Is there room for novel next generation ALK TKIs in 1L ALK+ NSCLC?

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Henry Ford Cancer Institute/Henry Ford Health

Disclosures

- Advisory Board- Genentech/Roche, Astellas, Amgen, Astra-Zeneca, Pfizer, Boehringer-Ingelheim, Takeda, Lilly, BMS, Daichii, Gilead, Bayer, Nuvation, Johnson and Johnson, Abbvie, Lilly, Regeneron
- IDMC- Astra-Zeneca
- Travel- Mirati, Merck

Objectives

- Recent Data
- Novel ALK TKIs
- Covalent Inhibitors, PROTACS
- Combination Treatments
- Vaccines
- Drug Tolerant Persister Cells and Co-Mutations
- Cancer Metabolism
- Lifestyle modifications

ALINA Updated Results

BERLIN 2025 ESMO congress

Updated results from the phase III ALINA study of adjuvant alectinib vs chemotherapy in patients with early-stage *ALK*+ non-small cell lung cancer (NSCLC)

R. Dziadziuszko[1], B.J. Solomon[2], Y. Wu[3], J.S. Ahn[4], M. Nishio[5], D.H. Lee[6], J. Lee[7], W. Zhong[3], H. Horinouchi[8], W. Mao[9], M.J. Hochmair[10], F. de Marinis[11], M.R. Migliorino[12], I. Bondarenko[13], T. Xu[14], A. Cardona[15], A. Scalori[16], V. McNally[16], A.A. Higgerson[17], F. Barlesi[18]

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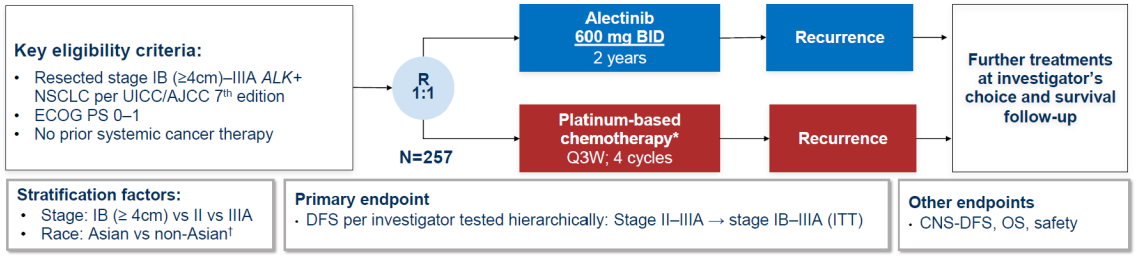
ALINA: background and study design

- **Alectinib**, an ALK inhibitor, is an approved **standard-of-care** for patients with **resected or advanced *ALK*+ NSCLC**[1–3]
  - Alectinib has **demonstrated efficacy and delayed disease progression in the CNS**[1–3]
  - Long-term data show alectinib is tolerable and has a manageable safety profile[1–3]
- **ALINA** is the only **positive phase III trial** of an ALK inhibitor in **resectable, stage IB–IIIA** (UICC/AJCC 7th edition), *ALK*+ NSCLC[2–4]
  - The primary analysis showed a **significant DFS benefit** with alectinib vs chemotherapy (**HR: 0.24**; 95% CI 0.13–0.43; p<0.0001)[2,3]



Here, we present updated data from the ALINA study with a median follow-up of 4 years
All patients in the alectinib arm had completed 2 years of treatment with ≥1 year of follow-up

NCT03456076. Crossover was not permitted prior to disease recurrence. *Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability. †Stratification by patient race recorded in the interactive voice/web response system. 1. Alecensa Prescribing Information Genentech Inc. 2024; 2. Solomon et al. ESMO 2023 (LBA2); 3. Wu et al. N Engl J Med 2024; 4. Ahn et al. ESMO Asia 2023 (LBA1). *ALK*, anaplastic lymphoma kinase; AJCC, American Joint Committee on Cancer; BID, twice daily; CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intention to treat; OS, overall survival; Q3W, every 3 weeks; R, randomisation; UICC, Union for International Cancer Control

Prof. Rafal Dziadziuszko

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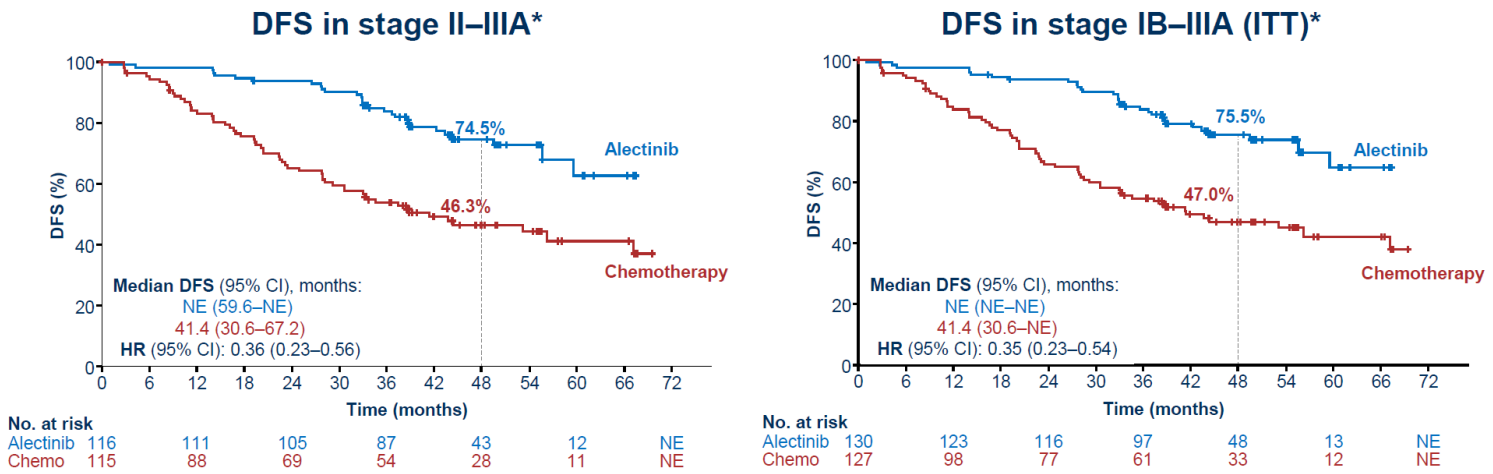
ALINA Updated Results

Disease-free survival



Median follow-up (ITT): alectinib, 48.0 months; chemotherapy, 47.4 months

DFS benefit was sustained with alectinib versus chemotherapy in the stage II–IIIA and stage IB-IIIA (ITT) populations

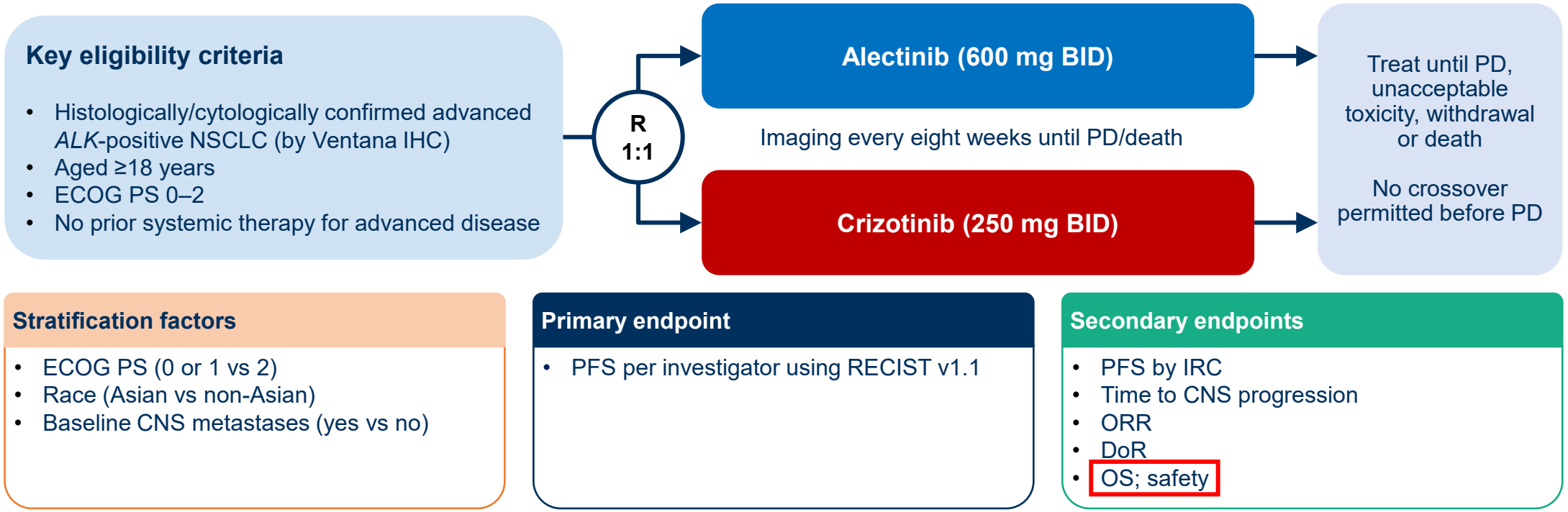
Data cut-off: 8 December 2024. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurred first
*Per UICC/AJCC 7th edition. Chemo, chemotherapy; NE, not estimable

Prof. Rafal Dziadziuszko

Alectinib was stopped at 2 years.

Patients did not receive adjuvant chemotherapy

ALEX: randomised, open-label, Phase 3 multicentre study



NCT02075840.

BID, twice daily; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumours.

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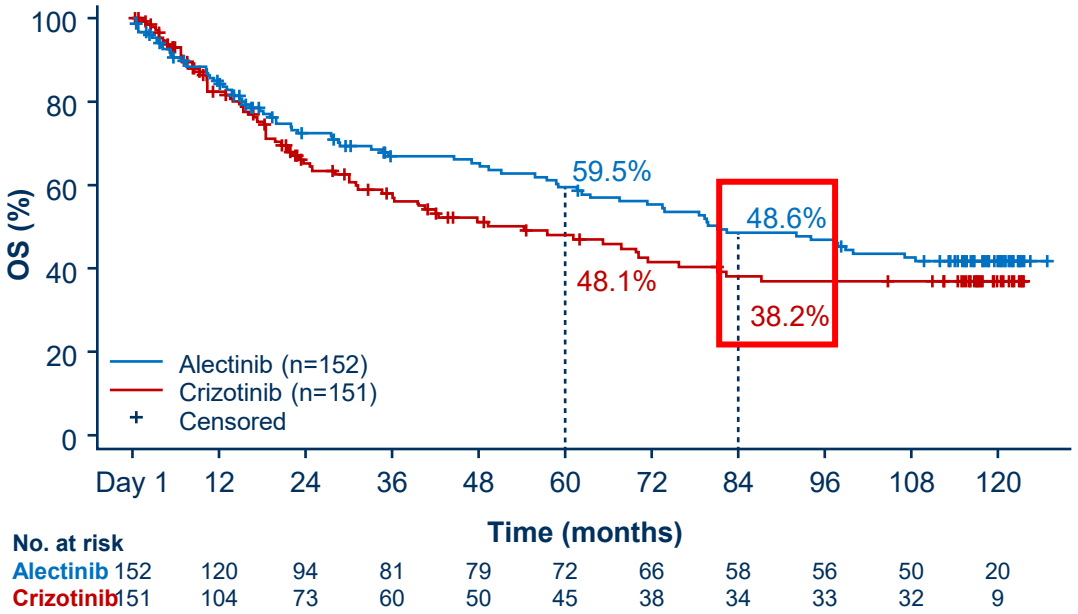
OS in the ITT population

- Median follow-up was 53.5 months with alectinib and 23.3 months with crizotinib
- 7-year OS rate: 48.6% with alectinib vs 38.2% with crizotinib



	Alectinib (n=152)	Crizotinib (n=151)
Patients with event, n (%)	76 (**50.0**)	73 (**48.3**)
Median, months (95% CI)	**81.1** (62.3–NE)	**54.2** (34.6–75.6)
Stratified HR (95% CI)	**0.78** (0.56–1.08)	
p-value (stratified log-rank)	0.1320	

Alectinib induced a clinically meaningful **OS benefit** compared with **crizotinib**

NCT02075840. Data cut-off date: 28 April 2025.

