Memorial Sloan Kettering
Cancer Center

Targeted therapy in Early-Stage Non-small cell lung cancer

Jamie E. Chaft, MD
Attending Physician
Thoracic Oncology Service

Disclosures

- AstraZeneca Consultant, Contracted Research support to institution
- BMS Consultant, Contracted Research support to institution
- Merck Consultant, Contracted Research support to institution
- Genentech Consultant, Contracted Research support to institution
- Beigene Contracted Research support to institution
- Guardant Consultant
- Janssen Consultant
- BI Consultant
- Lilly Consultant
- Roche Consultant

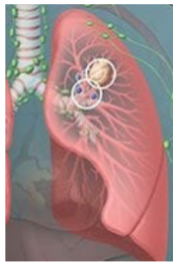
Early-Stage Lung Cancer Stats with Surgery Alone

Stage IA1: ≤ = 1cm ~92% 5-year survival

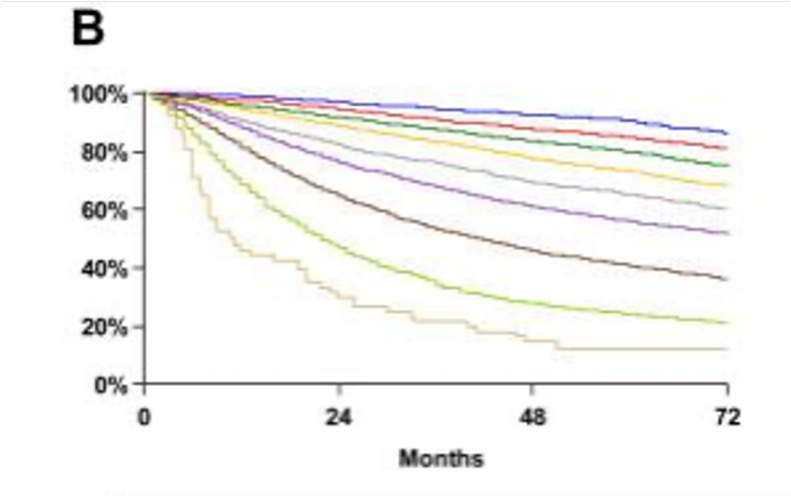
Stage IA2: >1-2 cm ~83% 5-year survival

Stage IA3: >2-3 ~77% 5-year survival

Stage IIA: >4 cm ~60% 5-year survival



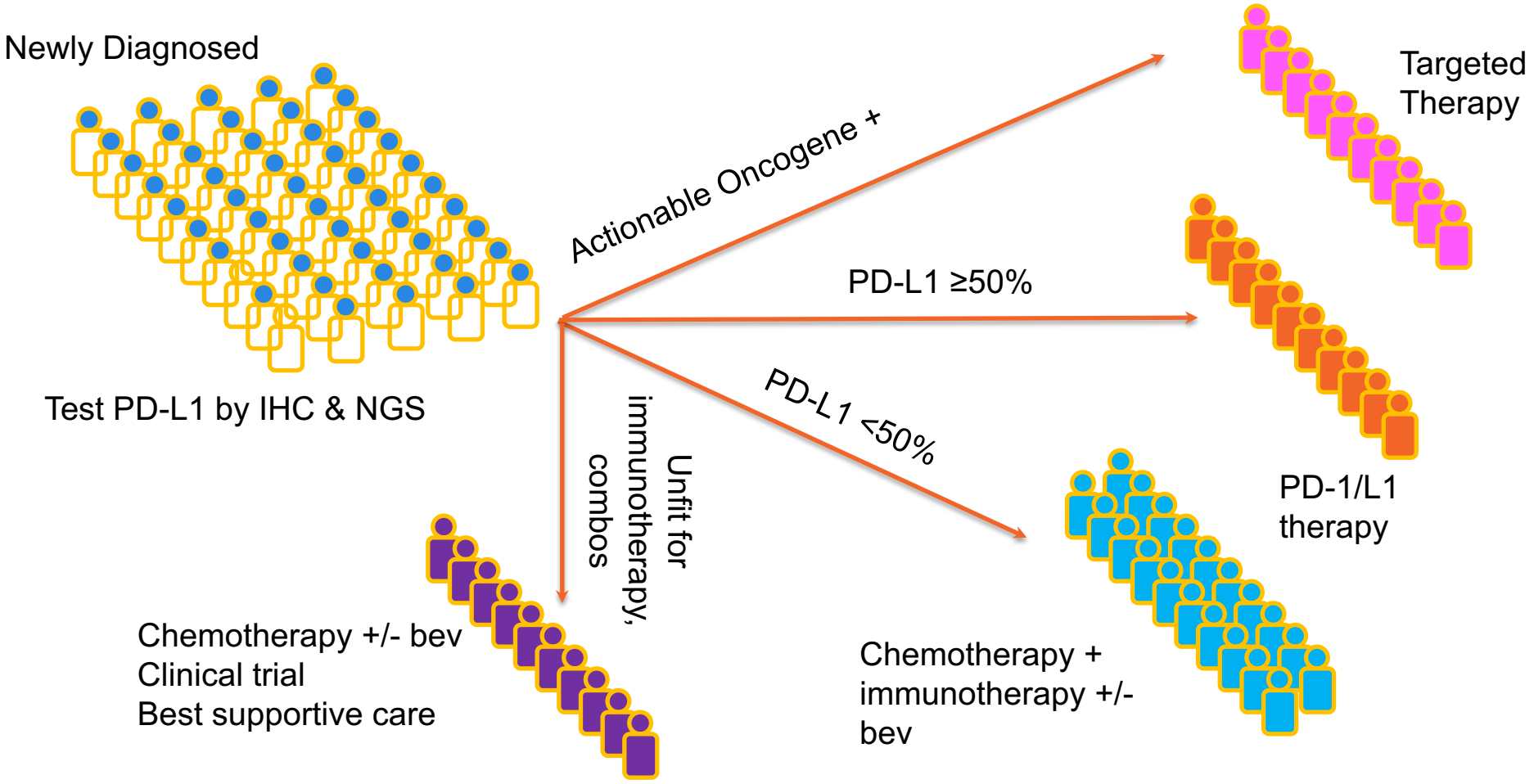
Once LNs are involved the risk of recurrence and death drastically increases



Survival based on pathologic stage

Memorial Sloan Kettering Cancer Center

Stage IV Lung Cancer – Today's 1st-line treatment



…yet for nearly 20 years all we had was adjuvant cis-based chemo for curable disease!

