Novel Strategies for Managing *EGFR*-mutated mNSCLC:

Expert Insights into the Latest Data and Recommendations

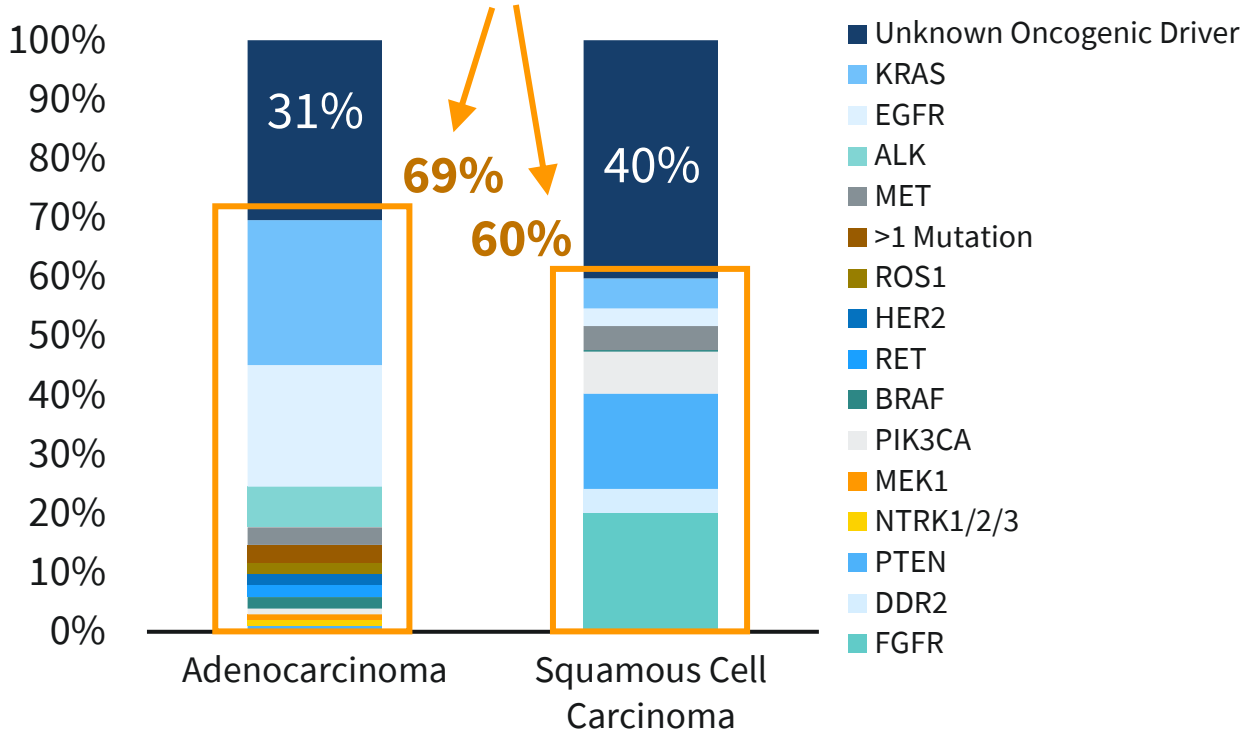
CORNERSTONE MEDICAL EDUCATION

AAACME®
AMERICAN ACADEMY OF CME, INC.

Why Biomarkers Matter

Examining the Empiric Role of Molecular Testing in *EGFR*-mutated NSCLC

Lung Adenocarcinoma and Squamous Cell Carcinoma Biomarker Frequency

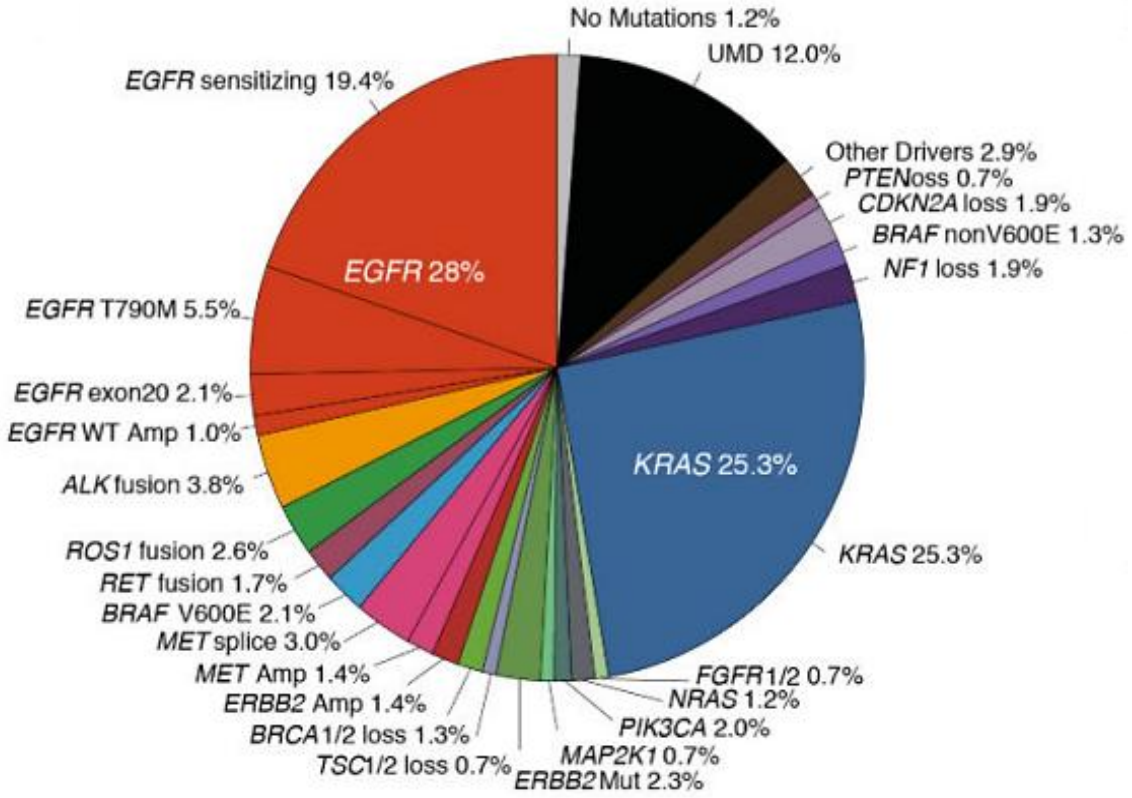


PD-L1 Expression in NSCLC Tumor Cells

Actionable for Immune Checkpoint Inhibitor Monotherapy

Kurzrock R, et al. *Cancer Metastasis Rev.* 2024.

Molecular Revolution: Targeted Therapy



Jordan EJ, et al. *Cancer Discov.* 2017.

Molecular Revolution: Targeted Therapy

PRINCIPLES OF BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE

Order does not imply preference. This is a listing for references.

***EGFR* Exon 19 Deletion or L858R Mutation**
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - (Carboplatin or Cisplatin)/ Osimertinib/Pemetrexed (nonsquamous)[7]
  - Erlotinib + Ramucirumab[8]
  - Erlotinib + Bevacizumab (nonsquamous)[9]
  - Lazertinib + Amivantamab-vmjw[10]
  - Lazertinib[10]
- Subsequent therapy
  - Osimertinib[11]
  - Carboplatin/Pemetrexed + Amivantamab-vmjw (nonsquamous)[12]
  - Datopotamab deruxtecan-dlnk (nonsquamous)[13]
  - Lazertinib + Amivantamab-vmjw[14,15]

***EGFR* S768I, L861Q, and/or G719X Mutations**
- First-line therapy
  - Afatinib[1,16]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,17]

***EGFR* S768I, L861Q, and/or G719X Mutations (continued)**
- Subsequent therapy
  - Osimertinib[11]
  - Datopotamab deruxtecan-dlnk (nonsquamous)[13]

***EGFR* Exon 20 Insertion Mutation**
- First-line therapy
  - Carboplatin/Pemetrexed + Amivantamab-vmjw (nonsquamous)[18]
- Subsequent therapy
  - Amivantamab-vmjw[19]
  - Sunvozertinib[20]
  - Datopotamab deruxtecan-dlnk (nonsquamous)[13]

***KRAS* G12C Mutation**[a]
- Subsequent therapy
  - Sotorasib[21]
  - Adagrasib[22]

***ALK* Gene Fusion**
- First-line therapy
  - Alectinib[23,24]
  - Brigatinib[25]
  - Ceritinib[26]
  - Crizotinib[23,27]
  - Ensartinib[28]
  - Lorlatinib[29]
- Subsequent therapy
  - Alectinib[30,31]
  - Brigatinib[32]
  - Ceritinib[33]
  - Ensartinib[34]
  - Lorlatinib[35]

***ROS1* Gene Fusion**
- First-line therapy
  - Crizotinib[36]
  - Entrectinib[37]
  - Repotrectinib[38]
  - Taletrectinib[39]
- Subsequent therapy
  - Lorlatinib[40]
  - Entrectinib[37]
  - Repotrectinib[38]
  - Taletrectinib[39]

***BRAF* V600E Mutation**
- First-line therapy
  - Dabrafenib/Trametinib[41]
  - Binimetinib/Encorafenib[42]
  - Dabrafenib[43]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/Trametinib[43,44]
  - Binimetinib/Encorafenib[42]

***NTRK1/2/3* Gene Fusion**
- First-line/Subsequent therapy
  - Larotrectinib[45]
  - Entrectinib[46]
  - Repotrectinib[47]

***MET* Exon 14 Skipping Mutation**[a]
- First-line therapy/Subsequent therapy
  - Capmatinib[48]
  - Crizotinib[49]
  - Tepotinib[50]

***RET* Gene Fusion**
- First-line therapy
  - Selpercatinib[51]
  - Pralsetinib[52]
- Subsequent therapy
  - Cabozantinib[53,54]

***ERBB2 (HER2)* Mutation**[a]
- First-line therapy
  - Zongertinib[55]
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[56]
  - Ado-trastuzumab emtansine[57]
  - Zongertinib[58]
  - Sevabertinib[59]

***NRG1* Gene Fusion**
- Subsequent therapy
  - Zenocutuzumab-zbco[60]

HER2-positive IHC 3+
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[61]

HGF receptor (c-Met) (≥50% IHC 3+ and *EGFR* wild-type)
- Subsequent therapy
  - Telisotuzumab vedotin-tllv (nonsquamous)[62]

