Management of EGFR-Mutation Positive Metastatic Non-Small Cell Lung Cancer

Leora Horn, MD, MSc
Vanderbilt-Ingram Cancer Center

Rogerio Lilenbaum, MD
Yale Cancer Center/Smilow Cancer Hospital

National Comprehensive Cancer Network®

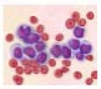
NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients

EGFR Mutation in Advanced NSCLC: NCCN, Florida 2016

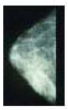
Rogerio Lilenbaum, MD
Professor of Medicine
Yale Cancer Center
Chief Medical Officer
Smilow Cancer Hospital

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Molecular Targeted Therapy in Cancer



BCR-ABL → Imatinib, Dasatinib, Nilotinib



ERBB2 (Her2) → Trastuzumab, Lapatinib, Pertuzumab, T-DM1

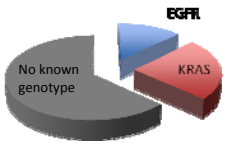
EGFR, ALK → Erlotinib, Crizotinib

KRAS → Cetuximab, Panitumumab

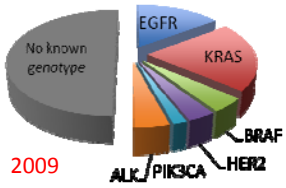
BRAF → Vemurafenib

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Personalized Medicine in Lung Cancer

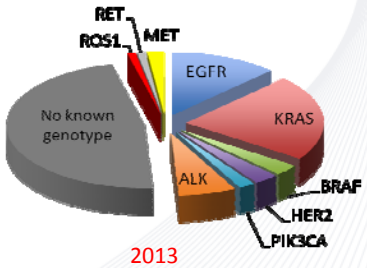


2004 - 2005



2009

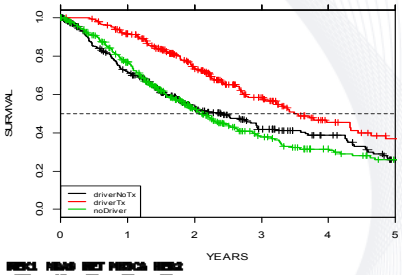
- Certain tumors arise as a result of aberrant activation of a single oncogene and become dependent on this activation
- This phenomenon is known as oncogenic addiction
- Identification of actionable oncogenic drivers creates the potential for highly active therapeutic interventions
- As an example, EGFR TKIs are now considered a standard first line treatment for patients with mutated tumors

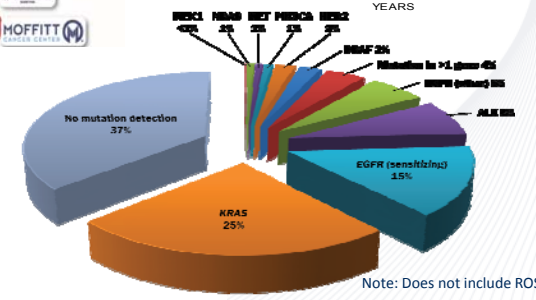


2013

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Molecular Alterations in Lung Adenocarcinoma





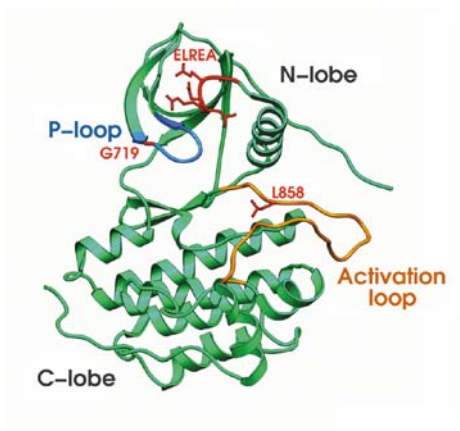
Note: Does not include ROS1 or RET

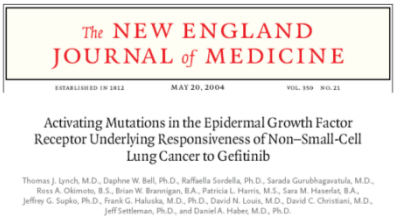
Sholl LM et al, 2015; Johnson BE, et al. ASCO 2013

Tumor Profiling at Yale

- Tier 1: Reflex testing using TaqMan platform
  - 5 to 7 days
- Tier 2: Oncomine Cancer Panel (143 genes and >40 translocations/fusions) on Ion Torrent
  - 2 weeks
- Tier 3: Whole exome sequencing with future custom panels per organ system specification
  - 2-3 weeks

EGFR Mutations




The NEW ENGLAND JOURNAL of MEDICINE

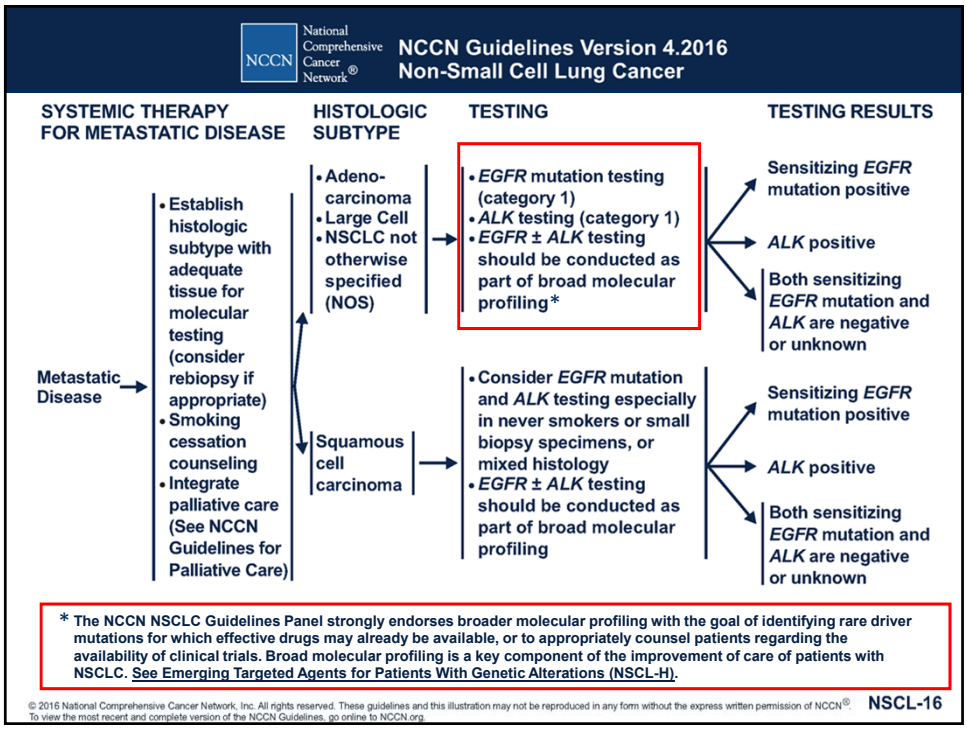
ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

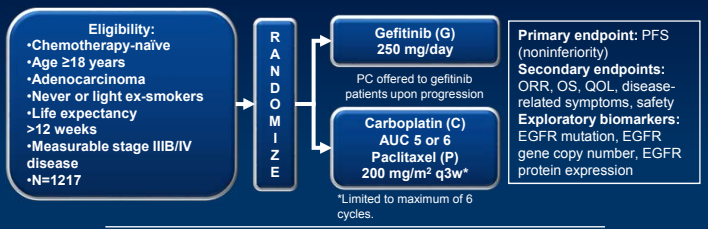
Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

- High ORR with EGFR TKIs with exon 19 deletion / exon 21 L858R point mutation
- Most common in never smokers, females, patients with East Asian ethnicity, and adenocarcinomas

Blencke S, et al. J Biol Chem 2003;15435–40
Lynch TJ, et al. N Engl J Med 2004;350:2129–39
Paez JG, et al. Science 2004;304:1497–500



Gefitinib vs Carboplatin/Paclitaxel for Clinically Selected Chemotherapy-Naïve Patients With Advanced NSCLC in Asia (IPASS)

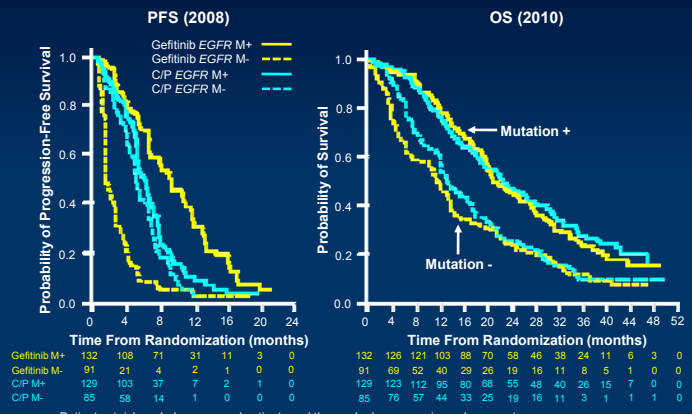


Endpoint	G N=609	C + P N=608	HR/OR (95% CI)
mPFS	5.7 mos	5.8 mos	**0.741** (0.65-0.85) *P*<0.0001
mOS	18.8 mos	17.4 mos	**0.90** (0.79-1.02) *P*=0.109
ORR (%)	43.0	32.2	**1.59** (1.25-2.01) *P*=0.0001

52% of patients on the C + P arm received subsequent TKI therapy

Mok, et al. *N Engl J Med*. 2009;361:947. Ohe, et al. *ASCO*. 2009 (abstr #8044). Yang, et al. *ESMO*. 2010 (abstr LBA2).

