Adjuvant TKI Therapy in NSCLC

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Disclosures

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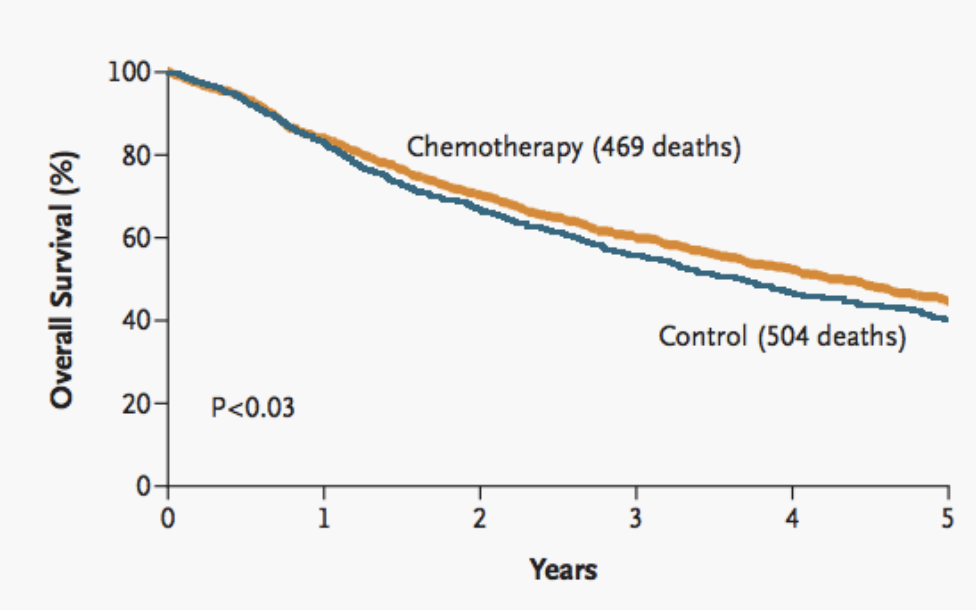
How have we learned to cure lung cancer?

