ALK & ROS1 RESISTANCE

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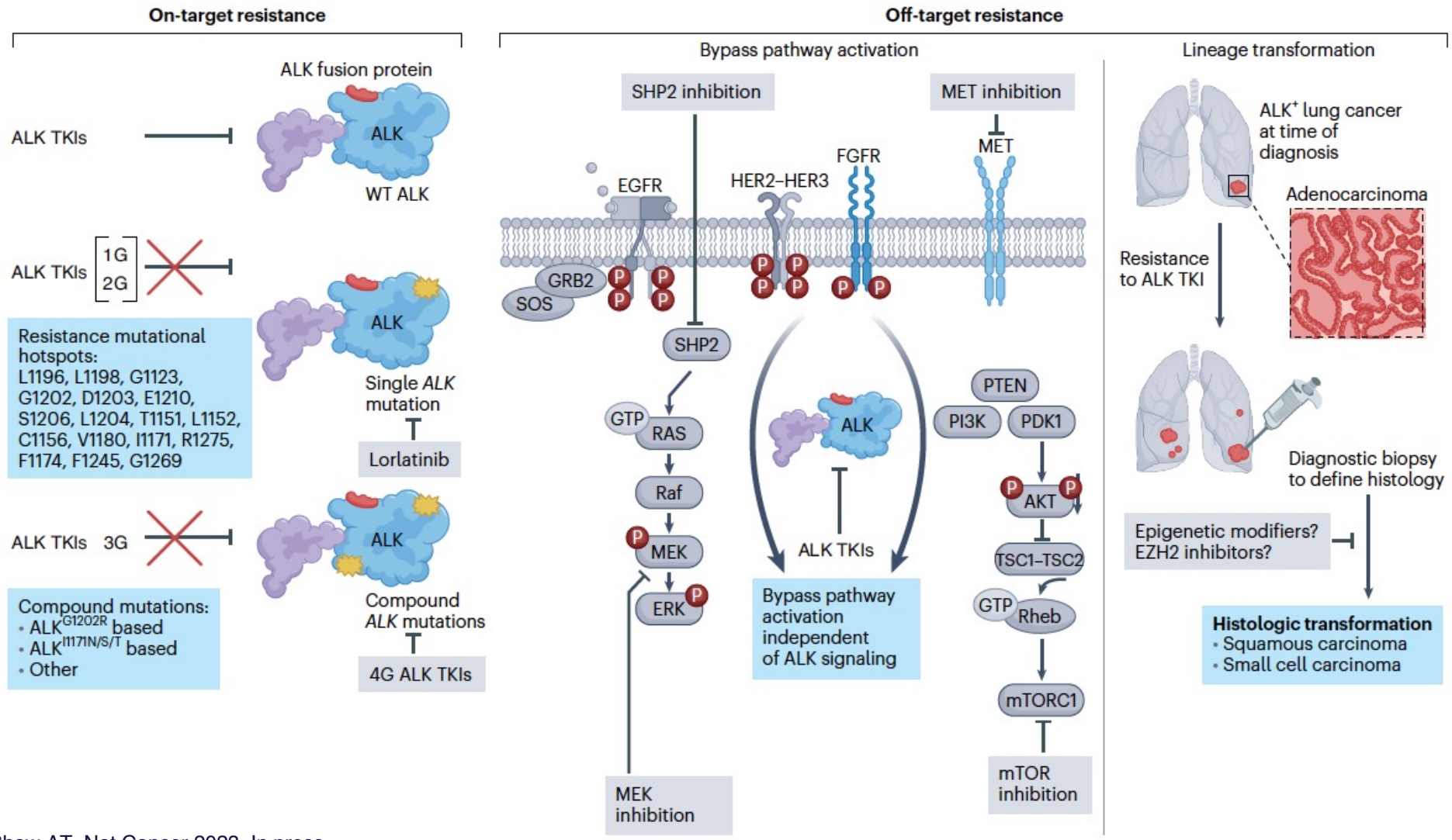
Broad Framework: Mechanisms of Resistance to ALK Inhibitors

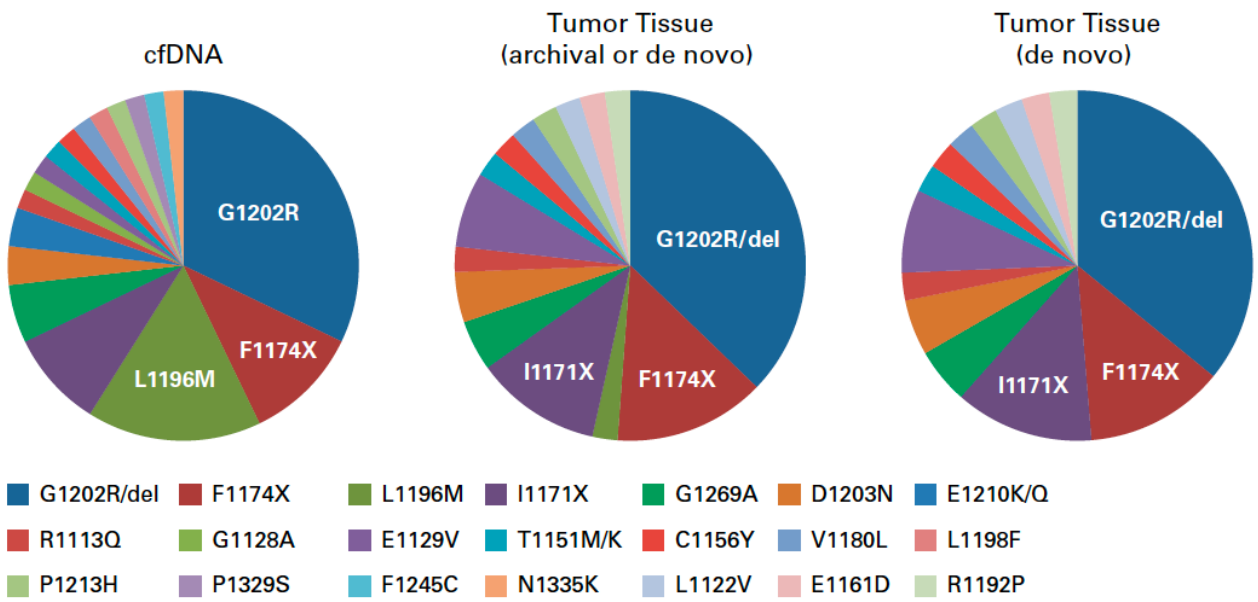


Schneider JL, Lin JJ, Shaw AT. Nat Cancer 2023. In press

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

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

Prior Second-Generation TKI(s) (EXP3B to EXP5)



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

Different ALK TKIs unique spectrum of activity against *ALK* mutations in preclinical models[2]

