

# FIRST-LINE EGFR TARGETED THERAPY: WITH OR WITHOUT CHEMOTHERAPY?

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**Portland, OR**

April 19, 2024

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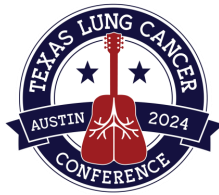


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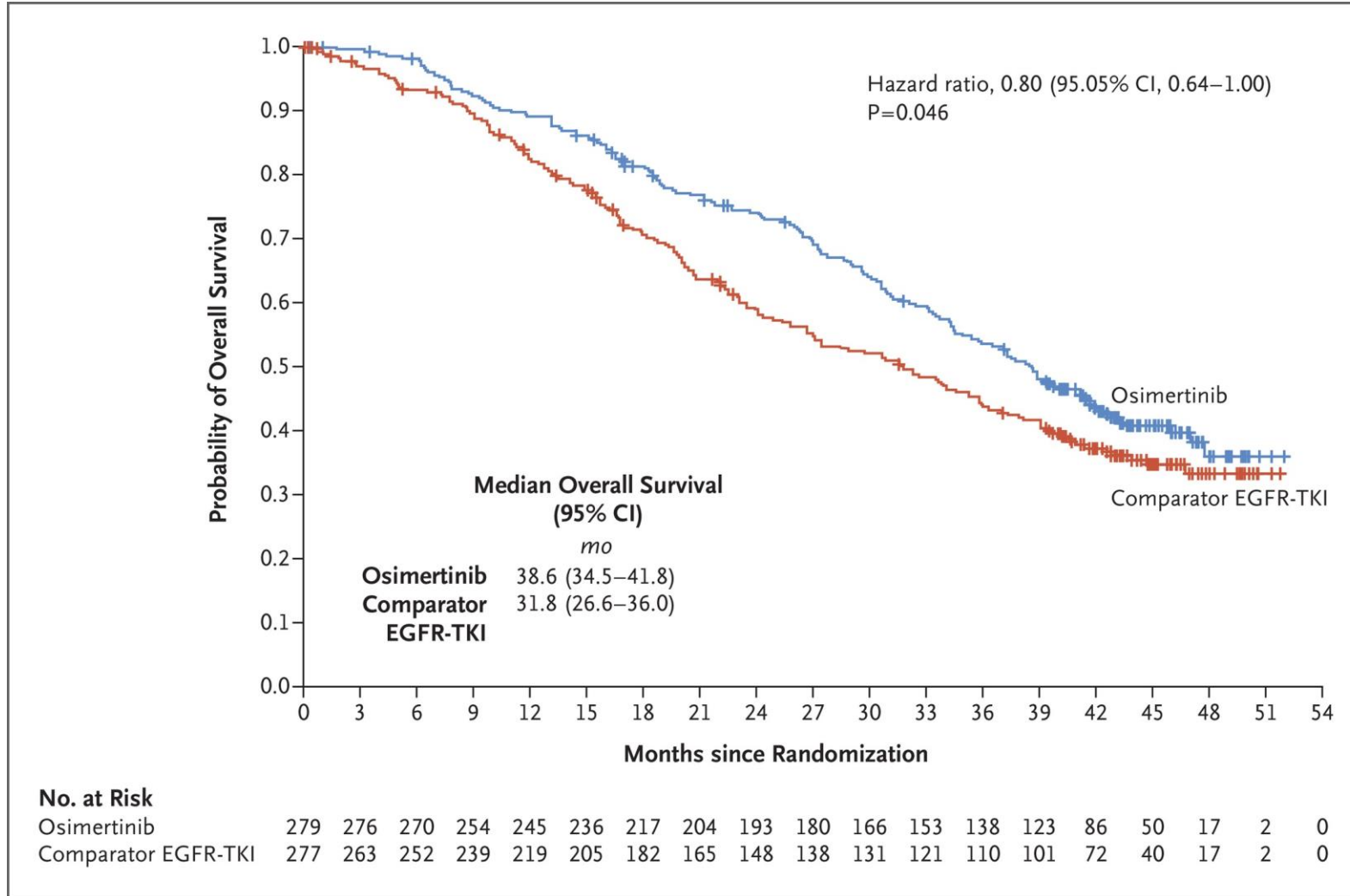
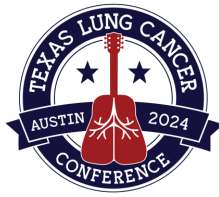
ORIGINAL ARTICLE

# Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC

S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators\*

N ENGL J MED 382;1 NEJM.ORG JANUARY 2, 2020

# FLAURA: Overall Survival

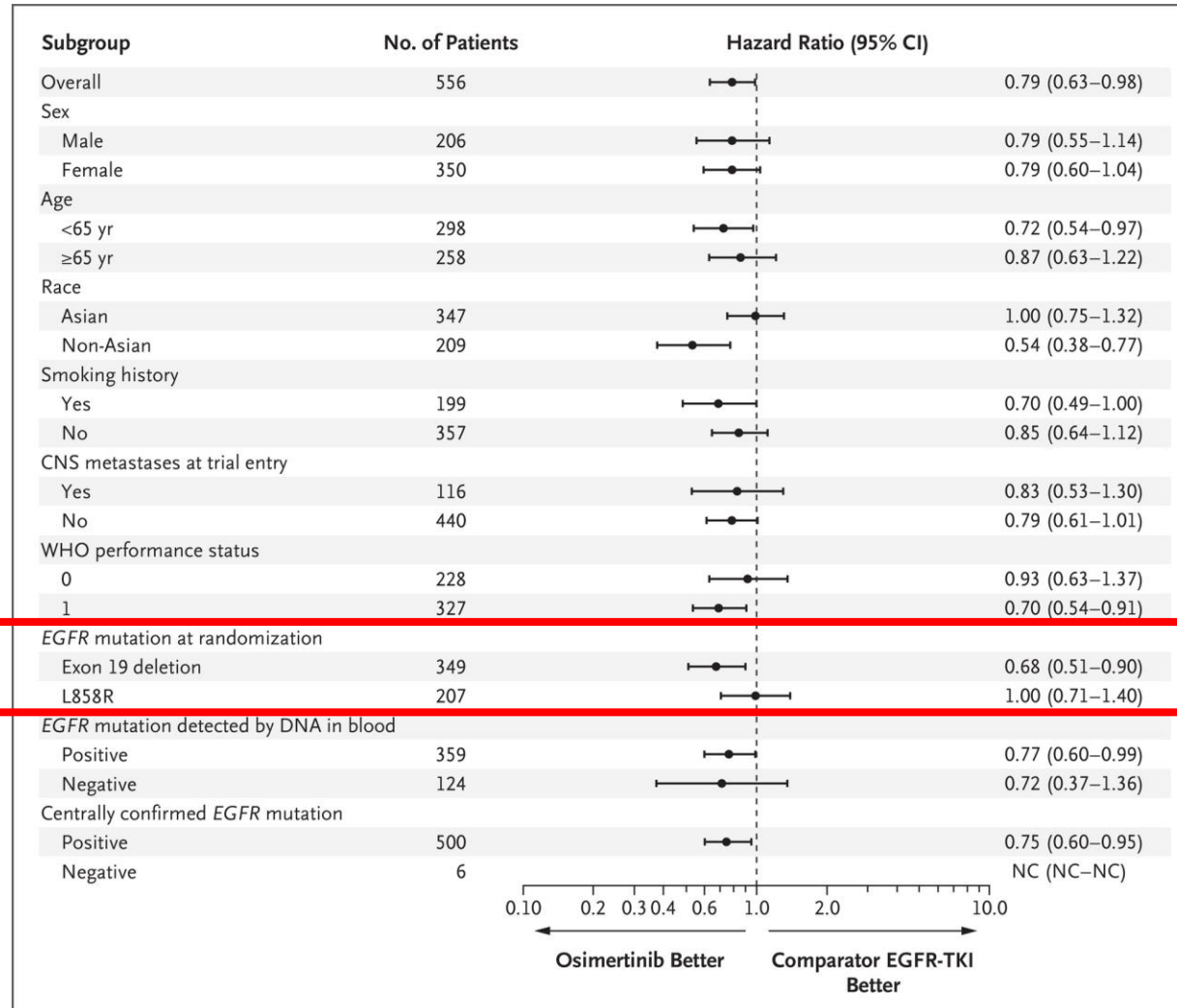
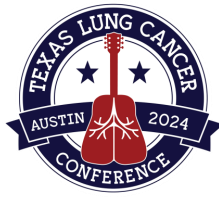


