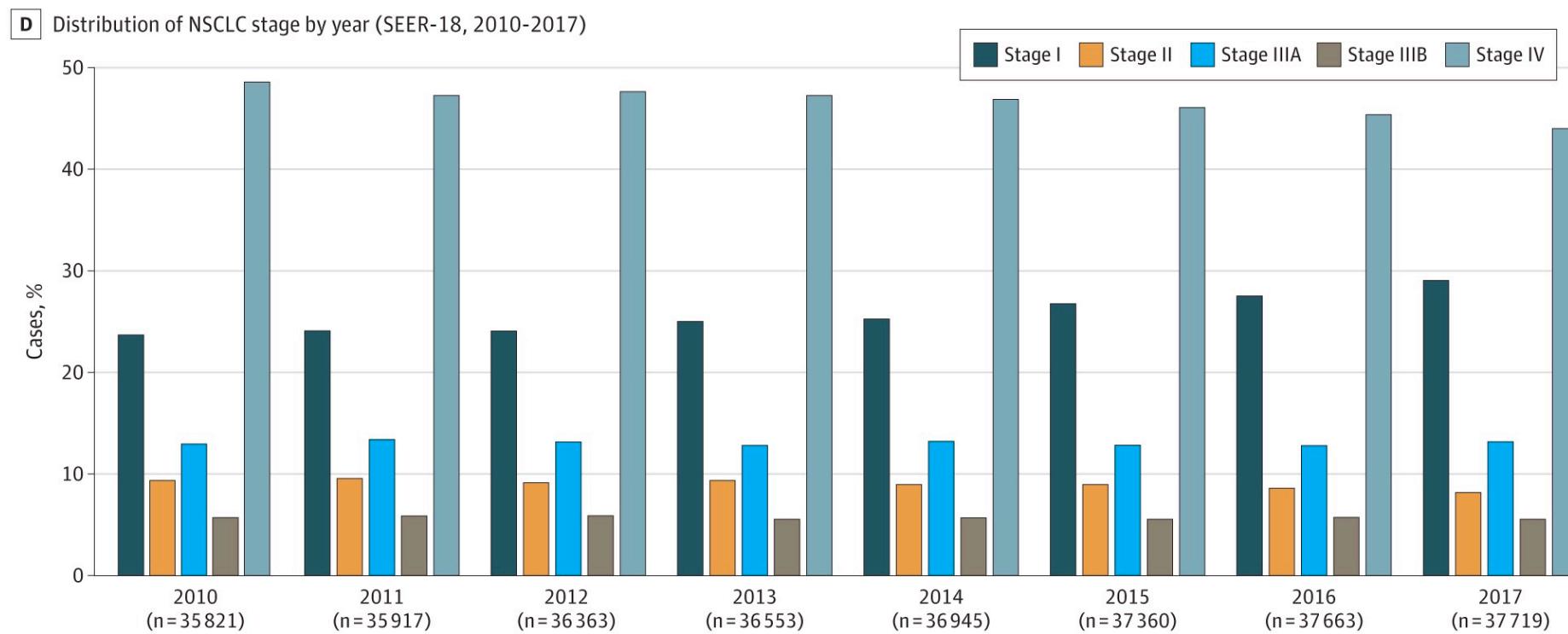


# Stage III Non-Small Cell Lung Cancer

Miheer Pujara

4/28/22

# Trend toward earlier diagnosis with screening



SEER-18 incidence per 100,000 persons per stage

	Stage I	Stage II	Stage IIIA	Stage IIIB	Stage IV
2010	9.8	3.9	5.3	2.3	19.8
2017	10.5	3.0	4.7	2.0	15.8

# Survival by stage (2010-2017)

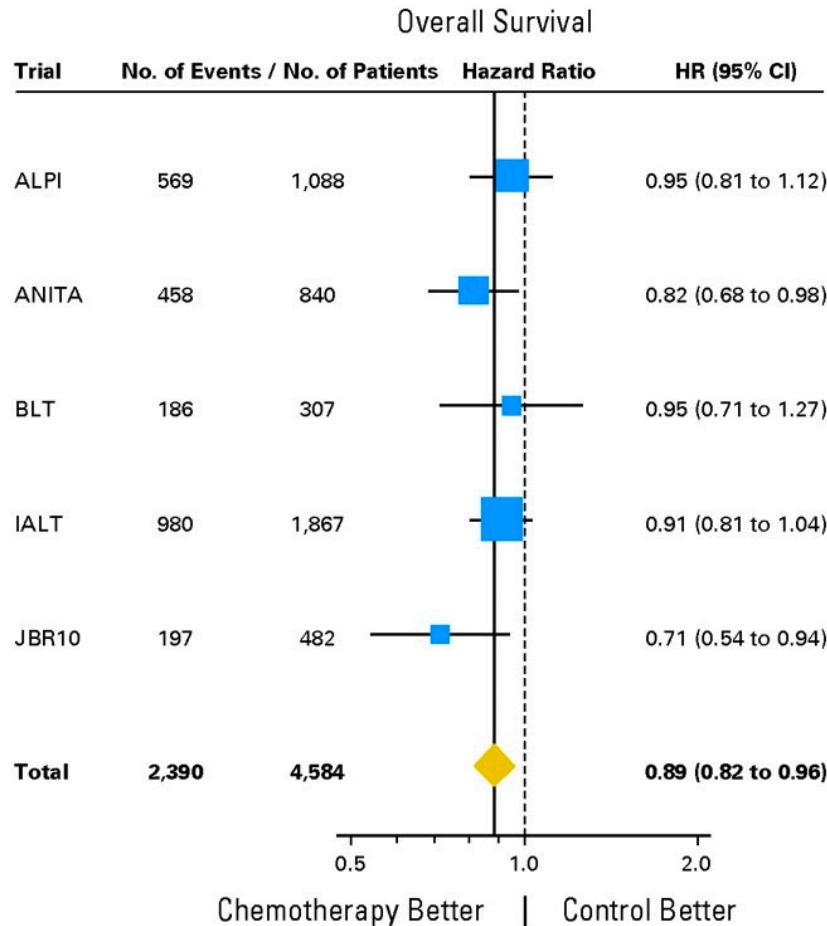
Table. Period Survival (SEER-18)

Characteristic	Period survival rate, %				
	1-year	2-year	3-year	4-year	5-year
Overall	55.1	41.0	33.8	29.5	26.4
Stage					
I	92.8	85.2	78.2	73.1	68.4
II	78.7	64.3	55.3	49.2	45.1
IIIA	66.5	47.3	37.2	30.6	26.2
IIIB	54.3	34.3	25.4	20.5	17.3
IV	31.3	16.6	10.6	7.5	5.8

# Learning objectives

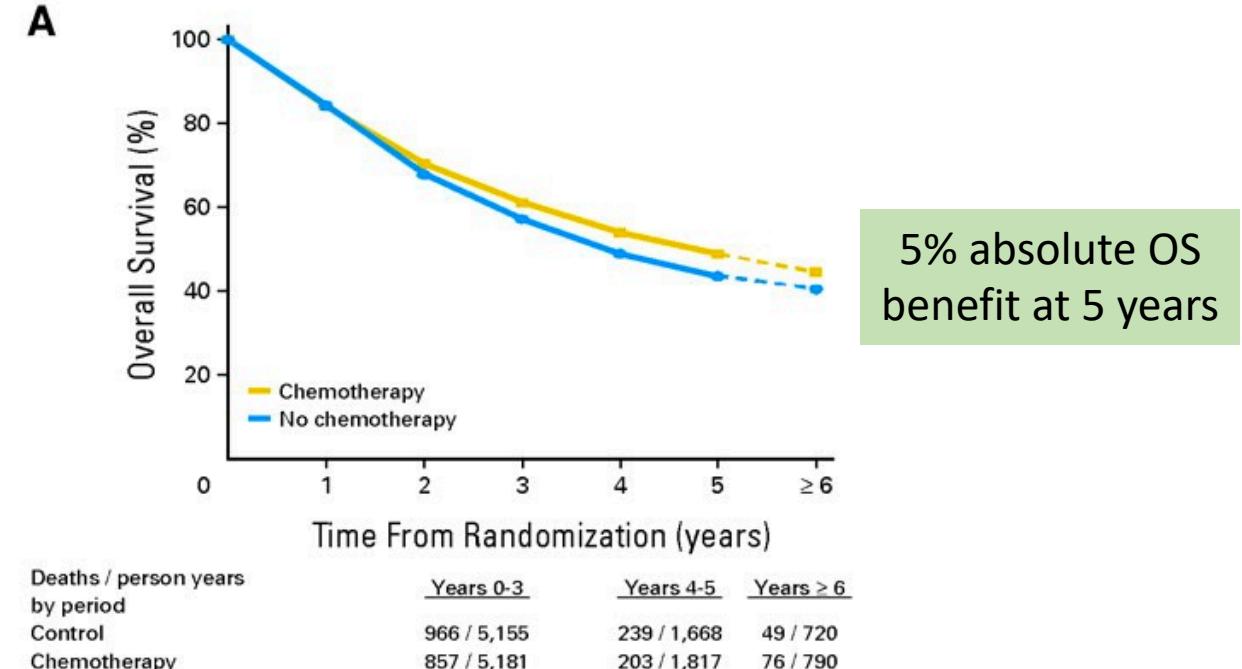
1. Recall the standard of care for non-metastatic NSCLC prior to the introduction of immunotherapy/targeted therapy
2. Identify changes from AJCC 7 to AJCC 8 staging
3. Appraise recent trials:
  - PACIFIC
  - ADAURA
  - IMpower010
  - PEARLS/KEYNOTE-091
  - Checkmate-816

# Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis (2008)

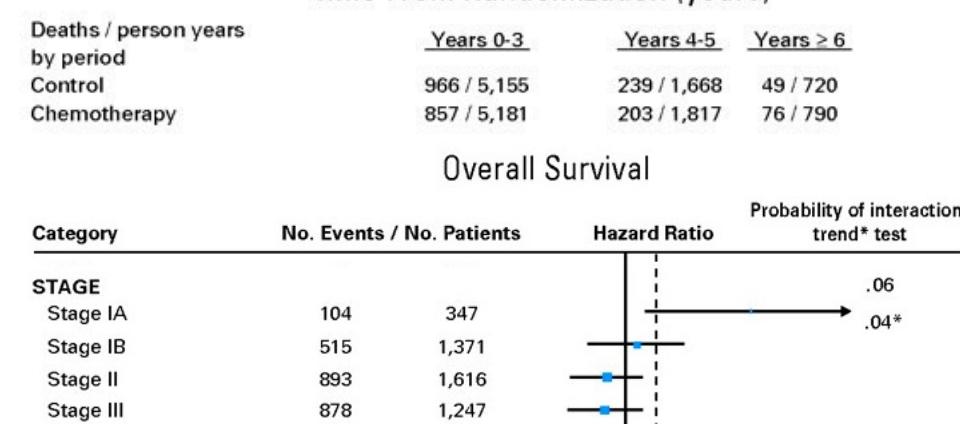


Chemotherapy effect: Logrank statistic = 8.5,  $P = .005$

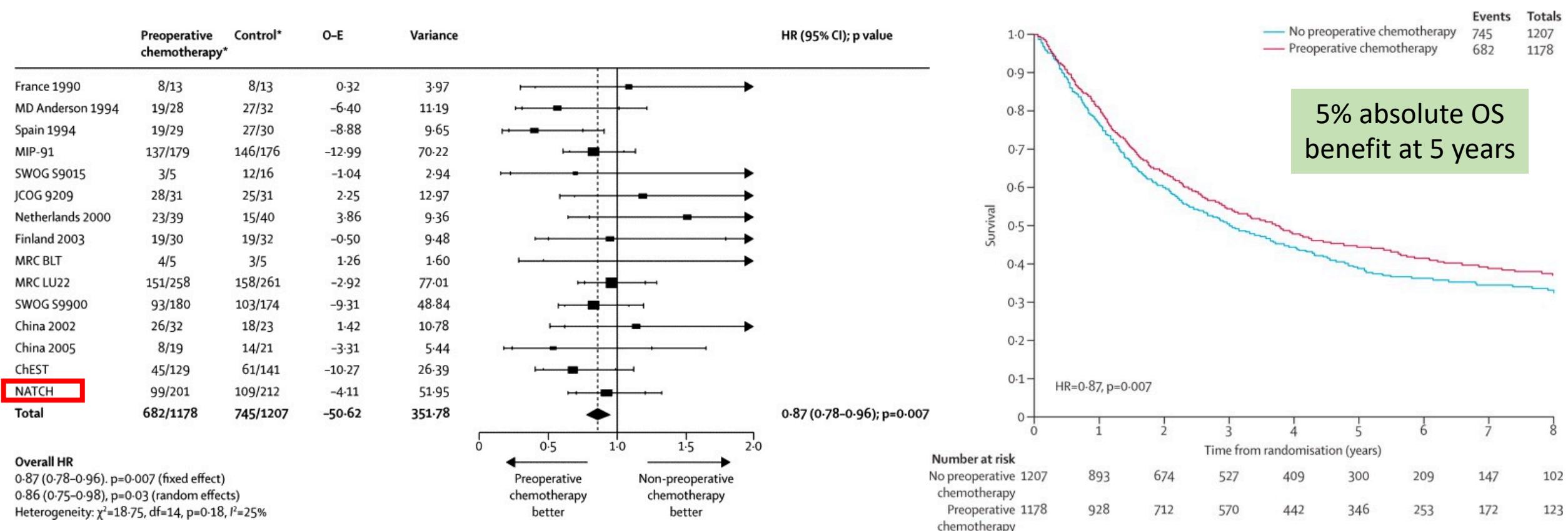
Test for heterogeneity:  $\chi^2_4 = 4.25$ ,  $P = .37$ ,  $I^2 = 6\%$



5% absolute OS  
benefit at 5 years



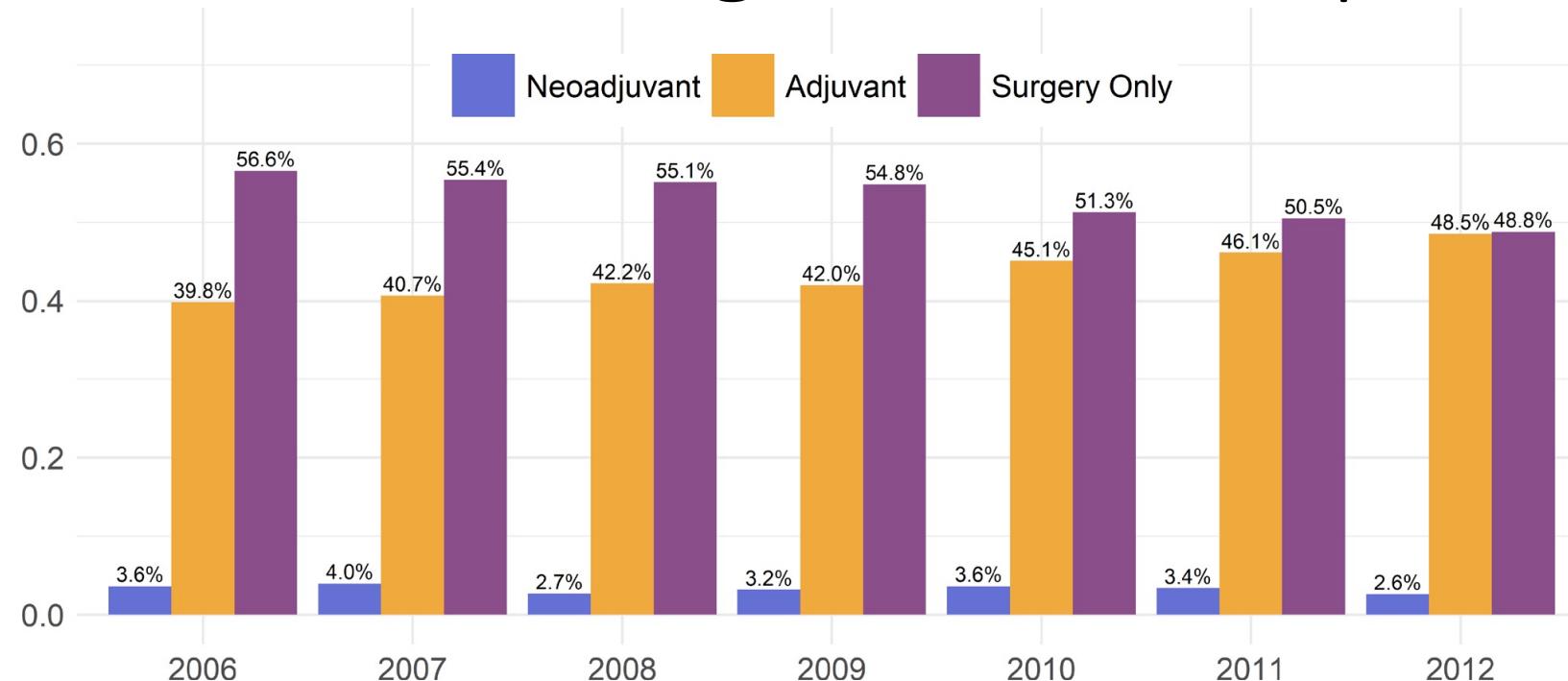
# NSCLC Meta-analysis Collaborative Group (2014): Neoadjuvant Platinum Doublet



