18th Annual

ATLANTA
LUNG CANCER SYMPOSIUM

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Treatment of ALK-Positive Advanced NSCLC

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Henry Ford Health System
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Disclosures

Advisory Board- Genentech/Roche, Mirati, Astra-Zeneca, Pfizer, Merck, Esai, GSK, Takeda, Lilly, BMS, Daichii, Gilead, Bayer

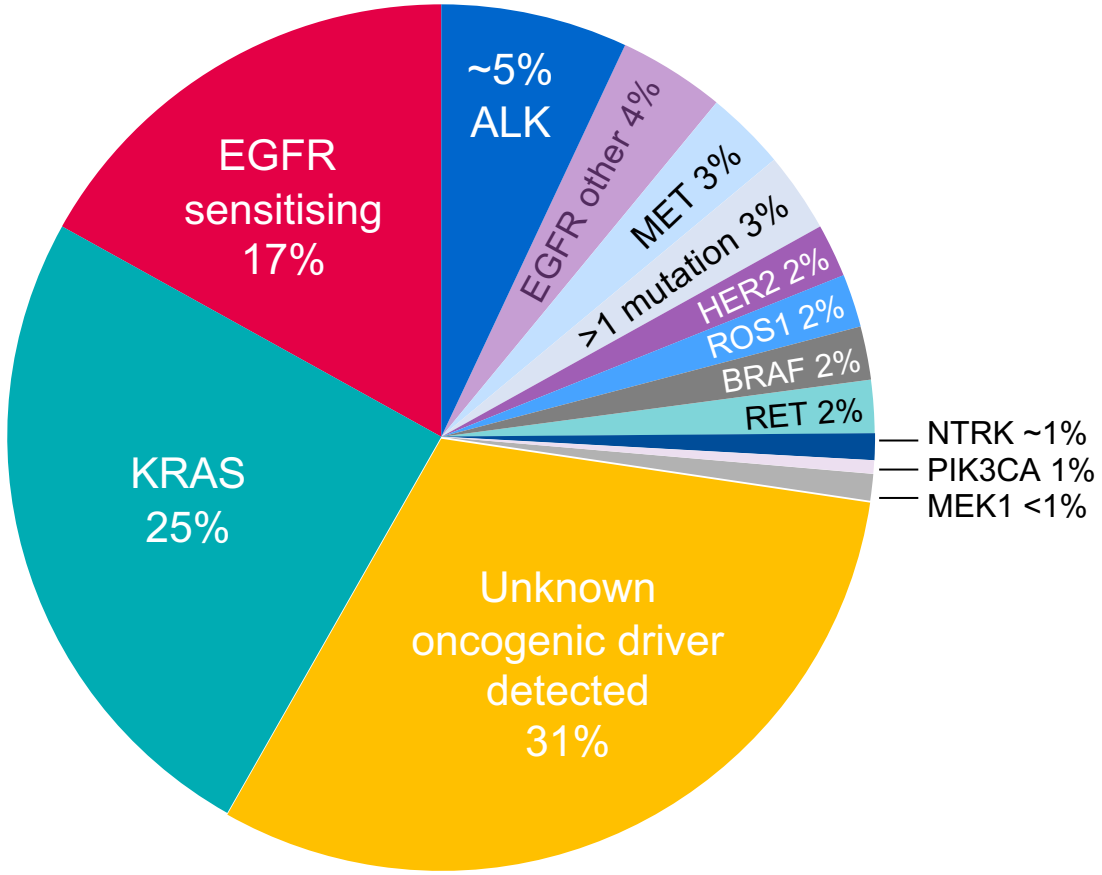
IDMC- Astra-Zeneca

Travel- Mirati

Slides- Dr. Stephen Liu

ALK is an oncogenic driver mutation for a distinct subset of NSCLC

Driver mutations in lung cancer[1]



Patients tend to be…

Younger[2–4]

Median age ~52 years versus ~70 years for other types of NSCLC

Never or light smokers[3,5,6]

~70% patients with *ALK*+ NSCLC have never smoked

Advanced disease at presentation[7–9]

- Pleural/pericardial effusion
- Multiple lesions/sites
- Symptomatic
- CNS metastases

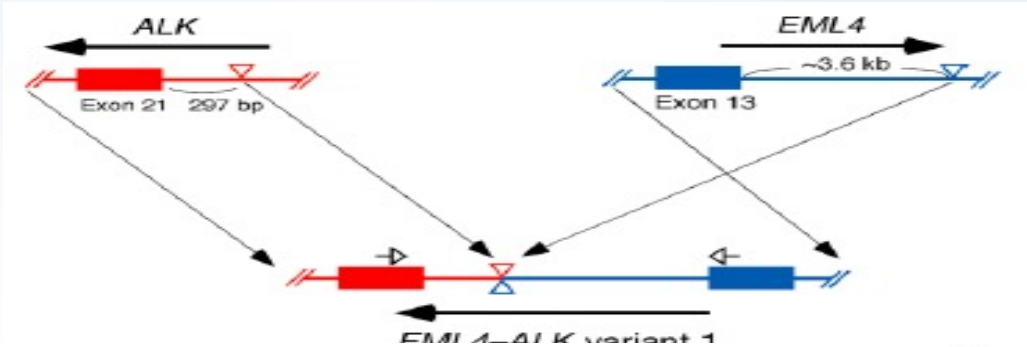
1. Tsao, et al. J Thorac Oncol 2016; 2. Chia, et al. Clin Epidemiol 2014; 3. Camidge, et al. Lancet 2012; 4. SEER Cancer Stat Fact Sheets Lung and Bronchus Cancer
5. Tao, et al. Thorac Cancer 2017; 6. Kayaniyil, et al. Curr Oncol 2016; 7. Solomon, et al. N Engl J Med 2014; 8. Soria, et al. Lancet 2017; 9. Peters, et al. N Engl J Med 2017

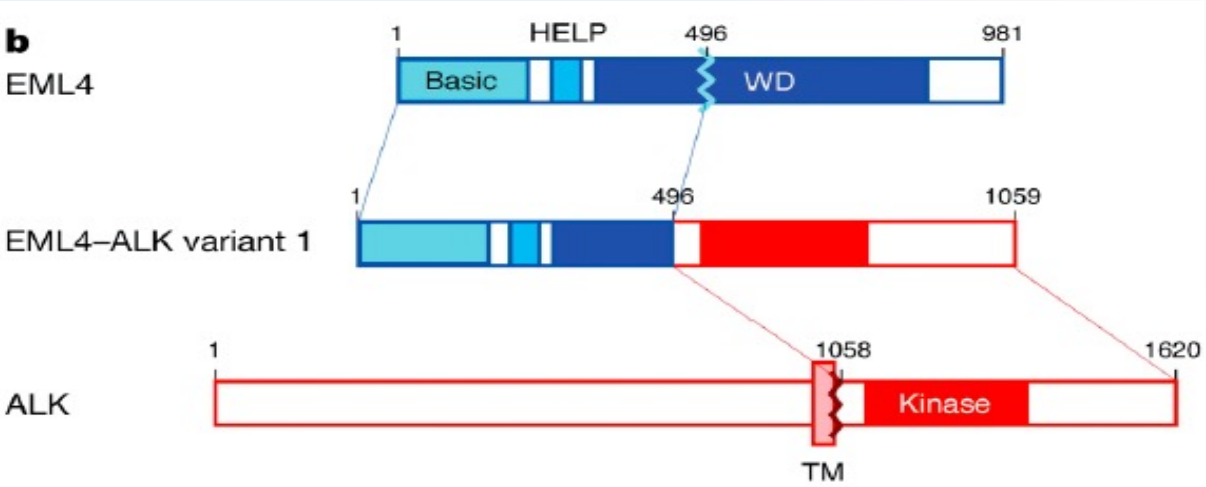
Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

