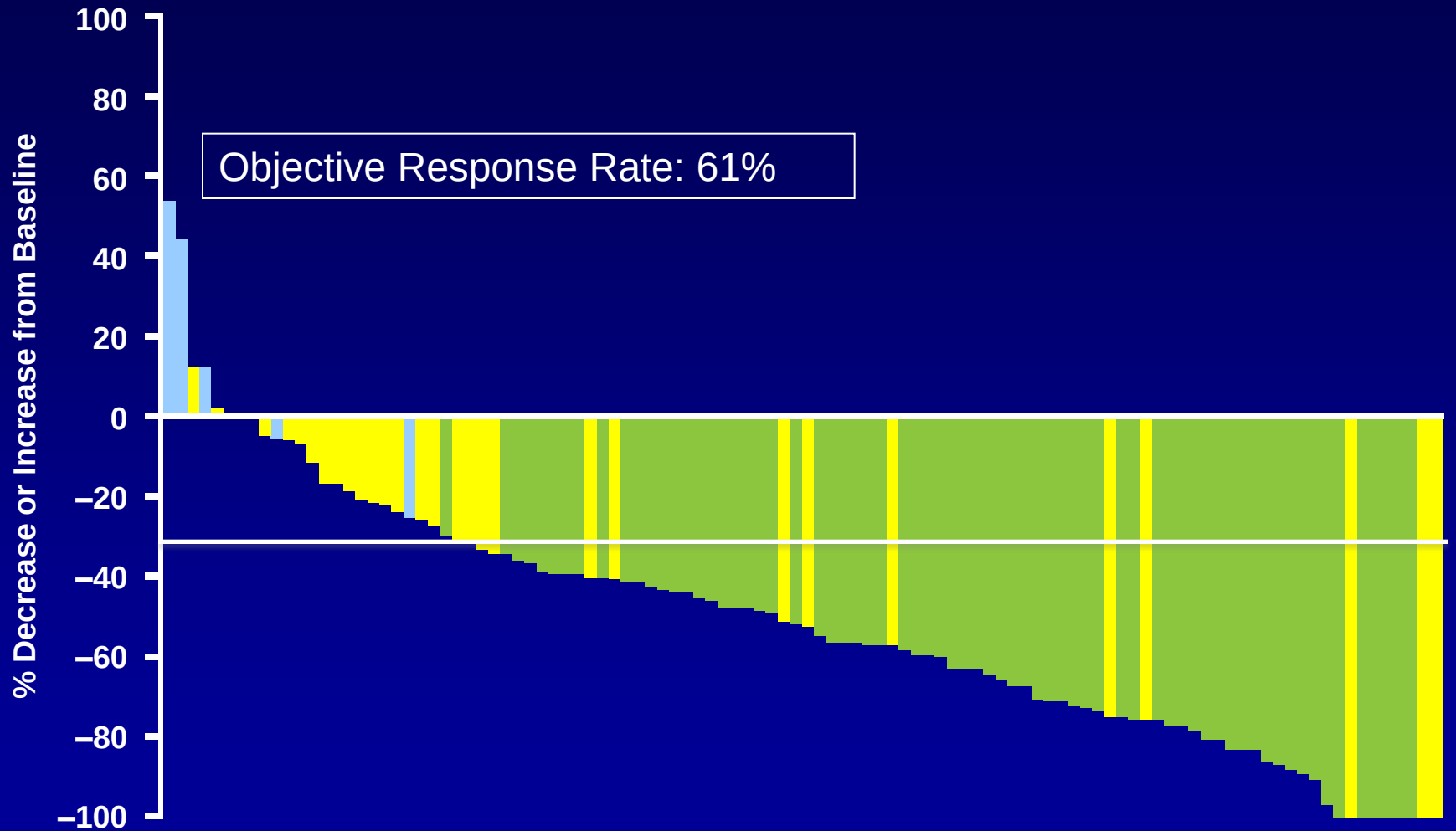
Targeting ALK: Clinical Trials with novel agents

ELCC 2016

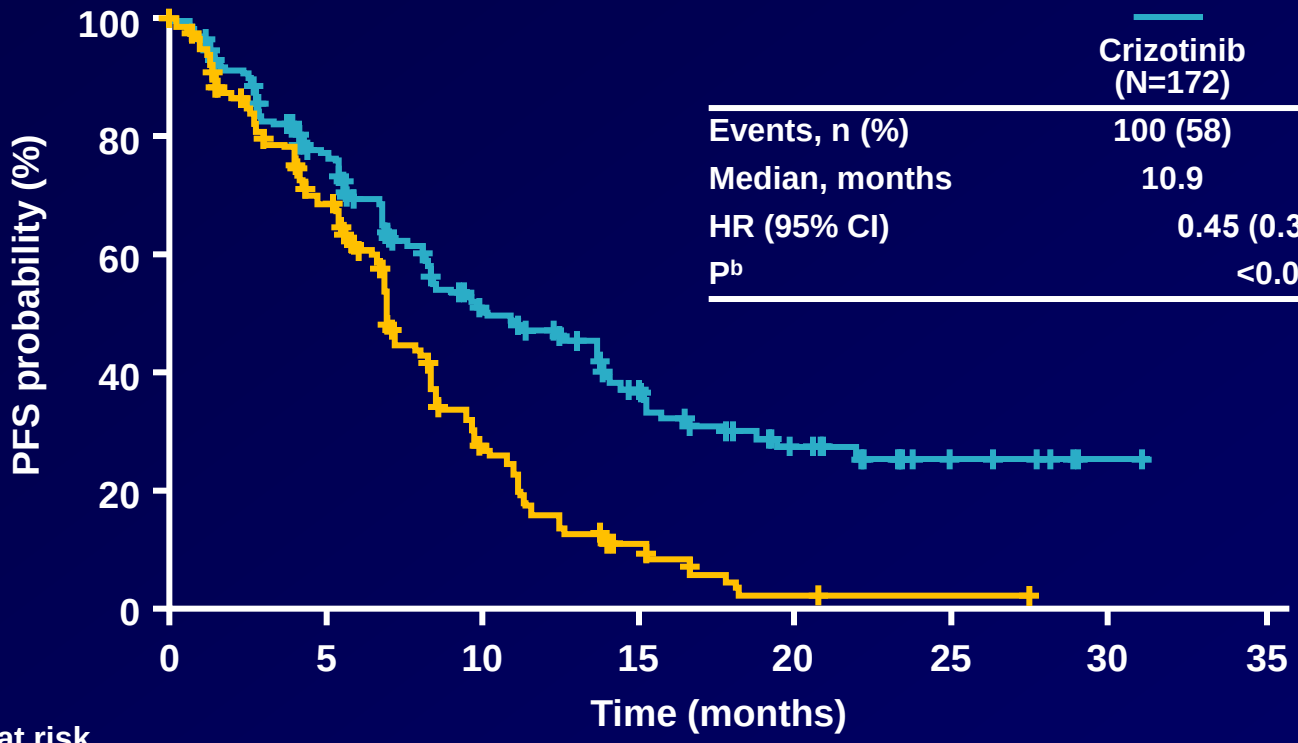
Ben Solomon
Peter MacCallum Cancer Centre

Responses in ALK+NSCLC patients treated on the crizotinib phase I study



Kwak NEJM 2010; Camidge Lancet Oncology 2012

PROFILE 1014: First-line Crizotinib vs Platinum-Pemetrexed in ALK+ NSCLC



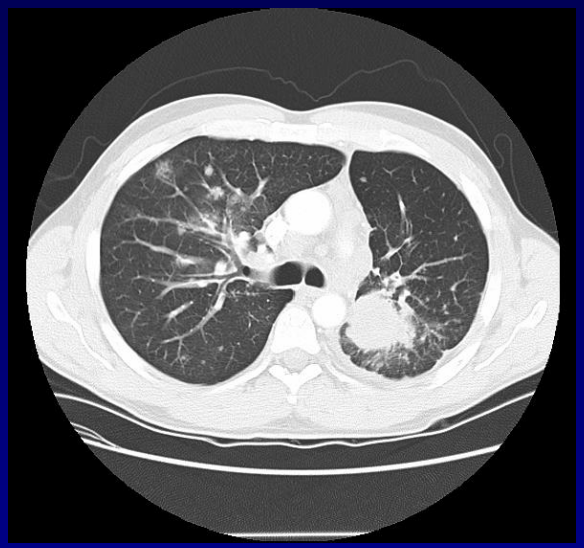
	Crizotinib (N=172)	Chemotherapy (N=171)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0[a]
HR (95% CI)	0.45 (0.35−0.60)	
P[b]	<0.0001	

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

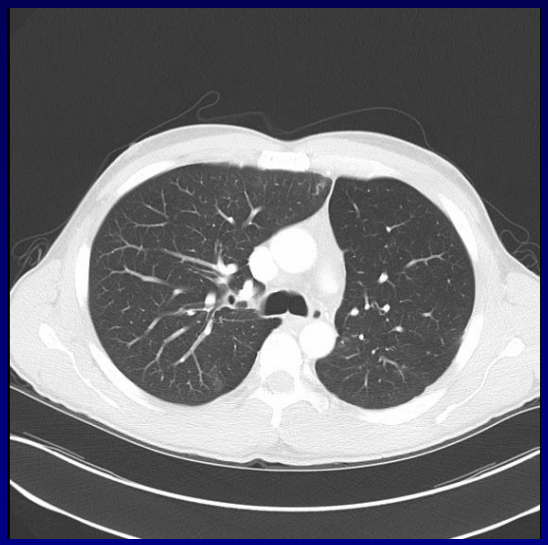
- **ORR: Crizotinib 74% vs Chemotherapy 45% P<001**

