EUROPEAN LUNG CANCER
CONFERENCE 2016

TARGETING ALK
SEQUENCING OF AGENTS

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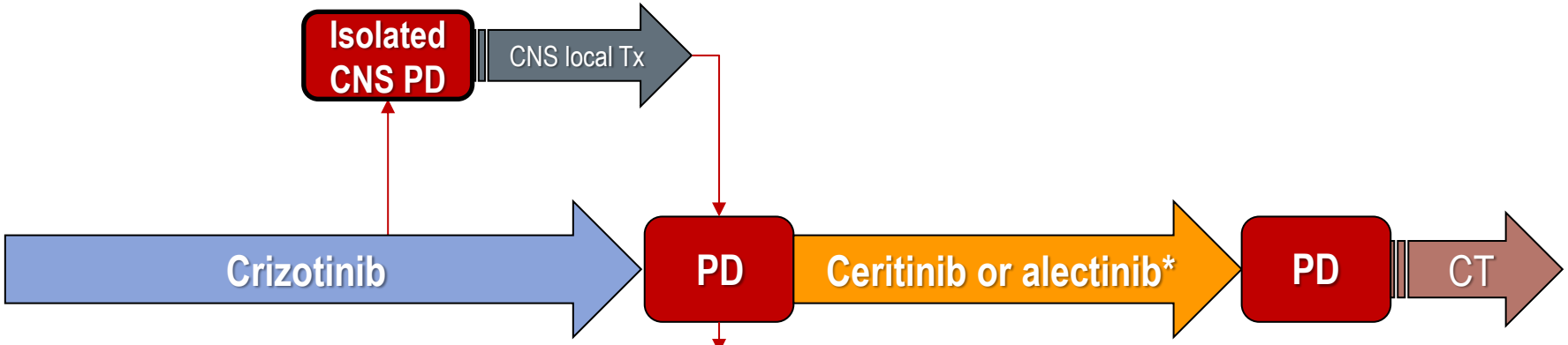
Disclosures Slide

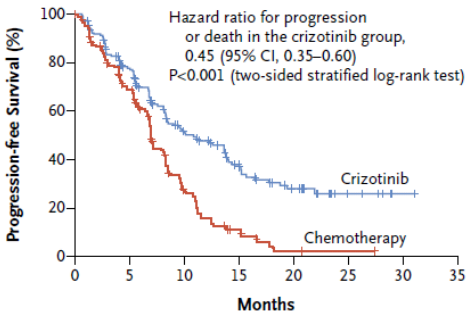
Advisory Boards: Eli Lilly, Roche, Genentech, Boehringer-Ingelheim, Astra-Zeneca, Pfizer, MSD, Clovis, Pierre Fabre, Bristol-Myers-Squibb, Novartis

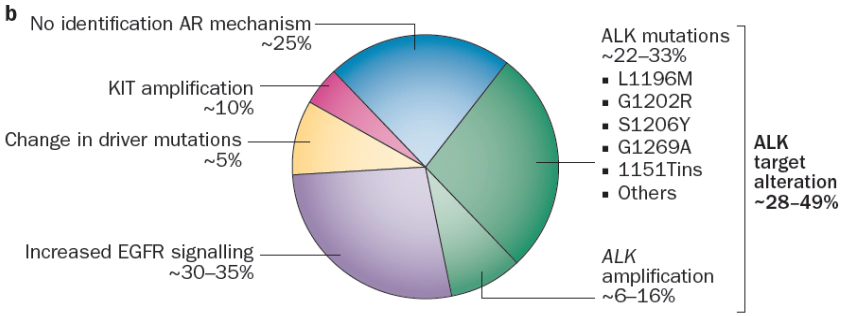
Symposia: Eli Lilly, Roche, Pfizer, Astra- Zeneca, Boehringer-Ingelheim, Novartis

Current Treatment Strategy for ALK+ Patients



*Available in Japan and US, not in EU

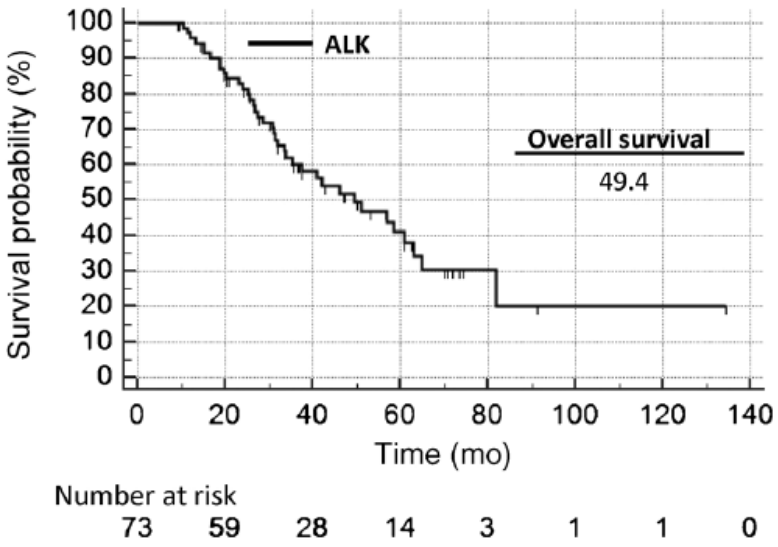




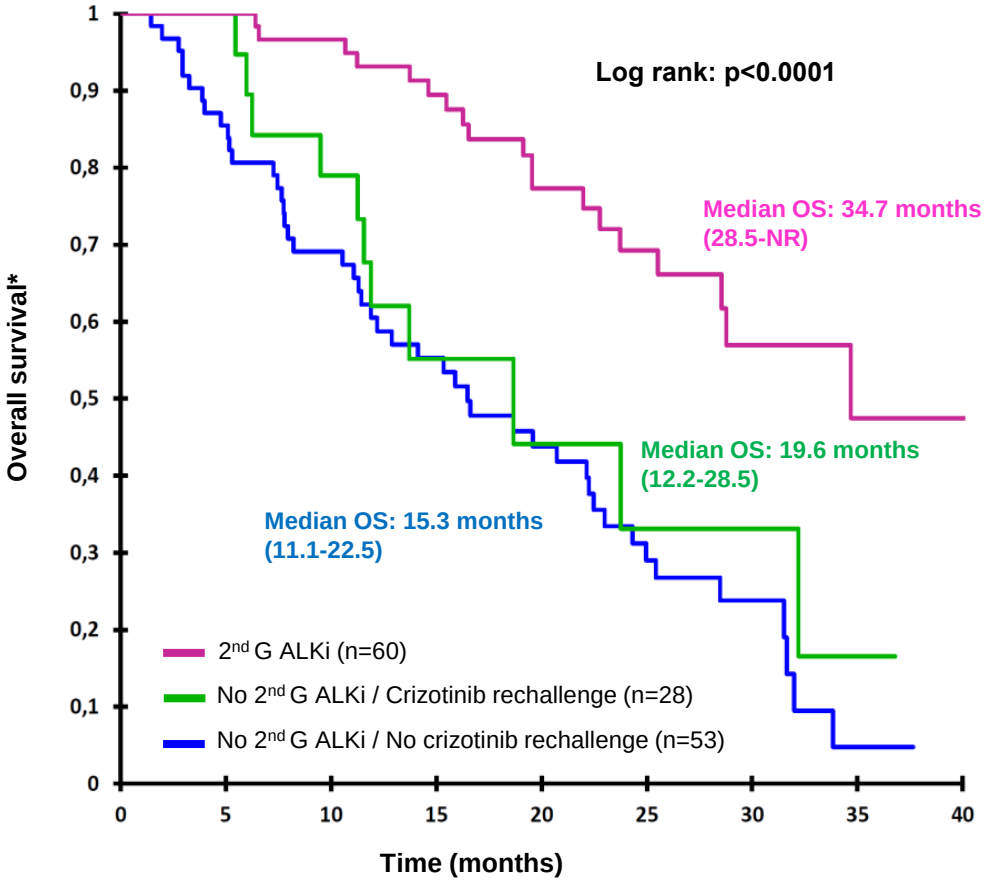
Solomon, NEJM 2014; Camidge, Nat Rev Clin Oncol 2014

Impact of the Current Strategy on ALK+ Patients OS

OS for patients treated with sequential crizotinib and ceritinib



Impact of 2nd generation ALK inhibitor on patients outcome after resistance to crizotinib



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Gainor, CCR 2015; Duruisseaux M, WCLC 2015

How to Improve the Current Strategy?

