Oncology Learning Network

Updates and Evidence-Based Strategies in Non-Small Cell Lung Cancer

A Focus on Molecular Testing, Targeted Treatment, and Adverse Event Management

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November 16, 2024

HMP Education

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Faculty Disclosures

- **Sheena Bhalla, MD**: Advisory Board—Novocure, AstraZeneca, Merus, Takeda; Independent Data Monitoring Committee—BMS
- **Christopher Fausel, PharmD, MHA, BCOP**, has disclosed no relevant financial relationship with any ineligible company (commercial interest)

Program Information

- This program is provided by HMP Education, an HMP Global company
- Supported by an educational grant from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, both are Johnson and Johnson companies.

Learning Objectives

- Assess current guideline recommendations for NSCLC molecular testing and treatment selection
- Evaluate the safety/efficacy data of current and emerging targeted treatment options in NSCLC
- Describe the role of oncology APs in NSCLC screening, treatment-related adverse event management, patient/caregiver education, and care coordination

NSCLC = non-small cell lung cancer; AP = advanced practitioner.

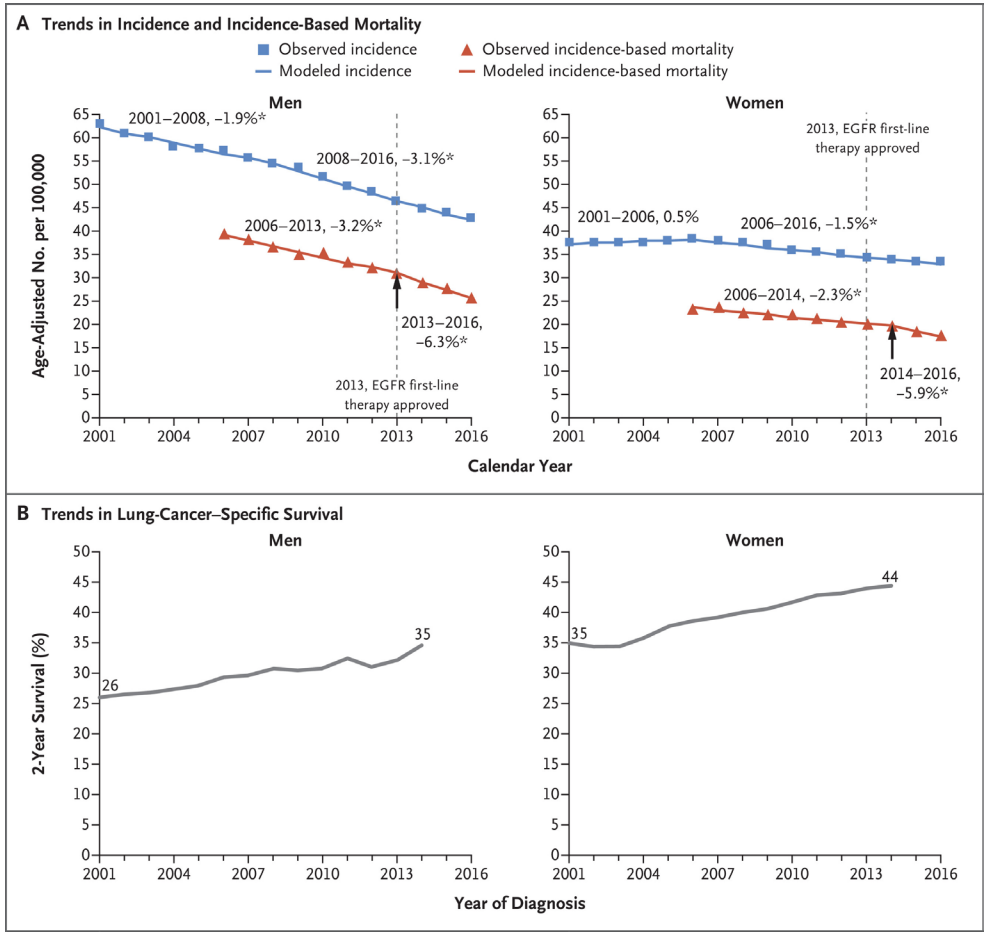
Lung Cancer Mortality

Estimated New Cases

	Males			Females	
Prostate	268,490	27%		Breast	287,850	31%
Lung & bronchus	117,910	12%		Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%		Colon & rectum	70,340	8%
Urinary bladder	61,700	6%		Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%		Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%		Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%		Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%		Pancreas	29,240	3%
Leukemia	35,810	4%		Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%		Leukemia	24,840	3%
All Sites	**983,160**	**100%**		**All Sites**	**934,870**	**100%**

Estimated Deaths

	Males			Females	
Lung & bronchus	68,820	21%		Lung & bronchus	61,360	21%
Prostate	34,500	11%		Breast	43,250	15%
Colon & rectum	28,400	9%		Colon & rectum	24,180	8%
Pancreas	25,970	8%		Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%		Ovary	12,810	4%
Leukemia	14,020	4%		Uterine corpus	12,550	4%
Esophagus	13,250	4%		Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%		Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%		Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%		Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**		**All Sites**	**287,270**	**100%**



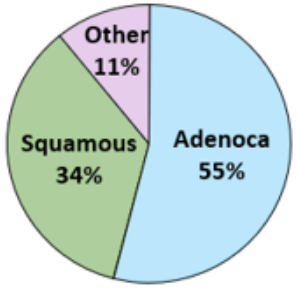
While lung cancer remains the leading cause of cancer-related deaths, mortality from lung cancer is decreasing with the use of targeted therapies.

***Annual percentage change is significantly different from zero (*P*<.05).**
EGFR = epidermal growth factor receptor.
Siegel RL, et al. *CA Cancer J Clin.* 2022;72(1):7-33. Howlader N, et al. *N Engl J Med.* 2020;383(7):640-649.

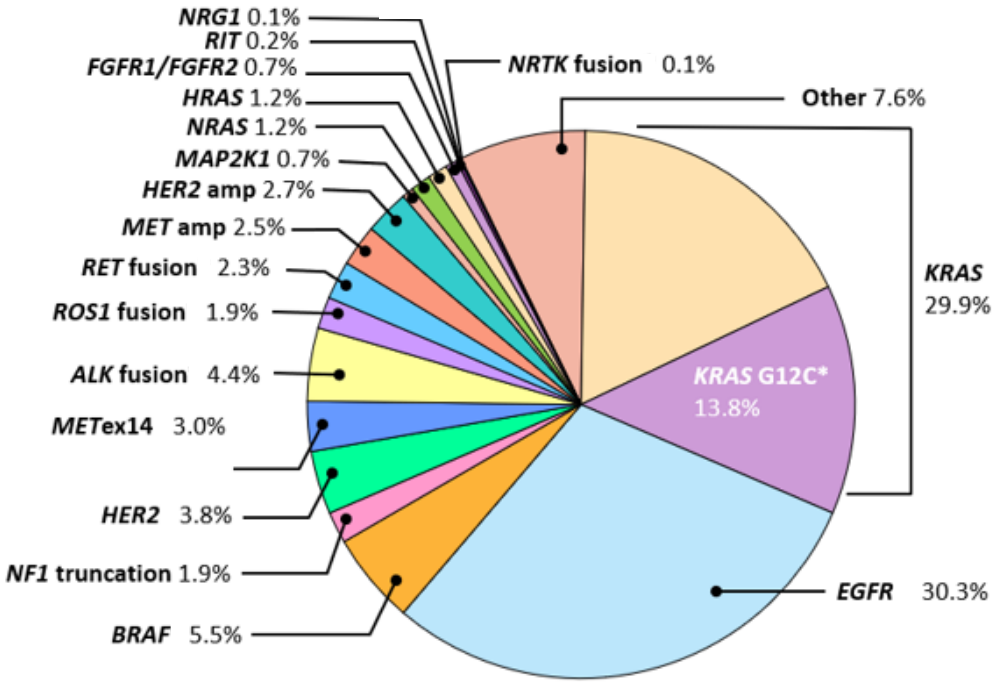
Histology and Prevalence of Driver Mutations in Advanced NSCLC

Disease Type

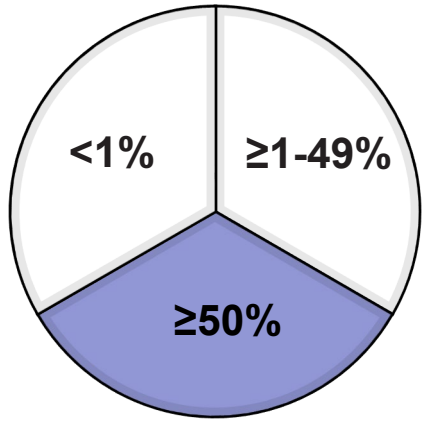
Histology Subtypes



Presence of a Targetable Mutation



PD-L1 Expression Level

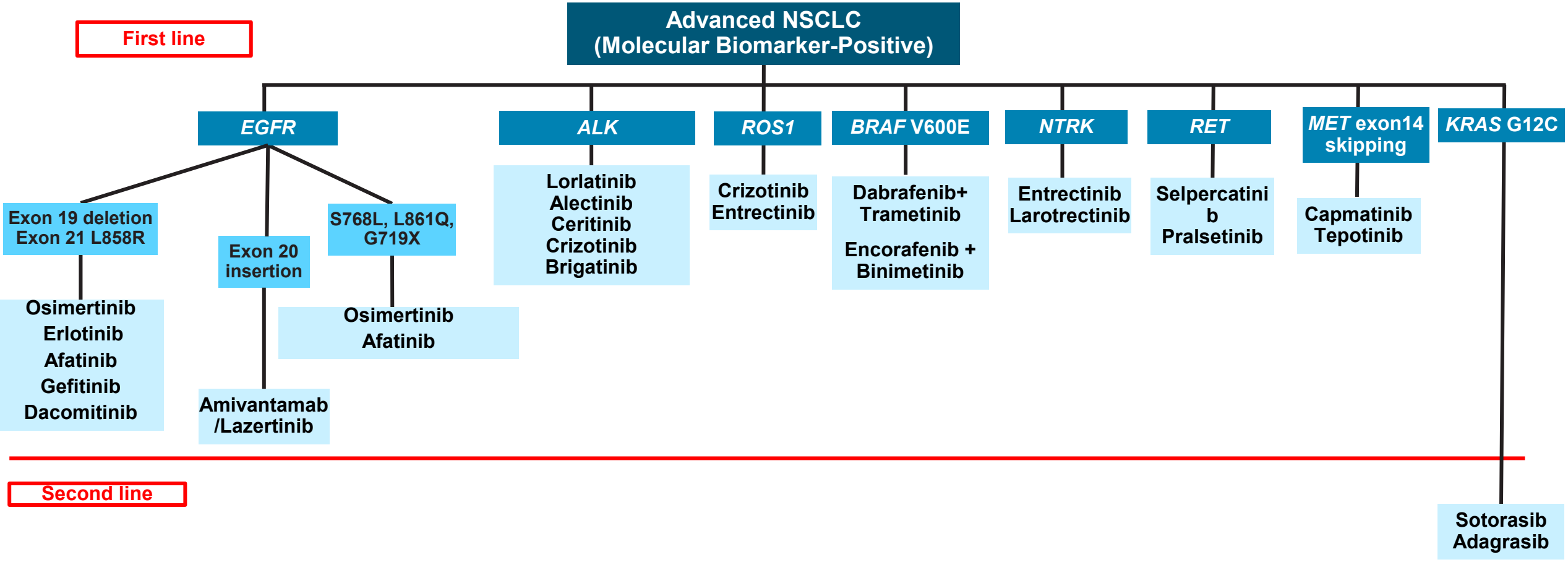


Co-mutations

STK11, KEAP1

Tsao AS, et al. *J Thorac Oncol*. 2016;11(5):613-638. Skoulidis F, et al. *Nat Rev Cancer*. 2019;19(9):495-509. Burnett H, et al. *PLoS One*. 2021;16(3):e0247620. Nassar AH, et al. *N Engl J Med*. 2021;384(2):185-187. Cooper WA, et al. *Pathology*. 2011;43(2):103-115. Langer CJ, et al. *J Clin Oncol*. 2010;28(36):5311-5320. Galon J, et al. *Immunity*. 2013;39(1):11-26. Pao W, et al. *Lancet Oncol.* 2011;12(2):175-180. Krigsfeld G, et al. Presented at: American Association for Cancer Research Annual Meeting; April 1-5, 2017; Washington, DC. Abstract CT143.

