JADPRO CE Regional Education

From Inquiry to Investigation to Insight: Clinical Clarity in Non–Small Cell Lung Cancer

Managing *EGFR*+ Metastatic NSCLC

Program Chair

Beth Eaby-Sandy
MSN, CRNP
Abramson Cancer Center

Faculty

Tyler Beardslee, PharmD
Winship Cancer Institute at Emory University

Marianne Davies
DNP, ACNP, AOCNP®
Yale School of Nursing

Elizabeth Gilbert
MS, PA-C
Abramson Cancer Center

Rasheda Persinger, NP-C
Johns Hopkins Sidney Kimmel Cancer Center

Faculty Financial Disclosures

- **Ms. Eaby-Sandy** has served as a consultant and on speakers bureaus for AstraZeneca, Helsinn, Merck, and Takeda.
- **Dr. Beardslee** has served as a consultant for AstraZeneca and Herron, and on the speakers bureau for AstraZeneca.
- **Dr. Davies** has served on speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Genentech, and Merck.
- **Ms. Gilbert** has no conflicts of interest to disclose.
- **Ms. Persinger** has served on speakers bureaus for Genentech and Guardant Health, and on the advisory board for AstraZeneca.

Planning Committee Financial Disclosures

- Elizabeth Waxman, RN, MSN, AOCN®, ANP-BC, has nothing to disclose.
- Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has nothing to disclose.
- Activity reviewers and the staff of the Annenberg Center for Health Sciences at Eisenhower and Harborside Medical Education have nothing to disclose.

This activity is supported, in part, by educational grants from AstraZeneca, Bristol-Myers Squibb Company and Lilly.
For further information concerning Lilly grant funding, visit www.lillygrantoffice.com.

Learning Objective

- Evaluate efficacy and safety data supporting the use of targeted and immune checkpoint inhibitor therapy used to treat NSCLC

Audience Response Question

Which *EGFR* mutation is not usually sensitive to EGFR inhibitors?

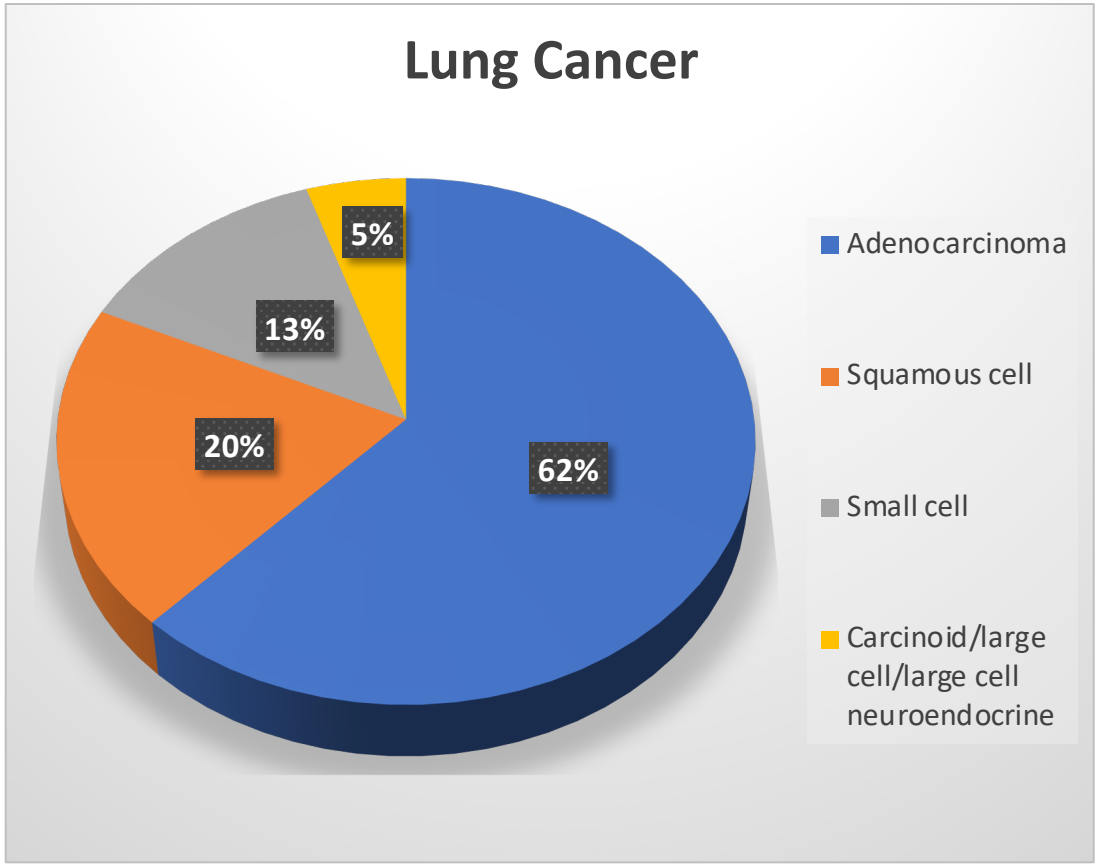
A. Exon 19 deletion
B. L858R
C. G719X
D. Exon 20 insertion
E. Unsure

Audience Response Question

For a patient needing treatment for an *EGFR*+ tumor, which would you choose based on its designation as the NCCN Guidelines' preferred first-line agent?

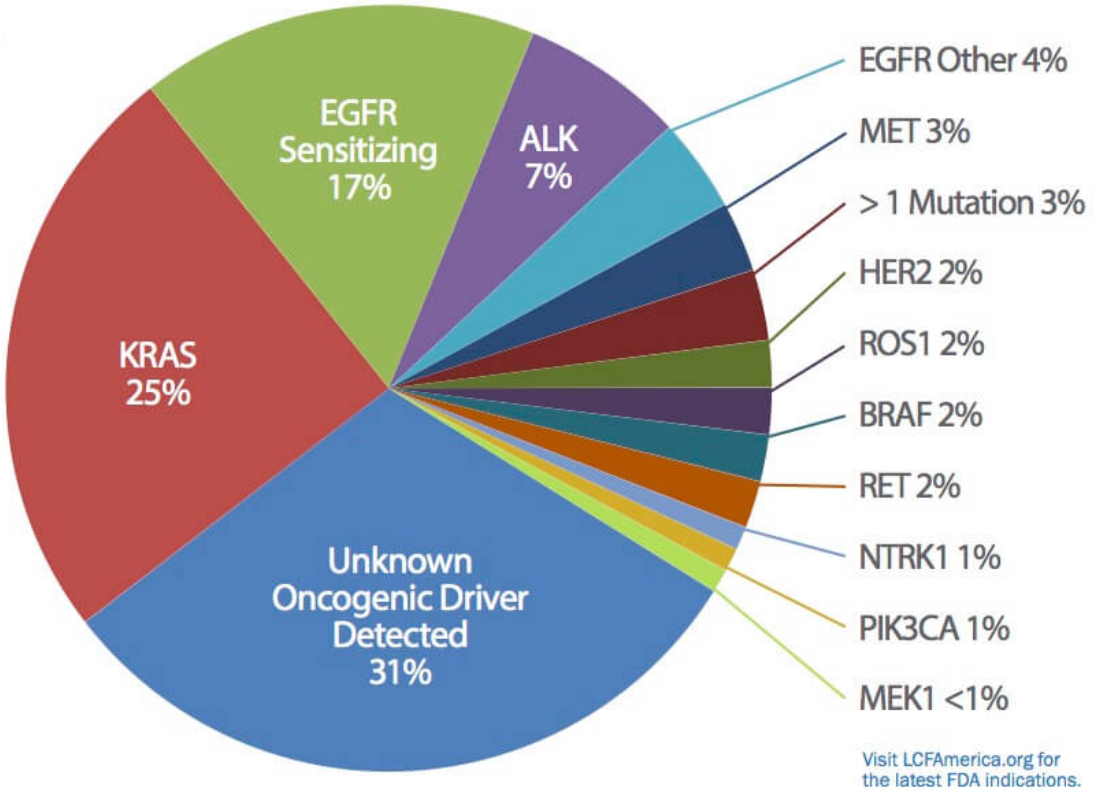
A. Afatinib
B. Erlotinib
C. Osimertinib
D. None; they are all FDA approved for first-line *EGFR*+ NSCLC
E. Unsure

EGFR in NSCLC



- Overwhelming majority of *EGFR* mutations found in adenocarcinoma type of NSCLC
- Rare in squamous but they can happen
- Also rare to have 2 different mutations (usually mutually exclusive)

