Advances in the Use of Targeted Therapies in the Management of Non–Small Cell Lung Cancer

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Learning Objectives

1. Recall updated clinical practice guidelines regarding genetic testing for targetable mutations in patients with metastatic NSCLC
2. Discuss efficacy and safety data from recent clinical trials of kinase inhibitors targeted against EGFR mutations and ALK rearrangements
3. Comment on best practices for managing side effects associated with EGFR and ALK inhibitors and BRAF
4. Apply recommended procedures for identifying and overcoming the T790M acquired resistance mutation

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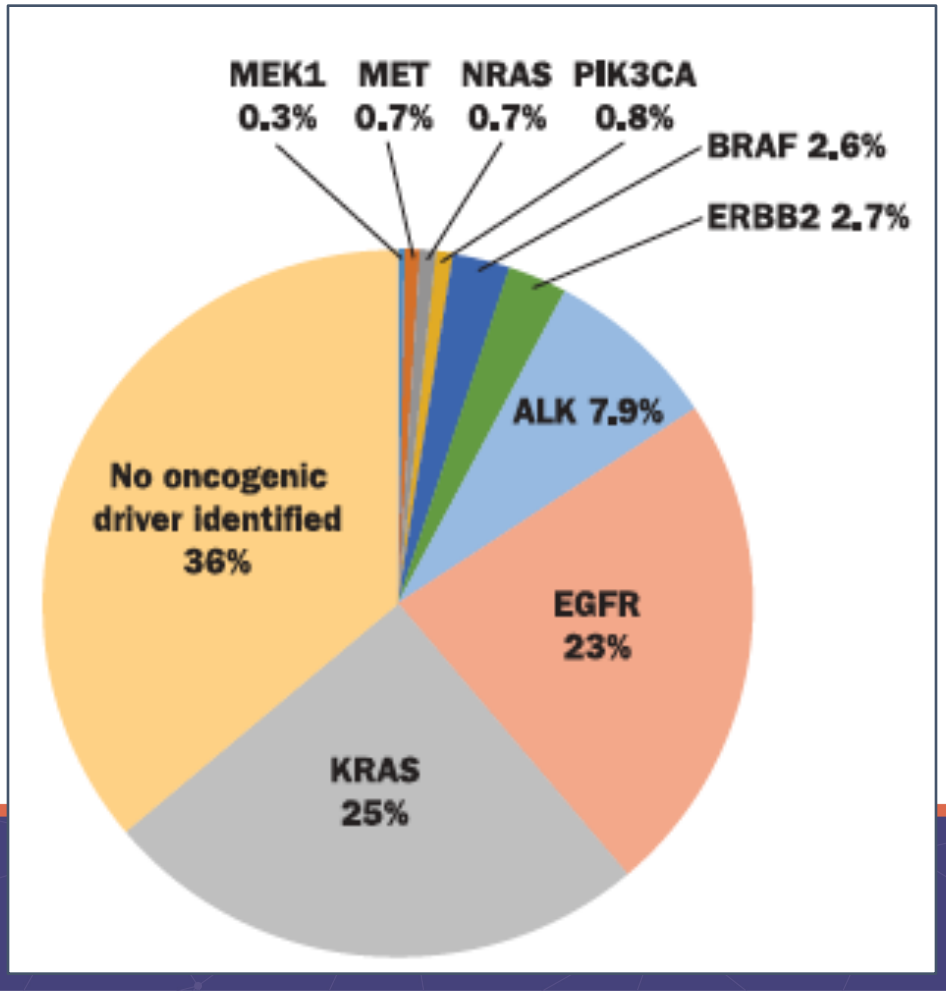
- Ms. Waxman has nothing to disclose.

Overview

- Tumor genetic testing
- EGFR driver mutations
- EGFR T790M
- ALK
- BRAF

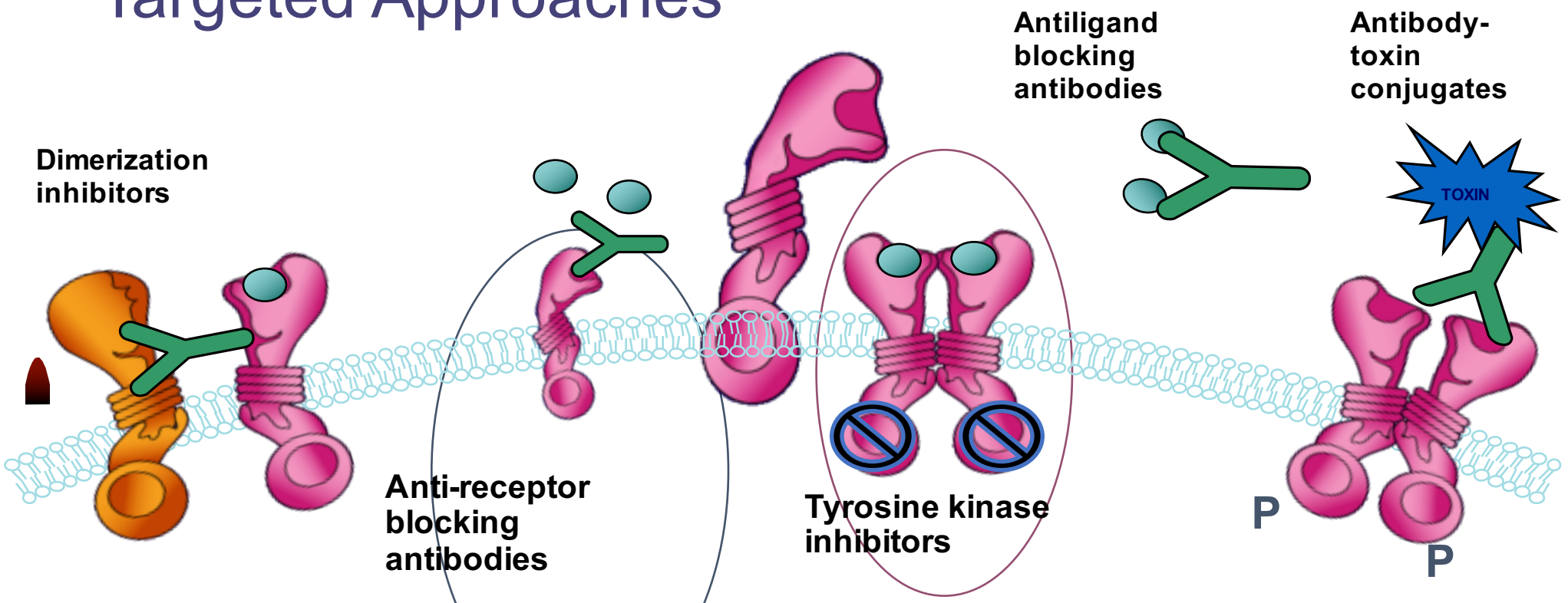
Genomic Driver Mutation in Lung Adenocarcinoma

n = 733 pts
14 institutions
of LCMC



Sholl LM, *J Thorac Oncol*. 2015;10(5):768-77.

Targeted Approaches



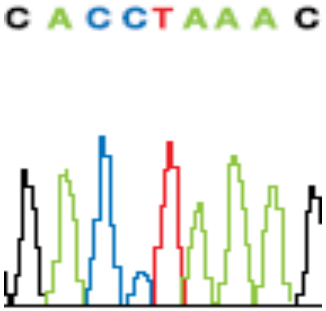
Adapted from Noonberg and Benz. *Drugs*. 2000;59:753.

Molecular Analysis

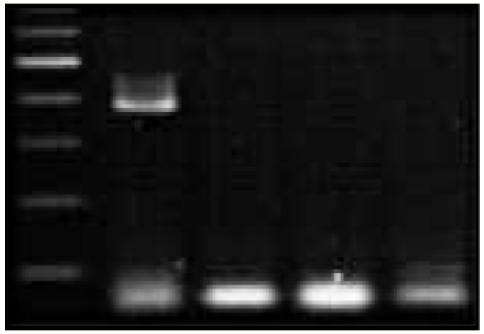
- Tumor tissue cancer genomic testing
  - Overview of methods of detection
  - Targeted DNA sequencing panels
- Blood-based cancer genomic testing
  - Sources
  - ctDNA technologies
  - Potential clinical applicability

Methods to Detect Mutations

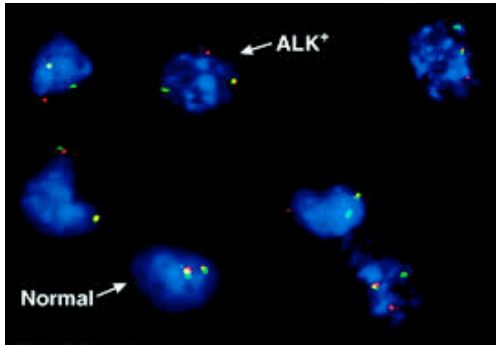
- DNA sequencing
- Reverse transcriptase polymerase chain reaction (RT-PCR)
- Fluorescence in situ hybridization (FISH)
- Immunohistochemistry (IHC)



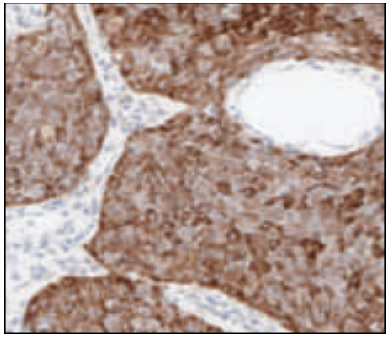
Sequencing



RT PCR

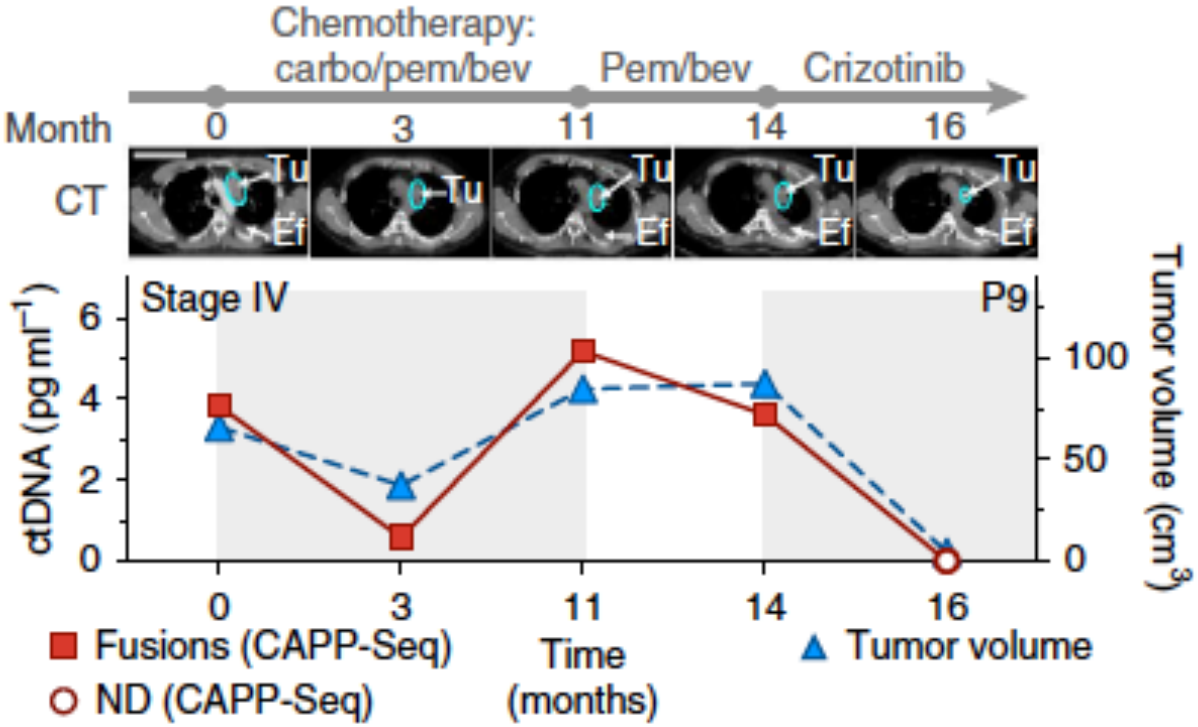


FISH



IHC

Monitoring Disease, Correlation With CT Imaging



Newman AM. *Nat Med*. 2014;20(5):548-54.

EGFR

Case 1

- JH is a 46-year-old woman who notes increasing dyspnea. She eventually gets a CXR and is found to have multiple small pulmonary nodules. A CT scan confirms a “miliary” pattern of nodules. A bronchoscopy confirms adenocarcinoma of the lung, and EGFR results reveal exon 19 deletion.
- She starts therapy with erlotinib at 150 mg and achieves a PR with resolution of dyspnea.
- 13 months later her dyspnea returns and her CT shows regrowth of multiple pulmonary nodules all ~4-7 mm and also growth of an adrenal metastases to 2 cm in size on the left.

A Case: 2nd Line

Would you consider getting a plasma assay for circulating tumor (ct)DNA to test for T790M?

A. Yes

B. No

A Case: 2nd Line (cont.)

A ctDNA assay is obtained which does not show T790M or exon19 deletion in EGFR.

Would you now obtain a tissue biopsy from the adrenal gland?

