SACRO CUORE DON CALABRIA

IRCCS
Istituto di Ricovero e Cura a Carattere Scientifico
Sacro Cuore - Don Calabria
Ospedale Classificato e Presidio Ospedaliero Accreditato - Regione Veneto

TUMORE DEL POLMONE:
dallo screening al trattamento

Venerdì 11 novembre 2022

SEDE: *Sala Convegni "Fr. Francesco Perez"*
IRCCS Sacro Cuore - Don Calabria
Via Don Angelo Sempreboni, 5
37024 Negrar di Valpolicella - Verona

NSCLC: Trattamento del NSCLC stadio I-II-III

Ruolo della Terapia Sistemica Antitumorale (adiuvante e neoadiuvante)

Alessandro Inno

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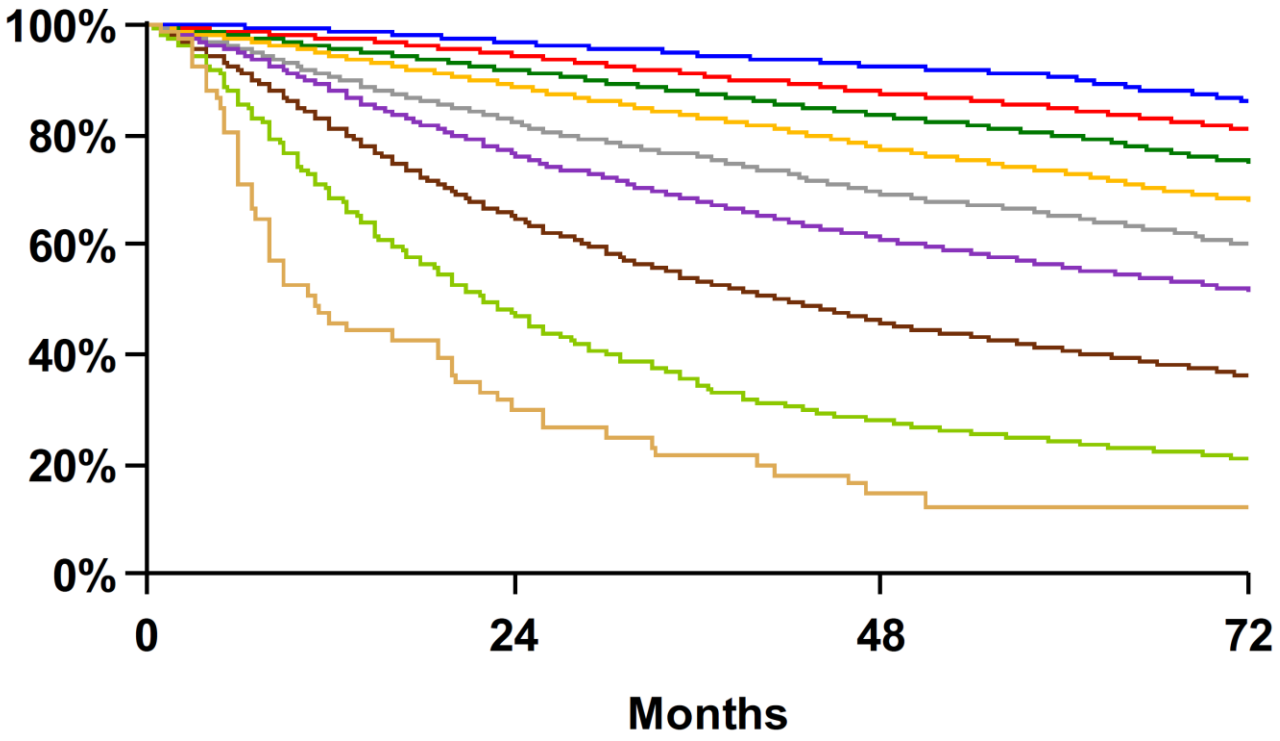
Oncologia Medica
IRCCS Ospedale Sacro Cuore Don Calabria
Negrar di Valpolicella (VR)

Sopravvivenza nel NSCLC stadio I-III



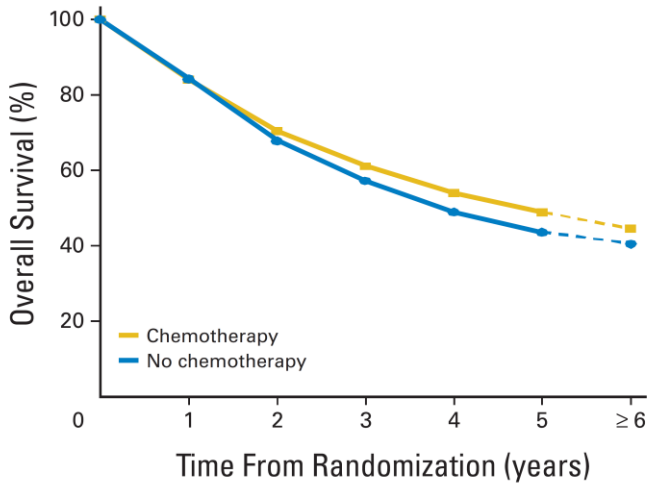
Proposed	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

- Circa il 25-30% dei pazienti con NSCLC si presenta con malattia resecabile alla diagnosi, candidata a chirurgia curativa (stadi I, II e IIIA)
- I tassi di sopravvivenza a 5 anni variano a seconda dello stadio (dal 90% nello stadio IA1 al 41% nello stadio IIIA)

Goldstraw P, et al. J Thorac Oncol 2016;11(1):39-51.

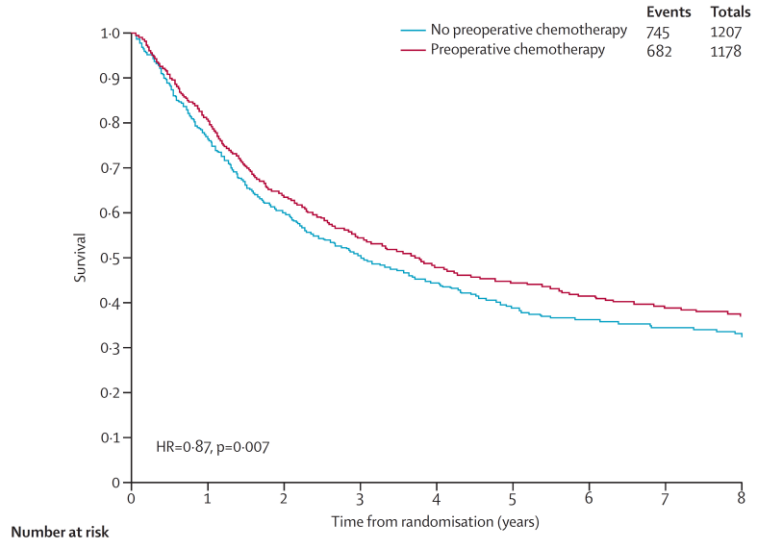
Chemioterapia perioperatoria nel NSCLC: impatto sulla OS

Adjuvant chemo



Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

Neoadjuvant chemo



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

LACE Collaborative Group. J Clin Oncol 2008;26(21):3552-9 NSCLC Meta-analysis Collaborative Group. Lancet 2014;383(9928):1561-71.

Chemioterapia negli stadi II-III: PDTA Regione Veneto 2022

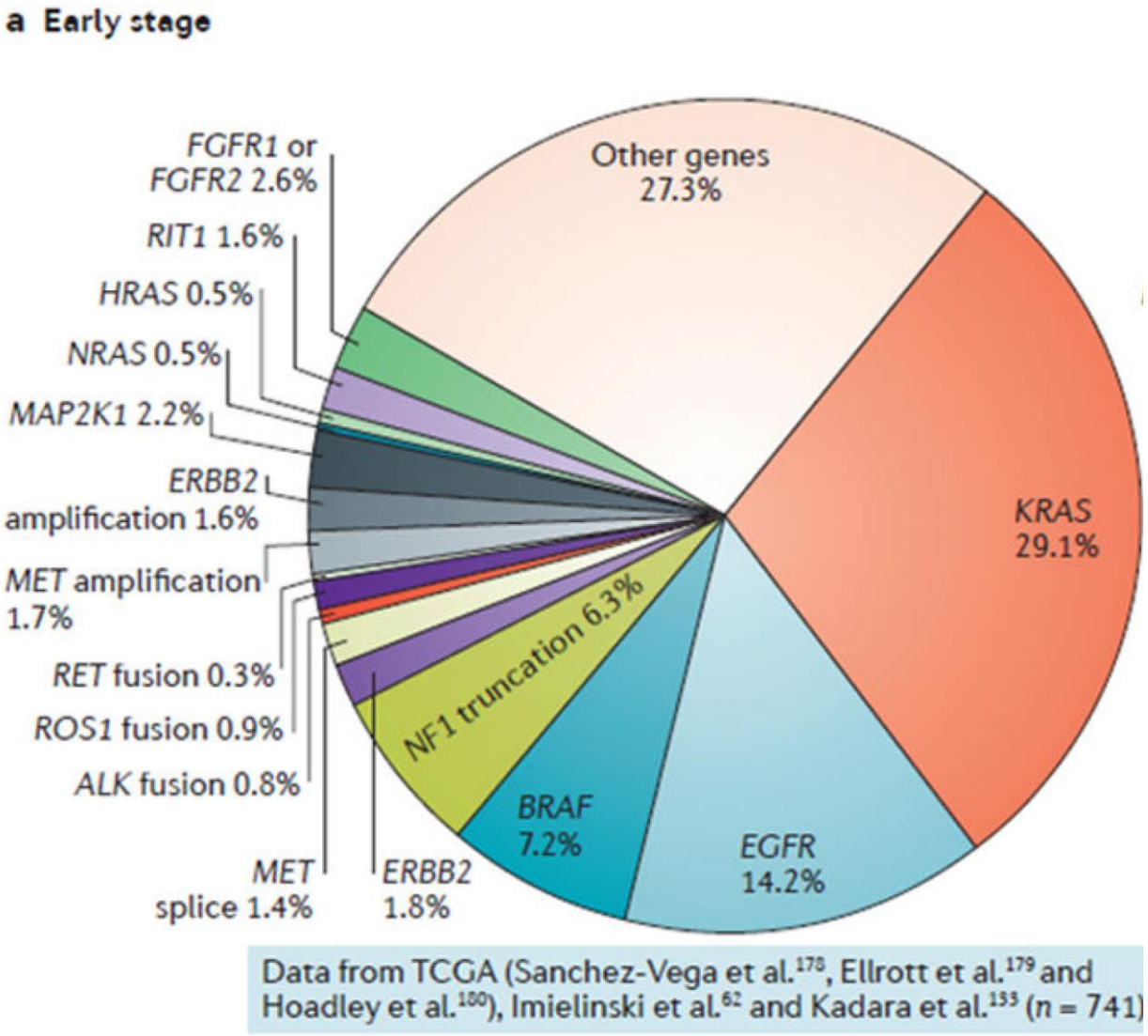
- **Adiuvante: stadi II-III (candidati a chirurgia diretta)**
- **Neoadiuvante: stadi III potenzialmente operabili**
- **Associata a RT definitiva +/- consolidamento con durvalumab: stadi III inoperabili**

Terapia Sistemica Antitumorale adiuvante/neoadiuvante: oltre la chemioterapia

Terapia target

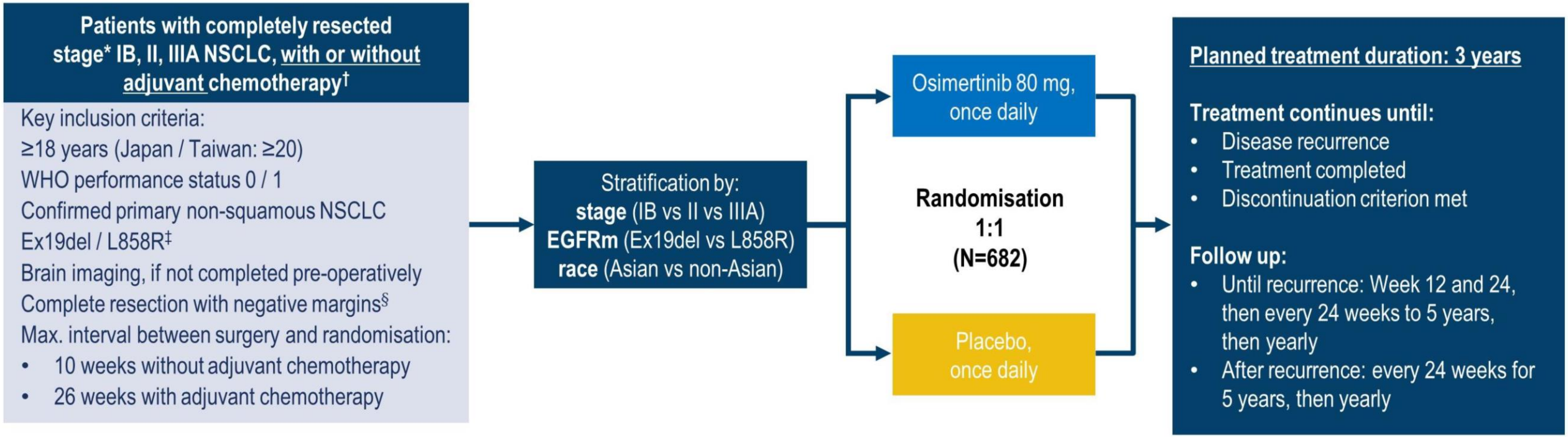
Immunoterapia

Alterazioni molecolari nel NSCLC in stadio precoce



Skoulidis F, Heymach JV. Nat Rev Cancer. 2019;19(9):495-509.