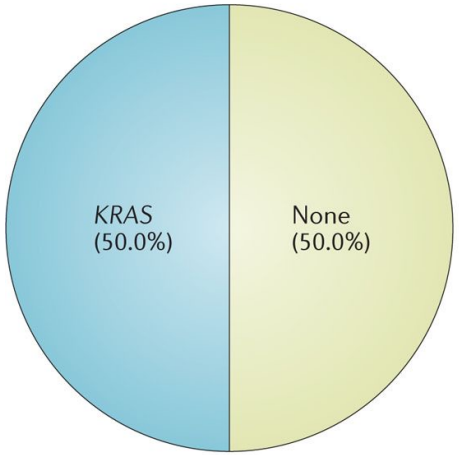
Memorial Sloan Kettering Cancer Center

Evolution of oncogenic biomarkers in NSCLC

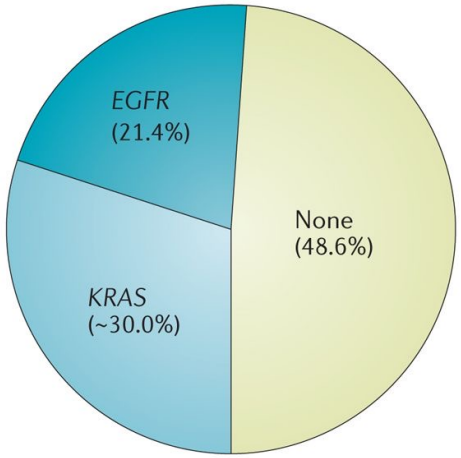
Novel drivers → Investigational targets → Clinical-grade predictive biomarkers in 2024

Targeted therapies

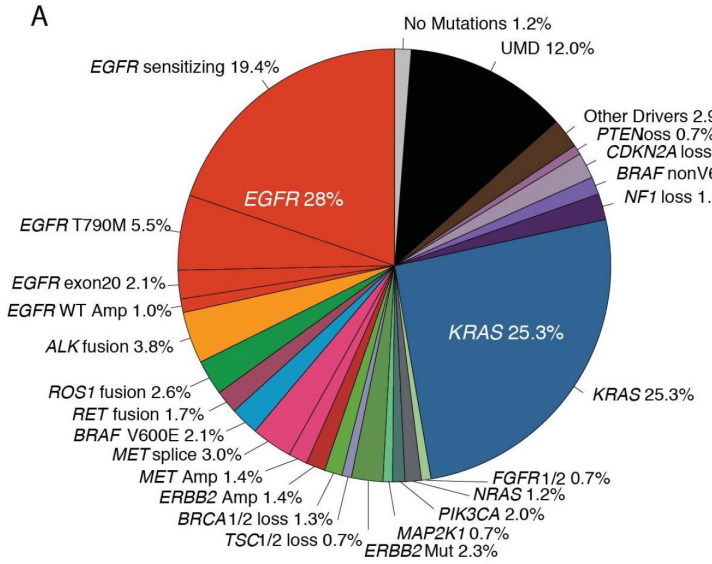
Immune checkpoint therapy

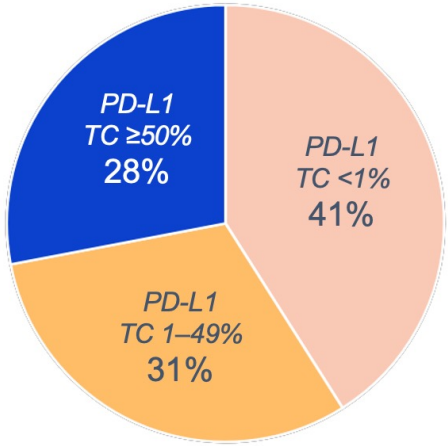


1987



2004





Vargas AJ, Harris CC. Nature Reviews Cancer. 2016 Aug;16(8):525; Jordan EJ et al. Cancer Discovery. 2017 Jun 1;7(6):596-609; Yang SR et al. Seminars in cancer biology 2022 Sep 1; Felip, et al. Lancet 2021; Carbone, et al. WCLC 2020; Forde, et al. N Engl J Med 2022; Kowanetz, et al. AACR 2018; Gandhi, et al. N Engl J Med 2018; Paz-Ares, et al. N Engl J Med 2018; Paz-Ares, et al. Lancet Oncol 2021

ADAURA

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Maximum interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

→ **Stratification by:**
Stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
Race (Asian vs non-Asian)

→ **Randomization 1:1 (N=682)**

- **Osimertinib 80 mg, once daily**
- **Placebo, once daily**

→ **Planned treatment duration: 3 years**

Treatment continued until:
- Disease recurrence
- Treatment completion
- Discontinuation criterion met

Follow-up:
- Until recurrence; Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II-IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB-IIIa), landmark DFS rates, OS, safety, health-related quality of life

*At the time of recruitment, staging was determined by the AJCC / UICC Staging Manual 7th edition. Patients with stage IB disease were not eligible in Japan. †Pre-operative, post-operative, or planned radiotherapy was not allowed. ‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment.

