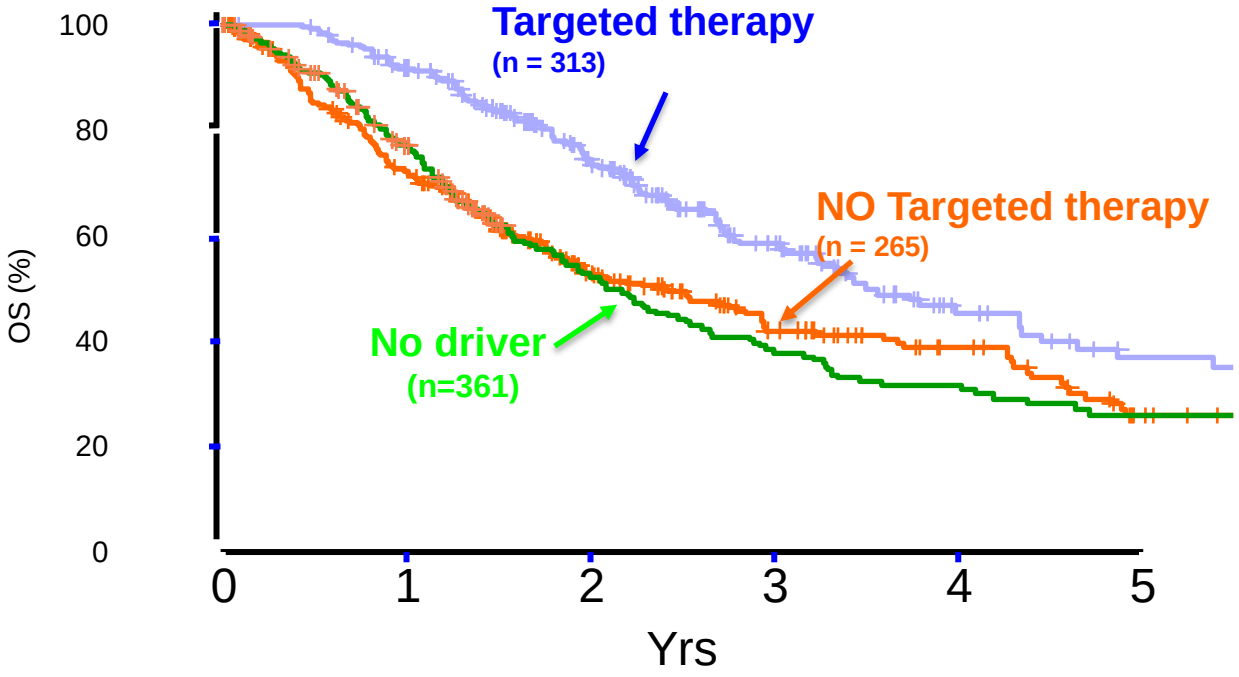
NSCLC oncogene addicted: Nuovi algoritmi alle porte

Dr. Rita Chiari

SC Oncologia Medica
Azienda Ospedaliera-Universitaria
di Perugia

Targeted therapy for oncogene-driven lung cancer



Kris MG et al, JAMA May 2014

JAMA | Original Investigation

Association of Broad-Based Genomic Sequencing With Survival Among Patients With Advanced Non–Small Cell Lung Cancer in the Community Oncology Setting

Carolyn J. Presley, MD; Daiwei Tang, BS; Pamela R. Soulos, MPH; Anne C. Chiang, MD, PhD; Janina A. Longtine, MD; Karin B. Adelson, MD; Roy S. Herbst, MD, PhD; Weiwei Zhu, MPH; Nathan C. Nussbaum, MD; Rachael A. Sorg, MPH; Vinayak Agarwala, MD, PhD; Amy P. Abernethy, MD, PhD; Cary P. Gross, MD

RESULTS Among 5688 individuals with advanced NSCLC (median age, 67 years [interquartile range, 41-85], 63.6% white, 80% with a history of smoking); 875 (15.4%) received broad-based genomic sequencing and 4812 (84.6%) received routine testing. Among patients who received broad-ba based on testing results, 9.8% r received no targeted treatment patients undergoing broad-bas routine testing. Using an instru between broad-based genomic death at 12 months, 41.1% for b difference −3.6% [95% CI, −18.4% to 11.1%]; $P = .63$). The results were consistent in the propensity score–matched survival analysis (42.0% vs 45.1%; hazard ratio, 0.92 [95% CI, 0.73 to 1.11]; $P = .40$) vs unmatched cohort (hazard ratio, 0.69 [95% CI, 0.62 to 0.77]; log-rank $P < .001$).

CONCLUSIONS AND RELEVANCE Among patients with advanced non–small cell lung cancer receiving care in the community oncology setting, broad-based genomic sequencing directly informed treatment in a minority of patients and was not independently associated with better survival.

From The JAMA Network

Redefining the Value Proposition of Precision Oncology
Can We Integrate Genomic Testing Without Overselling It?

Howard (Jack) West, MD

Outline

- **EGFR-mutated:**
  - Sequencing therapies for EGFR-mutation-positive NSCLC
  - The big question: First line Osimertinib or sequence after First-second generation EGFR-TKIs
- **ALK-rearranged:**
  - How alectinib changed 1st line
  - Update about lorlatinib
- **ROS.1 targeting agents and other targets**
- **Oncogene addicted NSCLC and immunotherapy**

Outline

- **EGFR-mutated:**
  - **Sequencing therapies for EGFR-mutation-positive NSCLC**
  - **The big question: First line Osimertinib or sequence after First-second generation EGFR-TKIs**
- **ALK-rearranged:**
  - How alectinib changed 1st line
  - Update about lorlatinib
- **ROS.1 targeting agents and other targets**
- **Oncogene addicted NSCLC and immunotherapy**

EGFR mutations and historical standard of care

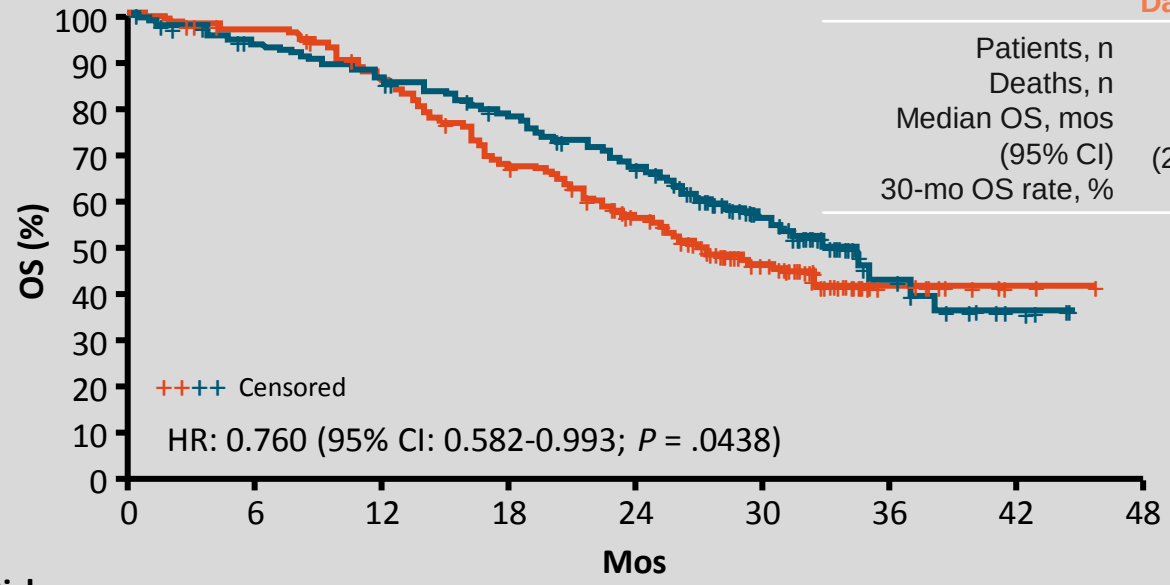
- Erlotinib, afatinib and gefitinib are AIFA approved first line treatments for pts with metastatic EGFR+ lung cancer

- Multiple randomized studies demonstrate superior mPFS with EGFR TKIs compared to chemotherapy as first line treatment

- No clear superior options among earlier generation EGFR inhibitors

a. Mok TS, et al. *N Engl J Med.* 2009;361:947-957; b. Maemondo M, et al. *N Engl J Med.* 2010;362:2380-2388;
c. Mitsudomi T, et al. *Lancet Oncol.* 2010;11:121-128; d. Zhou C, et al. *Lancet Oncol.* 2011;12:735-742;
e. Rosell R, et al. *Lancet Oncol.* 2012;13:239-246; f. Sequist LV, et al. *J Clin Oncol.* 2013;31:3327-3334;
g. Wu YL, et al. *Lancet Oncol.* 2014;15:213-222.

ARCHER 1050: Overall Survival…too LATE!!!



	Dacomitinib	Gefitinib
Patients, n	227	225
Deaths, n	103	117
Median OS, mos	**34.1**	**26.8**
(95% CI)	(29.5-37.7)	(23.7-32.1)
30-mo OS rate, %	56.2	46.3

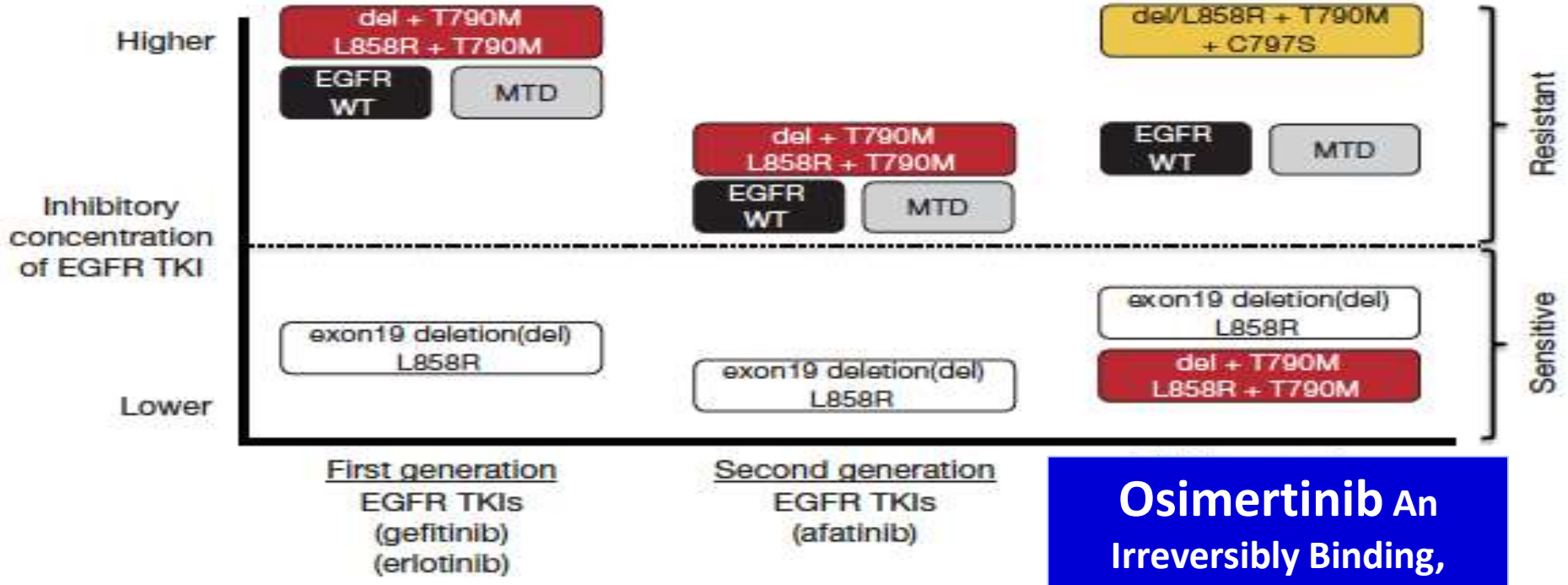
Patients at Risk, n

Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

Median follow-up: 31.3 mos

Mok T, et al. J Clin Oncol. 2018

The generation gap: different therapeutic window

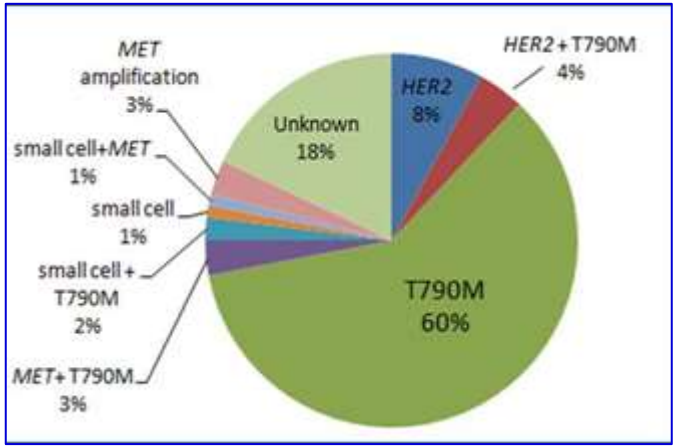


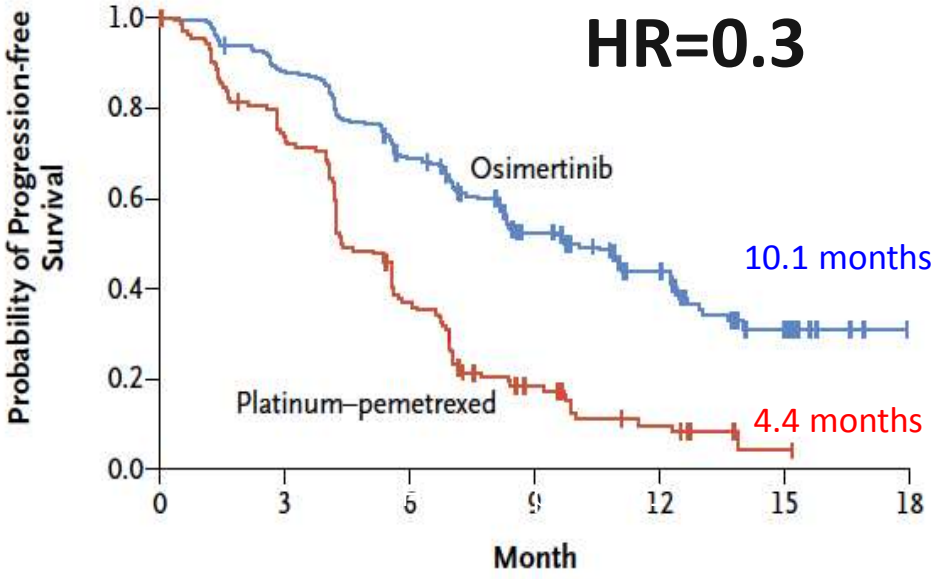
Osimertinib An Irreversibly Binding, Mutation-Specific, WT-Sparing EGFR TKI

Costa DB et al, Transl Lung Cancer Res 2015

AURA 3: Osimertinib is superior to platinum doublet in 2nd line in *EGFR*$^{T790M+}$

- T790M is a resistance mechanism to first and second generation EGFR TKIs[a]
  - Can arise as an early event or be acquired late





Mok T et al. NEJM 2016

CASE 1: 75-Year-Old Woman, Never smoker

Routine T790M identification of acquired resistance

Aug-Sep 2016

- CT: right pleural effusion, mediastinal LNs, bone mets
- MRI brain: multiple mets
- EBUS: TTF1+ adenocarcinoma stations 4R, 7
- Genotyping: *EGFR* del19
- Staging (v7): T3N3M1B

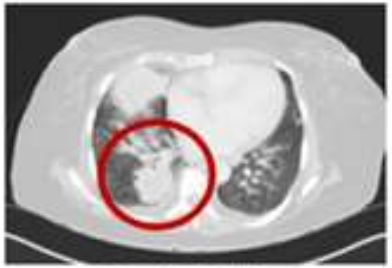
Oct 2016-Sep 2017

- Afatinib with good PR

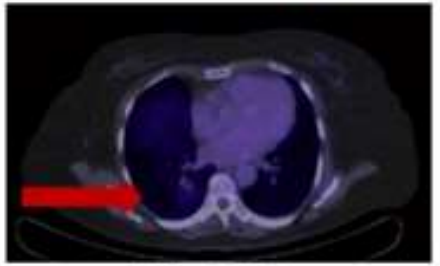
Oct 2017

- PD on PET; ctDNA del19 and T790M-positive
- Commenced osimertinib with good extracranial and intracranial PR (Feb 2018)

