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Novel Mechanisms of Resistance for ALK and ROS1 NSCLC

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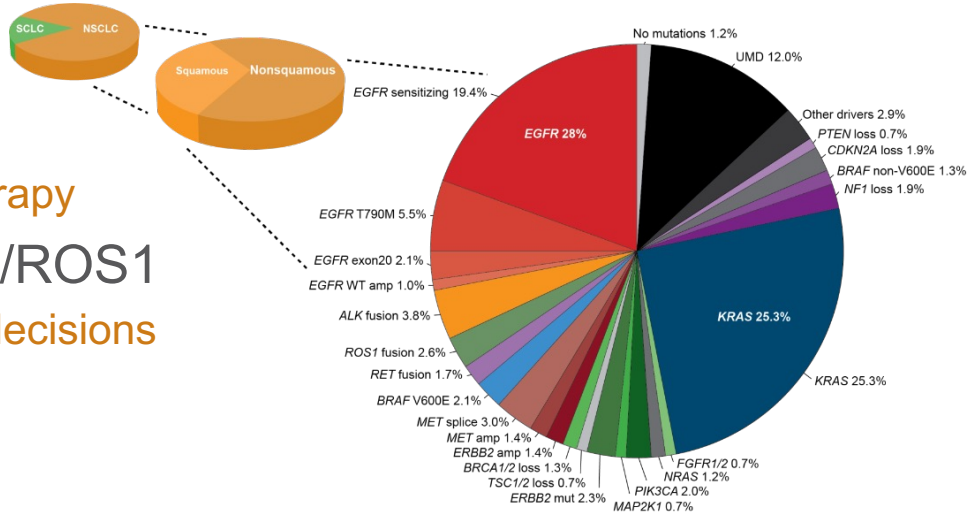
ALK and ROS1 NSCLC

- ALK and ROS1 fusions are important genomic events
  - Define biology
  - Guide treatment
    - To targeted therapy
    - Away from immunotherapy
  - Critical to test for ALK/ROS1
    - Necessary for proper decisions



Jordan, Cancer Disc 2017

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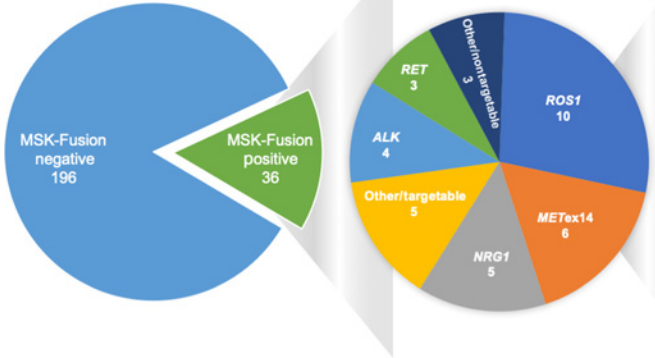
ALK and ROS1 NSCLC

- ALK fusions present in ~5% of advanced NSCLC
  - First described in 2007 in lung cancer
  - EML4–ALK most prevalent partner
- ROS1 fusions present in 1-2% of NSCLC
  - 2.4% in adenocarcinoma, 0.2% in non-adenocarcinoma
  - More common in non-smokers
- Validated therapeutic targets in NSCLC
  - Detection critical for proper management

Pacheco, JTO 2019

Detection of ROS1+

- RNA may be advantageous
  - 254 driver negative NSCLC cases subject to RNA-seq
    - Identified actionable alteration in 13% of cases, most frequently ROS1
      - Intron 31 poorly covered, two long interspersed nuclear elements



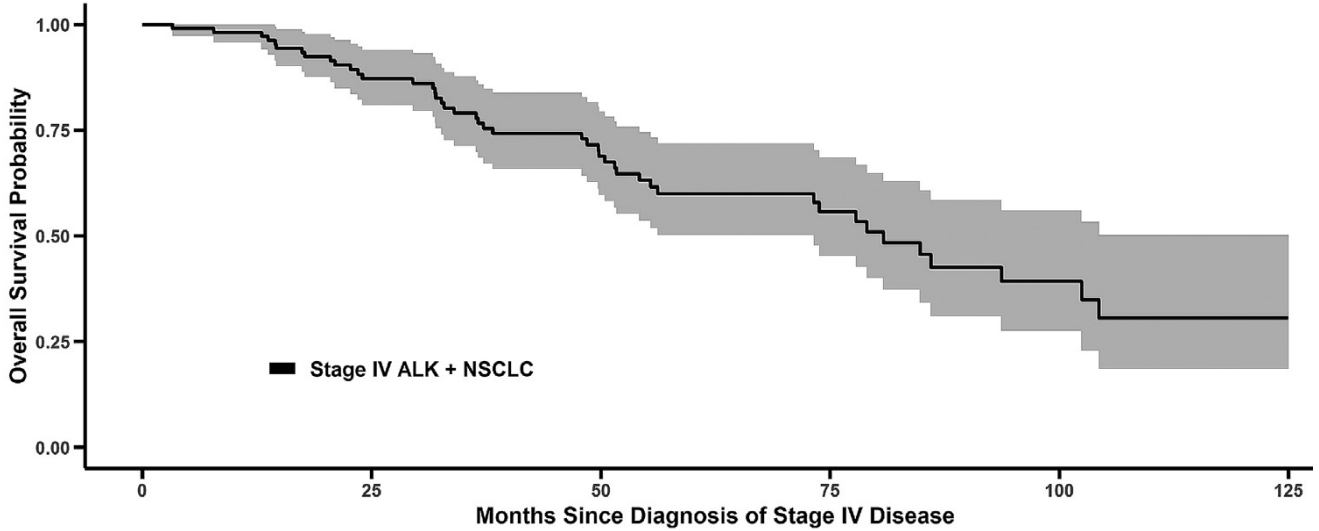
Clinical benefit of matched targeted therapy
(*n* = 10)

Rearrangement	Matched therapy	Best response*
EML4-ALK	Alectinib	SD
CD74-ROS1	Entrectinib	SD
SQSTM1-NTRK3	Larotrectinib	PR**
STRN-NTRK2	Larotrectinib	SD
CD74-ROS1	Entrectinib	PR**
CD74-NRG1	Afatanib	SD
MET Exon14 Skipping	Crizotinib	SD
SLC34A2-ROS1	Crizotinib	PD
SLC34A2-ROS1	Crizotinib	SD
SDC4-NRG1	Afatinib	PD

Benayed, CCR 2019; Davies, CCR 2019

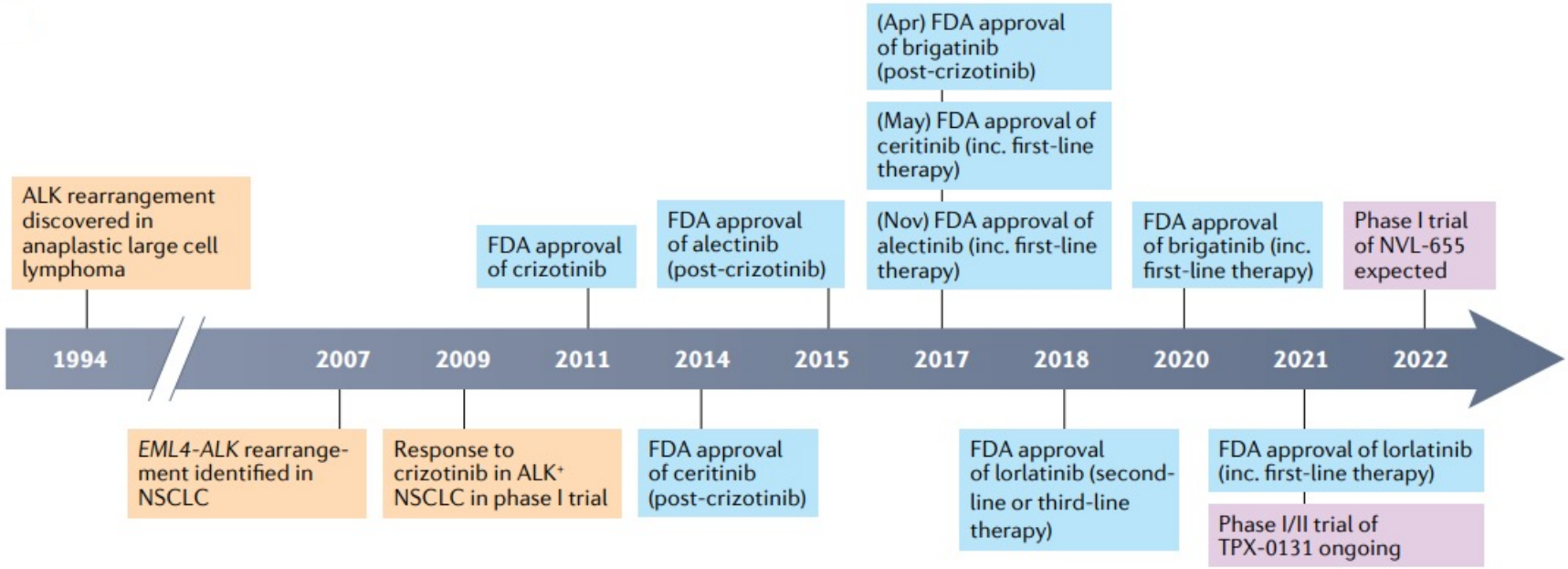
Survival in ALK+ NSCLC

- Median OS from diagnosis 81 months (6.8 years)
  - University of Colorado, 2009-2017



Pacheco, JTO 2019

ALK+ NSCLC: Speed of Development



Cooper, Nat Rev Clin Oncol 2022

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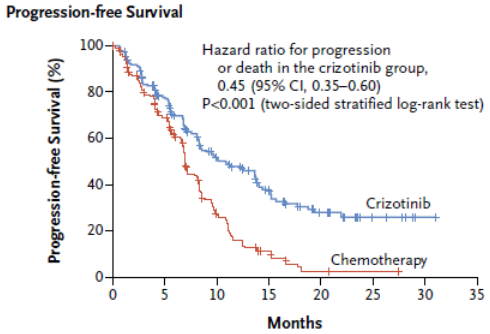
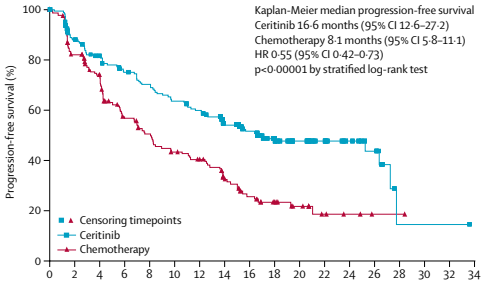
Early Generation Agents