Remove or Irradiate + Best Systemic Therapy

Implementation of adjuvant chemotherapy for patients with resected NSCLC

surgery → chemotherapy

After IALT, etc.
mid-2000's onward



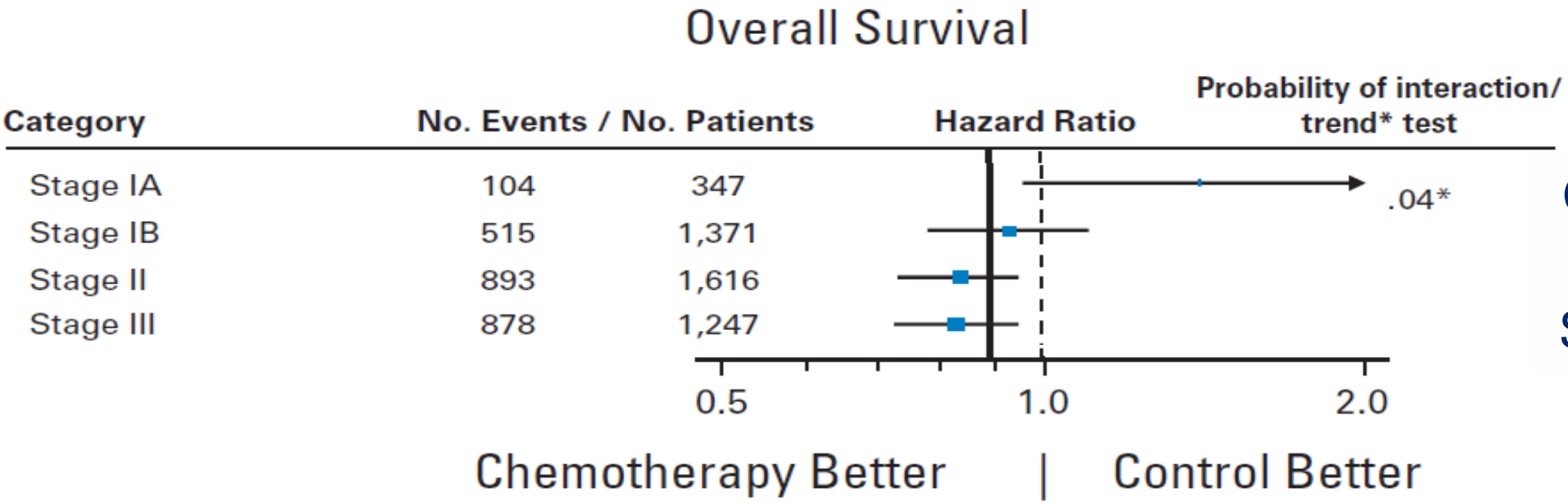
OS HR=0.86 p<0.03
DFS HR=0.83 p<0.003

Studies at this time gave:
cisplatin+ vinca alkaloids
or cisplatin + etoposide

IALT NEJM 2004

Adjuvant chemotherapy has clear benefits

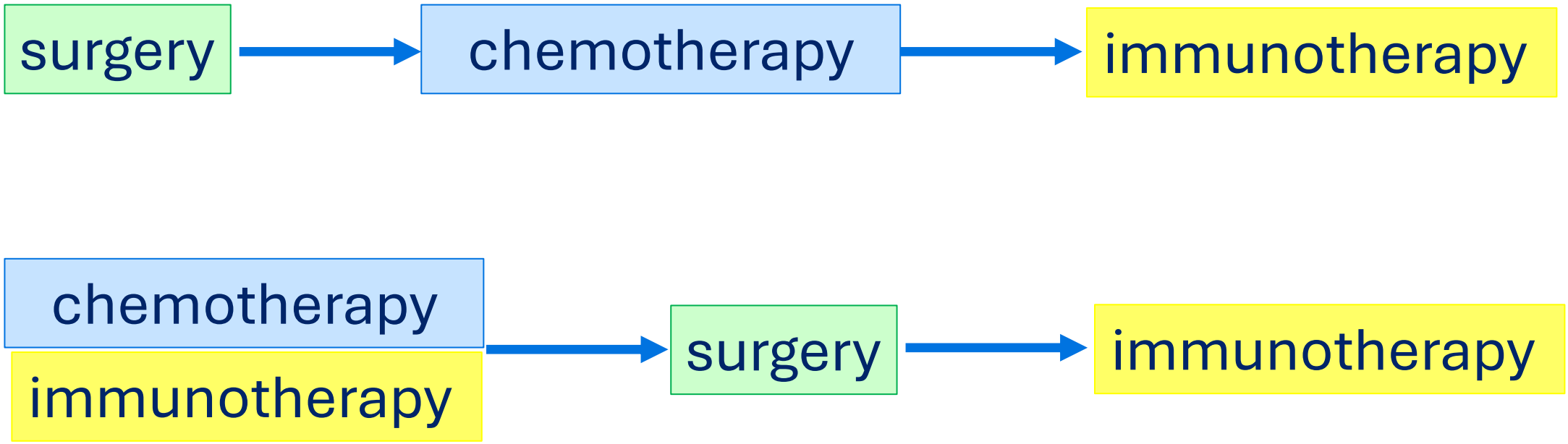
surgery → chemotherapy



Chemotherapy **useful** for Stages II and III

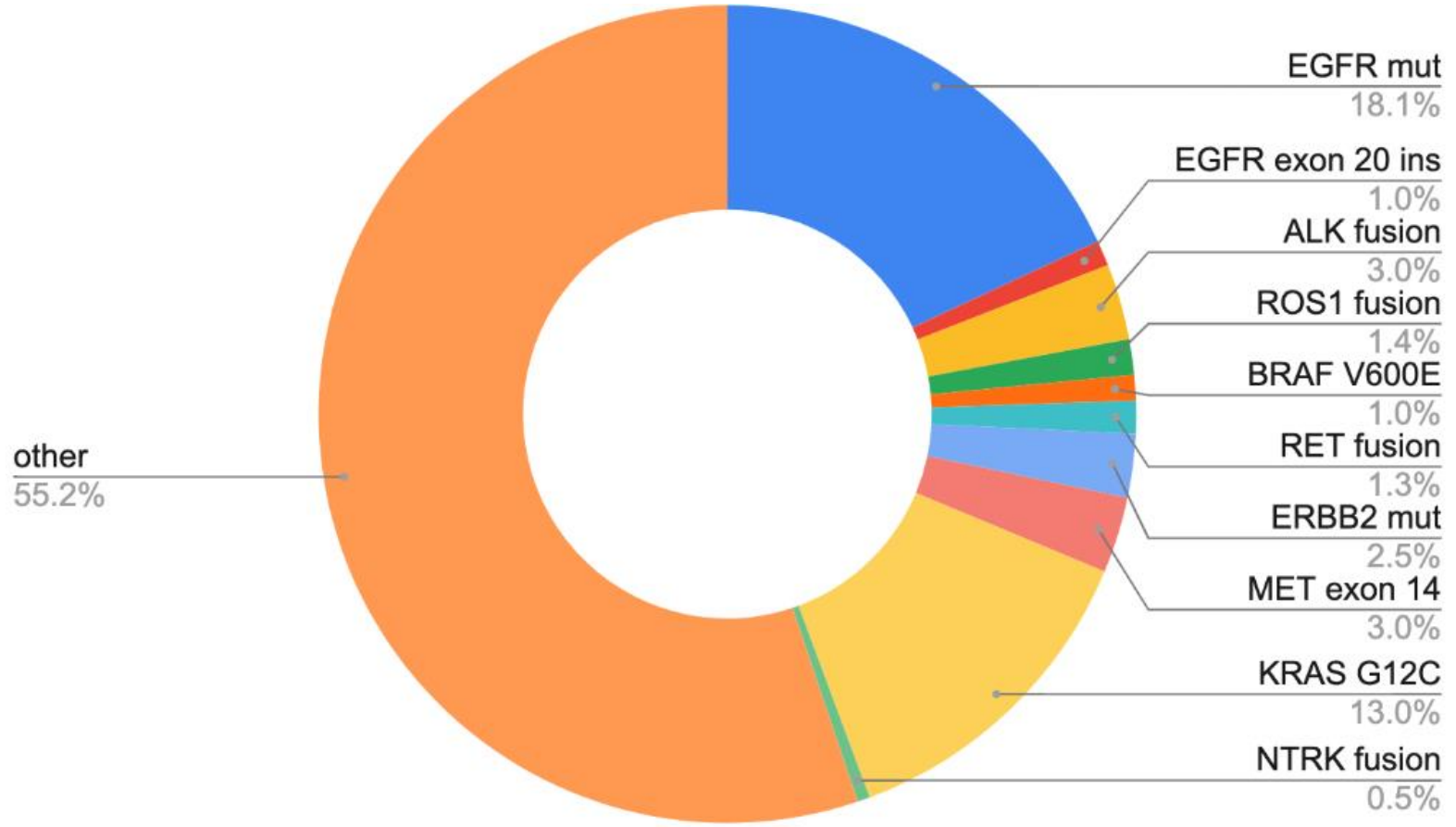
Modified from Pignon JP et al. J Clin Oncol 2008 Jul 20;26(21):3552-9

How do we treat early-stage NSCLC in 2024?



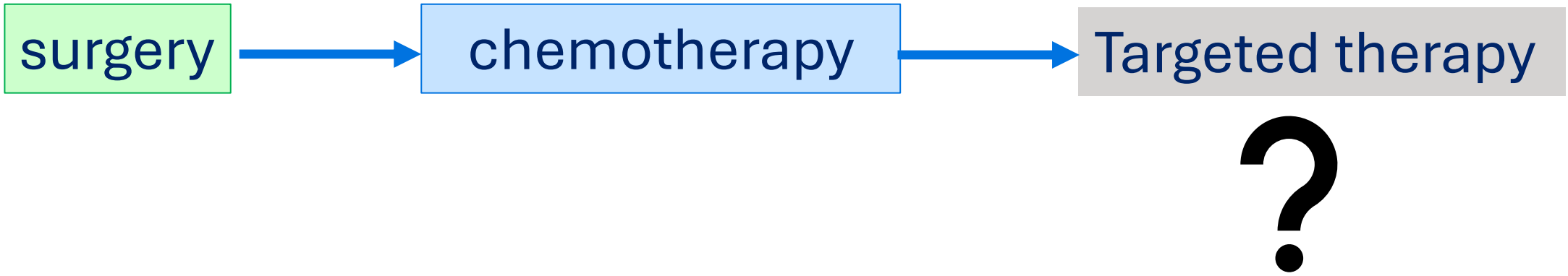
Is a combination of chemotherapy and immunotherapy the Best Systemic Therapy for all patients with NSCLC?

Lung cancer molecular subtypes with FDA-approved agents



AACR GENIE BPC lung, Choudhury et al, CCR 2023;
Data available at https://genie.cbioportal.org/

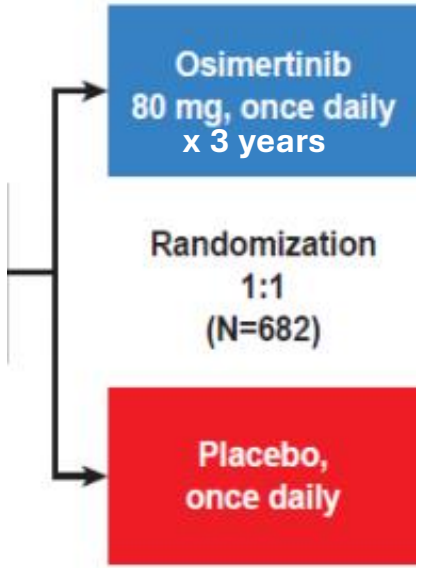
How do we treat early-stage NSCLC?



Phase III trial of adjuvant osimertinib

3rd generation EGFR TKI

Patients with:
- Completely resected IB-IIIA NSCLC
- EGFR exon 19 del or L858R
- With or without adjuvant chemotherapy
- <10 weeks from surgery (if no chemo)
- <26 weeks from surgery (if adjuvant chemo)