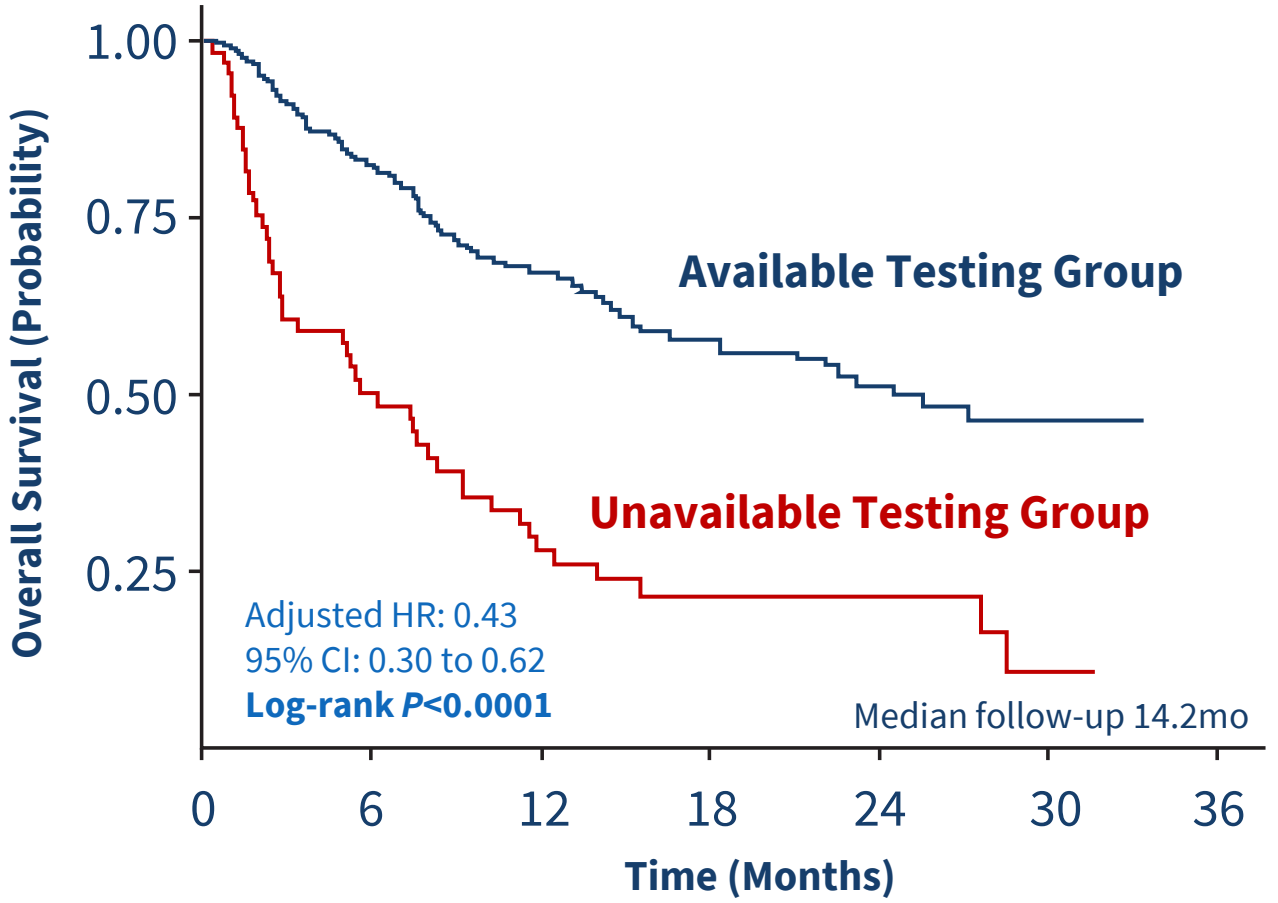
[a] For agents with a similar mechanism of action, it is not recommended to switch between these drugs at the time of progression.

NCCN Guidelines for NSCLC, Version 6.2026.

Importance of Biomarker Testing: OS Benefit in NSCLC

- Patients should **NOT be initiated on therapy** (except in emergent cases) **until results of biomarker testing are available**

Overall survival based on availability of results ***before first-line therapy*** in 236 mNSq NSCLC pts.



Aggarwal C, et al. *JCO Precis Oncol.* 2023.

Necessary Biomarker Testing for Lung Cancer

CLINICAL PRESENTATION

Advanced or metastatic disease →

- Establish histologic subtype[b] with adequate tissue for biomarker testing (consider rebiopsy[qq] or plasma testing if appropriate)
- Smoking cessation counseling
- Integrate palliative care[d] (NCCN Guidelines for Palliative Care)

HISTOLOGIC SUBTYPE[b] / **BIOMARKER TESTING[rr]**

- Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

→

- Biomarker testing, including:
  - *EGFR* mutation (category 1), *ALK* (category 1), *KRAS, ROS1, BRAF, NTRK1/2/3, MET* exon 14 skipping, *RET* (category 1), *ERBB2 (HER2), NRG1*, HER2 (immunohistochemistry [IHC]),[ss] HGF receptor (c-Met) IHC[ss]
  - Testing should be conducted as part of multigene panel testing (MGPT)[tt]
- PD-L1 testing (category 1)

→ Testing Results (NSCL-20)

Squamous cell carcinoma →

- Consider biomarker testing, including:[uu]
  - *EGFR* mutation, *ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET* exon 14 skipping, *RET, ERBB2 (HER2), NRG1*, HER2 (IHC)[ss]
  - Testing should be conducted as part of MGPT[tt]
- PD-L1 testing (category 1)

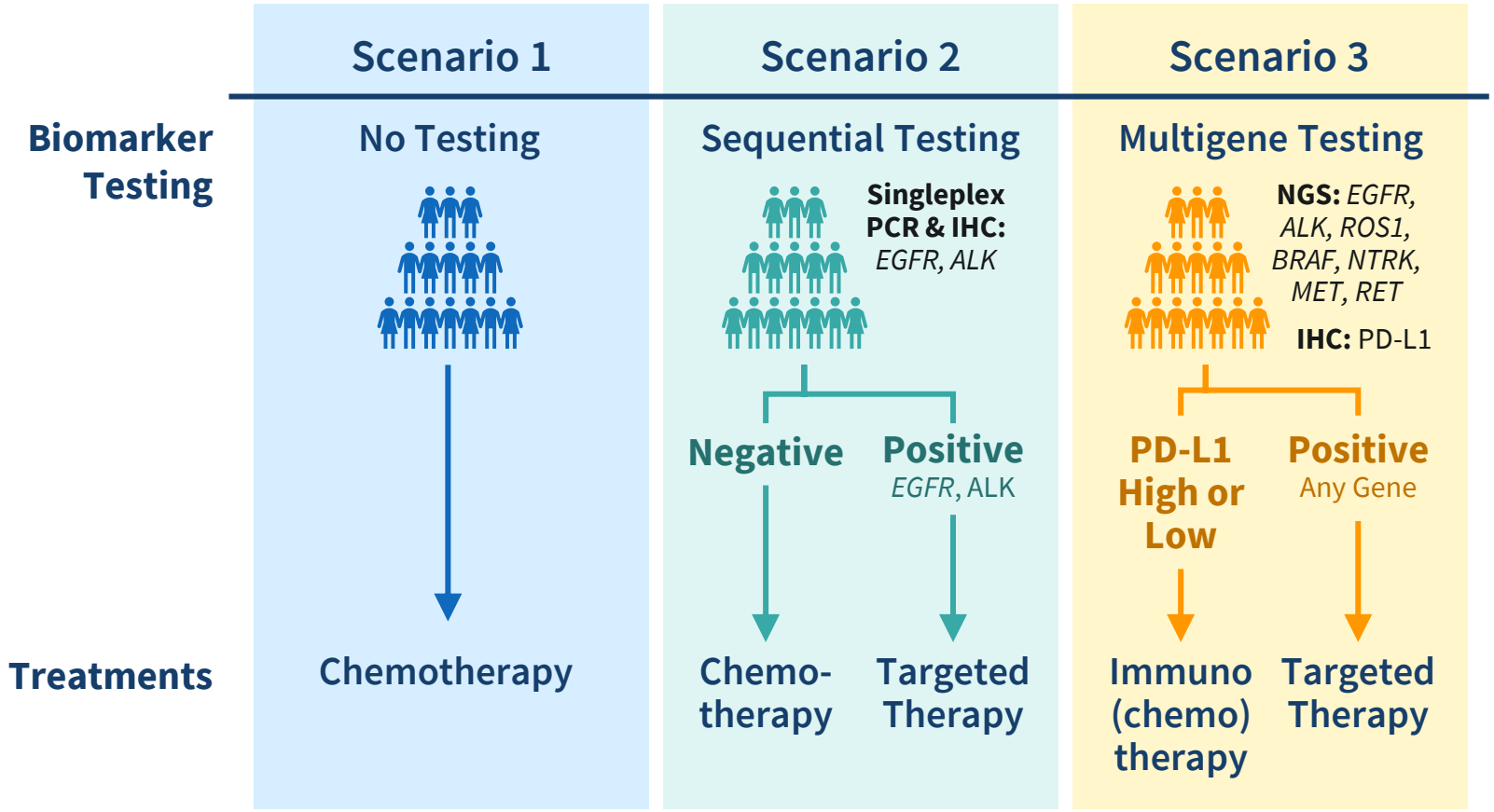
→ Testing Results (NSCL-20)

NCCN Guidelines for NSCLC, Version 6.2026.

How do we test for a biomarker? Sequential Single-gene vs. Comprehensive Multi-gene Testing

- **Broad molecular profiling** via next-generation sequencing (NGS) is guideline recommended.

Comprehensive NGS panel testing has been shown to be more efficient and cost-effective with quicker time to results.



Hofmarcher T, et al. *Front Med.* 2023; Pennell NA, et al. *JCO Precis Oncol*. 2019.

Tissue vs ctDNA (Liquid) Biopsy

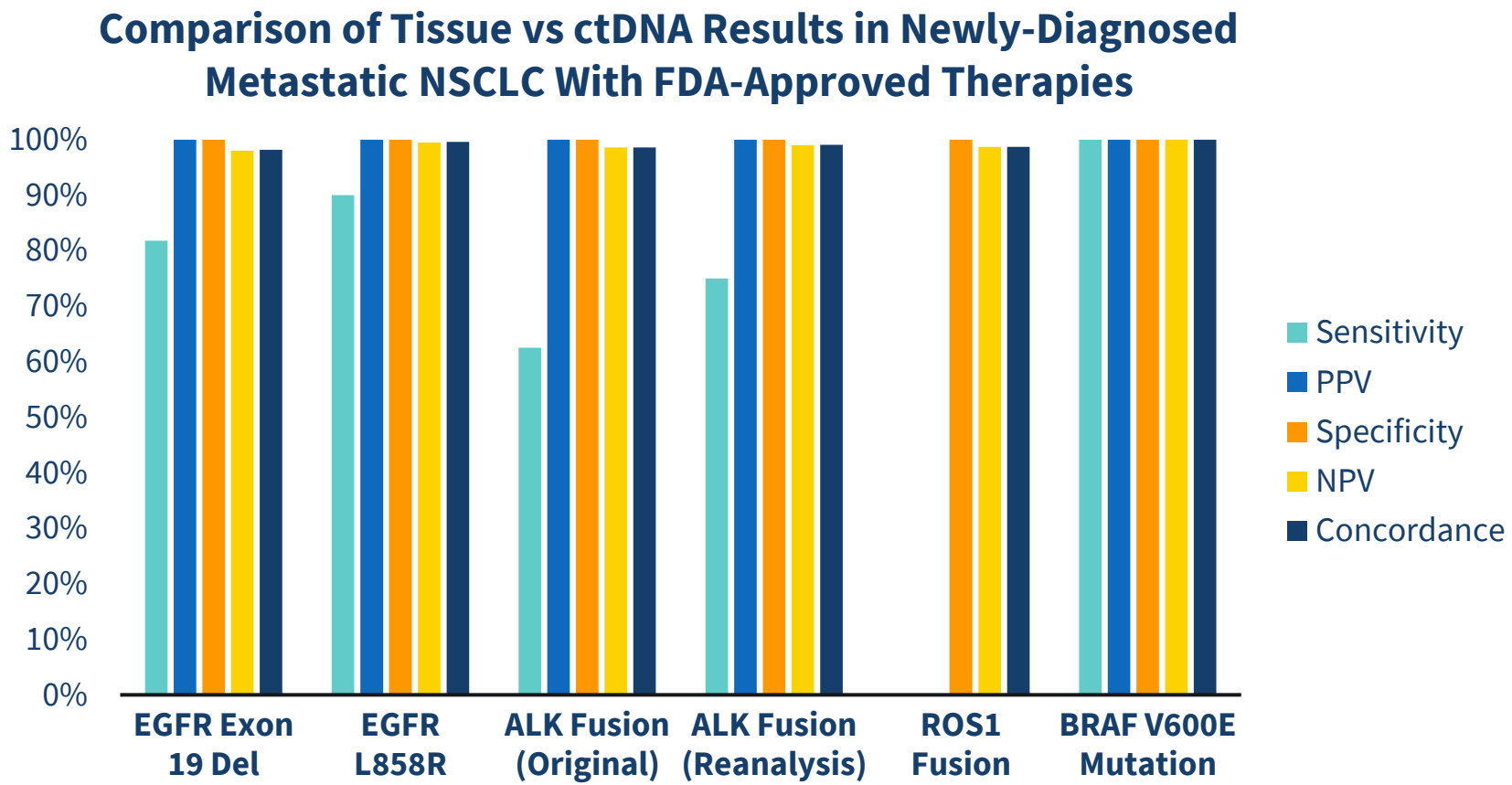
	Advantages	Disadvantages
Tissue Biopsy	• Pathology information • Assessment of DNA and non-DNA biomarkers • PD-L1 assessment	• Longer TAT • Limited tissue quantities • Invasive • At PD, re-biopsy not always feasible • Tumor heterogeneity
Liquid Biopsy (ctDNA)	• High concordance rate • Rapid TAT • Minimally invasive • Repeatable over time • Better capture tumor heterogeneity and clonal evolution	• Non-DNA biomarkers not evaluable • Increased costs if used concurrently with tissue testing • False negatives

PD: progressive disease;
TAT: turnaround time

Rolfo C, et al. *J Thorac Oncol*. 2021.

