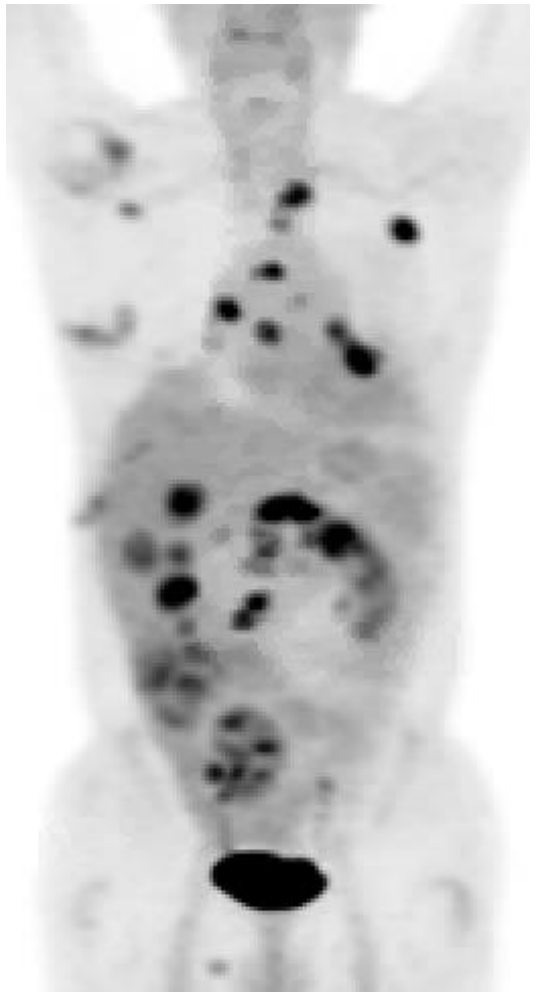
Case Session 2A: *EGFR*-Mutated Lung Cancer (Advanced Stage)

Case*

- A 65-year-old man never smoker presents with worsening cough and shortness of breath
- PET-CT showing a LLL primary with hypermetabolic lymphadenopathy in the hilum and mediastinum
- Widespread bone and liver metastases are also noted
- MRI brain with innumerable sub-cm brain metastases
- The patient has no CNS symptoms and Zubrod PS=1
- Biopsy of the primary lung lesion shows lung adenocarcinoma (TTF1+)
- The patient is stage IVB (pT3N3M1C) NSCLC-adenocarcinoma
- PD-L1 TPS = 90%
- Molecular testing: EGFR L858R + p53 and RB1 co-mutations



*Cases may have been modified for educational purposes

Question

Tissue and plasma NGS are both sent and they both show an EGFR L858R mutation with p53 and RB1 co-mutations.

Question 1: What would you initiate as 1L treatment for Stage IVB NSCLC-adenocarcinoma never-smoker PD-L1 90% (22C3) with EGFR L858R mutation/p53/RB1 co-mutations with sub-cm asymptomatic brain metastases? (Assuming all available)

1. **Osimertinib alone**
2. **Carboplatin/pemetrexed/osimertinib (FLAURA2)**
3. **Osimertinib + bevacizumab**
4. **WBRT + osimertinib concurrently**
5. **WBRT followed by osimertinib**

FLAURA2 Phase III Study Design

Safety run-in period (N=30)
Published in ESMO Open, 2021[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

Stratification by:

- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

Randomization 1:1 (N=557)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†

Osimertinib 80 mg (QD)

Follow-up:

- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

Janne et al WCLC 2023

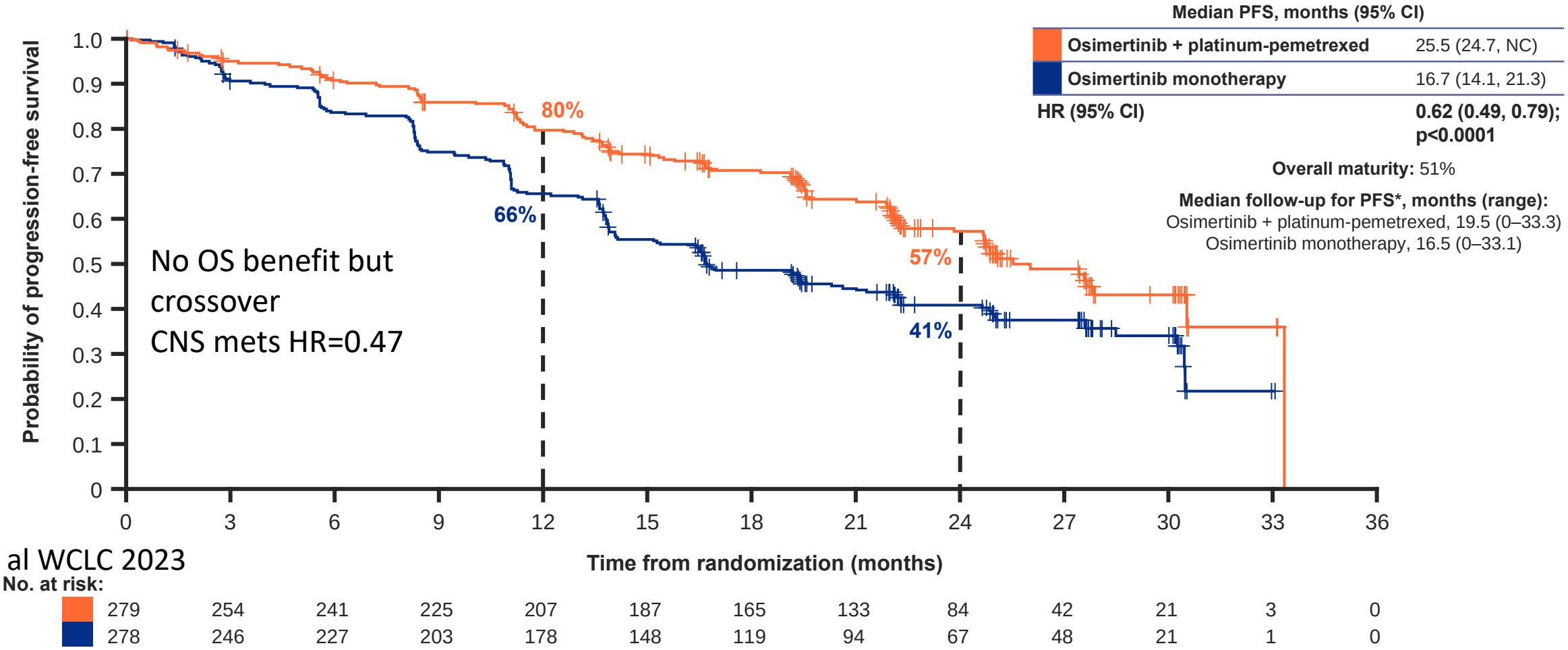
1. Planchard et al. ESMO Open 2021;6:100271

*Not requiring steroids for at least two weeks; †Pemetrexed maintenance continued until a discontinuation criterion was met; ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received, and safety analyses in the safety analysis set, defined as all randomized patients who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level

AE, adverse event; AUC, area under curve; BICR, blinded independent central review; CNS, central nervous system; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DoR, duration of response; EGFRm, epidermal growth factor receptor-mutated; EGFR-TKI, EGFR-tyrosine kinase inhibitor; Ex19del, exon 19 deletion; HR, hazard ratio; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; QD, once-daily; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO PS, World Health Organization performance status

PFS per Investigator

- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



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Data cut-off: 03 April 2023
*In all patients
CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

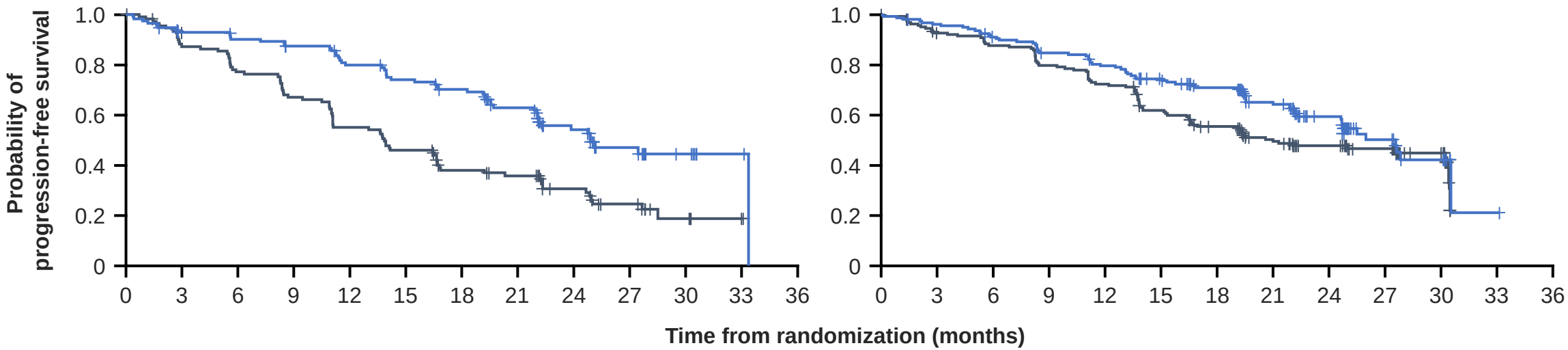
PFS per investigator with / without CNS metastases at baseline*

With CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	24.9 (22.0, NC)
Osimertinib monotherapy	13.8 (11.0, 16.7)
HR (95% CI)	**0.47 (0.33, 0.66)**

Without CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	27.6 (24.7, NC)
Osimertinib monotherapy	21.0 (16.7, 30.5)
HR (95% CI)	**0.75 (0.55, 1.03)**



No. at risk:

	116	101	98	93	84	77	70	58	34	19	8	2	0		163	153	143	132	123	110	95	75	50	23	13	1	0
	110	95	84	73	60	50	37	32	21	13	5	1	0		168	151	143	130	118	98	82	62	46	35	16	0	0

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MARIPOSA: Phase 3 Study Design

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

Stratification Factors

- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases[a] (yes or no)

Serial brain MRIs were required for all patients[a]

2:2:1 Randomization (N=1074)

- **Amivantamab + Lazertinib** (n=429; open-label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks
Lazertinib: 240 mg daily
Osimertinib: 80 mg daily

Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:

- **Amivantamab + lazertinib** vs **osimertinib**

Secondary endpoints of amivantamab + lazertinib vs osimertinib:

- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

[a]Baseline brain MRI was required for all patients and performed ≤28 days prior to randomization; patients who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis. Extracranial tumor assessments were conducted every 8 weeks for the first 30 months and then every 12 weeks until disease progression is confirmed by BICR.

[b]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS.

[c]These secondary endpoints (symptomatic and intracranial PFS) will be presented at a future congress.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

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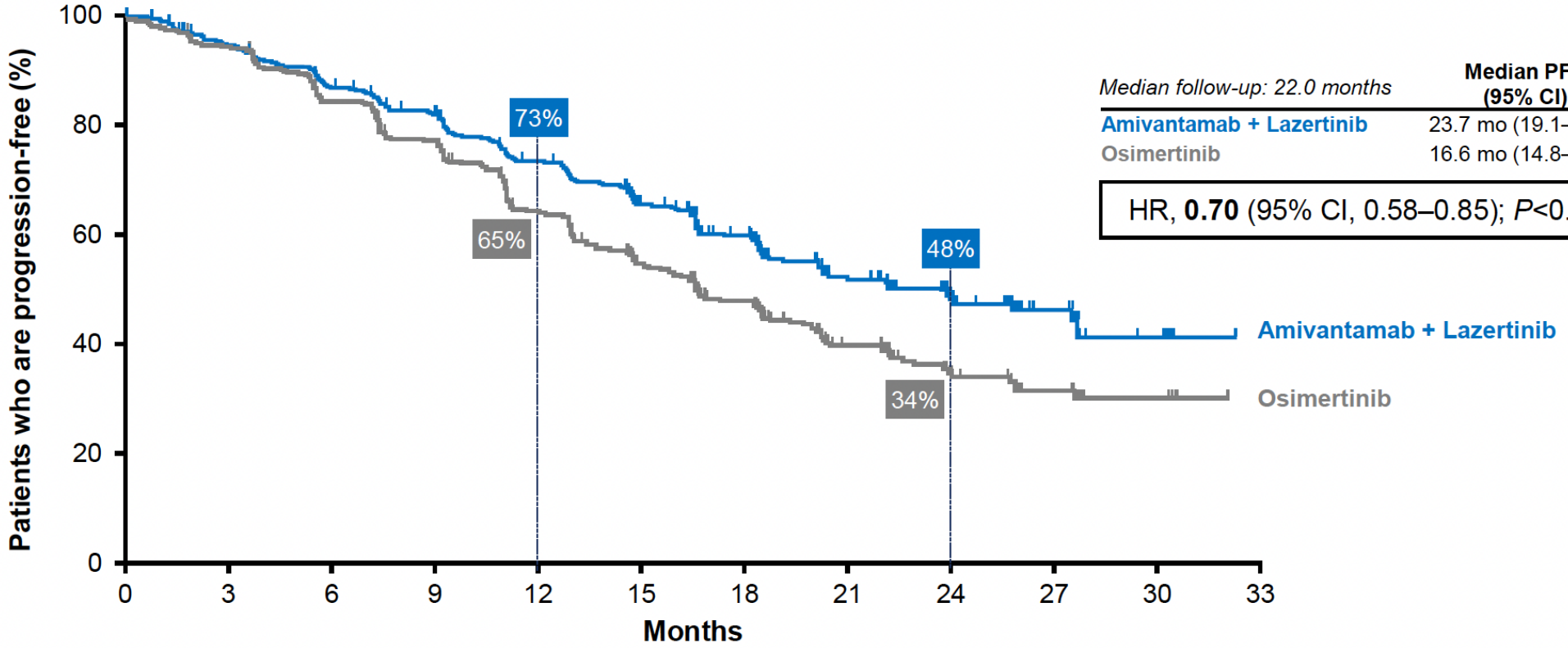
Primary Endpoint: PFS by BICR

