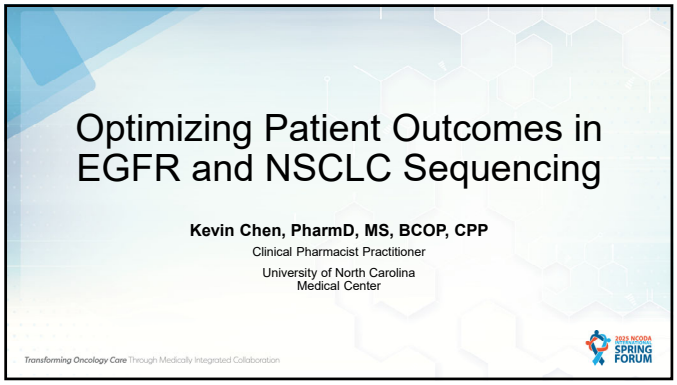
Optimizing Patient Outcomes in EGFR and NSCLC Sequencing
Kevin Chen, PharmD, MS, BCOP, CPP
Clinical Pharmacist Practitioner
University of North Carolina Medical Center
Transforming Oncology Care Through Medically Integrated Collaboration
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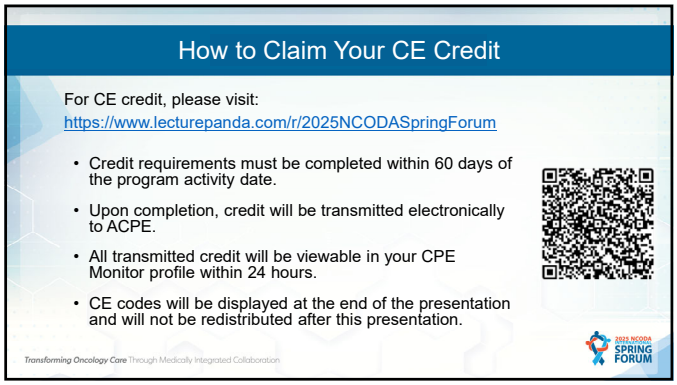
1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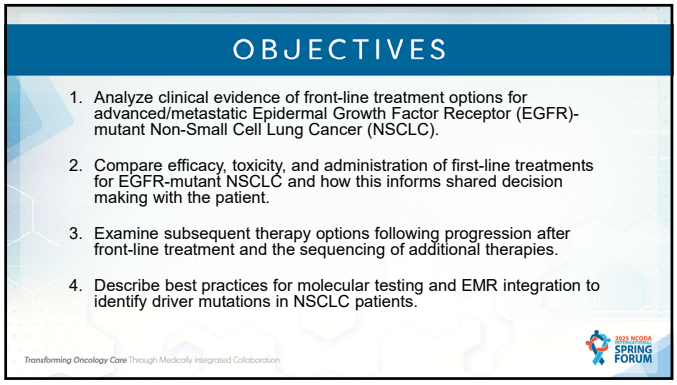
2


OBJECTIVES
1. Analyze clinical evidence of front-line treatment options for advanced/metastatic Epidermal Growth Factor Receptor (EGFR)-mutant Non-Small Cell Lung Cancer (NSCLC).
2. Compare efficacy, toxicity, and administration of first-line treatments for EGFR-mutant NSCLC and how this informs shared decision making with the patient.
3. Examine subsequent therapy options following progression after front-line treatment and the sequencing of additional therapies.
4. Describe best practices for molecular testing and EMR integration to identify driver mutations in NSCLC patients.
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3

DISCLOSURES

The following relevant financial relationships from the past 24 months have been identified and disclosed for the following faculty and planners of this CE activity:

- Kevin Chen, PharmD, MS, BCOP, CPP
  - Advisory boards member for Johnson & Johnson, Pfizer, Bristol Myers Squibb, Amgen, Daiichi Sankyo
  - Contracted Research for Eli Lilly and Company

No relevant financial relationships from the past 24 months have been identified for the following planners of this CE activity:

- Tahsin Imam, PharmD

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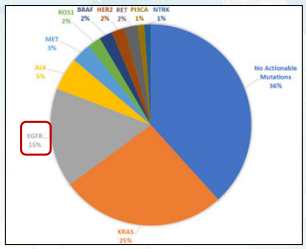
4

Background

- Lung cancer is the leading cause of cancer-related deaths
  - 1/6 deaths in light/non-smokers
- EGFR mutations are common
  - Younger
  - Female
  - East-Asian
  - Adenocarcinoma
  - Non-smokers
- Lung cancer screening is difficult



Saigal R, et al. CA Cancer J Clin. 2024;74(1):12-49. Pakkala S, Ramalingam SS. JCI Insight. 2018;3(15):e120858. Zhang YL, et al. Oncotarget. 2016;7(48):78985-78993.

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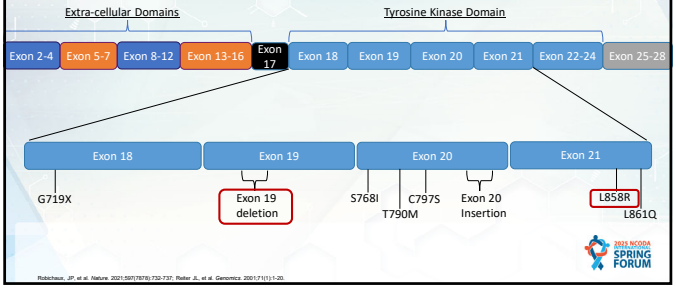
5

EGFR Mutations



Robichaux, JP, et al. Nature. 2021;597(7878):732-737. Reiter JL, et al. Genomics. 2001;71(1):1-20.

