NCCN 2025
Lung Cancer Congress

Managing *EGFR*-Positive Non-Small Cell Lung Cancer Across the Treatment Spectrum: A Team-Based Approach

Melina E. Marmarelis, MD
Assistant Professor
Medical Director, Penn Mesothelioma and Pleural Disease Program
Co-Director, Molecular Tumor Board
Faculty, Penn Center for Cancer Care Innovation (PC3I)
Abramson Cancer Center at the University of Pennsylvania

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Agenda

- *EGFR* across the stages
- Metastatic *EGFR*-mutated NSCLC
  - First-line treatment landscape
  - Subsequent treatments
- Special Populations
  - Atypical *EGFR* mutations
  - *EGFR* exon 20 insertions

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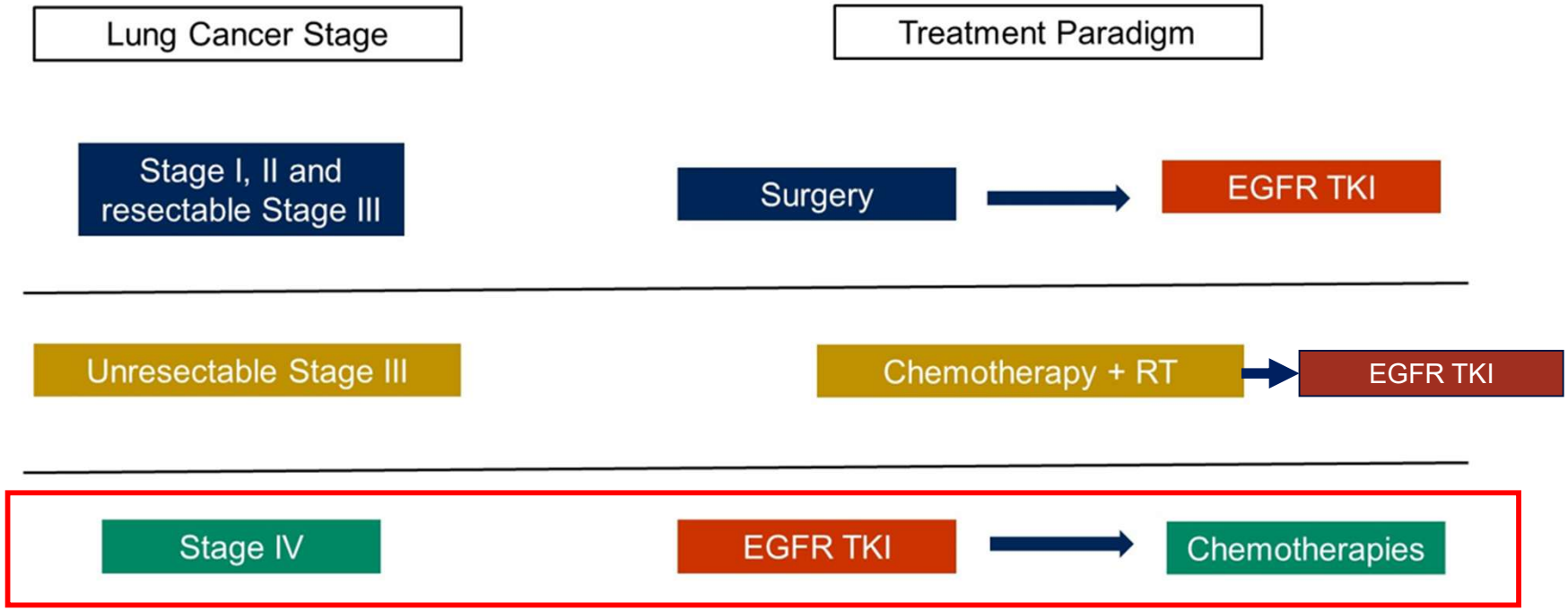
TESTING RESULTS[qq,rr]	
★ Classical Atypical Exon 20ins — *EGFR* exon 19 deletion or L858R mutation positive	NSCL-21
EGFR S768I, L861Q, and/or G719X mutation positive	NSCL-24
EGFR exon 20 insertion mutation positive	NSCL-25
KRAS G12C mutation positive	NSCL-26
ALK gene fusion positive	NSCL-27
ROS1 gene fusion positive	NSCL-30
BRAF V600E mutation positive	NSCL-32
NTRK1/2/3 gene fusion positive	NSCL-33
MET exon 14 skipping mutation positive	NSCL-34
RET gene fusion positive	NSCL-35
ERBB2 (*HER2*) mutation positive	NSCL-36
NRG1 gene fusion positive	NSCL-37
PD-L1 ≥1% and negative for actionable biomarkers above	NSCL-38
PD-L1 <1% and negative for actionable biomarkers above	NSCL-39