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



Median follow-up: 22.0 months	**Median PFS (95% CI)**
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

No. at risk												
Amivantamab + Lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

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[a]At time of the prespecified final PFS analysis, there were a total of 444 PFS events in the amivantamab + lazertinib and osimertinib arms combined.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

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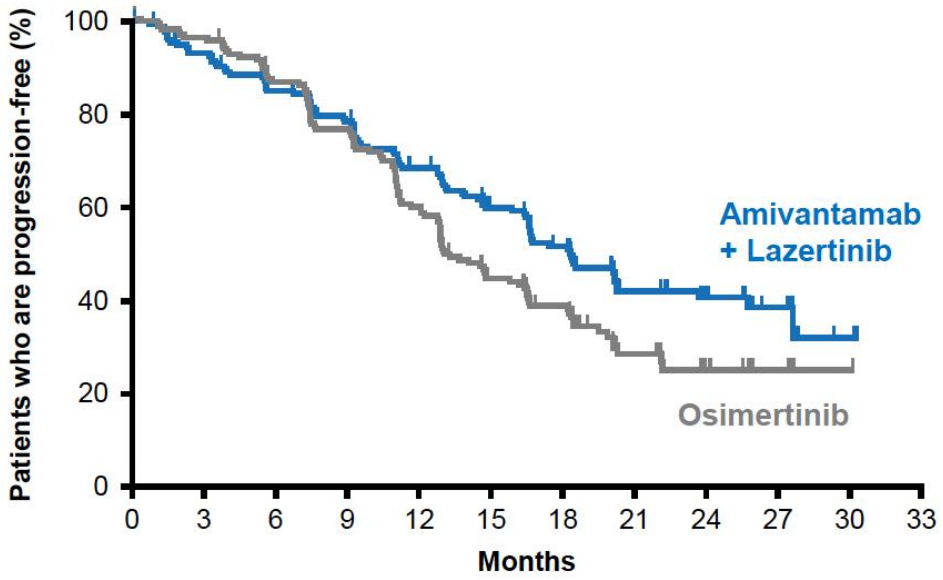
Consistent PFS (BICR) Benefit With or Without Brain Metastases

With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

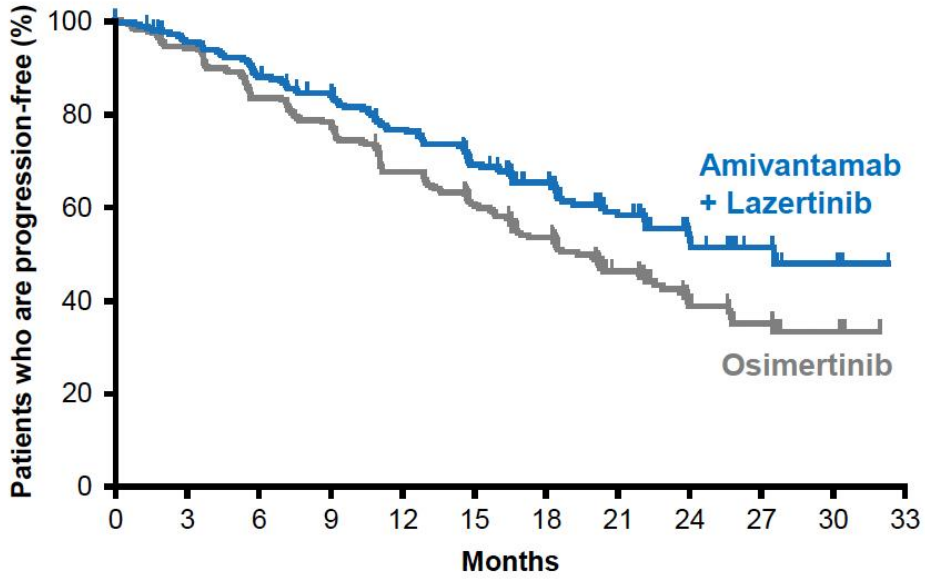
HR, **0.69** (95% CI, 0.53–0.92)



