

16th
CONGRESS
Lung **ON**
CANCER

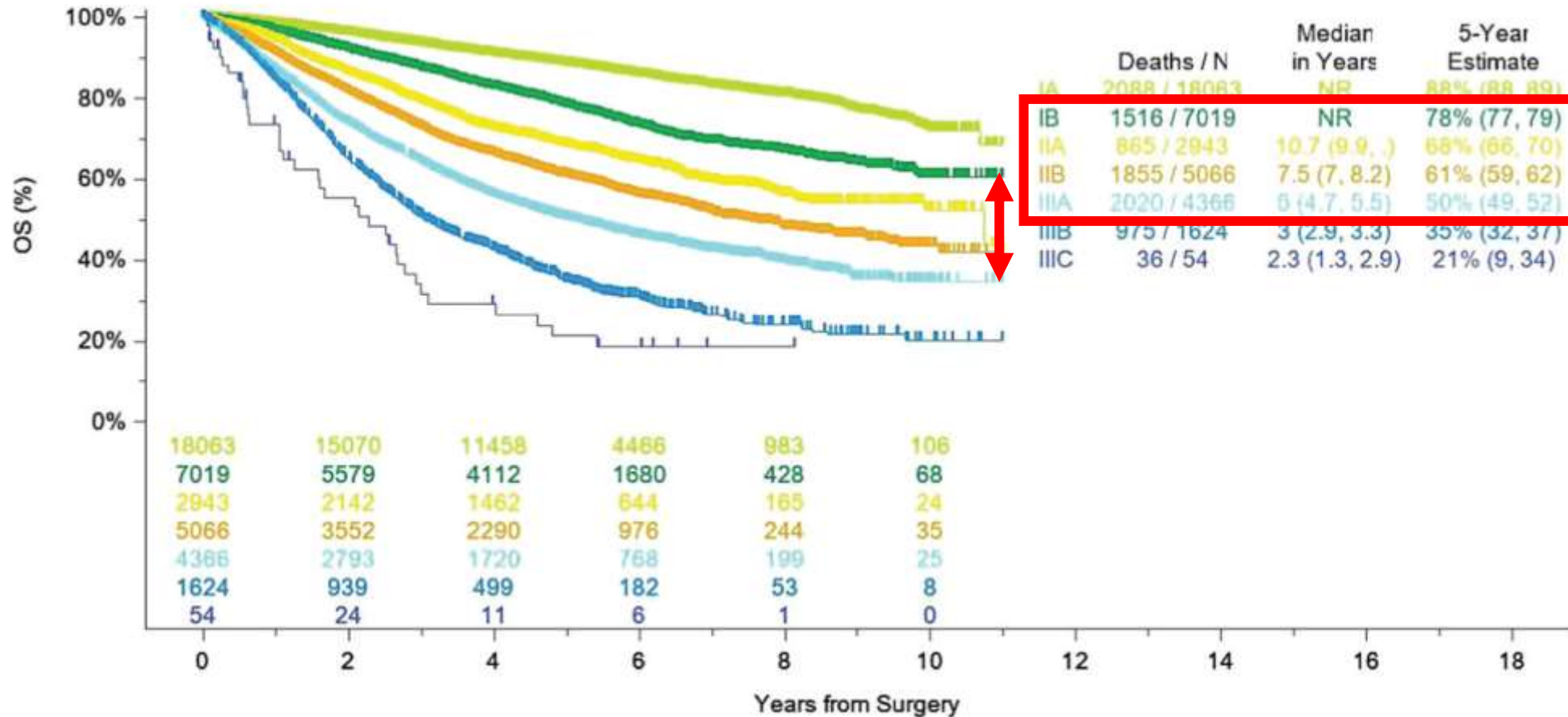
BARCELONA
27 / 28
NOVEMBER 2025

EARLY STAGES NSCLC.
**State of art: Neoadjuvant, adjuvant
and periadjuvant treatments**

Ramón Palmero Sánchez
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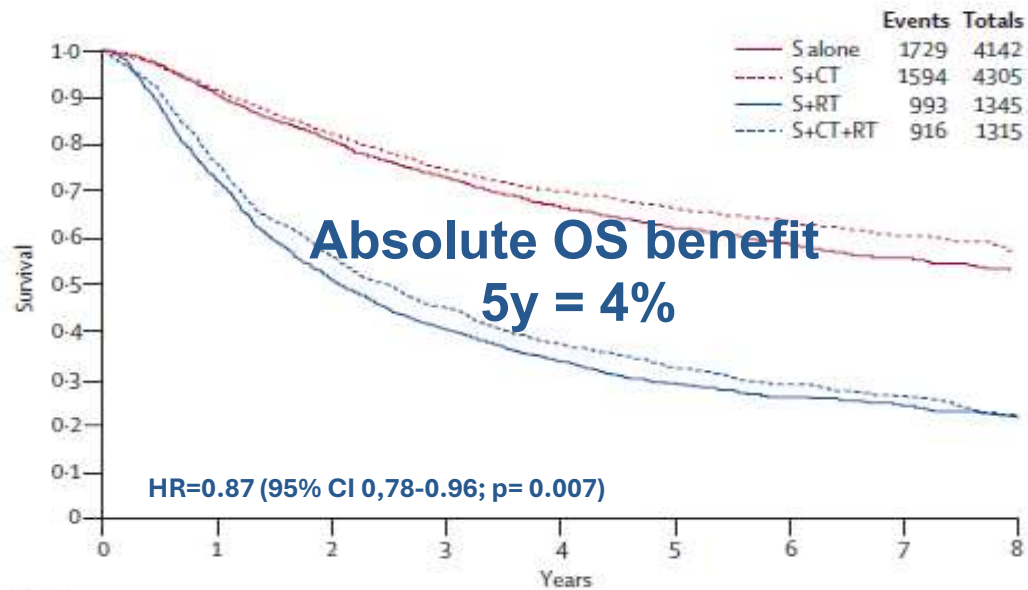
Los pacientes con CPNM estadio IB-III A operados tienen un elevado riesgo de recidiva y entre el 22-50% no están vivos a los 5 años

9th Edition pTNM



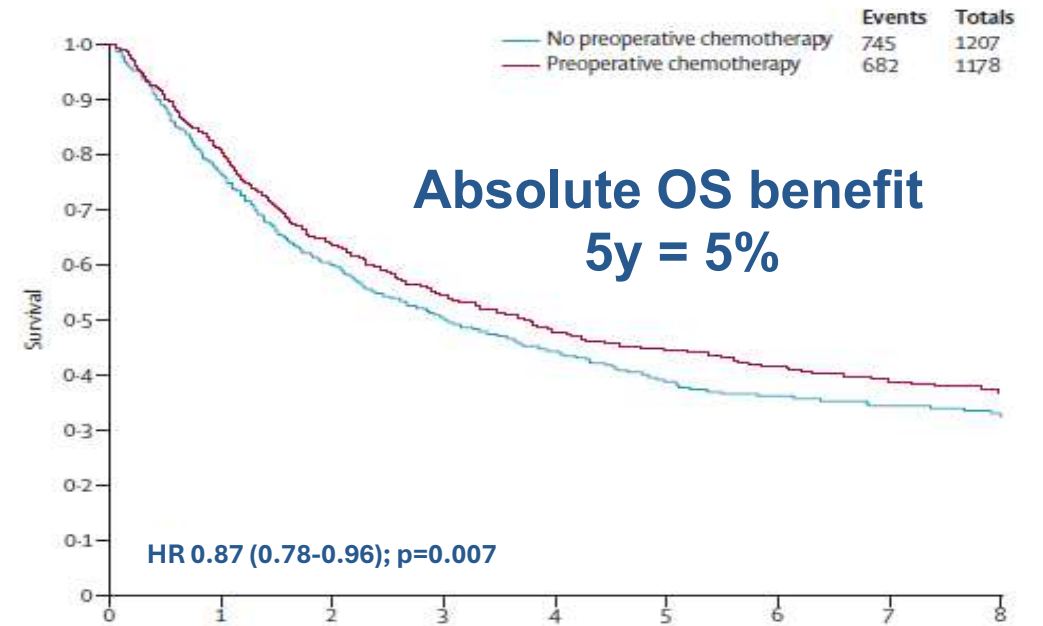
Perioperative treatment in resectable IB-IIIA NSCLC

Adjuvant platinum based chemo



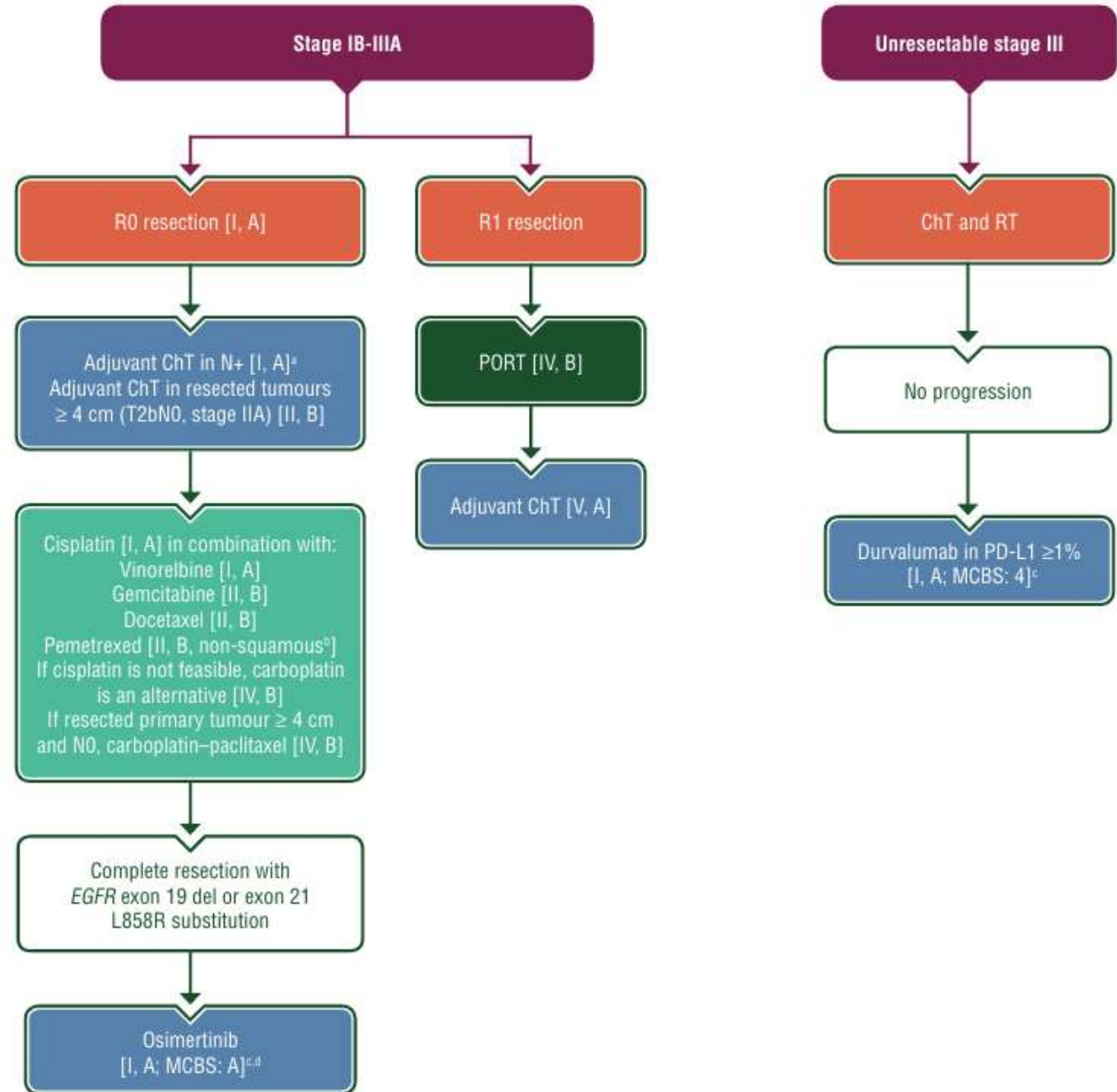
Number at risk	0	1	2	3	4	5	6	7	8
S alone	4142	3648	3102	2584	2083	1601	841	407	148
S+CT	4305	3809	3261	2746	2278	1785	936	473	165
S+RT	1345	956	660	503	376	282	202	141	85
S+CT+RT	1315	977	711	532	385	279	203	143	84

Neoadjuvant platinum based chemo

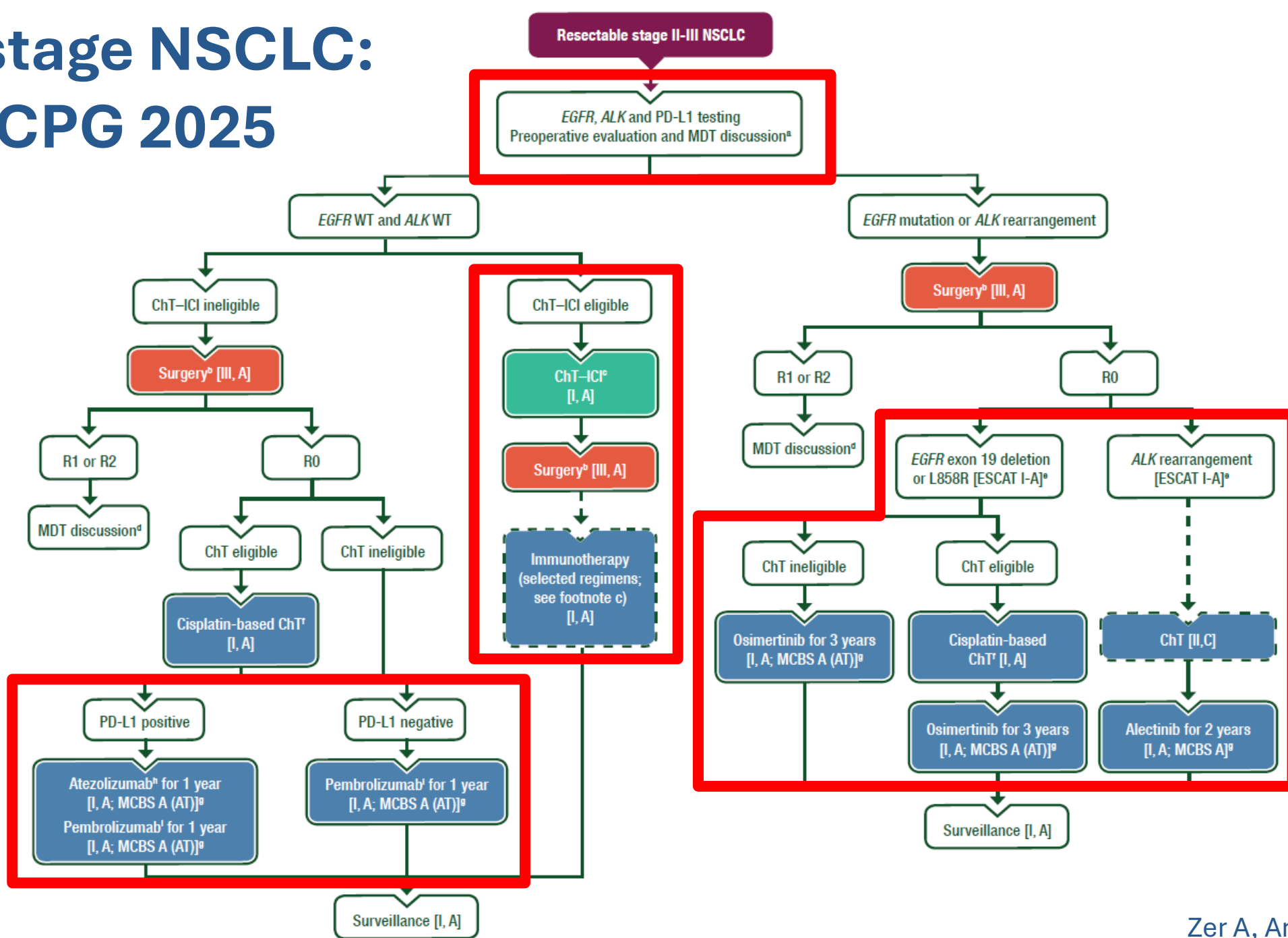


Number at risk	0	1	2	3	4	5	6	7	8
No preoperative chemotherapy	1207	893	674	527	409	300	209	147	102
Preoperative chemotherapy	1178	928	712	570	442	346	253	172	123