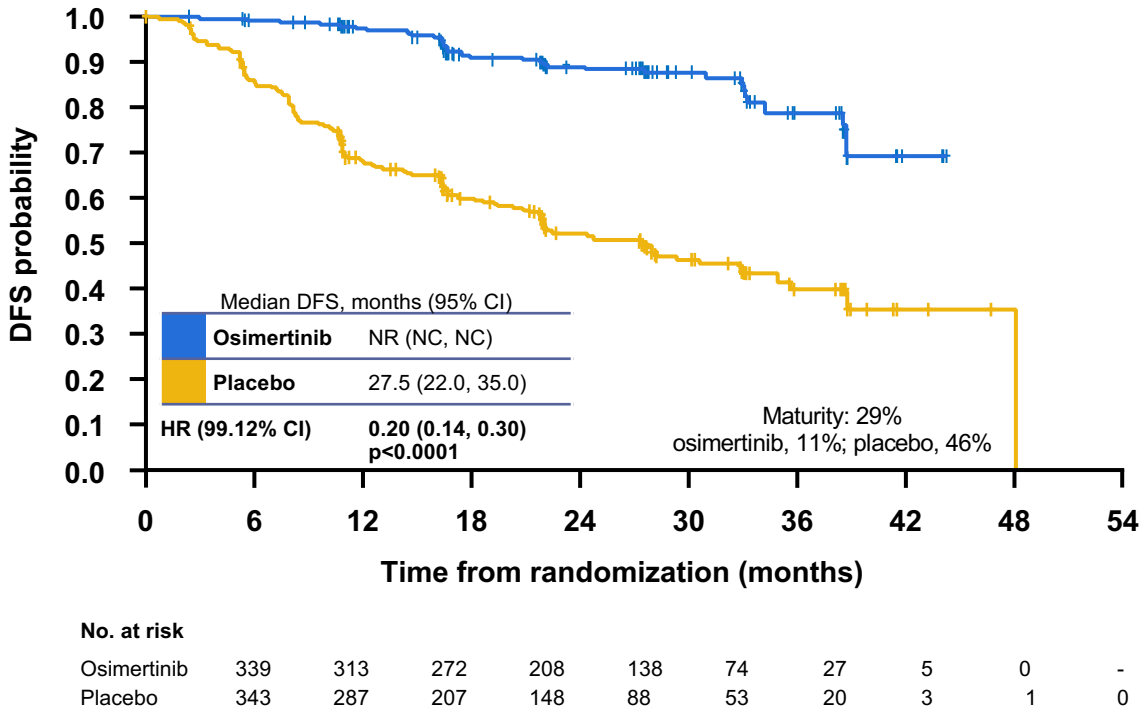
Herbst RS, et al. Oral presentation at ASCO 2023; June 7 2023; Chicago, IL. Abstract LBA3

Memorial Sloan Kettering Cancer Center

ADAURA: Adjuvant osimertinib x 3 yr significantly improved DFS vs placebo

ADAURA primary DFS analysis[1,2] (stage IB–IIIA)*

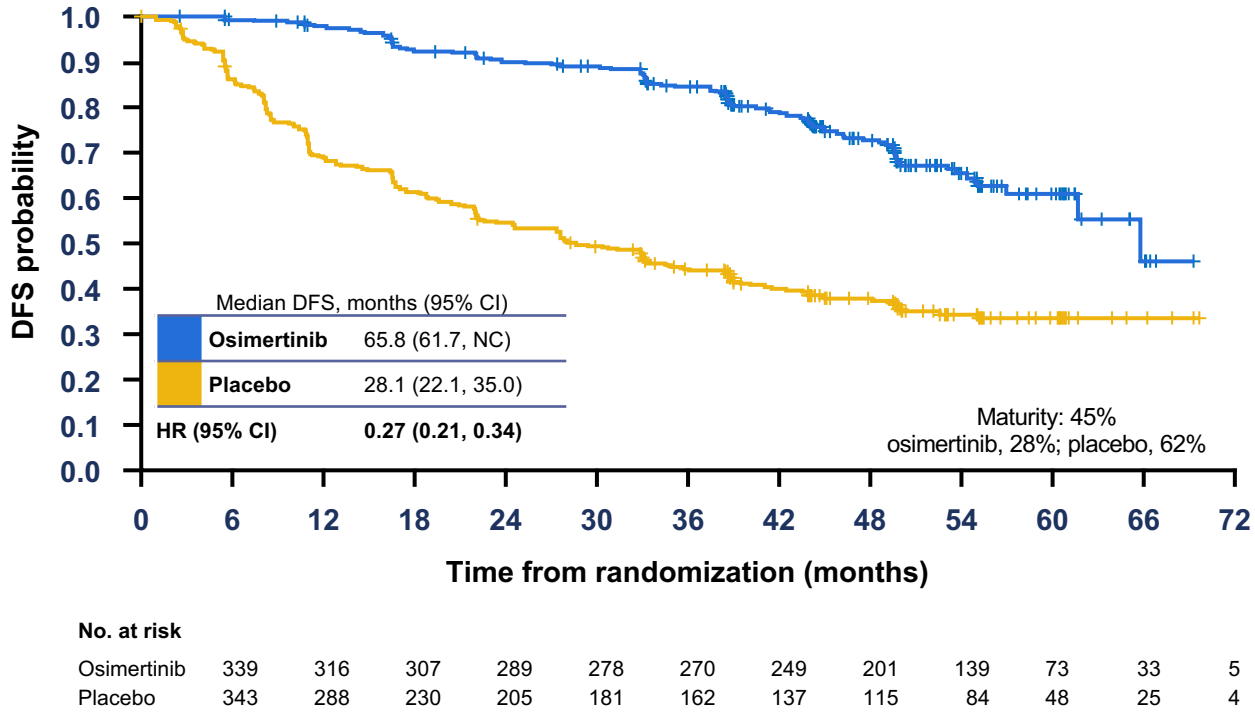
NEJM October 2020



No. at risk										
Osimertinib	339	313	272	208	138	74	27	5	0	-
Placebo	343	287	207	148	88	53	20	3	1	0