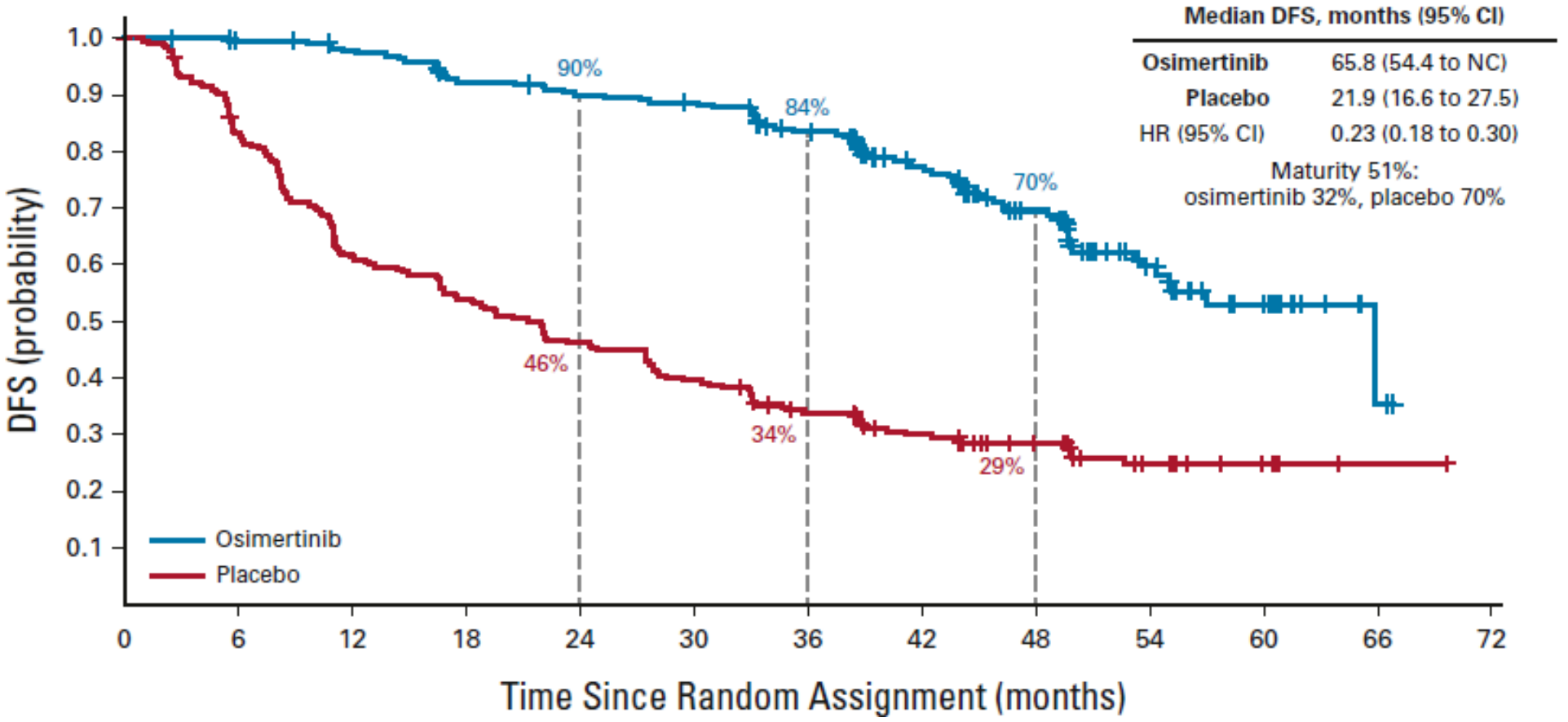


Primary endpoint:
disease free survival
in stage II-III

76% of stage II-II
26% of stage IB
} received chemo

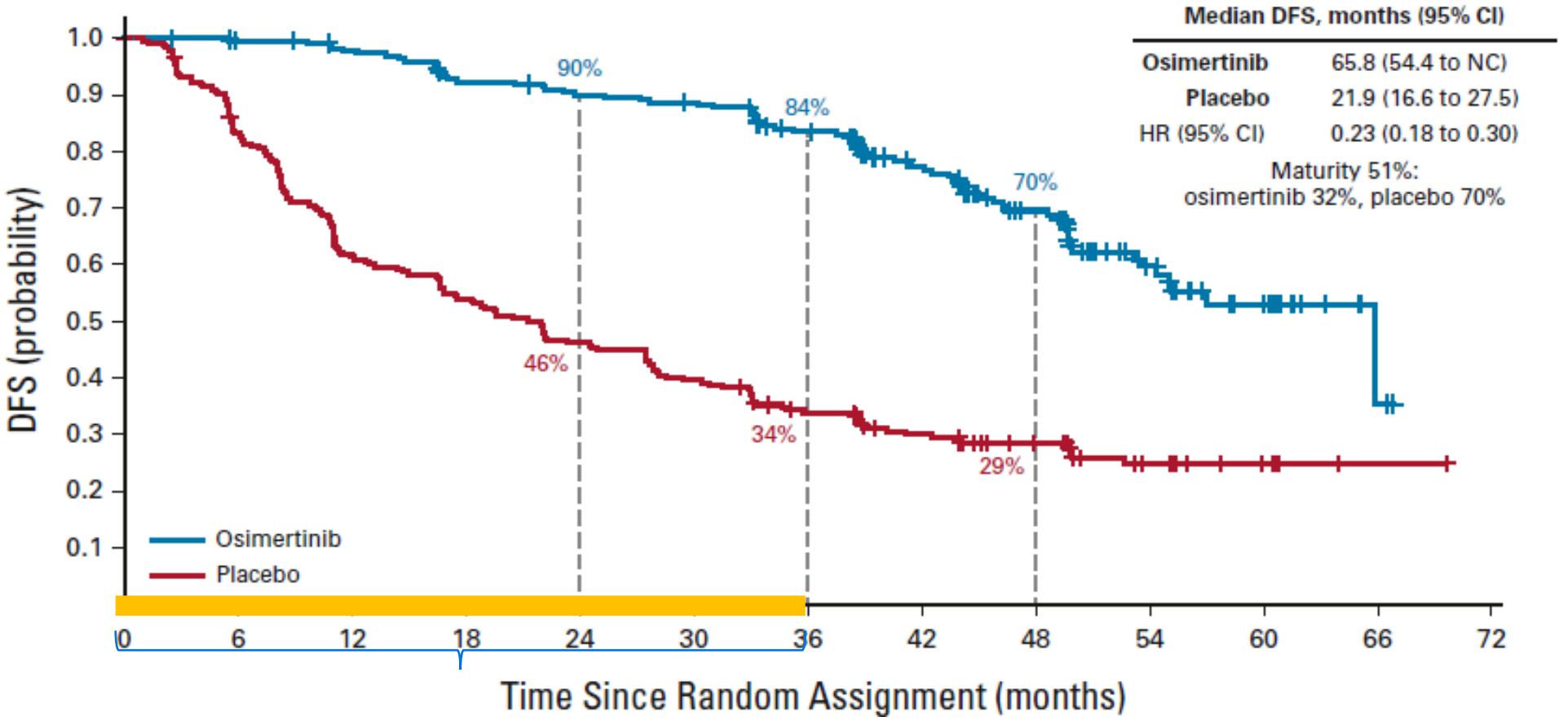
Modified from Wu et al NEJM 2020

DFS for Adjuvant Osimertinib (Stage II/IIa)



Herbst et al, JCO 2023

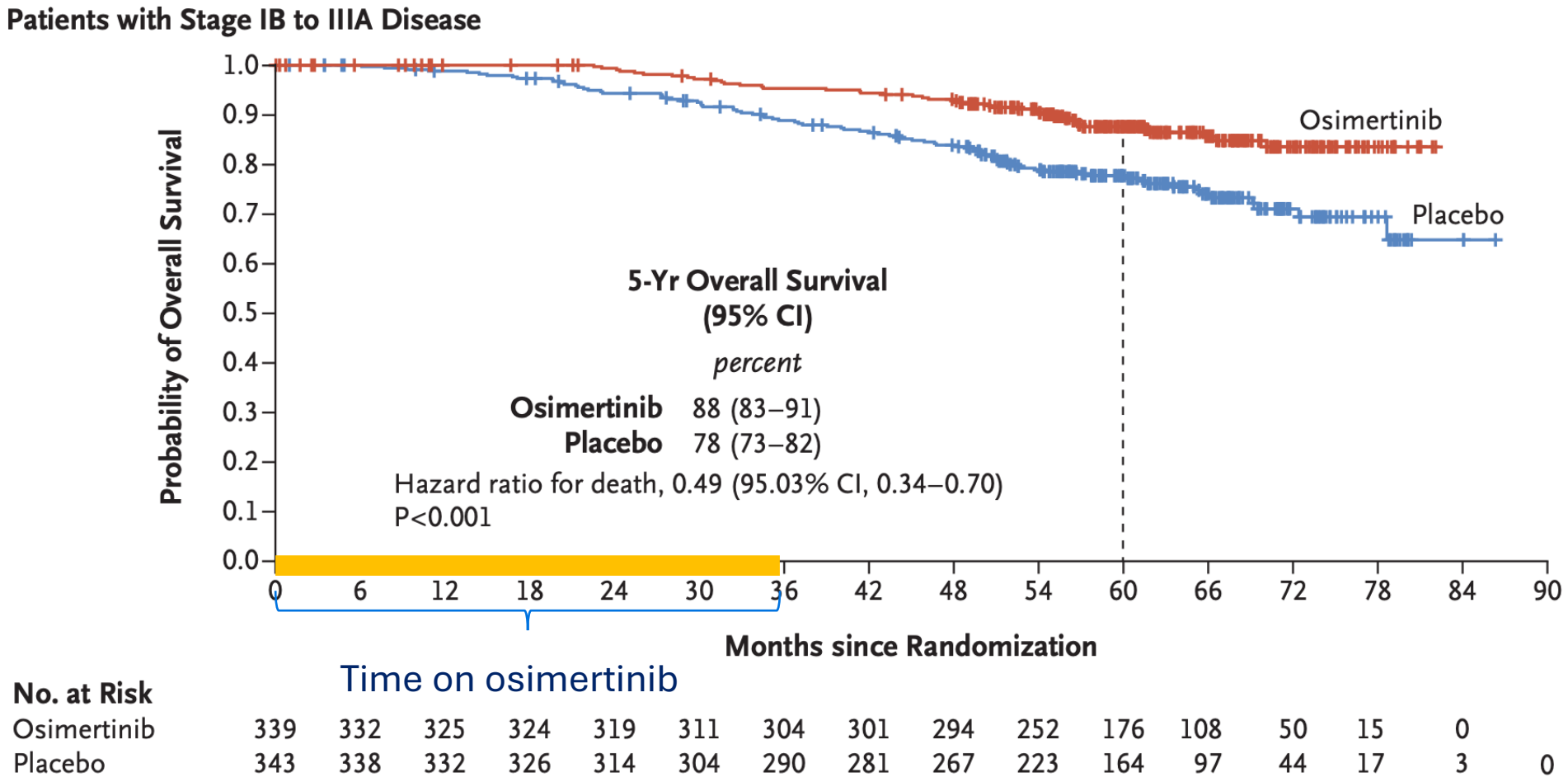
DFS for Adjuvant Osimertinib (Stage II/IIa)