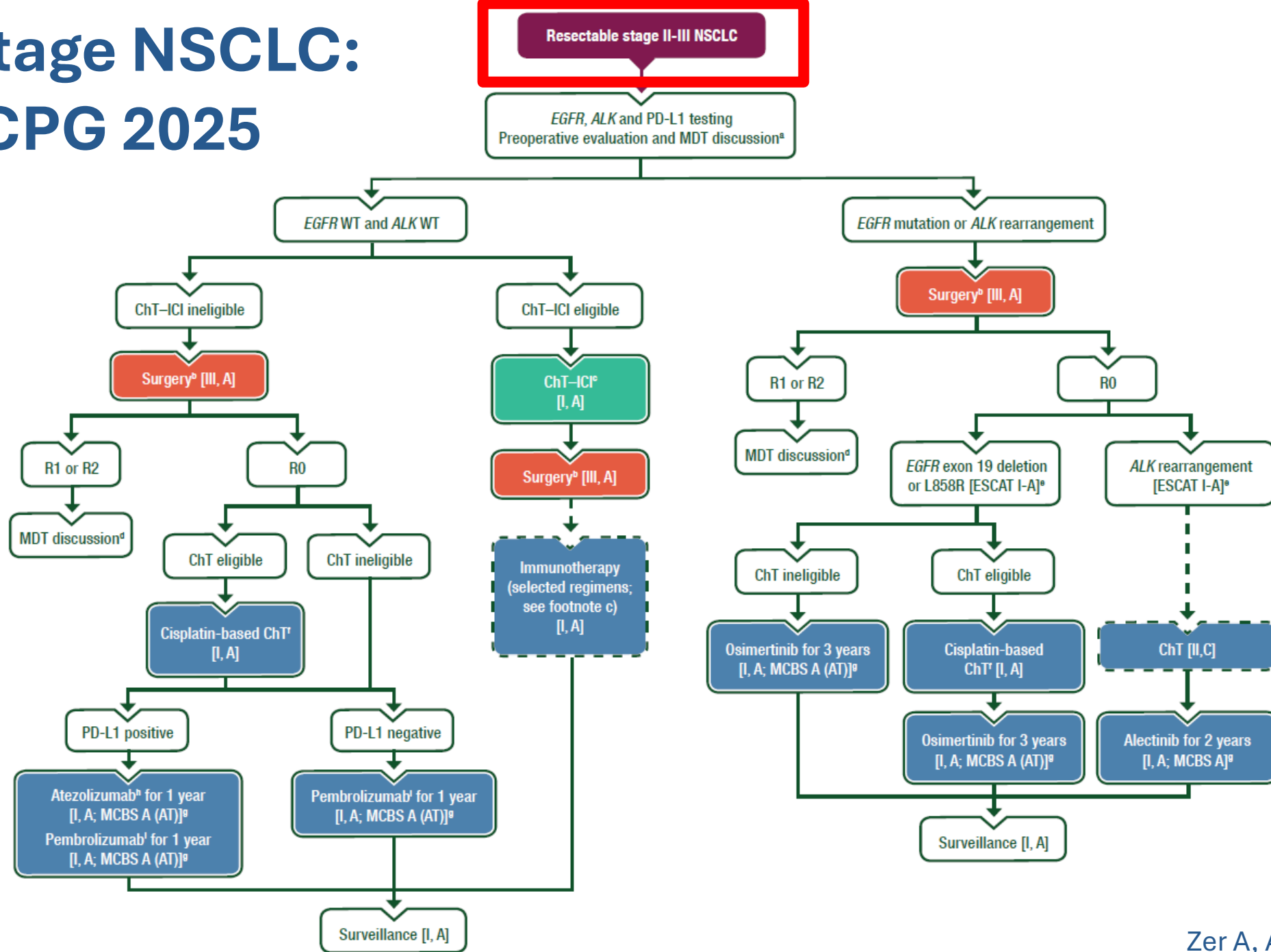
Early-stage NSCLC: ESMO CPG Express Update 2021



Early-stage NSCLC: ESMO CPG 2025



Early-stage NSCLC: ESMO CPG 2025



Consensual Definition of Stage III NSCLC Resectability: EORTC-Lung Cancer Group initiative with other scientific societies

Resectable disease

Unresectable disease

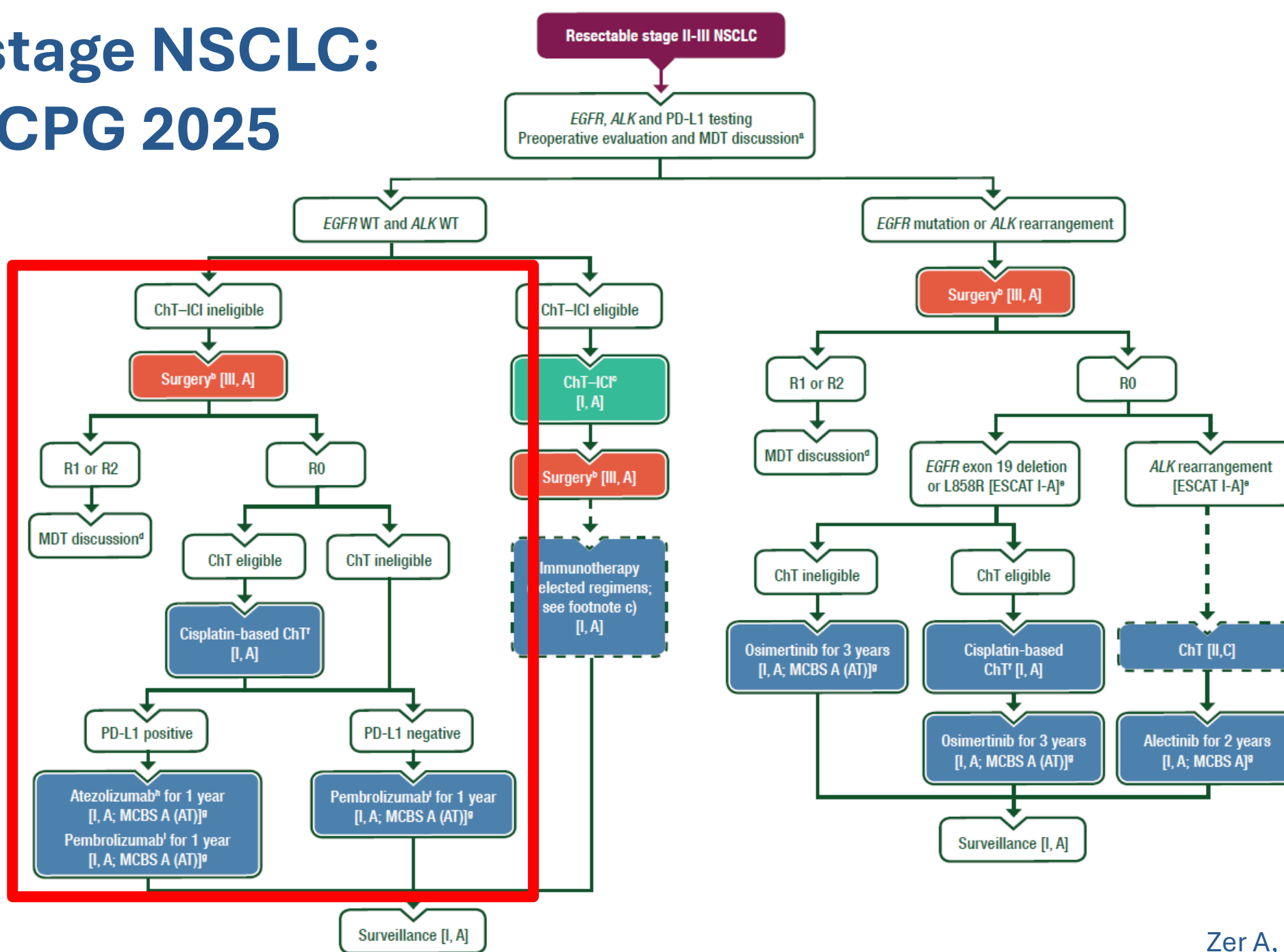
	Resectable disease				Unresectable disease		
	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY [¶]	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	MOSTLY UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	MOSTLY UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	MOSTLY UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE [§]	POTENTIALLY RESECTABLE [§]	POTENTIALLY RESECTABLE [§]	POTENTIALLY RESECTABLE* [§]	MOSTLY UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

*Multiple station N2: case-by-case discussion; the exact number of nodes/stations cannot be defined

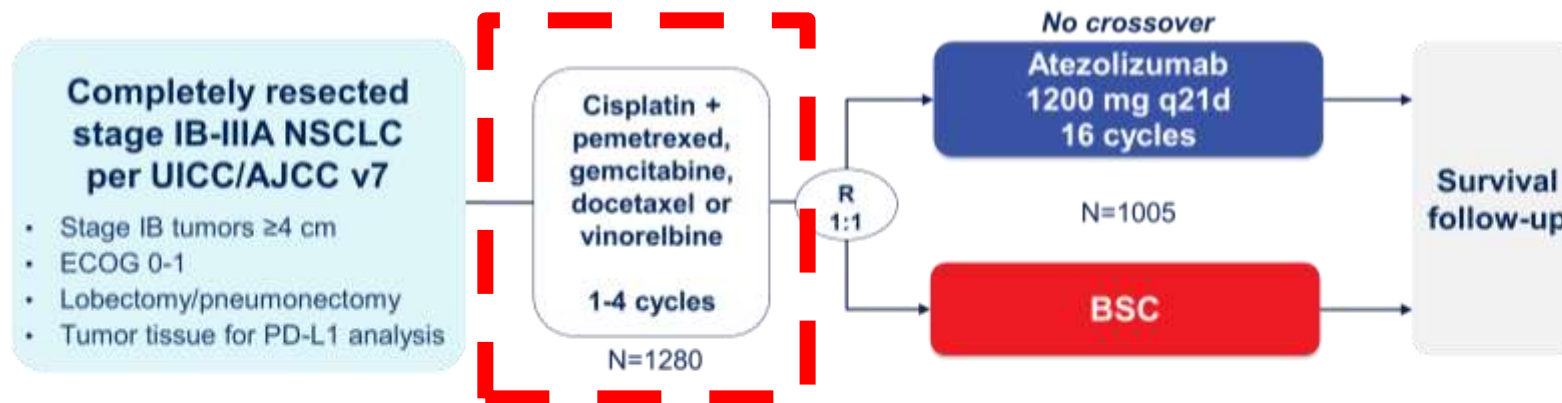
¶Bulky N2: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, consideration for including those patients in multidisciplinary trials with surgery as local therapy can be discussed

§Some T4 tumours by infiltration of major structures are considered unresectable, while others are potentially resectable – see Table 1

Early-stage NSCLC: ESMO CPG 2025



Adjuvant Atezolizumab: IMpower010 trial



Stratification factors

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

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

Primary endpoints

1) DFS in the PD-L1 $\geq 1\%$ in Stage II-IIIa

2) DFS in Stage II-IIIa

3) DFS in ITT (Stage IB-IIIa)

If 3) is positive

4) OS in ITT (Stage IB-IIIa)

- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA and FA
- Endpoint was not formally tested

Adjuvant Atezolizumab: IMpower010 trial

DFS FA and OS IA2 (Median follow-up = 65 months, CCOD: January 26, 2024)

Primary endpoints

1) DFS in the PD-L1 \geq 1% in Stage II-III A

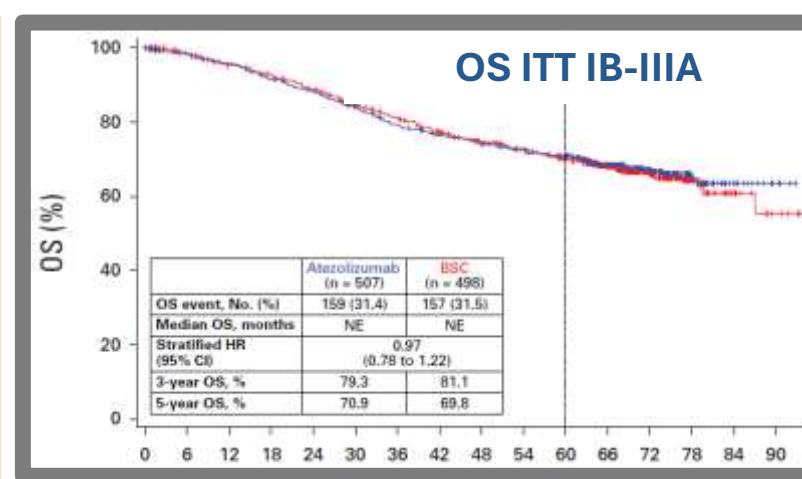
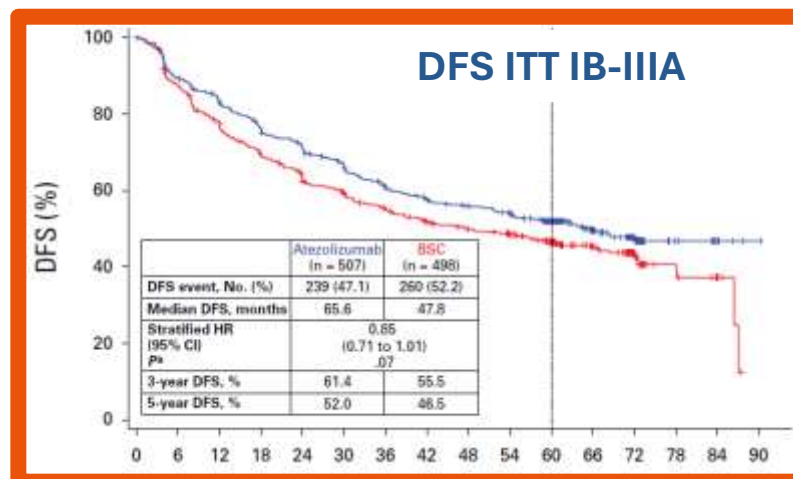
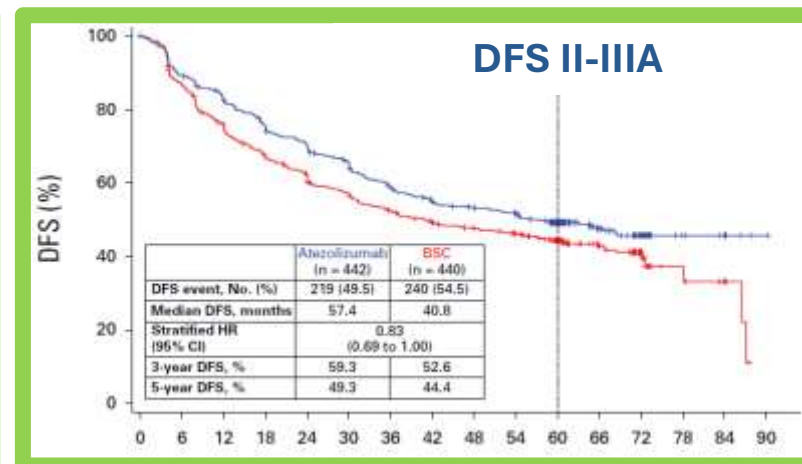
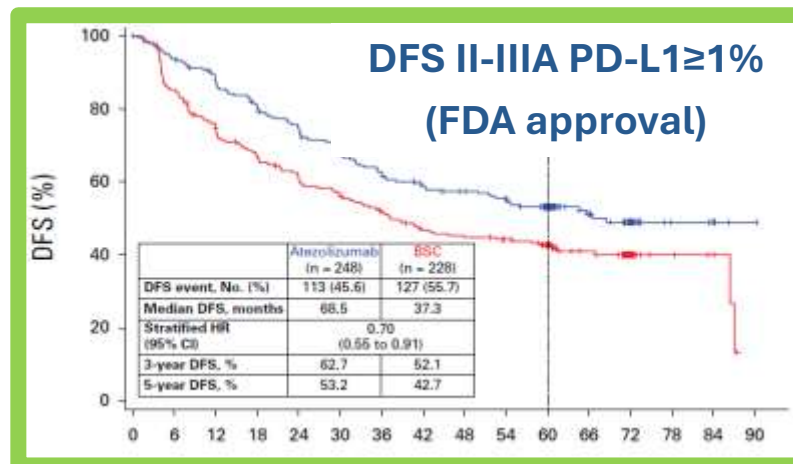
2) DFS in Stage II-III A