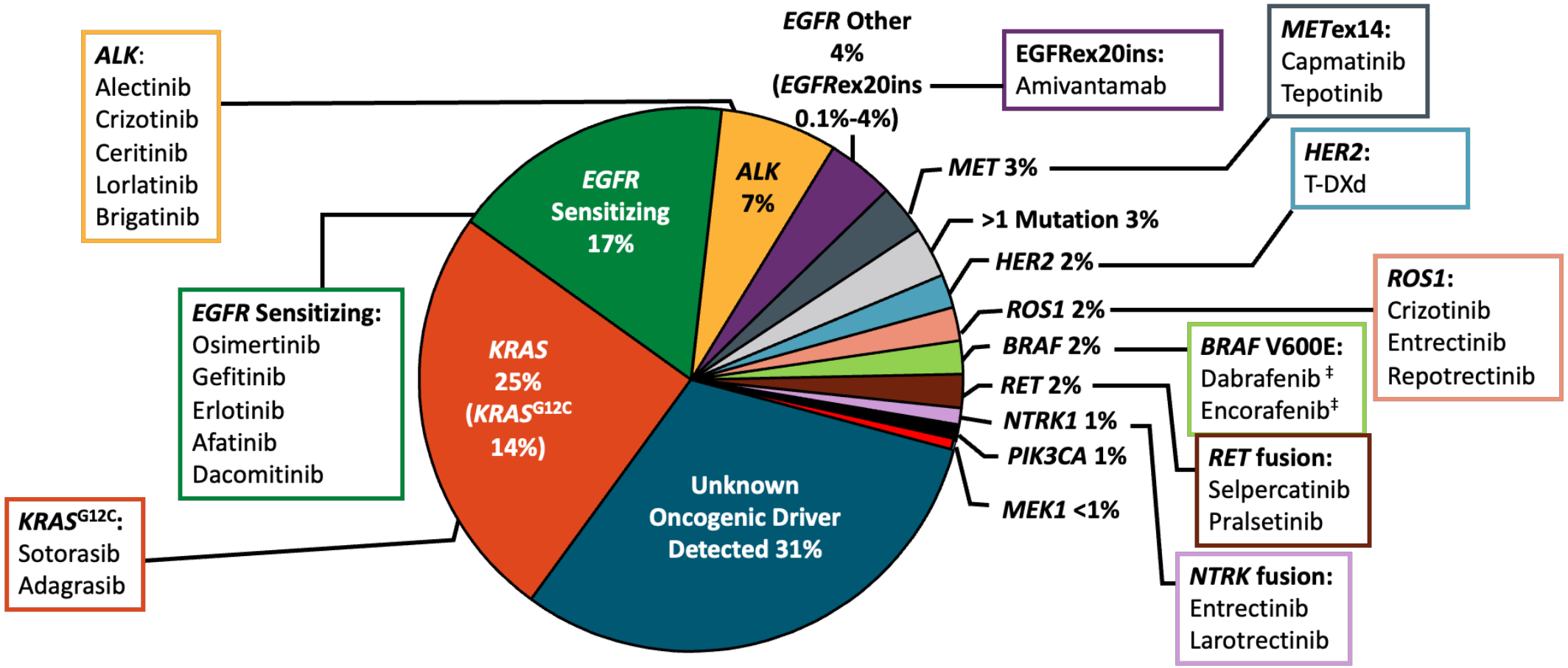
Treatment Landscape for Molecular Biomarker-Positive Advanced NSCLC



Singh N, et al. *J Clin Oncol*. 2023;41(15):e42-e50.

Guideline-Based Testing for Driver Mutations in Advanced NSCLC

50% of Patients with Advanced Non-Squamous NSCLC Have Targetable Alterations That Can Be Treated with FDA-Approved Therapy or Clinical Trial

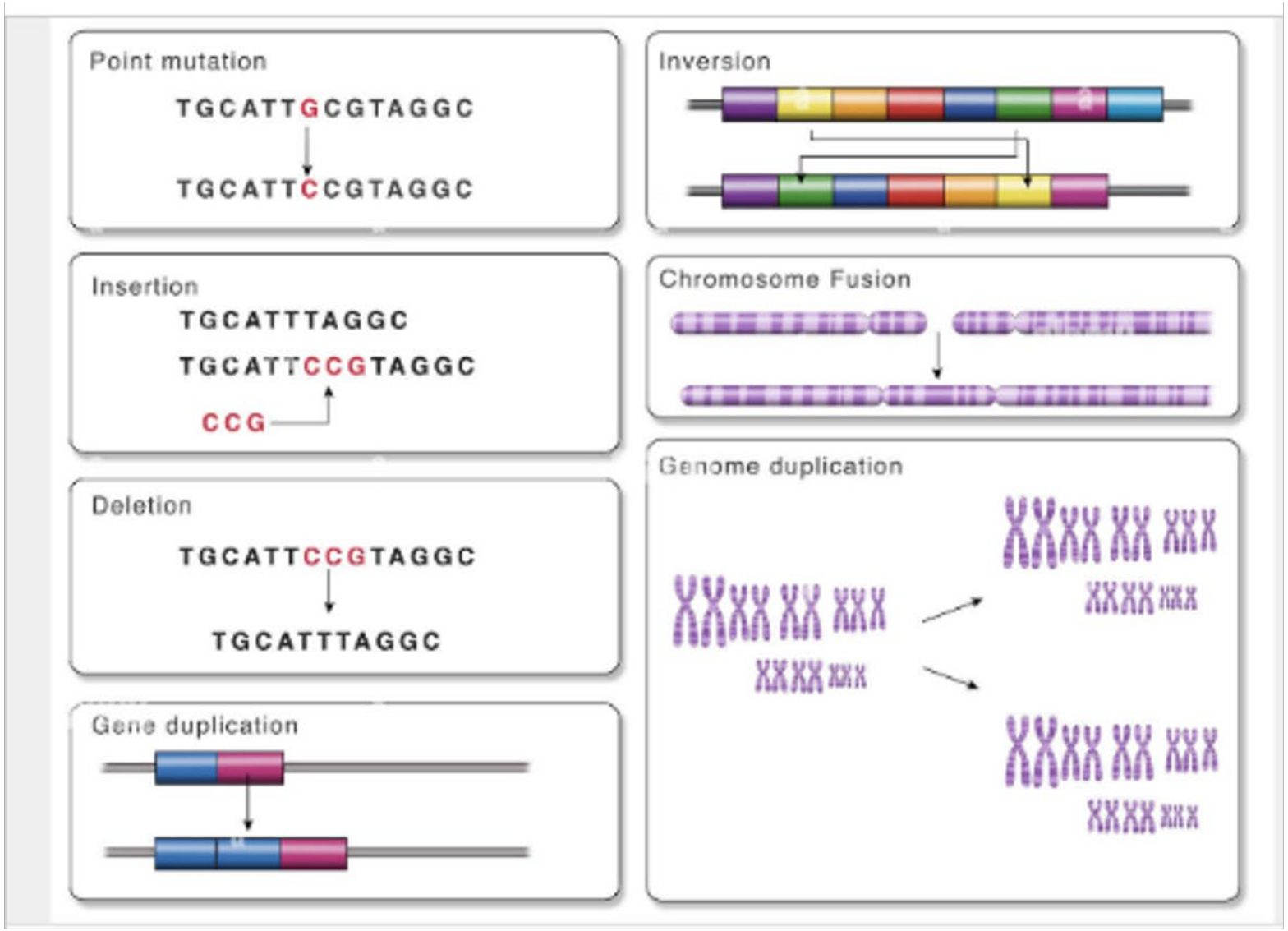


‡Approved with MEK inhibitor for *BRAF* V600E mutation.

Li T, et al. *J Clin Oncol*. 2013;31(8):1039-1049. Tsao AS, et al. *J Thorac Oncol*. 2016;11(5):613-638. Burnett H, et al. *PLoS One*. 2021;16(3):e0247620. Nassar AH, et al. *N Engl J Med*. 2021;384(2):185-187.

These Alterations Fall into Different Categories

EGFR
KRAS
BRAF
HER2



ALK
RET
NTRK
ROS1

EGFR
MET

Used with permission from Gerber D.

Broad NGS Testing for Advanced NSCLC

Cancer Type	Biomarker Testing Recommendations	
	NCCN	ASCO/CAP
NSCLC	*EGFR, ALK, ROS1, BRAF, KRAS, MET, RET, ERBB2/HER2, NTRK* fusions, PD-L1	*EGFR, ERBB2/HER2, ROS1, BRAF, KRAS, MET, RET, ALK*

Single gene testing or targeted panels may miss important alterations.

- For example, EGFR PCR misses ~50% of *EGFR* exon 20 insertion mutations

Best to use NGS testing with DNA- and RNA-based sequencing.

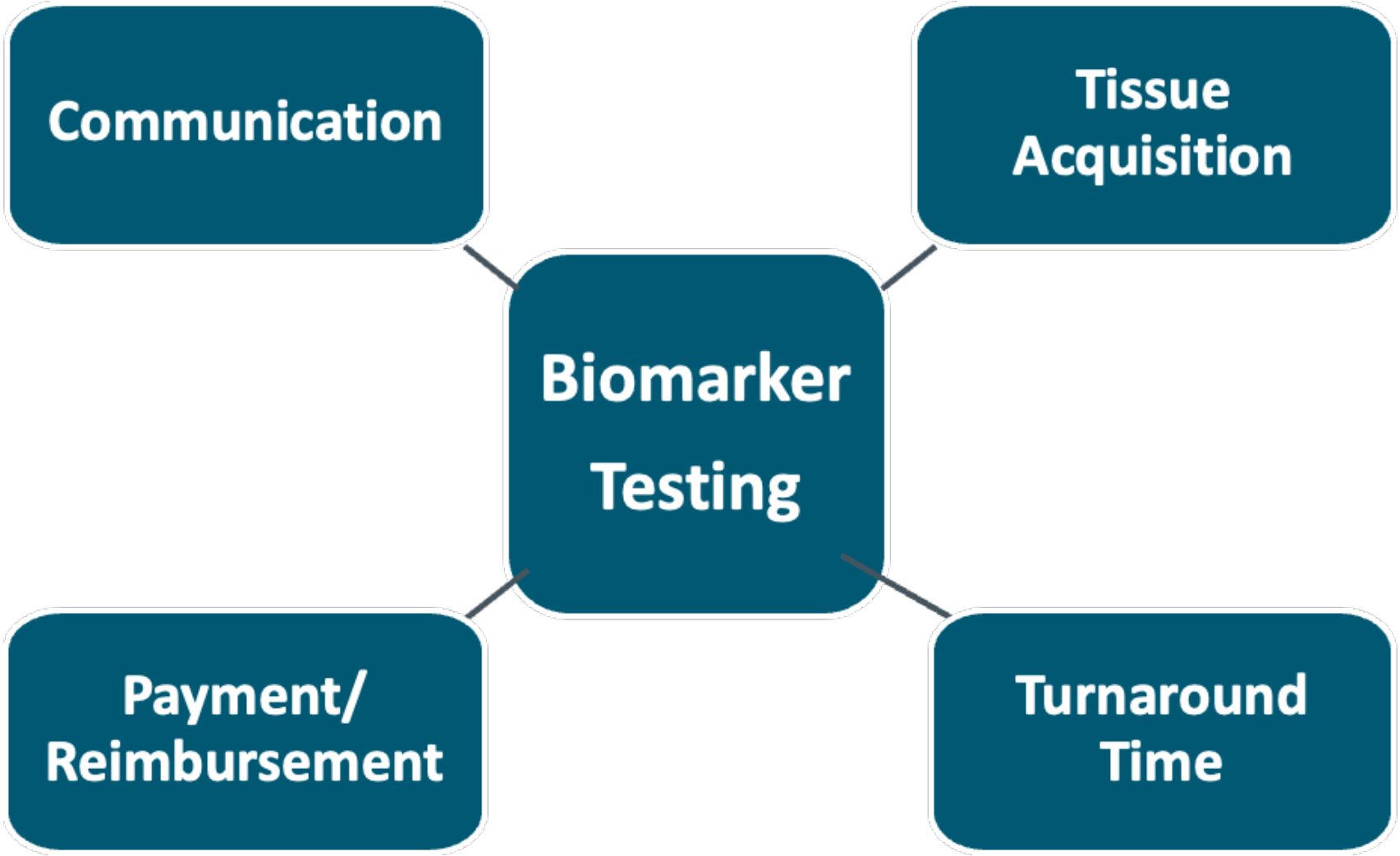
- RNA-based sequencing improves sensitivity of detecting fusions and rearrangements (ie, ALK, RET, ROS1, NTRK, MET exon 14 skipping)

Broad NGS testing will detect most alterations using the least amount of tissue.

