ALK, ROS1, and BRAF

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DISCLOSURES

Commercial Interest	Relationship(s)
CME Matters, Clinical Care Options CME, Research to Practice CME, Medscape CME, Biomedical Learning Institute CME, MLI Peerview CME, Prime Oncology CME, Projects in Knowledge CME, Rockpointe CME, MJH Life Sciences CME	Honoraria
AstraZeneca, Genentech/Roche, Exelixis, Jounce Therapeutics, Takeda Pharmaceuticals, Eli Lilly, Calithera Biosciences, Amgen, Iovance Biotherapeutics, Blueprint Pharmaceuticals, Regeneron Pharmaceuticals, Natera	Consulting or Advisory Role
Genentech/Roche, Merck, Novartis, Boehringer Ingelheim, Exelixis, Nektar Therapeutics, Takeda Pharmaceuticals, Adaptimmune, GSK	Research Funding
Up To Date	Royalties

Outline

ALK: Ensartinib, TKI quality of life and comparisons, resistance

ROS1 + BRAF: Not much new

Trends in biomarker testing among advanced NSCLC patients in oncology practice settings in the US

Authors:

Rebecca Levin,[1] Amy Sullivan,[1] Benjamin Li,[1] Vila Shetty,[1] Stan Krulewicz,[2] Lauren Bartolome[1]

Study design

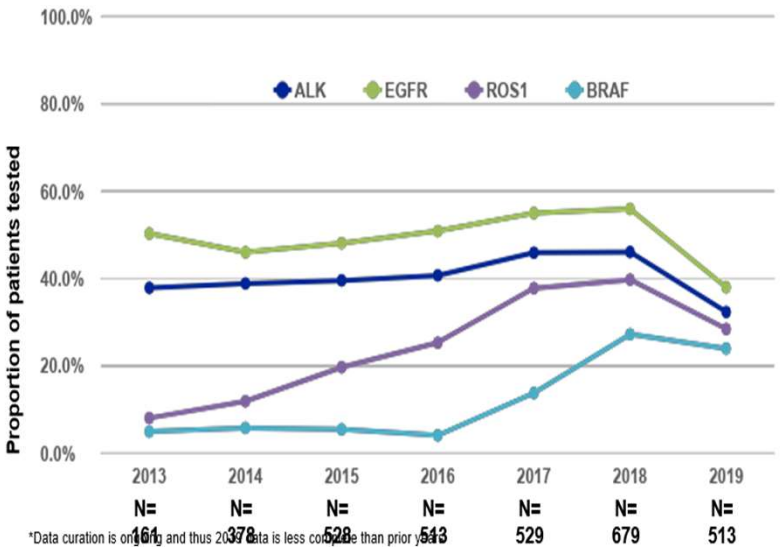
- Retrospective analysis of data from the ConcertAI Patient 360 electronic health record database
  - Nurse-curated EHR database from 350+ cancer clinics, representing 1,100+ active oncologists, and including over 4M oncology patients, with balanced representation of geographically diverse community and academic practices in the United States.
  - Data includes disease stage, treatment regimen, biomarker testing, and genomic variant detail.

Population

Adult patients diagnosed with advanced or metastatic (stage IIIb-IV) NSCLC (aNSCLC) from January 2013 – December 2019.

- All aNSCLC patients had dates of advanced staging populated in the database and were tested for at least one the following biomarkers of interest: ALK, BRAF, EGFR, or ROS1.

Figure 2 – Annual Biomarker Testing Trends for ALK, EGFR, ROS1, and BRAF



*Data curation is ongoing and thus 2019 data is less complete than prior years

- Testing rates appeared to increase for all biomarkers in recent years, with the largest increases observed in BRAF and ROS1 testing. (Figure 2)

2020 Presidential Symposium
AUGUST 8, 2020 | WORLDWIDE

Phase 3 Randomized Study of Ensartinib vs Crizotinib in Anaplastic Lymphoma Kinase (ALK)–Positive NSCLC Patients: eXalt3

Horn L,[1] Wang Z,[2] Wu G,[3] Poddubskaya E,[4] Mok T,[5] Reck M,[6] Wakelee H,[7] Chiappori A,[8] Lee DH,[9] Breder V,[10] Orlov S,[11] Cicin I,[12] Cheng Y,[13] Liu Y,[14] Fan Y,[15] Zhou J,[16] Oertel V,[16] Mao L,[16] Selvaggi G,[16] and **Wu Y**[17]

eXalt3: Global Phase 3, Open-Label, Randomized, Multicenter Study

- Stage IIIB/IV NSCLC
- ALK+ by local FDA-approved assays or central confimration by FISH by Abbott
- ECOG PS 0-2
- No prior ALK inhibitor
- ≤ 1 Prior chemotherapy regimen

NCT02767804

→ Randomized 1:1

- Ensartinib 225 mg QD
- Crizotinib 250 mg BID

Stratified by:
- Prior chemotherapy
- ECOG PS
- Asia Pacific vs ROW
- Brain metastases at BL