IC$_{50}$ ≤50 nM | IC$_{50}$ >50–<200 nM | IC$_{50}$ ≥200 nM

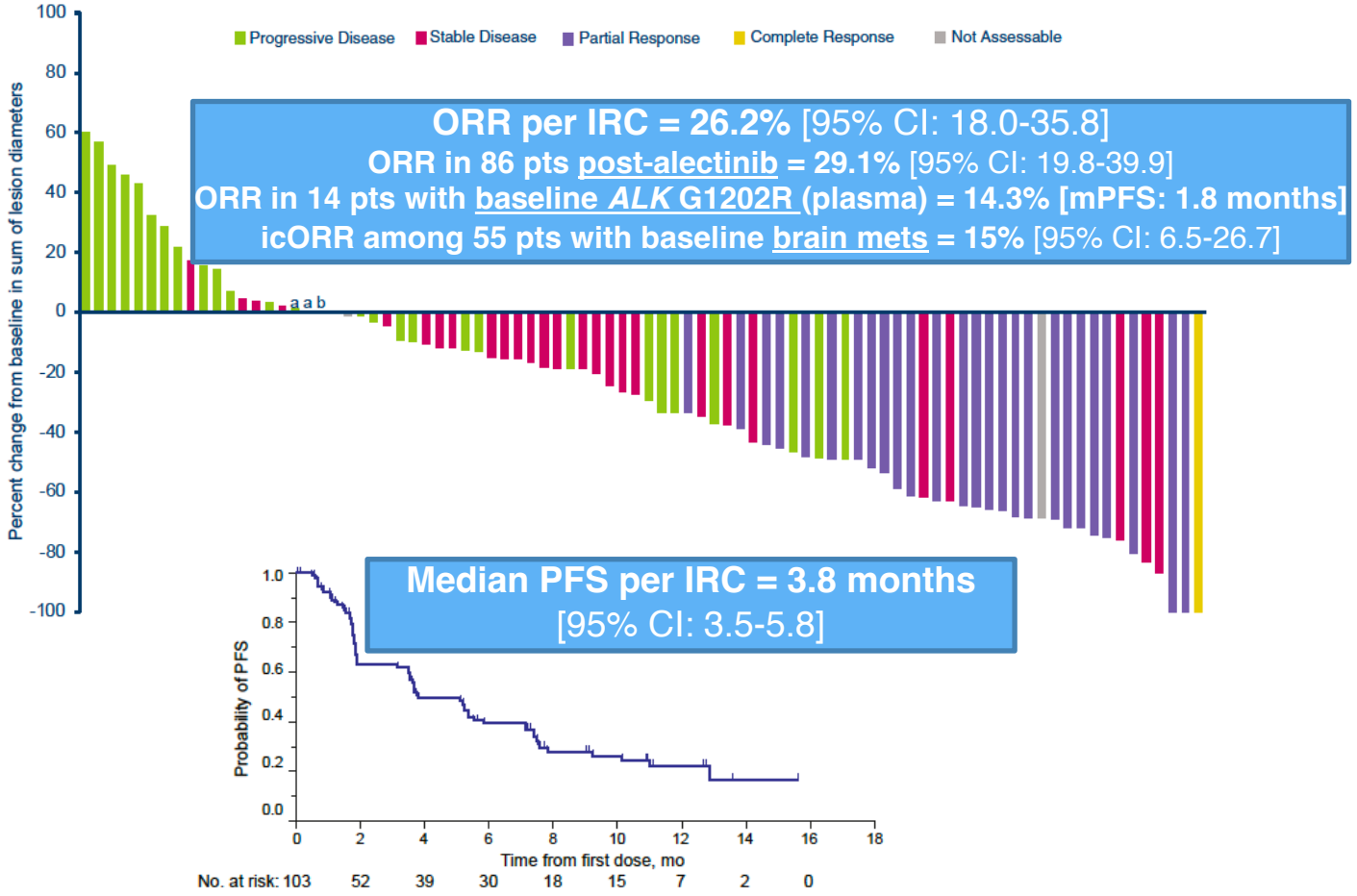
Cellular ALK Phosphorylation Mean IC$_{50}$ (nM)					
Mutation Status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
Parental BA/F3	763.9	885.7	890.1	2774.0	11293.8
V1	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	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

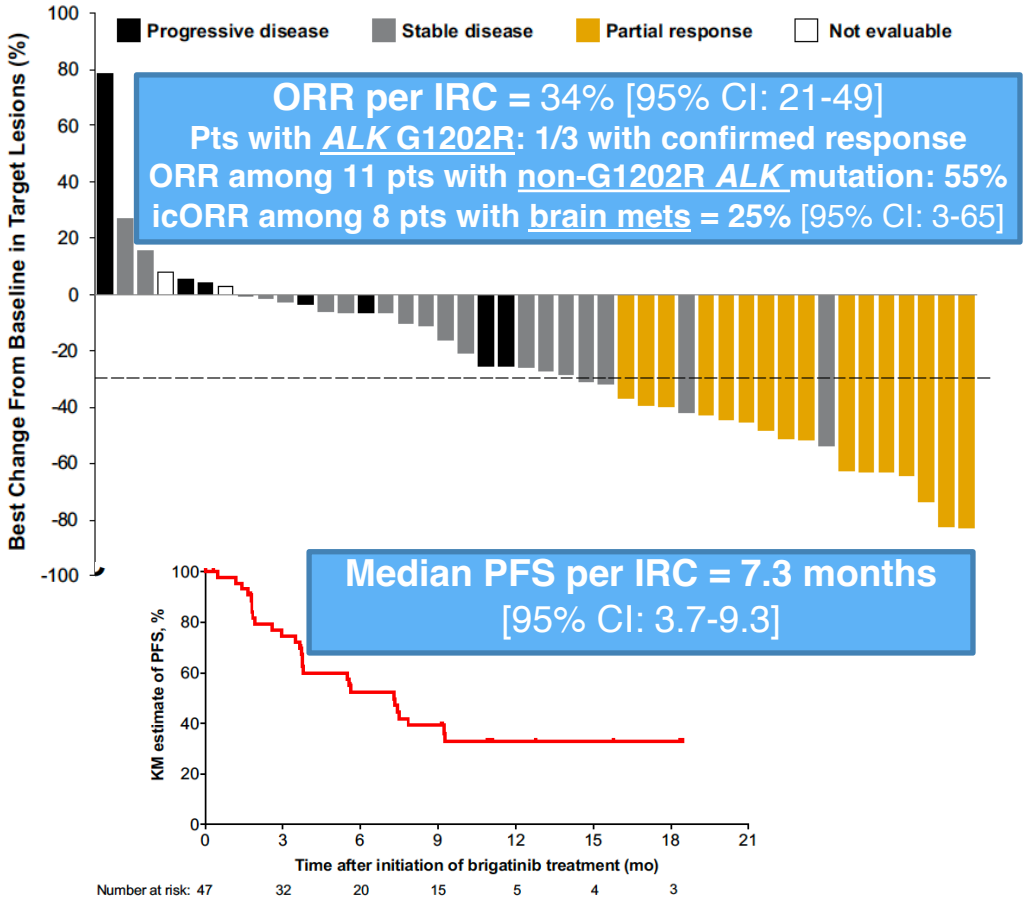
[2]Gainor JF, et al. *Cancer Discov.* 2016;6:1118–1133

Brigatinib After 2G ALK TKI (e.g. Alectinib)

Efficacy in patients who progressed on alectinib or ceritinib (n=103): Global phase II ALTA-2 trial[1]



Efficacy in patients who progressed on alectinib (n=47): Japanese phase II J-ALTA trial[2]