NATCH (2010): Phase III RCT, neoadjuvant vs adjuvant chemotherapy, underpowered
 

- 90.4% completed 3 cycles of neoadjuvant vs 60.9% adjuvant

# Analysis of 35,000 Stage II/III NCDB patients

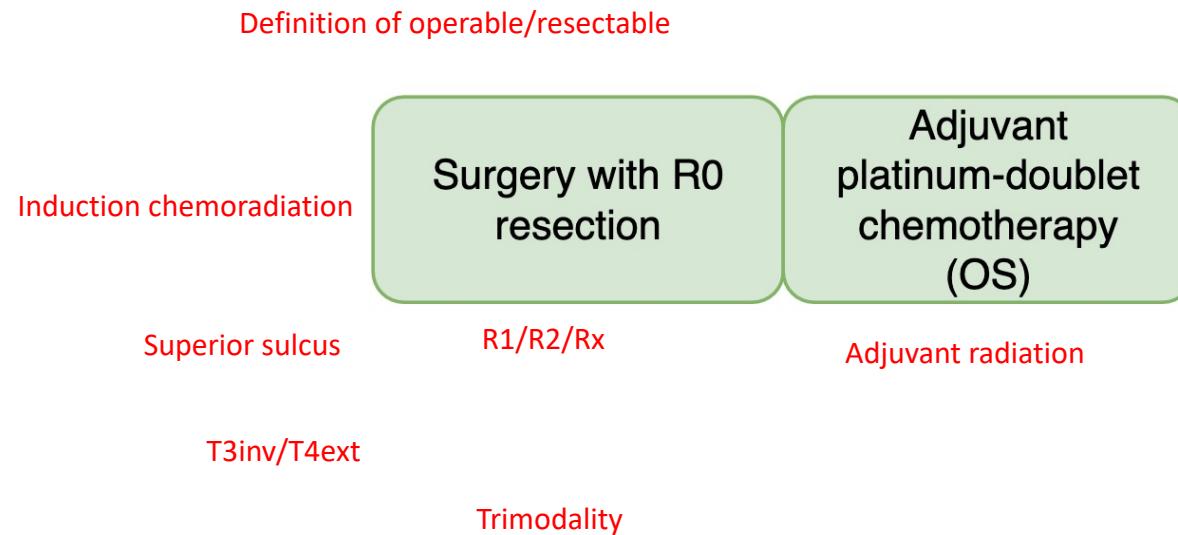


**Table 1: Clinical and demographic characteristics of patient cohort, including patients receiving surgery alone, adjuvant chemotherapy, and neoadjuvant chemotherapy**

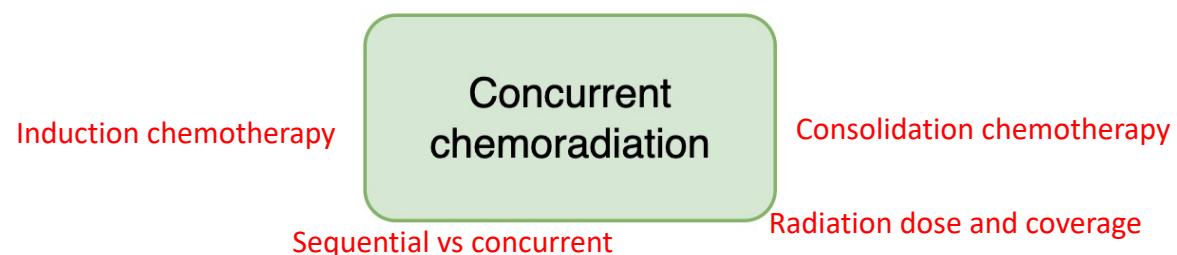
Characteristic	Stage II ( <i>n</i> = 23334)	Stage III ( <i>n</i> = 11800)	<i>p</i> -value
Treatment			<2.2e-16
Surgery Only	13385 (57.36%)	5299 (44.91%)	
Neoadjuvant	562 (2.41%)	592 (5.02%)	
Adjuvant	9387 (40.23%)	5909 (50.08%)	

# Standard of care in 2016

## Stage IB (>4cm) to IIIA



## Stage III, unresectable



# Landscape in 2022

Stage IB (>4cm) to IIIA

\*AJCC 7<sup>th</sup> edition

Checkmate-816

Neoadjuvant nivolumab  
and platinum-doublet  
chemotherapy

Surgery with R0  
resection

Adjuvant  
platinum-doublet  
chemotherapy  
(OS)

Adjuvant Osimertinib

ADAURA

Adjuvant  
Atezolizumab or  
Pembrolizumab

IMpower010

PEARLS/KEYNOTE-091

Stage III, unresectable

\*AJCC 7<sup>th</sup> edition

Concurrent  
chemoradiation

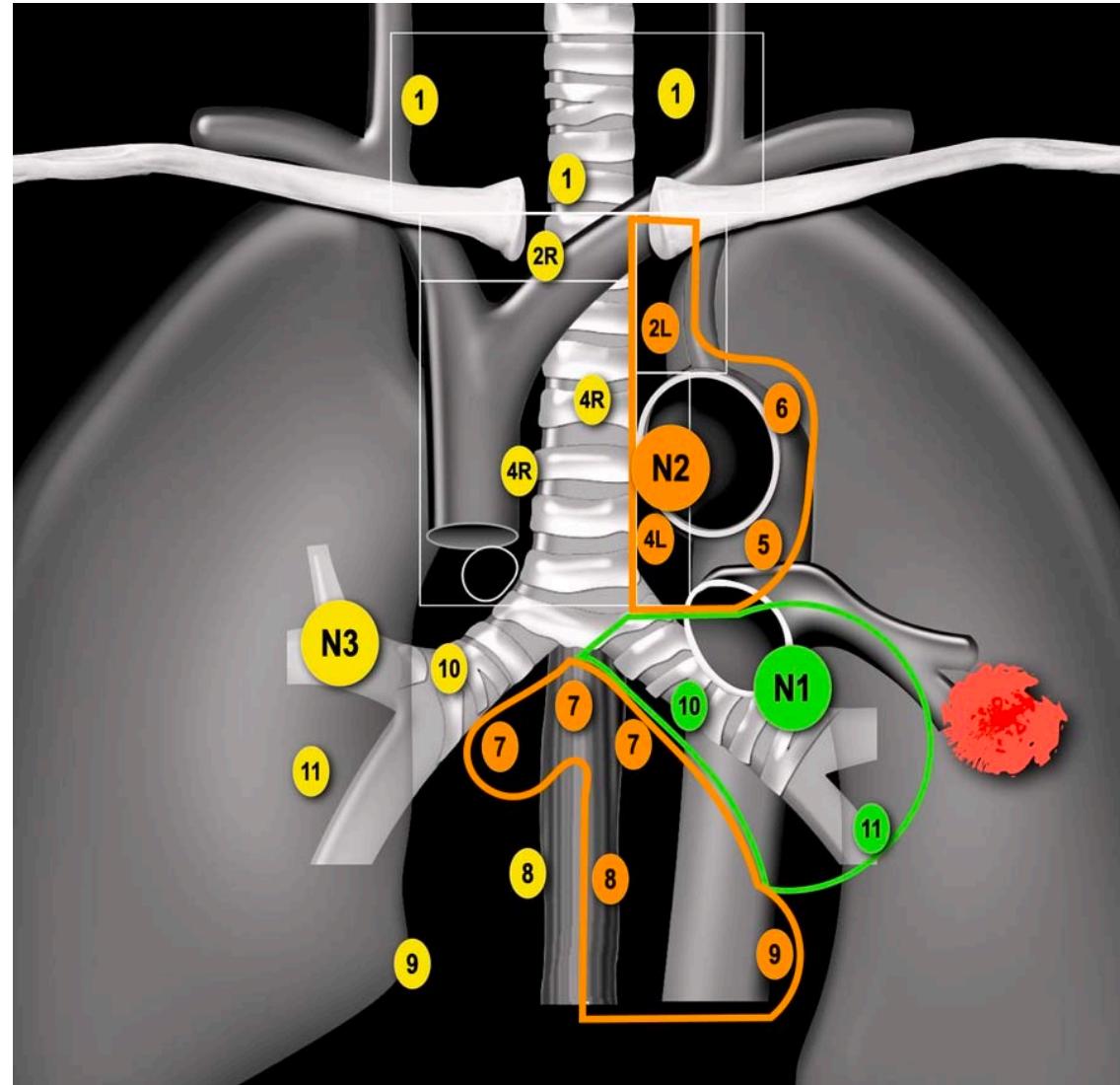
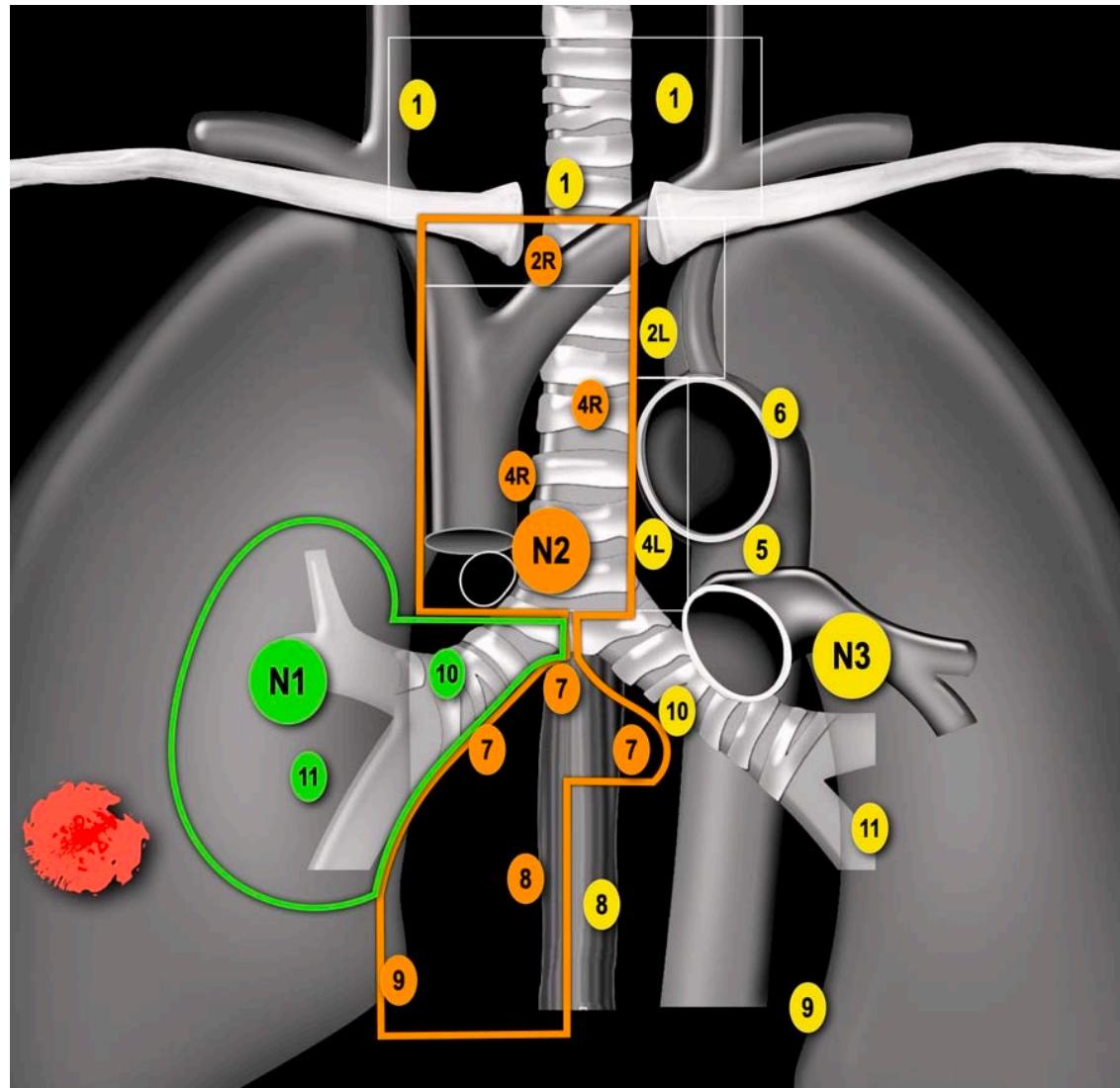
Consolidation  
Durvalumab

PACIFIC

# AJCC 8<sup>th</sup> edition staging (2017)

	TNM 7 <sup>th</sup> EDITION	TNM 8 <sup>th</sup> EDITION
<b>T</b>	- - - T1a ( $\leq 2$ cm) T1b ( $>2 - 3$ cm)	Tis Tmi Tss T1a ( $\leq 1$ cm) T1b ( $>1-2$ cm) T1c ( $>2-3$ cm)
	T2a ( $>3-5$ cm) T2b ( $>5-7$ cm)	T2a ( $>3$ cm but $\leq 4$ cm) T2b ( $>4$ cm but $\leq 5$ cm)
	T3 ( $>7$ cm) T3 - atelectasis/pneumonitis involving whole lung)	T4 T2 atelectasis/pneumonitis irrespective of involving lobe or whole lung
	T3 tumor involving the main bronchus $<2$ cm distance to carina	T2 - tumor involving the main bronchus irrespective of distance to carina
	T3 - invasion of the diaphragm	T4 (invasion of the diaphragm)
<b>N</b>	No changes	
<b>M</b>	M1b - distant metastasis	M1b - single extrathoracic metastasis M1c - multiple extrathoracic metastases

# Nodal staging is critical to determine resectability



# AJCC 8<sup>th</sup> edition: No changes in nodal staging

AJCC 7 Lung					
	N0	N1	N2	N3	M1ab
Tis	0				
T1a	IA	IIA	IIIA	IIIB	IV
T1b	IA	IIA	IIIA	IIIB	IV
T2a	IB	IIA	IIIA	IIIB	IV
T2b	IIA	IIB			
T3	IIIB		IIIA		
T4	IIIA	IIIA	IIIB		

AJCC 8 Lung					
	N0	N1	N2	N3	M1abc
Tis	0				
T1mi	IA1				
T1a	IA1				
T1b	IA2				
T1c	IA3	IIB	IIIA	IIIB	IVA/B/C
T2a	IB				
T2b	IIA				
T3	IIIB	IIIA	IIIB	IIIC	
T4	IIIA				

# Stage III NSCLC is a heterogeneous disease

AJCC 8 Lung					
	N0	N1	N2	N3	M1abc
Tis					
T1mi					
T1a					
T1b					
T1c					
T2a					
T2b					
T3					
T4	IIIA	IIIA	IIIB		
AJCC 7 Lung					
	N0	N1	N2	N3	M1ab
Tis					
T1a					
T1b					
T2a					
T2b					
T3					
T4	IIIA	IIIA	IIIB		
Tis					
T1mi					
T1a					
T1b					
T1c					
T2a					
T2b					
T3					
T4	IIIA	IIIA	IIIB	IIIC	

# Landscape in 2022

Stage IB (>4cm) to IIIA

Checkmate-816

Neoadjuvant nivolumab and platinum-doublet chemotherapy

Surgery with R0 resection

Adjuvant platinum-doublet chemotherapy (OS)

Adjuvant Osimertinib

ADAURA

Adjuvant Atezolizumab or Pembrolizumab

IMpower010

PEARLS/KEYNOTE-091

Stage III, unresectable

Concurrent chemoradiation

Consolidation Durvalumab

PACIFIC

# PACIFIC (2017): Consolidation Durvalumab

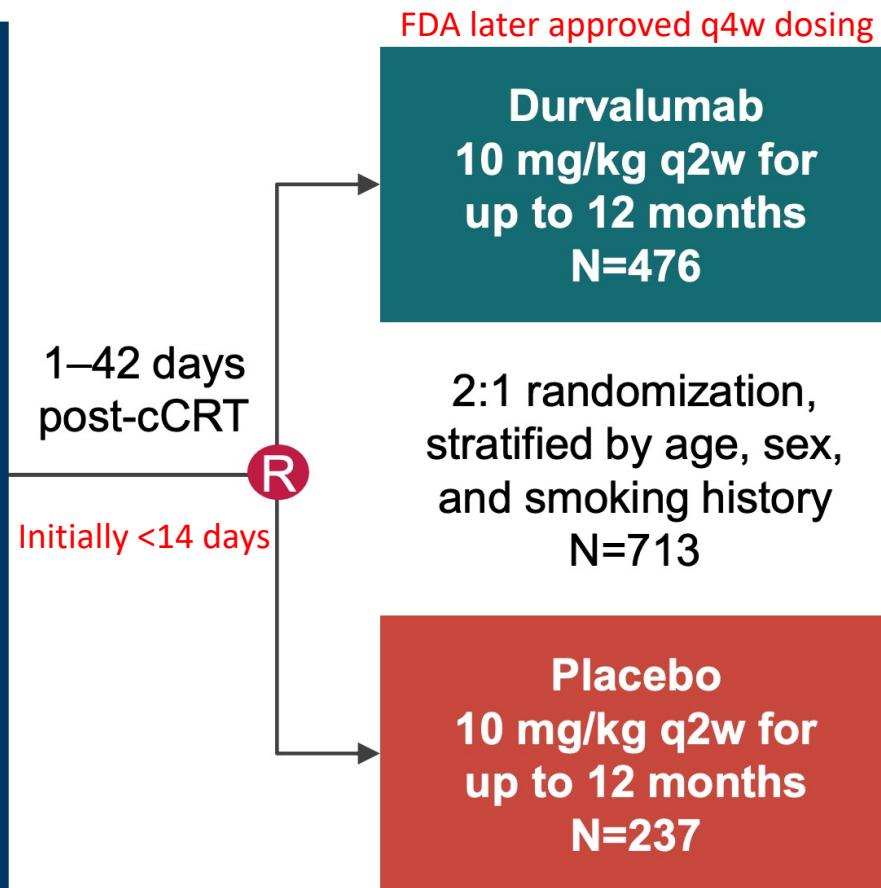
## Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

David R. Spigel, MD<sup>1</sup>; Corinne Faivre-Finn, MD, PhD<sup>2</sup>; Jhanelle E. Gray, MD<sup>3</sup>; David Vicente, MD<sup>4</sup>; David Planchard, MD, PhD<sup>5</sup>; Luis Paz-Ares, MD, PhD<sup>6</sup>; Johan F. Vansteenkiste, MD, PhD<sup>7</sup>; Marina C. Garassino, MD<sup>8,9</sup>; Rina Hui, PhD<sup>10</sup>; Xavier Quantin, MD, PhD<sup>11</sup>; Andreas Rimner, MD<sup>12</sup>; Yi-Long Wu, MD<sup>13</sup>; Mustafa Özgüroğlu, MD<sup>14</sup>; Ki H. Lee, MD<sup>15</sup>; Terufumi Kato, MD<sup>16</sup>; Maike de Wit, MD, PhD<sup>17</sup>; Takayasu Kurata, MD<sup>18</sup>; Martin Reck, MD, PhD<sup>19</sup>; Byoung C. Cho, MD, PhD<sup>20</sup>; Suresh Senan, PhD<sup>21</sup>; Jarushka Naidoo, MBBCH, MHS<sup>22</sup>; Helen Mann, MSc<sup>23</sup>; Michael Newton, PharmD<sup>24</sup>; Piruntha Thiagarajah, MD<sup>23</sup>; and Scott J. Antonia, MD, PhD<sup>3</sup>; on behalf of the PACIFIC Investigators

