Lung Cancer Immunotherapy

Luis E. Raez MD FACP FCCP
Chief Scientific Officer & Medical Director
Memorial Cancer Institute/Memorial Health Care System
Clinical Professor of Medicine/Herbert Wertheim College of Medicine
Florida International University
Past-President Florida Society of Clinical Oncology (FLASCO)

Memorial Cancer Institute

CANCER CENTER of EXCELLENCE Florida HEALTH

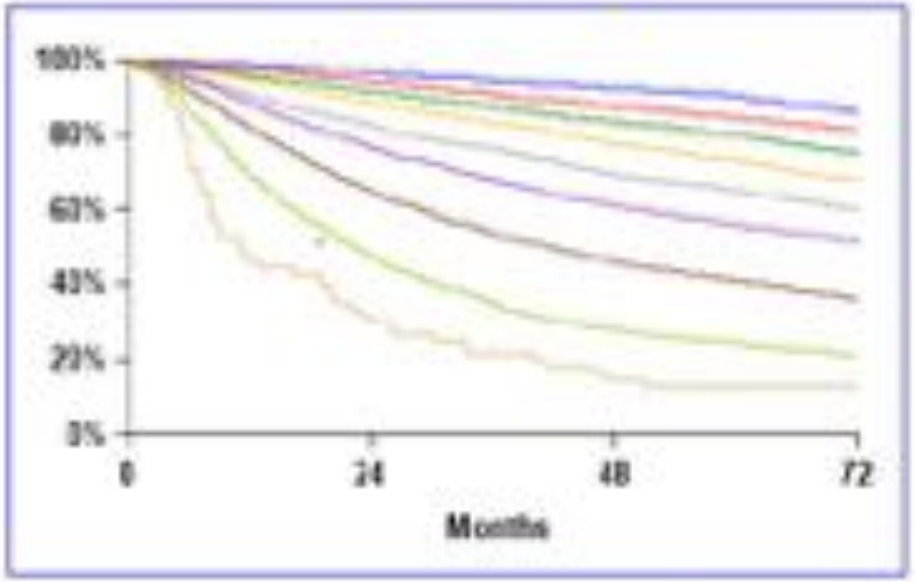
FAU I-HEALTH Florida Atlantic University

Lung Cancer Immunotherapy

- Neoadjuvant
- Adjuvant
- Metastatic

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%

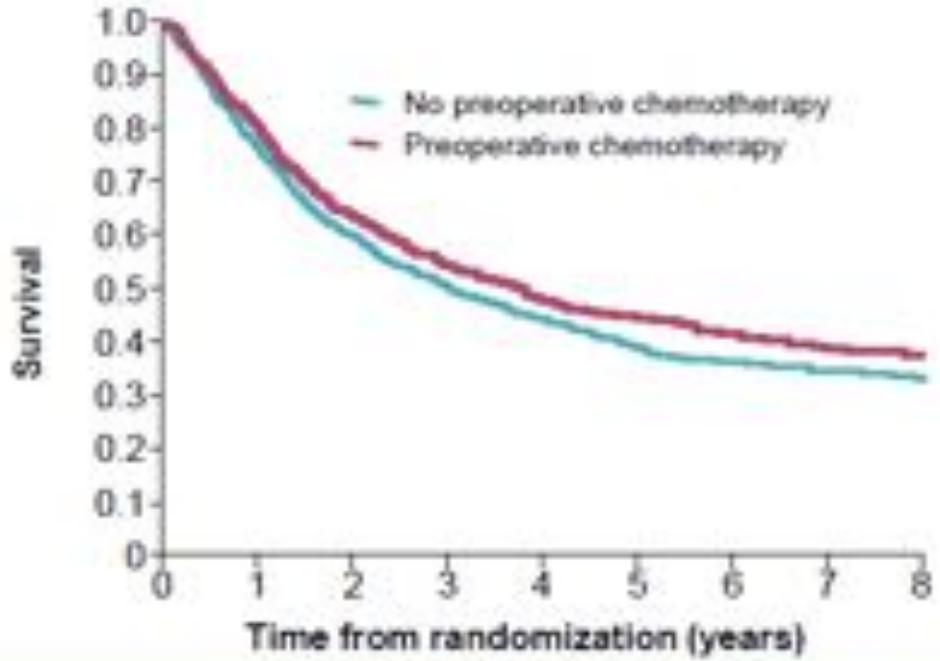
But there is a lot of room for improvement!

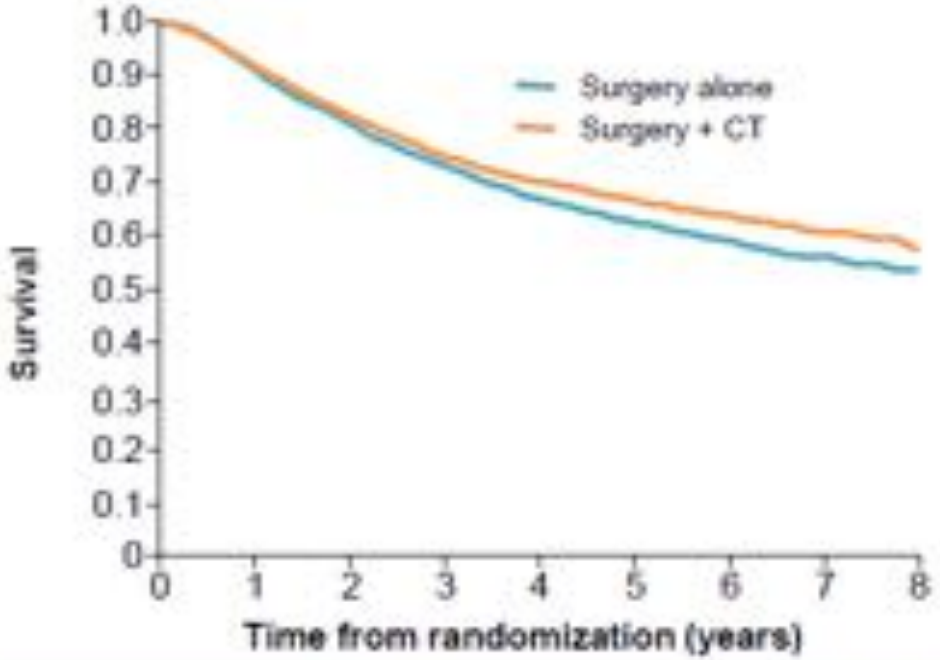
Goldstraw P et al. J Thorac Oncol 2016; 11: 39-51.

GECP

LUNG CANCER EARLY STAGES

Background & Current Situation

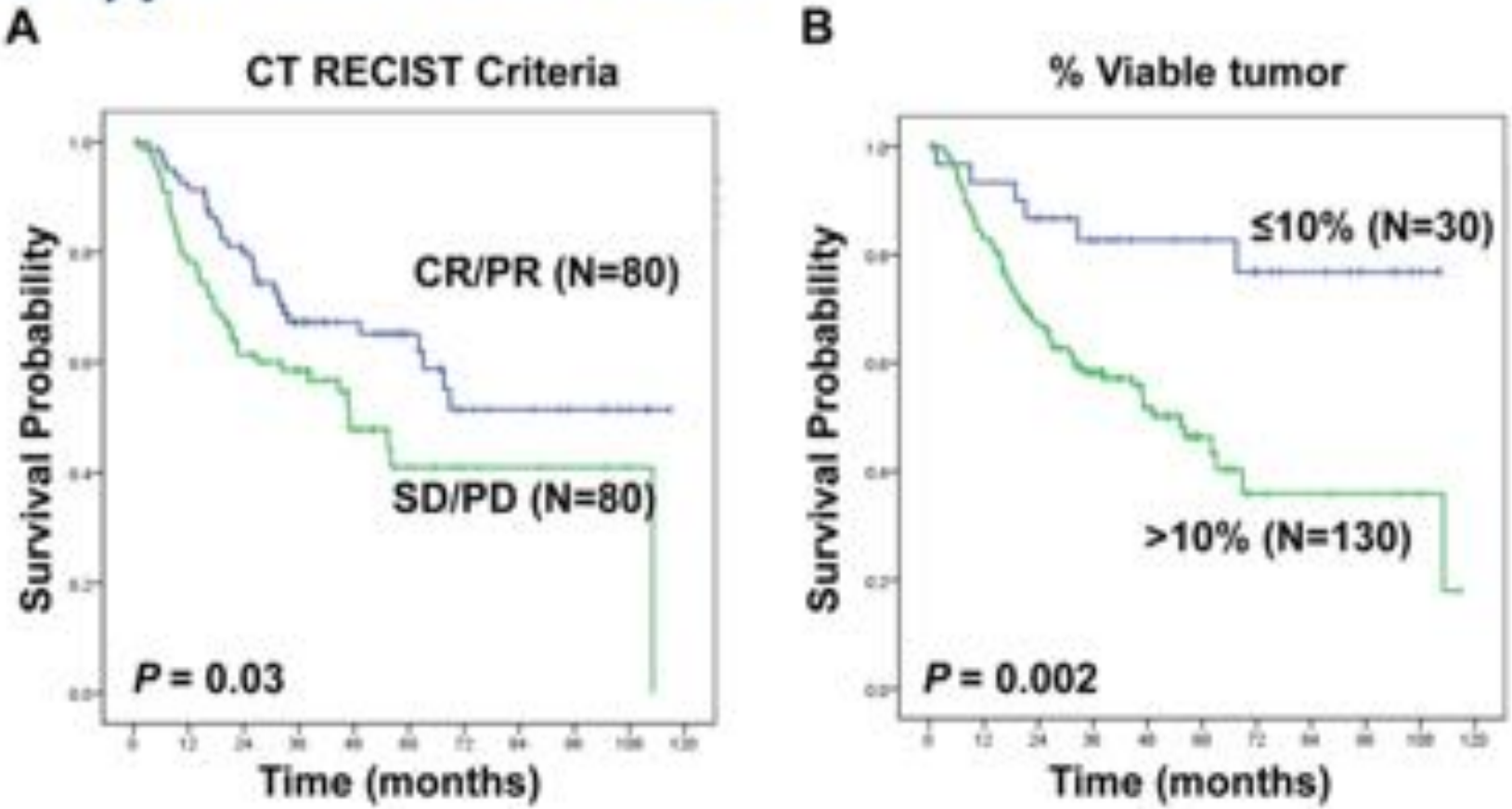




	N	Absolute Δ5 yr OS	HR	*P* value
Neoadjuvant Trials	2385	5%	0.87 (95% CI 0.78-0.96)	0.007
Adjuvant Trials	8447	4%	0.86 (95% CI 0.81-0.92)	<0.0001

Neoadjuvant Immunotherapy in NSCLC

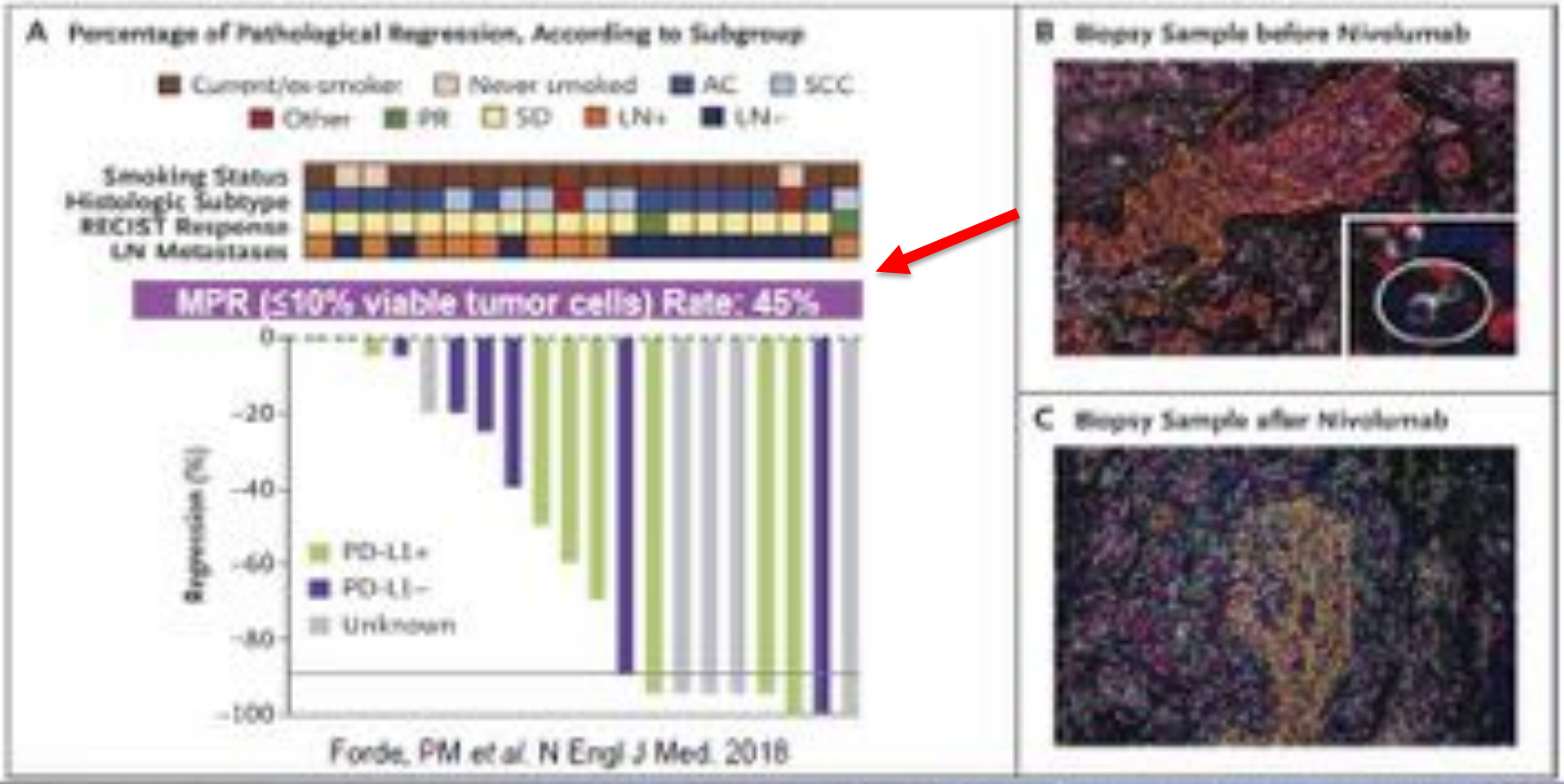
CT RECIST vs. MPR and prediction of OS after neoadjuvant chemotherapy in resectable NSCLC



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

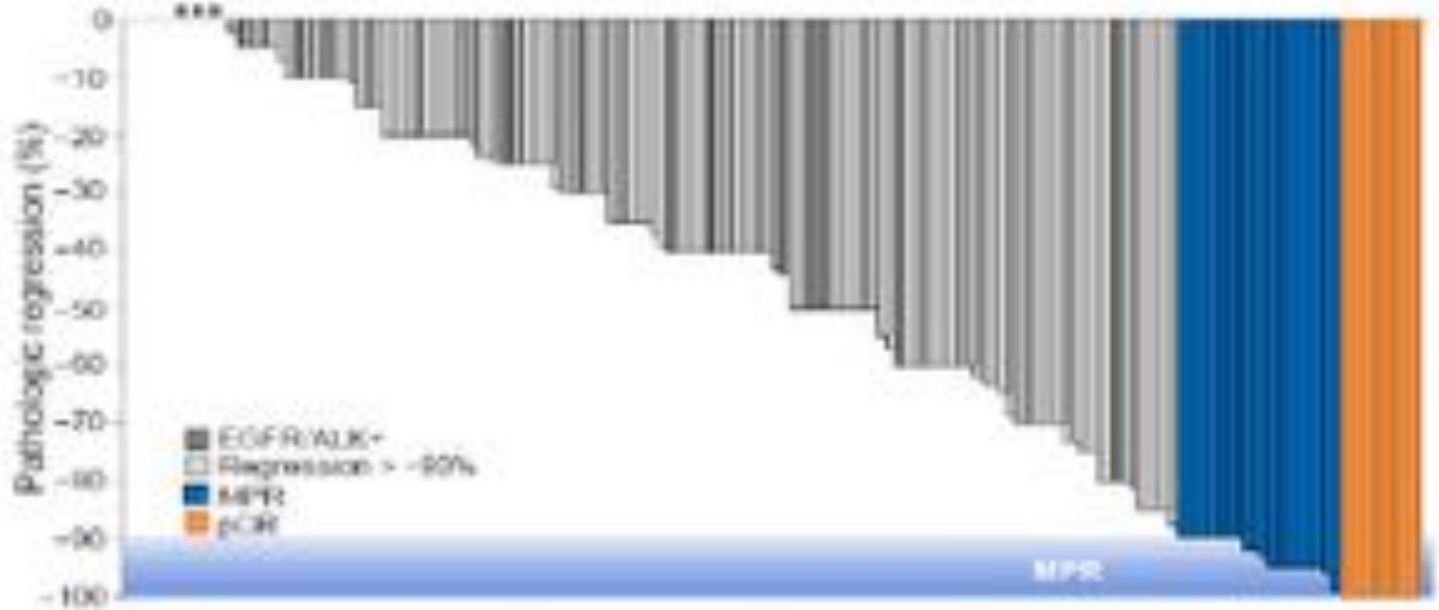
WN William et al. J Thorac Oncol. 2013 Feb; 8(2): 222-228

