Lung Cancer Immunotherapy

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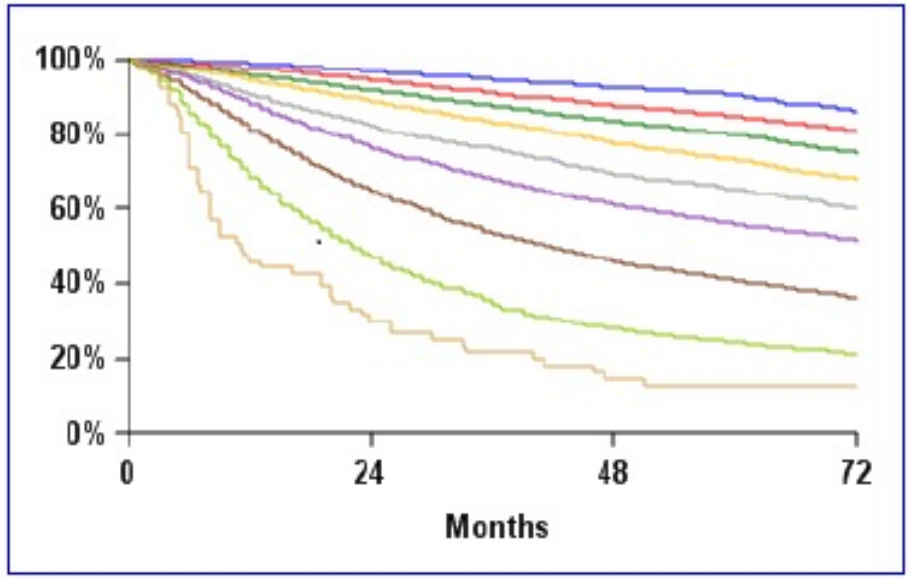
FAU I-HEALTH Florida Atlantic University

Lung Cancer Immunotherapy

- Neoadjuvant
- Adjuvant
- Locally Advanced

Surgery is still the intervention most likely to cure lung cancer

Pathological stage



	Events/N	MST	2 years	5 years
IA1	139/1389	NR	97%	90%
IA2	823/5633	NR	94%	85%
IA3	875/4401	NR	92%	80%
IB	1618/6095	NR	89%	73%
IIA	556/1638	NR	82%	65%
IIB	2175/5226	NR	76%	56%
IIIA	3219/5756	41.9	65%	41%
IIIB	1215/1729	22.0	47%	24%
IIIC	55/69	11.0	30%	12%

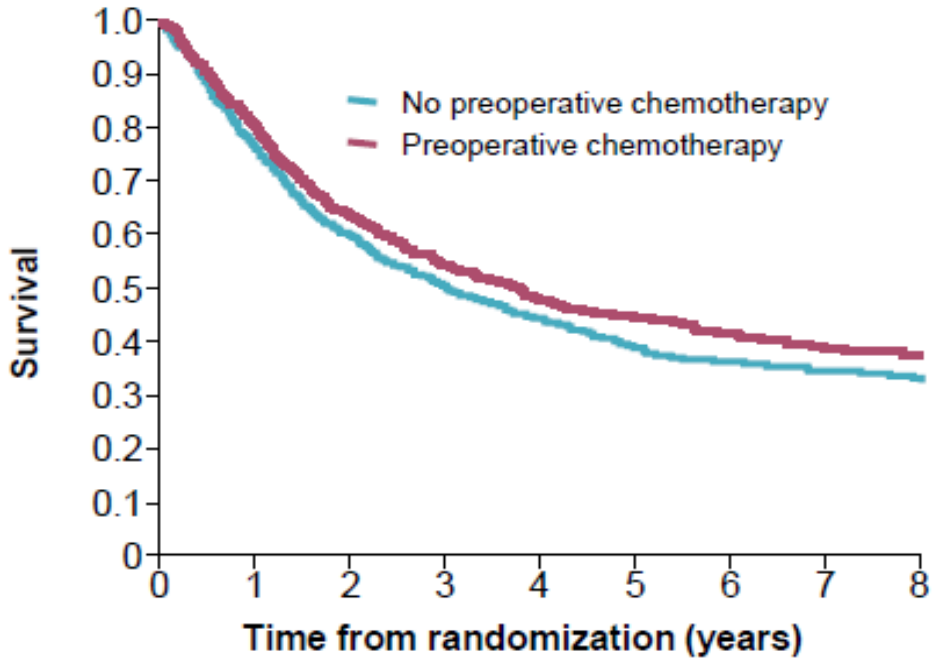
But there is a lot of room for improvement!

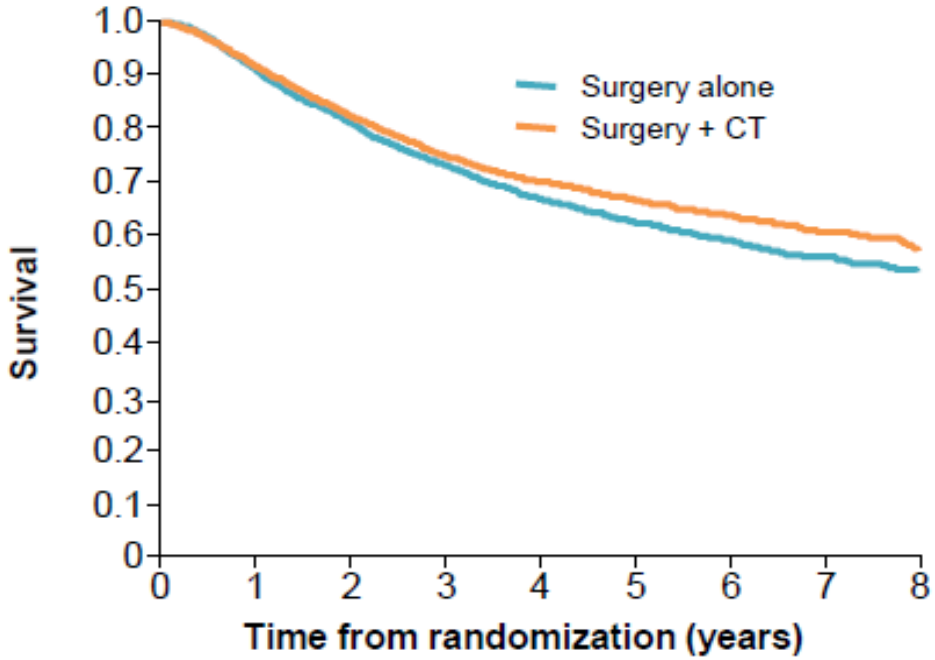
Goldstraw P et al. J Thorac Oncol 2016; 11: 39-51.

GECP lung cancer research

LUNG CANCER EARLY STAGES

Background & Current Situation

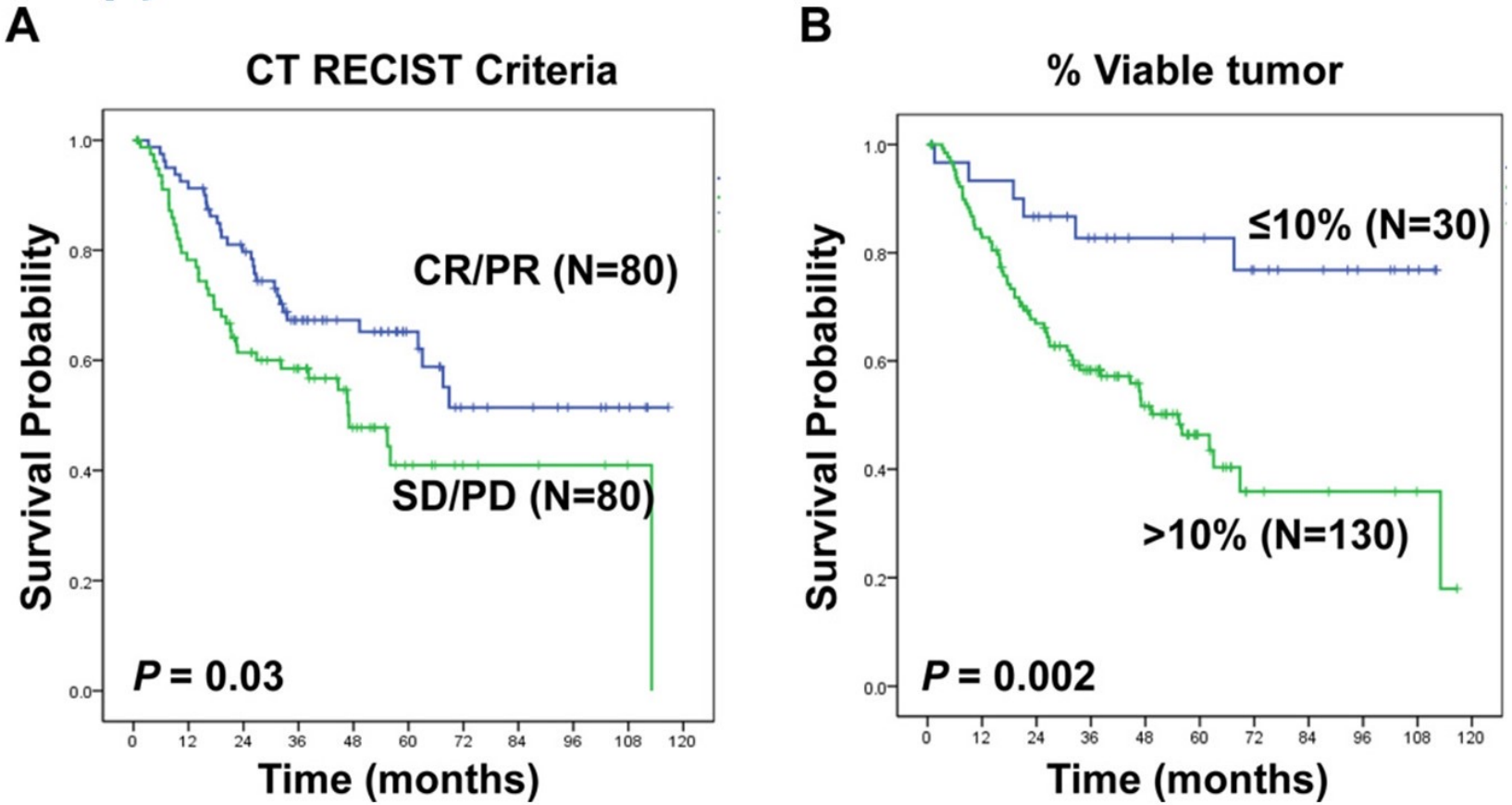




	N	Absolute Δ5 yr OS	HR	*P* value
Neoadjuvant Trials	2385	5%	0.87 (95% CI 0.78-0.96)	0.007
Adjuvant Trials	8447	4%	0.86 (95% CI 0.81-0.92)	<0.0001

Neoadjuvant Immunotherapy in NSCLC

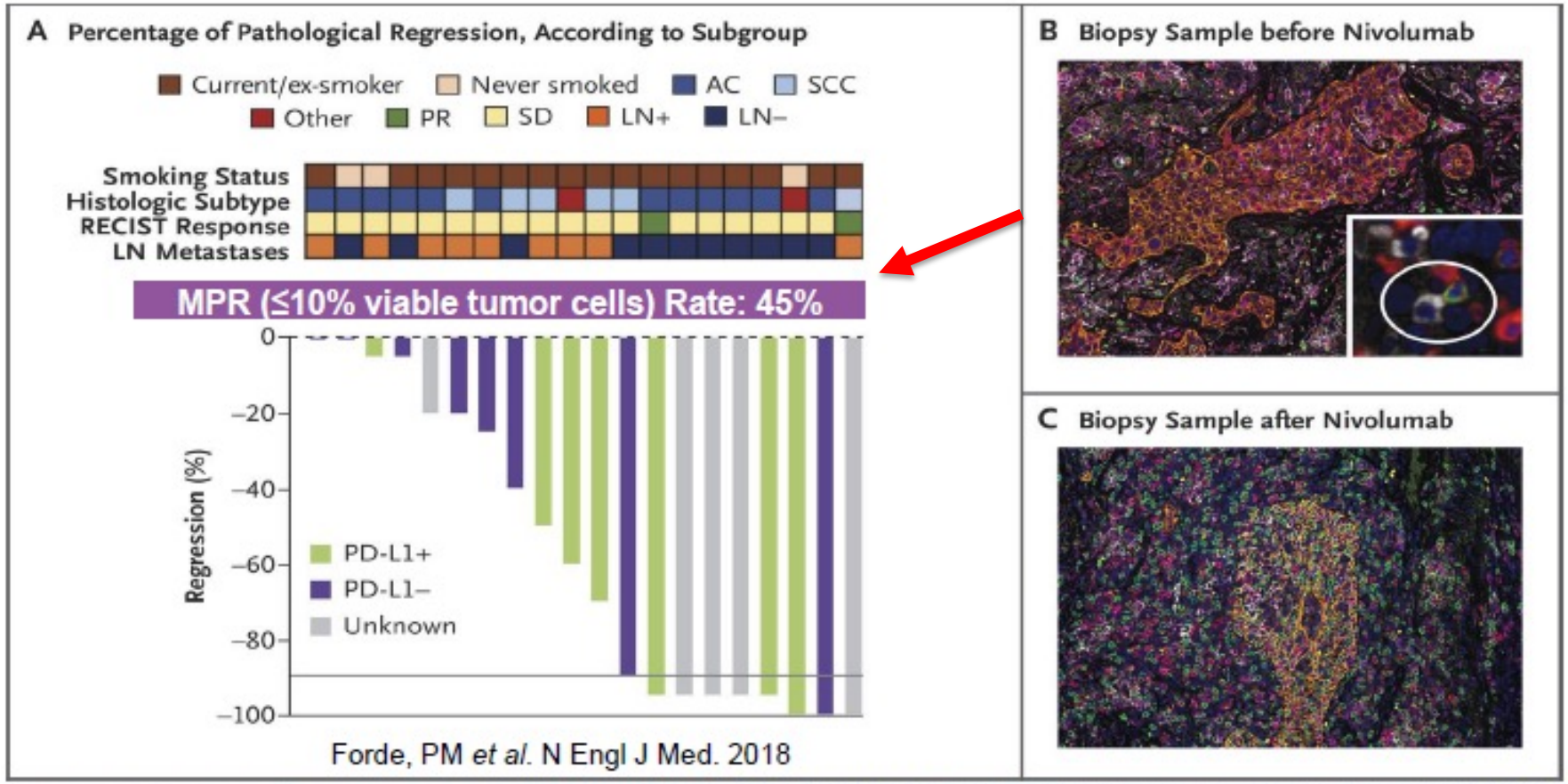
CT RECIST vs. MPR and prediction of OS after neoadjuvant chemotherapy in resectable NSCLC



