II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 6 Y 7 DE FEBRERO DE 2025

MECANISMOS DE RESISTENCIA DE **ALK** Y SU ENFOQUE TERAPÉUTICO

Enric Carcereny Costa

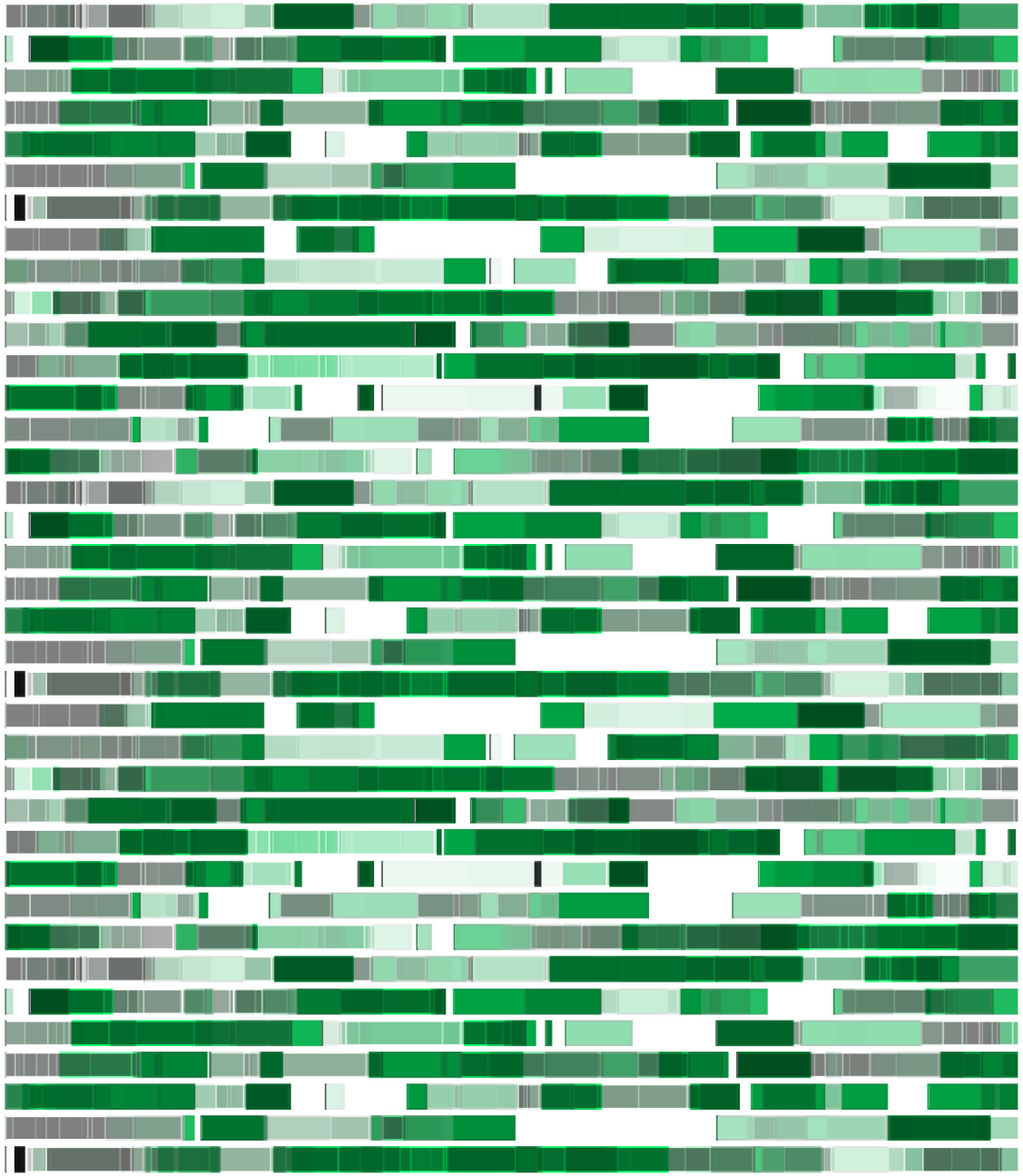
Coordinator of Thoracic, Brain and Sarcoma tumors Group

Medical Oncology Department, Catalan Institute of Oncology (ICO)-Badalona/Mataró

Badalona-Applied Research Group in Oncology (B-ARGO)

Organizador por:

HENDERE HEALTHCARE



DISCLOSURES

Advisory / Consultancy : AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Novartis, Roche, Takeda, Pfizer, Janseng-Cilag

- **Speaker Bureau / Expert testimony**: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Novartis, Pfizer, Roche, Takeda, Pierre-Fabre, Regeneron

- **Travel / Accommodation / Expenses** :Bristol-Myers Squibb, Pfizer, Roche, Takeda, Astra Zeneca

TO TAKE AWAY

- Currently, Lorlatinib is the leading and most clinically effective agent for treating ALK+ NSCLC, particularly known for its remarkable efficacy in managing CNS metastases.

- However, resistance to third-generation ALK TKIs can emerge through both on-target and off-target mechanisms.

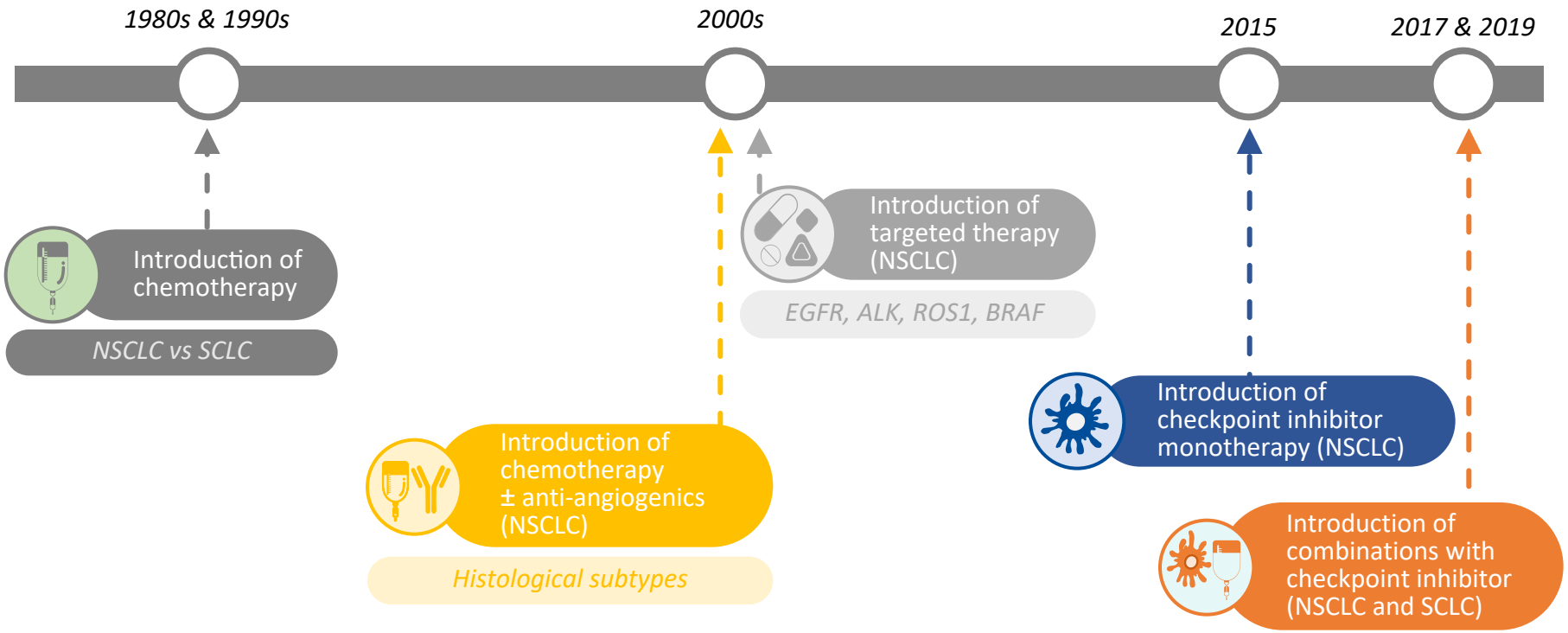
- To counteract on-target resistance, fourth-generation TKIs are in development, offering significant promise in addressing these challenges.

- Off-target resistance, which occurs more frequently, involves mechanisms such as the activation of bypass signaling pathways or phenotypic transformation, which can complicate treatment further.

- In order to tackle resistance beyond thrid-generation TKIs, a variety of innovative approaches are being explored. These include combination therapies, antibody-drug conjugates, …These advanced therapeutic approaches hold great potential for improving treatment outcomes and overcoming resistance in ALK+ NSCLC.

