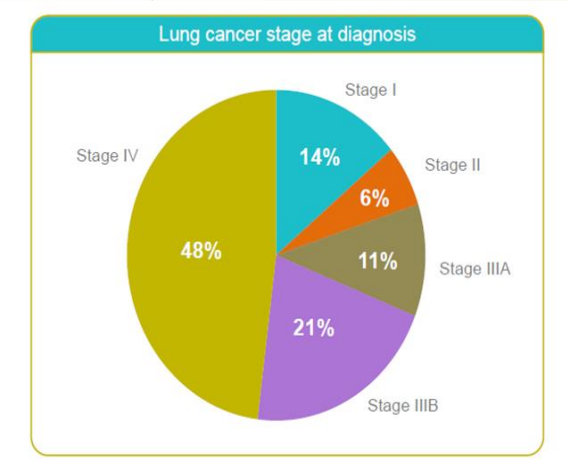
Optimal sequence of ALK inhibitors for ALK or ROS1 Mutant non-small cell lung cancer- marathon or sprint while choosing upfront TKI

Mor Moskovitz, MD

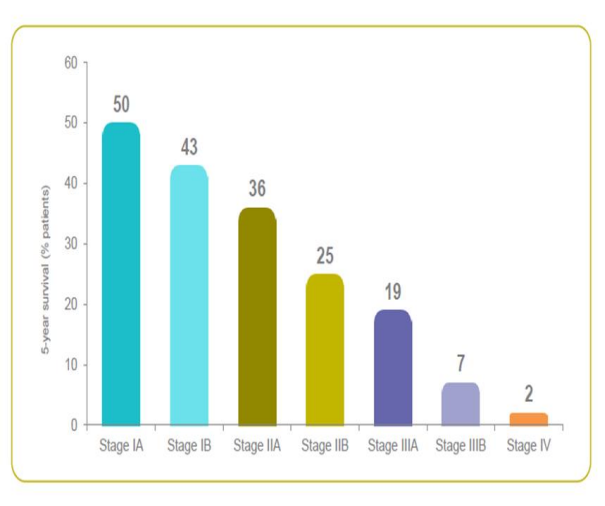
Rambam Health Care Campus

Haifa, Israel

Lung Cancer- The leading cause of cancer related death world-wide!



Most patients diagnosed at advanced stage



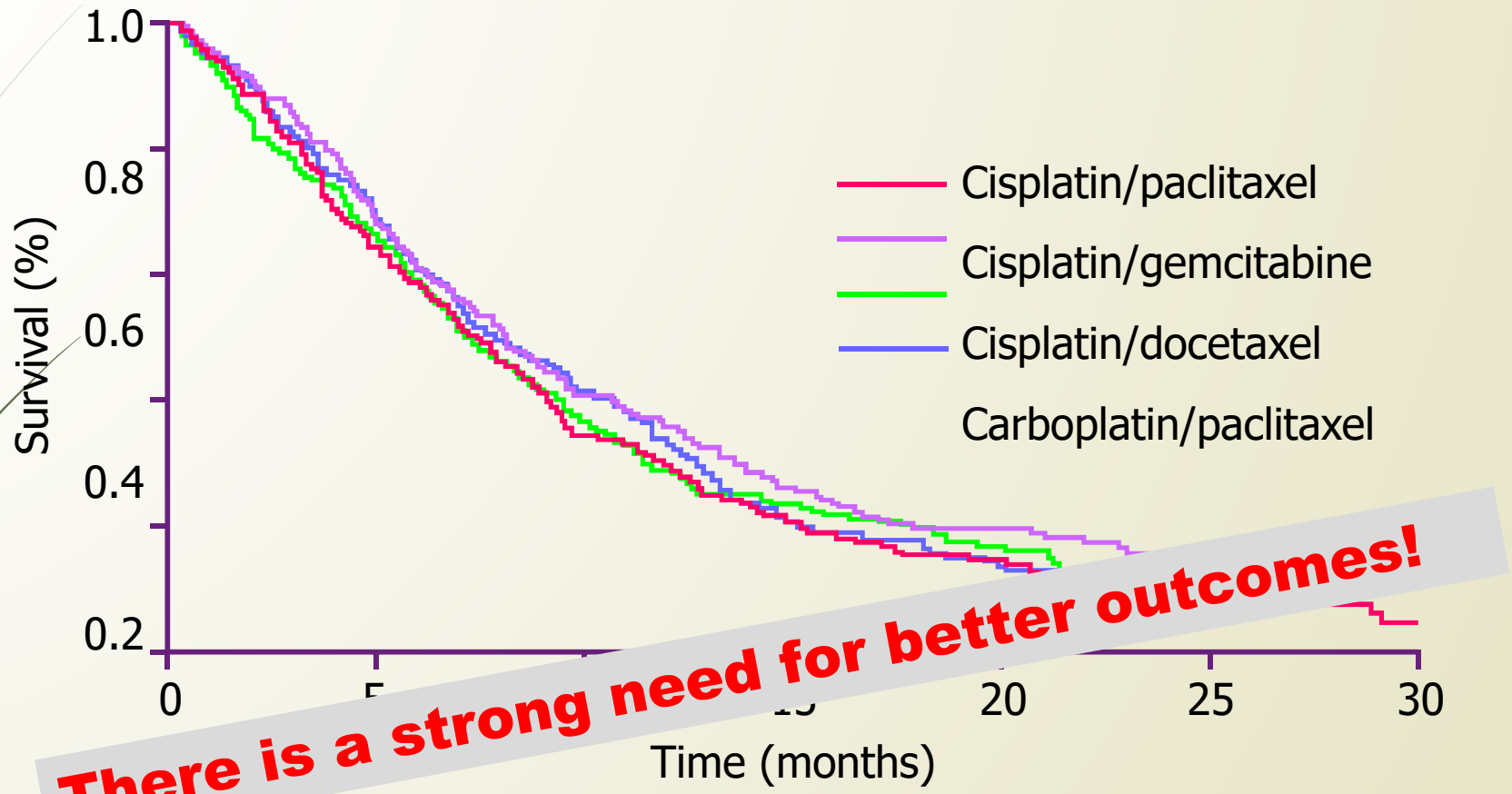
Leading Sites of New Cancer Cases and Deaths – 2015 Estimates

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 220,800 (26%)	Breast 231,840 (29%)	Lung & bronchus 86,380 (28%)	Lung & bronchus 71,660 (26%)
Lung & bronchus 115,610 (14%)	Lung & bronchus 105,590 (13%)	Prostate 27,540 (9%)	Breast 40,290 (15%)
Colon & rectum 69,090 (8%)	Colon & rectum 63,610 (8%)	Colon & rectum 26,100 (8%)	Colon & rectum 23,600 (9%)
Urinary bladder 56,320 (7%)	Uterine corpus 54,870 (7%)	Pancreas 20,710 (7%)	Pancreas 19,850 (7%)
Melanoma of the skin 42,670 (5%)	Thyroid 47,230 (6%)	Liver & intrahepatic bile duct 17,030 (5%)	Ovary 14,180 (5%)
Non-Hodgkin lymphoma 39,850 (5%)	Non-Hodgkin lymphoma 32,000 (4%)	Leukemia 14,210 (5%)	Leukemia 10,240 (4%)
Kidney & renal pelvis 38,270 (5%)	Melanoma of the skin 31,200 (4%)	Esophagus 12,600 (4%)	Uterine corpus 10,170 (4%)
Oral cavity & pharynx 32,670 (4%)	Pancreas 24,120 (3%)	Urinary bladder 11,510 (4%)	Non-Hodgkin lymphoma 8,310 (3%)
Leukemia 30,900 (4%)	Leukemia 23,370 (3%)	Non-Hodgkin lymphoma 11,480 (4%)	Liver & intrahepatic bile duct 7,520 (3%)
Liver & intrahepatic bile duct 25,510 (3%)	Kidney & renal pelvis 23,290 (3%)	Kidney & renal pelvis 9,070 (3%)	Brain & other nervous system 6,380 (2%)
All sites 848,200 (100%)	All sites 810,170 (100%)	All sites 312,150 (100%)	All sites 277,280 (100%)

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Most patients end up with advanced disease, and treated with systemic therapy

טיפולים כימותרפיים- תחילת 2000



Schiller JH, et al. N Engl J Med 2002;346:92–8

Two subtypes of NSCLC patient

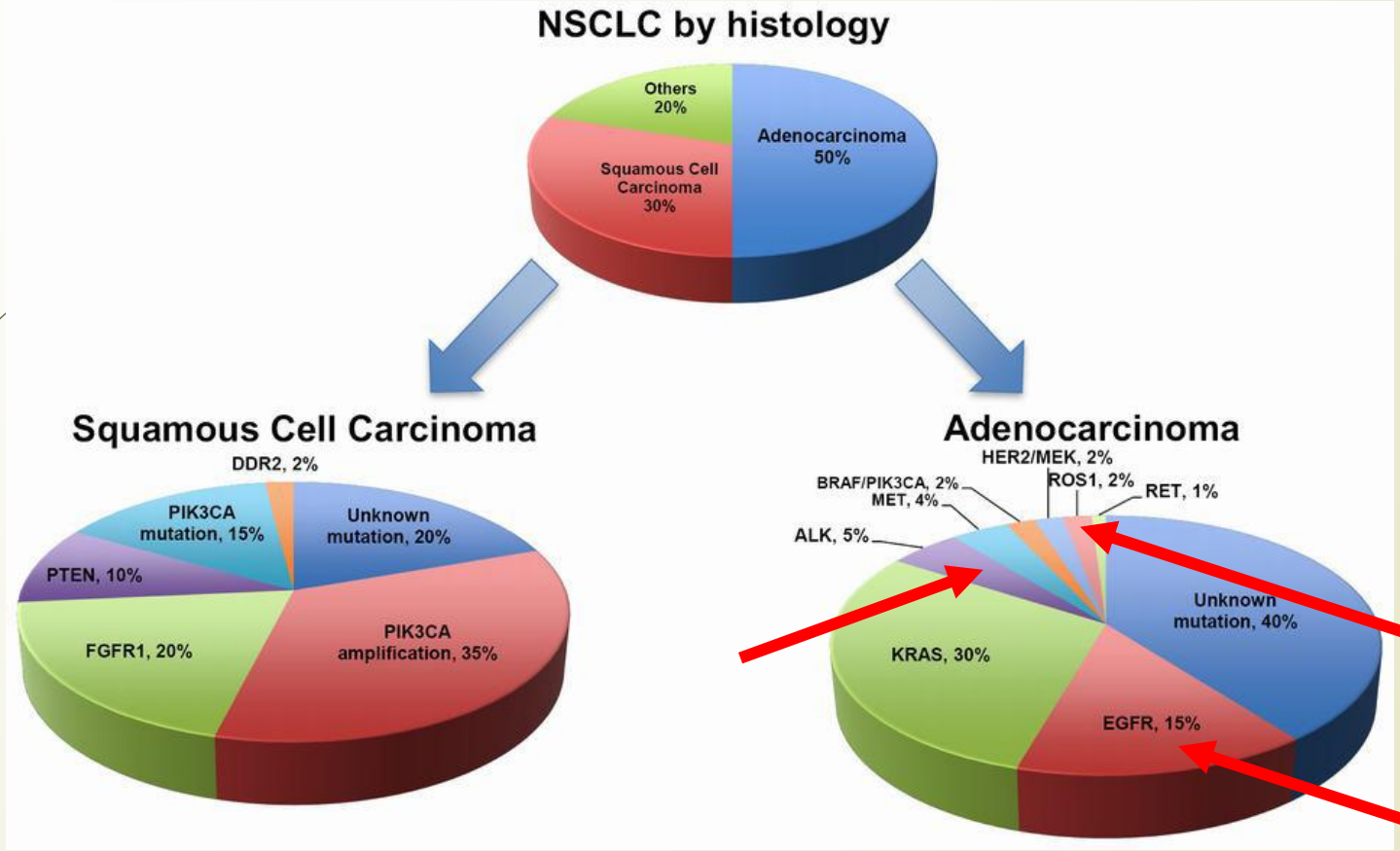
20%

80%

?

For those patients- tissue is the issue!

What are the common targets in Adenocarcinoma of the Lung?

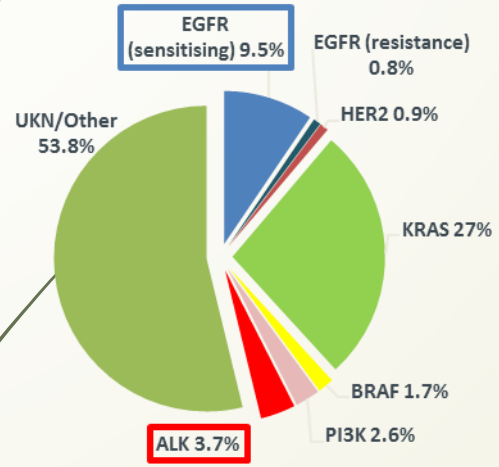


EGFR = epidermal growth factor receptor
ALK = anaplastic lymphoma kinase

ALK characteristics

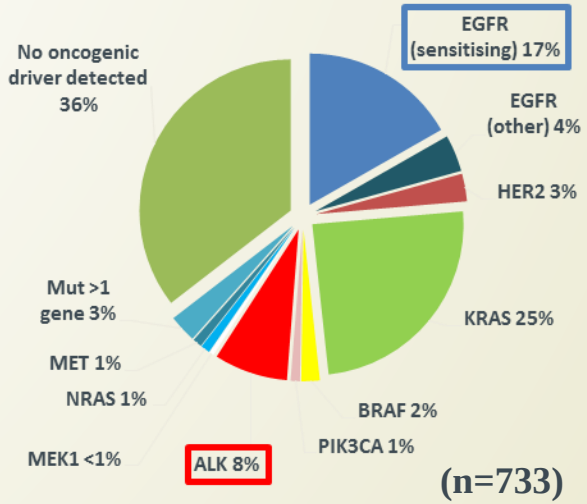
- Incidence of *ALK*+ NCSLC is Relatively Uniform across Ethnicities

Europe[1]
All histology



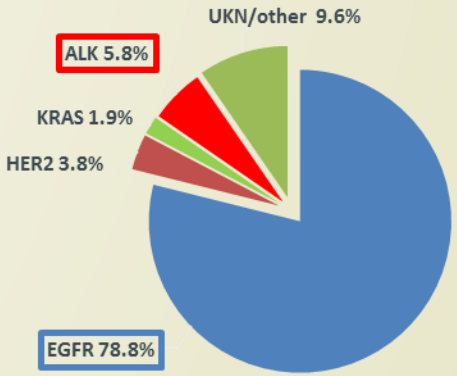
(n=9,911)

US[2]
Adenocarcinoma



(n=733)

East Asia[3]
Adenocarcinoma, never smokers



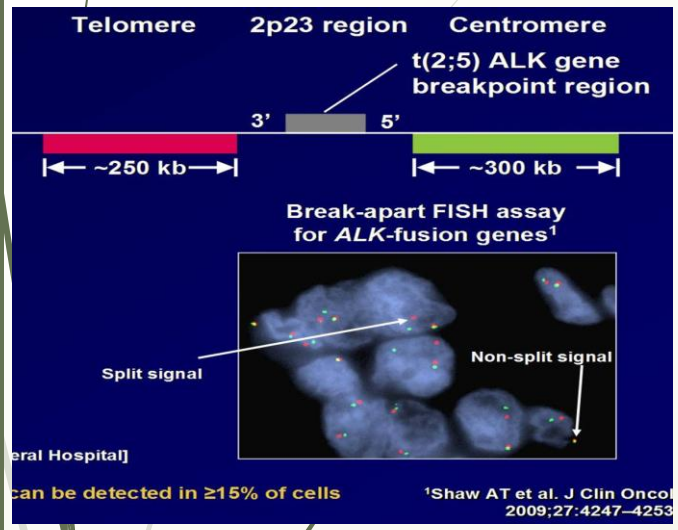
(n=52)

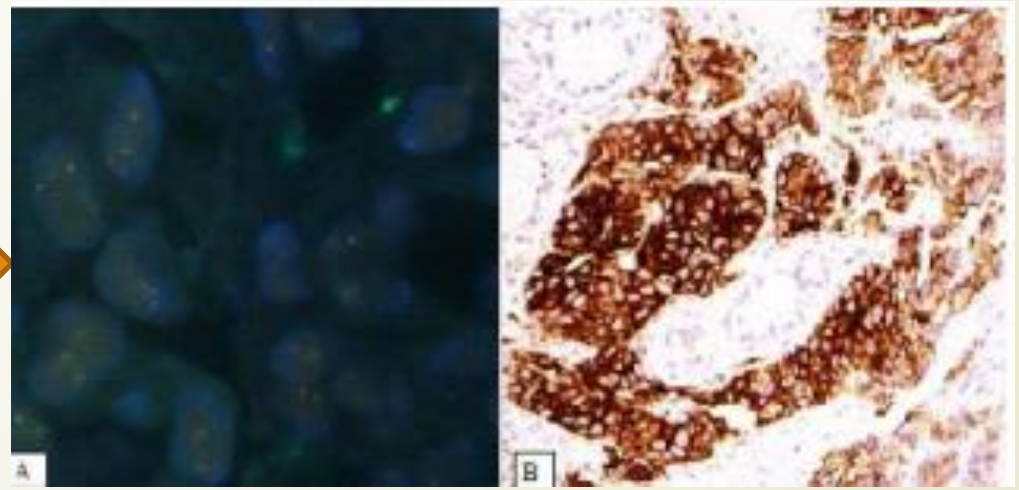
- *Younger and more male patients*
- Higher incidence of thrombo-embolic events

Barlesi, et al. ASCO 2013; 2. Johnson, et al. ASCO 2013; 3. Sun, et al. J Clin Oncol 2010

Zer, A., Moskovitz, M., Hwang, D.M., Hershko-Klement, A., Fridel, L., Korpanty, G.J., Dudnik, E., Peled, N., Shochat, T., Leighl, N.B. and Liu, G.,Shepherd F, 2017. ALK-Rearranged Non–Small-Cell Lung Cancer Is Associated With a High Rate of Venous Thromboembolism. Clinical lung cancer, 18(2), pp.156-161.

