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Next Generation ALK Inhibitors and Mechanisms of Resistance to Therapy

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Disclosures

- *Compensated consulting for Boehringer Ingelheim, Jounce Therapeutics, and Kyowa Hakko Kirin Pharmaceuticals*

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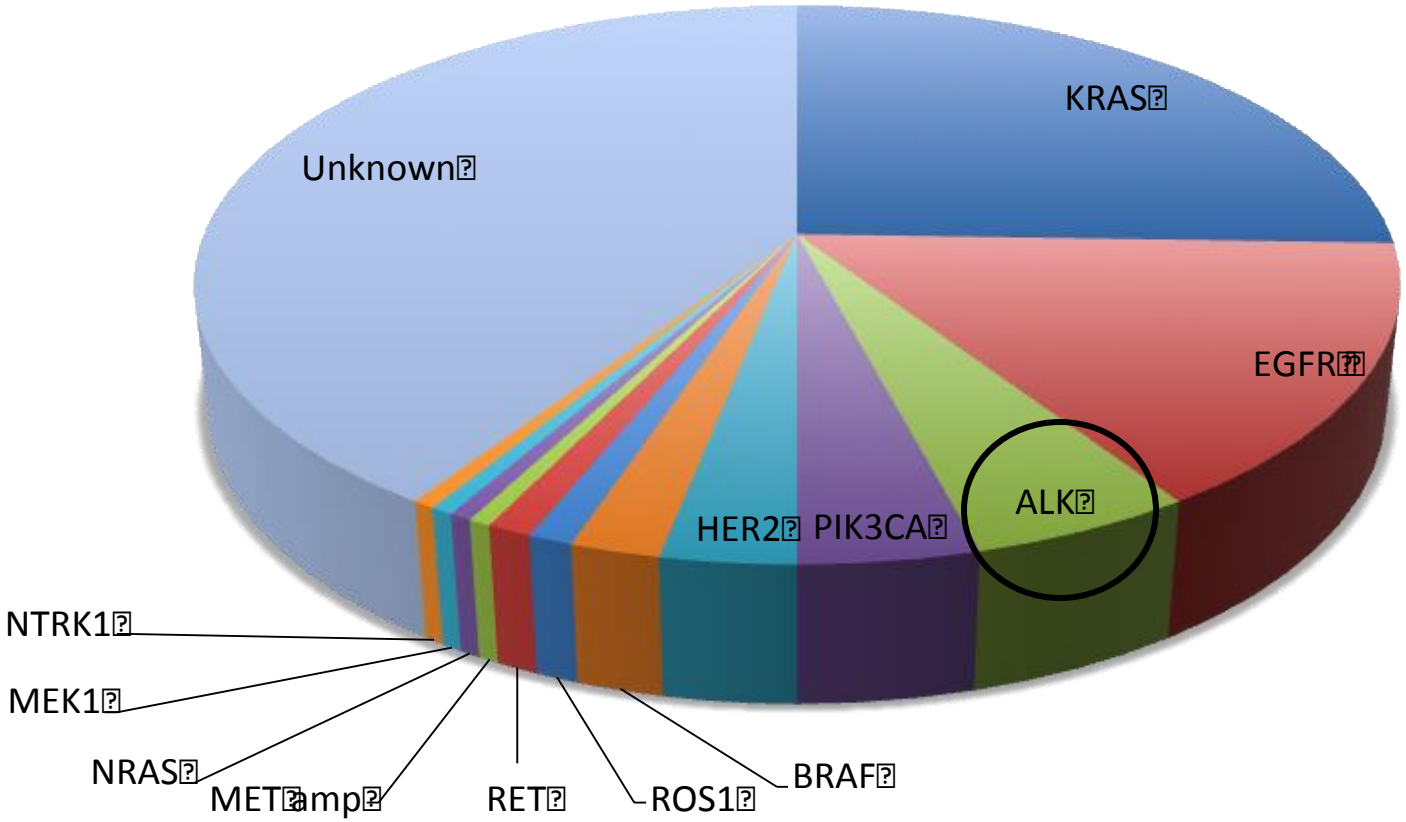
Distribution of Oncogenic Drivers in NSCLC



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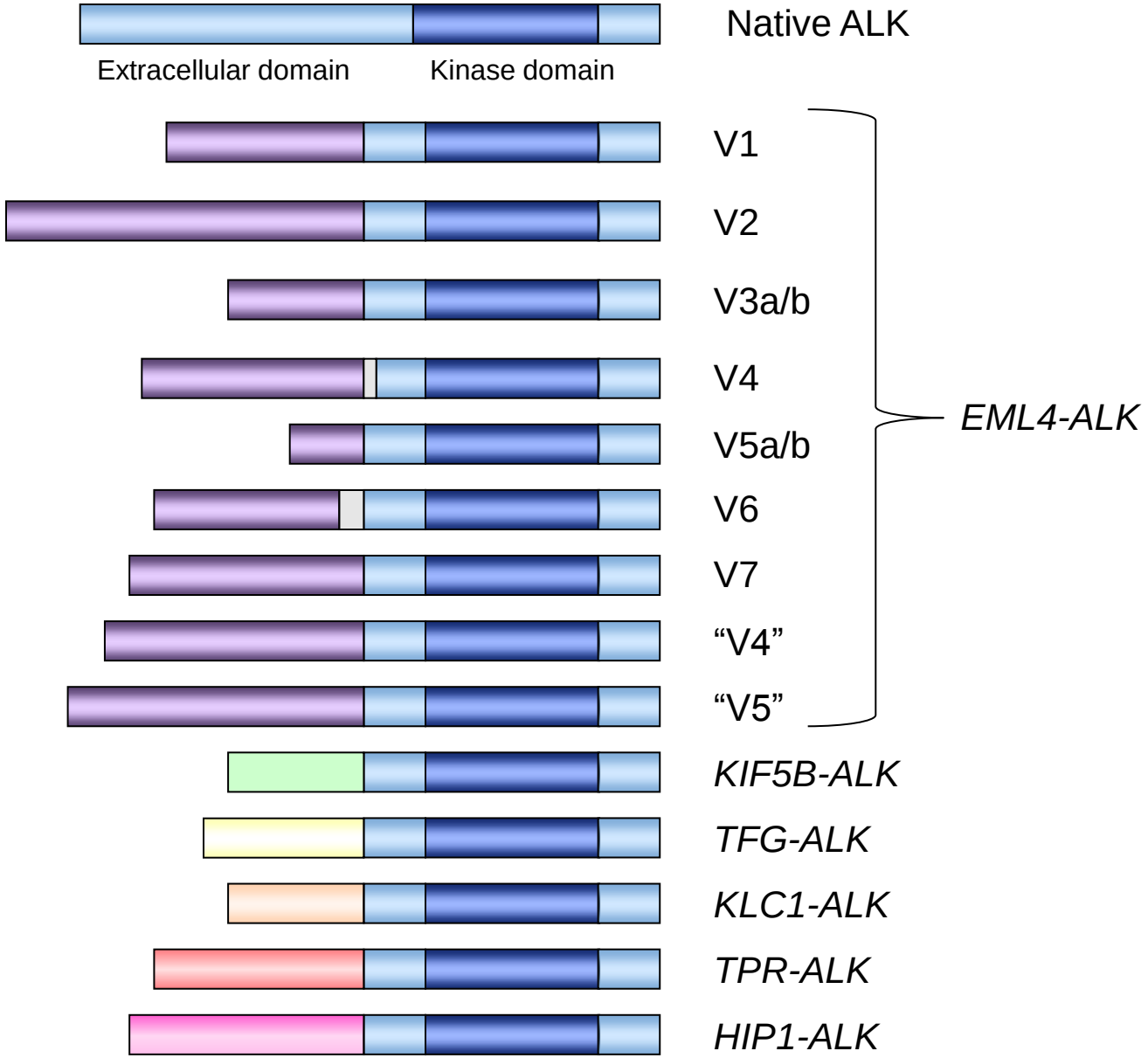
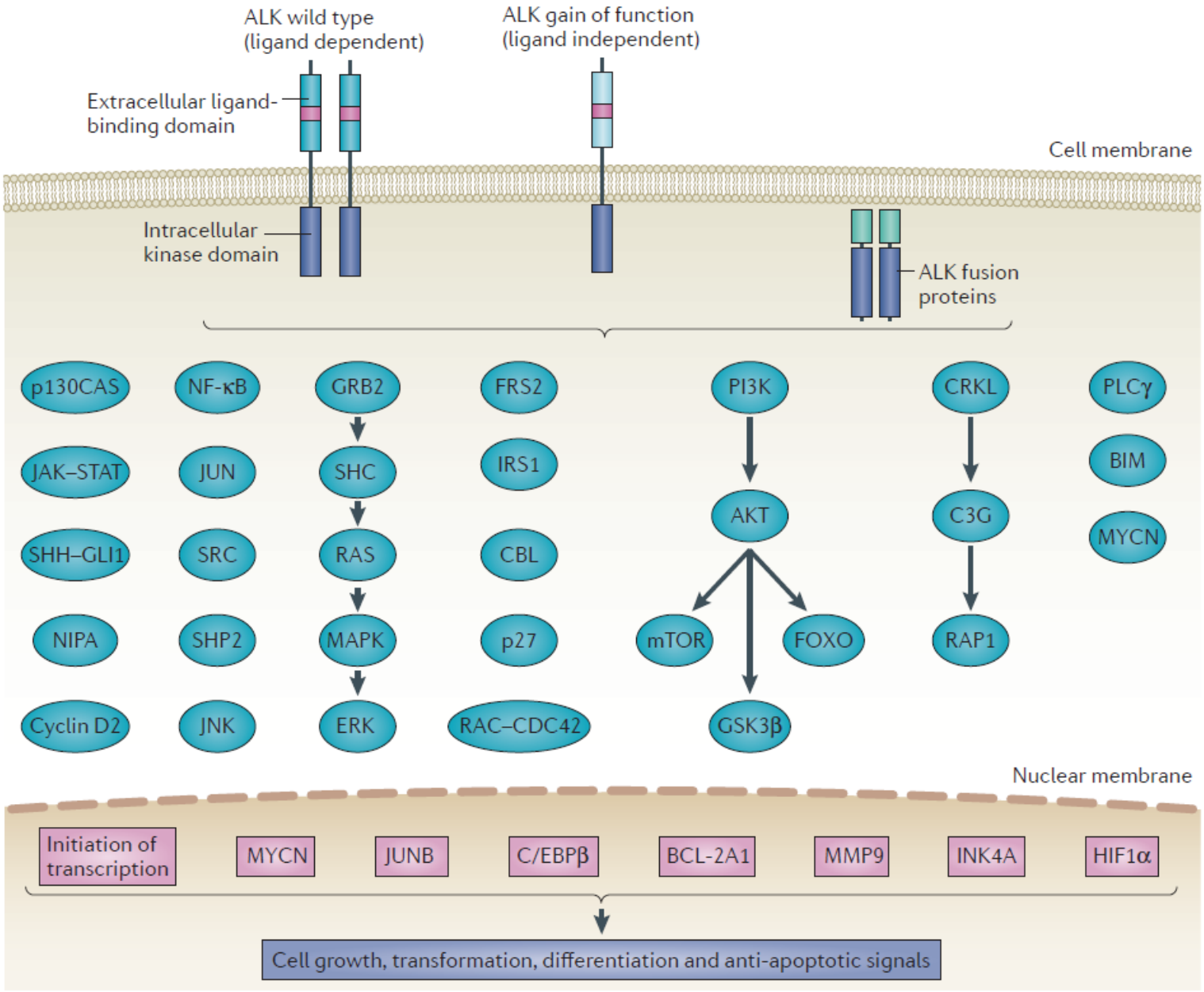
ALK Rearrangements in NSCLC