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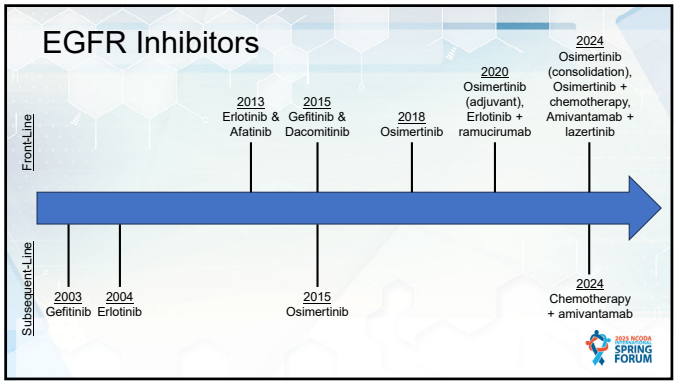
6


EGFR Inhibitors
Front-Line
Subsequent-Line
2013
Erlotinib & Afatinib
2015
Gefitinib & Dacomitinib
2018
Osimertinib
2020
Osimertinib (adjuvant), Erlotinib + ramucirumab
2024
Osimertinib (consolidation), Osimertinib + chemotherapy, Amivantamab + lazertinib
2003
Gefitinib
2004
Erlotinib
2015
Osimertinib
2024
Chemotherapy + amivantamab
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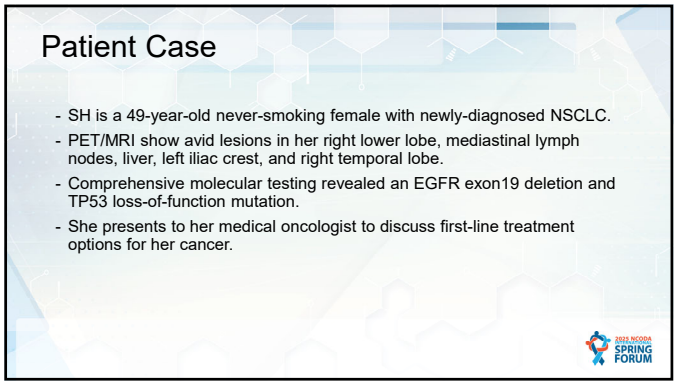
7


Patient Case
- SH is a 49-year-old never-smoking female with newly-diagnosed NSCLC.
- PET/MRI show avid lesions in her right lower lobe, mediastinal lymph nodes, liver, left iliac crest, and right temporal lobe.
- Comprehensive molecular testing revealed an EGFR exon19 deletion and TP53 loss-of-function mutation.
- She presents to her medical oncologist to discuss first-line treatment options for her cancer.
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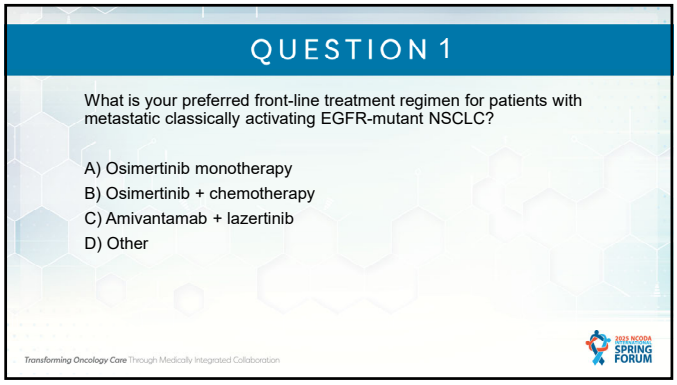
8


QUESTION 1
What is your preferred front-line treatment regimen for patients with metastatic classically activating EGFR-mutant NSCLC?
A) Osimertinib monotherapy
B) Osimertinib + chemotherapy
C) Amivantamab + lazertinib
D) Other
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9


Front-Line Treatments
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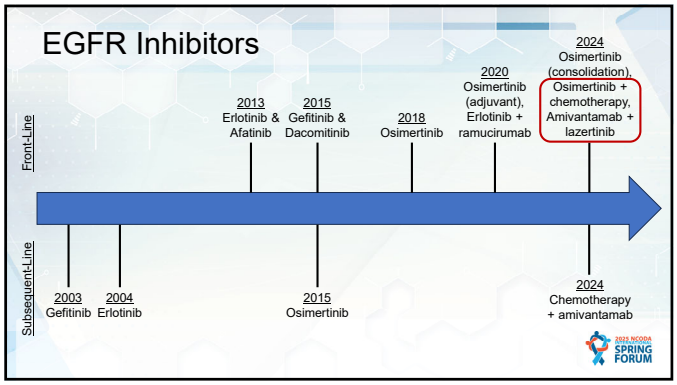
10


EGFR Inhibitors
Front-Line
2013 Erlotinib & Afatinib
2015 Gefitinib & Dacomitinib
2018 Osimertinib
2020 Osimertinib (adjuvant), Erlotinib + ramucirumab
2024 Osimertinib (consolidation), Osimertinib + chemotherapy, Amivantamab + lazertinib
Subsequent-Line
2003 Gefitinib
2004 Erlotinib
2015 Osimertinib
2024 Chemotherapy + amivantamab
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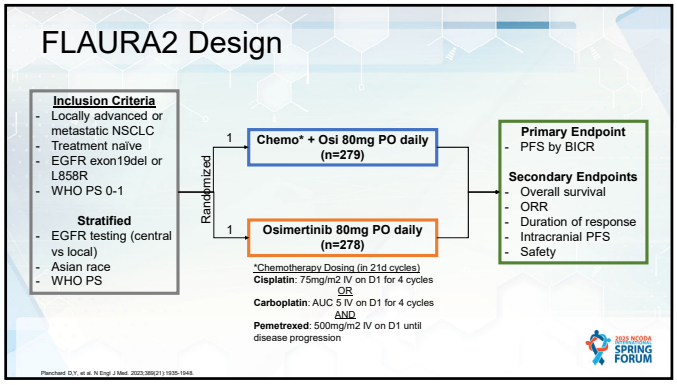
11


FLAURA2 Design
Inclusion Criteria
- Locally advanced or metastatic NSCLC
- Treatment naïve
- EGFR exon19del or L858R
- WHO PS 0-1
Stratified
- EGFR testing (central vs local)
- Asian race
- WHO PS
Randomized
1
Chemo* + Osi 80mg PO daily (n=279)
1
Osimertinib 80mg PO daily (n=278)
*Chemotherapy Dosing (in 21d cycles)
Cisplatin: 75mg/m2 IV on D1 for 4 cycles
OR
Carboplatin: AUC 5 IV on D1 for 4 cycles
AND
Pemetrexed: 500mg/m2 IV on D1 until disease progression
Primary Endpoint
- PFS by BICR
Secondary Endpoints
- Overall survival
- ORR
- Duration of response
- Intracranial PFS
- Safety
Planchard D.Y, et al. N Engl J Med. 2023;389(21):1935-1948.
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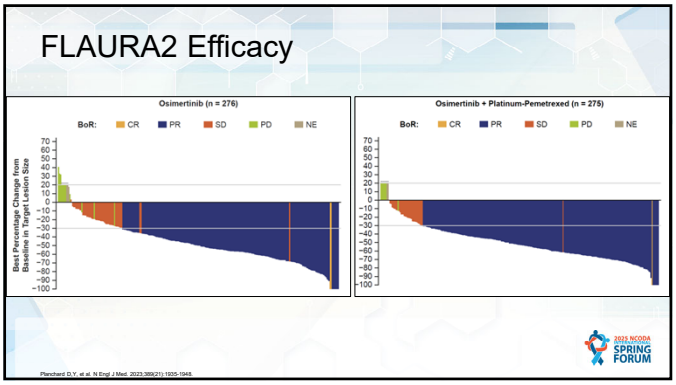
12