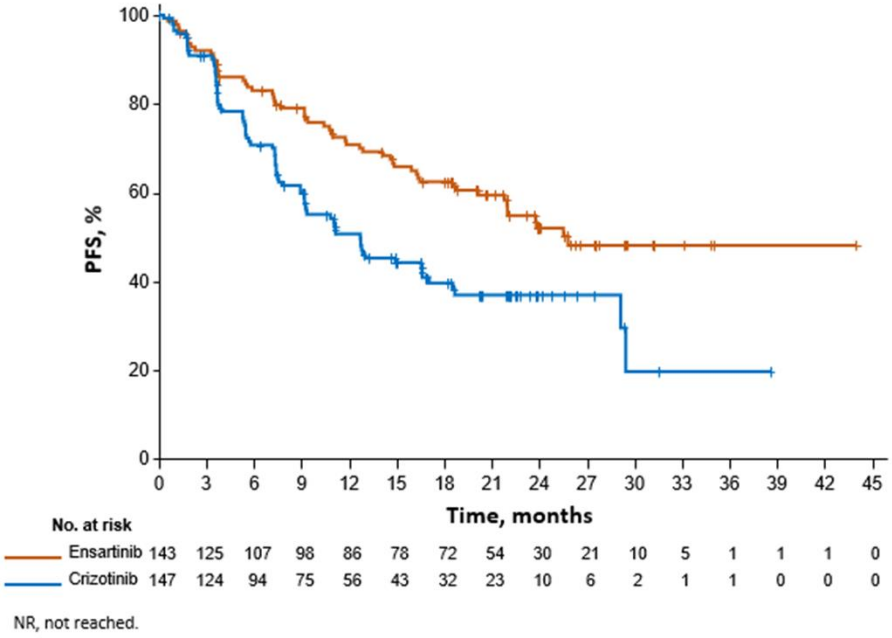
- No crossover allowed
- Trial fully accrued as of Nov 2018

Primary endpoint: blinded independent review committee (BIRC)–assessed median PFS (mPFS) per RECIST v1.1 in ITT population
Key secondary endpoints: OS, ORR/DOR (overall and brain), and TTF in the brain

BL, baseline; DOR, duration of response; ITT, intent to treat; ROW, rest of world; TTF, time to treatment failure.

Phase 3 Randomized Study of Ensartinib vs Crizotinib in Anaplastic Lymphoma Kinase (ALK)–Positive NSCLC Patients: eXalt3

BIRC-Assessed mPFS (ITT)



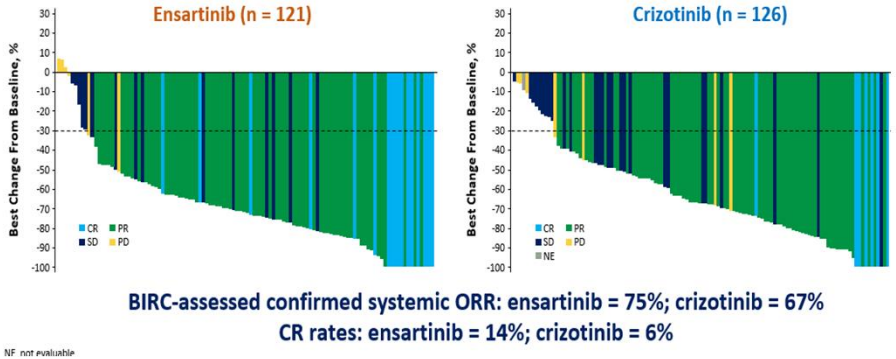
NR, not reached.

	Ensartinib (n = 143)	Crizotinib (n = 147)
mPFS (95% CI), mo	**25.8** (21.8-NR)	**12.7** (9.2-6.6)
Hazard ratio (95% CI)	**0.51** (0.35-0.72)	
P value (log-rank test)	**.0001**	

	Median follow-up (range), mo
Ensartinib	23.8 (0-44)
Crizotinib	20.2 (0-38)

Phase 3 Randomized Study of Ensartinib vs Crizotinib in Anaplastic Lymphoma Kinase (ALK)–Positive NSCLC Patients: eXalt3

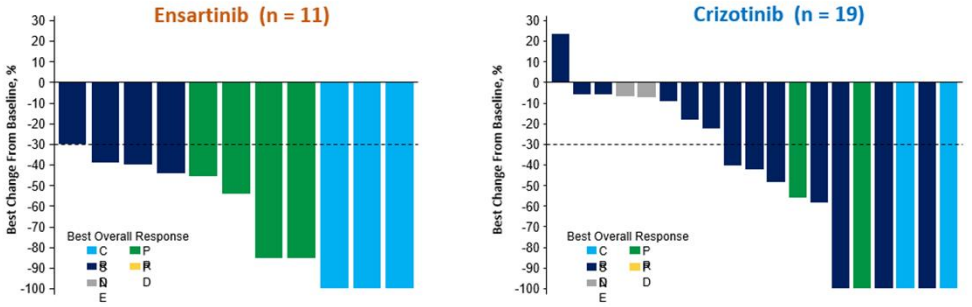
BIRC-Assessed Best Systemic Change From Baseline (mITT)



BIRC-assessed confirmed systemic ORR: ensartinib = 75%; crizotinib = 67%
CR rates: ensartinib = 14%; crizotinib = 6%

NE, not evaluable

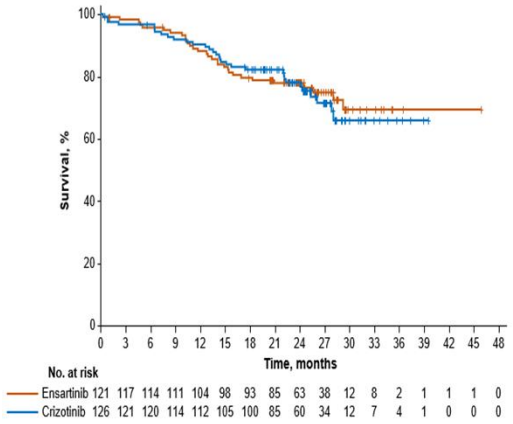
BIRC-Assessed Intracranial Best Change From Baseline in Patients With Measurable Brain Metastases (mITT)



