CARCINOMA POLMONARE:
QUALI NOVITÀ NEL 2022?

Il trattamento della malattia ALK positiva

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DISCLOSURES

No disclosure

AGENDA: ALK+ NSCLC in 2022, one more step to the future

The basements
- a wonderful story -

-First/second gen vs CT in pretreated *PROFILE 1007/ASCEND-5* (HR 0.49)
-First/second gen vs CT in 1L *PROFILE 1014/ASCEND-4*

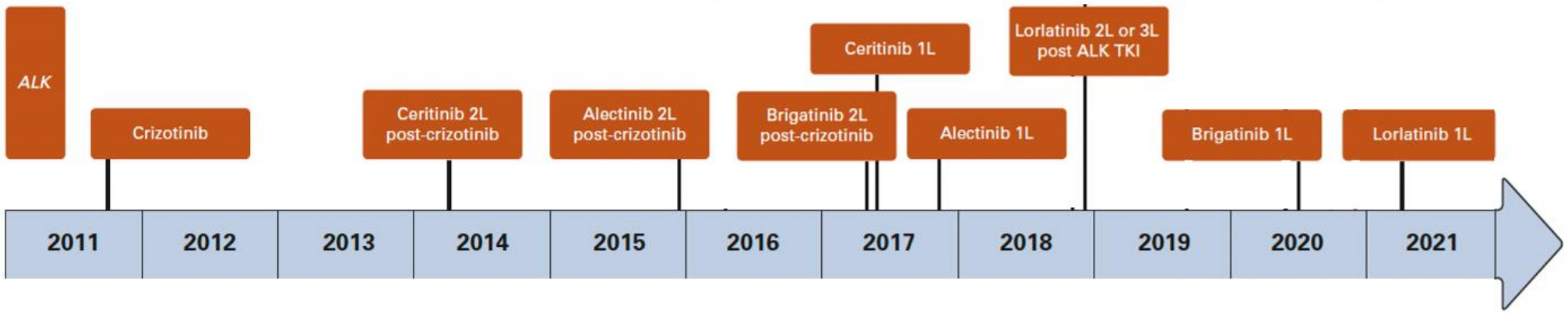
The current
- Treatment scenario -

-Second gen vs first gen ALK TKI
-Third gen vs first gen ALK TKI
-TKI sequencing

The future
- Are we ready for next steps? -

Room to improve:
-testing
-biology
-resistance
-patients selection

The evolving treatment landscape of ALK-positive NSCLC

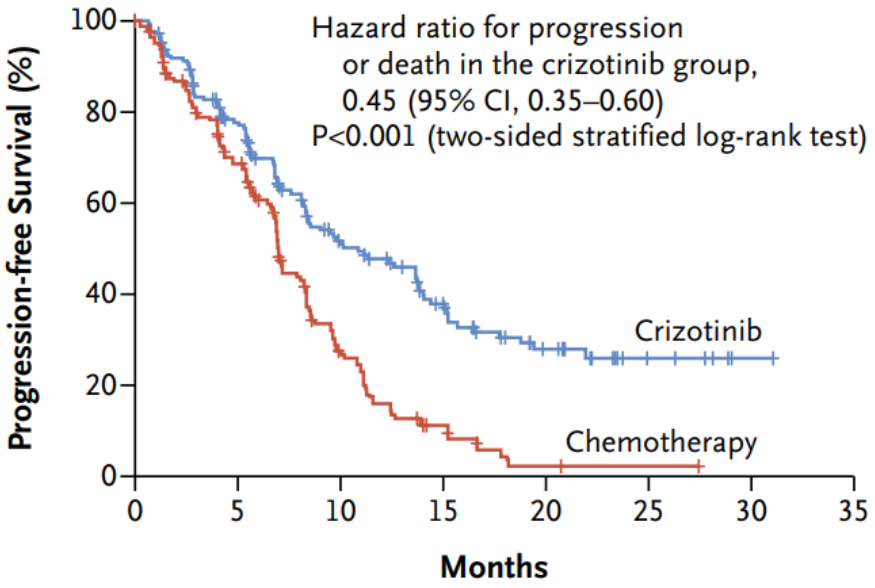


Adapted from Tan AC, J Clin Oncol 2022

1L ALK inhibitors vs chemotherapy

Crizotinib **PROFILE1014**

mPFS: 10.9 mos

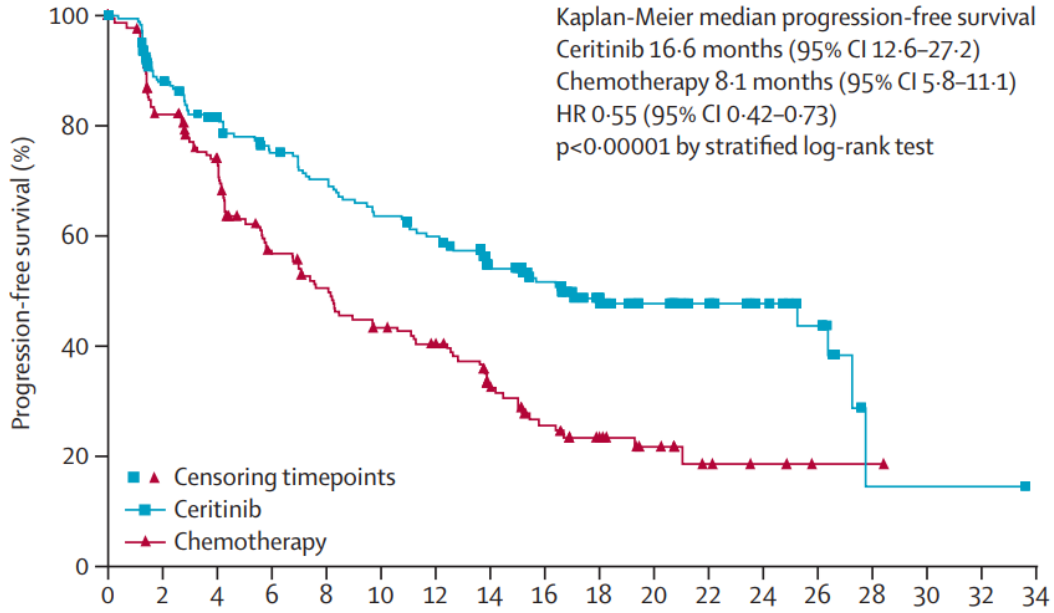


No. at Risk

Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

Ceritinib **ASCEND-4**

mPFS: 16.6 mos



Number at risk

Ceritinib	189	155	139	125	116	105	98	76	59	43	32	23	16	11	1	1	1	0
Chemotherapy	187	136	114	82	71	60	53	35	24	16	11	5	3	1	1	0	0	0

50% risk reduction of developing disease progression

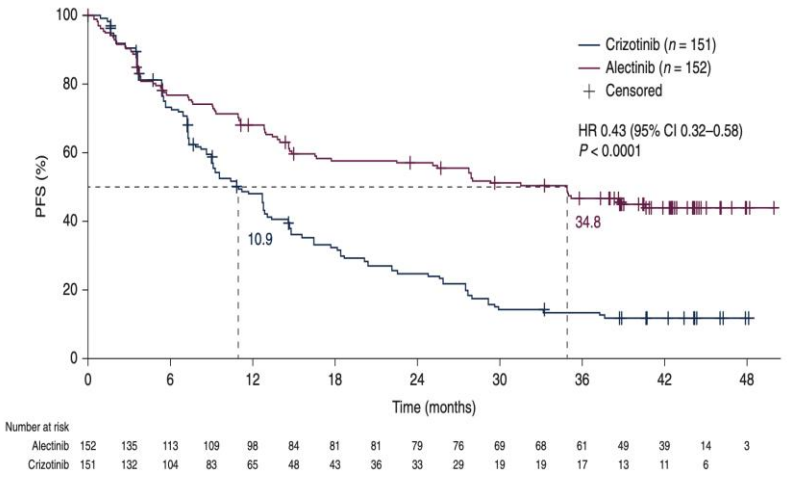
Solomon B NEJM 2014; Soria JC Lancet 2017

1L 2nd gen ALK inhibitors vs crizotinib

Alectinib **Global ALEX**

mPFS:

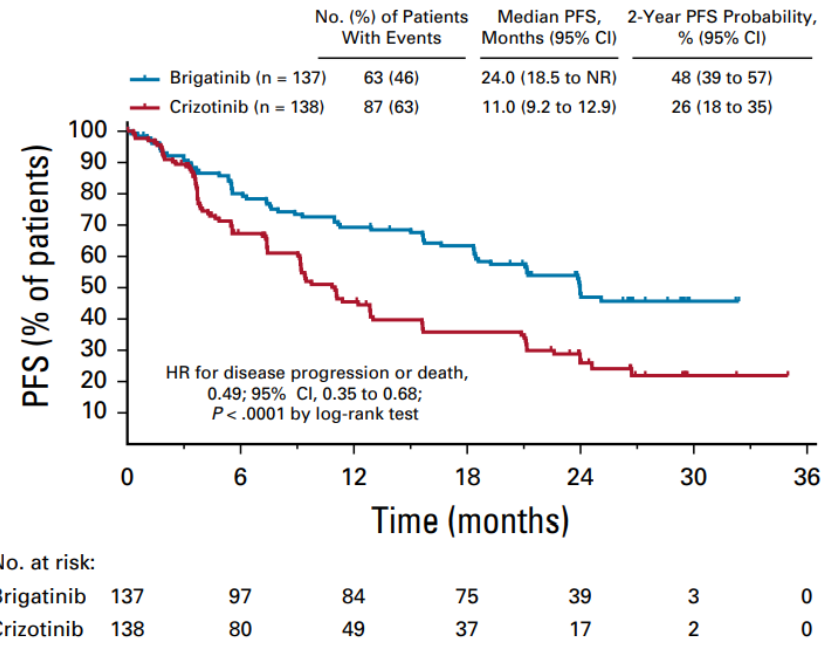
BIRC 25.7 m | Inv* 34.8 m



Brigatinib **ALTA-1L**

mPFS:

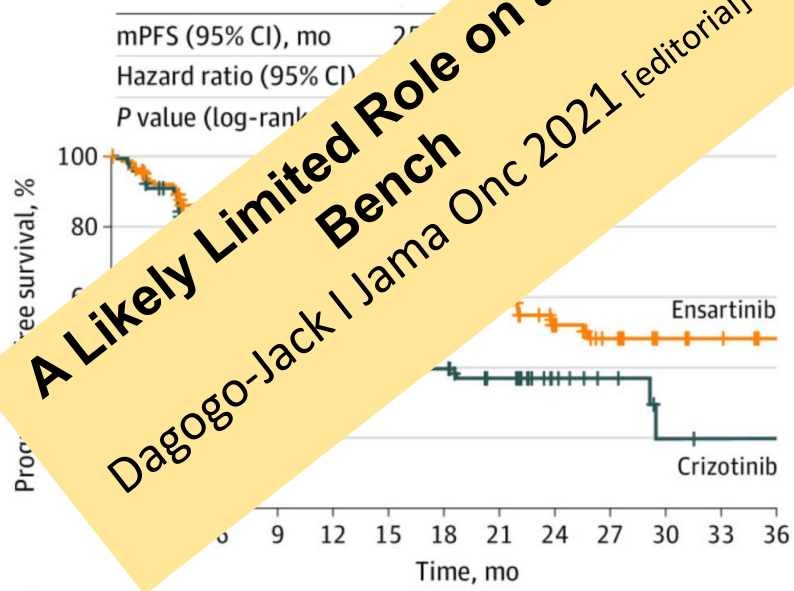
BIRC* 24 m | Inv 30.8 m



Ensartinib **eXALT3**

mPFS:

BIRC* 25



A Likely Limited Role on a Deep Bench

Dagogo-Jack I Jama Onc 2021 [editorial]

