Advances in ALK (+ve) mNSCLC

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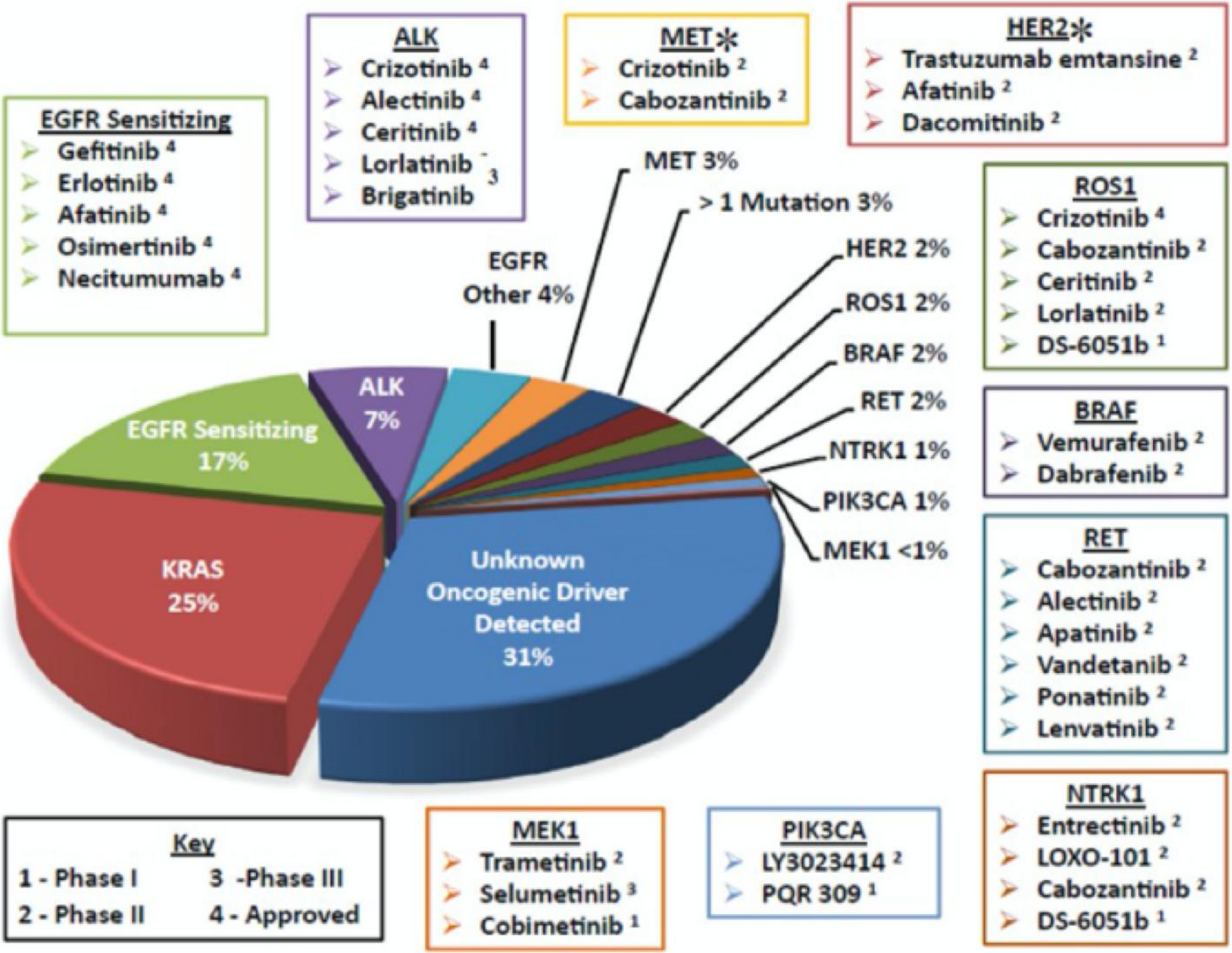
Disclosures

Consultant: BI, BMS, MSD, Roche


ALK
Crizotinib 4
Alectinib 4
Ceritinib 4
Lorlatinib 3
Brigatinib
MET*
Crizotinib 2
Cabozantinib 2
HER2*
Trastuzumab emtansine 2
Afatinib 2
Dacomitinib 2
EGFR Sensitizing
Gefitinib 4
Erlotinib 4
Afatinib 4
Osimertinib 4
Necitumumab 4
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
EGFR Other 4%
ALK 7%
EGFR Sensitizing 17%
KRAS 25%
Unknown Oncogenic Driver Detected 31%
ROS1
Crizotinib 4
Cabozantinib 2
Ceritinib 2
Lorlatinib 2
DS-6051b 1
BRAF
Vemurafenib 2
Dabrafenib 2
RET
Cabozantinib 2
Alectinib 2
Apatinib 2
Vandetanib 2
Ponatinib 2
Lenvatinib 2
Key
1 - Phase I
2 - Phase II
3 -Phase III
4 - Approved
MEK1
Trametinib 2
Selumetinib 3
Cobimetinib 1
PIK3CA
LY3023414 2
PQR 309 1
NTRK1
Entrectinib 2
LOXO-101 2
Cabozantinib 2
DS-6051b 1

ALK+ disease is a distinct subset of NSCLC

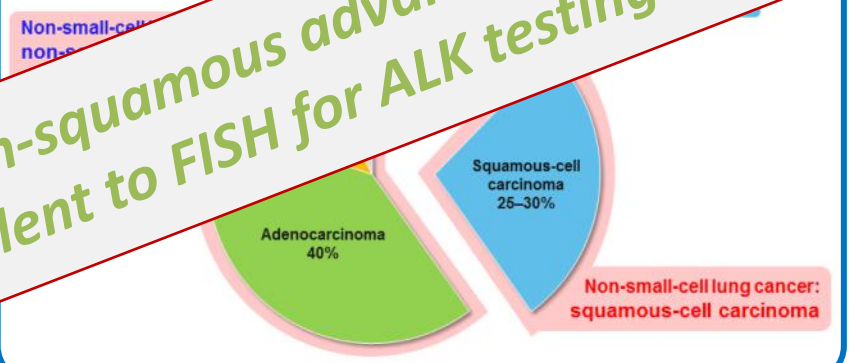
ALK+ disease occurs in ~5% of patients with advanced NSCLC[1–5]

More than 75,000 patients p… year diagnosed[7]

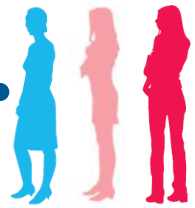
The incidence of … is …

- P…
- …mokers[2,8]
- … patients[2,8]
- Females[2]
- Patients who do not have *EGFR* or *KRAS* mutations[2,8]

Histological classificati… can…



ESMO guidelines: test **all** non-squamous advanced NSCLC IHC is considered equivalent to FISH for ALK testing



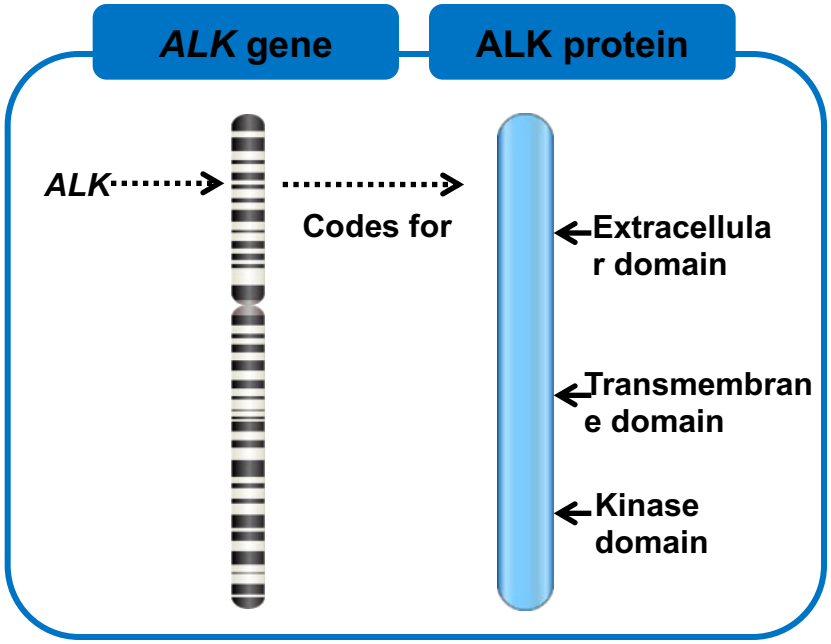
Clinical characteristics do not always predict the presence of *ALK*+ NSCLC[9,10]

ALK = anaplastic lymphoma kinase
EGFR = epidermal growth factor receptor
NSCLC = non-small cell lung cancer

1. Dearden, et al. Ann Oncol 2013; 2. Gridelli, et al. Cancer Treat Rev 2014
3. Hallberg, et al. Nat Rev Cancer 2013; 4. Rikova, et al. Cell 2007
5. Soda, et al. Nature 2007; 6. American Cancer Society 2013
7. Torre, et al. CA Cancer J Clin 2015; 8. Perez, et al. Lung Cancer 2014
9. Lindeman, et al. J Thorac Oncol 2013; 10. Leighl, et al. J Clin Oncol 2014

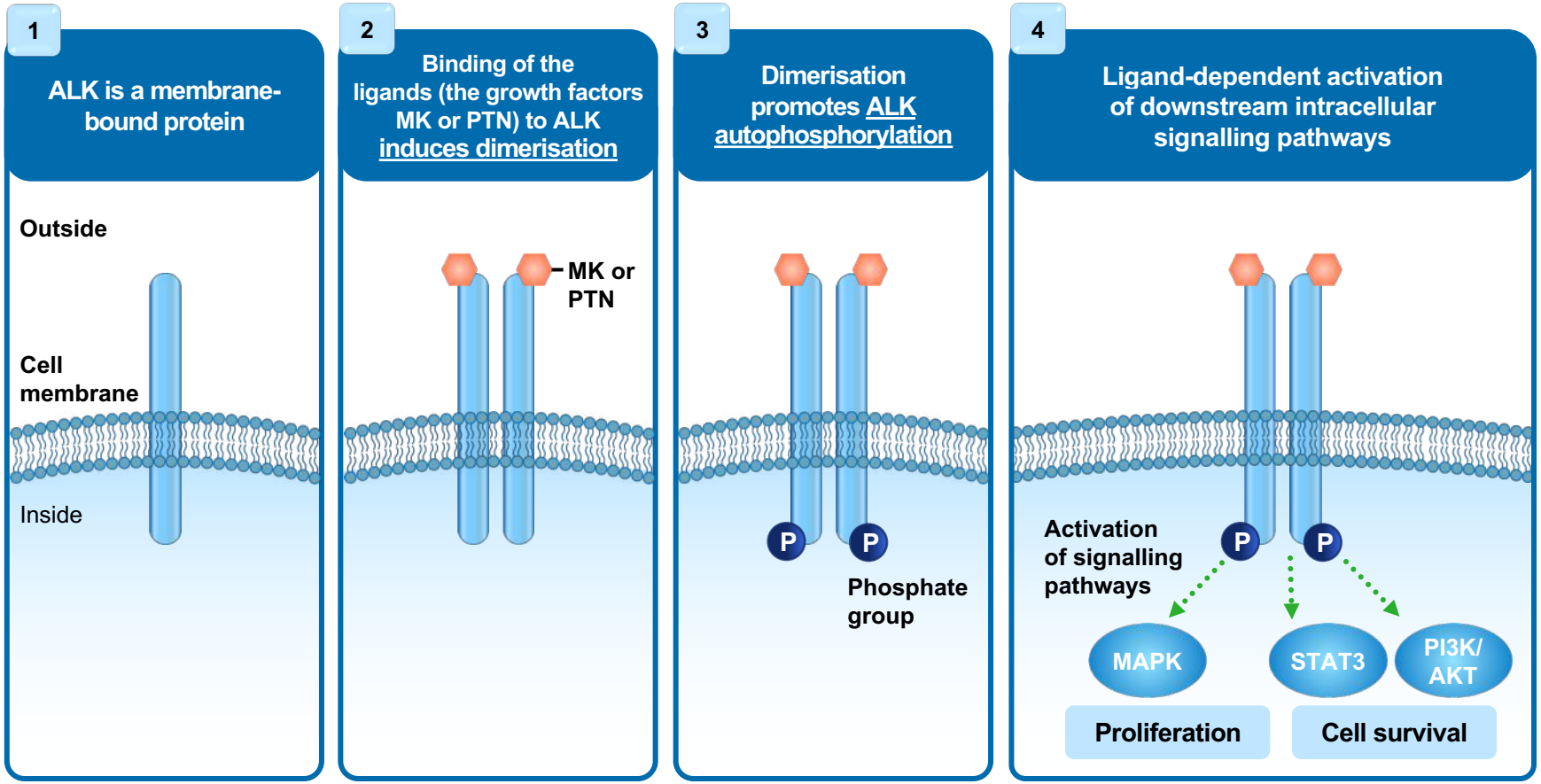
ALK signalling is involved in regulating the development of the CNS

