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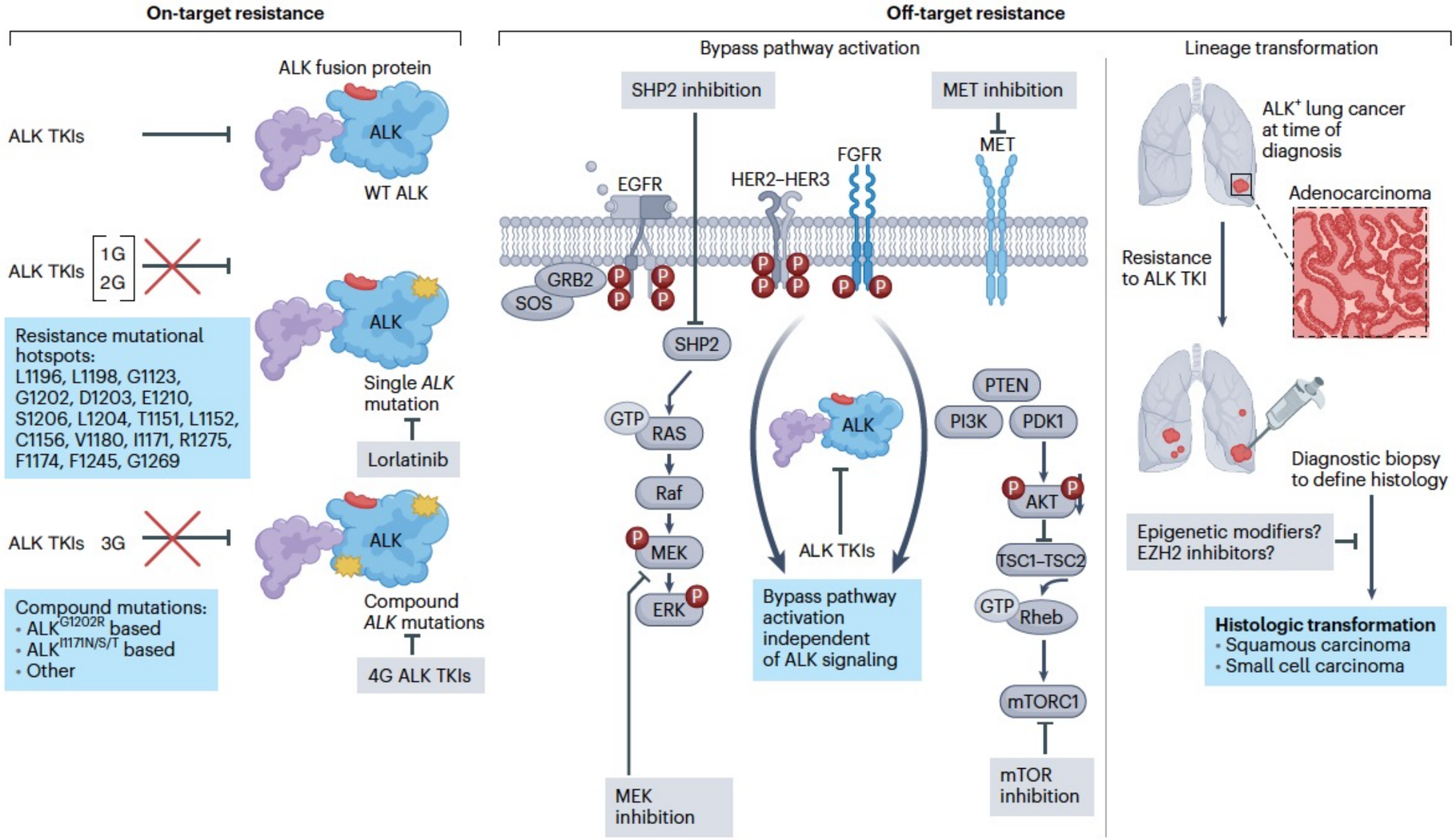
Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

Mechanisms of Resistance to ALK Inhibitors

Jessica J. Lin, M.D.
Massachusetts General Hospital
Harvard Medical School
Boston, MA

November 17, 2023

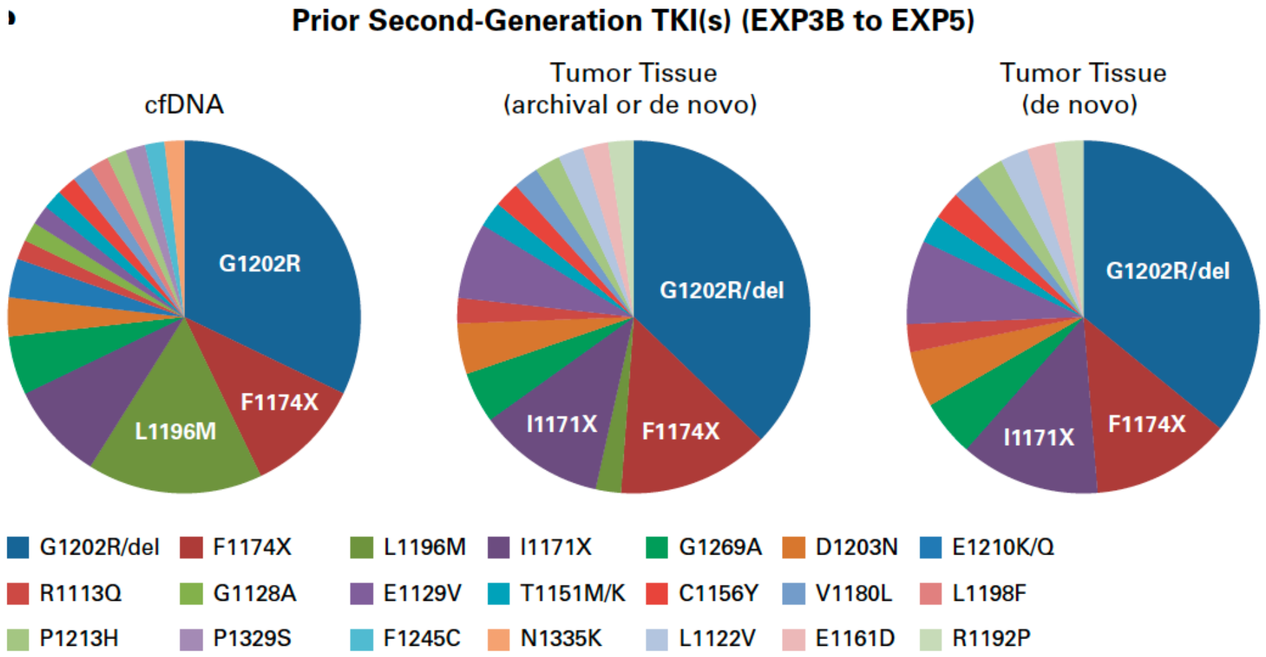
Broad Framework for Understanding Mechanisms of Resistance to ALK Inhibitors



Schneider JL et al. *Nat Cancer* 2023;4(3):330-43

On-Target Resistance to 2nd-Generation ALK TKI(s)

Distribution of *ALK* mutations identified in plasma or tumor biopsies from patients after 1 or more prior 2G ALK TKI(s)[1]



Most common *ALK* resistance mutations:
G1202R/del (detected in 53% and 55% of cfDNA and tumor tissue with an *ALK* mutation, respectively), I1171X, V1180L

Each ALK TKI harbors a unique spectrum of activity against *ALK* mutations in preclinical models[2]

IC_{50} ≤50 nM | IC_{50} >50–<200 nM | IC_{50} ≥200 nM

Cellular ALK Phosphorylation Mean IC_{50} (nM)					
Mutation Status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
Parental BA/F3	763.9	885.7	890.1	2774.0	11293.8
V1	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	50.1	58.8	95.8	5.2
D1203N	116.3	35.3	27.9	34.6	11.1
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0

[1]Shaw AT et al., J Clin Oncol 2019;37(16):1370-9

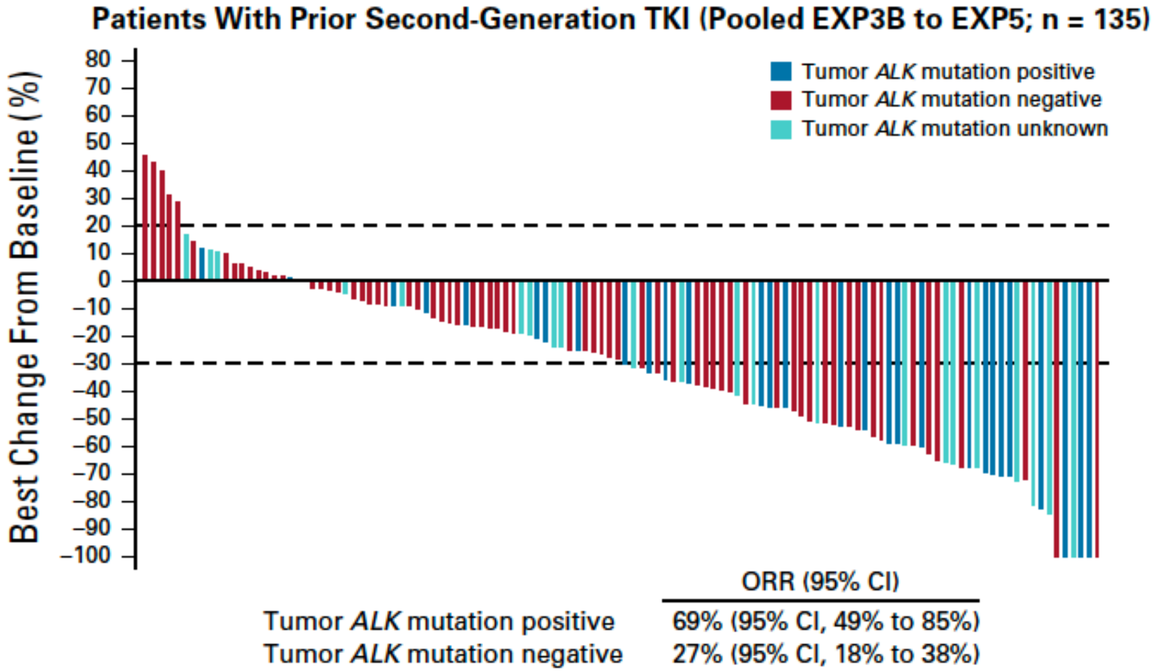
[2]Gainor JF, et al., Cancer Discov 2016;6:1118–1133