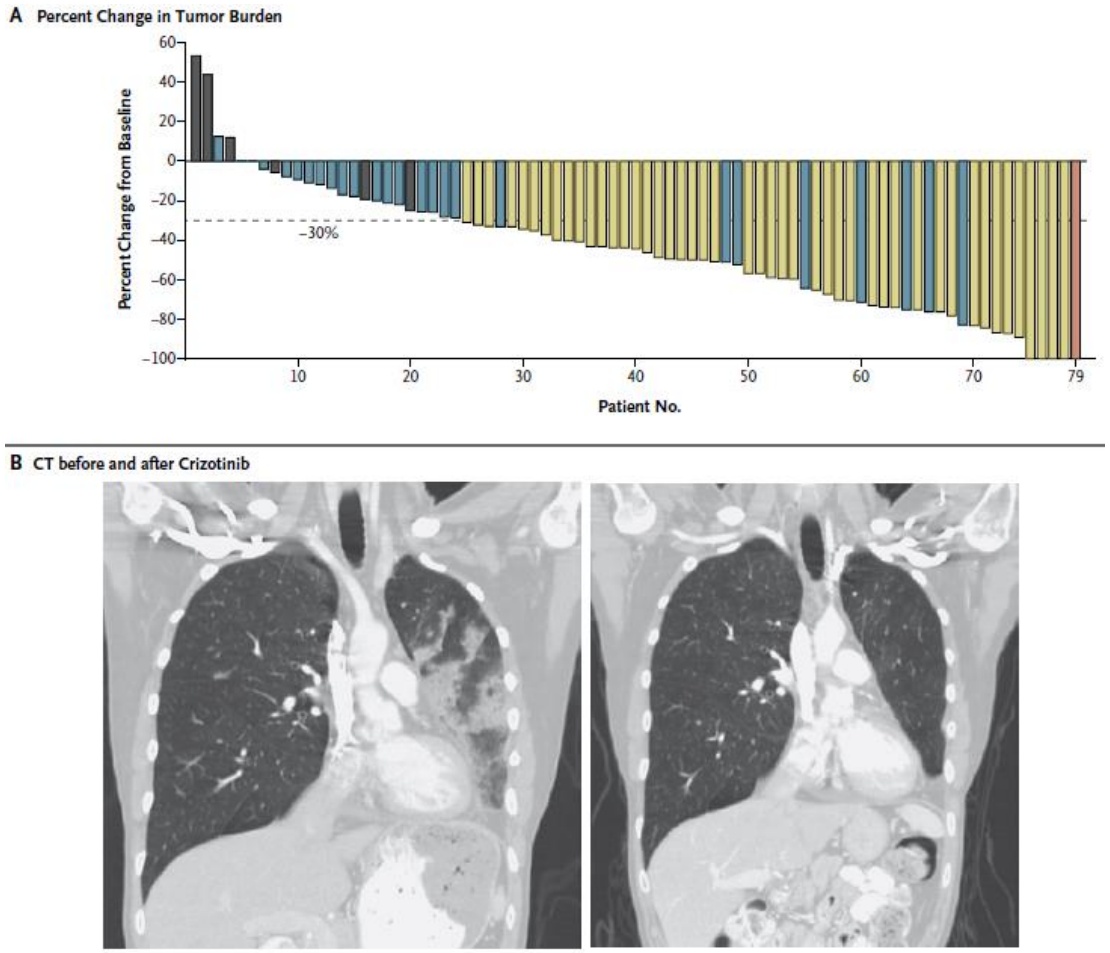


Shaw AT, Engelman JA, JCO 2013 (Adapted)



Hallberg B, Palmer RH. Nat Rev Cancer 2013

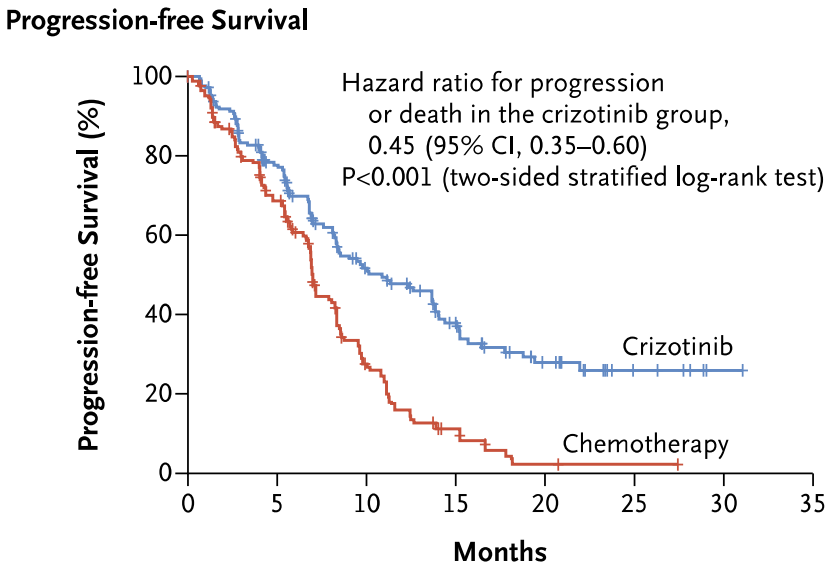
Crizotinib in ALK-Positive NSCLC



Kwak EL et al, NEJM 2010; Camidge DR et al. Lancet Oncol 2012; Shaw AT, J Clin Oncol 2009

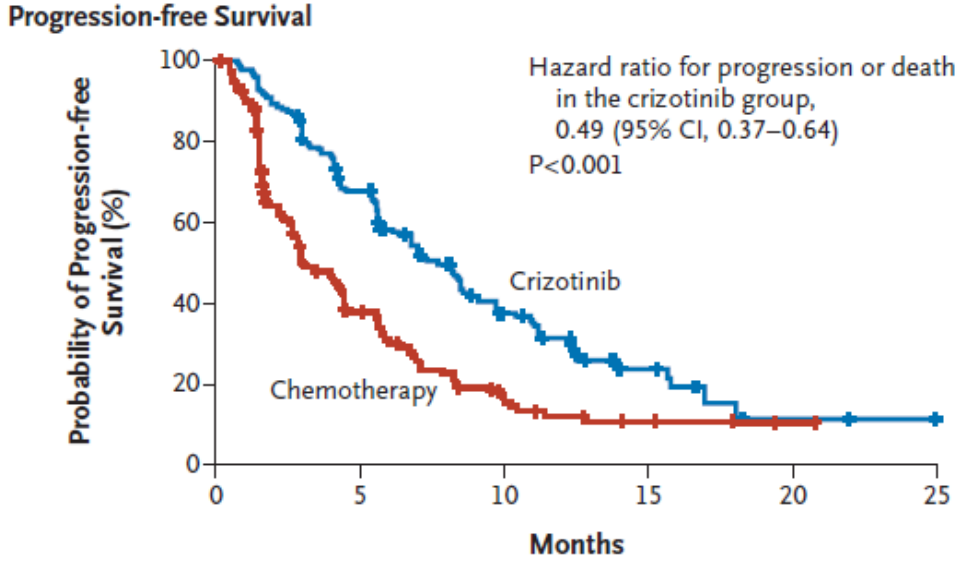
Crizotinib in ALK-Rearranged NSCLC

PROFILE 1014



No. at Risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

PROFILE 1007



No. at Risk						
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

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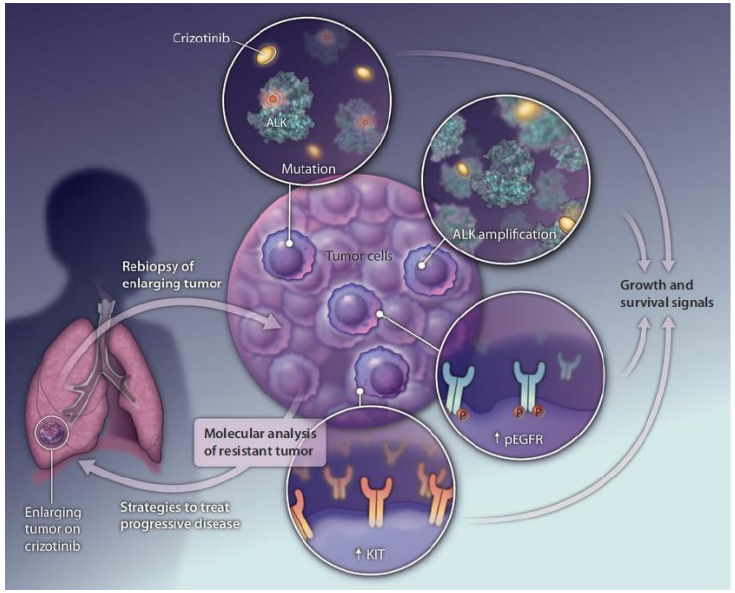
Solomon BJ, et al. NEJM 2014; Shaw AT, et al. NEJM 2013

Acquired Resistance to Crizotinib

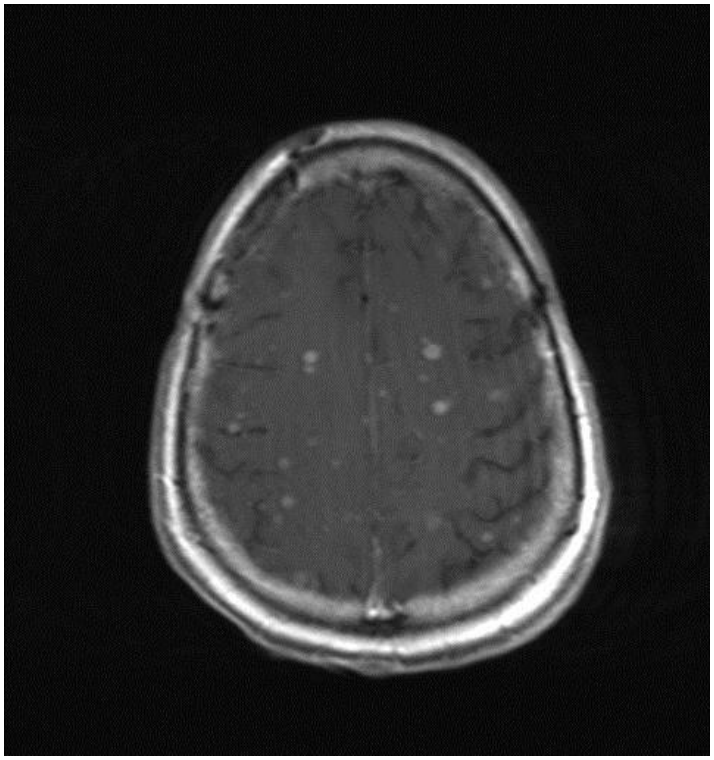
- Pharmacokinetic Failure
- *ALK* Resistance Mutations
- *ALK* Fusion Gene Amplification
- Bypass Signaling Pathways



Lovly CM, Pao W. Sci Tranl Med 2012

CNS Metastases in ALK+ NSCLC

- 26% of ALK+ patients have CNS metastases at initial diagnosis.
- CNS is among the most common sites of relapse on crizotinib.
- Among crizotinib-resistant patients entering trials of next-generation ALK inhibitors, rates of CNS metastases approach 60%.