FLAURA2 Efficacy



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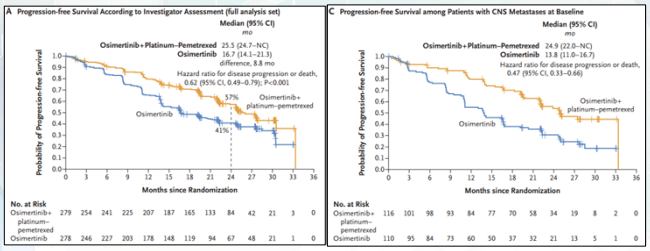
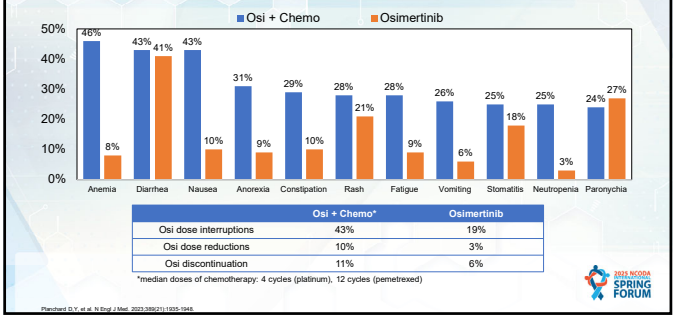
FLAURA2 Efficacy



14

FLAURA2 Safety

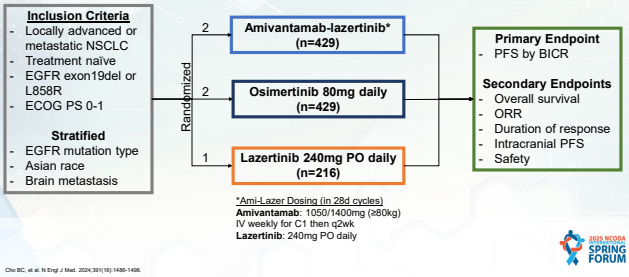


	Osi + Chemo*	Osimertinib
Osi dose interruptions	43%	19%
Osi dose reductions	10%	3%
Osi discontinuation	11%	6%

*median doses of chemotherapy: 4 cycles (platinum), 12 cycles (pemetrexed)

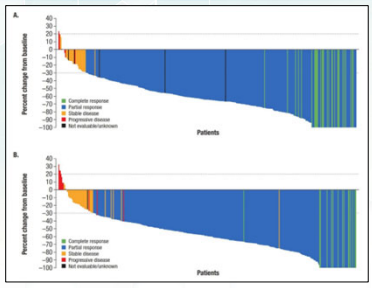
15

MARIPOSA Design



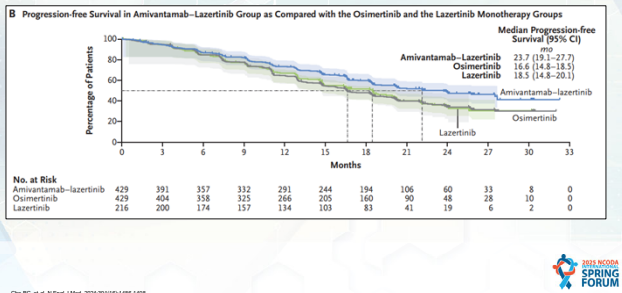
16

MARIPOSA Efficacy



17

MARIPOSA Efficacy



18

MARIPOSA High-Risk Groups

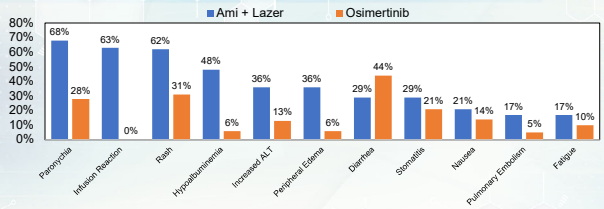
Patient Characteristics	Amivantamab + Lazertinib	Osimertinib
High risk features*	20.3 months	15.0 months
	0.72 (0.58–0.90)	
TP53 mutation	18.2 months	12.9 months
	0.65 (0.48–0.86)	
Brain Metastasis	18.3 months	13.0 months
	0.69 (0.53–0.92)	
Liver Metastasis	18.2 months	11.0 months
	0.58 (0.37–0.91)	
Baseline ctDNA detected	20.3 months	14.8 months
	0.68 (0.53–0.86)	

*high risk features identified in ~85% of patients in the MARIPOSA trial

Cho BC, et al. N Engl J Med. 2024;391(16):1486-1498; Felip E, et al. Ann Oncol. 2024;35(9):805-816.

19

MARIPOSA Safety



	Ami + Lazer	Chemotherapy
Dose Interruptions	83%	39%
Dose Reductions	59%	5%
Discontinuation	35%	14%

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

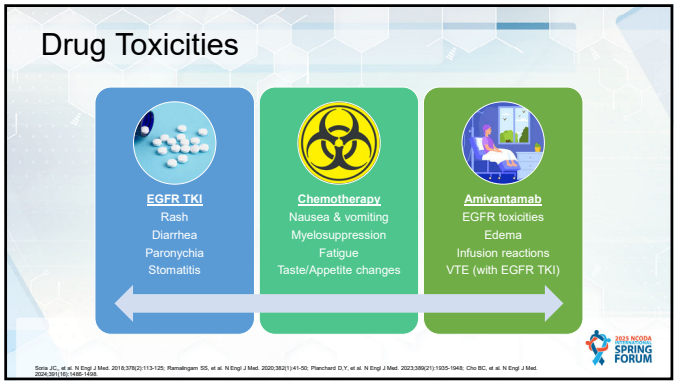
20

Front-line Regimens

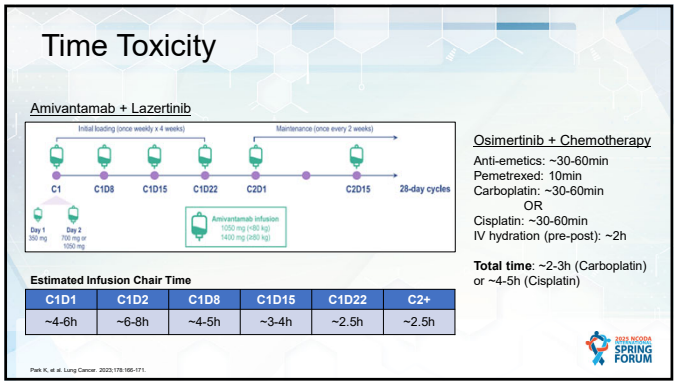
Osimertinib	Osimertinib + Chemotherapy	Amivantamab + Lazertinib
ORR: 80%	ORR: 83%	ORR: 86%
mPFS: 18.9mo	mPFS: 25.5mo	mPFS: 23.7mo
mOS: 38.6mo	mOS: NR	mOS: NR