NILE (Non-invasive vs Invasive Lung Evaluation) Study

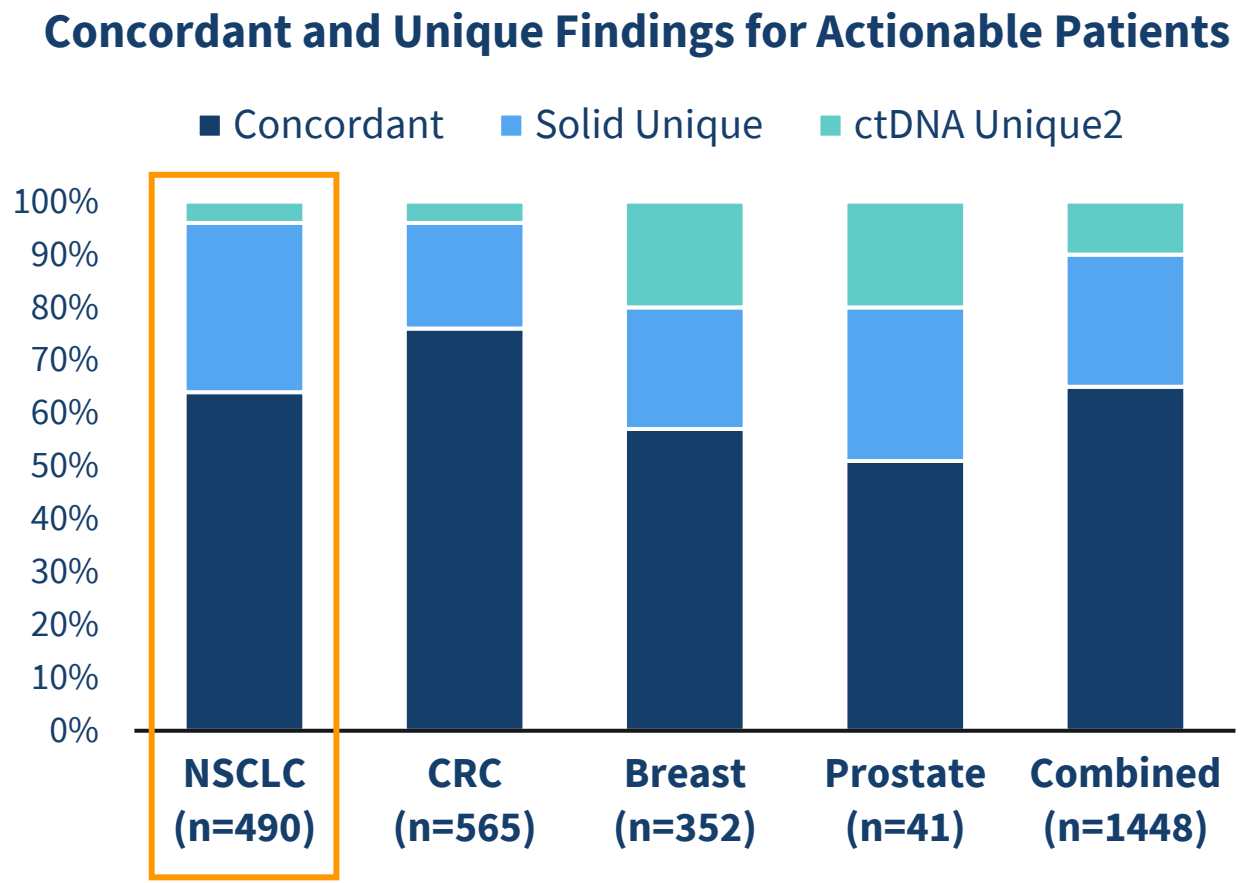
- Newly diagnosed advanced NSCLC (n = 282)
- Designed to test concordance between tissue & ctDNA (liquid) biopsy biomarker detection



Leighl NB, et al. *Clin Cancer Res*. 2019.

Concurrent NGS Testing Increases Detection Rates

- N = 3209 pts (May 2020 - December 2022)
- Patients had stage IV NSCLC, Breast, Prostate, or CRC
- Tissue and plasma ctDNA tested for genomic profiling
- Biopsies and blood draws must have occurred within 30 days



Iams WT, et al. *JAMA Netw Open.* 2024.

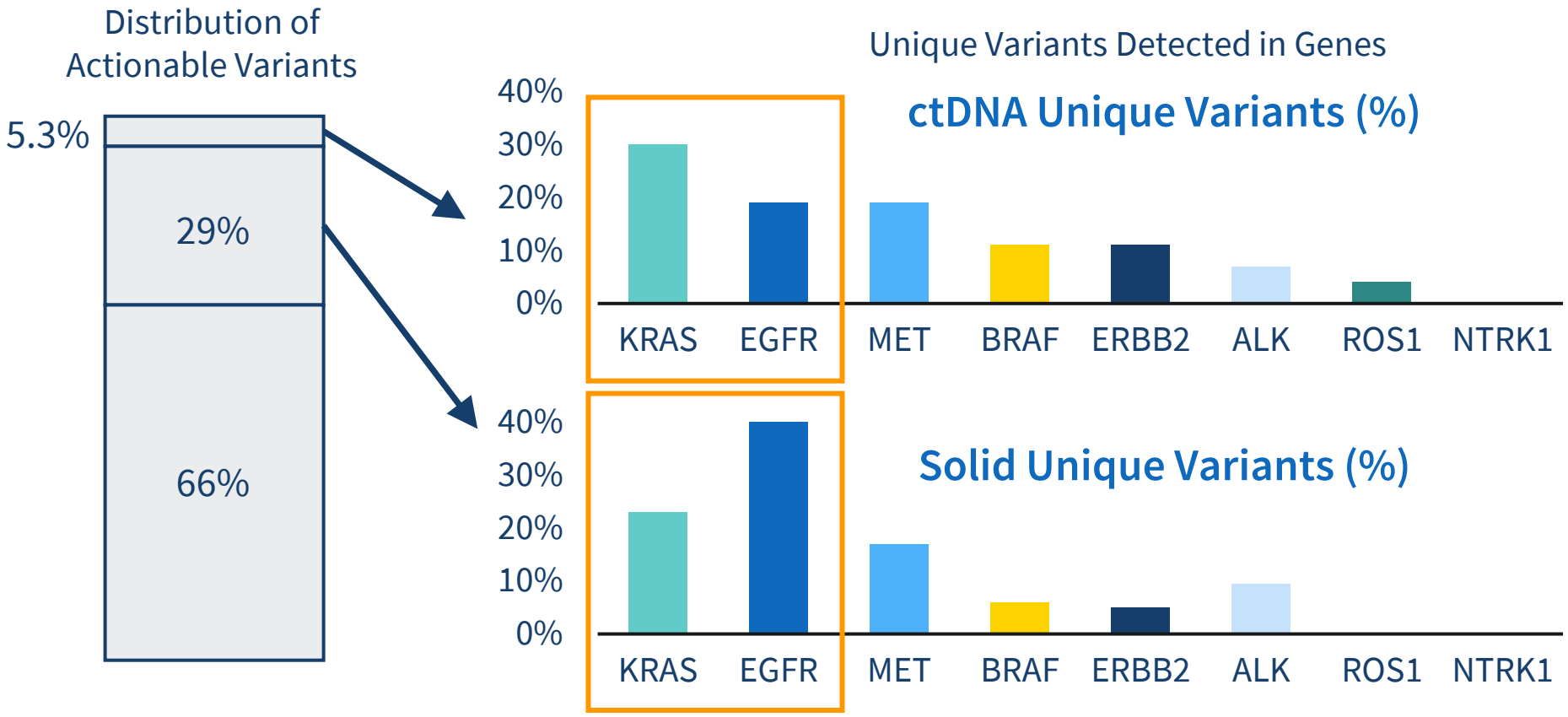
Guidelines: Concurrent vs Sequential Biomarker Testing in NSCLC

NCCN®[1]	Both ctDNA and tissue testing have appreciable false negative rates, supporting the complementarity of these approaches, and ***data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection***
ESMO®[2]	In treatment-naive NSCLC, **ctDNA can be considered complementary or alternative to tissue NGS for biomarker evaluation.** If available, tissue testing with such assays remains the gold standard compared with ctDNA, although any tissue assay can be limited by low tumour cellularity or quality
ASCO/IASLC®[3]	Although tissue-based testing remains the gold standard for tumor genotyping for many cancer patients, because of technical and biologic limitations of ctDNA analysis, **cfDNA analysis can be used either sequentially, when tumor tissue is insufficient/inadequate for testing, or concurrently, when tissue is scant or of uncertain adequacy for genotyping**

[1]NCCN Guidelines for NSCLC, Version 6.2026; [2]Pascual J, et al. *Ann Oncol*. 2022; [3]https://www.iaslc.org/iaslc-atlas-molecular-testing-targeted-therapy-lung-cancer.

Concurrent NGS Testing Increases Detection Rates

Actionable Variants Detected in Non–Small Cell Lung Cancer (NSCLC) Cohort



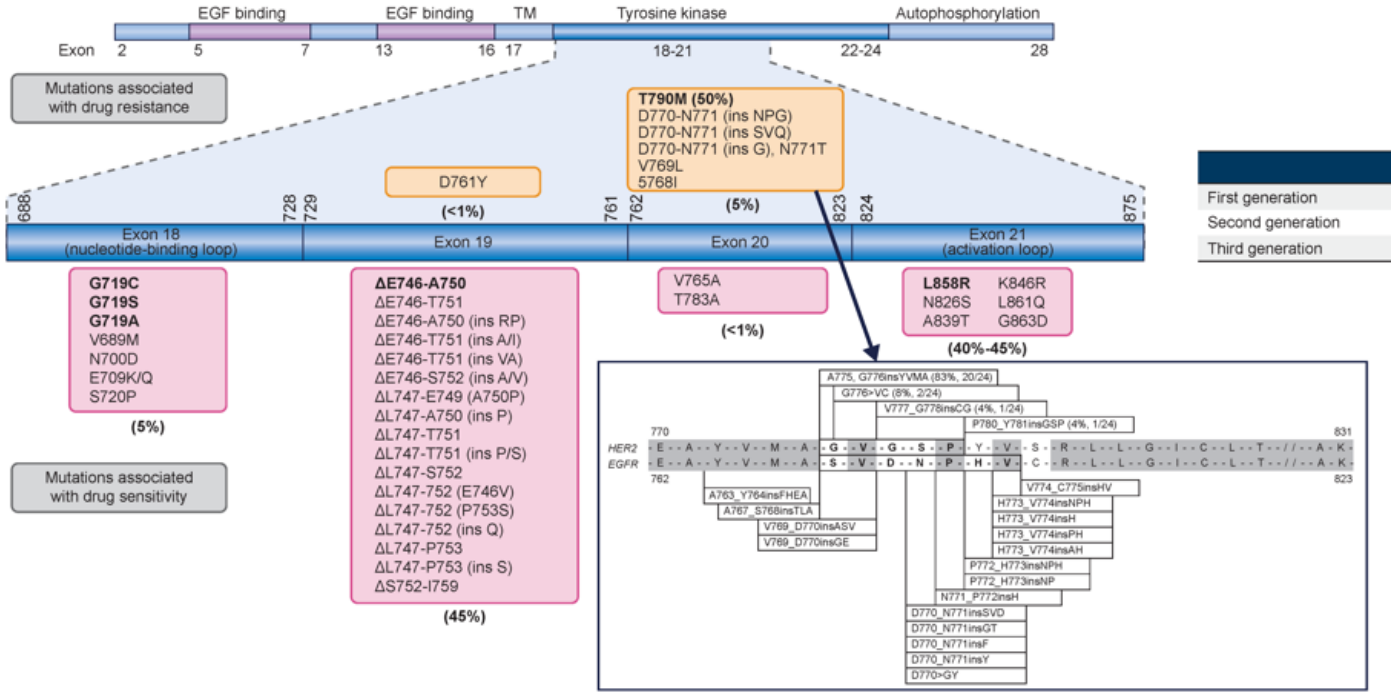
Most common variants detected were *KRAS* and *EGFR*

Iams WT, et al. *JAMA Netw Open.* 2024.

