Systemic Therapy Sequencing in Early Stage Resectable NSCLC ADJUVANT

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NACT vs Adjuvant

Early stage

Despite efforts directed toward lung cancer screening, stage at diagnosis remains high

- Stage I or II 20%
- stage III (locally advanced) 30%
- Stage IV 50%

Early stage (7^{th} vs 8^{th} Edition AJCC)

Major changes of TNM8 compared to TNM7 applicable to NSCLC

1. More refined tumor size cut points in every T-category, using 1 cm intervals up to the size of 5 cm
2. Classification of main bronchus involvement as T2, with removal of the 2 cm distance from the carina as a limit to separate pT2 and pT3 tumors
3. Classification of partial as well as total atelectasis as T2 instead of T3
4. Regarding diaphragm invasion as a T4 instead of T3 descriptor.
5. No changes in the N-category.

Descriptors and T and M categories of the eighth edition with seventh edition for comparison*

Descriptor in 7th edition	Descriptor in 8th edition	**N categories: 8th edition** (7th edition)			
		Overall stage			
		N0	**N1**	**N2**	**N3**
T1 ≤1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 >1 to 2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 >2 to 3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 >3 to 4 cm	T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2 >4 to 5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 >5 to 7 cm	T3	**IIB** (IIA)	**IIIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 >7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronchial: location/atelectasis 3 to 4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4 to 5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

* Where there is a change, the resultant stage groupings for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.

Current Role of Perioperative Systemic Therapy for Early-Stage NSCLC

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Detterbeck. Chest. 2017;151:193. Goldstraw. J Thorac Oncol. 2016;11:39.

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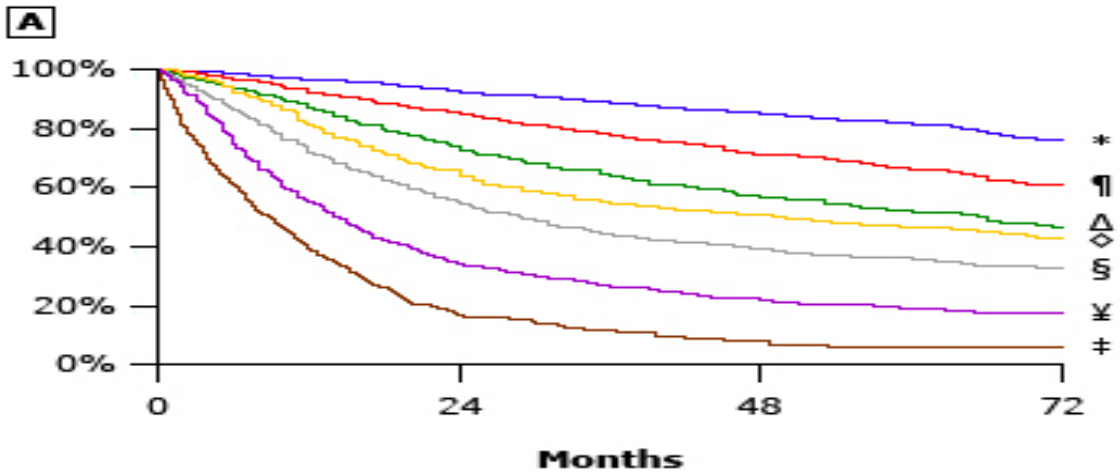
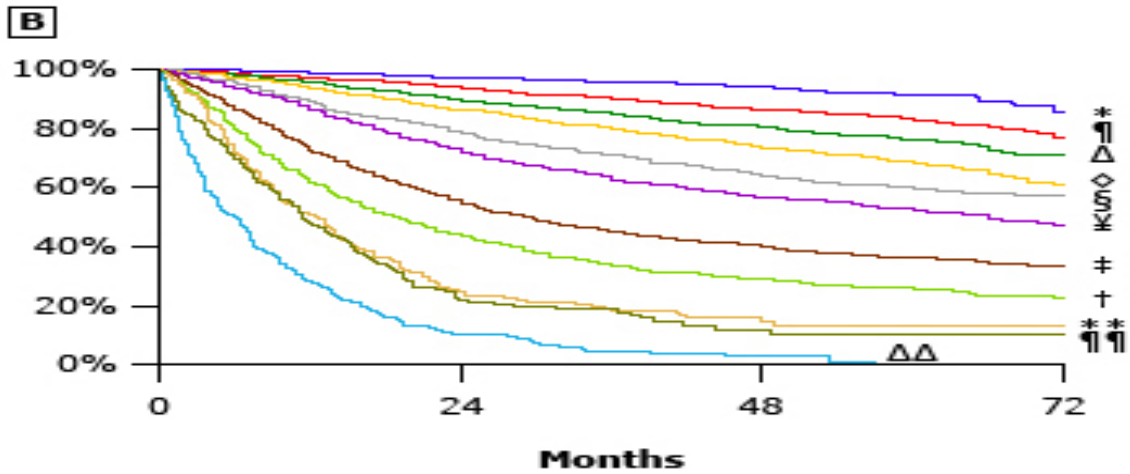
Overall survival by clinical stage according to the seventh edition (A) and the eighth edition (B) groupings using the entire database available for the eighth edition



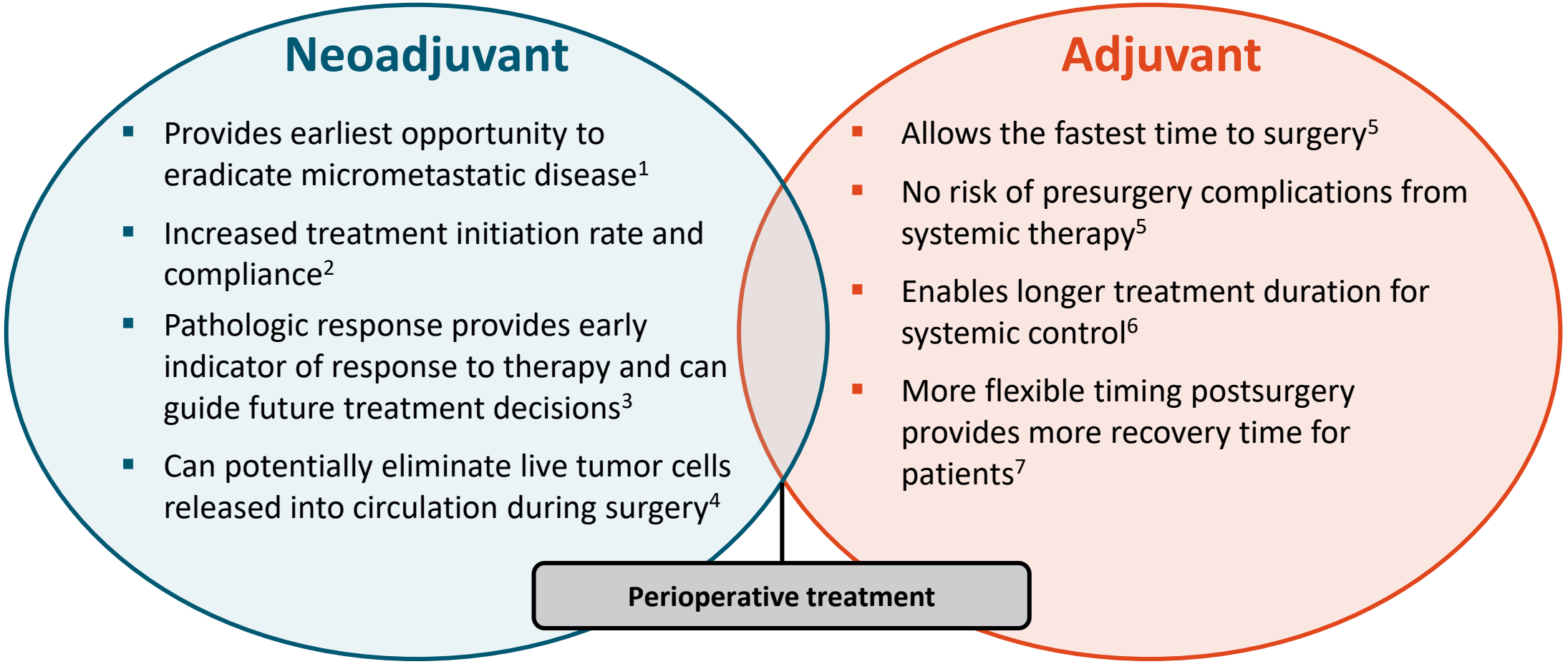


7th edition	Events / N	MST	24 month	60 month
* IA	1119 / 6303	NR	93%	82%
¶ IB	768 / 2492	NR	85%	66%
Δ IIA	424 / 1008	66.0	74%	52%
◇ IIB	382 / 824	49.0	64%	47%
§ IIIA	2139 / 3344	29.0	55%	36%
¥ IIIB	2101 / 2624	14.1	34%	19%
‡ IV	664 / 882	8.8	17%	6%

8th edition	Events / N	MST	24 month	60 month
* IA1	68 / 781	NR	97%	92%
¶ IA2	505 / 3105	NR	94%	83%
Δ IA3	546 / 2417	NR	90%	77%
◇ IB	560 / 1928	NR	87%	68%
§ IIA	215 / 585	NR	79%	60%
¥ IIB	605 / 1453	66.0	72%	53%
‡ IIIA	2052 / 3200	29.3	55%	36%
† IIIB	1551 / 2140	19.0	44%	26%
** IIIC	831 / 986	12.6	24%	13%
¶¶ IVA	336 / 484	11.5	23%	10%
ΔΔ IVB	328 / 398	6.0	10%	0%

Overall survival by clinical stage according to the seventh edition (A) and the eighth edition (B) groupings using the entire database available for the eighth edition. Survival is weighted by type of database submission:

Considerations for Timing of Treatment Options for Early-Stage NSCLC



1. Lewis. Front Oncol. 2018;8:5. 2. Felip. JCO. 2010;28:3138. 3. Hellmann. Lancet Oncol. 2014;15:e42. 4. Xie. Am J Cancer Res. 2021;11:2521.
5. McElnay. J Thorac Dis. 2014;6 Suppl 2:S224. 6. Yuan. Signal Transduct Target Ther. 2019;4:61. 7. Owen. J Thorac Dis. 2018;10(suppl 3):S404.

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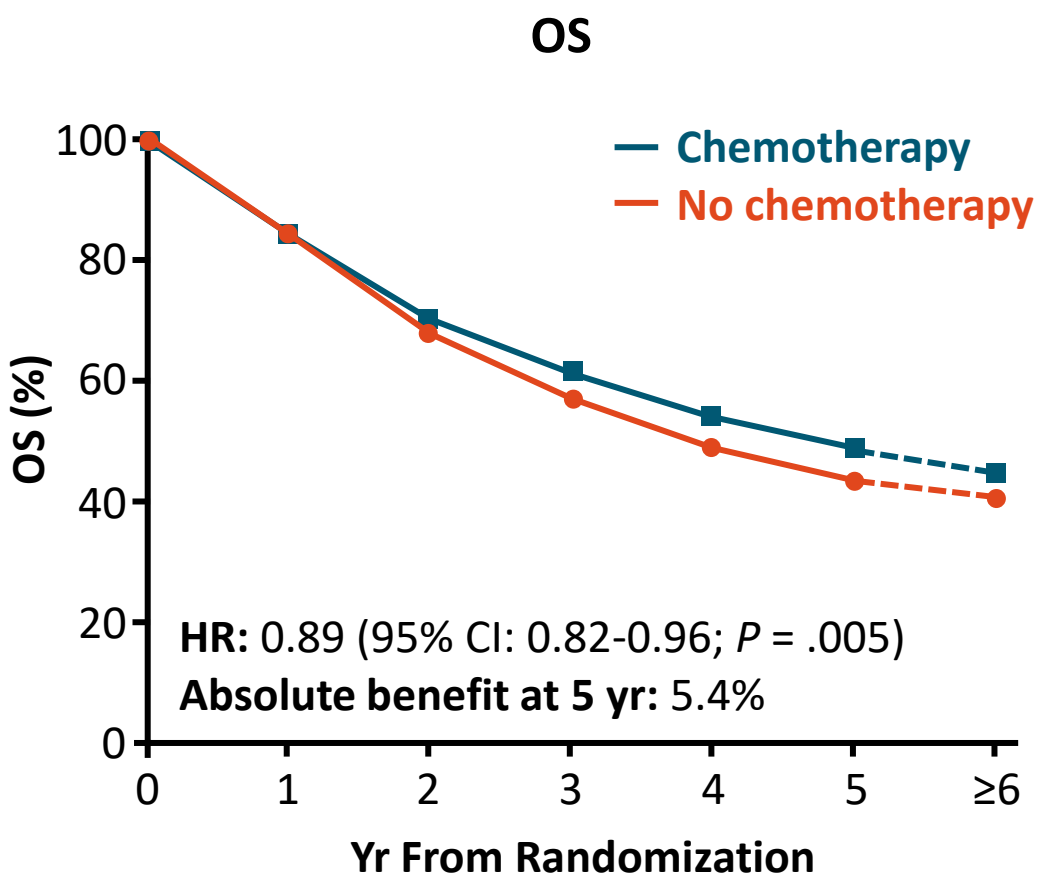
Meta-analysis: Lung Adjuvant Cisplatin Evaluation

- Pooled individual patient data from 5 studies of adjuvant cisplatin-based chemotherapy for completely resected early-stage NSCLC conducted after 1995 (N = 4584)
  - Studies: ALPI, ANITA, BLT, IALT, JBR10
- Overall HR: 0.89
  - Stg II 0.83. Stg IIIA 0.83. Stg IB 0.92
- Chemotherapy at Yr 5
  - ↓ **6.9%** lung cancer death
  - ↑ **1.4%** noncancer death



Pignon. JCO. 2016;26:3552.

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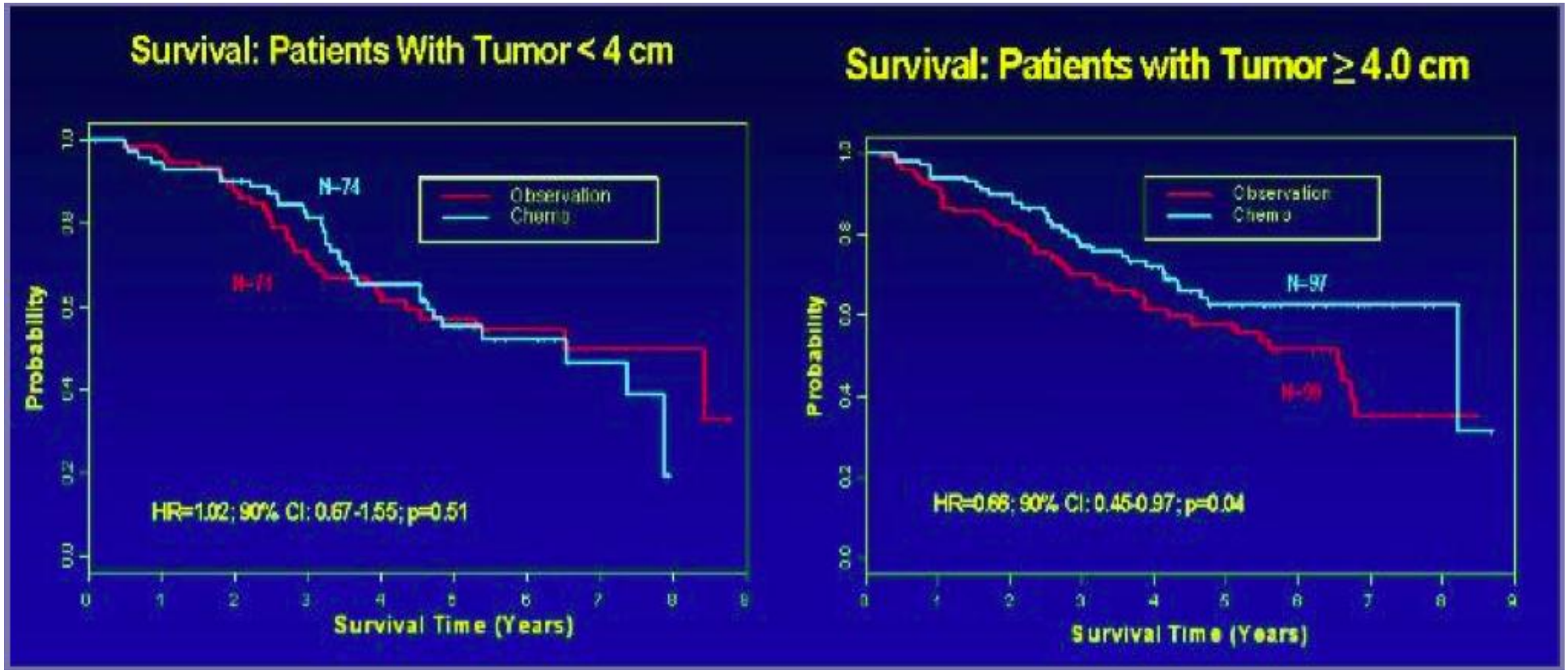
CALGB 9633


Survival: Patients With Tumor < 4 cm
Probability
N=74
Observation
Chemo
HR=1.02; 90% CI: 0.67-1.55; p=0.51
Survival Time (Years)
Survival: Patients with Tumor ≥ 4.0 cm
Probability
Observation
Chemo
N=97
HR=0.66; 90% CI: 0.45-0.97; p=0.04
Survival Time (Years)

