	South America	10.9	7.5
Smoking status, %	Current	26.0	25.4
	Former	60.1	59.6
	Never	13.9	15.0
Disease stage (AJCC 8th ed.), %	II	28.4	29.4
	IIIA	47.3	44.1
	IIIB	24.0	26.2
Histology, %	Squamous	46.2	51.1
	Non-squamous	53.6	47.9
PD-L1 expression, %	TC <1%	33.3	33.4
	TC 1–49%	36.9	38.0
	TC ≥50%	29.8	28.6
Planned neoadjuvant platinum agent, %	Cisplatin	27.3	25.7
	Carboplatin	72.7	74.3

DCO = Nov 10, 2022. *Characteristics with missing/other responses are histology (0.3% in the D arm and 1.1% in PBO arm had 'other' histology) and disease stage (0.3% in D arm had stage IV disease, and 0.3% in the PBO arm had stage III [NOS] disease, as reported per the electronic case report form [eCRF]). †All patients were M0 except one patient in the D arm who was classified as M1 (NOS). ‡Race was self-reported per the eCRF. NOS, not otherwise specified; TC, tumor cells.

EFS using RECIST v1.1 (BICR) (mITT)

First planned interim analysis of EFS

	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	



Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

No. at risk:

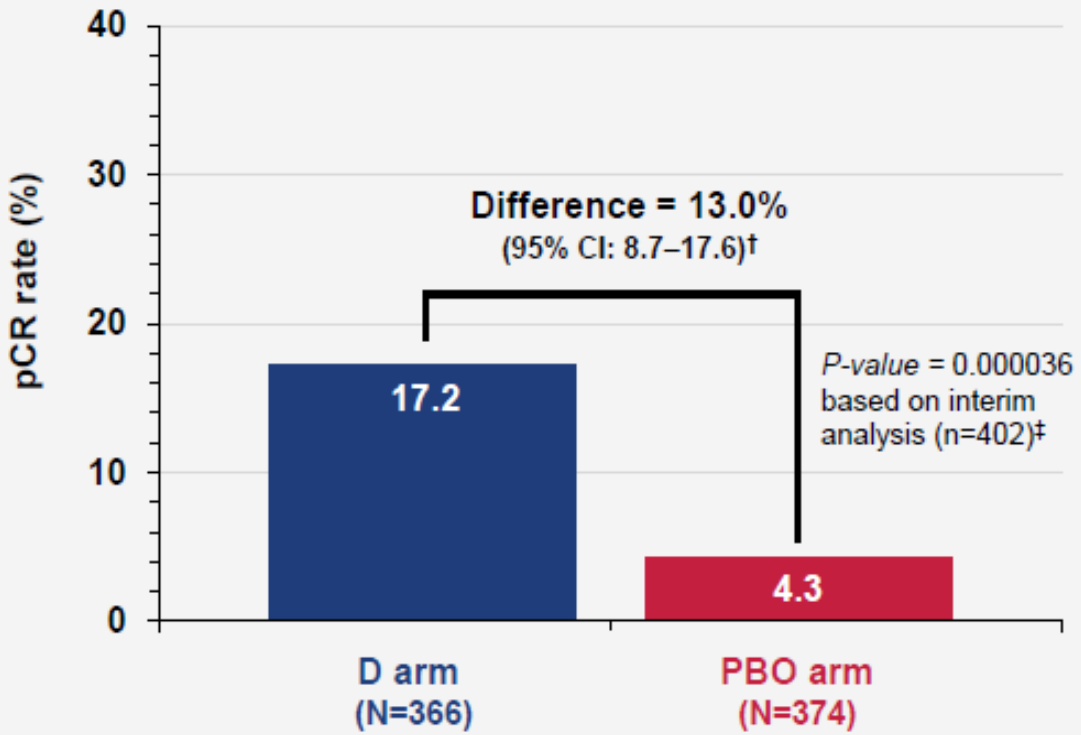
D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

DCO = Nov 10, 2022. EFS is defined as time from randomization to the earliest of: (A) progressive disease (PD) that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause. *HR <1 favors the D arm versus the PBO arm. Median and landmark estimates calculated using the Kaplan–Meier method; HR calculated using a stratified Cox proportional hazards model; and *P*-value calculated using a stratified log rank test. Stratification factors: disease stage (II vs III) and PD-L1 expression status (<1% vs ≥1%). Significance boundary = 0.009899 (based on total 5% alpha), calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary. mEFS, median EFS; NR, not reached.

