Quale sequenza terapeutica nella malattia ALK-traslocata?

Dr. Rita Chiari

SC Oncologia Medica
Azienda Ospedaliera-Universitaria
di Perugia

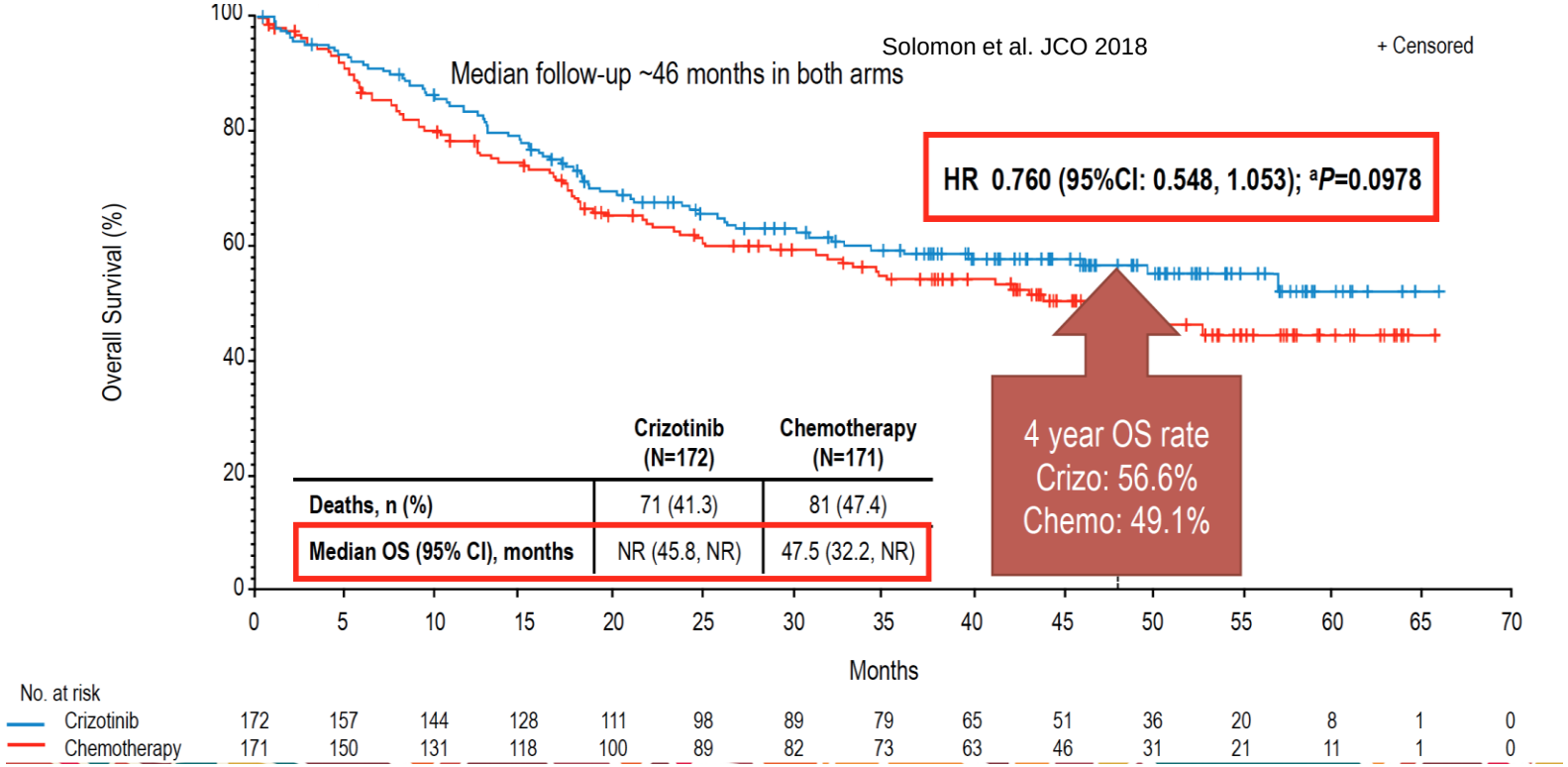
Outline

- **ALK-rearranged:**
  - The picture
  - How alectinib changed 1st line
  - Brigatinib: a new standard first line option?
  - The upcoming scenario in first line
  - Mechanisms underlying acquired resistanceto ALK-TKIs
  - Precision oncology in the era of NGS

Outline

- **ALK-rearranged:**
  - **The picture**
  - How alectinib changed 1st line
  - Brigatinib: a new standard first line option?
  - The upcoming scenario in first line
  - Mechanisms underlying acquired resistance to ALK-TKIs
  - Precision oncology in the era of NGS

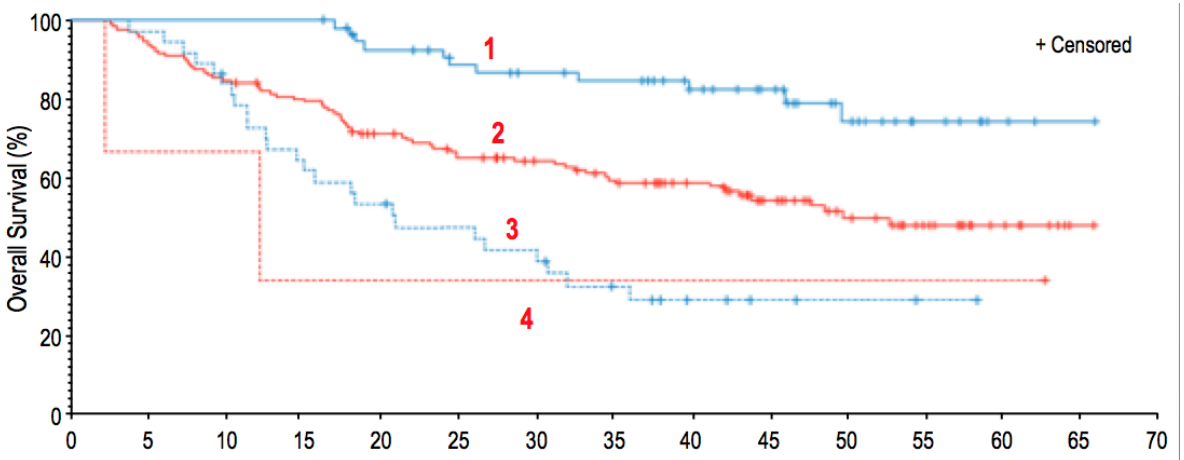
Crizotinib in First Line: OS final Analysis PROFILE 1014



Solomon et al. JCO 2018

Impact of Subsequent Therapy after Crizotinib 1st Line on OS:
ALK TKI versus Treatment Other Than ALK TKI - PROFILE 1014

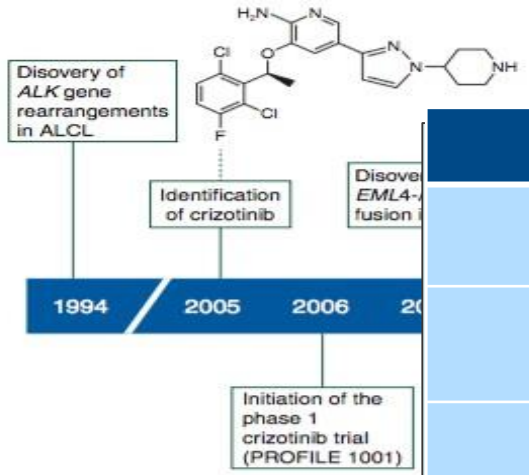
Crizotinib followed by another ALK TKI the best option!