Metanalysis Neoadjuvant

- 15 randomized trials and 2,385 patients

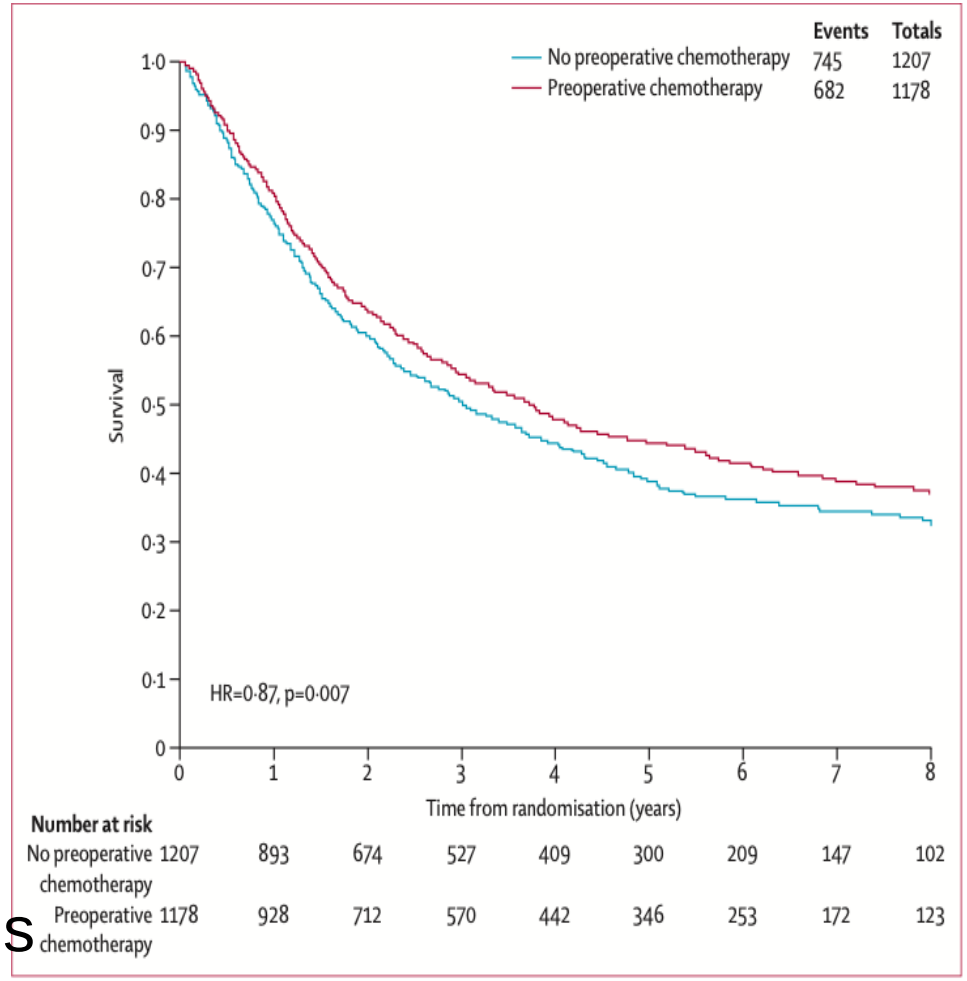
- Significant benefit of preoperative
- chemotherapy in OS

- Absolute survival improvement of 5% at 5 years

- HR, 0.87; 95% CI, 0.78–0.96; p 5 .007

Limitations

- 12 trials did not reach their target accrual
- Lack of using standard Cisplatin based regimens



Perioperative Therapy

- EGFR Mutation +
  - EGFR

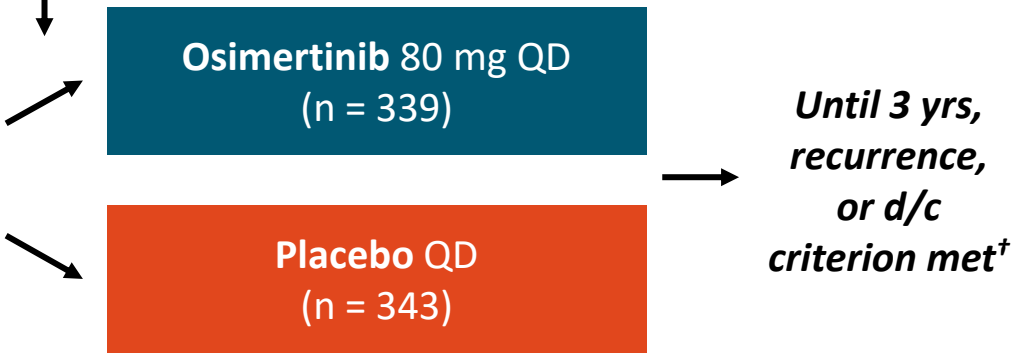
- EGFR Mutation –ve
  - Immunotherapy

ADAURA: Study Design

- International, randomized, double-blind phase III trial (data cutoff for interim analysis: 1/17/2020)
  - IDMC recommended early unblinding due to efficacy; at time of unblinding, trial had completed enrollment and all patients had ≥ 1 yr of follow-up

Patients with completely resected stage IB/II/IIIA NSCLC with negative margins; primary nonsquamous NSCLC with *EGFR* ex19del or L858R*; aged ≥ 18 yrs (≥ 20 yrs in Japan/Taiwan); WHO PS 0/1; brain imaging done; adj CT permitted; maximum time from surgery to randomization: 10 wks without adj CT, 26 wks with adj CT (N = 682)

Stratified by stage (IB vs II vs IIIA), EGFR mutation (ex19del vs L858R), race (Asian vs non-Asian)



*Confirmed centrally in tissue. †Follow-up: until recurrence, Wks 12 and 24, then Q24W to 5 yrs, then yearly; after recurrence, Q24W for 5 yrs, then yearly.

- Primary endpoint: investigator-assessed DFS in patients with stage II/IIIA disease
  - Trial designed to test superiority with assumed DFS HR of 0.70
- Secondary endpoints: DFS in overall population; landmark DFS rates at Yrs 2, 3, 4, and 5; OS; HRQoL; safety

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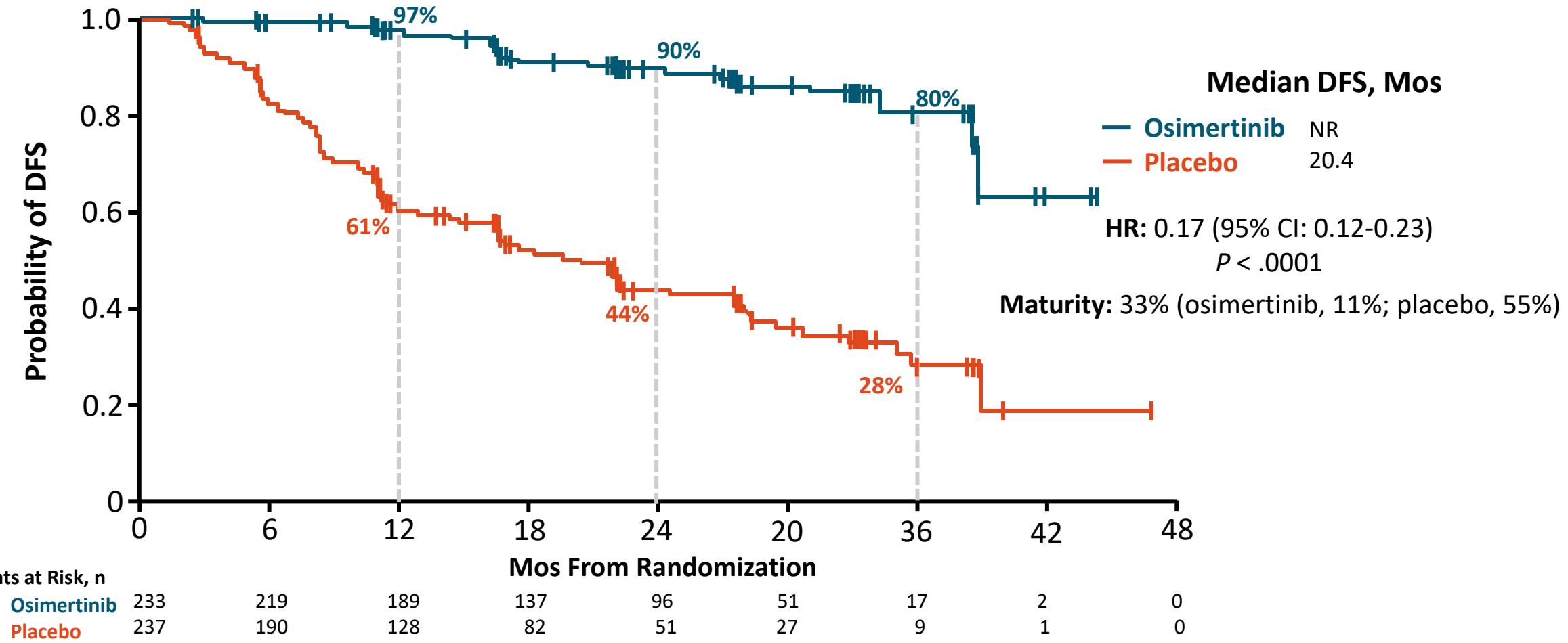
ADAURA: DFS in Patients With Stage II/IIIA NSCLC (Primary Endpoint)



- Adjuvant osimertinib significantly prolonged DFS vs placebo in stage II/IIIA disease ($P < .0001$)

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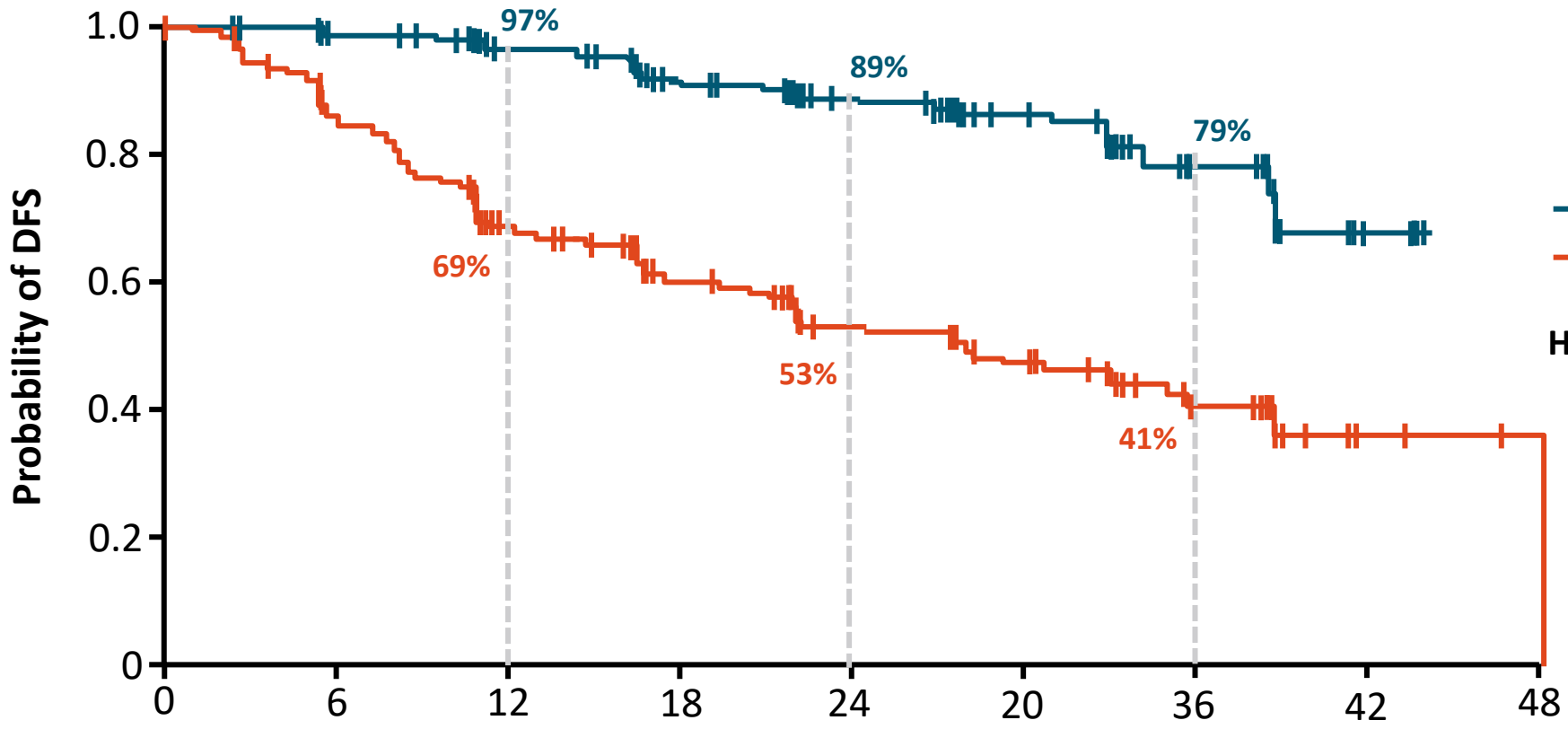
ADAURA: DFS in Overall Population With Stage IB/II/IIIA NSCLC (Secondary Endpoint)



Patients at Risk, n

Osimertinib	339	314	272	206	136	73	25	4	0
Placebo	343	288	209	149	87	53	20	3	1

Median DFS, Mos

Osimertinib	NR
Placebo	28.1

HR: 0.21 (95% CI: 0.16-0.28)
P < .0001

Maturity: 29%
(osimertinib: 12%;
placebo: 46%)

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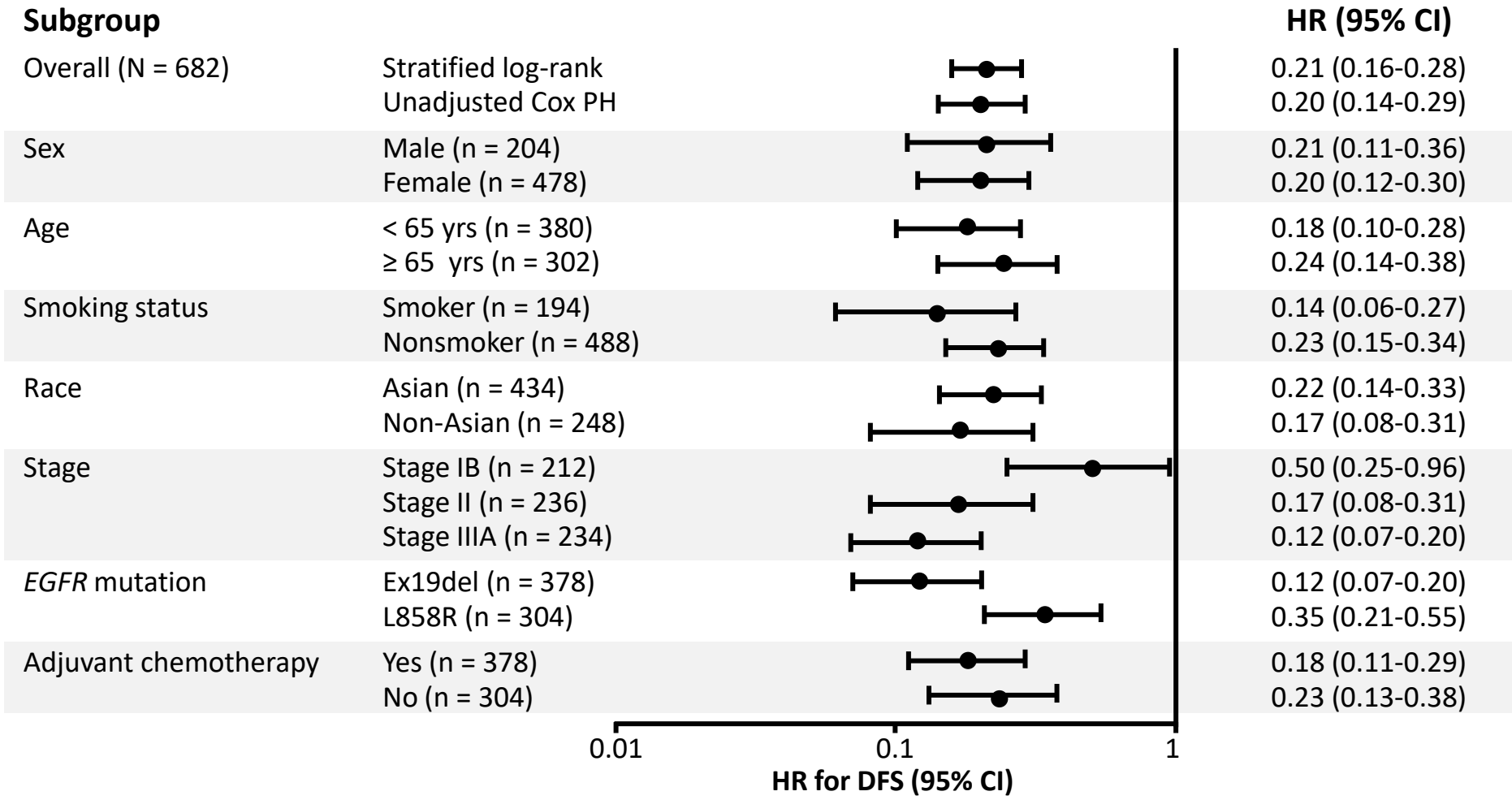
ADAURA: DFS by Subgroup in Overall Population



