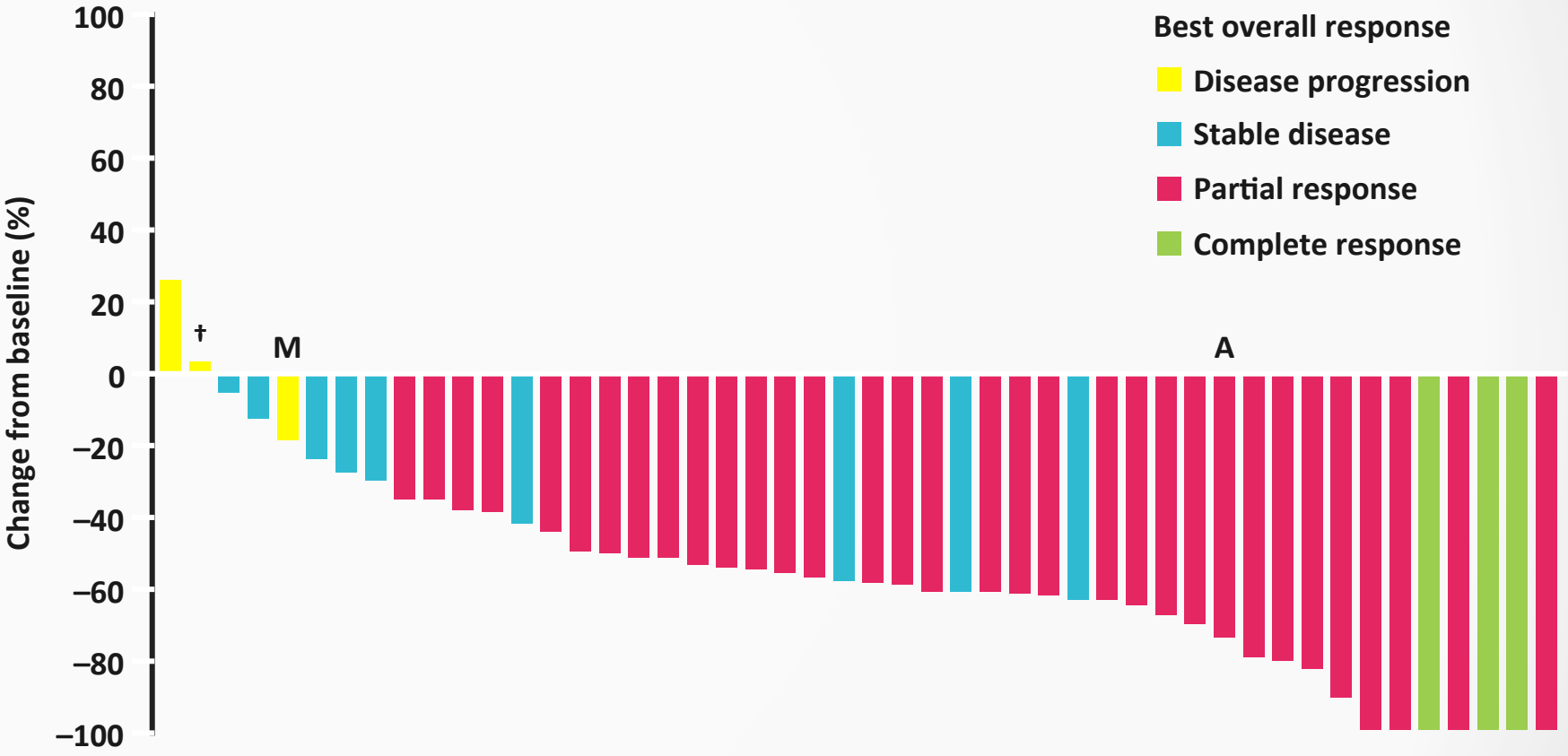
Respnse to crizotinib in ROS1-rearrangement NSCLC

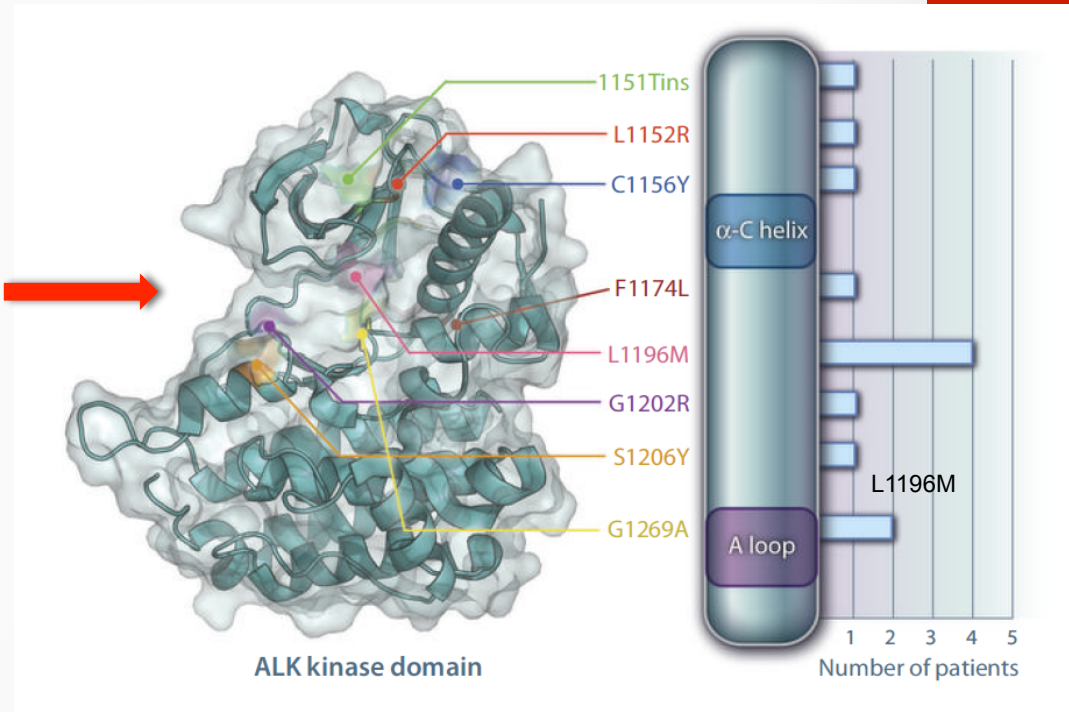


A, *ROS1*-negative, but *ALK*-positive
M, *ROS1*-positive and *MET* amplification-positive
†Tumor later shown to be *ROS1*-negative