- How to optimize the selection of second- and subsequent treatment lines if crizotinib is used in frontline setting?
- Should crizotinib remain the first-line treatment or should we use next-generation, more potent ALK inhibitors in frontline treatment?
- Which role for cytotoxic chemotherapy in ALK+ patients?
- Is there a room for treatment combinations?

Many Factors Have to Be Taken into Account to Define the Best Sequence

- Comparative activity of next-generation ALK inhibitors
  - For ALK TKI naïve patients and in post-crizotinib setting
  - According to resistance mechanisms (resistance mutations)
  - According to ALK fusion variants
  - In central nervous system
  - Role of 3rd generation ALK inhibitors (lorlatinib …)
- Role of other treatments beside ALK TKIs
  - Role of pemetrexed-based chemotherapy and maintenance pemetrexed
  - HSP90 inhibitors
  - Treatment of resistance consecutive to bypass activation
  - Room for brain radiotherapy
- Brain metastases present at baseline or during the disease course

How to optimize the selection of second- and subsequent treatment lines if crizotinib is used in frontline setting?

ALK Inhibitors after Crizotinib Failure
Systemic Efficacy and Tolerance

	Alectinib NP28673 (n=138)*	Alectinib NP28761 (n=87)*	Brigatinib (n=71)*	Ceritinib ASCEND-1 (prior ALKi) (n=163)**	Ceritinib ASCEND-2* (n=140)**
Population	n=122	n=69	n=70	n=163	n=140
ORR, %	**50**	**51**	**71**	**56**	**39**
DCR, %	**79**	**80**	**87**	**74**	**77**
mDoR, mos	**11.2**	**13.5**	**9.3**	**8.3**	**9.7**
mPFS, mos	**8.9**	**8.1**	**13.4**	**6.9**	**5.7**
Toxicity issues	**Very few**		**Dyspnea**	**GI (QoL)**	

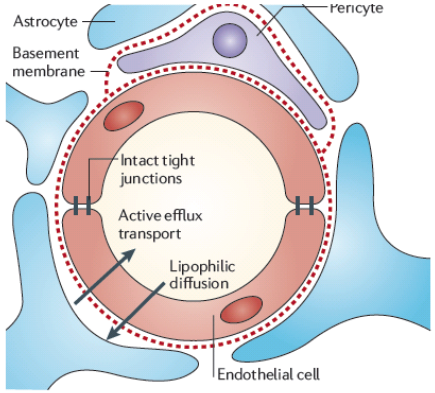
ORR: objective response rate; DCR: disease control rate; mDoR: median duration of response; mPFS: median progression-free survival

*By IRC; **By investigator

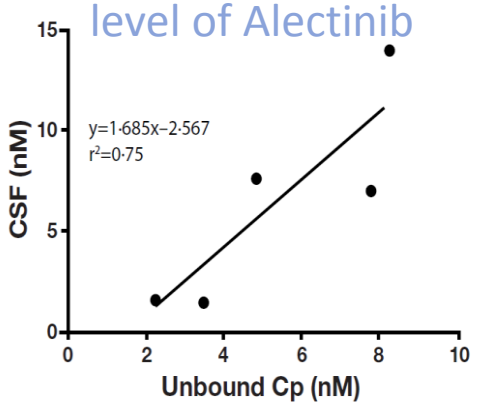
Ou, JCO 2016; Shaw, Lancet Oncol 2016; Camidge, ASCO 2015; Kim, Lancet Oncol 2016; Mok, ASCO 2015

CNS Metastases are a Difficult Problem in ALK+ Patients

- Increasing proportion of brain mets as patients fail increasing line of treatment
  - Cumulative incidence: 23.8, 45.5, and 58.4 % at 1, 2 and 3 yrs/diagnosis
- Control of CNS disease becomes crucial with the improvement of systemic disease control
- Importance of local treatments (WBRT, stereotactic RT, surgery)
  - Late toxicity of WBRT is of concern
- Variable CNS penetration of ALK TKIs
- Assessing ALKi in brain mets depends on several parameters
  - Symptomatic *vs* asymptomatic brain mets
  - Untreated lesions *vs* pretreated with previous WBRT
  - Crizotinib pretreated *vs* crizotinib naïve brain mets
  - Measurable lesions *vs* non-measurable lesions



Plasma/CSF level of Alectinib



ALK Inhibitors After Crizotinib Failure
CNS activity

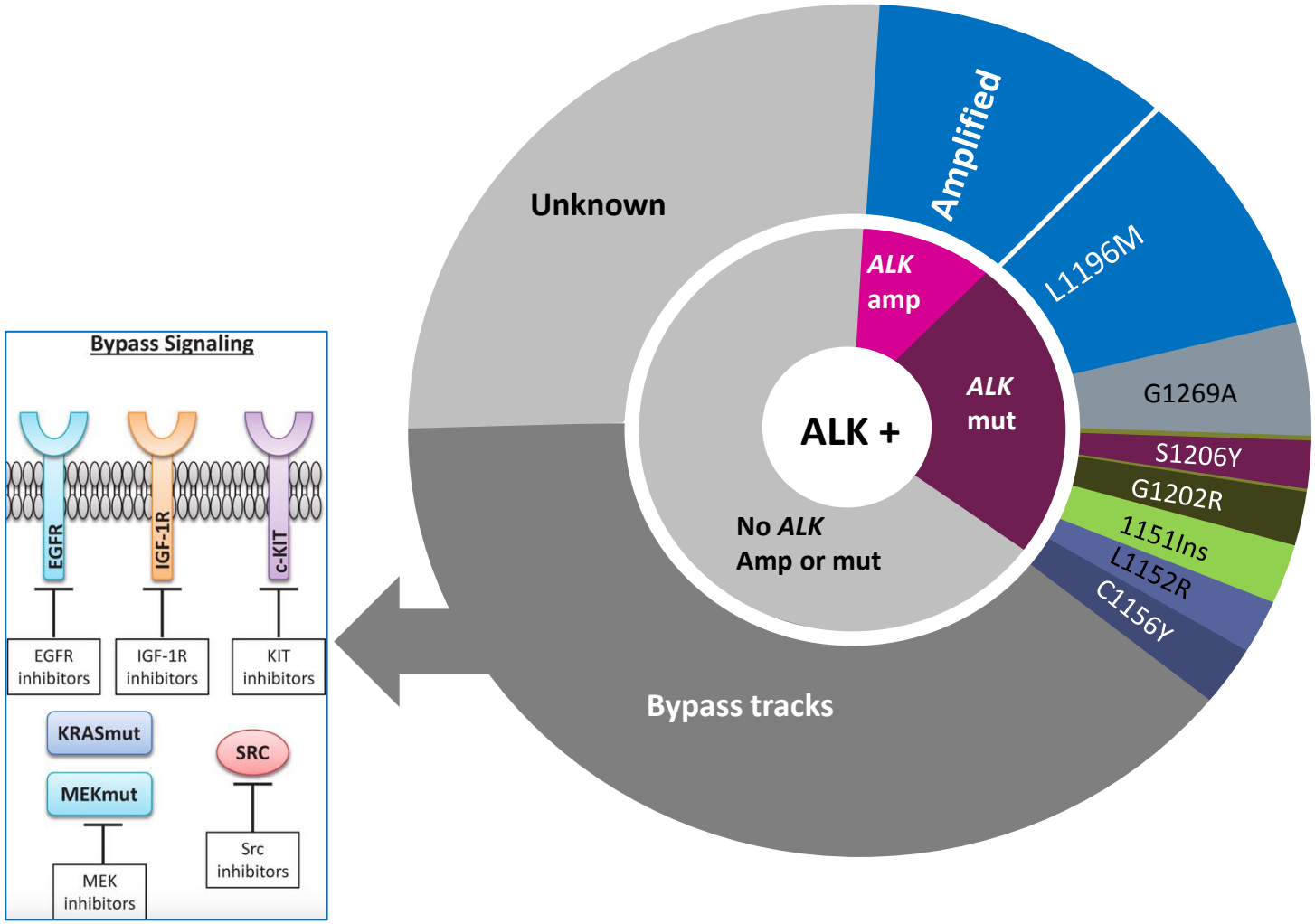
	Alectinib		Brigatinib*		Ceritinib		
	Measurable (n=60)	Measurable and non-measurable (n=138)	Measurable (n=15)	Non-measurable (n=33)	ASCEND-2 Measurable (n=20)	ASCEND-1 Measurable and non-measurable (n=75)	ASCEND-1 Measurable (n=28)
CNS ORR, %	64	43	53	33	45	19	36
CR, %	22	27	7	33	10	5	0
CNS DCR, %	80	86	87	88	80	65	61
CNS mDoR, months	10.8	11.1	18.9**		–	6.9	11.1

