University of Colorado Cancer Center
University of Colorado Hospital
University of Colorado Health Sciences Center



Adjuvant TKI therapy for early stage Lung Cancer with actionable genetic alterations

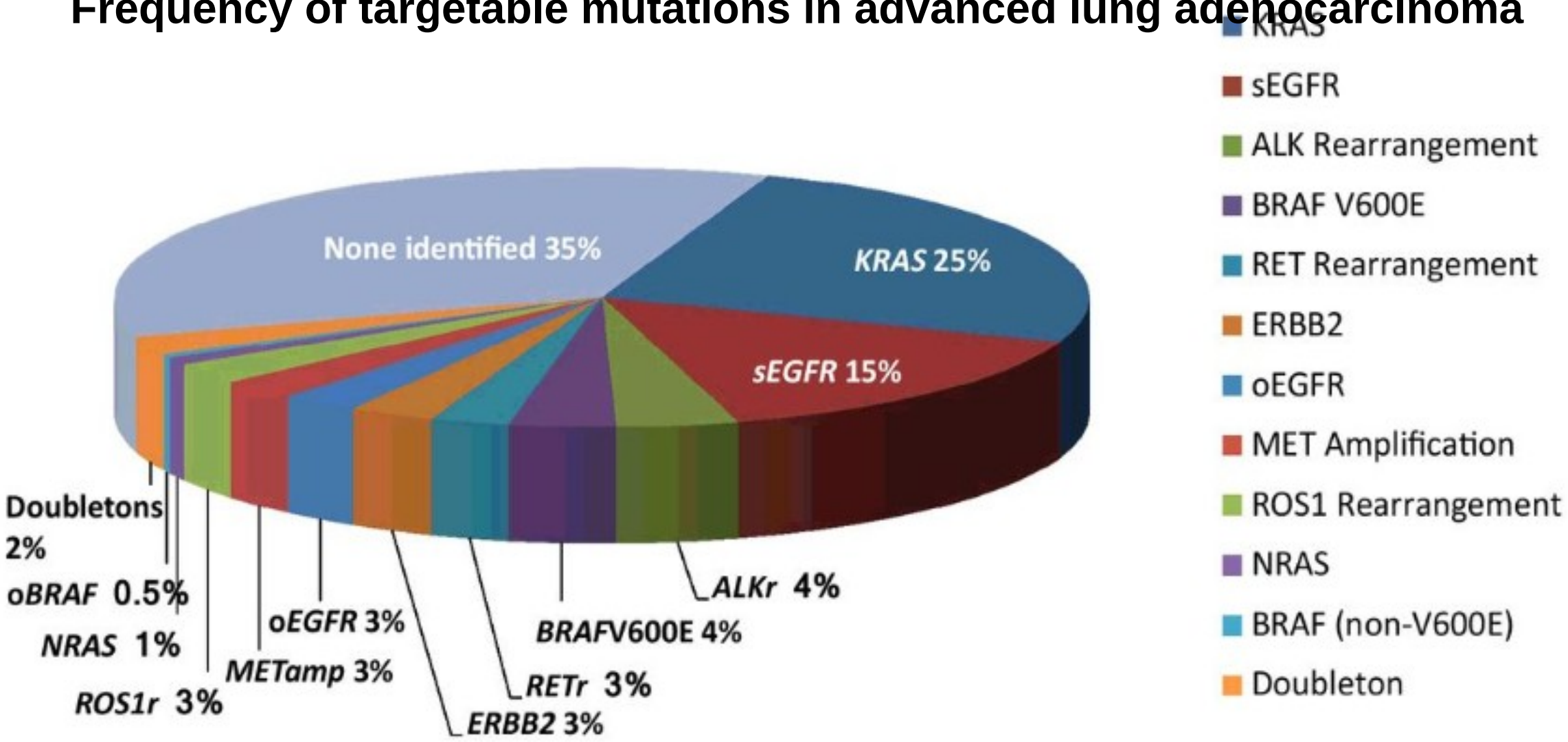
Paul A. Bunn, Jr, MD, Distinguished Professor and Dudley Endowed Chair, Univ. of Colorado Cancer Center, Aurora, CO, USA





DSMB: BMS,Merck, Daiichi
BO: Verastem
Consultant: Abbvie, AstraZeneca, Bayer, BMS, Daiichi-Sankyo, Eli Lilly, Merck, Novartis, Pfizer, Roche,Takeda

Frequency of targetable mutations in advanced lung adenocarcinoma



The Impact of Smoking and TP53 Mutations in Lung Adenocarcinoma Patients with Targetable Mutations—The Lung Cancer Mutation Consortium (LCMC2)

Dara L. Aisner, et al

DOI: 10.1158/1078-0432.CCR-17-2289 Published March 2018

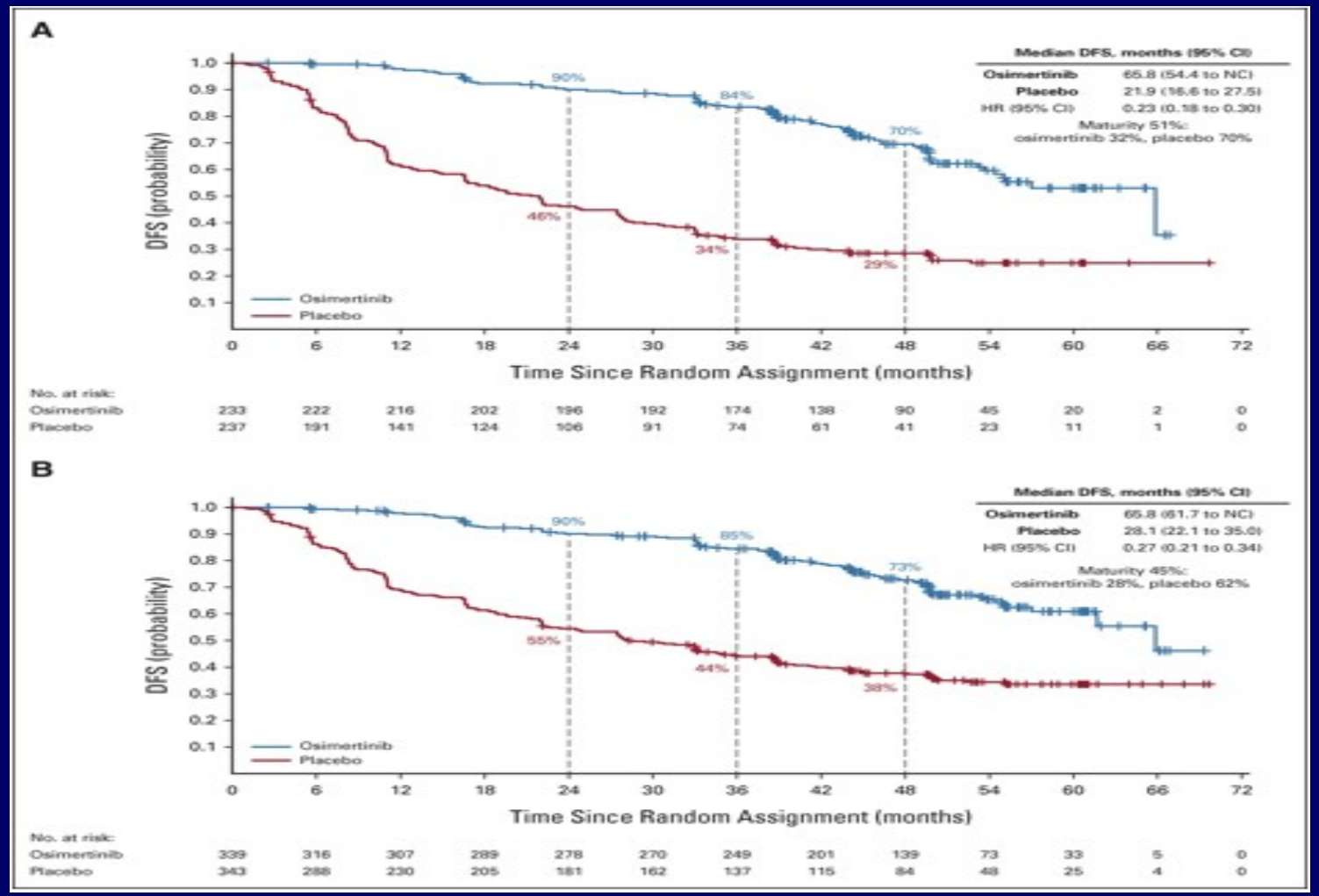
FDA Approved TKIs

- **EGFR TKIs**
  - gefitinib, erlotinib, afatinib, osimertinib, Lazertinib, aumolertinib
- **ALK TKIs**
  - crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, ensartinib
- **RET TKIs**
  selpercatinib, pralsetinib
- **NTRK TKIs**
  entrectinib, larotrectinib, repotrectinib
- **BRAF TKIs**
  dabrafinib/trametinib, vemurafinib/cobimetanib
- **ROS1 TKIs**
  repotrectinib,Larotrectinib, entrectinib, crizotinib
- **MET TKIs**
  crizotinib,topotinib,Glesatinib, capmatinib, others
- **HER2 TKIs**
- zongertinib, sevabertinib

Complete adjuvant trials, ongoing adjuvant trials

Genetic alteration	Approved agents	Approved in adjuvant setting	Reported/Ongoing neoadj/ adjuvant trials
EGFR mutation	Osimertinib,Lazertinib aumolertinib	osimertinib	Adura (osimertinib) Adura 2,Neoadura,ARTS
ALK fusions	Lorlatinib,alectinib, ensartinib	Alectinib,ensartinib,	Alina (alectiib) Elevate (ensartinib) Neoloro (lorlatinib)*
RET fusion	Selpercatinib,pralsetinib	selpercatinib	Libretto 432 (selpercatinib) Nautika (Pralsetinib)
Ros 1 fusion	Repotrectinib,Larotrectinib,entrectinib,crizotinib	none	Trust 4 (repotrectinib) Nautika (entrectinib)
HER2 exon 20	Zongertinib,sevabertinib, sunvocertinib	none	Beamion Lung-3 (zongertinib)
BRAF mutation	Encorafinib, binemetinib Drabrafinib/trametinib	none	Geometry1(dabrafenib+ trametinib),Nautika (vemurafenib+cobimetinib)
MET mutation/amplification	Capmatinib,topotinib, crizotinib	none	Geometry 1 (capmatinib)
NTRK	Entrectinib,Larotrectinib, Repotrectiniib,other	none	Nautika (entrecctinib)
KRAS G12C	Olomorasib	none	Sunray 02 (olomorasib)
KRAS G12D,V	multiple	none	pending
* Not yet recruiting			

ADURA Adjuvant Osi vs Placebo in EGFR mutant lung adenoca 4 Year DFS F/U



Unanswered questions

What is the optimal duration of therapy?