3) DFS in ITT (Stage IB-III A)

If 3) is positive

4) OS in ITT (Stage IB-III A)

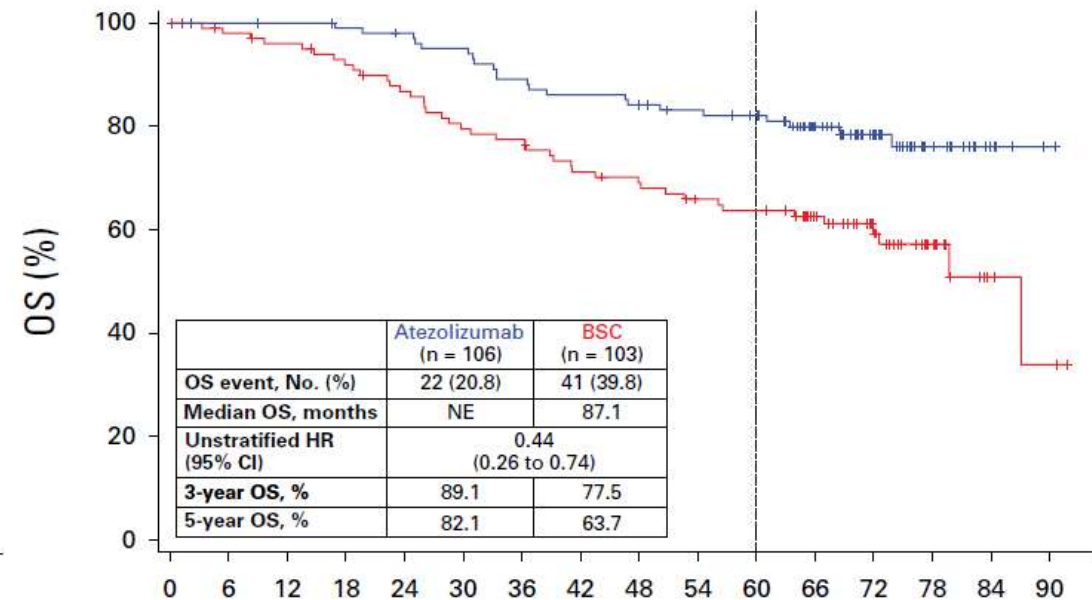
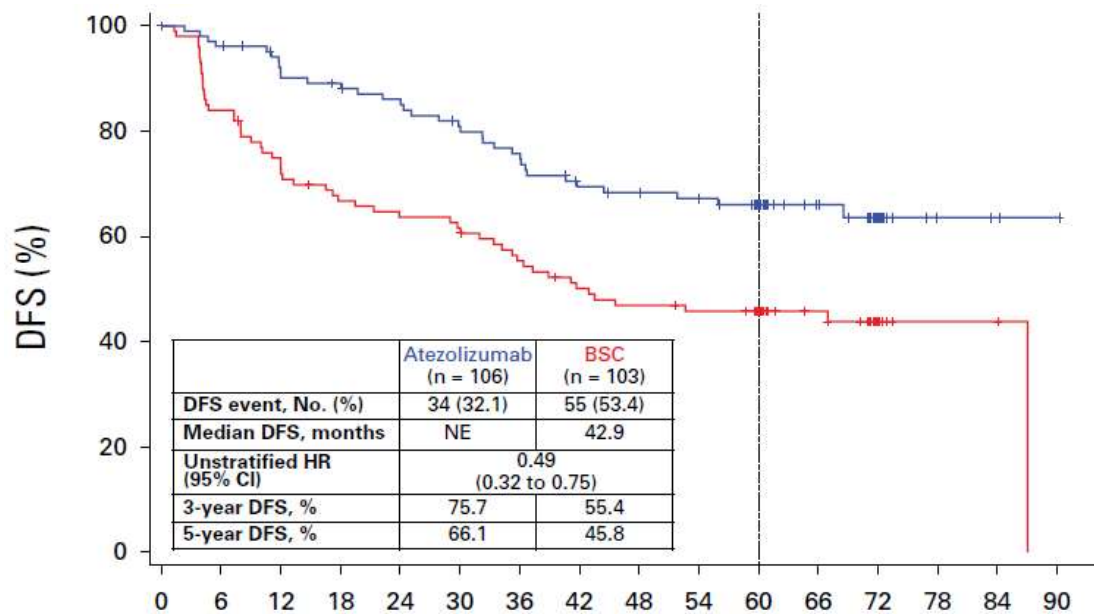
- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA and FA
- Endpoint was not formally tested



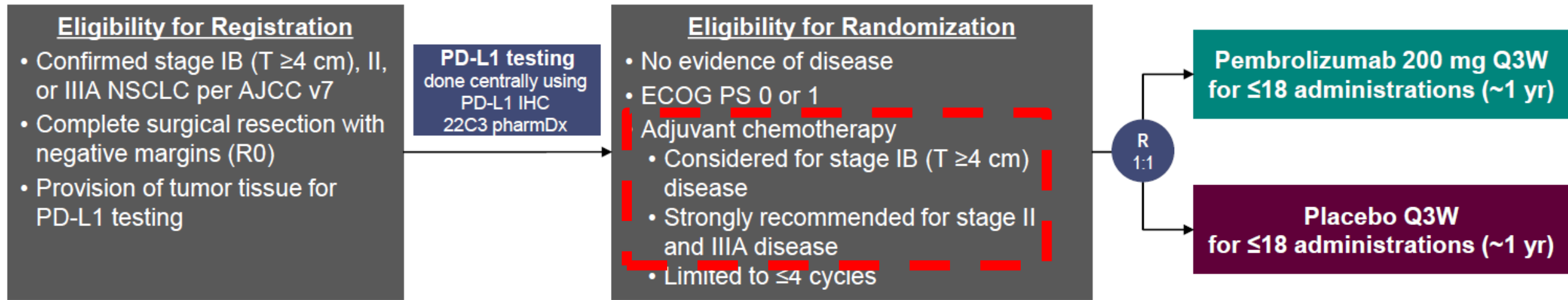
Adjuvant Atezolizumab: IMpower010 trial

DFS FA and OS IA2 (Median follow-up = 65 months, CCOD: January 26, 2024)

DFS and OS in stage II-III A PD-L1 \geq 50% w/o EGFR/ALK populations (EMA approval)



Adjuvant Pembrolizumab: PEARLS/KEYNOTE-091 trial



Stratification Factors

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

Dual Primary End Points

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

Secondary End Points

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

Adjuvant Pembrolizumab: PEARLS/KEYNOTE-091 trial

DFS IA3 (Median follow-up = 51.7 months, CCOD: January 24, 2023)

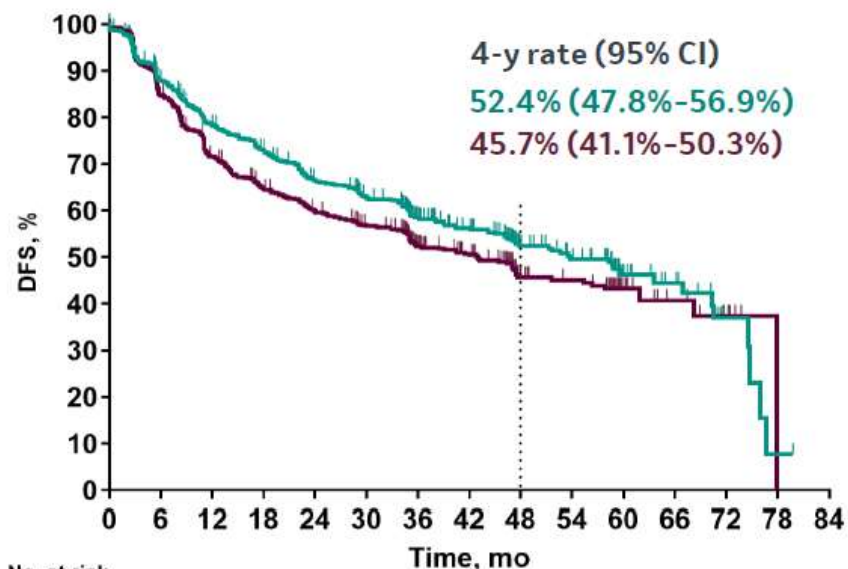
DFS (Overall Population; ITT)

HR,^a 0.81 (95% CI, 0.68-0.96)

Median (95% CI), mo

Pembrolizumab: 53.8 (46.2-67.0)

Placebo: 43.0 (35.0-51.6)



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Pembro	590	493	435	402	361	330	222	194	100	85	34	23	6	1	0
Placebo	587	493	411	366	337	309	202	180	82	73	23	13	5	0	0

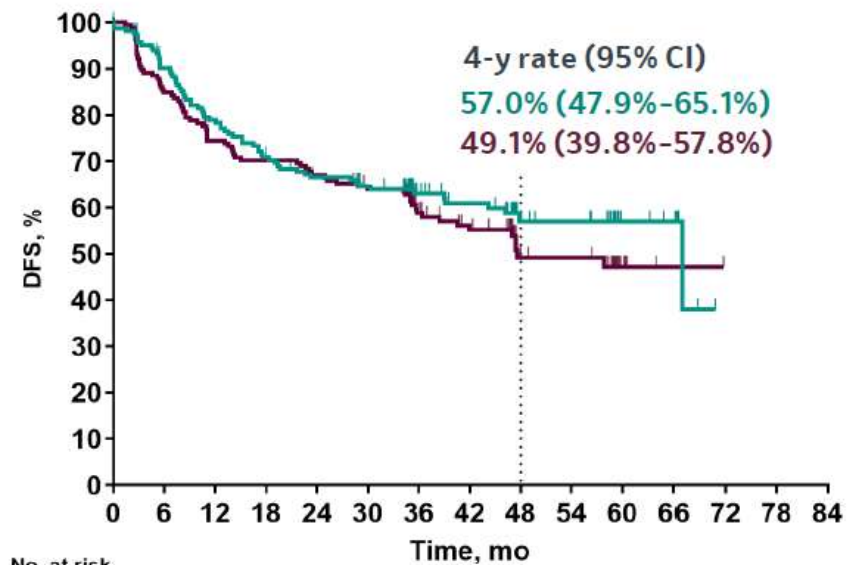
DFS (TPS ≥50%; ITT Population)

HR,^a 0.83 (95% CI, 0.59-1.16)
P=0.13^b

Median (95% CI), mo

Pembrolizumab: 67.0 (47.8-NR)

Placebo: 47.6 (36.4-NR)

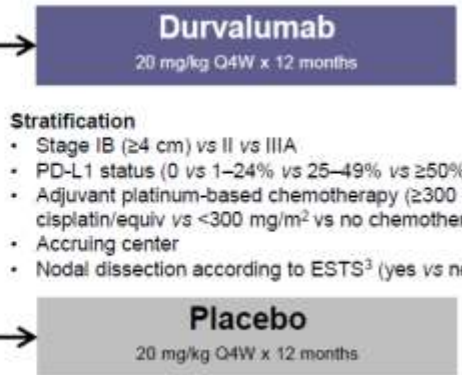
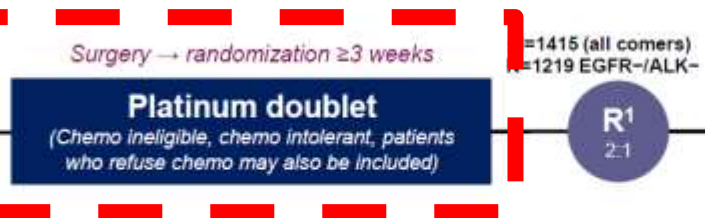


No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Pembro	168	145	127	114	104	97	66	59	30	27	8	6	0	0	0
Placebo	165	140	121	114	109	101	70	59	28	27	7	2	0	0	0

Adjuvant Durvalumab: CCTG BR.31 trial

Study population:

- Stage IB (≥4 cm)–IIIA NSCLC (AJCC 7th ed.)
- Complete resection
- ECOG PS 0–1
- EGFRm/ALK+ pts eligible



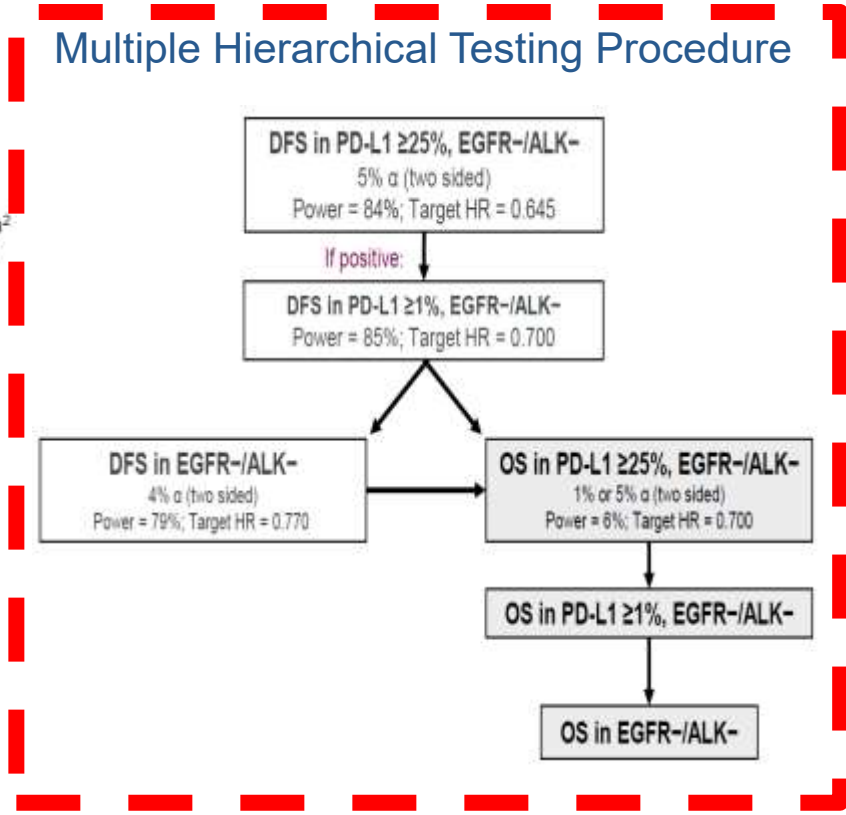
Primary endpoint

- DFS⁴ (Investigator Assessed) in patients with PD-L1 TC ≥25% and EGFR-/ALK-

Key secondary endpoints

- DFS in patients with:
 - PD-L1 TC ≥1% and EGFR-/ALK-
 - All PD-L1 TC ≥25%
 - All randomized patients
- OS (six patient subpopulations)
- AEs
- QoL