Neoadjuvant nivolumab is feasible, safe and active in operable NSCLC



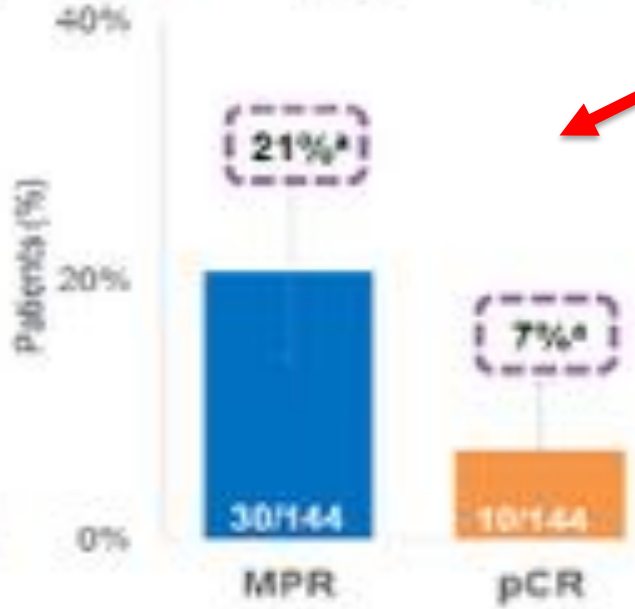
MPR to neoadjuvant atezolizumab in the LCMC3 study

Pathologic response in surgery population (n=159)



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

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



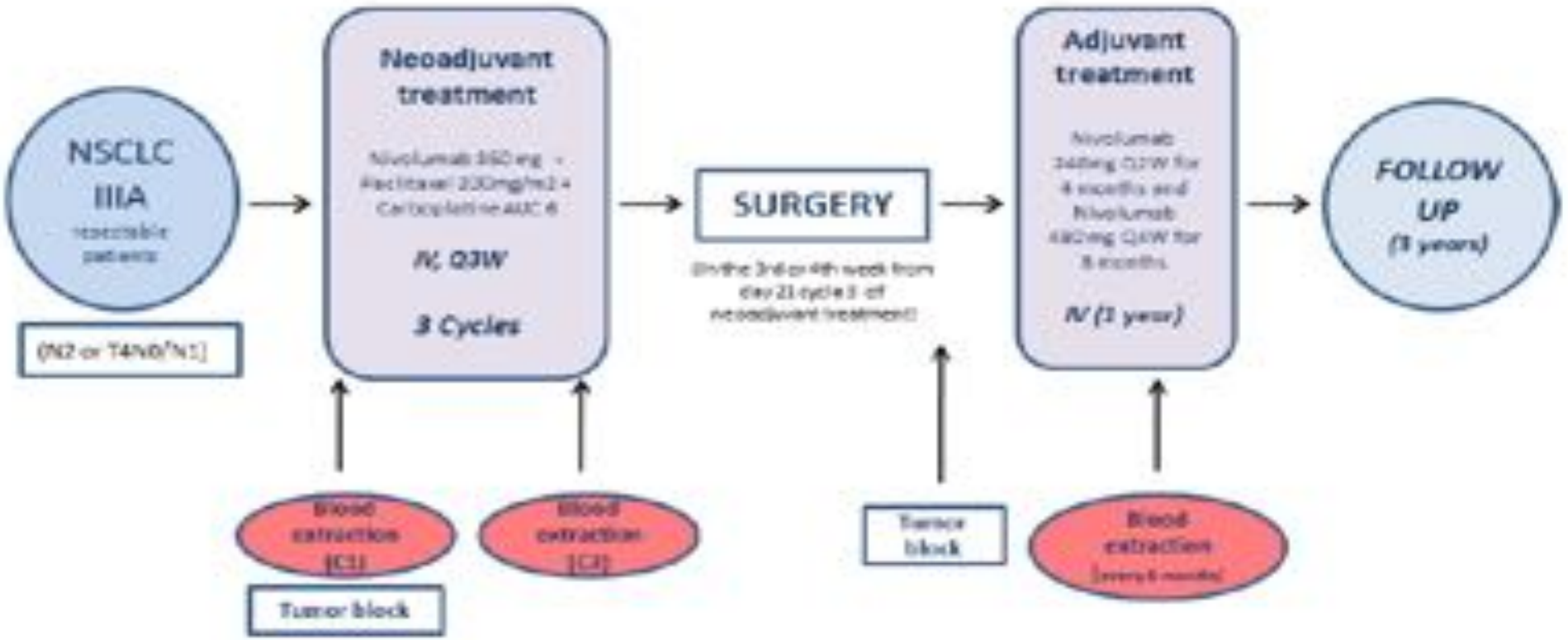
Lee JM, *et al.* WCLC 2021

Presented by Dr Jay M. Lee LCMC3: Neoadjuvant Atezolizumab in Resectable NSCLC JANUARY 29-31, 2021 | WORLDWIDE VIRTUAL EVENT

Neoadjuvant Chemo-Immunotherapy
NADIM: Study Design & Endpoints

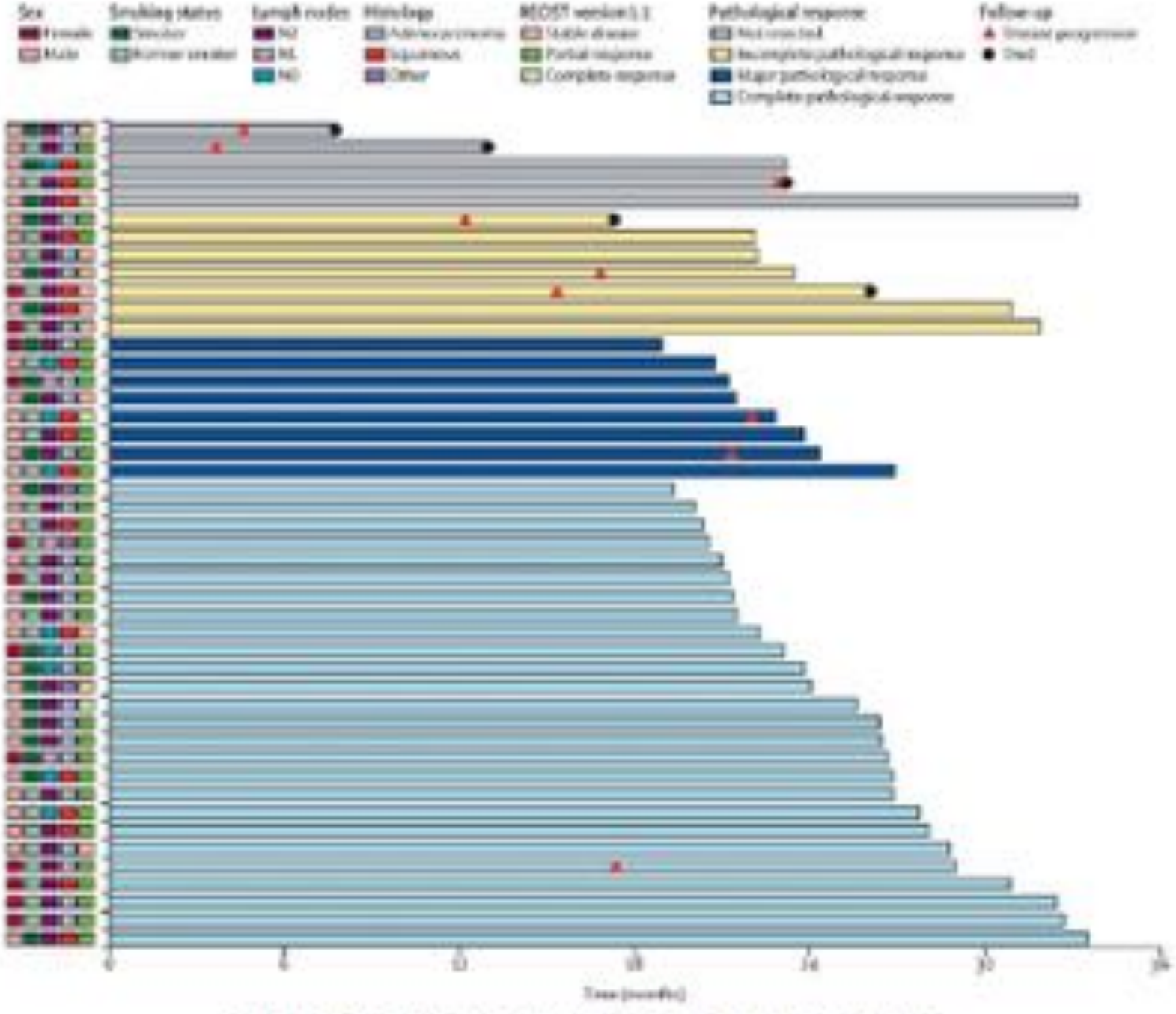
Primary Endpoint:
PFS at 24 months

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



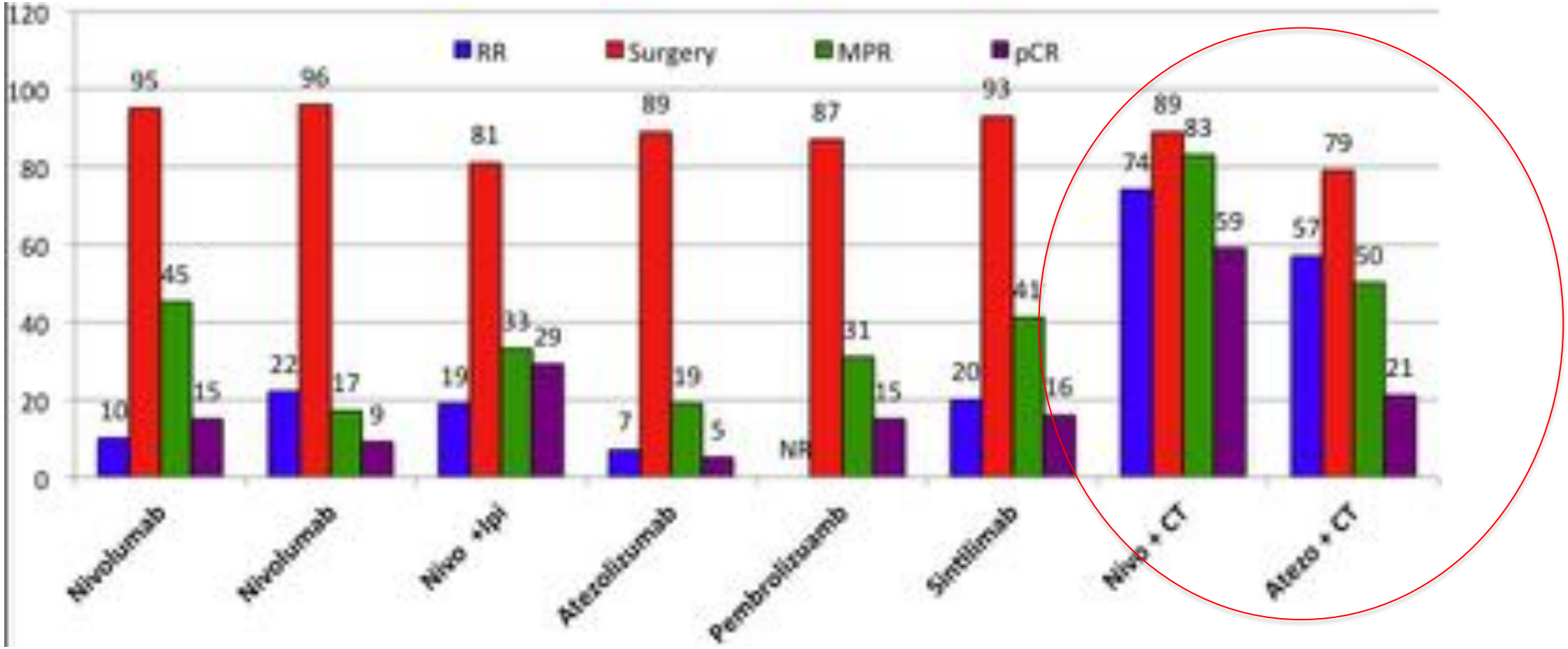
Key Results - NADIM

- 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**

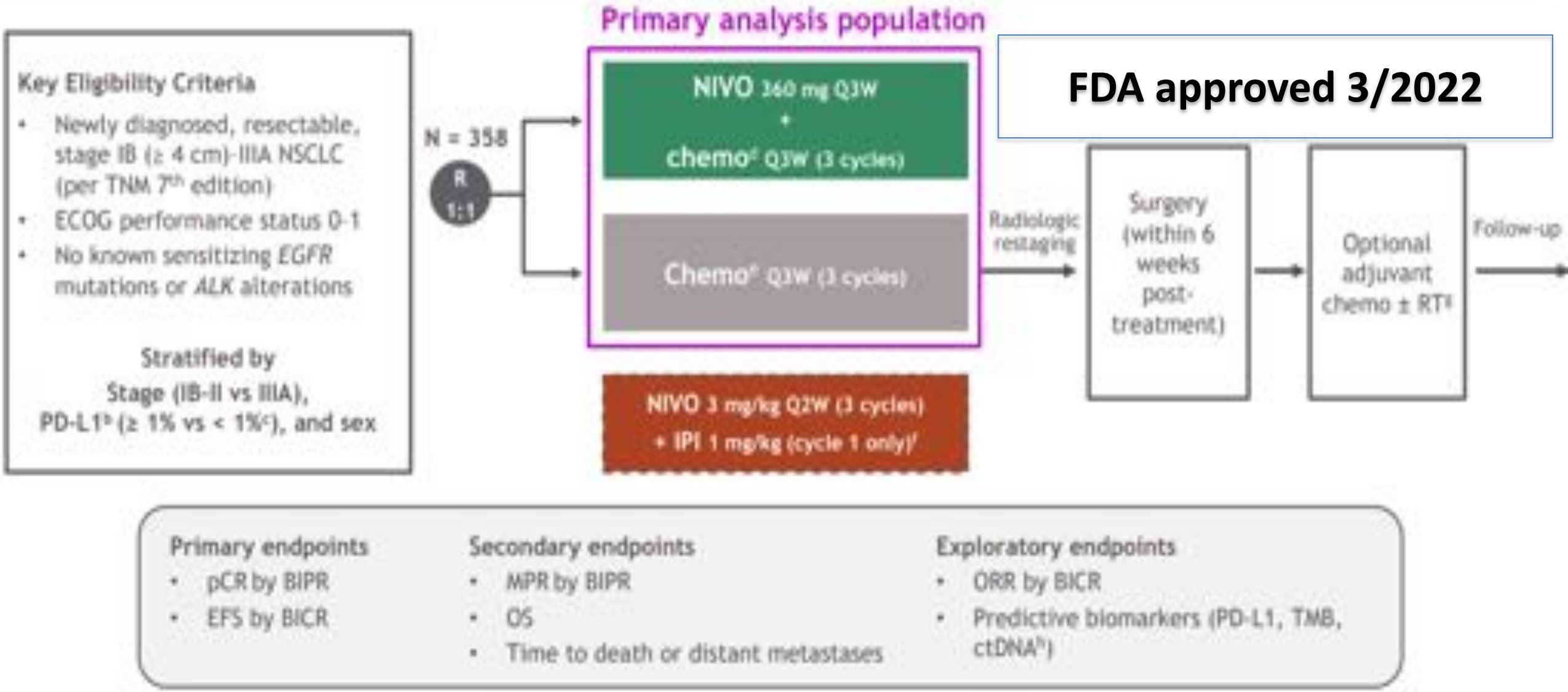


*2 pts elected not to have surgery, 3 pts had progressive disease

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



CheckMate 816 study design[a]