- Crizotinib and Ceritinib > Chemotherapy

Study	ALK+, n	Treatment	RR, %	PFS, months	PFS HR
PROFILE 1014 *Solomon, 2014*	343	Crizotinib Platinum/pemetrexed	74.0 45.0	10.9 7.0	HR 0.45
ASCEND-4 *Soria, 2017*	376	Ceritinib Platinum/pemetrexed	72.5 26.7	16.6 8.1	HR 0.55





Solomon, NEJM 2014; Soria, Lancet 2017

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CNS as Site of First Progression

- Crizotinib
  - Retrospective analysis of PROFILE 1005 and 1007
  - Patients with untreated brain metastases at baseline
    - In patients with nontarget or new lesions as PD, CNS progression in 70%
  - Patients with treated brain metastases at baseline
    - In patients with nontarget or new lesions as PD, CNS progression in 72%
  - Patients with no brain metastases at baseline
    - CNS metastases developed in 20% of patients (median of 30 weeks)
  - Randomized trials
    - CNS progression ~ 45%

Costa, JCO 2015

Next Generation Agents

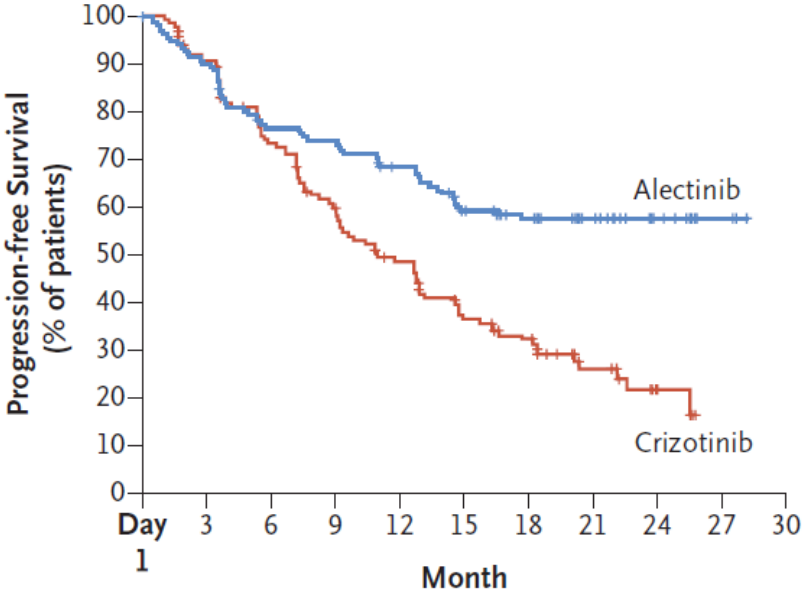
- Developed to overcome resistance, high CNS efficacy
  - Alectinib
  - Brigatinib
  - Lorlatinib
- All superior PFS over crizotinib in phase III trial
- All FDA approved as initial and subsequent therapy

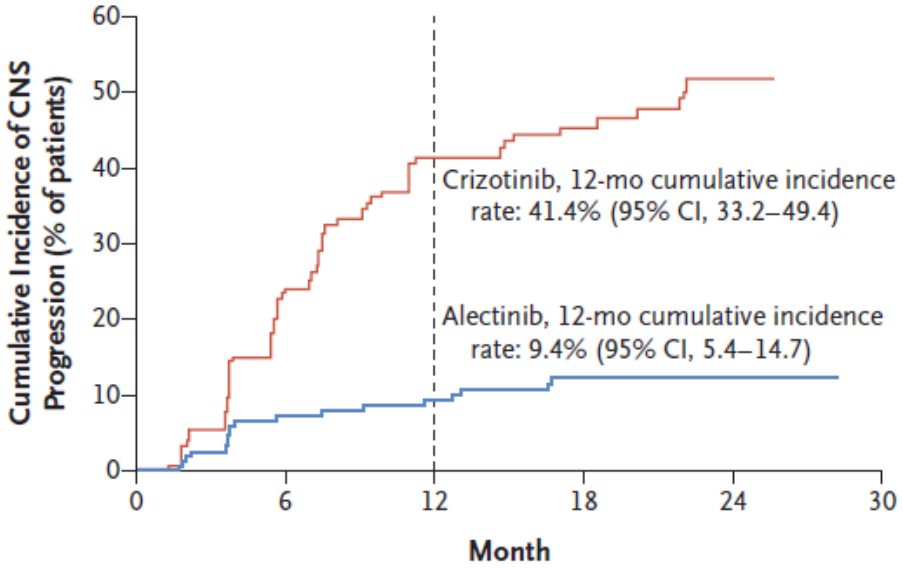
ALEX: Alectinib

- 303 patients randomized to alectinib or crizotinib
  - ALK+ by Ventana ALK D5F3 IHC
  - No prior systemic therapy
  - Brain metastases permitted
- Alectinib superior
  - Median f/u 18.6 months
  - Investigator PFS HR 0.47
  - IRC PFS 25.7 vs 10.7 months
    - HR 0.50

Peters, NEJM 2018

ALEX: Alectinib





November 7, 2017: FDA approval

Alectinib approved as first-line therapy for ALK+ NSCLC

Peters, NEJM 2018

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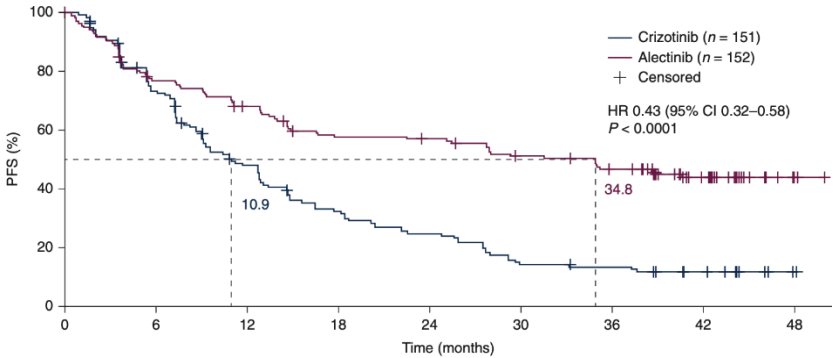
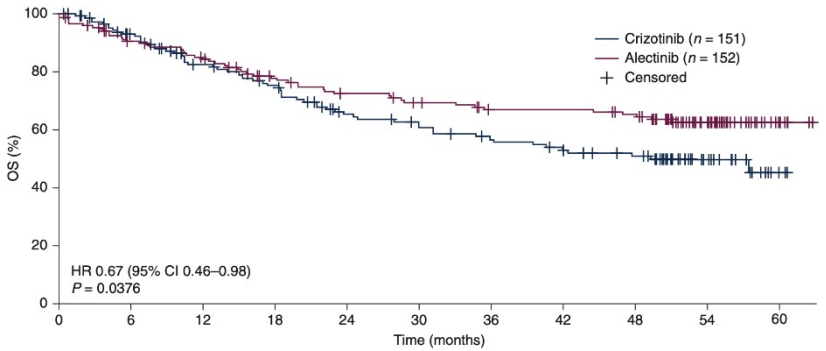
ALEX: Alectinib

- Alectinib 600mg bid vs crizotinib
  - Alectinib with superior RR and inv PFS (HR 0.43)
  - 5y OS rate 62.5% vs 45.5%, OS HR 0.67

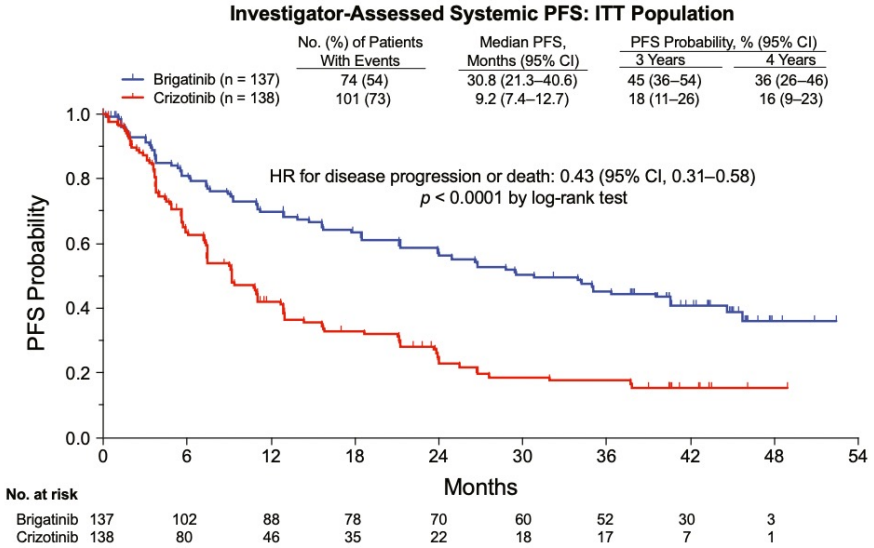




Mok, Ann Oncol 2020

ALTA-1L: Brigatinib

- Brigatinib 180mg qday vs crizotinib
  - Brigatinib with superior RR and inv PFS (HR 0.43)



Camidge, JTO 2021

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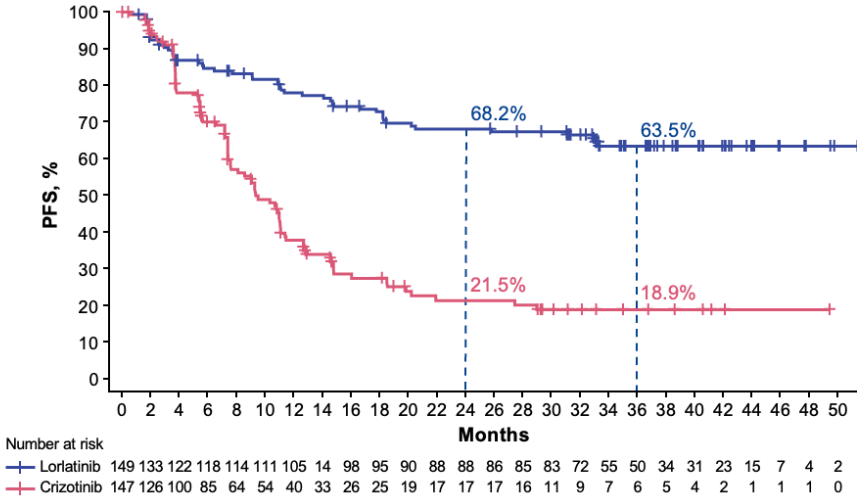
CROWN: Lorlatinib