# PACIFIC (2017): Consolidation Durvalumab

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT ( $\geq 2$  cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of  $\geq 12$  weeks
- Archived tissue was collected

**All-comers population**



## Co-primary endpoints

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

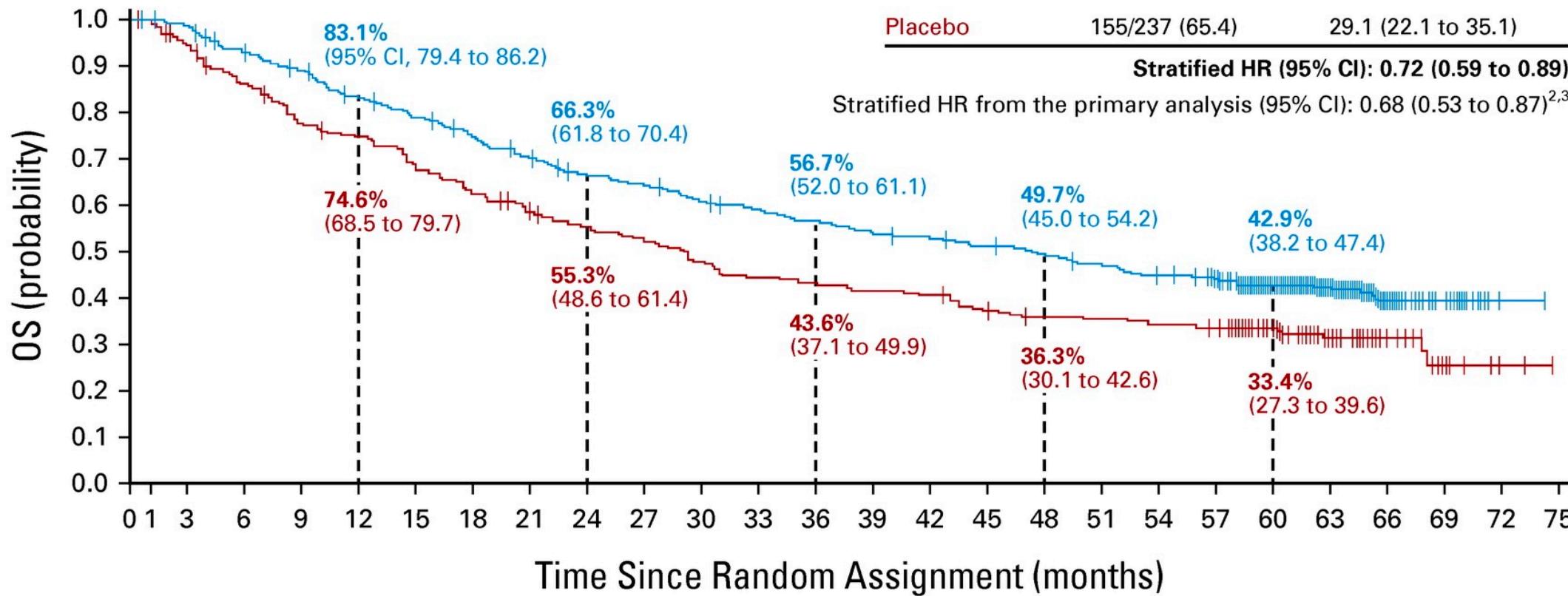
## Key secondary endpoints

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

# PACIFIC (2017): Consolidation Durvalumab

- Baseline characteristics:
  - 64yo, 70% male, 50% ECOG 0, 54% nonsquamous, 91% smokers
  - Stage: IIIA (53%), IIIB (45%), other (2%)
  - Radiation: 92% 54-66 Gy
  - Chemotherapy: 27% induction, 99% concurrent
  - Response to prior therapy: 2% CR, 48% PR, 47% stable disease
- Initial DFS benefit reported in 2017, OS benefit reported in 2018

# PACIFIC (2017): Consolidation Durvalumab

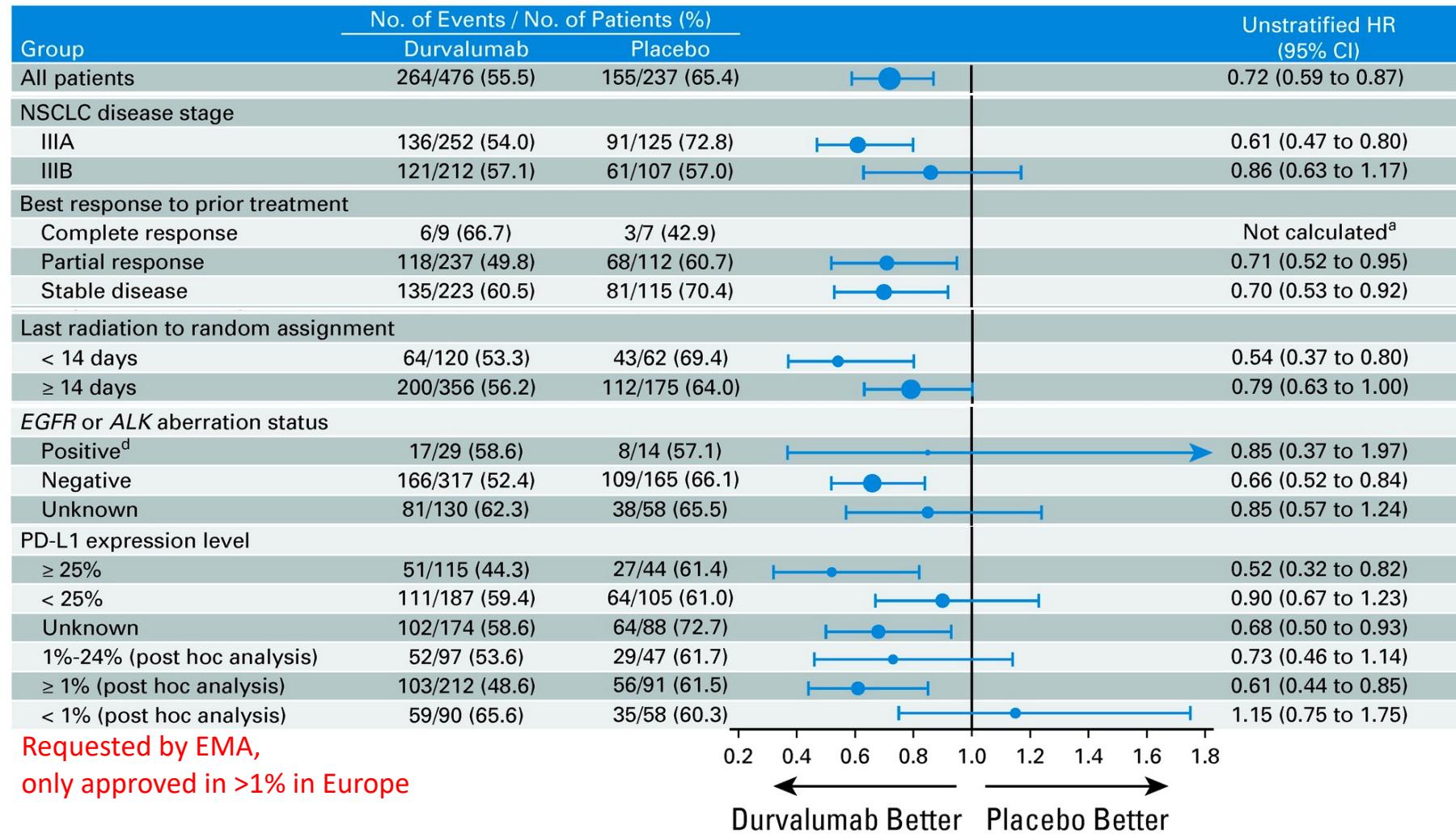


Characteristic	Period survival rate, %	
	5-year	
Overall	26.4	
Stage		
I	68.4	
II	45.1	
III A	26.2	
III B	17.3	
IV	5.8	

No. at risk:

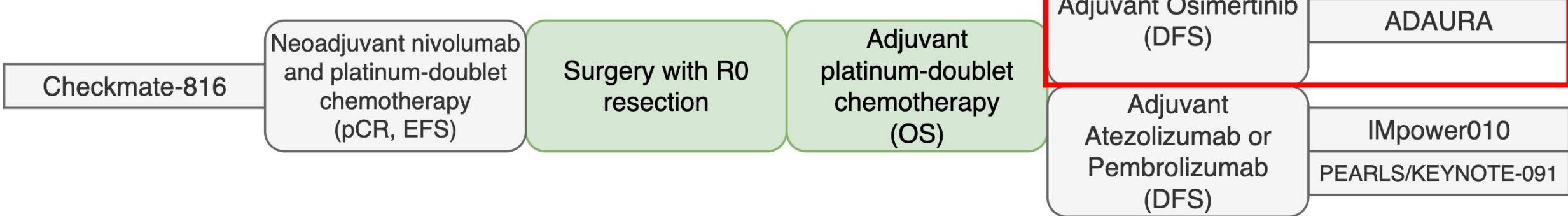
Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

# PACIFIC (2017): Consolidation Durvalumab

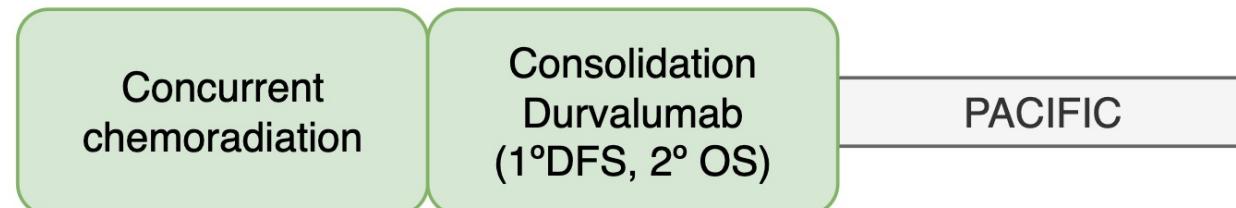


# Landscape in 2022

Stage IB (>4cm) to IIIA



Stage III, unresectable



# ADAURA (2020): Adjuvant Osimertinib

## The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

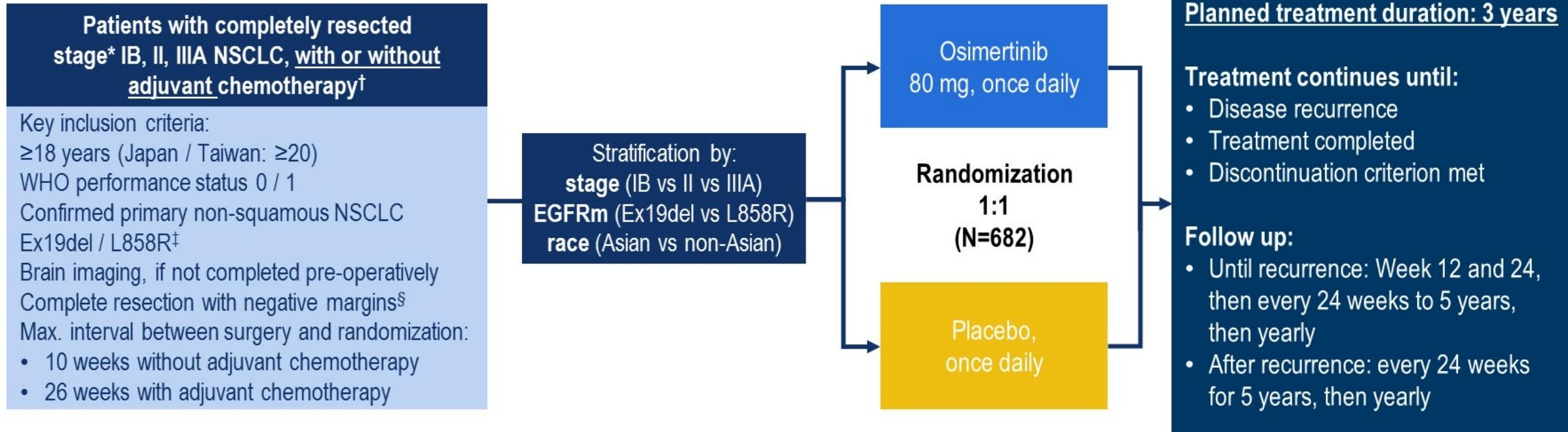
OCTOBER 29, 2020

VOL. 383 NO. 18

### Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators\*

# ADAURA (2020): Adjuvant Osimertinib



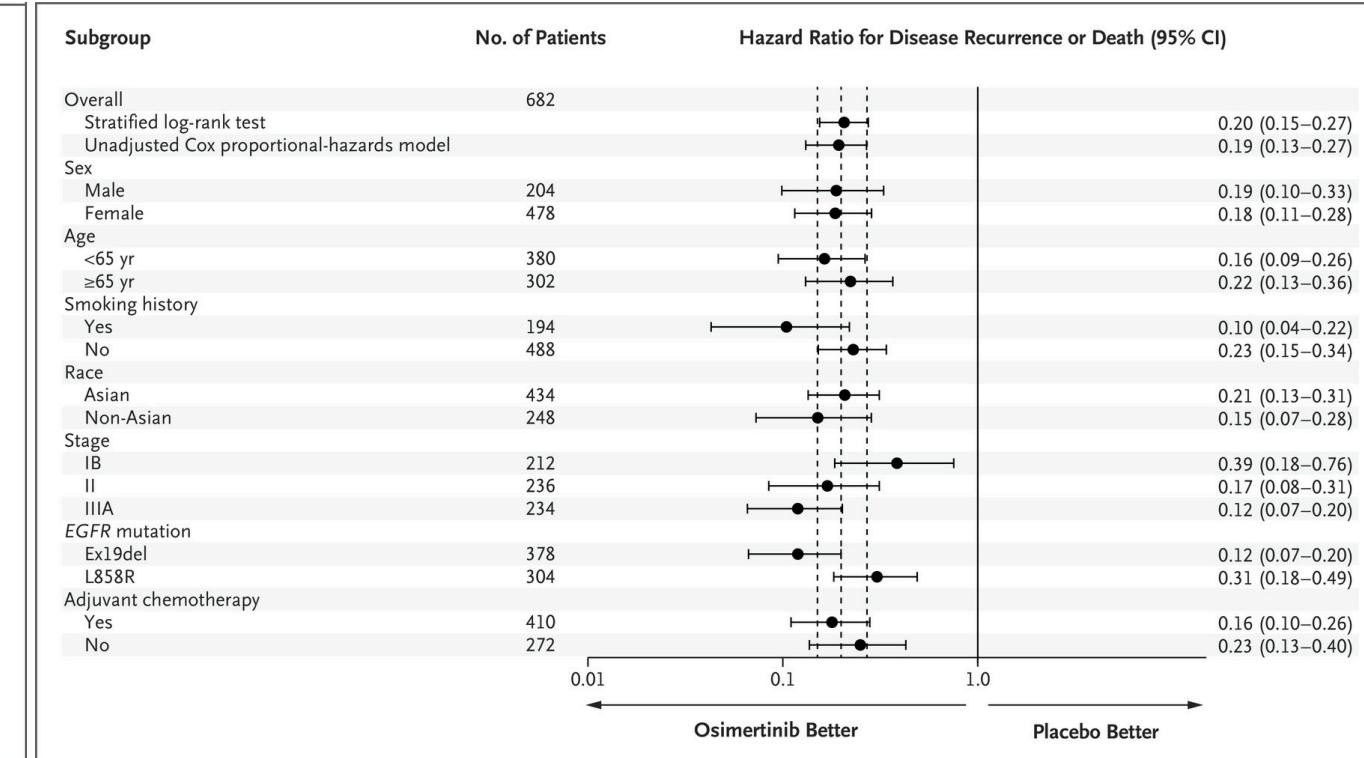
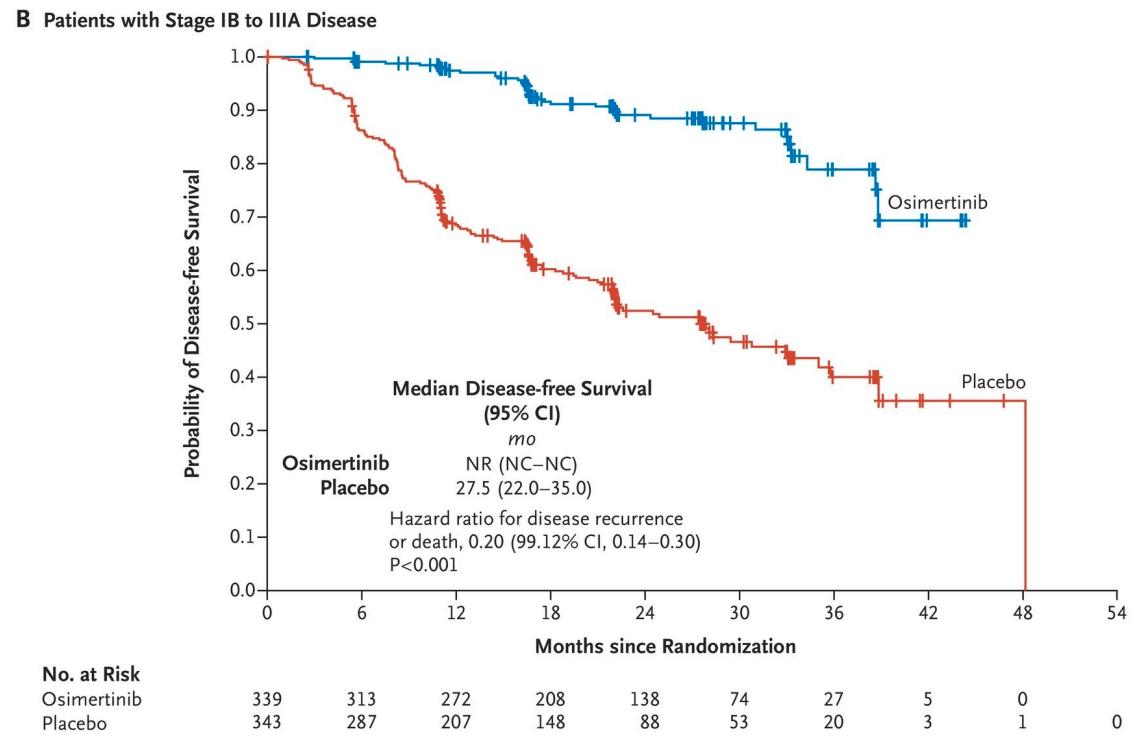
## Endpoints