The study was not powered for OS. Median follow-up was shorter than the additional 6-year follow-up time in this analysis due to patients who died, withdrew consent or were lost to follow-up. ITT, intent to treat; NE, not estimable.

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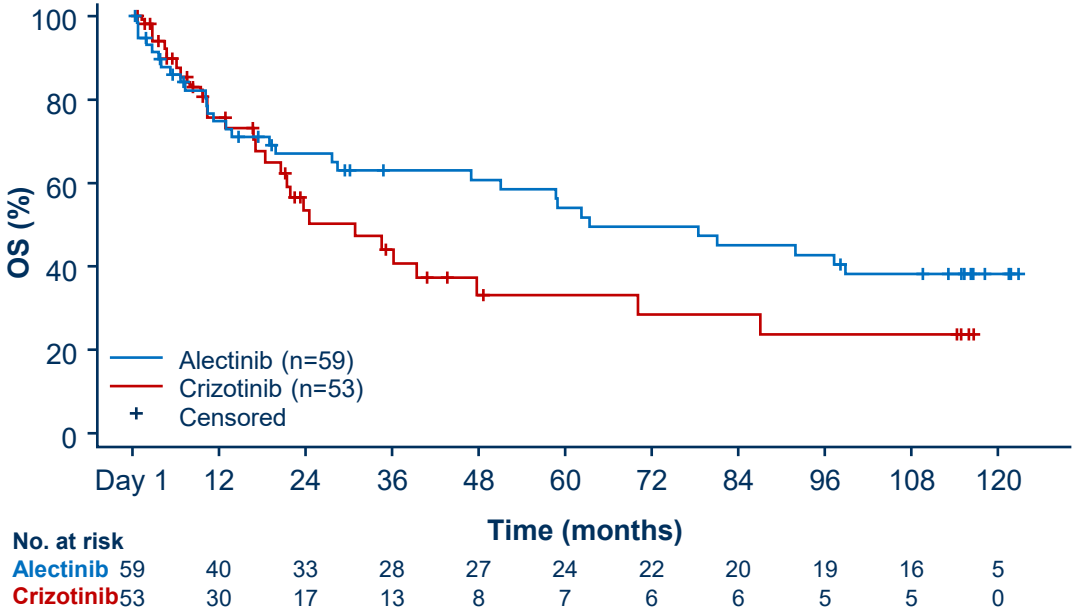
OS by CNS metastases* at baseline

Patients with CNS metastases at baseline

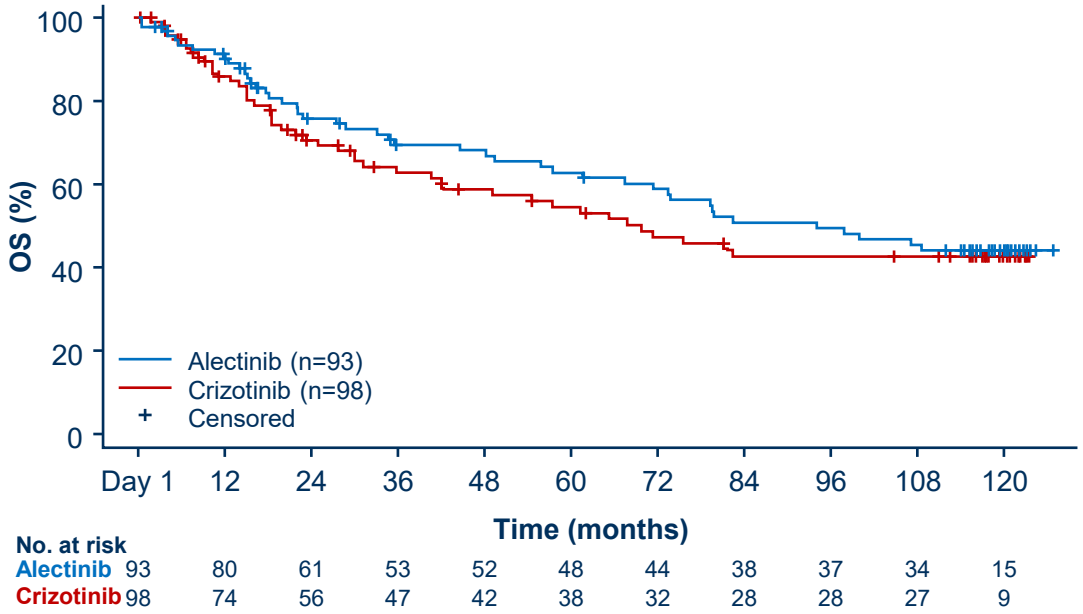
- Median OS: 63.4 months with alectinib vs 30.9 months with crizotinib (HR 0.68; 95% CI 0.40–1.15)



No. at risk											
Alectinib	59	40	33	28	27	24	22	20	19	16	5
Crizotinib	53	30	17	13	8	7	6	6	5	5	0

Patients without CNS metastases at baseline

- Median OS: 94.0 months with alectinib vs 69.8 months with crizotinib (HR 0.87; 95% CI 0.58–1.32)



No. at risk											
Alectinib	93	80	61	53	52	48	44	38	37	34	15
Crizotinib	98	74	56	47	42	38	32	28	28	27	9

Alectinib induced a clinically meaningful **OS benefit** compared with **crizotinib** in patients both **with** and **without CNS metastases**

NCT02075840. Data cut-off date: 28 April 2025.
*Assessed by investigator.

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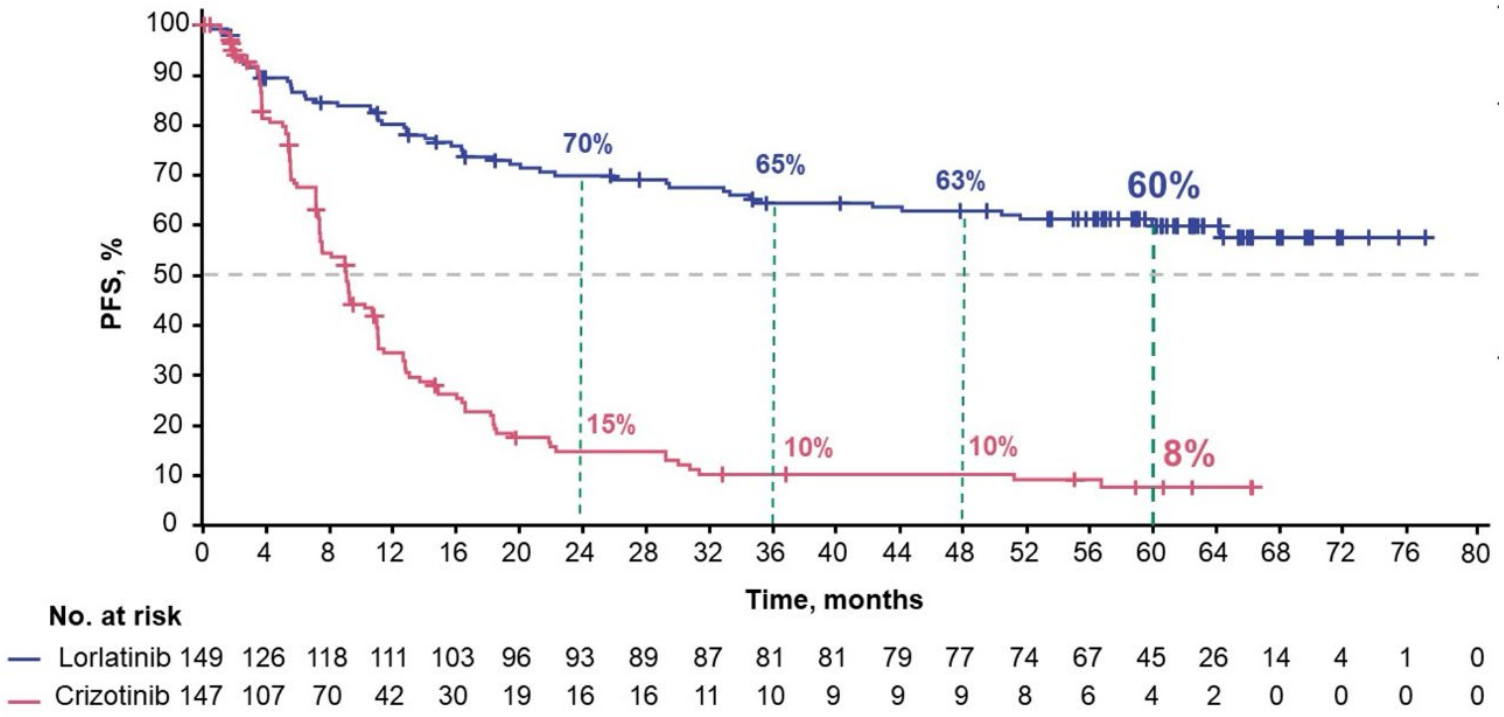
First Line Lorlatinib: CROWN

- 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)