- Lorlatinib 100mg qday vs crizotinib
  - Lorlatinib with superior RR and PFS (HR 0.27)
  - 3y PFS rate 63.5% vs 18.9%



Solomon, AACR 2022

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Next Generation ALK Inhibitors

Study *(ref)*	Treatment	n	RR (%)	PFS (inv, m)	PFS HR
ALEX *Mok, Ann Oncol 2018*	Alectinib 600mg bid Crizotinib 250mg bid	152 151	82.9 75.5	34.8 10.9	0.43
ALTA 1L *Camidge, JTO 2021*	Brigatinib 180mg qday Crizotinib 250mg bid	137 138	74 62	30.8 9.2	0.43
CROWN *Solomon, AACR 2022*	Lorlatinib 100mg qday Crizotinib 250mg bid	149 147	77.2 58.5	NR 9.3	0.27

Adverse Events

ALK Inhibitor	Rate of Dose Reduction	Rate of Discontinuation	Rate of Grade 3+ Adverse Events
Ceritinib 750mg qday ASCEND-4 *Soria et al, Lancet Oncol 2017*	80%	5%	78%
Alectinib 600mg bid ALEX *Mok et al, Ann Oncol 2020*	20%	15%	52%
Brigatinib 180mg qday ALTA-1L *Camidge et al, JTO 2021*	44%	13%	70%
Ensartinib 225mg qday eXalt3 *Horn et al, JAMA Oncol 2021*	24%	9%	45%
Lorlatinib 100mg qday CROWN *Shaw et al, NEJM 2020*	21%	7%	58%

Adverse Events

ALK Inhibitor	Rate of Dose Reduction	Rate of Discontinuation	G3+ AST	G3+ ALT	G3+ Nausea	G3+ Diarrhea
Ceritinib 750mg qday ASCEND-4 *Soria et al, Lancet Oncol 2017*	80%	5%	17%	31%	3%	5%
Alectinib 600mg bid ALEX *Mok et al, Ann Oncol 2020*	20%	15%	5%	5%	1%	1%
Brigatinib 180mg qday ALTA-1L *Camidge et al, JTO 2021*	44%	13%	4%	4%	2%	2%
Ensartinib 225mg qday eXalt3 *Horn et al, JAMA Oncol 2021*	24%	9%	1%	4%	1%	-
Lorlatinib 100mg qday CROWN *Shaw et al, NEJM 2020*	21%	7%	2%	3%	1%	1%

Adverse Events

ALK Inhibitor	Rate of Dose Reduction	Rate of Discontinuation	Special Toxicity Considerations
Ceritinib 750mg qday ASCEND-4 *Soria et al, Lancet Oncol 2017*	80%	5%	Discontinuation rates likely quite different in real world practice and in current treatment landscape. Alternate dosing schedules better tolerated.
Alectinib 600mg bid ALEX *Mok et al, Ann Oncol 2020*	20%	15%	Any grade AST/ALT elevation in 17%/18% Any grade bilirubin elevation in 22% Any grade myalgias in 17%
Brigatinib 180mg qday ALTA-1L *Camidge et al, JTO 2021*	44%	13%	EOPE with changes in DLCO Any grade pneumonitis seen in 6% of patients G3+ CPK elevation in 26%
Ensartinib 225mg qday eXalt3 *Horn et al, JAMA Oncol 2021*	24%	9%	Any grade rash in 59% G3+ rash in 11% Any grade pyrexia in 20%
Lorlatinib 100mg qday CROWN *Shaw et al, NEJM 2020*	21%	7%	G3+ hypercholesterolemia in 16% G3+ weight gain in 17% Any grade cognitive effects in 21%, G3+ in 2%

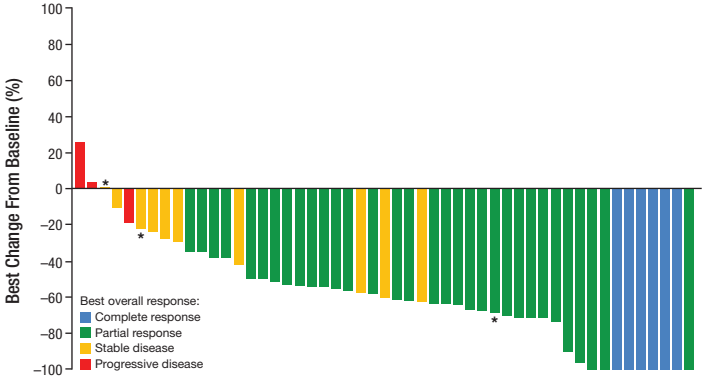
Treatment for ROS1+ NSCLC

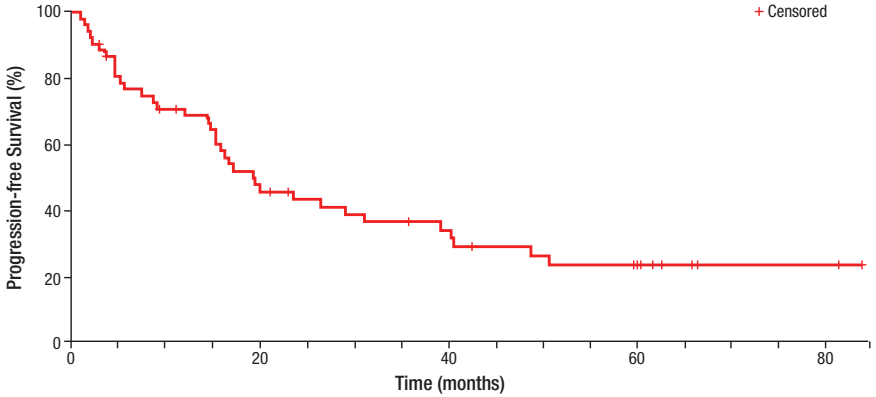
- Kinase domain has > 75% homology with ALK
  - Many ALK inhibitors are ROS1 inhibitors
  - Not all ALK inhibitors are ROS1 inhibitors
- Crizotinib is a multikinase inhibitor
  - ROS1, ALK, MET
- Phase I PROFILE 1001 study
  - Added ROS1 cohort in 2009
  - Crizotinib 250mg bid
  - Enrolled 50 patients (October 2010 – August 2013)

Shaw, NEJM 2014

Crizotinib

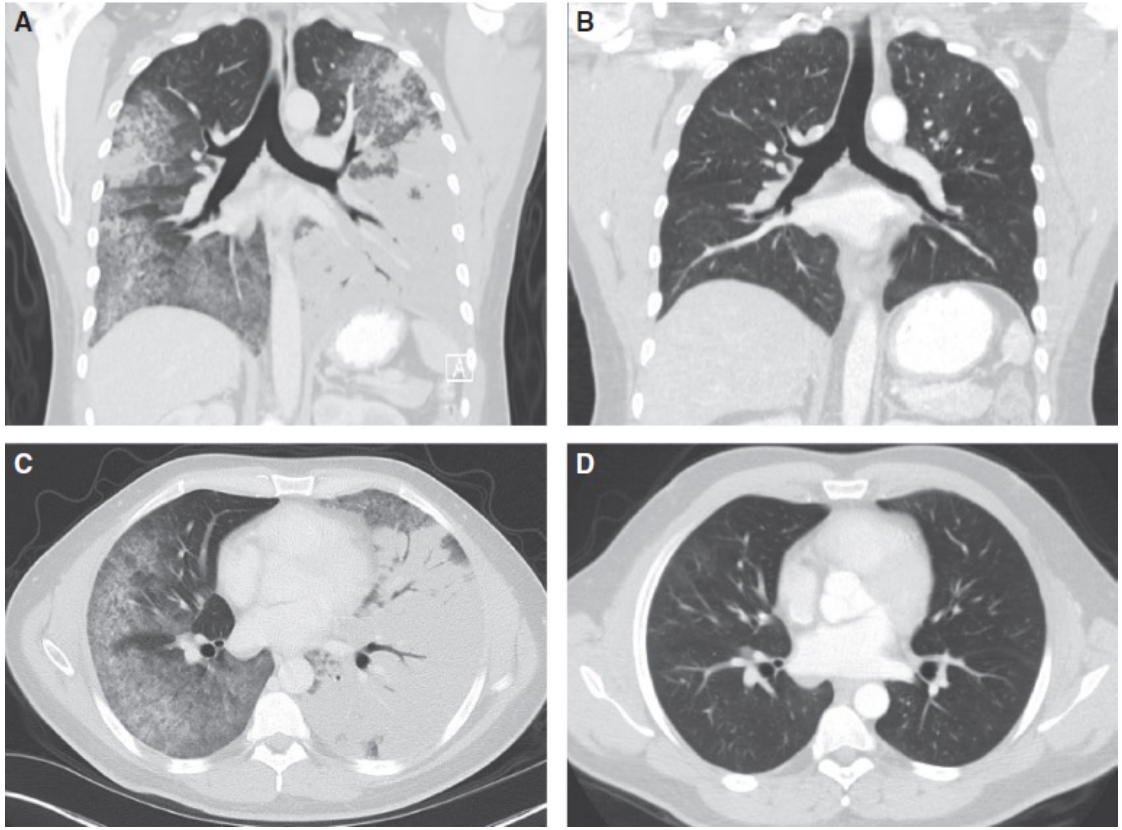
- Overall response rate 72%
  - Time to first response: 7.9 weeks
  - Duration of response 24.7 months
  - Median PFS 19.3 months





Shaw, Ann Oncol 2019

ROS1+ NSCLC Key Points



Shaw, NEJM 2014

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ROS1 and CNS

- Incidence of CNS metastases not well defined
  - Not consistently reported in early trials
  - Prospective trials note CNS metastases in 18-58%
  - MGH comparison of ROS1 (39) and ALK (196) NSCLC treated with crizotinib
    - Brain metastases at diagnosis: 19.4% (ROS1) vs 39.1% (ALK)
    - Cumulative risk at 5 years: 34% (ROS1) vs. 73% (ALK)
  - Colorado comparison of ROS1 (33) and ALK (115) NSCLC treated with crizotinib
    - Brain metastases at diagnosis: 36% (ROS1) vs 34% (ALK)
    - Brain as 1st site of progression in 47%

