NCCN 2025
Lung Cancer Congress

Toxicity and Symptom Management Related to Oral Agents and TKIs: What Every Team Member Should Know

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Learning Objectives

- **Identify common treatment-related toxicities in patients with lung cancer.**
- **Describe strategies for patient education and monitoring, managing, and mitigating key symptoms.**
- **Implement team-based strategies for assessing and managing treatment-related toxicities and symptoms in lung cancer, leveraging the roles of the interprofessional oncology care team to optimize patient outcomes.**

EGFR Inhibitors:

Rash is somewhat common, rarely severe depending on agent/regimen

EGFR Inhibitor	Any Grade Rash	Grade 3/4 Rash
Gefitinib	47%	2%
Erlotinib	75%	9%
Afatinib	90%	16%
Osimertinib	**58%**	**1%**
Dacomitinib	69%	23%
Amivantamab	**84%**	**4%**
Amivantamab + lazertinib	**86%**	**26%**
Sunvozertinib	60%	8%

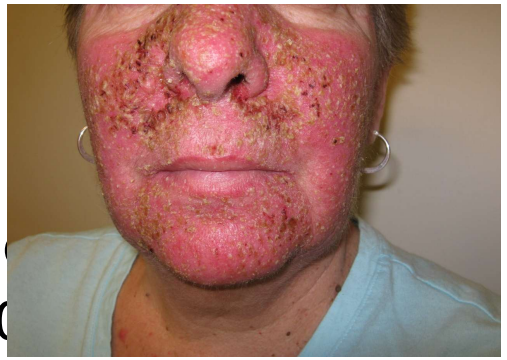
Gefitinib PI. Erlotinib PI. Afatinib PI. Osimertinib PI. Dacomitinib PI. Amivantamab PI. Sunvozertinib PI.

Pearls for EGFR Inhibitor rash

- For Osimertinib, given rash is generally moderate
  - Reactive doxycycline (or minocycline) 100mg BID
    - For Amivantamab or Afatinib this should be prophylactic
  - Topical clindamycin gel 1% (is drying, can be good or bad)
  - Moisturize with thick cream (from a tub), sunscreen
  - Protective clothing, avoid piping hot showers

Lacouture. Support Care Cancer. 2011;19:1079. Image courtesy of Beth Sandy

Pearls for EGFR Inhibitor rash



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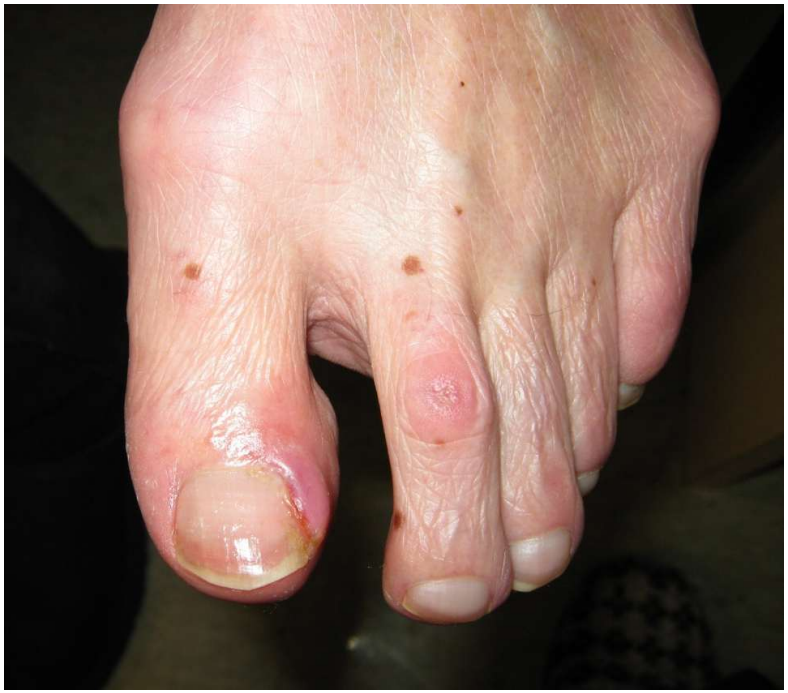
Paronychia: Inflammation Around Nail Beds