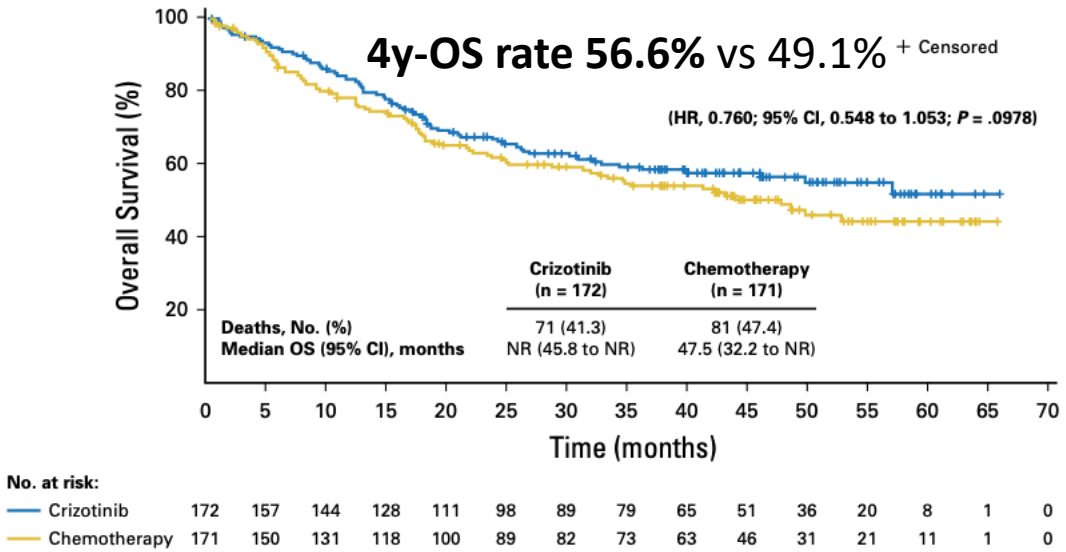
50% risk reduction of developing disease progression

* Primary endpoint

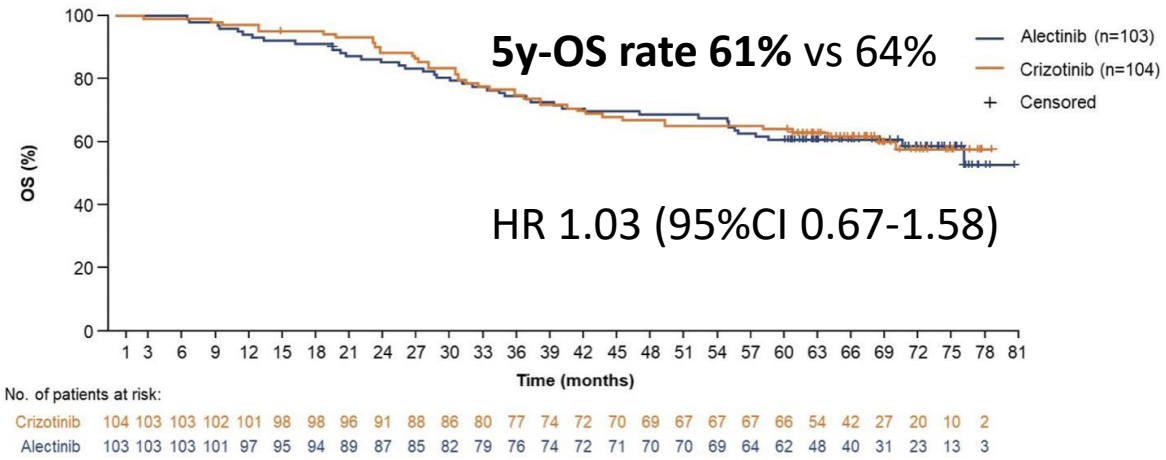
Mok T Ann Oncol 2020; Camidge RD NEJM 2018; Horn L JAMA Onc 2021

1L ALK inhibitors: Landmark OS results

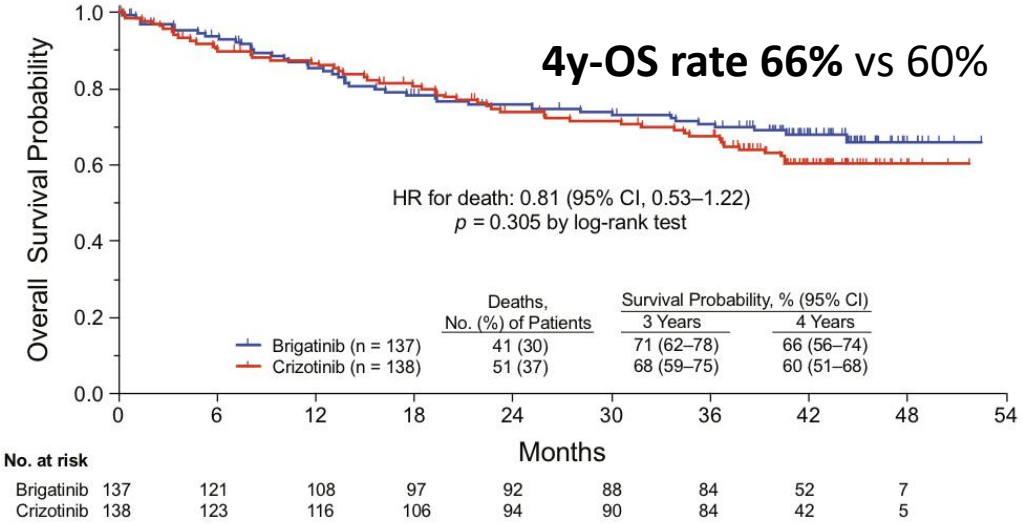
PROFILE1014



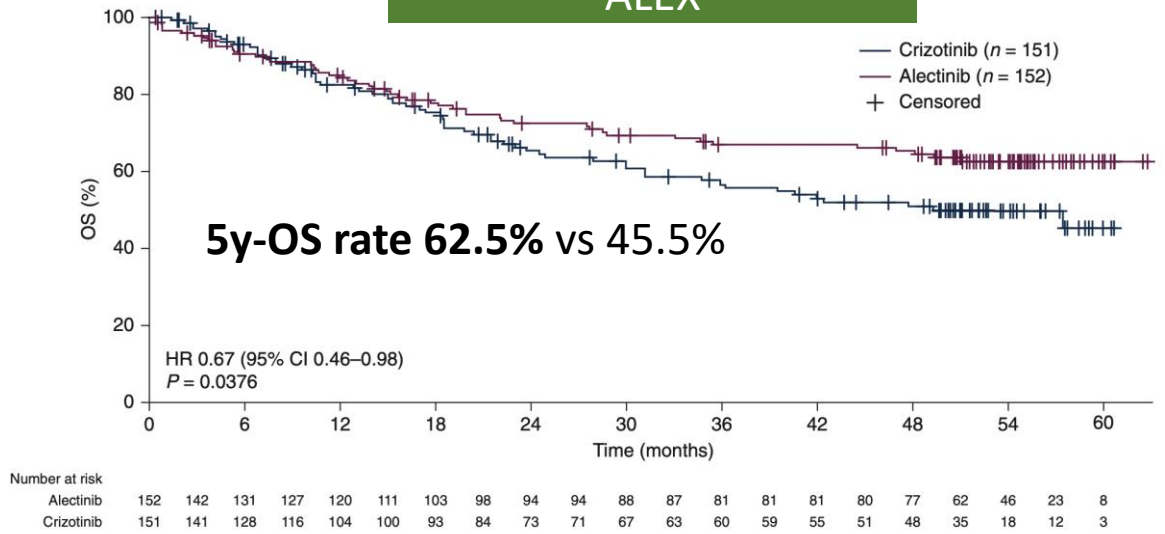
J-ALEX



ALTA-1L

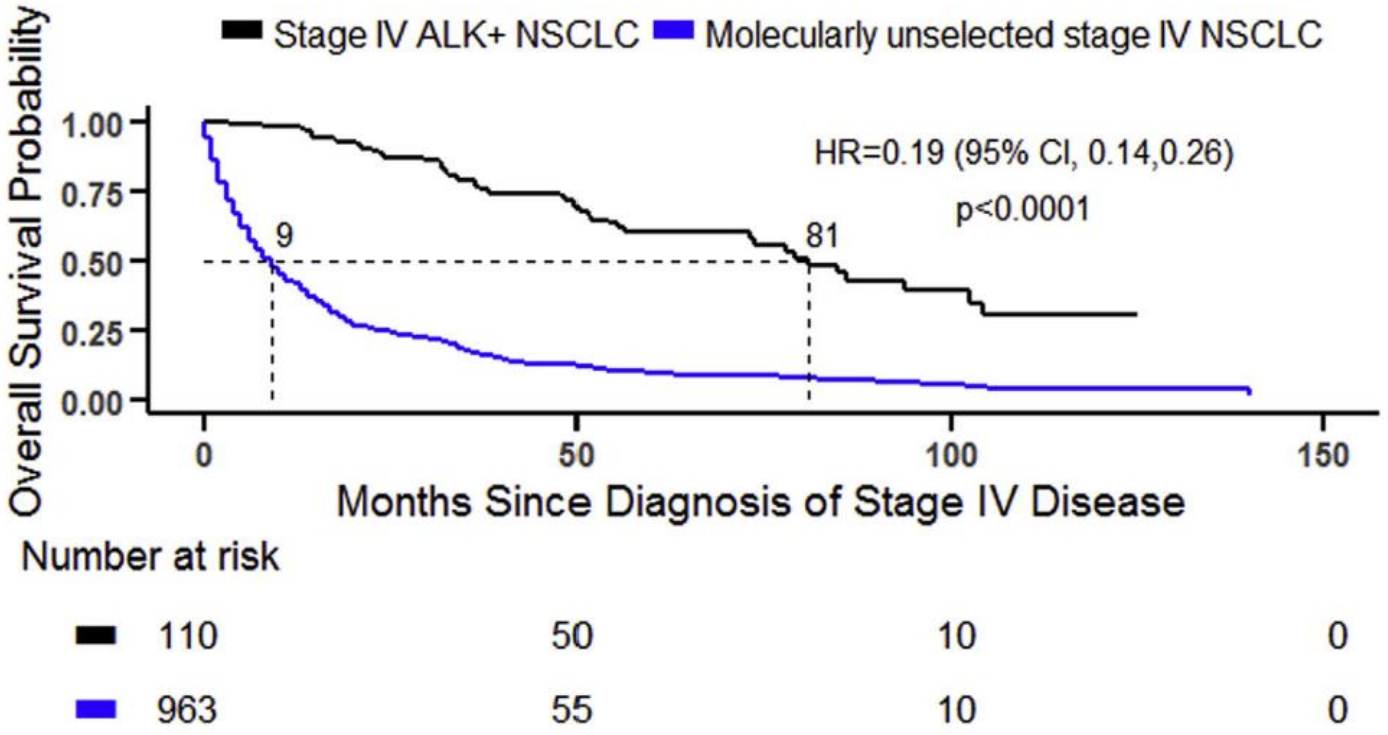


ALEX



Solomon B JCO 2018, Yoshioka ASCO 2021, Mok T Ann Oncol 2020, Camidge R JTO 2021

1L ALK inhibitors: the real impact on OS



[N=110 patients with ALK-positive NSCLC compared with all patients with NSCLC diagnosed at University of Colorado Cancer Center between 2004 and November 2017]

Pacheco JM et al, JTO 2019

1L ALK inhibitors: How to choose?