Shaw AT, *et al. N Engl J Med*
DATE [Epub ahead of print]

Resistance to ALK inhibitors

- **Intrinsic**
  - BIM polymorphism
  - Pre-existing resistance ALK mutations
  - Fusion partner specific
- **Acquired**
  - Histologic transformation
  - Resistance ALK mutations
  - "PK" failure
  - Bypass pathways
- **Pharmacodynamic failure**
  - Sanctuary sites



Modified from Lovly and Pao, Sci Transl Med 4(120): 120ps2, 2012

Beyond crizotinib ….. Newer Generation ALK Inhibitors

ALK TKI	Manufacturer	Status	Ongoing Studies
Ceritinib	Novartis	FDA Approved EMA Approved	Phase 3 (vs chemo)
Alectinib	Chugai Roche/Genetech	Approved in Japan FDA Approved	Phase 3 (vs crizotinib)
Brigatinib	Ariad	Investigational FDA Breakthrough Therapy	Phase 3 (vs crizotinib)
Ensartinib (X-396)	Xcovery	Investigational	Phase 3 (vs crizotinib)
Entrectinib	Ignyta	Investigational	Phase 2
Lorlatinib	Pfizer	Investigational	Phase 2

Cellular activity of different ALK Inhibitors

Cellular ALK Phosphorylation Mean IC50 (nM)

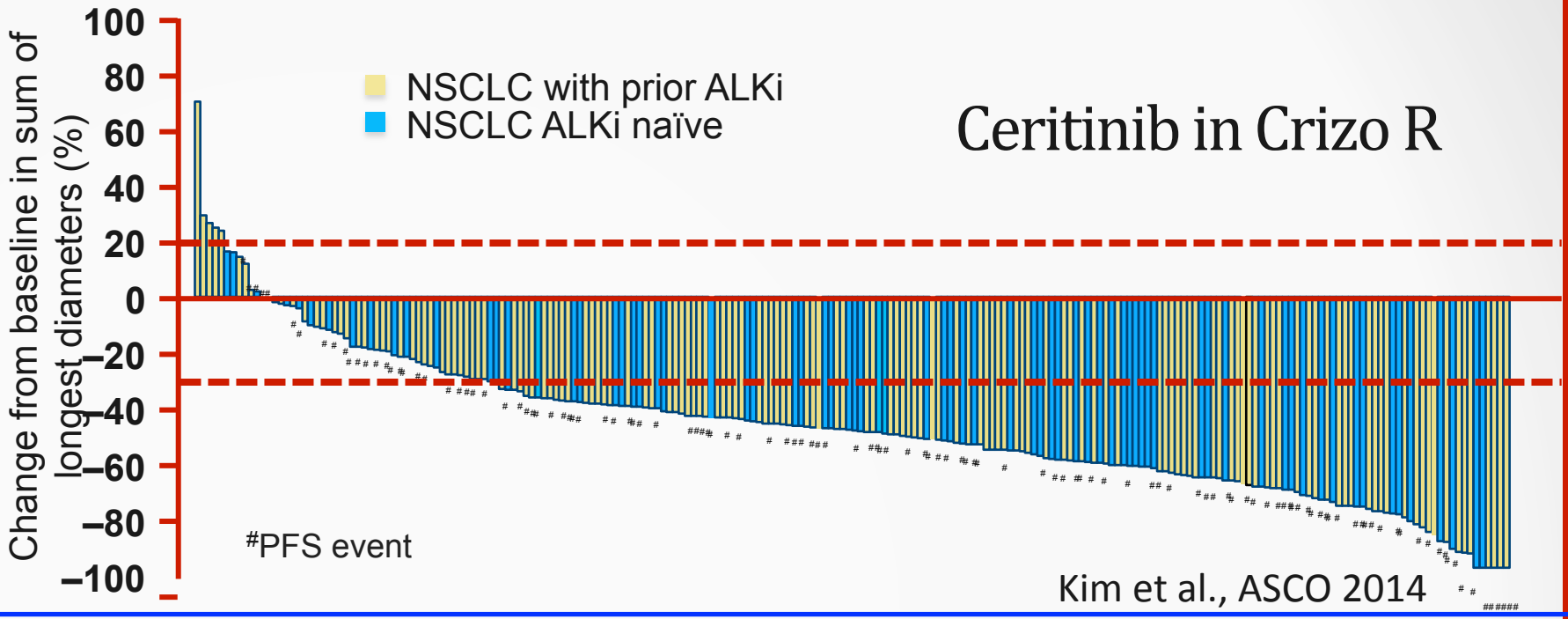
Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4-ALK V1	38.6	4.9	11.4	10.7	2.3
EML4-ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4-ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4-ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4-ALK I1171T	51.4	1.7	33.6[a]	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