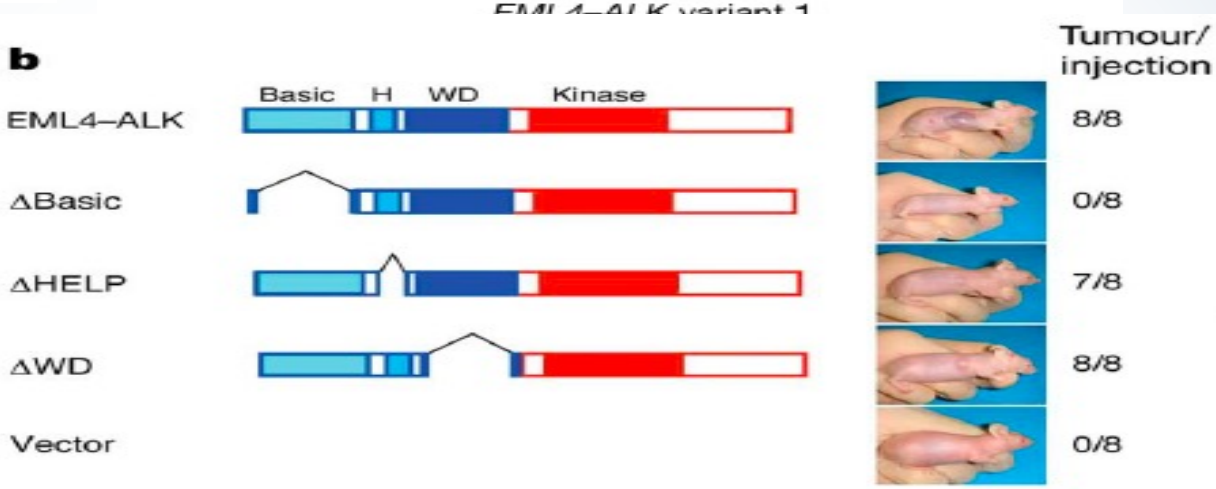
Soda et al. *Nature* 2007;448:561–6.

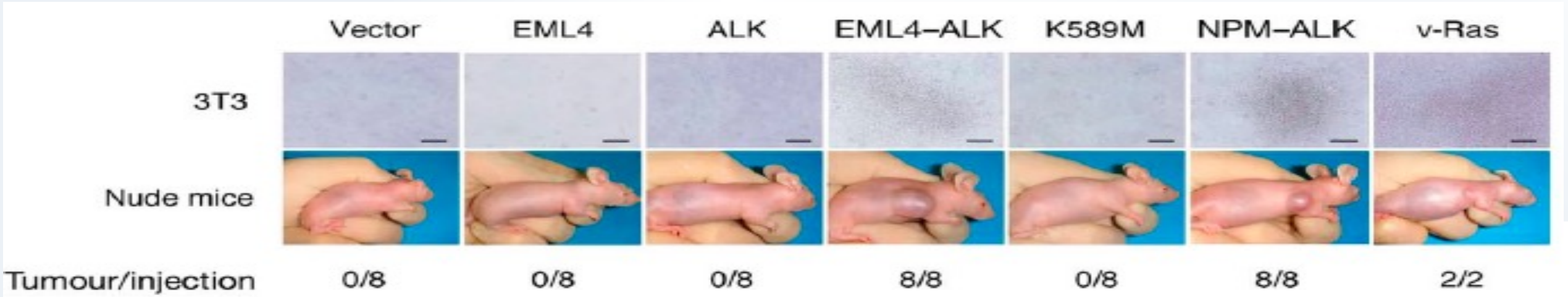
Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Ken[illegible]o[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshi[illegible]Hiroyuki Mano[1,7]