Current Landscape of Therapy for EGFR + NSCLC



Adapted from Lecia Sequist's ASCO '24 discussion

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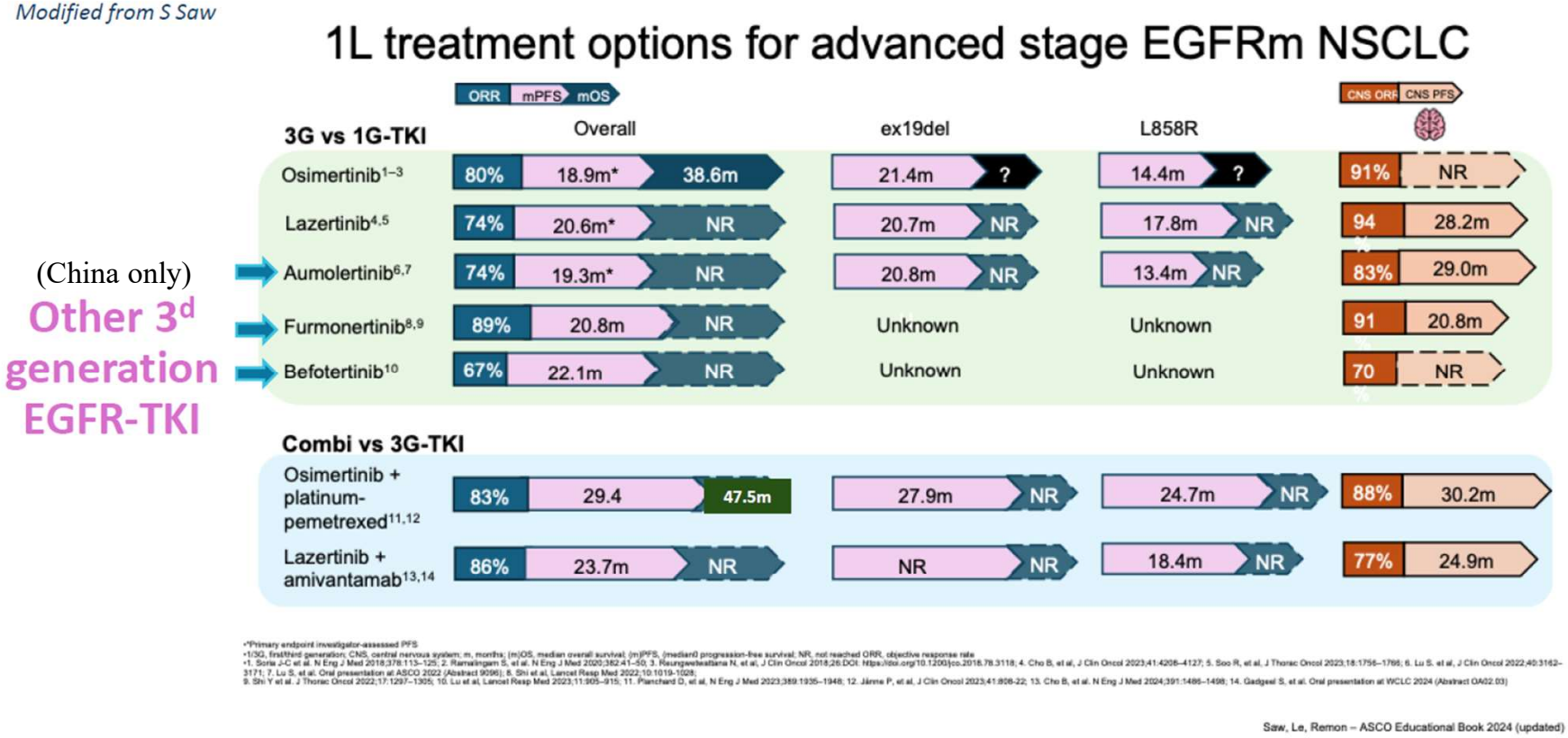
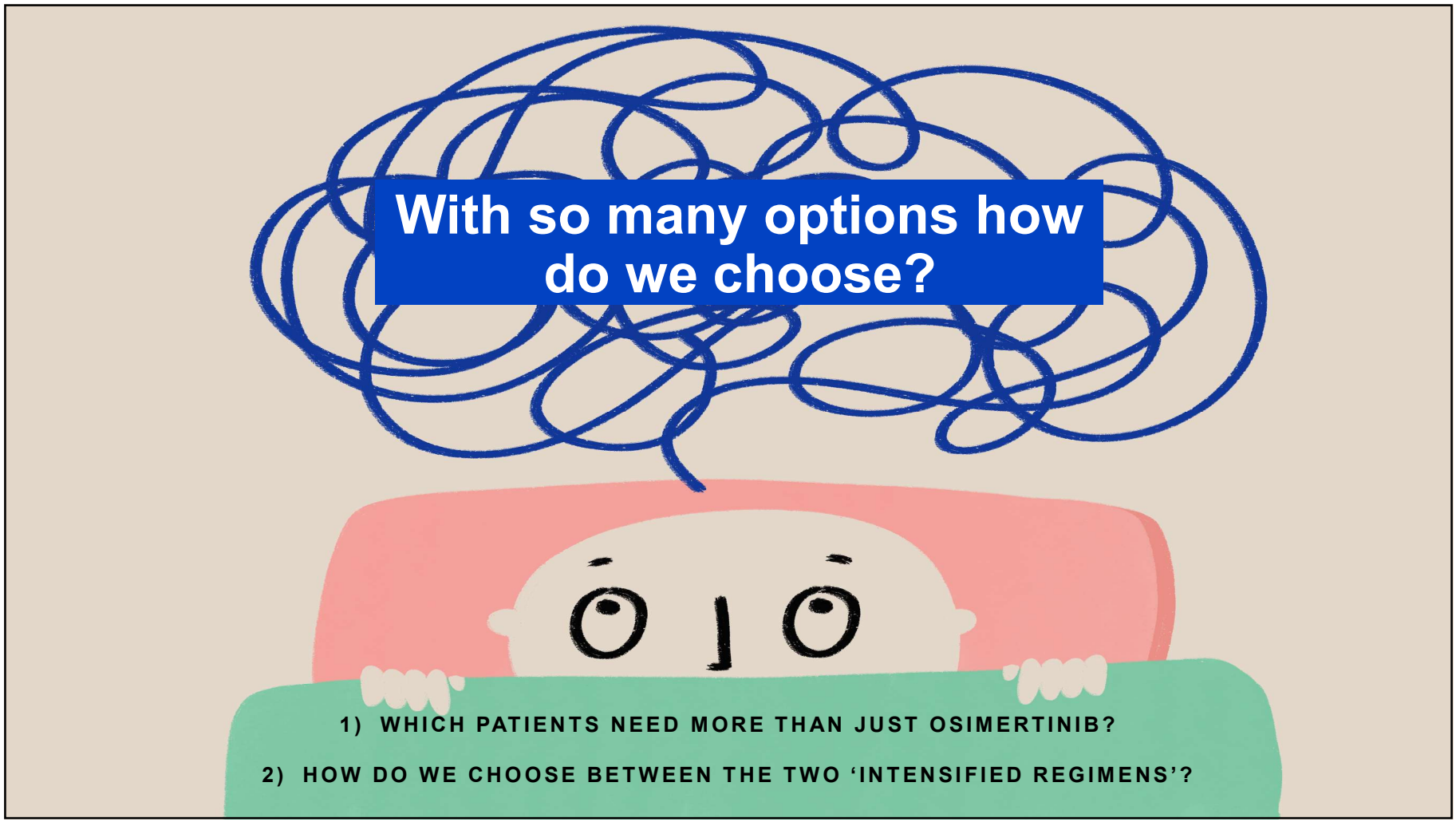
Metastatic *EGFR*m NSCLC