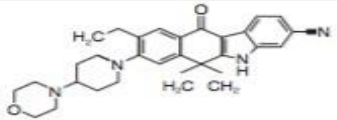


No. at risk														
Crizotinib followed by any ALK TKI	57	57	57	57	50	45	42	40	33	25	16	8	3	1	0
Crizotinib followed by any follow-up therapy other than ALK TKI	37	36	30	22	19	16	13	9	5	3	2	1	0	0	0
Chemotherapy followed by any ALK TKI	145	136	123	113	97	86	79	70	60	43	30	20	10	1	0
Chemotherapy followed by any follow-up therapy other than ALK TKI	3	2	2	1	1	1	1	1	1	1	1	1	1	0	0

Solomon et al. JCO 2018

Rapid clinical development of multiple ALK TKIs





ALK TKI	Additional Targets
Ceritinib	IGF-R1, IR, ROS1
Alectinib	LTK, GAK, RET[2]
Brigatinib	ROS1, EGFR
Ensartinib (X-396)	MET
Entrectinib	TrkA, TrkB, TrkC, ROS1
Lorlatinib	ROS1

Efficacy of next generation ALK-TKIs after CRIZ: updated evidence

ALK Inhibitors	ceritinib ASCEND-5[1]	alectinib ALUR[2]	lorlatinib Phase 1/2[4]	brigatinib ALTA[5]
Line of Therapy	2L ALK+	2L ALK+	1L/ 2L/ 3L ALK+	2L ALK+
Confirmed ORR	49% (Invest.) 45% (IRC)	37.5 (Invest.) 36.1 (IRC)	74% / 66% (Post-crizo only / +CT) 51% / 42% / 35% (Post 1 / 2 / 3 ALKi±CT)	Invest. [6]:54% IRC [7] 53%
Systemic DOR	6.9 Mos	9.3 (6.9 – NE) Months	5.5 Mos (1 prior ALKi ±CT) 6.9 Mos (2 or 3 prior ALKi±CT)	Invest.: 18.8 Mos IRC: 14.8 Mos
PFS	6.7 Mos (Invest.) 5.4 Mos (IRC)	9.6 Mos (Invest) 7.1 Mos(IRC)	N/A	Invest.: 15.6 Mos IRC 16.7 Mos
Confirmed CNS ORR	35%	54.2% (IRC Reviewed)	59% / 75% Post-crizo only / +CT 63% / 56% / 39% Post 1 / 2 / 3 ALKi±CT	IRC: 67%
Intracranial DOR	6.9 Mos	7.6 (5.8-10.3)[3] Mos	N/A	IRC: 16.6 Mos
Intracranial PFS (IRC<)	N/A	N/A	N/A	IRC: 18.4mos

1. ASCEND 5, Shaw et all. Lancet Oncol 2017;18;874-86 2: ALUR ESMO 2017 Novello S et al. abstr 1299. 3: WLCC 2017, Pooled response phase 1/II studies, Gadgeel S et al. 4. WCLC 2017 Phase 1/2 data Shaw et al 5. WLCC 2017 updated ALTA; Ahn MJ et al. 6: investigator assessed primary endpoint 7: IRC assessed secondary endpoint

Outline

- **ALK-rearranged:**
  - The picture
  - **How alectinib changed 1st line**
  - Brigatinib; a new standard first line option?
  - The upcoming scenario for first line
  - Mechanisms underlying acquired resistance to ALK-TKIs
  - Precision oncology in the era of NGS

ALEX: duration of follow up

ASCO 2018

Primary data cut-off 9 February 2017[1]

	Alectinib (n=152)	Crizotinib (n=151)
Duration of follow-up, months		
Mean (SD)*	17.08 (7.36)	15.50 (7.2)
Median	18.6	17.6
25%, 75% percentile*	12.91, 22.16	9.23, 20.60
Min, Max	0.5, 29.0	0.3, 27.0

164 PFS events observed:

- alectinib n=62/152 (41%)
- crizotinib n=102/151 (68%)

Updated data cut-off 1 December 2017[2]

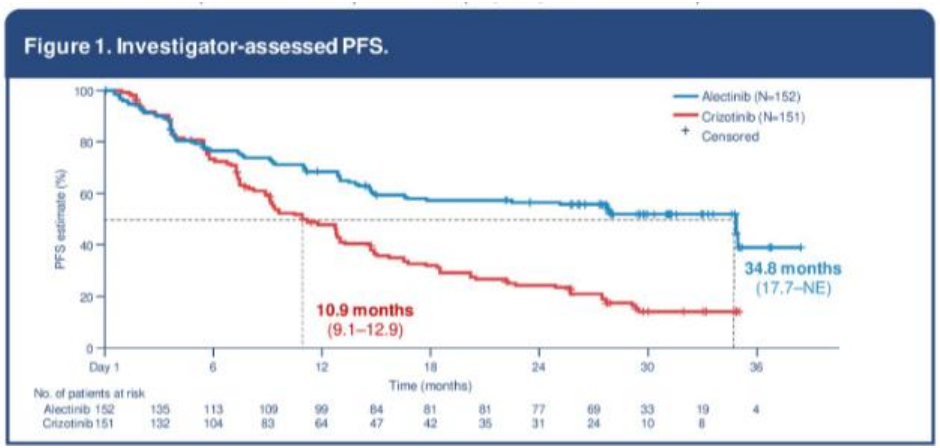
	Alectinib (n=152)	Crizotinib (n=151)
Duration of follow-up, months		
Mean (SD)*	23.02 (11.22)	20.09 (10.97)
Median	27.8	22.8
25%, 75% percentile*	14.05, 31.05	9.23, 29.37
Min, Max	0.5, 38.7	0.3, 36.7

188 PFS events observed:

- alectinib n=72/152 (47%)
- crizotinib n=116/151 (77%)

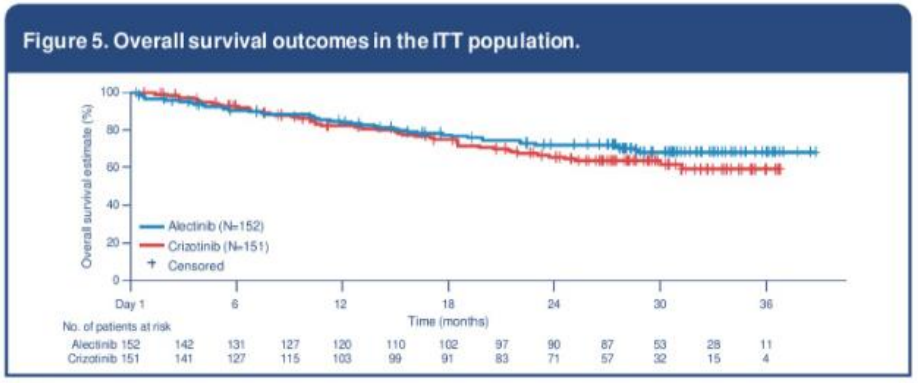
1.Peters, et al. NEJM 2017; 2. Camidge, et al. ASCO 2018

ALEX Trial: Outcomes Update



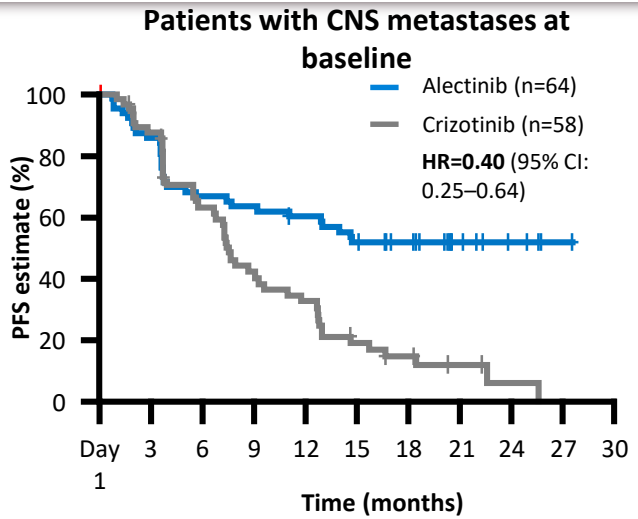
Median follow-up **27.8 months**
PFS HR 0.43 (95% CI 0.32-0.58)
mPFS 34.8 for AL vs 10.9 for CZ

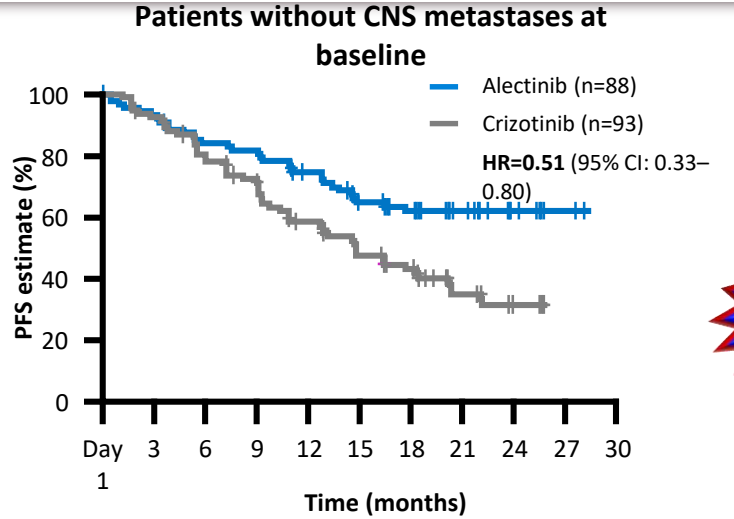
OS HR 0.76 (95% CI 0.50-1.15) **Median OS still immature**



