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Actionable Biomarkers in Lung Cancer: Clinical Applications for Nursing Practice

Saturday, September 10, 2022 | 1:50 PM PT
GLAONS – 6th Annual Oncology Care Summit
Los Angeles, CA

Supported by educational grants from AstraZeneca; Lilly; Merck Sharp & Dohme Corp.; Novartis Pharmaceuticals Corporation; Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme.

Faculty Presenter

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UCLA Santa Monica
Santa Monica, California

Blanca Ledezma, MSN, NP, has disclosed that she has received speaker fees from Amgen, AstraZeneca, Eisai, Helsinn, and Lilly.

A Quick Survey

Poll 1: If you are a practicing healthcare professional, how many patients with lung cancer do you provide care for in a typical month?

A. <5

B. 5-10

C. 11-15

D. 16-20

E. >20

Disease Overview

Patient Case #1

- A 76-year-old Hispanic woman hospitalized with COVID is found to have NSCLC, miliary spread throughout the lungs, stage IV
- Tissue biopsy is QNS for biomarker testing
- She is a never smoker, on oxygen at home and SOB at rest

Presurvey 1: When describing biomarker testing to a patient, all of the following statements are true EXCEPT:

A. Biomarker testing should only be done in the setting of advanced or metastatic NSCLC

B. Tissue testing is considered the gold standard method to test for actionable biomarkers

C. Completing comprehensive biomarker testing can identify if patients are eligible for targeted therapy

D. An advantage of liquid biopsy is that it is minimally invasive

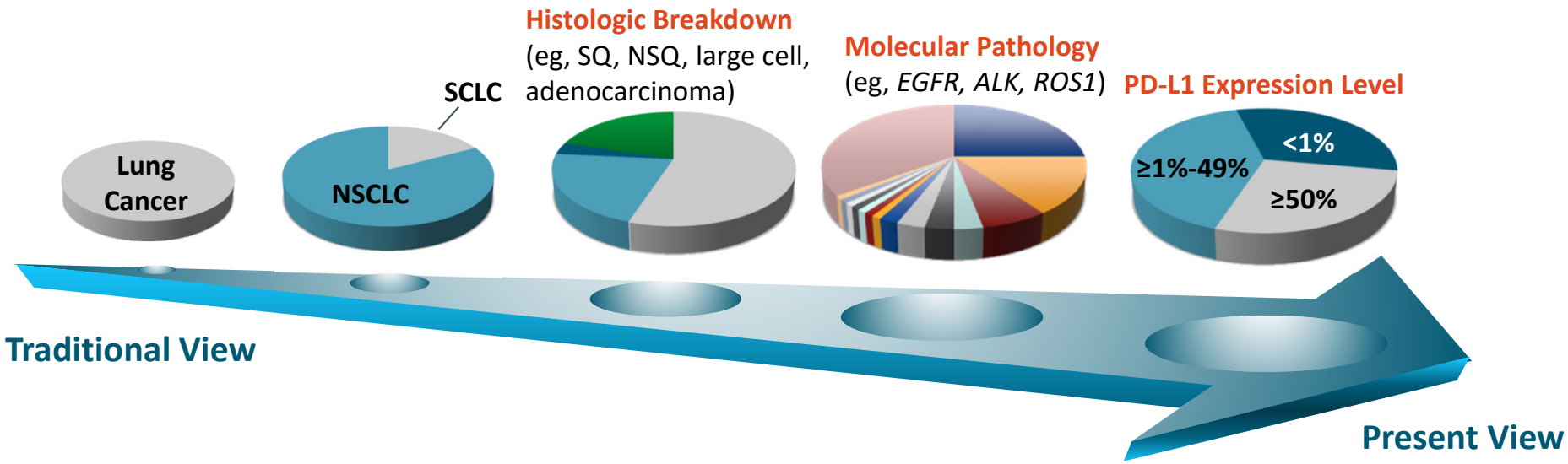
E. I'm not sure

Presurvey 2: When discussing treatment options for a patient with stage IIB NSCLC adenocarcinoma and *EGFR* exon 19 deletion, which of the following EGFR TKIs would you tell them has shown a DFS benefit in the adjuvant setting ?

A. Afatinib
B. Erlotinib
C. Mobocertinib
D. Osimertinib
E. I'm not sure

Evolution of Therapy in Lung Cancer

- Heterogeneous disease

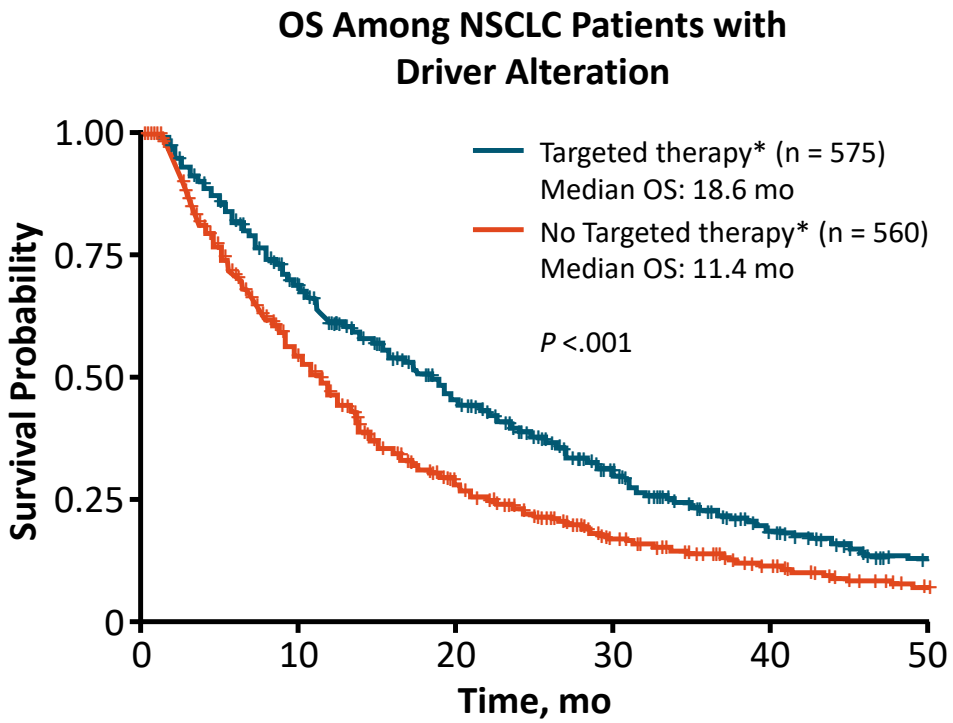


Cooper. Pathology. 2011;43:103. Langer. JCO. 2010;28:5311. Galon. Immunity. 2013;39:11.
Pao. Lancet Oncol. 2011;12:175. Krigsfeld. AACR 2017. Abstr CT143.

Slide credit: clinicaloptions.com

The Importance of Biomarker Testing in Non-Small-Cell Lung Cancer

- Studies have shown that patients with identified actionable mutations who receive appropriate targeted therapy have improved outcomes

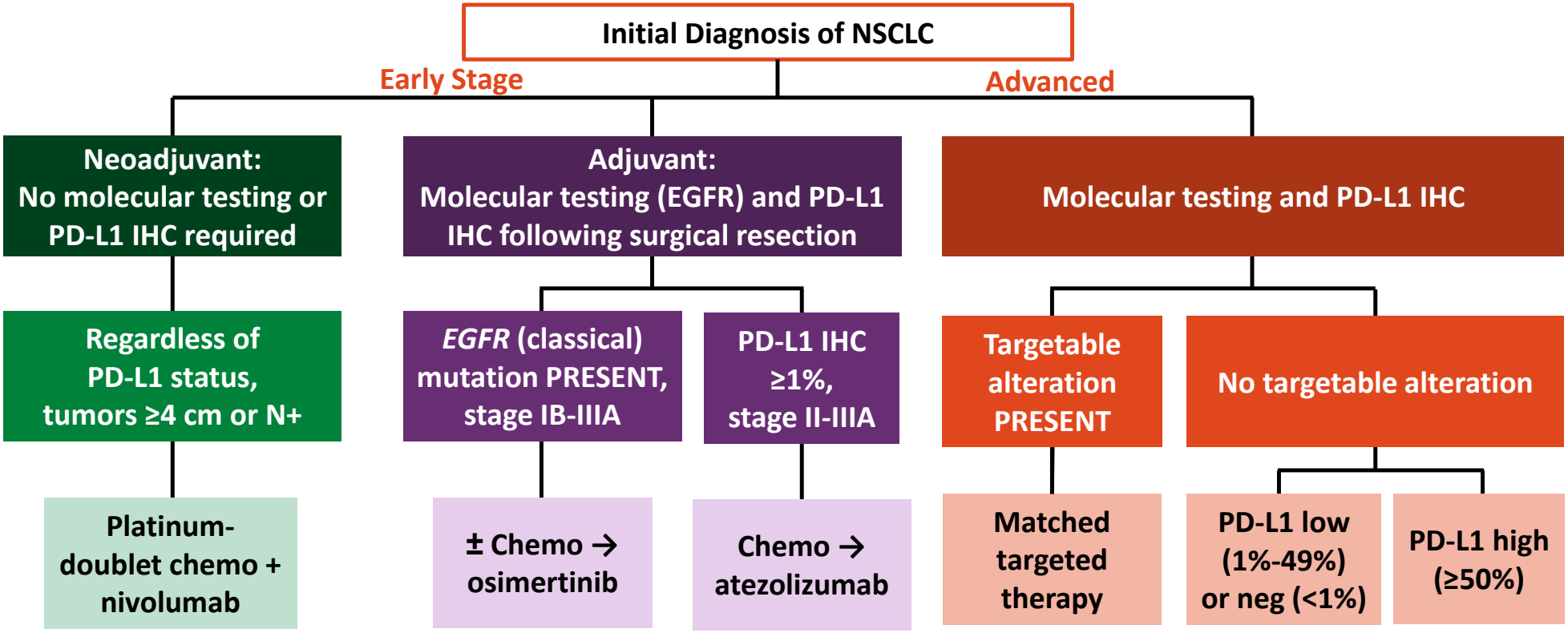


*Agents selected per NCCN recommendations for specific driver mutations

Singal. JAMA. 2019;321:1391.

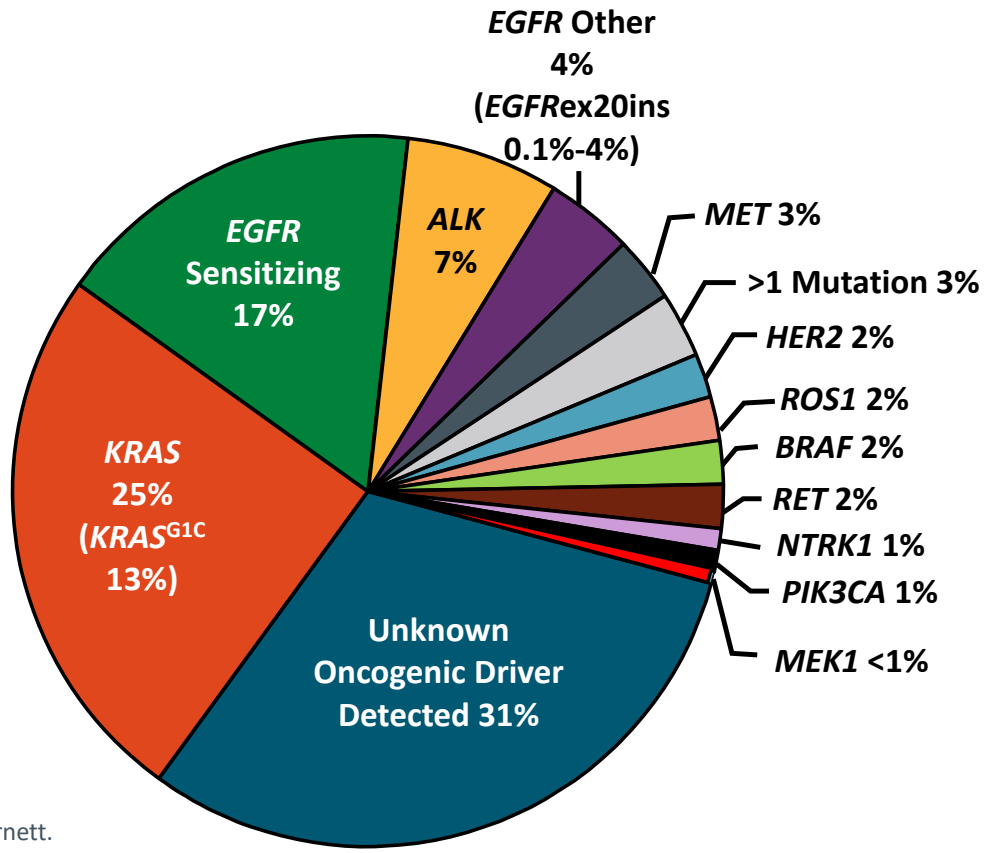
Slide credit: clinicaloptions.com

Molecular and PD-L1 Testing at Initial Diagnosis to Guide Treatment in NSCLC



Slide credit: clinicaloptions.com

~50% of Patients With Advanced Nonsquamous NSCLC Have an Actionable Driver Mutation



Li. JCO. 2013;31:1039. Tsao. JTO. 2016;11:613. Burnett. PLoS One. 2021;16:e0247620. Nassar. NEJM. 2021;384:185.