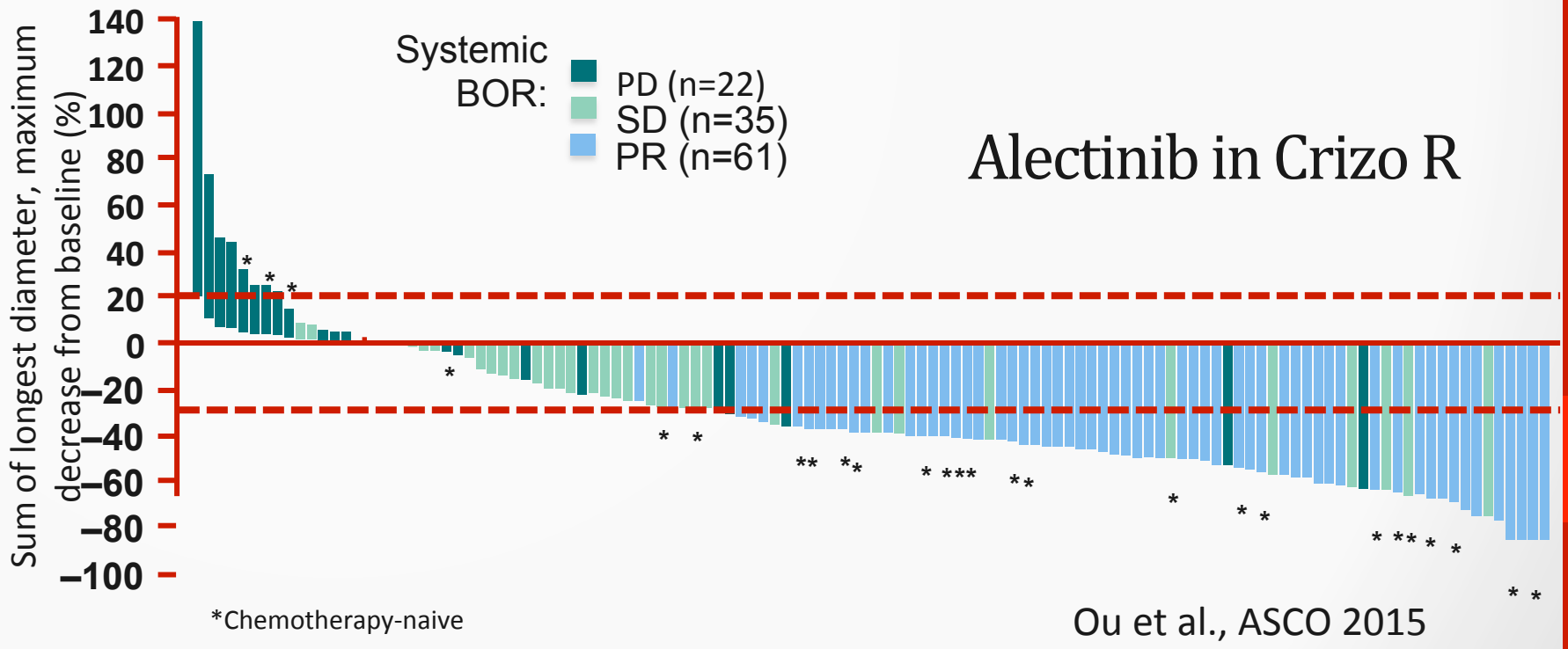
IC50 ≥ 200 nM

Gainor et al. *Cancer Discovery* 2016;6:1118-1133



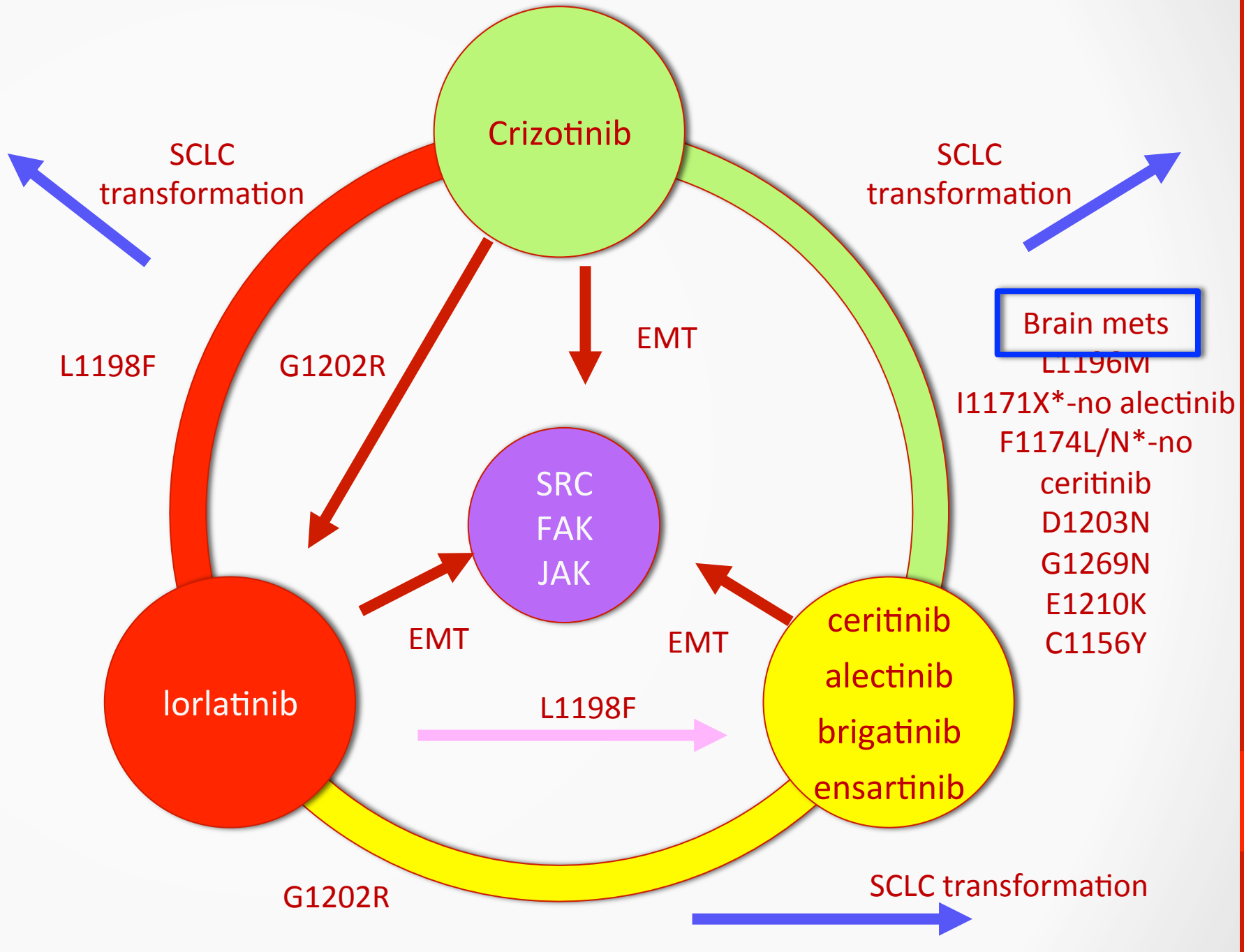
Ceritinib in Crizo R

Kim et al., ASCO 2014



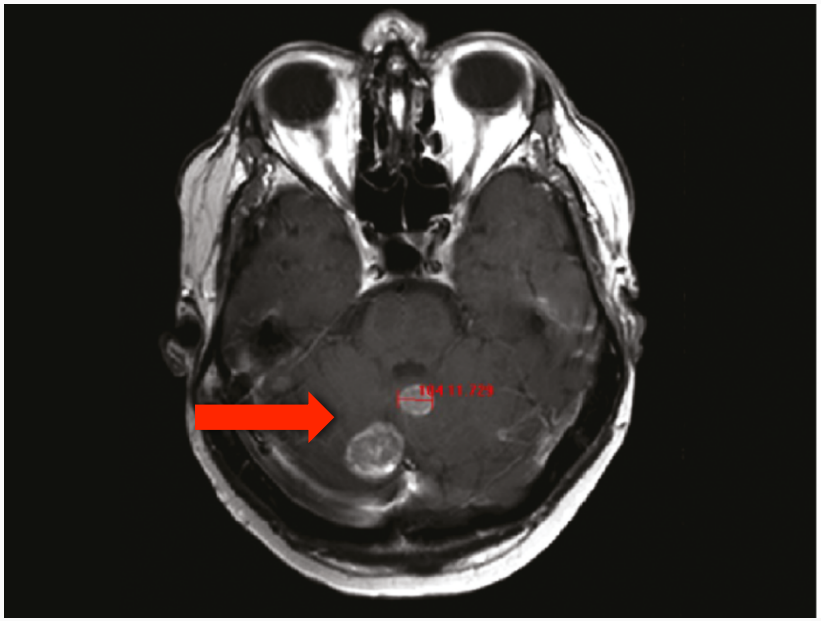
Alectinib in Crizo R

Ou et al., ASCO 2015

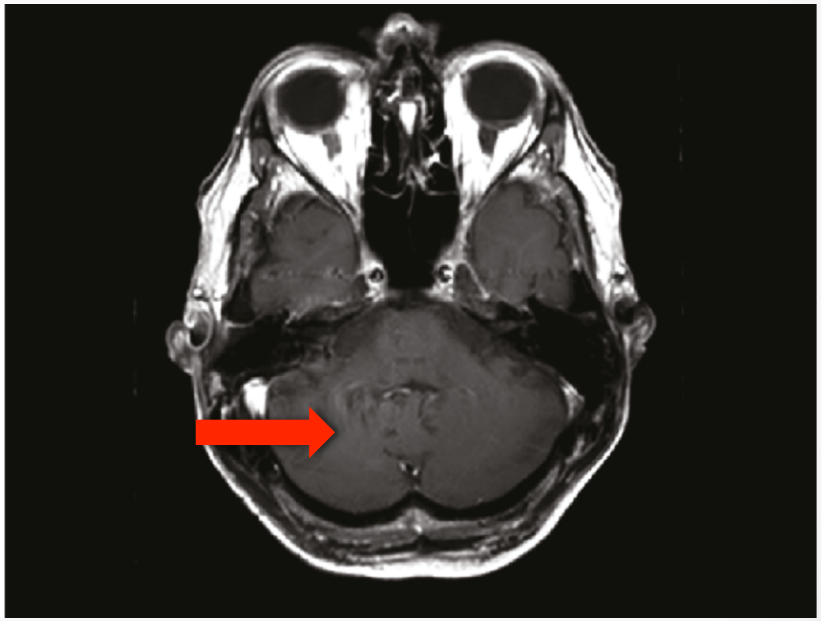

Crizotinib
SCLC transformation
SCLC transformation
Brain mets
L1196M
I1171X*-no alectinib
F1174L/N*-no ceritinib
D1203N
G1269N
E1210K
C1156Y
L1198F
G1202R
EMT
SRC
FAK
JAK
EMT
EMT
lorlatinib
L1198F
ceritinib
alectinib
brigatinib
ensartinib
G1202R
SCLC transformation

Brain metastases: Response to CERITINIB

MRI scans showing response in a ALK inhibitor-naïve patient (retrospective, independent readings)