- ✓ The anaplastic lymphoma kinase (*ALK*) gene is localised on chromosome 2 and was first discovered as part of a chromosomal rearrangement in anaplastic large-cell non-Hodgkin's lymphoma[1]
- ✓ ALK codes for a receptor tyrosine kinase, a member of the insulin receptor subfamily. *ALK* is primarily expressed in the developing CNS, and is also expressed to a lesser extent in the adult CNS.[1–3]
- ✓ The expression pattern of ALK, together with data from model organisms, suggest that ALK plays a role in the development of the CNS[2,4]



1. Morris, et al. Science 1994; 2. Iwahara, et al. Oncogene 1997
3. Pulford, et al. Blood 1997; 4. Hallberg, et al. Nat Rev Cancer 2013

Wild-type ALK activation is ligand-dependent



Ligand-dependent activation of ALK triggers intracellular signalling pathways involved in regulating proliferation and cell survival

MK = midkine
PTN = pleiotrophin

Iwahara, et al. Oncogene 1997; Morris, et al. Oncogene 1997
Bai, et al. Mol Cell Biol 1998; Fujimoto, et al. Proc Natl Acad Sci 1996; Bai, et al. Blood 2000; Zamo, et al. Oncogene 2002
Roskoski. Pharmacol Res 2013; Stoica, et al. J Biol Chem 2001; Stoica, et al. J Biol Chem 2002

EML4-ALK is the most common ALK fusion protein

ALK rearrangements can occur between *ALK* and several different genes, with the resulting proteins being potential therapeutic targets. The most common rearrangement is between *EML4* and *ALK* to produce the EML4-ALK fusion protein

Current evidence suggests all *ALK* rearrangements respond equally to ALK inhibitors

The breakpoint within *ALK* occurs at **exon 20** (A20)

The breakpoint within *EML4* can differ, thus generating **different variants** of the fusion protein

Breakpoints within EML4

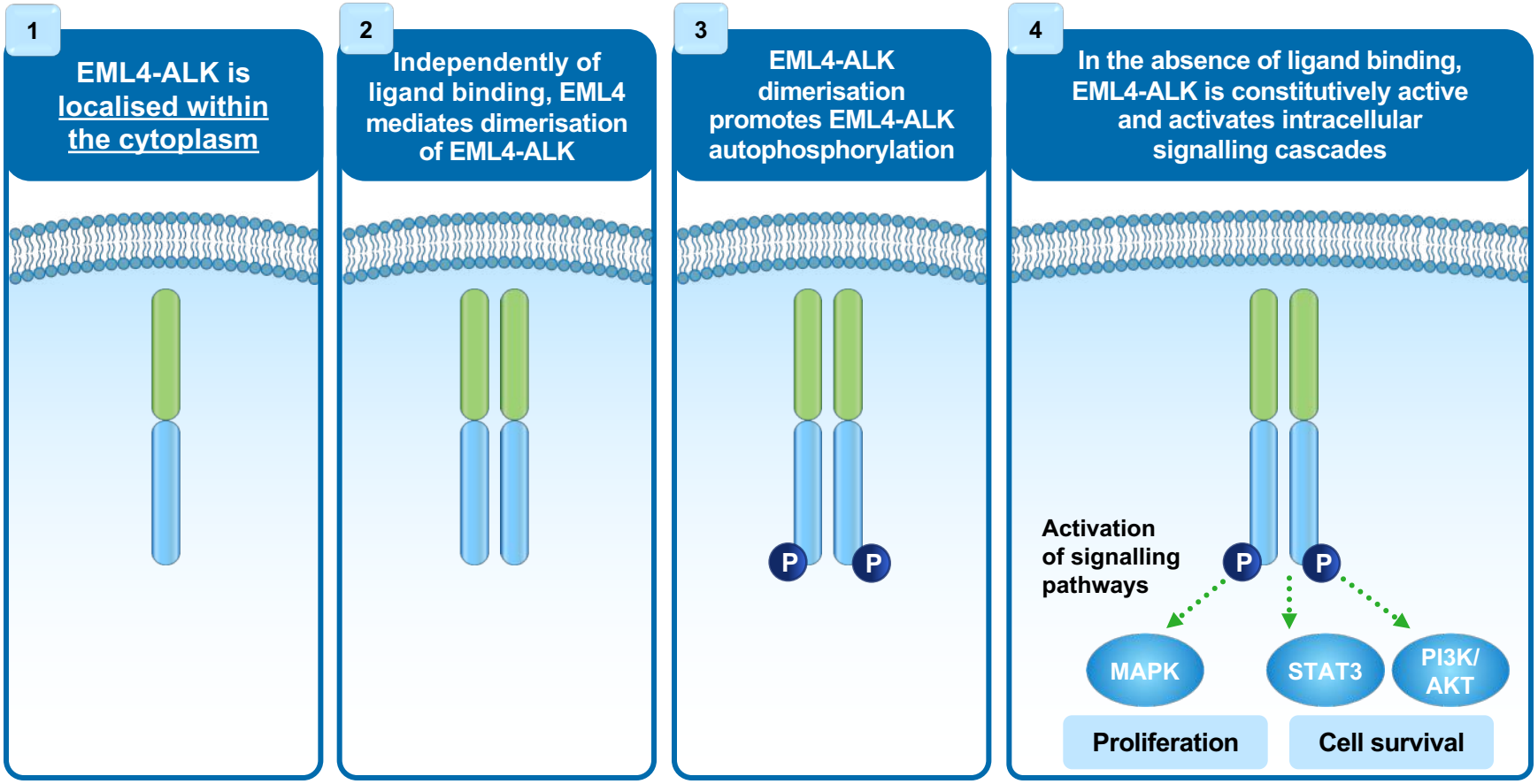
Summary of common variants of the ALK fusion protein

Fusion protein	Variant	Frequency in *ALK+* NSCLC
EML4–ALK	E13:A20	33%
EML4–ALK	E6a/b:A20	29%
EML4–ALK	E20:A20	9%
EML4–ALK	E14:A20	3%
EML4–ALK	E18:A20	2%
EML4–ALK	E15:A20	2%
EML4–ALK	E2:A20	2%
EML4–ALK	E17:A20	1%
KIF5B–ALK		0.5%
TFG–ALK		Unknown %
KLC1–ALK		
PTPN3–ALK		
STRN–ALK		

Exon A20

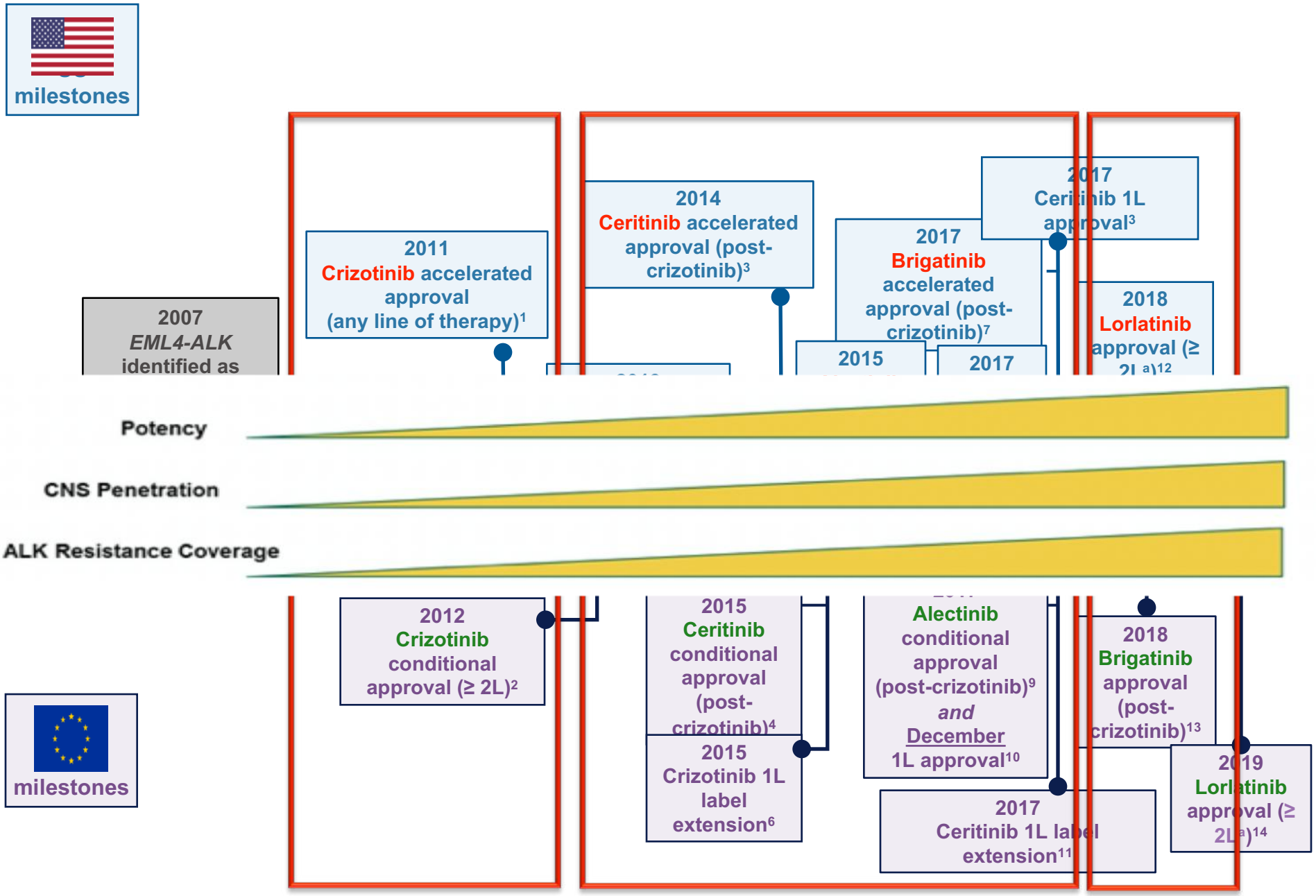
Soda, et al. Nature 2007; Rikova, et al. Cell 2007´D`Arcangelo, et al. Curr Opin Oncol 2013; Sasaki, et al. Eur J Cancer 2010´Gridelli, et al. Cancer Treat Rev 2014; Hallberg, et al. Nat Rev Cancer 2013; Ou, et al. Oncologist 2012

EML4-ALK activates signalling cascades in the absence of ligand binding



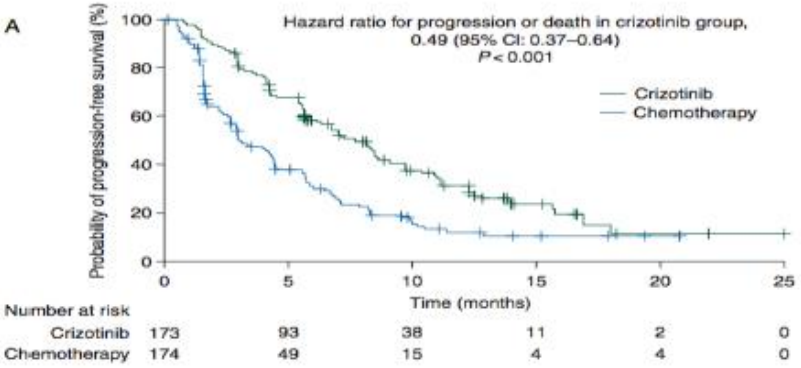
EML4-ALK promotes tumour cell growth and survival through the aberrant activation of pathways involved in regulating proliferation and cell survival

