Optimizing Use of Biomarkers in Managing Metastatic Non–Small Cell Lung Cancer

The Role of the Oncology Health Care Team

#NCODAForum21

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Educational Objectives for Pharmacists, Nurses, and Physicians

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After completion of this activity, participants will be able to:

- Examine the role, barriers, and trends of using molecular testing and biomarker results in non–small cell lung cancer (NSCLC)
- Investigate the evidence to support use of established and emerging biomarkers to guide treatment selection in NSCLC
- Illustrate the role of the oncology health care team in the care of patients with NSCLC

Pharmacy Technician Educational Objectives

After completion of this activity, participants will be able to:

- Recall the role of molecular testing and biomarkers in treatment plans for non–small cell lung cancer (NSCLC) treatment
- List targeted agents that may be selected for patients based on specific biomarker test results
- Review the role of the oncology health care team in the care of patients with NSCLC

Importance of Molecular Testing and Current Trends in NSCLC

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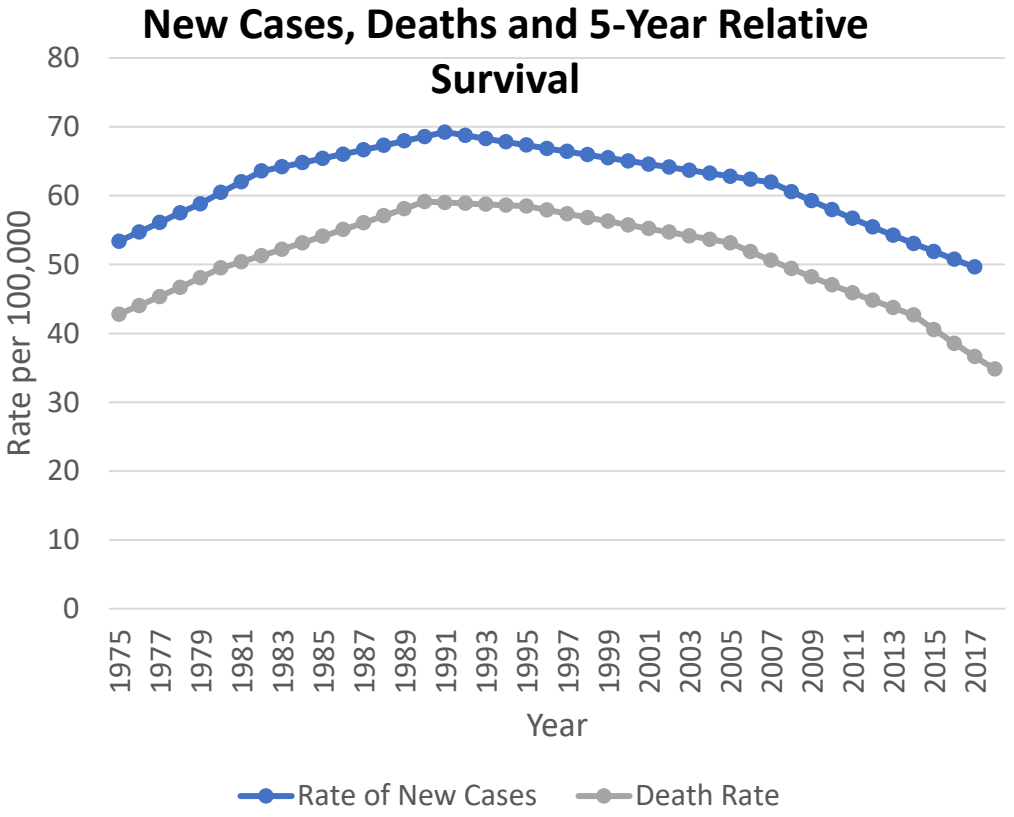
Lung Cancer Overview

- Leading cause of cancer death in the United States
- In 2020, estimated 228,820 new cases of lung and bronchial cancer diagnosed
  - 116,300 in men and 112,520 in women
- Areas of progress
  - Screening
  - Minimally invasive techniques
  - New treatment strategies, mainly targeted therapies and immunotherapies
    - Biomarker-directed treatment



NCCN Guidelines. Non-Small Cell Lung Cancer. Version 4.2021; Siegel RL, et al. *CA Cancer J Clin*. 2020;70(1):7-30; www.seer.cancer.gov