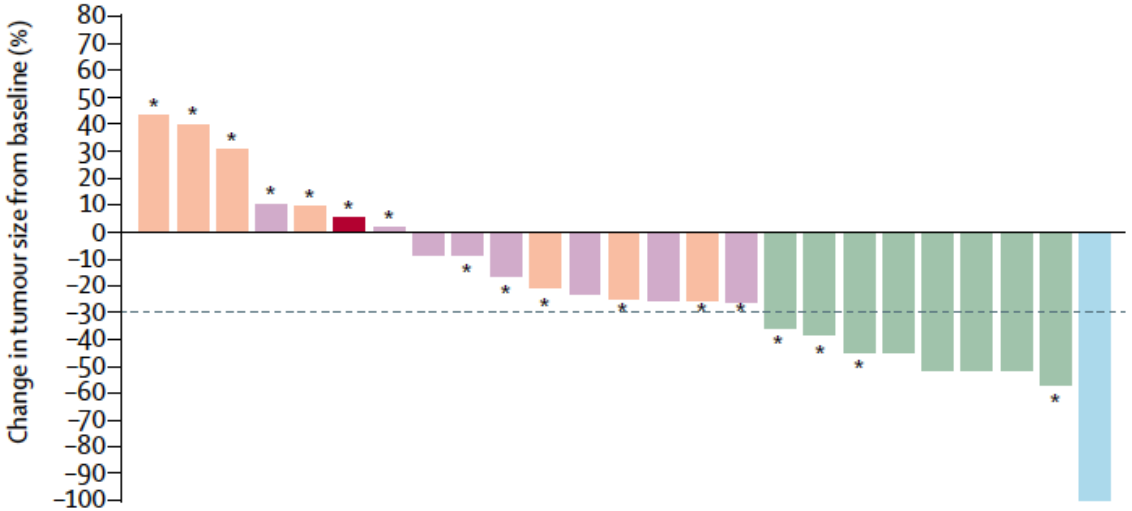


[1]Ou SI et al., J Thorac Oncol 2022;17(12):1404-14

[2]Nishio M et al., J Thorac Oncol 2021;16(3):452-63

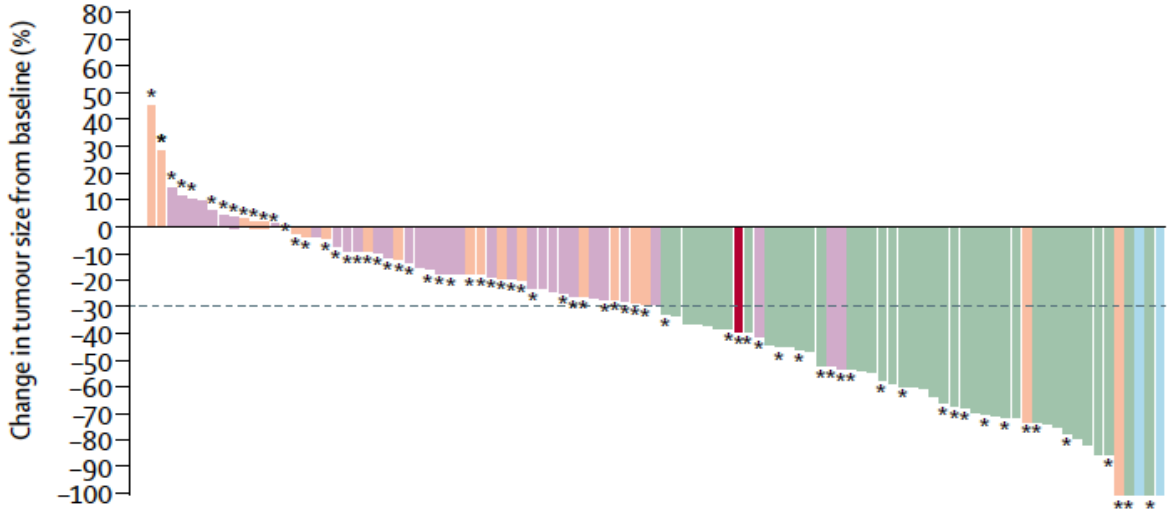
Lorlatinib After 2G ALK TKI(s)

EXP3B: Prior Non-Crizotinib ALK TKI ± Chemotherapy[1]



	EXP3B (n=28)
ORR, n/N (%) (95% CI)	**9/28 (32) (16, 52)**
IC ORR, n/N (%) (95% CI)	**5/9 (56) (21, 86)**
Median DOR, mo (95% CI)	NR (4.1, NR)
Median PFS, mo (95% CI)	**5.5 (2.9, 9.0)**

EXP4-5: 2-3 Prior ALK TKIs ± Chemotherapy[1]



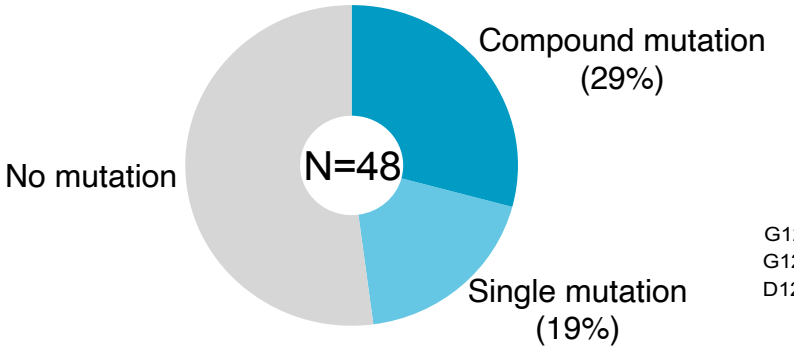
	EXP4+5 (n=111)
ORR, n/N (%) (95% CI)	**43/111 (39) (30, 49)**
IC ORR, n/N (%) (95% CI)	**26/49 (53) (38, 68)**
Median DOR, mo (95% CI)	NR (5.5, NR)
Median PFS, mo (95% CI)	**6.9 (5.4, 9.5)**

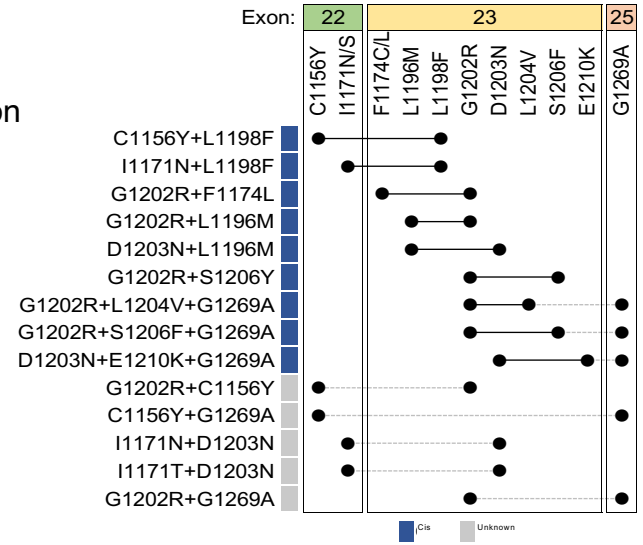
ORR in 29 pts with baseline *ALK* mutation in tissue = 69% [median PFS: 11.0 months][2]
ORR in 28 pts with baseline *ALK* G1202R/del (tissue or plasma) = 57% [median PFS: 8.2 months][2]

[1]Solomon BJ, et al. Lancet Oncol 2018;19:1654-67; [2]Shaw AT et al., J Clin Oncol 2019;37(16):1370-9