A. Yes

B. No

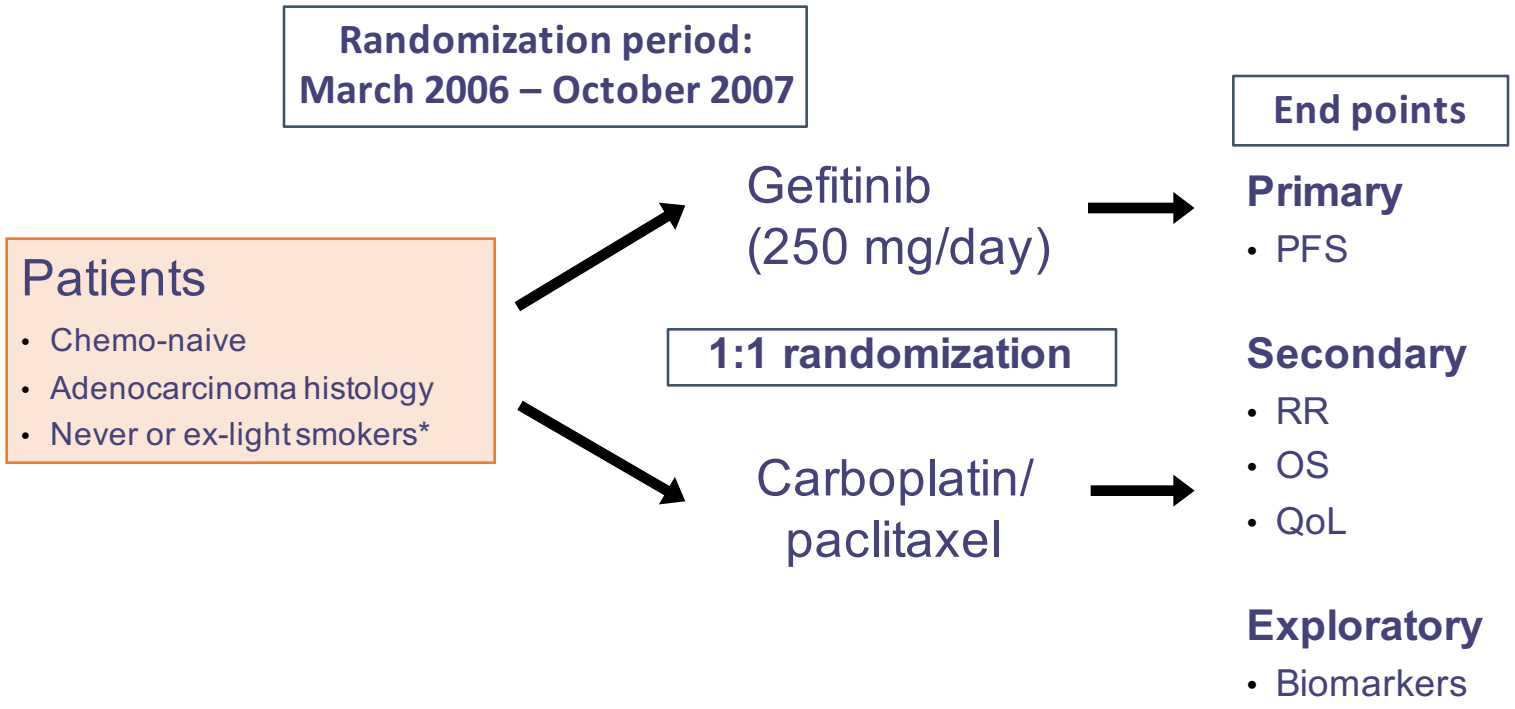
A Case: 2nd Line (cont.)

The tissue biopsy of the adrenal confirms the EGFR exon 19 mutation and shows development of T790M; PD-L1 by 22C3 assay is 60%

What would you offer her for treatment now?

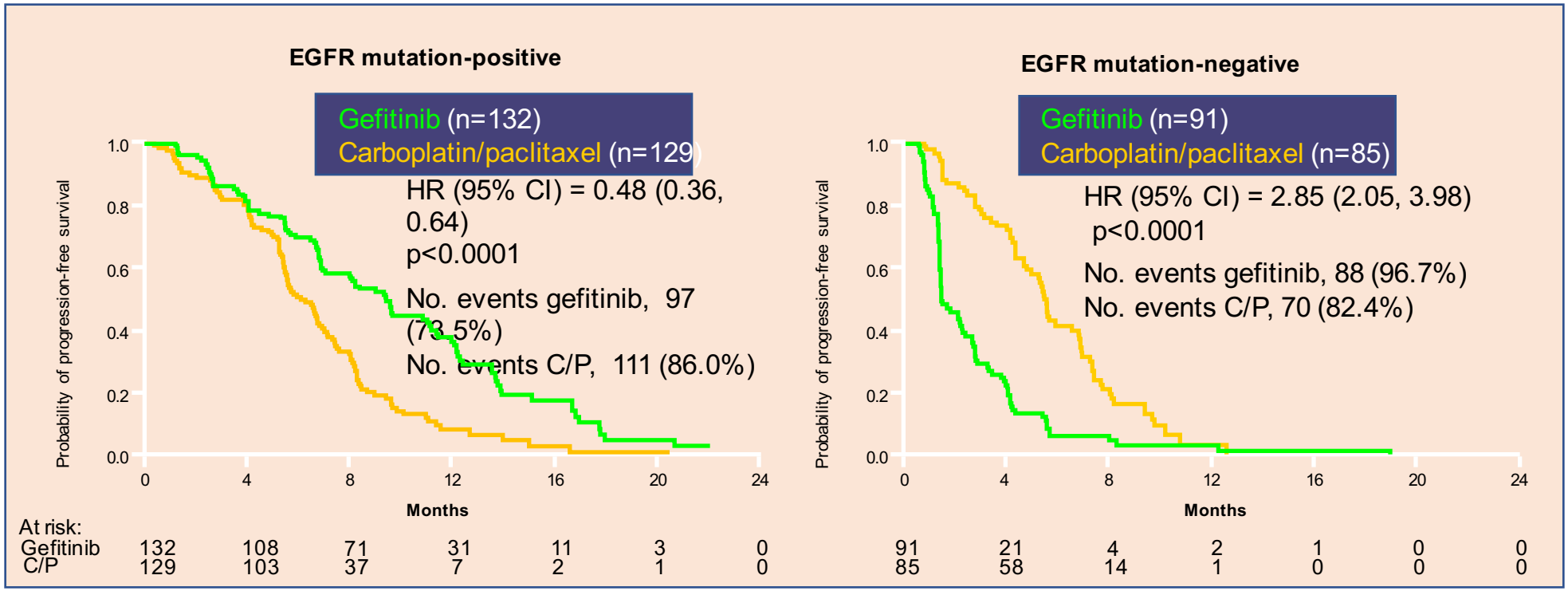
A. Osimertinib
B. Platinum/pemetrexed chemotherapy
C. Pembrolizumab
D. Alectinib
E. Dabrafenib

IPASS



Mok TS, et al. *N Engl J Med*. 2009;361:947-57.

IPASS: PFS in EGFR Mutation + vs. - Patients



Treatment by subgroup interaction test, p<0.0001

Mok TS, et al. *N Engl J Med*. 2009;361:947-57.

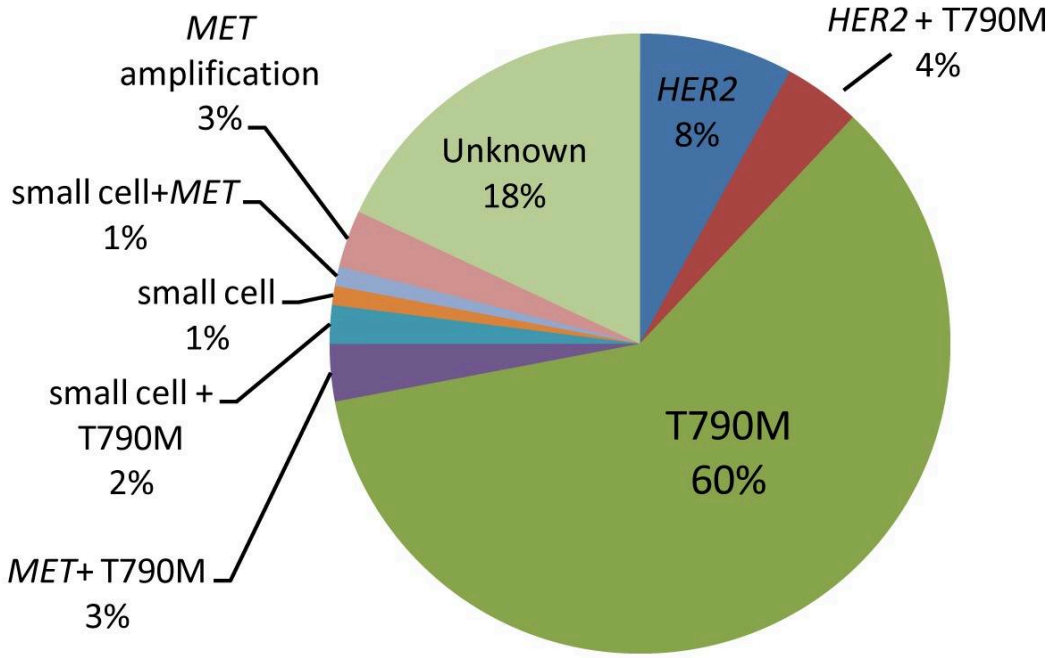
Incidence of EGFR mutation: 261/437 = 59.7%

Treatment-Naive EGFR^{mut} Patients
EGFR TKIs vs Chemotherapy

Study	Treatment	N	Median PFS, mo	Median OS, mo
Maemondo	Gefitinib vs carboplatin / paclitaxel	230	10.8 vs 5.4 (P < .001)	30.5 vs 23.6 (P = .31)
Mitsudomi	Gefitinib vs cisplatin / docetaxel	177	9.2 vs 6.3 (P < .0001)	36 vs 39 (HR: 1.19)
OPTIMAL	Erlotinib vs carboplatin / gemcitabine	165	13.1 vs 4.6 (P < .0001)	HR: 1.065 (P = .65)
EURTAC	Erlotinib vs platinum-based chemotherapy	174	9.7 vs 5.2 (P < .0001)	19.3 vs 19.5 (P = .87)
LUX-Lung 3	Afatinib vs cisplatin/pemetrexed	345	11.1 vs 6.9 (P = .001)	28.2 vs 28.2 HR 0.88, p.39
LUX-Lung 6	Afatinib vs cisplatin/gemcitabine	364	11.0 vs 5.6 (P < .0001)	23.1 vs 23.5 HR 0.93, p.61

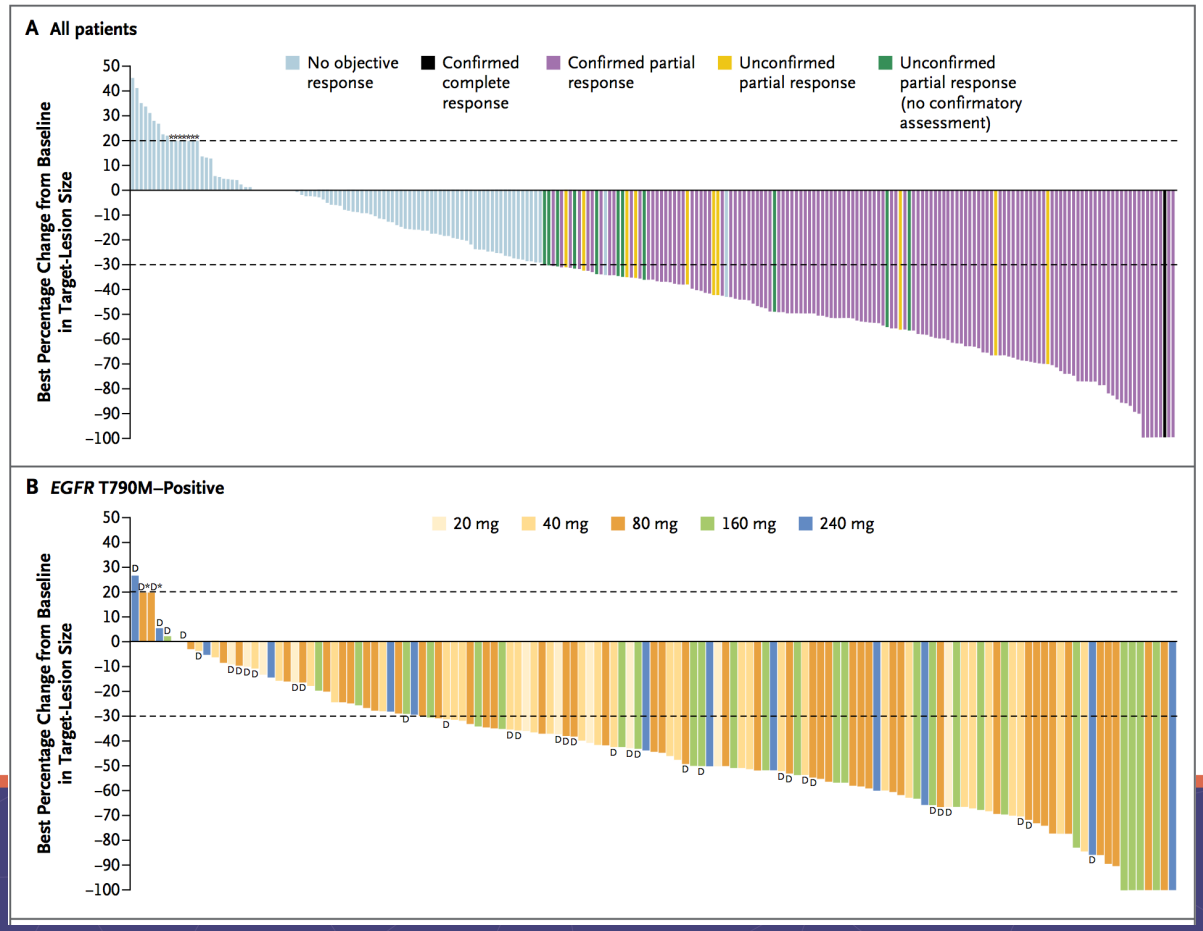
Maemondo M. *N Engl J Med.* 2010;362:2380-8; Mitsudomi T. *Lancet Oncol.* 2010;11:121-8, Abstract 7521; Zhou C, *Lancet Oncol.* 2011;12:735-42; Zhang C, et al. ASCO 2012, Abstract 7520; Rosell R, et al. *Lancet Oncol.* 2012;13:239-46; Sequist LV, et al. *J Clin Oncol.* 2013; Yang P, ASCO 2014; Wu YL, et al. *Lancet Oncol.* 2014;15:213-22, Yang JC, et al. *Lancet Oncol.* 2015;16:830-8.