How to diagnose ALK Rearrangement?



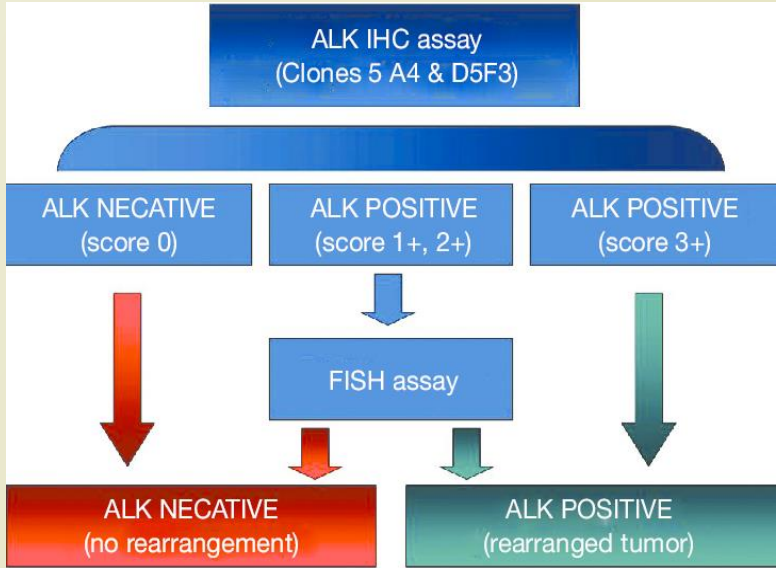


FISH break-apart test-

- Used to be the gold standard, but…
- Expensive
- Time consuming
- On some studies- missed up to 50% of ALK rearrangements compare to IHC and NGS

Immunohistochemistry-

- Less expensive
- faster



ROS1 rearrangement in NSCLC

- Found in 1% on Adenocarcinomas of the lung
- Younger patients, non-smokers
- Diagnosed with IHC (and FISH break-apart)
- No data on the risk of thromboembolic events, but clinical observations suggest increased risk

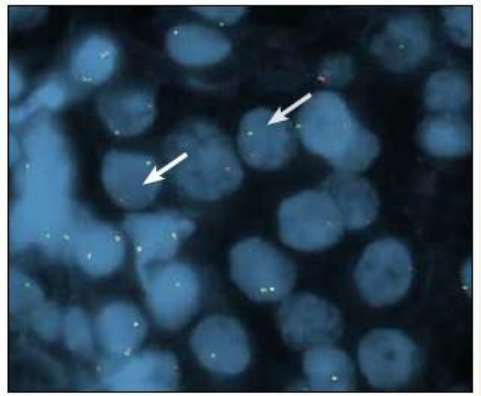
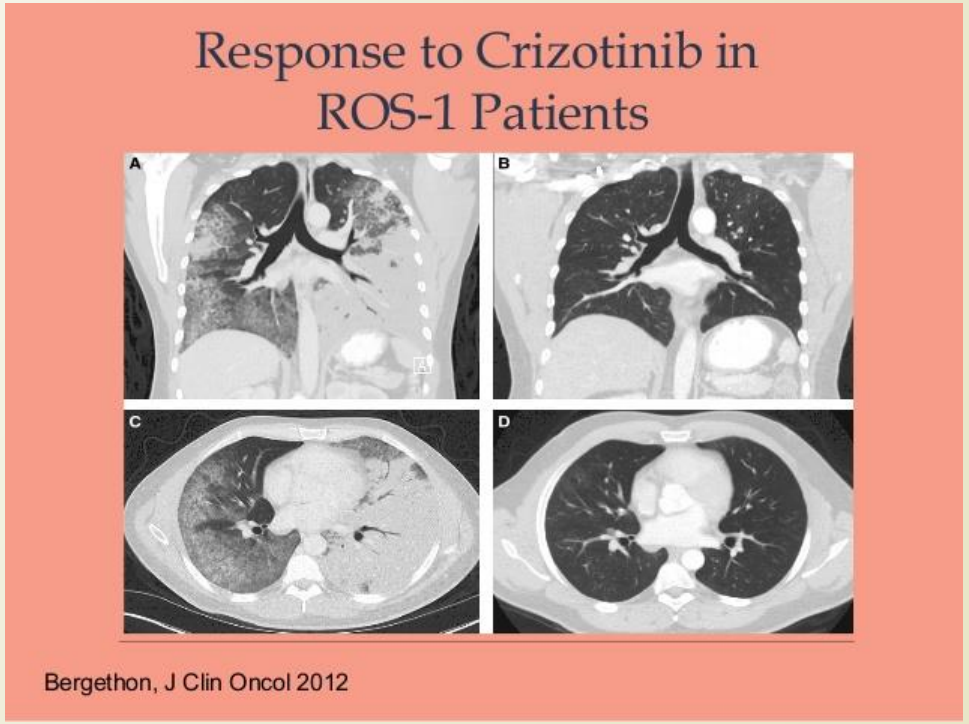


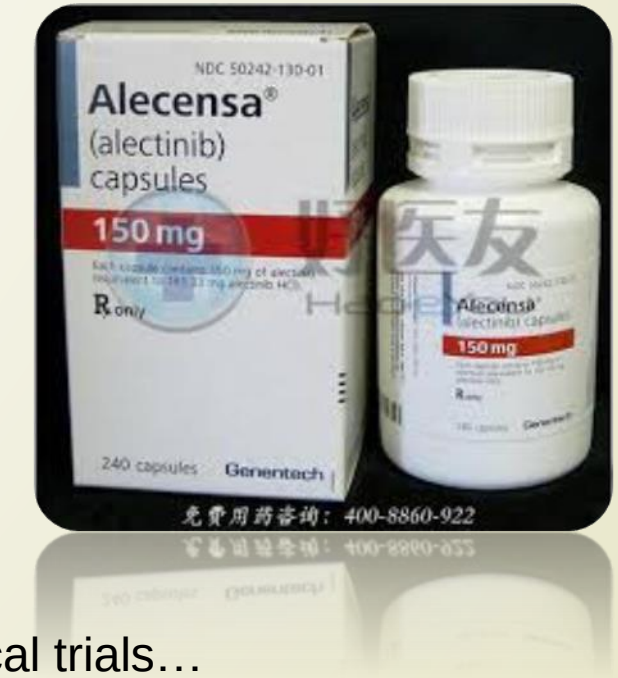
Figure 3. *ROS1* gene rearrangement in lung adenocarcinoma using a break-apart FISH assay, characterized by separation of red and green probes for *ROS1* gene in the tumor cells



When diagnosing ALK rearrangement…

Why?

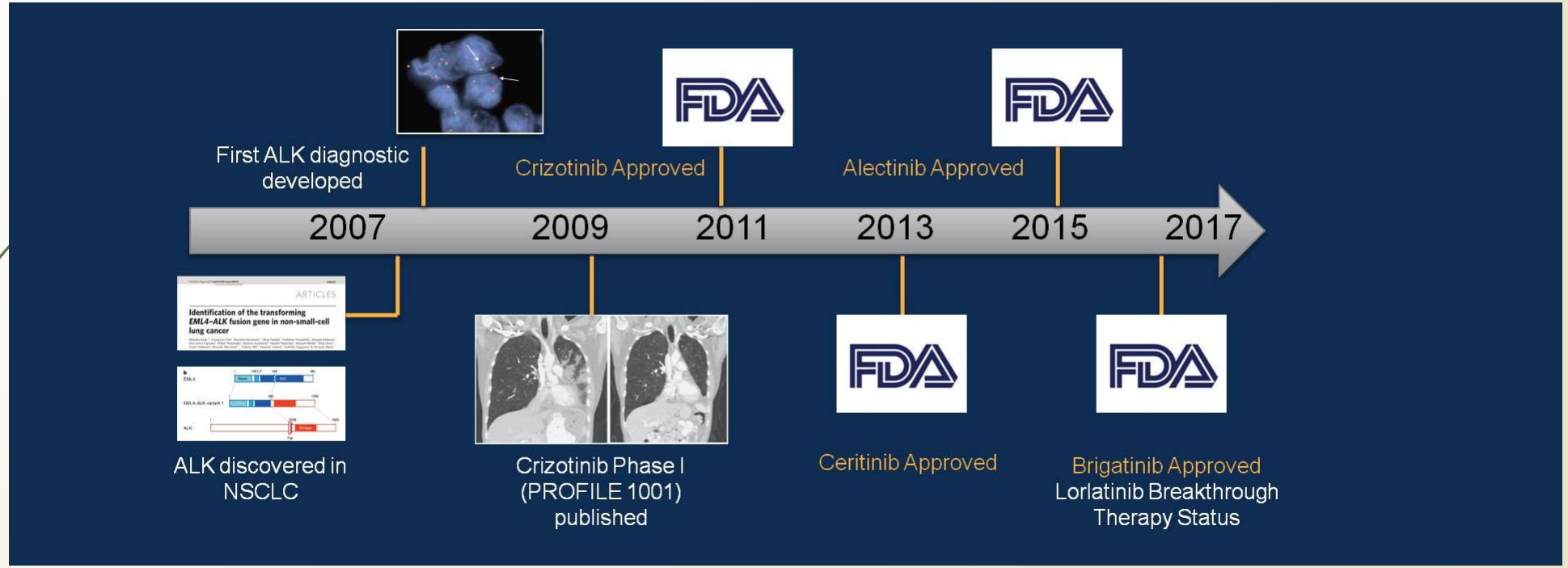
Because there are so many treatment options…and significant OS benefit



Lorlatinib, Ensartinib and many more in clinical trials…

How did it all start?

Treatment for ALK +ive NSCLC- the most rapid clinical translation!



Crizotinib is the 1st drug approved for ALK-rearrangement based on phase I trial

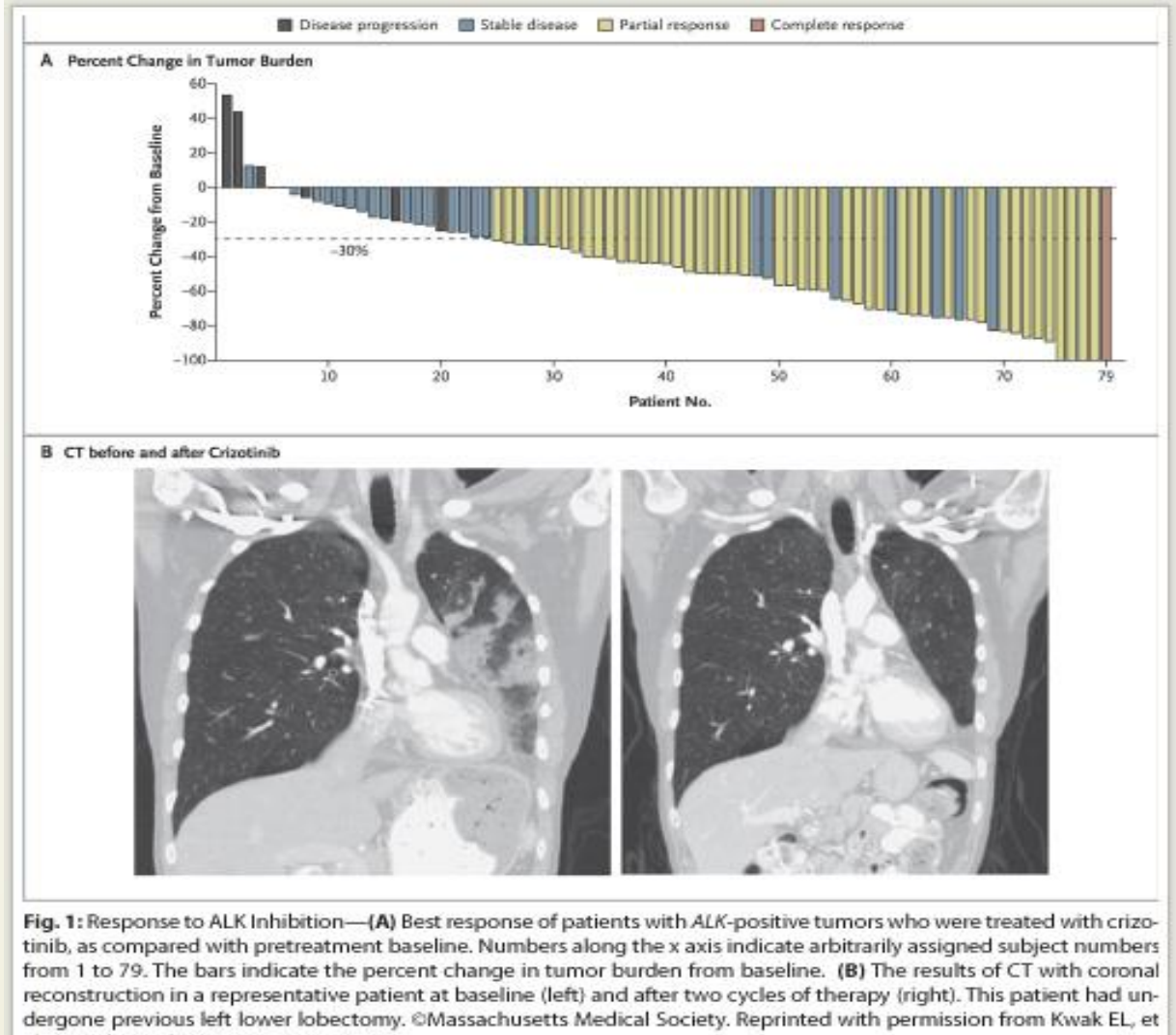


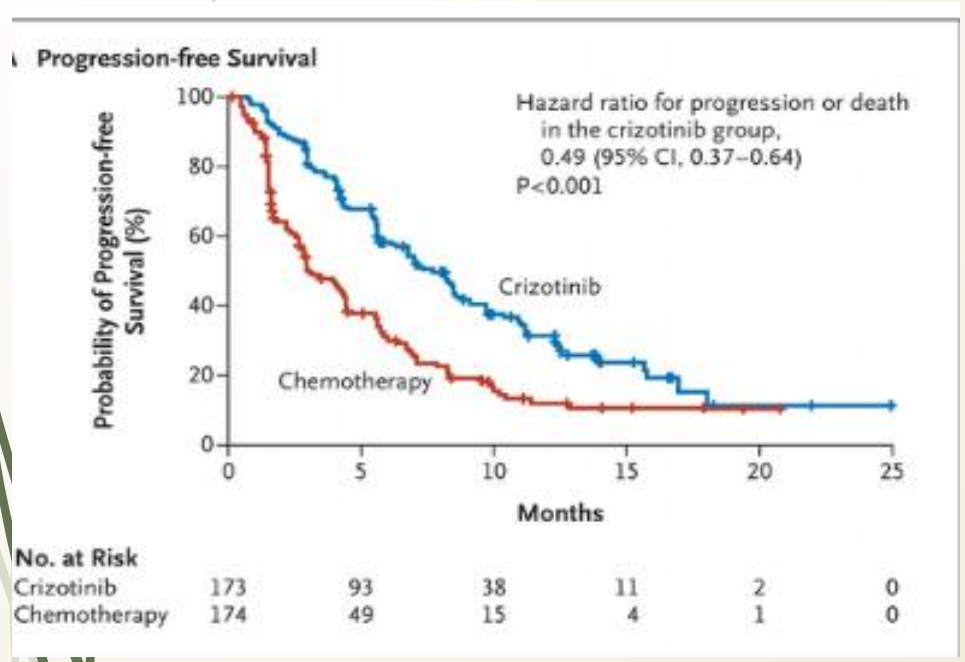
Fig. 1: Response to ALK Inhibition—**(A)** Best response of patients with *ALK*-positive tumors who were treated with crizotinib, as compared with pretreatment baseline. Numbers along the x axis indicate arbitrarily assigned subject numbers from 1 to 79. The bars indicate the percent change in tumor burden from baseline. **(B)** The results of CT with coronal reconstruction in a representative patient at baseline (left) and after two cycles of therapy (right). This patient had undergone previous left lower lobectomy. ©Massachusetts Medical Society. Reprinted with permission from Kwak EL, et

Side effects

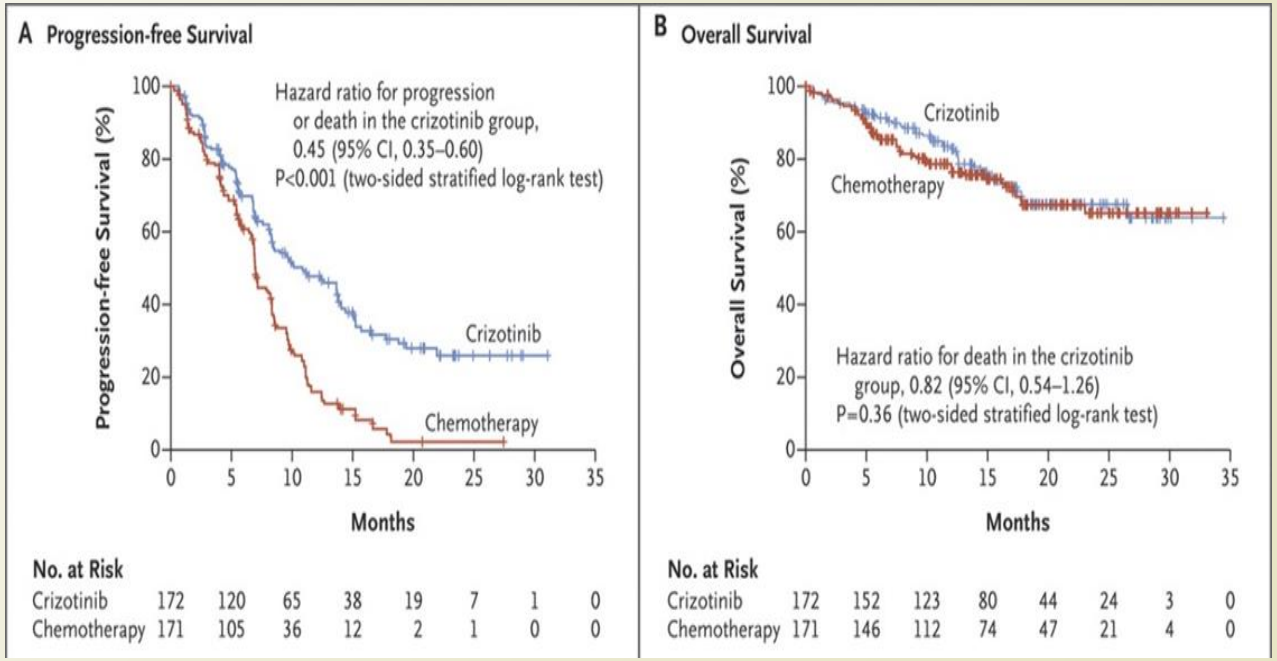
- Hepatotoxicity
- Pneumonitis
- Visual disturbance
- Nausea
- Edema