Median PFS of Alectinib in ALEX was 34 months

Solomon, ASCO 2024

CNS Activity: Updated Results

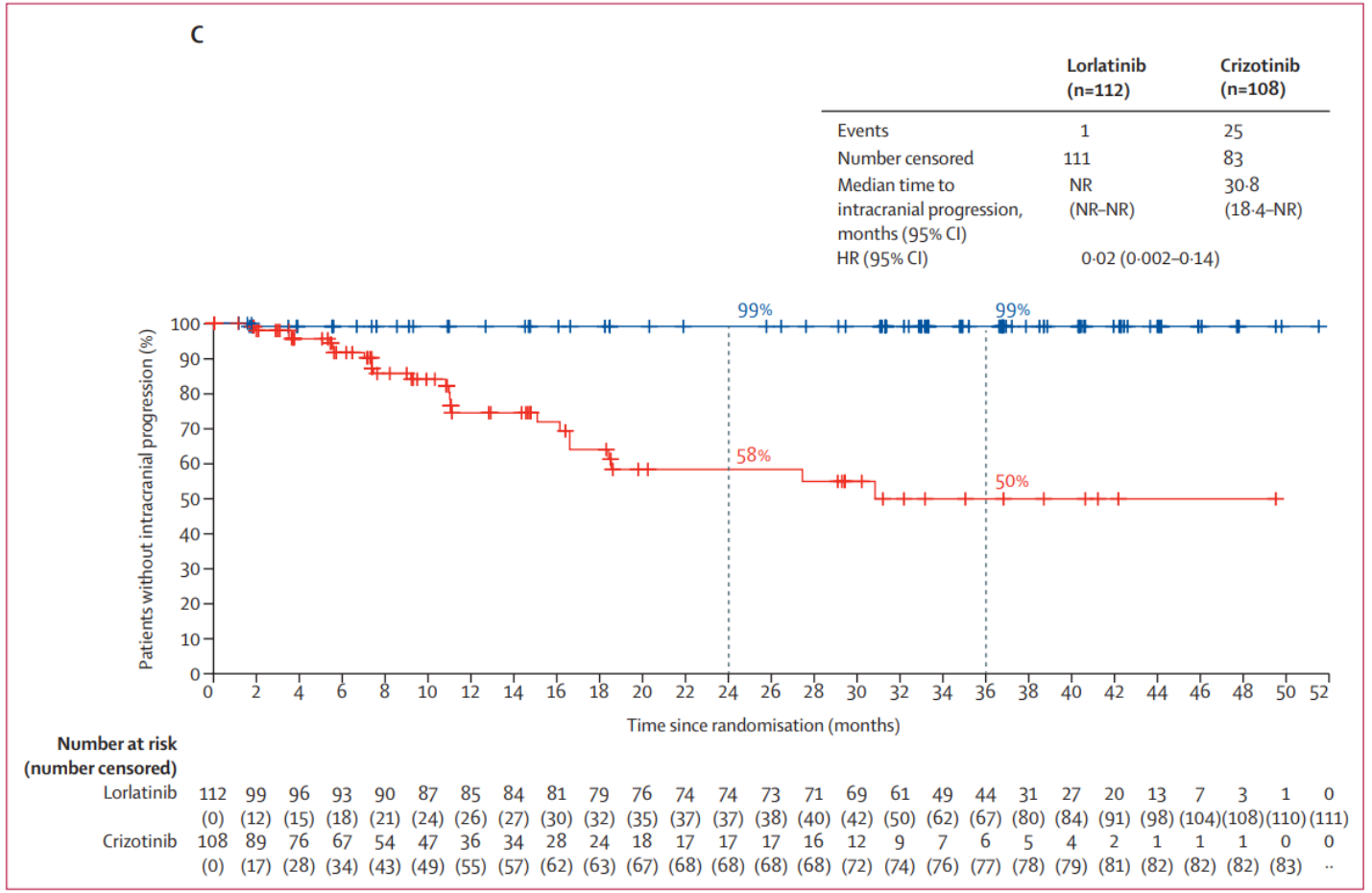


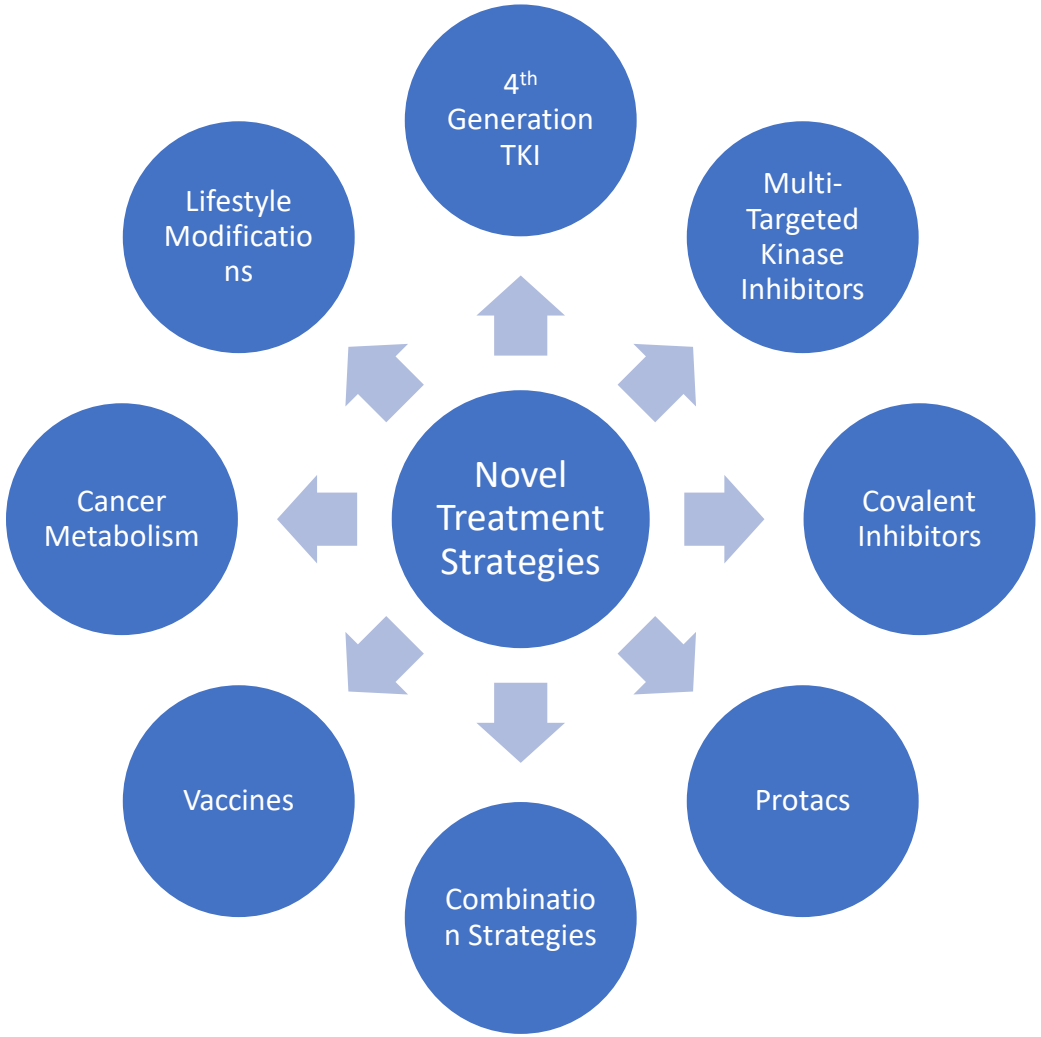
Figure 3: **Time to intracranial progression by blinded independent central review per modified Response Evaluation Criteria in Solid Tumours, version 1.1**
(A) Intracranial time to progression in the intention-to-treat population. (B) Intracranial time to progression in patients with baseline brain metastases.
(C) Intracranial time to progression in patients without baseline brain metastases. HR=hazard ratio. NR=not reached.

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%

Median PFS of second line Lorlatinib is 7-9 months
Preferred first-line agent in my practice is Lorlatinib

Novel Treatment Strategies in ALK+ NSCLC



Greater Benefit

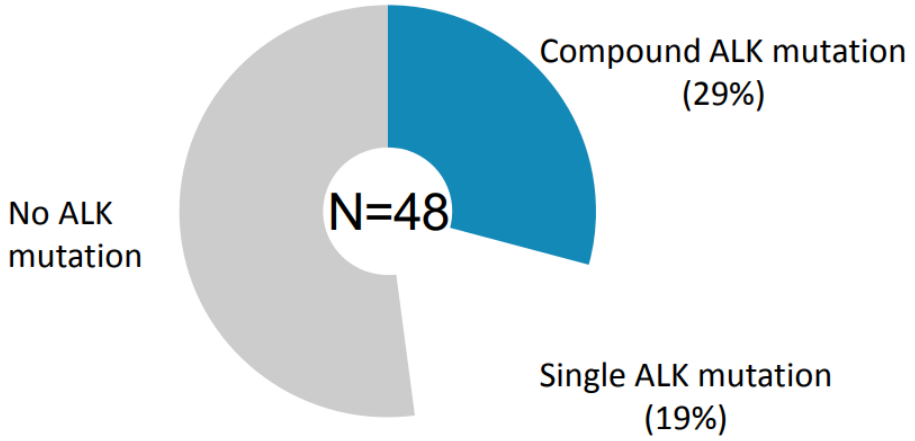
Overcome Resistance

Less Toxicities

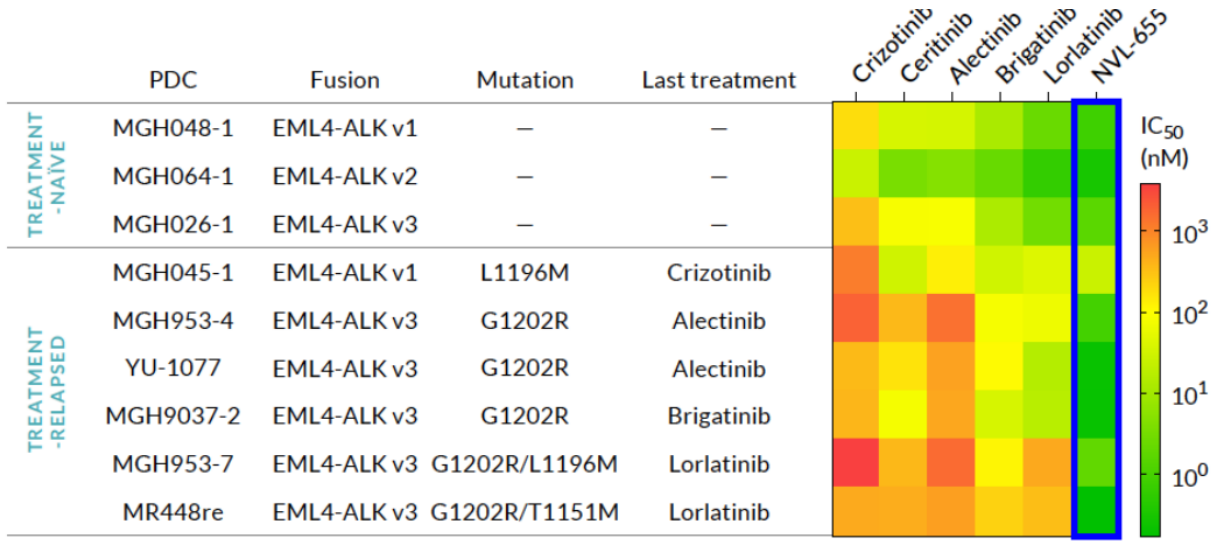
Live a Wholesome Life

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)

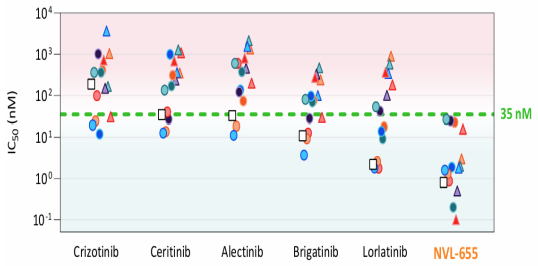


1. Solomon BJ, Lancet Oncol 2018; 2. Shiba-Ishii A, Nat Cancer 2021, 3. Fujino T, EORTC-NCI-AACR 2022

Neladalkib (NVL-655)

ALK Fusion and ALK Single/Compound Mutation Activity

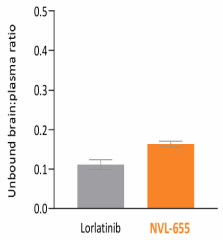
Potent activity (IC_{50} = 0.1 – 30 nM) against ALK-driven cell lines, including ALK single and compound mutants



