Treatment of ALK & ROS-1 Positive Advanced NSCLC
March 6-8 2024

Fiona Blackhall PhD FRCP

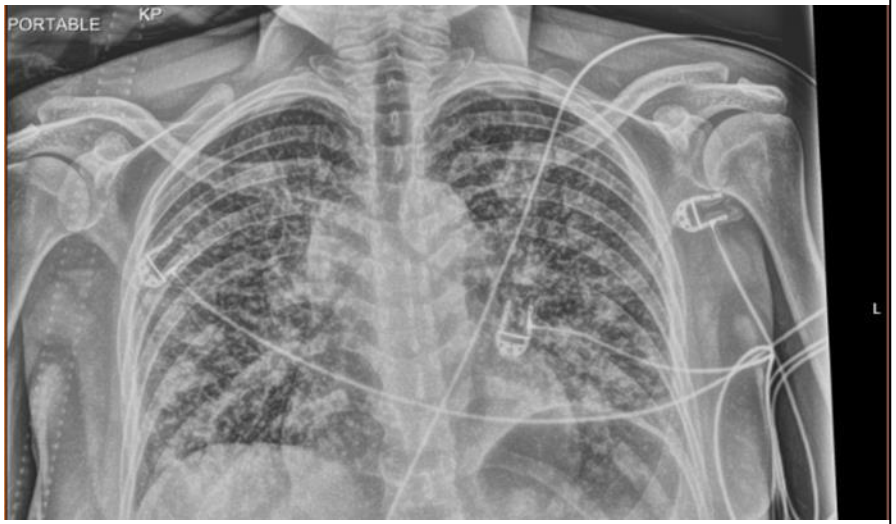
Medical Oncologist & Professor of Thoracic Oncology

The Christie Hospital & Manchester University of Manchester, Manchester, UK

• DISCLOSURE INFORMATION

•Honoraria for speaker engagements, advisory roles, research support :

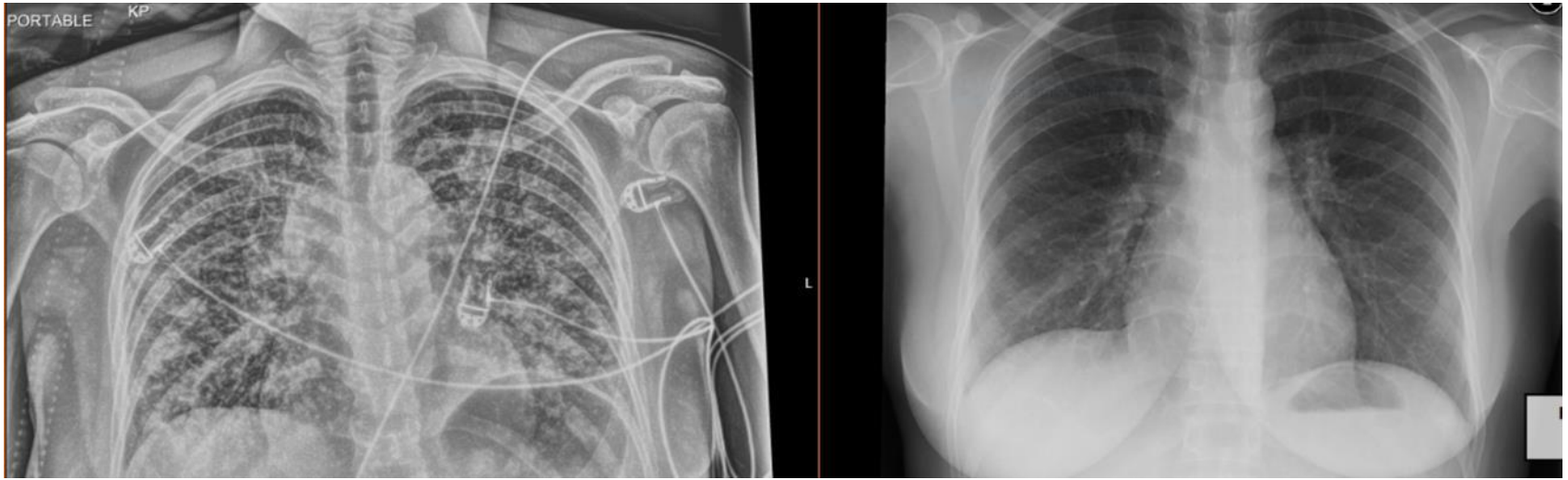
•Amgen, Astra Zeneca, Boehringher-Ingelheim



A 26 year old female

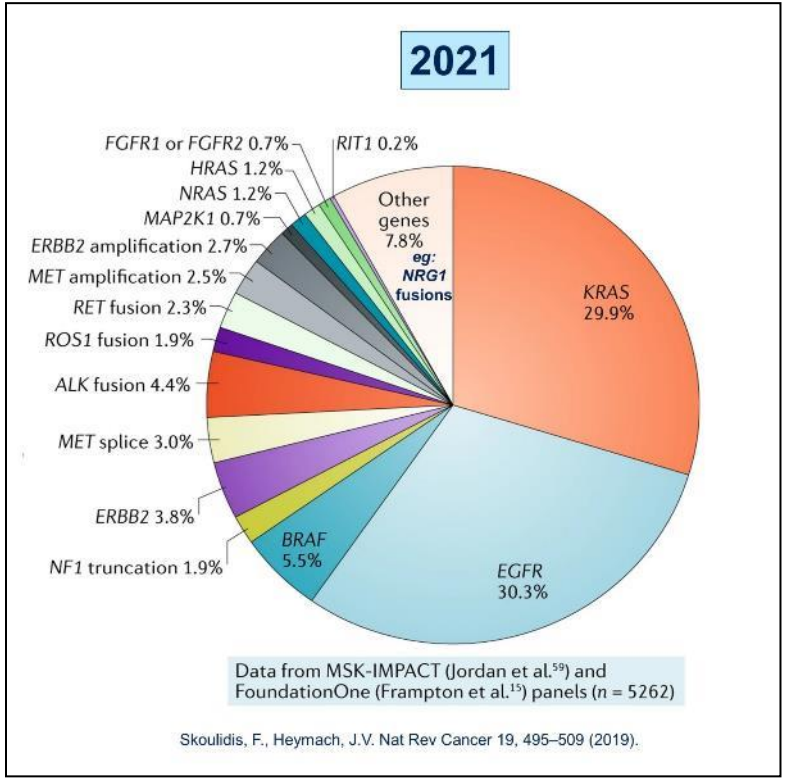
Acute breathlessness, fever, cough

Would you consider lung cancer ?



Within one week of starting alectinib

NSCLC is not a single disease



- > 50 % chance of an oncogene driver in a patient with a history of never or light former smoking
- ~ 6000 new diagnoses of non-smoking related lung cancer annually
- If considered a separate entity LC in never smokers is 8th most common cause of cancer related death in the UK
- 7th most prevalent cancer in the world

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.elsevier.com/locate/clon

ELSEVIER

Lung Cancer in the Non-smoker: A Patient View Focused on the Hopes and Challenges Facing the Non-smoker Population

J. Rawlinson

Personal Experience

told 'it's becoming more common in women who've never smoked, and

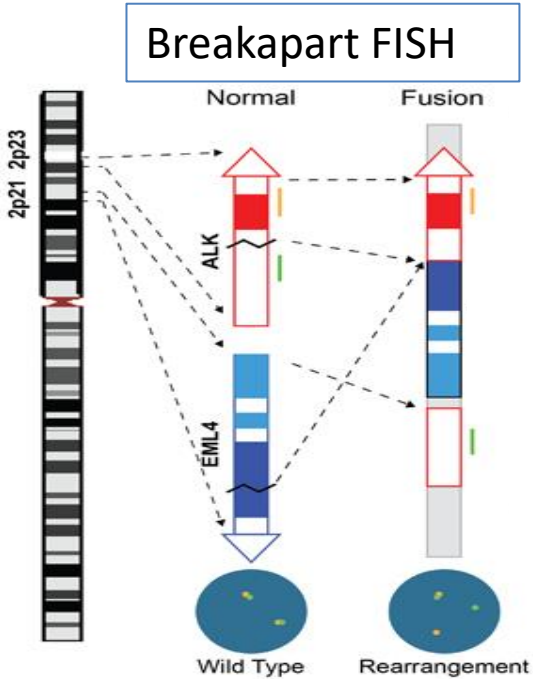
'You only need lungs to get lung cancer'

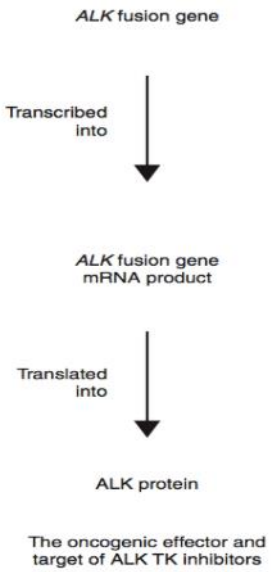
- ……the stigma that comes with lung cancer - even never smoking as folk assume you must have done.
- what caused it and why me ? …….was it the second hand smoke in hospitals and diesel buses or genes or just bad luck. Is it pollution in general?
- We had lives before cancer and different lives with it……In Feb 2014 I couldn't ever imagine being up a big hill again.
- Raising awareness is important to every never smoker LC patient I come across especially those of us who have no respiratory symptoms.
- Would I want a ctDNA test at a certain age..... and if so what age, we have teens and 20 year olds in the mutation club…….
- People all ages are being diagnosed age 17 upwards , lung cancer not only old men who have smoked all their lives which is what I thought .