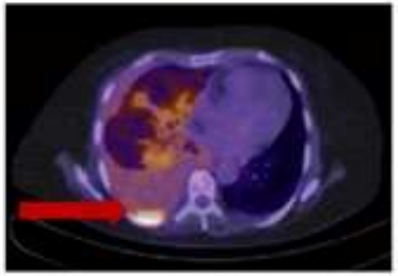
Sep 2016: Baseline



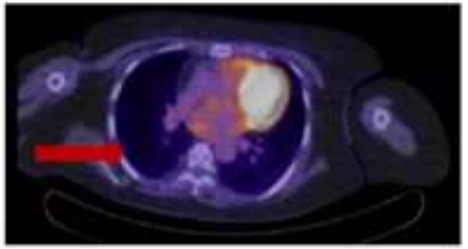
Apr 2017: Response to afatinib



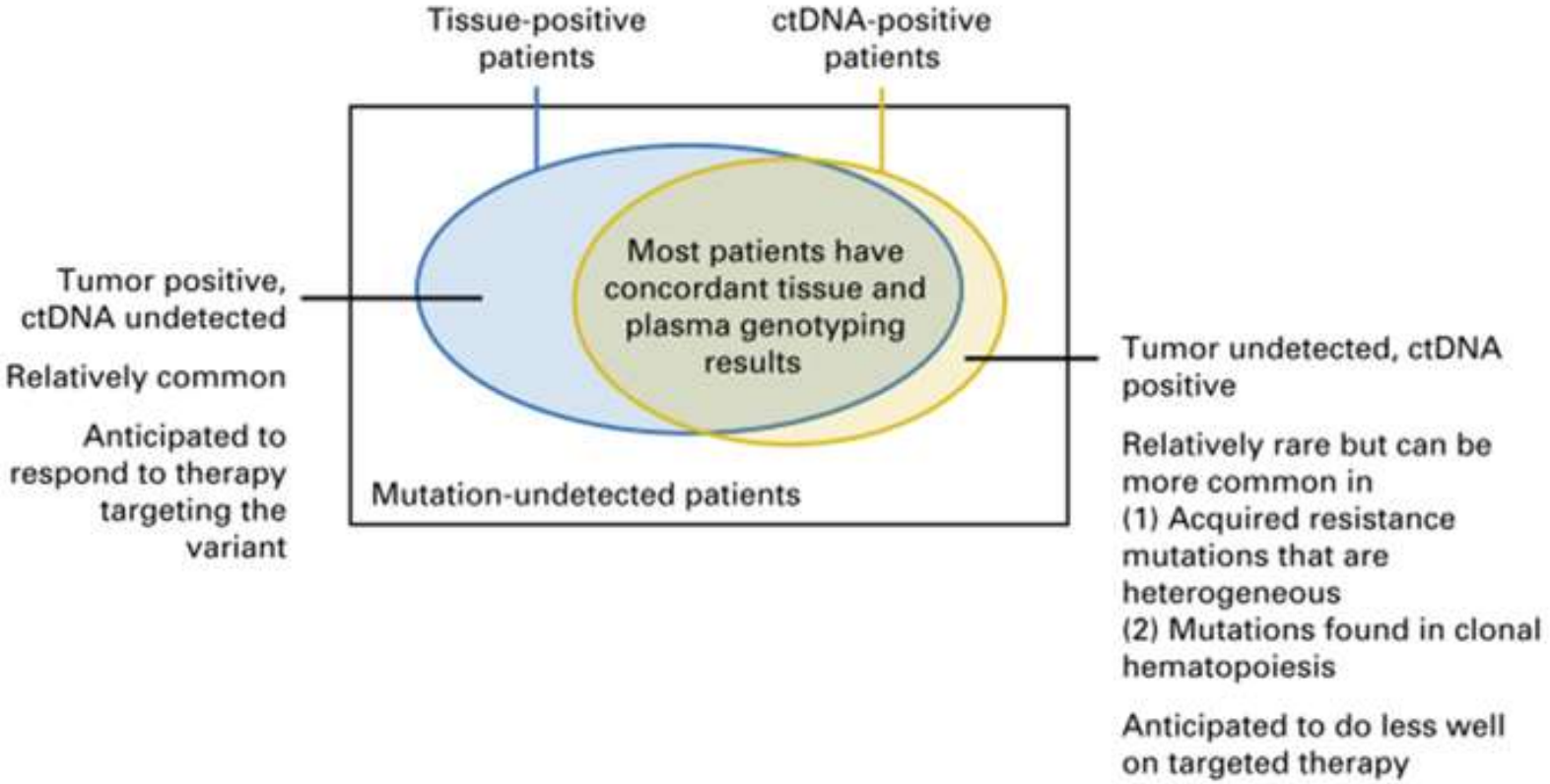
Oct 2017: PD 12 months of afatinib



Feb 2018: 4 months of osimertinib



Tissue and ctDNA can yield false negatives



Merker JD et al. JCO2018

CASE 2: 46-Year-Old Woman, Never smoker

Challenges in T790M identification

Sept 2015

- CT: LUL mass, L SCF adenopathy, no CNS mets
- Biopsy: TTF-1+ adenocarcinoma, PD-L1 1-49% TPS
- Genotyping: *EGFR* del19
- PET/CT: no additional findings
- Staging (v7): T2b N3 M1a

Oct 2015

- Commenced afatinib with good PR

Sept 2017

- PD on afatinib (23 months)

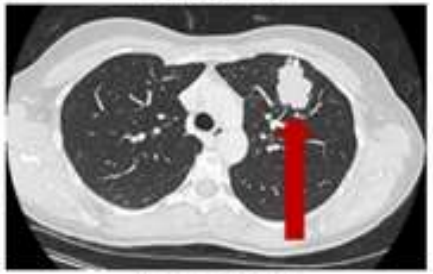
Oct 2017

- ctDNA: *EGFR* WT
- Biopsy *EGFR* del19 only
- Treatment beyond PD

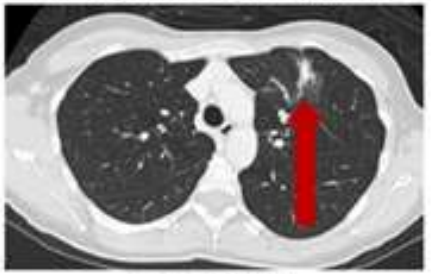
Jan 2018:

- Further PD on afatinib, ctDNA del19

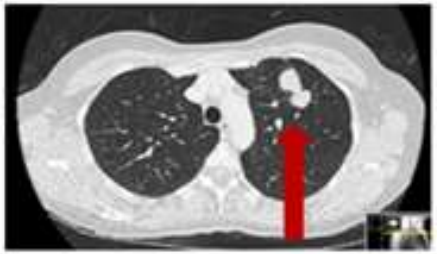
Oct 2015: Baseline



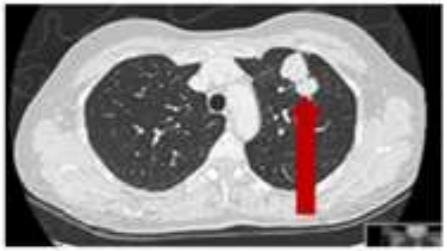
Dec 2015: 2 months on afatinib



Sep 2017: PD on afatinib



Jan 2018: Further PD on afatinib



What would you do next?

A. Repeat tissue biopsy
B. Switch to chemothe[illegible]y
C. Switch to immune c[illegible]kpoint inhibitor
D. Switch to alternativ[illegible]GFR TKI
E. Other

T790M+：Start Osimertinib on March 2018 obtaining PR still ongoing

Can preventing T790M clonal outgrowth Trough first-line osimertinib yield clinical benefit?

Practice changing data

PFS

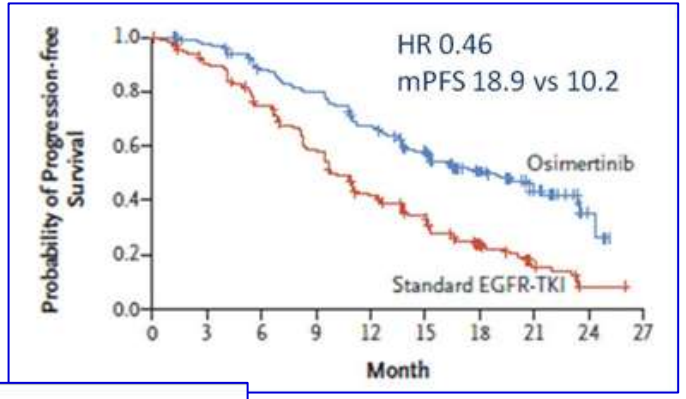
FLAURA: phase 3, double-blind trial

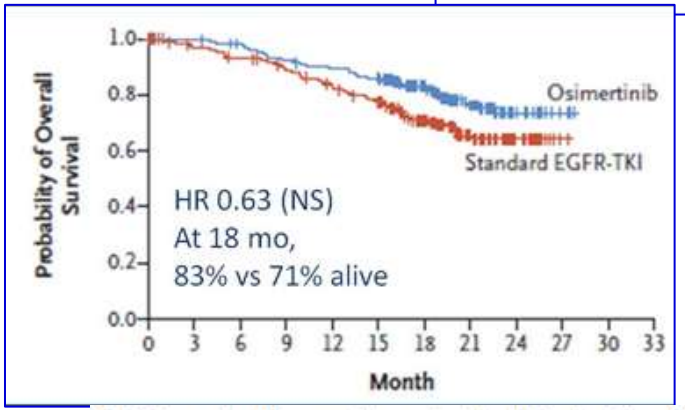
- Del19/L858R; stable CNS mets off steroids
- Osimertinib
- Standard EGFR TKI: gefitinib or erlotinib

Osimertinib vs standard EGFR TKI demonstrated:

- Longer mPFS -- HR = 0.46 (95% CI: 0.37, 0.57; *P* < .001); 18.9 vs 10.2 months
- Similar ORR -- 80% vs 76%
- Longer mDoR -- 17.2 months vs 8.5 months

OS data were immature at the time of analysis



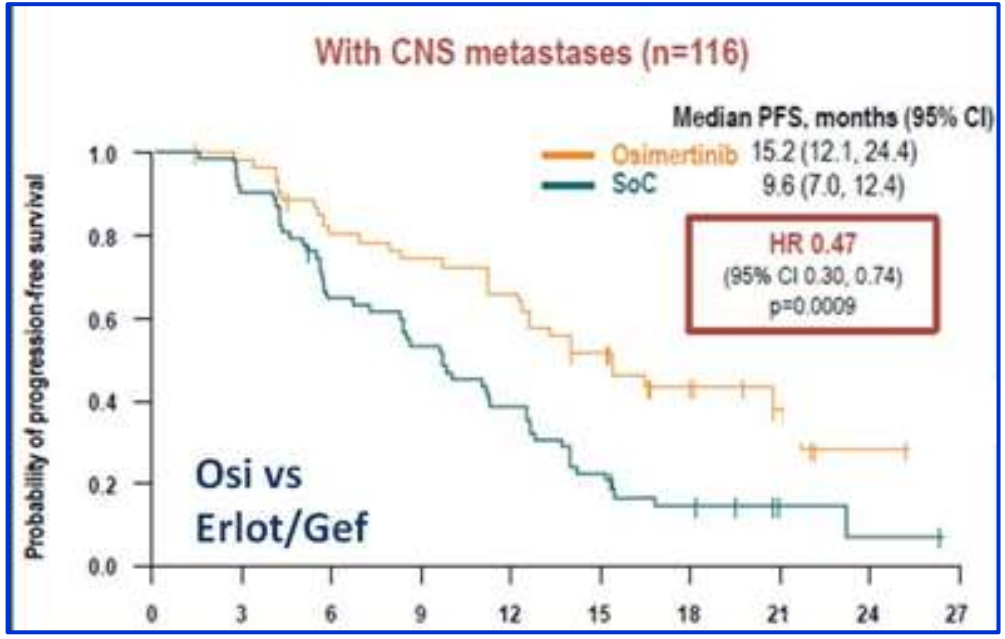


OS: interim analysis

25% maturity; osimertinib: 58 deaths (21%), SoC: 83 deaths (30%)

Osimertinib: CNS control

Practice-Changing Data



	Outcomes	
	mPFS, mo	*P* Value
With CNS Metastases		
Osimertinib (n = 53)	15.2	< .001
Standard EGFR TKI (n = 63)	9.6	
Without CNS Metastases		
Osimertinib (n = 226)	19.1	< .001
Standard EGFR TKI (n = 214)	10.9	

- Cumulative incidence of CNS involvement in EGFR+ LC is 60%
- Osimertinib with lower rate of CNS progression
- Local therapies improve local control but not overall survival
- New strategies to address CNS disease are needed

Ramalingam S et al. ESMO 2017 –Soria NEJM 2018

Case Example 3: 73-Year-Old Woman, Never Smoker

Front-Line Treatment Selection

Aug 2017

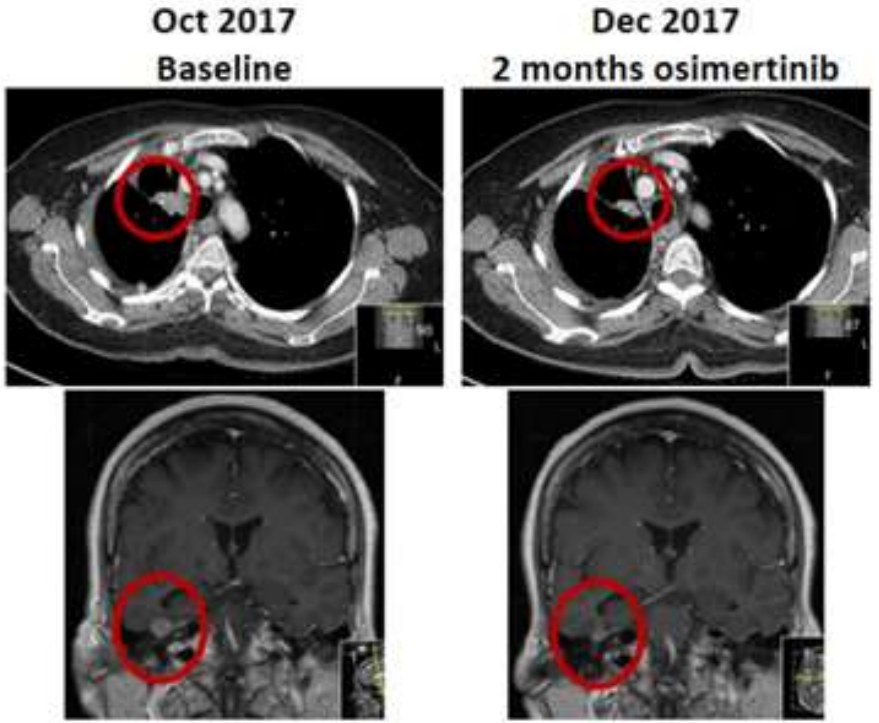
- CT: R pleural effusion, lung nodules, hilar lymph nodes
- MRI: solitary CNS metastasis
- Staging (v7): T3N1M1B
- Pleural tap: TTF1+ adenocarcinoma
- Cell pellet genotyping: *EGFR* WT

Sep 2017

- VATS biopsies and pleurodesis: TTF1+ adenocarcinoma, PD-L1 5% TPS
- Tissue NGS: *EGFR* del19

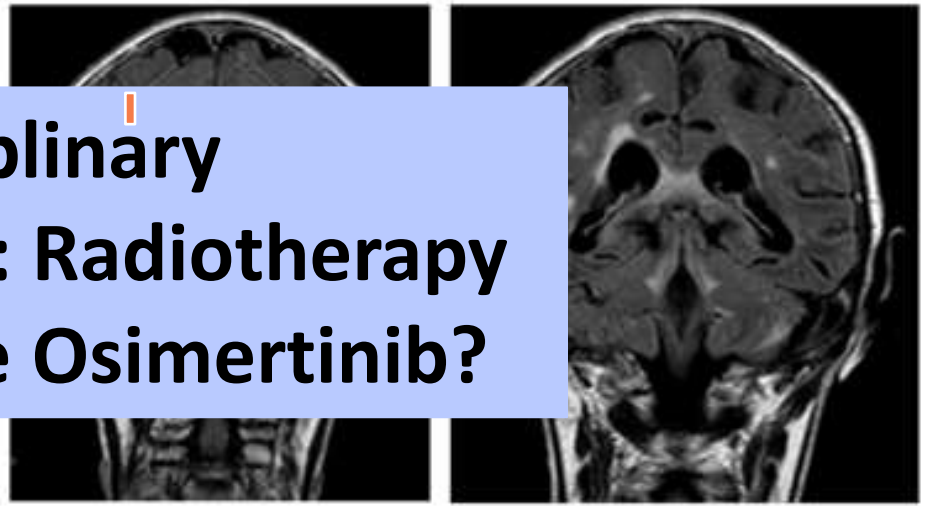
Oct 2017

- Commenced osimertinib
- Good PR



Case Example: First-Line Treatment Selection for *EGFR*-Positive Patients With CNS Involvement

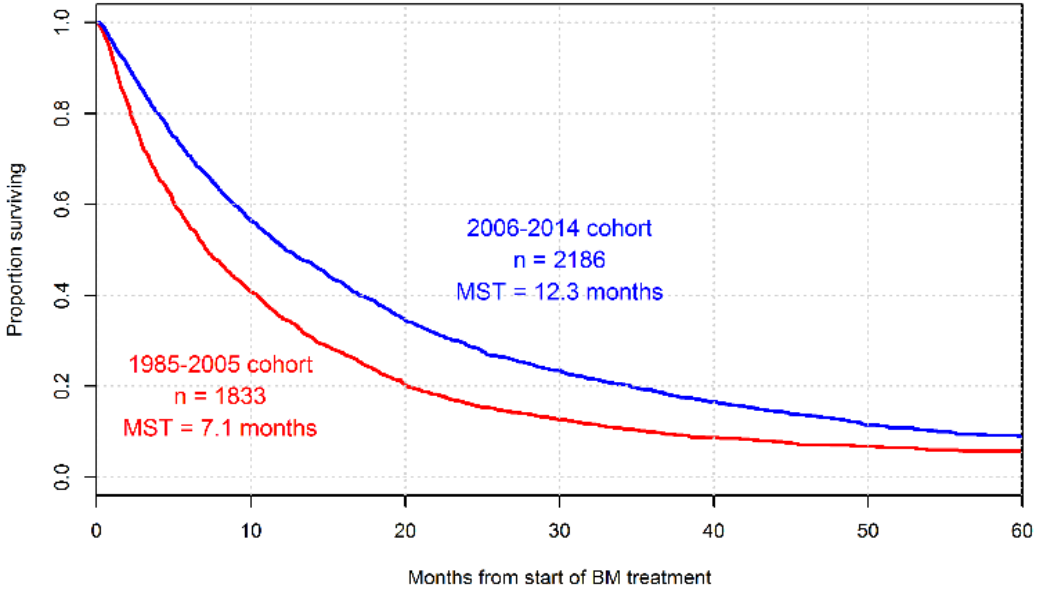
- Aged 76 years, never smoker, housewife
- January 2018: headache, confusion, and apraxia appeared
- CT scan:
  - Some small brain metastases
  - Lung tumor
  - Nodal and bone
- Brain MRI:
  - Leptomeningeal
- Pulmonary biopsy: a
  G3, mutated *EGFR* (c
- ECOG PS: 3
- Start dexamethasone 16 mg daily
  → no significant improvement in neurologic symptoms



Multidisciplinary discussion: Radiotherapy or first line Osimertinib?