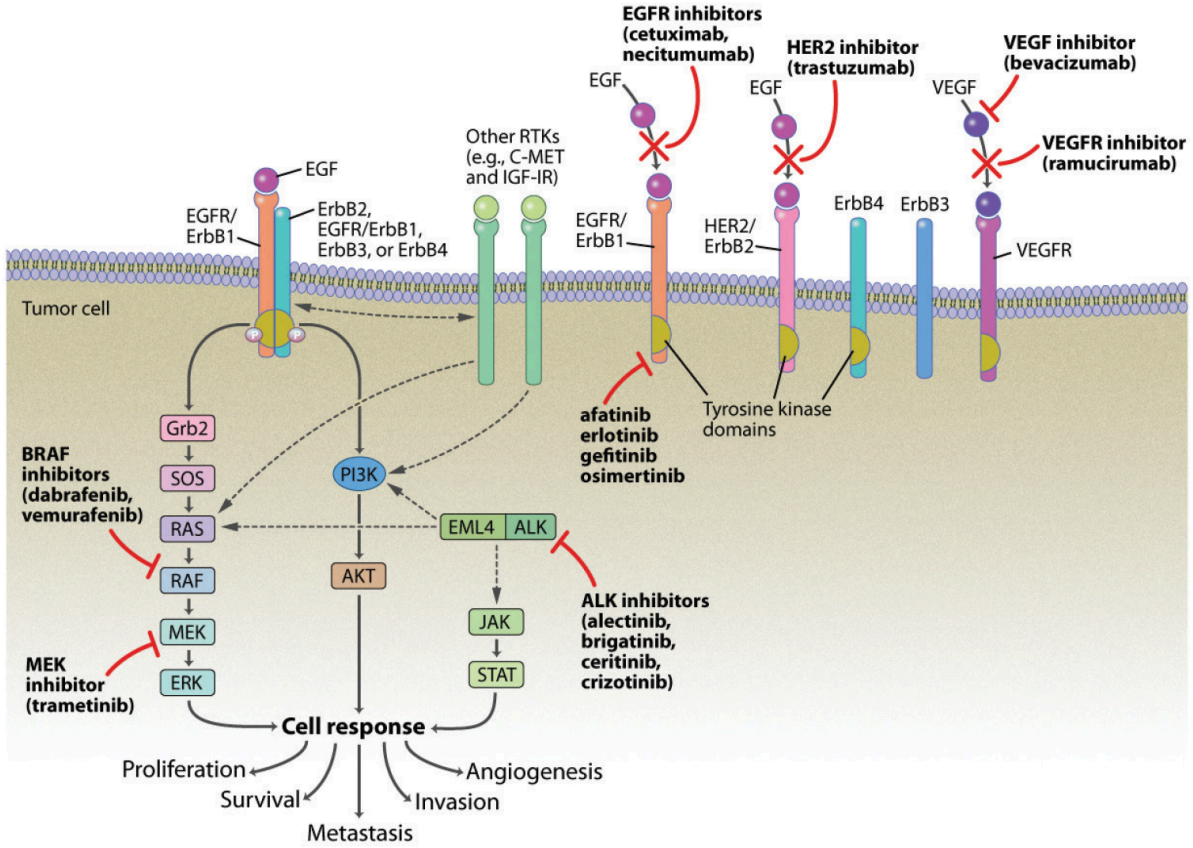
Sensitizing Mutations in NSCLC



Retrieved from https://lcfamerica.org/research-grants/therapies/available-targeted-therapies

Epidermal Growth Factor-Induced Signal Transduction and Tumorigenesis

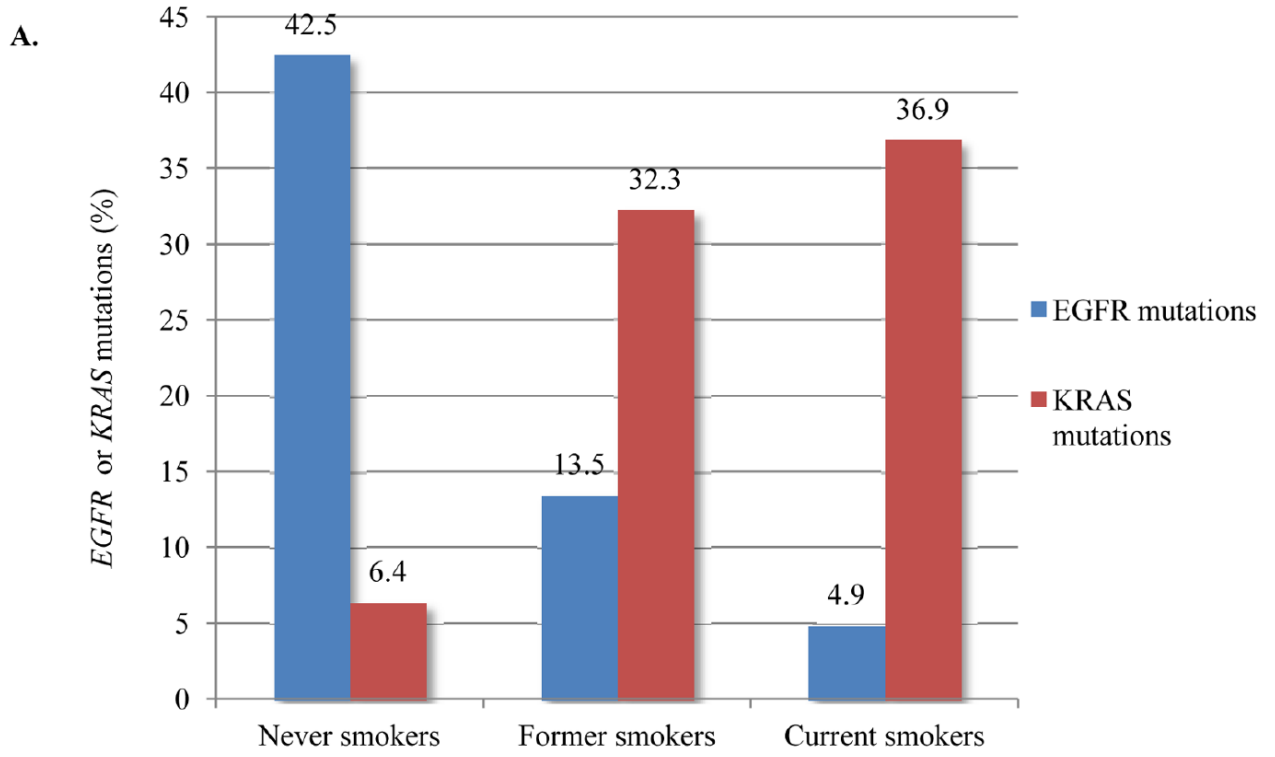
- Epidermal growth factor receptor (EGFR) is a tyrosine kinase growth factor receptor
- Activated by binding of natural ligands
  - TGF-α
  - EGF
- Activation of EGFR linked with
  - Increased cell proliferation
  - Angiogenesis
  - Metastasis
- EGFR expression correlates with
  - Poor response to treatment
  - Disease progression
  - Poor survival



1. Tanaka T, et al. *Int J Cancer*. 2010;126:651-655.
2. Ha SY, et al. *Oncotarget*. 2015;6:5465-5474.

Epidemiology of *EGFR*-mutated NSCLC

- *EGFR* mutations most common in
  - Females
  - Never/minimal smokers
  - Asian ethnicity
- Study of 3,026 lung adenocarcinomas
  - EGFR found in 43% of never smokers and 11% of smokers.

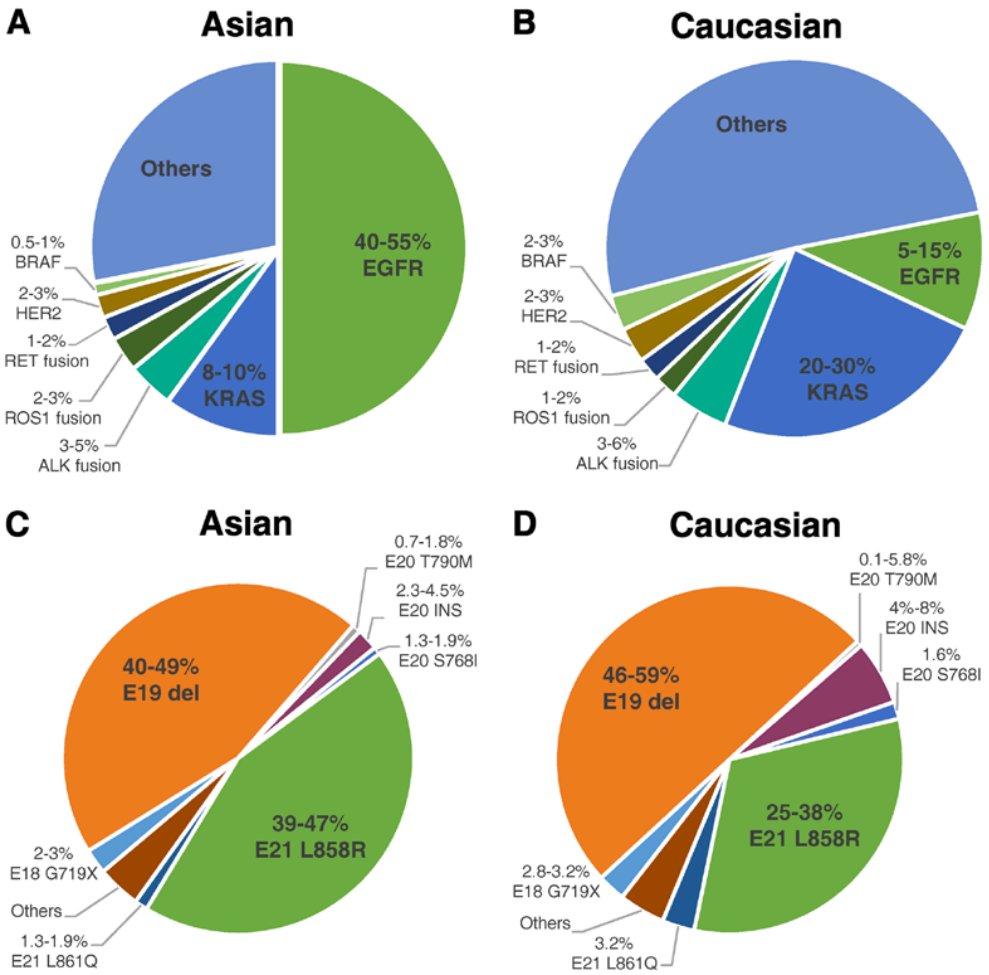


Former smoker defined as quit > 1 year ago

Tsao AS, Tang XM, Sabloff B, et al. Clinicopathologic characteristics of the EGFR gene mutation in non-small cell lung cancer. *J Thorac Oncol.* 2006;1:231-239.
Dogan S. et al. *Clin Cancer Res*. 2012 November 15; 18(22): 6169–6177. doi:10.1158/1078-0432.CCR-11-3265.