Molecular Testing

Guidelines (NCCN) recommend **broad molecular profiling** (NGS panels).

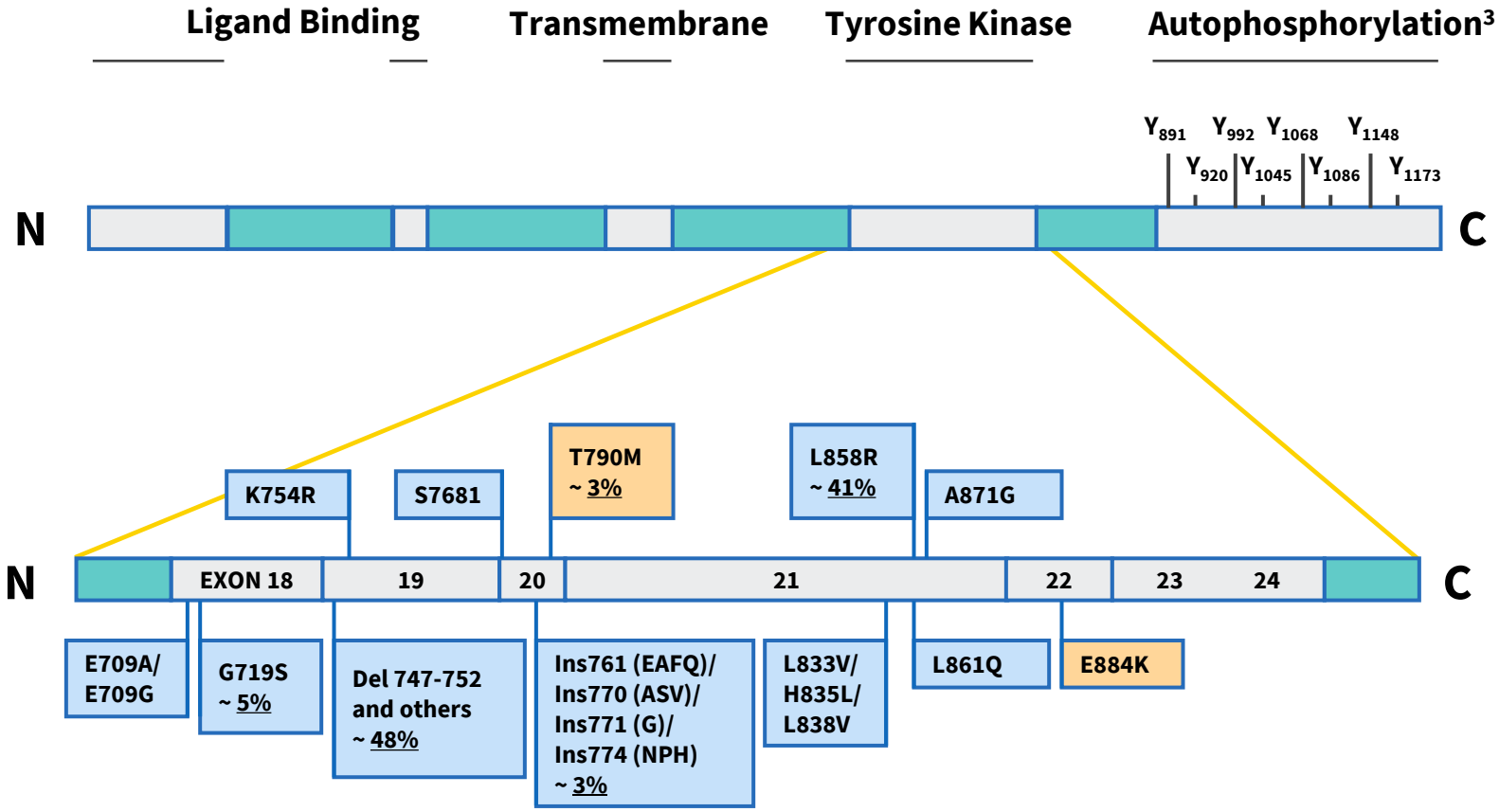
- **Comprehensive Profiling (NGS)**
  - Best for detecting rare variants and complex alterations in multiple genes in a single assay
- **PCR-based Assays**
  - Fewer alterations assayed
  - Can detect most common variants (L858R, ex19 del)
  - Fast TAT, less DNA required



NCCN Guidelines for NSCLC, Version 6.2026; Pirker R, et al. *J Thorac Oncol*. 2010.

EGFR Kinase Domain Mutations

- Encoded by exons 18–24[1]
- Mutation detection generally focused on 18–21[1]
- Sequencing has identified >600 described *EGFR* variants.[1,2]

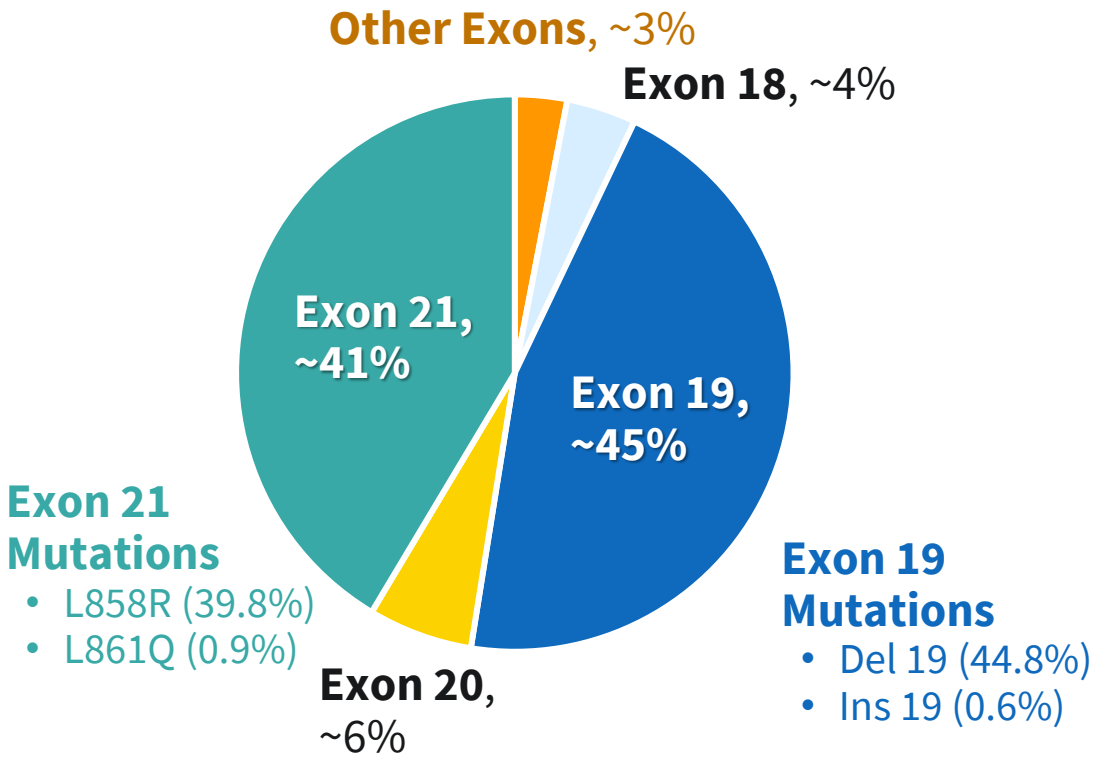


[1]Passaro A. *J Thorac Oncol*. 2021; [2]https://cancer.sanger.ac.uk; [3]Irmer D. *Oncogene*. 2007.

EGFR Mutations in NSCLC

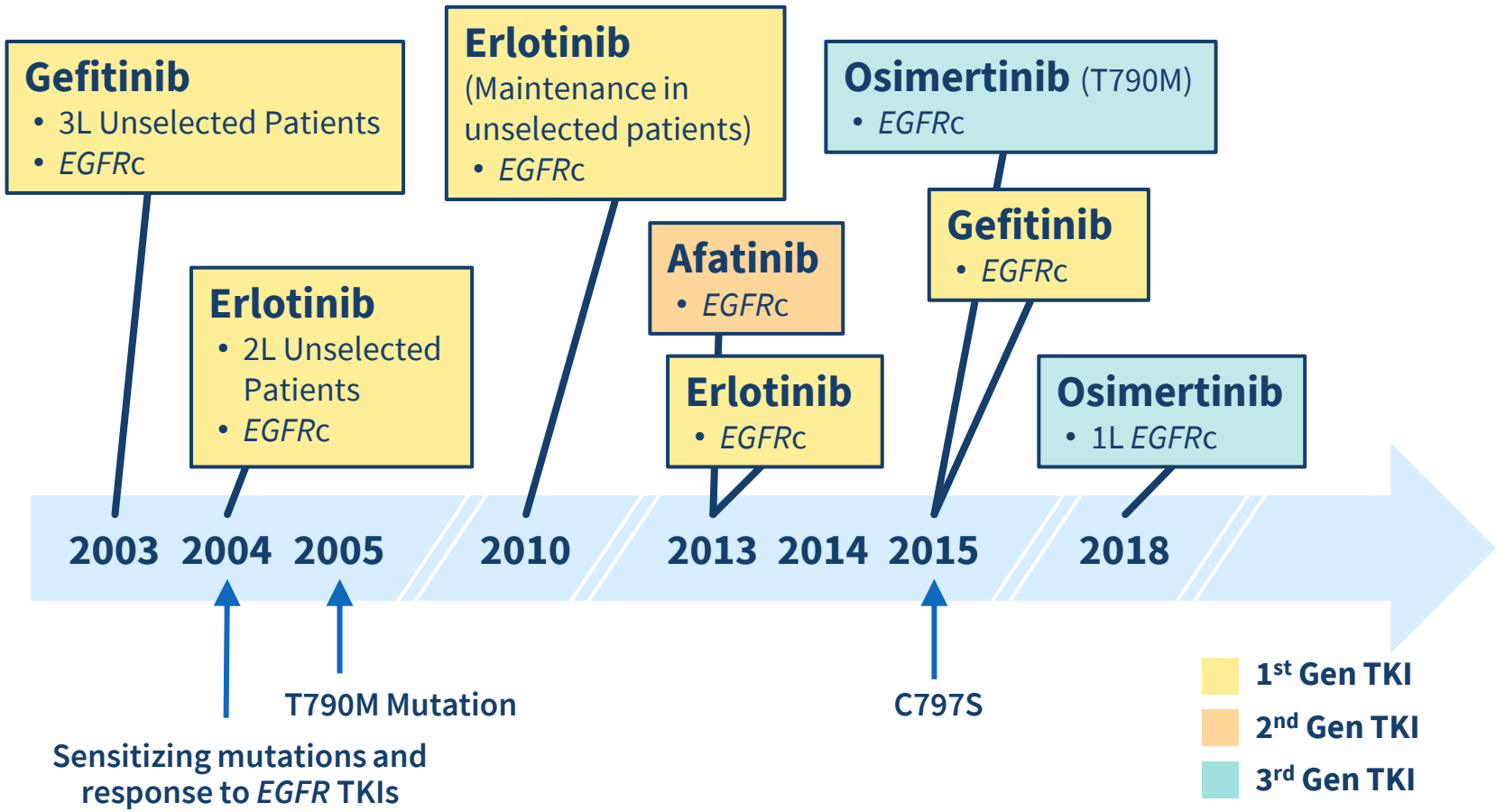
- The most common mutations are exon 19 deletions and L858R mutation in exon 21[1,2]
  - Detected in ~85% of all mutation cases
  - Clinically relevant as patients respond to *EGFR* tyrosine TKIs
- Exon 20 insertions are the third most common *EGFR* subtype[3,4]
  - SOC is amivantamab plus platinum-based chemotherapy
  - Prognosis is poorer compared to common *EGFR* mutations

Frequency of *EGFR* Mutations[1]



[1]Kobayashi Y, et al. *Cancer Sci*. 2016; [2]Girard N, et al. WCLC Annual Meeting 2021: Abstract 3390; [3]Remon J, et al. *Cancer Treat Rev*. 2020; [4]NCCN Guidelines for NSCLC, Version 6.2026.