Solomon, Mok *et al.* NEJM 2014

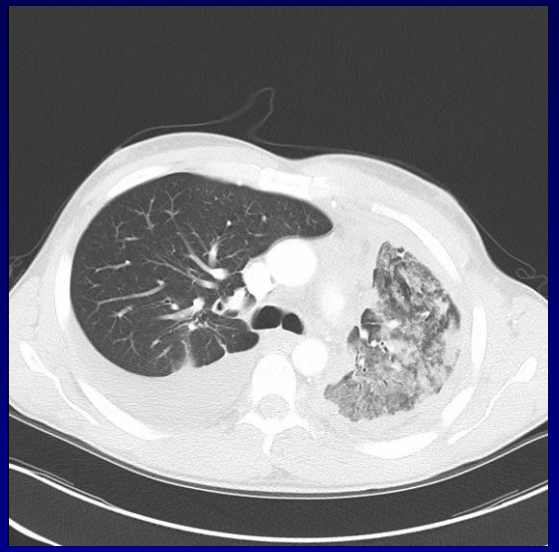
Acquired resistance to ALK inhibitors



April 2009

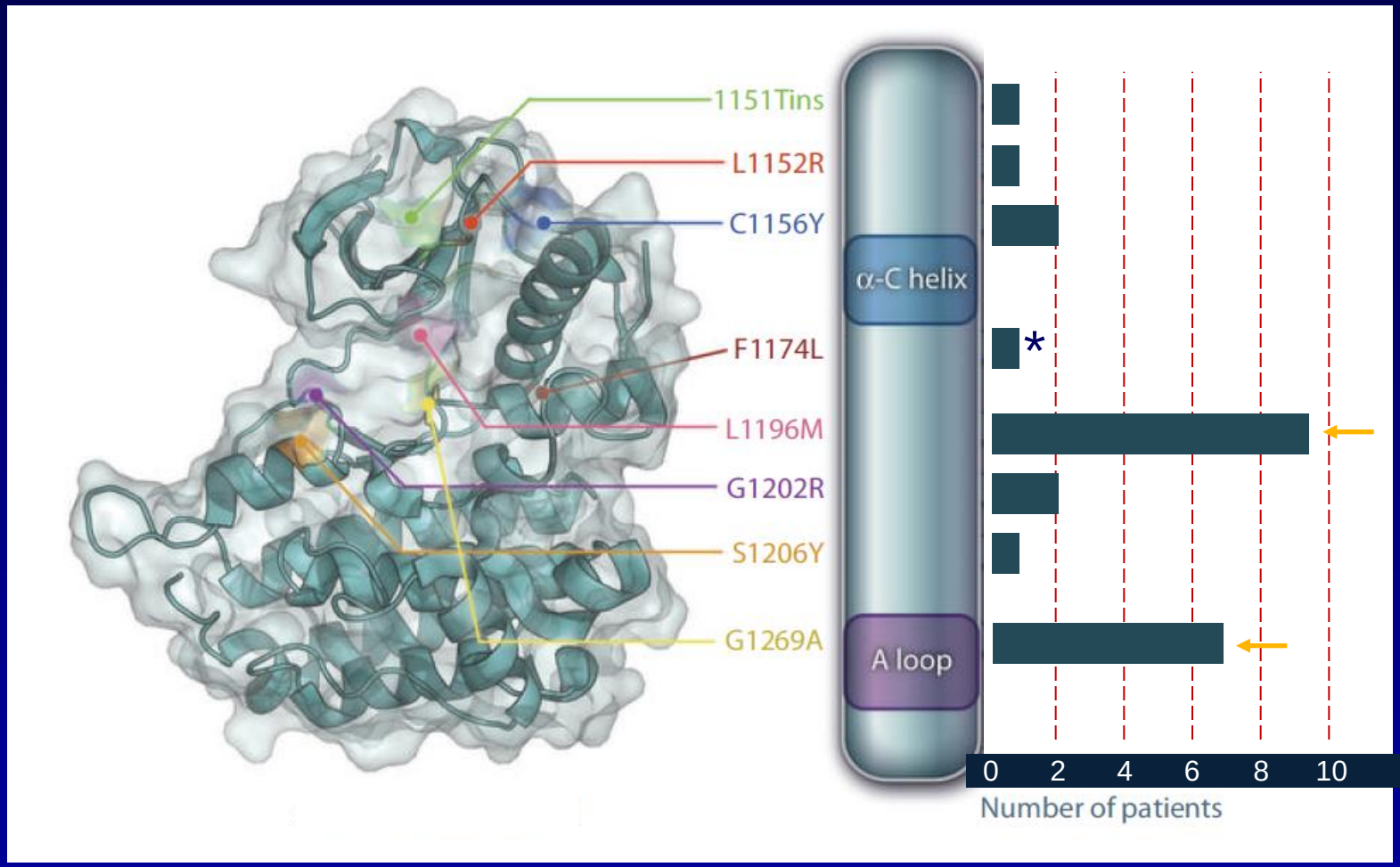


September 2010



September 2011

Crizotinib-resistance mutations in ALK+ NSCLC



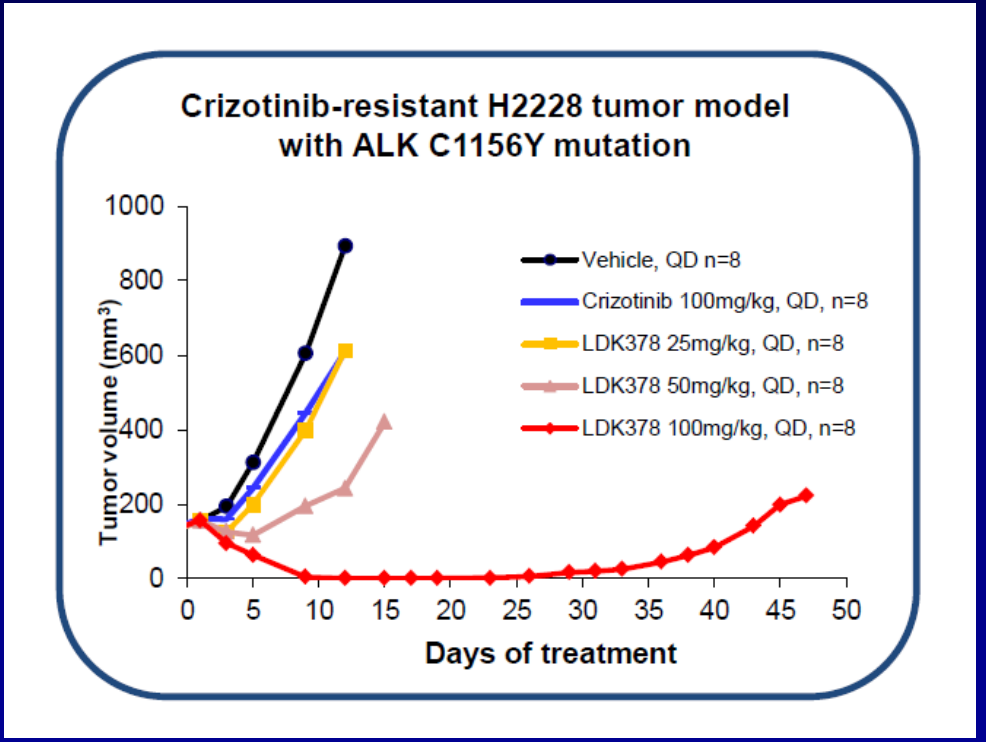
Adapted from Lovly CM, Pao W. *Sci Transl Med* 2012;4:120ps2.

Next Generation ALK Inhibitors

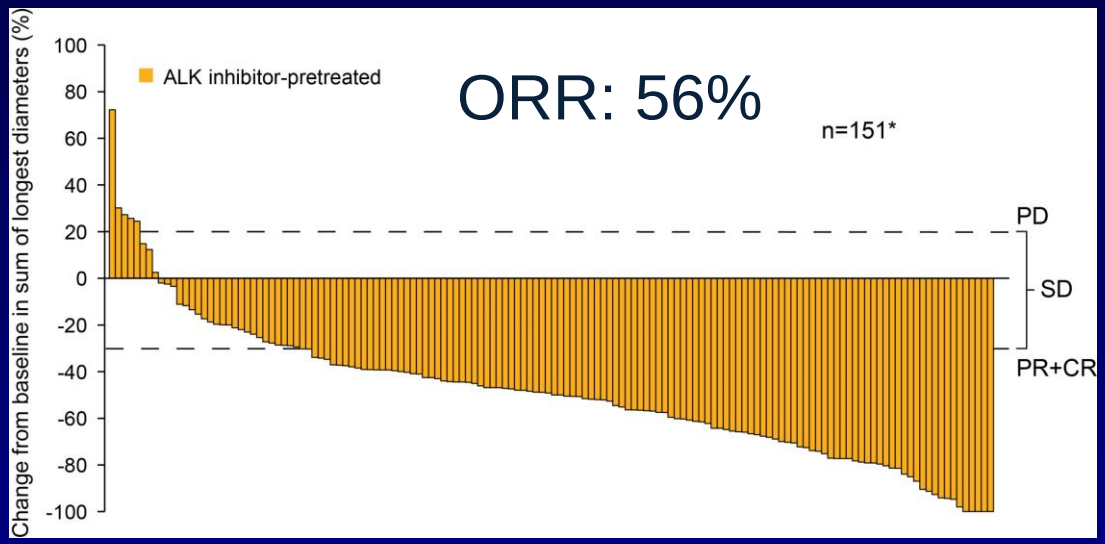
ALK TKI	Manufacturer	Status	Ongoing studies
Ceritinib	Novartis	**FDA approved** **EMA approved** *(post crizotinib)*	Phase 3 (vs chemo)
Alectinib	Chugai Roche/Genentech	**FDA approved** *(post crizotinib)*	Phase 3 (vs Crizotinib)
Brigatinib (AP26113)	Ariad	FDA breakthrough therapy	Phase 2 (90 vs 180 mg)
X-396	Xcovery	Investigational	Phase 1/2
TSR-011	Tesaro	Investigational	Phase 1/2a
RXDX-101	Ignyta	Investigational	Phase 1/2a
CEP-37440	Teva	Investigational	Phase 1
Lorlatinib (PF-06463922)	Pfizer	Investigational	Phase 1/2a

Ceritinib (LDK378) is a potent oral ALK inhibitor with activity against (some) mutations that confer resistance to crizotinib

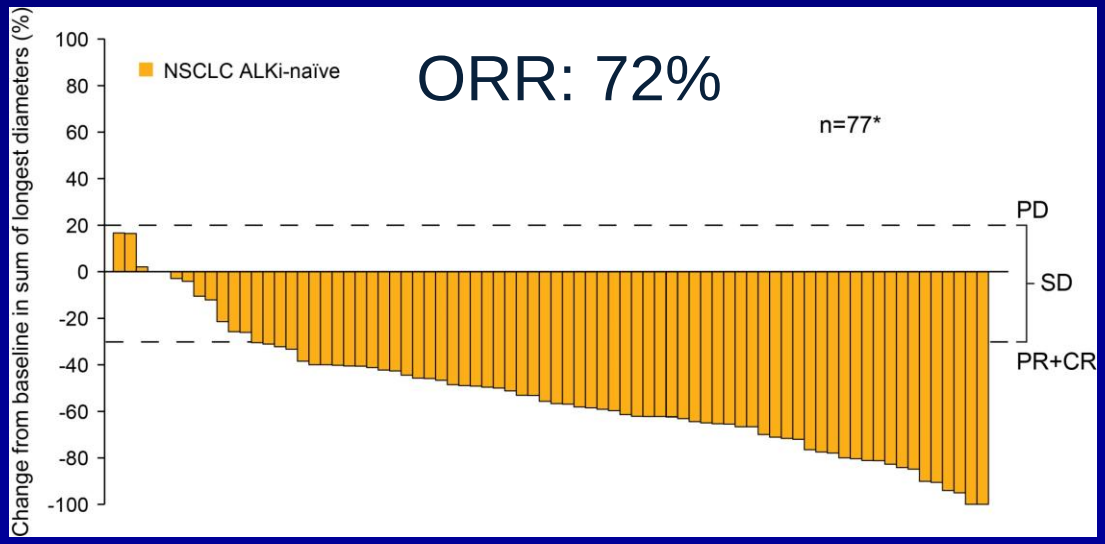
Assay	LDK378 IC_{50} (nM)	Crizotinib IC_{50} (nM)
Enzymatic		
ALK	0.15	3
IGF-1R	8	400
c-Met	3200	8
Cell-based		
EML4-ALK	20	120
- L1196M	60	810
- G1269S	140	1600
- G1202R	490	1020
- C1156Y	130	350



Activity of ceritinib (LDK378) in crizotinib naïve and crizotinib refractory ALK+ NSCLC in ASCEND-1