- Overall survival
- Progression free survival
- CNS activity
- Safety
- TKI sequencing
- Resistance mechanisms and biology

1L ALK inhibitors: CNS activity

	ALTA-1L		ALEX		eXalt3	
	Brigatinib	Crizotinib	Alectinib	Crizotinib	Ensartinib	Crizotinib
Patients with any brain mets at baseline, n	47	49	64	58	11	19
Confirmed IC-ORR, %	66	14	59	26	64	21
Complete IC response, %	45	2	45	9	27	10.5
Median IC-DoR (95% CI), months	27.1(16.9-42.6)	9.2(3.9-NR)	NE(17.3-NE)	3.7(3.2-6.8)	-	-
Patients with at least 1 measurable brain mets at baseline, n	18	23	22	21	11	19
Confirmed IC-ORR, %	78	26	81	50	64	21
Complete IC response, %	28	0	38	5	27	10.5
Median IC-DoR (95% CI), months	27.9(16.9-42.8)	9.2(3.9-NE)	17.3(14.8-NE)	5.5(2.1-17.3)	-	-

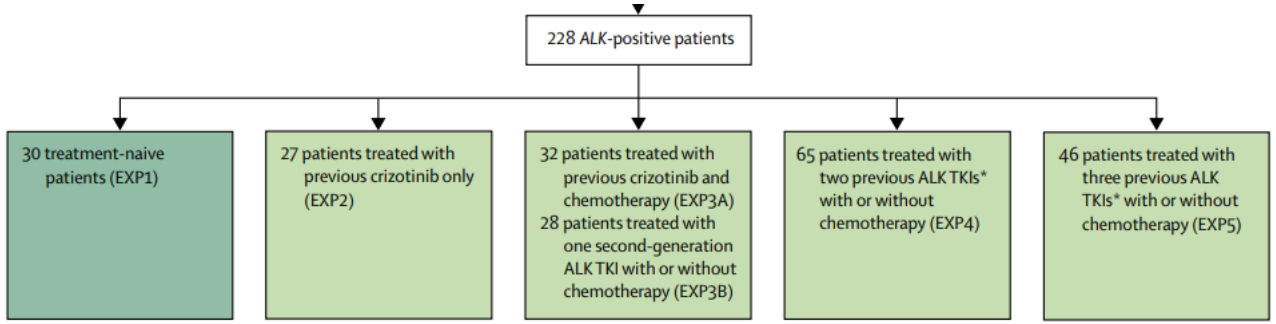
Camidge R, JTO 2021, Mok T Ann Oncol 2020, Horn WCLC Plenary 2020

1L ALK inhibitors: safety profile

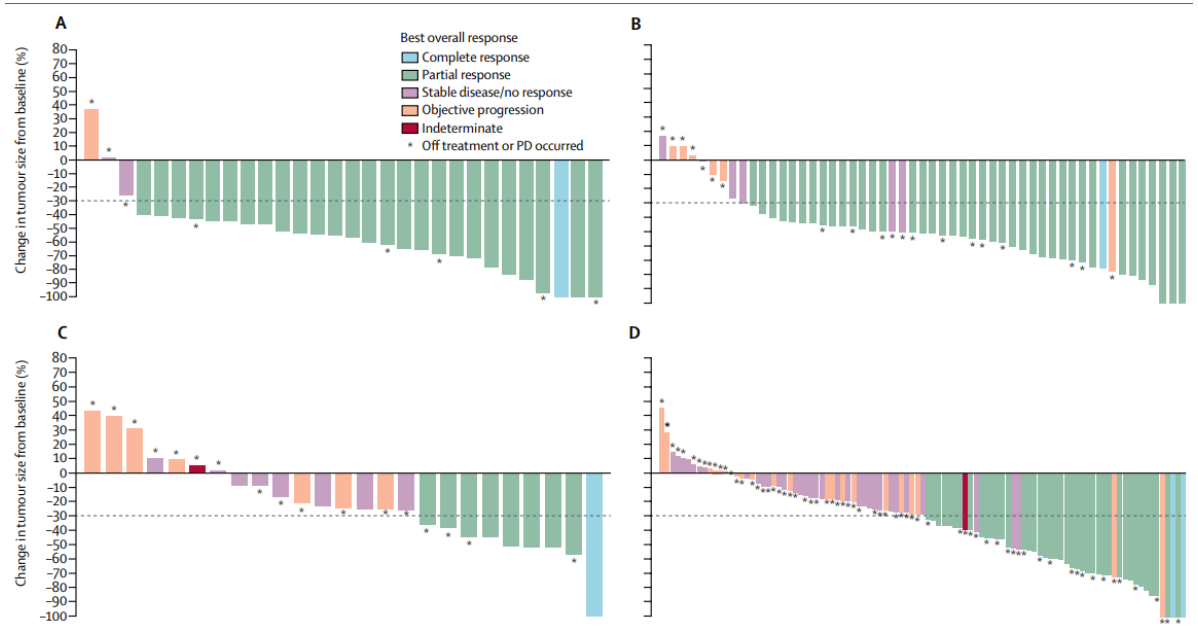
Drug (dose)	Serious TRAEs	TRAE leading to dose reduction (% pts)	TRAE leading to drug discontinuation (% pts)	TRAEs more common in study drug vs. crizotinib	Ref.
Alectinib (600mg po twice/day)	Alectinib = 28% Crizotinib = 29%	Alectinib = 16% Crizotinib = 21%	Alectinib = 11% Crizotinib = 13%	Anemia Myalgia Increased Bilirubin Increased weight Musculoskeletal pain Photosensitivity reaction	Initial Publication: Peters et al. *NEJM* 377;9 08/31/2017
Brigatinib (90mg po / day x 7 days, then 180mg po / day)	Brigatinib = 28% Crizotinib = 29%	Brigatinib = 28% Crizotinib = 29%	Brigatinib = 12% Crizotinib = 9%	Increased CK Cough Hypertension Increased Lipase Early onset ILD/pneumonitis	Initial Publication: Camidge et al. *NEJM* 379;21 11/22/2018
Ensartinib (225 mg po / day)	Ensartinib = 24% Crizotinib = 20%	Ensartinib = 24% Crizotinib = 20%	Ensartinib = 9% Crizotinib = 7%	Rash -- all grade ~70%, grade 1/2 ~60% Pruritis Pyrexia	Horn L et al. IASLC WCLC 08/08/2020

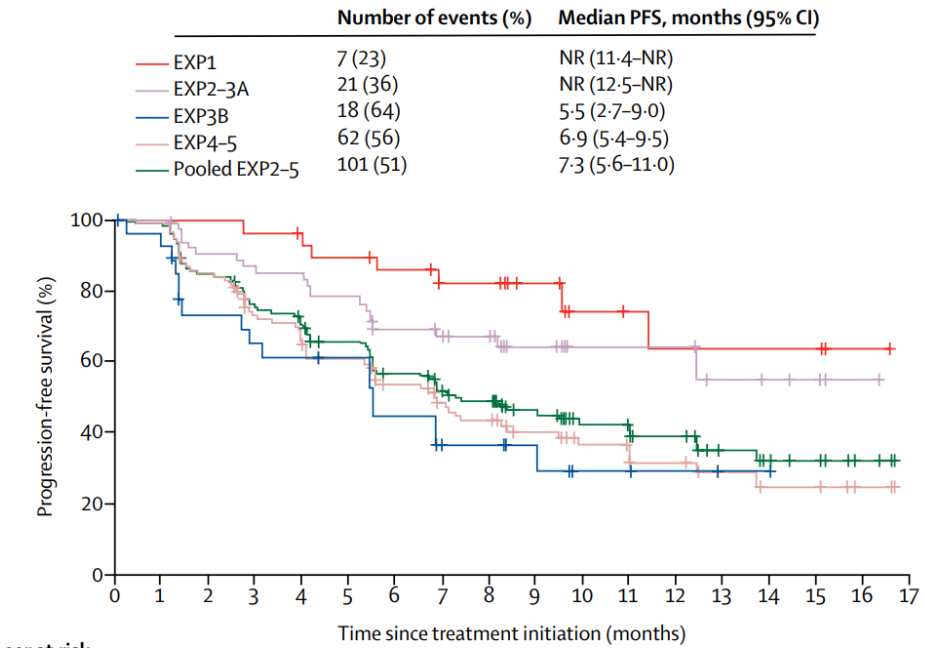
Adapted from Lovly WCLC Plenary 2020

1L ALK inhibitors: TKI sequencing – role of 3rd gen Lorlatinib in ALK-inh pretreated



Pooled EXP2-5 (up to 3 ALK-Is) ORR 50% mPFS 7.3 mos

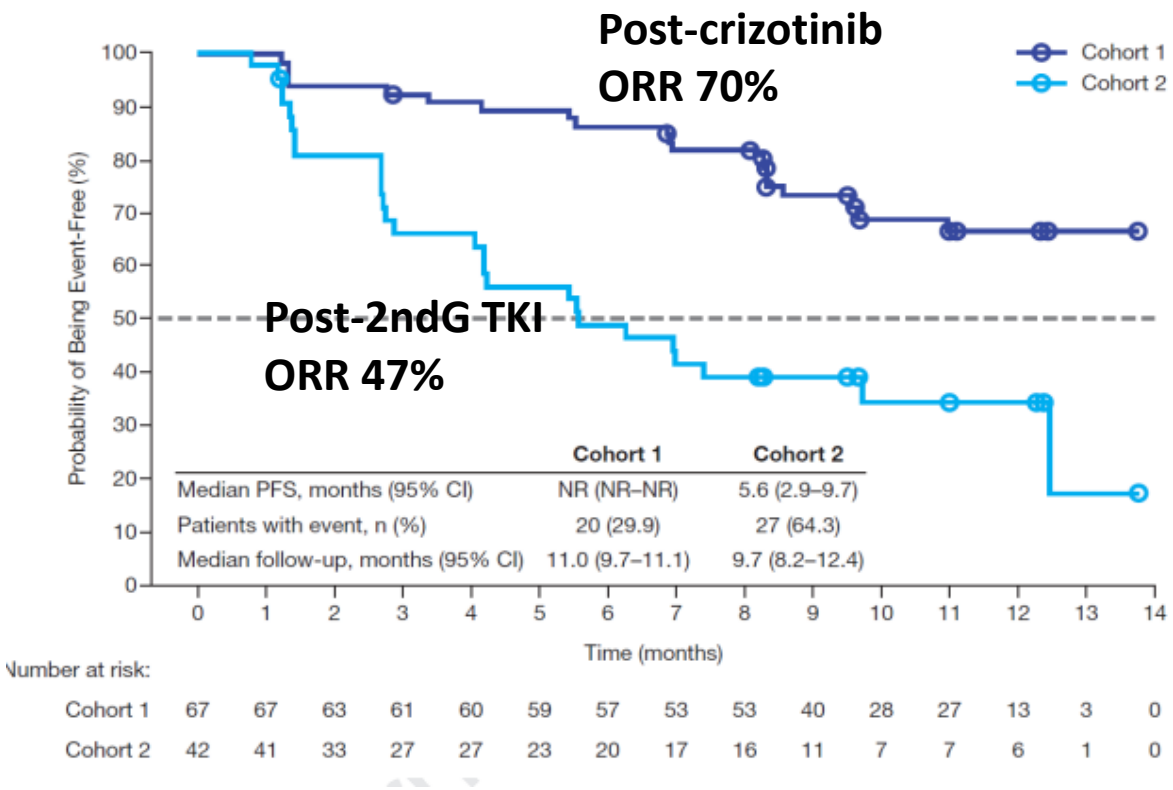




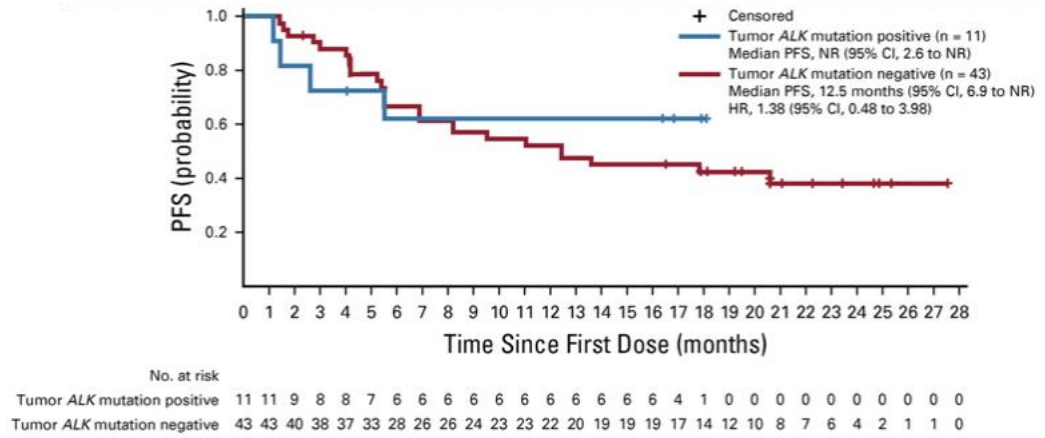
Solomon B Lancet Onc 2018

1L ALK inhibitors: TKI sequencing – Lorlatinib in ALK-inh pretreated according to prev TKI