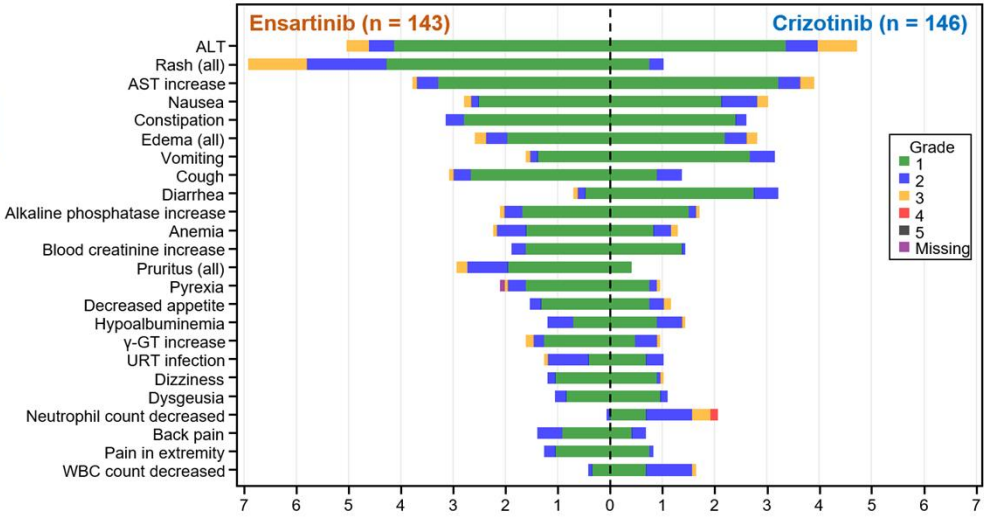
BIRC-assessed intracranial confirmed ORR: ensartinib = 64%; crizotinib = 21%

Phase 3 Randomized Study of Ensartinib vs Crizotinib in Anaplastic Lymphoma Kinase (ALK)–Positive NSCLC Patients: eXalt3

Overall Survival (mITT)



	Ensartinib (n = 121)	Crizotinib (n = 126)
Median OS (95% CI), mo	NR (NR-NR)	NR (NR-NR)
Hazard ratio (95% CI)	**0.88** (0.52-1.50)	
P value (log-rank test)	**.6470**	
24-mo OS (95% CI), %	78 (69-84)	78 (69-84)

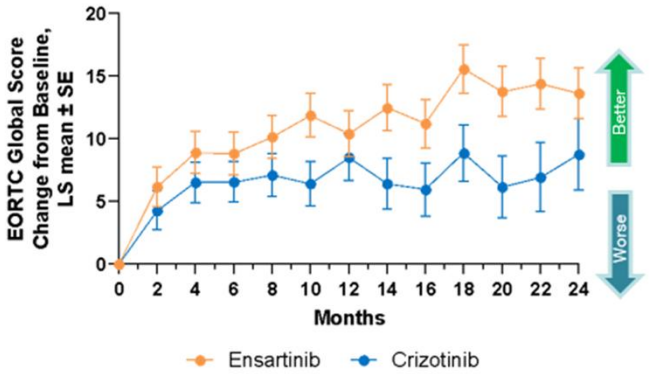


QUALITY-OF-LIFE OUTCOMES AND SUBGROUP ANALYSIS IN A PHASE 3 RANDOMIZED STUDY OF ENSARTINIB VS CRIZOTINIB IN ANAPLASTIC LYMPHOMA KINASE (ALK)-POSITIVE NSCLC PATIENTS: EXALT3

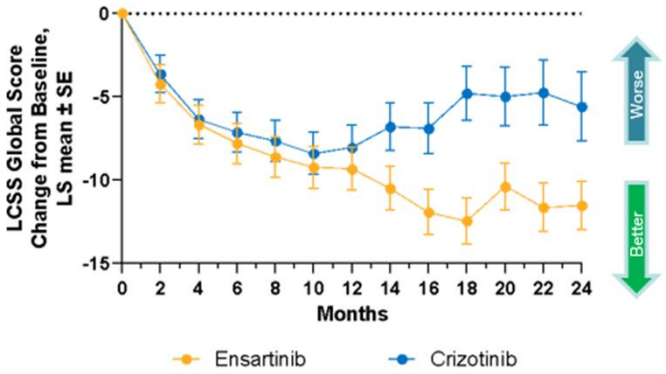
Wu Y,[1] Wang Z,[2] Wu G,[3] Poddubskaya E,[4] Mok T,[5] Reck M,[6] Chiappori A,[8] Lee DH,[9] Breder V,[10] Orlov S,[11] Cicin I,[12] Cheng Y,[13] Liu Y,[14] Fan Y,[15] Yen J,[16] Zhou J,[17] Liang C,[17] Mao L,[17] Selvaggi G,[17] Horn L,[18] Wakelee H[19]

QOL (ITT population)

Change from Baseline in EORTC



Change from Baseline in LCSS

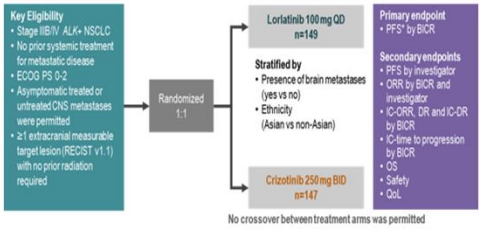


- Patients treated with ensartinib had better QOL scores on both the EORTC and LCSS
- Benefit appeared to be maintained over time

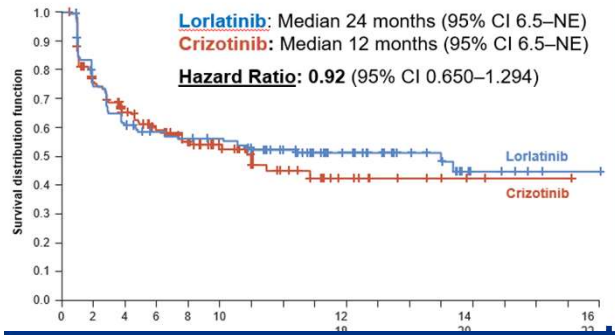
EORTC, European Organisation for Research and Treatment of Cancer; LCSS, Lung Cancer Symptom Scale; LS, least squares; QOL, quality of life.