Survival of NSCLC pts with BMs: Comparison of Current Data to Historical Controls

OBJECTIVE: to Update the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) based 4 factors: age, KPS, extracranial Ms, and number of BMs→**updated Lung-molGPA**

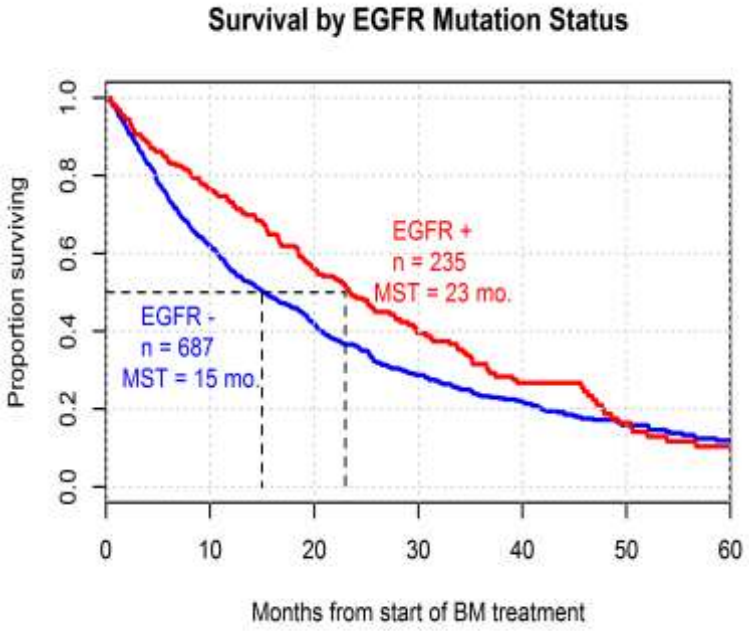


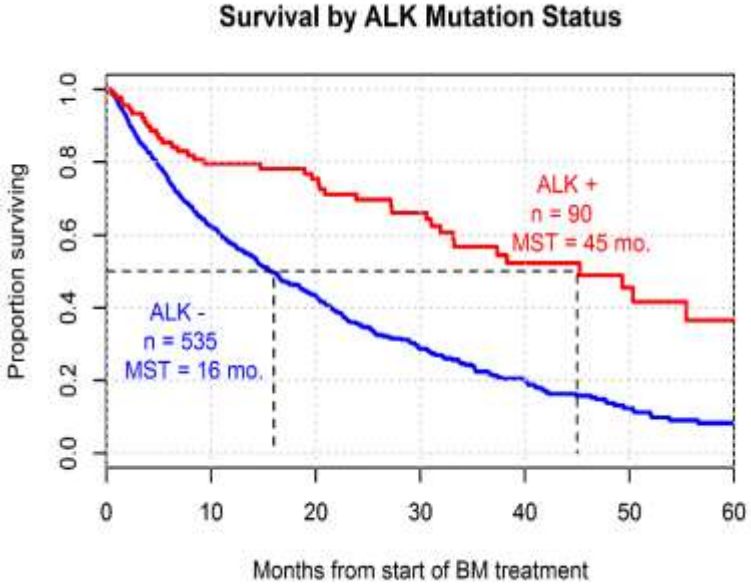
2324 pts with lung cancer
- 2186 NSCLC and BMs
  - 1521 adenocarcinoma
    - 993 mutation status

Largest reported series of gene mutations in pts with lung adc and BMs

Sperduto PW et al. JAMA2016

Survival of NSCLC pts with BMs: EGFR-mutated and ALK positive pts

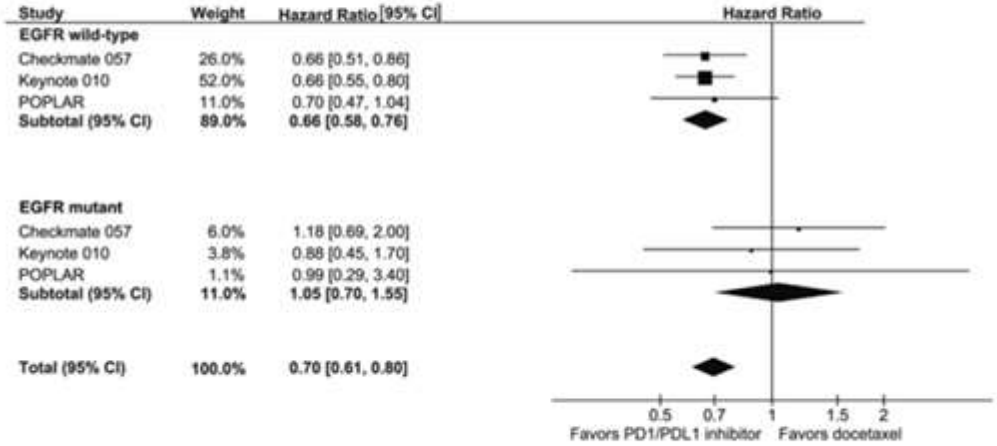




Sperduto PW et al. JAMA2016

T790M-Negative Options

- Local therapy (eg, oligoprogression)[a]
- Chemotherapy -- IMPRESS trial data[b]
- Immunotherapy is not favored in *EGFR*-positive disease[c]

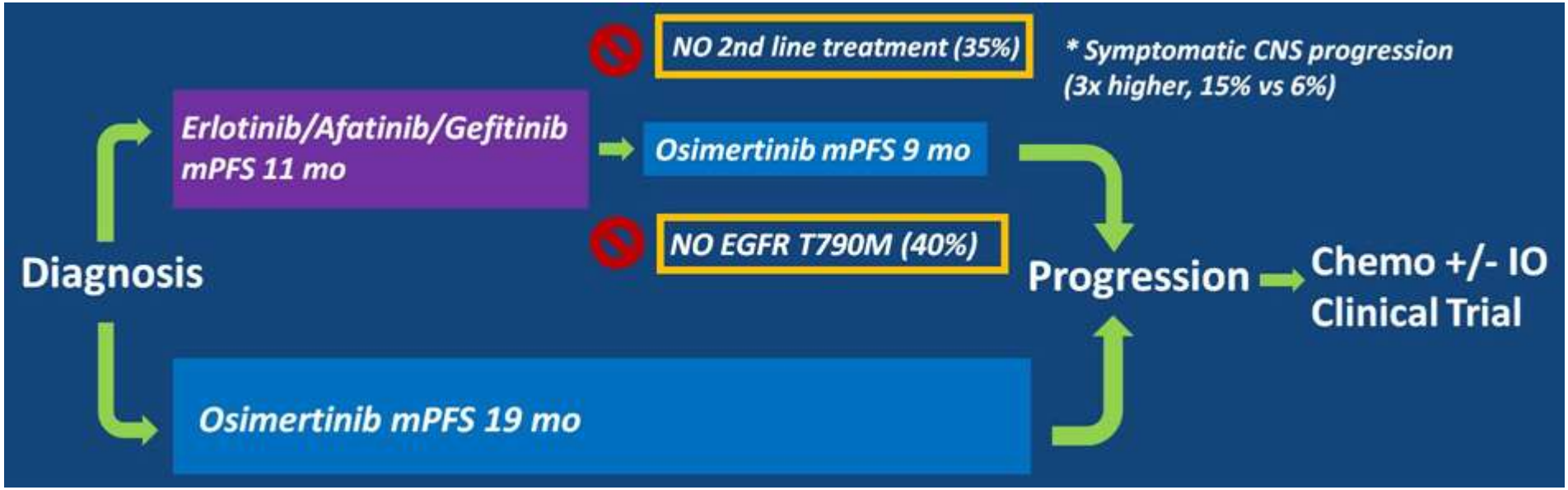


a. NCCN website. NSCLC; b. Soria J, et al. *Ann Oncol.* 2016:27. Abstract 1201O;
c. Lee CK, et al. *J Thorac Oncol.* 2017;12:403-407.

Outline

- **EGFR-mutated:**
  - •Sequencing therapies for EGFR-mutation-positive NSCLC
  - **•The big question: First line Osimertinib or sequence after First-second generation EGFR-TKIs**
- **ALK-rearranged:**
  - How alectinib changed 1st line
  - Update about lorlatinib
- **ROS.1 targeting agents and other targets**
- **Oncogene addicted NSCLC and immunotherapy**

Osimertinib is the best First line treatment



Always give your best treatments first: not everyone gets second line treatment.

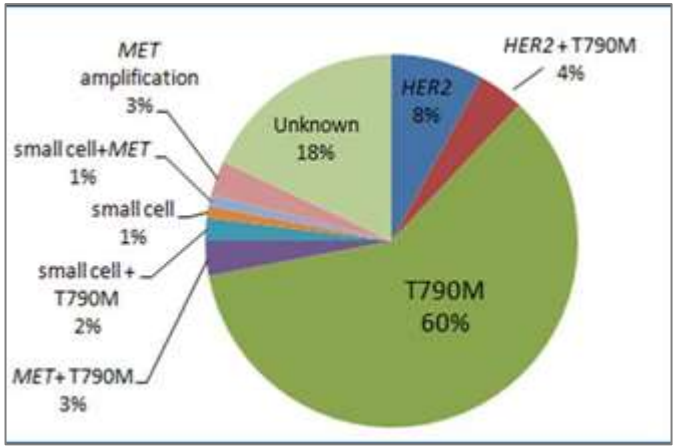
No “clear options” at the horizon after osimertinib

Acquired resistance to Osimertinib

EGFR-TKI
Afatinib
Dacomitinib
Erlotinib
Gefitinib

→ **Acquired resistance** →

T790M+
Osimertinib



↓

Acquired Resistance #2

EGFR-TKI
Osimertinib

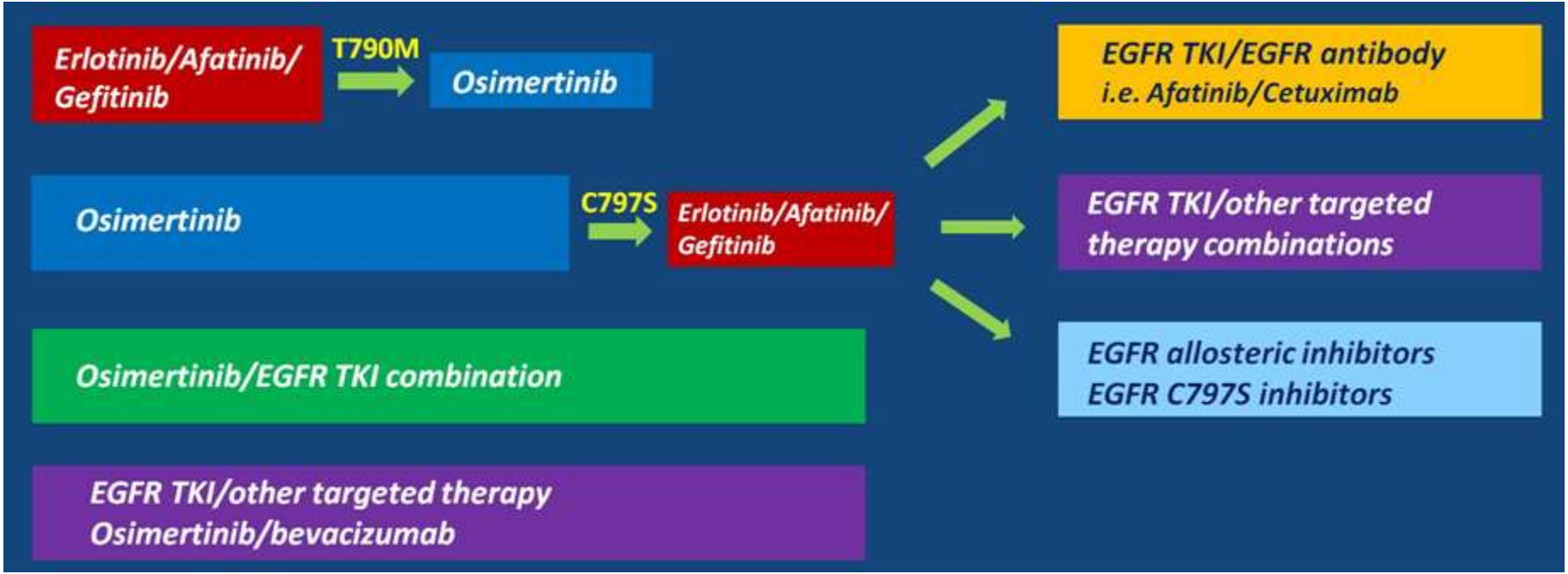
→ **???**

Treatment Selection After Osimertinib

Mutations identified	Where identified	Therapy
MET amplification	Tissue, plasma	MET inhibitor
HER2 amplification	Tissue, plasma	HER2 inhibitor
BRAF V600E	Tissue	BRAF/MEK inhibitor
PIK3CA	Plasma	PIK3CA inhibitor
KRAS mutation/amp	Plasma	--
EGFR amplification	Tissue, plasma	EGFR antibody
RB1 loss, p53 loss	Plasma	--
Small cell transformation	Tissue	Chemotherapy
Loss of EGFR T790M	Tissue, plasma	1st/2nd gen EGFR TKI

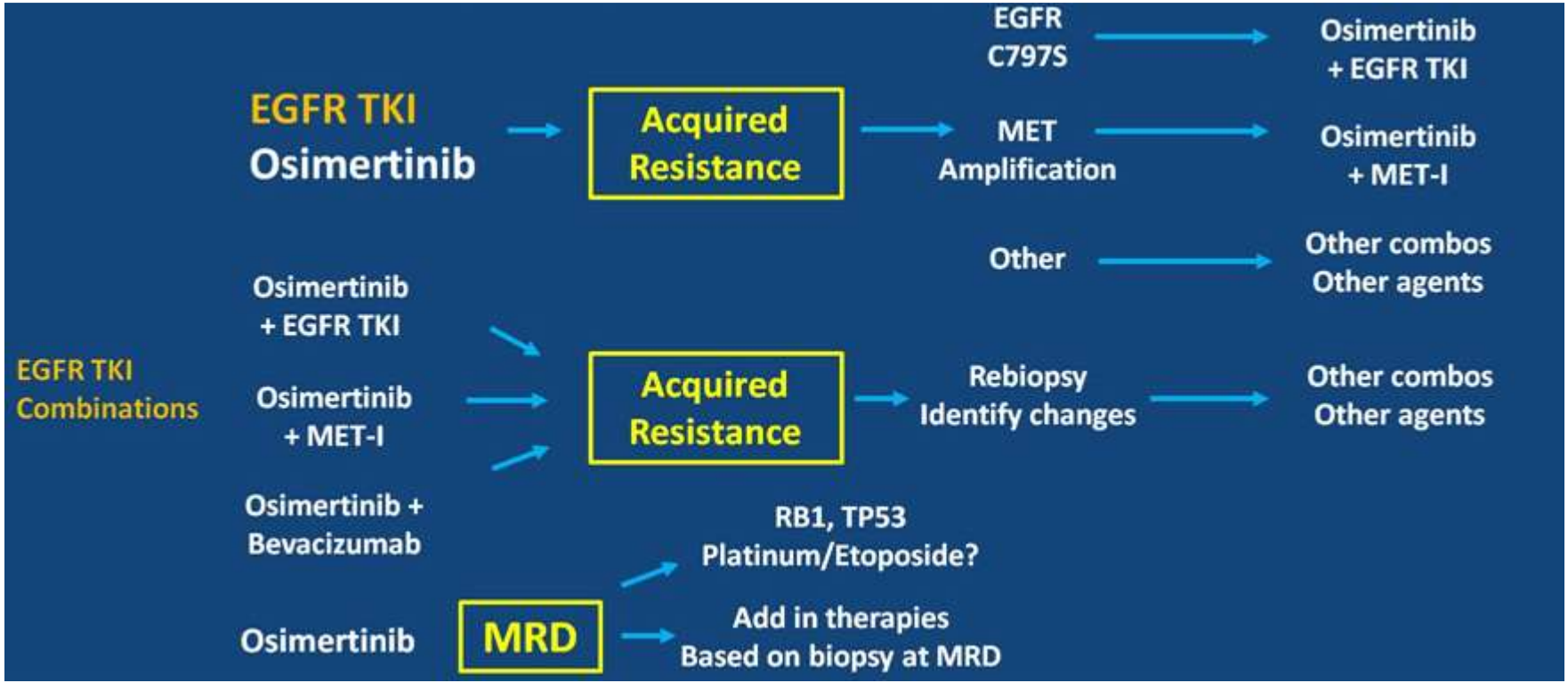
Mechanism of resistance should drive second-line treatment selection

AIM: to maximize TKI benefit trough sequencing or combinations



Combination treatment: which combos and when?