Camidge DR, Abstract 9043, ASCO 2018

ALEX: PFS by baseline CNS metastases status





ASCO 2018

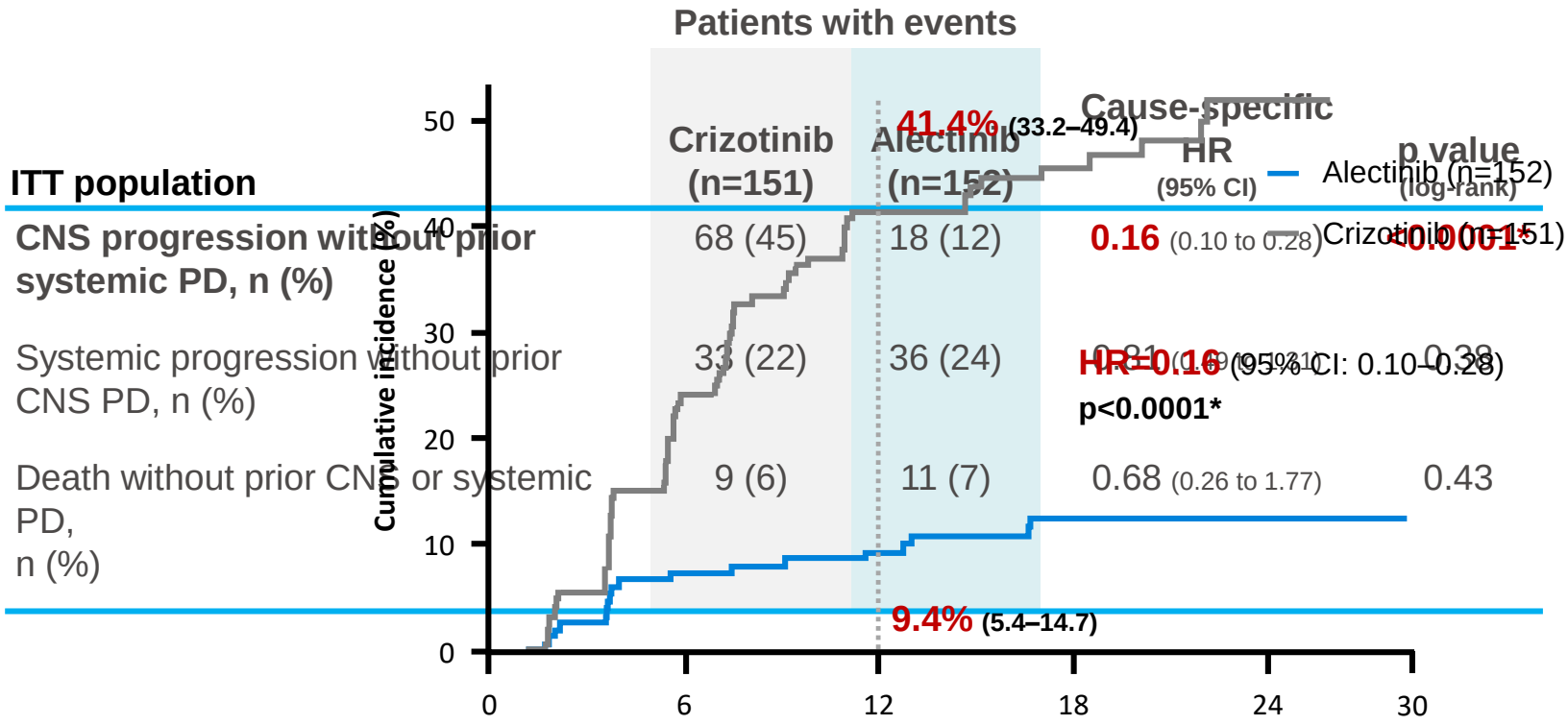
ASCO 2018

	Alectinib (n=64)	Crizotinib (n=58)
Median PFS (95% CI)	**27.7 (9.2–NE)**	**7.4 (6.6–9.6)**
HR (95% CI)	**0.35 (0.22–0.56)**	

	Alectinib (n=88)	Crizotinib (n=93)
Median PFS (95% CI)	**34.8 (22.4–NE)**	**14.7 (10.8–20.3)**
HR (95% CI)	**0.47 (0.32–0.71)**	

Peters et al; N Engl J Med. 2017 Camidge, et al. ASCO 2018

ALEX: risk of CNS progression

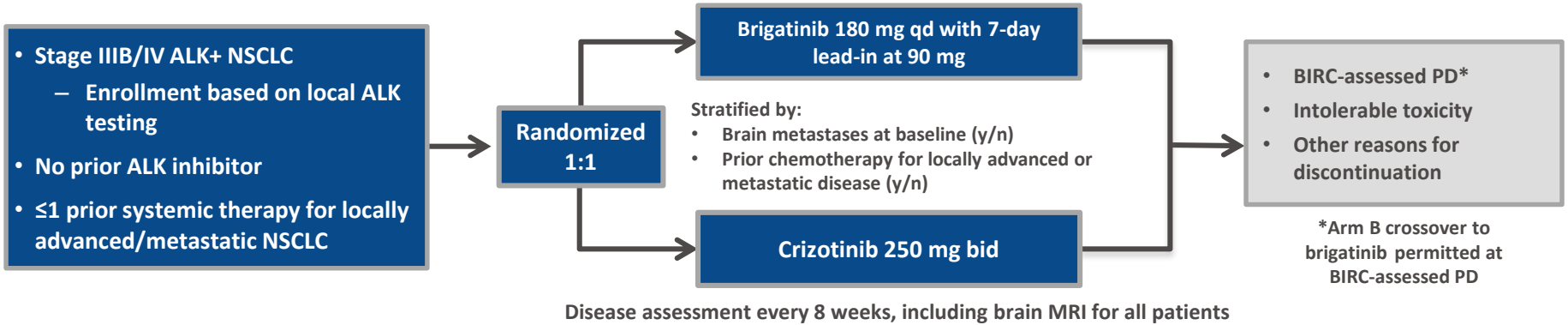


Peters et al; N Engl J Med. 2017

Outline

- **ALK-rearranged:**
  - The picture
  - How alectinib changed 1st line
  - **Brigatinib: a new standard first line option?**
  - The upcoming scenario in first line
  - Mechanisms underlying acquired resistance to ALK-TKIs
  - Precision oncology in the era of NGS

ALTA-1L: Phase 3, Open-label, Randomized, Multicenter



- **Primary endpoint: BIRC–assessed PFS per RECIST v1.1**
- Key secondary endpoints: Confirmed ORR, confirmed iORR, iPFS, OS, safety, and tolerability
- Statistical considerations: ~270 patients (198 events); 135 in each arm to detect a 6-month improvement in PFS (HR=0.625), assuming:
  - 10-month PFS in crizotinib arm
  - 2 planned interim analyses **at 99 (50%) and 149 (75%) total** expected events

Trial fully accrued in August 2017 (N=275)

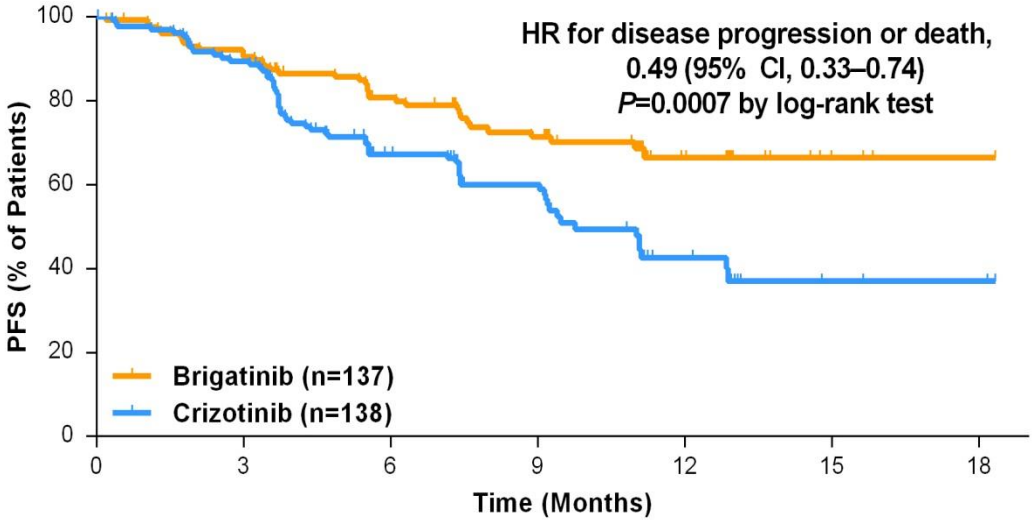
First interim analysis:

- **A total of 99 PFS events are included**
- **According to the prespecified O'Brien-Fleming Lan-DeMets alpha spending function, a 2-sided *P* value of 0.0031 was used to define the threshold for significance**

Camidge RD et al NEJM September 25th 2018

ALTA-1L Primary Endpoint: BIRC-Assessed PFS

- **Brigatinib met the prespecified threshold for statistical superiority vs crizotinib**

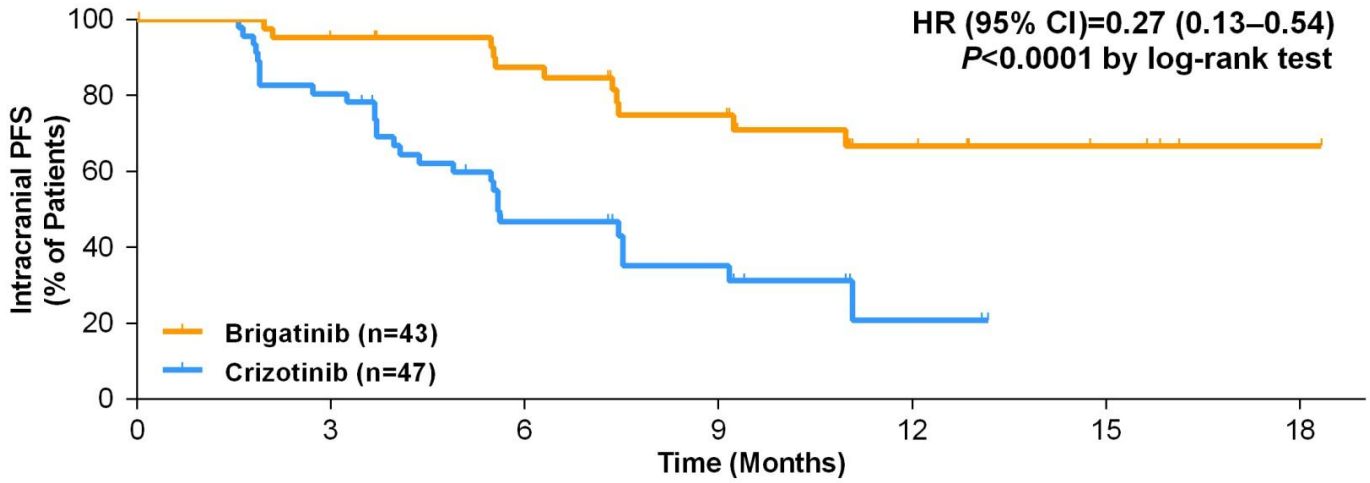


Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=137)	36 (26)	NR (NR–NR)	67 (56–75)
Crizotinib (n=138)	63 (46)	9.8 months (9.0–12.9)	43 (32–53)

- Investigator-assessed median PFS was NR (95% CI, NR–NR) in the brigatinib arm and 9.2 months (95% CI, 7.4–12.9 months) in the crizotinib arm (HR, 0.45 [95% CI, 0.30–0.68]; log-rank *P*=0.0001)
- 1-year OS probability: brigatinib, 85% (95% CI, 76%–91%); crizotinib, 86% (77%–91%)

Camidge RD et al NEJM September 25th 2018

Intracranial PFS in Patients With Any Brain Metastases at Baseline



Treatment	Median Intracranial PFS (95% CI)	1-Year PFS Probability, % (95% CI)
Brigatinib (n=43)	NR (11.0–NR)	67 (47–80)
Crizotinib (n=47)	5.6 months (4.1–9.2)	21 (6–42)

ALTA-1L Toxicity

	Brigatinib (n=136), %		Crizotinib (n=137), %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	49	1	55	2
Increased blood CPK	39	16	15	1
Nausea	26	1	56	3
Cough	25	0	16	0
Increased AST	23	1	25	6
Hypertension	23	10	7	3
Increased ALT	19	1	32	9
Increased lipase	19	13	12	5
Vomiting	18	1	39	2
Constipation	15	0	42	1
Increased amylase	14	5	7	1
Pruritus	13	1	4	1
Rash	10	0	2	0
Decreased appetite	7	1	20	3
Dermatitis acneiform	7	0	1	0

	Brigatinib (n=136), %		Crizotinib (n=137), %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Dyspepsia	6	0	13	0
Epistaxis	6	0	0	0
Bradycardia	5	1	12	0
Peripheral edema	4	1	39	1
Dysgeusia	4	0	19	0
Upper abdominal pain	4	1	13	1
Pain in extremity	4	0	12	1
Increased blood creatinine	2	0	14	1
Neutropenia	1	0	9	4
Pleural effusion	1	1	7	1
Photopsia	1	0	20	1
GERD	1	0	9	0
Hypoalbuminemia	1	0	6	1
Visual impairment	0	0	16	0
Deep vein thrombosis	0	0	6	0

- Interstitial lung disease (ILD)/pneumonitis at any time: brigatinib 4% (5/136); crizotinib 2% (3/137)
  - **Early-onset ILD/pneumonitis (within 14 days of treatment initiation): brigatinib, 3% (onset: Days 3–8); crizotinib, none reported**
- **Dose reduction due to AEs (brigatinib/crizotinib): 29%/21%; discontinuation due to AEs: 12%/9%**
  - For brigatinib, reductions for increased CPK (10.3%), lipase (5.1%); amylase (2.9%) and AST, hypertension, pneumonitis, pruritic rash (1.5% each)
- No clinical cases of pancreatitis; no difference in incidence of any grade myalgia between arms (brigatinib/crizotinib: 6%/4% and 4%/6%, respectively); no grade ≥3 myalgia reported

Camidge RD et al NEJM September 25th 2018

	ALTA-1L Camidge WCLC 2018		ALEX Peters NEJM 2017		ALEX : updated analysis Camidge ASCO 2018	
	Brigatinib	**Crizotinib**	**Alectinib**	**Crizotinib**	**Alectinib**	**Crizotinib**
Patients (N)	137	138	152	151	152	151
Median FU mths	11	9.25	18.6	17.6	27.8	22.8
ORR (%)	76	73	82.9	75.5		
Median PFS mths (95% CI)	**NR**** (NR, NR)	9.8 (9.0, 12.9)	**25.7**** (19.9, NR)	10.4 (7.7, 14.6)	**34.8*** (17.7-NR)	10.9*
HR (95%CI) Log rank p value	0.49 (0.33, 0.74) 0.0007		0.5 (0.36, 0.7) <0.001		0.43 (0.32, 0.58)	

** Investigator assessed ** Independent review committee assessed*

Intracranial Efficacy	ALTA-1L		ALEX	
	Brigatinib	**Crizotinib**	**Alectinib**	**Crizotinib**
Measurable Brain Metastases (N)	**18**	**21**	**21**	**22**
ORR % (95% CI)	**78** (52,94)	29 (11,52)	**81** (58,95)	50 (28,72)
Any brain metastases (N)	43	47	64	58
Median Intracranial PFS (95% CI)	NR (11,NR)	5.6 (4.1-9.2)	Not reported	
HR (95%CI) for PFS with any BM	**0.27 (0.13-0.54)**		**0.40 (0.25-0.64)**	
Cumulative incidence of CNS progression at 1 year % (95% CI)	Not reported		9.4 (5.4-14.7)	41.4 (33.2-49.4)

Outline

- **ALK-rearranged:**
  - The picture
  - How alectinib changed 1st line
  - Brigatinib; a new standard first line option?
  - **The upcoming scenario in first line**
  - Mechanisms underlying acquired resistance to ALK-TKIs
  - Precision oncology in the era of NGS