Should adjuvant chemotherapy be included?

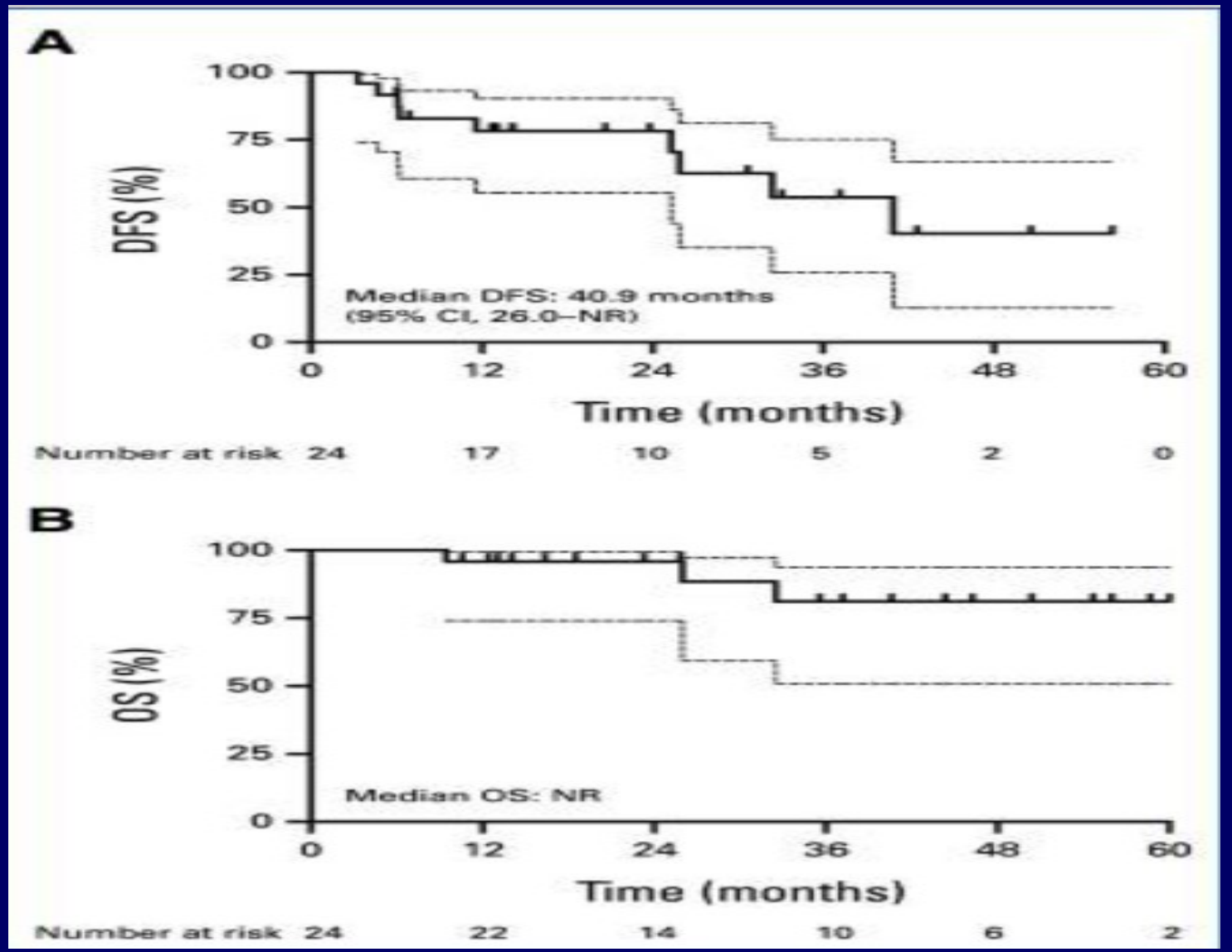
Should neoadjuvant induction therapy be given before surgery?

Does the control arm flatten around 5 years indicating potential Surgical cure?

Should adjuvant TKI therapy be continued until then?

About 1/3 of patients received no adjuvant chemo

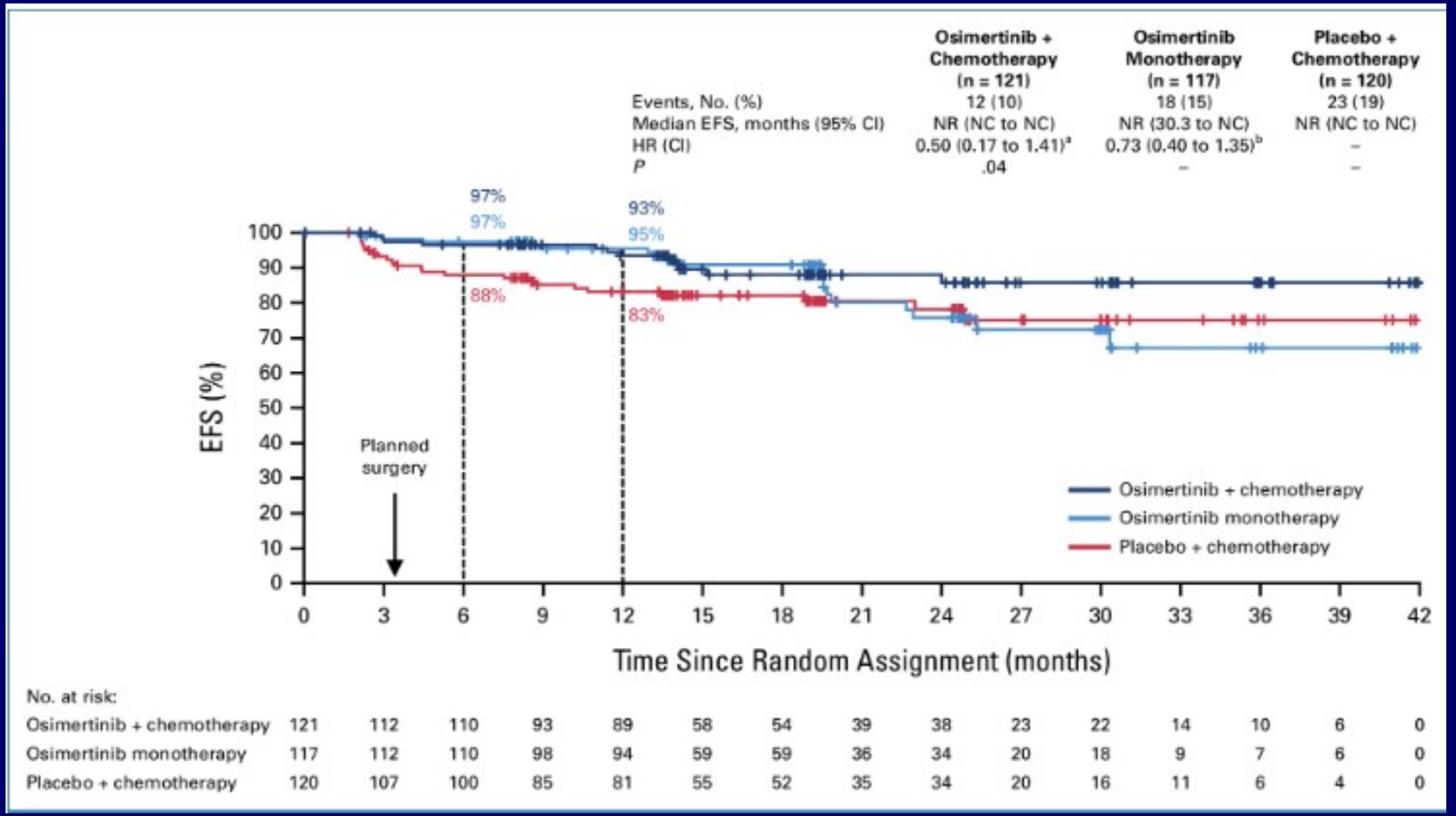
Phase 2 Neoadjuvant osimertinib in EGFR+ Lung adenoca



MPR= 15%
PCR= 0%
ORR=52%

Blakely c et al:. JCO 42:3105-3014,2024

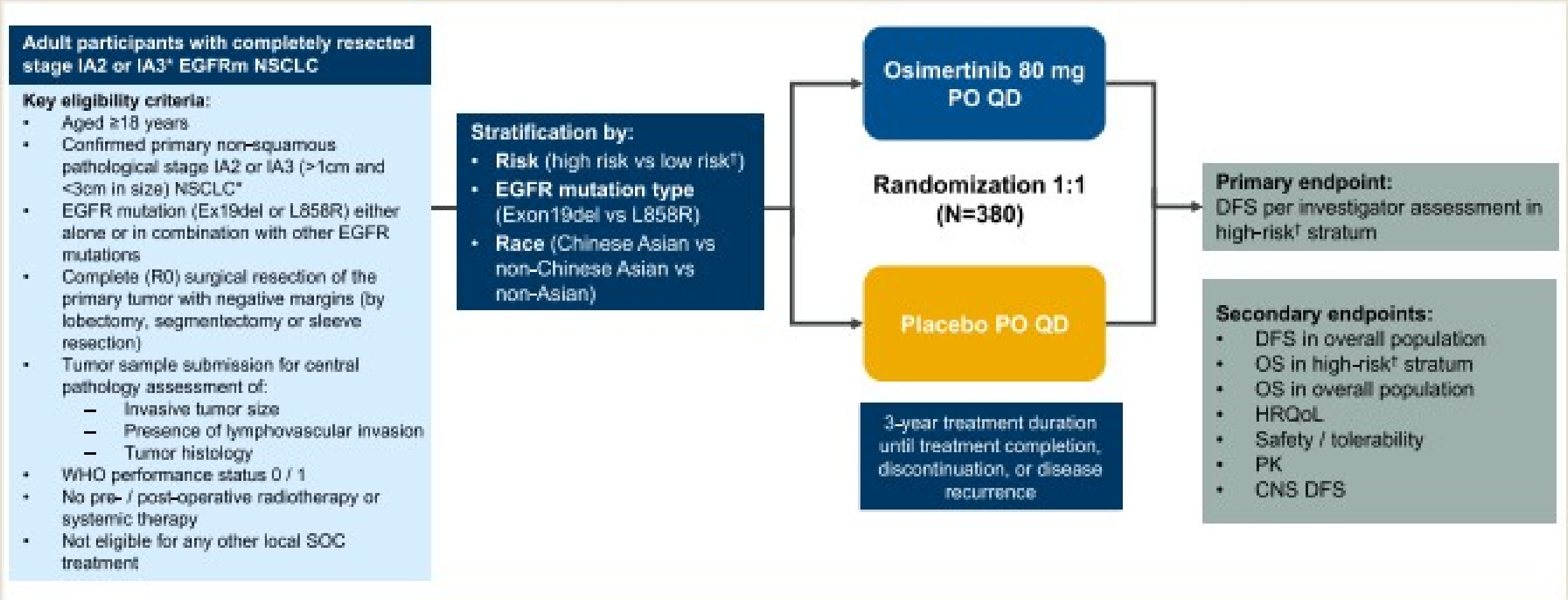
NEOADURA:Neoadjuvant osimertinib for resectable (1B and II) EGFR mutated NSCLC



