

Where Science Becomes Hope

TARGETING ALK AND MANAGING RESISTANCE?

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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

DISCLOSURES

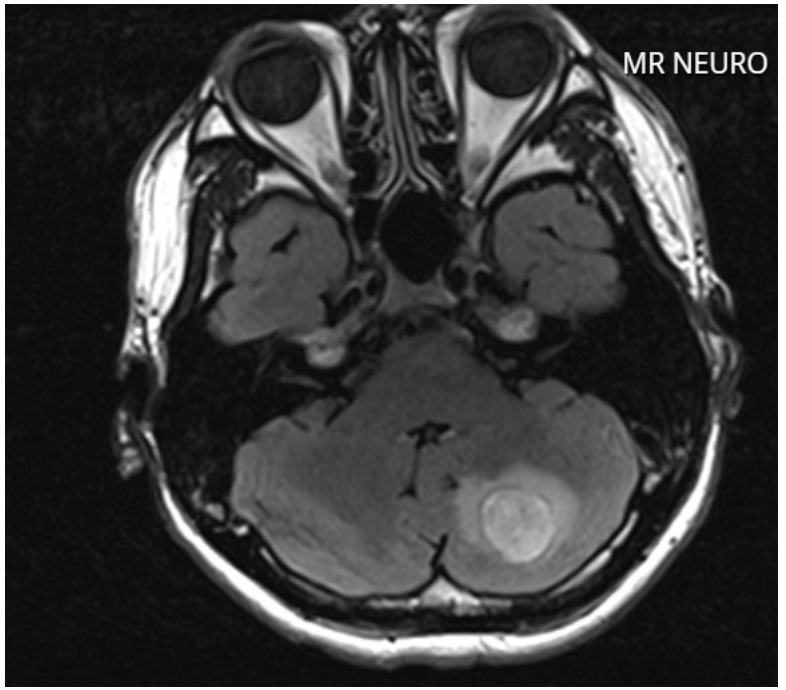
Advisory Board- Genentech/Roche, Amgen, Astra-Zeneca, Pfizer, Boehringer-Ingelheim, Bayer, Lilly, BMS, Daichii, Gilead, Johnson and Johnson, Abbvie, Sanofi, Summit, MBrace, Erasca.

IDMC- Astra-Zeneca

19-YEAR OLD MALE PATIENT



7/9/2026

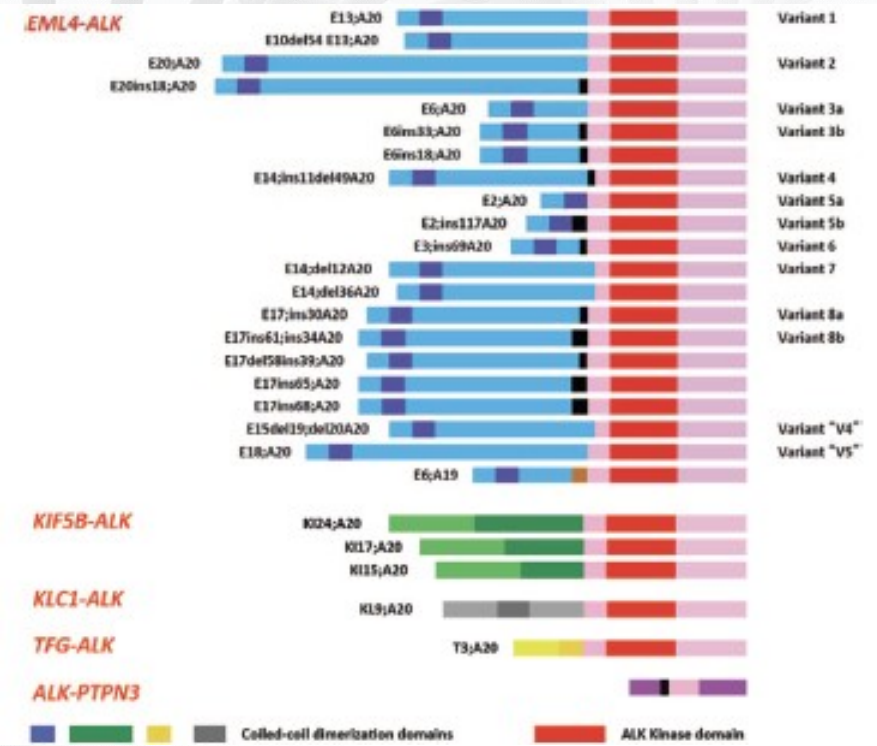


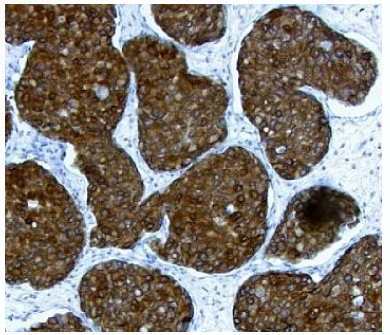
6/16/2026

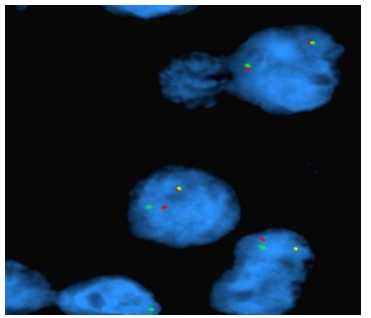
19 year old male patient had persistent cough.
No symptoms related to brain met.

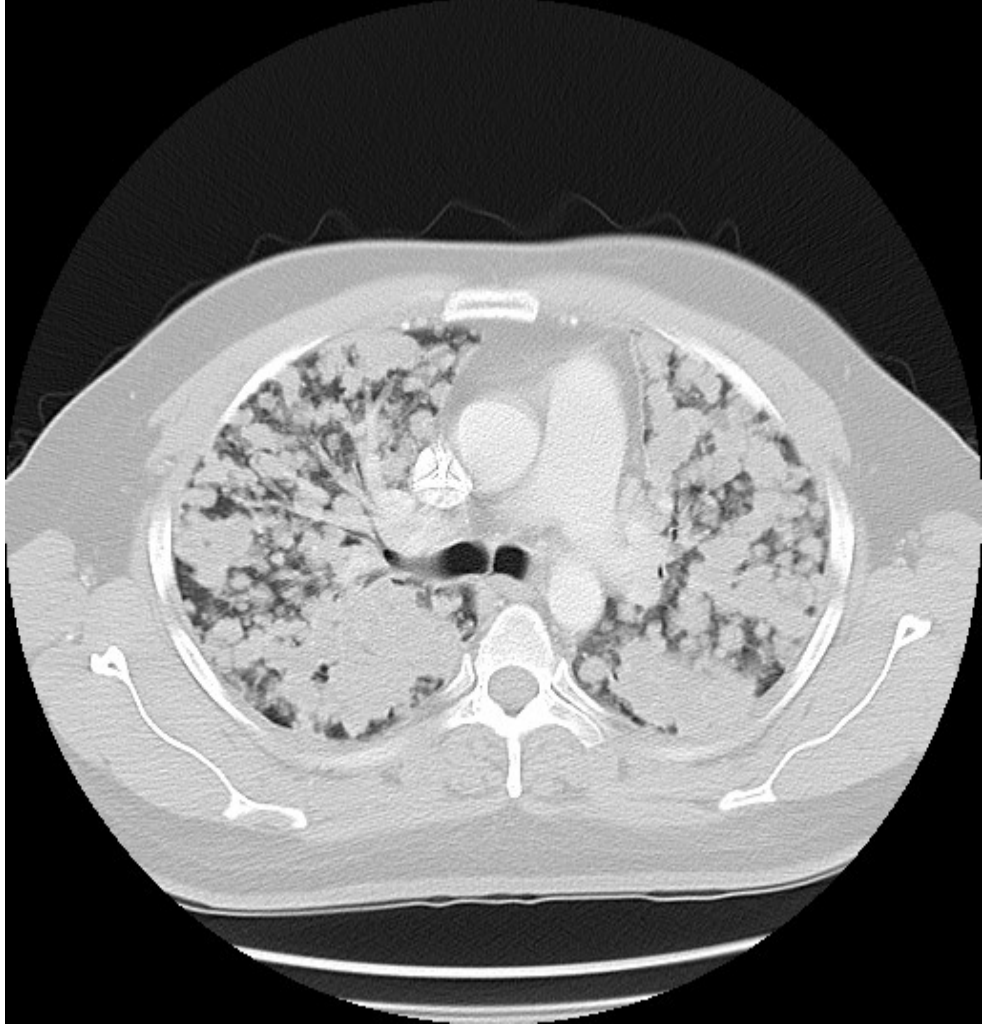
ALK GENE REARRANGEMENTS IN NSCLC

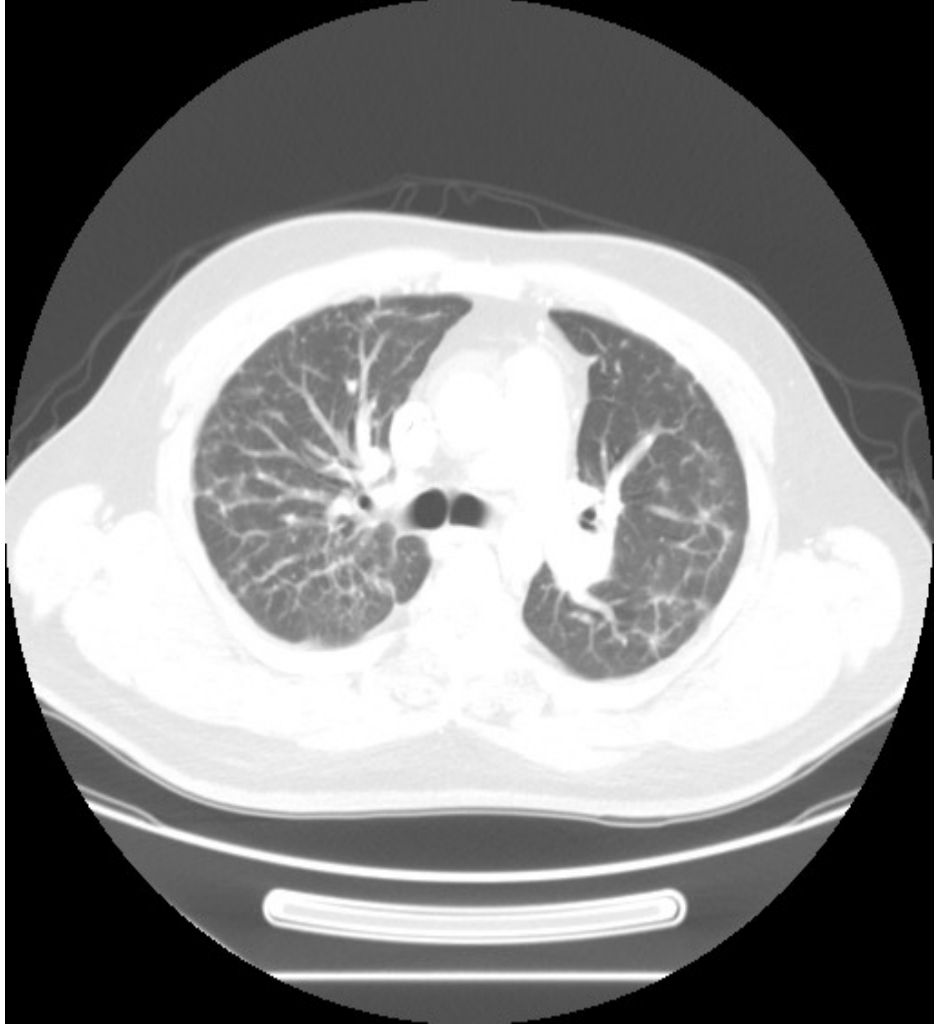
- ***EML4-ALK* and other ALK fusion variants present in 3-5% of NSCLC.**
  - Adenocarcinoma histology.
  - Typically (but not always!) younger & never smokers or light former smokers.
  - Propensity for brain metastases
  - Incidence very similar globally







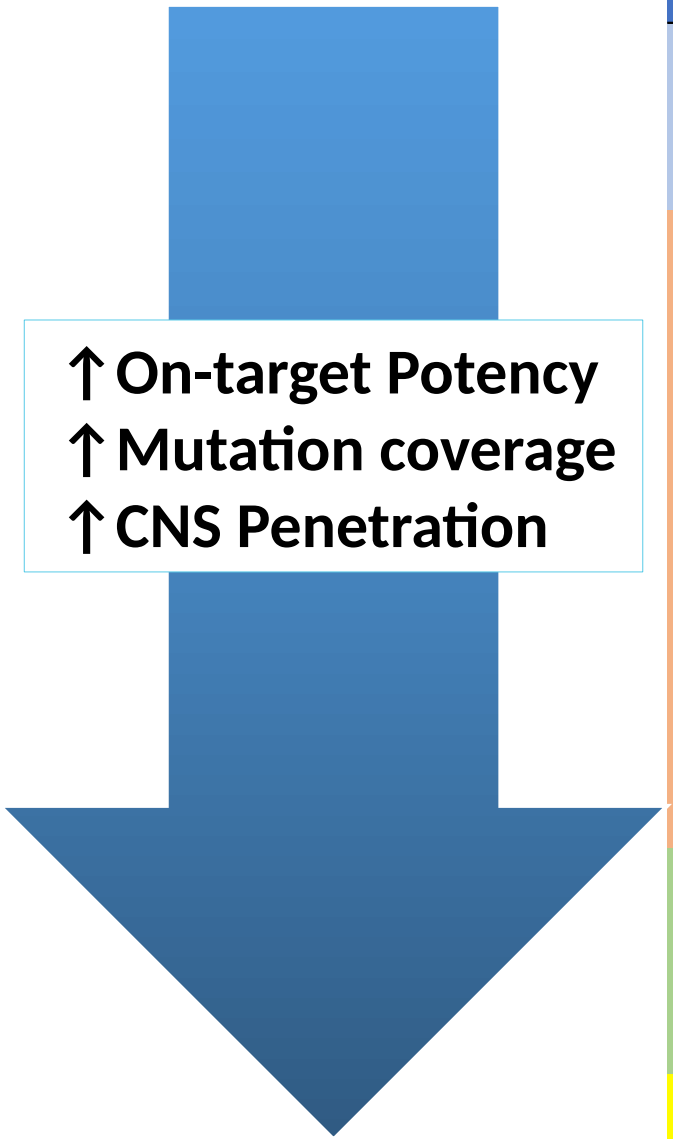




2/26/2010

5/25/2010

52 year old never smoker- Gem+Pem+Bev, Carbo+Pac,erlotinib
Treated with Crizotinib, ALK inhibitor