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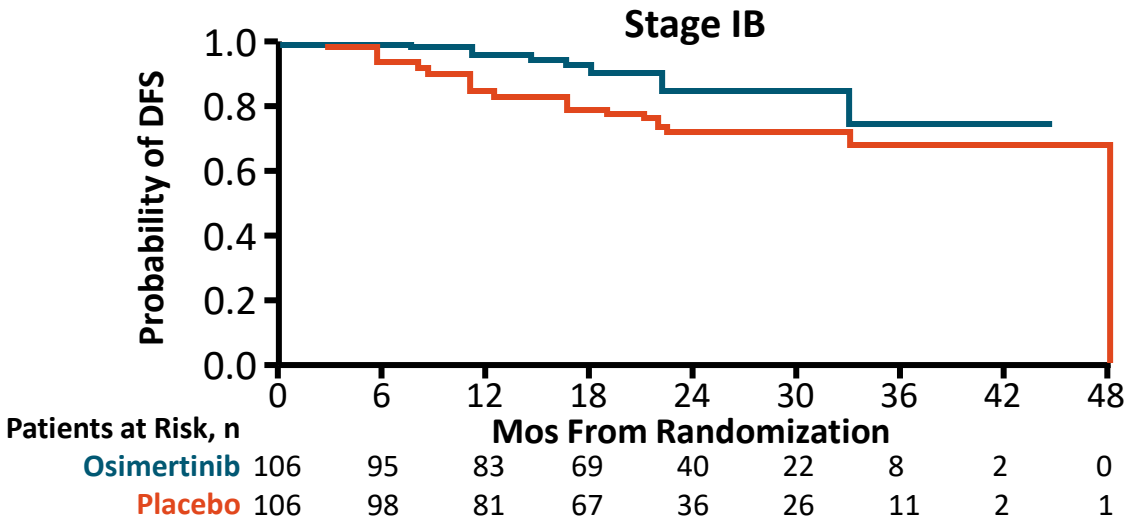
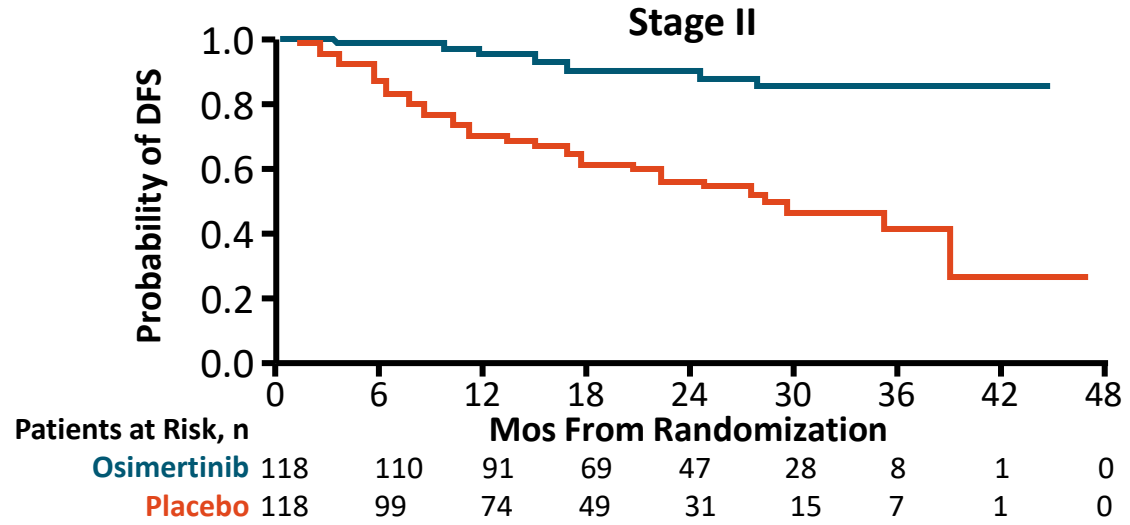
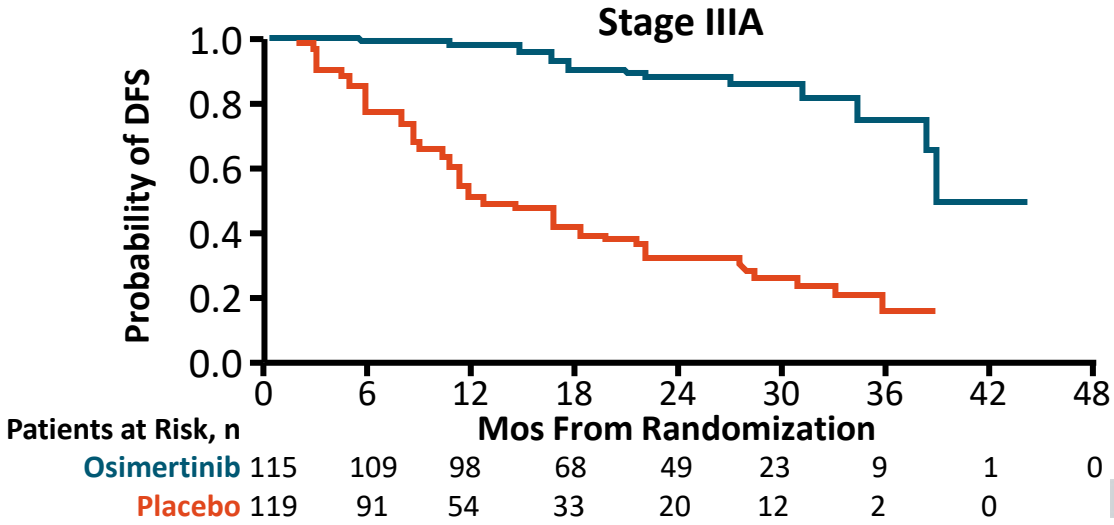
ADAURA: DFS by Stage of NSCLC





	Stage IB	Stage II	Stage IIIA
2-yr DFS rate, %			
Osimertinib	87	91	88
Placebo	73	56	32
Overall HR	0.50	0.17	0.12
(95% CI)	(0.25-0.96)	(0.08-0.31)	(0.07-0.20)



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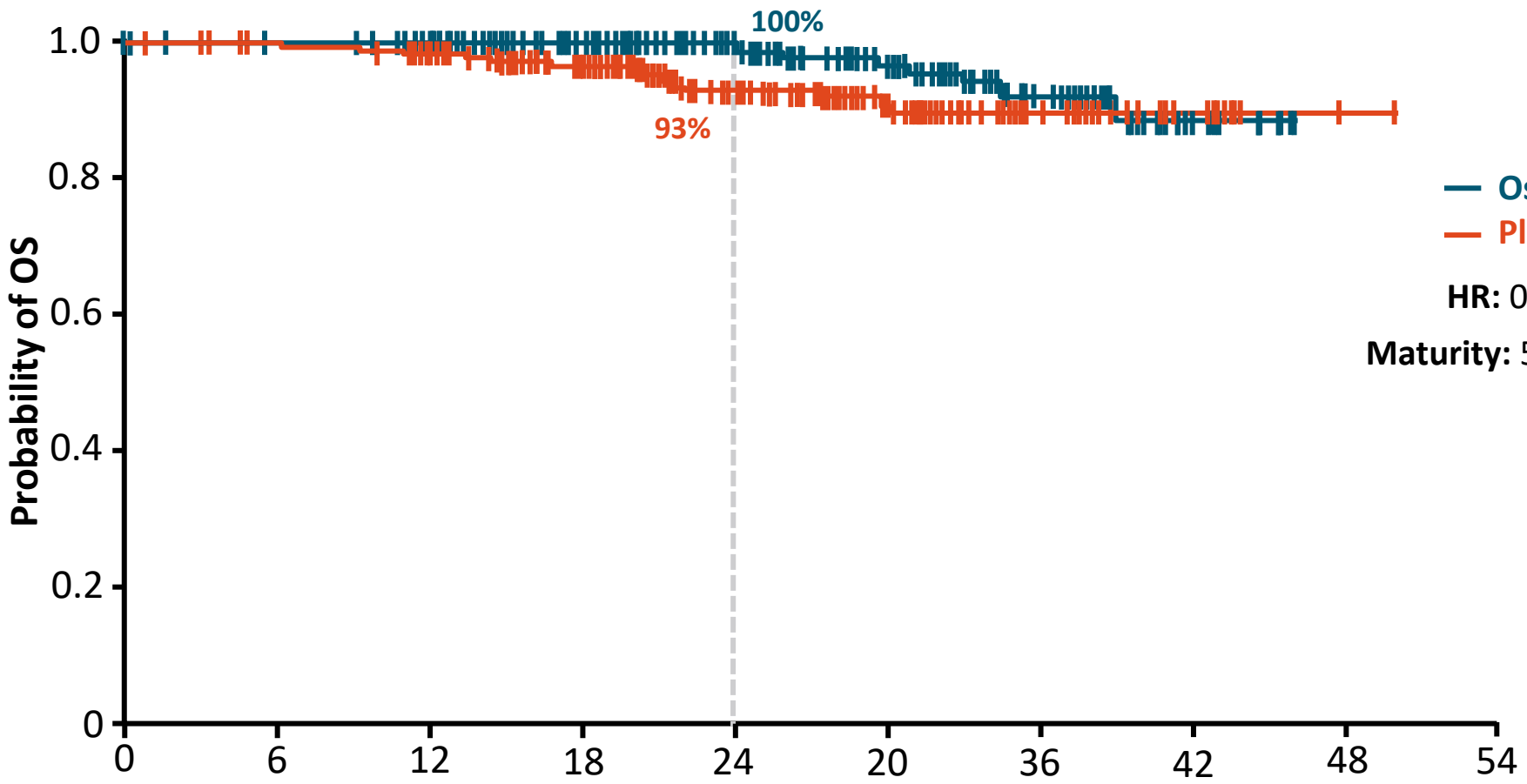
ADAURA: Early OS in Patients With Stage II/IIIA NSCLC



Median OS, Mos

Osimertinib	NR
Placebo	NR

HR: 0.40 (95% CI: 0.18-0.90)

Maturity: 5% (osimertinib: 3%; placebo: 7%)

Patients at Risk, n										
Osimertinib	233	229	221	192	137	82	39	10	0	
Placebo	237	231	221	190	127	69	32	11	1	0

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DATA SNAPSHOT

CNS Recurrence and DFS in Patients With NSCLC[6]

PREVENTING CNS RECURRENCE IS AN AREA OF UNMET NEED

- CNS is a common site of distant recurrence among patients with *EGFR*-mutant NSCLC who receive an EGFR TKI
- Compared with other TKIs, osimertinib (Tagrisso) has greater permeation of the blood-brain barrier

ADAURA EXPLORATORY ANALYSIS

- Data for disease recurrence patterns in ADAURA showed CNS recurrence in 1% of patients treated with osimertinib (n = 339) and 7% of patients with placebo (n = 343).
  - Disease recurrence rates for CNS in combination with other locations were less than 1% and 3%, respectively.
- The estimated probability of observing CNS recurrence at 18 months was less than 1% (95% CI, 0.2%–2.5%) with osimertinib versus 9% (95% CI, 5.9%–12.5%) with placebo.

CONCLUSION

- Osimertinib is a highly effective, practice-changing treatment for patients with stage IB/II/IIIA *EGFR*-mutant NSCLC following complete tumor resection.

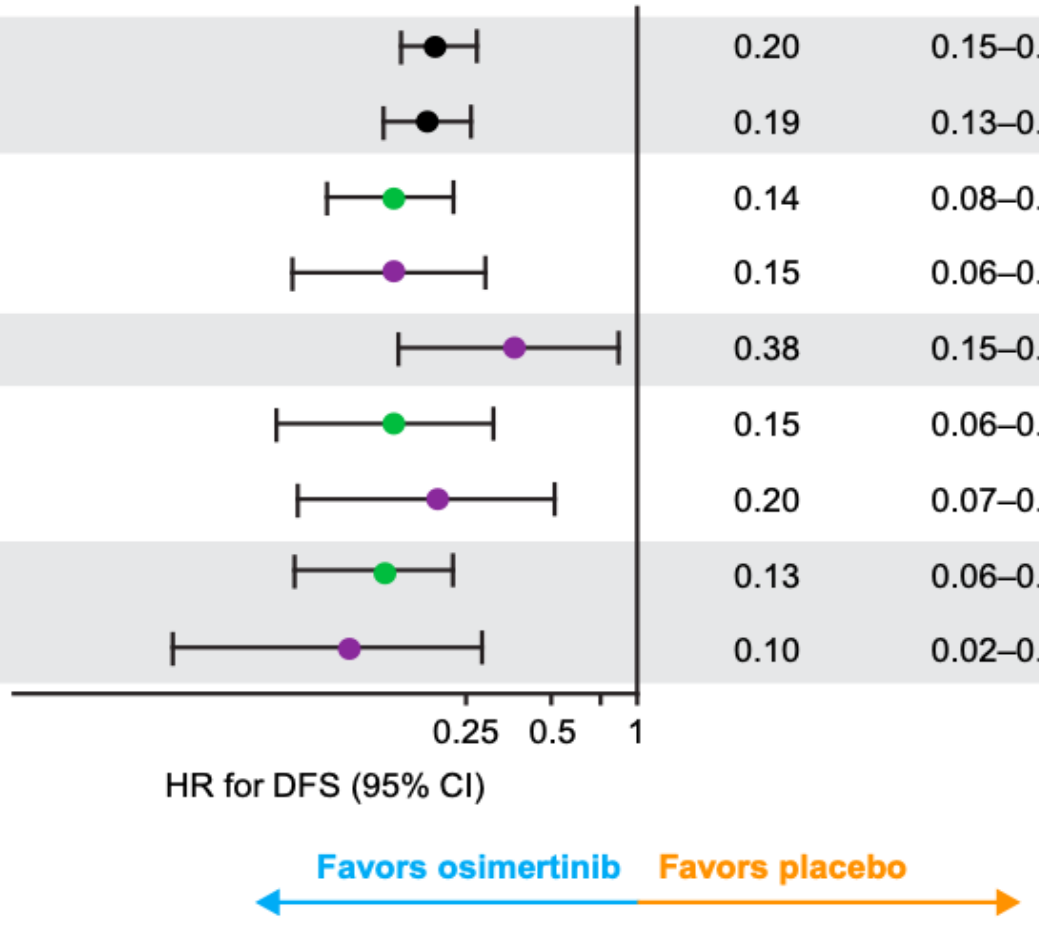
CNS, central nervous system; DFS, disease-free survival; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

TABLE 1. CNS DFS Outcomes in ADAURA[6]

Outcome	Osimertinib (n = 339)	Placebo (n = 343)
12-month CNS DFS	100%	97%
24-month CNS DFS	98%	85%
34-month CNS DFS	98%	82%
Median CNS DFS, months	NR (39–NC) (HR, 0.18; 95% CI, 0.10–0.33; *P* < .0001)	48.2 (NC–NC)

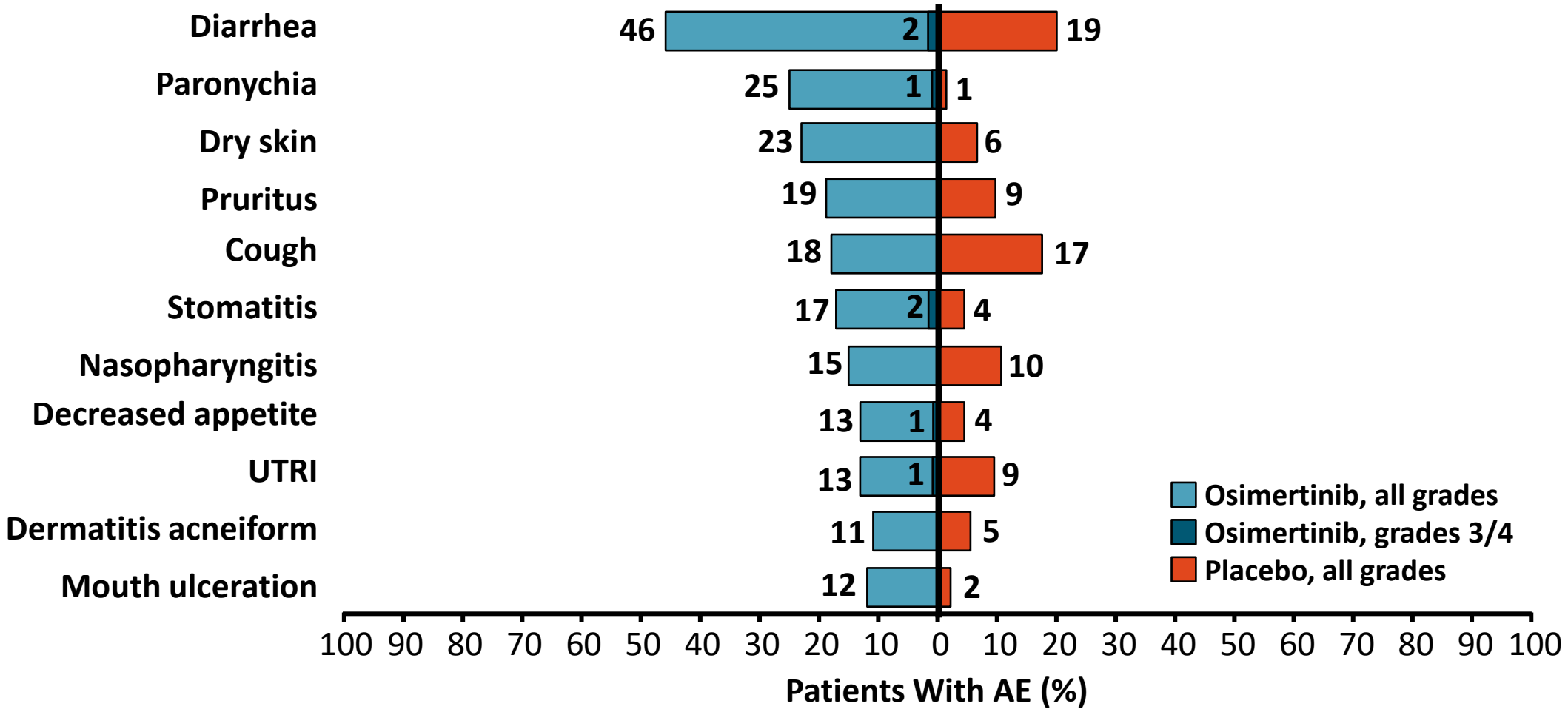
CNS, central nervous system; DFS, disease-free survival; NC, not calculable; NR, not reached.