IPASS: PFS and OS in *EGFR* Mutation–Positive and –Negative Patients



Patients at risk excludes censored patients and those who have experienced an event.
Yang, et al. *ESMO*. 2010 (abstr LBA2).

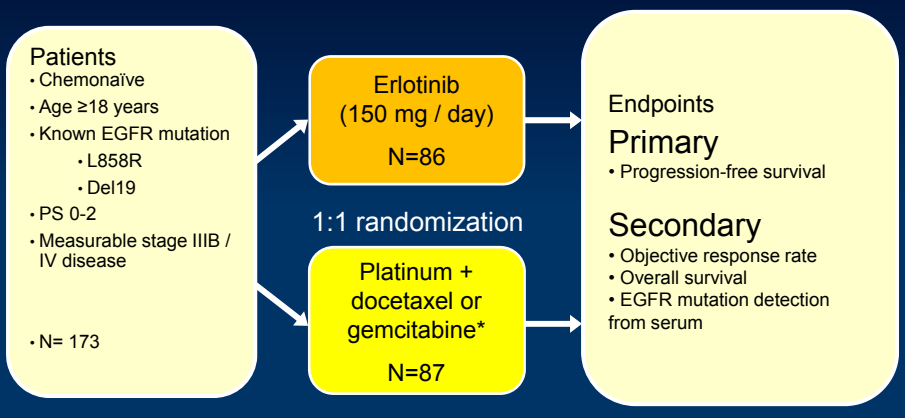
Randomized Trials of EGFR TKI vs CT in 1st Line Rx

Study	ORR	PFS (mo)	HR	OS
EURTAC	58% vs 15%	9.7 vs 5.2	0.37	ND
OPTIMAL	83% vs 36%	13.1 vs 4.6	0.16	ND
NEJ 002	74% vs 31%	10.8 vs 5.4	0.30	ND
WJTOG 3405	62% vs 31%	9.2 vs 6.3	0.49	ND
IPASS	71% vs 47%	9.5 vs 5.5	0.19	ND
LUX LUNG 3	56% vs 23%	11.1 vs 6.9	0.58	ND
LUX LUNG 6	67% vs 23%	11.0 vs 5.6	NR	NR

Mok et al. N Engl J Med 2009;361:947–57; Han et al. J Clin Oncol 2012;30:1122–8; Mitsudomi et al. Lancet Oncol 2010;11:121–8; Mitsudomi et al. J Clin Oncol 2012;30(Suppl.): Abstract 7521; Maemondo et al. N Engl J Med 2010;362:2380–8; Zhou et al. Lancet Oncol 2011;12:735–42; Zhou et al. J Clin Oncol 2012;30(Suppl.): Abstract 7520; Rosell et al. Lancet Oncol 2012;13:239–46.

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

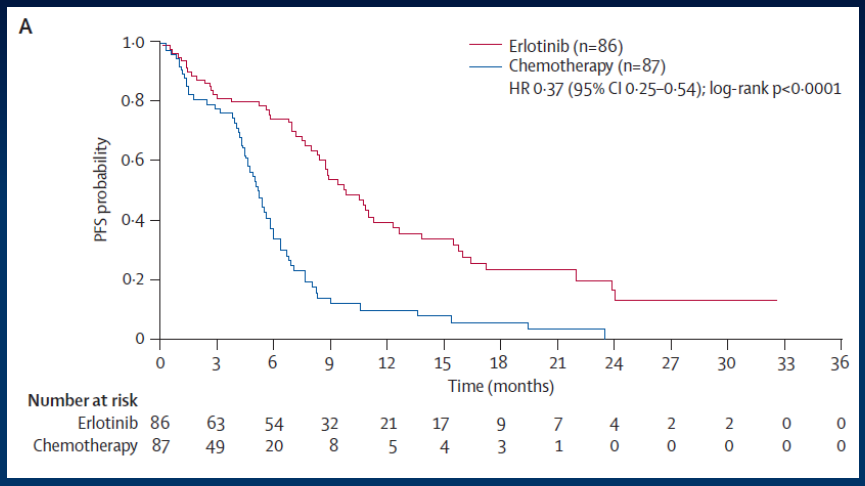
EURTAC Study



*Investigator could choose cisplatin or carboplatin and also docetaxel vs. gemcitabine
Chemotherapy was given for up to 4 cycles

Rosell et al, Lancet 2012

EURTAC Results



Rosell et al, Lancet 2012

LUX-Lung 3 and 6: design

- Stage IIIB/IV adenocarcinoma of the lung
- Presence of *EGFR* mutation in the tumor tissue*
- No prior treatment with chemotherapy for advanced/metastatic disease or EGFR inhibitors
- ECOG PS 0 or 1

Randomization

2:1

Stratification by EGFR mutation type: Del19/L858R/other and by race (LUX-Lung 3 only): Asian/non-Asian

Afatinib
40 mg orally once daily

LUX-Lung 3[1]:
Cisplatin + pemetrexed
up to 6 cycles

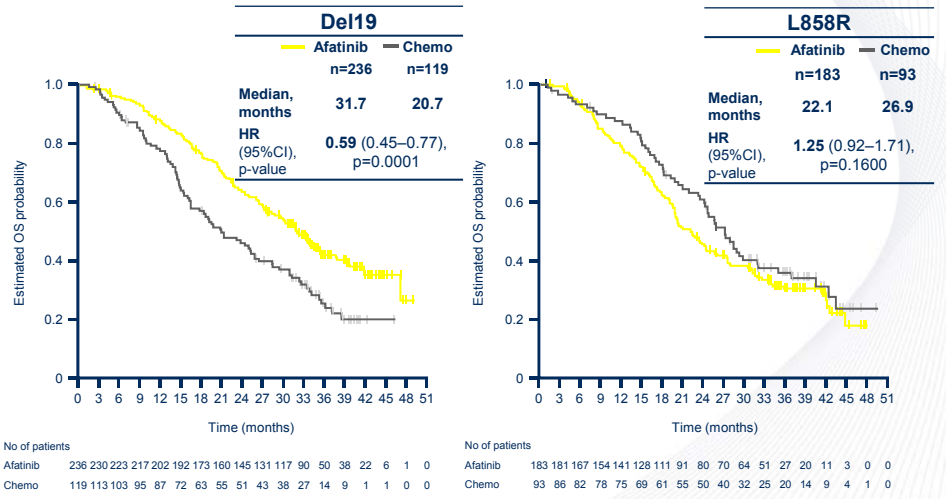
LUX-Lung 6[2]:
Cisplatin + gemcitabine
up to 6 cycles

Primary endpoint: PFS (independent review)
Secondary end points: ORR, DCR, OS, PRO, safety

*EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.
1. Sequist et al. *J Clin Oncol.* 2013;31:3327; 2. Wu et al. *Lancet Oncol.* 2014;15:213.

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

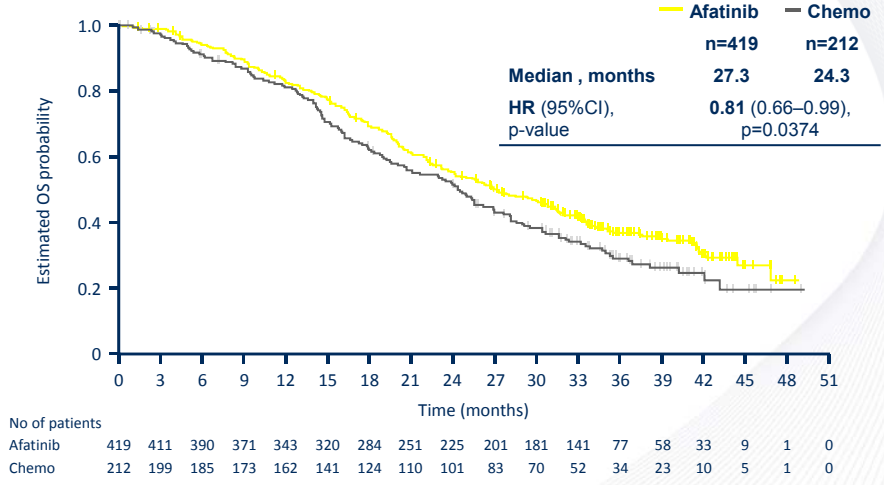
Overall Survival with Afatinib by EGFR mutation categories



Yang et al, 2015

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Afatinib vs Chemotherapy in the first-line setting: Combined OS analysis in patients with common EGFR mutations



Yang et al, 2015

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

LUX-Lung 7 - Study Design

- Stage IIIb/IV adenocarcinoma of the lung
- EGFR mutation (Del19 and/or L858R) in the tumor tissue#
- No prior treatment for advanced/metastatic disease
- ECOG PS 0-1

Randomization

Stratified by mutation type (Del19 vs L858R) and presence of brain metastases (yes vs no)

1:1

Afatinib 40 mg once daily | **Gefitinib 250 mg once daily**

Primary endpoints: PFS (independent review)#, **TTF, OS**

Secondary endpoints: ORR, time to and duration of response, duration of disease control, tumor shrinkage, HRQoL, safety

local or central test

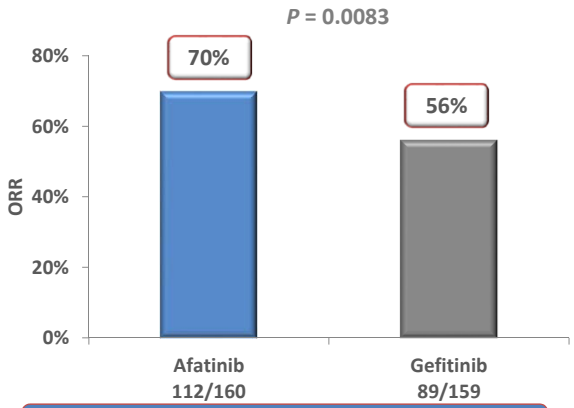
Tumor assessment performed at week 4, 8, every 8 weeks until w64 and every 12 weeks thereafter

Treatment beyond progression allowed if deemed beneficial by investigator.