He J,et al: JCO 43:2875-2887,2025

ADURA 2 (Stage 1A2 or 1A3) Study Design

Figure 1 ADAURA2 study design

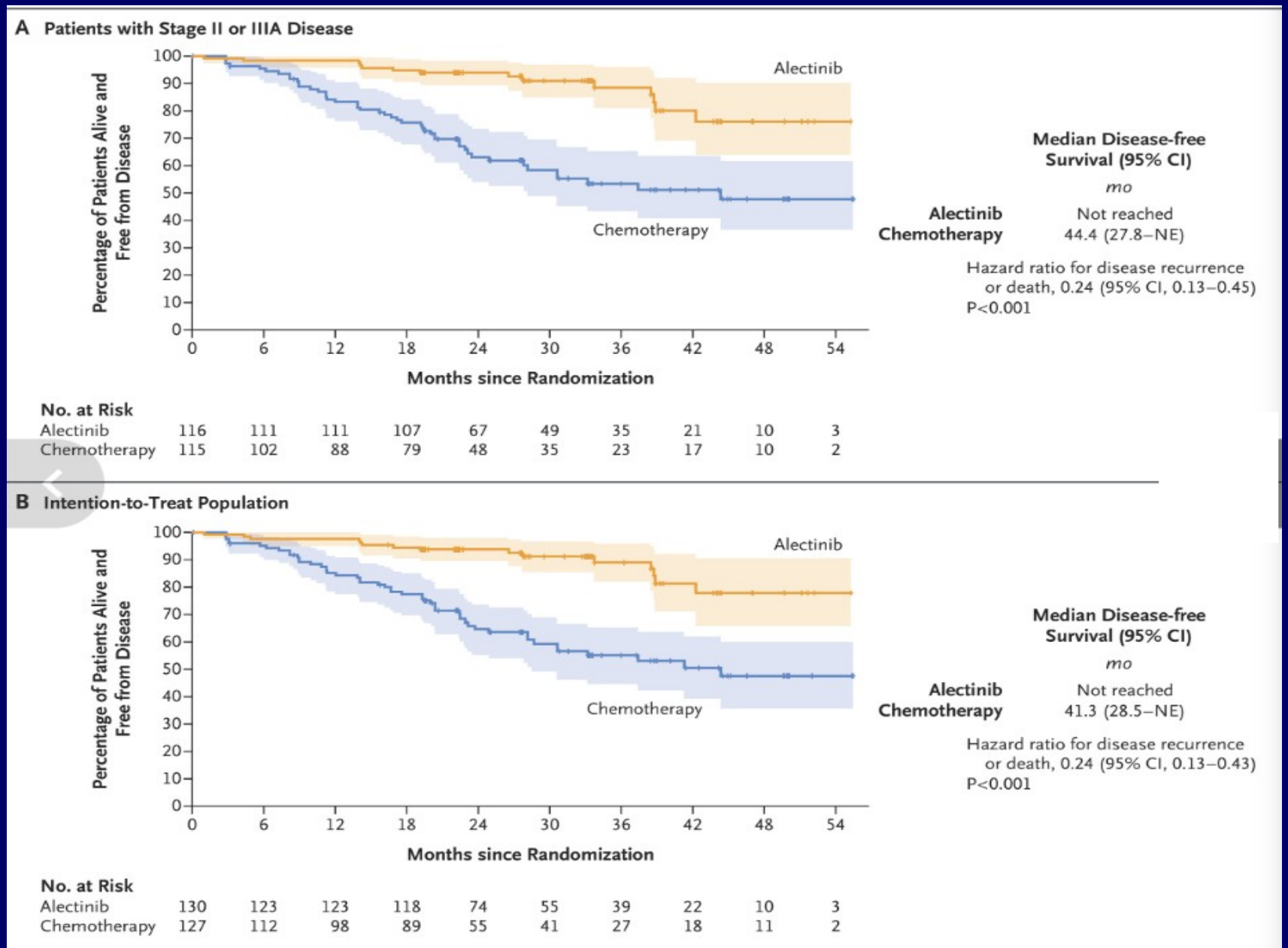


ARTS Trial of adjuvant aumolertinib

N=214 Chinese randomized to aumolertinib vs placebo post adj. Chemotherapy

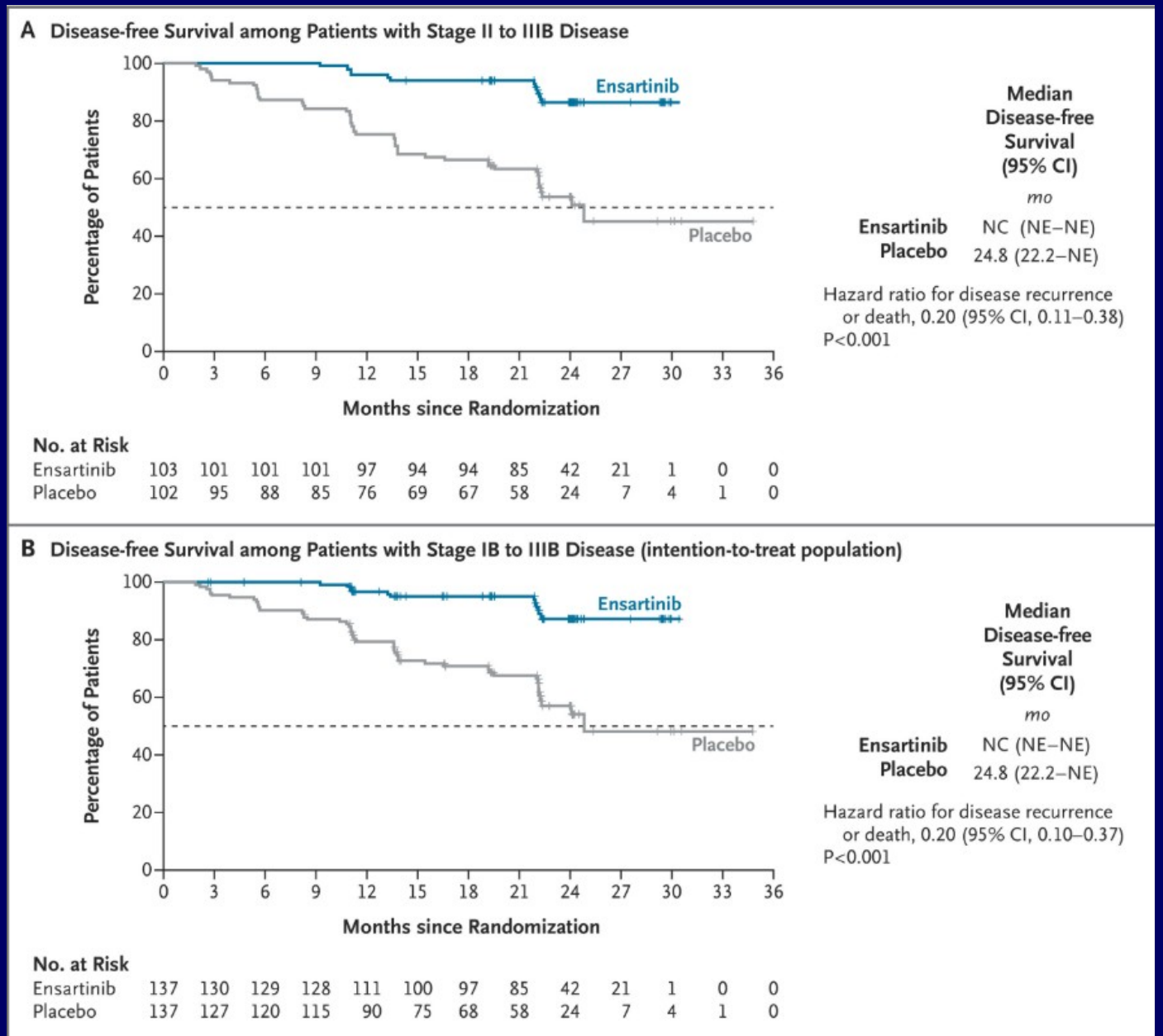
DFS aumolertinib: not reached vs 19.42 mo with placebo HR=0.17