ALK inhibitors currently approved

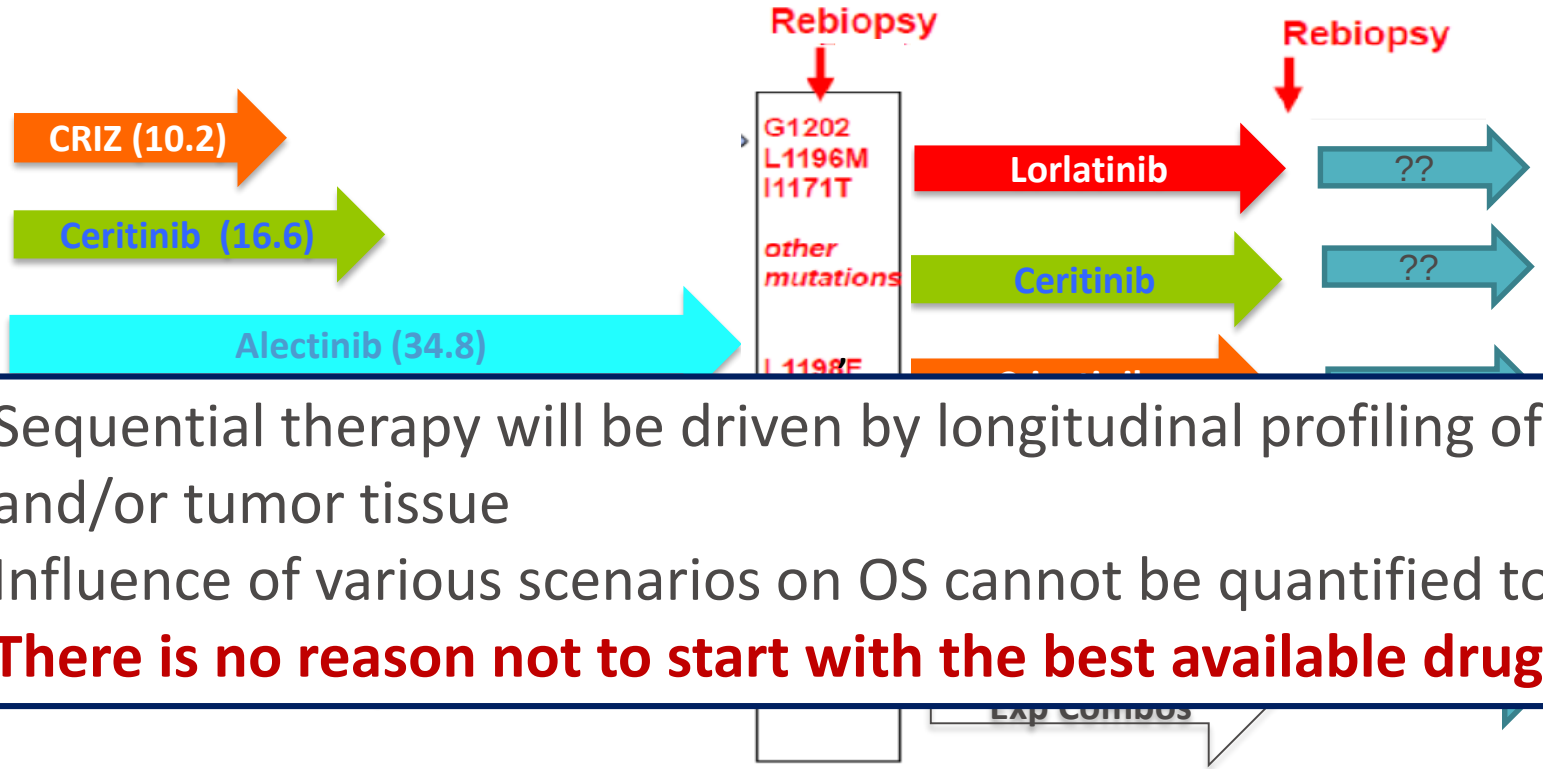
ALK TKi		Approved	First-line setting	mPFS (mo)	After crizotinib setting	mPFS (mo)
1° Generation	*Crizotinib 250mg bd	First-line (FDA/EMA/PMDA)	PROFILE 1014	10.9	--	--
2° Generation	*Alectinib 600mg bd	First-line and after crizotinib (FDA/EMA/PMDA)	JALEX	25.9	ALUR	9.6
			ALEX	34.8		
	*Ceritinib 750mg/die	First-line and after crizotinib (FDA/EMA/PMDA)	ASCEND 4	16.6	ASCEND 5	5.4
	Brigantinib 90mg x 7 days → 180 mg/die	After crizotinib (FDA)	ALTA 1L (ongoing)	NA	ALTA	15.6
3° Generation	Lorlatinib 150mg/die	Pending approval after crizotinib (FDA)	NCT03052628 (ongoing)	NA	NCT01970865	13.5

*** Approved drugs in Italy**

Solomon BJ. NEJM, 2014 - Peters S. NEJM, 2017 - Novello S. Annals of Oncol, 2018 - Soria JC. Lancet, 2017 - Shaw AT. Lancet, 2017 - Kim DW. J Clin Oncol, 2017 - Solomon B. JTO, 2017

How to incorporate new ALK Inhibitors into clinical practice ?

Molecular guided sequential therapy:



- Sequential therapy will be driven by longitudinal profiling of cfDNA and/or tumor tissue
- Influence of various scenarios on OS cannot be quantified to date
- **There is no reason not to start with the best available drugs**

OU et al., JTO, 2014, Ou et al., Lung Cancer 2015, Shaw et al., NEJM, 2016, Friboulet et l. Cancer Discov., 2014, Toyokawa et al., 2013

How to incorporate new ALK Inhibitors into clinical practice ?

To answer questions we need clinical trials

Quale sequenza terapeutica nella malattia ALK-traslocata?

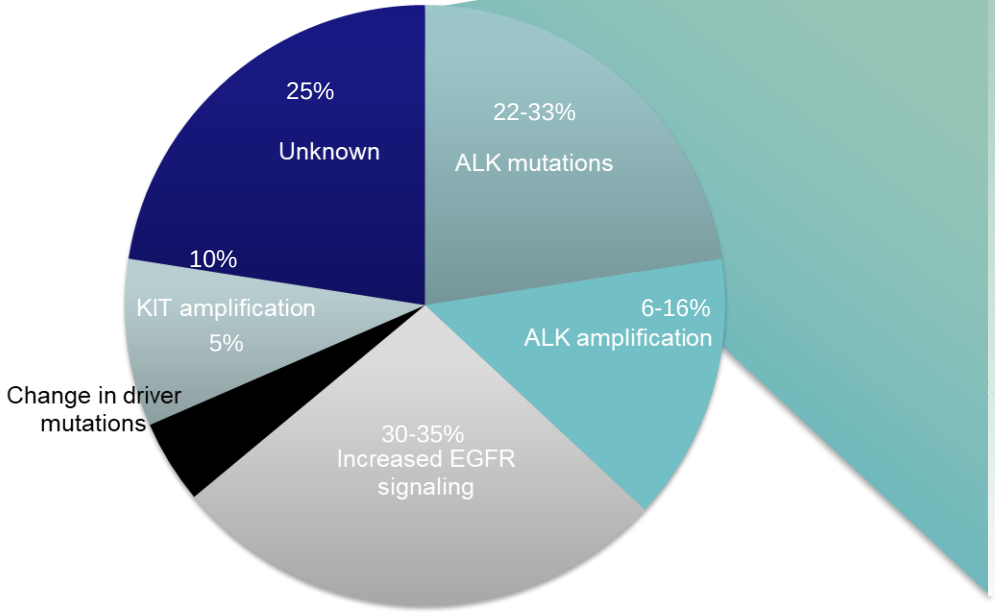
Outline

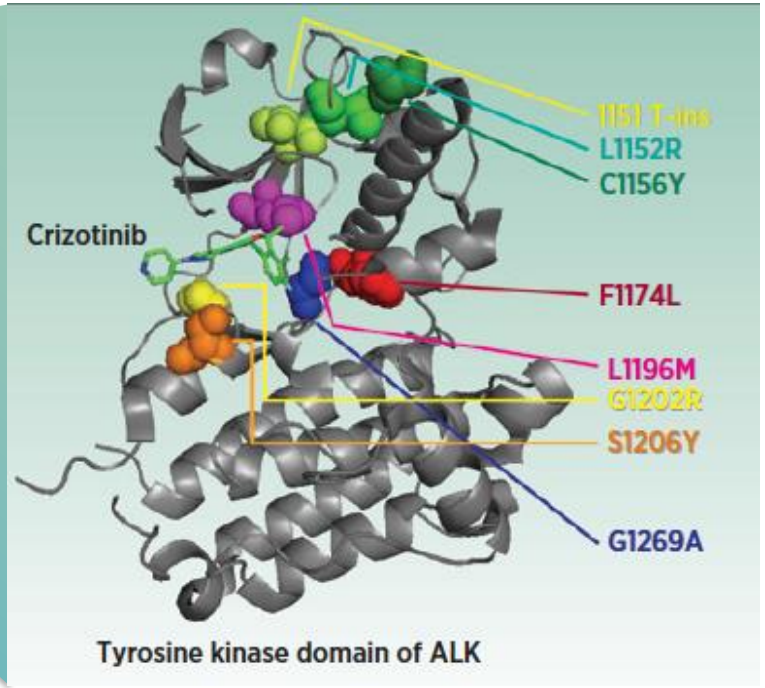
- **ALK-rearranged:**
  - The picture
  - How alectinib cha
  - Brigatinib; a new s
  - The upcoming sce
  - **Mechanisms underlying acquired resistance to ALK-TKIs**
  - Precision oncology in the era of NGS

Quale sequenza terapeutica nella malattia ALK-traslocata?

