TARGETED PERIOPERATIVE THERAPY FOR EARLY-STAGE NSCLC

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Conquering Thoracic Cancers Worldwide

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Perioperative Nivolumab and Chemotherapy in Stage III Non–Small-Cell Lung Cancer

M. Provencio, E. Nadal, J.L. González-Larriba, A. Martínez-Martí, R. Bernabé, J. Bosch-Barrera, J. Casal-Rubio, V. Calvo, A. Insa, S. Ponce, N. Reguart, J. de Castro, J. Mosquera, M. Cobo, A. Aguilar, G. López Vivanco, C. Camps, R. López-Castro, T. Morán, I. Barneto, D. Rodríguez-Abreu, R. Serna-Blasco, R. Benítez, C. Aguado de la Rosa, R. Palmero, F. Hernando-Trancho, J. Martín-López, A. Cruz-Bermúdez, B. Massuti, and A. Romero

Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer

J.V. Heymach, D. Harpole, T. Mitsudomi, J.M. Taube, G. Galffy, M. Hochmair, T. Winder, R. Zukov, G. Garbaos, S. Gao, H. Kuroda, G. Ostoros, T.V. Tran, J. You, K.-Y. Lee, L. Antonuzzo, Z. Papai-Szekely, H. Akamatsu, B. Biswas, A. Spira, J. Crawford, H.T. Le, M. Aperghis, G.J. Doherty, H. Mann, T.M. Fouad, and M. Reck, for the AEGEAN Investigators*

Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer

H. Wakelee, M. Liberman, T. Kato, M. Tsuboi, S.-H. Lee, S. Gao, K.-N. Chen, C. Dooms, M. Majem, E. Eigendorff, G.L. Martinengo, O. Bylicki, D. Rodríguez-Abreu, J.E. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari, and J.D. Spicer, for the KEYNOTE-671 Investigators*

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EGFR
ALK

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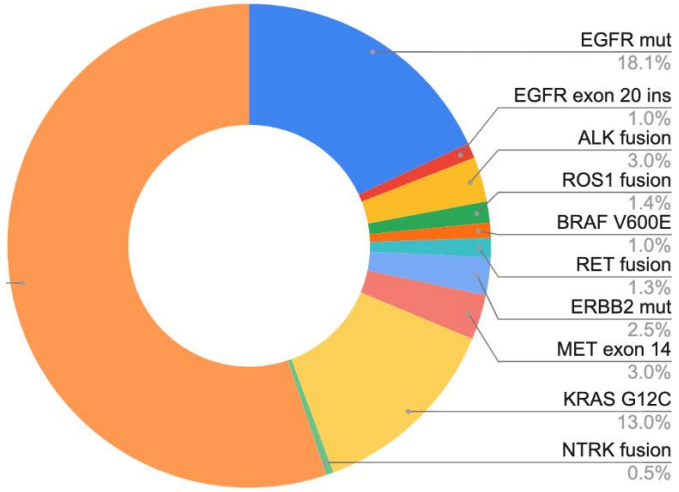
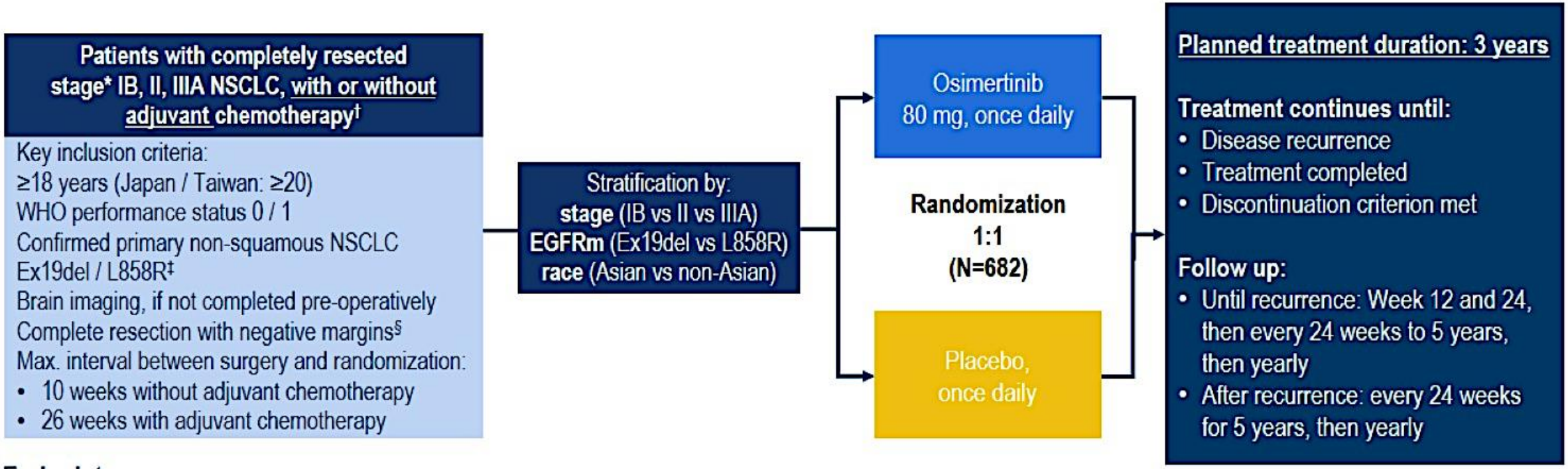


FOMO?