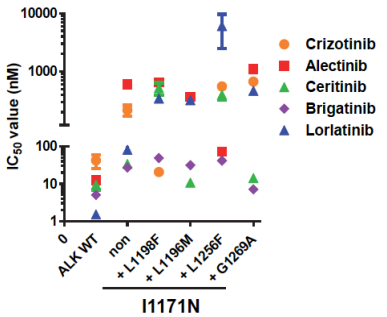
Resistance to Lorlatinib Following Prior ALK TKI(s): Compound *ALK* Mutations

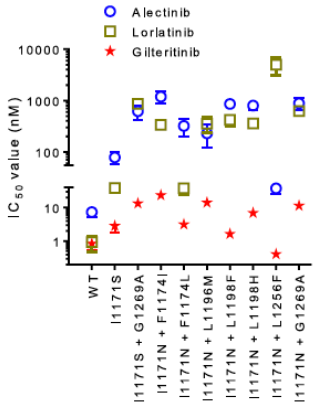
ALK mutations identified in lorlatinib-resistant tissue biopsies (with prior ALK TKI)[1]





A small subset of compound *ALK* mutations are sensitive to available ALK TKIs[2,3]





Many compound *ALK* mutations are refractory to all available ALK TKIs[1]

	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

- **~30% with on-target resistance to lorlatinib**
- No single predominant compound *ALK* mutation was identified; *however…*
- Among the 14 cases with ≥2 *ALK* mutations, 8 (57%) harbored *ALK* G1202R and 3 (21%) had *ALK* I1171N reflecting sequential ALKi therapy

[1]Shiba-Ishii A et al., Nat Cancer 2022;3:710-22; [2]Okada K et al., EBioMedicine 2019;41:105-119; [3]Mizuta H et al., Nat Commun 2021;12:1261

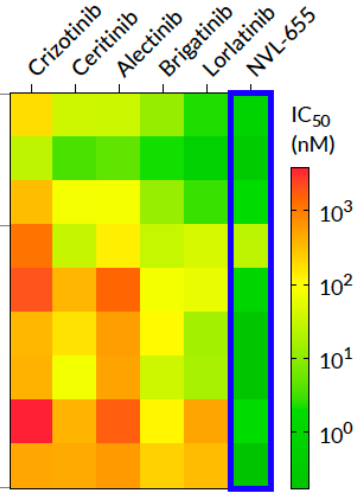
4G ALK TKI: Overcoming Lorlatinib-Resistant Compound *ALK* Mutations

NVL-655 (ALKOVE-1; NCT05384626)

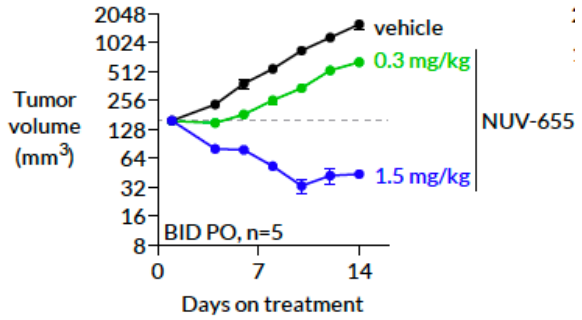
Coverage of lorlatinib-resistant *ALK* mutations in ALK+ cell lines

	Cell with ALK fusion	NUV-655	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
No kinase domain mutations	NCI-H2228 (EML4-ALK v3)	0.70	90	55	13	13	< 1.1
	NCI-H3122 (EML4-ALK v1)	2.0	180	48	22	22	3.5
	Wild-type	1.6	270	90	25	42	4.2
G1202R+ mutations	G1202R	< 0.73	950	570	1600	400	120
	G1202R/L1196M	7.0	1500	1400	2200	820	3900
	G1202R/G1269A	3.0	1100	350	1300	240	970
	G1202R/L1198F	2.0	170	1300	2200	470	720

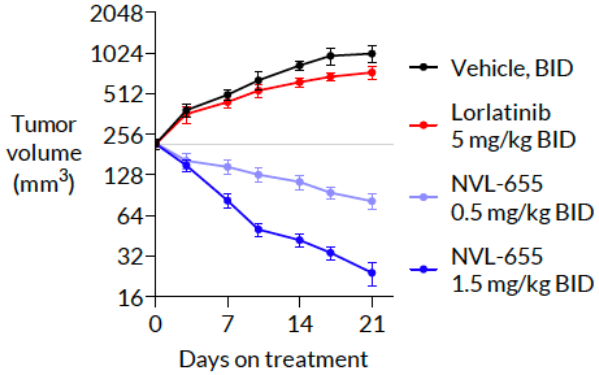
	PDC	Fusion	Mutation	Last treatment
TREATMENT-NAÏVE	MGH048-1	EML4-ALK v1	–	–
	MGH064-1	EML4-ALK v2	–	–
	MGH026-1	EML4-ALK v3	–	–
TREATMENT-RELAPSED	MGH045-1	EML4-ALK v1	L1196M	Crizotinib
	MGH953-4	EML4-ALK v3	G1202R	Alectinib
	YU-1077	EML4-ALK v3	G1202R	Alectinib
	MGH9037-2	EML4-ALK v3	G1202R	Brigatinib
	MGH953-7	EML4-ALK v3	G1202R/L1196M	Lorlatinib
	MR448re	EML4-ALK v3	G1202R/T1151M	Lorlatinib