ADAURA updated DFS analysis[3,4] (stage IB–IIIA)†

JCO January 2023



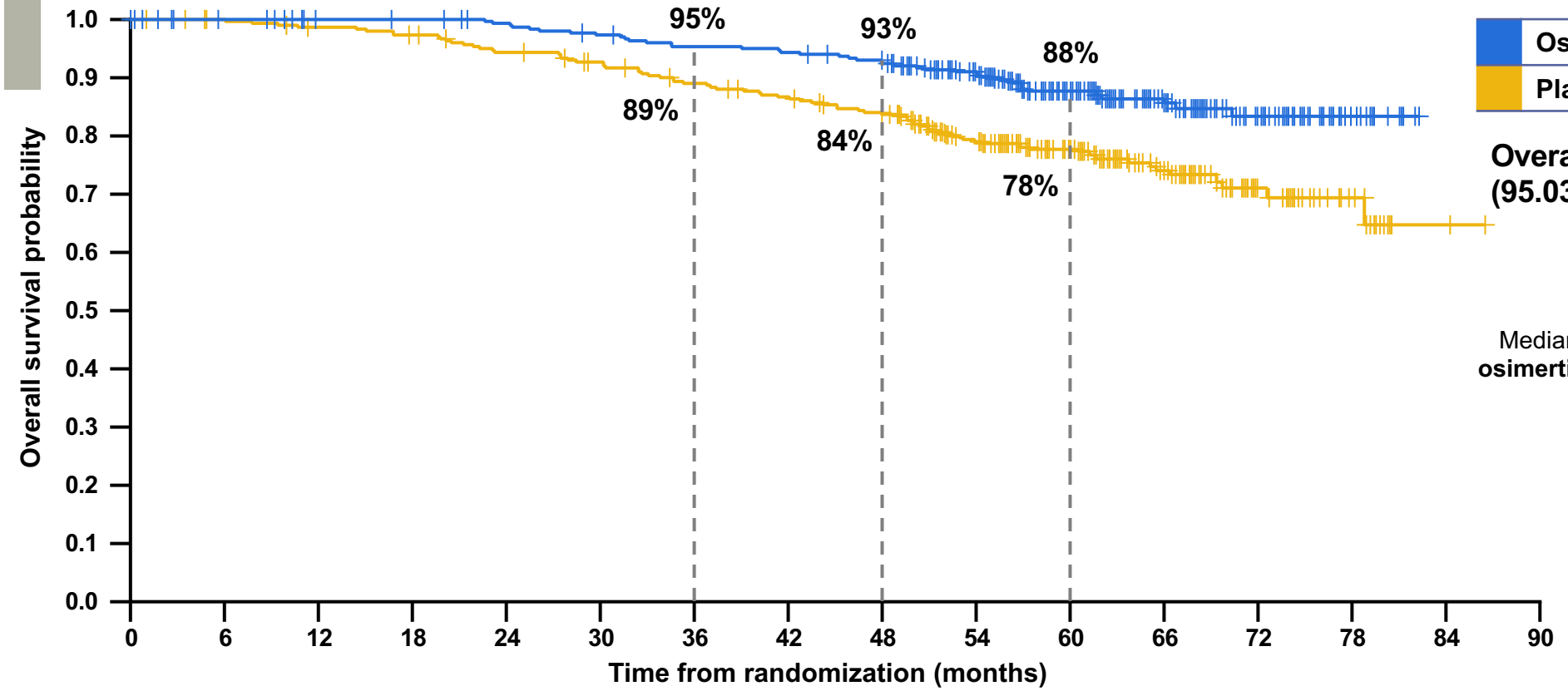
No. at risk												
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5
Placebo	343	288	230	205	181	162	137	115	84	48	25	4

CI, confidence interval; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer.
*Data cut-off: January 17, 2020. †Data cut-off: April 11, 2022.

1. Wu et al. N Engl J Med 2020;383:1711-1723; 2. Herbst et al. J Clin Oncol 2020;38(Suppl 18): abstract / oral LBA5; 3. Herbst et al. J Clin Oncol 2023;41:1830–1840; 4. Tsuboi et al. *Ann Oncol* 2022;33(Suppl 7): abstract / oral LBA47.

Memorial Sloan Kettering Cancer Center

ADAURA: Adjuvant osimertinib x 3 yrs—improved overall survival patients with stage IB / II / IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) **0.49 (0.34, 0.70); p<0.0001**