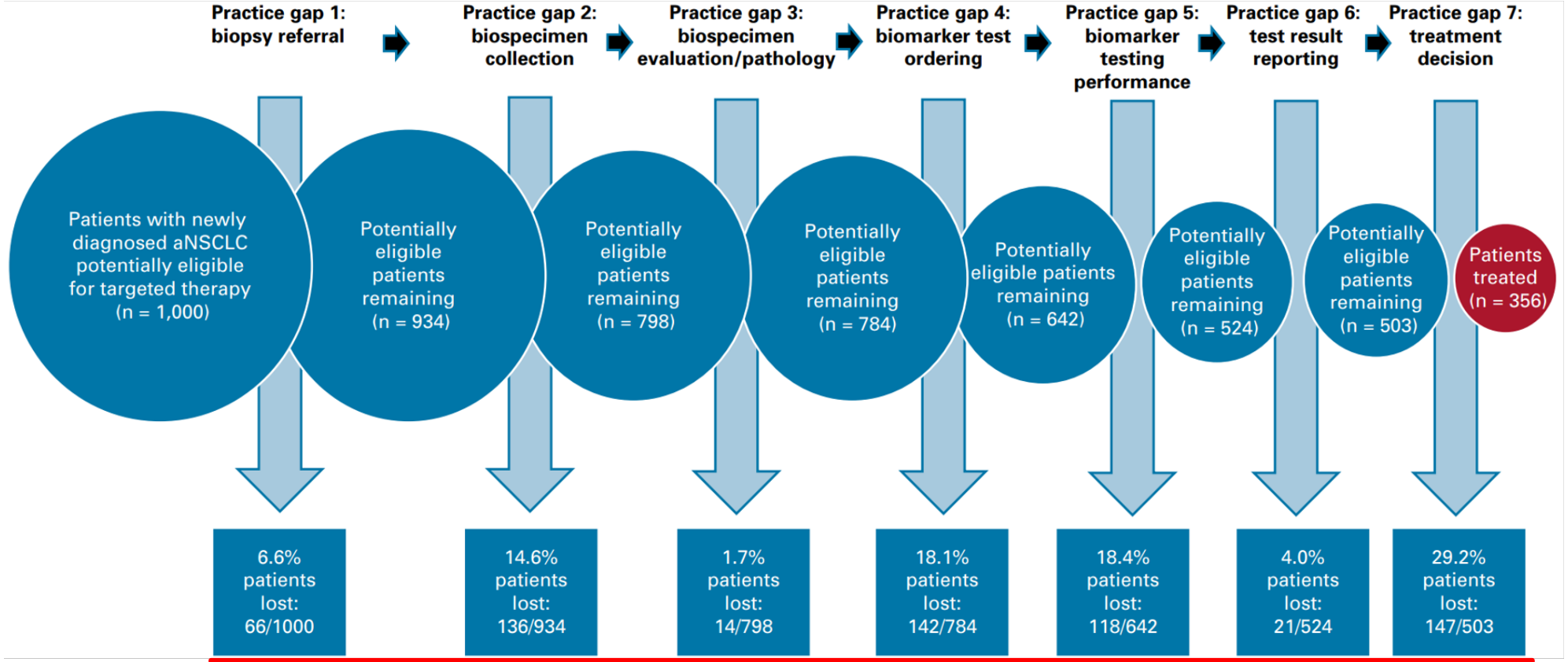
ASCO = American Society of Clinical Oncology; CAP = College of American Pathologists; PCR = polymerase chain reaction; NGS = next-generation sequencing.

National Comprehensive Cancer Network. Accessed November 8, 2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Lindemann NI, et al. *Arch Pathol Lab Med.* 2018;142(3):321-346. Merker JD, et al. *J Clin Oncol.* 2018;36(16):1631-1641.

There Are Several Significant Barriers to Universal Biomarker Testing



~50% of Patients with NSCLC Do Not Get Appropriate Biomarker Testing



Approximately 50% of patients are lost in precision oncology due to gaps in biospecimen processing and diagnostic testing.

aNSCLC = advanced NSCLC.

Sadik H, et al. *JCO Precision Oncol.* 2022;6:e2200246.

Sending Both Tissue and Blood ("Liquid Biopsy") for Molecular Testing May Increase Rate of Biomarker Detection

When do we use liquid biopsy?

- **Plasma-first approach:** when inadequate tissue biopsy—if negative, may proceed with re-biopsy for tumor tissue genotyping
- **Sequential approach:** tumor tissue adequate for genotyping—follow with cfDNA testing only when results from tissue incomplete
- **Complementary approach:** increases rate of biomarker detection
  - Prospective NILE study of 282 patients with untreated metastatic NSCLC showed that addition of cfDNA to tissue testing increased detection of an identifiable guideline-recommended biomarker by 48%

Advantages of liquid biopsy

- Minimally invasive
- Fast turnaround time (~1 week)
- May overcome tumor heterogeneity

Limitations of liquid biopsy

- Sensitivity 70% to 80%; specificity near 100%
- Negative result is noninformative (need to follow up negative test with tissue)
- Cannot assess histology or PD-L1

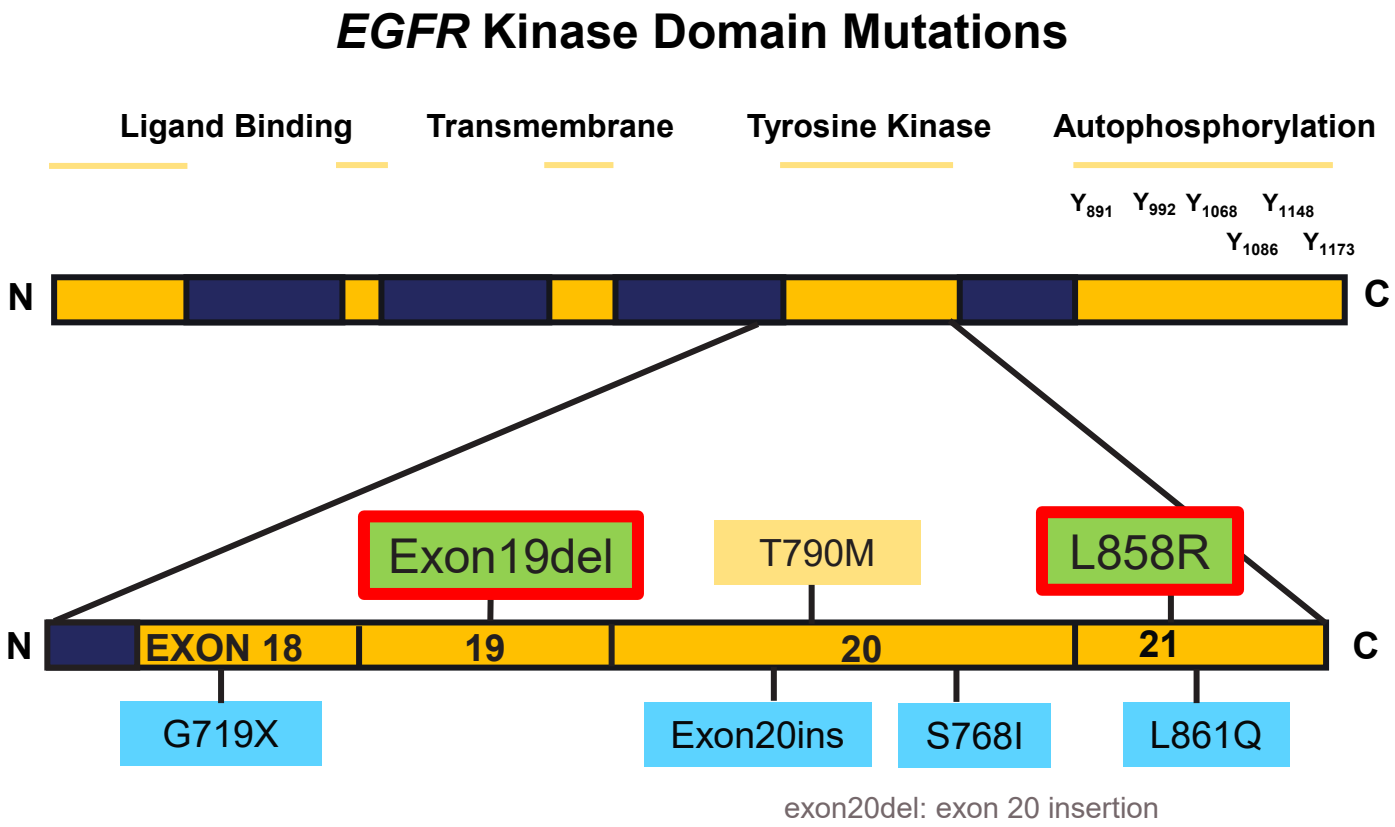
cfDNA = cell-free DNA.

Leighl NB, et al. *Clin Cancer Res*. 2019;25(15):4691-4700. Rothwell DG, et al. *Nat Med*. 2019;25(5):738-743. Bauml J, et al. *Clin Cancer Res*. 2018;24(18):4352-4354. Rolfo C, et al. *J Ther Oncol*. 2021;16(10):1647-1662. NIH. Accessed November 8, 2024. https://clinicaltrials.gov/study/NCT03615443.

Select Biomarker-Driven Therapies in NSCLC: EGFR Mutations

EGFR Mutations Are Seen in ~15% Patients with Stage IV NSCLC in the United States

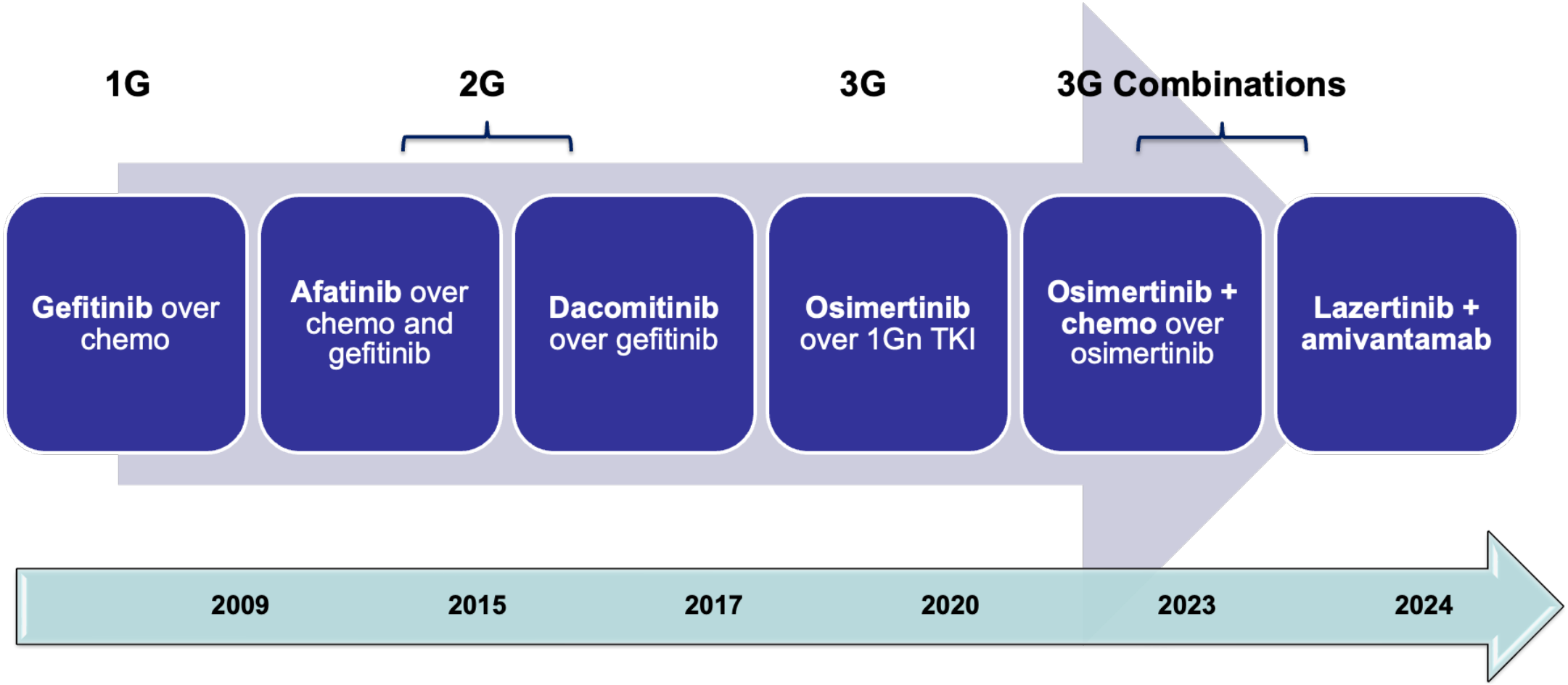
- **~15% all patients, ~40% never smokers**
  - More common in never/light smokers, Asians, women
- **Type of EGFR mutation impacts prognosis and treatment**
  - Classical *EGFR* mutations: exon 19 deletions, exon 21 L858R
  - Atypical *EGFR* mutations: G719X, L861Q, S768I
  - Exon 20 insertions
- **Molecular testing for EGFR mutations is advised for patients with NSCLC who are candidates for targeted therapy**



exon20del: exon 20 insertion

Irmer D, et al. *Oncogene*. 2007;26(39):5693-5701. Pao W, et al. *J Clin Oncol*. 2005;23(11):2556-2568. Wu YL, et al. *J Thorac Oncol*. 2007;2(5):430-439. Zhang YL, et al. *Oncotarget*. 2016:7(48):78985-78993. Fang S, et al. *Drug Des Devel Ther*. 2014;8:1595-1611. Shea M, et al. *Ther Adv Respir Dis*. 2016;10(2):113-129. Wang J, et al. *Onco Targets Ther*. 2016;9:3711-3726. Werutsky G, et al. Presented at: IASLC 17th World Conference on Lung Cancer; December 4-7, 2016; Vienna, Austria. Abstract P1.08.