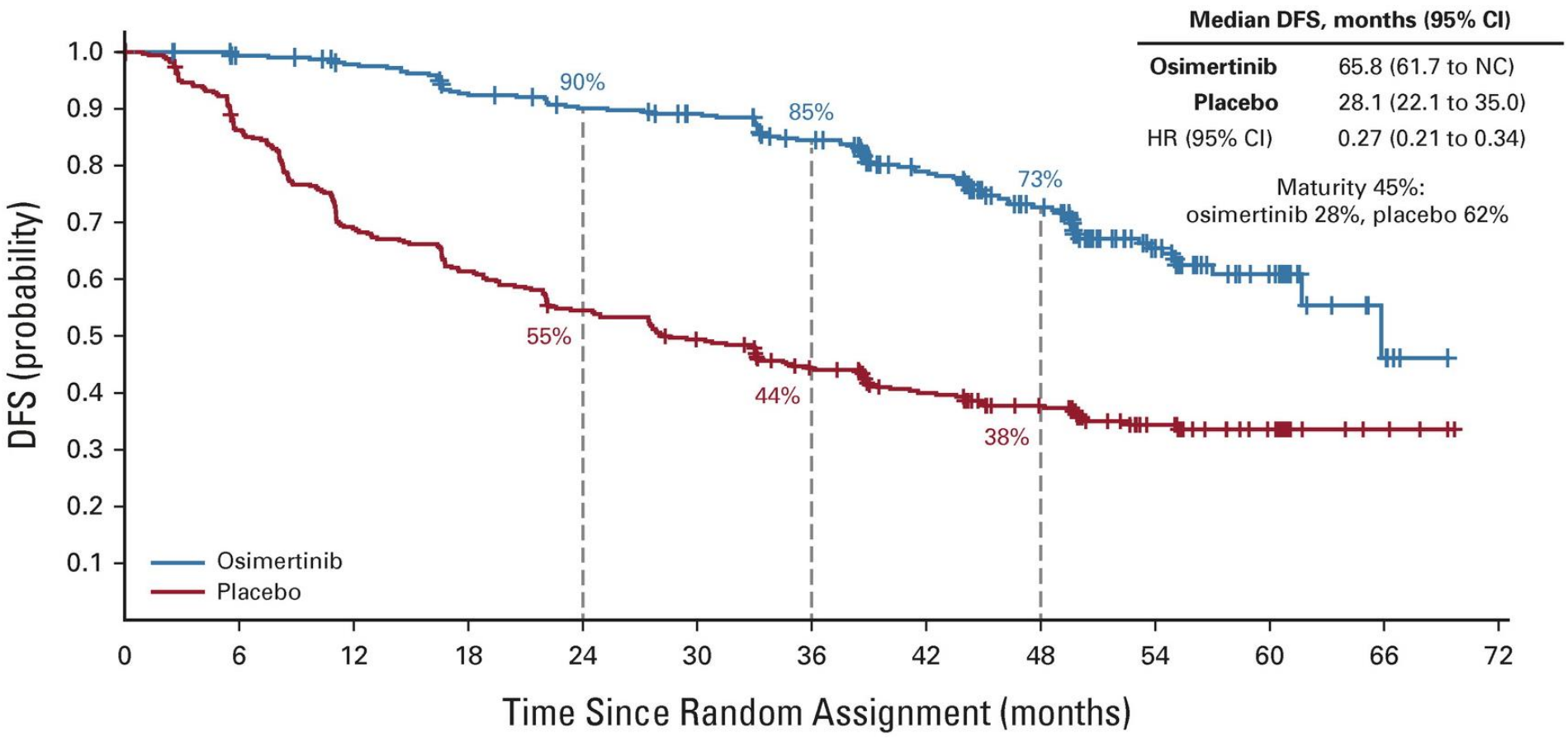
Evaluation of Adjuvant Osimertinib



Endpoints

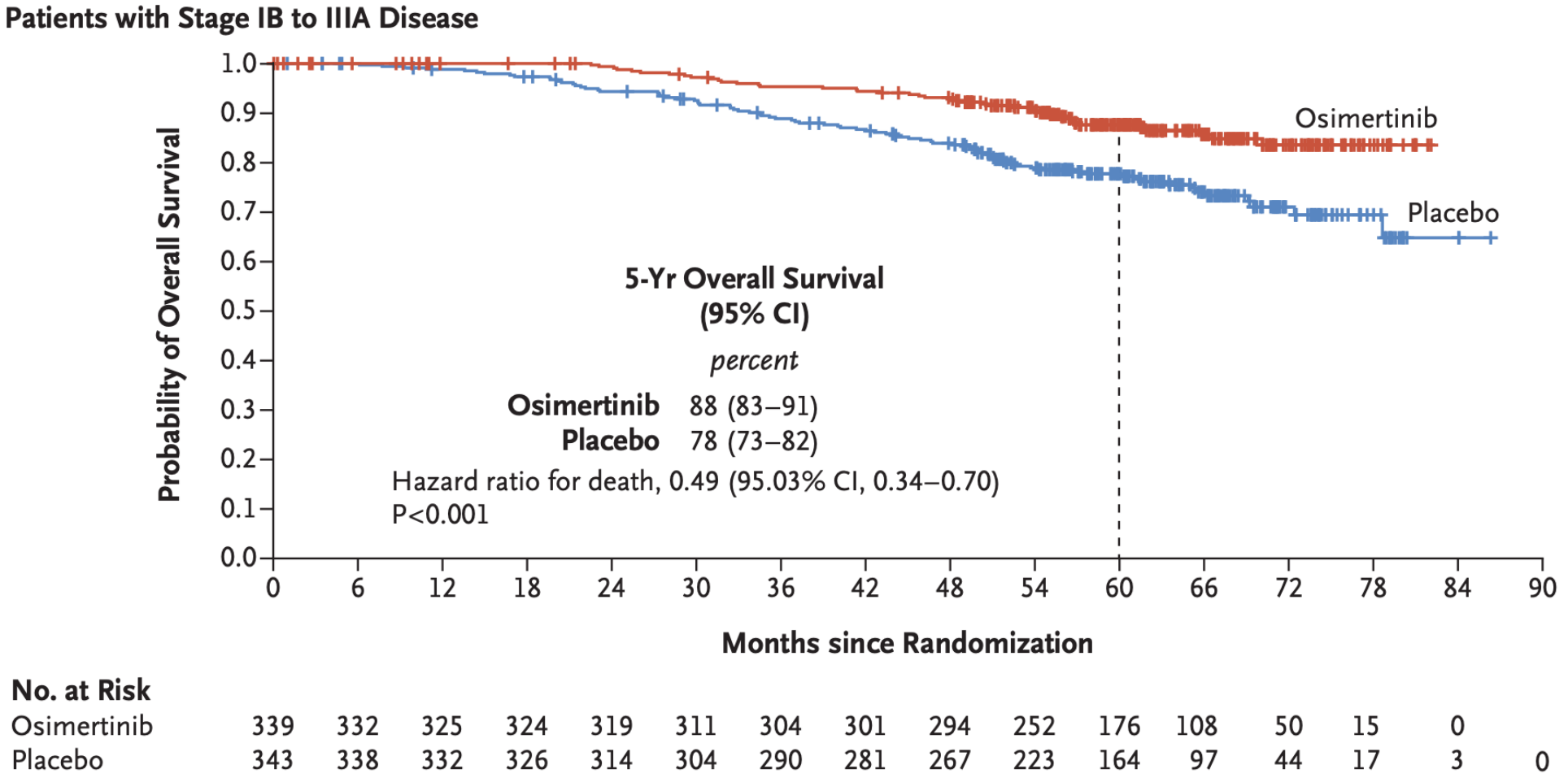
- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