Alina: Adj. Alectinib Results in ALK+ lung ca



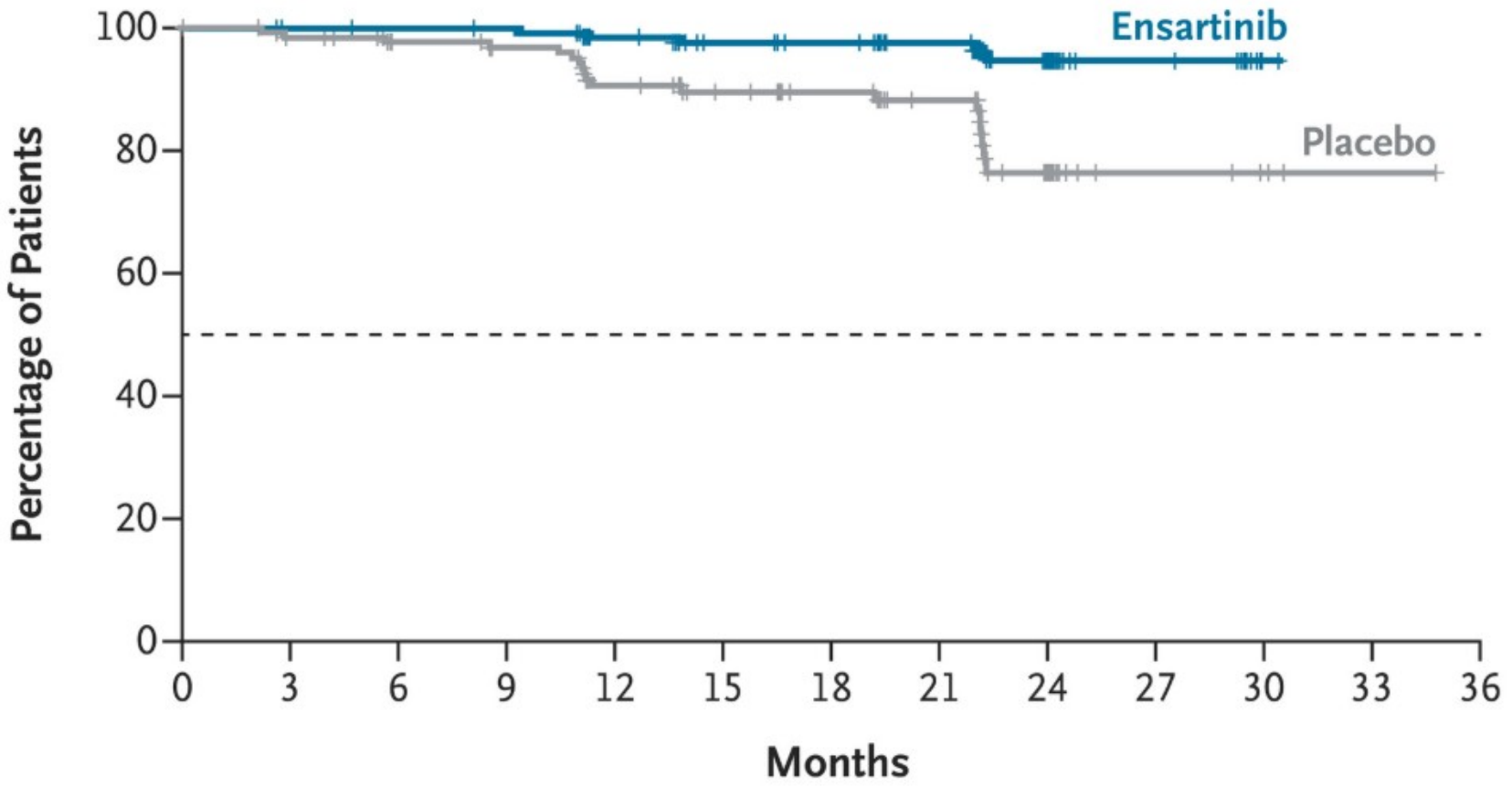
Wu,Y-L et al NEJM 390: 1265-1276,2024

Ensartinib in resected ALK-Positive NSCLC: ELEVATE Trial



Yue D, et al:NEJM 2026:395:151-61

Ensartinib in resected ALK-Positive NSCLC



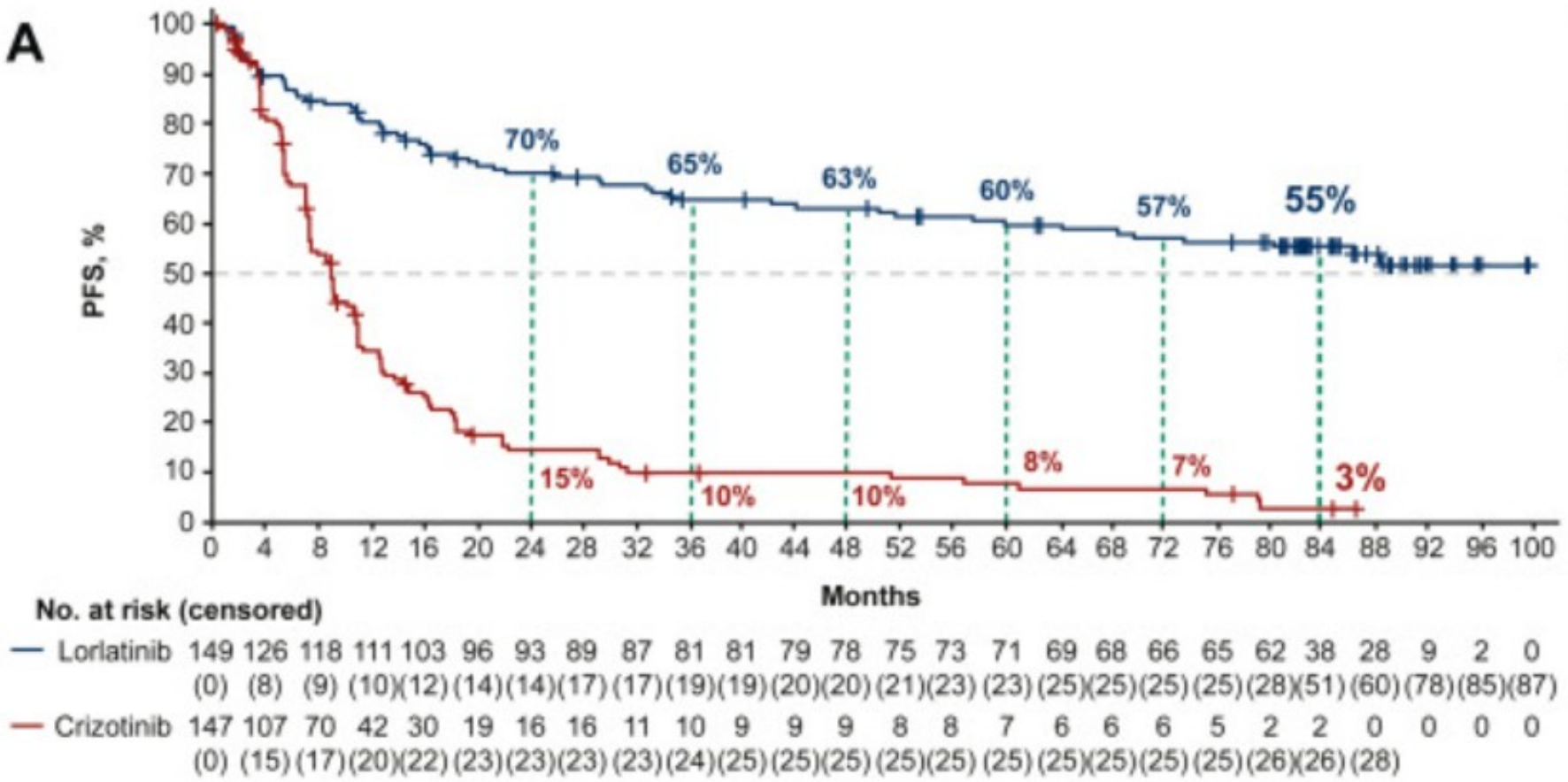
No. at Risk													
Ensartinib	137	130	129	128	111	100	97	85	42	21	1	0	0
Placebo	137	127	120	115	91	75	68	58	24	7	4	1	0

Median CNS Disease–free Survival (95% CI)	*mo*
Ensartinib	NC (NE–NE)
Placebo	NC (NE–NE)

Hazard ratio for CNS disease recurrence or death, 0.22 (95% CI, 0.08–0.60)

Yue D, et al NEJM 2026:395:151-61,

NEOLORA Randomized trial planned based on Lorlatinib vs Crizotinib in ALK+ Adv. Lung Adenoca

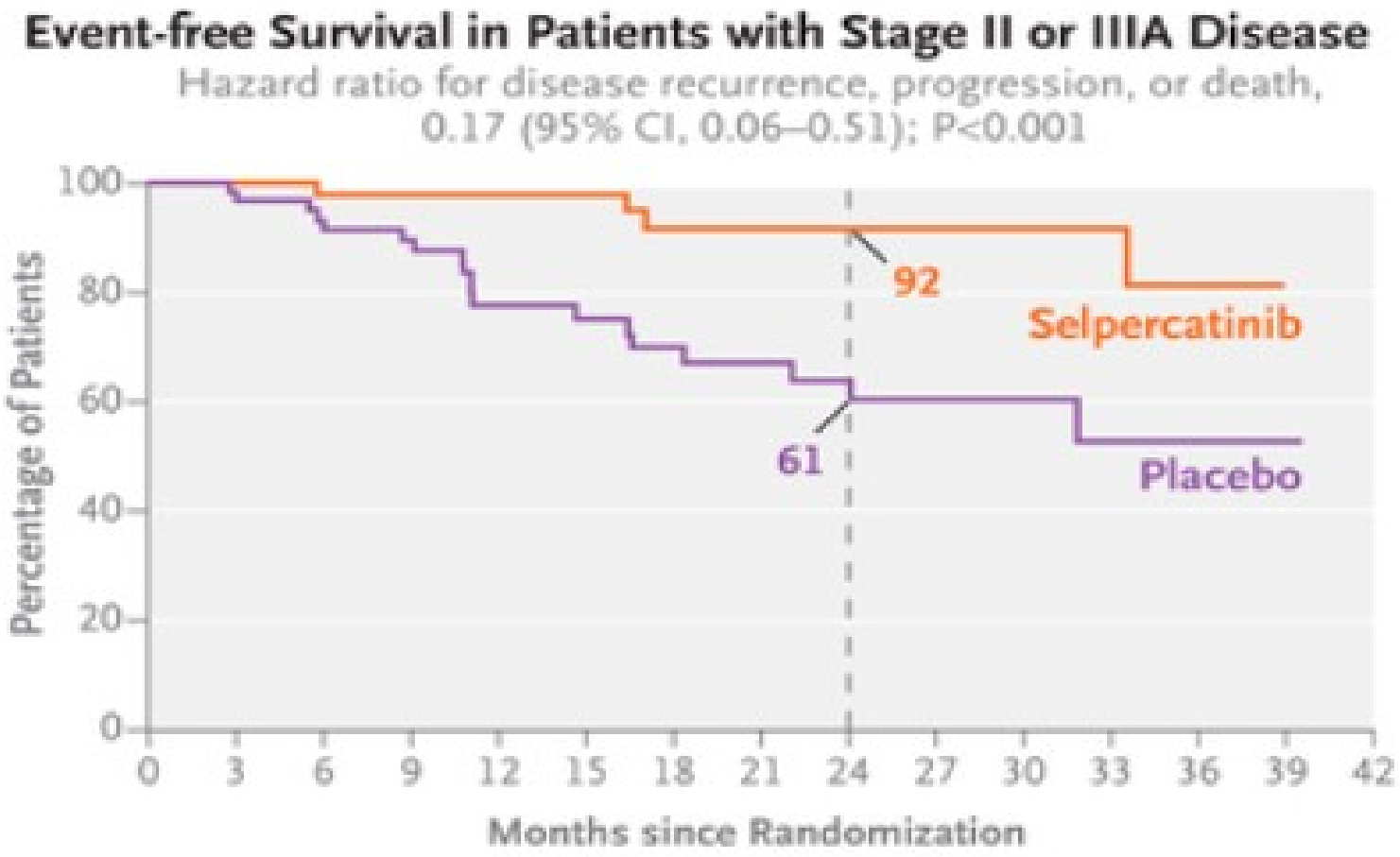


	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	62	119
PFS, months, median (95% CI)	NR (68.5-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.26)**	

Could it be superior in Adjuvant therapy?