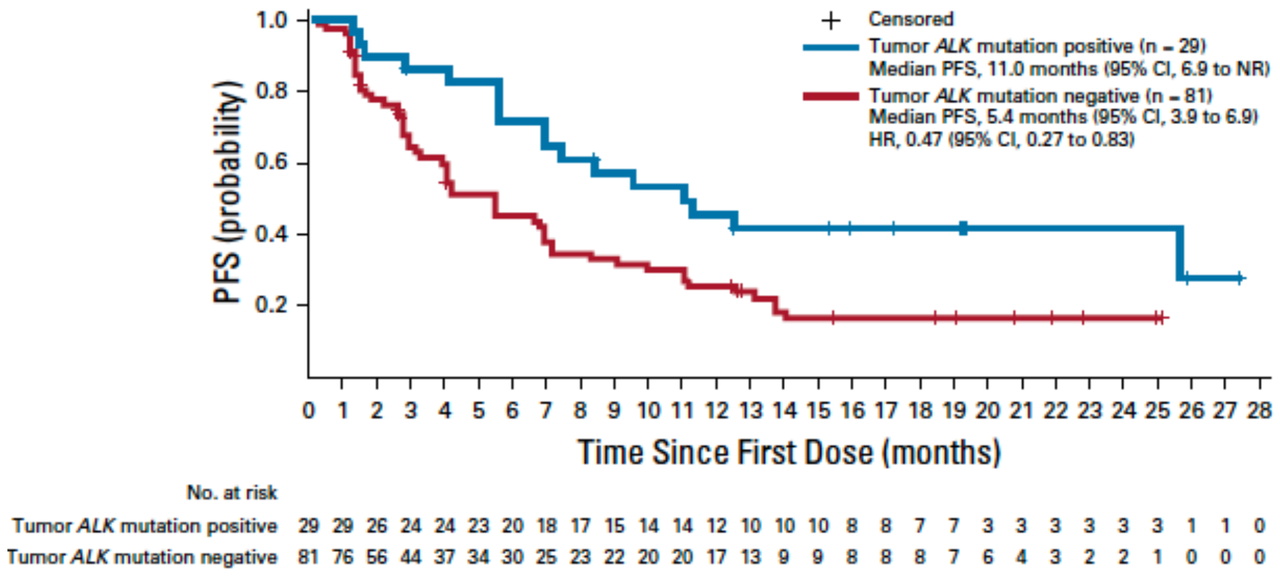
Efficacy of Lorlatinib (3G ALK TKI) After 2G ALK TKIs

Phase II study efficacy data

ORR s/p 2G ALK TKI(s) (n=139): **39.6%** (31.4-48.2)
Median DOR: 9.6 months (95% CI, 5.6-16.7)
Median PFS: 6.6 months (95% CI, 5.4-7.4)
IC-ORR: 56.1% (42.4-69.3)

Lorlatinib is recommended as a subsequent treatment option after progression on prior ALK TKIs in the NCCN Guidelines

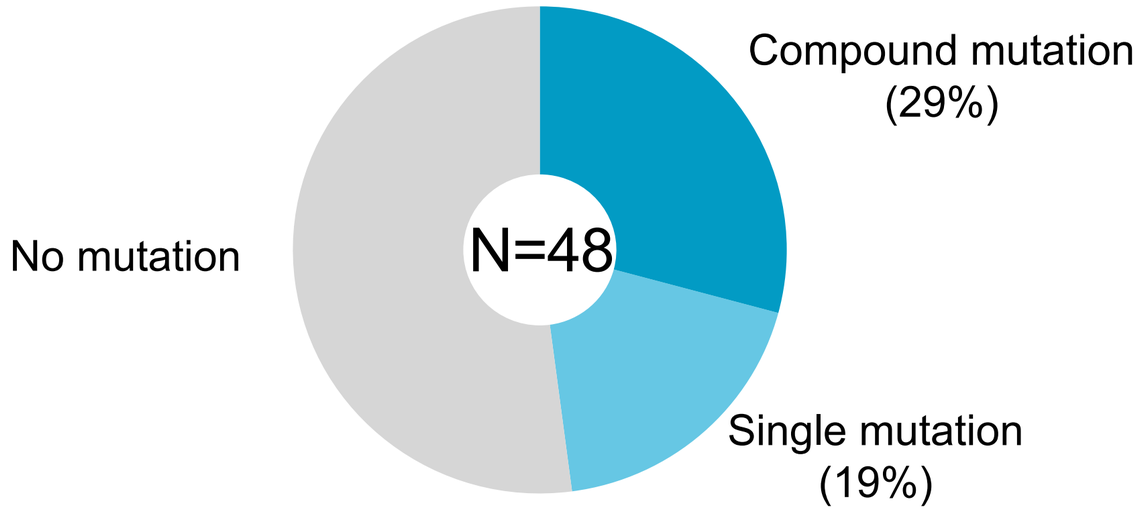


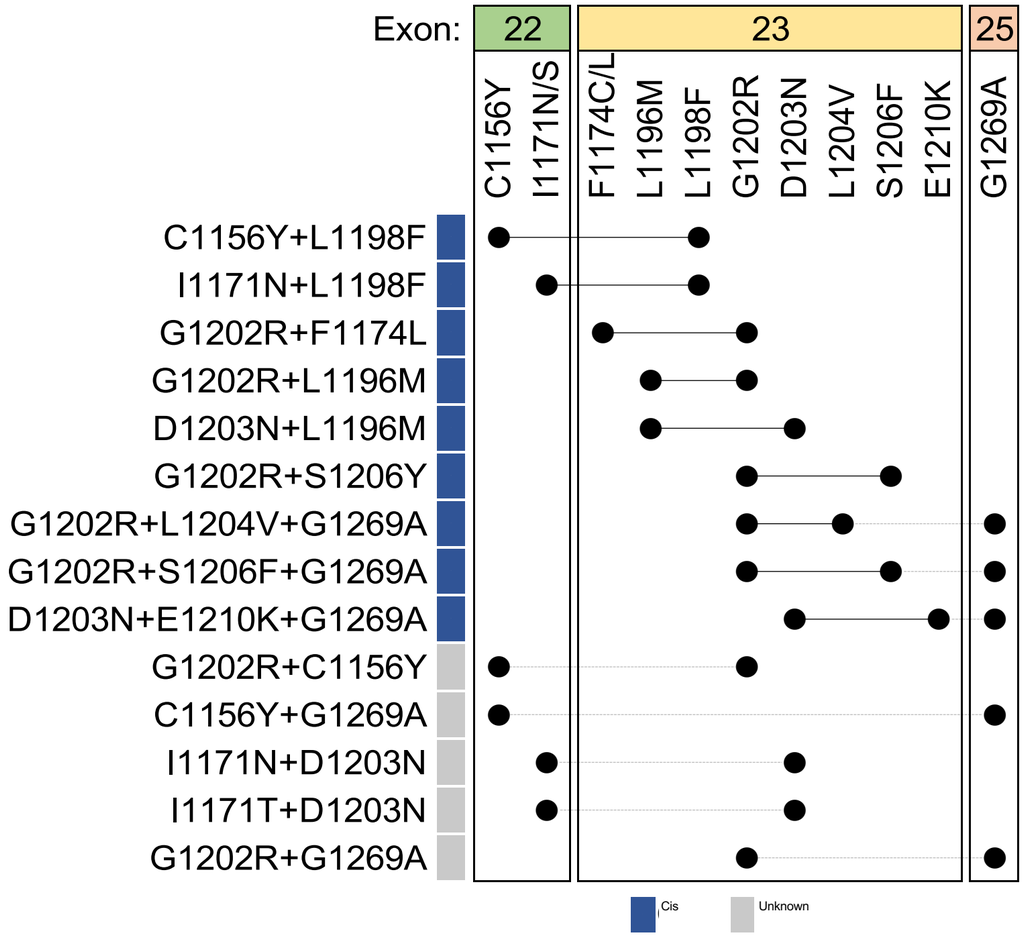


Felip E et al., Ann Oncol 2021;32(5)620-30
NCCN Guidelines Version 4.2023. Accessed 10/31/23
Shaw AT et al. *J Clin Oncol* 2019;37(16):1370-9

Resistance to Lorlatinib Following Prior ALK TKI(s): Compound *ALK* Mutations

Post-lorlatinib tissue biopsies (lorlatinib after prior ALK TKI)



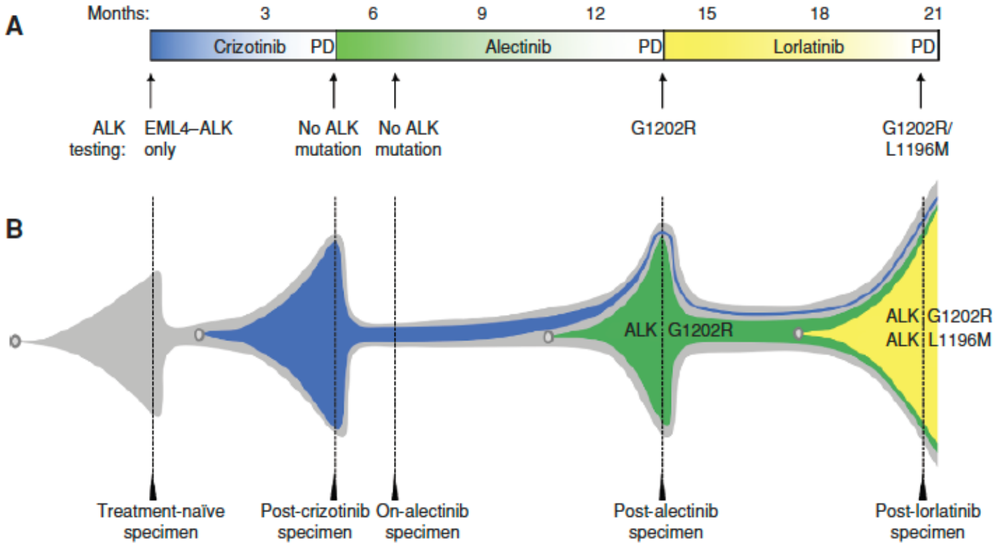


- No single predominant compound *ALK* mutation identified
- Among the 14 cases with ≥2 *ALK* mutations, 8 (57%) harbored *ALK* G1202R and 3 (21%) harbored *ALK* I1171N

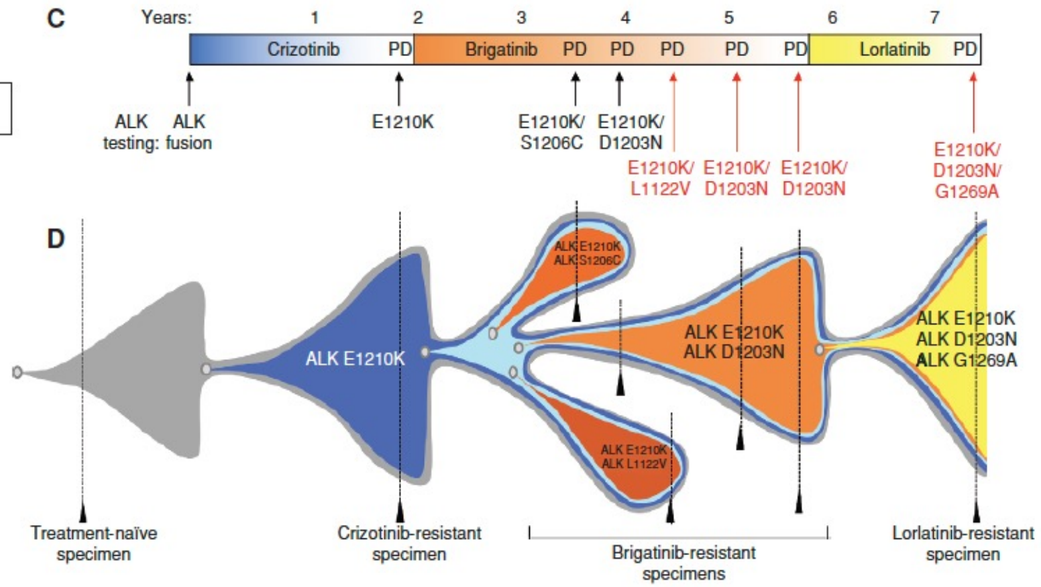
Shiba-Ishii A et al., Nat Cancer 2022;3:710-22