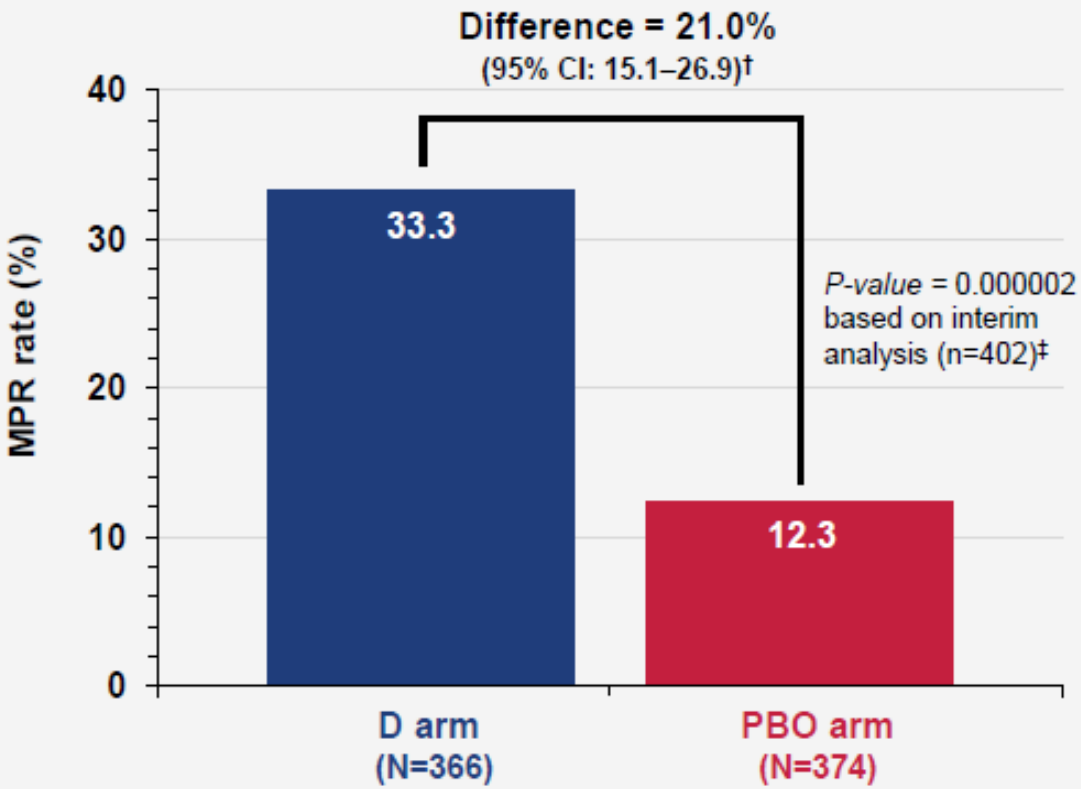
Pathologic response per IASLC 2020 methodology* (mITT)

Final analysis

pCR (central lab)



MPR (central lab)



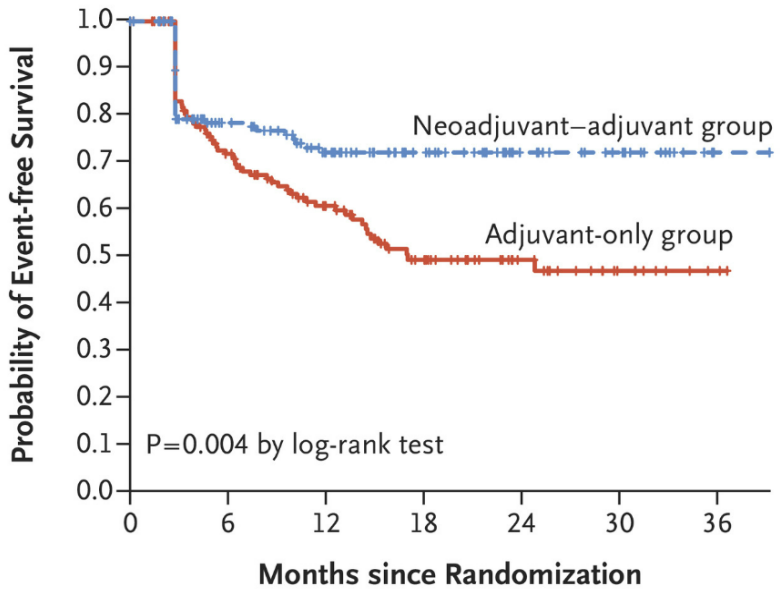
*Using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumor bed (Travis WD, et al. *J Thorac Oncol* 2020;15:709-40). pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR = less than or equal to 10% viable tumor cells in lung primary tumor after complete evaluation of the resected lung cancer specimen. To be eligible for pathologic assessment, patients needed to have received three cycles of neoadjuvant study Tx per protocol. Patients who were not evaluable were classified as non-responders. †CIs calculated by stratified Miettinen and Nurminen method. ‡No formal statistical testing was performed at the pCR final analysis (DCO: Nov 10, 2022; n=740 [data shown]). Statistical significance was achieved at the interim pCR analysis (DCO: Jan 14, 2022; n=402; *P*-value for pCR/MPR calculated using a stratified Cochran-Mantel-Haenszel test with a significance boundary = 0.000082 calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary).