Osimertinib adiuvante nei pazienti EGFR mutati: studio ADAURA



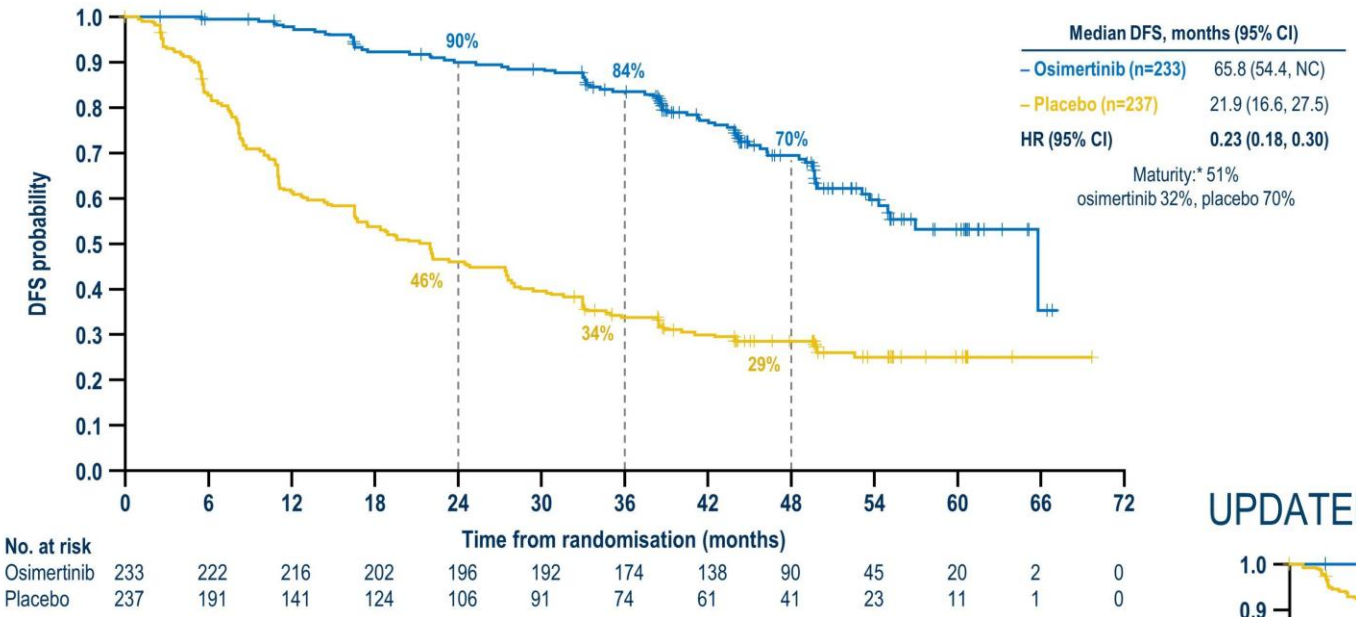
Endpoints

- **Primary endpoint:** DFS by investigator assessment in stage II / IIIA patients, designed for superiority under the assumed DFS HR of 0.70
- **Key secondary endpoints:** DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life
- **Pre-specified exploratory endpoints:** Patterns of recurrence, time to CNS disease recurrence or death (CNS DFS)

Wu YL, et al. N Engl J Med 2020;383(18):1711-1723.

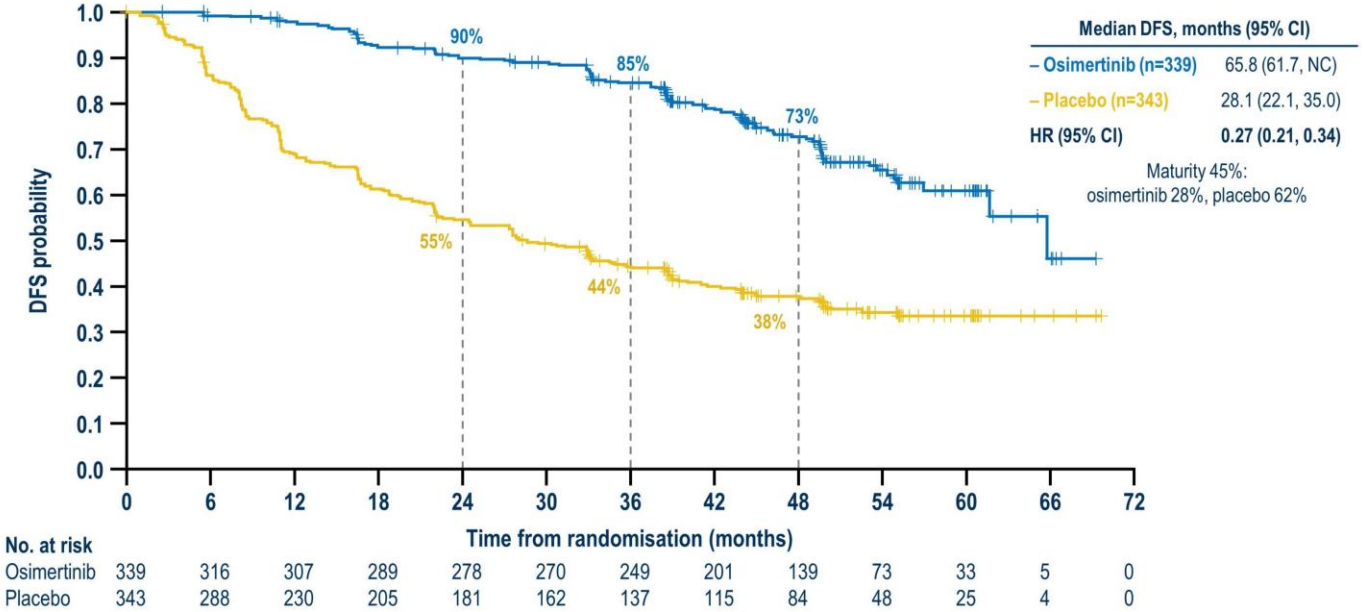
ADAURA: dati aggiornati di DFS

PRIMARY ENDPOINT: UPDATED DFS IN STAGE II / IIIA DISEASE



No. at risk													
Osimertinib	233	222	216	202	196	192	174	138	90	45	20	2	0
Placebo	237	191	141	124	106	91	74	61	41	23	11	1	0

UPDATED DFS IN THE OVERALL POPULATION (STAGE IB / II / IIIA DISEASE)



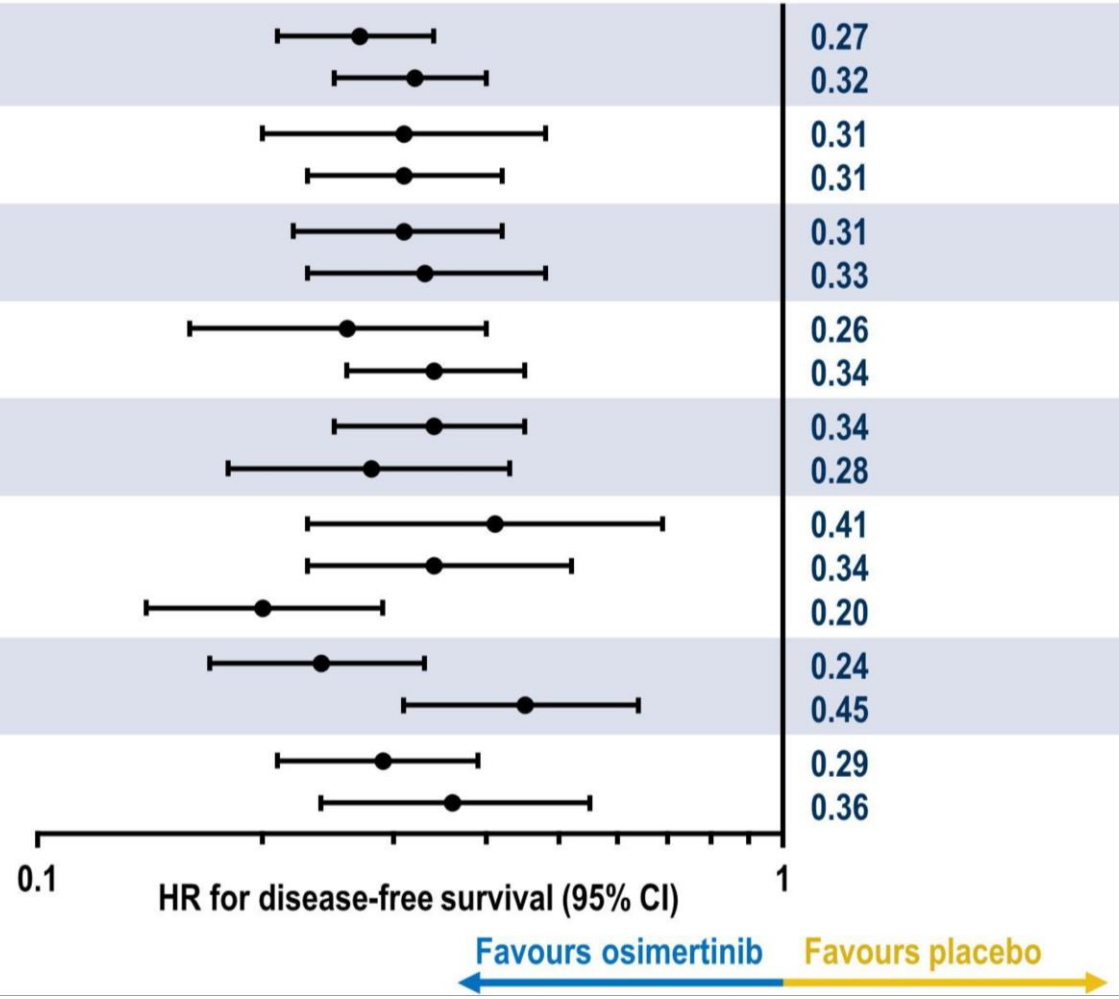
No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

Tsuboi M, ESMO 2022

ADAURA: dati aggiornati di DFS

- A DFS benefit with osimertinib was observed across all predefined subgroups

Subgroup		HR	95% CI
Overall (N=682)	Stratified log-rank	0.27	0.21, 0.34
	Unadjusted Cox PH	0.32	0.25, 0.40
Sex	Male (n=204)	0.31	0.20, 0.48
	Female (n=478)	0.31	0.23, 0.42
Age	<65 yr (n=380)	0.31	0.22, 0.42
	≥65 yr (n=302)	0.33	0.23, 0.48
Smoking history	Yes (n=194)	0.26	0.16, 0.40
	No (n=488)	0.34	0.26, 0.45
Race	Asian (n=434)	0.34	0.25, 0.45
	Non-Asian (n=248)	0.28	0.18, 0.43
Stage*	IB (n=212)	0.41	0.23, 0.69
	II (n=236)	0.34	0.23, 0.52
	IIIA (n=234)	0.20	0.14, 0.29
EGFR mutation	Ex19Del (n=378)	0.24	0.17, 0.33
	L858R (n=304)	0.45	0.31, 0.64
Adjuvant chemotherapy	Yes (n=410)	0.29	0.21, 0.39
	No (n=272)	0.36	0.24, 0.55