Crizotinib was assessed in 1st and 2nd line ALK-positive NSCLC in RCT vs. chemo

Crizotinib as 2nd line in ALK+ patients (PROFILE 1007)



Crizotinib as 1st line in ALK+ patients (PROFILE 1014)

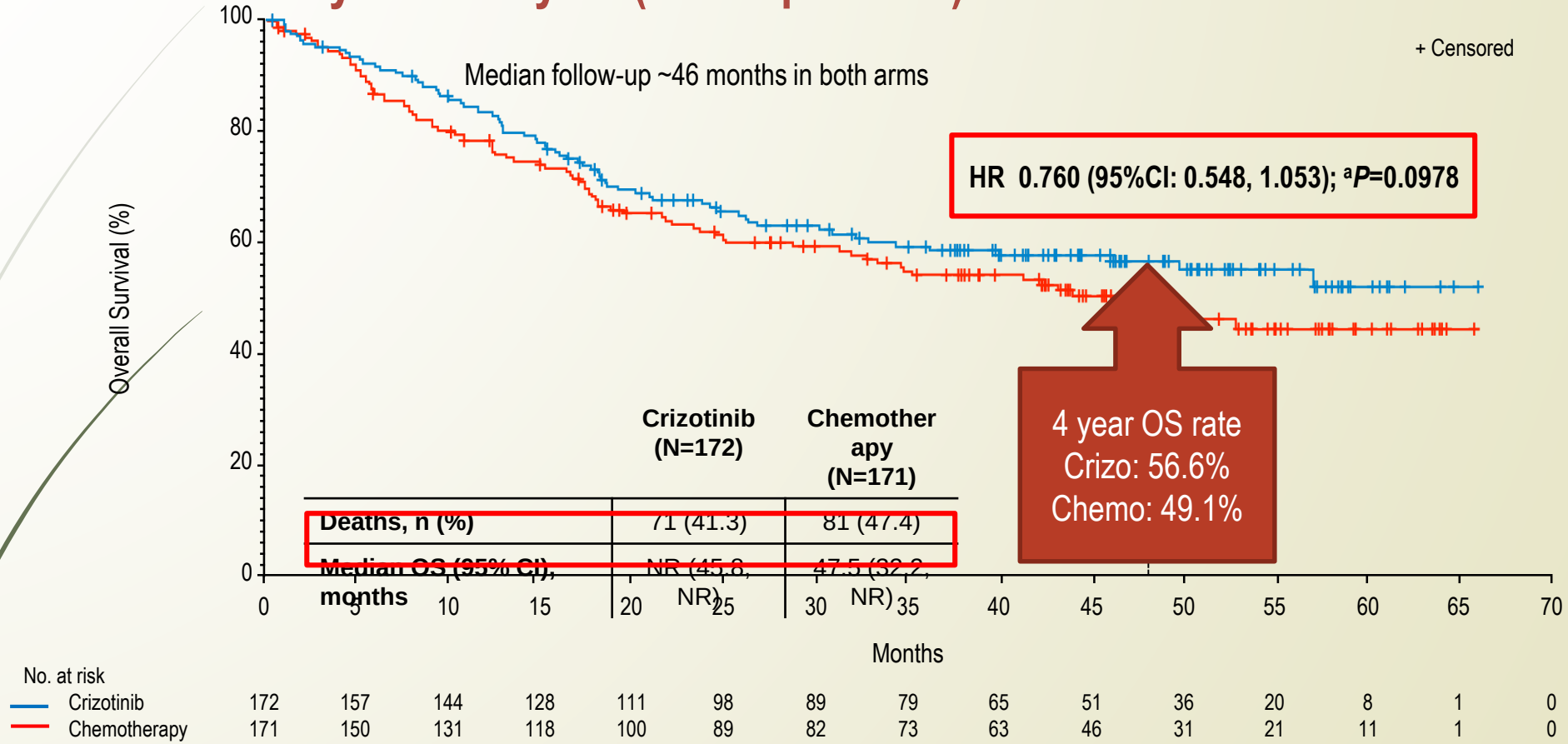


- **Median duration of treatment: Crizotinib, 10.9 months; chemotherapy, 4.1 months**

Shaw AT et al. N Engl J Med 2013;368:2385-2394.

Solomon BJ et al. N Engl J Med 2014;371:2167-2177. PROFILE 1014

Final Primary OS Analysis (ITT Population) PROFILE 1014



	Crizotinib (N=172)	Chemotherapy (N=171)
Deaths, n (%)	71 (41.3)	81 (47.4)
Median OS (95% CI), months	NR (45.8, NR)	47.5 (32.2, NR)

[a]2-sided p-value from the log-rank test stratified by ECOG PS, race, brain metastases.

Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced *ALK*-positive NSCLC

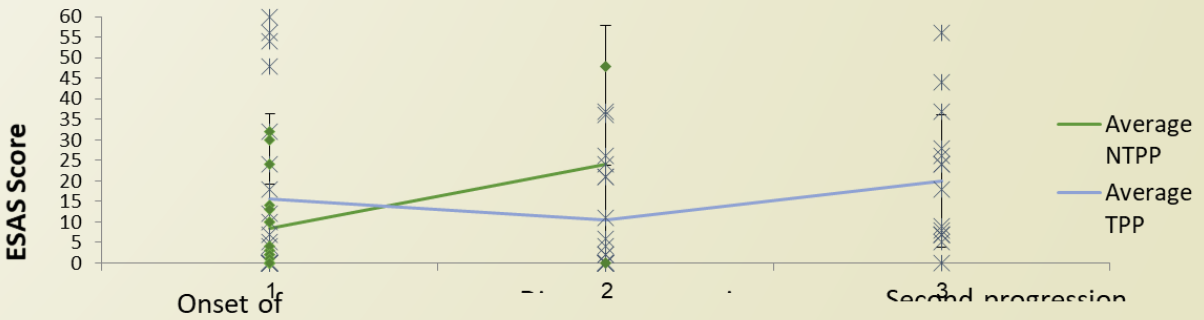
S.-H. I. Ou[1*,†], P. A. Jänne[2,†], C. H. Bartlett[3], Y. Tang[4], D.-W. Kim[5], G. A. Otterson[6], L. Crinò[7], P. Selaru[4], D. P. Cohen[4], J. W. Clark[8] & G. J. Riely[9]

Annals of Oncology 25: 415–422, 2014

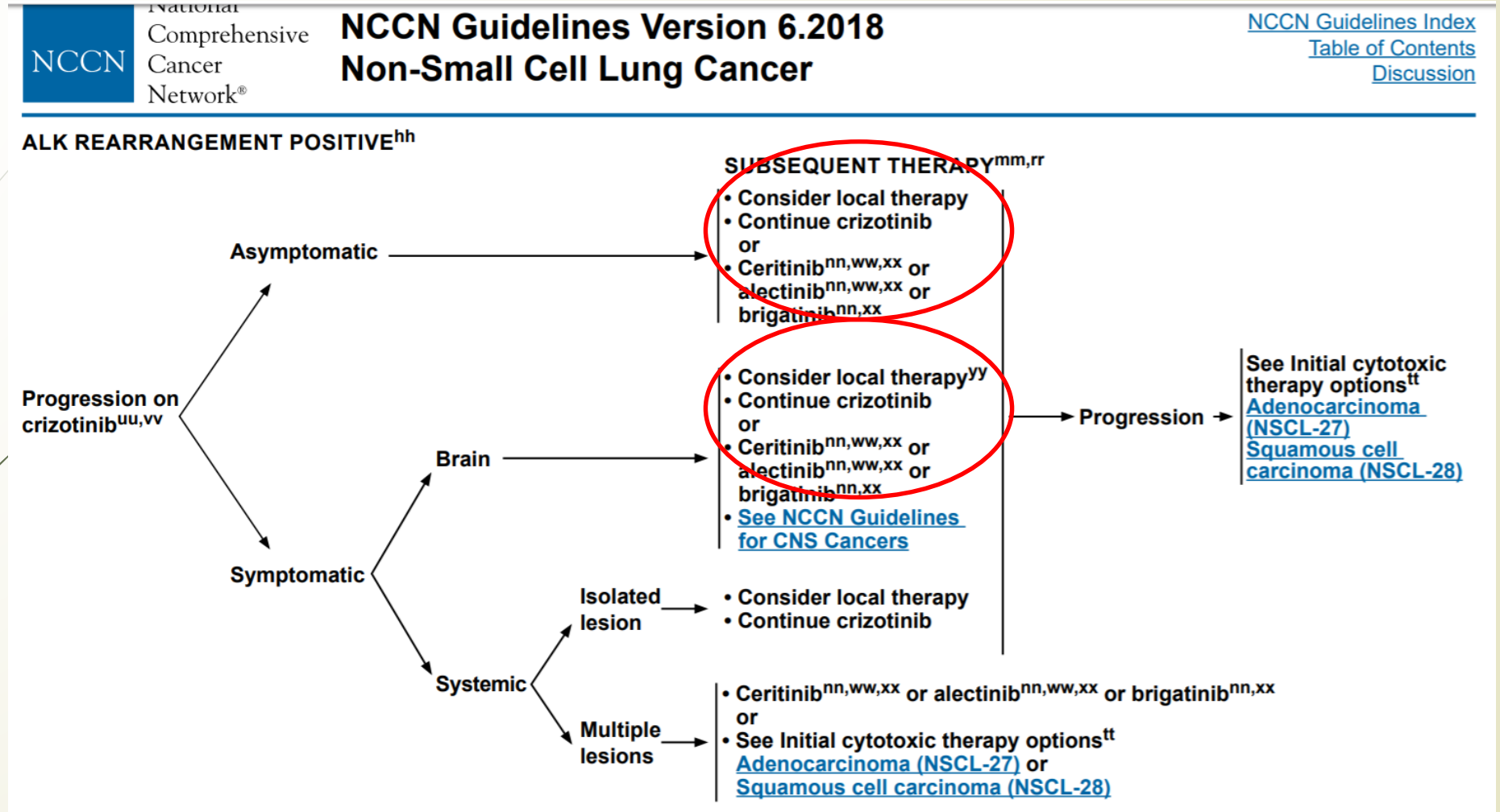
Site of initial disease progression
(New lesions and/or non-target lesions)

Site of disease progression	All patients (N = 138) (%)	CBPD (N=78) (%)	No CBPD (N = 60) (%)
Brain	57 (41)	40 (51)	17 (28)
Liver	34 (25)	12 (15)	22 (37)
Lung	22 (16)	10 (13)	12 (20)
Bone	13 (9)	8 (10)	5 (8)
Pleural effusion cavity	11 (8)	3 (4)	8 (13)
Lymph node	7 (5)	2 (3)	5 (8)
Other	30 (22)	10 (13)	20 (33)

Mean symptom burden during treatment with ALK inhibitors

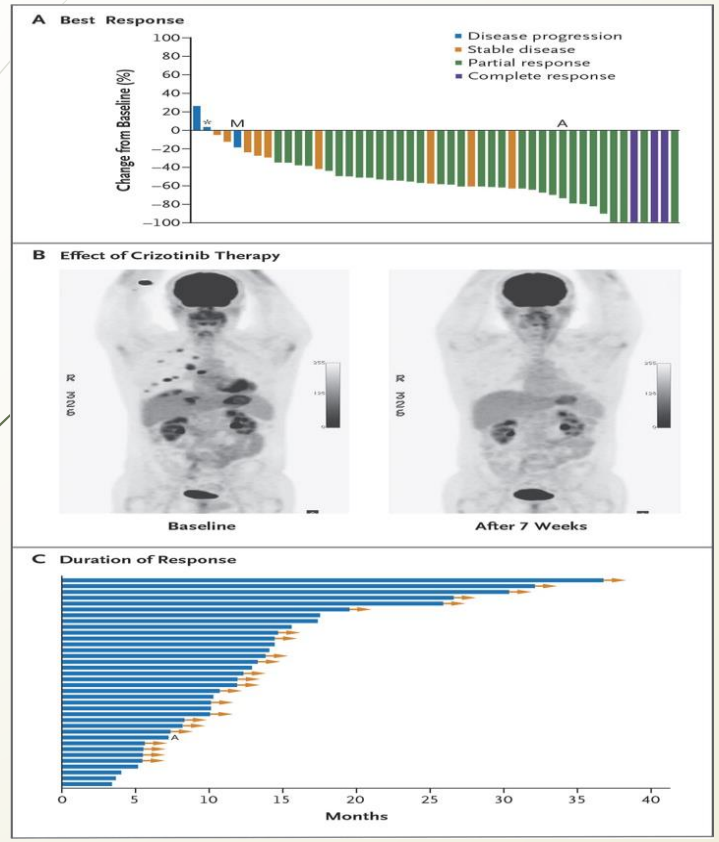


Treatment beyond disease progression: ALK inhibitors in *ALK*-rearranged advanced NSCLC
Mor Moskovitz, Priscilla Matthews, Alexandra Pavel, Dongyang Yang, Brendon Morganstein, Wei Xu, Penelope Bradbury, Geoffrey Liu, Frances Shepherd, Natasha B. Leighl Annals of Oncology 28.suppl_5 (2017).

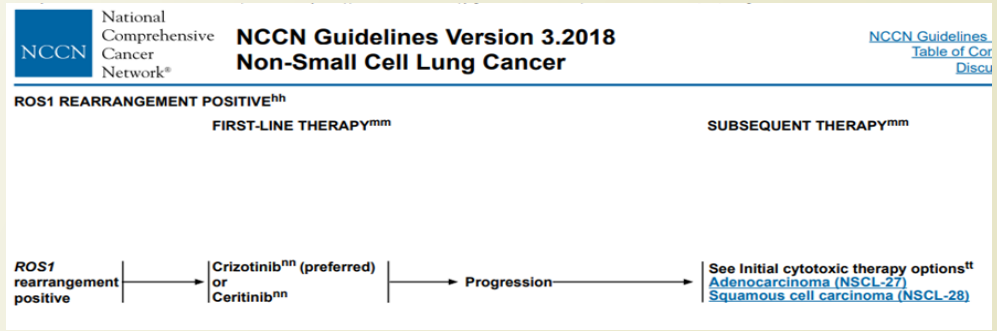


The NCCN suggest consider treatment past progression!

Tumor Responses to Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer.

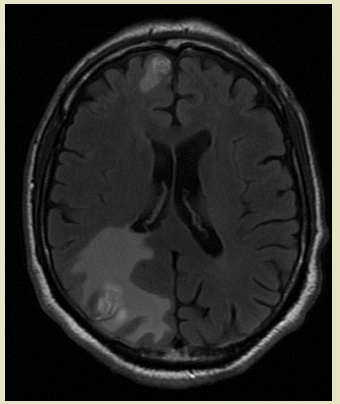


Shaw AT et al. N Engl J Med 2014;371:1963-1971.



The CNS- A sanctuary site

- 30-40% of ALK rearranged patients have brain mets at initial diagnosis.
- CNS is one of the most common sites of relapse on Crizotinib- first site of disease progression in 46% of patients!
- Among ALK rearranged patients entering trials with next-generation ALK TKIs, rates of CNS mets approaching 60%
- Brain metastases impact quality of life



What did we do with brain metastases in the past?