Soria JC., et al. N Engl J Med. 2018;378(2):113-125; Ramalingam SS, et al. N Engl J Med. 2020;382(1):41-50; Planchard D,Y, et al. N Engl J Med. 2023;389(21):1935-1948; Cho BC, et al. N Engl J Med. 2024;391(16):1486-1498.

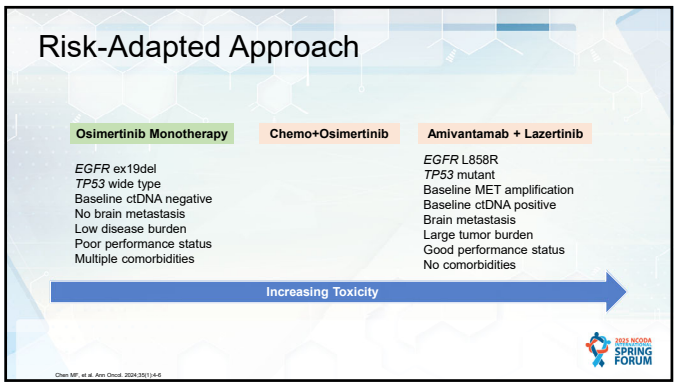
21


Drug Toxicities
EGFR TKI
Rash
Diarrhea
Paronychia
Stomatitis
Chemotherapy
Nausea & vomiting
Myelosuppression
Fatigue
Taste/Appetite changes
Amivantamab
EGFR toxicities
Edema
Infusion reactions
VTE (with EGFR TKI)

22


Time Toxicity
Amivantamab + Lazertinib
Initial loading (once weekly x 4 weeks)
Maintenance (once every 2 weeks)
C1
C1D8
C1D15
C1D22
C2D1
C2D15
28-day cycles
Osimertinib + Chemotherapy
Anti-emetics: ~30-60min
Pemetrexed: 10min
Carboplatin: ~30-60min
OR
Cisplatin: ~30-60min
IV hydration (pre-post): ~2h
Total time: ~2-3h (Carboplatin) or ~4-5h (Cisplatin)
Estimated Infusion Chair Time
C1D1 | C1D2 | C1D8 | C1D15 | C1D22 | C2+
~4-6h | ~6-8h | ~4-5h | ~3-4h | ~2.5h | ~2.5h

23


Risk-Adapted Approach
Osimertinib Monotherapy
EGFR ex19del
TP53 wide type
Baseline ctDNA negative
No brain metastasis
Low disease burden
Poor performance status
Multiple comorbidities
Chemo+Osimertinib
Amivantamab + Lazertinib
EGFR L858R
TP53 mutant
Baseline MET amplification
Baseline ctDNA positive
Brain metastasis
Large tumor burden
Good performance status
No comorbidities
Increasing Toxicity

24

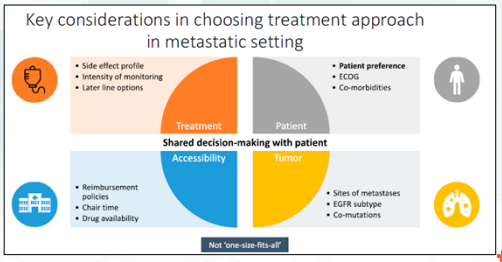
Patient Case

- SH is a 49-year-old never-smoking female with newly-diagnosed NSCLC. PET/MRI show avid lesions in her right lower lobe, mediastinal lymph nodes, liver, left iliac crest, and right temporal lobe. Comprehensive molecular testing revealed an EGFR exon19 deletion and TP53 loss-of-function mutation. She presents to her medical oncologist to discuss first-line treatment options for her cancer.

- She has an excellent performance score (ECOG: 0), with no other medical comorbidities and wants to pursue aggressive treatment. She would like to prefer avoiding her friends and co-workers knowing she has lung cancer.

25

Shared Decision Making



26

Subsequent Treatments

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27

Patient Case

- SH is a 49-year-old never-smoking female with widely metastatic EGFR-mutant NSCLC. She was started on first-line carboplatin, pemetrexed, and osimertinib given the presence of brain metastasis and TP53 mutation at baseline.
- Restaging scans performed ~2 years after she started treatment demonstrated two new hypodense lesions in her liver concerning for disease progression.

28

QUESTION 2

What is the next best treatment option for patient SH after progressing on front-line osimertinib + chemotherapy?

A) Local therapy and continue osimertinib
B) Chemotherapy + amivantamab
C) Amivantamab + lazertinib
D) HER3 or TROP2 directed antibody-drug conjugate

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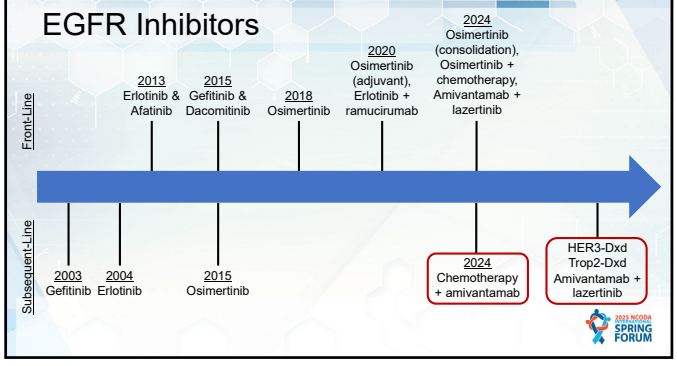
29