Park et al. *Ann Oncol*. 2015;26: (suppl 9; abstract LBA2).

Afatinib is approved in a number of markets, including the EU, Japan, Taiwan and Canada and in the U.S. for use in patients with distinct types of EGFR mutation-positive NSCLC. Registration conditions differ internationally, please refer to locally approved prescribing information. Afatinib is under regulatory review by health authorities in other countries worldwide.

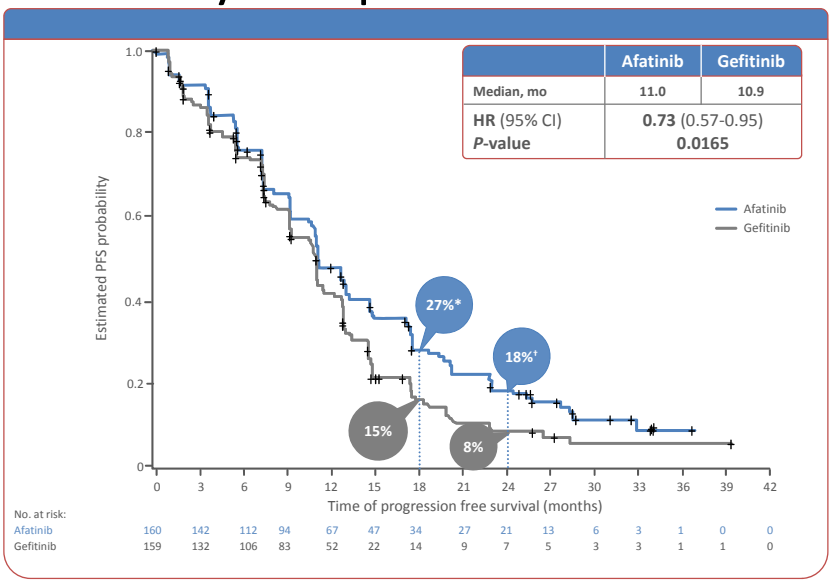
Objective Response and Disease Control Rates



Median DoR , months (95% CI)	10.1 (7.8, 11.1)	8.4 (7.4 – 10.9)
Disease control rate (N)	91.3% (146)	87.4% (139)

Park et al. *Ann Oncol*. 2015;26: (suppl 9; abstract LBA2).

PFS by Independent Review



Park et al. *Ann Oncol*. 2015;26: (suppl 9; abstract LBA2); * *P*=0.0176 †. *P*=0.0184

Common Adverse Events Following Use of EGFR TKIs

Adverse event, %	Afatinib (n=229)[1]		Erlotinib (n=84)[2]		Gefitinib (n=1126)[3]	
	Any grade	Grade 3+	Any grade	Grade 3+	Any grade	Grade 3+
Diarrhea	96	15	62	5	29	3
Rash	90	16	85	14	--	--
Paronychia	58	11	14	0	--	--
Stomatitis/mucositis*	71	9	18	1	7	0.3
Pruritus	21	0	16	0	--	--
Dry skin	31	0	21	1	--	--
Skin reactions†	--	--	--	--	47	2
Nail disorders††	--	--	--	--	5	0.1

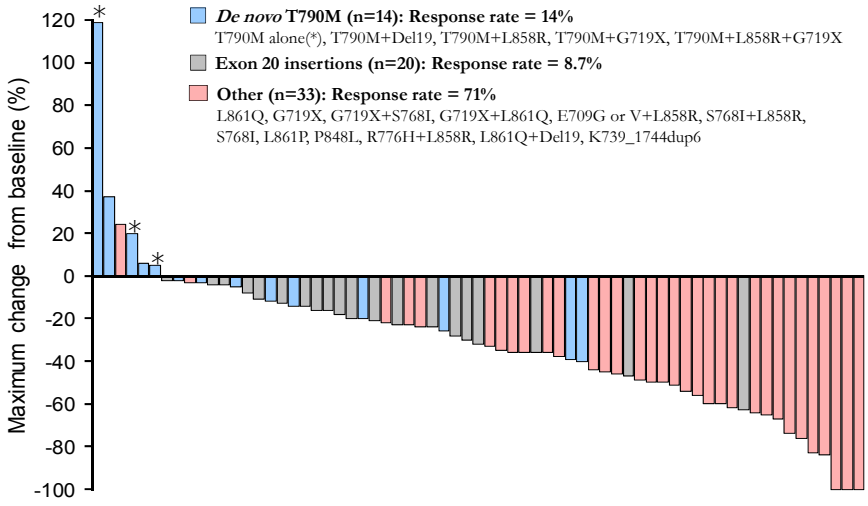
†Includes acne, acne pustular, dermatitis, dermatitis acneiform, dermatitis exfoliative, drug eruption, dry skin, erythema, exfoliative rash, folliculitis, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin toxicity, xeroderma

†† Includes ingrowing nail, nail bed infection, nail disorder, nail infection, onychoclasis, onycholysis, paronychia

*Only includes mucositis for erlotinib

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Tumor shrinkage in patients with uncommon mutations



†8 patients were not included due to insufficient data

Progression-free survival and overall survival in patients

	De novo T790M n=14	Exon 20 insertions n=23	Other n=38
Median PFS, months (range)	2.9 (0.3−13.8)	2.7 (0.4-11.9)	10.7 (0.0+-35.8+)
Median OS, months (range)	14.9 (1.5-30.5)	9.4 (0.4-32.2+)	18.6 (0.0+-51.3+)

T790M + L858R, n=6

Patient	PFS	OS
1	0.8	8.7
2	2.6	24.9
3	6.7	13.2
4	8.3	30.5
5	9.6*	24.4*
6	11.0	20.8
Median	**7.5**	**22.9**

T790M + Del19, n=3

Patient	PFS	OS
1	0.3	8.1
2	1.2	7.5
3	3.0	24.6
Median	**1.2**	**8.1**

+Patient data censored; NE = not estimable

Erlotinib +/- Bevacizumab Study Design

Chemotherapy-naïve
Stage IIIB/IV NSCLC or postoperative recurrence
Non-squamous
Activating *EGFR* mutations*
- Exon 19 deletion
- Exon 21 L858R

Age ≥20 years
PS 0–1
No brain metastasis

R
1:1

Erlotinib 150mg/d + Bevacizumab 15mg/kg q3w (*n* = 75) → PD

Erlotinib 150mg/d (n = 75) → PD

Stratification factors: sex, smoking status, clinical stage, *EGFR* mutation type

- **Primary endpoint:** PFS (RECIST v1.1, independent review)
- **Secondary endpoints:** OS, tumor response, QoL, safety
- **Exploratory endpoint:** biomarker assessment