- Radiotherapy- whole brain, stereotactic radiotherapy
- Changing crizotinib schedule

CASE REPORT

Effective Crizotinib Schedule for Brain Metastases in ALK Rearrangement Metastatic Non–Small-Cell Lung Cancer

Nir Peled, MD, PhD, Leor Zach, MD,† Ori Liran, MSc,* Maya Ilouze, PhD,* Paul A. Bunn Jr., MD,‡ and Fred R. Hirsch, MD, PhD‡*

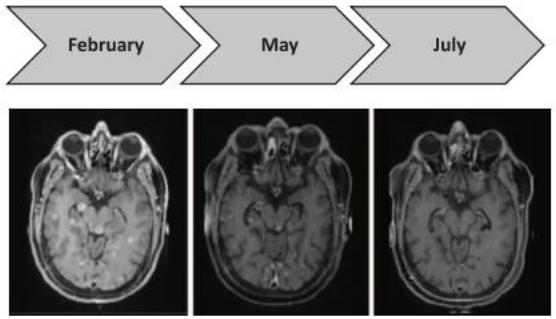
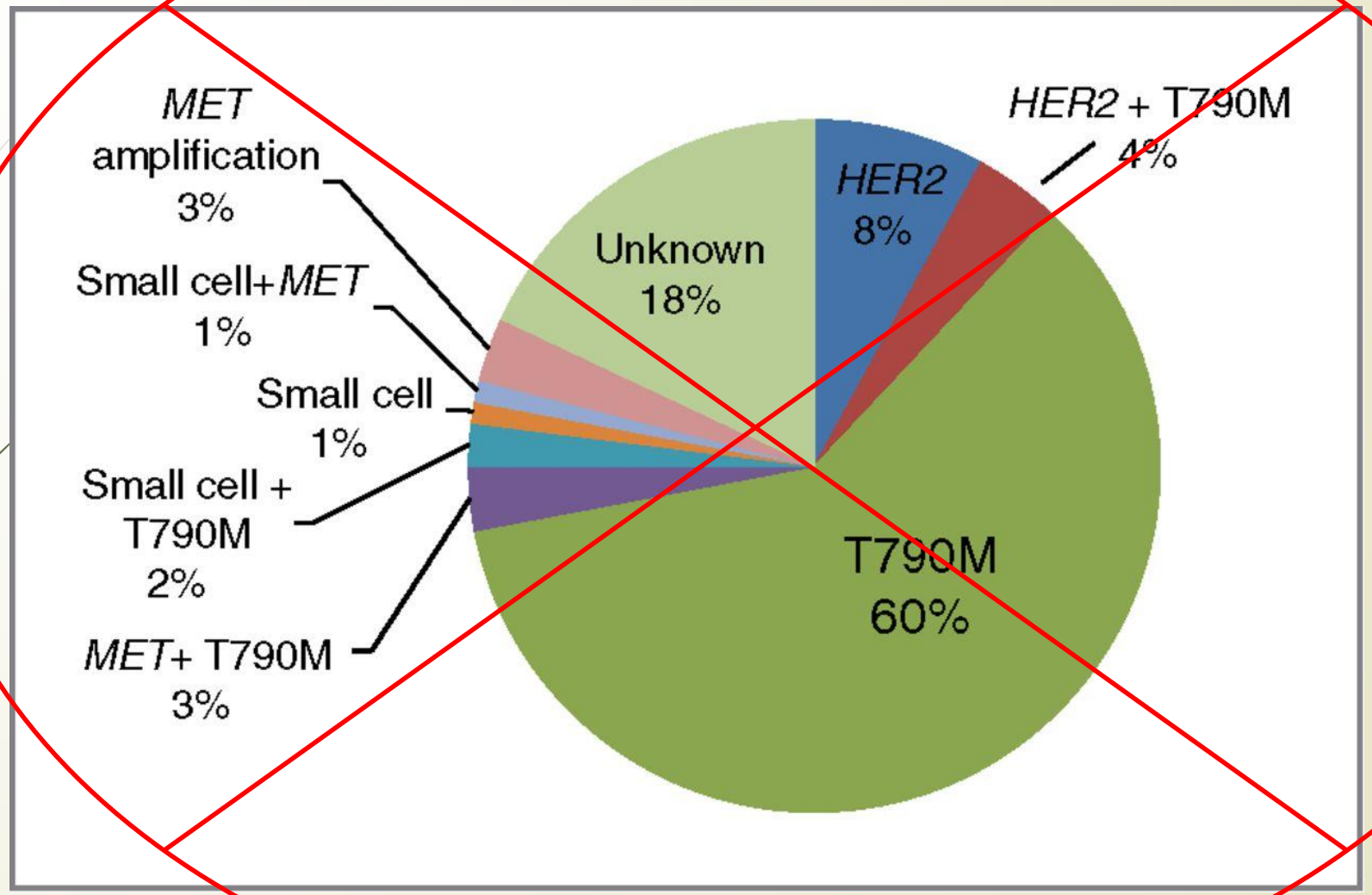


FIGURE 1. Brain MRIs (axial t1 with contrast images) in February, May, and July 2013. Brain metastases were diagnosed after 20 months of crizotinib therapy (250 mg twice daily). Whole-brain radiotherapy (3000 cGy/10fr) was administered while crizotinib was continued in standard dose (except for the radiation period). Follow-up MRI (May 2013) showed lack of response. Then, crizotinib was rescheduled for 500 mg X1/day, with a dramatic response 2 months later. MRI, magnetic resonance imaging.

Resistance pathways to EGFR TKI



Not so easy with ALK…

Helena A. Yu et al. Clin Cancer Res 2013;19:2240-2247

Clinical Cancer Research
AACR American Association for Cancer Research

Resistance – mostly due to ALK secondary mutation- and more…

Crizotinib: Acquired Resistance

Target-Independent Mechanisms	Reference
EGFR activation	Katayama et al. *Sci Transl Med* 2012
MAPK pathway reactivation	Doebele et al. *Clin Cancer Res* 2012
c-KIT amplification and SCF overexpression	Katayama et al. *Sci Transl Med* 2012
SRC activation	Crystal et al. *Science* 2014
IGF-1R activation	Lovly et al. *Nat Med* 2014
Ligand-mediated HER2/3 activation	Wilson et al. *Cancer Cell* 2015
Protein kinase C activation	Wilson et al. *Cancer Cell* 2015
Small cell transformation (rare)	Fujita et al. *J Thorac Oncol* 2016

Drug Sensitivity

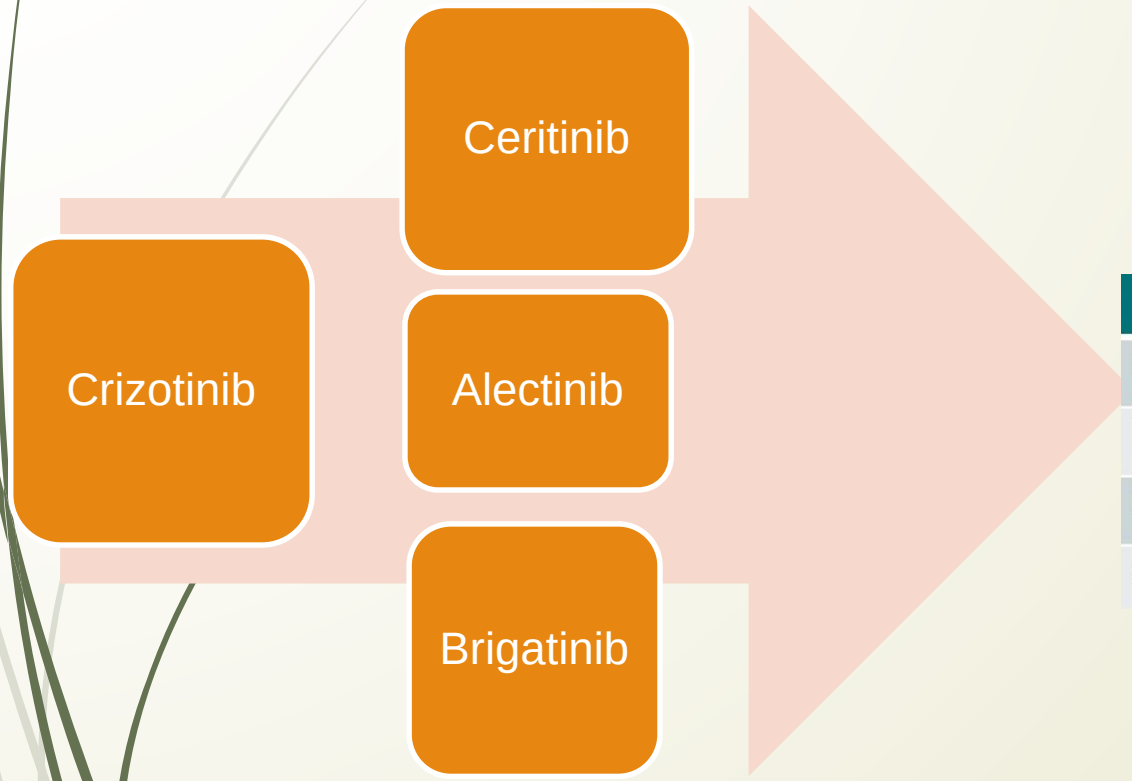
Different spectrum of activity to each drug-
but still no selection of treatment based on resistance profile…

$IC_{50} \leq 50$ nmol/L
$IC_{50} > 50 < 200$ nmol/L
$IC_{50} \geq 200$ nmol/L

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

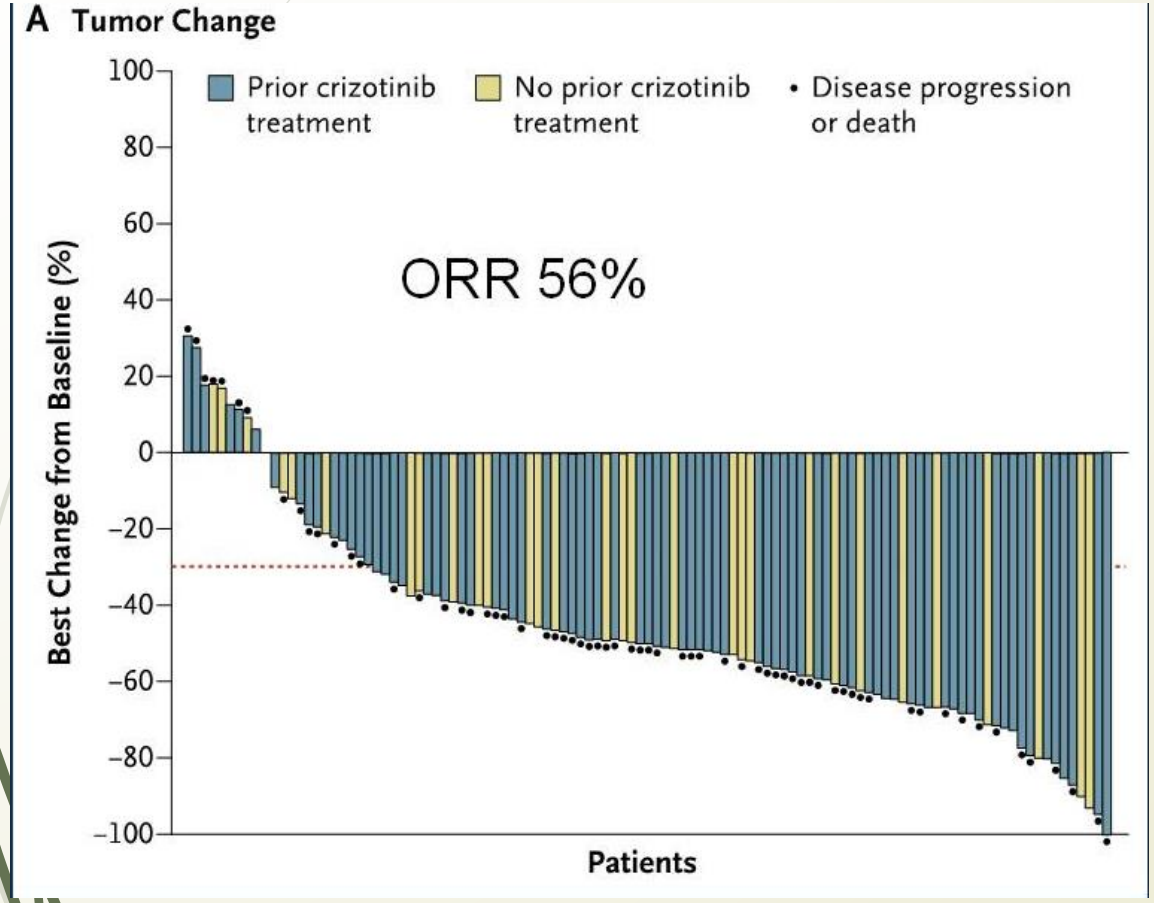
2nd line treatment after Crizotinib resistance



	Ceritinib	Alectinib	Brigatinib
ORR	39-56%	48-50%	45-62%
Median PFS	5.4-6.9 months	8.1-8.9 months	9.2-15.6
Intracranial ORR†	36-45%	57-75%	42-67%
Safety Considerations	GI toxicities	Constipation, myalgia	Pulmonary events

Ceritinib- the second ALK TKI

ASCEND-1



Study	Phase	Population	N	ORR	PFS (months)	Intracranial ORR†
ASCEND-1	I	Criz-naïve	83	72%	18.4	75% (N=4)
		Criz-resistant	163	56%	6.9	36% (N=28)
ASCEND-2	II	Criz-resistant‡	140	38.6%	5.7	45% (N=20)
ASCEND-3	II	ALKi-naïve	124	58.9%	11.1	59% (N=17)
ASCEND-4	III	Treatment-naïve	189	72.5%	16.6	73% (N=22)
ASCEND-5	III	Previous chemo and crizotinib	115	39.1%	5.4	NR

But….

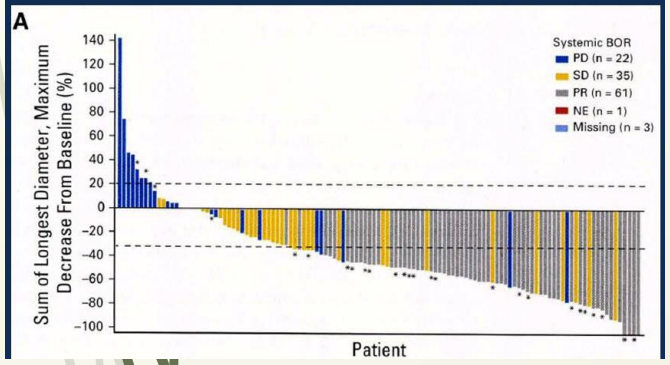
Select AEs (>30%)

Adverse Event	Grade 1-2	Grade 3	Grade 4
Diarrhea	80%	6%	0%
Nausea	77%	6%	0%
Vomiting	57%	4%	0%
Fatigue	38%	5%	0%
Abdominal pain	37%	1%	0%
Decreased appetite	36%	2%	0%

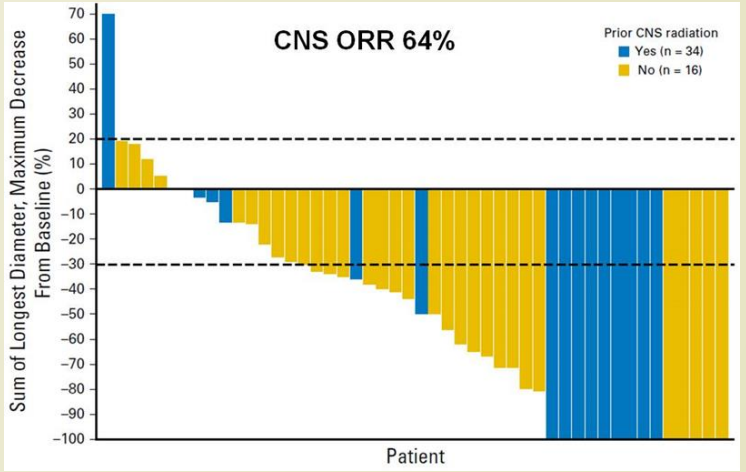
Significant toxicity!!!

Alectinib- early phases efficacy

Global Phase II (NP28673)
ORR 50%
Median PFS 8.9 months



Adverse Events	North American (NP28761)	Global (NP28673)
Constipation	36%	33%
Fatigue	33%	26%
Myalgia	24%	23%
Peripheral Edema	23%	25%



Phase II Studies: NP28761 and NP28673

Locally advanced or metastatic NSCLC
ALK+ disease
Prior crizotinib treatment
ECOG PS 0–2
NP28673 (n=138)
NP28761 (n=87)

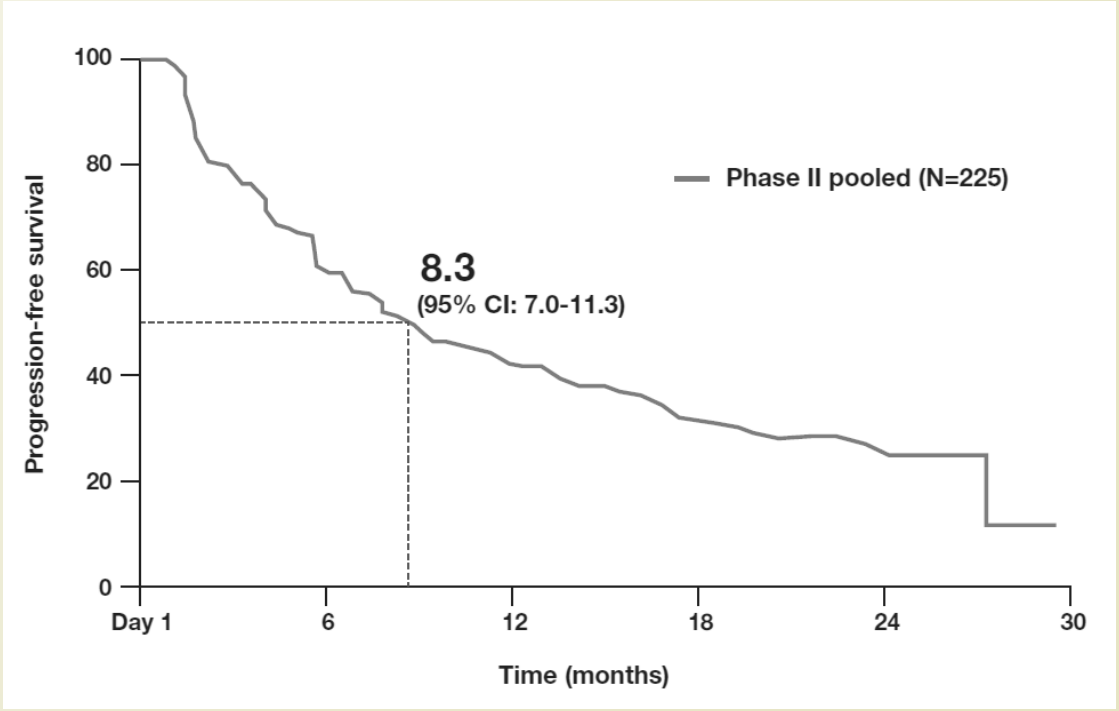
→ **Alectinib 600mg BID** → **PD**

Primary endpoint

- **ORR by IRC**
- **Co-primary endpoint for NP28673: ORR by IRC in patients with prior chemo**