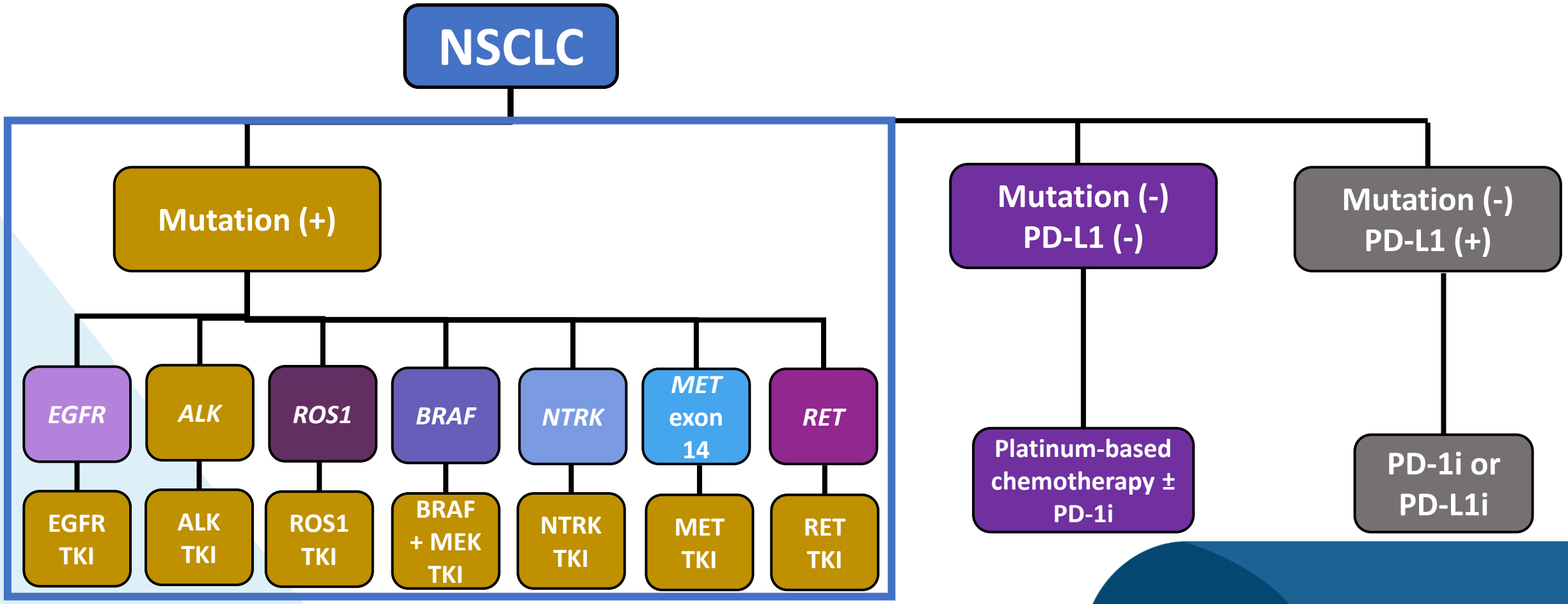
Frequency of Biomarker Mutations

Mutation	Nonsquamous	Squamous
EGFR	20%	6%
ALK	4%	1%
ROS1	1%	0%
BRAF	6%	2%
NTRK	<0.5%	<0.5%
MET	6%	3%
RET	2%	2%

**Generally seen in nonoverlapping fashion, although 1% to 3% of NSCLC may harbor concurrent alternations.

Calculated from Singal G, et al. *JAMA*. 2019;321(14):1391-1399; Farago AF, et al. *JCO Precis Oncol.* 2018;2018:PO.18.00037; NCCN Guidelines. Non-Small Cell Lung Cancer. Version 4.2021.

Biomarker-Driven Treatment



NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer, v4.2021.

PD-L1, programmed-death ligand 1; TKI, tyrosine kinase inhibitor.

Current NSCLC Molecular Testing Guidelines

- The National Comprehensive Cancer Network (NCCN) strongly advises next-generation sequencing (NGS) testing should be conducted as part of broader molecular profiling
- All patients with metastatic adenocarcinoma, large cell, or NSCLC not otherwise specified
  - Minimum of *EGFR, ALK, ROS1, BRAF, MET*ex14*, RET, NTRK*1/2/3
  - Immunohistochemistry (IHC) analysis testing for PD-L1 expression; category 1 recommendation
  - Regardless of clinical characteristics such as age, race, or smoking status

Lindeman N, et al. *Arch Pathol Lab Med*. 2018;142(3):321-346; NCCN Guidelines. Non-Small Cell Lung Cancer. Version 4.2021. Davis AA, Patel VG. *J Immunother Cancer*. 2019;7:278.

