Toxicity Management of Novel Agents in Lung Cancer

Khurrum Qureshi, PharmD, BCOP

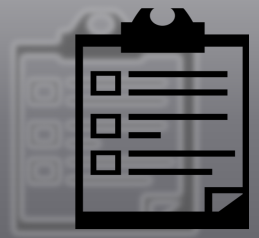
Pharmacy Clinical Specialist

Miami Cancer Institute | Baptist Health South Florida

Objectives

Recall recently approved novel targeted therapies used in the treatment of non-small cell lung cancer

Describe the adverse effect profile of novel therapies targeting *RET*, *MET*, and *KRAS G12C* mutations



Formulate a strategy to manage toxicities associated with novel targeted therapies

Targeted Therapy in Lung Cancer

- Lung cancer remains one of the most common and deadly types of cancers in the world
- Testing for molecular biomarkers is standard-of-care for non-small cell lung cancer (NSCLC) and drives treatment decisions
- Advent of targeted therapy has helped to improve treatment outcomes and quality of life
- When possible, targeted therapy has largely replaced chemotherapy as the preferred first-line treatment option for patients with metastatic NSCLC

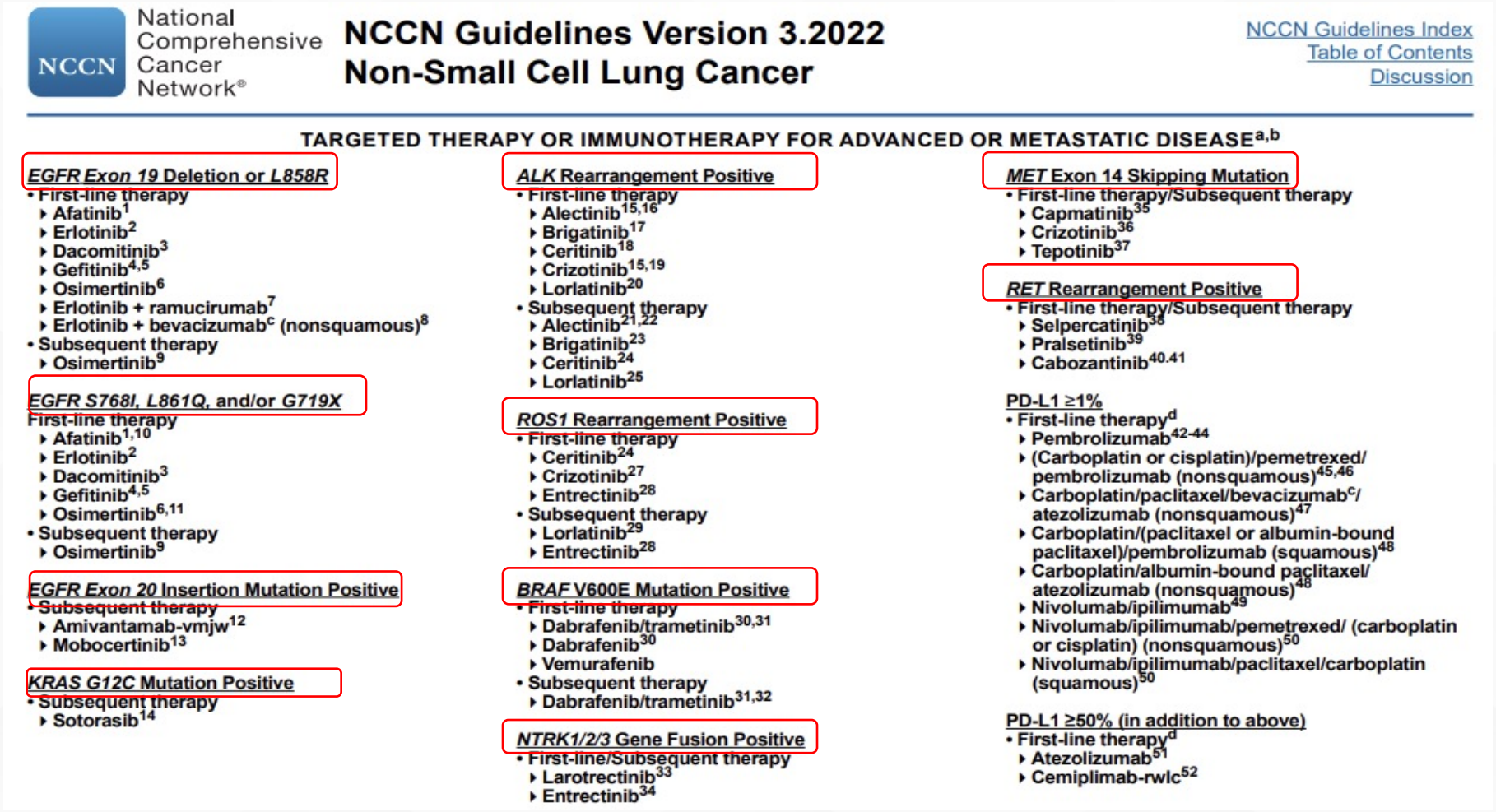
Signal Transduct Target Ther. 2019;4:61.