Vol 448|2 August 2007|doi:10.1038/nature05945

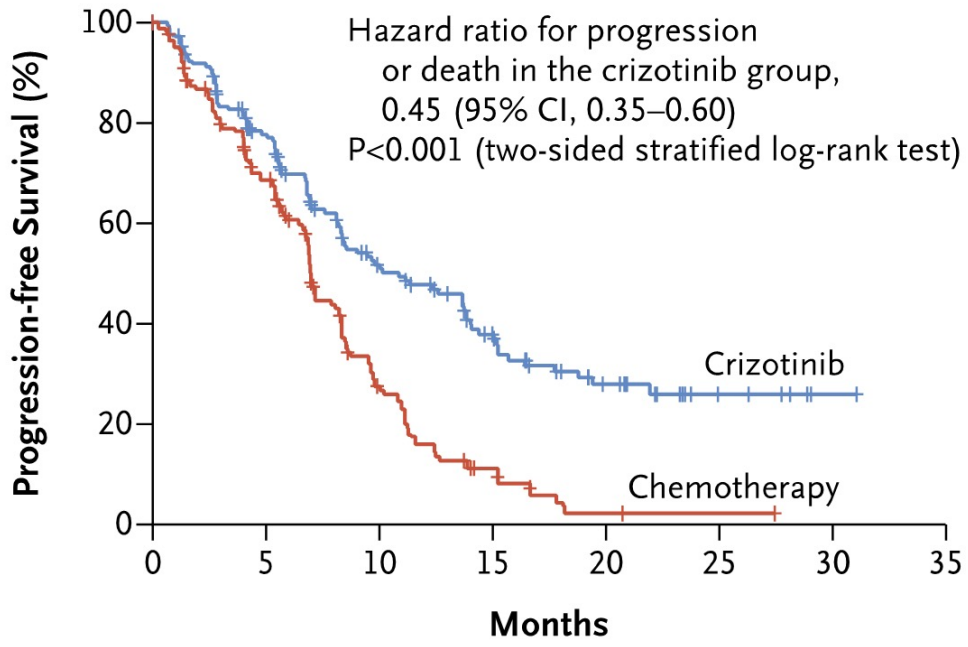








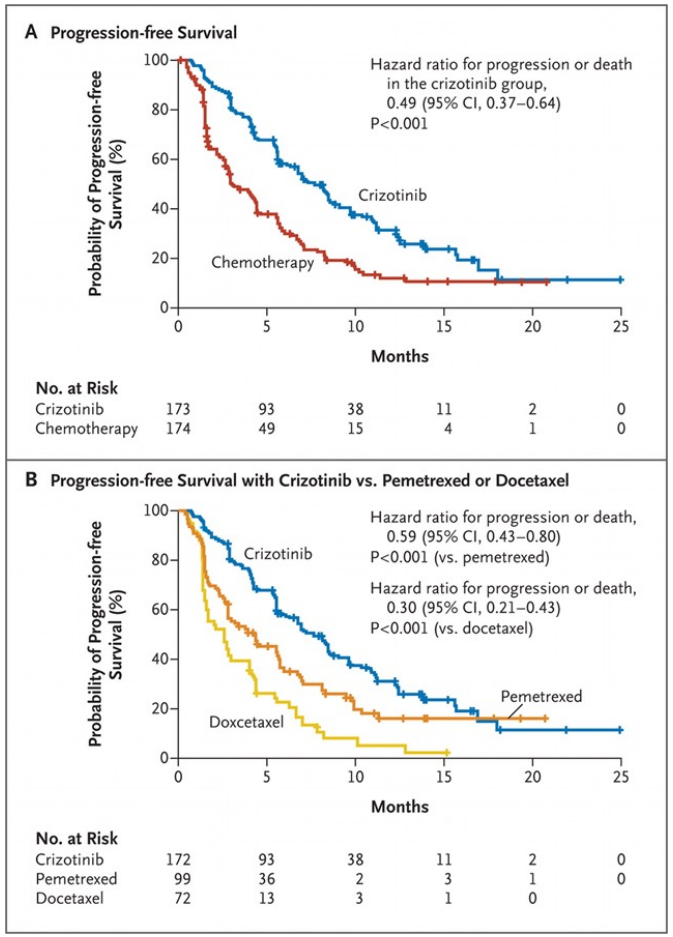
Crizotinib in ALK positive NSCLC



No. at Risk

Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

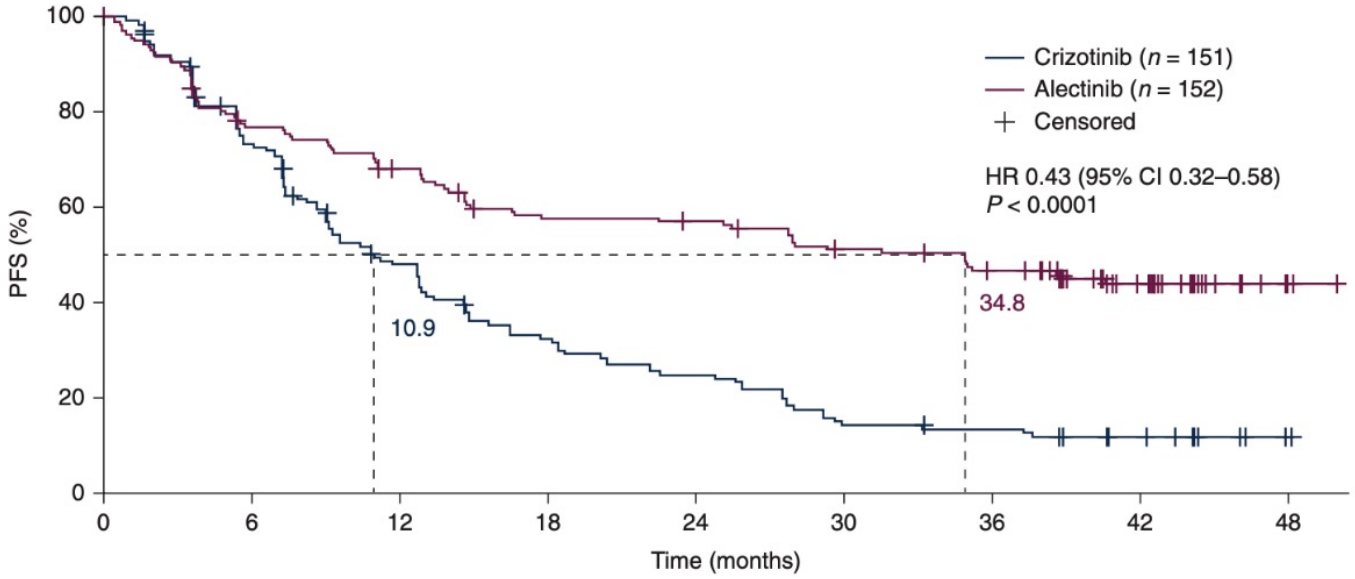
PROFILE 1014- Solomon B, NEJM 2014



PROFILE 1007
Shaw A,
NEJM 2013

First Line Alectinib: ALEX

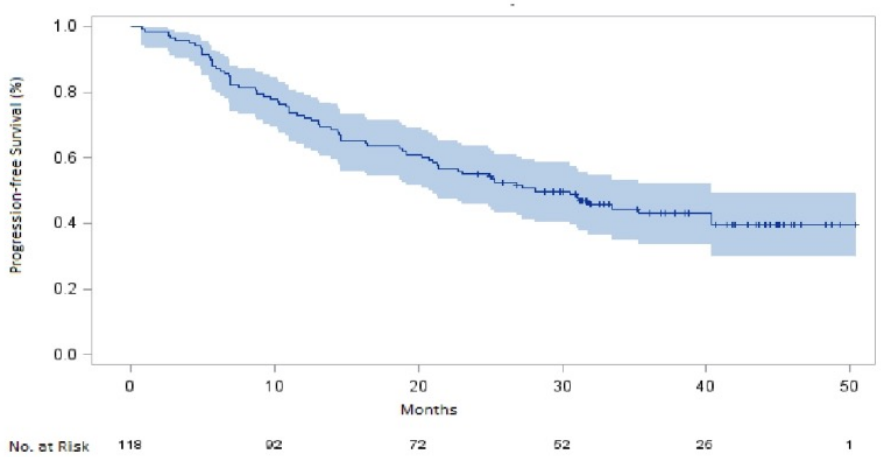
- 303 patients randomized to alectinib or crizotinib
- Alectinib superior
  - INV mPFS 34.8m vs 10.9m, PFS HR 0.43 (0.32-0.58)
  - OS HR 0.67 (0.46-0.98), 5y OS 62.5% vs 45.5%



Mok, Ann Oncol 2020

Real World Alectinib Outcomes

- Explore ALK study
  - Real world analysis from centers in France
  - First-line alectinib (n=119)
  - RR 79%, mDOR 27.4m, intracranial RR 72%, rwPFS 28.1m
  - rwPFS 28.1m



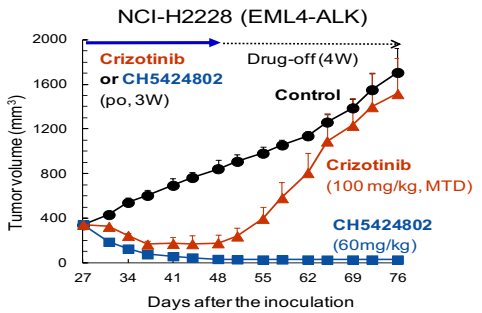
- US Flatiron data
  - 141 pts, 1L alectinib
  - rwPFS 24.5m