Controversies in Molecular Testing

- Testing in earlier-stage disease
- Challenges
  - Availability of assays
  - Variability of expression of PD-L1
  - Other methods of assessing PD-L1 expression (eg, tumor mutational burden) under evaluation
- Repeat testing?
  - Consider repeat panel testing or selected biomarker testing at progression on first-line therapy if a lesion can be accessed for sampling and testing
  - Recommended for *EGFR* inhibitor resistance
  - Potential role for liquid biopsies

Lindeman N, et al. *Arch Pathol Lab Med*. 2018;142(3):321-346; NCCN Guidelines. Non-Small Cell Lung Cancer. Version 4.2021; Colomer R, et al. *EClinicalMedicine*. 2020;25:100487; Davis AA, Patel VG. *J Immunother Cancer.* 2019;7:278. Garinet S, et al. *J Clin Med*. 2018;7(6):144.

Why Is Testing Important?

- Recent clinicogenomic database study
  - Included 4064 patients with advanced NSCLC
    - 85% treated in community setting
- **Less than half (48.3%) of patients** with advanced NSCLC, with an NCCN-driver alteration, **received NCCN-recommended therapy**
- Among patients with a mutation in an NCCN-listed gene with evaluable overall survival (OS), **exposure to NCCN-directed targeted therapy treatment was associated with longer OS**
  - Median OS 18.6 months vs 11.4 months, *P* <0.001

	NCCN-directed therapy N = 575	Did not receive NCCN-directed therapy N = 560	*P* value
Median OS	18.6 months	11.4 months	<0.001

Singal G, et al. *JAMA*. 2019;321(14):1391-1399.

Barriers and Access to Molecular Testing in NSCLC

- Rapidly changing recommendations
- Biopsy tissue samples often inadequate for biomarker testing and rebiopsies may pose additional risk and cost
- Test failures or discordant results between multiple tests
- Series of single gene tests rather than as broader NGS panel
- Payer coverage

Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542; Singal G, et al. *JAMA*. 2019;321(14):1391-1399.

Available Testing Options

NGS

- Preferred method, high specificity
- Panel of genes and abnormalities detected depends on specific NGS platform

PCR

- May be used for real-time testing on specific mutations

Fluorescence in situ hybridization (FISH)

- Used for many assays examining copy number, amplification, and structural alternations such as gene rearrangements