Ramalingam SS et al. N Engl J Med 2020;382:41-50



The NEW ENGLAND JOURNAL of MEDICINE

# FLAURA: Subgroup Analyses



Ramalingam SS et al. N Engl J Med 2020;382:41-50





# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

NOVEMBER 23, 2023

VOL. 389 NO. 21

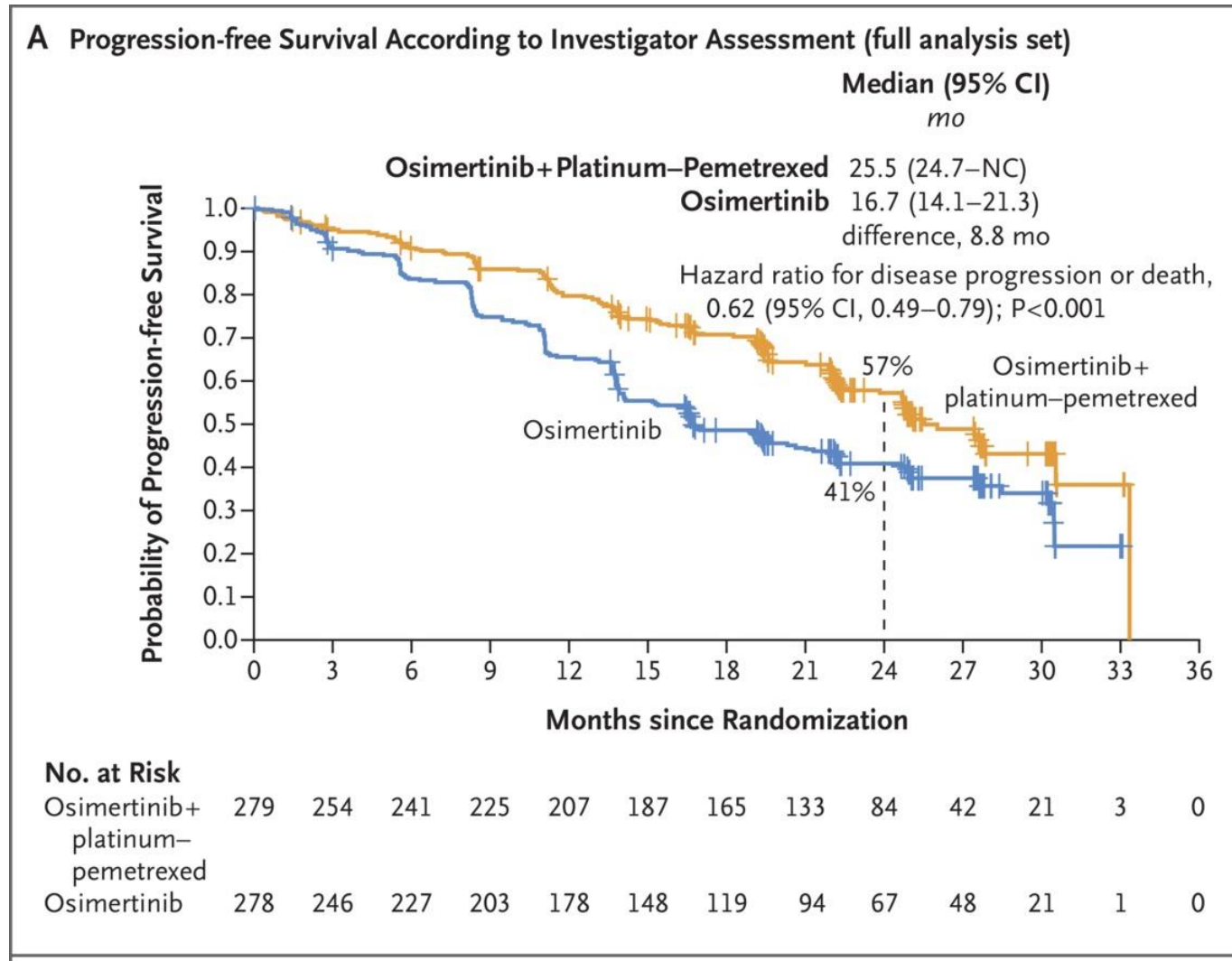
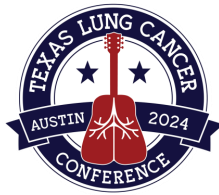
## Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC

D. Planchard, P.A. Jänne, Y. Cheng, J.C.-H. Yang, N. Yanagitani, S.-W. Kim, S. Sugawara, Y. Yu, Y. Fan, S.L. Geater, K. Laktionov, C.K. Lee, N. Valdiviezo, S. Ahmed, J.-M. Maurel, I. Andrasina, J. Goldman, D. Ghiorghiu, Y. Rukazenkov, A. Todd, and K. Kobayashi, for the FLAURA2 Investigators\*

N ENGL J MED 389;21 NEJM.ORG NOVEMBER 23, 2023



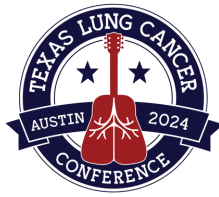
# FLAURA-2: PFS



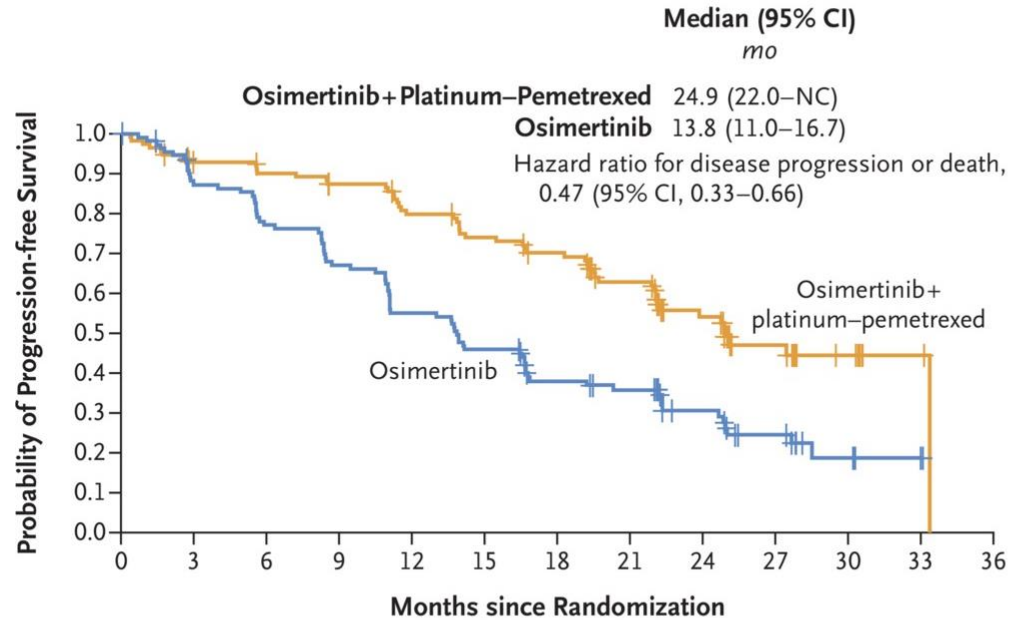
Planchard D et al. N Engl J Med 2023;389:1935-1948.