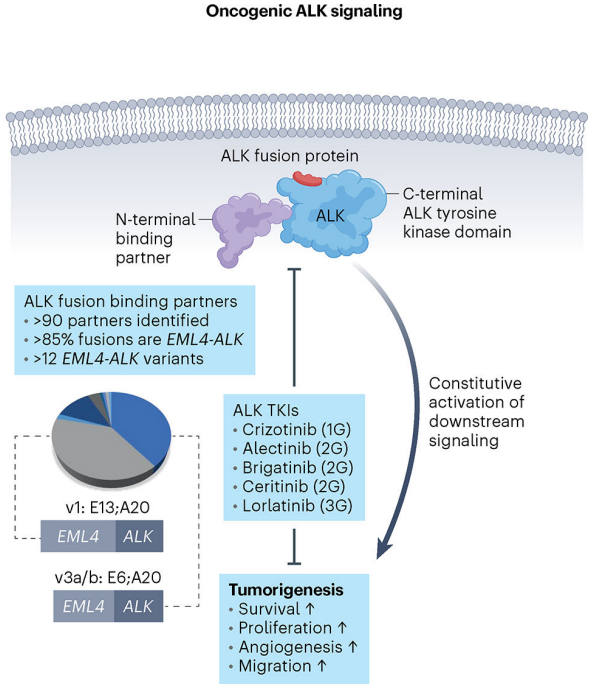
INTRODUCTION

INTRODUCTION



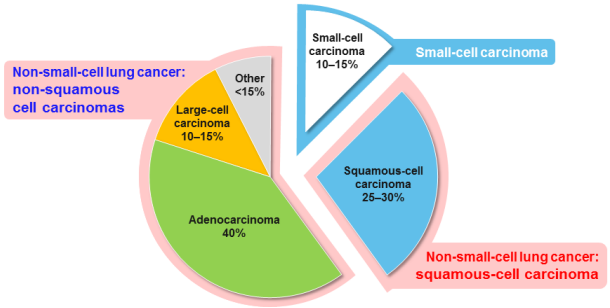
Bunn, Semin Oncol 1989; Bunn, et al. Clin Cancer Res 1998; Scagliotti, et al. J Clin Oncol 2002; Sandler, et al. N Engl J Med 2006 Shepherd, et al. N Engl J Med 2005; Brahmer, et al. N Engl J Med 2015; Horn, et al. N Engl J Med 2018

INTRODUCTION

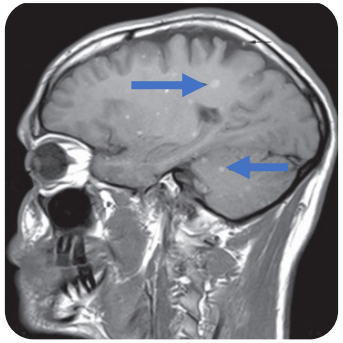


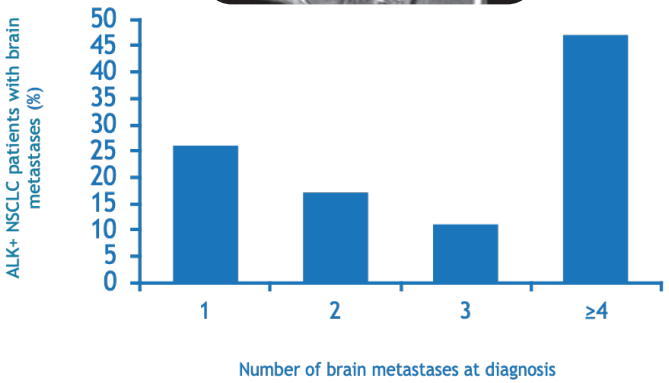
Chromosomal rearrangements lead to the production of ALK fusion proteins. The most common fusion partner with *ALK* is *EML4,* resulting in the expression of EML4-ALK on proteins

ALK+ disease occurs in ~5% of patients with advanced NSCLC



Brain metastases at present at diagnostis in approximately 15-35% ALK+ NSCLC patients



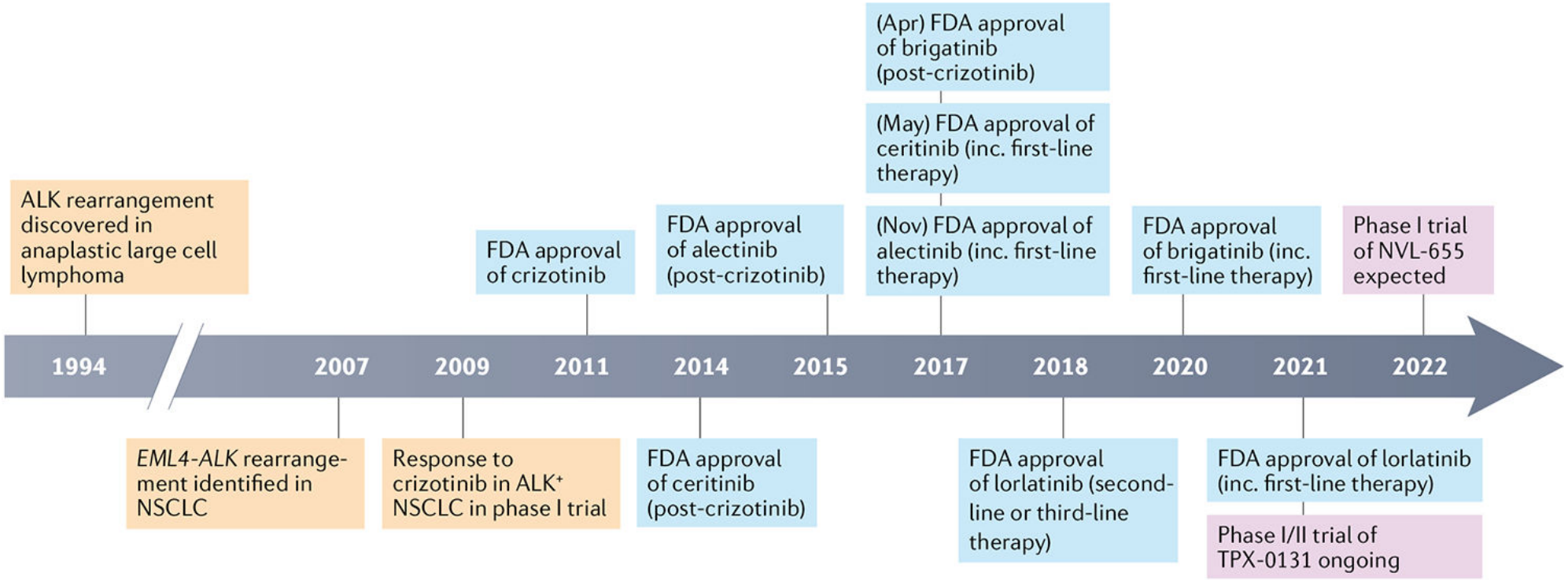


ALK+ NSCLC patients frequently present with brain metastases at diagnosis; aproximately 50% of patients with brain metastases at diagnosis have > 4 lesions

Costa et al JCO 2015: Johung, et al. J Clin Oncol 2015

INTRODUCTION

ALK-Driven Lung Cancer: A Breakthrough Target for Targeted Therapy



Cooper AJ et alNat Rev Clin Oncol. 2022 Aug;19(8):499-514.

INTRODUCTION

ALK-positive patients in the era of Lorlatinib

CROWN study: Lorlatinib vs crizotinib in treatment-naïve patients with advanced ALK+ non-small cell lung cancer

Key patient inclusion criteria
- Stage III/IV NSCLC
- ALK-positive
- No prior systemic treatment for metastatic disease
- Asymptomatic CNS metastases allowed
- ECOG PS 0–2

(n=296)

R 1:1

Lorlatinib 100 mg/day (n=149)

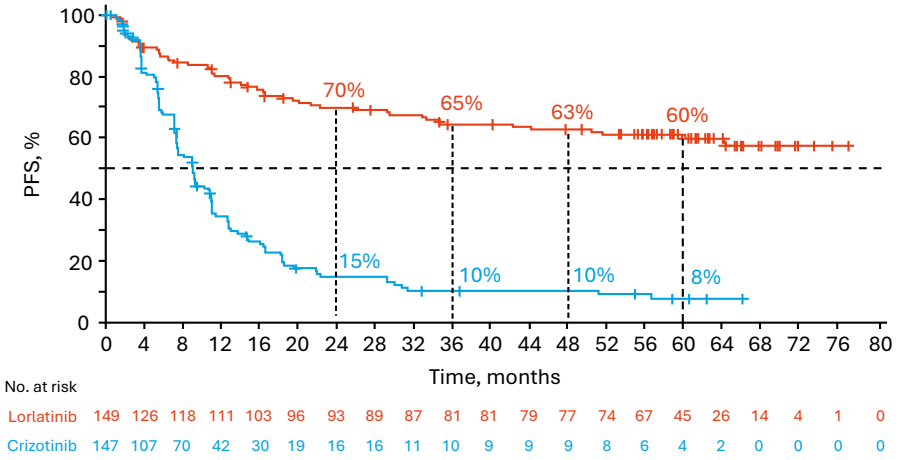
Crizotinib 250 mg BID (n=147)

Stratification
- Brain metastases (yes vs. no)
- Ethnicity (Asian vs. non-Asian)

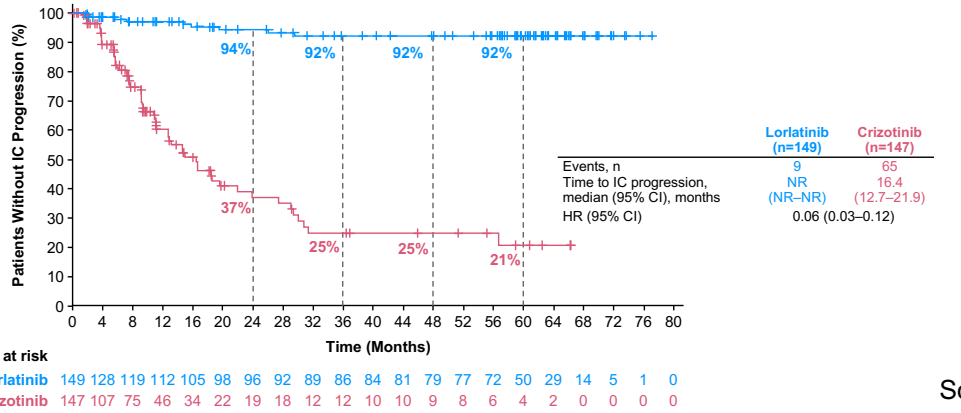
Primary endpoint
- PFS (BICR, RECIST v1.1)