Soda, et al. Nature 2007; Roskoski. Pharmacol Res 2013
Bai, et al, Mol Cell Biol 1998; Fujimoto, et al. Proc Natl Acad Sci 1996
Bai, et al. Blood 2000; Zamo, et al. Oncogene 2002


milestones
2007
EML4-ALK
identified as
2011
Crizotinib accelerated approval (any line of therapy)[1]
2014
Ceritinib accelerated approval (post-crizotinib)[3]
2015
2017
Brigatinib accelerated approval (post-crizotinib)[7]
2017
Ceritinib 1L approval[3]
2018
Lorlatinib approval (≥ 2L a)[12]
Potency
CNS Penetration
ALK Resistance Coverage
2012
Crizotinib conditional approval (≥ 2L)[2]
2015
Ceritinib conditional approval (post-crizotinib)[4]
2015
Crizotinib 1L label extension[6]
Alectinib conditional approval (post-crizotinib)[9] and December 1L approval[10]
2017
Ceritinib 1L label extension[11]
2018
Brigatinib approval (post-crizotinib)[13]
2019
Lorlatinib approval (≥ 2L a)[14]
milestones

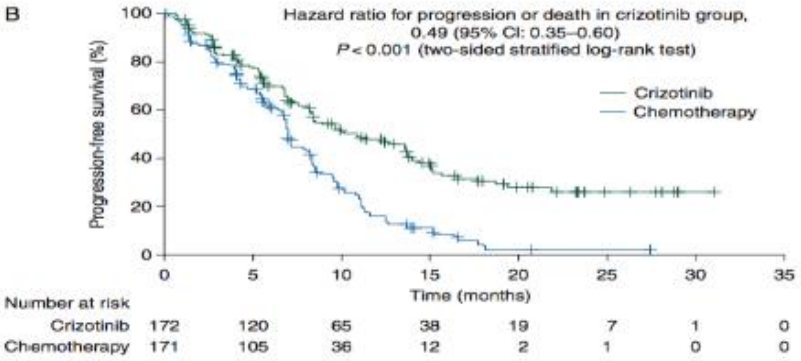
PROFILE: Phase III Trials of the ALK/TKI Crizotinib *vs* ChT

PROFILE 1007
Shaw et al.
NEJM 2013
(2nd line)



Response Rate
65 vs 20%

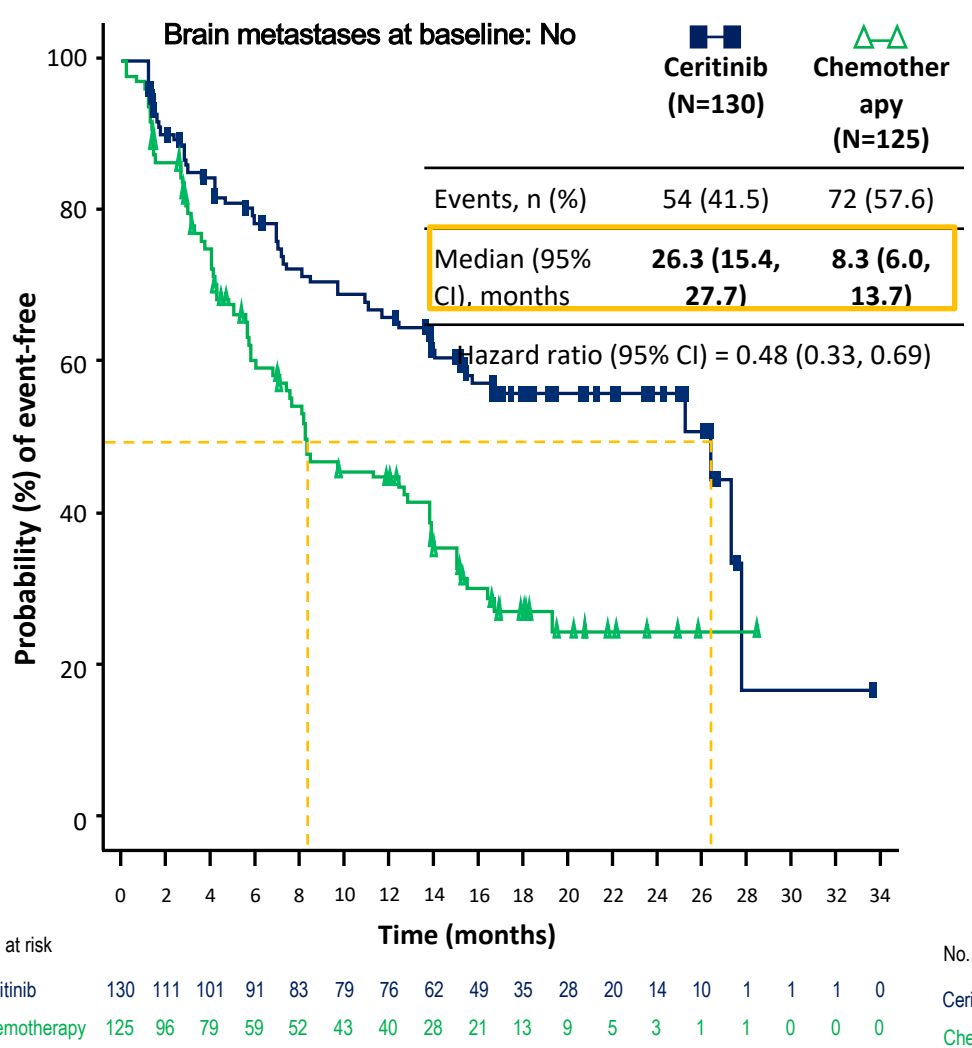
PROFILE 1014
Solomon et al
NEJM 2014
(1st line)

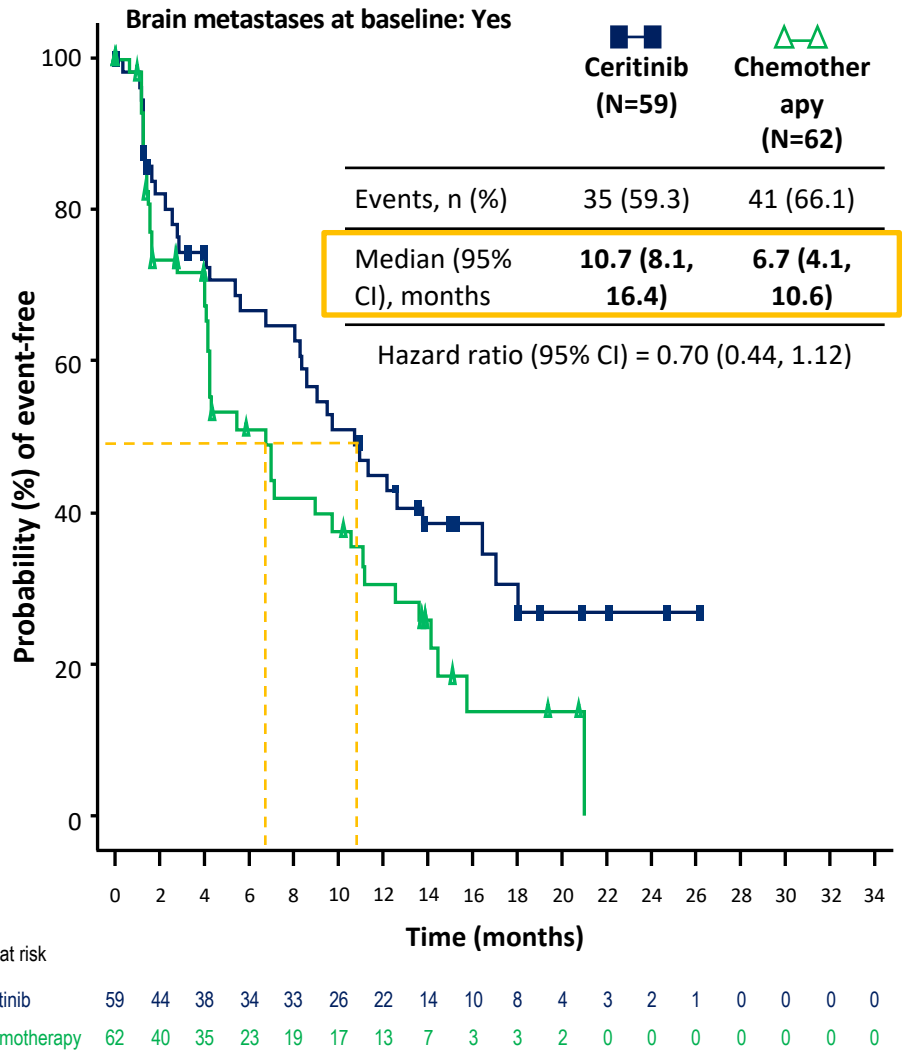


Response Rate
74 vs 45%

Blackhall & Cappuzzo Ann Oncol Supp 3 2016

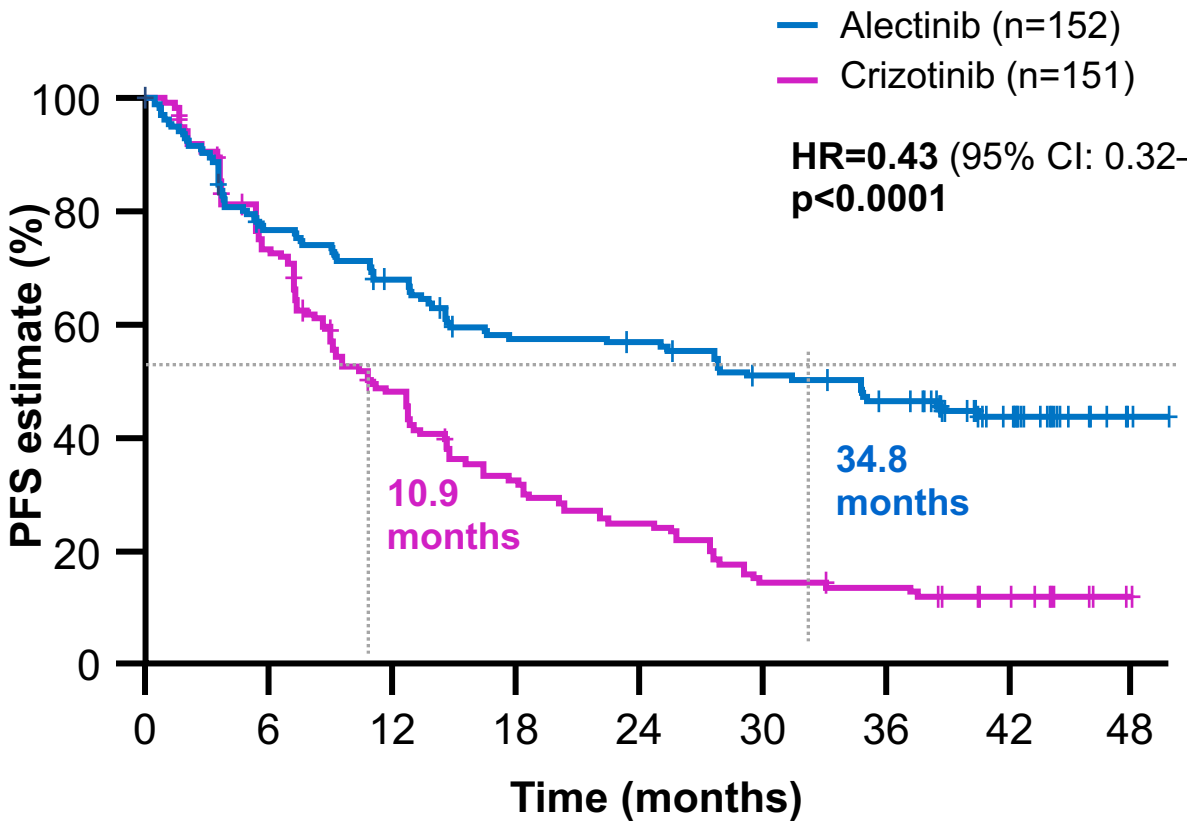
ASCEND: Phase III Trials of the ALK/TKI Ceritinib *vs* ChT