Patient-reported outcomes from the randomized Phase 3 CROWN study of first-line lorlatinib versus crizotinib in *ALK*+ NSCLC

Julien Mazieres,[1] Laura Iadeluca,[2] Alice T. Shaw,[3] Benjamin Solomon,[4] Todd M. Bauer,[5] Filippo de Marinis,[6] Enriqueta Felip,[7] Yasushi Goto,[8] Dong-Wan Kim,[9] Tony Mok,[10] Arlene Reisman,[2] Holger Thurm,[11] Anna Polli,[12] Geoffrey Liu[13]

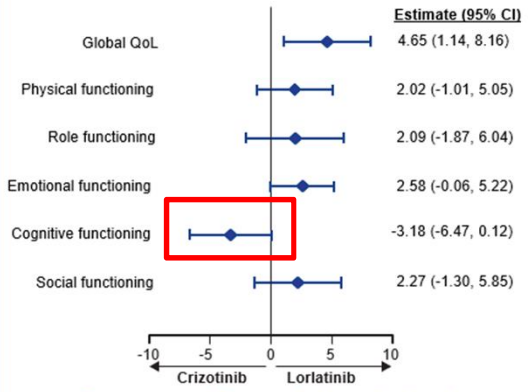


TIME TO DETERIORATION IN GLOBAL QoL



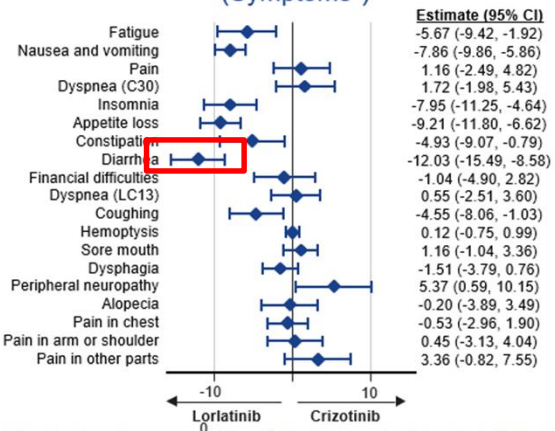
DIFFERENCES IN CHANGE FROM BASELINE UP TO BUT NOT INCLUDING EOT (MIXED MODEL)

EORTC QLQ-C30
(Global QoL and Functioning[a])



There were no differences between treatment arms in any functioning domain

EORTC QLQ-C30 and LC13
(Symptoms[b])



For diarrhea there was both a clinically meaningful and statistically significant difference favoring lorlatinib

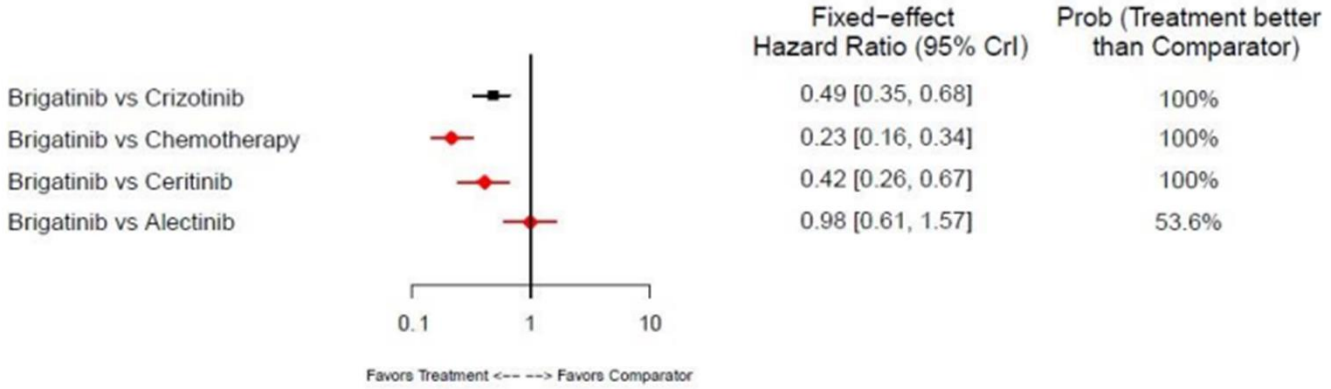
Included patients in the EORTC QLQ-C30 PRO analysis set with a score at baseline and post-baseline assessment. Analysis based on random-intercept, random-slope, mixed-effects model with an intercept term, treatment, time (as a continuous variable), treatment-by-time, baseline and randomization stratification factors as covariates. Analysis model included post-baseline assessments up to EOT, but not including EOT

First-line Brigatinib in Anaplastic Lymphoma Kinase-positive Non-small Cell Lung Cancer: A Network Meta-Analysis

Huamao M. Lin[1], Allie B. Cichewicz[2], Binod Neupane[3], Yanyu Wu[1], Lydia Vinals[4], Kyle Fahrbach[2], Karen L. Reckamp[5]

Brigatinib significantly reduced the risk of disease progression or death (IRC-assessed PFS) compared with ceritinib, crizotinib, and chemotherapy.

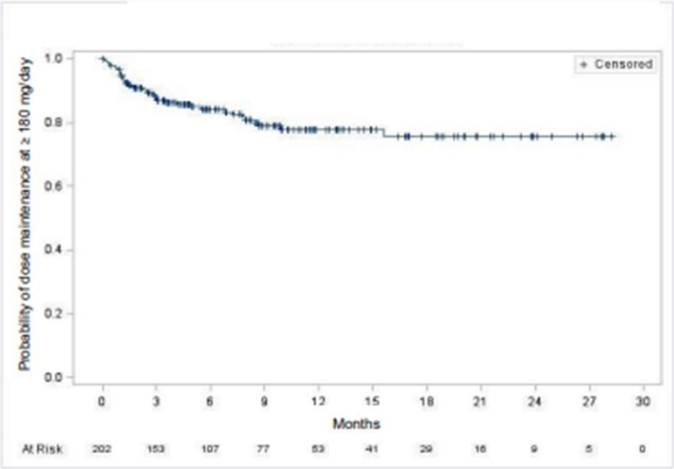
- No significant differences were observed between brigatinib and alectinib.