Rapidly Evolving Landscape

- **2003:** FDA approved the first targeted therapy for non-small cell lung cancer, gefitinib
- **2022:**

EGFR	ALK	ROS1	BRAF
KRAS G12C	NTRK	MET	RET

Rapidly Evolving Landscape



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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EGFR S768I, L861Q,* and/or *G719X
First-line therapy
- Afatinib[1,10]
- Erlotinib[2]
- Dacomitinib[3]
- Gefitinib[4,5]
- Osimertinib[6,11]

Subsequent therapy
- Osimertinib[9]

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PD-L1 ≥1%
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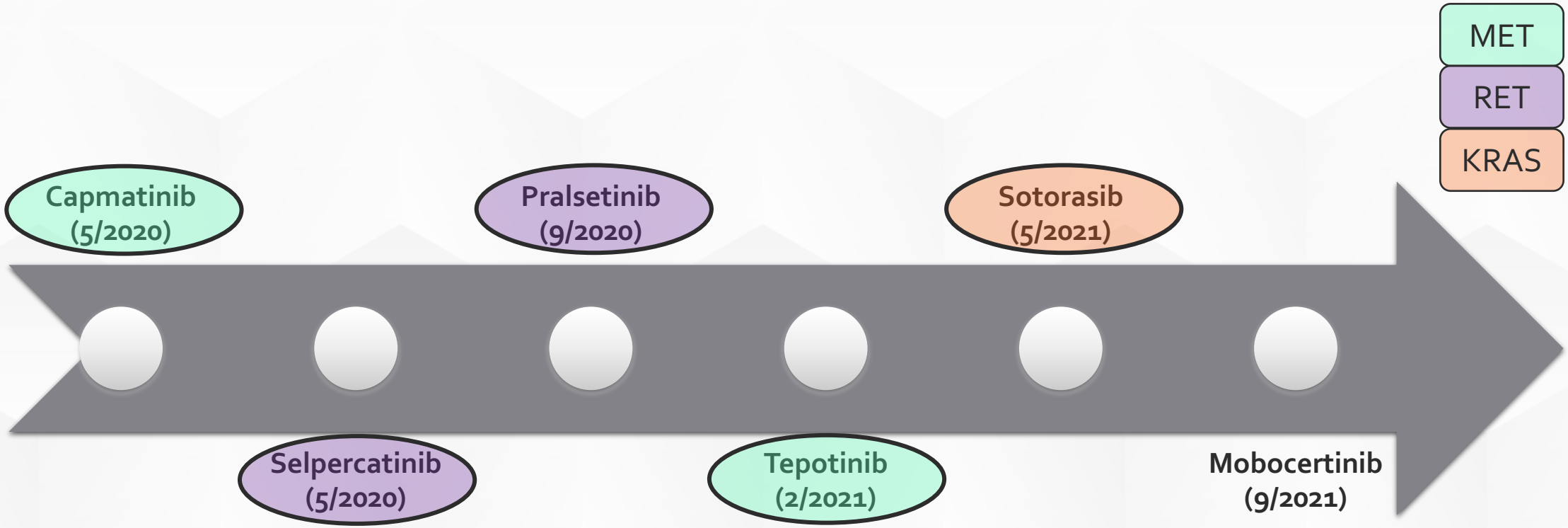
  - Cemiplimab-rwlc[52]