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

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

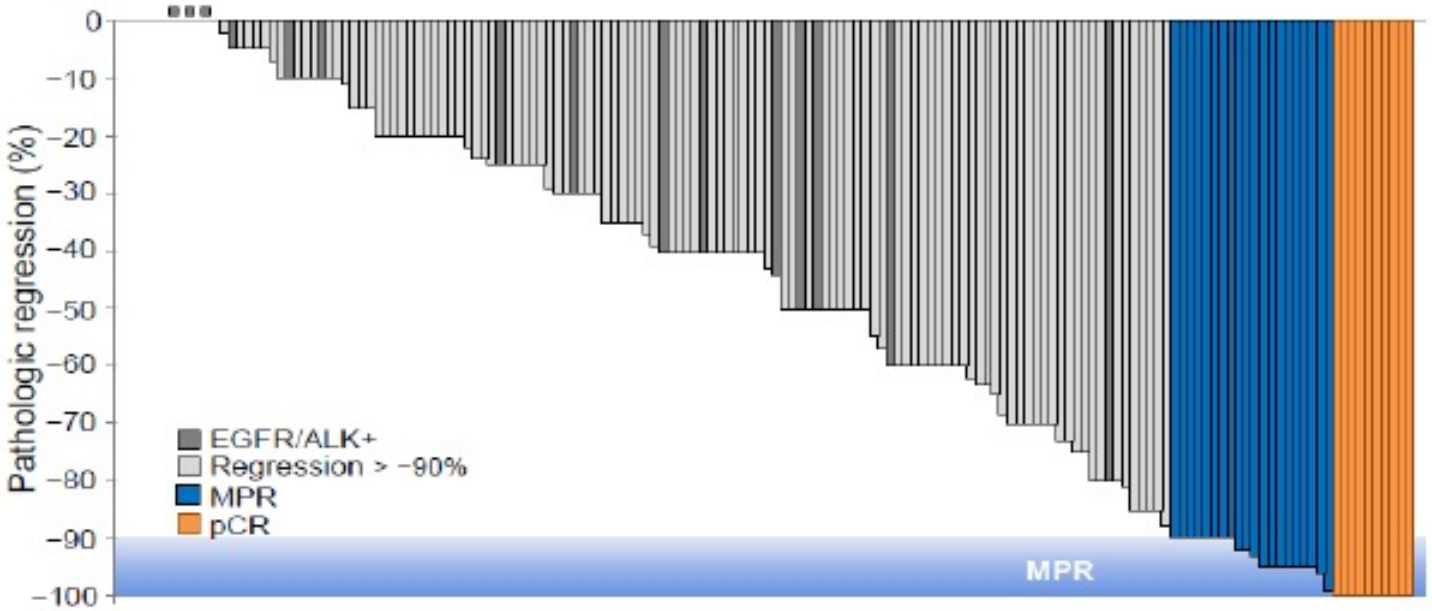
Neoadjuvant nivolumab is feasible, safe and active in operable NSCLC



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

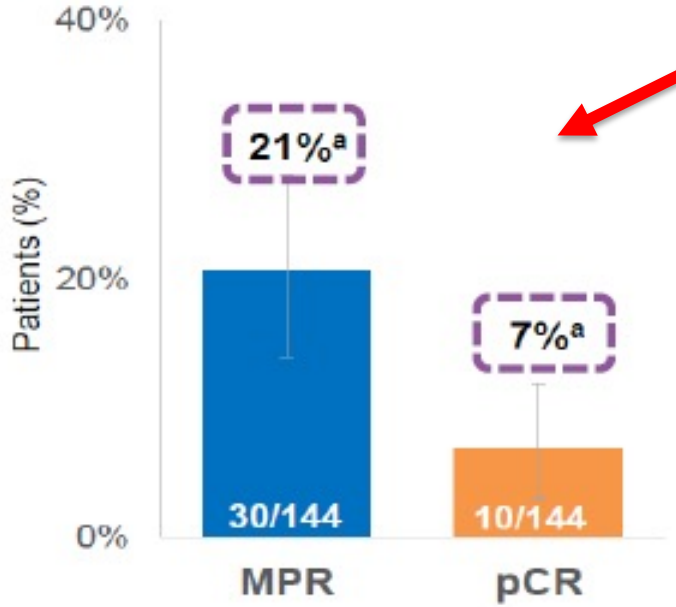
MPR to neoadjuvant atezolizumab in the LCMC3 study

Pathologic response in surgery population (n=159)