Challenge of Compound On-Target Mutations with Sequential Targeted Therapies

MGH953



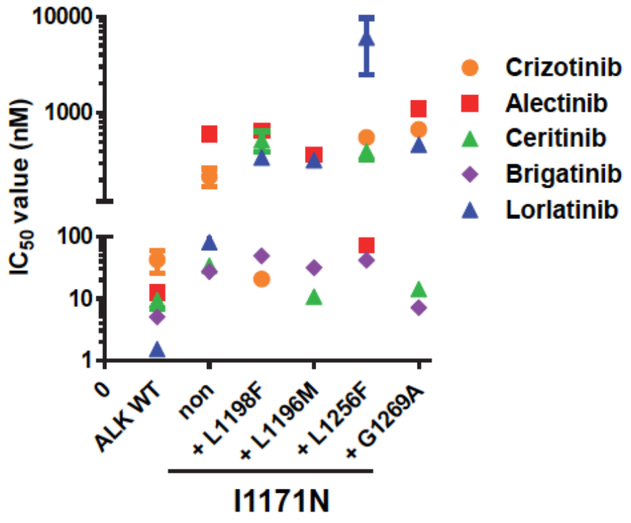
MGH086

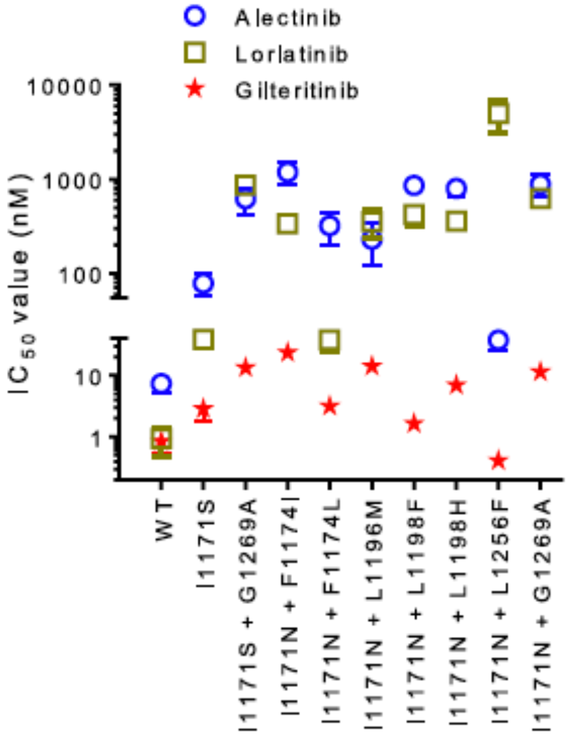


Yoda S et al., Cancer Discov 2018;8:714-29

Sensitivity Profile of Lorlatinib-Resistant Compound *ALK* Mutations

A small subset of compound *ALK* mutations are sensitive to available ALK TKIs





Many compound *ALK* mutations are refractory to all available ALK TKIs

	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
C1156Y+L1198F	20	447	133	29	123
I1171N+L1198F	16	416	2638	83	511
I1171N+D1203N	708	124	1219	139	478
G1202R+L1196M	1095	188	1763	126	674
G1202R+S1206F	570	651	1655	558	856
G1202R+G1269A	573	81	1606	91	502
G1202R+S1206F+G1269A	885	345	2275	304	1785

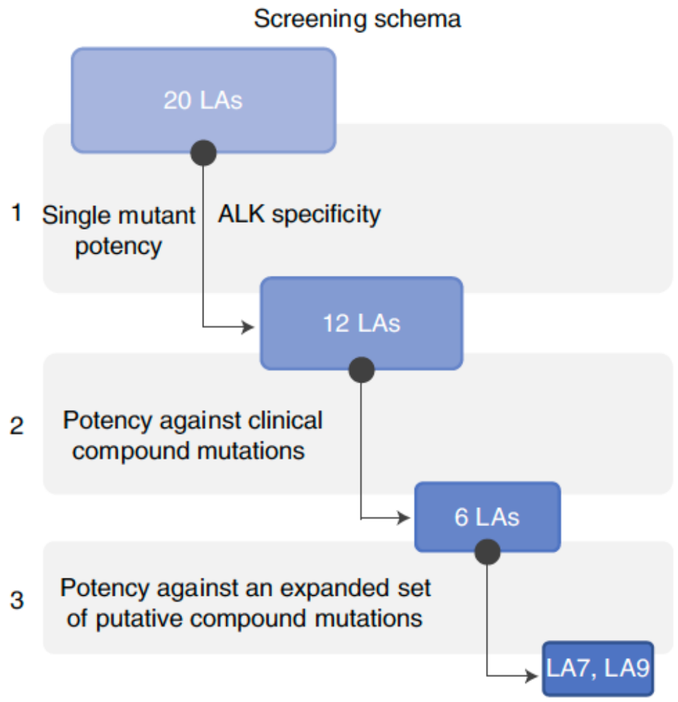
IC_{50}: 0 100 200 300

Okada K et al., EBioMedicine 2019;41:105-119; Mizuta H et al., Nat Commun 2021;12:1261

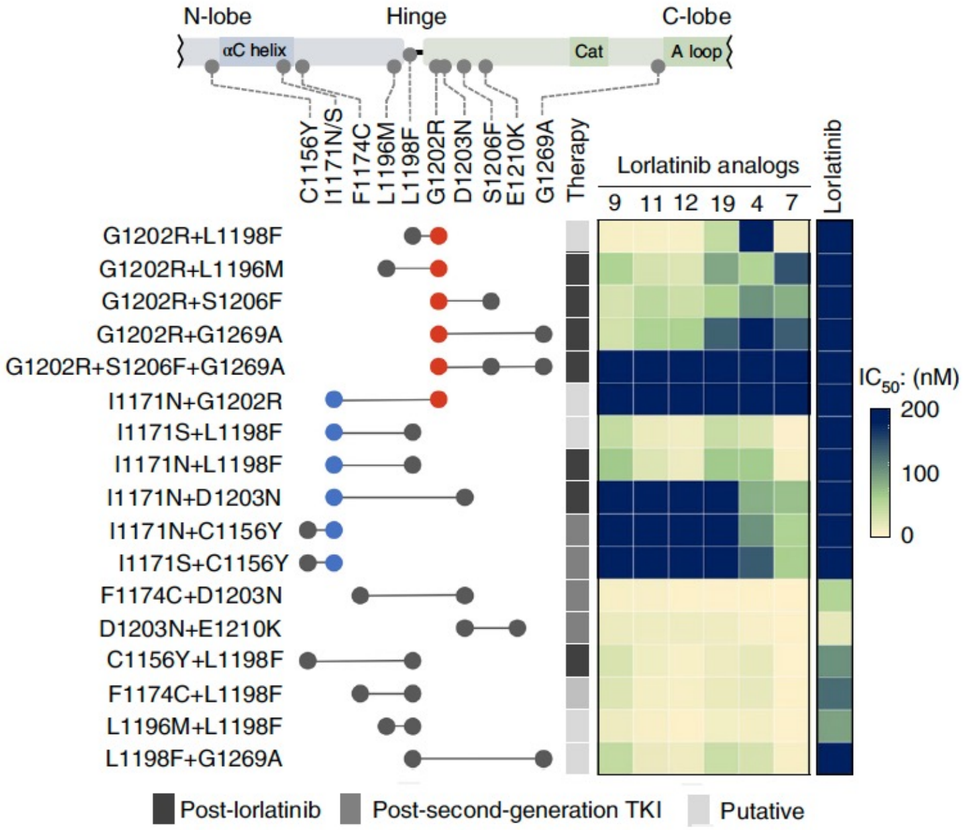
Shiba-Ishii A et al., Nature Cancer 2022;3:710-22

Distinct Therapeutic Strategies May Be Required to Overcome G1202R- vs I1171N/S-Based Compound *ALK* Mutations

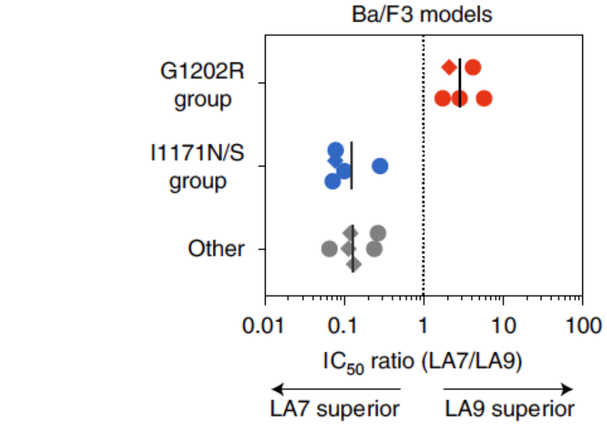
Functional Screening of Lorlatinib Analogs (LAs)