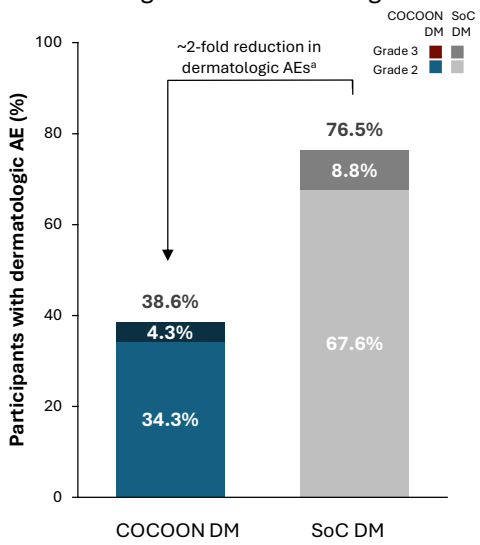
- Prevention: keep nails trimmed and clean, wear loose-fitting shoes, biotin
- Treat with topical steroids, systemic antibiotics
- Nail avulsion, silver nitrate
- Very dilute bleach soaks: ~1/4 cup bleach to 3 gallons water
- Chlorhexidine solution for nails recommended for amivantamab/lazertinib



Lacouture. Support Care Cancer. 2011;19:1079. Image courtesy of Beth Sandy.
Girard. ELCC 2025. Abstr. NCT06120140.

Amivantamab/Lazertinib Regimen Toxicities:
Can Be Significantly Reduced With Prophylactic Approaches

COCOON DM regimen- prophylactic antibiotics and topicals substantially reduced grade ≥2 dermatologic AEs[1]

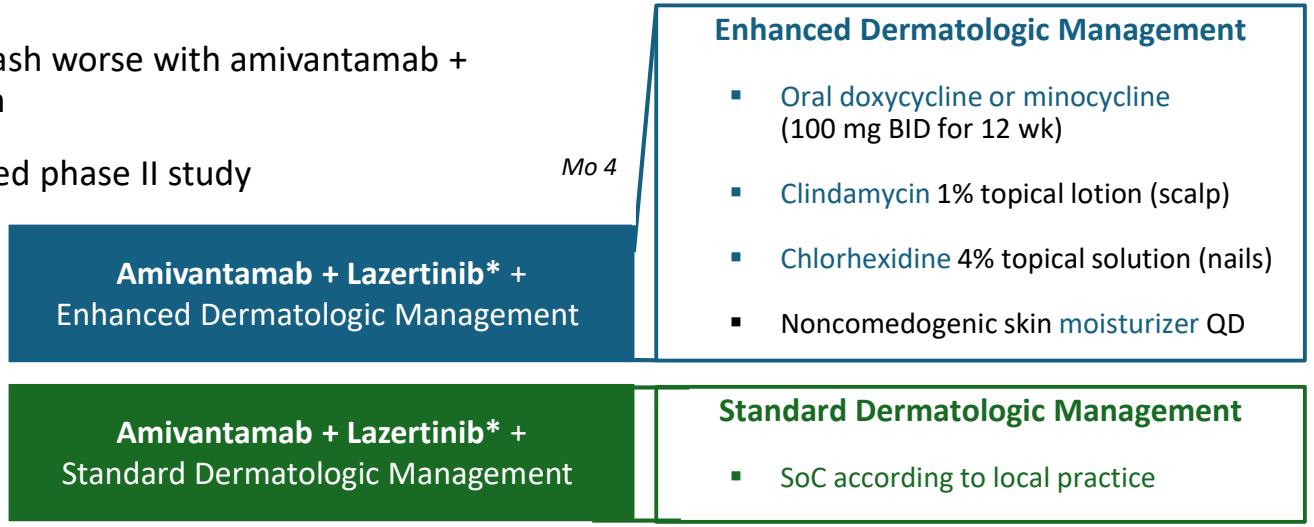


Presented by James Chih-Hsin Yang at the European Lung Cancer Congress (ELCC) Annual Meeting; March 26-29, 2025; Paris, France.