Secondary endpoints
- PFS (investigator-assessed), ORR, intracranial-ORR, intracranial-time to progression, OS, QoL, safety

Progression-free survival (investigator-assessed)



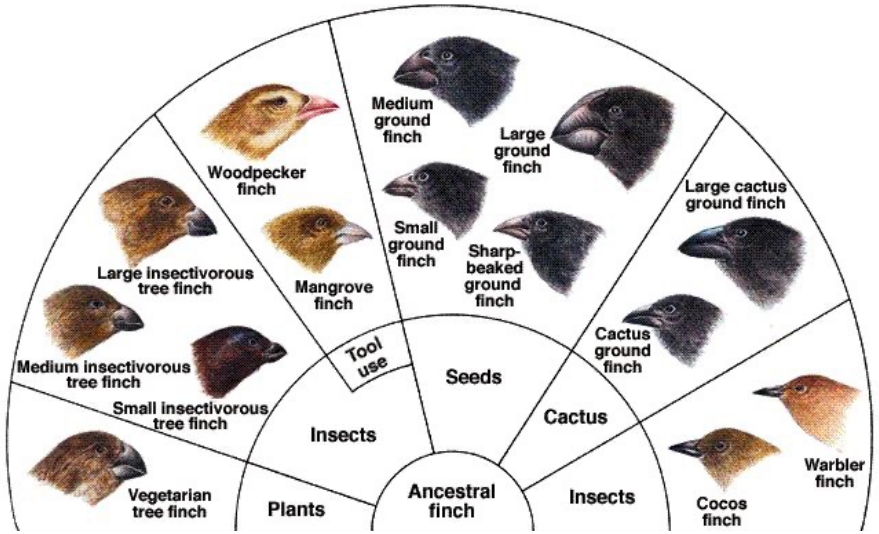
Time to IC Progression[a] by Investigator Assessment[1]

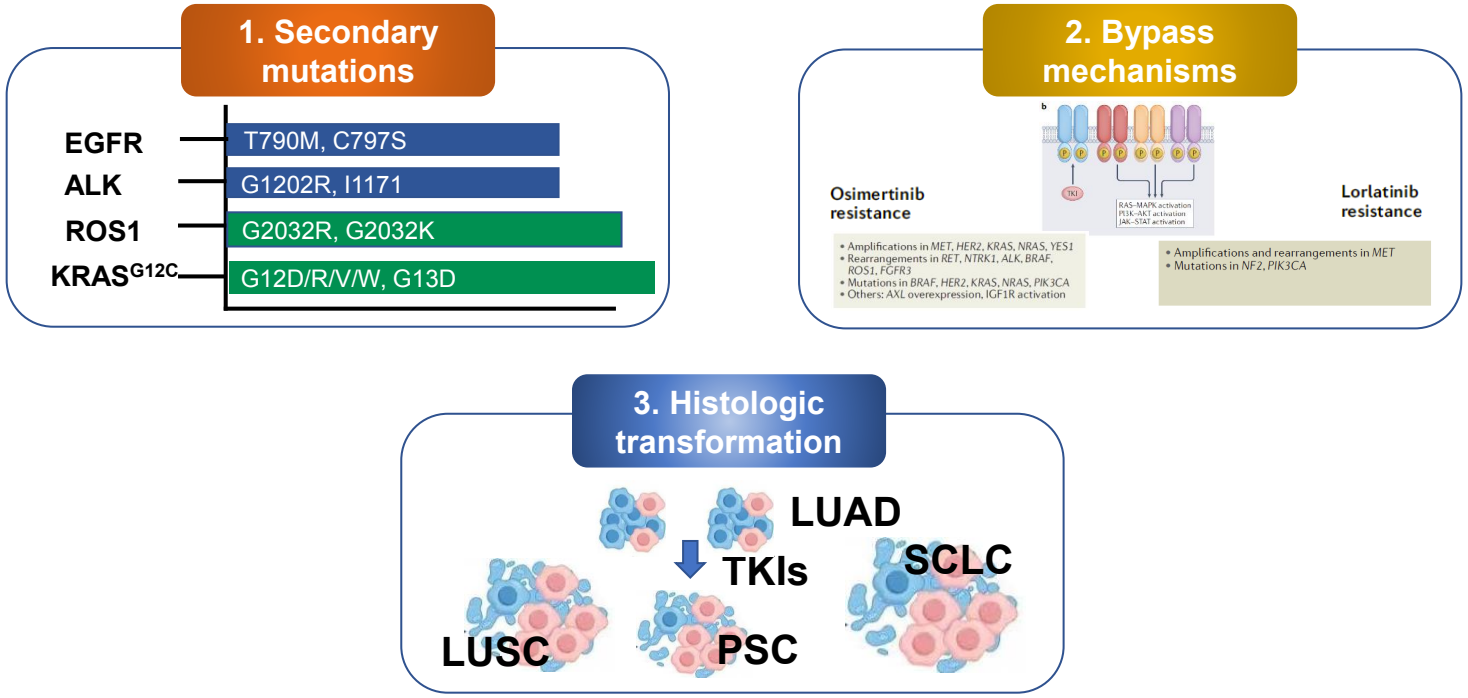


Solomon BJ, et al. J Clin Oncol 2024;42(suppl):Abstr LBA8503

MECHANISMS OF RESISTANCE

Darwinian Evolution and the Mechanisms of Resistance in ALK-targeted Therapies



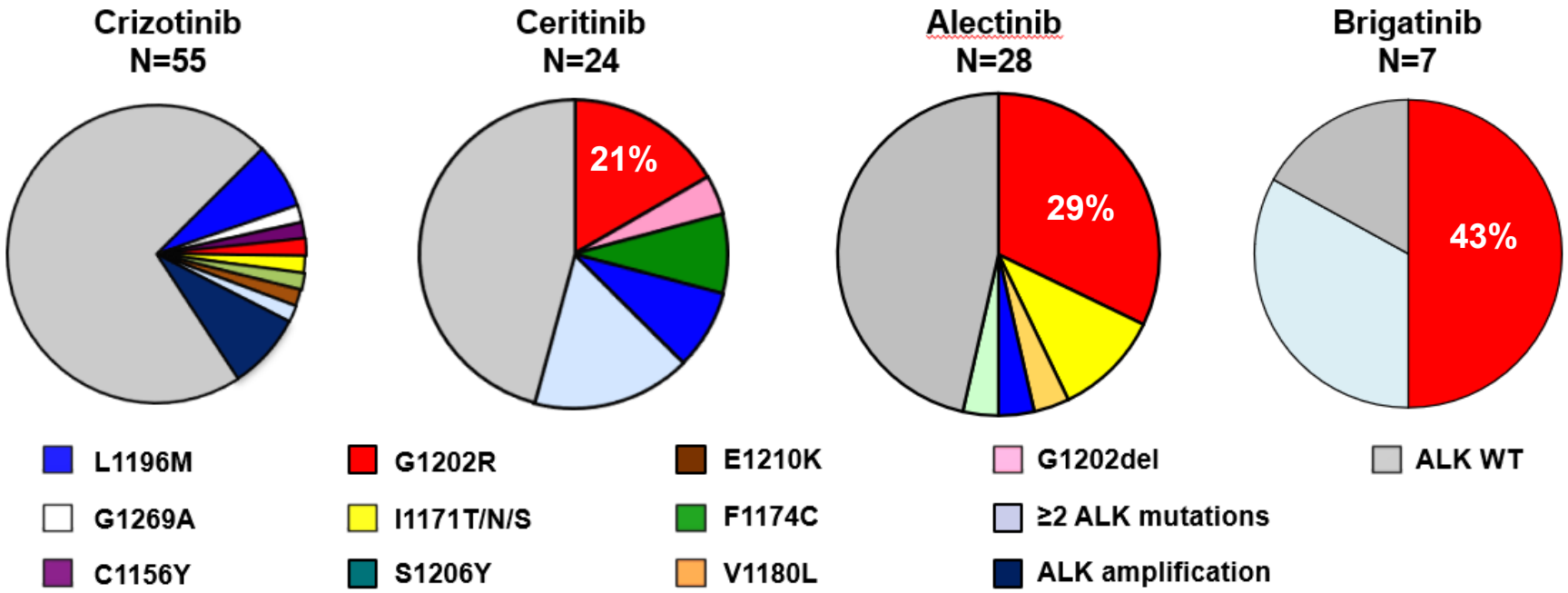


Without a pathway-impacting selection pressure, pathway should not alter

Gerber DE et al. Am Soc Clin Oncol Educ Book. 2014:e353-65

MECHANISMS OF RESISTANCE

Secondary Mutations: Unraveling Resistance to 1st and 2nd Generation ALK TKIs



We observed that the spectrum of ALK resistance mutations was different following progression on second-generation ALK inhibitors compared to crizotinib

The most common ALK mutant to second generation ALK inhibitors is G1202R (21%-43%)

EML4-ALK variant 3 is associated with high incidence of G1202R resistance

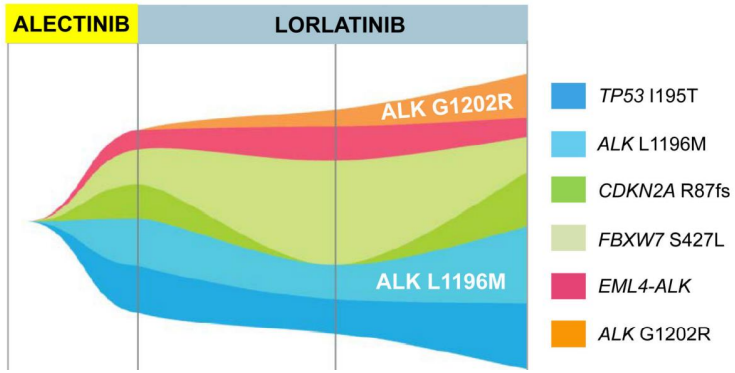
A minority of ALK-positive patients (~20%) developed ALK resistance mutations on crizotinib. By contrast, ALK resistance mutations were present in over one-half of patients progressing on second-generation ALK inhibitors, likely reflecting the greater potency and selectivity of these agents compared to crizotinib.