ALK TKI		STATUS
1st generation	Crizotinib	▪ FDA-approved, EMA-approved
2nd generation	Ceritinib	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Alectinib	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Brigatinib	▪ FDA / EMA approved, post crizotinib ▪ FDA/EMA approved, first line
	Ensartinib	▪ FDA approved
3rd generation	Lorlatinib	▪ FDA / EMA approved, in patients who have received 1 or more ALK inhibitors ▪ FDA/EMA approved firstline
4th Generation	Neladalkib (NVL-655)	▪ FDA Breakthrough designation

CROWN PHASE 3 STUDY DESIGN

Key Eligibility
- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST v1.1) with no prior radiation required

Randomized 1:1

Lorlatinib 100 mg QD n=149

Stratified by
- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

Crizotinib 250 mg BID n=147

No crossover between treatment arms was permitted

Primary endpoint
- PFS* by BICR

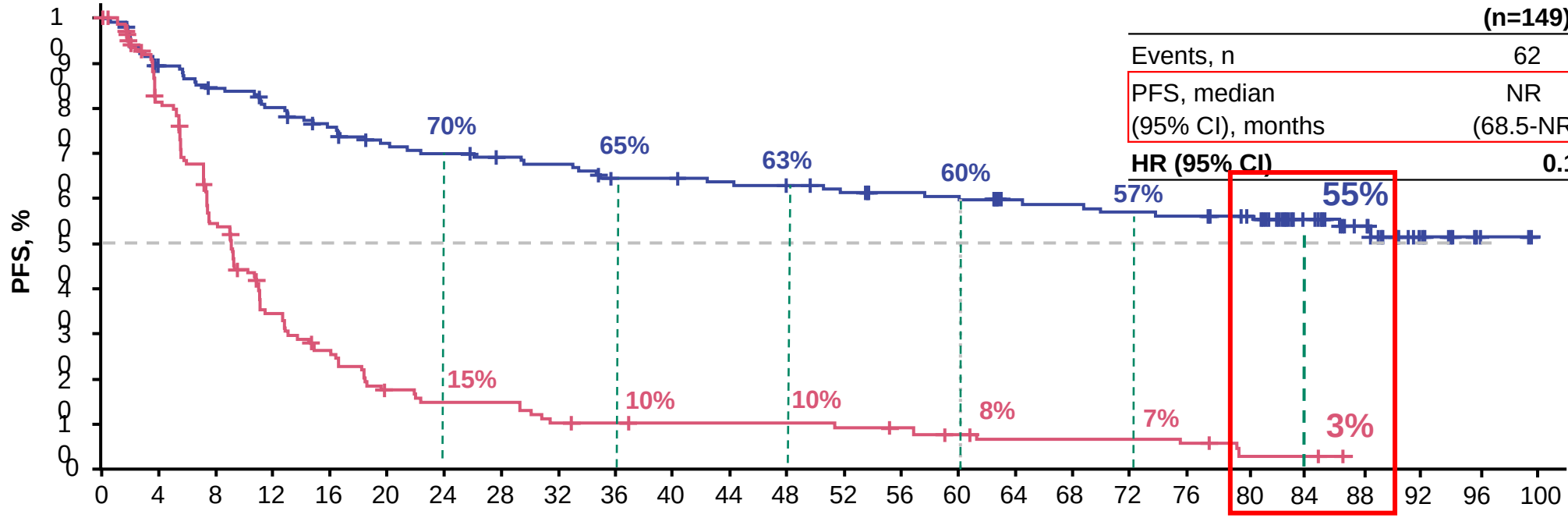
Secondary endpoints
- PFS by investigator
- ORR by BICR and investigator
- IC-ORR, DR and IC-DR by BICR
- IC-time to progression by BICR
- OS
- Safety
- QoL

*Defined as the time from randomization to RECIST-defined progression or death due to any cause.

PFS IN THE ITT POPULATION (7-YEAR FOLLOW-UP)

The median duration of follow-up for PFS was **83.0 months** (95% CI, 81.2-86.3) in the lorlatinib arm and **77.2 months** (95% CI, 36.8-not evaluable) in the crizotinib arm

	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	62	119
PFS, median (95% CI), months	NR (68.5-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.26)**	



No. at risk																									
Lorlatinib	149	126	118	111	103	96	93	89	87	81	81	79	78	75	73	71	69	68	66	65	62	38	28	9	2	0
Crizotinib	147	107	70	42	30	19	16	16	11	10	9	9	9	8	8	7	6	6	6	5	2	2	0	0	0	0

At the time of this analysis, median PFS by investigator was still not reached with lorlatinib

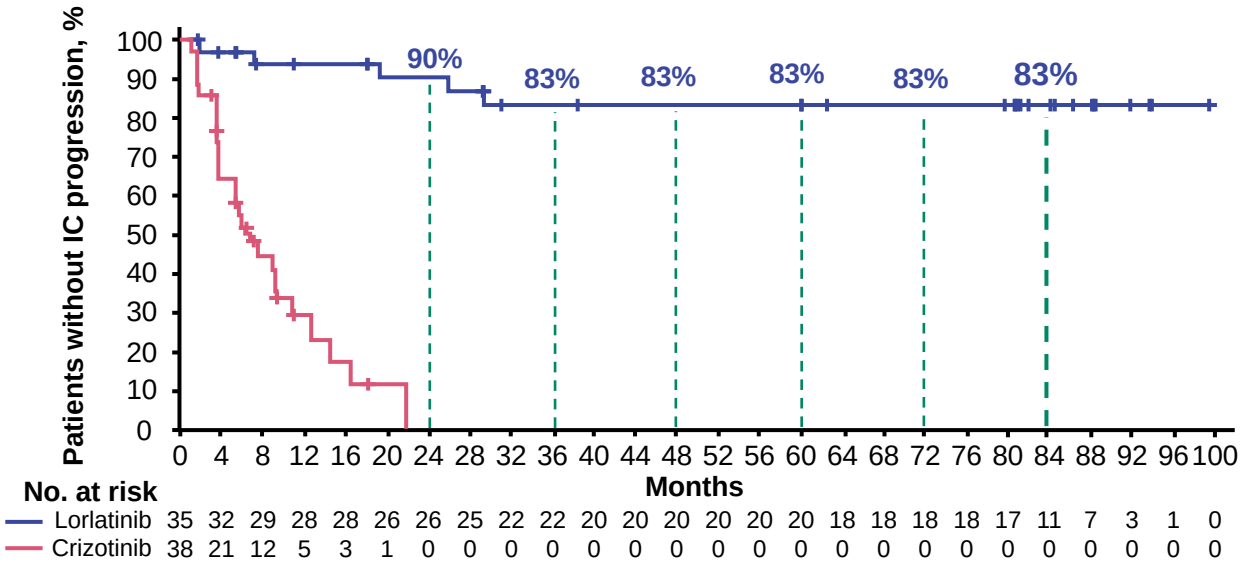
CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.

Tony S. K. Mok, MD (tony@clo.cuhk.edu.hk), ASCO 2026

TIME TO IC PROGRESSION BY BRAIN METASTASES

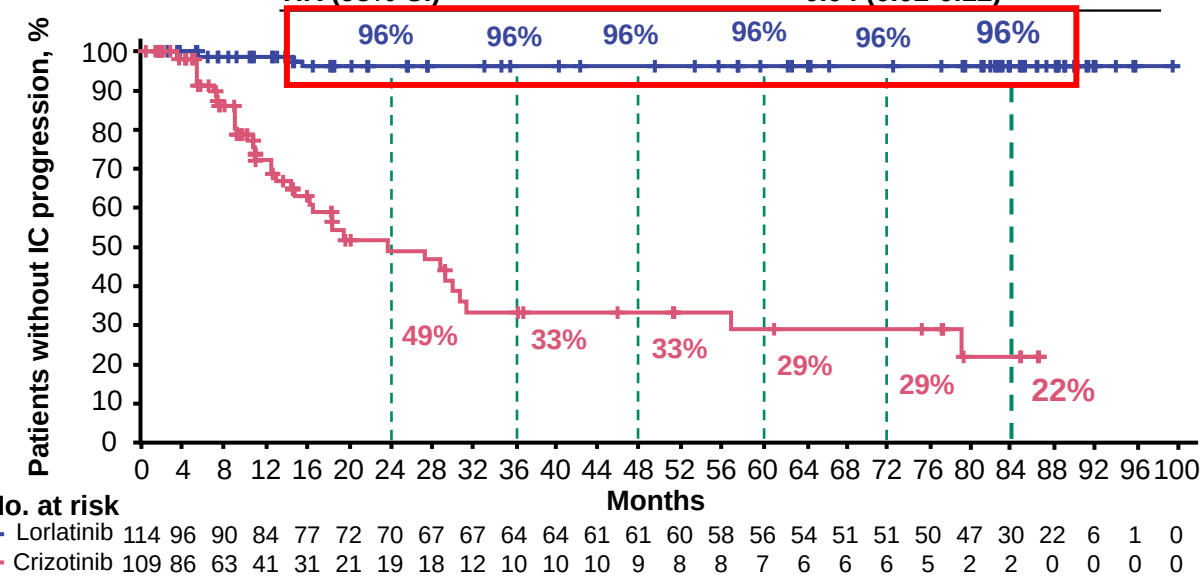
With baseline brain metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, months, median (95% CI)	NR (NR-NR)	7.2 (3.7-11.0)
HR (95% CI)	**0.03 (0.01-0.13)**	



Without baseline brain metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	4	40
Time to IC progression, months, median (95% CI)	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	**0.04 (0.02-0.12)**	



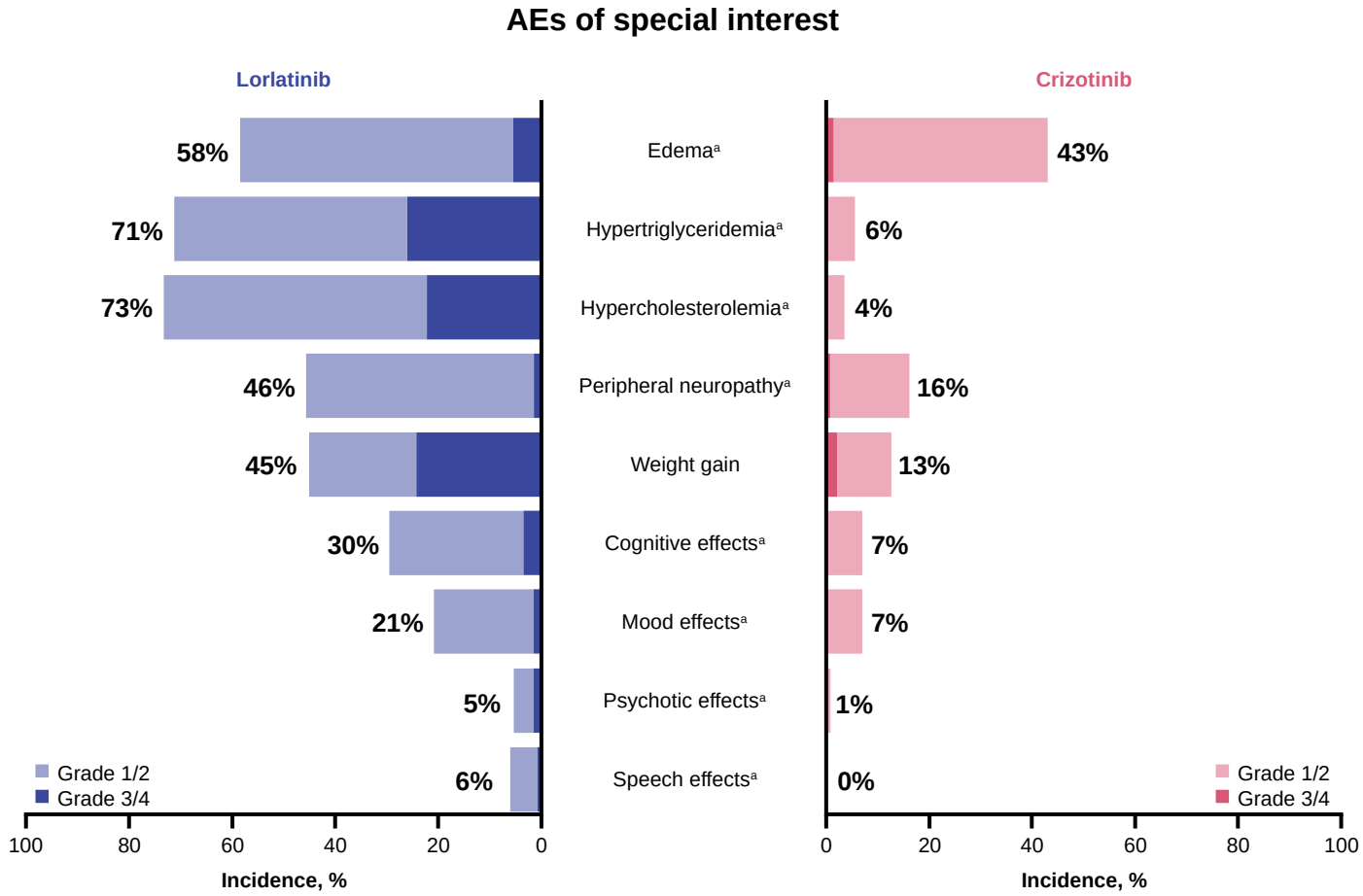
Sustained plateau in time to IC progression indicates a prolonged protective effect against the development of new brain metastases and a sustained control of the existing ones

CI, confidence interval; HR, hazard ratio; IC, intracranial; NR, not reached.