EGFR Inhibitors



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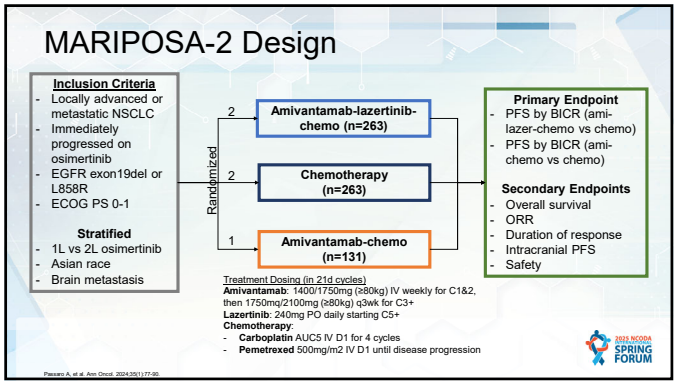
MARIPOSA-2 Design
Inclusion Criteria
- Locally advanced or metastatic NSCLC
- Immediately progressed on osimertinib
- EGFR exon19del or L858R
- ECOG PS 0-1
Stratified
- 1L vs 2L osimertinib
- Asian race
- Brain metastasis
Randomized
2
Amivantamab-lazertinib-chemo (n=263)
2
Chemotherapy (n=263)
1
Amivantamab-chemo (n=131)
Primary Endpoint
- PFS by BICR (ami-lazer-chemo vs chemo)
- PFS by BICR (ami-chemo vs chemo)
Secondary Endpoints
- Overall survival
- ORR
- Duration of response
- Intracranial PFS
- Safety
Treatment Dosing (in 21d cycles)
Amivantamab: 1400/1750mg (≥80kg) IV weekly for C1&2, then 1750mg/2100mg (≥80kg) q3wk for C3+
Lazertinib: 240mg PO daily starting C5+
Chemotherapy:
- Carboplatin AUC5 IV D1 for 4 cycles
- Pemetrexed 500mg/m2 IV D1 until disease progression
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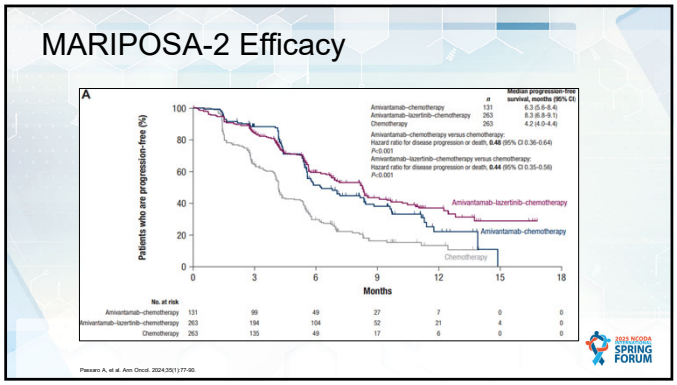
31


MARIPOSA-2 Efficacy
A
Patients who are progression-free (%)
Months
Amivantamab-lazertinib-chemotherapy
Amivantamab-chemotherapy
Chemotherapy
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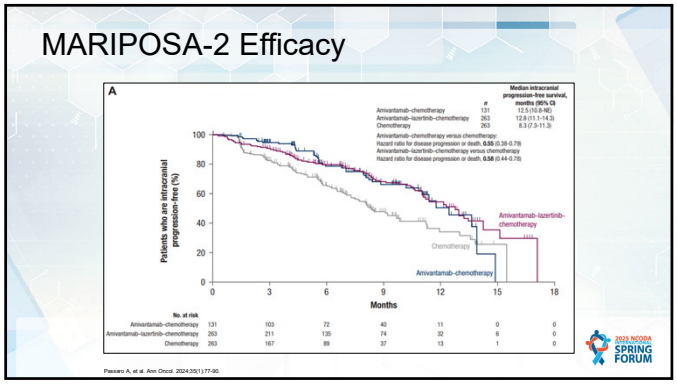
32


MARIPOSA-2 Efficacy
A
Patients who are intracranial progression-free (%)
Months
Amivantamab-lazertinib-chemotherapy
Chemotherapy
Amivantamab-chemotherapy
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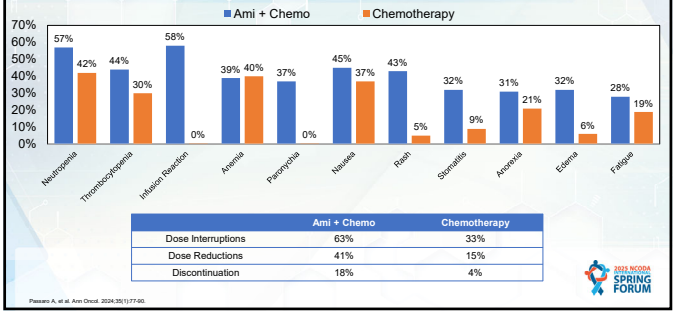
33

MARIPOSA-2 Safety



	Ami + Chemo	Chemotherapy
Dose Interruptions	63%	33%
Dose Reductions	41%	15%
Discontinuation	18%	4%

Passaro A, et al. Ann Oncol. 2024;35(1):77-90.

34

Antibody Drug Conjugate Efficacy

HERTHENA-Lung01

- Advanced/metastatic NSCLC, EGFR exon19del/L858R, ≥1 prior EGFR TKI & platinum-based chemotherapy
- Patritumab deruxtecan (HER3-Dxd): 5.6 mg/kg IV q3wks
- ORR: 29.8%, CNS ORR: 33%, mPFS: 5.5mo, mOS: 11.9mo

TROPION-Lung05 *(EGFR subset)*

- Advanced/metastatic NSCLC, EGFR mutation, 1-2 prior EGFR TKIs & cytotoxic therapies (including platinum doublet)
- Datopotamab deruxtecan (TROP2-Dxd): 6.0 mg/kg IV q3wks
- ORR: 43.6%, mPFS: 5.8mo, mOS: 18.3mo

Yu HA, et al. J Clin Oncol. 2023;41(35):5363-5375. Sands J, et al. J Clin Oncol. 2025;JCO2401349.