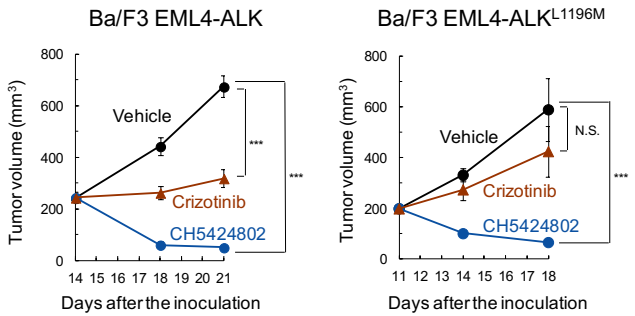
Swalduz, ASCO 2023; Zhang, JTO CRR 2023

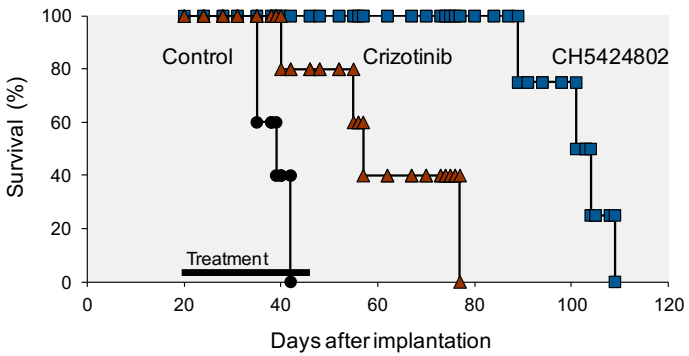
Next Generation ALK inhibitors

- Greater potency
- ALK mutations
- CNS activity
  - On Crizotinib

    CNS progression in 70%

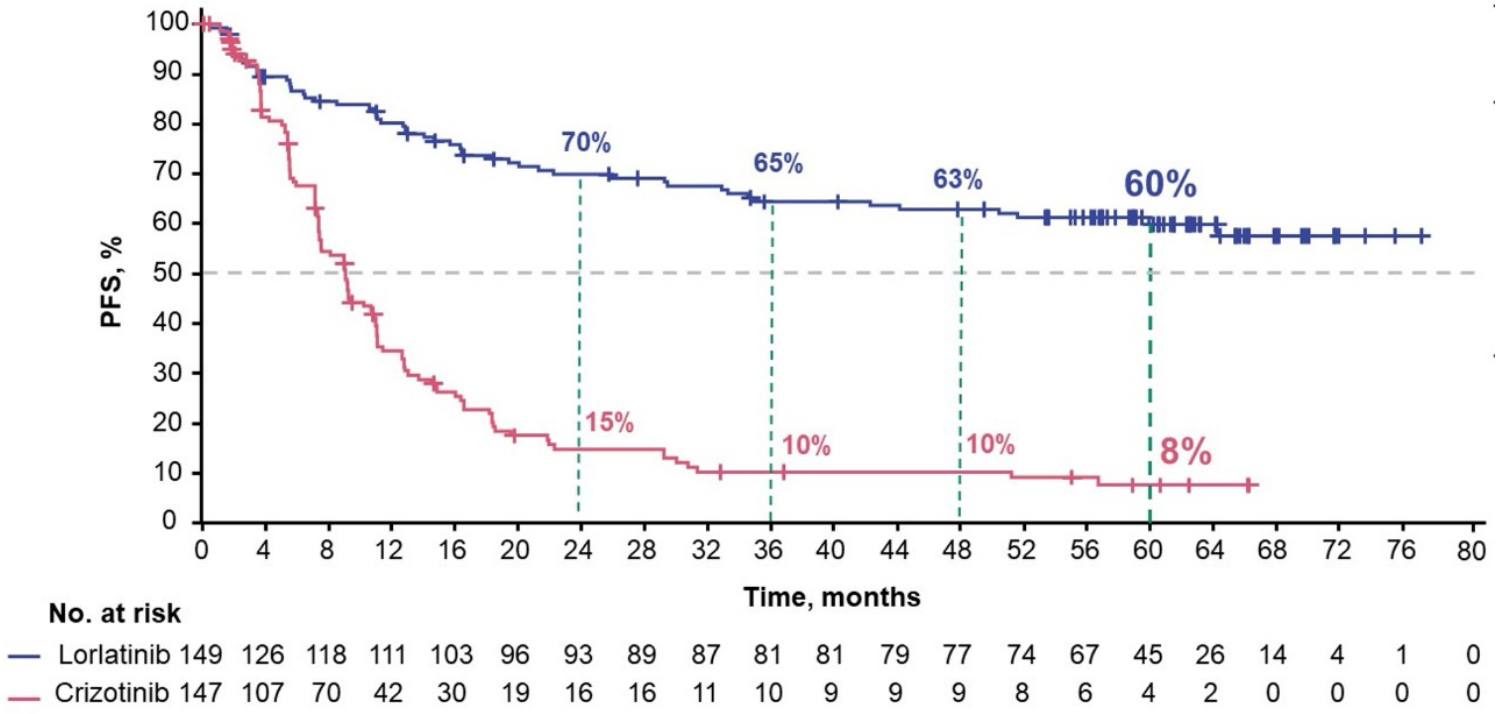






First Line Lorlatinib: CROWN

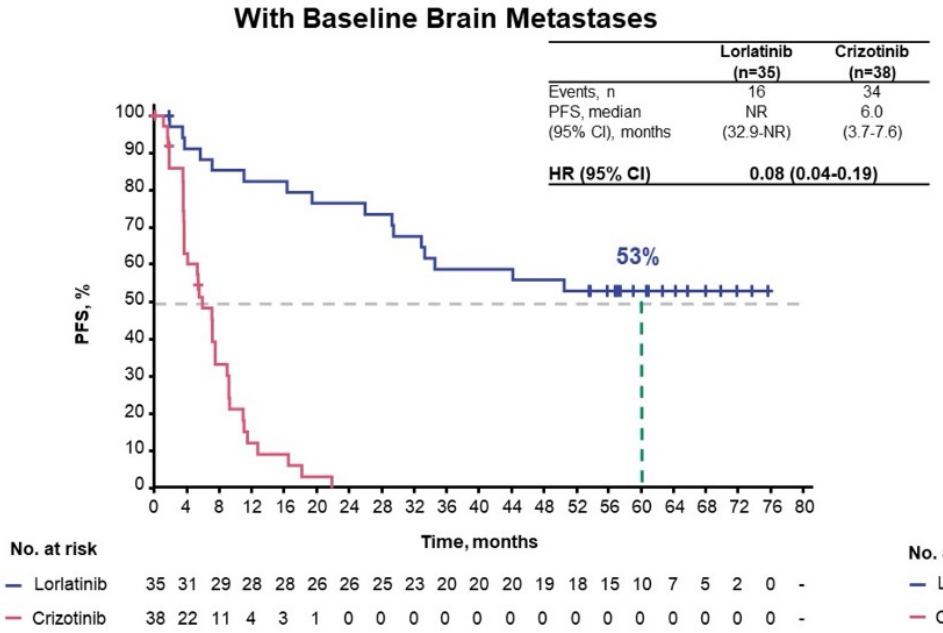
- 296 patients randomized to lorlatinib or crizotinib
  - 5y f/u: median PFS still not reached (vs 9.1m)
  - PFS HR 0.19 (0.13-0.27)

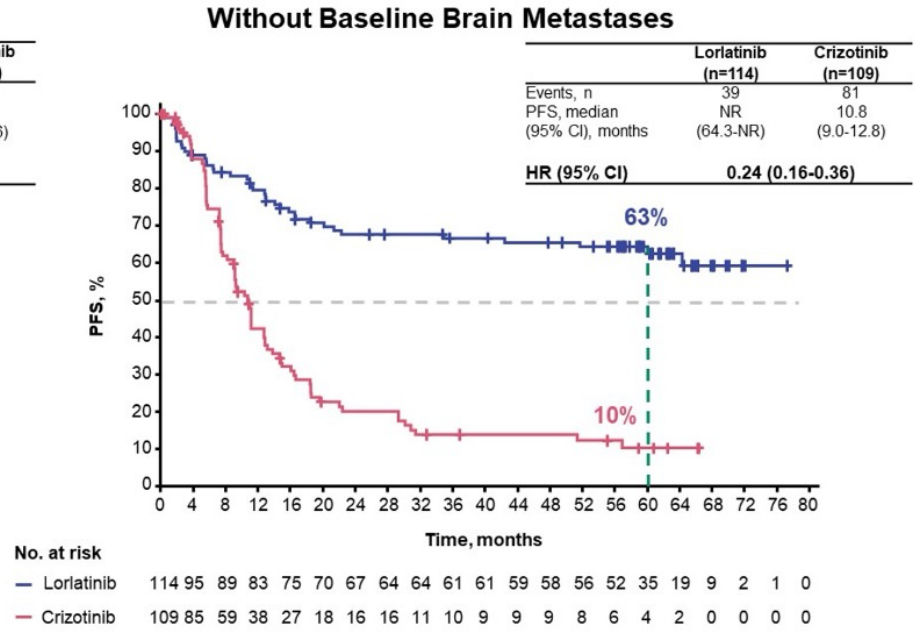


Solomon, ASCO 2024

First Line Lorlatinib: CROWN

- Lorlatinib superior with or without brain metastases
  - With baseline brain metastases, PFS HR 0.08 (!)
  - No baseline brain metastases, PFS HR 0.24