# FLAURA-2: CNS EFFICACY

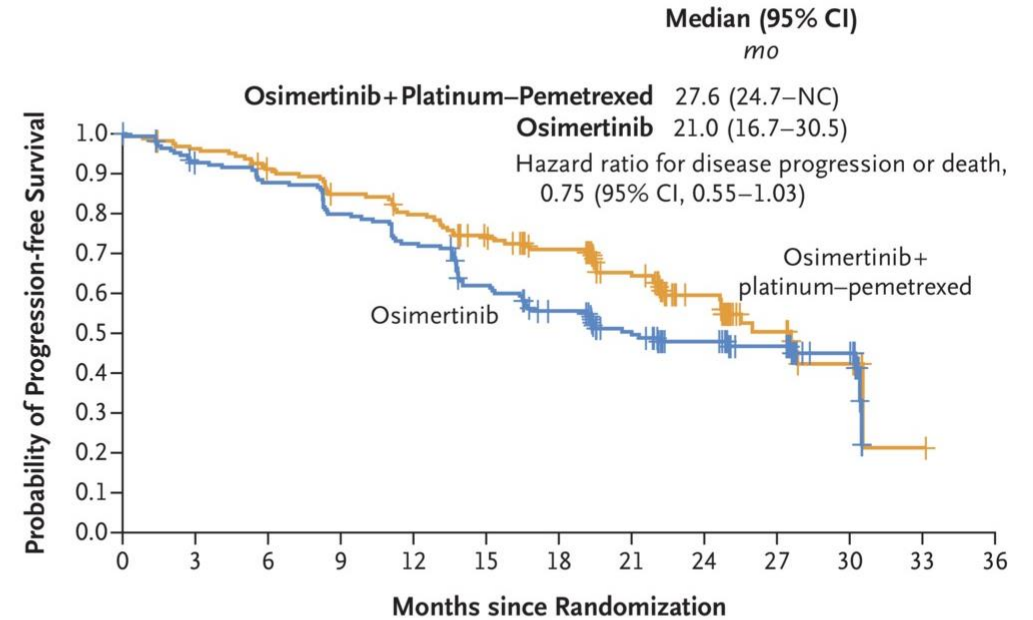


**C Progression-free Survival among Patients with CNS Metastases at Baseline**



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Osimertinib+ platinum-pemetrexed	116	101	98	93	84	77	70	58	34	19	8	2	0
Osimertinib	110	95	84	73	60	50	37	32	21	13	5	1	0