Treatment of EGFR+ NSCLC Continues to Evolve



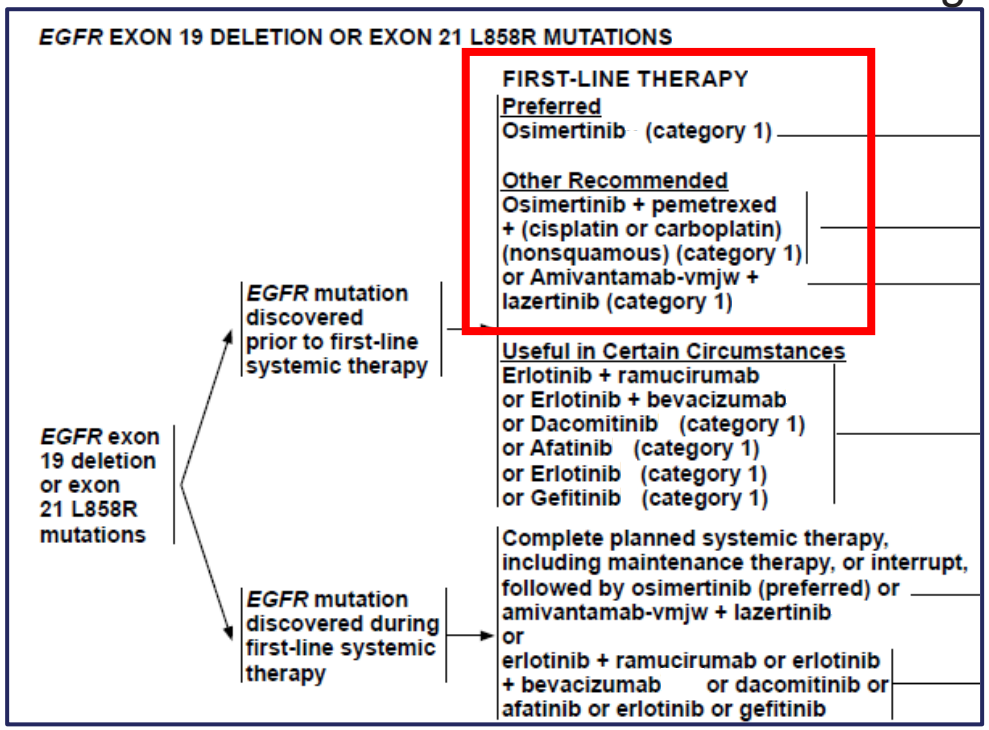
G = generation; TKI = tyrosine kinase inhibitor.

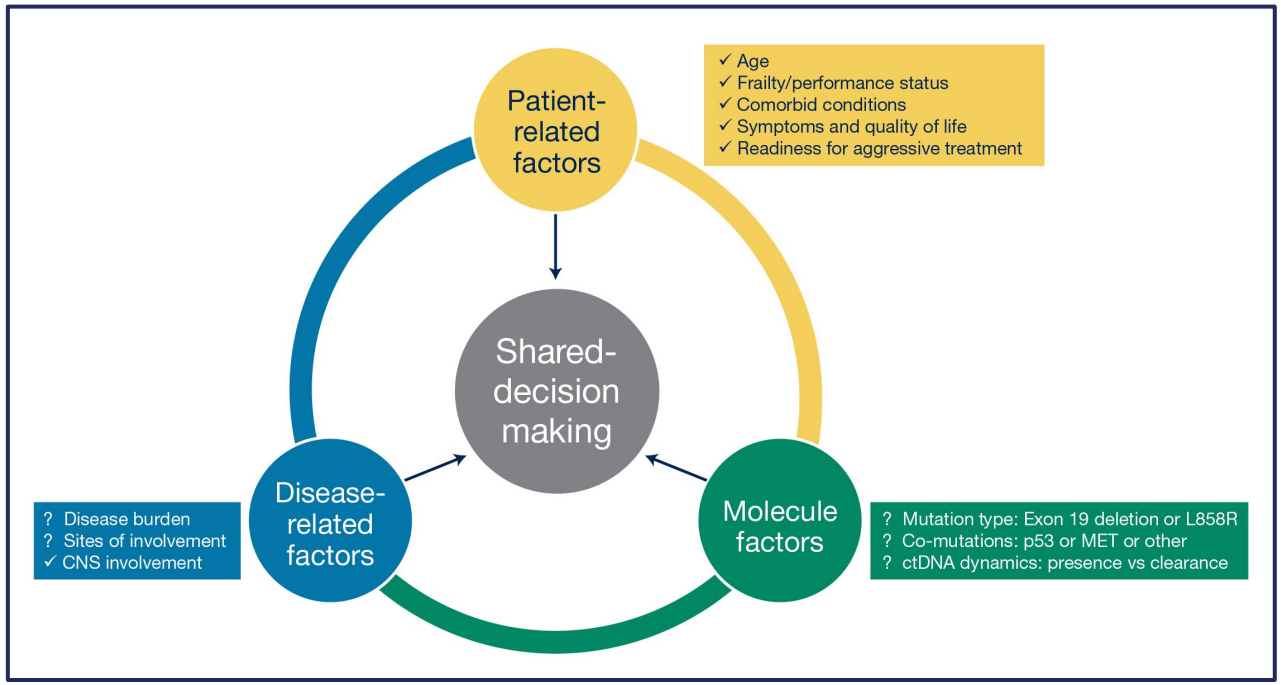
Soria JC, et al. *N Engl J Med.* 2018;378(2):113-125. Ramalingam SS, et al. *N Engl J Med.* 2020;382(1):41-50. Reungwetwattana T, et al. *J Clin Oncol.* 2018;JCO2018783118. Cho BC, et al. *J Clin Oncol.* 2023;41(26):4208-4217. Cho BC, et al. *J Thorac Oncol.* 2023;18(12):1731-1742. Lu S, et al. *J Clin Oncol.* 2022;40(27):3162-3171. Shi Y, et al. *Lancet Respir Med.* 2022;10(11):1019-1028. Lu S, et al. *Lancet Respir Med.* 2023;11(10):905-915. Janne PA, et al. *J Clin Oncol.* 2024;42(7):808-820. Planchard D, et al. *N Engl J Med.* 2023;389(21):1935-1948. Cho BC, et al. Presented at: European Society for Medical Oncology Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA14.

Considerations for Treatment

With multiple first-line treatment options for metastatic EGFR+ NSCLC, we need to take into account patient, disease, and molecular characteristics.

2024 NCCN Guidelines for Non-Small Cell Lung Cancer





NCCN = National Comprehensive Cancer Network; CNS = central nervous system; MET = methionine; ctDNA = circulating tumor DNA.

National Comprehensive Cancer Network. Accessed November 8, 2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
Singhi EK. ASCO Daily News. May 16, 2024. Accessed November 8, 2024. https://dailynews.ascopubs.org/do/deciding-between-frontline-regimens-advanced-stage-egfr--mutant-nsclc-there-place-more.

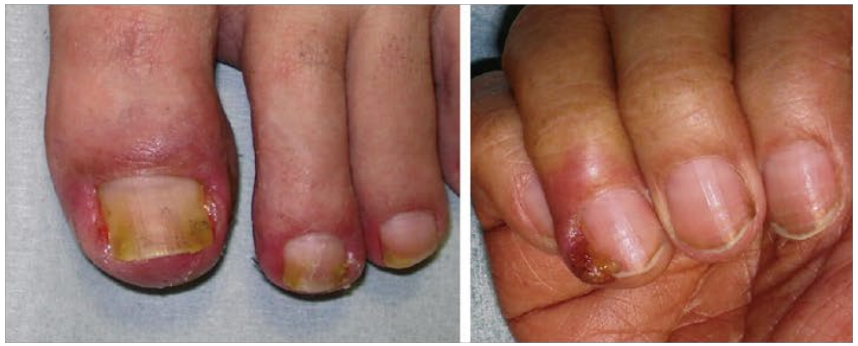
Osimertinib Improves PFS, OS, and Intracranial Response Compared to First-Generation TKIs

- Improves OS & PFS compared to 1st gen TKIs *(FLAURA: PFS 18m vs 10m, OS 36m vs 31m)*
- Improved intracranial response: 91% vs 1st gen TKI 68%

  Up to 60% pts with EGFR+ NSCLC will develop brain mets over course of disease
- More tolerable toxicity profile vs 1st/2nd gen TKIs (acneiform rash, diarrhea, nail toxicity)

Efficacy for Common *EGFR* Mutations Across Multiple Key Trials

TKI	ORR, %	mPFS, Mo	mOS, Mo
Osimertinib	80	17.7	38.6
Afatinib	70	11.0-13.6	23.6-31.6
Dacomitinib	75	14.7	34.1
Erlotinib	64-83	9.7-13.1	22.8-26.3
Gefitinib	56-72	9.2-10.8	27.7-34.8



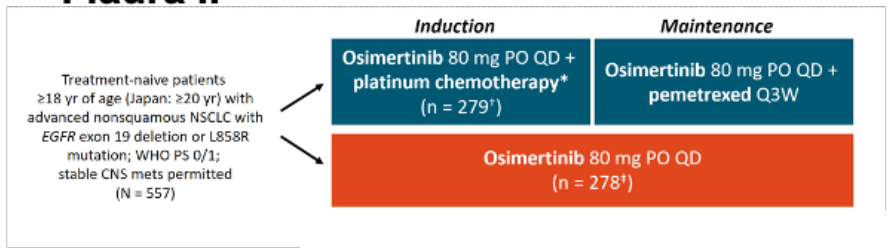
Paronychia related to erlotinib

PFS = progression-free survival; OS = overall survival; ORR = overall response rate; m = median.

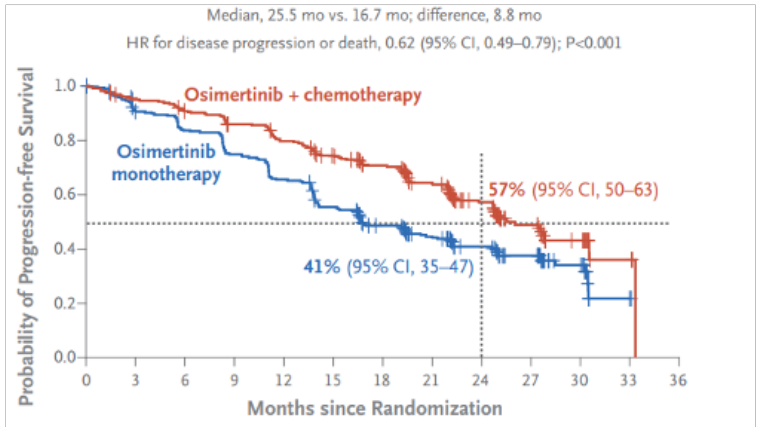
Soria JC, et al. *N Engl J Med.* 2018;378(2):113-125. Kiyohara et al. *J Am Acad Dermatol*. 2013;69(3):463-472. NIH. Accessed November 8, 2024. https://clinicaltrials.gov/study/NCT02296125.