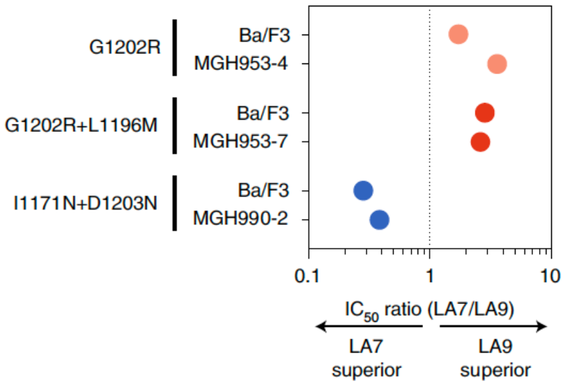


Distinct Patterns of LA Efficacy Against Groups of Compound *ALK* Mutations



LA7 and LA9 Differentially Target I1171N vs G1202R Compound *ALK* Mutations

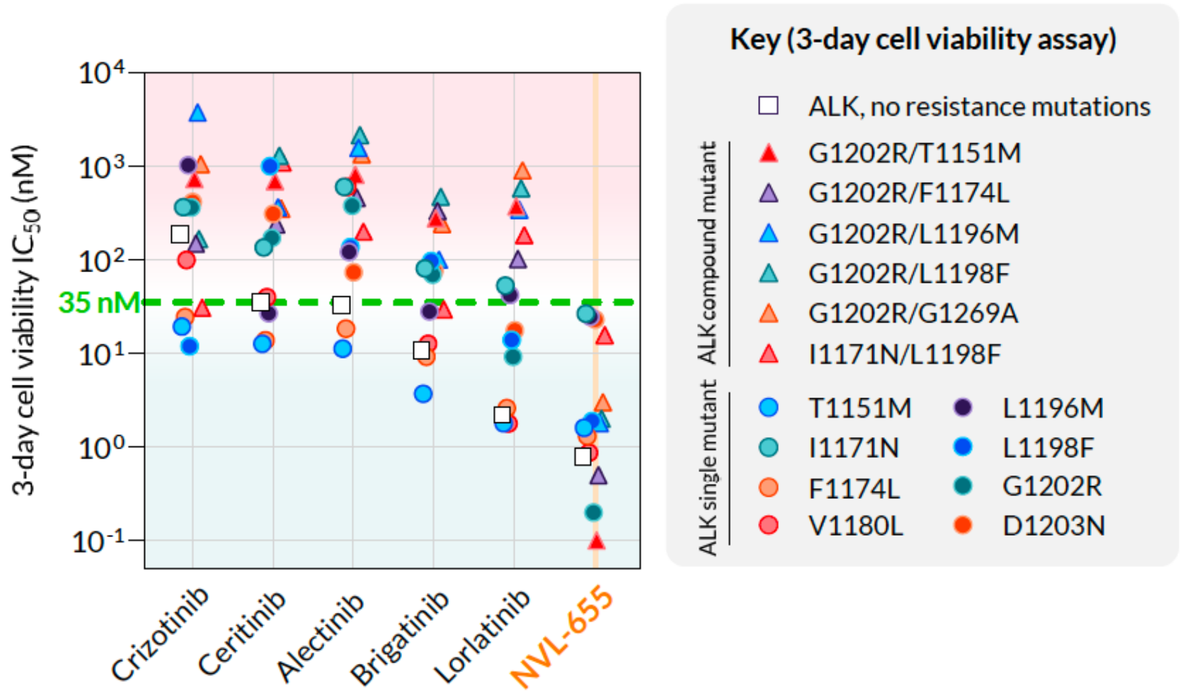




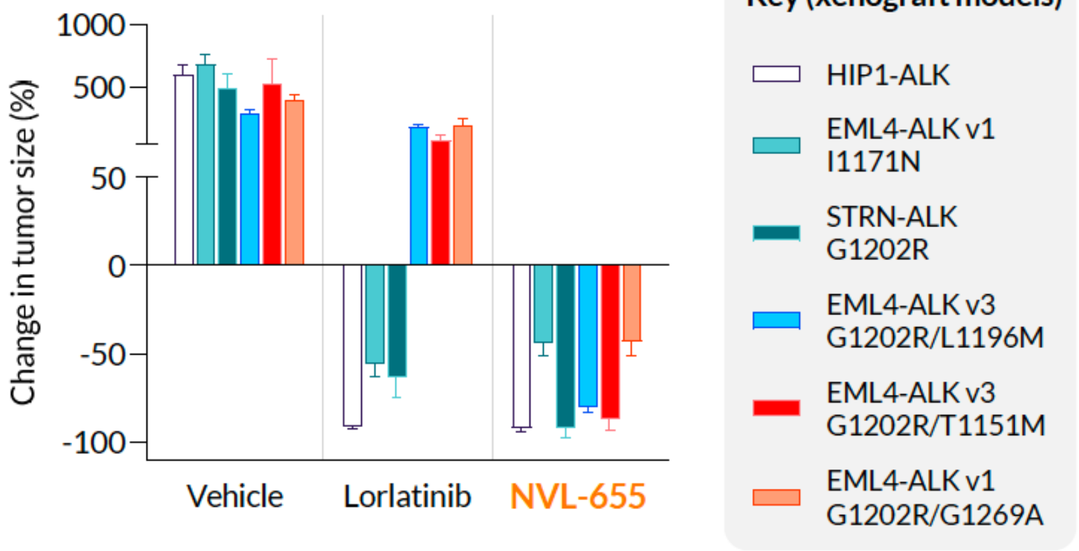
Shiba-Ishii A et al., Nature Cancer 2022;3:710-22

4G ALK TKI: NVL-655
Coverage of Single and Compound *ALK* Mutations

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



Tumor regression at well-tolerated doses in ALK models, including ALK single and compound mutants

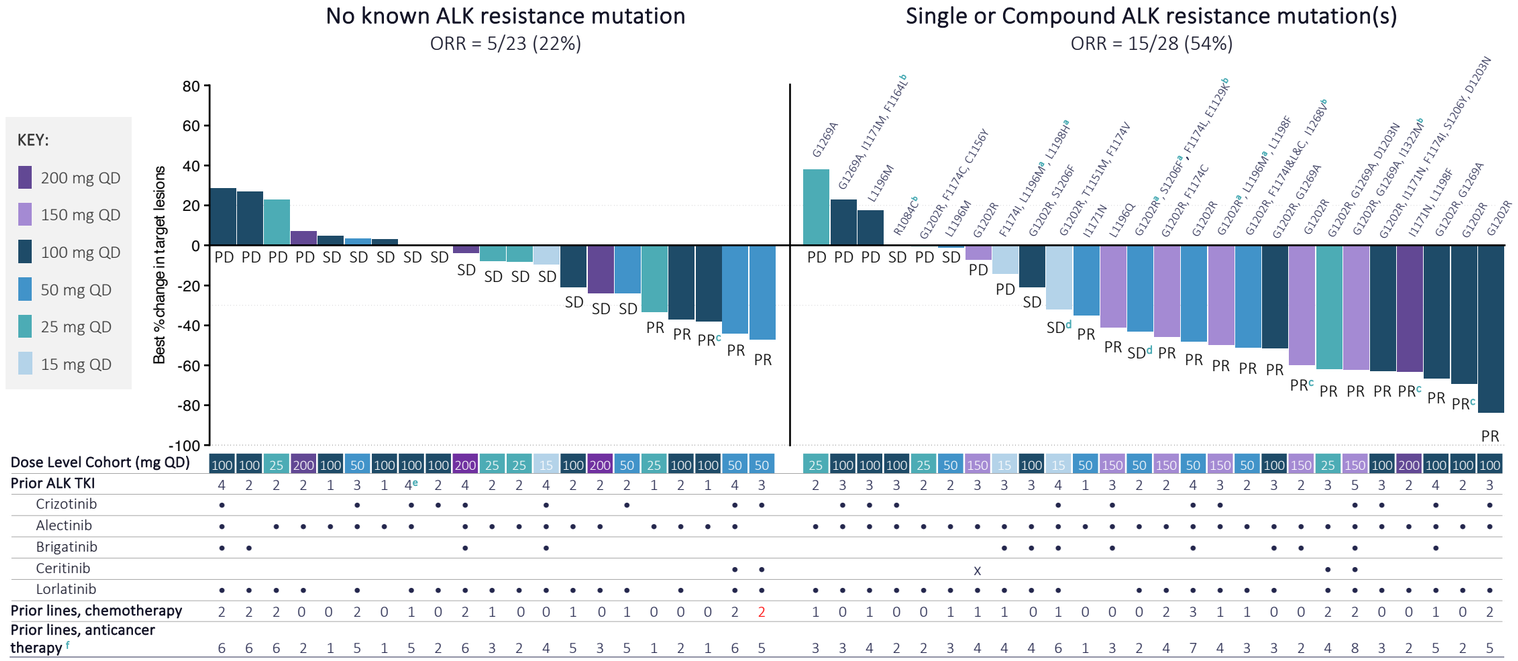


NVL-655: 0.5 - 7.5 mg/kg PO, BID
Lorlatinib: 5 mg/kg, PO, BID or 10 mg/kg, PO, QD
In some cases, dosing was not performed on weekends

Lin JJ et al., EORTC-NCI-AACR 2023

4G ALK TKI NVL-655: Preliminary Efficacy and Safety From the Global Phase I/II Study ALKOVE-1

- Coverage of **single and compound *ALK* mutations** demonstrated clinically
- Activity in heavily pre-treated patients including those with and without compound *ALK* resistance mutations [**ORR 56% (9/16) with compound mutations**], those who have received **prior lorlatinib [ORR 40% (10/25)]**, and those with history of **brain metastases [ORR 52% (15/29)]**

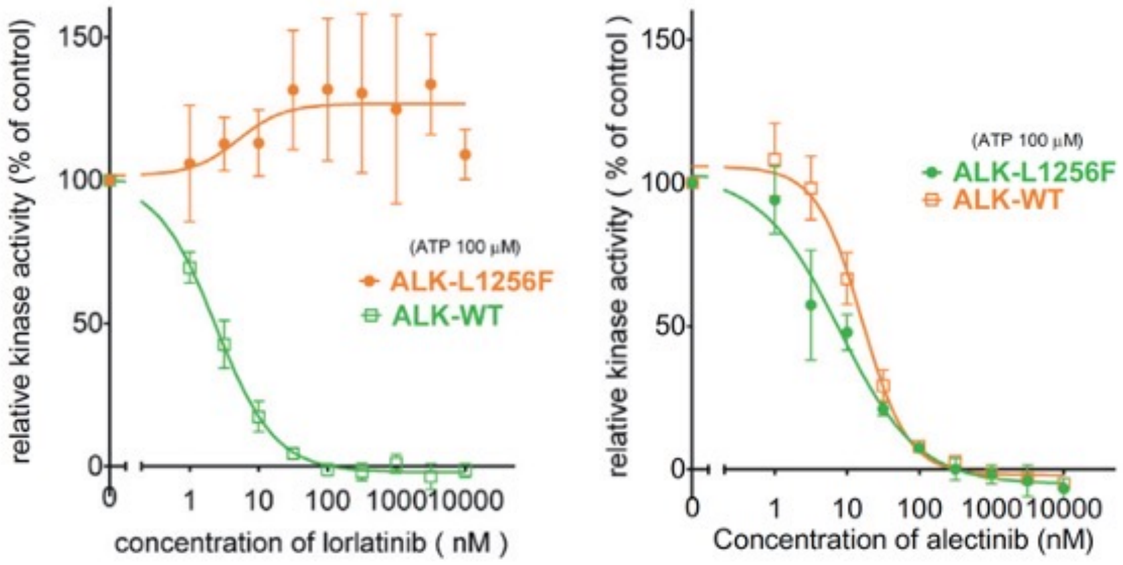


Lin JJ et al., AACR-NCI-EORTC 2023

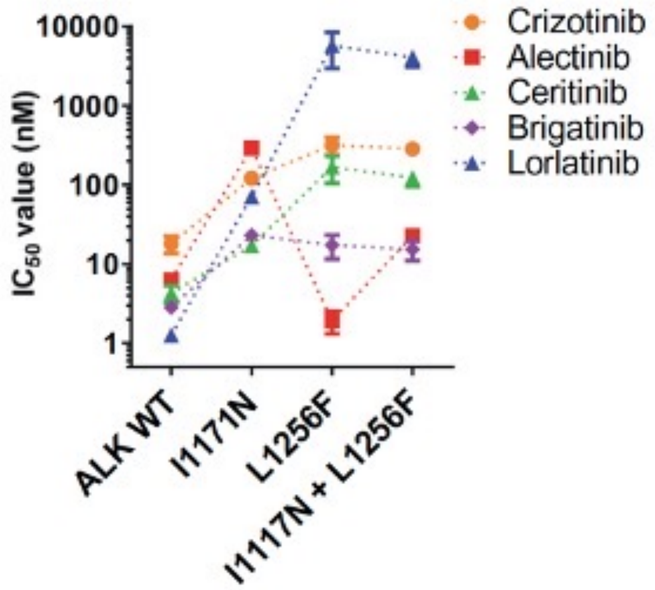
Landscape of Mechanisms of Resistance to 1L Lorlatinib Remains to Be Determined

ALK L1256F Single Mutation Confers Resistance to Lorlatinib But Is Sensitive to Alectinib

In vitro kinase assay



IC50's in Ba/F3 expressing WT or mutant ALK



Okada K et al., EBioMed 2019;41:105-19

Resistance Mechanisms to 1L Lorlatinib: Preliminary Insights from CROWN

Table 3: Summary of potential resistance mechanisms against lorlatinib or crizotinib

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.