Cell lines harboring EML4-ALK fusion
3-day cell viability assay

Brain Penetrance

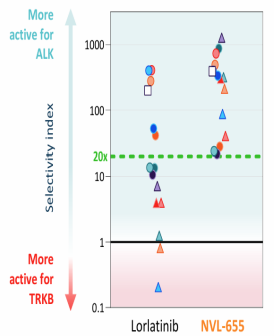
Preclinical pharmacokinetic data similar to lorlatinib



Wistar Han rats
10 mg/kg, single dose PO
1-hour timepoint

Avoidance of TRK Inhibition

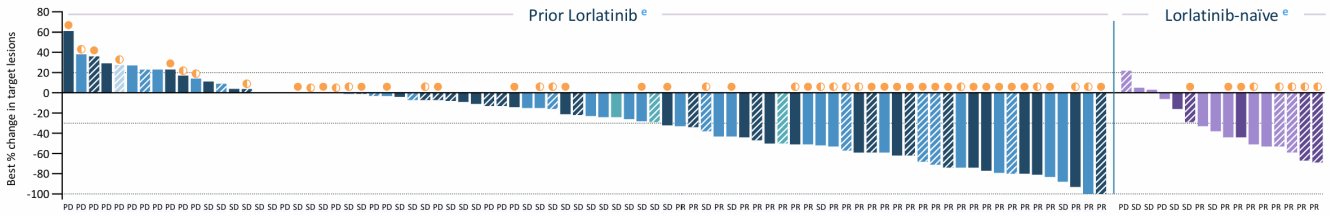
Selective inhibition of ALK and ALK mutants over TRK



$$\text{Selectivity index} = \frac{IC_{50}\ (pTRKB)}{IC_{50}\ (Ba/F3\ EML4\text{-}ALK)}$$

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

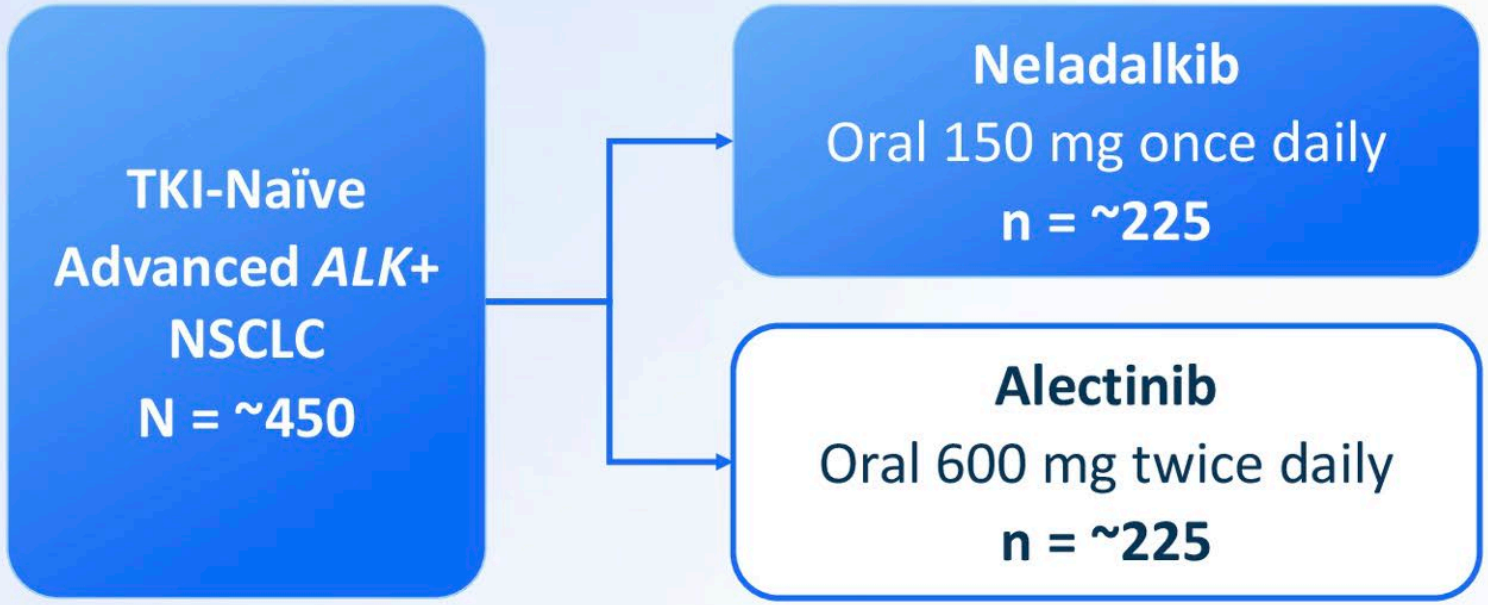
RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [b]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	**38%** (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

Global Phase 3 study of Neladalkib vs alectinib as firstline treatment for ALK+ NSCLC



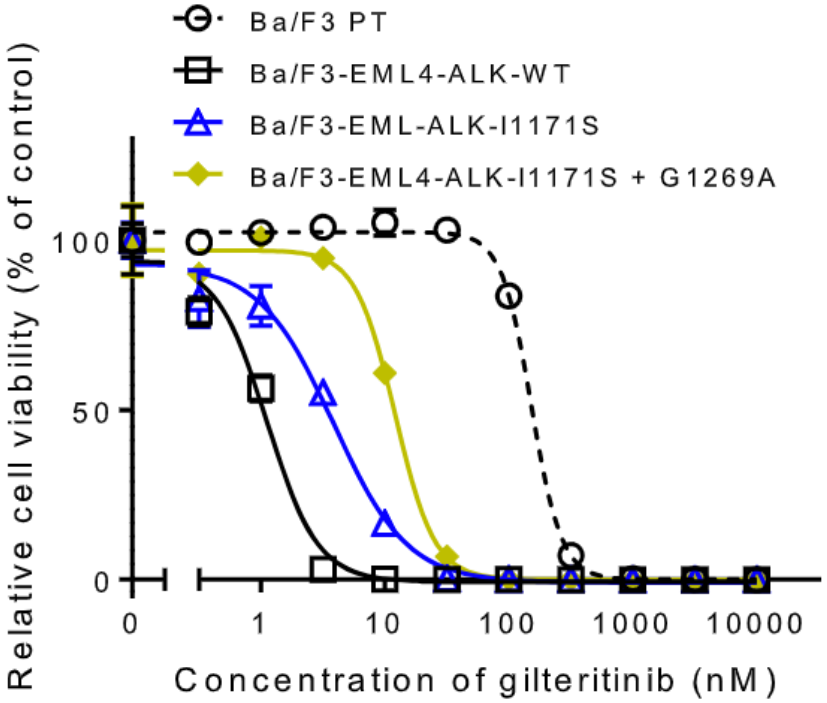
1:1 Randomization

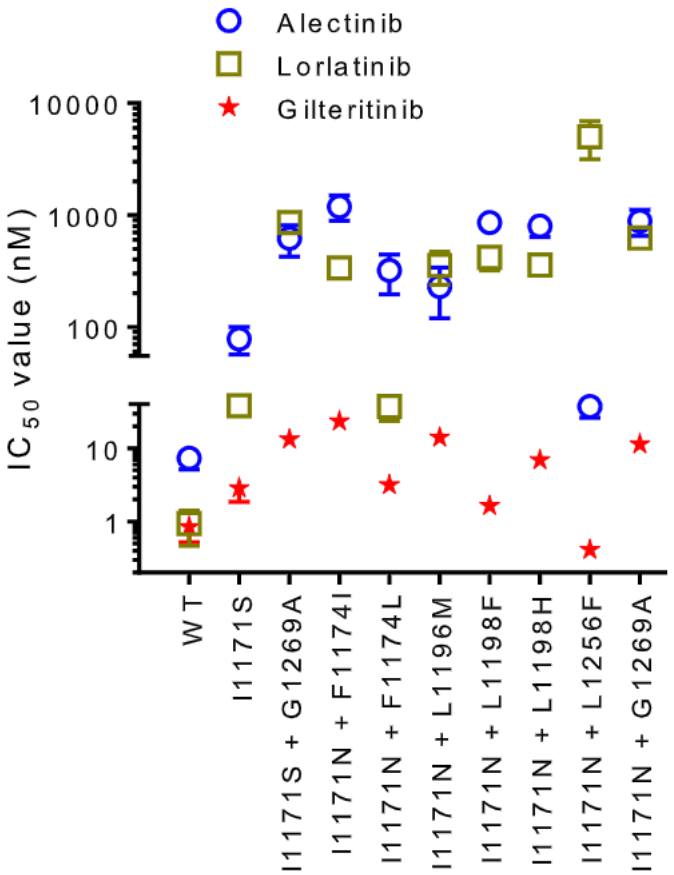
Stratification Factors:

- Brain metastases (yes vs. no)
- Ethnic origin (Asian vs. non-Asian)
- ECOG PS (0 vs. 1 vs. 2)

Primary Endpoint: **Progression Free Survival**

Gilteritinib for refractory ALK NSCLC

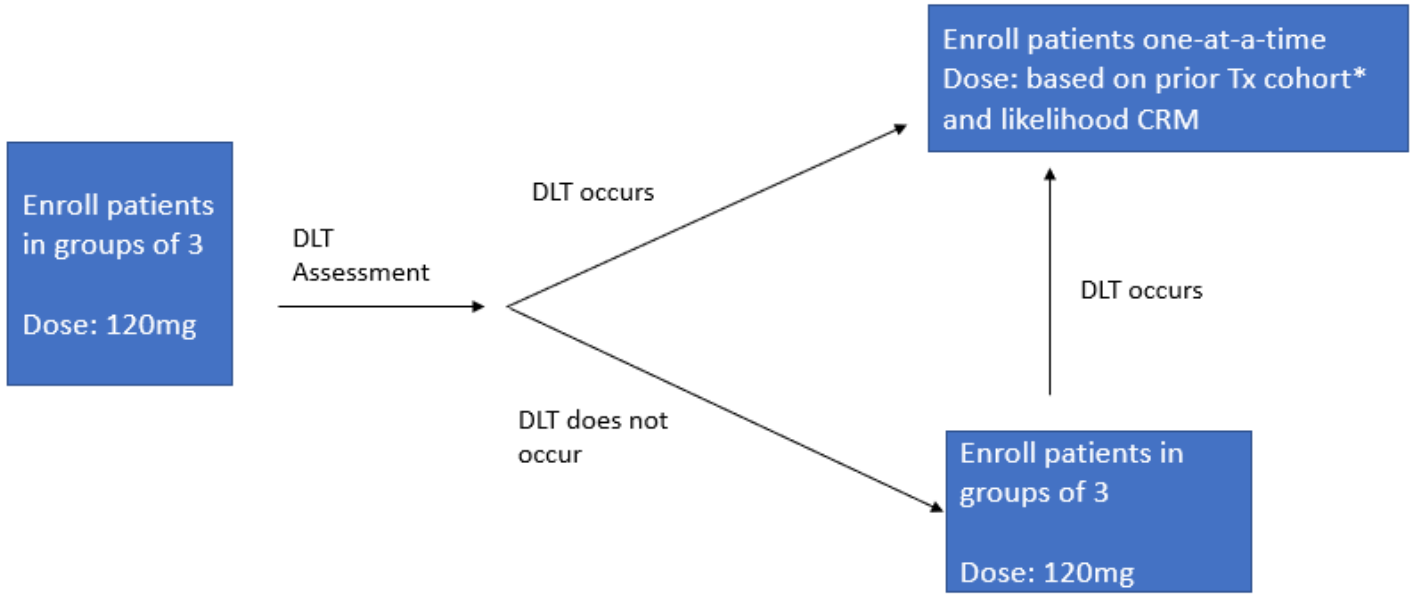




Gilteritinib has broad activity against compound ALK mutations and activity through FLT3, AXL, TRKA, and MER pathways