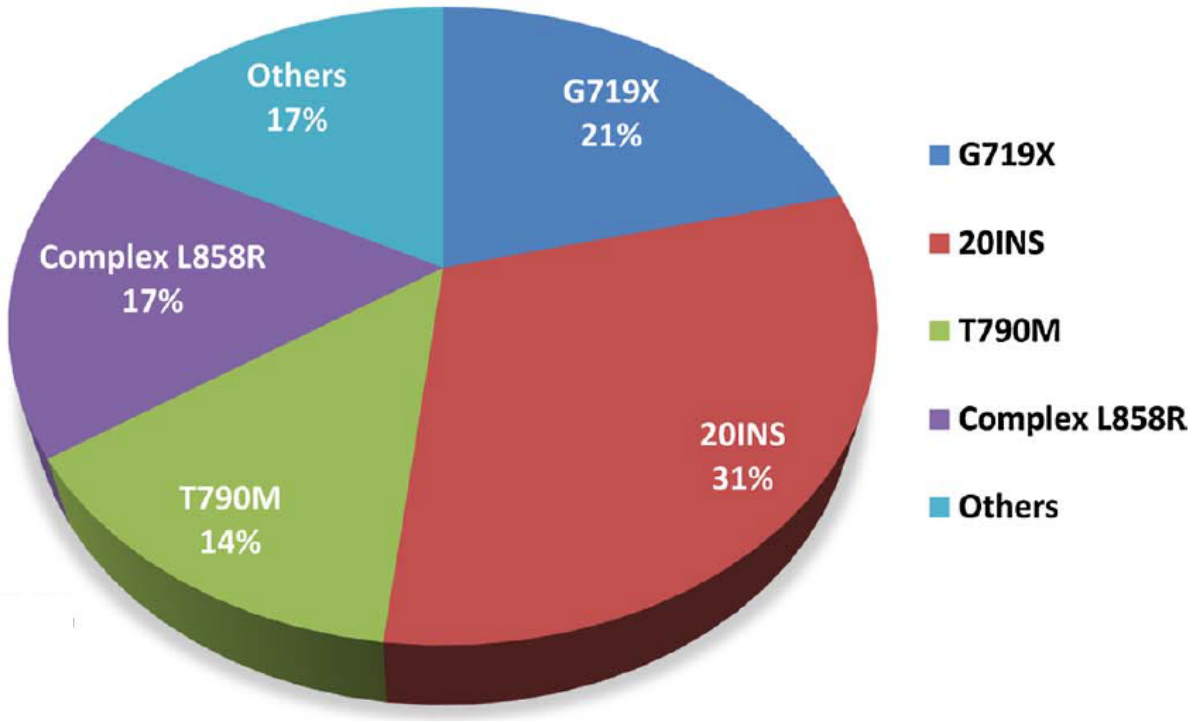
Mutation Frequency and Distribution in Asian and Caucasian Populations

- Graphs A and B: Mutations in Caucasians vs. Asians
- Graphs C and D: *EGFR* in both populations



Kaidi Li, Maojun Yang , Naixin Liang, and Shanqing Li. Determining EGFR-TKI sensitivity of G719X and other uncommon EGFR mutations in non-small cell lung cancer: Perplexity and solution (Review). ONCOLOGY REPORTS 37: 1347-1358, 2017

Uncommon *EGFR* Mutations



- 2 most common types
  - Exon 19 deletion mutation
  - Exon 21 (L858R) point mutation
- Uncommon *EGFR* mutations
  - Insertion 20 usually not sensitive to EGFR therapy
  - Some sensitive, some not, some similar to chemotherapy response rates

Hai-Yan T, et al. Lung Cancer. 144; 2017

How Do We Test for EGFR Mutations?

Tissue

- DNA Sequencing panel (NGS)
- Not an “expression”
- Not found on IHC or FISH
- Takes time due to NGS sequencing
- Not 100% sensitive—why?

Blood

- Can be detected on blood test that performs molecular profiling
- Quicker result that DNA sequencing panel
- Not 100% sensitive–why?

Who Do We Test for EGFR Mutations?

- You can never treat with an EGFR inhibitor if you never find the *EGFR* mutation!
- NCCN Guidelines
  - All patients with nonsquamous metastatic NSCLC (adenocarcinoma)
  - In squamous patients: Consider testing for *EGFR* in patients who exhibit clinical features: ie, never smokers

Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf; Version 4.2019

EGFR TKIs in NSCLC

Agent	Method of administration	Indication in NSCLC	Dose
Gefitinib	Oral	First line: EGFR exon 19 and exon 21 mutation+	250 mg daily (with or without food)
Erlotinib	Oral	First line: EGFR exon 19 and exon 21 mutation+	150 mg daily (empty stomach)
Afatinib	Oral	First line: EGFR exon 19 and exon 21 mutation+ As well as several uncommon *EGFR* mutations Second line: for squamous NSCLC	40 mg daily (empty stomach)
Osimertinib	Oral	First line: EGFR exon 19 and exon 21 mutation+ Second line: T790M + after progression on EGFR TKI therapy	80 mg daily (with or without food)
Dacomitinib	Oral	First line: EGFR exon 19 and exon 21 mutation+	45 mg daily (with or without food)

EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; NSCLC = non–small cell lung cancer; Data from package inserts 2019.

Gefitinib

- First drug on market approved around 2004 for metastatic NSCLC, second line (we were still trying to figure out what *EGFR* was at that time)
- Pulled from market due to futility over chemotherapy in general population
- Re-approved in the US many years later for only *EGFR*-mutated patients
- Was found to be inferior to afatinib in a head-to-head first-line study
- Causes less rash than most EGFR inhibitors

Park K, et al. *The Lancet Oncology.* 17 (5);2016.

Erlotinib

- Second EGFR inhibitor approved, initially similar to gefitinib in second-line setting of all metastatic NSCLC
- Once we figured out *EGFR* mutations, it was only approved in this setting where it was clearly superior to chemotherapy
- Caused more rash than gefitinib; however, was the mainstay of EGFR first-line therapy for years

Afatinib

- Third EGFR inhibitor approved
- Causes significantly more rash/diarrhea than either of its predecessors
- Superior to gefitinib in head-to-head studies
- Has niche approval in
  - Second-line squamous
  - First line for uncommon *EGFR* mutations
    - L861Q
    - G719X
    - S768I

Park K, et al. *The Lancet Oncology.* 17 (5);2016.

Osimertinib

- Fourth EGFR inhibitor to be approved
- Initially for T790M resistance mutation + in the second-line setting
- However, after FLAURA trial, now the “preferred” first-line treatment for *EGFR*-mutated NSCLC per NCCN guidelines.
  - FLAURA: significant improvement in PFS over either gefitinib or erlotinib in first-line setting
- Also causes less rash than prior EGFR inhibitors

Soria JC, et al. *N Engl J Med*. 2018;378:113-25.

Dacomitinib

- Fifth EGFR inhibitor approved, in 2018
- Is more toxic that most EGFR inhibitors, high rate of rash
- Head-to-head was superior to gefitinib in first-line setting for overall survival, with a median OS of 34.1 months vs. 26.8 months

Mok TS, et al. J Clin Oncol 36:2244-2250.

Which Drug to Use in First-Line Setting of Metastatic *EGFR*-Mutated NSCLC?