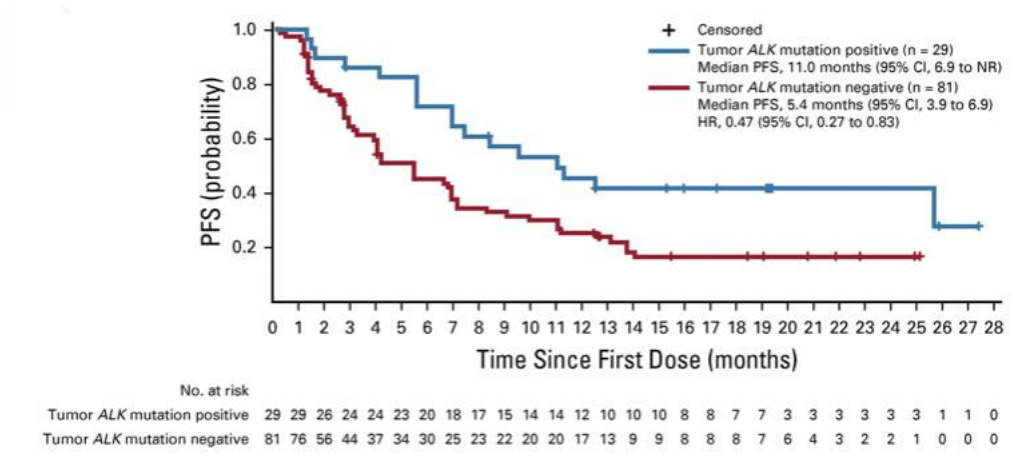
Phase 2 study in Chinese population



Phase 2 registrational study



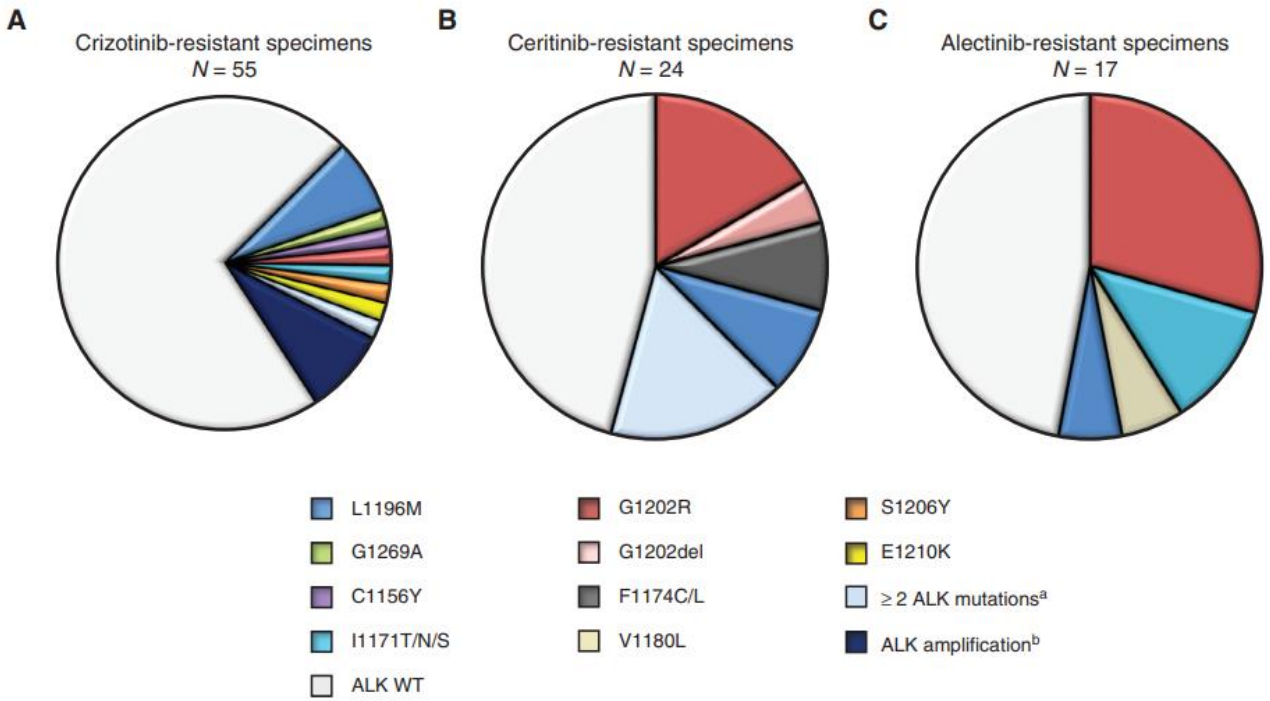
Lorl post crizo: no impact of ALK mut present/absent



Lorl post 2nd gen TKI: impact of ALK mut present/absent

Lu S JTO 2022 [in press], Shaw AT JCO 2019

1L ALK inhibitors: Resistance mechanisms – *on-target*



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

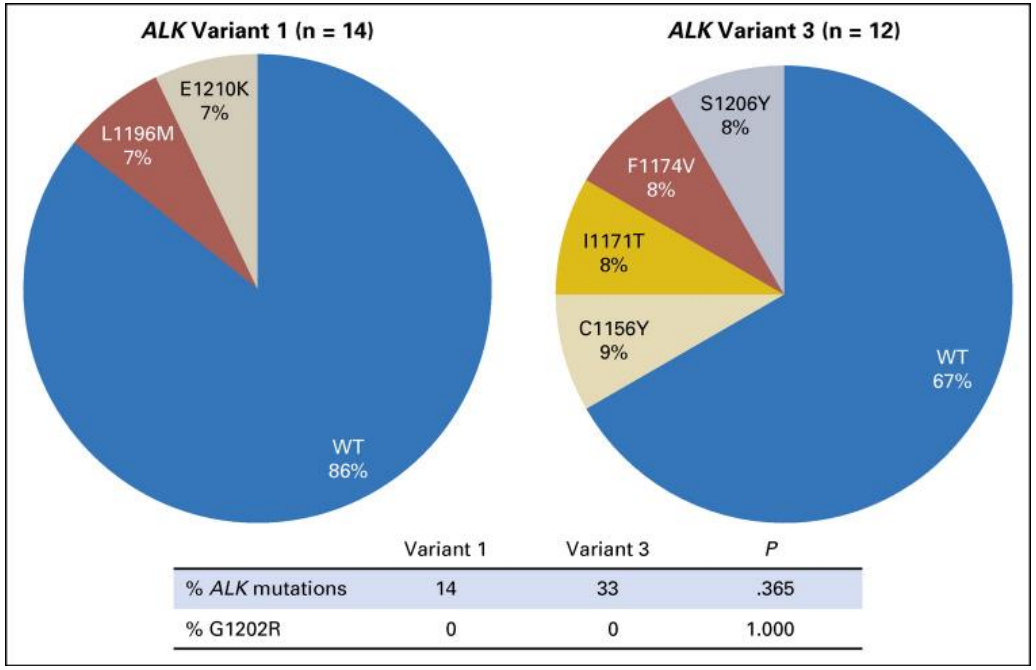
$IC_{50} \leq 50$ nmol/L

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

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

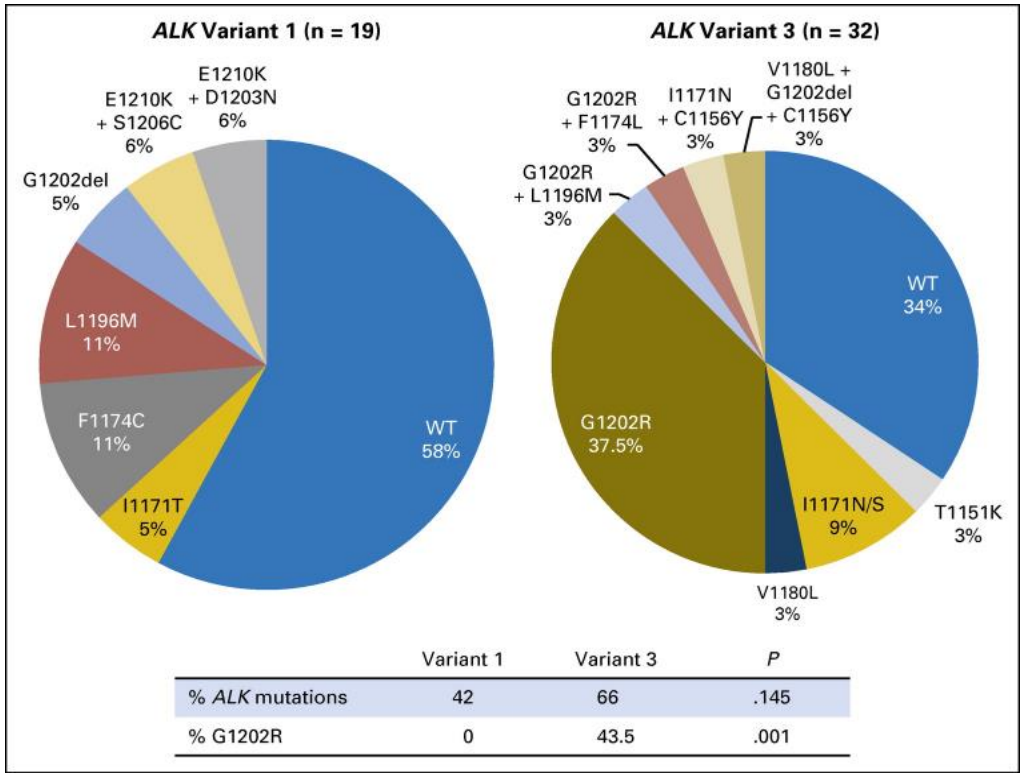
Gainor J, Cancer Discovery 2016

1L ALK inhibitors: Resistance mechanisms – *on-target by EML4-ALK variant*



	Variant 1	Variant 3	*P*
% *ALK* mutations	14	33	.365
% G1202R	0	0	1.000

Fig 4. Distribution of ALK resistance mutations in tumor biopsy specimens obtained after disease progression on crizotinib by EML4-ALK variant. WT, wild-type ALK.

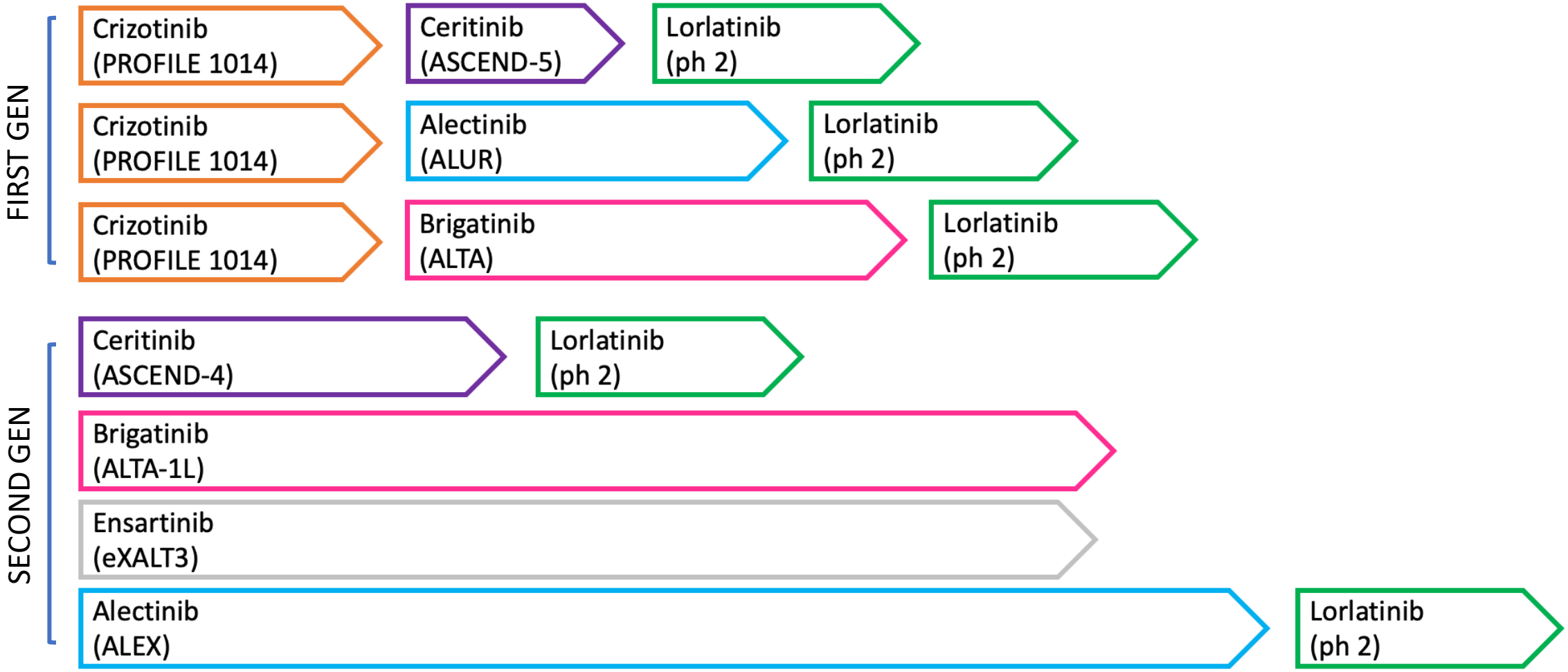


	Variant 1	Variant 3	*P*
% *ALK* mutations	42	66	.145
% G1202R	0	43.5	.001

Fig 3. Distribution of ALK resistance mutations in tumor biopsy specimens obtained after disease progression on a second-generation ALK inhibitor by EML4-ALK variant. WT, wild-type (nonmutated) ALK.