Mizuta, et al, Nature Communications 2021
Slide Courtesy Dr. Tejas Patil, TTLC 2025

Study schema



***Prior Treatment Cohorts**

Cohort 1: Prior 1st generation ALK TKI (crizotinib) and/or prior 2nd generation TKI (ceritinib, brigatinib, alectinib) and/or lorlatinib

Cohort 2: Prior 1st generation ALK TKI (crizotinib) and/or prior 2nd generation TKI (ceritinib, brigatinib, alectinib) and/orlorlatinib, and platinum-doublet chemotherapy

Cohort 3: Prior 1st generation ALK TK (crizotinib) and/or prior 2nd generation TKI (ceritinib, brigatinib, alectinib) and/or lorlatinib, platinum-doublet chemotherapy, and any other number of antineoplastic agents (including immunotherapy, standard or investigational)

NCT06225427; PI- Dr. Angel Qin, University of Michigan

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)

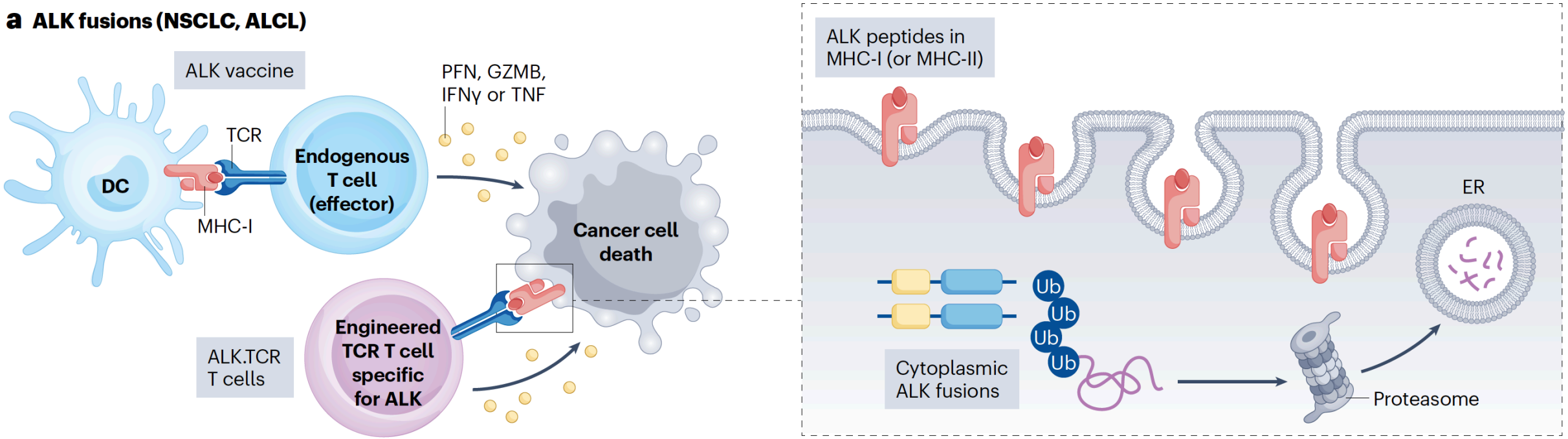
[a]Each sample could harbor >1 bypass mechanism.

Covalent Inhibitors and PROTACs

Covalent Inhibitors	Mechanism of Action	Clinical Status
ConB-1	Covalent bound to Cys1259	Pre-Clinical
BNP7787	Covalent bound to Cys1156	Pre-Clinical
PROTACS	**Mechanism of Action**	
TL13-112	ALK-TKI bound to E3 ubiquitin ligase or cereblon leading to degradation by proteasome system	Pre-Clinical
CPD-1224		Pre-Clinical
TD-004		Pre-Clinical

Voena, C, et al, Nature Reviews Cancer, 2025

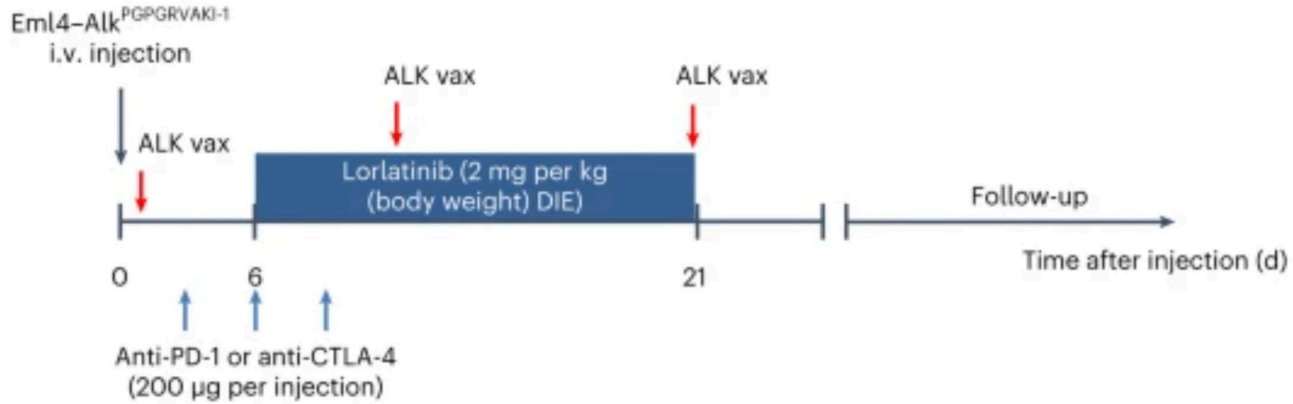
Engaging the immune system in ALK+ NSCLC

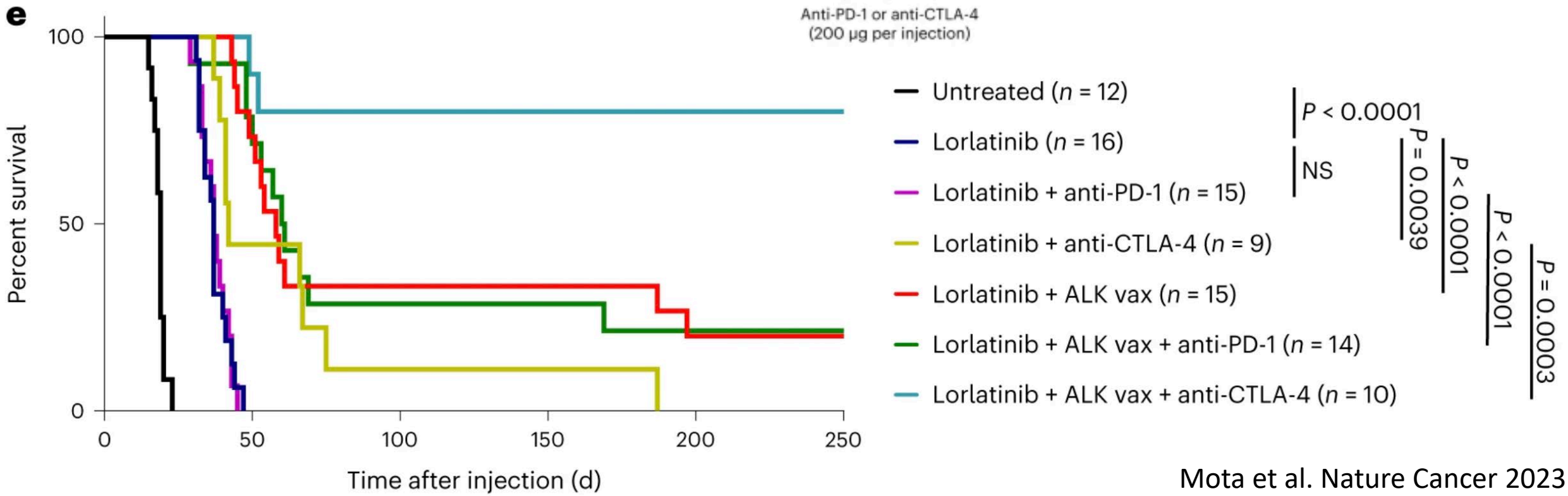


ALK can be immunogenic and its expression is restricted to tumor tissue
Titers of ALK antibodies in treatment naïve patients correlated with disease stage
ALK specific T-cells can be detected in peripheral blood in ALK patients

Voena, C, et al, Nature Reviews Cancer, 2025

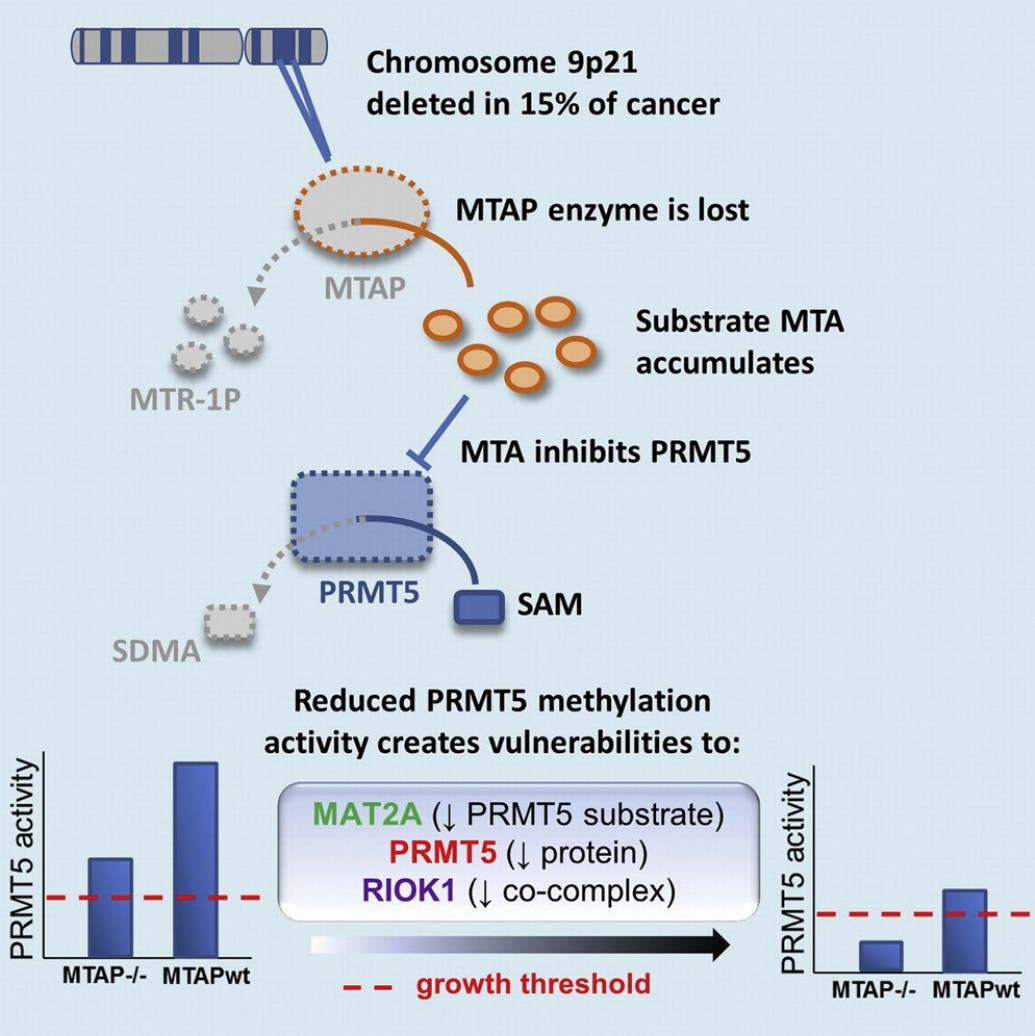
Engaging the immune system: Peptide ALK vaccines





Mota et al. Nature Cancer 2023

Cancer Metabolism- MTAP Deletion



MTAP is involved in methionine salvage pathway

Loss of MTAP leads to accumulation of MTA

MTA inhibits PRMT5 which regulates splicing, gene expression and cycle.