Real-World Brigatinib Dosing Patterns in Patients with Anaplastic Lymphoma Kinase Positive Non-Small Cell Lung Cancer in the United States

Huamao Mark Lin[1], Yanyu Wu[1], Magdaliz Gorritz[2], Catherine Balderston McGuiness[2], Wei-Ti Huang[2], Chi-Chang Chen[2], Kaili Ren[1], D. Ross Camidge[3]

Figure 2. Time to brigatinib dose reduction in patients who reached a dose of ≥ 180 mg/day



Time	N at Risk	Probability of Continued Therapy with Dose ≥ 180 mg/day
3 months	156	89.5%
6 months	104	86.0%
12 months	53	80.2%

Reduced Dose	N	%
<90 mg/day	6	18.8%
90 mg/day	7	21.9%
120 mg/day	14	43.8%
>120 mg/day	5	15.6%

- A total of 202 (84.2%) patients reached a dose of at least 180 mg/day, of which 87.1% were treated after 1+ prior lines.
- Of these 202 patients, 32 (15.8%) had a later dose reduction
- Of the patients with a dose reduction, the majority (59.4%) reduced to ≥ 120 mg/day

Drug (dose)	Clinical trial	# of patients	CNS Mets at Baseline	ORR (%) (95% CI)	PFS (months) in ITT (95% CI)	Intracranial Response Rate (%) (95% CI)	Ref.
Ensartinib (225 mg po / day)	eXalt-3 - *NCT02767804* - Phase 3 - Prior chemo allowed	290	Ensartinib: 33% Crizotinib: 39%	Ensartinib = 75% Crizotinib = 67%	Ensartinib: 25.8 mo Crizotinib: 12.7 mo HR 0.51 (0.35 - 0.72)	Ensartinib: 64% (Not reported) Crizotinib: 21% (Not reported)	Horn et al. IASLC WCLC 08/08/2020
Alectinib (600mg po twice/day)	ALEX trial - *NCT02075840* - Phase 3 - No prior chemo	303	Alectinib: 38% Crizotinib: 42%	Alectinib: 82.9% (76.0 - 88.5) Crizotinib: 75.5% (67.8 - 82.1)	Alectinib: 25.7 mo (19.9 - NE) Crizotinib: 10.4 mo (7.7 - 14.6) HR 0.50 (0.36 – 0.70) ASCO 2020 (investigator assessed) + Brain mets: Alectinib 25.4 mo; Crizotinib 7.4 mo; HR 0.37 No Brain mets: Alectinib 38.6 mo; Crizotinib 14.8 mo; HR 0.46	Alectinib: 81% (58 – 95) Crizotinib: 50% (28 – 72) HR 0.32 (0.15 - 0.64)	Initial Publication: Peters et al. *NEJM* 377;9 08/31/2017 Updated: Peters et al. *J Clin Oncol*. 2020;38(suppl 15)
Brigatinib (90mg po / day x 7 days, then 180mg po / day)	ALTA-1L - NCT02737501 - Phase 3 - Prior chemo allowed	275	Brigatinib: 29% Crizotinib: 30%	Brigatinib: 71% (62 - 78) Crizotinib: 60% (51 – 68)	Brigatinib: not reached (NR) Crizotinib: 9.8 mo (9.0 - 12.9) HR 0.49 (0.33 - 0.74) ESMO Asia 2019 (investigator assessed) + Brain mets: Brigatinib NR; Crizotinib 5.9 mo; HR 0.24 No Brain mets: Brigatinib 29.4 mo; Crizotinib 12.9 mo; HR 0.57	Brigatinib: 78% (52 – 94) Crizotinib: 29% (11 - 52)	Initial Publication: Camidge et al. *NEJM* 379;21 11/22/2018 Updated: Camidge et al. ESMO Asia Congress 2019. 11/23/2019
Lorlatinib (150mg po / day)	CROWN - *NCT03052608* - Phase 3 - No prior chemo	296 *Aug 5, 2020 Press release – primary endpoint met*	Note: Experimental Arm 1 of the Lorlatinib Phase 1 trial included treatment naïve patients. Response rate was 90% (27/30). (reference: Solomon B et al. The Lancet Vol 19 December 2018.)		Note: The next-generation ALK TKI, **Ceritinib**, was also tested in the first line setting. In this case, the comparator was cisplatin / carboplatin + pemetrexed, in the ASCEND-4 study (reference: Soria JC, et al. Lancet. 2017 Mar 4;389(10072):917-929.)		

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Associate Professor of Medicine, Division of Hematology
Ingram Associate Professor of Cancer Research
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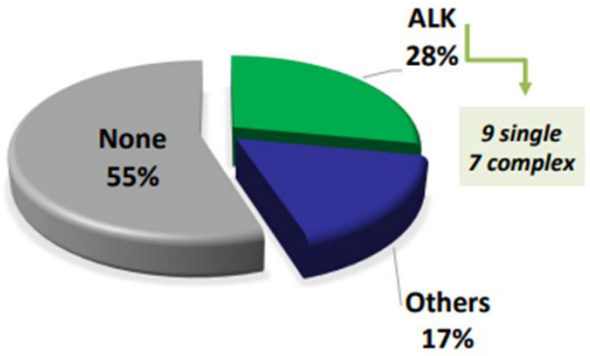
Nashville, TN U.S.A.