Lin JJ, JCO 2018

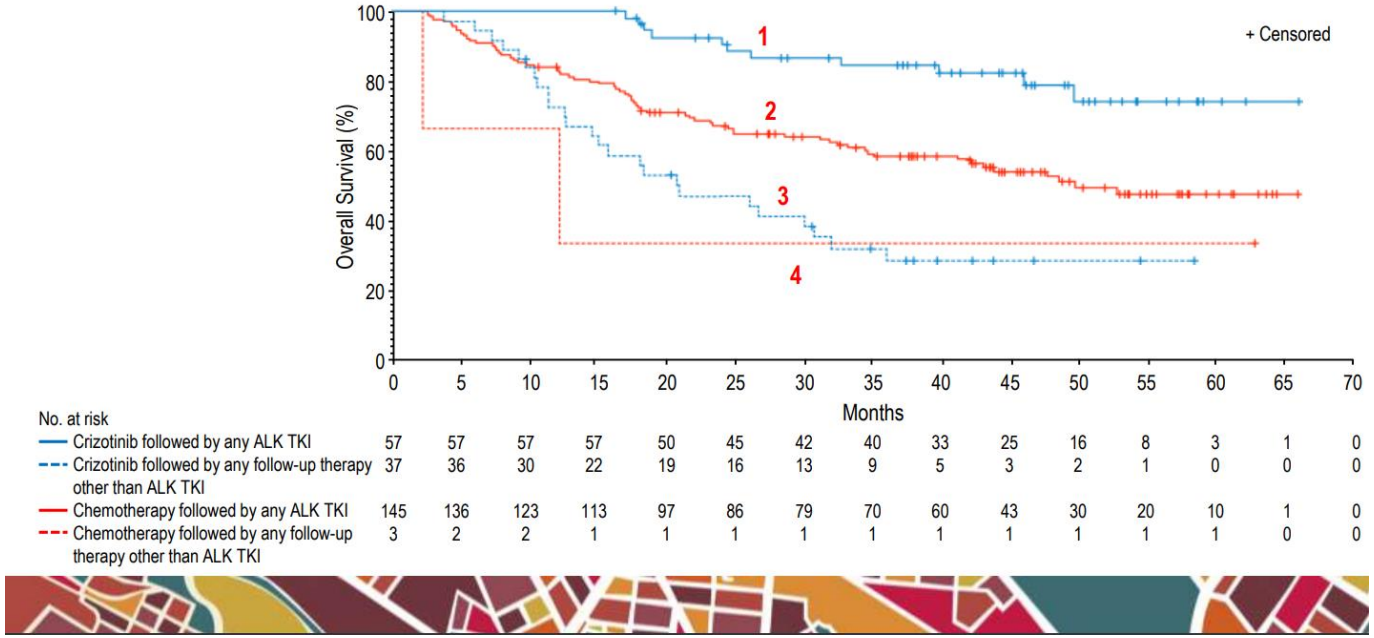
1L ALK inhibitors: TKI sequencing



1L ALK inhibitors: TKI sequencing – where is the room for chemotherapy?

PROFILE1014

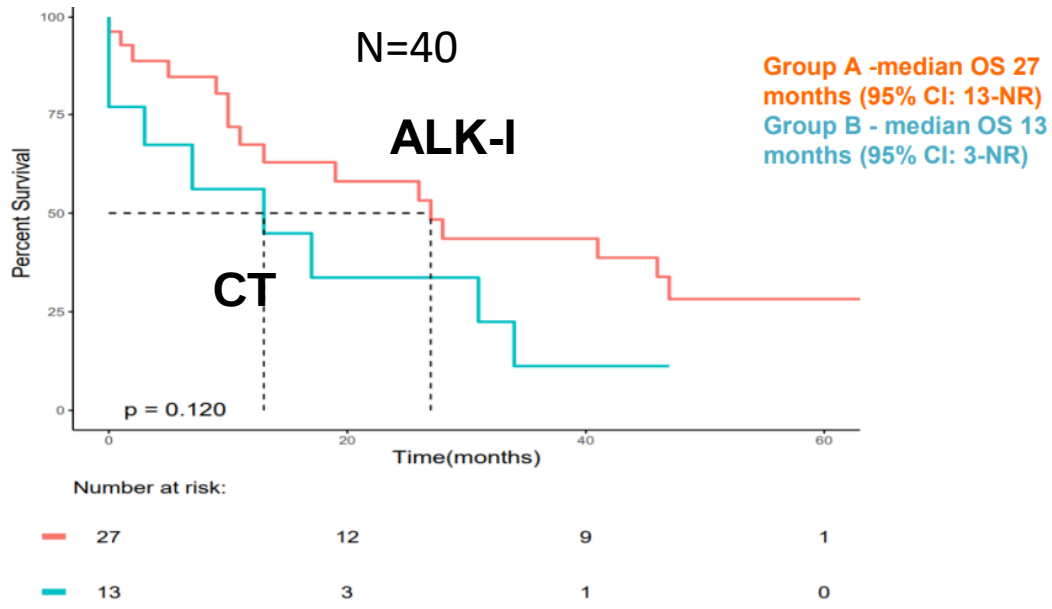
Impact of Subsequent Therapy on OS: ALK TKI versus Treatment Other Than ALK TKI



…KEEP IT AS THE LAST OPTION

REAL-WORLD

OS from initiation of third-line of interest of ALK + patients according to the treatment given; further ALKi (group A) or chemotherapy (group B)



Mok T, ESMO 2017; Moskovitz M, Real world data WCLC 2020

ALK-positive NSCLC in 2022: The CROWN

Key eligibility criteria
- Stage IIIB/IV *ALK* + NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1 N=296

Lorlatinib 100 mg QD n=149

Stratified by:
- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

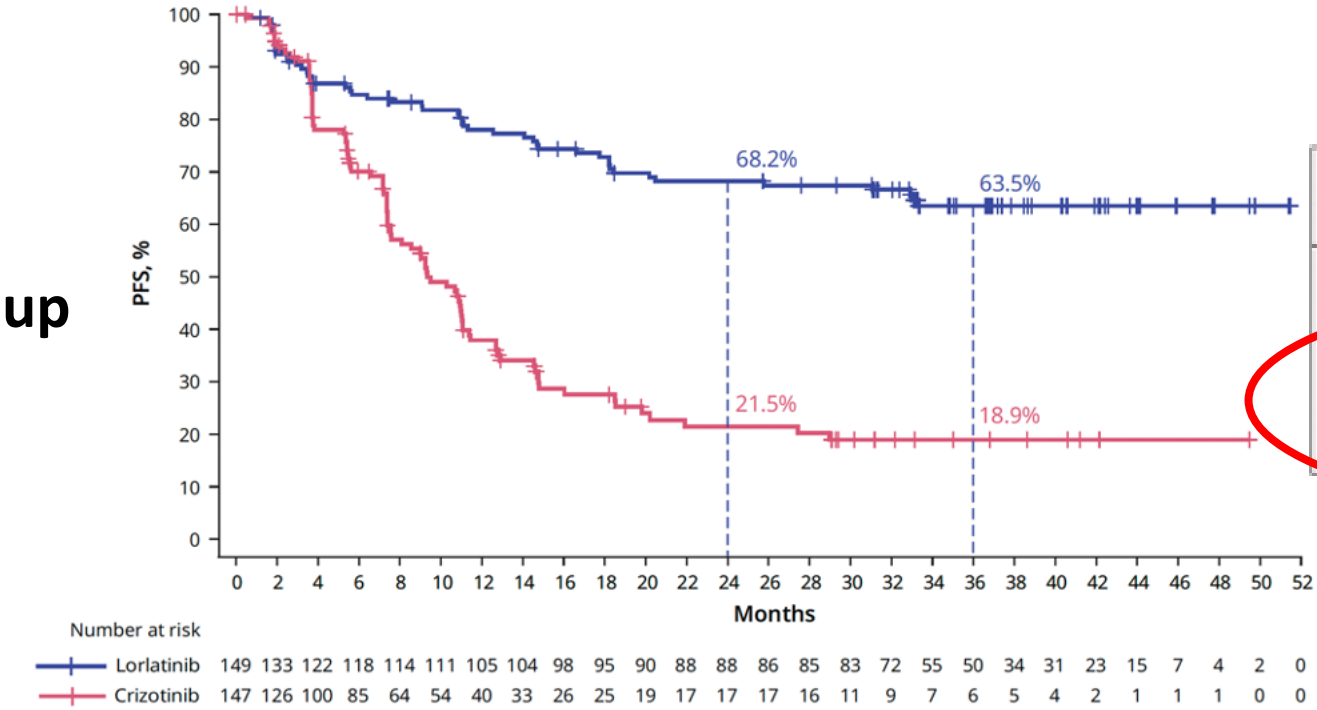
Crizotinib 250 mg BID n=147

Primary endpoint
- PFS[a] by BICR

Secondary endpoints
- Overall survival
- PFS by investigator
- ORR by BICR and investigator
- DOR, IC ORR, and IC DOR by BICR
- IC TTP by BICR
- TTR and IC TTR by BICR
- Safety
- Quality of life

A. ITT population

3-y follow up



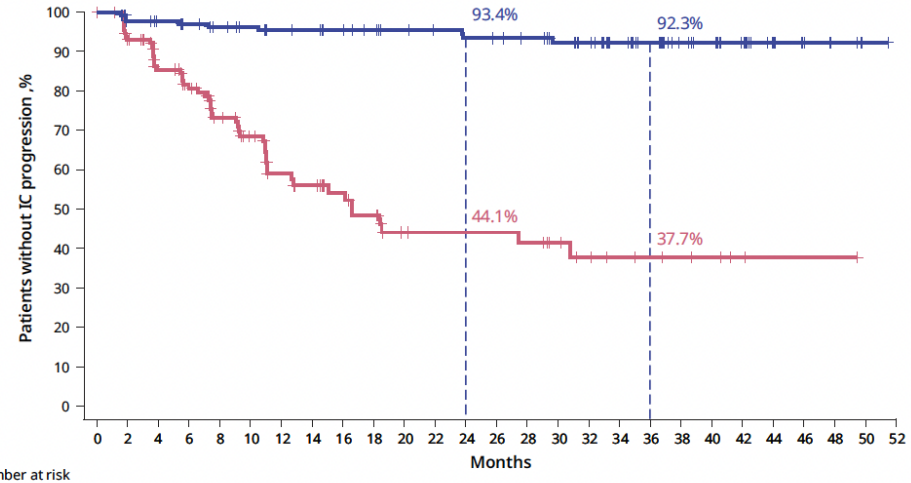
	Lorlatinib (n=149)	Crizotinib (n=147)
Events	49	92
PFS, median (95% CI), months	NR (NR-NR)	9.3 (7.6-11.1)
HR (95% CI)	0.27 (0.184-0.388)	

