# NON-SMALL CELL LUNG CANCER MANAGING TOXICITIES OF TYROSINE KINASE INHIBITORS: EFGR & ALK

JANE ARBOLEDA, APRN

MIAMI CANCER INSTITUTE

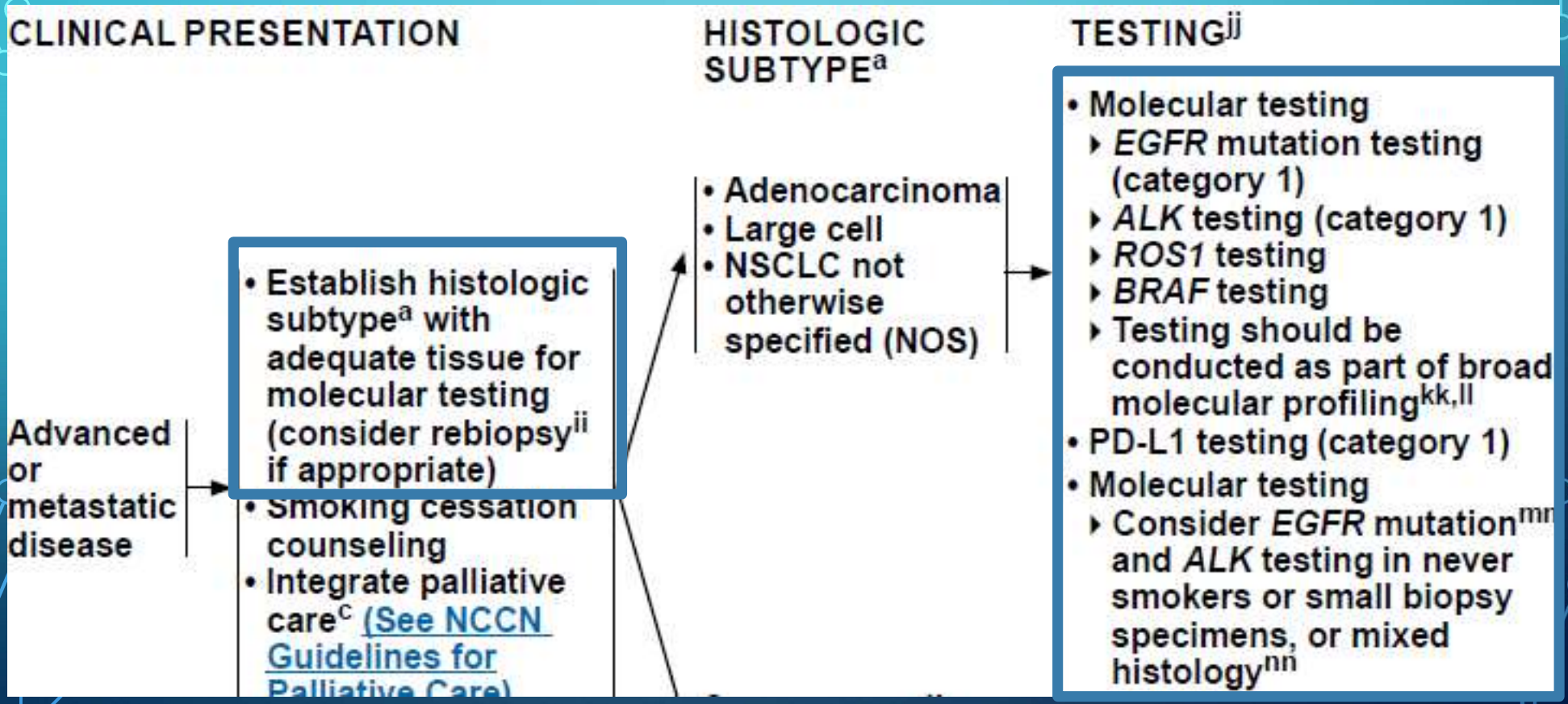
BAPTIST HEALTH SOUTH FLORIDA

9th Annual
Winter Cancer Symposium (WCS)
San Juan, PR
March 6-8, 2020

# OBJECTIVES

- NCCN Guidelines to treat Non-Small Cell Lung Cancer (NSCLC)
- Oral Targeted Therapies
  - EGFRi and ALKi
- Common Side Effects (SEs) and Adverse Events (AEs) of TKIs
- Improves quality of life
- Management of SEs/AEs