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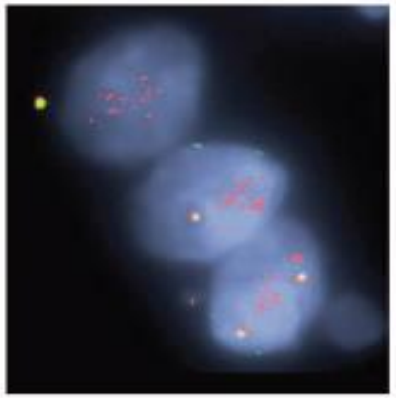
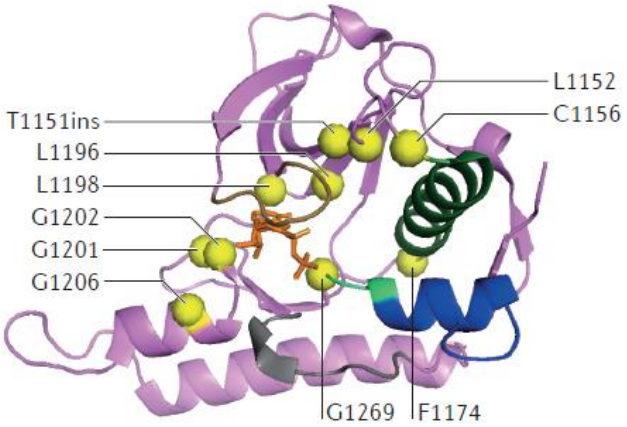
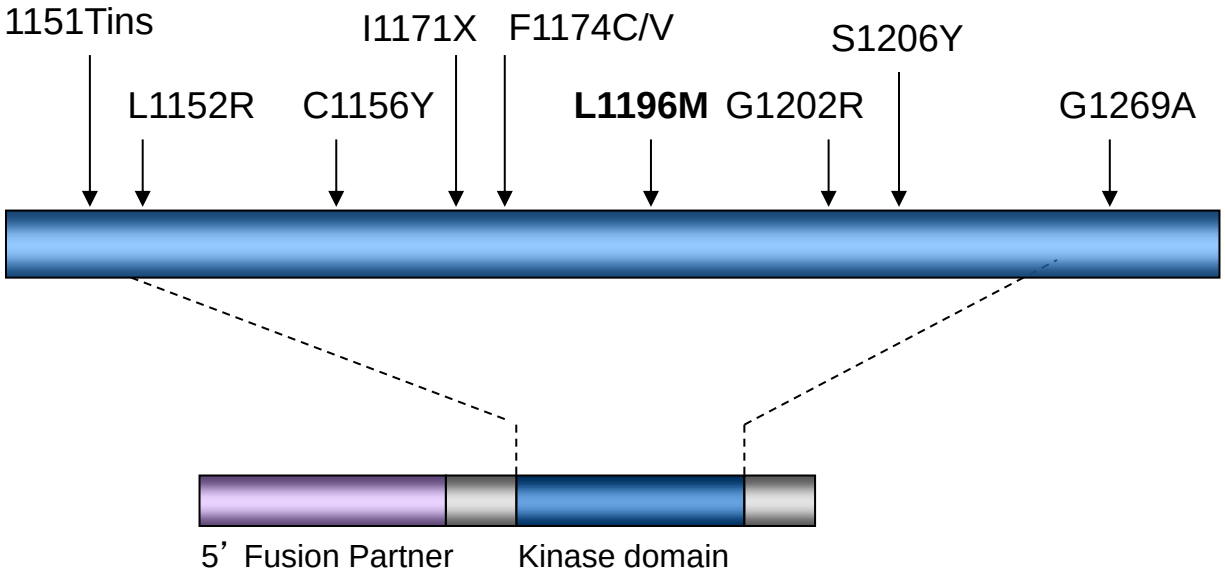
Solomon BJ et al. NEJM 2014; Camidge DR et al. Lancet Oncol 2012; Kim DW et al. ASCO 2014

Molecular Mechanisms of Crizotinib Resistance

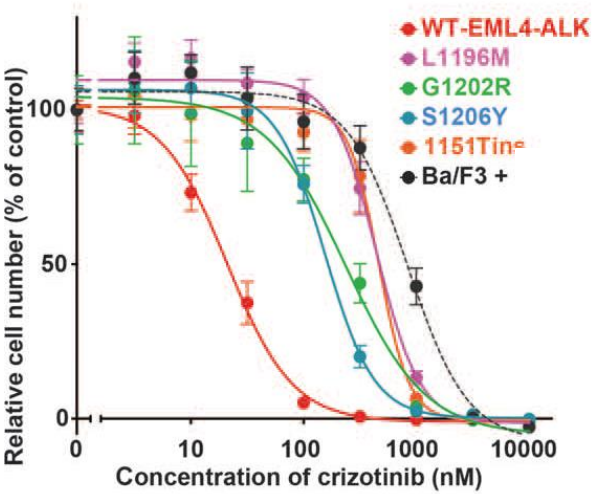


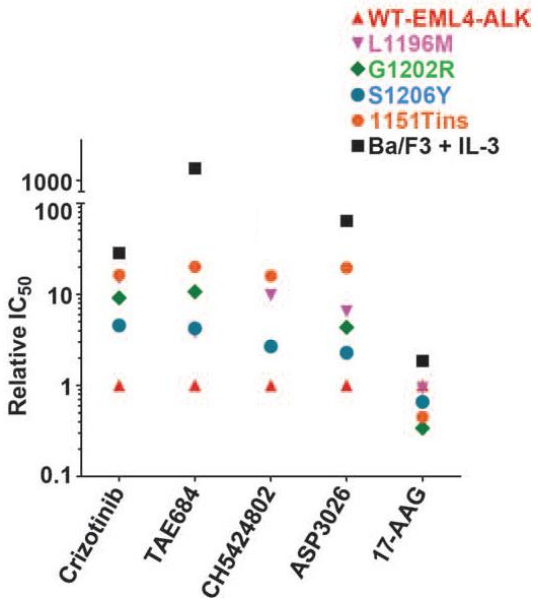


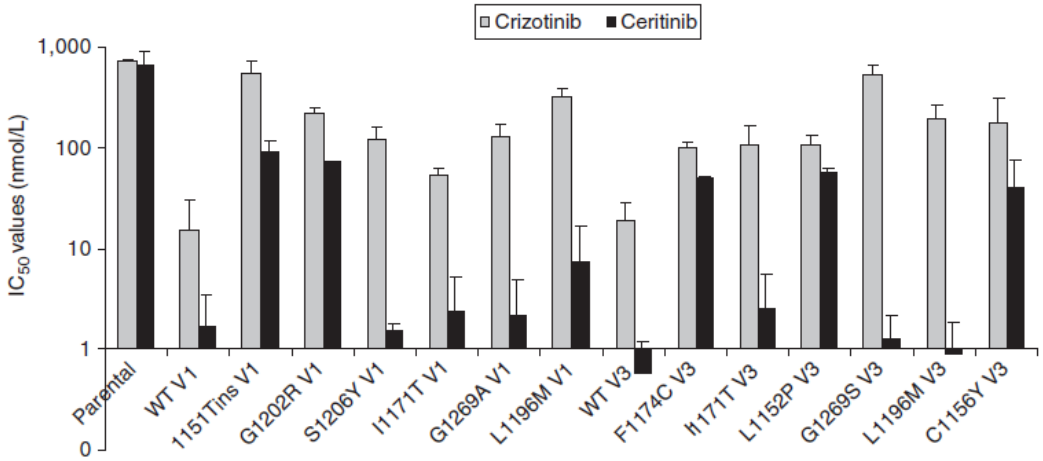


Katayama R et al. Sci Transl Med 2012; Doebele RC et al CCR 2012; Hallberg B, Palmer RH. Nat Rev Cancer 2013

ALK Resistance Mutations Confer Differential Sensitivities to Next Generation ALK Inhibitors







Katayama R et al. Sci Transl Med 2012; Friboulet L et al. Cancer Discovery 2014

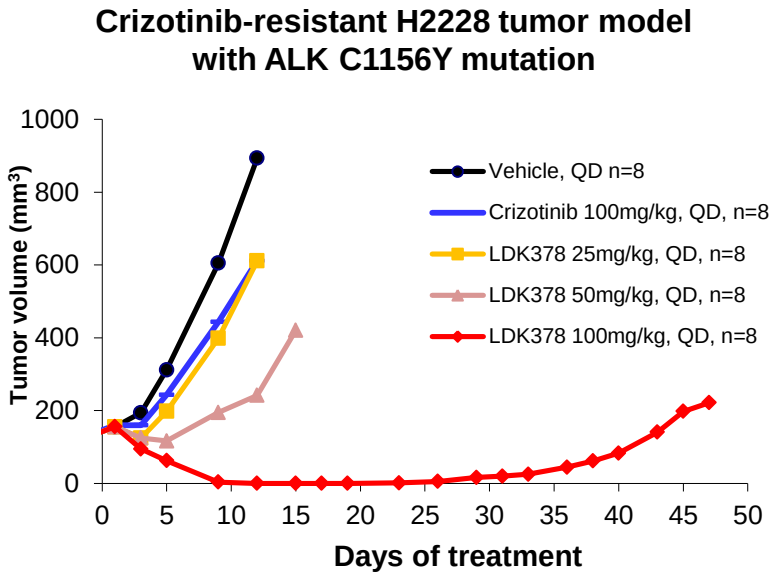
Next Generation ALK TKIs

Agent	Company
Ceritinib (LDK378)	Novartis
Alectinib (CH5424802)	Roche
AP26113	Ariad
CEP-37440	Teva
Entrectinib (RXDX-101)	Ignyta
PF-06463922	Pfizer
TSR-011	Tesaro
X-396	Xcovery

Preclinical Studies of Ceritinib (LDK378)

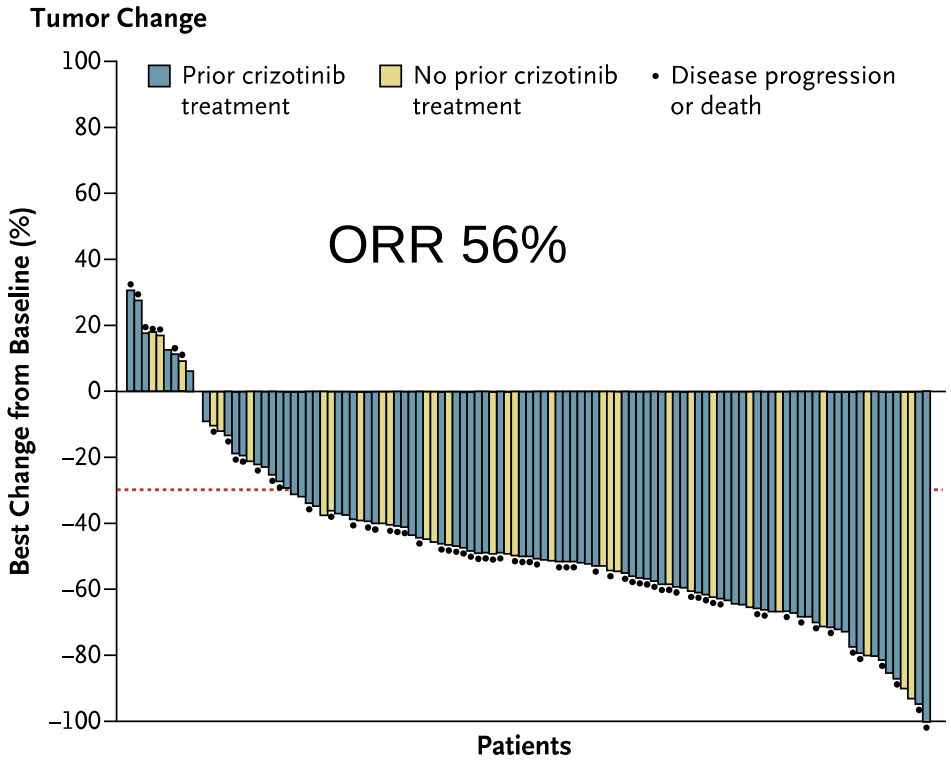
- Ceritinib is a potent and selective ALK inhibitor
- Potent activity in enzymatic and cell based assays
- Significant activity in crizotinib-resistant, in vivo models.