Felip E et al. ESMO 2022

Resistance: Bypass Pathways in TKI-Refractory ALK+ NSCLC

Bypass mechanism	Prior ALK TKI[a]	Prevalence	Refs
MET amplifications	Second-generation TKIs	12% in first or later lines	121
	Lorlatinib	22% in later lines	121
MET rearrangements	Alectinib or lorlatinib	3% in later lines	121
MET exon 14 mutations	Alectinib	Unknown, data limited to case reports	146
RET rearrangements	Brigatinib	Unknown, data limited to case reports	125
EGFR activation	Crizotinib	44% in first line	151
EGFR mutations	Crizotinib	9–14% in first line	152,153
HER2 amplifications	Crizotinib, alectinib	Unknown, data limited to case reports	148,149
KIT amplifications/activation	Crizotinib	15% in first line	151
IGF1R activation	Crizotinib	80% in first line	154
SHP2 signalling	Ceritinib	Preclinical data only	157
NF2 mutations	Lorlatinib	20% in later lines	107
YES1 amplifications	Crizotinib, ceritinib	11.8% in later lines	141
KRAS mutations	Crizotinib	18% in first line	153
$BRAF^{V600E}$ mutations	Alectinib	Unknown, data limited to case reports	147
MAP2K1 mutations	Ceritinib	Unknown, data limited to case reports	150
DUSP6 loss	Crizotinib	83%	166
PIK3CA mutations	Lorlatinib or ceritinib	Unknown, data limited to case reports	100,150
AXL overexpression	Earlier-generation TKIs	Preclinical data only	155,156

This table includes selected studies and is not intended to reflect the entirety of clinical and preclinical work on bypass mechanisms in *ALK*-rearranged NSCLC. NSCLC, non-small-cell lung cancer; TKI, tyrosine kinase inhibitor. [a]The ALK TKI received immediately before biopsy sampling is reported here.

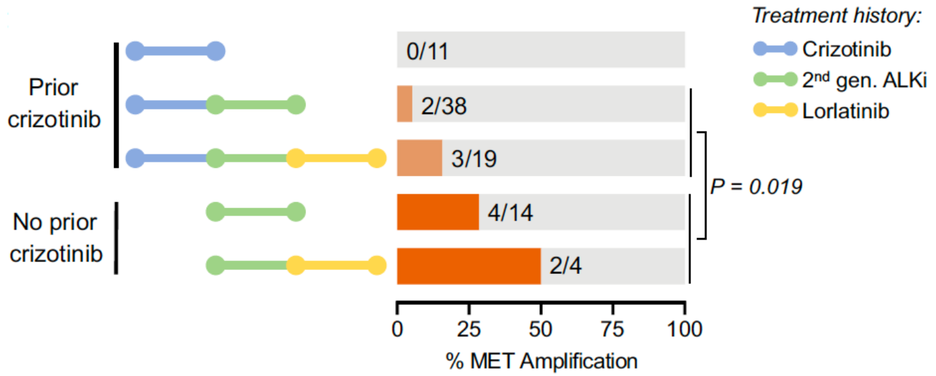
Cooper AJ, Sequist LV, Lin JJ. Nat Rev Clin Oncol 2022;19(8):499-514

ALK: Addressing Resistance with Combinations
Example of ALKi + METi Targeting *MET* Amplification

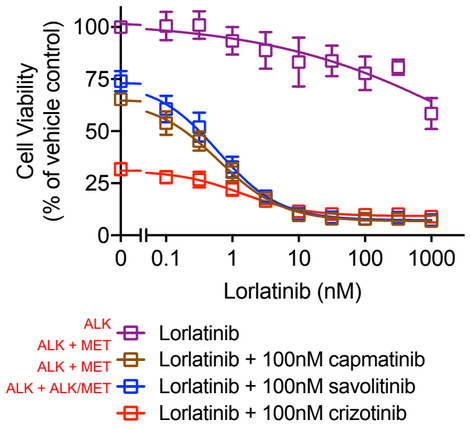
***MET* amplification identified in[1]:**

12% of patients progressing on 2G ALK TKI

22% of patients progressing on 3G ALK TKI (lorlatinib)



Patient-derived ALK+ cell line with *MET* amplification is sensitive to ALK/MET co-inhibition



Case series[2], n=12

ALK/MET co-targeting strategies, ORR 42% (5/12)

Patient	ALK/MET Therapy	Best Response Time on Treatment	Pre-ALK/MET Targeted Therapy Biopsy Findings
1	Crizotinib 250 mg BID	PD <1 month	**MET/CEP7 ≥ 25**, *TP53* R273C, *TP53* Q192*, *SETD2* V2280fs*89
2	Crizotinib 250 mg BID	PR (-38%) 3.5 months	**MET/CEP7 ≥ 25**, *TSC2* D1612N, *TP53* A161T
3	Lorlatinib 75 mg QD#+ Crizotinib 250 mg BID	PR (-30%) 3 months	**MET/CEP7 5.7**, *ATM* S378G, *MDM4* splice region variant, *ARID1A* D1193N, *PIK3CA* E453K
4	Lorlatinib 50 mg QD+ Crizotinib 250 mg BID	PD <1 month	**MET/CEP7 2.4**, *NF1* G2379R, *TP53* V274G, *MYC* gain
5	Lorlatinib 50 mg QD# + Crizotinib 250 mg BID	PR (-60%) 11 months**	**MET/CEP7 ≥ 25**, *APC* Y1642_V1644del
6	Lorlatinib 50 mg QD+ Crizotinib 250 mg BID	PD <1 month	**MET/CEP7 5.5**, *TP53* R273C
7	Lorlatinib 50 mg QD + Crizotinib 250 mg BID	PR (-51%) 6 months	***MET* amplification (2.5)**, *TP53* E346*, *MYC* amplification (3.8) by plasma
8	Lorlatinib 50 mg QD + Crizotinib 250 mg BID	PD <1 month	***MET* amplification (5.4)**, *TP53* C135F (4.6), *BRCA2* D3188fs (2.4), *APC* M314T (0.6), *STK11* A43V (0.3)
9	Alectinib 600 mg BID#+ Capmatinib 400 mg BID	SD (Non-CR/Non-PD) 9 months	**MET/CEP7 ≥ 25**, *SMARCA4* P47T, *EGFR* P596L
10	Alectinib 600 mg BID + Capmatinib 400 mg BID#	SD (-8%) 10 months	**MET/CEP7 ≥ 25**, *TP53* E180*, *APC* E1156K
11	Alectinib 600 mg BID + Capmatinib 300 mg BID	PR (-70%) 7 months	**MET/CEP7 7.7**, *TP53* N131Y, *SMARCA4* D1183N
12	Alectinib 600 mg BID+ Crizotinib 200 mg BID	SD (-26%) 6 months	***MET* amplification** by NGS, *TP53* E285K

[1]Dagogo-Jack I et al., Clin Cancer Res 2020;26(11):2535-45
[2]Dagogo-Jack I et al., JTO Clin Res Rep 2023; in press, DOI: 10.1016/j.jtocrr.2023.100534

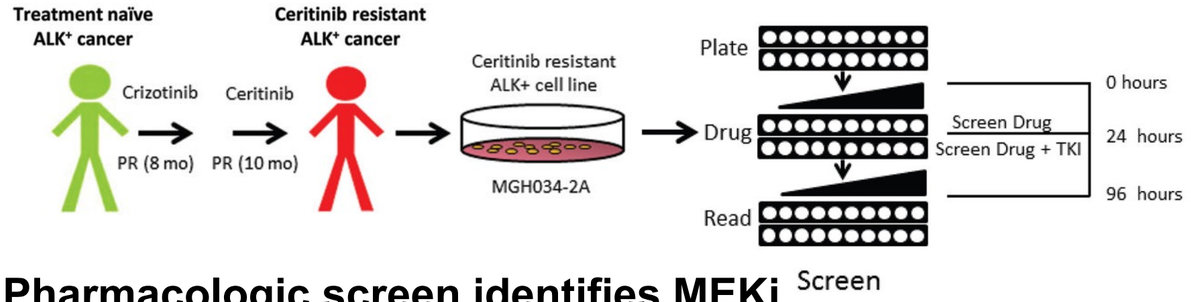
Overcoming ALK-Independent Resistance:

Combination Strategies Outside of ALKi + METi Targeting MET-Driven Resistance

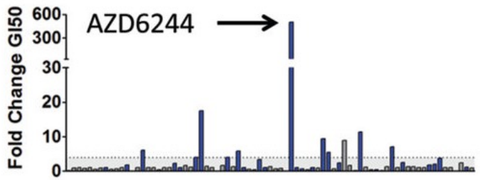
Combination	Bypass Pathway Targeted	Sponsor	ClinicalTrials.gov
Alectinib + Cobimetinib	MEK	MGH	NCT03202940
Brigatinib + Binimetinib	MEK	UCSF	NCT04005144
Ceritinib + Trametinib	MEK	UCSF	NCT03087448
Lorlatinib + Binimetinib	MEK	MGH	NCT04292119
Lorlatinib + PF-07284892	SHP2	Pfizer	NCT04800822
Lorlatinib + TNO155	SHP2	MGH	NCT04292119
Ceritinib + Everolimus	mTOR	MD Anderson	NCT02321501
Brigatinib + Bevacizumab	VEGF	City of Hope	NCT04227028

ALK: Addressing Resistance with Combinations
Rationale for ALK-MEK Co-Blockade

MGH034-2A, ceritinib-resistant patient-derived ALK+ cell line*



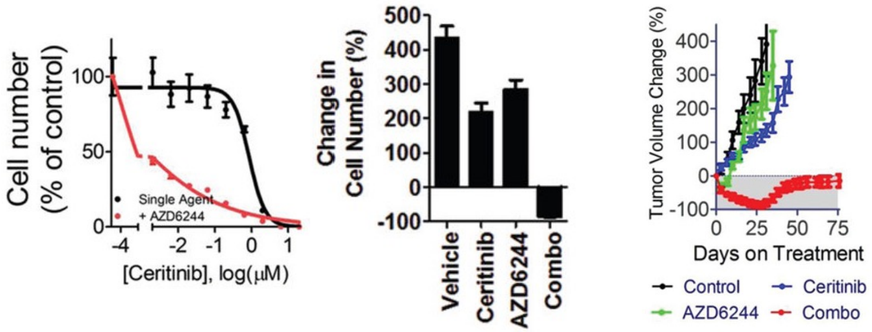
Pharmacologic screen identifies MEKi as a hit in combination with ceritinib