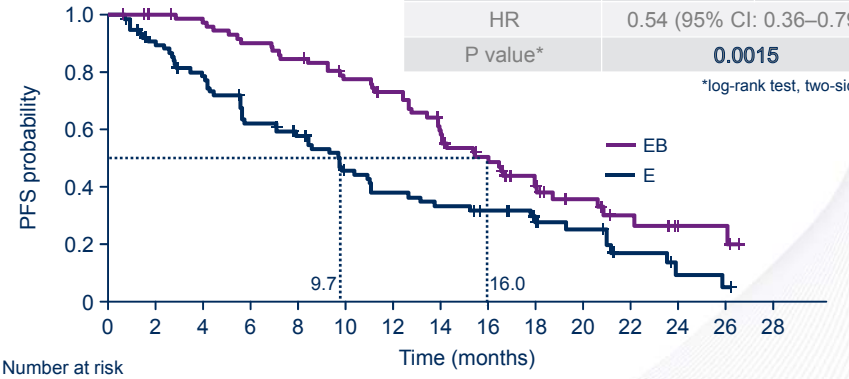
*T790M excluded

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

First-Line Erlotinib +/- Bevacizumab

	EB	E
Median (months)	16.0	9.7
HR	0.54 (95% CI: 0.36–0.79)	
P value*	0.0015	

*log-rank test, two-sided

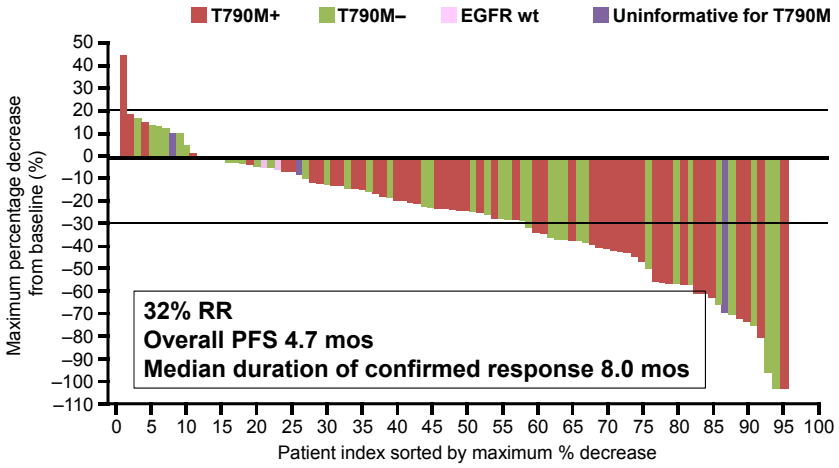


Number at risk

EB	75	72	69	64	60	53	49	38	30	20	13	8	4	4	0
E	77	66	57	44	39	29	24	21	18	12	10	5	2	1	0

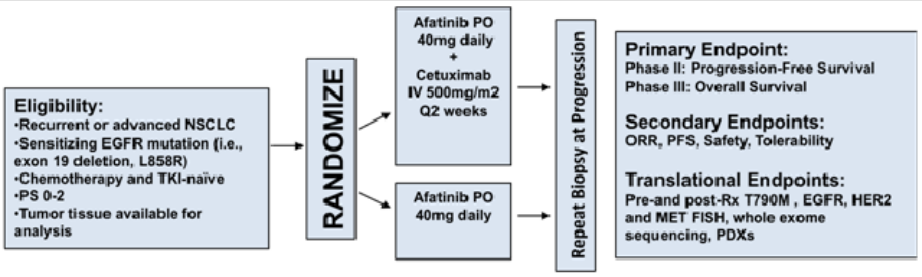
Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Afatinib + Cetuximab at MTD: Responses by T790M mutation



Janjigian et al ESMO '12

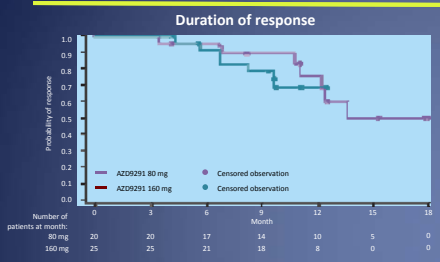
S1403: A randomized phase II/III trial of afatinib plus cetuximab versus afatinib alone in treatment-naïve patients with advanced, *EGFR* mutation positive NSCLC

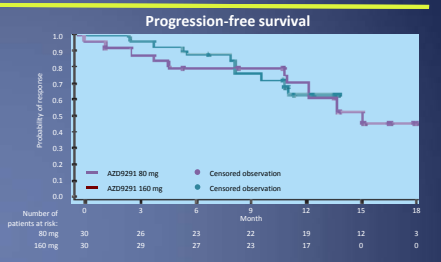


PIs: Goldberg; Politi; Lilenbaum

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

DoR and PFS in osimertinib (AZD9291) first-line cohorts (investigator assessed)



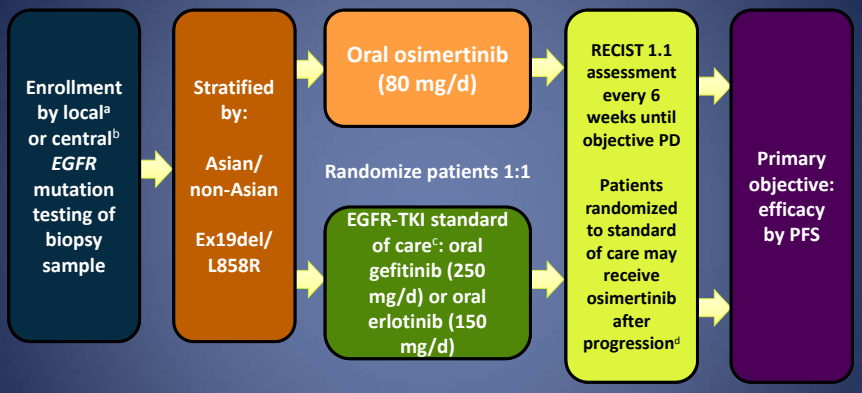


	80 mg N=20	160 mg N=25	Total N=45
Median DoR, months (95% CI)	13.6 (11.1, NC) Maturity: 35%	NC (9.7, NC) Maturity: 28%	NC (12.3, NC) Maturity: 31%
Maximum DoR, months	18.0+	12.6+	18.0+
Remaining in response, % (95% CI)			
9 months	89 (64, 97)	78 (56, 90)	83 (68, 92)
12 months	76 (46, 90)	69 (45, 84)	71 (53, 83)

	80 mg N=30	160 mg N=30	Total N=60
Median PFS, months (95% CI)	NC (12.3, NC) Maturity: 40%	NC (11.1, NC) Maturity: 30%	NC (13.7, NC) Maturity: 35%
Maximum PFS, months	19.2+	13.8+	19.2+
Remaining alive and progression-free, % (95% CI)			
9 months	83 (64, 93)	80 (60, 90)	81 (69, 89)
12 months	75 (55, 87)	69 (48, 82)	72 (58, 82)

Ramalingam SS et al. *Proc ASCO* 2015

FLAURA Study Design



[a]With central laboratory assessment performed for sensitivity; [b]cobas™ EGFR Mutation Test; [c]Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; [d]Patients randomized to the standard-of-care treatment arm may receive open-label treatment with osimertinib on central confirmation of both objective disease progression and T790M positive tumor.

PFS2 = second progression-free survival (time from randomization to second progression).

NCT02296125. Clinical study report available at http://clinicaltrials.gov

Conclusions

- Gefitinib, erlotinib, and afatinib are appropriate options
- Afatinib has demonstrated an OS benefit in patients with Del 19 mutations
- Afatinib showed superior ORR, PFS, and TTF in 1st line therapy against gefitinib
- At the current recommended doses, afatinib has a higher rate of toxicity
- Combination of bevacizumab and erlotinib showed better PFS compared to erlotinib alone
- Ongoing studies are evaluating the role of cetuximab in combination with afatinib vs afatinib alone
- Osimertinib is being evaluated in 1st line

Yale CANCER CENTER | SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

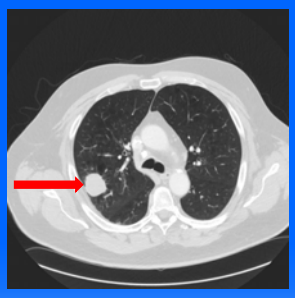
Management of EGFR-Mutation Positive Metastatic Non-Small Cell Lung Cancer

Treatment of Patients With Sensitizing EGFR Mutation Positive NSCLC and Acquired Resistance to EGFR TKIs

Leora Horn, MD MSc
Associate Professor of Medicine
Clinical Director of Thoracic Oncology Research Program
Associate Vice Chancellor for Faculty Development
Vanderbilt Ingram Cancer Center
Nashville, TN USA

Case One

- 64 year old, Caucasian, male former smoker diagnosed with stage IV non-small cell lung cancer, adenocarcinoma histology, positive for EGFR exon deletion 19. He is treated with erlotinib 150 mg daily and after 4 years is found to have progression in a single lung lesion.



What do you recommend?

1. Biopsy the lung lesion
2. Switch to chemotherapy
3. Start on afatinib
4. Start on osimertinib
5. Radiation to the lung lesion

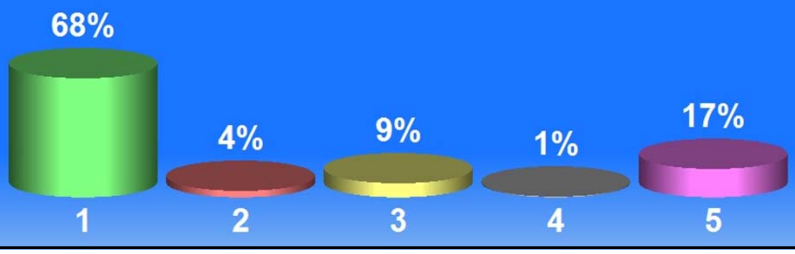
Audience Polling Results

Case One

64 year old, Caucasian, male former smoker diagnosed with stage IV non-small cell lung cancer, adenocarcinoma histology, positive for EGFR exon deletion 19. He is treated with erlotinib 150 mg daily and after 4 years is found to have progression in a single lung lesion.

What do you recommend?