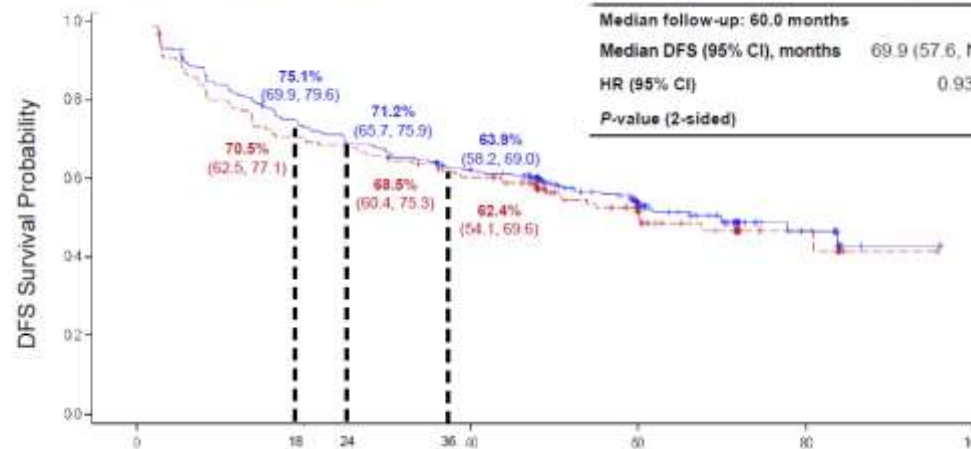
Today, we will present the final DFS analysis from three EGFR-/ALK- populations



Adjuvant Durvalumab: CCTG BR.31 trial

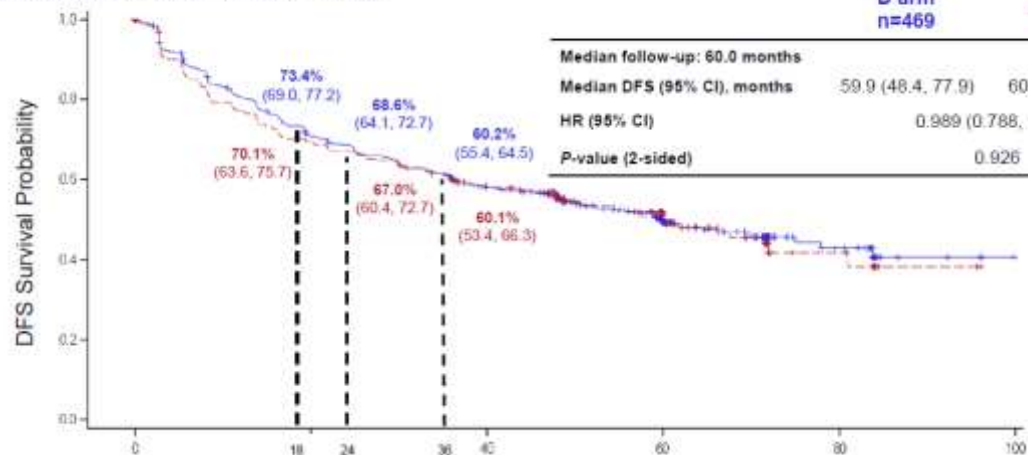
DFS FA (Median follow-up = 60 months)

DFS in PD-L1 \geq 25% EGFR-/ALK-



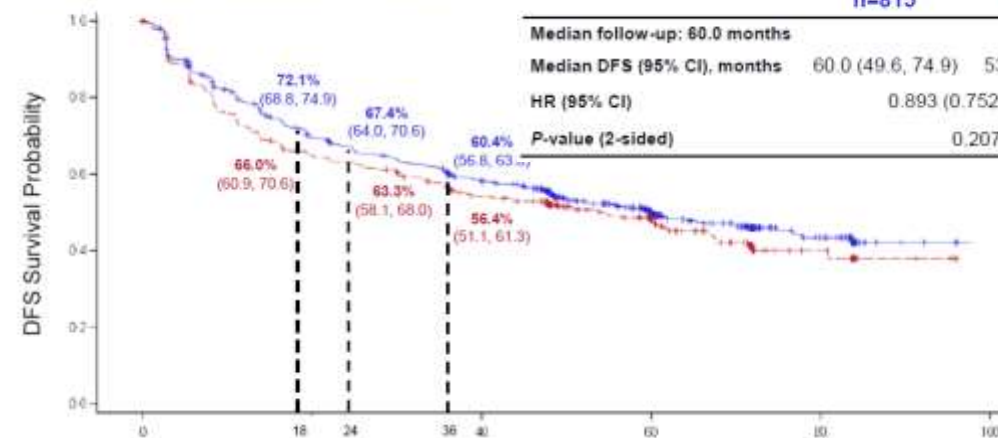
	D arm n=316	PBO arm n=161
Median follow-up: 60.0 months		
Median DFS (95% CI), months	69.9 (57.6, NR)	60.2 (47.7, NR)
HR (95% CI)	0.935 (0.706, 1.247)	
P-value (2-sided)	0.642	

DFS in PD-L1 \geq 1% EGFR-/ALK-



	D arm n=469	PBO arm n=240
Median follow-up: 60.0 months		
Median DFS (95% CI), months	59.9 (48.4, 77.9)	60.3 (43.8, 80.9)
HR (95% CI)	0.989 (0.788, 1.248)	
P-value (2-sided)	0.926	

DFS in PD-L1 All Comers EGFR-/ALK-



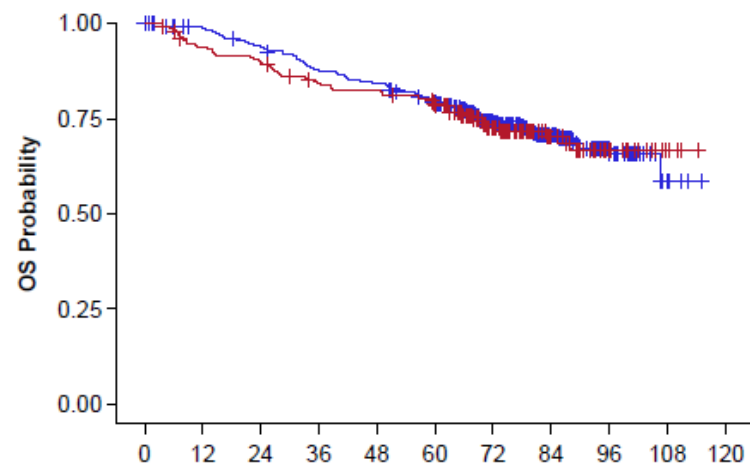
	D arm n=815	PBO arm n=404
Median follow-up: 60.0 months		
Median DFS (95% CI), months	60.0 (49.6, 74.9)	53.9 (36.7, 67.3)
HR (95% CI)	0.893 (0.752, 1.065)	
P-value (2-sided)	0.207	

Adjuvant Durvalumab: CCTG BR.31 trial

OS FA (Median follow-up = >70 months)

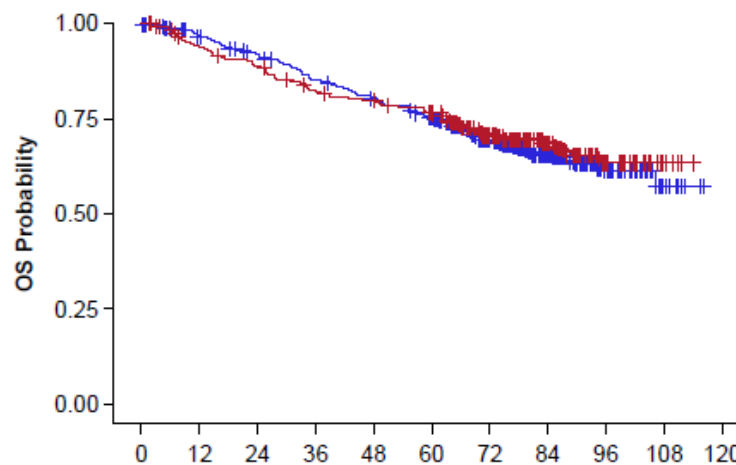
PD-L1 \geq 25% and *EGFR-ALK-*

	D arm n=316	PBO arm n=161
No. of events (%)	88 (27.8)	45 (28.0)
Median OS (95% CI), months	NR (106.8–NR)	NR (NR–NR)
Stratified HR (95% CI)	0.98 (0.69–1.42)	
P-value (2-sided)	0.93	



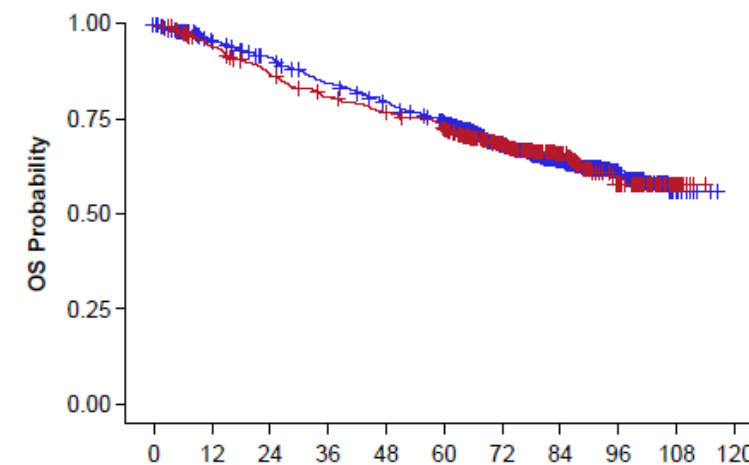
PD-L1 \geq 1% and *EGFR-ALK-*

	D arm n=469	PBO arm n=240
No. of events (%)	149 (31.8)	72 (30.0)
Median OS (95% CI), months	NR (106.8–NR)	NR (NR–NR)
Stratified HR (95% CI)	1.10 (0.83–1.47)	
P-value (2-sided)	0.52	

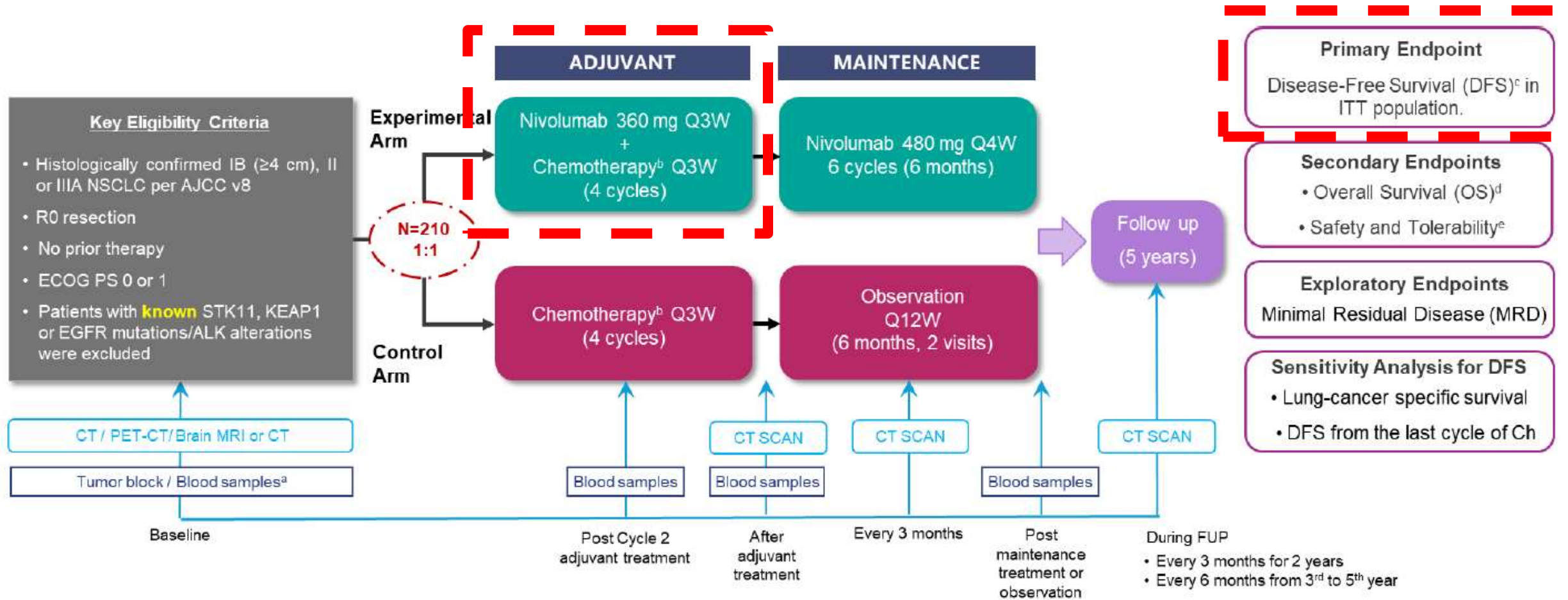


PD-L1 All Comers and *EGFR-ALK-*

	D arm n=815	PBO arm n=404
No. of events (%)	266 (32.6)	135 (33.4)
Median OS (95% CI), months	NR (106.8–NR)	NR (NR–NR)
Stratified HR (95% CI)	1.00 (0.81–1.23)	
P-value (2-sided)	0.96	