3 years of osimertinib improves disease-free survival



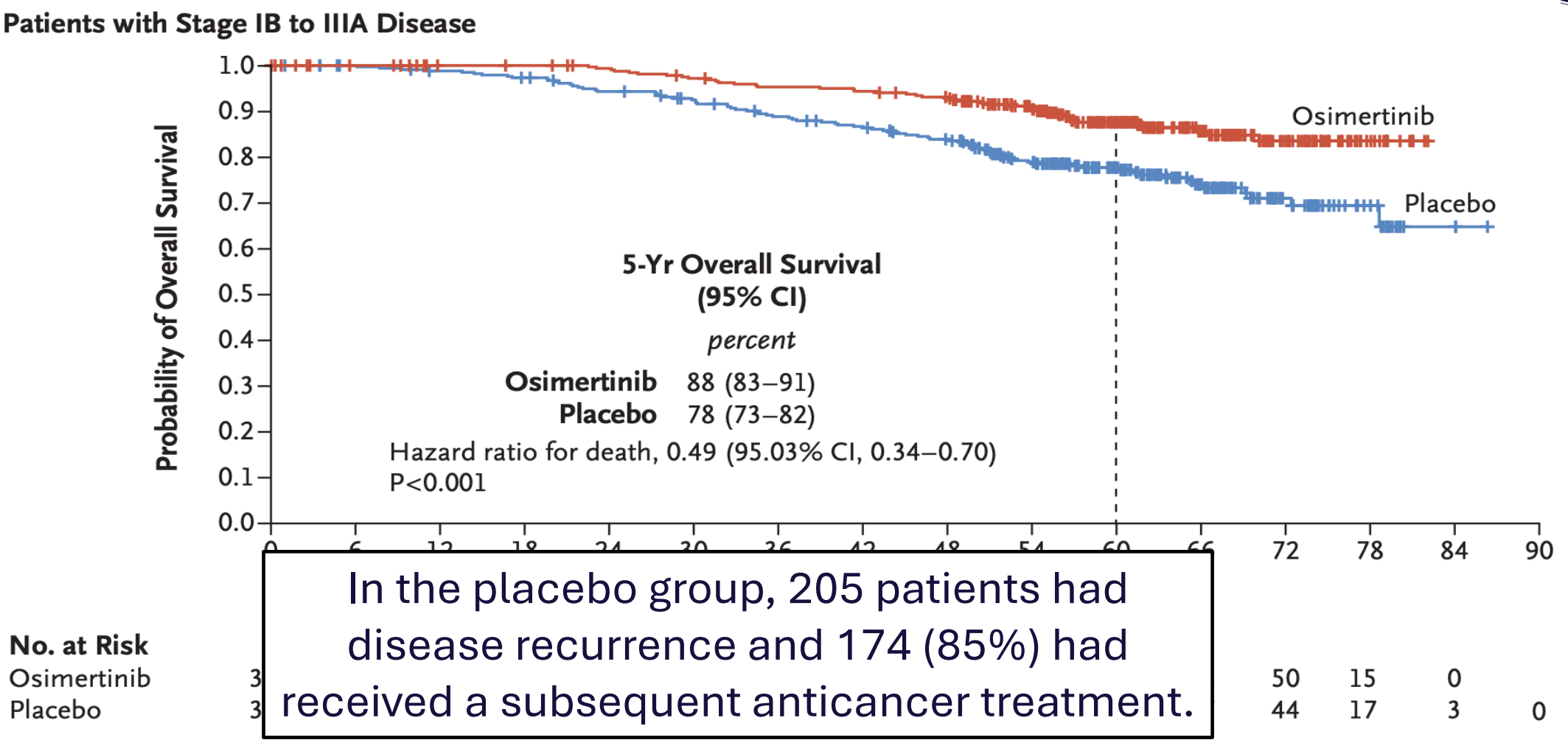
Herbst et al, JCO 2023

3 years of osimertinib improves survival



Tsuboi et al, NEJM 2023

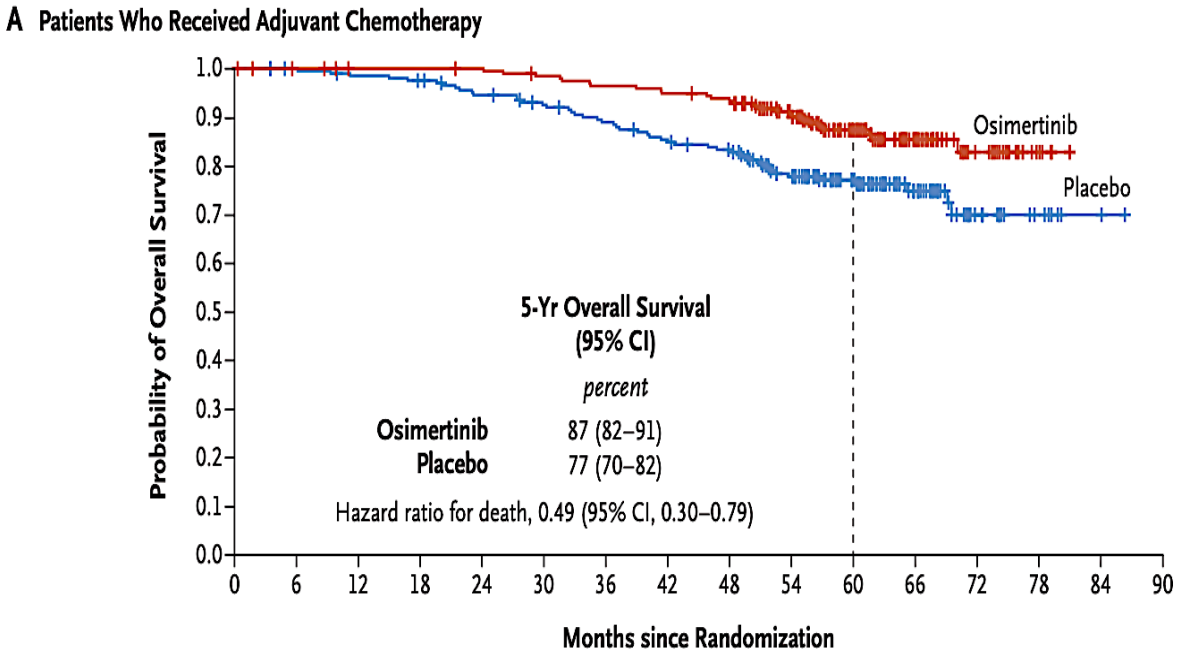
3 years of osimertinib improves survival

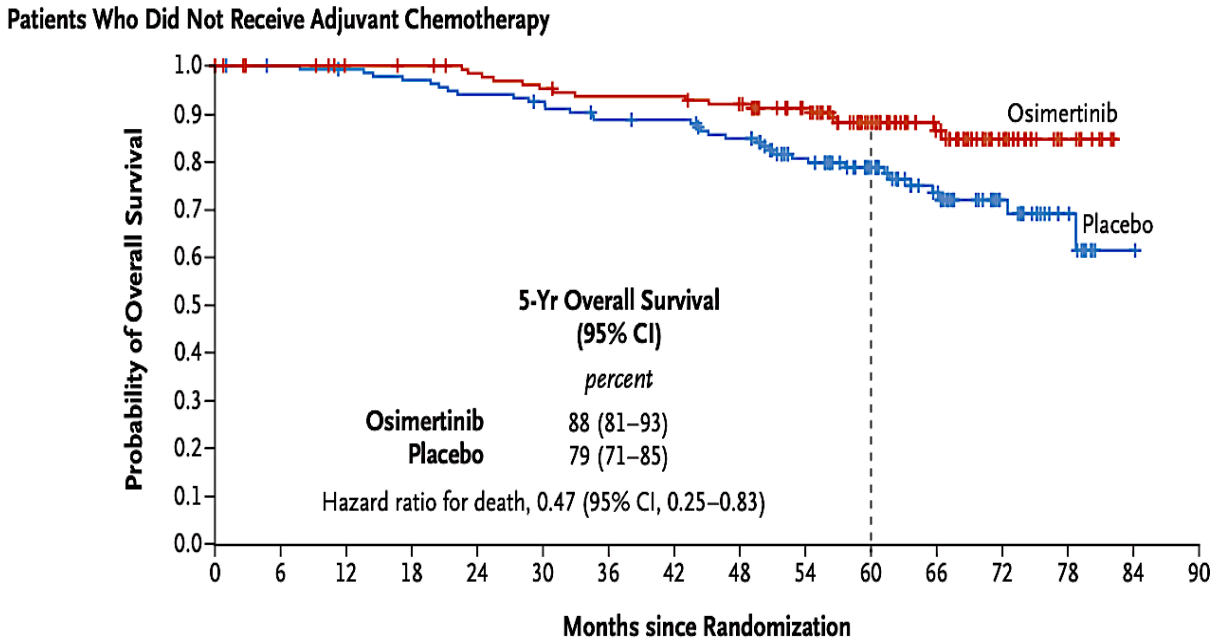


In the placebo group, 205 patients had disease recurrence and 174 (85%) had received a subsequent anticancer treatment.

Tsuboi et al, NEJM 2023

Do these patients still need chemo?