The ARIA study:
Activity of Next-generation ALK TKIs based on *ALK* Resistance mutations detected by liquid biopsy in *ALK* positive NSCLC patients

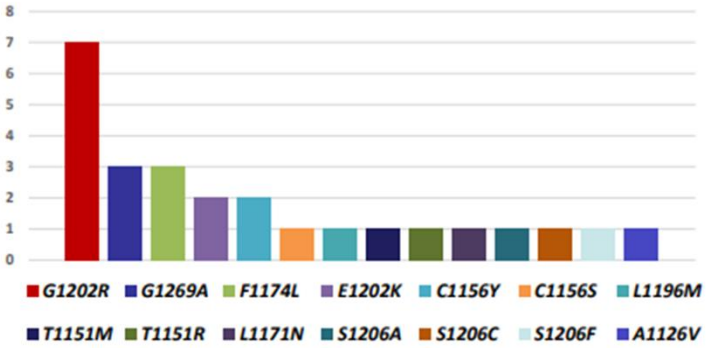
L. Mezquita[1,2], A. Swalduz[3], E. Auclin[4], M. Carter[5], C. Steendam[6], M. Aldea[2], M. Scheffler[7], J. Corral[8], S. Viteri[9], E. Segui[1], A. Barba[10], E.J. Dubbink[6], D. Planchard[2], D. Vasseur[2], R. Reyes[1], C. Caramella[2], G. Recondo[2], P. Saintigny[3], F. Blackhall[5], A.M. Dingemans[6], B. Besse[2]

- ***ALK*m were detected in 28% of patients**



5 post-alectinib; 5 post-ceritinib; 6 post-brigatinib

- **16 Cases with *ALK*m on blood**
  - Wide spectrum of *ALK*m detected
  - Range: 1- 6 *ALK*m per sample



RESULTS: Lorlatinib outcomes by ctDNA mutations

- **N=13 cases with *ALK* resistance mutations** →
  - ***ALK single (3 cases):*** *G1202R*
  - ***ALK single:*** *C1156Y*
  - ***ALK single:*** *L1171N*
  - ***ALK single:*** *F1174V*

- ***ALK single + others:*** *T1151R+TP53*
- ***ALK single + others:*** *I1171M+EGFR+EGFRamp*
- ***ALK complex:*** *.G1202R+G1269A+T1151M+C1156Y+F1174L+S1206F*
- ***ALK complex:*** *G12023+A1126V*
- ***ALK complex + others:*** *G1202R+F1174L+TP53*
- ***ALK complex + others:*** *F1774L+S1206C+G1202R+S1206A+L1196M+E1210K+BRCA2+TP53+METamp+EGFRamp*
- ***ALK complex + others:*** *D1203N+L1196M+KRAS+TP53*

	Overall	*ALK* mutations	Others	None
	N= 42	**n= 13**	**n= 7**	**n= 22**
PFS, median (95% CI)	**7.6 months (5.26- 11.14)**	**6.5 months (3.61-NR)**	**7.6 months (5.22-NR)**	**7.3 months (4.63-NR)**
12 months-PFS rate	**29.5% (17.7-49.1)**	**30% (12.0-74.7)**	**28.6% (8.9-92.2)**	**30% (14.6-61.6)**
ORR	38% (16/58)	**46% (6/13)**	71% (5/7)	23% (5/22)
ORR CNS	62% (18/29)	**56% (5/9)**	60% (3/5)	67% (10/15)
OS*, median (95% CI)	55.5 months (45.0-NR)	**62.6 months (54.8-NR)**	45.0 months (24.5-NR)	NR (41.9-NR)

PFS: progression-free survival; ORR: objective response rate; CNS: central nervous system; OS: overall survival; *since systemic therapy start

GLASS: Global Lorlatinib for *ALK*(+) and *ROS1*(+) retrospective Study: real world data of 123 NSCLC patients

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Extracranial best response to Lorlatinib treatment – ROS1+

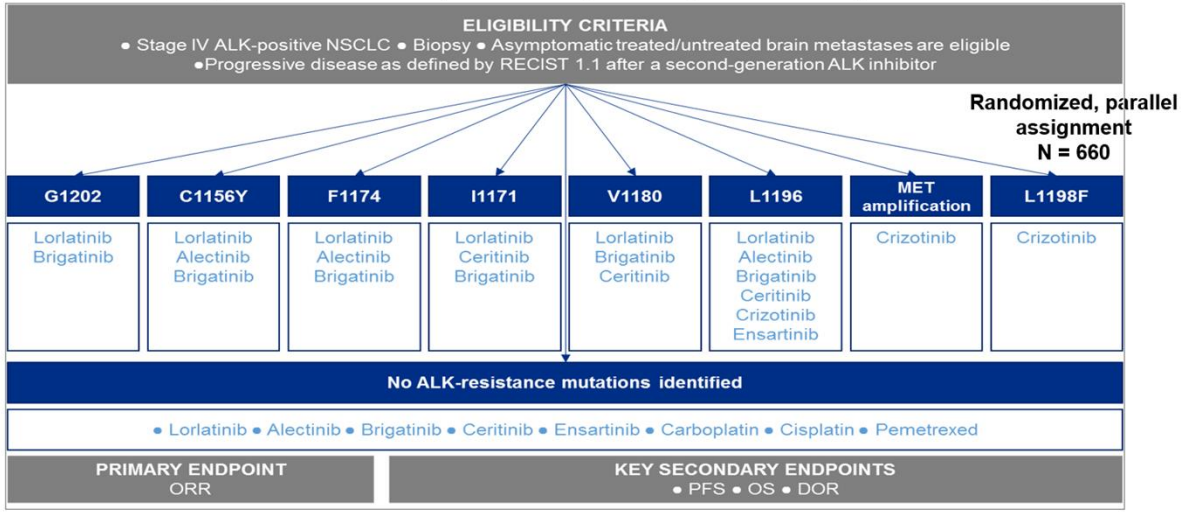
Systemic Best response to Lorlatinib treatment	Summary of cases	2nd Line	3rd Line	4th Line	5th Line	6th Line	7th Line	8th Line
ORR	**8 (62%)**	**1 (25%)**	**4 (100%)**	**1 (33%)**			**1 (100%)**	**1 (100%)**
DCR	12 (92%)	4 (100%)	4 (100%)	2 (67%)			1 (100%)	1 (100%)
CR	0 (0%)							
PR	8 (61%)	1 (25%)	4 (100%)	1 (33%)			1 (100%)	1 (100%)
SD	4 (31%)	3 (75%)		1 (33%)				
PD	1 (8%)			1 (33%)				
Available data	13 (100%)	4 (100%)	4 (100%)	3 (100%)			1 (100%)	1 (100%)
Indeterminate/ Missing Data	4	2	2					
Total ROS1(+) cases	17	6	6	3			1	1