Upfront Combination Therapies May Improve PFS Further

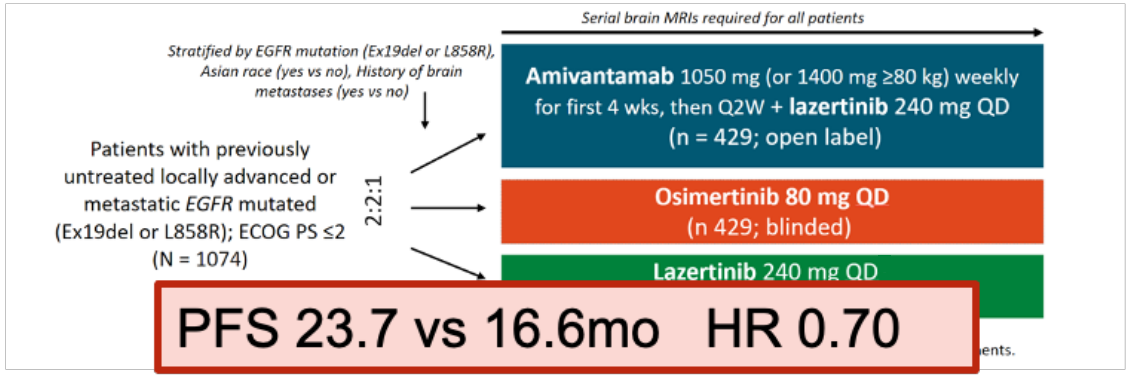
Flaura II



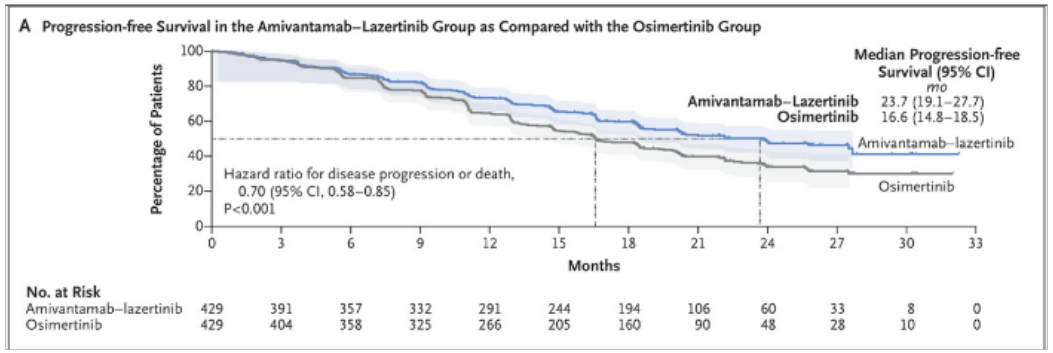
PFS 25.5 vs 16.7mo HR 0.62



Mariposa



PFS 23.7 vs 16.6mo HR 0.70



*Pemetrexed 500 mg/m^2 + carboplatin AUC5 or cisplatin 75 mg/m^2 every 3 weeks for 4 cycles; †n=276 received treatment; ‡n=275 received treatment.

HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; QD = daily.

Planchard D, et al. *N Engl J Med.* 2023;389(21):1935-1948. Cho BC, et al. *N Engl J Med.* 2024;391(16):1486-1498. Cho BC, et al. Presented at: European Society for Medical Oncology Congress; October 20-24, 2023; Madrid, Spain Abstract LBA14. NIH. Accessed November 8, 2024. https://clinicaltrials.gov/study/NCT04035486; NCT04487080.

Subgroup Analysis of FLAURA, FLAURA2, and MARIPOSA by Mutation Type and CNS Disease

PFS	FLAURA		FLAURA-2		MARIPOSA4	
	Gefitinib/Erlotinib	Osimertinib	Osimertinib	Osimertinib/Chemotherapy	Osimertinib	Amivantamab/Lazertinib
Overall	10.2	18.9	16.7	25.5	16.6	23.7
Exon 19	11.0	21.4	19.4	27.9	NA	NA
L858R	9.5	14.4	13.9	24.7	NA	NA
CNS disease	9.6	15.2	13.8	24.9	13.0	18.3

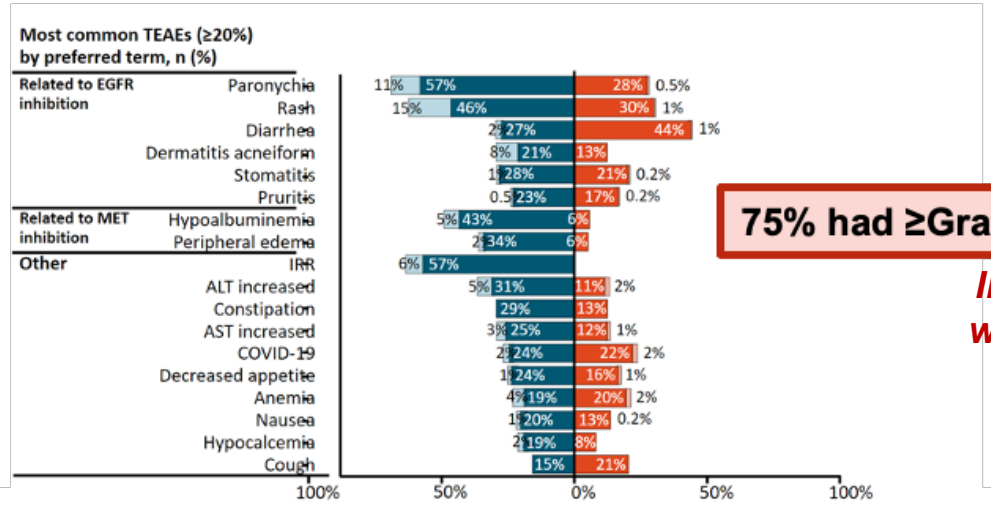
- **Table not meant for cross-trial comparisons**
- Pending mature survival data for FLAURA2 and MARIPOSA

May consider osimertinib + chemotherapy in patients with high-risk features and good performance status

Singhi EK. ASCO Daily News. May 16, 2024. Accessed November 8, 2024. https://dailynews.ascopubs.org/do/deciding-between-frontline-regimens-advanced-stage-egfr--mutant-nsclc-there-place-more.

Combination Strategies Result in Increased Toxicities

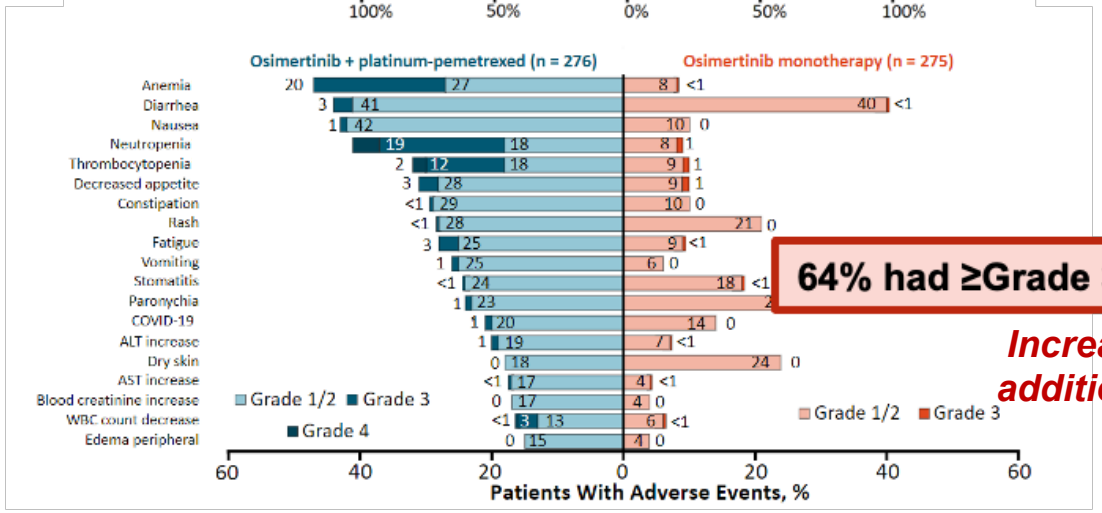
Mariposa



75% had ≥Grade 3 AEs (vs 43% with osimertinib)

Increased dermatological toxicities with the addition of amivantamab to EGFR TKI

Flaura II



64% had ≥Grade 3 AEs (vs 27% with osimertinib)

Increased myelosuppression with the addition of chemotherapy to EGFR TKI

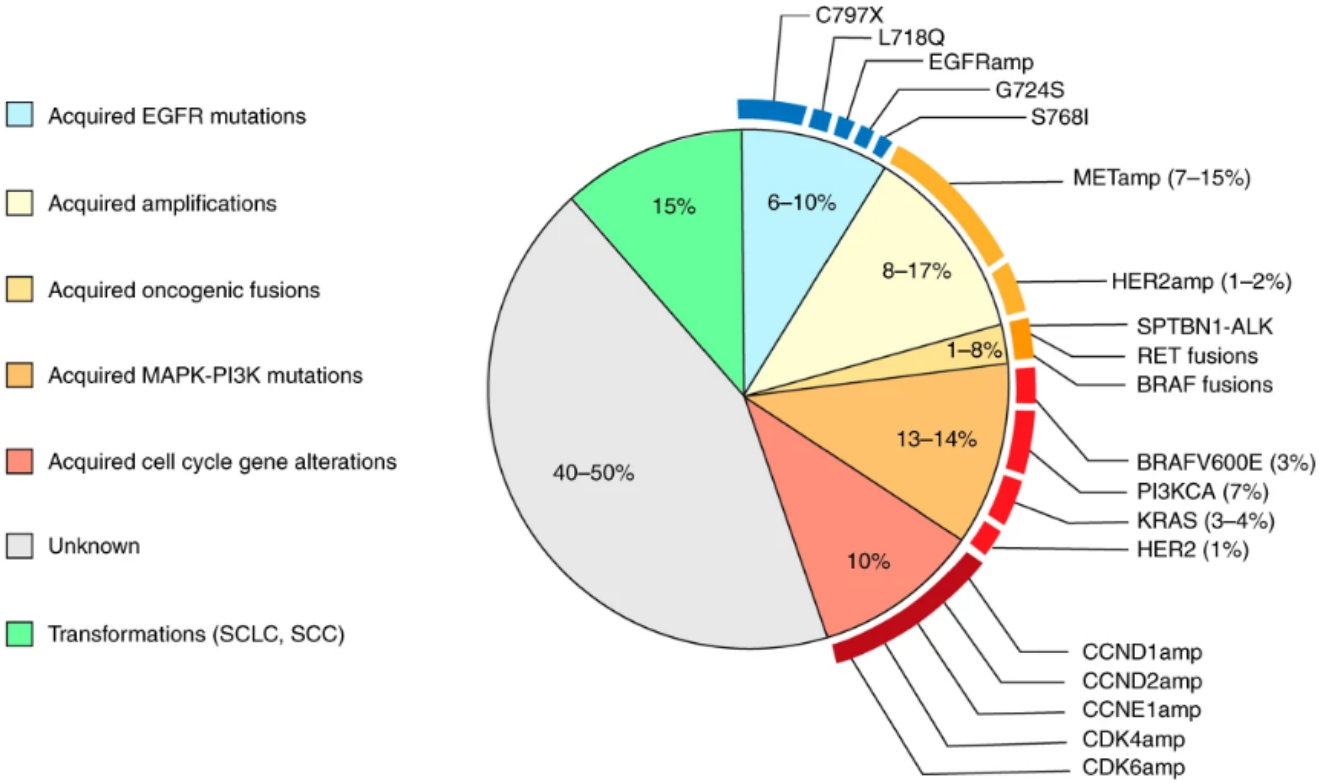
TEAE = treatment-emergent adverse event; IRR = infusion-related reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AE = adverse event.

Cho BC, et al. Presented at: European Society for Medical Oncology Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA14.

Planchard D, et al. *N Engl J Med.* 2023;389(21):1935-1948.