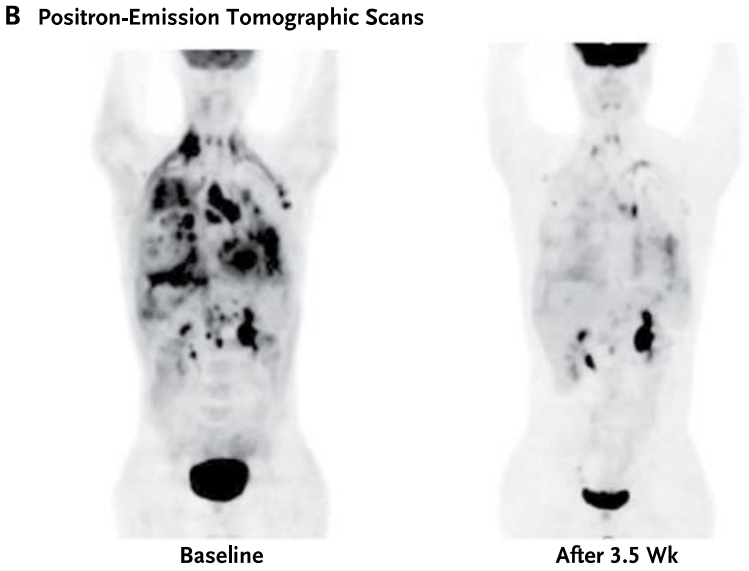
Assay	Ceritinib IC_{50} (nM)	CRZ IC_{50} (nM)
Enzymatic		
ALK	0.15	3
IGF-1R	8	400
c-Met	3200	8
Cell-based[3]		
EML4-ALK	20	120
- L1196M	60	810
- G1269S	140	1600
- G1202R	490	1020
- C1156Y	130	350



Shaw et al., ASCO 2013

Ceritinib is Active in Crizotinib-Resistant NSCLC





Shaw AT, NEJM 2014

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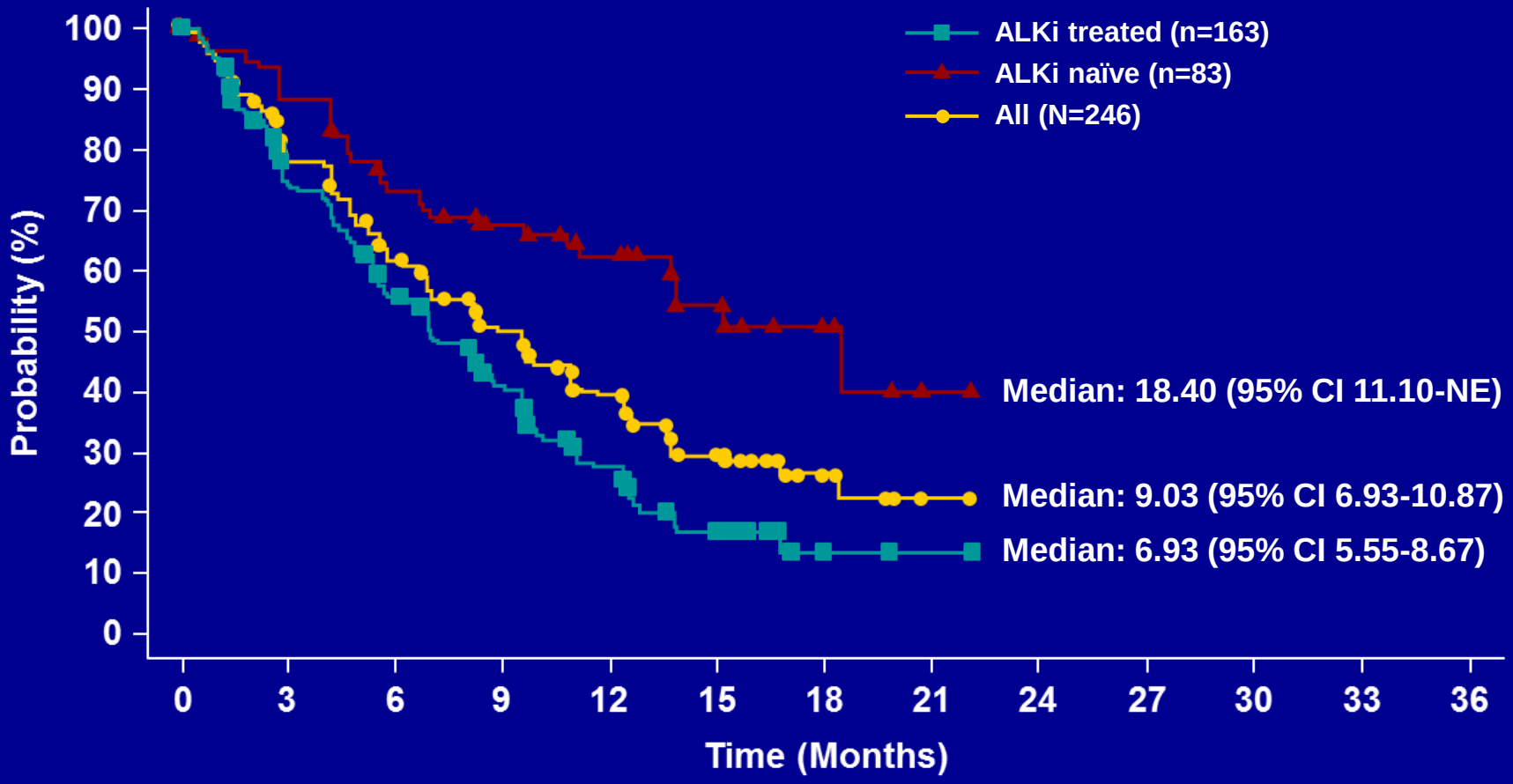
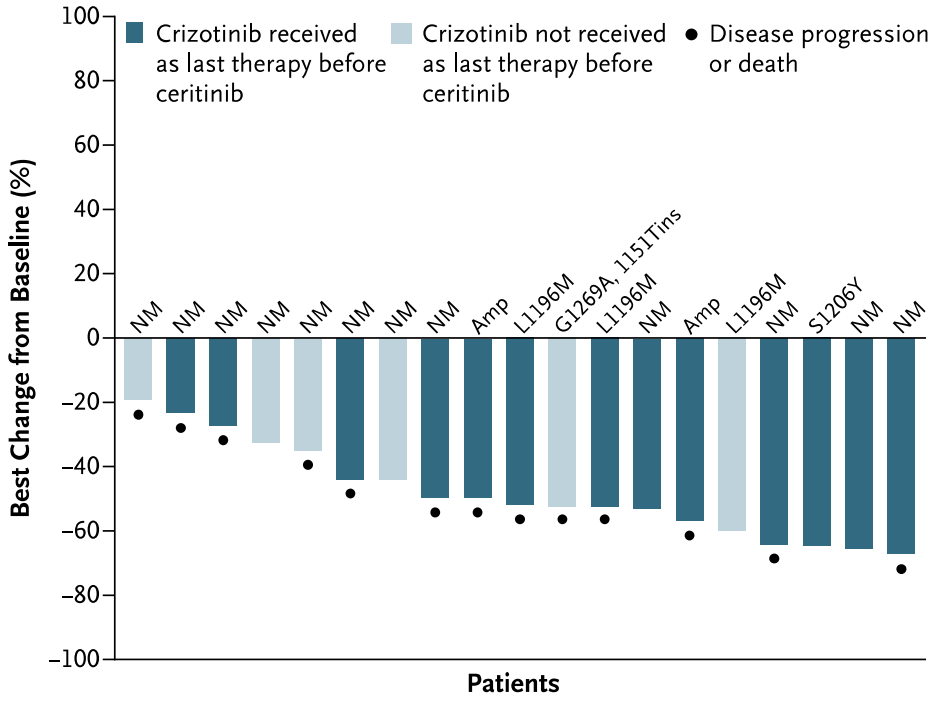
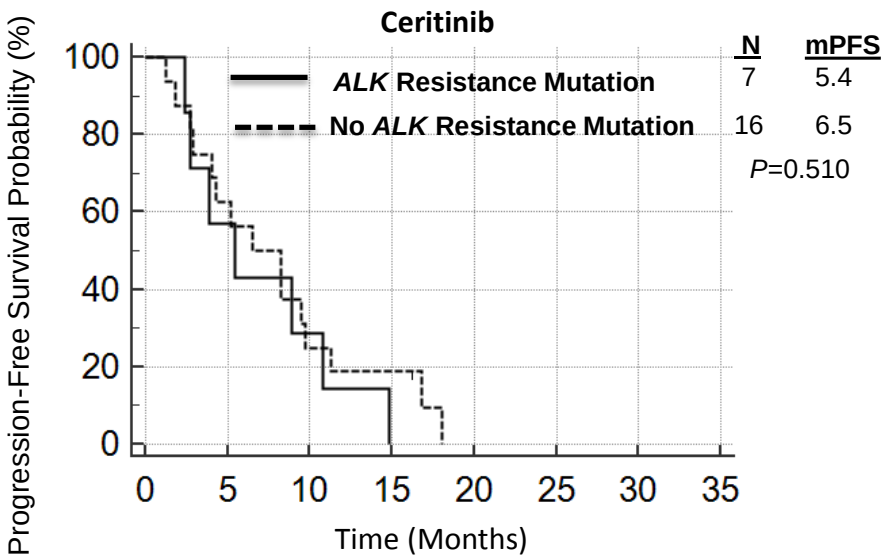
Progression-Free Survival with Ceritinib