- **Primary:** DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary:** DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life
- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

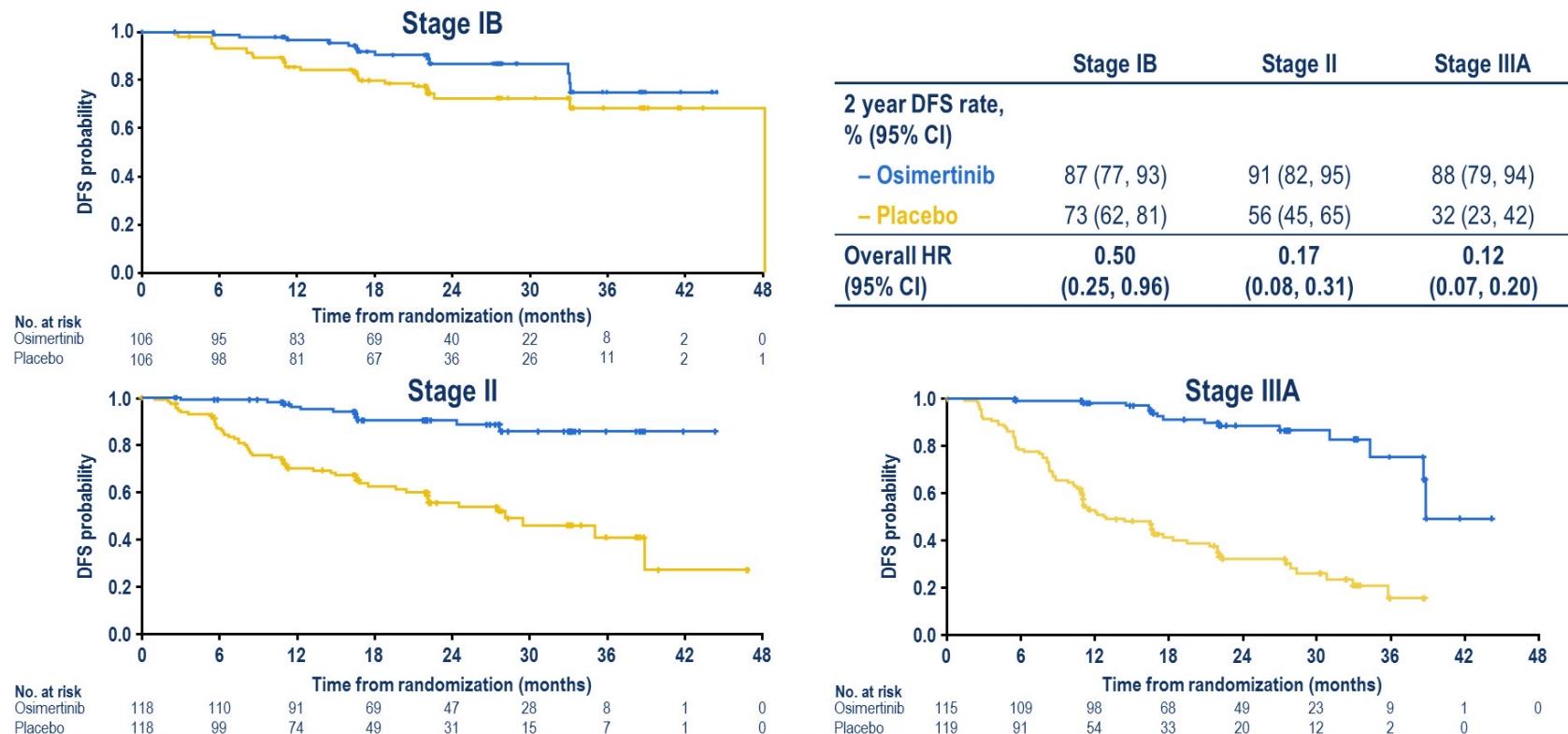
# ADAURA (2020): Adjuvant Osimertinib

- Baseline characteristics:
  - 63yo, 70% female, 70% never smokers, 64% Asian, 64% ECOG 0
  - 96% adeno, 95% lobectomy
  - 1/3<sup>rd</sup> each: stage IB, II, IIIA
  - 40% N0, 30% N1, 30% N2
  - 60% received adjuvant chemotherapy

# ADAURA (2020): Adjuvant Osimertinib



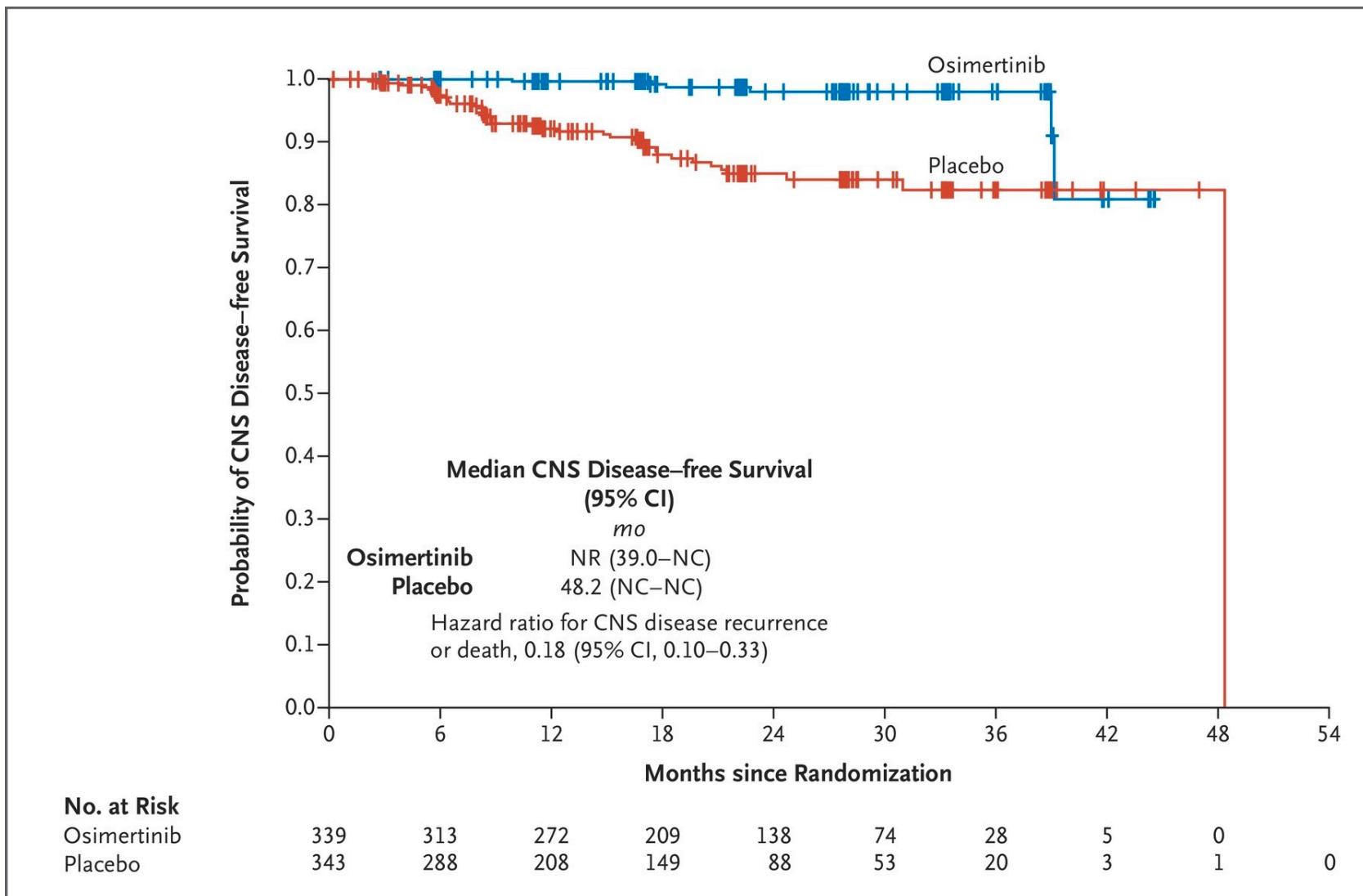
# ADAURA (2020): Adjuvant Osimertinib



**Table S2. Delivery of adjuvant platinum-based chemotherapy, by disease stage**

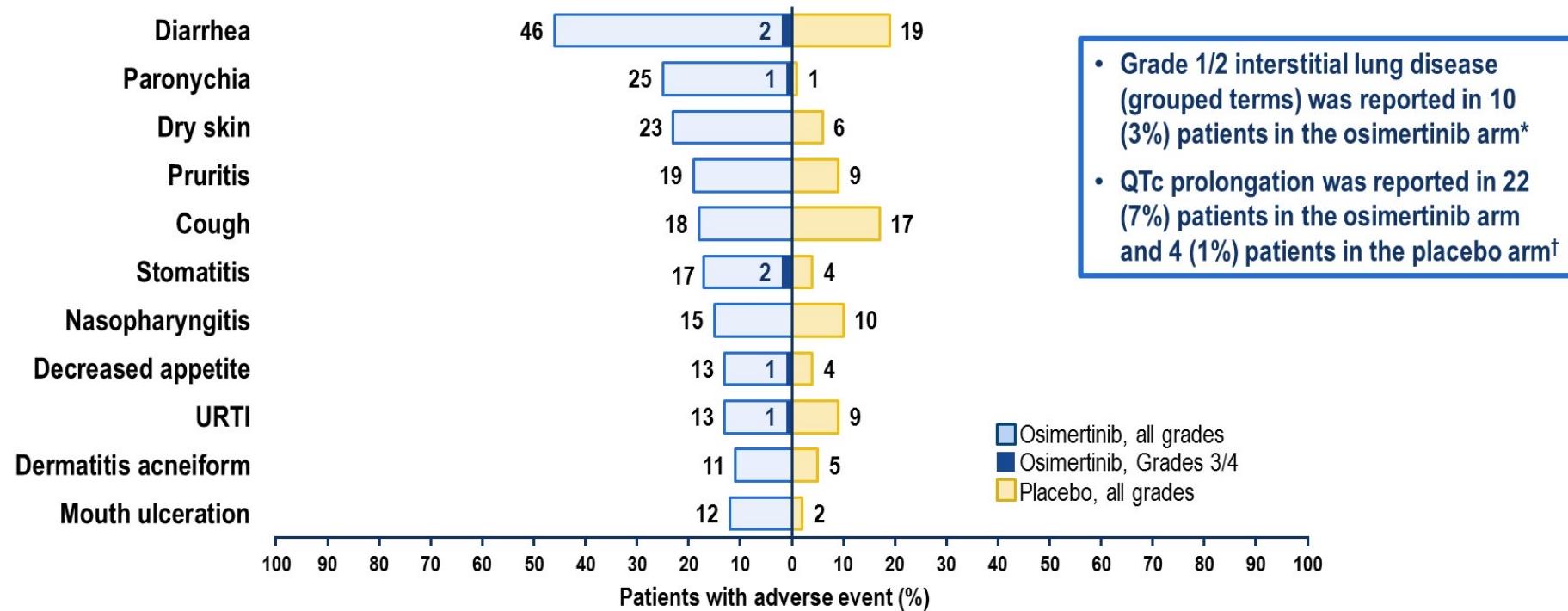
<b>Number of patients, n (%)</b>	<b>Stage IB</b>		<b>Stage II</b>		<b>Stage IIIA</b>	
	<b>Osimertinib (n=107)</b>	<b>Placebo (n=109)</b>	<b>Osimertinib (n=115)</b>	<b>Placebo (n=116)</b>	<b>Osimertinib (n=117)</b>	<b>Placebo (n=118)</b>
Adjuvant platinum-based chemotherapy	27 (25)	30 (28)	80 (70)	85 (73)	95 (81)	92 (78)
No adjuvant platinum-based chemotherapy	80 (75)	79 (72)	35 (30)	31 (27)	22 (19)	26 (22)

# ADAURA (2020): Adjuvant Osimertinib



# ADAURA (2020): Adjuvant Osimertinib

Median duration of exposure: osimertinib: 22.3 months (range 0 to 43), placebo: 18.4 months (range 0 to 48)



- Grade 1/2 interstitial lung disease (grouped terms) was reported in 10 (3%) patients in the osimertinib arm\*
- QTc prolongation was reported in 22 (7%) patients in the osimertinib arm and 4 (1%) patients in the placebo arm†

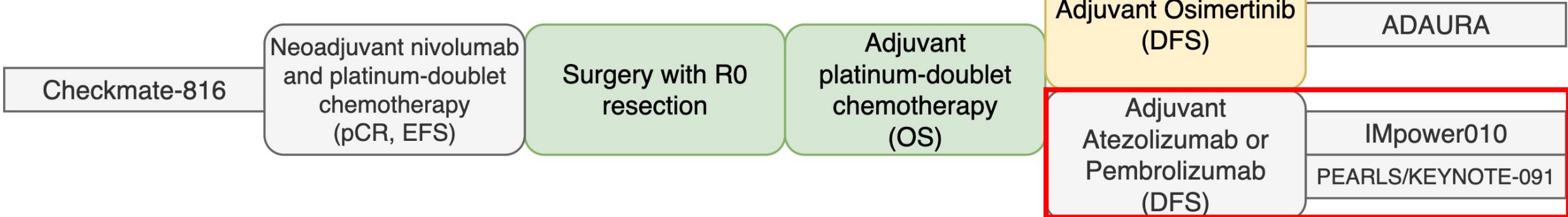
- Dose interruptions: 24% vs 11%
- Dose reductions: 9% vs 1%
- Discontinuation of the trial regimen owing to adverse events: 11% vs 3%
- Completed 3 years of therapy (at time of publication): 12% vs 10%

# ADAURA (2020): Adjuvant Osimertinib

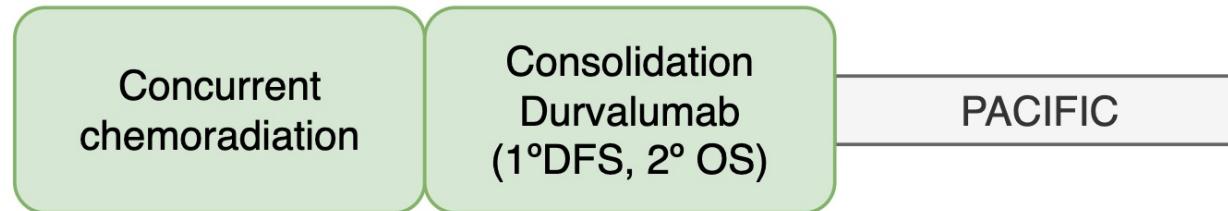
- Trial unblinded early due to substantial DFS benefit across all subgroups
- OS data not yet mature
  - Sequencing not yet clear: adjuvant vs. treatment at relapse?
- Chemotherapy not mandated, 24% of stage II-III did not receive
- No grade 4-5 toxicity; 3% pneumonitis, 7% QT prolongation; 11% discontinued drug

# Landscape in 2022

Stage IB (>4cm) to IIIA



Stage III, unresectable



# IMpower010 (2021): Adjuvant Atezolizumab

## **Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial**

*Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszsi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators\**

*Lancet* 2021; 398: 1344-57

# IMpower010 (2021): Adjuvant Atezolizumab

**Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7**

- Stage IB tumors  $\geq 4$  cm
- ECOG 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis

Allowed EGFR and ALK

## Stratification factors

- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status<sup>a</sup>: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Mandated chemotherapy

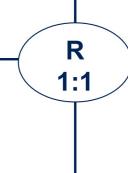
Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine  
1-4 cycles

N=1280

No crossover  
**Atezolizumab 1200 mg q21d 16 cycles**

N=1005

**BSC**



**Survival follow-up**

Hierarchical assessment

**DFS in PD-L1 TC  $\geq 1\%$  stage II-IIIA population**  
2-sided  $\alpha=0.05$

If positive:

**DFS in all-randomized stage II-IIIA population**  
2-sided  $\alpha=0.05$

If positive:

**DFS in ITT population (stage IB-IIIA)**  
2-sided  $\alpha=0.05$

If positive:

**OS in ITT population**  
2-sided  $\alpha=0.05$

## Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC  $\geq 1\%$  (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