No. at risk												
ivantamab + Lazertinib	178	162	146	134	115	92	71	34	24	12	3	0
Osimertinib	172	164	146	126	95	64	47	21	11	6	1	0

Without History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	27.5 mo (22.1–NE)
Osimertinib	19.9 mo (16.6–22.9)

HR, **0.69** (95% CI, 0.53–0.89)



No. at risk												
Amivantamab + Lazertinib	251	229	211	198	176	152	123	72	36	21	5	0
Osimertinib	257	240	212	199	171	141	113	69	37	22	9	0

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BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; PFS, progression-free survival.

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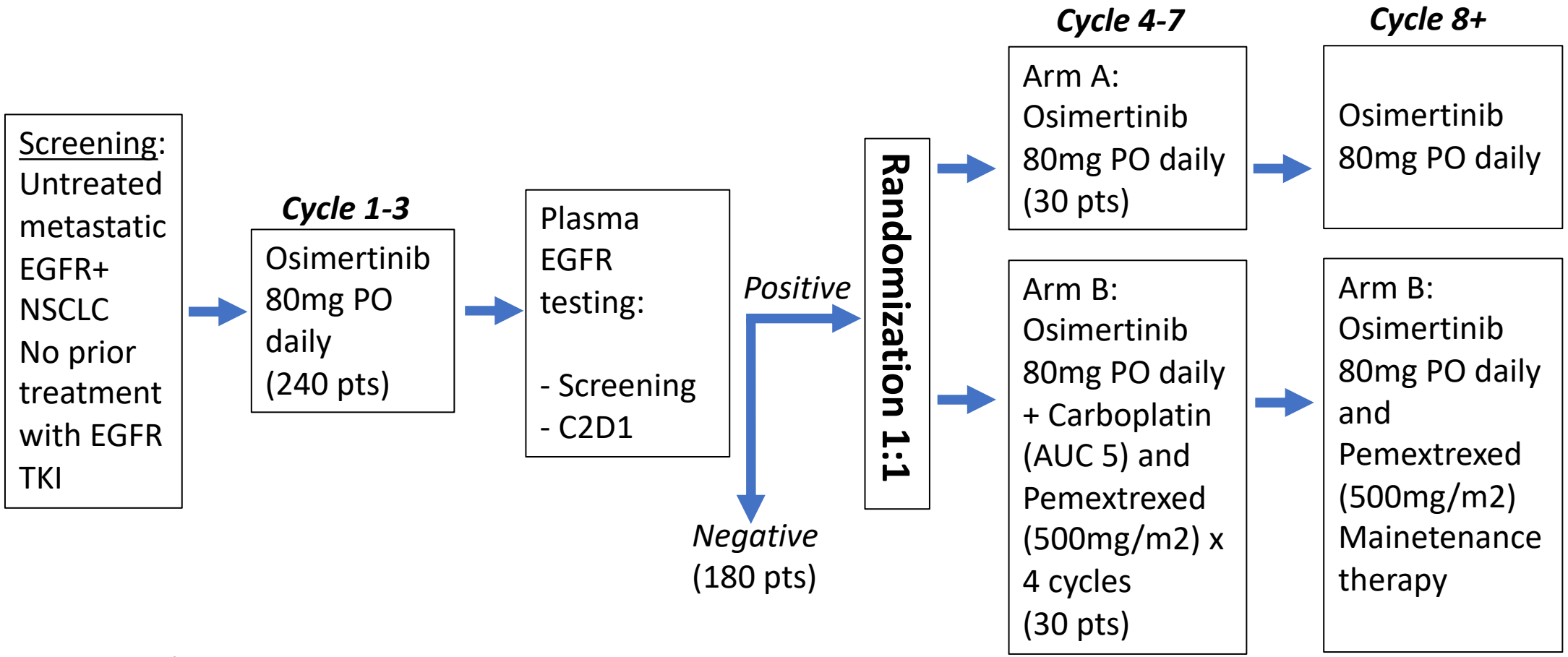
Who are the bad actors?