Shaw AT,et al: Ann Oncol 37:1242-1252,2026
Adjuvant NEOLORO trial in progress

Selpercatinib in resected RET fusion Positive NSCLC: Libretto 432



For participants receiving selpercatinib, median EFS was not reached, For those in the placebo group, the median EFS was 31.8 months.

At 2 years, the EFS rate was 91.5% vs. 61.1% for people in the placebo group.

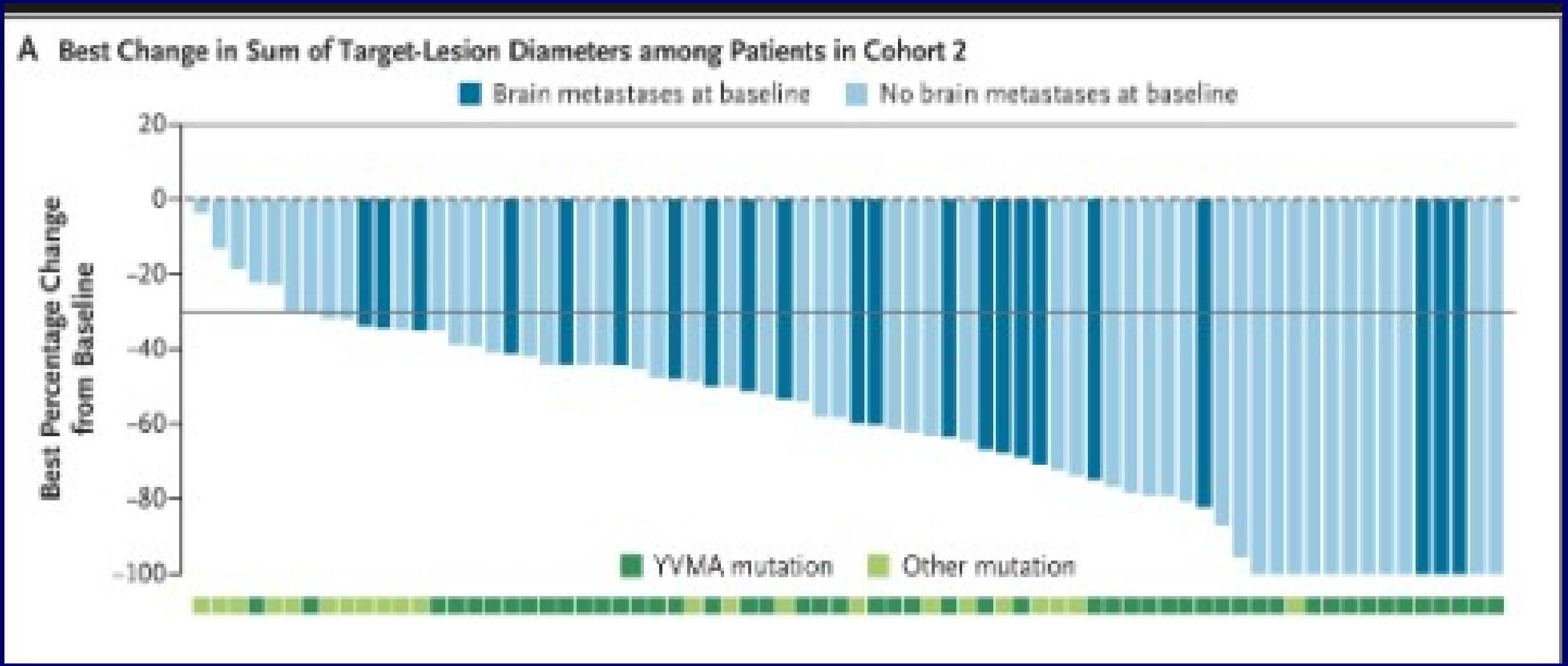
Overall, selpercatinib reduced the risk of recurrence or death by about 83% compared to the placebo

Wu Y-L et al: NEJM 395:660-670,2026

TRUST 4 Taletrectinib Adjuvant trial in ROS1 fusion + lung adenoca

Ongoing trial: planned N=180 with 2:1 randomization to taletrectinib or placebo. The primary endpoint is disease-free survival (DFS) by investigator assessment. Select secondary endpoints include: DFS rates at 2, 3, 4, and 5 years; DFS by blinded independent central review; overall survival; CNS-DFS; and safety.

1st line zongertinib in HER-2 mutatnt NSCLC



Heymach JE et al NEJM 394:1675-84,2026

Beamion LUNG-3 Zongertinib Adj Trial (NCT07195695) For HER2 mutatnt lung adenoca

(

Ongoing, global Phase III trial (n==400) investigating zongertinib as adjuvant monotherapy compared with SoC (immunotherapy [IO] or observation) in patients with early-stage, resectable *HER2*-mutant NSCLC.

Geometry 1: Adj. capmetinib in MET+ Resectable lung ca

Adults with resectable, histologically confirmed NSCLC stage IB-IIIA, N2 and select IIIB (T3N2 or T4N2) with either *MET*ex14 (cohort A) or high-level *MET*amp (gene copy number ≥10; cohort B) are eligible. Patients will receive capmatinib 400 mg twice daily for 8 weeks before surgical resection, followed by 3 years of adjuvant capmatinib.

In the 2-stage design, stage 1 will enroll 9 patients per cohort, with MPR evaluated in each cohort after 9 patients have completed neoadjuvant therapy; stage 2, enrolling 10 more patients in a cohort, will proceed only if ≥1 of 9 participants has an MPR.

About 42 patients will be enrolled, with 19 evaluable patients per cohort. Primary endpoint is MPR rate (local assessment). Secondary endpoints are complete pathological response rate (central and local review), ORR (local assessment), DFS, and safety. Following treatment, there will be a 2-year survival follow-up. Enrollment has started; expected first patient first visit: March 31, 2022. Clinical trial information: NCT04926831.

Lee J et al:J Clin Oncol 40, 2022 (suppl 16; abstr TPS8590)

Geometry 1: Adj.dabrafenib + trametinib in BRAF mutated Resectable lung ca

Eligible patients with BRAF V600 mutations will receive dabrafenib 150mg bid plus trametinib 2mg qd for 8 weeks before a surgical resection (neoadjuvant), and followed by up to 4 cycles of adjuvant chemotherapy, if receive adjuvant chemotherapy, up to four cycles, chemo regimen according to investigators' choice, and up to 2 years of adjuvant targeted therapy with dabrafenib plus trametinib.

Nautika 1Phase II Neoadjuvant/Adjuvant Trial

Genetic Alteration	Therapy
ALK	alectinib
ROS1	entrectinib
NTRK	entrectinib
BRAFv600E	Vemurafinib/cobemetinib
RET	pralsetinib
KRAS12C	diverasib

Nautika 1 Alectinib Results

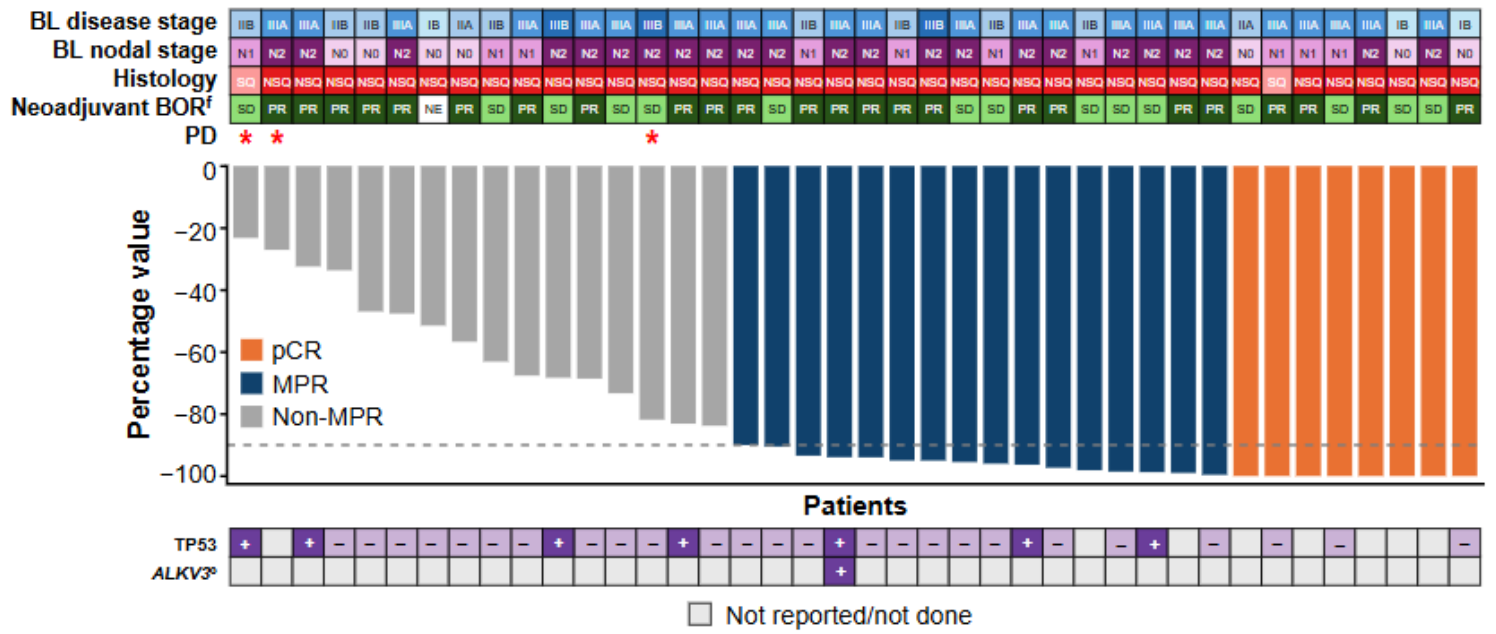
Pathologic and radiographic[a] responses and 2-year time-to-event outcomes[b]