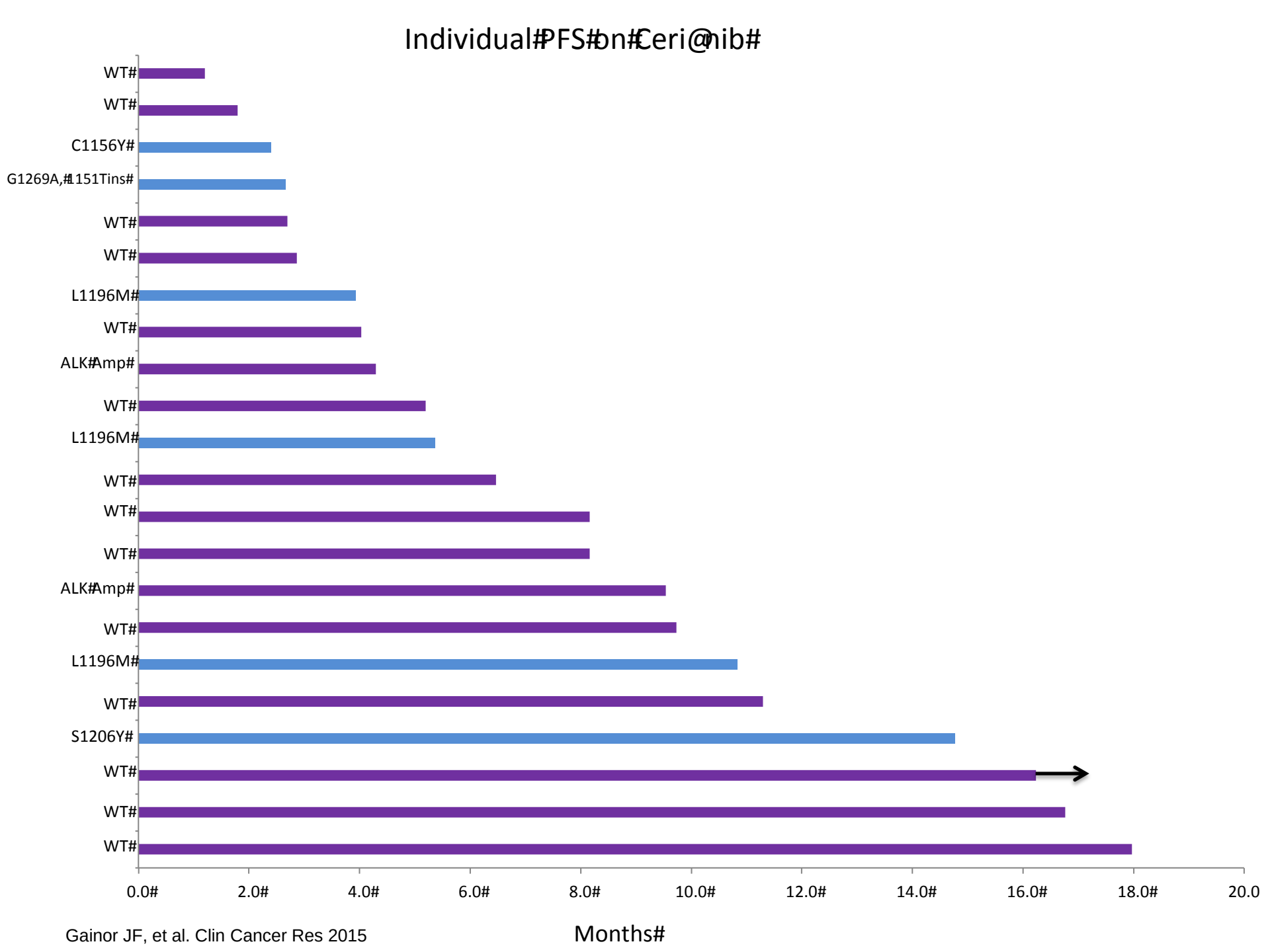
Felip et al., ESMO 2014

Ceritinib – Influence of *ALK* Secondary Mutations



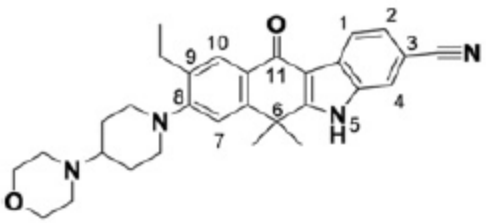


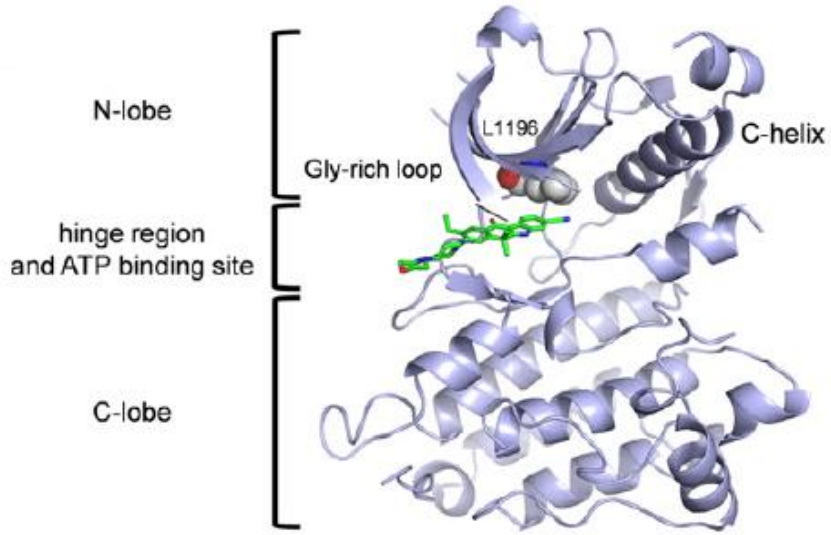
Shaw AT, et al. NEJM 2014; Gainor JF, et al. Clin Cancer Res 2015



Gainor JF, et al. Clin Cancer Res 2015

Alectinib

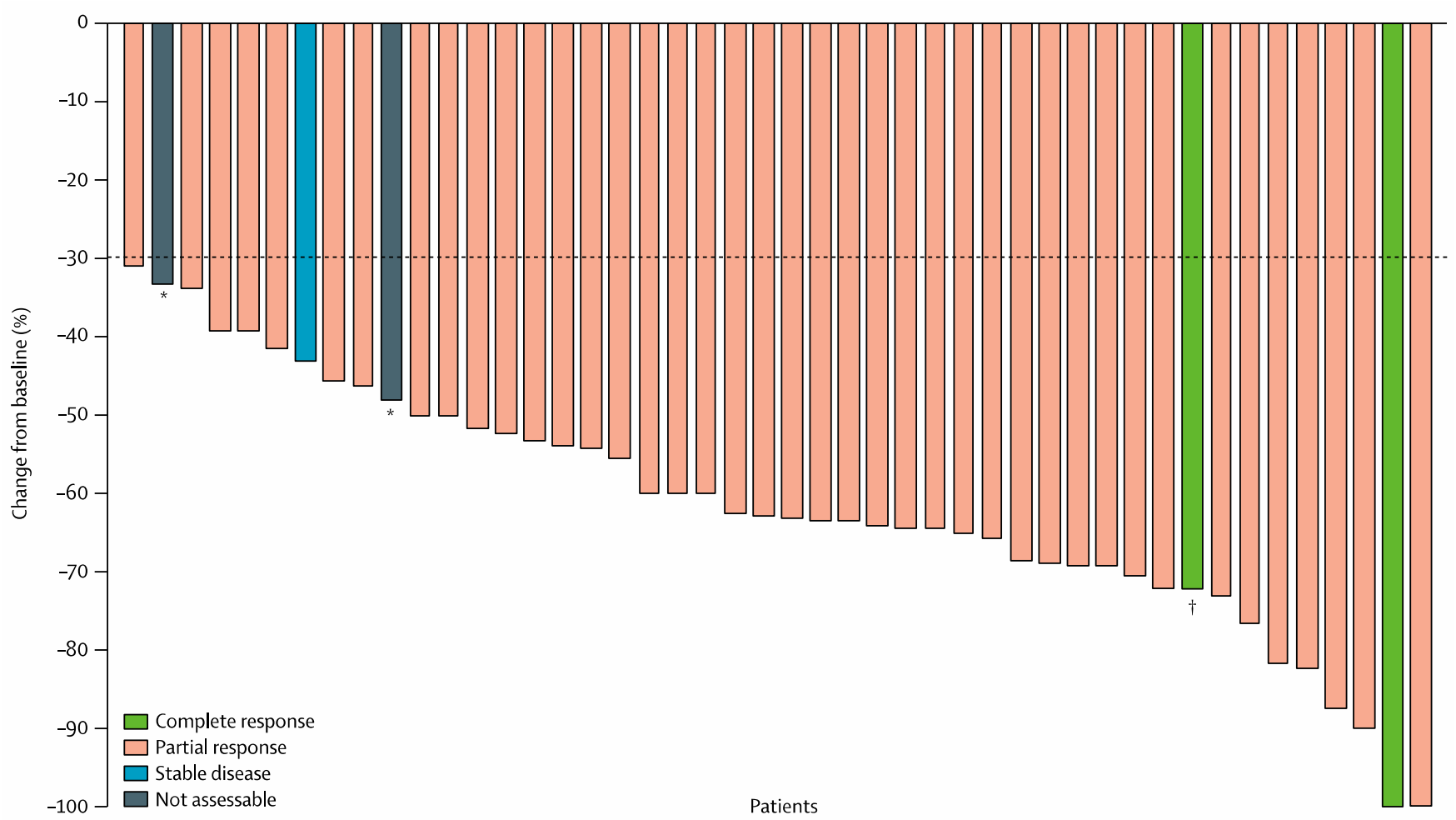




Tyrosine Kinase	IC_{50} (nM)
ALK	1.9
ALK F1174L	1.0
ALK R1275Q	3.5
RET	4.8
INSR	550
KDR	1400
ABL	>5000
EGFR	>5000
FGFR2	>5000
HER2	>5000
IGF1R	>5000
JAK1	>5000
MET	>5000