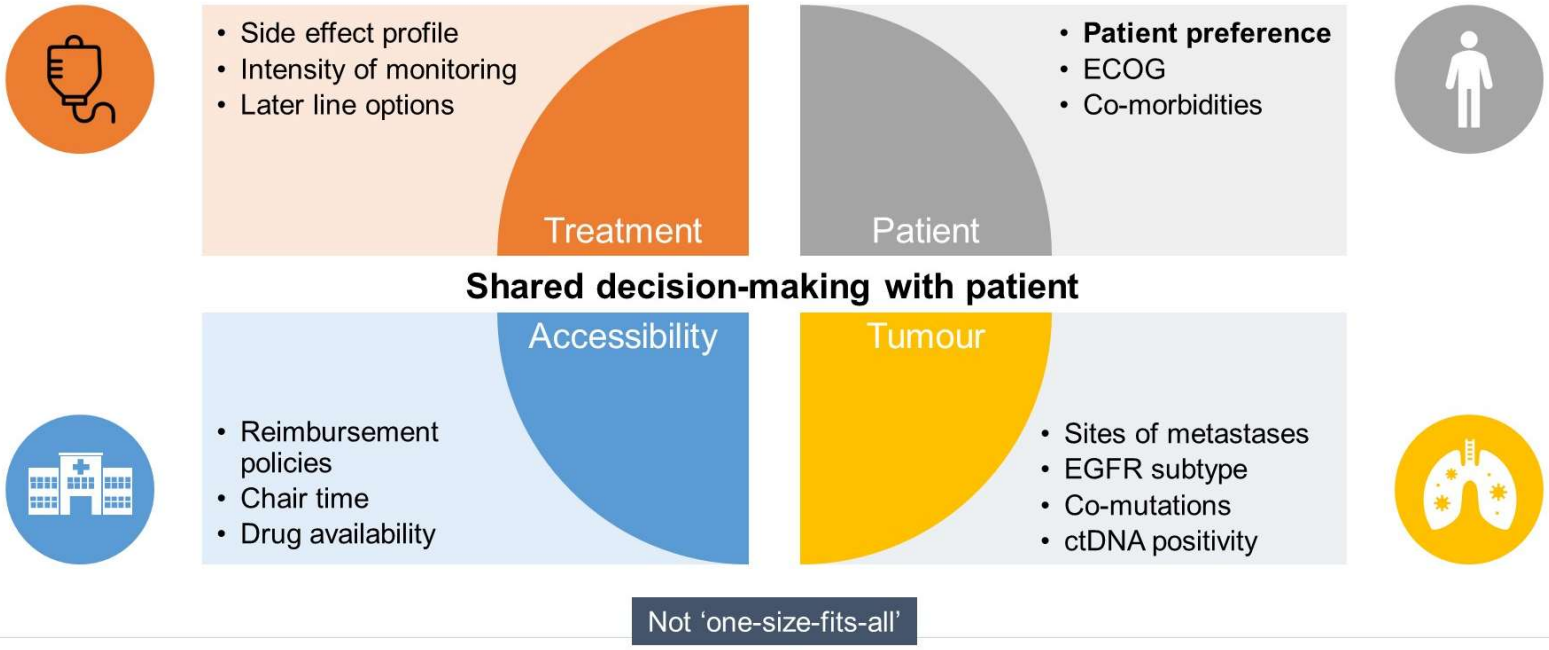
Modified from S Saw



Saw, Le, Remon – ASCO Educational Book 2024 (updated)



*EGFR*m 1L Metastatic: How do we choose?



Adapted from Presentation by Stephanie Saw @ASCO 2024

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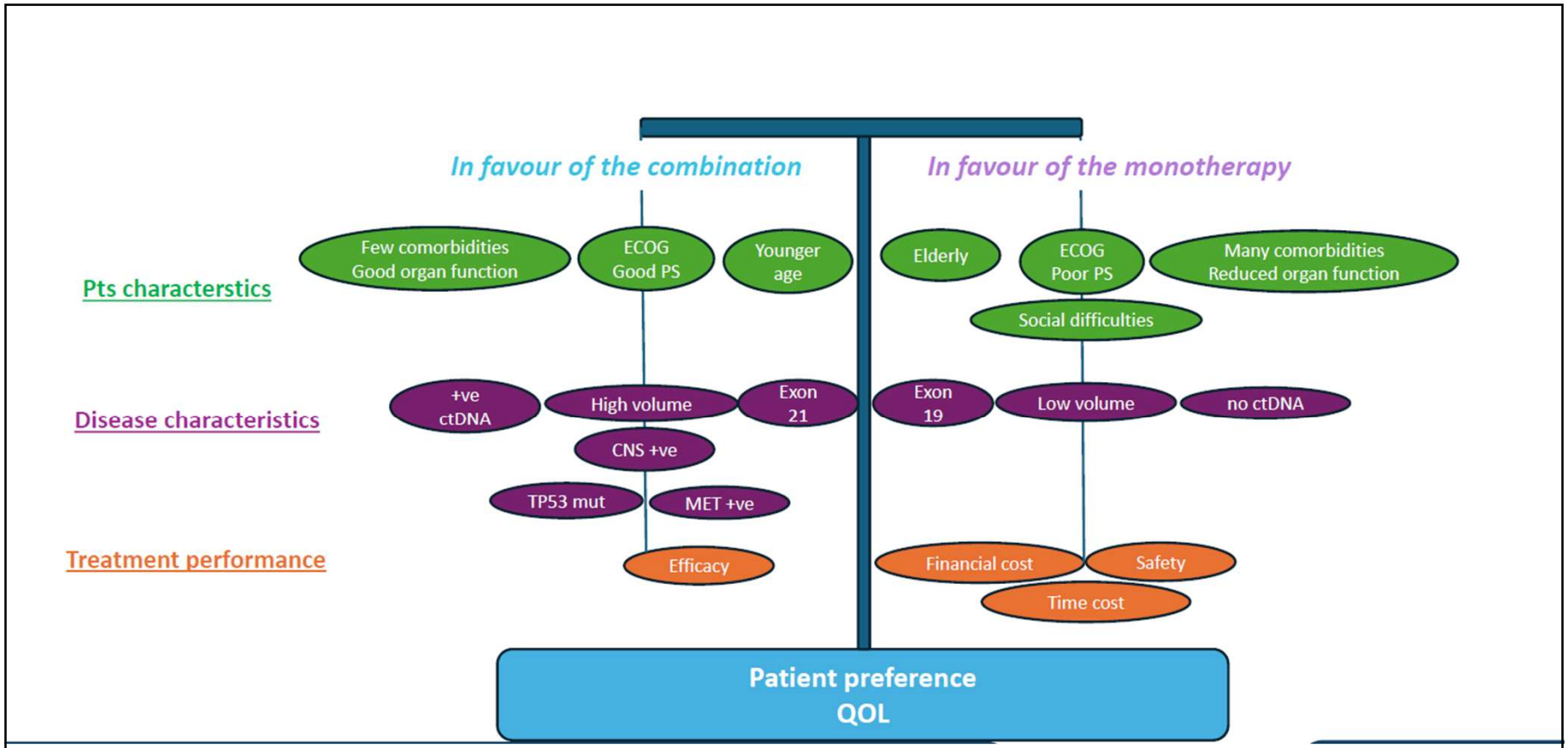