Ultimately, Most Patients Develop Resistance to EGFR-Targeted Therapies

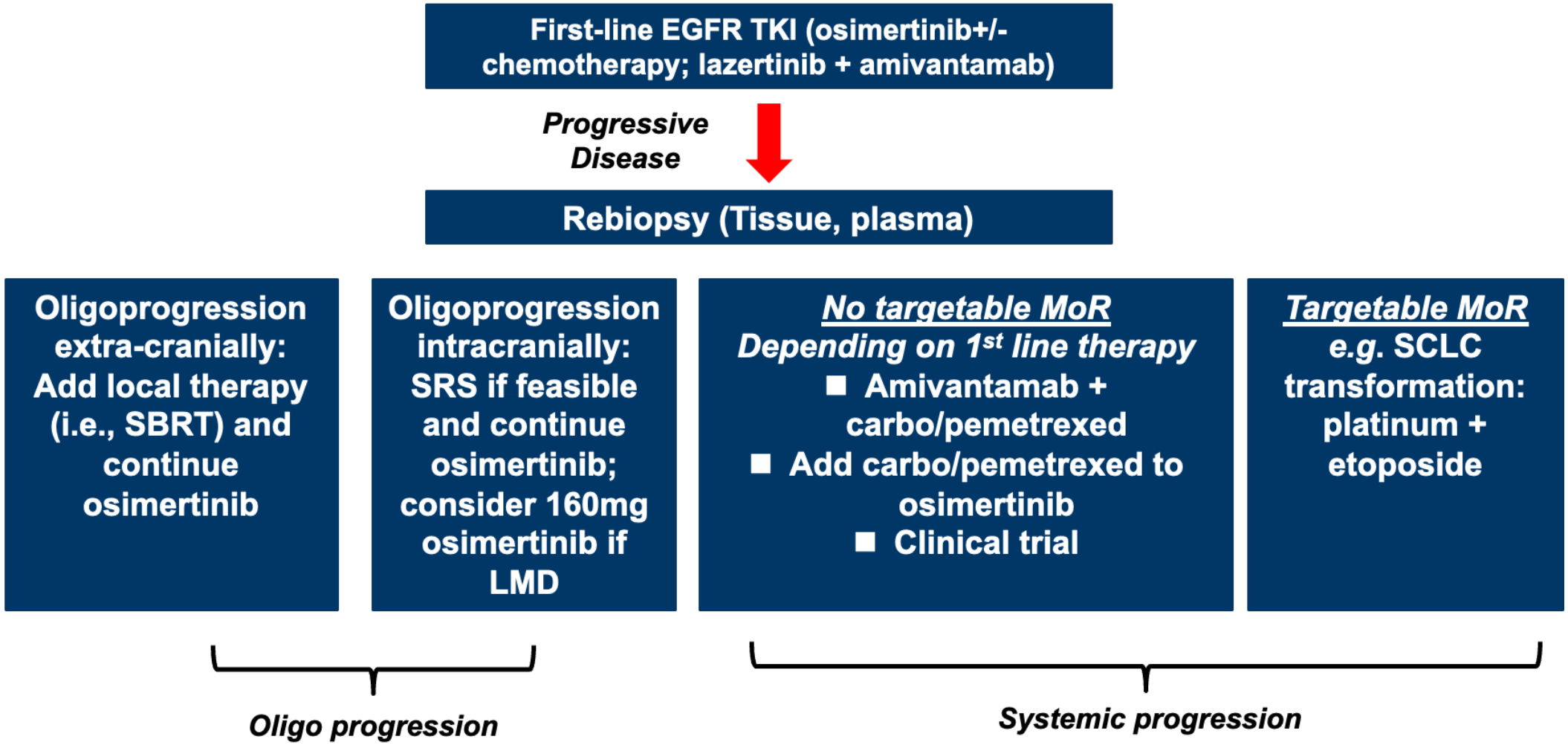
Resistance Mechanisms to First-Line Osimertinib



When feasible, re-biopsy is critical to rule out small cell transformation and assess resistance mechanisms that may impact treatment decisions.

Leonetti A, et al. *Br J Cancer*. 2019;121(9):725-737.

Stage IV NSCLC with Classical EGFR Mutation: Possible Treatment Strategies at Progression



SBRT = stereotactic body radiotherapy; SRS = stereotactic radiosurgery; LMD = leptomeningeal metastasis; MoR = mu (μ)-opioid receptor; SCLC = small-cell lung cancer.

Patritumab Deruxtecan Is under Investigation for Patients Who Have Progressed on Prior EGFR TKI

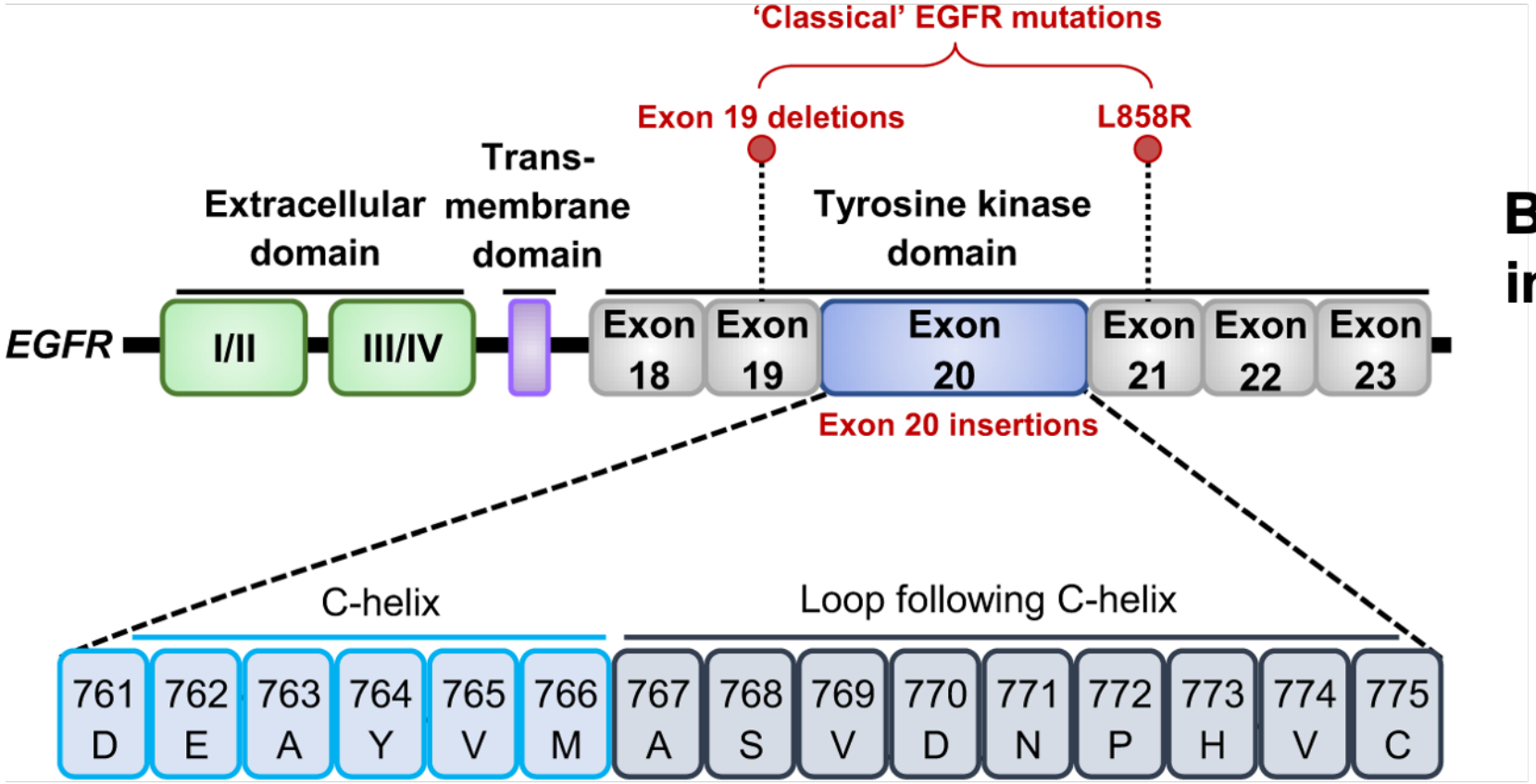
- HER3 expression is broadly observed in EGFR+ NSCLC and is an attractive molecular target for treatment
- HER3 antibody drug conjugate with clinical activity in EGFR TKI-resistant cancers is in early-phase clinical trials
- Awaiting results from phase III study of patritumab deruxtecan vs doublet chemotherapy following prior EGFR TKI therapy

Result	All Patients (n = 225)
Confirmed ORR, % (95% CI)	29.8 (23.9-36.2)
CR, No. (%)	1 (0.4)
Partial response, No. (%)	66 (29.3)
Stable disease/non-CR/non-PD, No. (%)	99 (44.0)
PD, No. (%)	43 (19.1)
Not evaluable, No. (%)	16 (7.1)
Disease control rate, % (95% CI)	73.8 (67.5-79.4)
Duration of response, months, median (95% CI)	6.4 (4.9-7.8)
Patients with DOR ≥6 months, %	43.3
Progression-free survival, months, median (95% CI)	5.5 (5.1-5.9)
Overall survival, months, median (95% CI)	11.9 (11.2-13.1)

ORR: 30%
Median PFS: 5.5 months
CNS ORR: 33%

CR = complete response; PD = progressive disease; DOR = duration of response.
Yu HA, et al. *J Clin Oncol*. 2023;41(35):5363-5375.

EGFR Exon 20 Insertions Account for about 5-10% of EGFR Mutations in NSCLC

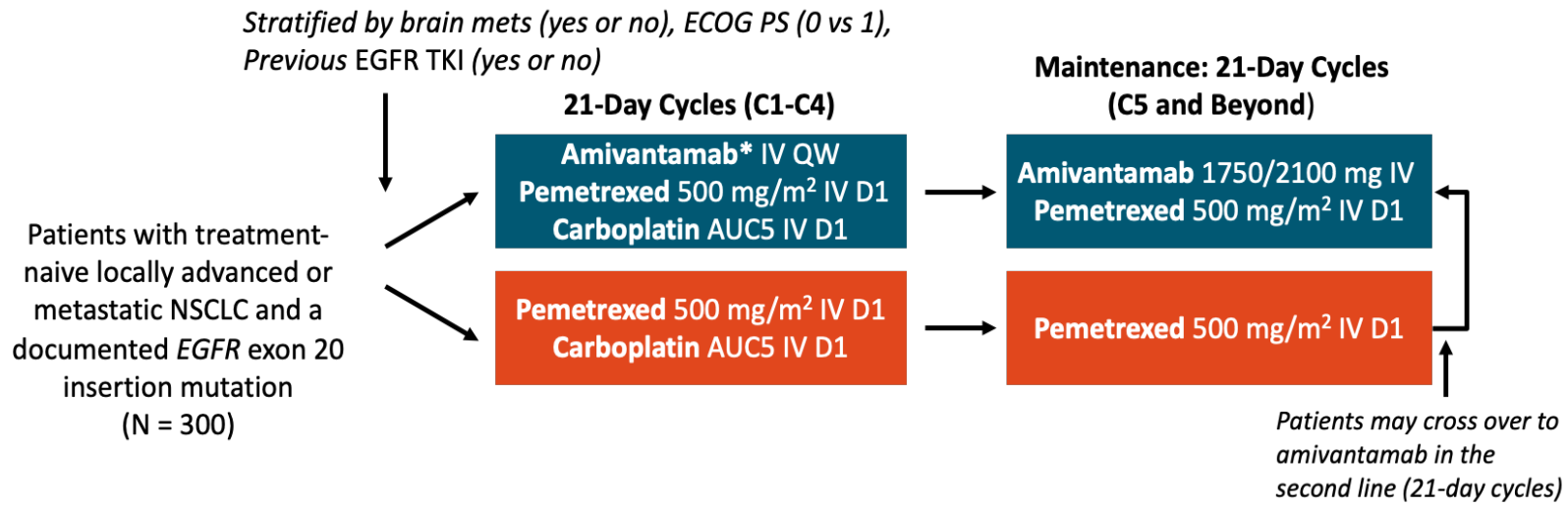


Based on conformation in binding pocket, exon 20 insertions are relatively resistant to traditional EGFR inhibitors

Vyse S, et al. *Sig Transduct Target Ther.* 2019;4:5.