*8% patients with CNS mets at baseline were crizotinib-naïve; **n=16

ORR: objective response rate; CR: complete response; DCR: disease control rate; mDoR: median duration of response

Gadgeel, WCLC 2015; Camidge, ASCO 2015; Kim, Lancet Oncol 2016; Mok, ASCO 2015

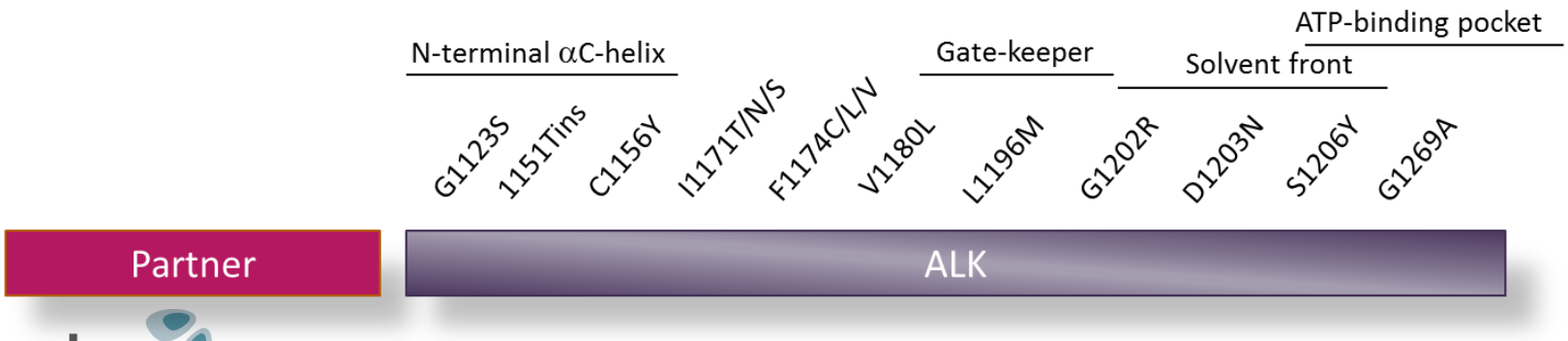
Acquired Resistance to Crizotinib



Camidge, Nat Rev Clin Oncol 2014 ; Shaw, ECC 2015; Doebele, JTO 2014

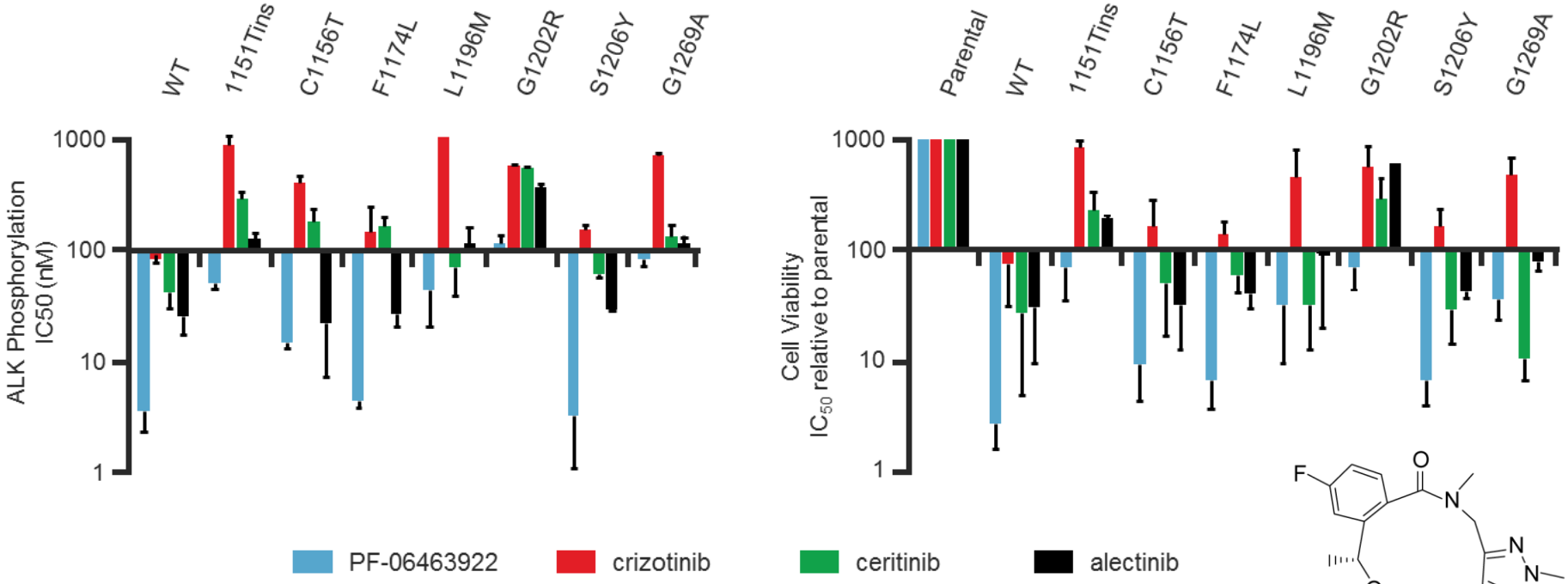
Which Next-Generation ALKi to Select for Post-Crizotinib Systemic Progression?

	L1196M	G1269A/S	C1156Y	R1275Q	S1206Y	I1171T	V1180L	F1174V/L	D1203N	G1202R	Other kinases
Crizotinib	-	-	-	-	-	+	+	-	-	-	ROS1, MET
Ceritinib	+	+	-	+	+	+	+	-	-	-	ROS1, IGF1R
Alectinib	+	+	+	+	+	-	-	+	+	-	RET
Brigatinib	+	+				+	+	+		+	EGFR



Shaw et al. ASCO 2013; Sakamoto et al. Cancer Cell 2011; Kodama et al. Mol Cancer Ther 2014; Katayama et al. Sci transl Med 2012; Doebele et al. Clin Cancer Res 2012; Friboulet et al. Cancer Discov 2014; Ou et al. J Thorac Oncol 2014; Katayama et al. Clin Cancer Res 2014

PF-06463922 Appears as the Most Potent Inhibitor Against All Clinically-Relevant ALK-Resistant Mutants