35

Antibody Drug Conjugate Toxicities

HER3-Dxd

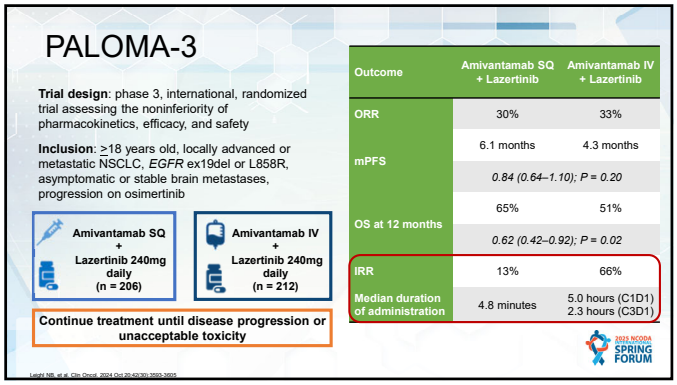
Adverse Event (all grade)	Patritumab Deruxtecan (n=225)
Nausea	66%
Thrombocytopenia	44%
Anorexia	42%
Neutropenia	36%
Constipation	34%
Anemia	33%
Fatigue	31%
Diarrhea	28%
Alopecia	25%
Stomatitis	12%
ILD	5.3%

TROP2-Dxd

Adverse Event (all grade)	Datopotamab Deruxtecan (n=137)
Stomatitis	65.7%
Nausea	54.7%
Alopecia	49.6%
Ocular events	26.3%
Anorexia	20.4%
Fatigue	19.0%
Infusion reaction	16.1%
Constipation	15.3%
Rash	13.9%
ILD	3.6%

Yu HA, et al. J Clin Oncol. 2023;41(35):5363-5375. Sands J, et al. J Clin Oncol. 2025;JCO2401349.

36


PALOMA-3
Trial design: phase 3, international, randomized trial assessing the noninferiority of pharmacokinetics, efficacy, and safety
Inclusion: ≥18 years old, locally advanced or metastatic NSCLC, EGFR ex19del or L858R, asymptomatic or stable brain metastases, progression on osimertinib
Amivantamab SQ + Lazertinib 240mg daily (n = 206)
Amivantamab IV + Lazertinib 240mg daily (n = 212)
Continue treatment until disease progression or unacceptable toxicity
Outcome
Amivantamab SQ + Lazertinib
Amivantamab IV + Lazertinib
ORR
30%
33%
mPFS
6.1 months
4.3 months
0.84 (0.64–1.10); P = 0.20
OS at 12 months
65%
51%
0.62 (0.42–0.92); P = 0.02
IRR
13%
66%
Median duration of administration
4.8 minutes
5.0 hours (C1D1)
2.3 hours (C3D1)
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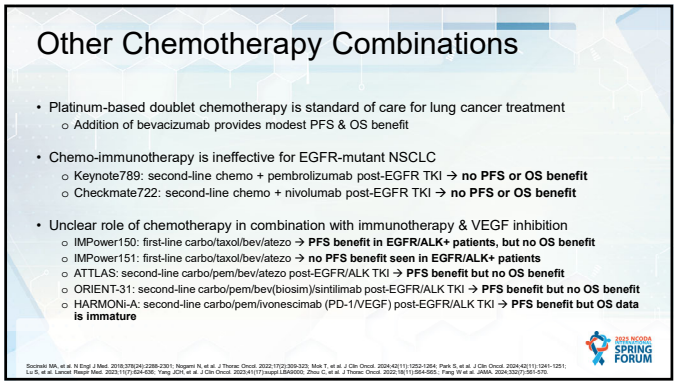
37


Other Chemotherapy Combinations
Platinum-based doublet chemotherapy is standard of care for lung cancer treatment
Addition of bevacizumab provides modest PFS & OS benefit
Chemo-immunotherapy is ineffective for EGFR-mutant NSCLC
Keynote789: second-line chemo + pembrolizumab post-EGFR TKI → no PFS or OS benefit
Checkmate722: second-line chemo + nivolumab post-EGFR TKI → no PFS or OS benefit
Unclear role of chemotherapy in combination with immunotherapy & VEGF inhibition
IMPower150: first-line carbo/taxol/bev/atezo → PFS benefit in EGFR/ALK+ patients, but no OS benefit
IMPower151: first-line carbo/taxol/bev/atezo → no PFS benefit seen in EGFR/ALK+ patients
ATTLAS: second-line carbo/pem/bev/atezo post-EGFR/ALK TKI → PFS benefit but no OS benefit
ORIENT-31: second-line carbo/pem/bev(biosim)/sintilimab post-EGFR/ALK TKI → PFS benefit but no OS benefit
HARMONi-A: second-line carbo/pem/ivonescimab (PD-1/VEGF) post-EGFR/ALK TKI → PFS benefit but OS data is immature
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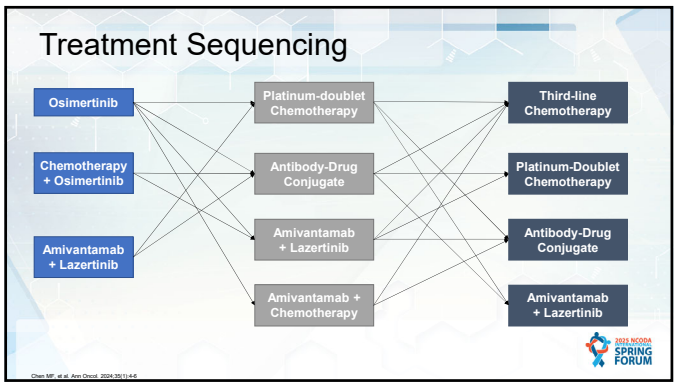
38


Treatment Sequencing
Osimertinib
Chemotherapy + Osimertinib
Amivantamab + Lazertinib
Platinum-doublet Chemotherapy
Antibody-Drug Conjugate
Amivantamab + Lazertinib
Amivantamab + Chemotherapy
Third-line Chemotherapy
Platinum-Doublet Chemotherapy
Antibody-Drug Conjugate
Amivantamab + Lazertinib
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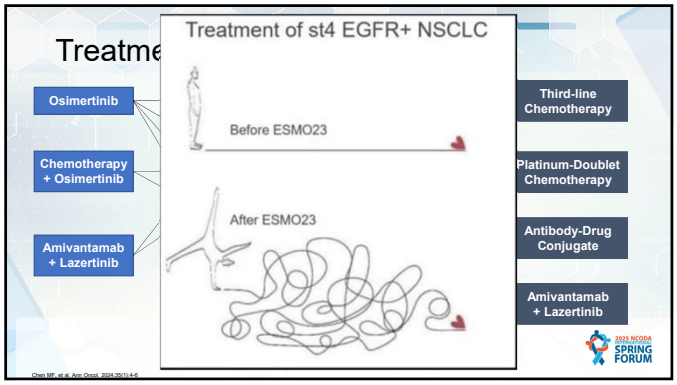
39