COCOON: Enhanced Dermatologic Prophylaxis with Amivantamab + Lazertinib

- Skin toxicities, facial rash worse with amivantamab + lazertinib combination
- Open-label, randomized phase II study

Adults with locally advanced/metastatic NSCLC with *EGFR* ex19del or ex21 L858R, no prior treatment for advanced disease (N = 201)



- Grade ≥2 dermatologic AEs were reduced from 77% with standard prophylaxis vs 39% with enhanced prophylaxis

Girard. ELCC 2025. Abstr. NCT06120140.

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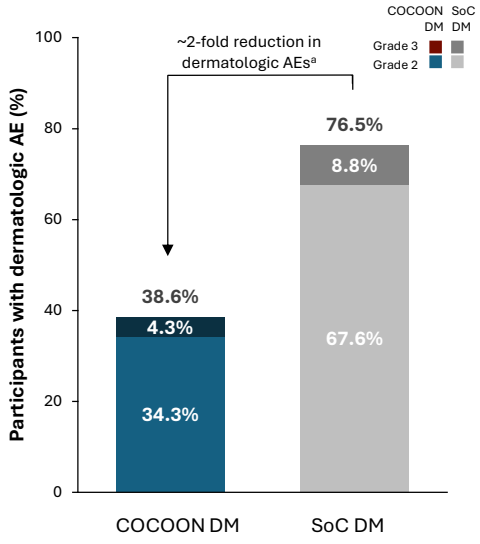
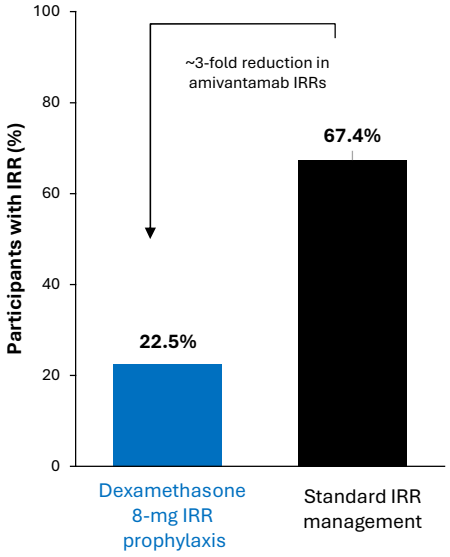


SKIPPirr regimen – prophylactic dexamethasone substantially reduced IRRs[2]



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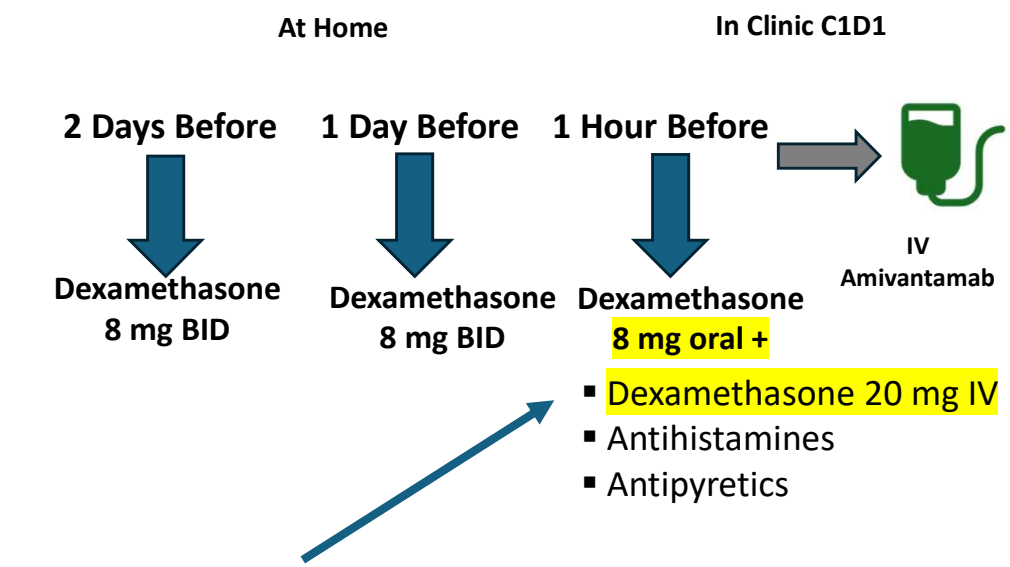
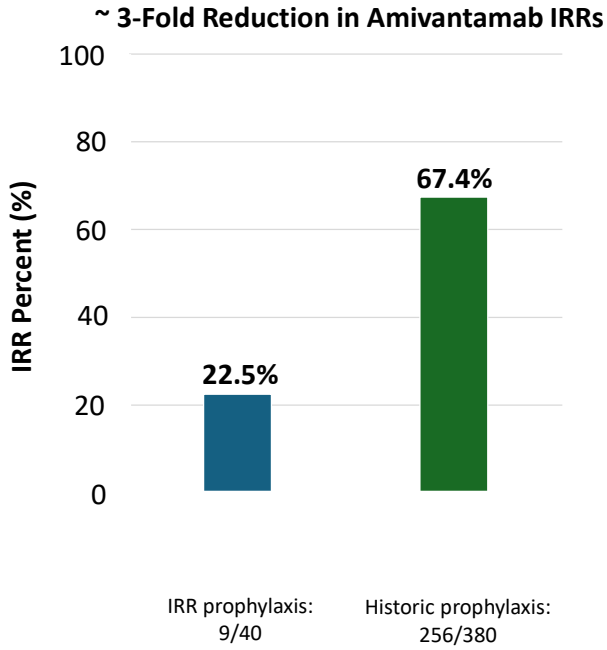
SKIPPirr: IRR Rate With Dexamethasone Prophylaxis