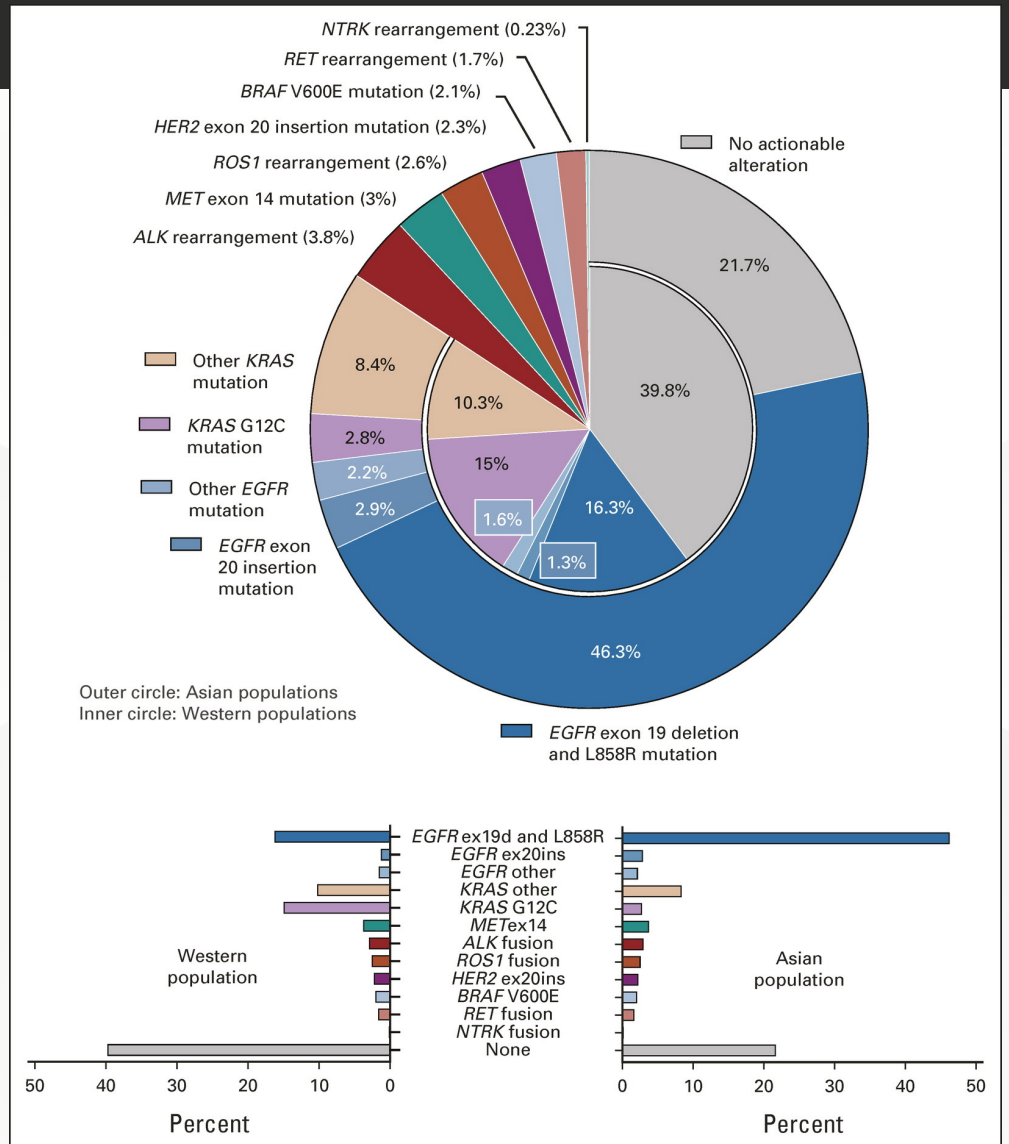
National Comprehensive Cancer Network. NSCLC (Version 3.2022) Accessed March 17th, 2022

Novel Oral Targeted Agents



Tan AC, et al. *J Clin Oncol*. 2022;40(6):611-625.

Oncogenic Driver Molecular Alterations



Tan AC, et al. *J Clin Oncol*. 2022;40(6):611-625.

Missing the Target ?

- Some targeted therapy agents do not exhibit high specificity between mutant genes and wild-type counterparts
- On-target toxicity is associated with mechanism of action and may or not be associated with response
- Other toxicities are off-target and may be due to class of agent or toxic metabolites
- Identifying the cause of toxicity helps to better understand the appropriate management strategy

Liu S, et al. *Cancer Treat Rev*. 2014;40(7):883-891.

MET Kinase Inhibitors

FDA approved therapy	Clinical Trial	ORR (%)	mPFS (mo.)	mOS (mo.)
Capmatinib	GEOMETRY	41/68	5.4/12.4	13.6/20.8
Tepotinib	VISION	46	8.5	17.1*

- Adverse events leading to discontinuation:
  - Capmatinib: 16 %
  - Tepotinib: 11 %
- **Warnings:** Interstitial lung disease, hepatotoxicity, embryo-fetal toxicity, photosensitivity (capmatinib)

Majeed U, et al. *J Hematol Oncol*. 2021;14(1):108.

* Not mature

MET Inhibitors: Safety Profile

	Capmatinib		Tepotinib	
Adverse Effect	Grade 1-2 AEs (%)	Grade 3-4 AEs (%)	Grade 1-2 AEs (%)	Grade 3-4 AEs (%)
Peripheral edema	42	9	56	7
Nausea	43	2	25	1
Diarrhea	17	1	21	1
Serum creatinine increased	24	0	17	1
Hypoalbuminemia	NR	NR	14	2
Amylase/lipase increased	7	8	15	6
Fatigue	11	3	7	1
Decreased appetite	12	1	7	1

Wolf J, et al. *N Engl J Med*. 2020;383(10):944-957.
Paik PK, et al. *N Engl J Med*. 2020;383(10):931-943.

NR: Not reported

MET Inhibitors: Peripheral Edema

- Exact etiology is unclear but thought to be due to attenuated HGF-mediated signaling in the peripheral vascular endothelium
  - HGF normally protects against VEGF-induced endothelial hyperpermeability
  - Inhibition of this pathway results in endothelial leak
- Patient counseling
  - Educate patients to set expectations
  - Elevate legs when sitting or lying down
  - Avoid high sodium diet
  - Record weight daily and keep a log

Kunimasa K, et al. *Thorac Cancer*. 2021;12(24):3426-3428.