Subsequent tissue NGS reveals an activating *MAP2K1* mutation at multiple TKI-resistant sites

Site	MAP2K1 K57N	PIK3CA H1047R
Lung - RLL1	0.22	0.00
Lung - RLL2	0.20	0.00
Lung - RLL3	0.27	0.00
Lung - RLL4	0.22	0.00
Lung - Left apex	0.22	0.00
Lung - LUL1	0.00	0.00
Lung - LUL2	0.29	0.00
Lung - LUL3	0.24	0.00
Liver - Medial	0.00	0.28
Liver - Lateral	0.00	0.00
Liver - Posterior	0.00	0.00
Heart (Normal)	0.00	0.00

ALKi+MEKi overcomes TKI resistance



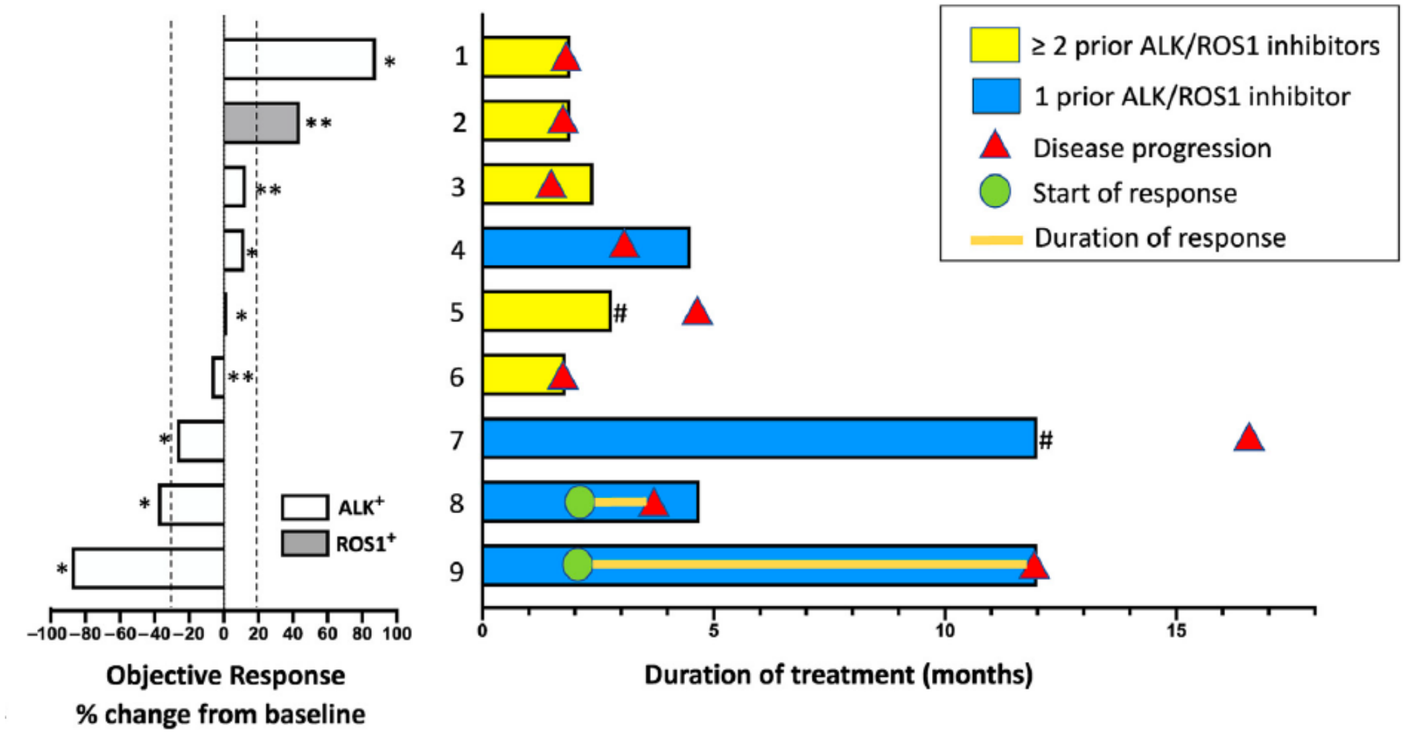
*Crystal AS et al., Science 2014;346(6216):1480-6

RAS-MAPK dependence underlies a rational polytherapy strategy in EML4-ALK–positive lung cancer

Gorjan Hrustanovic[1,2], Victor Olivas[1,2], Evangelos Pazarentzos[1,2], Asmin Tulpule[1,2], Saurabh Asthana[1,2], Collin M Blakely[1,2], Ross A Okimoto[1,2], Luping Lin[1,2], Dana S Neel[1,2], Amit Sabnis[1,2], Jennifer Flanagan[1,2], Elton Chan[1,2], Marileila Varella-Garcia[3,4], Dara L Aisner[4], Aria Vaishnavi[3], Sai-Hong I Ou[5,6], Eric A Collisson[1,2], Eiki Ichihara[7], Philip C Mack[8,9], Christine M Lovly[7], Niki Karachaliou[10], Rafael Rosell[10], Jonathan W Riess[8,9], Robert C Doebele[3] & Trever G Bivona[1,2]

One strategy for combating cancer-drug resistance is to deploy rational polytherapy up front that suppresses the survival and emergence of resistant tumor cells. Here we demonstrate in models of lung adenocarcinoma harboring the oncogenic fusion of ALK and EML4 that the GTPase RAS–mitogen-activated protein kinase (MAPK) pathway, but not other known ALK effectors, is required for tumor-cell survival. EML4-ALK activated RAS-MAPK signaling by engaging all three major RAS isoforms through the HELP domain of EML4. Reactivation of the MAPK pathway via either a gain in the number of copies of the gene encoding wild-type K-RAS (*KRAS*^{WT}) or decreased expression of the MAPK phosphatase DUSP6 promoted resistance to ALK inhibitors *in vitro*, and each was associated with resistance to ALK inhibitors in individuals with EML4-ALK–positive lung adenocarcinoma. Upfront inhibition of both ALK and the kinase MEK enhanced both the magnitude and duration of the initial response in preclinical models of EML4-ALK lung adenocarcinoma. Our findings identify RAS-MAPK dependence as a hallmark of EML4-ALK lung adenocarcinoma and provide a rationale for the upfront inhibition of both ALK and MEK to forestall resistance and improve patient outcomes.

Phase I Study of Ceritinib + Trametinib



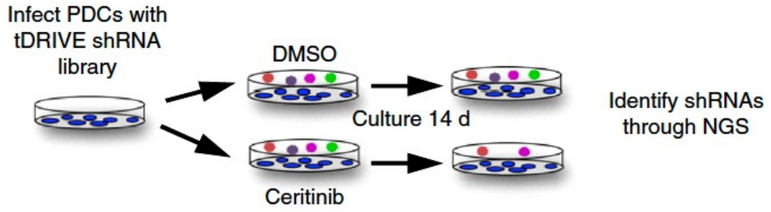
- N=6 at DL1 (ceritinib 300 mg QD with food + trametinib 1.5 mg QD without food
- N=3 at DL2 (ceritinib 450 mg QD with food + trametinib 1.5 mg QD without food)
- **Study stopped early due to low accrual**

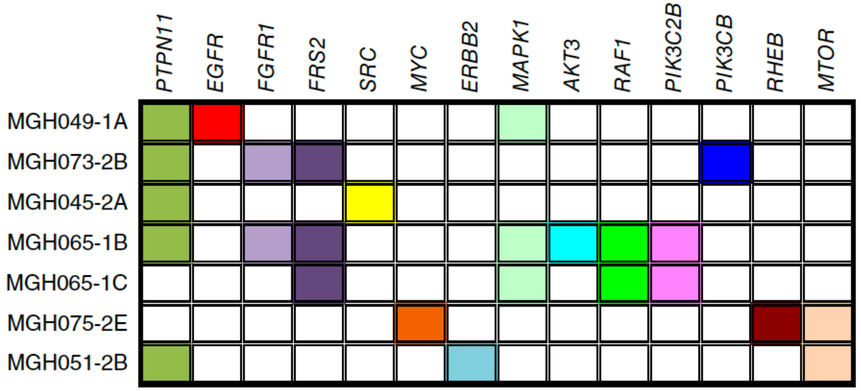
- **ORR 22%**
  - 2/8 patients with ALK+ NSCLC had confirmed PR
    - Both had received 1 prior ALK TKI (alectinib or crizotinib)
  - 4 patients with PD as best response had received 3-5 prior TKIs
- **Median PFS 3.0 months**

Lara MS et al., JTO Clin Res Rep 2022;3:100436

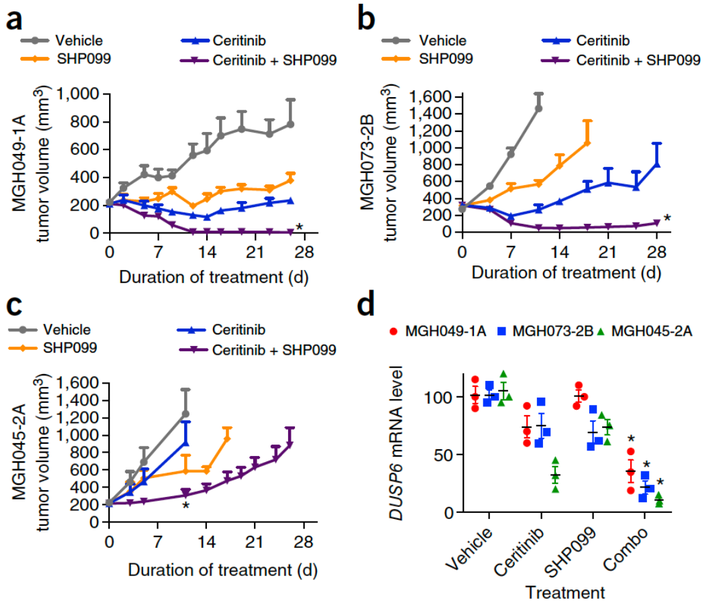
ALK: Addressing Resistance with Combinations Rationale for ALK-SHP2 Co-Blockade

shRNA screen identifies top candidate genes driving resistance to ceritinib in ALK+ PDCs