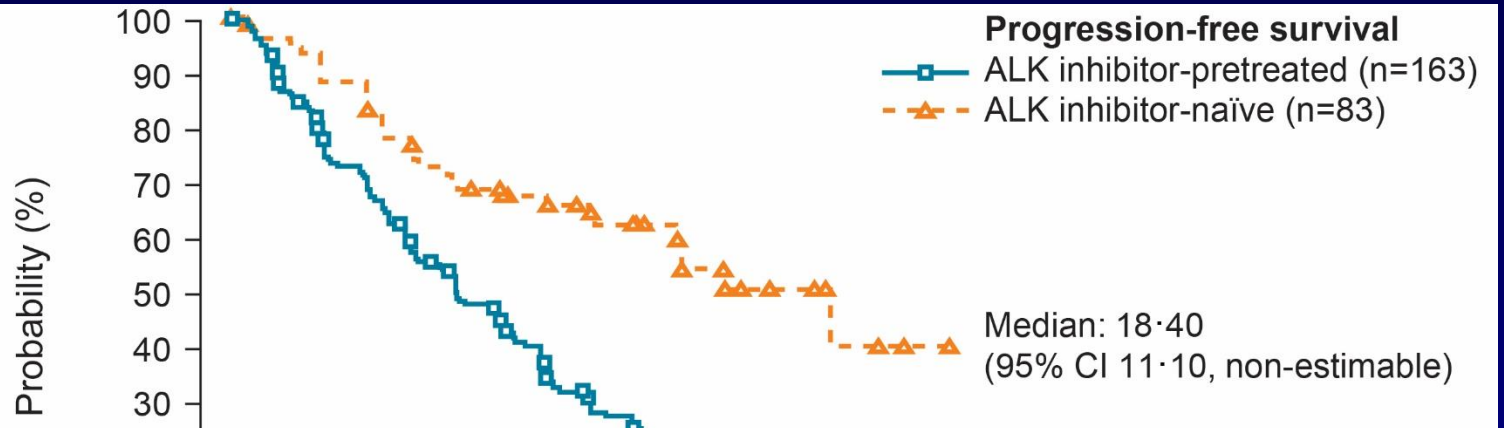
Crizotinib refractory patients: ORR: 56%



ALK TKI naïve patients: ORR: 72%

Kim DW et al. Lancet Oncol. 2016

Ceritinib shows durable responses in both pre-treated and previously ALK inhibitor naïve patients (ASCEND-1)



Number of patients still at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36
NSCLC with prior ALKi	163	108	79	52	29	13	2	1	0	0	0	0	0
NSCLC ALKi-naïve	83	69	55	43	32	17	6	2	0	0	0	0	0

Median PFS in ALK inhibitor pre-treated patients 6.9 months

Median PFS in ALK inhibitor naïve patients was 18.4 months

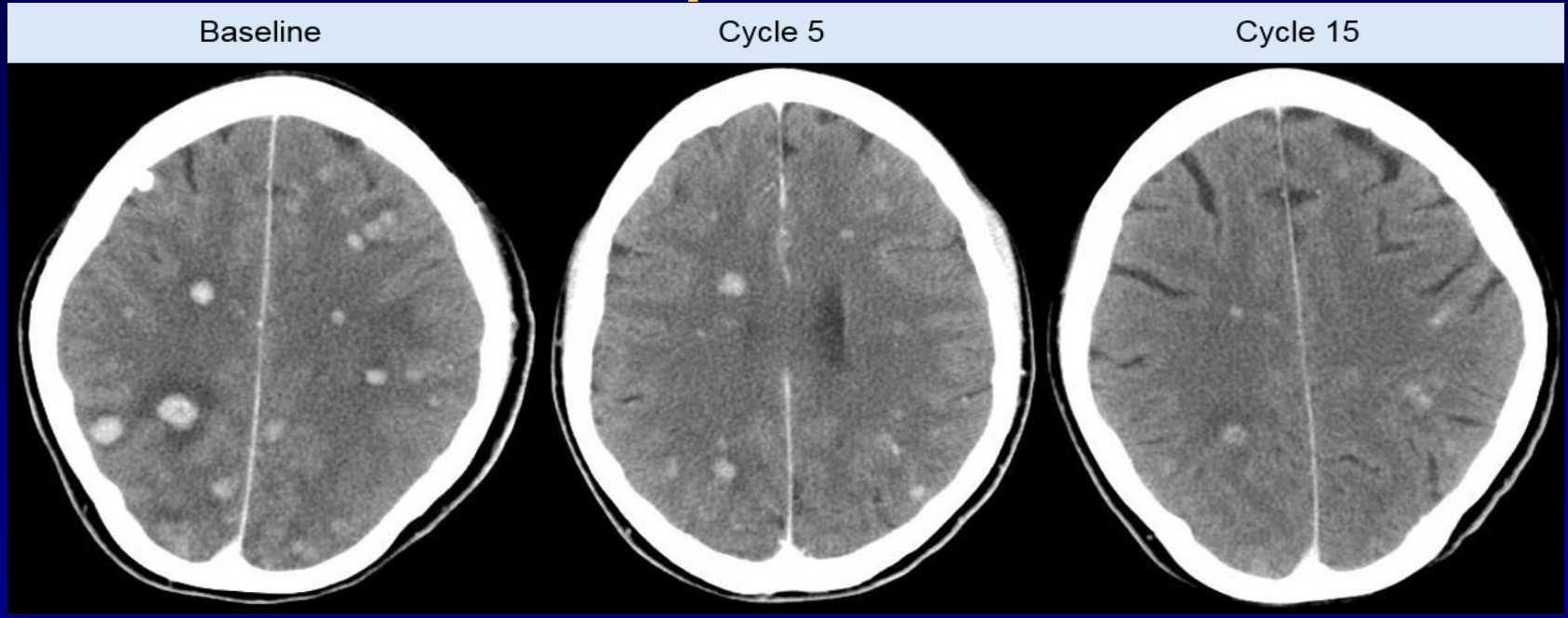
Kim DW et al. Lancet Oncol. 2016

Response rates and PFS in crizotinib refractory and crizotinib naïve patients confirmed in phase 2 studies (ASCEND-2 and ASCEND3)

	ALKi-naïve		ALKi pre-treated	
	ASCEND -1[1]	ASCEND-3[2]	ASCEND-1[1]	ASCEND-2[3]
patients	**83**	**124**	**163**	**140**
Overall Response rate (ORR)	**72%**	**64%**	**56%**	**50%**
Median PFS (M)	**18.4**	**NE***	**6.9**	**7.2**

1. Kim et al Lancet Oncology 2016
2 Felip et al ASCO 2015
3 Mok et al ASCO 2015

CNS activity of Ceritinib in crizotinib pretreated patients



Ceritinib achieved durable intracranial responses in ALK+ NSCLC patients with BM at baseline in both crizotinib-pretreated and ALKi-naïve patients

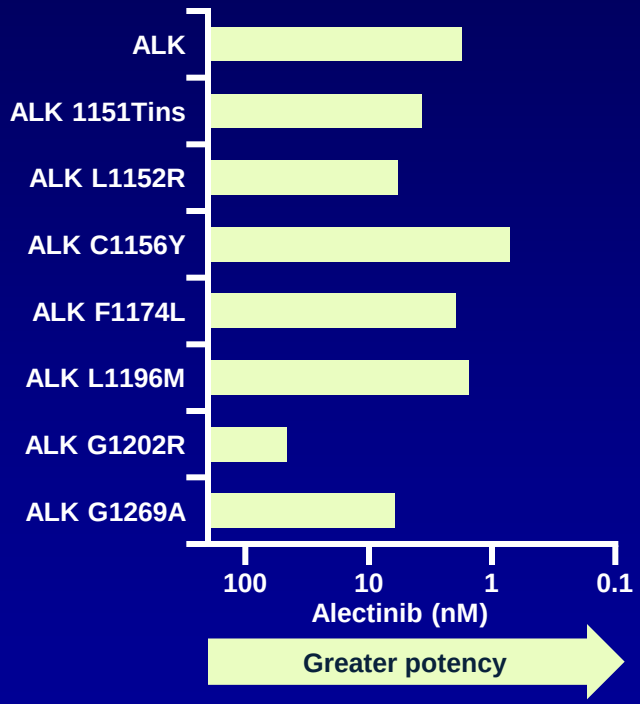
OIRR (95% CI): 13/33 - 39.4% (22.9, 57.9) in crizotinib-pretreated;
10/17 - 58.8% (32.9, 81.6) in ALKi-naïve patients

(DATA from ASCEND -2 and ASCEND -3)

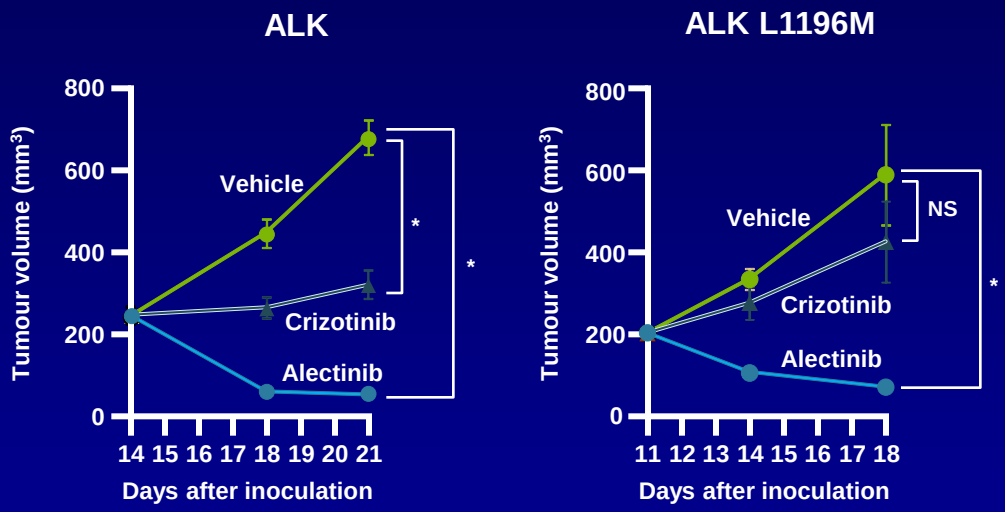
Park K et al, ESMO-Asia 2015.

Alectinib a potent, selective ALK inhbitor active against various ALK mutations

Activity of alectinib against various ALK kinases *in vitro*[1]



Alectinib maintains efficacy against the gatekeeper mutation *ALK L1196M* [§ 2]



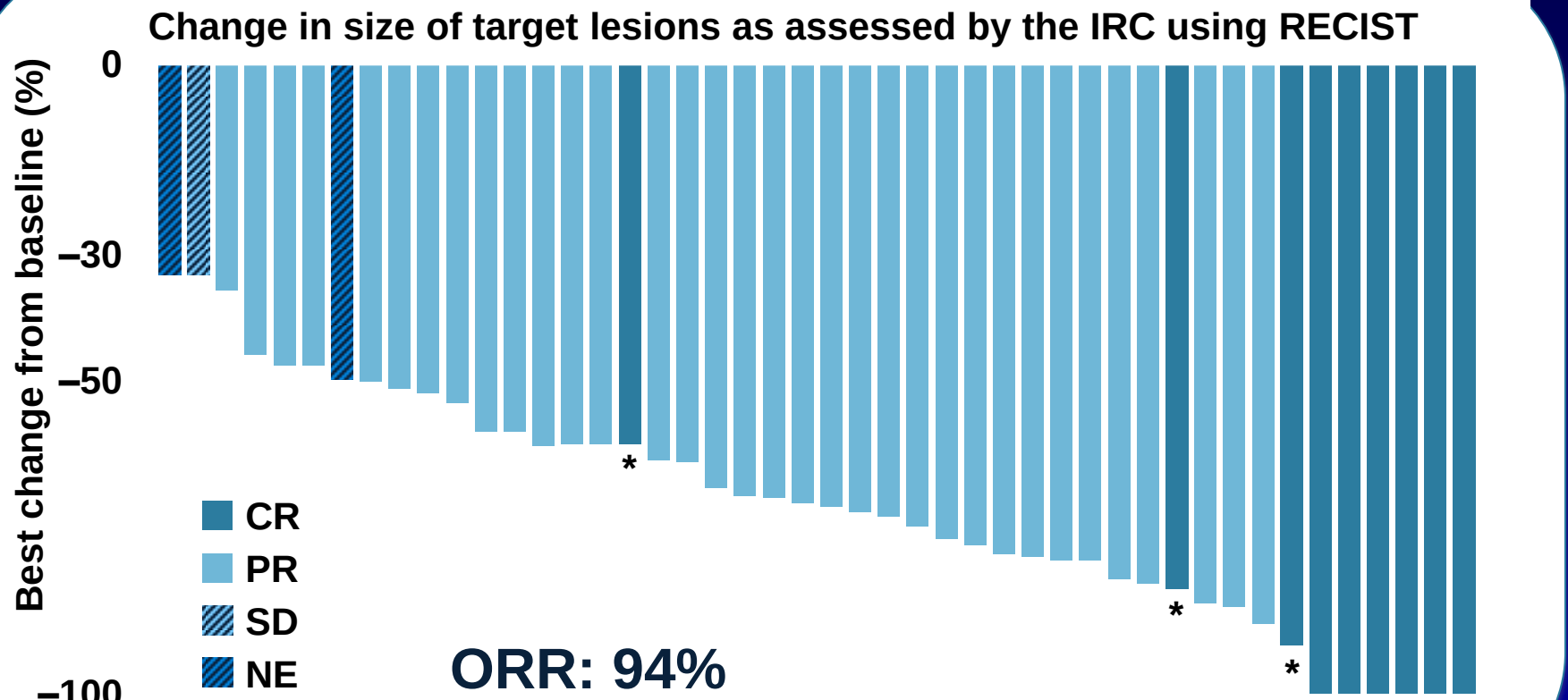
*p<0.001

§ Mouse xenograft models bearing Ba/F3 cells expressing native *EML4-ALK* and *EML4-ALK L1196M*