ALEX
HR- 0.37, PFS- 25.4 mo

Solomon, ASCO 2024; MOK ESMO 2019

Adverse Events

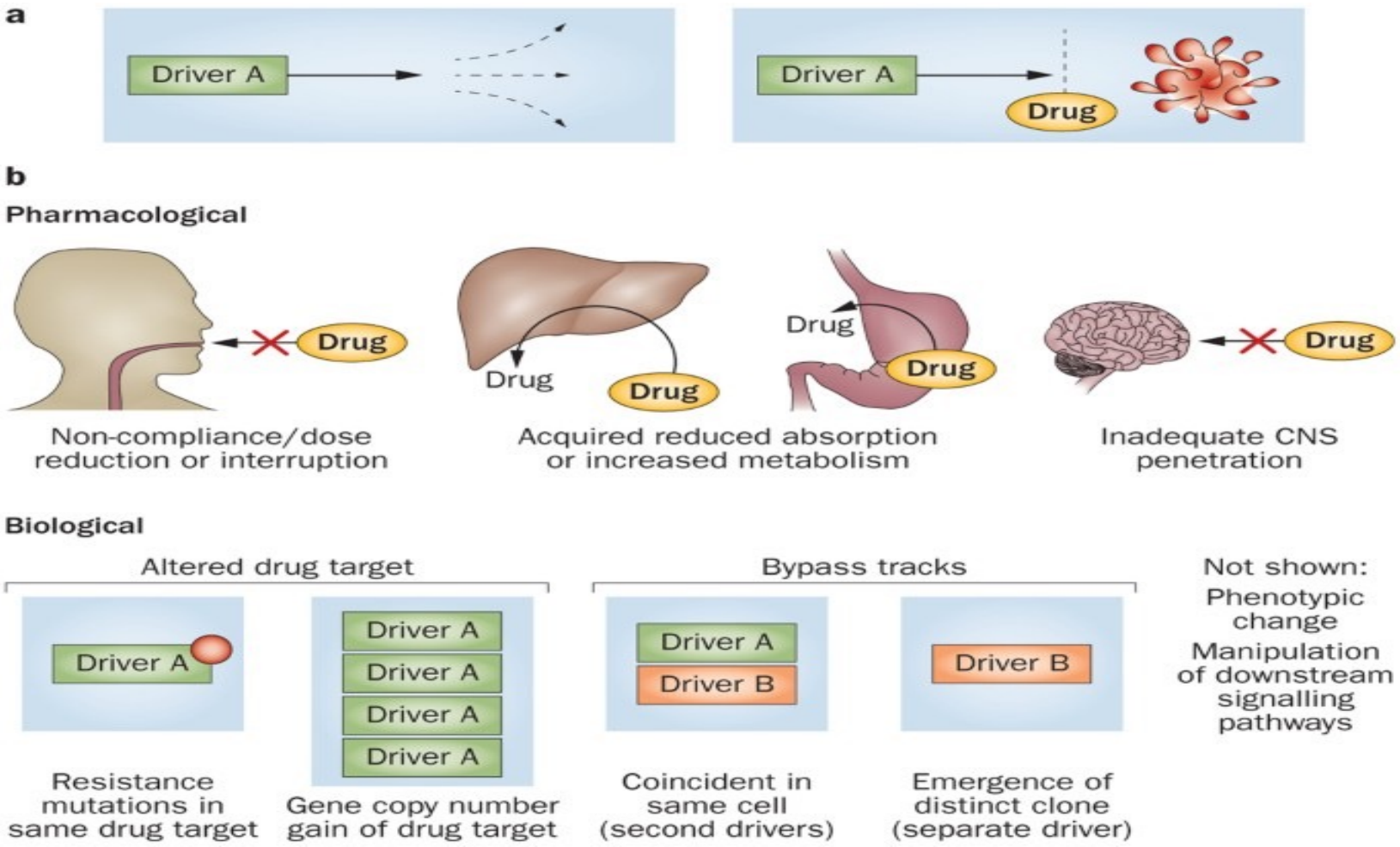
ALK Inhibitor	Rate of Dose Reduction	Rate of Discontinuation	Special Toxicity Considerations
Alectinib 600mg bid ALEX *Mok, Ann Oncol 2020*	20%	15%	Any grade AST/ALT elevation in 17/18% Any grade bilirubin elevation in 22% Any grade myalgias in 17%
Brigatinib 180mg qday ALTA-1L *Camidge, JTO 2021*	44%	13%	EOPE with changes in DLCO Any grade pneumonitis seen in 6% of pts G3+ CPK elevation in 26%
Lorlatinib 100mg qday CROWN *Solomon, ASCO 2024*	23%	11%	G3+ hypertriglyceridemia in 25% G3+ weight gain in 23% CNS AEs in 42%, G3+ in 14%

Selection of Initial ALK Therapy

- Lorlatinib offers longest PFS with unique toxicities
- Unanswered questions
  - How will real world first-line lorlatinib perform?
    - rwPFS
    - rw dose reduction / discontinuation rates
      - In 2L+ setting, rw rates were similar to trials
- Phase II basket study of lorlatinib
  - Exp3B: 28 pts with one prior non-crizotinib ALK inhibitor
    - 31% alectinib, 24% ceritinib, 4% brigatinib
    - RR 32.1%, mDOR not reached
    - Median PFS 5.5 months

Alexander, JTOCRR 2023; Solomon, ASCO 2024; Solomon Lancet Oncol 2018

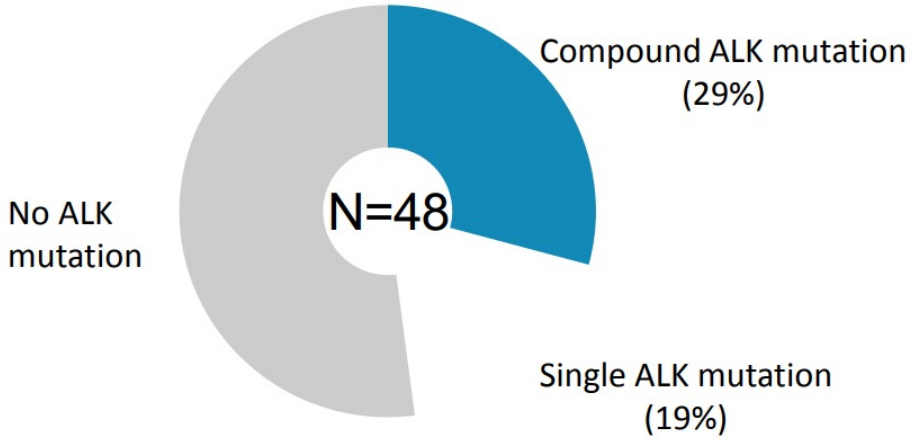
Mechanisms of resistance to TKIs



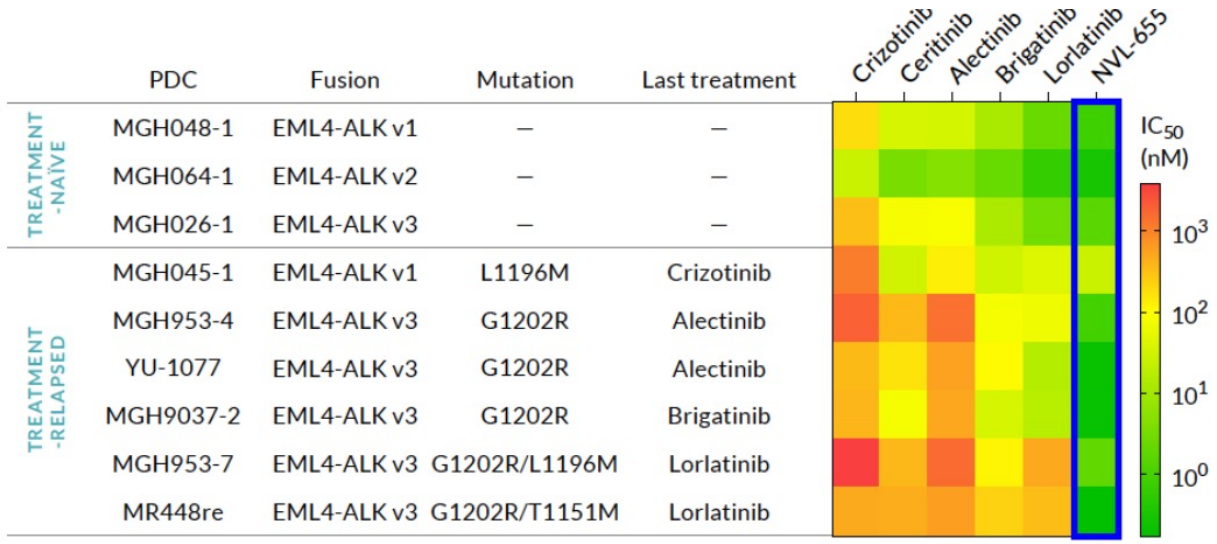
Camidge, Nature Reviews Clinical Oncology

Resistance to 2nd Line lorlatinib[1]

Post-lorlatinib tissue biopsies[2] (with prior ALK TKI)