1. Biopsy the lung lesion
2. Switch to chemotherapy
3. Start on afatinib
4. Start on osimertinib
5. Radiation to the lung lesion



Acquired Resistance to EGFR TKIs

- When treated with EGFR TKIs, 70% of patients with activating mutations will have tumor regression and a median PFS of 1 year.
- Once these responding patients progress, they have developed acquired resistance to gefitinib, erlotinib or afatinib.
- In "Acquired Resistance"
  - Oncogene addiction persists
  - Median post-progression survival is 16 months

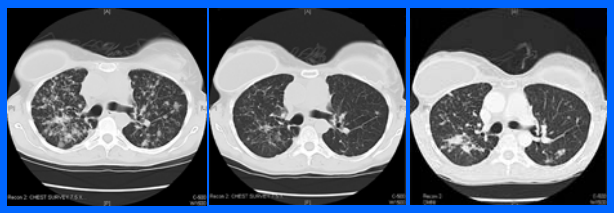
Mok T et al NEJM 2009; Jackman D et al JCO 2009

Criteria for Acquired Resistance

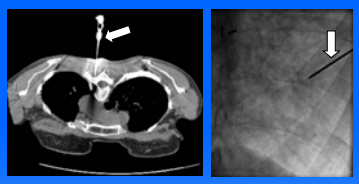
- Previously received treatment with single-agent sensitizing EGFR TKI (gefitinib, erlotinib or afatinib).
- Either of the following:
  - Documented partial response (PR) or complete response (CR) or
  - Durable (> 6 months) clinical benefit (stable disease) while on sensitizing EGFR TKI
- Systemic progression of disease while on continuous treatment with sensitizing EGFR TKI during the last 30 days.
- No intervening systemic therapy between cessation of sensitizing EGFR TKI and initiation of new therapy.

Jackman D et al JCO 2009

Acquired Resistance to EGFR TKIs in Lung Cancer



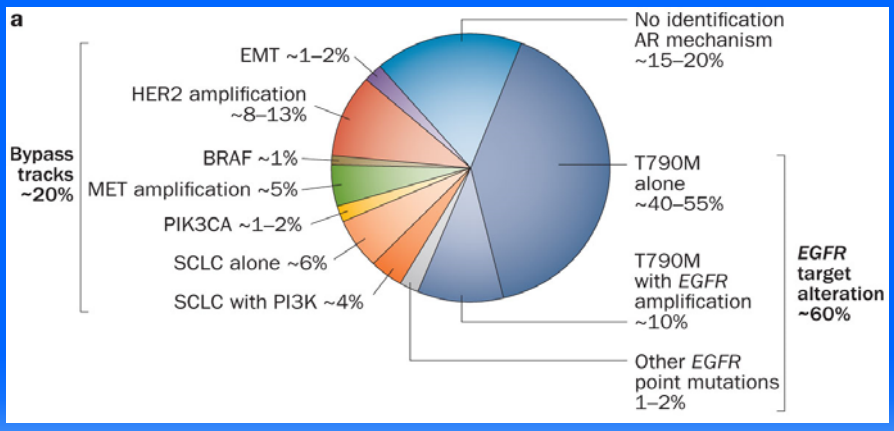
Day 0 4 months 25 months



Growing bone lesion Growing lung lesion

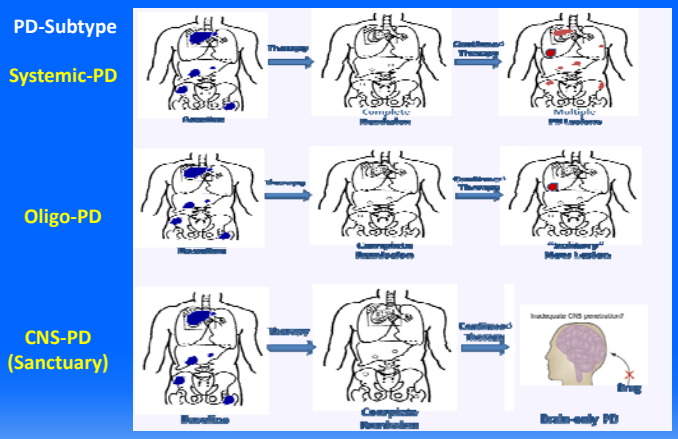
Pao W et al PLoS Med 2: e73 2005

Mechanism of Acquired Resistance to EGFR TKIs



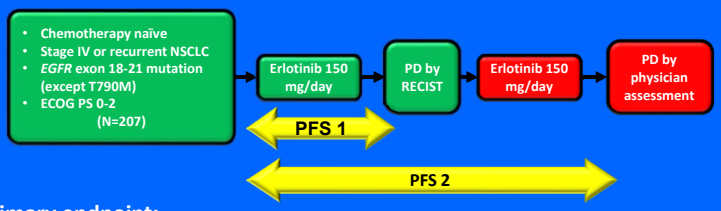
Camidge, D. R. et al Nat. Rev. Clin. Oncol. 2014+

Type of Progression Drives Therapy: Three PD Subtypes



Gandara et al., Clinical Lung Cancer 2013

ASPIRATION: Phase II First-line Erlotinib in Sensitizing EGFR Mutation–Positive NSCLC Continued After Progression – Study Design



Primary endpoint:

- PFS (time to RECIST PD or death)

Secondary endpoints:

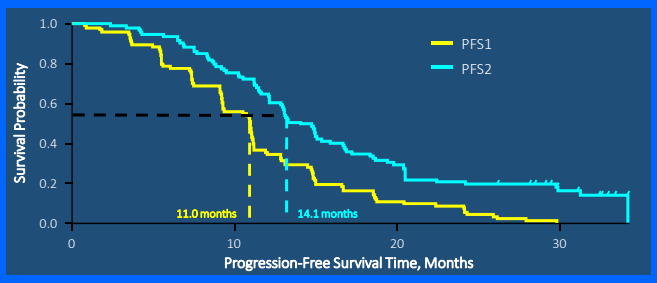
- PFS2 (time to off-erlotinib PD if erlotinib was extended beyond RECIST PD), PFS1 in exon 19 deletion/L858R subsets, OS, ORR/DCR/BOR, safety

BOR=best overall response; ECOG PS=Eastern Cooperative Oncology Group performance status.

Park, et al. Presented at: ESMO. 2014 (abstr 1223O).

ASPIRATION: PFS1 and PFS2

- In patients receiving post-PD erlotinib (n=93)
  - PFS1 was 11.0 months
  - **Difference between PFS1 and PFS2 was an additional 3.1 months**



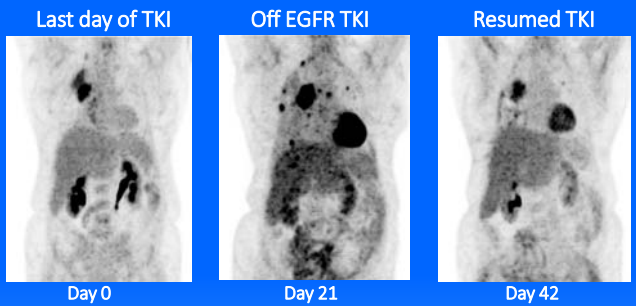
- Secondary endpoints, ITT population
  - ORR : 66.2%
  - DCR : 82.6%
  - Median OS: 31.0 months (95% CI, 27.3-not reached)

PD=progressive disease.

Park, et al. Presented at: ESMO. 2014 (abstr 1223O).

Disease Flare

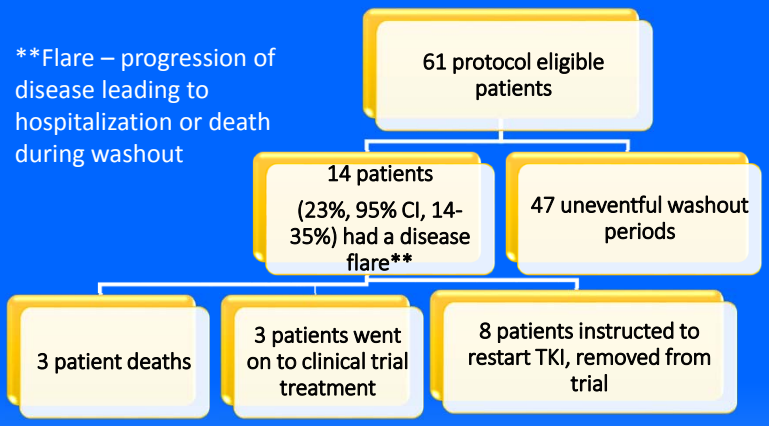
Rapid acceleration of disease progression resulting in hospitalization and/or death after discontinuation of gefitinib or erlotinib and before initiation of study drug.