Treatme
Treatment of st4 EGFR+ NSCLC
Osimertinib
Chemotherapy + Osimertinib
Amivantamab + Lazertinib
Before ESMO23
After ESMO23
Third-line Chemotherapy
Platinum-Doublet Chemotherapy
Antibody-Drug Conjugate
Amivantamab + Lazertinib
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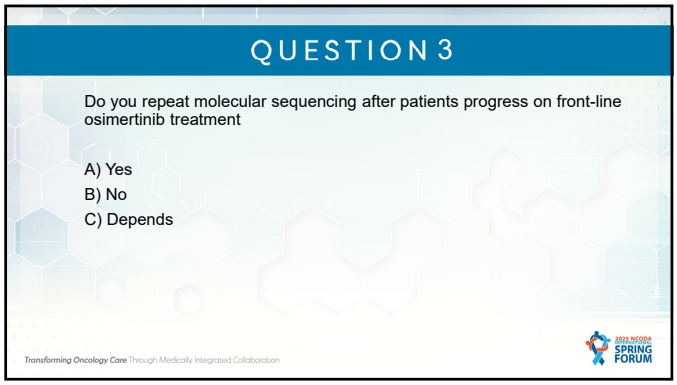
40


QUESTION 3
Do you repeat molecular sequencing after patients progress on front-line osimertinib treatment
A) Yes
B) No
C) Depends
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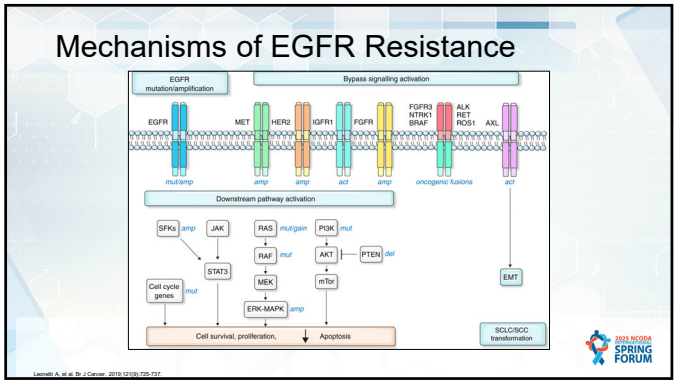
41


Mechanisms of EGFR Resistance
EGFR mutation/amplification
Bypass signalling activation
EGFR
MET
HER2
IGFR1
FGFR
FGFR3 NTRK1 BRAF
ALK RET ROS1
AXL
mut/amp
amp
amp
act
amp
oncogenic fusions
act
Downstream pathway activation
SFKs amp
JAK
STAT3
Cell cycle genes mut
RAS mut/gain
RAF mut
MEK
ERK-MAPK amp
PI3K mut
AKT
PTEN del
mTor
EMT
Cell survival, proliferation,
Apoptosis
SCLC/SCC transformation
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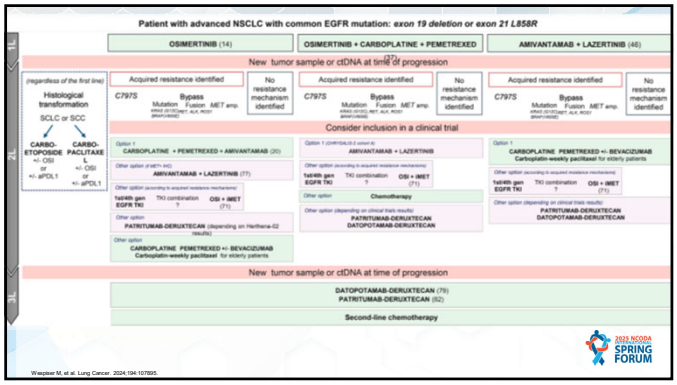
42


Patient with advanced NSCLC with common EGFR mutation: exon 19 deletion or exon 21 L858R
OSIMERTINIB (14)
OSIMERTINIB + CARBOPLATINE + PEMETREXED
AMIVANTAMAB + LAZERTINIB (46)
New tumor sample or ctDNA at time of progression
Acquired resistance identified
No resistance mechanism identified
C797S
Bypass
Mutation
Fusion
MET amp.
Histological transformation
SCLC or SCC
CARBO-ETOPOSIDE +/- OSI or +/- aPDL1
CARBO-PACLITAXEL +/- OSI or +/- aPDL1
Consider inclusion in a clinical trial
CARBOPLATINE + PEMETREXED + AMIVANTAMAB (20)
AMIVANTAMAB + LAZERTINIB (77)
3rd/4th gen EGFR TKI
TKI combination ?
OSI + MET (71)
Chemotherapy
PATRITUMAB-DERUXTECAN (depending on Herthena-02 results)
PATRITUMAB-DERUXTECAN
DATOPOTAMAB-DERUXTECAN
CARBOPLATINE PEMETREXED +/- BEVACIZUMAB
Carboplatin-weekly paclitaxel for elderly patients
New tumor sample or ctDNA at time of progression
DATOPOTAMAB-DERUXTECAN (79)
PATRITUMAB-DERUXTECAN (82)
Second-line chemotherapy
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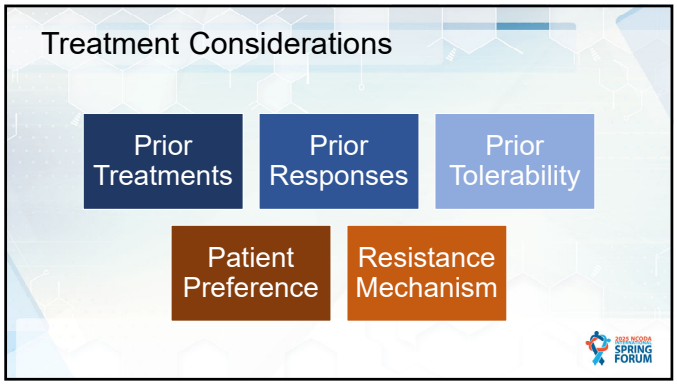
43


Treatment Considerations
Prior Treatments
Prior Responses
Prior Tolerability
Patient Preference
Resistance Mechanism
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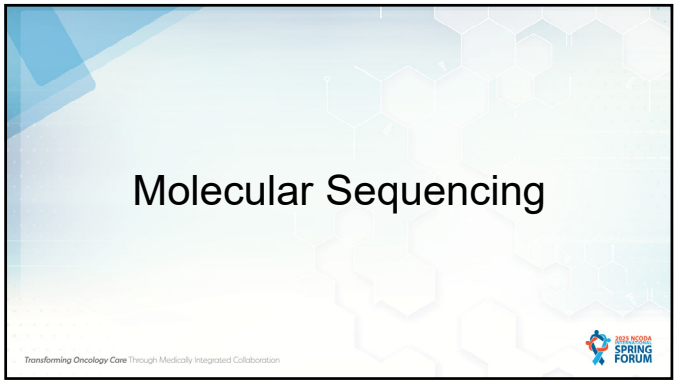
44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45