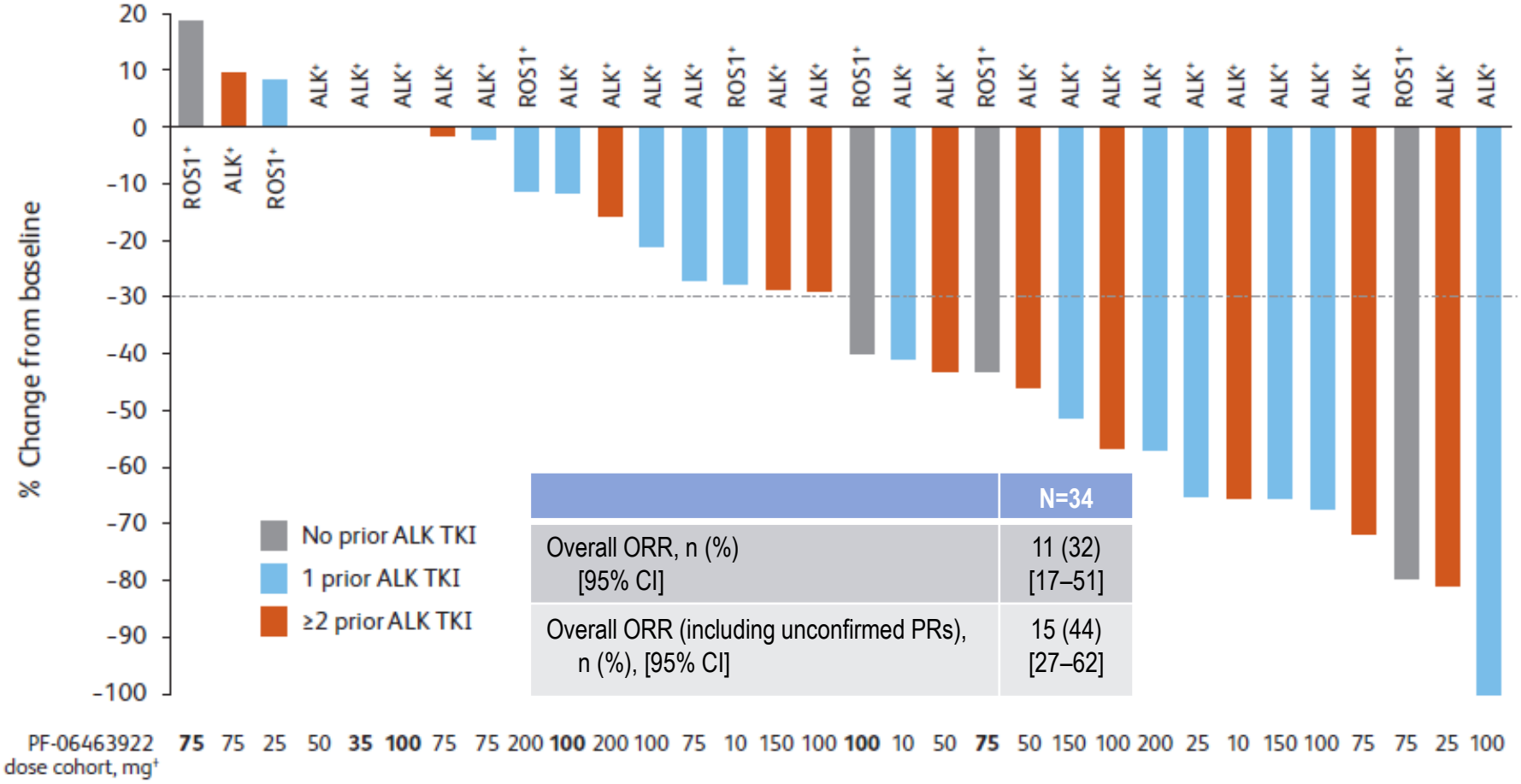


(C) IC_{50} values of PF-06463922, crizotinib, ceritinib, and alectinib on ALK phosphorylation (left) and cell viability (right) across different Ba/F3 cell lines expressing wild-type or mutated EML4-ALK relative to parental interleukin-3-dependent Ba/F3 cells

PF-06463922

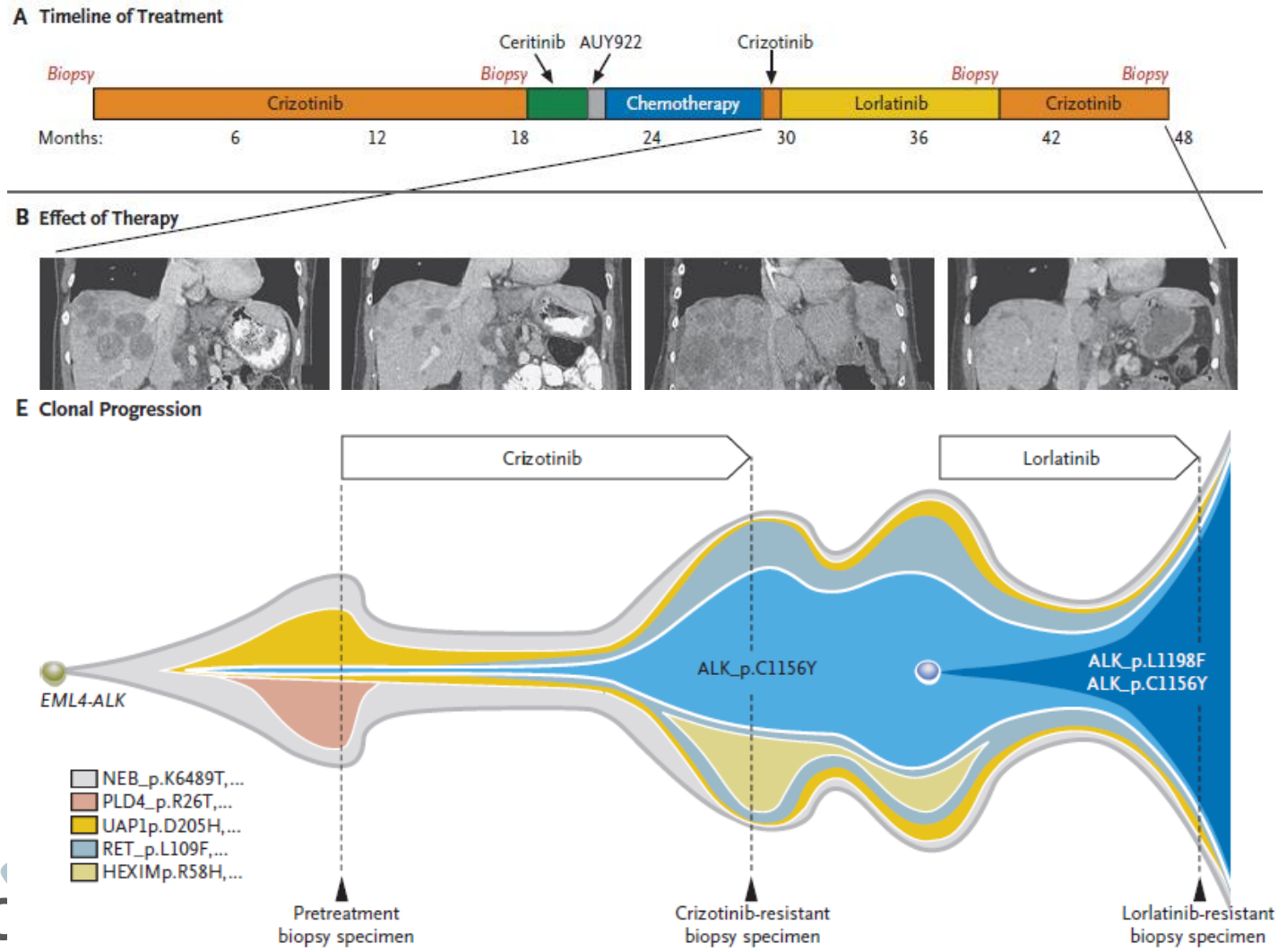
Zou HY et al. Cancer Cell 2015;28:70–81

Phase 1 Study of PF-06463922 in Patients with Advanced NSCLC with Specific Molecular Alterations