Subgroup		HR	95% CI
Overall (N = 682)	Stratified log-rank	0.20	0.15–0.27
	Unadjusted Cox PH	0.19	0.13–0.27
Stage II / IIIA	With adjuvant chemotherapy (n = 352)	0.14	0.08–0.23
	Without adjuvant chemotherapy (n = 118)	0.15	0.06–0.30
Stage IB*	Without adjuvant chemotherapy (n = 154)	0.38	0.15–0.88
Stage II	With adjuvant chemotherapy (n = 166)	0.15	0.06–0.32
	Without adjuvant chemotherapy (n = 70)	0.20	0.07–0.52
Stage IIIA	With adjuvant chemotherapy (n = 186)	0.13	0.06–0.23
	Without adjuvant chemotherapy (n = 48)	0.10	0.02–0.29



- Overall population
- Patients with adjuvant chemotherapy
- Patients without adjuvant chemotherapy

ADAURA: All-Causality AEs in ≥ 10% of Patients



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CONCLUSION

- DFS benefit : 79% reduction in risk of recurrence or death
- Benefit seen across all subgroups irrespective of chemotherapy
- Well tolerated drug grade 3 / 4 toxicities very few
- OS data immature : Important to follow
- PRESENTLY, Adjuvant Osimertinib is Standard of Care in EGFR exon 19 del and Exon 21 mutation

Role of NACT in EGFR +

- Lengthy time for biomarker testing: barriers to preoperative TKI
- Whether TKI still be required after Neoadjuvant use - Probably yes
- Risk of progression and inoperabiliy in few patients
- Lack of Randomised phase III study
- In a Systematic Review, higher Response Rates for neoadjuvant EGFR-TKI treatment did not translate in better surgical outcomes

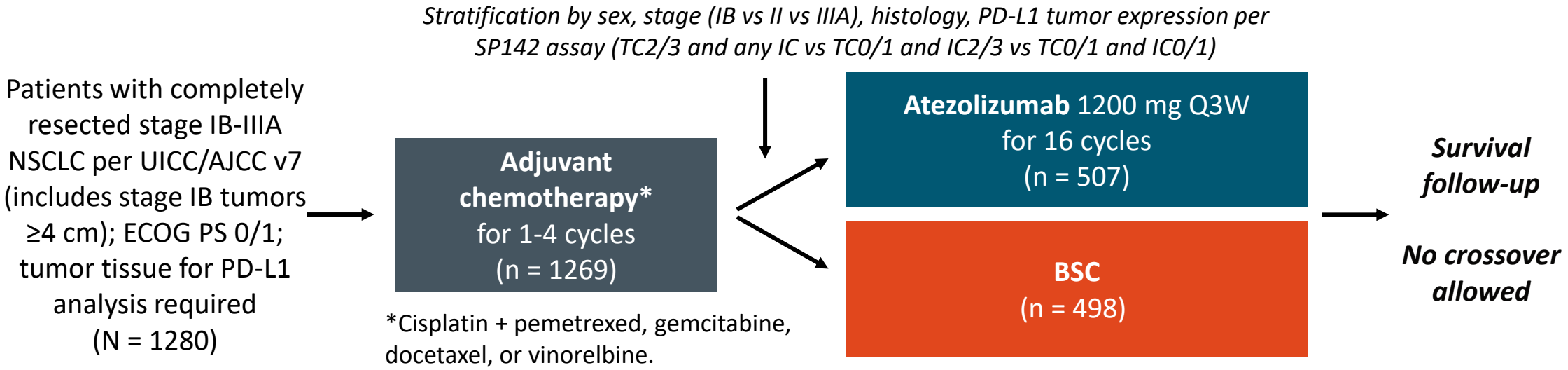
EGFR Mutation Positive Early Stage resectable Lung Cancer – Osimertinib x 3 yrs

Immunotherapy as Perioperative Therapy inEGFR Negative

IMpower010: Study Design

IMpower010: Study Design

- Randomized, open-label phase III trial (data cutoff for interim analysis: January 21, 2021)



- Primary endpoint: hierarchical evaluation of investigator-assessed DFS in 3 populations
  - Stage II-IIIA with PD-L1 TC ≥1% (by PD-L1 SP264 IHC assay) → all randomized stage II-IIIA → ITT population (stage IB-IIIA)
- Key secondary endpoints: OS (ITT); DFS in stage II-IIIA with PD-L1 TC ≥50 (by PD-L1 SP264 IHC assay); 3-yr and 5-yr DFS in all 3 populations; safety

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IMpower010: Baseline Characteristics

Median age 62,
2 /3 rd were males and
2 / 3 rd Nonsquamous and
> 2 /3 rd were white population
Stg Ib 12%, 40-45 % each in stage II and IIIA.
PDL1 > 1% 55%
EGFR +. 11% and ALK = 3.3 %.

Wakelee. ASCO 2021. Abstr 8500.

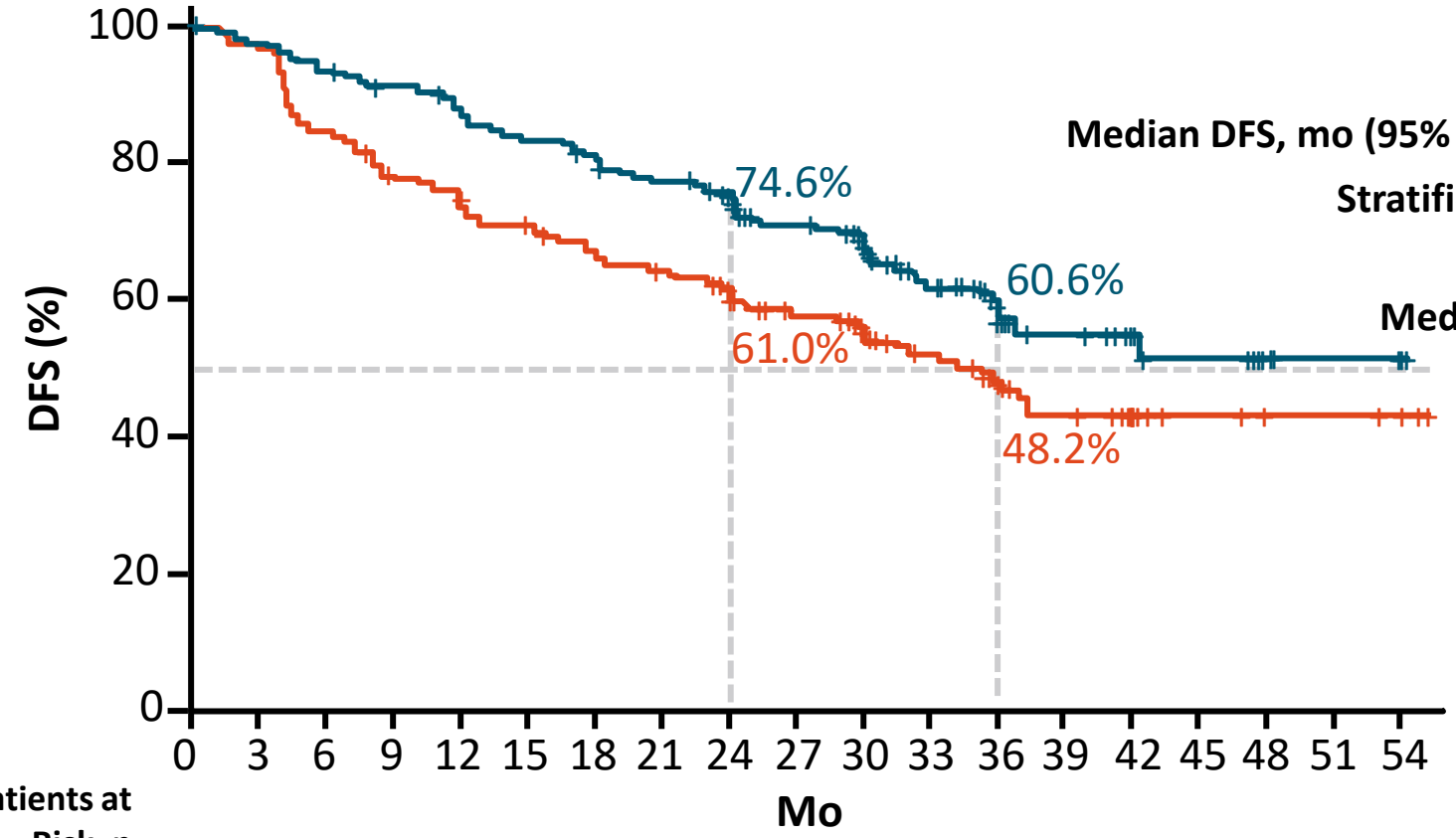
IMpower010 Subgroup Analysis: Patient and Treatment Characteristics

Characteristic	Atezolizumab (n = 507)	BSC (n = 498)
Median age, yr (range)*	62 (33-83)	62 (26-84)
Male, n (%)	337 (66.5)	335 (67.3)
ECOG PS 0/1, %	53.8/45.8	56.8/43.0
Nonsquamous histology, n (%)	328 (64.7)	331 (66.5)
PD-L1 TC ≥1%,† n (%)	283 (57.4)	252 (51.9)
Stage, n (%)		
▪ IB	65 (12.8)	58 (11.6)
▪ IIA	147 (29.0)	148 (29.7)
▪ IIB	90 (17.8)	84 (16.9)
▪ IIIA	205 (40.4)	208 (41.8)
Mediastinal LN dissection, n (%)	402 (79.3)	409 (82.1)
Mediastinal LN sampling, n (%)	93 (18.3)	88 (17.7)

Characteristic	Atezolizumab (n = 507)	BSC (n = 498)
Regional LN status (pN), n (%)		
▪ N0	183 (36.1)	169 (33.9)
▪ N1	170 (33.5)	178 (35.7)
▪ N2	154 (30.4)	151 (30.3)
Surgery type, n (%)		
▪ Lobectomy	394 (77.7)	391 (78.5)
▪ Pneumonectomy	77 (15.2)	83 (16.7)
▪ Bilobectomy	31 (6.1)	19 (3.8)
Median time from surgery to first atezolizumab/BSC treatment, mo (range)	5.2 (2.4-7.7)	5.1 (2.3-8.0)
Chemotherapy, n (%)		
▪ Cisplatin/docetaxel	77 (15.2)	75 (15.1)
▪ Cisplatin/gemcitabine	88 (17.4)	77 (15.5)
▪ Cisplatin/vinorelbine	152 (30.0)	151 (30.3)
▪ Cisplatin/pemetrexed	190 (37.5)	195 (39.2)

*Approximately 40% of patients in each arm were ≥65 yr of age.
†By PD-L1 SP263 IHC assay.

IMpower010: DFS in Stage II-IIIA NSCLC With PD-L1 TC ≥1% (Primary Endpoint)



	Atezolizumab (n = 248)	BSC (n = 228)
Median DFS, mo (95% CI)	NE (36.1-NE)	35.3 (29.0-NE)

Stratified HR: 0.66 (95% CI: 0.50-0.88; *P* = .004)
(crossed significance boundary)

Median follow up: 32.8 mo (range: 0.1-57.5)

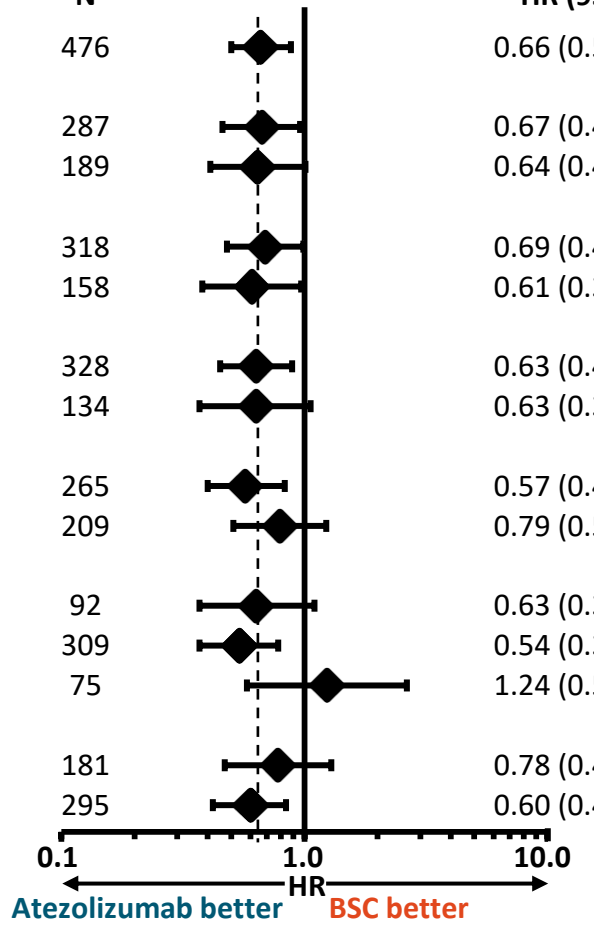
Patients at Risk, n

Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
BSC	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3

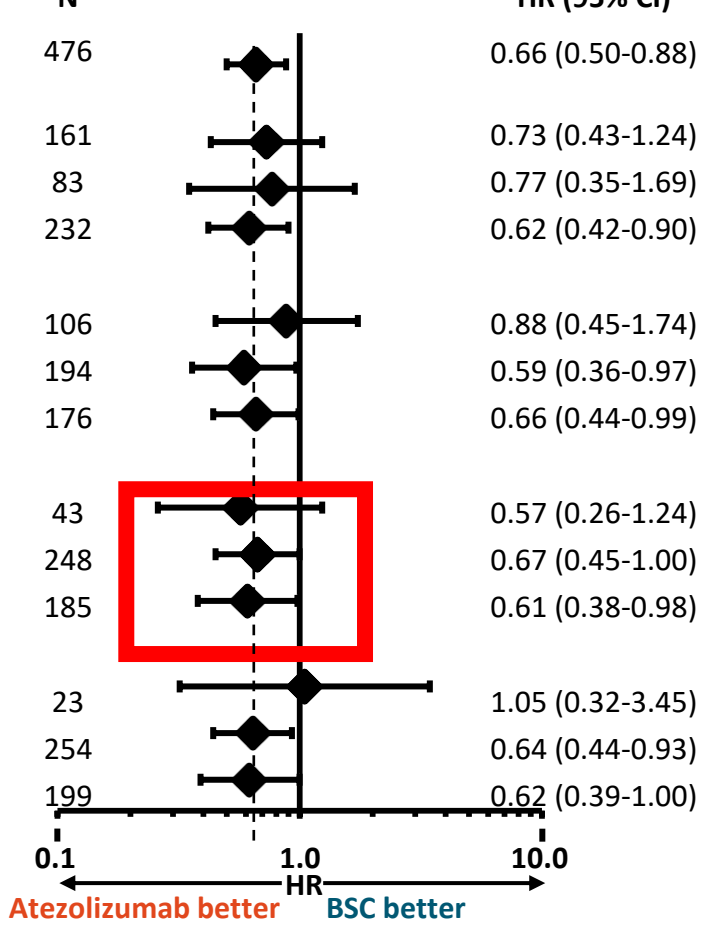
PD-L1 expression by SP263 assay.