Testing Considerations

- Who
  - Histology (non-squamous vs squamous)
- How
  - Tissue vs blood (ctDNA)
  - Single-gene vs broad panel
  - DNA vs RNA
- When
  - Non-metastatic
  - Metastatic disease
  - Disease recurrence

46

Sample Considerations

Tissue	Blood (ctDNA)*
Advantages: - Tumor specific - Improved sensitivity Disadvantages: - Longer turnaround time - Invasive biopsy required - Cannot use certain samples (e.g. bone) - Cannot assess tumor heterogeneity	Advantages: - Non-invasive - Shorter turnaround time - Reflects tumor heterogeneity Disadvantages: - Sensitivity varies based on tumor burden - May contain false positives (e.g. CHIP) - Difficulty detecting fusions or amplifications

*unable to determine histologic transformation using ctDNA assay

Hofman P, Cancers (Basel). 2024;16(19):3340.

47

Patient Case

- JR is a 65-year-old male with newly diagnosed NSCLC. Comprehensive molecular sequencing and PD-L1 22C3 IHC revealed the following:
  - PD-L1: 90%
  - TMB: 15 mut/Mb
  - EGFR: A763_Y764insFQEA
  - TP53: P151S
- Are you comfortable selecting a first-line treatment option for this patient?

48

Patient Case

- JR is a 65-year-old male with newly diagnosed NSCLC. Comprehensive molecular sequencing and PD-L1 22C3 IHC revealed the following:
  - PD-L1: 90%
  - TMB: 15 mut/Mb
  - EGFR: A763_Y764insFQEA (exon 20 insertion)
  - TP53: P151S
- Are you comfortable selecting a first-line treatment option for this patient?

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49

Sequencing Results

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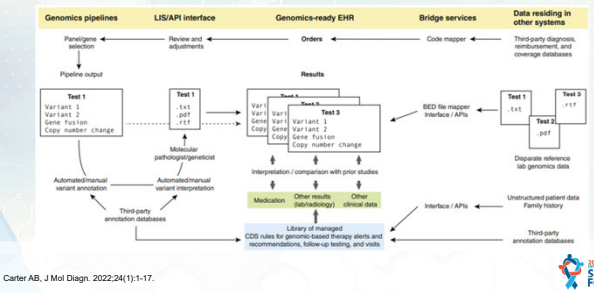
50

EMR Integration



Carter AB, J Mol Diagn. 2022;24(1):1-17.

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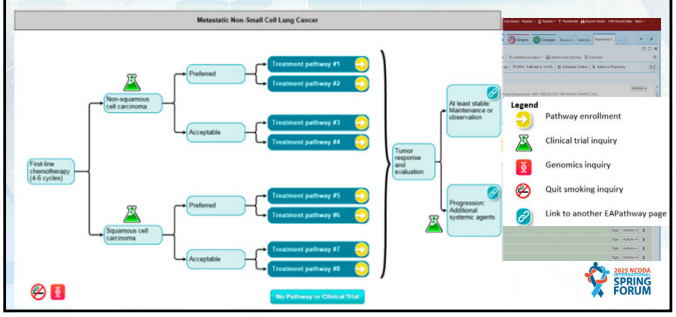
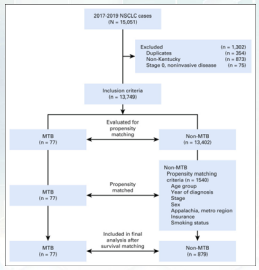
51

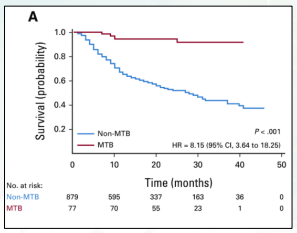
Clinical Decision Support



52

Molecular Tumor Boards





Huang B. JCO Precis Oncol. 2021;5:PO.21.00210

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53

SUMMARY

- Front-line intensification strategies have improved efficacy over osimertinib monotherapy
- Challenges in additional toxicities and complex administration warrant patient centered discussion to select optimal treatment
- Subsequent line therapies should consider prior therapies received and a patient's individual treatment goals
- Integrating molecular sequencing results into existing EMR platforms is challenging, but is essential for selection the optimal treatment
- Clinical decision support tools and molecular tumor boards may assist in selecting the most appropriate biomarker-directed therapies

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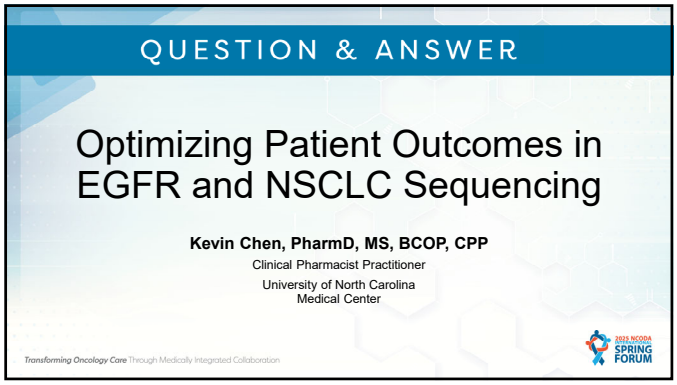
54


QUESTION & ANSWER
Optimizing Patient Outcomes in EGFR and NSCLC Sequencing
Kevin Chen, PharmD, MS, BCOP, CPP
Clinical Pharmacist Practitioner
University of North Carolina Medical Center
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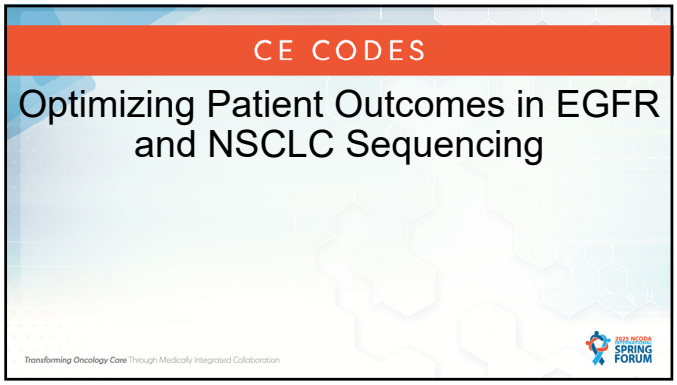
55


CE CODES
Optimizing Patient Outcomes in EGFR and NSCLC Sequencing
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56