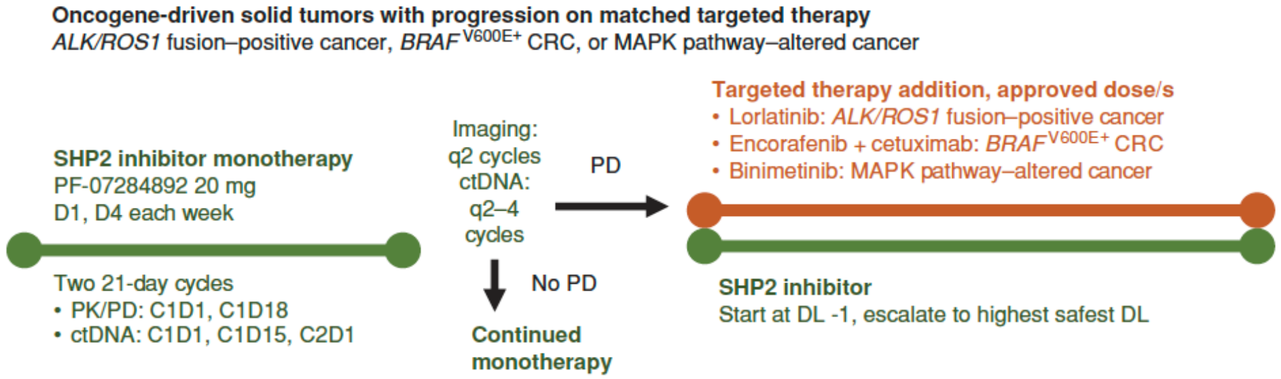
Ceritinib + SHP2 inhibitor overcomes resistance to ALK TKI

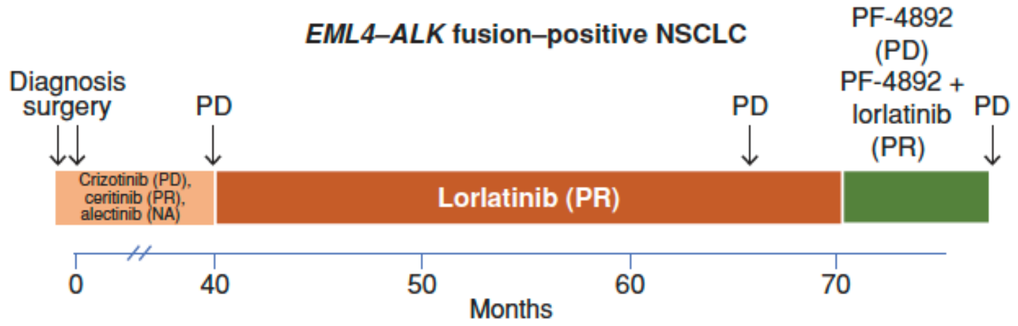


Dardaei L et al., Nat Med 2018;24(4):512-7

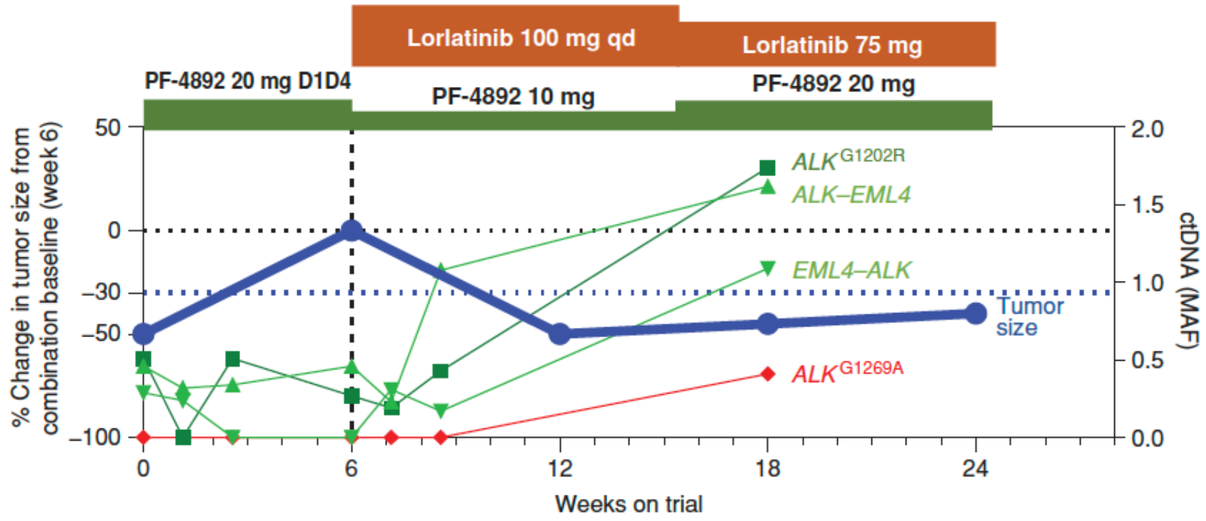
ALK: Addressing Resistance with Combinations
ALK-SHP2 Co-Blockade

FIH Phase 1 Study of SHP2i PF-07284892 as monotherapy and in combination with targeted therapies in treatment-resistant oncogene-driven solid tumors





PF-07284892 + lorlatinib in ALK+ NSCLC, prior ALK TKIs including lorlatinib



Drilon A et al., Cancer Discov 2023;13(8):1789-801

Overcoming ALK-Independent Resistance:

Combination Strategies Outside of ALKi + METi Targeting MET-Driven Resistance

Combination	Bypass Pathway Targeted	Sponsor	ClinicalTrials.gov
Alectinib + Cobimetinib	MEK	MGH	NCT03202940
Brigatinib + Binimetinib	MEK	UCSF	NCT04005144
Ceritinib + Trametinib	MEK	UCSF	NCT03087448
Lorlatinib + Binimetinib	MEK	MGH	NCT04292119
Lorlatinib + PF-07284892	SHP2	Pfizer	NCT04800822
Lorlatinib + TNO155	SHP2	MGH	NCT04292119
Ceritinib + Everolimus	mTOR	MD Anderson	NCT02321501
Brigatinib + Bevacizumab	VEGF	City of Hope	NCT04227028

None with clinical biomarker

Limited Evidence Regarding Role for Chemo + Anti-PD(L)1 +/- Anti-VEGF – Borrowing Data Mostly from EGFRmut NSCLC

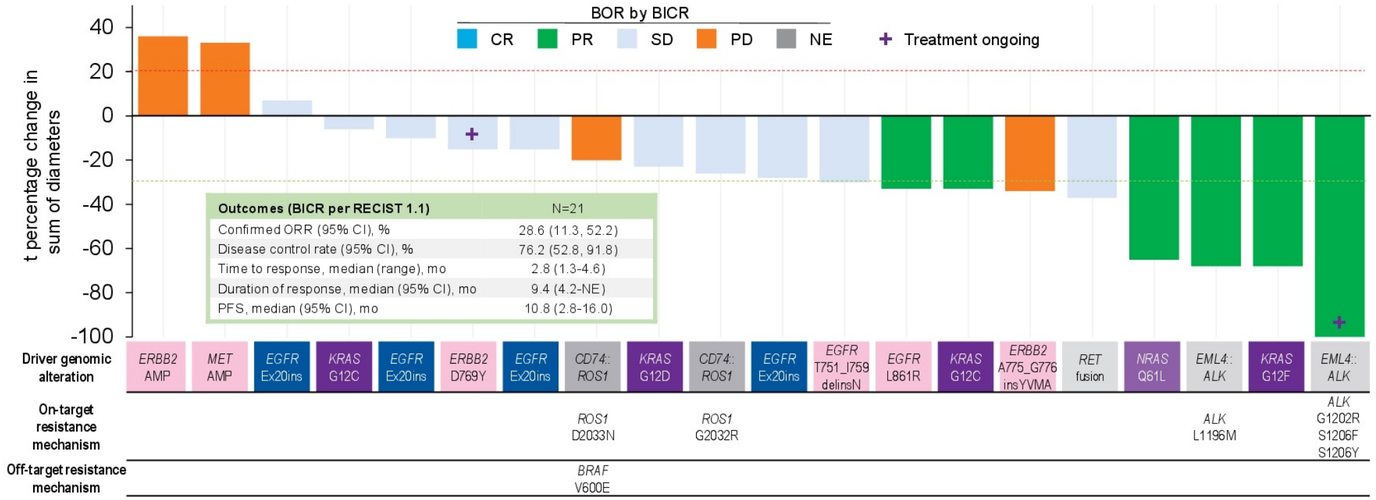
Trial	Treatment	Genotype	N	ORR	PFS	OS
KEYNOTE-789[1]	**Pembrolizumab** + platinum/pem vs platinum/pem	EGFR	245 vs 247	29.0% vs 27.1%	**HR 0.80 (0.65-0.97)** **5.6 mo vs 5.5 mo**	**HR 0.84 (0.69-1.02)** **15.9 mo vs 14.7 mo**
CheckMate-722[2]	**Nivolumab** + platinum/pem vs platinum/pem	EGFR	144 vs 150	31% vs 27%	**HR 0.75 (0.56-1.00)** **5.6 mo vs 5.4 mo**	**HR 0.82 (0.61-1.10)** **19.4 mo vs 15.9 mo**
ORIENT-31[3]	**Sintilimab** + IBI305 + cis/pem (arm A) vs **sintilimab** + cis/pem (arm B) vs cis/pem (arm C)	EGFR	158 vs 158 vs 160	48.1% vs 34.8% vs 29.4%	**Arm A vs C: HR 0.51** (0.39-0.67) **Arm B vs C: HR 0.72** (0.55-0.94) **7.2 mo vs 5.5 mo vs 4.3 mo**	**Arm A vs C: HR 0.98** (0.72-1.34) **Arm B vs C: HR 0.97** (0.71-1.32) **21.1 mo vs 20.5 mo vs 19.2 mo**
IMpower150[4,5]	**Atezolizumab** + **bev** + carbo/pac vs **atezolizumab** + carbo/pac vs **bev** + carbo/pac	EGFR subgroup	34 vs 45 vs 44	70.6% vs 35.6% vs 41.9%	**ABCP vs BCP HR 0.61** (0.36-1.03) **ACP vs BCP HR 1.14** (0.73-1.78) **10.2 mo vs 6.9 mo vs 6.9 mo**	**ABCP vs BCP HR 0.91** (0.53-1.59) **ACP vs BCP HR 1.16** (0.71-1.89) **26.1 mo vs 21.4 mo vs 20.3 mo**
IMpower151[6]	**Atezolizumab** + **bev** + carbo + pem/pac vs **bev** + carbo + pem/pac	EGFR/ALK subgroup	81 vs 82	-----	**HR 0.86 (0.61, 1.21)** **8.5 mo vs 8.3 mo**	-----
ATTLAS, KCSG-LU19-04[7]	**Atezolizumab** + **bev** + carbo/pac vs PT/pem	EGFR/ALK	154 vs 74	**69.5% vs 41.9%**	**HR 0.62 (0.45-0.86)** **8.48 mo vs 5.62 mo**	**HR 1.01 (0.69-1.46)** **20.63 mo vs 20.27 mo**

[1]Yang J et al., ASCO 2023; [2]Mok T et al., ESMO Asia 2022; [3]Lu S et al., Lancet Respir Med 2023;11(7):624-36; [4]Reck M et al., Lancet Respir Med 2019;7(5):387-401; [5]Nogami N et al., J Thorac Oncol 2022;17(2):309-23; [6]Zhou C et al., WCLC 2023; [7]Ahn MJ et al., ESMO 2023