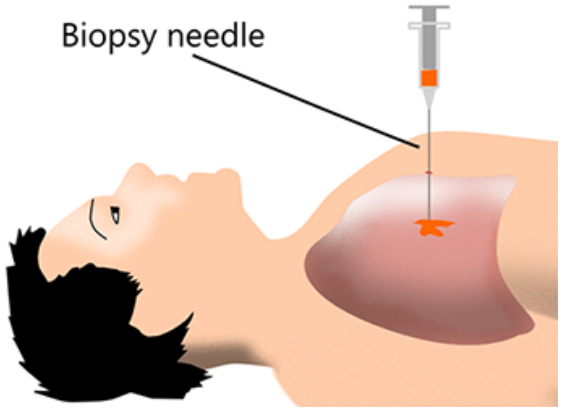
Slide credit: clinicaloptions.com

Biomarker Testing: Benefits and Limitations

Tissue Testing in NSCLC

Benefits

- Tissue available from biopsy
- Considered "gold standard" for biomarker testing



Challenges

- Lung cancer biopsies are less cellular than other solid tumors
  - QNS: quality or quantity not sufficient. (need 10%-20% of viable cancer cells in sample for reliable results)
- Bone biopsies yield poor samples due to decalcification which degrades DNA
- Logistical: timing of DNA sequencing can take weeks. Centralized vs sent to distant laboratory

Vanderlaan. Lung Cancer. 2014;84:39. Hiley. Lancet. 2016;388:1002.

Slide credit: clinicaloptions.com

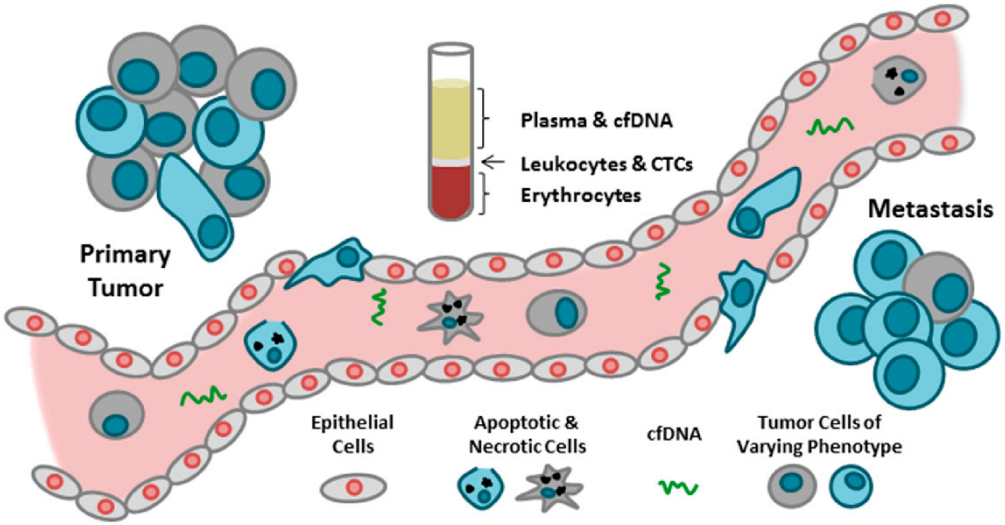
Methods of Tissue Testing in NSCLC

Tissue Testing Method	Detection
DNA sequencing/NGS/PCR	▪ Detects insertions, point mutations, deletions ▪ Detects aberrations in *EGFR, KRAS, BRAF, HER2, MET* – Single-gene or full NGS panel
RNA sequencing panel	▪ Detects fusion abnormalities ▪ More sensitive for *ALK, ROS1, RET, NTRK*
IHC/FISH	▪ FISH: Detects *ALK/ROS1*, highly specialized, can be faster ▪ IHC: – Detects *ALK/ROS1*, easy test, fast, but not reliable or sensitive enough to guide treatment – Detects PD-L1

Vanderlaan. Lung Cancer. 2014;84:39. Hiley. Lancet. 2016;388:1002. Shim. J Path Trans Med. 2017;51:242.

Liquid Biopsy

- Blood sample containing cell-free (cf) DNA from multiple sources, including DNA shed from tumor



CTC = circulating tumor cell.

Bauml. Clin Cancer Res. 2018;24:4352. Leighl. Clin Cancer Res. 2019;25:4691. Rothwell. Nat Med. 2019;25:738.

When do we use liquid biopsy?

- **Plasma-first approach**: for inadequate or no tissue biopsy—if negative, rebiopsy for tumor tissue
- **Sequential approach**: tumor tissue adequate for genotyping—follow with cfDNA testing only when results from tissue incomplete
- **Complementary approach**: increases rate of biomarker detection
- Resistance to TKIs

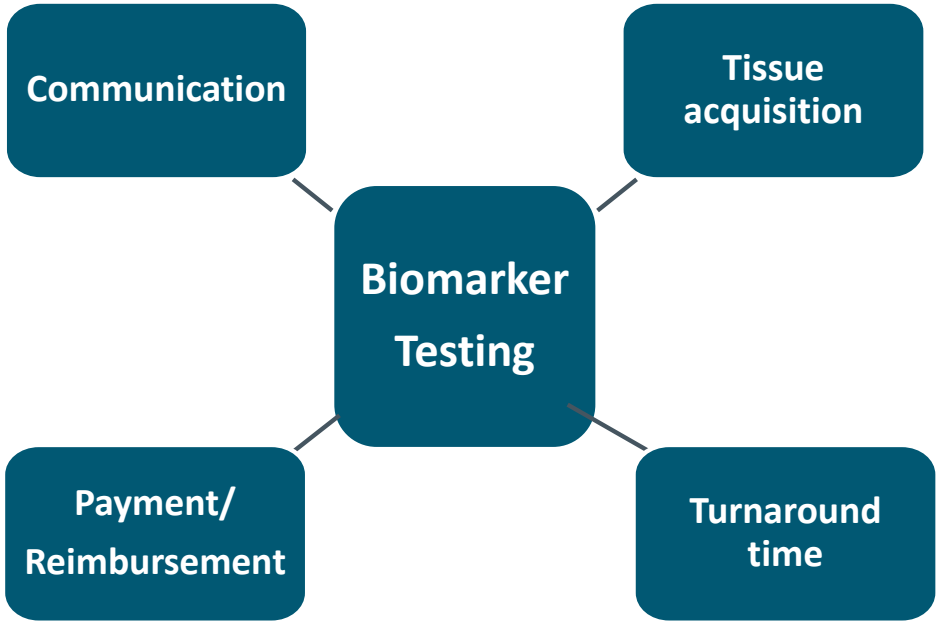
Advantages: minimally invasive, may overcome tumor heterogeneity

Limitations: Sensitivity (70%-80%), specificity near 100%; negative result is noninformative; cannot assess histology or PD-L1

Slide credit: clinicaloptions.com

Barriers to Universal Biomarker Testing

- Not enough tissue in small biopsies—up to 25% lack sufficient tumor
- Turnaround time not fast enough—recommended <14 calendar/10 working days from biopsy
- Poor communication—lack of reflex testing, differing sites for biopsy and treatment
- Who pays?

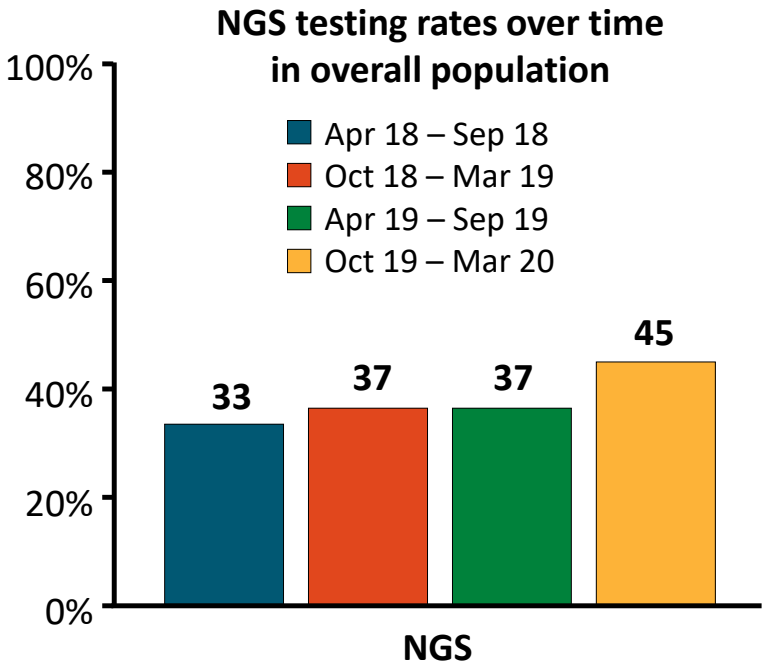


Ferry-Galow. J Oncol Pract. 2018;14:JOP1800092. Pennell. ASCO Educ Book. 2019;39:531.

Slide credit: clinicaloptions.com

MYLUNG Consortium Study of Biomarker Testing in Metastatic NSCLC

- N = 3474 patients in US Oncology Network (2018-2020)
  - Adenocarcinoma: 75%



Biomarker, %	Overall (N = 3474)	Nonsquamous (n = 2820)
EGFR	70	76
ALK	70	76
ROS1	68	73
BRAF	55	59
PD-L1	83	83
Any of the 5 biomarkers	90	91
All 5 biomarkers	46	49
NGS	37	39

Robert. ASCO 2021. Abstract 9004.

Slide credit: clinicaloptions.com

When to Test?

- Initial diagnosis
  - Stage IB-IIIA, resected: EGFR
  - Stage II-IIIA, resected: PD-L1
  - Metastatic disease: comprehensive biomarker testing (NGS panel)
  - Locally advanced, receiving definitive chemoradiation
    - Currently no indications for approvals, but consideration….
- Disease progression
  - In EGFR, can be resistance mechanisms that are targetable (T790M, SCLC transformation, MET or HER2 resistance, clinical trials)
  - For other biomarkers, mostly informational for clinical trials
- Disease recurrence
  - Try to retest, especially if has been a long interval from definitive therapy

Slide credit: clinicaloptions.com

Disparities in Biomarker Testing

Racial Disparities in Biomarker Implementation in NSCLC: Retrospective Cohort Study

- Overall population (N = 14,768) and nonsquamous subpopulation (n = 10,333) diagnosed with advanced/metastatic NSCLC from 1/1/2017 to 10/31/2020
- Rates of biomarker testing low overall (76.5% ever tested, 48.7% ever NGS tested)
  - **Rate of NGS testing significantly lower in Black vs White patients** at any time during their care (39.8% vs 50.1%; *P* <.0001); nonsquamous cohort (43.8% vs 54.7%; *P* <.0001)
  - Rates of targeted therapy use similar between groups (9.2% vs 10.2% first line, 13.2% vs 13.5% any line); nonsquamous cohort trend toward inferior first-line targeted therapy use in Black patients (12.3% vs 14.3%; *P* = .09)
- **Rate of clinical trial participation by Black patients one half that of White patients** in nonsquamous population (1.9% vs 3.9%; *P* = .0002)

Bruno. ASCO 2021. Abstr 9005.