The Arrival of a New Targeted Therapy Paradigm in *EGFR*-mutated Metastatic NSCLC

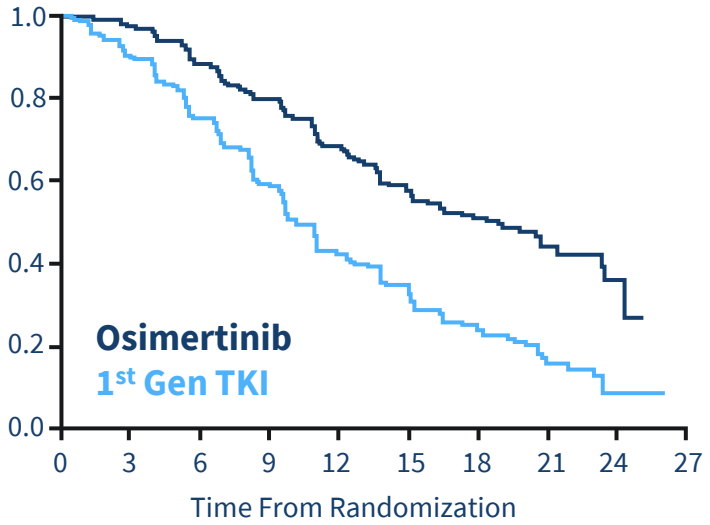


Role for Combination Strategies

Adapted from Zhou F, et al. *Nat Rev Clin Oncol*. 2025.

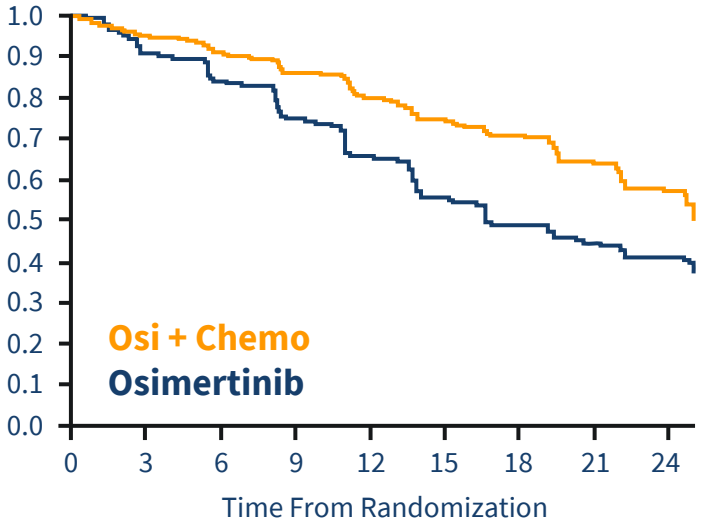
Options for 1L Treatment for *EGFR*+ NSCLC

FLAURA
Osi Mono



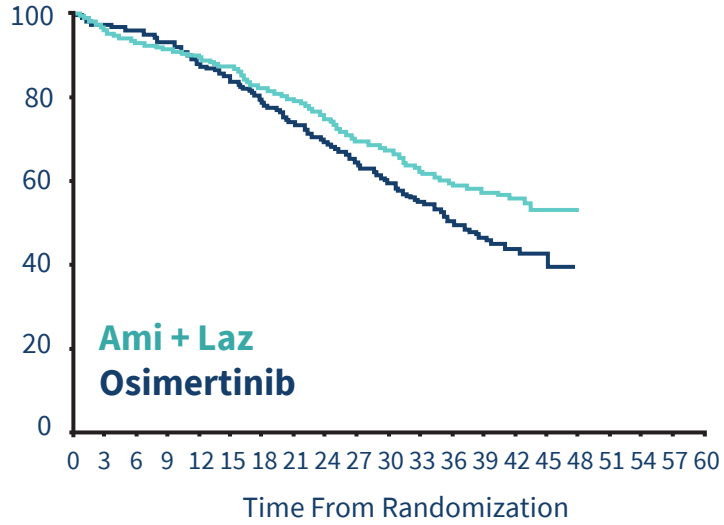
Progression-Free Survival		Overall Survival	
Osimertinib	18.9 mo	Osimertinib	38.6 mo
1st Gen TKI	10.2 mo	1st Gen TKI	31.8 mo

FLAURA 2
Osi + Chemo



Progression-Free Survival	
Osi + Chemo	25.5 mo
Osimertinib	16.7 mo

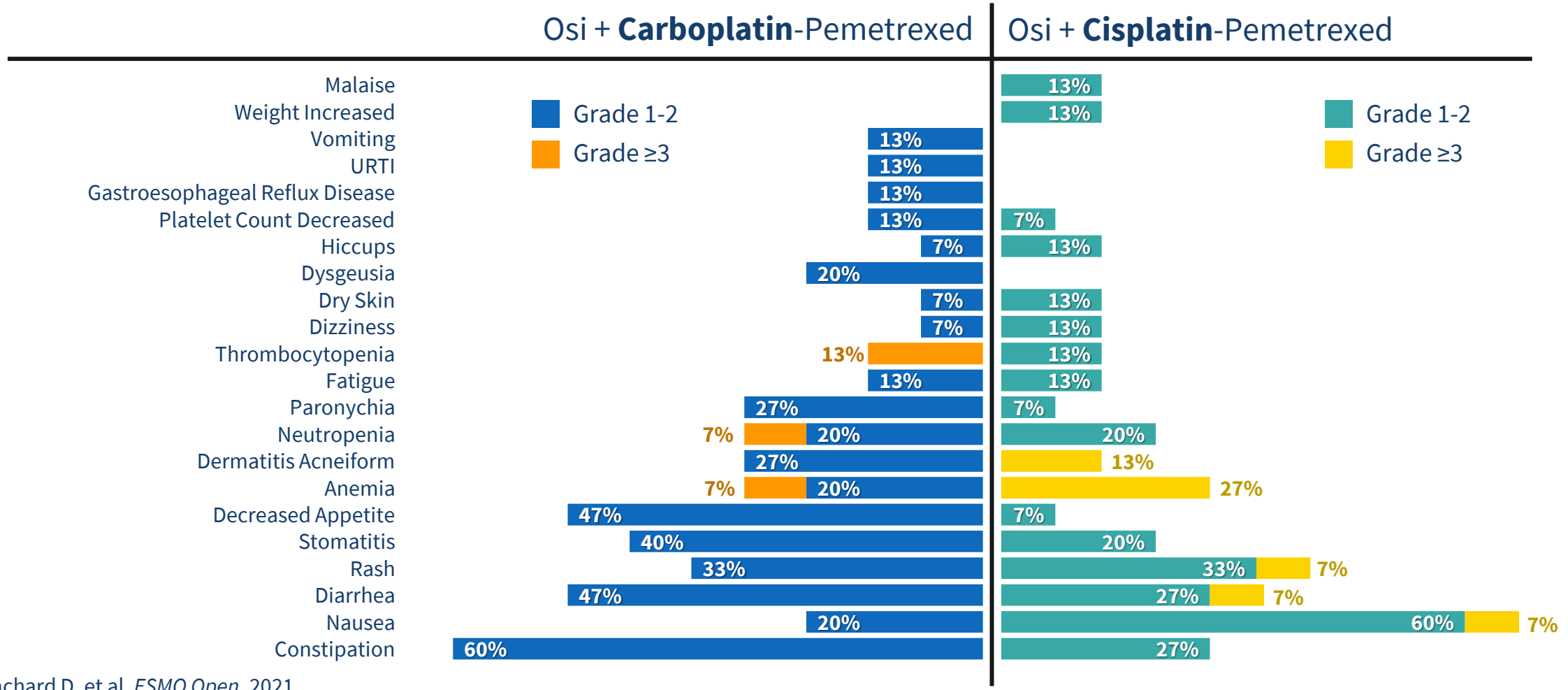
MARIPOSA
Ami + Lazertinib



Progression-Free Survival		Overall Survival	
Ami + Laz	23.7 mo	Ami + Laz	NR
Osimertinib	16.6 mo	Osimertinib	36.7 mo

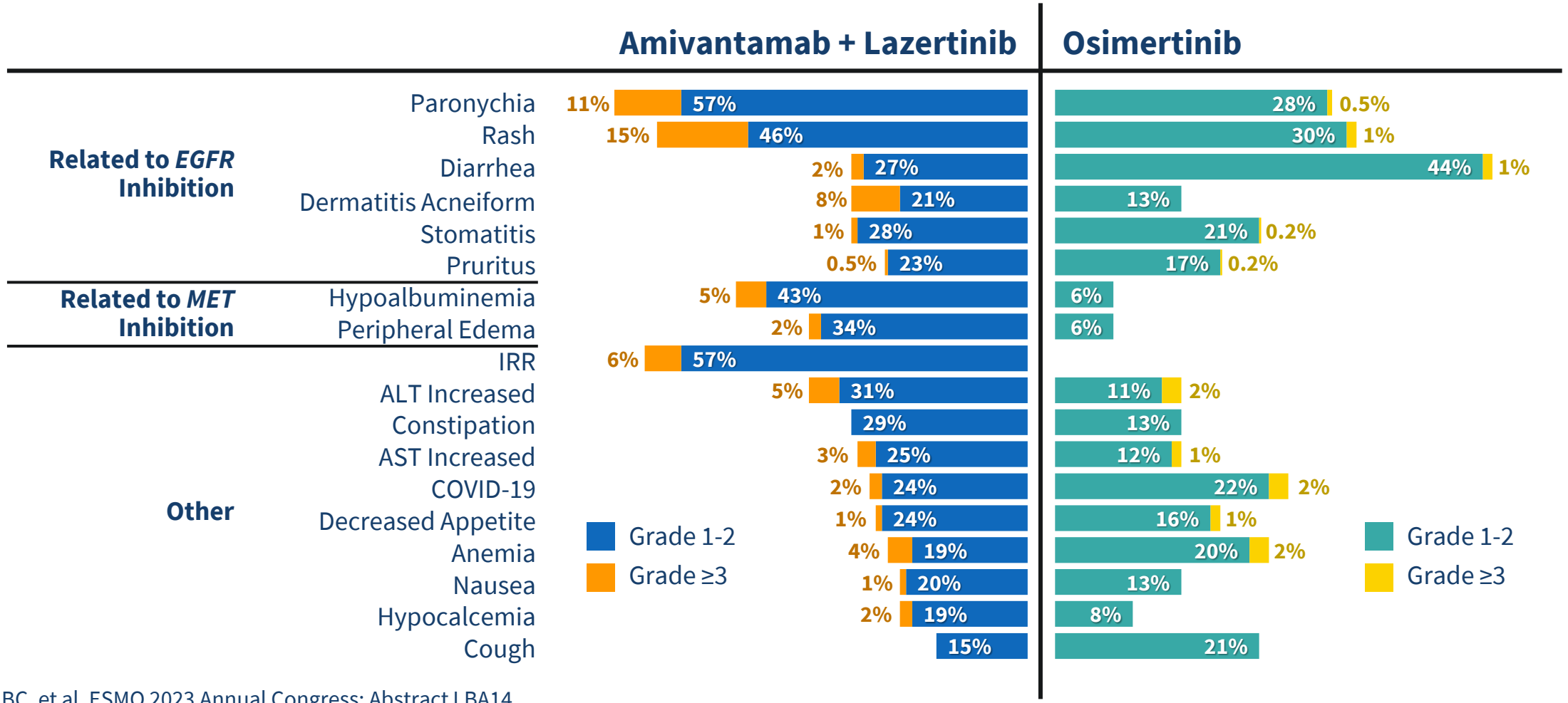
Soria JC, et al. *N Engl J Med*. 2018; Planchard D, et al. *N Engl J Med*. 2023; Cho BC, et al. *N Engl J Med*. 2024.

Safety Profiles: Osimertinib + Chemo



Planchard D, et al. *ESMO Open*. 2021.

Safety Profiles: Amivantamab + Lazertinib



Cho BC, et al. ESMO 2023 Annual Congress: Abstract LBA14.

Patients With *EGFR*m NSCLC Eventually Develop *EGFR* TKI Resistance and Disease Progression

Stage IV*

*Some stage IIIb patients may be treated as stage IV patients depending on disease characteristics.