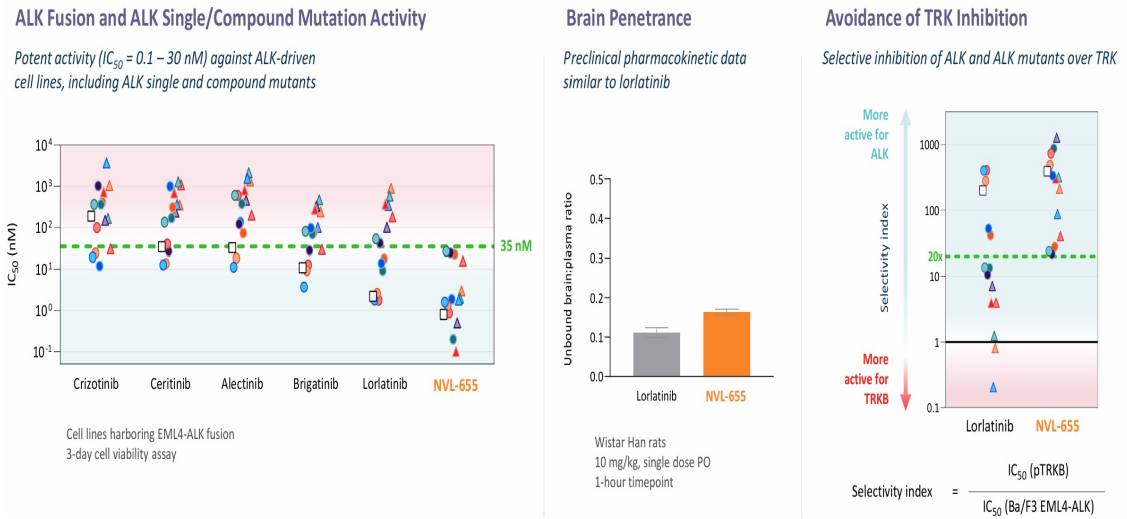


NVL-655, preclinical activity[3] (phase I evaluation ongoing; ALKOVE-1 – NCT05384626)



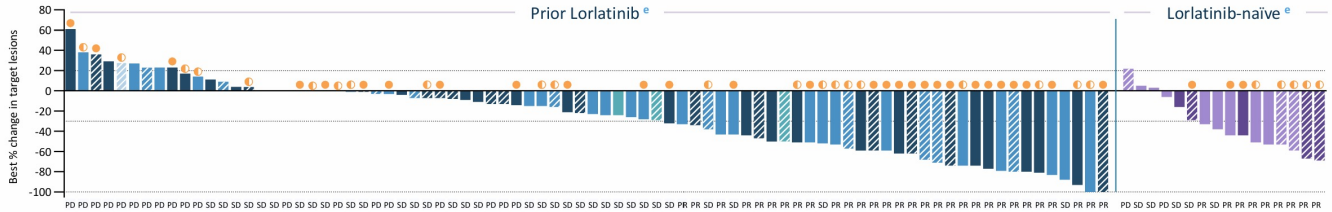
1. Solomon BJ, Lancet Oncol 2018; 2. Shiba-Ishii A, Nat Cancer 2021, 3. Fujino T, EORTC-NCI-AACR 2022

NVL-655



Preliminary Activity: Radiographic Tumor Responses Across Previously Treated Patients with ALK+ NSCLC

RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [b]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	**38%** (39/103)	**52%** (30/58)	**69%** (22/32) [d]	**35%** (30/85)	**47%** (23/49)	**54%** (15/28)	**53%** (9/17)	**88%** (7/8)
RP2D	**38%** (15/39)	**55%** (12/22)	**71%** (10/14)	**35%** (11/31)	**50%** (8/16)	**64%** (7/11)	**57%** (4/7)	**80%** (4/5)



Most common toxicities were AST/ALT elevation

15% required dose reduction

2% Drug discontinuation

Drilon, A, ESMO 2024

Resistance to 1st line lorlatinib

Felip E, ESMO 2022- CROWN

Resistance mutation at EOT	Lorlatinib n=26	Crizotinib n=80
New single *ALK* mutation, n (%)	0	6 (8)
ALK compound mutation, n (%)	0	2 (2)
Bypass mechanism, n (%)[a]	9 (35)	10 (12)
MAPK pathway aberration	3 (12)	1 (1)
PI3K/mTOR/PTEN pathway aberration	2 (8)	0
RTK pathway aberration	4 (15)	5 (6)
Cell cycle pathway aberration	2 (8)	5 (6)
Other mutation, n (%)	9 (35)	15 (19)

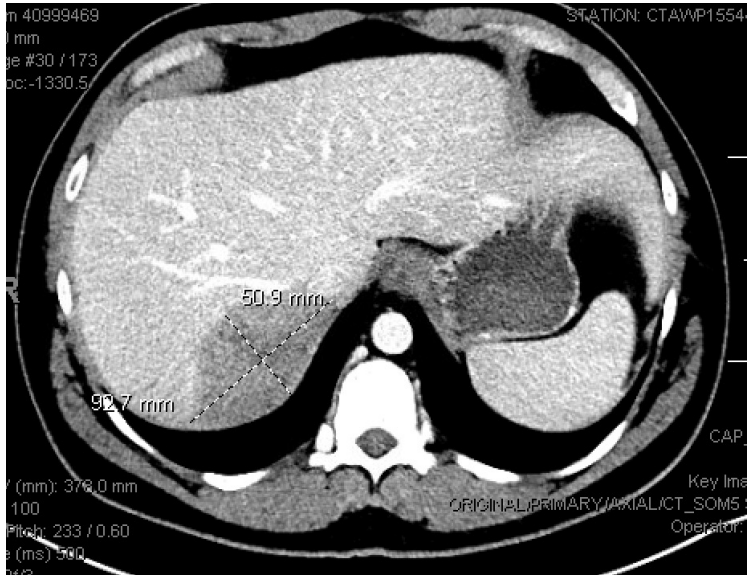
[a]Each sample could harbor >1 bypass mechanism.

MET Amplification in ALK positive NSCLC patient

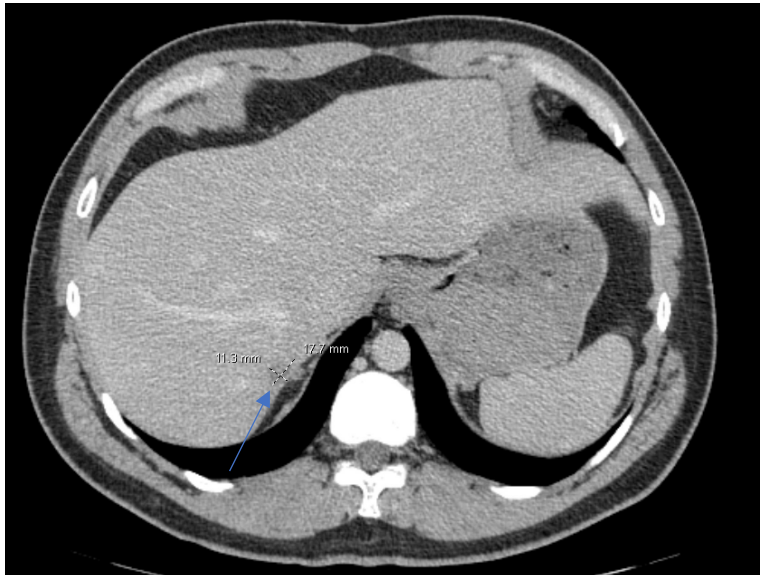
Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY ✓ Approved in indication ~ Approved in other indication ✗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 5)	% cfDNA or Amplification
EML4-ALK Fusion	✓ Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib	Yes	3.3%
MET Amplification	~ Capmatinib, Crizotinib, Tepotinib	Yes	Medium (++)
TP53 Splice Site SNV	None	Yes	5.1%
TP53 D391Y	None	Yes	4.8%



June 8th 2023
Lorlatinib (ALK inhibitor)

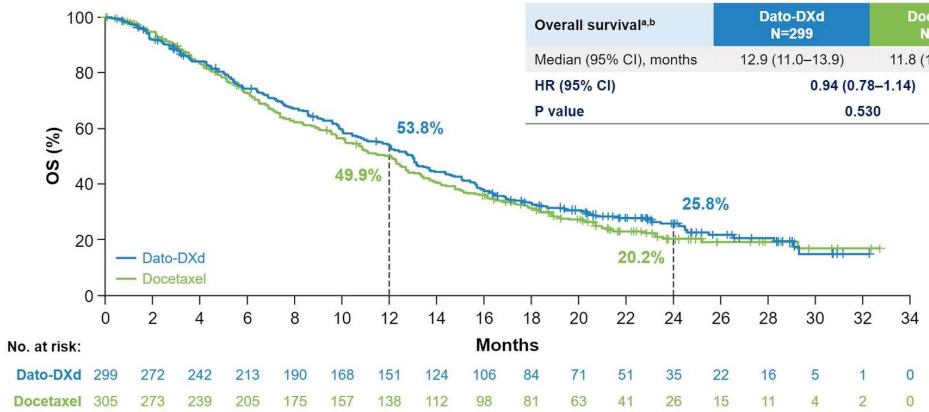


August 8th 2024
Lorlatinib (ALK inhibitor) +
Capmatinib (MET inhibitor)

Antibody Drug Conjugates in AGA NSCLC

Overall Survival: ITT

TROPION-Lung01



Overall survival[a,b]	Dato-DXd N=299	Docetaxel N=305
Median (95% CI), months	12.9 (11.0–13.9)	11.8 (10.0–12.8)
HR (95% CI)	0.94 (0.78–1.14)	
P value	0.530	

[a]Median (95% CI) OS follow-up was 23.1 (22.0, 24.8) months for Dato-DXd and 23.1 (21.7, 24.2) months for docetaxel. [b]At primary OS analysis (data cutoff: March 1, 2024), 433 OS events (IF) were observed.
IF, information fraction.