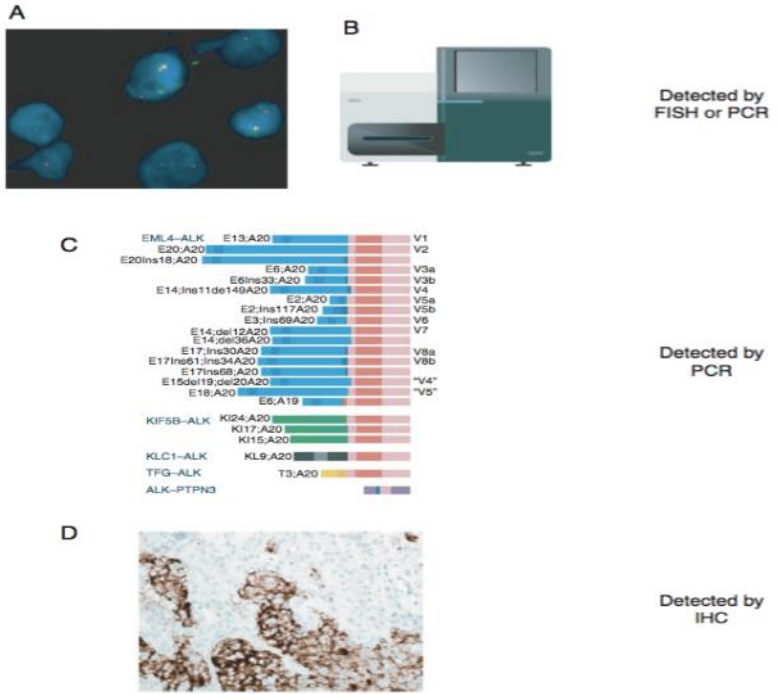
Clinical Features of ALK + and ROS + NSCLC

- *Typically adenocarcinoma histology*
- *Typically (but not always !) never smokers or light former smokers*
- *Younger age*
- *ALK gene fusions : present in 3-7% of NSCLC*
- *ROS1 gene fusions : present in 1–2% of NSCLC patients*
- *Brain metastases are common at presentation (~ 30%)*
- *Aetiology is not known*

Diagnostic methods for Gene Fusions







Schematic diagram of *EML4-ALK* fusion

Kerr & Lopez-Rios Ann Oncol supp 3 2016

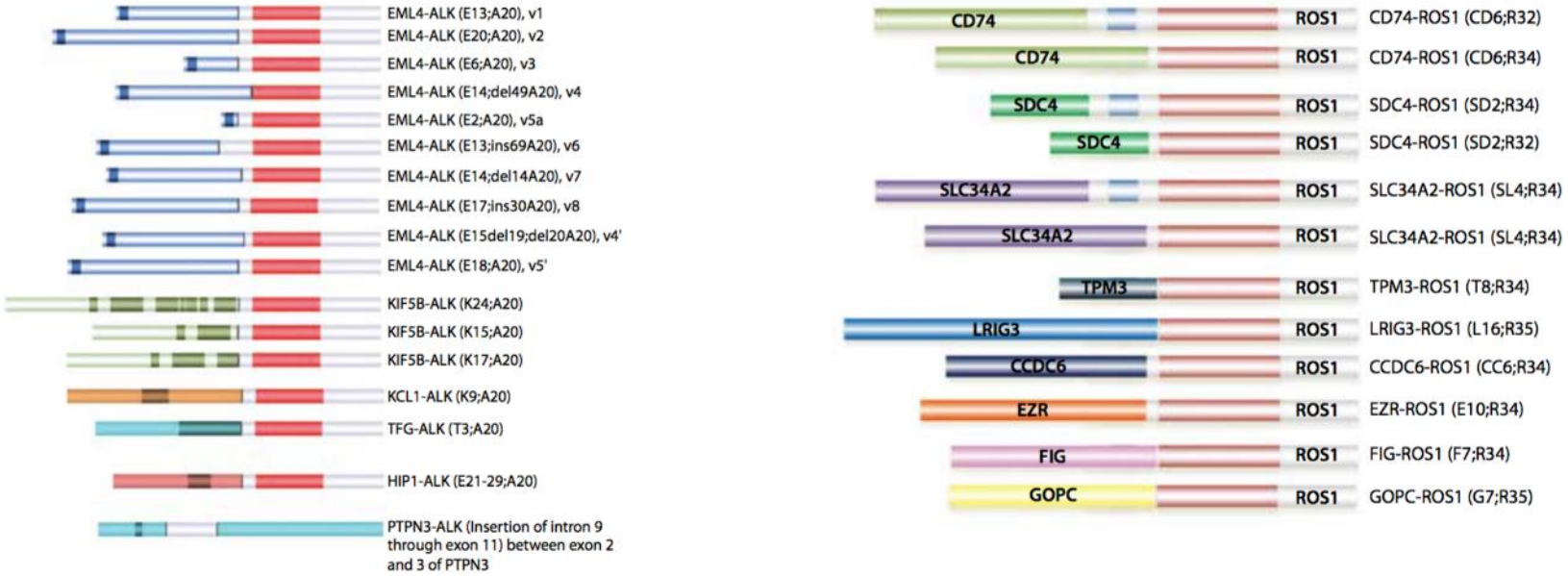
IASLC/CAP/AMP Guidelines for ALK testing

- Testing for *ALK* rearrangements must be ordered at the time of diagnosis or at the time of recurrence or progression in patients who may not have been tested at earlier stages of disease[1]
  - Test results should be available within 2 weeks of the specimen being received
- Since the 2018 guideline update, IHC is now considered to be an equivalent alternative to FISH for ALK testing[2]
- Two step method : IHC screen and then molecular confirmation by FISH or NGS
- *Increasing use of 'one stop shop' NGS (next generation sequencing) of tissue or plasma (DNA) or tissue (RNA) using comprehensive genomic profiling methods eg guardant 360, Foundation liquid due to multiple druggable drivers eg EGFR, ALK, ROS, RET, NTRK, BRAF, MET exon 14, KRAS…..*
- *If plasma is negative a tissue screen is needed*

AMP, Association for Molecular Pathology; CAP, College of American Pathologists; IASLC, International Association for the Study of Lung Cancer

1. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors. J Thorac Oncol 2013;8:823–59;
2. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors. J Thorac Oncol 2018;13:323–58

ALK & ROS-1 fusion kinases : high degree of homology between the ALK and ROS-1 tyrosine kinase domains



Figures from IASLC Atlas of ALK and ROS1 testing in lung cancer 2nd edition, editors Tsao, Hirsch, Yatabe

1st, 2nd and 3rd Generation ALK inhibitors, structurally different - some but not all (!) with activity against ROS-1

Inhibitor	Generation	Other Targets
Crizotinib	1st	MET, ROS-1
Ceritinib	2nd	IGFR-1, ROS-1
Alectinib	2nd	RET, LTK
Brigatinib	2nd	Mutant EGFR, ROS-1
Ensartanib	2nd	MET, ABL, Axl, EPHA2, LTK, SLK
Entrectinib	2nd	TRK, ROS-1
Lorlatinib	3rd	ROS-1
Repotrectinib	3rd	NTRK, ROS-1
Taletrectinib (DS-6501)	3rd	ROS-1/NTRK

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

L. E. Hendriks[1], K. M. Kerr[2], J. Menis[3], T. S. Mok[4], U. Nestle[5,6], A. Passaro[7], S. Peters[8], D. Planchard[9], E. F. Smit[10,11], B. J. Solomon[12], G. Veronesi[13,14] & M. Reck[15], on behalf of the ESMO Guidelines Committee*

[1]Department of Pulmonology, GROW School for Oncology and Reproduction, Maastricht University Medical Center, Maastricht, The Netherlands; [2]Aberdeen Royal Infirmary, Aberdeen University Medical School, Aberdeen, UK; [3]Medical Oncology Department, University and Hospital Trust of Verona, Verona, Italy; [4]Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China; [5]Department of Radiation Oncology, University Hospital Freiburg, Freiburg; [6]Department of Radiation Oncology, Kliniken Maria Hilf, Moenchengladbach, Germany; [7]Division of Thoracic Oncology, European Institute of Oncology IRCCS, Milan, Italy; [8]Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland; [9]Department of Medical Oncology, Thoracic Group, Gustave-Roussy, Villejuif, France; [10]Thoracic Oncology Service, Netherlands Cancer Institute, Amsterdam; [11]Department of Pulmonary Diseases, Leiden University Medical Center, Leiden, The Netherlands; [12]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [13]Faculty of Medicine and Surgery-Vita-Salute San Raffaele University, Milan; [14]Division of Thoracic Surgery, IRCCS San Raffaele Scientific Institute, Milan, Italy; [15]Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, Lung Clinic, Grosshansdorf, Germany

CHECK FOR UPDATES

Available online 23 January 2023

ESMO Guidelines : Stage IV ALK translocation

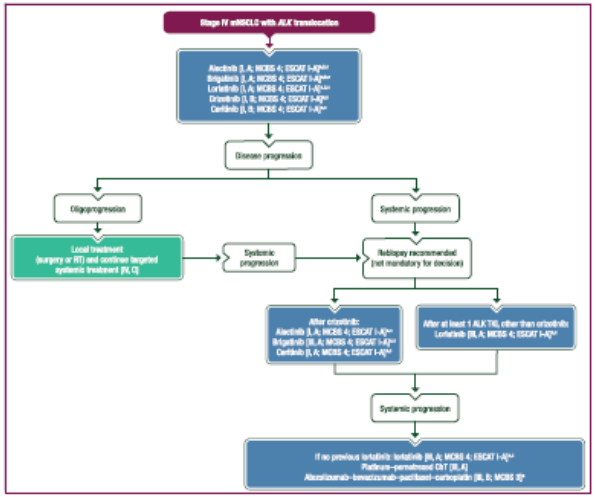


Figure 3. Treatment algorithm for stage IV mNSCLC with *ALK* translocation.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ALK, anaplastic lymphoma kinase; ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mNSCLC, metastatic non-small-cell lung cancer; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
[a]ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[b]Preferred option.
[c]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[4] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.009 for more information on ESCAT scores.