Solomon BJ, Abstr #CT223 AACR22

1L Lorlatinib in ALK+ NSCLC: IC progression

A. ITT population

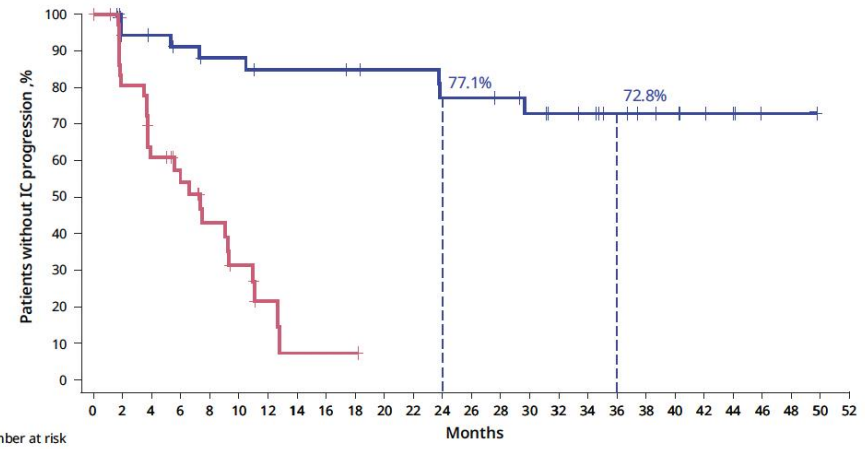
	Lorlatinib (n=149)	Crizotinib (n=147)
Events	9	51
PFS, median (95% CI), months	NR (NR-NR)	16.6 (11.1-NR)
HR (95% CI)	0.08 (0.040-0.174)	



Number at risk

Lorlatinib	149	131	127	122	117	114	109	108	105	102	98	96	94	93	90	86	75	62	54	39	34	25	17	8	4	1	0
Crizotinib	147	118	97	83	65	54	39	35	29	25	18	17	17	17	16	12	9	7	6	5	4	2	1	1	1	0	0

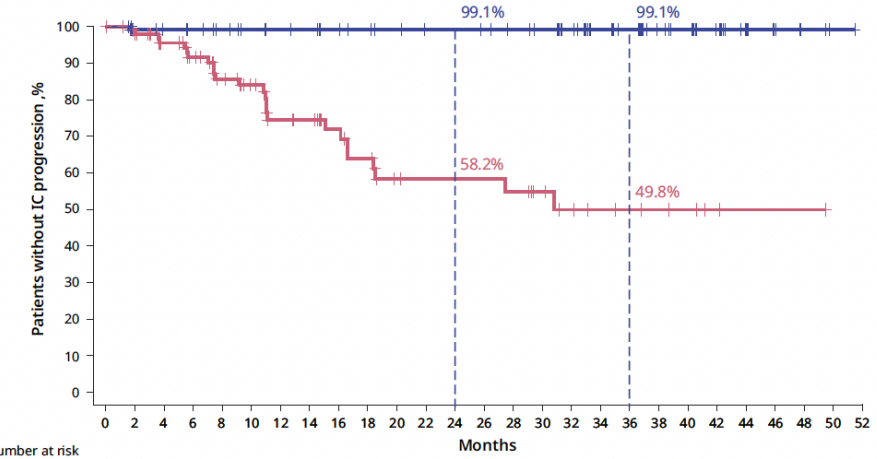
B. Patients with baseline brain metastases



Number at risk

Lorlatinib	37	32	31	29	27	27	24	24	24	23	22	22	20	20	19	17	14	13	10	8	7	5	4	1	1	0	0
Crizotinib	39	29	21	16	11	7	3	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

C. Patients without baseline brain metastases



Number at risk

Lorlatinib	112	99	96	93	90	87	85	84	81	79	76	74	74	73	71	69	61	49	44	31	27	20	13	7	3	1	0
Crizotinib	108	89	76	67	54	47	36	34	28	24	18	17	17	17	16	12	9	7	6	5	4	2	1	1	1	0	0

Solomon BJ, Abstr #CT223 AACR22

1L ALK inhibitors: CNS activity

	ALTA-1L		ALEX		eXalt3		CROWN	
	Brigatinib	Crizotinib	Alectinib	Crizotinib	Ensartinib	Crizotinib	Lorlatinib	Crizotinib
Patients with any brain mets at baseline, n	47	49	64	58	11	19	37	39
Confirmed IC-ORR, %	66	14	59	26	64	21	64.9	17.9
Complete IC response, %	45	2	45	9	27	10.5	59.5	12.8
Median IC-DoR (95% CI), months	27.1(16.9-42.6)	9.2(3.9-NR)	NE(17.3-NE)	3.7(3.2-6.8)	-	-	NR(NR-NR)	9.4 (6.0-11.1)
Patients with at least 1 measurable brain mets at baseline, n	18	23	22	21	11	19	18	13
Confirmed IC-ORR, %	78	26	81	50	64	21	83.3	23.1
Complete IC response, %	28	0	38	5	27	10.5	72.2	7.7
Median IC-DoR (95% CI), months	27.9(16.9-42.8)	9.2(3.9-NE)	17.3(14.8-NE)	5.5(2.1-17.3)	-	-	NR(NR-NR)	10.2(9.4-11.1)

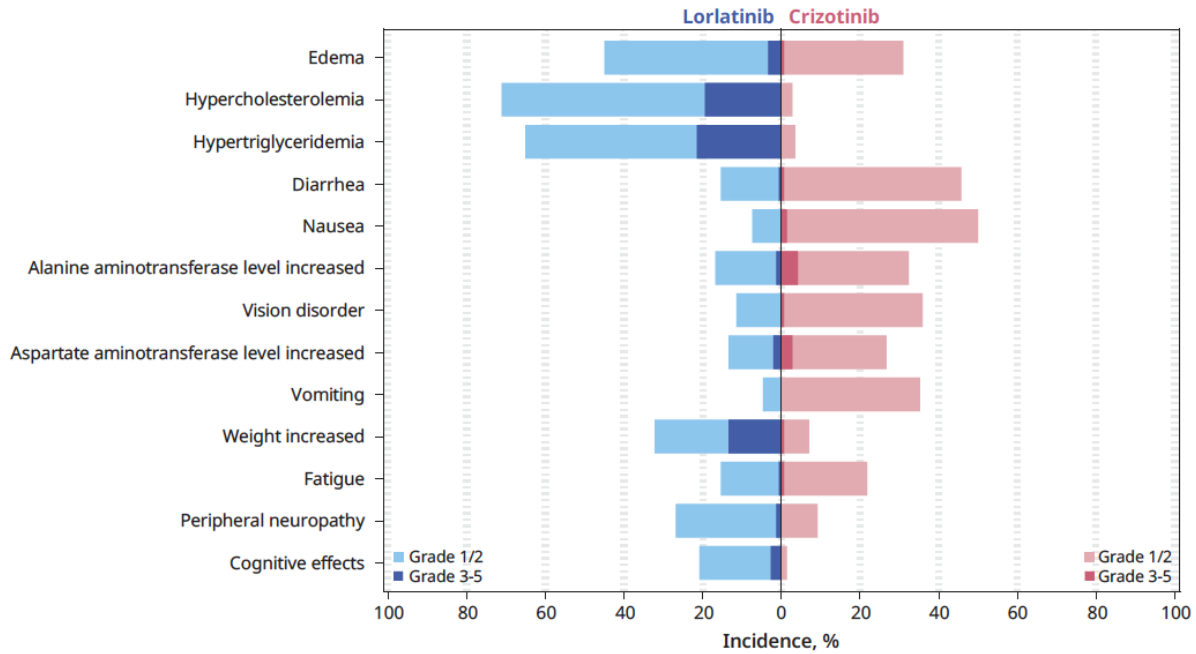
Camidge R, JTO 2021, Mok T Ann Oncol 2020, Horn WCLC Plenary 2020, Solomon B AACR2022

1L ALK inhibitors: safety profile

Table 2: Summary of AEs

	n (%)	
	Lorlatinib (n=149)	Crizotinib (n=142)
Any-grade AE	149 (100.0)	140 (98.6)
Treatment related	145 (97.3)	133 (93.7)
Grade 3/4 AE	113 (75.8)	81 (57.0)
Treatment related	94 (63.1)	54 (38.0)
Death	10 (6.7)	7 (4.9)
Treatment related	2 (1.3)	0
Any serious AE	57 (38.3)	44 (31.0)
Treatment related	13 (8.7)	9 (6.3)
AEs leading to dose reduction	32 (21.5)	21 (14.8)
AEs leading to temporary discontinuations	84 (56.4)	69 (48.6)
AEs leading to permanent treatment discontinuation	11 (7.4)	14 (9.9)

Figure 4: Any-grade treatment-related AEs in ≥20% of patients within either treatment arm

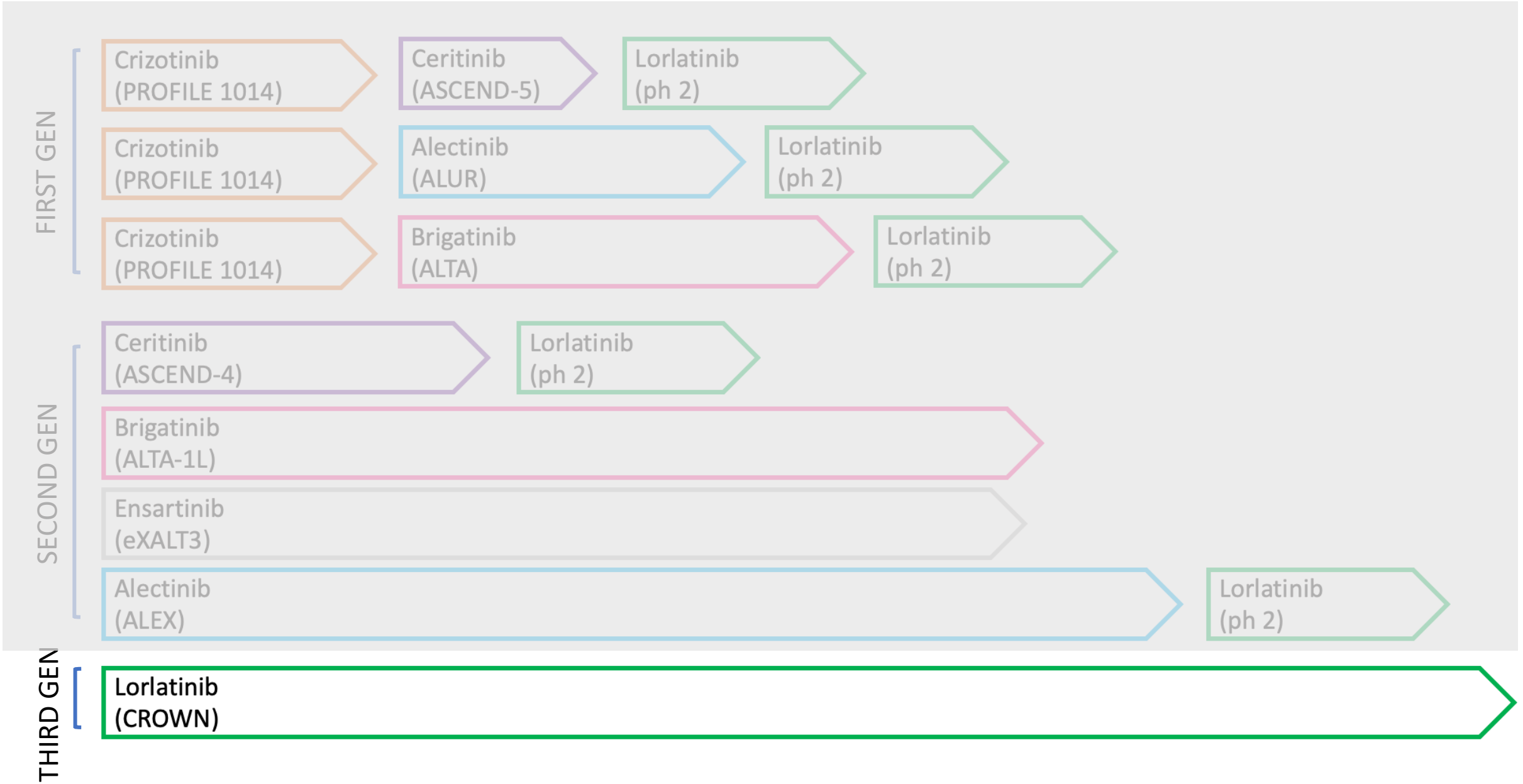


- The incidence of treatment-related grade 3/4 AEs in the lorlatinib arm was largely due to frequent occurrence of altered lipid levels such as hypercholesterolemia and hypertriglyceridemia (**Figure 4**)

- Treatment-related cognitive effects occurred in 20.8% of patients in the lorlatinib arm; however, most (27 of 31) cognitive effects were grade 1/2 and no grade 4 event was observed
- AEs leading to permanent treatment discontinuation were reported in 7.4% of patients in the lorlatinib arm and 9.9% in the crizotinib arm

Solomon BJ, Abstr #CT223 AACR22

1L ALK inhibitors: TKI sequencing



Are we really ready for the future?