Cancer cells with MTAP deletion makes them sensitive to further PRMT5 inhibition

MTAP deletion could be seen in 25% of ALK+ NSCLC

Marjon K, et al, Cell Reports 2016; Ikushima, H, etal ESMO Open 2025

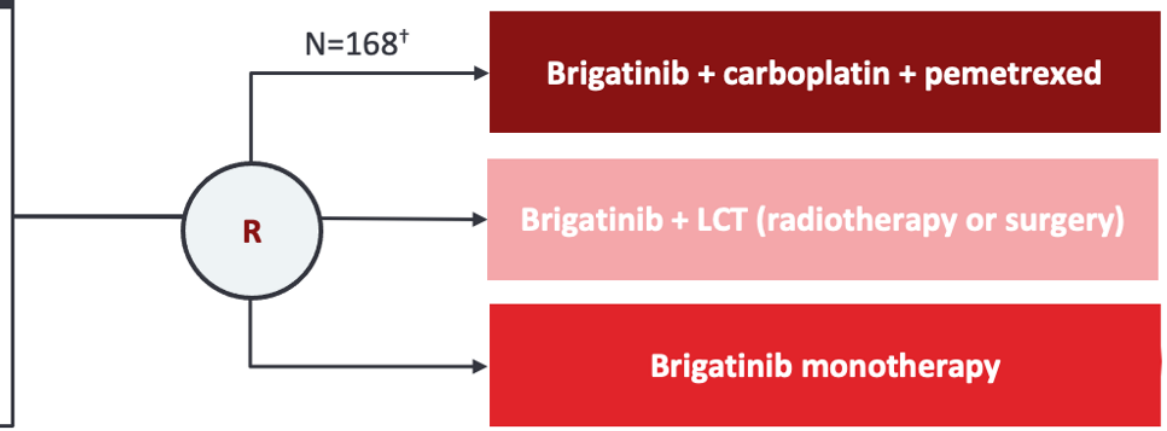
Trial in progress: BRIGHTSTAR2

Brigatinib + chemotherapy or local consolidative therapy (LCT) in TKI-naive *ALK*+ NSCLC

NCT06522360: Randomized, open-label, Phase 2 trial of 1L brigatinib monotherapy versus brigatinib + carboplatin + pemetrexed or brigatinib + LCT in advanced ALK+ *NSCLC (US)*

SELECT INCLUSION CRITERIA

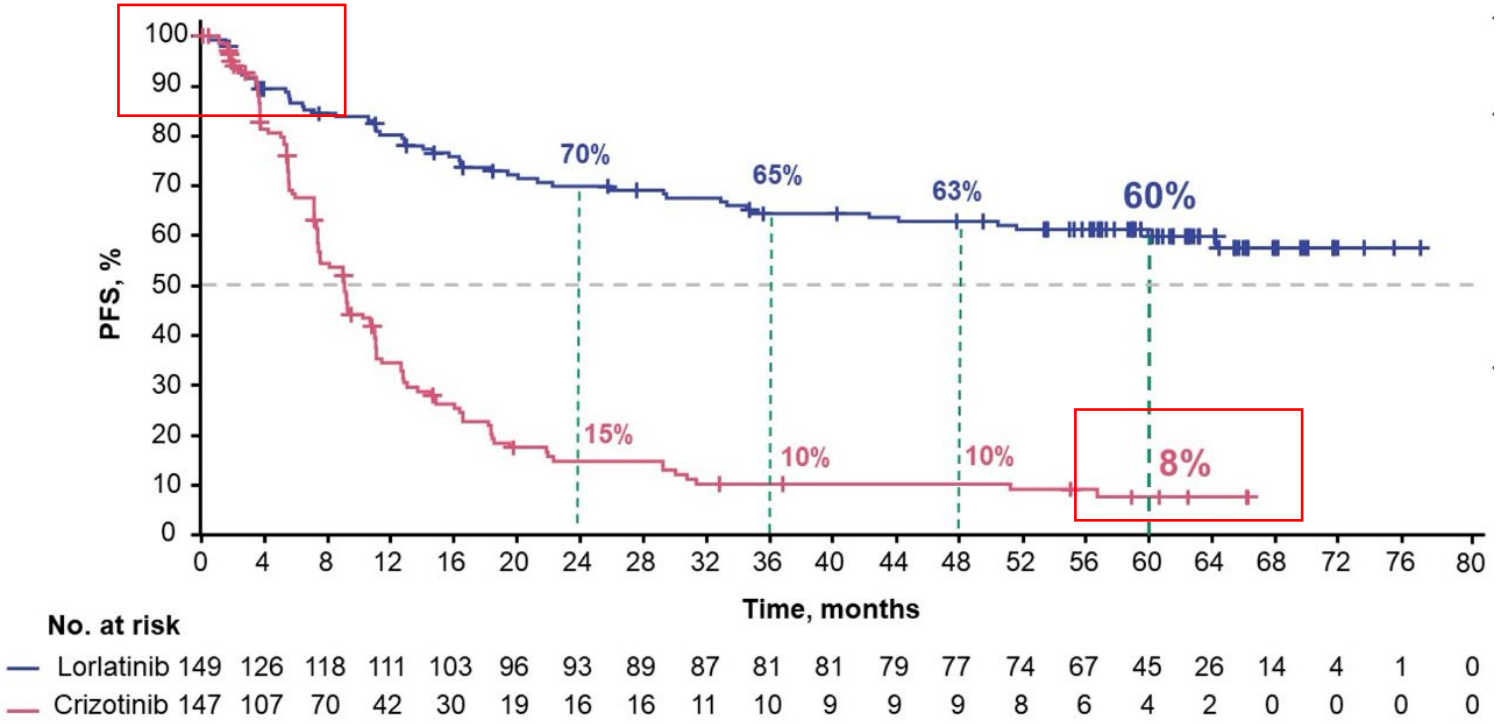
- Age ≥18 years
- Histologically or cytologically confirmed Stage IV *ALK*+ NSCLC (or recurrent NSCLC not a candidate for definitive multimodality therapy)
- ECOG PS 0–2
- TKI-naive*



PRIMARY ENDPOINT	SECONDARY ENDPOINTS
• Incidence of AEs according to NCI CTCAE v5.0	• 2-year PFS • OS • TTP of non-LCT lesions (brigatinib + LCT arm only) • Safety and tolerability

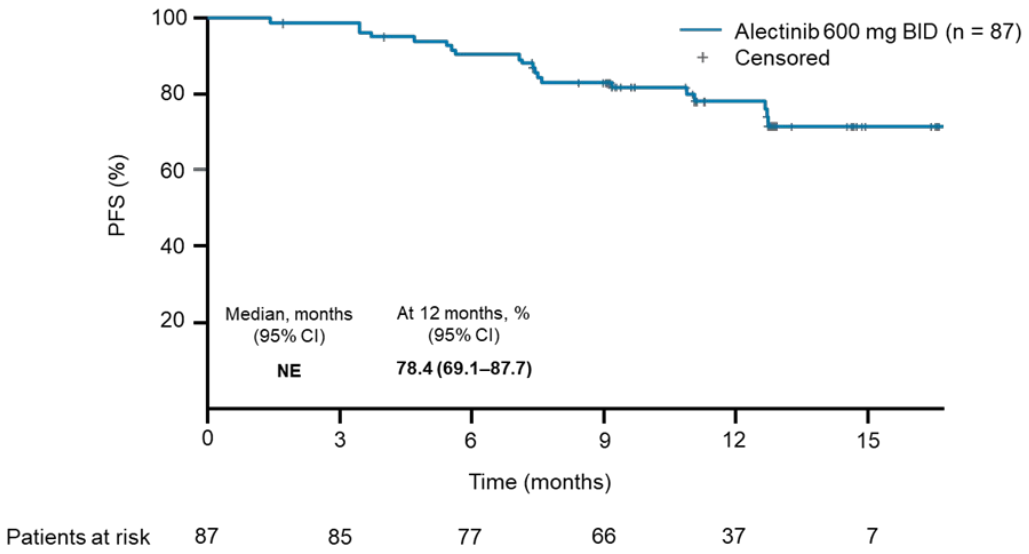
First Line Lorlatinib: CROWN

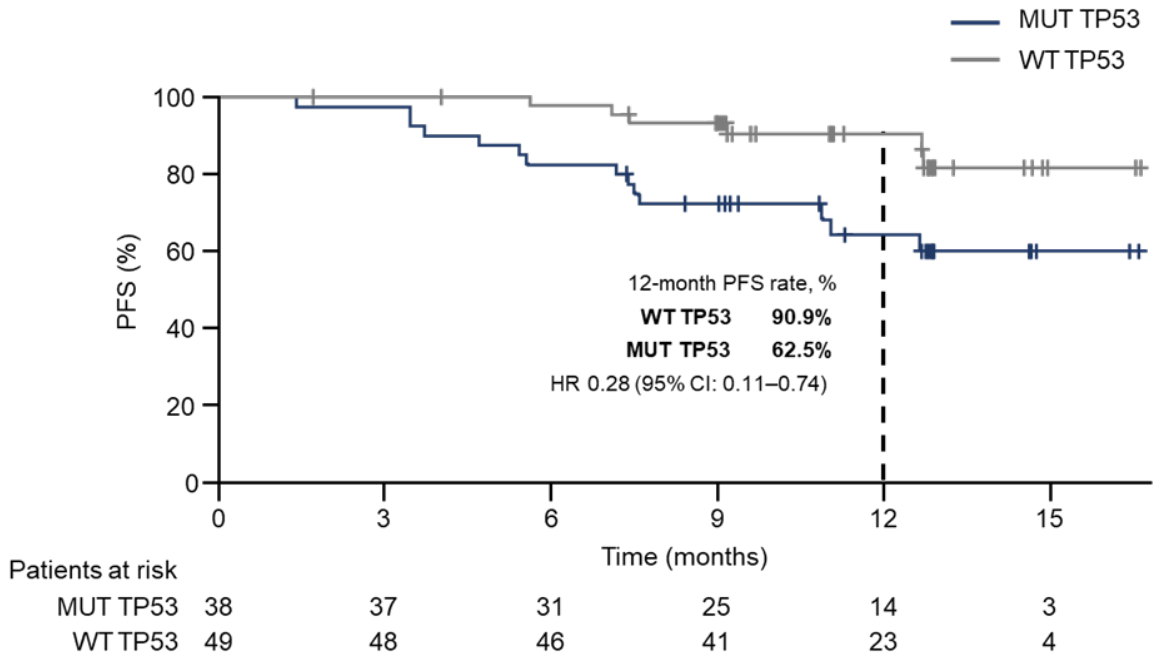
- 296 patients randomized to lorlatinib or crizotinib
  - 5y f/u: median PFS still not reached (vs 9.1m)
  - PFS HR 0.19 (0.13-0.27)