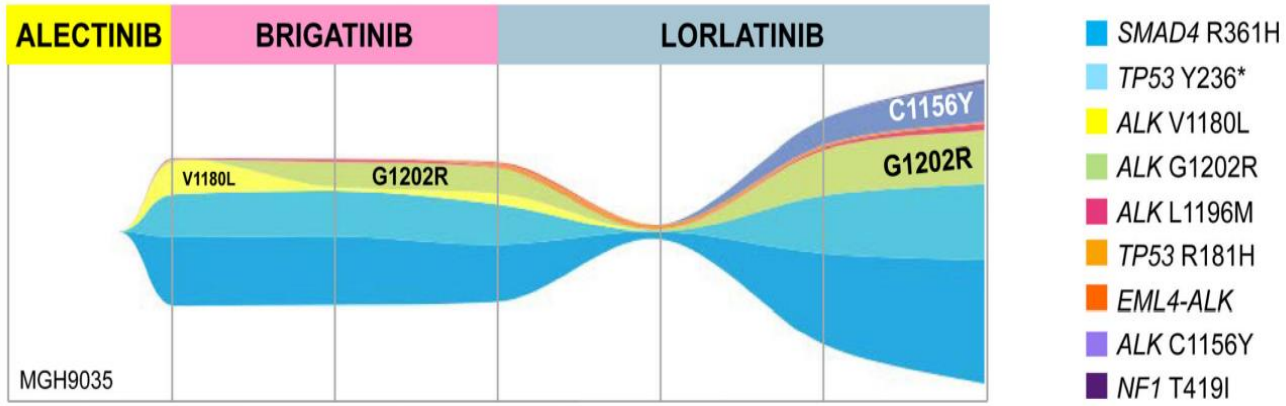
Gainor JF et al Cancer Discov. 2016 Oct;6(10):1118-1133.

MECHANISMS OF RESISTANCE

Secondary Mutations: The Evolution of ALK Resistance During Sequential Treatment

High incidence of compound mutations with sequential use of 2nd and 3rd G TKIs

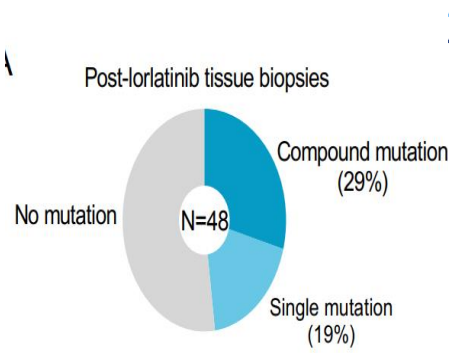


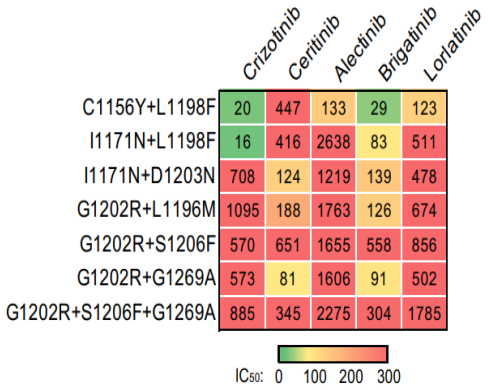


Compound ALK mutations accounts for ~ 30% in resistance to lorlatinib in the later-line setting

Most of compound ALK mutations are refractory to all available ALK TKIs

As the initial ALK mutation provides the substrate for generating compound mutations





Dagogo-Jack I et al. Clin Cancer Res. 2019 Nov 15;25(22):6662-6670.

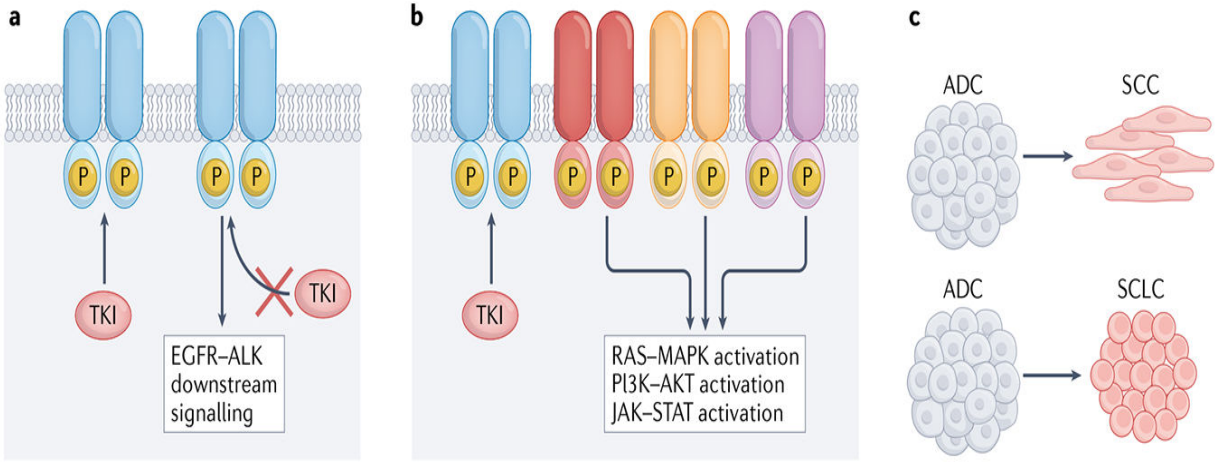
MECHANISMS OF RESISTANCE

Shifting Resistance Mechanisms: The Impact of Lorlatinib

Mechanisms of acquired resistance

On target — **Secondary mutations**

Off target — **Bypass downstream pathways. Cell transformation**



Lorlatinib resistance

- *ALK* compound mutations, including those containing G1202R, I1171N/T/S, L1198F*
- ALK L1256F

- Amplifications and rearrangements in *MET*
- Mutations in *NF2*, *PIK3CA*

- Small-cell transformation
- Squamous-cell transformation
- EMT

Mechanisms of resistance en Crown trial

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.

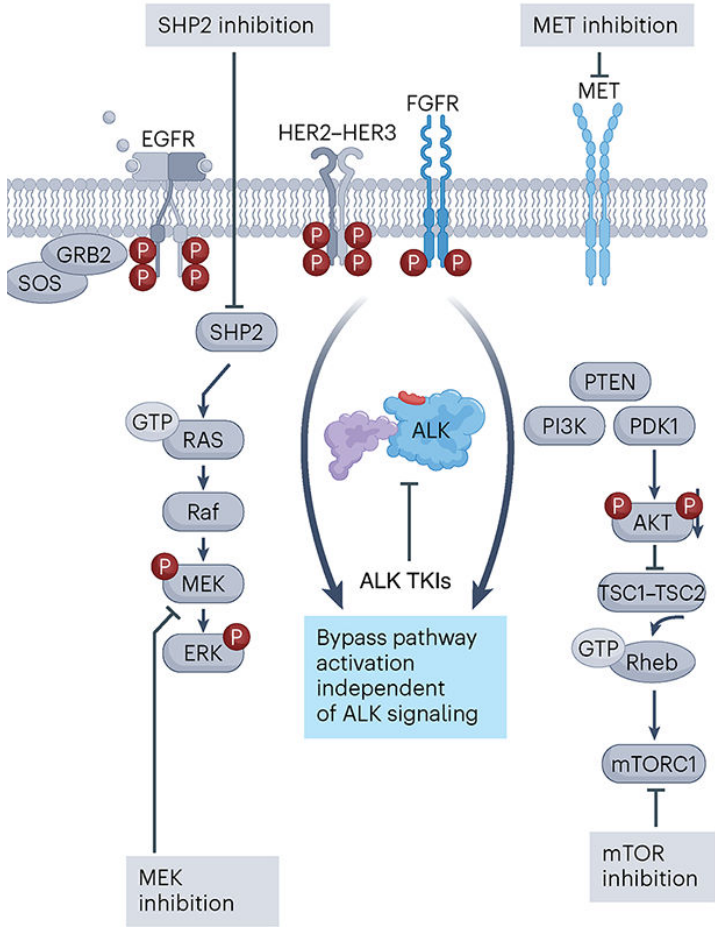
Cooper AJ et alNat Rev Clin Oncol. 2022 Aug;19(8):499-514.