Overall Survival: Subgroup Analyses

TROPION-Lung01

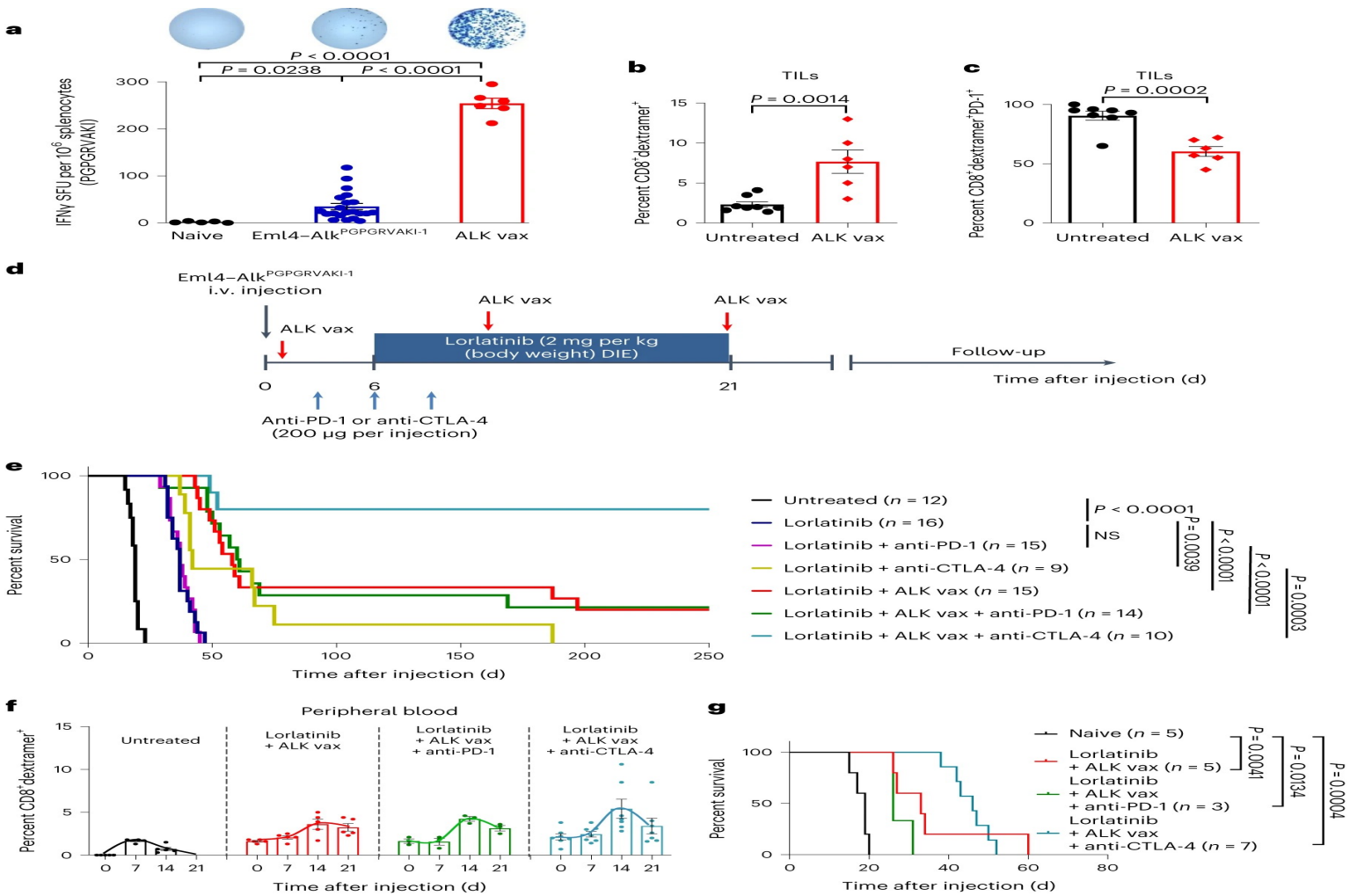
		No. of events/No. of patients Dato-DXd	Docetaxel	HR
Age at randomization	<65 years	117/162	112/155	0.88
	≥65 years	98/137	106/150	0.97
Sex	Male	136/183	156/210	0.93
	Female	79/116	62/95	0.97
Race	White	90/123	95/126	0.85
	Asian	83/121	79/120	0.92
	Black/African American	4/6	2/4	1.61
	Other	33/43	35/47	1.05
Smoking status	Never	43/60	31/52	1.22
	Former/current	172/239	186/251	0.88
Brain metastases at baseline	With	37/50	31/47	1.09
	Without	178/249	187/258	0.89
Histology	Nonsquamous	160/234	163/234	0.84
	Squamous	55/65	55/71	1.32
Actionable genomic alterations[a]	Absent	182/249	185/254	0.97
	Present	33/50	33/51	0.66

Data cutoff: March 1, 2024.
[a]Regardless of histology.