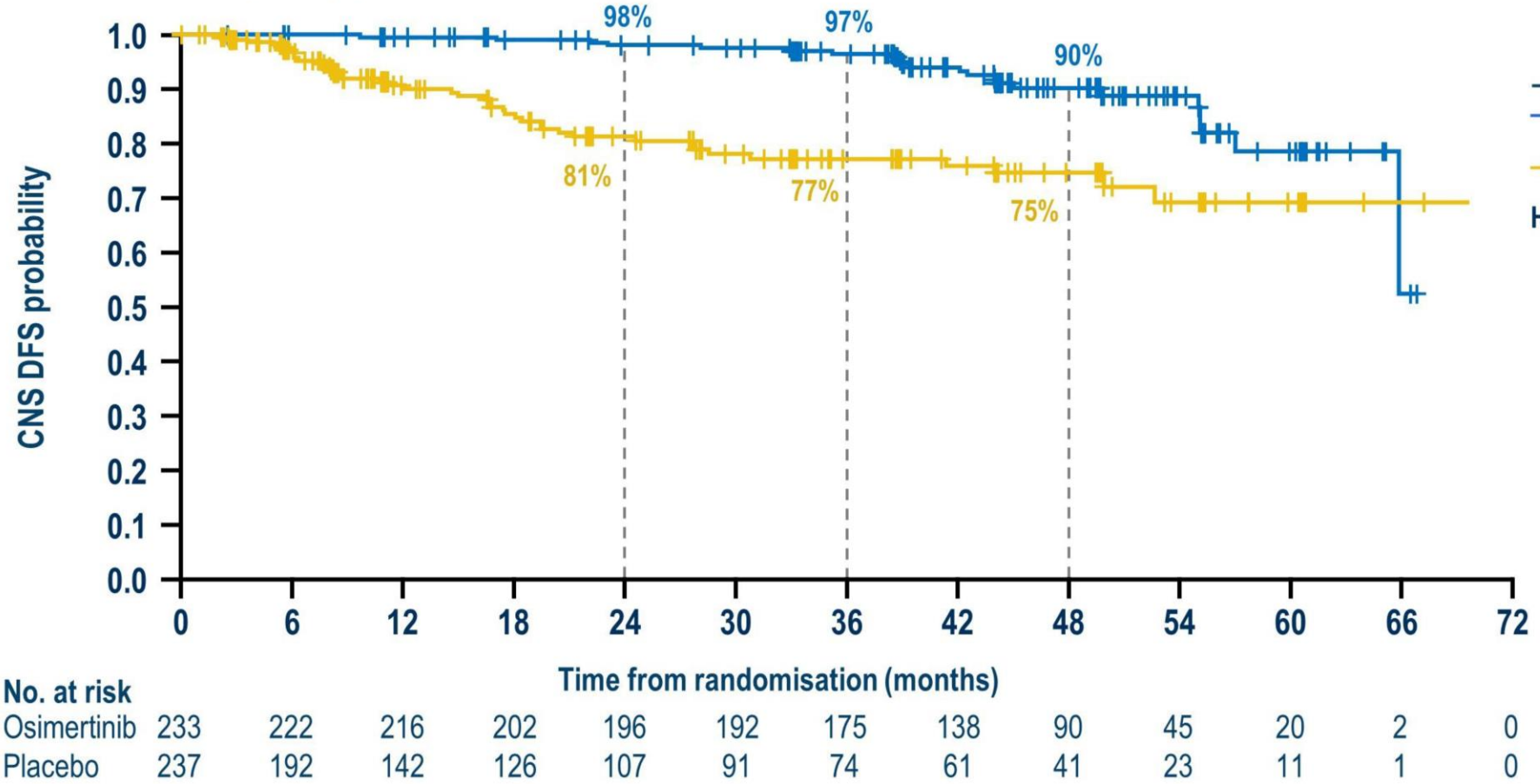


Tsuboi M, ESMO 2022

ADAURA: dati aggiornati di DFS per metastasi al SNC

UPDATED CNS DFS IN PATIENTS WITH STAGE II / IIIA DISEASE

- Overall, 63 patients (osimertinib n=22, placebo n=41) had CNS DFS events:*
  - 3 (14%) patients were on treatment at the time of CNS recurrence with osimertinib, versus 29 (71%) with placebo



No. at risk													
Osimertinib	233	222	216	202	196	192	175	138	90	45	20	2	0
Placebo	237	192	142	126	107	91	74	61	41	23	11	1	0

Median CNS DFS, months (95% CI)	
– Osimertinib	NR (65.8, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.24 (0.14, 0.42)**

Maturity 13%:
osimertinib 9%, placebo 17%

PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

Median follow-up: osimertinib 44.2 months, placebo 20.4 months; DFS by investigator assessment; Tick marks indicate censored data.
*Defined as CNS as the first site of disease recurrence, or death without any disease recurrence.

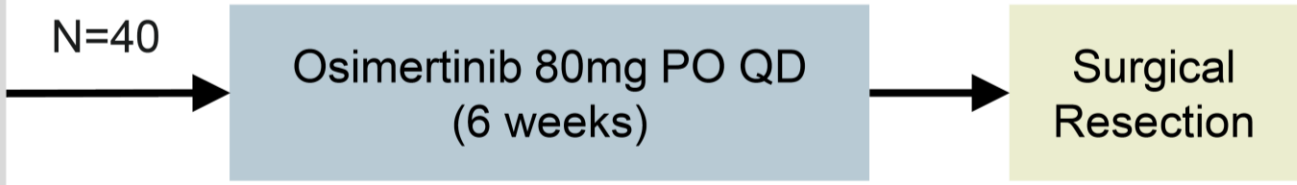
CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; HR, hazard ratio; NC, not calculable; NR, not reached
Data cut-off: April 11, 2022.

Osimertinib neoadiuvante: studio NEOS

Phase II, multicenter study of neoadjuvant osimertinib in EGFRm resected NSCLC

Key inclusion criteria

- Resectable lung carcinoma
- Stage II–IIIB N2 (AJCC v8)
- EGFRm NSCLC (Ex19del/L858R)
- ECOG PS 0-1

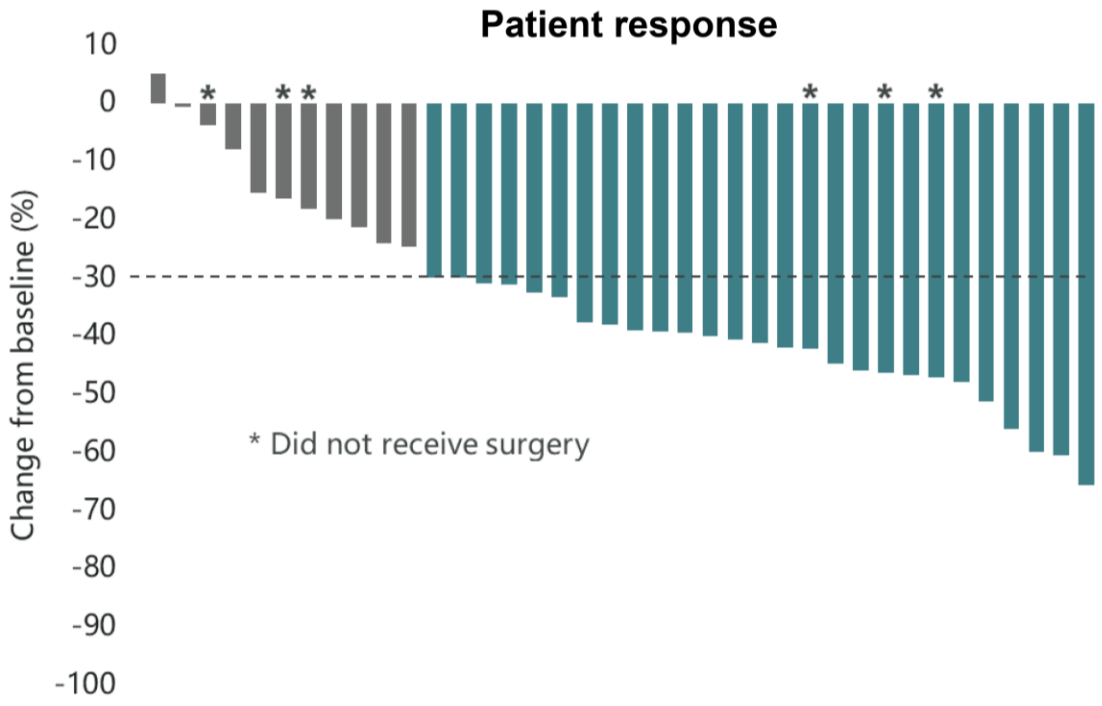


Endpoints

Primary: Objective response rate (ORR) assessed by investigator per RECIST v1.1.
Secondary: Safety, R0 resection rate, major pathologic response (MPR) rate, pathological complete response (pCR) rate, N2 downstaging rate, quality of life.

Studio NEOS: analisi di efficacia

- The objective response rate (ORR) was 71.1% (27/38) and the disease control rate (DCR) was 100%.
- Of the pathological evaluable patients, 11% (3/28) achieved MPR, including one pCR (4%). 46% (13/28) patients had a pathological response of ≥50%.

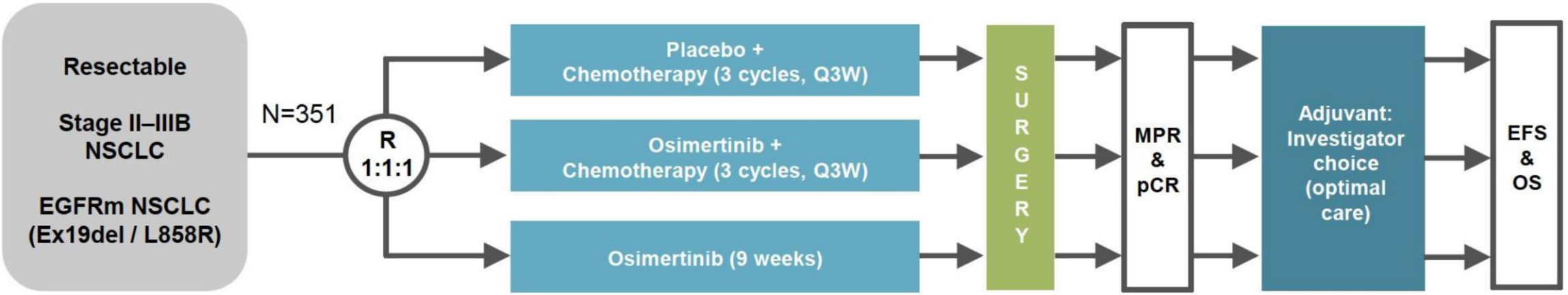


Endpoint		N=38
Tumor Response, n (%)	CR	0 (0%)
	PR	27 (71%)
	SD	11 (29%)
	PD	0 (0%)
ORR		71% (27/38)
DCR		100% (38/38)
R0 resection		94% (30/32)
MPR		11% (3/28)
pCR		4% (1/28)
Pathological response ≥50%		46% (13/28)

- **ORR:** objective response rate; **DCR**: disease control rate
- **MPR**: major pathological response rate, defined as the proportion of patients with no more than 10% residual viable tumor cells.
- **pCR**: pathological complete response rate, defined as the proportion of patients without residual viable tumor cells evaluated by pathologists.