**D Progression-free Survival among Patients without CNS Metastases at Baseline**

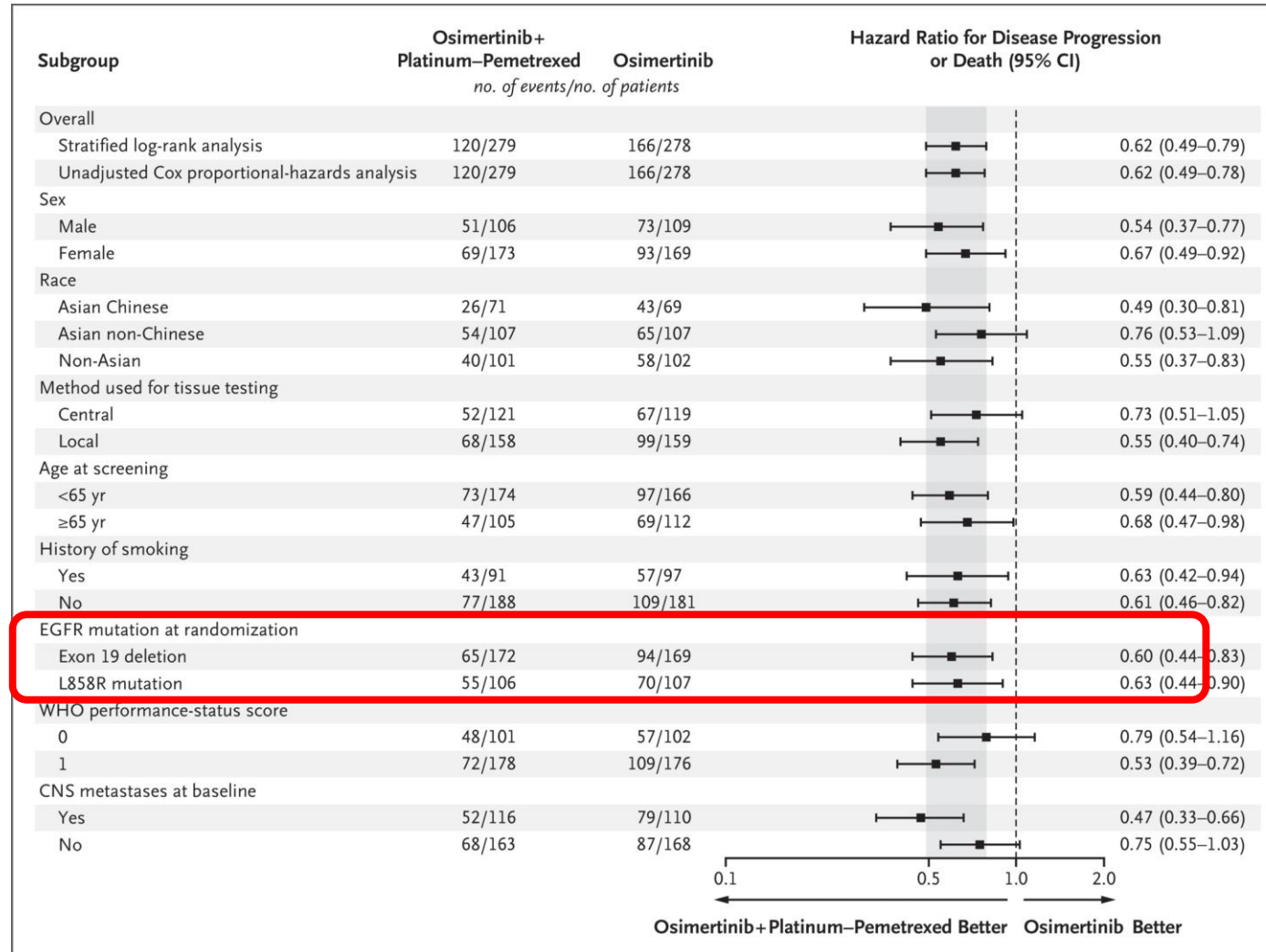
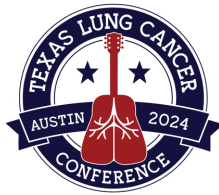


No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Osimertinib+ platinum-pemetrexed	163	153	143	132	123	110	95	75	50	23	13	1	0
Osimertinib	168	151	143	130	118	98	82	62	46	35	16	0	0

Planchard D et al. N Engl J Med 2023;389:1935-1948.



# FLAURA-2: Subgroup Analyses, PFS

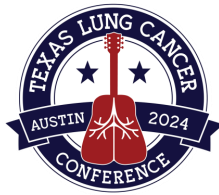


Planchard D et al. N Engl J Med 2023;389:1935-1948.