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

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



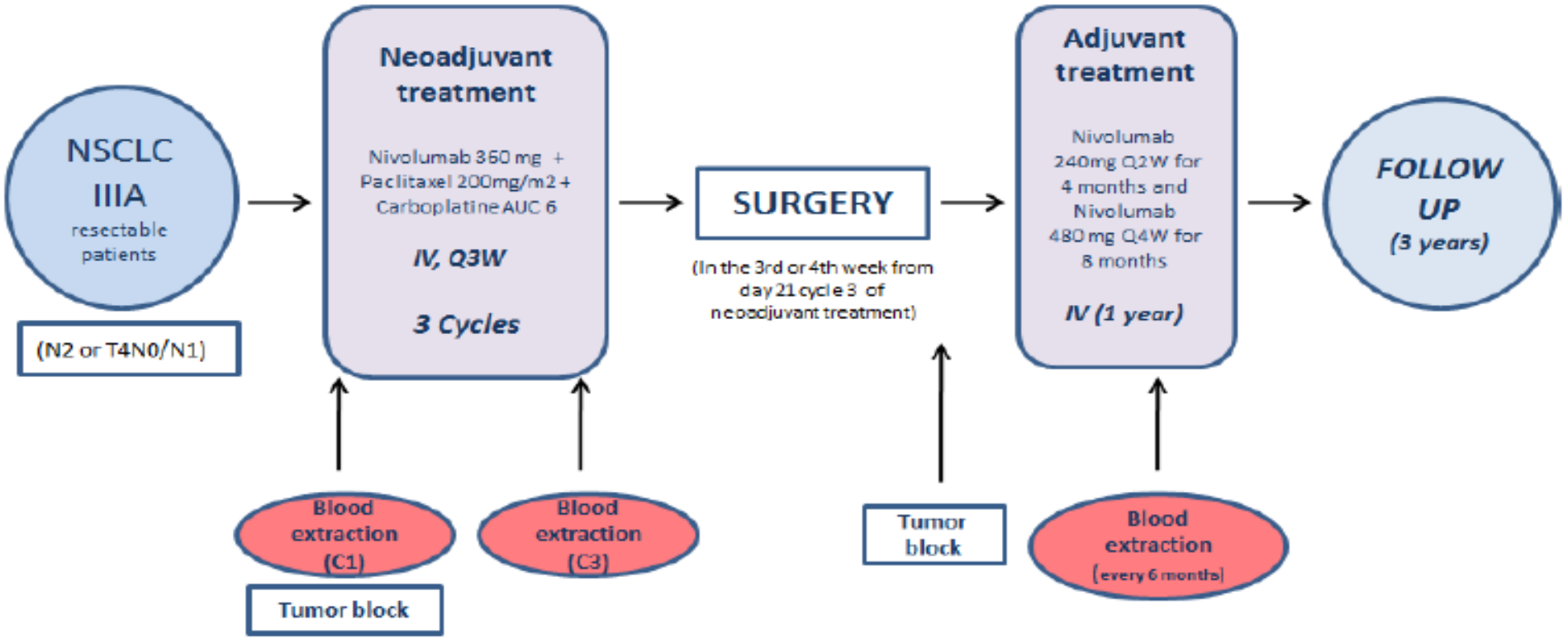
Lee JM, *et al.* WCLC 2021

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

Neoadjuvant Chemo-Immunotherapy
NADIM: Study Design & Endpoints

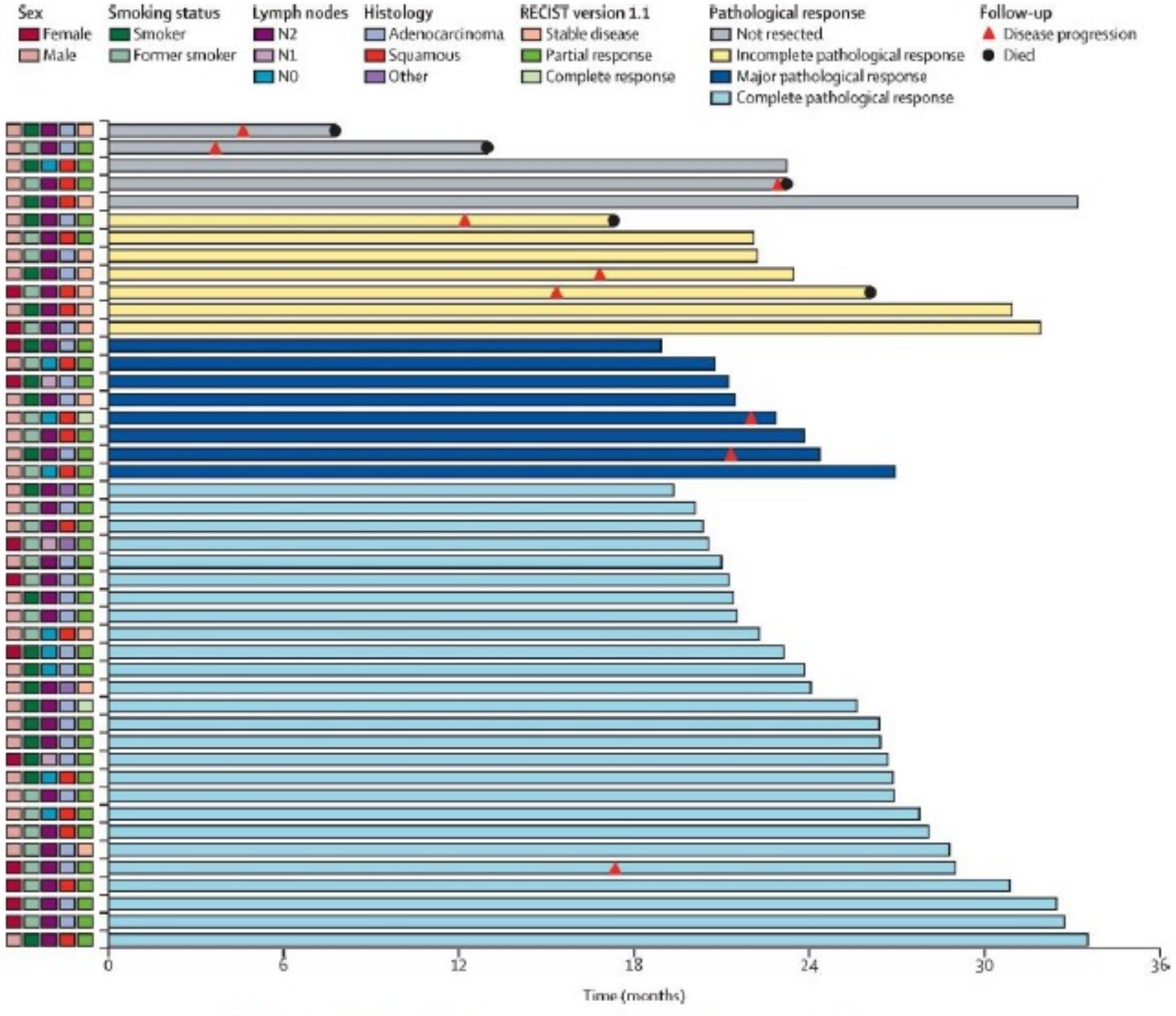
Primary Endpoint:
PFS at 24 months

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



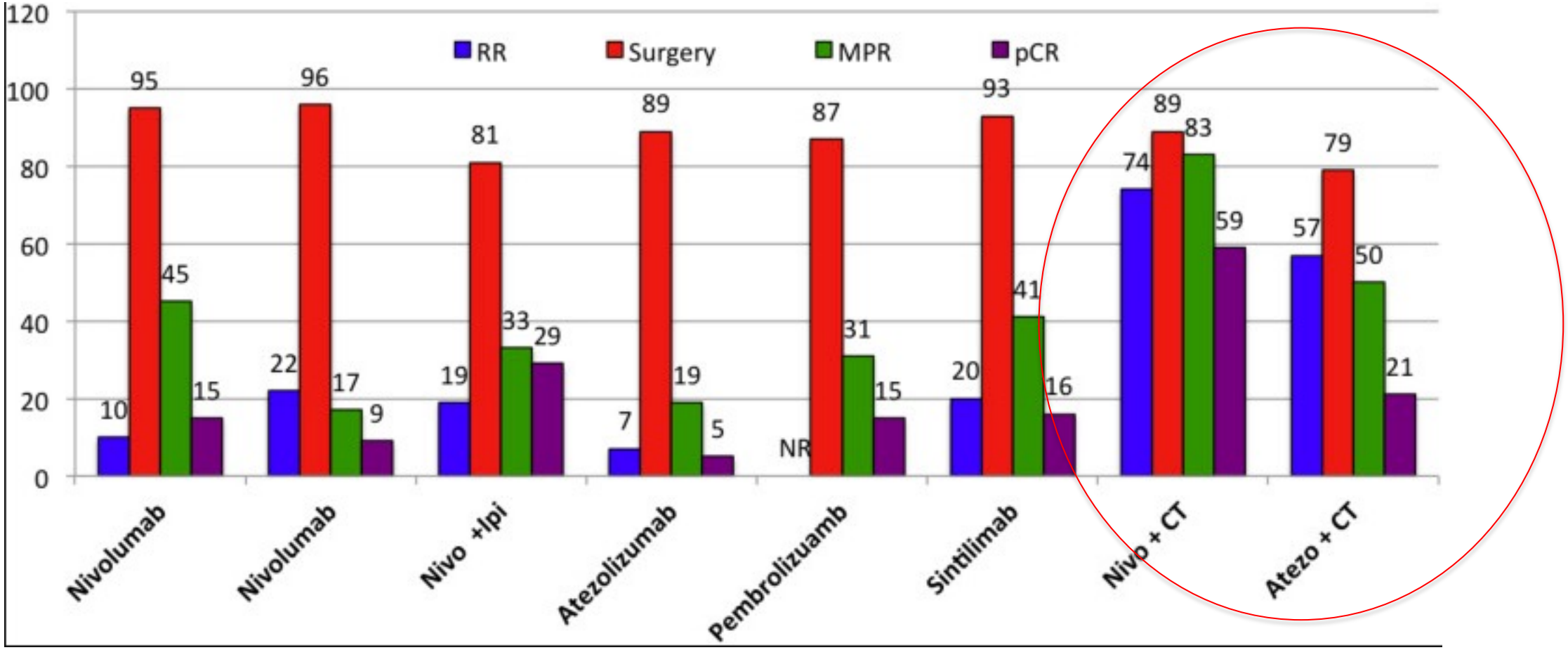
Key Results - NADIM

- 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

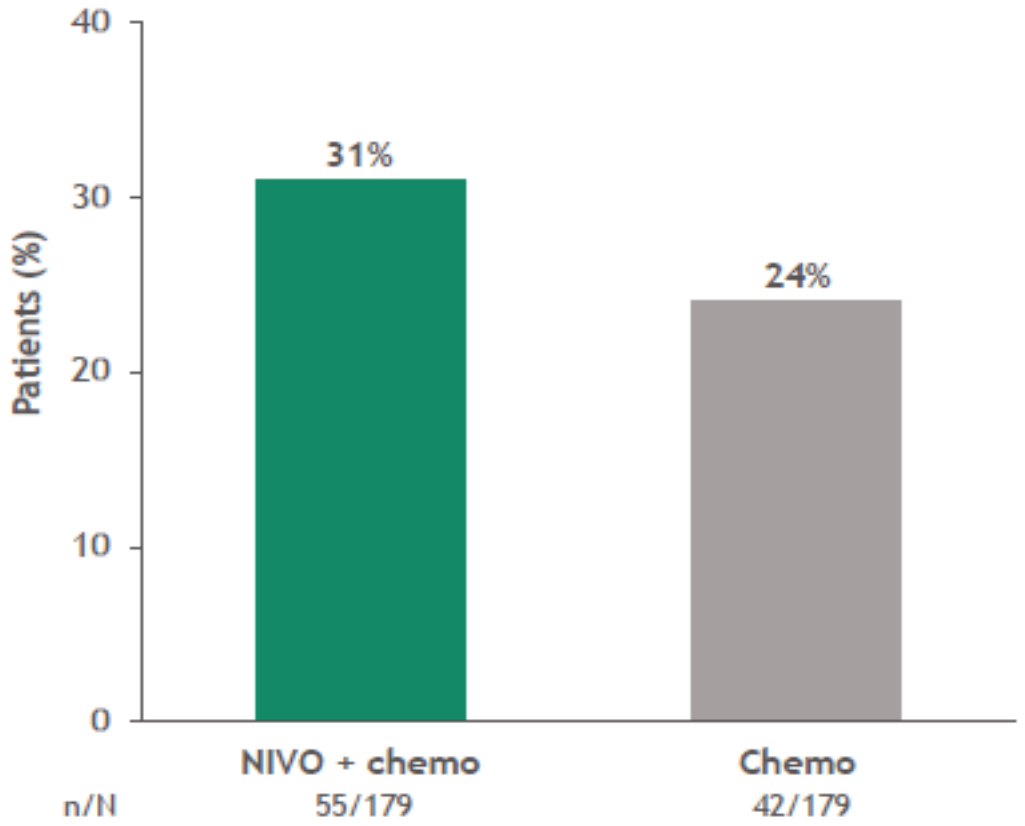
Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

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)

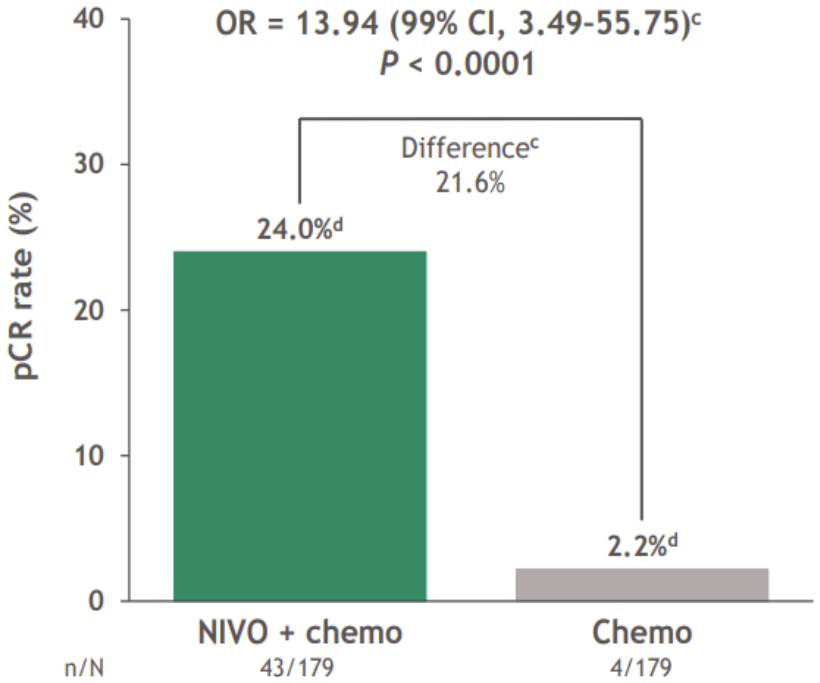
Patients with radiographic down-staging[c]



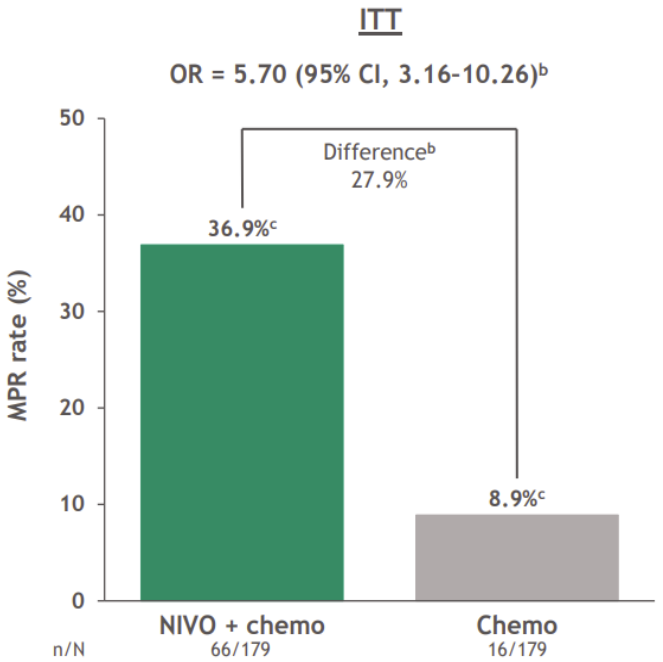
[a]Objective response rate was up to the presurgical scan; [b]ORR rates 95% CI: NIVO + chemo, 46-61; chemo, 30-45; [c]Decrease in stage from baseline to presurgical scan.

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.

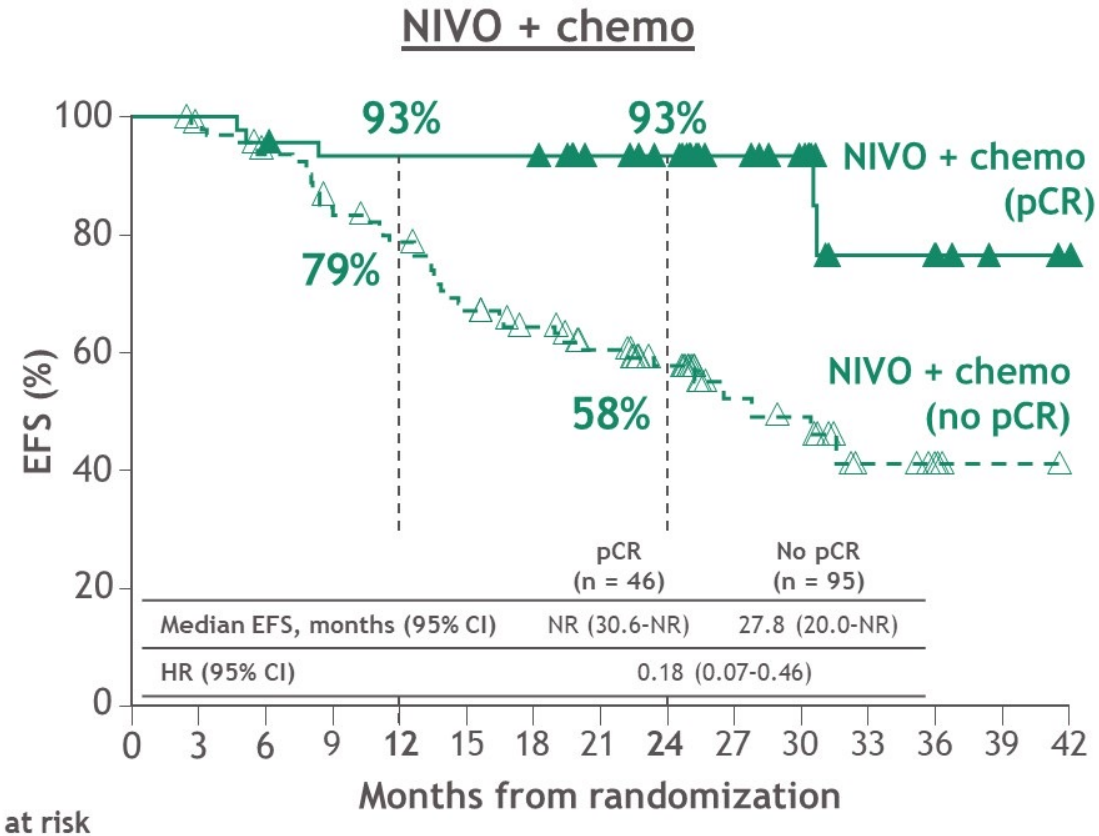
CheckMate 816 Summary—Neoadjuvant Nivolumab Plus Chemotherapy vs Chemotherapy for Resectable NSCLC

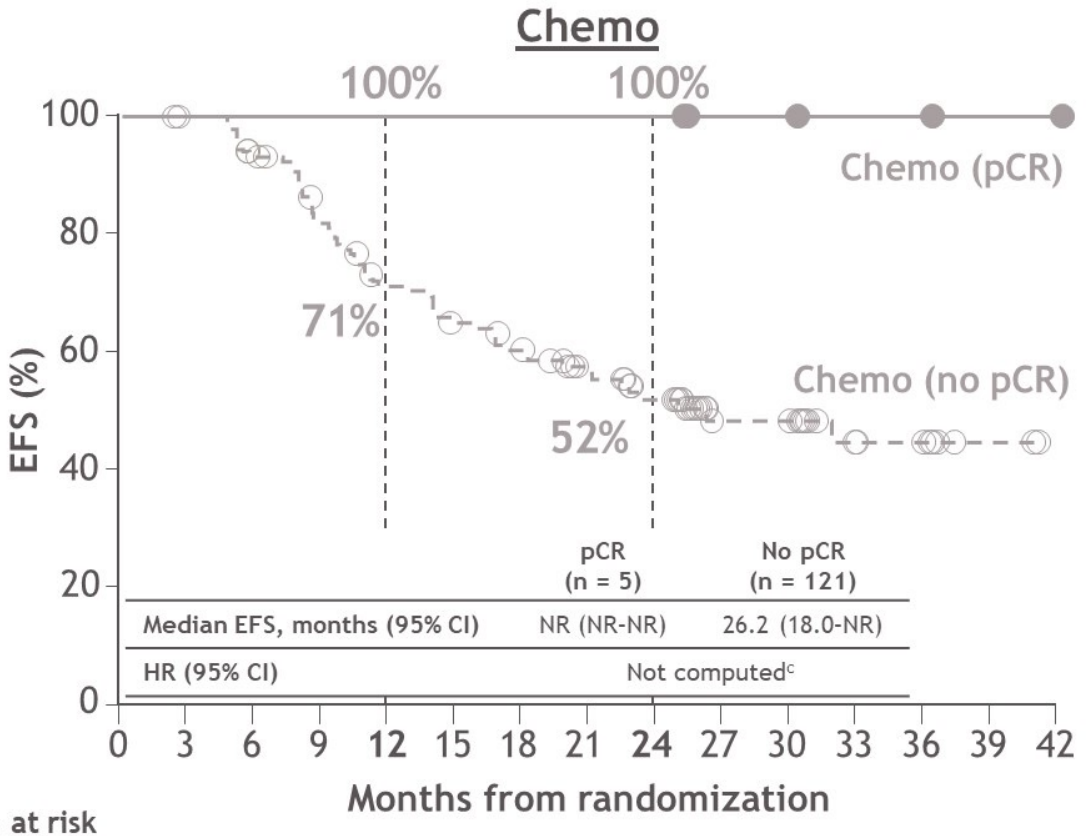
- CheckMate 816 showed a statistically significant improvement in the primary endpoint of pCR (OR = 13.94 [99% CI, 3.49–55.75]; *P* <.0001), and benefit was consistent across disease stages, histologies, TMB, and PD-L1 expression levels
  - MPR and ORR were also improved
  - The study reportedly also now positive for EFS
- The addition of neoadjuvant nivolumab to chemotherapy maintained a tolerable safety profile and did not impede the feasibility of surgery
- In an exploratory subset analysis, ctDNA clearance was more frequent with nivolumab plus chemotherapy vs chemotherapy alone and appeared to be associated with pCR
- CheckMate 816 is the first phase III study to show the benefit of neoadjuvant immunotherapy plus chemotherapy combination for resectable NSCLC

Abbreviations: ctDNA, circulating tumor DNA; EFS, event-free survival; MPR, major pathologic response; NSCLC, non-small cell lung cancer; ORR, objective response rate; pCR, pathologic complete response; TMB, tumor mutational burden.

Forde PM, et al. Abstract CT003. Presented at: 2021 AACR; April 10–15, 2021.