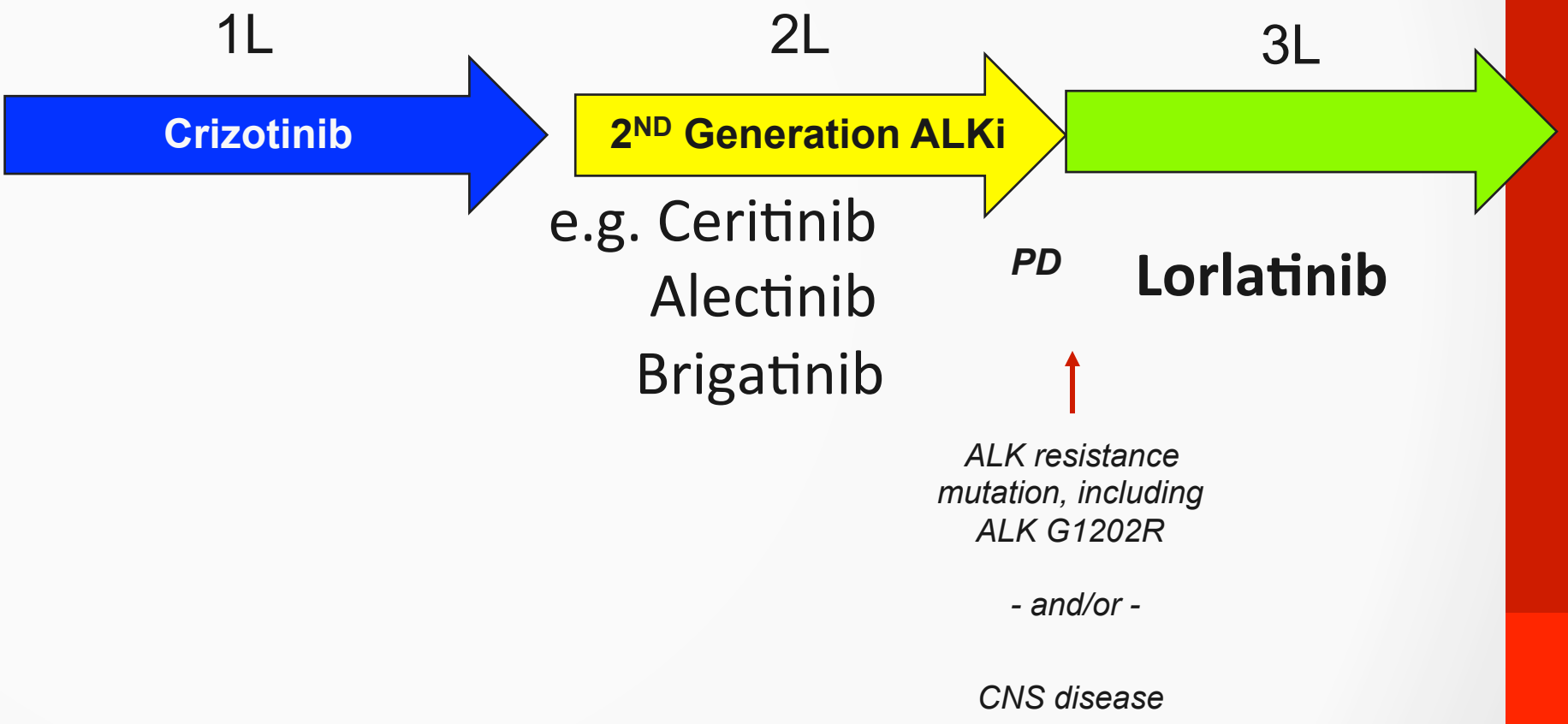


Baseline

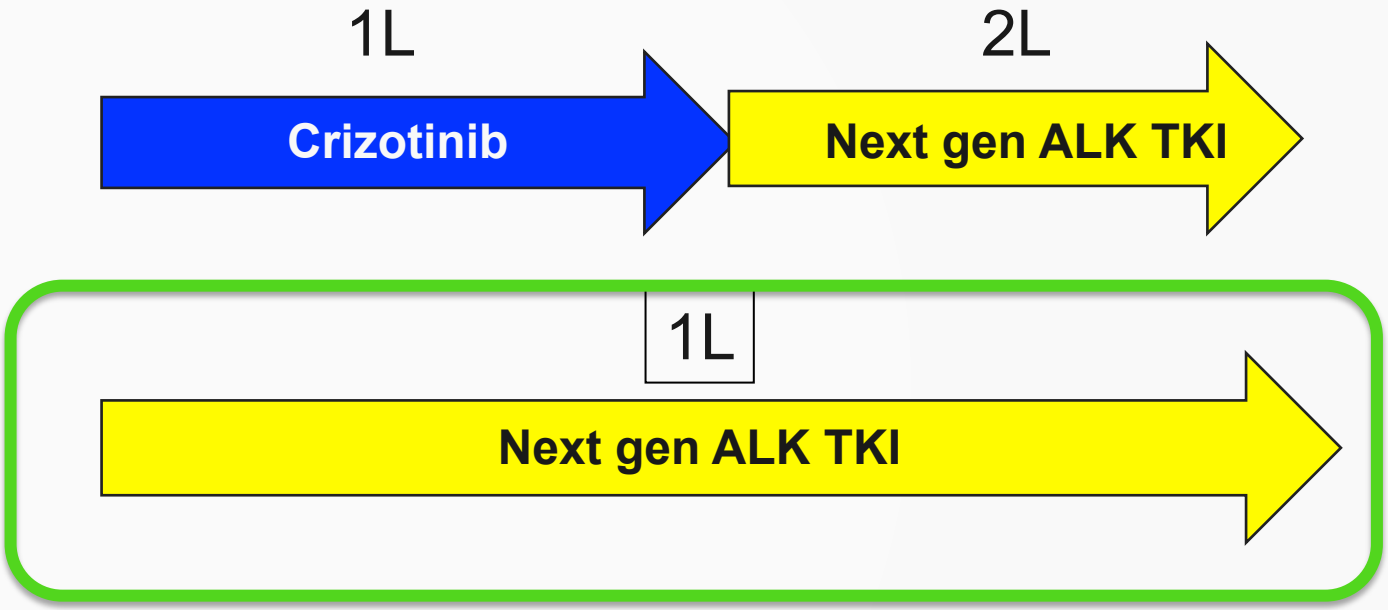


12 Months

Role for Multiple Sequential ALK Inhibitors



What is Optimal 1° line for Advanced ALK+ NSCLC ?