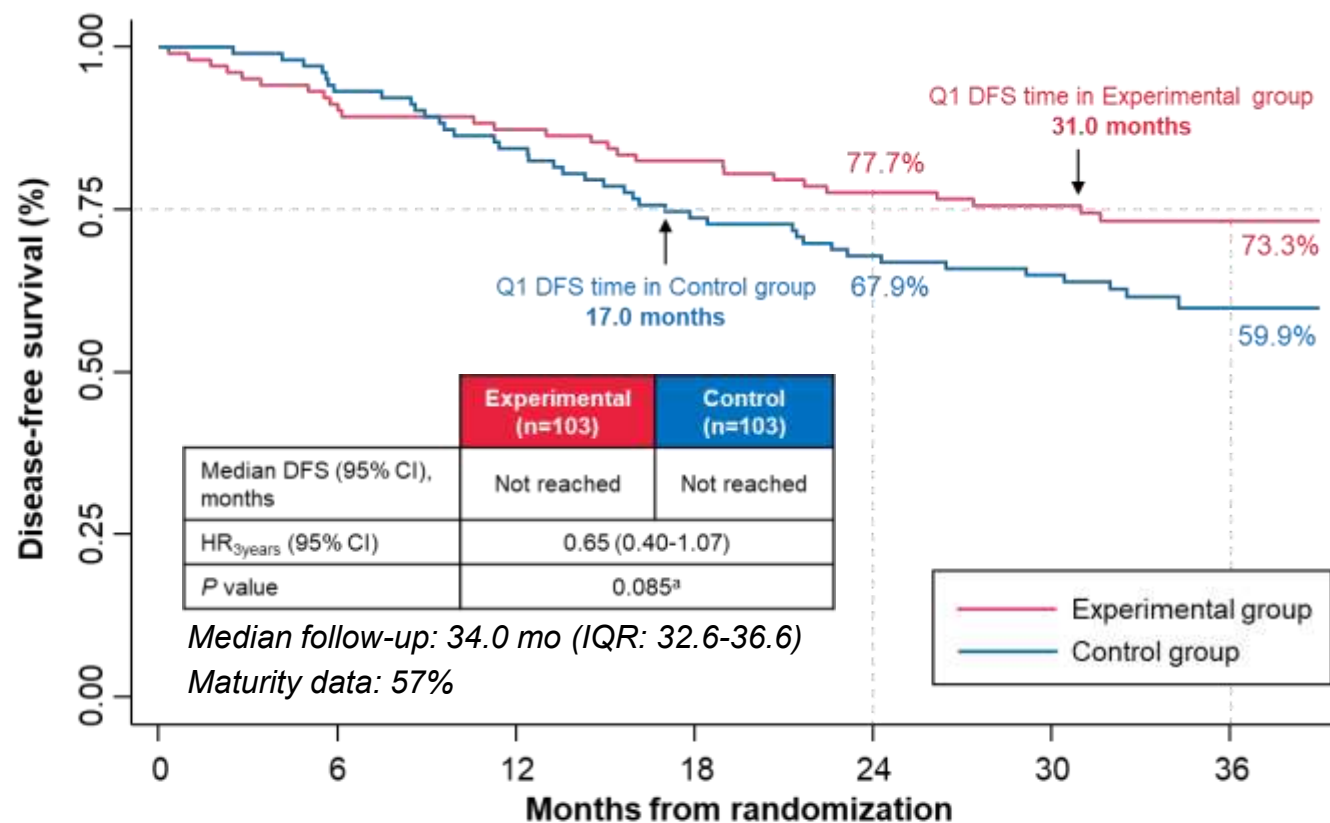


Adjuvant Nivolumab + Chemo: NADIM Adj trial



Adjuvant Nivolumab + Chemo: NADIM Adj trial

DFS IA1 (Median follow-up = 34 months, DBL: June 13, 2025)

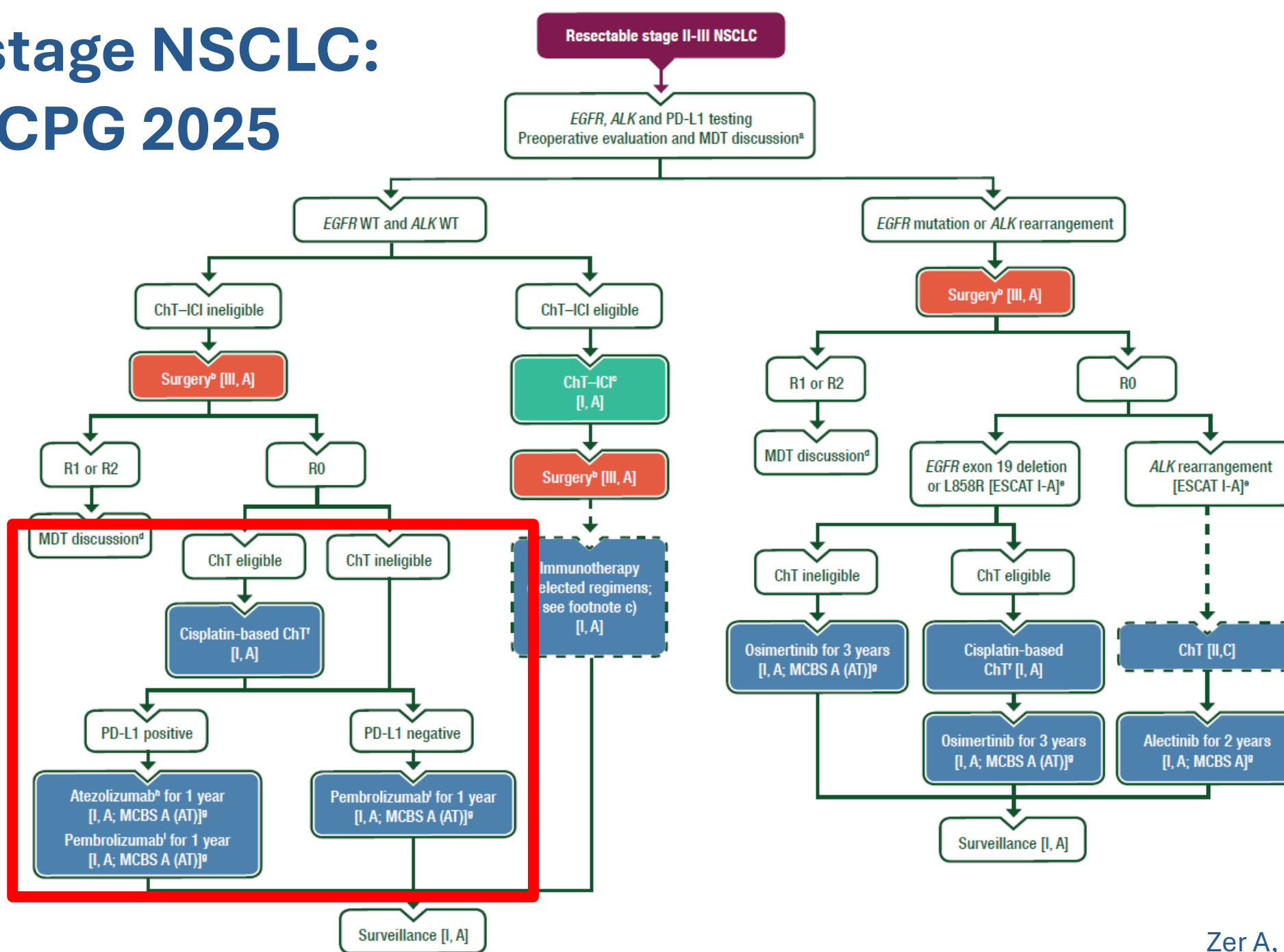


Number at risk (events)

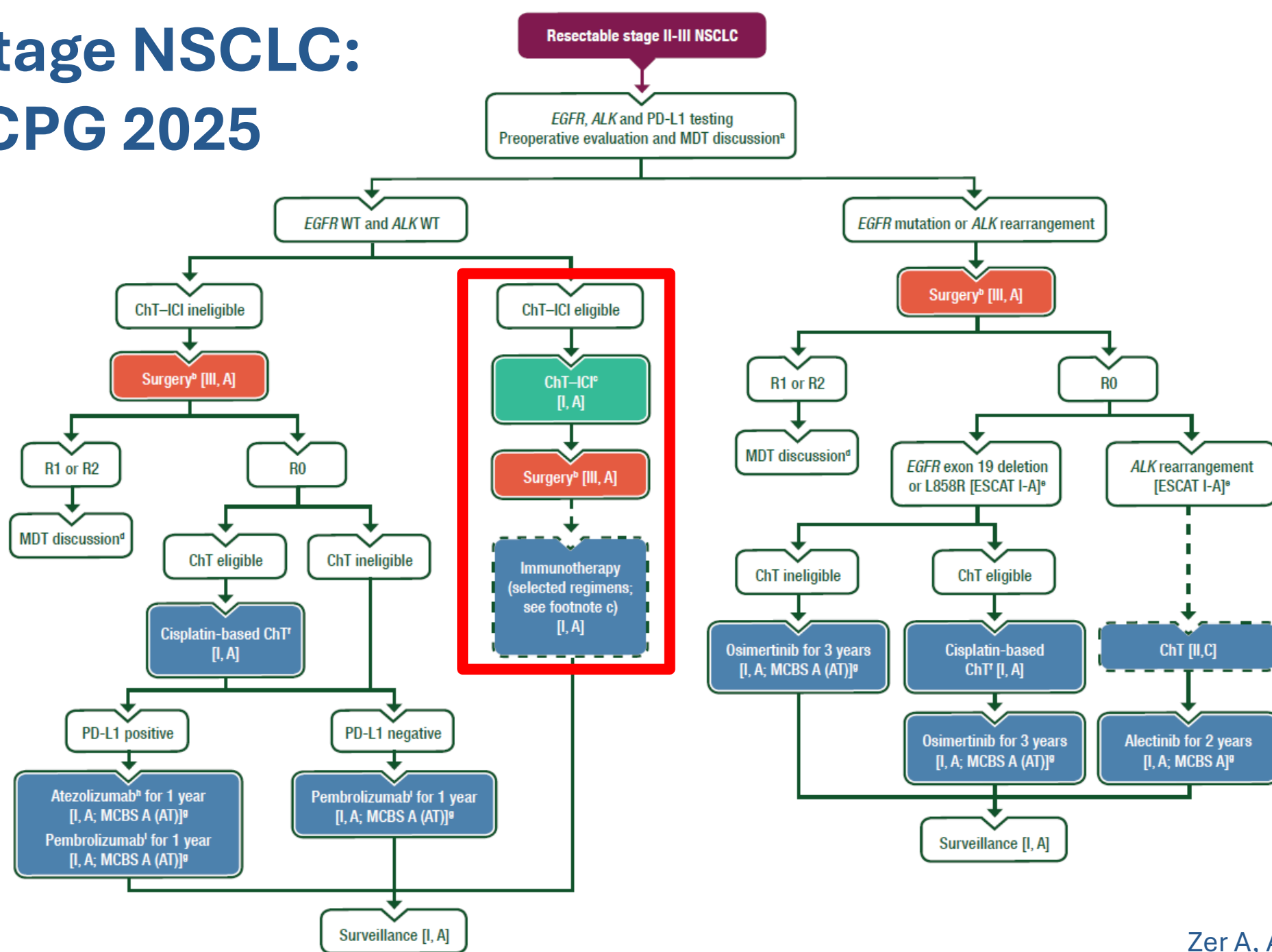
	0	6	12	18	24	30	36
Experimental group	103	(9) 94	(4) 90	(5) 85	(5) 80	(2) 67	(2) 21
Control group	103	(7) 96	(9) 87	(11) 76	(6) 70	(3) 63	(4) 18

^a At the interim analysis (57% information fraction), the early efficacy threshold was $p < 0.0126$; the observed $p = 0.085$ did not cross this boundary.

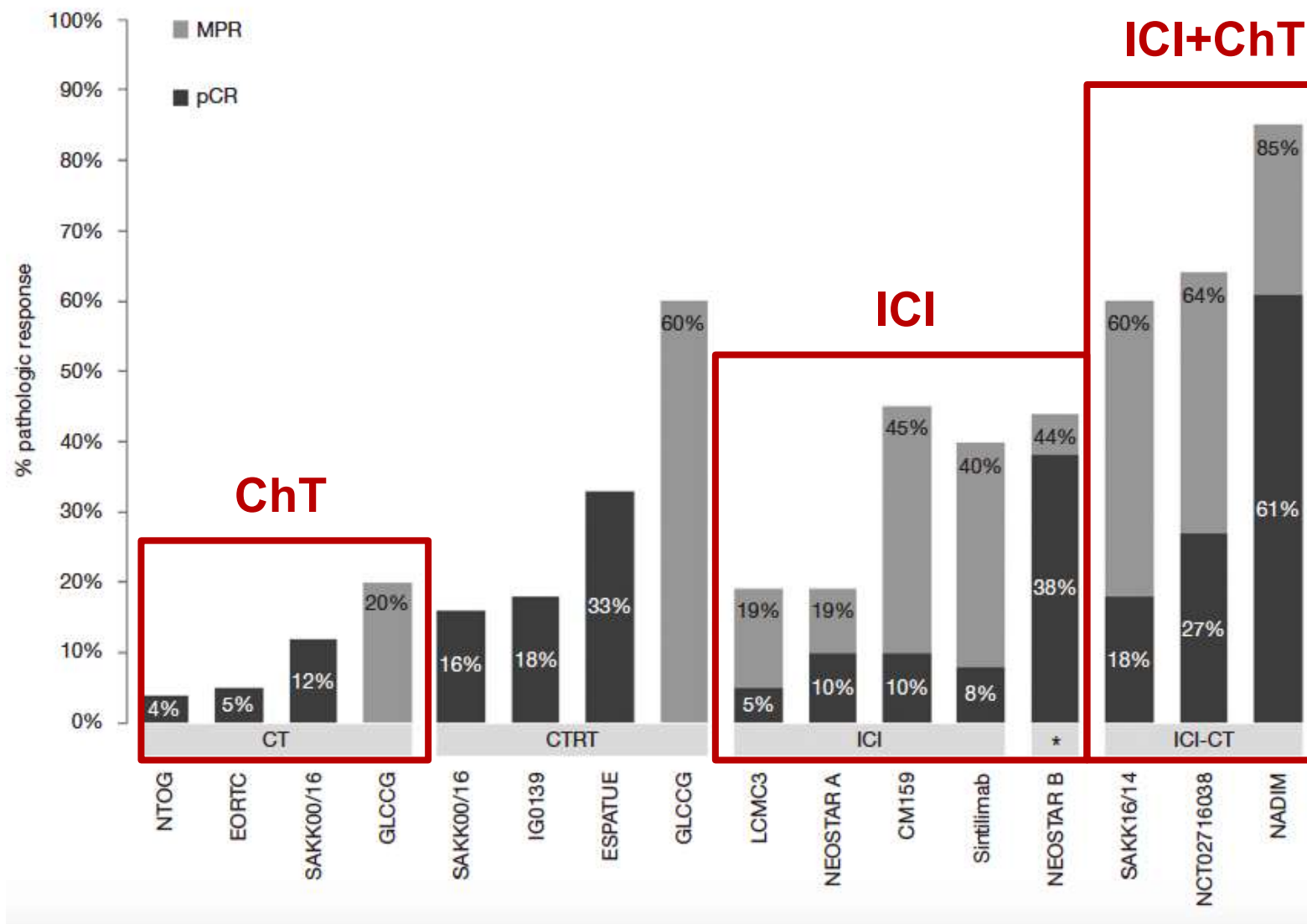
Early-stage NSCLC: ESMO CPG 2025



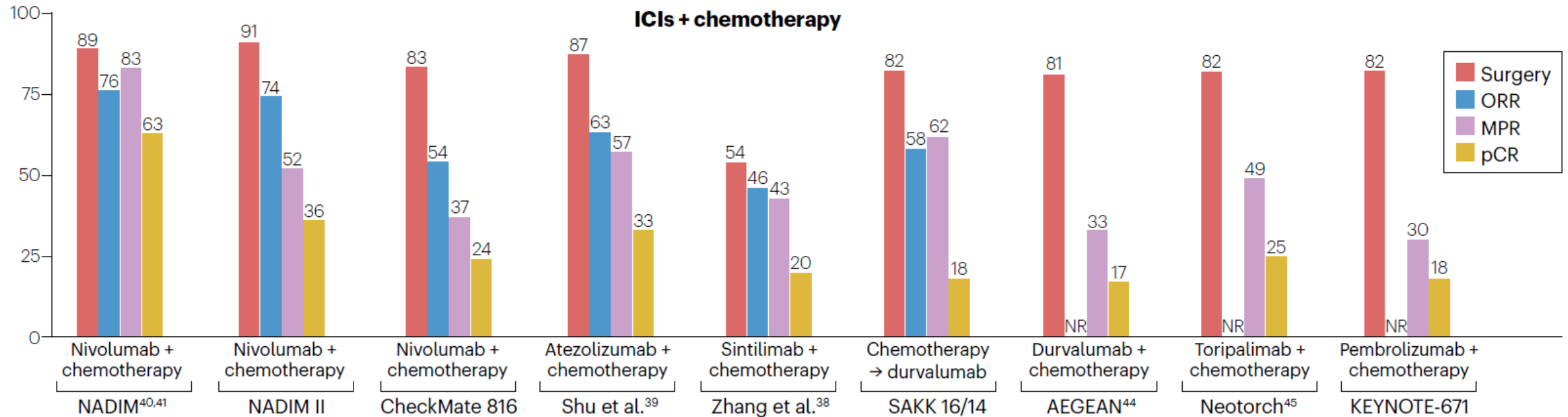
Early-stage NSCLC: ESMO CPG 2025



Higher responses (ORR, MPR, pCR) with neoadj ICI+chemo than ICI or chemo alone (Ph2 cross-trial comparison)