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

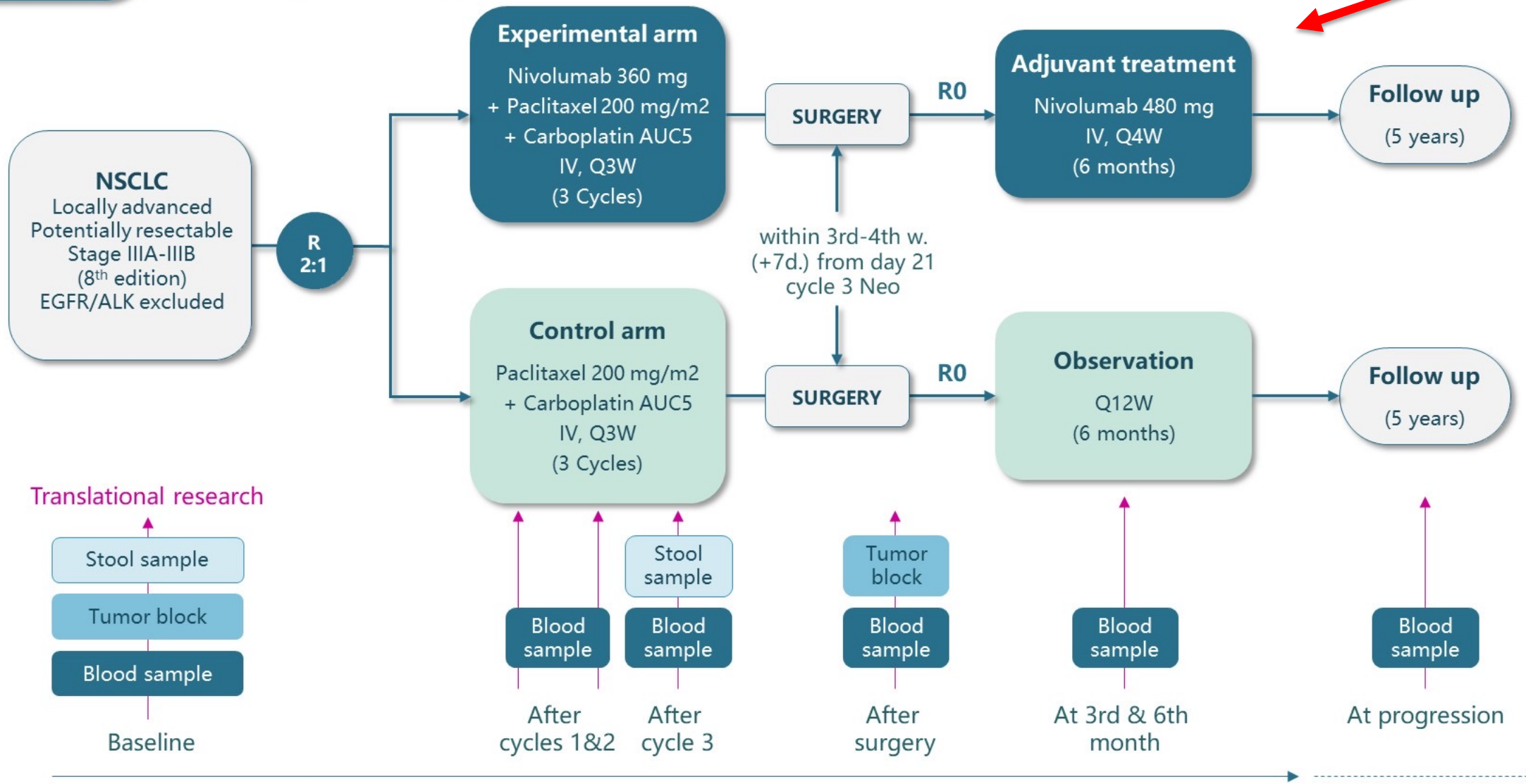
pCR	5	5	5	5	5	5	5	5	5	3	2	2	2	1	0
No pCR	121	119	108	93	79	71	64	53	44	21	20	10	8	2	0

- 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

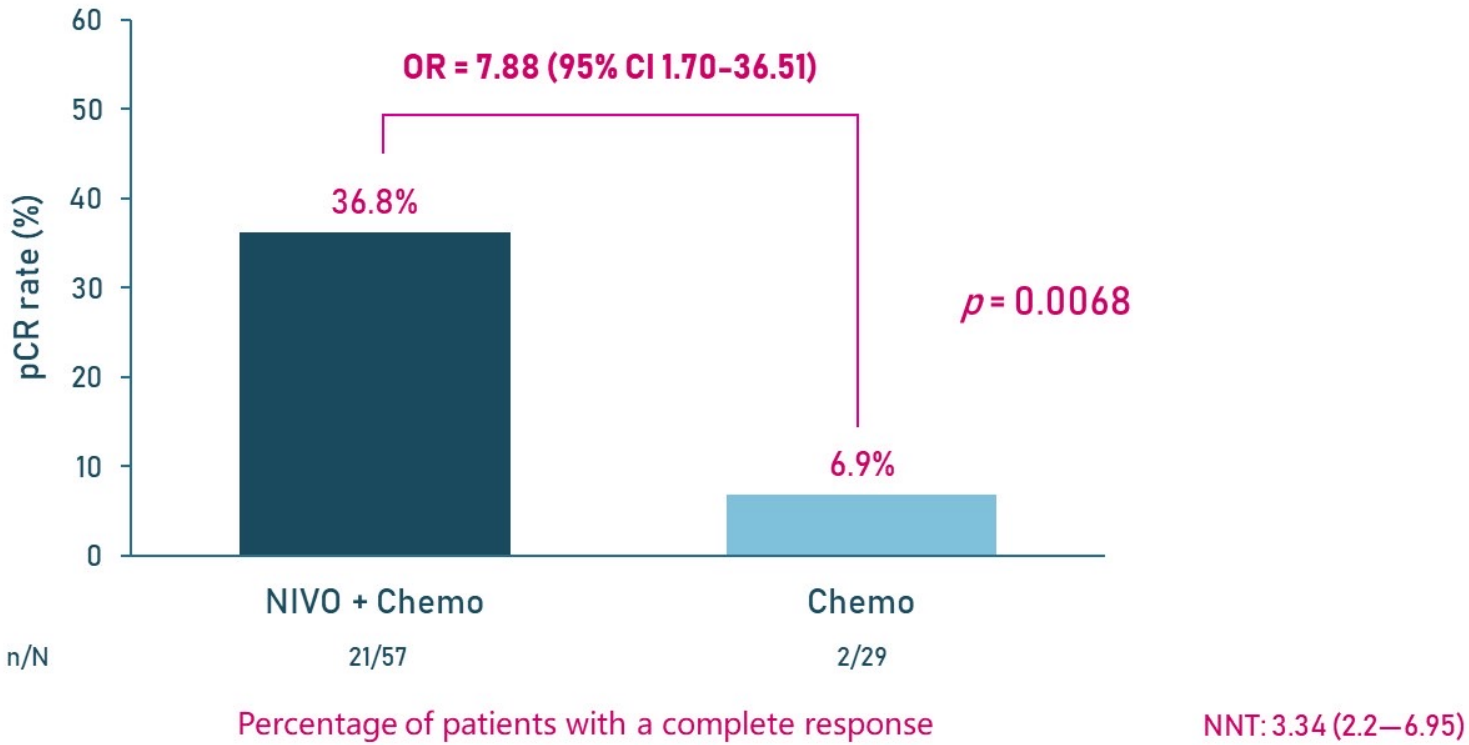


NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

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)

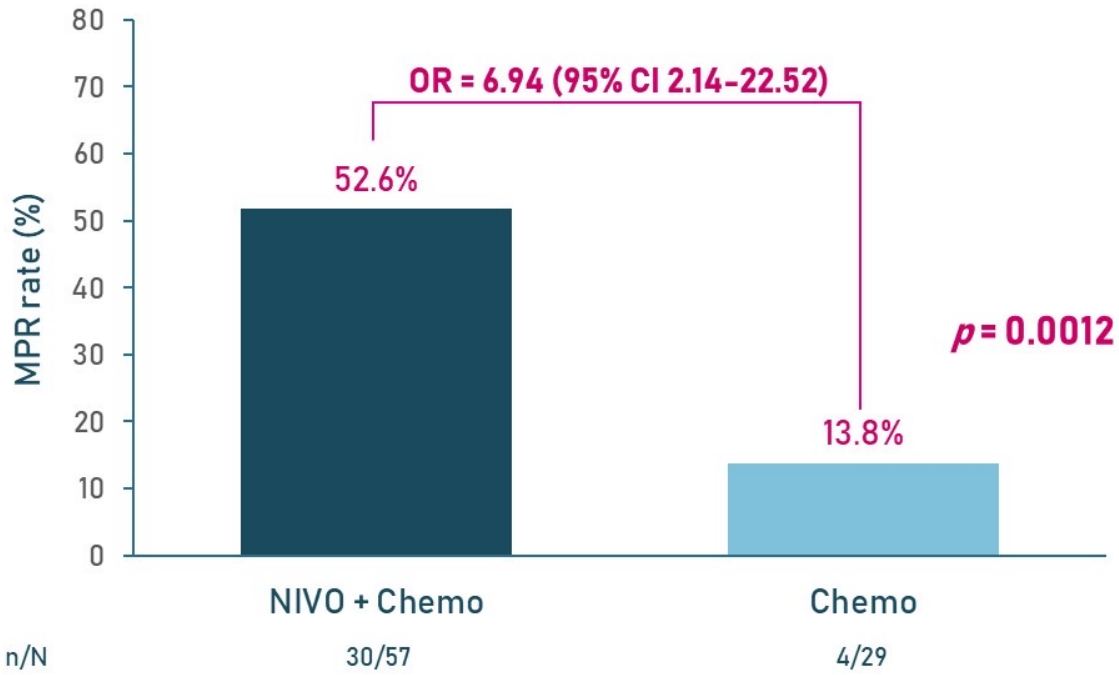
[a]pCR was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders

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.**
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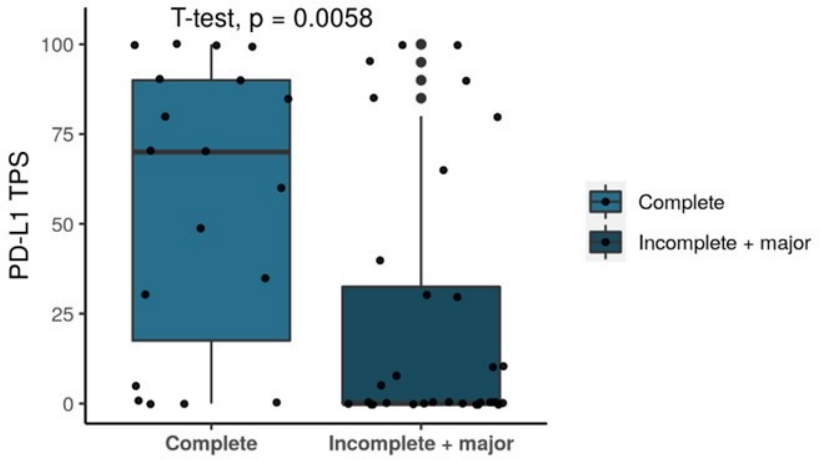
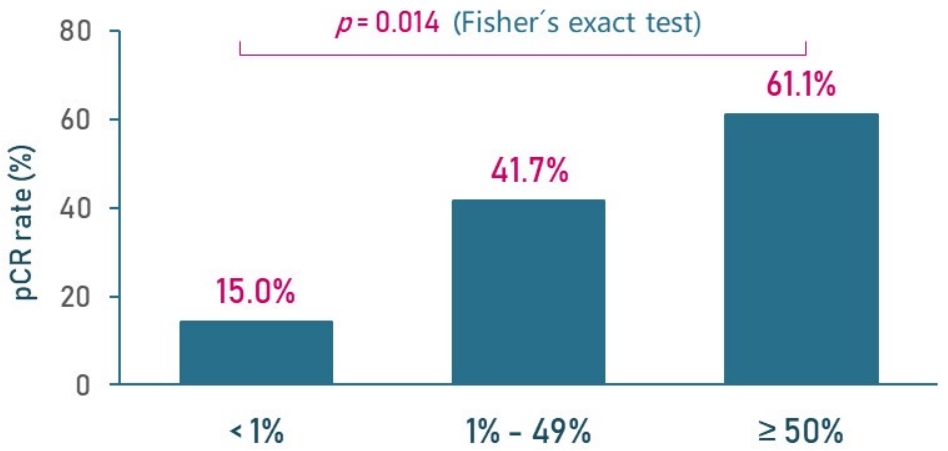
Secondary endpoints – Predictive biomarkers

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.**
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IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

NIVOLUMAB + CHEMOTHERAPY vs CHEMOTHERAPY AS NEOADJUVANT TREATMENT FOR RESECTABLE IIIA-B NSCLC

Progression-free survival and overall survival results from the phase 2 NADIM II trial