Sakamoto H et al. Cancer Cell 2011; Kodama T et al. Mol Cancer Ther 2014

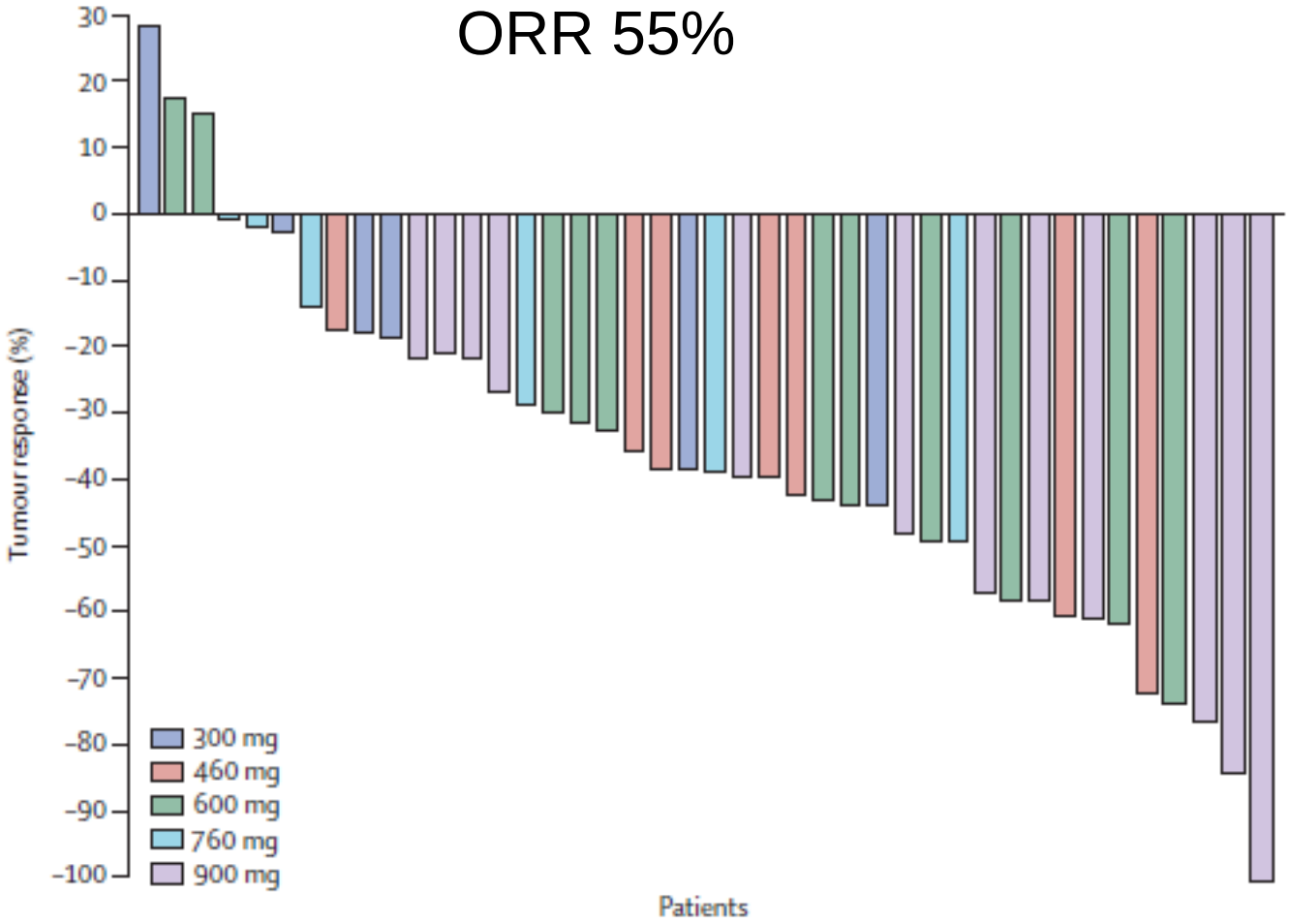
Alectinib in ALK-TKI Naïve Patients



Seto et al. Lancet Oncol 2013

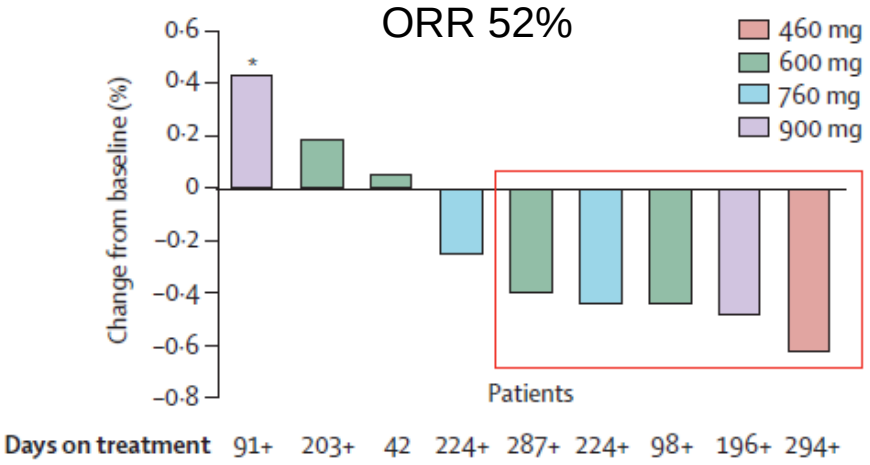
Activity of Alectinib in Crizotinib-Resistant Disease

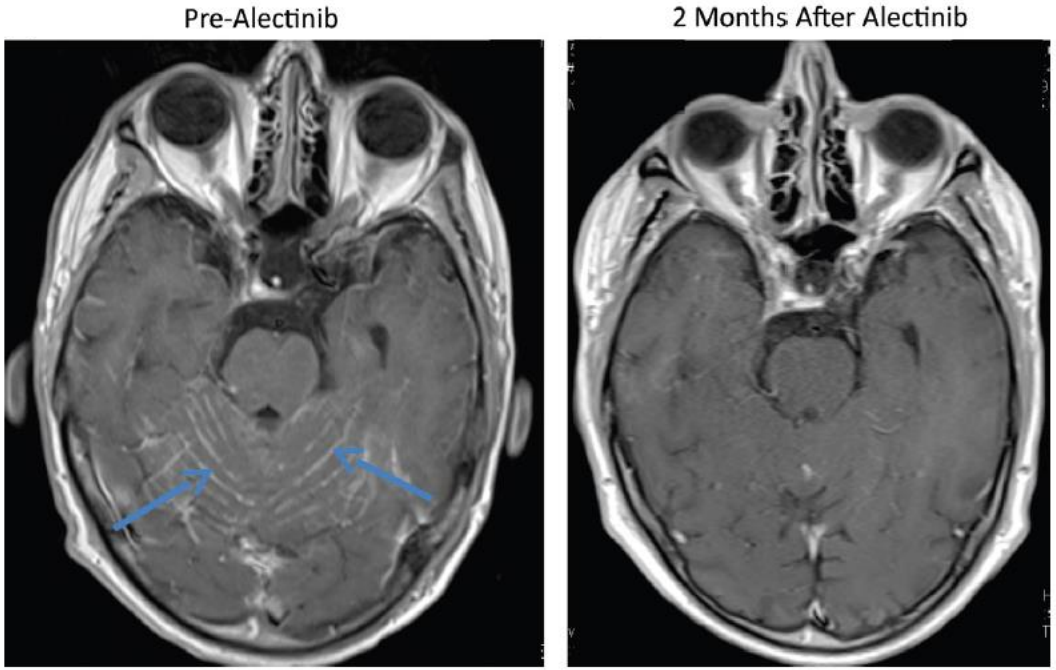
ORR 55%



Gadgeel SM et al. Lancet Oncol 2014

Activity of Alectinib in the CNS





Gadgeel SM et al. Lancet Oncol 2014; Gainor JF et al. JTO 2015

Activity of Next-Generation ALK Inhibitors in Crizotinib-Resistant Disease

	Ceritinib	Alectinib	AP26113
Sponsor	Novartis	Roche	Ariad
Sample Size	163	44	65
ORR	55%	55%	69%
Confirmed/Unconfirmed Responses	Confirmed	Confirmed & Unconfirmed	Confirmed & Uncomfirmed
Median PFS	6.93 months	-	47.3 weeks

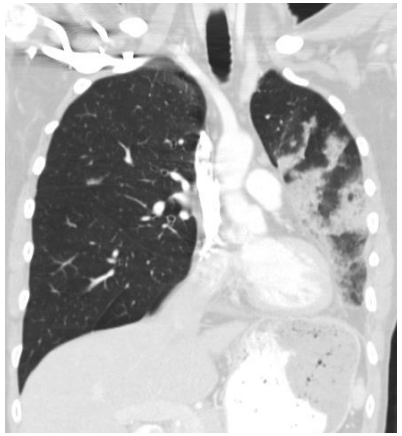
Shaw AT et al. NEJM 2014; Felip et al. ESMO 2014; Gadgeel et al. Lancet Oncol 2014; Gettinger et al. ESMO 2014

Resistance to Next Generation ALK Inhibitors

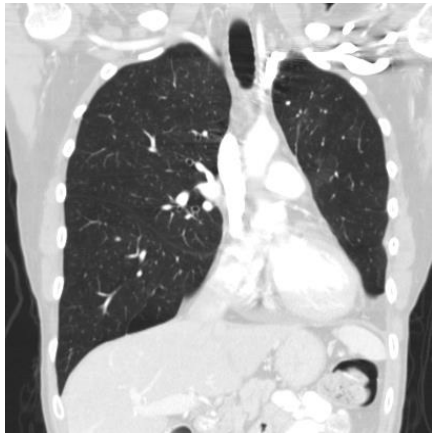
Patient ID	*EML4–ALK* sequence at crizotinib resistance
MGH011	S1206Y
MGH015	WT
MGH023	WT
MGH034	WT
MGH049	WT
MGH051	WT
MGH057	N/A
MGH061	WT
JFCR013	N/A
JFCR021	G1269A (right lung)