# NCCN Guidelines Version 2.2020
# Non-Small Cell Lung Cancer




https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

# NCCN GUIDELINES – NON-SMALL CELL LUNG CANCER (NSCLC)

- Molecular diagnostic studies which help to determine if target gene alterations are present
- Targeted therapy very effective in pts with specific gene mutations or rearrangements (**50-80%**) compared to chemo alone
- It is key to follow pts closely to assess safety and manage tolerability

# NCCN GUIDELINES–NSCLC TYROSINE KINASE INHIBITORS (TKIs)

**Sensitizing *EGFR* Mutation Positive**

- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
- Subsequent therapy
  - Osimertinib[7]

**Preferred 1st Line Drug**

**ALK Rearrangement Positive**

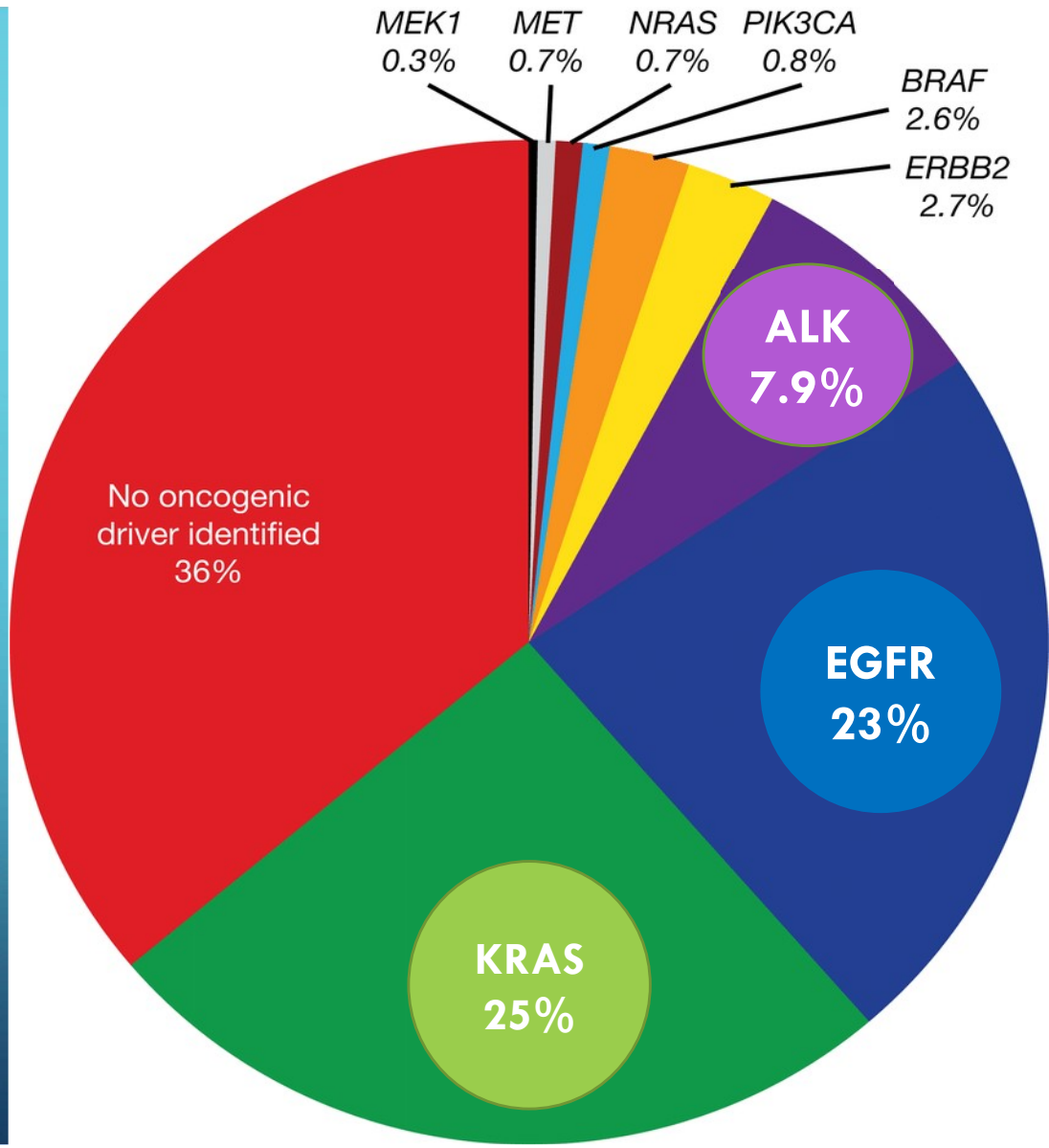
- First-line therapy
  - Alectinib[8,9]
  - Brigatinib[10]
  - Ceritinib[11]
  - Crizotinib[8,12]
- Subsequent therapy
  - Alectinib[13,14]
  - Brigatinib[15]
  - Ceritinib[16]
  - Lorlatinib[17]

https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
https://doi.org/10.1016/j.pharmthera.2018.08.007