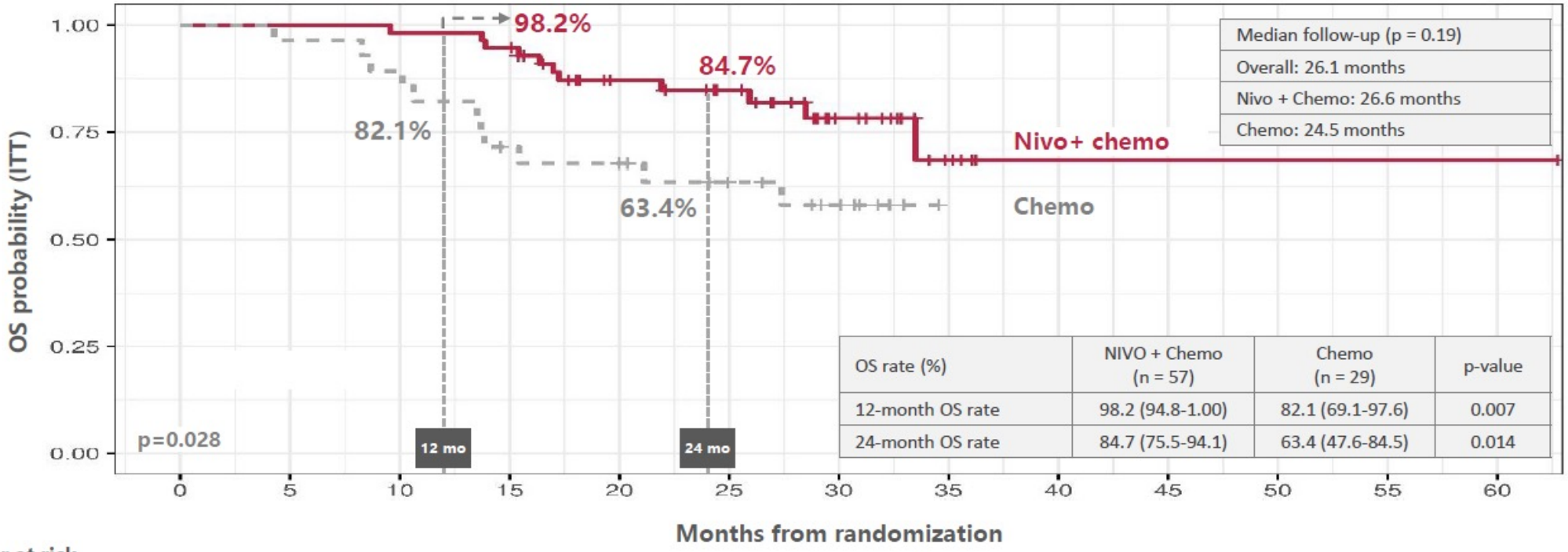
Dr. Mariano Provencio

Hospital Universitario Puerta de Hierro-Majadahonda, Madrid

SPAIN

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

SECONDARY ENDPOINTS – Overall survival



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

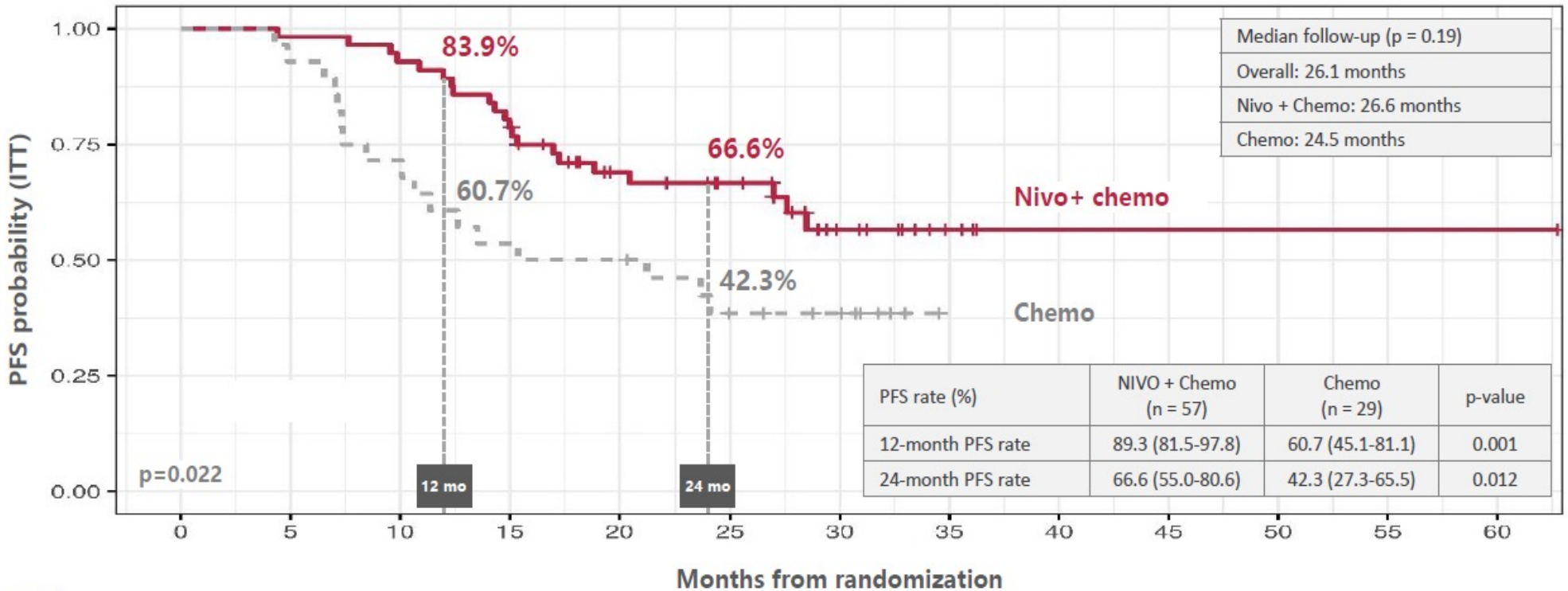
OS rate (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)	p-value
12-month OS rate	98.2 (94.8-1.00)	82.1 (69.1-97.6)	0.007
24-month OS rate	84.7 (75.5-94.1)	63.4 (47.6-84.5)	0.014

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

ADJUVANT IMMUNOTHERAPY IN NSCLC

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

IMpower010: Overall survival interim analysis of a phase III study of atezolizumab vs best supportive care in resected NSCLC

Enriqueta Felip,[1] Nasser Altorki,[2] Eric Vallieres,[3] Ihor O. Vynnychenko,[4] Andrey Akopov,[5] Alex Martinez-Marti,[1] Antonio Chella,[6] Igor Bondarenko,[7] Shunichi Sugawara,[8] Yun Fan,[9] Hirotsugu Kenmotsu,[10] Yuh-Min Chen,[11] Yu Deng,[12] Meilin Huang,[12] Virginia McNally,[13] Elizabeth Bennett,[12] Barbara J. Gitlitz,[12] Caicun Zhou,[14] Heather A. Wakelee[15]

[1]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]NewYork-Presbyterian Hospital, Weill Cornell Medicine, New York, NY, USA; [3]Swedish Cancer Institute, Seattle, WA, USA; [4]Regional Municipal Institution Sumy Regional Clinical Oncology Dispensary, Sumy State University, Sumy, Ukraine; [5]Pavlov State Medical University, Saint Petersburg, Russia; [6]Pneumology Unit, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; [7]Dnipro State Medical University, Dnipro, Ukraine; [8]Sendai Kousei Hospital, Miyagi, Japan; [9]Zhejiang Cancer Hospital, Hanzhou, China; [10]Shizuoka Cancer Center, Shizuoka, Japan; [11]Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei, Taiwan; [12]Genentech Inc, South San Francisco, CA, USA; [13]Roche Products Ltd, Welwyn Garden City, United Kingdom; [14]Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China; [15]Stanford University School of Medicine/Stanford Cancer Institute, Stanford, CA, USA.

IMpower010: Phase III randomised trial of atezolizumab vs BSC in early-stage NSCLC

Completely resected stage IB-IIIA[a] NSCLC

- Stage IB tumors ≥4 cm
- ECOG 0-1
- Lobectomy
- Tumor tissue for PD-L1 analysis

Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

1-4 cycles

N=1280

R 1:1

No crossover

Atezolizumab 1200 mg q21d x 16 cycles or 1 year

N = 1005

BSC

Survival follow-up

Stratification factors

- Sex | Stage | Histology | PD-L1 status

Primary endpoint

- Investigator-assessed DFS tested hierarchically

Key secondary endpoints

- OS in ITT | DFS in PD-L1 TC ≥50% | 3-yr and 5-year DFS

Key exploratory endpoints

- OS biomarker analyses

Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule. ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.
[a] Per UICC/AJCC staging system, 7th edition. [b] Two-sided α=0.05.

Hierarchical statistical testing of endpoints

DFS in PD-L1 TC ≥1% stage II–IIIA population[b]

If positive:

DFS in all-randomized stage II–IIIA population[b]

If positive:

DFS in ITT population (stage IB-IIIA)[b]

If positive:

OS in ITT population[b]

Endpoint was met at DFS IA

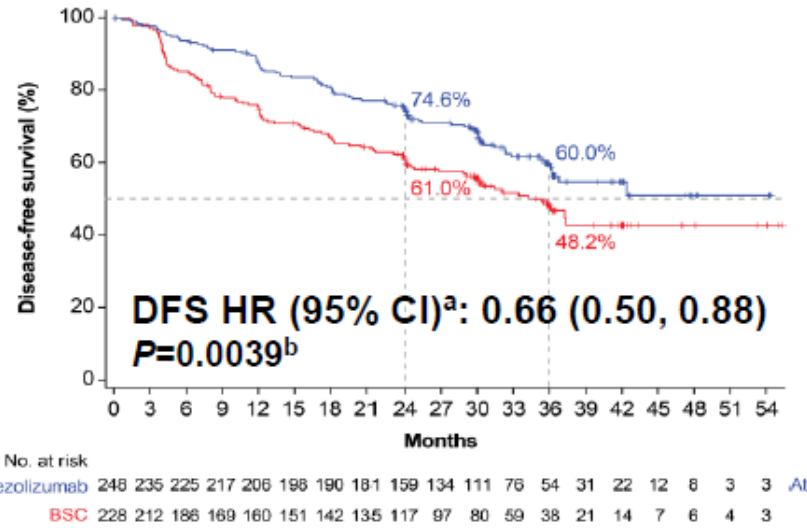
Endpoint was not met at DFS IA and follow up is ongoing

Endpoint was not formally tested

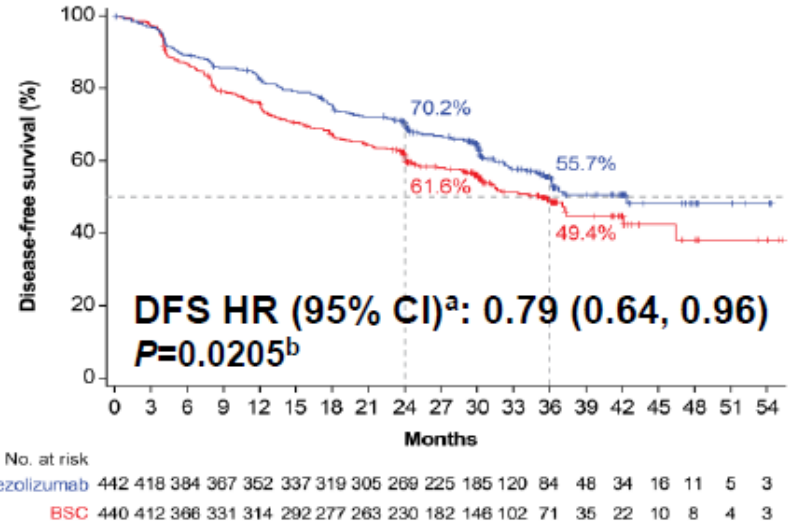
Recap of DFS and OS data from the DFS IA[1,2]

(data cutoff: 21 Jan '21, median follow-up: 32 months)

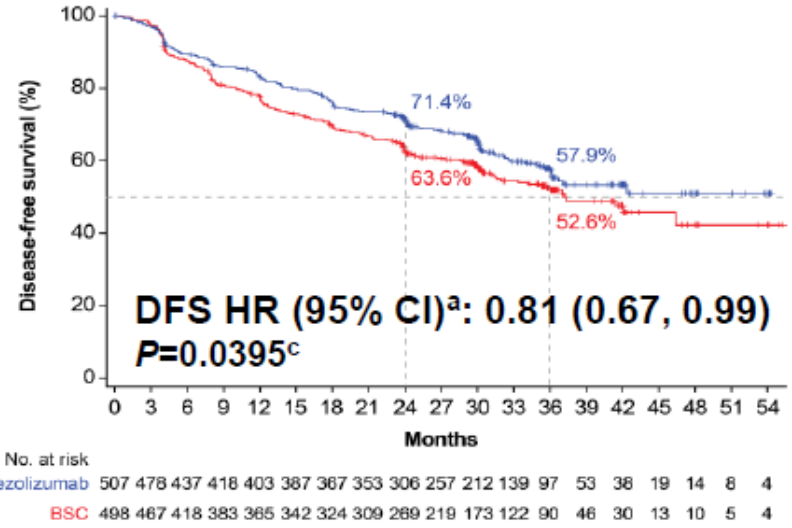
DFS: PD-L1 TC ≥1% stage II-IIIA population



DFS: All-randomised stage II-IIIA population



DFS: ITT (randomised stage IB-IIIA) population



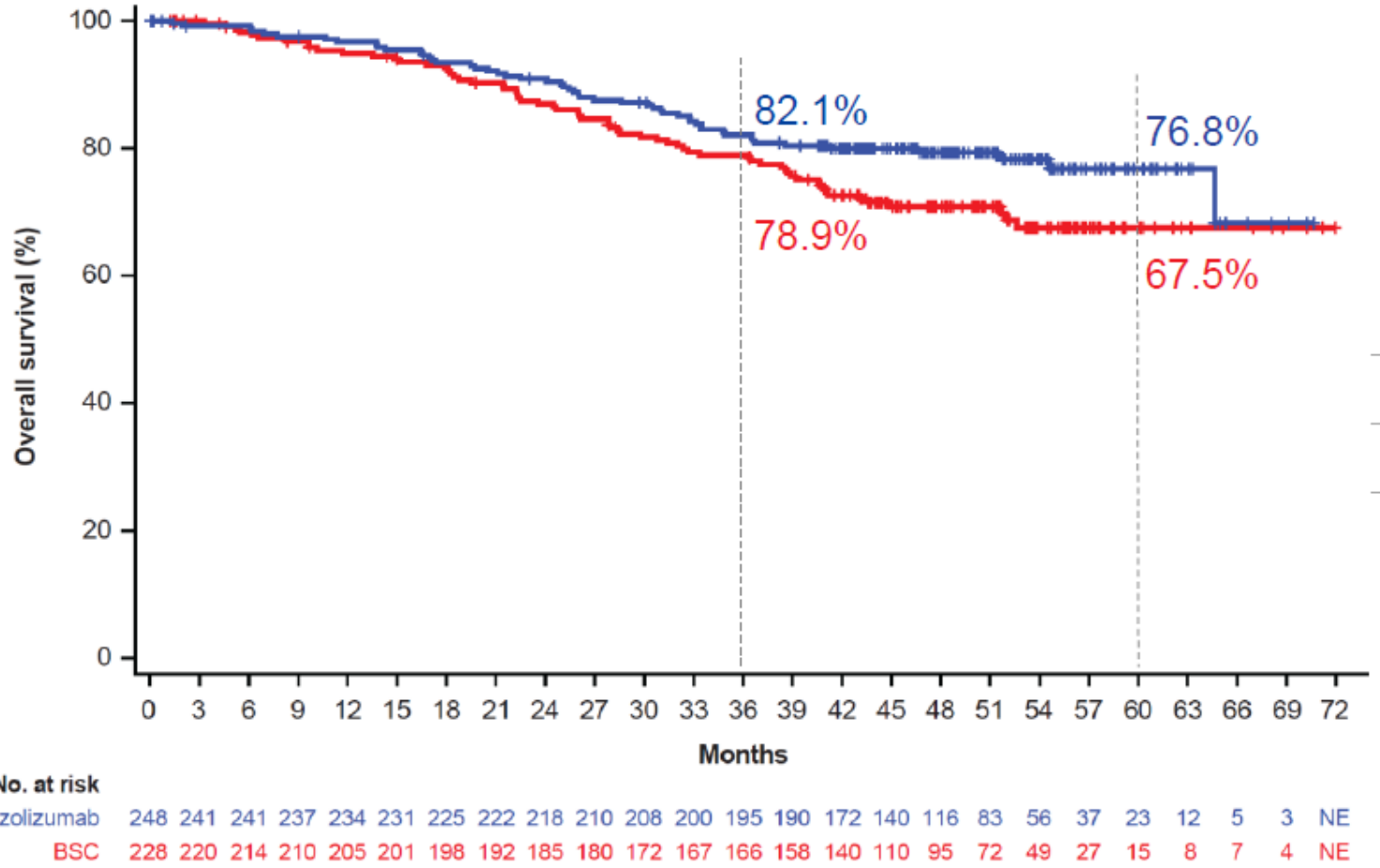
- **OS data** were not mature (event to patient ratio in ITT was 19% in atezolizumab arm, 18% in BSC arm)
  - PD-L1 TC ≥1% stage II-IIIA population: OS HR, 0.77 (95% CI: 0.51, 1.17)[a]
  - All-randomised stage II-IIIA population: OS HR, 0.99 (95% CI: 0.73, 1.33)[a]
  - ITT (randomised stage IB-IIIA) population: OS HR, 1.07 (95% CI: 0.80, 1.42)[a]

Clinical cutoff: 21 Jan 2021. [a] Stratified. [b] Statistical significance boundary for DFS crossed. [c] Statistical significance boundary for DFS not crossed.