Mechanisms of Resistance to EGFR TKI Therapy: T790M Gatekeeper Mutation in 60%



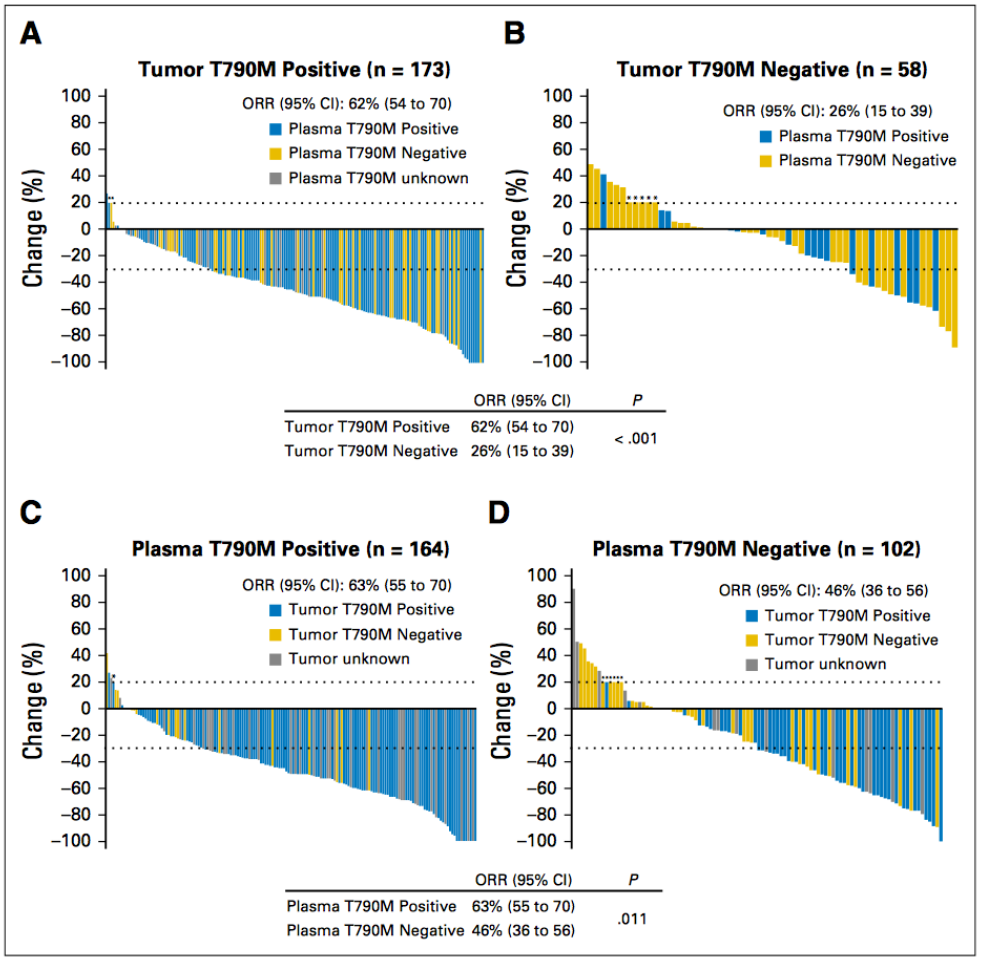
Yu H, et al. *Clin Cancer Res*. 2013 Apr 15;19(8):2240-7.

Osimertinib Single-Agent Activity: 2nd Line+



Janne NEJM 2015

Osimertinib Activity by Plasma/Tumor T790M- 2nd Line+



Oxnard JCO 34 (28): 2016

EGFR Cross-Comparison Plasma Testing

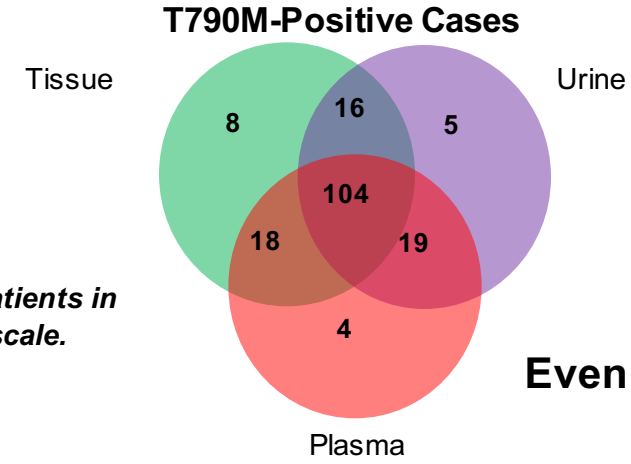
	Cobas	ARMS (therascreen)	ddPCR	BEAMing
Exon 19				
Sensitivity	82%	82%		82%
Specificity	97%	100%		97%
L858R				
Sensitivity	87%	78%	90%	87%
Specificity	97%	100%	100%	97%
T790M				
Sensitivity	73%	29%	71%	81%
Specificity	67%	100%	83%	58%

72 plasma samples (65 for T790M)

Non-digital PCR (Cobas)
Therascreen EGFR amplification refractory mutation system (ARMS)
Digital detection droplet PCR (ddPCR)
Beads, emulsion, amplification and magnetics (BEAM)ing dPCR

Plasma, Tissue, and Urine Identify Unique and Overlapping Subsets of T790M-Positive Patients

- 181 samples had matched pretreatment T790M results in plasma, tissue, and urine
  - 7 were T790M-negative or inadequate by all 3 sample types (4%)
  - 174 were T790M-positive by at least 1 sample type (96%)



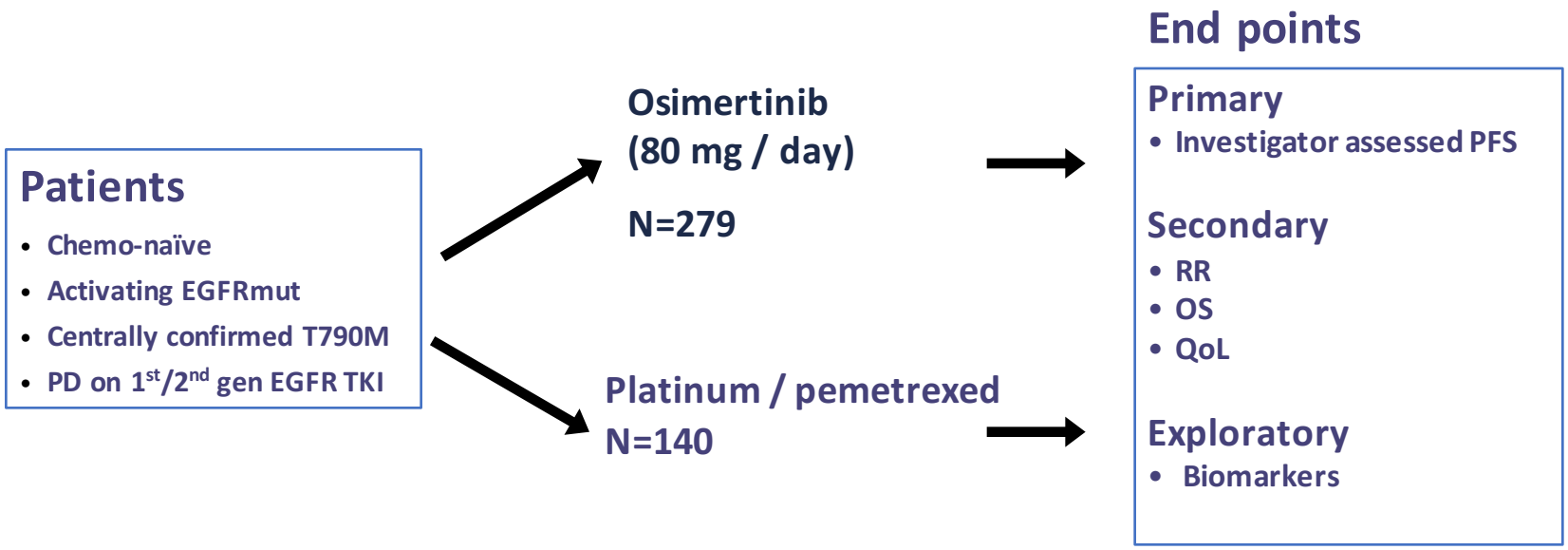
Proportion of patients in diagram not to scale.

Total positive by tissue: 146 of 181
Total positive by plasma: 145 of 181
Total positive by urine: 144 of 181

104 (57%) were positive by all 3 sample types

Even with multiple tests we can miss some T790M

AURA-3


Patients
• Chemo-naïve
• Activating EGFRmut
• Centrally confirmed T790M
• PD on 1st/2nd gen EGFR TKI
Osimertinib
(80 mg / day)
N=279
Platinum / pemetrexed
N=140
End points
Primary
• Investigator assessed PFS
Secondary
• RR
• OS
• QoL
Exploratory
• Biomarkers

AURA3: Post 1st Gen EGFR TKI Osimertinib vs Chemotherapy

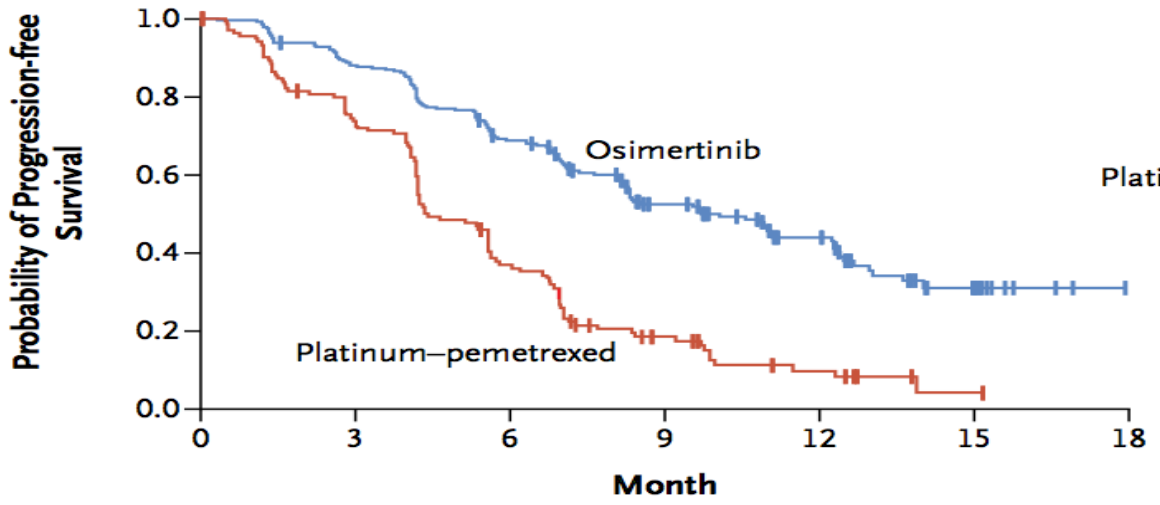
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Osimertinib (N=279)	Platinum–Pemetrexed (N=140)
Median age (range) — yr	62 (25–85)	63 (20–90)
Female sex — no. (%)	172 (62)	97 (69)
Race — no. (%)†		
White	89 (32)	45 (32)
Asian	182 (65)	92 (66)
Other	8 (3)	3 (2)
No history of smoking — no. (%)	189 (68)	94 (67)
Disease classification — no. (%)		
Adenocarcinoma histology not otherwise specified	232 (83)	122 (87)
Metastatic disease	266 (95)	138 (99)
CNS metastases‡	93 (33)	51 (36)
Extrathoracic visceral metastases§	145 (52)	80 (57)
Type of *EGFR* mutation — no. (%)¶		
T790M‖	275 (99)	138 (99)
Exon 19 deletion	191 (68)	87 (62)
Exon 21 L858R	83 (30)	45 (32)
G719X	4 (1)	2 (1)
S768I	1 (<1)	1 (1)
Exon 20 insertion	1 (<1)	2 (1)
No. of previous anticancer regimens for advanced disease — no. (%)**		
1	269 (96)	134 (96)
2	9 (3)	6 (4)
3	1 (<1)††	0
Previous EGFR-TKI therapy — no. (%)	279 (100)	139 (99)
Gefitinib	166 (59)	87 (62)
Erlotinib	96 (34)	49 (35)
Afatinib	20 (7)	4 (3)