Osimertinib+/-other drugs is the first-line treatment of choice



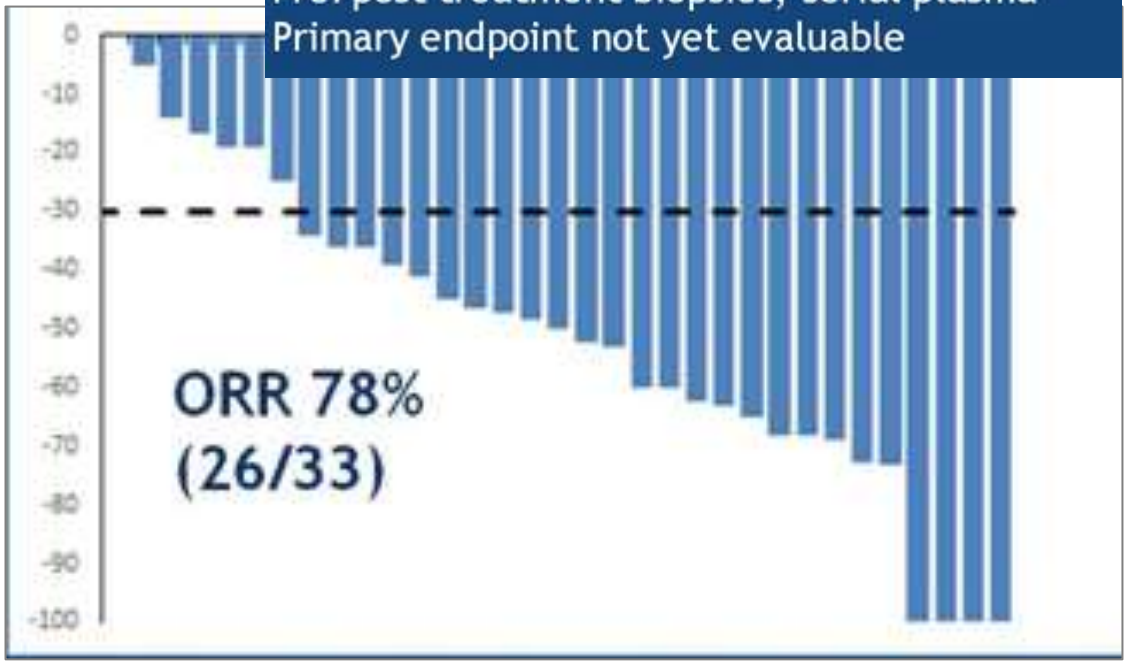
Osimertinib and Bevacizumab

Patient population:
Untreated Metastatic EGFR+ LC
No prior EGFR TKI
No contraindications to Bev

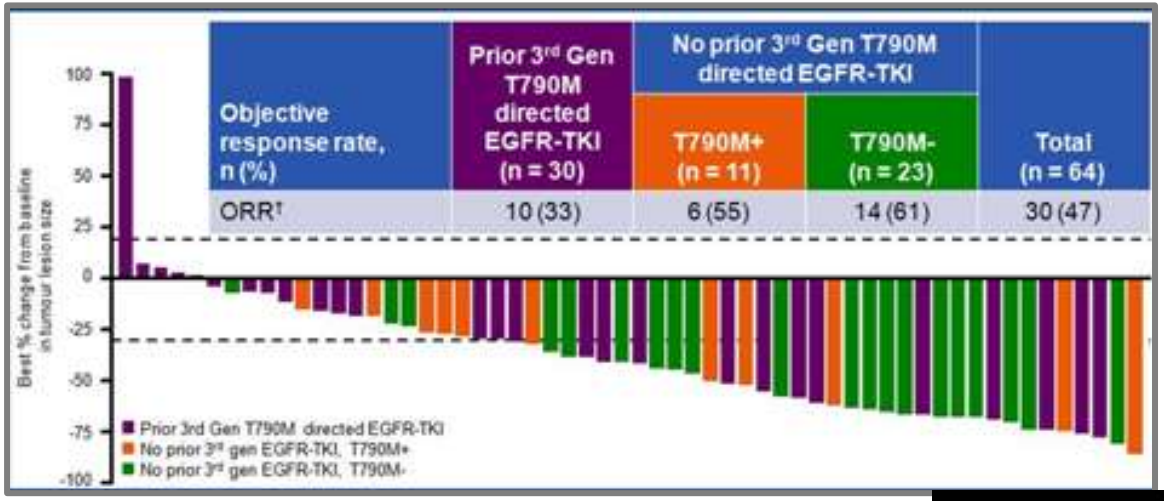
Phase 1:
3+3 Dose de-escalation design
Dose level 1: Full doses both drugs

Phase 2:
MTD from Phase 1
Primary endpoint: PFS at 12 months
Accrual=49

37 ongoing on treatment
Reasonable toxicity profile
No CNS progression (mandated interval MRIs)
Pre/post treatment biopsies, serial plasma
Primary endpoint not yet evaluable



Osimertinib and MET inhibition



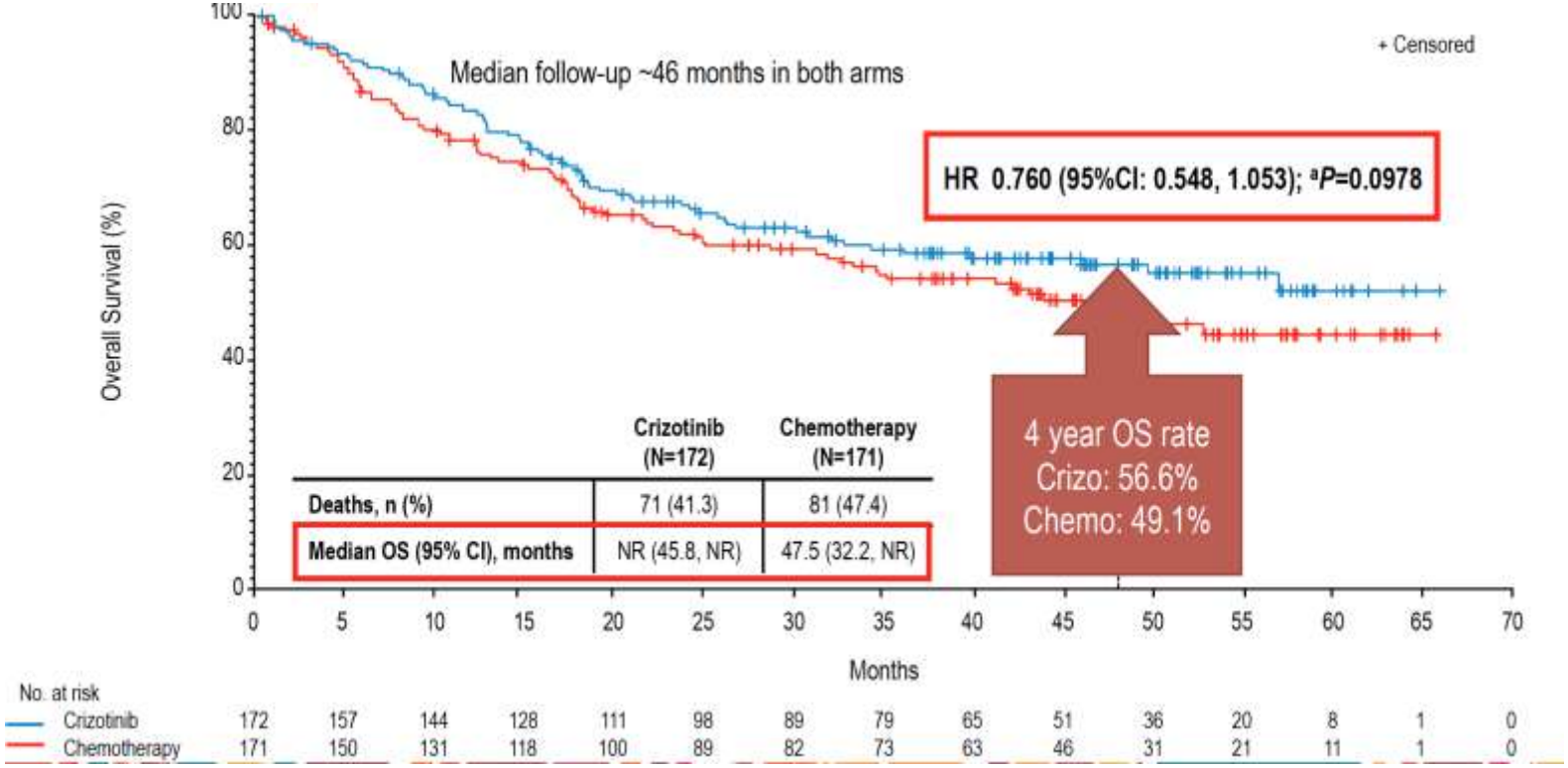
Objective response rate, n (%)	Prior 3rd Gen T790M directed EGFR-TKI (n = 30)	No prior 3rd Gen T790M directed EGFR-TKI		Total (n = 64)
		T790M+ (n = 11)	T790M- (n = 23)	
ORR†	10 (33)	6 (55)	14 (61)	30 (47)

- MET amplification is seen at baseline in ~5% of EGFR+ NSCLC
- MET amplification in up to 30% of patients at progression on osimertinib
- In TATTON study, in patients with MET amplification after osimertinib, ORR 33%.

Outline

- EGFR-mutated:
  - Sequencing therapies for EGFR-mutation-positive NSCLC
  - The big question: First line Osimertinib or sequence after First-second generation EGFR-TKIs
- **ALK-rearranged:**
  - **How alectinib changed 1st line**
  - Update about lorlatinib
- ROS.1 targeting agents and other targets
- Oncogene addicted NSCLC and immunotherapy

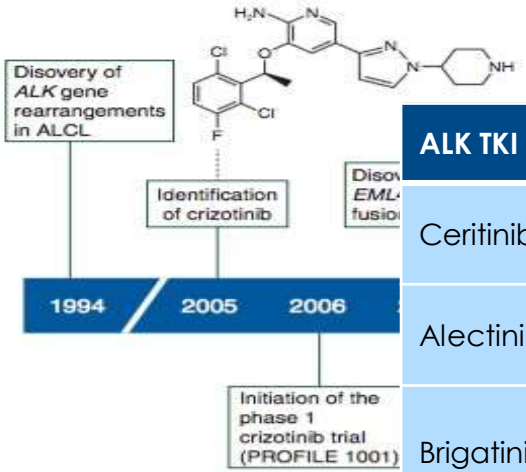
Crizotinib in First Line: OS final Analysis (ITT Population) PROFILE 1014

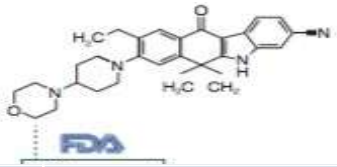


d p-value from the log-rank test stratified by ECOG PS, race, brain metastases

Mok T et al, ESMO 2017

Rapid clinical development of multiple ALK TKIs

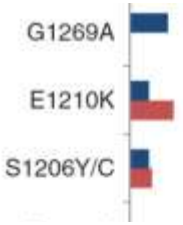


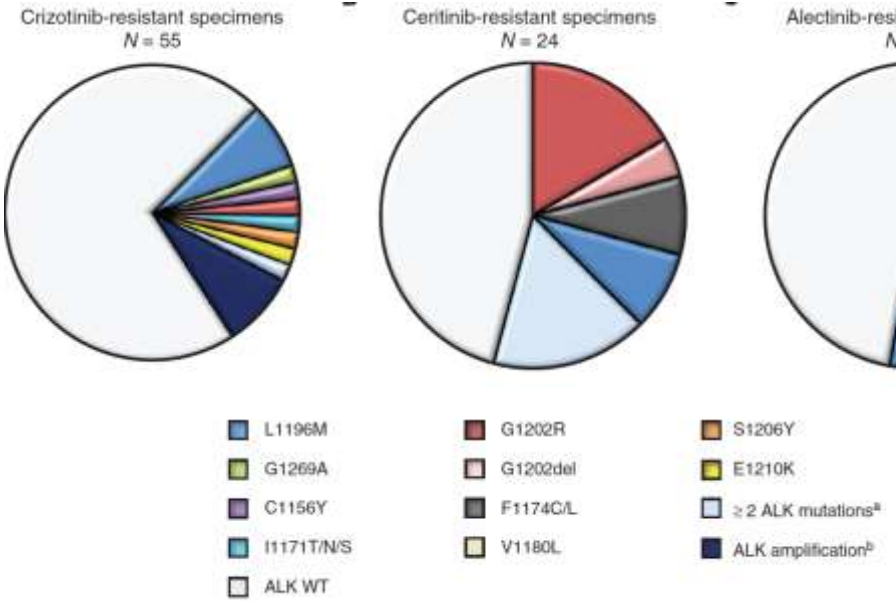


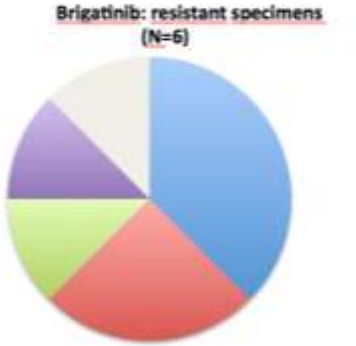
ALK TKI	Additional Targets	Status	Ongoing Studies
Ceritinib	IGF-R1, IR, ROS1	Approved in EU and US	Phase 3 (vs chemotherapy)
Alectinib	LTK, GAK, RET[2]	Approved in Japan and US	Phase 3 (vs crizotinib)
Brigatinib	ROS1, EGFR	Investigational FDA Breakthrough Therapy Designation	Phase 2 (RP2) Phase 3 (vs crizotinib)
Ensartinib (X-396)	MET	Investigational	Phase 1/2 Phase 3 (vs crizotinib)
Entrectinib	TrkA, TrkB, TrkC, ROS1	Investigational	Phase 1/2
Lorlatinib	ROS1	Investigational	Phase 1/2

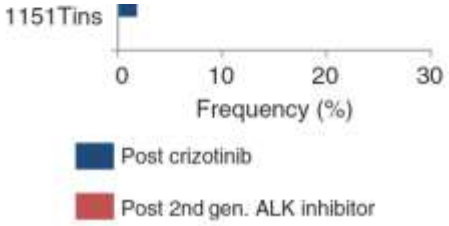
Secondary Resistance: Alk mutations

- **ALK resistance mutations in 20% of pts progressing on crizotinib and in 53-71% of pts progressing on next-generation Alk-TKI**









*21 prior crizotinib

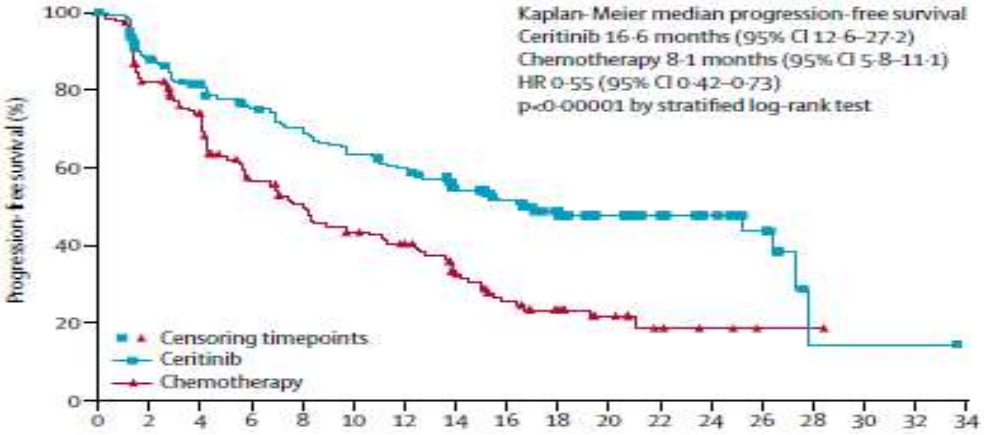
§ 17 prior crizotinib, 3 prior crizotinib and ceritinib

Gainor JF et al, Cancer Discovery

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

Lancet 2017; 389: 917–29

Jean-Charles Soria, Daniel S W Tan, Rita Chiari, Yi-Long Wu, Luis Paz-Ares, Juergen Wolf, Sarayut L Geater, Sergey Orlov, Diego Cortinovis, Chong-Jen Yu, Maximillian Hochmair, Alexis B Cortot, Chun-Ming Tsai, Denis Moro-Sibilot, Rosario G Campelo, Tracey McCulloch, Paramita Sen, Margaret Dugan, Serafino Pantano, Fabrice Branle, Cristian Massacesi, Gilberto de Castro Jr



	Ceritinib (n=189)		Chemotherapy (n=175)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any adverse event	189 (100%)	148 (78%)	170 (97%)	108 (62%)
Diarrhoea	160 (85%)	10 (5%)	19 (11%)	2 (1%)
Nausea	130 (69%)	5 (3%)	97 (55%)	9 (5%)
Vomiting	125 (66%)	10 (5%)	63 (36%)	10 (6%)
Alanine aminotransferase increased	114 (60%)	58 (31%)	38 (22%)	5 (3%)
Aspartate aminotransferase increased	100 (53%)	32 (17%)	34 (19%)	3 (2%)
Gamma-glutamyltransferase increased	70 (37%)	54 (29%)	18 (10%)	3 (2%)
Decreased appetite	64 (34%)	2 (1%)	55 (31%)	2 (1%)
Blood alkaline phosphatase increased	55 (29%)	14 (7%)	8 (5%)	1 (1%)
Fatigue	55 (29%)	8 (4%)	52 (30%)	5 (3%)
Abdominal pain	47 (25%)	4 (2%)	13 (7%)	0
Cough	46 (24%)	0	28 (16%)	0
Weight decreased	45 (24%)	7 (4%)	26 (15%)	1 (1%)
Blood creatinine increased	42 (22%)	4 (2%)	17 (10%)	0
Upper abdominal pain	39 (21%)	3 (2%)	10 (6%)	0
Non-cardiac chest pain	38 (20%)	2 (1%)	17 (10%)	1 (1%)
Back pain	36 (19%)	3 (2%)	32 (18%)	4 (2%)
Constipation	36 (19%)	0	38 (22%)	0
Pyrexia	34 (18%)	0	24 (14%)	2 (1%)
Asthenia	33 (17·5)	5 (3%)	36 (21%)	6 (3%)
Headache	31 (16%)	0	21 (12%)	2 (1%)
Dyspnoea	29 (15%)	4 (2%)	35 (20%)	11 (6%)
Anaemia	28 (15%)	4 (2%)	62 (35%)	13 (7%)
Neutropenia	9 (5%)	1 (1%)	38 (22%)	19 (11%)
White blood cell count decreased	7 (4%)	0	31 (18%)	7 (4%)

Data are n (%).