1. Felip, E et al Lancet 2021; 938; 1344-1357; 2. Wakelee. HA et al ASCO 2021; abs #8500.

Results of OS IA: PD-L1 TC ≥1%[a] (stage II-IIIA)

(data cutoff: 18 Apr '22, median follow-up: 46 months)



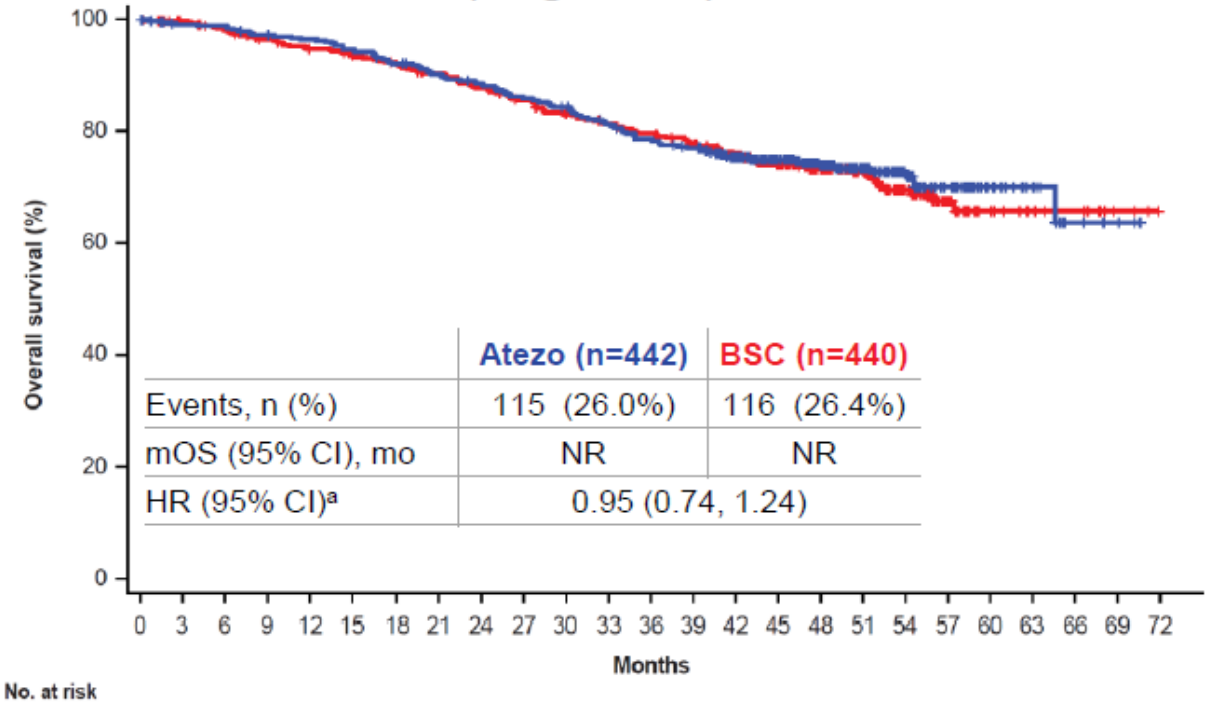
	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[b]	0.71 (0.49, 1.03)	

mOS, median overall survival; NR, not reached. [a]By SP263 assay. [b]Stratified.

Results of OS IA: other primary populations

(data cutoff: 18 Apr '22, median follow-up: 45 months)

All randomised (stage II-IIIA)

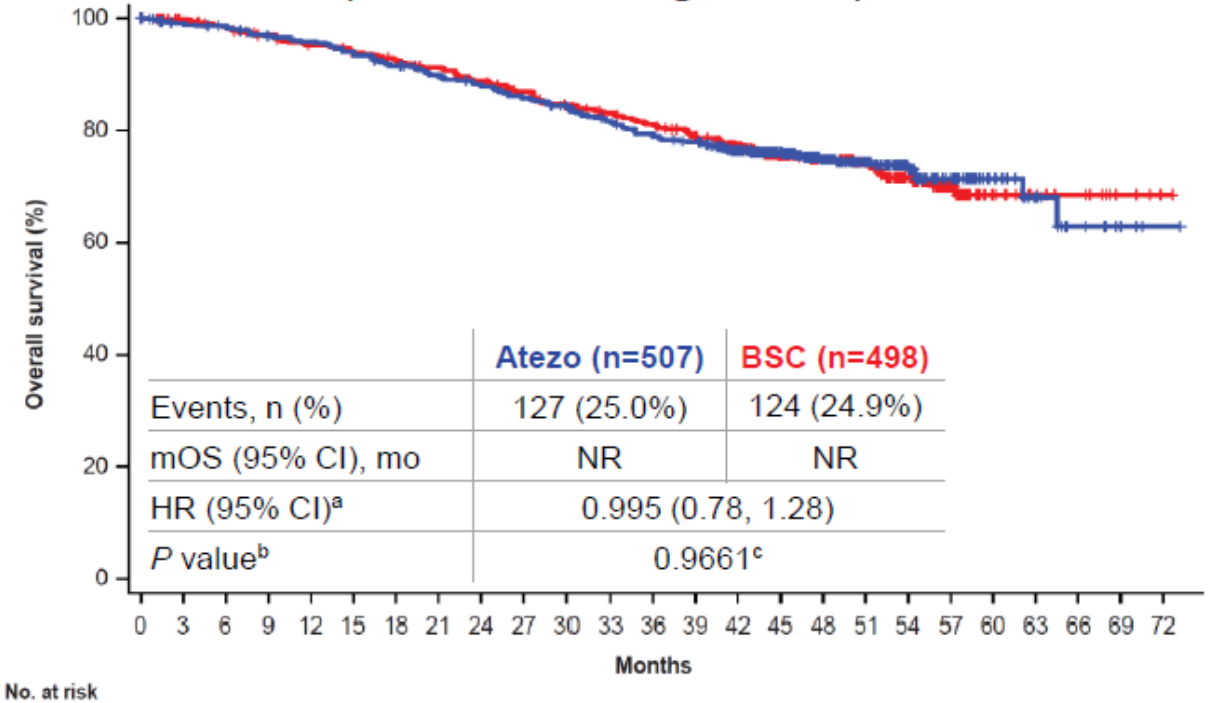


	Atezo (n=442)	BSC (n=440)
Events, n (%)	115 (26.0%)	116 (26.4%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.95 (0.74, 1.24)	

No. at risk

Atezolizumab	442	429	428	420	416	408	396	386	378	367	359	344	332	323	287	228	179	128	85	56	27	15	6	3	NE
BSC	440	426	416	405	396	389	382	373	362	350	337	328	320	310	279	215	178	125	81	42	20	11	9	4	NE

ITT (randomised stage IB-IIIA)



	Atezo (n=507)	BSC (n=498)
Events, n (%)	127 (25.0%)	124 (24.9%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.995 (0.78, 1.28)	
P value[b]	0.9661[c]	

No. at risk

Atezolizumab	507	492	488	478	472	463	450	439	430	419	408	393	381	372	328	262	203	144	96	61	30	17	8	4	1
BSC	498	484	473	462	452	444	437	428	417	405	391	381	371	357	325	253	207	148	101	57	25	14	11	5	1

Clinical cutoff: 18 April 2022.[a] Stratified. [b] No formal testing until statistical significance observed for DFS in the ITT population due to the prespecified testing hierarchy.
[c] Descriptive purposes only.

PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial

Eligibility for Registration

- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing
done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomization

- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R 1:1

- Pembrolizumab 200 mg Q3W for 18 administrations (~1 yr)
- Placebo Q3W for 18 administrations (~1 yr)

Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

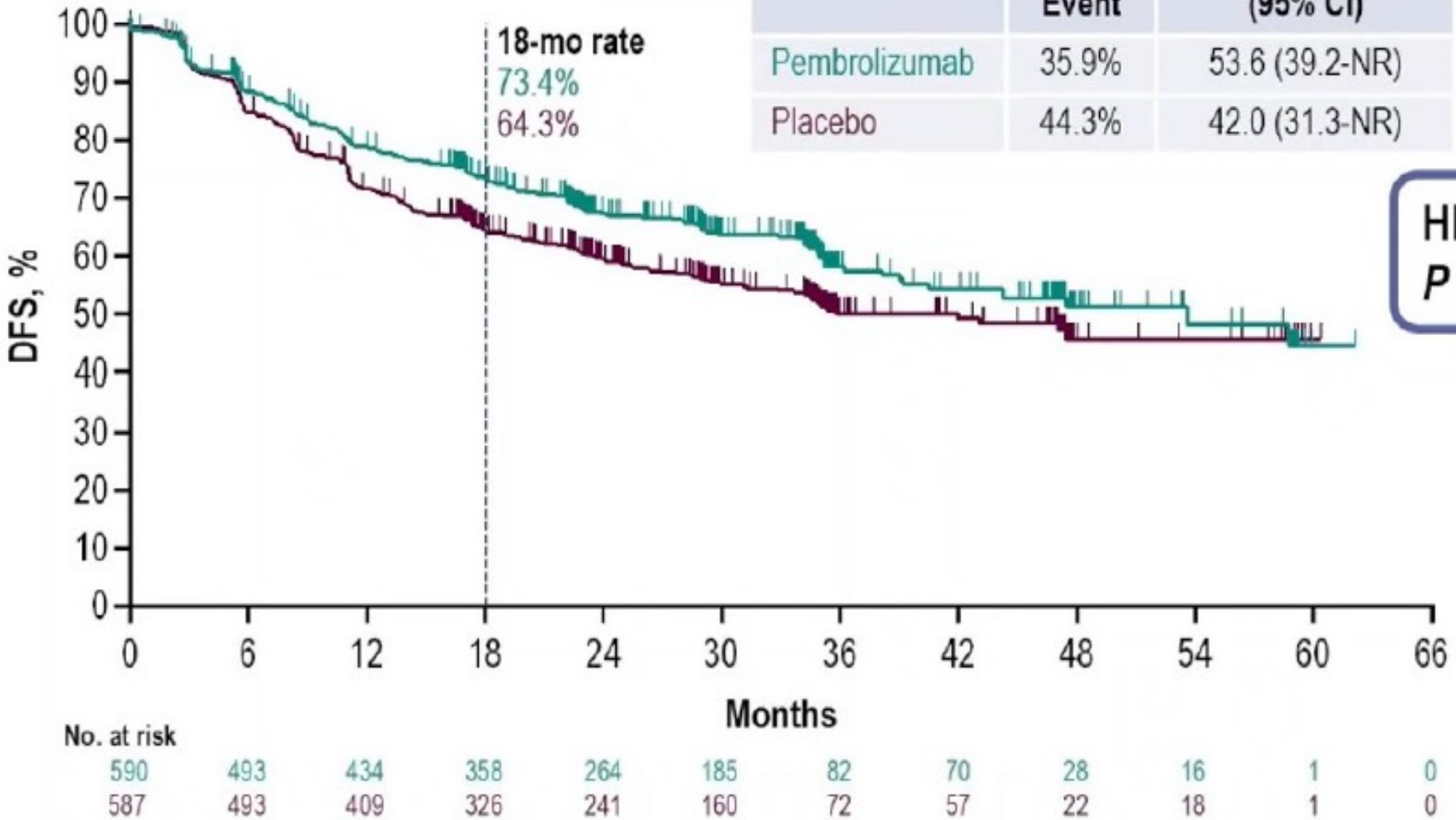
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

ESMO VIRTUAL PLENARY

ClinicalTrials.gov number, NCT02504372.

DFS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)



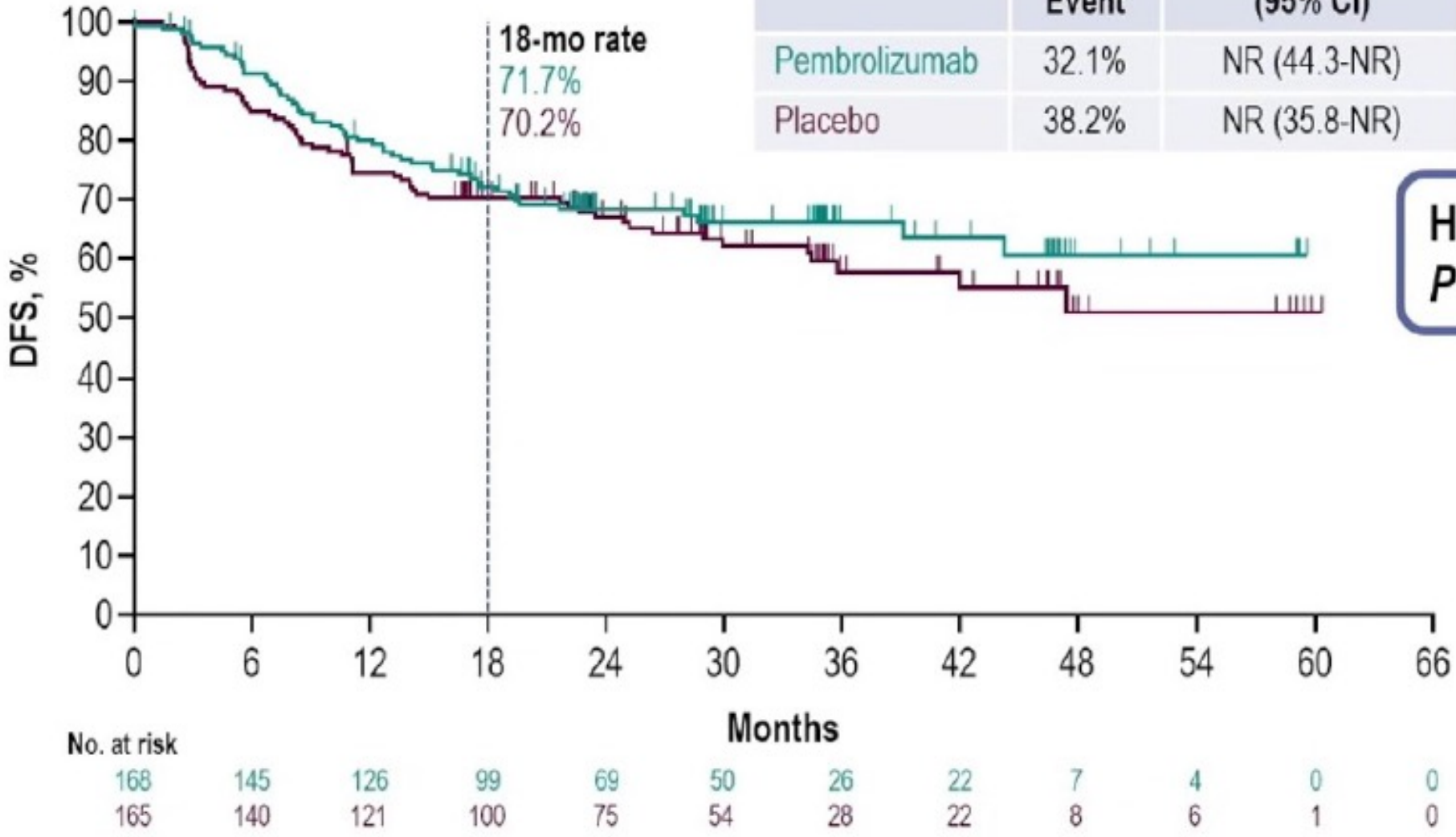
HR 0.76 (95% CI, 0.63-0.91)
P = 0.0014

ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

DFS, PD-L1 TPS ≥50% Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)