Friboulet L, et al. Cancer Discovery 2014

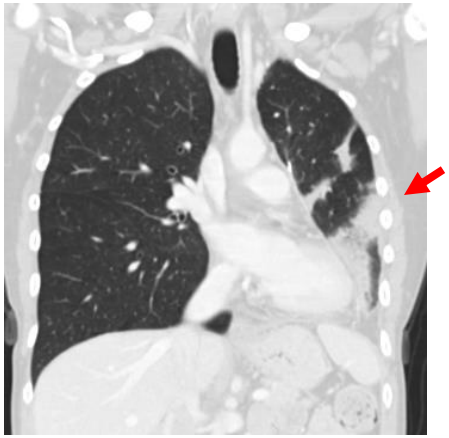
Evolution of ALK TKI Resistance



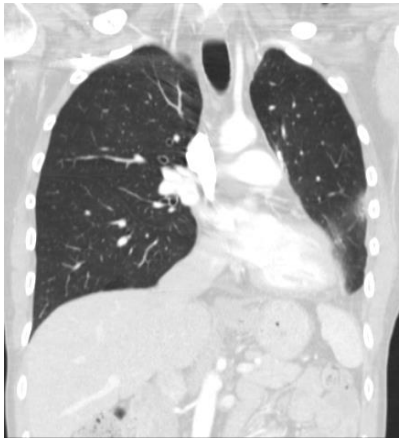
Baseline



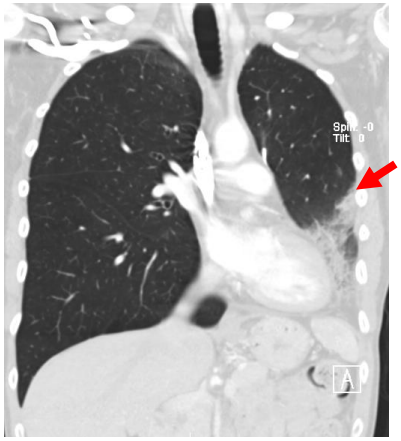
After 8 weeks of crizotinib



After 34 months of crizotinib
S1206Y



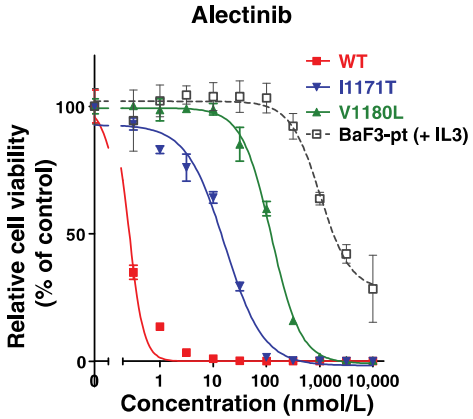
After 12 weeks of ceritinib

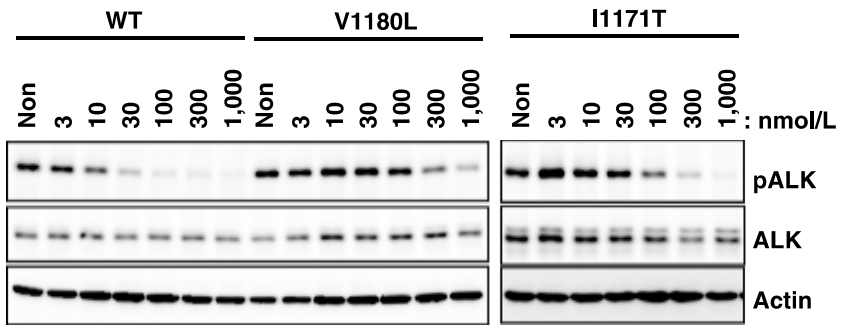


After 15 months of ceritinib
G1202R

Friboulet L, et al. Cancer Discovery 2014

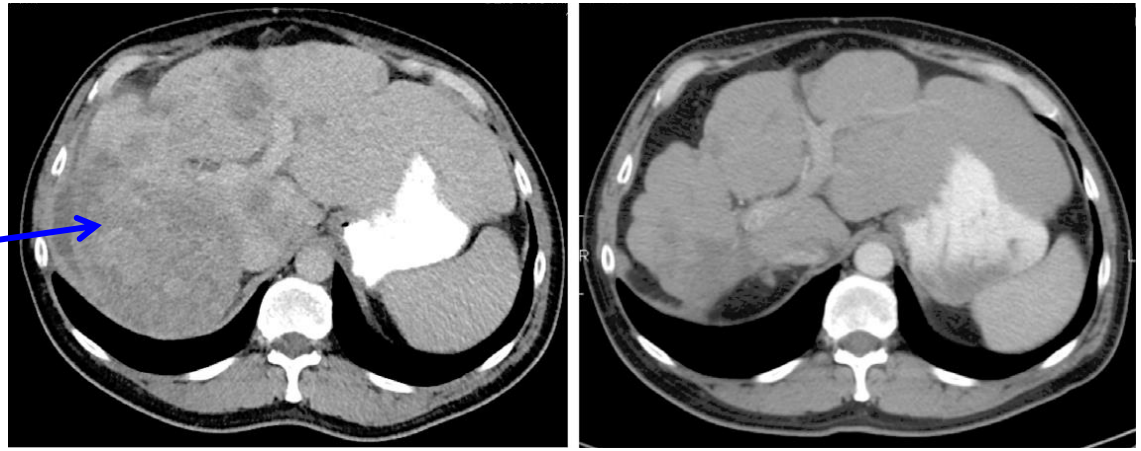
ALK Resistance Mutations May Differ Across Next Generation ALK Inhibitors





I1171T

MGH056



After alectinib
(Pre-ceritinib)

On ceritinib
(best response to ceritinib)

Evolution of *ALK* Resistance Mutations

Crizotinib	Ceritinib	Alectinib
1151Tins		
L1152R		
C1156Y		
F1174V/L	**F1174V/C**	
L1196M		
G1202R	**G1202R**	**G1202R**
D1203N	**D1203N**	
S1206Y		
G1269A		
		I1171T
		V1180L

Katayama et al., Sci Transl Med 4(120): 120ra17, 2012; Doebele et al., CCR 18(5): 1472-82, 2012; Friboulet et al., Cancer Discov 4(6): 662-73, 2014; Ou et al., JTO 9(4): 549-53, 2014; Doebele, ELCC 2014; Katayama et al., CCR, 2014

Additional Mechanisms of ALK TKI Resistance: Bypass Signaling

ALK TKI	Bypass Pathway	Reference(s)
Crizotinib	EGFR Activation	*Katayama et al. 2012* *Doebele et al. 2012* *Sasaki et al. 2011*
	cKIT Amplification	*Katayama et al. 2012*
	IGF-1R Signaling	*Lovly et al. 2014*
	SRC Signaling	*Crystal et al. 2014*
Crizotinib/Ceritinib	MAPK Pathway Activation	*Doebele et al. 2012* *Crystal et al. 2014*
Alectinib	*MET* Amplification	*Gouji et al. 2014*

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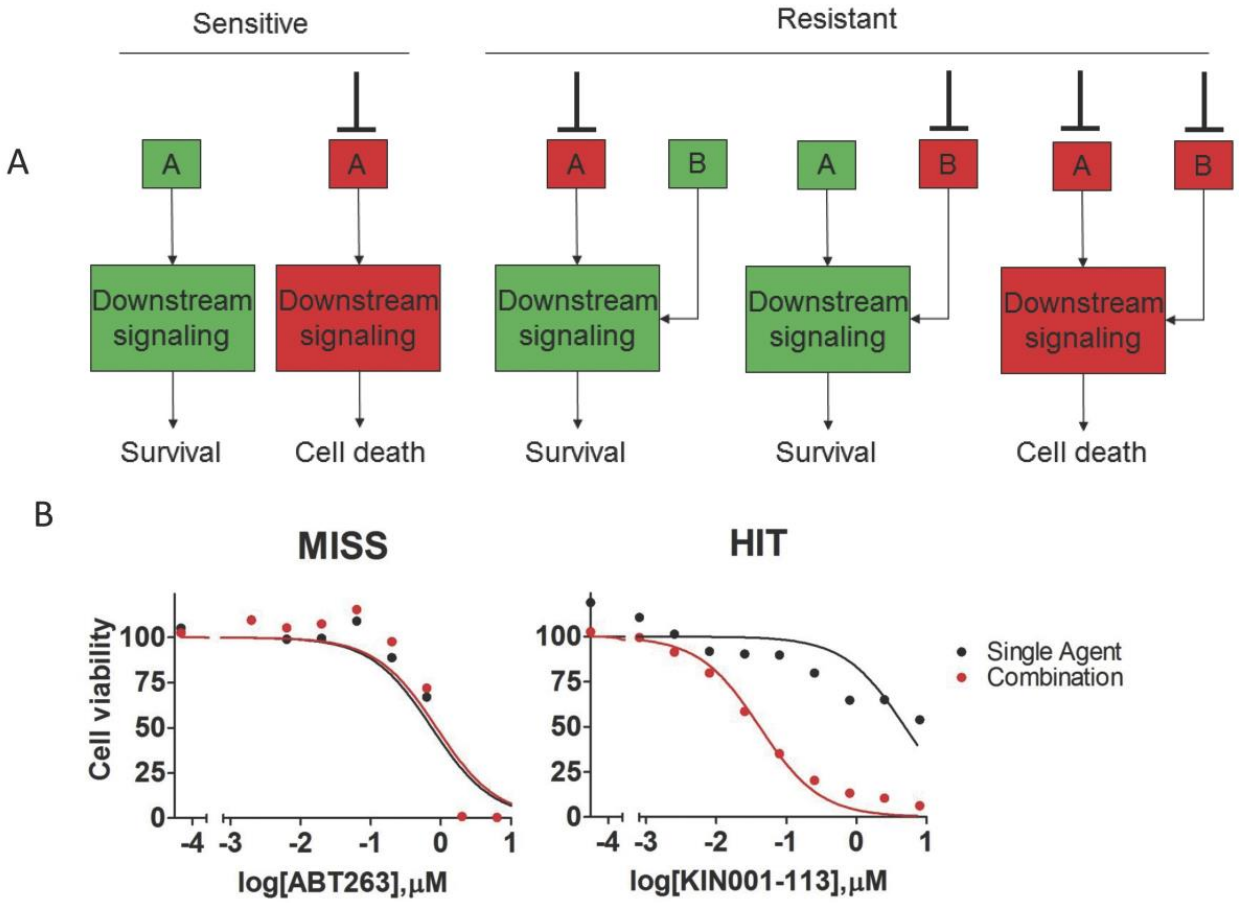
Targeting Bypass Signaling Pathways



Crystal AS, et al. Science 2014

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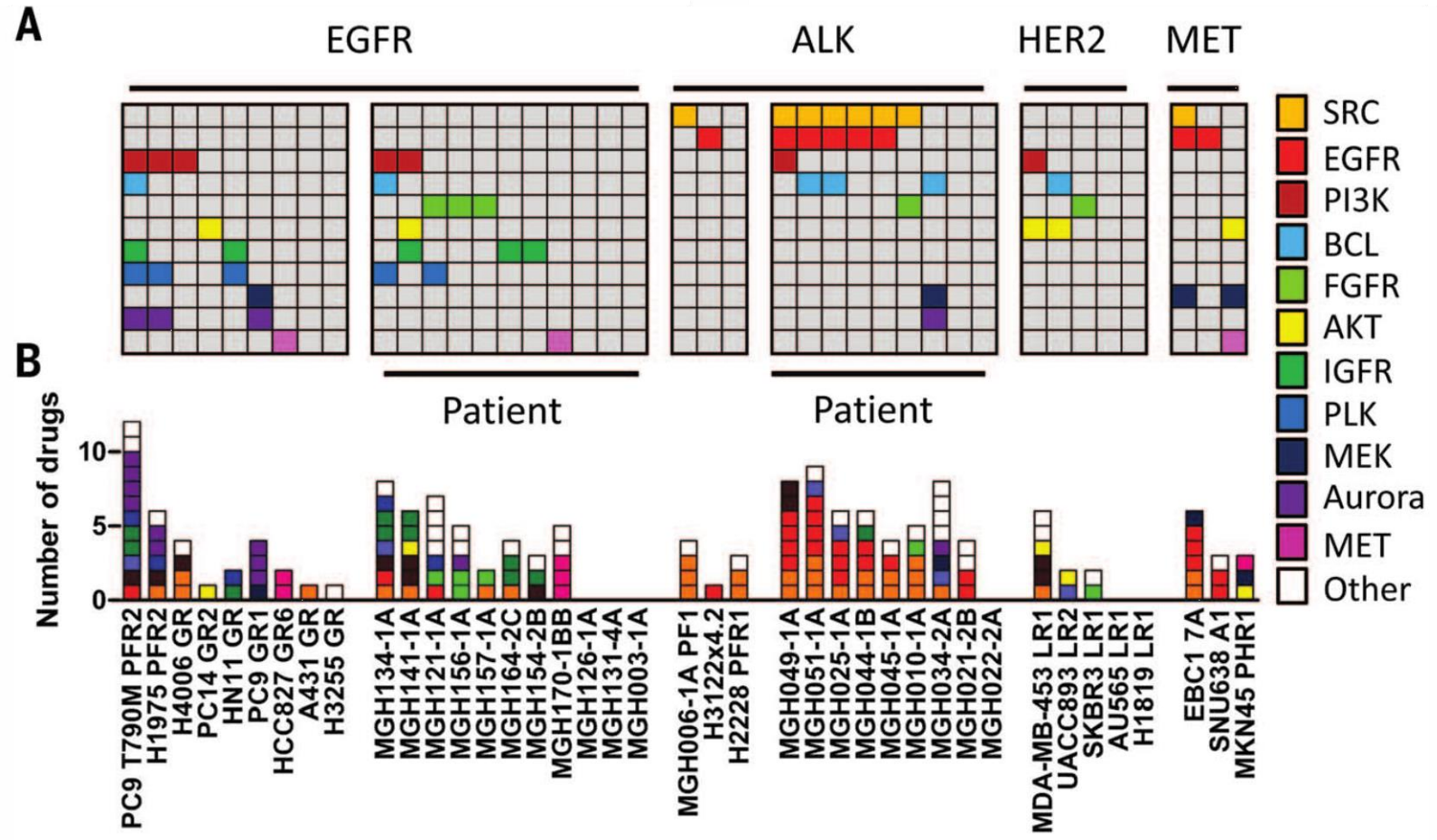
Targeting Bypass Signaling Pathways