Ou, Lung Cancer 2019; Gainor, JCO PO 2018; Patil, JTO 2018

Crizotinib

- Real world data with crizotinib in ROS1+ NSCLC
  - Single institution retrospective analysis
  - 35 patients from Fudan University, Shanghai Cancer Center
  - 23% with brain metastases
  - RR 71.4%
  - PFS 11.0 months
  - OS 41.0 months
- Most common site of progression was brain (47.6%)
- Crizotinib FDA approved for ROS1+ NSCLC 3/11/16

Liu, Target Oncol 2019

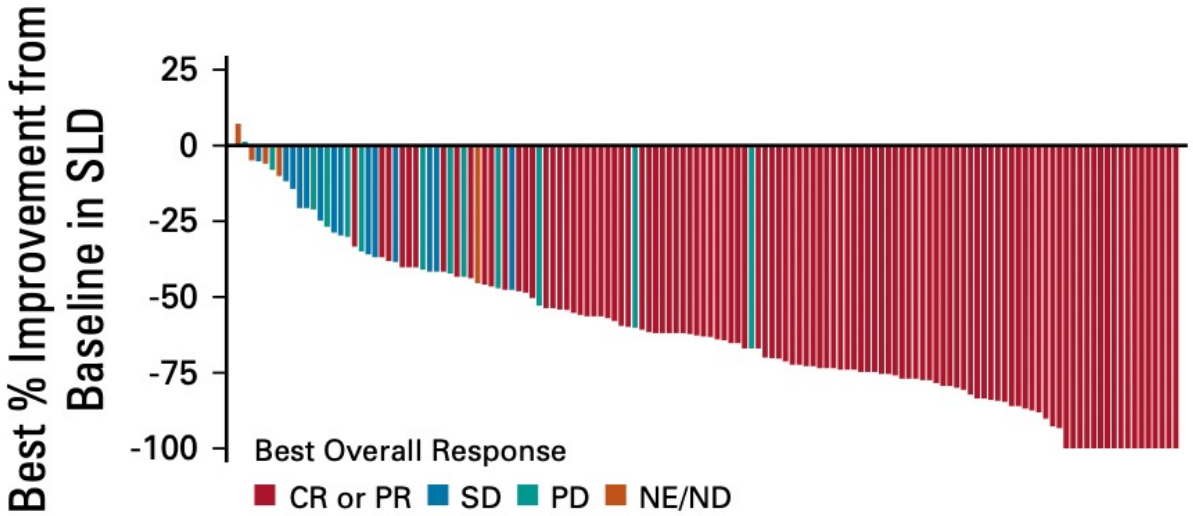
Entrectinib

- Entrectinib is a potent multikinase inhibitor
  - Activity at ROS1, TRK, ALK
  - Highly CNS penetrant
- Integrated analysis of 3 clinical trials
  - ALKA-372-001 (Phase I)
  - STARTRK-1 (Phase 1)
  - STARTRK-2 (Phase 2)
- Included 161 patients with ROS1 fusion+ NSCLC
  - Entrectinib 600mg daily

Dziadziuszko, JCO 2021

Entrectinib

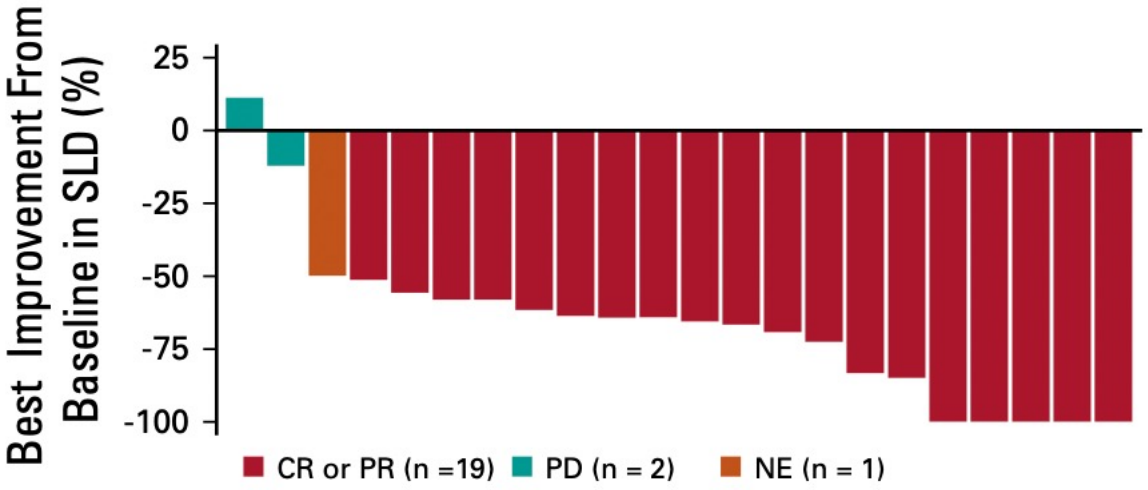
- RR 67.1% (9% CR), mDOR 15.7m, mPFS 15.7m
- mOS not reached, 12m OS rate 81%



Dziadziuszko, JCO 2021

Entrectinib

- BICR of scans from pts with measurable CNS mets
  - Intracranial RR 79.2% (12.5% CR)
  - Median time to response < 1m, intracranial PFS 8.3m



Dziadziuszko, JCO 2021

Entrectinib

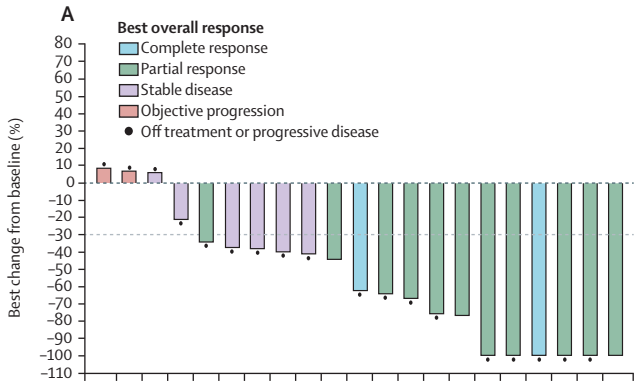
- Monitor for toxicity
  - Often mediated by NTRK
  - Paresthesias, dizziness
  - Weight gain, polyphagia
  - Withdrawal pain
- FDA approval 8/15/19

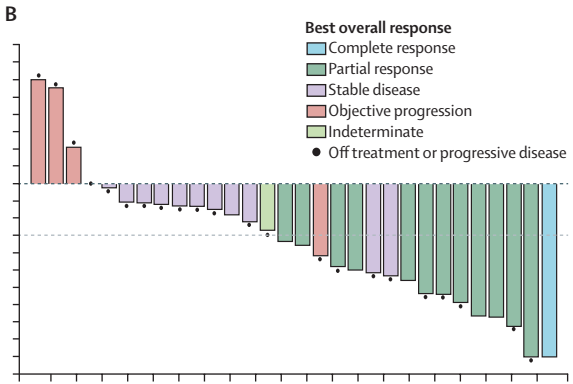
Treatment-Related Adverse Event	*ROS1* Fusion–Positive Safety-Evaluable Population[a] (N = 210)		
Patients, n (%)	**Grades 1-2**	**Grade 3**	**Grade 4**
Dysgeusia	90 (42.9)	1 (0.5)	0
Dizziness	72 (34.3)	1 (0.5)	0
Constipation	66 (31.4)	0	0
Fatigue	62 (29.5)	1 (0.5)	0
Diarrhea	50 (23.8)	6 (2.9)	0
Weight increased	43 (20.5)	17 (8.1)	0
Paresthesia	39 (18.6)	0	0
Blood creatinine increased	38 (18.1)	1 (0.5)	0
Nausea	37 (17.6)	2 (1.0)	0
Edema peripheral	37 (17.6)	1 (0.5)	0
Myalgia	33 (15.7)	2 (1.0)	0

Dziadziuszko, JCO 2021; Liu, Ann Oncol 2020

Lorlatinib

- 3rd generation ALK/ROS1 kinase inhibitor
  - Enrolled 69 patients w/ ROS1+ NSCLC (Jan 2014 – Oct 2016)
    - 21 TKI naïve, 40 post-crizotinib, 8 with other/further ROS1 TKI therapy
  - ROS1 TKI naïve, RR 62%, DOR 25.3m, PFS 21m
  - Post crizotinib, RR 35%, DOR 13.8m, PFS 8.5m





Shaw, Lancet Oncol 2019

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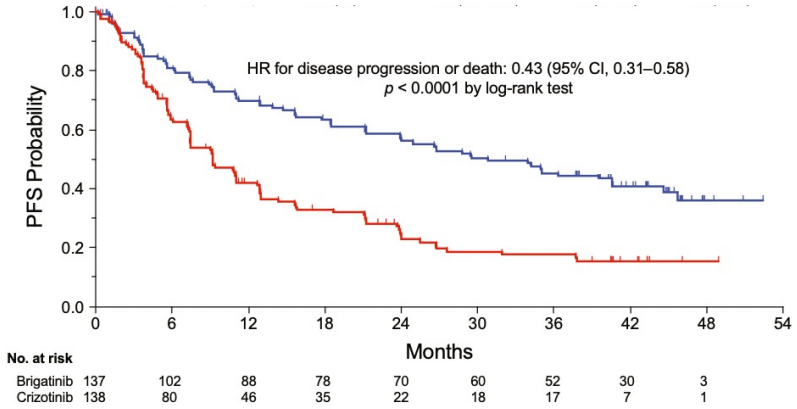
ALK and ROS1 NSCLC

- ALK inhibitors approved for ALK+ NSCLC
  - Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib
- ROS1 inhibitors approved for ROS1+ NSCLC
  - Crizotinib, entrectinib



- Very effective and more durable than many other targeted agents
- Resistance still expected