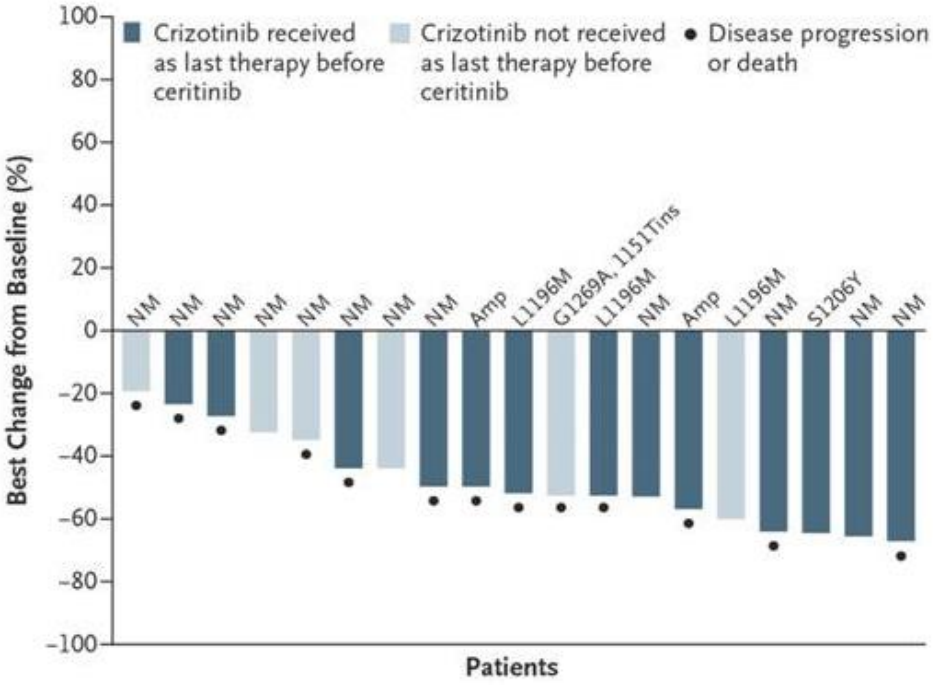
Bauer TM et al. WCLC 2015

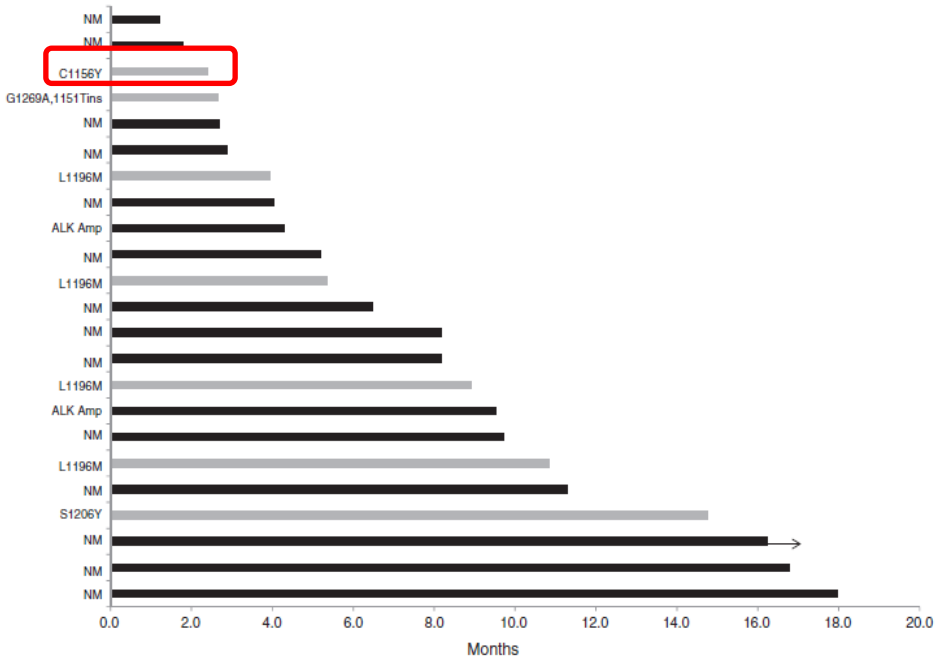
Importance of Repeated Biopsy on Treatment Sequencing in ALK+ Patients



Shaw, NEJM 2015

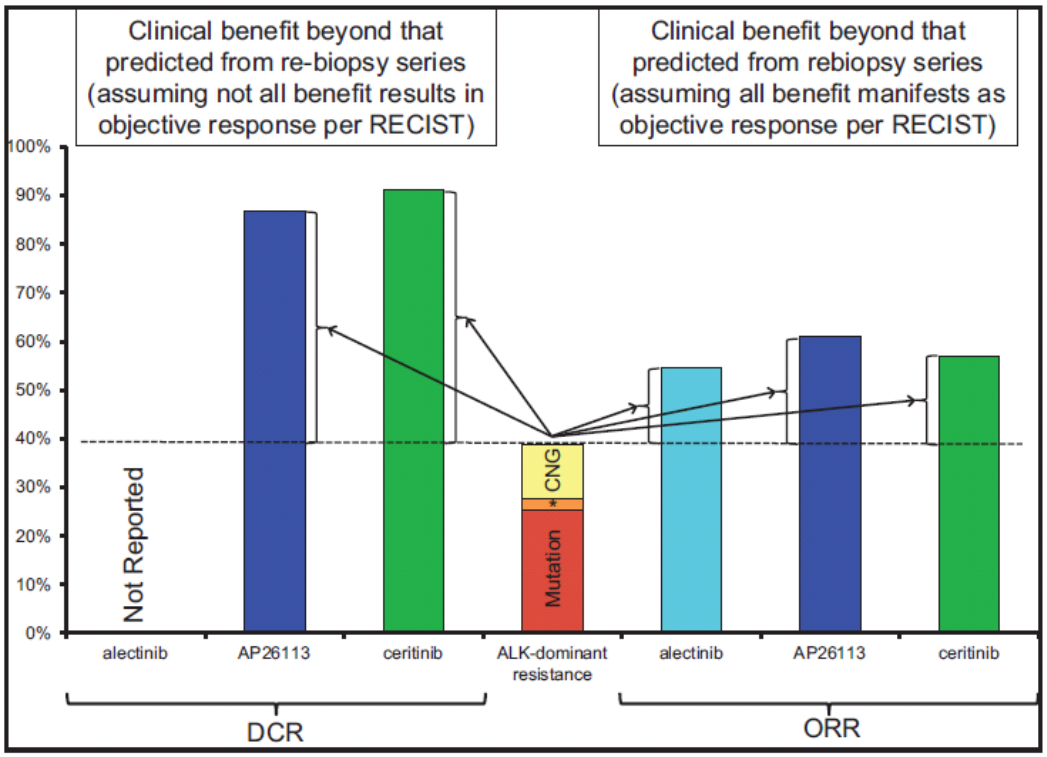
Activity of Ceritinib Seems Partially Independent from Resistance Mutation Subtype





Shaw, NEJM 2014; Gainor, CCR 2015

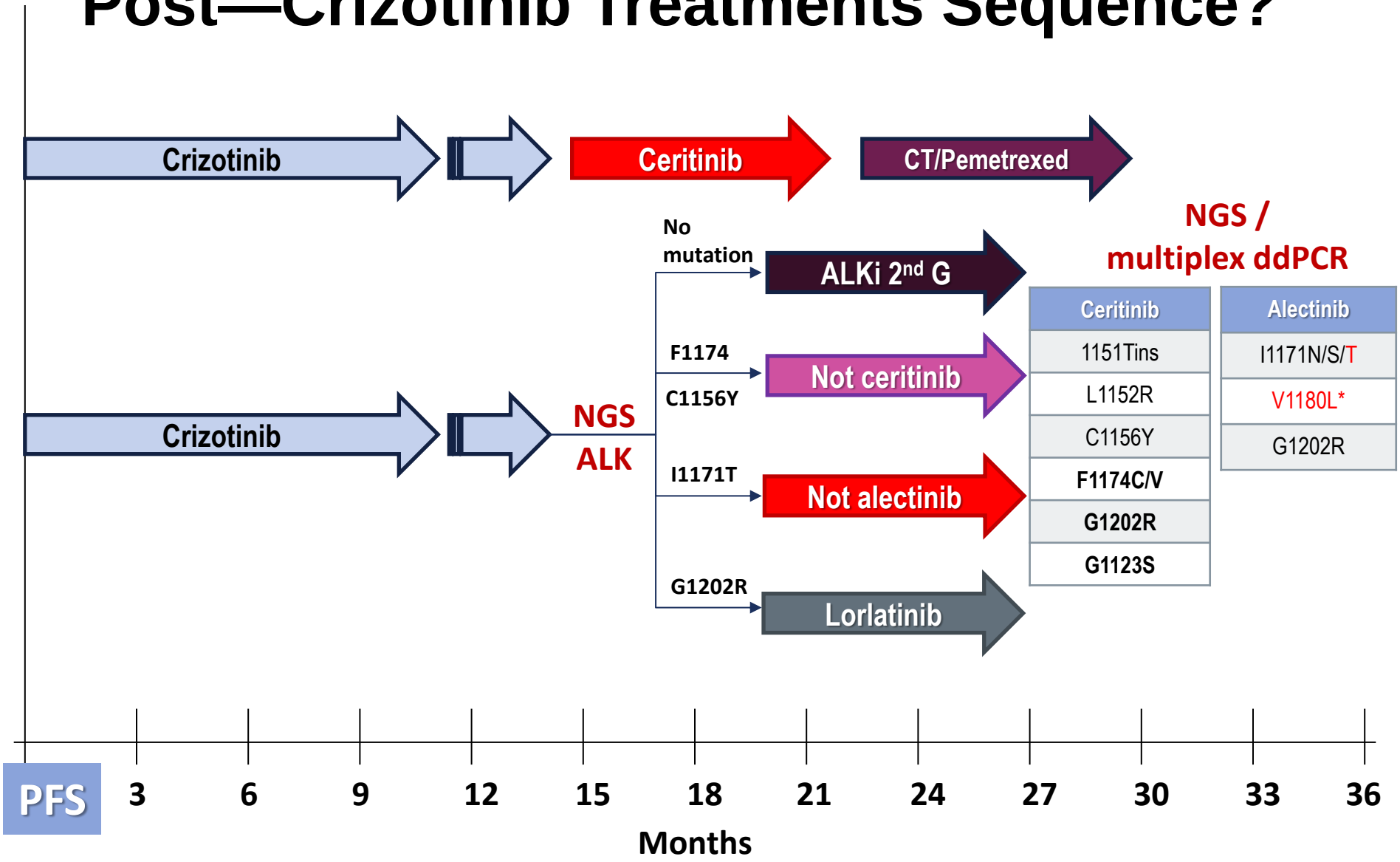
Clinical Benefit of Next-Generation ALKi is Beyond That Expected from Re-biopsy Series



- Some crizotinib failures due to PK causes?
- Underestimation of resistance mutation frequency?
- Tumor heterogeneity?
- Activity on some bypass (IGF-1R)?
- Chemotherapy between crizotinib and NG ALKi?