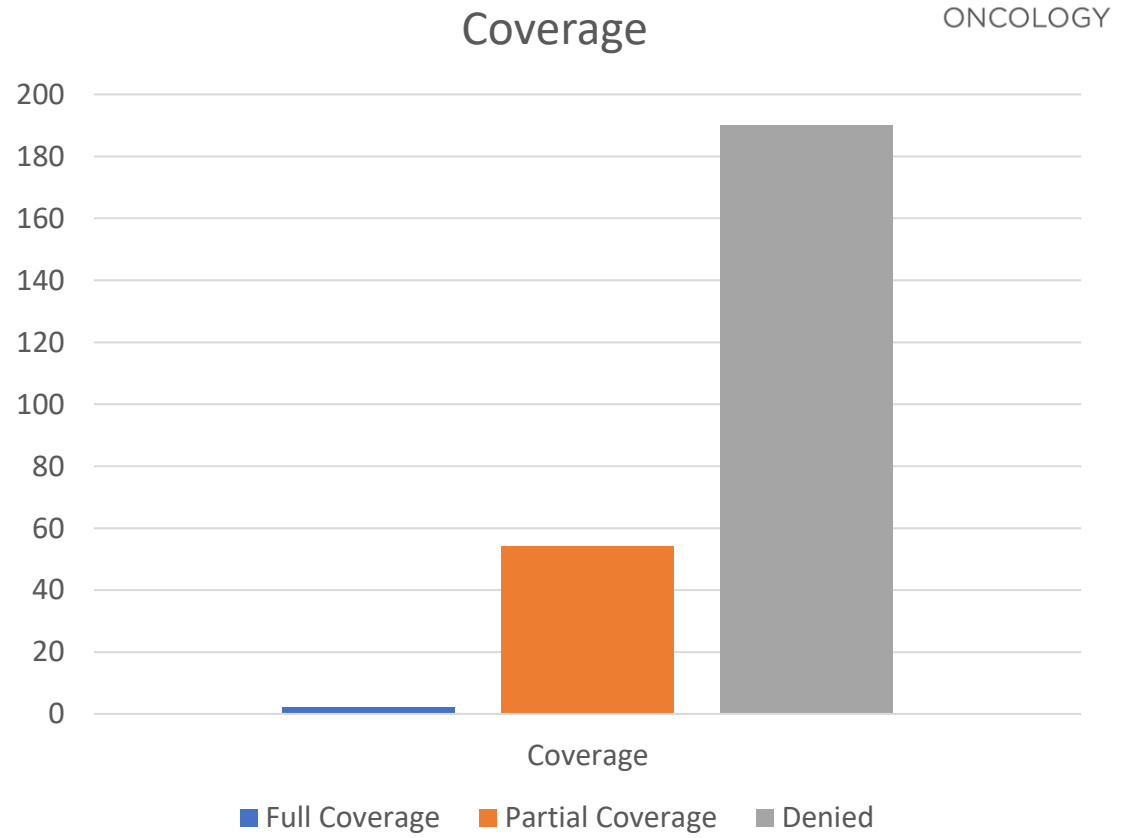
Immunohistochemistry

- May be used for specific analyses, useful surrogate for screening assays
- Predictive IHC analyses for targeted therapy distinct from studies to identify tumor type and lineage

NCCN Guidelines. Non-Small Cell Lung Cancer. Version 3.2021.

Costs Associated With Testing

- Recent study among 246 cases in New York showed **majority of tests denied payer coverage (77%, n = 190) and only 10.75% of the total NGS service charge was reimbursed**
- In 2018, centers for Medicare & Medicaid Services (CMS) released a National Coverage Determination (NCD) for NGS testing for Medicare beneficiaries with advanced cancer
  - Limited to patients who have not been previously tested using the same NGS test for the same primary cancer diagnosis
- Coverage through private payers may be variable



Hsiao S, et al. *JCO Precis Oncol* 2020;4:1038-1048; Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542.

Targets With Approved Therapies in NSCLC

Immune Checkpoint Inhibitors and PD-L1 Expression

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Metastatic Nonsquamous NSCLC

Sensitizing mutation (+):

Treat with targeted therapy

Higher response rates than standard ICI or chemotherapy in the first-line setting

Mutation (–), PD-L1 <1%, contraindications to ICI:

Treat with platinum doublet or single-agent chemotherapy

Mutation (–), no contraindications to ICI, PS 0-1:

ICI monotherapy (pembrolizumab), chemotherapy + pembrolizumab

Mutation (–), PD-L1 (+) (>50%):

ICI monotherapy (atezolizumab, cemiplimab-rwlc, pembrolizumab) or ICI + chemotherapy

NCCN Clinical Practice Guidelines in Oncology. NSCLC, v4.2021.

Summary of ICIs in NSCLC

- ICIs have demonstrated prolonged OS compared with platinum-based chemotherapy
- ICI + chemotherapy should be considered standard-of-care for patients with metastatic nonsquamous NSCLC with good PS without contraindications to ICI treatment
- Patients with metastatic NSCLC and PD-L1 ≥1% with a targetable driver oncogene variant (eg, *EGFR, ALK, ROS1*) should receive first-line targetable treatment
- Common strategies should be individualized to each patient:
  - PD-L1 ≥50% ICI monotherapy alone is recommended
  - PD-L1 ≤50% ICI + chemotherapy followed by ICI maintenance
  - Patients contraindicated to chemotherapy: nivolumab + ipilimumab

NCCN Clinical Practice Guidelines in Oncology. NSCLC, v4.2021.

FDA-Approved Targeted Therapies

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EGFR	*ALK*	*ROS1*	*BRAF* V600E	*NTRK*	*RET*	*MET* exon 14 skipping
Afatinib Dacomitinib Gefitinib Erlotinib Osimertinib	Alectinib Brigatinib Ceritinib Crizotinib Lorlatinib	Crizotinib Entrectinib	Dabrafenib + Trametinib	Entrectinib Larotrectinib	Pralsetinib Selpercatinib	Capmatinib Tepotinib

FDA Prescribing Information.