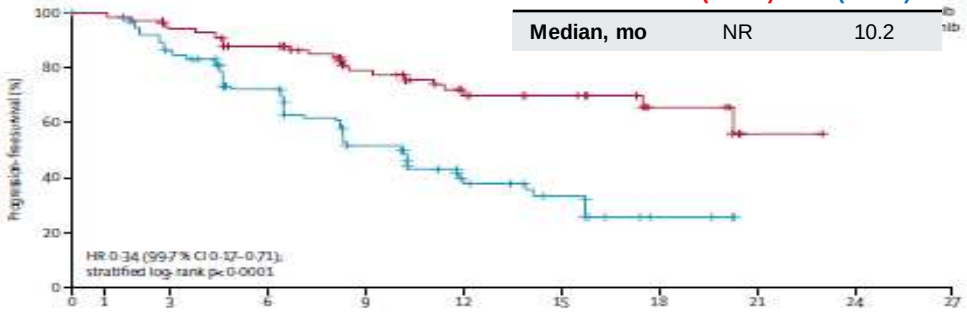
Table 3: Adverse events regardless of study drug relationship in the safety set (>15% of patients in either group)

Alectinib versus crizotinib in patients with *ALK*-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial

Toyoaki Hida, Hiroshi Nokihara, Masashi Kondo, Young Hak Kim, Koichi Azuma, Takashi Seto, Yuichi Takiguchi, Makoto Nishio, Hiroshige Yoshioka, Fumio Imamura, Katsuyuki Hotta, Satoshi Watanabe, Koichi Goto, Miyako Satouchi, Toshiyuki Kozuki, Takehito Shukuya, Kazuhiko Nakagawa, Tetsuya Mitsudomi, Noboyuki Yamamoto, Takashi Asakawa, Ryoichi Asabe, Tomohiro Tanaka, Tomohide Tamura

www.thelancet.com Published online May 10, 2017

PFS	Alectinib (n=103)	Crizotinib (n=104)
Median, mo	NR	10.2



	Alectinib	Crizotinib
Assessed by IRF		
Total	83	90
Objective response	92% (85·6–97·5)	79% (70·5–87·3)
Complete response	2 (2%)	2 (2%)
Partial response	74 (89%)	69 (77%)
Stable disease	4 (5%)	12 (13%)
Time to response (months)	1·0 (1·0–1·1)	1·0 (1·0–1·0)
Duration of response (months)	NE (NE–NE)	11·1 (7·5–13·1)
Assessed by investigators		
Total	103	104
Objective response	85% (78·6–92·3)	70% (61·4–79·0)
Complete response	5 (5%)	2 (2%)
Partial response	83 (81%)	71 (68%)
Stable disease	13 (13%)	19 (18%)
Time to response (months)	1·0 (1·0–1·1)	1·0 (1·0–1·0)
Duration of response (months)	NE (16·7–NE)	11·2 (8·5–13·9)

Data are n, % (95% CI), n (%), or median (95% CI). IRF=independent review facility. NE=not estimable.

Table 2: Summary of response data

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D.,

N Engl J Med 2017;377:829-38.

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.34–0.65)
P<0.001 by log-rank test

PFS	Alectinib (n=152)	Crizotinib (n=151)
Median, mo	25.7	10.4

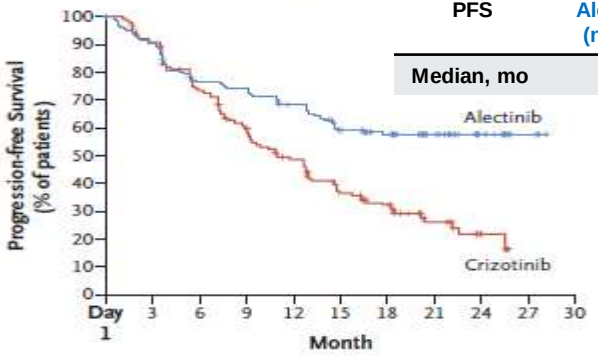


Table 2. Objective Response Rates in the Intention-to-Treat Population and among Patients with CNS Lesions at Baseline.*

Variable	Crizotinib	Alectinib
Intention-to-treat population		
No. of patients	151	152
Response		
No. of patients	114	126
% (95% CI)	75.5 (67.8–82.1)	82.9 (76.0–88.5)†
Complete response — no. (%)	2 (1)	6 (4)
Partial response — no. (%)	112 (74)	120 (79)
Stable disease — no. (%)	24 (16)	9 (6)
Median duration of response (95% CI) — mo	11.1 (7.9–13.0)	NE (NE)

Updated efficacy and safety data from the global phase III ALEX study

Pts with BM at baseline: PFS 27.7m vs 7.4m (**HR 0.35**, 95% CI 0.22–0.56)

(n receiving WBRT (n = 16 ALC, n = 17 CZ) or SRS (n = 4 ALC, n = 6 CZ) and n° of BL lesions (median 2 per arm)balanced].

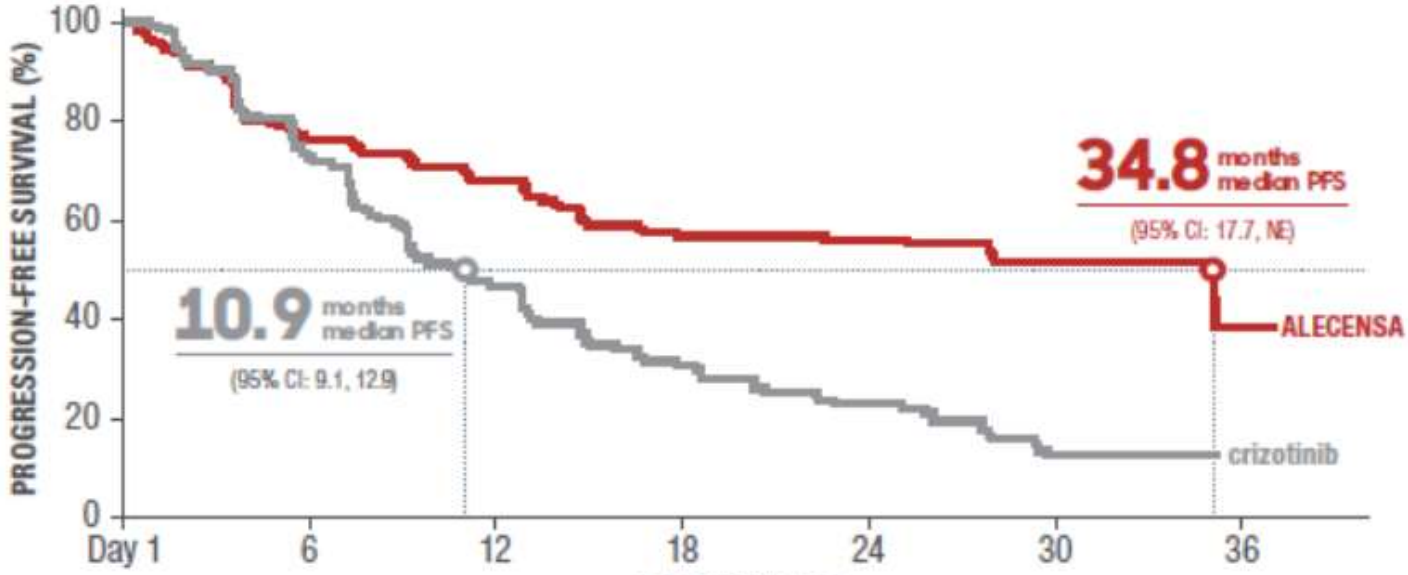
Pts without BM at baseline: PFS 34.8m vs 14.7m (**HR 0.47**, 95% CI 0.32–0.71).

Updated secondary endpoint data (INV):

- ✓ ORR 82.9% (95% CI 75.95–88.51; n = 152) vs 75.5% (95% CI 67.84–82.12; n = 151);
- ✓ DOR 33.3m (95% CI 31.1–NE; n = 126) vs 11.1m (95% CI 7.5–13.0; n = 114), HR 0.33, 95% CI 0.23–0.48.
- ✓ **OS data are still immature** (events ALC 28.3%, CZ 31.8%; HR 0.76, 95% CI 0.50–1.15).
- ✓ **AEs leading to dose reduction** (16.4% vs 20.5%) **or interruption** (22.4% vs 25.2%) **were lower with ALC vs CZ**. ..despite significantly longer treatment (Tx) duration with ALC (27.0m vs 10.8m),
- ✓ grade 3–5 AEs (44.7% vs 51.0%)
- ✓ pts with AEs leading to discontinuation: 13.2% each arm.
- ✓ Fatal AEs: 5% CZ (2 Tx-related AEs) and 4% ALC pts (0 Tx related).

Abstract No: 9043- presented at ASCO18

PRIMARY ENDPOINT: PFS (N=303)[1,13]



Number at Risk

ALECENSA	152	135	113	109	99	84	81	81	77	69	33	19	4
crizotinib	151	132	104	83	64	47	42	35	31	24	10	8	

INV

DATA CUTOFF: DEC. 1, 2017

57%

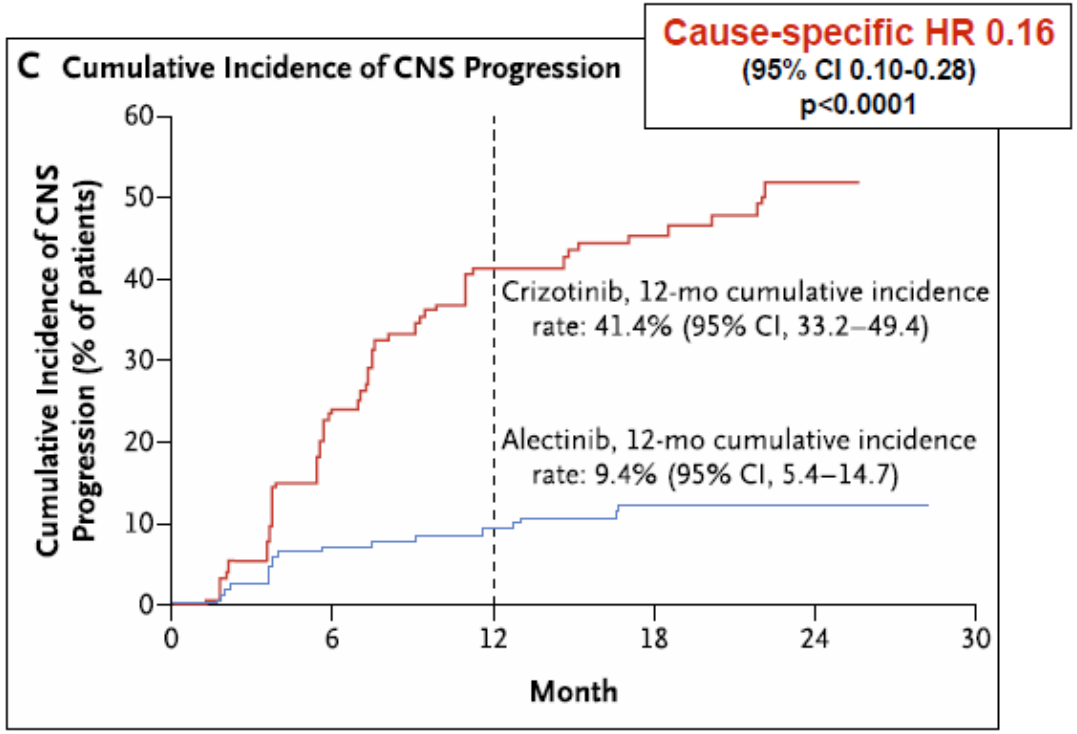
REDUCTION IN RISK

HR=0.43

(95% CI: 0.32, 0.58)

ALEX-Prevention of brain mets:

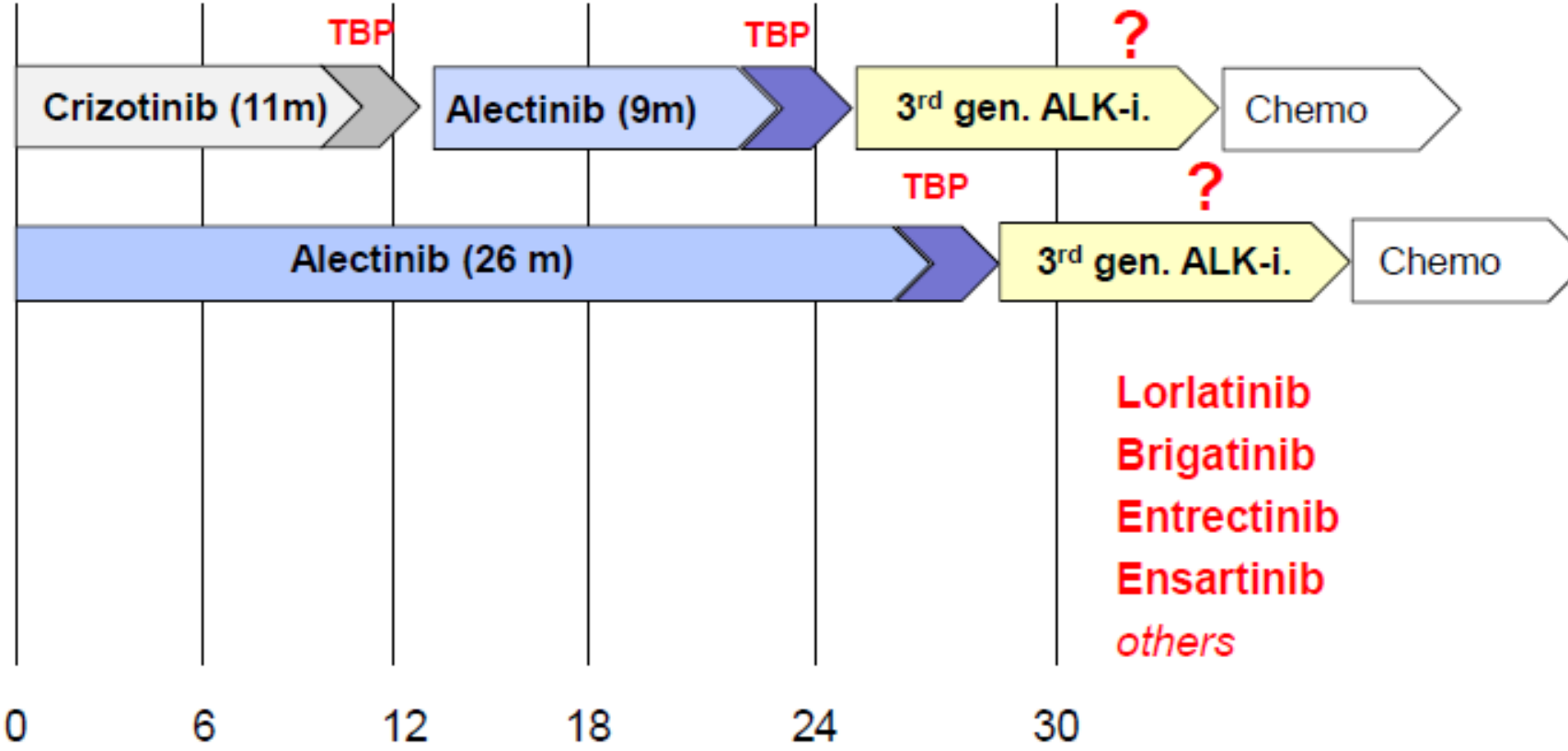
Cumulative incidence at 12 months



Peters, NEJM 2017

Sequential therapy with Alk-inhibitors: OS

What is the role of other next generation alk inhibitors?

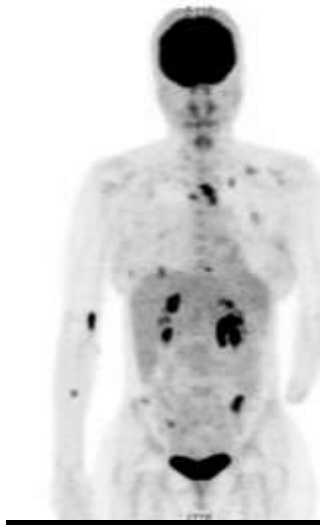


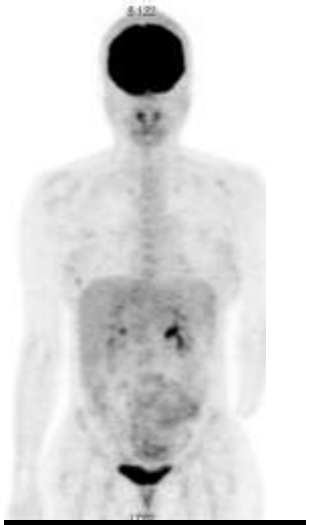
Case # 3: Up-front Alectinib, does TKIs generation matter?

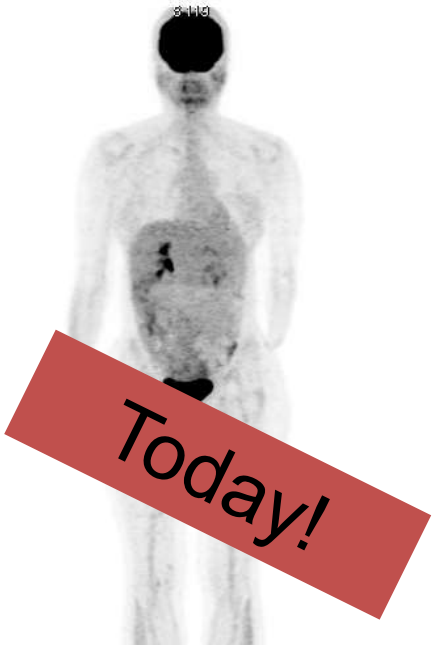
- March 2015: diagnosis of stage IV

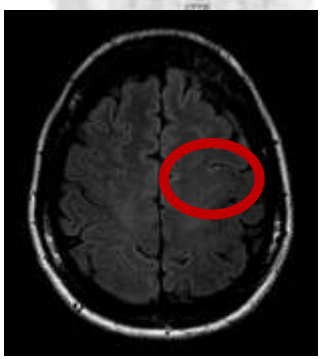
ALK-rearranged metastatic lung adenocarcinoma (Brain +)

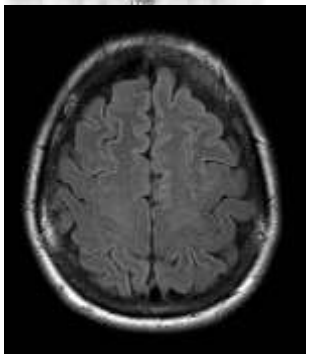
- April 2015: She stared Alectinib 600 mg bid (ALEX trial) with PR afer 21 days→ still ongoing **(+ 42 months)**

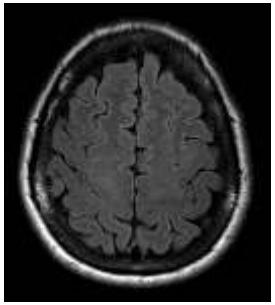












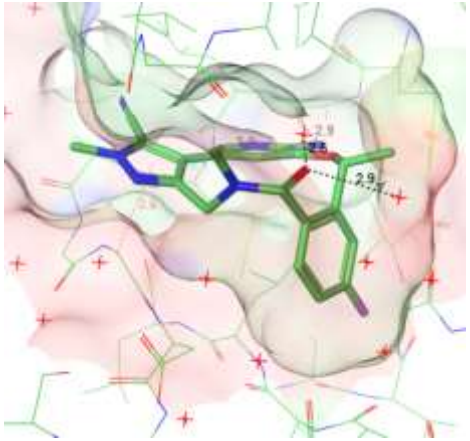
March 2015

April 2015

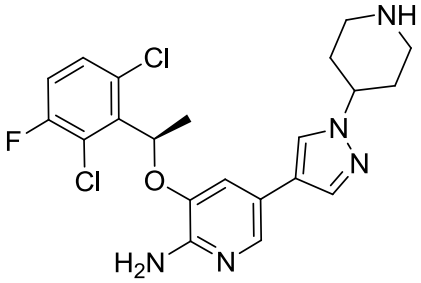
Outline

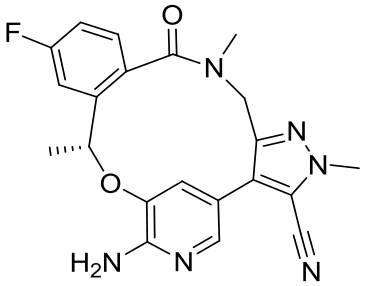
- **EGFR-mutated:**
  - Sequencing therapies for EGFR-mutation-positive NSCLC
  - The big question: First line Osimertinib or sequence after First-second generation EGFR-TKIs
- **ALK-rearranged:**
  - How alectinib changed 1st line
  - **Update about lorlatinib**
- **ROS.1 targeting agents and other targets**
- **Oncogene addicted NSCLC and immunotherapy**

Lorlatinib is a Third-Generation Potent, Selective, CNS-Penetrant ALK/ROS1 TKI



Lorlatinib/ALK L1196M bound structure





	Crizotinib		Lorlatinib
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**

ALK, anaplastic lymphoma kinase; CSF, cerebrospinal fluid; D, distribution coefficient; IC_{50}, half-maximal inhibitory concentration; MDR, multidrug-resistant transporter; nM, nanomolar; ROS1, c-ros oncogene 1; WT, wild-type

Zou HY, et al. *Proc Natl Acad Sci* 2015;112:3493-8.