Doebele, JTO 2014

How to Optimize Post—Crizotinib Treatments Sequence?

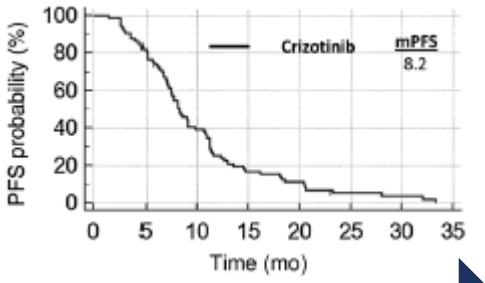


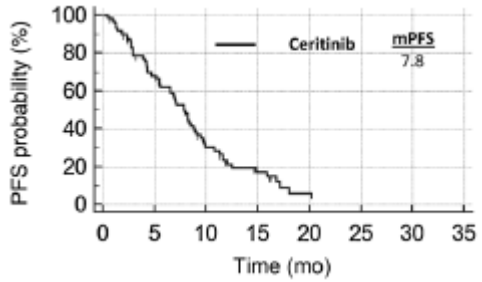
Should crizotinib remain the first-line treatment or should we use next-generation ALK inhibitors in frontline treatment?

Two Different Strategies

- "Interventional" approach
  - Start with crizotinib and adaptation of subsequent treatments to mechanisms of resistance
  - Next-generation ALKi are able to overcome resistance to crizotinib in most cases
  - **Hypothesis: PFS $_{\text{crizo /1}^{st}\text{ line}}$ + PFS $_{\text{ALKi 2}^{nd}\text{ G /2}^{nd}\text{ line}}$ > PFS $_{\text{ALKi 2}^{nd}\text{ G /1}^{st}\text{ line}}$**
  - Risk: rapid emergence of brain metastases, shorter disease control duration
- "Preventive" approach
  - To obtain deeper and longer responses with NG ALKi more potent than crizotinib
  - To prevent or delay emergence of resistances
  - More penetrable-brain blood barrier ALKi would delay or prevent CNS metastases
  - **Hypothesis: PFS $_{\text{ALKi 2}^{nd}\text{ G /1}^{st}\text{ line}}$ > PFS $_{\text{crizo /1}^{st}\text{ line}}$ + PFS $_{\text{ALKi 2}^{nd}\text{ G /2}^{nd}\text{ line}}$**
  - Risk: strategy leading to highly resistant disease with cross-resistance to other ALKi

"Interventional" *vs* "Preventive" Strategy





Median PFS
crizotinib + ceritinib:
17.4 months

Crizotinib → **PD** → **Next-G ALKi**

11 months

17-18 months

Next-G ALKi →

17-18 months > 24 months

elcc

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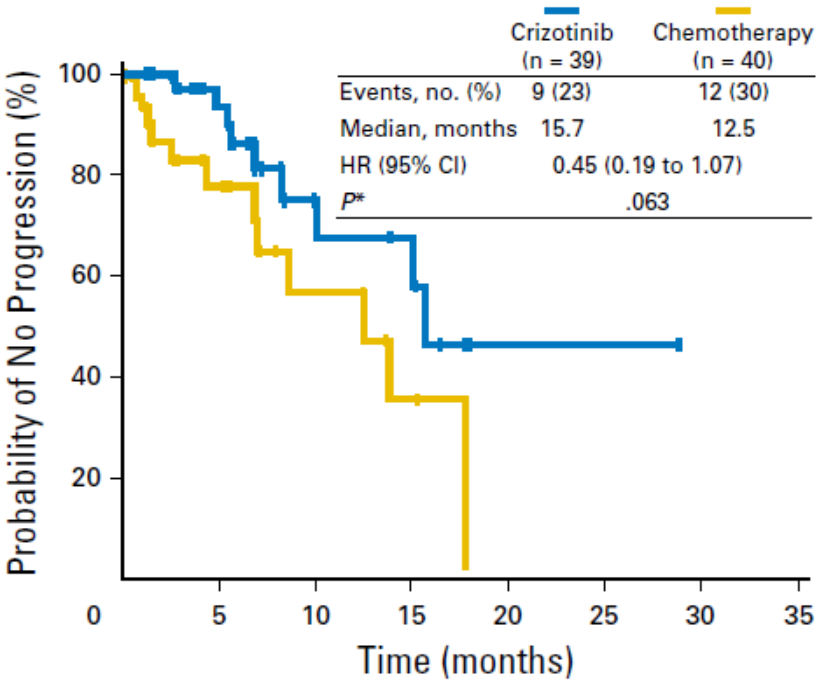
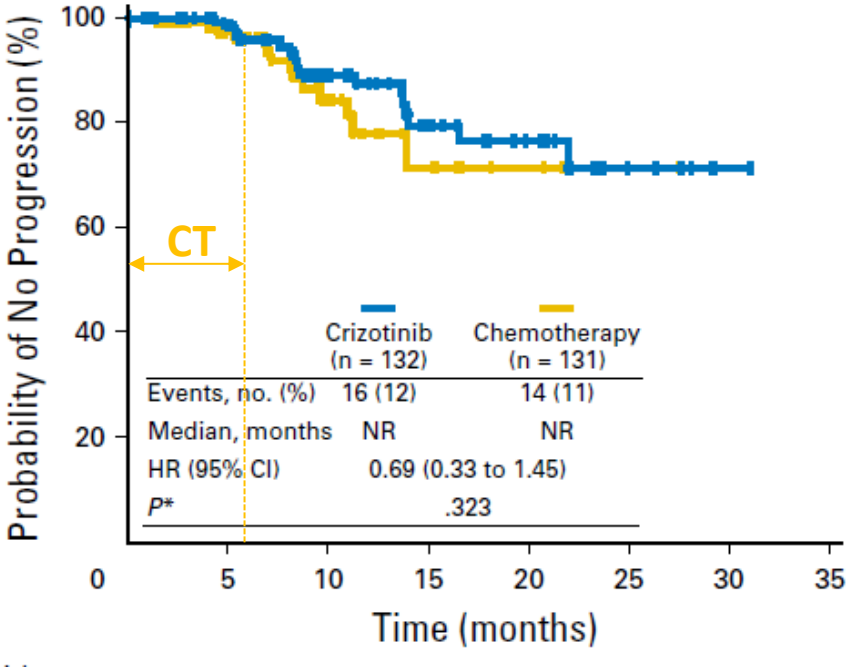
Gainor, CCR 2014; adapted from Shaw, ECC 2015

Intracranial TTP[a] by IRR in Patients with/without Brain Metastases at Baseline (Profile 1014)

Pretreated brain metastases present



Brain metastases absent



NR, not yet reached

[a]Time from randomization to first documentation of intracranial tumor progression