Osimertinib neoadiuvante: studio NeoADAURA

NeoADAURA (NCT04351555): Phase III, Randomized, Controlled, Multicenter Study of Neoadjuvant Osimertinib in EGFRm Resectable NSCLC



Stratification:

- Stage II/III
- Non-Asian/Chinese/ other Asian
- Ex19del/L858R

Double-blind treatment arms:

1. Placebo QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2
2. Osimertinib 80 mg QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2

Open-label (sponsor-blind) treatment arm:

3. Osimertinib 80 mg QD

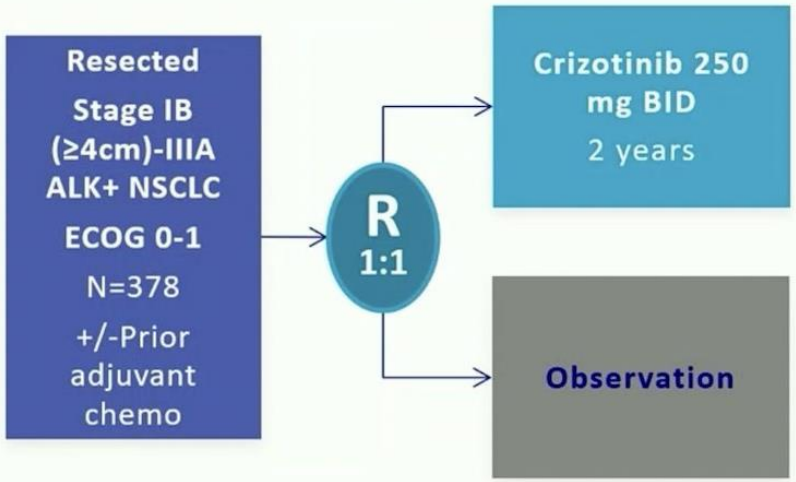
Adjuvant therapy and follow-up:

- Patients will be followed up for OS until 5 years from surgery, with evaluation at 12 and 24 weeks post-surgery, then every 24 weeks, until disease recurrence or withdrawal of consent
- Osimertinib will be offered to all patients who complete surgery (+/- post-surgical chemotherapy) for up to 3 years or until disease recurrence

Tsuboi M, et al. Future Oncol 2021;17(31):4045-4055.

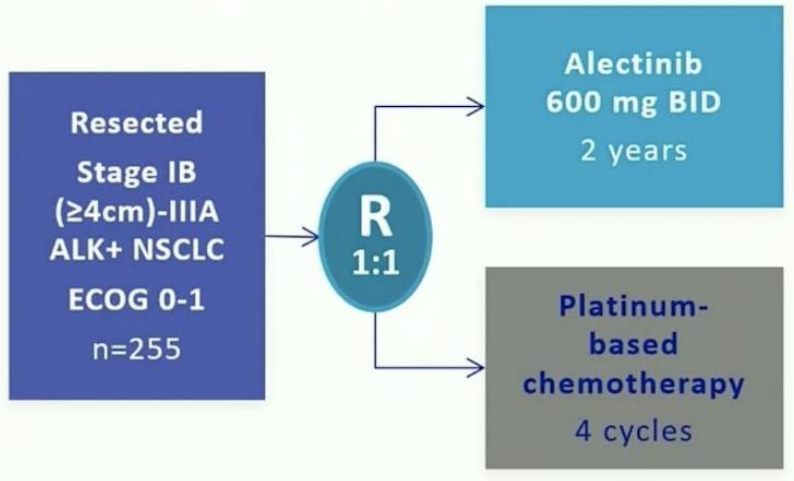
Studi nella malattia ALK+ early stage

Adjuvant Crizotinib phase 3 trial
E4512 – ALCHEMIST[1]



ALK, anaplastic lymphoma kinase; BID; two times a day; ECOG, Eastern Cooperative Oncology Group NSCLC, non small cell lung cancer.

Adjuvant Alectinib phase 3 trial
ALINA (BO40336)[2]



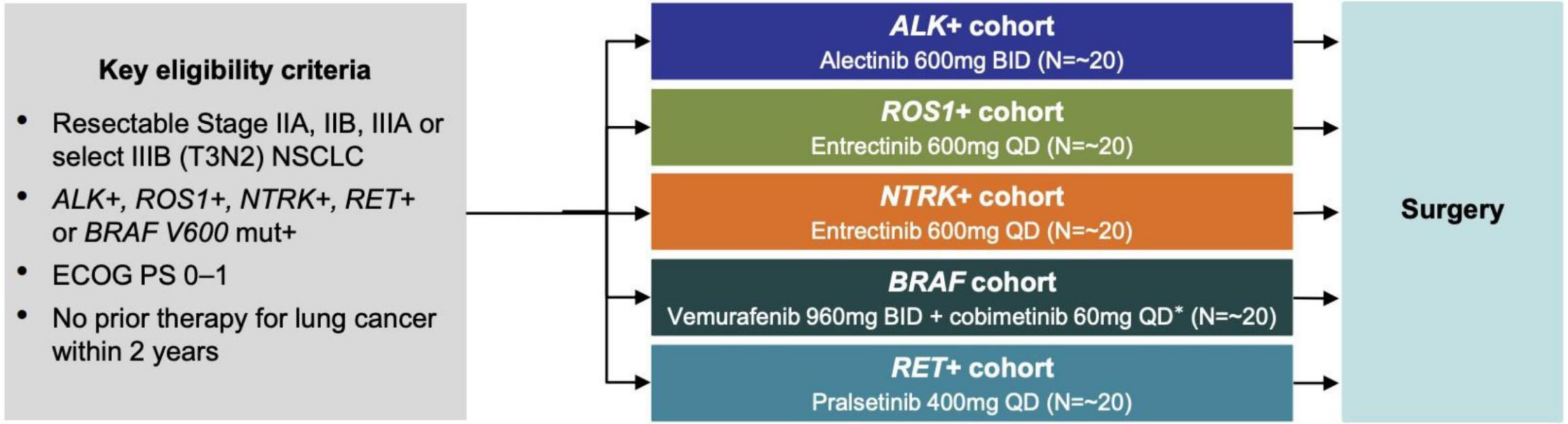
1.Clinicaltrials.gov, https://clinicaltrials.gov/ct2/show/NCT02201992 (accessed 19 August 2021); 2.Clinicaltrials.gov, https://www.clinicaltrials.gov/ct2/show/NCT03456076. (accessed 19 August 2021)

Neoadjuvant Alectinib phase 2 trial
ALNEO

Primary Endpoint: MPR
Secondary Endpoints: pCR, OR, EFS, DFS, OS, AEs

Umbrella trials

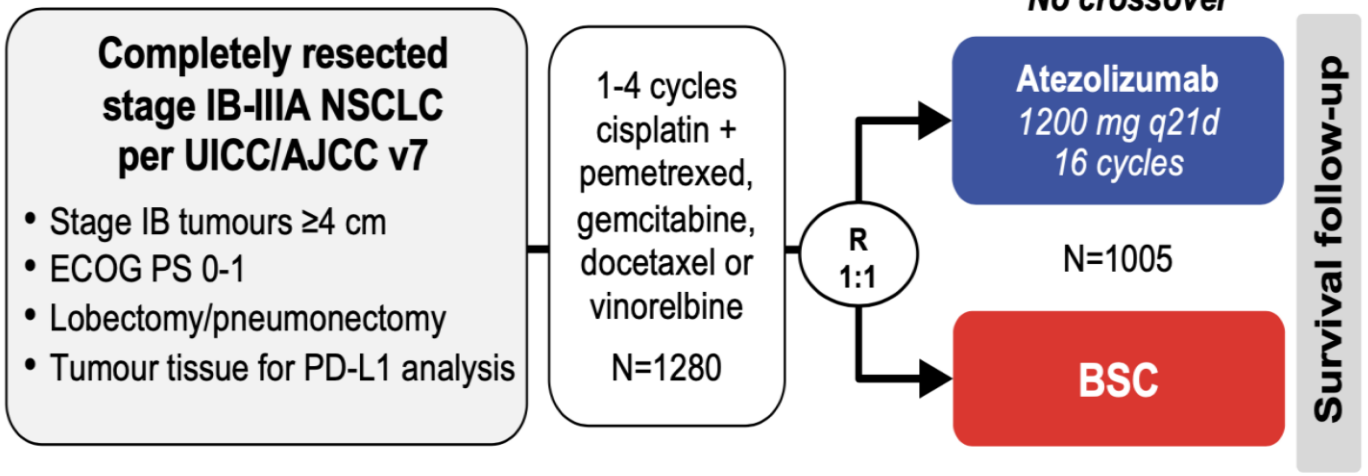
NAUTIKA1: study design overview (neoadjuvant treatment)



Neoadjuvant treatment and response assessment

- Patients will be assigned a neoadjuvant therapy based on their driver mutation
  - Patients will receive 8 weeks (2 cycles) of neoadjuvant therapy
- PET/CT scans will be performed at screening and pre-surgery to determine tumour response

IO adiuvante: Studio IMpower010



Stratification factors

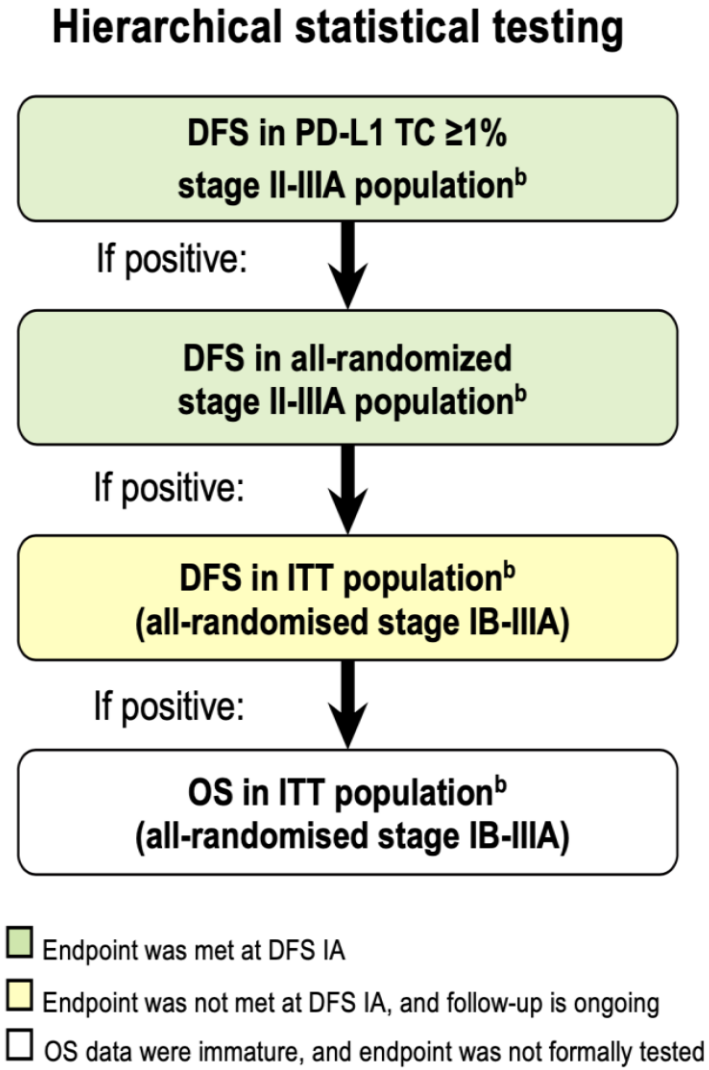
- Sex
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumour expression status (TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1)[a]

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (SP263) stage II-IIIA population
  2. All-randomised stage II-IIIA population
  3. ITT (all-randomised stage IB-IIIA) population