Adapted from Jessica Menis, WCLC 25 presentation

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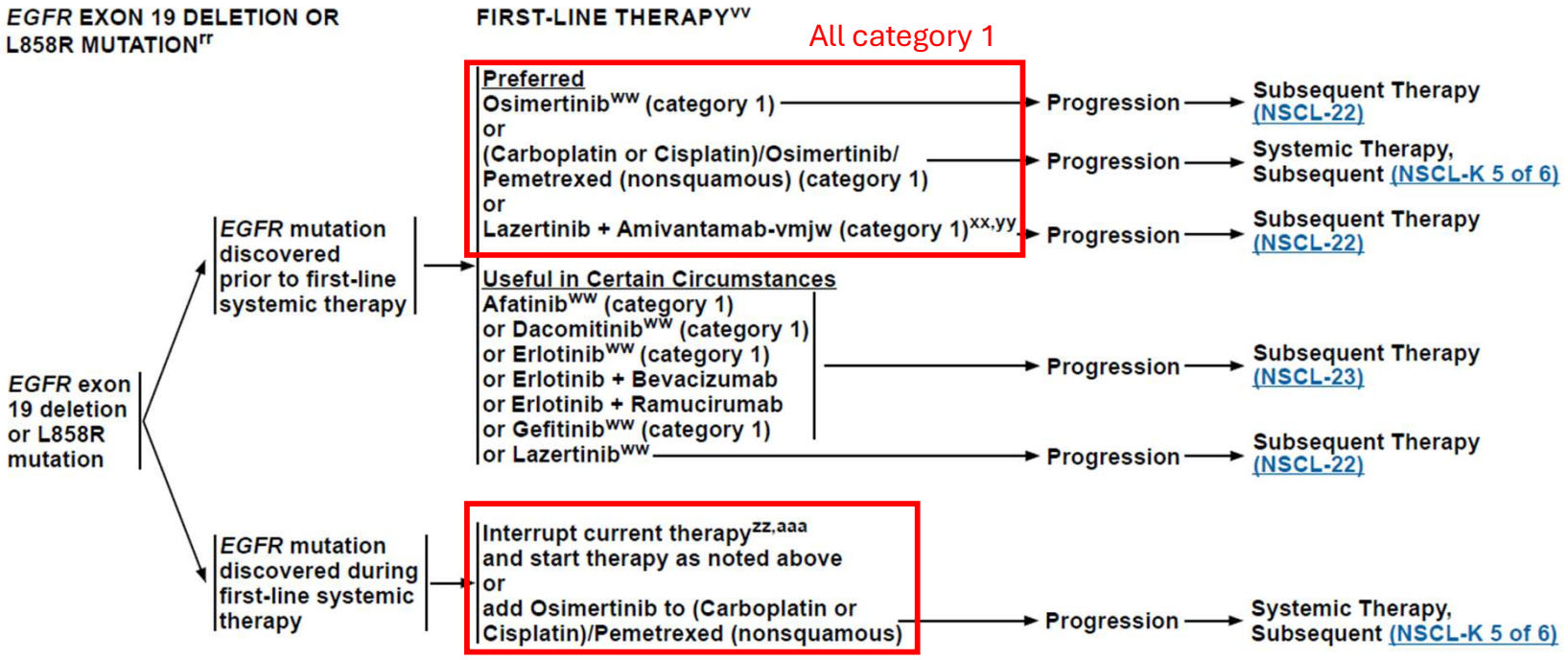
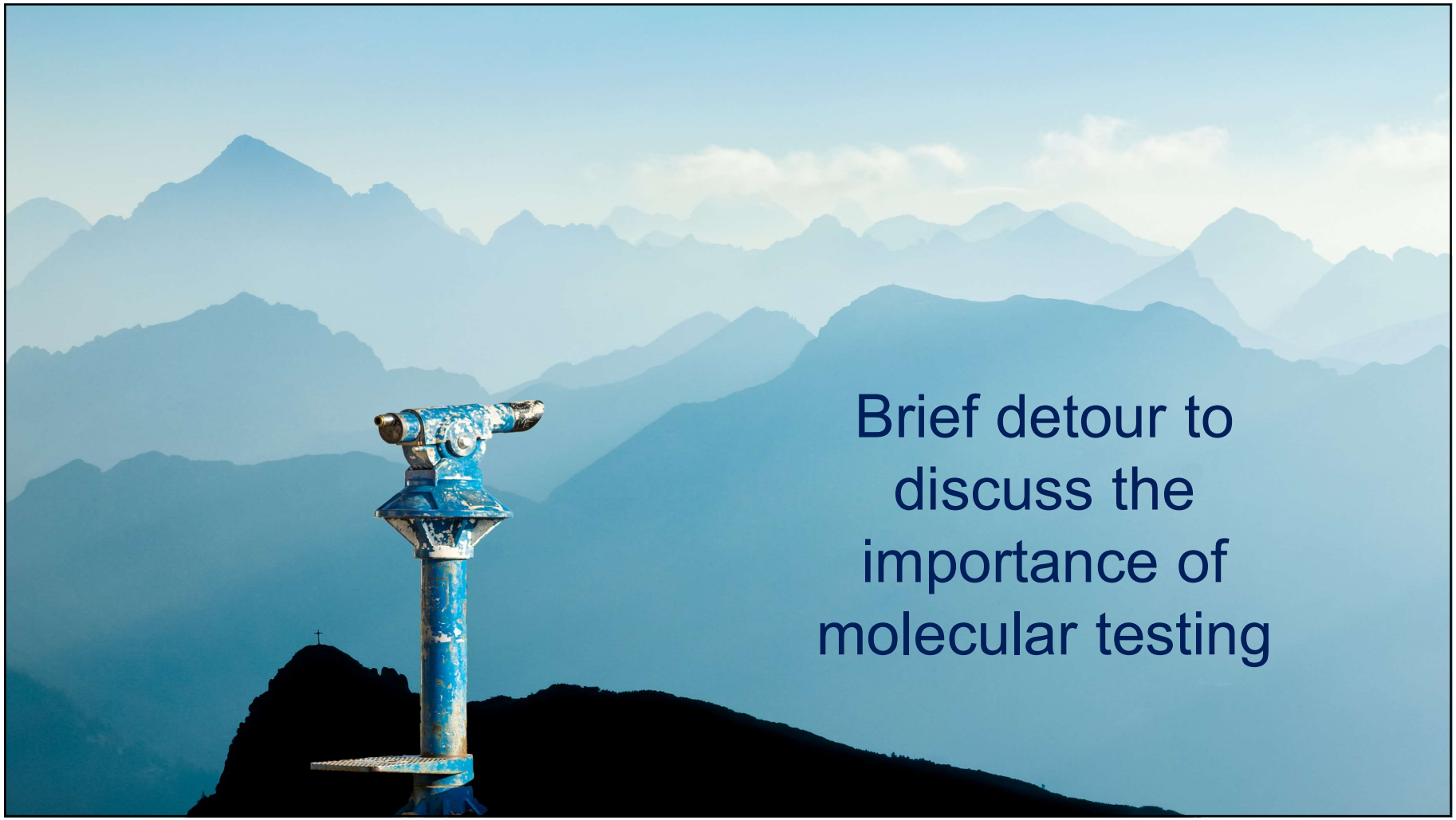
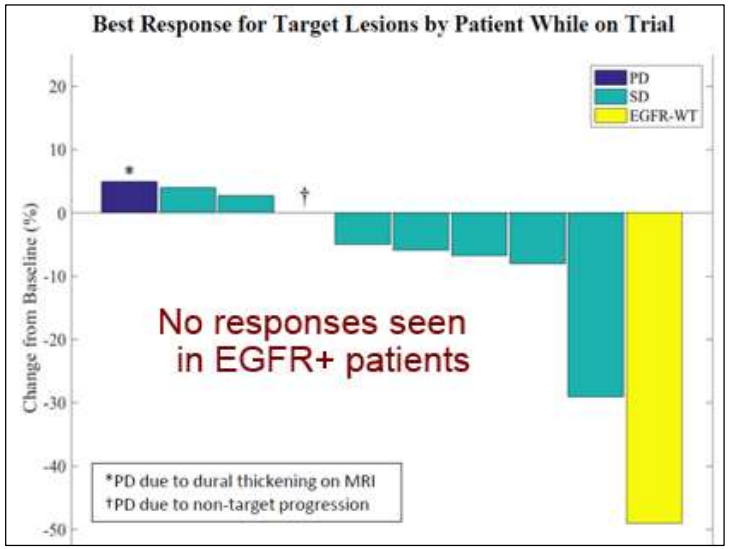


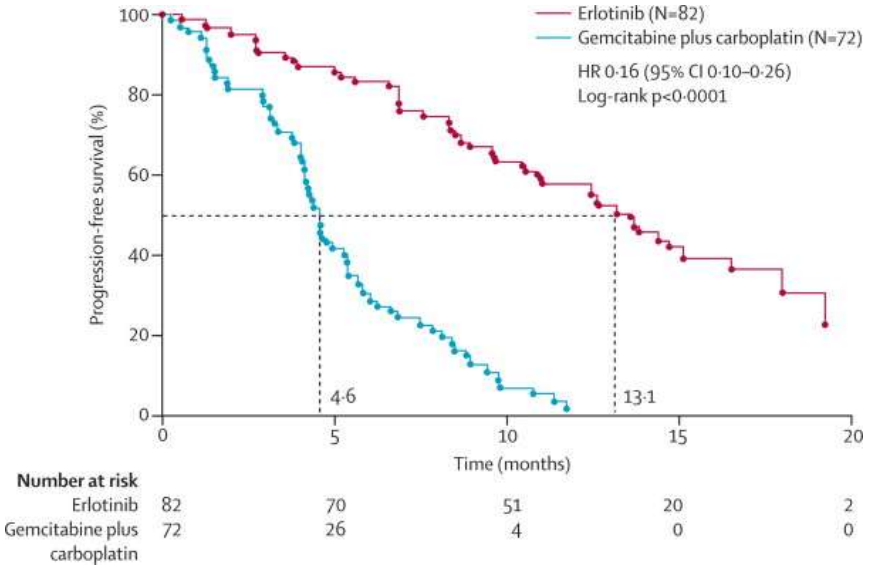
If *EGFR* mutation is found while on 1L, **SWITCH** to EGFR Targeted therapy!