Higher responses (ORR, MPR, pCR) with neoadj ICI+chemo than ICI or chemo alone (Neoadj/Periop RCTs)

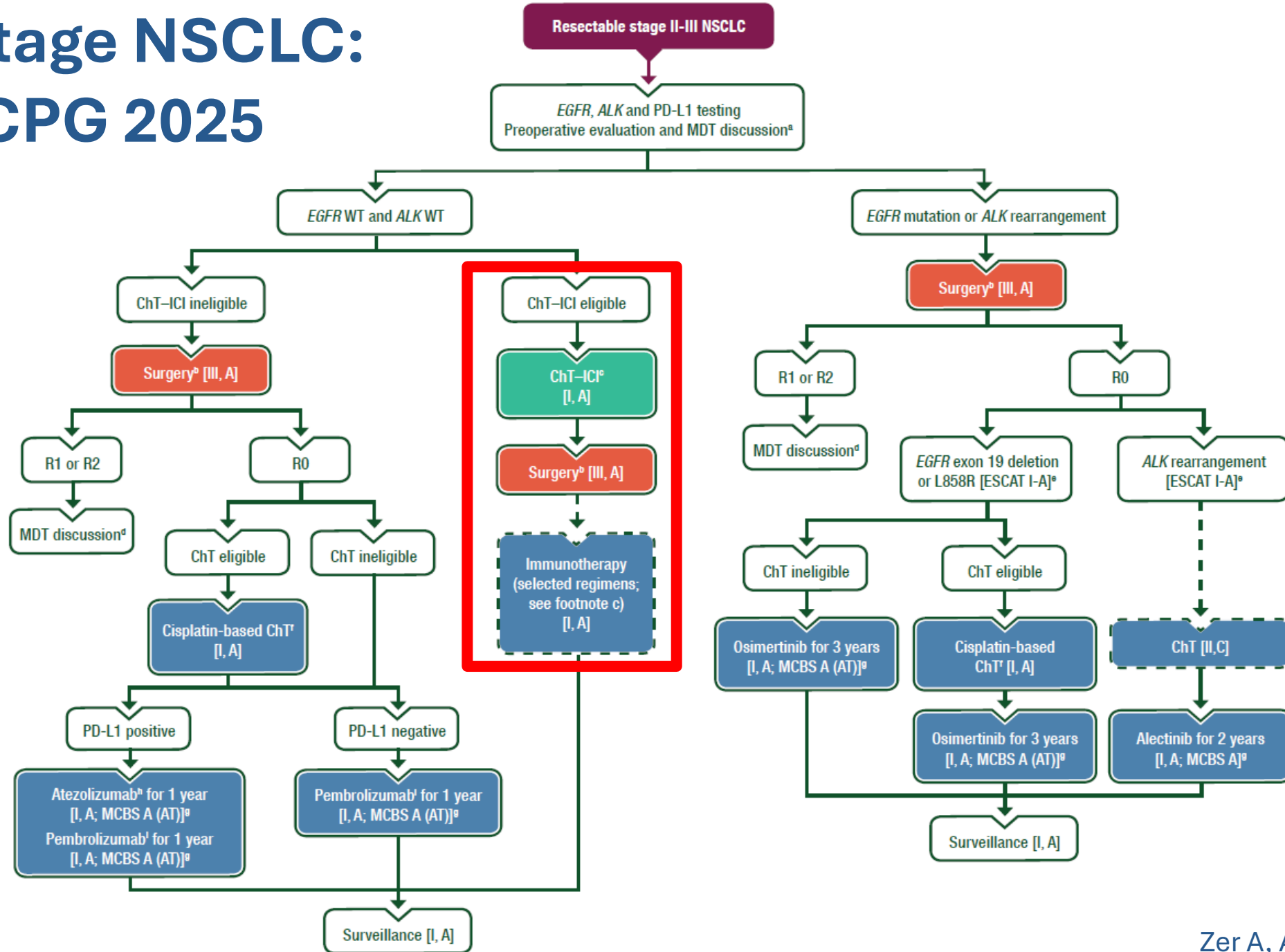


Endpoint	ICI + Chemo
Resection rate	82-91%
ORR	46-76%
MPR	30-83%
pCR	17-63%

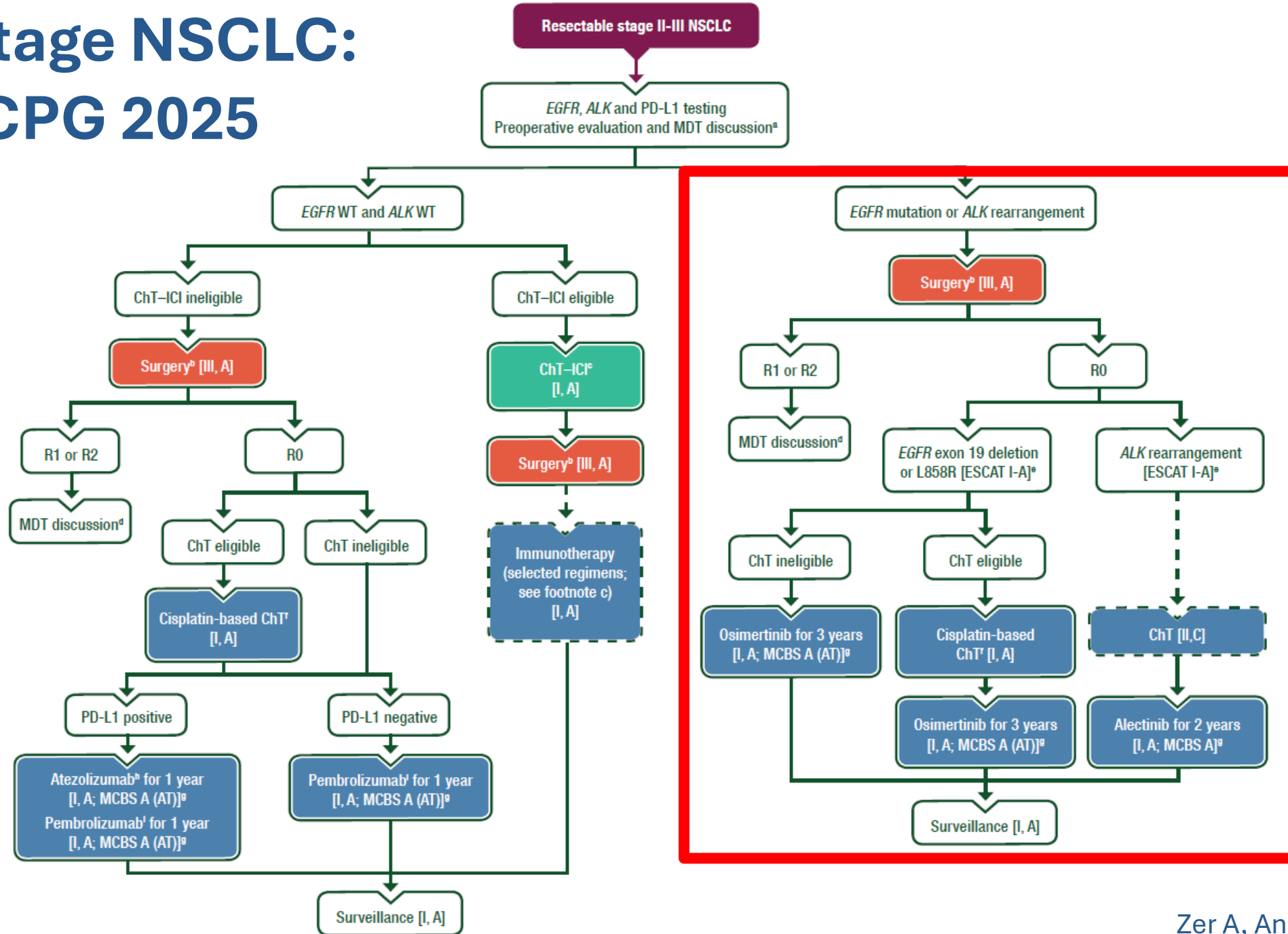
Neoadj/Periop ICI-Chemo RCTs

Trial	Stage (ed)	Intervention	Last report	Median f-u	EFS HR	OS HR
CHECKMATE 816	IB-III A (7 th)	Neoadj Nivo	Forde P, ASCO 2025	60m	0.68 (0.51-0.91)	0.72 (0.52-0.99)
NADIM2	III A/B (8 th)	Periop Nivo	Provencio M, NEJM 2023	26.1m	0.47 (0.25-0.88)	0.43 (0.19-0.98)
KEYNOTE 671	IIA-III A (8 th)	Periop Pembro	Wakelee H, ESMO 2025	60m	0.58 (0.48-0.69)	0.74 (0.59-0.92)
IMPOWER 030	II-III B (8 th)	Periop Atezo	NR	NR	NR	NR
AEGEAN	IIA-III B (8 th)	Periop Durva	Heymach JV, WCLC 2025	25.9m	0.69 (0.55-0.88)	0.89 (0.70-1.14)
CHECKMATE 77T	IIA-III B (8 th)	Periop Nivo	Cascone T, ASCO 2025	41m	0.61 (0.46-0.80)	0.85 (0.58-1.25)
RATIONALE 315	II-III A (8 th)	Periop Tislelizumab	Yue D, WCLC 2025	38,5m	0.58 (0.43-0.79)	0.65 (0.45-0.93)
NEOTORCH	II-III B (8 th)	Periop Toripalimab	Lu S, JAMA 2024	18,3m	0.40 (0.28-0.57)	NR

Early-stage NSCLC: ESMO CPG 2025

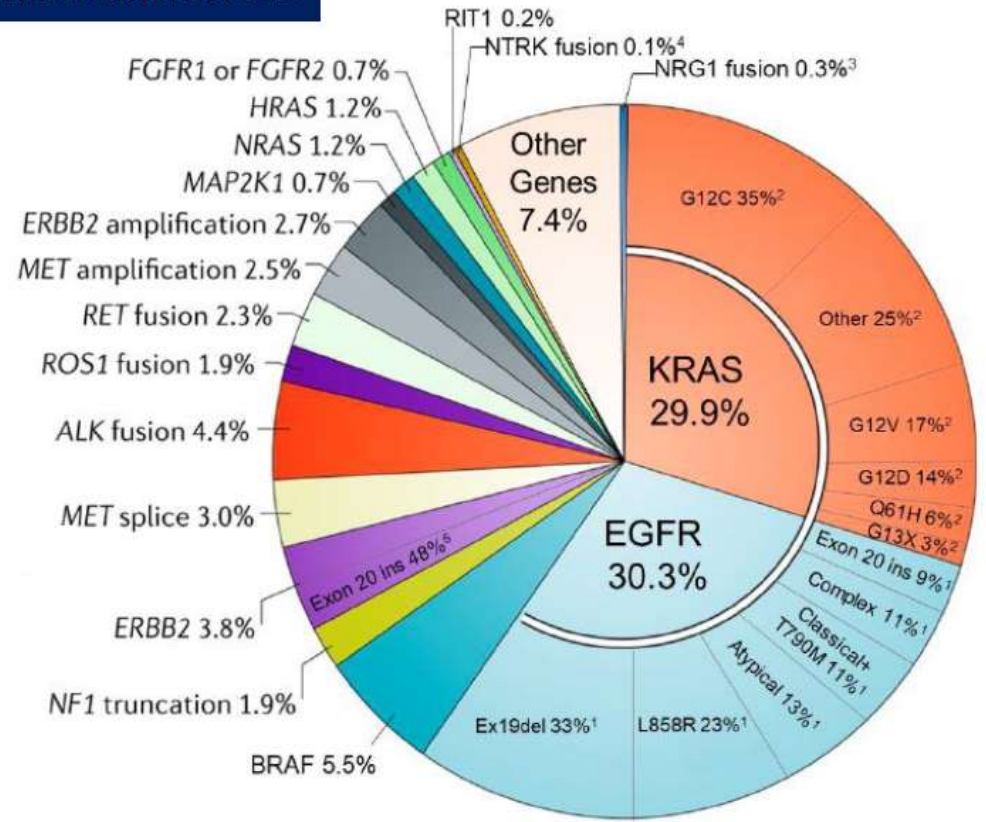


Early-stage NSCLC: ESMO CPG 2025

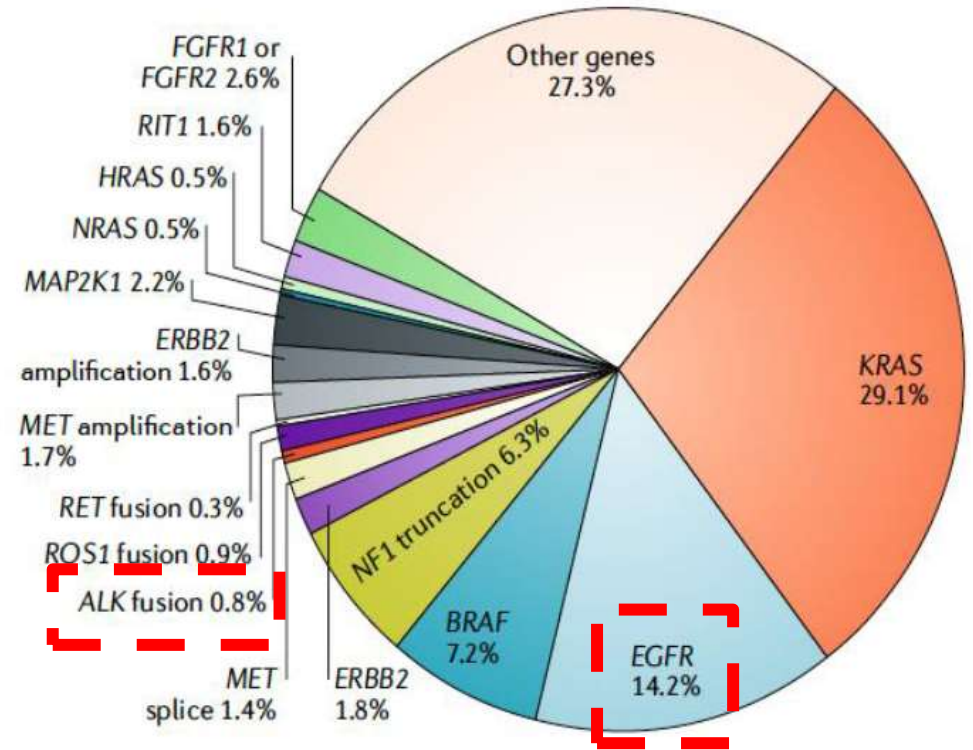


Spectrum of Genomic Alterations in Early and Late Stage NSCLC

Metastatic NSCLC



Early-stage NSCLC

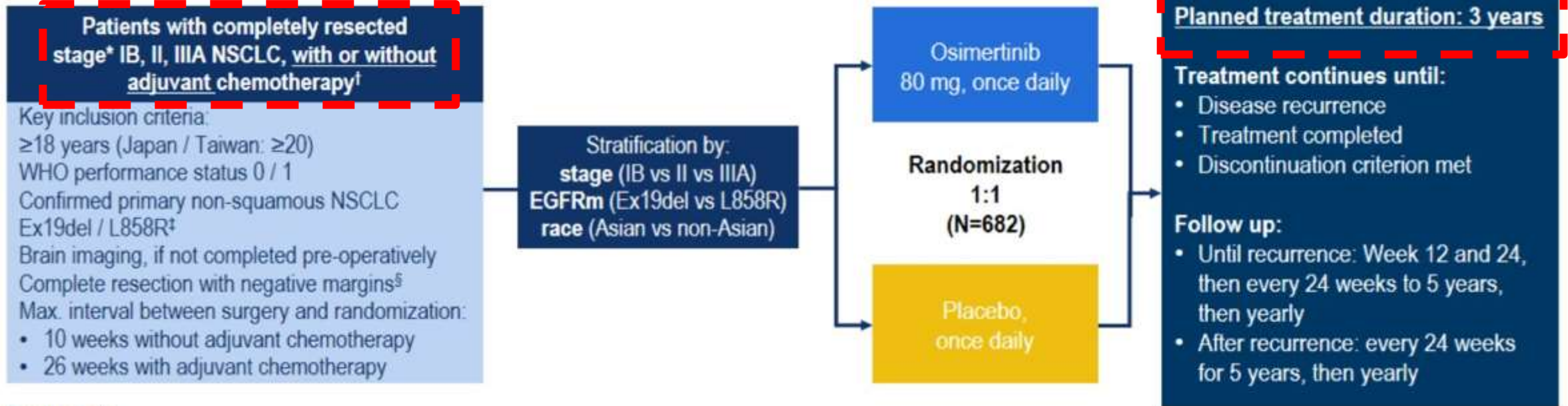


ORIGEN study: EGFRmut 14.5% in Spain
(Varela M, TLCR 2025)