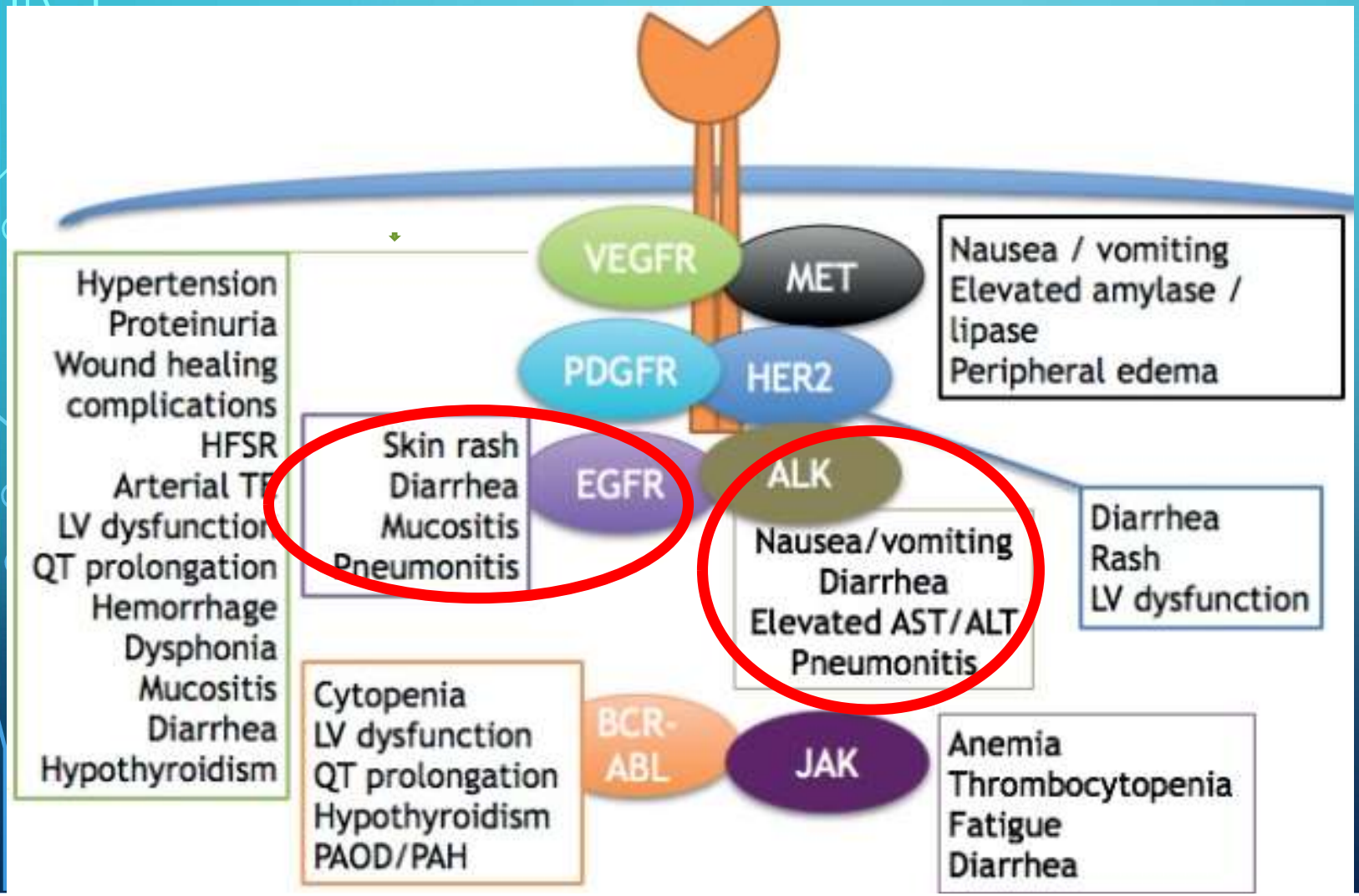
# MOST COMMON GENE ALTERATIONS

- Gene mutations or rearrangements
- Oncodriver or driver mutations
- Biomarkers

https://www.researchgate.net/figure/EGFR-driver-mutations-identified-in-the-Lung-Cancer-Mutation-Consortium-cohort-lung_fig2_323817383