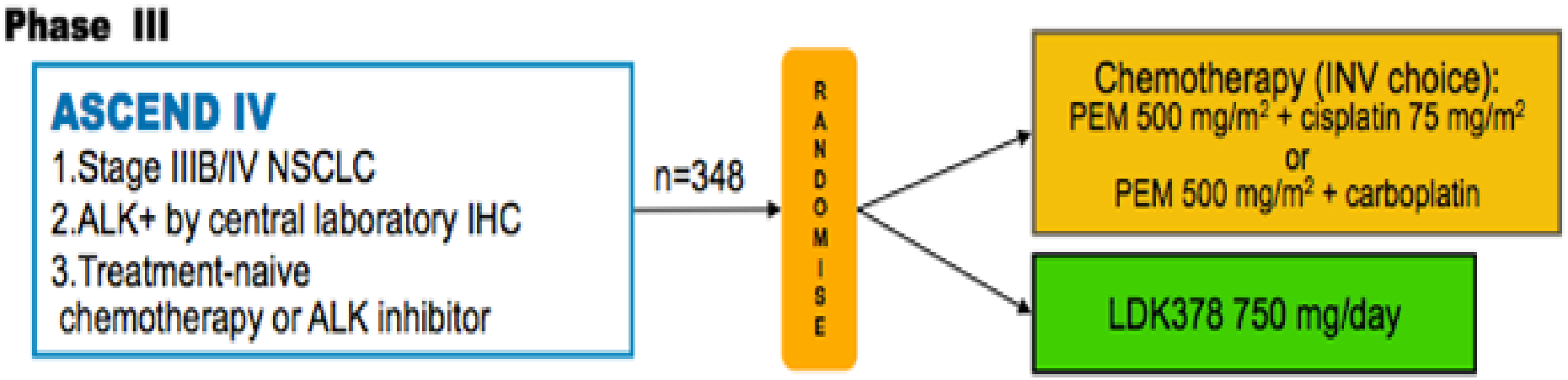
[b]2-sided log-rank test

ALK TKIs Activity in ALK+, Crizotinib-Naïve Patients

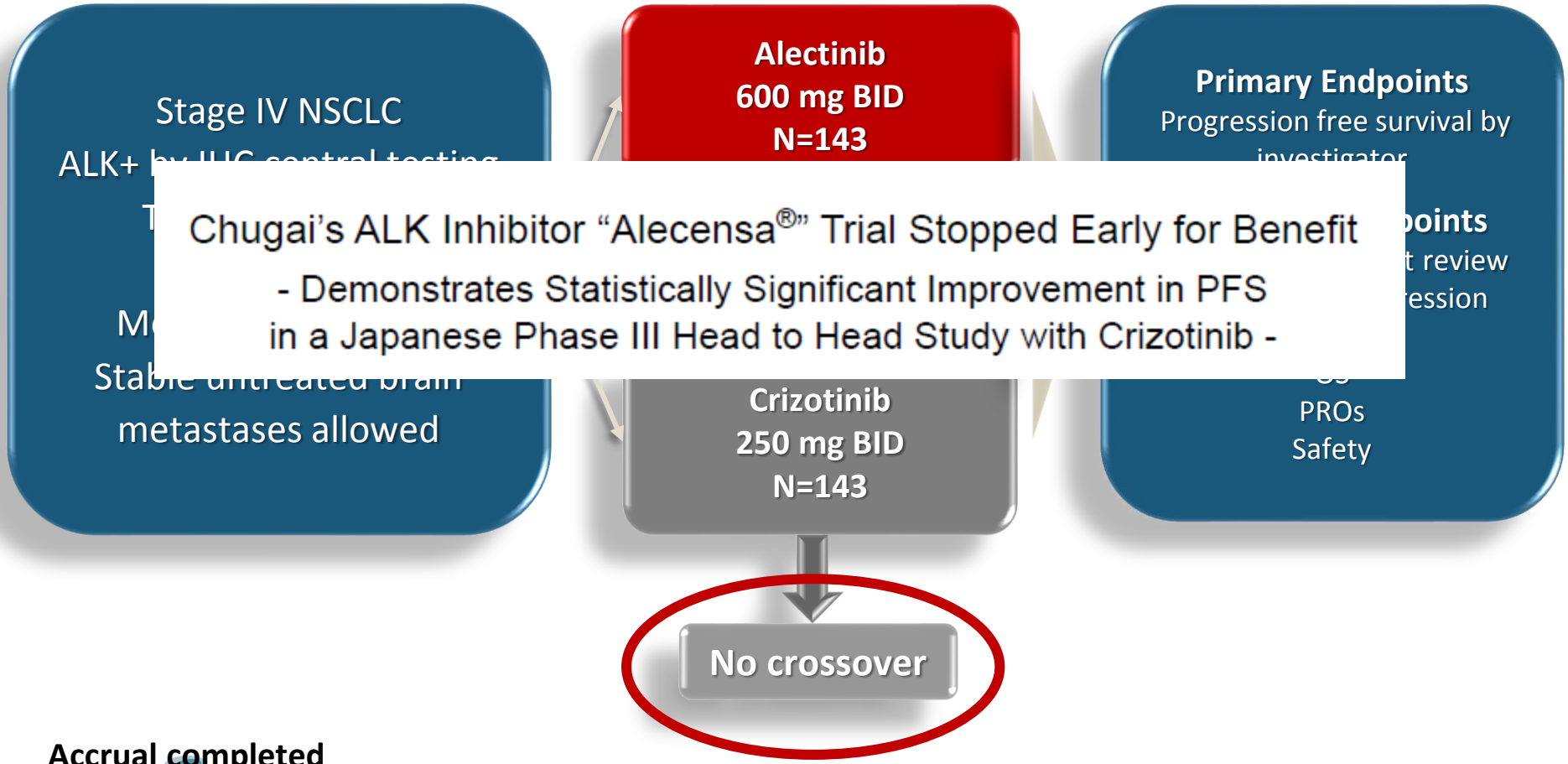
	Crizotinib Profile 1014	Crizotinib Profile 1007	Ceritinib Ascend 1	Ceritinib Ascend 2	Alectinib AF-001 JP	Brigatinib
Phase	III	III	I	II	I/II	I
Countries	Global	Global	Global	Global	Japan	USA /Spain
ALK fusion diagnosis	FISH (central)	FISH (central)	FISH (local)	FISH (central)	IHC + FISH (central)	FISH (local)
Treatment line	1	≥1	≥1	≥1	≥1	≥1
Patients	172	173	83	124	46	8
ORR	**74%**	**65%**	**72%**	**64%**	**94%**	**100%**
Median PFS, mos	**10.9**	**7.7**	**18.4**	**11.1**	**27.7**	**Not reached**

Solomon, NEJM 2014; Shaw, NEJM 2013; Ou, JCO 2016; Seto, Lancet Oncol 2013; Camidge, ASCO 2015; Kim, Lancet Oncol 2016; Mok, ASCO 2015