NS = not significant

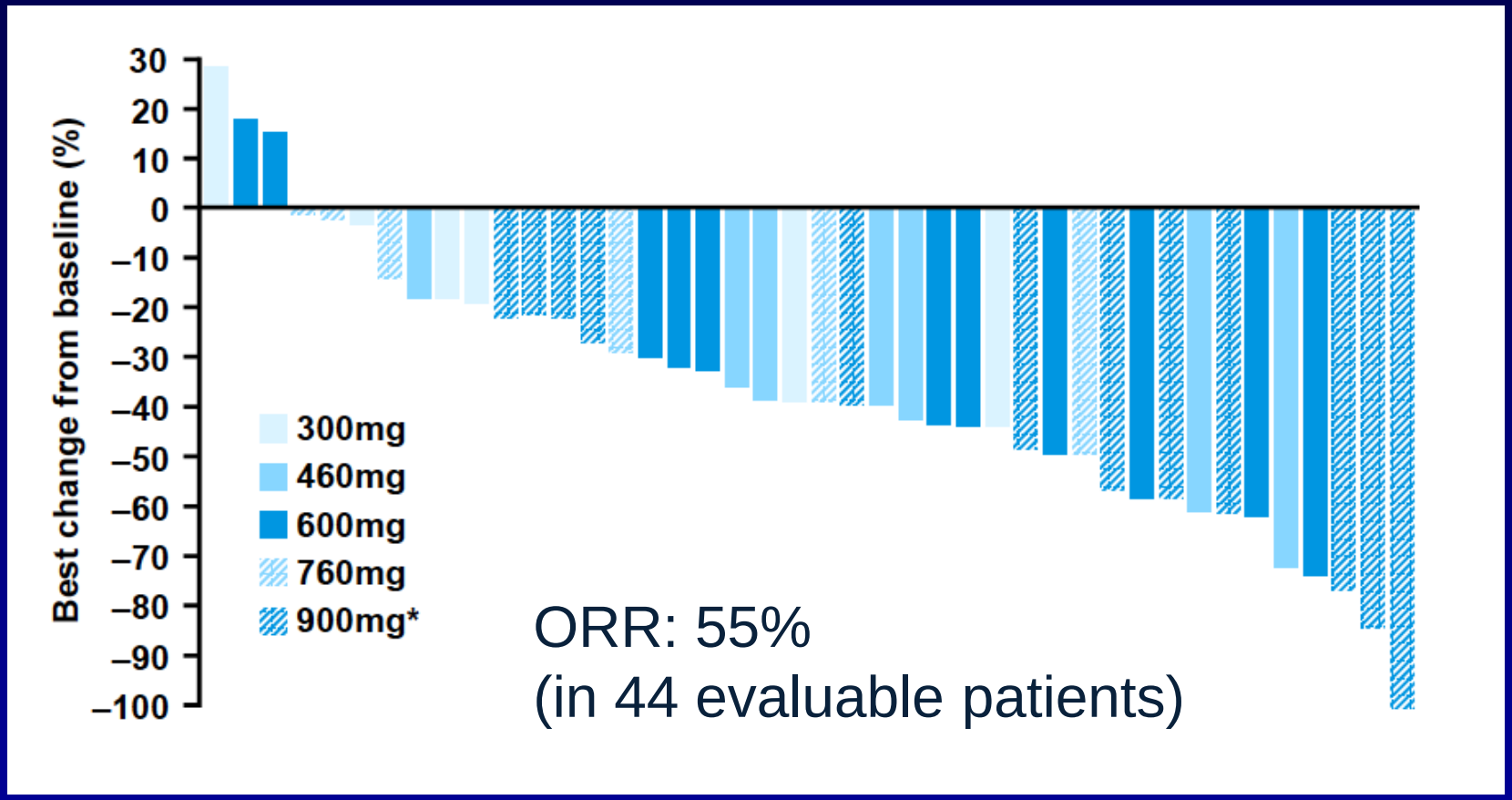
1. Kodama, et al. Cancer Lett 2014
2. Sakamoto, et al. Cancer Cell 2011

Alectinib in crizotinib naïve ALK rearranged NSCLC; Japanese phase 1/2 study(AF001JP) – 300mg bid



Ohe, et al. ASCO 2015

Alectinib in crizotinib refractory ALK rearranged NSCLC: AF-002JG/NP28761 – RP2D 600mg bid



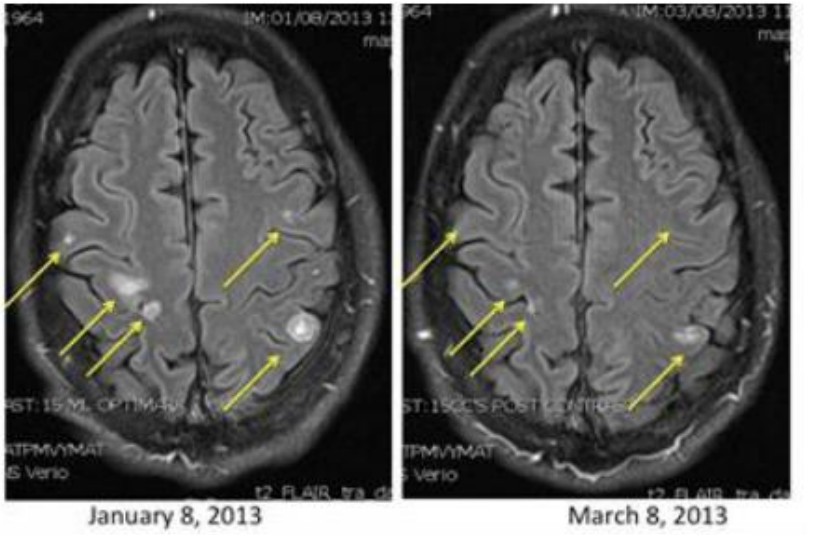
Gadgeel, et al. Lancet Oncol 2014

Alectinib in Crizotinib-refractory ALK positive NSCLC (600mg bid)

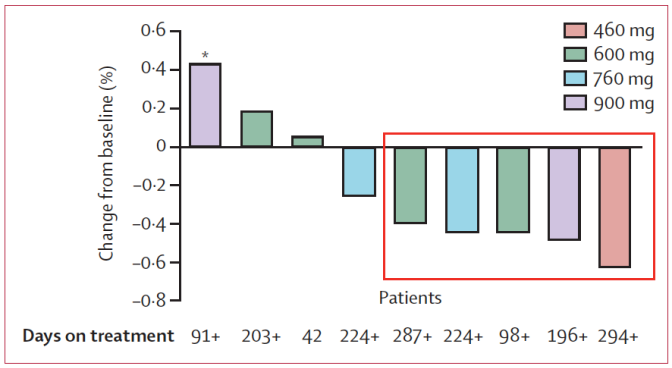
	AF-002JG (phase I)	NP28761 (phase 2)	NP28673 (phase 2)
patients	47	87	138
Countries	N. America	N. America	Global
Response rate	55%	52%	51%
Median PFS (M)	NR	8.1	8.9

Gadgeel, et al. Lancet Oncol 2014
Shaw et al. Lancet Oncology 2015
Ou et al. JCO 2015

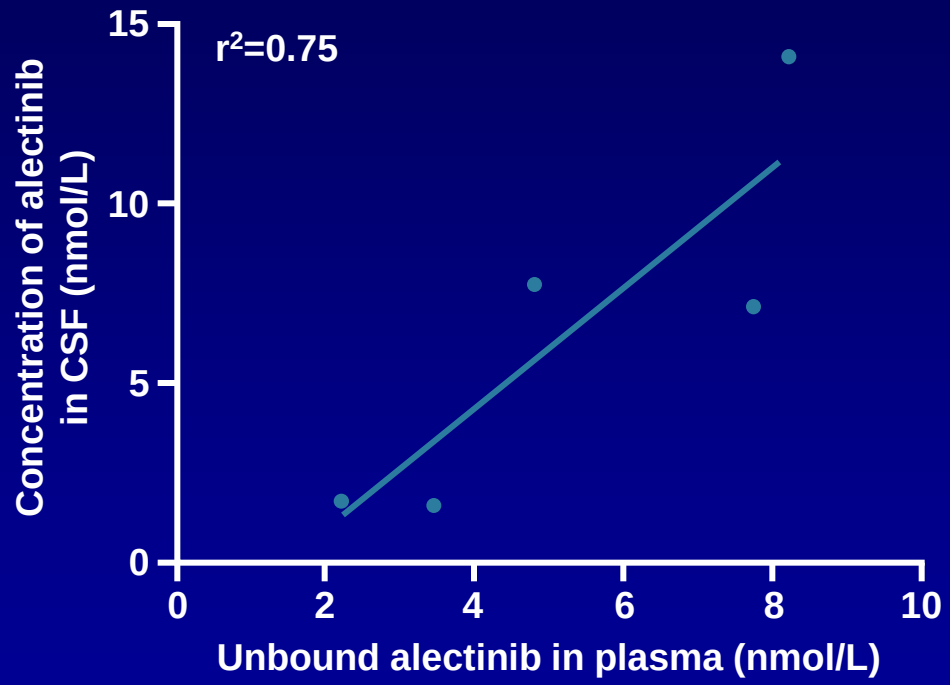
CNS Responses with Alectinib in Crizotinib-Resistant Patients (AF-002JG Study)



IRR: 52%
(confirmed and unconfirmed responses)



Alectinib penetrates into the CNS where it is able to exceed the in-vitro concentration required for ALK inhibition



Ou et al., ESMO 2013; Gadgeel et al., Lancet Onc 15(10):1119-28, 2014

Pooled CNS analysis from phase 2 studies (NP28761 and NP28673)