Lopes. WCLC 2024. Abstr MA12.08. Spira. J Thorac Oncol. 2025;20:809.

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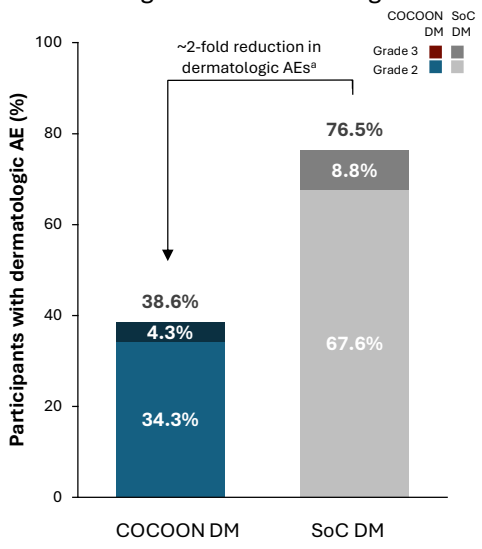

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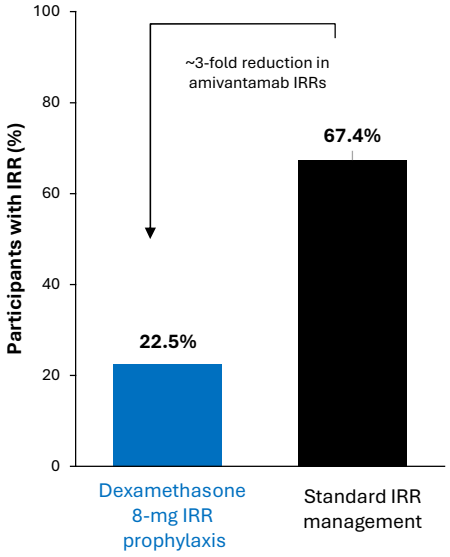
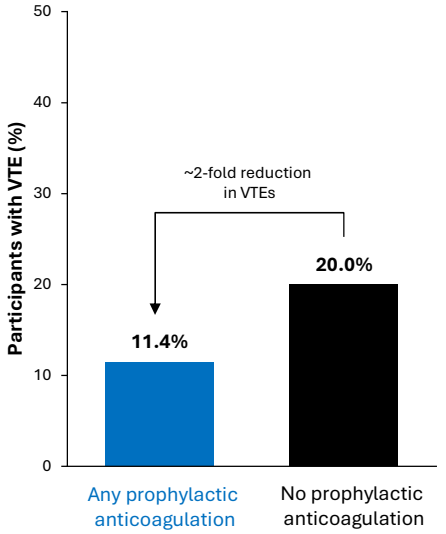