Tsuboi et al, NEJM 2023

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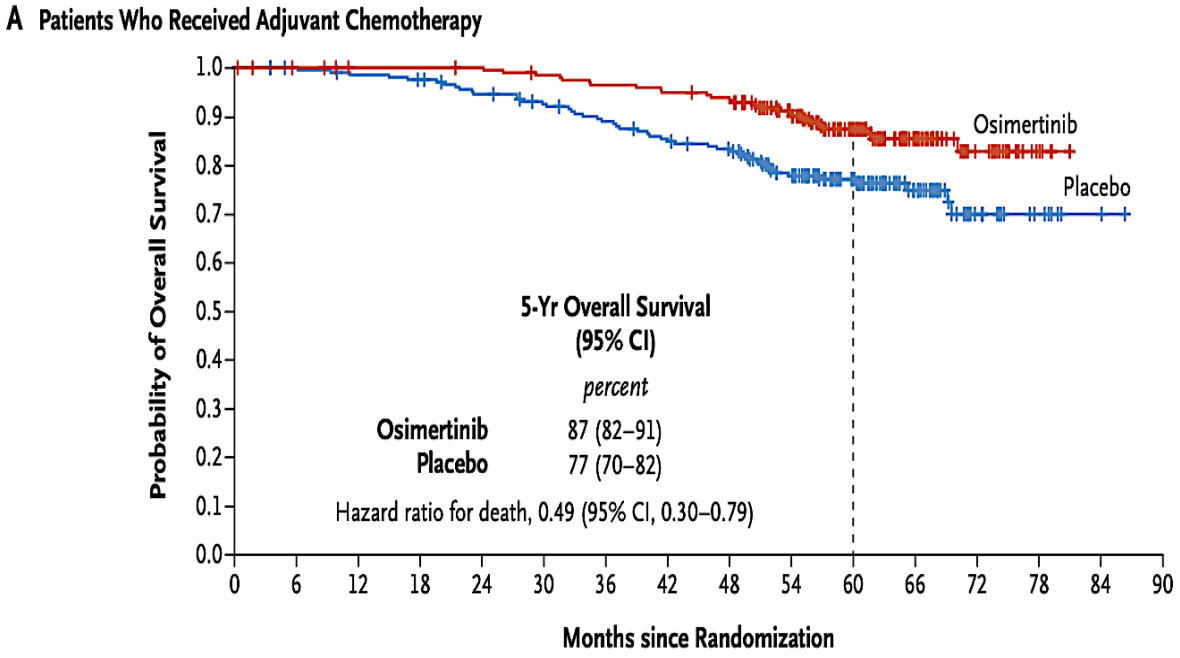
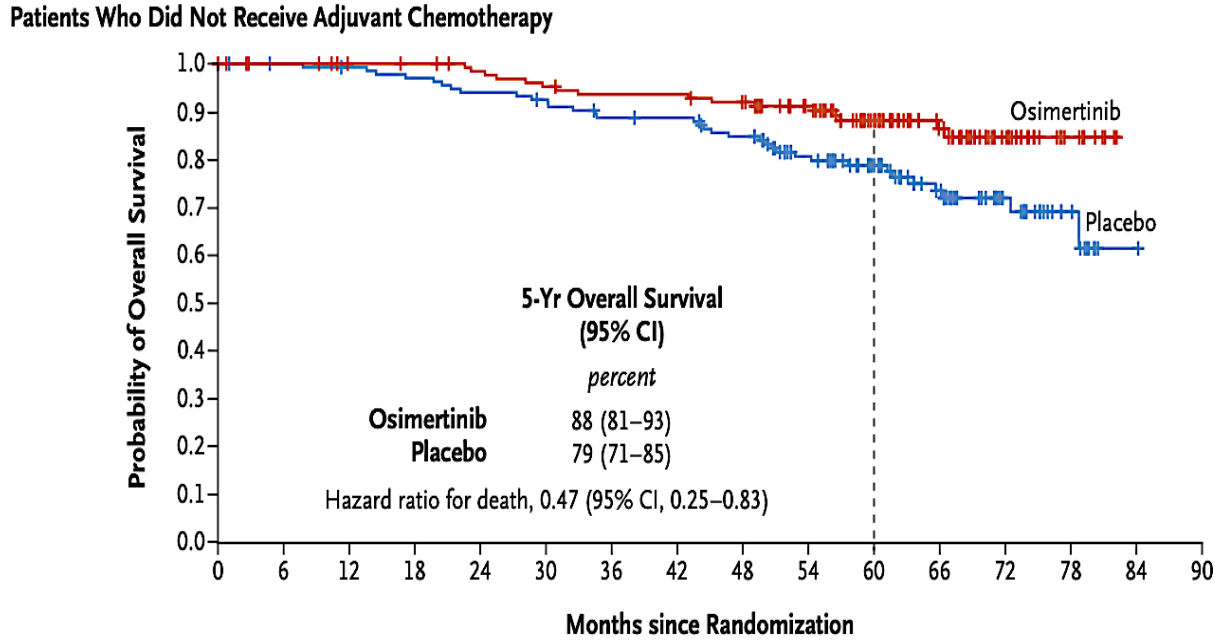




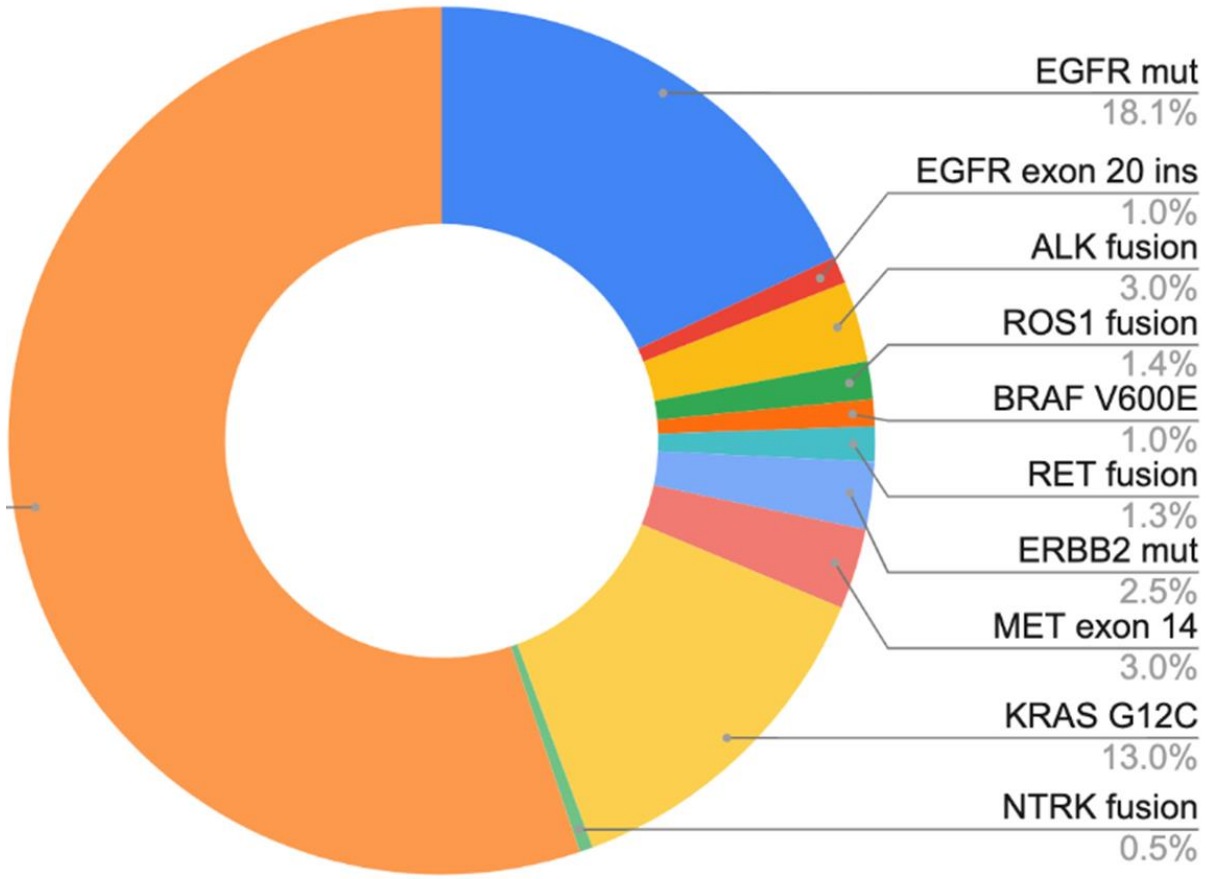
But, this is a mix of stages, so the “no chemotherapy” group, had more patients with Stage Ib