- ctDNA positive on treatment
- Co-mutations p53/RB1, RBM10
- CNS metastases
- Tumor volume/disease burden?

Shedders Trial



PI: Helena Yu, MD

Trial	Treatment	PFS (Months)	OS	Adverse Events of Interest
FLAURA	Osimertinib vs. gefitinib/erlotinib	18.9 vs. 10.2, P<0.001	38.6 vs. 30.8 months, p=0.046	
FLAURA2	Carbo/Pem/Osi vs. Osi	25.5 vs. 16.8, P<0.001	Immature HR=0.9	Chemo side effects
MARIPOSA	lazertinib/amivantamab vs. osi vs lazertinib	23.7 vs. 17, p<0.001 (lazertinib 18.5)	Immature HR, 0.80 (95% CI, 0.61 1.05); P =0.11	infusion reaction,VTE (37% vs. 9%), rash

Soria et al NEJM 2018, Ramalingam et al NEJM 2020, Janne et al. WCLC 2023, Cho et al. ESMO 2023

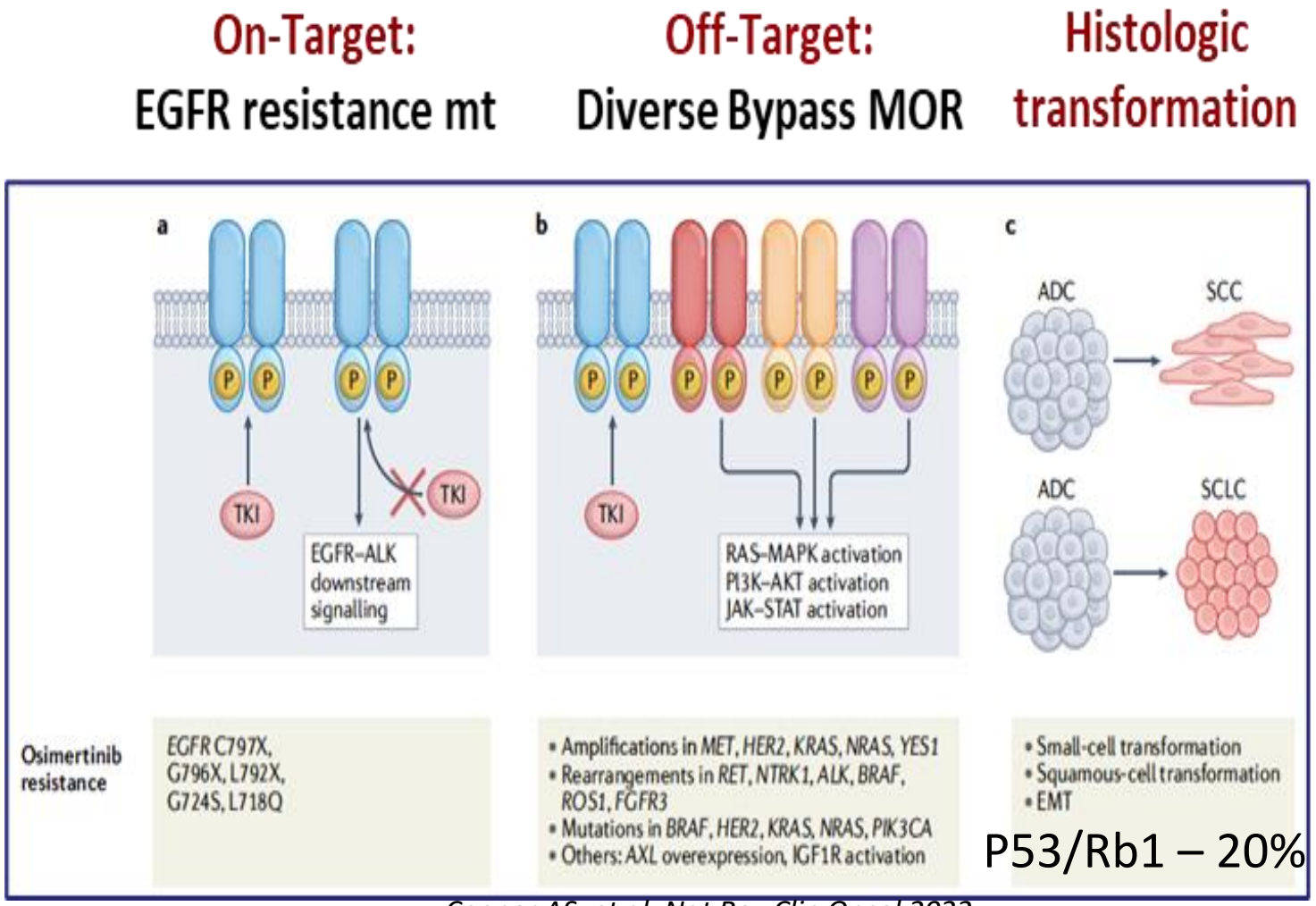
Question

The patient is initiated on osimertinib with an initial response and resolution of brain metastases. 12 months later the patient develops diffuse progressive disease in liver, lung and lymph nodes with continued resolution of brain metastases.