First Line Options

Alectinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Brigatinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Lorlatinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Crizotinib [I, B; MCBS 4; ESCAT I-A][a,c]
Ceritinib [I, B; MCBS 4; ESCAT I-A][a,c]

Second Line Options

After crizotinib:
Alectinib [I, A; MCBS 4; ESCAT I-A][a,c]
Brigatinib [III, A; MCBS 4; ESCAT I-A][a,c]
Ceritinib [I, A; MCBS 4; ESCAT I-A][a,c]

After at least 1 ALK TKI, other than crizotinib:
Lorlatinib [III, A; MCBS 4; ESCAT I-A][a,c]

Third Line Options

If no previous lorlatinib: lorlatinib [III, A; MCBS 4; ESCAT I-A][a,c]
Platinum–pemetrexed ChT [III, A]
Atezolizumab–bevacizumab–paclitaxel–carboplatin [III, B; MCBS 3][a]

ESMO Guidelines : Stage IV ROS translocation

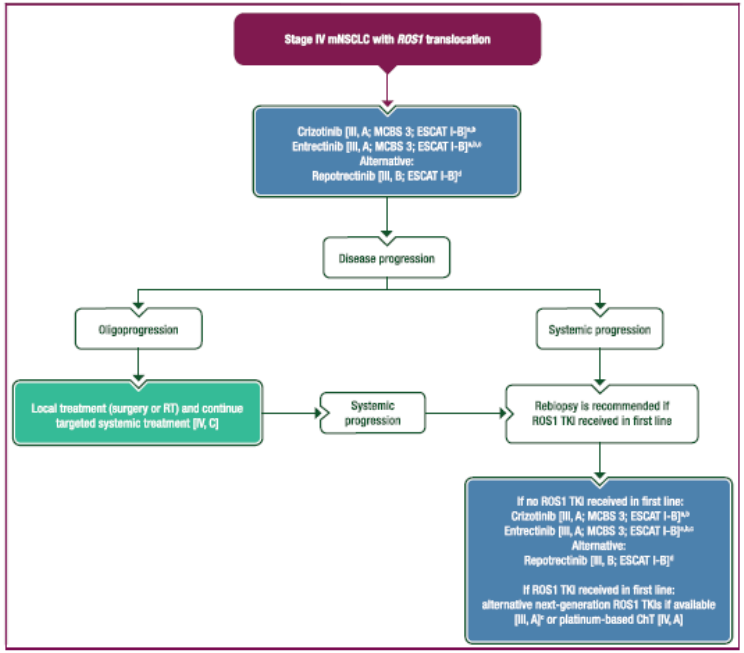


Figure 4. Treatment algorithm for stage IV mNSCLC with *ROS1* translocation.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mNSCLC, metastatic non-small-cell lung cancer; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
[a]ESMO-MCBS v1.1[111] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[b]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[6] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.009 for more information on ESCAT scores.
[c]Preferred over crizotinib in patients with brain metastases.
[d]Not EMA approved.

First Line Options

Crizotinib [III, A; MCBS 3; ESCAT I-B][a,b]
Entrectinib [III, A; MCBS 3; ESCAT I-B][a,b,c]
Alternative:
Repotrectinib [III, B; ESCAT I-B][d]

Second Line Options

If no ROS1 TKI received in first line:
Crizotinib [III, A; MCBS 3; ESCAT I-B][a,b]
Entrectinib [III, A; MCBS 3; ESCAT I-B][a,b,c]
Alternative:
Repotrectinib [III, B; ESCAT I-B][d]

If ROS1 TKI received in first line:
alternative next-generation ROS1 TKIs if available
[III, A][c] or platinum-based ChT [IV, A]

View Online Article

Check for updates

ASCO Special Articles

Therapy for Stage IV Non–Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2023.3

Ishmael A. Jaiyesimi, MD, MS[1]; Natasha B. Leighl, MD[2]; Nofisat Ismaila, MD[3]; Krishna Alluri, MD[4]; Narjust Florez, MD[5]; Shirish Gadgeel, MD[6]; Gregory Masters, MD[7]; Erin L. Schenk, MD, PhD[8]; Bryan J. Schneider, MD[9]; Lecia Sequist, MD[10]; Navneet Singh, MD, DM[11]; Lyudmila Bazhenova, MD[12]; Elizabeth Blanchard, MD[13]; Janet Freeman-Daily, MS, Engr[14]; Naoki Furuya, MD, PhD[15]; Balazs Halmos, MD[16]; Ibrahim Hanna Azar, MD[17]; Sara Kuruvilla, MD[18]; Michael Mullane, MD[19]; Jarushka Naidoo, MD[20]; Joshua E. Reuss, MD[21]; David R. Spigel, MD[22]; Dwight H. Owen, MD, MS[23]; and Jyoti D. Patel, MD[24]

DOI https://doi.org/10.1200/JCO.23.02744

ABSTRACT

Living guidelines are developed for selected topic areas with rapidly evolving evidence that drives frequent change in recommended clinical practice. Living guidelines are updated on a regular schedule by a standing expert panel that systematically reviews the health literature on a continuous basis, as described in the ASCO Guidelines Methodology Manual. ASCO Living Guidelines follow the ASCO Conflict of Interest Policy Implementation for Clinical Practice Guidelines. Living Guidelines and updates are not intended to substitute for independent professional judgment of the treating provider and do not account for individual variation among patients. See complete disclaimer in Appendix 1 and Appendix 2 for more. Updates are published regularly and can be found at https://ascopubs.org/

ACCOMPANYING CONTENT

Article, 10.1200/JCO.22.00824

Appendix

Data Supplement

Accepted January 18, 2024
Published February 28, 2024

TABLE 1. Summary of all Recommendations

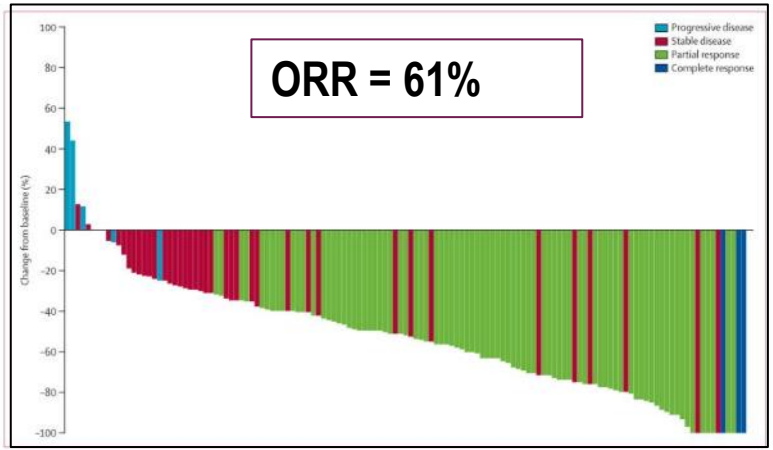
Driver Alteration	Recommendation	Type	Evidence Quality	Strength of Recommendation
NOTE: For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored to each patient incorporating both efficacy and toxicity All biomarkers should be available at the time of decision-making				
Clinical question 1: What are the most effective first-line treatment options for patients' status based on the driver alterations:				
ALK	1.6. Clinicians should offer alectinib or brigatinib or lorlatinib	Evidence-based	High	Strong
	1.7. If alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib	Evidence-based	High	Strong
ROS1	1.8. Clinicians may offer crizotinib or entrectinib	Evidence-based	Moderate	Strong
	1.9. If crizotinib or entrectinib are not available or not tolerated, clinicians may offer ceritinib or lorlatinib	Evidence-based	Low	Weak

Clinical question 2: What are the most effective second-line and subsequent treatment options for patients based on the driver alterations:
NOTE: Due to development of potentially targetable resistance mechanisms, every effort should be made to assess for presence of new mutation by tissue and/or blood NGS testing. If patients have received all targeted options, or if no targeted options are available, clinicians may offer standard therapy following the non-driver alteration guideline

ALK	2.4. For patients who have previously received crizotinib, clinicians should offer alectinib, brigatinib, or ceritinib and may offer lorlatinib	Evidence-based	Moderate	Strong
	2.5. For patients who have previously received other *ALK* inhibitors including alectinib or brigatinib, clinicians may offer lorlatinib	Evidence-based	Low	Strong
ROS1	2.6. For patients who have previously received crizotinib or entrectinib or ceritinib, clinicians may offer lorlatinib	Evidence-based	Low	Weak
	2.7. Clinicians should offer platinum-based chemotherapy following the non-driver alteration guideline	Informal consensus	Low	Strong

Crizotinib : 1st in class 1st generation ALK & ROS-1 TKI

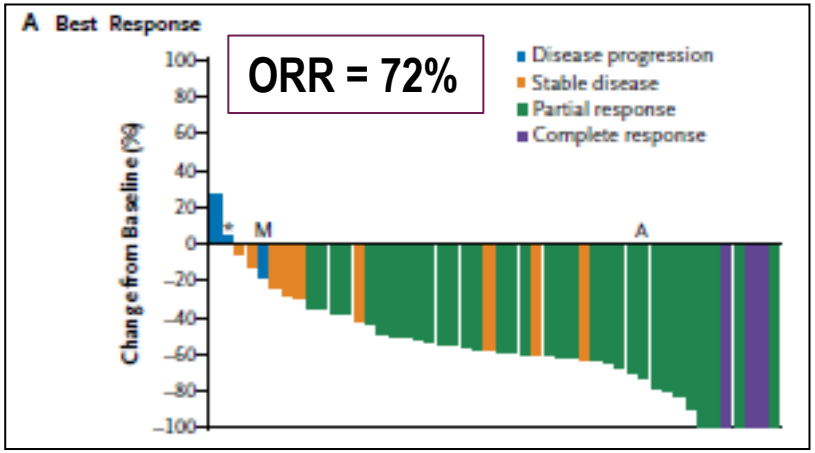
ALK + cohort



Phase I PROFILE 1001

Camidge et al. Lancet Oncol 2012

ROS1 + cohort



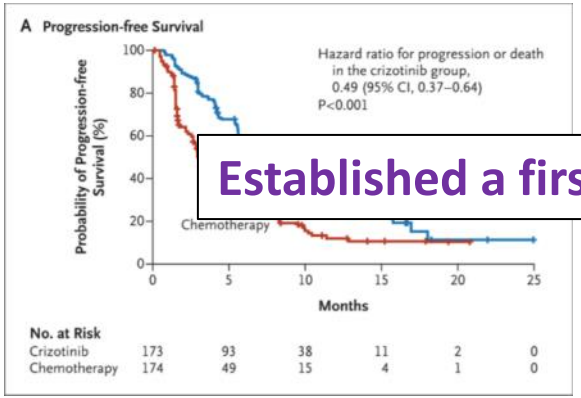
Phase I PROFILE 1001

Shaw et al. NEJM 2014

Proof of the principle of early phase drug development in biomarker selected / enriched populations