Chaft J et al CCR 2011

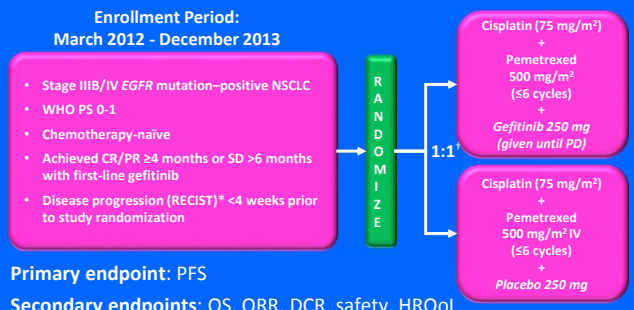
Results

**Flare – progression of disease leading to hospitalization or death during washout



Chaft J et al CCR 2011

IMPRESS: Phase III Trial of Gefitinib vs Gefitinib + CT Beyond Progression in Sensitizing EGFR Mutation–Positive NSCLC



Primary endpoint: PFS

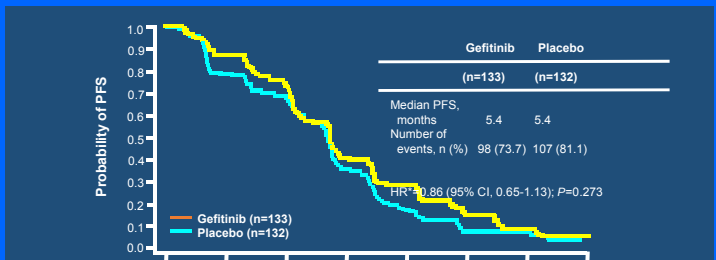
Secondary endpoints: OS, ORR, DCR, safety, HRQoL

Exploratory endpoint: Biomarkers

*Progressive disease based on radiological evaluation (modified Jackman's criteria) and RECIST version 1.1. Tumor assessments were performed ≤4 weeks before start of treatment (baseline) and every 6 weeks (±7 days) after randomization until progressive disease.
†Randomization did not include stratification factors; analyses were adjusted for 2 covariates; age (<65 vs ≥65 years) and prior response to gefitinib (SD vs PR+CR).
CR=complete response; CT=chemotherapy; DCR=disease control rate; HRQoL=Health-Related Quality of Life; ORR=objective response rate; PR=partial response; SD=stable disease; WHO PS=World Health Organization performance status.

Mok, et al. Presented at: ESMO. 2014; Lancet Oncology 16:990-8 (2015)

IMPRESS: PFS (Primary Endpoint; ITT)



	Gefitinib (n=133)	Placebo (n=132)
Median PFS, months	5.4	5.4
Number of events, n (%)	98 (73.7)	107 (81.1)

HR* 0.86 (95% CI, 0.65-1.13); *P*=0.273

Patient Characteristics were Balanced with the Exception of:	Gefitinib (n=133)	Placebo (n=132)
≥65 years, %	32	26
Brain metastases (baseline), %	33	23
CR or PR/SD to first-line gefitinib, %	68/32	76/24

*Primary cox analysis with covariates. An HR <1 implies a lower risk of progression with gefitinib.

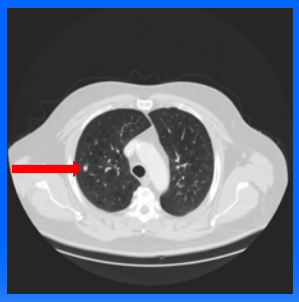
Mok, et al. Presented at: ESMO. 2014; Lancet Oncology 16:990-8 (2015)

Case Continued

- He is treated with SBRT to the primary lung lesion but 12 months later develops new disease in the bones and hip pain as well and small bilateral lung nodules.

What do you recommend?

1. Biopsy of a growing lesion
2. Switch to chemotherapy
3. Start on afatinib
4. Start on osimertinib
5. Do something else



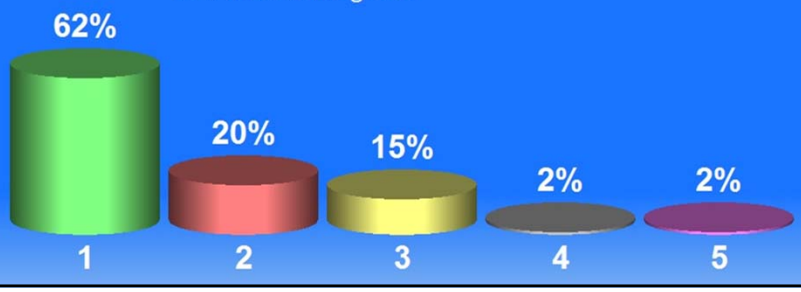
Audience Polling Results

Case Continued

He is treated with SBRT to the primary lung lesion but 12 months later develops new disease in the bones and hip pain as well and small bilateral lung nodules.

What do you recommend?

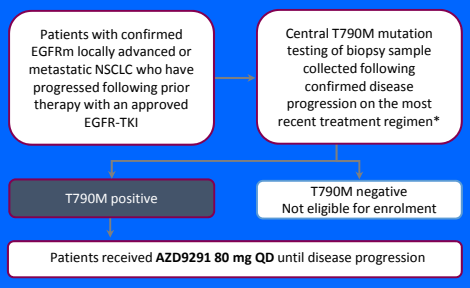
1. Biopsy of a growing lesion
2. Switch to chemotherapy
3. Start on afatinib
4. Start on osimertinib
5. Do something else



Osimertinib (AZD9291)

Primary endpoint

- AURA extension: to investigate the safety, tolerability and efficacy (ORR) of AZD9291 (assessed by BICR).
- AURA2: ORR according to RECIST 1.1 (assessed by BICR).



Key inclusion criteria

- Aged ≥18 (≥20 in Japan).
- Confirmation of tumor EGFR mutation associated with EGFR-TKI sensitivity (including G719X, exon 19 del, L858R, L861Q).
- Measurable disease at baseline.
- WHO performance status 0 or 1.
- Acceptable organ function.
- Stable brain metastases allowed.

For patients ≥third line

- AURA extension: disease progression following at least two lines of prior therapy including at least one EGFR-TKI.
- AURA2: disease progression following at least two lines of prior therapy including both an EGFR-TKI and a platinum-based doublet chemotherapy.

*T790 EGFR mutation identified by EGFR Mutation Test

BICR, blinded independent central review; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor; WHO, World Health Organization

Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress

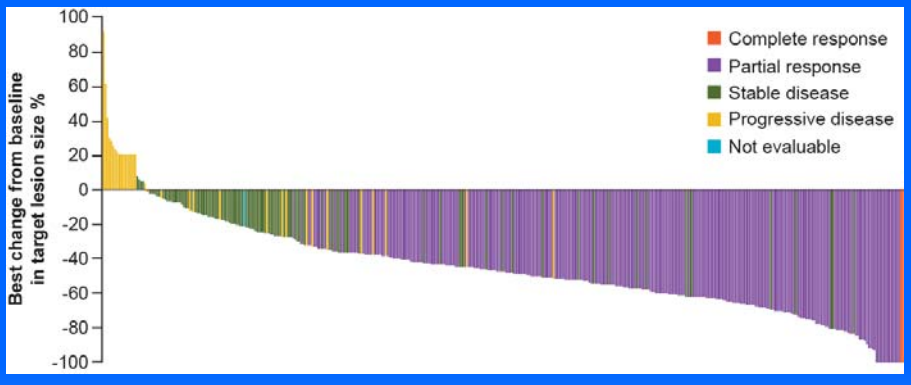
Baseline demographics and disease characteristics

Characteristic, %	AURA extension (n=201)	AURA2 (n=210)	Total (n=411)*
Sex: male / female	34 / 66	30 / 70	32 / 68
Age: median (range), years	62 (37–89)	64 (35–88)	63 (35–89)
Race: White / Asian / other / not reported	38 / 57 / 3 / 2	34 / 63 / 3 / 0	36 / 60 / 3 / 1
Histology: adenocarcinoma / other	97 / 3	96 / 4	97 / 3
WHO performance status: 0 / 1 / 2	34 / 66 / 1†	40 / 60 / 0	37 / 63 / 0
Brain metastases	37	41	39
Treatment: second line / ≥third line	30 / 70	32 / 68	31 / 69
EGFR-TKI as last therapy:‡ <30 days ≥30 days	79 52 27	75 53 22	77 53 25
EGFR mutation type by last test: Exon 19 del / L858R / G719X / S7681 / Exon 20 ins	71 / 25 / 2 / 2 / 1	65 / 32 / 2 / 1 / 1	68 / 29 / 2 / 2 / 1

*Full analysis set: n=411. Evaluable for response analysis set: n=398; 13 patients did not have measurable disease at baseline by independent central review
†Protocol deviation: inclusion criteria states patients should have a WHO performance status of 0 or 1
‡Last regimen prior to start of treatment with AZD9291
EGFR, epidermal growth factor receptor; TKI, tyrosine kinase receptor; WHO, World Health Organization

Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress

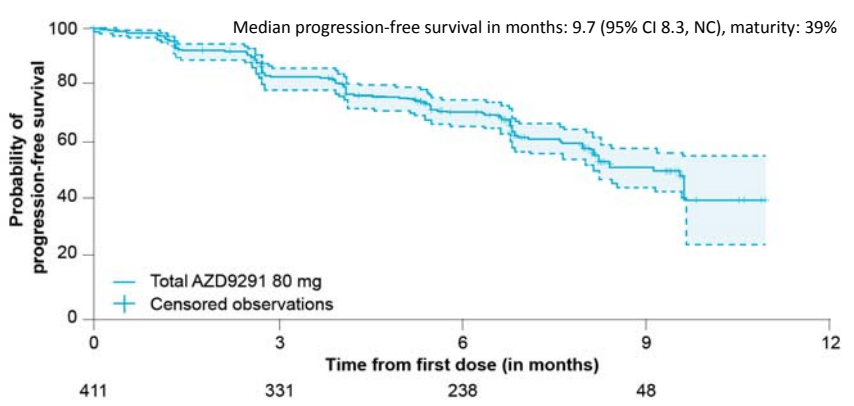
Response rate



By blinded independent central review. Evaluable for response analysis set (n=398). Mean best percentage change in target lesion size -45%, standard deviation 28.0 (median best percentage change -47.6%; range: -100% to +90.8%)

Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress

Progression-free survival



By blinded independent central review. Patients with confirmed objective response (n=263), maturity 23%. Blue dotted lines represent 95% CI
CI, confidence interval; NC, not calculated

Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress

Most frequent adverse events (all-causality)

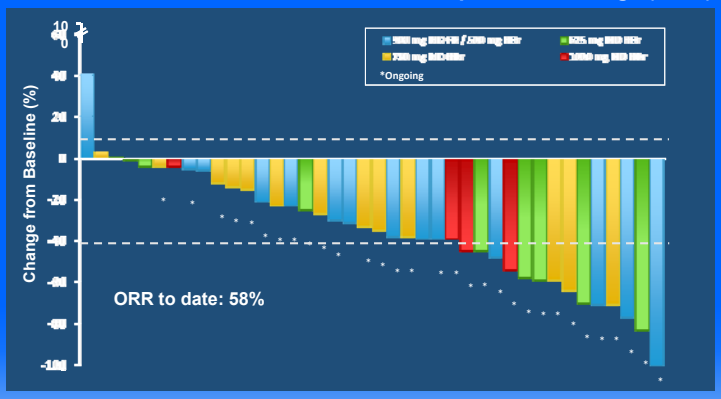
AE, number (%) of patients	Grade 1	Grade 2	≥Grade 3	Unknown	Total (n=411)
AE by preferred term occurring in ≥15% of patients overall					
Diarrhea	147 (36)	21 (5)	4 (1)	2 (1)	174 (42)
Rashes and acnes (grouped terms)	149 (36)	18 (4)	2 (1)	1 (0)	170 (41)
Dry skin	88 (21)	7 (2)	0	0	95 (23)
Paronychia	52 (13)	20 (5)	0	0	72 (18)
Nausea	58 (14)	9 (2)	2 (1)	0	69 (17)
Decreased appetite	49 (12)	13 (3)	3 (1)	0	65 (16)
Constipation	50 (12)	8 (2)	1 (0)	3 (1)	62 (15)
Select AEs of interest					
ILD and pneumonitis	4 (1)	0	7 (2)	0	11 (3)
Hyperglycemia	3 (1)	1 (0)	1 (0)	0	5 (1)
QT prolongation	9 (2)	3 (1)	5 (1)	0	17 (4)

AE, adverse event; ILD, interstitial lung disease

Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress

Rociletinib (CO-1686): Best response in Phase 1 and early Phase 2 expansion cohort patients

Centrally confirmed T790M+ patients within therapeutic dose range (N=40)



Sequist et al., ASCO 2014; NEJM 372:1700-1709 (2015)

Adverse events

Treatment-related adverse events* occurring in >10% of CO-1686 patients (N=72) treated at efficacious doses, % (n)

Preferred term	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	19 (14)	14 (10)	1 (1)	0
Hyperglycemia and IGT	19 (14)	11 (8)	22 (16)	0
Diarrhea	19 (14)	4 (3)	0	0
Vomiting	13 (9)	1 (1)	3 (2)	0
Decreased appetite	10 (7)	10 (7)	1 (1)	0
Myalgia	10 (7)	1 (1)	0	0
QTc prolonged	4 (3)	4 (3)	7 (5)	0

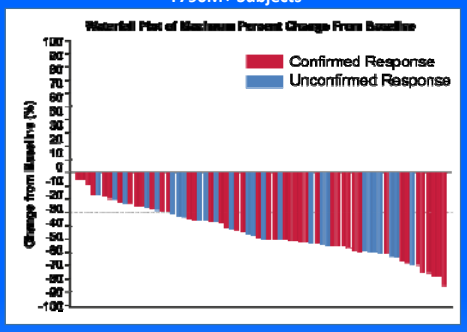
*excluding malignancy-related adverse events (eg, disease progression)

4% (3) patients with any form of rash, all Grade 1

Sequist et al., ASCO 2014

ASP8273: Preliminary Results: Phase 1/2 Study in Asian Subjects (Phase 2 Part)

Best Change (%) from Baseline of Target Lesions in T790M+ Subjects[a]



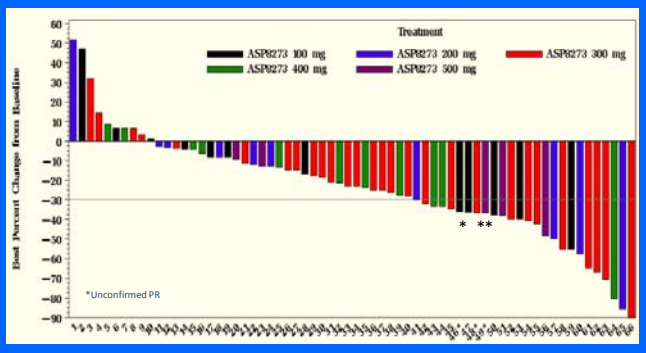
Preliminary ORR:

- 64% (n=45/70)
- Both confirmed and unconfirmed responses
- Investigator assessment

[a] Investigator assessment of target lesion changes only
‡ Indicates unconfirmed response in target lesions, but ORR is progressive disease based on new or non-target lesions
* Subject was withdrawn from the study with unconfirmed stable disease in target lesions;

Azuma K., Nokihara H., Murakami H., et al: Japanese Lung Cancer Society Meeting Nov 2015

ASP8273 Preliminary Results: US Phase 1 Study



Antitumor activity has been observed at doses of ≥ 100 mg:
ORR: 36.8% (25/68)

- T790M+: 40.9% (18/44)
- 50% (1/2) exon 20 insertion

Yu H., Oxnard G., Spira A., et al. AACR-EORTC-NCI Meeting Nov 2015 Boston

Preliminary Results: US Phase 1 Study Treatment Emergent AE's (> 10%)

- 95 patients received a dose of ASP8273 (25 – 500mg)
- Table reflects doses which will be utilized in future studies and events which occurred in at least 10% of pts

Treatment-Emergent Adverse Events Occurring in ≥10% of the Total Population, n (%)		100 mg (n=12)	200 mg (n=12)	300 mg* (n=48)	Total (N=72)
Diarrhea	Overall	1 (8)	2 (17)	17 (35)	20 (28)
	Grade ≥3	0	0	1 (2)	1 (1.4)
Nausea	Overall	3 (25)	4 (33)	10 (21)	17 (24)
	Grade ≥3	1 (8)	0	0	1 (1.4)
Fatigue	Overall	3 (25)	2 (17)	6 (13)	11 (15)
	Grade ≥3	0	0	0	0
Constipation	Overall	2 (17)	3 (25)	6 (13)	11 (15)
	Grade ≥3	0	0	0	0
Hyponatremia	Overall	2 (17)	2(17)	6 (13)	10 (14)
	Grade ≥3	2 (17)	1 (8)	4 (8)	7 (10)
Vomiting	Overall	1 (8)	3 (25)	7 (15)	11 (15)
	Grade ≥3	1 (8)	0	0	1 (1.4)
Dizziness	Overall	1 (8)	3 (25)	7 (15)	11 (15)
	Grade ≥3	0	0	1 (2)	1 (1.4)
Paraesthesia	Overall	0	1 (8)	5 (10)	10 (11)
	Grade ≥3	0	0	0	0
Cough	Overall	1 (8)	3(25)	3 (6)	7 (10)
	Grade ≥3	0	0	0	0

Yu H., Oxnard G., Spira A., et al. AACR-EORTC-NCI Meeting Nov 2015 Boston, modified

Lux Lung 1

- Randomized Phase II/III comparing afatinib to placebo in patients who had progressed following at least 12 weeks of gefitinib or erlotinib (EGFR mutation not required)
- RR was 7% for afatinib vs. 1% for placebo
- 141 patients had tumors available for molecular testing
  - 96 patients: sensitizing EGFR mutation positive, 76 (79%) had common mutations,
  - Median PFS was 3.3 months for afatinib vs. 1.1 months placebo (HR 0.38; $p < 0.0001$) in patients with sensitizing EGFR mutation positive NSCLC
  - Median PFS was 1.8 months for both afatinib and placebo in patients negative for sensitizing EGFR mutations
- Median overall survival was 10.3 months for afatinib vs. 12.0 months for placebo (HR 1.08; $p = 0.74$)

Miller et al., Lancet Oncology 5:528 (2012)

Phase Ib Study: Afatinib+ Cetuximab

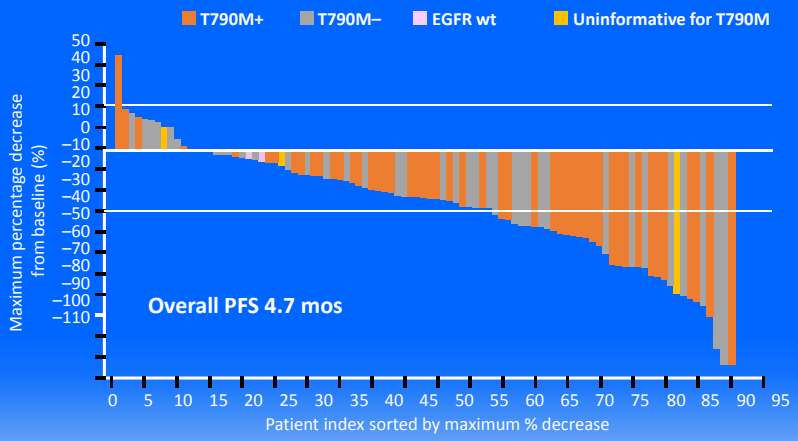
- Phase Ib, open-label, multicenter trial in the US and The Netherlands
- Primary endpoints: RECIST 1.1 Response and PFS, with imaging at Week 4, 8, 12, and every 8 weeks thereafter
- Key eligibility criteria:

Inclusion	Exclusion
Pathologically confirmed NSCLC	Prior treatment with EGFR targeting antibodies
Presence of EGFR drug-sensitizing mutations or RECIST response, or SD ≥6 months on prior EGFR TKI	Symptomatic brain metastases or disease progression only in CNS
Gefitinib/erlotinib as last systemic treatment	
Disease progression on treatment with erlotinib or gefitinib within 30 days	
Biopsy (available) at time of acquired resistance	
ECOG PS 0–2	

SD = stable disease; i.v. = intravenous; RECIST = Response Evaluation Criteria in Solid Tumors .