Response endpoint	
Pathological response, n[c]	**43[d]**
MPR, n (%) [95% CI]	24 (**56**) [40, 71]
pCR, n (%) [95% CI]	8 (**19**) [8, 33]
Radiographic response, n	**45[e]**
ORR, n (%) [95% CI]	27 (**60**) [44, 74]
PR	27 (**60**) [44, 74]
SD	16 (**36**) [22, 51]
PD, n (%) [95% CI]	1 (**2**) [<1, 12]
NE,[f] n (%)	1 (**2**)

2-year event rates, % (95% CI)	
EFS (n=45)	**90** (81, 99)
DFS (n=39)[g]	**97** (91, 100)
OS rate (n=45)	**98** (93, 100)

Median follow-up: 23.0 months

Weighted percentage pathologic regression (n=40)[h]



Robust pathologic regression and radiographic responses were observed with neoadjuvant alectinib

Lee JM, et al: WCLC 2026

Nautika 1 divarasib Results

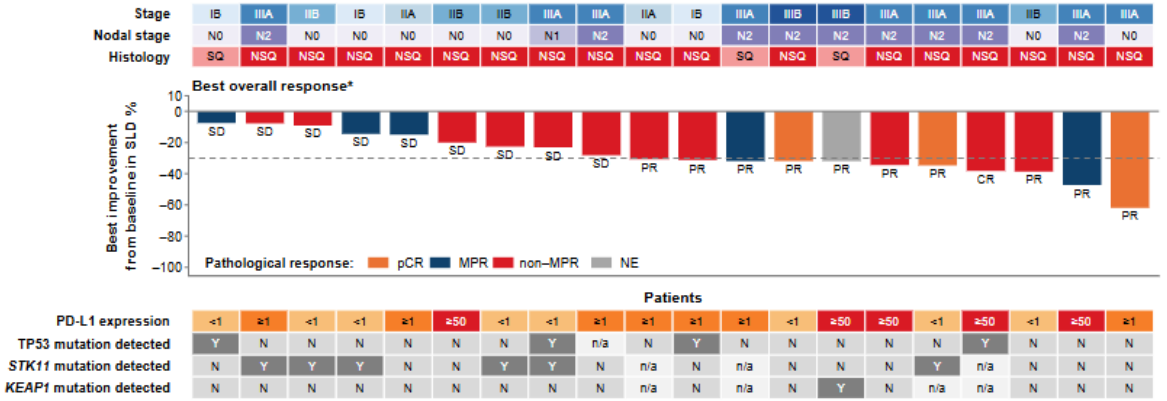
Antitumor activity with neoadjuvant divarasib

Pathological response, n (%) [95% CI]	n=19*
MPR	8 (42) [20–67]
pCR	3 (16) [3–40]
Radiographic response, n (%)	**n=20†**
ORR (by investigator), n (%) [95% CI]	11 (55) [32–77]
Complete response	1 (5)
Partial response	10 (50)
Stable disease	9 (45)
Progressive disease	0