Time on osimertinib
(for osimertinib arm)

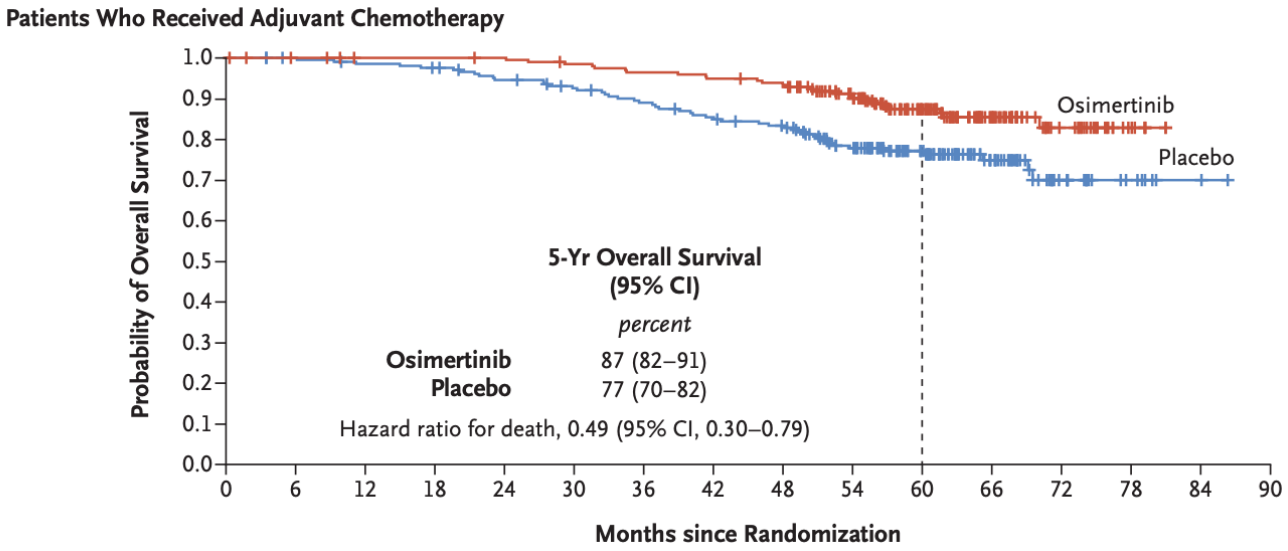
Herbst et al, JCO 2023

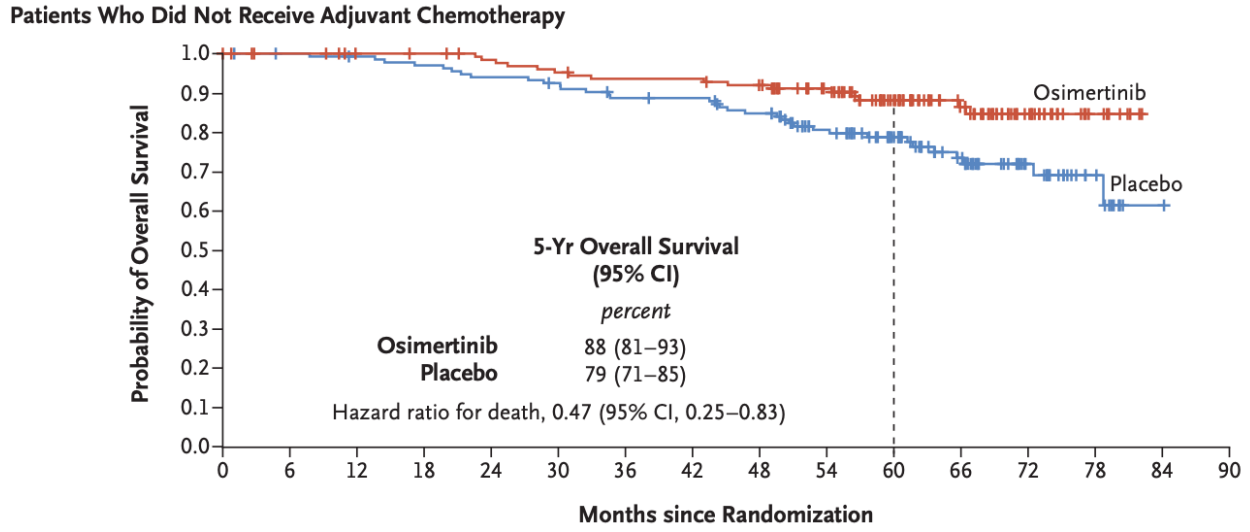
Three Years of Osimertinib Improves Survival



Tsuboi M, et al NEJM 2023

Do These Patients Still Need Chemo?