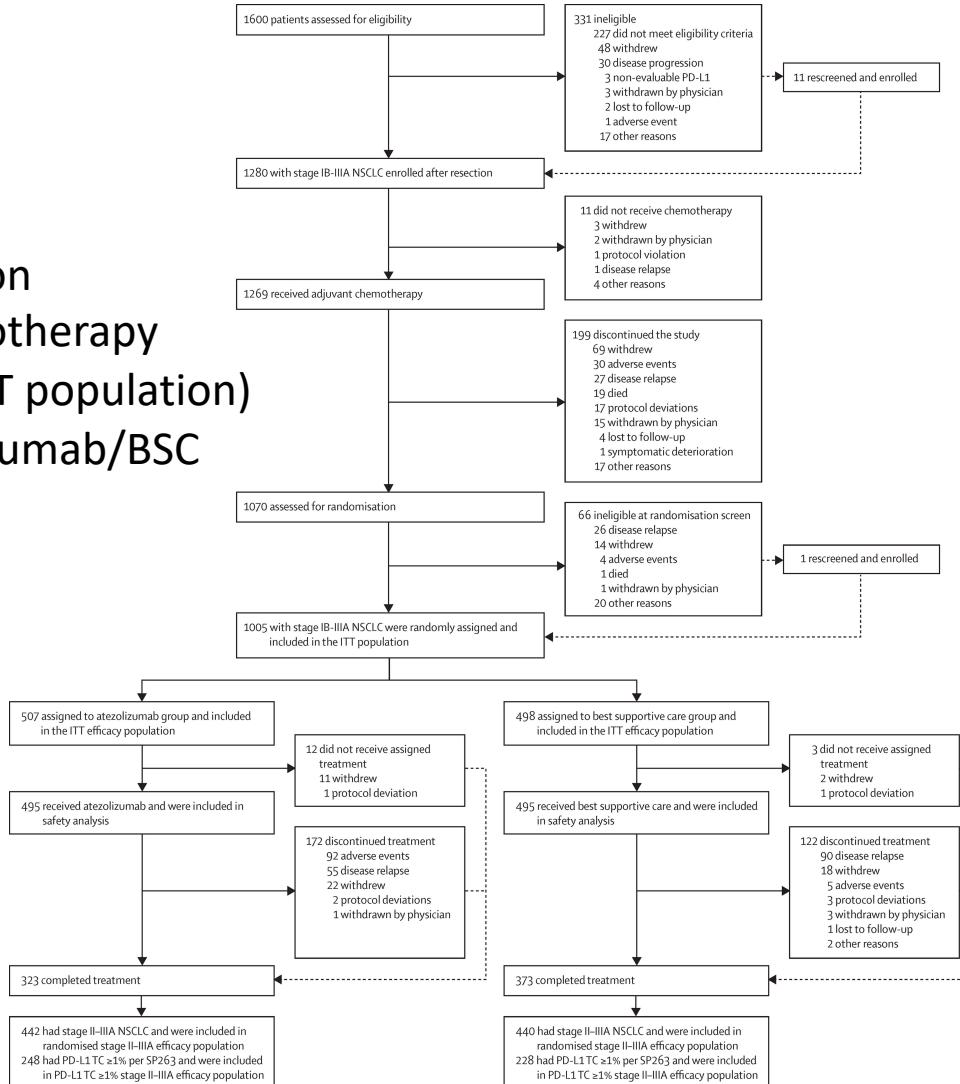
## Key secondary endpoints

- OS in ITT population
- DFS in PD-L1 TC  $\geq 50\%$  (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Protocol amended to change from SP142 to SP263 PDL1 assay after randomization

# IMpower010 (2021): Adjuvant Atezolizumab

1280 enrolled after resection  
1269 (99%) received chemotherapy  
1005 (78%) randomized (ITT population)  
990 (77%) received atezolizumab/BSC

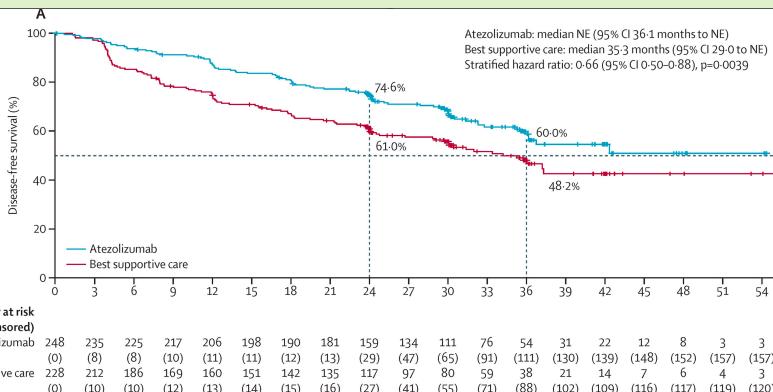


# IMpower010 (2021): Adjuvant Atezolizumab

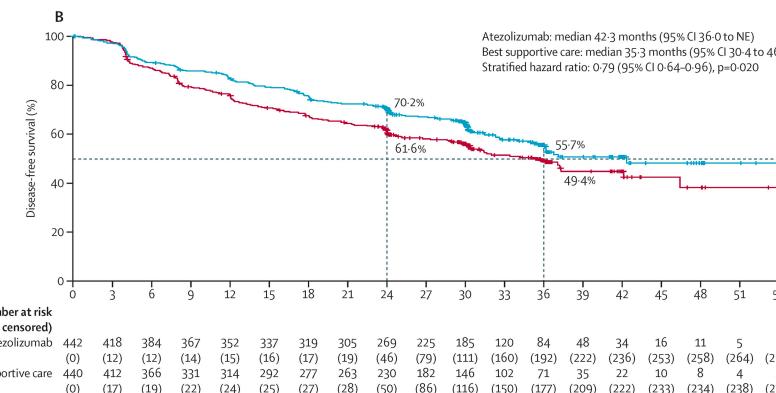
- Baseline characteristics:
  - 62yo, 66% male, 70% white/30% Asian, 55% ECOG 0, 66% nonsquamous, 80% smokers
  - Stage: 13% IB, 30% IIA, 17% IIB, 40% IIIA
  - Surgery: 78% lobectomy, 16% pneumonectomy
  - PD-L1: 50% ( $\geq 1\%$ )
  - Mutations: 12% EGFR, 4% ALK
- Chemotherapy: 100% received, 85% completed 4 cycles

# IMpower010 (2021): Adjuvant Atezolizumab

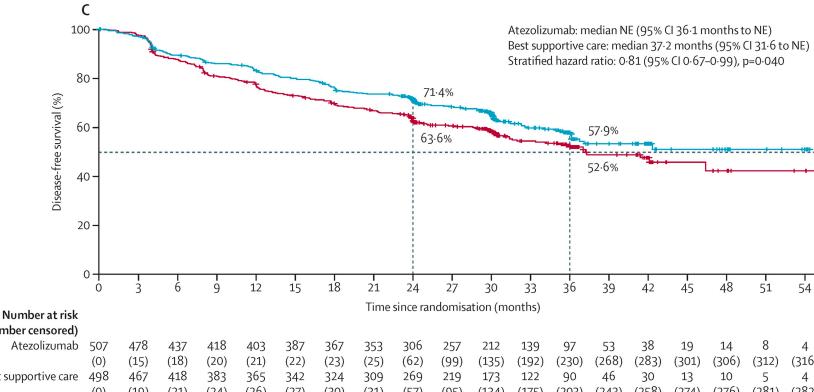
**DFS in PD-L1 TC  $\geq 1\%$  stage II-IIIA population**  
2-sided  $\alpha=0.05$



**DFS in all-randomized stage II-IIIA population**  
2-sided  $\alpha=0.05$



**DFS in ITT population (stage IB-IIIA)**  
2-sided  $\alpha=0.05$

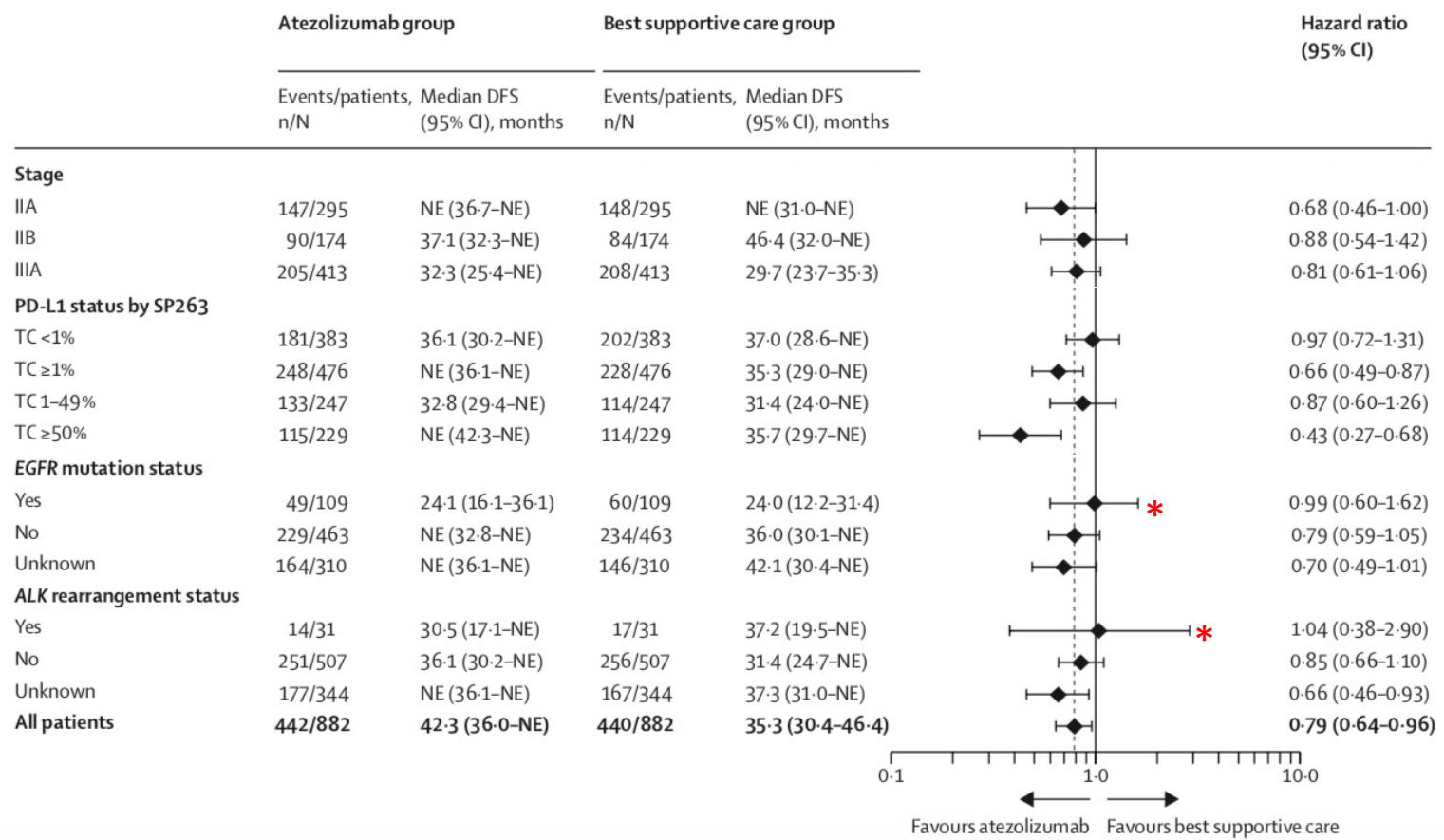


**OS in ITT population**  
2-sided  $\alpha=0.05$

# IMpower010 (2021): Adjuvant Atezolizumab

## Subgroups in Stage II-III ITT population

B



# IMpower010 (2021): Adjuvant Atezolizumab

- 23% of trial patients enrolled did not receive adjuvant IO/BSC
- DFS benefit starts early and is maintained at 3y in stage II-III
  - Driven by PD-L1 >1% population and strongest in >50% population
  - No benefit so far in PD-L1 <1% subgroup
  - No benefit in EGFR/ALK
- OS data immature
  - Will DFS predict OS for adjuvant immunotherapy as it did in PACIFIC?

# PEARLS/KEYNOTE-091 (2022): Adjuvant Pembrolizumab

**ESMO VIRTUAL PLENARY**

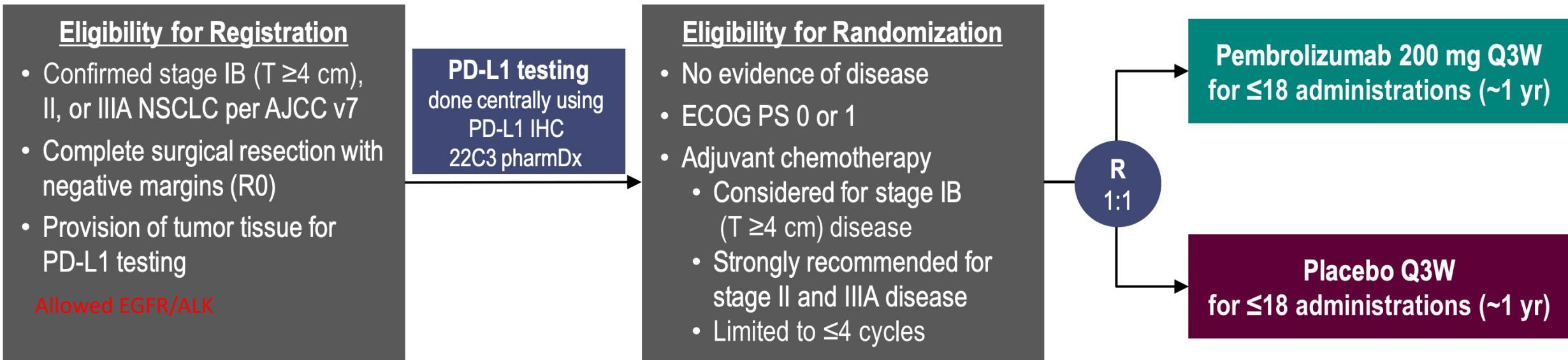
**Pembrolizumab Versus Placebo For Early-Stage NSCLC Following Complete Resection and Adjuvant Chemotherapy When Indicated: Randomized, Triple-Blind, Phase 3 EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Study**

L. Paz-Ares,<sup>1\*</sup> M. O'Brien,<sup>2\*</sup> M. Mauer,<sup>3</sup> U. Dafni,<sup>4</sup> K. Oselin,<sup>5</sup> L. Havel,<sup>6</sup> E. Esteban,<sup>7</sup> D. Isla,<sup>8</sup> A. Martinez-Martí,<sup>9</sup> M. Faehling,<sup>10</sup> M. Tsuboi,<sup>11</sup> J.S. Lee,<sup>12</sup> K. Nakagawa,<sup>13</sup> J. Yang,<sup>14</sup> S.M. Keller,<sup>14</sup> N. Jha,<sup>3</sup> S. Marreaud,<sup>3</sup> R. Stahel,<sup>15</sup> S. Peters,<sup>16\*\*</sup> B. Besse<sup>17\*\*</sup> on behalf of the PEARLS/KEYNOTE-091 Investigators

<sup>1</sup>Hospital Universitario 12 de Octubre, CNIO, Ciberonc & Universidad Complutense, Madrid, Spain; <sup>2</sup>Royal Marsden Hospital, London, UK; <sup>3</sup>European Organisation for Research and Treatment of Cancer, Headquarters Brussels, Belgium; <sup>4</sup>National and Kapodistrian University of Athens and Frontier Science Foundation Hellas; <sup>5</sup>North Estonia Medical Centre, Tallinn, Estonia; <sup>6</sup>Charles University and Thomayer Hospital, Prague, Czech Republic; <sup>7</sup>Hospital Universitario Central de Asturias, Oviedo, Spain; <sup>8</sup>University Hospital Lozano Blesa, IIS Aragon, Zaragoza, Spain; <sup>9</sup>Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; <sup>10</sup>Klinikum Esslingen, Esslingen, Germany; <sup>11</sup>National Cancer Center Hospital East, Kashiwa, Japan; <sup>12</sup>Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; <sup>13</sup>Kindai University Faculty of Medicine, Osaka, Japan; <sup>14</sup>Merck & Co., Inc., Kenilworth, NJ, USA; <sup>15</sup>European Thoracic Oncology Platform, Bern, Switzerland; <sup>16</sup>Lausanne University Hospital, Lausanne, Switzerland; <sup>17</sup>Institut Gustave Roussy, Villejuif, France  
\*Drs. Paz-Ares and O'Brien contributed equally to this presentation. \*\*Drs. Peters and Besse contributed equally to this presentation.