Prophylactic anticoagulation substantially reduced VTEs[3]



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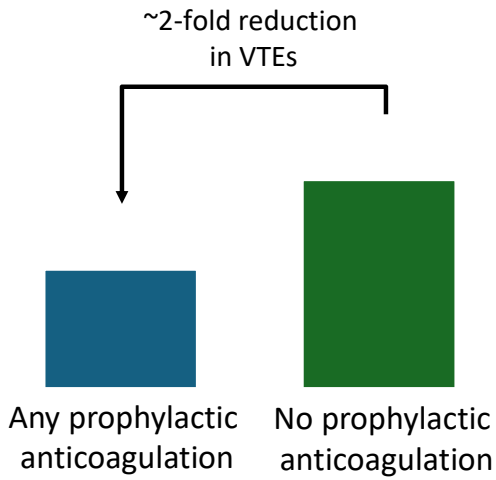
MARIPOSA: VTE Risk

Prophylactic anticoagulation
substantially reduced VTEs



- At the time of first VTE:
  - Most patients not on anticoagulants
  - Majority in the amivantamab + lazertinib arm occurred within the first 4 mo
- Prophylactic dose anticoagulation is now recommended for the initial 4 months of treatment. DOAC or LMH recommended

1. Girard. ELCC 2025. Abstr 10MO. 2. Spira. J Thorac Oncol. 2025:[Epub].
3. Lim. ASCO 2024. Abstr LBA8612. 4. Yang. ELCC 2025. Abstr 4O.

Diarrhea With EGFR TKIs

- More common with the oral TKIs
  - Afatinib: 96%; 15% grade 3/4
  - Osimertinib: 58%; 2.2% grade 3/4
  - Sunvozertinib: 73%; 2.2% grade 3/4
- Less common with amivantamab; constipation more frequent than diarrhea
- Diarrhea usually easily manageable with diphenoxylate
- Can require dose reduction

Afatinib PI. Osimertinib PI. Amivantamab PI. Sunvozertinib PI.

EGFR TKIs and ILD/Pneumonitis

- ILD/pneumonitis: uncommon, but a class effect of EGFR TKIs in the range of 1%-4%; can be fatal
- Evaluate for acute onset SOB with PE protocol CT chest
- Unlike IO rechallenge, TKI rechallenge is not recommended (permanently discontinue)
- **Word of caution: osimertinib given in short timeframe after immunotherapy causes significantly increased rate and severity of pneumonitis!**

Osimertinib PI. Schoenfeld. Ann Oncol. 2019;30:839.

EGFR: Osimertinib and Cardiac Concerns

- Cardiomyopathy (Pulm edema, CHF, decreased EF, cardiac failure)
  - Occurred in 3.8% of patients, 0.1% fatal.
  - “conduct cardiac monitoring including LVEF in patients with cardiac risk factors at baseline and during treatment”
- QT interval prolongation:
  - 1.1% greater than 500 msec, 4.3% increase by 60 msec from baseline
  - PI states “periodic monitoring” with ECG and electrolytes for patients with congenital conditions, CHF, abnormal lytes, or on concomitant meds known to prolong QT interval.

Osimertinib PI. 2025

Sunvozertinib

- Approved 2nd-line for EGFR Exon 20 insertion mutation
- 200mg daily oral, with food
- Diarrhea 73% and 2% grade 3/4
- Rash 60% and 8% grade 3/4
- ILD rare 1.7%
- Due to supply/distribution issue, unavailable right now?

Sunvozertinib PI. 2025

ALK Inhibitors:

- Class effects:
  - ILD uncommon 1-4%, more common with brigatinib
  - Edema
  - Bradycardia
  - CPK elevation with or without myalgias

DRUG	DOSE
Crizotinib	250mg twice a day (250mg, 200mg capsules)
Ceritinib	450mg daily (150mg capsules)
Alectinib	600mg twice a day (150mg capsules)
Brigatinib	90mg daily X 1 week, then 180mg daily (30 mg, 90mg and 180mg)
Lorlatinib	100mg daily (25mg, 100mg)
Ensartinib	225mg daily (25mg, 100mg)