Slide credit: clinicaloptions.com

Assessment 1: When describing biomarker testing to a patient, all of the following statements are true EXCEPT:

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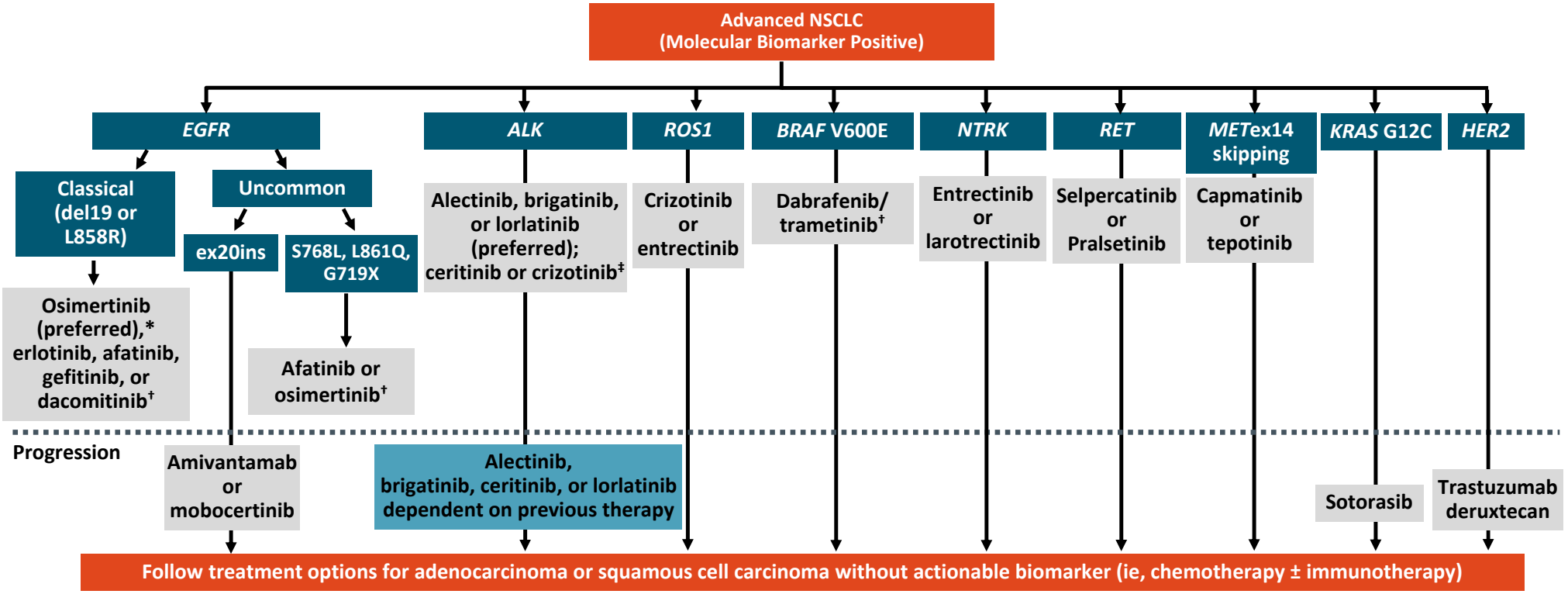
D. An advantage of liquid biopsy is that it is minimally invasive

E. I'm not sure

Presurvey 3: For a patient with *RET* fusion-positive NSCLC, which of the following would you recommend?

A. Selpercatinib or pralsetinib
B. Osimertinib or afatinib
C. Amivantamab or mobocertinib
D. Entrectinib or larotrectinib
E. I'm not sure

2022 Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC



*Osimertinib also approved as second-line therapy for *EGFR* T790M–positive disease after an earlier-generation EGFR TKI. †Afatinib, dacomitinib, erlotinib (alone or in combination with ramucirumab), gefitinib, and osimertinib approved for *EGFR* exon19del, exon 21 L858R; afatinib for *EGFR* G719X, S768I, L861Q. Osimertinib also a preferred option for *EGFR* G719X, S768I, L861Q per NCCN guidelines. ‡Or as second-line after CT.

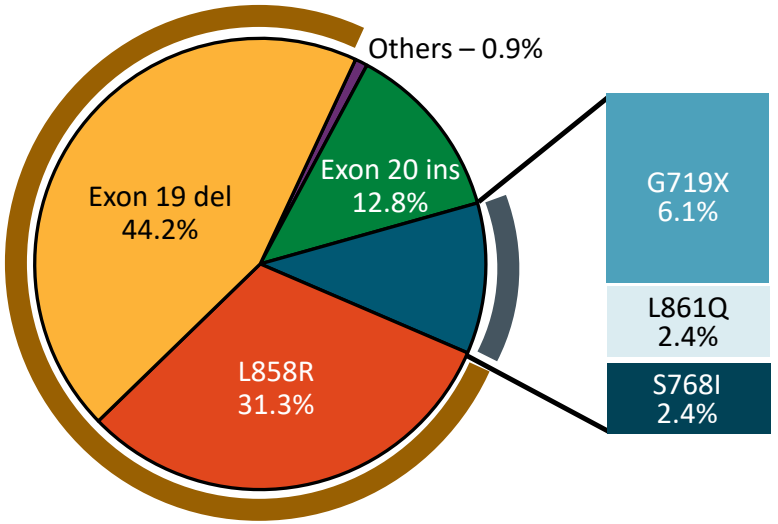
Afatinib PI. Alectinib PI. Amivantamab PI. Capmatinib PI. Ceritinib PI. Crizotinib PI. Dabrafenib PI. Dacomitinib PI. Entrectinib PI. Erlotinib PI. Gefitinib PI. Lorlatinib PI. Larotrectinib PI. Mobocertinib PI. Osimertinib PI. Pralsetinib PI. Selpercatinib PI. Sotorasib PI. Trametinib PI. Trastuzumab deruxtecan PI. NCCN. Clinical practice guidelines in oncology: NSCLC. v.3.2022.

Biomarkers for Targeted Therapies in NSCLC: *EGFR*

EGFR Mutations in NSCLC: Overview

- More common (but not exclusively)
  - Never/minimal smokers, East Asians, Women
- Classical mutations make up majority
  - Exon 19del
  - Exon 21point/L858R
- Atypical/uncommon EGFR mutations
  - Including G719X, L861Q, S768I
  - Some are sensitive to traditional EGFR inhibitors
  - More study needed

Uncommon *EGFR* mutations in NSCLC



- Exon 20 insertions
  - Resistant to traditional EGFR inhibitors
  - New drugs approved

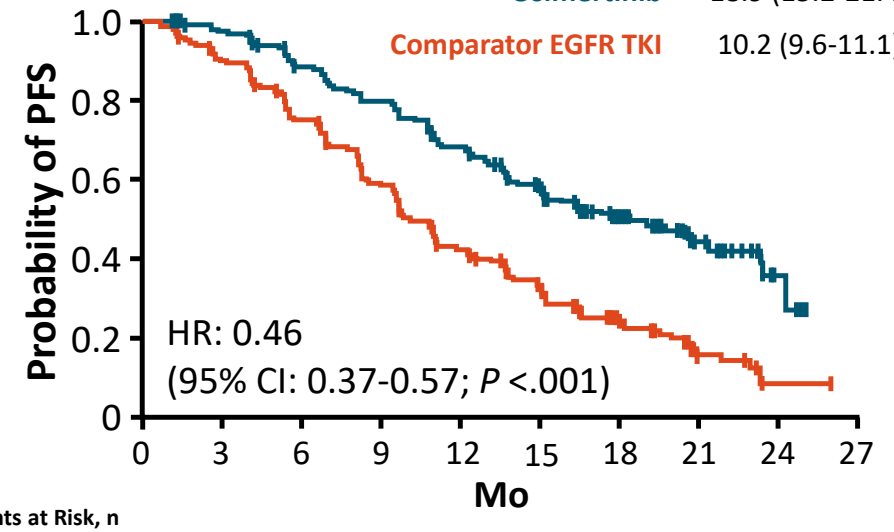
Sehgal. Oncologist. 2021;26:281.

Slide credit: clinicaloptions.com

FLAURA Trial: First-line Osimertinib vs Erlotinib or Gefitinib for NSCLC w/Classical *EGFR* Mutations

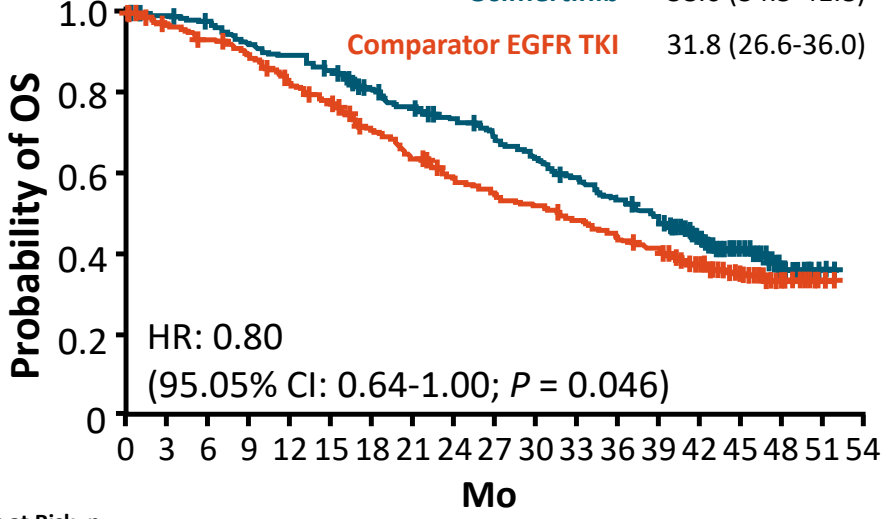
- 5 drugs approved for NSCLC with *EGFR* Ex19del and Ex21L858R mutations: Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib
- Osimertinib 80 mg once daily preferred first-line treatment over other TKIs[1]

PFS[2]



Patients at Risk, n										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Comparator EGFR TKI	277	239	197	152	107	78	37	10	2	0

Updated OS[3]



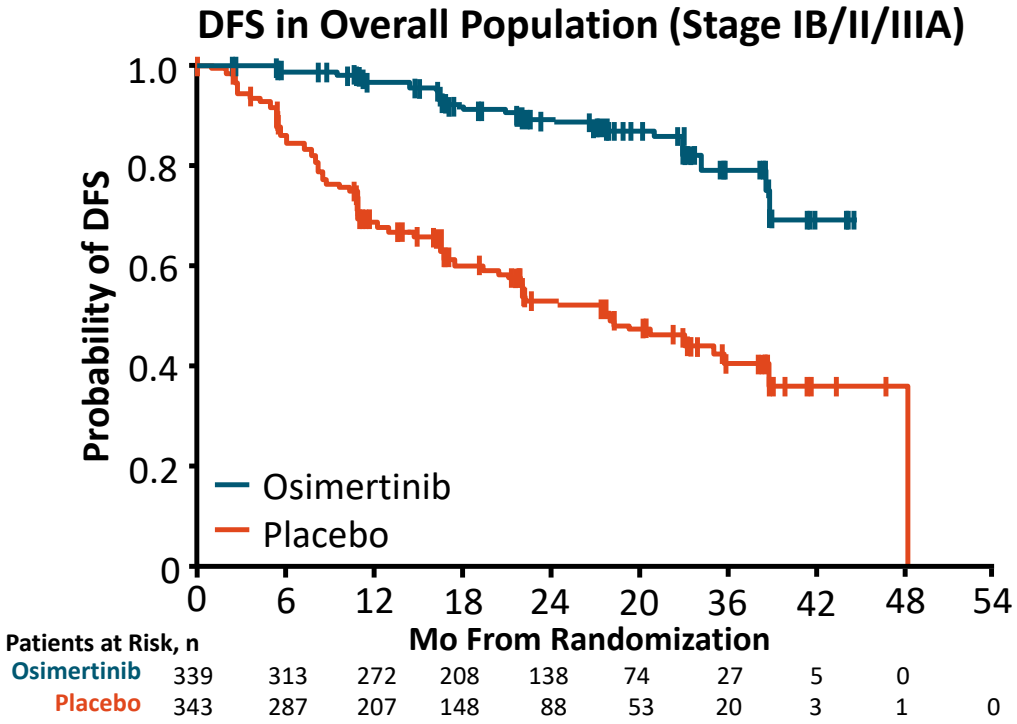
Patients at Risk, n																				
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

1. NCCN Clinical Practice Guidelines in Oncology: NSCLC (v.3.2022). 2. Soria. NEJM. 2018;378:113. 3. Ramalingam. NEJM. 2020;282:41-50.