Mok/Wu NEJM 2016

AURA3: Post 1st gen EGFR TKI Osimertinib vs Chemotherapy

A Patients in Intention-to-Treat Population



No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

	No. of Patients	Median Progression-free Survival *mo (95% CI)*
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

ORR 71% vs 31%:
Odds ratio 5.39 (3.47-8.48), p<0.001
Grade 3 AEs 23% vs 47%

Mok/Wu NEJM 2016

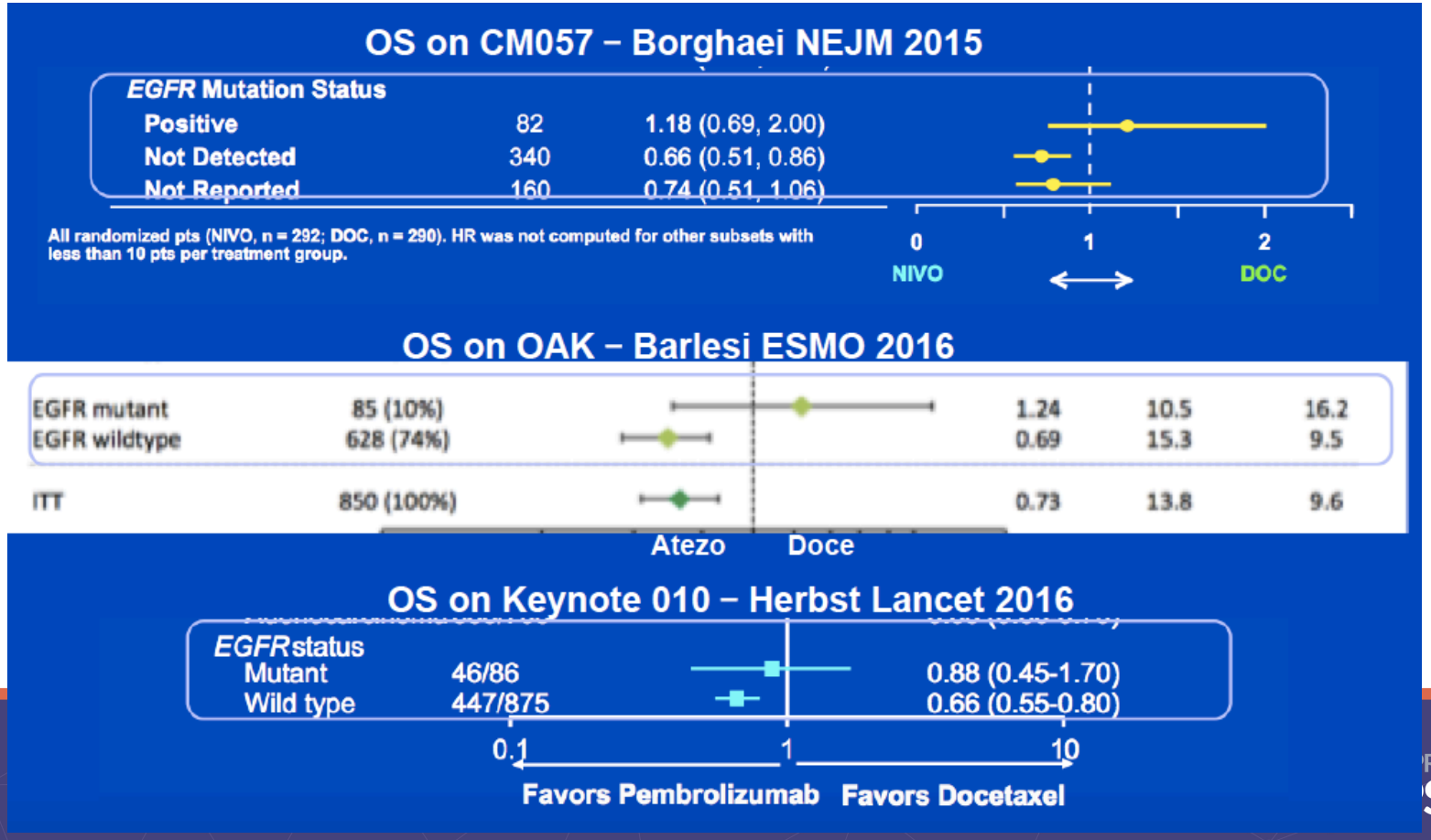
AURA3: Toxicity

Adverse Event	Osimertinib (N=279)		Platinum–Pemetrexed (N=136)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Diarrhea	113 (41)	3 (1)	15 (11)	2 (1)
Rash†	94 (34)	2 (1)	8 (6)	0
Dry skin†	65 (23)	0	6 (4)	0
Paronychia†	61 (22)	0	2 (1)	0
Decreased appetite	50 (18)	3 (1)	49 (36)	4 (3)
Cough	46 (16)	0	19 (14)	0
Nausea	45 (16)	2 (1)	67 (49)	5 (4)
Fatigue	44 (16)	3 (1)	38 (28)	1 (1)
Stomatitis	41 (15)	0	21 (15)	2 (1)
Constipation	39 (14)	0	47 (35)	0
Pruritus	35 (13)	0	6 (4)	0
Vomiting	31 (11)	1 (<1)	27 (20)	3 (2)
Back pain	29 (10)	1 (<1)	12 (9)	1 (1)
Thrombocytopenia†	28 (10)	1 (<1)	27 (20)	10 (7)
Nasopharyngitis	28 (10)	0	7 (5)	0
Headache	28 (10)	0	15 (11)	0
Dyspnea	24 (9)	3 (1)	18 (13)	0
Neutropenia†	22 (8)	4 (1)	31 (23)	16 (12)
Leukopenia†	22 (8)	0	20 (15)	5 (4)
Anemia†	21 (8)	2 (1)	41 (30)	16 (12)
Asthenia	20 (7)	3 (1)	20 (15)	6 (4)
Pyrexia	18 (6)	0	14 (10)	0
Alanine aminotransferase elevation	18 (6)	3 (1)	15 (11)	1 (1)
Aspartate aminotransferase elevation	14 (5)	3 (1)	15 (11)	1 (1)
Malaise	11 (4)	0	14 (10)	0

PD-(L)1 Inhibitors and EGFR^{mut} NSCLC

In KN010, CM057 and OAK, the ONLY subgroup that did not show superior survival with the PD-(L)1 inhibitor vs docetaxel were the patients with EGFR mutations.

OS on 2nd Line Docetaxel vs IO Therapy by EGFR^{mut} Status



Borghaei. NEJM 2015

FLAURA Double-Blind Study Design

FLAURA data cut-off: 12 June 2017; NCT02296125

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria
- ≥18 years*
- WHO performance status 0 / 1
- Exon 19 deletion / L858R (enrolment by local# or central‡ EGFR testing)
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

Stratification by **mutation status** (Exon 19 deletion / L858R) and **race** (Asian / non-Asian)

Randomised 1:1

Osimertinib (80 mg p.o. qd) (n=279)

EGFR-TKI SoC§; **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) (n=277)

RECIST 1.1 assessment every 6 weeks¶ until objective progressive disease

Crossover was allowed for patients in the **SoC** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 to 14.1 mo) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 wk after 18 mo.

Ramalingam S, et al. ESMO 2017, Abstract LBA2_PR.

FLAURA: Baseline Characteristics

FLAURA data cut-off:
12 June 2017

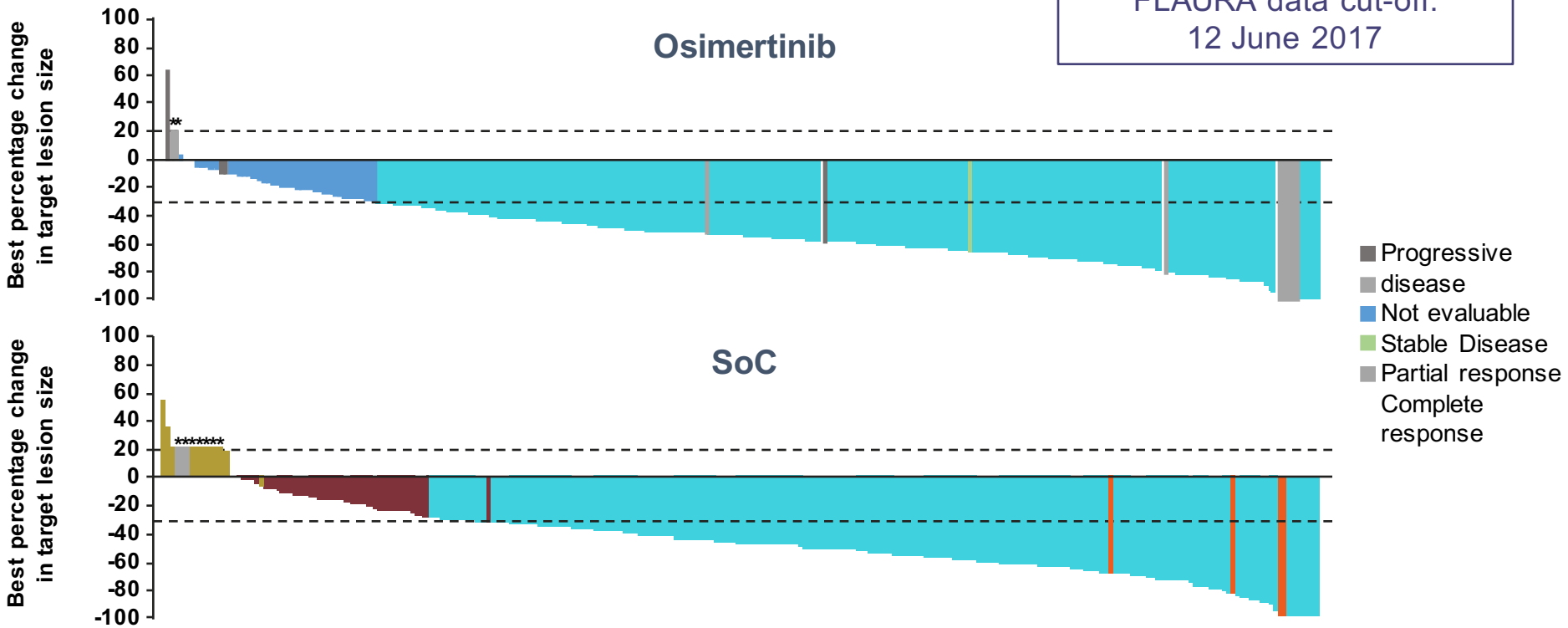
Characteristic, %	Osimertinib (n=279)	SoC* (n=277)
Sex: male / female	36 / 64	38 / 62
Age, median (range), years	64 (26–85)	64 (35–93)
Race: White / Asian / other#	36 / 62 / 1	36 / 62 / 1
Smoking status: never / ever	65 / 35	63 / 37
CNS metastases at study entry‡	19	23
WHO performance status§: 0 / 1	40 / 60	42 / 58
Overall disease classification¶: metastatic / advanced	95 / 5	95 / 5
Histology: adenocarcinoma / other	99 / 1	98 / 2
EGFR mutation at randomisation**: Exon 19 deletion / L858R	63 / 37	63 / 37

*In the SoC arm, 66% of patients received gefitinib and 34% received erlotinib; #Including Black or African American and American Indian or Alaska Native. Race was missing for 1 patient in the osimertinib arm and 1 patient in the SoC arm; ‡CNS metastases determined programmatically from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy; §WHO performance status was missing for one patient in the SoC arm; ¶Overall disease classification was missing for one patient in the osimertinib arm; **Local or central test.

Ramalingam S, et al. ESMO 2017, Abstract LBA2_PR.