Camidge, JTO 2021

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ALK and ROS1 TKI Resistance

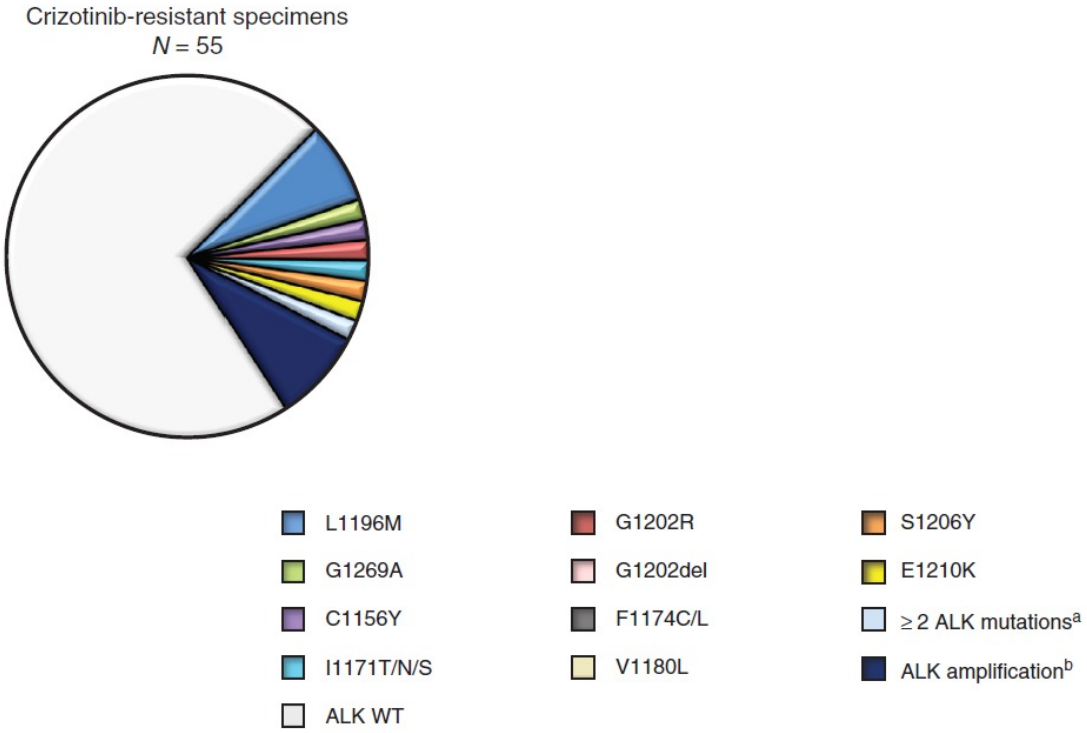
- CNS-only resistance
  - Potentially a PK problem
- Solutions
  - Increase dose?
  - Change to a more CNS-penetrant agent
  - Local therapies

ALK and ROS1 TKI Resistance

- Kinase-dependent resistance
  - ALK/ROS1 amplification
  - ALK/ROS1 mutation
- Next-generation ALK/ROS1 kinase inhibitors
  - Rational design to overcome resistance mutations

Lovly, ASCO 2018

ALK TKI Resistance



Gainor, Cancer Disc 2017

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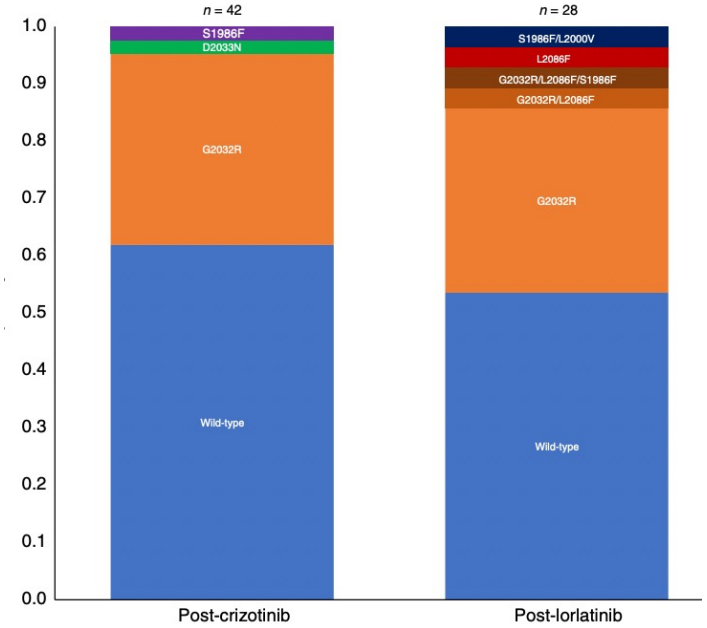
ROS1 TKI Resistance

- 42 post-crizotinib
  - 38% with ROS1 mutations
- 28 post-lorlatinib
  - 46% with ROS1 mutations
- ROS1 G2032R in ~ 1/3



Lin CCR 2021

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Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

ALK Variant	TKI Activity, IC_{50} (nM)			
	Crizotinib 250 mg twice daily	Ceritinib 750 mg once daily	Alectinib 600 mg twice daily	Brigatinib 180 mg once daily
Native	107	37	25	14
1151Tins	1109[b]	283	201	114
L1152R	844[b]	437[b]	62	11
L1152P	721	451	48	20
C1156Y	529[b]	195	67	45
I1171N	532[b]	119	724[b]	124
F1174C	238	109[b]	31	58
F1174L	253[b]	117	44	55
F1174V	257[b]	121[b]	46	64
V1180L	170	16	597	11
L1196M	589[b]	67	133	41
L1198F	17	697	84	82
G1202R	617[b]	354[b]	695[b]	184
D1203N	459[b]	159	42	79
S1206F	199[b]	39	34	43
S1206Y	179[b]	42	19	36
E1210K	240	80	59	107
G1269A	509[b]	29	56	9

Gainor, Cancer Disc 2017; Kim, JCO 2016

ROS1 TKI Resistance

IC_{50} (nmol/L)	Crizotinib	Entrectinib	Lorlatinib	Repotrectinib	Cabozantinib	Ceritinib	Brigatinib	Taletrectinib	Alectinib
Parental	840.5	1,801.0	>3,000	1,218.0	>3,000	1,117.0	>3,000	>3,000	1,207.0
Nonmutant	5.4	2.7	0.7	2.0	2.8	16.4	9.4	2.6	995.4
G2032R	609.6	436.3	196.6	23.1	17.5	346.4	472.7	53.3	1,091.0
L2000V	37.1	25.9	2.5	10.1	7.6	124.9	78.9	29.8	985.0
L2086F	536.8	440.0	>3,000	587.9	3.6	226.9	159.3	1,265.0	672.5
S1986F/L2000V	159.4	36.1	2.4	7.2	5.1	86.9	62.5	20.3	1,080.0
S1986F/L2086F	469.7	344.2	>3,000	241.2	1.3	154.8	48.5	662.6	919.9
G2032R/L2086F	498.6	335.4	>3,000	248.9	5.0	573.9	450.9	744.2	1,254.0
S1986F/G2032R	594.4	718.5	990.6	65.1	70.1	614.7	717.0	105.4	1,137.0
S1986F/G2032R/L2086F	562.8	1,111.0	2,131.0	1,178.0	9.4	1,116.0	1,341.0	2,432.0	1,150.0

$IC_{50} \leq 50$ nmol/L

50 nmol/L < IC_{50} <200 nmol/L

$IC_{50} \geq 200$ nmol/L

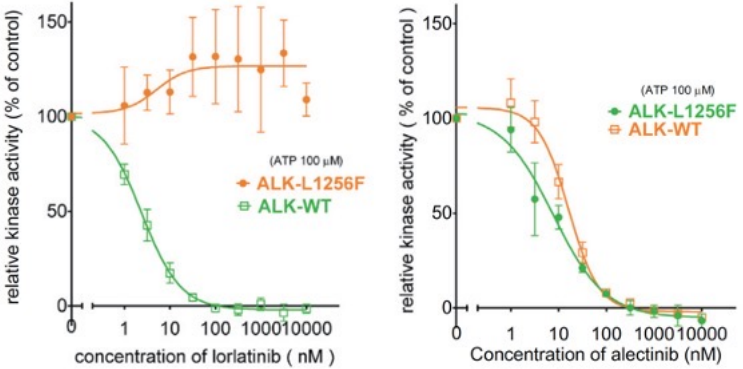
Lin CCR 2021

Georgetown | Lombardi

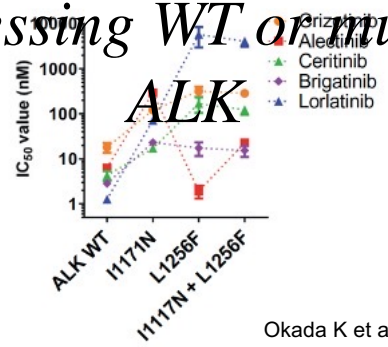
Landscape of Mechanisms of Resistance to 1L Lorlatinib Remains to Be Determined

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

In vitro kinase



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

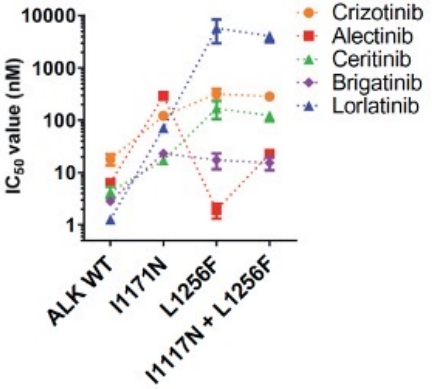


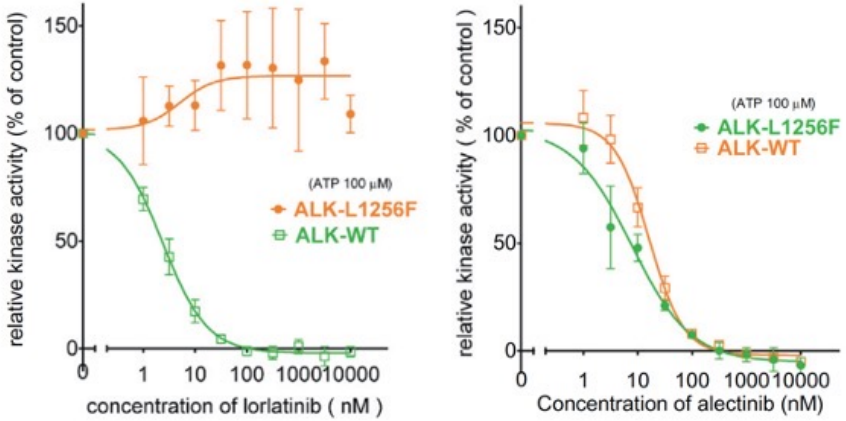
Okada K et al., EBioMed 2019;41:105-19

After 1L lorlatinib in CROWN, 21 of 33 patients (63.6%) who received ≥ 1 subsequent therapy received an ALK TKI (alectinib, 12), of whom 6 (28.6%) had objective responses *(Solomon BJ et al., ASCO 2022)*