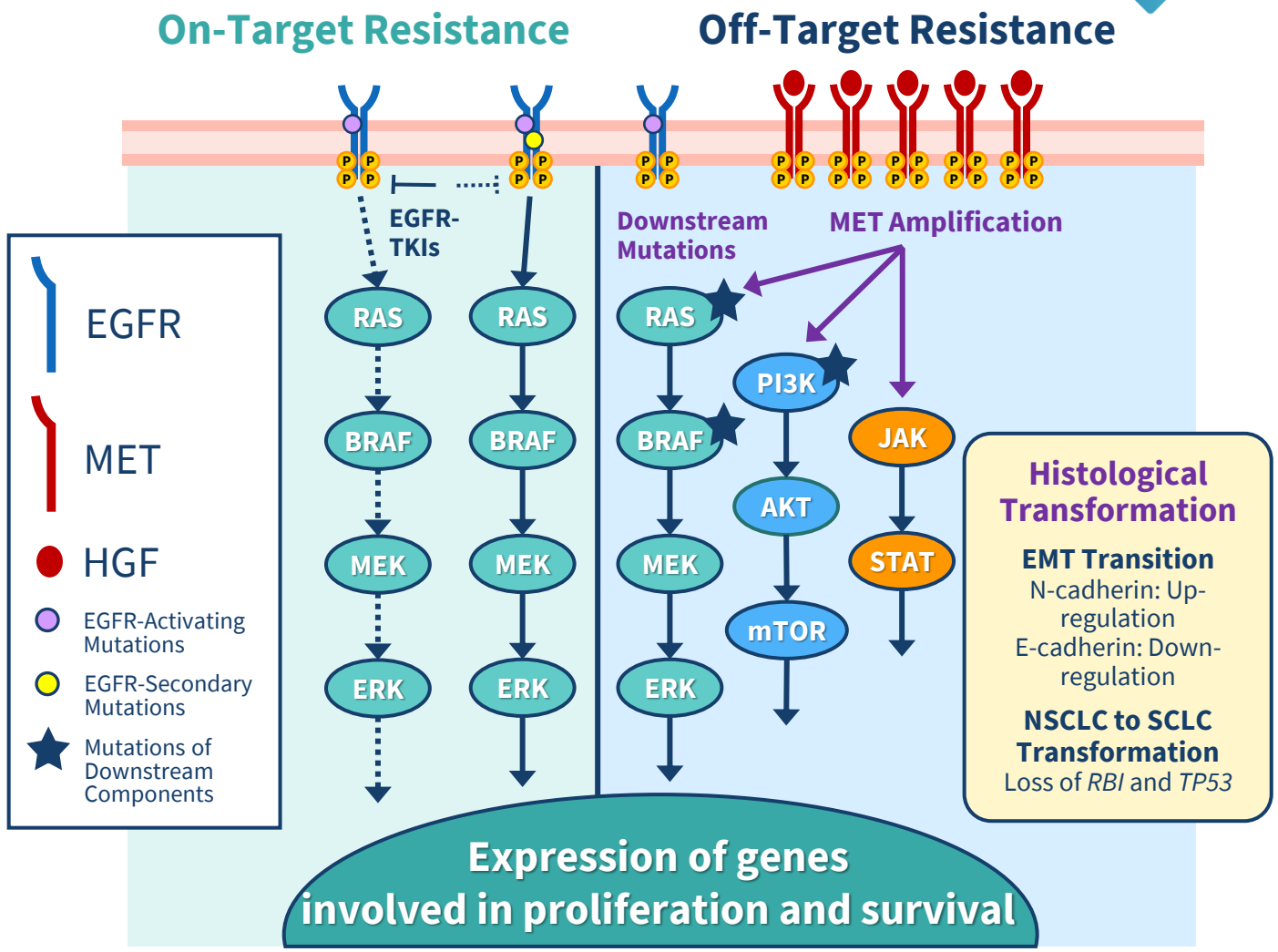
Patients With Stage IV *EGFR*m NSCLC*

	L858R and Ex19del (~79%)	Ex20ins (~12%)
1L	Historical SOC: **Osimertinib** mPFS: 18.9 months mOS: 38.6 months	Historical SOC: **Platinum Chemo** mPFS: 5.5 months mOS: 16.2 months
2L	Historical SOC: **Platinum-Based Chemotherapy** mPFS: 5.4 months mOS: 19.5 months	Historical SOC: **Docetaxel** mPFS: 3 months mOS: 12.5 months

Reiss JW, et al. *J Thorac Oncol*. 2018; Ramalingam SS, et al. *N Engl J Med*. 2020; Soria JC, et al. *Lancet Oncol*. 2015.

Overcoming Resistance – Combination Strategies

- Selective (On target resistance)
  - *EGFR* T790M, C797S, G724S
    - Acquired vs de novo
  - 3rd and 4th generation *EGFR* TKI
- Non-selective (Off target resistance)
  - *MET / BRAF / RET / ALK / HER2 / PI3K*
  - EMT State transformation
  - **Novel MOA**
    - Bispecifics
    - T-cell Engagers
    - Antibody drug conjugates
    - Conventional chemotherapy combinations



Houssein C, et al. *Cancer*. 2023.

MARIPOSA 2

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Documented EGFR Ex19del or L858R
- Progressed on or after osimertinib monotherapy, as most recent line of therapy
- ECOG PS 0 or 1
- Stable brain metastases were allowed:
  - Radiation or definitive therapy was not required (untreated)

Stratification Factors

- Osimertinib line of therapy (first vs second)
- Asian race (yes or no)
- History of brain metastases (yes or no)

2:2:1 Randomization (N=657)

- **Amivantamab-Lazertinib-Chemotherapy** (n=263)
- **Chemotherapy** (n=263)
- **Amivantamab-Chemotherapy** (n=131)

Dual Primary Endpoint of PFS[c] by BICR per RECIST v1.1

Amivantamab-Lazertinib-Chemotherapy vs Chemotherapy

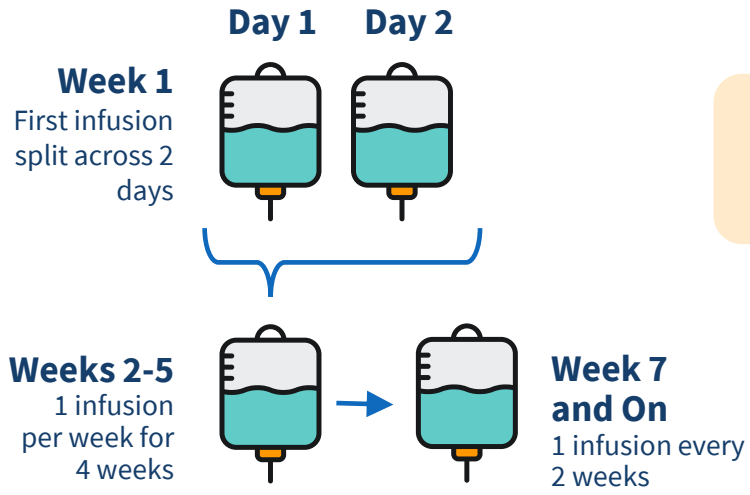
Amivantamab-Chemotherapy vs Chemotherapy

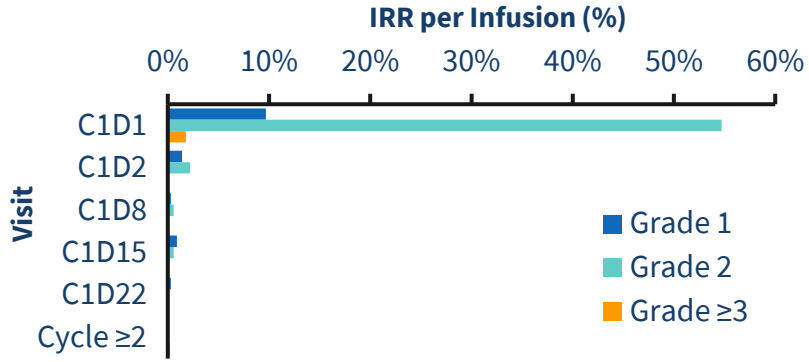
Secondary Endpoints

- Objective Response Rate (ORR)[c]
- Duration of Response (DoR)
- Overall Survival (OS)[c]
- Intracranial PFS
- Time to Subsequent Therapy[d]
- PFS After First Subsequent Therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

Passaro A, et al. *Ann Oncol*. 2024.

Infusion Related Reaction





Park K, et al. *Ann Oncol*. 2021.

The initial infusion should be administered in split doses on Week 1, Day 1 and 2

Prior to initial infusion (Week 1), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs

For subsequent doses, antihistamines and antipyretics should be administered.

Patients should be treated in a setting with appropriate medical support to treat IRRs.

Infusions should be interrupted at the first sign of IRRs of any severity and additional medicinal products* should be administered as clinically indicated

Upon resolution of symptoms, the infusion should be resumed at 50% of the previous rate.

For recurrent Grade 3 or Grade 4 IRRs, amivantamab should be permanently discontinued.

*e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics.

SKIPPirr (WCLC2024)

Can We Prevent Infusion Related Reactions? SKIPPirr Study Design

IV **Amivantamab**
1050 mg (<80 kg)
1400 mg (≥80 kg)
Once weekly for 4 weeks; every 2 weeks thereafter
+
Oral **Lazertinib**
240 mg QD

Stage 1

Cohort A
Oral Dexamethasone (4 mg)

Cohort A2
Oral Dexamethasone (8 mg)

Cohort B
Oral Montelukast (10 mg)

Cohort C
SC Methotrexate (25 mg)

If IRR ≤3/6 pt, proceed to Stage 2

Stage 2

Enroll up to **10** additional patients per cohort.

If IRR ≤8/16 pt, proceed to Expansion Stage

Expansion Stage

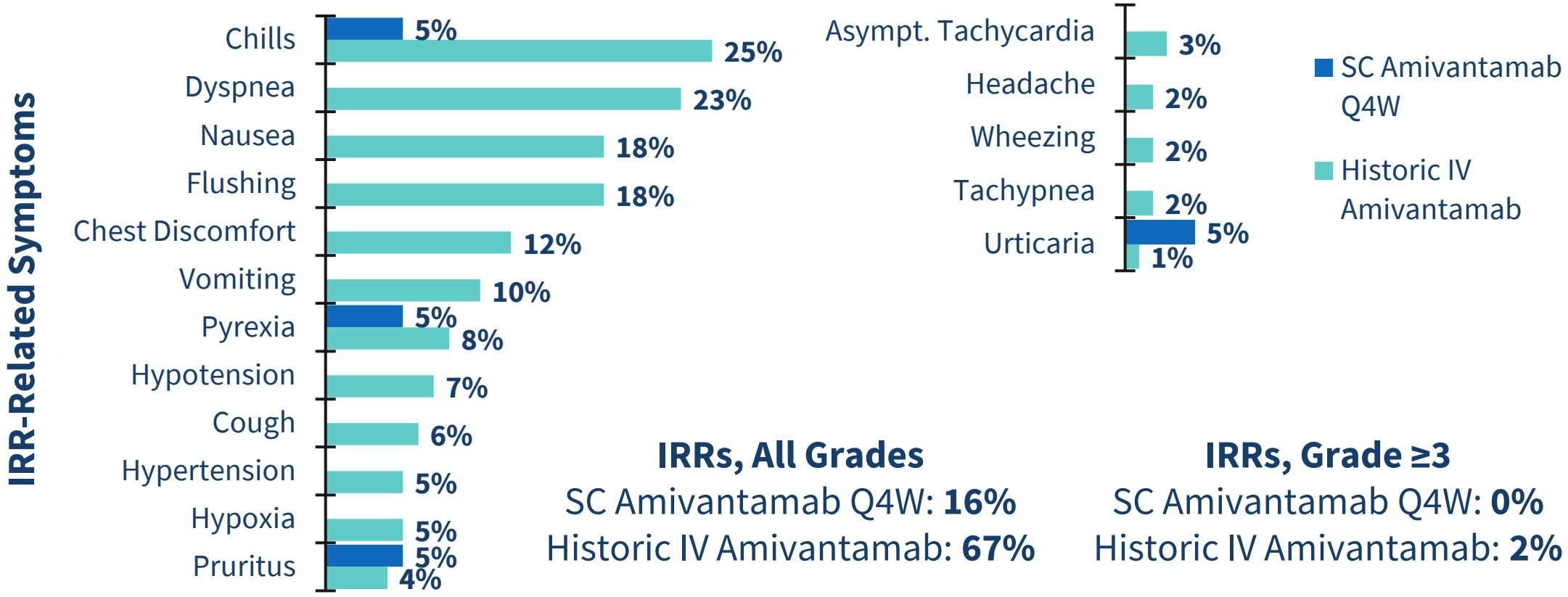
Enroll up to **24** additional patients per cohort.