Neoadjuvant divarasib demonstrated promising antitumor activity

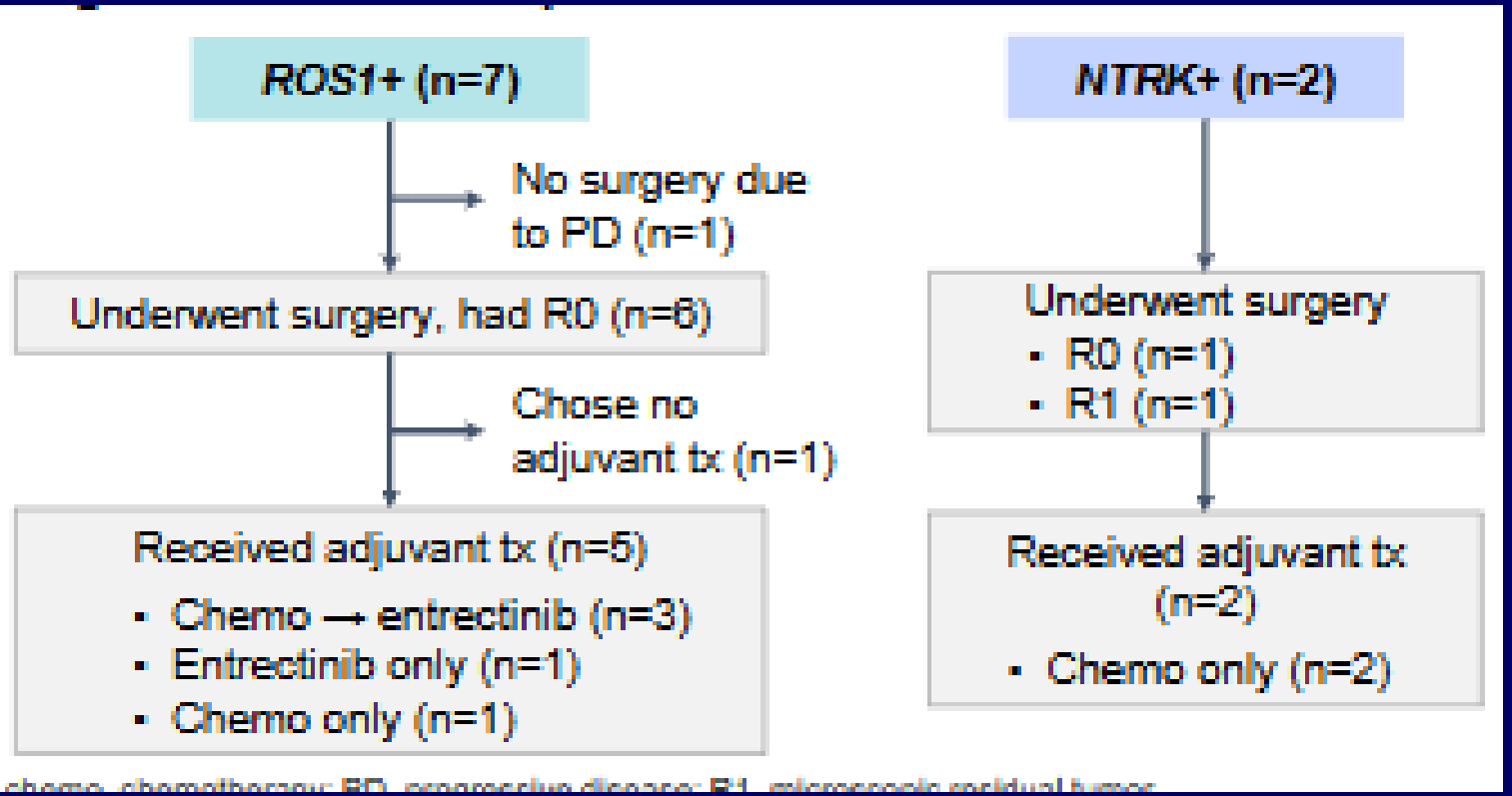
Chaft JE et al: WCLC 2026

Best percent change in SLD from baseline with neoadjuvant divarasib

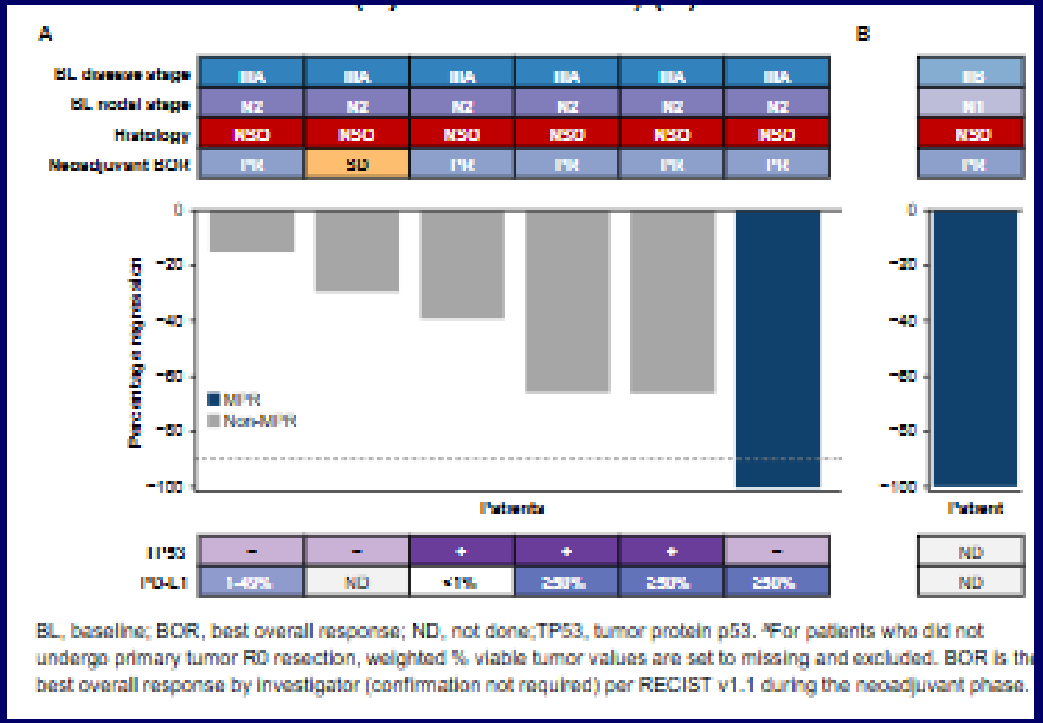


Tumor regression was observed across PD-L1, *TP53*, and *STK11* status

Nautika 1 Entrectinib in both ROS1 & NTRK



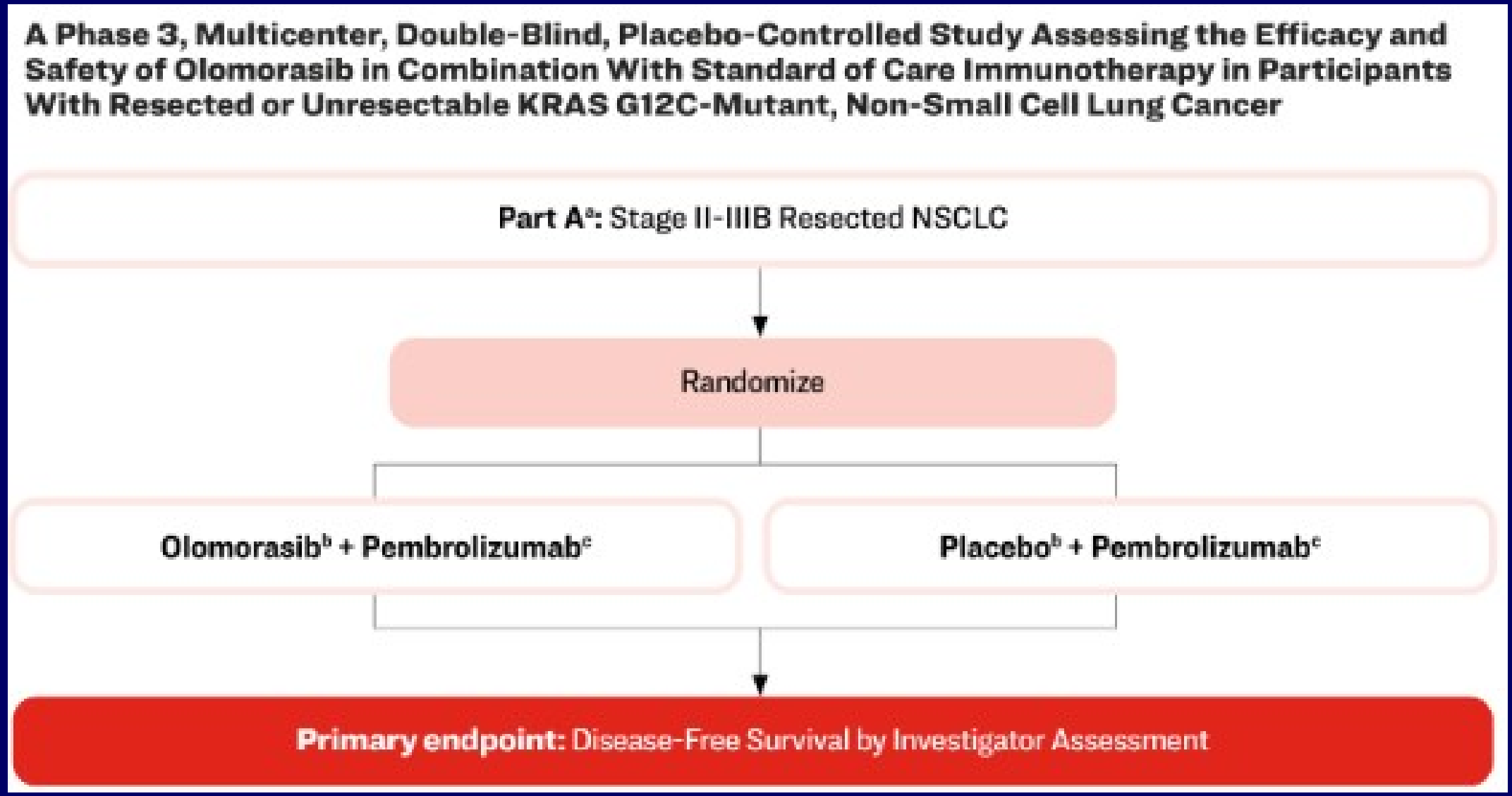
ROS1 Entrectinib NTRK



BL, baseline; BOR, best overall response; ND, not done;TP53, tumor protein p53. [a]For patients who did not undergo primary tumor R0 resection, weighted % viable tumor values are set to missing and excluded. BOR is the best overall response by investigator (confirmation not required) per RECIST v1.1 during the neoadjuvant phase.

Chaft JE et al: WCLC 2026

SUNRAY 02 TRIAL of Olomorasib in KRAS G12C Mutant Adenoca

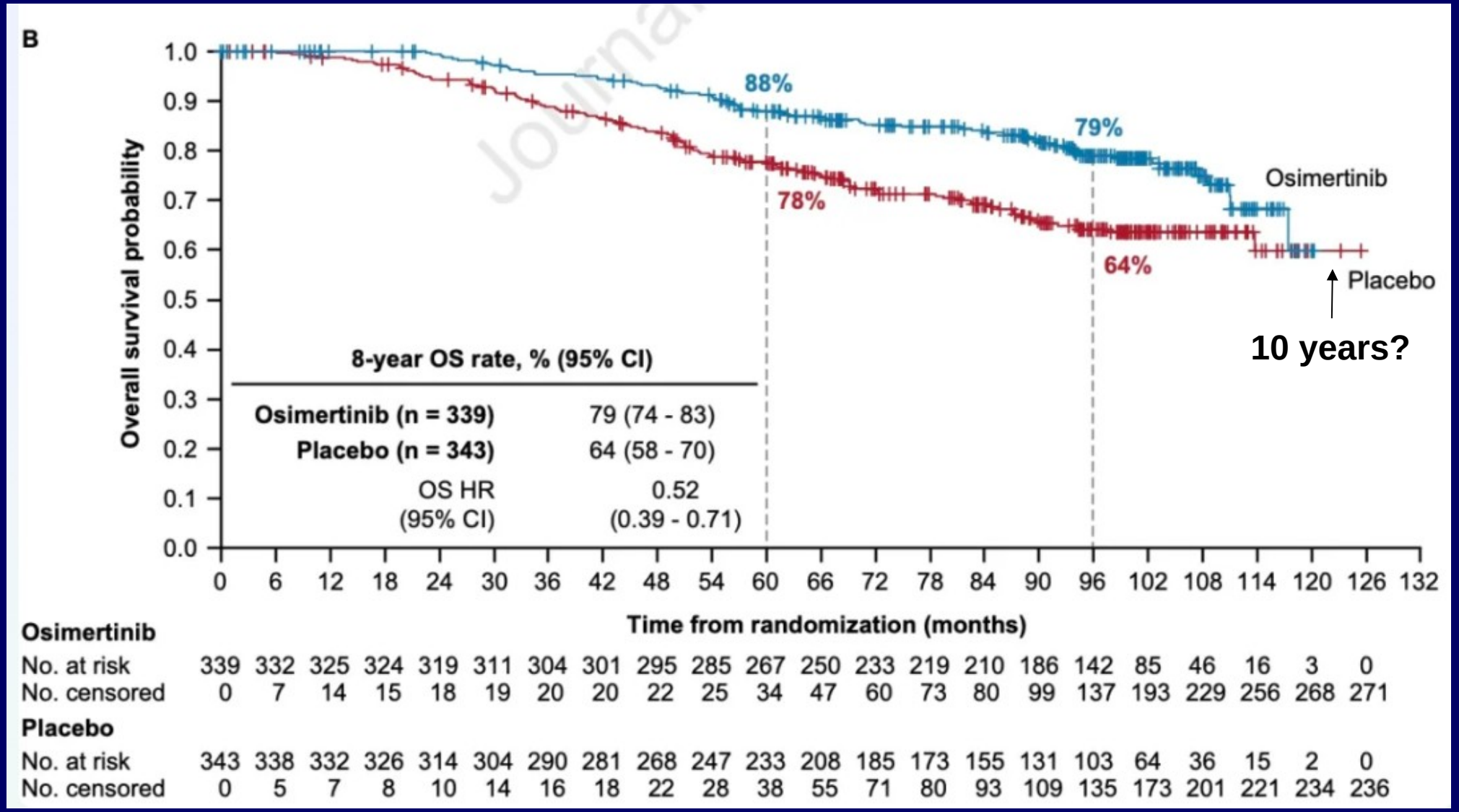


Remaining Questions

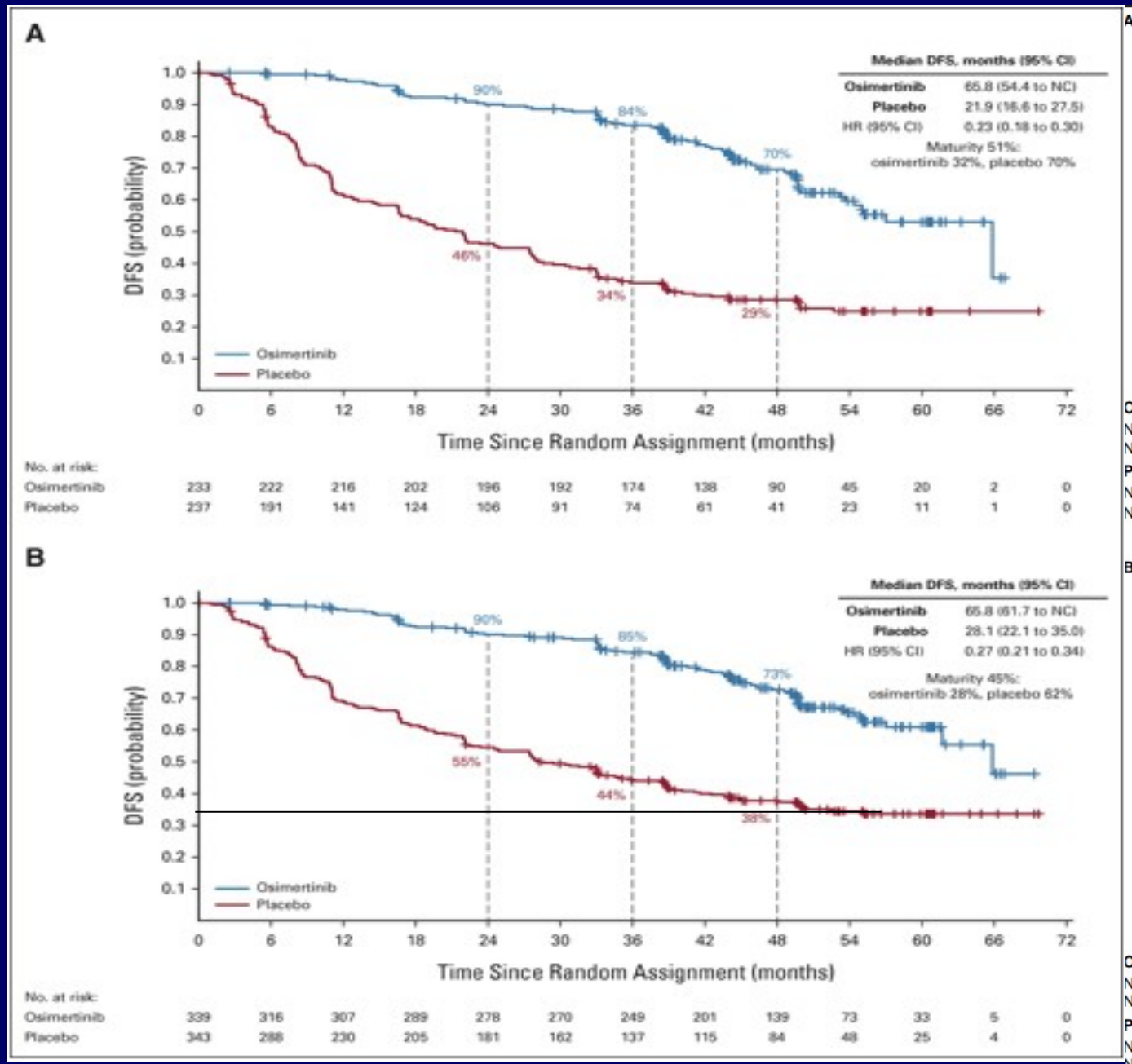
Should neoadjuvant chemotherapy be given?
Should adjuvant chemotherapy be given?
Should neoadjuvant TKI therapy be given?
Should adjuvant TKI therapy be given for 3 years or until PD?