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

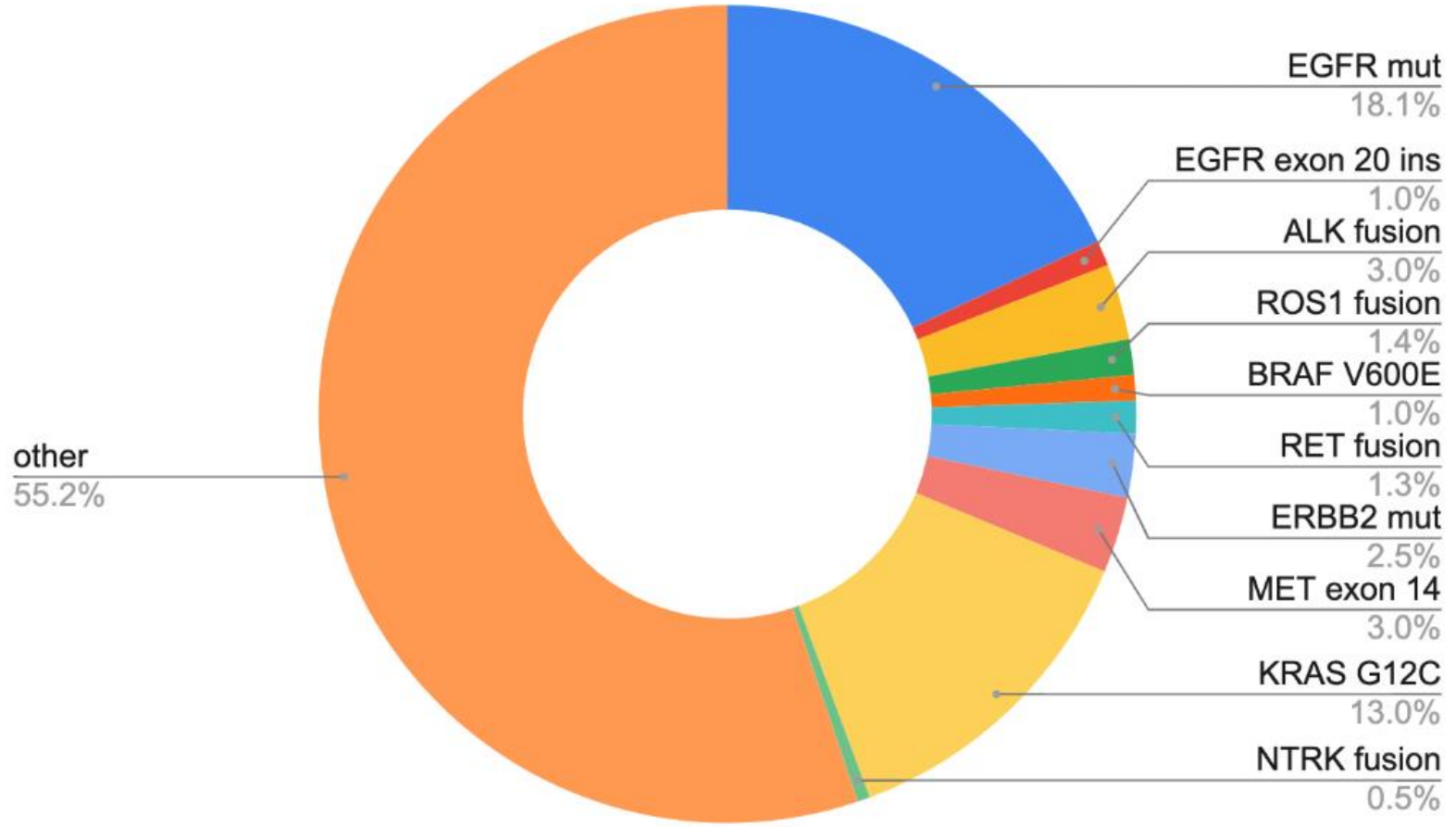
Tsuboi M, et al NEJM 2023

Among Patients with Stage II-III NSCLC

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

Tsuboi M, et al NEJM 2023

Lung cancer molecular subtypes with FDA-approved agents



AACR GENIE BPC lung, Choudhury et al, CCR 2023;
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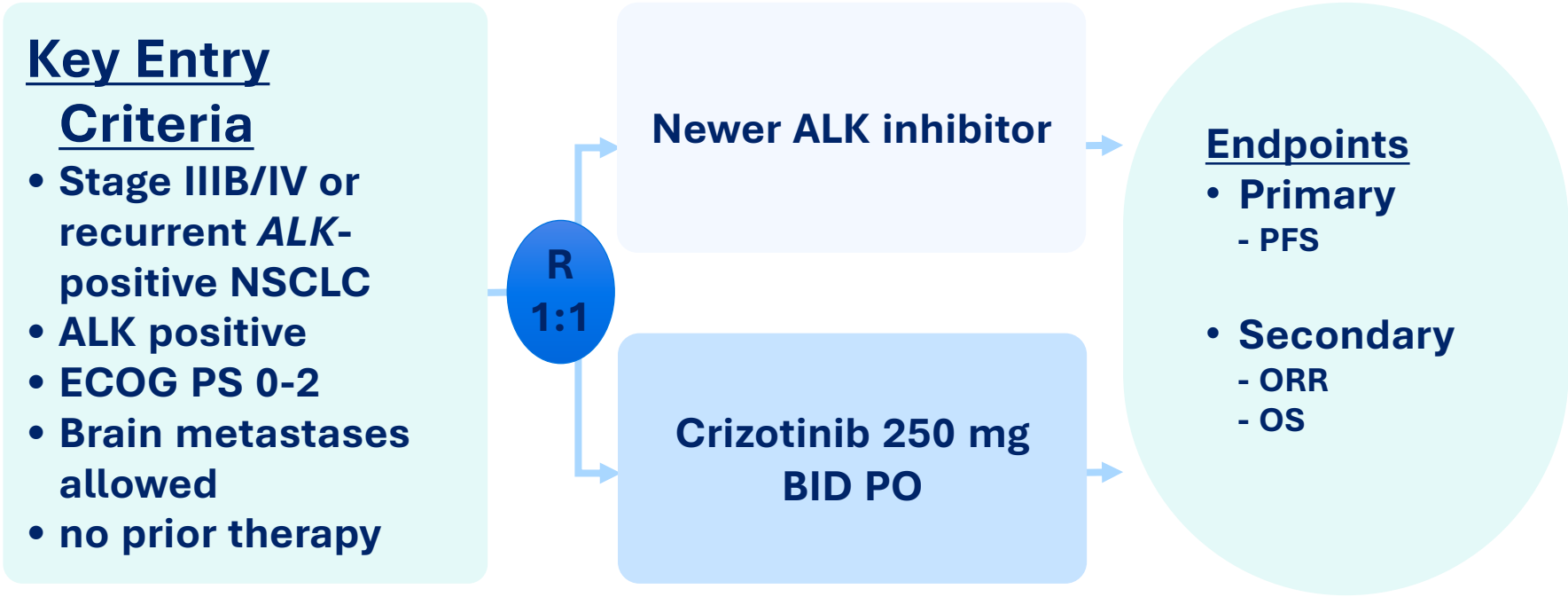
Evaluating Newer ALK inhbitors in ALK+ NSCLC

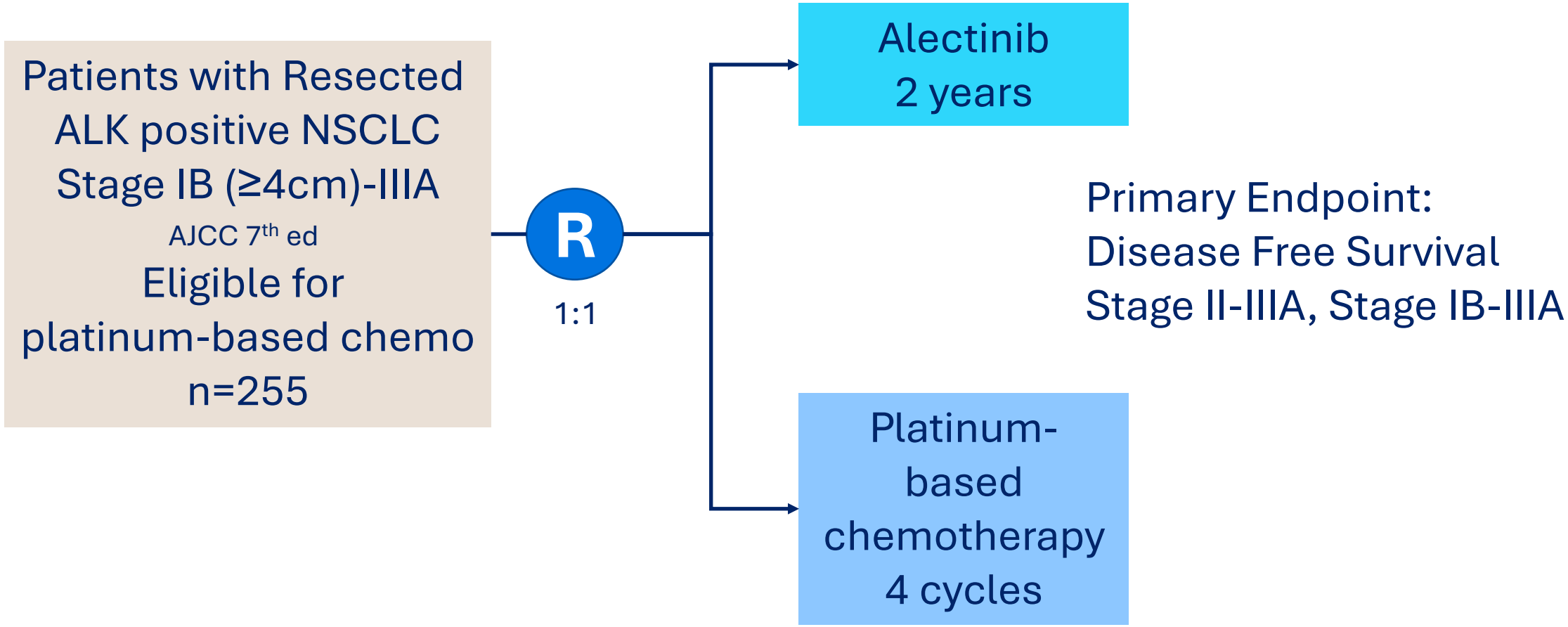


Comparing newer ALK inhibitors in ALK+ NSCLC

	RR (vs crizotinib)	12 month PFS (vs crizotinib)	PFS HR
Alectinib	83% vs 76%*	68% vs 49%	0.47
Brigatinib	71% vs 60%	67% vs 43%	0.49
Lorlatinib	76% vs 58%	78% vs 59%	0.28