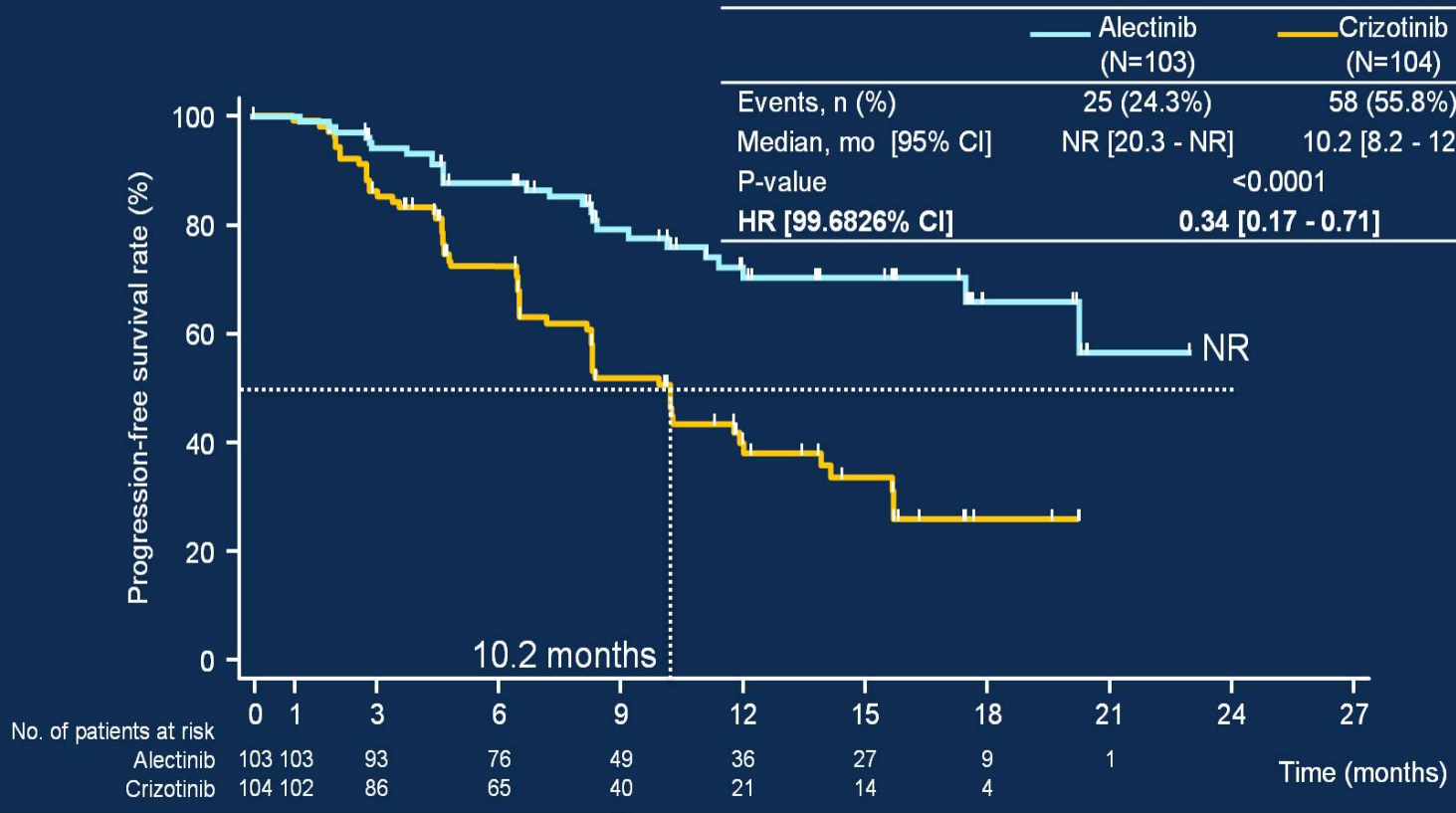


Firstline Phase 3 studies of novel ALK inhibitors in NSCLC

- ALEX: Alectinib vs Crizotinib
- ASCEND 4: Ceritinib vs Chemotherapy
- ALTA: Brigatinib vs. crizotinib
- eXalt3: Ensartinib vs. Crizotinib

J-ALEX

Primary Endpoint: PFS by IRF (ITT Population)



ALK-TKI in 1° e linee successive: conclusioni

- Necessario ricercare la traslocazione ALK (in nonSQ) alla diagnosi
- Il trattamento di I linea dei pazienti ALK traslocati dovrebbere essere con ALK-TKI (**crizotinib**).
- La maggior parte dei tumori resistenti al crizotinib rimangono dipendenti dalla pathway di ALK concedendo l'uso sequenziale di altri inibitori di ALK
- **Ceritinib ed alectinib** potrebbero essere le terapie standard per i pazienti recidivati a crizotinib
- **Lorlatinib** ha un'alta permeabilità nel SNC e copre un largo spettro di mutazioni di resistenza a crizotinib
- L'assessment delle mutazioni ALK alla progressione potrebbe guidare la scelta del ALK-TKI.