# OVERVIEW OF TOXICITIES ASSOCIATED WITH DIFFERENT TKI TARGETS




https://cancerworld.net/wp-content/uploads/2016/12/Overview-of-Toxicities-associated-with-different-TKI-targets.jpg

# ALK INHIBITOR-MOST COMMON ADVERSE EVENTS

| | crizotinib | ceritinib | brigatinib | alectinib |
|---|---|---|---|---|
| **Overall AEs** | 97.7 | 95.8 | NA | 96.9 |
| **Grade 3-5 AEs** | 40.8 | 54.2 | NA | 33.8 |
| **SAEs** | 18.6 | 13.2 | NA | 19.1 |
| **TRD** | 1.5 | 2 | 2.3 | 0.7 |
| **Dose reduction** | 12.3 | 61.2 | 20 | 15.9 |
| **Drug discontiunation** | 6.2 | 7.7 | 7.9 | 8.3 |
| **Common AEs** | | | | |
| Diarrhea | 54.9 | 81 | 39.5 | 10.8 |
| Nausea | 55.1 | 75.4 | 46.5 | 14.2 |
| Vomitting | 43.9 | 63.3 | 22.1 | 9 |
| Constipation | 35.7 | 25 | 16.9 | 34.2 |
| Increased ALT | 27.8 | 46.1 | 11.3 | 12.8 |
| **Response rate** | 69 | 52.5 | 70 | 71.8 |

Journal of Thoracic Oncology Vol. 12 No. 11S2

# EGFR INHIBITORS- SAFETY PROFILE

## Dermatological (37-89%)

- Within approx. 10-14 days of initiating treatment
  - face, scalp, neck, upper chest, and back
  - Acne-like or pustular rash
- Inflammation
- Dry skin
- Nail changes: brittle, Paronychia
- Hair alterations
  - Curling or thinning on scalp
  - Increase in eyes lashes; inverted

"erythematous papules and pustules that develop on the face, scalp, and upper trunk within the first month in > 90% of patients. Not only does the rash have a cosmetic impact, but it is frequently associated with pain, infections, and pruritus"

*Mario E. Lacouture, MD*

https://www.ascopost.com/issues/may-15-2013/prevention-and-treatment-of-acneiform-rash-caused-by-egfr-inhibitors/

# EGFR INHIBITORS- SAFETY PROFILE CON'T

- Diarrhea Approx (approx. 70%)
- Stomatitis/Mouth Sores (tingling, ulcers, cracks on side of mouth)
- Fatigue
- Loss of appetite
- Ocular-Related Toxicity
  - conjunctivitis/blepharitis/dry eye and keratitis
- Interstitial Lung Disease/pneumonitis (non-infectious)

https://doi.org/10.6004/jadpro.2016.7.7.4

https://amp.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html

# ALK INHIBITORS- SAFETY PROFILE CON'T

- Nausea/Vomiting
- Diarrhea
- Constipation
- Elevated ALT/AST
- Fatigue
- Edema (lower ext)
- Visual disturbances

https://amp.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html

# GRADE 1

# GRADE 2

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5902152/#A34

# GRADE 2

https://www.ascopost.com/issues/may-15-2013/prevention-and-treatment-of-acneiform-rash-caused-by-egfr-inhibitors/