FDA-Approved Targeted Therapies for Metastatic NSCLC

1st and 2nd Line Therapies

	EGFR		*ALK*		*ROS1*		*BRAF* V600E		*NTRK*		*RET*		*MET* exon 14	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Afatinib	X													
Dacomitinib	X													
Erlotinib	X													
Gefitinib	X													
Osimertinib	X	X[1]												
Alectinib			X											
Brigatinib			X											
Ceritinib			X											
Crizotinib			X		X									
Lorlatinib			X			X								
Dabrafenib + Trametinib							X							
Entrectinib[2]					X					X				
Larotrectinib[2]										X				
Pralsetinib											X			
Selpercatinib											X			
Capmatinib													X	
Tepotinib													X	

[1]T790M; [2]Must have progressed following treatment or have no satisfactory alternative therapy

NCCN Guidelines. Non-Small Cell Lung Cancer. Version 4.2021 FDA Prescribing Information.

Newly Approved and Emerging Biomarkers/Therapies

Capmatinib: *MET* exon 14 skipping

GEOMETRY Mono-1

Eligibility

- Stage IIIB/IV NSCLC
- *MET* exon 14 skipping (*MET*ex14) mutation
- Performance status 0-1
- Treatment naïve and pretreated (2nd/3rd line)

→ Capmatinib 400 mg PO twice daily

End Points	N = 69 Previously treated N = 28 Treatment naïve
Overall response rate (ORR), %	
Previous treatment	41%
Treatment naïve	68%
Median progression-free survival (PFS), months (95% CI)	
Previous treatment	5.4 months (95% CI, 4.2-7.0)
Treatment naïve	12.4 months (95% CI, 8.2-not estimated)

Summary: Led to accelerated FDA approval in May 2020 for patients with metastatic NSCLC and *MET*ex14 skipping mutation; found to be well-tolerated with mostly grade 1/2 peripheral edema (51%) and nausea (45%).

Wolf J, et al. *N Engl J Med*. 2020;383(10):944-957; Tabrecta. Prescribing information. Novartis Pharmaceuticals Corporation; May 2020.

Tepotinib: *MET* exon 14 skipping

VISION

Eligibility

- Stage IIIB/IV NSCLC
- *MET* exon 14 skipping (*MET*ex14) mutation
- Performance status 0-1
- Treatment naïve and pretreated (2nd/3rd line)

Tepotinib 450 mg PO once daily

Treatment naïve (n = 69)

- ORR, 43% (95% CI, 32-56)
- Median duration of response (DOR), 10.8 months (95% CI, 6.9-not estimated)

Previously treated (n = 83)

- ORR, 43% (95% CI, 33-55)
- Median DOR, 11.1 months (95% CI, 9.5-18.5)

Adverse effects: grade ≥3 peripheral edema (7%)

Summary: Led to accelerated FDA approval in February 2021 for patients with metastatic NSCLC and *MET*ex14 skipping alteration.

Paik P, et al. *N Engl J Med*. 2020;383(10):931-943; Tepmetko. Prescribing information. Merck KGaA; February 2021.

Selpercatinib: *RET* Fusion+

LIBRETTO-001

Eligibility

- Stage IIIB/IV NSCLC
- *RET* fusion
- Performance status 0-2
- Treatment naïve and prior platinum chemotherapy

→ Selpercatinib 160 mg PO twice daily

Treatment naïve (n = 39)

- ORR, 85%
- DOR (median, months), NE (12-NE)
- PFS (median, months), NE (14-NE)

Prior platinum chemotherapy (n = 105)

- ORR, 64%
- DOR (median), 18 (12-NE)
- PFS (median, months), 17 (14-NE)
- Intracranial response (n = 11), 91%

Central nervous system ORR: 82% overall

Grade ≥3 adverse effects: hypertension (14%), increased liver function tests (LFTs) (10%-12%), hyponatremia (6%), lymphopenia (6%)

Summary: Based on efficacy, including CNS activity, FDA approved in May 2020 for patients with metastatic NSCLC and *RET* gene fusions, regardless of treatment history.

Drilon A, et al. *N Engl J Med.* 2020;383(9):813-824; Retevmo. Prescribing information. Eli Lilly and Company; January 2021.