What trials should have priority? Cooperative groups?

ADURA OS Adjuvant Osi vs Placebo in EGFR mutant lung adenoca



Or should therapy be continued for 10 yrs or until PD?


A
Median DFS, months (95% CI)
Osimertinib 65.8 (54.4 to NC)
Placebo 21.9 (16.6 to 27.5)
HR (95% CI) 0.23 (0.18 to 0.30)
Maturity 51%:
osimertinib 32%, placebo 70%
DFS (probability)
90%
84%
70%
46%
34%
29%
Osimertinib
Placebo
Time Since Random Assignment (months)
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
B
Median DFS, months (95% CI)
Osimertinib 65.8 (61.7 to NC)
Placebo 28.1 (22.1 to 35.0)
HR (95% CI) 0.27 (0.21 to 0.34)
Maturity 45%:
osimertinib 28%, placebo 62%
DFS (probability)
90%
85%
73%
55%
44%
38%
Osimertinib
Placebo
Time Since Random Assignment (months)
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

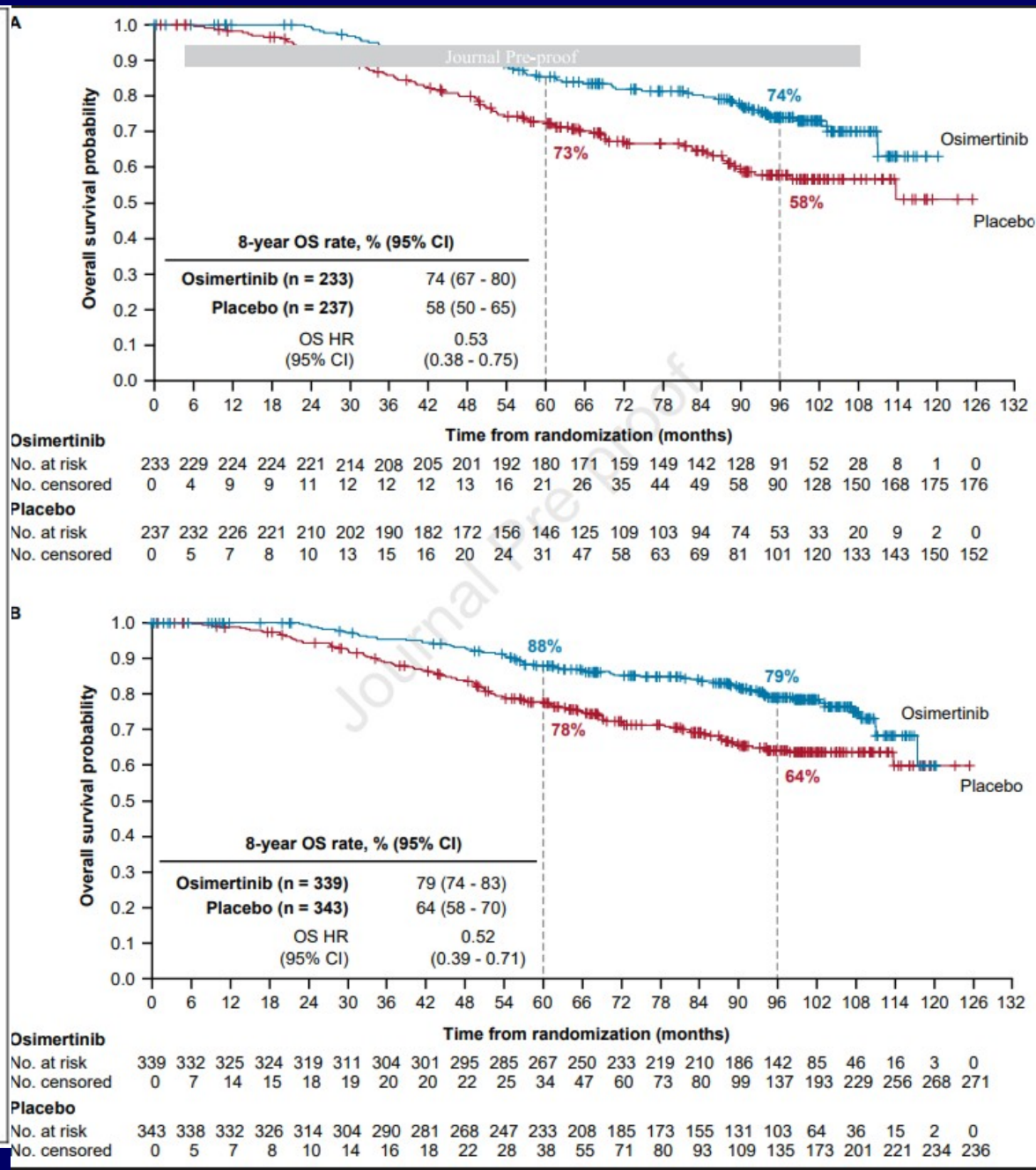

A
Journal Pre-proof
Overall survival probability
74%
73%
58%
Osimertinib
Placebo
8-year OS rate, % (95% CI)
Osimertinib (n = 233) 74 (67 - 80)
Placebo (n = 237) 58 (50 - 65)
OS HR (95% CI) 0.53 (0.38 - 0.75)
Time from randomization (months)
Osimertinib
No. at risk 233 229 224 224 221 214 208 205 201 192 180 171 159 149 142 128 91 52 28 8 1 0
No. censored 0 4 9 9 11 12 12 12 13 16 21 26 35 44 49 58 90 128 150 168 175 176
Placebo
No. at risk 237 232 226 221 210 202 190 182 172 156 146 125 109 103 94 74 53 33 20 9 2 0
No. censored 0 5 7 8 10 13 15 16 20 24 31 47 58 63 69 81 101 120 133 143 150 152
B
Overall survival probability
88%
79%
78%
64%
Osimertinib
Placebo
8-year OS rate, % (95% CI)
Osimertinib (n = 339) 79 (74 - 83)
Placebo (n = 343) 64 (58 - 70)
OS HR (95% CI) 0.52 (0.39 - 0.71)
Time from randomization (months)
Osimertinib
No. at risk 339 332 325 324 319 311 304 301 295 285 267 250 233 219 210 186 142 85 46 16 3 0
No. censored 0 7 14 15 18 19 20 20 22 25 34 47 60 73 80 99 137 193 229 256 268 271
Placebo
No. at risk 343 338 332 326 314 304 290 281 268 247 233 208 185 173 155 131 103 64 36 15 2 0
No. censored 0 5 7 8 10 14 16 18 22 28 38 55 71 80 93 109 135 173 201 221 234 236

Table. Ongoing Trials of ALK TKIs in Neoadjuvant/Adjuvant/Perioperative NSCLC

Trial name	Phase	Setting	Stage	Study drug	Intervention and regimen	Primary endpoint	Status/key results
ALNEO[5] (NCT05015010)	2	Perioperative	Resectable stage III *ALK*+ NSCLC	Alectinib	Neoadjuvant alectinib 600 mg BID × 8 wk → surgery → adjuvant alectinib × 96 wk	MPR	46% MPR, 12% pCR, 67% ORR; 94% alive at median 15.2 mo (33 pts)
NAUTIKA-1[4] (NCT04302025)	2	Perioperative	Resectable stage IB-III selected NSCLC	Alectinib	Neoadjuvant alectinib 600 mg BID × 8 wk → surgery → chemo → adjuvant alectinib (~2 yrs)	MPR (ALK+ arm)	66.7% MPR, 33.3% pCR in *ALK*+ cohort (9 pts)
HORIZON-2 (NCT06624059)	3	Perioperative	Stage II-select IIIB *ALK*+ NSCLC	Alectinib	B1: adjuvant alectinib + chemo → alectinib (~5 yrs); B2: neoadjuvant alectinib + chemo → surgery → alectinib (~5 yrs)	pCR	Recruiting as of August 2025
ALINA[3] (NCT03456076)	3	Adjuvant	Resected stage IB (≥ 4 cm)-IIIA *ALK*+ NSCLC	Alectinib	Adjuvant alectinib 600 mg BID × 24 mo vs platinum chemo × 4 cycles	DFS	2-yr DFS 93.8% vs 63.0% (HR 0.24); FDA approval April 2024[2]
Ensartinib adjuvant (NCT05241028)	2	Adjuvant	Resected stage IB-IIIA *ALK*+ NSCLC	Ensartinib	Adjuvant ensartinib ~225 mg QD for up to 3 yrs	DFS	Recruiting as of August 2025
Ensartinib neoadjuvant (NCT05380024)	2	Neoadjuvant	Stage II-IIIB *ALK*+ NSCLC	Ensartinib	Neoadjuvant ensartinib 225 mg QD × 8 wk	MPR	Active and recruiting
Brigatinib "window" (NCT05361564)	2	Neoadjuvant	Resectable stage I-IIIA *ALK*+ NSCLC	Brigatinib	Neoadjuvant brigatinib lead-in then 4-10 wk	Mechanistic	Small cohort; not yet publicly recruiting
NEOLORA (NCT06682884)	2	Neoadjuvant	Stage IB-IIIB *ALK*+ NSCLC	Lorlatinib	Lorlatinib 100 mg QD for 6-8 wk	pCR	Planning stage; not yet widely recruiting