Brigantinib, Alectinib, Lorlatinib, Crizotinib PI's. 2025

Unique Toxicities with Lorlatinib 100mg
N=149 patients in the first-line Crown Study

- Goal for LDL < 100mg/dl
- Goal for Triglycerides < 200mg/dl
- Mild/Mod (grade 1/2)
  - Rosuvastatin 10mg
  - Rosuvastatin 10mg + Ezetimibe 10mg
- Severe (grade 3/4)
  - Rosuvastatin 20mg +/- Ezetimibe 10mg
  - Evolocumab or Alirocumab + Rosuvastatin 20mg +/- Ezetimibe 10mg

Lorlatinib 100mg	All grades	Grade 3/4
Hypertriglyceridemia	95%	22%
Hypercholestolemia	91%	19%
Psychiatric: Mood	16%	2%
Peripheral Neuropathy	34%	2%
Cognitive Effects	21%	2%
Edema	56%	4%
Weight Gain	38%	17%
Hypertension	18%	10%

NCI CTCAE grading criteria V5.0; Lorlatinib PI accessed 10/2025;
Arriola E, et al Clinical Drug Investigation (2024) 44:553–576

Unique toxicities with Lorlatinib 100mg N=149 patients in the first-line Crown study

- Weight gain or Metabolic syndrome:
  - Increased weight with elevated blood sugar and hyperlipidemia
  - Weight gain seemingly independent of edema
  - Grade 3 is greater than 20% baseline weight
- Use of GLP-1 agonists
  - Case studies using semaglutide, return to baseline weight, improved HgbA1c and lipid panel
  - Consider PET scans may be with less uptake with these meds on board?

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Pietroluongo E, et al. ClinicalLungCancer,Vol.26,No.5,429–433; Lee ATM, Ou SI, Lisberg A. Letter to Editor. Re "de Leeuw SP, et al. Analysis of Serious Weight Gain in Patients Using Alectinib for ALK Positive Lung Cancer," Semaglutide a Potential Treatment for Serious Weight Gain From ALK Tyrosine Kinase Inhibitors? J Thorac Oncol 2023;18:e97-e99; NCI CTCAE grading criteria V5.0; Lorlatinib PI accessed 10/2025.

ROS1 and *NTRK*

	Approved for ROS1 NSCLC	Approved for *NTRK* Fusion + NSCLC	Dizziness	Weight Gain	Dysgeusia	Paresthesia
Crizotinib	★		18%	NR	26%	19%
Entrectinib	★	★	16-26%	10-28%	21-47%	16-29%
Larotrectinib		★	25-32%	4-14%	13%	10%
Repotrectinib	★		57%	NR	51%	29%
Taletrectinib	★		22%	NR	15%	17%

Management:

- Weight gain- GLP-1's
- Dizziness: meclinizine; scopolamine. Midodrine or Fludrocortisone if orthostatic
- Paresthesia: NSAIDs, opioids, Gaba analogs

Liu D, et al. Annals of Oncology. 2020; 31(9); Lim JSJ, Tan, DSP. Annals of Oncology. 2020; 31(9); crizotinib PI and Talotrectinib PI accessed 10/2025

KRAS G12C: Sotorasib and Adagrasib

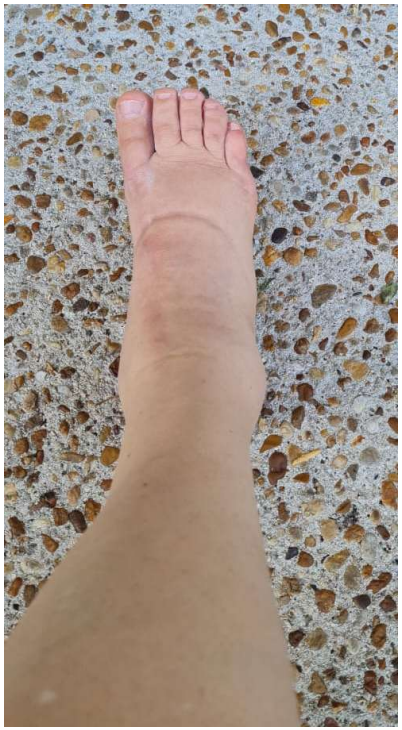
- Both approved in 2nd line NSCLC post progression on Chemotherapy +/- Immunotherapy
- Sotorasib:
  - DDI with PPI's, avoid completely with all PPI's and H2 blockers
    - Some data to take with soda
- Adagrasib: QT interval issue
- Both drugs cause diarrhea, Adagrasib more frequent, but less grade 3/4