Maturity: 18%
osimertinib 12%, placebo 24%

Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

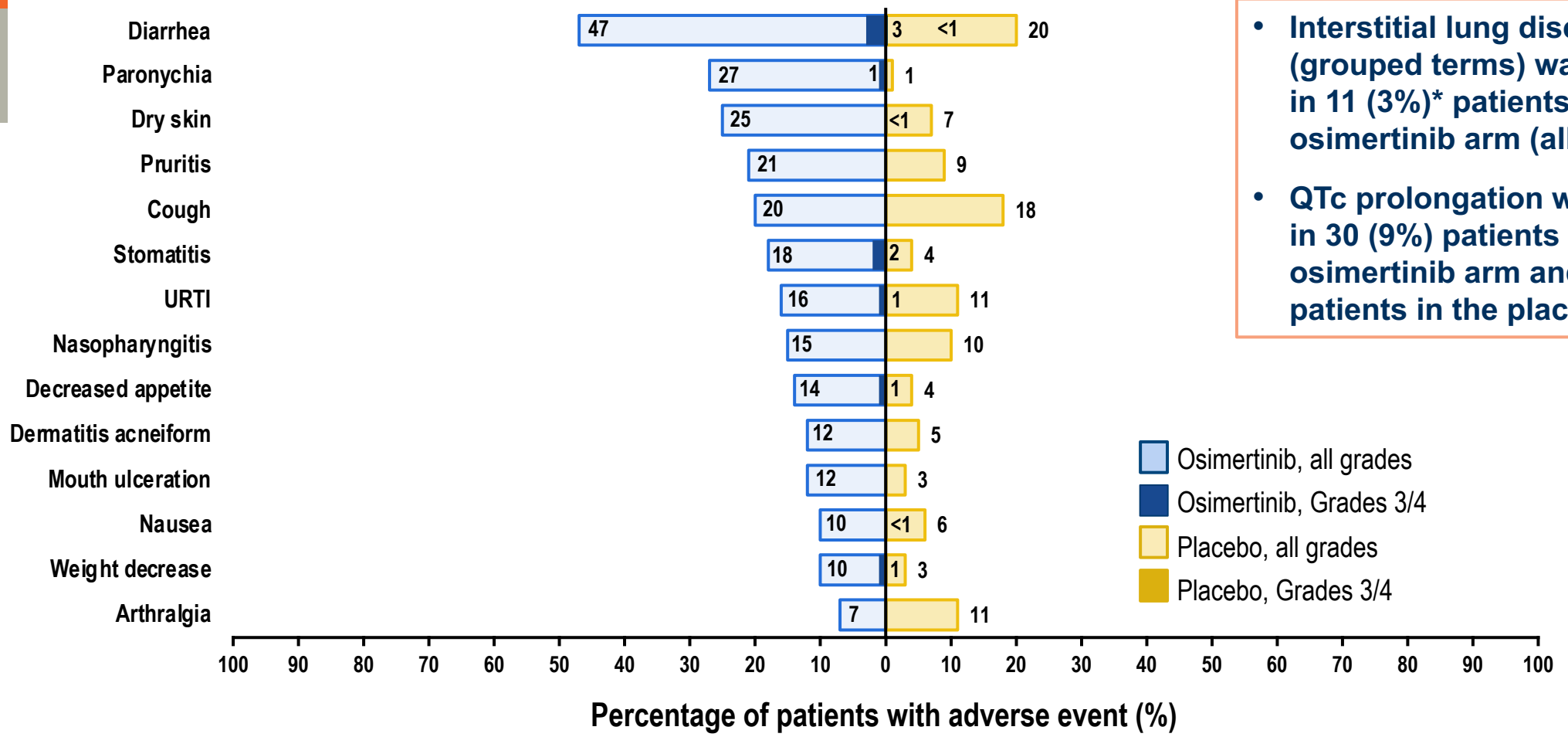
No. at risk

Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	-
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

CI, confidence interval; HR, hazard ratio; OS, overall survival
Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.

Memorial Sloan Kettering Cancer Center

All Causality Adverse Events (≥10% of Patients)

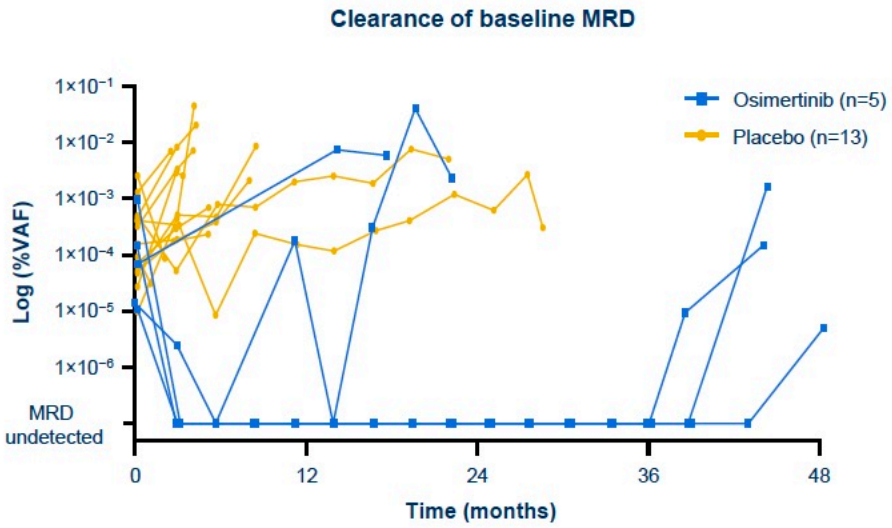


- **Interstitial lung disease (grouped terms) was reported in 11 (3%)* patients in the osimertinib arm (all Grade 1/2)†**
- **QTc prolongation was reported in 30 (9%) patients in the osimertinib arm and 8 (2%) patients in the placebo arm‡**

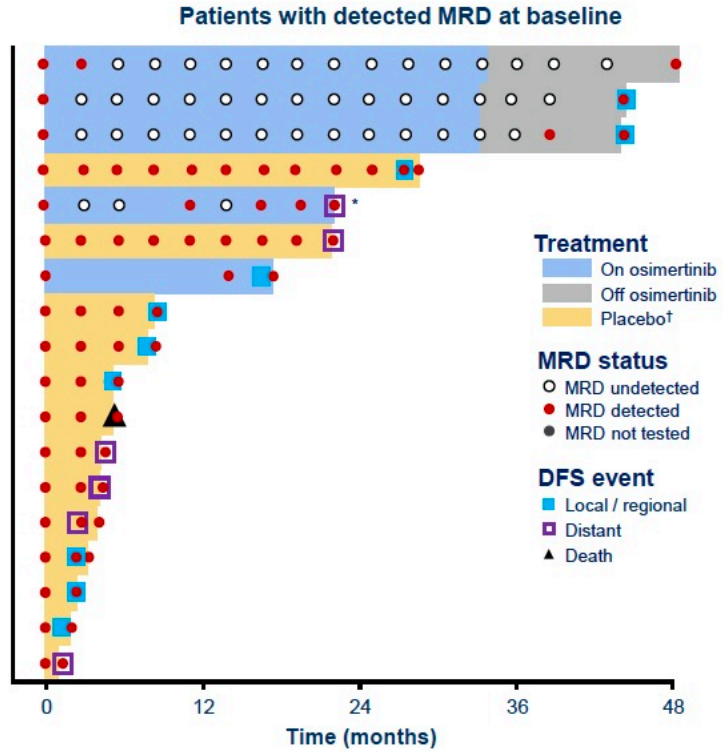
*Compared with the January 17, 2020 data cut-off, 1 additional patient reported interstitial lung disease (grouped term): pneumonitis, Grade 2;
†Grade 1, n=6; Grade 2, n=5; Grade 3, n=0; ‡Osimertinib: Grade 1, n=16; Grade 2, n=10; Grade 3, n=4; placebo: Grade 1, n=7; Grade 2, n=0; Grade 3, n=1.
QTc, electrocardiogram QT; URTI, upper respiratory tract infection.
Data cut-off: April 11, 2022.

Memorial Sloan Kettering Cancer Center

ctDNA dynamics



- Of 18 patients with detected MRD at baseline
  - 4 / 5 patients receiving osimertinib cleared MRD
  - 0 / 13 patients receiving placebo cleared MRD