Tumor Response[a]

FLAURA data cut-off:
12 June 2017



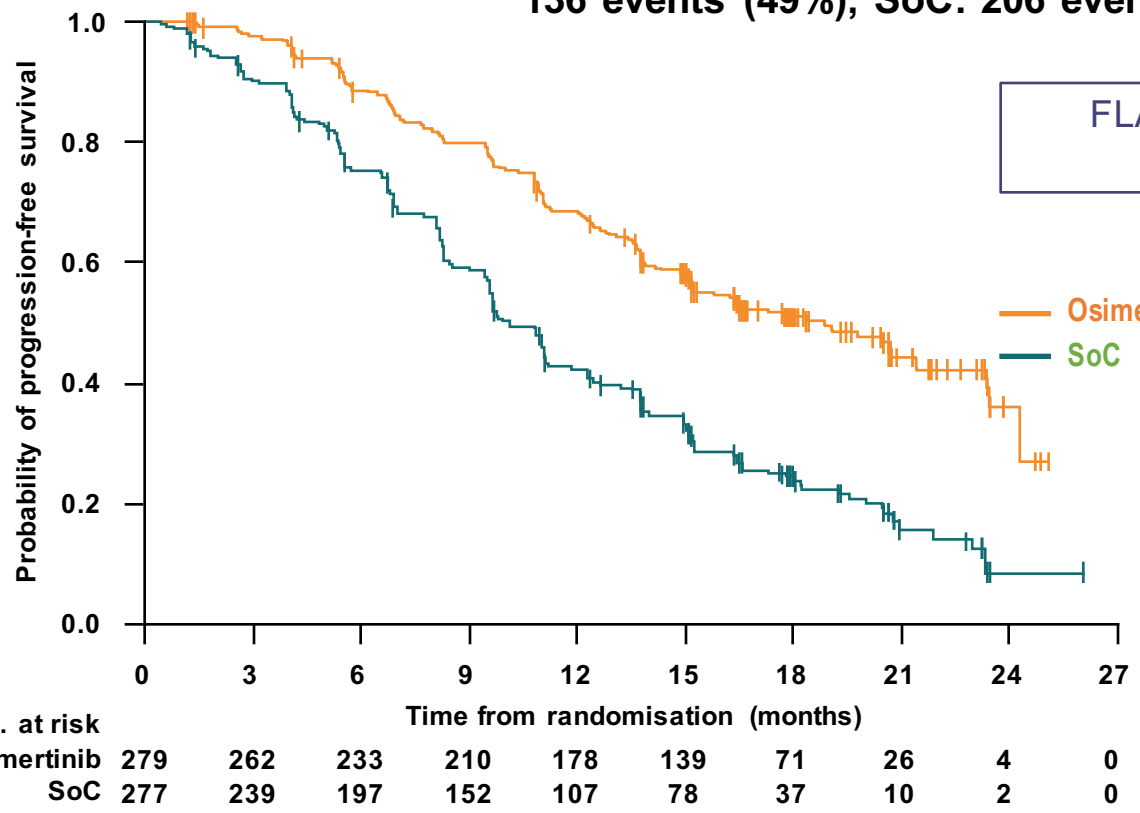
Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase. *Represents imputed values: if it is known that the patient has died, has new lesions or progression of assessments, best change will be imputed as 20%

[a]By investigator assessment; CI, confidence interval; SD, standard deviation; SoC, standard-of-care.

Ramalingam S, et al. ESMO 2017, Abstract LBA2_PR.

FLAURA Primary Endpoint: PFS by Investigator Assessment

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)



FLAURA data cut-off: 12 June 2017

Median PFS, mo (95% CI)

Osimertinib **18.9 (15.2, 21.4)**

SoC **10.2 (9.6, 11.1)**

HR 0.46
(95% CI 0.37, 0.57)
p<0.0001

Tick marks indicate censored data.

FLAURA Safety Summary

FLAURA data cut-off:
12 June 2017

AE, any cause*, n (%)	Osimertinib (n=279)	SoC (n=277)
Any AE	273 (98)	271 (98)
Any AE Grade ≥3	94 (34)	124 (45)
Any AE leading to death	6 (2)	10 (4)
Any serious AE	60 (22)	70 (25)
Any AE leading to discontinuation	37 (13)	49 (18)
AE, possibly causally related#, n (%)		
Any AE	253 (91)	255 (92)
Any AE Grade ≥3	49 (18)	78 (28)
Any AE leading to death	0	1 (<1)
Any serious AE	22 (8)	23 (8)

*Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories; #As assessed by the investigator. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication

Ramalingam S, et al. ESMO 2017, Abstract LBA2_PR.

EGFR Overview

- 10% of all cases of NSCLC have an EGFR mutation
- >50% in never-smoking Asian woman with lung cancer
- 5 drugs now available as first-line therapy (1st/2nd gen)
  - Most very expensive >$10,000 per month
- Addition of bevacizumab or ramucirumab may improve outcomes but cost >$10,000 per dose
- Osimertinib: clear superiority vs chemotherapy after 1st/2nd generation EGFR TKI
- Osimertinib new option as first-line EGFR TKI (prolong PFS)
- Checkpoint inhibitors are inferior in EGFRmut NSCLC

EGFR Toxicities

- Dermatologic
- GI
- Ophthalmic
- Cardiac

Toxicity Discussion

EGFR Inhibitors

- Afatinib
- Erlotinib
- Geftinib
- Osimertinib

Incidence of Rash

- Afatinib: 81-89%, 16% grade 3 or 4
- Erlotinib: 75-80%, 13% grade 3 or 4
- Gefitinib: 37-66%, 3% grade 3 or 4
- Osimertinib: 41%, 0.5% grade 3 or 4

Mok, TS, et al. *N Engl J Med*. 2009;361:947-57; Rosell, R, et al. *Lancet Oncol*. 2012;13(3):239-46; Sequist, LV, et al. *J Clin Oncol*. 2013;31(27):3327-34; Burotto, M, et al. *Oncolgist*. 2015;20(4):400-10; Douillard, JY, et al. *Br J Can*. 2014;110:55-62.

Rash: Pathophysiology

EGF

- Found in normal epidermal and follicular keratincoytes
- Primarily serves to regulate differentiation and provide protection from UV rays or other cellular damage
- Can help hasten wound healing and inhibit inflammation
- If inhibited, the skin begins to thin and dry; may result in recruitment of the immune system, leading to a pustular eruption

Mitchell, EP, et al. *Oncology*. 2007;21(11 suppl 5):4-9; Lacouture, ME. *Nat Rev Cancer*. 2006;6:803-12.

Clinical Presentation

- Sudden onset of papulopustular eruption
- Usually involves face, scalp, neck, upper chest, back
- Rash may be indicative of clinical benefit
- Low-grade rash affects quality of life

Galimont-Collen, AF, et al. *Eur J Cancer*. 2007;43(5):845-51; Liu, HB, et al. *PloS One*. 2013;8(1):E55128; Joshi, SS, et al. *Cancer*. 2010;116(16):3916-23.

Management: Prophylaxis

- No standard treatment for EGFR skin rash
- MASCC and NCCN guidelines and strategies
- Prophylaxis: daily skin care with thick, alcohol-free emollient to moisturize the skin
- Minimize sun exposure, wear protective clothing, and use sunscreen with SPF 15 or higher.
- Take lukewarm showers, baths
- Avoid perfume- and alcohol-containing skin products

Hasenbank, C. *J Adv Pract Oncol*. 2017;8(suppl 1):43-50; Hirsh, V. *Curr Oncol*. 2011;18(3):126-138.

Rash Management

- Depends on severity/grade of rash
- Grade 1: no intervention may be needed. Consider topical steroid/antibiotic ointment, lotion, gel, such as hydrocortisone 2.5%, clindamycin 1%
- Grade 2: hydrocortisone 2.5% plus oral antibiotic, either doxycycline 100 mg BID or minocycline 100 mg BID
- Grade 3/4: same as grade 2, consider methylprednisolone dose pack

Vogel, WH, et al. *J Adv Pract Oncol* 2016;7(7):723-35

Rash Management

Other interventions

- Hold drug and treat rash; consider dose reduction of drug depending on severity of rash and response to interventions
- Refer to dermatology

GI Toxicities: Diarrhea

- Most common GI toxicity associated with EGFR inhibitors
- Due to presence of EGFR in GI mucosa
- Afatinib has the highest incidence of diarrhea (83-95%), often dose limiting/dose reducing
- Ceritinib has the highest incidence of diarrhea for the ALK inhibitors (83%)

Vogel, WH, et al. *J Adv Pract Oncol* 2016;7(7):723-35; Soria, J-C, et al. (2015). *Lancet Oncol*. 2015;16(8):897-907; Novartis Pharmaceuticals Corporation, 2016. Hasenbank. C. *J Adv Pract Oncol*. 2017;8(suppl 1):43-50.

Diarrhea Prophylaxis

- Avoid foods that irritate the GI tract: dairy, spicy, greasy foods
- Hydrate
- Good eating habits, healthy diet

Diarrhea

- Usually occurs during first month of starting erlotinib and gefitinib, and within 1 week of starting afatinib
- Rule out other potential causes of diarrhea including *C. diff*, medications (laxatives, antibiotics)

Hasenbank. C. *J Adv Pract Oncol*. 2017;8(suppl 1):43-50; Hirsh, V, et al. *Curr Oncol*. 2014;21(6):329-36; Melosky, B., Hirsh, V. *Front Oncol*. 2014;4:238; Vogel, WH, et al. *J Adv Pract Oncol* 2016;7(7):723-35.

Diarrhea Treatment

- BRAT diet: bananas, rice, applesauce, toast
- Hydrate/electrolyte replacement
- Loperamide
- Diphenoxylate: atropine if loperamide is not effective.
- Intravenous hydration if grade 3 (> 7 episodes/day)
- Consider holding drug, and possible dose reduction

Ophthalmic Issues

- EGFR present on several anatomic sites surrounding and related to the eyes, including: eyelids, eyelash follicles, tear glands, conjunctiva, and cornea.
- Patients on afatinib likely to experience conjunctivitis (11%).
- Conjunctivitis, blepharitis, dry eyes, keratitis (rarely) are associated with gefitinib

Davis, ME. *Onc Nurs Forum*. 2016;43(2):235-43; Saint-Jean, A.,et al. *Ophthalmology*. 2012;119(9):1798-1802; Hasenbank. C. *J Adv Pract Oncol*. 2017;8(suppl 1):43-50; Vogel, WH, et al. *J Adv Pract Oncol* 2016;7(7):723-35.

Ophthalmic Issues

- 18% of patients on erlotinib have reported: dry eyes, eyelash growth disturbances (trichomegaly), keratitis
- 19% of patients on osimertinib have experienced: dry eyes, cataracts, keratitis, blurry vision, eye irritation

Genetech, USA, Unc. (2016). Package insert. AstraZeneca (2016). Package insert. Pfizer Inc. (2016). Package insert.

Ophthalmic Treatment

Refer to ophthalmologist

ALK

Case 2

- RJ is a 47-year-old man who smoked a few cigarettes daily for 10 years. He presents with progressive right-sided chest pain.
- CXR reveals pleural thickening and a mass
- CT reveals right adrenal mass, right lung mass (3 cm), and pleural studding on the right
- Biopsy is c/w adenocarcinoma
- PET/brain MRI show no other areas of disease
- Initially ALK FISH is negative, and rapid EGFR is negative

Case 2 (cont.)

A biopsy is performed of the liver metastases and NGS reveals an ALK rearrangement. He does well with crizotinib for 10 months until disease progression. He then has a biopsy which reveals V1180L ALK resistance mutation.

What do you start?

A. Brigatinib
B. Ceritinib
C. Restart pemetrexed
D. Alectinib
E. Nivolumab or pembrolizumab
F. Lorlatinib or ensartinib or other on trial

Resistance Mechanisms in ALK+ NSCLC

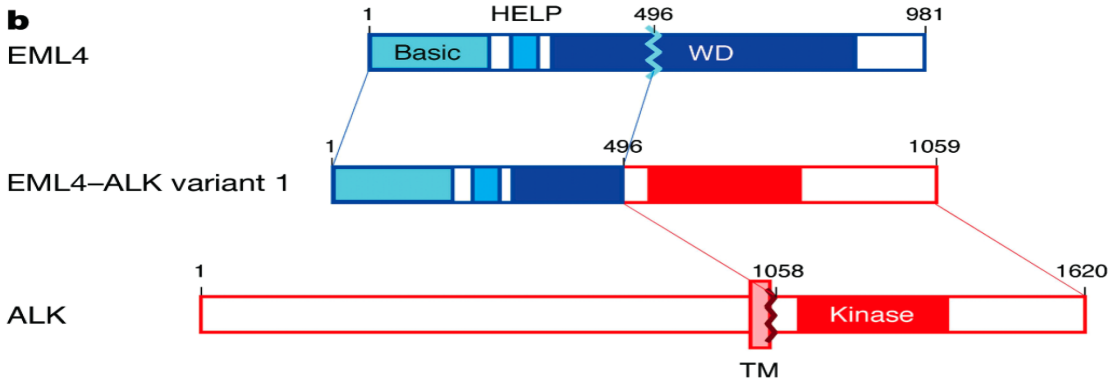
	1st gen	2nd gen			3rd gen
	Crizotinib	**Alectinib**	**Brigatinib**	**Ceritinib**	**Lorlatinib**
G1123S	Res	Sens[2]	N/D	Res[2]	N/D
1151Tins	Res	Res[3]	N/D	Res[7]	Sens[9]
L1152P/R	Res	Sens	N/D	Res[7]	Sens[9]
C1156Y/T	Res	Sens	N/D	Res[7]	Sens[9]
I1171T/N	Res	Res[4,5]	N/D	Sens[4,5,7]	N/D
F1174C/L/V	Res	Sens	Sens[6]	Res[7]	Sens[9]
V1180L	Res	Res[4]	N/D	Sens[4]	N/D
L1196M	Res	Sens[3]	Sens[6]	Sens[7]	Sens[9]
L1198F	Sens[1]	Res[1]	Res[1]	Res[1]	Res[1]
G1202R	Res	Res[3]	N/D	Res[7]	Sens[9]
S1206C/Y	Res	Sens[3]	Res[6]	Sens[7]	Sens[9]
F1245C	Res[8]	N/D	N/D	Sens[8]	N/D
G1269A/S	Res	Sens	N/D	Sens[7]	Sens[9]