1st gen adj EGFR TKI DFS benefit does not translate to OS

Trial	Country	Stage	N	TKI	DFS (mo.) HR; p-value	OS (mo.) HR; p-value	Crossover
RADIANT*	Internat.	IB–IIIA	161	Erlotinib x 2 y vs. PI	46.4 vs 28.5; 0.61 (0.34–0.98)	1.09 (0.54–2.16)	NR
CORIN	China	IB	128	Icotinib x 1y vs. PI	NR vs NR; 0.38 (0.18–0.83); 0.012	0.45 (0.02–1.27)	83%
IMPACT	Japan	II–IIIA	234	Gefitinib x 2y vs. CT	35.9 vs 25.1; 0.92 (0.67–1.28); 0.63	NR vs NR; 1.03 (0.65–1.65); 0.89	52%
CTONG1104 ADJUVANT	China	II–IIIA	222	Gefitinib x 2y vs. CT	30.8 vs 19.6; 0.56 (0.40–0.97); 0.0001	75.5 vs 62.8; 0.92 (0.62–1.36); 0.67	52%
EVAN	China	III	102	Erlotinib x 2y vs. CT	42.4 vs 21.0; 0.38 (0.20–0.70); 0.001	84.2 vs 61.1; 0.32 (0.15–0.67)	37%
EVIDENCE	China	II–IIIA	332	Icotinib x 2y vs. CT	47.0 vs 22.1; 0.36 (0.24–0.55); 0.0001	0.91 (0.42–1.94)	NR
ICTAN	China	II–IIIA	251	Icotinib x 12–6 mo. vs. CT	0.40 (0.27–0.61); 0.0001 0.41 (0.27–0.62); 0.0003	0.55 (0.32–0.96); 0.035 0.56 (0.32–0.98); 0.041	76%

Adjuvant Osimertinib: ADAURA trial



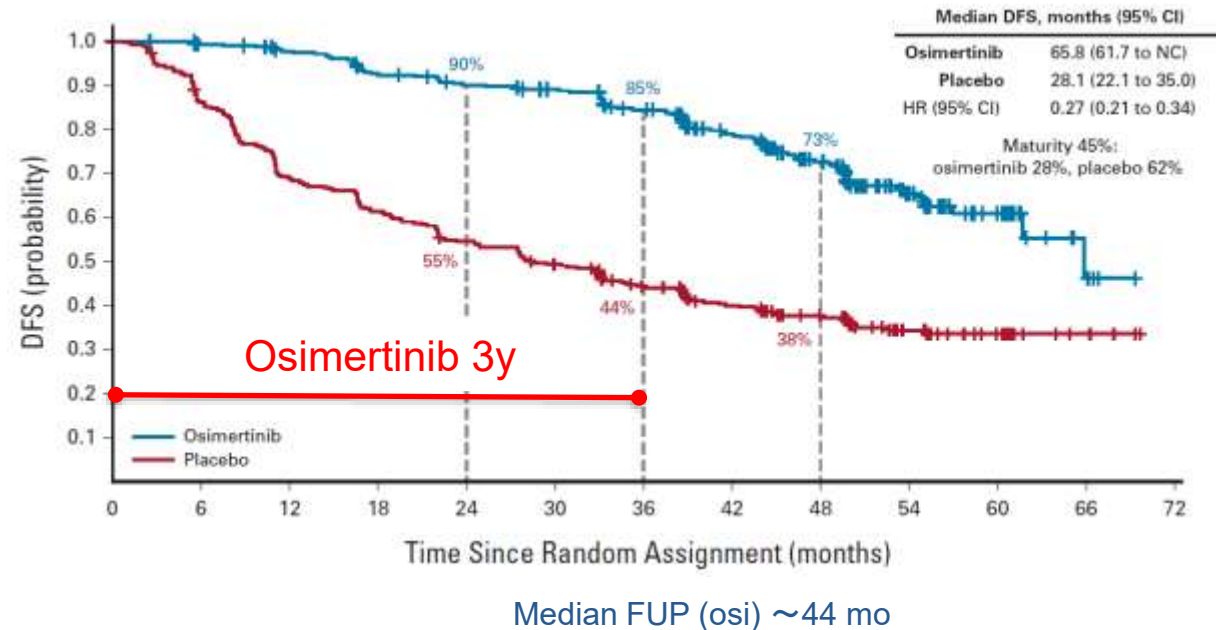
Endpoints

- **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

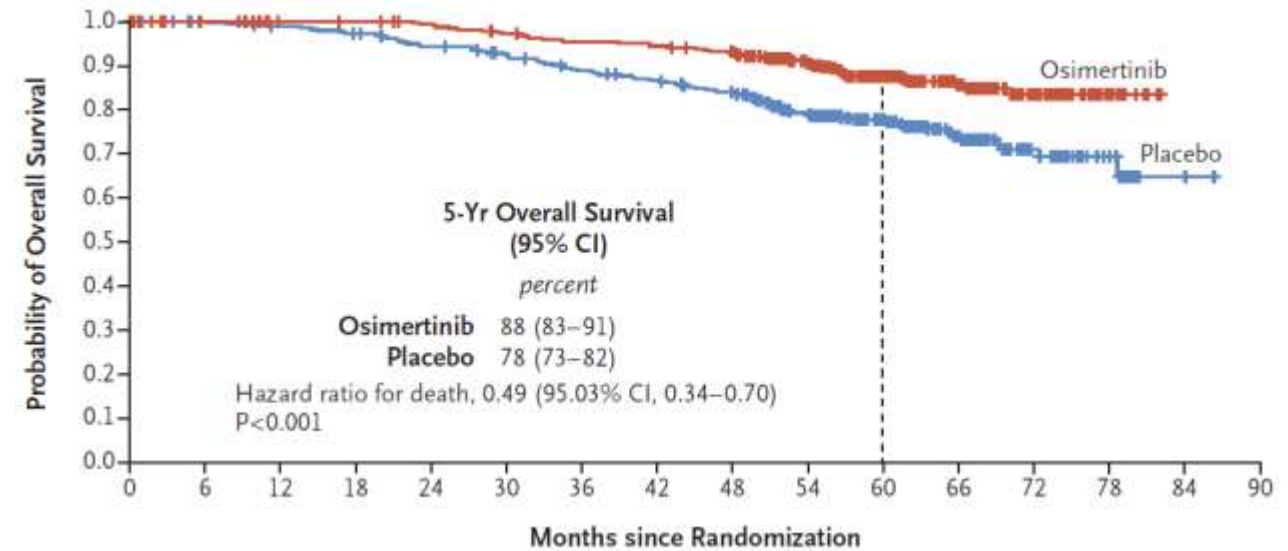
- Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis
- At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year

Adjuvant Osimertinib: ADAURA trial

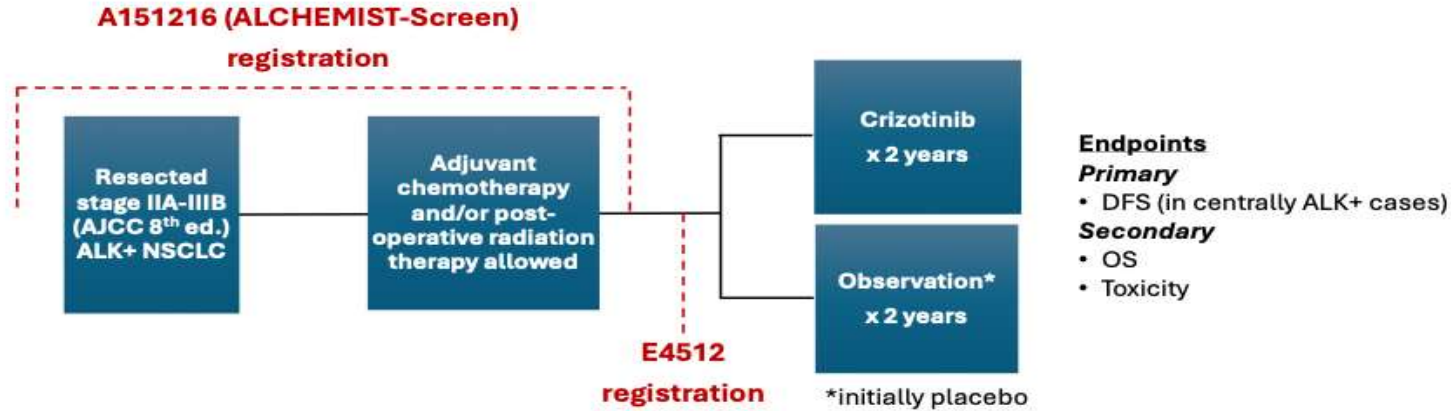
Updated DFS in stage IB–IIIA



Updated OS in stage IB–IIIA



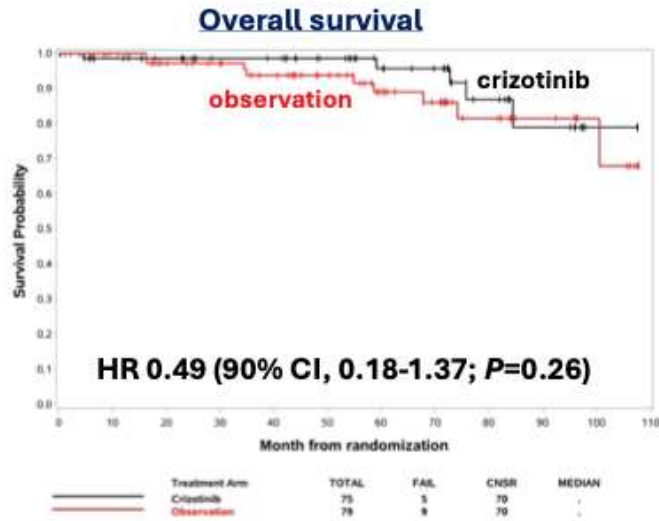
Adjuvant Crizotinib: ALCHEMIST trial (E4512)



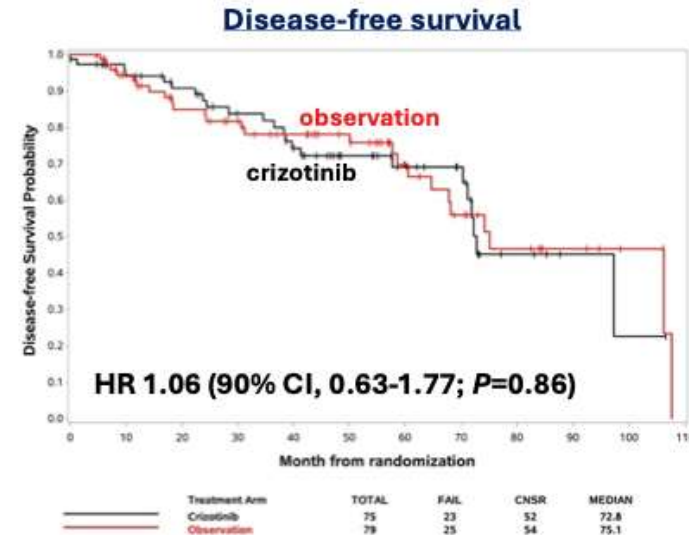
Stratification factors

- Stage: IIA/IIB/IIIA (T3N1) vs. IIIA (N2)/IIIB (N2) (AJCC 8th ed.)
- Prior RT: yes vs. no
- Sex: male vs. female

ALCHEMIST, Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials

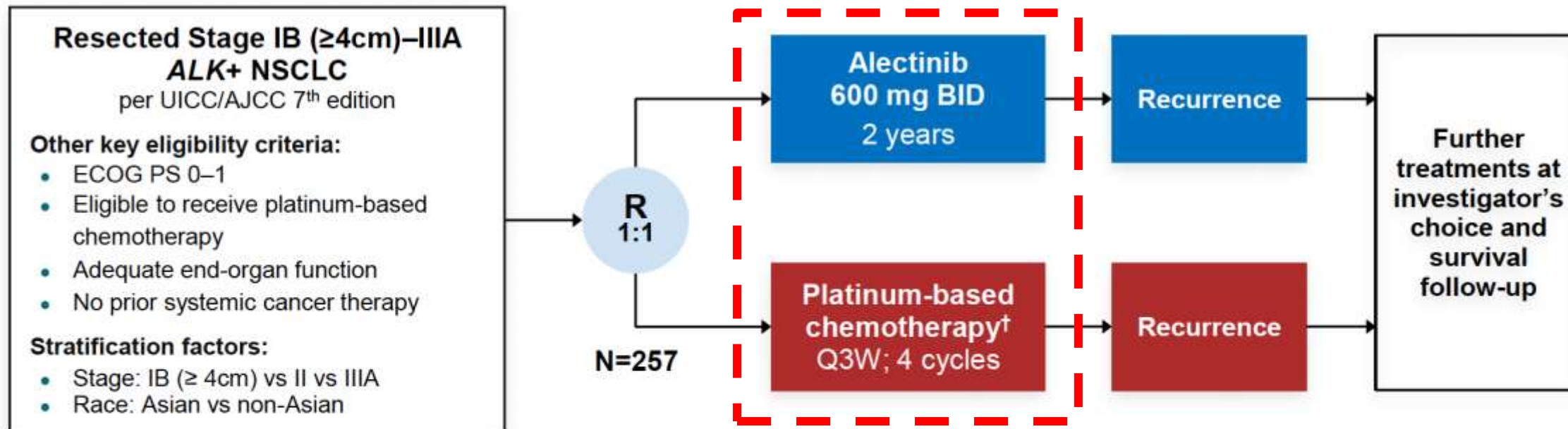


Median follow-up = 58.3 months



Median follow-up = 58.3 months

Adjuvant Alectinib: ALINA trial



Primary endpoint

- DFS per investigator,[‡] tested hierarchically:
 - Stage II–IIIA → ITT (Stage IB–IIIA)