Why is it important to get molecular data?



Front line trial of Pembro monotherapy in *EGFR* MT patients with PD-L1>1%



Targeted EGFR therapy (erlotinib) vs chemotherapy in NSCLC patients with *EGFR* mutations

Lisberg et al, JTO 2018; Zhou Lancet Oncology, 2011

Is molecular testing also important in locally advanced NSCLC?

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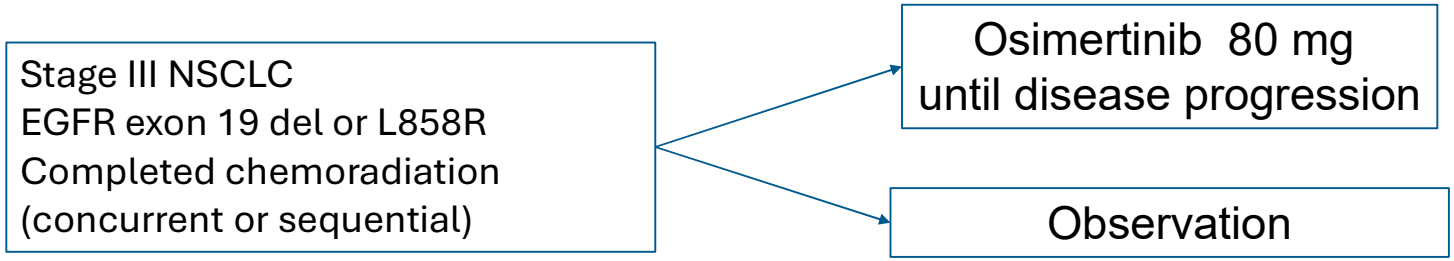
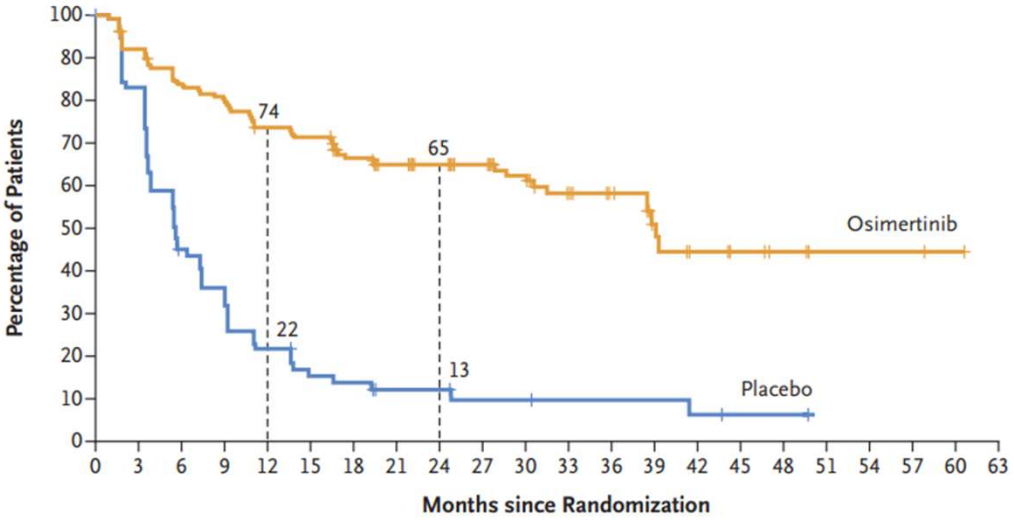
Unresectable
Stage III EGFR mutant NSCLC



Primary endpoint: PFS
Secondary endpoints: OS, time to CNS progression

Lu et al, NEJM 2024

Osimertinib improves PFS in Patients with Stage III NSCLC previously treated with chemoRT



No. at Risk																					
Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Median Progression-free Survival (95% CI)	*mo*
Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

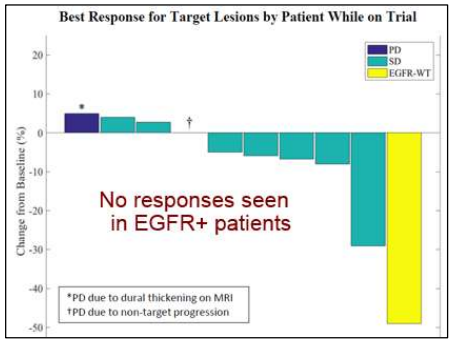
Hazard ratio for disease progression or death, 0.16 (95% CI, 0.10–0.24)
P<0.001

PFS in favor of Osi
OS data is immature

Figure 1. Progression-free Survival According to Blinded Independent Central Review.

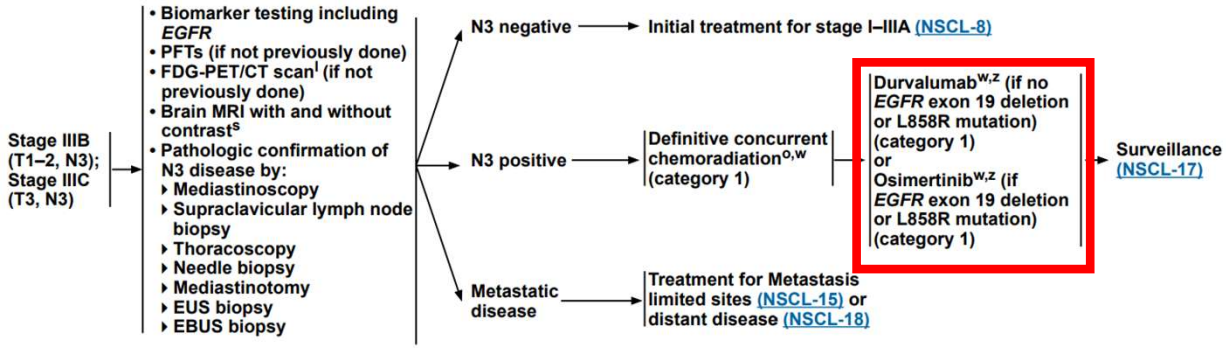
Lu et al, NEJM 2024

Immunotherapy alone is not effective in EGFR+ NSCLC



Front line trial of Pembro monotherapy in *EGFR* MT patients with PD-L1>1%

Indefinite Adjuvant Osimertinib after Chemoradiation in Stage III EGFR+ NSCLC



Use Osimertinib in place of Durvalumab after chemoradiation.

Lisberg et al, JTO 2018; Zhou Lancet Oncology, 2011

What about the second-line setting?