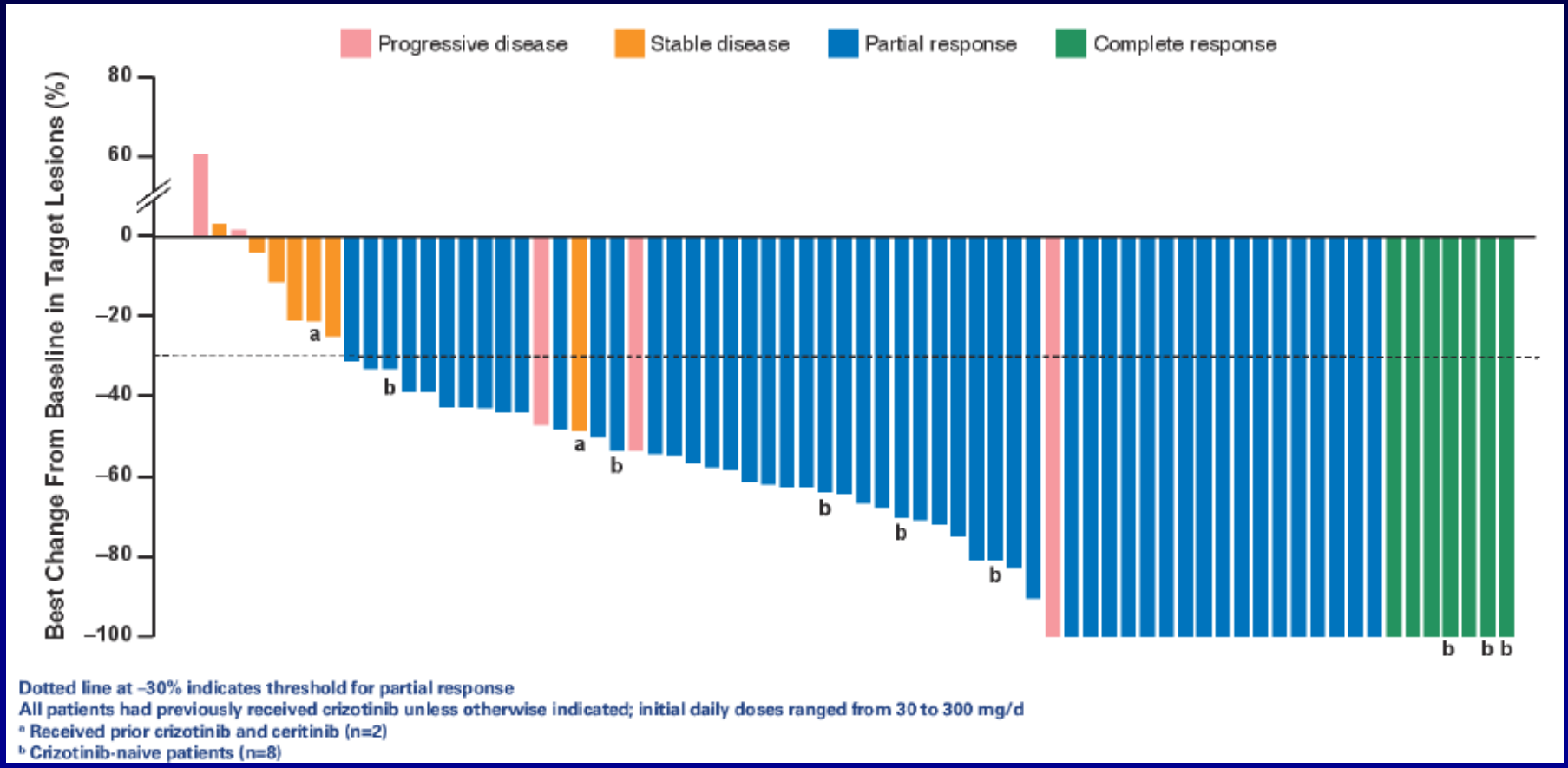
Response, %	Alectinib 600mg BID	
	Measurable CNS disease (n=50)*	Measurable and non-measurable CNS disease (n=136)*
CNS ORR	**64**	**43**
CR	22	27
PR	42	15
SD	26	43
PD	6	9
CNS DCR	**90**	**85**
Median CNS DoR, months	**10.8**	**11.1**

Median duration of follow-up was 12.4 months (range: 4.1–85.7)

CNS CR in 27% of patients with measurable and non-measurable disease at baseline

Gadgeel, et al. WCLC 2015

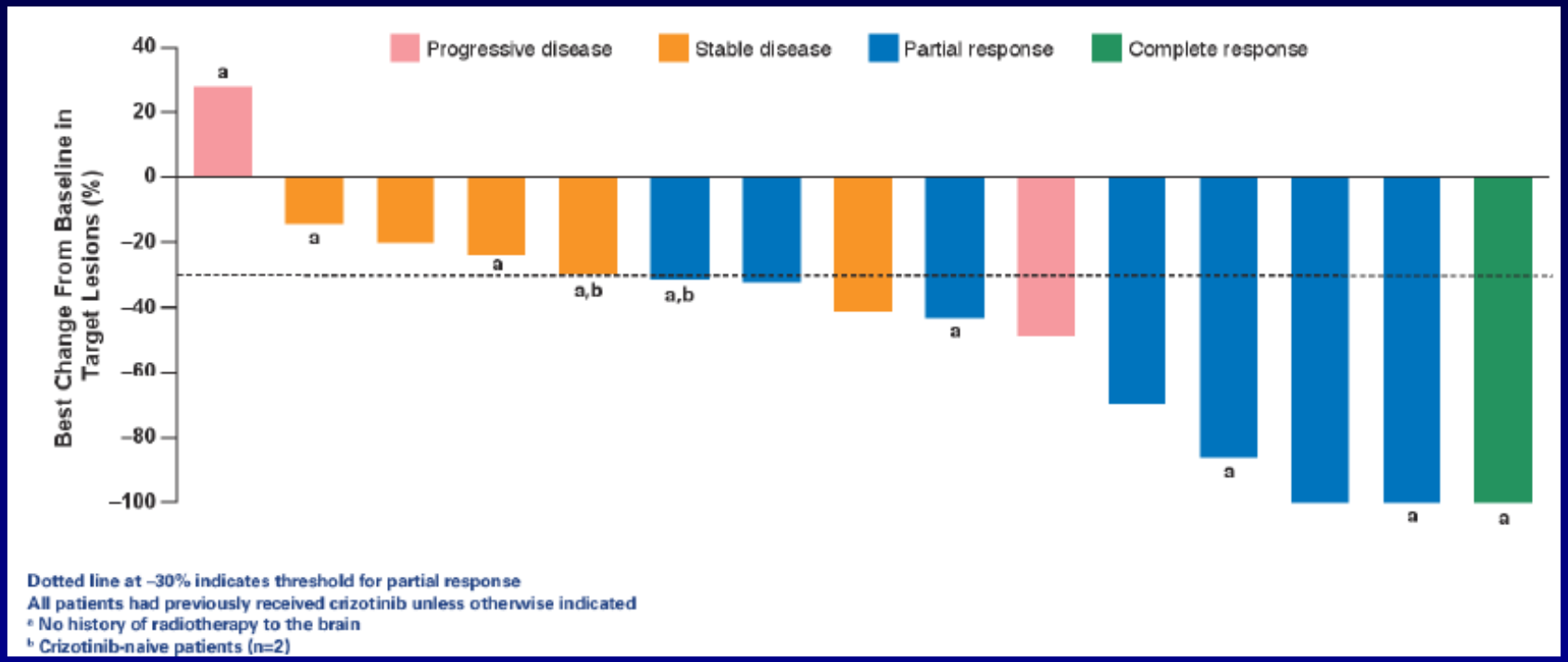
Brigatinib (AP26113) in ALK positive NSCLC



ORR: 50/70 (71%) in pts with prior crizotinib with mPFS 13.4 M
ORR: 8/8 in crizotinib naïve NSCLC

Camidge et al. ASCO 2015

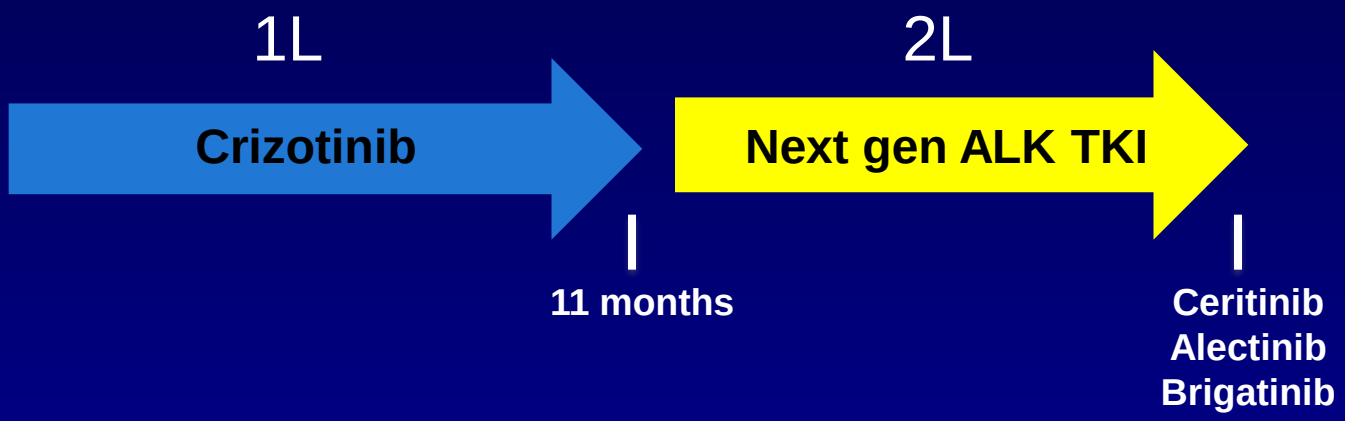
Activity of Brigatinib in CNS disease



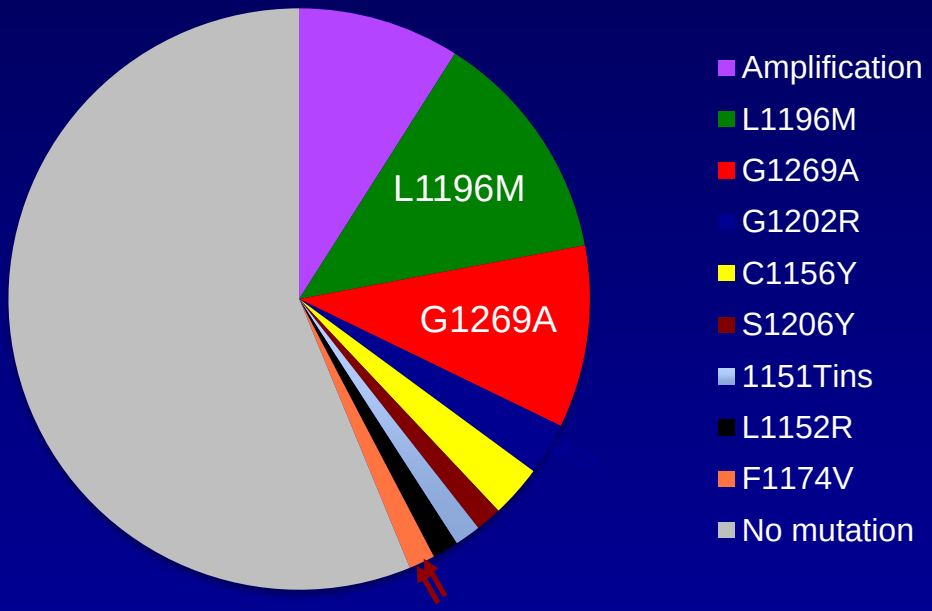
8/15 (53%) of patients with measurable intracranial disease had a partial response

Camidge et al. ASCO 2015

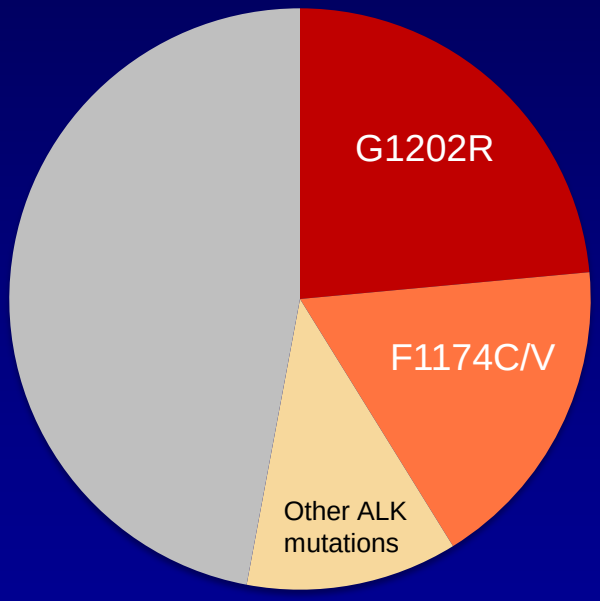
Role for Multiple Sequential ALK Inhibitors