Acquired Resistance to Crizotinib

- Alk target alteration (mutation or amplification)
- Alternative pathway activation
- Histologic trasformation



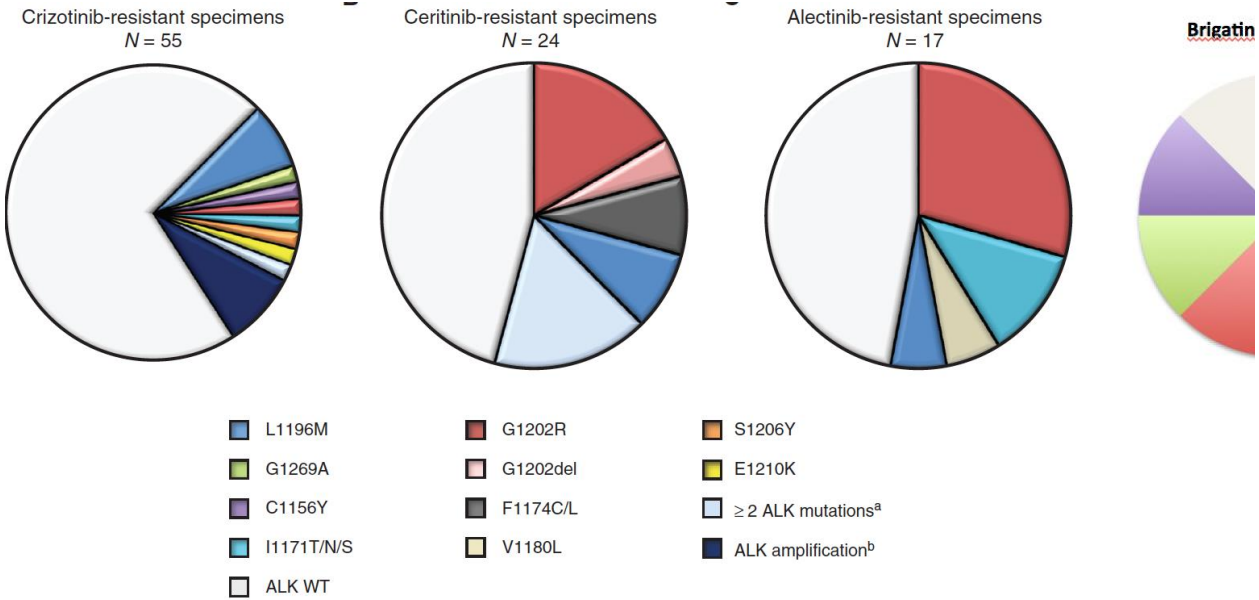


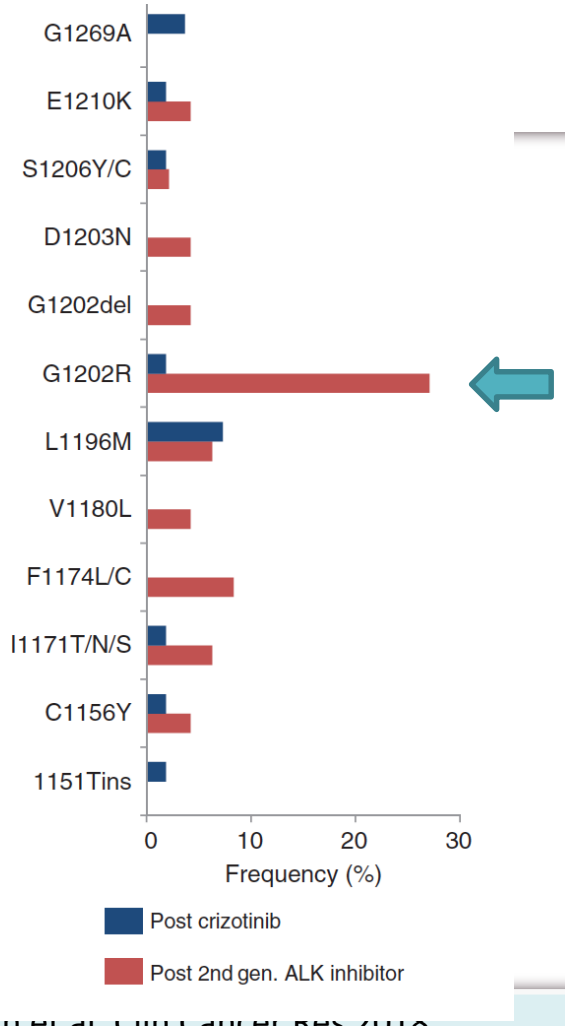
Camidge et al., Nature Rev Clin Oncol, 2014

Katayama, et al, Sci Trasl Med 2012

Alk mutations % is proportional to the s

ALK resistance mutations[a]	Crizotinib (*N* = 55)	Ceritinib (*N* = 24)	Alectinib (*N* = 17)	Brigatinib (*N* = 7)
ALK mutations[b]	20%	54%	53%	71%





*21 prior crizotinib

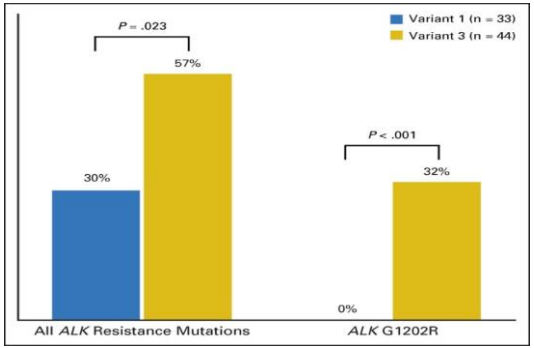
§ 17 prior crizotinib, 3 prior crizotinib and ceritinib

Gainor JF et al, Cancer Discovery 2016 - McCoach et al. Clin Cancer Res 2018

Preclinical activity of next generation ALK-TKIs in resistance mutants

IC_{50} ≤50 nM | IC_{50} >50–<200 nM | IC_{50} ≥200 nM

Cellular ALK Phosphorylation Mean IC_{50} (nM)					
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
EML4-ALK	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0[a]	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	5			
D1203N	116.3	3			
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0



Lin J et al. JCO 2018

G1202R resistance mutation is most common in variant 3 EML4-ALK and sensitive to lorlatinib > brigatinib > other 1st and 2nd generation ALKis

IC_{50}, half-maximal inhibitory concentration

Gainor JF, et al. Cancer Discov. 2016

Secondary Resistance: evidence

1. **Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers.** Katayama R et al. Sci Transl Med 2012

2. **Molecular Mechanisms of Resistance to 1st- and 2nd-Generation ALK Inhibitors in ALK-Rearranged Lung Cancer.** Gainor JF et al. Cancer Discov. 2016 Oct;6(10):1118-1133

3. **Impact of EML4-ALK Variant on Resistance Mechanisms and Clinical Outcomes in ALK-Positive Lung Cancer.** Lin JJ et al. J Clin Oncol. 2018 Apr 20;36(12):1199-1206

4. **Clinical Utility of Cell-Free DNA for the Detection of *ALK* Fusions and Genomic Mechanisms of ALK**

5.