Tsuboi et al, NEJM 2023

Among patients with Stage II-III NSCLC…best survival comes in those who get chemo AND osimertinib

Treatment	5-year OS
No Chemotherapy/placebo	66%
Chemotherapy/placebo	75%
No Chemotherapy/ 3 yrs osimertinib	80%
Chemotherapy/3 yrs osimertinib	87%

From Supplementary Figure S4, Tsuboi et al, NEJM 2023



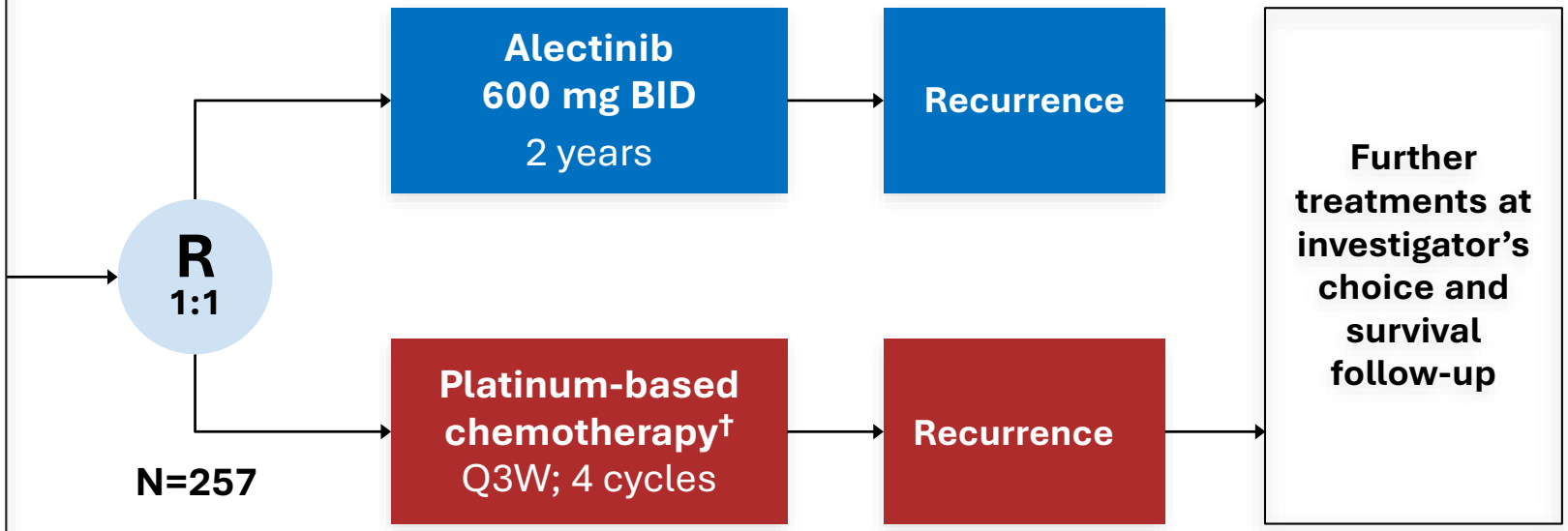
What about the other targets?

Evaluation of Adjuvant Alectinib

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

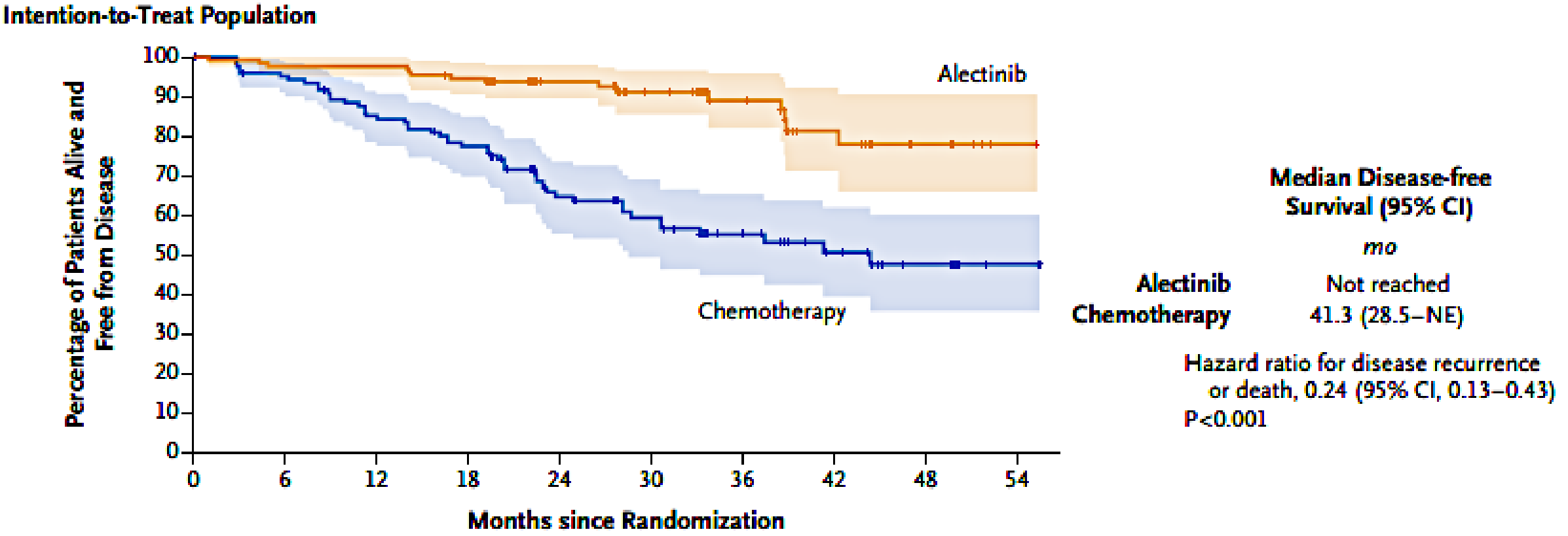


Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

False dichotomy!