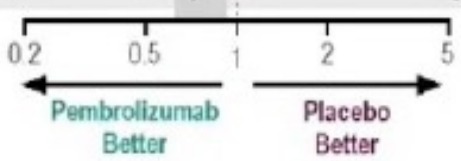
HR 0.82 (95% CI, 0.57-1.18)
P = 0.14

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

DFS in Key Subgroups, Overall Population

Subgroup	No. Events/ No. Participants	Hazard Ratio (95% CI)
Overall	472/1177	0.76 (0.63-0.91)
Age		
<65 years	213/558	0.73 (0.56-0.96)
≥65 years	259/619	0.84 (0.66-1.07)
Sex		
Female	158/373	0.73 (0.54-1.00)
Male	314/804	0.81 (0.65-1.01)
Geographic region		
Asia	96/211	0.74 (0.49-1.10)
Eastern Europe	90/229	0.84 (0.56-1.27)
Western Europe	245/604	0.77 (0.60-1.00)
Rest of world	41/133	0.74 (0.40-1.39)
ECOG performance status		
0	288/723	0.78 (0.62-0.99)
1	184/454	0.79 (0.59-1.06)
Smoking status		
Current	53/165	0.42 (0.23-0.77)
Former	340/859	0.84 (0.68-1.04)
Never	79/153	0.72 (0.47-1.13)

Subgroup	No. Events/ No. Participants	Hazard Ratio (95% CI)
Overall	472/1177	0.76 (0.63-0.91)
Pathologic stage		
IB	46/169	0.76 (0.43-1.37)
II	246/667	0.70 (0.55-0.91)
IIIA	178/339	0.92 (0.69-1.24)
Received adjuvant chemotherapy		
No	84/167	1.25 (0.76-2.05)
Yes	408/1010	0.73 (0.60-0.89)
Histology		
Nonsquamous	330/761	0.67 (0.54-0.83)
Squamous	142/416	1.04 (0.75-1.45)
PD-L1 TPS		
<1%	195/465	0.78 (0.58-1.03)
1-49%	160/379	0.67 (0.48-0.92)
≥50%	117/333	0.82 (0.57-1.18)
***EGFR* mutation**		
No	186/434	0.78 (0.59-1.05)
Yes	40/73	0.44 (0.23-0.84)
Unknown	246/670	0.82 (0.63-1.05)

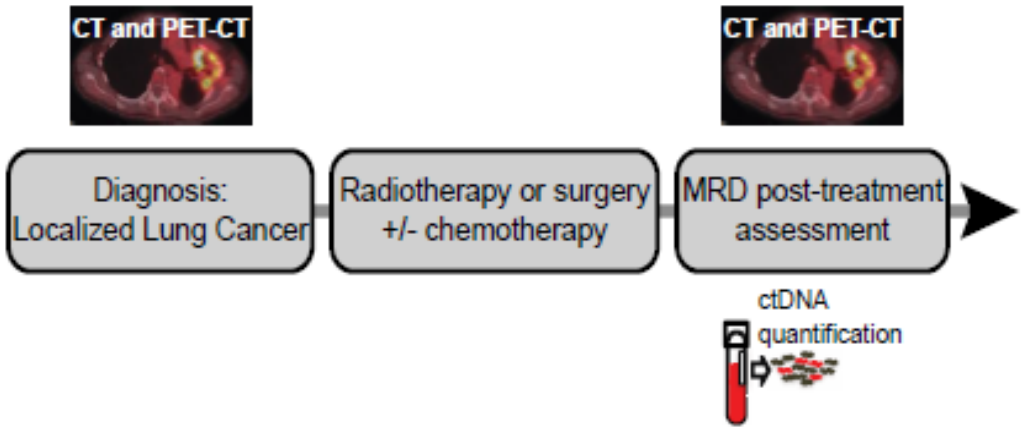


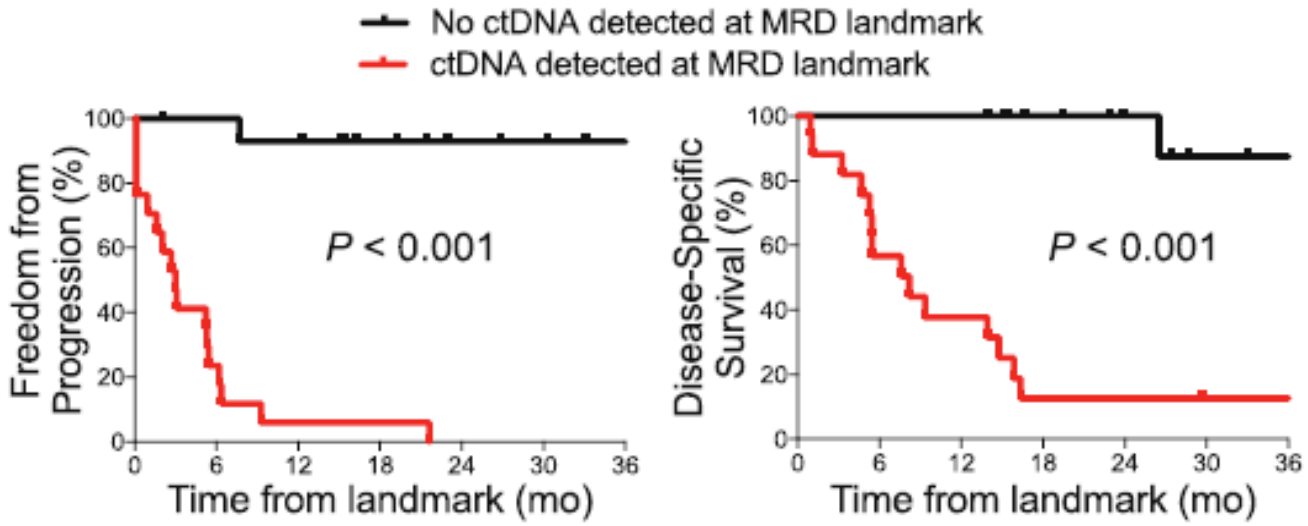
Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

Summary and Conclusions

- Pembrolizumab provided statistically significant, clinically meaningful DFS improvement versus placebo in the overall population
  - Median DFS of 53.6 months with pembrolizumab vs 42.0 months with placebo (HR, 0.76)
  - Generally consistent DFS benefit in participants with PD-L1 TPS <1%, 1-49%, and ≥50%
  - OS data are immature
  - DFS in the PD-L1-defined populations and OS will be tested at future analyses according to the analysis plan
- Pembrolizumab safety profile as expected
- **Data suggest pembrolizumab has the potential to be a new adjuvant treatment option for patients with stage IB (T ≥4 cm) to IIIA NSCLC following complete resection and adjuvant chemotherapy when recommended, regardless of PD-L1 expression**

ctDNA Minimal Residual Disease in Localized Lung Cancer

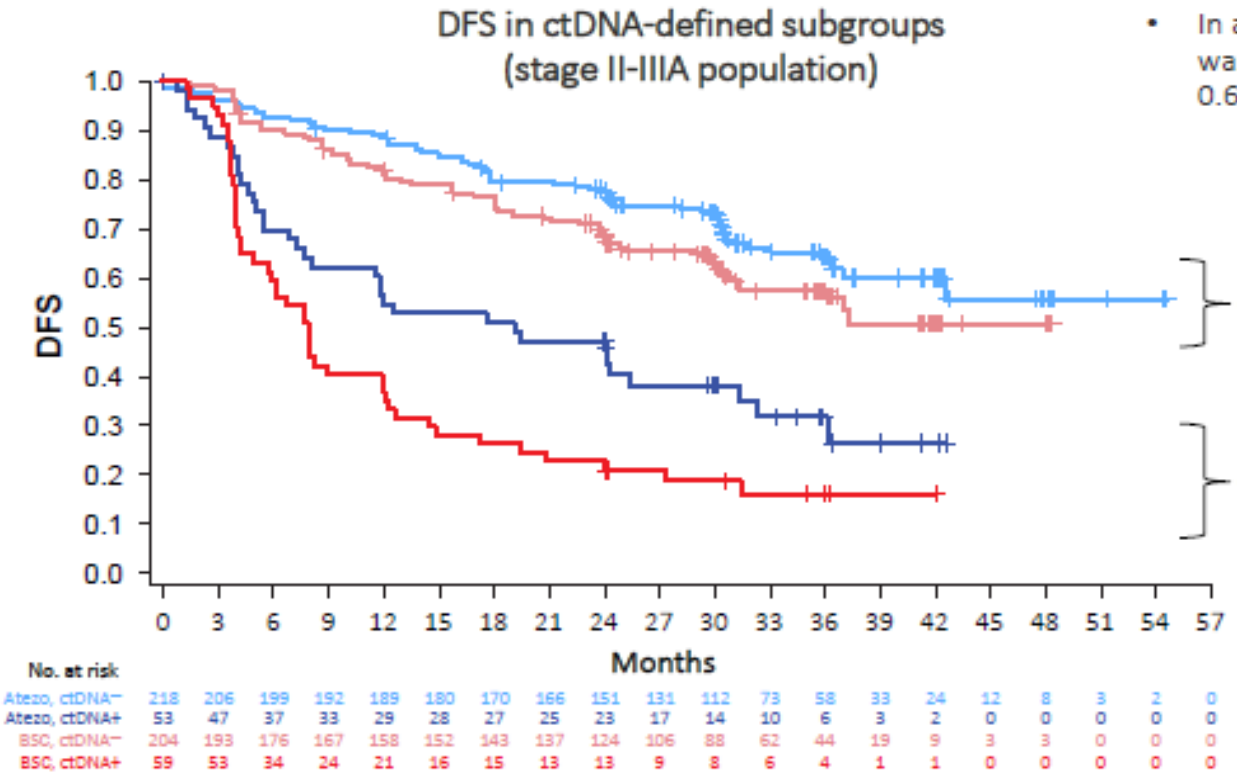




Residual ctDNA after completion of therapy is associated with an extremely high risk of recurrence

Chaudhuri et al. *Cancer Discovery* 2017

IMpower010 ctDNA MRD Analysis



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Benefit of consolidation immunotherapy is strongest in ctDNA-positive patients

Zhou et al. *ESMO Immuno-Oncology* 2021

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A081801

INTEGRATION OF IMMUNOTHERAPY INTO ADJUVANT THERAPY FOR RESECTED NSCLC: ALCHEMIST CHEMO-IO

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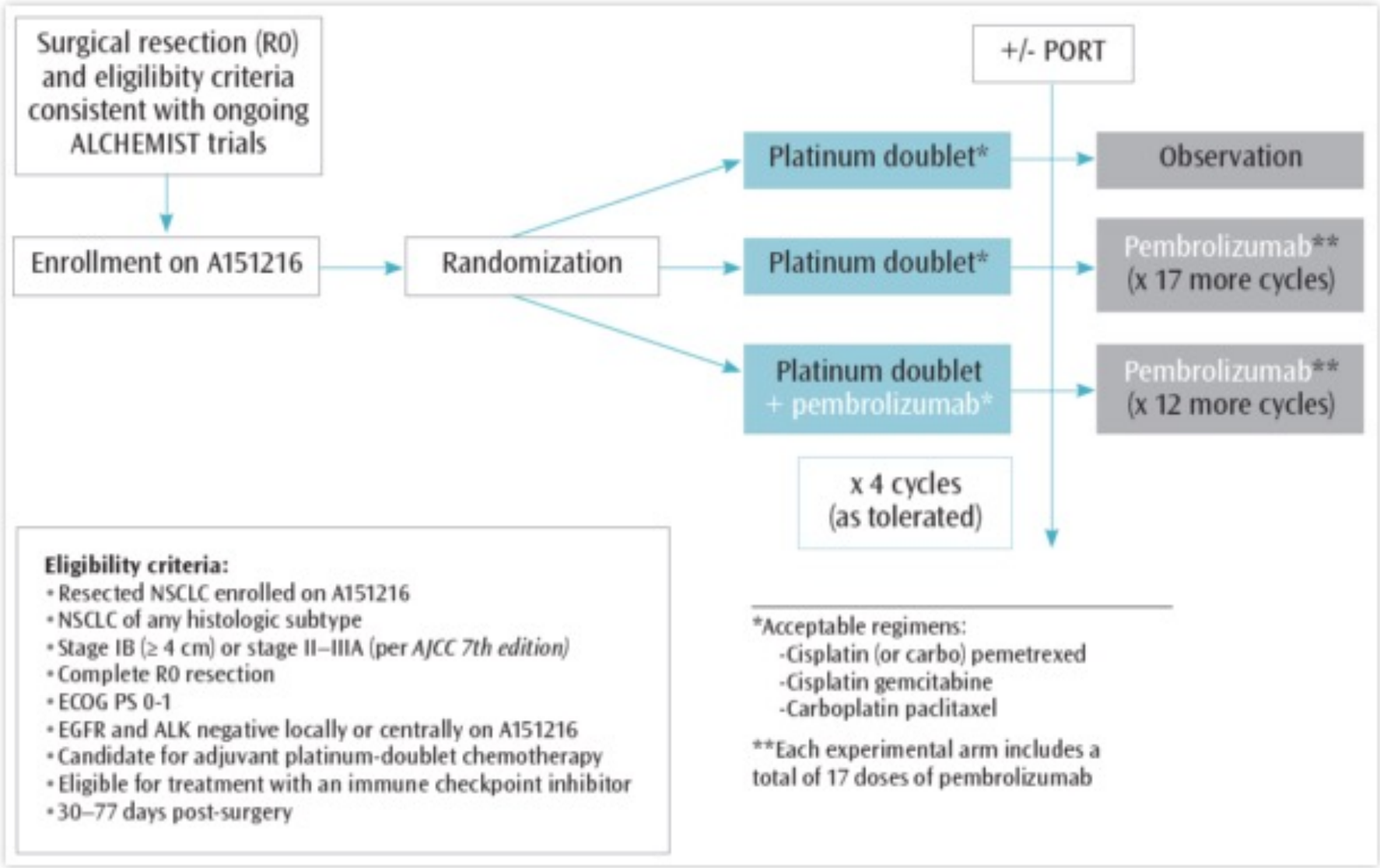
Figure 1. Schema: ALCHEMIST CHEMO-IO