Exploring resistance mechanism-agnostic approaches

ADCs in TKI-Resistant Fusion-Addicted NSCLC

Activity of patritumab deruxtecan in NSCLC with non-classical EGFRmut AGAs[1]



Activity of datopotamab deruxtecan in NSCLC with AGAs[2] 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)

- **Patritumab deruxtecan** (**anti-HER3 ADC**)[1] & **datopotamab deruxtecan** (**anti-TROP2 ADC**)[2] have shown signals of activity in patients with fusion-driven NSCLC (small n's)
- In early data, clinical activity of ADCs across AGA subsets appears **irrespective of** the spectrum of known or unknown **resistance mechanisms**[1-3]

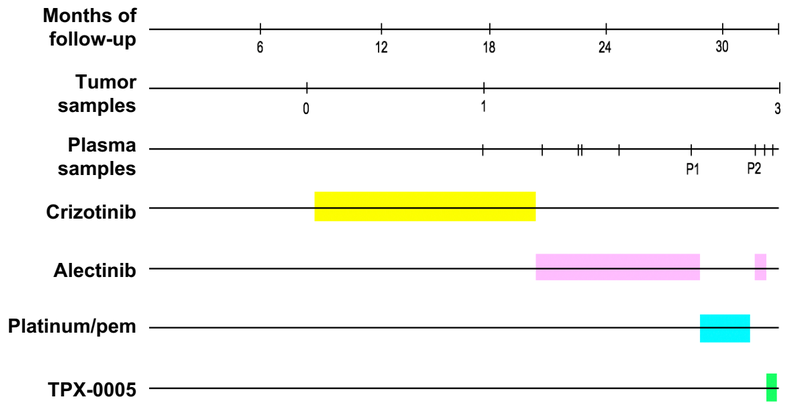
[1]Steuer C et al., ASCO 2022; [2]Paz Ares L et al., ESMO 2023
[3]HA et al., J Clin Oncol 2023; doi: 10.1200/JCO.23.01476

Histologic Transformation in ALK+ NSCLC

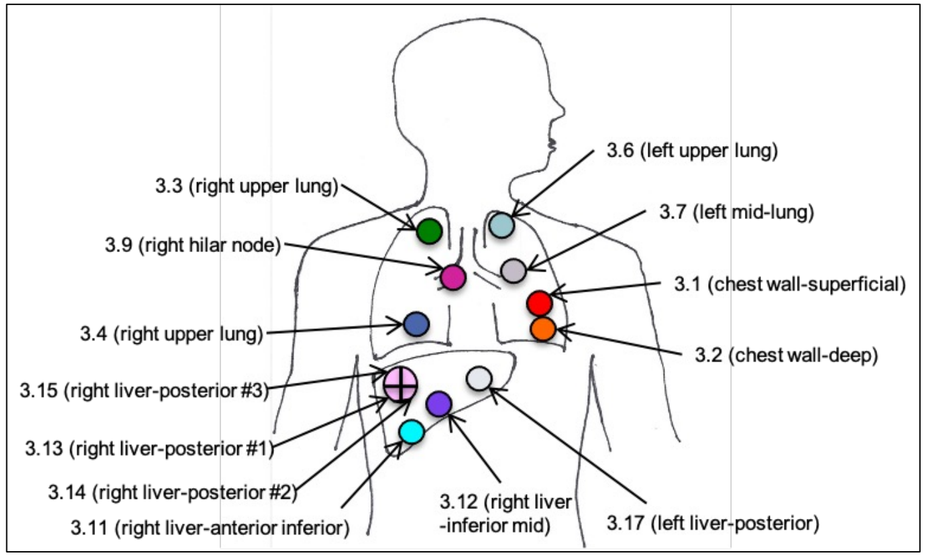
- **Small cell transformation** is a well recognized phenomenon across TKI-refractory oncogene-addicted lung cancers including ALK+ NSCLC:
  - ALK+ NSCLC refractory to next-generation ALK TKIs: 1.2% (2/168)[1]
- **Squamous cell transformation** has also been reported in TKI-refractory ALK+ NSCLC[2]
- Above frequencies most likely represent **underestimates** given the overall low prevalence of **repeat biopsies** **following disease progression resulting in under-diagnosis**

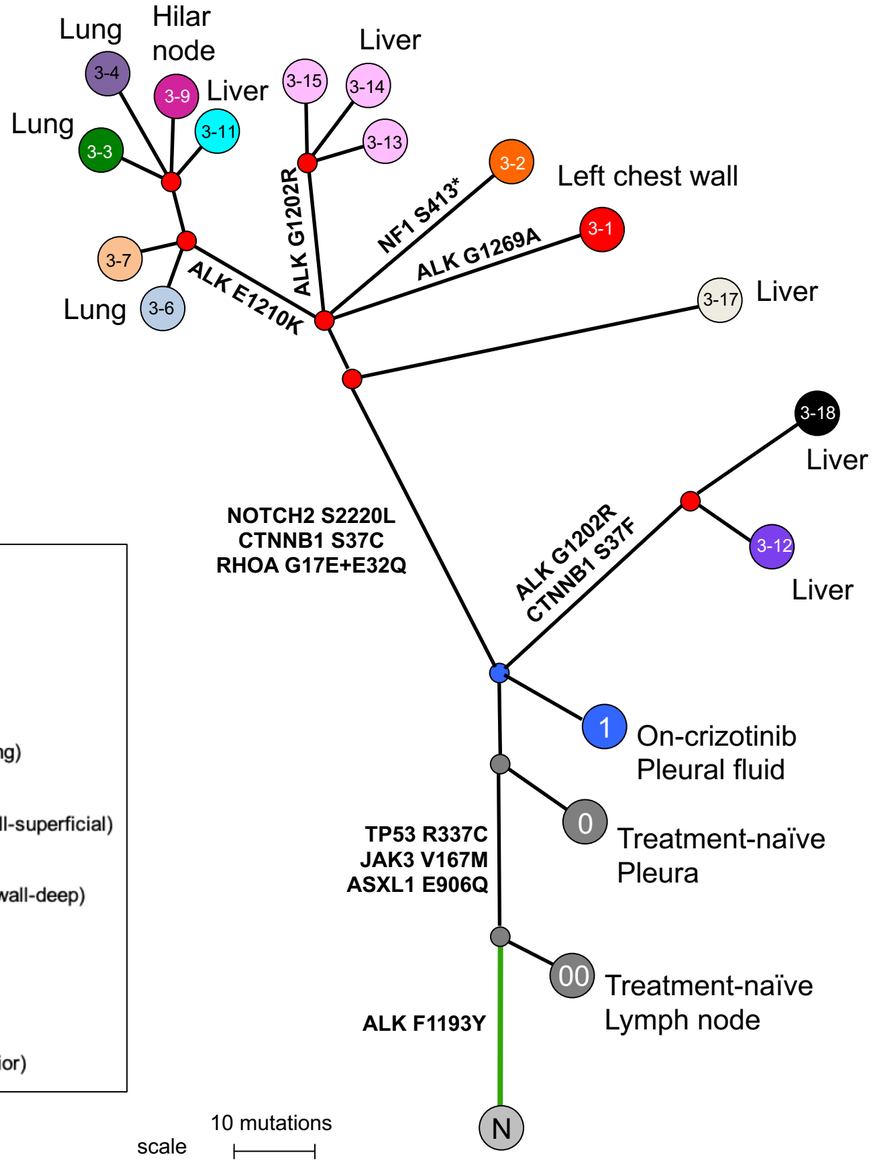
[1]Lin JJ et al., NPJ Precis Oncol 2020;4:21
[2]Schneider JL et al., Nat Cancer 2023;4(3):330-43

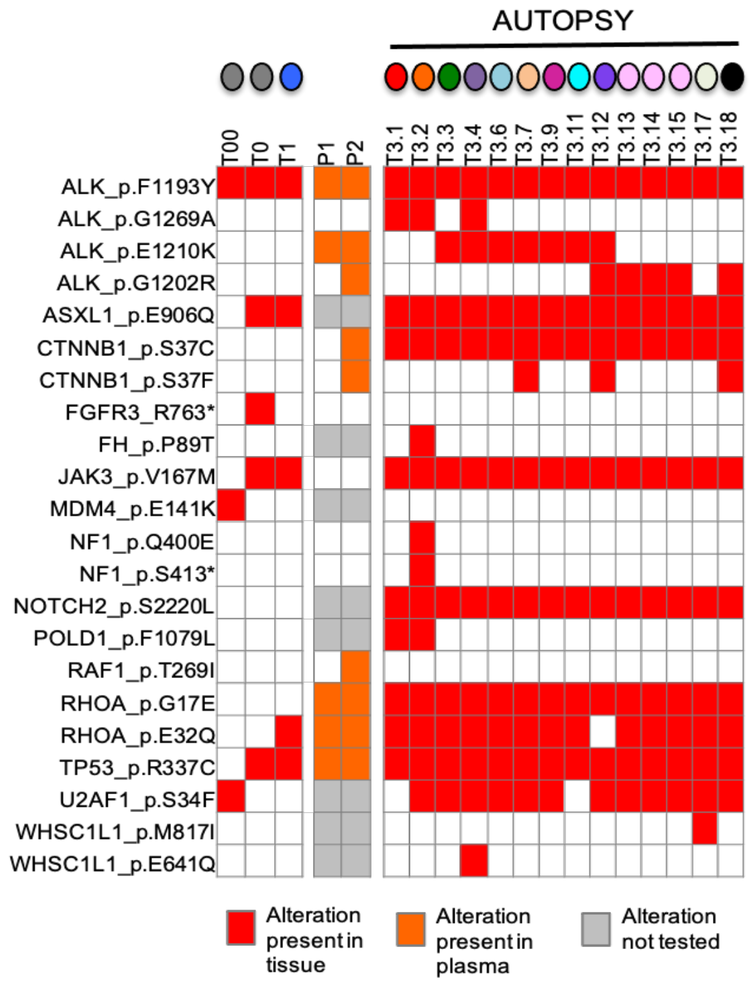
Intra-Patient Heterogeneity in Mechanisms of Resistance After ALK TKIs



Tumor sites harvested at autopsy







Unpublished data – Please do NOT post
Collaboration with Michael Lawrence, MGH

Summary

- Sequential ALK TKI therapy can result in the successive acquisition of on-target (*ALK*) resistance mutations leading to refractory compound *ALK* resistance mutations
- Next-generation ALK TKIs with activity against single and compound ALK mutations are in clinical development
- Off-target mechanisms of resistance are common after potent ALK TKIs, only some of which are actionable (e.g., *MET* amplification), with combination strategies being evaluated in clinical trials
- Standard-of-care for patients with TKI-refractory ALK+ NSCLC remains chemotherapy [limited evidence to support addition of anti-PD(L)1]
- An unmet need exists for resistance mechanism-agnostic therapeutic strategies (such as ADCs) and for approaches to overcome or prevent polyclonal resistance (e.g., upfront rational combination approaches)