LUX-Lung 3, EURTAC, IPASS: PFS and ORR
First-Line Reversible EGFR TKI in EGFR M+ NSCLC

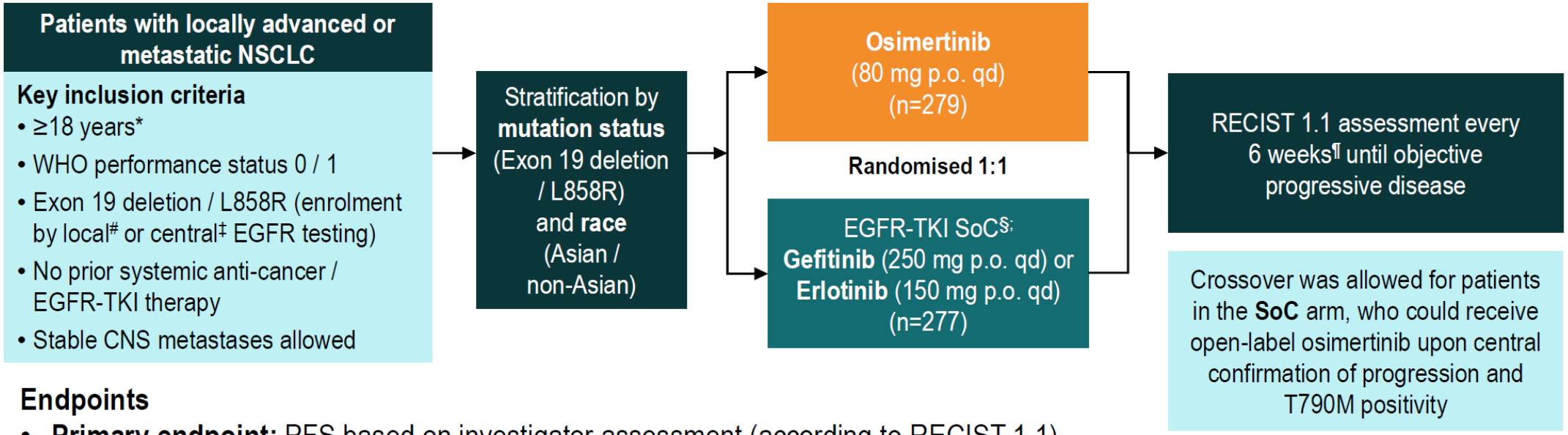
Trial	CT	Mutations	ORR	PFS	Hazard ratio (95% CI)	Primary endpoint assessment
LUX-Lung 3[1] Afatinib N = 345	Pem/Cis x 6	EGFR Del19/L858R (89%)	56 vs. 23 61 vs. 22	11.1 vs. 6.9 13.6 vs. 6.9	0.58 (0.43, 0.78) 0.47 (0.34, 0.65)	Independent
		EGFR	69 vs. 44	11.1 vs. 6.7	0.49 (0.37, 0.65)	Investigator
EURTAC[2,3] Erlotinib N = 173	Cis (Carbo) + Doc/Gem x 4	Del19/L858R (100%)	–	10.4 vs. 5.4	0.47 (0.28, 0.78)	Independent
		Del19/L858R (100%)	58 vs. 15	9.7 vs. 5.2	0.37 (0.25, 0.54)	Investigator
IPASS[4] Gefitinib N = 1,217	Carbo/Paclitaxel x 6	EGFR Del19/L858R (96%)	71 vs. 47 NR	9.5 vs. 6.3 NR	0.48 (0.36, 0.64) NR	Investigator

Carbo = carboplatin; Cis = cisplatin; CT = chemotherapy; Doc = docetaxel; EGFR = epidermal growth factor receptor; Gem = gemcitabine; NR = not reported; NSCLC = non-small cell lung cancer; ORR = objective response rate; Pem = pemetrexed; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

1. Yang JC, et al. *Lancet Oncol*. 2015;16(2):141-151; 2. Rosell R, et al. *Lancet Oncol* 2012;13:239–246; 3. EU CHMP Variation Assessment Report, Tarceva, July 21 2011; 4. Mok T, et al. *N Engl J Med.* 2009;361:947–957.

First-line Osimertinib Trial vs. Gefitinib

FLAURA DOUBLE-BLIND STUDY DESIGN

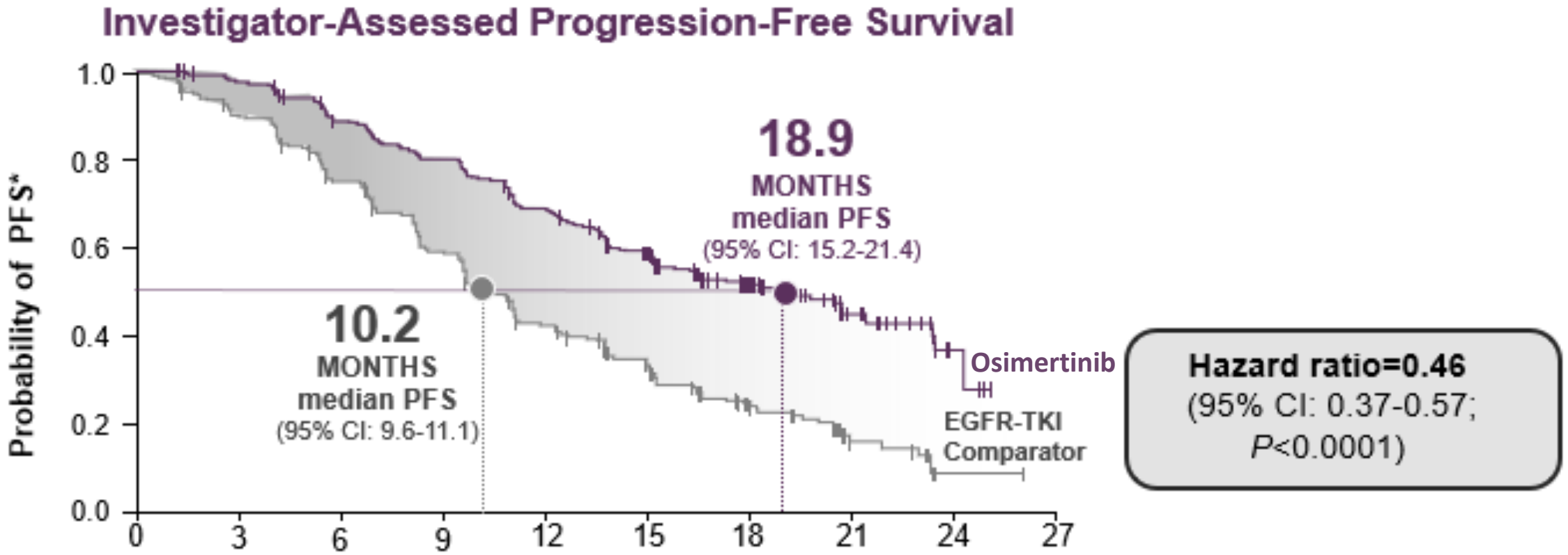


Endpoints

- **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 an improvement in median PFS from 10 months to 14.1 months) 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

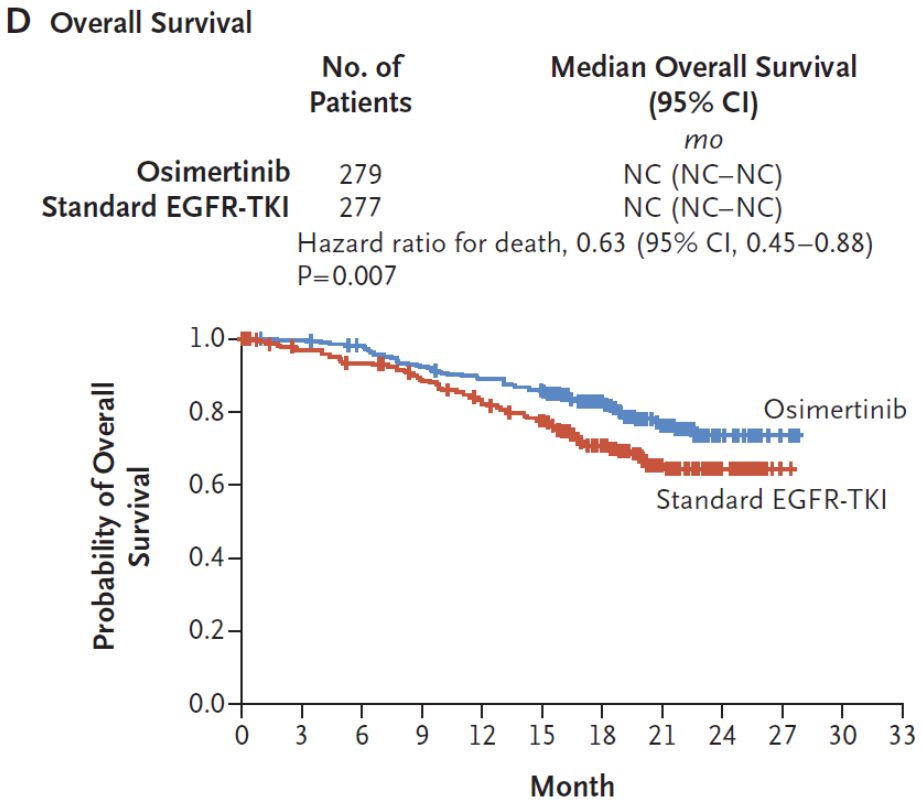
Slide adapted from 2017 ESMO Congress in Madrid, Spain, presented by S.S. Ramalingam

FLAURA: First-Line Osimertinib vs. Erlotinib or Gefitinib



Soria JC, et al. *N Engl J Med*. 2018;378:113-25.