	Crizotinib	Ceritinib	Ensartinib	Alectinib	Brigatinib	Lorlatinib
WT	23.30 16.23 to 33.46	12.47 7.813 to 19.92	1.281 1.073 to 1.530	1.377 1.044 to 1.818	0.959 0.794 to 1.158	0.267 0.212 to 0.337
G1123S	27.17 16.75 to 44.09	661.6 271.7 to 1611	0.983 0.711 to 1.358	1.559 1.167 to 2.082	11.14 7.082 to 17.53	2.855 2.238 to 3.642
L1152R	361.3 205.5 to 635.1	167.3 145.2 to 968.4	34.75 23.42 to 51.56	3.501 3.110 to 3.943	0.798 0.640 to 0.995	7.402 8.190 to 20.24
C1156Y	306.0 100.6 to 931.3	199.7 54.09 to 737.4	27.27 9.057 to 82.12	13.61 5.461 to 33.91	7.659 3.999 to 14.67	8.938 4.206 to 18.99
I1171T	471.9 190.3 to 1171	165.1 59.20 to 460.4	69.25 339.21 to 122.3	379.8 126.4 to 1141	25.85 10.58 to 63.14	52.53 23.42 to 117.8
F1174C	294.4 72.52 to 1195	205.1 69.89 to 601.6	58.55 24.82 to 138.1	19.22 9.222 to 40.05	29.10 12.31 to 68.78	9.786 5.047 to 18.98
F1174V	57.91 33.13 to 100.7	51.28 24.74 to 106.3	6.992 5.689 to 8.593	1.988 1.700 to 2.325	5.165 4.110 to 6.491	2.100 1.732 to 2.545
V1180L	114.5 44.44 to 295.0	11.87 7.962 to 17.70	4.436 3.401 to 5.786	1902 1186 to 3051	1.563 1.233 to 1.983	1.650 1.394 to 1.953
L1196M	637.1 246.7 to 1645	133.8 59.24 to 302.4	59.53 31.25 to 113.4	58.74 23.75 to 145.3	20.09 8.841 to 45.65	56.52 30.07 to 106.2
L1198F	27.97 14.30 to 54.73	1722 587.6 to 5045	0.323 0.199 to .524	201.9 125.2 to 325.5	48.53 29.15 to 80.80	56.61 26.51 to 120.9
G1202del	179.9 59.72 to 541.6	319.1 165.9 to 614.0	138.9 68.17 to 283.0	963 614.7 to 1509	25.02 14.85 to 42.15	11.15 5.858 to 21.21
G1202R	289.5 197.4 to 424.4	252.4 147.7 to 413.3	316.0 212.4 to 470.2	1918 1151 to 3197	30.92 233.47 to 40.72	31.18 26.41 to 36.81
S1206Y	177.5 65.38 to 482.0	53.14 25.64 to 110.1	31.45 21.92 to 45.14	7.216 3.878 to 13.43	17.56 8.543 to 36.10	4.704 2.795 to 7.918
E1210K	4027 887.6 to 20981	345.6 147.4 to 809.1	3010 1015 to 9077	5065 2991 to 8557	299.2 144.7 to 622	38.04 10.67 to 139.3
F1245C	197.6 68.43 to 571.3	216.3 87.17 to 536.6	22.03 11.88 to 40.85	13.62 6.995 to 26.53	26.00 12.48 to 54.18	7.357 4.538 to 11.93
G1269A	699.3 176.9 to 2765	67.13 29.22 to 154.3	221.8 97.82 to 503.1	58.66 42.83 to 80.35	11.41 5.492 to 23.72	76.39 31.93 to 182.7

1000nM
800nM
600nM
400nM
200nM

Schema for NCI ALK Protocol

A Phase II study biomarker-driven protocol for previously treated ALK-positive NSCLC patients