ALK TKI Resistance

- ALK L1256F mutation
  - Confers resistance to lorlatinib
  - Still retains sensitivity to alectinib





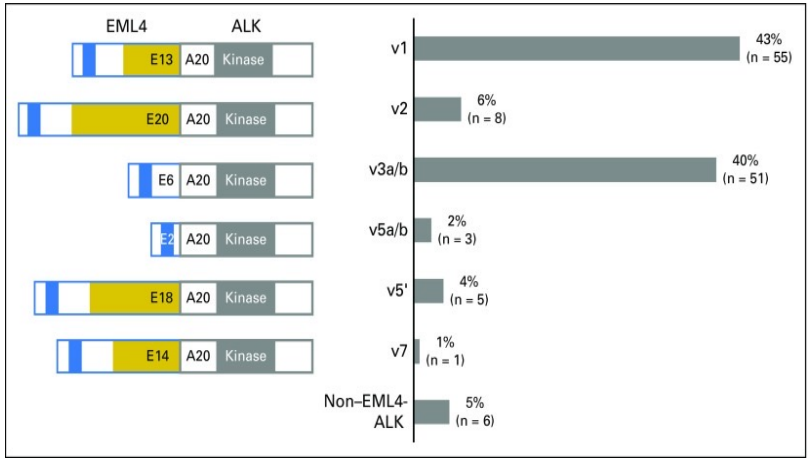
Lin, NACLC22, Okada, EBioMed 2019,

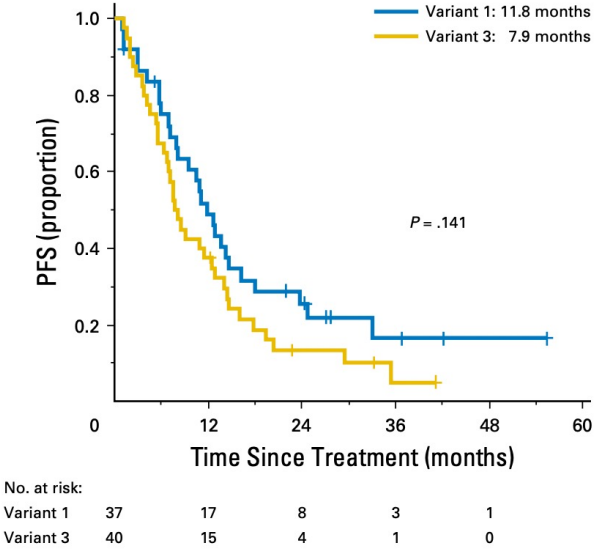
ALK/ROS1 TKI Resistance

- Identification of acquired solvent front mutations possible with biopsy or plasma testing
  - Challenges
    - Heterogeneity (intratumor, intertumor)
    - Clinical relevance (mostly preclinical)
    - Practical concerns: risk of biopsy, time, cost (NGS), sensitivity
  - May help guide therapy in the future
    - Is it necessary? Is it helpful?
  - Can we predict mutations and anticipate resistance?

ALK Variants

- Many different EML4–ALK fusion variants
  - Variants 1 and 3 most common
  - Variant impacts outcomes





Lin, JCO 2018

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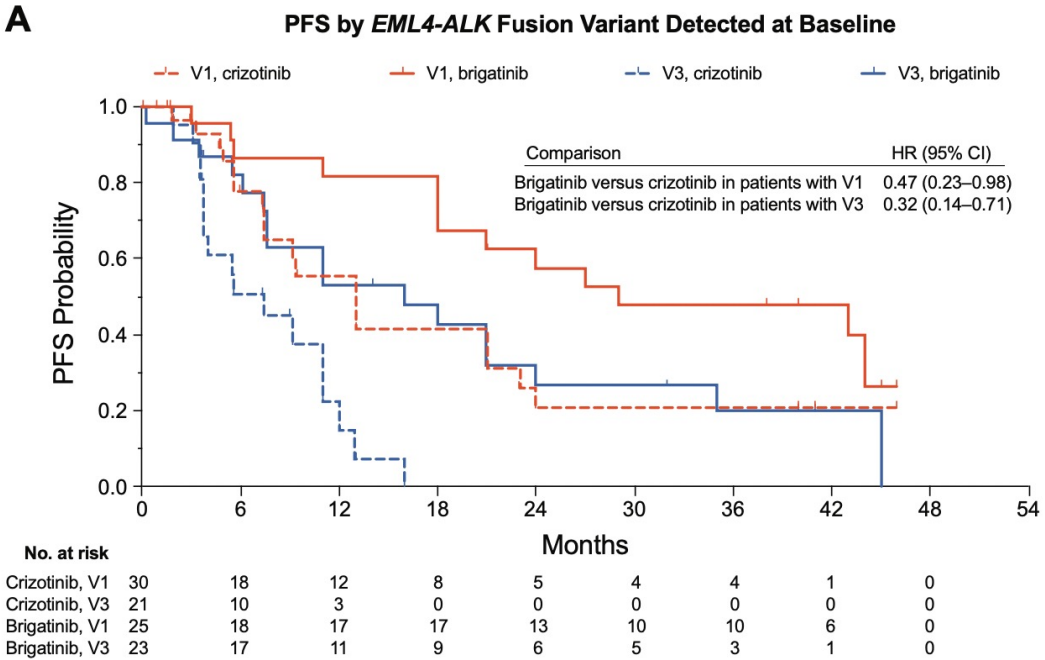
ALK Variants