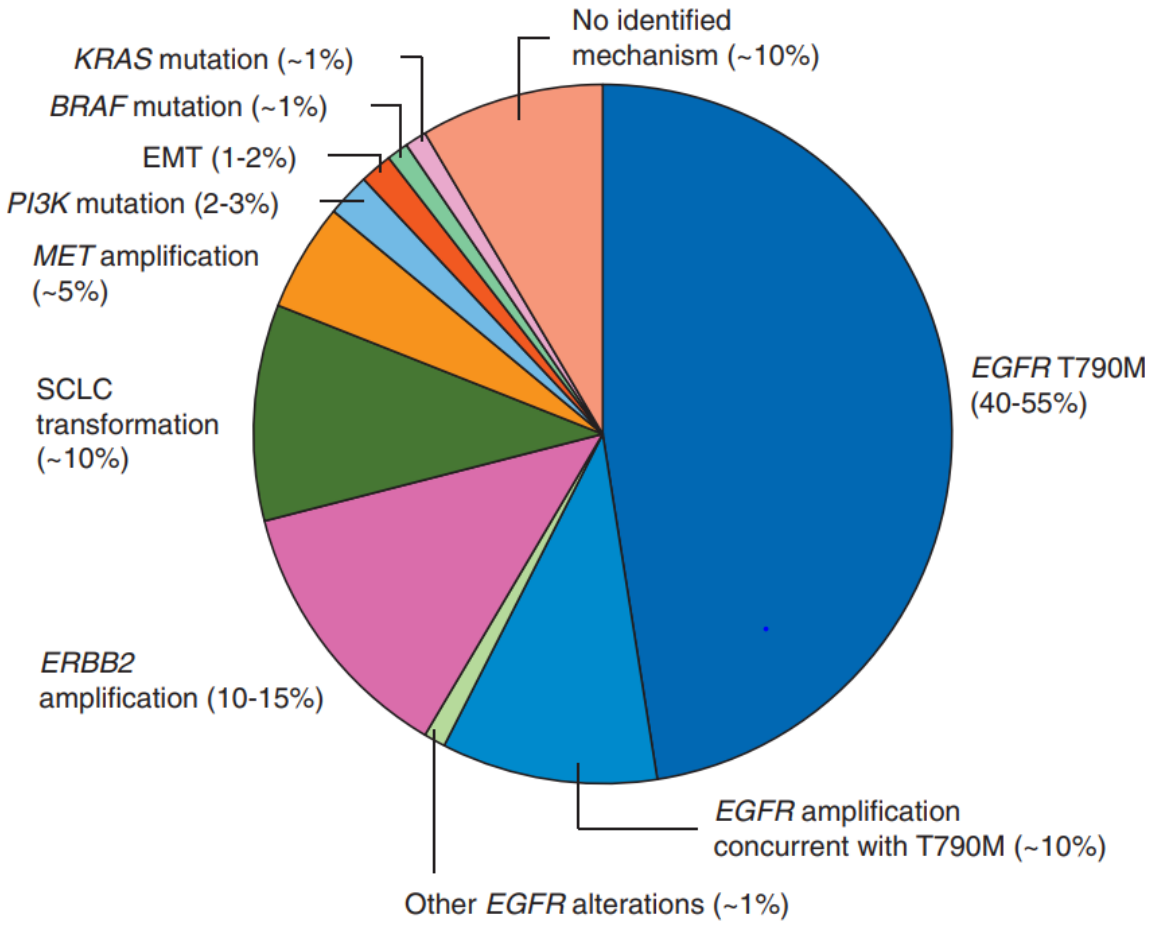
FLAURA Overall Survival Data: Not Reached, But Apparently Has Been Reached and Will Be Presented in Late 2019—Stay Tuned!



Soria JC, et al. *N Engl J Med*. 2018;378:113-25.

Mechanisms of Acquired Resistance to EGFR

- Multiple possibilities
- Many can be detected on blood test
- Can/should also rebiopsy if possible
  - Blood will not detect small cell transformation
- Other than SCLC, other resistance mechanisms hard to manage outside of clinical trial
- C797S is common tertiary resistance mechanism to EGFR T790M

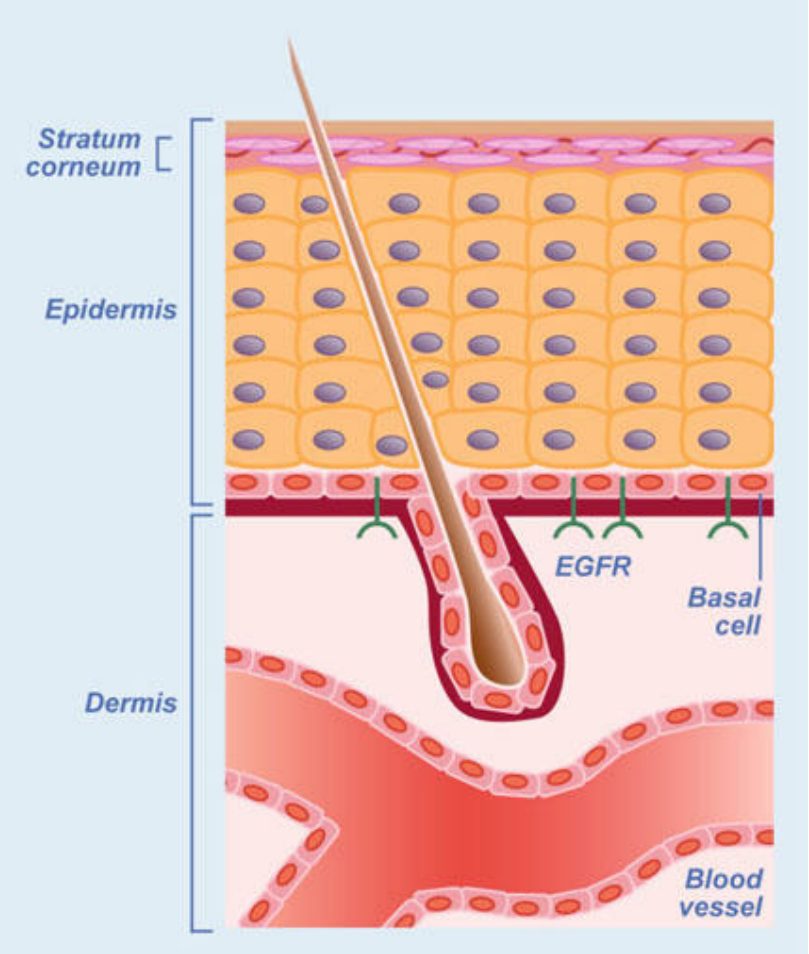


Westover D, et al. *Annals of Oncology* 29 (Supplement 1): i10–i19, 2018
Duffield, E. Mechanisms of Acquired Resistance to Targeted Therapy in NSCLC. Davies M, Eaby-Sandy B (Eds). Targeted Therapies in Lung Cancer: Management Strategis for Nurses and Practitioner.
Springer Publishing 2019.

Toxicities of EGFR Inhibitors

Why Does EGFR Inhibitor Rash Occur?

- The epidermis relies on EGF
- The keratinocytes located in the basal layers of the epidermis express elevated level of EGF
- Inhibition of EGF will result in negative effects on cell growth in this layer of the epidermis
- This results in thinning, which decreases ability of skin to hold in moisture
- The damage also causes recruitment of the immune system response and thus, a pustular eruption



Adapted from Lacouture, *Nat Rev Cancer*; 6:803-812.

Meta-Analysis on EGFR Rash and Clinical Benefit

- Liu and colleagues (2013) reviewed 33 studies of EGFR TKIs which reported rash and clinical benefit
- Rash was a significant predictor of clinical benefit for NSCLC patients receiving EGFR inhibitor therapy
- Rash predicted overall response rate, longer PFS, and longer OS

Liu et al, 2013. *PLOS One*. DOI:10.1371/journal.pone.0055128

Rash Incidence by Drug

EGFR inhibitor	Any grade rash	Grade 3/4 rash
Gefitinib	66%	3%
Erlotinib	85%	14%
Afatinib	89%	16%
Osimertinib	58%	1%
Dacomitinib	69%	23%

Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361:10.
Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012;13:239-246.
Sequist LV, Yang JC-H, Yamamoto N, et al. LUX-Lung 3: Phase III study of afatinib or cisplatin plus pemetrexed in patients EGFR mutations. *J Clin Oncol.* 2013;31:3327-3334.
Soria J-C, Ohe Y, vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-125.
* Dacomitinib package insert.