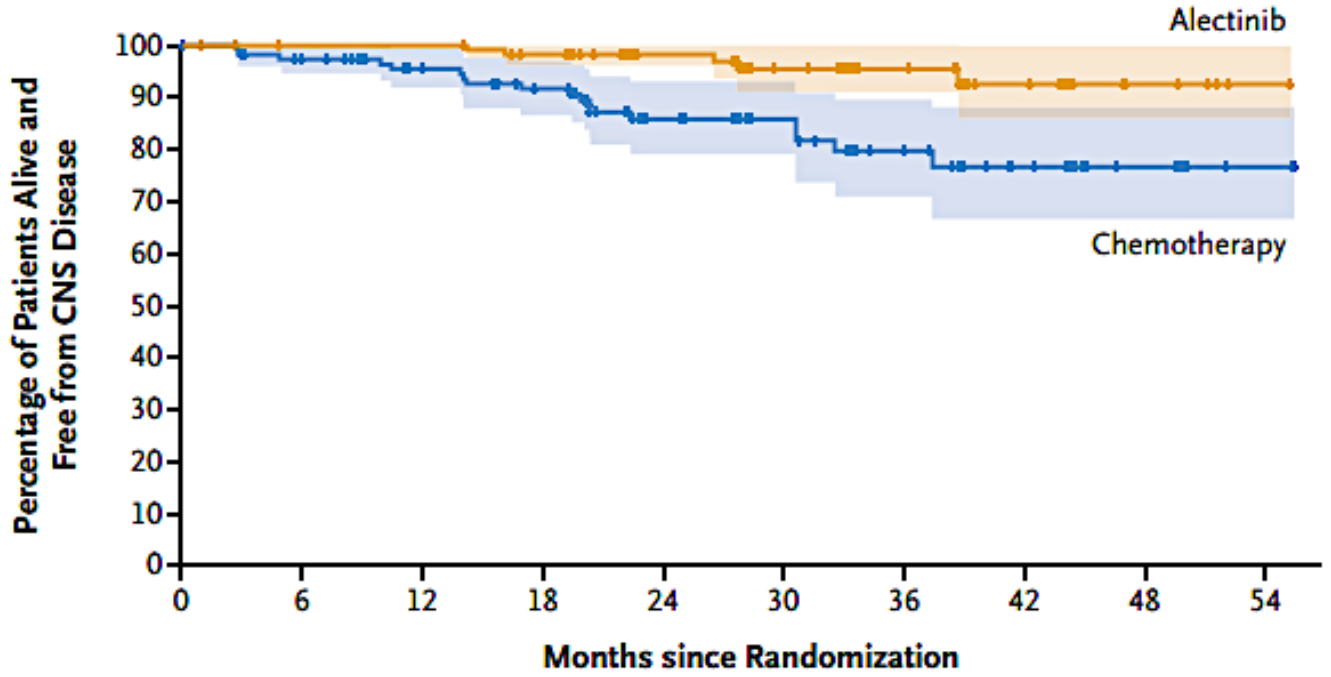
Wu et al, NEJM 2024

2 years of Alectinib improves disease-free survival



Wu et al, NEJM 2024

2 years of Alectinib improves CNS disease-free survival



No. at Risk										
Alectinib	130	124	124	118	74	55	39	22	10	3
Chemotherapy	127	113	98	90	57	43	27	18	11	2

CNS Disease–free Survival (95% CI) at 24 Months

percent

Alectinib	98.4 (96.1–100)
Chemotherapy	85.8 (78.8–92.8)

Hazard ratio for CNS disease recurrence or death, 0.22 (95% CI, 0.08–0.58)

Wu et al, NEJM 2024

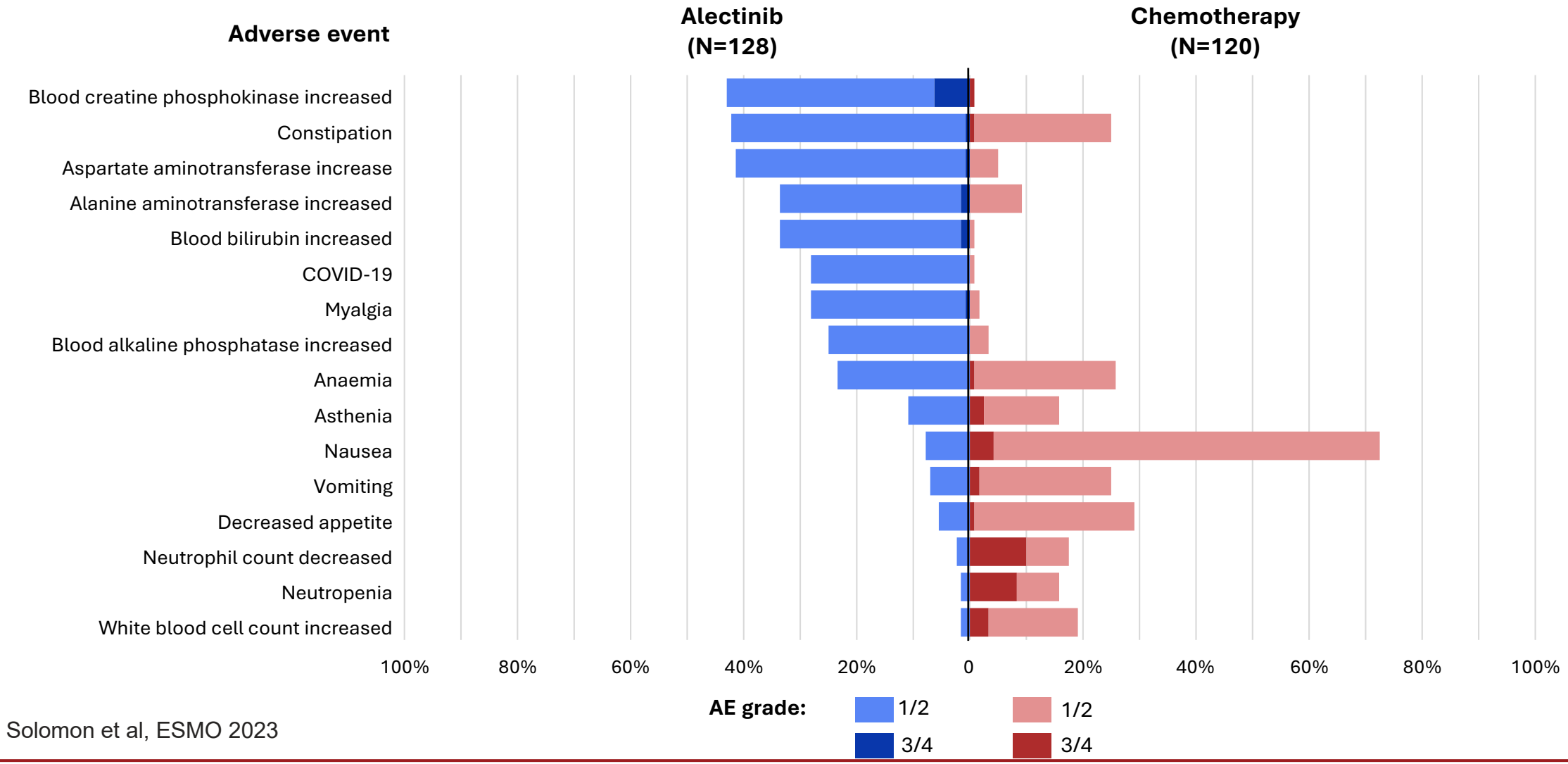
Adjuvant Alectinib: Adverse events

Table 2. Adverse Events Occurring in at Least 10% of Patients in Either Trial Group (Safety-Evaluable Population).*