Tony S. K. Mok, MD (tony@clo.cuhk.edu.hk)

ADVERSE EVENTS

- No increase in frequency of grade 3 or 4 AEs since the 5-year analysis (77%)
  - Majority were due to an increase in lipid values
- Despite higher rates of hyperlipidemia with lorlatinib, no increase in cardiovascular AEs was observed compared with crizotinib
- All treatment-related discontinuations (5%) occurred within the first 26 months



Safety profile of lorlatinib was consistent with prior analyses with no new safety signals with longer follow-up

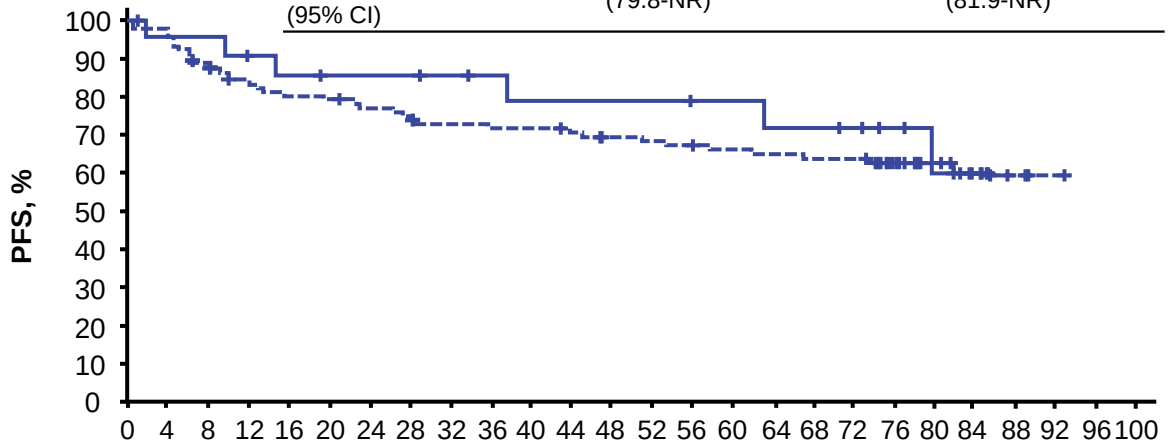
AE, adverse event; CNS, central nervous system.
[a]Comprised a cluster of AEs that may represent similar clinical symptoms or syndromes.

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EFFICACY IN PATIENTS WITH AND WITHOUT DOSE REDUCTION WITHIN 26 WEEKS

PFS

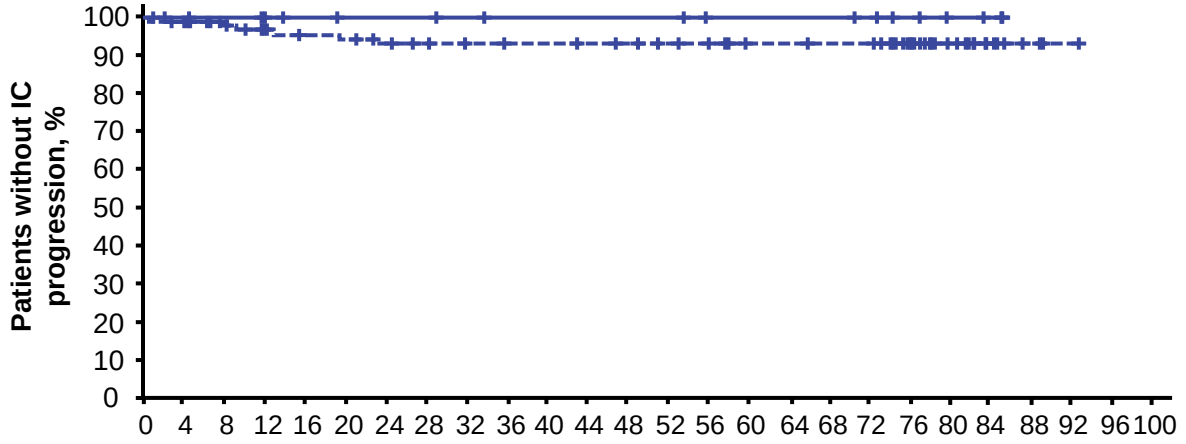
	With dose reduction (n=23)	Without dose reduction (n=98)
Events, n	6	36
PFS, months, median (95% CI)	NR (79.8-NR)	NR (81.9-NR)



No. at risk																									
With dose reduction	23	21	20	18	17	15	15	15	14	13	12	12	12	12	11	11	10	10	9	7	5	3	0	0	0	0
Without dose reduction	98	96	86	79	76	75	72	70	67	66	66	64	61	60	59	57	56	55	55	37	24	12	5	2	0	0

Time to IC progression

	With dose reduction (n=24)	Without dose reduction (n=99)
Events, n	0	6
Time to IC progression, months, median (95% CI)	NR (NR-NR)	NR (NR-NR)



No. at risk																									
With dose reduction	24	21	20	18	17	15	15	15	14	13	13	13	13	13	11	11	11	11	10	8	5	3	0	0	0	0
Without dose reduction	99	96	88	82	79	78	75	73	70	68	68	67	66	64	63	58	58	57	57	39	25	12	5	2	0	0

Long-term efficacy with lorlatinib was similar between patients with and without dose reduction within 26 weeks. PFS and IC TTP were also consistent across lorlatinib dose levels (100, 75, or 50 mg)

CI, confidence interval; IC, intracranial; NR, not reached; PFS, progression-free survival.

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MANAGING LORLATINIB TOXICITIES

1. Starting Dose- I start at 100 mg

2. Close follow up for the first 2-3 months

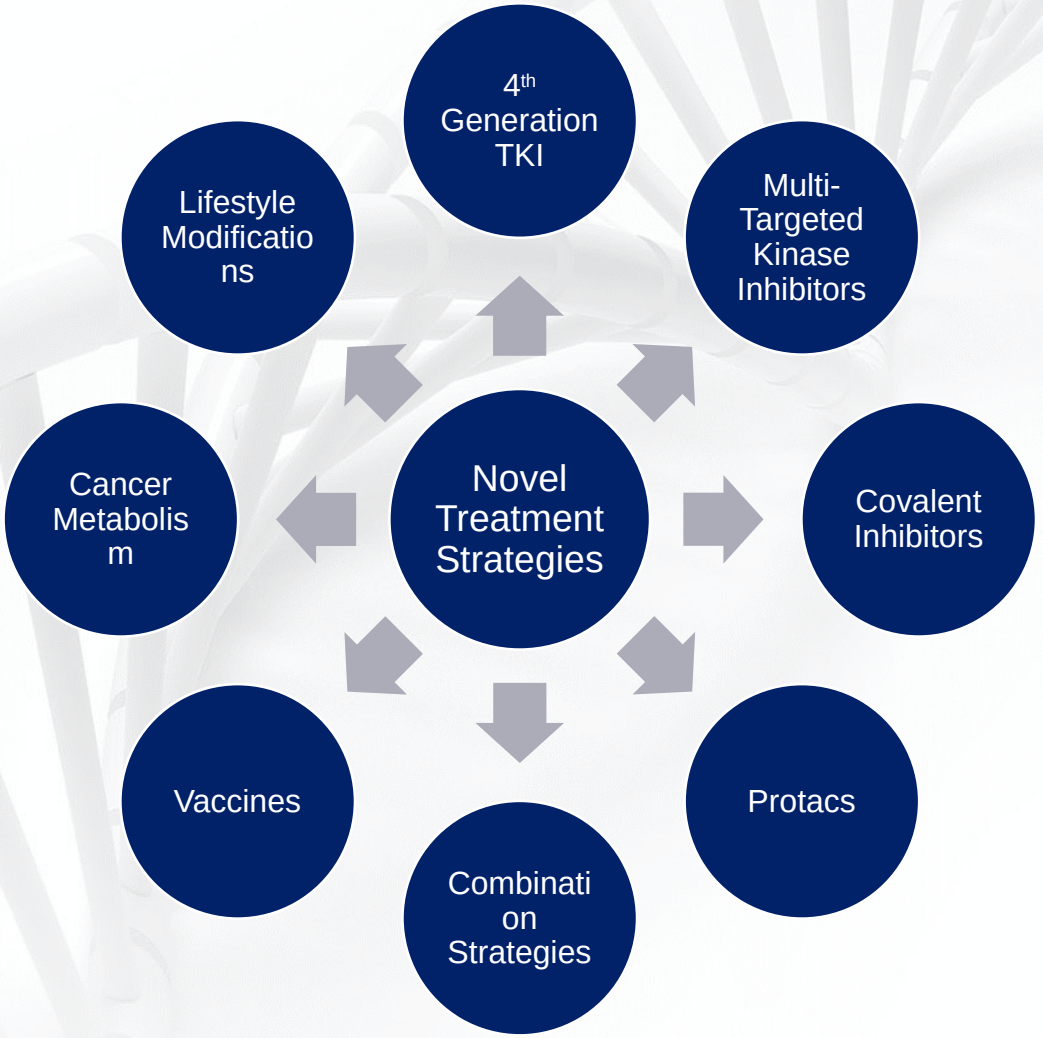
3. Engagement of Significant Other

4. Liver enzyme elevation with initiation of Statins

5. Evolocumab for cholesterol control

TOMORROW'S PROMISE BUILT ON PAST ACHIEVEMENTS





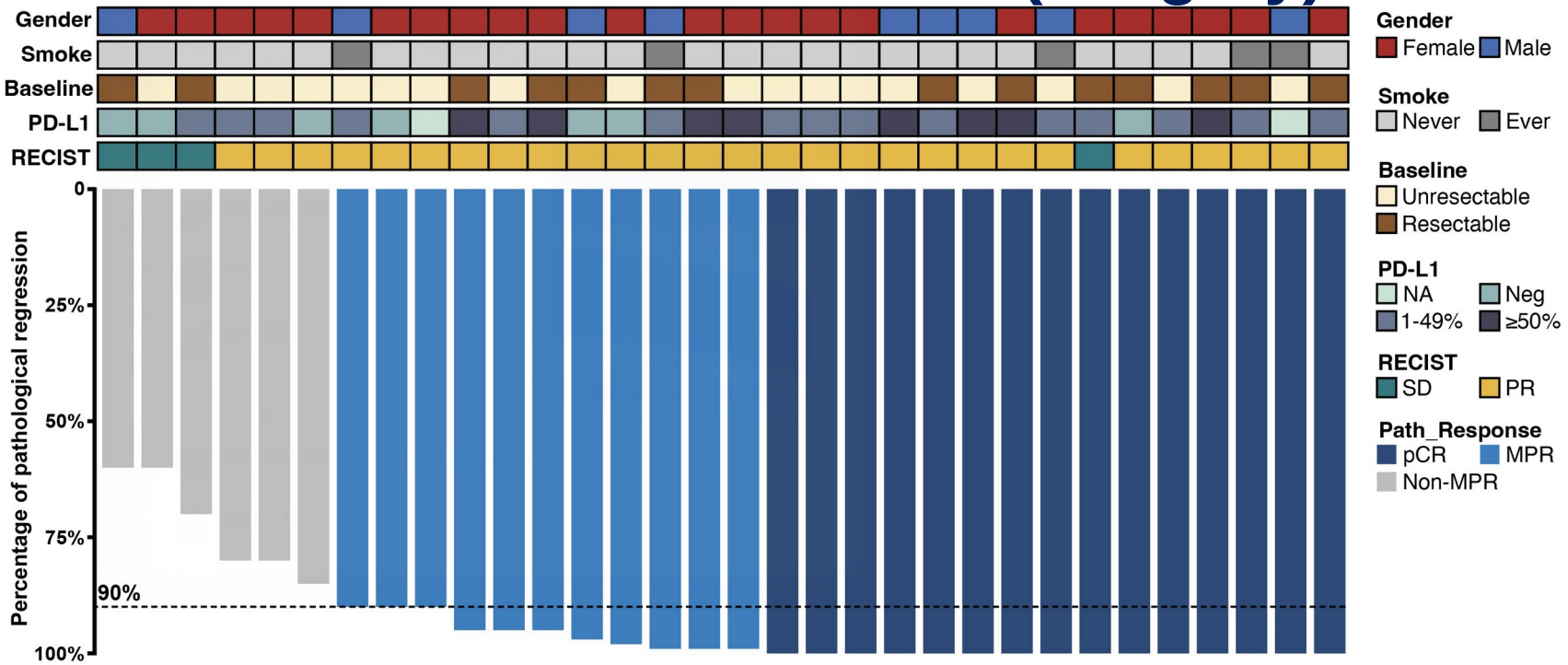
Early Stage

Novel Therapeutics/ Overcome Resistance

Biomarkers

Healthy Survival

LORIN: Primary Endpoint—pCR (Surgery)