EML4-ALK G1202R/L1196M fusion Ba/F3 xenograft model

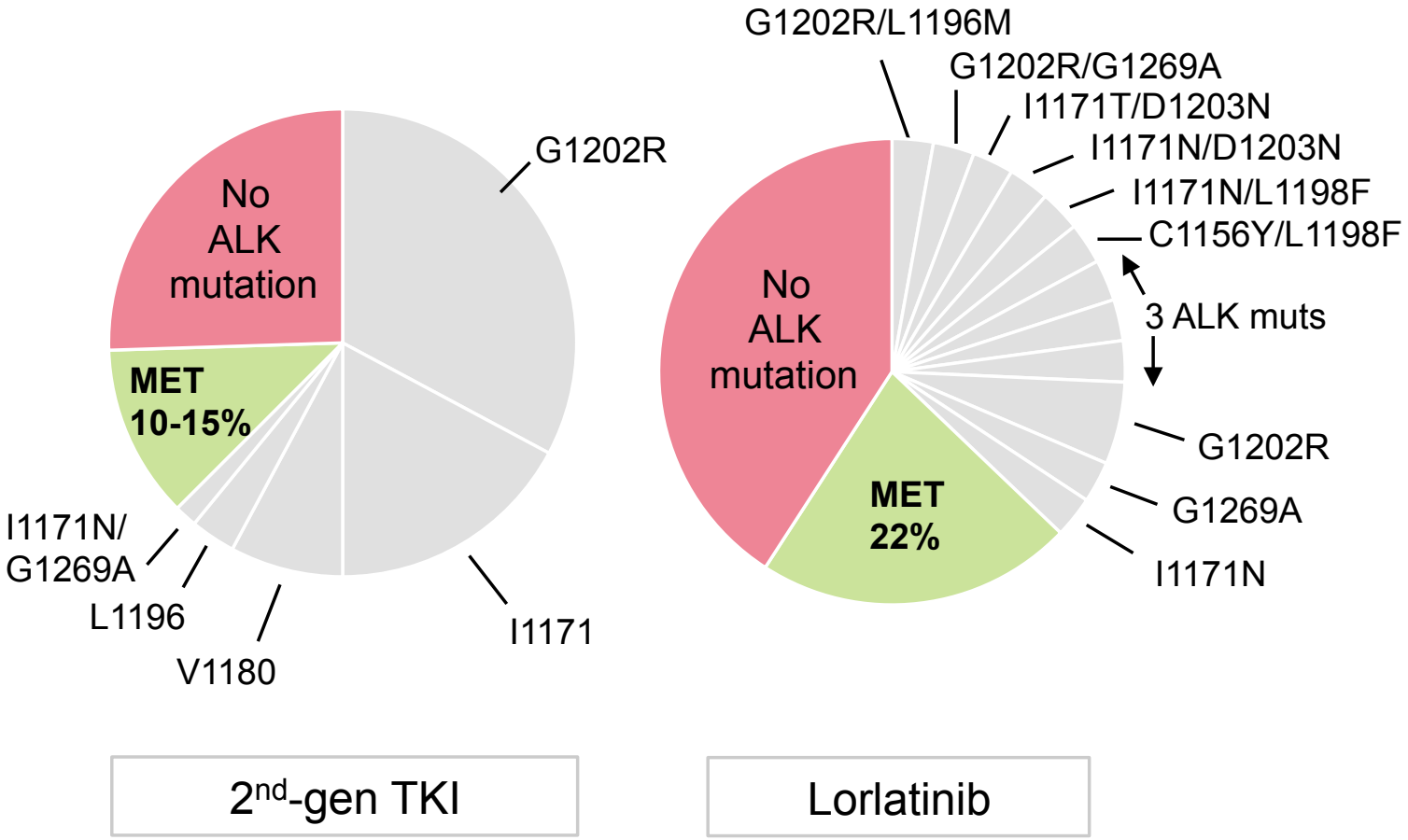


EML4-ALK G1202R/L1196M fusion MGH953-7 PDX



Pelish HE et al., AACR 2021; Fujino T et al., EORTC-NCI-AACR 2022

MET Amplification as an Off-Target Resistance Mechanism Following Next-Gen ALK TKI(s)

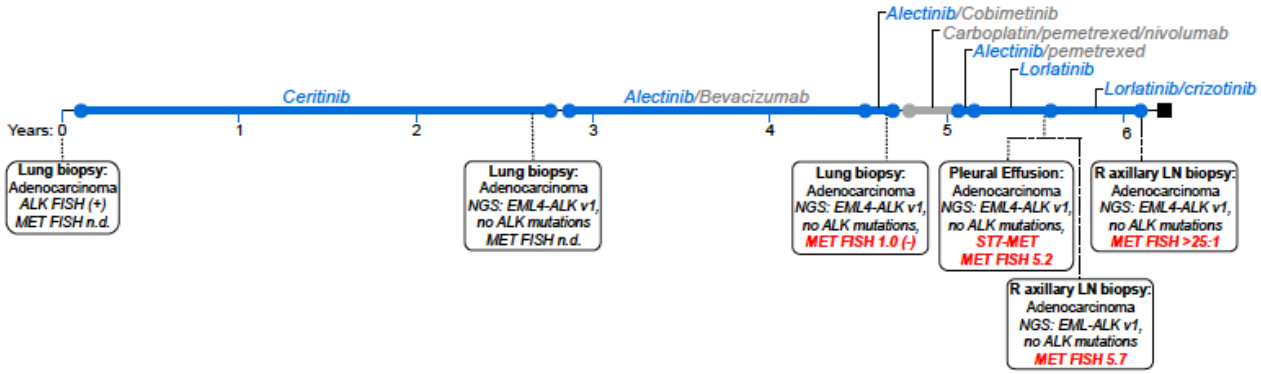


Dagogo-Jack I et al. Clin Cancer Res 2020;26:2535-45

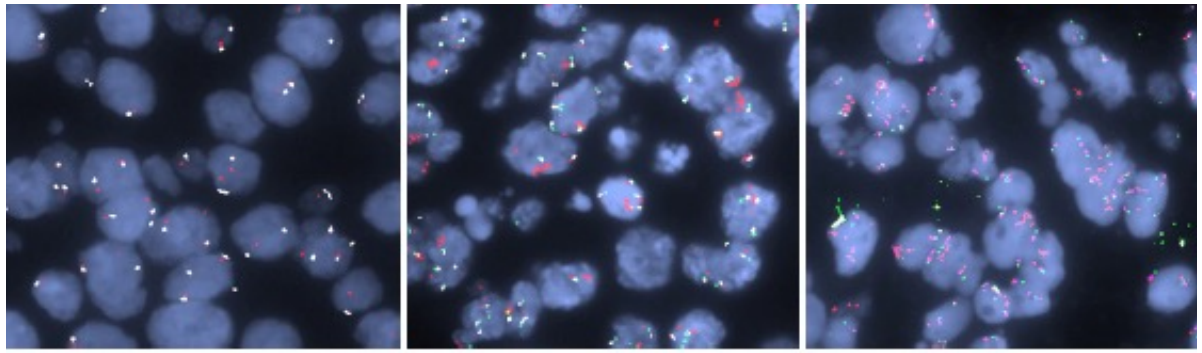
Dagogo-Jack I et al. Clin Cancer Res 2020;26:2535-45

Targeting *MET* amplification in ALK+ NSCLC with ALK/MET Co-Inhibition

MET amplification and fusion identified in tissue biopsies from a patient progressing on lorlatinib



Progression on alectinib + bev | Progression on lorlatinib (pleural fluid) | Progression on lorlatinib (axillary LN)

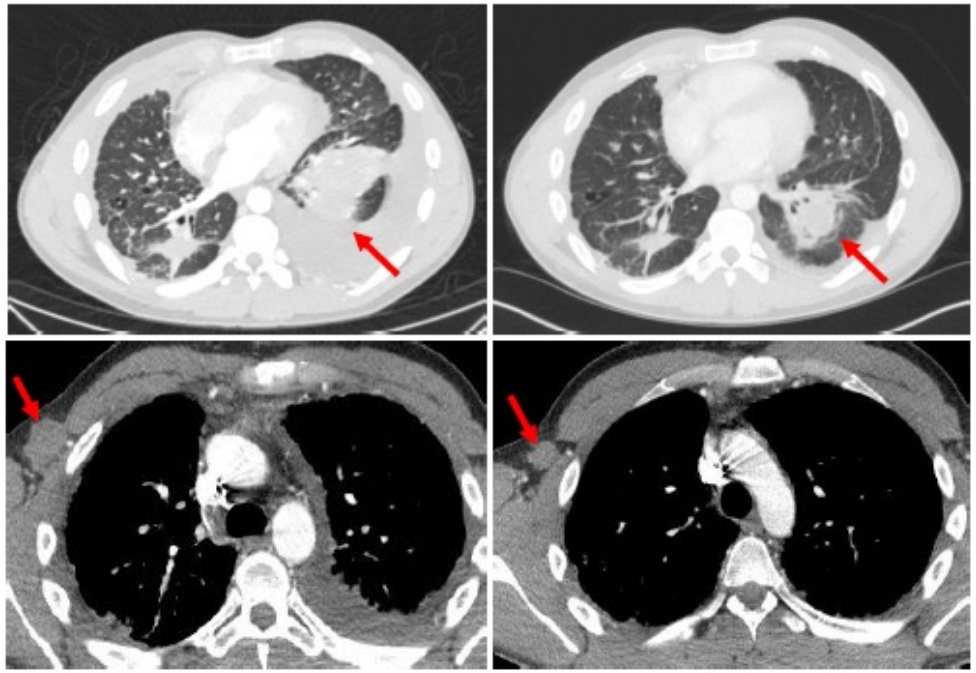


MET/CEP7 1.0 | MET/CEP7 5.2 | MET/CEP7 5.7

Dagogo-Jack I et al. Clin Cancer Res 2020;26:2535-45

Targeting MET-driven resistance to ALKi with dual ALK/MET blockade

Progression on **lorlatinib** | Response to **lorlatinib + criz**



Combinations (Investigational): Overcoming Off-Target ALKi Resistance

Resistance: Bypass Pathways in ALK+ NSCLC[1]

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.