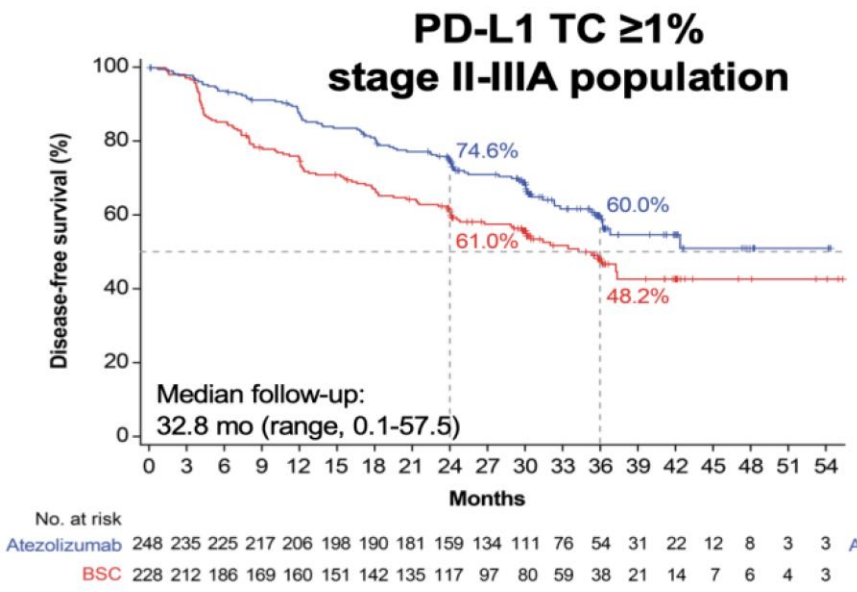
Key secondary endpoints

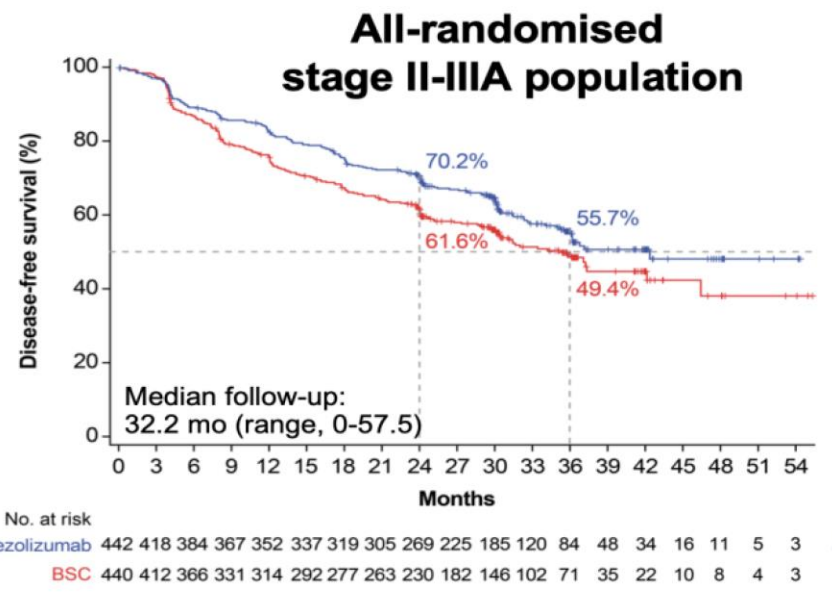
- OS in ITT (all-randomised stage IB-IIIA) population
- DFS in PD-L1 TC ≥50% (SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

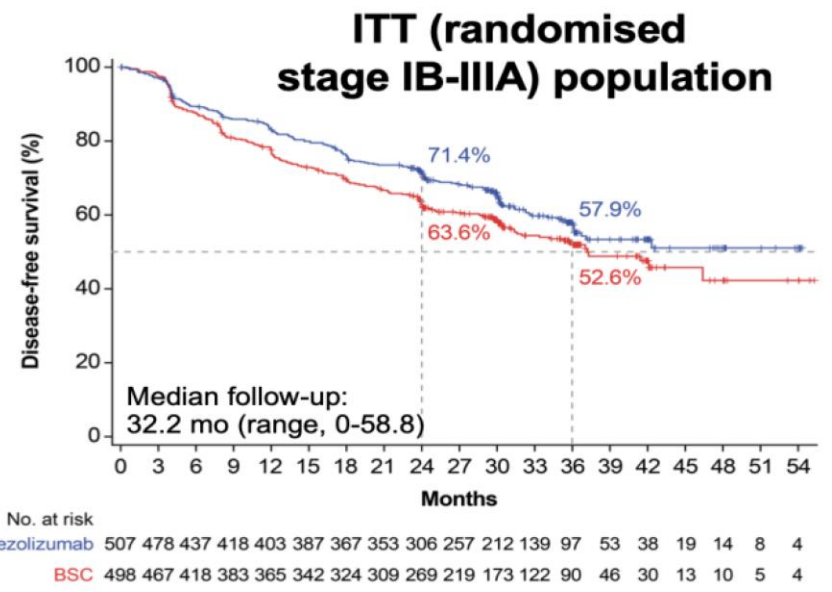


Felip E et al. Lancet 2021;398(10308):1344-1357

IMpower010: DFS







	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

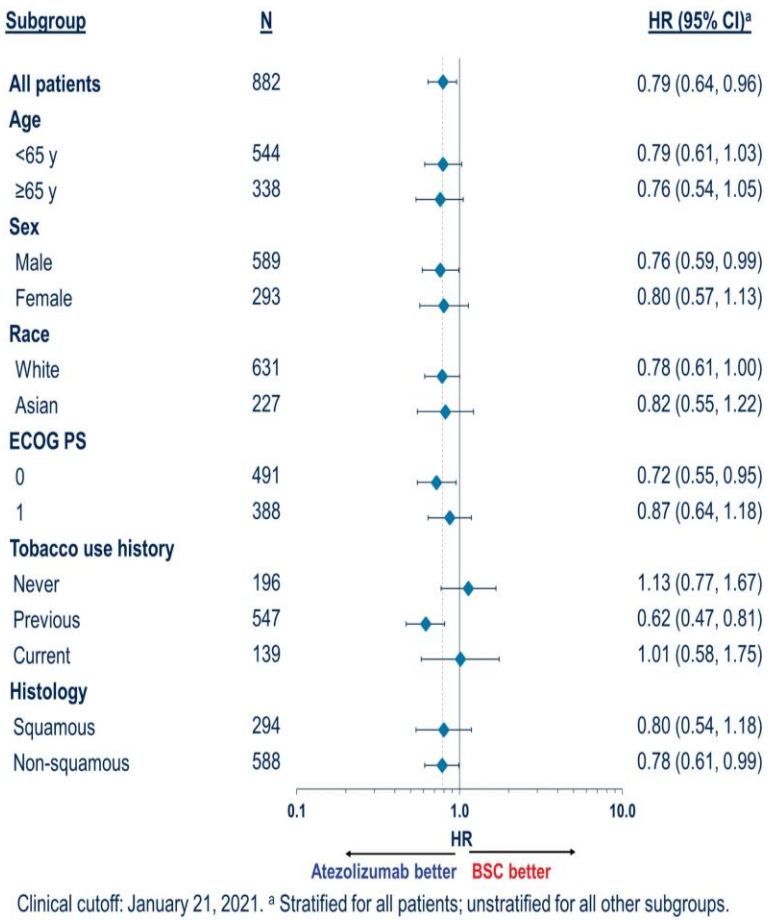
	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[b]	0.02[c]	

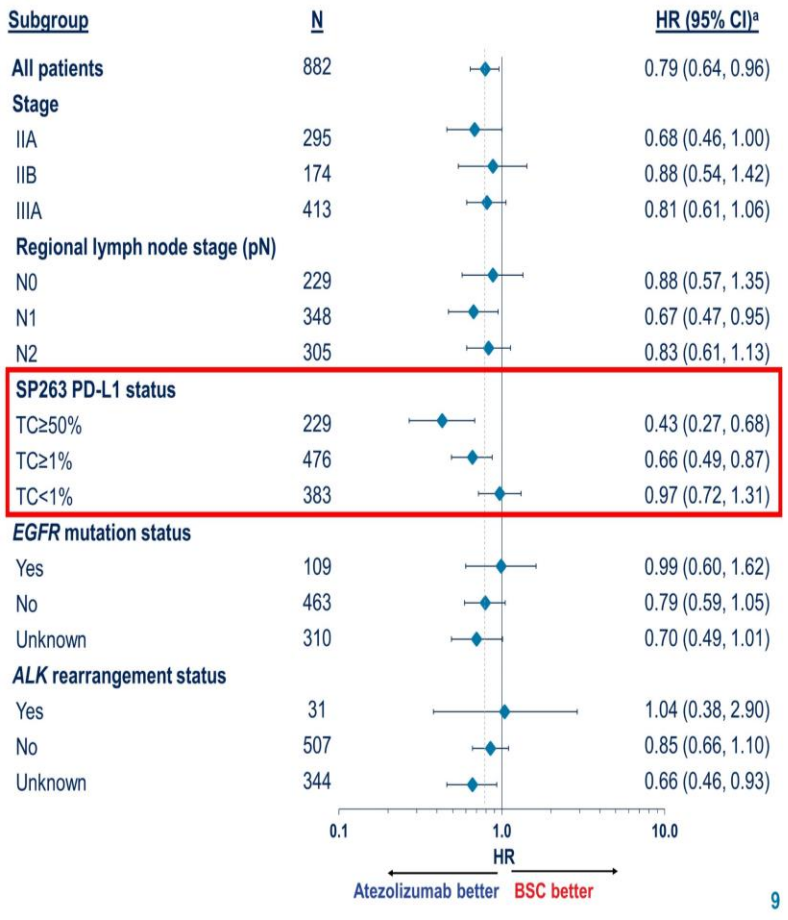
	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

Clinical cut-off: 21 January 2021. [a.] Per SP263 assay [b.] Stratified log-rank. [c.] Crossed the significance boundary for DFS. [D.] The statistical significance boundary for DFS was not crossed

Felip E et al. Lancet 2021;398(10308):1344-1357

IMpower010: DFS nei sottogruppi di pazienti allo stadio II-IIIA





Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

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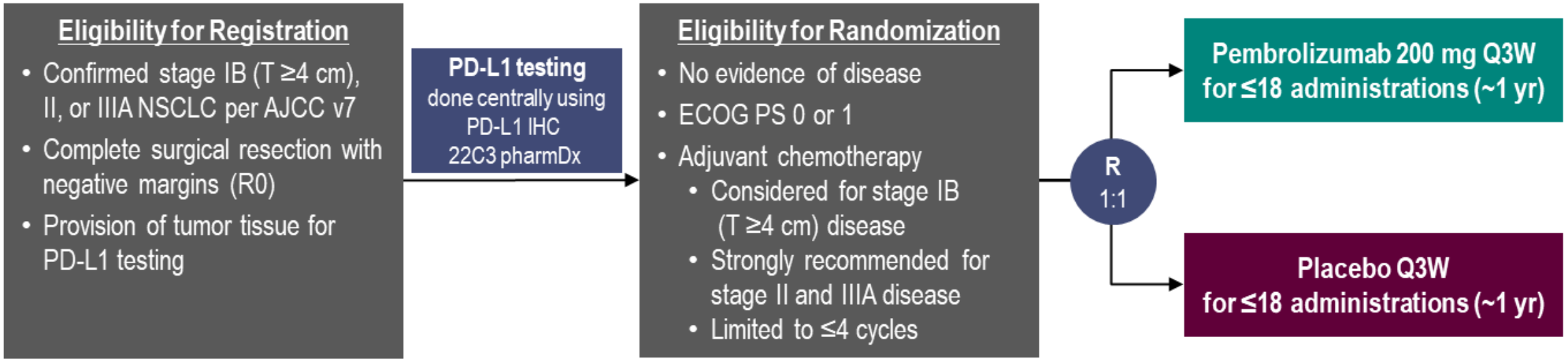
Population analyzed for DFS[1,2]	n	HR (95% CI)
PD-L1 TC ≥1%[a] Stage II-IIIA	476	0.66 (0.50, 0.88)[b]
PD-L1 TC 1-49% Stage II-IIIA[2]	247	0.87 (0.60, 1.26)[c]
PD-L1 TC ≥50% Stage II-IIIA	**229**	**0.43 (0.27, 0.68)[c]**
All-randomised Stage II-IIIA	882	0.79 (0.64, 0.96)[b]
ITT (randomised Stage IB-IIIA)	1005	0.81 (0.67, 0.99)[b]

Felip E et al. Lancet 2021;398(10308):1344-1357; Felip E, ELCC 2022

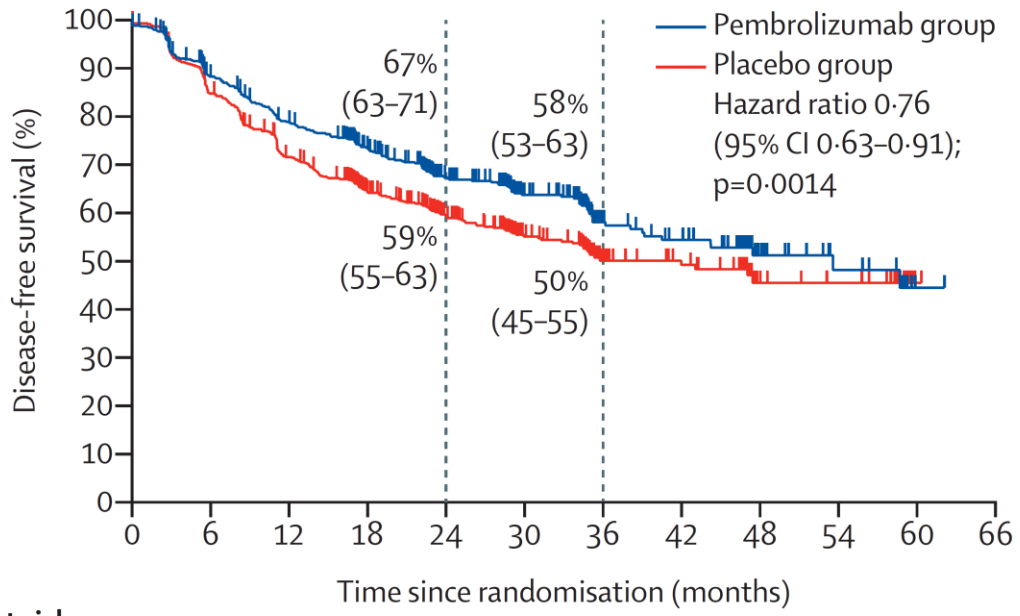
IO adiuvante: PEARLS/Keynote-091



O'Brien M, et al. Lancet Oncol 2022;23(10):1274-1286.