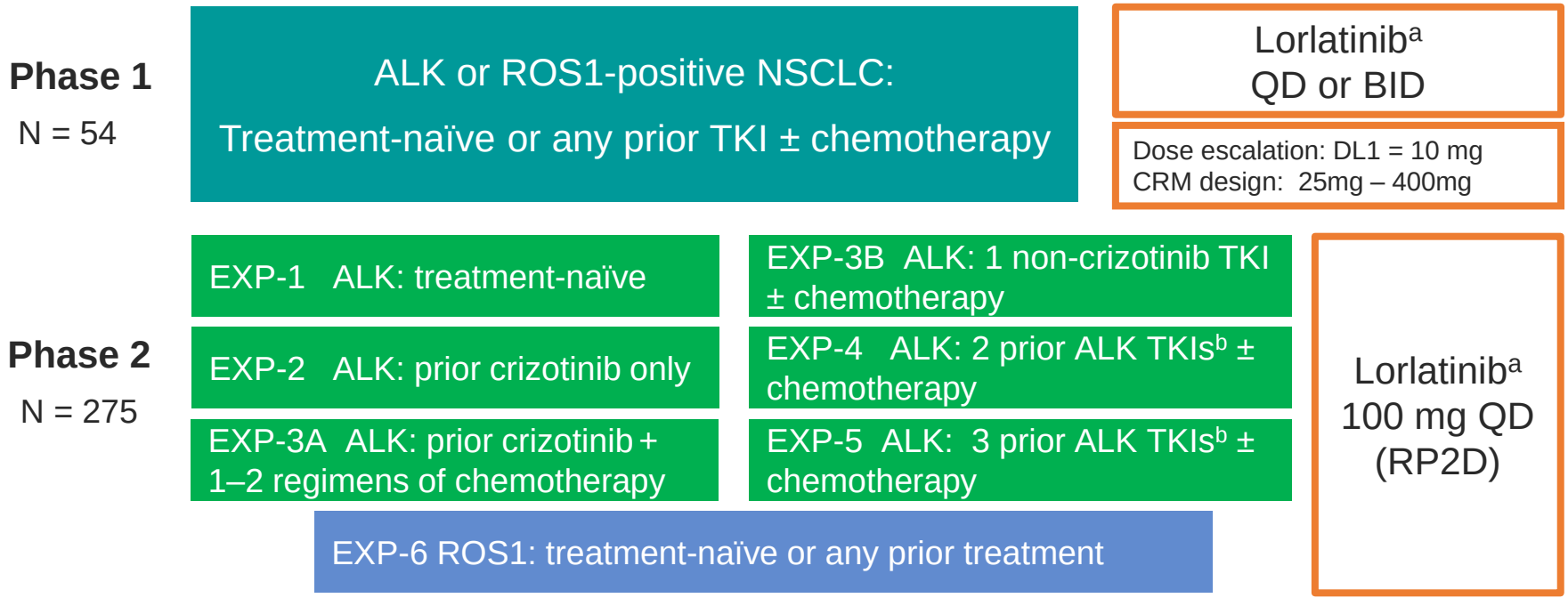
6. **of Circulating Tumor DNA.** Dagogo-Jack I et al. JCO Precis Oncol. 2018;2018

7. **Accumulation of Concomitant Mutations Involved in Drug Resistance in the Sequential ALK TKI Treatments of ALK-Positive NSCLC.** Shun Lu, et al. (Oral at WCLC 2018)

Materials and methods:

We used a combination of next generation sequencing (NGS), multiplex mutation assay, direct DNA sequence and FISH

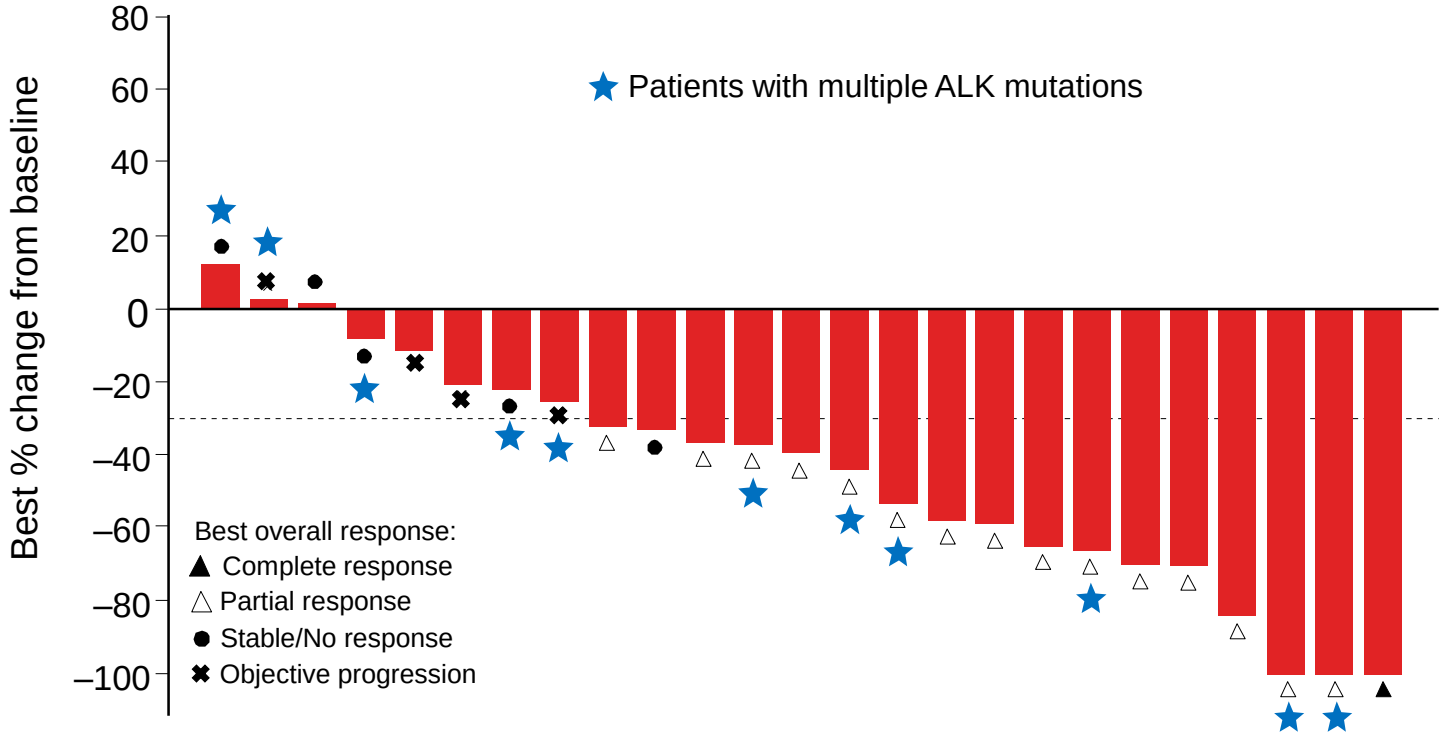
Phase 1/2 Study of Lorlatinib: Design and Patient Populations



Asymptomatic brain mets were allowed in all cohorts. [a]Treatment until PD or unacceptable toxicity. [b]Lines of therapy (if the same TKI is given twice, this is counted as 2 prior lines of treatment).

BID, twice daily; PD, progressive disease; QD, once daily.

Best Response in Patients Harboring the ALK G1202R or G1202del Mutation[a] (EXP2–5)