Crizotinib vs chemotherapy in Advanced ALK + NSCLC

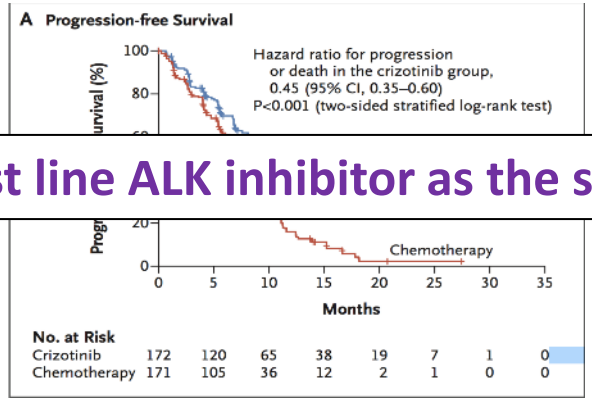
PROFILE 1007
Shaw et al. NEJM 2015



1014	PFS	HR	ORR
crizotinib	7.7	0.49	65 %
chemoT	3.0		20 %

2nd Line

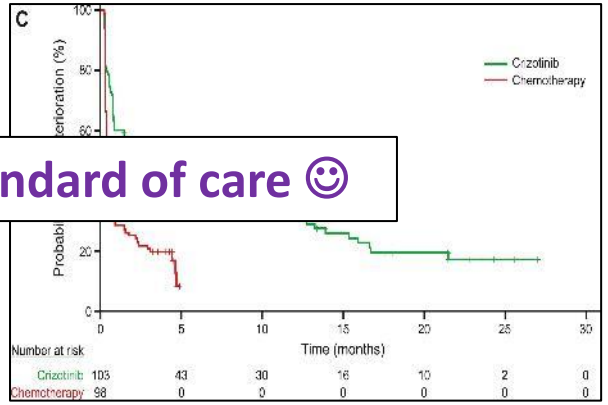
PROFILE 1014
Solomon et al. NEJM 2014



1014	PFS	HR	ORR
crizotinib	10.9	0.45	74 %
chemoT	7.0		45%

1st Line

PROFILE 1029
Wu et al. JTO 2018



1029	PFS	HR	ORR
crizotinib	11.1	0.40	87 %
chemoT	6.8		48%

1st Line

Established a first line ALK inhibitor as the standard of care ☺

Efficacy of Crizotinib in ROS1 + NSCLC

Study	1001	EUROS 1*	ACSe	EUCROSS	OxOnc
Patients	53	29	34	31	127
ORR %	69.8	80	71	66.7	71.7
PFS months	19.3	9.1	10	NR	15.9

No randomised trials of crizotinib compared with chemotherapy in ROS1 + NSCLC

Shaw Ann Oncol 2016; Mazieres JCO 2015;Moro-Sibilot JCO 2015; Michels JTO 2017; Wu JCO 2018

*Abbreviations : ORR objective response rate, PFS progression free survival, NR not reached *retrospective*

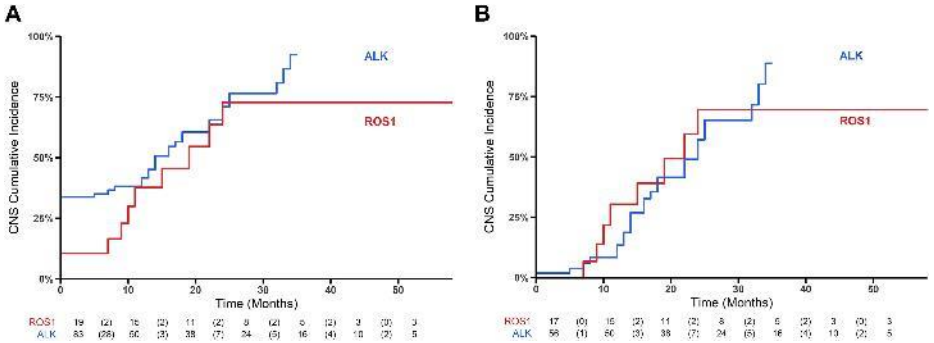
The strategy for treatment of ROS1+ NSCLC was informed by experience with ALK+ NSCLC

Crizotinib for treating ROS1 positive advanced non-small cell lung cancer UK NICE Technology appraisal guidance [TA529] Published 04 July 2018

- 'Evidence for crizotinib in ROS1-positive advanced NSCLC comes from a small, single-arm study that included mostly people with previously treated disease. Although the study showed crizotinib to be effective at shrinking tumours and slowing disease progression, the lack of data comparing it with other treatments makes the size of the benefit uncertain.'
- 'Because of the limited evidence in ROS1-positive NSCLC, the company presented data from 2 randomised controlled trials for crizotinib in ALK-positive NSCLC instead (comparing crizotinib with chemotherapy)* as proxy data for ROS1-positive advanced NSCLC. However, using data from a proxy population is far from ideal, and makes the assessment of clinical and cost effectiveness highly uncertain'.

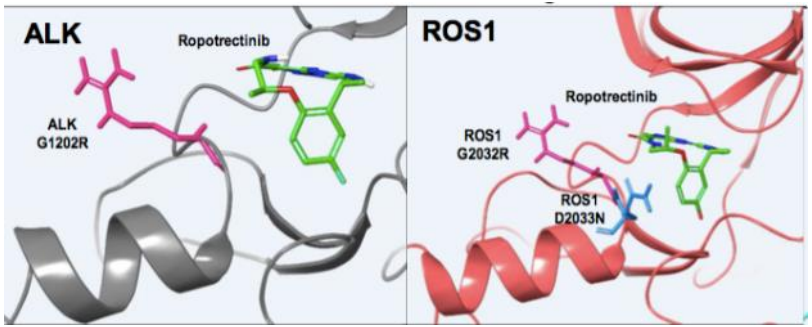
*PROFILE 1007, 1014

Patterns of Progression & Mechanisms of Resistance to Crizotinib



Cumulative development of brain metastases in ALK & ROS1 + NSCLC patients treated with crizotinib

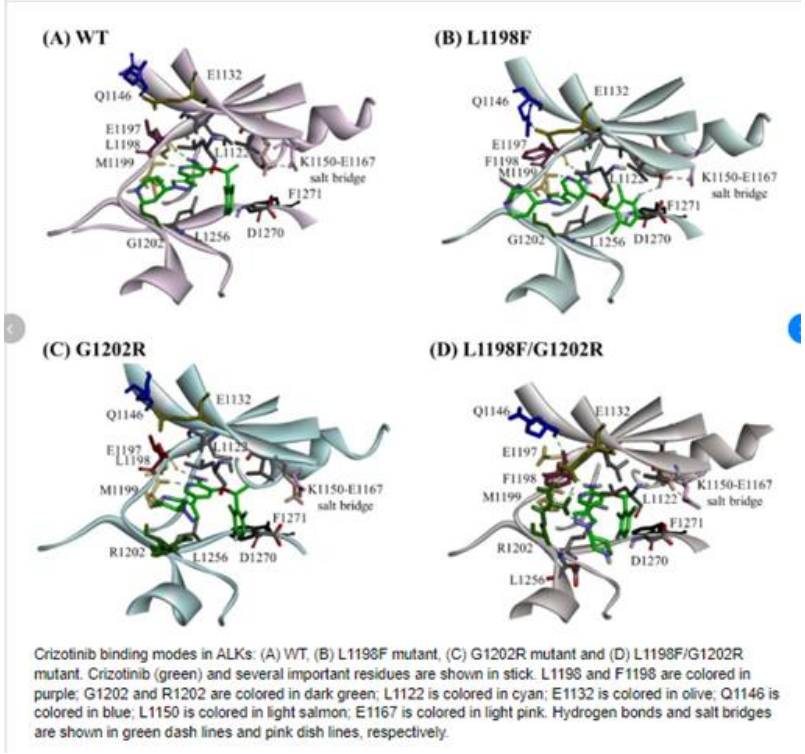
Patil, et al. J Thorac Oncol 2018



On Target Kinase domain resistance mutations in ALK (G1202R) and ROS-1 (G2032R) on treatment with crizotinib

Schram AM, et al. Nature Reviews Clinical Oncology 2017, 14:735-748 ; Drilon et al ASCO 2018

MUNICH 2018 ESMO congress



Crizotinib binding modes in ALKs: (A) WT, (B) L1198F mutant, (C) G1202R mutant and (D) L1198F/G1202R mutant. Crizotinib (green) and several important residues are shown in stick. L1198 and F1198 are colored in purple; G1202 and R1202 are colored in dark green; L1122 is colored in cyan; E1132 is colored in olive; Q1146 is colored in blue; L1150 is colored in light salmon; E1167 is colored in light pink. Hydrogen bonds and salt bridges are shown in green dash lines and pink dish lines, respectively.

Scientific reports 2019

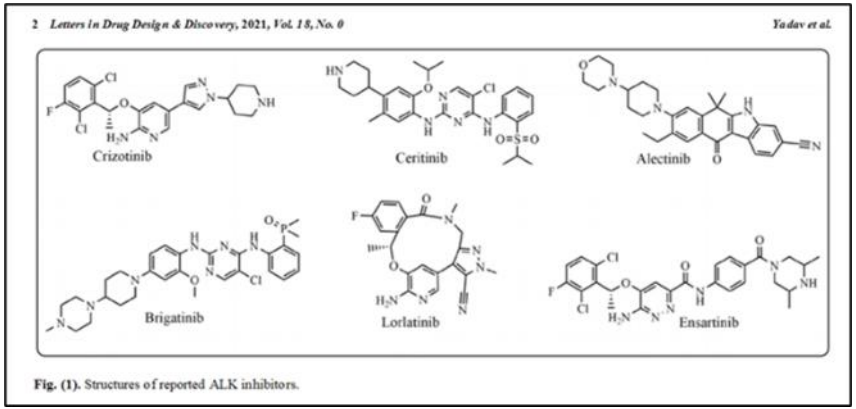


Fig. (1). Structures of reported ALK inhibitors.