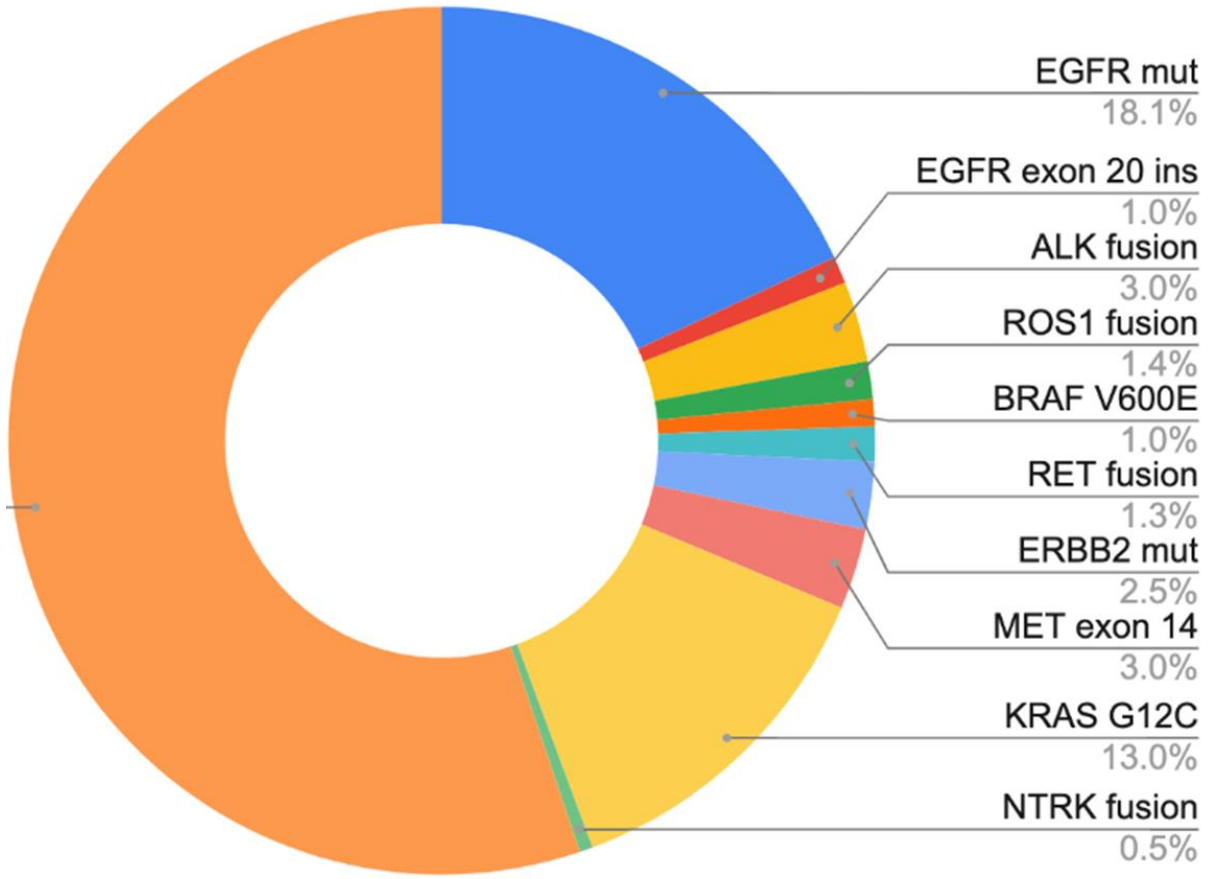
Adverse Event	Alectinib (N=128)		Chemotherapy (N=120)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	126 (98.4)	38 (29.7)	112 (93.3)	37 (30.8)
Nausea	10 (7.8)	0	87 (72.5)	5 (4.2)
Creatine kinase increased	55 (43.0)	8 (6.2)	1 (0.8)	1 (0.8)
Constipation	54 (42.2)	1 (0.8)	30 (25.0)	1 (0.8)
Aspartate aminotransferase increased	53 (41.4)	1 (0.8)	6 (5.0)	0
Alanine aminotransferase increased	43 (33.6)	2 (1.6)	11 (9.2)	0
Blood bilirubin increased	43 (33.6)	2 (1.6)	1 (0.8)	0
Decreased appetite	7 (5.5)	0	35 (29.2)	1 (0.8)
Covid-19	37 (28.9)	0	1 (0.8)	0
Myalgia	36 (28.1)	1 (0.8)	2 (1.7)	0
Anemia	30 (23.4)	0	31 (25.8)	1 (0.8)
Vomiting	9 (7.0)	0	30 (25.0)	2 (1.7)
Alkaline phosphatase increased	32 (25.0)	0	4 (3.3)	0
White-cell count decreased	2 (1.6)	0	23 (19.2)	4 (3.3)
Neutrophil count decreased	3 (2.3)	0	21 (17.5)	12 (10.0)
Asthenia	14 (10.9)	0	19 (15.8)	3 (2.5)
Neutropenia	2 (1.6)	0	19 (15.8)	10 (8.3)
Creatinine increased	19 (14.8)	1 (0.8)	6 (5.0)	0
Cough	19 (14.8)	1 (0.8)	4 (3.3)	0
Fatigue	18 (14.1)	1 (0.8)	16 (13.3)	2 (1.7)
Rash	18 (14.1)	1 (0.8)	7 (5.8)	0

Modified from Wu et al, NEJM 2024

Adjuvant Alectinib: Adverse events

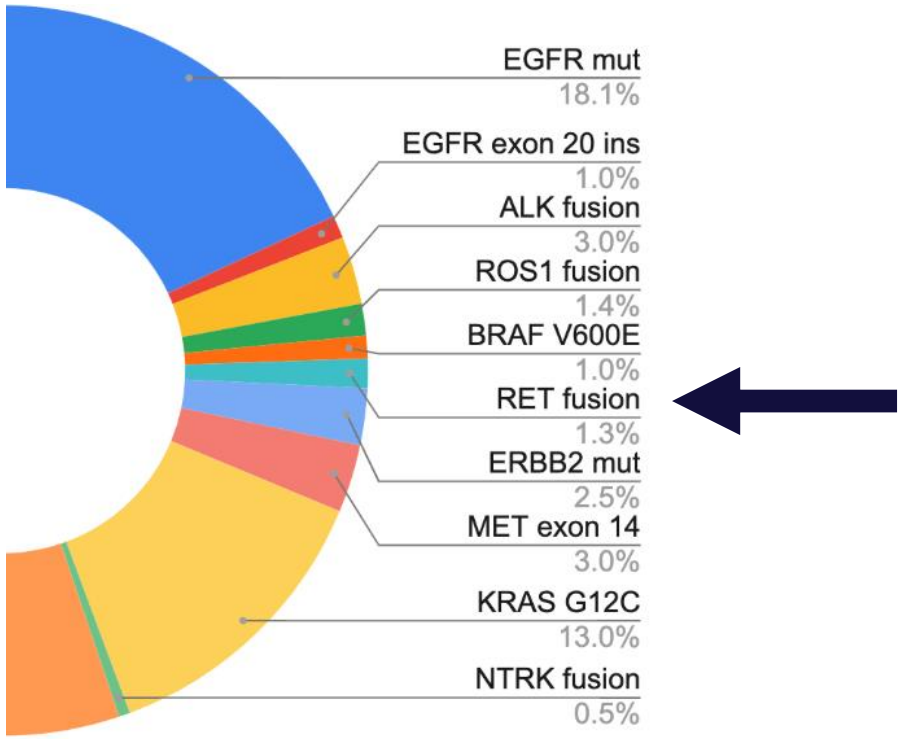


Solomon et al, ESMO 2023



What about the other targets?