Pralsetinib: *RET* Fusion+

ARROW

Eligibility

- Stage IIIB/IV NSCLC
- *RET* fusion+
- Treatment naïve and pretreated

→ Pralsetinib 400 mg PO once daily

Summary: Pralsetinib shows clinical response in patients with metastatic *RET* fusion+ NSCLC, regardless of past therapy. Led to FDA approval in September 2020 in patients with metastatic *RET* fusion+ NSCLC, along with the companion diagnostic Oncomine Dx Target test.

End Points	N = 116
ORR, % = 65	
Previous treatment	61%
Treatment naïve	73%
CNS response rate, % = 50	
Median DOR, months (95% CI)	
Treatment naïve	Not reached (95% CI, 11.3-NR)
Grade 3/4 AEs: hypertension (14%), pneumonitis (2.7%), increased AST/ALT (5%/6%), hemorrhagic events (2.5%)	

AST/ALT, aspartate aminotransferase/alanine aminotransferase

Gainor JF, et al. *J Clin Oncol.* 2020;38(suppl 15):Abstract 9515; Gavreto. Prescribing information. Blueprint Medicines Corporation; December 2020.

FDA-Approved Targeted Therapies for Metastatic NSCLC

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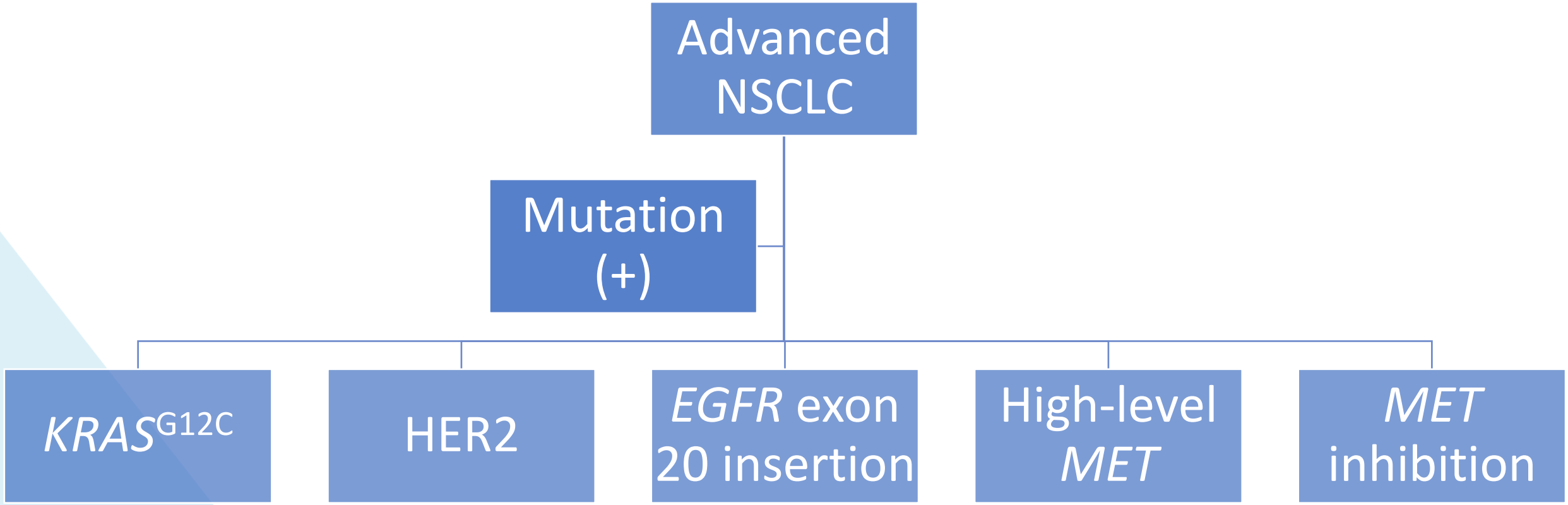
1st and 2nd line therapies	*NTRK*		*RET*		*MET* exon 14	
	1st	2nd	1st	2nd	1st	2nd
Entrectinib[1]		X				
Larotrectinib[1]		X				
Pralsetinib			X			
Selpercatinib			X			
Capmatinib					X	
Tepotinib					X	

[1]Must have progressed following treatment or have no satisfactory alternative therapy.

NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer, v4.2021; Hematology/oncology (cancer) approvals and safety notifications. US FDA. Updated April 1, 2021. Accessed April 6, 2021. www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications

Emerging Targets in NSCLC

Novel Biomarker-Driven Treatment Strategies



NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer, v4.2021.

Sotorasib: *KRAS*^{G12C} CodeBreaK: Phase 1/2 Trial

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Eligibility

- Locally advanced/metastatic solid tumors
- For NSCLC: received prior platinum chemotherapy
- *KRAS*^{G12C} mutation
- Performance status 0-2
- Treatment naïve and prior platinum chemotherapy

Sotorasib

960 mg PO daily

End Points	N = 124
Confirmed response	46 (37.1%)
Disease control rate	99 (80.6%)
DOR, median	10 months
Median PFS	6.8 months

Summary:

- Sotorasib is associated with positive results in patients with previously treated, locally advanced or metastatic NSCLC and *KRAS*^{G12C} mutation
- Granted priority review by the FDA in February 2021; Prescription Drug User Fee Action (target action date) August 2021

Hong DS, et al. *N Engl J Med.* 2020;383(13):1207-1217; Terry M. Amgen moves one step closer to first approved KRAS inhibitor for lung cancer. BioSpace. February 17, 2021. Accessed March 30, 2021. biospace.com/article/fda-grants-amgen-s-sotorasib-priority-review-for-lung-cancer; Li BT, et al. Presented at 2020 World Conference on Lung Cancer. Abstract PS01.07.

HER2 Antibody-Drug Conjugates

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Ado-trastuzumab emtansine

- 3.6 mg/kg intravenous (IV) every 3 weeks
- Phase 2 study; patients with HER2-mutant lung cancer (n = 18)
- Median number of prior therapies = 2
- Partial response rate: 44%
- Response seen in patients with HER2 ex20ins and other point mutations

Trastuzumab deruxtecan:

DESTINY-Lung01

- 6.4 mg/kg IV every 3 weeks
- Ongoing phase 2 study in patients with nonsquamous NSCLC overexpressing HER2 or with HER2-activating mutation (n = 42)
- Median number of prior therapies = 2
- ORR: 62%

Summary: HER2-targeted therapies demonstrate efficacy in patients with NSCLC and HER2 overexpression or mutation. Clinical trials are ongoing.

Li BT, et al. *J Clin Oncol.* 2018;36(24):2532-2537; Smit EF, et al. *J Clin Oncol*. 2020;38(suppl 15):Abstract 9504.

EGFR exon 20 Insertion-Directed Therapies

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Amivantamab: CHRYSALIS

- Anti-*EGFR-MET* bispecific antibody
- Ongoing phase 1 study (n = 39)
- Median number of prior therapies: 1 (0-7)
- ORR (≥ partial response): 36% (95% CI, 21-53)
- Median PFS:
  - Response-evaluable patients: 8.3 months (95% CI, 3.0-14.8)
  - Prior platinum-based chemotherapy: 8.6 months (95% CI, 3.7-14.8)

Mobocertinib

- Oral *EGFR*/HER2 inhibitor
- Ongoing phase 1/2 study (n = 28)
- ≥2 prior therapies: 86%
- ORR: 43%
- Median PFS: 7.3 months

Cho JH, et al. *J Clin Oncol.* 2020;38(suppl 15): Abstr 9512; Riely G, et al. *Ann Oncol.* 2020;31(suppl 4):S754-S840.

Capmatinib* High-Level *MET* Amplification
GEOMETRY MONO-1

Eligibility

- Stage IIIB/IV NSCLC
- *MET*ex14 mutation
- Performance status 0-1
- Treatment naïve and pretreated (2nd/3rd line)
- Randomized based on *MET*ex14 vs *MET* amplification

→ Capmatinib 400 mg PO twice daily

End Points (GCN ≥10)	N = 69 Previously Treated N = 15 Treatment Naïve
ORR, %	
Previous treatment	29%
Treatment naïve	40%
Median PFS, months (95% CI)	
Previous treatment	4.1 months (95% CI, 2.9-4.8)
Treatment naïve	4.2 months (95% CI, 1.4-6.9)

*Not FDA approved at this time for this indication.

GCN, gene copy number.