Overall	N=32 (n, %)
pCR	**15 (47)**
MPR	26 (81)
Median/Mean RVT	**1%/7%**

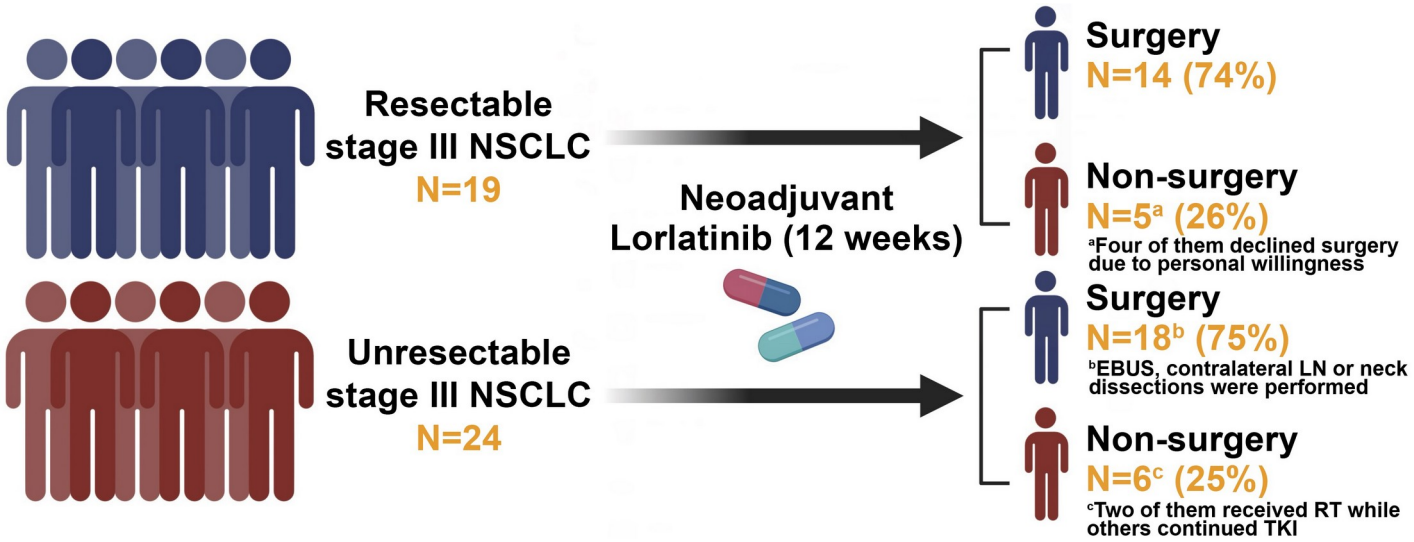
Resectability	pCR/MPR
Resectable	50%/86%
Unresectable	44%/78%

	Median PD-L1 exp.
MPR/pCR	25%
Non-MPR	1%
	p value <0.01

Among patients who underwent surgery, the pCR and MPR rates were **46.9% (15/32) (95%CI, 29.1%-65.2%) [34.9% for ITT]** and **81.3% (26/32) [60.5% for ITT]**, respectively, reaching the primary endpoint.

PR, partial response; SD, stable disease; pCR, pathological complete response; MPR, major pathological response; NA, not assessed; Neg, negative; RVT, residual viable tumor

LORIN: Surgical Outcomes



Overall pN downstaging **90%**

cN-pN shift	Num. (%)
cN3(n=18) → pN3	1 (6)
cN3(n=18) → pN1/N2	**4 (22)**
cN3(n=18) → pN0	**13 (72)**
cN2(n=12) → pN2	1 (8)
cN2(n=12) → pN1	**0 (0)**
cN2(n=12) → pN0	**11 (92)**

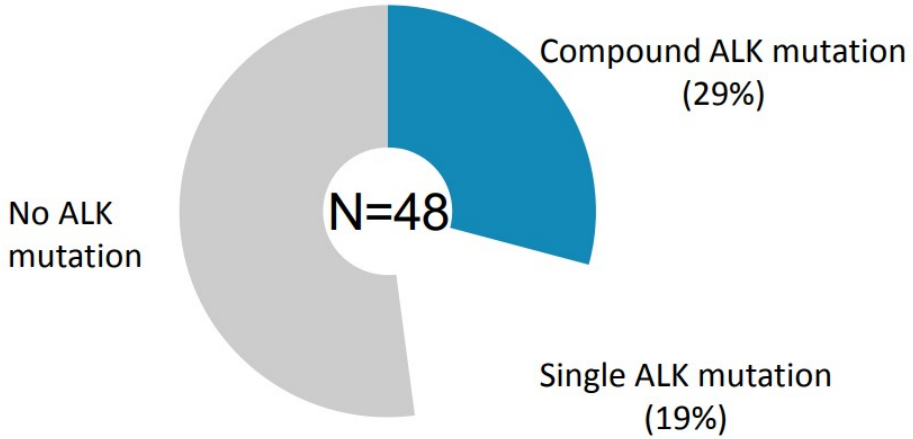
Operation	N=32
R0 resection, n (%)	31 (97)*
Types of surgery, n (%)	
VATS#/RATS/Open surgery	27(84) /2(7) /3(9)
Conversion to open surgery	3 (9)

Operation details	N=32
Median surgical duration	180mins (90-315)
Median harvested LNs	12 (7-31)
Median estimated blood loss	50ml (30-800)
Clavien-Dindo (grade II)	5 (16%)

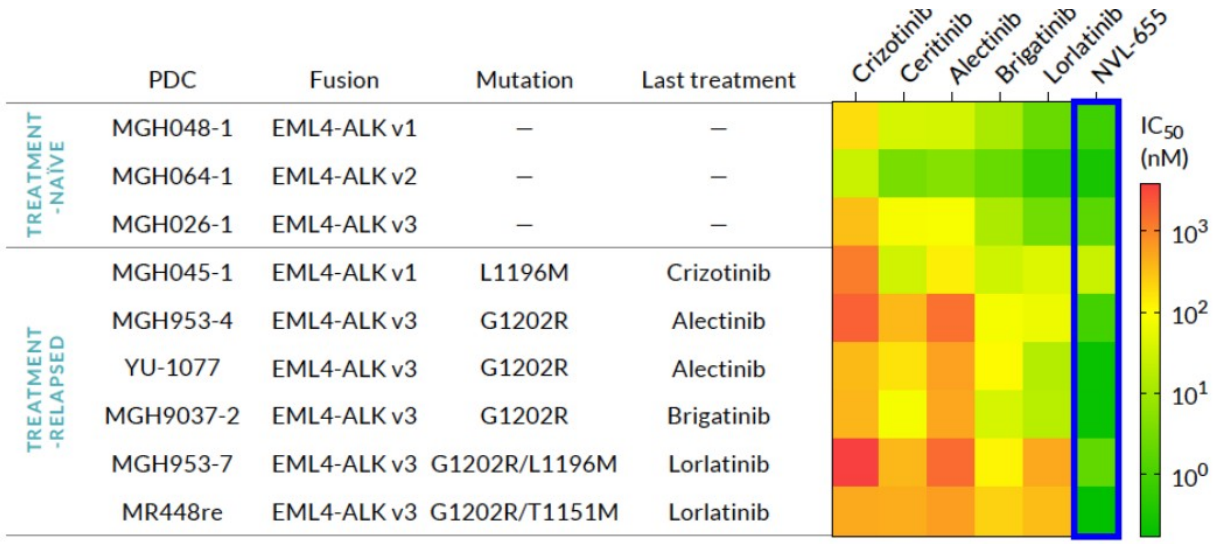
*One patient had pathologically confirmed N3 positive after lorlatinib and surgery; #All patients underwent lobectomy with 3 underwent bilobectomy

RESISTANCE TO 2ND LINE LORLATINIB[1]

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

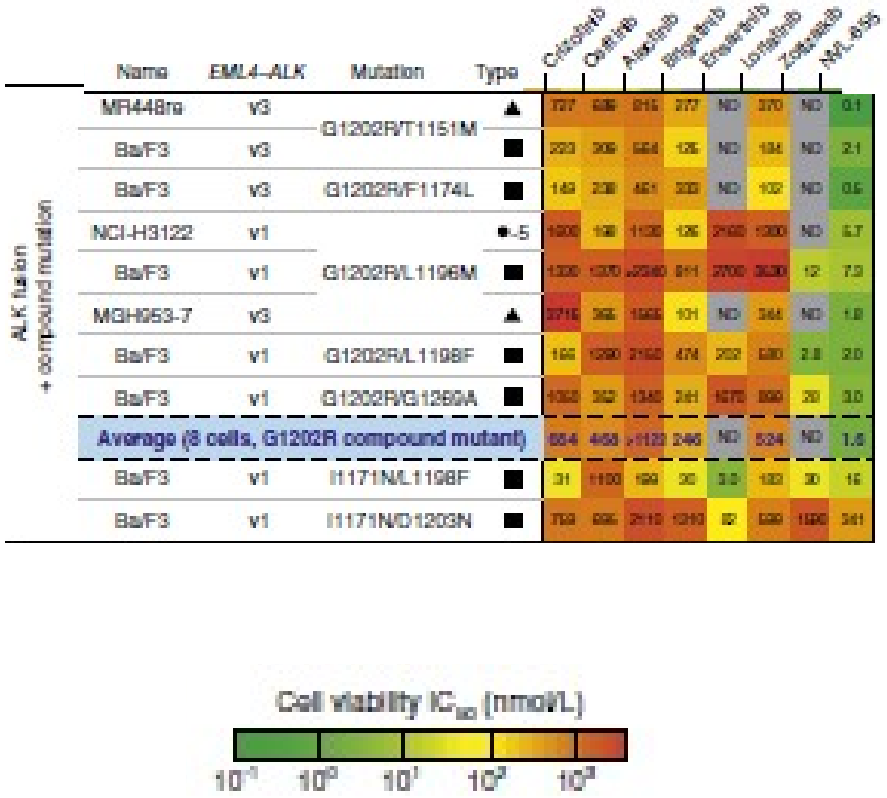


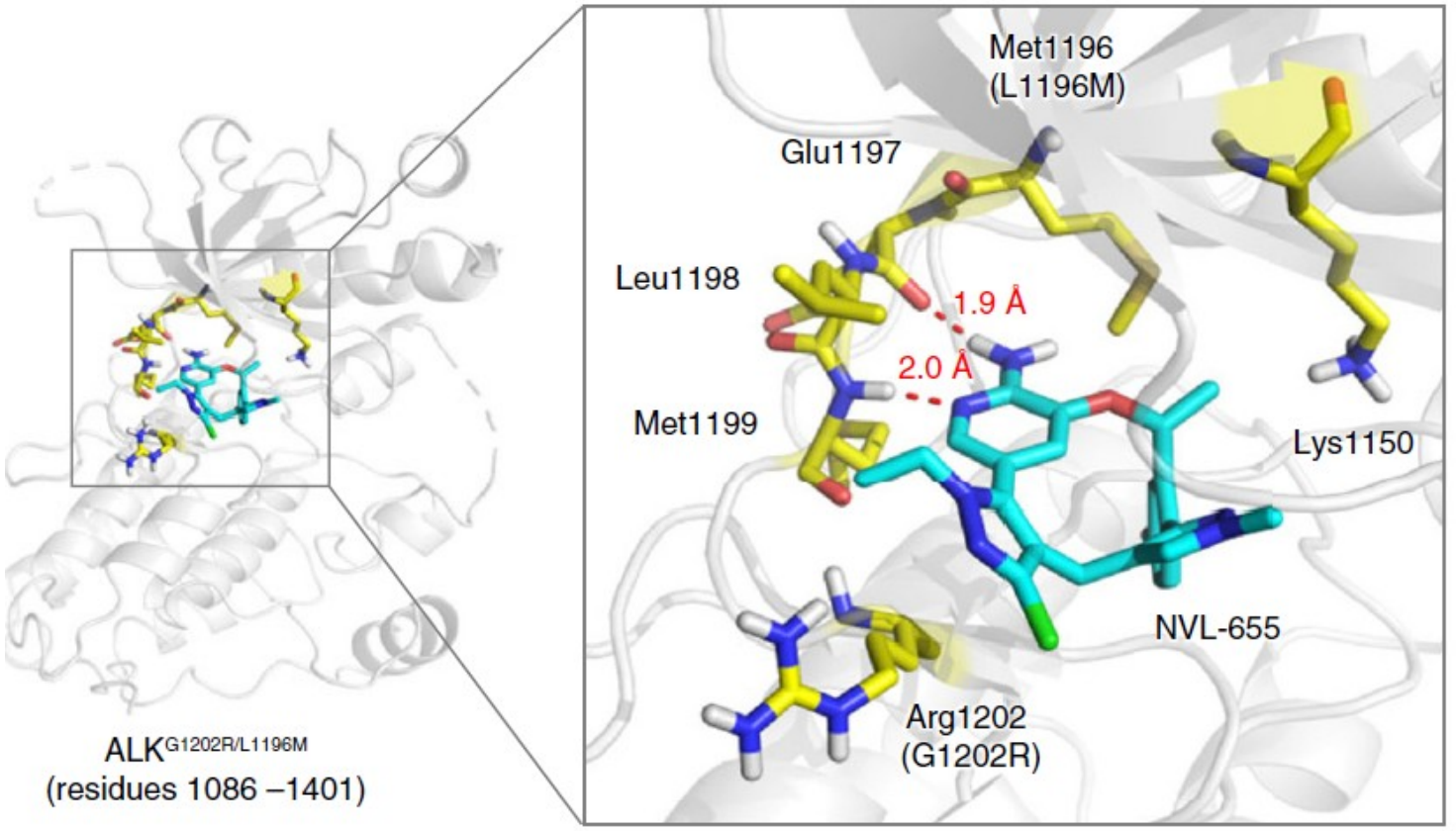
NVL-655, preclinical activity[3] (phase I evaluation ongoing; ALKOVE-1 – NCT05384626)



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

Neladalkib(NVL-655) has activity against compound mutations e.g. G1202R/L1196M





Structure of Human Anaplastic Lymphoma Kinase (ALK) harboring the **G1202R/L1196M Compound Mutation** in Complex with **NVL-655**