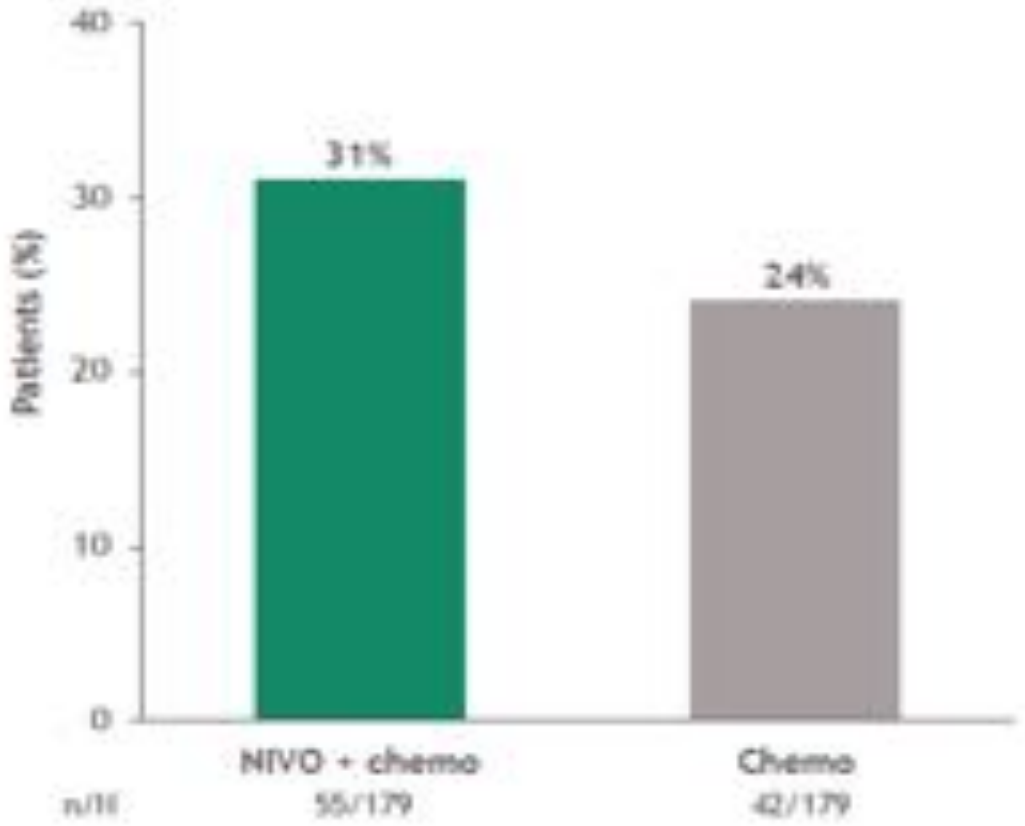


Objective response rate and radiographic down-staging

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)

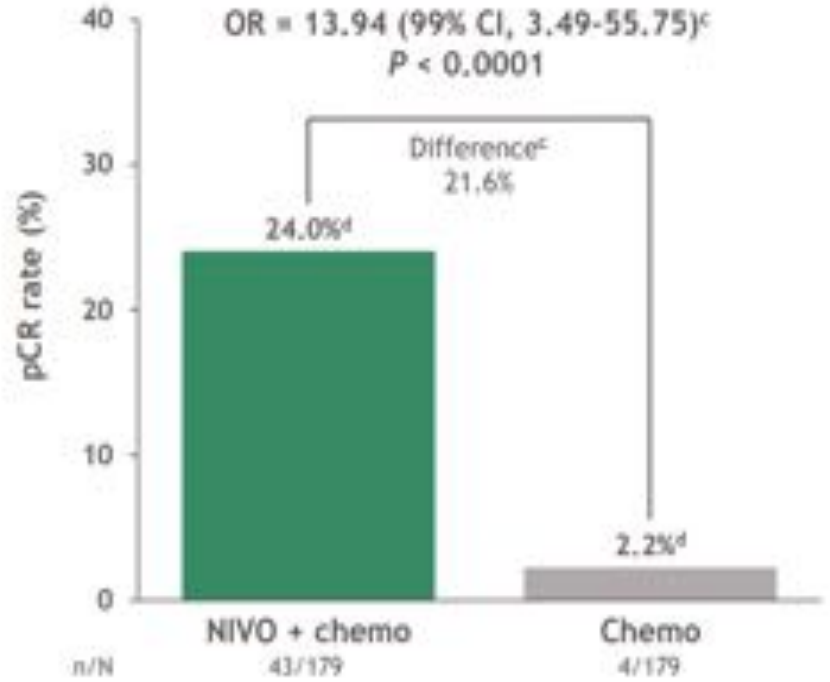
Patients with radiographic down-staging[c]



[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.

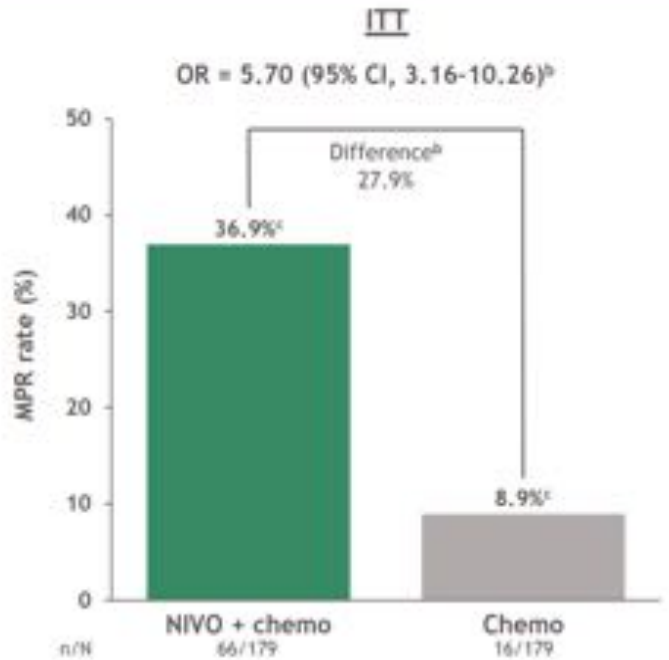
Primary endpoint: pCR[a] rate with neoadjuvant NIVO + chemo vs chemo

Primary endpoint: ITT (ypT0N0)[b]



CheckMate 816: pCR with neoadjuvant NIVO + chemo in resectable NSCLC

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.

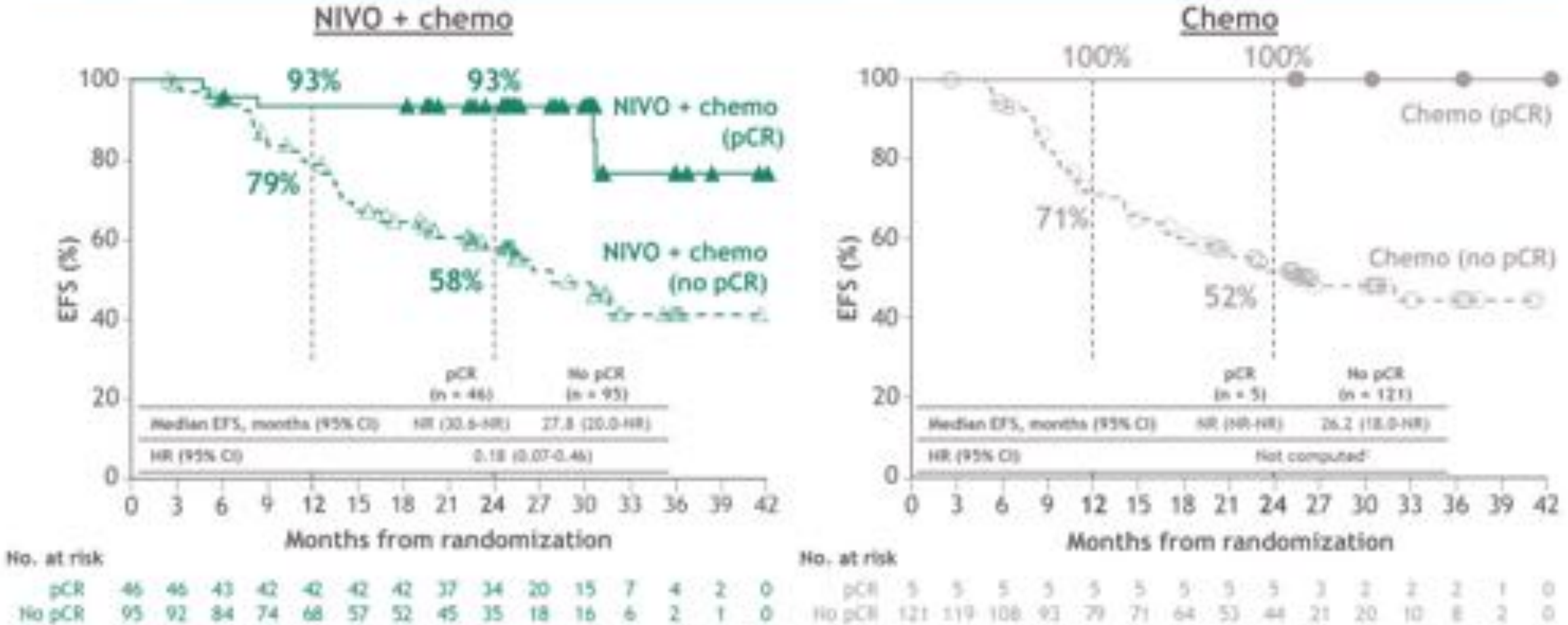
CheckMate 816 Summary—Neoadjuvant Nivolumab Plus Chemotherapy vs Chemotherapy for Resectable NSCLC

- **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

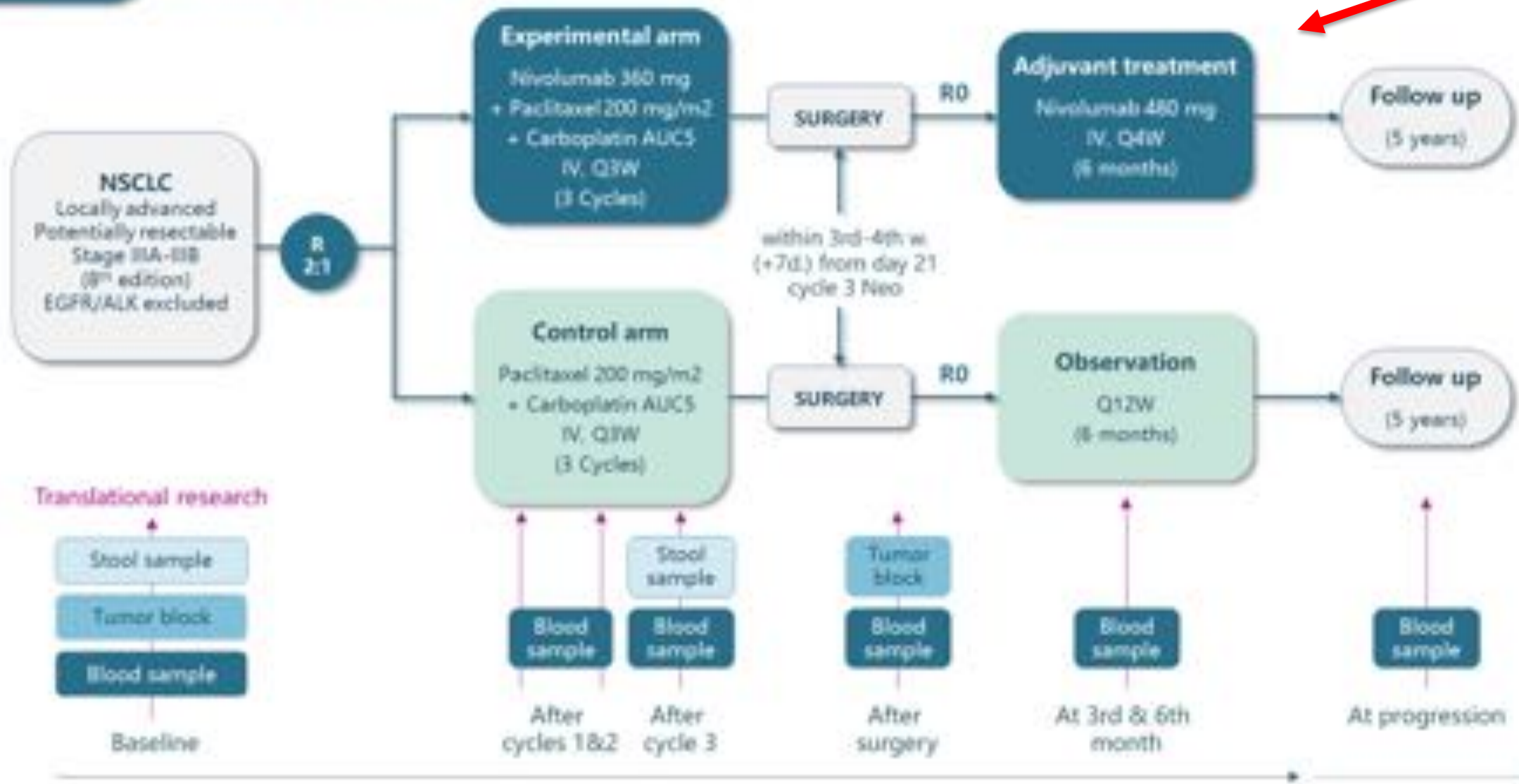


- EFS was also improved in patients with MPR[b] in the primary tumor compared with those without; HR (95% CI) was 0.26 (0.14-0.50) for NIVO + chemo and 0.48 (0.22-1.05) for chemo, respectively

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

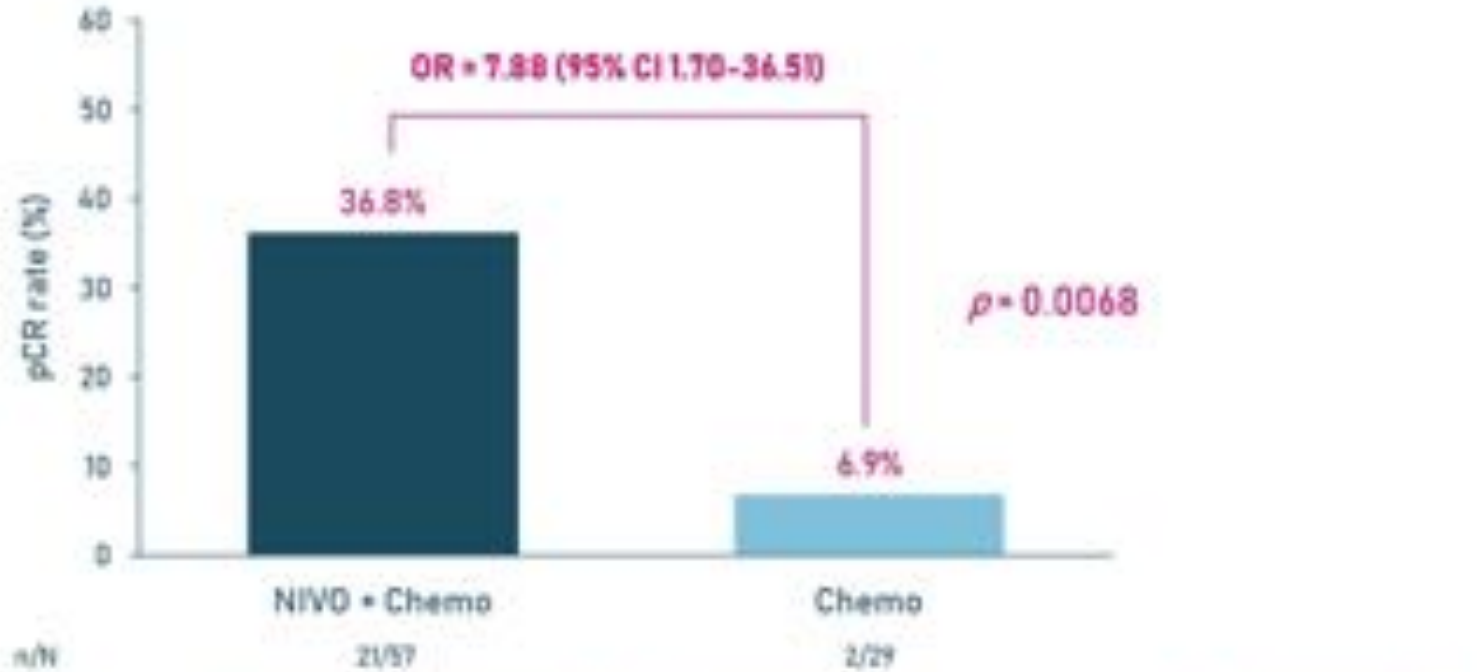


NADIM II (NCT03081159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

Presented by: Mariano Provencio MD, PhD.
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