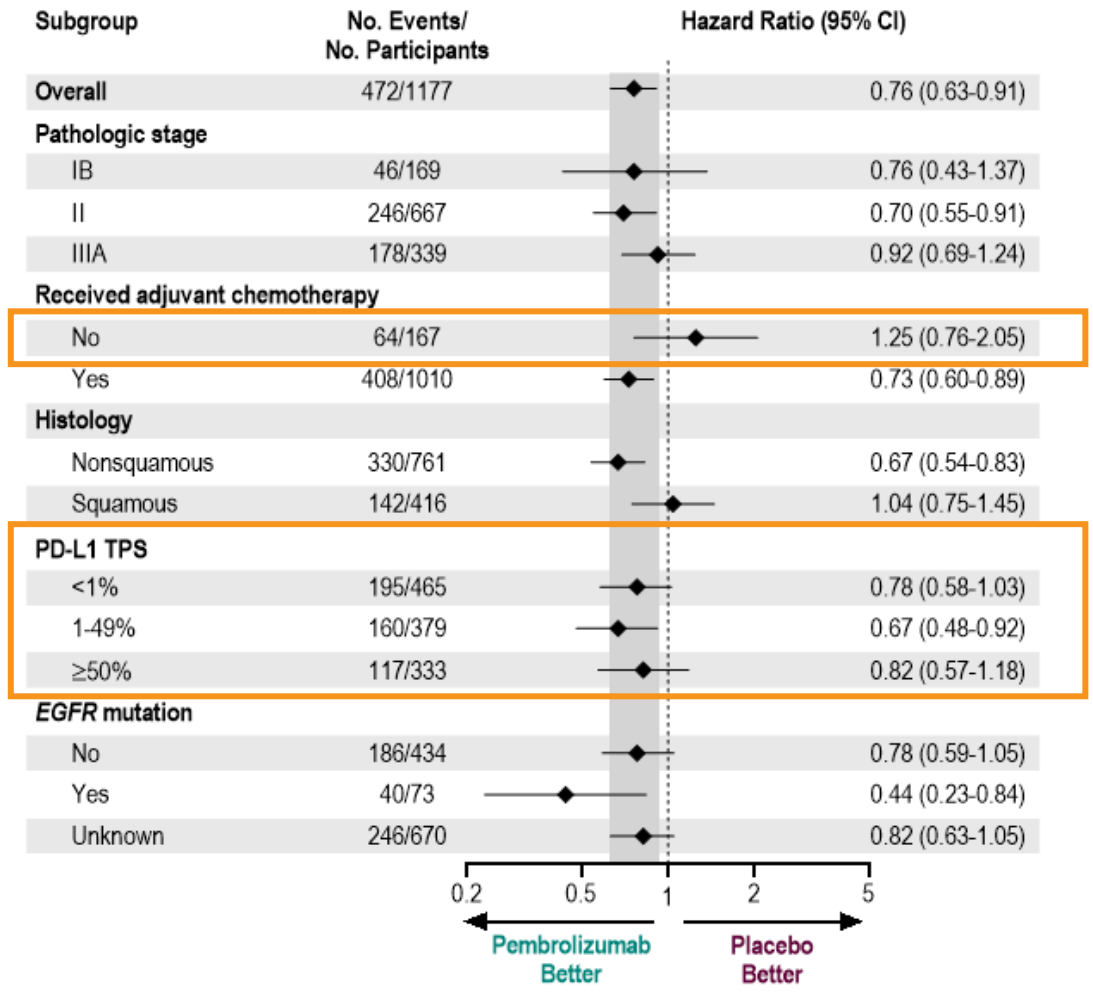
PEARLS/Keynote-091: DFS

A

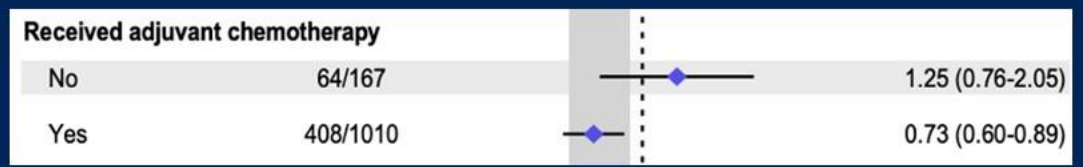


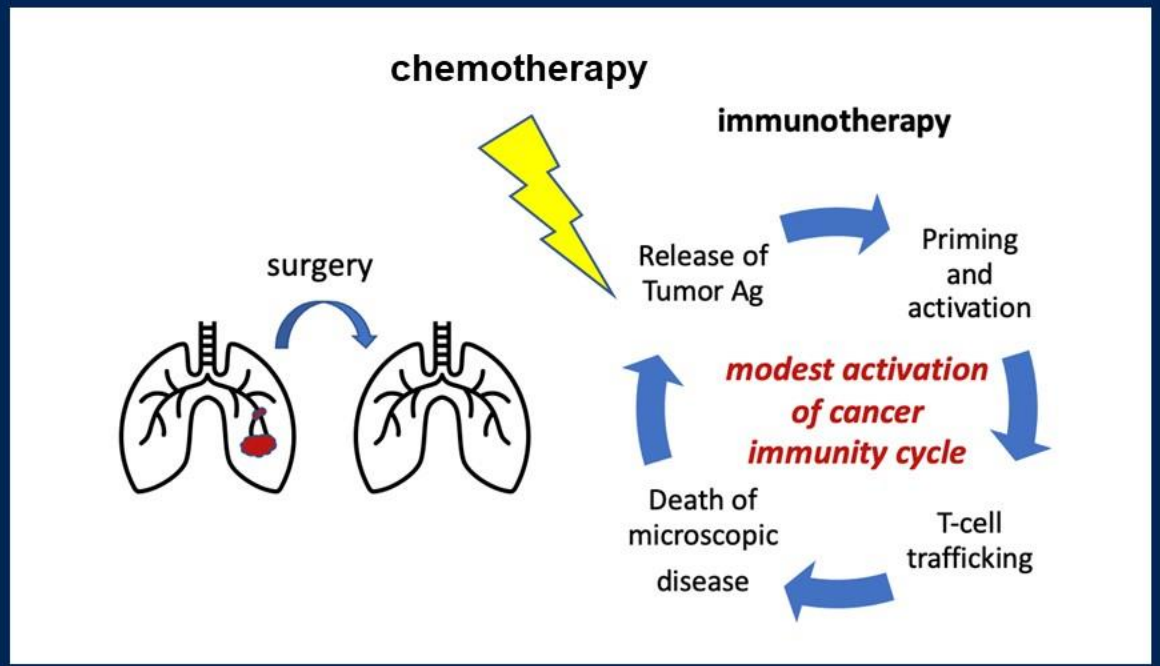
Number at risk (number censored)

Pembrolizumab	590	493	434	358	264	185	82	70	28	16	1	0
	(0)	(30)	(36)	(84)	(150)	(216)	(306)	(313)	(352)	(363)	(377)	(378
Placebo	587	493	409	326	241	160	72	57	22	18	1	0
	(0)	(5)	(13)	(56)	(118)	(183)	(259)	(273)	(305)	(309)	(326)	(327



Adjuvant Therapy Required for IO?



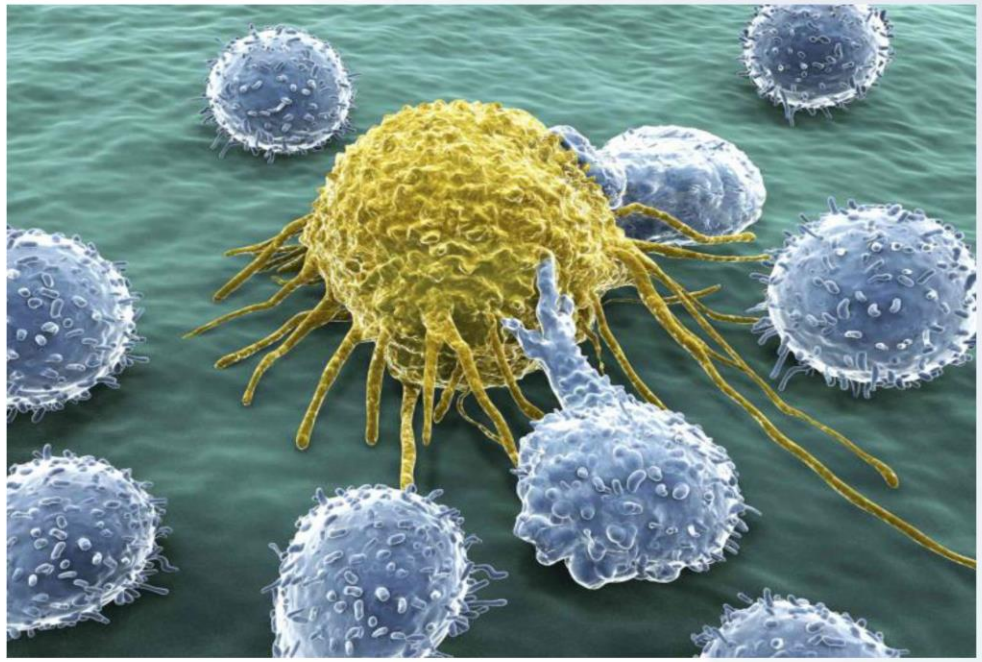


PRESENTED BY:
Jyoti D. Patel, MD FASCO
Northwestern University

Main considerations for Neoadjuvant Therapy in resectable early-stage lung cancers

The case for Neoadjuvant therapy

- Powerful systemic anti-tumor immune response
  - Activation of tumor infiltrating T-cells prior to surgery
  - Memory T-cells that may provide long-term protection
  - Tumor resection may reduce the neoantigen repertoire
  - Better drug delivery presurgery
  - Better tolerability presurgery
  - Early treatment of micrometastatic disease
  - Tumor downstaging/Improved resectability
  - Disruption of several immunological pathways by surgical stress