Slide credit: clinicaloptions.com

Phase III ADAURA Trial: Adjuvant Osimertinib for Early-Stage *EGFR*-Mutated NSCLC

- International, randomized, double-blind phase III trial (data cutoff for interim analysis: 1/17/2020)



	Median DFS, Mo	24-Mo DFS,%
Osimertinib	NR	89
Placebo	27.5	52

HR: 0.20 (99.12% CI: 0.14-0.30; *P* <.001)

Maturity: 33% (osimertinib: 11%; placebo: 55%)

Approved by the FDA in December 2020 for adjuvant treatment of adults with stage IB-IIIA *EGFR+* (del19 or L585R) NSCLC following tumor resection ± adjuvant CT

Wu. NEJM. 2020;383:1711. Osimertinib PI.

Slide credit: clinicaloptions.com

CHRYSALIS Phase I Trial: Amivantamab in NSCLC w/*EGFR* Exon 20 Insertion and PD on Plt-Doublet CT

- Outcomes in efficacy population (n= 81) †
  - ORR 40% (95% CI, 29-51)
  - Median DoR 11.1 months (95% CI, 6.9-NR)
  - Median PFS 8.3 months (95% CI 6.5-10.9)
  - Median OS 22.8 months (95% CI, 14.6-NR)

	Amivantamab
FDA approval	▪ Accelerated approval May 21, 2021
Indication	▪ Advanced/metastatic *EGFR* exon 20 insertion mutation–positive NSCLC + PD on platinum chemo
Dose, route	▪ Weight <80 kg: 1050 mg ▪ Weight ≥80 kg: 1400 mg ▪ Administer wkly* x 4, then Q2W beginning Wk 5
Available dosage	▪ 350-mg/7-mL single-dose vial
Common AEs, all grades (≥20%):	▪ Rash, IRR, fatigue, edema, paronychia, musculoskeletal pain, dyspnea, cough, nausea, stomatitis, constipation, vomiting
Common laboratory abnormalities (≥25%):	▪ Decreased albumin, phosphate, magnesium, sodium, potassium, lymphocytes ▪ Increased glucose, alk phos, creatinine, ALT, AST, GGT
Warnings/Precautions:	▪ IRR, ILD/pneumonitis, dermatologic AEs, ocular toxicity, EFT
Significant DDIs:	▪ None listed

† Data cutoff: June 8, 2020.

*Initial dose split on Week 1 Day 1 and Day 2

Park. JCO. 2021;39:3391.
Amivantamab PI. 2021.

Amivantamab: Select Adverse Event Monitoring and Management

Infusion-Related Reactions (66%; 97% grade 1-2)

- Premedicate with glucocorticoid*, antihistamine, and antipyretic
- Split initial dose on Week 1 Day 1 and Day 2
- Monitor for s/s of infusion reactions during infusion
- Interrupt therapy for:
  - Grade 1-3 reaction
  - Administer supportive medications for grade 3
  - May resume at reduced rate upon symptom resolution
- Discontinue therapy for
  - Grade 4

ILD/Pneumonitis (3.3%; 0.7% grade 3)

- Monitor for new/worsening pulmonary symptoms (eg, dyspnea, cough, fever)
- Hold therapy if ILD/pneumonitis suspected
- Discontinue if ILD/pneumonitis confirmed

Dermatologic AEs (including rash, 74%)

- Initiate supportive management† for grade 2
- Hold therapy for grade 3
- Discontinue therapy for grade 4 or severe bullous, blistering, or exfoliating skin conditions

*Week 1, Days 1 and 2 only
†topical corticosteroids and topical and/or oral antibiotics; add oral steroids and consider dermatologic consultation for grade 3.

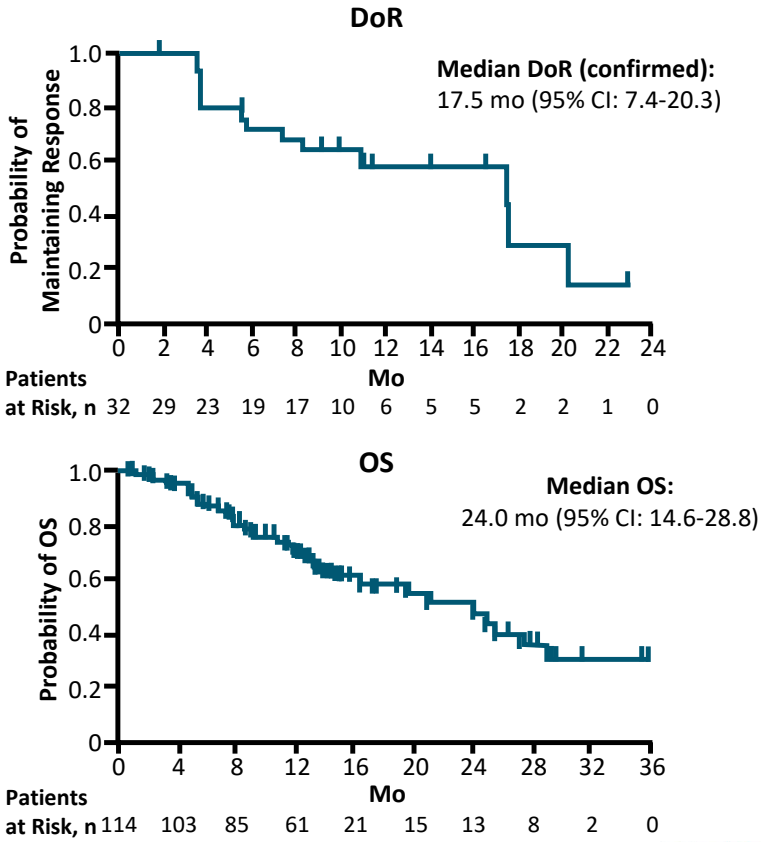
Amivantamab PI. 2021.

Slide credit: clinicaloptions.com

Mobocertinib in *EGFR* Ex20ins+ Advanced NSCLC: Efficacy

- Mobocertinib (TAK-788): orally active, first-in-class, irreversible EGFR TKI that targets *EGFR*ex20ins mutations[1]

	Mobocertinib
FDA approval	▪ Accelerated approval September 15, 2021
Indication	▪ Advanced/metastatic *EGFR* exon 20 insertion mutation–positive NSCLC + PD on platinum chemo
Dose, route	▪ 160 mg QD ± food
Available dosage	▪ 40-mg capsule
Common AEs, all grades (≥20%):	▪ Diarrhea, stomatitis, vomiting, decreased appetite, nausea, decreased weight, rash, paronychia, dry skin, pruritis, fatigue, cough
Common laboratory abnormalities (≥25%):	▪ Decreased RBC, lymphocytes, platelets, leukocytes, potassium ▪ Increased creatinine, amylase, lipase, alk phos
Warnings/Precautions:	▪ ILD/pneumonitis, cardiac toxicity, diarrhea, EFT
Significant DDIs:	▪ Strong, moderate CYP3A inhibitors, inducers



Data cutoff: November 1, 2020.

1. Riely. Cancer Discov. 2021;11:1688. 2. Zhou. JAMA Oncol. 2021;7:e214761. 3. Mobocertinib PI. 2021.

Slide credit: clinicaloptions.com

Mobocertinib: Select Adverse Event Monitoring and Management

Diarrhea (93%; 20% grade 3; 0.4% grade 4)

- Monitor electrolytes
- Advise patients to start antidiarrheal agent at 1st sign of diarrhea or increased BM frequency
- - Increase fluid and electrolyte intake
- Hold therapy for intolerable or recurrent grade 2-4
- Discontinue for recurrent grade 4

ILD/Pneumonitis (4.3%; 0.8% grade 3; 1.2% fatal)

- Monitor for new/worsening pulmonary symptoms (eg, dyspnea, cough, fever)
- Hold therapy if ILD/pneumonitis suspected
- Discontinue if ILD/pneumonitis confirmed

QTc Interval Prolongation and TdP (QTc > 500 msec in 1.2%; gr 4 TdP 0.4%)

- Assess QTc, electrolytes at baseline
- Monitor and correct lab imbalances as indicated
- Monitor and review concomitant medications
- Interrupt therapy for grade 2-3
- Discontinue therapy for grade 4

Decreased EF or Heart Failure (2.7%)

- Assess LVEF at baseline and during treatment
- Hold therapy for grade 2 decreased EF
- Discontinue therapy for grade ≥2 heart failure or grade 3/4 decreased EF

Mobocertinib PI. 2021.

CCO

Slide credit: clinicaloptions.com

Uncommon *EGFR* Mutations in NSCLC: Point Mutations Across Exons 18-21

- The targetable "uncommons" are G719X (S,A,C,D), S768I, L861Q[1]
  - They are often compounded together with the common mutations
  - Less responsive than the classical EGFR mutations to EGFR TKIs
- Afatinib: sole FDA-approved agent, based on data in >100 patients[2]
  - ORR: 60% (77% if compounded)[1]
- Osimertinib[3]
  - Data in 36 patients: ORR varied depending on mutation (38%-78%)

1. Yang. J Thorac Oncol. 2020;15:803. 2. Afatinib PI. 2021. 3. Cho. J Clin Oncol. 2019;38:488.

Assessment 2: When discussing treatment options for a patient with stage IIB NSCLC adenocarcinoma and *EGFR* exon 19 deletion, which of the following EGFR TKIs would you tell them has shown a DFS benefit in the adjuvant setting ?