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

PACIFIC: Study Design

Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Study

- Patients with Stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks

All-comers population

1-42 days post-CRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
N=237

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

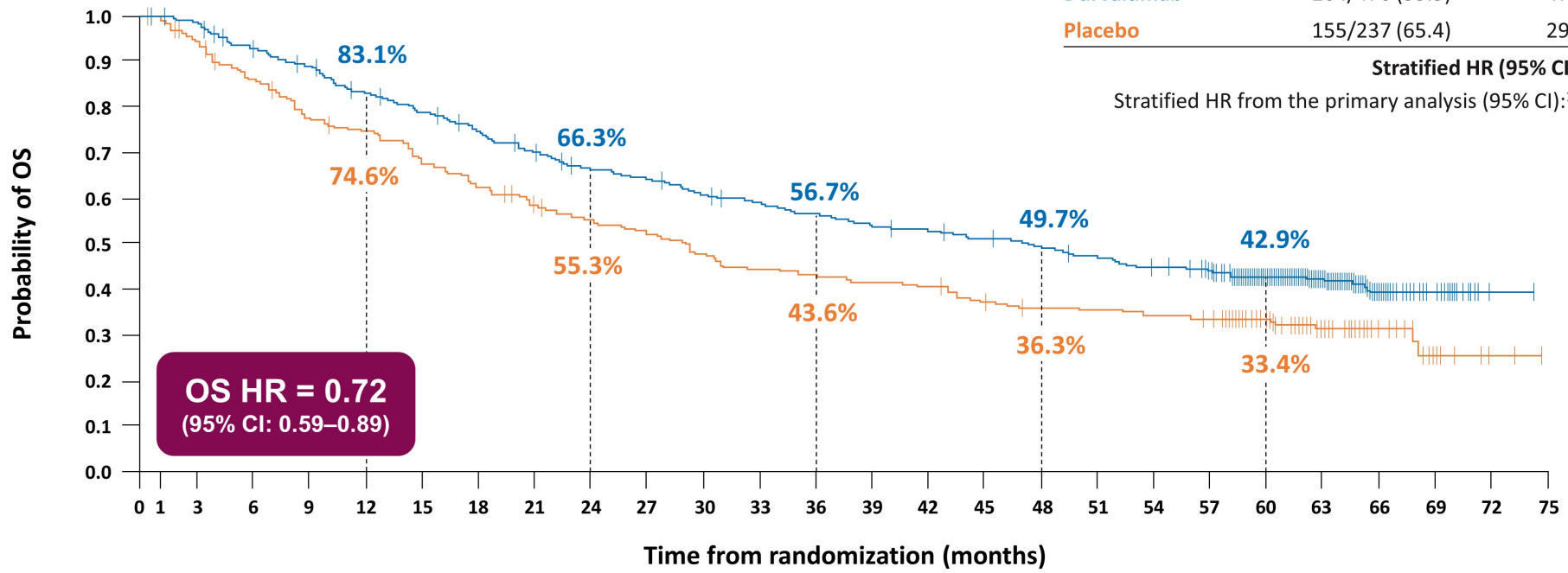
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

Updated OS (ITT)

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	264/476 (55.5)	47.5 (38.1–52.9)
Placebo	155/237 (65.4)	29.1 (22.1–35.1)

Stratified HR (95% CI): 0.72 (0.59–0.89)

Stratified HR from the primary analysis (95% CI):[1,2] 0.68 (0.53–0.87)



No. at risk

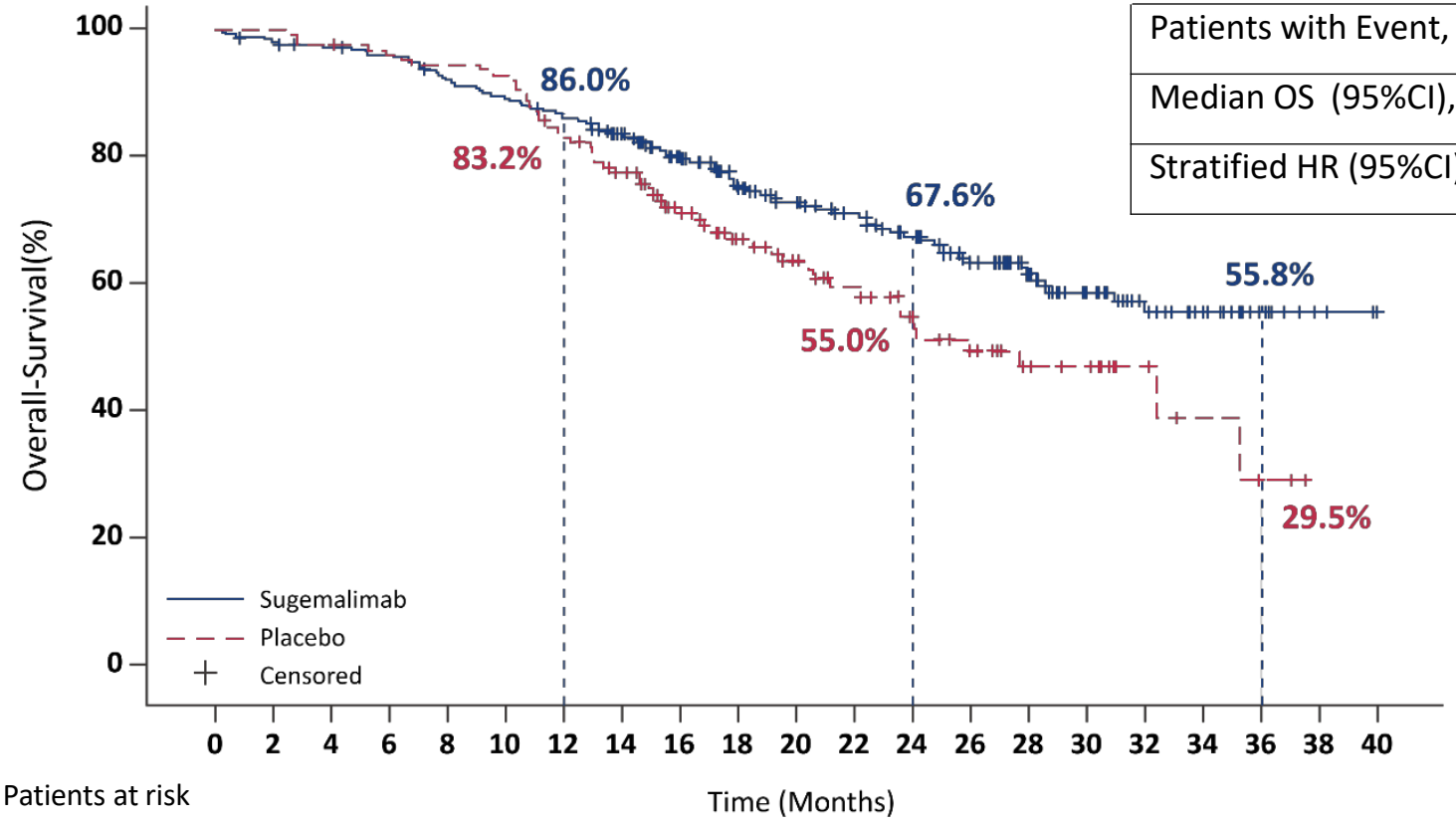
Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).

1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

Overall Survival



Patients at risk

Sugemalimab	255	249	245	241	230	223	214	199	172	146	131	119	107	87	69	49	34	25	12	3	0
Placebo	126	126	123	120	118	116	103	93	74	61	51	42	32	26	17	14	7	4	2	0	0

	Sugemalimab	Placebo
Patients with Event, %	33.3%	42.9%
Median OS (95%CI), months	NR (31.0, NR)	25.9 (21.2, NR)
Stratified HR (95%CI)	0.69 (0.49, 0.97)	

Median follow-up time ***27.1*** vs ***23.5*** months

OS data were immature at the data cutoff date, no formal analysis was performed

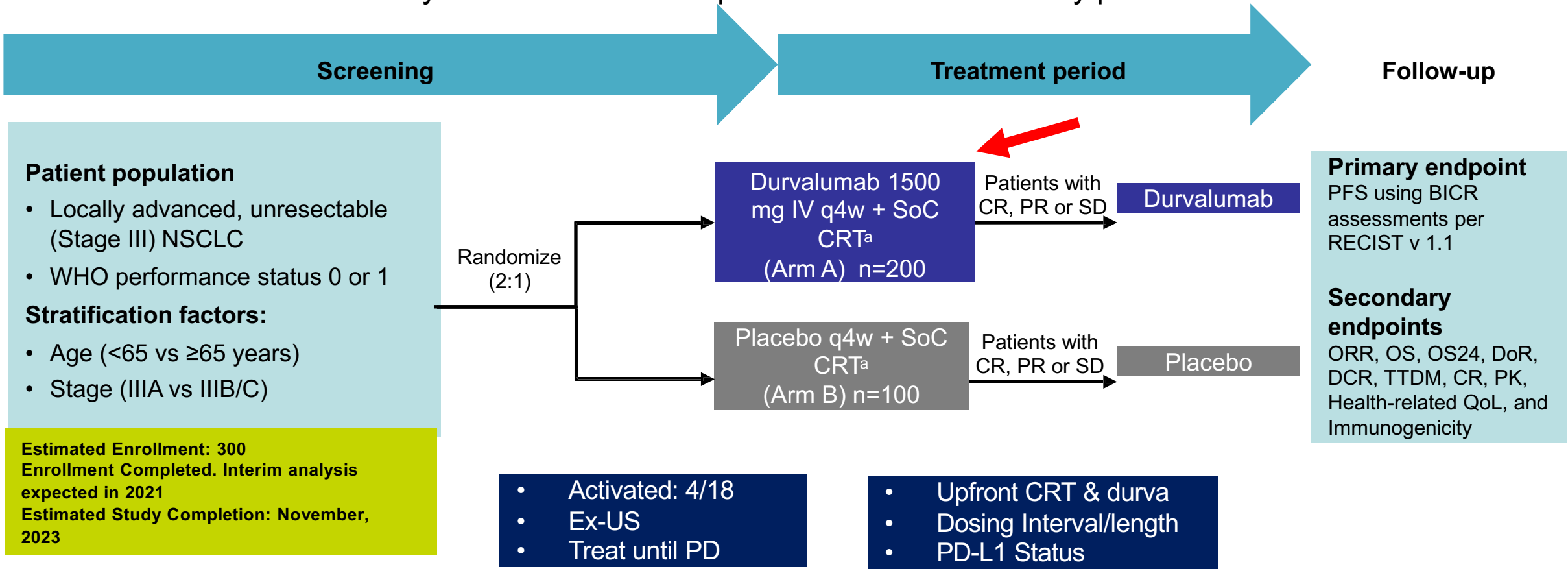
Cutoff date: 1 Mar 2022

NR: not reached

PACIFIC 2 Study Design:

Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study[1,2]

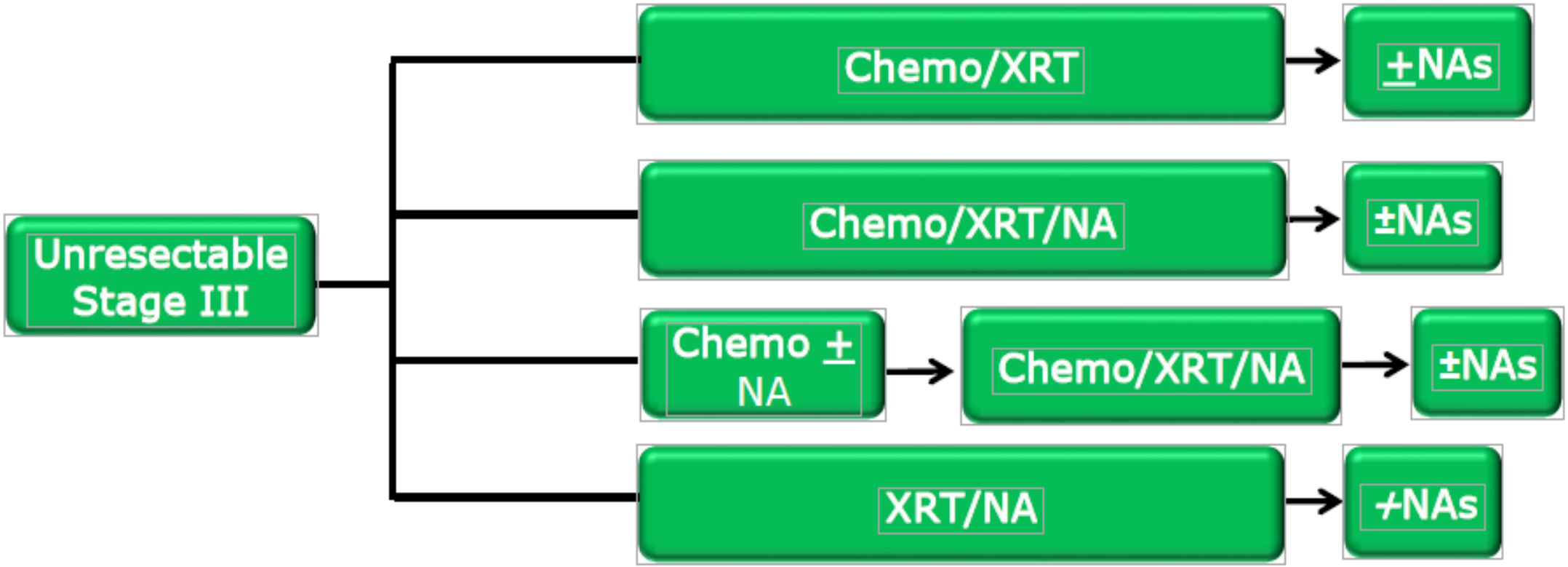
Durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo



[a]Platinum-based chemotherapy regimens include cisplatin/ etoposide, carboplatin/paclitaxel, pemetrexed/cisplatin (nonsquamous only) or pemetrexed/carboplatin (nonsquamous only), alongside radiation therapy (5 fractions/week for ~6 weeks [±3 days; total 60 Gy]).

1. Bradley JD et al. Poster presented at: ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL. Poster TPS8573; 2. Study NCT03519971. ClinicalTrials.gov website.

How do we incorporate novel agents (NAs) into treatment regimens of unresectable Stage III lung cancer?



Memorial Cancer Institute

CANCER CENTER of EXCELLENCE Florida HEALTH

FAU I-HEALTH Florida Atlantic University