# GRADE 3

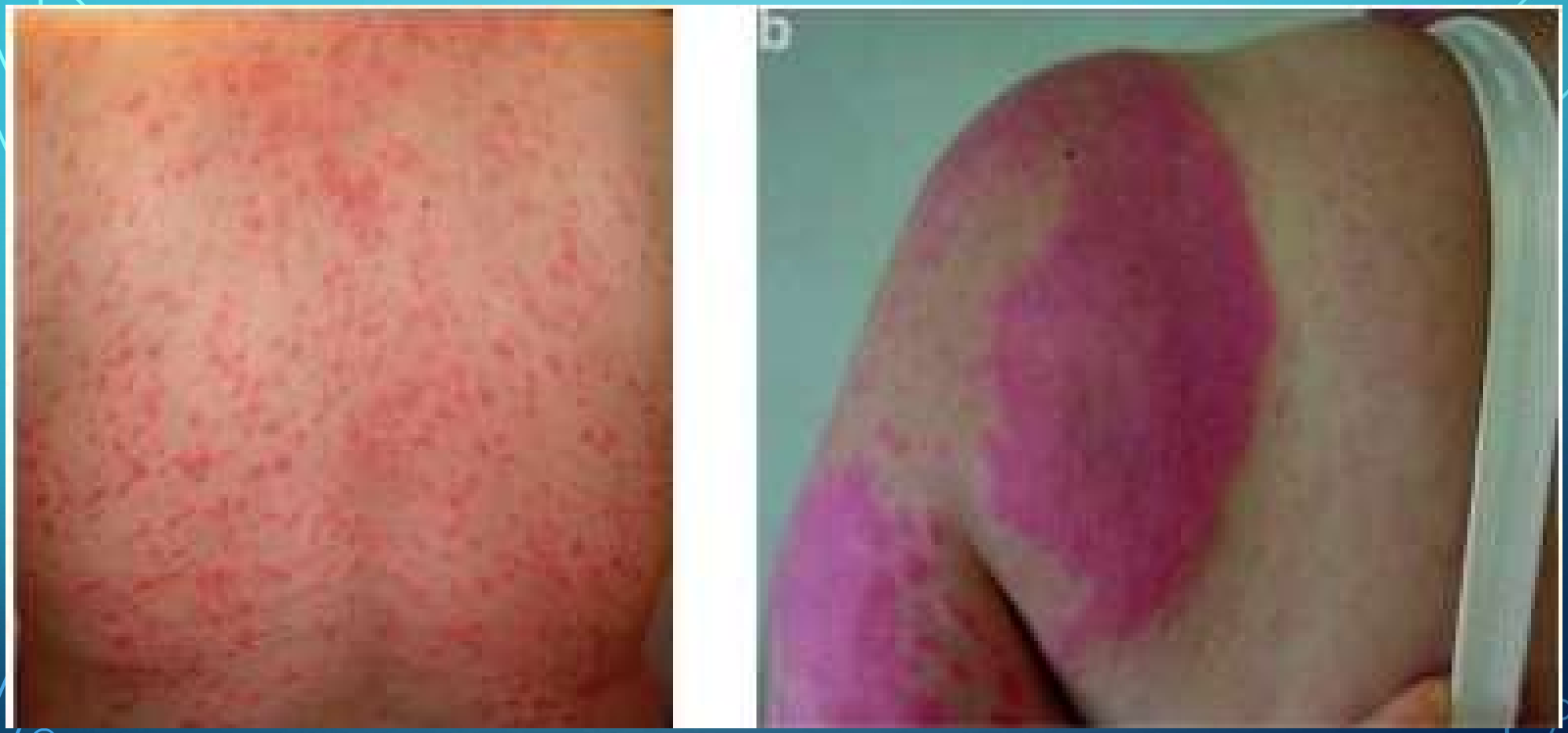
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5902152/#A34

# GRADE 4

https://cancerworld.net/wp-content/uploads/2016/12/Grades-and-types-of-rash-with-EGFR-TKIs.jpg

Betamethasone valerate 0.1% lotion QD-BID (medium/low potency)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6103195/pdf/APJON-5-430.pdf



https://cancerworld.net/wp-content/uploads/2016/12/Grades-and-types-of-rash-with-EGFR-TKIs.jpg

# CONSIDERATIONS TO MANAGE TOXICITY AGGRESSIVELY

Secondary to dermatologic toxicity:

- 2/3 of oncologist dose reduce/modify EGFRi due to rash alone
- Decreased QOL
- 1/3 of oncologist will stop EGFRi b/c of rash alone
- Only 8% of pts are referred to dermatologist

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6103195/pdf/APJON-5-430.pdf

| GRADE | ACNEIFORM RASH- CTCAE GRADING |
|---|---|
| 1 | Papules or pustules, covering **< 10%** BSA, +/- pruritus or tenderness; generally localized; minimally symptomatic; no impact on ADLs; No sign of superinfection |
| 2 | Papules or pustules, covering **10–30%** BSA, which +/- pruritus or tenderness; Mild symptoms i.e. pruritus, tenderness Minimal impact on ADL; no sign of superinfection |
| 3 | Papules or pustules, covering **> 30%** BSA, +/- pruritus or tenderness; Severe symptoms; potential for superinfection |
| 4 | Papules or pustules, **covering any percentage** BSA, +/-pruritus or tenderness; **extensive superinfection- intravenous antibiotics may be indicated**; Life-threatening consequences |

https://cancerworld.net/wp-content/uploads/2016/12/Management-of-EGFR-associated-rash.jpg