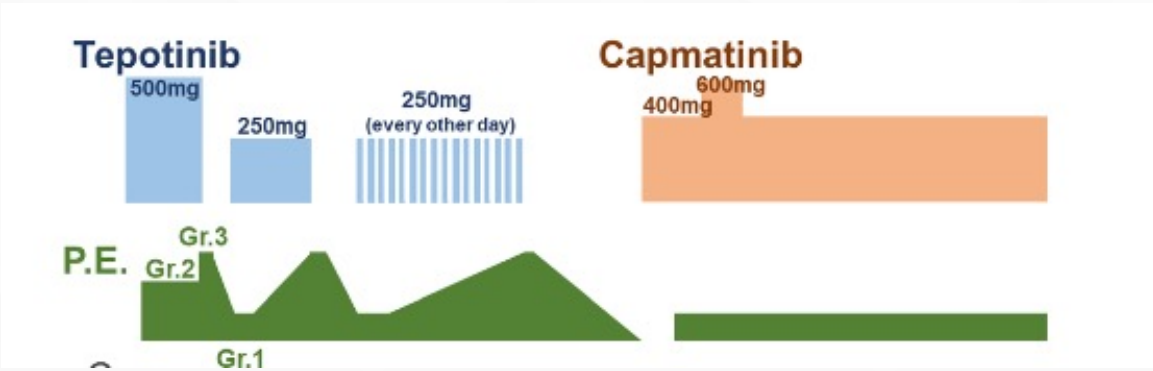
MET Inhibitors: Peripheral Edema

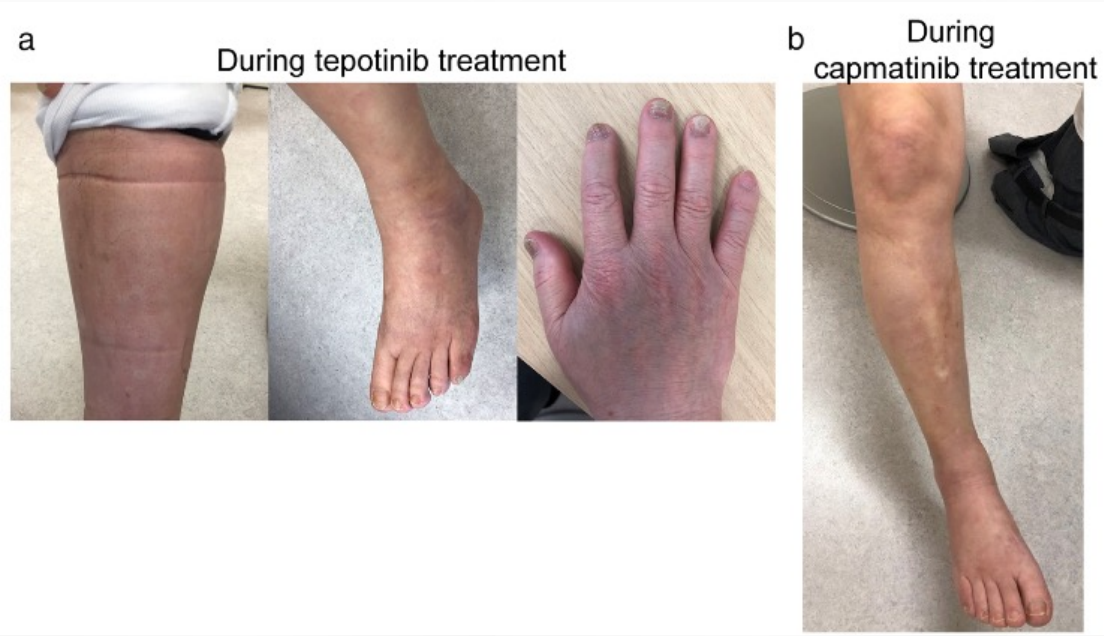
- Dose reduction/ dose interruption:
  - **Grade 2:** Maintain dose level. If intolerable, consider withholding until resolved & resume at reduced dose.
  - **Grade 3:** Interrupt treatment until resolved & resume at reduced dose
  - **Grade 4:** Permanently discontinue
- Use of compression garments
- Diuretics: edema tends to be resistant

Capmatinib [prescribing information].
Tepotinib [prescribing information].

Kunimasa K, et al. *Thorac Cancer*. 2021;12(24):3426-3428.

MET Inhibitors: Peripheral Edema





- Case report of 72 year-old man initially treated with tepotinib and subsequently developed grade 3 peripheral edema
- Recurred despite dose reduction and use of diuretics

Kunimasa K, et al. *Thorac Cancer*. 2021;12(24):3426-3428.

MET Inhibitors: Hepatotoxicity

- Median time to onset
  - **Capmatinib:** 1.4 months
  - **Tepotinib:** 1 month
- Monitoring recommendations for ALT, AST, and total bilirubin
  - Baseline
  - Every 2 weeks during first 3 months
  - Thereafter, monthly or as clinically indicated

Capmatinib [prescribing information].
Tepotinib [prescribing information].