# PEARLS/KEYNOTE-091 (2022): Adjuvant Pembrolizumab



## Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs  $\geq 50\%$ )
- 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  $\geq 50\%$  population

## Secondary End Points

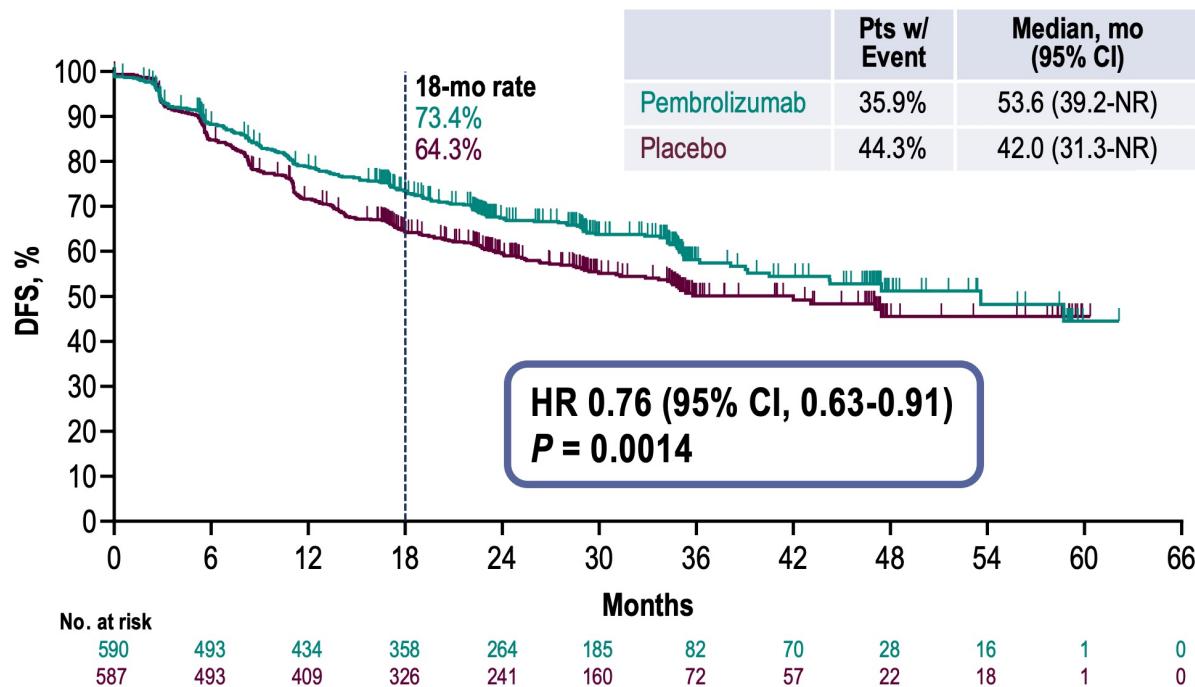
- DFS in the PD-L1 TPS  $\geq 1\%$  population
- OS in the overall, PD-L1 TPS  $\geq 50\%$ , and PD-L1 TPS  $\geq 1\%$  populations
- Lung cancer-specific survival in the overall population
- Safety

# PEARLS/KEYNOTE-091 (2022): Adjuvant Pembrolizumab

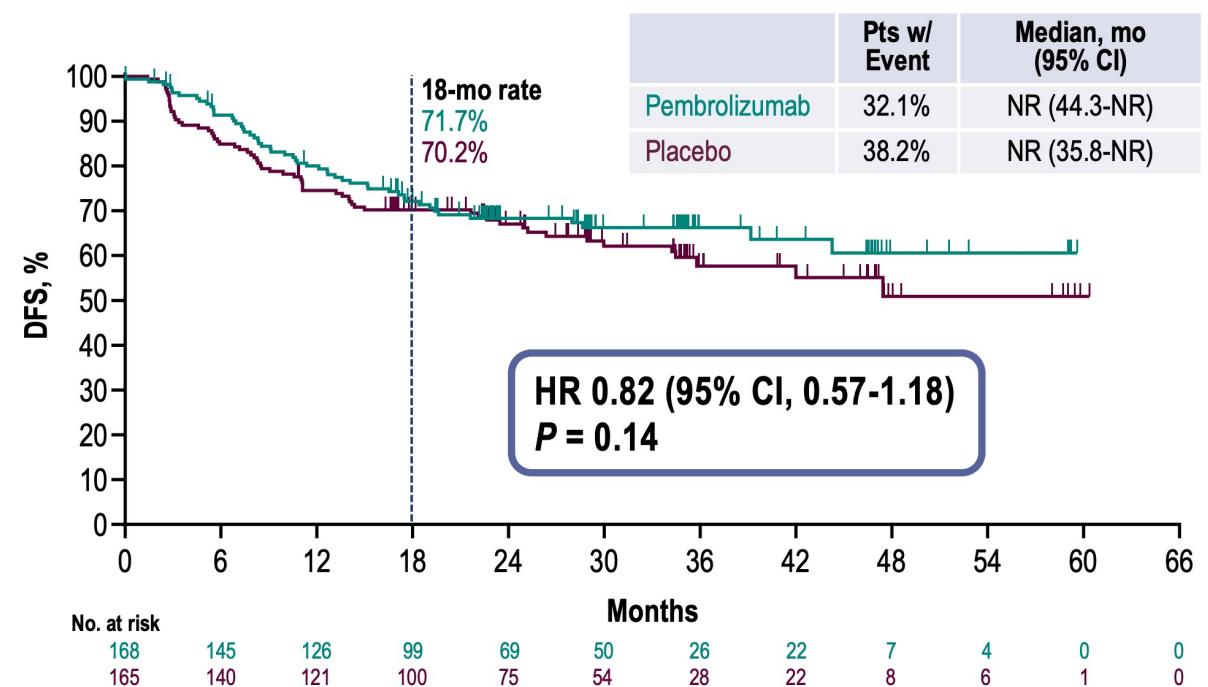
- Baseline characteristics:
  - 65yo, 68% male, 64% nonsquamous, 85% smokers
  - ECOG 1: 35% vs 41% placebo
  - Stage: 14% IB, 56% II, 30% III
  - PD-L1: 39.5% (<1%), 32% (1-49%), 28% ( $\geq 50\%$ )
  - Mutations: 6% EGFR, 1% ALK

# PEARLS/KEYNOTE-091 (2022): Adjuvant Pembrolizumab

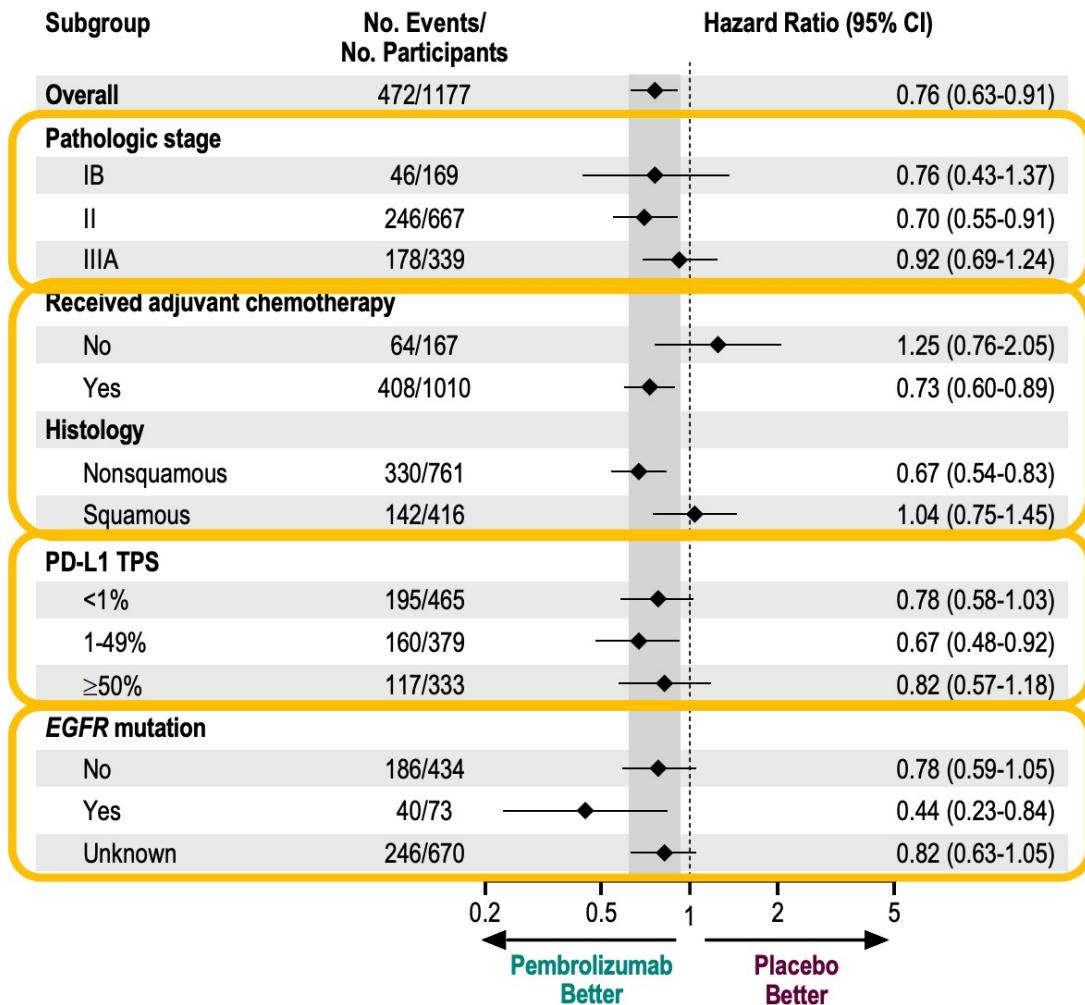
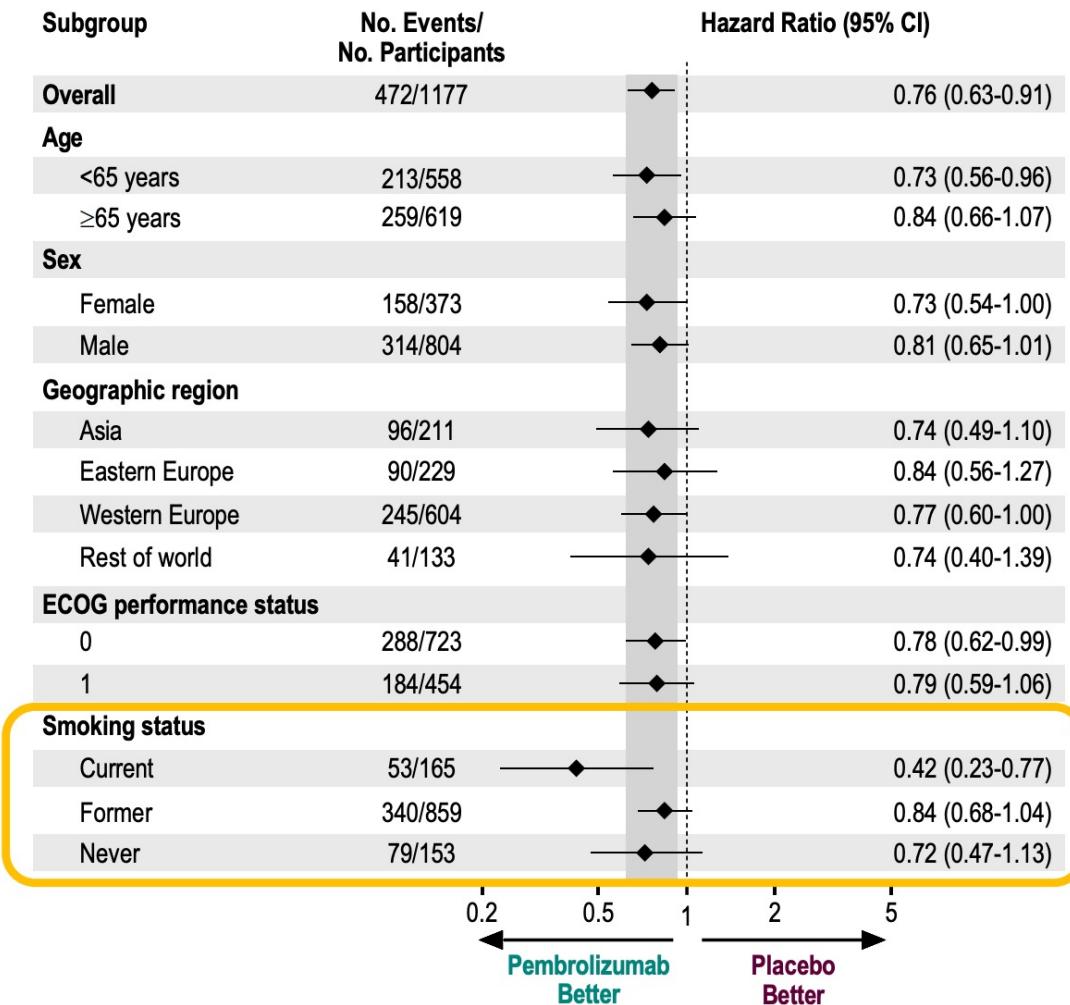
## DFS, Overall Population



## DFS, PD-L1 TPS ≥50% Population



# PEARLS/KEYNOTE-091 (2022): Adjuvant Pembrolizumab



# Comparison: Baseline Characteristics

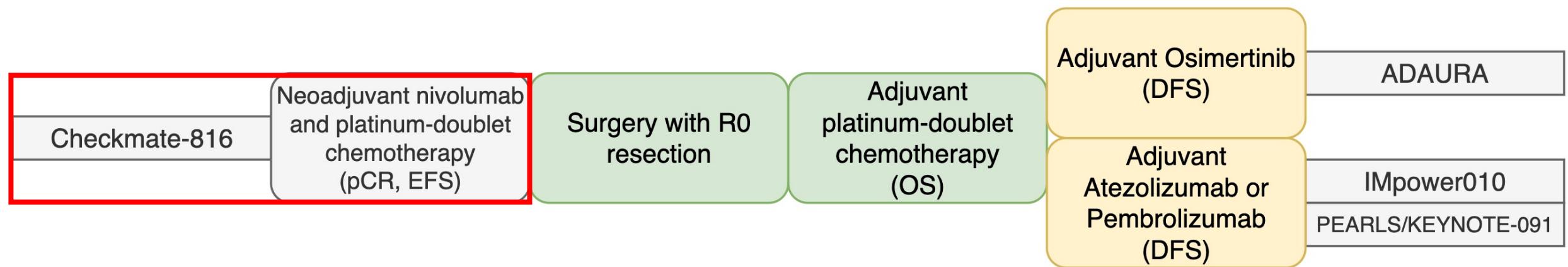
- IMpower010:
  - 62yo, 55% ECOG 0
  - Stage: 13% IB, **47% II**, **40% IIIA**
  - Surgery: 16% pneumonectomy
  - PD-L1: **50% ( $\geq 1\%$ )** by SP263
  - Mutations: 12% EGFR, 4% ALK
- Chemotherapy: 100% received, 85% completed 4 cycles
- PEARLS/KEYNOTE-091:
  - 65yo, 60% ECOG 0
  - Stage: 14% IB, **56% II**, **30% IIIA**
  - Surgery: ?
  - PD-L1: **60% ( $\geq 1\%$ )** by 22C3
  - Mutations: 6% EGFR, 1% ALK
- Chemotherapy: 85% received

# PEARLS/KEYNOTE-091 (2022): Adjuvant Pembrolizumab

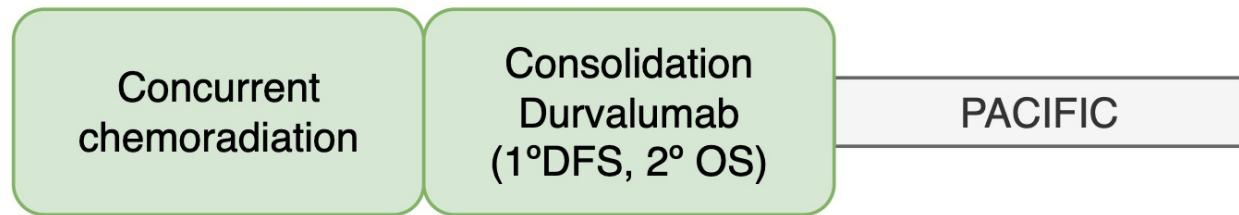
- DFS benefit at 18 months
  - Incongruent results in PD-L1 >50% population as well as other subgroups
  - Immature data at 18 months? (vs 36 months in IMpower010)
- OS data immature
- Limited information without publication