IMpower010: DFS in Stage II-IIIA NSCLC With PD-L1 TC ≥1% Across Key Subgroups

Subgroup	N	HR (95% CI)
All patients	476	0.66 (0.50-0.88)
Age		
<65 yr	287	0.67 (0.46-0.96)
≥65 yr	189	0.64 (0.41-1.01)
Sex		
Male	318	0.69 (0.48-0.99)
Female	158	0.61 (0.38-0.97)
Race		
White	328	0.63 (0.45-0.89)
Asian	134	0.63 (0.37-1.06)
ECOG PS		
0	265	0.57 (0.40-0.83)
1	209	0.79 (0.51-1.23)
Tobacco use history		
Never	92	0.63 (0.37-1.10)
Previous	309	0.54 (0.37-0.78)
Current	75	1.24 (0.58-2.64)
Histology		
Squamous	181	0.78 (0.47-1.29)
Nonsquamous	295	0.60 (0.42-0.84)



Subgroup	N	HR (95% CI)
All patients	476	0.66 (0.50-0.88)
Stage		
IIA	161	0.73 (0.43-1.24)
IIB	83	0.77 (0.35-1.69)
IIIA	232	0.62 (0.42-0.90)
Regional lymph node stage (pN)		
N0	106	0.88 (0.45-1.74)
N1	194	0.59 (0.36-0.97)
N2	176	0.66 (0.44-0.99)
***EGFR* mutation status**		
Yes	43	0.57 (0.26-1.24)
No	248	0.67 (0.45-1.00)
Unknown*	185	0.61 (0.38-0.98)
***ALK* rearrangement status**		
Yes	23	1.05 (0.32-3.45)
No	254	0.64 (0.44-0.93)
Unknown*	199	0.62 (0.39-1.00)



PD-L1 expression by SP263 assay. *89.2% and 80.7% in ITT population with unknown *EGFR* or *ALK* status, respectively, had squamous NSCLC and were not required to undergo testing.

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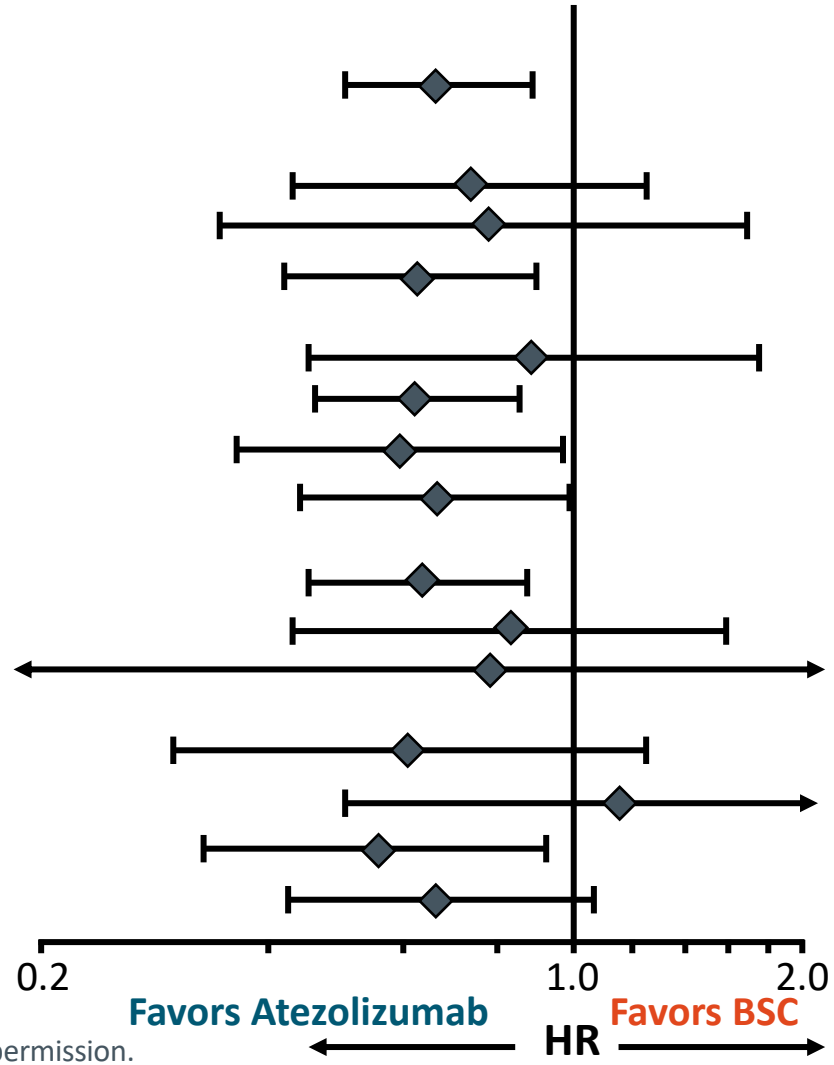
IMpower010 Subgroup Analysis: DFS in Patients with Stage II-IIIA NSCLC and PD-L1 TC ≥1%

Subgroup	n	HR (95% CI)	Atezolizumab	BSC
All patients	**476**	**0.66 (0.50-0.88)**	**NE**	**35.3**
Disease stage				
IIA	161	0.73 (0.43-1.24)	NE	NE
IIB	83	0.77 (0.35-1.69)	NE	NE
IIIA	232	0.62 (0.42-0.90)	42.3	26.7
Regional lymph node stage (pN)				
N0	106	0.88 (0.45-1.74)	36.7	NE
N+	370	0.62 (0.46-0.85)	NE	31.4
N1	194	0.59 (0.36-0.97)	NE	NE
N2	176	0.66 (0.44-0.99)	32.3	21.3
Type of surgery				
Lobectomy	359	0.63 (0.45-0.87)	NE	33.4
Pneumonectomy	85	0.83 (0.43-1.58)	36.1	NE
Bilobectomy	24	0.78 (0.18-3.33)	36.7	NE
CT regimen				
Cisplatin-docetaxel	71	0.60 (0.30-1.23)	36.1	18.0
Cisplatin-gemcitabine	75	1.14 (0.50-2.61)	36.1	NE
Cisplatin-vinorelbine	161	0.55 (0.33-0.92)	NE	34.2
Cisplatin-pemetrexed	169	0.66 (0.42-1.06)	NE	31.4



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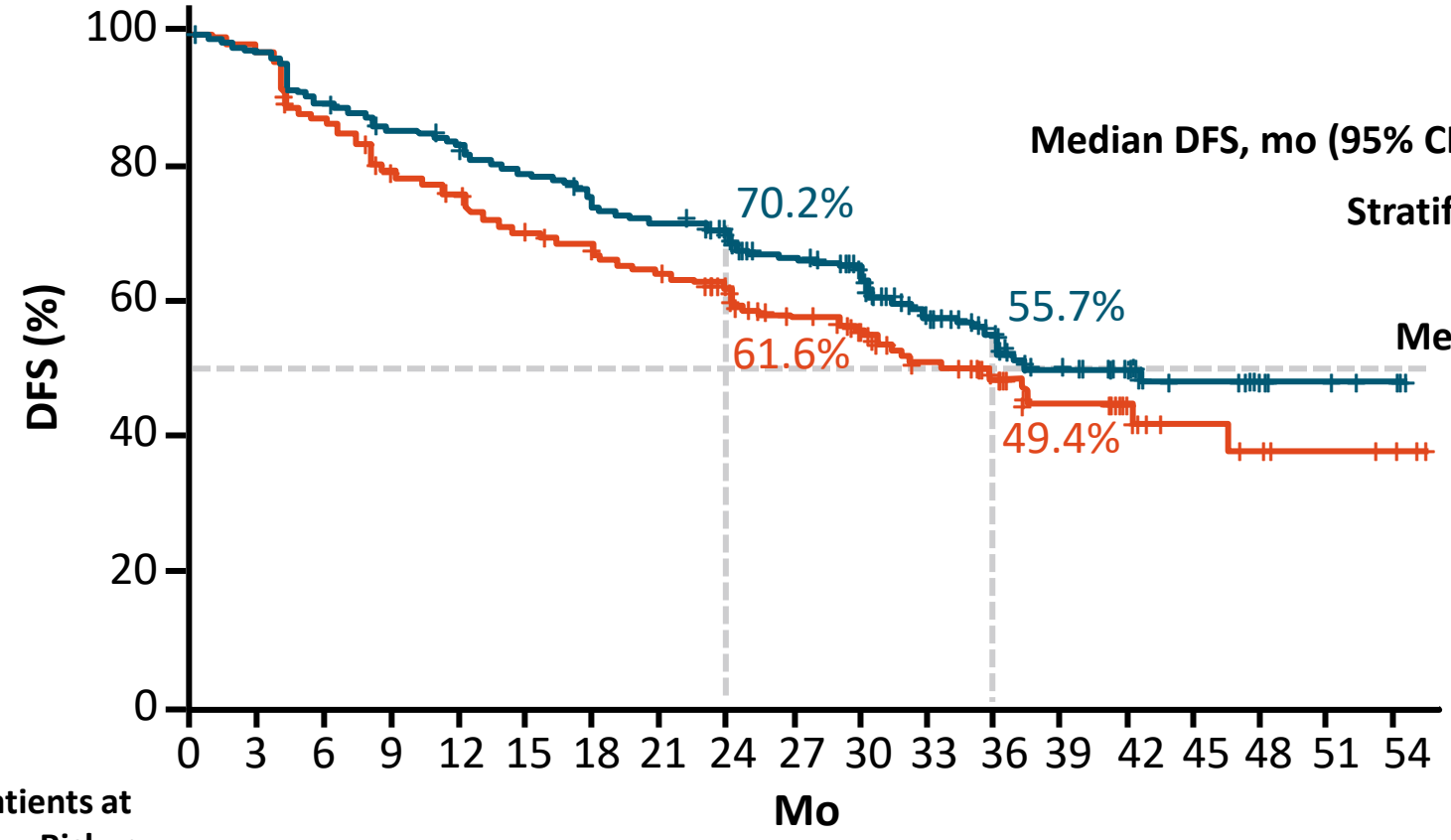
IMpower010: DFS in All Randomized Stage II-IIIA NSCLC (Primary Endpoint)



	Atezolizumab (n = 442)	BSC (n = 440)
Median DFS, mo (95% CI)	42.3 (36.0-NE)	35.3 (30.4-46.4)

Stratified HR: 0.79 (95% CI: 0.64-0.96; *P* = .02)
(crossed significance boundary)

Median follow up: 32.2 mo (range: 0-57.5)

Patients at Risk, n																		
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

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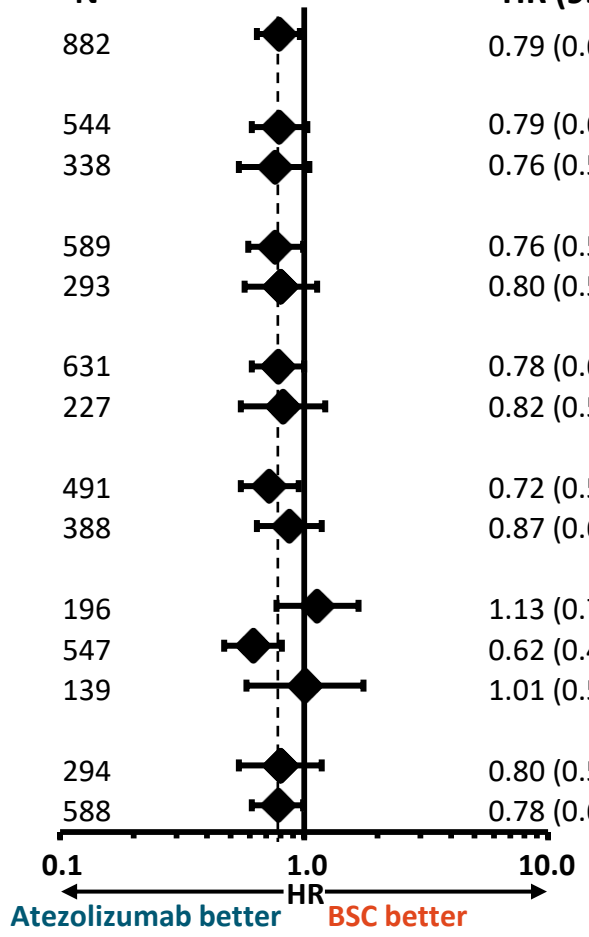
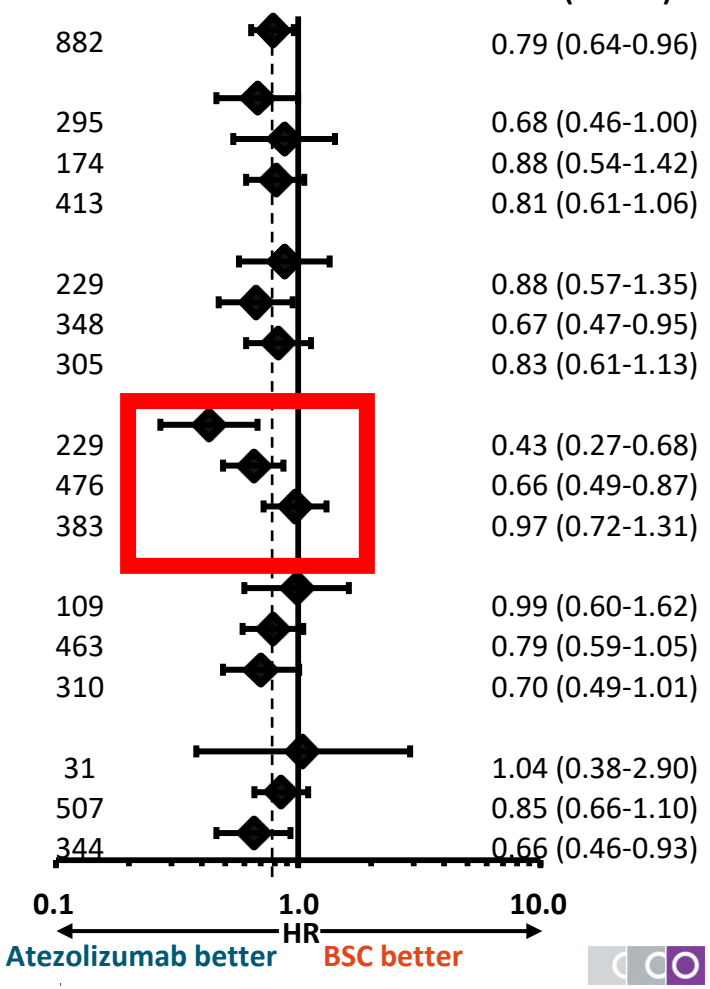
IMpower010: DFS in All Randomized Stage II-IIIA NSCLC Across Key Subgroups

Subgroup	N	HR (95% CI)
All patients	882	0.79 (0.64-0.96)
Age		
<65 yr	544	0.79 (0.61-1.03)
≥65 yr	338	0.76 (0.54-1.05)
Sex		
Male	589	0.76 (0.59-0.99)
Female	293	0.80 (0.57-1.13)
Race		
White	631	0.78 (0.61-1.00)
Asian	227	0.82 (0.55-1.22)
ECOG PS		
0	491	0.72 (0.55-0.95)
1	388	0.87 (0.64-1.18)
Tobacco use history		
Never	196	1.13 (0.77-1.67)
Previous	547	0.62 (0.47-0.81)
Current	139	1.01 (0.58-1.75)
Histology		
Squamous	294	0.80 (0.54-1.18)
Nonsquamous	588	0.78 (0.61-0.99)



Subgroup	N	HR (95% CI)
All patients	882	0.79 (0.64-0.96)
Stage		
IIA	295	0.68 (0.46-1.00)
IIB	174	0.88 (0.54-1.42)
IIIA	413	0.81 (0.61-1.06)
Regional lymph node stage (pN)		
N0	229	0.88 (0.57-1.35)
N1	348	0.67 (0.47-0.95)
N2	305	0.83 (0.61-1.13)
SP263 PD-L1 status		
TC ≥50%	229	0.43 (0.27-0.68)
TC ≥1%	476	0.66 (0.49-0.87)
TC <1%	383	0.97 (0.72-1.31)
***EGFR* mutation status**		
Yes	109	0.99 (0.60-1.62)
No	463	0.79 (0.59-1.05)
Unknown	310	0.70 (0.49-1.01)
***ALK* rearrangement status**		
Yes	31	1.04 (0.38-2.90)
No	507	0.85 (0.66-1.10)
Unknown	344	0.66 (0.46-0.93)



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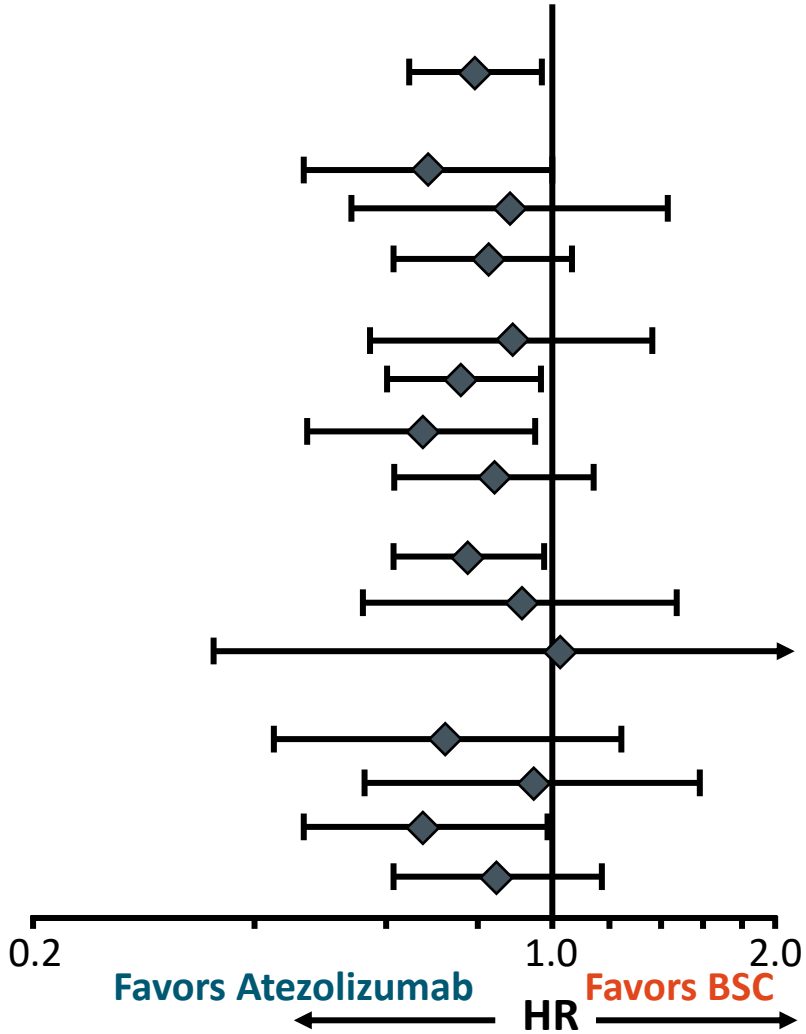
IMpower010 Subgroup Analysis: DFS in All Randomized Patients With Stage II-IIIA NSCLC