Lorlatinib Covers the Broadest Range of ALK Resistance Mutations

- Secondary mutations in the ALK kinase domain can induce resistance to first- and second-generation ALK TKIs[1]
- Lorlatinib has broad-spectrum potency against most known ALK resistance mutations, including ALK G1202R[1,2]

IC_{50} ≤50 nM | IC_{50} >50–<200 nM | IC_{50} ≥200 nM

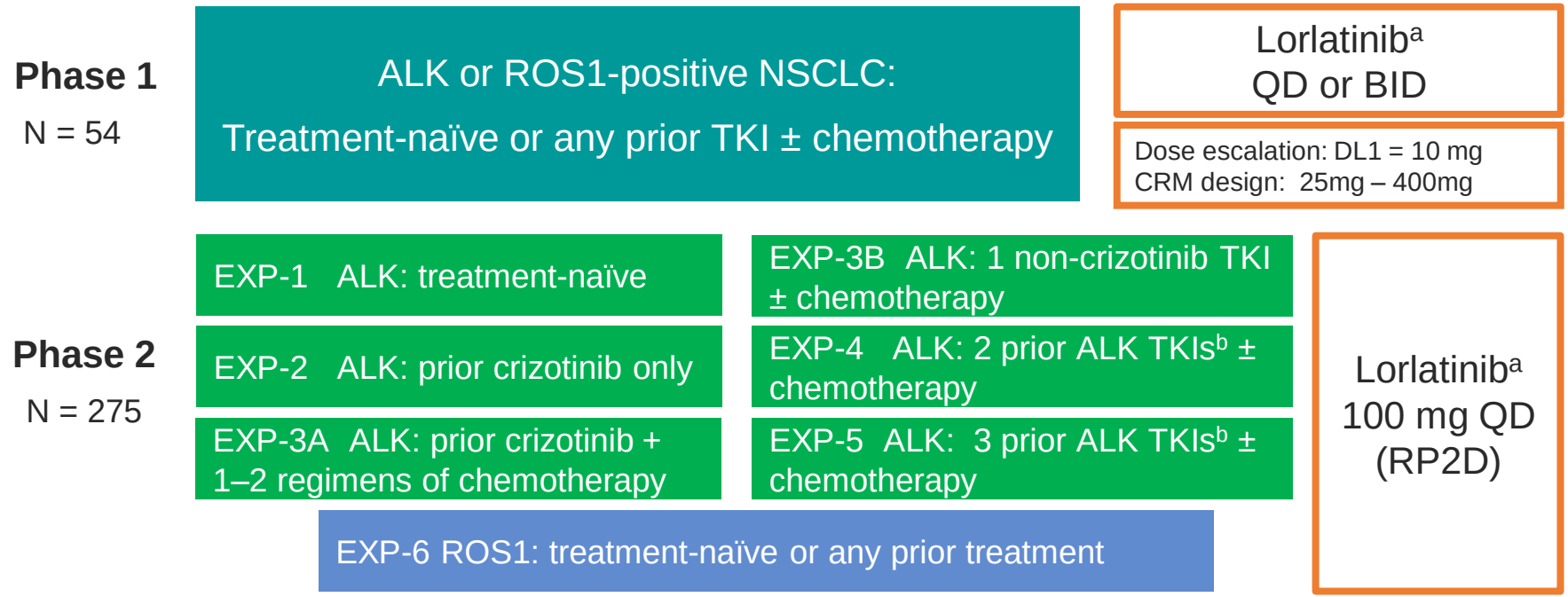
	Cellular ALK Phosphorylation Mean IC_{50} (nM)				
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
EML4-ALK	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0[a]	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	50.1	58.8	95.8	5.2
D1203N	116.3	35.3	27.9	34.6	11.1
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0

Adapted from Gainor JF, et al. *Cancer Discov.* 2016;6:1118–33.

IC_{50}, half-maximal inhibitory concentration; ND, not done

1. Gainor JF, et al. *Cancer Discov.* 2016;6:1118–1133.
2. Johnson TW, et al. *J Med Chem.* 2014;57:4720–4744.

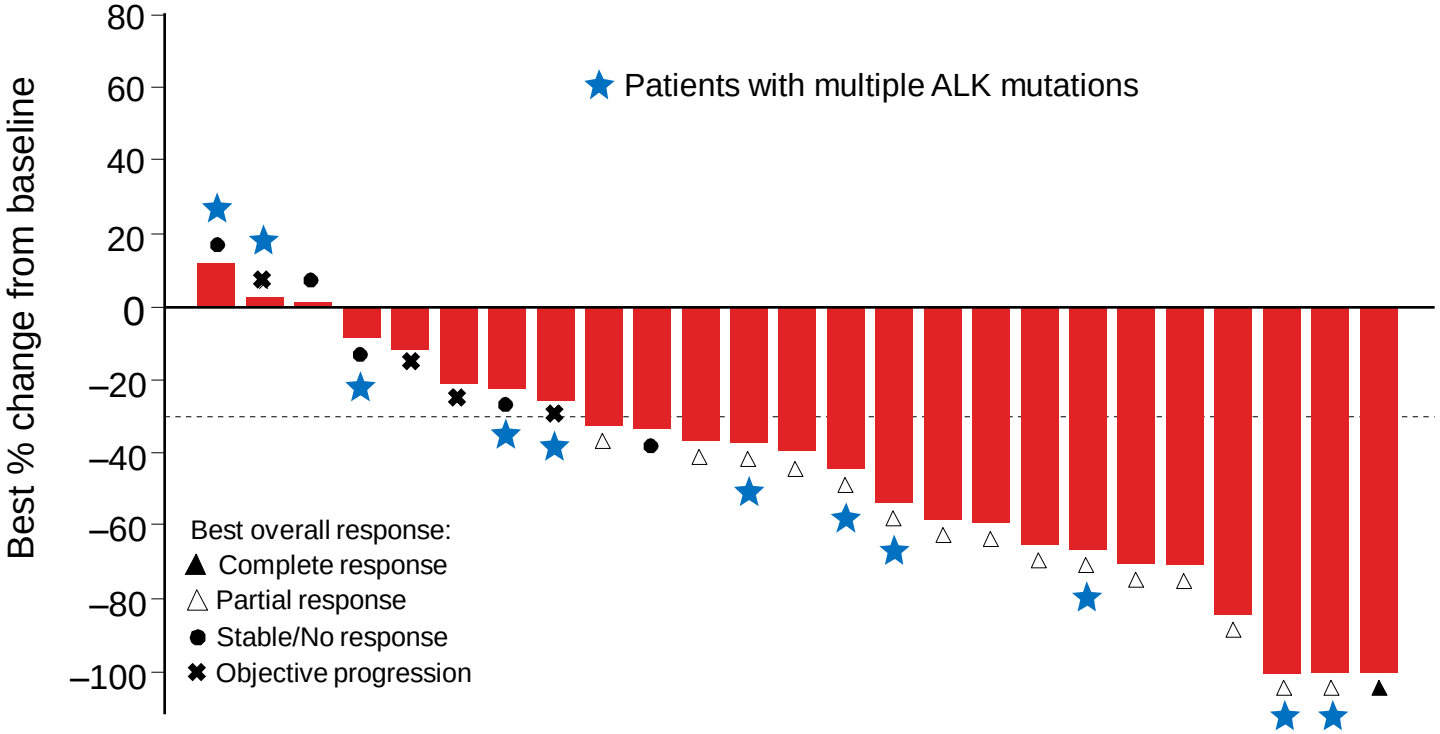
Phase 1/2 Study of Lorlatinib: Design and Patient Populations



Asymptomatic brain mets were allowed in all cohorts. [a]Treatment until PD or unacceptable toxicity.
[b]Lines of therapy (if the same TKI is given twice, this is counted as 2 prior lines of treatment).

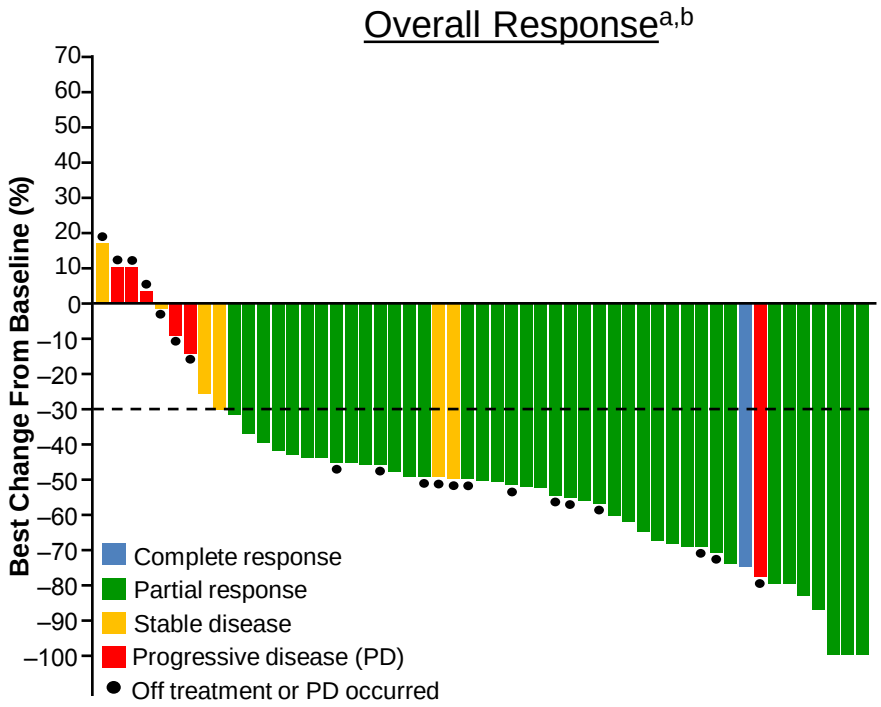
BID, twice daily; PD, progressive disease; QD, once daily.

Best Response in Pts Harboring the ALK G1202R or G1202del Mutation[a] (EXP2–5)



[a]Detected in either cfDNA or tumor tissue (archival or de novo) analysis sets

Efficacy in ALK+ Pre Treated with Crizotinib ± Chemotherapy (EXP2–3A)



	EXP2–3A: Prior crizotinib ± 1–2 chemo (n=59)
ORR, n/N (%) (95% CI)	41/59 (69) (56, 81)
IC ORR, n/N (%) (95% CI)	25/37 (68) (50, 82)

Solomon BJ, et al. J Thorac Oncol:2017;12:abs1756 (Data cut-off: 15 Mar 2017).

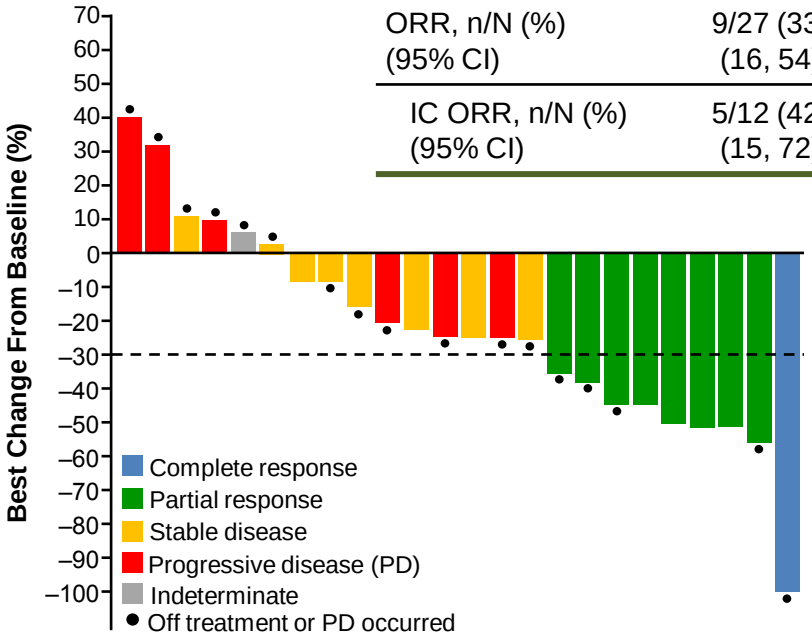
[a] Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.

[b] Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, reversion to normal node size (<10 mm) prevented the percent change from baseline from reaching –100%. Some patients with a total change from baseline of –100% are shown as partial responses due to the inclusion of non-target lesions in the summary.

Efficacy in ALK+ Pts Pre-Treated with 2nd-gen ALK TKIs (EXP3B and EXP4–5)

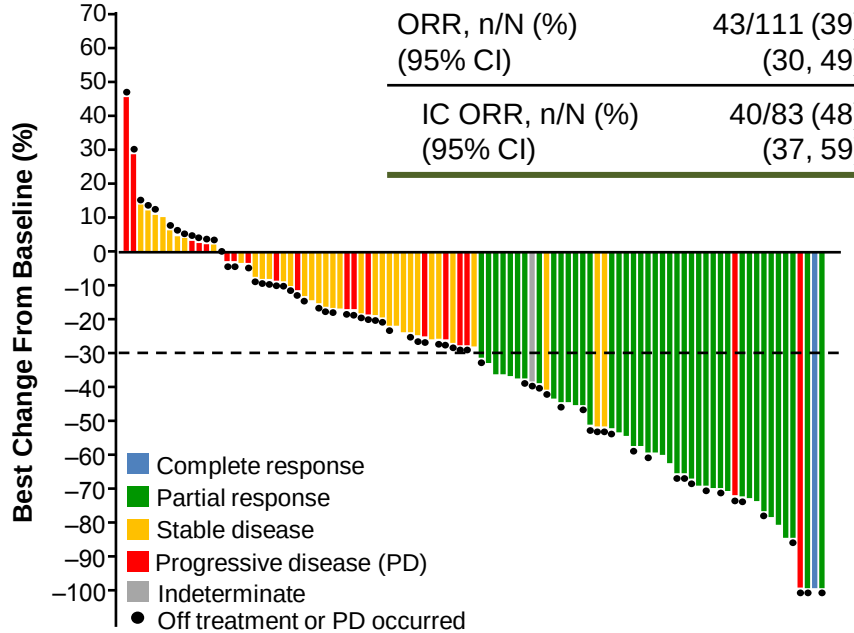
Overall[a,b]

	EXP3B: 1 non-crizotinib TKI ± chemo (n=27)
ORR, n/N (%) (95% CI)	9/27 (33) (16, 54)
IC ORR, n/N (%) (95% CI)	5/12 (42) (15, 72)



Overall[a,b]

	EXP4–5: ≥2 prior ALK TKIs ± chemo (n=111)
ORR, n/N (%) (95% CI)	43/111 (39) (30, 49)
IC ORR, n/N (%) (95% CI)	40/83 (48) (37, 59)



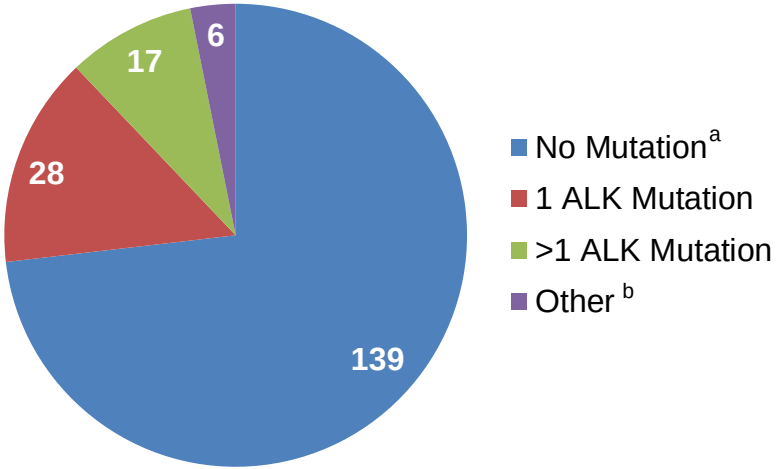
Solomon BJ, et al. J Thorac Oncol:2017;12:abs1756 (Data cut-off: 15 Mar 2017).