Conclusions

- Perioperative durvalumab + neoadjuvant CT significantly improved both pCR and EFS among patients with resectable NSCLC versus neoadjuvant CT alone
  - Difference in pCR rate = 13.0% (95% CI: 8.7–17.6)
  - EFS HR = 0.68 (95% CI: 0.53–0.88); *P* = 0.003902; median follow-up of 11.7 months and 31.9% maturity
  - The AEGEAN study continues for assessment of longer-term EFS, as well as DFS and OS
- Improvements in both pCR and EFS were largely consistent across predefined subgroups
  - EFS benefit was observed regardless of the planned neoadjuvant platinum agent: the HR was 0.59 (95% CI: 0.35–1.00) for cisplatin and 0.73 (95% CI: 0.54–0.98) for carboplatin
- Perioperative durvalumab + neoadjuvant CT was associated with a manageable safety profile that was consistent with the known safety profiles of durvalumab and CT
  - The addition of durvalumab did not impact completion of neoadjuvant CT (4 cycles) or surgery
- AEGEAN is the first phase 3 study to describe the benefit of perioperative immunotherapy + neoadjuvant CT
- Perioperative durvalumab + neoadjuvant CT is a potential new treatment for patients with resectable NSCLC

Neoadjuvant is better? At least in Melanoma

- Phase 2 trial, randomly assigned pts with stage IIIB to IVC melanoma that was amenable to surgical resection to 3 doses of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab (NEO–ADJ) or to surgery followed by pembrolizumab for 18 doses) for approximately 1 year (ADJ).
- NEO-ADJ group (154 pts) had longer EFS than the ADJ-only group (159 pts) (P=0.004).
- EFS at 2 years was 72% (NEO-ADJ) and 49% (ADJ).
- Grades 3 AEs or higher 12% in the NEO-ADJ and
  14% in the ADJ.



Patel S et al. N Engl J Med 2023; 388:813-823
DOI: 10.1056/NEJMoa2211437

Neoadjuvant				
Trial (ClinicalTrials.gov Identifier)	**Phase**	**Stage**	**Treatment**	**End Points**
KEYNOTE -671 (NCT03425643)	III	II–IIIA, resectable IIIB	Experimental arm: pembrolizumab and chemotherapy (cisplatin + gemcitabine/pemetrexed) × 4 cycles → adjuvant pembrolizumab × 13 cycles Comparator arm: placebo and chemo × 4 cycles→ adjuvant placebo	EFS, OS
CheckMate 77T (NCT04025879)	III	II–IIIB	Experimental arm: Neoadjuvant nivolumab + platinum-based doublet chemotherapy × 4 cycles → adjuvant nivolumab for 1 year Comparator arm: Neoadjuvant Placebo + platinum-based doublet chemotherapy × 4 cycles → adjuvant placebo	EFS
IMpower030 (NCT03456063)	III	II–IIIB	Experimental arm: atezolizumab + platinum-based chemotherapy × 4 cycles → adjuvant atezolizumab × 16 cycles Placebo Comparator: placebo + platinum-based chemotherapy × 4 cycles → adjuvant placebo	EFS
AEGEAN (NCT03800134)	III	II–IIIB	Experimental arm: durvalumab + platinum-based chemotherapy × 4 cycles Placebo Comparator: placebo + platinum-based chemotherapy × 4 cycles	EFS, pCR
NEOpredict (NCT04205552)	II	IB–IIIA	Nivolumab or nivolumab/relatlimab × 2 cycles	Feasibility

Memorial Cancer Institute

CANCER CENTER of EXCELLENCE Florida HEALTH

FAU I-HEALTH Florida Atlantic University