Shifting profile of ALK resistance mutations depending on the ALK inhibitor



Post-Crizotinib
(N=69)



Post-Ceritinib
(N=17)

Alice Shaw, MGH

Lorlatinib is active against all known ALK resistance mutations, including G1202R

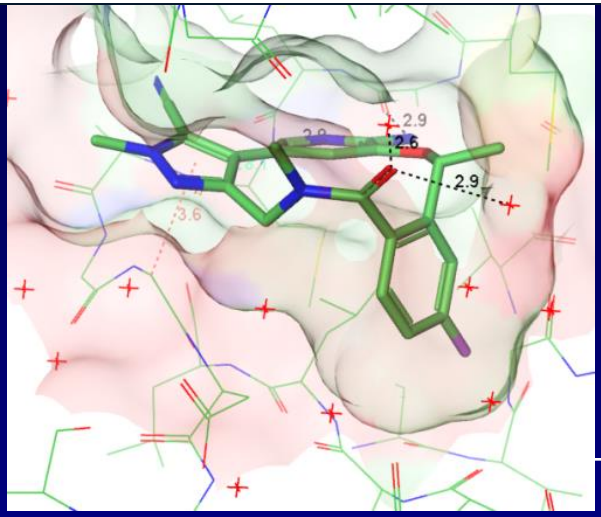
Mutation status	Cell line	Cellular ALK phosphorylation mean IC_{50} (nM) Lorlatinib (PF-06463922)	Crizotinib	Ceritinib (LDK-378)	Alectinib (CH-5424802)
EML4-ALK v1	NIH3T3	1.3	80	NA	62
	BaF3	3.6	90	41	24
EML4-ALK L1196M	NIH3T3	21	843	NA	250
	BaF3	43	1154	70	113
EML4-ALK G1269A	NIH3T3	15	605	NA	NA
	BaF3	80	689	134	112
EML4-ALK G1202R	NIH3T3	77	1003	>1000	>10,000
	BaF3	113	562	549	362
EML4-ALK I1151Tins	NIH3T3	38	1268	1066	1770
	BaF3	50	902	296	126
EML4-ALK S1206Y	NIH3T3	4.2	626	NA	NA
	BaF3	3.2	152	60	29
EML4-ALK C1156Y	NIH3T3	1.6	478	NA	NA
	BaF3	15	406	177	21
EML4-ALK F1174L	NIH3T3	0.2	165	NA	NA
	BaF3	1.0	150	161	26

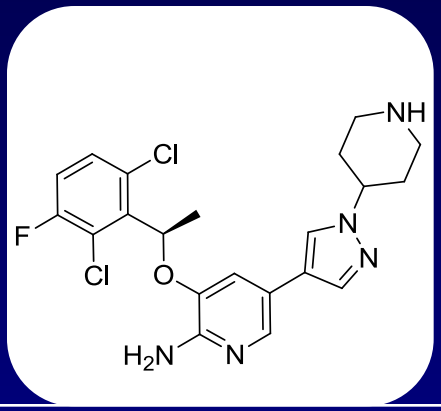
- IC_{50} < 100 nM
- IC_{50} ≥ 100 < 200 nM
- IC_{50} ≥ 200 nM

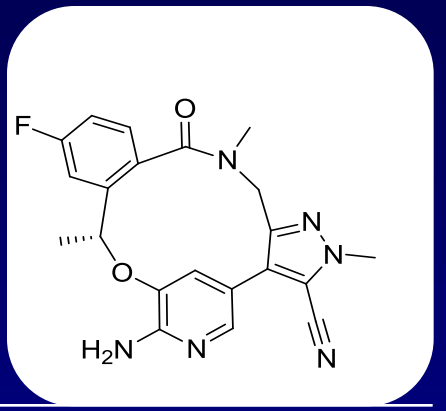
Zou HY, et al. *Proc Natl Acad Sci U S A* 2015;112:3493–3498.

Lorlatinib (PF-06463922) is a potent and CNS penetrant ALK/ROS1 TKI

PF-06463922/L1196M-ALK bound structure



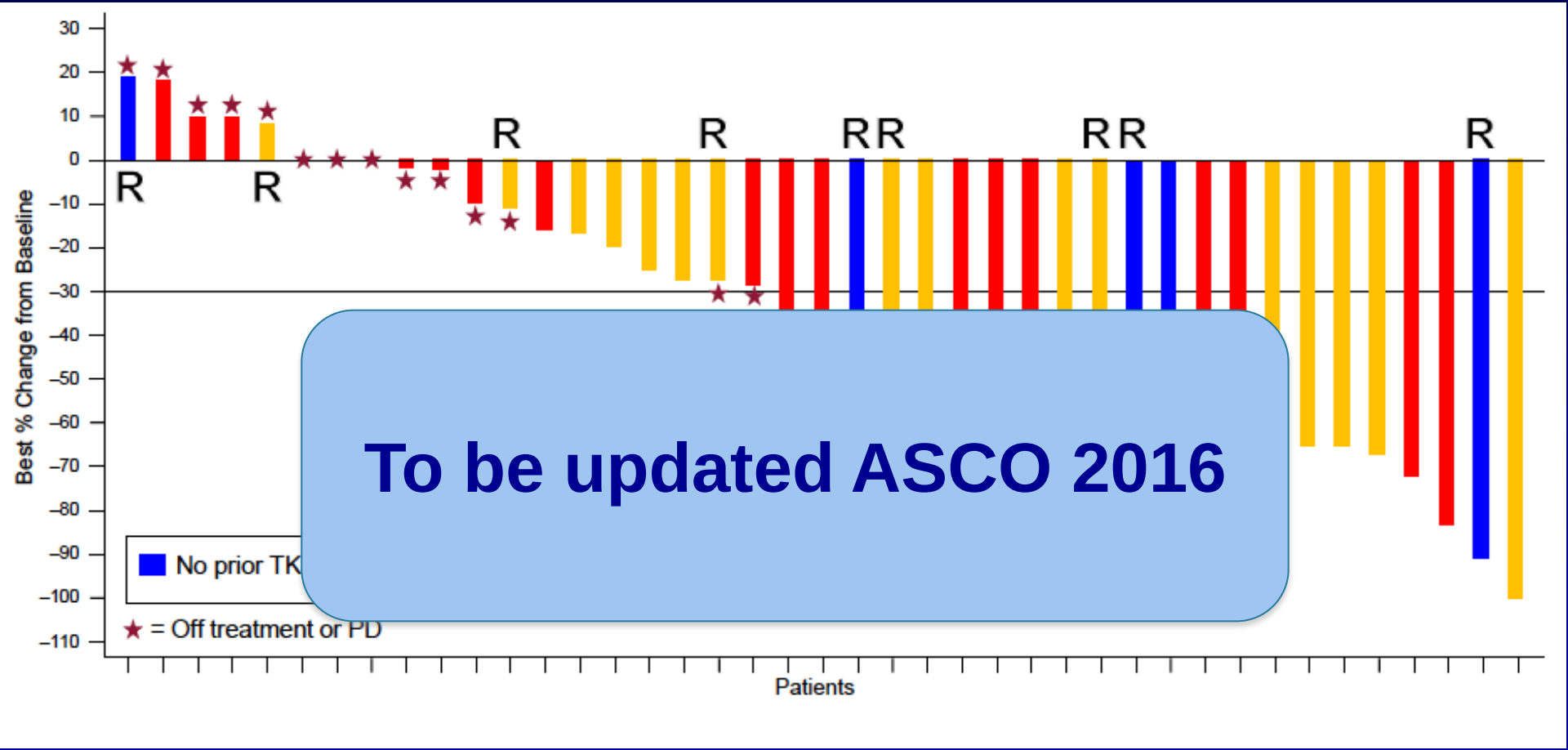




	crizotinib		PF-06463922
ALK WT NIH3T3 IC_{50} (nM)	**80**	53x	**1.5**
ALK L1196M NIH3T3 IC_{50} (nM)	**843**	40x	**21**
ROS1-CD74 IC_{50} (nM)	**11**	45x	**0.24**
MDR BA/AB	**45**		**1.5**
CSF or free brain:free plasma (rodent)	--		0.23 – 0.33
Log D	2.0		2.3

Zou HY, et al. *Proc Natl Acad Sci U S A* 2015;112:3493–3498.

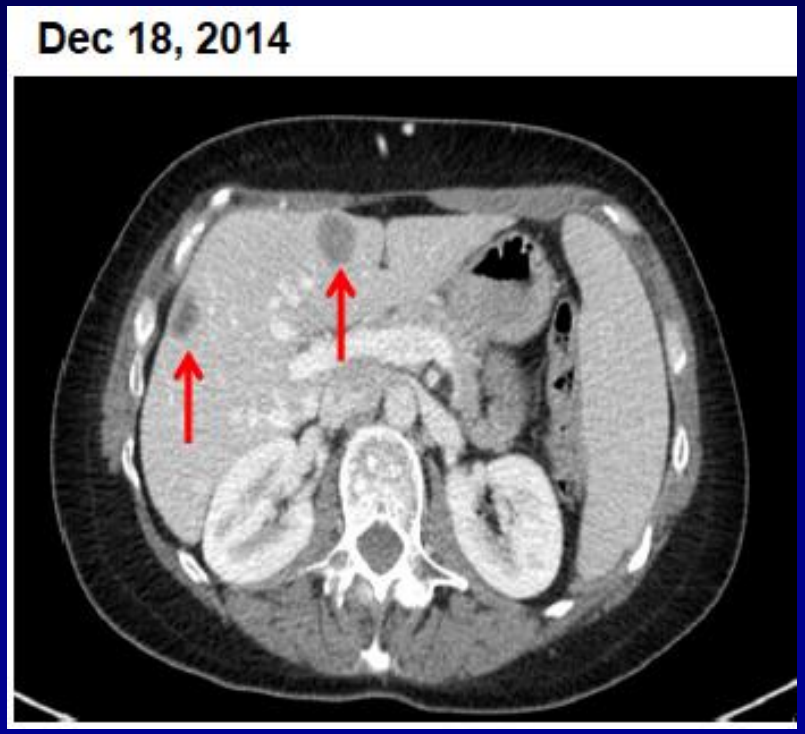
Clinical activity of Lorlatinib in advanced ALK+ (and ROS1+) NSCLC