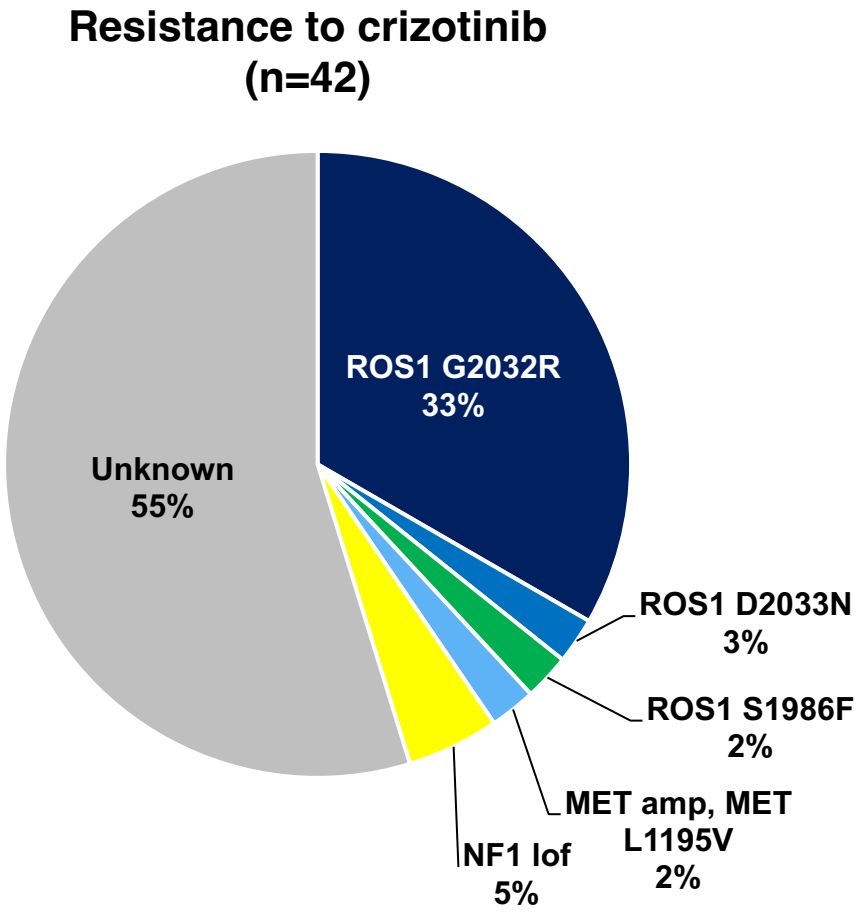
Summary of ongoing trials with combination therapy in ALK+ NSCLC[2]

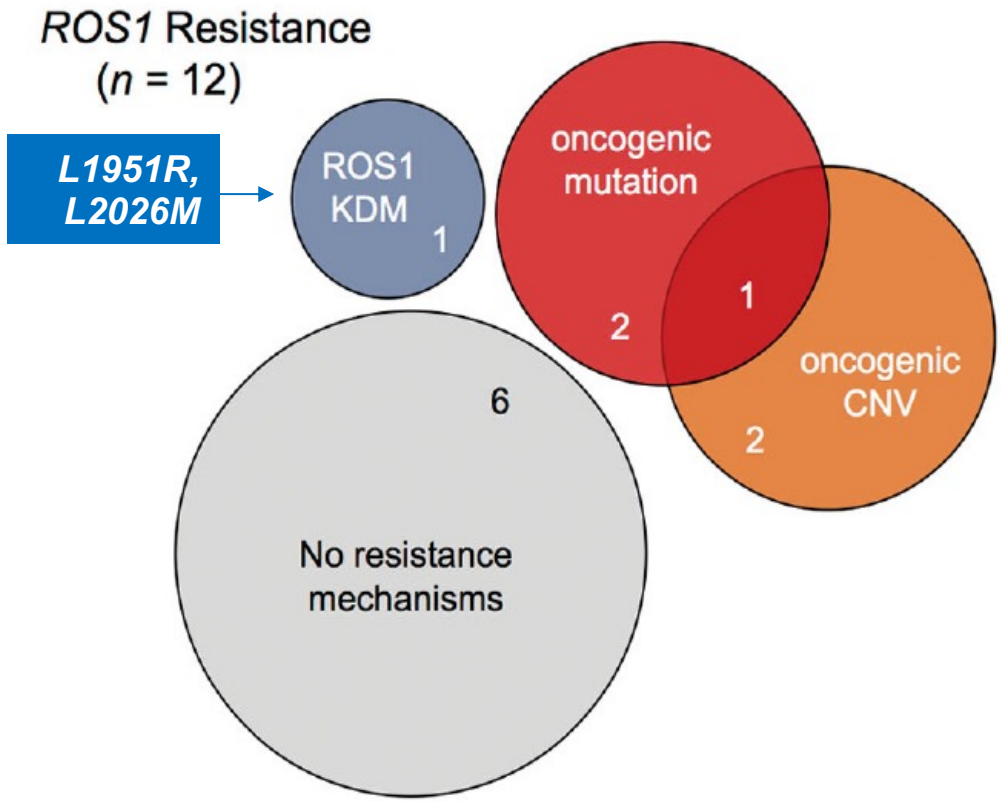
Clinical trial identifier	Drugs		Bypass pathway targeted	Phase	Biomarker required outside of ALK
	ALK TKI	Other agent			
NCT02321501	Ceritinib	Everolimus	mTOR	1	No
NCT03202940	Alectinib	Cobimetinib	MAPK (MEK)	1–2	No
NCT04005144	Brigatinib	Binimetinib	MAPK (MEK)	1	No
NCT04227028	Brigatinib	Bevacizumab	VEGF	1	No
NCT04292119	Lorlatinib	Binimetinib	MAPK (MEK)	1–2	No
		Crizotinib	MET		Yes (*MET* amplification)
		TNO155	SHP2		No
NCT04800822	Lorlatinib	PF-07284892	SHP2	1	No

mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

1Cooper AJ, Sequist LV, Lin JJ. Nat Rev Clin Oncol 2022;19(8):499-514
2Schneider JL, Lin JJ, Shaw AT. Nat Cancer 2023. In press

On-Target Resistance to 1L ROS1 Inhibitor (Crizotinib or Entrectinib)