NADIM II Primary endpoint - pCR

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

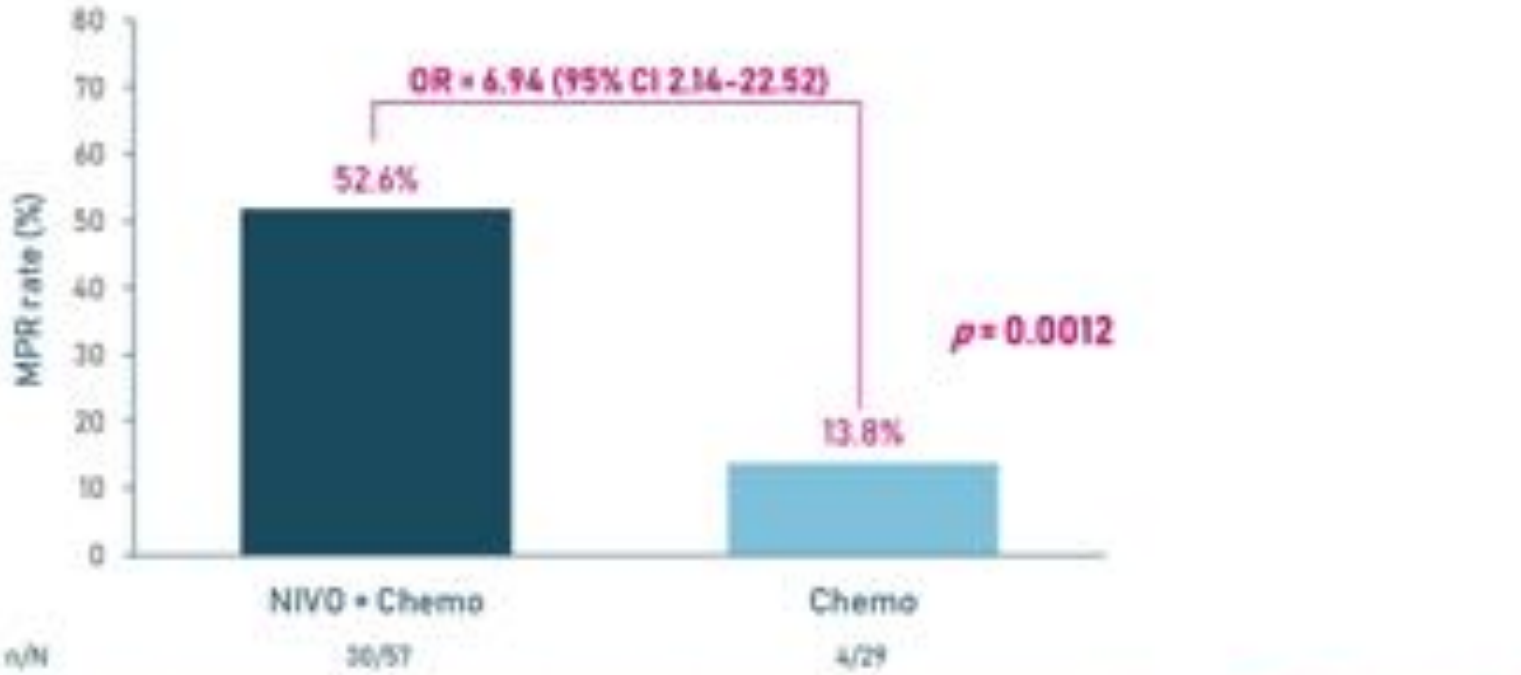


[a]pCR was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders
Chemo, chemotherapy; ITT, intention-to-treat; Nivo, nivolumab; pCR, pathological complete response; RR, risk ratio

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

NADIM II 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 (1.74-4.81)

[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

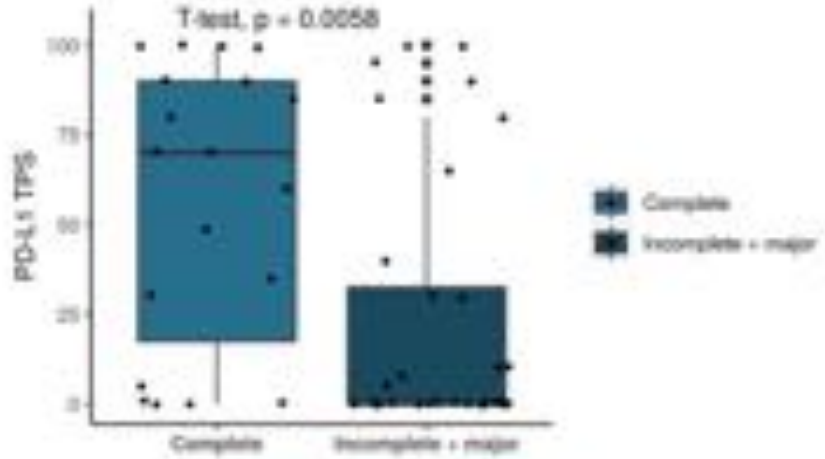
Chemo, chemotherapy; ITT, intention-to-treat; MPR, major pathological response; Nivo, nivolumab; RR, risk ratio

Presented by: Mariano Provencio MD, PhD.
Hospital Puerta de Hierro Majadahonda-Madrid; SPAIN
Spanish Lung Cancer Group

NADIM II 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

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

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

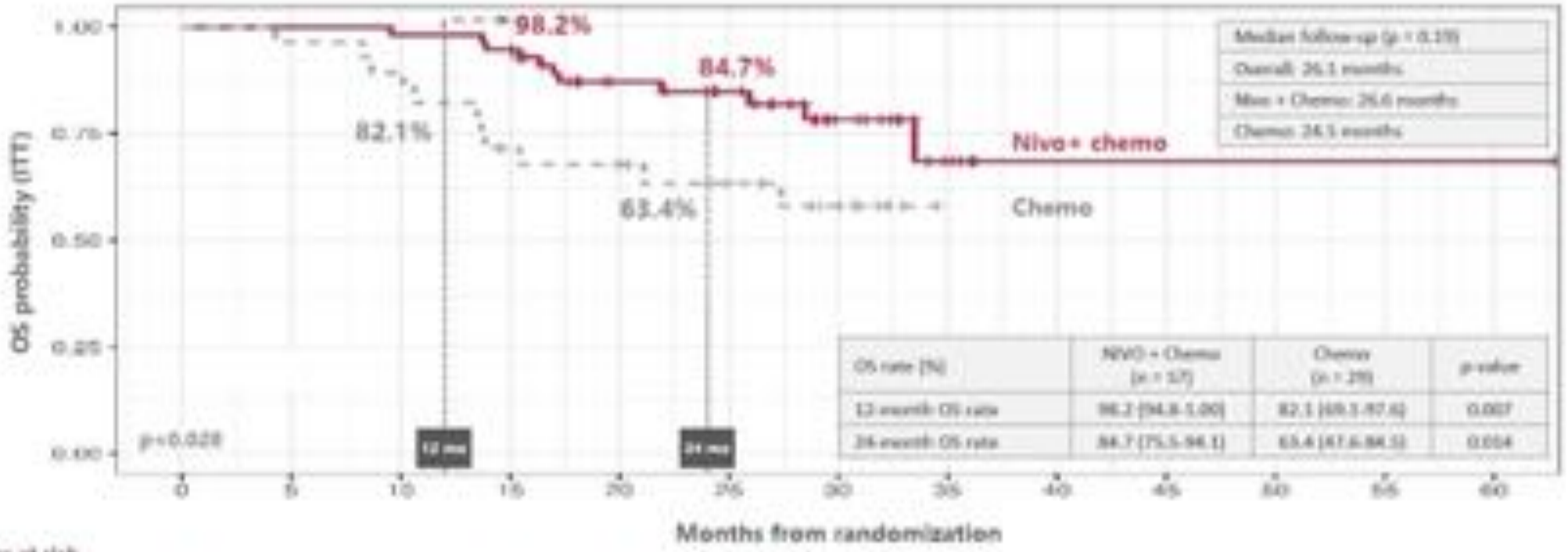
Dr. Mariano Provencio

Hospital Universitario Puerta de Hierro-Majadahonda, Madrid

SPAIN

NADIM II (NCT03081559) 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

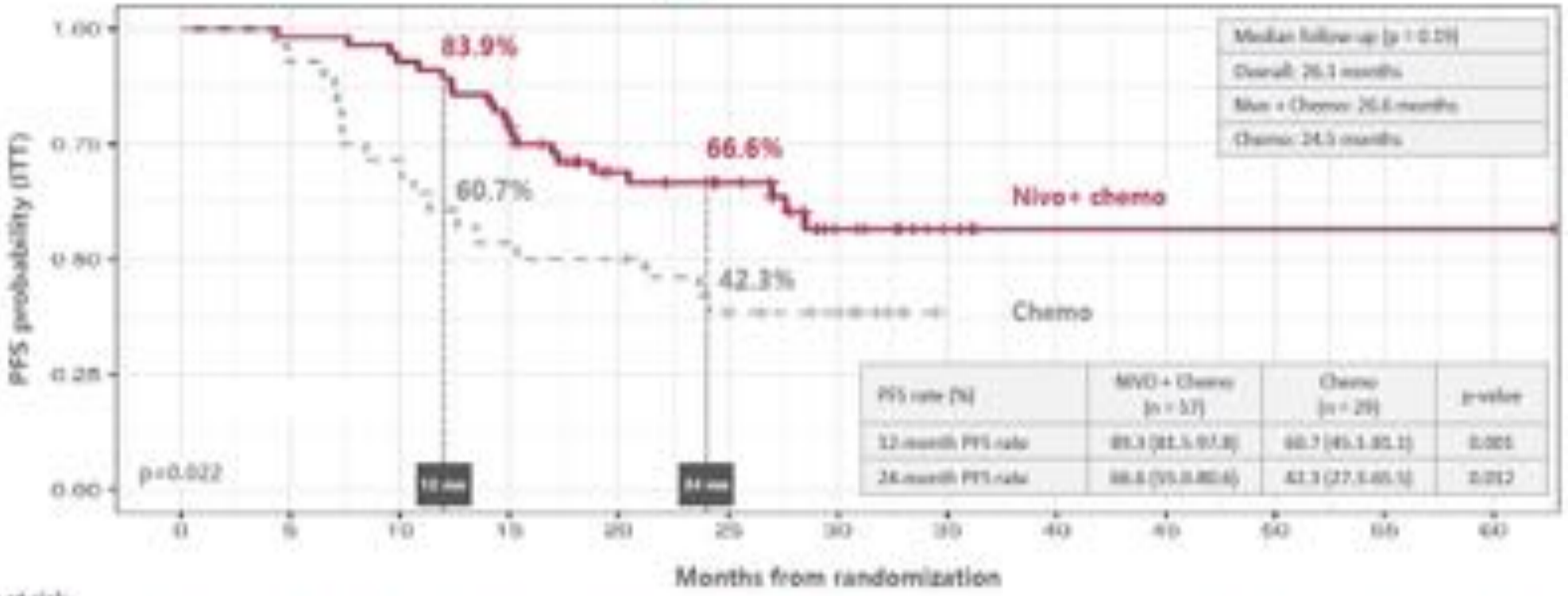


Number at risk

Nivo + chemo	58	56	55	53	37	33	15	5	1	1	1	1	1
Chemo	29	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



PFS rate (%)	MVD + 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 (27.5, 65.1)	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

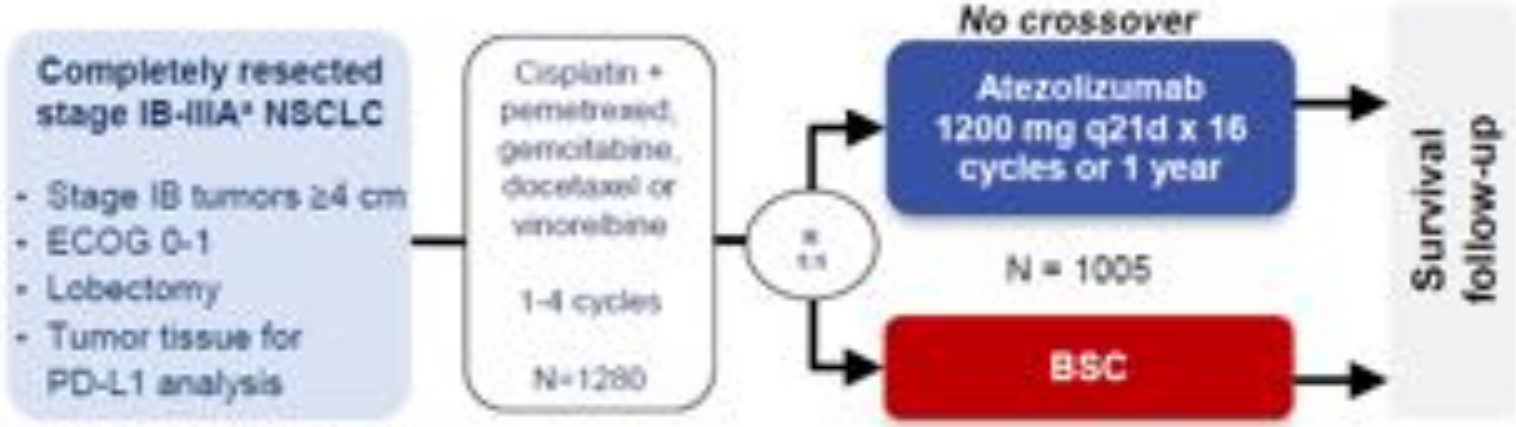
IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

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

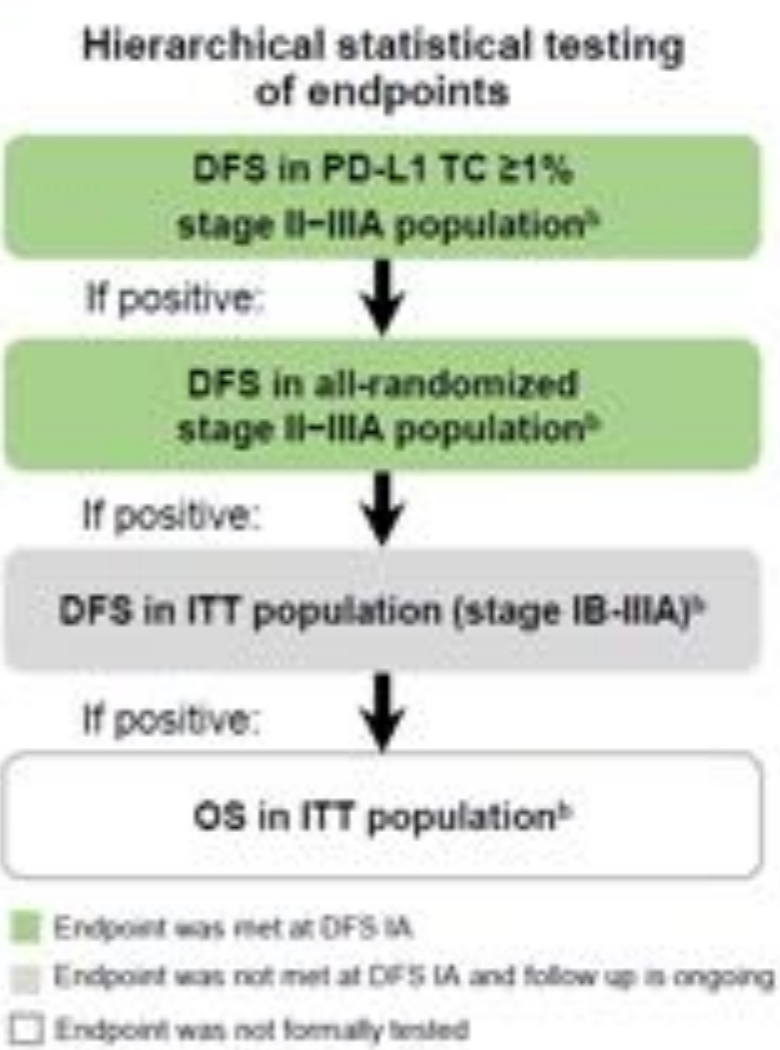


Stratification factors
- Sex | Stage | Histology | PD-L1 status

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.