Secondary endpoints

- **CNS ORR**
- **CNS DoR**
- **PFS**
- **DCR**
- **Safety**

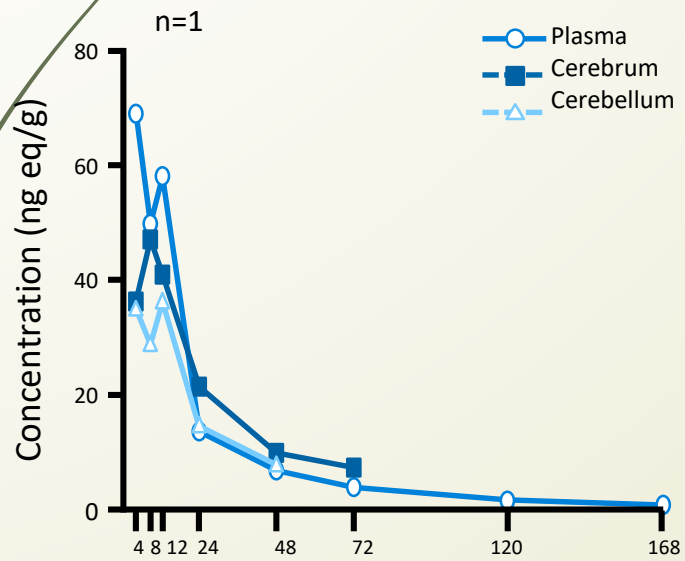


Shaw et al., Lan Onc 2016
Ou SH et al., JCO 2015

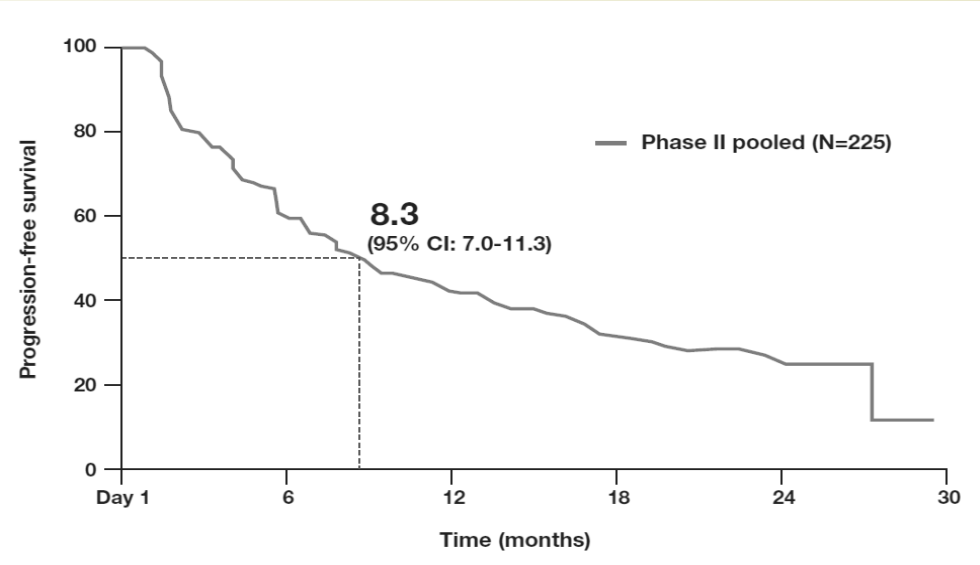
CNS: First Place of Progression in 46% of 1L Patients

Alectinib is not a substrate for the drug efflux transporter P-gp3, and is therefore not actively transported out of the brain[1]

^{14}C-labelled Alectinib administration shows similar CSF and Plasma Concentration[1]



Alectinib is clinically active in the CNS irrespective of prior radiation[2]

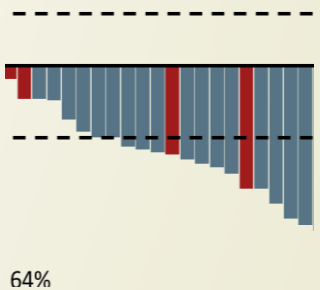


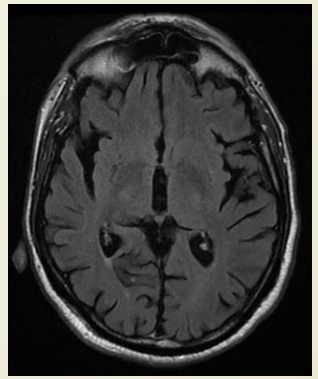
. Gadgeel, et al. J Clin Oncol 20162. Kodama, et al. Cancer Chemother Pharmacol 2014 , 1

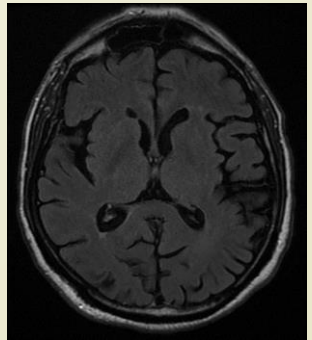
Patient case

- 76 y male, diagnosed 10/2015 with NSCLC Adenocarcinoma, stage IIIA
- Resection and adjuvant chemo-radio
- 06/2017- metastases in brain and lymph nodes
- Treated with Crizotinib with good systemic response, stable CNS disease
- 11/2017- PD in brain
- 12/2017- started Alectinib

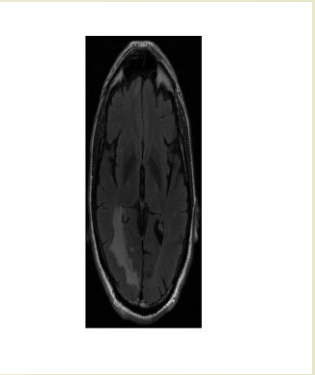
November 2017

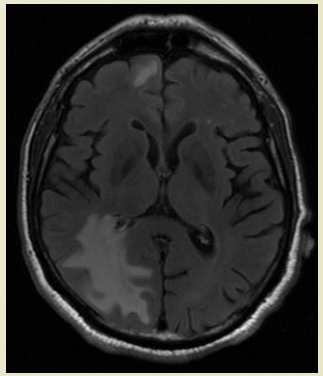


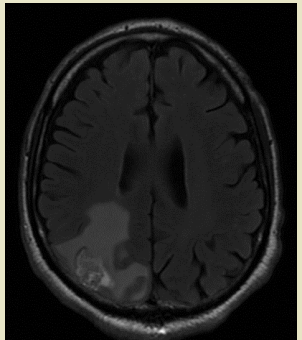




February 2018





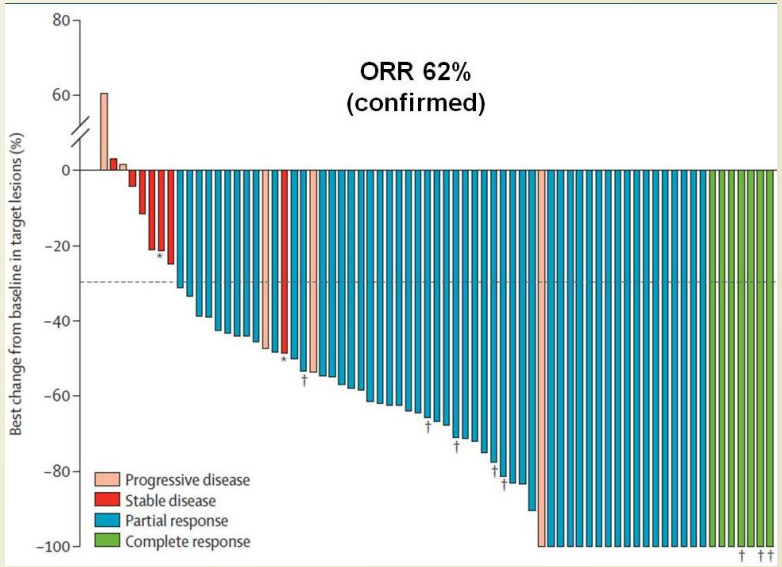


Brigatinib-next generation ALK inhibitor

Mechanism of Action

- Brigatinib is a tyrosine kinase inhibitor with in vitro activity against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-IR), and FLT-3, as well as EGFR deletion and point mutations
- It inhibits autophosphorlylation of ALK and ALK-mediated phosphorylation of downstream signaling proteins STAT3, AKT, ERK1/2, and S6
- It is also inhibits in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins

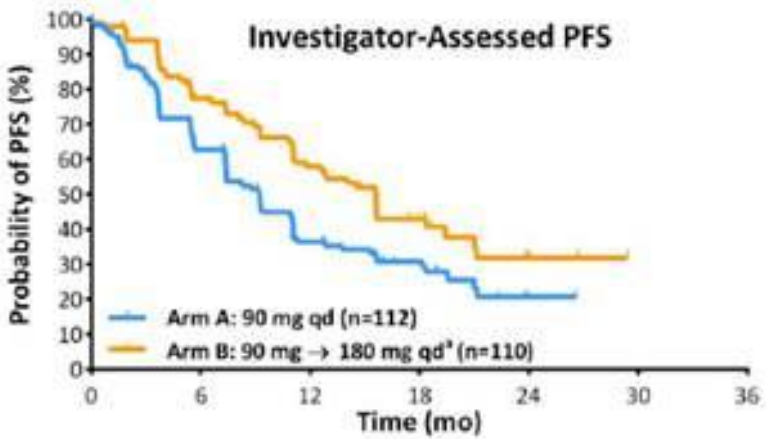
Phase I

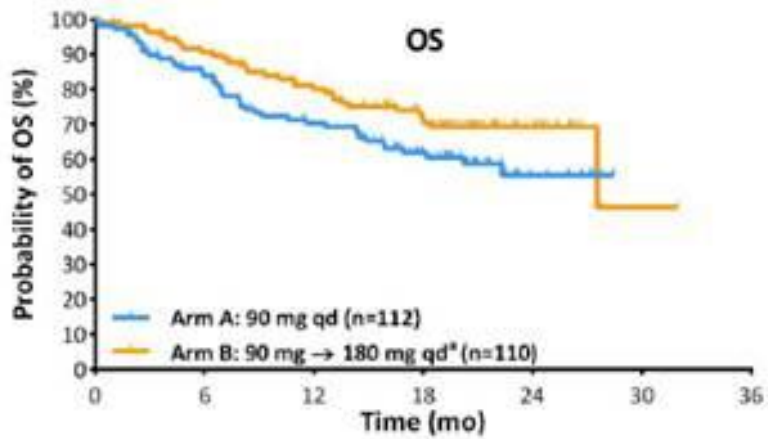


Brigatinib- efficacy and safety in the 2nd line

Randomised phase II- ALTAtrial

Survival in Crizotinib-Resistant Patients





Treatment	Median PFS (95% CI)	HR (95% CI)
Arm A: 90 mg qd (% events = 65)	9.2 months (7.4–11.1)	0.64 (0.45–0.91)
Arm B: 90 mg → 180 mg qd[a] (% events = 50)	15.6 months (11.1–19.4)	

Treatment	Median OS (95% CI)	HR (95% CI)
Arm A: 90 mg qd (% events = 38)	NR (20.2–NR)	0.67 (0.42–1.06)
Arm B: 90 mg → 180 mg qd[a] (% events = 29)	27.6 months (27.6–NR)	

[a] 180 mg qd with 7-day lead-in at 90 mg. HR, hazard ratio; NR, not reached; qd, once daily

- IRC-assessed median PFS was 9.2 months (95% CI, 7.4–12.8 months) in Arm A and 16.7 months (95% CI, 11.6–NR months) in Arm B

Mechanism of Action

- Brigatinib is a tyrosine kinase inhibitor with in vitro activity against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1R), and FLT-3, as well as EGFR deletion and point mutations
- It inhibits autophosphorylation of ALK and ALK-mediated phosphorylation of downstream signaling proteins STAT-3, AKT, ERK1/2, and S6
- It is also inhibits in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins

Intra-cranial response

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

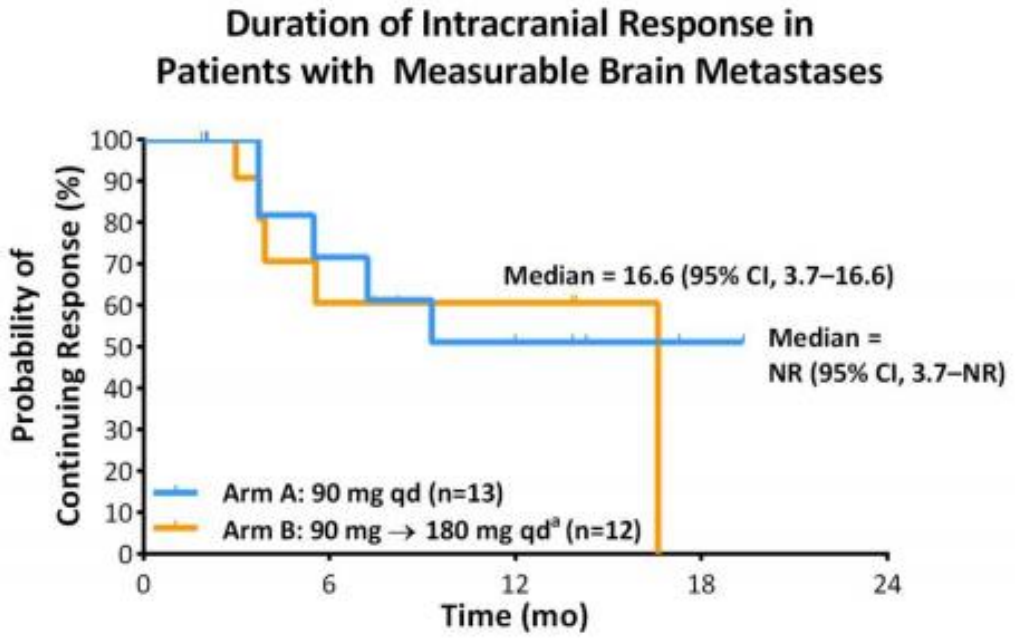
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

IRC-Assessed Intracranial Response in Patients With Baseline Brain Metastases

IRC-Assessed Efficacy Parameter, % (95% CI)	Patients With Measurable Brain Metastases	
	Any	
	Arm A, n=26	Arm B,[a] n=18
Confirmed intracranial ORR	50 (30–70)	67 (41–87)
Intracranial disease control rate	85 (65–96)	83 (59–96)
	Active Brain Lesions	
	Arm A, n=19	Arm B,[a] n=15
Confirmed intracranial ORR	47 (24–71)	73 (45–92)
Intracranial disease control rate	84 (60–97)	93 (68–99.8)

[a] 180 mg qd with 7-day lead-in at 90 mg

- Complete response in patients with only nonmeasurable intracranial CNS metastases at baseline:
  - 7% (4/54) and 18% (10/55) in Arms A and B, respectively



Last scan date: January 24, 2017
[a] 180 mg qd with 7-day lead-in at 90 mg
NR, not reached

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

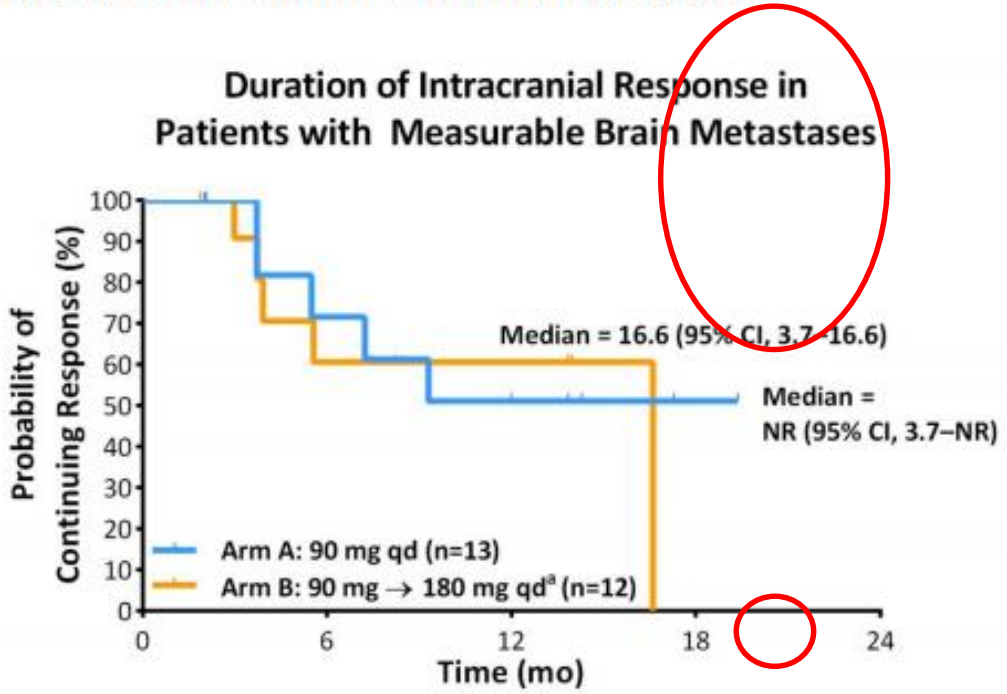
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

IRC-Assessed Intracranial Response in Patients With Baseline Brain Metastases

IRC-Assessed Efficacy Parameter, % (95% CI)	Patients With Measurable Brain Metastases	
	Any	
	Arm A, n=26	Arm B,[a] n=18
Confirmed intracranial ORR	50 (30–70)	67 (41–87)
Intracranial disease control rate	85 (65–96)	83 (59–96)
	Active Brain Lesions	
	Arm A, n=19	Arm B,[a] n=15
Confirmed intracranial ORR	47 (24–71)	73 (45–92)
Intracranial disease control rate	84 (60–97)	93 (68–99.8)

[a] 180 mg qd with 7-day lead-in at 90 mg

- Complete response in patients with only nonmeasurable intracranial CNS metastases at baseline:
  - 7% (4/54) and 18% (10/55) in Arms A and B, respectively

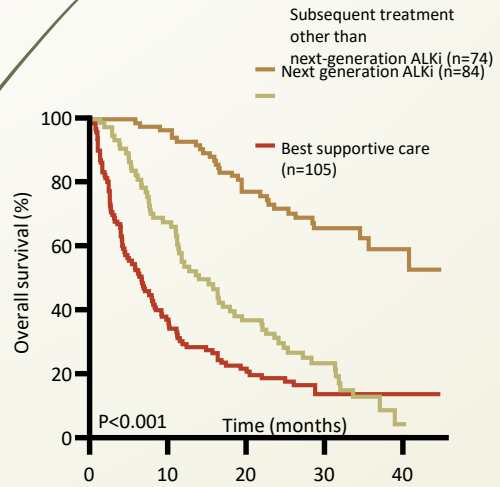


Last scan date: January 24, 2017
[a] 180 mg qd with 7-day lead-in at 90 mg
NR, not reached

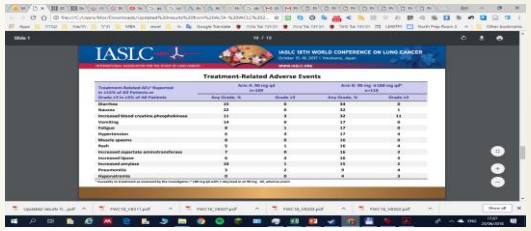
ALK+ NSCLC: sequence of crizotinib followed by next generation inhibitor: mOS of 89.6 months