*Oncol Clin Pract 2016;12(4):113-118*

| GRADE | ACNEIFORM RASH MANAGEMENT/TREATMENT |
|---|---|
| 0 | Moisturize regularly (for all grades)<br>Protect against excessive exposure to sunlight<br>Use SPF 30 UVA and UVB Sunscreen |
| 1 | No treatment or<br>Hydrocortisone 1% or 2.5% cream and/or clindamycin 1% gel<br>Continue TKI EGFR at the current dose |
| 2 | Hydrocortisone 2.5% cream or clindamycin 1% gel or pimecrolimus 1% cream<br>Doxycycline or minocycline 100mg BID PO $\geq$ 2wks<br>Continue TKI EGFR at the current dose or hold if intolerable |
| 3 & 4 | Topical treatment as grade 2 management<br>Antibiotic from the tetracycline group $\geq$ 2wks as above grade 2<br>Start methylprednisolone orally or prednisone 0.5mg/kg X 7 days<br>TKI dose interruption until improved to grade 1<br>Refer to dermatologist who specializes in drug-related cutaneous AEs |

https://www.ascopost.com/issues/may-15-2013/prevention-and-treatment-of-acneiform-rash-caused-by-egfr-inhibitors/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4532717/figure/Fig1/?report=objectonly Oncol Clin Pract 2016;12(4):113-118

# ANTIBIOTIC ALTERNATIVES-ACNEIFORM RASH

- If intolerant to tetracycline family antibiotics may consider:
  - Cefadroxil 1-2 g/day PO q12-24 hrs
  - Amoxicillin/clavulanate 500mg/125mg or 875mg/125mg PO q 12 hrs
  - Cephalexin 500mg PO q 6-12 hrs
  - Evidence does not support treating rash prophylactically

# STEROID OPTIONS-ACNEIFORM RASH

- Apply **low** potency steroids to face
- Duration may be up to 6-8 wks BID
- Hydrocortisone 0.5%, 1%, 2.5%-ointment, cream, lotion
  - 0.025% cream or lotion- low
  - 0.25% ointment- medium/low
  - 0.1% ointment- medium
  - 0.1% cream or lotion-medium
  - 0.5% ointment-high
  - 0.5% cream- high/medium
- Alclometasone 0.05% ointment or cream-medium/low
- Triamcinolone 0.9% Apply 2-4 X day
- Betamethasone valerate 0.1% lotion QD-BID (medium/low potency)

https://www.ascopost.com/issues/may-15-2013/prevention-and-treatment-of-acneiform-rash-caused-by-egfr-inhibitors/


# GRADE 1

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4399609/figure/f1-conc-22-123/

# GRADE 2

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4399609/figure/f1-conc-22-123/

# GRADE 3

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4399609/figure/f1-conc-22-123/

# GRADE

1 2 3

https://theoncologist.onlinelibrary.wiley.com/doi/10.1634/theoncologist.12-5-610

# PARONYCHIA CTCAE GRADING

| | |
|---|---|
| 1 | Nail fold edema or erythema; disruption of the cuticle |
| 2 | Nail fold edema or erythema with pain; associated with discharge or nail plate separation;<br>Limits iADLs<br>Localized intervention indicated; oral intervention indicated (i.e. antibiotics, antifungal) |
| 3 | Limits self-care activities of daily living; Surgical intervention or IV antibiotics indicated |

https://current-oncology.com/index.php/oncology/article/view/2430/1764#t5-conc-22-123

*Oncol Clin Pract 2016;12(4):113-118*

# PARONYCHIA MANAGEMENT

| | |
|---|---|
| 0 | Local care: Petroleum jelly emollient; antimicrobial soaks (diluted white vinegar); cushioning of affected areas; no aggressive manicures; use of gloves when cleaning |
| 1-2 | Maintain dose level of TKI; Same supportive care as above<br>Apply betamethasone valerate 2-3 times a day PRN |
| 3 | Temporary hold TKI for 2-4 wks; Same supportive care as above<br>Upon improvement ≤ grade 1, restart TKI at lower dose or per MD discretion; if no improvement may consider discontinuation<br>Apply clobetasol cream 2-3 times a day PRN<br>If Refractory to tx: Apply mupirocin ointment |

https://current-oncology.com/index.php/oncology/article/view/2430/1764#t5-conc-22-123

*Oncol Clin Pract 2016;12(4):113-118*

| GRADE | DIARRHEA-CTCAE GRADING |
|---|---|
| 1 | Increase of fewer than 4 stools per day |
| 2 | Increase of 4–6 stools per day over baseline |
| 3 | Increase of 7 or more stools per day over baseline; incontinence<br>Limits self-care activities of daily living<br>Hospitalization indicated |
| 4 | Life-threatening consequences<br>Urgent intervention indicated |

S/S: pallor skin and mucous membranes, shortness of breath, palpitations, soft systolic murmurs, lethargy, and fatigability