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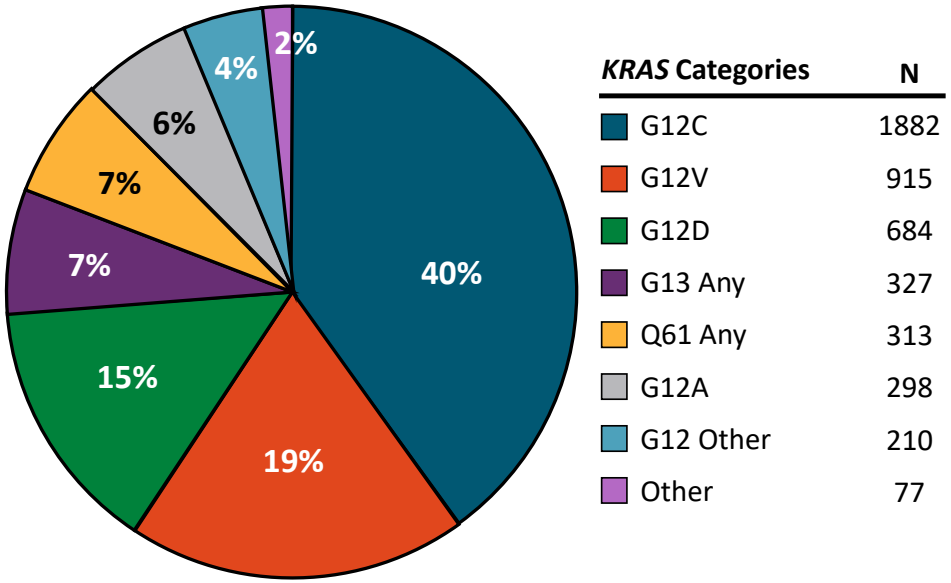
B. Erlotinib
C. Mobocertinib
D. Osimertinib
E. I'm not sure

Biomarkers for Targeted Therapies in NSCLC: *KRAS*

KRAS Mutations in Advanced NSCLC

- Most common oncogenic driver in NSCLC
  - Present in ~25% nonsquamous, 3% squamous
  - Significant heterogeneity with specific mutations, comutations
- *KRAS* G12C most common variant
  - Comprise 40% to 50% of *KRAS* mutations overall
  - ~13% incidence in adenocarcinoma
- Patient characteristics associated with *KRAS* mutations: younger age, female, Caucasian, smokers, adenocarcinoma

Incidence of *KRAS* Mutation Variants in Advanced NSCLC

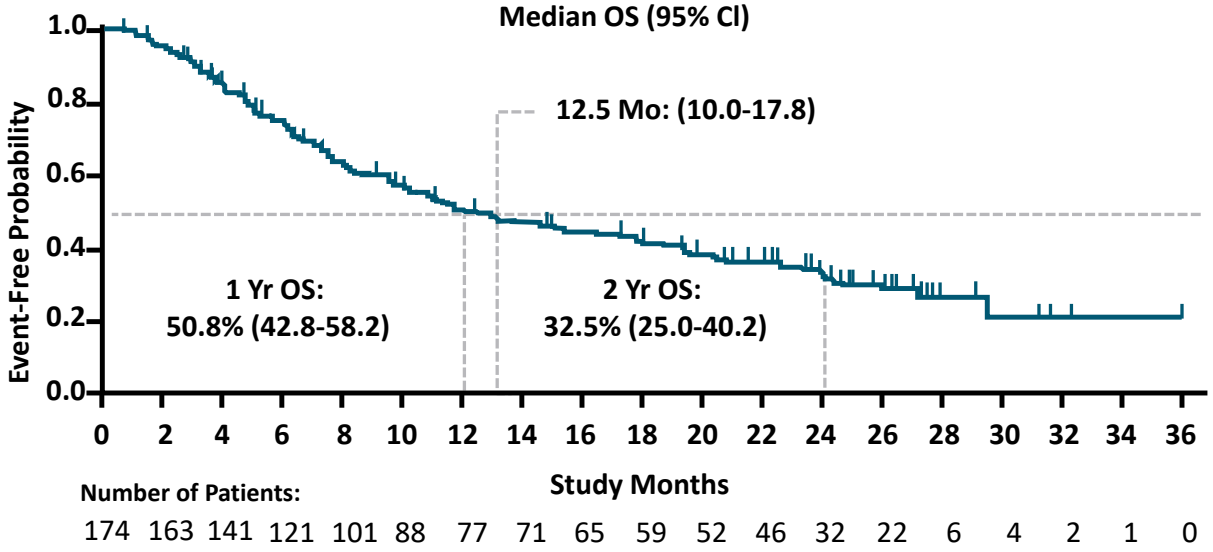


Liu. ASCO 2020. Abstr 9544. Kempf. Eur Resp Rev. 2016;25:71.

Slide credit: clinicaloptions.com

CodeBreaK100 Trial: Sotorasib in Pretreated Advanced *KRAS* G12C Mutation–Positive NSCLC

- Phase II trial evaluating sotorasib 960 mg PO daily in patients with *KRAS* G12C mutation–positive NSCLC who progressed on 1-3 prior standard therapies
  - 82.8% with both prior platinum-based CT and IO



Sotorasib	
FDA approval	▪ Accelerated approval May 28, 2021
Indication	▪ Locally advanced or metastatic NSCLC with *KRAS* G12C mutation, after at least 1 prior systemic therapy
Dose, route	▪ 960 mg orally daily, with or without food
Available dosage	▪ 120-mg tablet
Common AEs, all grades (≥20%):	▪ Diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity. ILD/pneumonitis, rash, cough
Common laboratory abnormalities (≥25%):	▪ Decreased calcium, sodium, lymphocytes, hemoglobin ▪ Increased AST, ALT, alkaline phosphatase, urine protein
Warnings/ Precautions:	▪ ILD/pneumonitis, hepatotoxicity
Significant DDIs:	▪ AVOID concomitant use of PPI and H2RA; OTC acid-reducing medication optional* ▪ Avoid strong CYP3A4 inducers

*Take sotorasib 4 hours before or 10 hours after local antacid

Skoulidis. NEJM. 2021;384:2371. Dy. AACR 2022. CT008. Sotorasib PI. 2021.

Slide credit: clinicaloptions.com

Sotorasib: Select Adverse Event Monitoring and Management

Diarrhea (42% all grades)*

- Initiate appropriate supportive care (including anti-diarrheal therapy)
- Hold therapy if grade 3/4

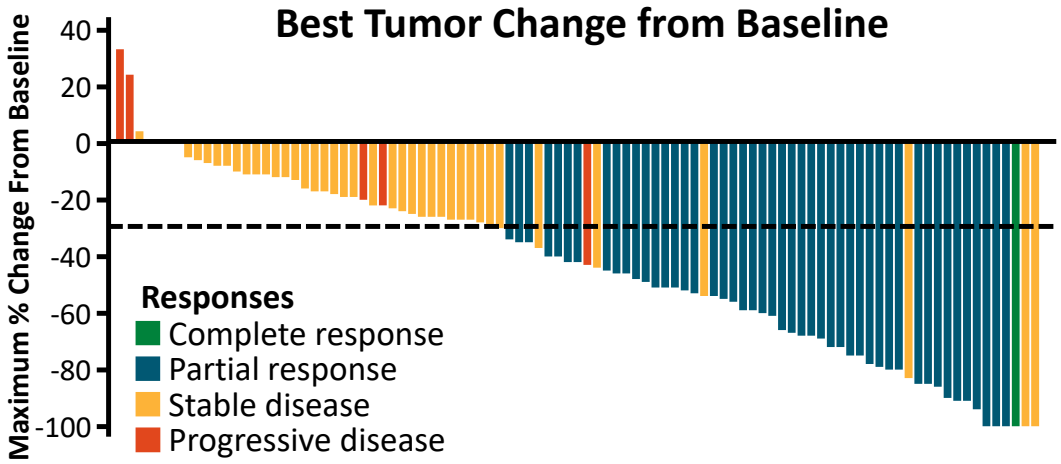
Hepatotoxicity

- Monitor hepatic function at baseline, Q3W x 3 months, then monthly or as indicated
- Hold therapy for grade 2 AST/ALT ↑ with symptoms or grade 3/4 AST/ALT ↑
- Discontinue if AST/ALT >3x ULN w/total bilirubin >2x ULN†

* Despite appropriate supportive care (including antidiarrheals) † In absence of alternative causes.

Sotorasib PI. 2021.

Adagrasib in Pretreated Advanced *KRAS* G12C Mutation–Positive NSCLC



Outcome	Phase II Cohort (n = 112)
ORR, n (%)	48 (43)
DCR, n (%)	89 (80)
Median PFS, mos (95% CI)	6.5 (4.7-8.4)
Median OS, mos (95% CI)	12.6 (9.2-19.2)

TRAE, %	All Cohorts (N = 116)	
	Any Grade	Grade 3/4
Any	97	43
▪ Diarrhea	63	<1
▪ Nausea	62	4
▪ Vomiting	47	<1
▪ Fatigue	41	4
▪ ALT increased	28	4
▪ Blood creatinine increased	26	<1
▪ AST increased	25	3
▪ Decreased appetite	24	3

- Grade 1–2 TRAEs: 53% of patients
- 2 grade 5 TRAEs (pneumonitis, cardiac failure)
- TRAEs leading to dose reduction: 52%
- TRAEs leading to discontinuation: 7%

Spira. ASCO 2022. Abstr 9002. Jänne. NEJM. 2022;[Epub].

Slide credit: clinicaloptions.com

Biomarkers for Targeted Therapies in NSCLC: ALK/ROS1

ALK and ROS1 Inhibition in NSCLC: Approved Agents

- *ALK* rearrangements present in ~4%-6% of NSCLC[1]
  - Younger on average, non-smokers most common
  - Fusion gene, most commonly with *EML4*
- 5 TKIs approved, 3 are preferred in first-line setting[2]
  - Alectinib, brigatinib, lorlatinib
  - Also available: crizotinib, ceritinib

- *ROS1* rearrangements present in 1%-2% of NSCLC[3]
  - Younger age, light or never-smokers
  - Fusion gene (14 identified partners; CD74 most common)
- 2 TKIs approved and preferred in first-line setting[2]
  - Crizotinib and entrectinib
  - Also available: ceritinib

1. Chia. Clin Epidemiol. 2014;6:423. 2. NCCN Clinical Practice Guidelines in Oncology: NSCLC (v3.2022).
3. Almquist. JCO Oncol Pract. 2021;17:7.

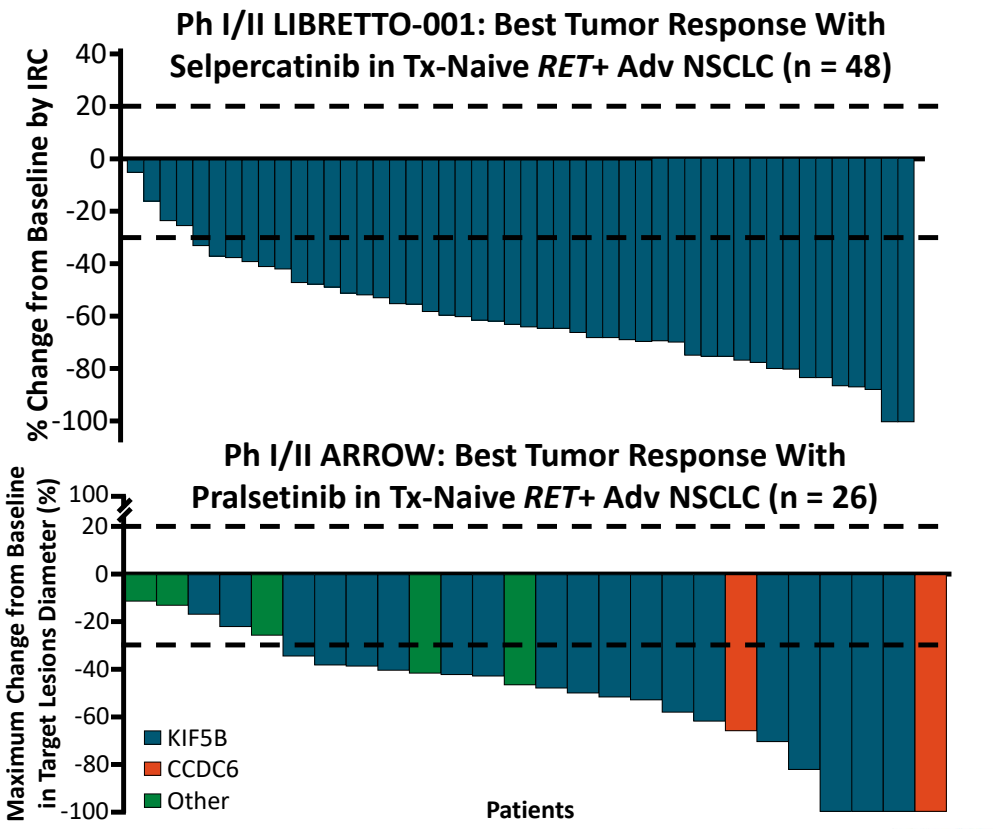
Biomarkers for Targeted Therapies in NSCLC: RET

Selpercatinib and Pralsetinib: 2 Approved Selective RET Inhibitors for *RET* Fusion–Positive Advanced NSCLC

- Incidence: 1-2% of nonsquamous NSCLC

Response	Prior Plt-Based CT	Tx Naive
Selpercatinib	(n = 247)	(n = 69)
▪ ORR, %	61.1	84.1
▪ Median DoR, mo	28.6	20.2
▪ Median PFS, mo	24.9	22.0
Pralsetinib	(n = 87)	(n = 27)
▪ ORR, %	61	70
▪ Median DoR, mo	NR	9.0
▪ Median PFS, mo	17.1	9.1

- FDA approvals for metastatic *RET*+ NSCLC
  - Selpercatinib: May 2020
  - Pralsetinib: September 2020



Drilon. ELCC 2022. Abstr 27P. Besse. ASCO 2021. Abstr 9065.
Gainor. Lancet Oncol. 2021;22:959. Selpercatinib PI. Pralsetinib PI.