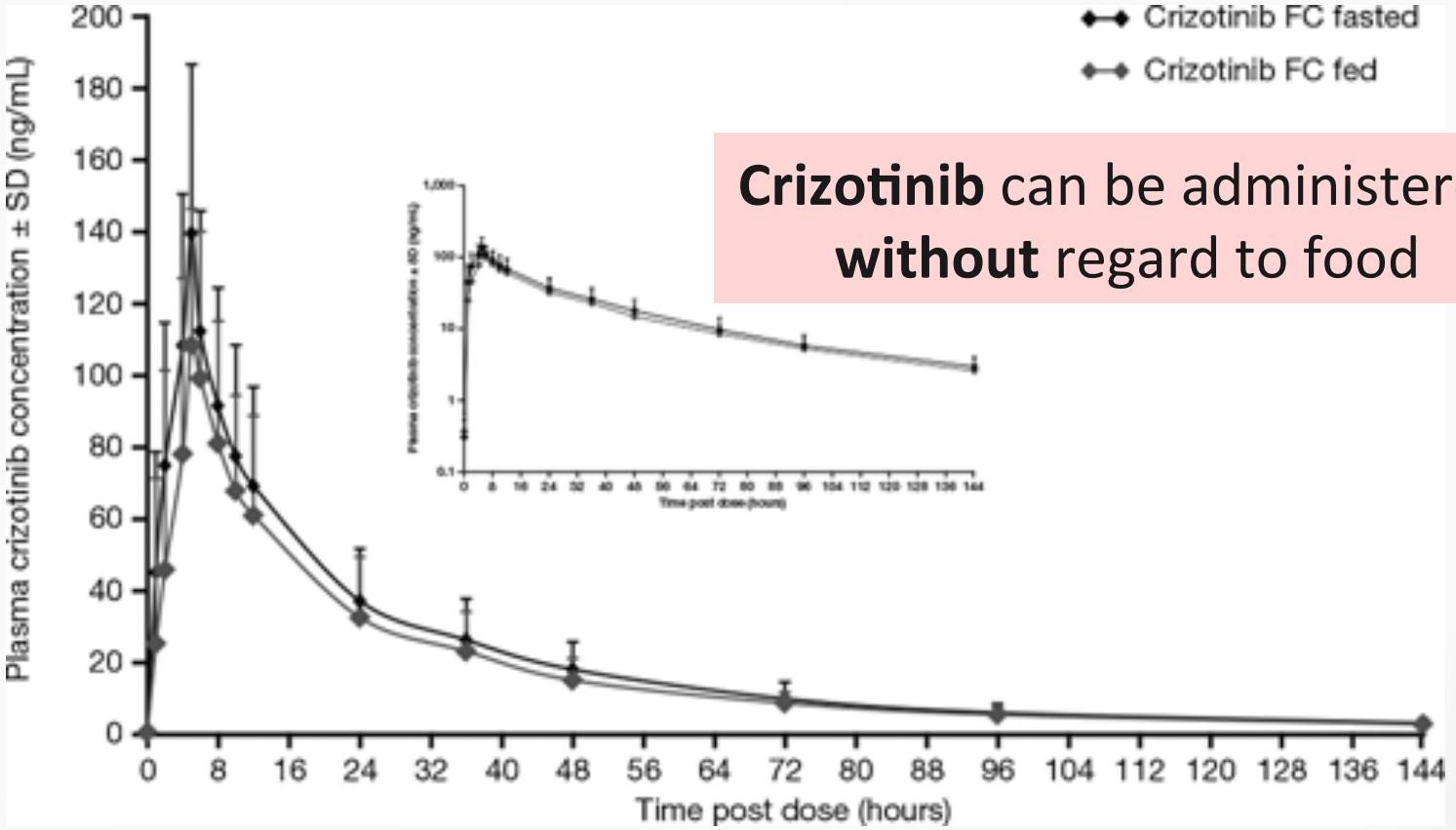
AGENDA

- INIBITORI TKI DI EGFR
  - ✓ 1° linea
  - ✓ 2° linea
  - ✓ Interazioni
- INIBITORI TKI DI ALK
  - ✓ 1° linea
  - ✓ Linee successive
  - ✓ **Interazioni**

ALK-TKI ed alimenti

Study A8081011, open-label randomized, crossover, single-dose phase I (healthy subjects)

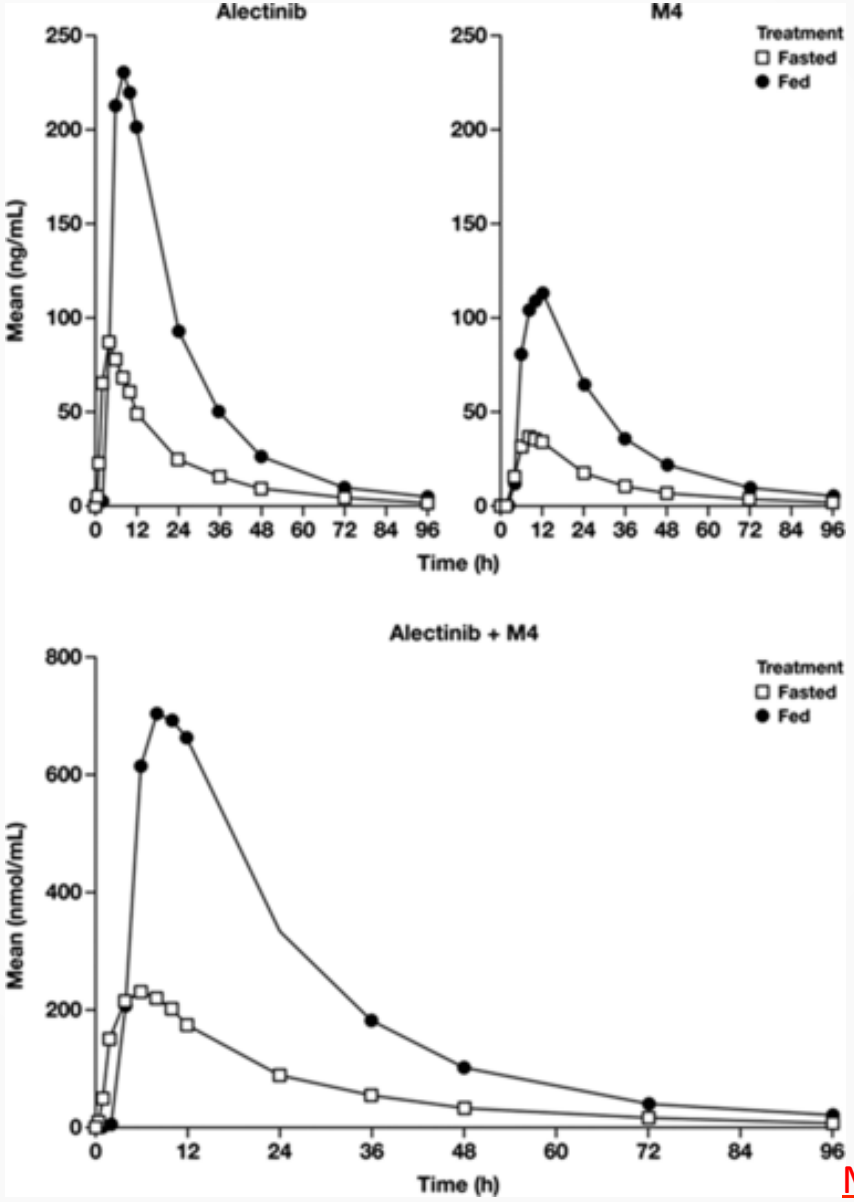
- High-fat meal -> slight reduction of 14% crizotinib exposure
- Reduction NOT clinically meaningful