John T, et al. ASCO 2024. Chicago, IL

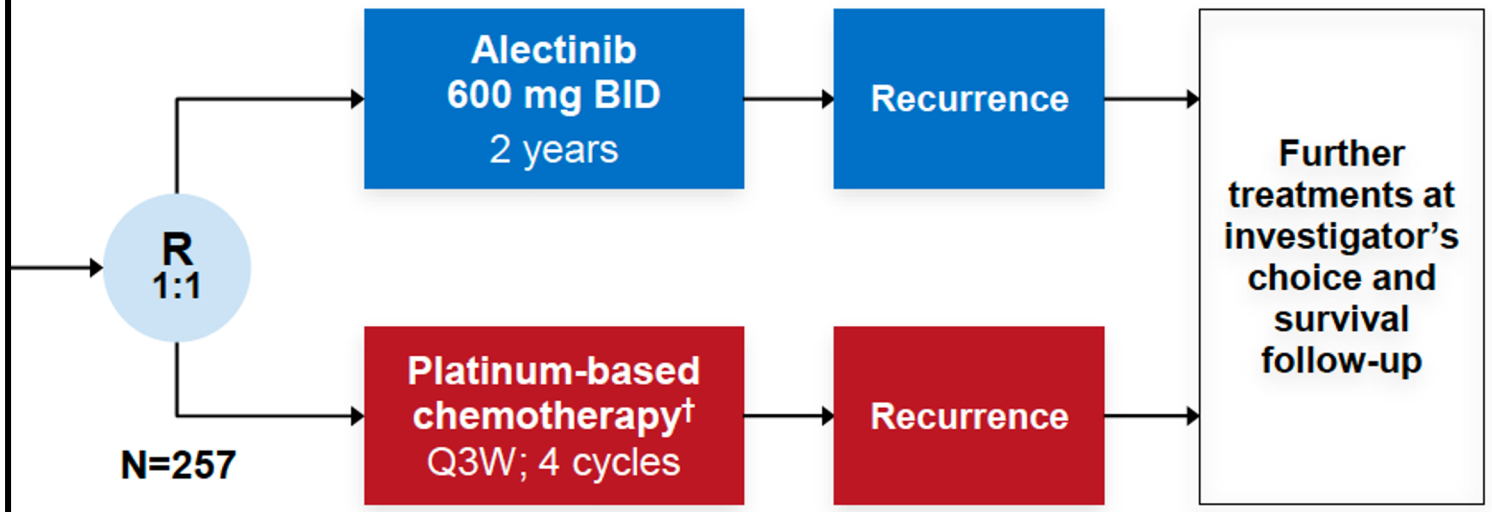
Memorial Sloan Kettering Cancer Center

ALINA

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 (≥4 cm) vs II vs IIIA
- Race: Asian vs non-Asian



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

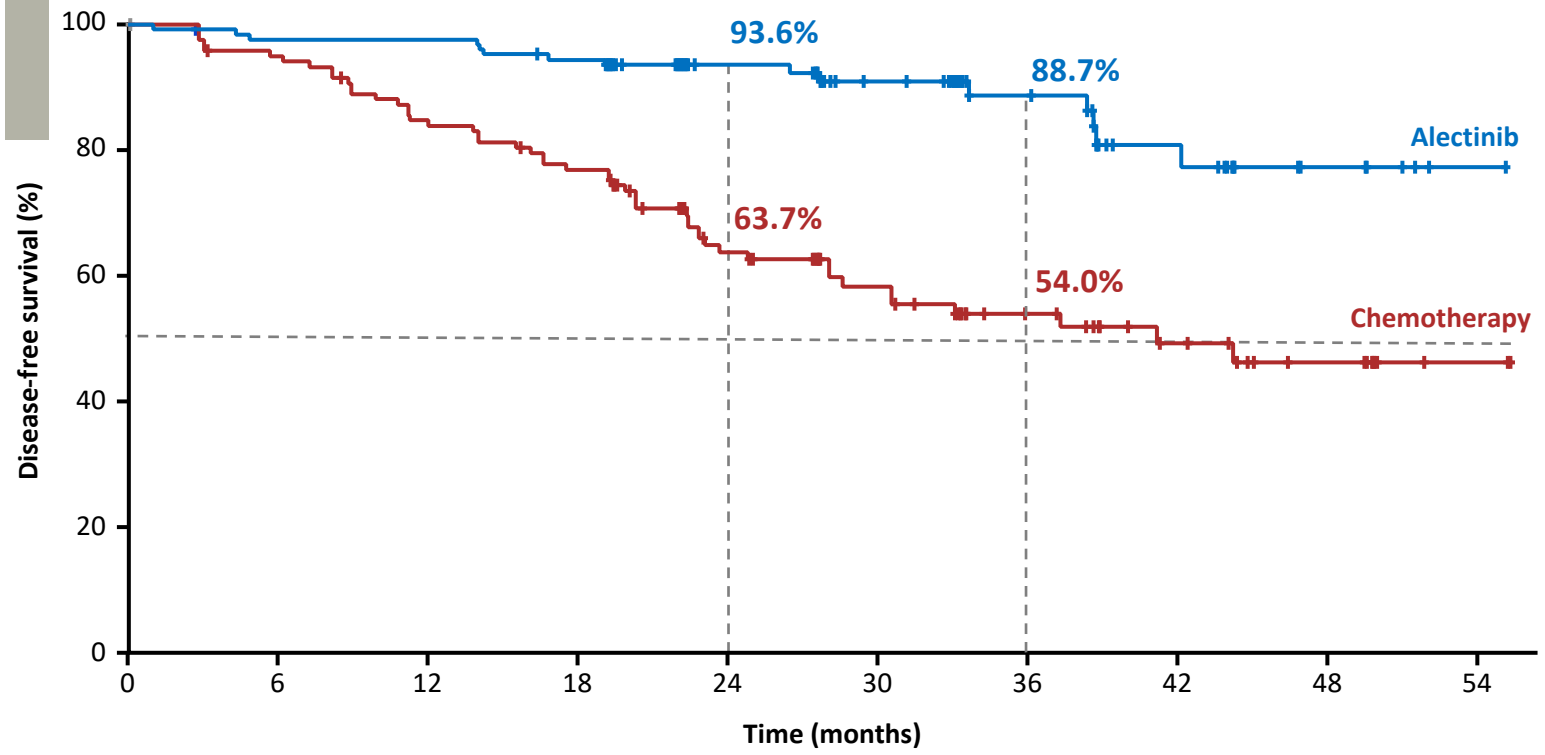
Other endpoints
- CNS disease-free survival
- OS
- Safety

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

Wu Y-L, et al. N Engl J Med. 2024;390(14):1265-1276.