Felip et al ESMO 2023

MECHANISMS OF RESISTANCE

Bypass pathwat activation

Bypass mechanism	Prior ALK TKI[a]	Prevalence
MET amplifications	Second-generation TKIs	12% in first or later lines
	Lorlatinib	22% in later lines
MET rearrangements	Alectinib or lorlatinib	3% in later lines
MET exon 14 mutations	Alectinib	Unknown, data limited to case reports
RET rearrangements	Brigatinib	Unknown, data limited to case reports
EGFR activation	Crizotinib	44% in first line
EGFR mutations	Crizotinib	9–14% in first line
HER2 amplifications	Crizotinib, alectinib	Unknown, data limited to case reports
KIT amplifications/activation	Crizotinib	15% in first line
IGF1R activation	Crizotinib	80% in first line
SHP2 signalling	Ceritinib	Preclinical data only
NF2 mutations	Lorlatinib	20% in later lines
YES1 amplifications	Crizotinib, ceritinib	11.8% in later lines
KRAS mutations	Crizotinib	18% in first line
BRAF^{V600E} mutations	Alectinib	Unknown, data limited to case reports
MAP2K1 mutations	Ceritinib	Unknown, data limited to case reports
DUSP6 loss	Crizotinib	83%
PIK3CA mutations	Lorlatinib or ceritinib	Unknown, data limited to case reports
AXL overexpression	Earlier-generation TKIs	Preclinical data only

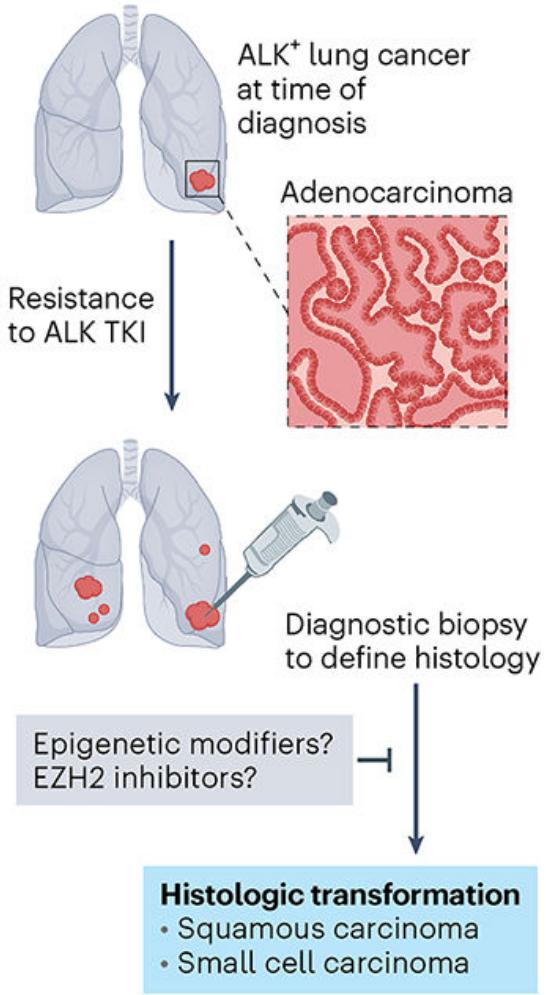


Bypass pathway activation can occur through genetic mechanisms (amplifications, activation mutations, structural alterations) and non-genetic mechanisms (receptor hyperactivation), resulting in activation of signaling pathways that bypass ALK dependency

Cooper AJ et alNat Rev Clin Oncol. 2022 Aug;19(8):499-514. Schneider JL et al. Nat Cancer. 2023 Mar;4(3):330-343.

MECHANISMS OF RESISTANCE

Lineage Transformation: Unveiling the Power Behind Tumor Evolution and Resistance



Transformation of a tumor to a different histologic subtype is associated with loss of reliance on the oncogenic driver, leading to drug resistance

Although virtually all cases of newly diagnosed ALK+ NSCLC are adenocarcinoma, small cell lung cancer transformation has been identified in patients with ALK+ lung cancer after treatment with all generations of ALK TKIs, albeit at low frequency (<3% according to retrospective analysis)

Diagnostic biopsies to define histology are necessary to select histology-specific chemotherapy regimens in squamous cell- or small cell-transformed tumors.

Studies are underway to determine whether histologic changes are reversible and whether epigenetic modifiers may resensitize tumor cells to ALK inhibition. GRB2, growth factor receptor-bound protein

Given the rarity of transformed ALK+ lung cancers, randomized prospective trials to inform treatment strategies following phenotypic changes are not feasible

Schneider JL et al. Nat Cancer. 2023 Mar;4(3):330-343.

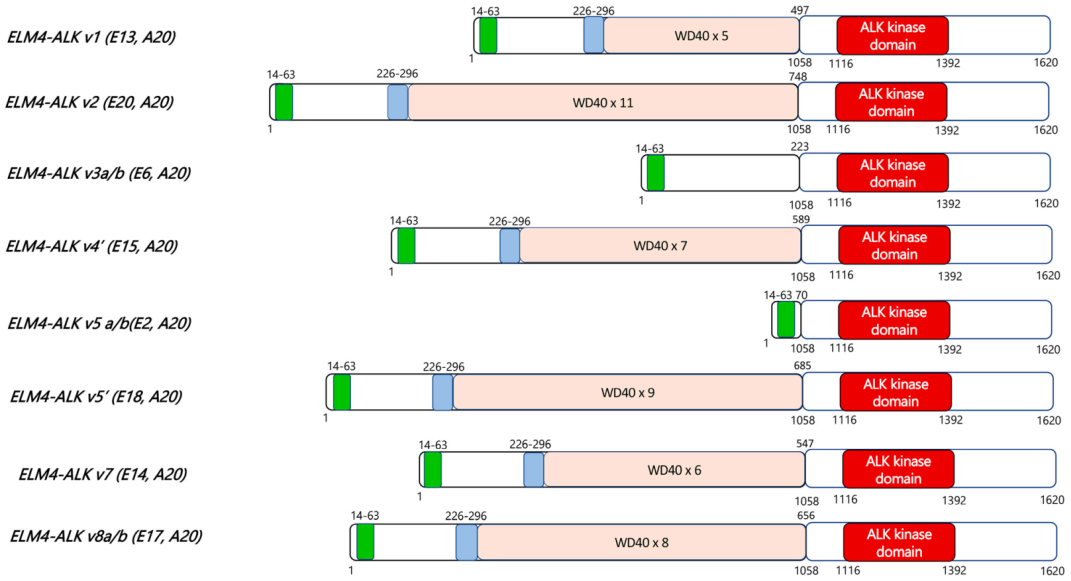
MECHANISMS OF RESISTANCE

ALK Variants: Key Drivers of Resistance?

15 EML4-ALK variants have been identified and variant 1 and 3 being the most common (75-80%)

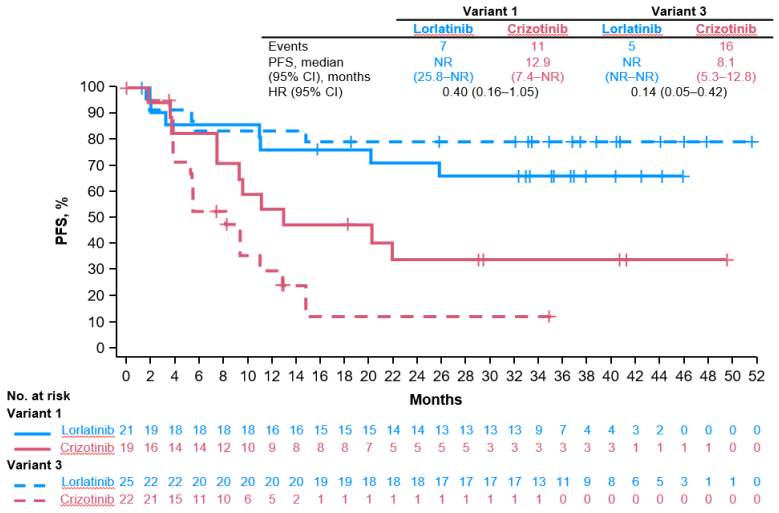
Many trials demonstrated differential clinical outcomes between “short” and “long” variants

ALK G1202R is more prone to develop EML4-ALK v3 following sequential use of next G ALK TKIs



PFS based in ALK variant subtype in CROWN study

Based on tumor DNA



- Based on tumor DNA, in the lorlatinib arm, median PFS was not reached for patients with either variant 1 or variant 3; in the crizotinib arm, median PFS was 12.9 months and 8.1 months, respectively

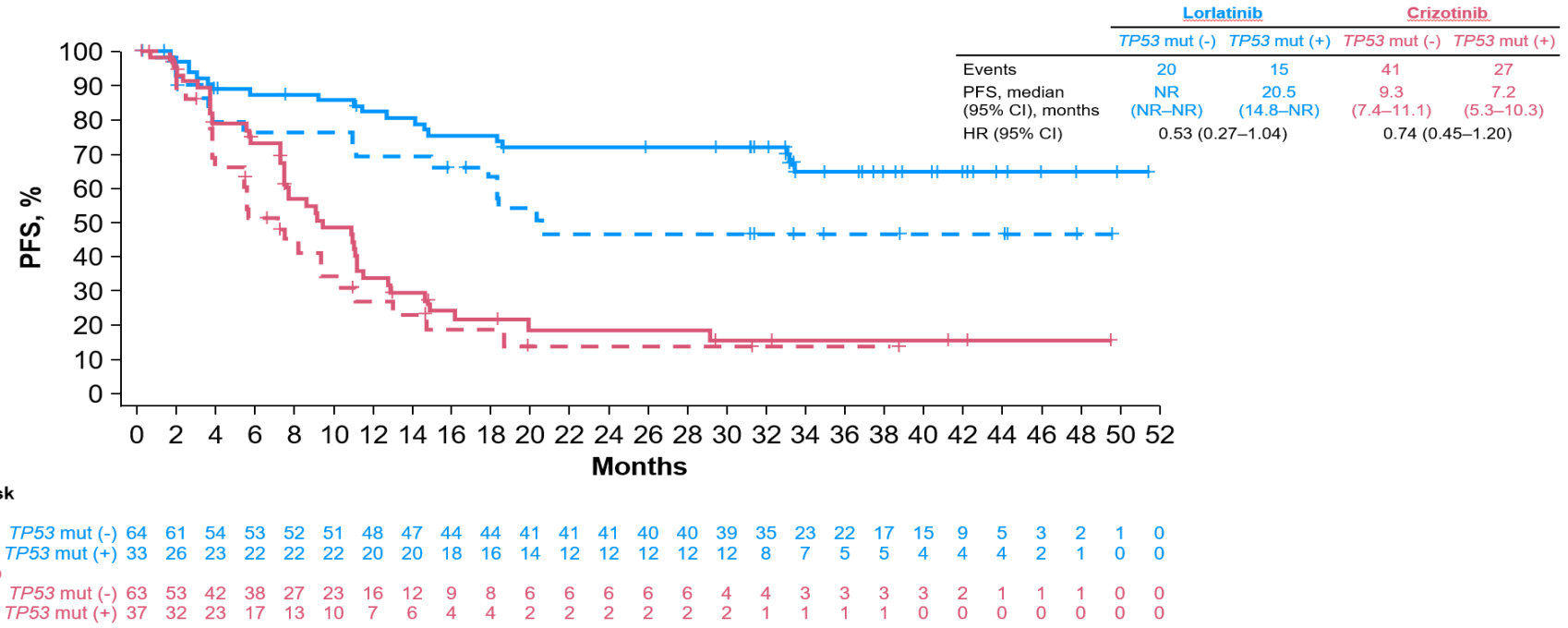
Zhang SS et al Lung Cancer 2021;158:126-136 *Bearz A et al ASCO 2022*