Lorlatinib come monoterapia è indicato per il trattamento di pazienti adulti affetti da cancro del polmone non a piccole cellule (Non-small Cell Lung Cancer, NSCLC) in stadio avanzato positivo per la chinasi del linfoma anaplatico (Alk) la cui malattia è PROGREDITA dopo:

- **Alectinib o ceritinib** come terapia di prima linea con un inibitore della tirosin chinasi (TKI) ALK;
- Oppure **crizotinib e almeno un altro TKI ALK**

AIFA 3 Aug 2021

1L treatment of ALK+ NSCLC: how to improve? – *TESTING*

ALEX: 39 pts FISH neg

Table 3. Objective Response Rate According to *ALK* Status (Response-Assessable Population)

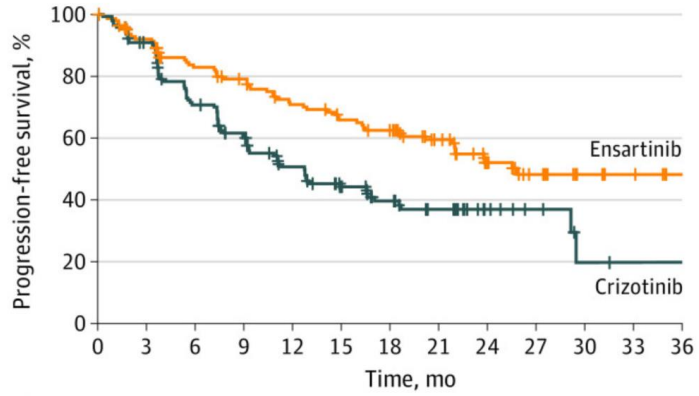
ORR	Alectinib	Crizotinib	Stratified OR (95% CI)
ALK IHC-positive and FISH-positive	n = 106	n = 97	–
ORR, n (%)	96 (90.6)	79 (81.4)	2.22 (0.97-5.07)
CR	6 (5.7)	3 (3.1)	–
PR	90 (84.9)	76 (78.4)	–
SD	4 (3.8)	14 (14.4)	–
PD	2 (1.9)	3 (3.1)	–
Missing or unassessable	4 (3.8)	1 (1.0)	–
ALK IHC-positive and FISH-uninformative[a]	n = 25	n = 36	–
ORR, n (%)	24 (96.0)	27 (75.0)	9.29 (1.05-81.88)
CR	0	0	–
PR	24 (96.0)	27 (75.0)	–
SD	0	5 (13.9)	–
PD	0	3 (8.3)	–
Missing or unassessable	1 (4.0)	1 (2.8)	–
ALK IHC-positive and FISH-negative	n = 21	n = 18	–
ORR, n (%)	6 (28.6)	8 (44.4)	0.45 (0.12-1.74)
CR	1 (4.8)	0	–
PR	5 (23.8)	8 (44.4)	–
SD	5 (23.8)	5 (27.8)	–
PD	6 (28.6)	4 (22.2)	–
Missing or unassessable	4 (19.0)	1 (5.6)	–

Table 4. Duration of Response According to *ALK* Status (Response-Assessable Population)

DoR	Alectinib	Crizotinib
ALK IHC-positive and FISH-positive	n = 106	n = 97
Median DoR, mo (95% CI)	33.1 (31.3-NE)	11.1 (7.4-14.7)
Stratified HR (95% CI)	0.34 (0.22-0.53), $p < 0.0001$	
ALK IHC-positive and FISH-uninformative[a]	n = 25	n = 36
Median DoR, mo (95% CI)	26.1 (9.4-NE)	9.1 (6.6-12.9)
Stratified HR (95% CI)	0.37 (0.17-0.80), $p = 0.0087$	
ALK IHC-positive and FISH-negative	n = 21	n = 18
Median DoR, mo (95% CI)	NE (NE)	NE (7.4-NE)
Stratified HR (95% CI)	0.24 (0.02-2.62), $p = 0.2181$	

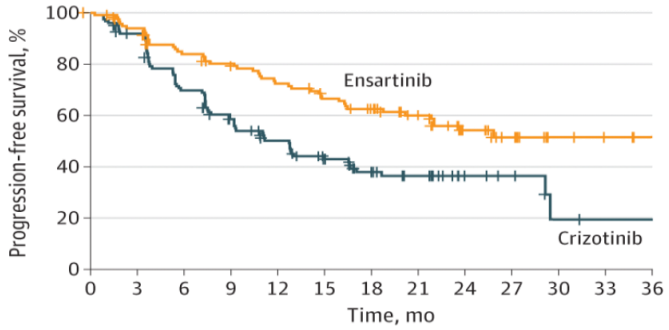
eXALT3: 43 pts excluded by central FISH testing in mITT

mPFS (95% CI), mo	25.8 (21.8-NR)	12.7 (9.2-16.6)
Hazard ratio (95% CI)	0.51 (0.35-0.72)	
P value (log-rank test)	<.001	



A PFS in the mITT population

	Ensartinib (n = 121)	Crizotinib (n = 126)
mPFS (95% CI), mo	NR (20.2-NR)	12.7 (8.9-16.6)
Hazard ratio (95% CI)	0.45 (0.30-0.66)	
P value (log-rank test)	<.001	

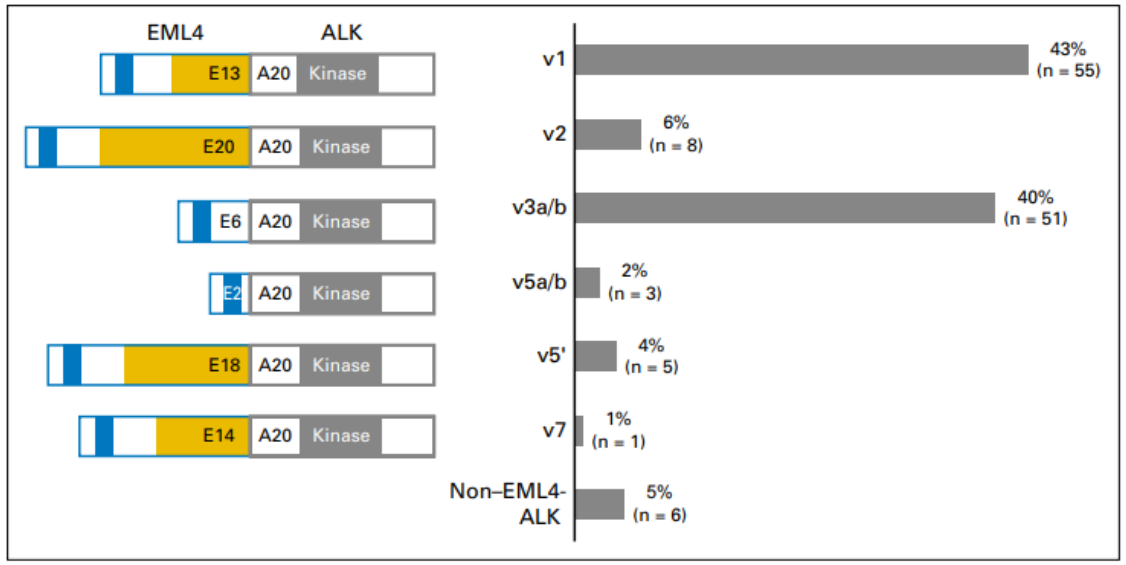


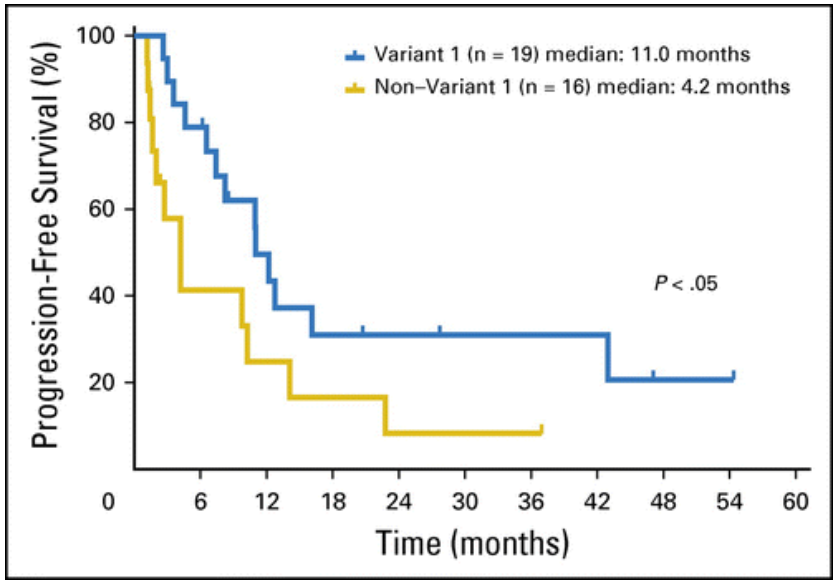
No. at risk

Ensartinib	121	107	90	84	75	67	61	45	24	16	6	4	1
Crizotinib	126	109	82	66	50	38	28	20	9	6	2	1	1

Mok T JTO 2020; Horn L JAMA Oncol 2021

1L treatment of ALK+ NSCLC: how to improve? – Role of *ALK variants*





ALTA-1L

- Efficacy of brigatinib in pts with V1, V2, V3 (plasma NGS, n=250 pts):

ORR higher in all three variants

mPFS 29 m V1 , 16 m V2 and V3

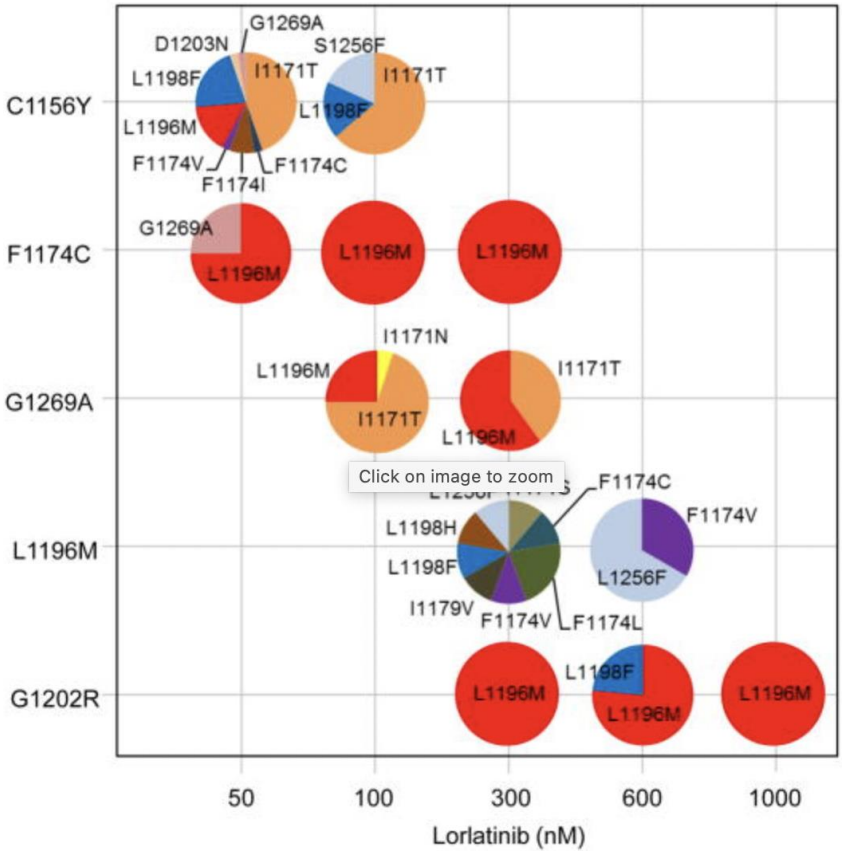
ALEX

- EMLA4-ALK variants were detectable in 135/222 patient plasma samples and 124/203 tissue samples (NGS):