Progression-Free and Overall Survival of Patients With *ALK* Rearrangement–Positive Non–Small Cell Lung Cancer Treated Sequentially With Crizotinib and Alectinib

Satomi Watanabe,[1] Hidetoshi Hayashi,[1] Kunio Okamoto,[2] Kimiko Fujiwara,[3] Yoshikazu Hasegawa,[4] Hiroyasu Kaneda,[2] Kaoru Tanaka,[1] Masayuki Takeda,[1] Kazuhiko Nakagawa[1]



Median OS = 89.6 months



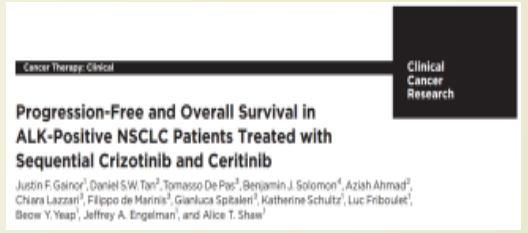
www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 13), pp: 21903-21917

Research Paper

Overall survival with crizotinib and next-generation ALK inhibitors in *ALK*-positive non-small-cell lung cancer (IFCT-1302 CLINALK): a French nationwide cohort retrospective study

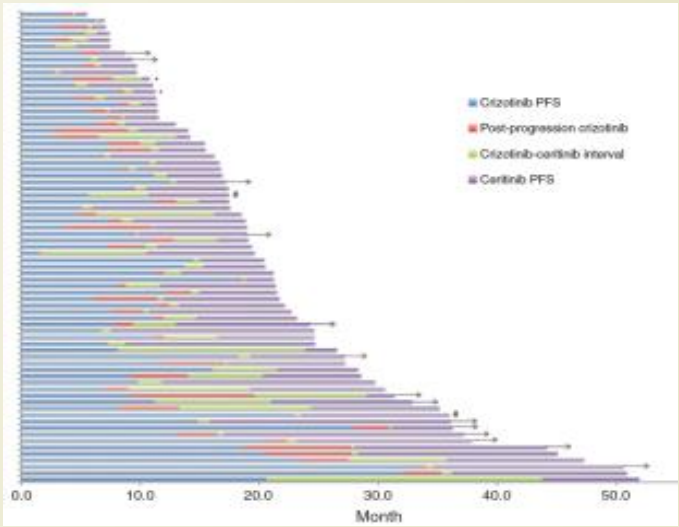
Michaël Duruisseaux[1], Benjamin Besse[2], Jacques Cadranel[3], Maurice Pérol[4], Bertrand Mennecier[5], Laurence Bigay-Game[6], Renaud Descourt[7], Eric Dansin[8], Clarisse Audigier-Valette[9], Lionel Moreau[10], José Hureaux[11], Remi Veillon[12], Josiane Otto[13], Anne Madroszyk-Flandin[14], Alexis Cortot[15], François Guichard[16], Pascaline Boudou-Rouquette[17], Alexandra Langlais[18], Pascale Missy[19], Franck Morin[19], Denis Moro-Sibilot[1]

Median combined PFS: 17.4 months
Median OS: 49.4 months



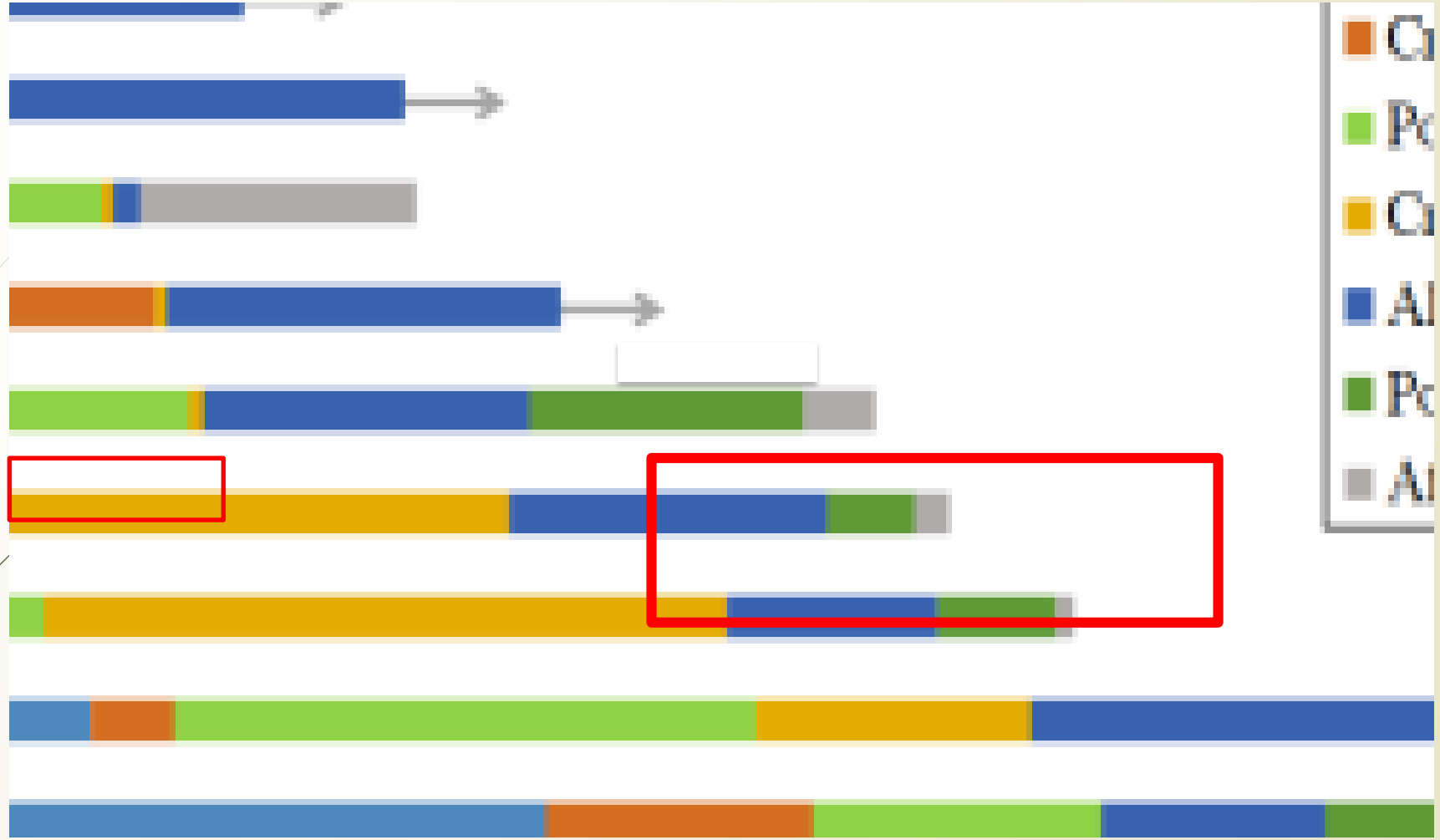
Progression-Free and Overall Survival in ALK-Positive NSCLC Patients Treated with Sequential Crizotinib and Ceritinib

Justin F. Gainor[1], Daniel S.W. Tan[2], Tomasso De Pas[3], Benjamin J. Solomon[4], Azish Ahmad[5], Chiara Lazzari[3], Filippo de Marinis[3], Gianluca Spitaleri[3], Katherine Schultz[1], Luc Friboulet[1], Beow Y. Yeap[1], Jeffrey A. Engelman[1], and Alice T. Shaw[1]



Median combined PFS: 18.2 months
Median OS: 51.1 months

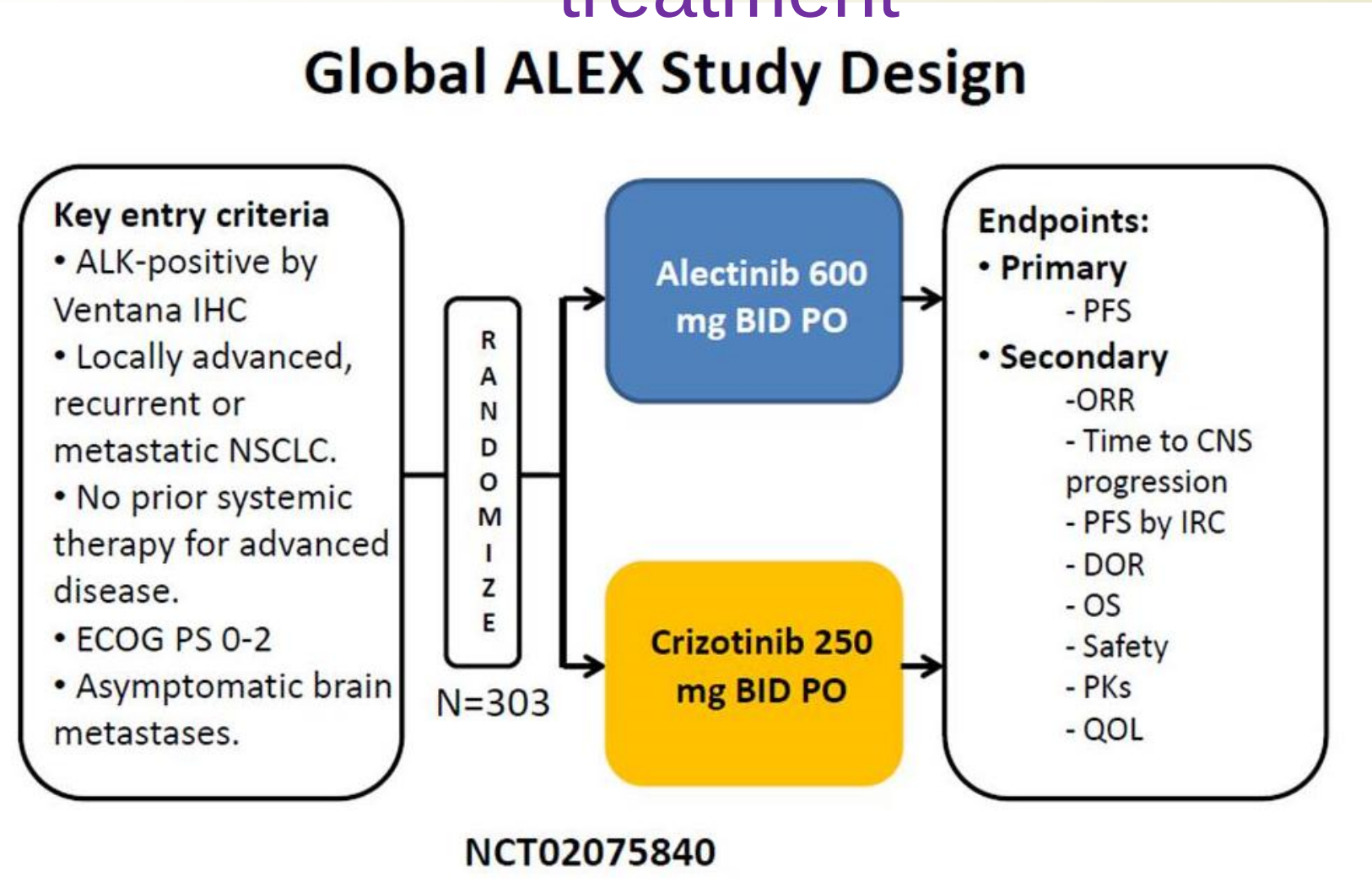
Duruisseaux M, et al. Oncotarget 2017; Gainor JF, et al. Clin Cancer Res 2015; Watanabe S, et al. Clin Lung Cancer 2016



Unmet need in the first line-

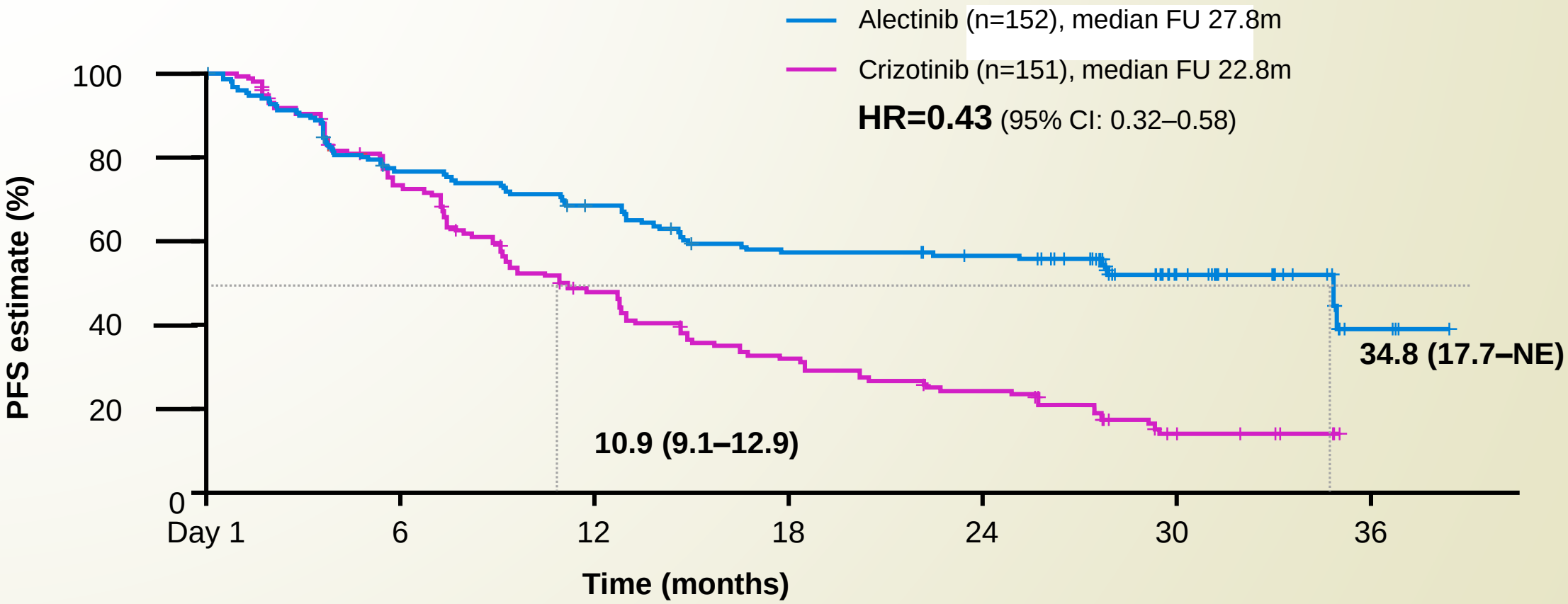
- **50% of patients progress within 1 year** on treatment with Crizotinib
- **CNS is the first site of disease progression in 46%** of patients
- A significant portion of patients will not continue 2L treatment (Poor PS)

ALEX- alectinib vs. crizotinib in the 1st line of treatment



ALEX: Investigator Assessed PFS

57% reduction in risk to progression vs. SoC



	Alectinib	Crizotinib
Events, n (%)	72 (47)	116 (77)