[a] Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.

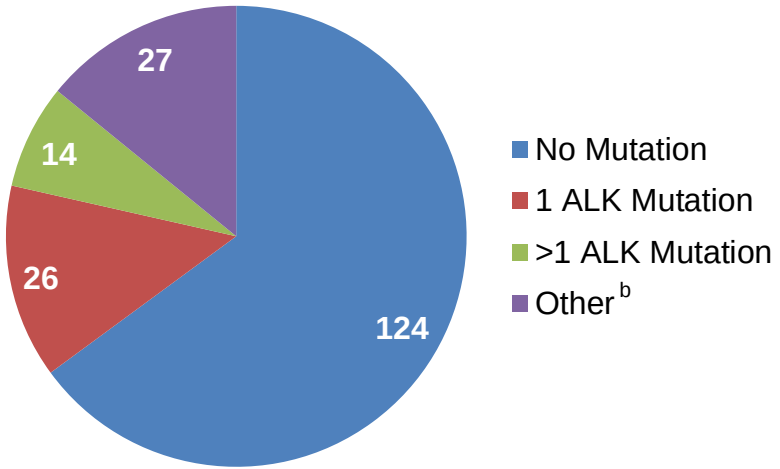
[b] Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, reversion to normal node size (<10 mm) prevented the percent change from baseline from reaching –100%. Some patients with a total change from baseline of –100% are shown as partial responses due to the inclusion of non-target lesions in the summary.

ALK Kinase Domain Mutation Detected in Pre-treated ALK+ Pts (EXP2–5)

cfDNA analysis:
- 45/190 patients with 1 or more ALK kinase domain mutations

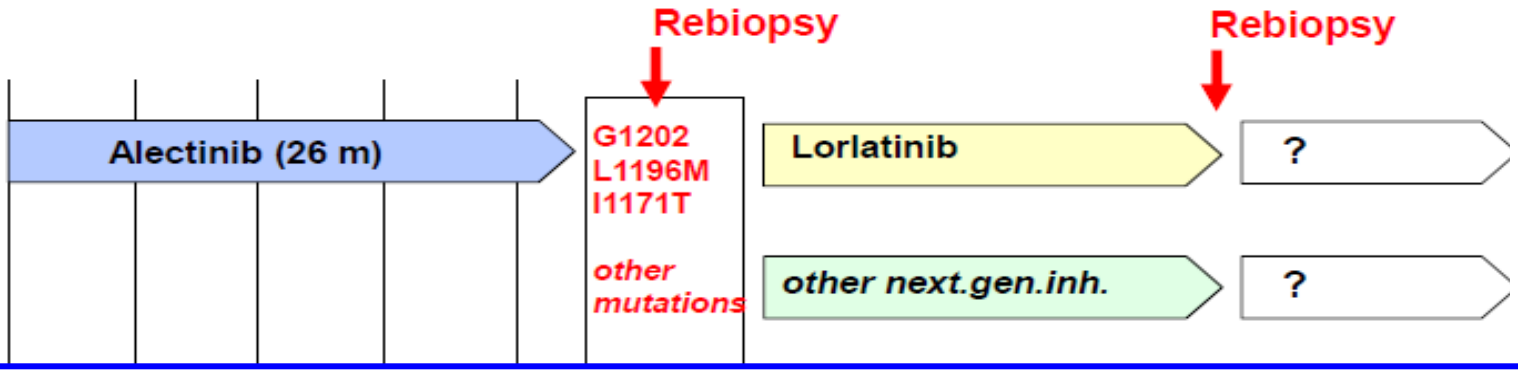


Tumor tissue analysis (archival or de novo):
- 40/191 patients with 1 or more ALK kinase domain mutations



[a]No mutation includes samples with no cfDNA was detected; [b]Other includes samples which failed analysis, were uninformative or not analyzed.

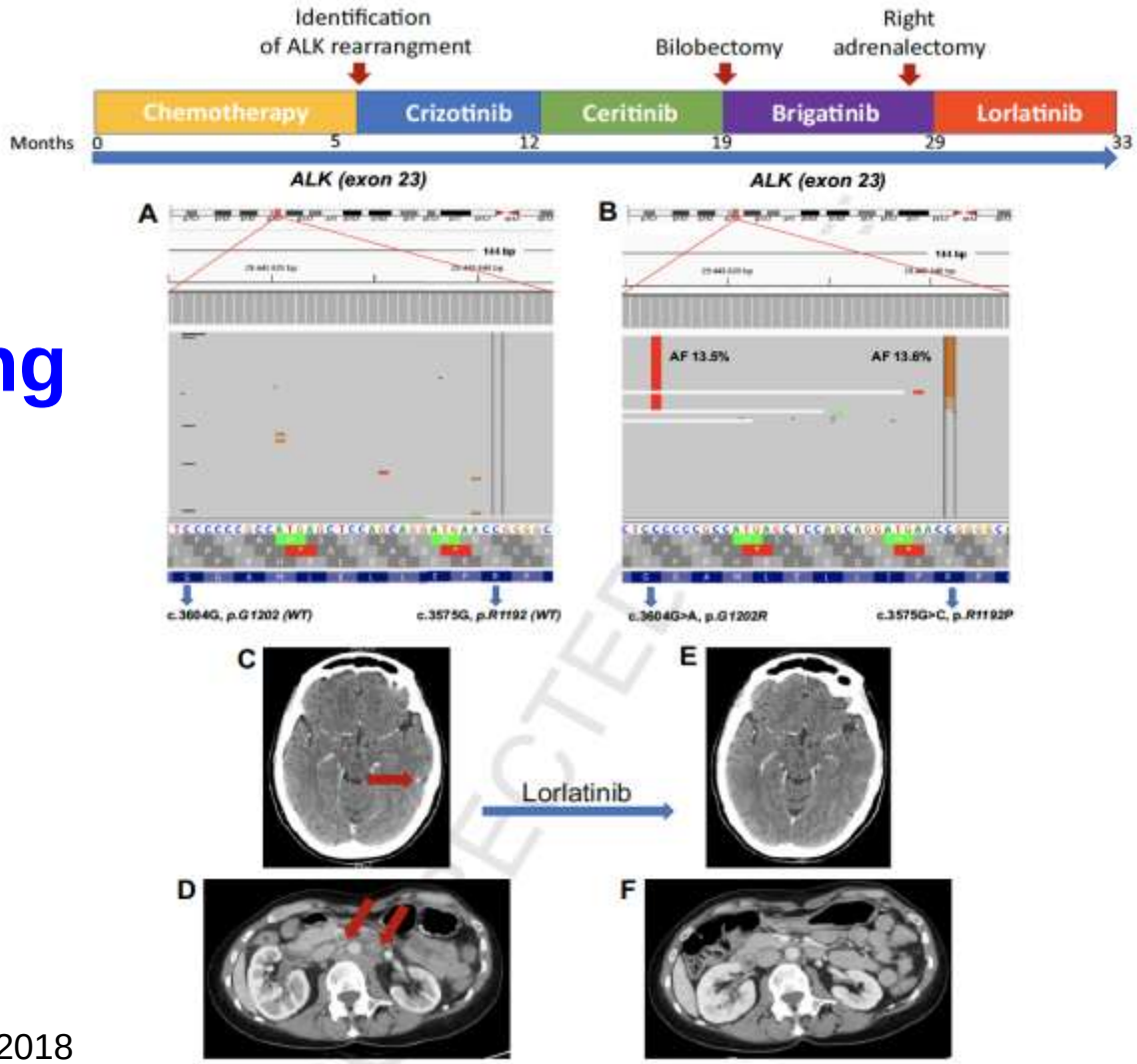
Molecular guided sequential therapy: OS?



- Sequential therapy will be driven by longitudinal profiling of cfDNA and/or tumor tissue
- Influence of various scenarios on OS cannot be quantified to date (OS will be longer for sure)
- There is no reason not to start with the best available drug

Shaw. et al, NEJM 2016, Gainor et al, Cancer Disc. 2016, Lin, Rieley, Shaw Cancer Disc. 2017

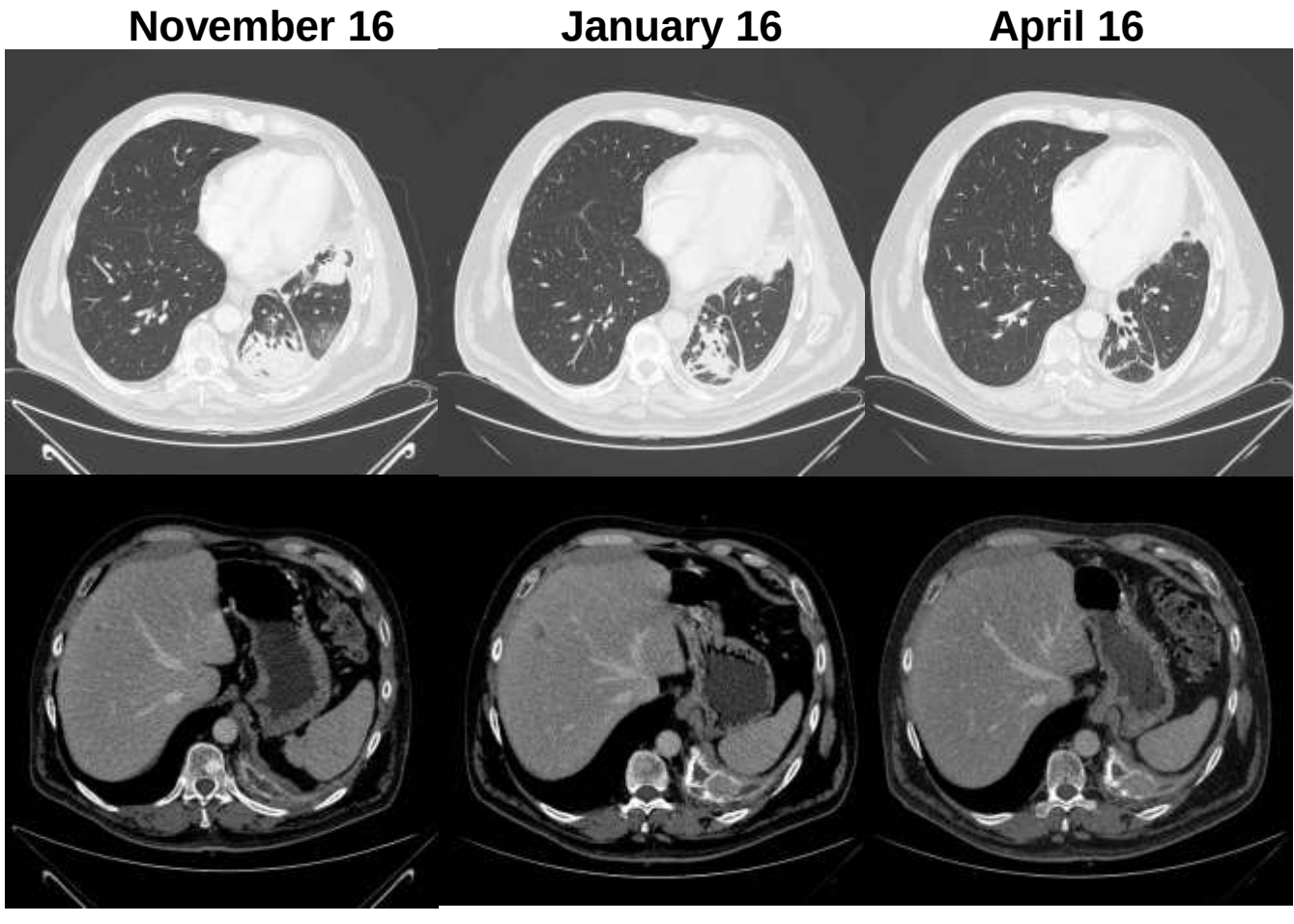
Case # 4: Tailoring treatment with secondary mutations



Baglivo et al. JTO 2018

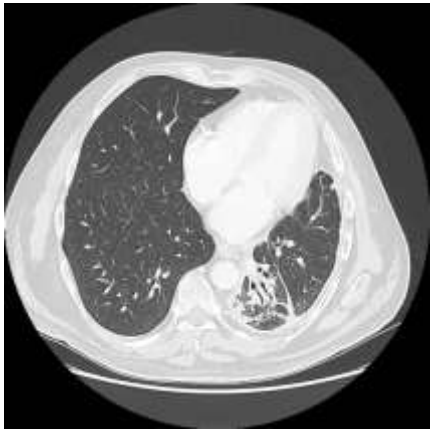
Case # 5: What if secondary mutations do not arise?

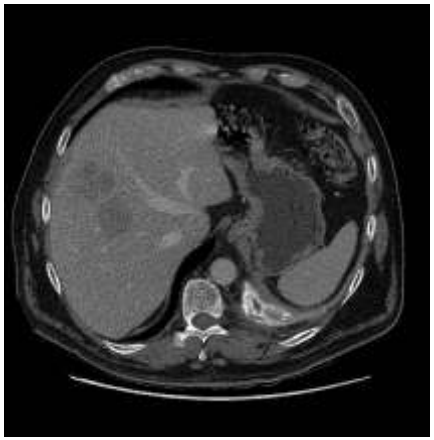
- November 2016: Diagnosis of ALK-positive lung adenocarcinoma (stage IV, liver-pleura)
- The patient started Crizotinib within a clincal trial
- The patinet progressed after 2 months and was swithed to II line brigatinib with PR (april 2017)
- December 2017: liver and lung progression
- No secondary mutations were detected upon PD to brigatinib
- Dembmber 2017: he started platinum/pemetrexed with PR

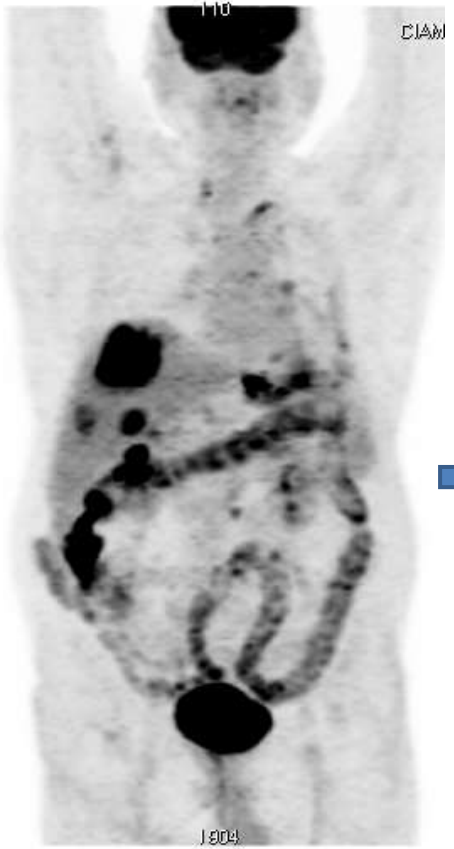


Case # 5: What if secondary mutations do not arise?

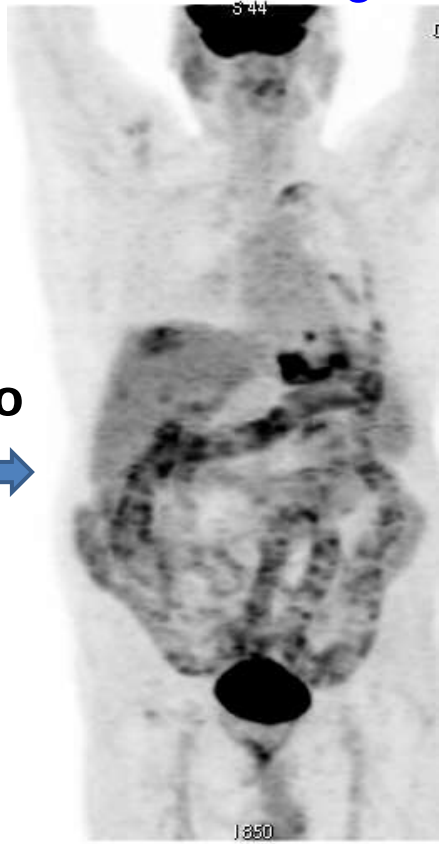
Do not forget chemotherapy!







Chemo



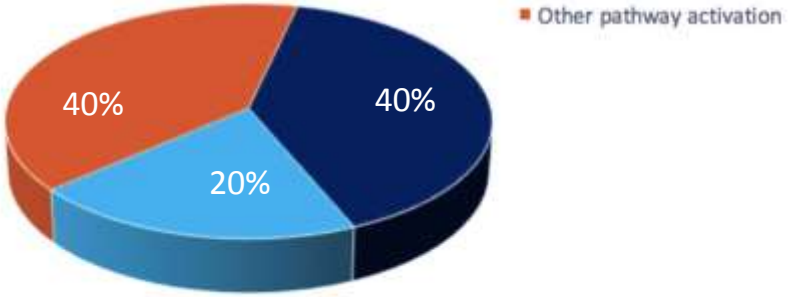
December

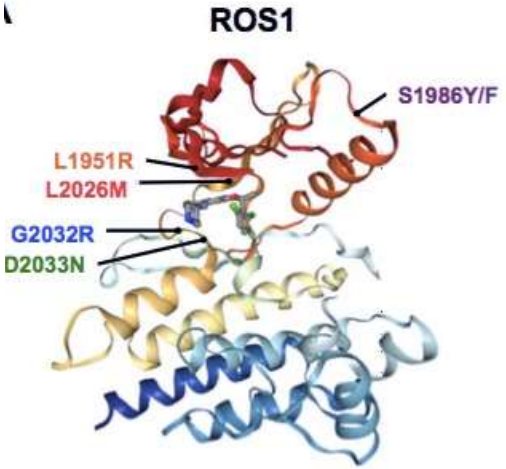
January 2018

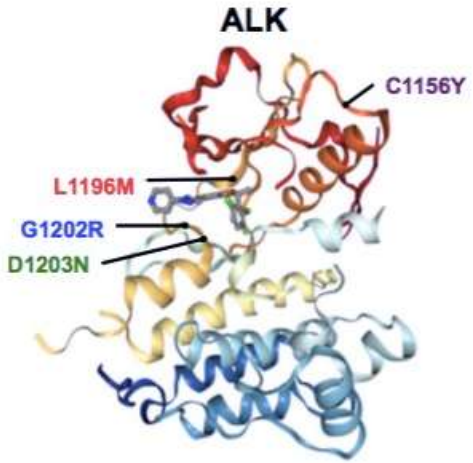
Outline

- **EGFR-mutated:**
  - Sequencing therapies for EGFR-mutation-positive NSCLC
  - The big question: First line Osimertinib or sequence after First-second generation EGFR-TKIs
- **ALK-rearranged:**
  - How alectinib changed 1st line
  - Update about lorlatinib
- **ROS.1 targeting agents and other targets**
- **Oncogene addicted NSCLC and immunotherapy**

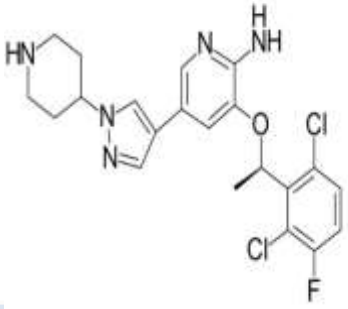
Not all anti-ALK TKIs are also anti-ROS1 agents!!!!