ASCEND IV
Ceritinib First-Line Phase III Trial



ALEX Alectinib First-Line Phase III Trial

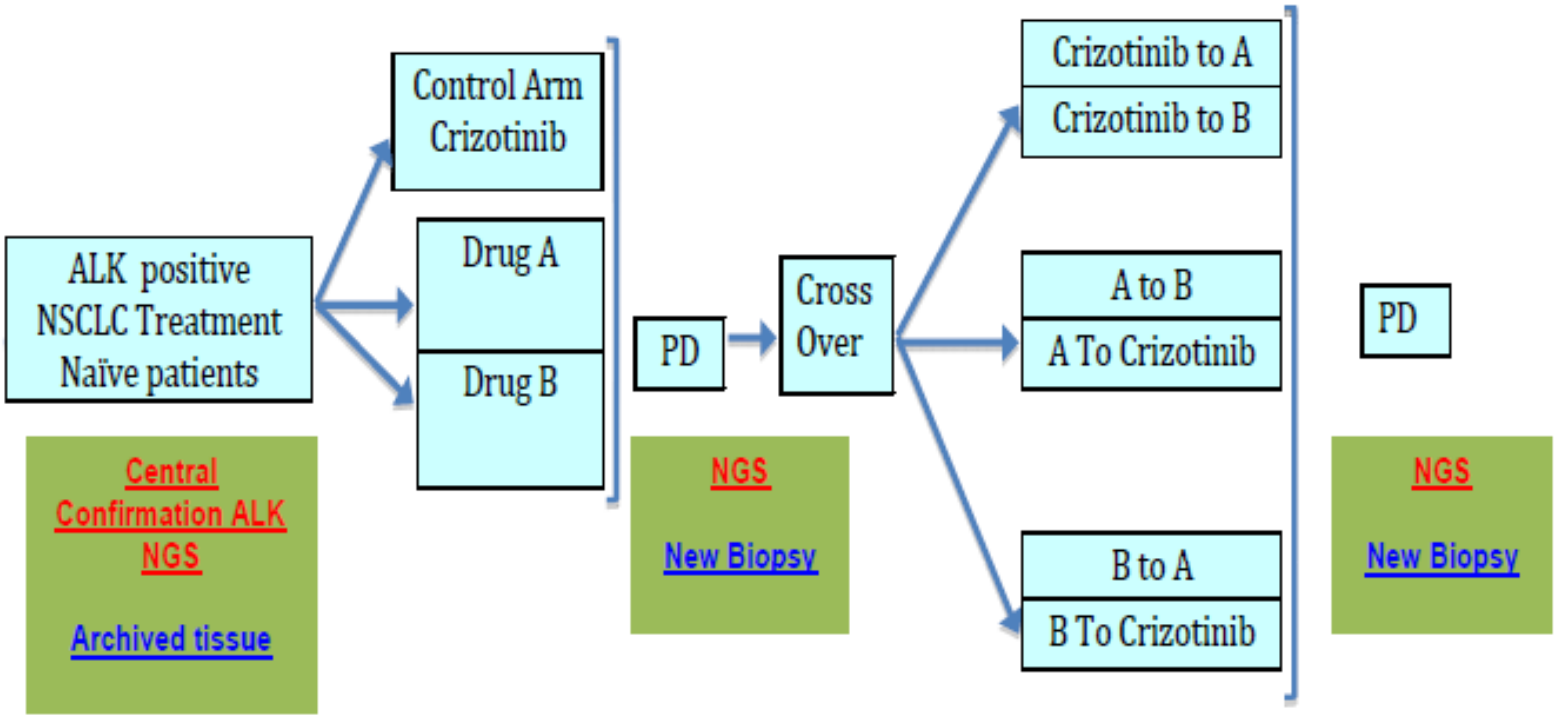


Chugai's ALK Inhibitor "Alecensa®" Trial Stopped Early for Benefit

- Demonstrates Statistically Significant Improvement in PFS in a Japanese Phase III Head to Head Study with Crizotinib -

Accrual completed

ALK Master Protocol in Advanced Lung Adenocarcinoma



PIs: Alice Shaw, Shakun Malik

Ariad- AP26113 (brigatinib)
Ignyta- RXDX-101
Novartis - Ceritinib
Pfizer- PF-06463922 (lorlatinib)
Roche/Chugai - Alectinib
Tesaro - TSR-011
Xcovery-X-396

Which Room for Cytotoxic Chemotherapy? Pemetrexed Activity in ALK+ NSCLC Patients

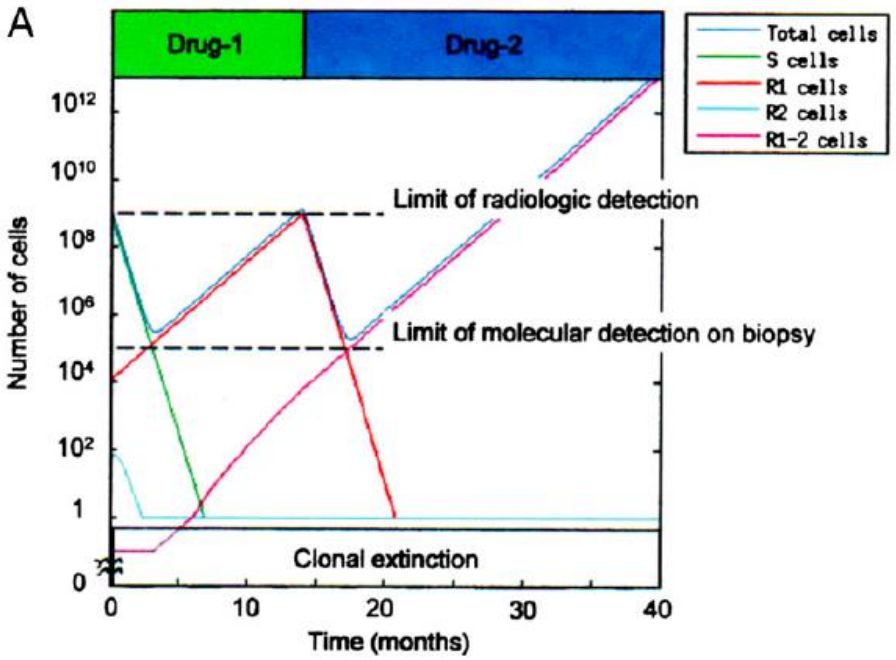
	Cisplatin-pemetrexed 1st line			Pemetrexed 2nd line		Docetaxel 2nd line	
Tumor	ALK+	EGFR +	Adc.	ALK+	Adc.	ALK+	Adc.
ORR	45%	23%	29%	29%	13%	7%	10%
Median PFS (months)	7.0	6.9	5.5	4.2	3.5	2.6	3.5

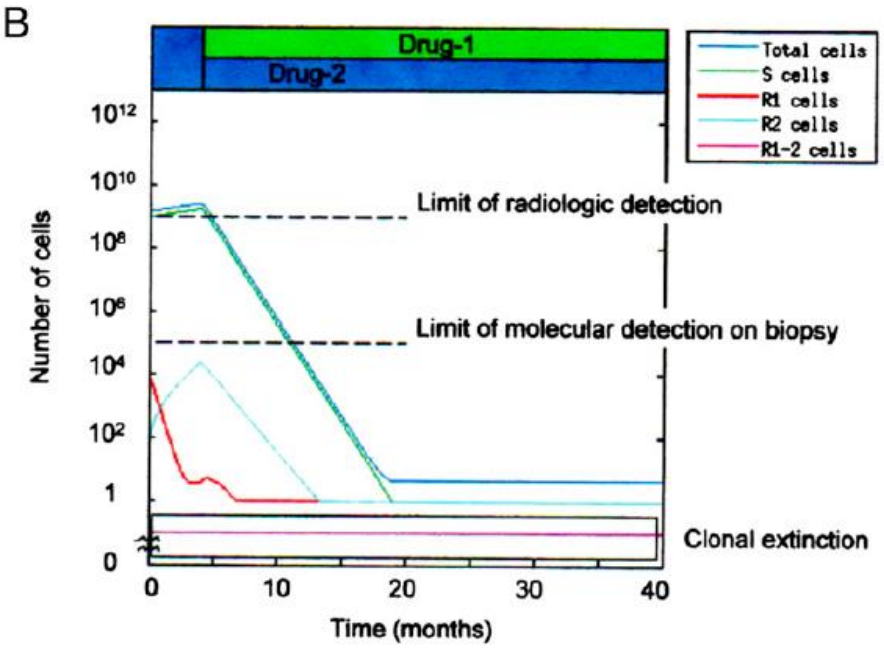
- All ALK+ patients will receive chemotherapy at one point of their disease course
- Platinum-pemetrexed combinations seem the most active regimen
  - Positioning of chemotherapy should be early enough to allow administration of platinum-based regimen
- Role of maintenance pemetrexed should be addressed by ASCEND IV phase III trial
- Role in case of two successive ALK TKI failures, multiple asymptomatic brain metastases, between two ALK TKIs treatments?

Solomon, NEJM 2014; Shaw, NEJM 2013; Sequist, JCO 2013; Hanna, JCO 2004

ALKi in Combination with Other Agents

- ALKi + pemetrexed-based chemotherapy
- ALKi + HSP90 inhibitors
  - Phase I crizotinib + ganetespib: RP2D C 250 mg BID, G 150 mg/m2 D1-8 q3 wks, ORR: 8/12 (67%)
- ALKi + TKI adressing bypass mechanisms of resistance
- ALKi + IOs





Riely G, ASCO 2015; Beckman R, PNAS 2012

Targeting ALK: Sequencing of Agents

- Current standard approach with crizotinib followed by 2nd generation ALKi provides an unprecedented survival duration for ALK+ NSCLC pts
- This "interventional" strategy is supported by some points
  - Crizotinib provides a median PFS of 10 months with a good safety profile
  - A majority of crizotinib-resistant pts respond to next-generation ALKi
  - Some next-generation ALKi resistances are sensitive to other ALK TKIs
  - Repeated biopsies and/or cfDNA can be useful to select the ALKi most likely to be active
- Issues of CNS involvement, CT positioning

Targeting ALK: Sequencing of Agents

- The "preventive" strategy remains to be validated yet
  - Importance to prevent or delay CNS metastases
  - ALEX phase III results should be available at the end of 2016
    - Alectinib might be used in first-line treatment
  - The answer might only be provided by trials like ALK Master Protocol (cross over)
  - Optimizing treatment sequences will anyway need a repeated knowledge of successive resistance mechanisms
    - Impact of cfDNA remains to be assessed in this setting

Acknowledgments

- **Alexis CORTOT, Lille University Hospital, France**