FLAURA Trial Adverse Events

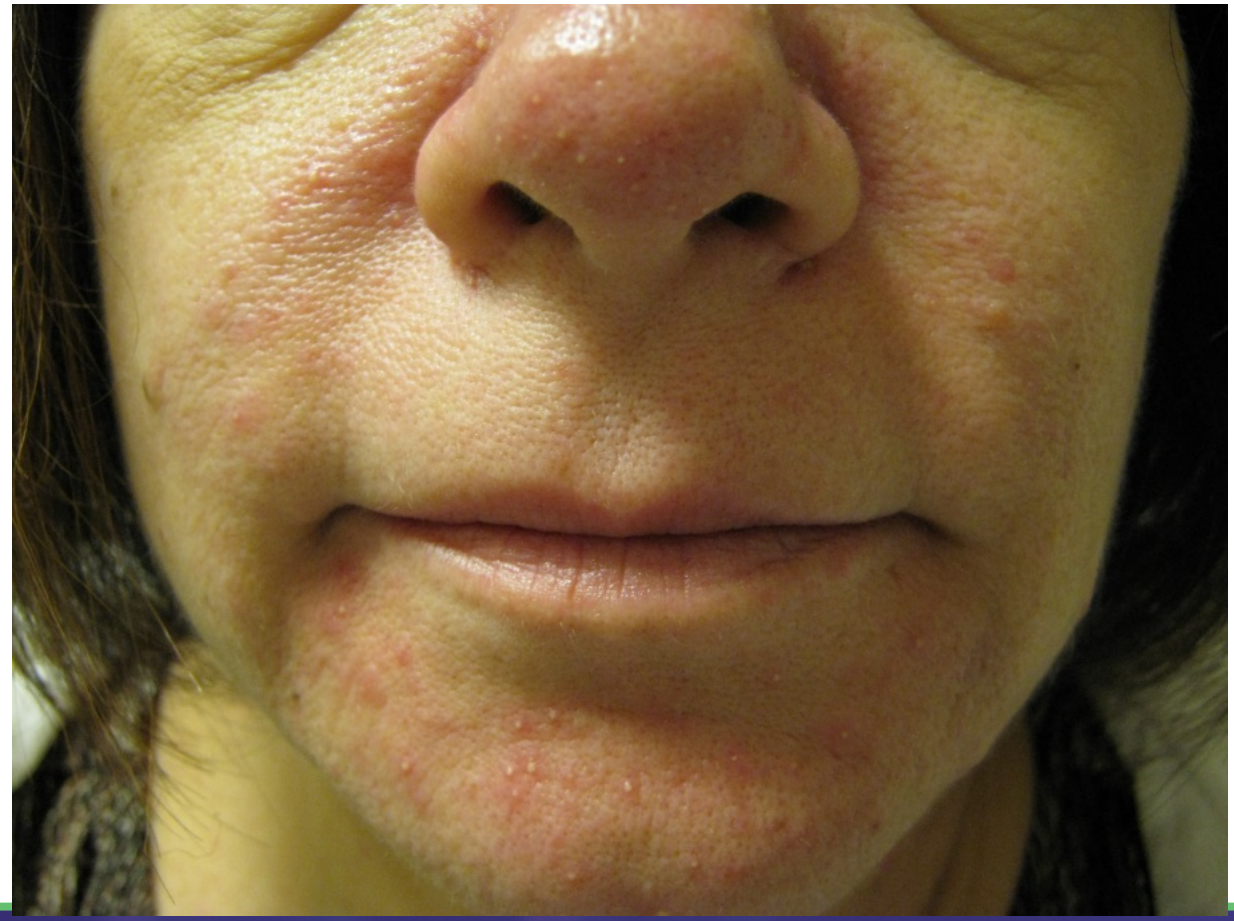
Median duration of exposure: osimertinib: 16.2 months (range 0.1 to 27.4), SoC: 11.5 months (range 0 to 26.2)

AEs by preferred term, n (%)	Osimertinib (n=279)					SoC (n=277)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	161 (58)	120 (43)	35 (13)	6 (2)	0	159 (57)*	116 (42)	35 (13)	6 (2)	0
Dry skin	88 (32)	76 (27)	11 (4)	1 (<1)	0	90 (32)	70 (25)	17 (6)	3 (1)	0
Paronychia	81 (29)	37 (13)	43 (15)	1 (<1)	0	80 (29)	46 (17)	32 (12)	2 (1)	0
Stomatitis	80 (29)	65 (23)	13 (5)	1 (<1)	1 (<1)	56 (20)	47 (17)	8 (3)	1 (<1)	0
Dermatitis acneiform	71 (25)	61 (22)	10 (4)	0	0	134 (48)	71 (26)	50 (18)	13 (5)	0
Decreased appetite	56 (20)	27 (10)	22 (8)	7 (3)	0	51 (18)	24 (9)	22 (8)	5 (2)	0
Pruritis	48 (17)	40 (14)	7 (3)	1 (<1)	0	43 (16)	30 (11)	13 (5)	0	0
Cough	46 (16)	34 (12)	12 (4)	0	0	42 (15)	25 (9)	16 (6)	1 (<1)	0
Constipation	42 (15)	33 (12)	9 (3)	0	0	35 (13)	28 (10)	7 (3)	0	0
AST increased	26 (9)	18 (6)	6 (2)	2 (1)	0	68 (25)	38 (14)	18 (6)	12 (4)	0
ALT increased	18 (6)	11 (4)	6 (2)	1 (<1)	0	75 (27)	31 (11)	19 (7)	21 (8)	4 (1)

Slide adapted from 2017 ESMO Congress in Madrid, Spain, presented by S.S. Ramalingam

Grade 2 EGFR Rash

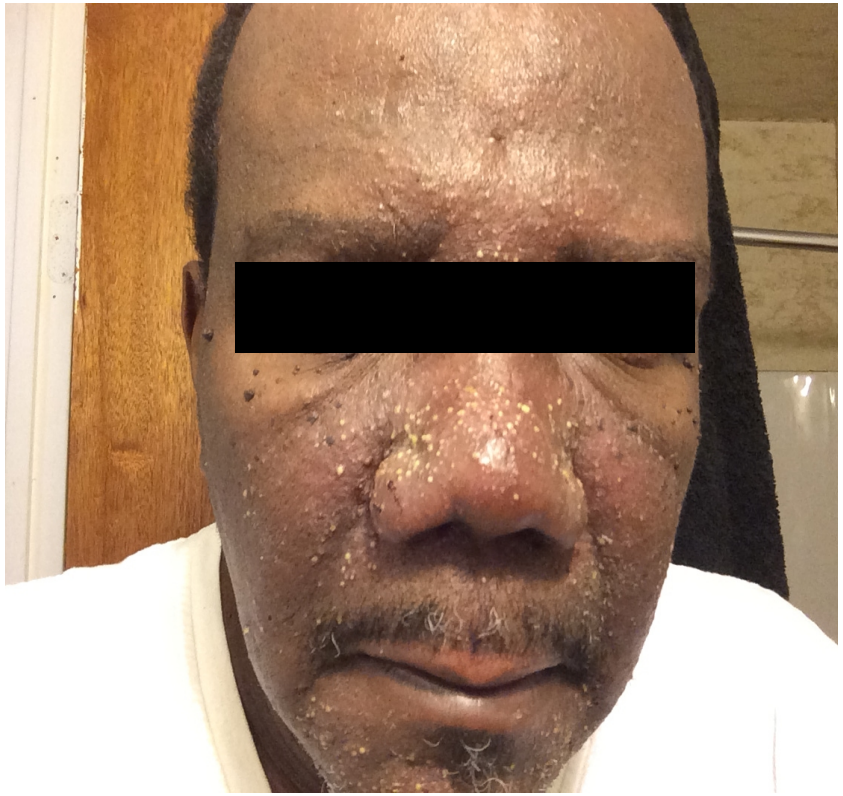
- Moisturize thick cream, no fragrances or dyes
- Topical either clindamycin gel or fluocinonide 0.05% cream
- May add oral doxycycline or minocycline
- Not recommended: vit K cream or acitretin

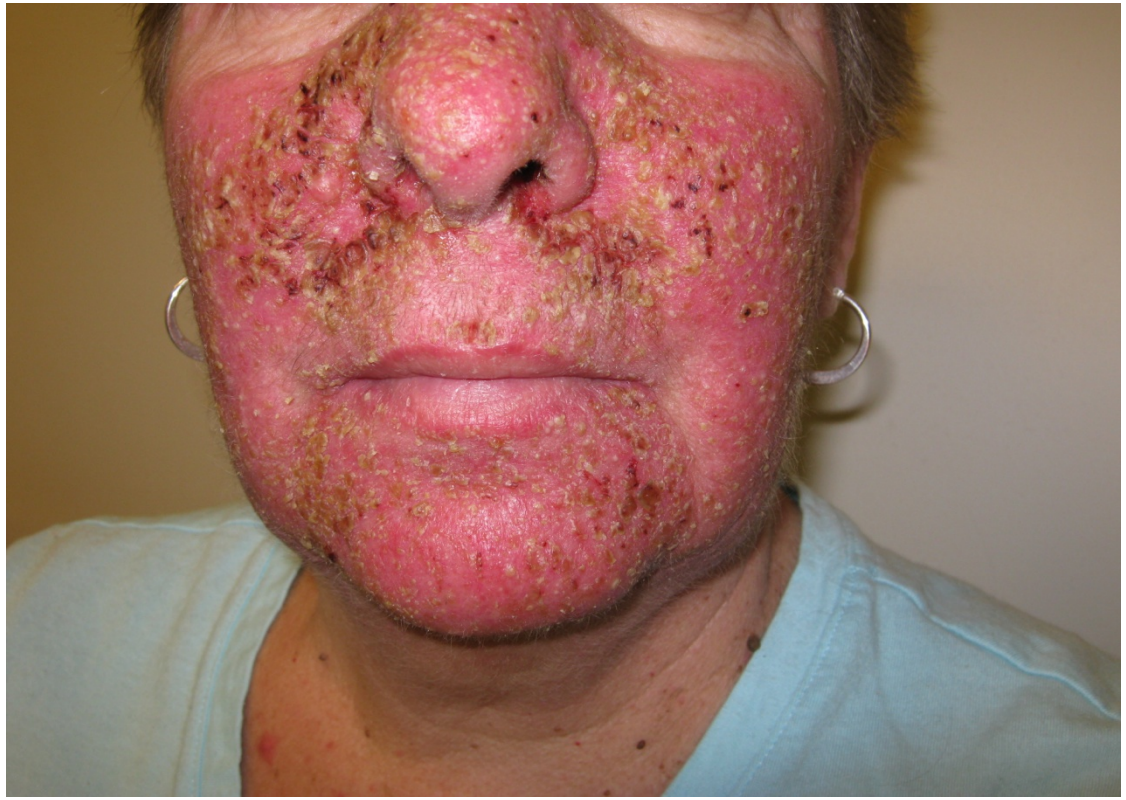


Lacouture ME, Anadkat MJ, Bensadoun R-J, et al. Clinical practice guidelines for the prevention and treatments of EGFR-inhibitor associated dermatologic toxicity. *Support Care Cancer* (2011) 19:1079–1095. DOI 10.1007/s00520-011-1197-6