PL03: G de Castro et al. IASLC 17th WCLC, Vienna, December 2016

ALEX: Phase III Trials of the ALK/TKI Alectinib *vs* Crizotinib



	Alectinib	Crizotinib
Events, n (%)	80 (53)	122 (81)

Consistent with the primary[1] analysis and the first exploratory[2] analysis,

final median PFS was significantly longer with alectinib (34.8 months) versus crizotinib (10.9 months)[3]

Exploratory data cut-off 2 (30 November 2018)
CI = ; HR = ; PFS =

1. Peters, et al. N Engl J Med 2017; 2. Camidge, et al. J Thorac Oncol 2019; 3. Mok, et al. ESMO 2019

ALEX: final PFS by baseline CNS metastases status

Patients with CNS metastases at baseline

	Alectinib (n=64)	Crizotinib (n=58)
Median PFS, months	**25.4**	**7.4**
HR (95% CI)	**0.37 (0.23–0.58)**	

Patients without CNS metastases at baseline

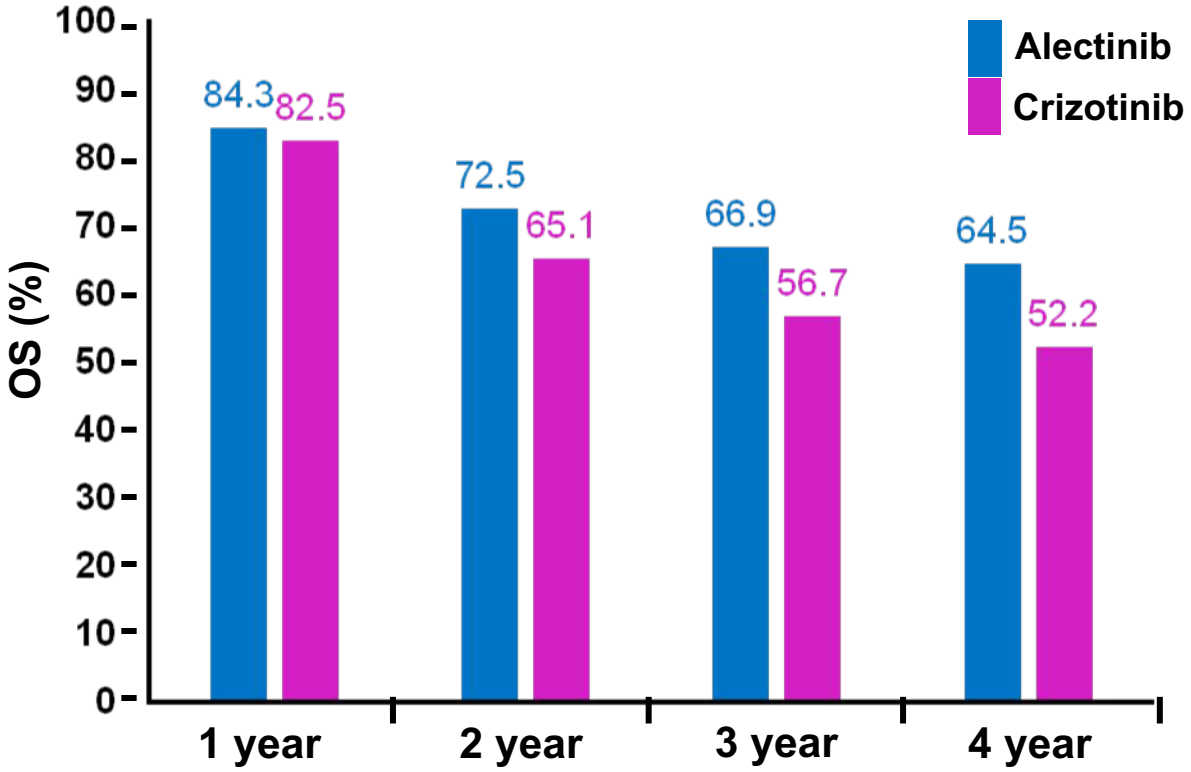
	Alectinib (n=88)	Crizotinib (n=93)
Median PFS, months	**38.6**	**14.8**
HR (95% CI)	0.46 (0.31–0.68)	

At this most recent data cut (30 November 2018), alectinib demonstrated a PFS benefit over crizotinib **in patients with or without CNS metastases at baseline**[3], consistent with the primary[1] analysis and exploratory analysis [1,2]

Exploratory data cut-off 2 (30 November 2018)
CNS = ; HR = ; PFS =

1. Peters, et al. N Engl J Med 2017; 2. Camidge, et al. J Thorac Oncol 2019; 3. Mok, et al. ESMO 2019

ALEX: Phase III Trials of the ALK/TKI Alectinib *vs* Crizotinib



4- year OS rates:

Alectinib: 64.5%
(95% CI, 55.6–73.4)

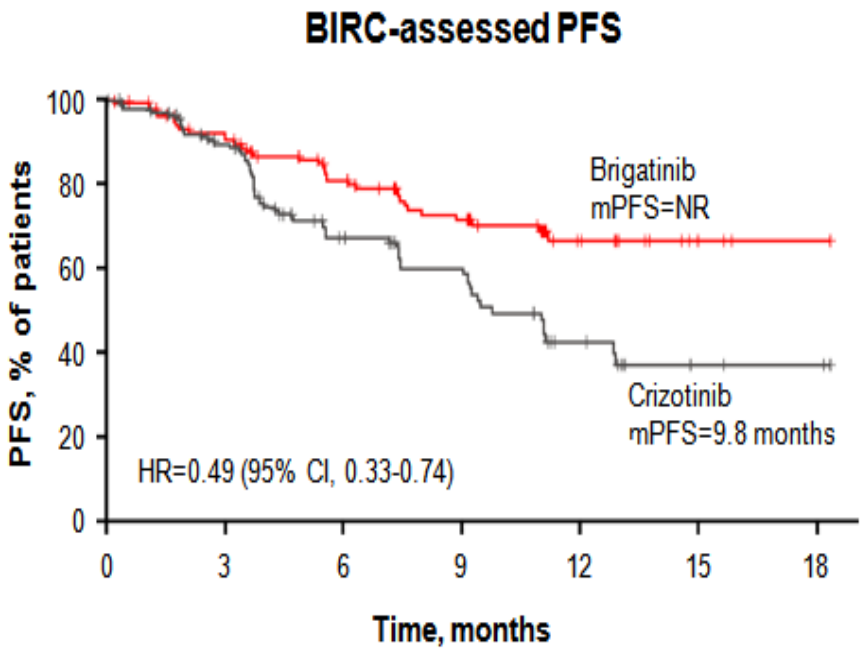
Crizotinib: 52.2%
(95% CI, 42.6–64.8)

OS data remain immature, with 32% of events recorded (stratified HR 0.69, 95% CI: 0.47–1.02)

Exploratory data cut-off 2 (30 November 2018)
CI = confidence interval; HR = hazard ratio; OS = overall survival

Mok, et al, ESMO 2019

First-line brigatinib (ALTA-1L): systemic efficacy and safety



Median follow-up was 11 months with brigatinib and 9.3 months with crizotinib

	Brigatinib (n=137)	Crizotinib (n=138)
Confirmed ORR, % (95% CI)	71 (62-78)	60 (51-68)
Median PFS, months (95% CI)	NR (NR-NR)	9.8 (9.0-12.9)
1-year PFS, % (95% CI)	**67 (56-75)**	**43 (32-53)**
HR (95% CI)	0.49 (0.33-0.74); *P*=0.0007[a]	

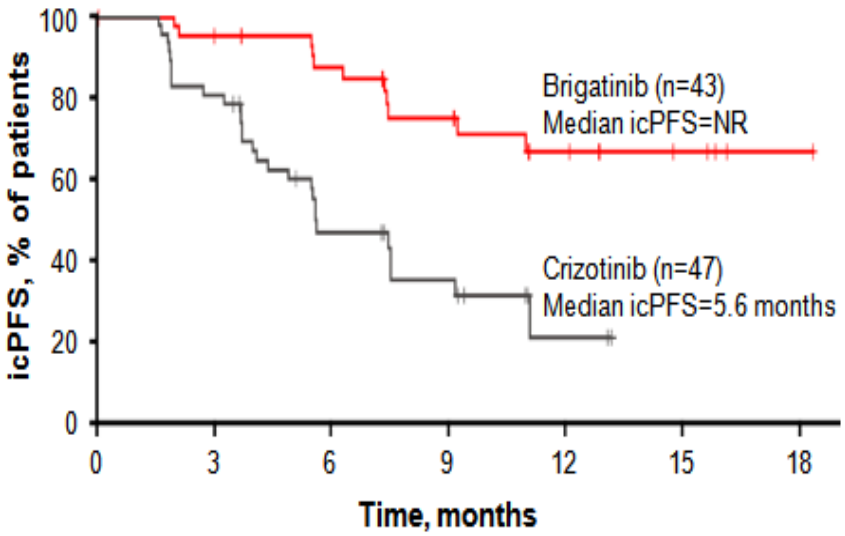
- The most common AEs that occurred at a higher rate with brigatinib by ≥5% included increased creatine kinase level (39% vs 15%), cough (25% vs 16%), hypertension (23% vs 7%), and an increased lipase level (19% vs 12%)
- Early-onset ILD/pneumonitis (within 14 days of treatment initiation): brigatinib, 3% (onset: days 3-8); crizotinib, none reported
- Treatment discontinuation attributable to AEs: 12% with brigatinib and 9% with crizotinib
- Treatment reduction attributable to AEs: 29% with brigatinib and 21% with crizotinib

Brigatinib is not approved in the first-line setting.

As of the first interim analysis (data cutoff: February 19, 2018). [a]Log-rank test.
AE, adverse event; ALT, alanine aminotransferase; BIRC, blinded independent review committee; CI, confidence interval; HR, hazard ratio; ILD, interstitial lung disease; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; PFS, progression-free survival.
Camidge DR, et al. Brigatinib versus crizotinib in ALK-positive non–small-cell lung cancer. *N Engl J Med*. 2018 [Epub ahead of print].
Camidge DR, et al. Presented at: IASLC WCLC. 2018 (abstr PL02.03).

First-line brigatinib (ALTA-1L): CNS efficacy

icPFS in patients with any brain metastases at baseline[1]



Median follow-up was 11 months with brigatinib and 9.3 months with crizotinib

Measurable[a] brain metastases at baseline[2]	Brigatinib (n=18)	Crizotinib (n=21)
Confirmed icORR,[b] % (95% CI)	78 (52-94)	29 (11-52)
CR, %	11	0
PR, %	67	29
icORR at ≥1 assessment (confirmed and unconfirmed),[b] % (95% CI)	83 (59-96)	33 (15-57)
Any brain metastases at baseline	**(n=43)**	**(n=47)**
Confirmed icORR,[b] % (95% CI)	67 (51-81)	17 (8-31)
CR, %	37	4
PR, %	30	13
icORR at ≥1 assessment (confirmed and unconfirmed),[b] % (95% CI)	79 (64-90)	23 (12-38)
Median icPFS,[b] months (95% CI)	NR (11.0-NR)	5.6 (4.1-9.2)
HR (95% CI)	0.27 (0.13-0.54); *P*<0.0001[c]	

Brigatinib is not approved in the first-line setting.