*Oncol Clin Pract 2016;12(4):113-118*

| GRADE | DIARRHEA MANAGEMENT/TREATMENT |
|---|---|
| 1 | -Adjust diet<br>-Loperamide at the beginning 4 mg orally, then 2 mg Q2–4 hrs after 12 hrs without diarrhea<br>-Continue TKI therapy |
| 2 | -See grade 1 recommendations for supportive care<br>-Diphenoxylate/atropine 2.5mg/0.025mg tab, 1-2 tabs BID-QID/day prn (reduce dose when symptoms controlled) |
| 3 & 4 | -See grade 1 recommendations for supportive care<br>-Hospitalization and parenteral hydration is recommended<br>-Hold TKI until regression of the side effects to grade 1 |

*Oncol Clin Pract 2016;12(4):113-118*


https://current-oncology.com/index.php/oncology/article/view/2430/1764

| GRADE | STOMATITIS/MUCOSITIS-CTCAE GRADING |
|---|---|
| 1 | Asymptomatic or mild symptoms; no intervention |
| 2 | Moderate pain; not interfering with oral intake; modified diet indicated |
| 3 | Severe pain; interfering with oral intake |
| 4 | Life-threatening consequences; Urgent intervention indicated |

https://current-oncology.com/index.php/oncology/article/view/2430/1764

| GRADE | STOMATITIS/MUCOSITIS MANAGEMENT |
|---|---|
| 0 | Mild symptom of general mouth sensitivity and/or tingling:<br>-Gargle with benzydamine rinse 15 mL for 30 sec and spit 3X day PRN<br>-Brush teeth and tongue with a soft-bristled brush and floss<br>-Rinse with vitamin B7 or normal saline (1 tsp of salt to 1 qt of water) |
| 1 | -Maintain dose level of TKI<br>-Apply triamcinolone in dental paste 2-3 times daily PRN |
| 2 | -Maintain dose level of TKI<br>-Apply triamcinolone in dental paste 2-3 times daily PRN<br>-Erythromycin 250-350 mg daily PO OR Minocycline 50mg daily PO |
| 3 & 4 | -Temporary hold TKI for 2-4 wks;<br>-Upon improvement to Grade ≤2 restart TKI dose per MD discretion<br>-Apply clobetasol ointment 2-3 X day<br>-Erythromycin 500 mg daily PO OR Minocycline 100mg daily PO |

https://current-oncology.com/index.php/oncology/article/view/2430/1764 https://cancerworld.net/wp-content/uploads/2015/11/CW_69-grandround.pdf

# MAGIC MOUTHWASH: AKA MARY'S OR DUKE'S

*"Evidence shows it is **NO** more effective for management of oral mucositis than salt and sodium bicarbonate rinses"*

Ingredients may include 3 or more:

- Antihistamine or anticholinergic agent (i.e. diphenhydramine)
- A local anesthetic (i.e. viscous lidocaine)
- Antacid (i.e. magnesium or aluminum hydroxide
- Antifungal (i.e. nystatin)
- Corticosteroid (i.e. dexamethasone)
- Antibiotic

Side effects of magic mouthwash may include:

- Problems with taste
- Burning or tingling sensation in the mouth
- Dryness
- Drowsiness
- Constipation
- Diarrhea
- Nausea

**Not usually covered by insurance; very expensive**

https://www.aannet.org/initiatives/choosing-wisely/choosing-wisely---magic-mouthwash
https://www.mayoclinic.org/tests-procedures/chemotherapy/expert-answers/magic-mouthwash/faq-20058071

# OTHER HELPFUL TIPS

Preventative:

- Stop Smoking
- Avoid alcohol, irritating foods, such as those that are spicy, hot, acidic or coarse
- May use foam toothbrushes with antibacterial rinse
- Use toothpaste with fluoride
  - Use biotene enzyme based products
  - Chlorhexidine gluconate 0.12%

https://oralcancerfoundation.org/complications/mucositis/

# OTHER HELPFUL TIPS CONTINUED

Preventative:

- If toothpaste too irritating:
  - Dissolve 1 teaspoon of salt in 4 cups of water
  - Mix 1 teaspoon baking soda in 2 cups of water
- Gently floss your teeth once daily
- Avoid whitening agents
- Rinse mouth (swish and spit) before and after meals and at bedtime:
  - normal saline (1 tsp of table salt to 1 quart of water)
  - salt and soda (one-half teaspoon of salt and 2 tablespoons of sodium bicarbonate in 1 quart of warm water)

https://oralcancerfoundation.org/complications/mucositis/

# OTHER HELPFUL TIPS CONTINUED

Treating Mucositis:

- Increase brushing q4 hours and at bedtime
- Keep mouth moisturized to prevent infections
- Rinse frequently with antiseptic mouth rinses
  - Chlorhexidine gluconate 0.12%
- Mix 1 teaspoon of baking soda in 8 ounces of water
- ½ teaspoon salt and 2 tablespoons of sodium bicarbonate dissolved in 4 cups of water
- Sores:
  - Rinse with 1 part of 3% hydrogen peroxide with 1 tsp of salt water dissolved in 4 cups of water

https://oralcancerfoundation.org/complications/mucositis/

# CTCAE GRADING- NAUSEA

- Gr 1: lose of appetite w/o alteration in eating habits
- Gr 2: oral intake ↓ without major wt loss, dehydration, or malnutrition
- Gr 3: Inadequate oral caloric or fluid intake:
  tube feeding, TPN, or hospitalization
- Gr 4 & 5: not assigned

https://www.ncbi.nlm.nih.gov/books/NBK66056/

https://www.researchgate.net/figure/Acute-nausea-and-vomiting-grade-CTCAE-v40_tbl1_257805185

# CTCAE GRADING-VOMITING

- Gr 1: 1 to 2 episodes in 24 h; no intervention required
- Gr 2: 3-5 episodes in 24 h (separated by 5 min); out-pt IV hydration & medical intervention with anti-emetics
- Gr 3: ≥6 episodes in 24 h (separated by 5 min); tube feeding, TPN, or hospitalization
- Gr4: Life-threatening consequences; **urgent** intervention indicated
- Gr 5: Death

https://www.researchgate.net/figure/Acute-nausea-and-vomiting-grade-CTCAE-v40_tbl1_257805185
https://current-oncology.com/index.php/oncology/article/view/2430/1764

# PNEUMONITIS-TKI INDUCED

- S/S: Acute or subacute, progressive dyspnea with or without cough and/or fever
- Hold TKI
- Rule out other causes:
  - infections, occupational, recreational or environmental exposures; asthma; and systemic diseases; Respiratory distress; hx: of immunotherapy/chest RT
- Work up: Chest CT scan, bronchofibroscopy to rule out infectious causes
- Treat:
  - Corticosteroids
  - Supportive treatment: bronchodilators, supplementary oxygen, and mechanical ventilation
  - Hospitalization

https://cancerworld.net/wp-content/uploads/2015/11/CW_69-grandround.pdf

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6894986/

# SUMMARY

- 1st-line treatment with TKI if EGFR positive or ALK rearrangement positive
- Safety (AEs) and tolerability will guide treatment and management
- Evaluate prior to initiating tx with EGFR and q2wks during the first month and/or after dose modification
- Consider dose modification if grade 2 identified (per provider discretion)
- Goal is to maintain pt on targeted therapy to provide:

  improved QOL, prolong both PFS and OS

# REFERENCES


- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4532717/figure/Fig1/?report=objectonly
- Oncol Clin Pract 2016;12(4):113-118
- https://wwwncbi.nlm.nih.gov/pmc/articles/PMC4399609/figure/f1-conc-22-123
- https://cancerworld.net/wp-content/uploads/2016/12/Grades-and-types-of-rash-with-EGFR-TKIs.jpg
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6103195/pdf/APJON-5-430.pdf
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5902152/#A34
- https://amp.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html
- https://doi.org/10.6004/jadpro.2016.7.7.4
- Journal of Thoracic Oncology Vol. 12 No. 11S2
- https://cancerworld.net/wp-content/uploads/2016/12/Overview-of-Toxicities-associated-with-different-TKI-targets.jpg
- https://www.researchgate.net/figure/EGFR-driver-mutations-identified-in-the-Lung-Cancer-Mutation-Consortium-cohort-lung_fig2_323817383

# REFERENCES


- https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
- https://doi.org/10.1016/j.pharmthera.2018.08.007
- https://cancerworld.net/wp-content/uploads/2015/11/CW_69-grandround.pdf
- https://current-oncology.com/index.php/oncology/article/view/2430/1764
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6894986/
- https://www.ascopost.com/issues/may-15-2013/prevention-and-treatment-of-acneiform-rash-caused-by-egfr-inhibitors/
- https://oralcancerfoundation.org/complications/mucositis/
- https://www.mayoclinic.org/tests-procedures/chemotherapy/expert-answers/magic-mouthwash/faq-20058071
- https://www.aannet.org/initiatives/choosing-wisely/choosing-wisely---magic-mouthwash