	Sotorasib	**Adagrasib**
Trial	CodeBreaK 100	Krystal-1
# of patients	126	116
Primary endpoint		
ORR	41%	42.9%
DCR	84%	79.5%
Toxicity	All grades/grade 3/4	
Diarrhea	42%/5%	70%/0.9
Prolonged QT	N/A	19.8%/6%

Jänne P, et al. N Engl J Med 2022;387:120-31; Dy, G et al. 2023 J Clin Oncol 41:3311-3317; Sotorasib PI. 10/6/2023

MET TKIs: Capmatinib and Tepotinib

Edema, %	Capmatinib	Tepotinib
Any grade	52	70
▪ Grade ≥3	9	9



Management

- Elevation, compression stockings, diuretics sparingly

- Dose reductions if it becomes unbearable, emotional toll or stress on cardiovascular system

Capmatinib PI. 2020. Tepotinib PI. 2021

RET: Selpercatinib and Pralsetinib

Hypertension

38% [18% gr 3] pralsetinib

41% [20% gr 3] selpercatinib

- Optimize blood pressure prior to therapy initiation; do not initiate if uncontrolled
- Monitor blood pressure after 1 week, then at least monthly or as indicated
- Hold therapy if grade 3

Edema: all grades

44% w/pralsetinib (0% grade 3/4)

49% w/selpercatinib (1% grade 3/4)

QT Interval Prolongation: Selpercatinib only

QTc interval > 500 ms in 6%

- Assess QT interval, electrolytes, TSH at baseline and periodically
- Monitor and correct lab imbalances as indicated; concomitant medications
- Hold therapy if grade 3
- Discontinue if grade 4

Selpercatinib PI. 2025. Pralsetinib PI. 2025

Management of HTN in Patients with Cancer

- Work with clinical pharmacist to chose meds that do not have DDI with cancer meds
- Tailor antihypertensive therapy to comorbidities
- Lifestyle modification, though may not be applicable or appropriate for many patients with cancer

Table 2: Suggested choice of antihypertensive drugs by comorbidity.

Comorbidity	Suggested antihypertensive medication
DM, diabetic nephropathy, proteinuria, CKD	ACE-I/ARB SGLT2i
CHF, LV systolic dysfunction	ACE-I/ARB/ARNI SGLT2i BB MRA Loop diuretic
CAD	BB ACE-I/ARB Nitrates
Arrhythmia	BB
Resistant HTN	MRA Nitrates and/or hydralazine
Elderly, isolated systolic HTN	Dihydropyridine CCB

DM, diabetes mellitus; CHF, congestive heart failure; HTN, hypertension; LV, left ventricular; ARNI, angiotensin receptor/neprilysin inhibitor; BB, beta blocker.

Pandey S, et al. Clinical Kidney Journal , 2023, vol. 16, no. 12, 2336–2348

BRAF V600E mutation+ NSCLC:

- Dabrafenib/Trametinib approved in *BRAF* V600E
  - Common toxicity fever (non-infectious): 43%, 6% grade 3/4
  - Treatment acetaminophen, hold drug and restart at same dose
  - In resistant cases, can add prednisone
- Encorafenib and Binimetinib approved in 2024
  - Fever 22%, but 0 grade 3/4
  - Diarrhea 52% all grades
  - Nausea/Vomiting 58%/37% (4%/1% grade 3/4)

Garutti M, et al. Cancers 2023, 15, 141; Encorafenib and binimetinib PI 2025.