Lin et al., Cancer Discovery

- CNS penetrant
- Relative sparing of TRK relative to

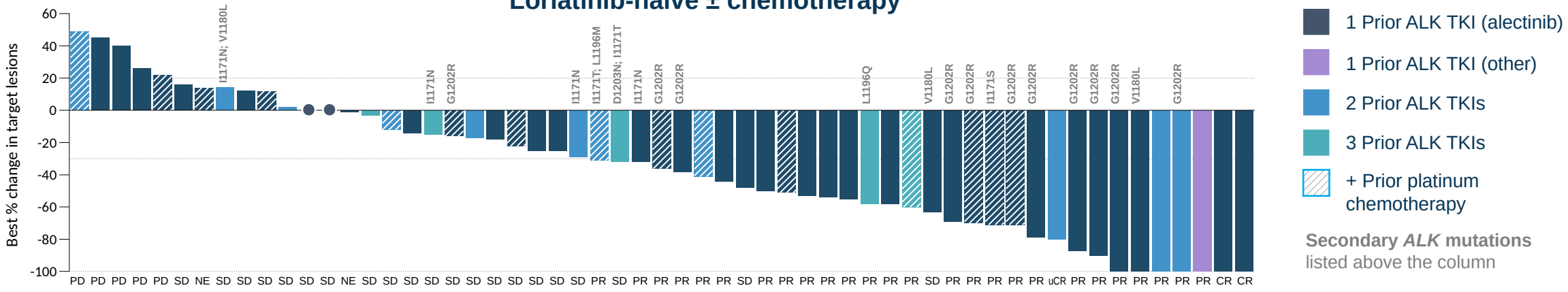
ALKOVE-1: OBJECTIVE RESPONSE IN ALK TKI-PRETREATED PATIENTS

Advanced *ALK*+ NSCLC RECIST v1.1 by BICR	**Any prior ALK TKI** [a] (1–5 prior ALK TKIs ± chemotherapy) **N = 253**	**Lorlatinib-naive** (1–3 prior ALK TKIs ± chemotherapy) **N = 63**	**Lorlatinib-experienced** (1–5 prior ALK TKIs ± chemotherapy) **N = 190**
ORR, % (n/N) [95% CI]	**31%** (79/253) [b] [26, 37]	**46%** (29/63) [33, 59]	**26%** (50/190) [b] [20, 33]
CR, % (n/N)	2% (6/253) [c]	5% (3/63) [d]	2% (3/190) [d]

[a] Median duration of follow-up of 11.3 months. [b] Includes 2 single-timepoint PR pending confirmation for ongoing patients. [c] Includes 2 single-timepoint CR pending confirmation in ongoing patients with prior confirmed PR. [d] Includes 1 single-timepoint CR pending confirmation in ongoing patient with prior confirmed PR.

- **Prior alectinib only ± chemotherapy:** ORR = **48%** (21/44, 5% CR)
- **≥ 2 prior ALK TKIs ± chemotherapy:** ORR = **28%** (56/198) [b]

Lorlatinib-naïve ± chemotherapy



BICR, blinded independent central review; **CI**, confidence interval; **CR**, complete response; **NE**, not evaluable; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **TKI**, tyrosine kinase inhibitor.

Jessica J. Lin, Mass General Brigham Cancer Institute, Boston, MA, USA

ALKOVE-1: SAFETY IN ADVANCED *ALK*+ NSCLC

Dose reduction due to TEAE: 17%

- Most common (≥1% of patients):
  ALT increased (10%), AST increased (8%) [a]

Discontinuation due to TEAE: 5%

- Most common (≥1% of patients):
  ALT increased (2%), AST increased (1%)

Most common TEAE were transaminase elevations

- Most were asymptomatic lab abnormalities, and observed to be low-grade, transient, and reversible with dose interruptions or reductions
- Preliminary data suggest increased incidence in less heavily pre-treated patients
- Enhanced monitoring and prompt dose interventions implemented in the protocol for the Phase 3 ALKAZAR trial

Overall safety profile consistent with avoiding TRK-related neurotoxicities

All Treatment-Emergent Adverse Events (TEAEs) in ≥ 15% of TKI-Naïve or TKI-Pretreated Patients with Advanced *ALK*+ NSCLC Receiving Neladalkib 150 mg QD (N = 656)

Preferred Term	Any Grade	Grade ≥3
ALT increased	**47%**	**20%**
AST increased	**44%**	**16%**
Constipation	28%	0.2%
Dysgeusia	23%	0
Peripheral edema	18%	0.3%
Cough	16%	0.5%
Nausea	16%	0.8%

Data pooled for patients in the Phase 1 or Phase 2 portion of ALKOVE-1 with a data cut-off of August 29, 2025. Patients received at least 1 dose of neladalkib at RP2D of 150 mg QD with median duration of exposure of 6.0 months (range: 0.1, 28.4). **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **NSCLC**, non-small cell lung cancer; **RP2D**, recommended phase 2 dose; **QD**, once-daily; **TEAE**, treatment emergent adverse event; **TKI**, tyrosine kinase inhibitor.

[a] Not mutually exclusive: Dose reduction due to any transaminase elevation observed in 11% of patients.

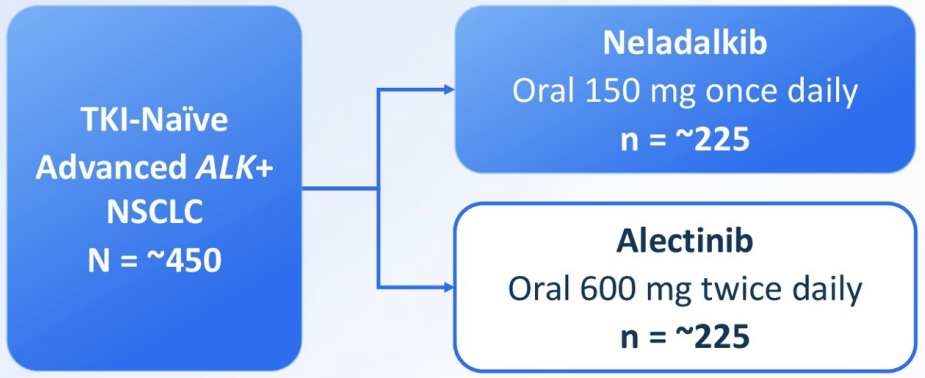
Jessica J. Lin, Mass General Brigham Cancer Institute, Boston, MA, USA

ALKAZAR

GLOBAL PHASE 3 STUDY OF NELADALKIB VS ALECTINIB AS FIRSTLINE TREATMENT FOR ALK+ NSCLC

ALK TKI-naïve, BICR	Response-evaluable N = 44
ORR, % (n/N)	**86%** (38/44) [a]
CR, % (n/N)	9% (4/44) [b]
% DOR ≥ 12 months [95% CI] [c]	**91%** [70, 98]
DOR range	1.7+ to 14.8+ months

[a] Includes 2 single-timepoint PR pending confirmation for ongoing patients. [b] Includes 1 single-timepoint CR pending confirmation in ongoing patient with prior confirmed PR. [c] Analyses of DOR based on Kaplan-Meier estimates.



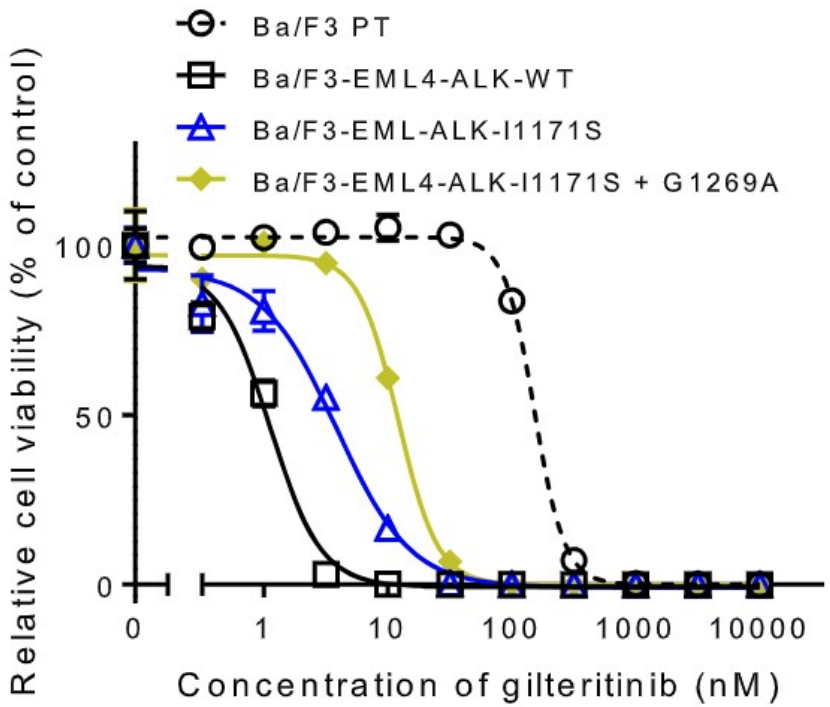
1:1 Randomization

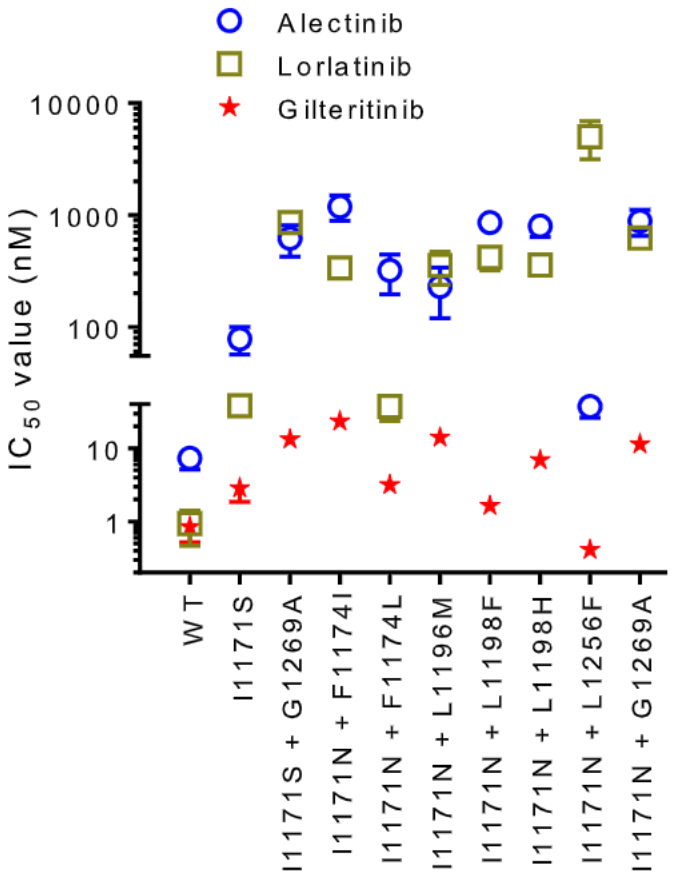
Stratification Factors:

- 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

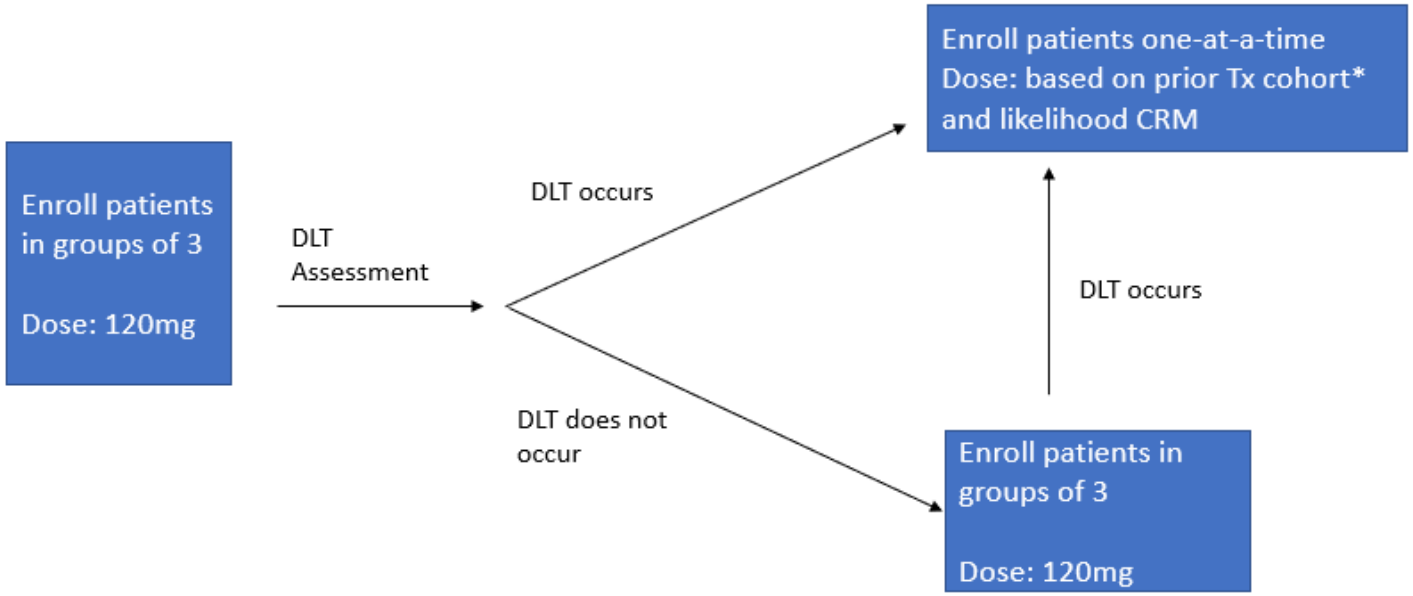




Gilteritinib has broad activity against compound ALK mutations and activity through FLT3, AXL, TRKA, and MER pathways