EML4-ALK Translocations in NSCLC

Vol 448|2 August 2007|doi:10.1038/nature05945 nature

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

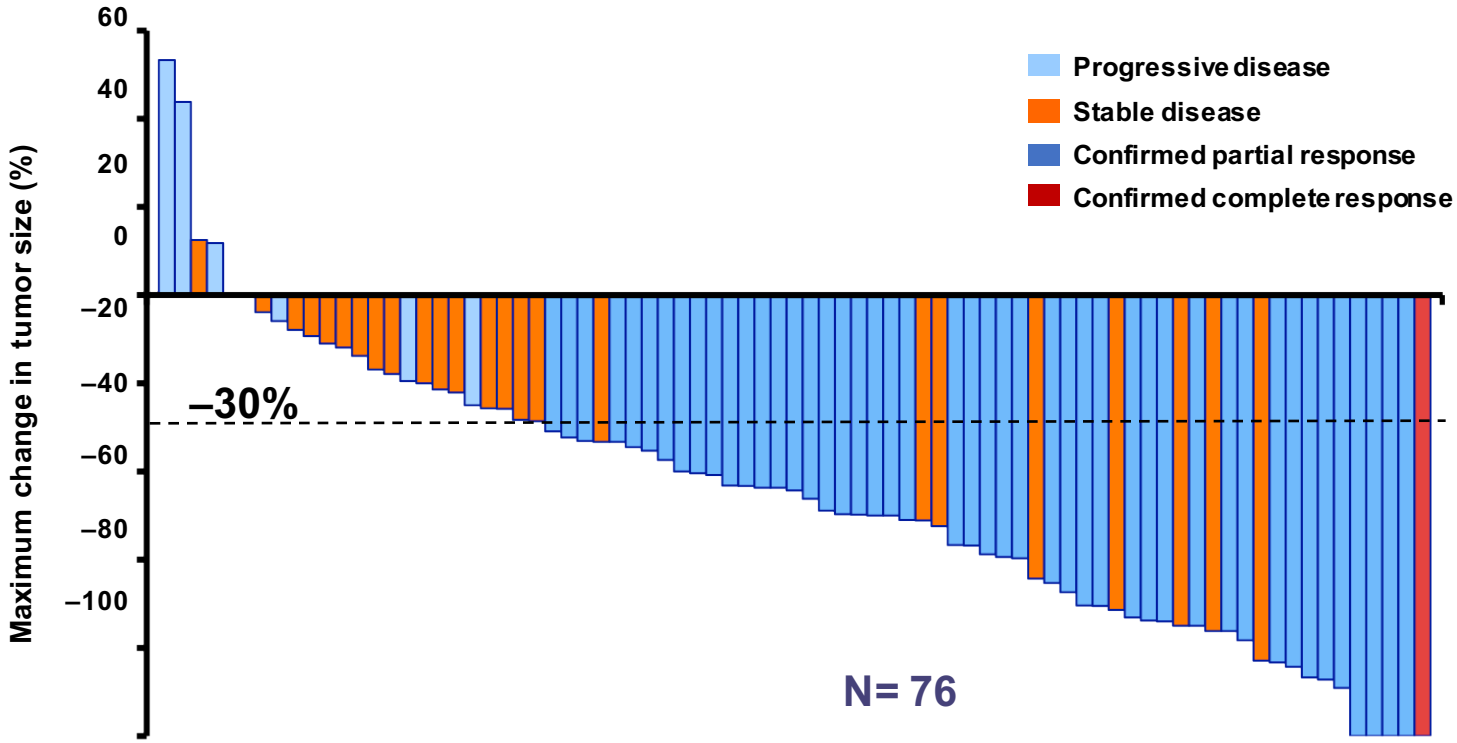
Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



EML4-ALK frequency: ~4% (64/1709) Primarily lung adenocarcinoma

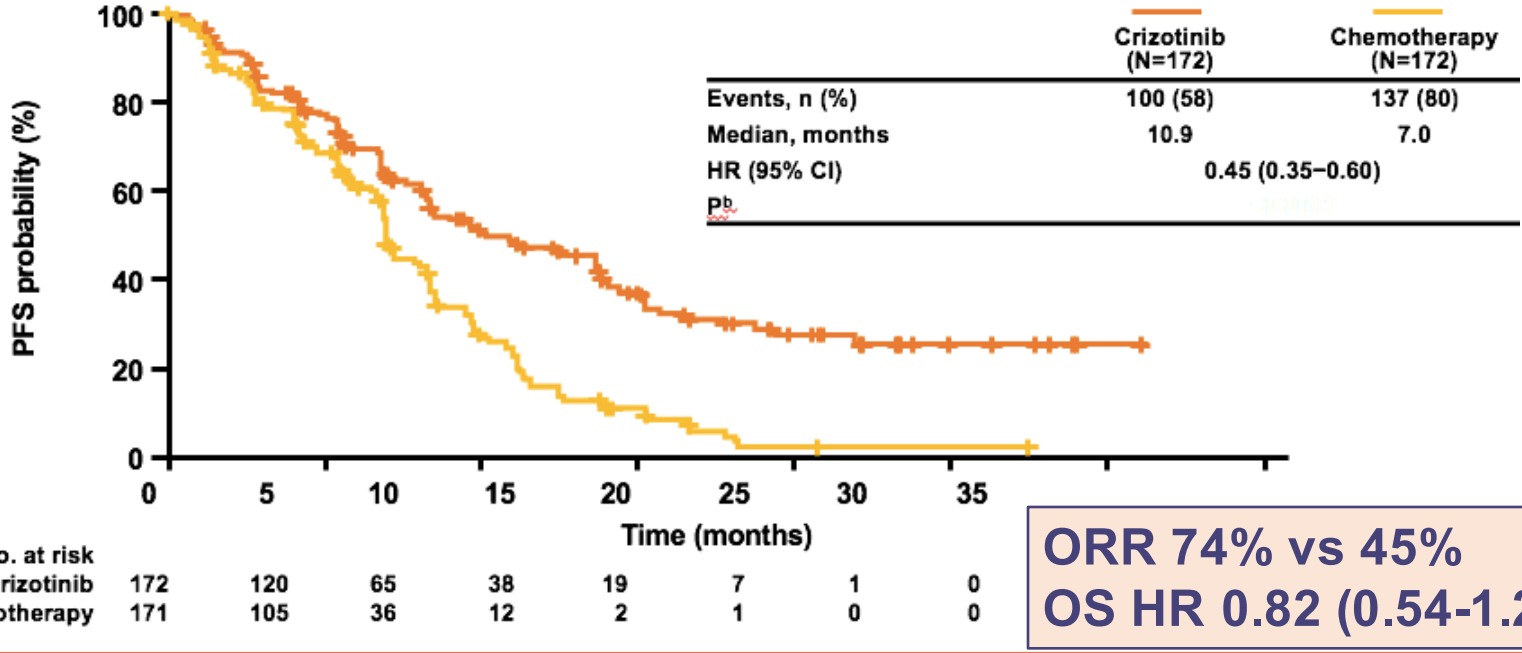
Soda M, et al. *Nature*. 2007;448:561-6.

Tumor Responses to Crizotinib for Patients With ALK-Positive NSCLC



Primary Endpoint Met: Crizotinib Superior to Pemetrexed-Based Chemotherapy in Prolonging PFS[a]

Data cutoff: 11/30/13



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

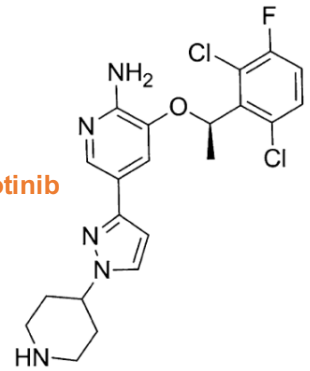
ORR 74% vs 45%
OS HR 0.82 (0.54-1.26), NS

[a]Assessed by IRR; [b]1-sided stratified log-rank test.

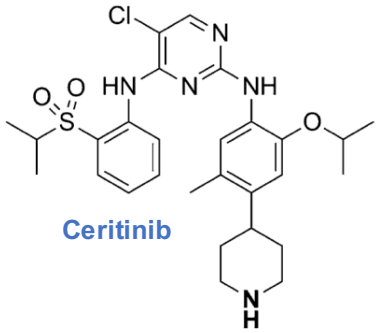
Mok ASCO 2014, Solomon NEJM 2014, Solomon JCO 2016

Next-Generation ALK Inhibitors

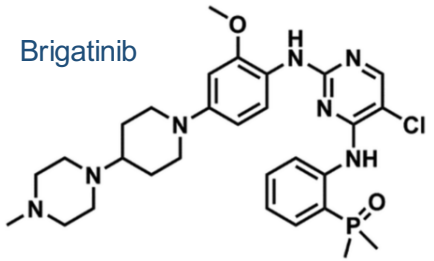
Crizotinib



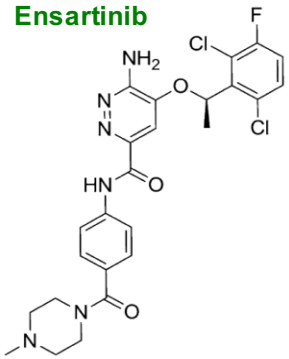
Ceritinib



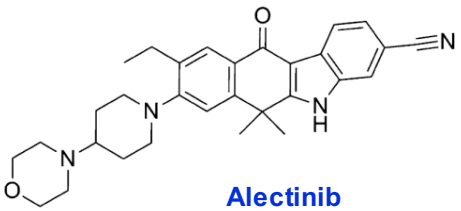
Brigatinib



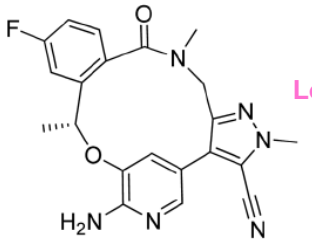
Ensartinib



Alectinib



Lorlatinib



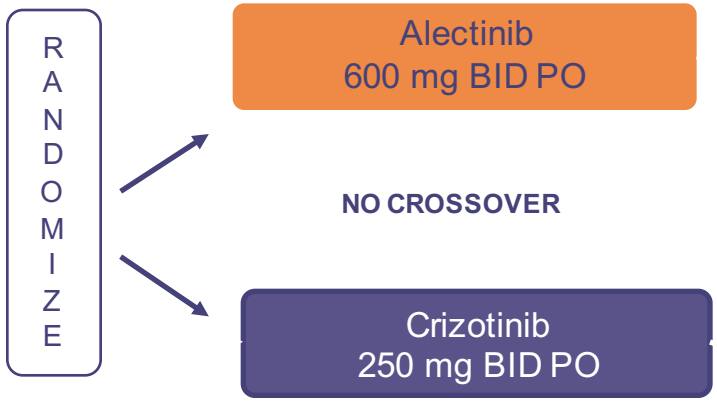
Courtesy Solange Peters

Chen J, et al. *J Med Chem.* 2013;56:5673-4. Huang W-S, et al. *J Med Chem.* 2016;59:4948-64; Johnson TW, et al. *J Med Chem.* 2014;57:4720-44. Marsilje TH, et al. *J Med Chem.* 2013;56:5675-90.

ALEX Study Design

KEY ELIGIBILITY

- *ALK*+ by central IHC testing
- Advanced or metastatic *ALK*+ NSCLC
- Treatment-naïve
- ECOG PS 0–2
- Measurable disease
- Asymptomatic brain metastases allowed



ENDPOINTS

- Primary
  - PFS (RECIST 1.1), by investigator review
- Secondary
  - PFS by IRC
  - Time to CNS progression
  - ORR, DOR
  - OS
  - Safety and tolerability
  - Patient-reported outcomes

ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; IRC, independent review committee; CNS, central nervous system; ORR, objective response rate; DOR, duration of response; OS, overall survival.

Stratification factors:
- ECOG PS (0/1 vs 2)
- Race (Asian vs non-Asian)
- Brain metastases (present vs absent)

Peters S, et al. *N Engl J Med*. 2017;377:829-38.