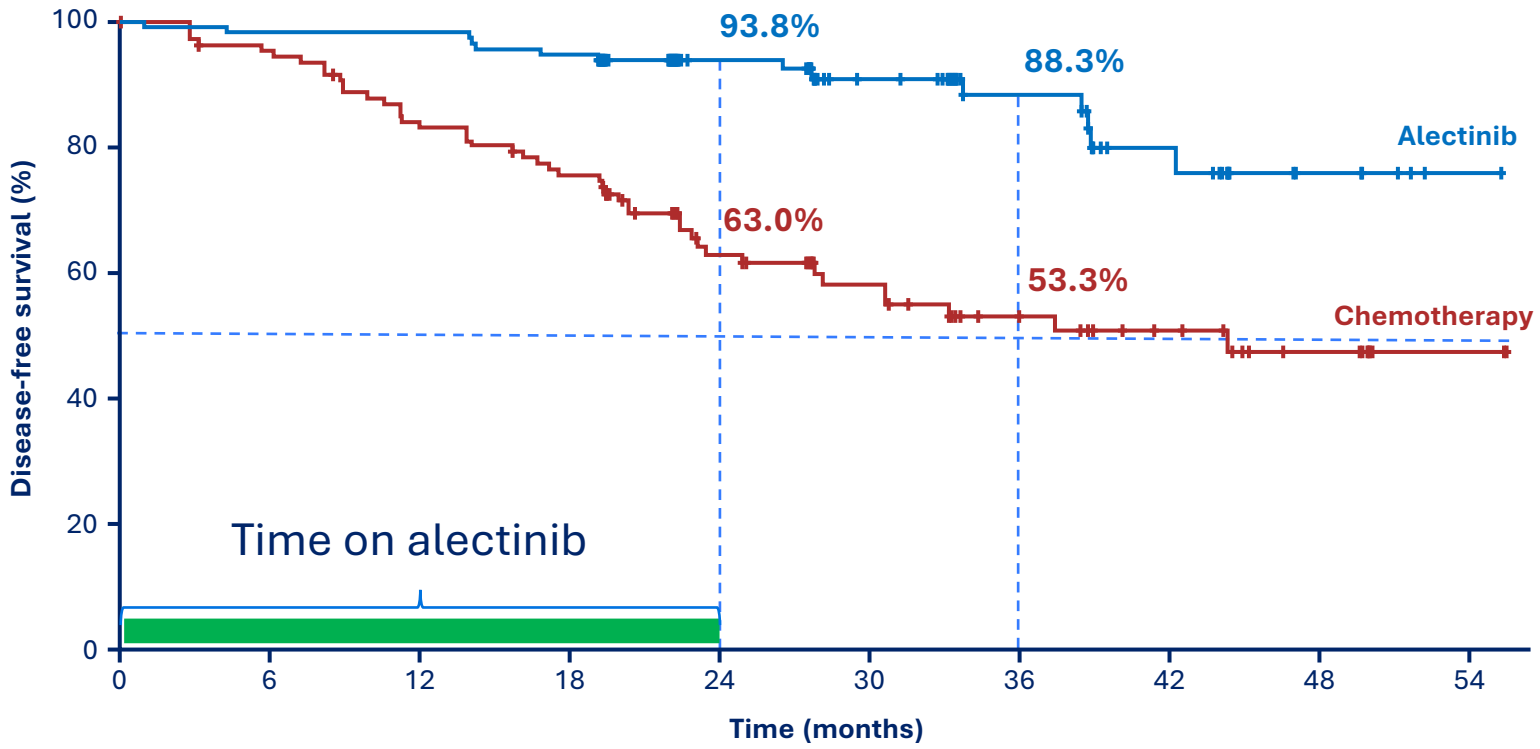
*confirmed objective response rate not reported

Exploring ALK inhibition in early-stage disease



Solomon et al, ESMO 2023

Alectinib vs Chemotherapy in Resected NSCLC
Disease-free survival: stage II–IIIA



No. at risk

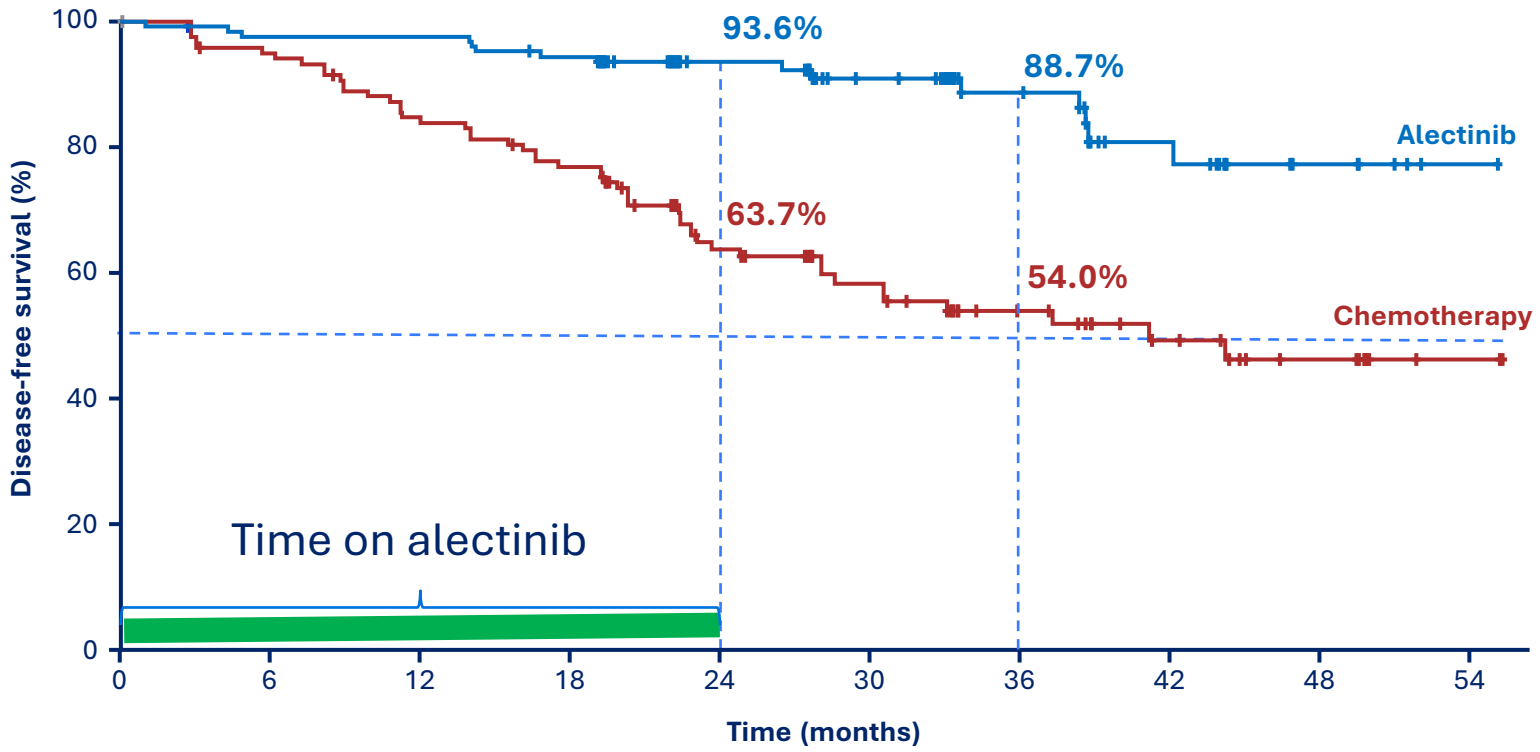
Alectinib	116	111	111	107	67	49	35	21	10	3
Chemo	115	102	88	79	48	35	23	17	10	2

	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

Modified from Solomon et al, ESMO 2023

Alectinib vs Chemotherapy in Resected NSCLC Disease-free survival: ITT (stage IB–IIIA)



No. at risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemo	127	112	98	89	55	41	27	18	11	2