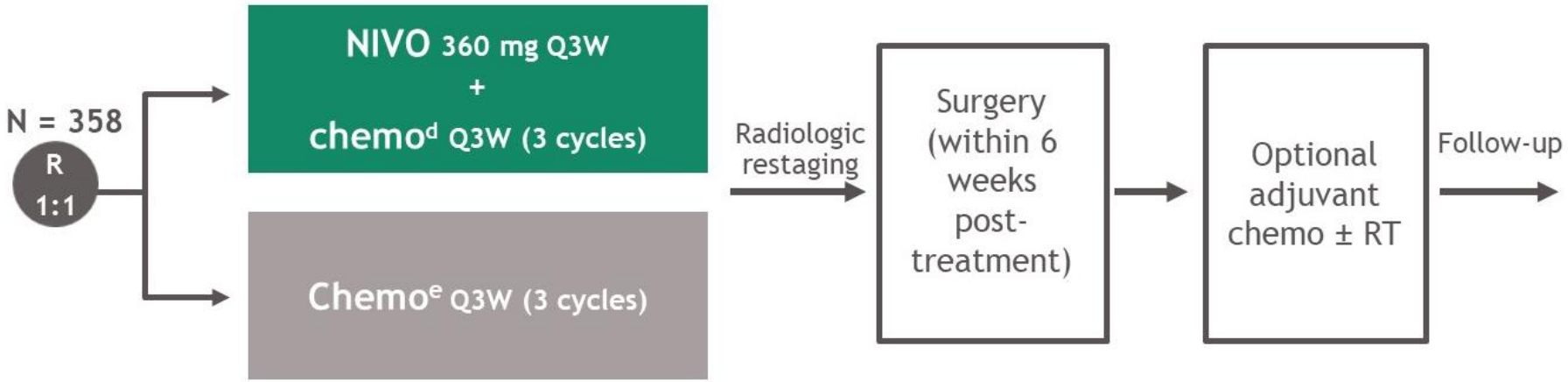


Checkmate 816: study design

Key eligibility criteria

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

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



Primary endpoints

- pCR by BIPR
- EFS by BICR

Key secondary endpoints

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

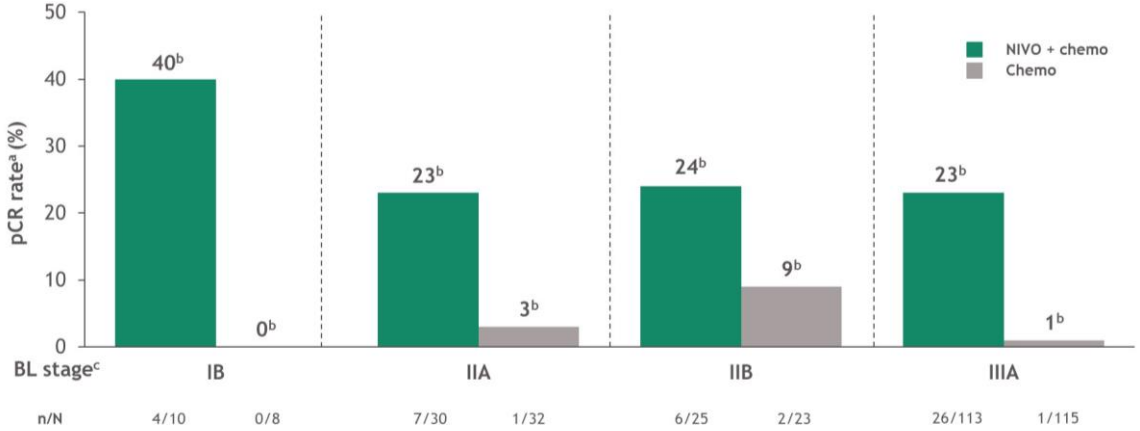
Key exploratory endpoints included

- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

Forde PM, et al. N Engl J Med 2022;386(21):1973-1985.

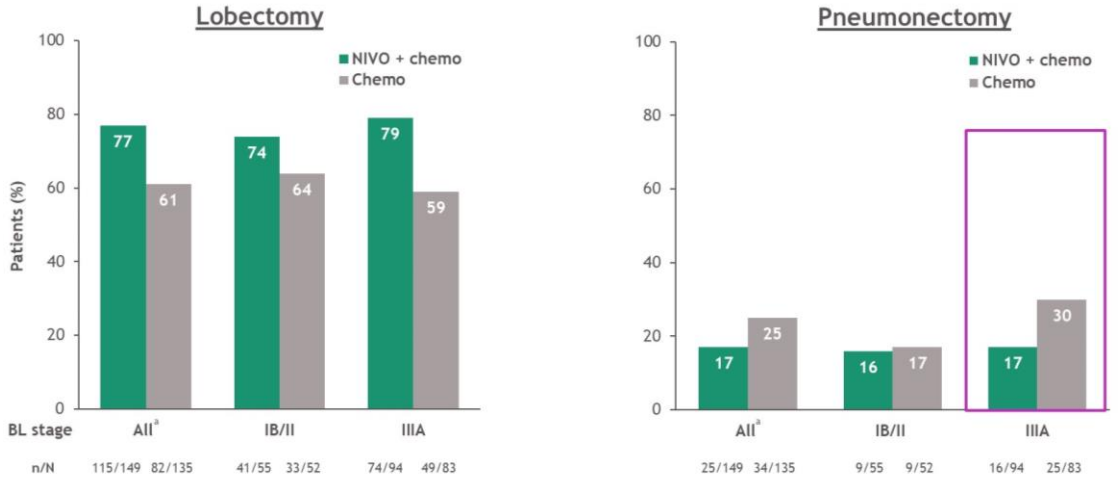
Checkmate 816: outcomes chirurgici

pCR by baseline stage

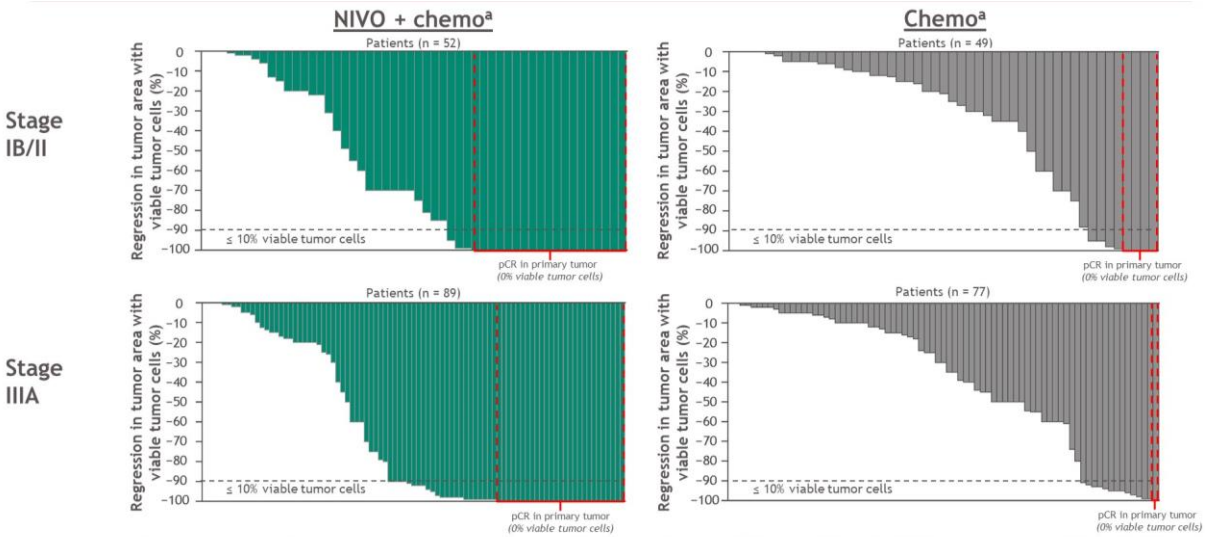


- pCR improvement with NIVO + chemo vs chemo was observed regardless of radiologic down-staging[d]

Type of surgery by baseline stage



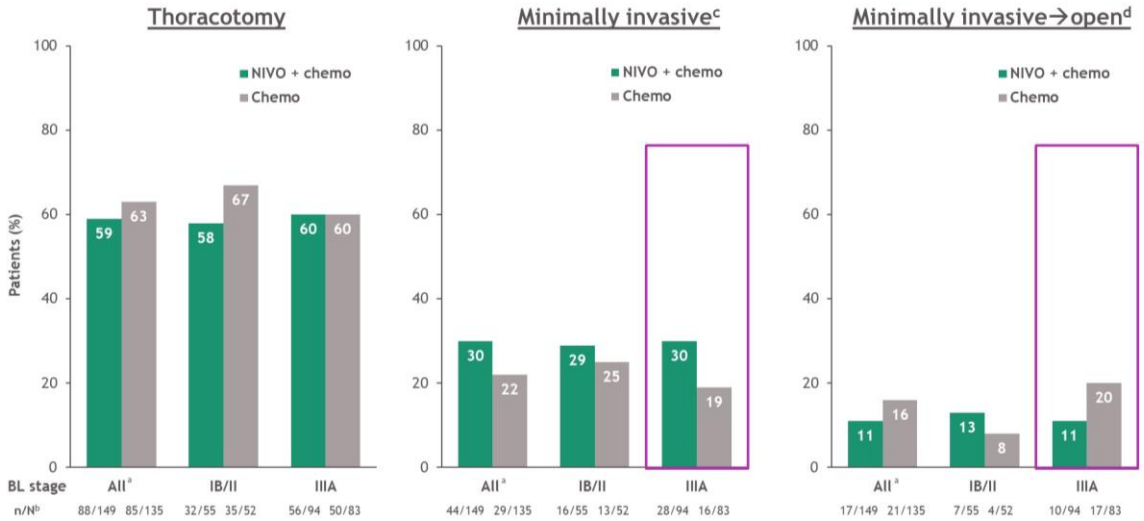
Depth of pathological regression



- The median residual viable tumor percentage in stage IB/II and IIIA was 28% and 8% with NIVO + chemo vs 79% and 70% with chemo, respectively

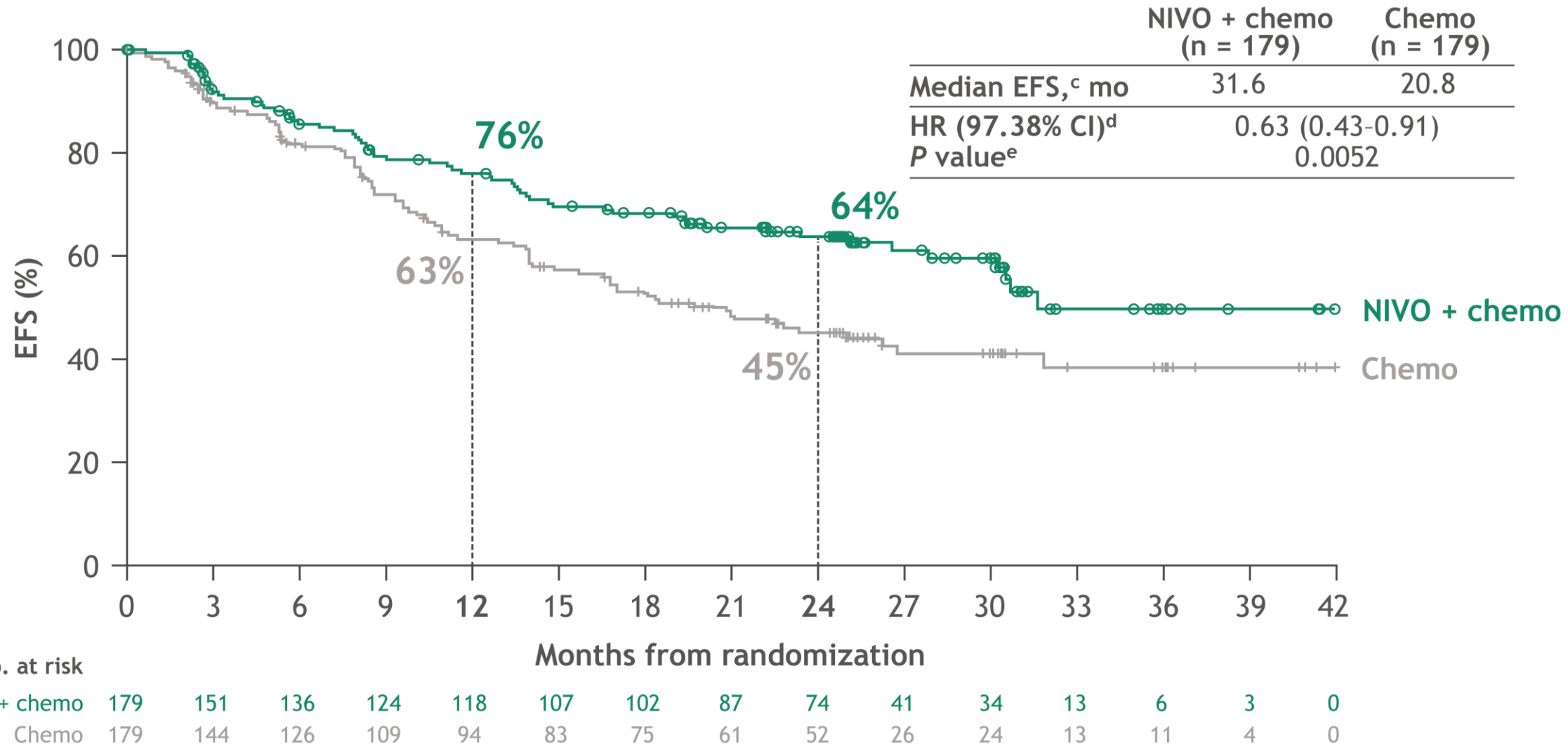
[a]Response-evaluable patients.