RET positive NSCLC - selpercatinib



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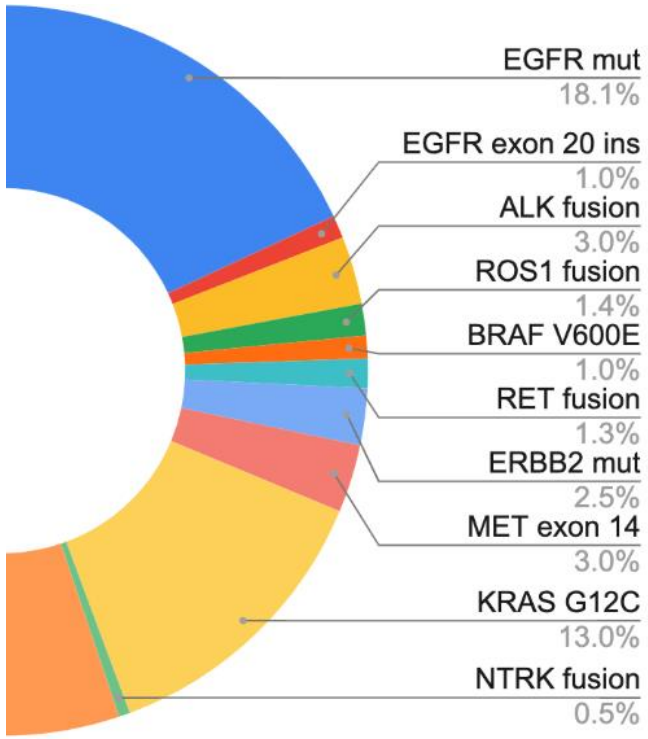
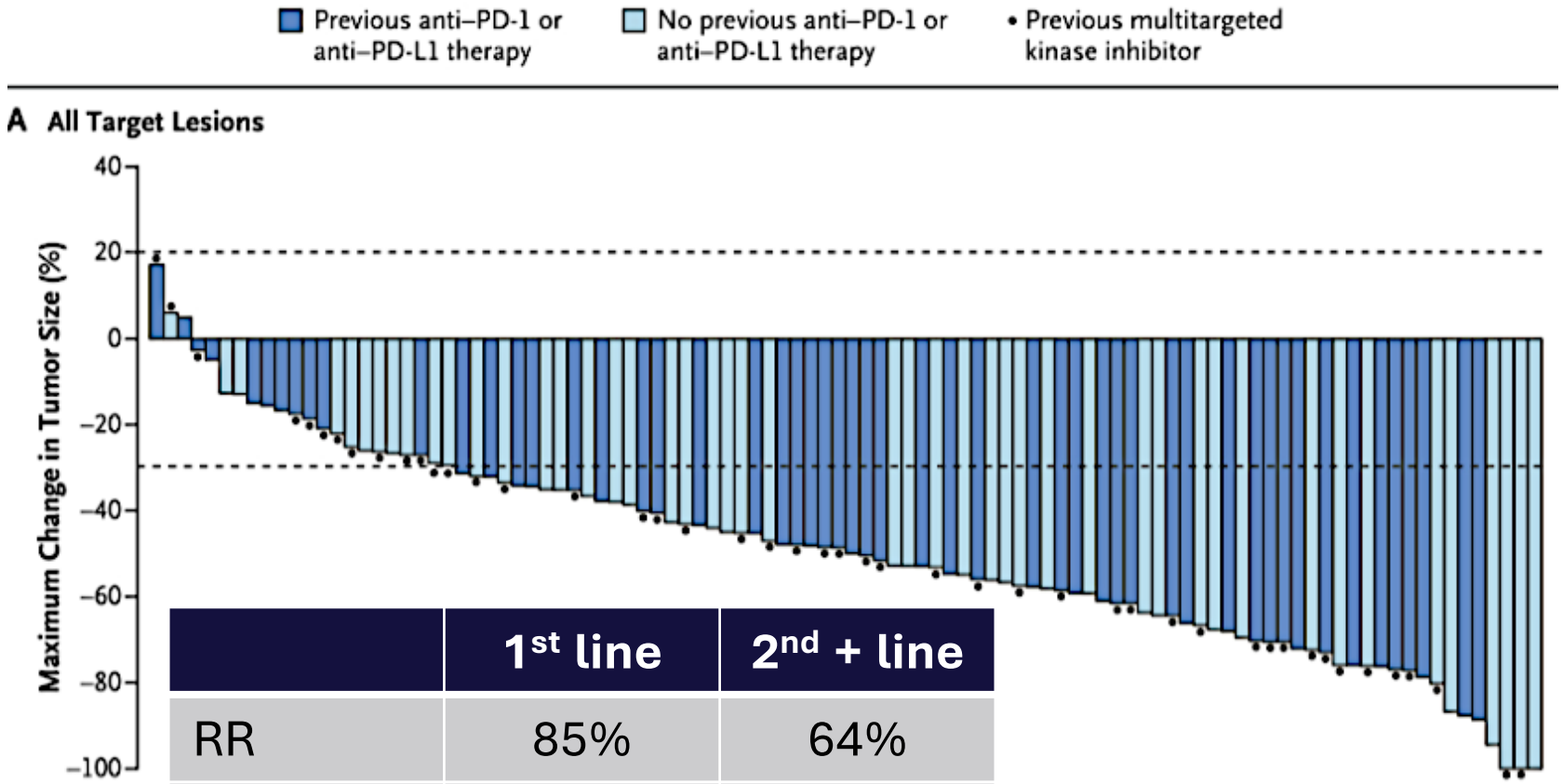
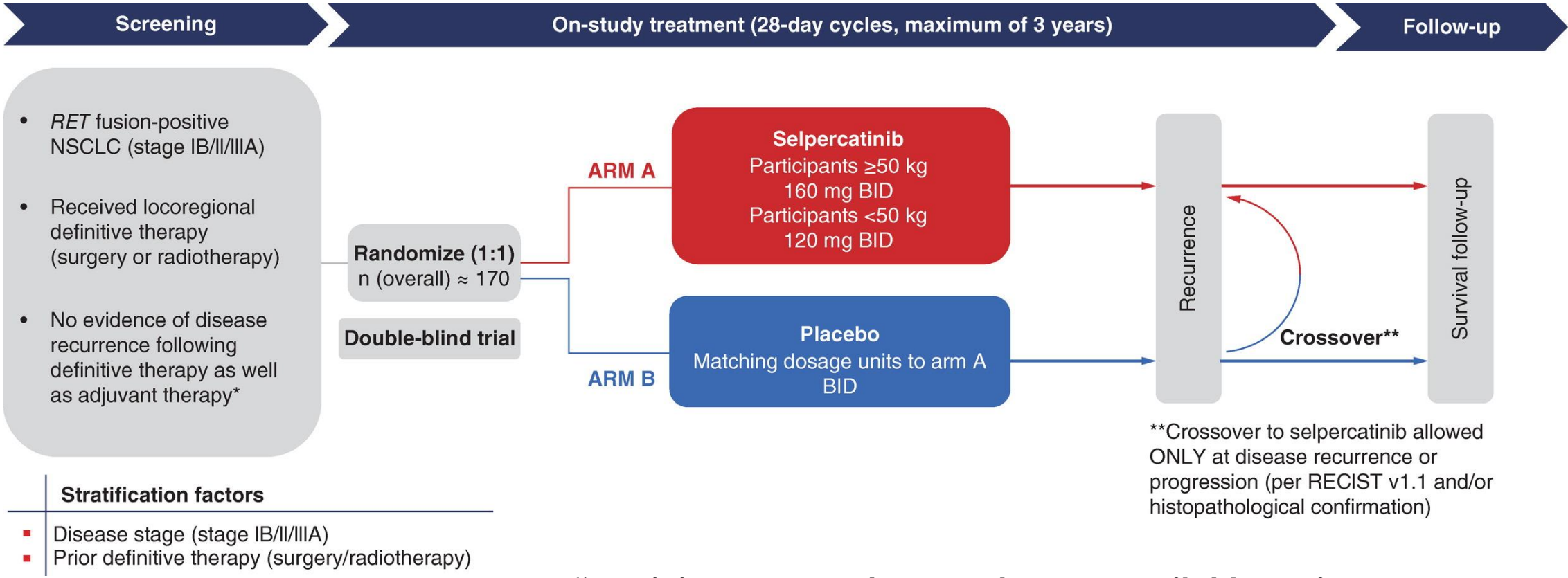


Drilon et al, NEJM 2020



	1st line	2nd + line
RR	85%	64%
mPFS	NE	17 mo

RET targeting in the adjuvant setting



"participants must have undergone available anti-cancer therapy (including chemotherapy or durvalumab) or not be suitable for it"

Tsuboi et al, Future Oncology 2022

Conclusions

- For patients with resected stage II-III, EGFR mutant NSCLC, 3 years of adjuvant osimertinib improves disease-free survival, CNS-disease-free survival, and overall survival for patients with resected stage II-III NSCLC.
- For patients with EGFR mutant NSCLC, outcomes are better if patients also receive chemotherapy.
- For patients with resected stage II-III ALK positive NSCLC, 2 years of adjuvant alectinib improves disease-free survival and CNS-disease-free survival.
- Years of therapy leads to years of toxicities

Open questions

- **How does chemotherapy contribute?**
- **When do we invest the patient resources in these trials?**
  - First in class or best in class?
  - After achieving some efficacy bar?
  - What about rare targets?
- **Do very early-stage patients benefit (i.e. stage IA)?**
- **How long should adjuvant therapy be given (2 years, 3 years, 5 years, forever)?**
- **How do we manage long-term toxicity in these patients?**