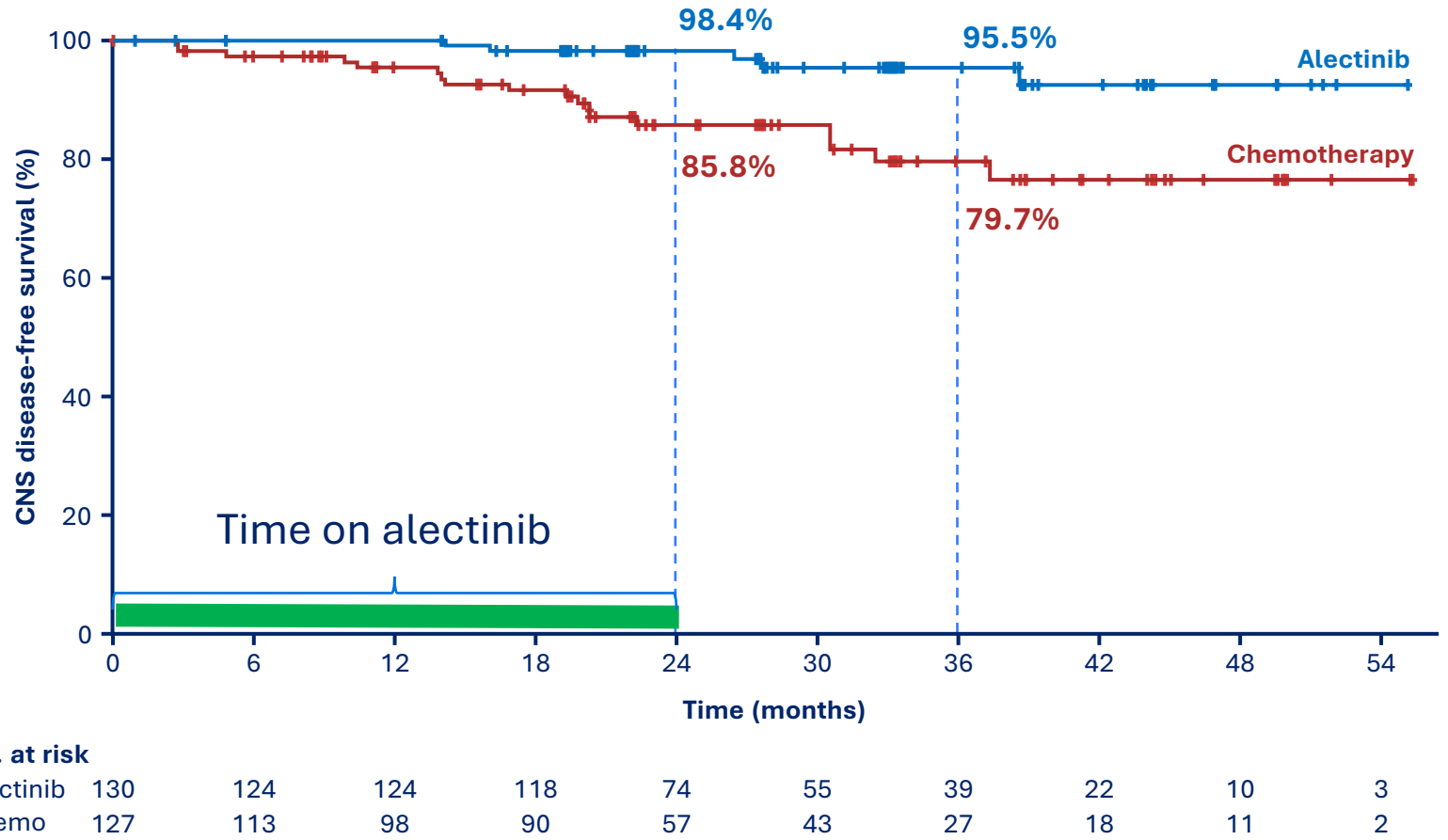
	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported‡

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Modified from Solomon et al, ESMO 2023

Alectinib vs Chemotherapy in Resected NSCLC
CNS disease-free survival in the ITT population

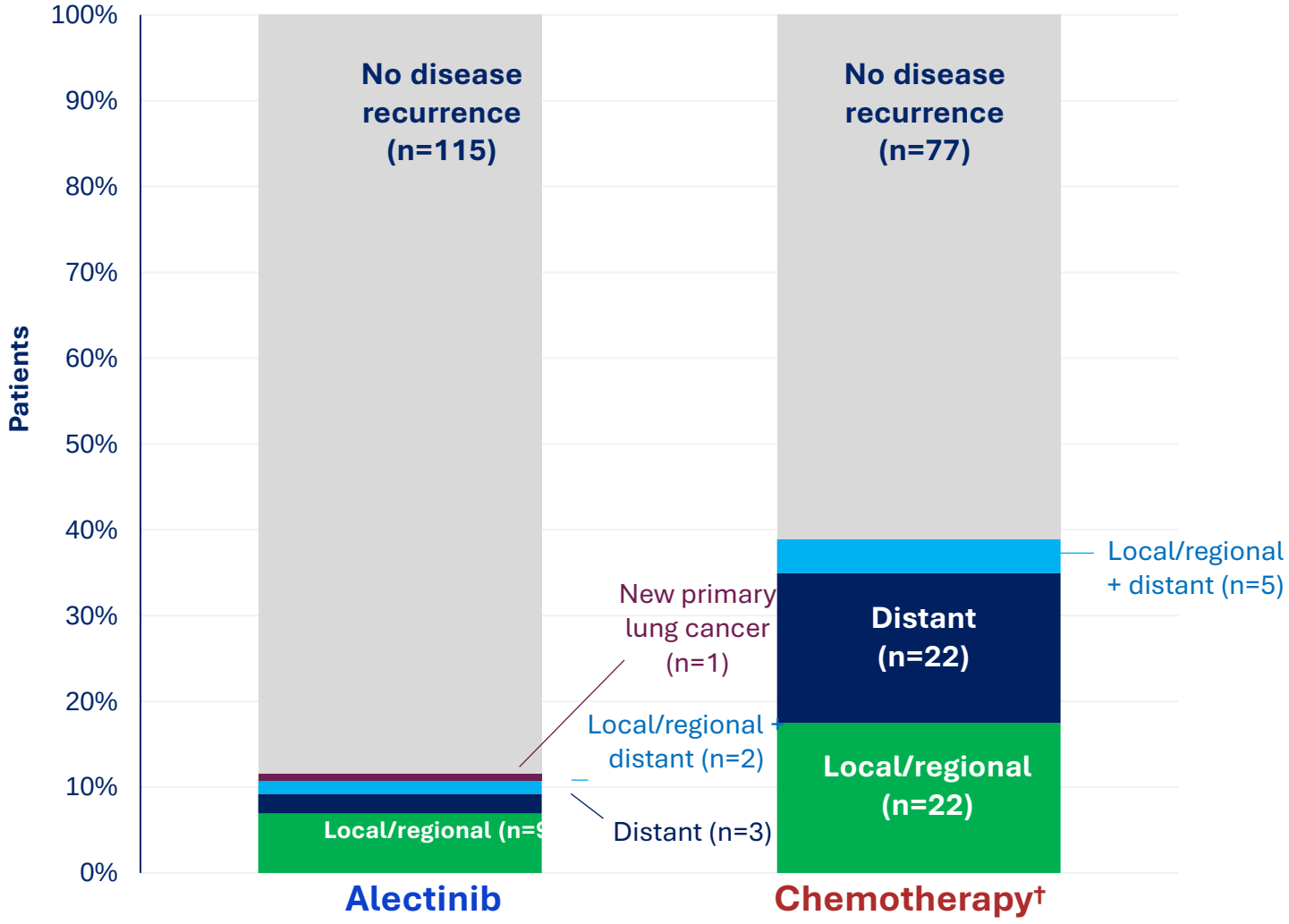


	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	**0.22** (0.08, 0.58)	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Modified from Solomon et al, ESMO 2023