Slide credit: clinicaloptions.com

Comparison of Approved RET Inhibitors

	Selpercatinib	Pralsetinib
Dose, oral	▪ <50 kg: 120 mg twice daily ± food ▪ ≥50 kg: 160 mg twice daily ± food	▪ 400 mg once daily on an empty stomach
Available dosage (capsule)	▪ 40 mg, 80 mg	▪ 100 mg
Common AEs, all grades (≥20%):	▪ Dry mouth, diarrhea, constipation, nausea, abdominal pain, hypertension, fatigue, edema, rash, headache	▪ Constipation, hypertension, fatigue, edema, musculoskeletal pain, diarrhea, pyrexia, cough
Common laboratory abnormalities (≥25%):	▪ Decreased albumin, calcium, sodium, leukocytes, platelets ▪ Increased AST, ALT, glucose, creatinine, alkaline phosphatase, total cholesterol	▪ Decreased calcium, albumin, phosphate, sodium, neutrophils, hemoglobin, lymphocytes, platelets ▪ Increased AST, ALT, alkaline phosphatase, creatinine, potassium
Warnings/Precautions:	▪ Hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, TLS, impaired wound healing, embryo-fetal toxicity	▪ ILD/pneumonitis, hepatotoxicity, hypertension, hemorrhagic events, TLS, impaired wound healing, embryo-fetal toxicity
Significant DDIs (avoid):	▪ PPI and H2RA: may take with food (w/PPI) or adjust administration time (w/H2RA*) ▪ Strong, moderate CYP3A4 inducers, inducers	▪ Strong CYP3A4 inhibitors and inducers, combined P-gp and strong CYP3A4 inhibitors

*Take selpercatinib 2 hrs before or 10 hos after H2RA, or 2 hrs before or 2 hrs after antacid

Selpercatinib PI. Pralsetinib PI.

CCO

Slide credit: clinicaloptions.com

RET Inhibitors: Select Adverse Event Monitoring and Management (Common)

Hypertension (29% [14% gr 3] w/pralsetinib, 35% [17% gr 3] w/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‡

Hepatotoxicity (↑AST/ALT 69%/46% w/pralsetinib, 51%/45% w/selpercatinib)

- Monitor hepatic function at baseline, Q2W x 3 mo, then monthly or as indicated
- Hold therapy if grade 3/4

Edema (20% w/pralsetinib, 35% w/selpercatinib, all grades)

QT Interval Prolongation* (QTcF interval > 500 ms in 6%)

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

‡Persistent hypertension despite optimal antihypertensive therapy

*Selpercatinib only

Selpercatinib PI. 2021. Pralsetinib PI. 2020.

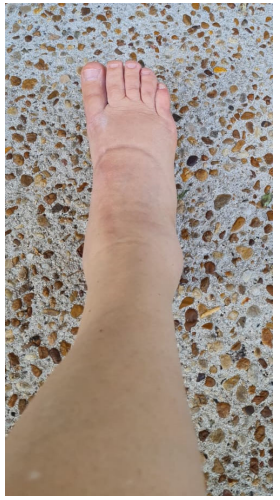
Assessment 3: For a patient with *RET* fusion-positive NSCLC, which of the following would you recommend?

A. Selpercatinib or pralsetinib
B. Osimertinib or afatinib
C. Amivantamab or mobocertinib
D. Entrectinib or larotrectinib
E. I'm not sure

Biomarkers for Targeted Therapies in NSCLC: MET

Patient Case #2

- A 50-year-old female was diagnosed with metastatic adenocarcinoma of the lung in 2018. She smoked cigarettes on occasion. Biomarker testing at the time of diagnosis was negative for EGFR, ALK, and ROS1; PD-L1 20%
- She was initially treated with chemotherapy, followed by 2nd-line immune checkpoint inhibitor, which yielded a durable PFS benefit
- She experienced disease progression in 2021, at which time both archival and new tissue sent for NGS testing
  - Both samples positive for *MET* exon 14 skipping mutation
- Patient initiated on MET inhibitor
  - She developed response on imaging; however, she reported significant extremity swelling and redness
  - Patient was upset about weight gain from the fluid



Presurvey 4: All of the following would be recommended to manage edema with MET inhibitors EXCEPT:

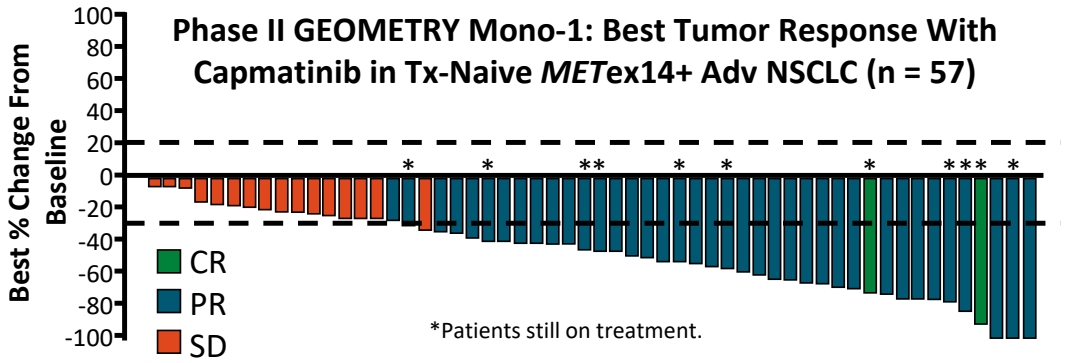
A. Rule out DVT, cellulitis
B. Elevation, compression stockings
C. Consider dose reduction of MET inhibitor
D. Permanently discontinue MET inhibitor
E. I’m not sure

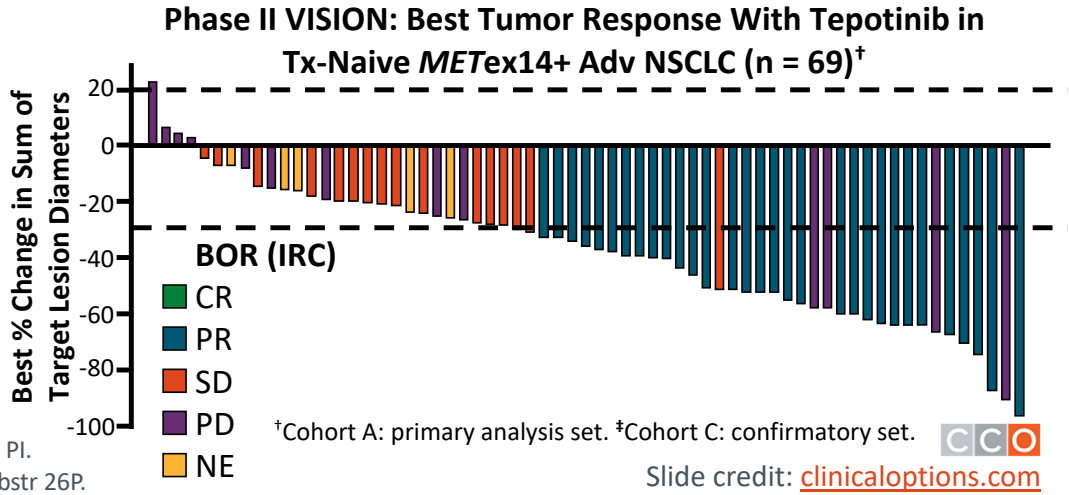
Capmatinib and Tepotinib: 2 Approved Selective MET Inhibitors for *MET*ex14-Positive Advanced NSCLC

- Incidence: 3% to 4% of nonsquamous 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 DoR, mo	9.7	12.6
▪ Median PFS, mo	5.5	12.3
Tepotinib (Cohort A†/C‡)	(n = 83/66)	(n = 69/95)
▪ ORR, %	43.4/47.0	50.7/60.0
▪ Median DoR, mo	12.4/12.6	46.4/NE
▪ Median PFS, mo	10.9/12.1	10.3/15.9

- FDA approvals for metastatic *MET*ex14+ NSCLC
  - Capmatinib: May 2020
  - Tepotinib: February 2021





Capmatinib PI. Le. Clin Cancer Res. 2022;28:1117. Paik. NEJM. 2020;383:931. Tepotinib PI. Thomas. WCLC 2022. Abstr OA03.05. Wolf. ASCO 2021. Abstr 9020. Wolf. ELCC 2022. Abstr 26P.

Slide credit: clinicaloptions.com

Comparison of Approved MET Inhibitors

	Capmatinib	Tepotinib
Dose, oral	▪ 400 mg BID with or without food	▪ 450 mg QD with food
Available dosage (tablets)	▪ 150 mg, 200 mg	▪ 225 mg
Common AEs, all grades (≥20%):	▪ Peripheral edema, fatigue, nausea, vomiting, dyspnea, decreased appetite	▪ Edema, fatigue, nausea, diarrhea, musculoskeletal pain, dyspnea
Common laboratory abnormalities (≥20%):	▪ Decreased albumin ▪ Increased creatinine, ALT, alkaline phosphatase, amylase, gamma-glutamyltransferase, lipase, AST	▪ Decreased albumin, sodium ▪ Increased creatinine, alkaline phosphatase, ALT, AST, potassium, amylase, gamma-glutamyltransferase
Warnings/Precautions:	▪ ILD/pneumonitis, hepatotoxicity, photosensitivity, embryo-fetal toxicity	▪ ILD/pneumonitis, hepatotoxicity, embryo-fetal toxicity
Significant DDIs (avoid):	▪ Strong, moderate CYP3A inducers	▪ Dual strong CYP3A + P-gp inhibitors, strong CYP3A inducers

1. Capmatinib PI. 2020. 2. Tepotinib PI. 2021.

Edema: Common Concern with MET and RET inhibitors

- Edema from MET and RET inhibitors very common
- Rule out DVT, cellulitis
  - Usually not cellulitis despite sometimes red appearance

Edema, %	Capmatinib	Tepotinib	Selpercatinib	Pralsetinib
Any grade	52	70	35	29
▪ Grade ≥3	9	9	0.3	0

- Management
  - Elevation, compression stockings, diuretics sparingly
  - Dose reductions if it becomes unbearable, emotional toll

Capmatinib PI. 2020. Tepotinib PI. 2021. Selpercatinib PI. 2020. Pralsetinib PI. 2020.