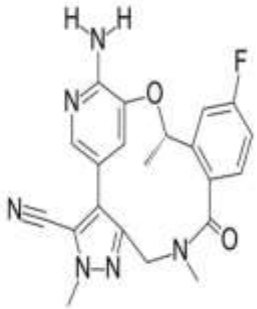




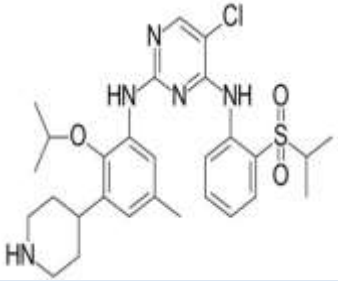
(A) Crizotinib



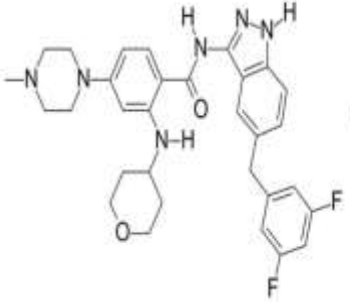
(B) Lorlatinib



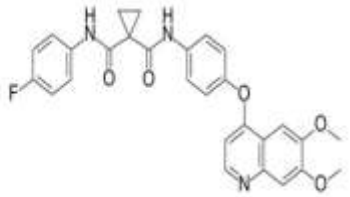
(C) Ceritinib



(D) Entrectinib

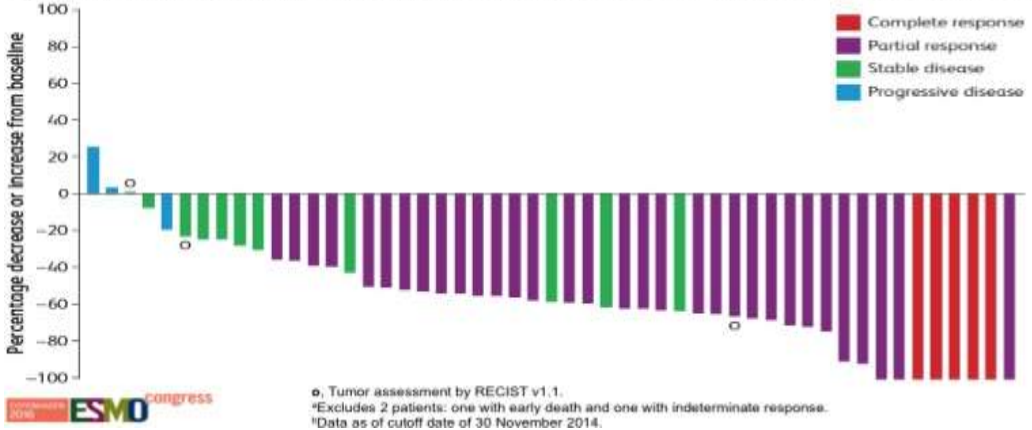


(E) Cabozantinib



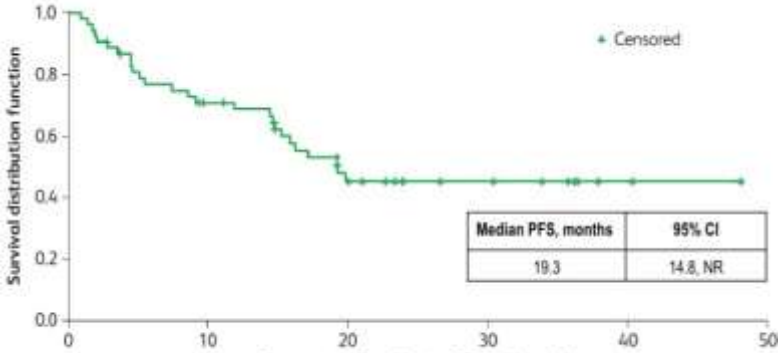
Crizotinib in *ROS1*-pos NSCLC: Updated Results from PROFILE 1001

Best Percent Change From Baseline in Size of Target Lesions (n=51)[a,b]



o, Tumor assessment by RECIST v1.1.
[a]Excludes 2 patients: one with early death and one with indeterminate response.
[b]Data as of cutoff date of 30 November 2014.

Progression-Free Survival[a]



ORR 69.8 %

- **CR n=5**
- **PR n=32**
- **SD n=11**

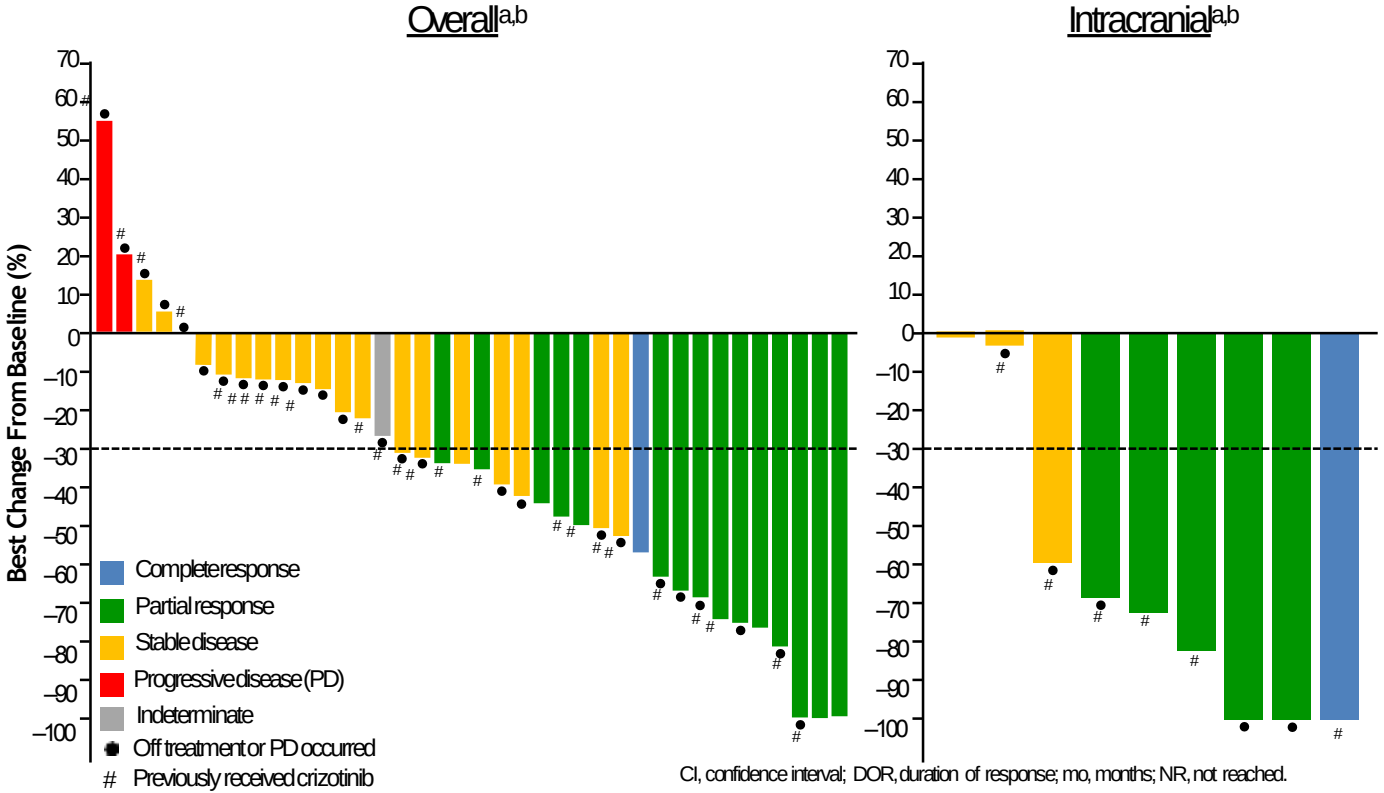
mPFS 19.3 m

Shaw et al. Annals of Oncology (2016) 27 (6): 416-454.

Efficacy in EXP6 (ROS1+ With Any Prior Treatment)

	EXP6 (n=47)
ORR, n/N (%) (95% CI)	17/47 (**36**) (23, 52)
IC ORR, n/N (%) (95% CI)	14/25 (**56**) (35, 76)
Median DOR, mo (95% CI)	13.8 (11.1, NR)
DOR ≥6 mo, n[0]/n (%)	12/17 (71)
Median PFS, mo (95% CI)	9.6 (4.7, NR)

- 25 patients (53%) had brain metastases at baseline.



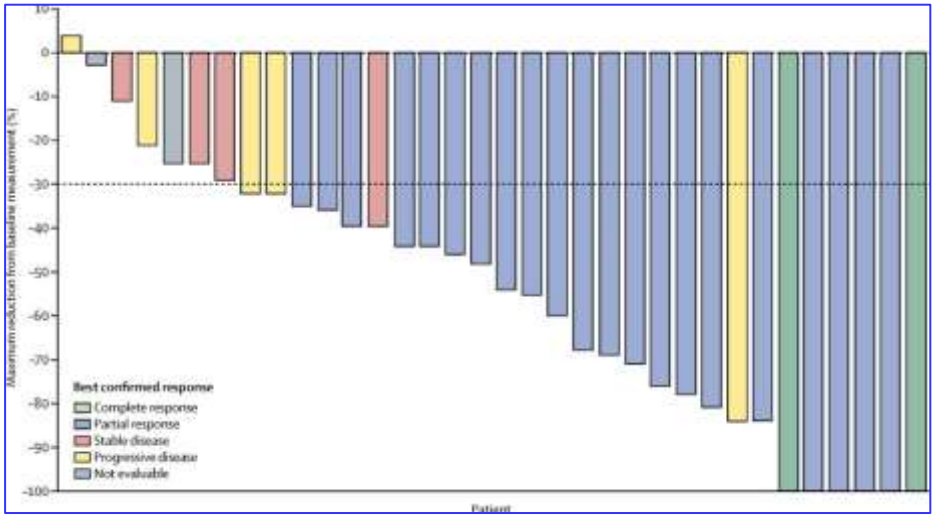
CI, confidence interval; DOR, duration of response; mo, months; NR, not reached.

[a] Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.
[b] Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, reversion to normal node size (<10 mm) prevented the percent change from baseline from reaching –100%. Some patients with a total change from baseline of –100% are shown as partial responses due to the inclusion of non-target lesions in the summary.

Dabrafenib/trametinib in previously untreated BRAF V600E patients

BRAF mutations in up to 3% NSCLC

V600E	**~55%**
G469A	**~35%**
D594G	**~10%**



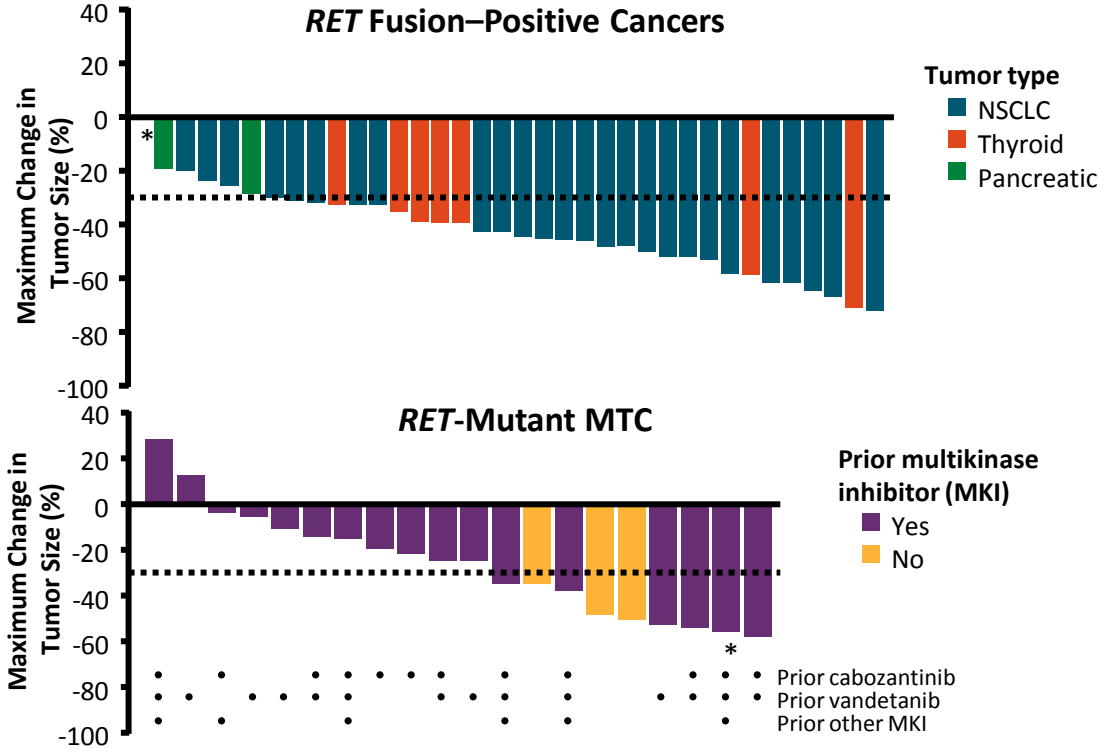
ORR 64%
DCR 72%
mPFS 14.6 mo (independent review, n=36)

Planchard et al. Lancet Oncol. 2017 Oct;18(10):1307-1316.

RET – Rearranged during Transfection – in 1-2% of NSCLC

- *RET* fusions or mutations can lead to *RET* activation in cancers[1-3]
  - *RET* fusions observed in 10% to 20% of papillary and other thyroid cancers, **1% to 2% of NSCLC**, < 1% of pancreatic and other cancers[1,2]
  - *RET* mutations observed in 40% to 60% of sporadic and > 90% of hereditary medullary thyroid cancers[3]
- **LOXO-292:** investigational, highly selective RET inhibitor with preclinical activity against diverse RET fusions/mutations in xenograft models and orthotopic brain mouse models[4]
  - Active against MKI-resistant *RET* V804M gatekeeper mutation

LIBRETTO-001: Efficacy



- In *RET*-altered cancers, responses independent of *RET* fusion partner, *RET* mutation type, LOXO-292 starting dose, and prior therapy

*Patient with no change in tumor size.

Drilon AE, et al. ASCO 2018. Abstract 102. Reproduced with permission.

NTRK1-2 and 3 fusions in 0,21% of all cancer types

- More common in rare tumors including salivay (MASC)and secretory breast cancer
- Low incidence in other audult and pediatric cancers including brain, colon, colangiocarcinoma, GIST, NSCLC
- TRK .-specific inhbitor: **Larotrectinib:** breaktrough therapy designation from FDA
- TRK/ALK/ROS specific inhibitors: **Entrectinib**:breaktrough therapy designation from FDA

VIEWPOINT

Arthur J. Barsky, MD
Department of Psychiatry, Brigham & Women's Hospital, Boston, Massachusetts

The Iatrogenic Potential of the Physician's Words

Information is an important mediator of the variability in the relationship between disease and symptoms.

•Medscape Coverage from the (ASCO) 2017 Annual Meeting

'Dealing With the Hype': Communicating and the Art of Oncology Leonard B. Saltz, MD

REMEMBER… those patients already saw the FILM Once or twice!

Outline

- **EGFR-mutated:**
  - Sequencing therapies for EGFR-mutation-positive NSCLC
  - The big question: First line Osimertinib or sequence after First-second generation EGFR-TKIs
- **ALK-rearranged:**
  - How alectinib changed 1st line
  - Update about lorlatinib
- **ROS.1 targeting agents and other targets**
- **Oncogene addicted NSCLC and immunotherapy**

ImmunoTarget: Efficacy of immune-checkpoint inhibitors in NSCLC patients harboring activating molecular alterations

Driver	n	RR	PFS	OS	Impact of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.6	16.1					Overall poor outcome
KRAS	271	26%	3.2	13.5	□	□	□	□	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	□	□	□	□	Could be considered in PDL1 + after TKIs exhausted
BRAF	43	24%	3.1	13.6	□	□	□	□	Could be considered in smokers
MET	36	16%	3.4	18.4	□	□	□	□	Could be considered
HER2	29	7%	2.5	20.3	□	□	□	NA	Could be considered
ALK	23	0	2.5	17	□	□	□	□	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

Mazieres J, et al. ASCO 2018. Abstract 9010.

TAKE HOME MESSAGES

- 1st-, 2-generation EGFR-TKIs and Crizotinib **have been** the first-line standard of care for oncogene-addicted NSCLC
- Osimertinib **is** the new standard of care in first-line *EGFR*$^{mut+}$ NSCLC
- Alectinib **is** the new standard of care in first-line ALK-rearranged NSCLC **but is not** an anti-ROS1
- Osimertinib and Alectinib are effective in preventing and treating brain metastases → After multidisciplinary discussion ostpone brain radiotherapy if using these drugs in first line!
- At the time of Osimertinib and Alectinib failure, therapeutic options remain undefined

Thank you for your attention!

rita.chiari@unipg.it