Next generation ALK / ROS1 Inhibitors : Better CNS penetration, more potent & active against on target / kinase domain resistant mutations

Cellular ALK Phosphorylation Mean IC50 (nM)

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

IC50 ≤ 50 nM

IC50 > 50 <200 nM

IC50 ≥ 200 nM

Gainor et al. Cancer Discovery 2016

ALK G1202R Lorlatinib > Repotrectinib

ROS1 G2032R Repotrectinib > Lorlatinib

Table 1. Ropotrectinib Potently Inhibited WT and Mutant ALK/ROS1/TRK in Ba/F3 Cell Proliferation IC_{50} (nM

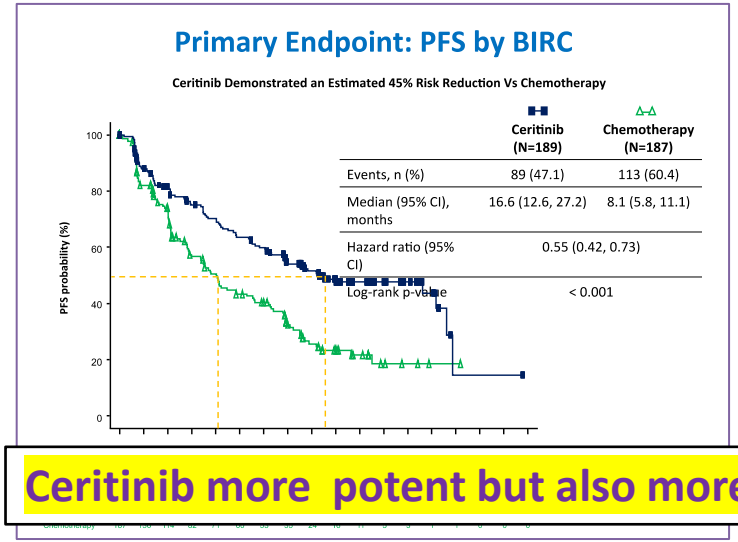
	EML4-ALK V1		CD74-ROS1			LMNA-TRKA		ETV6-TRKB		ETV6-TRKC		
Inhibitor	WT	G1202R	WT	G2032R	D2033N	WT	G595R	WT	G639R	WT	G623R	G623E
Ropotrectinib	27	63.6	<0.2	3.3	1.3	<0.2	0.4	<0.2	0.6	<0.2	3	1.4
Crizotinib	55.7	400	14.6	266.2	200.9							
Ceritinib	7.1	965	42.8	1813	169.2							
Alectinib	11.6	417										
Brigatinib	10.9	190.5	21	1172	128.4							
Lorlatinib	0.5	41.5	0.2	160.7	3.3							
Ensartinib			39.5	371.8	401.9							
Entrectinib			10.5	1813	169.2	0.5	705	<0.5	1384	0.6	1623	1351
Larotrectinib						4	1024	10.9	3000	10.2	3293	742.3

Drilon et al ASCO 2018

MUNICH 2018 ESMO congress

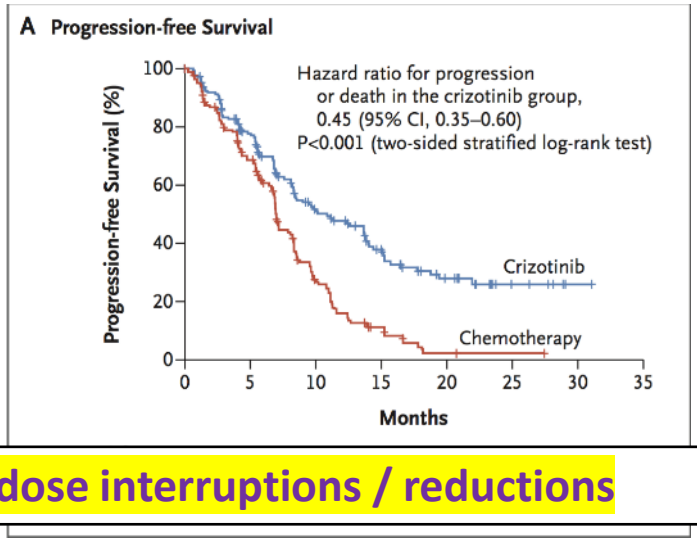
ASCEND-4

De Castro et al. WCLC 2016



PROFILE 1014

Solomon et al. NEJM 2014



Ceritinib more potent but also more toxic – GI / dose interruptions / reductions

ASCEND-4	PFS [95% CI]	HR (95%CI)	ORR
ceritinib	**16.6** (12.6,27.2)	**0.55**(0.42,0.73)	72.5%
chemoT	**8.1** (5.8,11.1)		26.7%

PROFILE	PFS [95% CI]	HR (95%CI)	ORR
crizotinib	**10.9** (8.3,13.9)	**0.45**(0.35,0.60)	74 %
chemoT	**7.0** (6.8,8.2)		45%

How to improve on crizotinib ?

Next generation ALK (ROS-1) inhibitors were first tested in patients with progression on acquired resistance to crizotinib

	Ceritinib		Alectinib		Brigatinib	
Reference	Kim et al. Lancet Oncol 2016	Crino et al. JCO 2016	Ou et al. JCO 2016	Shaw et al. Lancet Oncol 2016	Gettinger et al. Lancet Oncol 2016	Kim et al JCO 2017 (ALTA) 90mg/ 90*-180mg
Patients (N)	163	140	138	87	70	112 / 110
ORR (%)	56	38	50	48	71	45 / 54
Median PFS (mths)	6.9	5.7	8.9	8.1	13.4	9.2 / 12.9 16.7 mths**

**90mg 7 day run in then increase to 180mg*

****Updated analysis of ALTA ORR for Brigatinib on 180mg dose Ahn et al. JTO 2017**

Caution : Cross-trial comparisons cannot be made due to differences in trial design and study populations

CNS activity of 2nd generation ALK inhibitors in patients with progression on crizotinib

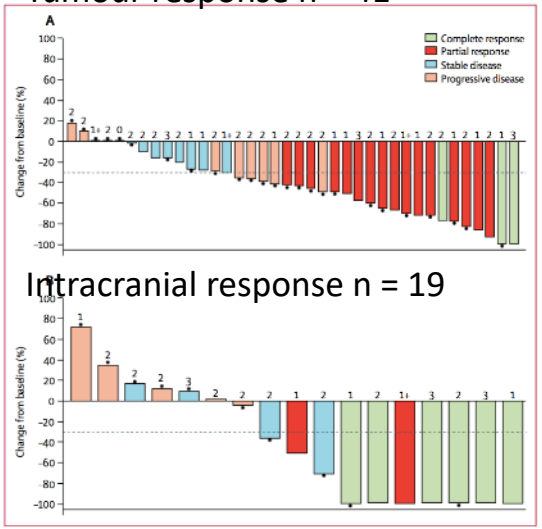
	Ceritinib (Crino JCO 2016)	Alectinib (Gadgeel JCO 2016)		Brigatinib (Camidge et al. JCO 2018)		
Study	Crino JCO 2016 ASCEND 2	Ou et al. JCO 2016	Shaw et al. Lancet Oncol 2016	Gettinger et al. Lancet Oncol 2016	Kim et al JCO 2017 (ALTA) 90mg	Kim et al JCO 2017 (ALTA) 90*-180mg
Patients (N) with measurable disease	20	50		15	26	18
Intracranial ORR	45%	64%		53%	46%	67%

Cross-trial comparisons cannot be made due to differences in trial design and study populations

3rd Generation Lorlatinib : Phase I efficacy in ALK + G1202R NSCLC

Shaw et al. Lancet Oncol 2017

Tumour response n = 41



Intracranial response n = 19

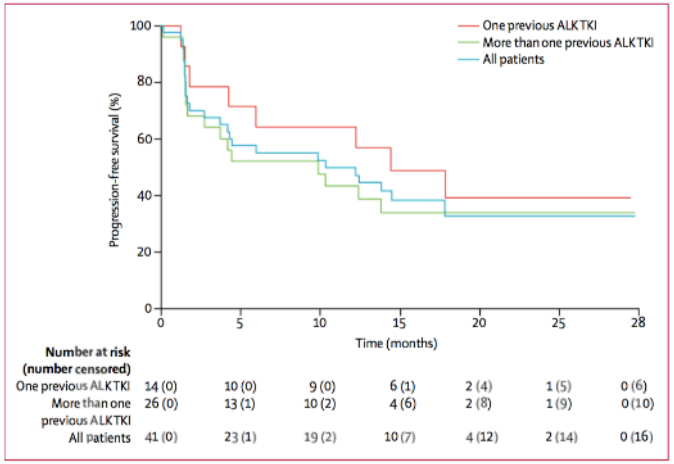
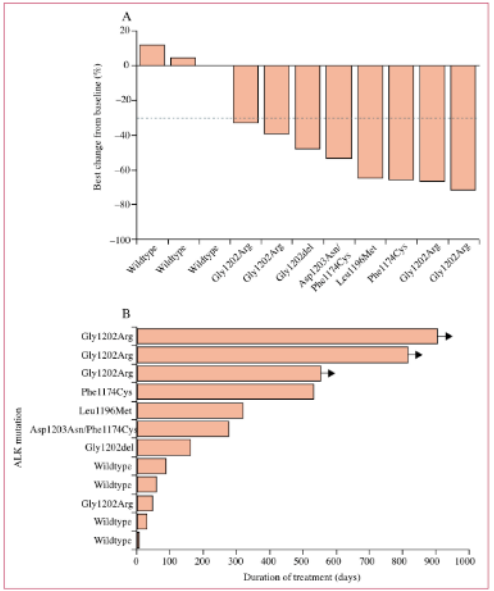


Figure 2: **Progression-free survival in patients with *ALK*-positive non-small-cell lung cancer treated with lorlatinib**

ALK=anaplastic lymphoma kinase. TKI=tyrosine kinase inhibitor.