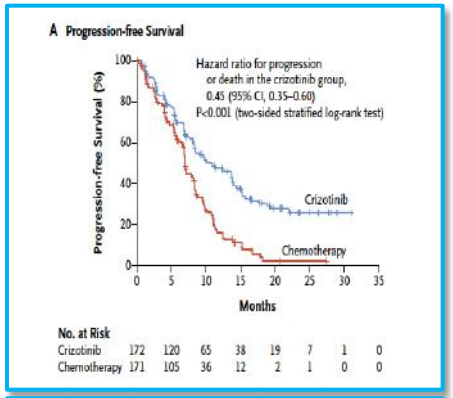
As of the first interim analysis (data cutoff: February 19, 2018). [a]≥10 mm in diameter; [b]BIRC assessed; [c]Log-rank test.
BIRC, blinded independent review committee; CI, confidence interval; CNS, central nervous system; CR, complete response; HR, hazard ratio; icORR, intracranial objective response rate; icPFS, intracranial progression-free survival; NR, not reached; PR, partial response.

1. Camidge DR, et al. Brigatinib versus crizotinib in ALK-positive non–small-cell lung cancer. *N Engl J Med*. 2018 [Epub ahead of print]. Copyright © 2018 Massachusetts Medical Society.
2. Popat S, et al. Poster. ESMO. 2018 (abstr LBA58).

PROFILE 1014[1]

crizotinib vs chemotherapy

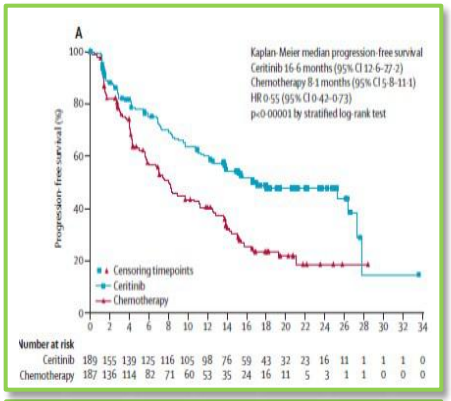
Median PFS 10.9 months vs 7.0 months (IRC) HR=0.45 (95% CI, 0.35-0.60)[a]



ASCEND-4[2]

ceritinib vs chemotherapy

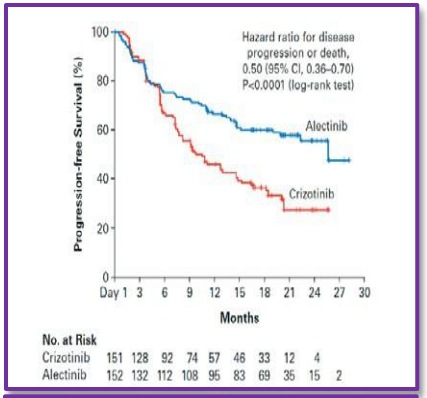
Median PFS 16.6 months vs 8.1 months (IRC) HR=0.55 (95% CI, 0.42-0.73)[a]



ALEX[3]

alectinib vs crizotinib

Median PFS 34.8 months vs 10.9 months (INV) HR=0.43 (95% CI, 0.32-0.58)[a]



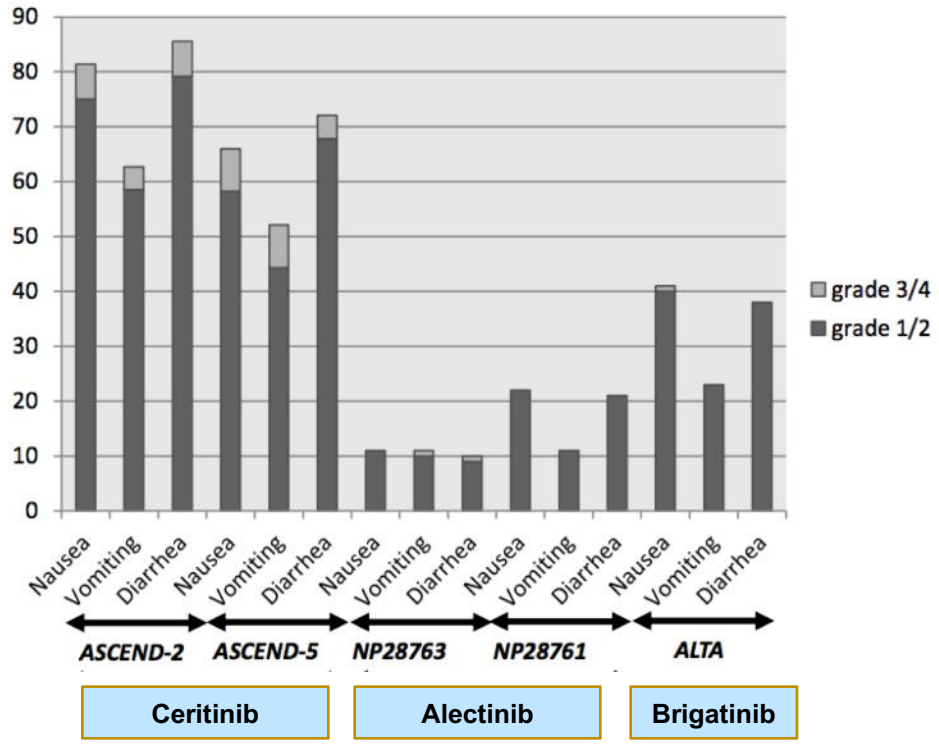
Indirect comparison for illustration only

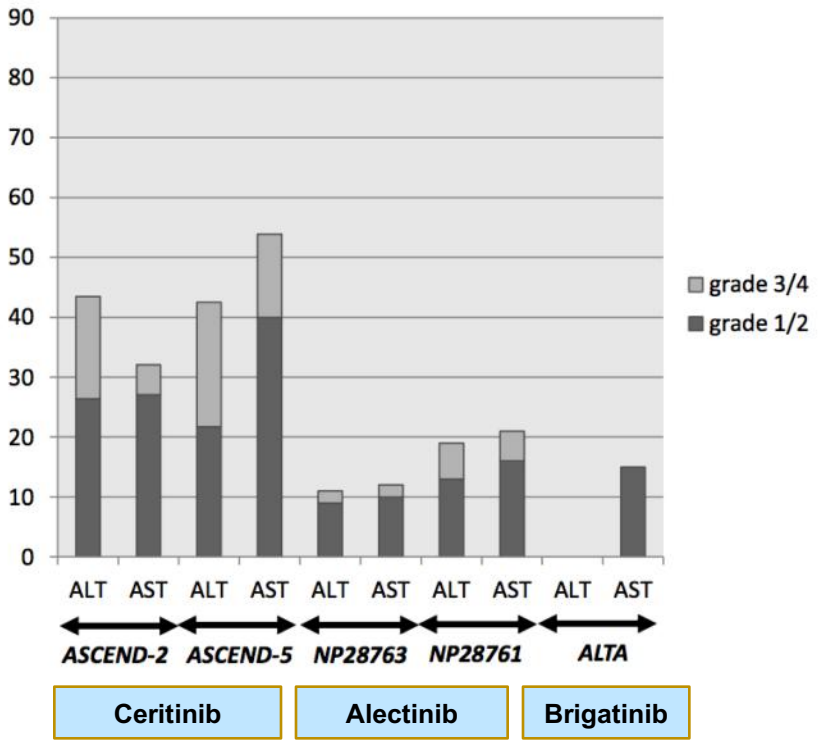
[a]IRC assessed.

CI, confidence interval; HR, hazard ratio; IRC, independent review committee; PFS, progression-free survival.

1.Solomon BJ, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167-2177. 2. Soria J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. 2017;389:917-929. © 2017, 3.Peters S, et al. *N Engl J Med*. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung. cancer. 2017;377:829-838. Copyright © 2017 Massachusetts Medical Society., Mok et al ESMO 2019

2nd generation ALK-TKIs according to toxicity profile





Metro et al. Lung Cancer 2017

2nd generation ALK-TKIs according to toxicity profile

CERITINIB

NAUSEA
DIARRHEA
VOMITING
ALT, AST, GAMMA-GT
ALP

ALECTINIB

ALT, AST, GAMMA-GT
OEDEMA
FATIGUE
MYALGIA
LUNG TOXICITY
(LATE ONSET)

BRIGATINIB

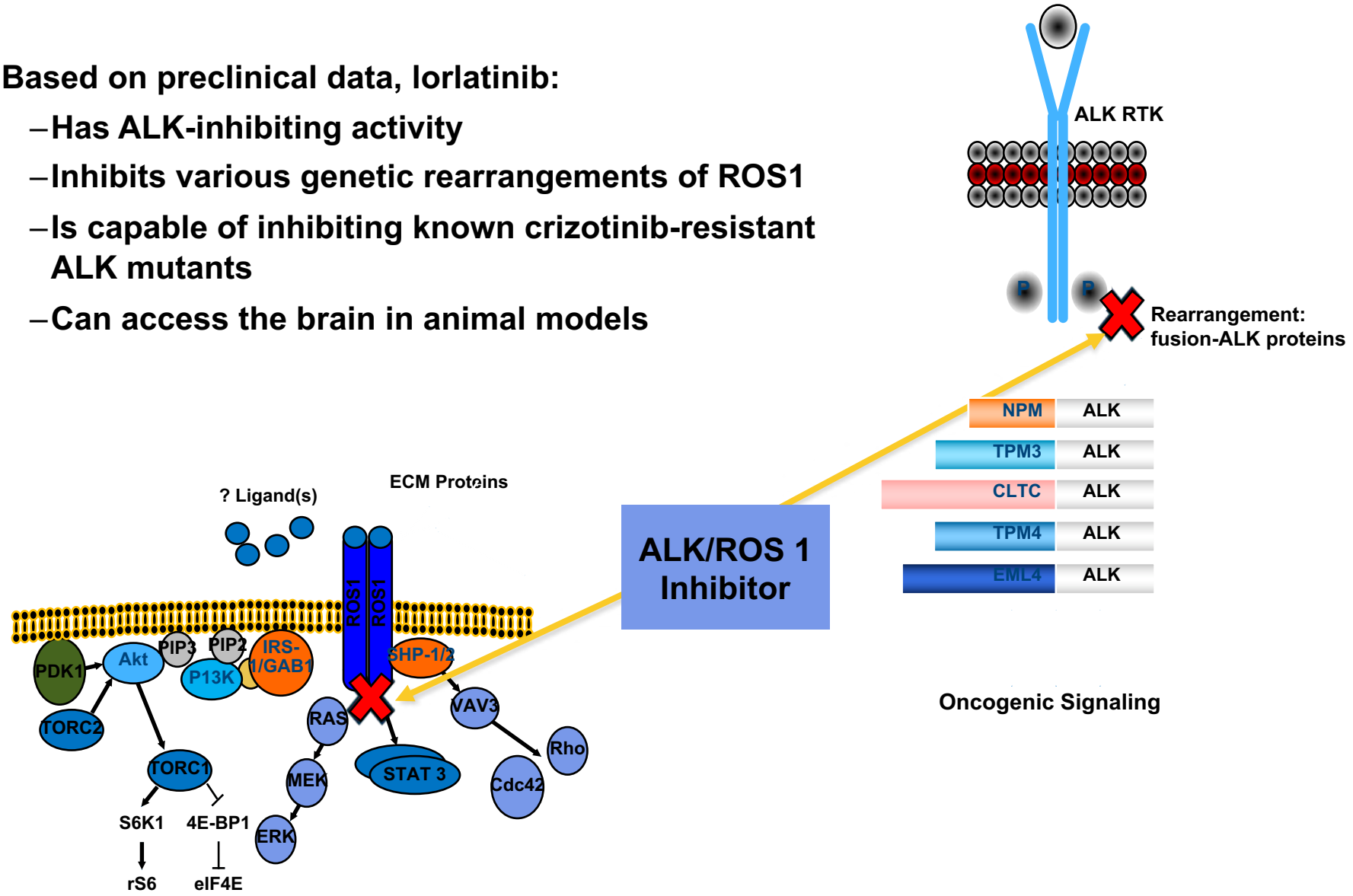
CPK
HYPERTENSION
LIPASE
AMYLASE
DIARRHEA

LUNG TOXICITY
(EARLY ONSET)