If both Cohorts A and A2 have positive results, only one will move on to Stage 2 as determined by the SET.

Prophylaxis with 8mg oral dexamethasone resulted in reduction in IRR compared to historical data

Lopes G, et al. WCLC Annual Meeting 2024: Abstract MA12.08.

Incidence of IRR and IRR Related Symptoms PALOMA (Subcutaneous)



IRRs, All Grades
SC Amivantamab Q4W: **16%**
Historic IV Amivantamab: **67%**

IRRs, Grade ≥3
SC Amivantamab Q4W: **0%**
Historic IV Amivantamab: **2%**

Leighl NB, et al. ELCC 2024: Abstract 6MO.

Nursing Considerations: Amivantamab

- Confirm pre-medications were taken
- Verify weight: 80kg vs >80kg – different dosing
- Use a peripheral IV line for Week 1 and Week 2
- During infusion: Monitor for IRR
  - chills, dyspnea, flushing, fever, nausea, chest discomfort, hypotension, and vomiting
- Grade 1–2: Interrupt infusion immediately. Monitor until symptoms resolve. Resume at 50% of the infusion rate at which the reaction occurred. If no additional symptoms after 30 minutes, the rate may be escalated
- Grade 3: Interrupt infusion and administer supportive care medications. Continuously monitor until symptoms resolve. Resume at 50% rate; escalate after 30 minutes if tolerated. Add corticosteroid premedication for subsequent doses. For recurrent grade 3 → permanently discontinue
- Grade 4 or any grade anaphylaxis: Permanently discontinue amivantamab
- Subcutaneous amivantamab:
  - Offers patients safety and convenience vs IV formulation
  - Safety profile is similar to IV formulation, with reduced infusions reactions (13% vs 66% of patients receiving IV formulation)

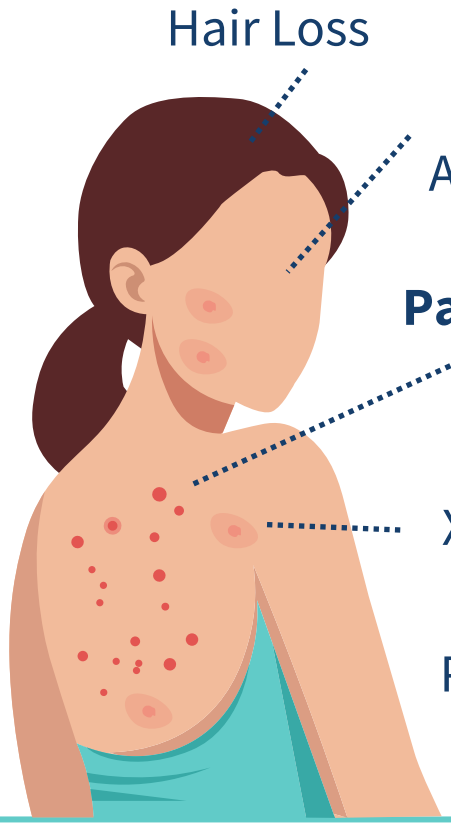
Leighl NB, et al. *J Clin Oncol.* 2024; Expert Opinion.

First-line Combination Therapies

- **Toxicity:** more toxicity and for longer
- **Quality of life:** intravenous therapy every 2-3 weeks vs newly available subcutaneous option
- Financial cost to patient and healthcare system
- **Over-treatment:**
  - Significant heterogeneity in response to osimertinib
  - Consider osimertinib monotherapy

EGFR Inhibition Mediated Cutaneous Toxicities

Cutaneous



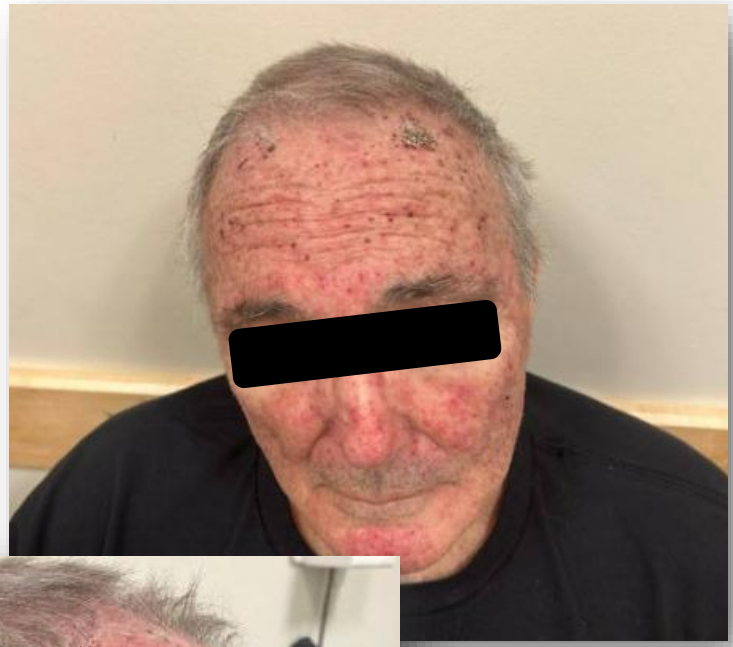
Hair Loss

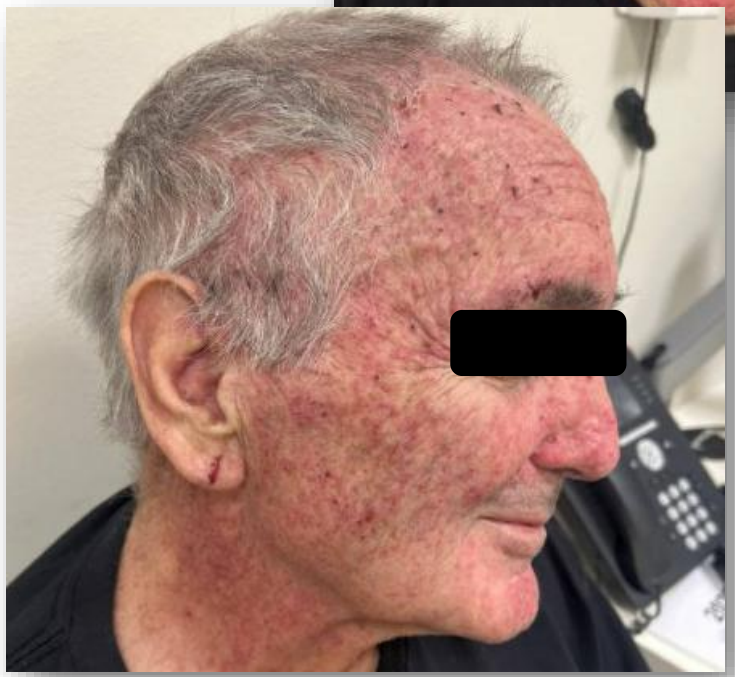
Eye/Eyelash Abnormalities

Papulopustular Rash

Xerosis/Pruritus

Periungual/Nail Alterations





Images courtesy of Dr. Sherry.

EGFR Inhibition Mediated Cutaneous Toxicities: Nursing interventions

- Moisturize skin
- Avoid hot water/sun
- Wash face with gentle cleanser
- Triamcinolone cream 0.5%
- Clindamycin gel
- Minocycline or Doxycycline BID
- Scalp: head and shoulders shampoo

Expert Opinion.

EGFR TKI Toxicity (CTCAE v5.0)
Rash acneiform

*__Rash__ is defined as a disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest, and back.

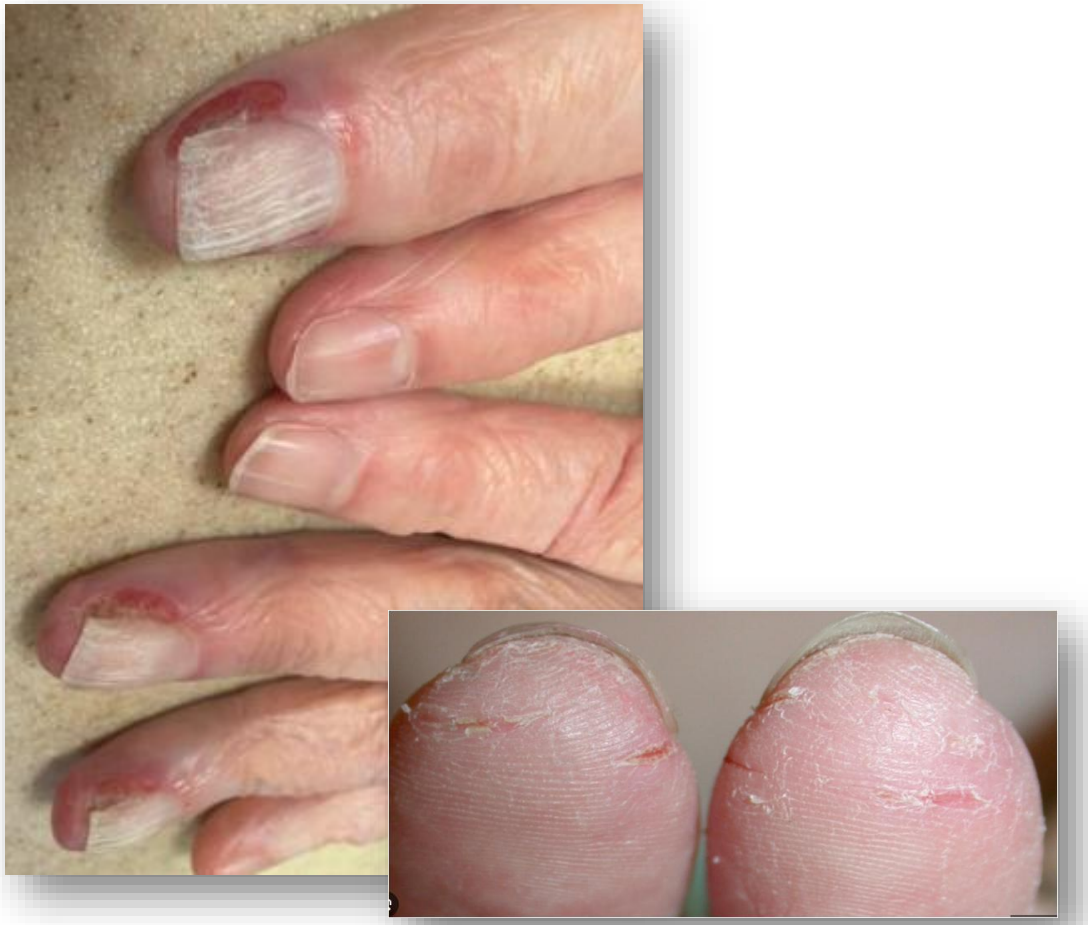
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe or medically significant, but not immediately life-threatening	Life-threatening consequences	Death related to AE
Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10%–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering >30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death

Instrumental ADL—preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Self-care ADL—bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