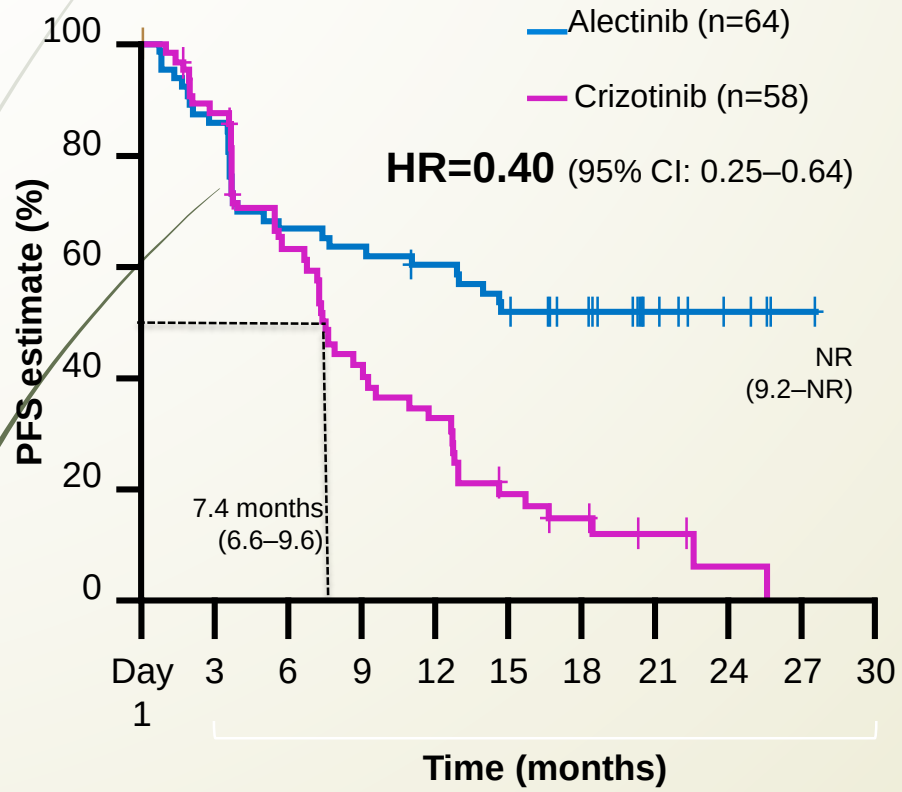
NE = not estimable; FU = Follow Up

NCT02075840

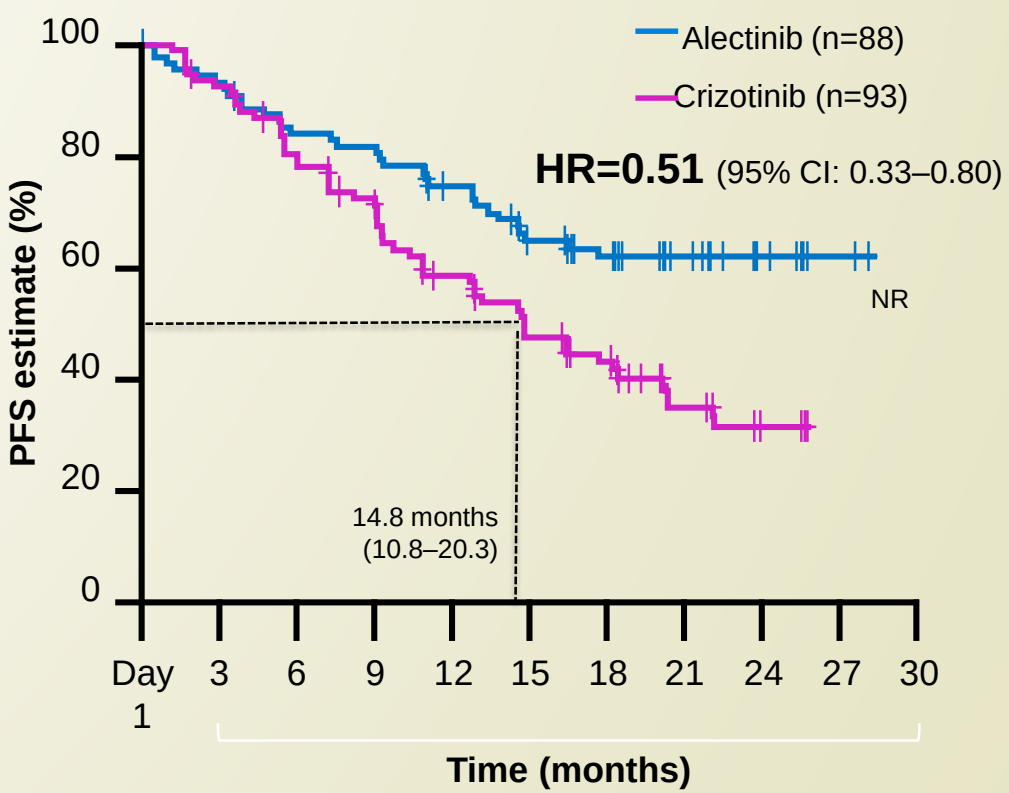
Camidge, et al. ASCO 2018

ALEX- PFS was improved regardless of CNS metastases status

Pts with CNS mets at baseline



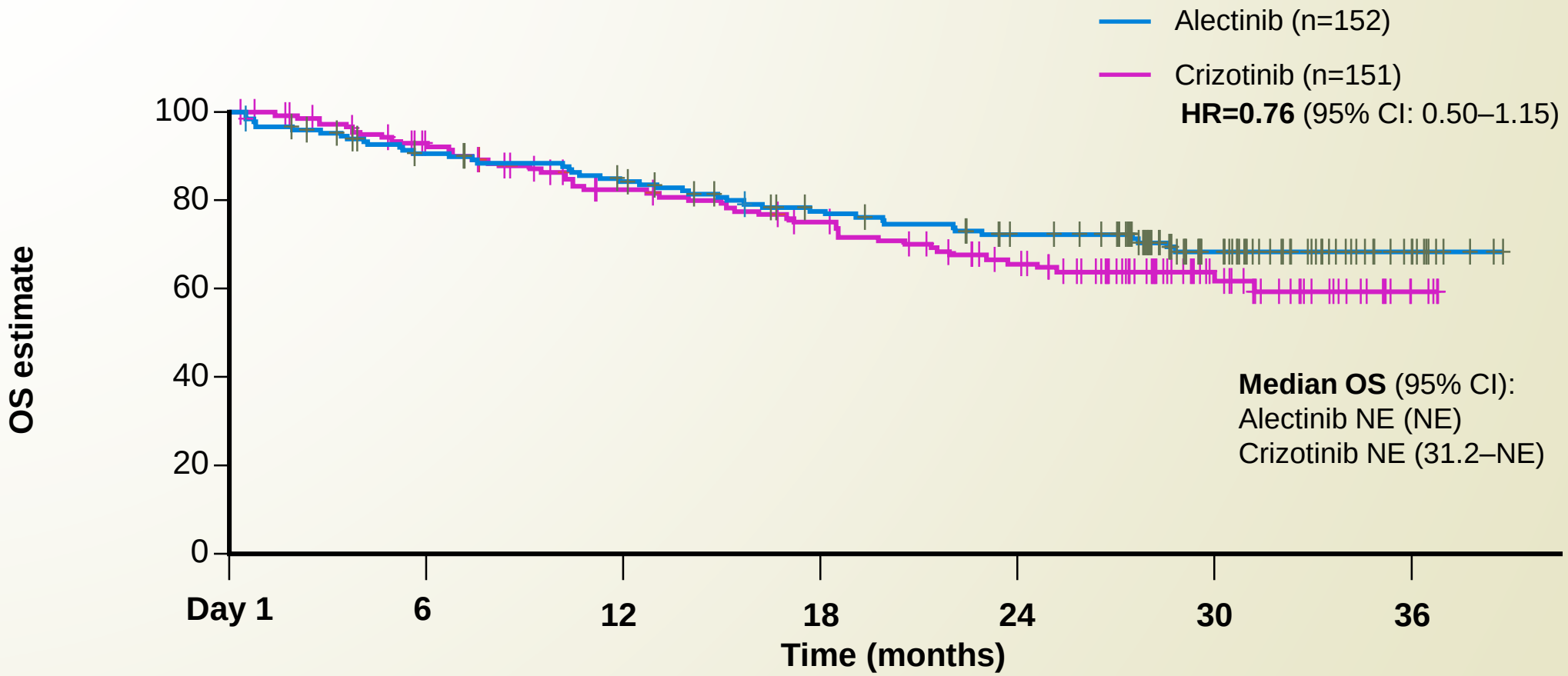
Pts without CNS mets at baseline



Investigator assessed

Peters, et al. NEJM 2017; Shaw et al. ASCO 2017

ALEX: Updated Overall survival is still immature



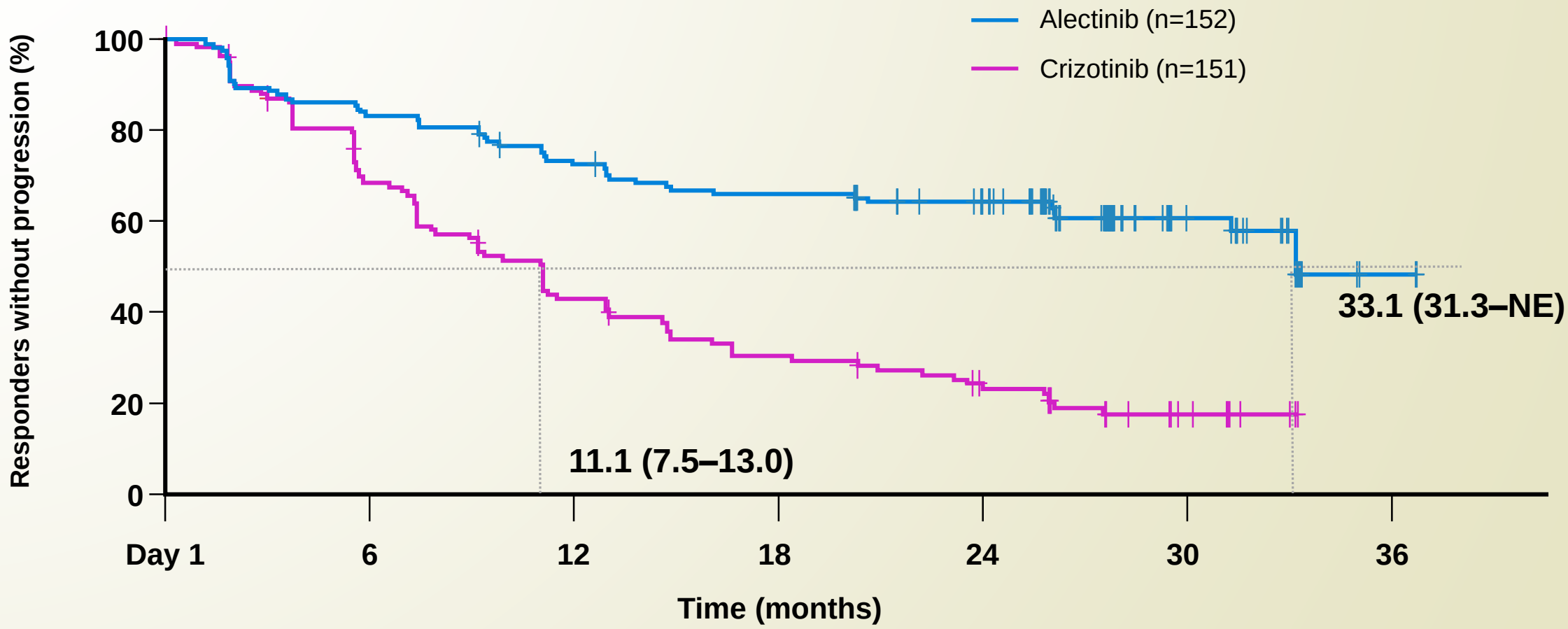
	Alectinib	Crizotinib
Events, n (%)	43 (28)	48 (32)

Updated data cut-off (1 December 2017)

NCT02075840

Camidge, et al. ASCO 2018

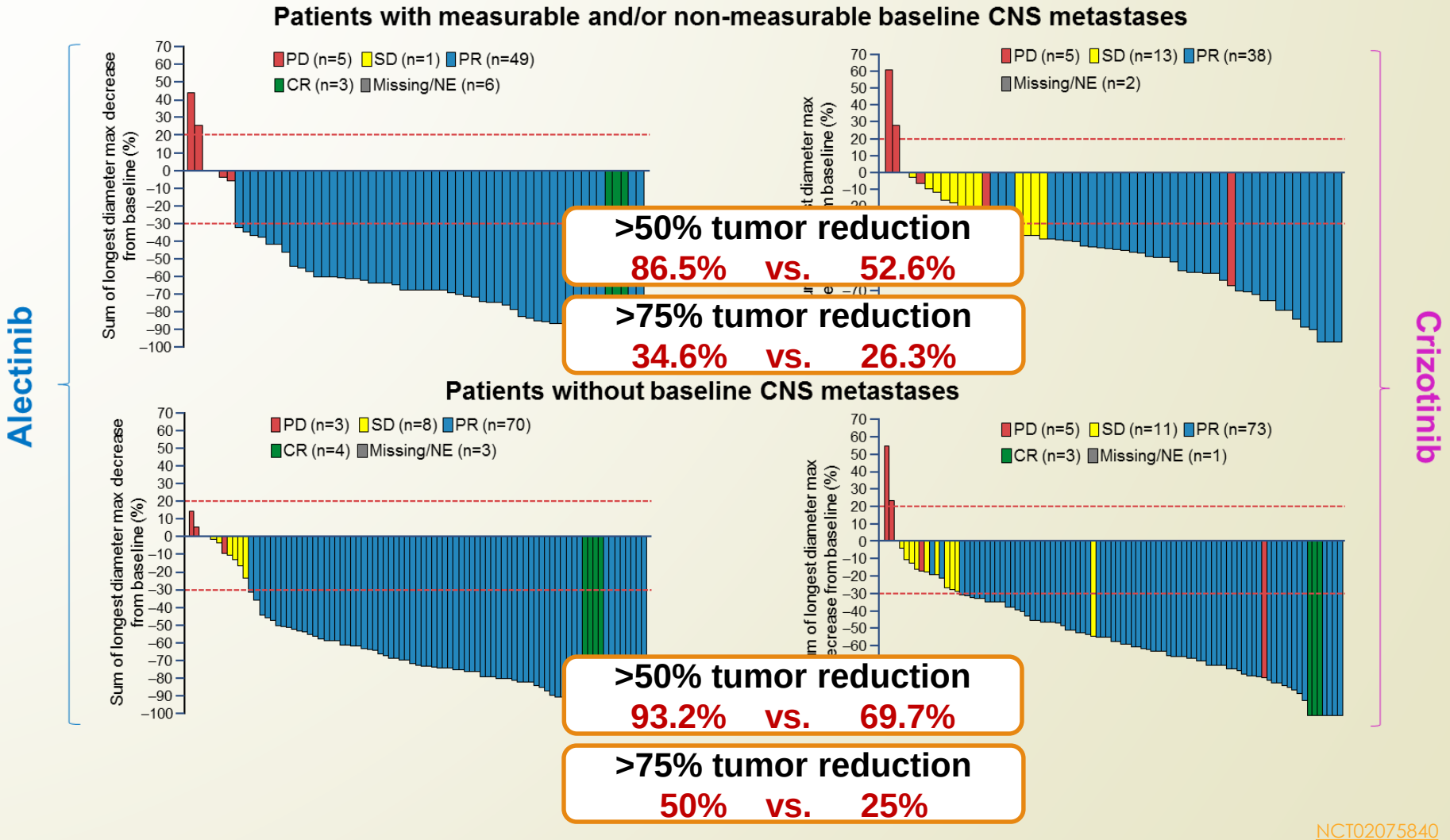
ALEX: Updated Duration of Response



Updated data cut-off (1 December 2017)
Investigator assessed
NE = not estimable

NCT02075840
Camidge, et al. ASCO 2018

ALEX: best overall response by baseline CNS metastases (updated analysis)



Updated data cut-off (1 December 2017)

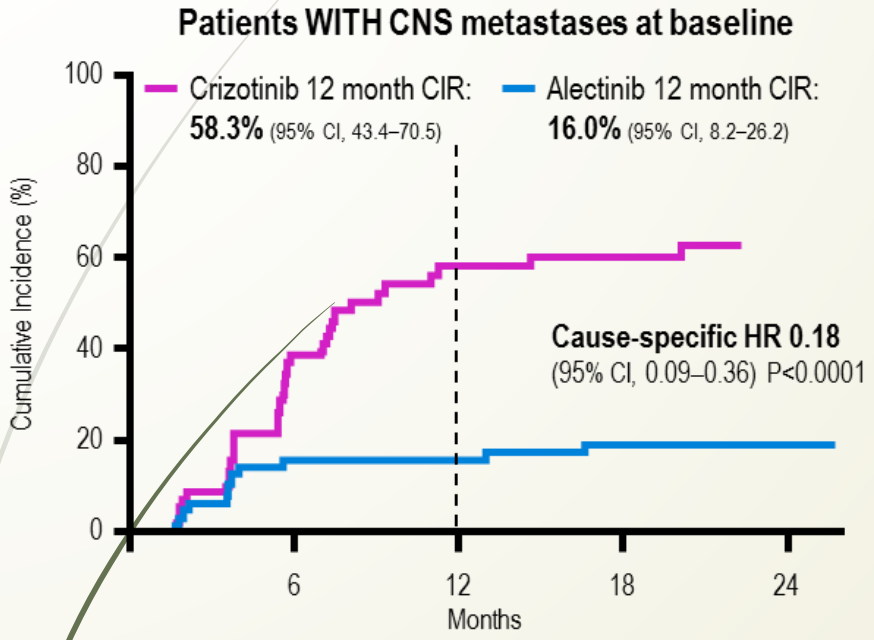
NCT02075840

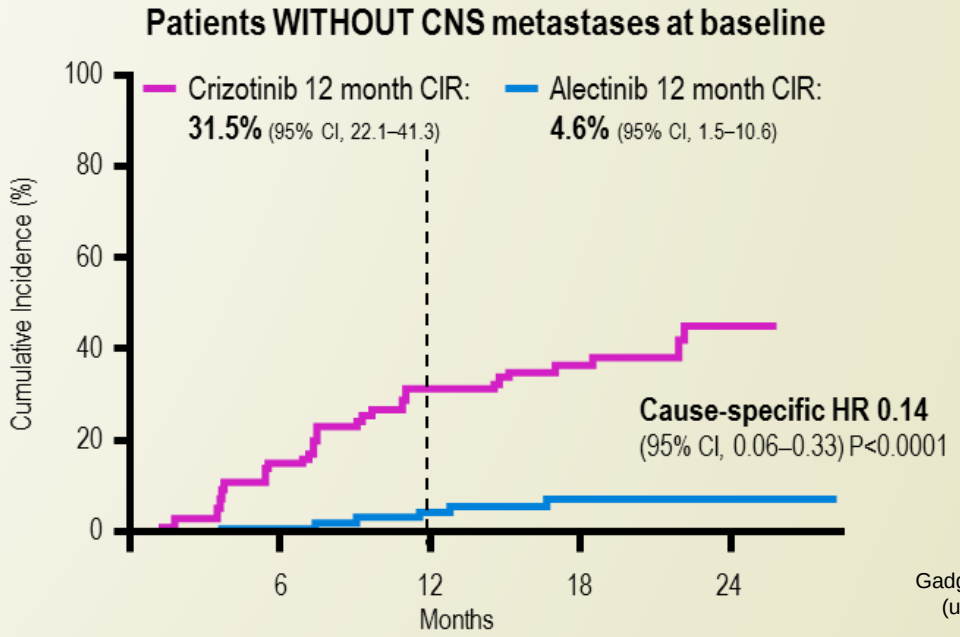
Camidge, et al. ASCO 2018

ESMO 2017

ALEX: Alectinib Significantly Reduced CNS Progression/Appearance

Patients with or without CNS mets at baseline

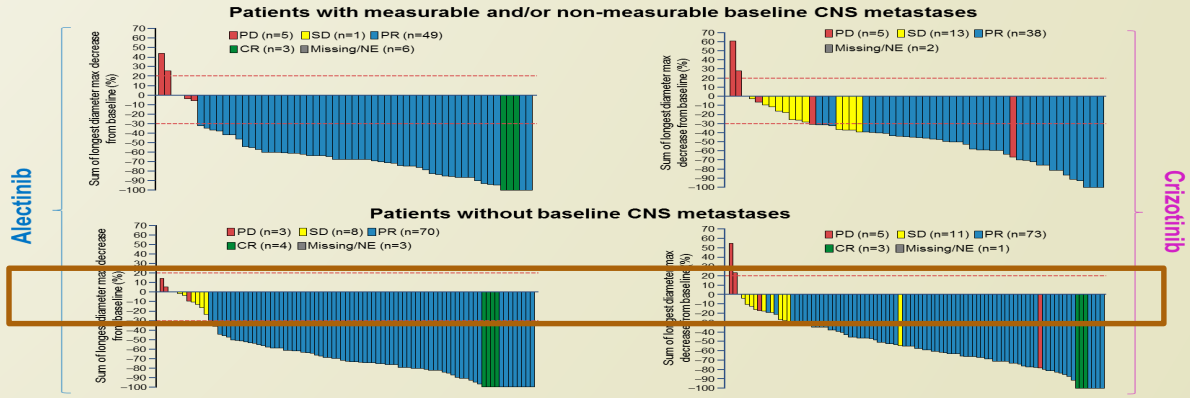




Gadgeel, et al. ESMO 2017 (Abstract 1298O)
(updated data from congress presentation)