MET Inhibitors: Hepatotoxicity

Adverse Reaction	Dose Adjustment
ALT and/or AST **without** increased total bilirubin	Grade 3 (> 5 x ULN) : Withhold until recovery to baseline ALT and/or AST. If recovered to baseline within 7 days, then resume at the same dose; otherwise resume at a reduced dose.
	Grade 4 (> 20 x ULN): Permanently discontinue.
Increased ALT and/or AST **with** increased total bilirubin	ALT and/or AST >3 x ULN with total bilirubin >2 x ULN: Permanently discontinue.
Increased total bilirubin **without** concurrent increased ALT and/or AST	Grade 3 (> 3 x ULN): Withhold until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume at a reduced dose; otherwise permanently discontinue.
	Grade 4 (> 10 x ULN): Permanently discontinue.

Capmatinib [prescribing information].
Tepotinib [prescribing information].

MET Inhibitors: Nausea/Vomiting

- Emetic risk is minimal to low per NCCN Guidelines
  - **Version 1.2022, capmatinib removed from 'Moderate to high emetic risk'**
  - Routine prophylaxis is not required
  - As needed medications are recommended
  - If the patient experiences nausea/vomiting:
    - Metoclopramide
    - Prochlorperazine
    - Short-acting 5HT3 receptor antagonist

National Comprehensive Cancer Network. Antiemesis (Version 1.2022) Accessed February 7th, 2022

MET Inhibitors: Interstitial Lung Disease

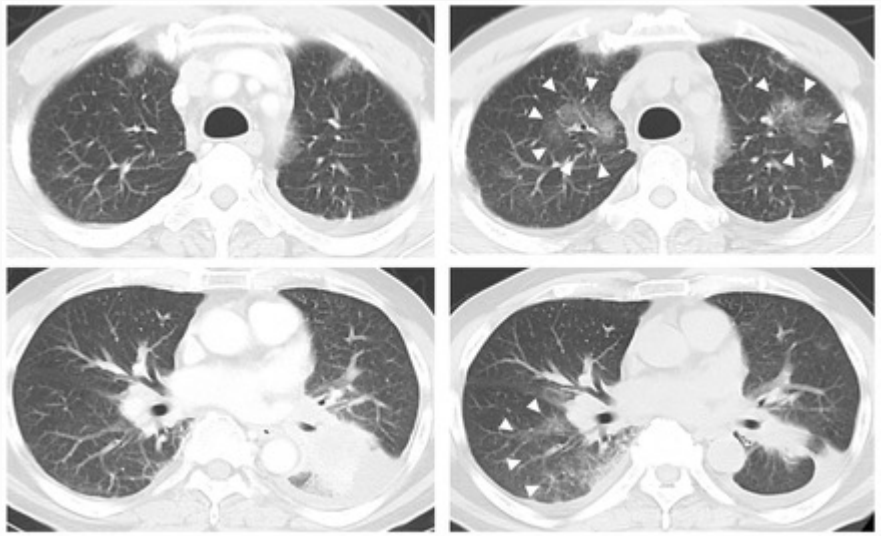
- Median time to onset: 1.4 months (Range: 0.2 months – 1 year)
- ILD comprises a large group of fibrotic lung disease
  - Rare but potentially serious side effect of TKIs used in the treatment of lung cancer
  - HGF and its MET receptor exerts anti-fibrotic effects, however, unclear if MET TKIs influence this role
- Immediately withhold if ILD or pneumonitis suspected
- Permanently discontinue if confirmed

Kanemura H, et al. *Thorac Cancer*. 2021;12(4):549-552.

ILD: Interstitial lung disease
HGF: Hepatocyte growth factor

MET Inhibitors: Interstitial Lung Disease

- Clinical signs
  - Cough, fever, acute or subacute dyspnea
- Important to rule out infectious causes
- Radiographic findings often our only evidence
- Management
  - Discontinue causative agent
  - Supplemental oxygen
  - Systemic corticosteroids
  - Careful evaluation of risk vs. benefit if considering re-challenge



Kanemura H, et al. *Thorac Cancer*. 2021;12(4):549-552.
Nishino M, et al. *JCO Precis Oncol*. 2017;1:PO.17.00026.

MET Inhibitors: Dose Modification

Capmatinib	Dosing	Tepotinib
400 mg twice daily	Initial dose	450 mg once daily
300 mg twice daily	1st reduction	225 mg once daily
200 mg twice daily	2nd reduction	Discontinue

Capmatinib [prescribing information].
Tepotinib [prescribing information].

RET Kinase Inhibitors

FDA approved therapy	Clinical Trial	ORR (%)	mPFS (mo.)	mOS (mo.)
Selpercatinib	LIBRETTO-001	65/85	19.3/ NE	NR
Praseltinib	ARROW	57/70	16.5/ 13.0	NR

- Adverse events leading to discontinuation
  - Selpercatinib: 2 %
  - Praseltinib: 4 %
- **Warnings:** Hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, tumor lysis syndrome, impaired wound healing, embryo-fetal toxicity, pulmonary toxicity (praseltinib)

Drilon A, et al. *N Engl J Med*. 2020;383(9):813-824.