Subgroup	n	HR (95% CI)	Atezo	BSC
All patients	**882**	**0.79 (0.64-0.96)**	**42.3**	**35.3**
Disease stage				
IIA	295	0.68 (0.46-1.00)	NE	NE
IIB	174	0.88 (0.54-1.42)	37.1	46.4
IIIA	413	0.81 (0.61-1.06)	32.3	29.7
Regional lymph node stage (pN)				
N0	229	0.88 (0.57-1.35)	NE	46.4
N+	653	0.76 (0.60-0.96)	42.3	31.4
N1	348	0.67 (0.47-0.95)	NE	36.0
N2	305	0.83 (0.61-1.13)	30.2	24.1
Type of surgery				
Lobectomy	675	0.77 (0.61-0.97)	42.3	32.0
Pneumonectomy	150	0.91 (0.56-1.47)	36.1	42.1
Bilobectomy	47	1.02 (0.35-2.98)	36.7	NE
CT regimen				
Cisplatin-docetaxel	124	0.72 (0.42-1.23)	36.1	37.3
Cisplatin-gemcitabine	138	0.94 (0.56-1.57)	36.1	46.4
Cisplatin-vinorelbine	271	0.67 (0.46-0.99)	NE	37.0
Cisplatin-pemetrexed	349	0.84 (0.61-1.16)	42.3	31.4



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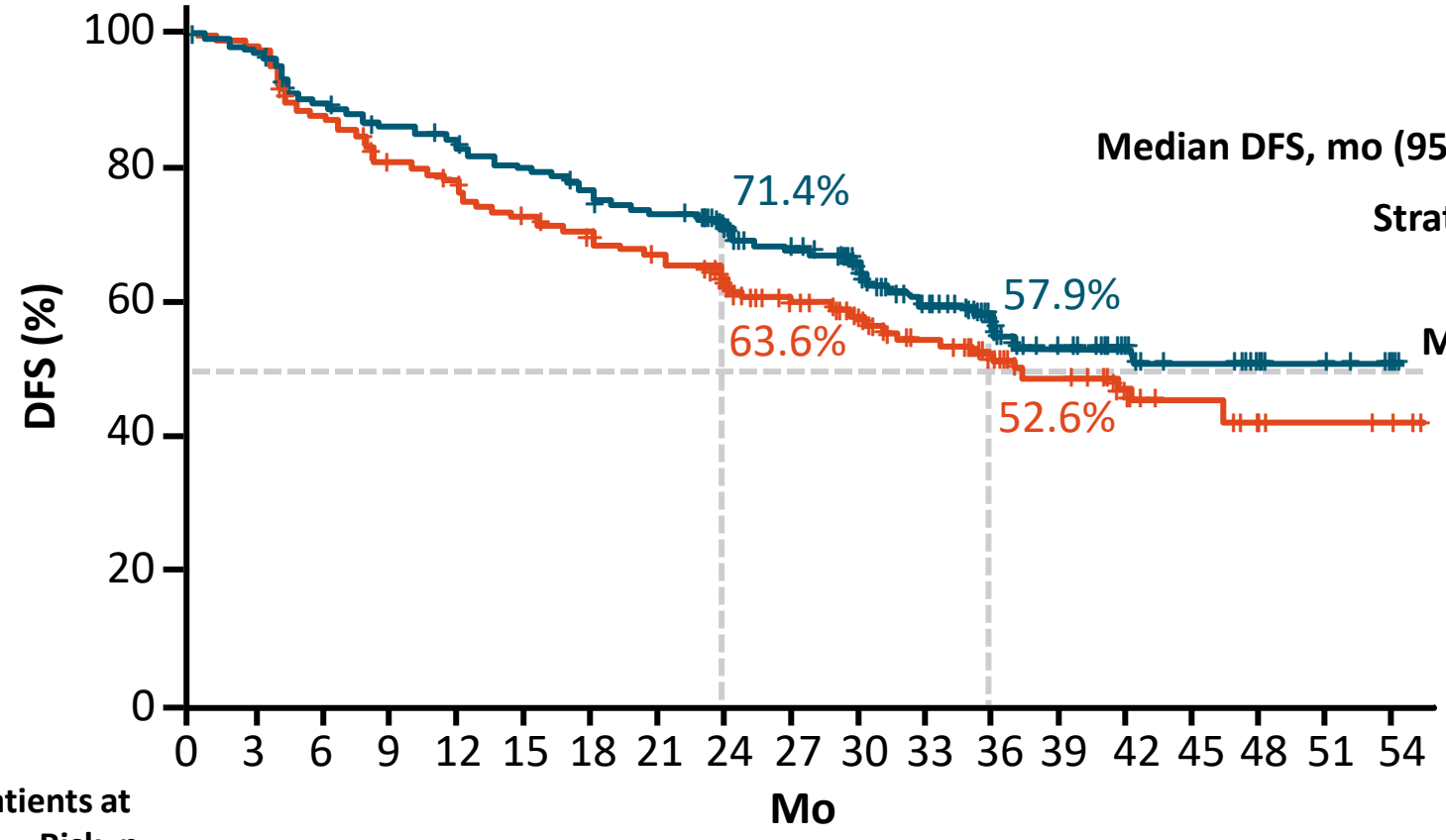
IMpower010: DFS in ITT Population (Stage IB-IIIA NSCLC; Primary Endpoint)



	Atezolizumab (n = 507)	BSC (n = 498)
Median DFS, mo (95% CI)	NE (36.1-NE)	37.2 (31.6-NE)

Stratified HR: 0.81 (95% CI: 0.67-0.99; *P* = .04)
(did not cross significance boundary)

Median follow up: 32.2 mo (range: 0-58.8)

Because DFS in ITT population did not cross significance boundary at this interim analysis, testing in this population will continue to final DFS analysis

Patients at Risk, n

Atezolizumab	507	478	437	418	403	387	367	353	306	257	212	139	97	53	38	19	14	8	4
BSC	498	467	418	383	365	342	324	309	269	219	173	122	90	46	30	13	10	5	4

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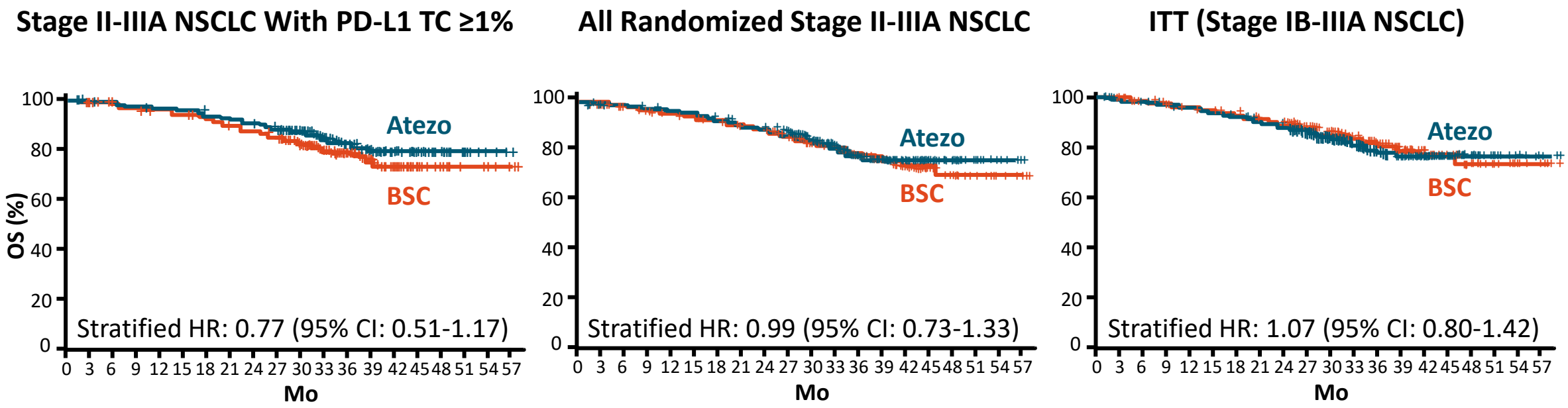
IMpower010: Early OS



- OS data immature at pre-planned interim DFS analysis, not formally tested

IMpower010: Safety

Safety Event, n (%)	Atezolizumab (n = 495)	BSC (n = 495)
Any AE ▪ Treatment related	459 (92.7) 335 (67.7)	350 (70.7) --
Grade 3/4 AEs ▪ Treatment related	108 (21.8) 53 (10.7)	57 (11.5) --
Serious AEs ▪ Treatment related	87 (17.6) 37 (7.5)	42 (8.5) --
Grade 5 AEs ▪ Treatment related	8 (1.6)* 4 (0.8)	3 (0.6)† --
AE leading to atezolizumab dose interruption	142 (28.7)	--
AE leading to atezolizumab discontinuation	90 (18.2)	--
Immune-mediated AEs ▪ Grade 3/4 ▪ Requiring use of systemic corticosteroids	256 (51.7) 39 (7.9) 60 (12.1)	47 (9.5) 3 (0.6) 4 (0.8)

Safety population included all randomized patients who received ≥1 atezolizumab dose or for BSC, had ≥1 postbaseline assessment.
*Deaths with atezolizumab: those related to tx per inv include interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, AML; others include pneumothorax, CVA, arrhythmia, acute cardiac failure. †Deaths with BSC: pneumonia; pulmonary embolism; cardiac tamponade/ septic shock in the same patient.

PD-L1 TC ≥1% stage II-IIIA population – Relapse Pattern

n (%)	Atezo[a] n=73	BSC[a] n=102
Relapse sites		
Locoregional only	35 (48)	42 (41)
Distant only	28 (38)	40 (39)
Distant only - CNS only	8 (11)	12 (12)
Locoregional and distant	9 (12)	17 (17)
Second primary lung	1 (1)	3 (3)
Post-relapse tx		
Systemic anticancer therapy	51 (70)	68 (67)
Systemic anticancer therapy - immunotherapy	8 (11)	36 (35)
Radiotherapy	32 (44)	48 (47)
Surgery	12 (16)	11 (11)

Conclusion

- DFS benefit
- stage II –A PDL1 TC ≥1% Stage II and IIIA and all comers
- Higher benefit with PDL1 > 50%
- EGFR mutation: ADAURA
- Finances ? Restrict to patients with Max benefit (PDL1 > 50%)

FDA approval in II – IIIA. PDL1 > = 1 %

EMA approval II – IIIA PDL1 >=50% and EGFR / ALK Negative

Phase 3 KEYNOTE-091 (EORTC-1416-LCG/ETOP-8-15/PEARLS): Adjuvant Pembrolizumab in Stage IB-IIIA NSCLC[1,2]

PEARLS/KEYNOTE-091 Study Design: A Randomized, Blinded 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 endpoint

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

Secondary endpoints

- DFS in 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

[a] EGFR status unknown for 333 (56.4%) in pembro arm and 337 (57.4%) in placebo arm.
[b] ALK status unknown for 357 (60.5%) in pembro arm and 390 (66.4%) in placebo arm.
[c] 2 (0.3%) participants in the placebo group had stage IV disease.

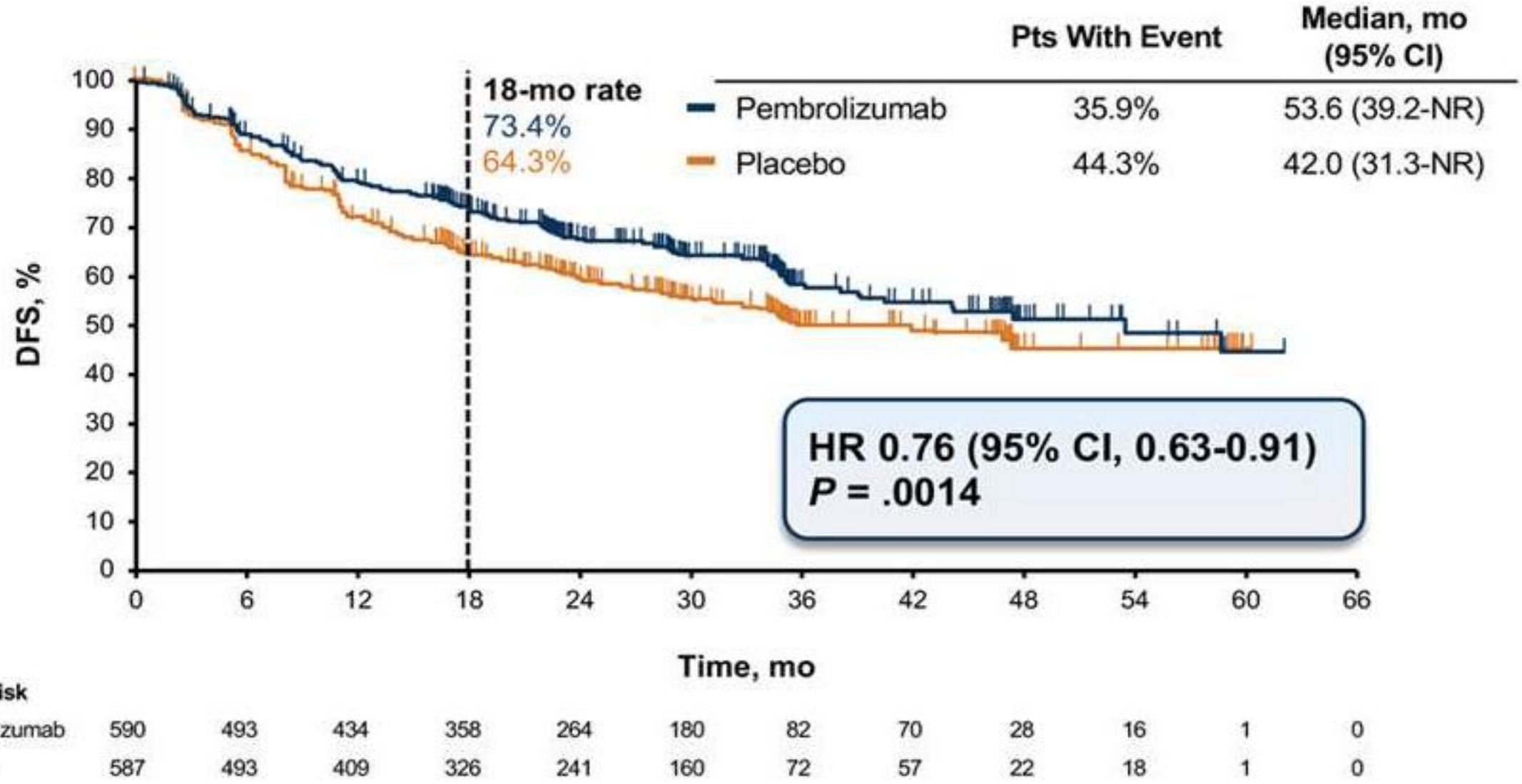
1. Paz-Ares L et al. ESMO 2022. Abstract VP3-2022.