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

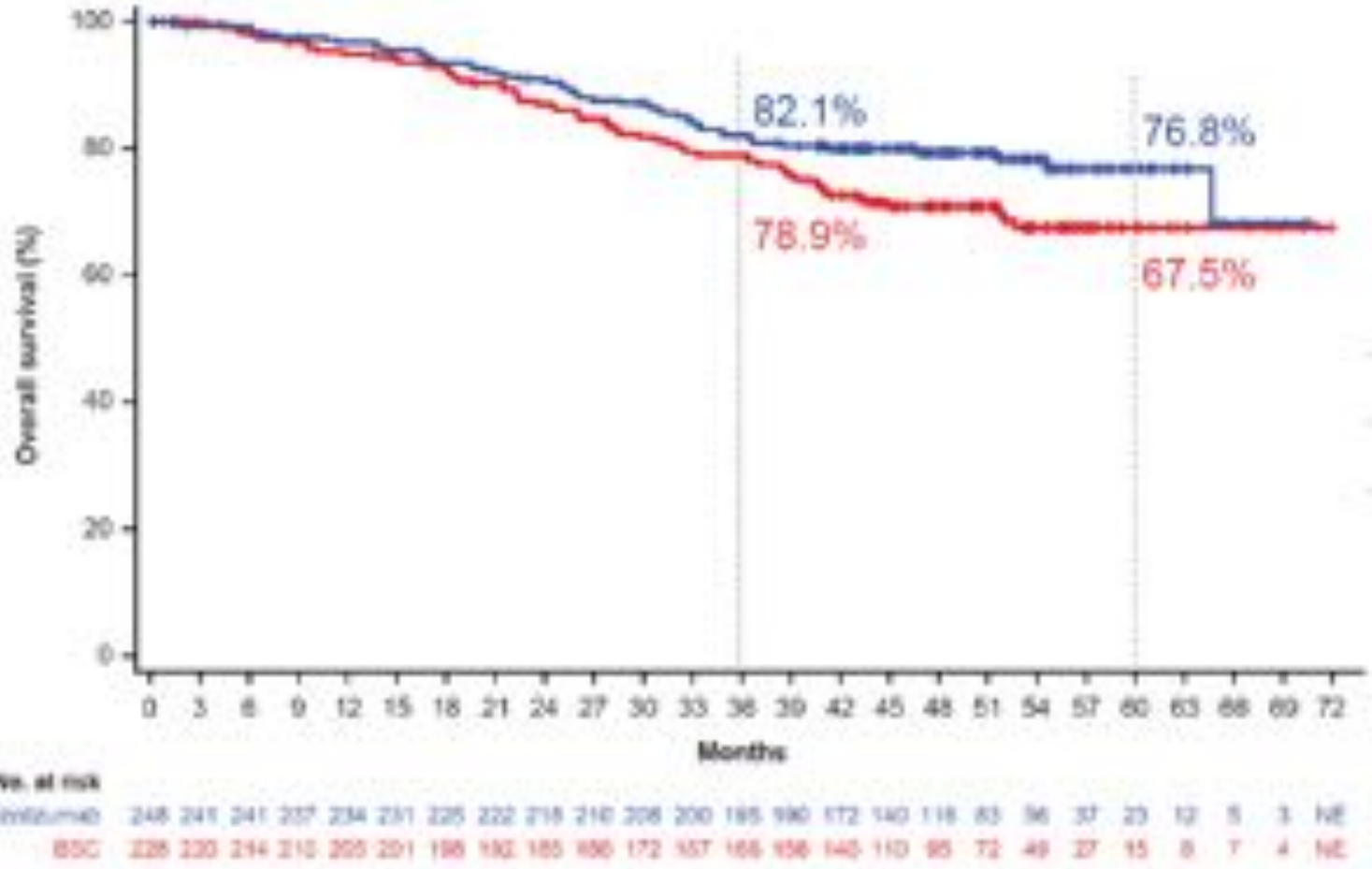
- **OS data** were not mature (event to patient ratio in ITT was 19% in atezolizumab arm, 18% in BSC arm)
  - PD-L1 TC ≥1% stage II-IIIA population: OS HR, 0.77 (95% CI: 0.51, 1.17)[a]
  - All-randomised stage II-IIIA population: OS HR, 0.99 (95% CI: 0.73, 1.33)[a]
  - ITT (randomised stage IB-IIIA)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



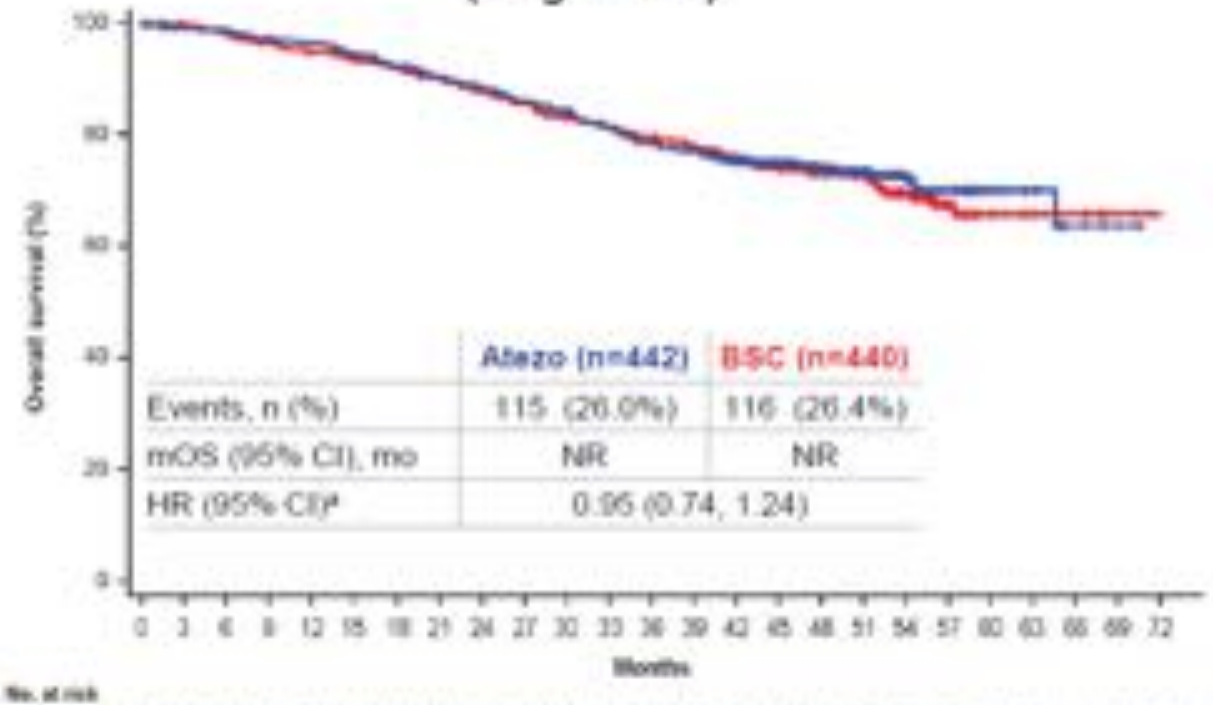
	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[b]	0.71 (0.49, 1.03)	

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)

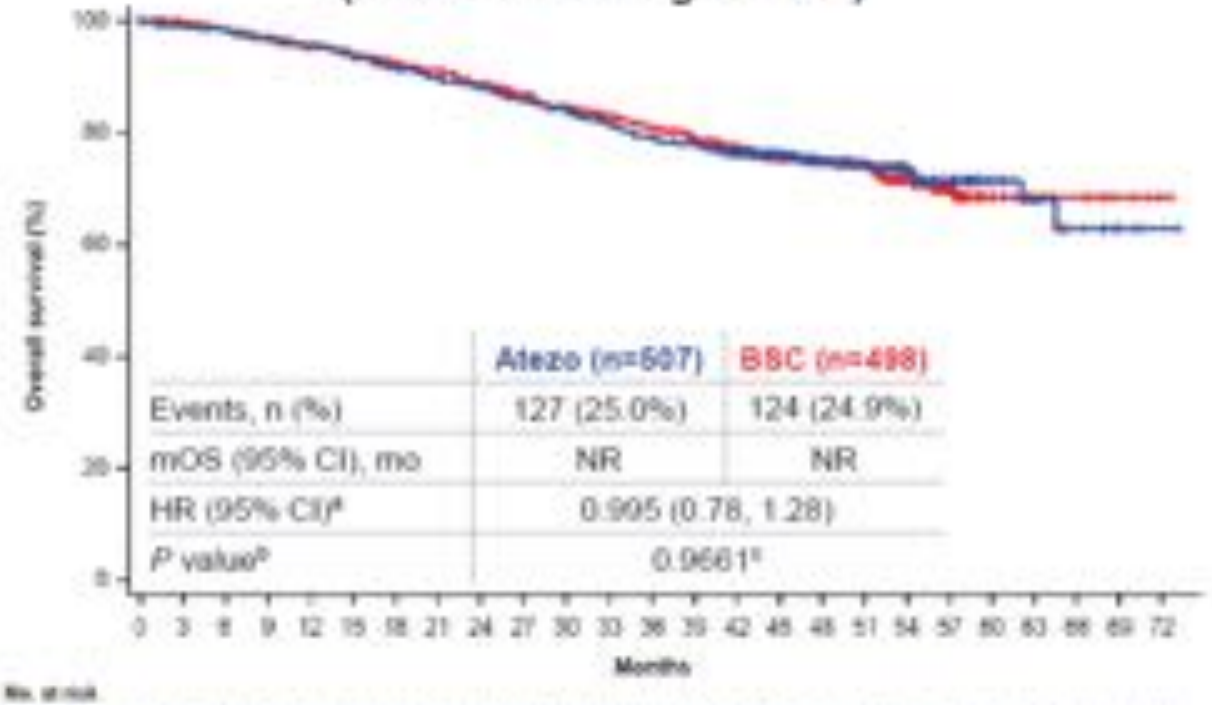


	Atezo (n=442)	BSC (n=440)
Events, n (%)	115 (26.0%)	116 (26.4%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.96 (0.74, 1.24)	

No. at risk

Atezo/durva	442	423	428	423	416	409	399	399	378	367	359	344	332	323	297	228	179	128	89	59	27	15	9	3	NE
BSC	440	426	419	403	396	389	382	372	362	350	337	326	320	310	279	213	179	125	87	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

Atezo/durva	507	492	488	479	472	463	456	450	430	419	406	390	381	372	328	262	203	144	96	61	33	17	8	4	1
BSC	498	484	473	462	452	444	437	428	417	406	391	381	371	357	325	252	207	146	101	67	23	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

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

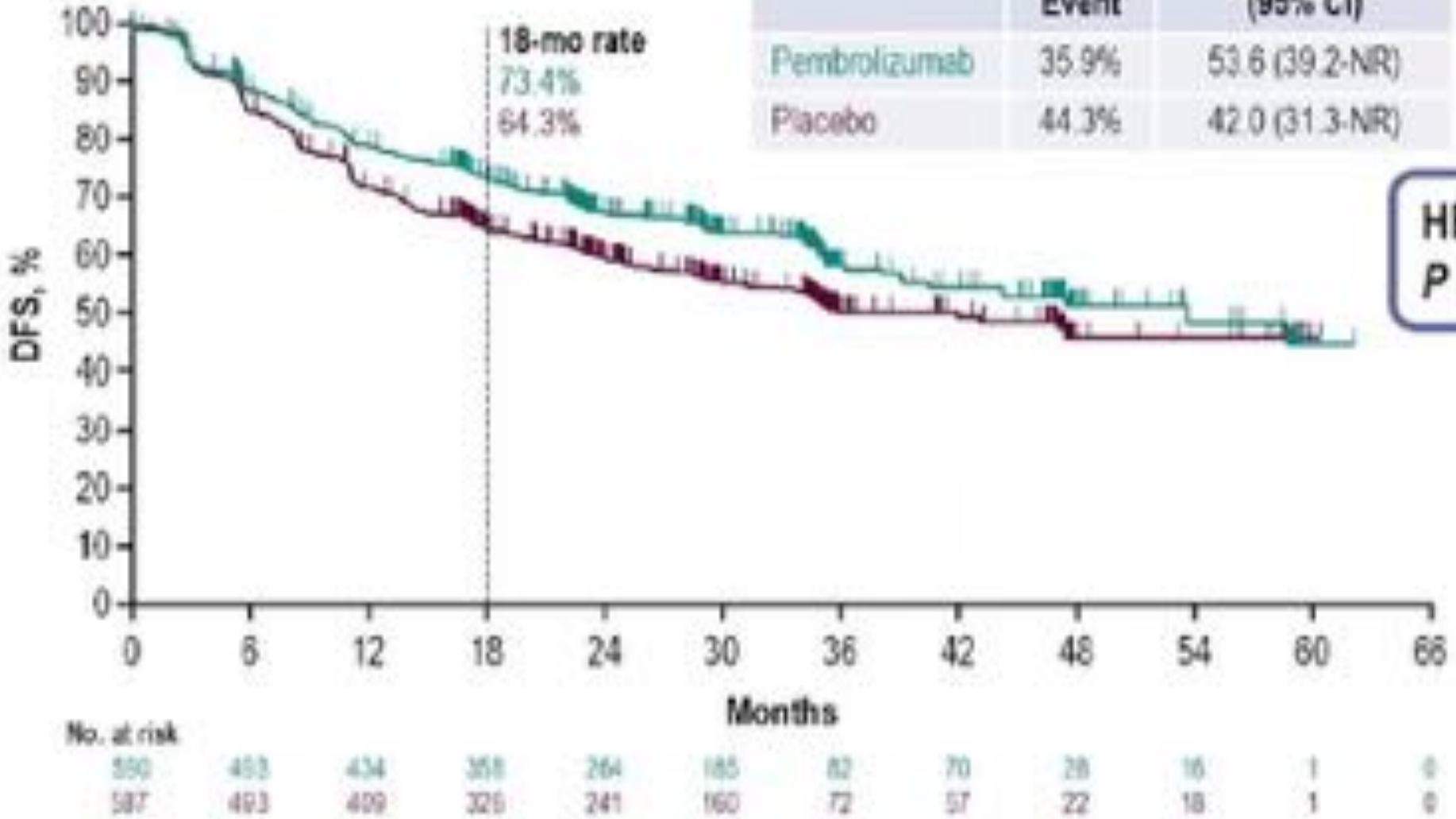
Secondary End Points

- 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

ClinicalTrials.gov number: NCT02578433

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)

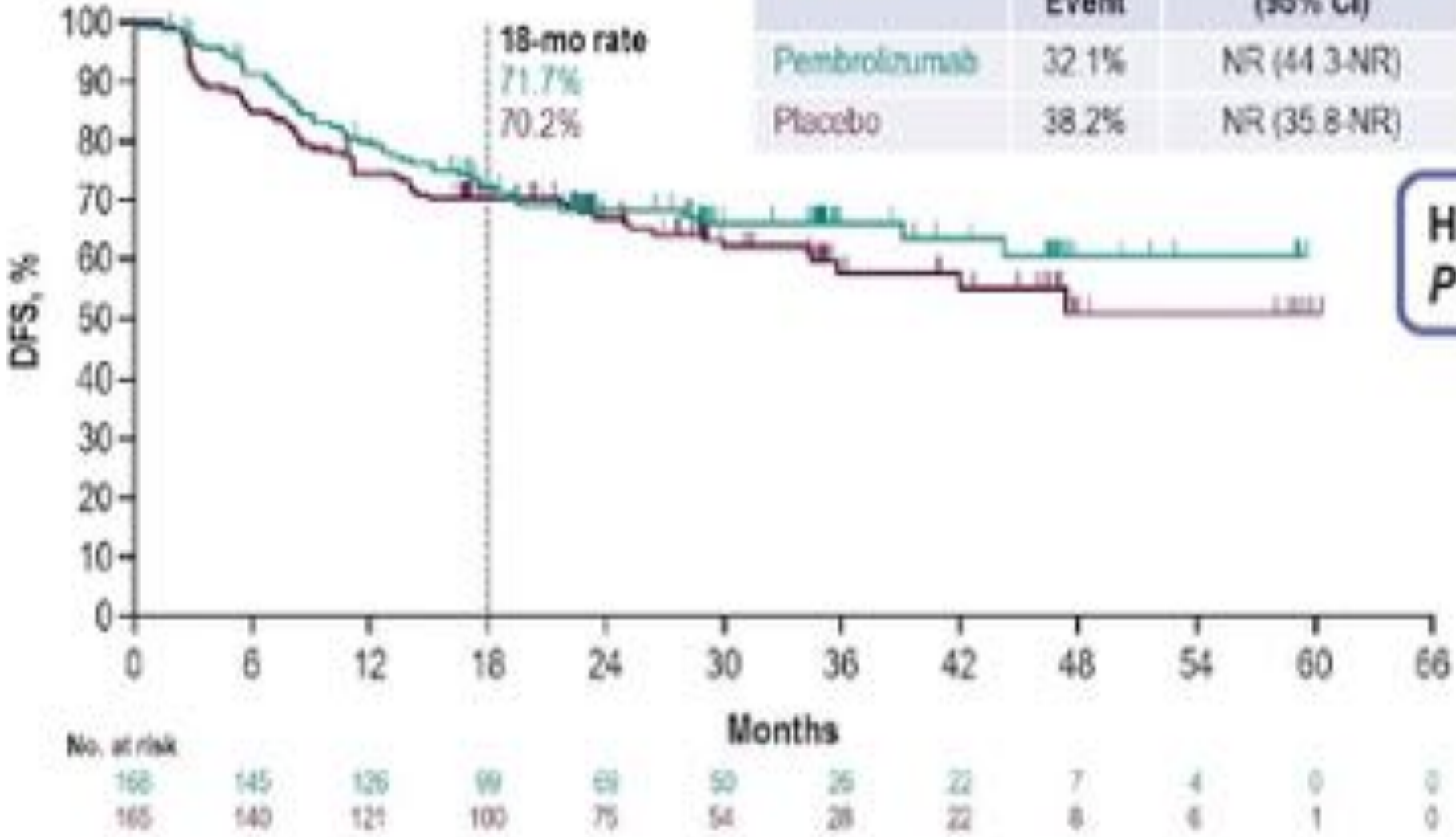


HR 0.76 (95% CI, 0.63-0.91)
***P* = 0.0014**

Response assessed per RECIST v1.1 by investigator review
Data cutoff date: September 30, 2021