Slide credit: clinicaloptions.com

MET Inhibitors: Select Adverse Event Monitoring and Management

Hepatotoxicity (↑ ALT/AST 13%)

- Monitor hepatic function at baseline, Q2W x 3 months, then monthly or as indicated
- Hold therapy for
  - Grade 3 ALT/AST ↑ without total bilirubin ↑
  - Grade 2*/3 total bilirubin ↑ without ALT/AST ↑
- Discontinue therapy for
  - Grade 4 ALT/AST ↑ without total bilirubin ↑
  - ALT/AST >3x ULN + total bilirubin >2x ULN
  - Grade 4 total bilirubin ↑ without ALT/AST ↑

Photosensitivity*

- Limit direct ultraviolet exposure (eg, sunscreen, protective clothing)

*Capmatinib only

Capmatinib PI. 2020. Tepotinib PI. 2021

Slide credit: clinicaloptions.com

Assessment 4: All of the following would be recommended to manage edema with MET inhibitors EXCEPT:

A. Rule out DVT, cellulitis
B. Elevation, compression stockings
C. Consider dose reduction of MET inhibitor
D. Permanently discontinue MET inhibitor
E. I'm not sure

Biomarkers for Targeted Therapies in NSCLC: NTRK

TRK Inhibitors Are Active in *NTRK* Fusion+ Lung Cancer

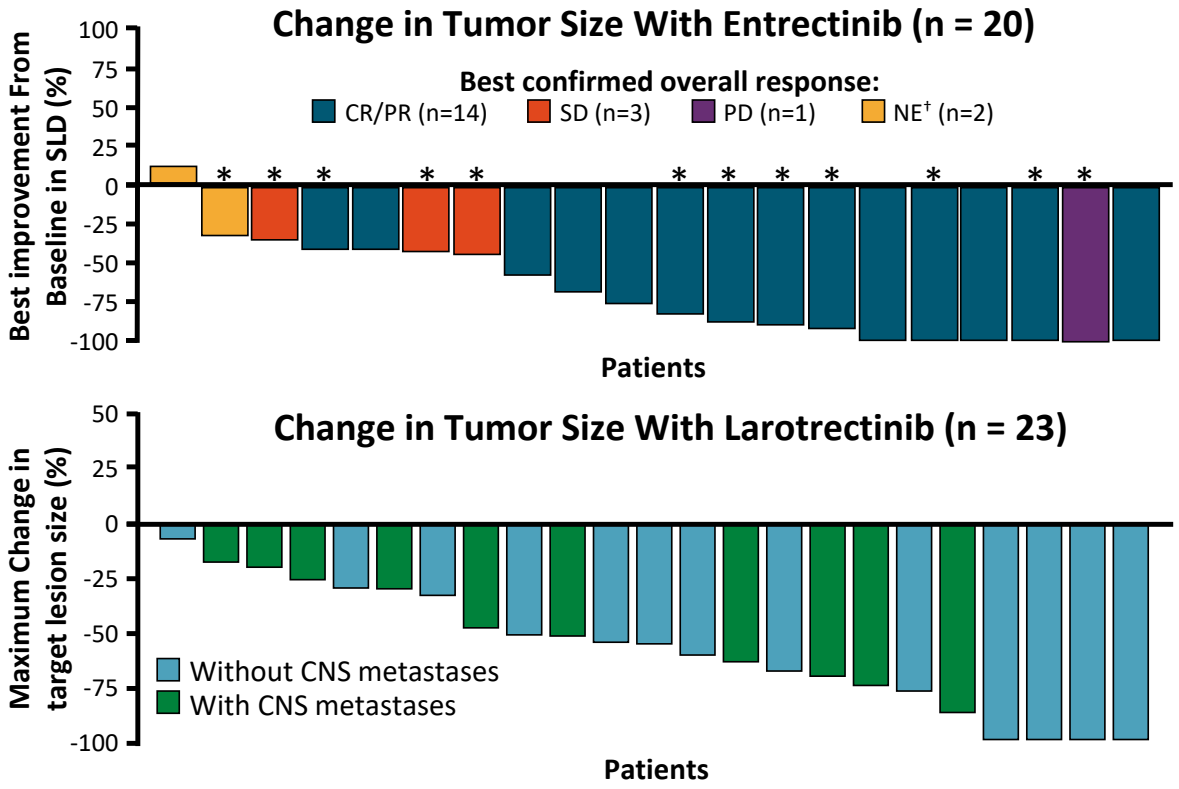
- Incidence: 0.21% across all tumor types; ~0.2% in lung cancer

Entrectinib	N = 22
ORR, % (95% CI)	63.6 (40.7-82.8)
Median DoR, mo*	19.9
Median PFS, mo	14.9
Median OS, mo	NE
Median f/u, mo	19.2

*Among the 14 pts who responded.

Larotrectinib	N = 26
ORR, % (95% CI)*	83 (61-95)
Median DoR, mo†	NR
Median PFS, mo*	NR
Median OS, mo	40.7
Median f/u, mo	12.9-14.6‡

*Among the 23 evaluable pts. †Among the 19 pts who responded. ‡12.9 mo for DoR, OS; 14.6 mo for PFS.



Investigator-assessed as per RECIST v1.1. *Patients with investigator-assessed CNS metastases at baseline. †Patient with measurable intracranial disease and 100% reduction intracranial target lesions.

Cho. ELCC 2022. Abstr 110P. Moreno. WCLC 2022. Abstr EP08.02-148.

Slide credit: clinicaloptions.com

Comparison of Approved NTRK Inhibitors for NSCLC

	Entrectinib*	Larotrectinib
FDA Accelerated Approval	▪ August 15, 2019	▪ November 26, 2018
Indication	▪ Treatment of adult + pediatric patients with metastatic or unresectable disease + *NTRK* gene fusion and lacking alternative therapy (tumor agnostic indication)	
Dose, oral (adults)	▪ 600 mg once daily ± food	▪ 100 mg twice daily ± food
Available dosage (capsules)	▪ 100 mg, 200 mg	▪ 25 mg, 100 mg†
Common AEs, all grades (≥20%):	▪ Fatigue, edema, pyrexia, constipation, diarrhea, nausea, vomiting, dysgeusia, dizziness, dysesthesia, **cognitive impairment**, dyspnea, cough, myalgia, arthralgia, ↑ weight, vision disorders	Musculoskeletal pain, fatigue, pyrexia, cough, dizziness, constipation, diarrhea, nausea, vomiting, abdominal pain
Common laboratory abnormalities (≥25%):	▪ Anemia, lymphopenia, neutropenia, decreased calcium, phosphorus, albumin ▪ Increased creatinine, uric acid, AST, ALT, sodium, lipase, amylase, potassium, alkaline phosphatase, glucose	▪ Increased AST, ALT, alkaline phosphatase ▪ Hypoalbuminemia, hypocalcemia, anemia, neutropenia, leukopenia
Warnings/Precautions:	▪ Congestive heart failure, CNS effects, fractures, hepatotoxicity, hyperuricemia, QT interval prolongation, vision disorders, embryo-fetal toxicity	▪ CNS effects, skeletal fractures, hepatotoxicity, embryo-fetal toxicity
Significant DDIs (avoid):	▪ Moderate, strong CYP3A4 inhibitors, inducers	▪ Strong CYP3A4 inhibitors and inducers

*Also approved for adult patients with metastatic *ROS1*-positive NSCLC; †Also available in 20 mg/mL oral solution.

Entrectinib PI. 2019. Larotrectinib PI. 2021.

CCO

Slide credit: clinicaloptions.com

Biomarkers for Targeted Therapies in NSCLC: BRAF

BRAF V600E Mutations in NSCLC

- *BRAF* mutations found in 1%-3% of NSCLC cases[1]
  - Most common: *BRAF* V600E
  - More common in smokers
  - Patients often respond to chemoimmunotherapy
- Only 1 drug regimen approved in this setting: dabrafenib/trametinib[2]
  - Notable AE: pyrexia (55% all grade with dabrafenib + trametinib in NSCLC)
  - Fever can be complicated by hypotension, rigors, chills, dehydration, or renal failure
  - Recommended to hold therapy for temperature ≥ 100.4°F
  - Antipyretics for secondary prophylaxis; corticosteroids for second/subsequent pyrexia if temperature persists x 3 days or if associated with complications

1. Roviello. Invest New Drugs. 2021;39:879. 2. Dabrafenib PI.

Biomarkers for Targeted Therapies in NSCLC: HER2

HER2-Mutations in NSCLC

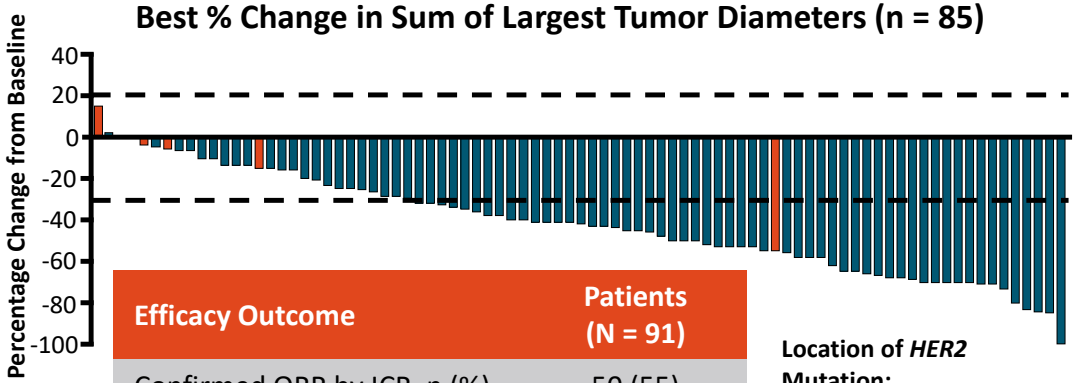
- *HER2 (ERBB2)* present in 3%-5% of NSCLC adenocarcinomas
  - Mostly exon 20 in-frame insertions
  - Mutually exclusive with other mutations
  - Mostly seen in never smokers
  - Worse OS than other subtypes in Lung Cancer Mutation Consortium
- In NSCLC, *HER2* mutation and amplification must be identified using an NGS DNA panel (similar to breast cancer)
- IHC used to assess HER2 overexpression, seen in 59% of NSCLC cases
  - 2-3+: up to 30%

Pillai. Cancer. 2017;123:4099. Hirsch. Lancet. 2017;389:299. Paudya. Cancer Sci. 2010;101:1045.

Phase II DESTINY-Lung01: Trastuzumab Deruxtecan (T-DXd) in Pretreated *HER2*-Mutated Metastatic NSCLC

- Incidence: 2-3% of nonsquamous NSCLC
- **T-DXd:** HER2-targeted ADC coupling an anti-HER2 mAb with trastuzumab AA sequence to topoisomerase I inhibitor payload using a tumor-selectable cleavable linker

Best % Change in Sum of Largest Tumor Diameters (n = 85)



Efficacy Outcome	Patients (N = 91)
Confirmed ORR by ICR, n (%)	50 (55)
DCR, % (95% CI)	92 (85-97)
Median DoR, mo (95%)	9.3 (5.7-14.7)
Median PFS, mo (95%)	8.2 (6.0-11.9)

Drug-Related AEs in ≥20% of Patients,* %	Patients (N = 91)			
	Gr 1/2	Gr 3	Gr 4	All
Nausea	64	9	0	73
Vomiting	36	3	0	40
Neutropenia	16	15	3	35
Anemia	23	10	0	33
Diarrhea	29	2	1	32
Decreased appetite	30	0	0	30
Leukopenia	19	4	0	23
Constipation	22	0	0	22

*Not shown: any-grade fatigue (53%) and alopecia (46%).
Adjudicated drug-related ILD: n = 24 (26%); Gr 1, n = 3; Gr 2, n = 15; Gr 3, n = 4; Gr 5, n = 2. Median time to onset: 141 d (range: 14-462). Median duration: 43 d. Glucocorticoids received by 21 of 24 patients. ILD resolved in 13 of 24 at data cutoff.

- FDA approved in August 2022 for treatment of adults with unresectable or metastatic *HER2*-mutated NSCLC who received a prior systemic therapy

Li. NEJM. 2022;386:241. Trastuzumab deruxtecan PI.