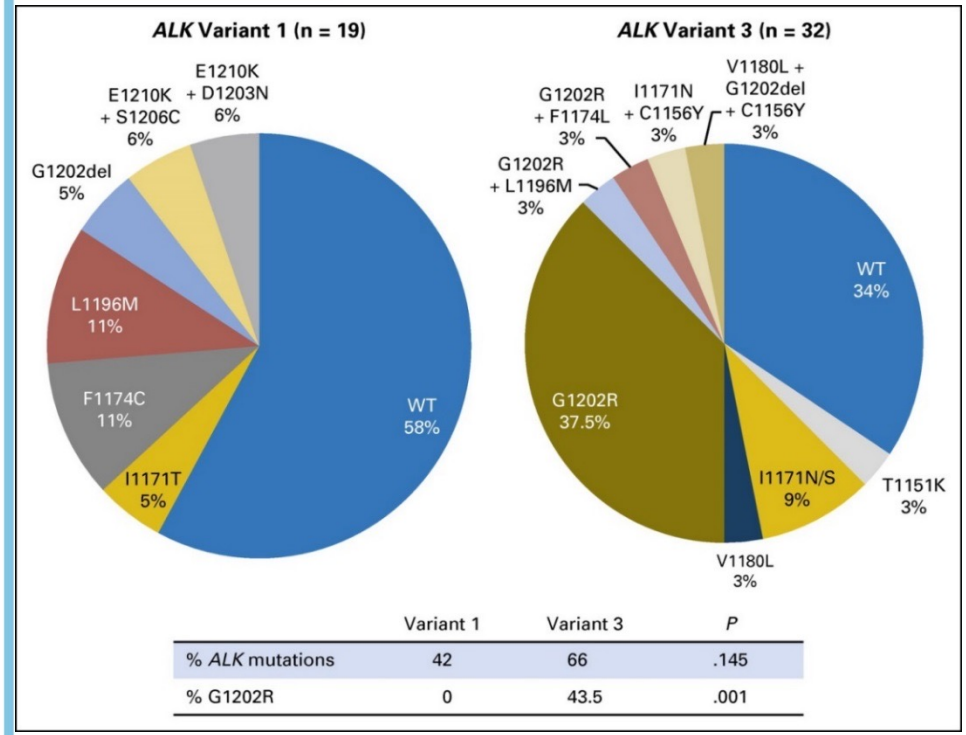
- EML4–ALK variant impacts outcomes



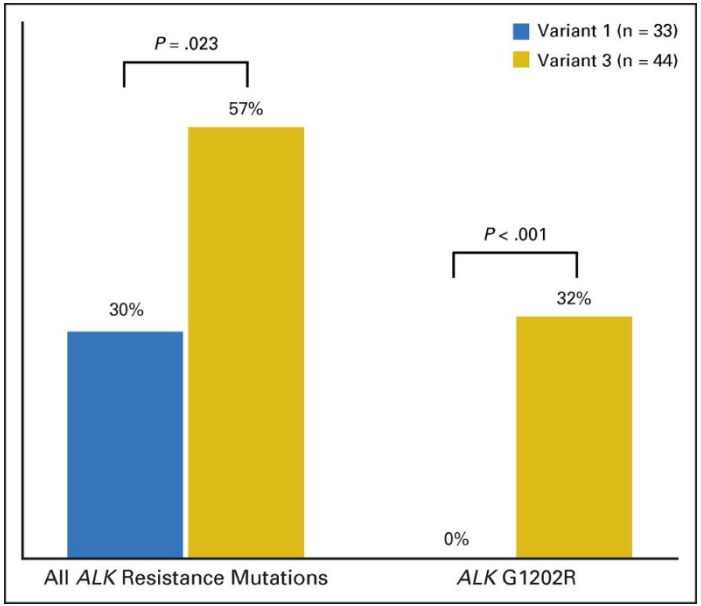
Camidge, JTO 2021

Georgetown | Lombardi

ALK TKI Resistance



	Variant 1	Variant 3	*P*
% *ALK* mutations	42	66	.145
% G1202R	0	43.5	.001



Lin, JCO 2018

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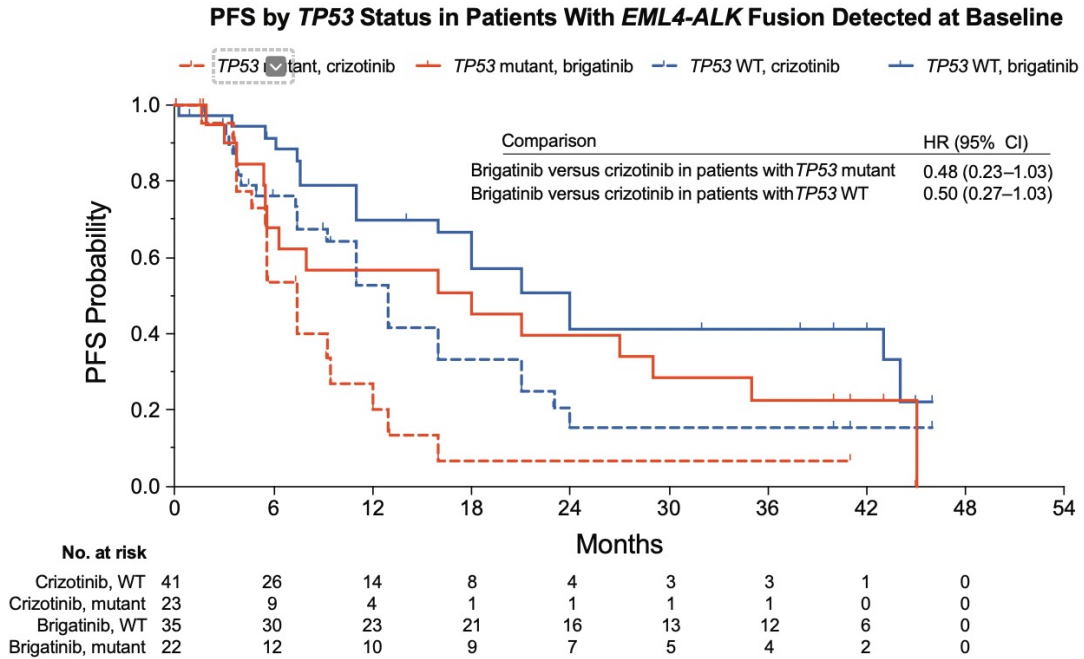
ALK Variants

- Co-mutations may also impact outcomes



Camidge, JTO 2021

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Complex Resistance

- Fewer progression events is preferred
  - Each event carries clinical risk
  - Each line influences resistance
    - Solvent front mutations develop
    - Complex mutations expected

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

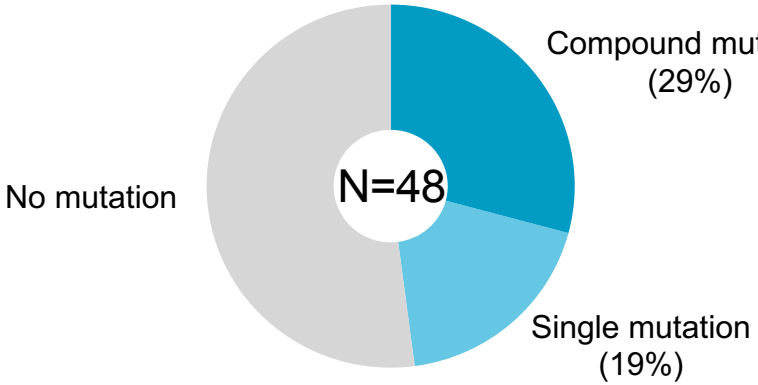
Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

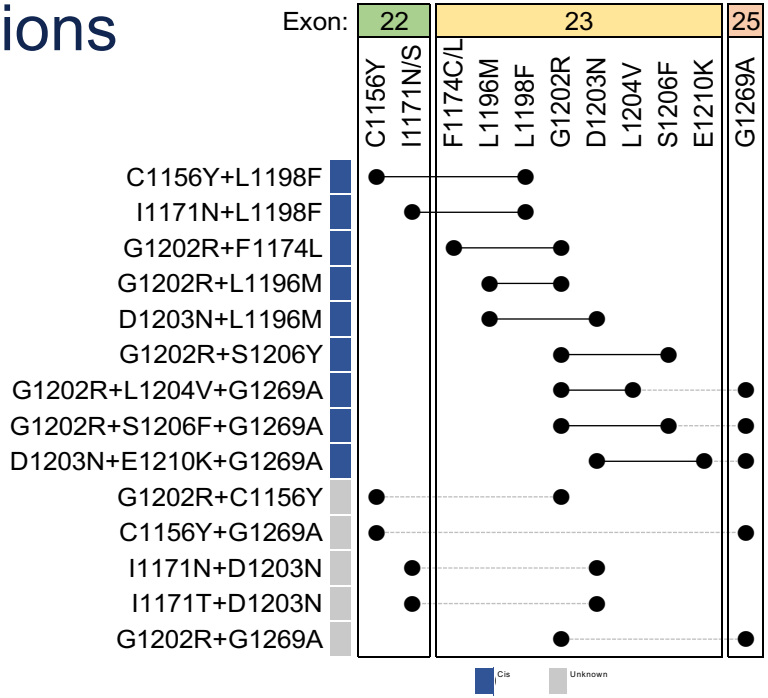
Gainor, Cancer Disc 2017;

Complex Resistance

- Complex / compound mutations

Post-lorlatinib tissue biopsies (with prior ALK TKI)

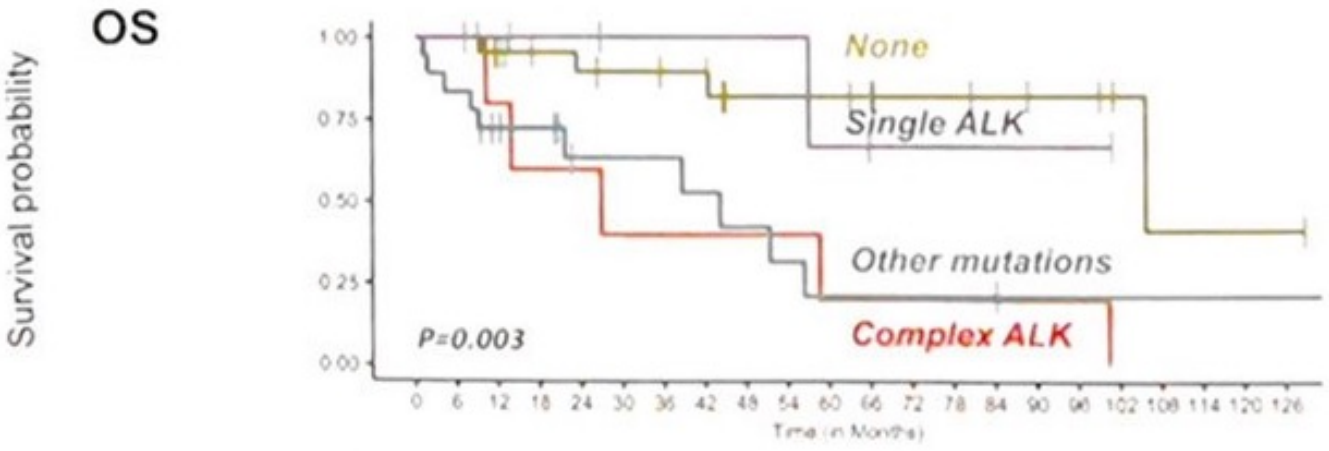




Shiba-Ishii, Nat Cancer 2022; Lin, NACLC 2022

Complex Resistance

- French study exploring ctDNA and TKI efficacy
  - Collected 74 samples at progression on ALK TKI therapy
  - Presence of complex mutations associated with poor OS



Mezquita, ASCO 2019

Overcoming On-Target Resistance

- NVL-655 (ALKOVE-1)

	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

Mezquita, ASCO 2019

Overcoming On-Target Resistance

- TPX-0131 (FORGE1)

Ba/F3 EML4-ALK		TPX-0131	Crizotinib[a]	Alectinib[a]	Brigatinib[a]	Ceritinib[a]	Loriatinib[a]
L1196M/L1198F	N=3	<0.2	252	2250	253	1410	1310
L1198F/C1156Y	N=3	<0.2	19.3	776	102	1310	140
G1202R/C1156Y	N=3	0.2	745	2420	810	1300	521
G1202R/L1196M	N=3	0.7	808	>10000	1100	1260	4780
G1202R/L1198F	N=3	<0.2	188	3000	2040	2010	1710
G1202R/G1269A	N=3	9.9	705	7200	164	303	636
G1202R/G1269A/L1204V	N=3	14.9	634	6740	176	345	673
G1202R/G1269A/L1198F	N=3	0.2	596	>10000	907	1670	6330

[a] Proxy reagents purchased from commercial sources

Mezquita, ASCO 2019

Repotrectinib (TPX-005)

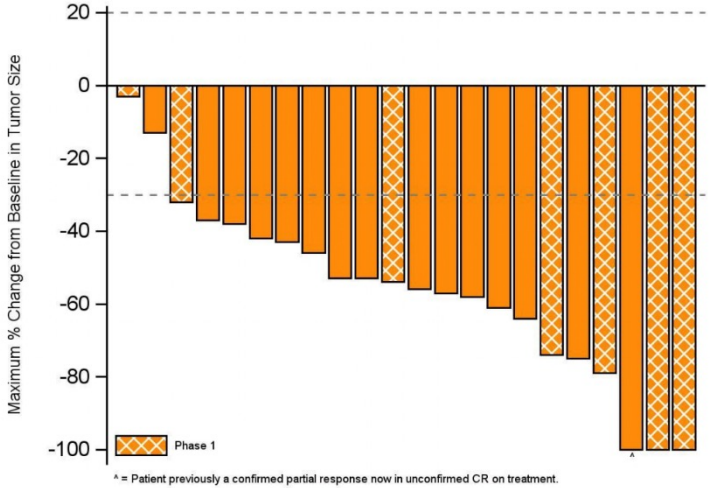
- Next-generation ROS1/TRK inhibitor
  - FDA Breakthrough Therapy Designation for ROS1+ NSCLC