MECHANISMS OF RESISTANCE

comutations: Key Drivers of Resistance?

Presence of TP53 mutations is poor prognostic factor for PFS and OS

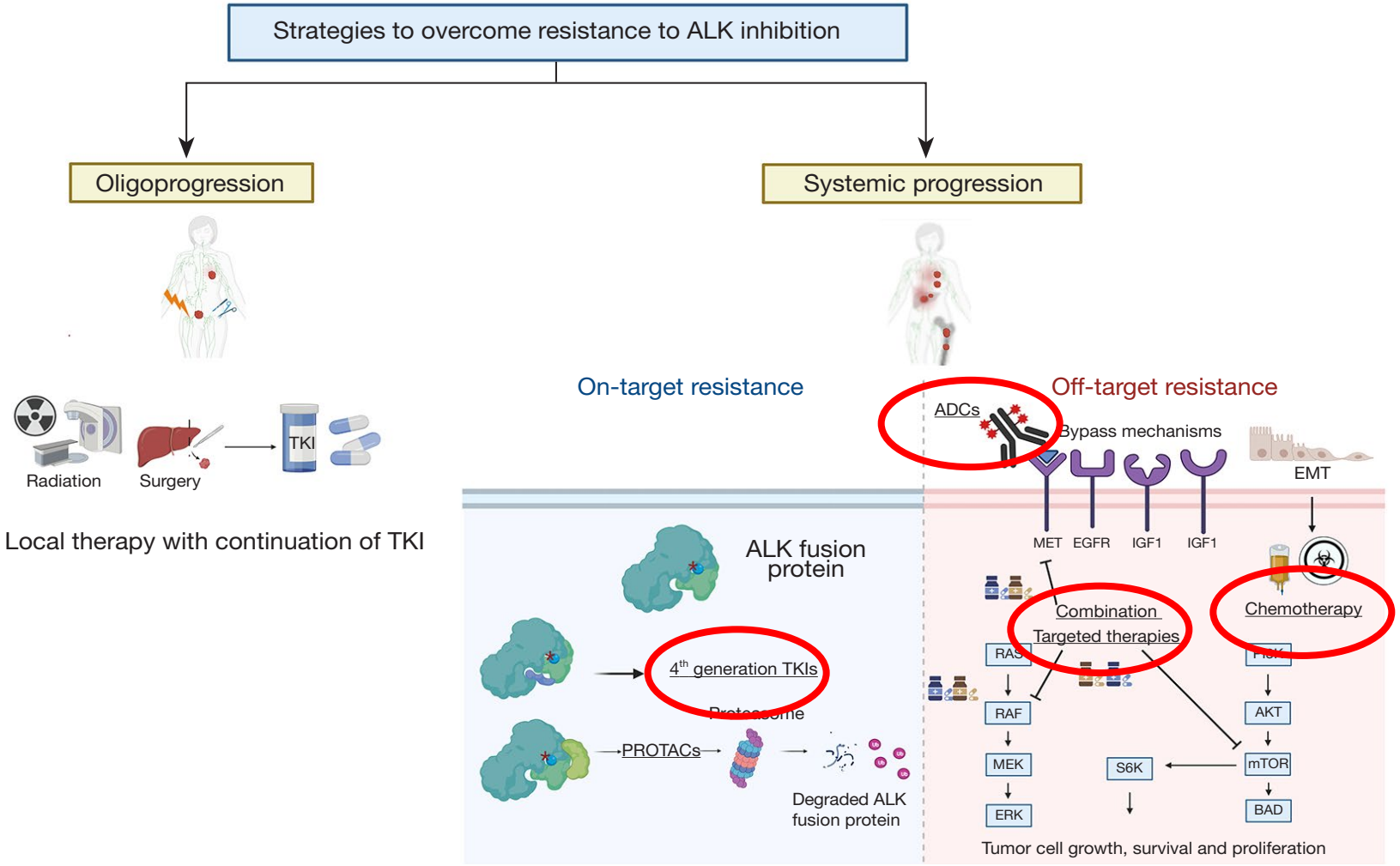
PFS Based on BICR by *TP53* Mutation Status



BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.
Bearz A, et al. ASCO Annual Meeting. June 3-7, 2022. Abstract 9070.

Bearz A et al ASCO 2022

STRATEGIES TO OVERCOME RESISTANCE TO ALK INHIBITION



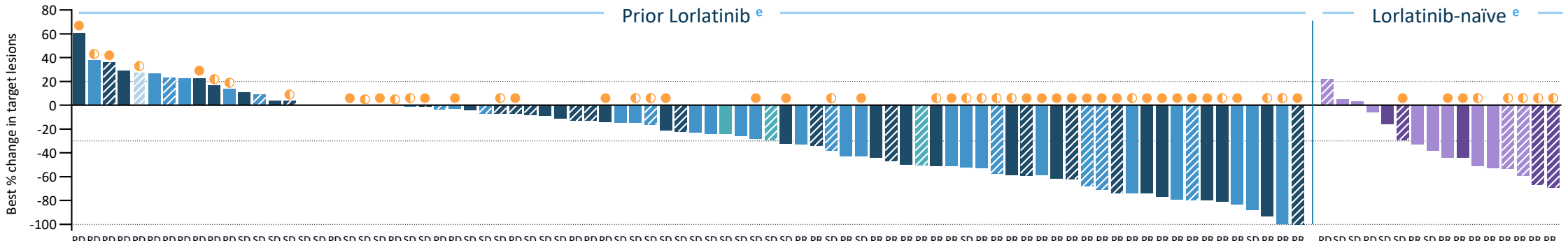
Desai A et al Transl Lung Cancer Res 2023;12(3):615-628

STRATEGIES TO OVERCOME RESISTANCE TO ALK INHIBITION

Novel 4th generation TKIs

Neladalkib (NVL-655), 4G ALK TKI: Preliminary Efficacy (ALKOVE-1 Global Phase II Trial – NCT05384626)

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)



KEY: PATIENT DETAILS

Lorlatinib Pre-treated:
- ≥ 3 prior ALK TKI
- 2 prior, 2G + lorlatinib
- 2 prior, 1G + lorlatinib
- 1 prior (lorlatinib only)

Lorlatinib-naïve:
- ≥ 2 prior ALK TKIs
- 1 prior, alectinib

Patient treated at RP2D

ALK single resistance mutation

ALK compound (≥2) resistance mutation

Drilon A et al., ESMO 2024

STRATEGIES TO OVERCOME RESISTANCE TO ALK INHIBITION

Revolutionizing Treatment with Novel 4th Generation TKIs in Cancer Therapy

Neladalkib (NVL-655): CNS Activity

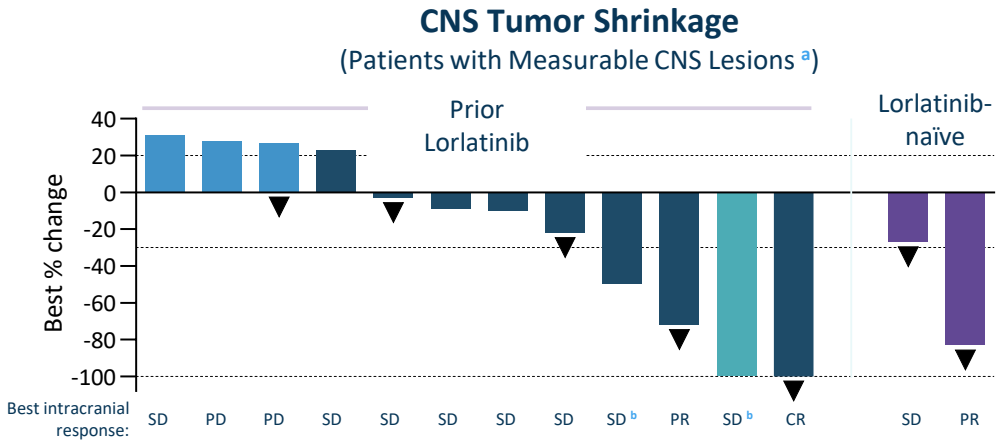
IC-ORR (patients with measurable CNS lesions):