Question 2: What would you do next in this patient with EGFR L858R/p53mut/RB1mut lung adenocarcinoma?

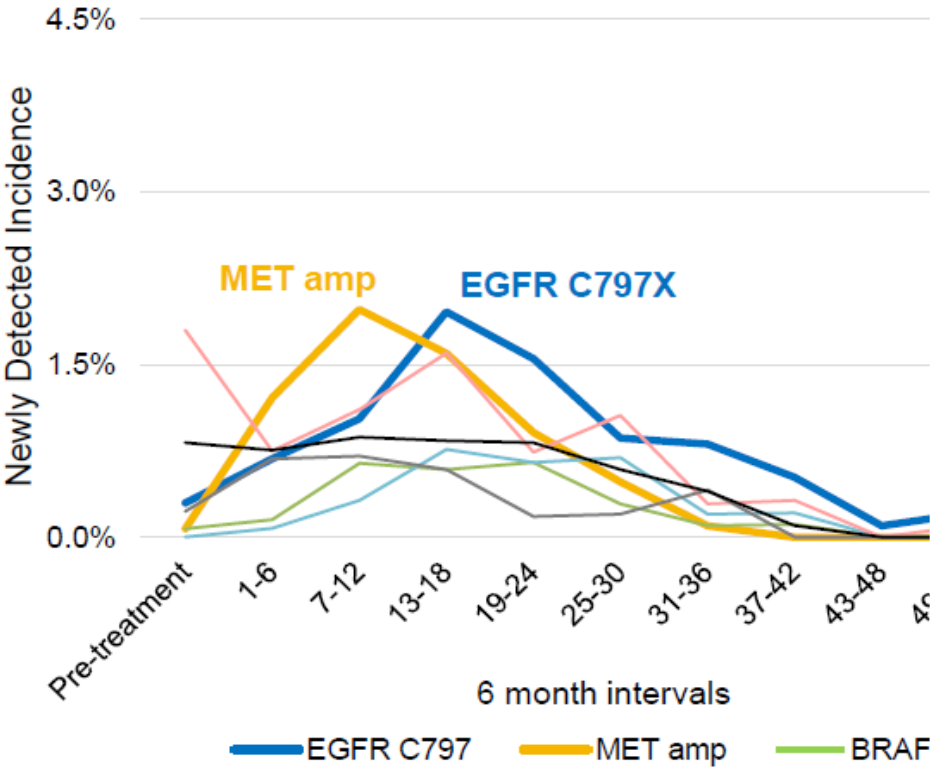
1. Check plasma ctDNA
2. Send both plasma ctDNA and tissue for NGS
3. Send only tissue for NGS (do not send plasma ctDNA)
4. Proceed to next line of treatment without blood or tissue biopsy

Mechanisms of Osimertinib Resistance



P53/Rb1 – 20%

Cooper AS, et al, Nat Rev Clin Oncol 2022



Presented by S. Ramalingam WCLC 2022

Question

In view of PD on osimertinib, you decide to perform repeat tissue biopsy. It shows mainly small cell lung cancer with a residual component of adenocarcinoma.

NGS continues to show EGFR L858R, with an increase in VAF of p53 mutation/RB1. No detectable molecular resistance mechanisms such as secondary EGFR mutations (C797S)

He has diffuse PD on osimertinib

Question 3: What would you do next for systemic treatment? (assuming all available)

1. **Add carboplatin and pemetrexed to osimertinib**
2. **Carboplatin + etoposide only**
3. **Carboplatin + etoposide + osimertinib**
4. **Carboplatin + etoposide + atezolizumab (or durvalumab)**
5. **Carboplatin + etoposide + atezolizumab + osimertinib**