Gainor JF, et al. *Lancet Oncol*. 2021;22(7):959-969.

NR: Not reported
NE: Not estimable

RET Inhibitors: Safety Profile

Adverse Effect	Selpercatinib		Praseltinib	
	Grade 1-2 AEs (%)	Grade 3-4 AEs (%)	Grade 1-2 AEs (%)	Grade 3-4 AEs (%)
Fatigue	33	2	33	2
Constipation	24	1	34	1
Hypertension	17	18	14	14
Diarrhea	34	3	21	3
Increased ALT	36	9	47	2
Increased AST	43	8	72	2
Prolonged QT Interval	13	4	0	0
Hemorrhage	13	2	NR	2.5

Drilon A, et al. *N Engl J Med*. 2020;383(9):813-824.
Gainor JF, et al. *Lancet Oncol*. 2021;22(7):959-969.

NR: Not reported

RET Inhibitors: Hypertension

- RET inhibitors also inhibits VEGF receptors
- **Hypothesis:** ERK activation & upregulation of CD47 → Endothelial dysfunction → Hypertension
- Patient counseling
  - Monitor & record blood pressure routinely
  - Contact provider for symptoms such as headache, dizziness, chest pain, shortness of breath, fluid retention or swelling

van Dorst DCH, et al. *Circ Res*. 2021;128(7):1040-1061.

RET Inhibitors: Management of Hypertension

- Screen for cardiovascular risk factors
- Optimize blood pressure management prior to starting anticancer treatment
  - Recommended goal < 130/80 mmHg
  - At least < 140/90 mmHg before starting treatment with pro-hypertensive effects
- Initiate or optimize pharmacologic therapy for BP > 140/90 mmHg
  - Guidance on best antihypertensive agent in cancer population is lacking
  - Consider adverse effects, co-morbidities, and drug interactions

van Dorst DCH, et al. *Circ Res*. 2021;128(7):1040-1061.

RET Inhibitors: Management of Hypertension

- Dihydropyridine CCBs such as amlodipine or nifedipine
- Mir, et al. published a retrospective study demonstrating 31/36 (86%) of patients with bevacizumab-induced hypertension were controlled with amlodipine 5 mg within 7 days
- Combination therapy with more than one class of anti-hypertensive
- Dose interruption or reduction
  - **Grade 3:** Withhold for grade 3 HTN that persists despite management with optimal therapy. Resume at reduced dose when HTN resolves.
  - **Grade 4:** Discontinue agent

van Dorst DCH, et al. *Circ Res*. 2021;128(7):1040-1061.
Mir O, et al. *Invest New Drugs*. 2012;30(2):702-707.

RET Inhibitors: Hepatotoxicity

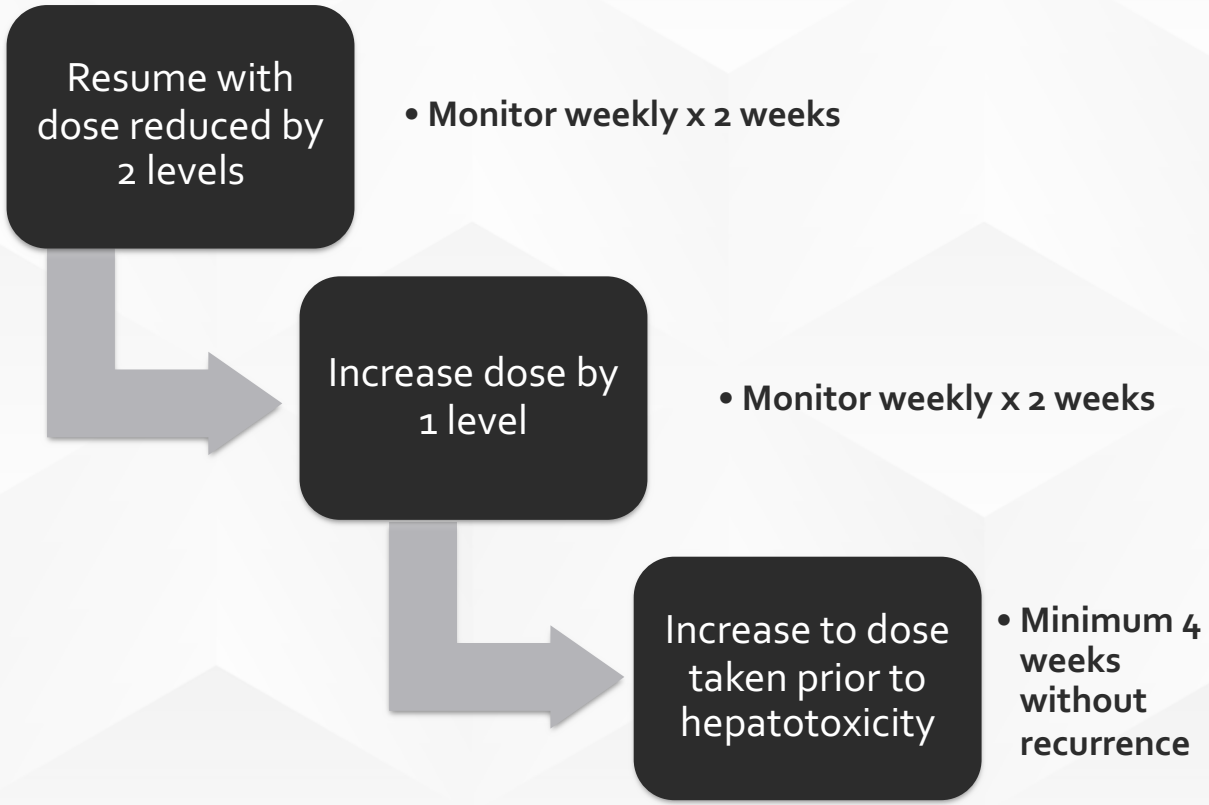
- Median time to onset
  - **Selpercatinib:** 4.1 weeks (Range: 5 days – 2 years)
  - **Praseltinib:** 2.1 weeks (Range: 5 days – 1.7 years)
- Monitoring recommendations for ALT, AST, and total bilirubin
  - Baseline
  - Every 2 weeks during first 3 months
  - Thereafter, monthly or as clinically indicated