PAPILLON: Amivantamab + Carboplatin/Pemetrexed Is First-Line Treatment for Stage IV NSCLC with EGFR Exon 20 Insertion Mutation

- A global randomized, open-label, phase III study

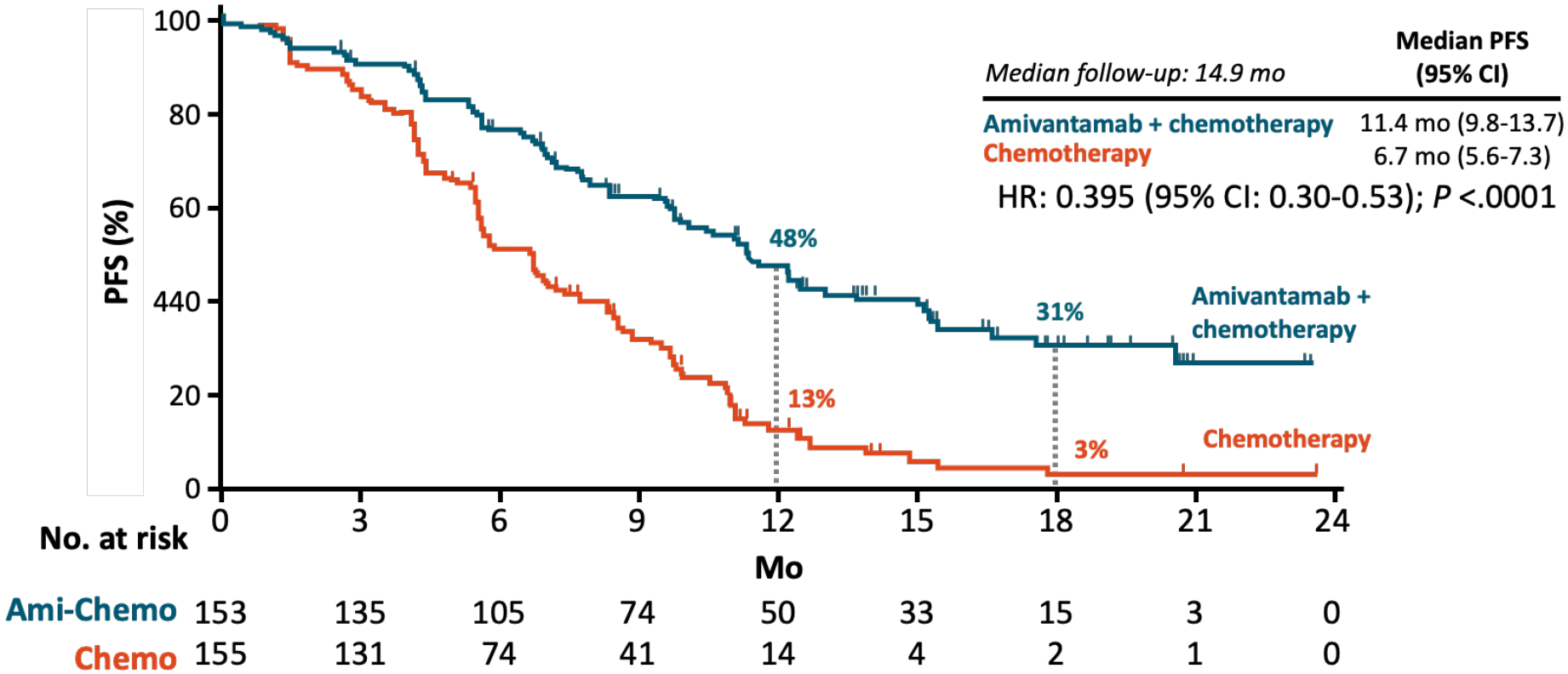


Primary endpoint: PFS by BICR per RECIST v1.1

Secondary endpoints: ORR, DoR, OS, TST, PFS2, safety

***1400/1759 mg by weight (<80 kg/≥80 kg) until C2D1 (on C1D1/2 [split dose], 8, 15, and on C2D1); 1750/2100 mg by weight (<80 kg/≥80 kg) C3D1 and C4D1 (escalated doses).**
C = cycle; QW = weekly; IV = intravenous; D1 = day 1; BICR = blinded independent central review; RECIST = response evaluation criteria in solid tumors; TST = time to start treatment; PFS2 = time from randomization to progression on second-line therapy.
NIH. Accessed November 8, 2024. https://clinicaltrials.gov/study/NCT04538664. Agrawal T, et al. Presented at: IASLC 21st World Conference on Lung Cancer; January 28-31, 2021; Virtual. Abstract P76.74. Zhou C, et al. *N Engl J Med.* 2023;389(22):2039-2051. Girard N, et al. Presented at: European Society for Medical Oncology Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA5.

PAPILLON: Amivantamab + Chemotherapy Improves Progression-Free Survival Compared to Chemotherapy Alone



- Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR: 0.38; 95% CI: 0.29-0.51; *P* <.0001)

Girard N, et al. Presented at: European Society for Medical Oncology Congress; October 20-24, 2023; Madrid, Spain. Abstract LBA5. Zhou C, et al. *N Engl J Med.* 2023;389(22):2039-2051.

Common AE Profile and Management for EGFR Therapies

Osimertinib/Chemotherapy vs Osimertinib: Grade ≥III Toxicity

Event	Osimertinib/Chemo (n=276)	Osimertinib (n=275)
Anemia	20%	1%
Diarrhea	3%	0
Decreased appetite	3%	0
Constipation	1%	1%
Rash	1%	0
Fatigue	3%	1%
Vomiting	1%	1%
Stomatitis	1%	1%
Neutropenia	14%	1%
Paronychia	1%	1%
ALT increase	1%	1%
Thrombocytopenia	7%	1%
Dry skin	0	0
AST increase	1%	1%
SCr increase	0	0
WBC decrease	4%	1%
Peripheral edema	0	0

SCr = serum creatinine; WBC = white blood cell.

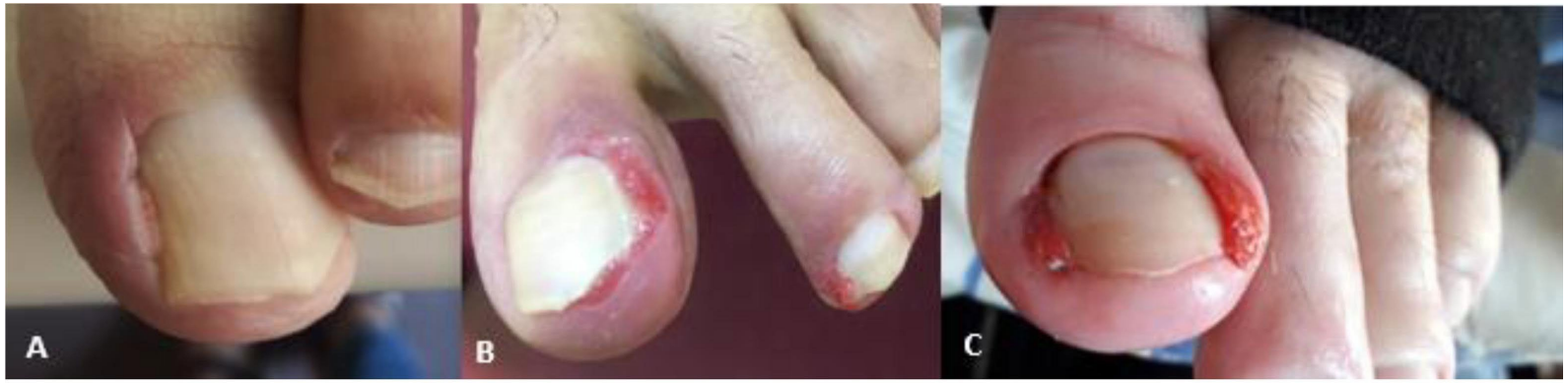
Planchard D, et al. *N Engl J Med.* 2023;389(21):1935-1948.

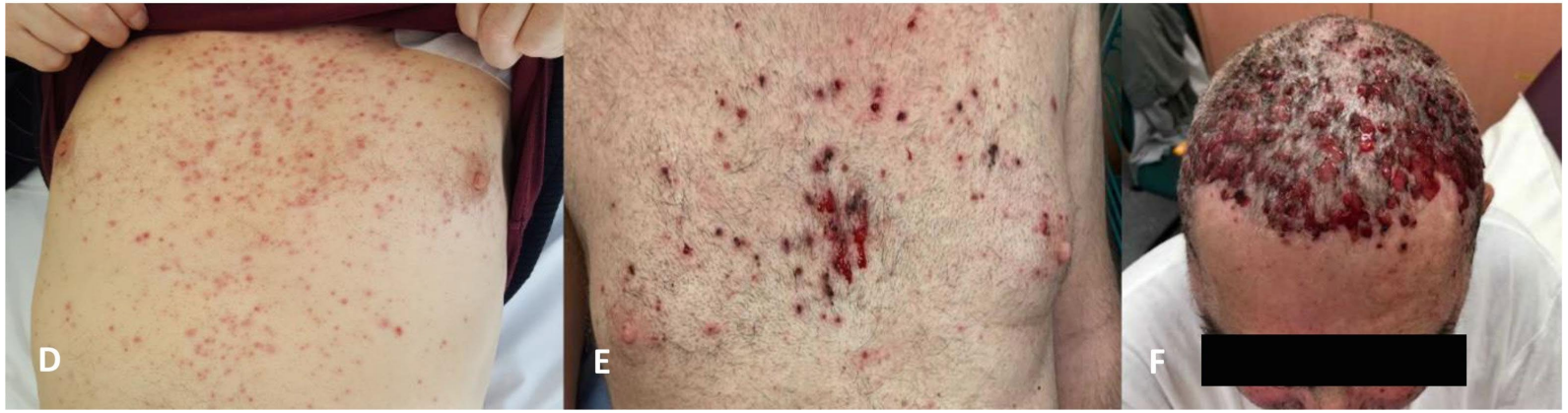
Amivantamab/Lazertinib vs Osimertinib: Grade ≥III Toxicity

Event	Amavantamab/Lazertinib (n=421)	Osimertinib (n=428)
Paronychia	11%	1%
Infusion-related reaction	6%	0
Rash	15%	1%
Hypoalbuminemia	5%	0
Increased ALT	5%	2%
Peripheral edema	2%	0
Diarrhea	2%	1%
Dermatitis acneiform	8%	0
Stomatitis	1%	1%
Increased AST	3%	1%
Decreased appetite	1%	1%
Pruritis	1%	1%
Anemia	4%	2%
Nausea	1%	1%
Hypocalcemia	2%	0
Asthenia	3%	1%
Pulmonary embolism	8%	2%

Cho BC, et al. *N Engl J Med.* 2024;391(16):1486-1498.

Rash and Paronychia Are Common AEs with EGFR Therapies That Can Significantly Impact Quality of Life





Multidisciplinary team care is necessary to prevent, diagnose, and follow dermatological AEs.

Basse C, et al. *Lung Cancer*. 2022;173:116-123.

Acneiform Rash Management

	Guidelines on the Management of Amivantamab Acneiform Rash	Management of EGFR TKI-Induced Acneiform Rash
Prevention	▪ **Moisturizing** 2/day with adapted topics (balm) ▪ **Prophylactic antibiotic therapy** by tetracycline 50 mg 2/day	
Grade 1	▪ **Moisturizing** 2/day with adapted topics (balm) ▪ **Prophylactic antibiotic therapy** by tetracycline 50 mg 2/day	▪ Apply hydrocortisone valerate topically twice daily as needed
Grade 2	▪ **Moisturizing** to continue at same posology ▪ **Increase posology of antibiotic therapy** (tetracycline 100 mg 2/day) ▪ **Potent topical corticoids** (with clobetasol propionate) once/day for 7 days ▪ **Cancer treatment suspension is an option to consider if inefficient result**	▪ Oral minocycline 100 mg twice daily for 4 wk AND hydrocortisone valerate topically twice/day as needed
Grade 3	▪ **Moisturizing** to continue at same posology ▪ **Antibiotic therapy** (tetracycline 100 mg 2/day) ▪ **Potent topical corticosteroids** (with clobetasol propionate) once/day for 7 days ▪ **If poor response: Suspension of cancer therapy is highly recommended** ▪ **Dose reduction to consider hospitalization in dermatology department for specific care**	▪ Oral minocycline 100 mg twice/day for 4 wk AND hydrocortisone valerate topically twice/day as needed
Additional advice	▪ Noncomedogenic makeup can be used to fade skin toxicity ▪ Taper topical corticosteroids after long-term application (>15 days)	

Basse C, et al. *Lung Cancer*. 2022;173:116-123.

Counsel Patients Regarding High Likelihood of Infusion-Related Reaction with First Dose of Amivantamab

- **Nearly 70% of patients experience infusion reaction with first dose**
  - >90% are mild and able to rechallenge
  - Only 1% with subsequent doses
  - First dose is split dose on day 1 and day 2

Recommended Concomitant Medicinal Products			
Prior to infusion (Wk 1, Days 1 and 2)			
Premedication	**Dose**	**Route of administration**	**Recommended dosing window prior to amivantamab administration**
Antihistamine	Diphenhydramine (25-50 mg) or equivalent	IV	15-30 min
		Oral	30-60 min
Antipyretic	Paracetamol/acetaminophen (650-1000 mg)	IV	15-30 min
		Oral	30-60 min
Glucocorticoid	Dexamethasone (10 mg) or methylprednisolone (40 mg) or equivalent	IV	45-60 min
Postinfusion medicinal products: Administration as clinically indicated			

FDA. Accessed November 13, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761210s000lbl.pdf.