Solomon, ASCO 2024

BFAST- Relevance of p53 co-mutations

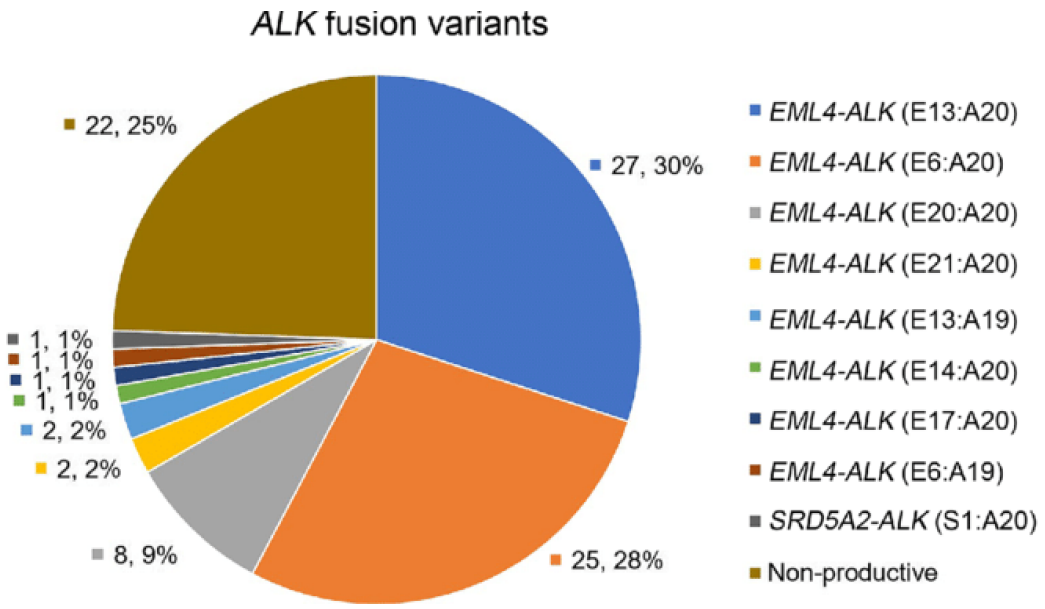


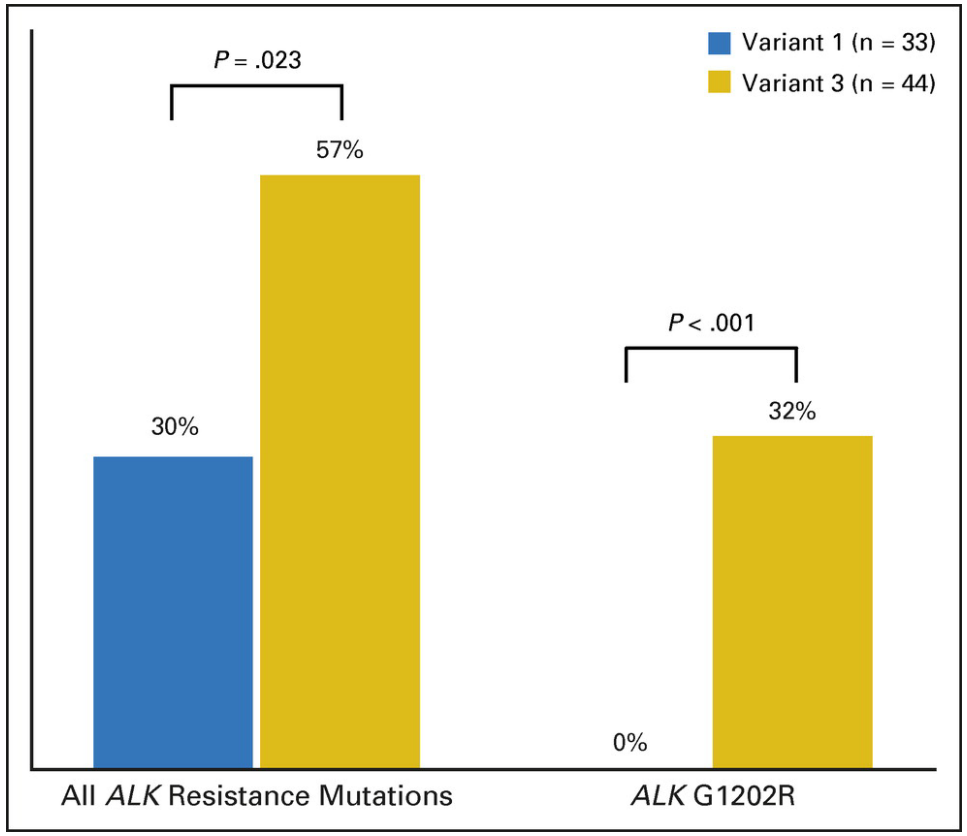


	PFS- Overall Population		PFS- p53 mutated and p53 wild type	
***TP53* co-mutation vs *TP53* wild type**	38 (44) vs 49 (56)	18.7 (12.6–40.5) vs 39.5 (31.5–NE)	1.68 (1.00–2.82)	

Gadgeel, ESMO 2019, ESMO 2023

Fusion Variants





Variants based on partner gene may have different tumor biology

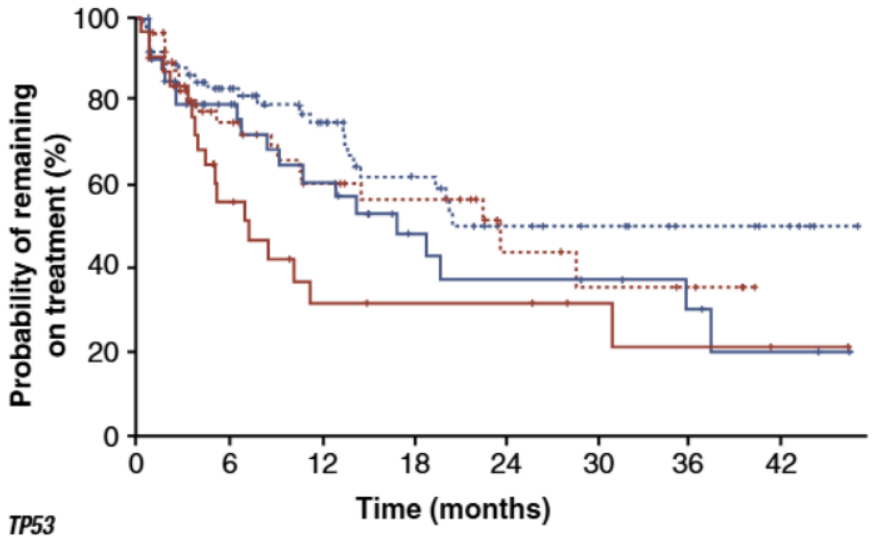
Lorlatinib had better efficacy in variant 3

Zhao, Molecular Diagnosis and Therapy 2019; Lin J, J Clin Oncol 2018

Additive effects of co-occurring risk factors in ALK NSCLC

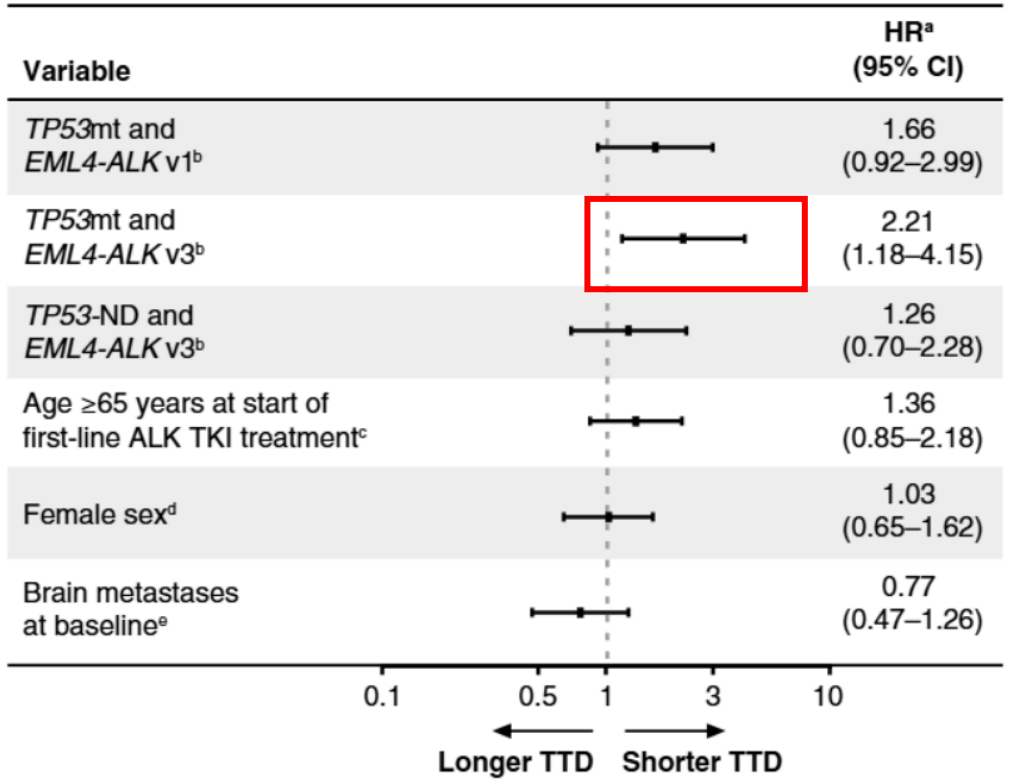
C

EML4-ALK fusion	*TP53* mutation	Median TTD (95% CI), months	HR[a] (95% CI)	*P* value[a]
v1	mt	17.1 (8.7–37.5)	1.66 (0.92–2.99)	0.0929
v3	mt	7.4 (4.2–31.1)	2.21 (1.18–4.15)	0.0137
v1	ND	NE (14.3–NE)	Reference	
v3	ND	23.8 (9.4–NE)	1.26 (0.70–2.28)	0.4445



EML4-ALK fusion	*TP53* mutation	No. at risk							
v1	mt	42	24	16	9	7	6	4	2
v3	mt	32	13	6	5	5	3	2	1
v1	ND	75	48	34	23	14	11	7	5
v3	ND	52	28	19	15	6	4	3	0