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

Study schema



***Prior Treatment Cohorts**

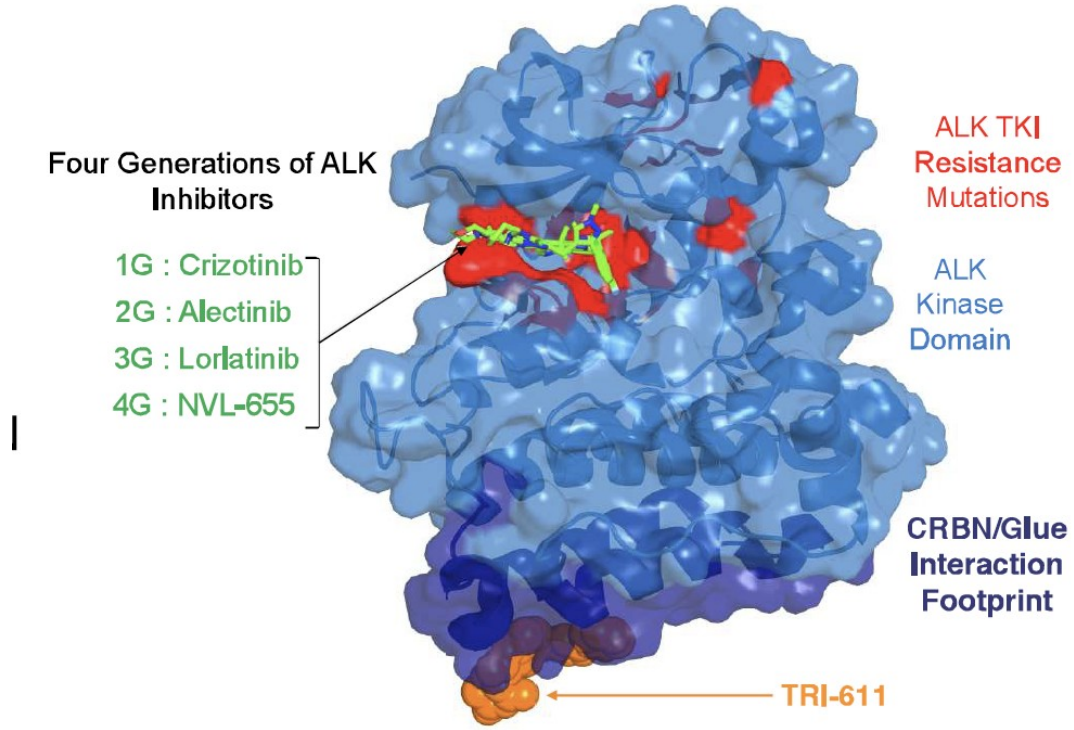
Cohort 1: Prior 1st generation ALK TKI (crizotinib) and/or prior 2nd generation TKI (ceritinib, brigatinib, alectinib) and/or lorlatinib

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

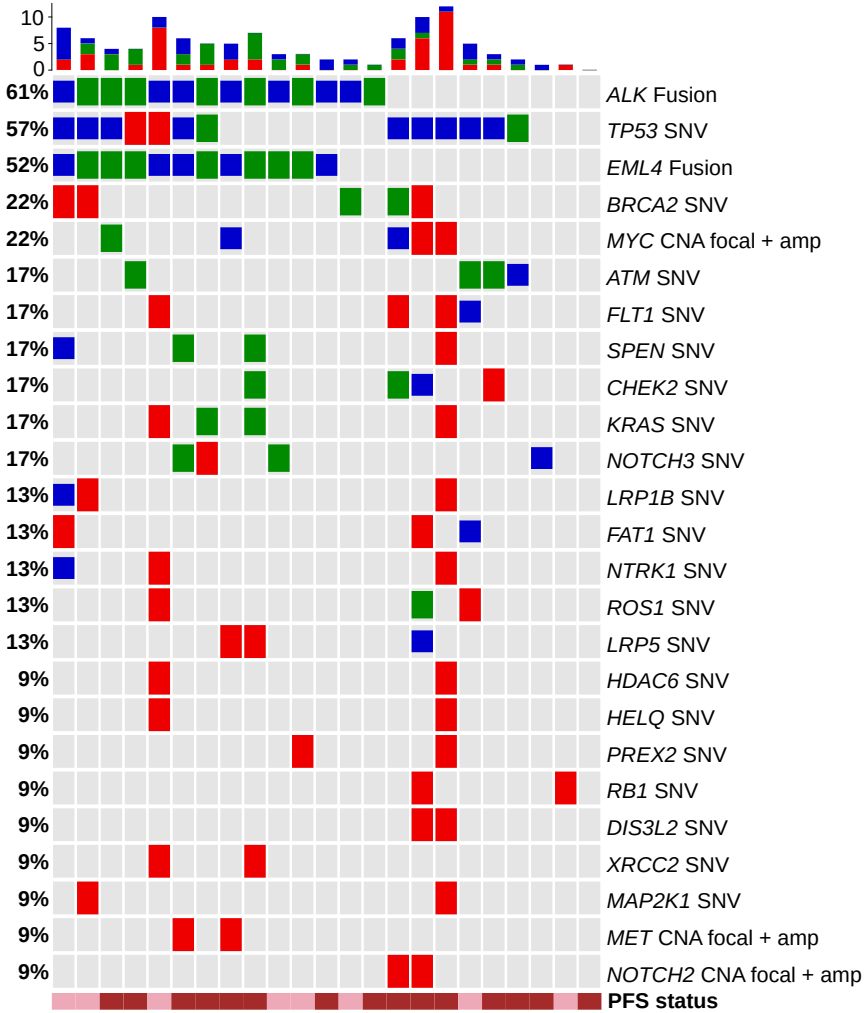
TRI-611 A MOLECULAR GLUE DEGRADER



- The site of TRI-611 engagement is distal from ALK TKI resistance alleles, colored in red
- TRI-611 is expected to engage and promote the degradation of any TKI resistance allele

NO ALK G1202R or L1196M mutations in ctDNA at EOT With Lorlatinib in CROWN trial

Genes with ≥2 gain or loss alterations at EOT (n=23[a])



PFS early: PFS ≤12 months
PFS intermediate: PFS >12 to <84 months
[a]17 patients discontinued due to progressive disease and 6 discontinued due to adverse events.

Previously identified resistance mechanisms

- *RTK*/*RAS*/*MAPK* pathways: *MAP2K1*, *MET*, *KRAS, and NTRK1*
- Tumor suppressors: *RB1*, *LRP5*, and *FAT1*
- Amplified oncogenes (copy number ≥2.1): *MYC*, *MET,* and *NOTCH2*

New putative resistance mechanisms

- Angiogenesis pathway: *FLT1*/*VEGFR1*
- DNA damage repair: *XRCC2*
- Epigenetic regulation pathway: *HDAC6*

No emerging new *ALK* resistance mutations were detected in the ctDNA samples collected at end of lorlatinib treatment

amp, amplification; CNA, copy number alteration; ctDNA, circulating tumor DNA; EOT, end of treatment; PFS, progression-free survival; SNV, single-nucleotide variation.

Tony S. K. Mok, MD (tony@clo.cuhk.edu.hk)

MET AMPLIFICATION IN ALK POSITIVE NSCLC PATIENT

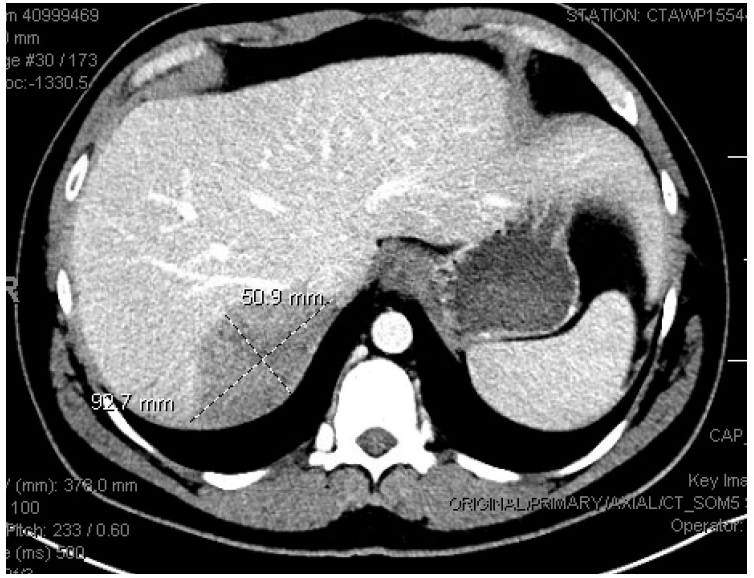
Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

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

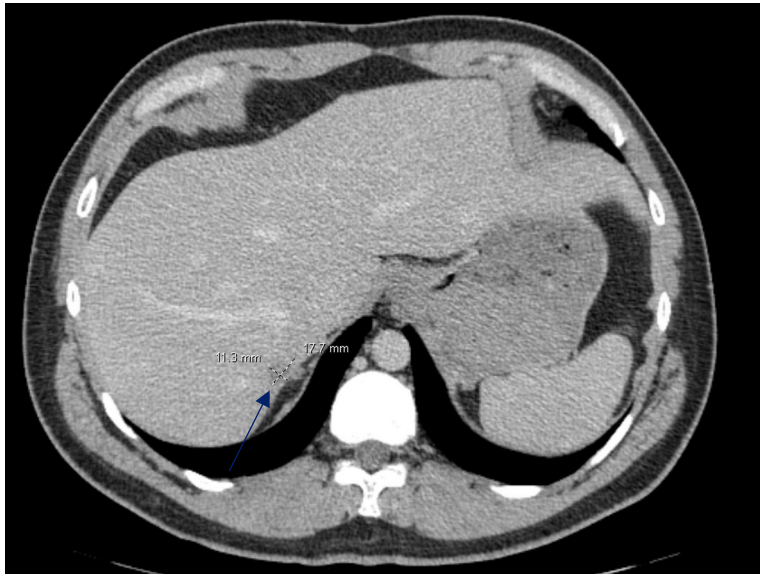
Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 5)	% cfDNA or Amplification
EML4-ALK Fusion	✓ Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib	Yes	3.3%
MET Amplification	~ Capmatinib, Crizotinib, Tepotinib	Yes	Medium (++)
TP53 Splice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

42% RR with MET combination
(N = 12 patients)

Dagogo-Jack, JTO CRR, 2023

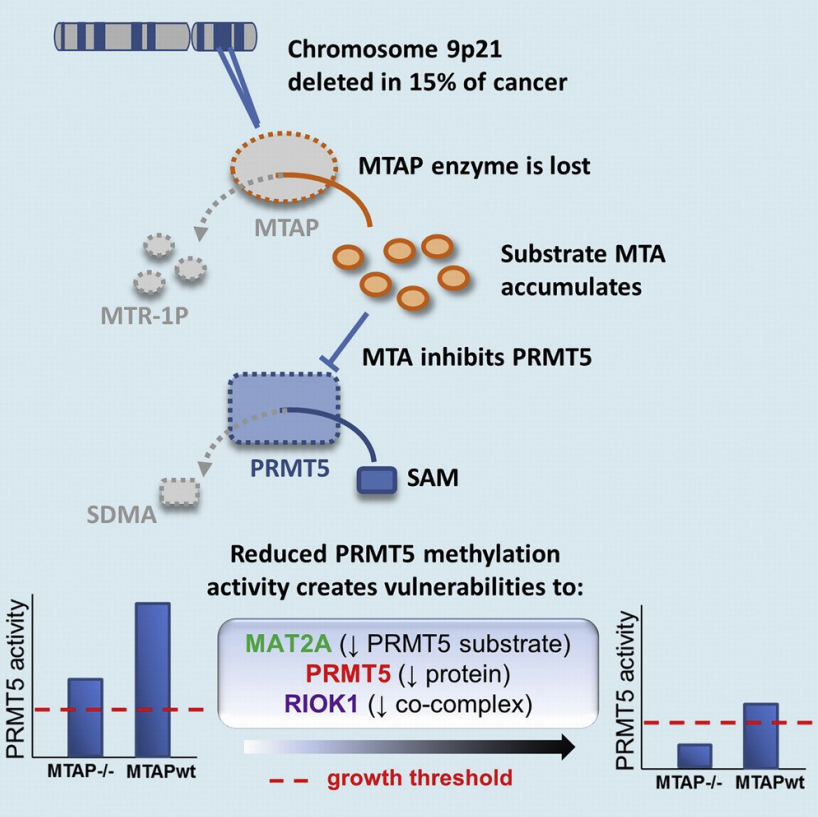


June 8th 2023
Lorlatinib (ALK inhibitor)



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

CO-MUTATIONS- MTAP DELETION

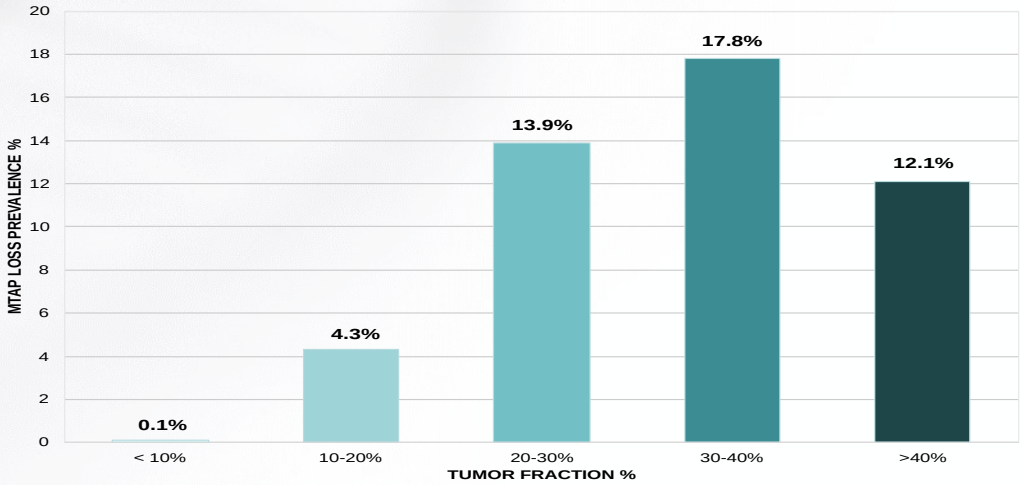


MTAP is involved in methionine salvage pathway

Loss of MTAP leads to accumulation of MTA

MTA inhibits PRMT5 which regulates gene expression and cell cycle.