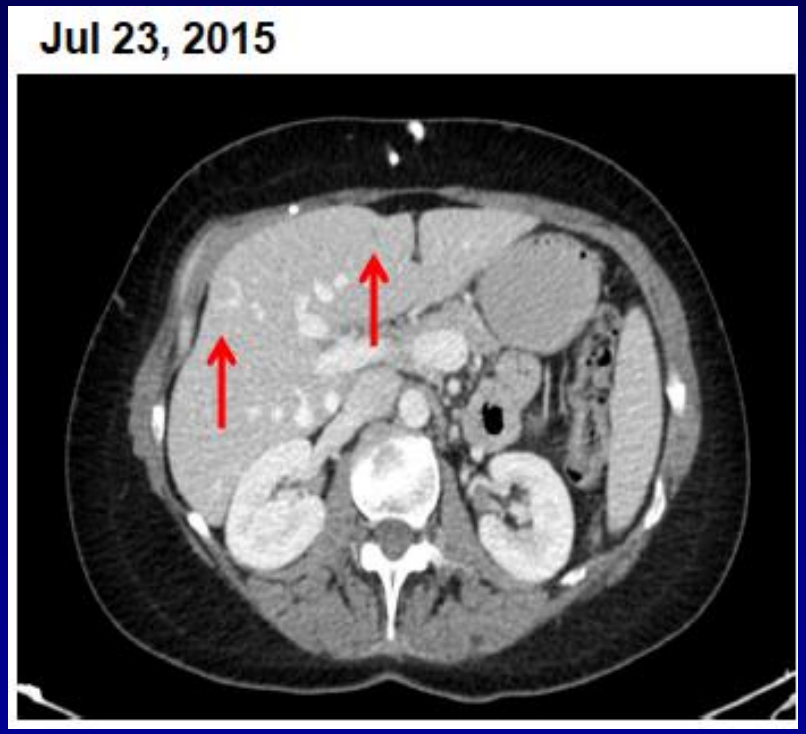


To be updated ASCO 2016

Bauer WCLC 2015

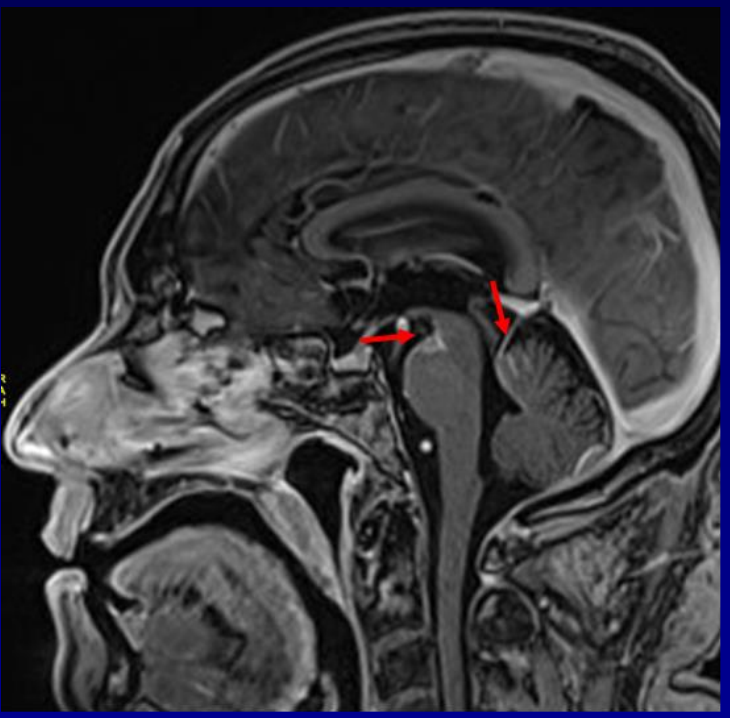
Activity of Lorlatinib in a patient with ALK G1202R mutation



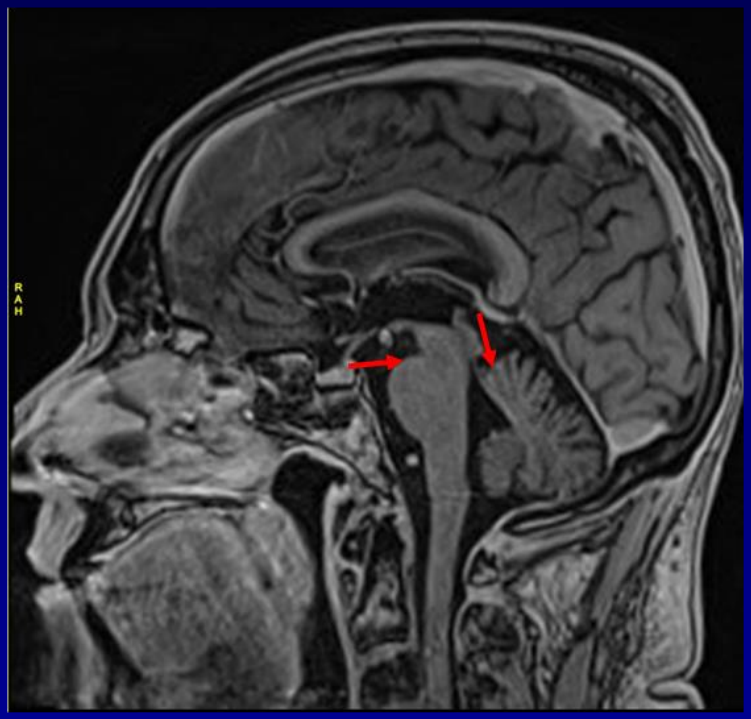


Partial Response to Lorlatinib in a 40 y.o. woman with ALK+ NSCLC (G1202R+) with prior crizotinib and Alectinib treatment

Resolution of leptomeningeal disease arising after 3 prior ALK TKIs



June 10, 2015



July 26, 2015

ALK+ NSCLC
Post-Crizotinib,
Ceritinib, Alectinib

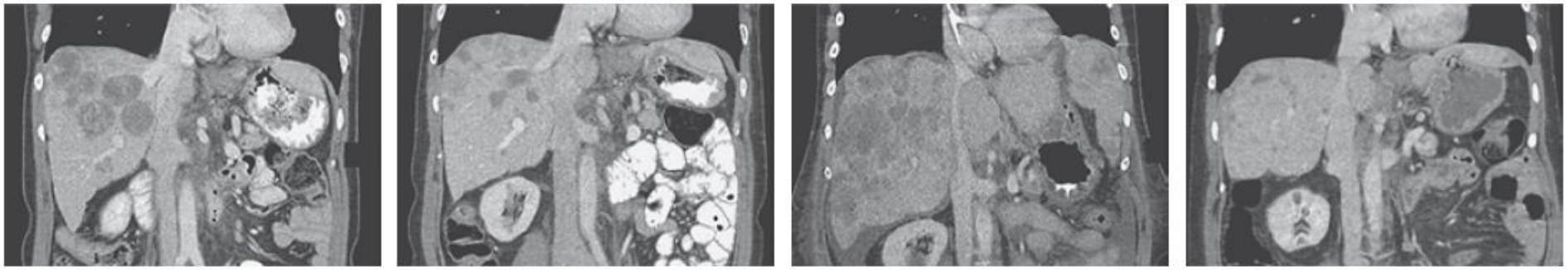
Start Lorlatinib
(PF-06463922)
at 100 mg QD
on June 18 2015

Bauer TM, et al. WCLC 2015 (Abstr. 295).

Resistance to Lorlatinib by the ALK mutation L1198F can result in resensitisation to crizotinib

Acquired Resistance to crizotinib mediated by C1156Y mutation

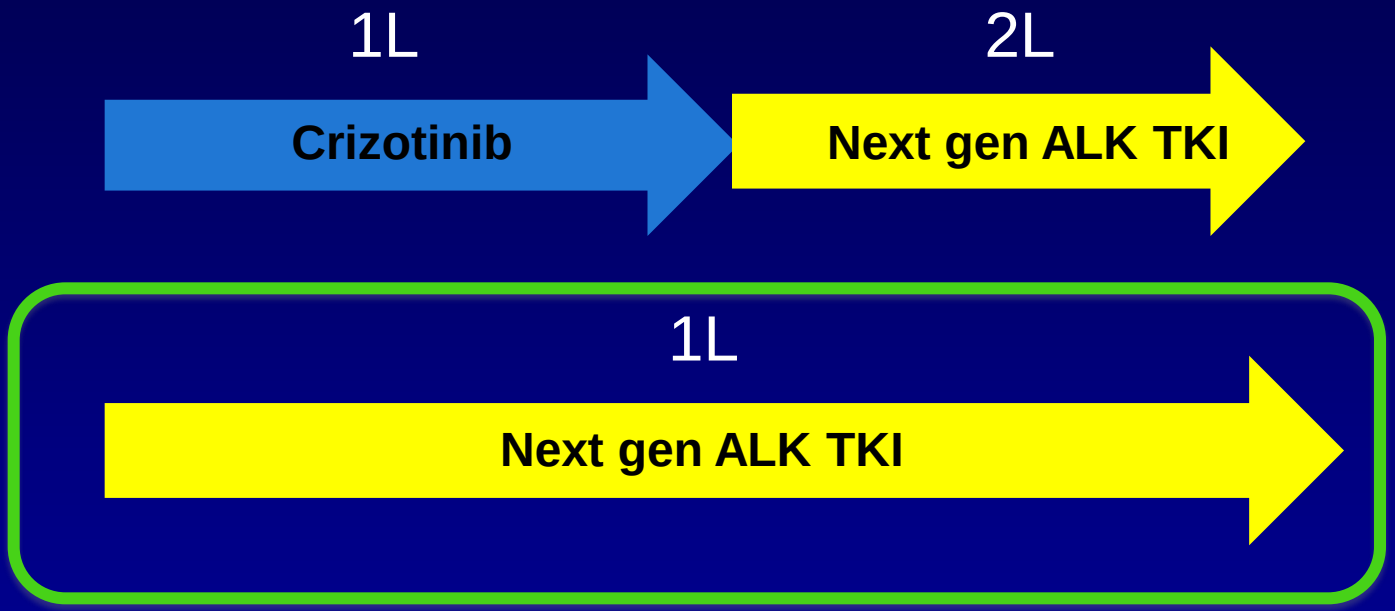
Acquired Resistance to Loratinib with C1156Y mutation and L1198F mutations



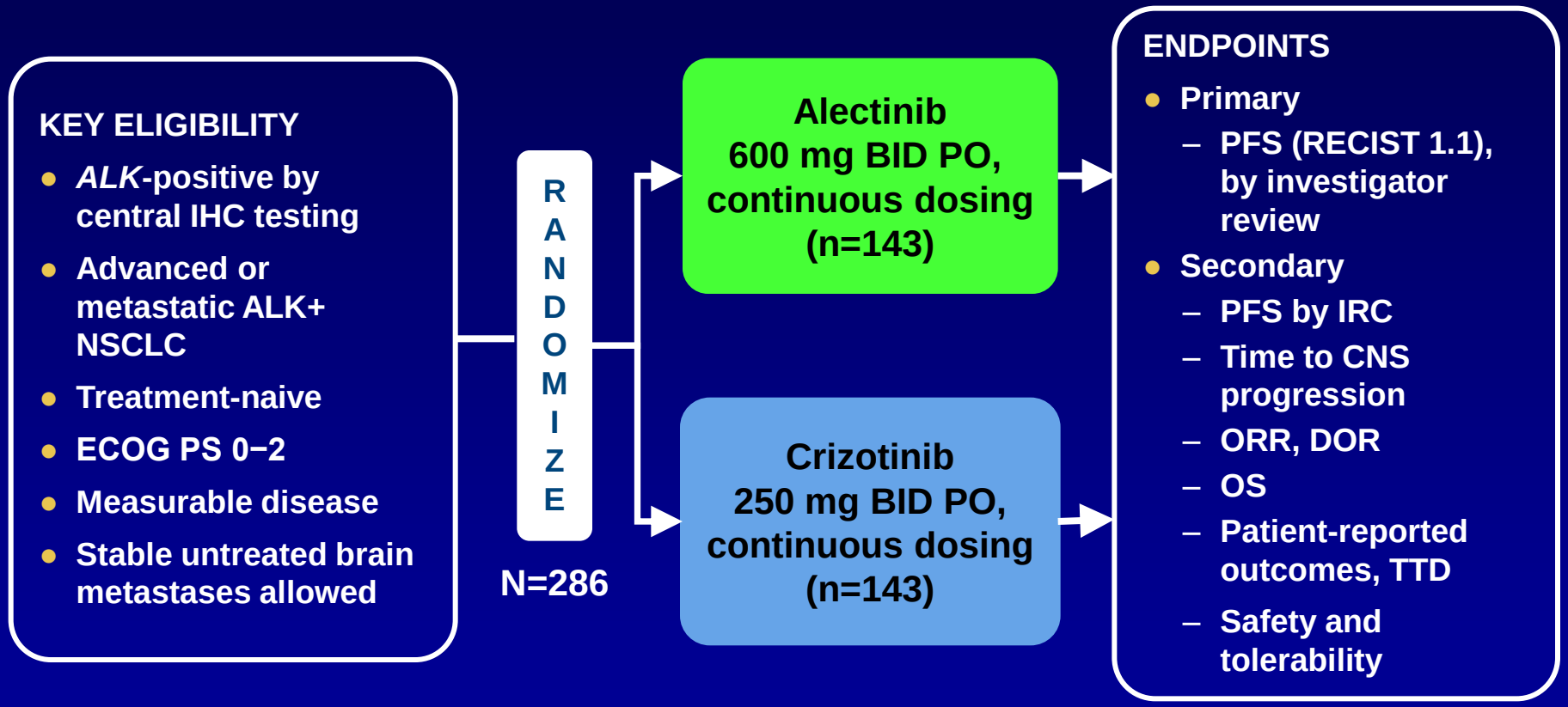
Before Lorlatinib | Response to Lorlatinib | Resistance to Lorlatinib | Response to Crizotinib

Shaw NEJM 2016

What is Optimal Therapeutic strategy for Advanced ALK+ NSCLC?