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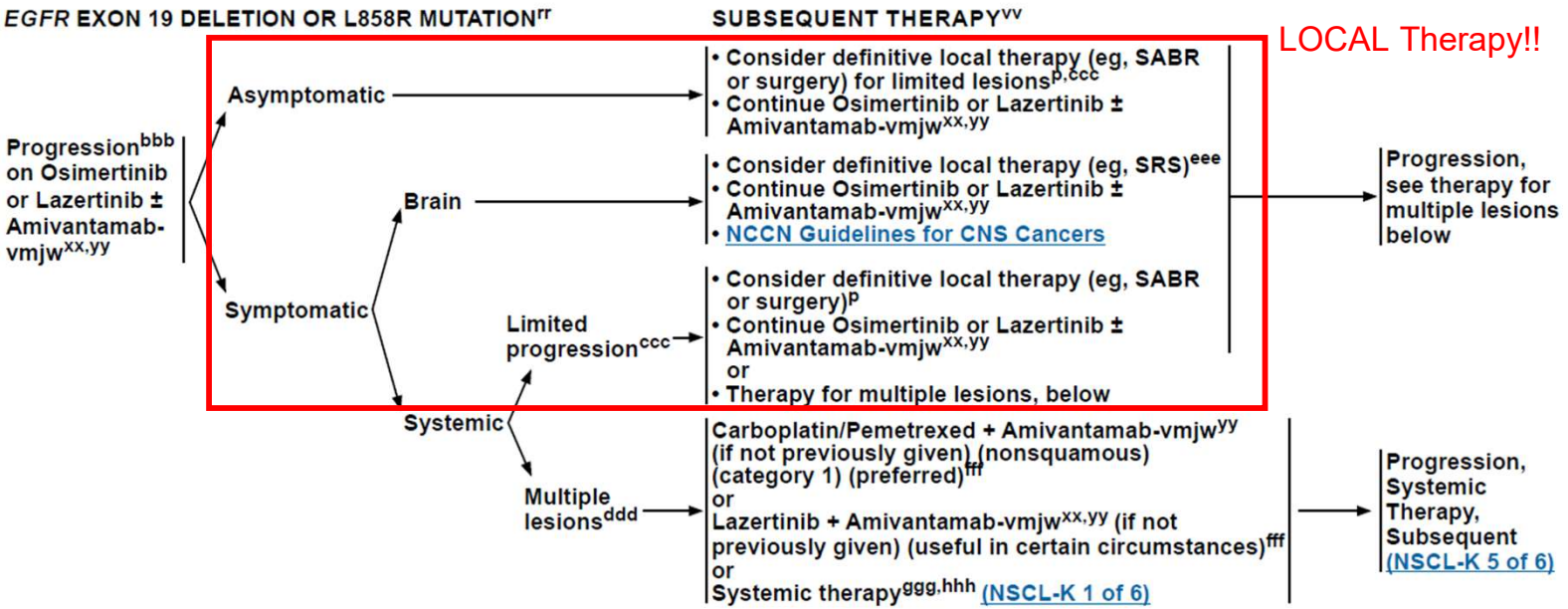

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Investigating Resistance to *EGFR*-targeted therapy

- Liquid biopsy and tissue biopsy for NGS ☑
- Send tissue biopsy for MET FISH (or IHC) ☑
- Target resistance mechanism
- If no targetable resistance mechanism, then
  - Chemotherapy (with continued EGFR-targeted therapy)
  - Datopotamab deruxtecan
- If SCLC transformation
  - Carboplatin, etoposide
  - Consider continuing osimertinib if CNS disease

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Atypical *EGFR* Mutations

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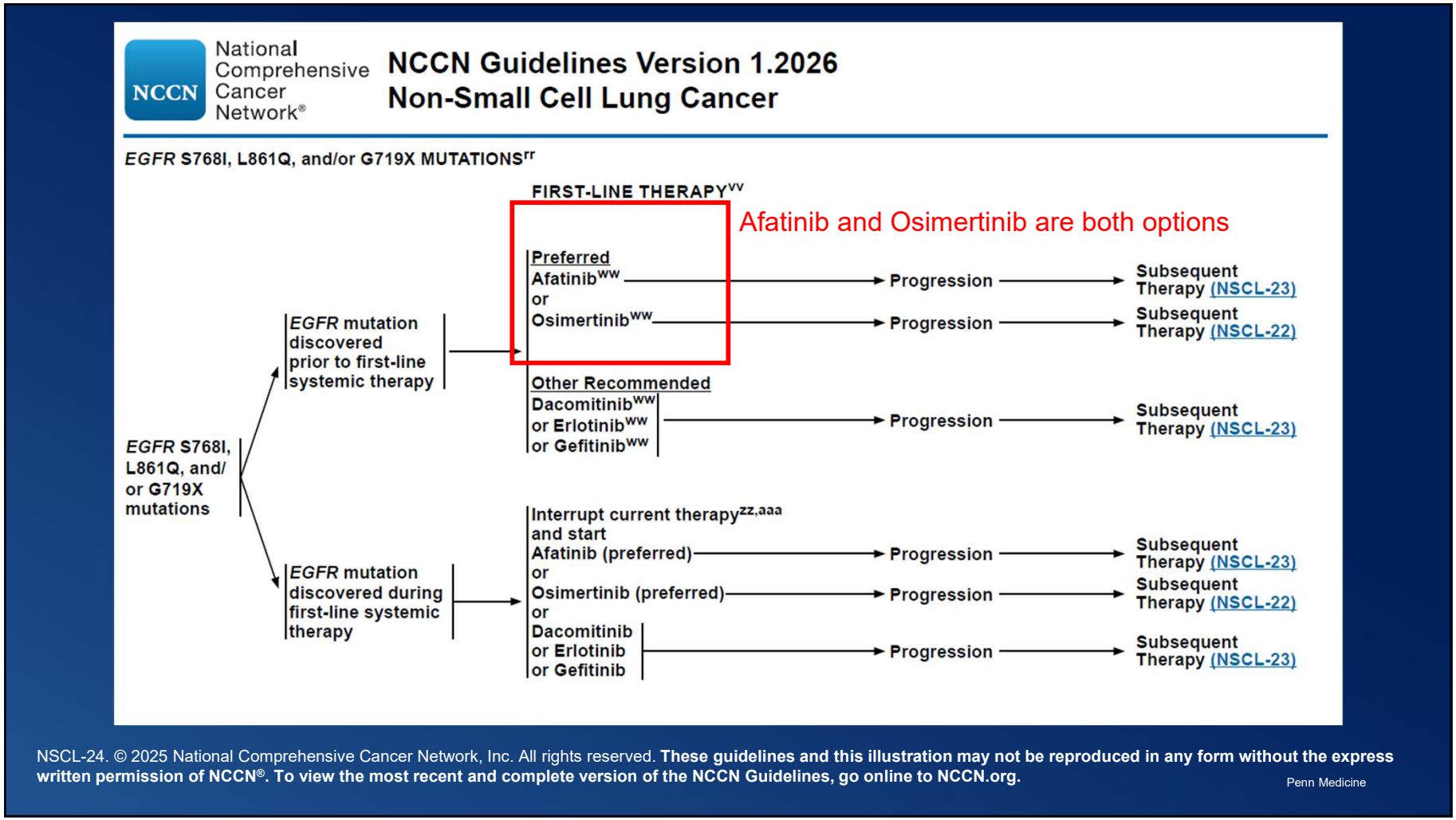

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Type of Atypical *EGFR*m may matter