Memorial Sloan Kettering Cancer Center

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‡

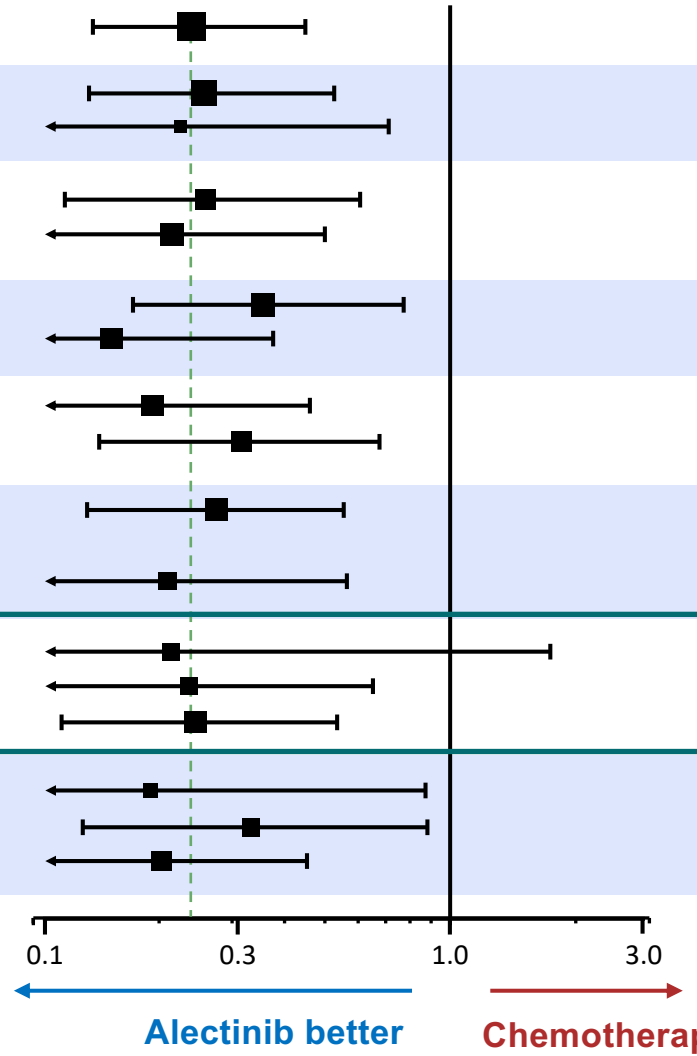
Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months
*Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first
Wu Y-L, et al. N Engl J Med. 2024;390(14):1265-1276, Wu et al. AATS 2024

Memorial Sloan Kettering Cancer Center

Disease-free survival subgroup analysis (ITT)

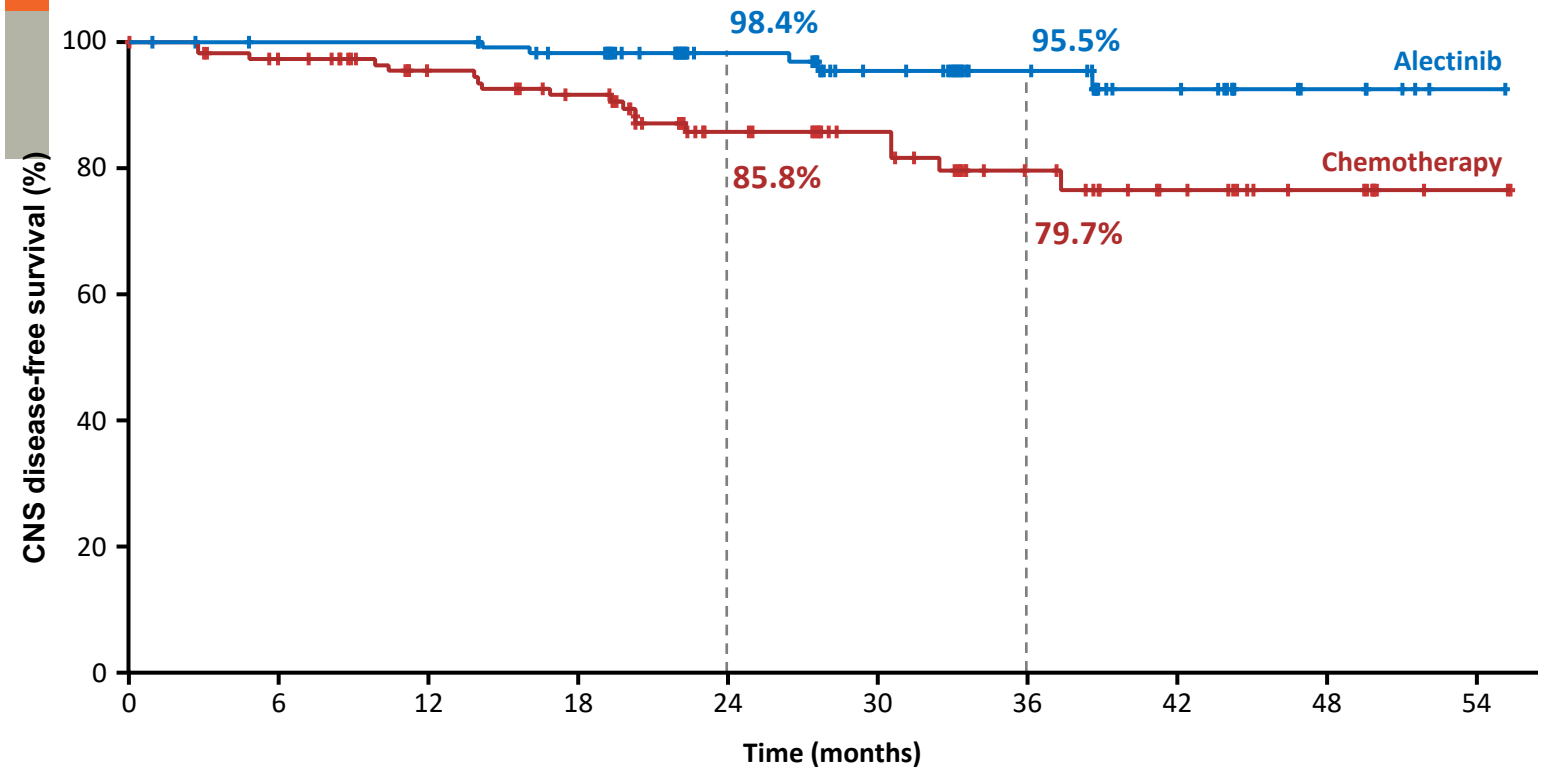
Subgroup		No. of events / patients	DFS HR (95% CI)
All patients		65 / 257	0.24 (0.14–0.43)
Age	<65	43 / 196	0.26 (0.13–0.52)
	≥65	22 / 61	0.24 (0.08–0.71)
Sex	Male	35 / 123	0.26 (0.11–0.60)
	Female	30 / 134	0.22 (0.10–0.50)
Race	Asian	31 / 143	0.36 (0.17–0.79)
	Non-Asian	34 / 114	0.16 (0.06–0.38)
ECOG PS at baseline	0	32 / 137	0.20 (0.09–0.46)
	1	33 / 120	0.31 (0.14–0.69)
Tobacco use history	Never	37 / 154	0.27 (0.13–0.55)
	Current	0 / 8	NE
	Previous	28 / 95	0.22 (0.08–0.57)
Stage*	Stage IB	6 / 26	0.21 (0.02–1.84)
	Stage II	22 / 92	0.24 (0.09–0.65)
	Stage IIIA	37 / 139	0.25 (0.12–0.53)
Regional lymph node status	N0	11 / 39	0.19 (0.04–0.88)
	N1	20 / 88	0.34 (0.13–0.89)
	N2	34 / 130	0.21 (0.09–0.47)