DFS, PD-L1 TPS ≥50% Population

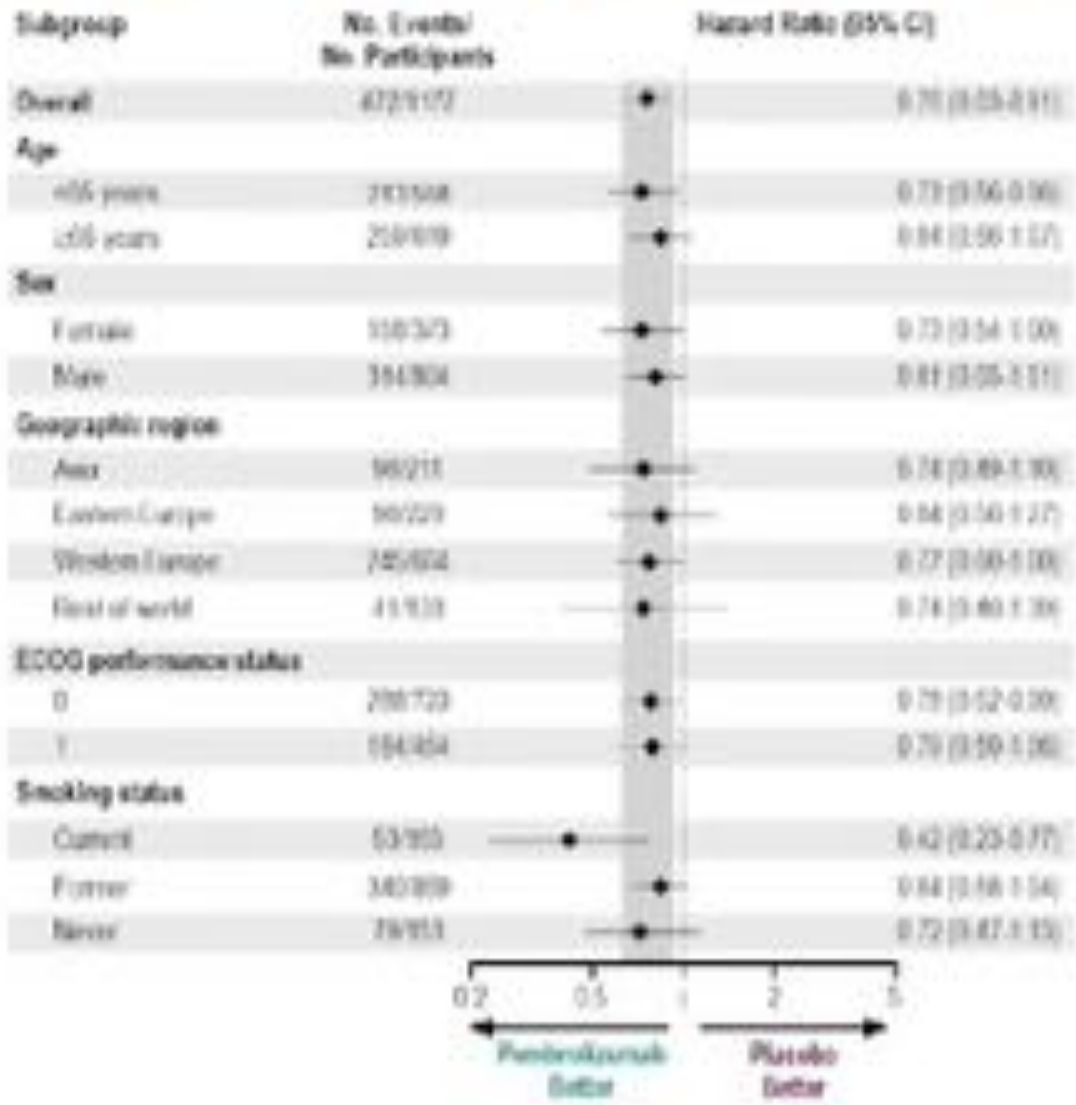
	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)

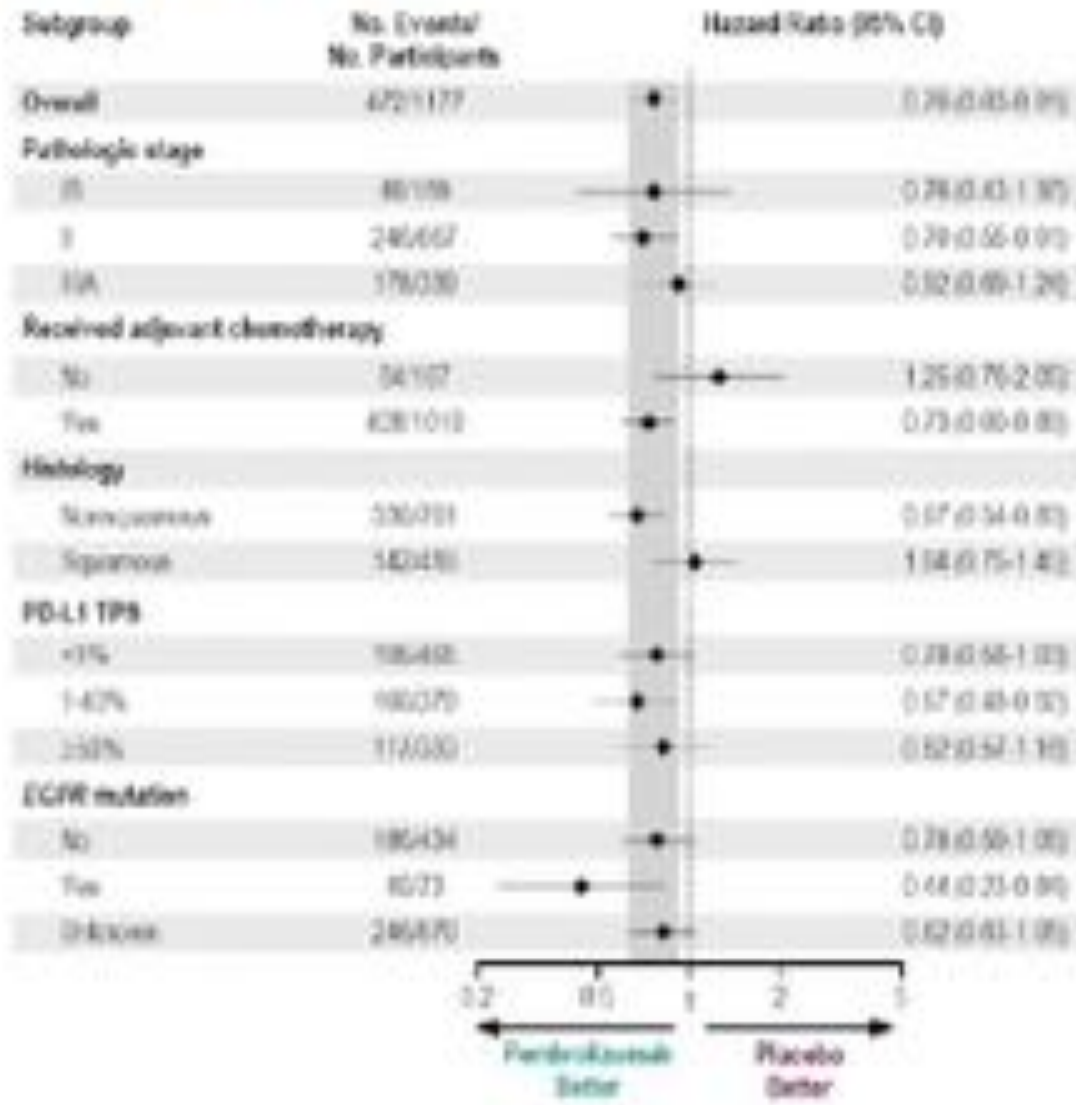


HR 0.82 (95% CI, 0.57-1.18)
P = 0.14

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

DFS in Key Subgroups, Overall Population



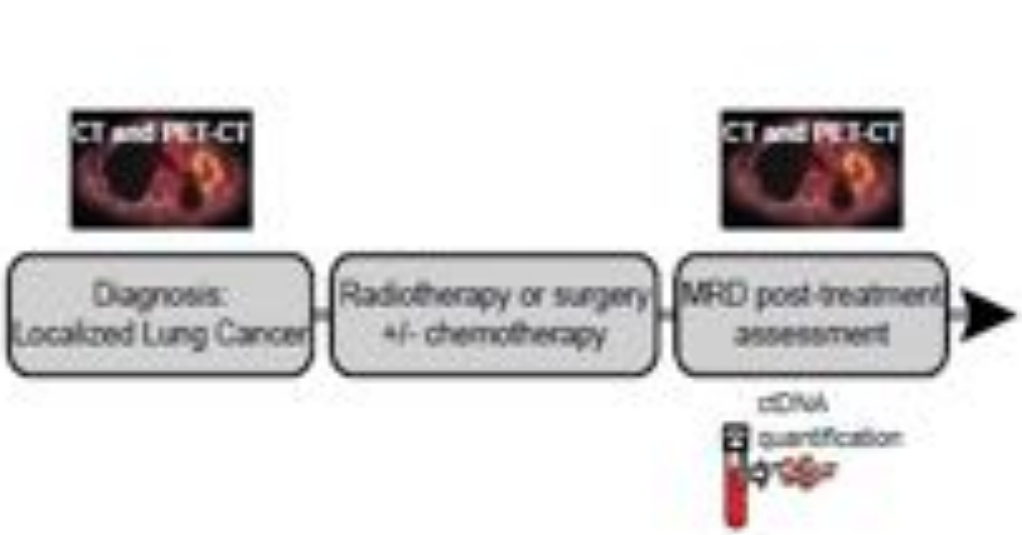


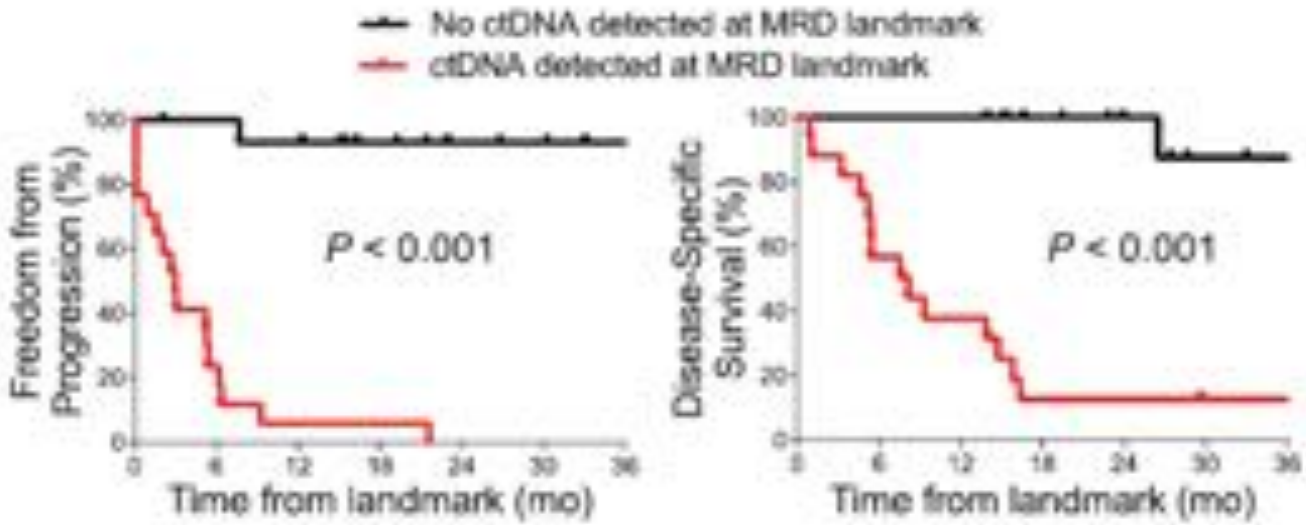
Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

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

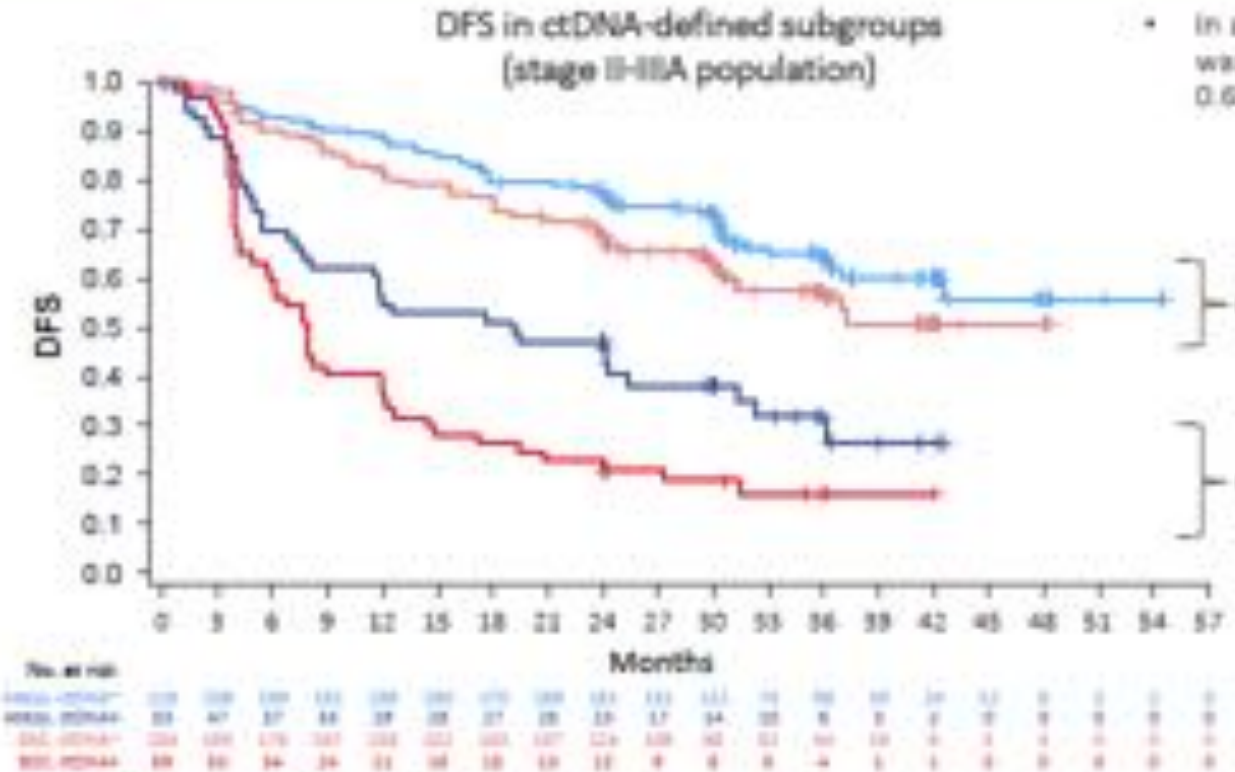




Residual ctDNA after completion of therapy is associated with an extremely high risk of recurrence

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

Study Chair
Jacob Sands, MD
450 Brookline Ave
Boston, MA 02215
Tel: 617-632-6049 Fax: 617-582-7199