Pooled analysis of CNS response to Alectinib-

Based on the 2 pivotal studies



ALEX: CNS response

Measurable and non-measurable CNS lesions at baseline		
	Crizotinib (n=58)	Alectinib (n=64)
CNS responders (%)	26	59
CNS CR (%)	9*	45†
Median DoR, months (95% CI)	3.7 (3.2–6.8)	NE (17.3–NE)

CNS Complete Response: Alectinib (45%) vs. Crizotinib (9%)

IRC RECIST. *Includes one patient who received prior brain radiotherapy and one patient who received concomitant radiotherapy; †Includes five patients who received prior brain radiotherapy and one patient who received concomitant radiotherapy

Peters, et al. NEJM 2017

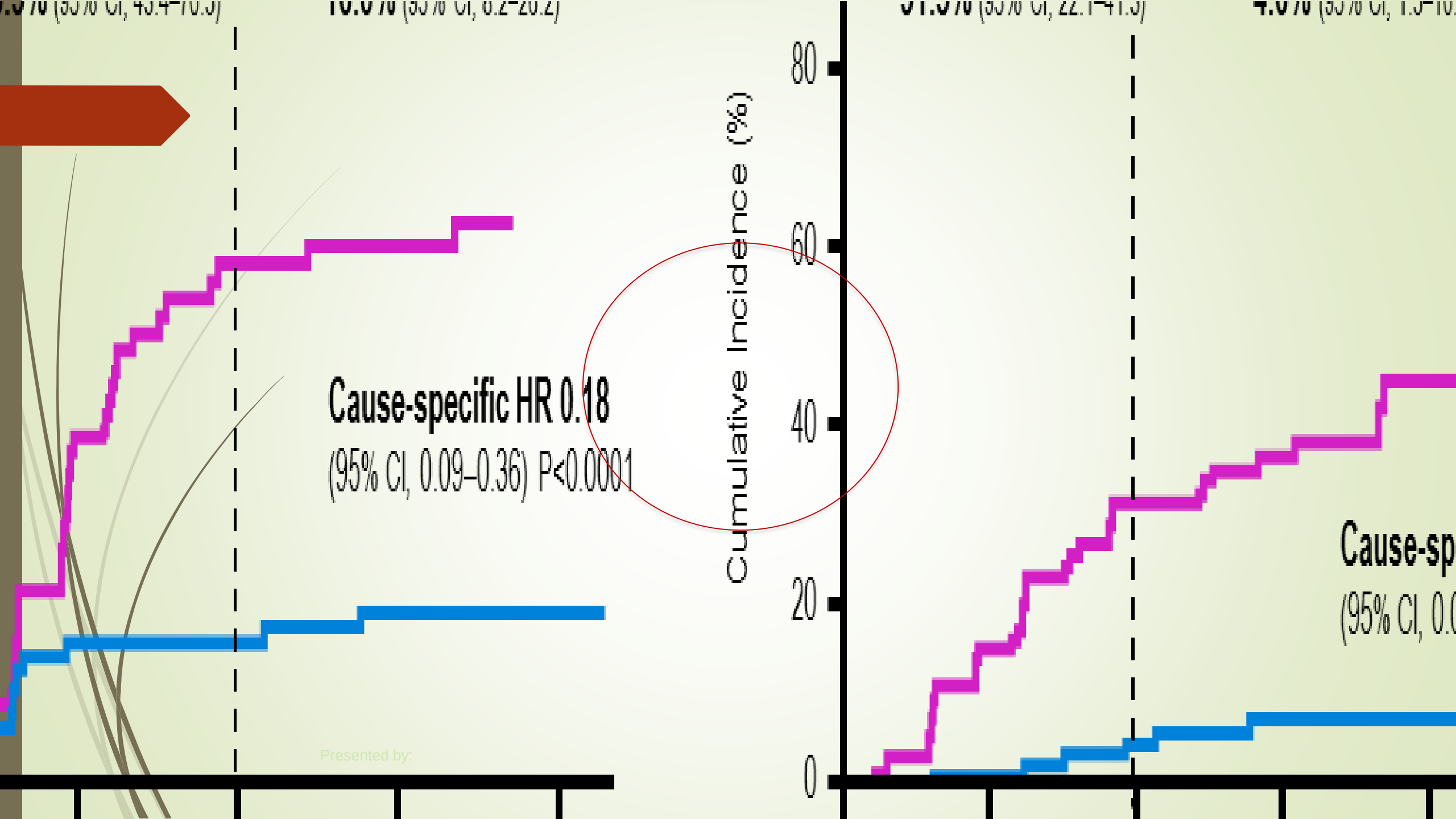
ALEX: Safety

Selected Adverse Events

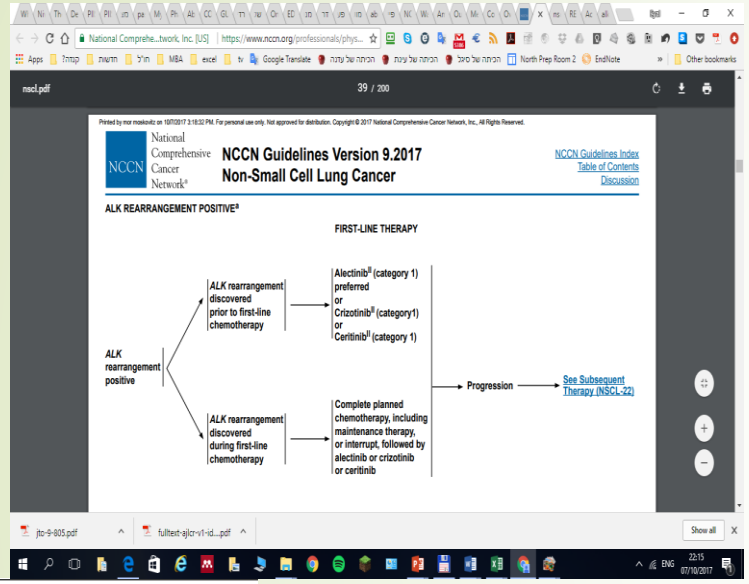
	Crizotinib n=151		Alectinib n=152	
N, (%)	**Any grade**	**Grade 3–5**	**Any grade**	**Grade 3–5**
Constipation	49 (33)	0	52 (34)	0
Nausea	72 (48)	5 (3)	21 (14)	1 (1)
Diarrhoea	68 (45)	3 (2)	18 (12)	0
Vomiting	58 (38)	5 (3)	11 (7)	0
Peripheral edema	42 (28)	1 (1)	26 (17)	0
ALT increased	45 (30)	22 (15)	23 (15)	7 (5)
AST increased	37 (25)	16 (11)	21 (14)	8 (5)
Arthralgia	11 (7)	0	3 (2)	0
Myalgia	3 (2)	0	24 (16)	0
Visual impairment	18 (12)	0	2 (1)	0

*Two events in crizotinib and none in alectinib were reported as related to study treatment; †Roche data on file
AE = adverse event; SD = standard deviation

Peters, et al. NEJM 2017; Shaw et al. ASCO 2017


Cumulative Incidence (%)
80
60
40
20
0
Cause-specific HR 0.18
(95% CI, 0.09–0.36) P<0.0001
Cause-sp
(95% CI, 0.0
Presented by:

Alectinib- first line treatment for ALK+

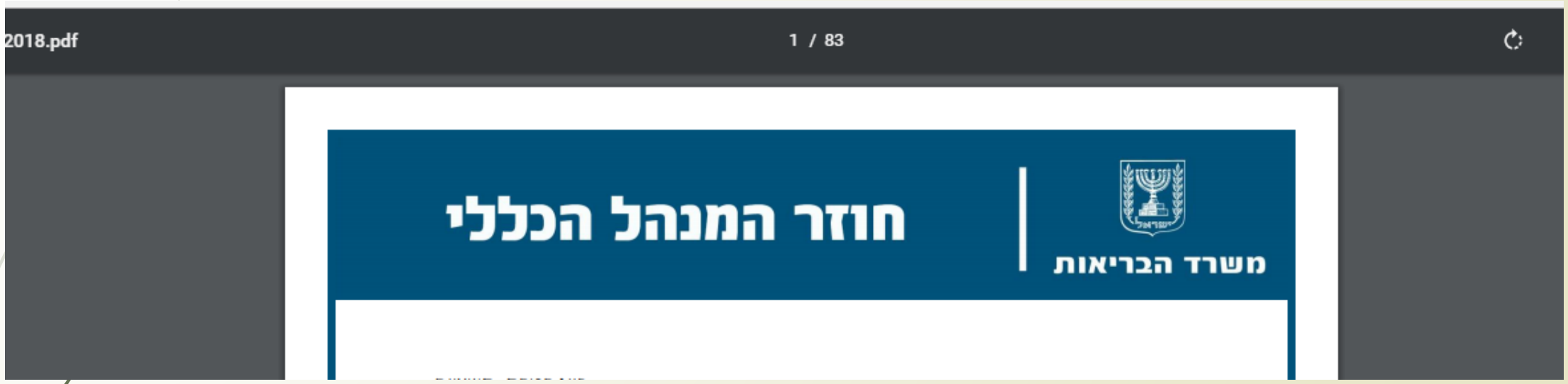


	Alectinib 600mg BID	
	Measurable CNS disease (n=60)*	Measurable and non-measurable CNS disease (n=136)*
CNS ORR, % (95% CI)	64.0 (49.2–77.1)	42.6 (34.2–51.4)
Complete response, n (%)	11 (22.0)	37 (27.2)
Partial response, n (%)	21 (42.0)	21 (15.4)
Stable disease, n (%)	13 (26.0)	58 (42.6)
Progressive disease, n (%)	3 (6.0)	12 (8.8)
CNS DCR, n (%)	45 (90.0)	116 (85.3)
[95% CI]	[78.2–96.7]	[78.2–90.8]
Median CNS DOR, months (95% CI)	10.8 (7.6–14.1)	11.1 (10.3–NE)

Approved by the Israeli ministry of health and reimbured in the 1st line setting since January 2018

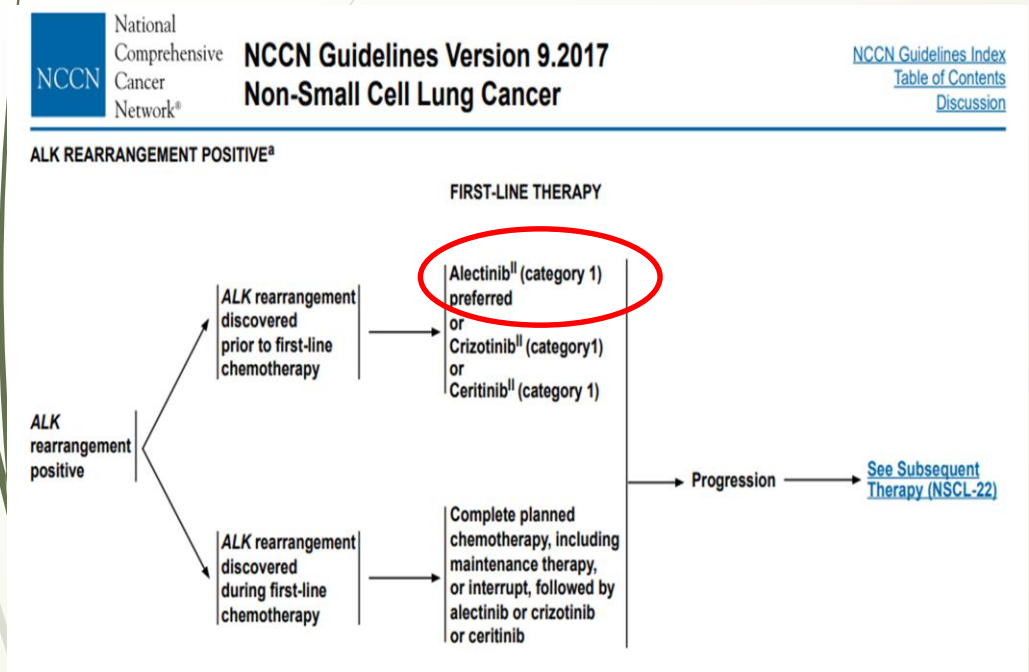
ology - Life Sciences

Whats next? To be presented at WCLC 2018

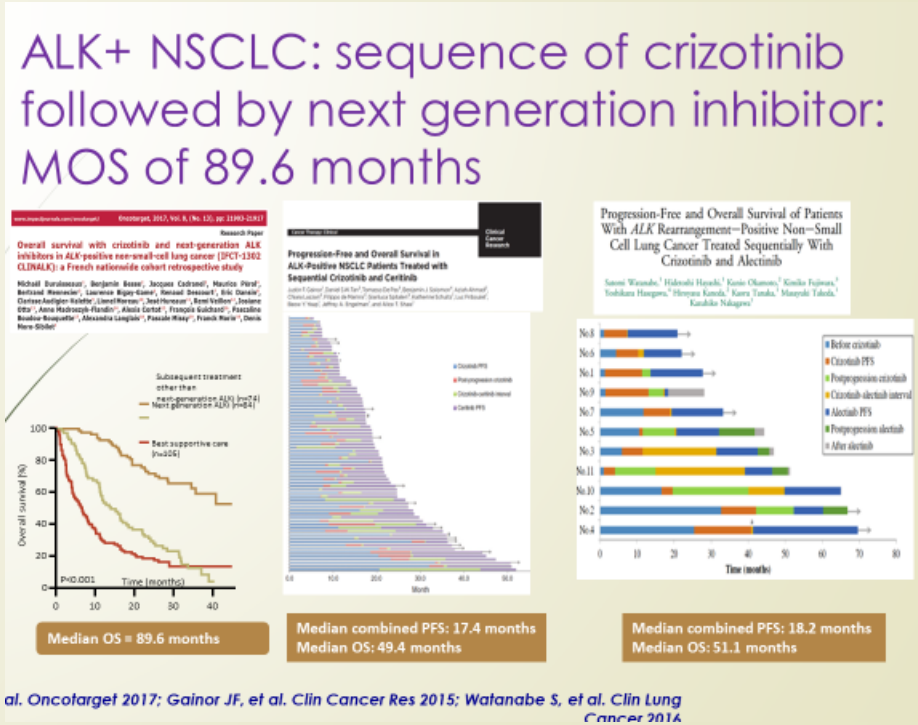


טיפול בפגיעה בראיה על רקע DME (בצקת מקולרית סוכרתית) כקו טיפול מתקדם אחרי Bevacizumab (במהלך	Eylea	Aflibercept

The choice of 1st line ALK- evidence based sequence or go with the best drug first?



Or



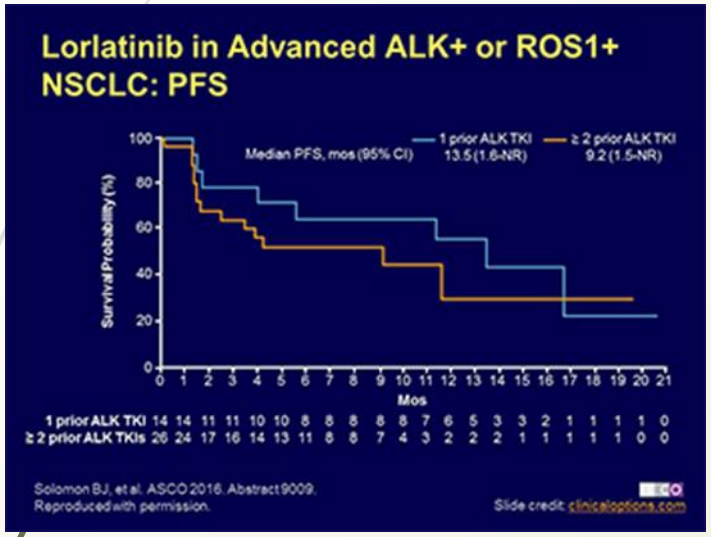
My index case

- 40 year old lady, healthy, never smoker
- 2013- Diagnosed with NSCLC, adenocarcinoma, mets to lung, bone, lymph nodes, EGFR and ALK pending
- Started chemotherapy- carboplatin and paclitaxel
- ALK positive!
- Started crizotinib after 4 cycles of chemo
- Complete response!

- 8 months later- dizziness, headache
- Diagnosed with multiple brain metastases
- Started whole brain radiotherapy
- Continue with crizotinib? Change to other ALK?

- After WB, the patient continued crizotinib
- PD in brain, with hydrocephalus
- Deceased 2 months after diagnosis of brain metastases
- Sometimes we only have 1 chance!

How about ROS1? Not much debate here yet…



- Of the 12 patients with *ROS1* -positive NSCLC, six (50%) achieved a confirmed partial response and two (17%) had stable disease
- Two patients had received previous crizotinib, and the other four patients were crizotinib naive but had received platinum doublet chemotherapy.
- Median duration of response was 12·0 months (95% CI 5·7–NR).
- Brigatinib, cabozantinib, enteractinib in advanced line of treatment show efficacy (very little evidence)
- Our experience shows prolonged survival with crizotinib- and 1 patient on the lorlatinib access program survived 4 years.

Lorlatinib in non-small-cell lung cancer with *ALK* or *ROS1* rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial Shaw, Alice T et al. The Lancet Oncology , Volume 18 , Issue 12 , 1590 - 1599

Summary- treatment of ALK +ive NSCLC

- ALK and ROS1rearrangement- mainly in non smokers with Adenocarcinoma
- Diagnosed mainly by IHC
- Crizotinib was the first ALK inhibitor- showed efficacy in 1st line with median OS of 5-7 years
- Alectinib-preferred drug for ALK in 1st line
- Alectinib, Ceritinib, Brigatinib demonstrated efficacy in 2nd line post crizotinib- no definite sequence yet-, but real world and prospective evidence are on the way…

Thank you!


RAMBAM 80
Health Care Campus
Eighty years of Excellence, Innovation and Humanity