Crizotinib can be administered **without** regard to food

Xu H., J Clin Pharmacol. 2015 Jan;55(1):104-13

ALK-TKI ed alimenti



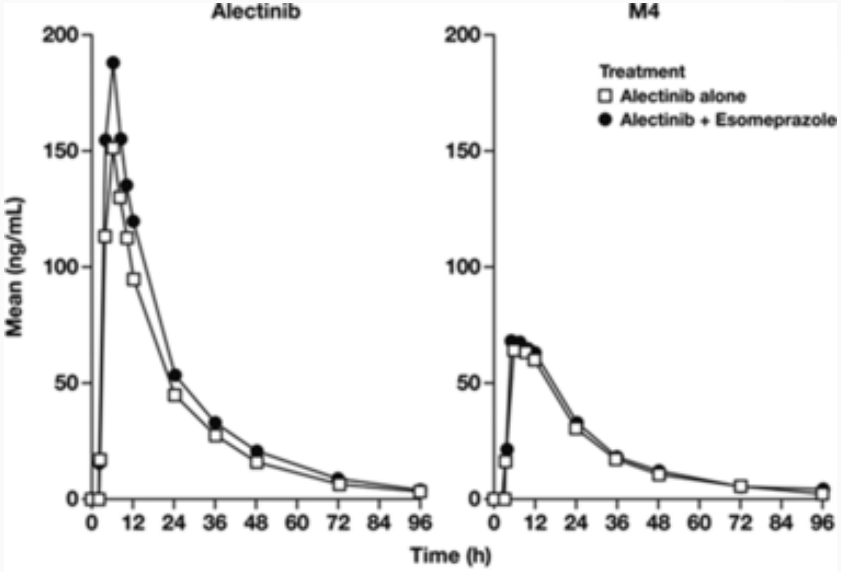
Open-label, 2-group study in healthy subjects

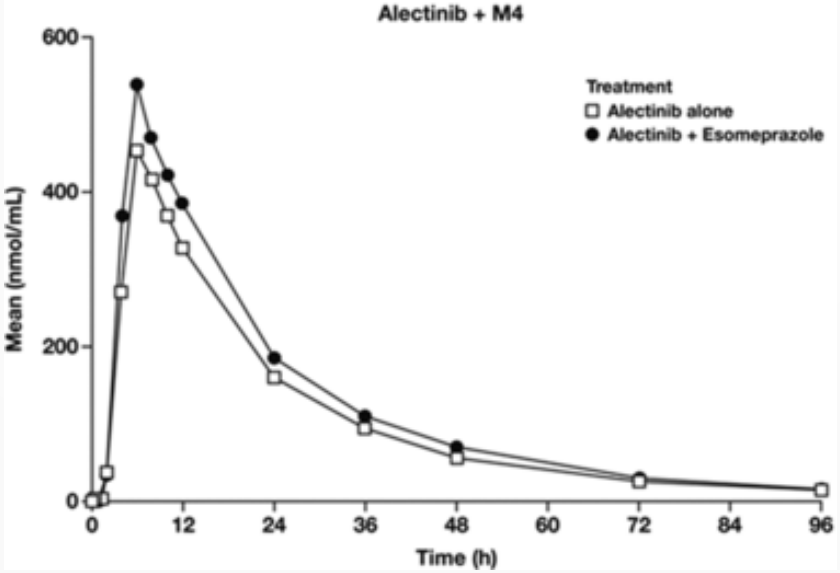
- High-fat meal -> increased exposure to alectinib by 2.7 and 2.92-fold for for Cmax and AUC

Alectinib should be administered **under fed conditions** to maximize bioavailability

Morcos P.N., Clin Pharmacol Drug Dev. 2016 Aug 22

ALK-TKI e PPI (esomeprazolo)





Open-label, 2-group study in healthy subjects

- Esomeprazole -> minor increased in exposure of alectinib, similar exposure of M4
- NOT clinically relevant

Alectinib and esomeprazole could be co-administred

Morcos P.N., Clin Pharmacol Drug Dev. 2016 Aug 22

TAKE HOME MESSAGES (1)

① **Ricercare, dove indicato, con costanza e caparbietà la presenza di mutazioni/traslocazioni sia alla diagnosi che alla progressione (cito-istologico e biopsia liquida).**

② **Intrapprendere il trattamento di prima linea avendo a disposizione i dati biomolecolari, talora anche a scapito del ritardo di inizio del trattamento di qualche giorno.**

③ **I trattamenti per pazienti "oncogene addicted" sono molto efficaci in termini di ORR e PFS, MA non portano MAI a guarigione il paziente.**

TAKE HOME MESSAGES (2)

④ **Le tossicità sono minori rispetto alla CT, o meglio, sono diverse.**

⑤ **Dobbiamo fare attenzione a possibili interazioni con farmaci concomitanti, CAM e cibo. Potrebbero influenzare sia l'efficacia sia la tollerabilità.**

AGGIORNAMENTO SULLE PATOLOGIE POLMONARI: IL TRATTAMENTO DEL CARCINOMA DEL POLMONE NON A PICCOLE CELLULE

Palmanova (UD), 24 maggio 2017

Grazie dell'attenzione

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