# Landscape in 2022

## Stage IB (>4cm) to IIIA



## Stage III, unresectable



# Checkmate-816 (2022): Neoadjuvant Nivolumab + Platinum-doublet

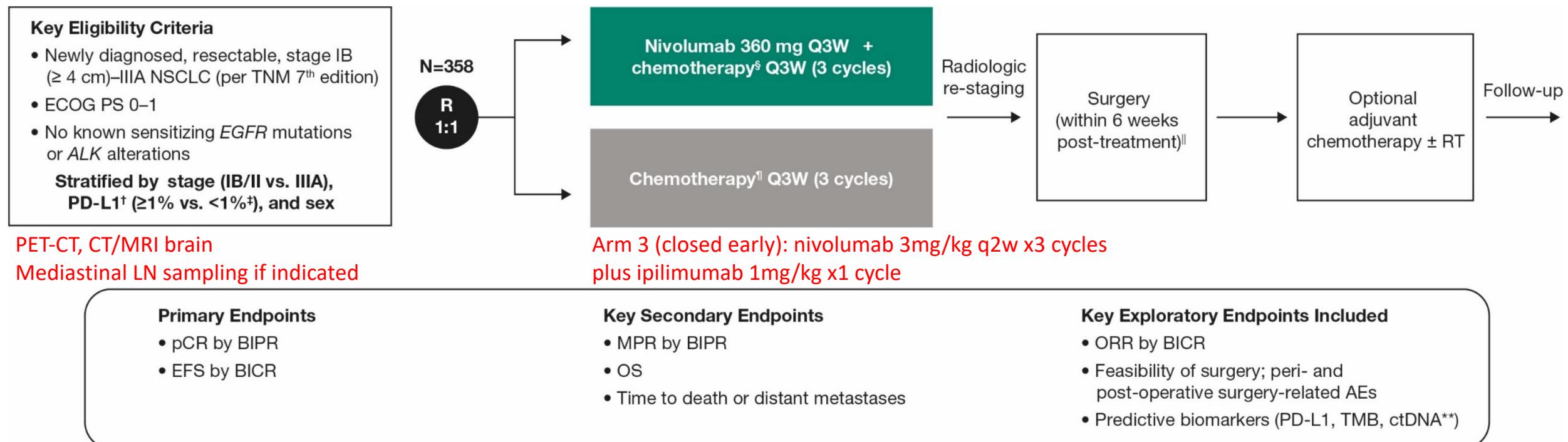
ORIGINAL ARTICLE

## Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

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

# Checkmate-816 (2022): Neoadjuvant Nivolumab + Platinum-doublet

**Figure S1.** Study Design.\*

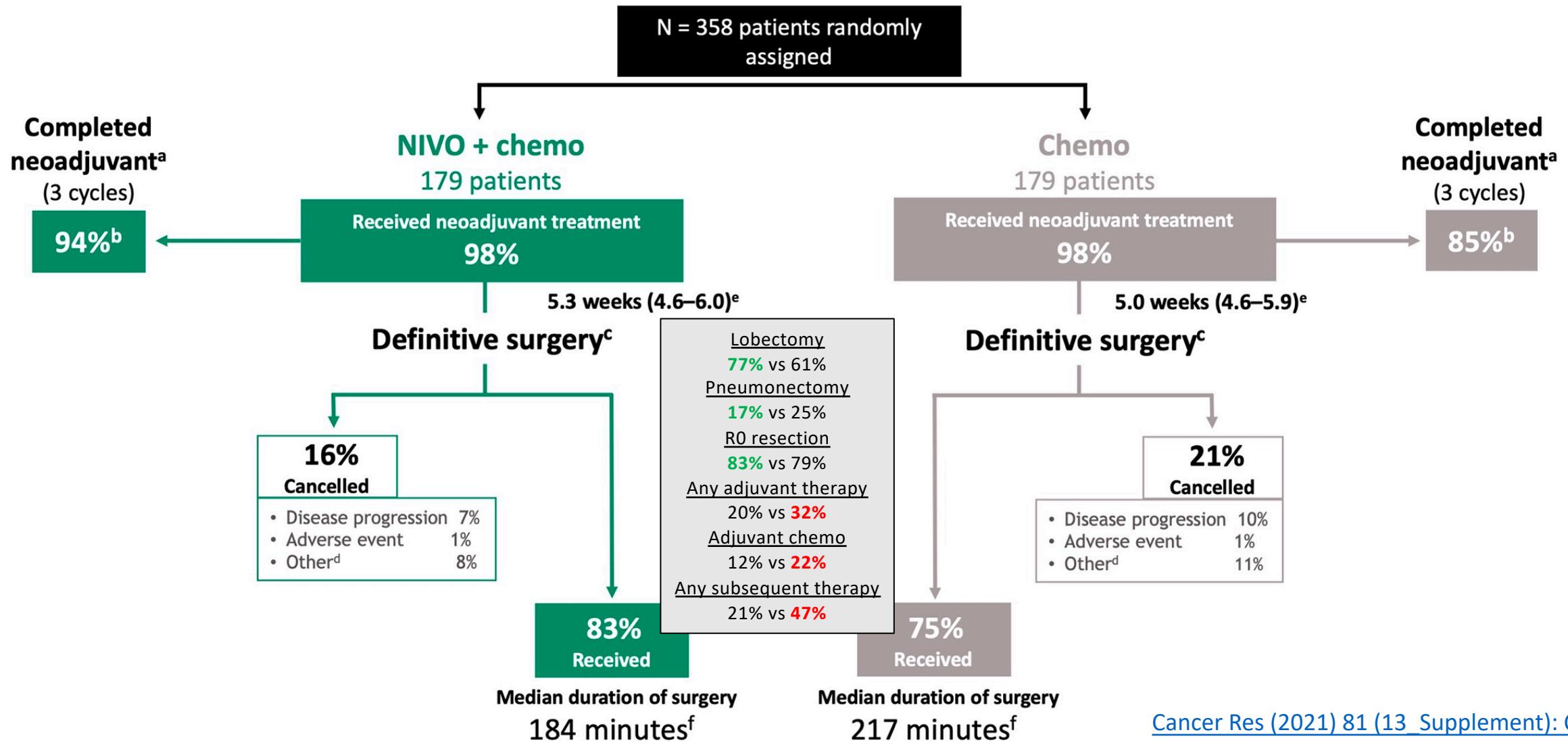


# Checkmate-816 (2022): Neoadjuvant Nivolumab + Platinum-doublet

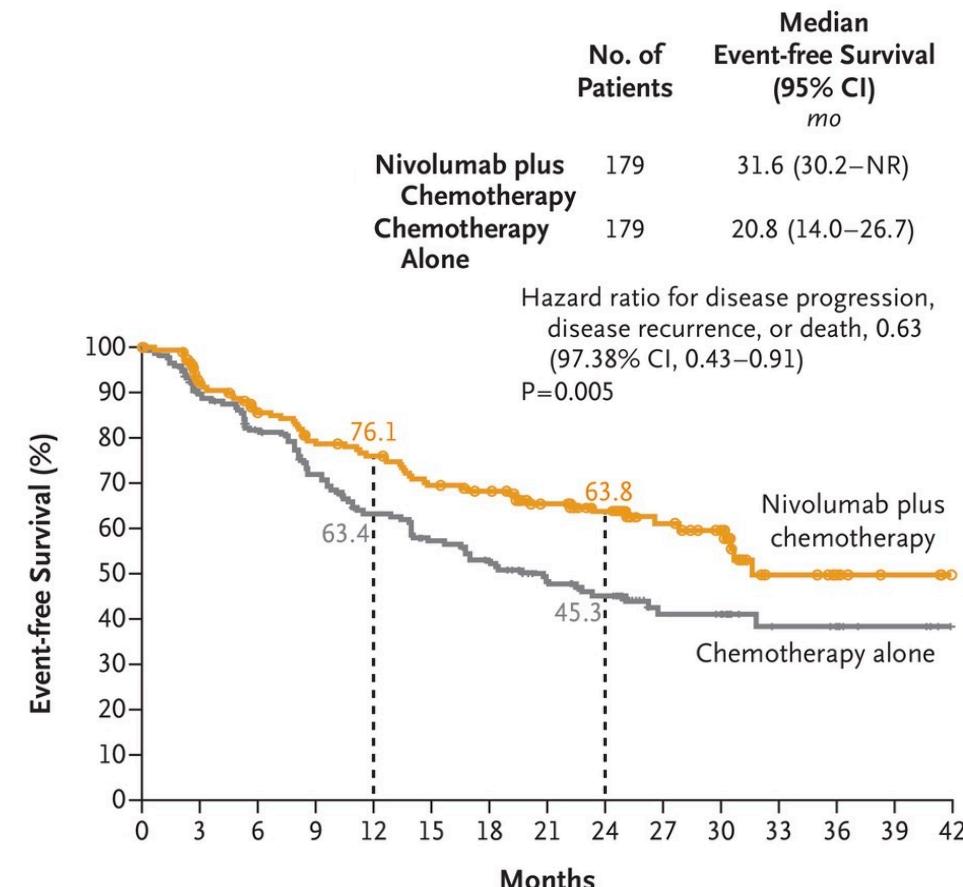
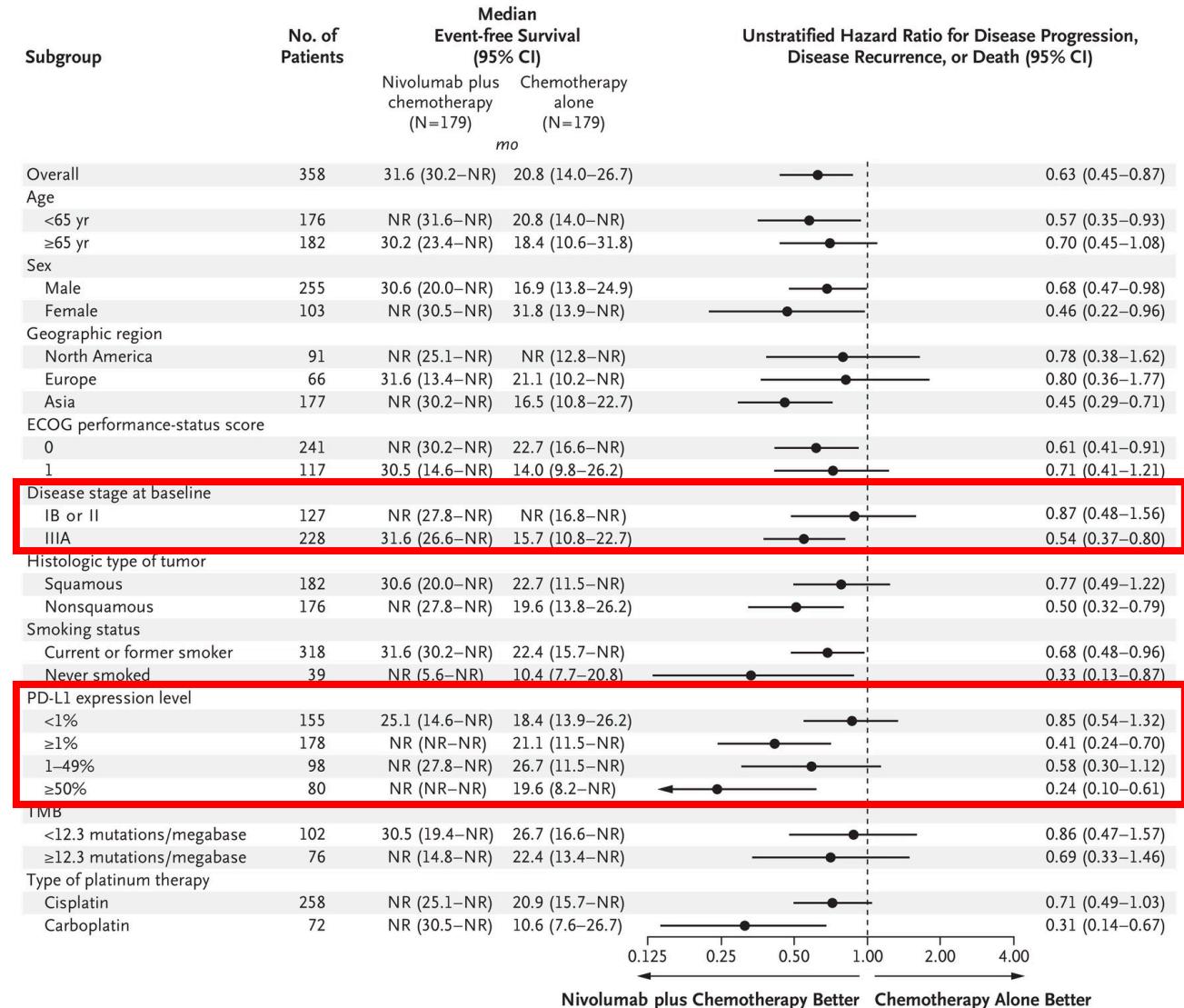
- Baseline Characteristics

- 64yo, 71% male, 67% ECOG 0, 50% nonsquamous, 89% smokers
- Stage: 36% IB or II, 64% IIIA
- PD-L1 : 43% (<1%), 27%(1-49%), 22% (>50%), 7% (n/a) by 28-8
- Chemotherapy: 70% cisplatin

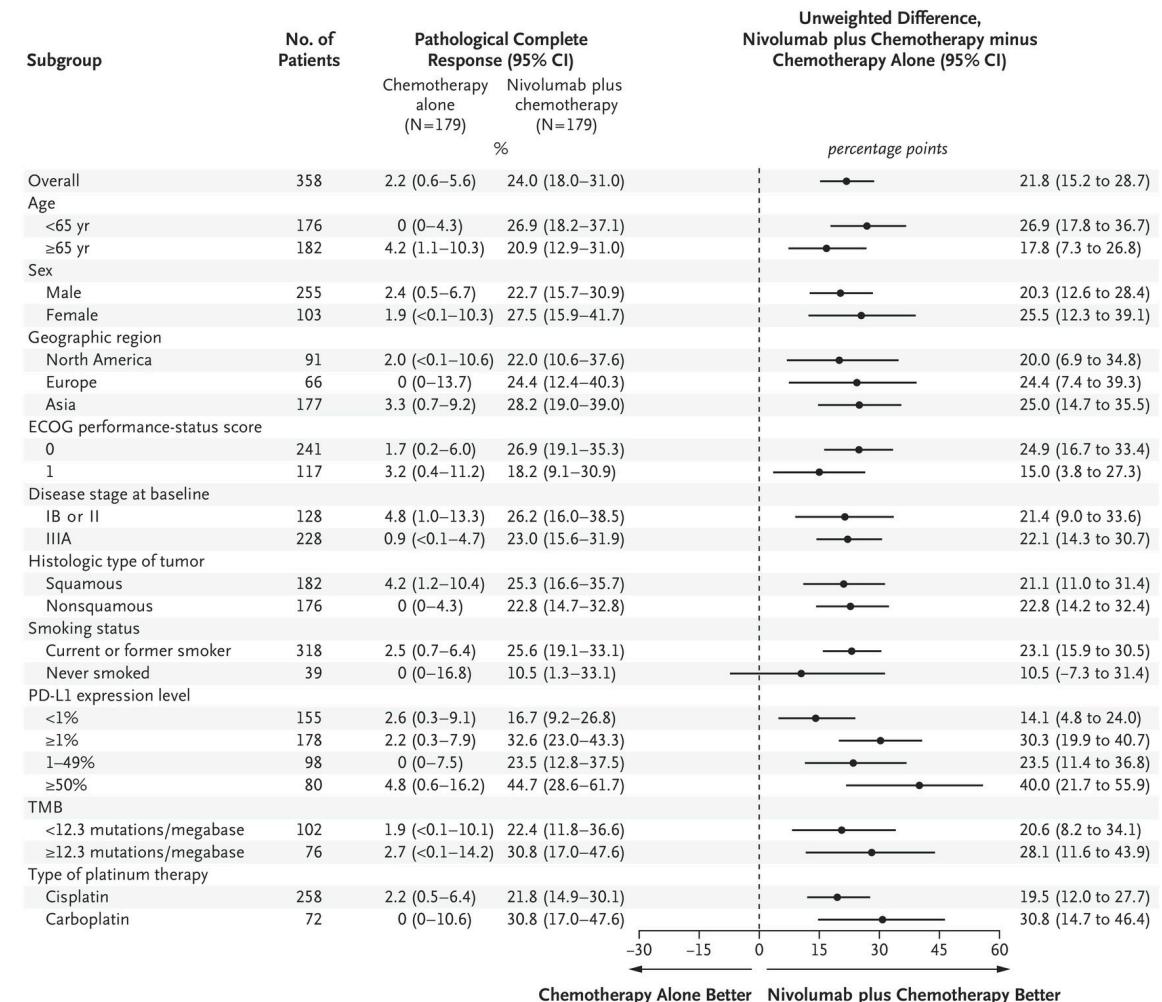
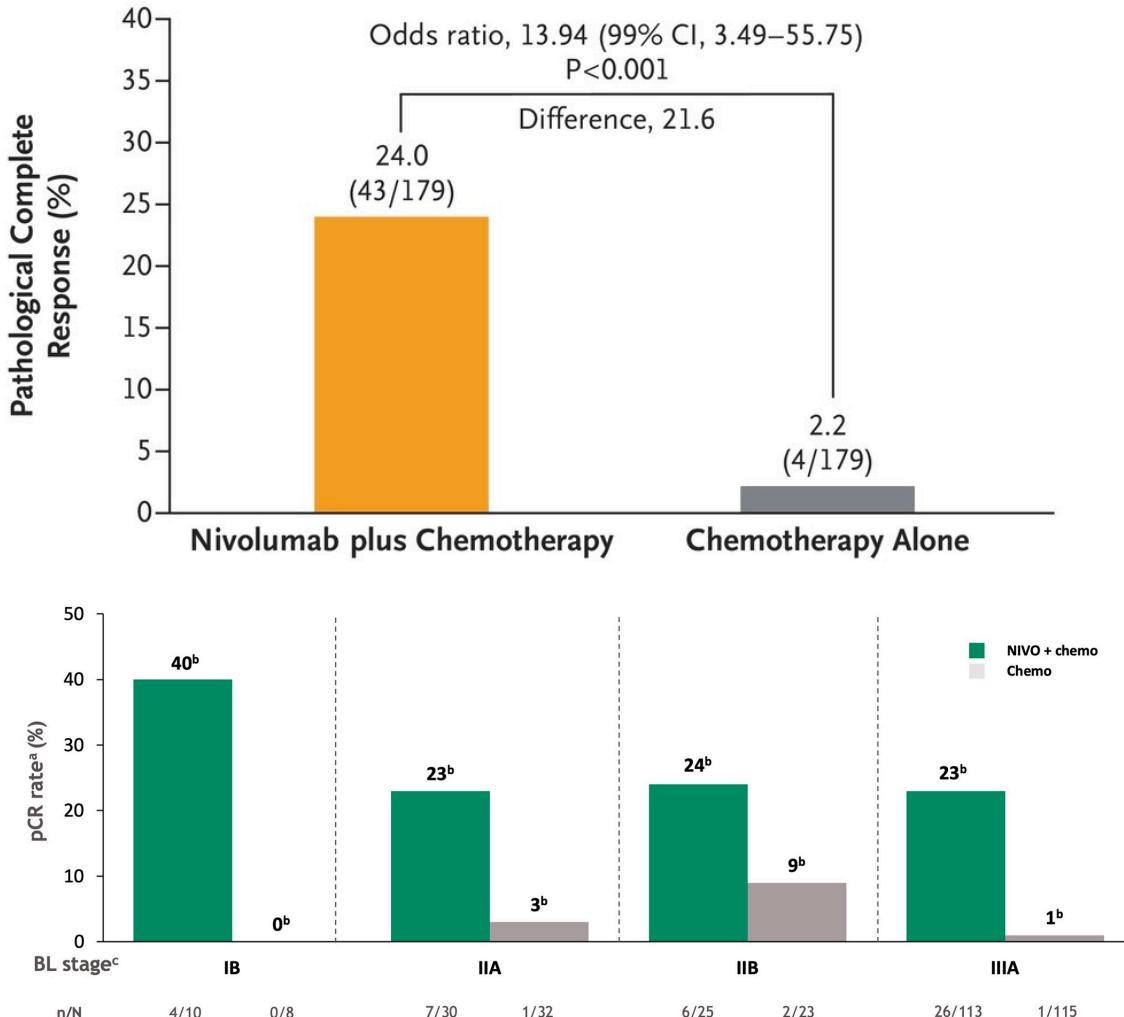
# Checkmate-816 (2022): Neoadjuvant Nivolumab + Platinum-doublet