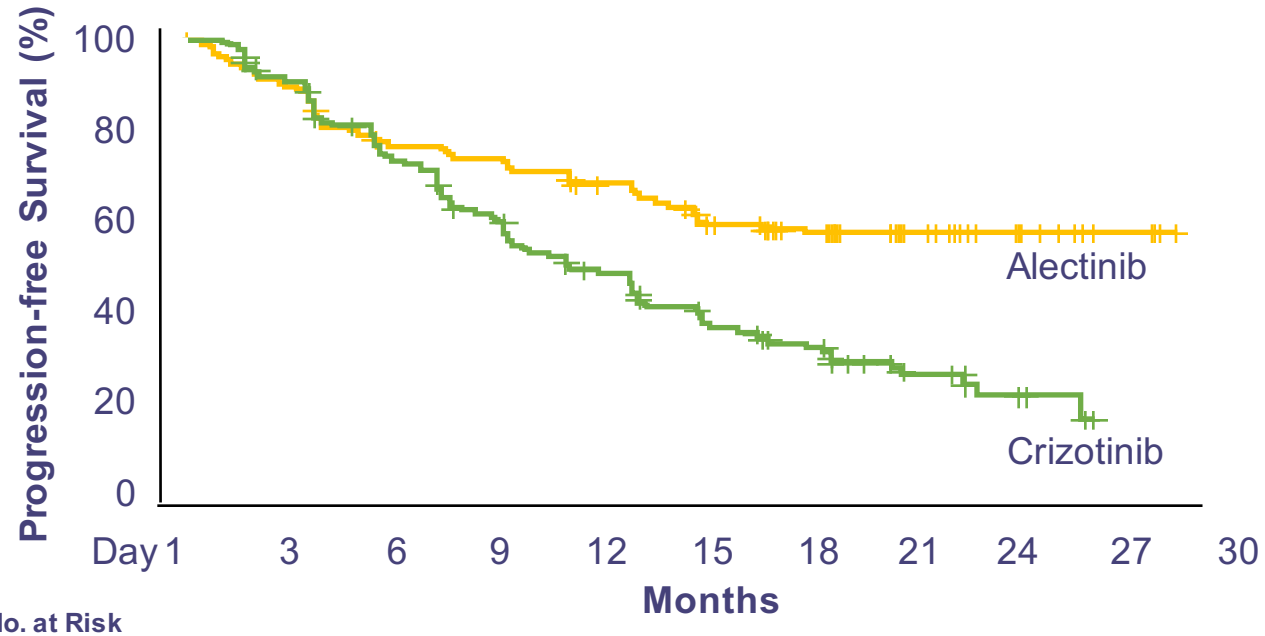
ALEX: Objective Response Rate*

	Crizotinib (N=151)		Alectinib (N=152)
Responders, n (%)	114 (76)		126 (83)
(95% CI)	(68–82)		(76–89)
P value		0.09	
Complete response, n (%)	2 (1)		6 (4)
Partial response, n (%)	112 (74)		120 (79)
Stable disease, n (%)	24 (16)		9 (6)
Median DOR (months)	11.1		NE
(95% CI)	(7.9–13.0)		(NE)

*Investigator assessment

Peters S, et al. *N Engl J Med*. 2017;377:829-38.

Primary Endpoint: PFS, Investigator-Assessed



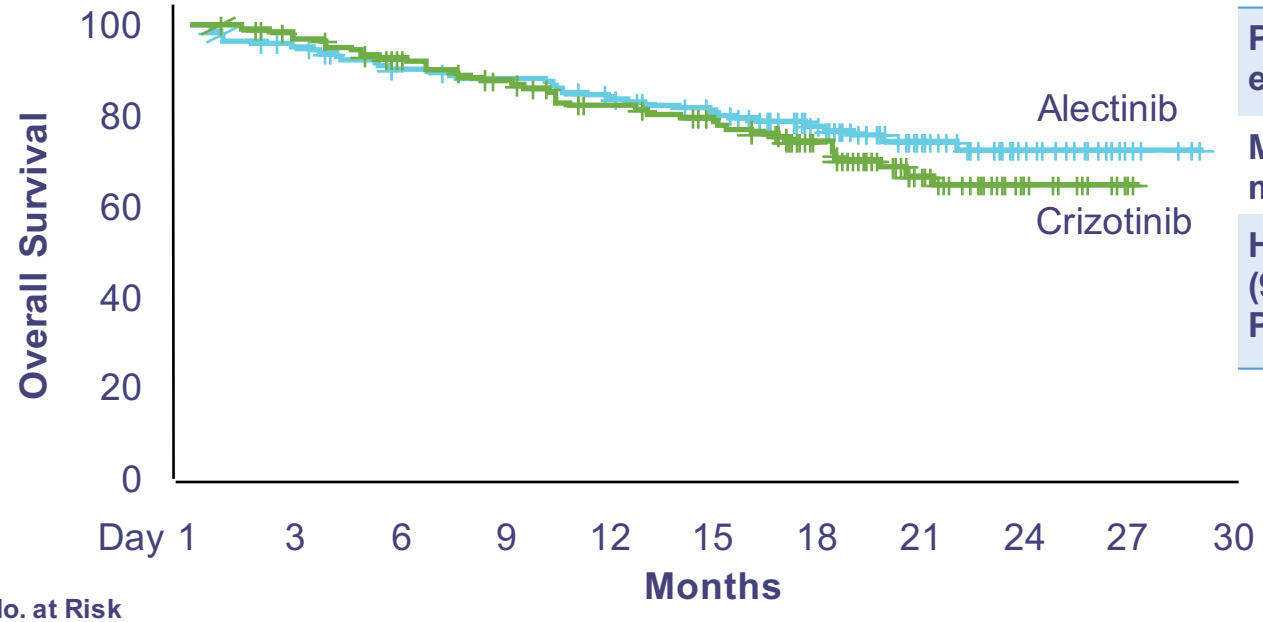
No. at Risk

Crizotinib	151	132	104	84	65	46	35	16	5	
Alectinib	152	135	113	109	97	81	67	35	15	3

	Crizotinib (N=151)	Alectinib (N=152)
Patients with events, n (%)	102 (68)	62 (41)
Median PFS, months (95% CI)	**11.1** (9.1–13.1)	**NE** (17.7–NE)
HR (95% CI)	**0.47** (0.34–0.65)	
P-value (log-rank test)	P<0.0001	

Peters S, et al. *N Engl J Med*. 2017;377:829-38.

Secondary Endpoint: OS



No. at Risk

Crizotinib	151	141	127	115	103	95	73	33	13	1
Alectinib	152	142	131	127	119	107	87	51	24	5

	Crizotinib (N=151)	Alectinib (N=152)
Patients with events, n (%)	40 (27)	35 (23)
Median OS, months (95% CI)	NE (NE)	NE (NE)
HR (95% CI) P value	0.76 (0.48–1.20) P=0.24	

ALK Summary

- First-line ALK TKI therapy remains the standard of care for patients with ALK translocations
  - Crizotinib, ceritinib, alectinib approved first-line options
  - 2nd line + ceritinib, alectinib, brigatinib now approved
  - Multiple other ALK inhibitors in development
- Toxicities variable
  - Crizotinib: edema, bradycardia, vision changes, N/V, transaminitis
  - Ceritinib: N/V, fatigue, rash, diarrhea

Costs are >$10,000 per month for all of these agents.
PERHAPS market forces will now start to bring down price?

Toxicity Discussion

ALK inhibitors

- Alectinib
- Brigatinib
- Ceritinib
- Crizotinib

ALK Toxicities

- Dermatologic
- GI
- Ophthalmic
- Cardiac
- Hyperglycemia

Adverse Events, ≥10% in Either Treatment Arm (ALEX Trial)

	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)
Diarrhea	68 (45)	3 (2)	18 (12)	0
Vomiting	58 (38)	5 (3)	11 (7)	0
Peripheral edema	42 (28)	1 (1)	26 (17)	0
Fatigue	25 (17)	0	29 (19)	1 (1)
ALT increased	45 (30)	22 (15)	23 (15)	7 (5)
AST increased*	37 (25)	16 (11)	21 (14)	8 (5)
Blood bilirubin increased	2 (1)	0	23 (15)	3 (2)
Dizziness	21 (14)	0	12 (8)	0
Dysgeusia	29 (19)	0	4 (3)	0
Arthralgia	11 (7)	2 (1)	17 (11)	0
Myalgia	3 (2)	0	24 (16)	0
Anemia	7 (5)	1 (1)	30 (20)	7 (5)
Rash	14 (9)	0	17 (11)	1 (1)
Visual impairment	18 (12)	0	2 (1)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase.

Ophthalmic Issues

- 61-70% of patients on crizotinib may develop visual changes: common side effect is difficulty with light and dark accommodation
- Visual effects: most common side effect of crizotinib; onset less than 2 weeks
- Shimmering/flashing lights, streamers, strings, floaters, overlapping shadows, afterimages
- No interruption in therapy or dose adjustments
- Baseline ophthalmologic assessment not required, but if visual effects persist, refer

Crizotinib package insert.

Cardiac Toxicities: Sinus Bradycardia

- Retrospective analysis from two studies of patients on crizotinib showed 75.3% of patients experienced sinus bradycardia, heart rate between 50 and 59.
- The average decrease in heart rate was 25 beats/minute.
- Patients with baseline heart rate less than 70 beats/minute were significantly more likely to experience bradycardia.

Hasenbank, C. *J Adv Pract Oncol*. 2017;8(suppl 1):43-50; Ou, S-HI, et al. *Cancer Med*. 2016;5(4):617-22.

Cardiac Toxicities: Sinus Bradycardia

- Patients who experienced sinus bradycardia did so after approximately 20 weeks on treatment.
- Patients who did not experience sinus bradycardia had their lowest heart rate near week 12 of treatment.

Hasenbank, C. *J Adv Pract Oncol*. 2017;8(suppl 1):43-50; Ou, S-HI, et al. *Cancer Med*. 2016;5(4):617-22.

Cardiac Toxicities: Sinus Bradycardia

- Grade 1: Patient asymptomatic. Majority of patients (83%) had grade 1 sinus bradycardia.
- Grades 2, 3, and 4: Hold drug until recovery of normal heart rate. Review all medications to determine if any contribute to bradycardia.

Hasenbank, C. *J Adv Pract Oncol.* 2017;8(suppl 1):43-50; Ou, S-HI, et al. *Cancer Med.* 2016;5(4):617-22.

Cardiac Toxicities: Sinus Bradycardia

- For grade 2 and 3 sinus bradycardia: if no medications are identified as contributing to bradycardia, resume treatment with ALK inhibitor at reduced dose. If medication is identified as contributing to bradycardia, adjust dose of that medication, and resume ALK inhibitor at full dose.
- Grade 4: As above; however, if no medications are identified as contributing to bradycardia, permanently discontinue ALK inhibitor

Ou, S-HI, et al. *Cancer Med*. 2016;5(4):617-22.

Cardiac Toxicities: QT Prolongation

- Crizotinib, ceritinib, are osimertinib all carry boxed warnings for QT prolongation
- Be aware of patient's PMH and medications
- Baseline and periodic EKGs

Hasenbank, C. *J Adv Pract Oncol*. 2017;8(suppl 1):43-50.

Hyperglycemia

- Mainly seen with ceritinib and alectinib
- Due to ability of ALK inhibitors to inhibit insulin-like growth factor receptor

Au, TH, et al. *J Oncol Pharm Pract*. 2017;23:602-14; Hasenbank. C. *J Adv Pract Oncol*. 2017;8(suppl 1):43-50.

Hyperglycemia

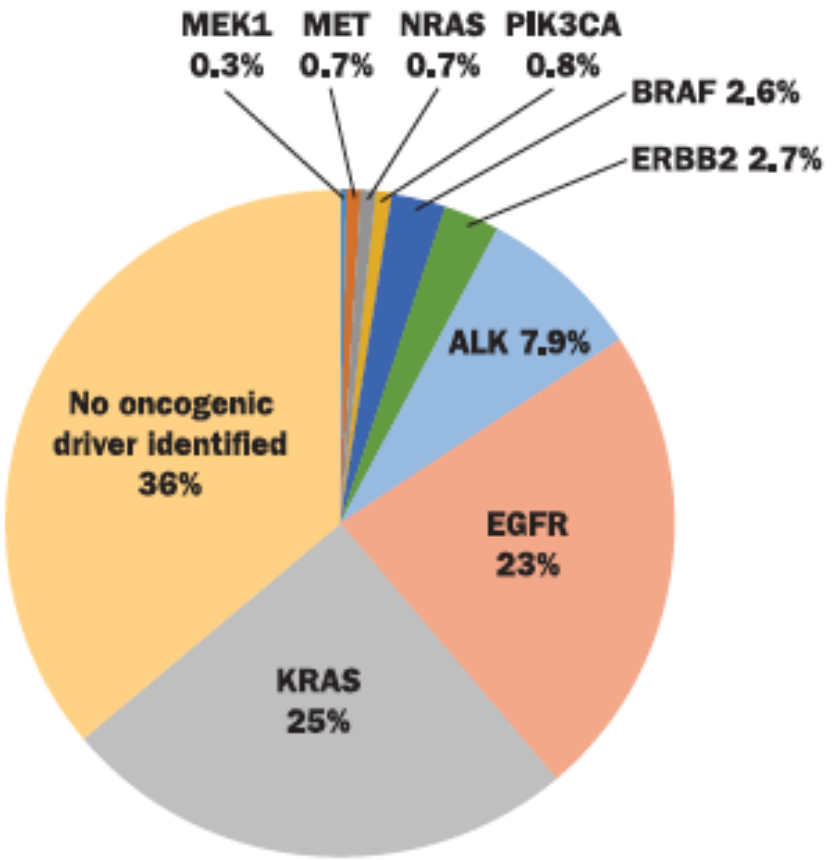
- Treat patients based on current diabetes guidelines
- Hold drug until blood glucose is under control, then resume ALK inhibitor at lower dose
- If the patient's blood glucose remains uncontrolled, discontinue ALK inhibitor

Hasenbank, C. *J Adv Pract Oncol*. 2017;8(suppl 1):43-50; Novartis Pharmaceuticals Corporation (2016). Package Insert.

Other Targets

Genomic Driver Mutation in Lung Adenocarcinoma

N = 733 pts
14 institutions
of LCMC



Sholl LM, et al. *J Thorac Oncol*. 2015;10:768-77.

Case 3

- TV is a 58-year-old Asian American woman who notices increasing shortness of breath
- On PE, she has dullness 1/3 up on left lung
- CXR confirms an effusion, and CT reveals a LLL mass and moderate effusion as well as multiple smaller pulmonary nodules bilaterally
- Cytology of effusion is c/w adenocarcinoma
- PET/brain MRI show no other areas of disease
- Cytologic sample is used for rapid EGFR testing and ALK FISH. Both are negative. No tissue remains for further testing.