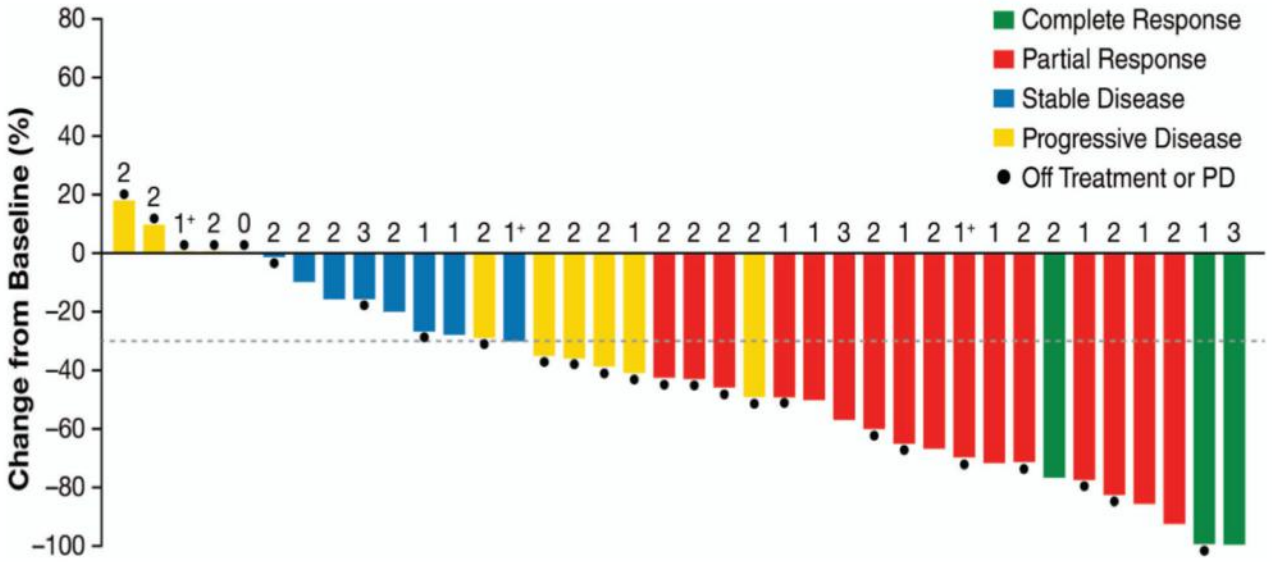
3rd Generation ALK/ROS1 Inhibitor: Lorlatinib

Based on preclinical data, lorlatinib:

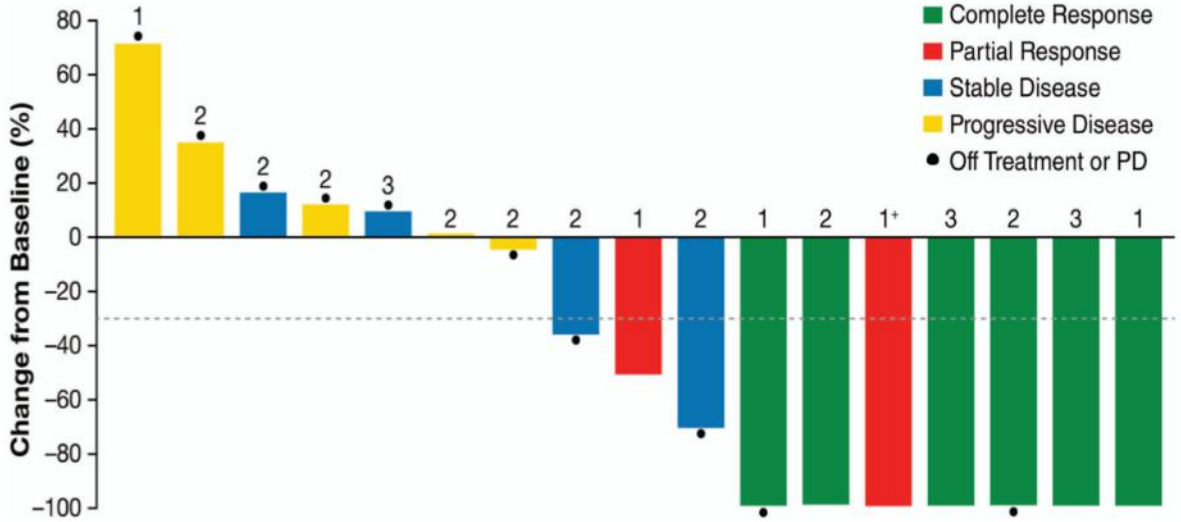
- **Has ALK-inhibiting activity**
- **Inhibits various genetic rearrangements of ROS1**
- **Is capable of inhibiting known crizotinib-resistant ALK mutants**
- **Can access the brain in animal models**



3rd Generation ALK Inhibitor: Lorlatinib

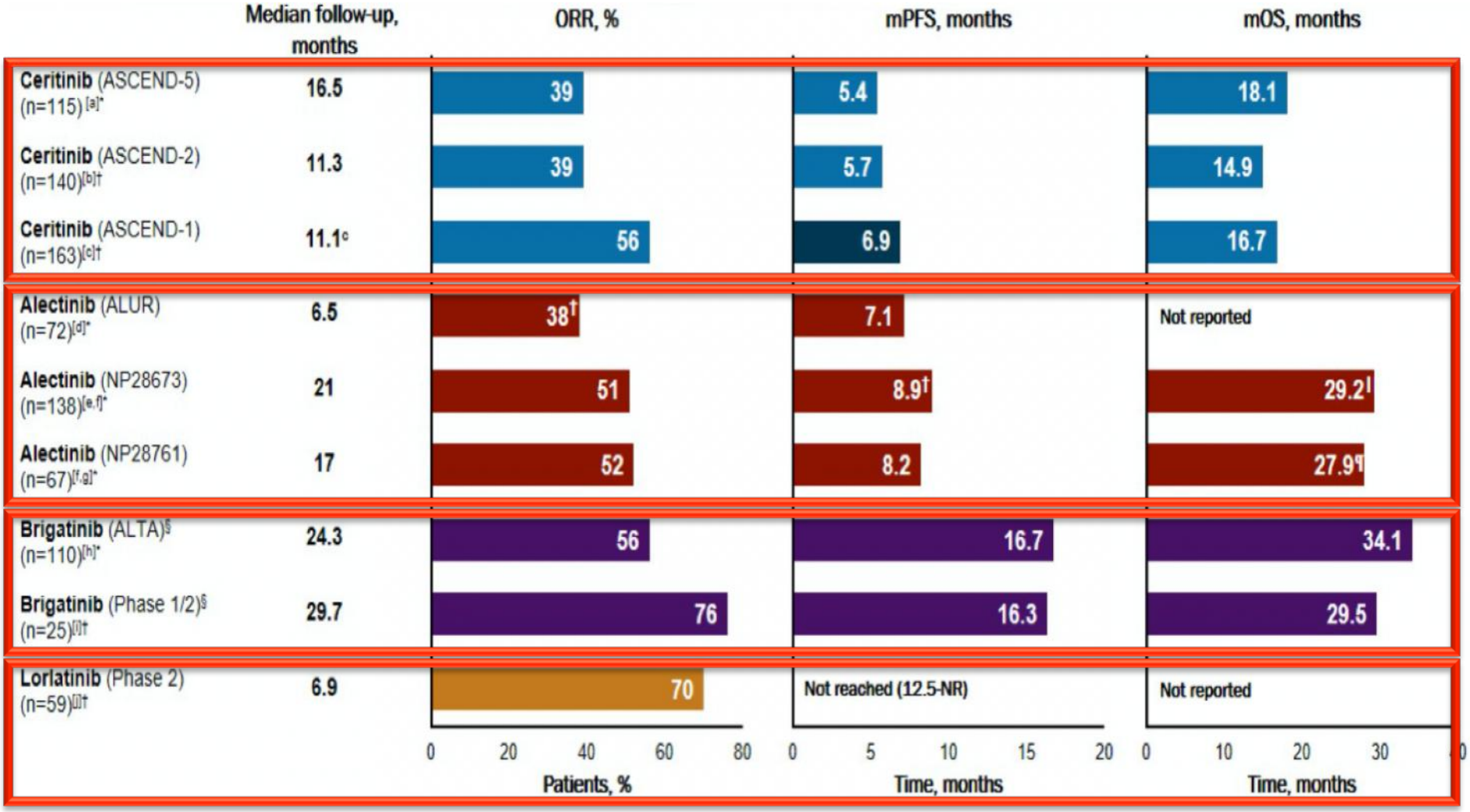


Best confirmed tumor responses



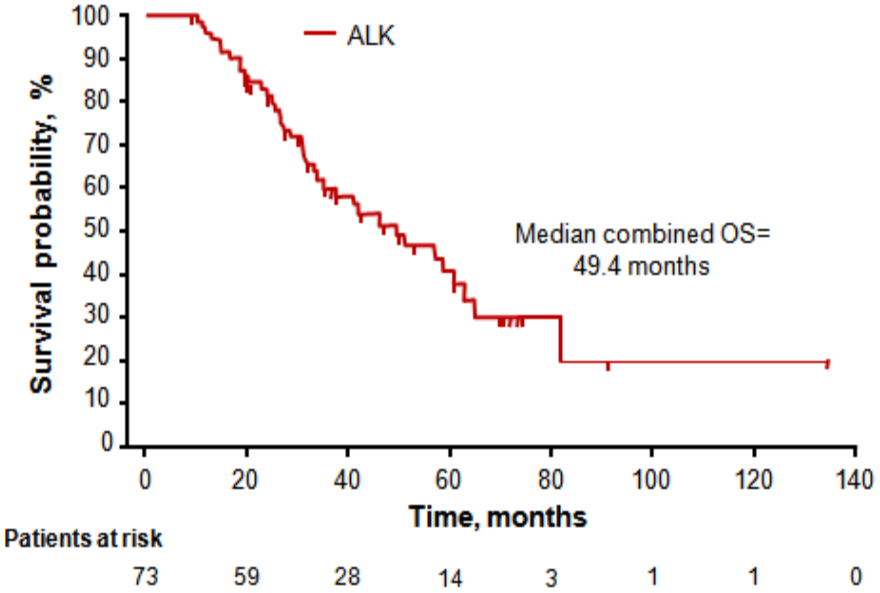
Best intracranial tumor response

Evolving treatment options in ALK +ve NSCLC



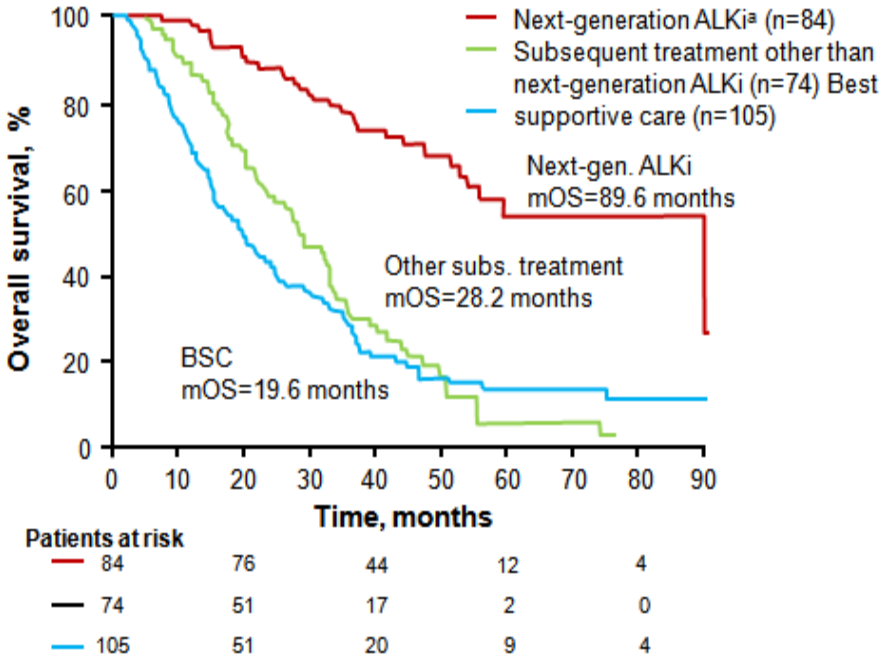
Sequential ALK inhibitor treatment substantially prolongs survival in ALK+ NSCLC patients