Data cut-off: 26 June 2023
Arrows indicate lower bound of the CI<0.1; *Per UICC/AJCC 7th edition

Memorial Sloan Kettering Cancer Center

CNS disease-free survival in the ITT population



No. at risk

Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

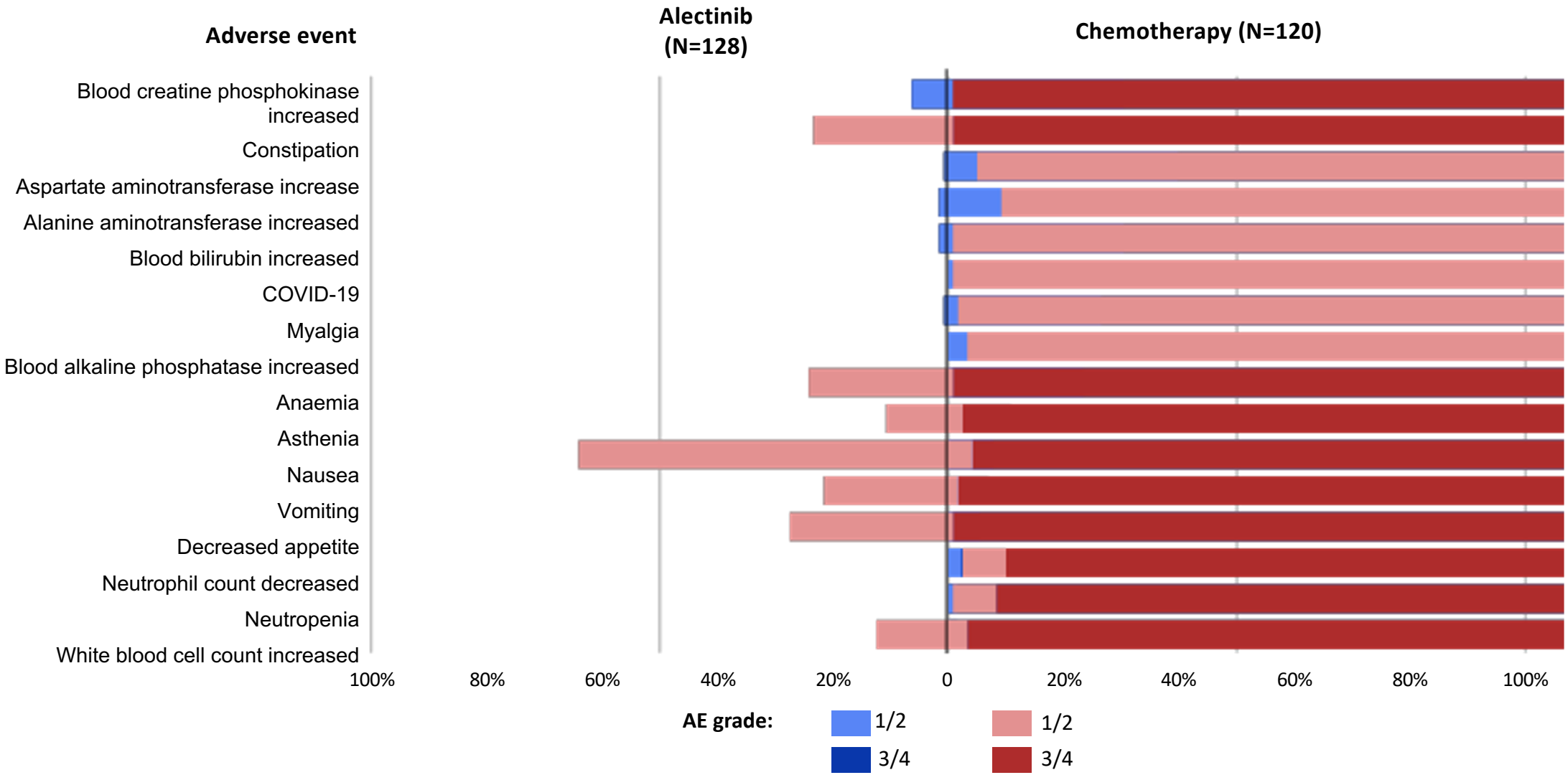
	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	**0.22** (0.08, 0.58)	

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

Data cut-off: 26 June 2023
*Stratified analysis with race and stage as stratification factors
CNS-DFS defined as time from randomisation to the first documented recurrence of disease in the CNS or death from any cause
Wu Y-L, et al. N Engl J Med. 2024;390(14):1265-1276.

Memorial Sloan Kettering Cancer Center

AEs occurred in ≥15% of patients



Data cut-off: 26 June 2023
Median treatment duration was 23.9 months in the alectinib arm and 2.1 months in the chemotherapy arm. No grade 5 events were observed.
Wu Y-L, et al. N Engl J Med. 2024;390(14):1265-1276.

Memorial Sloan Kettering Cancer Center

Finally making progress in early-stage disease