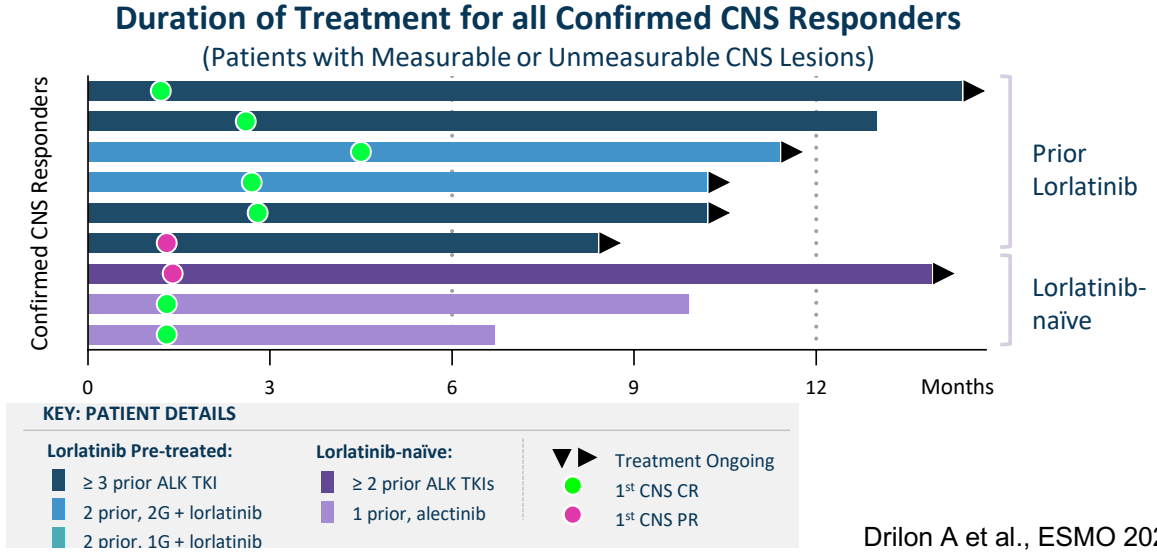
- Lorlatinib-naïve: 50% (1/2)
- Prior lorlatinib: 15% (2/13)

— 31% (4/13) including 2 CNS uPRs not confirmed due to discontinuation of treatment in absence of CNS progression

• No CNS progression among confirmed CNS responders, including in patients who previously received the brain-penetrant TKI lorlatinib (measurable or unmeasurable CNS lesions)

— Treatment duration: 6.7 - 14.4+ months





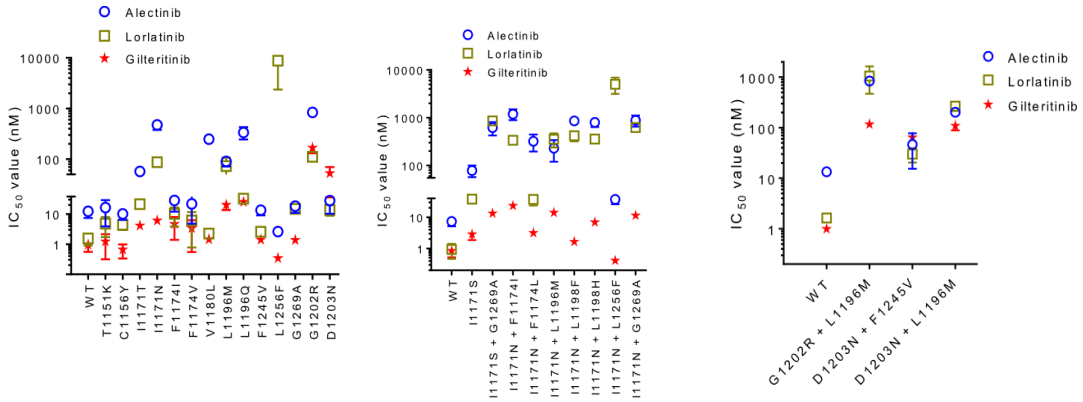
Drilon A et al., ESMO 2024

STRATEGIES TO OVERCOME RESISTANCE TO ALK INHIBITION

Revolutionizing Treatment with Novel 4th Generation TKIs in Cancer Therapy

Gilteritinib: Another ALK TKI (Multikinase Inh.) in Trial (Phase 1 Trial at UMich -- NCT06225427)

- TKI approved by the FDA for relapsed/refractory FLT3 mutated AML
- Activity against FLT3, ALK, AXL, TRK A, ROS, RET and MER kinases



TPX-0131 potent inhibitor f wild-type ALK and a broad spectrum of single ALK resistance mutations

Effective against a broad spectrum of adquired resistance mutations, specially the SFM G1202R, the gatekeeper mutation L1196M and compund mutations

Cell proliferation IC_{50} values (nM)						
EML4-ALK	**TPX-0131**	**Crizotinib**	**Alectinib**	**Brigatinib**	**Ceritinib**	**Lorlatinib**
Single EML4-ALK mutations						
Wild-type	0.4	50	7.4	12	3.9	0.8
I1171N	516	254	4310	49	72	48
I1171S	189	188	306	31	27	31
I1171T	316	232	210	33	29	25
L1196M	0.5	274	50	21	5.4	38
L1198F	<0.2	18	397	74	618	30
G1202R	0.2	434	2690	188	329	52
G1269A	13	451	197	20	15	49
G1269S	701	1390	671	46	97	191
Compound EML4-ALK mutations						
L1196M/L1198F	<0.2	252	2250	253	1410	1310
L1198F/C1156Y	<0.2	19.3	776	102	1310	140
L1198F/I1171N	1.6	626	236	55.1	64.1	78.7
G1202R/C1156Y	0.2	745	2420	810	1300	521
G1202R/L1196M	0.7	808	>10000	1100	1260	4780
G1202R/L1198F	<0.2	188	3000	2040	2010	1710
G1202R/G1269A	9.9	705	7200	164	303	636
G1202R/G1269A/L1204V	14.9	634	6740	176	345	673
G1202R/G1269A/L1198F	0.2	596	>10000	907	1670	6330

Mizuta H et al. Nat Commun 2021;12:1261
https://clinicaltrials.gov/study/NCT06225427?term=gilteritinib%20alk&rank=1

STRATEGIES TO OVERCOME RESISTANCE TO ALK INHIBITION

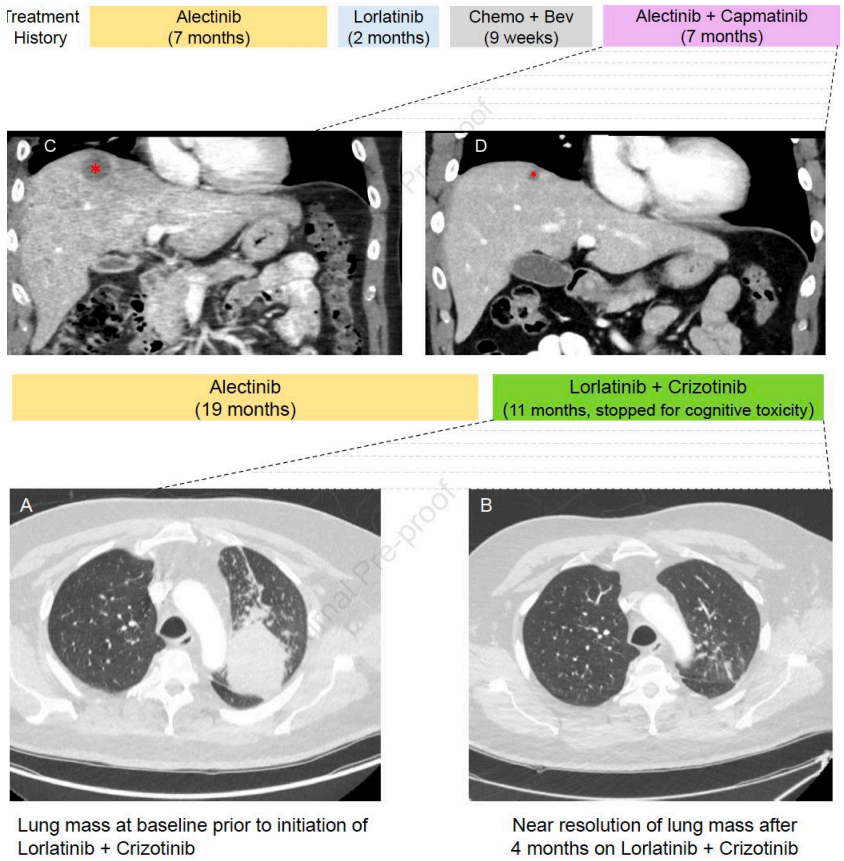
Unlocking the Potential of ALKi + METi Therapy in ALK+ NSCLC with MET Amplification

Cohort of patients (12) with ALK+ lung cancer and acquired *MET*amplification (identified by tissue or plasma) who received regimens targeting both ALK and MET.