Crizotinib → ceritinib[1]



- Retrospective analysis of 73 ALK+ patients

Multiple ALK TKIs post-crizotinib[2]



- Retrospective analysis of 214 ALK+ patients

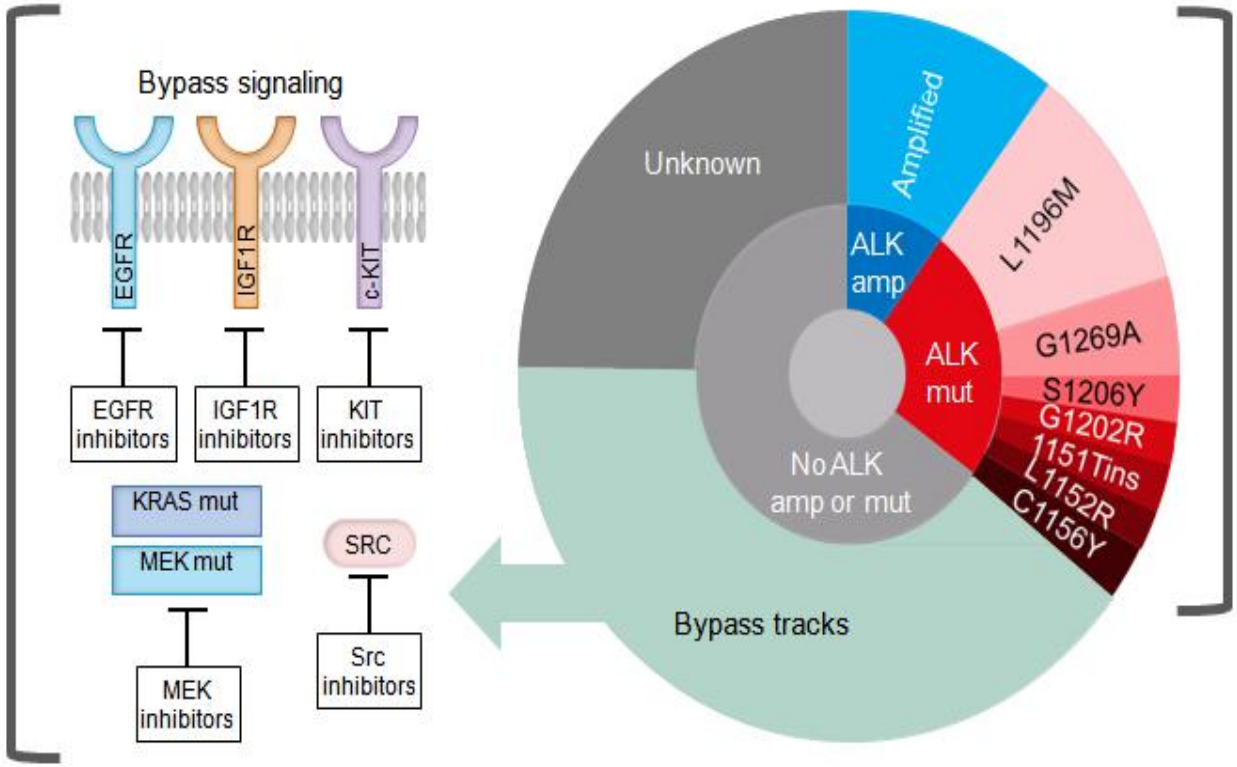
[a]The next-generation ALKis administered were ceritinib, alectinib, ceritinib followed by alectinib, ceritinib followed by lorlatinib, or alectinib followed by ceritinib.
ALK, anaplastic lymphoma kinase; ALKi, ALK inhibitor; BSC, best supportive care; mOS, median overall survival; NSCLC, non–small cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

1. Gainor JF, et al. Progression-free and overall survival in ALK-positive NSCLC patients treated with sequential crizotinib and ceritinib. *Clin Cancer Res*. 2015;21:2745-2752.

2. Duruisseaux M, et al. *Oncotarget*. 2017;8:21903-21917 3.0 license acoessible at https://creativecommons.org/licenses/by/3.0/us/legalcode.

Mechanisms of resistance to crizotinib

ALK-independent mechanisms of resistance

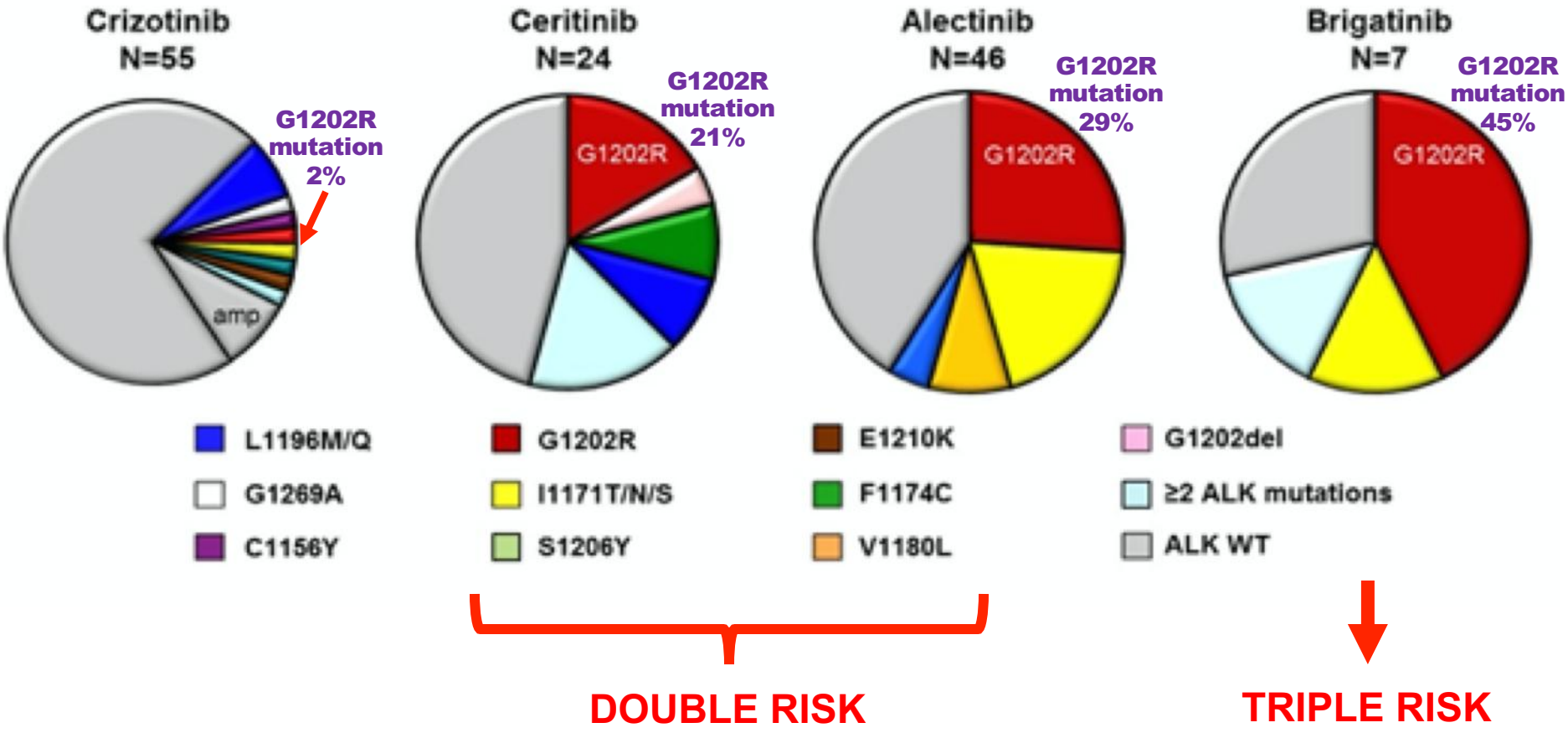


ALK-dependent genetic alterations

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; IGF1R, insulin-like growth factor 1 receptor; KIT, CD117; MEK, mitogen-activated protein kinase (MAPK) kinase; mut, mutation; SRC, sarcoma.

Camidge DR, et al. *Nat Rev Clin Oncol*. 2014;11:473-481. Hallberg B, Palmer RH. *Nat Rev Cancer*. 2013;13:685-700. Katayama R, et al. *Clin Cancer Res*. 2015:2227-2235. Lin JJ, et al. *Cancer Discov*. 2017;7:137-155.

Secondary resistance mutations are more common with 2nd generation ALK TKIs



Mutational sensitivity of established ALK TKIs

	Cellular ALK phosphorylation mean IC_{50} (nmol/L)				
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