Selpercatinib [prescribing information].
Praseltinib [prescribing information].

RET Inhibitors: Hepatotoxicity

Adverse Reaction	Dose Adjustment
ALT and/or AST elevation	Grade 3 or 4 (> 5 x ULN) : Withhold and monitor AST/ALT once weekly until resolution to grade 1 or baseline **Selpercatinib:** See diagram. **Praseltinib:** Resume at reduced dose. If grade ≥ 3 hepatotoxicity recurs, discontinue.

Resuming selpercatinib



Selpercatinib [prescribing information].
Praseltinib [prescribing information].

RET Inhibitors: Tumor Lysis Syndrome

Laboratory TLS (≥2 present)	Clinical TLS (≥1 present)
Uric acid ≥8 mg/dL, or 25% increase from baseline	Creatinine >1.5 times the upper limit of normal
Potassium ≥6 mmol/L, or 25% increase from baseline	Cardiac arrhythmia/sudden death
Phosphorus ≥4.5 mg/dL (adults), or 25% increase from baseline	Seizure
Calcium <7 mg/dL, or 25% decrease from baseline	

- Tumor lysis syndrome (TLS): metabolic abnormalities caused by the release of intracellular contents; subsequent clinical manifestations include renal impairment, cardiac arrhythmias, seizures and death
- Patients with rapidly growing tumors, high tumor burden, renal dysfunction or dehydration are at risk

Robbins, et al. J Hematol Oncol Pharm. 2022;12(1):19-23.

RET Inhibitors: Tumor Lysis Syndrome

- Most solid tumors are considered low-risk for TLS
- Renal dysfunction elevates risk level to the next tier
- Patients at low-risk should be encouraged to maintain adequate fluid intake & monitored closely
- Prevention: Address underlying renal dysfunction & hypovolemia

Jones GL, et al. *Br J Haematol*. 2015;169(5):661-671.

RET Inhibitors: Tumor Lysis Syndrome

Management of Tumor Lysis Syndrome		
Aggressive Hydration	Goal urine output of at least 2 mL/kg/hr	
Uric Acid Lowering Agents	**Allopurinol**	100 mg/m2 q8h or 10 m/kg/day Does not alter level of circulating uric acid
	Febuxostat	40 mg once daily; may increase to 80-120 mg daily
	Rasburicase	Studies support single 3 mg dose with repeat doses based on uric acid levels Decreases circulating uric acid
Hyperkalemia	**Potassium binders**	Sodium polystyrene, sodium zirconium, patiromer
	Calcium gluconate	If concurrent EKG changes; 1 gram
	Insulin & dextrose	10 units followed by 25 g of D50W intravenously
Hyperphosphatemia	**Restrict IV & PO intake**	Medications and dietary sources
	Phosphate binders	Sevelamer, aluminum hydroxide (with meals)

Jones GL, et al. *Br J Haematol*. 2015;169(5):661-671.

RET Inhibitors: Hemorrhagic Events

Adverse Reaction	Dose Adjustment
Hemorrhagic Events	Grade 3 or 4: Withhold until recovery to grade 0 or 1 or to baseline
	Severe or life-threatening: Permanently discontinue.

- Grade 3 (per CTCAE v5.0): Transfusion indicated; invasive intervention; hospitalization
- Grade 4 (per CTCAE v5.0): Life-threatening consequences; urgent intervention indicated

Selpercatinib [prescribing information].
Praseltinib [prescribing information].