Community Onc Co-chair
Luis Raez, MD
Memorial Cancer Institute

Thoracic Surgery Co-chair
Dennis Wigle, MD
Mayo Clinic

Correlatives Co-chair
Geoffrey Oxnard, MD
Dana Farber Cancer Institute

Medical Oncology Co-Chair
Govindan Ramaswamy, MD
Tel: 314-362-5737

Radiation Oncology Co-Chair
Joseph K. Salama, MD
Tel: 888-275-3853

Quality of Life Co-Chair
Apar Ganti, MD
Tel: 402-559-8300

Primary Statistician
Sumithra Mandrekar, PhD

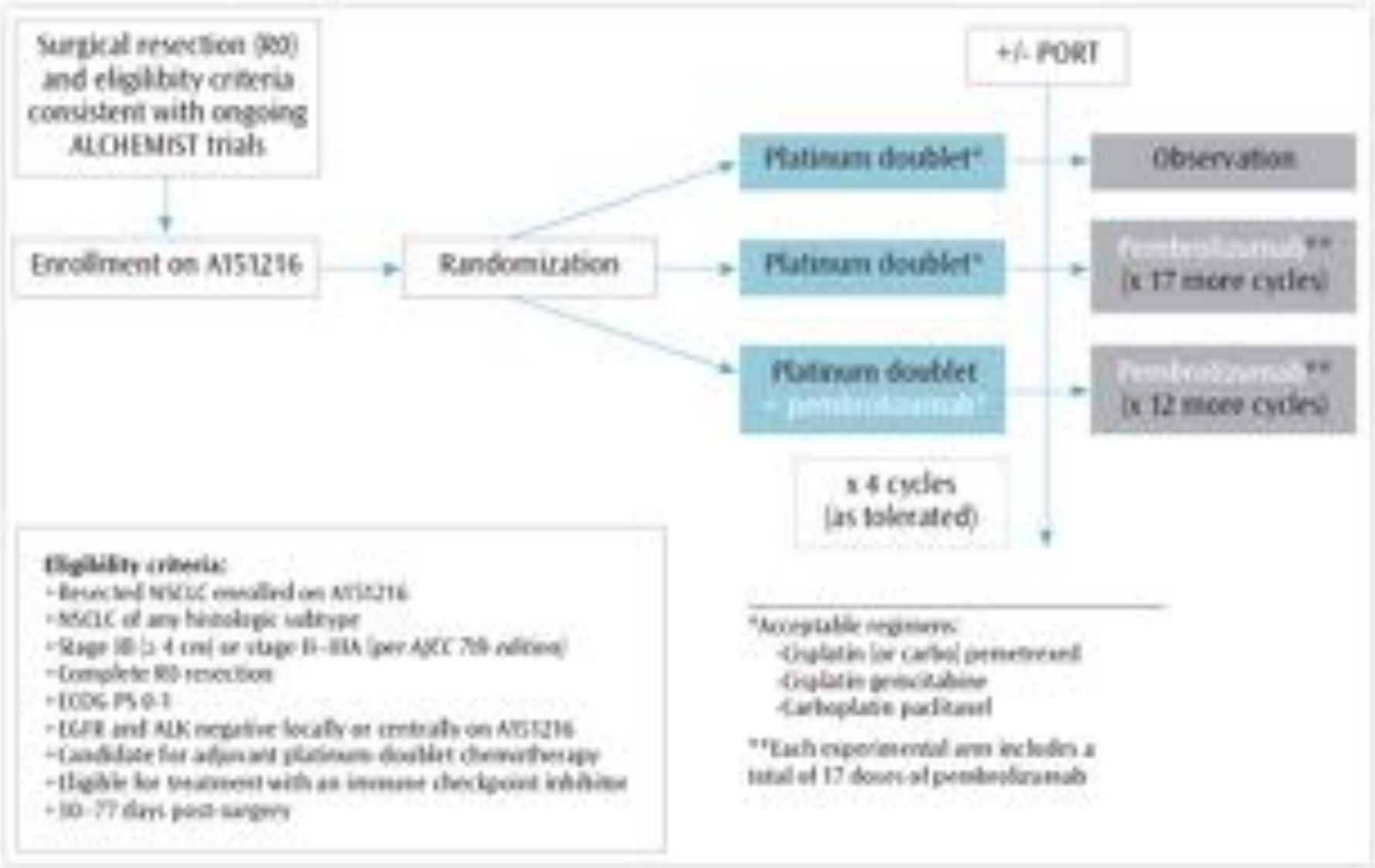
QOL Statistician
Gina Mazza, PhD

Secondary Statistician
Nathan Foster, MS

Protocol Coordinator
Colleen Watt
Tel: 773-702-4670 Fax: 312-345-0117

Data Manager
Adam Eggert
Tel: 507-538-1760

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

Metastatic NSCLC with no actionable genes

First Line Lung Cancer Therapy with no actionable genes

NSQCC:

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]

SQCC:

- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]

NSQCC and SQCC:

- Cemiplimab/Chemotherapy [Empower Lung-3]

IO single Agent (NSQCC OR SQCC)

- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab [Empower Lung-1]

Immunotherapy combinations:

- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

ORR slightly in favor of combination

	KN 24 (TPS > 50%)	KN 42 (TPS > 50%)	IMPW 10 TC3/IC3 (>50% and >10%)	KN 407 (TPS > 50%)	KN 189 (TPS > 50%)
ORR	45%	39.5%	30.7%	60.3%	61.4%
DOR	Nr (1.8-20.6 m)	20.2 m	Nr (1.8-29.3m)	7.7 m (all patients)	11.2 m (all patients)

Reck M, NEJM 2016, Mok T et al, Lancet 2019, Paz Ares, NEJM 2018, Ghandi, NEJM 2018

Adverse Events

	KN-42		KN-24		KN-189		KN-407	
	Pembro	CT	Pembro	CT	Pembro + CT	CT	Pembro + CT	CT
All TRAE (%)	62.7%	89.9%	76.6%	90.0%	99.8%	99.0%	98.2%	97.9%
Grade 3-5 TRAE (%)	17.8%	41%	31.2%	53.3%	67.2%	65.0%	69.8%	68.2%
Discontinuation rate (any) (%)	9%	9.4%	13.6%	10.7%	27.7%	14.9%	23.4%	11.8%
Led to death	0.2%	0%	1.3%	2.0%	6.7%	5.9%	8.3%	6.4%

2022 ASCO ANNUAL MEETING

FDA

Outcomes of anti-PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score ≥50%: FDA Pooled Analysis

Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Vellanki[1], Nicole Drezner[1], Mathieu Luckson[1], Shenghui Tang[1], Martha Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration

[2]Oncology Center of Excellence, U.S. Food and Drug Administration

Oladimeji Akinboro, MD, MPH

Clinical trials of first-line Chemo-IO and IO regimens included in FDA pooled analysis

Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab + Ipilimumab****
CheckMate-9LA	**Nivolumab + Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy immunotherapy; IO=immunotherapy.
* Cohort G
** Control arms: Platinum-based doublet chemotherapy
*** Control arm in IMpower150: Bevacizumab plus platinum-based doublet chemotherapy

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

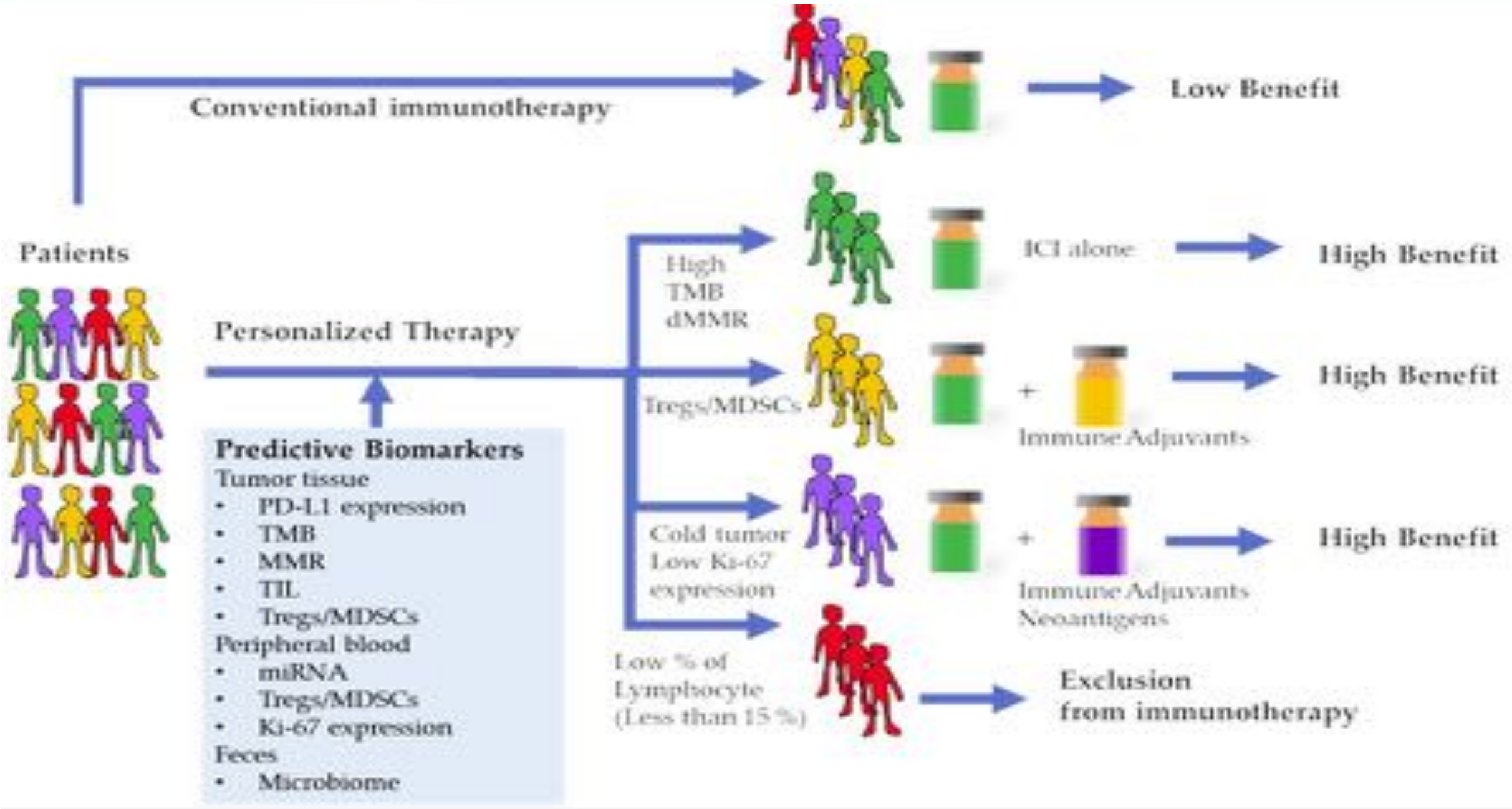
Exploratory OS, PFS, and ORR: NSCLC PD-L1 ≥50%

FDA

	Chemo-IO (*N*=455)		IO-alone (*N*=1,298)
OS			
Median, months (95% CI)	25.0 (19.0, NE)		20.9 (18.5, 23.1)
HR (95% CI)		0.82 (0.62, 1.08)	
PFS			
Median, months (95% CI)	9.6 (8.4, 11.1)		7.1 (6.3, 8.3)
HR (95% CI)		0.69 (0.55, 0.87)	
ORR			
% (95% CI)	61 (56, 66)		43 (41, 46)
Odds ratio		1.2 (1.1, 1.3)	

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR=hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.


Cancer
Immune-desert tumour
Tolerance
No priming
Immune-excluded tumour
Stromal interactions
Inflamed tumour
B cells
Regulatory T cells
Exhausted or hyper-exhausted T cells
Myeloid suppressors
Cancer-associated fibroblasts
Tumour cells
Metabolic ignorance

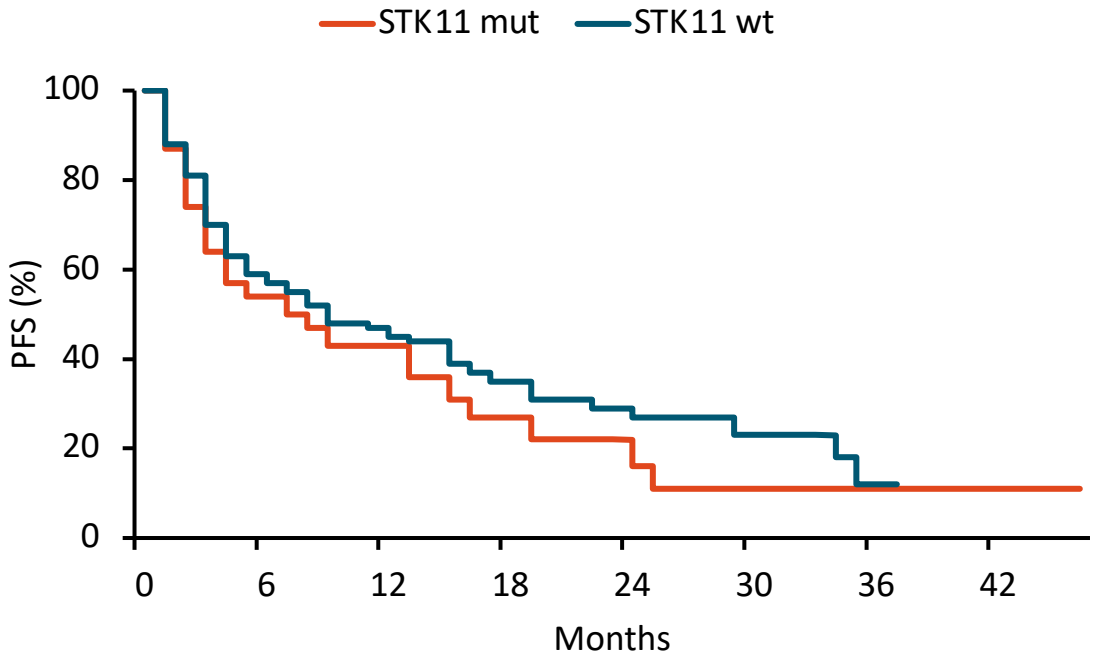

Conventional immunotherapy
Low Benefit
Patients
Personalized Therapy
High
TMB
dMMR
ICI alone
High Benefit
Tregs/MDSCs
+
Immune Adjuvants
High Benefit
Cold tumor
Low Ki-67
expression
+
Immune Adjuvants
Neoantigens
High Benefit
Low % of
Lymphocyte
(Less than 15 %)
Exclusion
from immunotherapy
Predictive Biomarkers
Tumor tissue
• PD-L1 expression
• TMB
• MMR
• TIL
• Tregs/MDSCs
Peripheral blood
• miRNA
• Tregs/MDSCs
• Ki-67 expression
Feces
• Microbiome

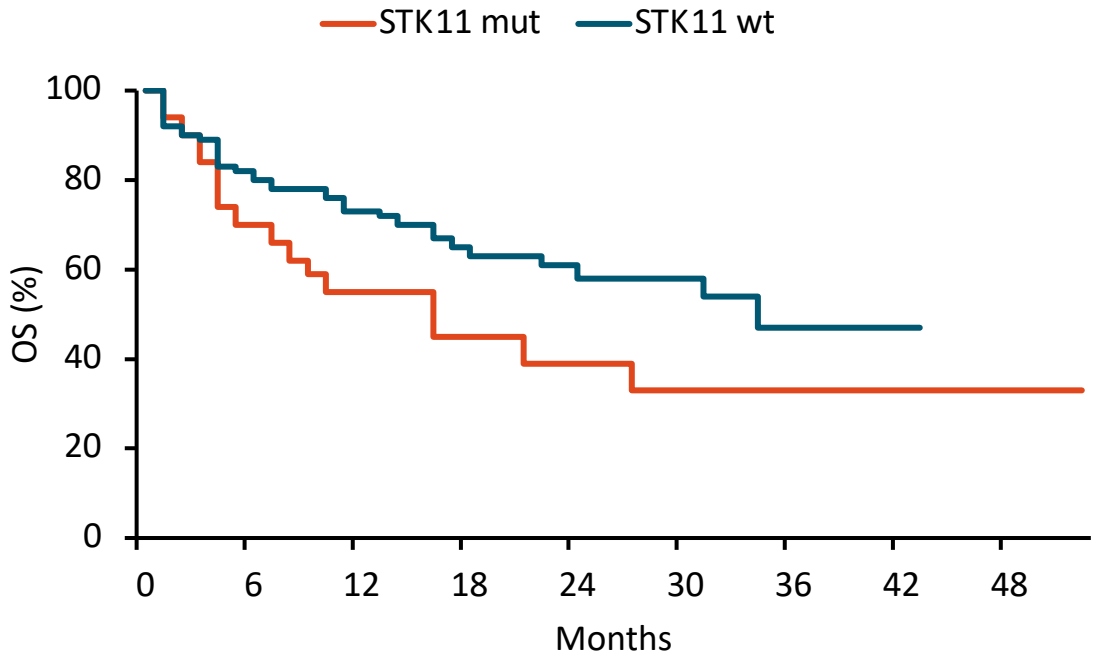
STK11/LKB1, KRAS mutations and immune-related adverse events as predictors of response to immunotherapy in lung cancer

Luis E. Raez, MD[1]; Richie Uba, PharmD[2,3]; Aaron North, PharmD[2,3]; Katerine Dumais, PharmD, MPH[1]; Hermán W. Powery II, PharmD, BCOP[1]; Gelenis Domingo, MD[1]; Brian Hunis, MD[1]; Paola Izquierdo, ARNP[1]; Frank Gentile, PharmD, BCOP[1]

[1]Memorial Cancer Institute, Pembroke Pines, FL; [2]Florida A&M University, Davie, FL; [3]Memorial Regional Hospital, Hollywood, FL