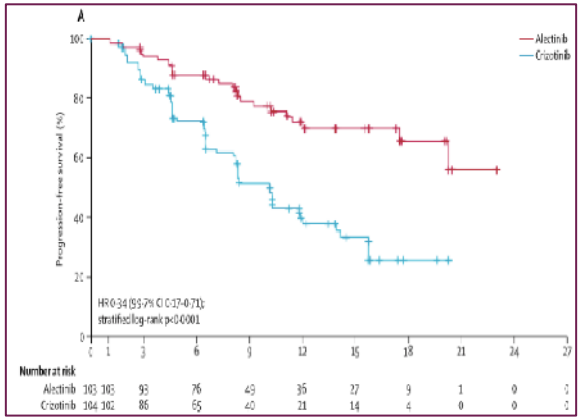


Correlation of response with ALK Resistance mutations n=12

1L treatment of ALK + NSCLC : head to head trials of TKIs

J-ALEX

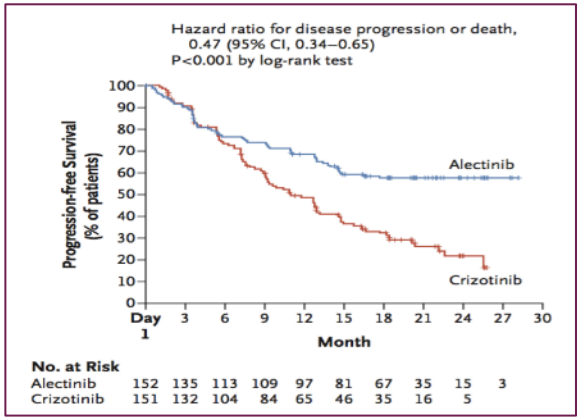
Hida et al. Lancet 2017



J-ALEX	PFS	HR	ORR
alectinib	NR	0.34	91.6 %
crizotinib	10.2		78.9%

ALEX

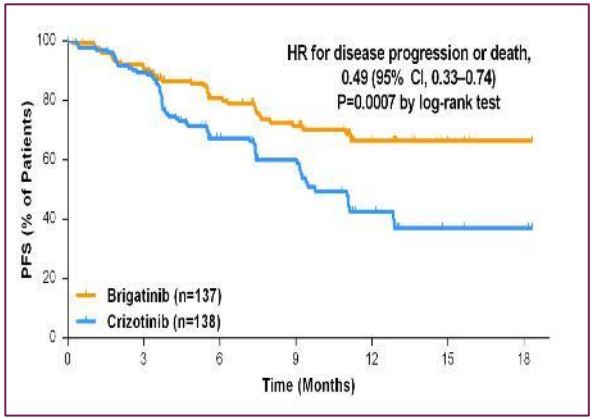
Peters et al. NEJM 2017



ALEX	PFS	HR	ORR
alectinib	25.7	0.5	82.9%
crizotinib	10.4		75.5%

ALTA 1L

Camidge et al. NEJM 2018



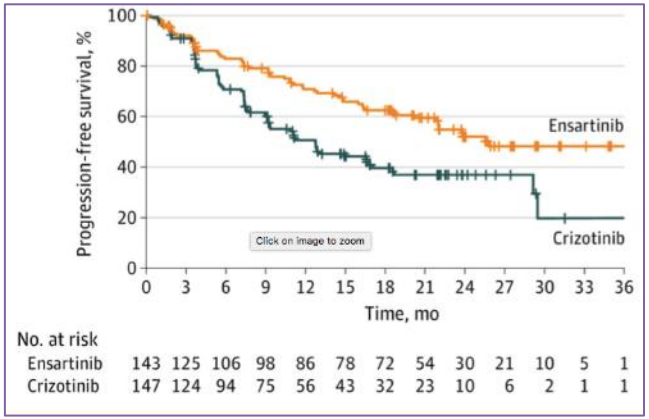
ALTA 1L	PFS	HR	ORR
brigatinib	NR	0.49	76%
crizotinib	9.6		73%

Conclusion : Next generation superior to first generation – moved into first line SOC

1L treatment of ALK + NSCLC : head to head trials of TKIs

eXalt3

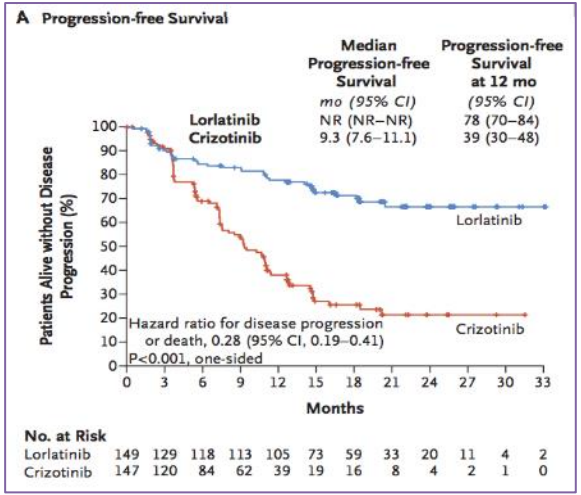
Horn et al. JAMA 2021



eXalt3	PFS	HR	ORR
ensartanib	25.8	0.51	74 %
crizotinib	12.7		67%

CROWN

Shaw et al. NEJM 2020



CROWN	PFS	HR	ORR
lorlatinib	NR	0.28	76%
crizotinib	10.4		58%

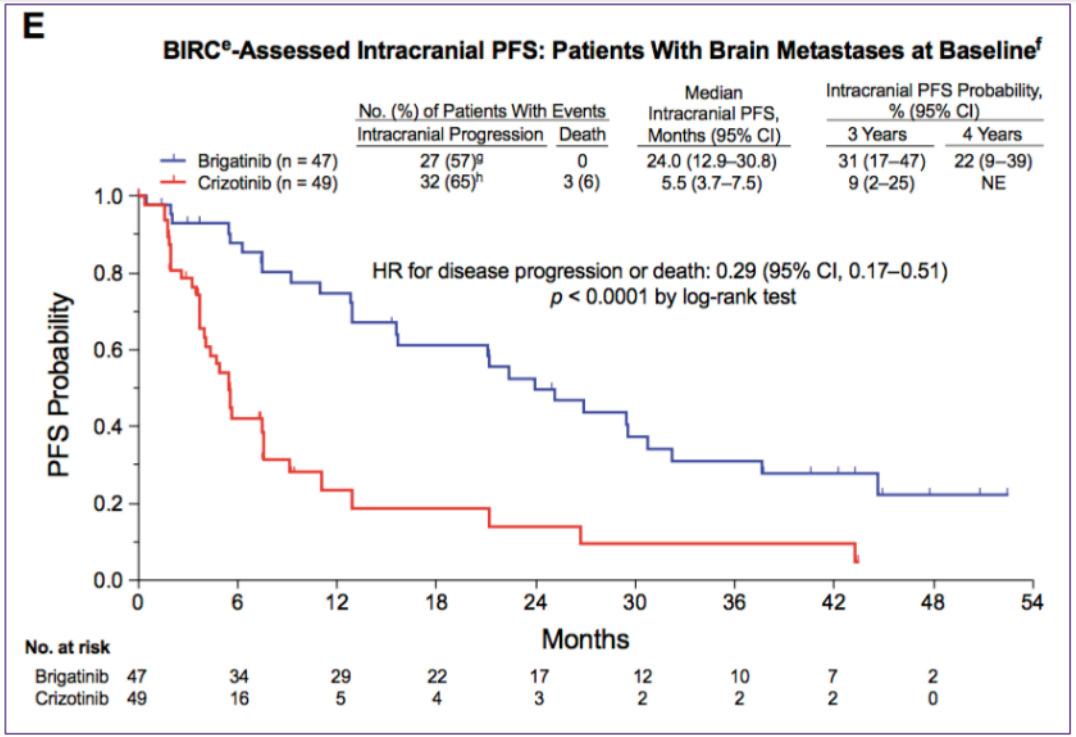
Importance of Baseline Brain Scan

Study	Drug	PFS months Brain mets	PFS months No brain mets	Reference
ALEX	Alectinib Crizotinib	25.4 7.4 HR 0.37	38.6 14.8 HR 0.46	ASCO 2020
ALTA-1L	Brigatinib Crizotinib	NR 5.9 HR 0.24	29.4 12.9 HR 0.57	ESMO Asia 2019
CROWN	Lorlatinib	HR 0.2	HR 0.32	ESMO 2020

PFS progression free survival; HR Hazard ratio

CNS Progression : Brigatinib vs Crizotinib

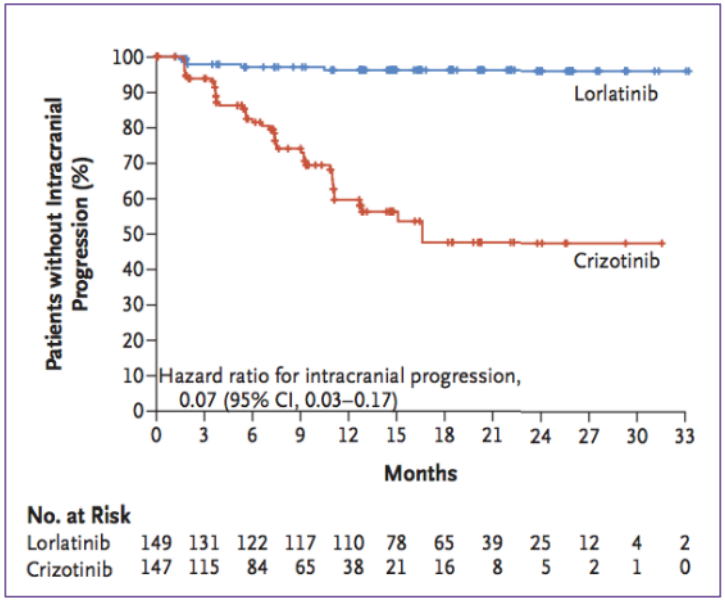
Camidge et al JTO 2021



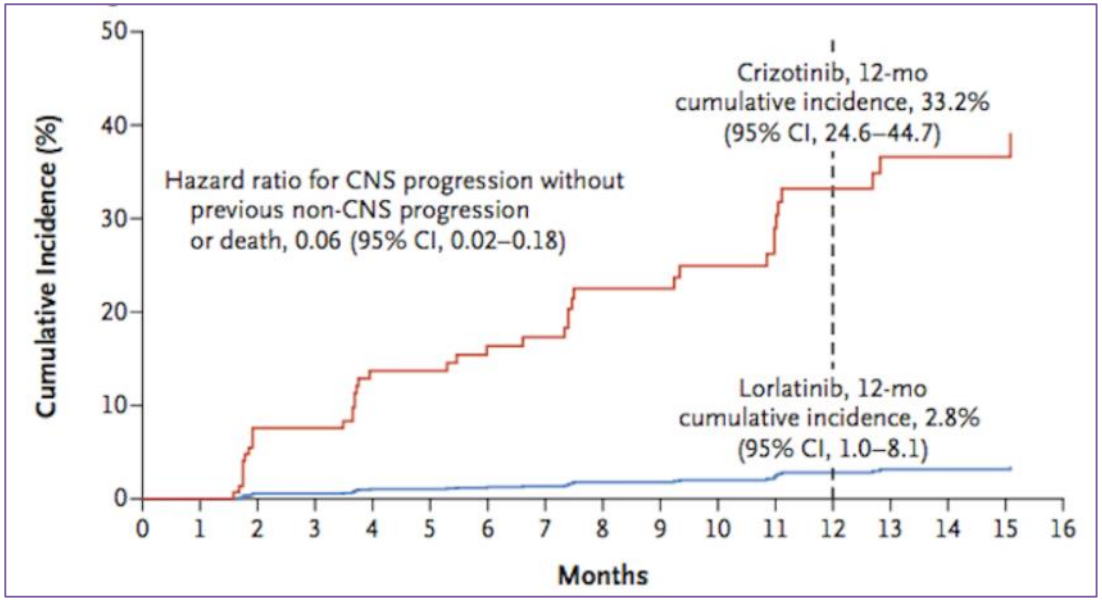
Median intracranial PFS : Brigatinib 24 months , Crizotinib 5.5 months