CTCAE: Common Terminology Criteria for Adverse Events

RET Inhibitors: Dose Modification

Praseltinib	Dosing	Selpercatinib
400 mg once daily	Initial dose	120 / 160 mg twice daily
300 mg once daily	1st reduction	80 / 120 mg twice daily
200 mg once daily	2nd reduction	40 / 80 mg twice daily
100 mg once daily	3rd reduction	40 mg once / twice daily
		Pts < 50 kg / ≥ 50 kg

Selpercatinib [prescribing information].
Praseltinib [prescribing information].

KRAS G12C Inhibitor

FDA approved therapy	Clinical Trial	ORR (%)	mPFS (mo.)	mOS (mo.)
Sotorasib	CodeBreak 100	32	6.3	12.5

- Adverse events leading to discontinuation: 7.1 %
- Adverse events leading to dose reduction: 22.2 %

- **Warnings:** Hepatotoxicity & interstitial lung disease/pneumonitis

Hong DS, et al. *N Engl J Med*. 2020;383(13):1207-1217.

Sotorasib: Safety Profile

Adverse Effect	Sotorasib	
	Grade 1-2 AEs (%)	Grade 3-4 AEs (%)
Diarrhea	28	4
Nausea	19	0
Vomiting	8	0
ALT Increased	9	6
AST Increased	9.5	5.6
Fatigue	11	0
Maculopapular rash	5.6	0

Hong DS, et al. *N Engl J Med*. 2020;383(13):1207-1217.

Sotorasib: Management of Diarrhea

- Patient Counseling
  - Maintain adequate hydration
  - Avoid high-fiber foods
  - Avoid foods that cause gas
  - Avoid "trigger" foods (lactose, fatty or spicy foods)
- Loperamide (max: 16 mg or eight 2 mg tablets per day)
- **Grade 3 or 4:** Withhold until recovery to grade ≤ 1 or baseline, then resume at the next lower dose level

Sotorasib [prescribing information].

Sotorasib: Hepatotoxicity

- Etiology of hepatocellular injury has not been identified
  - Case reports published of hepatitis in patients receiving sotorasib after immune checkpoint inhibitor therapy
  - Preclinical studies showed sotorasib may induce a proinflammatory tumor microenvironment
- Median time to onset: 9 weeks
- Monitoring (AST, ALT, and total bilirubin):
  - Baseline
  - Every 3 weeks for the first 3 months
  - Then once a month or as clinically indicated

Sotorasib [prescribing information].
Begum P, et al. *JTO Clin Res Rep*. 2021;2(9):100213.

Sotorasib: Hepatotoxicity

Adverse Reaction	Dose Adjustment
ALT and/or AST elevation	Grade 2 (>3-5 x ULN**) with symptoms:** Withhold until recovery to grade ≤ 1 or baseline, then resume at next lower dose level
	Grade 3 or 4 (> 5- 20 x ULN): Withhold until recovery to grade ≤ 1 or baseline, then resume at next lower dose level
Increased ALT and/or AST **with** increased total bilirubin	ALT and/or AST >3 x ULN with total bilirubin >2 x ULN: Permanently discontinue

- Some patients in CodeBreak 100 received corticosteroids for management of hepatotoxicity in addition to dose interruption or reduction

Sotorasib [prescribing information]. .

Sotorasib: Pulmonary Toxicity

- Interstitial lung disease or pneumonitis may occur and can be fatal
- Median time to onset: 2 weeks
- **Any grade**
  - Immediately withhold if ILD or pneumonitis suspected
  - Permanently discontinue if confirmed

Sotorasib [prescribing information]. .

Sotorasib: Dose Modification

Dosing	Sotorasib
Initial dose	960 mg once daily
1st reduction	480 mg once daily
2nd reduction	240 mg once daily

Sotorasib [prescribing information].

Improving Outcomes in Patients with Toxicity

- Patients who experienced adverse drug reactions to targeted cancer therapies have poor treatment compliance, higher rates of discontinuation and undergo frequent changes & adjustments to their medications
- Repetitive education to the patient on how to identify, manage, and escalate signs of toxicity is crucial
- Pharmacists providing follow-up calls can serve to improve pharmacovigilance for patients on oral targeted therapy
  - Study showed over a 6-month duration, 22 % of ADRs reported to pharmacist over the phone were not reported to the healthcare provider by the patient

Du R, et al. *BMC Cancer*. 2021;21(1):206.
Monestime S, et al. *J Am Pharm Assoc (2003)*. 2021;61(1):53-59.

Conclusion

Several novel agents have been approved by the FDA in the treatment of NSCLC that allow practitioners to target molecular alterations in *MET, RET, and KRAS G12C*

The growing landscape of targeted therapy used in lung cancer requires healthcare providers to understand the etiology and frequency of expected toxicities

Healthcare providers can utilize various avenues of supportive care, dose reductions and interruptions in order to provide an individualized treatment plan for patients presenting with toxicities from targeted therapy