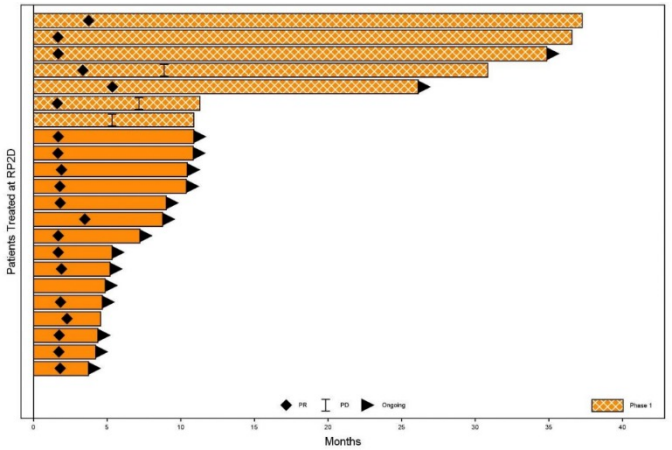
ROS1+ Advanced NSCLC				*NTRK*+ Advanced Solid Tumors	
EXP-1 ROS1 TKI naïve (n=55)	**EXP-2** 1 prior ROS1 TKI AND 1 platinum-based chemotherapy (n=60)	**EXP-3** 2 prior ROS1 TKIs AND No prior chemotherapy (n=40)	**EXP-4** 1 prior ROS1 TKI AND No prior chemotherapy (n=60)	**EXP-5** TRK TKI naïve (n=55)	**EXP-6** TRK TKI pretreated (n=40)
ORR **86% (6/7)** 95% CI, 42–100	**ORR** **40% (2/5)** 95% CI, 5–85	**ORR** **40% (2/5)** 95% CI, 5–85	**ORR** **67% (4/6)** 95% CI, 22–96	**Not Reported**	**ORR** **50% (3/6)** 95% CI, 12–88

Cho, WCLC 2020

Repotrectinib (TPX-005)

- In TKI-naïve, RR 91% (n=22)
  - Phase I median time on treatment: 30.9m (29% ongoing)
  - Phase II median time on treatment: 5.3m (93% ongoing)





Cho, WCLC 2020

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Overcoming On-Target Resistance

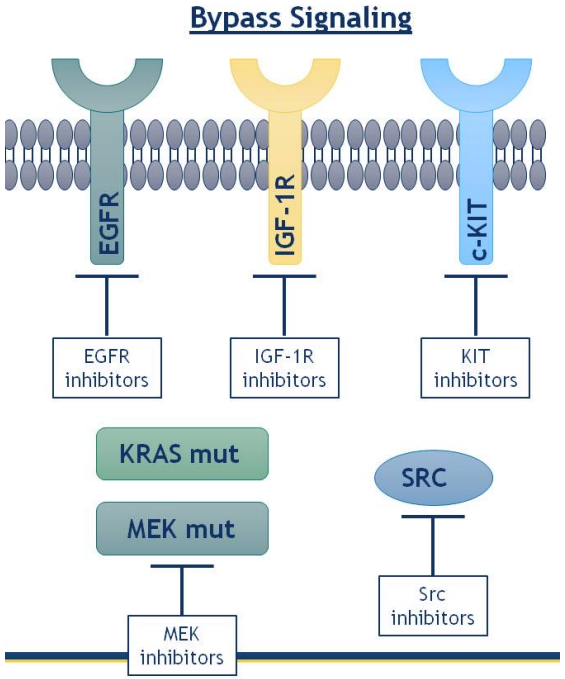
- NVL-520 (ARROS-1)

ROS1	NUV-520	Crizotinib	Entrectinib	Lorlatinib	Repotrectinib
Wild-type	1.2 nM	40 nM	23 nM	1.3 nM	4.4 nM
G2032R	3.5 nM	960 nM	1500 nM	300 nM	25 nM
S1986F	< 0.58 nM	39 nM	26 nM	< 0.27 nM	0.84 nM
L2026M	1.5 nM	110 nM	41 nM	0.77 nM	3.3 nM
D2033N	1.0 nM	77 nM	79 nM	0.44 nM	2.5 nM

Mezquita, ASCO 2019

ALK/ROS1 TKI Resistance

- Bypass tracts
  - Mutation/amplification of other drivers/pathways
  - KRAS
  - MET
- Histologic transformation (EMT)
  - Squamous cancer
  - Small cell lung cancer



Lovly ASCO Educ Book 2015

Overcoming ALK-Independent Resistance: Combination Strategies

Combination	Partner Target	Sponsor	ClinicalTrials.gov
Lorlatinib + Crizotinib	MET	MGH	NCT04292119
Alectinib + Cobimetinib	MEK	MGH	NCT03202940
Brigatinib + Binimetinib	MEK	UCSF	NCT04005144
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

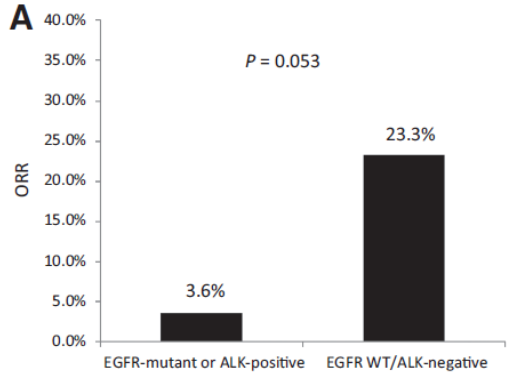
ALK/ROS1 and Chemotherapy

- Among NSCLC, retrospective analysis of patients treated with pemetrexed-based therapy
  - PFS in KRAS+ was 7.0 months
  - PFS in EGFR+ was 5.5 months
  - PFS in ALK+ was 9.0 months
- Retrospective analysis of patients with NSCLC receiving pemetrexed based chemotherapy
  - 102 EGFR+, 32 ALK+, 19 ROS1+
  - ROS1 cohort had best outcomes: RR 58%, PFS 7.5m

Chen, JTO 2016; Camidge, JTO 2011

Immunotherapy

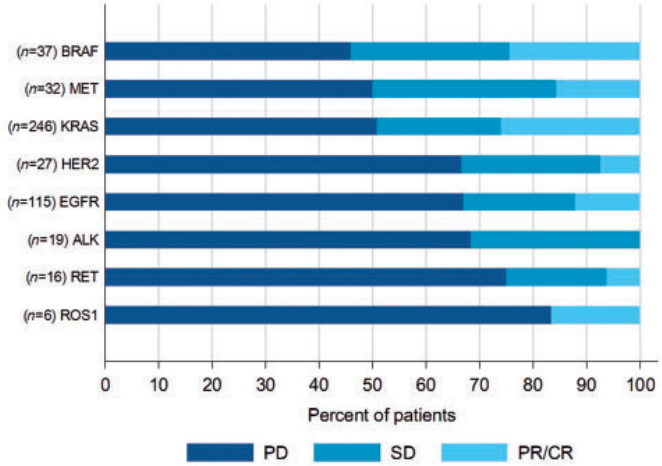
- EGFR/ALK+ tumors can (highly) express PD-L1
- In EGFR/ALK+ NSCLC treated with PD-(L)1 inhibitors
  - Response rate 3.6% (vs. 23.3% in wild type)
- Among light/never smokers
  - Response rate 4.2% (vs. 20.6%)



Gainor, CCR 2016

ROS1 and Immunotherapy

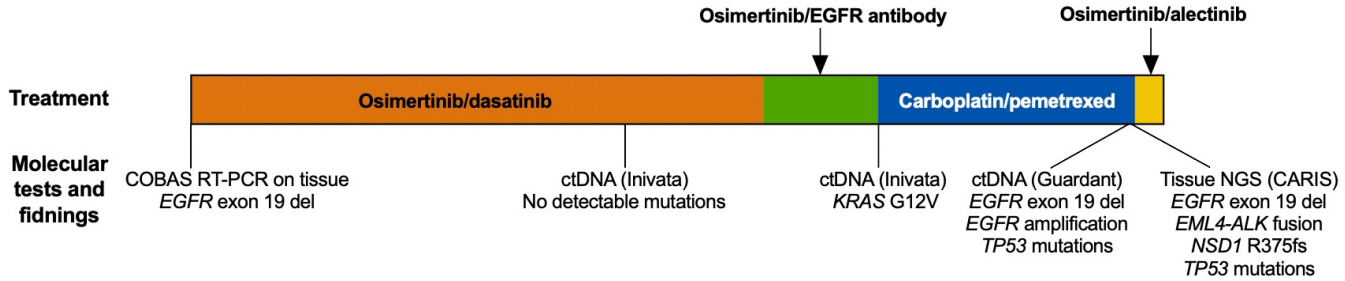
- Retrospective analysis included 7 patients with ROS1+ NSCLC treated with PD(L)1 monotherapy
  - Median PDL1 expression was 90%
  - RR 17%
    - Rapid PD in 42.9%



Mazieres, Ann Oncol 2019

ALK Mediating Resistance

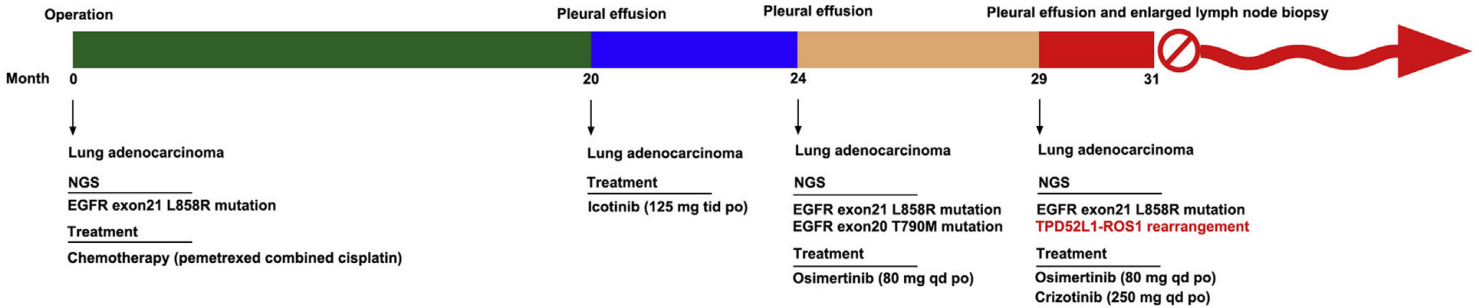
- Acquired ALK fusion mediating EGFR TKI resistance
  - EGFR del19 with initial response to osimertinib
  - Chemotherapy at progression
  - Biopsy after progression revealed EGFR del19 and an acquired EML4 ALK fusion



Xu, JTO 2020

ROS1 Mediating Resistance

- Acquired ROS1 fusion mediating EGFR TKI resistance
  - EGFR L858R with initial response to chemotherapy, icotinib, and osimertinib
  - Biopsy after progression on osimertinib showed ROS1 fusion
  - Responded to osimertinib + crizotinib



Xu, JTO 2020

Summary

- Next–generation ALK and ROS1 TKIs effective
  - Long PFS and high CNS efficacy
  - High landmark PFS and OS rates
  - Consistently well tolerated
- Resistance is still expected
  - Understanding resistance can permit overcoming resistance and eventually, preventing resistance
  - Kinase dependent, independent, histologic transformation