G719X (40%) **S768I (10%)** **L861Q (15%)**

G719X

- mTTD: **afatinib** vs osi (20.3m vs 9.4, **p=0.047**)
- mOS: **afatinib** vs osi (42.3m vs 17.4, **p=0.043**)

S768I

- mTTD: afatinib vs osi (7.0 vs 1.0; p=0.317)
- mOS: afatinib vs osi (19.4 vs 12.4; p=0.620)

L861Q

- mTTD: afatinib vs **osi** (1.3 vs 7.2; **p=0.004**)
- mOS: afatinib vs osi (12.7 vs 18.9, p=0.215)

Barsouk, Lung Cancer, 2025

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EGFR exon 20 insertions

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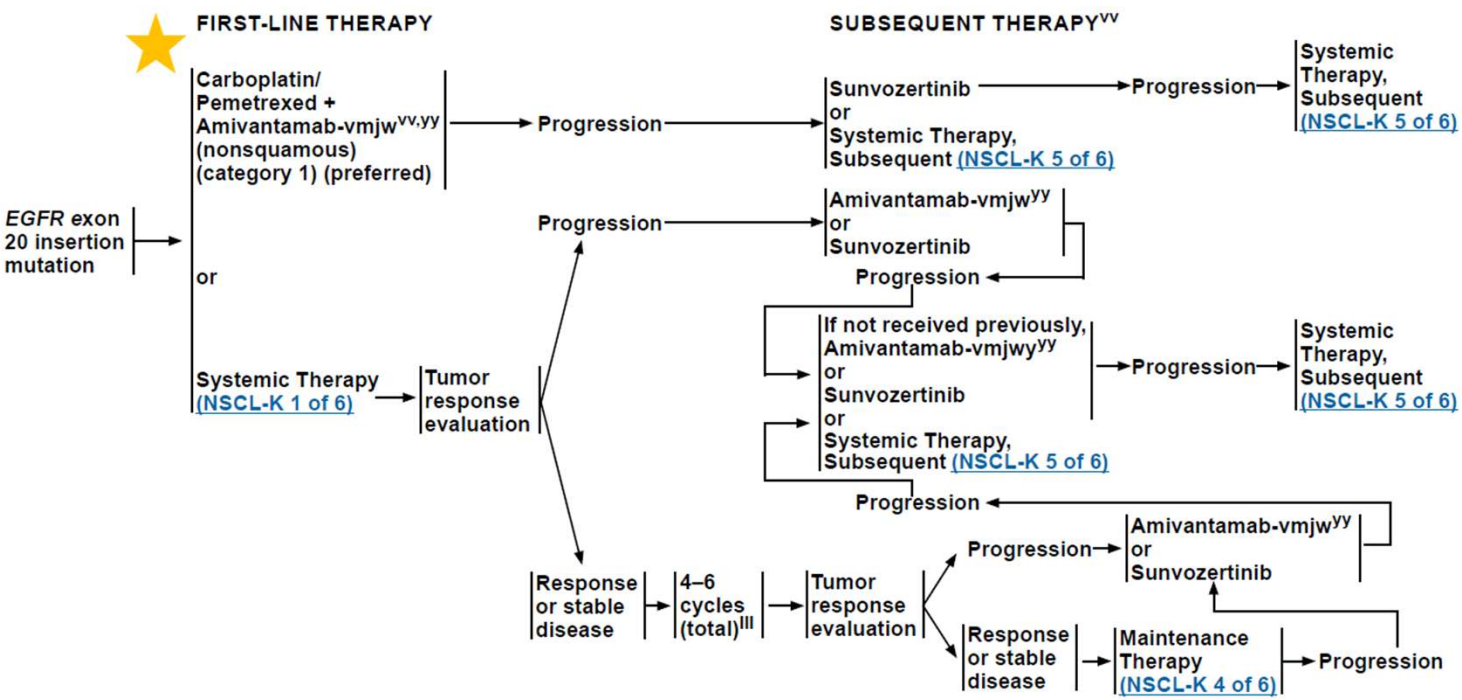
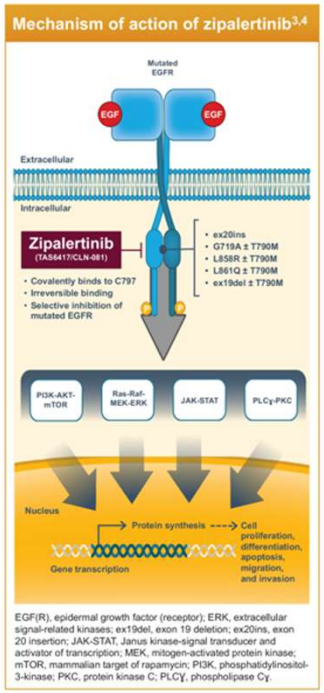


EGFR exon 20 insertion

- Amivantamab + Chemo is the clear first-line option currently
- Additional agents on the horizon

Approved but not available in US…
Sunvozertinib, Presented by Dr. Yang @ASCO '24

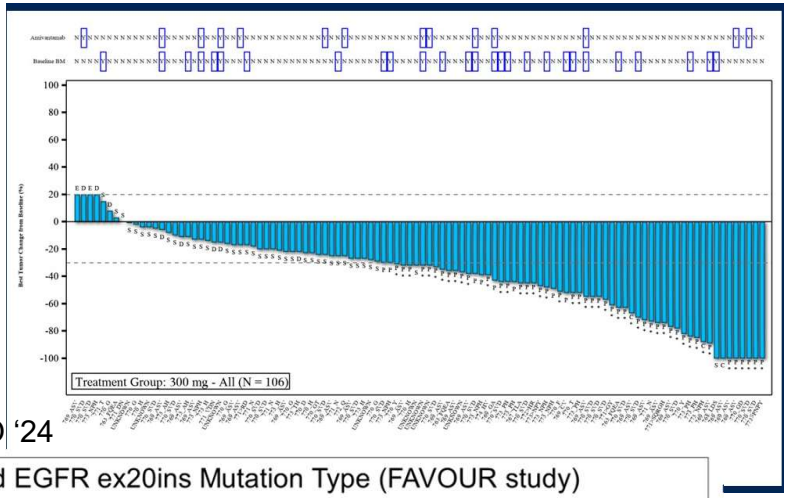


Zipalertinib, Presented by Dr. Yu @ASCO '24

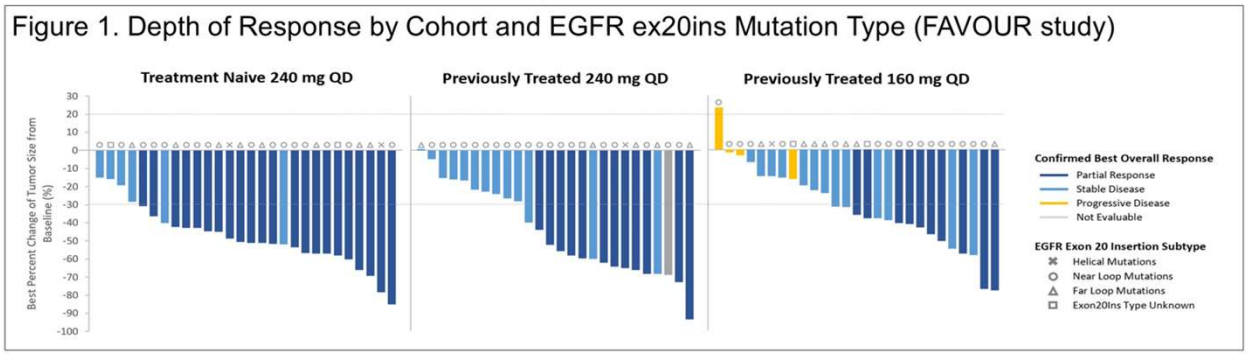
Zipalertinib 100 mg orally twice daily

Cohort A[a]	Cohort B[a]	Cohort C	Cohort D[a]
Patients with *EGFR* ex20ins mutations who have progressed on or after first-line platinum-based chemotherapy and prior therapy targeting ex20ins mutations (administered together or separately) for advanced disease	Patients with *EGFR* ex20ins mutations who have not received prior treatment for advanced disease	Patients with ex20ins, other uncommon single or compound *EGFR* mutations, and active brain metastases (including LMD) and who may or may not have received prior treatment for advanced disease	Patients harboring other, uncommon, non-ex20ins, single or compound *EGFR* mutations who have progressed on or after standard systemic therapy

[a]Patients with brain metastases must be neurologically stable.
EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertions; LMD, leptomeningeal disease.