Higher Rates of VTE with the Addition of Amivantamab

	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	157 (37)	39 (9)
Grade 1	5 (1)	0
Grade 2	105 (25)	24 (6)
Grade 3	43 (10)	12 (3)
Grade 4	2 (0.5)	1 (0.2)
Grade 5	2 (0.5)	2 (0.5)
Any VTE leading to death, n (%)	2 (0.5)	2 (0.5)
Any VTE leading to any discontinuation, n (%)	12 (3)	2 (0.5)
Anticoagulant use at time of first VTE, n (%)		
On anticoagulants	5 (1)	0
Not on anticoagulants	152 (36)	39 (9)
Median onset to first VTE	84 days	194 days
Within first 4 months, n (%)	97 of 157 (62)	13 of 39 (33)

Prophylactic dose anticoagulation is recommended with treatment initiation with amivantamab + lazertinib.

VTE = venous thromboembolism.

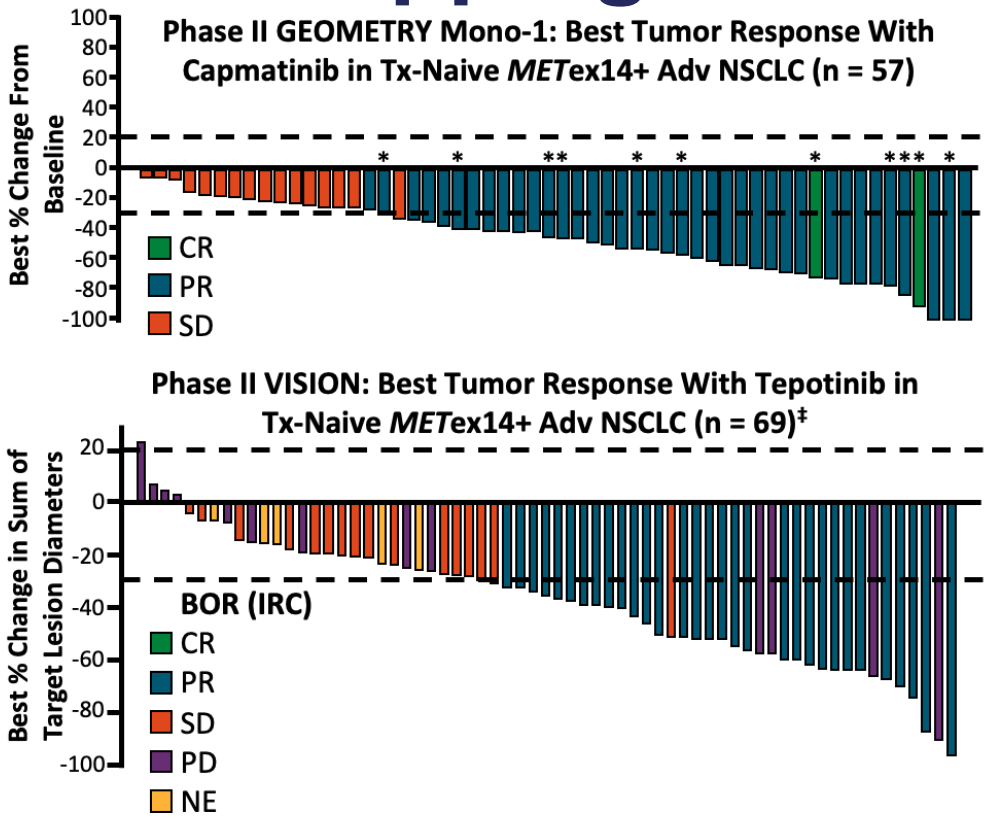
Cho BC, et al. *N Engl J Med.* 2024;391(16):1486-1498. National Comprehensive Cancer Network. Accessed November 8, 2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Select Biomarker-Driven Therapies in NSCLC: MET and HER2 Mutations

Capmatinib and Tepotinib Approved for Stage IV NSCLC with *MET* Exon 14 Skipping Mutation

- **Incidence: 3% to 4% NSCLC; 20% to 30% of sarcomatoid cancers**

Response	Prior Plt-Based CT	Tx Naive
Capmatinib	(n = 100)	(n = 60)
▪ ORR, %	44.0	66.7
▪ Median PFS, mo	5.5	12.3
Tepotinib†	(n = 66)	(n = 95)
▪ ORR, %	43.4	60.0
▪ Median PFS, mo	10.9	15.9



*Patients still on treatment; †Cohort C (confirmatory); ‡Cohort A (primary analysis).
CT = chemotherapy; Tx = treatment.

FDA. Accessed November 11, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203469lbl.pdf; 2021/214096s000lbl.pdf. Le X, et al. *Clin Cancer Res.* 2022;28(6):1117-1126. Paik PK, et al. *N Engl J Med.* 2020;383(10):931-943. Yang R, et al. Presented at: IASLC 22nd World Conference on Lung Cancer; August 6-9, 2022; Vienna, Austria. Abstract OA03.05. Wolf J, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 4-8, 2021; Virtual. Abstract 9020. Wolf J, et al. Presented at: European Lung Cancer Congress; March 30–April 2, 2022; Virtual. Abstract 26P.

Trastuzumab Deruxtecan Is Second-Line Treatment Option for Stage IV HER2 Mutated NSCLC

- HER2 mutation incidence: 2%-3% of non-squamous NSCLC
- More common in females, younger patients, patients with limited smoking history
- T-DXd is a HER2 antibody drug conjugate approved for HER2 mutations (exon 20 most common) based on phase II data

Efficacy Outcome	T-DXd 5.4 mg/kg (n = 52)
Confirmed ORR by BICR, % (95% CI)	57.7 (43.2-71.3)
Median DoR, mo (95% CI)	8.7 (7.1-NE)

Drug-Related ILD/Pneumonitis, n (%)	T-DXd 5.4 mg/kg (n = 101)
Any grade	15 (14.9)
▪ Grade 1	4 (4.0)
▪ Grade 2	9 (8.9)
▪ Grade 3	1 (1.0)
▪ Grade 4	0
▪ Grade 5	1 (1.0)
In patients *with* prior anti–PD-1/PD-L1 treatment, %	
▪ >3 mo before T-DXd	11.4
▪ ≤3 mo before T-DXd	20.0
In patients *without* prior anti–PD-1/PD-L1 treatment, %	14.8

Close monitoring for drug-related ILD/pneumonitis

ILD = interstitial lung disease.

Zeng J, et al. *J Natl Cancer Cent*. 2021;(2):58-73. Riudavets M, et al. *ESMO Open*. 2021;6(5):100260. Zhao J, et al. *JCO Precis Oncol*. 2020;4:411-425. Hyman DM, et al. *Nature*. 2018;554(7691):189-194. Janne, et al. Presented at: American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2024; Chicago, Illinois. Abstract 8543.

Common AE Profile and Management for MET and HER2 Therapies

Capmatinib: Grade III/IV Toxicity

Event	Grade III/IV Toxicity (n=364)
Peripheral edema	9%
Nausea	2%
Vomiting	2%
Increased serum creatinine	0
Dyspnea	7%
Fatigue	4%
Decreased appetite	1%
Constipation	1%
Diarrhea	1%
Cough	1%
Back pain	1%
Pyrexia	1%
ALT increased	6%
Asthenia	4%
Pneumonia	5%
Weight loss	1%
Non-cardiac chest pain	1%

Wolf J, et al. *N Engl J Med*. 2020;383(10):944-957.

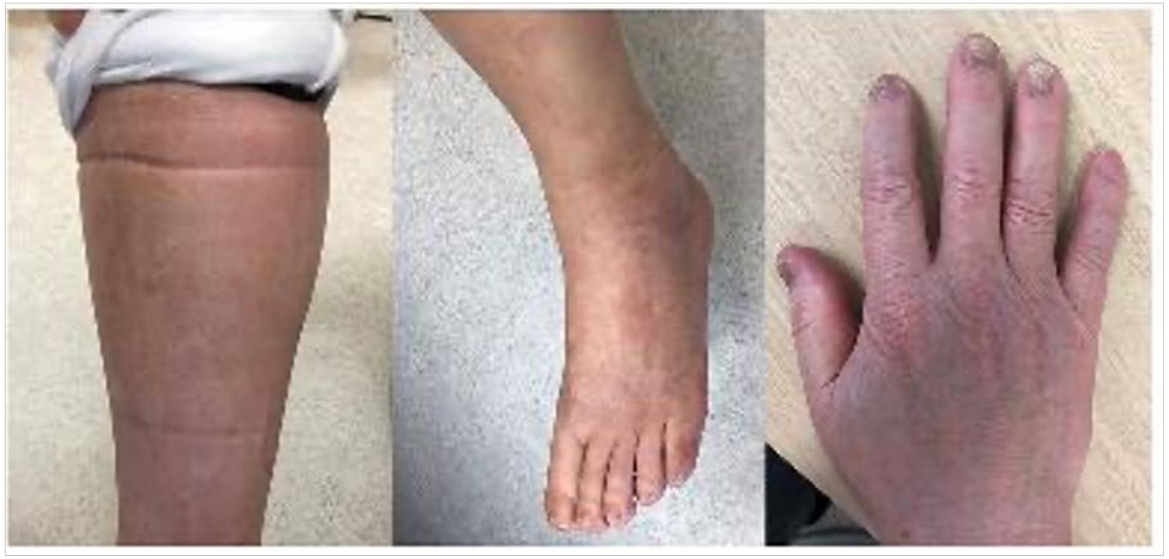
Tepotinib: Grade III/IV Toxicity

Event	Grade III/IV Toxicity (n=152)
Peripheral edema	7%
Nausea	1%
Diarrhea	1%
Increased serum creatinine	1%
Hypoalbuminemia	2%
Increased amylase	3%
Increased lipase	3%
Asthenia	1%
Decreased appetite	1%
Pleural effusion	3%
Alopecia	0
Fatigue	1%
Increased ALT	3%
Increased AST	2%
Vomiting	0
General edema	3%
Upper abdominal pain	0

Paik PK et al. *N Engl J Med*. 2020;383(10):931-943.

Peripheral Edema Is Dominant Toxicity of MET Inhibitors

Incidence of Peripheral Edema, n (%)	Capmatinib (N = 373)	Tepotinib (N = 152)
Any grade	202 (54.2)	96 (63)
Grade 3/4	36 (9.7)	11 (7)



- **Edema management strategies**
  - Elevation
  - Compression stockings or sleeves
  - Physical therapy referral
  - Diuretics—but not very effective here
  - Often not able to manage and may require dose reductions depending on patient's quality of life

Wolf J, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 4-8, 2021; Virtual. Abstract 9020. Paik PK, et al. *N Engl J Med.* 2020;383(10):931-943.

Trastuzumab Deruxtecan: Grade III/IV Toxicity

Event	Grade III/IV Toxicity (n=91)
Nausea	9%
Fatigue	7%
Alopecia	0
Vomiting	3%
Neutropenia	18%
Anemia	10%
Diarrhea	3%
Decreased appetite	0
Leukopenia	4%
Constipation	0
Pneumonitis*	2%

***Included 2 fatalities.**

Li BT, et al. *N Engl J Med*. 2021;386(3):241-251.

Drug-Drug Interactions

Agent	CYP450 Mediated Drug Interaction	QTc Interval Prolongation
Osimertinib	Strong CYP3A inducers - ↓ osimertinib	YES
Lazertinib*	Strong CYP3A inducers - ↓ lazertinib Weak CYP3A inhibitor - ↑ object drug	NO
Capmatinib	Strong CYP3A inducers - ↓ capmatinib Strong CYP3A inhibitor - ↑ capmatinib CYP1A2 substrate - ↑ object drug	NO
Tepotinib	No CYP450 mediated interactions P-gp inhibitor	NO

***Administer VTE prophylaxis when administered with amivantamab.**

FDA. Accessed November 11, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208065s000lbl.pdf; 2024/219008s000lbledt.pdf; 2020/213591s000lbl.pdf; 2021/214096s000lbl.pdf.

Key Learning Points

- NCCN recommends molecular testing for EGFR mutations in patients with NSCLC who are candidates for targeted therapy
- There may be advantages to sending both tissue and blood (“liquid biopsy”) for molecular testing
- Amivantamab/chemotherapy resulted in significantly longer progression-free survival compared to chemotherapy alone in patients with advanced NSCLC and EGFR exon 20 insertions
- EGFR therapies often cause AEs that can significantly impact quality of life, including rash and paronychia

Thank you