Patient	ALK/MET Therapy	Best Response Time on Treatment
1	Crizotinib 250 mg BID	PD <1 mo
2	Crizotinib 250 mg BID	PR (−38%) 3.5 mo
3	Lorlatinib 75 mg QD[a] + crizotinib 250 mg BID	PR (−30%) 3 mo
4	Lorlatinib 50 mg QD + crizotinib 250 mg BID	PD <1 mo
5	Lorlatinib 50 mg QD[a] + crizotinib 250 mg BID	PR (−60%) 11 mo[b]
6	Lorlatinib 50 mg QD + crizotinib 250 mg BID	PD <1 mo
7	Lorlatinib 50 mg QD + crizotinib 250 mg BID	PR (−51%) 6 mo
8	Lorlatinib 50 mg QD + crizotinib 250 mg BID	PD <1 mo
9	Alectinib 600 mg BID[a] + capmatinib 400 mg BID	SD (non-CR/non-PD) 9 mo
10	Alectinib 600 mg BID + capmatinib 400 mg BID[a]	SD (−8%) 10 mo
11	Alectinib 600 mg BID + capmatinib 300 mg BID	PR (−70%) 7 mo
12	Alectinib 600 mg BID + crizotinib 200 mg BID	SD (−26%) 6 mo

4 regimens: crizotinib (n=2), lorlatinib + crizotinib (n=6), alectinib + capmatinib (n=3), alectinib + crizotinib (n=1)

ORR: 42% (5/12)



Dagogo-Jack I et al. JTO Clin Res Rep 2023; 4(8):100534

STRATEGIES TO OVERCOME RESISTANCE TO ALK INHIBITION

Exploring Innovative Combination Strategies Beyond ALKi

Combination	Bypass Pathway Targeted	Phase	ClinicalTrials.gov
Alectinib + Cobimetinib	MEK	1-2	NCT03202940
Brigatinib + Binimetinib	MEK	1	NCT04005144
Ceritinib + Trametinib	MEK	1	NCT03087448
Lorlatinib + Binimetinib	MEK	1-2	NCT04292119
Lorlatinib + PF-07284892	SHP2	1	NCT04800822
Lorlatinib + TNO155	SHP2	1-2	NCT04292119
Ceritinib + Everolimus	mTOR	1	NCT02321501
Brigatinib + Bevacizumab	VEGF	1	NCT04227028

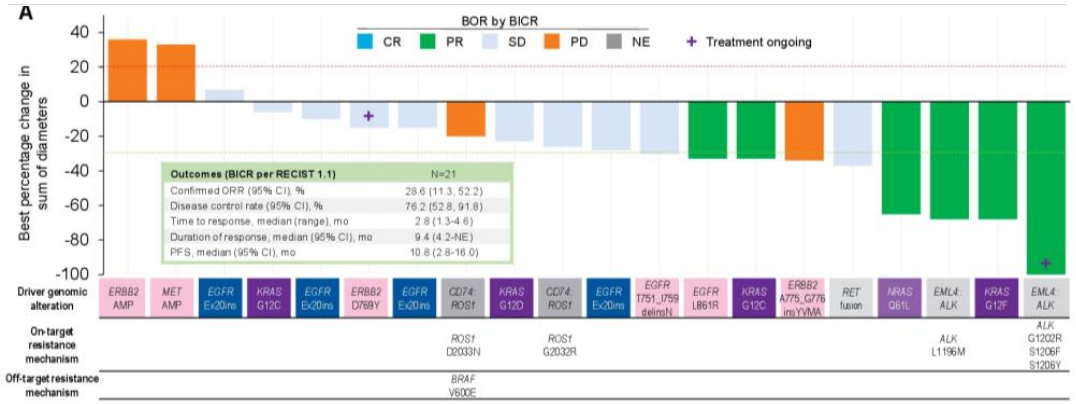
None with clinical biomarker

Schneider JL, Lin JJ, Shaw AT. Nat Cancer 2023;4(3):330-43

STRATEGIES TO OVERCOME RESISTANCE TO ALK INHIBITION

ADCs: A Promising Therapeutic Approach in TKI-Resistant ALK+ NSCLC

Activity of patritumab deruxtecan in NSCLC with non-classical EGFRmut AGAs



- Patritumab deruxtecan (anti-HER3 ADC)1 & datopotamab deruxtecan (anti-TROP2 ADC) have shown signals of activity in patients with ALK+ NSCLC (small number)

- Clinical activity of ADCs across AGA subsets appears irrespective of the spectrum of known or unknown resistance mechanisms

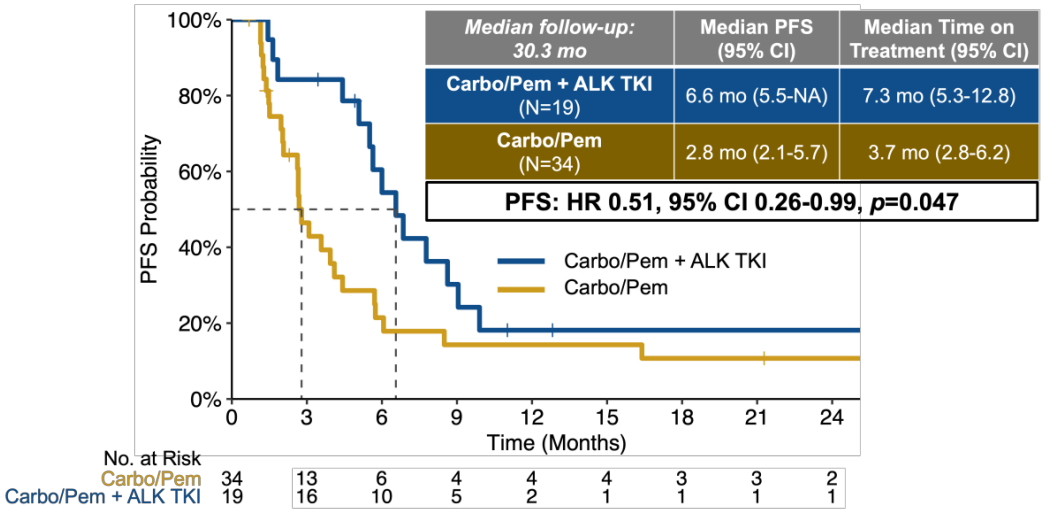
Activity of datopotamab deruxtecan in NSCLC withAGAs including EGFR and ALK

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

. Steuer C et al., ASCO 2022; . Paz Ares L et al., ESMO 2023; HA et al., WCLC 2023;

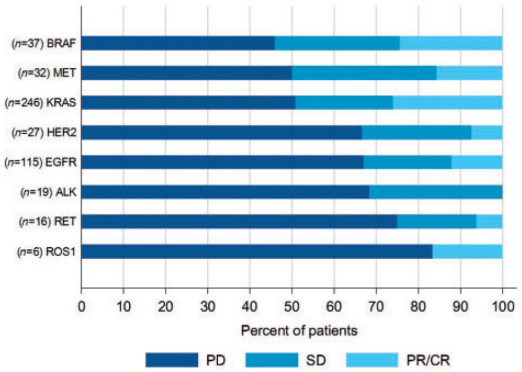
STRATEGIES TO OVERCOME RESISTANCE TO ALK INHIBITION

SOC Post-ALK TKI Therapy Remains Chemotherapy (+/- Next-Generation ALK TKI)



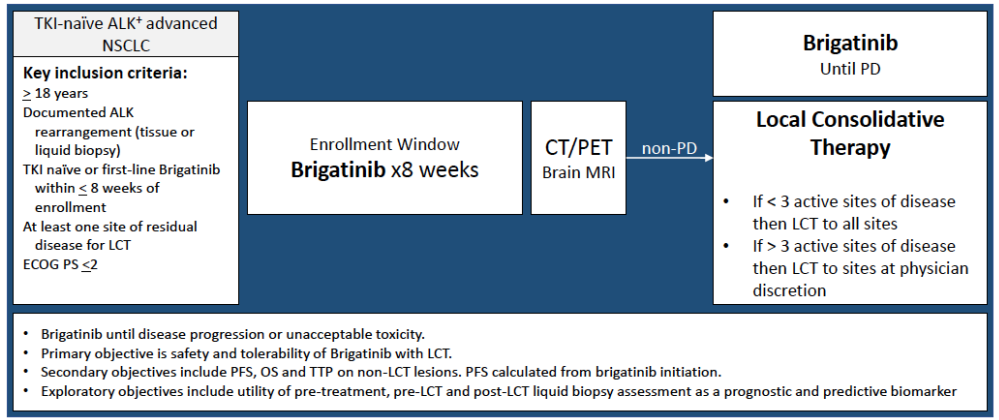
Median follow-up: 30.3 mo	Median PFS (95% CI)	Median Time on Treatment (95% CI)
Carbo/Pem + ALK TKI (N=19)	6.6 mo (5.5-NA)	7.3 mo (5.3-12.8)
Carbo/Pem (N=34)	2.8 mo (2.1-5.7)	3.7 mo (2.8-6.2)

PFS: HR 0.51, 95% CI 0.26-0.99, *p*=0.047



Mazieres J et alAnn Oncol. 2019 Aug 1;30(8):1321-1328.

BRIGHTSTAR (NCT03707938)



32/34 patients completed planned LCT (79% RT, 9% surgery, 6% surgery + RT, 3% no LCT- amenable residual disease)

PFS Rate	BrightStar	ALTA 1L* (first line single agent brigatinib)
1-yr	94%	80%
2-yr	76%	56%
3-yr	66%	47%

Elamin Y et al., WCLC 2023

Waliany S et al. TTLC 2024

TO TAKE AWAY

- Currently, Lorlatinib is the leading and most clinically effective agent for treating ALK+ NSCLC, particularly known for its remarkable efficacy in managing CNS metastases.

- However, resistance to third-generation ALK TKIs can emerge through both on-target and off-target mechanisms.

- To counteract on-target resistance, fourth-generation TKIs are in development, offering significant promise in addressing these challenges.

- Off-target resistance, which occurs more frequently, involves mechanisms such as the activation of bypass signaling pathways or phenotypic transformation, which can complicate treatment further.

- In order to tackle resistance beyond thrid-generation TKIs, a variety of innovative approaches are being explored. These include combination therapies, antibody-drug conjugates, …These advanced therapeutic approaches hold great potential for improving treatment outcomes and overcoming resistance in ALK+ NSCLC.

GRacias!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025