Image courtesy of Beth Eaby-Sandy, Abramson Cancer Center, Hospital of the University of Pennsylvania

Examples of EGFR Grade 3/4 Rash





Images courtesy of Beth Eaby-Sandy, Abramson Cancer Center, Hospital of the University of Pennsylvania

For Grade 3 or 4 Rash

- Moisturize, sun protection, minimize exposure to heat/hot water
- Hold drug and likely dose reduce
- Topical clindamycin or higher potency steroid creams: alclometasone, fluocinonide, betamethasone
- Oral doxycycline 100 mg bid or minocycline 100 mg daily
  - Be aware of photosensitivity on these antibiotics
- Systemic steroids are not recommended in MASCC paper, however, at times have been used for inflammation

MASCC = Multinational Association of Supportive Care in Cancer

Lacouture ME, Anadkat MJ, Bensadoun R-J, et al. Clinical practice guidelines for the prevention and treatments of EGFR-inhibitor associated dermatologic toxicity. *Support Care Cancer* (2011) 19:1079–1095. DOI 10.1007/s00520-011-1197-6

Paronychias

- Very diluted bleach soaks: approx. ¼ cup bleach to 3 gallons water
- Prevent: keep nails trimmed and clean, loose fitting shoes, biotin
- Topical steroids or antibx
- Systemic antibiotics
- Nail avulsion, silver nitrate

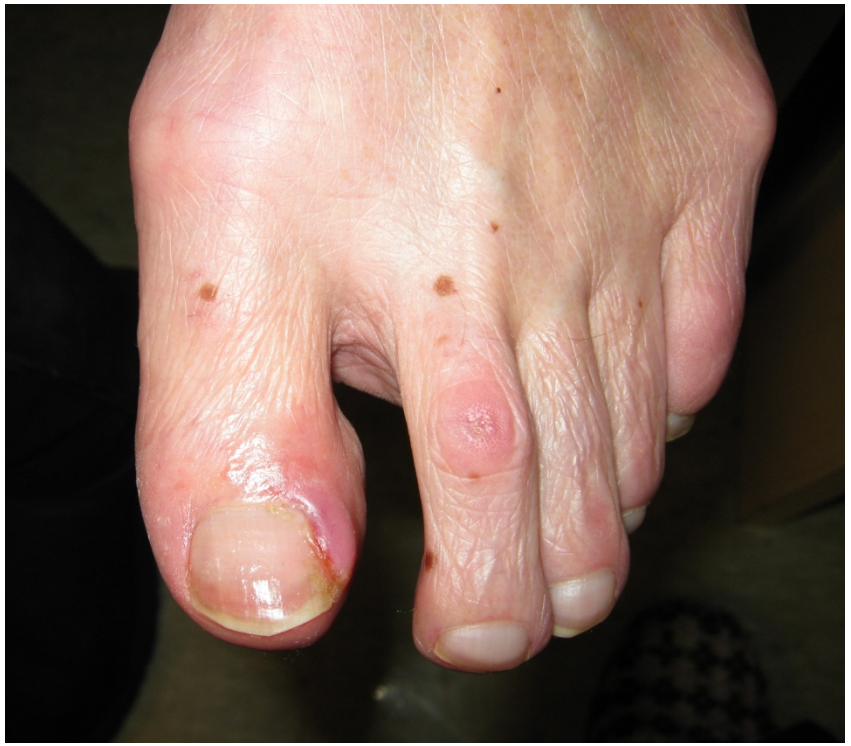


Image courtesy of Beth Eaby-Sandy, Abramson Cancer Center, Hospital of the University of Pennsylvania

Lacouture ME, Anadkat MJ, Bensadoun R-J, et al. Clinical practice guidelines for the prevention and treatments of EGFR-inhibitor associated dermatologic toxicity. *Support Care Cancer* (2011) 19:1079–1095. DOI 10.1007/s00520-011-1197-6

Scalp Rash

- Moisturizing shampoos with selenium, brands that are sold for dandruff
- Topical solutions either in shampoo form or liquid solution that you apply and leave in: fluocinolone shampoo or solution

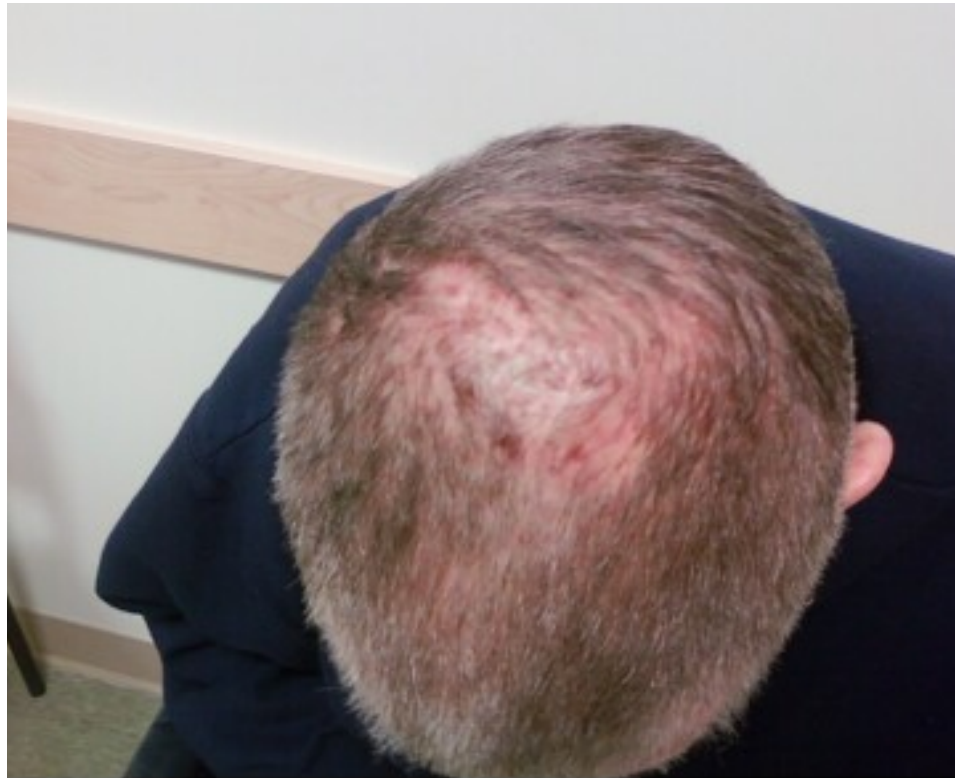


Image courtesy of Beth Eaby-Sandy, Abramson Cancer Center, Hospital of the University of Pennsylvania

Lacouture ME, Anadkat MJ, Bensadoun R-J, et al. Clinical practice guidelines for the prevention and treatments of EGFR-inhibitor associated dermatologic toxicity. Support Care Cancer (2011) 19:1079–1095. DOI 10.1007/s00520-011-1197-6

Fissuring

- Prevent: wear gloves, prevent exposure
- Thick moisturizers
- Liquid glues to seal cracks
- Steroid tapes

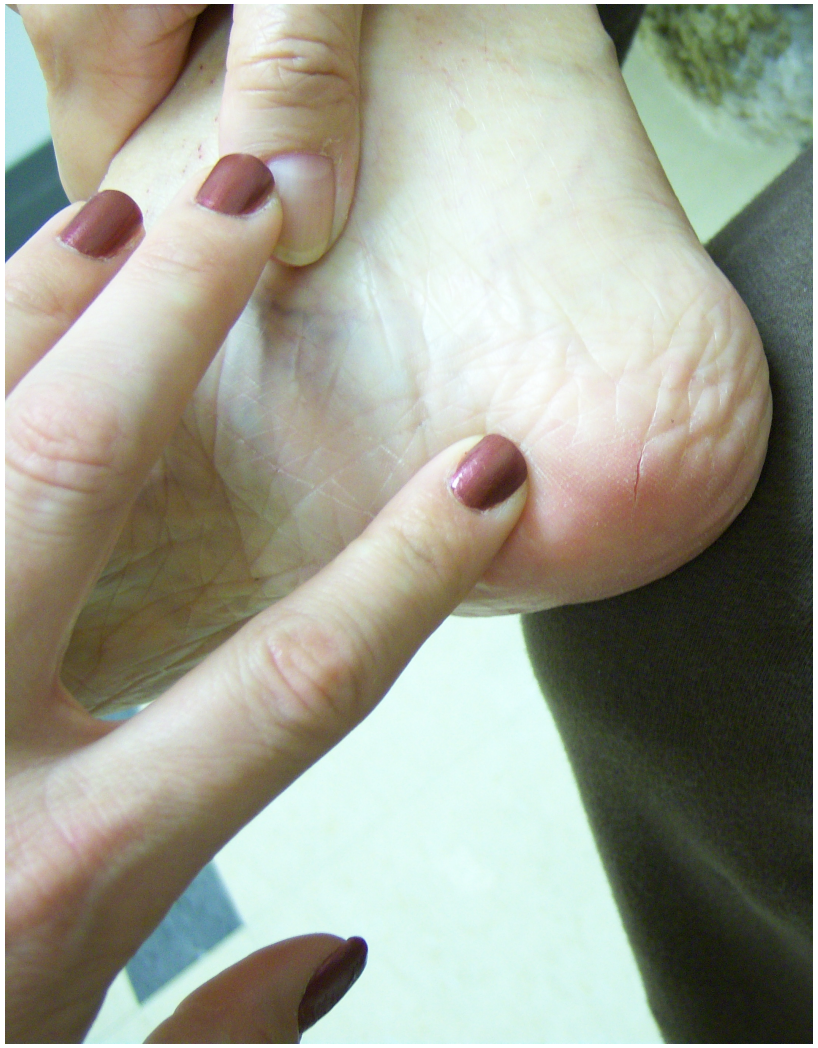


Image courtesy of Beth Eaby-Sandy, Abramson Cancer Center, Hospital of the University of Pennsylvania