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



Rate of MTAP deletion is about 25% in NSCLC

Marjon K, Cell Reports 2016; Ikushima, H ESMO Open 2025; Gadgeel AACR 2026

ARCHER STUDY DESIGN

ALK-Vac is synthetic long peptide vaccine with Poly-ICLC adjuvant targeting 7 common resistance mutations

G1202R, L1196M, I1171T/N/S, D1203N, E1210K

Key Inclusion

- Advanced or unresectable ALK+ NSCLC
- Without known resistance alterations targeted by the peptide vaccine
- Disease control for ≥ 4 months on standard of care TKI



Endpoints

Co-primary

- Safety
- Vaccine induced immune response

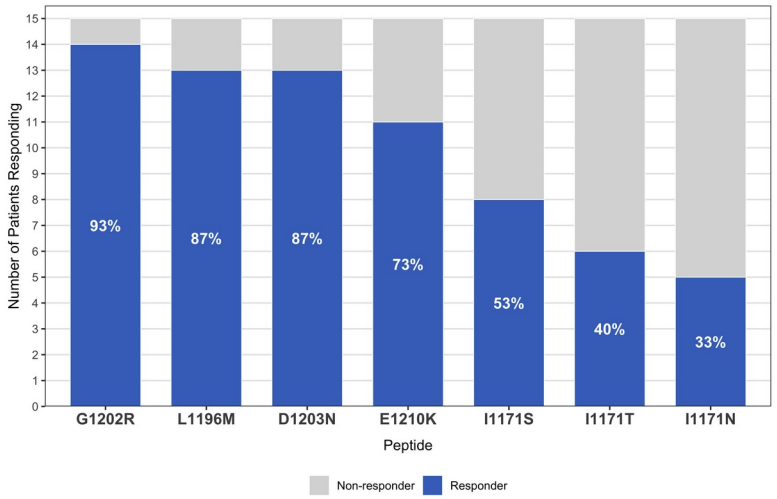
Secondary

- Post-progression genomic alterations
- PFS
- OS

Single center, Phase 1b (NCT05950139)

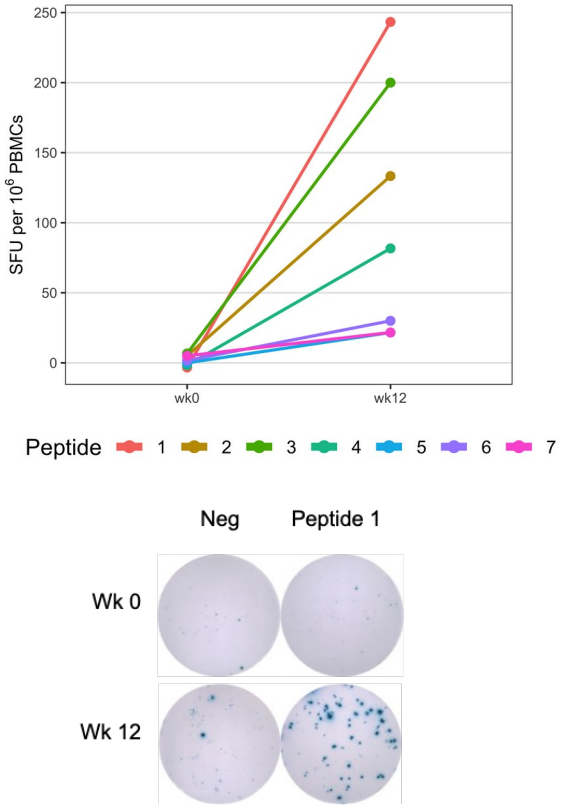
ALK-VAC INDUCED DE NOVO RESPONSES AGAINST ALL TARGETED ANTIGENS

ELISpot responses observed across all peptides



- Positive response = SFU fold-change ≥ 2 at Wk12
- Median fold-change 11.4 (IQR 5.8 – 22.3)

Representative patient response



No pt had a detectable pre-existing immune response

93% (14/15) of pts mounted a response to at least one targeted antigen

33% (5/15) of pts mounted a response to all targeted antigens

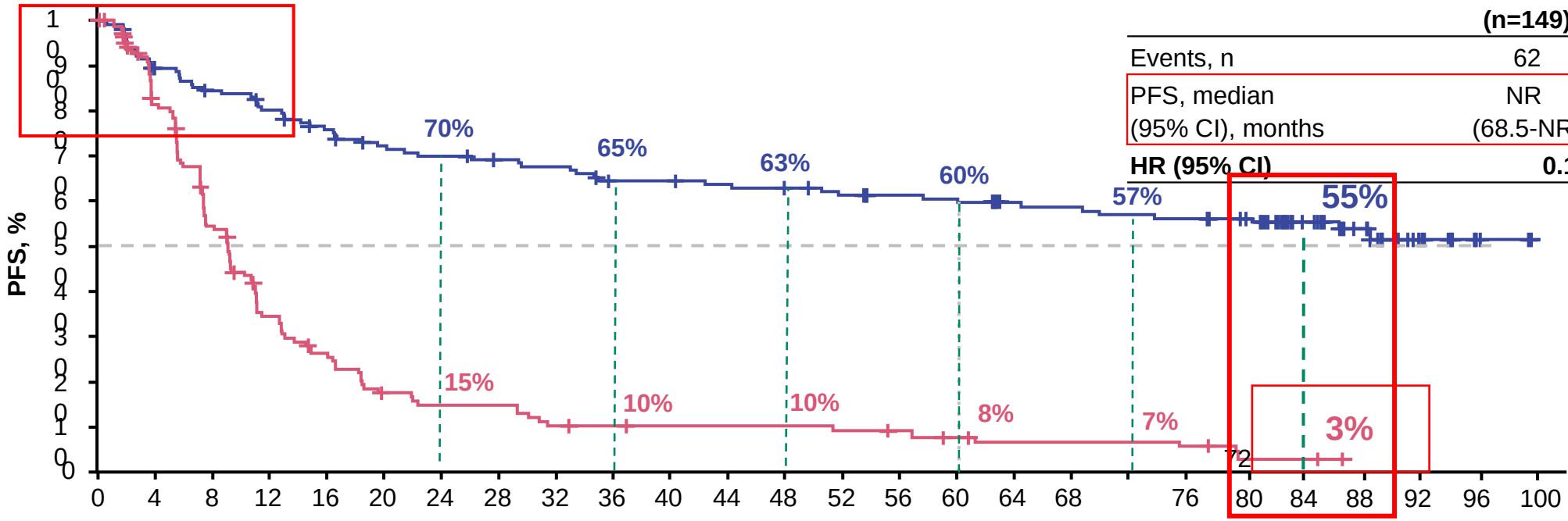
The most common resistance mutation (G1202R) had the highest response rate (93%)

Vincent K. Lam, M.D., Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

PFS IN THE ITT POPULATION (7-YEAR FOLLOW-UP)

The median duration of follow-up for PFS was **83.0 months** (95% CI, 81.2-86.3) in the lorlatinib arm and **77.2 months** (95% CI, 36.8-not evaluable) in the crizotinib arm

	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	62	119
PFS, median (95% CI), months	NR (68.5-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.26)**	



No. at risk																									
Lorlatinib	149	126	118	111	103	96	93	89	87	81	81	79	78	75	73	71	69	68	66	65	62	38	28	9	2	0
Crizotinib	147	107	70	42	30	19	16	16	11	10	9	9	9	8	8	7	6	6	6	5	2	2	0	0	0	0

36 year old female died within 11 months of diagnosis. Tumor had MET amplification

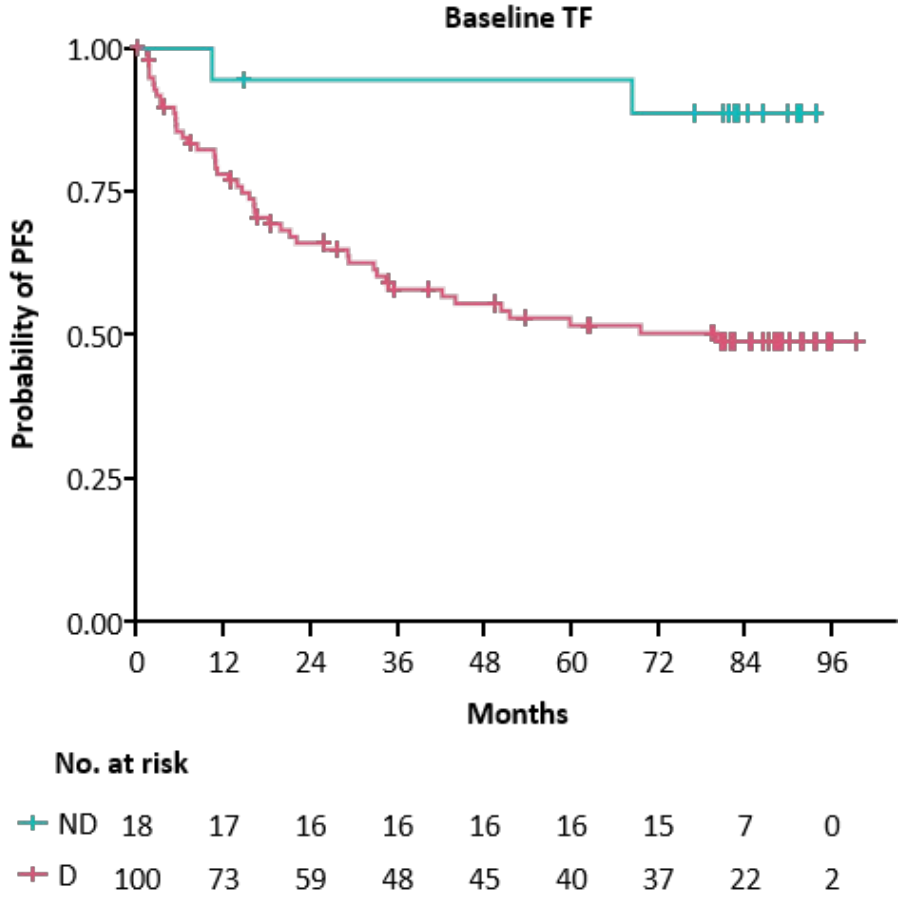
At the time of this analysis, median PFS by investigator was still not reached with lorlatinib

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.

Tony S. K. Mok, MD (tony@clo.cuhk.edu.hk)

7-year PFS by baseline methylation-based TF detection in the lorlatinib group

- The Guardant Infinity ctDNA next-generation sequencing assay assesses genomic alterations across 755 genes and uses a non-destructive methylation-based technology to quantify tumor fraction
- Baseline methylation-based TF level was prognostic for PFS, with longer PFS in patients with TF ND vs D at baseline[a]



	ND n=18	D n=100
PFS, median (95% CI), months	NR (NR-NR)	80.3 (34.6-NR)
HR (95% CI), ND vs D	0.17 (0.04-0.69)	

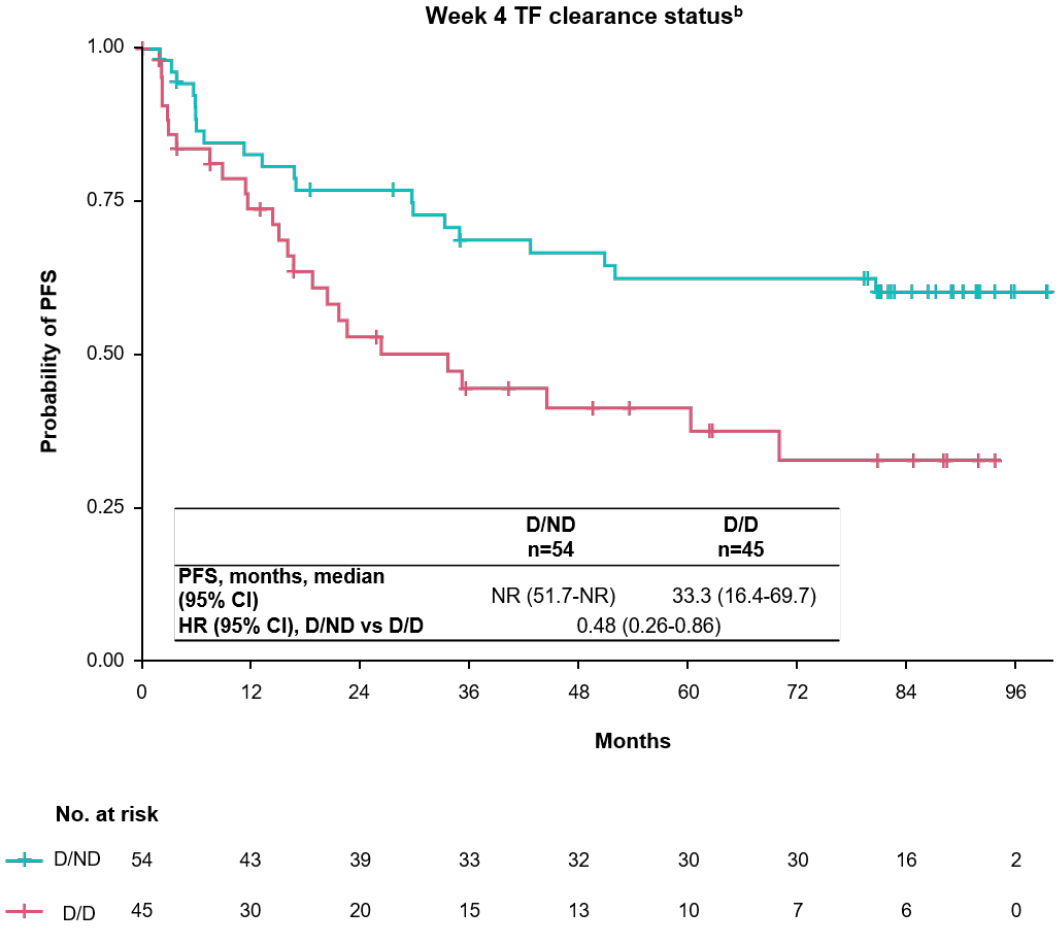
D, detected; HR, hazard ratio; ND, not detected; NR, not reached; PFS, progression-free survival; TF, tumor fraction.