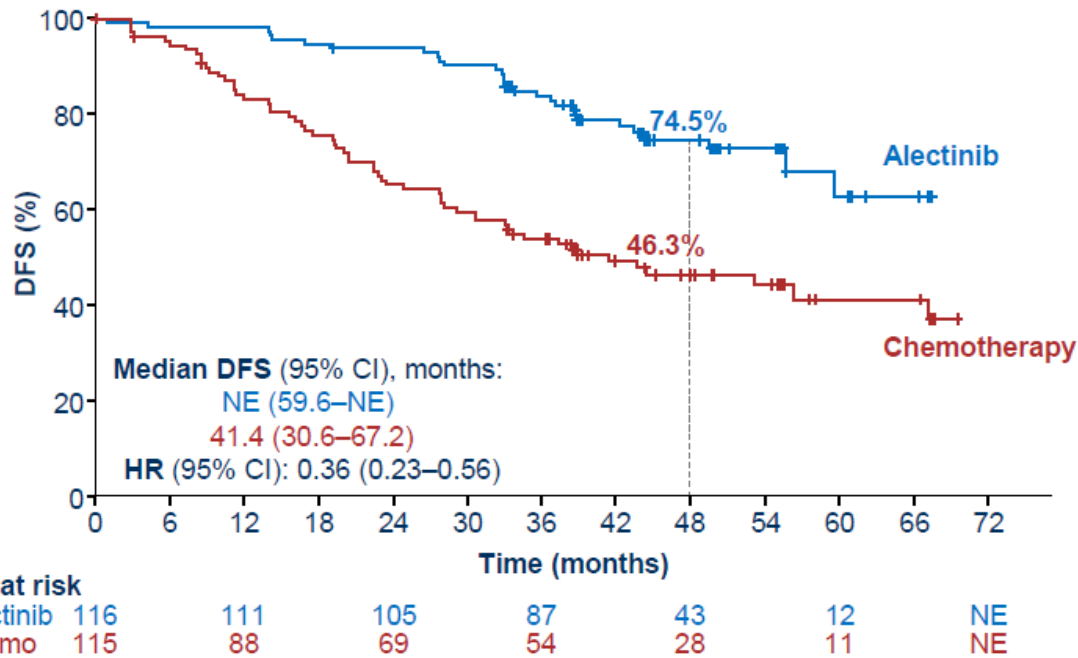
Other endpoints

- CNS disease-free survival
- OS
- Safety

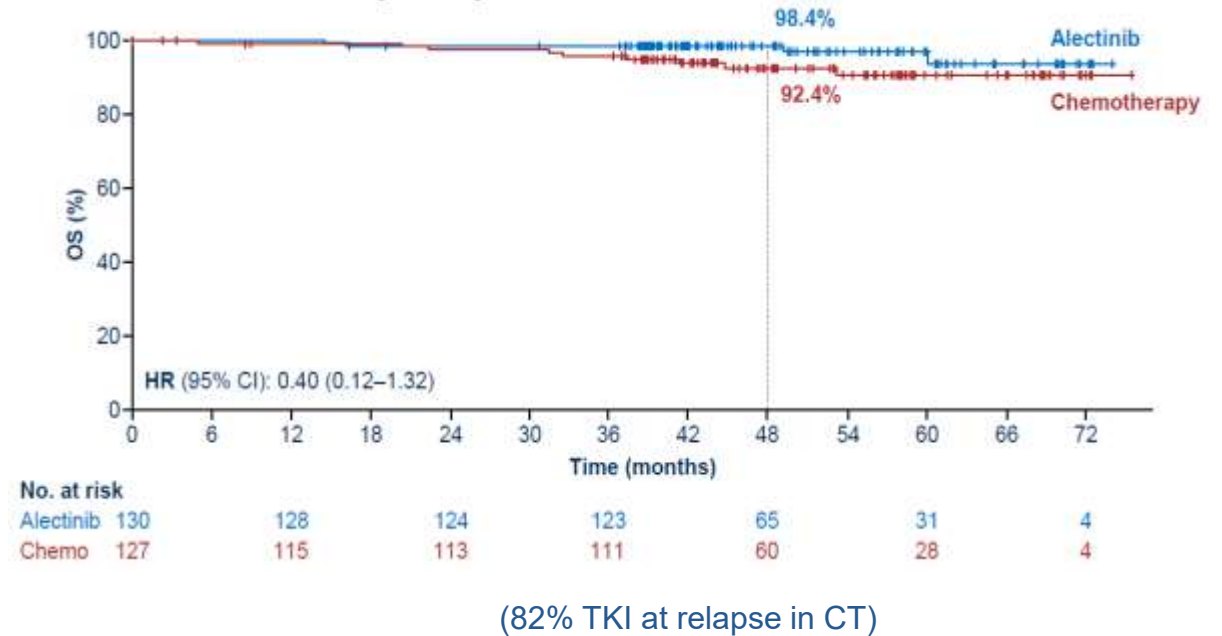
Disease assessments (including brain MRI)[§] were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

Adjuvant Alectinib: ALINA trial

DFS in stage II–IIIA*



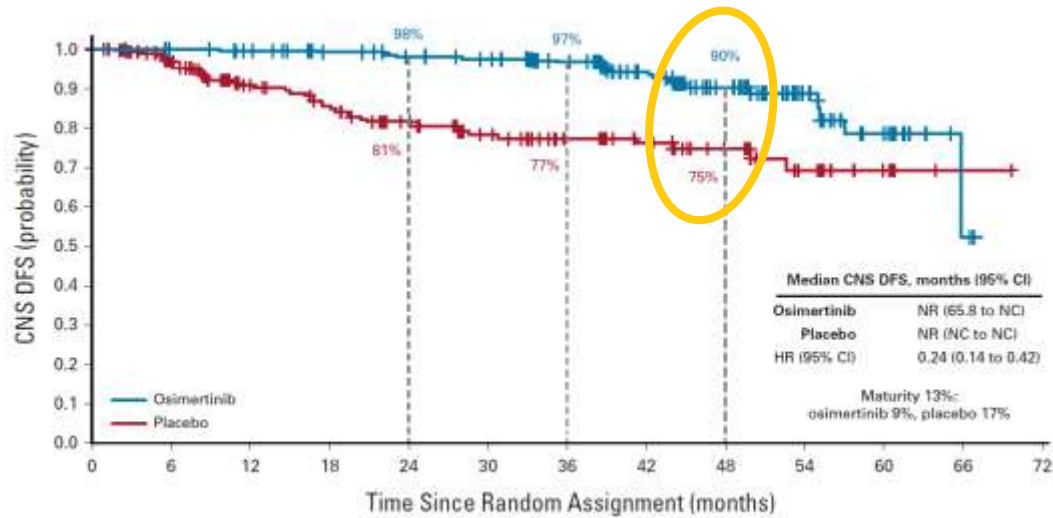
OS in stage IB–IIIA (ITT)



Median follow-up (ITT): alectinib, 48.0 months; chemotherapy, 47.4 months

CNS Disease-free survival (ITT)

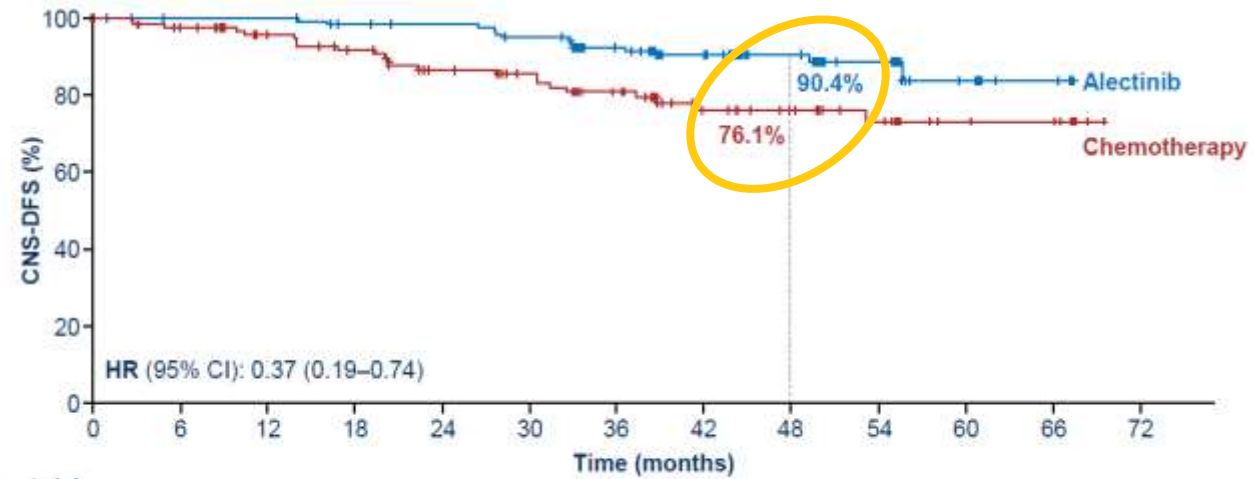
ADAURA trial



No. at risk:	0	6	12	18	24	30	36	42	48	54	60	66	72
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

4y CNS-DFS: 90% vs 75% (HR 0.24)

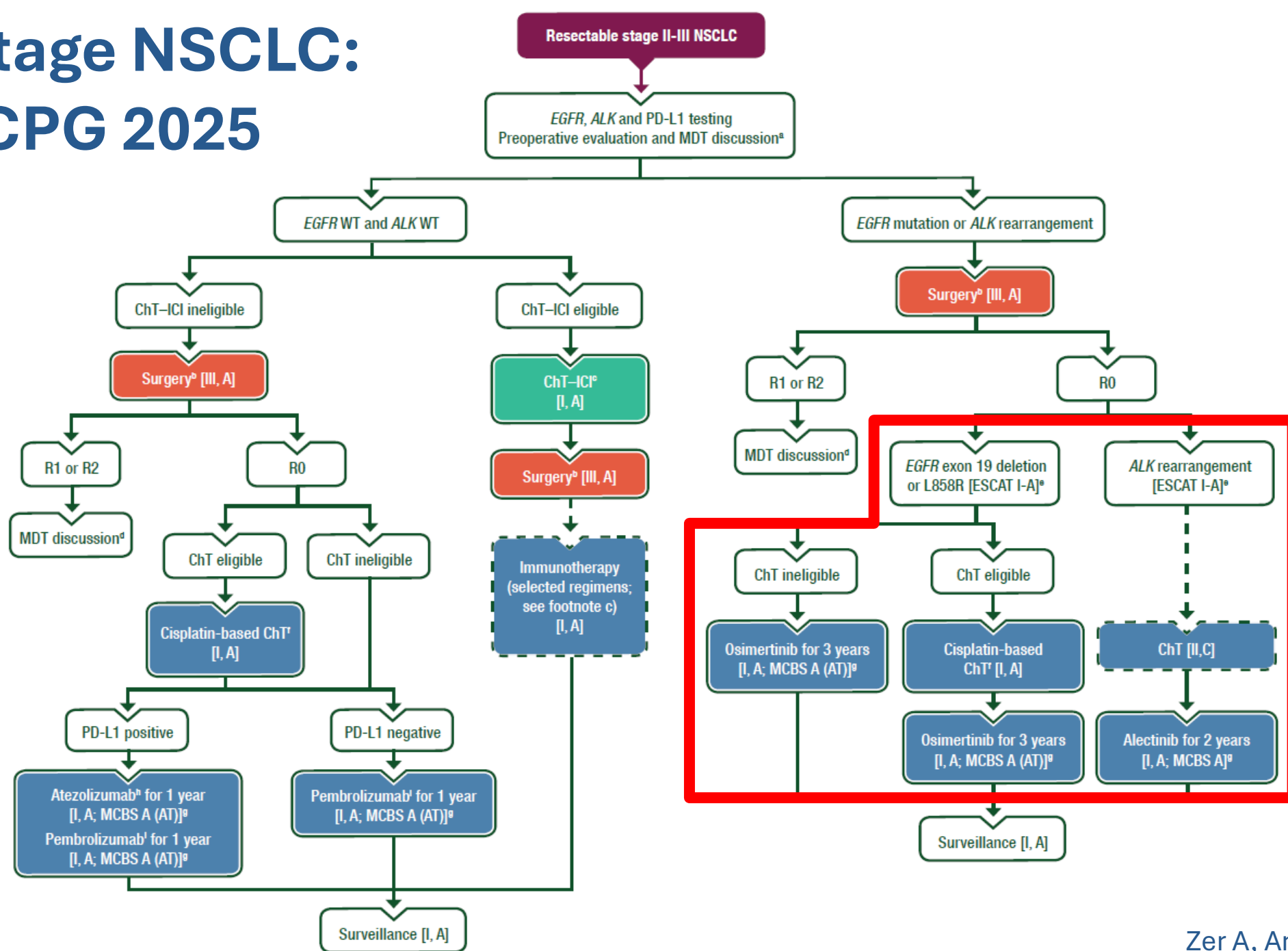
ALINA trial



No. at risk:	0	6	12	18	24	30	36	42	48	54	60	66	72
Alectinib	130	124	117	98	49	13	NE						
Chemo	127	99	80	61	33	13	NE						

4y CNS-DFS: 90% vs 76% (HR 0.37)

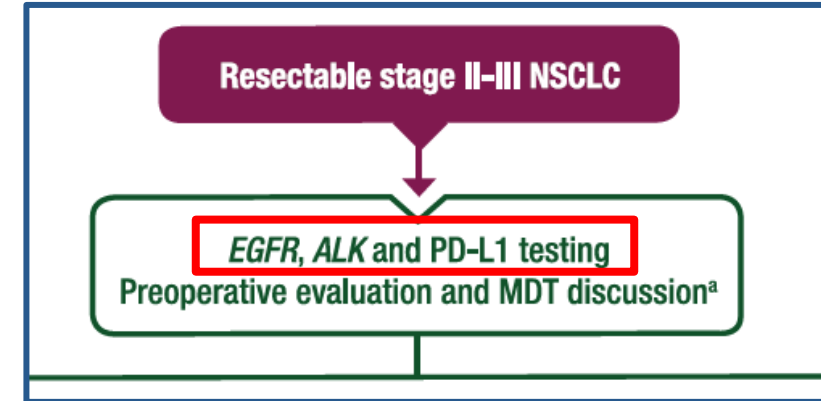
Early-stage NSCLC: ESMO CPG 2025



Early-stage NSCLC: ESMO CPG 2025

Table 1. Work-up for diagnosis and staging

	Mandatory	Optional
General	Medical history Physical examination Assess comorbidities, weight loss and PS	
Imaging	FDG—PET and contrast-enhanced CT Brain MRI (for clinical stage II-III)	Contrast-enhanced brain CT if MRI not possible
Laboratory	CBC Chemistry profile	
Preoperative cardiopulmonary evaluation	FEV ₁ DLCO CPET	
Tissue acquisition	Bronchoscopy EBUS or EUS CT-guided biopsy US-guided biopsy	Mediastinoscopy
Pathology	TTF-1 IHC staining p40 IHC staining EGFR molecular testing ALK molecular testing PD-L1 testing	



“While current data support testing of EGFR and ALK only, routine implementation of broad NGS in patients with stage II-III non-squamous NSCLC may be more pragmatic, although more time-consuming, and is likely to be beneficial in the future, as the number of targets with clinical significance is expected to increase”.

This is the state of the art, but... still many questions

- Which is the value of adjuvant therapy after neoadjuvant therapy?
- Do we have predictive factors for pCR in the neoadjuvant setting?
- How to improve neoadjuvant strategies?



16th
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NOVEMBER 2025

THANK YOU