CNS Progression : Lorlatinib vs Crizotinib

Shaw et al. NEJM 2020



Survival without CNS Progression



Cumulative incidence of CNS Progression as First Event

Summary of trials of ROS-1 inhibitors

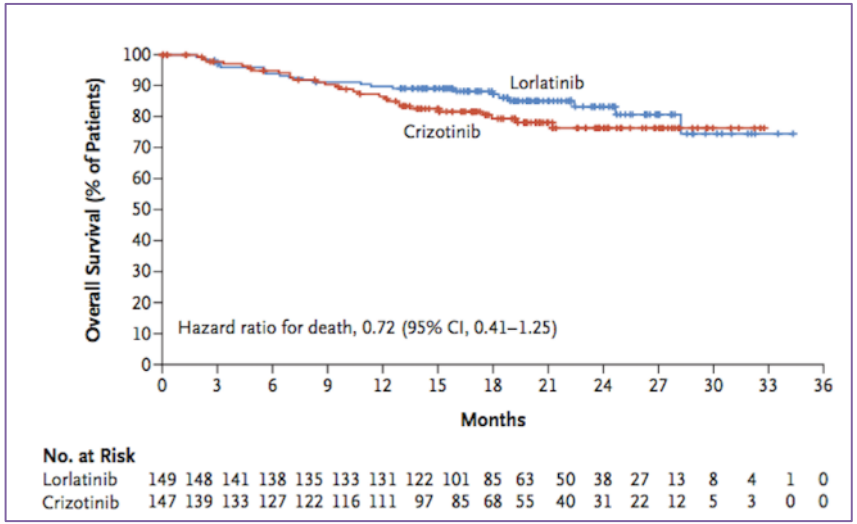
	crizotinib	entrectinib	ceritinib	lorlatinib	repotrectinib
Phase/study	I/ PROFILE 1001	I-II/ALKA-372-001, STARTRK-1, STARTRK-2	II	I-II	I-II TRIDENT-1 NEJM 2024
No. patients	53	161	32	69	71 (56*)
ORR %	72	67	62	62 (35*)	79 (38*)
mPFS	19.3	15.7	19.3		35.7 (9*)
mOS	51.4	Not reached	24		
CNS mets(N)		24		11 (24*)	9 (13*)
Intracranial ORR		79%		64 (50*)	89 (38*)
mPFS		12		25.3 (13.8*)	
mOS		28.3			

Results include TKI naïve and pretreated patients with TKI and /or chemotherapy * prior crizotinib

Overall Survival

CROWN

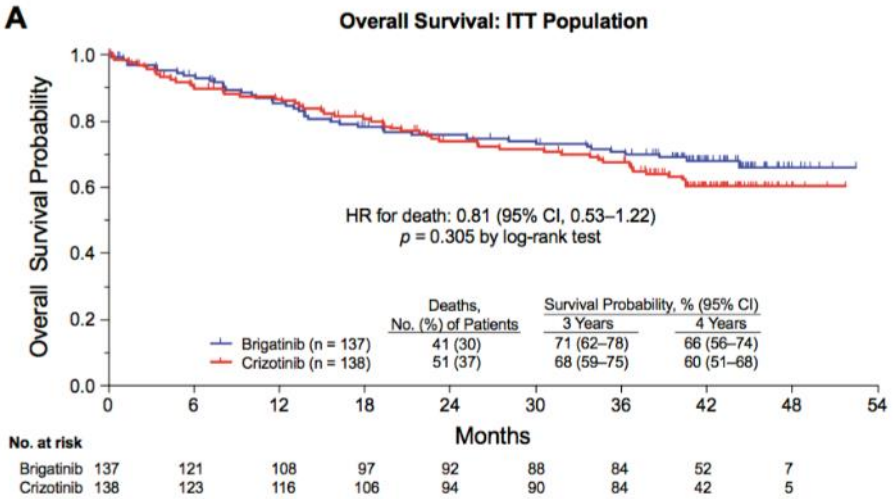
Shaw et al. NEJM 2020



Hazard ratio for death 0.72

ALTA 1L

Camidge et al. JTO 2021



Hazard ratio for death 0.81

Side Effect Profiles of Next Generation ALK/ROS Inhibitors

Drug	Study	Serious TRAEs	Dose reduction	Dose Discontinuation	Treatment Related Adverse Effects (TRAEs) more common than crizotinib
Alectinib	ALEX	28%	16%	11%	Anaemia, Mylagia, Raised bilirubin, weight gain, musculoskeletal pain, photosensitivity reaction
Brigatinib	ALTA-1L	28%	28%	12%	Raised Creatine Kinase, Cough, Hypertension, Raised lipase, Early onset pneumonitis
Ensartinib	eXalt-3	24%	24%	9%	Rash (70%), pruritis, pyrexia
Lorlatinib	CROWN	35%	49%	7 %	Hypercholesterolaemia, hypertriglyceridaemia, weight increase, peripheral neuropathy, cognitive effects
Entrectinib	STARTRK	No randomised data; commonest : fatigue, constipation, dysgeusia, oedema, dizziness, dysaesthesia			

- Elevated transaminases are very common for all ALK-TKIs
- Often difficult to separate ‘paper’ toxicities from clinically significant toxicities
- Long term effects of low grade TRAEs are not known eg elevated creatine kinase

References : Peters et al. NEJM 2017, Camidge et al NEJM 2018, Horn et al IASLC WCLC 2020, Solomon ESMO 2020

ALK, anaplastic lymphoma kinase.

TLCR 2023

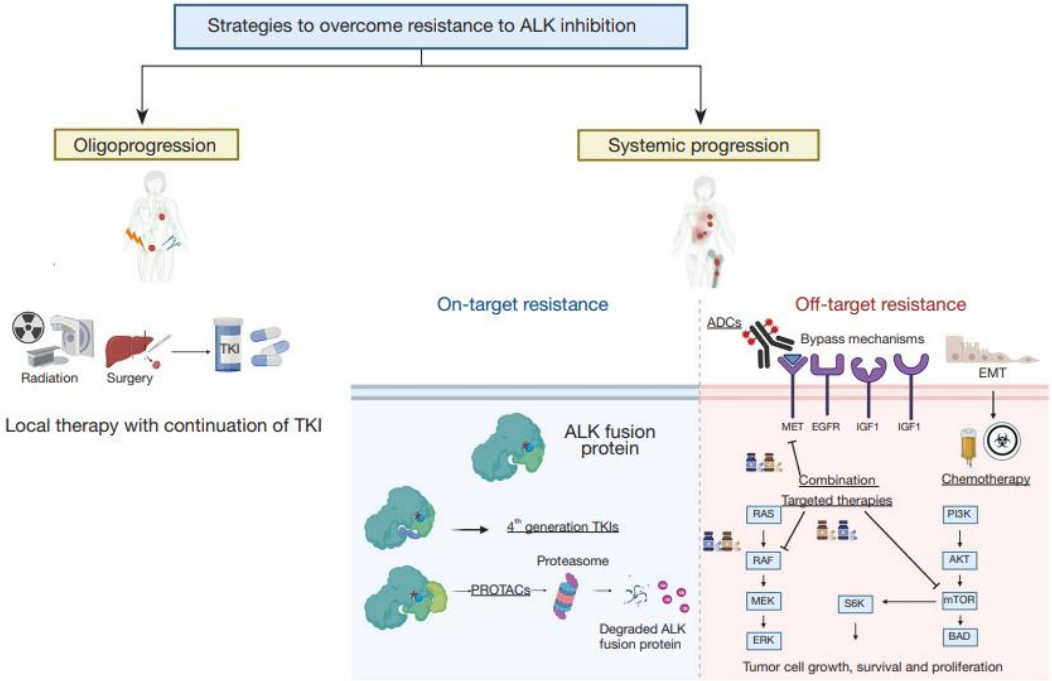


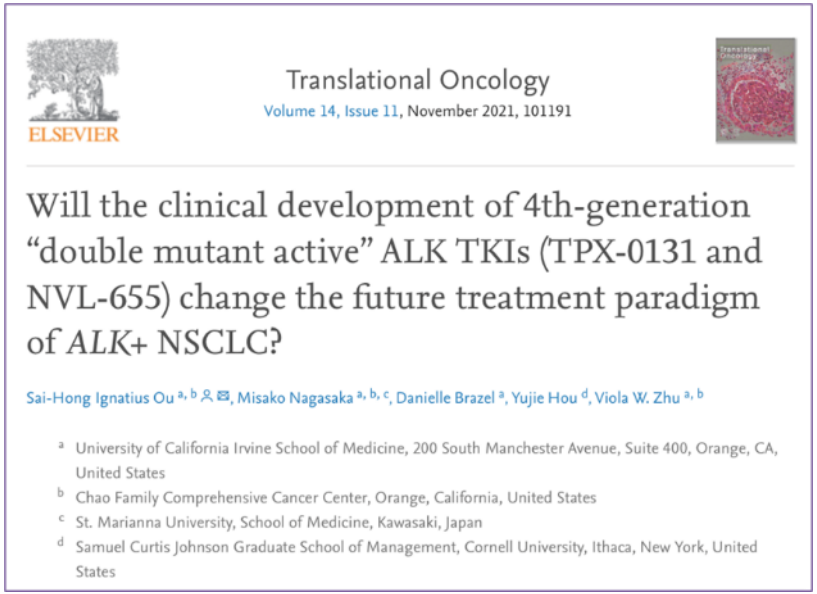
Figure 1 Strategies to overcome resistance to ALK inhibition. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; ADC, antibody drug conjugate; EMT, epithelial to mesenchymal transition; PROTACs, proteolysis-targeting chimeras.