Left: Lin JJ et al., Clin Cancer Res 2021;27:2899-909

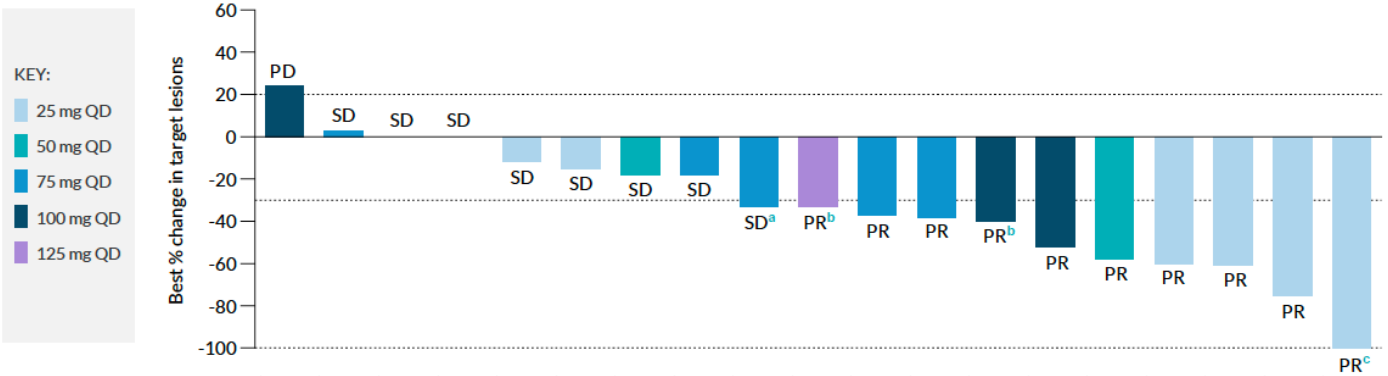
Right: McCoach CE et al., Clin Cancer Res 2018;24:3334-47

ROS1 TKIs with Activity in Crizotinib/TKI-Pretreated ROS1 Fusion+ NSCLC Demonstrated in Phase 2 Trials

	Lorlatinib (Phase 1/2)	Repotrectinib (TRIDENT-1 Phase 1/2)	Taletrectinib (TRUST Chinese Phase 2)
Patients	N=40	N=56	N=38
ORR	35%	38% (1 prior ROS1 TKI, no chemo)	50%
Median PFS	8.5 months	NR	NR
CNS activity	12/24 (50%) patients with measurable or nonmeasurable intracranial disease	5/12 (42%) patients with baseline measurable CNS metastases	11/12 (92%) patients with baseline measurable CNS metastases (TKI-naive and crizotinib-pretreated combined)
Clinical ROS1 G2032R activity	Response in 0/6 (0%) patients with a baseline ROS1 G2032R in plasma	Responses in 10/17 (59%) patients with a baseline ROS1 G2032R (1-2 prior ROS1 TKIs, +/- chemo)	Response in 4/5 (80%) patients with a baseline ROS1 G2032R
Most common treatment-related or treatment-emergent AEs (all grades)	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, cognitive effects, weight increased, dizziness, mood effects, lipase increased	Dizziness, dysgeusia, constipation, paresthesia, dyspnea, anemia, fatigue, nausea, muscular weakness, ataxia	Diarrhea, nausea, vomiting, ALT increase, AST increase, anemia, neutrophil count decrease
Reference	Shaw et al., Lancet Oncol 2019	Cho et al., AACR-NCI-EORTC 2022	Li W et al., ASCO 2022

NVL-520: Brain-Penetrant, ROS1-Selective, TRK-Sparing TKI Preliminary Efficacy and Safety from the Phase 1 ARROS-1 Trial

	All Response-Evaluable	ROS1 G2032R Resistance Mutation	History of CNS Metastases	≥2 Prior ROS1 TKI and ≥1 Chemotherapy	Prior Lorlatinib or Repotrectinib [d]
NSCLC Response-Evaluable Patients	n = 21	n = 9	n = 11	n = 17	n = 18
ORR (RECIST 1.1)	10 (48%)	7 (78%)	8 (73%)	9 (53%)	9 (50%)



Dose Level Cohort (mg QD)	100	75	100	125	25	25	50	75	75	125	75	75	100	100	50	25	25	25	25
Prior ROS1 TKI	1	1	3[d]	2	1	2	2	2	2	3[d]	2	2	2	2	2	2	2	1	2
Crizotinib			•	•				•		•	•	•	•	•		•	•	•	•
Entrectinib	•					•	•	•	•						•				
Lorlatinib			•	•					•	•		•	•	•		•	•		•
Repotrectinib		•			•	•	•				•				•				
Prior lines, chemotherapy	3	1	6	1	0	2	3	1	1	2	1	1	2	2	1	2	1	0	3
Prior lines, anticancer therapy [e]	3	2	11	3	1	4	6	3	3	6	3	4	4	4	3	5	4	2	6

Data as of 13 Sep 22, for response-evaluable patients with NSCLC treated by 01 Sep 2022. Two patients (25 mg QD and 125 mg QD dose cohorts, both with prior therapies consisting of crizotinib, lorlatinib and chemotherapy) not shown due to incomplete or missing post-baseline tumor assessments in the setting of PD and symptomatic deterioration. PD, progressive disease, PR, partial response, QD, once daily; SD, stable disease; TKI, tyrosine kinase inhibitor. [a] Single-timepoint PR not confirmed. [b] Ongoing partial responses pending confirmation. [c] Best response PR due to residual nontarget disease. [d] Additional prior ROS1 TKI was ceritinib. [e] Including immunotherapy, bevacizumab, and investigational therapy.