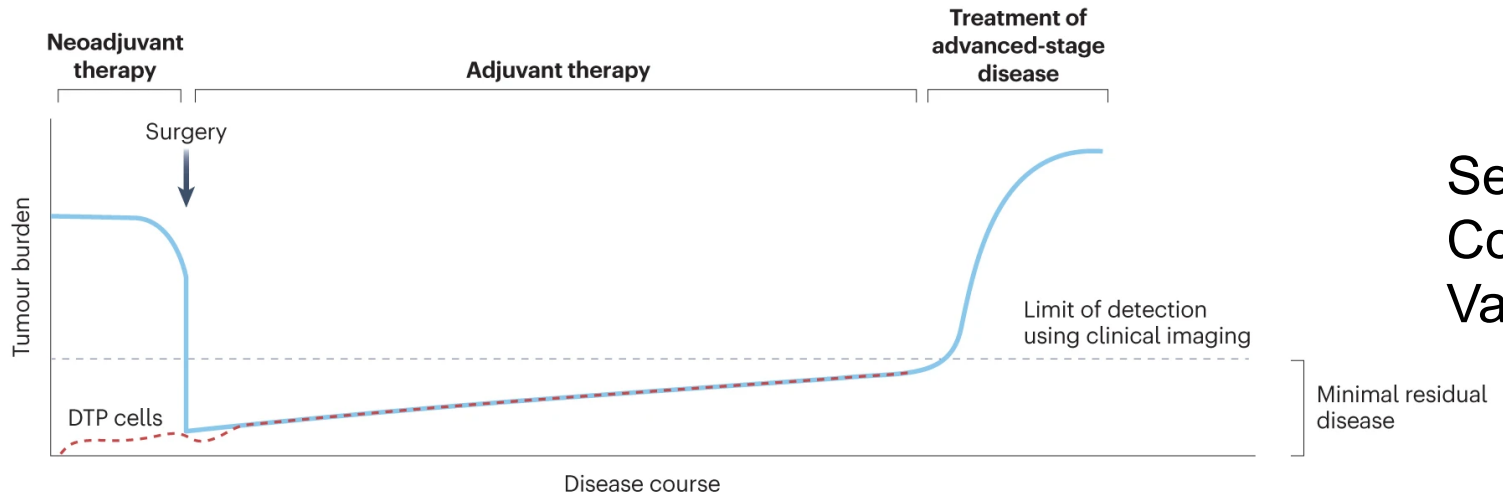
D



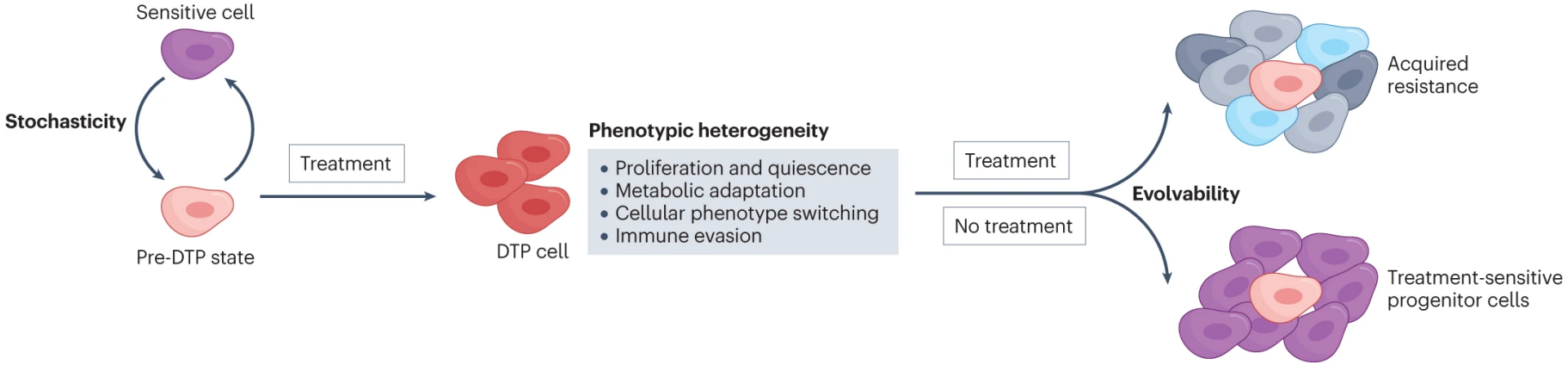
Note that **dual** TP53 and variant 3a/b did worse.

Parikh *J Thorac Oncol* 2023

Drug Tolerant Persister Cells (DTPCs)

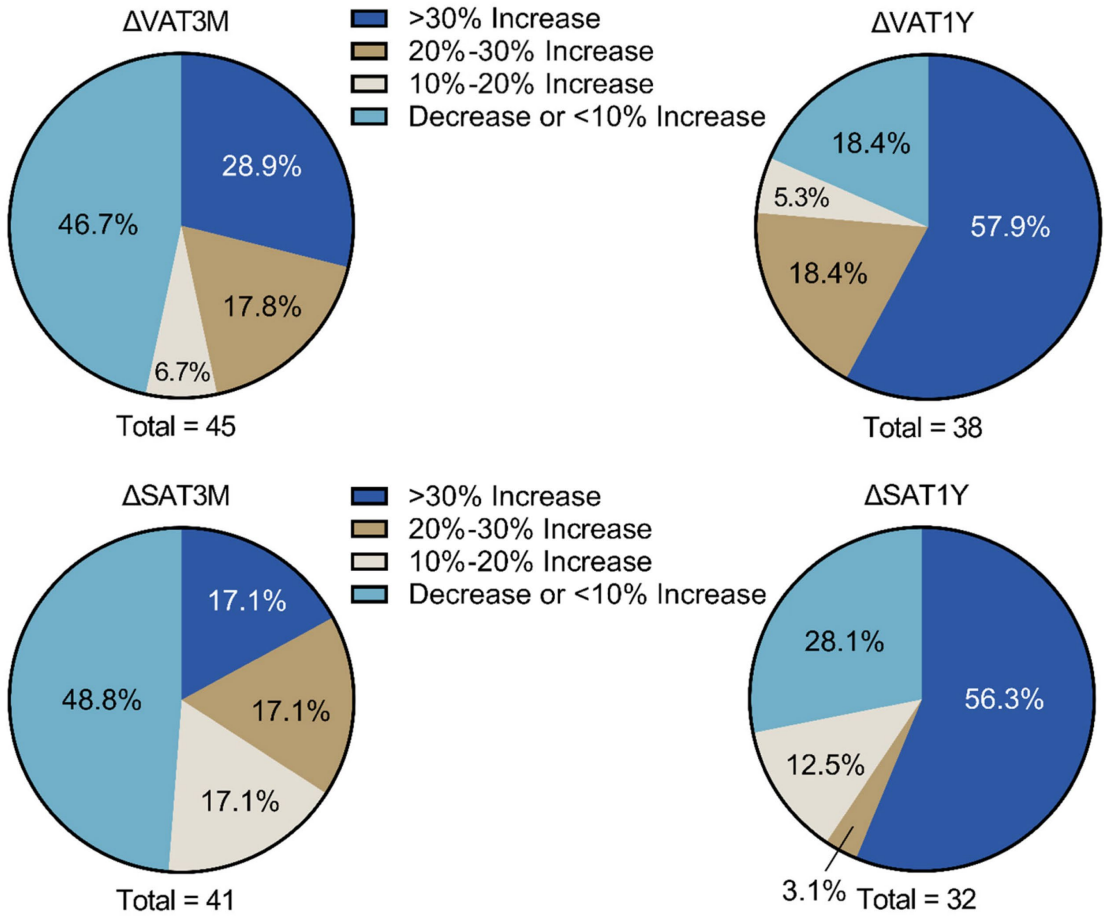


Selection of ALK-TKIs
Combination Strategies
Vaccines



Yi Pu, et al Nature Reviews Clinical Oncology, 2023

Lifestyle Modifications



Mean waist circumference increase- 9cm

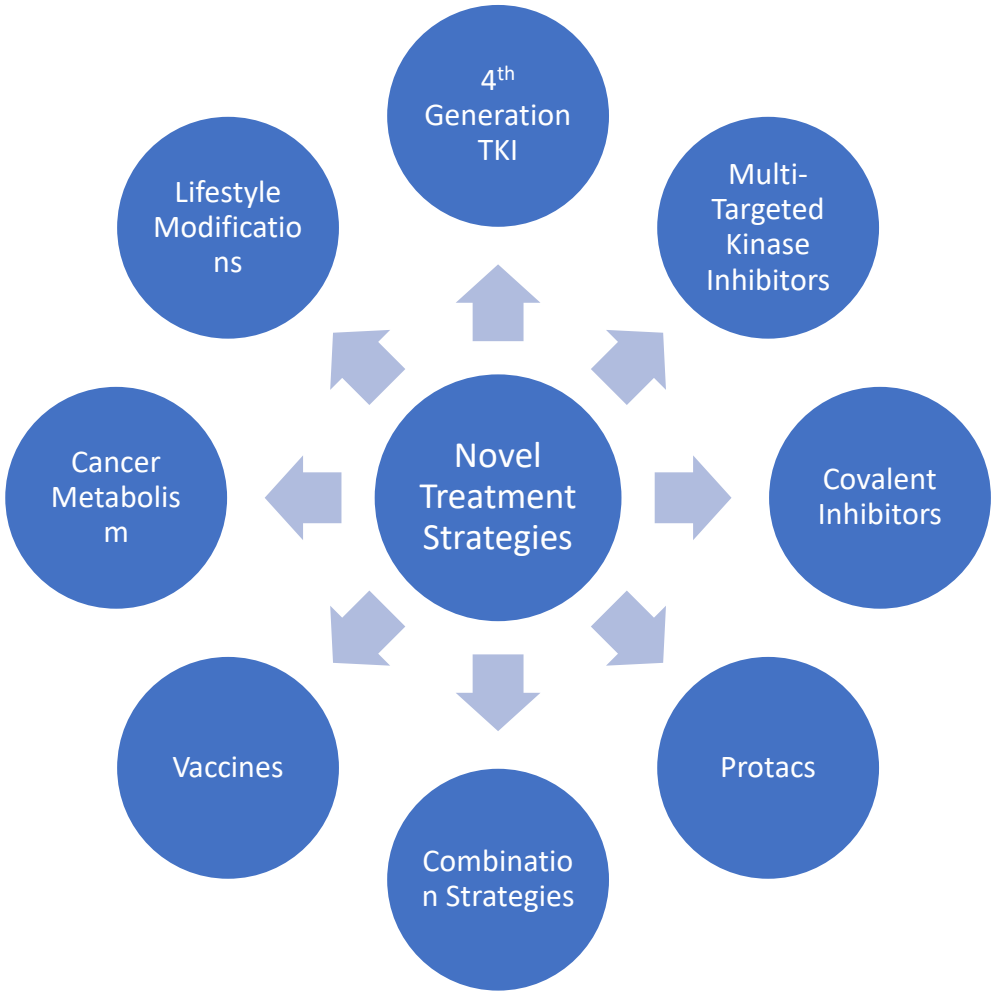
Abdominal Obesity increase- 40%

Lifestyle Interventions- Diet, Exercise, GLP-1 inhibitors?

Psychological and Physical Health

de Leeuw S, et al J Thorac Oncol 2023

Conclusions



- Shared Decision Making has become extremely critical
- Median PFS > 5 years with Lorlatinib
- Several Novel Strategies being investigated
- Better understanding of each patient's cancer biology
- Lifestyle modifications for long term survival