PFS was longer for alectinib than for crizotinib across EML4-ALK V1,V2 V3

Lin JJ JCO 2018, Yoshida JCO 2016, Camidge R, JTO 2021, Camidge R JTO 2019

1L treatment of ALK+ NSCLC: Lorlatinib resistance



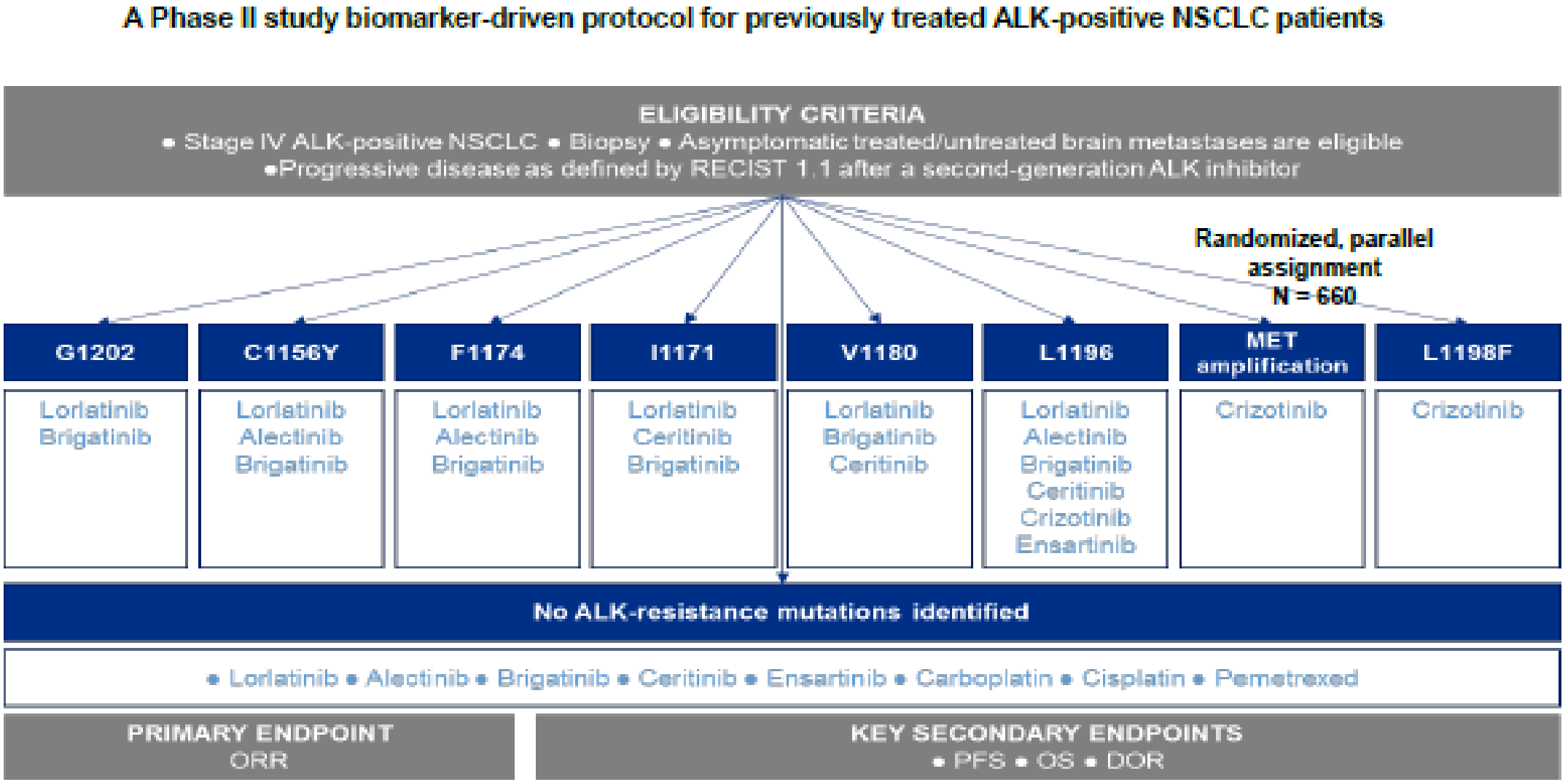
Acquired sequential resistance mutations

- More frequent ALK compound mutations after lorlatinib than after second gen TKIs (48% vs 23%)
- Plasma samples more informative to detect compound mutations (24% vs 2% in tissue samples)

→ New compounds in development to target ALK compound mutations

Yoda S et al, Cancer Discov 2018, Dagogo-Jack CCR 2019

1L treatment of ALK+ NSCLC: how to improve? – the *ALK MASTER Protocol*



NCT03737994

1L treatment of ALK+ NSCLC: how to improve? – *combos*

Immune Checkpoint Inhibitors + ALK TKI

Trial	Drugs	Cohort	ORR (dose exp)	Gr ≥ 3 TRAE (safety & dose exp)
Checkmate 370 (NCT02574078) Spigel D et al. JTO 2018; 13	Crizotinib Nivolumab	ALK+ / TKI naïve	38%	62% - 38% hepatitis (15% gr 5) - 7% pneumonitis
NCT0251184 Patel S et al. Oncologist 2020;25	Crizotinib Pembrolizumab	ALK+ / TKI naïve	Terminated early 9 pts enrolled	- 3/9 pts with grade 3 transaminitis - 1/9 pts with grade 4 pneumonitis

VEGFR inhibitors + ALK TKI

Target	Drug	Trial
VEGF-A	Bevacizumab (+ Alectinib) Bevacizumab (+Atezolizumab + Carboplatin + Paclitaxel)	NCT02521051 NCT03991403

Targeted Therapies + ALK TKI

Target	Drug	Trial
MEK	Combimetinib (+alectinib) Trametinib (+ceritinib) Binimetinib (+lorlatinib)	NCT03202940 NCT03087448 NCT04292119
HSP90	Ganetespib (+crizotinib) AUY922 (+ceritinib)	NCT01579994 NCT01772797
CDK 4/6	Ribociclib (+ceritinib)	NCT02292550
MET	Crizotinib (+lorlatinib)	NCT04292119
SHP2	TNO155	NCT03114319 – phase 1 includes EGFR and KRAS (ALK hopefully soon?)

Chemotherapy + ALK TKI

** This slide is not a comprehensive list of all studies **

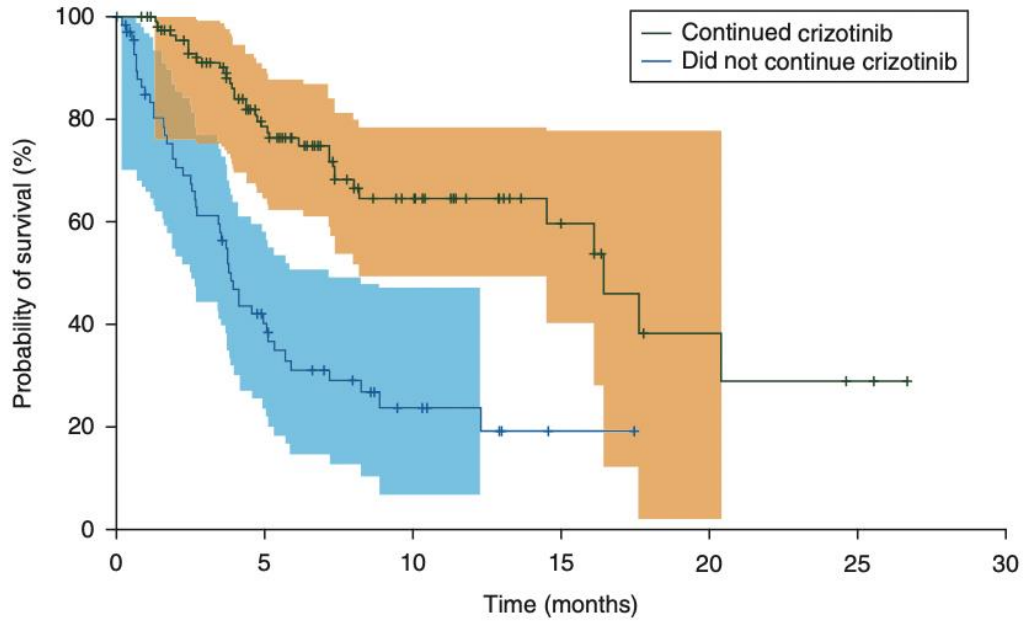
…Not yet the time for combos

Lovly C, WCLC Virtual Plenary 2020

1L treatment of ALK+ NSCLC: do not forget the basements

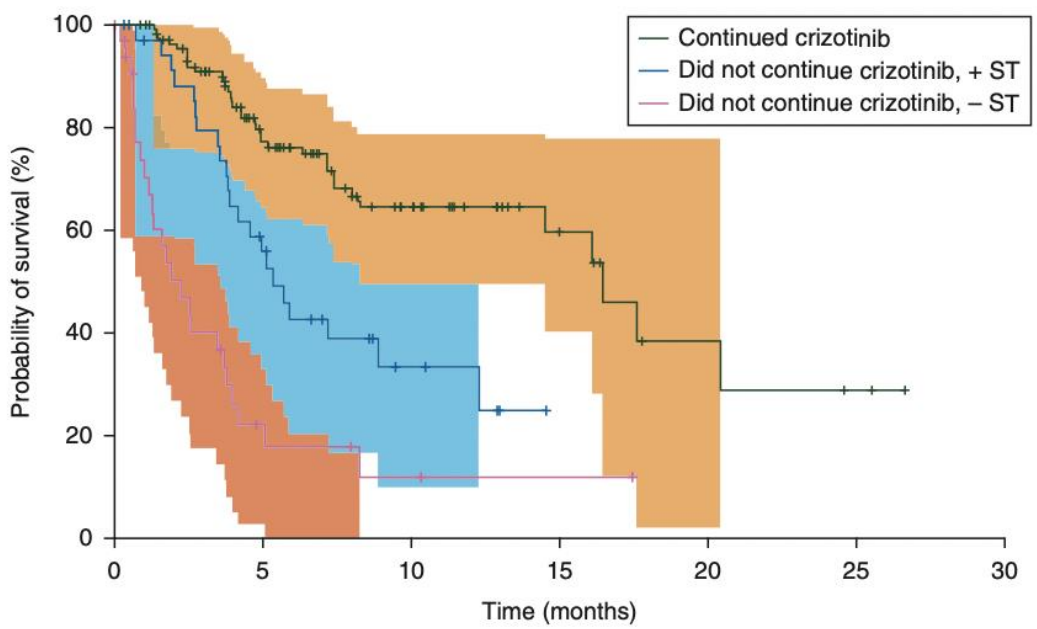
Treatment beyond progression & Locoregional approaches

A



Number at risk				
Continued	120	29	4	0
Did not continue	74	7	0	

B



Number at risk				
Continued	120	29	4	0
Did not continue, + ST	37	5	0	
Did not continue, – ST	37	2	0	

Ou SH-I Ann Oncol 2014

Final remarks

- ALK rearreanged NSCLC: to date our favourite story
- Current treatment landscape include 1L second/third gen ALK TKIs
- Lorlatinib PFS results (CROWN trial) might revert the current TKI sequencing approach
- Treatment selection: duration of benefit, CNS activity, toxicity profile/long-term side effects
- Patients' selection at disease progression: patterns of relapse, resistance mechanisms