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

Savolitinib: *MET* Inhibitor

- Selective once-daily oral MET tyrosine kinase inhibitor (TKI)
- Phase 1b trial in combination with third-generation *EGFR* TKI osimertinib
- Patients with locally advanced or metastatic, *MET* amplified, *EGFR*+ NSCLC after disease progression on prior *EGFR* TKI (n = 144)

- **Patients with prior third-generation *EGFR* TKI**
  - Response rate, 38%
  - Median time to response, months: 1.4 (95% CI, 1.4-1.6)
  - PFS (median), months: 5.4 (95% CI, 4.1-8)
- **No prior third-generation *EGFR* TKI, T790M negative**
  - RR: 64%
  - Median time to response, months: 1.4 (95% CI, 1.3-1.5)
  - PFS (median), months: 9.1 (95% CI, 5.4-12.9)
- **Grade 3/4 adverse effects:** nausea/diarrhea/vomiting, decreased absolute neutrophil count (ANC), anaphylaxis
  - All <10% incidence

Sequist L, et al. *J Clin Oncol*. 2020;21(3):373-386.

The Role of the Multidisciplinary Team

Patient Counseling

Biomarker	Drug	Dosing/ Administration	AEs	Pearls
RET	Pralsetinib	400 mg by mouth once daily; empty stomach	Hepatotoxicity, hypertension, interstitial lung disease (ILD)	• CYP3A4, P-gp interactions • Hold for medical procedures
	Selpercatinib	120 mg or 160 mg by mouth twice daily	QTc prolongation, hepatotoxicity, hypertension, hemorrhage	• Weight-based dosing • CYP3A, CYP2C8, acid suppressant interactions • Hold for medical procedures
***MET*ex14**	Capmatinib	400 mg by mouth twice daily	Hepatotoxicity, ILD, edema	CYP3A4 interactions
	Tepotinib	450 mg by mouth once daily; with food		CYP3A4, P-gp interactions
NTRK	Entrectinib	600 mg by mouth once daily	Edema, hepatotoxicity, neurotoxicity, QTc prolongation, visual changes	• Baseline ejection fraction, LFTs, uric acid required • Withdrawal pain syndrome • CYP3A4 interactions
	Larotrectinib	100 mg by mouth twice daily	Hepatotoxicity, neurotoxicity	• Withdrawal pain syndrome • CYP3A4 interactions

Gavreto. Prescribing information. Blueprint Medicines Corporation; December 2020; Retevmo. Prescribing information. Eli Lilly and Company; January 2021; Tabrecta. Prescribing information. Novartis Pharmaceuticals Corporation; May 2020; Tepmetko. Prescribing information. Merck KGaA; February 2021; Rozlytrek. Prescribing information. Genentech; August 2019; Vitrakvi. Prescribing information. Bayer HealthCare Pharmaceuticals Inc; March 2021.

Oncology Team Collaboration

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Molecular Review

- Review patient's molecular profile results/next-generation sequencing
- Participate in molecular tumor board
- Recommend appropriate target-based therapy to optimize response rate, progression-free survival, overall survival

Patient Education

- Medication dosing and administration
- Instructions for missed doses
- Food considerations, drug interactions
- Potential adverse effects and management
- Adherence strategies
- Safe handling, storage, and disposal of medications
- Patient follow-up/monitoring plan

Singal G, et al. *JAMA*. 2019;321(14):1391-1399; Segal E, et al. *J Oncol Pharm Practice*. 2019;25(8):1945-1967.

Conclusion

- Overall, improved response rates and survival outcomes are seen with the use of FDA-approved targeted therapies for NSCLC driver mutations
- Molecular testing at the point of diagnosis is vital to quickly identify any targetable mutations to ensure improved outcomes for patients who qualify for these novel therapies
- The field of molecular driver-metastatic NSCLC is rapidly expanding, and the oncology care team must be vigilant in monitoring for new approvals that can significantly improve patient outcomes
- The oncology care team plays a vital role in recommending therapy based on tumor sequencing, monitoring/managing AEs with targeted therapy, and educating patients and caregivers

Additional Resources

Resource	How to Access
Lung Cancer and COVID-19 Resources	www.lungcancerresearchfoundation.org/for-patients/lung-cancer-covid19-resources/
NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer	www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
Oral Chemotherapy Education Sheets	oralchemoedsheets.com
Yuan M, Huang LL, Chen JH, Wu J, Xu Q. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. *Signal Transduct Target Ther*. 2019;4:61. doi: 10.1038/s41392-019-0099-9	

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