Phase 3 KEYNOTE-091 (EORTC-1416-LCG/ETOP-8-15/PEARLS): Baseline Characteristics, Overall Population[1]

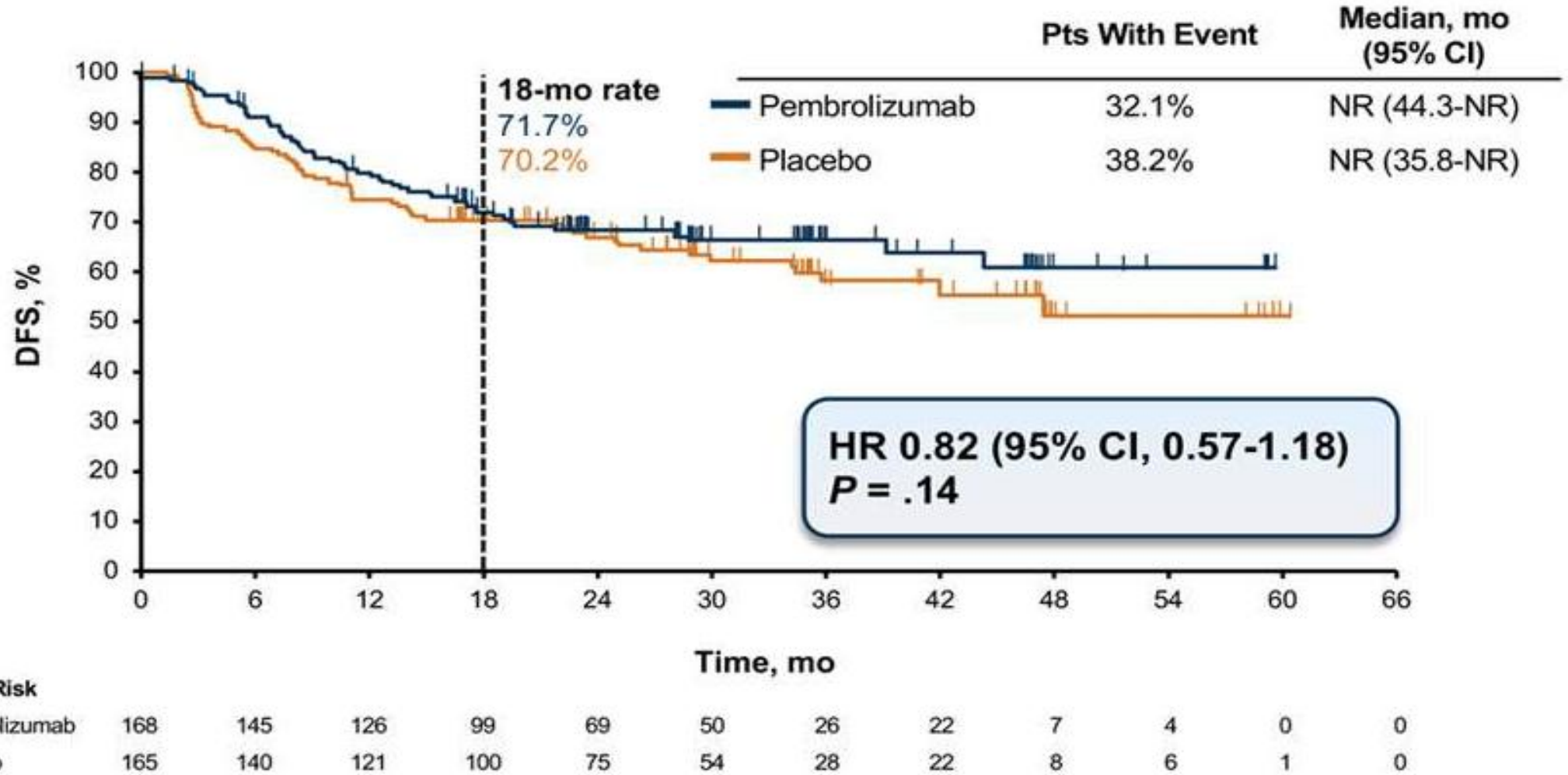
	Pembrolizumab (N = 590)	Placebo (N = 587)
Median age, y (range)	65 (31-87)	65 (37-85)
Male, n (%)	401 (68.0)	403 (68.7)
Geographic location		
Asia, n (%)	106 (18.0)	105 (17.9)
Eastern Europe, n (%)	116 (19.7)	113 (19.3)
Western Europe, n (%)	303 (51.4)	301 (51.3)
Rest of world, n (%)	65 (11.0)	68 (11.6)
ECOG PS 1, n (%)	210 (35.6)	244 (41.6)
Current/former smoker, n (%)	503 (85.3)	521 (88.8)
***EGFR* mutation[a], n (%)**	39 (6.6)	34 (5.8)
***ALK* translocation[b], n (%)**	7 (1.2)	7 (1.2)

	Pembrolizumab (N = 590)	Placebo (N = 587)
Nonsquamous histology, n (%)	398 (67.5)	363 (61.8)
Pathologic stage[c]		
IB, n (%)	84 (14.2)	85 (14.5)
II, n (%)	329 (55.8)	338 (57.6)
IIIA, n (%)	177 (30.0)	162 (27.6)
Received adjuvant chemotherapy		
Yes, n (%)	506 (85.8)	504 (85.9)
No, n (%)	84 (14.2)	83 (14.1)
PD-L1 TPS		
<1%, n (%)	233 (39.5)	232 (39.5)
1-49%, n (%)	189 (32.0)	190 (32.4)
≥50%, n (%)	168 (28.5)	165 (28.1)

DFS, Overall population



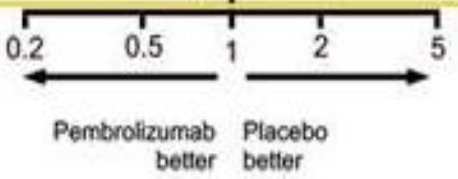
DFS, TPS >=50% population



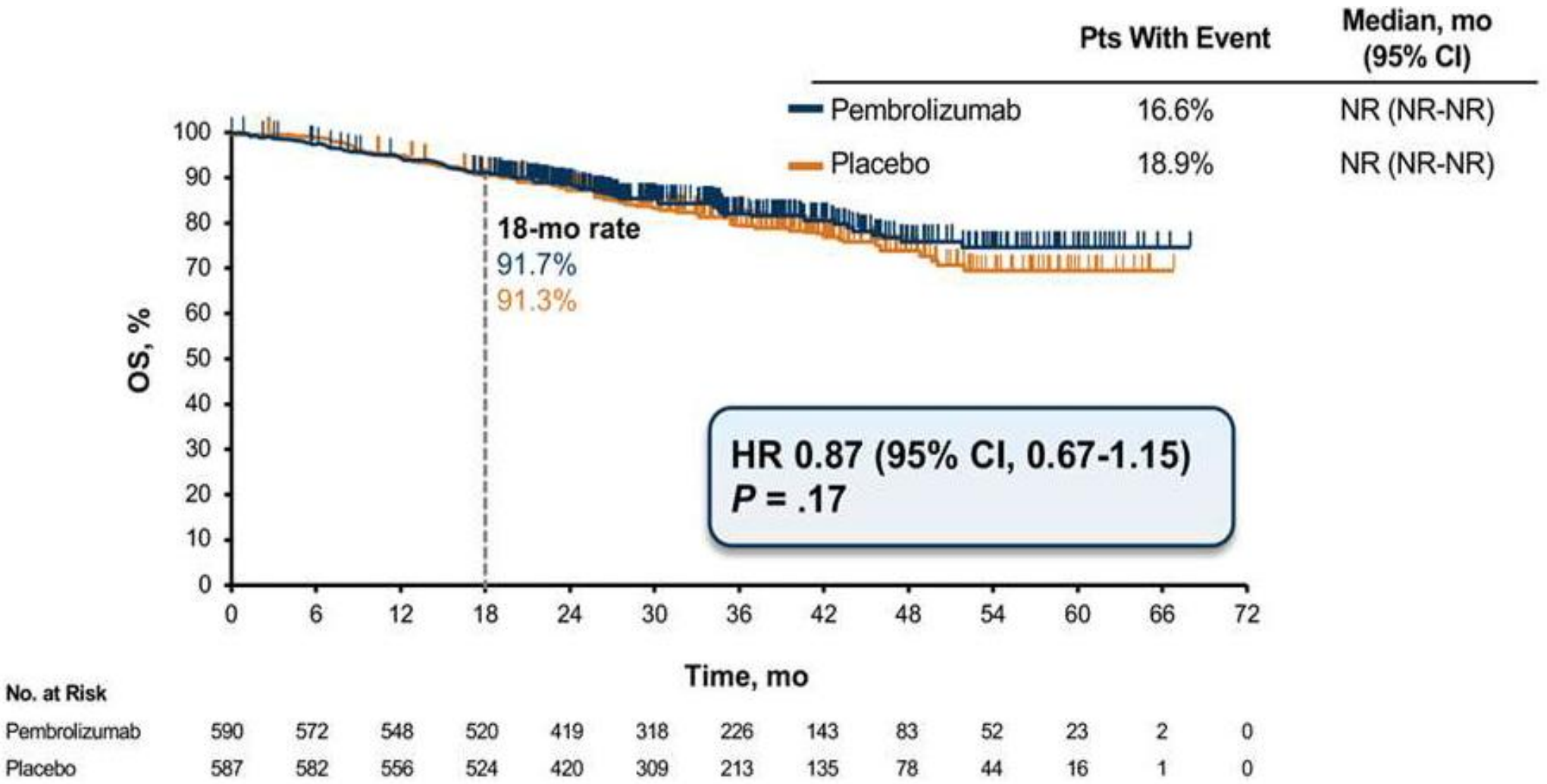
DFS in key subgroups, Overall population

Subgroup	No. Events/No. Participants	HR (95% CI)
Overall	472/1,177	0.76 (0.63-0.91)
Age		
<65 y	213/558	0.73 (0.56-0.96)
≥65 y	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 PS		
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	HR (95% CI)
Overall	472/1,177	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 chemo		
No	64/167	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)



OS, overall population



Conclusion

- DFS benefit irrespective of PDL1 status in Resectable Early stage
- OS data important
- PDL1 < 1 % by SP263, Pembrolizumab adjuvant may be an option
- No approvals yet

Adjuvant treatment

- Allows the fastest time to surgery
- Longer treatment duration for systemic control.
- Financial toxicity

IALT: Stage IB-IIIA resected NSCLC	• Surgery → Observation: 2-year DFS 55.5% • Surgery → Platinum chemotherapy: 2-year DFS 61.0%
ADAURA: Stage IB-IIIA resected NSCLC EGFR+	• Surgery → Platinum chemotherapy: 2-year DFS 52.0% • Surgery → Platinum chemotherapy → 3 years of osimertinib: 2-year DFS 89.0%
IMpower010: Stage II-IIIA resected NSCLC PD-L1 ≥ 1%	• Surgery → Platinum chemotherapy: 2-year DFS 61.0% • Surgery → Platinum chemotherapy → 1 year of atezolizumab: 2-year DFS 75.0%

Ongoing Phase III Trials of Adjuvant CT + Anti–PD-(L)1 Antibody Therapy in Early-Stage NSCLC

Study Title (Planned Accrual)	Status*	Disease Stage (TNM Edition)	Adjuvant CT Intervention	Adjuvant IO Intervention	Primary Endpoint(s)
IMpower010 (N = 1280)[1,2]	Completed accrual	IB-IIIA (7th)	1-4 cycles of cis + pemetrexed, gem, doc, or vin	Sequential atezolizumab vs BSC	DFS
ANVIL (N = 903)[3,4]	Completed accrual	IB-IIIA (7th)	CT and/or RT permitted	Sequential nivolumab vs observation	DFS, OS
PEARLS (N = 1177)[5,6]	Completed accrual	IB-IIIA (7th)	CT permitted	Sequential pembrolizumab vs placebo	DFS
BR31 (N = 1360)[7]	Completed accrual	IB-IIIA (8th)	CT permitted	Sequential durvalumab vs placebo	DFS
ALCHEMIST Chemo-IO (N = 1263)[8]	Accrual ongoing	IB-IIIA (7th)	1-4 cycles of carbo or cis + pemetrexed, pac, or gem	Concurrent pembrolizumab followed by pembrolizumab vs sequential pembrolizumab vs observation	DFS, OS

*As of August 2021.

1. NCT02486718. 2. Wakelee. ASCO 2021. Abstr 8500. 3. NCT02595944. 4. Chaft. ASCO 2018. Abstr TPS8581.
5. NCT02504372. 6. O'Brien. ASCO 2016. Abstr TPS8571. 7. NCT02273375. 8. NCT04267848

Indications of NACT

- Potentially Resectable disease
- Single station N2 (mediastinal nodal involvement)
- Superior sulcus or chest walll invasion(T4) in N1 nodal nodal involvement
- Comorbidities requiring optimization prior to surgery

CheckMate 816 Pathologic Response and Survival: Background

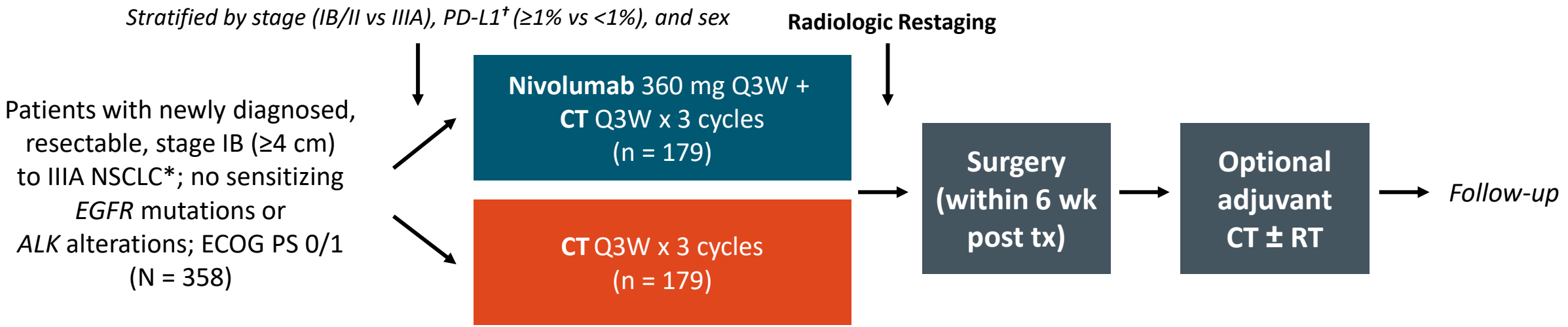
- In the phase III CheckMate 816 trial, neoadjuvant nivolumab + chemotherapy significantly improved EFS and pCR compared with chemotherapy alone in patients with resectable NSCLC
  - Median EFS: 31.6 mo vs 20.8 mo (HR: 0.63; *P* = .0052)
  - pCR: 24.0% vs 2.2% (OR: 13.94; *P* <.0001)

- Nivolumab + chemotherapy is approved by FDA as neoadjuvant treatment for patients with resectable (tumors ≥4 cm or node positive) NSCLC[2]

1. Forde. NEJM. 2022;386:1973. 2. Nivolumab PI. 3. Provencio-Pulla. ASCO 2022. Abstr LBA8511.

CheckMate 816 Pathologic Response and Survival: Study Design

- Randomized, open-label phase III trial



*By TNM 7th edition. †PD-L1 28-8 pharmDx IHC assay.

- **Primary endpoints:** pCR (by BIPR), EFS (by BICR)
- **Key secondary endpoints**: OS, MPR (by BIPR), time to death or distant metastasis

Provencio-Pulla. ASCO 2022. Abstr LBA8511.