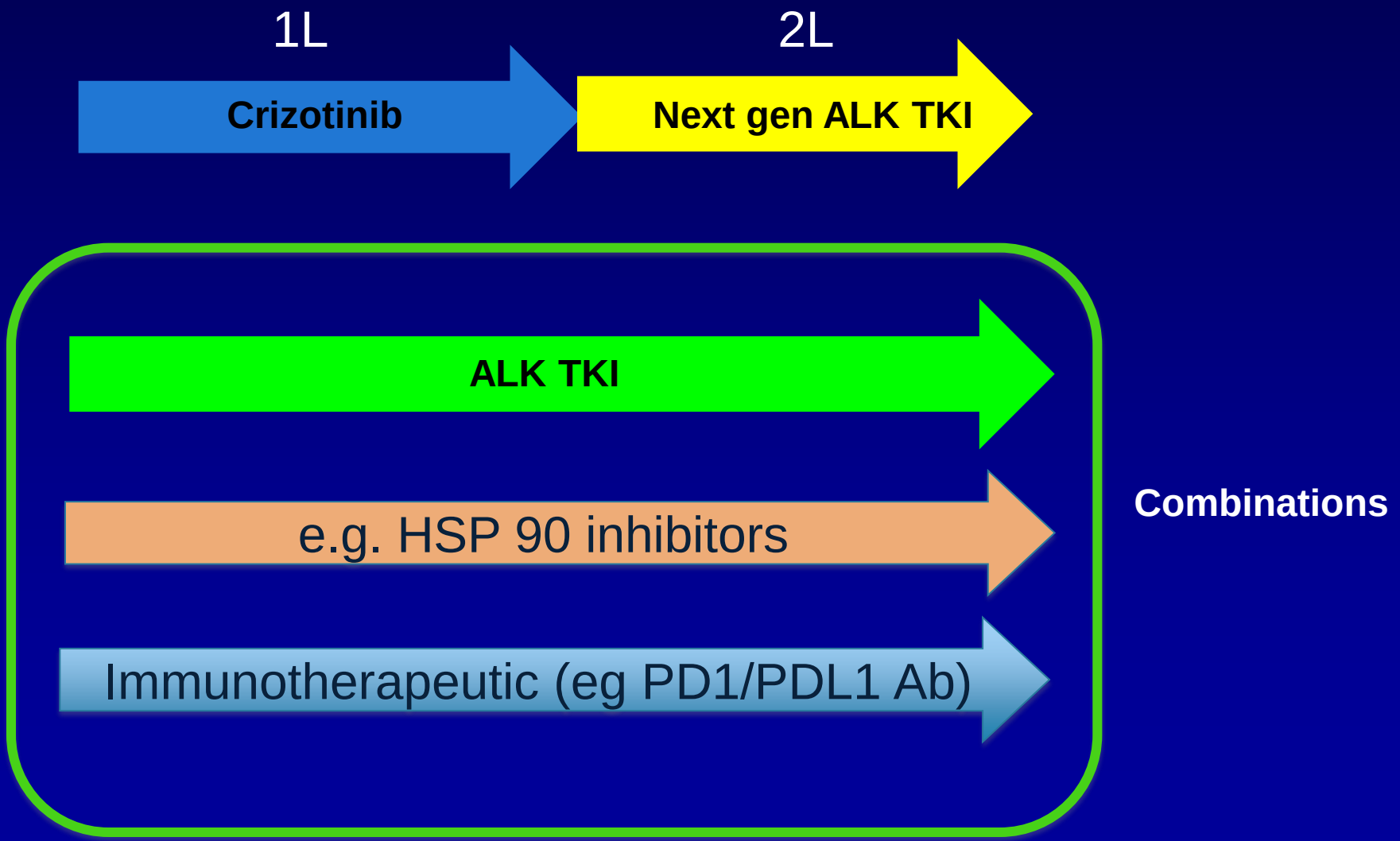


First-Line Phase 3 Studies: ALEX: Alectinib *vs* Crizotinib



First-Line phase 3 studies: Ceritinib vs. Chemotherapy
Brigatinib vs. crizotinib

What is Optimal Therapeutic strategy for Advanced ALK+ NSCLC?

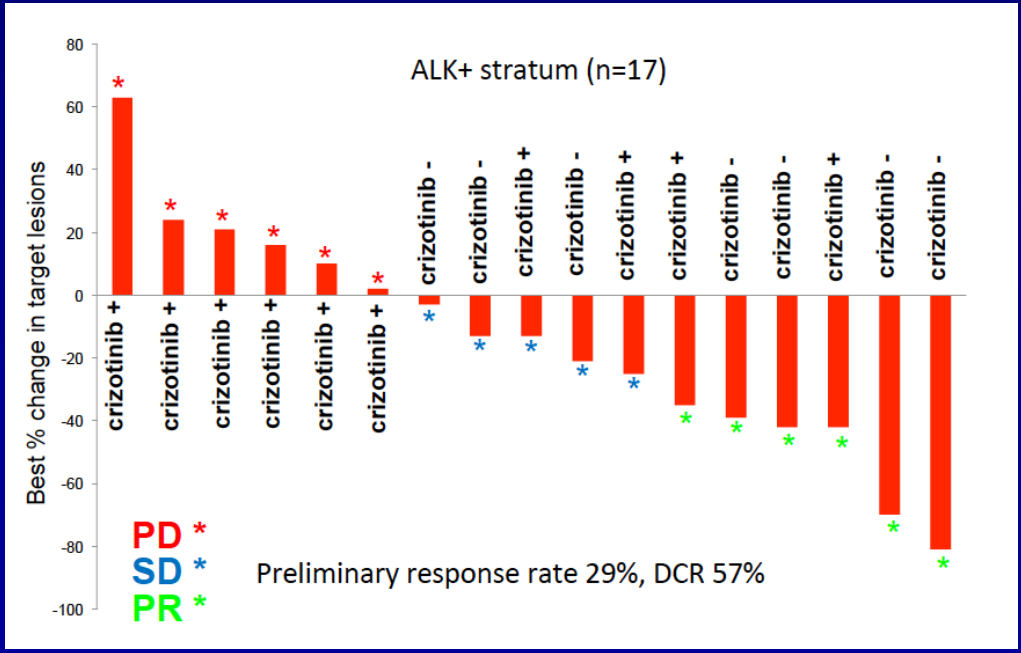


HSP 90 inhibitors in ALK + NSCLC

NPM-ALK and EML4ALK are client proteins for HSP90

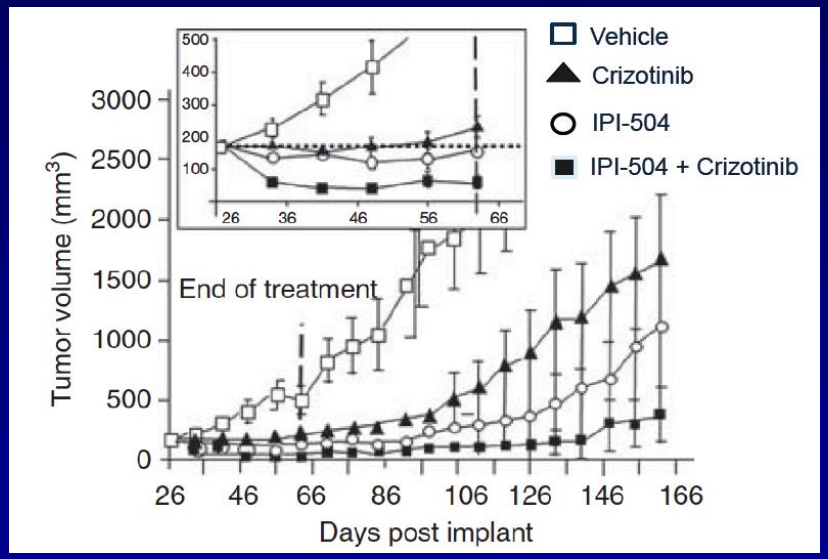
Preclinical treatment with HSP90 inhibitors results in rapid degradation of ALK protein and antitumour activity in ALK driven tumor models

Modest activity has been observed in phase II studies of single agents ganatespib, IPI-504 and AUY-922 in ALK+ NSCLC



AUY922 in ALK+ NSCLC

Combinations of ALK inhibitors with HSP90 inhibitors



ALK inhibitor	HSP90 inhibitor	Trial number
Crizotinib	Ganatespib	NCT01579994
Crizotinib	AT13387	NCT01712217
Ceritinib	AUY922	NCT01772797

Activity of IPI-504 and crizotinib alone and in combination in H3122 xenografts

Normant E, et al. *Oncogene.* 2011;30:2581–2586

Combinations of ALK TKIs with Immunotherapy: PDL1 + TIL expression in ALK+NSCLC

	ALK-Rearranged		
	Pre-Crizotinib (N=21)	**Post-Crizotinib (N=14)**	***P*-value[a]**
PD-L1 ≥ 50%[b]	7 (33%)	2 (14%)	0.552
PD-L1 ≥ 5%	11 (52%)	3 (21%)	0.284
CD8+ TILs[b] 0 1+ 2+ 3+	 3 (21%) 3 (21%) 7 (50%) 1 (7%)	 3 (25%) 8 (67%) 1 (8%) 0 (0%)	0.500
PD-L1 ≥ 50% and High CD8+ TILs (gr 2-3+)	1/14 (7%)	0/12 (0%)	ND[c]
PD-L1 ≥ 5% and High CD8+ TILs (gr 2-3+)	4/14 (29%)	0/12 (0%)	ND[c]

Gainor ASCO 2015

Combinations of ALK TKIs with Immunotherapy

ALK Inhibitor	PD1/PDL1 inhibitor
Ceritinib	Nivolumab
Alectinib	Atezolizumab
Crizotinib	Pembrolizumab
Lorlatinib	Avelumab

www.clinicaltrials.gov

Conclusions

Clinical trials with newer Generation ALK inhibitors e.g. Ceritinib, Alectinib, and Brigatinib show significant activity and allow sequential therapy in crizotinib-refractory patients in whom many tumours remain ALK dependent.

Optimal sequencing of ALK inhibitors; how to chose between drugs; and how to combine these agents with other agents e.g. immunotherapy remain to be established.