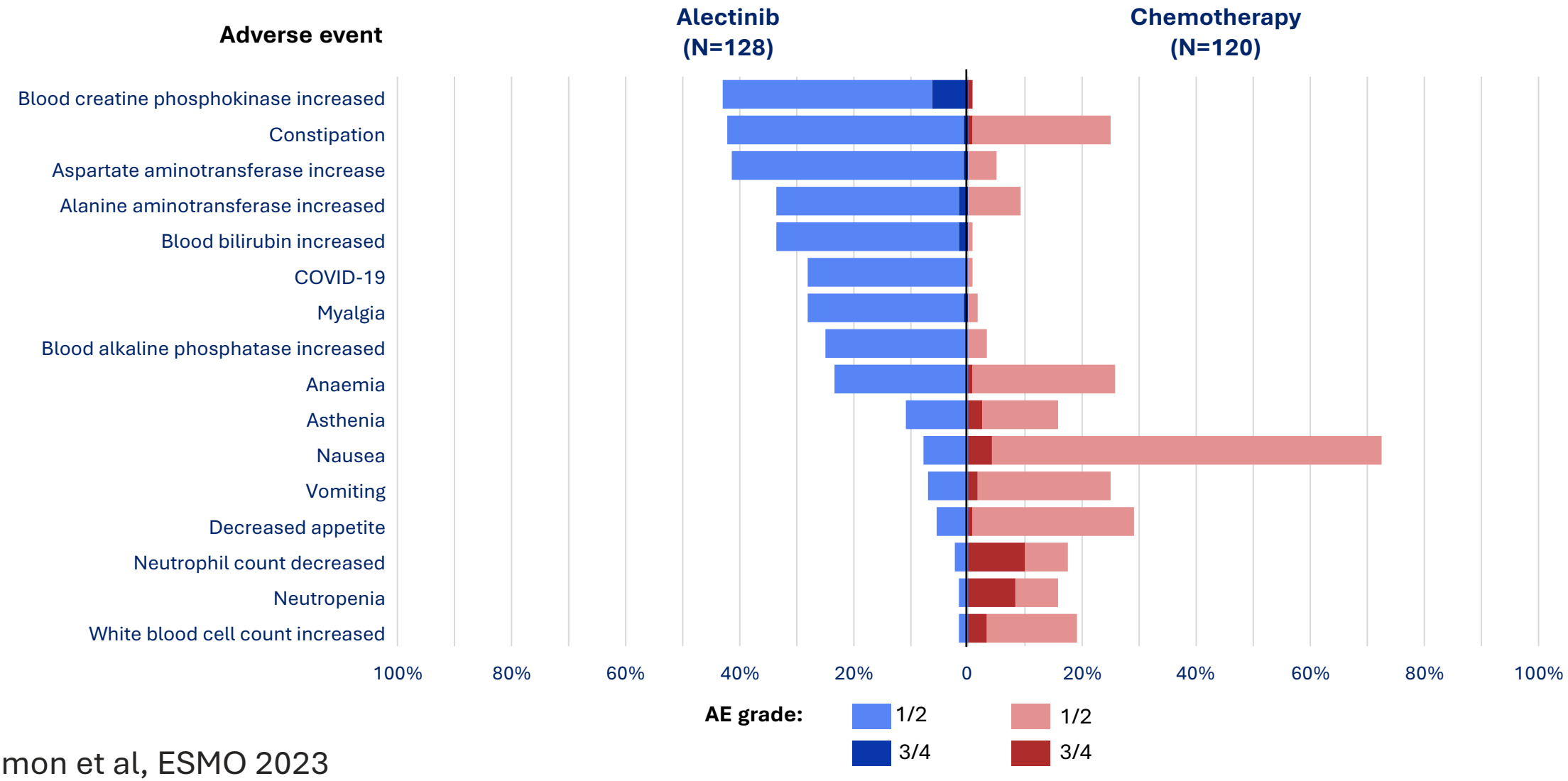
Alectinib vs Chemotherapy in Resected NSCLC
Sites of disease recurrence (ITT)



Site(s) of distant recurrence*	Alectinib (n=130)	Chemotherapy (n=127)
Brain	4	14
Bone	1	8
Adrenal gland	0	3
Lymph node	0	2
Kidney	0	1
Peritoneum	0	1
Other	1	0

Solomon et al, ESMO 2023

Alectinib vs Chemotherapy in Resected NSCLC
AEs occurring in ≥15% of patients



Solomon et al, ESMO 2023

Open Questions

- Long duration of disease control for patients with metastatic disease mean it's harder to judge based on early timepoints whether effects of treatment are durable beyond completion of the TKI, but survival is improved.
- What's the right duration of TKI? 2 years…3 years…10 years
- Do we incorporate chemotherapy into these regimens? How?

What are characteristics of treatment approaches that have proven to be useful in adjuvant setting

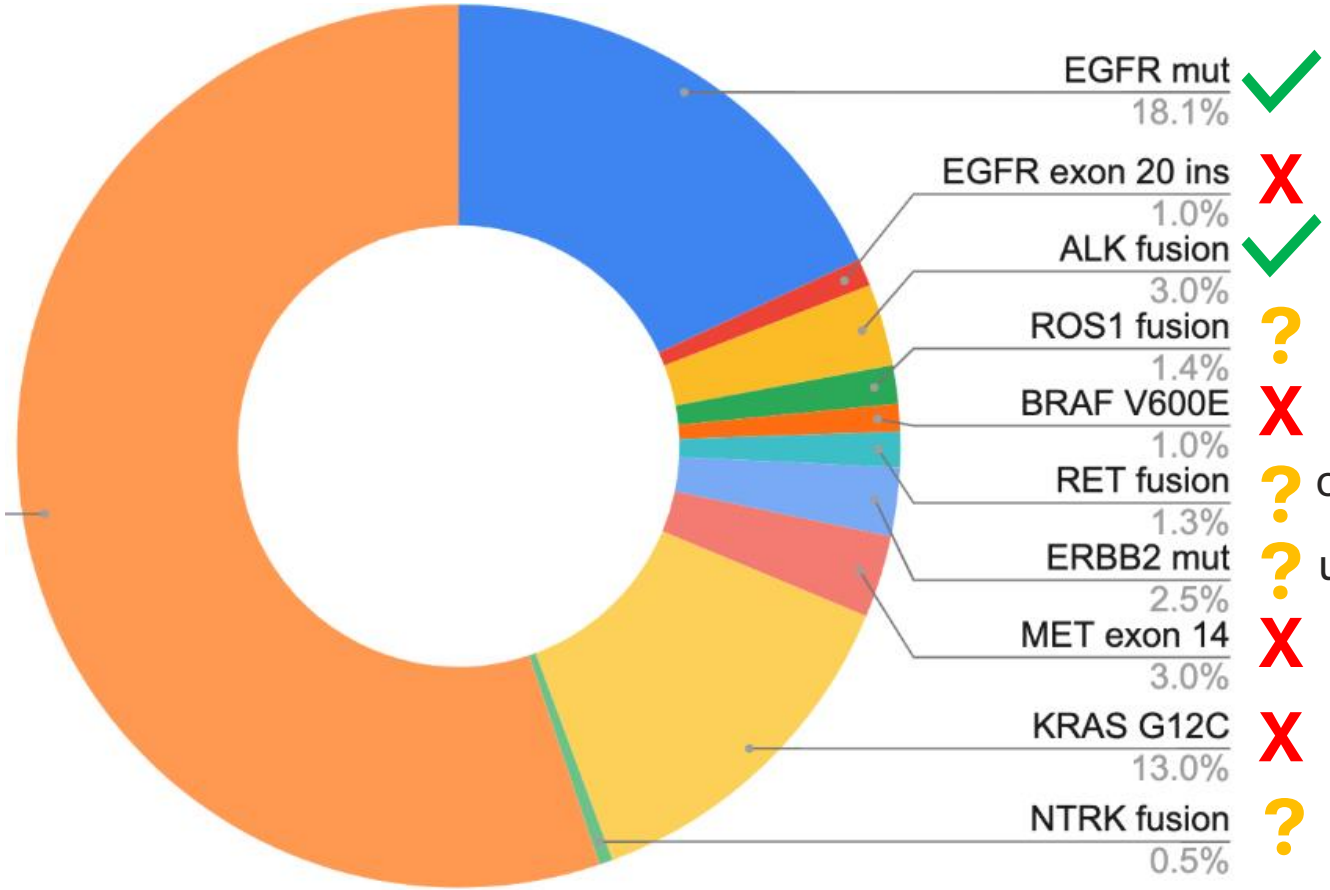
- Manageable toxicity profile (higher bar for longer duration of adjuvant therapy)
- High response rate
- Long median PFS
- Long median OS

Conclusions

- For patients with completely resected EGFR mutant NSCLC
  - 3 years of osimertinib improves overall survival
  - Benefits of chemotherapy appear additive
  - I recommend chemotherapy followed by osimertinib

- For patients with completely resected ALK positive
  - 2 years of alectinib improves disease free survival
  - Trial inappropriately required a choice between adjuvant chemotherapy and alectinib
  - I recommend chemotherapy followed by alectinib

For what oncogenes do these lessons apply?



✓
X
✓
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X
? ongoing trial (selpercatinib)
? upcoming trial neoadjuvant/adjuvant(TDXD)
X
X upcoming trial neoadjuvant/adjuvant
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AACR GENIE BPC lung, Choudhury et al, CCR 2023;
Data available at https://genie.cbioportal.org/