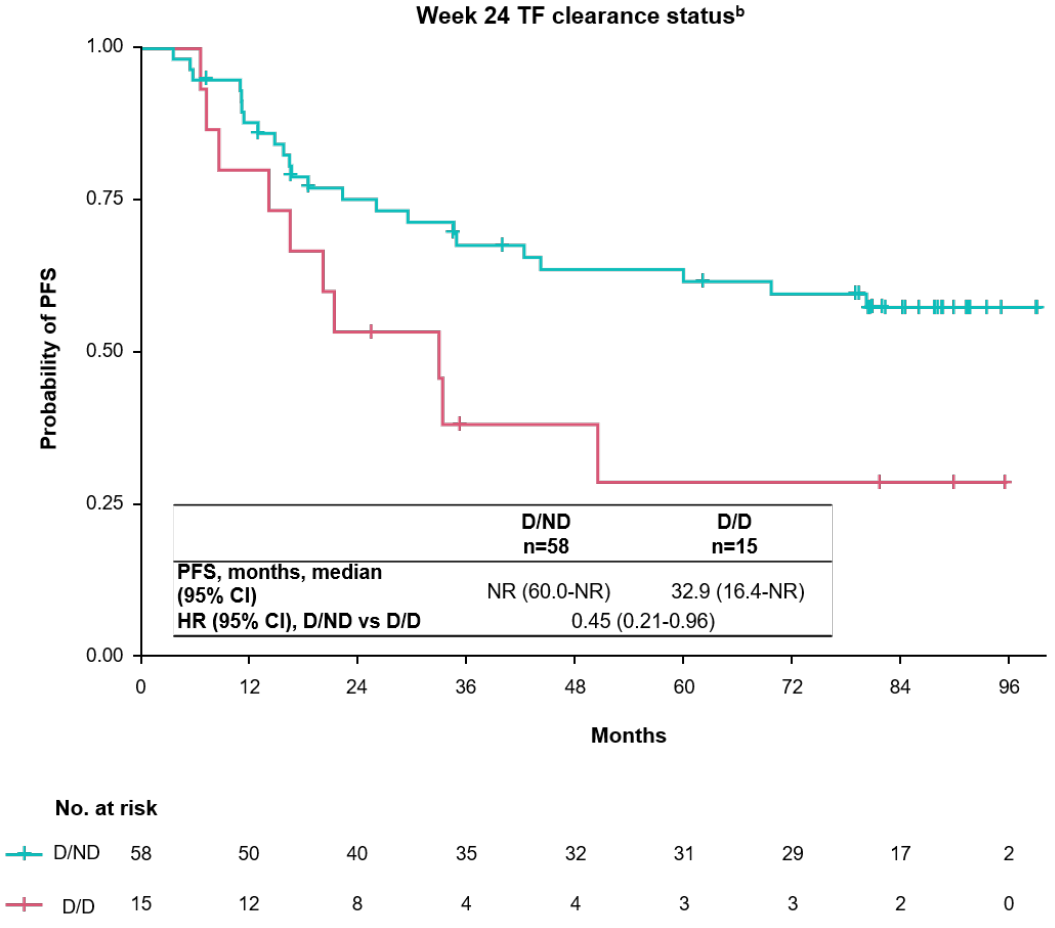
[a]TF is defined as the ratio of observed tumor-specific methylation signals to methylation levels across constitutively methylated and unmethylated regions. ND means TF=0.

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7-year PFS by on-treatment TF clearance in the lorlatinib group

- Among patients with TF detected at baseline, TF clearance (D/ND) was associated with longer PFS vs persistent TF detected (D/D) as early as week 4 (HR 0.48) and the association held at week 24 (HR 0.45)[a]





D, detected; HR, hazard ratio; ND, not detected; NR, not reached; PFS, progression-free survival; TF, tumor fraction.

[a]TF is defined as the ratio of observed tumor-specific methylation signals to methylation levels across constitutively methylated and unmethylated regions. ND means TF=0.

[b]The clearance analyses at Week 4 and Week 24 are based on patients with both a detectable baseline sample and an evaluable paired sample at the respective visit.

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19-YEAR OLD MALE PATIENT



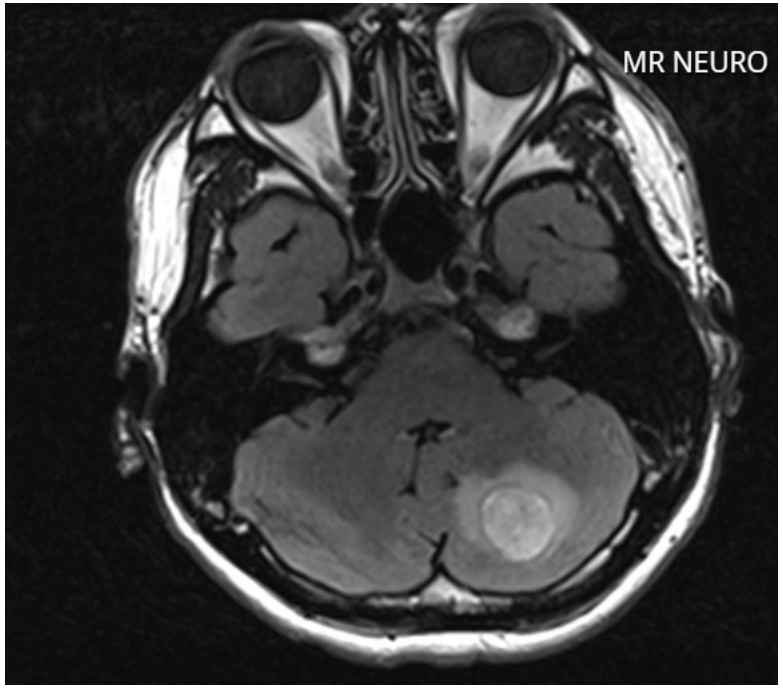
7/9/2026



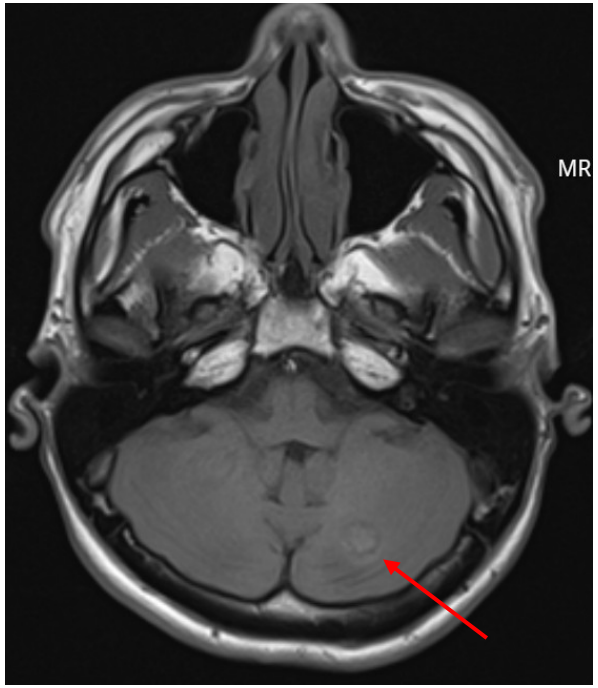
8/23/2026

19 year old male patient had persistent cough.
No symptoms related to brain met.

19-YEAR OLD MALE PATIENT



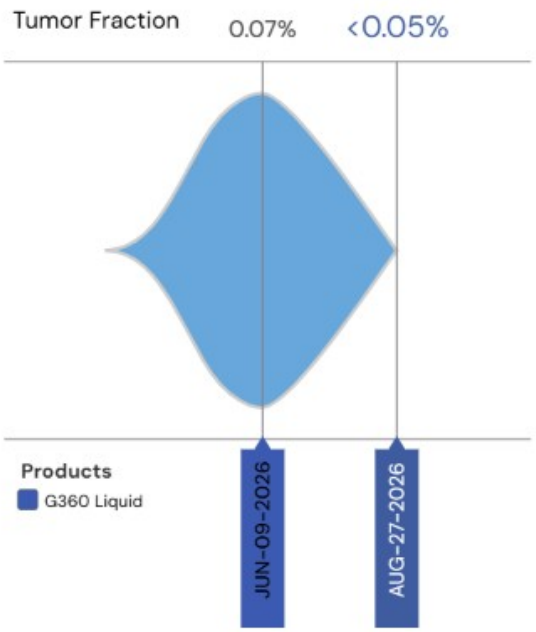
6/16/2026



8/23/2026

19 year old male patient had persistent cough.
No symptoms related to brain met.

CT DNA CHANGES



EML4-ALK Fusion

and 1 other alterations

Amplifications not graphed.

	ND n=18	D n=100
PFS, median (95% CI), months	NR (NR-NR)	80.3 (34.6-NR)
HR (95% CI), ND vs D	0.17 (0.04-0.69)	

INTENSIFICATION OF THERAPY

Clinical Factor- Brain Metastases, Tumor Burden

Co-Mutations- p53, CDKN2A,

ctDNA changes on therapy

ADVANCED LUNG CANCER SURVIVORSHIP HEALTHY SURVIVAL

Advanced lung cancer survivorship

Physical symptoms
Dyspnea, fatigue, pain

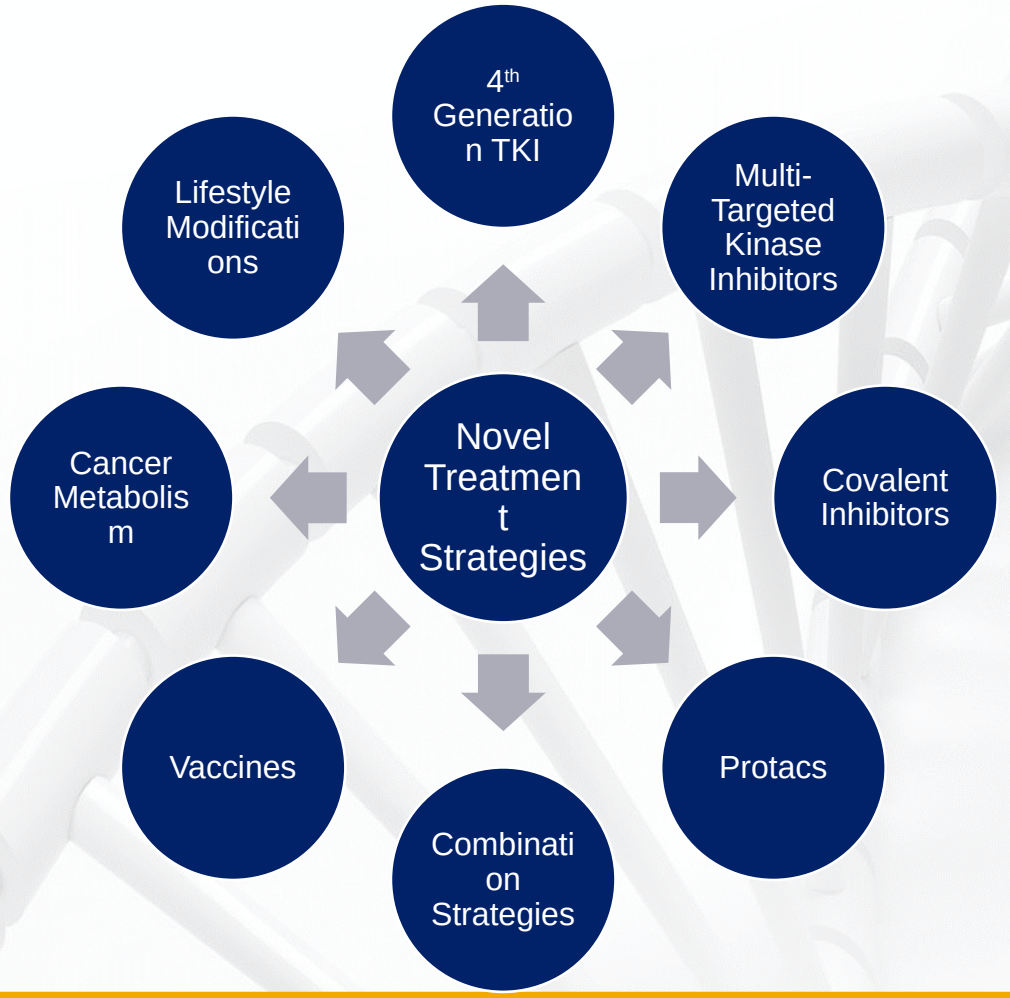
Psychological
Anxiety and distress

Financial toxicity
Costs and income loss

Social & role changes
Relationship and caregiver strain

Ongoing surveillance
Scans, specialists, monitoring

CONCLUSIONS



Shared Decision Making has become extremely critical

Median PFS > 7 years with Lorlatinib

Several Novel Strategies being investigated

Biomarkers to Personalize Therapy

Lifestyle modifications for Healthy Survival

ADVANCED ALK+VE NSCLC PATIENT



Patient has provided verbal permission to show picture

THANK YOU

Thoracic Oncology Team
Winship Cancer Institute/Emory University





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