Surgical approach by baseline stage



Forde PM, et al. N Engl J Med 2022;386(21):1973-1985.

Checkmate 816: EFS



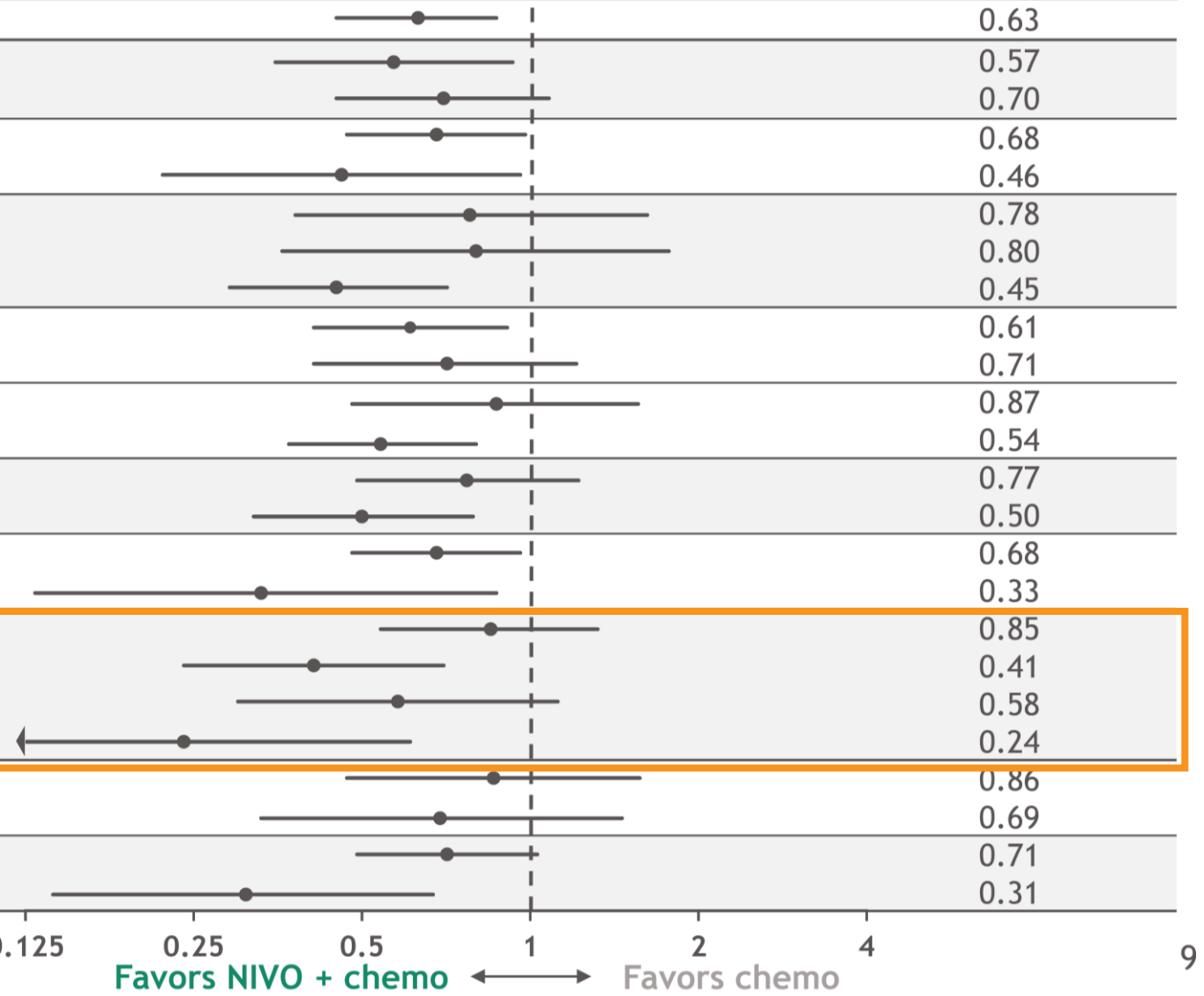
Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]Per BICR; [b]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy; [c]95% CI = 30.2-NR (NIVO + chemo) and 14.0-26.7 (chemo); [d]95% CI = 0.45-0.87; [e]The significance boundary at this interim analysis was 0.0262.

Forde PM, et al. N Engl J Med 2022;386(21):1973-1985.

Checkmate 816: EFS

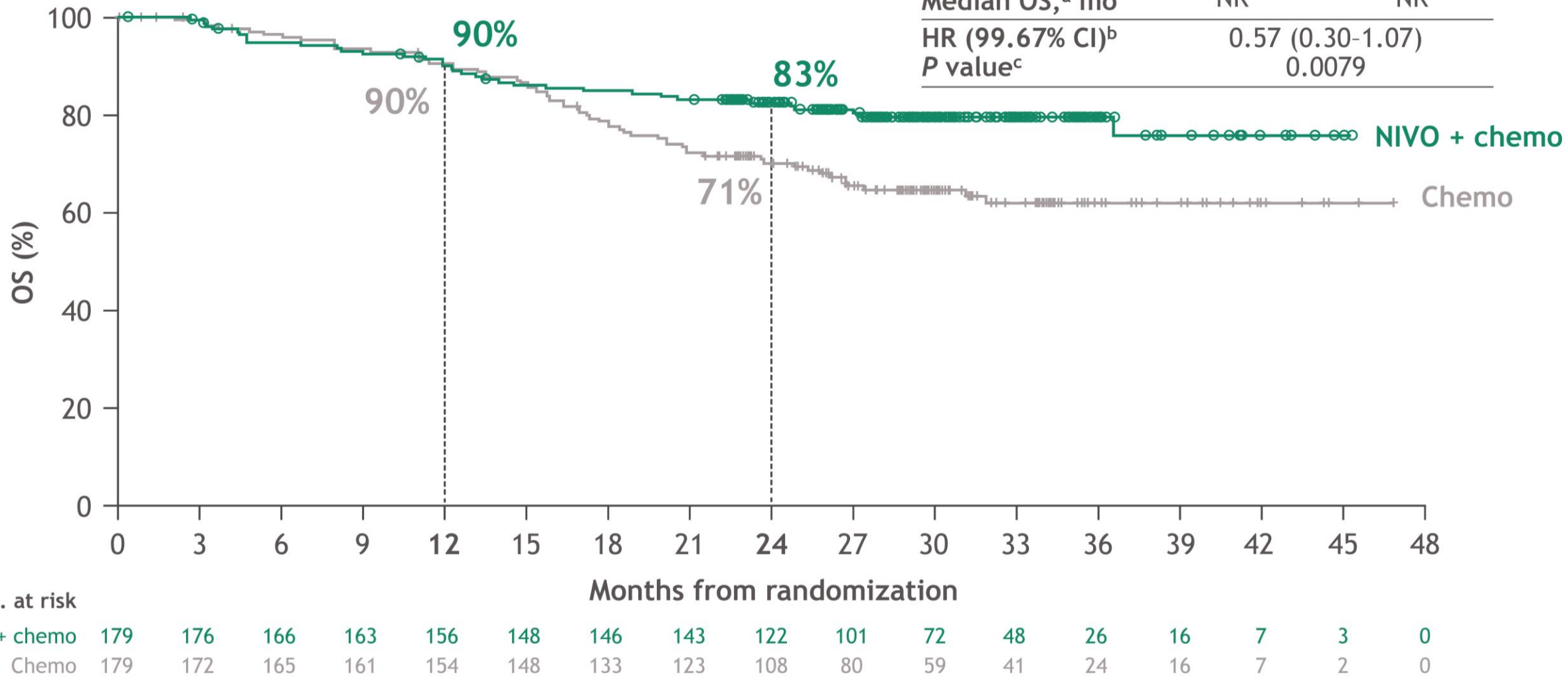
	Median EFS[a], mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	32	21		0.63
< 65 years (n = 176)	NR	21		0.57
≥ 65 years (n = 182)	30	18		0.70
Male (n = 255)	31	17		0.68
Female (n = 103)	NR	32		0.46
North America (n = 91)	NR	NR		0.78
Europe (n = 66)	32	21		0.80
Asia (n = 177)	NR	16		0.45
ECOG PS 0 (n = 241)	NR	23		0.61
ECOG PS 1 (n = 117)	30	14		0.71
Stage IB-II (n = 127)	NR	NR		0.87
Stage IIIA (n = 228)	32	16		0.54
Squamous (n = 182)	31	23		0.77
Non-squamous (n = 176)	NR	20		0.50
Current/former smoker (n = 318)	32	22		0.68
Never smoker (n = 39)	NR	10		0.33
PD-L1 < 1% (n = 155)	25	18		0.85
PD-L1 ≥ 1% (n = 178)	NR	21		0.41
PD-L1 1-49% (n = 98)	NR	27		0.58
PD-L1 ≥ 50% (n = 80)	NR	20		0.24
TMB < 12.3 mut/Mb (n = 102)	30	27		0.86
TMB ≥ 12.3 mut/Mb (n = 76)	NR	22		0.69
Cisplatin (n = 258)	NR	21		0.71
Carboplatin (n = 72)	NR	11		0.31



[a]Per BICR.

Forde PM, et al. N Engl J Med 2022;386(21):1973-1985.

Checkmate 816: analisi ad interim di OS



	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR
HR (99.67% CI)[b]	0.57 (0.30-1.07)	
P value[c]	0.0079	

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

[a]95% CI = NR-NR (NIVO + chemo) and NR-NR (chemo); [b]95% CI = 0.38-0.87; [c]Significance boundary for OS (0.0033) was not met at this interim analysis.

Forde PM, et al. N Engl J Med 2022;386(21):1973-1985.

IO neoadiuvante: studi in corso

Trial	Inclusion criteria	Treatment arms	Post-SUR therapy
CheckMate 816	Resectable stage IB (≥4 cm)-IIIA N=350	CT (3C) followed by SUR vs CT+nivolumab (3C) followed by SUR	
Impower030	Resectable stage II, IIIA, selected IIIB (T3N2) N=450	CT+placebo (4C) followed by SUR vs CT+atezolizumab (4C) followed by SUR	BSC vs Atezolizumab (1 yr)
Keynote-671	Resectable stage II, IIIA, selected IIIB (T3-T4N2) N=786	CT+placebo (4C) followed by SUR vs CT+pembrolizumab (4C) followed by SUR	Placebo vs Pembrolizumab (1 yr)
AEGEAN	Resectable stage II-III N=300	CT+placebo (4C) followed by SUR vs CT+durvalumab (4C) followed by SUR	Placebo vs Durvalumab (1 yr)
CheckMate 77T	Resectable stage IIA, IIIA, IIIB (T3N2) N=452	CT+placebo (4C) followed by SUR vs CT+nivolumab (4C) followed by SUR	Placebo vs Nivolumab (1 yr)

Take home messages

- La chemioterapia neoadiuvante/adiuvante a base di cisplatino aumenta la sopravvivenza a 5 anni nei pazienti in stadio II-III di circa il 5%
- Osimertinib adiuvante nuovo standard per i tumori in stadio IB-IIIA EGFRmut radicalmente operati
- Atezolizumab adiuvante nuova opzione (dopo chemioterapia) per i tumori in stadio II-IIIA radicalmente operati e con alta espressione di PDL1
- Nel prossimo futuro, la Chemio-IO cambierà lo scenario terapeutico del trattamento del NSCLC in stadio precoce

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