Case 3

She is started on platinum/pemetrexed and does not tolerate it well. She does not want any further chemotherapy but would consider other options that are available. She has systemic lupus so immune therapy is not an option.

What do you to?

A. Repeat biopsy for NGS
B. Send “liquid biopsy” for NGS
C. Initiate hospice

Case 3: BRAF

A “liquid biopsy” is obtained and reveals BRAF V600E

What do you start?

A. Erlotinib/bevacizumab
B. Osimertinib
C. Dabrafenib/trametinib
D. Alectinib
E. Brigatinib

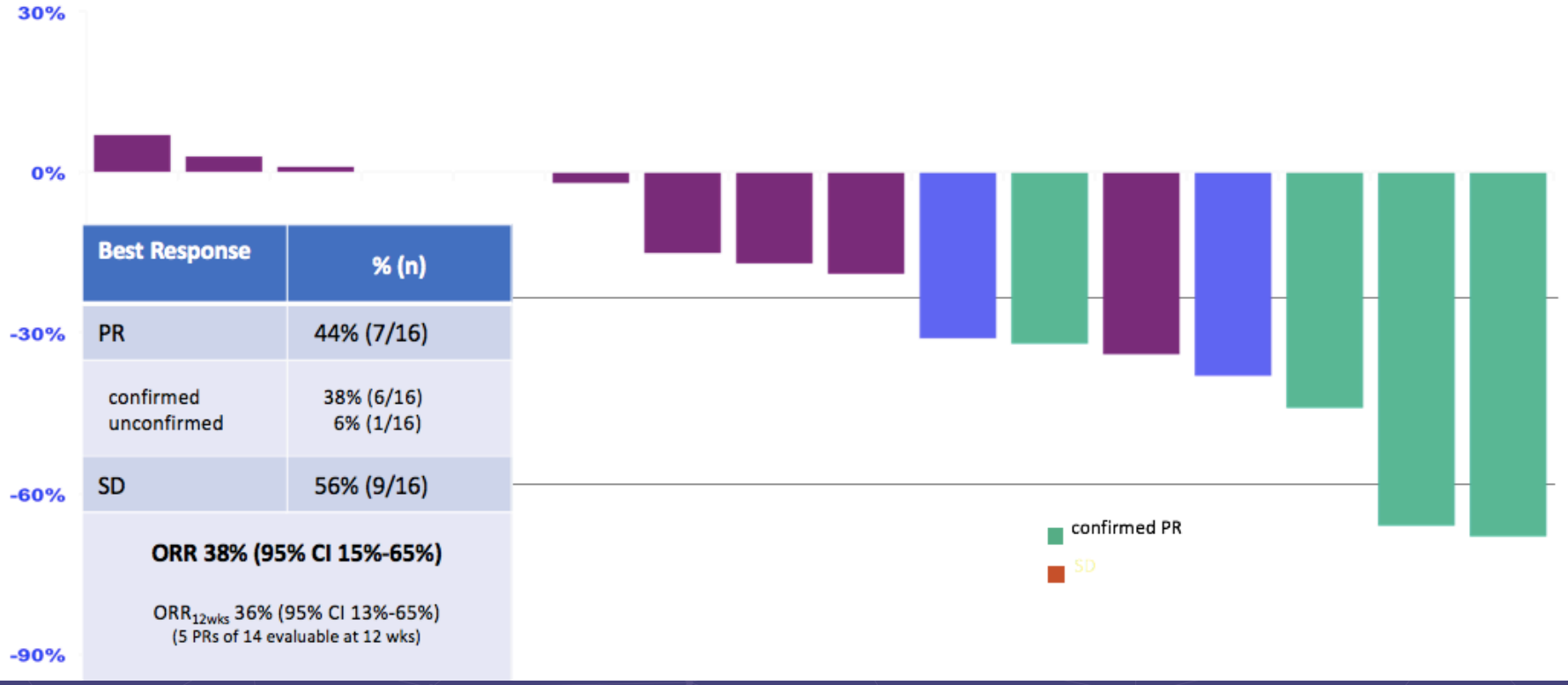
Case 3: BRAF

Drabrafenib/trametinib was started, and she has had a rapid clinical improvement in symptoms from her pleural effusion. It is well tolerated.

Phase II Dabrafenib (D) + Trametinib (T) in pts With prev Rx BRAF V600E–mut adv NSCLC (BRF113928): N = 57

- BRAF inhibitor combo therapy of dabrafenib (D) + trametinib (T) is active in BRAF V600E-mutant melanoma
- Dosing: D 150 mg po bid + T 2 mg po qd
- Median age 64 yr (range: 41–88); 51% female
- All patients had nonsquamous histology; 73% current/former smokers
- ORR 63% in 52 pts evaluable for efficacy (confirmed response); 50% still with response at the time of analysis
- Safety
  - Most common AEs (> 25%) included pyrexia, nausea, vomiting, diarrhea, asthenia, decreased appetite, dry skin

Response to Cabozantinib in Patients With RET-Rearranged Lung Adenocarcinomas



Best Response	% (n)
PR	44% (7/16)
confirmed unconfirmed	38% (6/16) 6% (1/16)
SD	56% (9/16)

ORR 38% (95% CI 15%-65%)

ORR_{12wks} 36% (95% CI 13%-65%)
(5 PRs of 14 evaluable at 12 wks)

Drilon, ASCO 2016, abstract 108.

RET Inhibitors: Efficacy Summary

Agent	*RET* testing	n	ORR (%)	PFS (months)	OS (months)
Cabozantinib (Drilon, ASCO 2015)	FISH/NGS	Stage I, 16	38	7	10
Cabozantinib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	13	31	3.6	4.9
Vandetanib (Sato, ASCO 2016)	FISH/RT-PCR	19/17	47/53	4.7	47% 1-year
Vandetanib (Lee, ASCO 2016)	FISH confirmed	18	17	4.5	11.6
Vandetanib (Gautschi, ASCO16)	FISH/NGS/RT-PCR	11	18	2.9	10.2
Sunitinib (Gautschi, ASCO 2016)	FISH/NGS/RT-PCR	9	22	2.2	6.8
Any RET inhibitor (Gautschi, ASCO 16)	FISH/NGS/RT-PCR	41	23	2.9	6.8

Reckamp KL, discussant ASCO 2016.

MET Exon 14 Splice Variant

- MET exon 14 splice variant ~4% adeno (TCGA)
- 8/18 (44%) pts responded to crizotinib
  - Additional 5/18 (28%) unconfirmed
- Dramatic responses to cabozantinib reported

Paik PK, et al. *Cancer Disc*. 2015;5(8):842-9: Drilon, ASCO 2016, abstract 108.

MET Exon 14 Splice Variant

- MET exon 14 splice variant ~4% adenocarcinoma (TCGA)
- Responses to crizotinib and cabozantinib

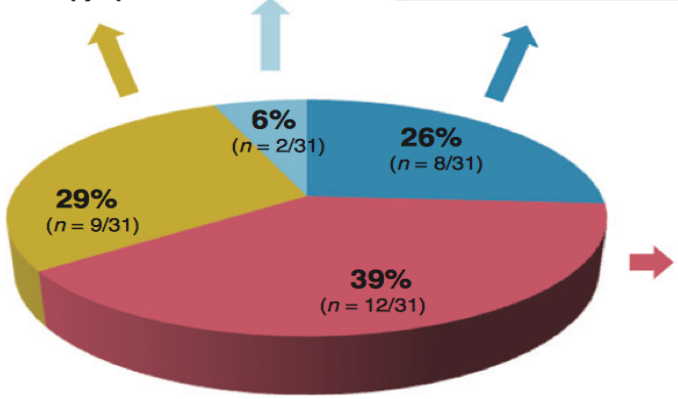
Paik PK, et al. *Cancer Disc*. 2015;5(8):842-9.

HER2-mutant NSCLC

- 69% women, 100% adeno, 50% never-smoker
- ORR 50% and DCR 93% with trastuzumab + chemotherapy
- High RR to afatinib (100% DCR)
- Time to progression relatively short (< 6 mo)

Mazieres J, et al. *J Clin Oncol*. 2013;31:1997-2003.

NGS in Patients With “No Genomic Alterations”



Genomic alteration with targeted therapy in NCCN guidelines	Tumor from same procedure as tumor subjected to non-NGS testing	Patient's clinical course
EGFR G719A	Yes	Recently started erlotinib, response evaluation pending
*BRAF*V600E	Yes	Subsequently passed away
SOCS5-ALK	Yes	**Disease shrinkage (<30%) with crizotinib**
HIP1-ALK	Yes	**Partial response to crizotinib**
CD74-ROS1	Yes	Recently started crizotinib, response evaluation pending
KIF5B-RET	Yes	**Partial response to cabozantinib**
KIF5B-RET	No	**Disease shrinkage (<30%) with cabozantinib**
CCDC6-RET	Yes	Candidate for cabozantinib after progression on chemotherapy

Genomic alteration with targeted agent available on or off a clinical trial	Targeted therapeutic (clinicaltrials.gov number) with potential activity available at institution
CDKN2A loss	CDK4/6 inhibitor (NCT01237236)
EGFR L747P	erlotinib, afatinib
EGFR exon 18 del (*n* = 2)	pan-ERBB inhibitor (NCT01858389)
EGFR exon 20 ins	pan-ERBB inhibitor (NCT01858389)
ERBB2 L755F	pan-ERBB/mTOR inhibitor (NCT01953926)
FGFR1 T141R	FGFR inhibitor (NCT01948297)
KRAS G12C	ERK inhibitor (NCT01781429)
KRAS Q61H	ERK inhibitor (NCT01781429)
MDM2 amp (*n* = 3)	MDM2 inhibitor (NCT01877382)

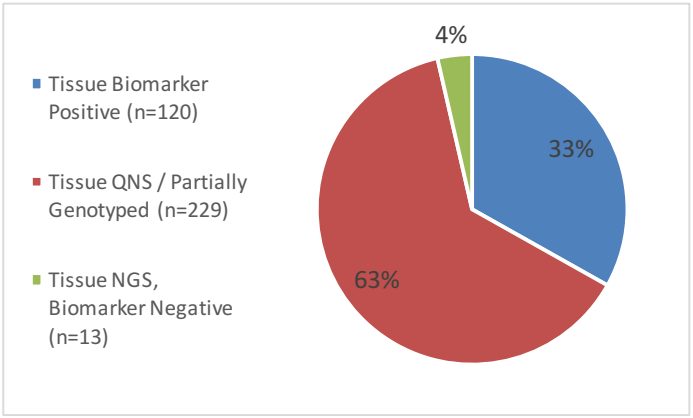
Figure 2.
Clinical NGS and targeted therapy use. The results of NGS of lung adenocarcinomas that harbored no genomic alterations (GA) in 11 genes (*EGFR*, *ERBB2*, *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, *PIK3CA*, *AKT1*, *ALK*, *ROS1*, and *RET*) via a focused panel of non-NGS testing in never or ≤15 pack-year smokers are shown. The percentage of patients with results that fall into 1 of 4 categories is depicted in the pie chart.

Drilon A, et al. *Clin Cancer Res*. 2015;21:3631-9.

ctDNA Utility in Undergenotyped NSCLC

Tissue Genotyping Status

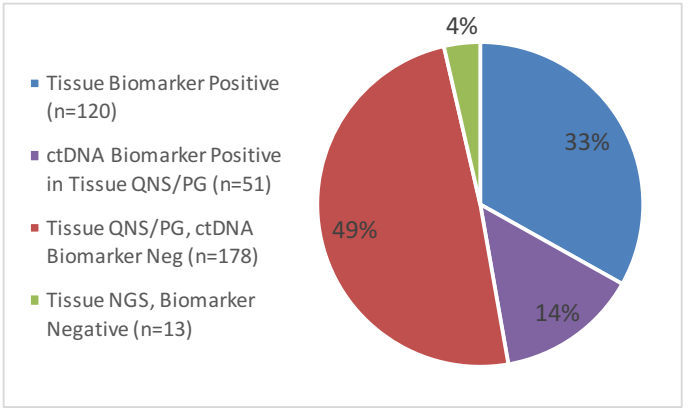
(n=362 non-squamous NSCLC)



Biomarker	N in Tissue	Biomarker	N in Tissue
EGFR	98	*RET* fusion	1
KRAS	11	*BRAF*^{V600E}	1
ALK fusion	5	*MET/ERBB2* amp	2
ROS1 fusion	2	**TOTAL**	**120**

ctDNA NGS Increased Biomarker Yield by 42%

(51 additional biomarkers identified in tissue QNS/PG cases)



Biomarker	N in ctDNA*	Biomarker	N in ctDNA*
EGFR	8	*RET* fusion	3
KRAS	28	*BRAF*^{V600E}	4
ALK fusion	1	*MET/ERBB2* amp	7
ROS1 fusion	0	**TOTAL**	**51**

*among Tissue QNS/PG

Mack PC. ASCO 2016.

Conclusions

- Promising new EGFR TKIs with T790M+ activity
  - Osimertinib, others
- Promising ALK TKIs with activity 1st/2nd line+
- New insights with recent publications on resistance mechanisms, ongoing combination/sequencing trials
- Multiple other clinically relevant targets with active agents being identified
- Consider repeat testing
- Serum testing: the next step
- Many patients living years in this setting but with medication costs of >$100,000 annually

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