HER2 mutation + NSCLC: Oral Drug Zongertinib

- Generally well tolerated
- Diarrhea, but rare for grade 3/4
  - Mostly grade 1/2 which is 1-6 stools over baseline

Adverse Reaction	All grades	Grade 3/4
Diarrhea	52%	1%
Nausea	24%	1%
Rash	32%	1%

Zongertinib PI. 2025

Adherence with Orals in Cancer

- In meta-analysis of interventions, less than 1/2 of interventions improved adherence
- Best data is for pharmacist-led programs for monitoring and routine/consistent provider follow up
- Use alarms, text reminders, pill boxes
- When reviewing meds, ask how you take medication:
  - Case study: well-educated, 48 y/o male, new to alectinib. At 2-week follow up after starting medication, I asked him, “how are you taking your cancer medication?” He said, “4 tabs once a day”. (should be twice a day).
  - Found out, he literally read the bottle wrong.

Rosenberg, SM, et al. JNCI J Natl Cancer Inst (2020) 112(5): djz244

Conclusions:

- Many orals in NSCLC
- They have different s/e even within the same class sometimes
- Newer toxicities offer challenges for oncology providers
- Adherence very important

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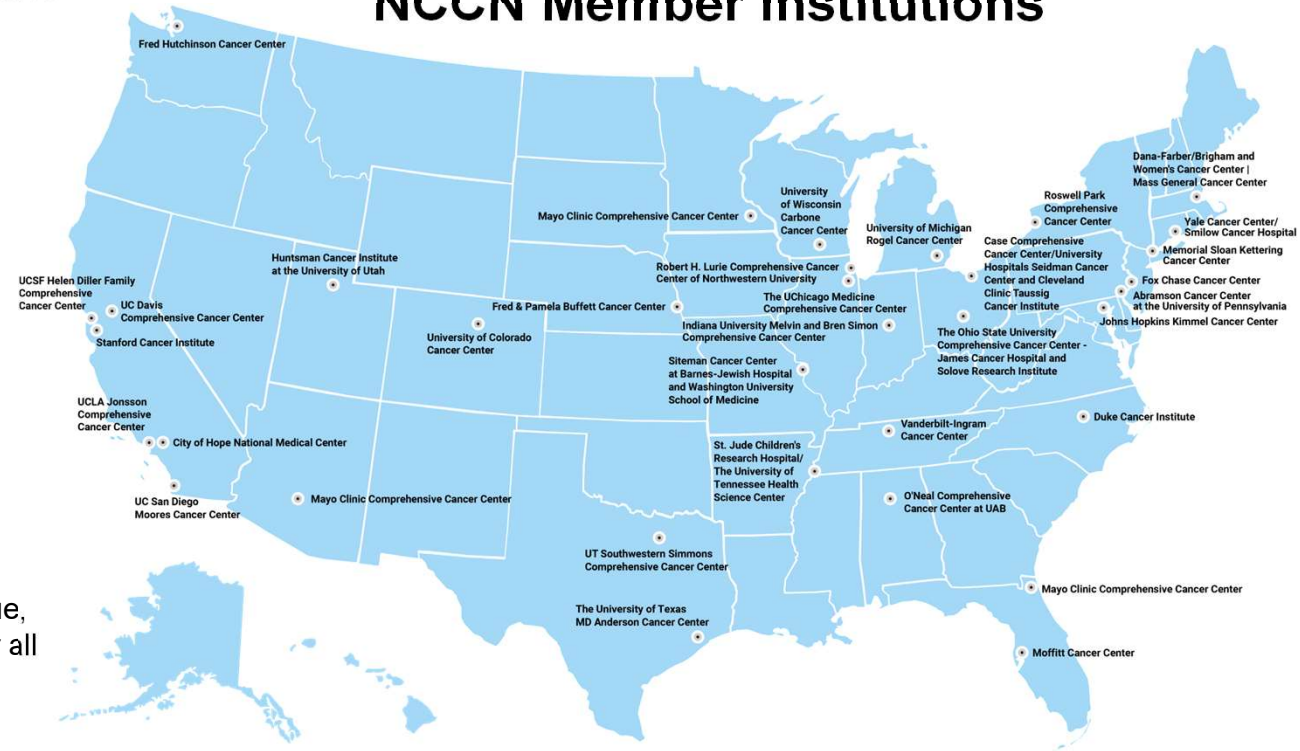

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An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To define and advance quality, effective, equitable, and accessible cancer care and prevention so all people can live better lives

Our Vision

Access to high-quality, high-value, patient-centered cancer care for all people globally

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