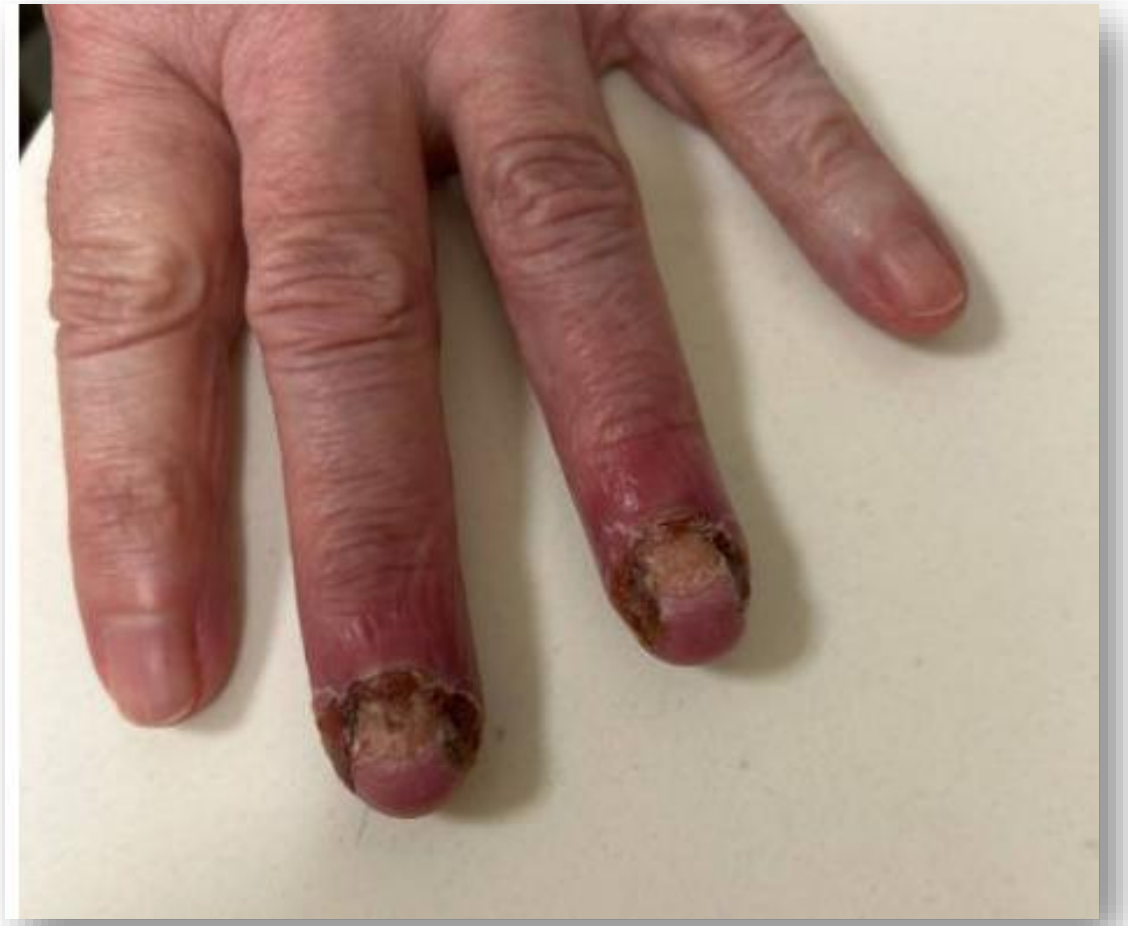
Paronychia/Nail Alterations

- Soak in 3:1 warm water/vinegar or bleach (15 mins on, 15 mins off)
- Mupirocin ointment
- 4% Chlorhexidine
- Timolol 0.5% ophthalmic solution (1-2 gtts BID)
- Dermatology/podiatry/surgery consult
- Nail avulsion
- Superglue (fissures)



Expert Opinion.

Paronychia/Nail Alterations

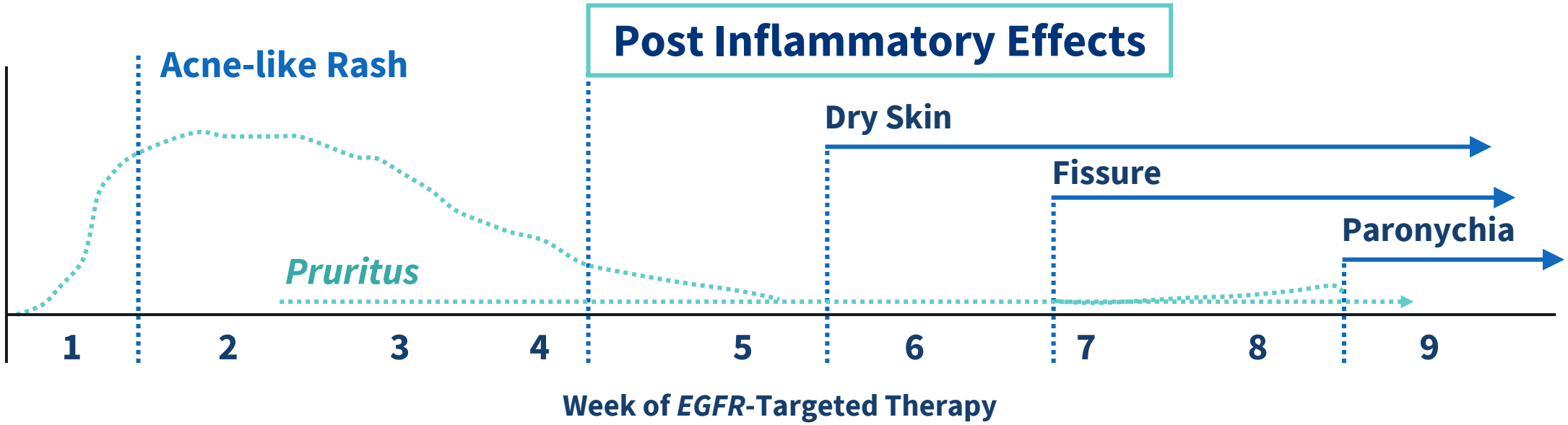


Cocoon Trial: First-line Ami/Laz With Enhanced Dermatologic Care

	Dermatologic Prophylactic Regimen (COCOON)	
Antibiotic Prophylaxis	**Weeks 1-12** 100 mg BID Doxycycline or Minocycline	**Weeks 13+** 1% Topical Clindamycin Lotion on the scalp daily
Nail Cleaning Agent	**Weeks 1+** 4% Chlorhexidine on the fingernails and toenails daily for 12 months	
Long-Acting Skin Hydration	**Weeks 1+** Ceramide-based moisturizer at least daily for 12 months.	

Basse C, et al. *Lung Cancer*. 2022; COCOON (ClinicalTrials.gov Identifier: NCT0612014).

Timing of *EGFR*i Associated Dermatologic Toxicities

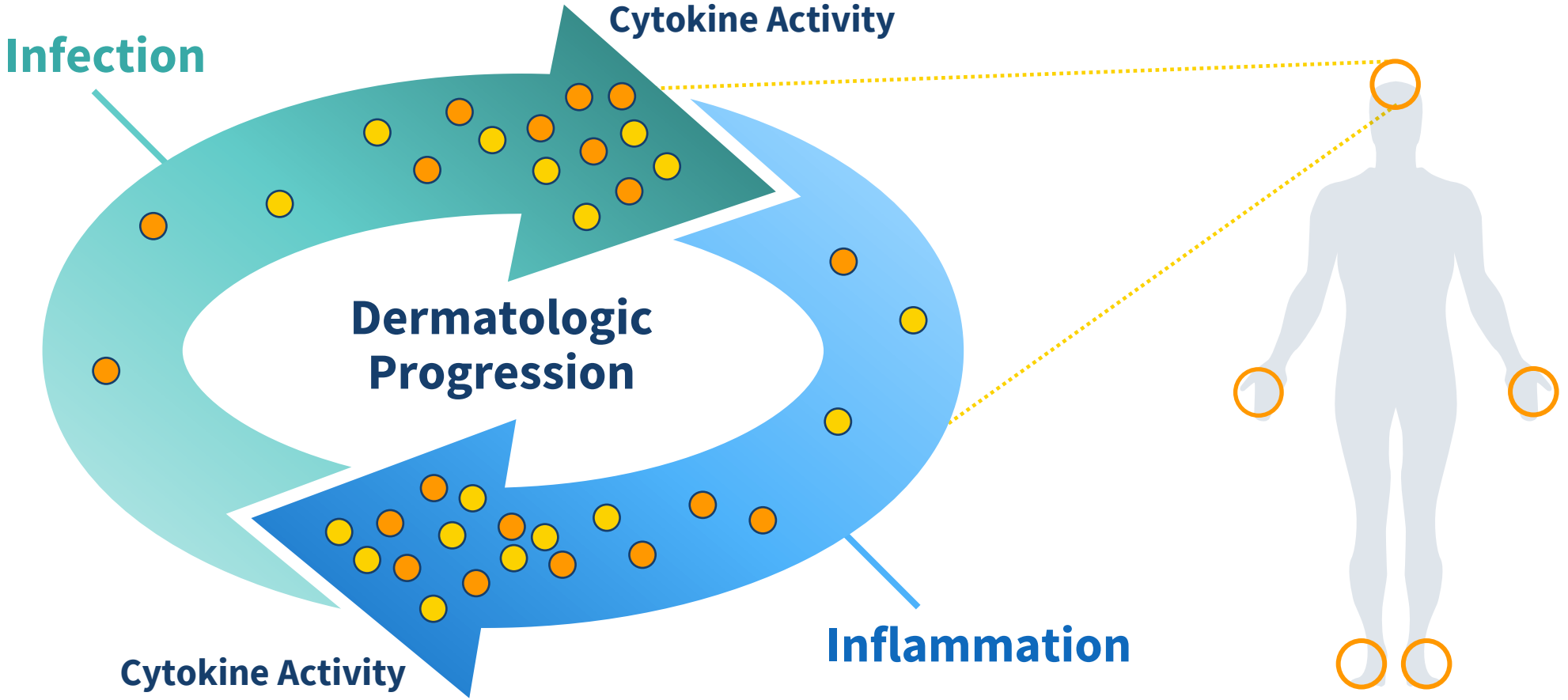


34

Clinical sequelae of **skin drying and cracking** emphasize the important role of **proactive management**

Van Cutsem E. *Oncologist*. 2006; Lacouture ME, et al. *J Clin Oncol*. 2010; Scope A, et al. *J Clin Oncol*. 2007.

Cycle of Dermatologic Toxicities



Key Takeaways

- Biomarker Testing Is Not Optional — It Is the Standard of Care
- *EGFR*-Mutated NSCLC Has Entered a New Combination Therapy Era — But With Important Trade-Offs
- Resistance Is Inevitable — But Now Targetable
- Nurses Are Central to Optimizing Outcomes

Interprofessional/Multidisciplinary Team Overview

- Providers (Physicians, Advanced practice providers: NPs and PAs)
- Nurses/Nurse coordinators
- Pharmacists
- Social workers
- Psychologists
- Dieticians
- Among others

Reflect on What You Have Learned

How will you apply what you have learned to your practice and with your interprofessional and interdisciplinary oncology care team?

ASCO 2026: EGFR Key Data

- **Sunvozertinib (WU-KONG28 Trial):** Phase III results showed that sunvozertinib significantly outperformed standard platinum-based chemotherapy as a first-line treatment for advanced NSCLC with EGFR exon 20 insertions. It yielded a higher confirmed objective response rate (ORR) of 58.9% (vs 31.1%) and a median progression-free survival (PFS) of 10.3 months (vs. 7.5 months).
- **Amivantamab + Lazertinib (CHRYSALIS-2):** For the historically hard-to-treat atypical EGFR-mutant population, first-line use of this combination achieved a median overall survival (OS) of 41.0 months. This contrasts to the real-world cohort that received physician-selected first-line TKIs, which showed a median OS of 15.2 months.
- **ctDNA-Guided Therapy (FLAME Trial):** Data revealed that in EGFR-mutant NSCLC where ctDNA is persistent, utilizing ctDNA to guide the addition of chemotherapy to the EGFR TKI osimertinib significantly improved PFS compared to osimertinib alone.
- **Novel Inhibitors (Silevertinib & DZD6008):** Silevertinib, a 4th-generation CNS-penetrant inhibitor, yielded a 60% ORR in non-classical EGFR mutations. For C797X-resistant mutations, DZD6008 achieved a 41.7% ORR with durable disease control.
- **Brain Metastases (ESAONA Study):** Frontline asandeutertinib demonstrated improved intracranial ORR and intracranial PFS compared to osimertinib in EGFR-mutated NSCLC patients with brain metastases.

Neal J, et al. *J Clin Oncol.* 2026; Rotow J, et al. *J Clin Oncol*. 2026; Wang M, et al. *J Clin Oncol*. 2026; Zhou Q, et al. *J Clin Oncol*. 2026.

Novel Strategies for Managing *EGFR*-mutated mNSCLC:

Expert Insights into the Latest Data and Recommendations

CORNERSTONE MEDICAL EDUCATION

AAACME®
AMERICAN ACADEMY OF CME, INC.