# Checkmate-816 (2022): Neoadjuvant Nivolumab + Platinum-doublet

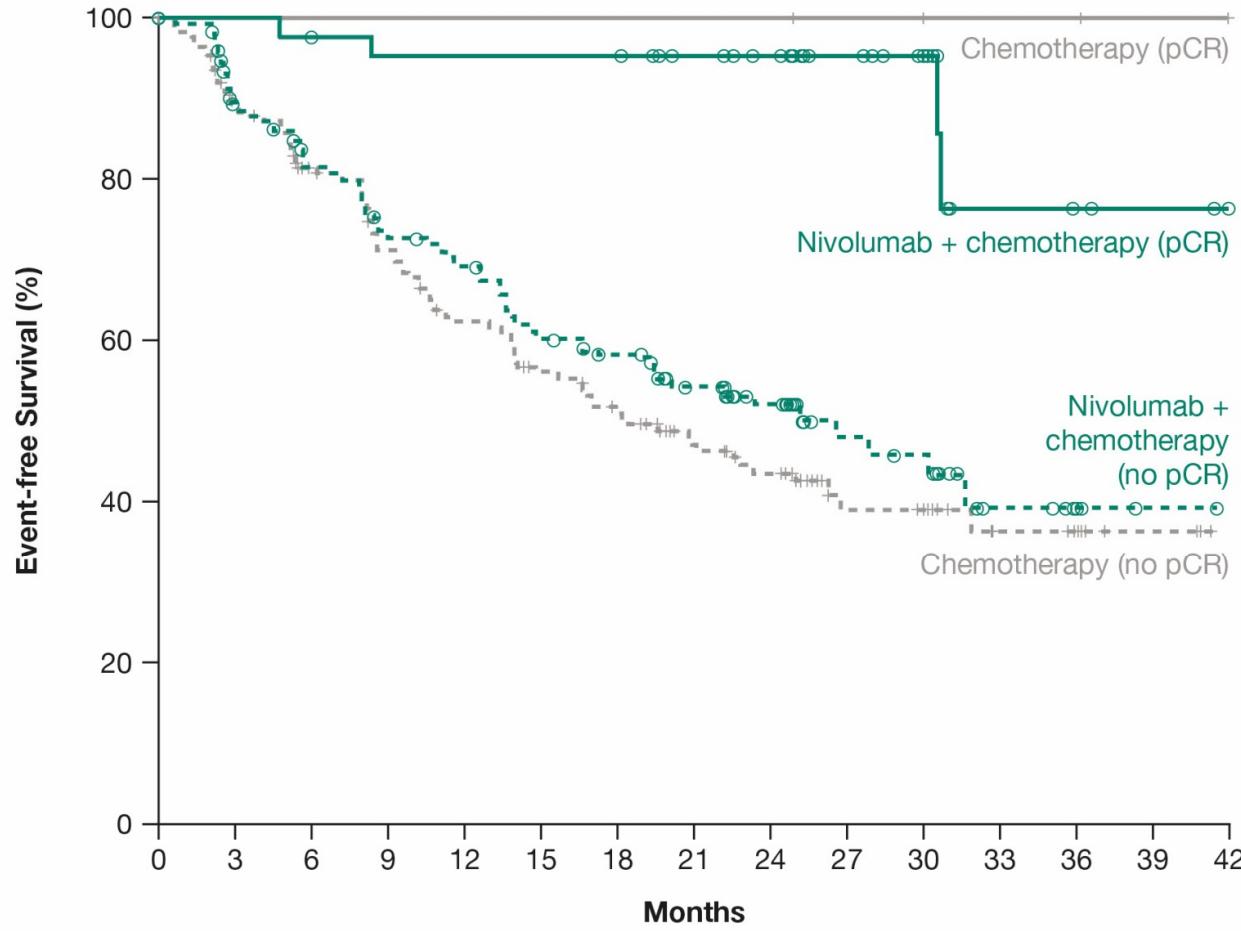


# Checkmate-816 (2022): Neoadjuvant Nivolumab + Platinum-doublet



<sup>a</sup> pCR improvement with NIVO + chemo vs chemo was observed regardless of radiologic down-staging<sup>d</sup>

# Checkmate-816 (2022): Neoadjuvant Nivolumab + Platinum-doublet



	Nivolumab + chemotherapy		Chemotherapy	
	pCR (n=43)	No pCR (n=136)	pCR (n=4)	No pCR (n=175)
Median EFS, mo (95% CI)	NR (30.6–NR)	26.6 (16.6–NR)	NR (NR–NR)	18.4 (13.9–26.2)
HR (95% CI)*	0.13 (0.05–0.37)		Not computed†	

No. at Risk														
Nivolumab + chemotherapy (pCR)	43	43	41	40	40	40	35	32	19	14	6	3	2	0
Chemotherapy (pCR)	4	4	4	4	4	4	4	4	3	2	2	1	0	
Nivolumab + chemotherapy (no pCR)	136	108	95	84	78	67	62	52	42	22	20	7	3	0
Chemotherapy (no pCR)	175	140	122	105	90	79	71	57	48	23	22	11	9	0

# Checkmate-816 (2022): Neoadjuvant Nivolumab + Platinum-doublet

- pCR and DFS benefit, particularly in PD-L1  $\geq 1\%$  and  $\geq 50\%$
- Less invasive surgery, less adjuvant therapy
- Short course of treatment (3 cycles vs 1 year)

# Immunotherapy Adverse Events

**Table 3.** Adverse Events of Any Cause.

Event	PACIFIC			
	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
number of patients with event (percent)				
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

\* Included are events that were reported in at least 10% of the patients in either group. Grade 5 adverse events of any cause occurred in 21 patients (4.4%) who received durvalumab (4 [0.8%] with pneumonitis, 2 [0.4%] with cardiac arrest, and 1 each [0.2%] with the following: pneumonia, bacterial pneumonia, pneumococcal pneumonia, sepsis, septic shock, cardiomyopathy, cardiopulmonary failure, myocardial infarction, aortic dissection, dyspnea, emphysema, hemoptysis, respiratory distress, respiratory failure, radiation pneumonitis, right ventricular failure, increased level of brain natriuretic peptide, and unknown cause). Grade 5 adverse events of any cause occurred in 13 patients (5.6%) who received placebo (3 each [1.3%] with pneumonitis and pneumonia and 1 each [0.4%] with the following: pneumonia streptococcal, West Nile virus infection, cardiac arrest, eosinophilic myocarditis, hemoptysis, intestinal obstructions, radiation pneumonitis, and unknown cause). Each patient could have had more than one grade 5 adverse event.

† Pneumonitis or radiation pneumonitis was assessed by investigators with subsequent review and adjudication by the study sponsor. In addition, pneumonitis is a grouped term that includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis.

**IMpower 010**

	Atezolizumab group (n=495)	Best supportive care group (n=495)
<b>Adverse event</b>		
Any grade	459 (93%)	350 (71%)
Grade 3-4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
<b>Immune-mediated adverse events</b>		
Any grade	256 (52%)	47 (9%)
Grade 3-4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

Data are n (%). \*Interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, and acute myeloid leukaemia (all four events related to atezolizumab), and pneumothorax, cerebrovascular accident, arrhythmia, and acute cardiac failure. †Pneumonia; pulmonary embolism; and cardiac tamponade and septic shock in the same patient. ‡Atezolizumab-related.

**PEARLS/KEYNOTE-091**

	Pembrolizumab (N = 580)	Placebo (N = 581)
<b>Any</b>	556 (95.9%)	529 (91.0%)
<b>Grade 3-5</b>	198 (34.1%)	150 (25.8%)
<b>Led to death</b>	11 (1.9%)	6 (1.0%)
Treatment-related	4 (0.7%) <sup>a</sup>	0 (0.0%)
<b>Serious</b>	142 (24.5%)	90 (15.5%)
<b>Led to treatment discontinuation</b>	115 (19.8%)	34 (5.9%)
<b>Led to treatment interruption</b>	221 (38.1%)	145 (25.0%)

<sup>a</sup> 1 participant each with myocarditis + cardiogenic shock, myocarditis + septic shock, pneumonia, and sudden death.

# Landscape in 2022

## Stage IB (>4cm) to IIIA

Checkmate-816

Neoadjuvant nivolumab and platinum-doublet chemotherapy (pCR, EFS)

Surgery with R0 resection

Adjuvant platinum-doublet chemotherapy (OS)

Adjuvant Osimertinib (DFS)

Adjuvant Atezolizumab or Pembrolizumab (DFS)

ADAURA

IMpower010

PEARLS/KEYNOTE-091

## Stage III, unresectable

Concurrent chemoradiation

Consolidation Durvalumab (1°DFS, 2° OS)

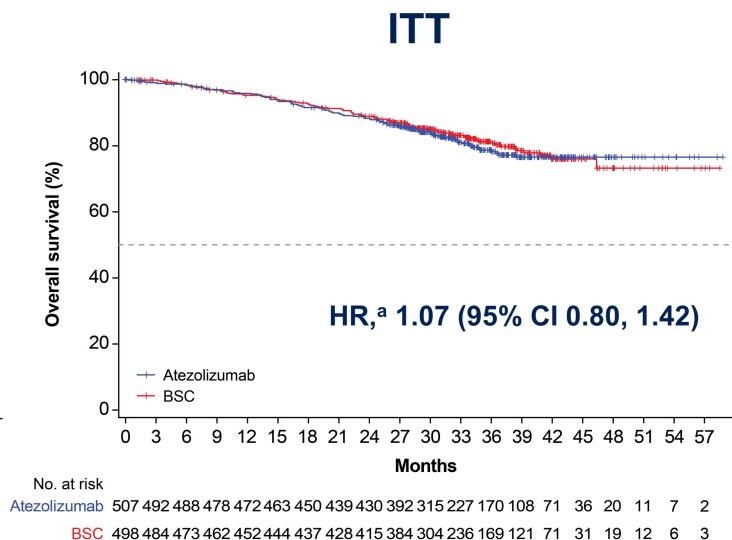
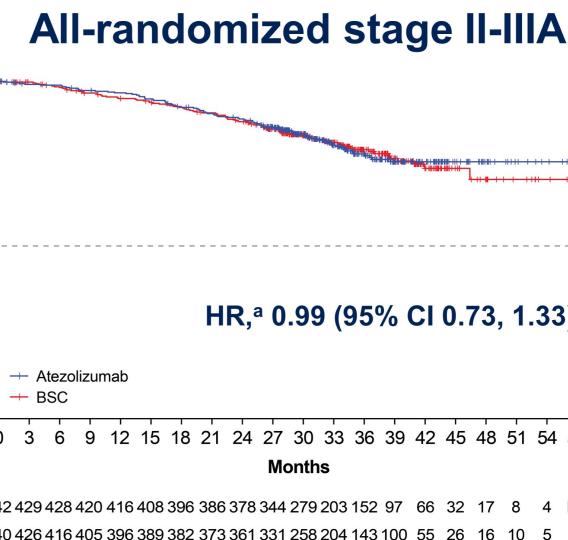
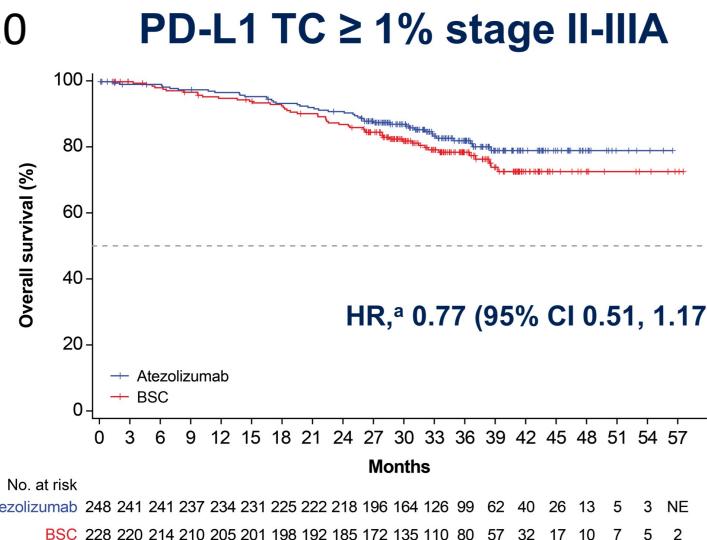
PACIFIC

# Estimated cost (UpToDate wholesale price)

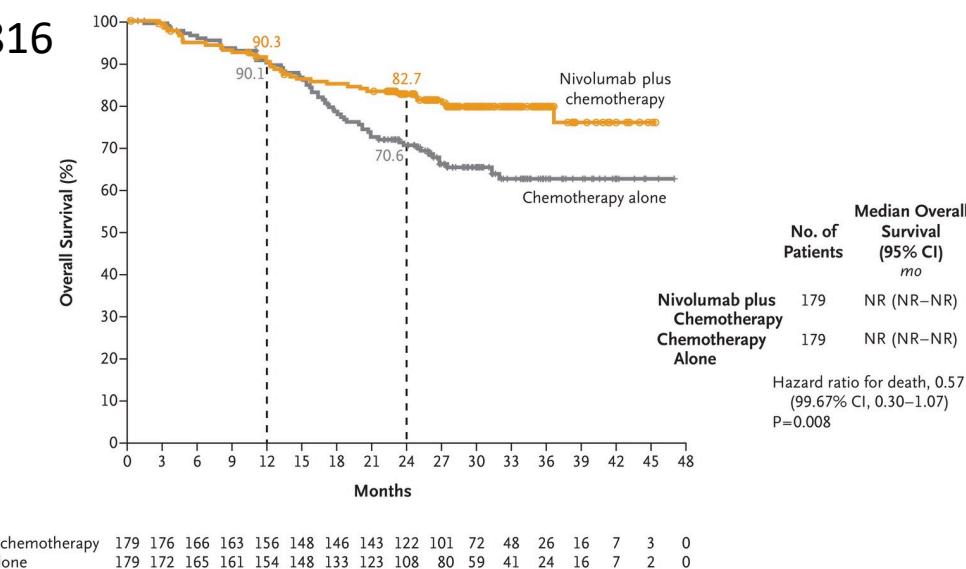
- Osimertinib (Tagrisso Oral)
  - 40 mg (per each): \$626.59
  - 80 mg (per each): \$626.59 x 365d x 3y = **\$686,116.05**
- Atezolizumab (Tecentriq Intravenous)
  - 840 mg/14 mL (per mL): \$590.92
  - 1200 mg/20 mL (per mL): \$590.92 x 16 cycles = **\$9,454.72** + facility fees
- Pembrolizumab (Keytruda Intravenous)
  - 100 mg/4 mL (per mL): \$1,571.11 x 2 (200mg q3w) x 16 cycles = **\$50,275.52** + facility fees
- Durvalumab (Imfinzi Intravenous)
  - 120MG/2.4ML (per mL): \$453.10
  - 500 mg/10 mL (per mL): \$453.09 x 3 (1500mg q4w) x 16 cycles = **\$17,670.51** + facility fees
- Nivolumab (Opdivo Intravenous)
  - 40 mg/4 mL (per mL): \$345.75
  - 100 mg/10 mL (per mL): \$345.75
  - 120MG/12ML (per mL): \$345.75
  - 240MG/24ML (per mL): \$345.75 x2 (360mg q3w) x 3 cycles = **\$2,074.5** + facility fees

# Unofficial not statistically significant OS data

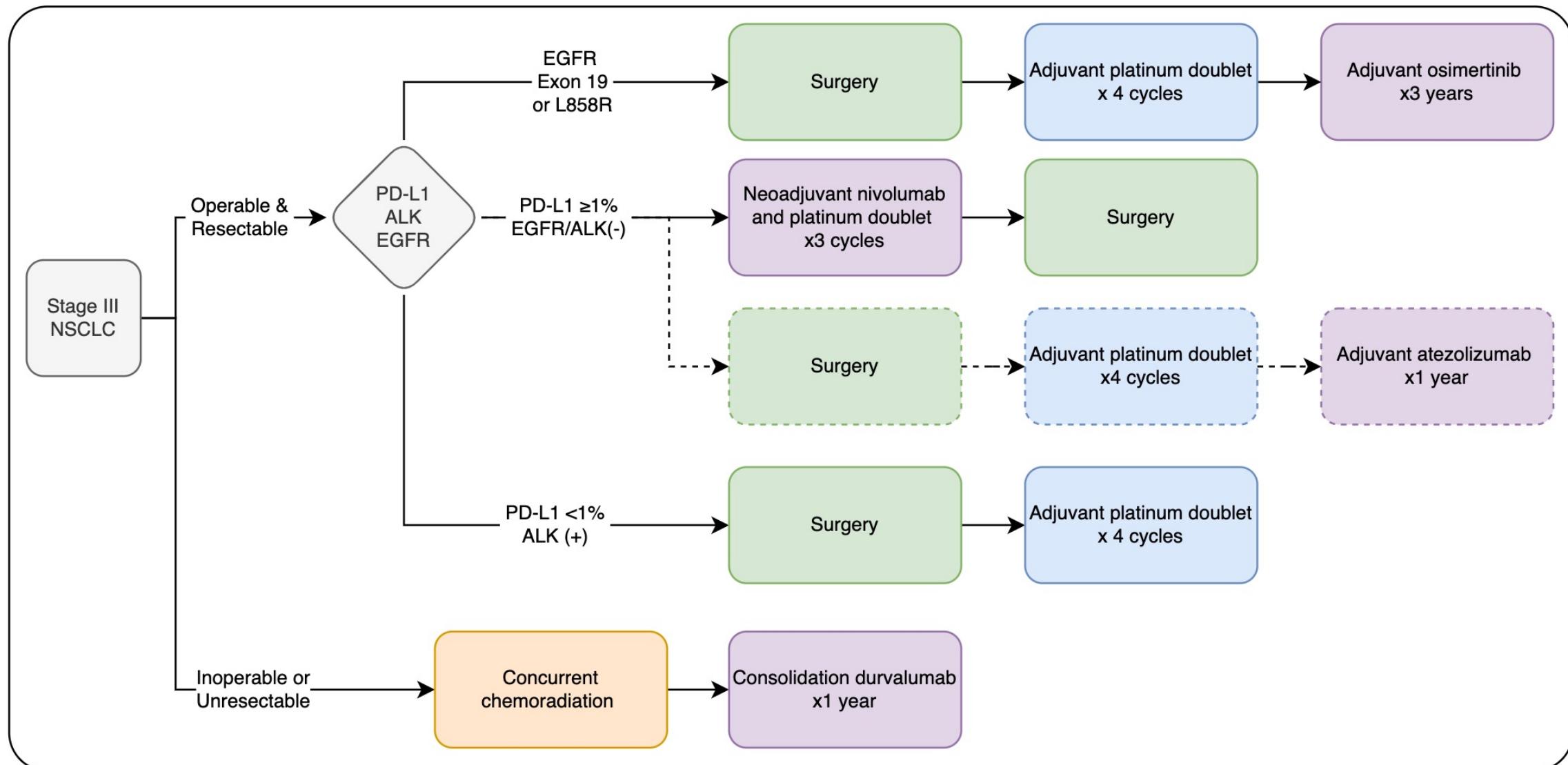
IMpower010



Checkmate-816



# “Put your nickel down”



Thank you



*Amir, unimpressed with zebra (2022)*