Slide credit: clinicaloptions.com

Biomarkers for Targeted Therapies in NSCLC: Immunotherapy

Presurvey 5: All of the following ICIs are approved as monotherapy in the first-line setting for patients with advanced NSCLC and PD-L1 ≥50% with no actionable biomarkers EXCEPT:

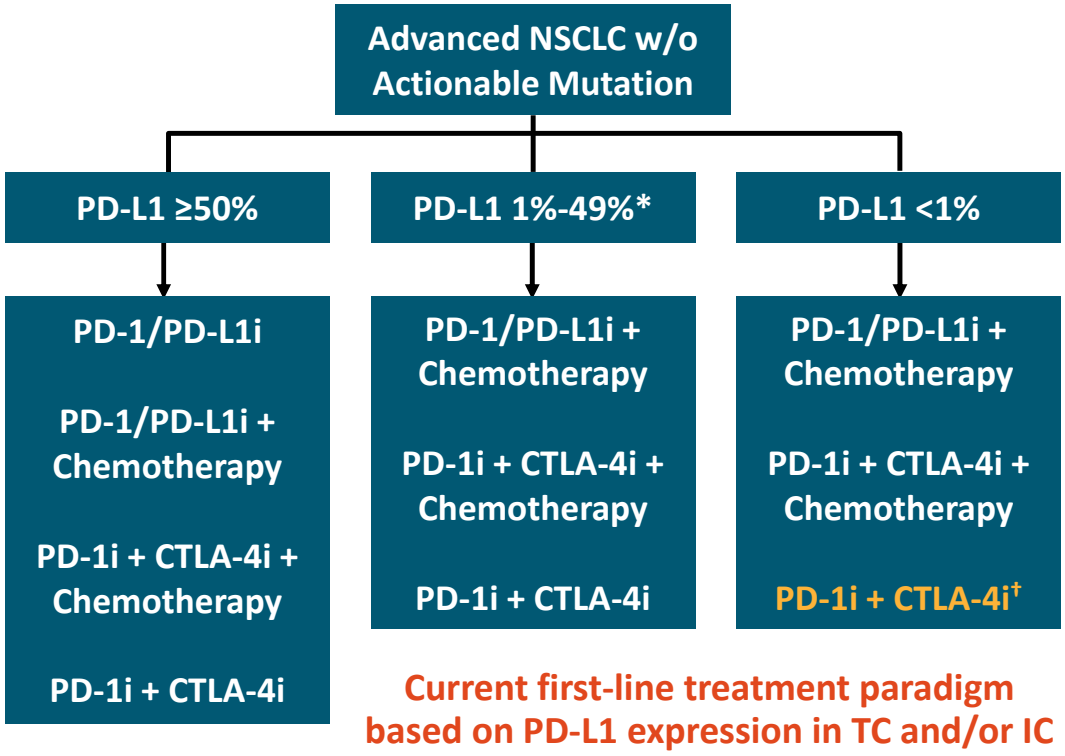
A. Atezolizumab
B. Cemiplimab
C. Nivolumab
D. Pembrolizumab
E. I'm not sure

Biomarkers for Immunotherapy in NSCLC: A Controversial Topic

- PD-L1: sole current biomarker able to guide immunotherapy
  - Imperfect: PD-L1 negative tumors can still respond, albeit mostly when added to chemotherapy. Synergistic effect?
- TMB: former marker for response, not currently used[1,2]
  - Conflicting correlation with survival in the CheckMate studies
- MSI high/MMR: not used, or relevant, in lung cancer
- LAG-3: possibly related to resistance to immunotherapy, being studied[3]

1. Hellmann. Cancer Cell. 2018;33:843. 2. Bravaccini. Int J Mol Sci. 2021;22:6536. 3. Shi. Front Immunol. 2022;12:785091.

2022 Paradigm for Immunotherapy in Advanced NSCLC Without an Actionable Mutation



Current first-line treatment paradigm based on PD-L1 expression in TC and/or IC

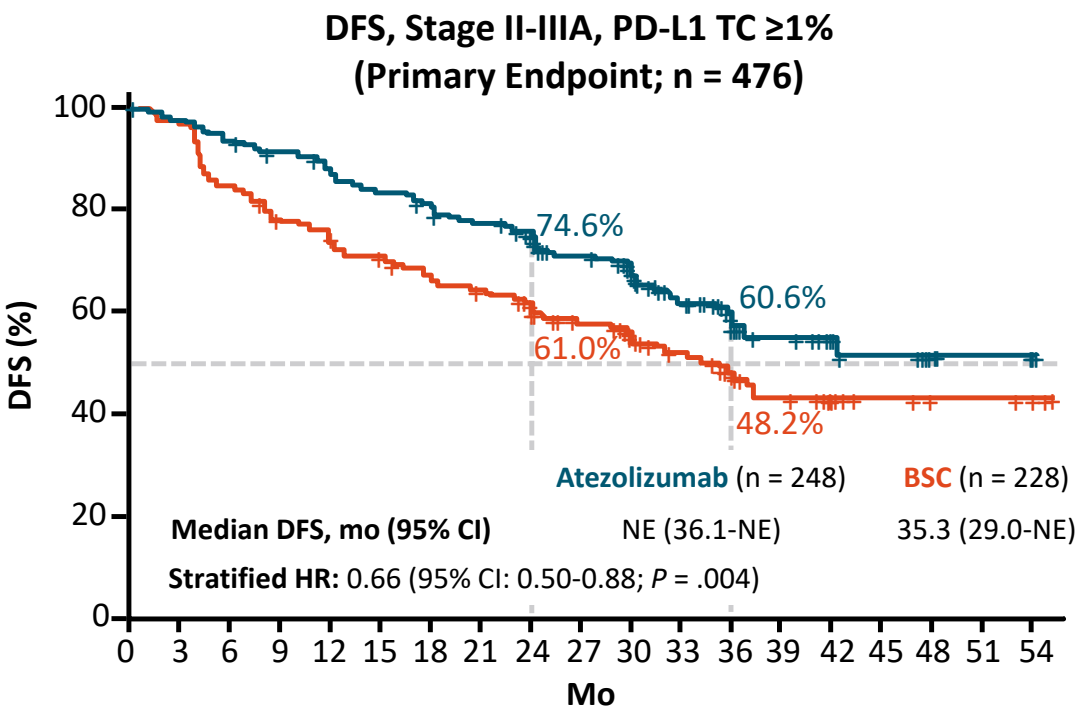
- ICI monotherapy: pembrolizumab,* atezolizumab, cemiplimab
- ICI + chemotherapy
  - Pembrolizumab/carboplatin or cisplatin/pemetrexed (Nsq)
  - Atezolizumab/carboplatin/paclitaxel/ bevacizumab (Nsq)
  - Atezolizumab/carboplatin/nab-paclitaxel (Nsq)
  - Pembrolizumab/carboplatin/taxane (Sq)
  - Nivolumab/ipilimumab + 2 cycles of CT (Sq/Nsq)
- ICI combination: nivolumab/ipilimumab

*Single-agent pembrolizumab also approved for ≥1% PD-L1 but not broadly recommended by experts; guideline-recommended for PD-L1 1-49% if poor PS or contraindications to combining w/CT. †Not an FDA approved indication, but guideline recommended.

NCCN. Clinical practice guidelines in oncology: NSCLC. v.3.2022. nccn.org.

Slide credit: clinicaloptions.com

Phase III IMpower010: Adjuvant Atezolizumab vs BSC in Resected Stage IB-IIIA NSCLC After Adjuvant CT

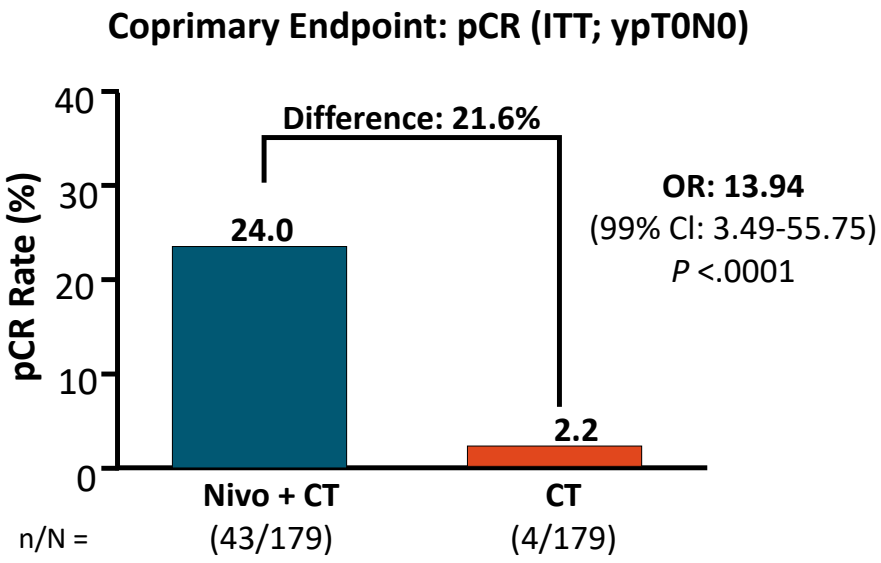


Median follow-up: 32.8 mo (range: 0.1-57.5).

- DFS benefit by PD-L1 status assessed by SP263 IHC: HR (95% CI)
  - TC ≥50%: 0.43 (0.27-0.68)
  - TC ≥1%: 0.66 (0.49-0.87)
  - TC <1%: 0.97 (0.72-1.31)
- FDA approved in October 2021 for adj treatment following resection and adj plt-based CT for adults with stage II-IIIA NSCLC, PD-L1 TC ≥1%
- First pre-specified interim analysis of OS showed trend in favor of atezolizumab in stage II-IIIA with PD-L1 TC ≥1% and ≥50% but not in all randomized stage II-IIIA or ITT populations

Wakelee. ASCO 2021. Abstr 8500. Felip. Lancet. 2021;398;1344. Felip. WCLC 2022. Abstr PL03.09.

Phase III CheckMate 816: Neoadjuvant Nivolumab + Platinum CT for Resectable Stage IB-IIIA NSCLC



- FDA approved in March 2022 for adults with resectable NSCLC (tumors ≥4 cm or N+) in combination with platinum doublet CT in the neoadjuvant setting

Surgery-Related Parameter in All Randomized Patients	Nivolumab + CT (n = 179)	CT (n = 179)
Surgery received/cancelled, %	83.2/15.6	75.4/20.7
Median duration of surgery, min (IQR)	185 (133-260)*	213.5 (150-283)†
Surgery approach, %		
▪ Thoracotomy	59.1‡	63§
▪ Minimally invasive	29.5‡	21.5§
▪ Minimally invasive → open	11.4‡	15.6§
Type of surgery, %#		
▪ Lobectomy	77.2‡	60.7§
▪ Pneumonectomy	16.8‡	25.2§
Complete resection (R0), %	83.2	77.8

*n = 122. †n = 121. ‡n = 149. §n = 135. #Calculated from patients who received definitive surgery. Patients may have had ≥1 surgery type.

Forde. NEJM. 2022;386:1973.

Slide credit: clinicaloptions.com

Assessment 5: All of the following ICIs are approved as monotherapy in the first-line setting for patients with advanced NSCLC and PD-L1 ≥50% with no actionable biomarkers EXCEPT:

A. Atezolizumab
B. Cemiplimab
C. Nivolumab
D. Pembrolizumab
E. I'm not sure

Summary

- Because of highly effective targeted therapies (and lack of efficacy with immunotherapy), testing for *EGFR/ALK/ROS1/BRAF/NTRK/MET*ex14*/RET* at diagnosis is mandatory for all patients with advanced NSCLC
  - Broad testing with NGS for both required and emerging biomarkers is highly recommended!
- PD-L1 testing still important in initial decision making, but biomarker testing is necessary to determine optimal treatment for the patient. For patients with most actionable mutations, targeted therapy is preferred regardless of PD-L1 status
- Molecular testing is moving into the early-stage setting—biomarker-directed targeted therapy and immunotherapy options now approved as adjuvant therapy for these patients
  - Approval of neoadjuvant nivolumab in combination with chemotherapy regardless of PD-L1 expression

Questions?

Go Online for More CCO Coverage of Lung Cancer!

CE-certified on-demand webcast of a live workshop (*coming soon*)

Downloadable slideset with slides from today's presentation (*available now*)

Downloadable clinical resource (*coming soon*)

clinicaloptions.com/LungONSLocal2022Program