Results: PFS and OS by STK11 Status

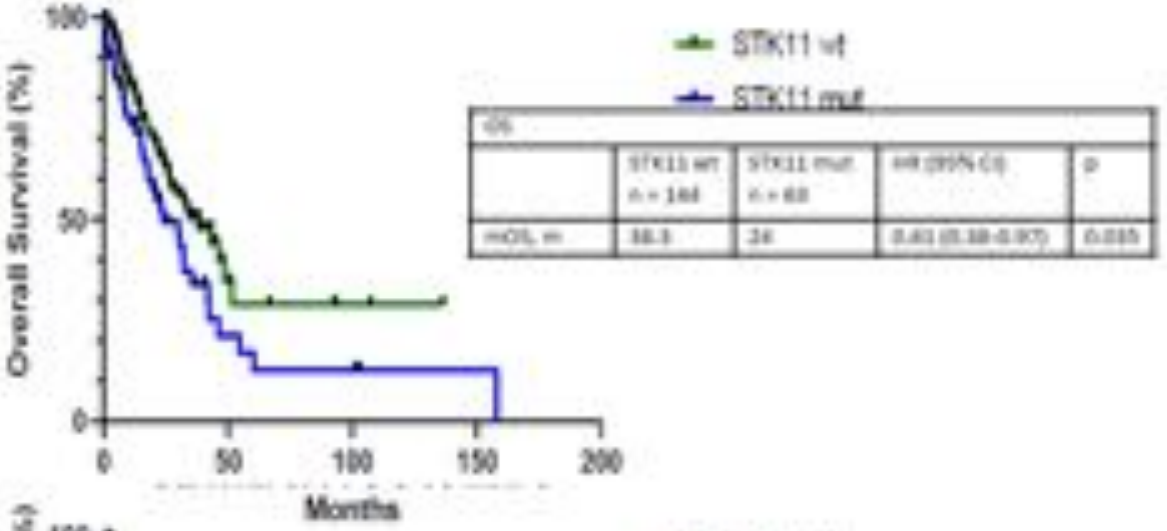




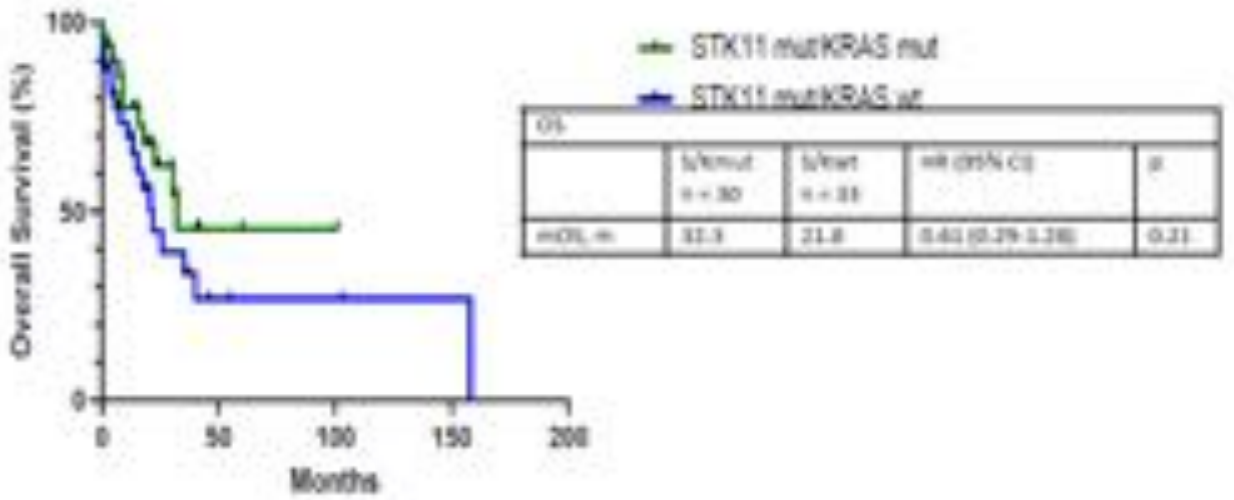
	STK11 wt n = 96	STK11 mut n = 31	HR (95% CI)	p
mPFS	6.3m	5.6m	1.35 (0.76-2.1)	0.35
12-m PFS	45%	43%	-	0.85

	STK11 wt n = 96	STK11 mut n = 31	HR (95% CI)	p
mOS	12.1m	8.6m	1.7 (1.0-3.6)	0.03
12-m OS	73%	55%	-	0.03

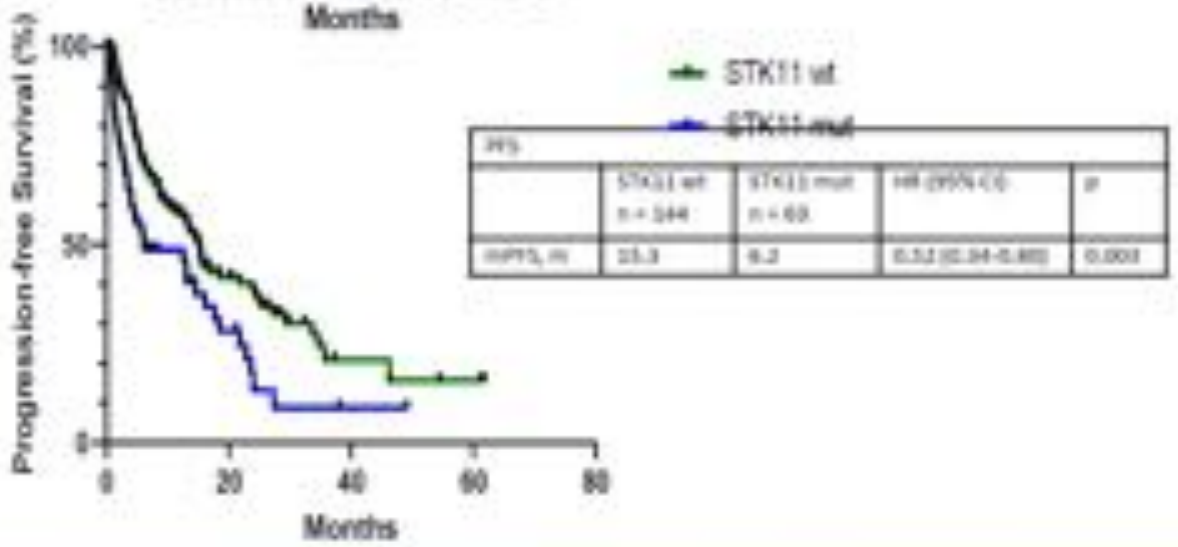
Favorable survival with co-mutation of STK11 and KRAS



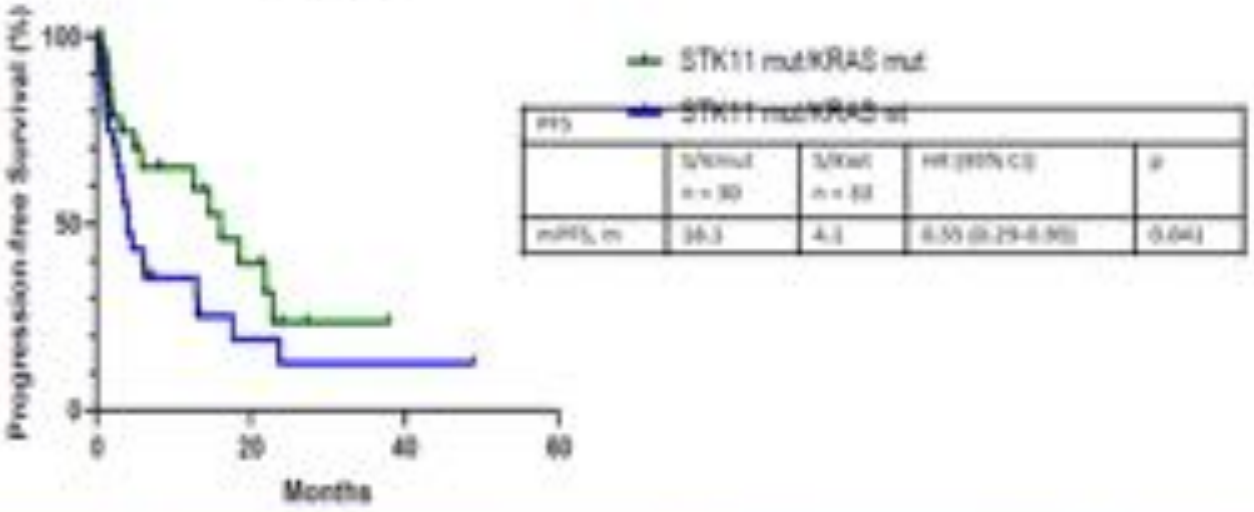
OS				
	STK11 wt n = 168	STK11 mut n = 63	HR (95% CI)	p
mOS, m	38.3	24	0.63 (0.46-0.87)	0.035



OS				
	S/Kmut n = 30	S/Kwt n = 33	HR (95% CI)	p
mOS, m	32.3	21.8	0.61 (0.29-1.28)	0.21



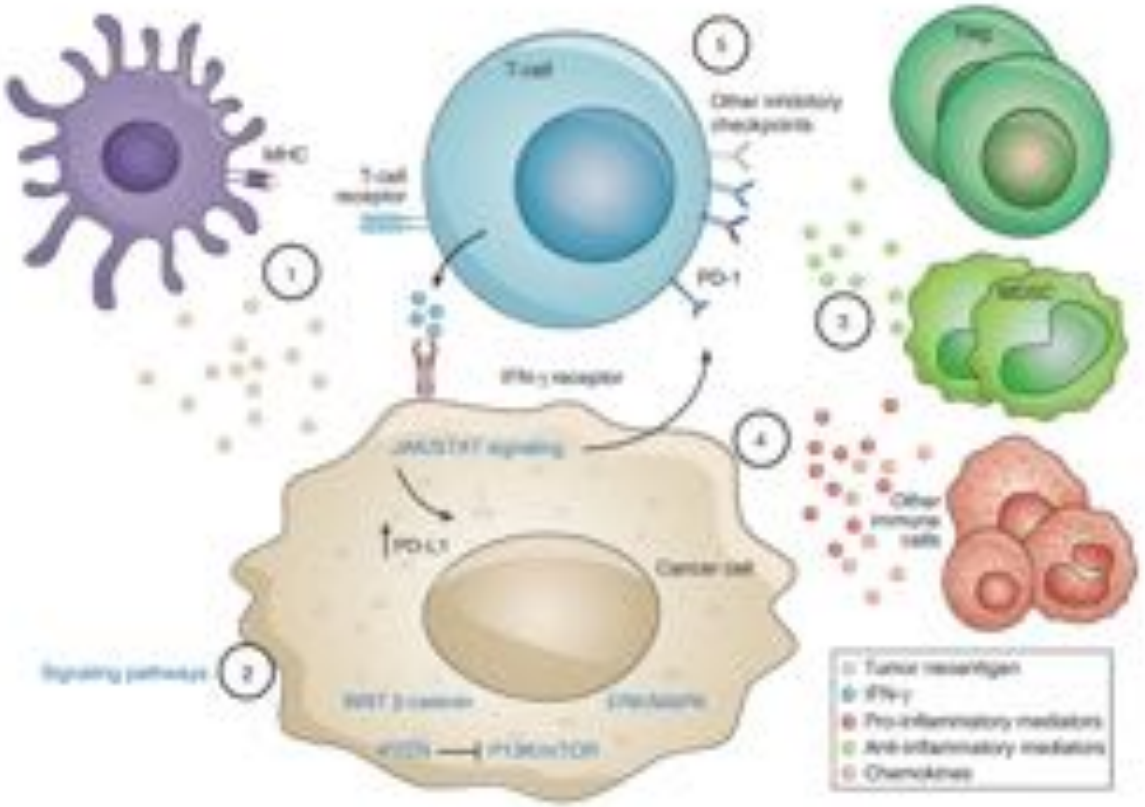
PFS				
	STK11 wt n = 144	STK11 mut n = 63	HR (95% CI)	p
mPFS, m	15.3	6.2	0.52 (0.34-0.80)	0.003



PFS				
	S/Kmut n = 30	S/Kwt n = 33	HR (95% CI)	p
mPFS, m	16.3	4.1	0.55 (0.29-0.95)	0.041

Basher F, Raez et al. WCLC 2021

Mechanisms of resistance to checkpoint inhibitors



1) Changes in tumor neoantigen presentation

2) Alterations in oncogenic signaling pathways

} Ricciuti et al.

3 and 4) Changes in tumor immune microenvironment including decreased anti-tumor inflammation and increase in protumorigenic inflammation

Paulus et al.
Zhao et al.

5) Dependence on alternate immune checkpoints

Hu-Lieskovan et al., Future Oncol 2021

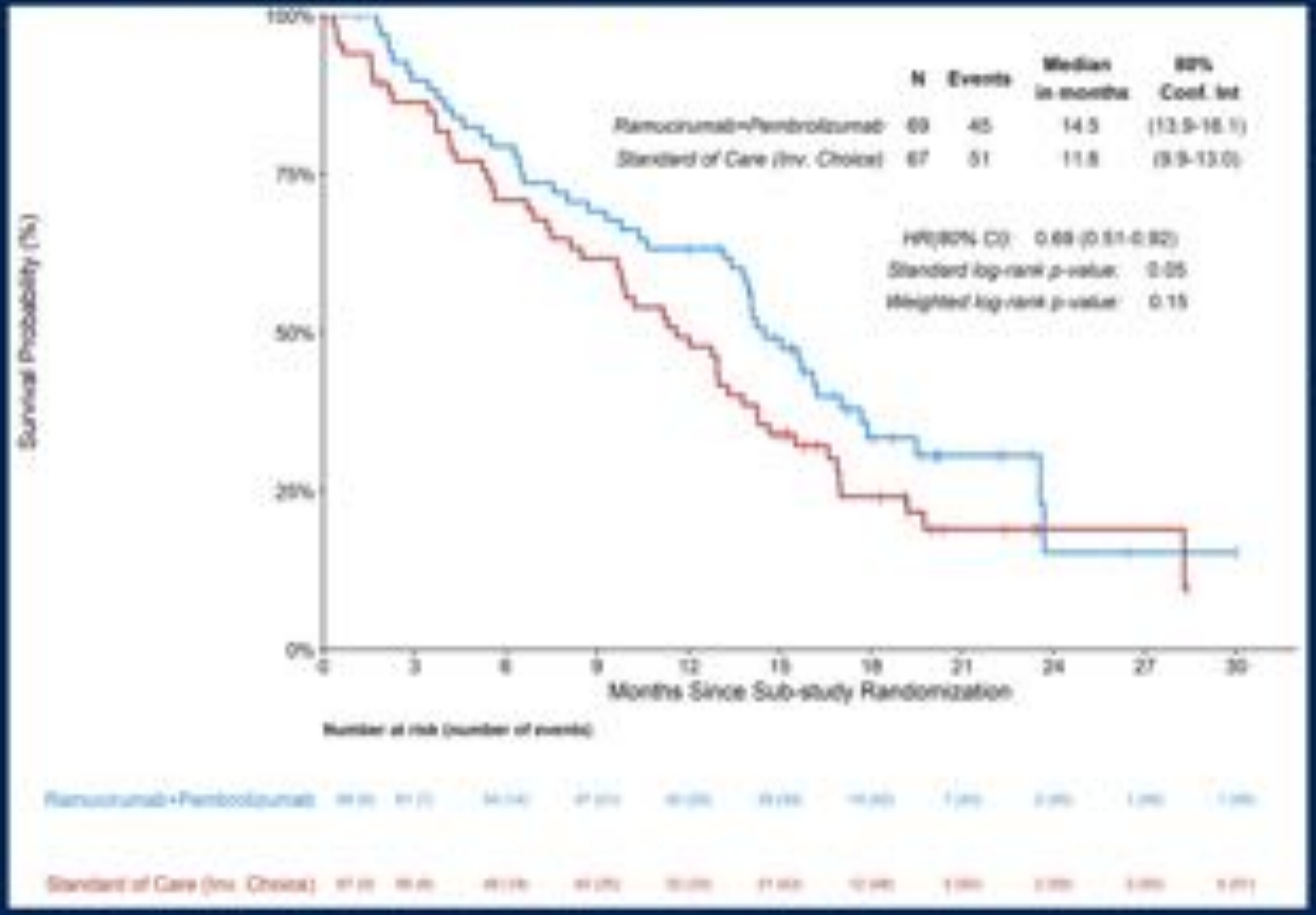
2022 ASCO ANNUAL MEETING

Overall survival from a phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with immunotherapy—Lung-MAP non-matched sub-study S1800A

Karen L. Reckamp, M.D.[1], Mary W. Redman, PhD[2], Konstantin H. Dragnev, M.D.[3], Liza Villaruz, M.D.[4], Bryan Faller, MD[5]; Tareq Al Baghdadi, MD[6], Susan Hines, MD[7], Lu Qian, M.S.[2], Katherine Minichiello, M.S.[2], David R. Gandara, M.D.[8], Karen Kelly, MD[8], Roy S. Herbst, M.D., Ph.D.[9]

[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]SWOG Statistics and Data Management Center & Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Dartmouth-Hitchcock Norris Cotton Cancer Center, Lebanon, NH/Alliance for Clinical Trials in Cancer; [4]University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center; [5]Missouri Baptist Medical Center, St. Louis, MO/Heartland NCORP; [6]IHA Hematology Oncology Consultants-Ann Arbor/Michigan CRC NCORP; [7]Novant Health Cancer Institute - Mount Airy/Southeast Clinical Oncology Research Consortium NCORP); [8]UC Davis Comprehensive Cancer Center, Sacramento, CA; [9]Yale University, New Haven, CT

Overall survival



- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)


Memorial
Cancer Institute
CANCER CENTER
of
EXCELLENCE
Florida
HEALTH
FAU
I-HEALTH
Florida Atlantic University