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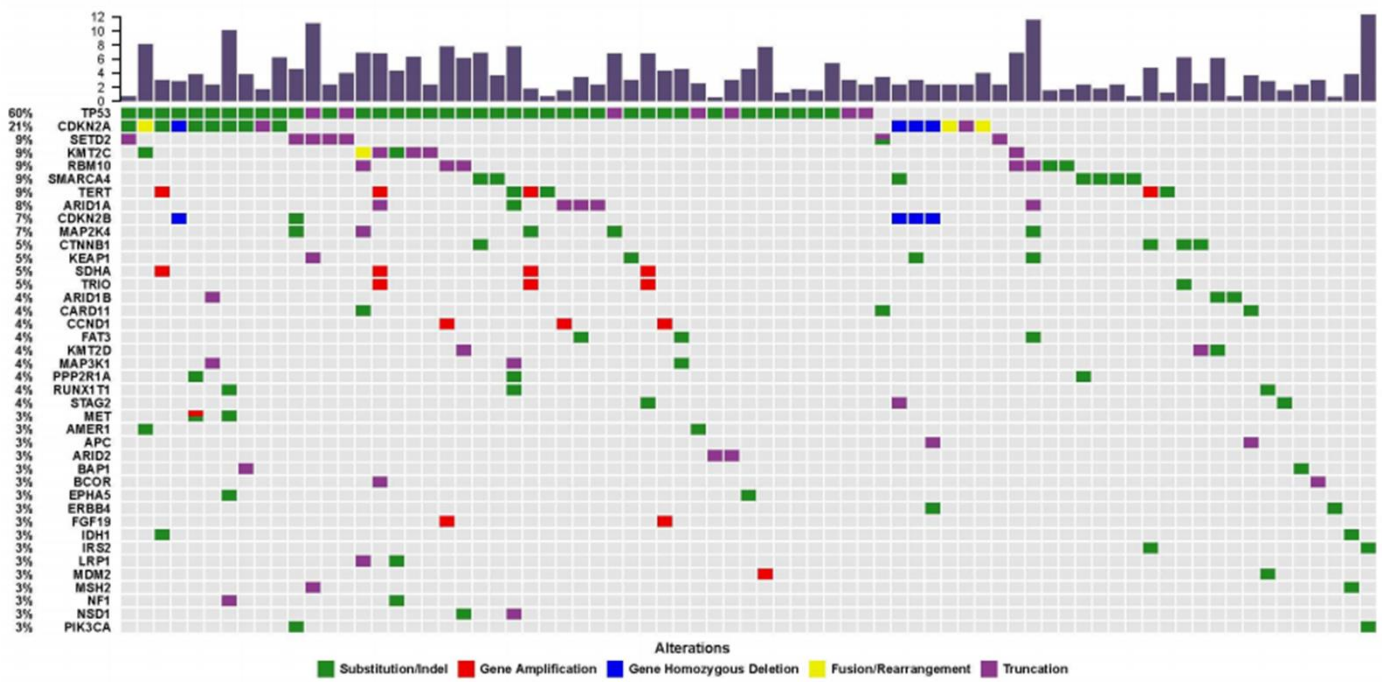
P88.01 - Hanlin Xu

Comprehensive Profiling of ROS1 Fusions in Chinese Non-Small Cell Lung Cancer Patients

N=102 patients with ROS1



Comparative effectiveness of crizotinib versus entrectinib in ROS1-positive non-small cell lung cancer (NSCLC) using clinical trial and real-world data

Michael Groff[1], Gabriel Tremblay[1], Laura Iadeluca[2], Keith Wilner[3], Robin Wiltshire[4], Lauren Bartolome[2], Tiziana Usari[5], Joseph C. Cappelleri[6], D. Ross Camidge[7]

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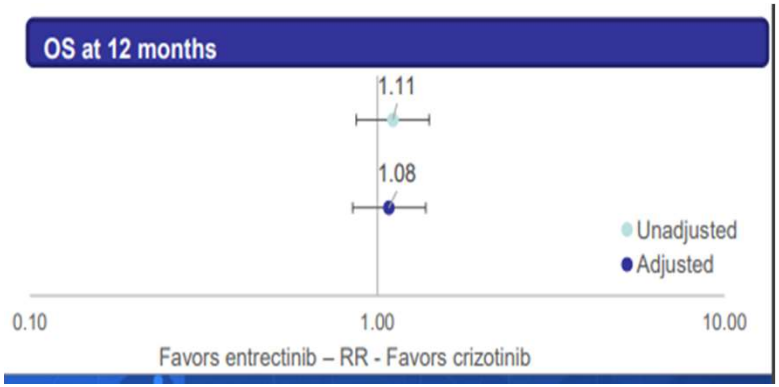

Conclusions

- Large differences were observed between the crizotinib clinical trial endpoint values and the crizotinib endpoints from RWD, both Flatiron and US Oncology/McKesson.
- RWD sources were not consistent in their effectiveness assessments.
- Population adjusted analyses suggest a portion of the difference is attributable to imbalances in known and potentially unknown patient characteristics between the clinical trial and real-world populations. This raises concerns about RWD head-to-head comparisons.
- Overall, RWD, ITC and STC comparisons of treatments may all be subject to imbalances and biases and direct head-to-head comparisons in appropriately stratified randomized trials should remain the gold standard.

Clinical characteristics and outcome of patients with non-small cell lung cancer harboring BRAF Mutations

Mina. Zhang, H. Wang, Z. Ma, X. Zhang, G. Zhang, P. Li, X. Yan;
Affiliated cancer hospital of zhengzhou university, Zhengzhou， China

Results 46/3217 (1.4%) NSCLC had BRAF mutation, 35(76%)V600E mutation and11non-V600E mutation. more common for V600E had concomitant mutation, 2 had a concomitant mutation in EGFR 19 del,1 in L858R ,1 inTP53 and 1 in PIK3CA ; Clinical and pathological features

BRAF Mutation And Peridiagnosis Thromboembolic Events In Advanced NSCLC Patients

Inmaculada Aparicio Salcedo, Blanca Morón, Miguel García Pardo , Íñigo Martínez , Manuel Alva, Marta Arregui, Victoria Tirado, Mar Galera, Rosa Álvarez, Laura Ortega, Andrés J. Muñoz, Antonio Calles

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BRAF mutation was identified in 11/192 patients (**incidence 5.7%**):

The incidence rate of **TEE was 36.4%** (4/11 patients).

- If these results are confirmed in larger cohorts, prophylactic anticoagulation may be recommended in these patients.

Take Home Messages

- Don’t forget to test for ALK, ROS1, and BRAF (among others)!
- 5 ALK inhibitors are approved, plus ensartinib emerging?
- Alectinib or brigatinib are the current 1st line standard of care.
- Test for ALK kinase domain mutations (tissue or ctDNA) - may predict response to other ALK inhibitors.
- For ROS1 continue to offer crizotinib or entrectinib (esp with brain mets)
- For BRAF V600E continue to offer dabrafenib + trametinib (VTE?)