Strategies to overcome resistance to ALK inhibitors in non-small cell lung cancer: a narrative review

Aakash Desai[1], Christine M. Lovly[2,3]

ALKOVE-1 : A Phase 1/2 Study of the Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor NVL-655 in Patients With Advanced NSCLC and Other Solid Tumors NCT05384626

Phase 2 (N ≈ 160)				
COHORT	N	TUMOR TYPE	PRIOR ALK TKI [4]	Prior Chemo and/or IO
2a	40	ALK fusion+ NSCLC	1 prior 2nd generation (ceritinib, alectinib, or brigatinib)	0-2 lines
2b	40	ALK fusion+ NSCLC	2-3 prior 1st or 2nd generation (crizotinib, ceritinib, alectinib, or brigatinib)	0-2 lines
2c	40	ALK fusion+ NSCLC	2-3 prior with lorlatinib in 2nd or 3rd line of therapy	0-2 lines
2d [5]	40	Other ALK+ solid tumors & other ALK+ NSCLC not eligible for 2a-c	≥ 1 prior systemic therapy (or for whom no satisfactory standard therapy exists)	Any
Efficacy endpoints include ORR (primary), DOR, measures of intracranial activity Pre-specified analyses include patients with NSCLC and ALK resistance mutations of interest				



ELSEVIER

Translational Oncology

Volume 14, Issue 11, November 2021, 101191

Will the clinical development of 4th-generation "double mutant active" ALK TKIs (TPX-0131 and NVL-655) change the future treatment paradigm of *ALK*+ NSCLC?

Sai-Hong Ignatius Ou [a, b], Misako Nagasaka [a, b, c], Danielle Brazel [a], Yujie Hou [d], Viola W. Zhu [a, b]

[a] University of California Irvine School of Medicine, 200 South Manchester Avenue, Suite 400, Orange, CA, United States
[b] Chao Family Comprehensive Cancer Center, Orange, California, United States
[c] St. Marianna University, School of Medicine, Kawasaki, Japan
[d] Samuel Curtis Johnson Graduate School of Management, Cornell University, Ithaca, New York, United States

Table 2 Ongoing clinical trials for ALK + non-small cell lung cancer

NCT identifier (trial name)	Phase	Line of therapy	Mechanism of investigational agent	Treatment arm(s)
NCT04405401 (SUPRESS-NSCLC)	2	First-Line	Radiation (for oligoprogression)	SABR *vs.* standard of care
NCT03256981 (HALT)	2	Second-Line	Radiation (for oligoprogression)	SBRT and continued TKI therap *vs.* continued TKI therapy alone
NCT02756793 (STOP)	2	Second-Line	Radiation (for oligoprogression)	SABR *vs.* standard of care
NCT04849273 (FORGE-1)	1–2	Second line or later	4th Gen TKI	TPX-0131
NCT05384626 (ALKOVE-1)	1–2	Second line or later	4th Gen TKI	NVL-655
NCT0429119	1–2	Second line or later	ALK inhibitor + ALK inhibitor	Lorlatinib + crizotinib
			ALK inhibitor + MEK inhibitor	Lorlatinib + binimetinib
			ALK inhibitor + SHP2 inhibitor	Lorlatinib + TNO155
NCT04005144	1	Second line or later	ALK inhibitor + MEK inhibitor	Brigatinib with binimetinib
NCT03202940	1–2	Second line	ALK inhibitor + MEK inhibitor	Alectinib and cobimetinib
NCT04800822	1	Second line or later	ALK inhibitor + SHP2 inhibitor	Lorlatinib + PF-07284892
NCT02321501	1	Second line or later	ALK inhibitor + mTOR inhibitor	Ceritinib + Everolimus
NCT04227028	1	Second line or later	ALK inhibitor + VEGF inhibitor	Brigatinib + bevacizumab
NCT04484142 (Tropion Lung-05)	2	Third line or later	Trop-2 ADC	Datopotamab deruxtecan
NCT04644237 (Destiny Lung-02)	2	Second line or later	HER-2 ADC	Trastuzumab deruxtecan
NCT04495153	2	Second line or later	Oncolytic viral therapy	Gene Mediated Cytotoxic Immunotherapy (GMCI™)
NCT03645928	2	Second line or later	Tumor infiltrating lymphocytes	Autologous tumor infiltrating lymphocytes
NCT03313778	1	Second line or later	mRNA-based vaccine	mRNA-4157 + pembrolizumab
NCT04302025 (NAUTIKA1)	2	Neoadjuvant and Adjuvant	2nd generation TKI	Neoadjuvant and adjuvant alectinib *vs.* standard of care
NCT03456076 (ALINA)	3	Adjuvant	2nd generation TKI	Chemotherapy followed by alectinib *vs.* chemotherapy alon

Current status of clinical trial enrollment is obtained from clinicaltrials.gov with status updated as found on 25th Se
anaplastic lymphoma kinase; NCT, National Clinical Trial; TKI, tyrosine kinase inhibitor; ADC, antibody drug conjugate
ablative radiotherapy; SBRT, stereotactic body radiation.

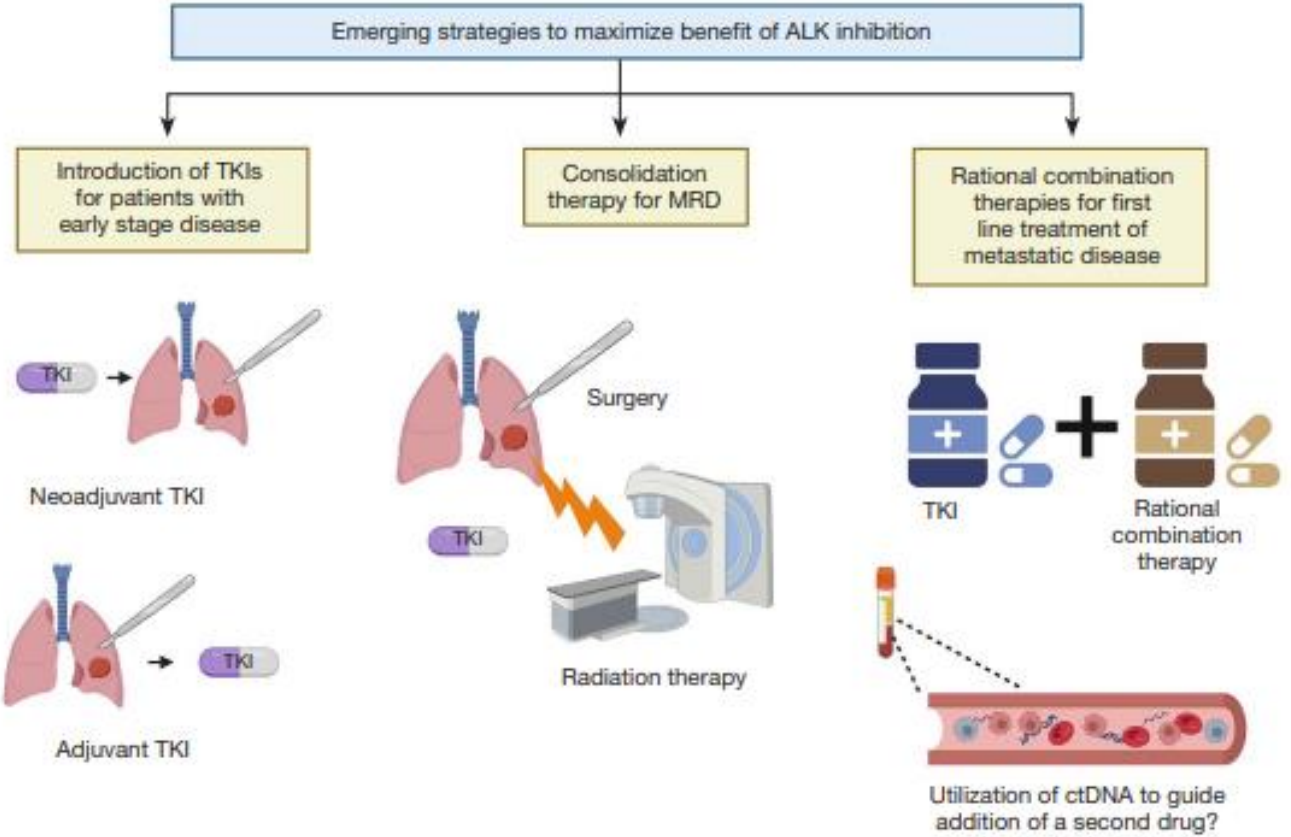


Figure 2 Emerging strategies to maximize benefit of ALK inhibition. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; MRD, minimal residual disease; ctDNA, circulating tumor DNA.

ALKALINE

Ann Oncol 2023

1509TiP **The 1825-EORTC, ALKALINE: Activity of lorlatinib based on ALK resistance mutations on blood in ALK positive NSCLC patients previously treated with second generation ALK inhibitor**

L. Mezquita[1], E. Xenophontos[2], Y. Pretzenbaher[3], C. Sureda[4], E. Nadal[5], K. Al-Rabi[6], G. Rousseau Bussac[7], S. Ponce Aix[8], I.G. Sullivan[9], A. Calles Blanco[10], N. Cloarec[11], J. De Langen[12], T. Berghmans[13], R. Descourt[14], L. Hendriks[15], P. Garrido Lopez[16], A. Helland[17], E. Carcereny[18], B. Besse[19], A-M.C. Dingemans[20]

Trial design: ALKALINE is a phase II, open-label, multicenter, single-arm study in 84 pts with *ALK+* aNSCLC progressing on 2nd gen. ALK TKI. ctDNA is performed before lorlatinib to stratify pts in 3 cohorts: A: if $\geq$ 1 ctDNA *ALK* mutations, B: non-*ALK* mutations and C: no ctDNA detected. Eligible patients receive lorlatinib until disease progression (PD), unacceptable toxicity or occurrence of any withdrawal criterion. Lorlatinib beyond PD is allowed if clinical benefit. Imaging, including brain MRI and ctDNA are performed every 2 months until week 40 and then 3 monthly. A prospective sub-study will assess the time to emergence of resistance mutations and its impact on outcomes in patient on treatment with 2nd gen. ALKi. ctDNA is collected 3 monthly until PD to 2nd gen. ALK inh. (RECIST v.1.1). Pts in the sub-study will enter the main study during PD based on RECIST v1.1. Primary endpoint is progression-free survival rate at 12 months in cohort A as assessed by Blinded Independent Central Review based on RECIST v1.1. Secondary objectives will evaluate activity in cohorts B and C, toxicity and patient reported outcomes. The estimated duration of the ALKALINE is 72 months, with an enrolment period of 42 months.

Take home messages for everyday practice

ALK (and ROS-1) positive NSCLC are clinically and biologically heterogeneous

We have a growing menu of ALK and ROS-1 TKIs that vary in chemistry/potency, efficacy, CNS penetrance, toxicity…..... Cost?

Living longer will generate new questions on how best to optimise care for the individual patient

We lack head to head 2nd vs 3rd Gen TKI data

Most important !
Ensure that ALK and ROS-1 are tested for
Assess early & regularly for intracranial disease