HR in AGA- 0.66; NSQ- 0.84;ITT- 0.94

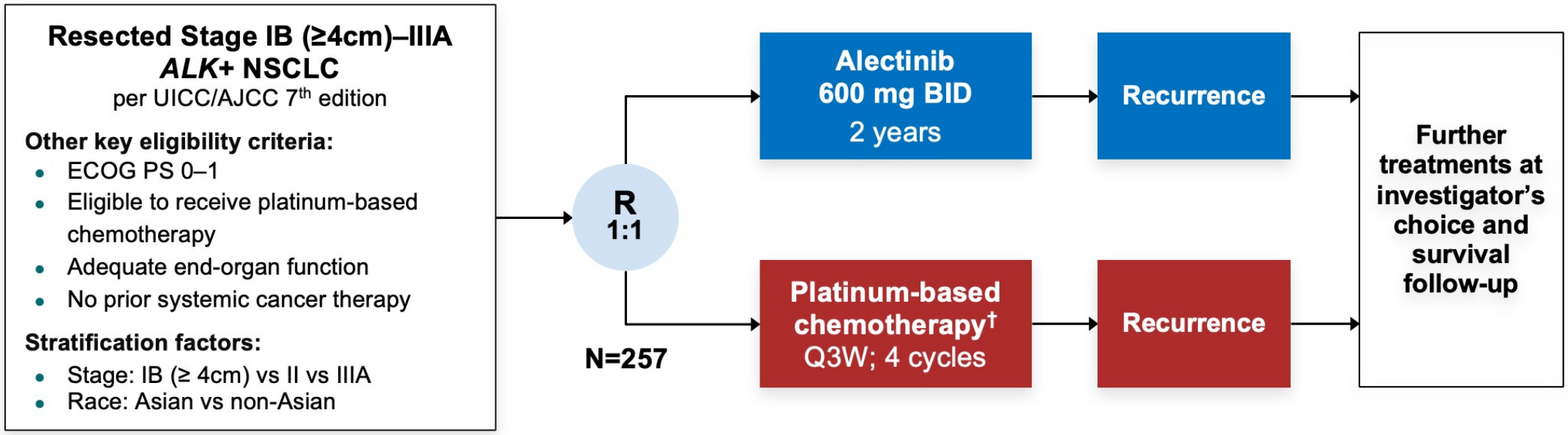
Sands, et al WCLC 2024

ALK Vaccine



Mota, et al Nature Cancer 2023

ALINA: Adjuvant ALK Inhibition

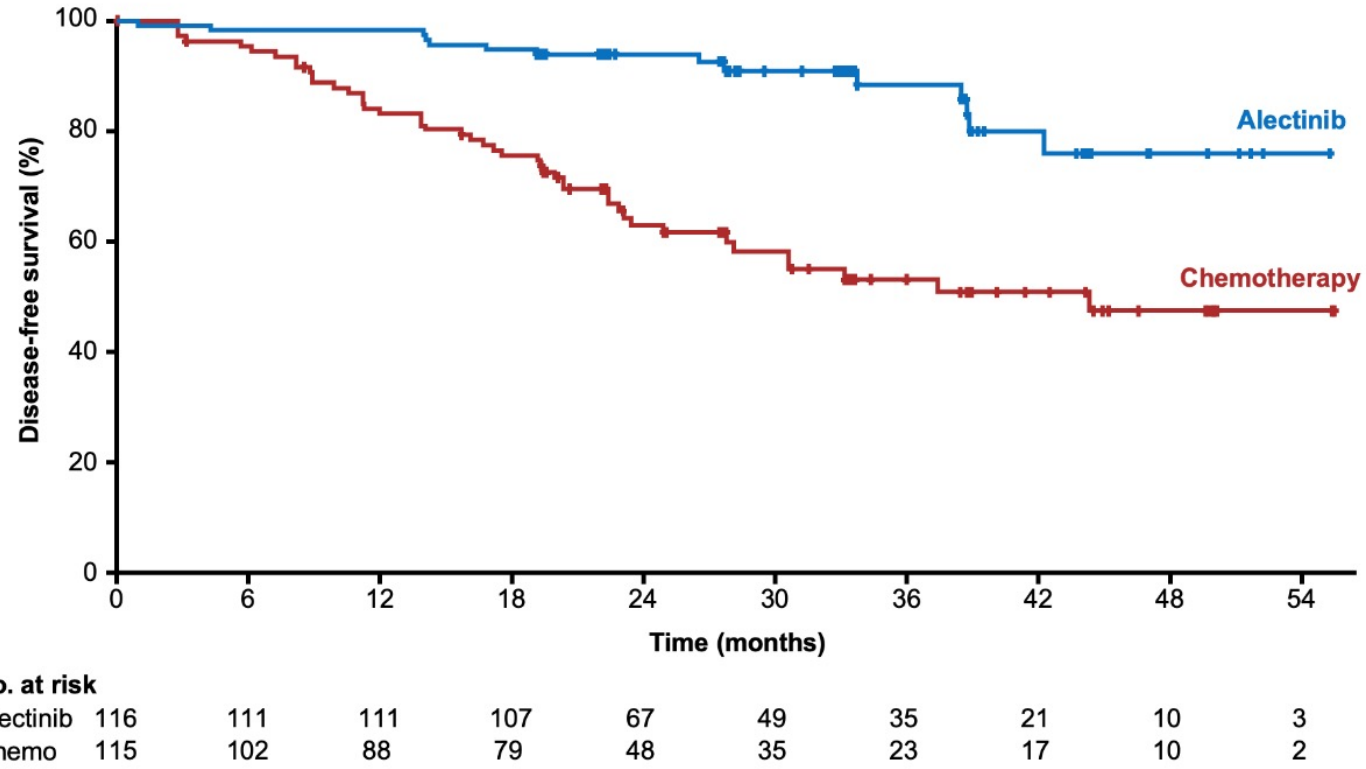


- ALINA
  - 2y adjuvant alectinib versus chemotherapy

Solomon, ESMO 2023

ALINA: Adjuvant ALK Inhibition

- Alectinib superior, DFS HR 0.24, CNS DFS HR 0.22



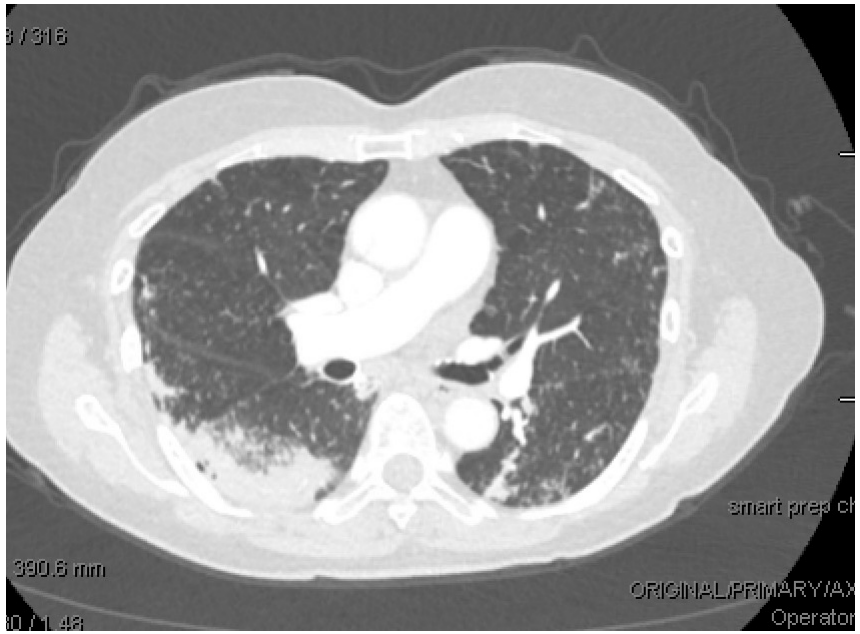
	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Solomon, ESMO 2023

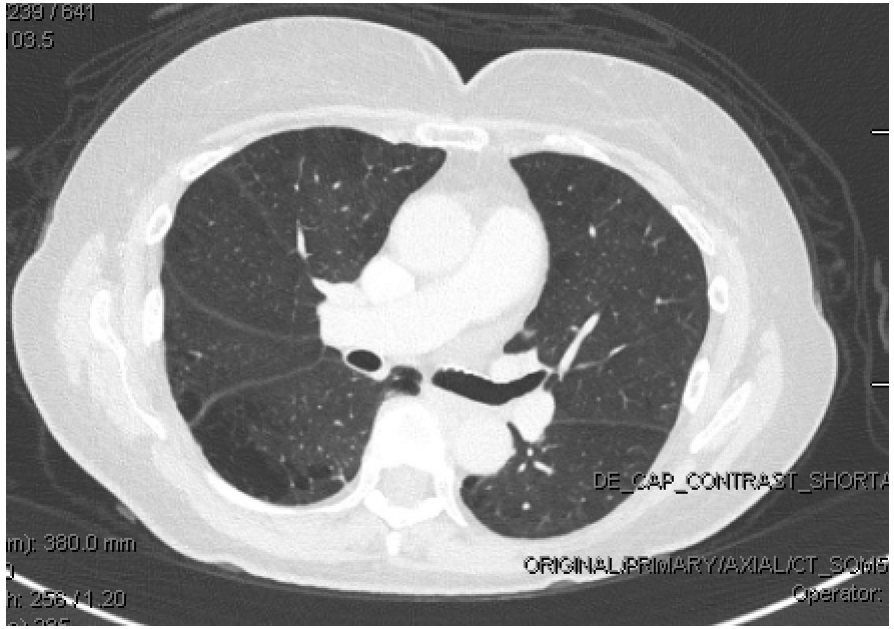
Questions

- Should chemotherapy be considered in stage II/III NSCLC or should it be alectinib alone?
  - Yes- Lymph Node positive disease
- Post-Chemo/RT in Stage III disease
  - Yes.
- Duration of Therapy?
  - Longer in More Lymph node positive disease
- Role of MRD assessment.
- Should neoadjuvant alectinib be considered?

Advanced ALK+ve NSCLC Patient



July 2021



December 2022

Advanced ALK+ve NSCLC Patient

Patient has provided verbal permission to show picture

Conclusions

- Lorlatinib offers the longest PFS in the front-line setting
  - Unique Adverse Events
- Some patients do exceedingly well with Alectinb or Brigatinib
  - Biomarkers to identify patients who do well
- Adjuvant Alectinib improves DFS
- ADCs, Vaccines and Cell Therapy