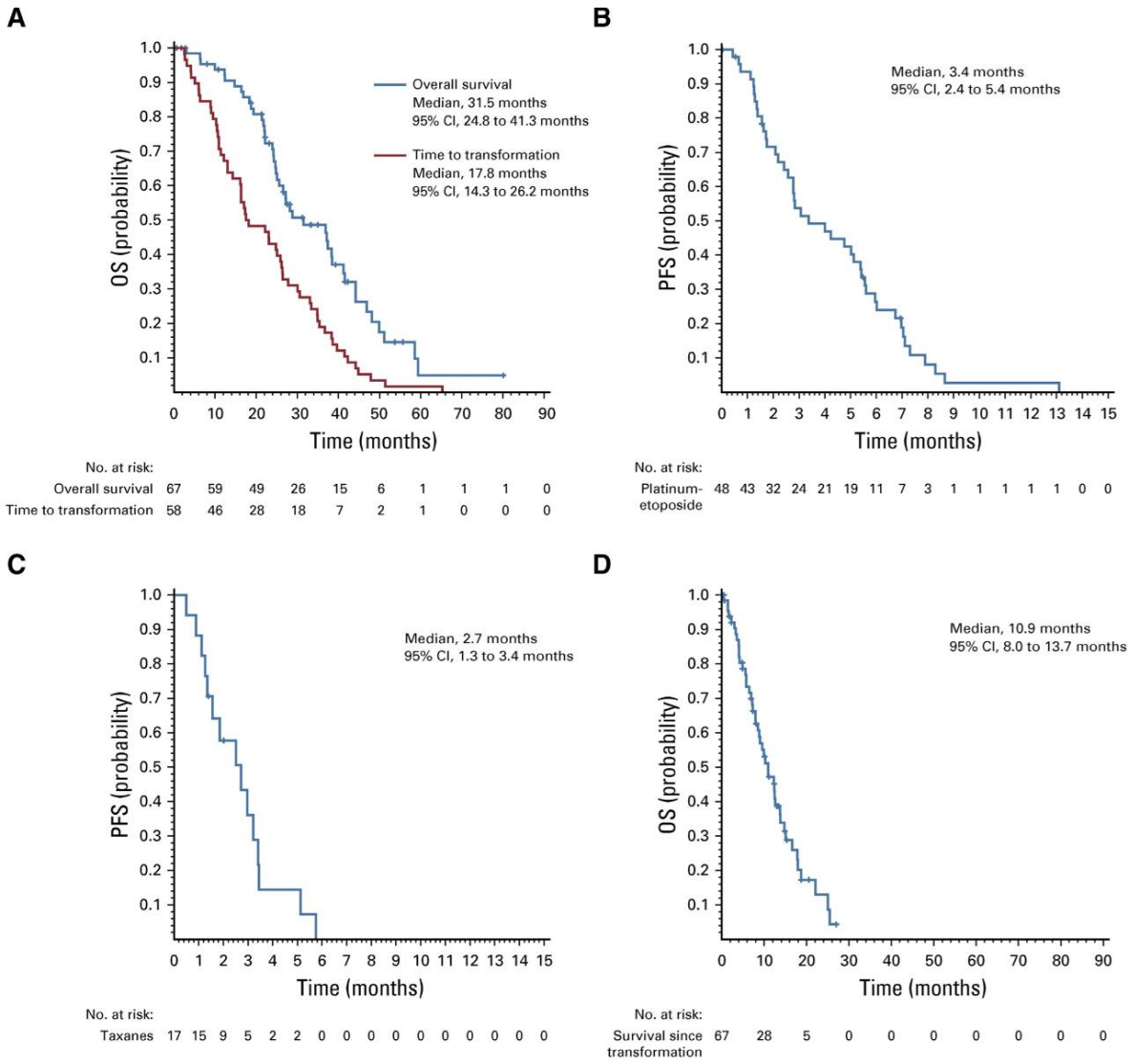
SCLC Transformation Management

Received after SCLC transformation (or after diagnosis for de novo SCLC)	n = 65*
Cytotoxic chemotherapy	63 (97)
Platinum-etoposide	53 (82)
Other platinum-combination	7 (11)
Taxane	21 (32)
Campthotecin (topotecan, irinotecan)	12 (18)
Temozolamide	4 (6)
EGFR TKI	34 (52)
Checkpoint inhibitor	17 (26)
PD-1 or PD-L1 monotherapy	9 (14)
Ipilumumab plus nivolumab	8 (12)

NOTE. Only treatments received by at least four patients are listed and patients are listed more than once if they received more than one regimen.

- ~5% EGFR mutant NSCLC p53/RB1 comutated
- ~20-25% of these develop SCLC (or de novo)

Offin et al JTO 2019



Marcoux et al. JCO 2019