$IC_{50} \leq 50$ nmol/L

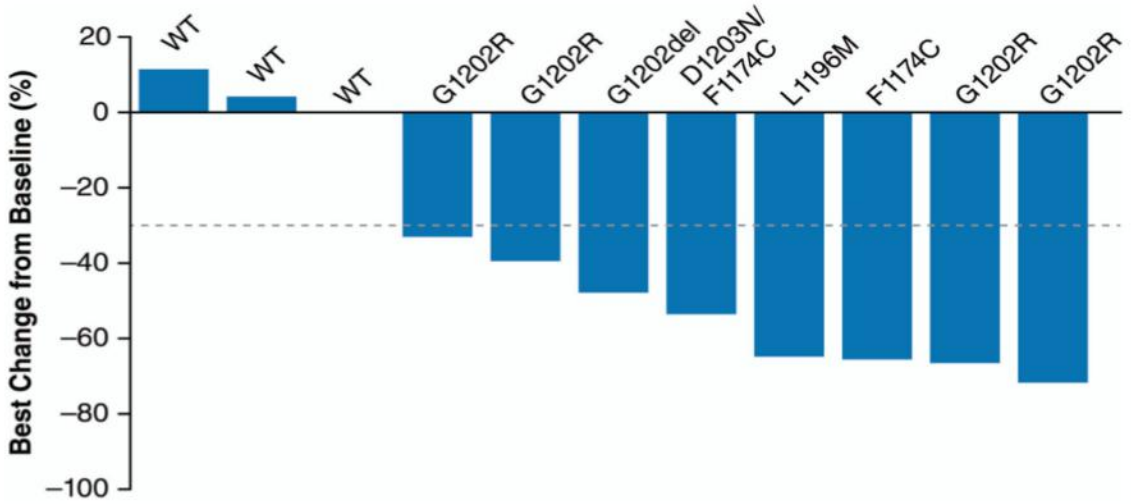
$IC_{50} > 50 < 200$ nmol/L

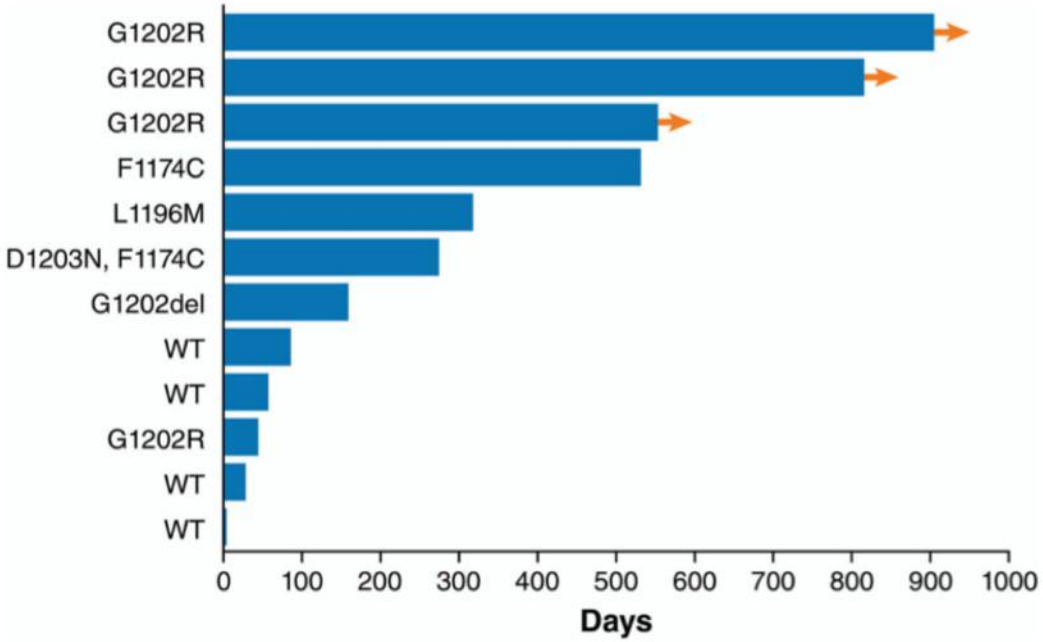
$IC_{50} \geq 200$ nmol/L

G1202R

3rd Generation ALK Inhibitor: Lorlatinib

Response according to ALK resistance mutations

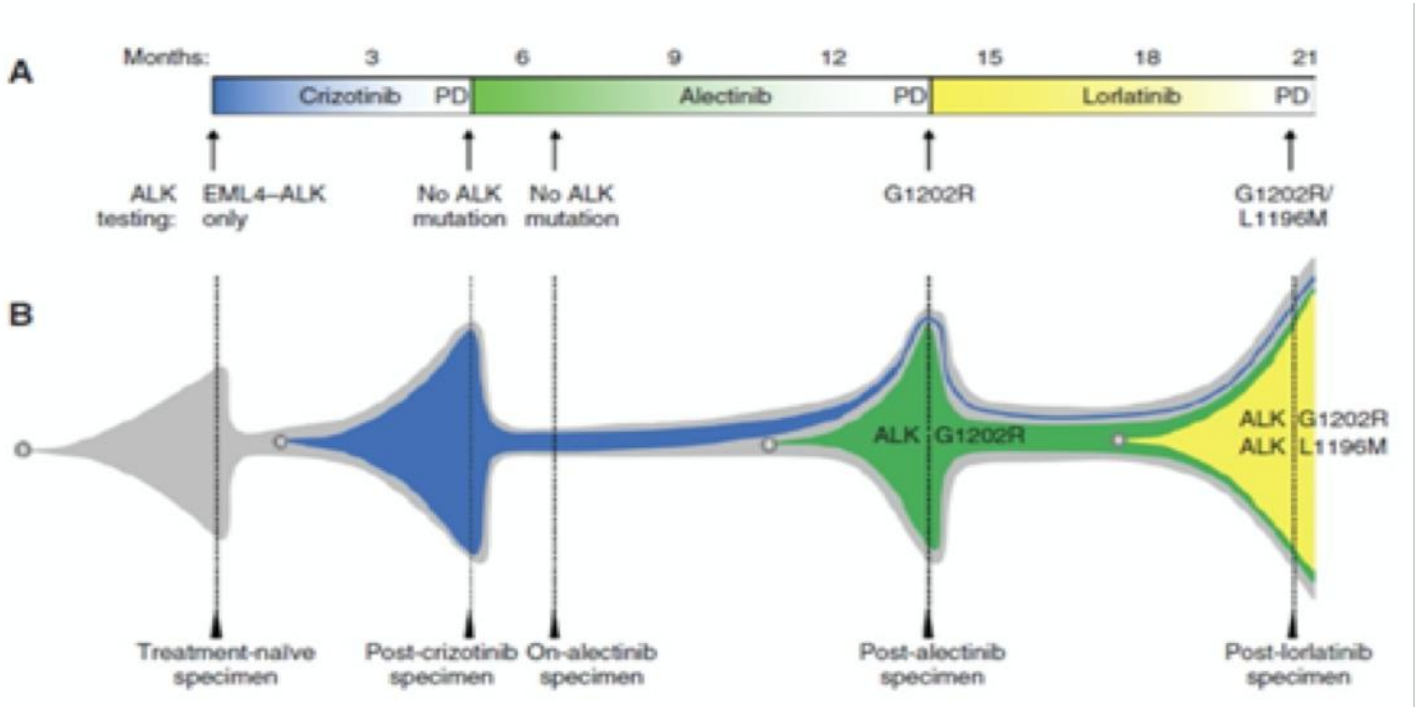


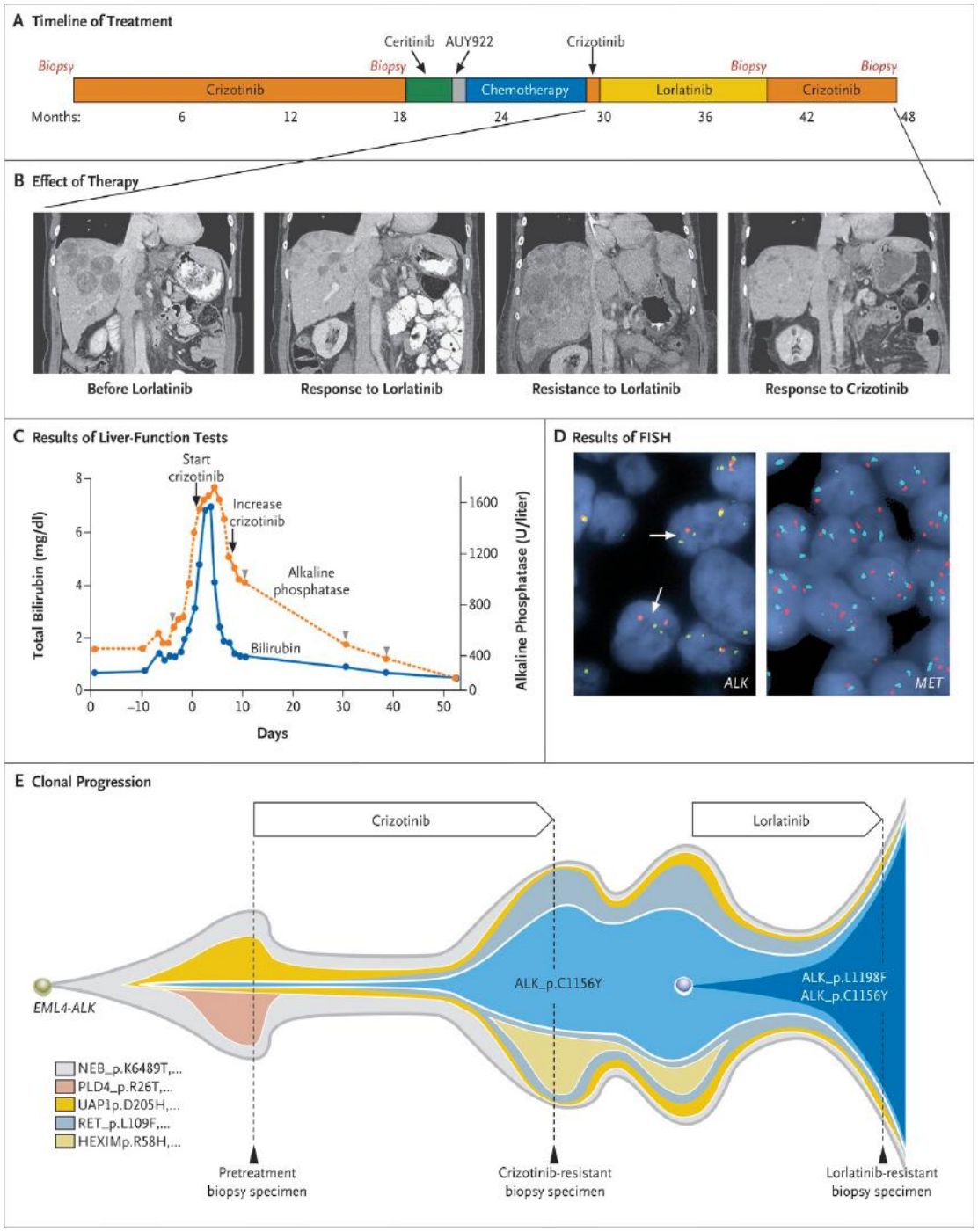


Duration of treatment according to ALK resistance mutations >2 prior TKIs

Clonal evolution of resistance to sequential ALK inhibitor therapy throughout lorlatinib

MGH953





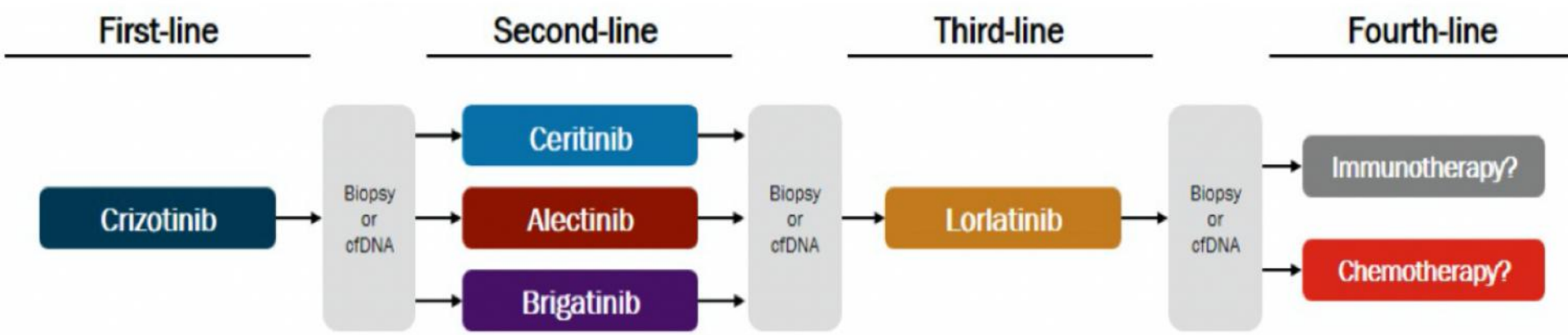
Clonal evolution of resistance to sequential ALK inhibitor therapy throughout lorlatinib

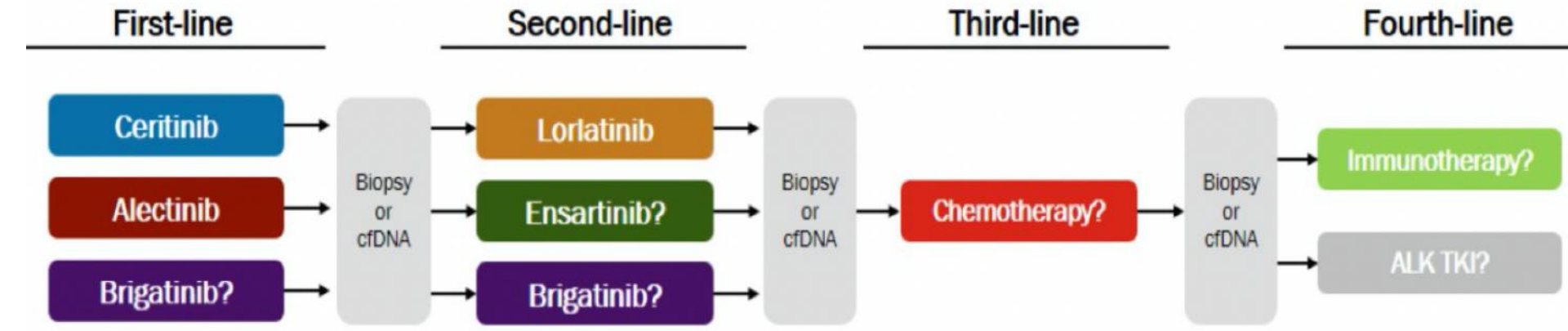
and resensitization to crizotinib

Take Home Message

- **ALK targeting has been a fundamental part in the development of targeting therapies.**
- **Development of resistance to ALK inhibitors follows a Darwinian pattern of selection of resistant clones and represents a model in cancer evolution.**
- **The molecular pattern of resistance and the most appropriate treatment option and sequencing remain to be defined when second-generation ALK inhibitors are used as first-line treatment.**
- **Because of multiple mechanisms driving resistance to ALK inhibitors, genotype monitoring at progression may help to guide evolving treatment decisions.**

Proposed therapeutic algorithm in ALK-positive NSCLC





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