Lacouture ME, Anadkat MJ, Bensadoun R-J, et al. Clinical practice guidelines for the prevention and treatments of EGFR-inhibitor associated dermatologic toxicity. Support Care Cancer (2011) 19:1079–1095. DOI 10.1007/s00520-011-1197-6

Hypertrichosis

- Trim lashes carefully
- See ophthalmology

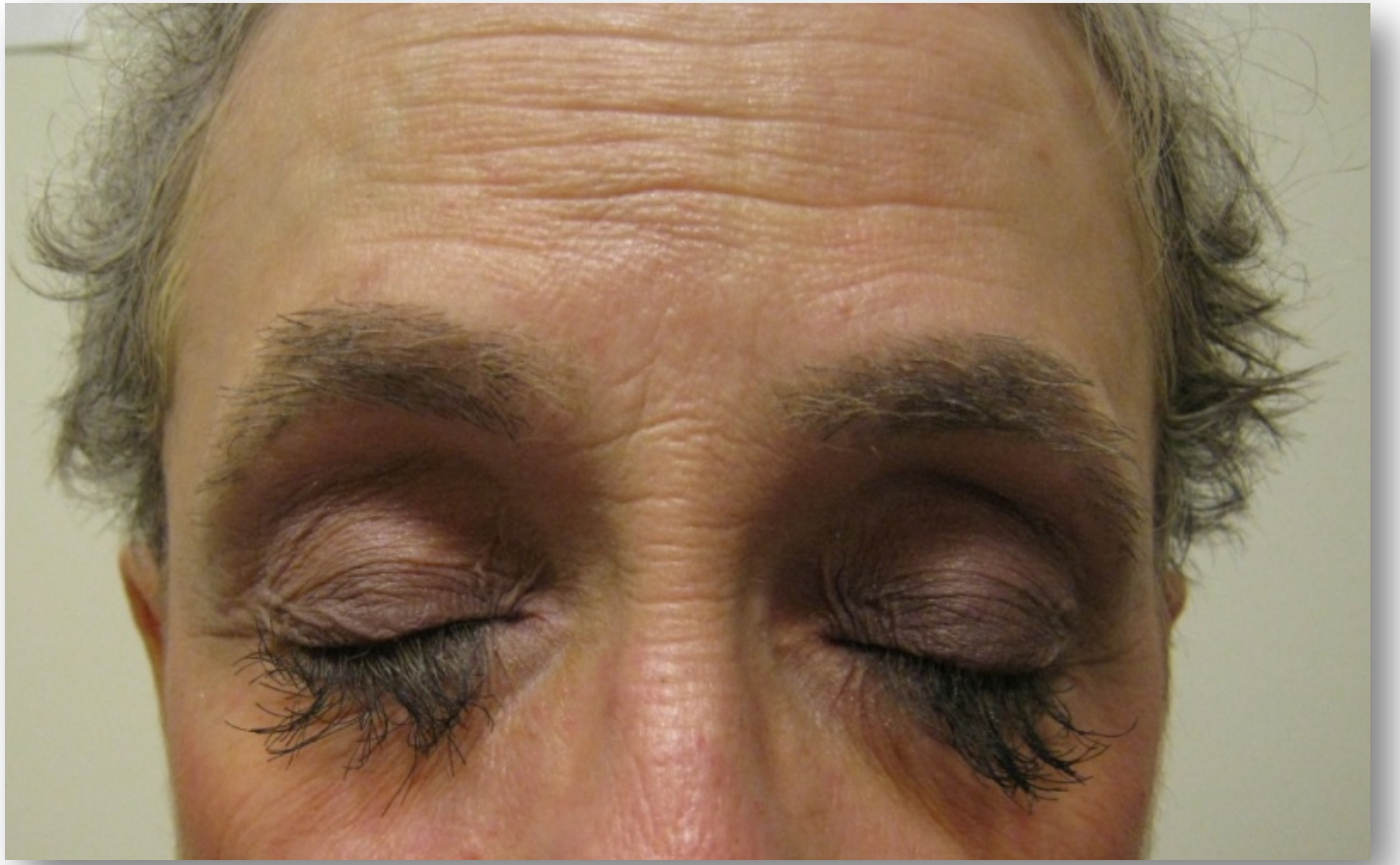


Image courtesy of Beth Eaby-Sandy, Abramson Cancer Center, Hospital of the University of Pennsylvania

Lacouture ME, Anadkat MJ, Bensadoun R-J, et al. Clinical practice guidelines for the prevention and treatments of EGFR-inhibitor associated dermatologic toxicity. *Support Care Cancer* (2011) 19:1079–1095. DOI 10.1007/s00520-011-1197-6

Other EGFR Inhibitor Toxicities

- Diarrhea: similar across agents, about 50%. More in afatinib.
- Usually easily manageable with OTC diphenoxylate
- Rarely requires dose reduction

Median duration of exposure: osimertinib: 16.2 months (range 0.1 to 27.4), SoC: 11.5 months (range 0 to 26.2)

AEs by preferred term, n (%)	Osimertinib (n=279)					SoC (n=277)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	161 (58)	120 (43)	35 (13)	6 (2)	0	159 (57)*	116 (42)	35 (13)	6 (2)	0
Dry skin	88 (32)	76 (27)	11 (4)	1 (<1)	0	90 (32)	70 (25)	17 (6)	3 (1)	0
Paronychia	81 (29)	37 (13)	43 (15)	1 (<1)	0	80 (29)	46 (17)	32 (12)	2 (1)	0
Stomatitis	80 (29)	65 (23)	13 (5)	1 (<1)	1 (<1)	56 (20)	47 (17)	8 (3)	1 (<1)	0
Dermatitis acneiform	71 (25)	61 (22)	10 (4)	0	0	134 (48)	71 (26)	50 (18)	13 (5)	0
Decreased appetite	56 (20)	27 (10)	22 (8)	7 (3)	0	51 (18)	24 (9)	22 (8)	5 (2)	0
Pruritis	48 (17)	40 (14)	7 (3)	1 (<1)	0	43 (16)	30 (11)	13 (5)	0	0
Cough	46 (16)	34 (12)	12 (4)	0	0	42 (15)	25 (9)	16 (6)	1 (<1)	0
Constipation	42 (15)	33 (12)	9 (3)	0	0	35 (13)	28 (10)	7 (3)	0	0
AST increased	26 (9)	18 (6)	6 (2)	2 (1)	0	68 (25)	38 (14)	18 (6)	12 (4)	0
ALT increased	18 (6)	11 (4)	6 (2)	1 (<1)	0	75 (27)	31 (11)	19 (7)	21 (8)	4 (1)

Slide adapted from 2017 ESMO Congress in Madrid, Spain, presented by S.S. Ramalingam

Other EGFR Inhibitor Toxicities (cont.)

- ILD/pneumonitis: uncommon, but a class effect of EGFR TKIs. In the range of 1%–4%, however, can be fatal.
  - Evaluate for acute onset SOB with PE protocol CT chest
  - Different from IO pneumonitis in that NEVER rechallenge, it is permanent discontinuation.
  - **Word of caution:** recent data shows that osimertinib given in short time frame after immunotherapy causes significantly increased rate and severity of pneumonitis!

Shoenfeld AJ, Arbour KC, Rizvi H et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. *Annals of Oncology*, Volume 30, Issue 5, May 2019, Pages 839–844, https://doi.org/10.1093/annonc/mdz077

Clinical Pearls

- Can’t treat an *EGFR* mutation if you never find it. MUST TEST.
- Several drugs available: osimertinib is the preferred first-line treatment based on current data
- Several toxicities, usually many are manageable.

Audience Response Question

Which *EGFR* mutation is not usually sensitive to EGFR inhibitors?

A. Exon 19 deletion
B. L858R
C. G719X
D. Exon 20 insertion
E. Unsure

Audience Response Question

For a patient needing treatment for an *EGFR*+ tumor, which would you choose based on its designation as the NCCN Guidelines' preferred first-line agent?

A. Afatinib
B. Erlotinib
C. Osimertinib
D. None; they are all FDA approved for first-line *EGFR*+ NSCLC
E. Unsure

Questions?