Firmonertinib, Presented by Dr. Spira @ASCO '24

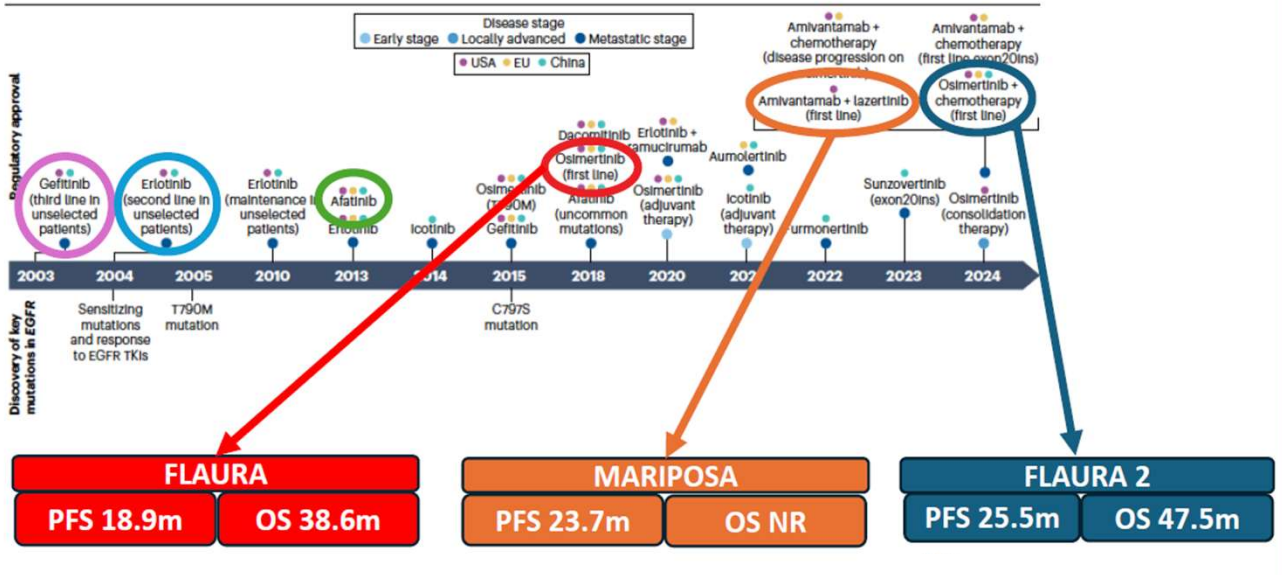


Waterfall plot was based on patients with at least one tumor assessment post baseline;
Near-loop region: A767-P772; far-loop region: H773-C775; Helical region: E762-M766

We are making Progress!!!!!

Changing treatment scenario of EGFR common

Trial	TKi	mOS
IPASS	Gefitinib	21.6m
NEJ002	Gefitinib	27.7m
WJTOG 3405	Gefitinib	34.8m
EURTAC	Erlotinib	19.3m
OPTIMAL	Erlotinib	22.8m
LL3	Afatinib	28.2m
LL6	Afatinib	23.1m



Thank you

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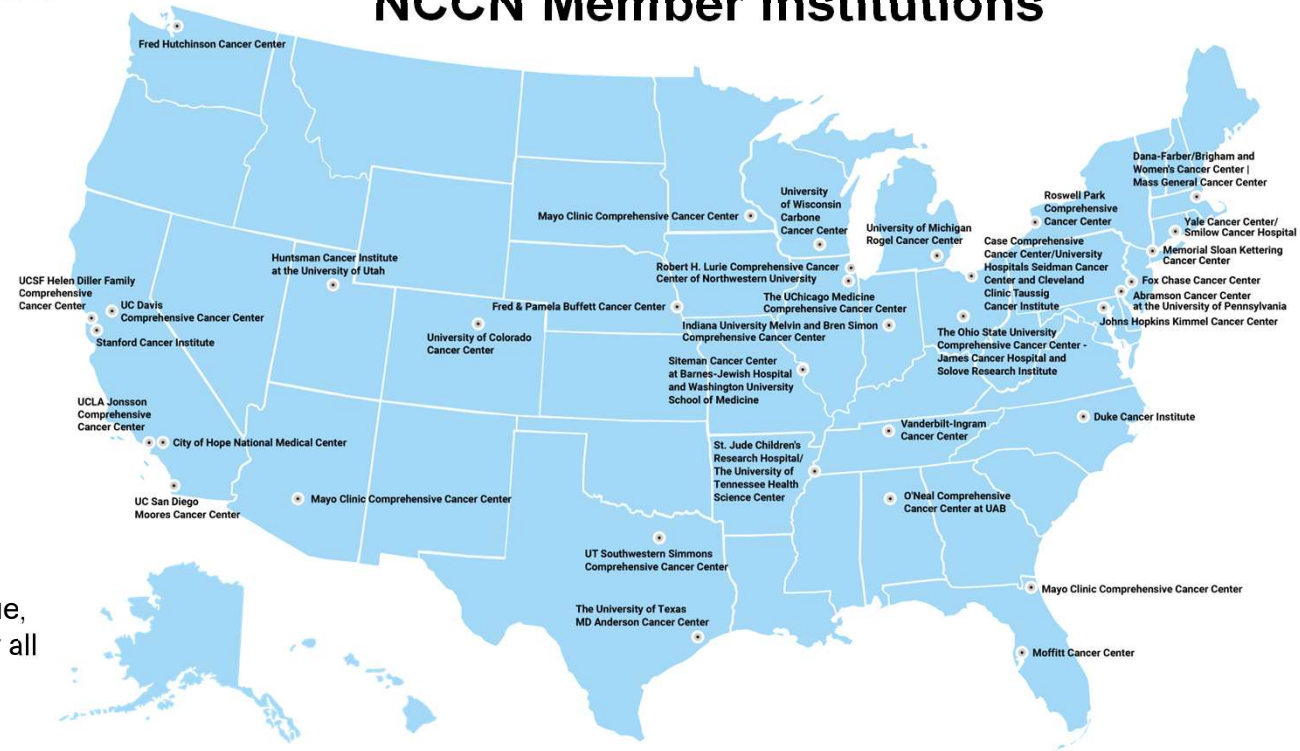

Who We Are

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

Our Mission

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

Our Vision

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

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