Treatment-Related Adverse Events (TRAEs) in >1 Patient

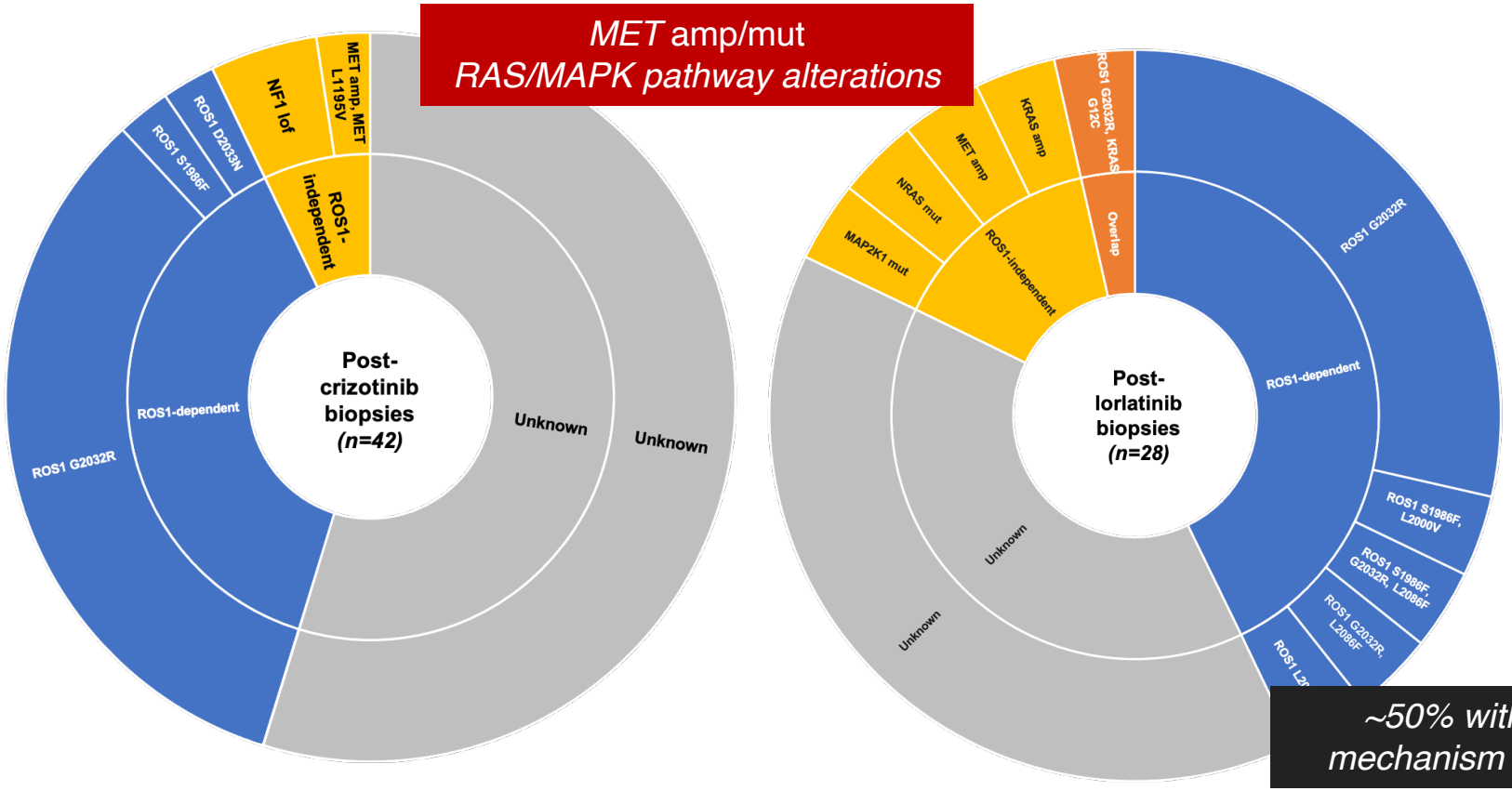
All Treated Patients (N = 35)

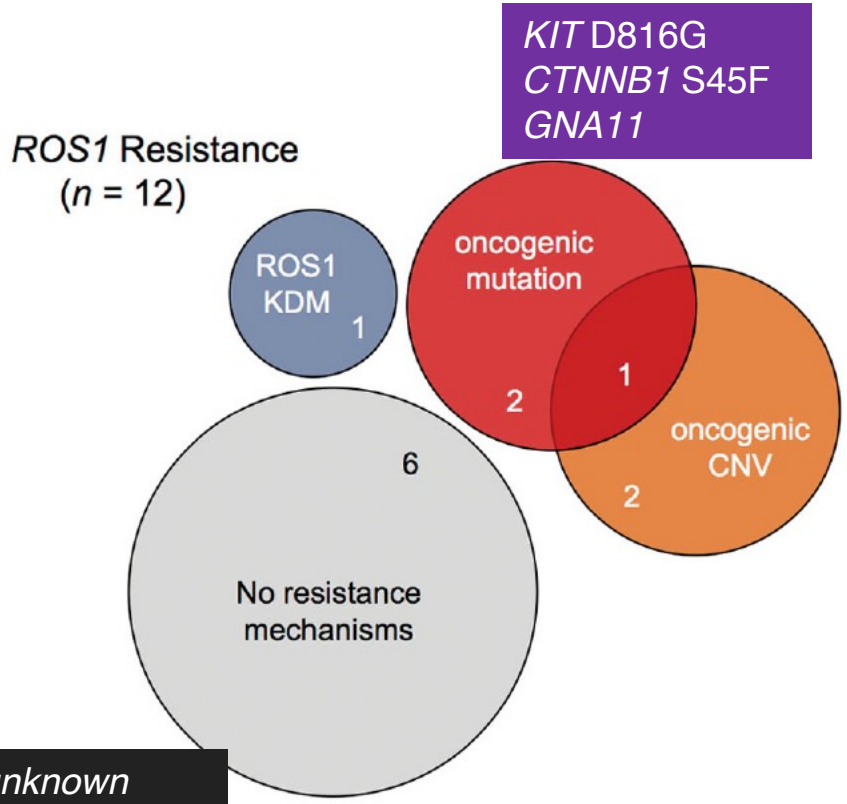
	Grade 1 n (%)	Grade 2 n (%)	Grade ≥3 n (%)	Any Grade N (%)
Fatigue	4 (11%)	-	-	4 (11%)
Nausea	3 (9%)	-	-	3 (9%)
ALT increased	2 (6%)	-	-	2 (6%)
AST increased	2 (6%)	-	-	2 (6%)
Oedema [a]	1 (3%)	1 (3%)	-	2 (6%)
Myalgia	2 (6%)	-	-	2 (6%)

- No DLTs
- No treatment-related SAEs
- No AEs leading to dose reduction or discontinuation
- No treatment-related dizziness

Drilon A et al., EORTC-NCI-AACR 2022

Off-Target Resistance to ROS1 Inhibitors





Left: Lin JJ et al., Clin Cancer Res 2021;27:2899-909

Right: McCoach CE et al., Clin Cancer Res 2018;24:3334-47

Histologic Transformation and Lineage Change: A Shared Mechanism of Resistance Across Lung Cancer

Prior ALK TKI	Reference
Crizotinib, ceritinib, brigatinib, lorlatinib	Coleman N et al., Lung Cancer 2019
Crizotinib	Zhu Y et al., Onco Targets Ther 2017
Ceritinib, alectinib, lorlatinib	Ou S et al., Lung Cancer 2017
Crizotinib, ceritinib	Levacq D et al., Lung Cancer 2016
Crizotinib, alectinib	Takegawa N et al., Ann Oncol 2016
Crizotinib	Caumont C et al., Lung Cancer 2016
Crizotinib	Cha YJ et al., J Thorac Oncol 2016
Crizotinib, alectinib	Fujita S et al., J Thorac Oncol 2016
Crizotinib, alectinib	Miyamoto S et al., Jpn J Clin Oncol 2016

Frequencies of small cell transformation in ALK/ROS1 fusion lung cancers appear low*:

1.2% (2/168) ALK+ lung cancer resistant to next-gen ALK TKI(s)

1.5% (1/65) ROS1 fusion+ lung cancer resistant to ROS1 TKI(s)

*Likely representing underestimates given the overall low prevalence of re-biopsies following disease progression

Lin JJ et al., NPJ Precis Oncol 2020;4:21

Summary

- ALK and ROS1 fusion-positive lung cancers represent disease subsets in which we have highly effective targeted therapies available

- Upon disease progression due to resistance to the first-line ALK or ROS1 inhibitor, we often have the ability to sequence TKIs, using next-generation TKIs, which may have:
  - Coverage of on-target resistance driver mutations
  - Superior CNS penetration and activity

- Re-biopsies can be helpful in determining the mechanism of resistance (e.g., actionable on-target resistance mutation versus off-target mechanism) and refining the range of subsequent therapeutic options