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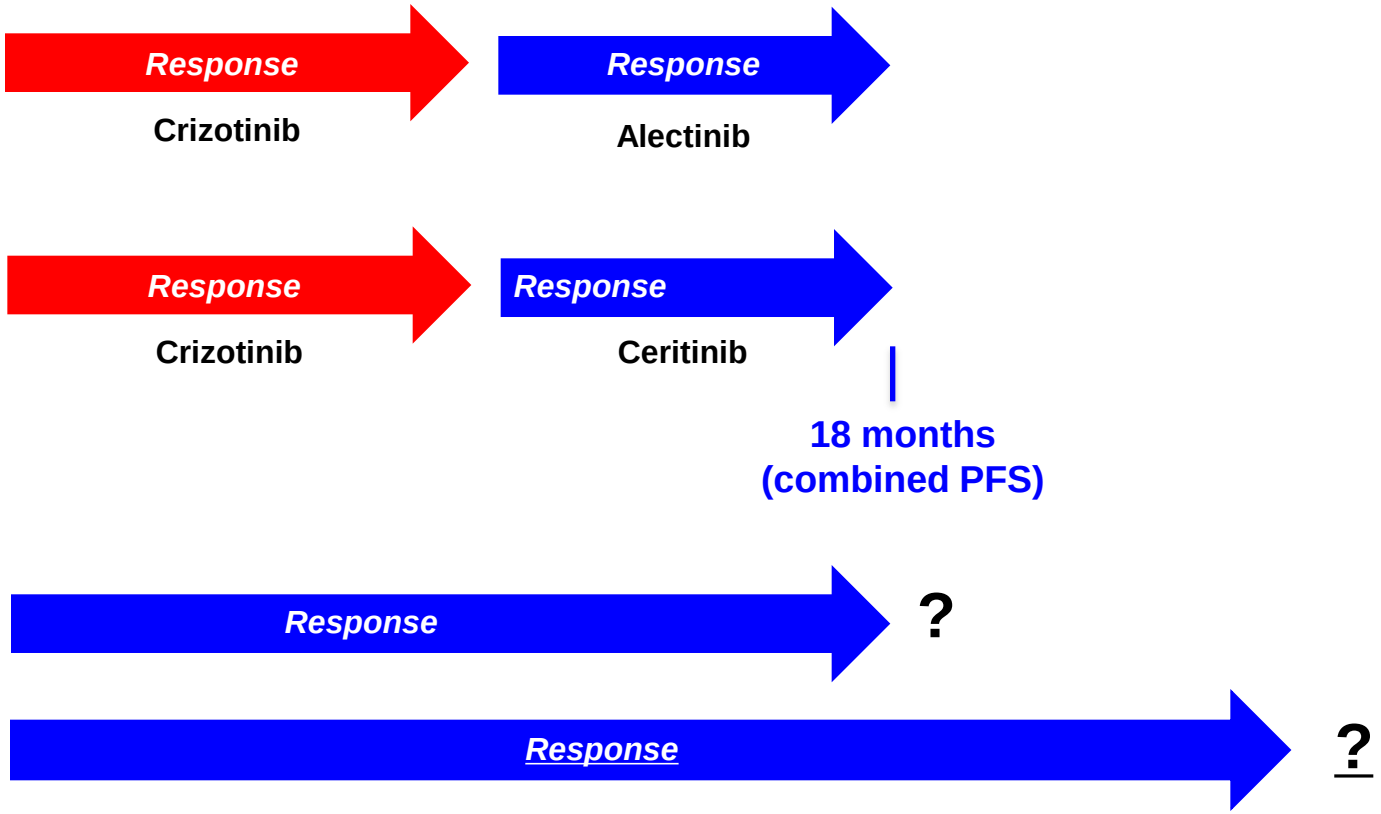
Crystal AS, et al. Science 2014

Sequencing of ALK TKIs Moving Forward?



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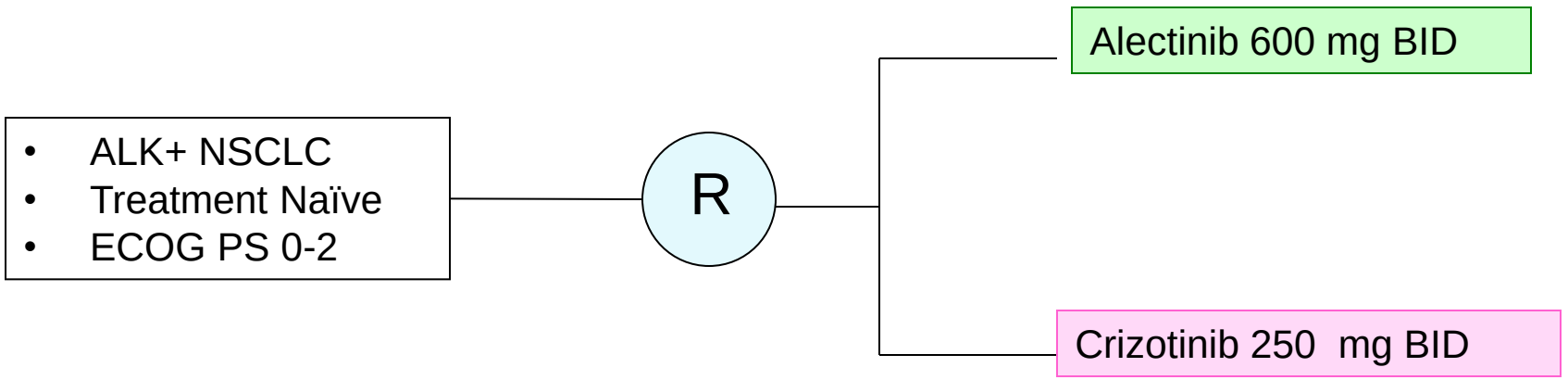
ALEX Study (NCT02075840)



Primary Endpoint:
- PFS

Secondary Endpoints:
- ORR
- OS
- Time to CNS Progression
- Quality of Life Measures

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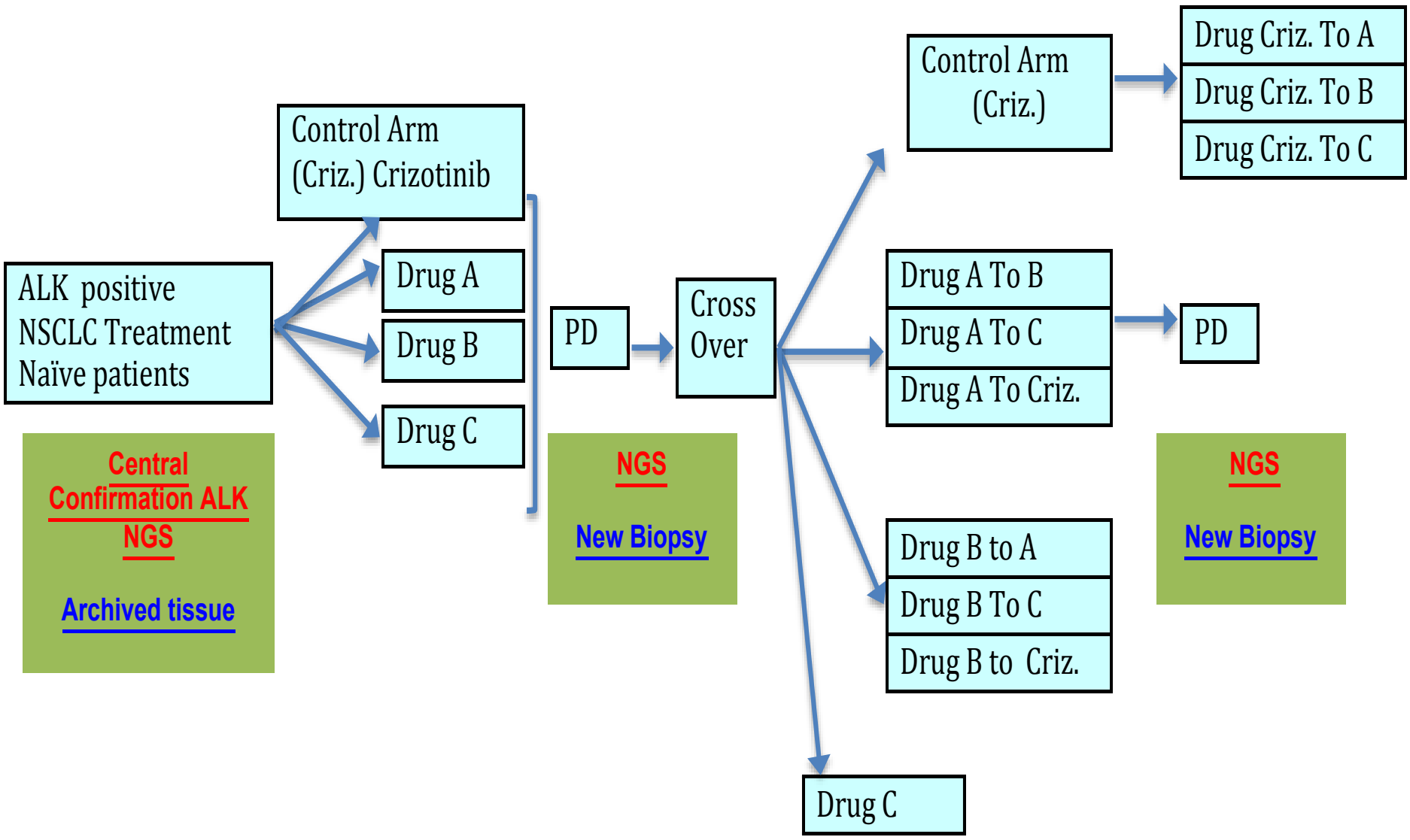
NCI ALK MP


ALK positive NSCLC Treatment Naïve patients
Central Confirmation ALK NGS
Archived tissue
Control Arm (Criz.) Crizotinib
Drug A
Drug B
Drug C
PD
NGS
New Biopsy
Cross Over
Control Arm (Criz.)
Drug Criz. To A
Drug Criz. To B
Drug Criz. To C
Drug A To B
Drug A To C
Drug A To Criz.
PD
NGS
New Biopsy
Drug B to A
Drug B To C
Drug B to Criz.
Drug C

Conclusions

- Mechanisms of resistance to crizotinib include: PK failure (e.g., CNS), *ALK* amplification, *ALK* resistance mutations, and bypass signaling.
- Next-generation ALK inhibitors have shown promising anti-tumor activity in early phase studies.
- *ALK* resistance mutations confer differential sensitivities to next-generation ALK inhibitors.
- Certain *ALK* resistance mutations (e.g., G1202R) confer high levels of resistance to available ALK TKIs.
- Questions remain regarding the optimal sequencing of ALK inhibitors.

Acknowledgements

- **Alice Shaw**
- **Jeff Engelman**
- Luc Friboulet
- Ryohei Katayama
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- Kate Schultz
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MGH Thoracic Team

- Lecia Sequist
- Rebecca Heist
- Jennifer Temel
- Christopher Azzoli
- Anna Farago
- Inga Lennes

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