Janjigian et a., Cancer Discover 2014

Afatinib + Cetuximab at MTD: Responses by T790M mutation

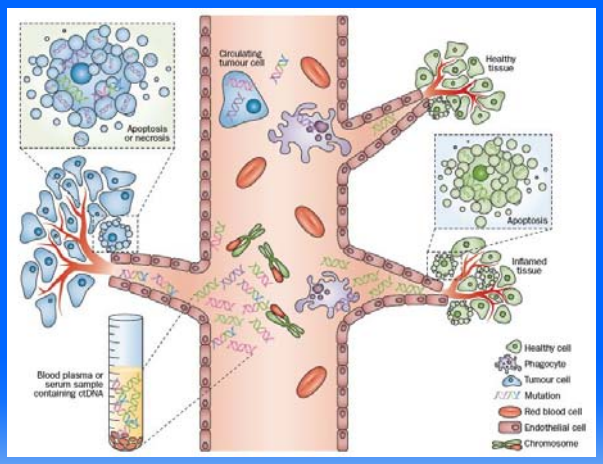


Janjigian et a., Cancer Discover 2014

Most Frequent Adverse Events

Adverse event	n=61	
	Grade ≥3 n (%)	All Grades n (%)
Rash	5 (8)	53 (87)
Diarrhea	3 (5)	40 (66)
Xerosis	1 (2)	34 (56)
Fatigue	2 (3)	31 (51)
Skin fissures		29 (48)
Nausea		27 (44)
Headache	2 (3)	25 (41)
Paronychia	1 (2)	18 (30)
Vomiting	1 (2)	18 (30)

Blood-Based Testing (cfDNA) in detection of biomarkers



Crowley E et al. Nat Rev Clin Oncol. 2013;10(8):472-84.

Blood-Based Testing in TIGER-X Trial: Sensitivity and Specificity of cfDNA Analysis

Plasma Testing for T790M has Good Sensitivity and Likely Good Specificity

		Tissue*			Total
		Positive	Negative	Inadequate tissue	
Plasma*	Positive	155	23	12	190
	Negative	37	12	8	57
Total		192	35	20	247

*patients at all doses

- When inadequate tissue specimens are factored in, plasma testing identifies as many patients as T790M+ as tissue testing
- T790M tissue⁻plasma⁺ are not false positives – T790M confirmed in plasma on subsequent testing in 5/7 samples

Tissue as reference:	T790M	Activating mutations
Positive percent agreement	81% (155/192)	87% (193/221)

Reference: Sequist, L. ASCO Annual Meeting, 2015.

Blood-Based Testing in TIGER-X: ORR by Tumor or cfDNA Analysis

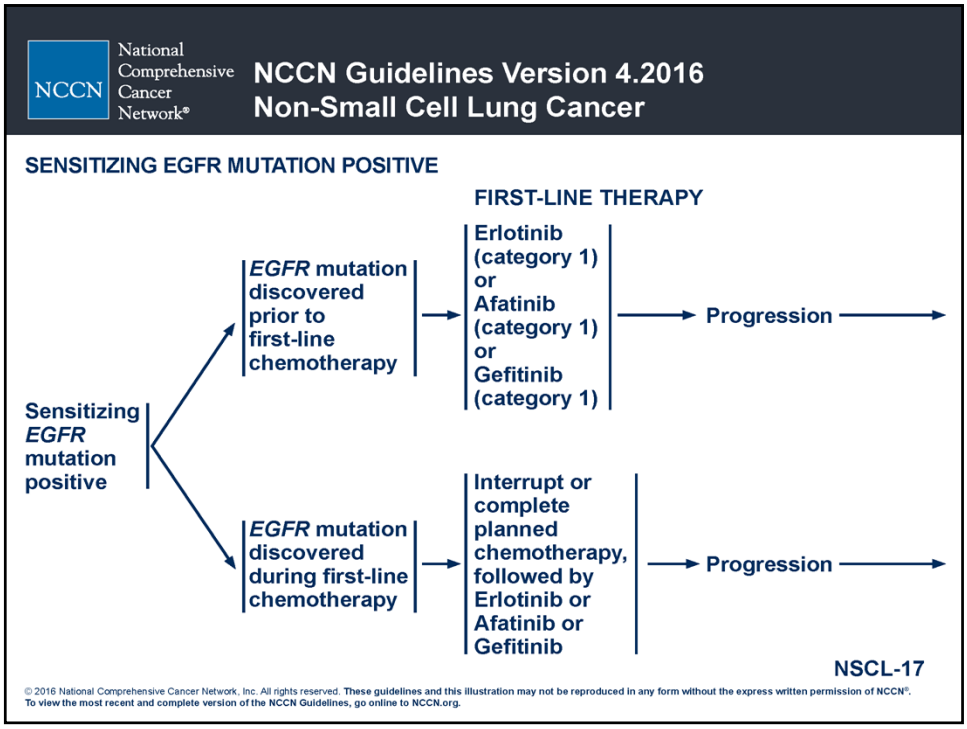
T790M Plasma Testing is a Viable Alternative to Tissue Testing

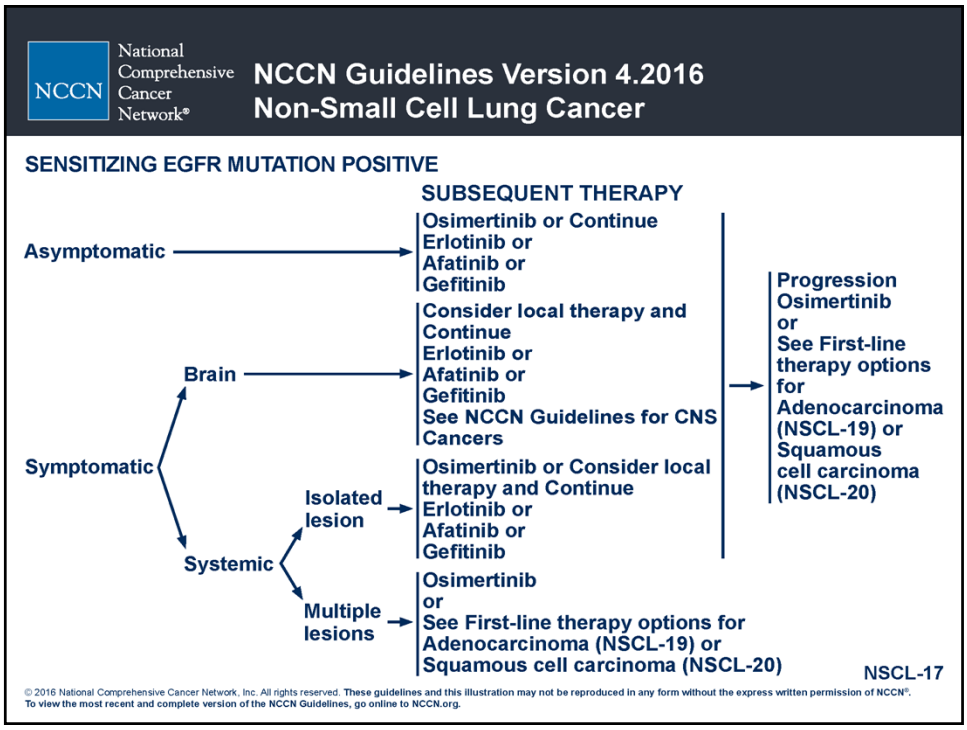
Objective response rate for 188 evaluable patients with both central T790M tissue test result and plasma T790M result

		Plasma T790M		
		+	-	
Tissue T790M	+	55% (72/130)	43% (13/30)	53% (85/160)
	-	35% (6/17)	27% (3/11)	32% (9/28)
		53% (78/147)	39% (16/41)	

- Similar ORR observed when detecting T790M in either tissue or plasma
- Not all patients with progression on first-line TKI are candidates for tissue re-biopsy

Sequist, L. ASCO Annual Meeting, 2015.





Conclusions

- In patients with sensitizing EGFR mutation positive NSCLC who progress on a first or second generation EGFR TKI, the type of progression determines treatment option
- All patients should have a biopsy to evaluate for T790M prior to switching systemic therapy
- In patients where a tissue biopsy is not possible, a serum based test for T790M is reasonable
- Osimertinib is approved for patients who are T790M positive (with more agents on the way)