[a]Detected in either cfDNA or tumor tissue (archival or de novo) analysis sets

Phase 2 Study Objectives

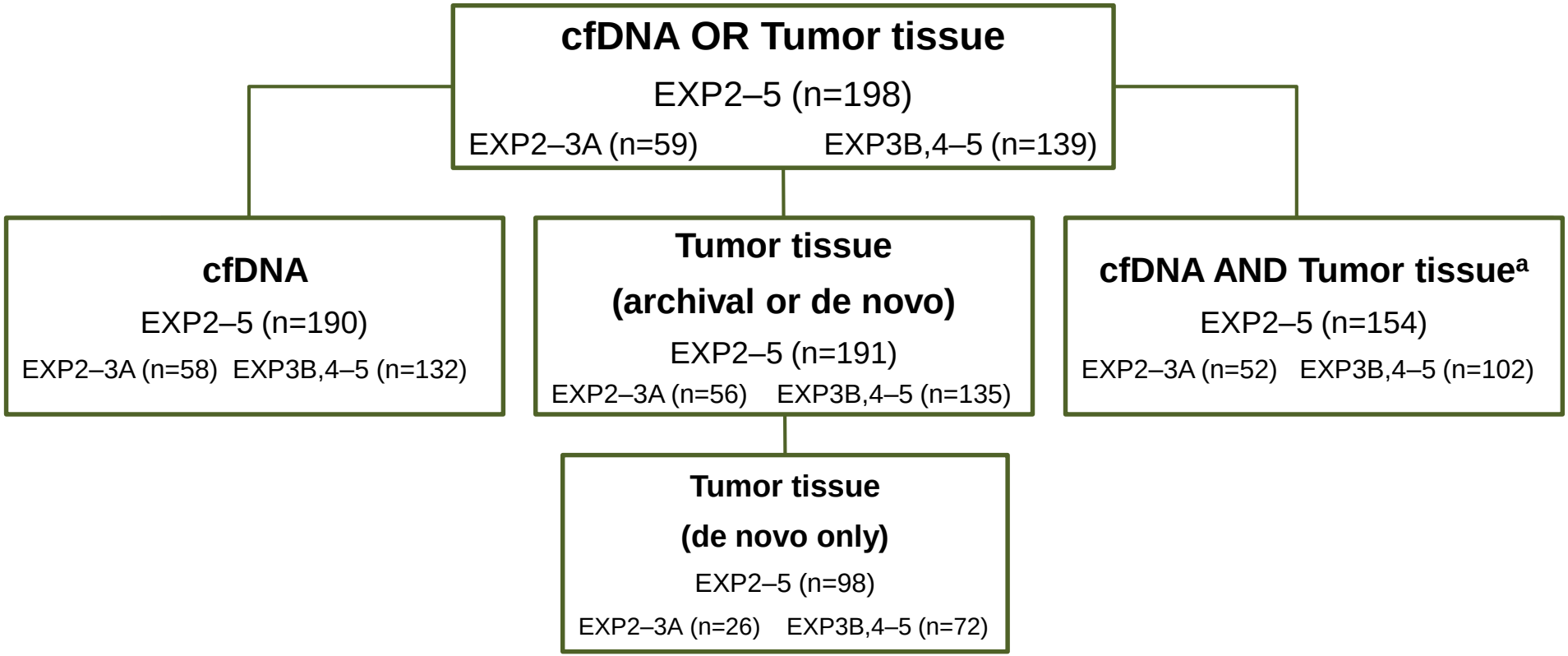
Primary Objective

- Overall and intracranial antitumor activity measured as confirmed overall and intracranial response by independent central review

Secondary Objectives

- Secondary measures of clinical efficacy
- Safety and tolerability
- Patient-reported outcomes
- **Selected molecular profiling**

Patients Included in Biomarker Analyses



[a]Only patients with mutation status of “Mutation(s)” or “No Mutation” in both cfDNA and tumor DNA are counted.

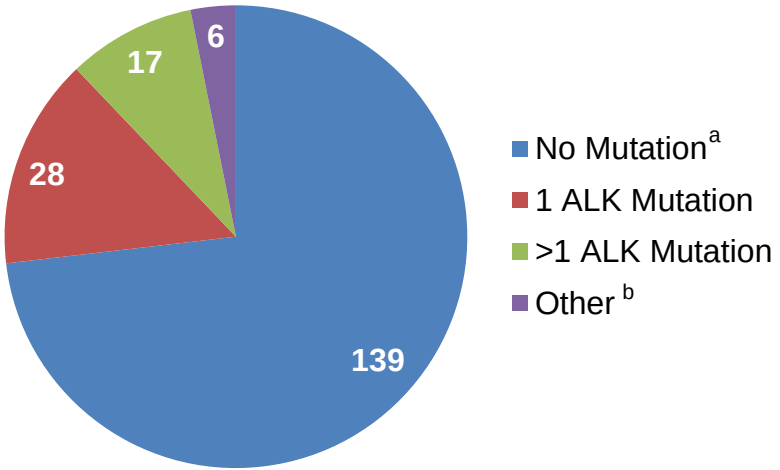
ALK Kinase Domain Mutation Detected in Previously Treated ALK+ Patients (EXP2–5)

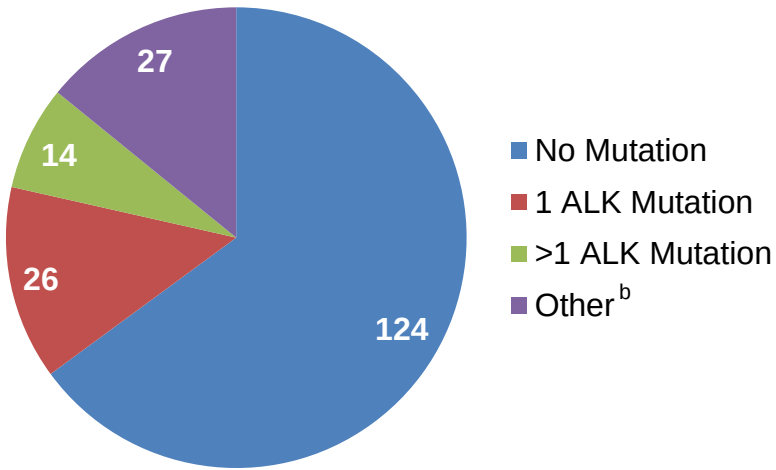
cfDNA analysis:

- 45/190 **(23,6%)** pts with 1 or more ALK kinase domain mutations

Tumor tissue analysis (archival or de novo):

- 40/191 **(20,9%)** ts with 1 or more ALK kinase domain mutations





[a]No mutation includes samples with no cfDNA was detected; [b]Other includes samples which failed analysis, were uninformative or not analyzed.

Concordance Assessment of ALK Mutation Status by cfDNA and Tumor Tissue (Archival or De Novo)

	≥1 prior ALK TKI EXP2–5
Patients with blood and tumor tissue data, N	**154**
Same mutations in blood and tumor, n (%)	112 (72.7)
Different mutations in blood and tumor, n (%)	42 (27.3)
Patients with blood and tumor tissue (de novo only) data, N	**69**
Same mutations in blood and tumor, n (%)	41 (59.4)
Different mutations in blood and tumor, n (%)	28 (40.6)

Patients who have blood CNA data only or tumor DNA data (archival or de novo) only are counted as not available (n=44).
Patients who have blood CNA data only or tumor DNA data (de novo) only are counted as not available (n=126).

Best Overall Response by Presence/Absence of ALK Mutation

	EXP2–3A: Post-Crizotinib (N=59)[a]	
	No Mutation[b] (n=43)	≥1 Mutation[b] (n=15)
BOR, n (%)		
CR	1 (2.3)	0
PR	30 (69.8)	11 (73.3)
SD	8 (18.6)	0
PD	4 (9.3)	2 (13.3)
IND	0	2 (13.3)
ORR, n (%)	**31 (72.1)**	**11 (73.3)**
95% CI	**56.3, 84.7**	**44.9, 92.2**

[a]1 patient sample was non-analyzable
[b]Detected in either cfDNA or tumor tissue (archival or de novo) analysis sets

	EXP3B,4–5: Prior 2nd-gen TKI (N=139)[a]	
	No Mutation[b] (n=87)	≥1 Mutation[b] (n=49)
BOR, n (%)		
CR	2 (2.3)	1 (2.0)
PR	21 (24.1)	29 (59.2)
SD	36 (41.4)	10 (20.4)
PD	21 (24.1)	5 (10.2)
IND	7 (8.0)	4 (8.2)
ORR, n (%)	**23 (26.4)**	**30 (61.2)**
95% CI	**17.6, 37.0**	**46.2, 74.8**

[a]3 patients samples were non-analyzable
[b]Detected in either cfDNA or tumor tissue (archival or de novo) analysis sets

BOR, best overall response; CR, complete response; IND, indeterminate, ORR, objective response rate, PD, progressive disease; PR, partial response, SD, stable disease.

Outline

- **ALK-rearranged:**
  - The picture
  - How alectinib changed 1st line
  - Brigatinib; a new standard first line option?
  - The upcoming scenario in first line
  - **Precision oncology in the era of NGS**

JAMA | Original Investi

Association
With Surviva
Lung Cancer

Carolyn J. Presley, MD; Daiwei
Karin B. Adelson, MD; Roy S. H
Vinodh Agarwala, MD, PhD; A

RESULTS Among 5688
range, 41-85], 63.6% w
broad-based genomic
patients who received
based on testing result
received no targeted t
patients undergoing b
routine testing. Using a
between broad-based
death at 12 months, 41
difference −3.6% [95%
propensity score–matc
to 1.11]; *P* = .40) vs unm
P < .001).

y
It?

ll lung cancer
uencing directly
ciated with

Summary

- Crizotinib has been the first-line standard of care for patients with ALK positive NSCLC
- Alectinib is and Brigatinib is going to become the two new 1st line standard of care
- This has implications for current 1L trials in which crizotinib is the control arm
- Alectinib and Brigatinib are effective in preventing and treating brain metastases → After multidisciplinary discussion postpone brain radiotherapy if using these drugs in first line!
- In the absence of direct comparison of next generation ALKis a 'best' ALK inhibitor will remain unknown (MASTER PROTOCOL)
- At the time of Alectinib/Brigatinib failure, therapeutic options remain undefined

Right Patient, Right Target & Right Drug –
Improving cancer care through innovative patient-driven collaborations.

Zofia Piotrowska, MD, MHS
Massachusetts General Hospital
Instructor, Harvard Medical School
Boston, USA

Thank you for your attention!

rita.chiari@unipg.it