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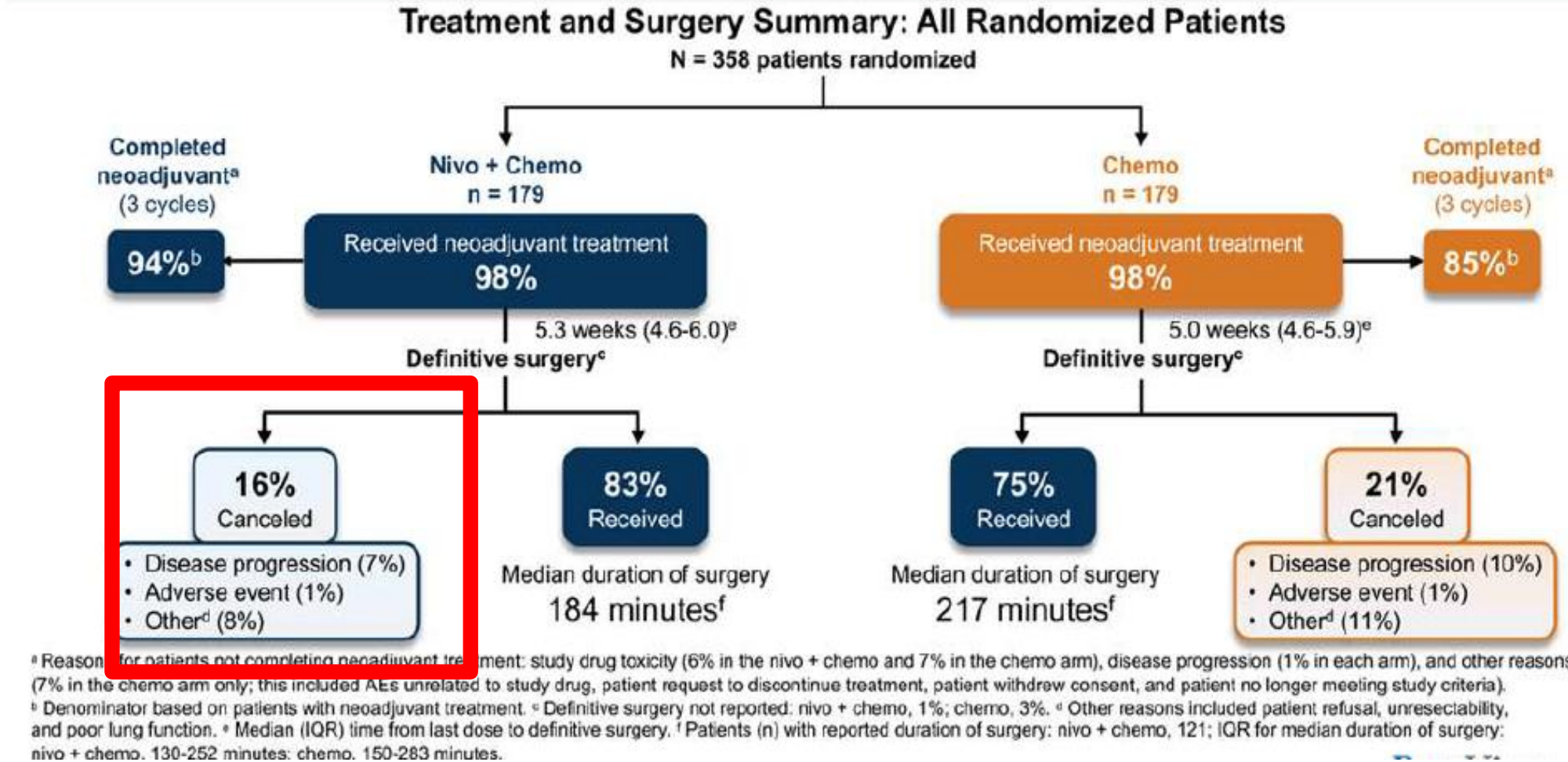
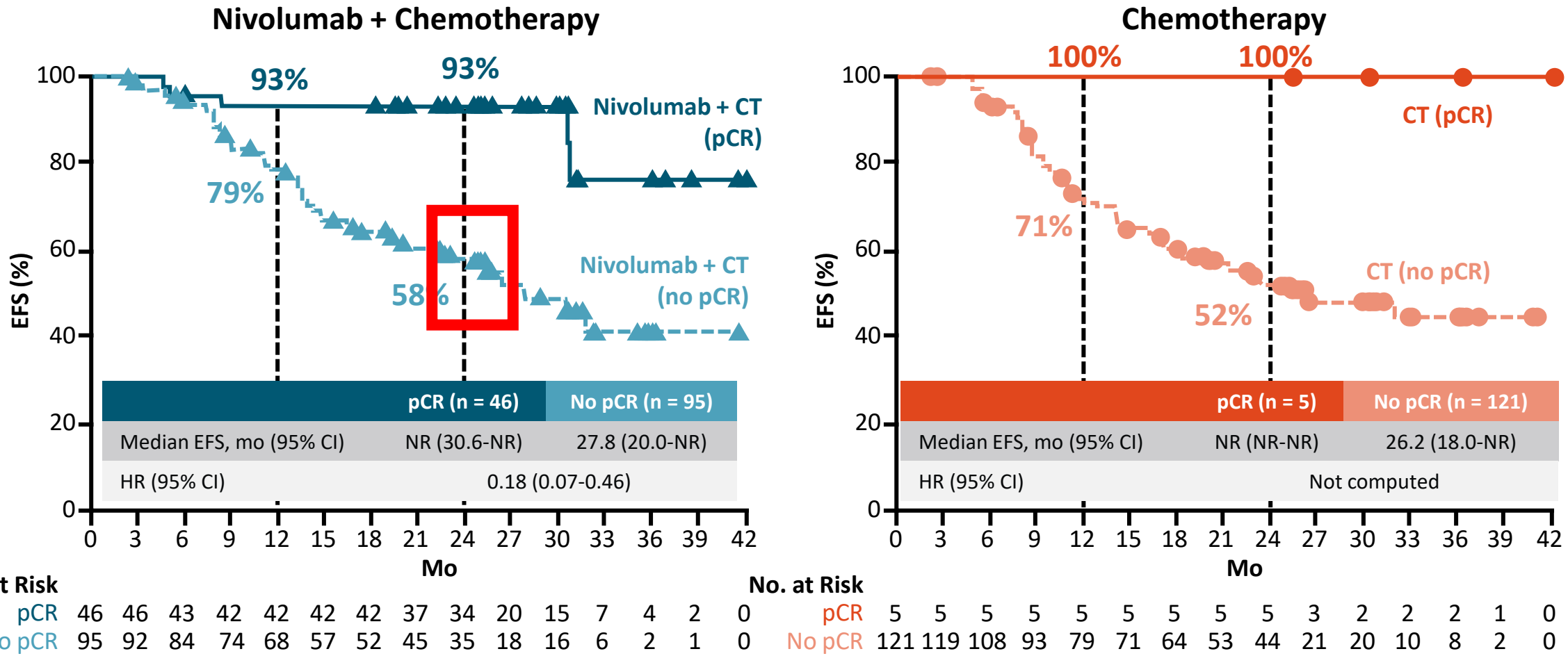
CheckMate -816: Surgical Outcomes With Neoadjuvant Nivolumab Plus Chemo in Resectable NSCLC[1]



[a] Reason for patients not completing neoadjuvant treatment: study drug toxicity (6% in the nivo + chemo and 7% in the chemo arm), disease progression (1% in each arm), and other reasons (7% in the chemo arm only; this included AEs unrelated to study drug, patient request to discontinue treatment, patient withdrew consent, and patient no longer meeting study criteria). [b] Denominator based on patients with neoadjuvant treatment. [c] Definitive surgery not reported: nivo + chemo, 1%; chemo, 3%. [d] Other reasons included patient refusal, unresectability, and poor lung function. [e] Median (IQR) time from last dose to definitive surgery. [f] Patients (n) with reported duration of surgery: nivo + chemo, 121; IQR for median duration of surgery: nivo + chemo, 130-252 minutes; chemo, 150-283 minutes.

CheckMate 816 Pathologic Response and Survival: EFS by pCR Status*



*Primary tumor pCR status.

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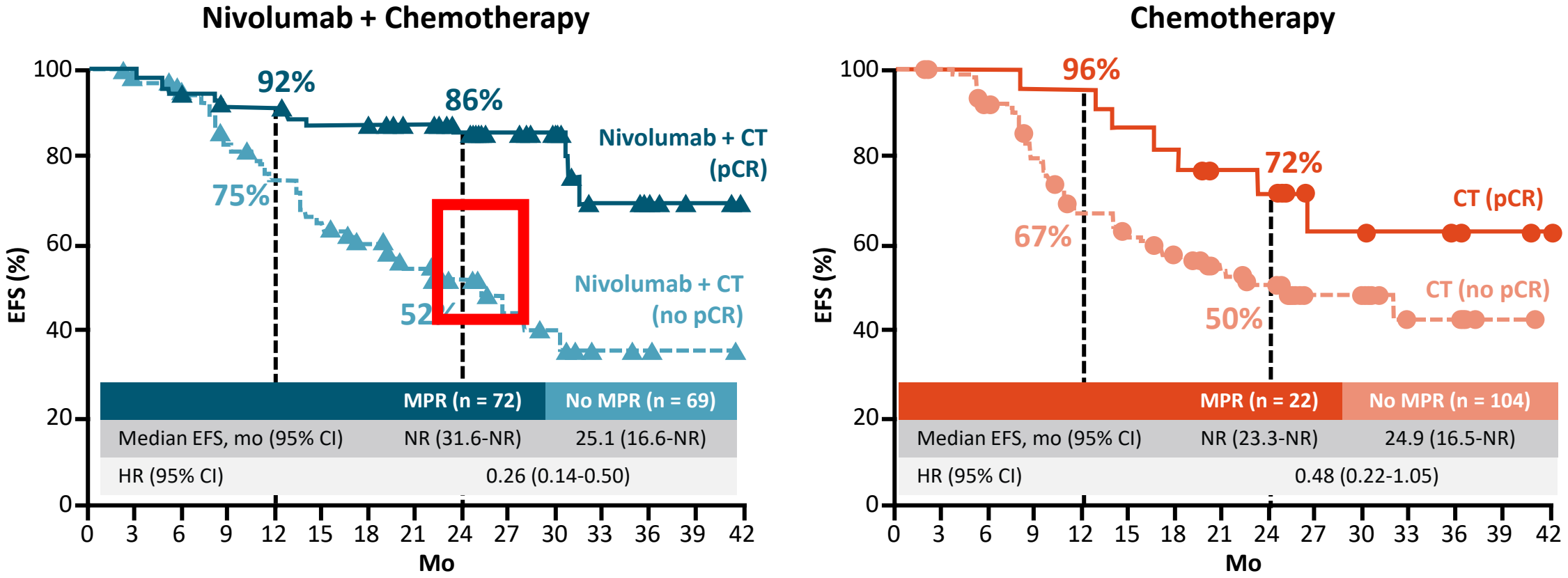
CheckMate 816 Pathologic Response and Survival: EFS by Primary Tumor MPR Status



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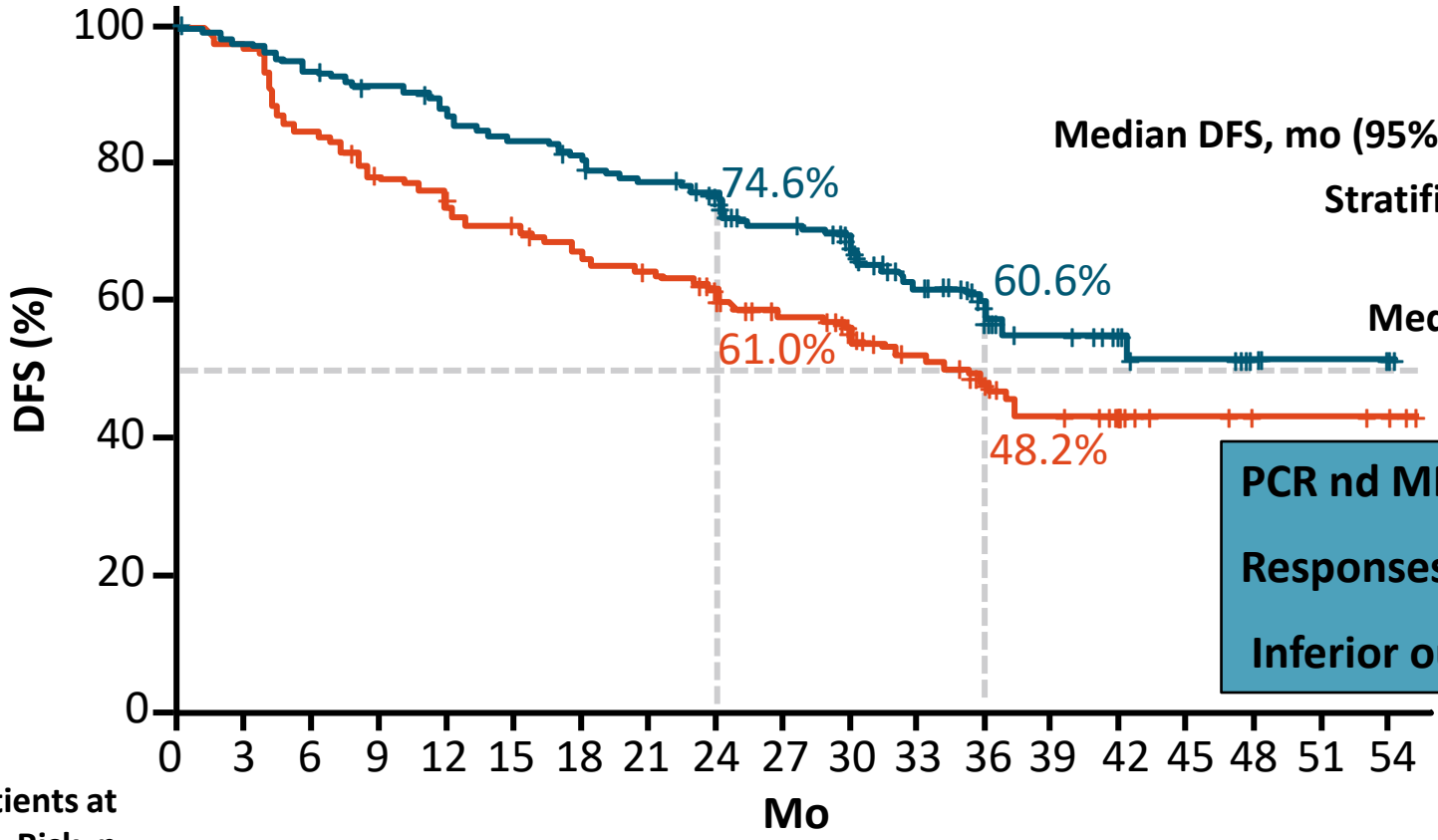
IMpower010: DFS in Stage II-IIIA NSCLC With PD-L1 TC ≥1% (Primary Endpoint)



	Atezolizumab (n = 248)	BSC (n = 228)
Median DFS, mo (95% CI)	NE (36.1-NE)	35.3 (29.0-NE)

Stratified HR: 0.66 (95% CI: 0.50-0.88; *P* = .004)
(crossed significance boundary)

Median follow up: 32.8 mo (range: 0.1-57.5)

PCR nd MPR were doing better .

Responses < MPR or > 10% Residual viable tumor

Inferior outcomes

Patients at Risk, n																		
Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
BSC	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3

PD-L1 expression by SP263 assay.

Conclusion

- 16 % surgeries cancelled and deprived of Cure
- Role of Biomarker monitoring in NACT setting
- Responses < MPR inferior to Adjuvant Immunotherapy cross trial comparison
- Better surgical outcomes : Reduce Pnemonectomies and major surgical complications
- Good option for (Stage IIIA)T4 or N2 Stage where surgeries might be challenging and Relapses are high
- Long term OS and DFS awaited

NADIM

- Phase II trial
- N- 46
- Single Arm

- NADIM : Path CR. 63%
- Checkmate 816 : Path CR : 24% vs 2.2% in chemotherapy arm.

Why so much difference?

Ongoing Phase III Trials of Neoadjuvant CT + Anti–PD-(L)1 Antibody Therapy in Early-Stage NSCLC

Study Title (Planned Accrual)	Status*	Disease Stage (TNM Edition)	CT Backbone	Neoadjuvant Intervention	Adjuvant IO Treatment	Primary Endpoint(s)
CheckMate 816 (N = 358)[1,2]	Completed accrual	IB-IIIA (7th)	3 cycles of cis/pemetrexed, carbo/pac, cis/gem, carbo/pac (nivolumab arm) ***or*** cis/pemetrexed, cis/vin, cis/doc, cis/gem, carbo/pac (CT arm)	± Nivolumab†	No	pCR, EFS
KEYNOTE-671 (N = 786)[3]	Accrual ongoing	II-IIIB (8th)	≥4 cycles of cis/(gem or pemetrexed)	Pembrolizumab or placebo	13 x 3-wk cycles of pembrolizumab or placebo	EFS, OS
IMpower030 (N = 450)[4]	Accrual ongoing	II-IIIB (8th)	4 cycles of carbo/pemetrexed, carbo/nab-pac, cis/pemetrexed, or cis/gem	Atezolizumab or placebo	16 x 3-wk cycles of atezolizumab or BSC	EFS
AEGEAN (N = 800)[5,6]	Accrual ongoing	IIA-IIIB (8th)	4 cycles of carbo/pac, carbo/pemetrexed, cis/gem, or cis/pemetrexed	Durvalumab or placebo	12 x 4-wk cycles of durvalumab or placebo	pCR, EFS
CheckMate 77T (N = 452)[7,8]	Accrual ongoing	IIA-IIIB (8th)	≥4 cycles carbo/pac, cis/doc, carbo/pemetrexed, cis/pemetrexed, or carbo/pac	Nivolumab or placebo	Nivolumab or placebo for 1 yr	EFS

*As of August 2021. †Nivolumab + ipilimumab arm closed.

1. NCT02998528. 2. Spicer. ASCO 2021. Abstr 8503. 3. NCT03425643. 4. NCT03456063.
5. NCT03800134. 6. Heymach. WCLC 2019. Abstr P1.18-02. 7. Cascone. ASCO 2020. Abstr TPS9076. 8. NCT04025879.

Pending Data in Each Study

- ADAURA : OS data awaited , although the study was not powered for OS as aprimary end point.
- CheckMate 816 study awaits EFS follow-up and data to show a correlation between pCR and EFS.
- IMPOWER 010: Await mature data on the benefit of adjuvant atezolizumab in lymph node–negative tumors 4-5 cm in size, the OS data, and analysis of benefit in the population with tumors that express PD-L1 in 1%-49% of cells.

SYSTEMIC THERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

Preferred (nonsquamous)
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[1]

Preferred (squamous)
- Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[2]
- Cisplatin 75 mg/m² day 1, docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[3]

Other Recommended
- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[4]
- Cisplatin 100 mg/m² day 1, vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5,6]
- Cisplatin 75–80 mg/m² day 1, vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[5]

Useful in Certain Circumstances
- Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[7]
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[8]
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles[9]

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

Neoadjuvant Systemic Therapy
- Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[10,*]
  - Platinum-doublet chemotherapy options include:
    - ◊ Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
    - ◊ Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (non-squamous)
    - ◊ Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)

Adjuvant Systemic Therapy
- Osimertinib 80 mg daily[11]
  - Osimertinib for patients with completely resected stage IB–IIIA *EGFR* (*exon 19* deletion, *L858R*) NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[12]
  - Atezolizumab for patients with completely resected stage IIB–IIIA or high risk stage IIA PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

Conclusion

- Absence of direct comparisons
- Both valid options for different patient subset
- Potentially Resectable or questionable fitness - Neoadjuvant
- Undergone resection, negative margins and have adequate fitness to undergo adjuvant chemotherapy.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