# FLAURA-2: Adverse Events



**Table 3. Adverse Events.\***

Event	Osimertinib + Platinum–Pemetrexed (N=276)					Osimertinib Monotherapy (N=275)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	128 (46)	30 (11)	43 (16)	55 (20)	0	22 (8)	15 (5)	6 (2)	1 (<1)	0
Diarrhea	120 (43)	83 (30)	29 (11)	8 (3)	0	112 (41)	89 (32)	22 (8)	1 (<1)	0
Nausea	119 (43)	81 (29)	34 (12)	4 (1)	0	28 (10)	22 (8)	6 (2)	0	0
Decreased appetite	85 (31)	49 (18)	28 (10)	8 (3)	0	26 (9)	18 (7)	6 (2)	2 (1)	0
Constipation	81 (29)	60 (22)	20 (7)	1 (<1)	0	28 (10)	23 (8)	5 (2)	0	0
Rash	77 (28)	55 (20)	21 (8)	1 (<1)	0	57 (21)	46 (17)	11 (4)	0	0
Fatigue	76 (28)	45 (16)	23 (8)	8 (3)	0	26 (9)	24 (9)	1 (<1)	1 (<1)	0
Vomiting	73 (26)	50 (18)	20 (7)	3 (1)	0	17 (6)	13 (5)	4 (1)	0	0
Stomatitis	68 (25)	40 (14)	27 (10)	1 (<1)	0	50 (18)	32 (12)	17 (6)	1 (<1)	0
Neutropenia	68 (25)	4 (1)	27 (10)	30 (11)	7 (3)	9 (3)	3 (1)	4 (1)	2 (1)	0
Paronychia	65 (24)	28 (10)	35 (13)	2 (1)	0	73 (27)	37 (13)	35 (13)	1 (<1)	0
Neutrophil count decrease	62 (22)	5 (2)	26 (9)	25 (9)	6 (2)	16 (6)	6 (2)	8 (3)	2 (1)	0
Covid-19†	57 (21)	23 (8)	31 (11)	2 (1)	0	39 (14)	18 (7)	21 (8)	0	0
ALT increase	56 (20)	36 (13)	16 (6)	4 (1)	0	21 (8)	17 (6)	3 (1)	1 (<1)	0
Platelet count decrease	51 (18)	19 (7)	11 (4)	18 (7)	3 (1)	19 (7)	18 (7)	1 (<1)	0	0
Thrombocytopenia	51 (18)	19 (7)	13 (5)	16 (6)	3 (1)	12 (4)	6 (2)	3 (1)	3 (1)	0
Dry skin	50 (18)	43 (16)	7 (3)	0	0	66 (24)	62 (23)	4 (1)	0	0
AST increase	48 (17)	42 (15)	5 (2)	1 (<1)	0	13 (5)	12 (4)	0	1 (<1)	0
Blood creatinine increase	46 (17)	33 (12)	13 (5)	0	0	12 (4)	10 (4)	2 (1)	0	0
White-cell count decrease	44 (16)	7 (3)	28 (10)	8 (3)	1 (<1)	18 (7)	9 (3)	8 (3)	1 (<1)	0
Peripheral edema	42 (15)	33 (12)	9 (3)	0	0	12 (4)	9 (3)	3 (1)	0	0

\* Safety analyses included all the patients who received at least one dose of trial treatment (safety analysis set), according to the treatment received. Each patient has been represented only with the maximum reported Common Terminology Criteria for Adverse Events grade for each preferred term. Listed are adverse events from any cause, according to preferred term that were reported in at least 15% of patients in either group. Adverse events with an onset date on or after the date of first dose and up to and including 28 days after the discontinuation of treatment but before the start of a subsequent anticancer therapy are reported. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.  
 † One patient in the group that received osimertinib plus platinum–pemetrexed died from coronavirus disease 2019 (Covid-19).

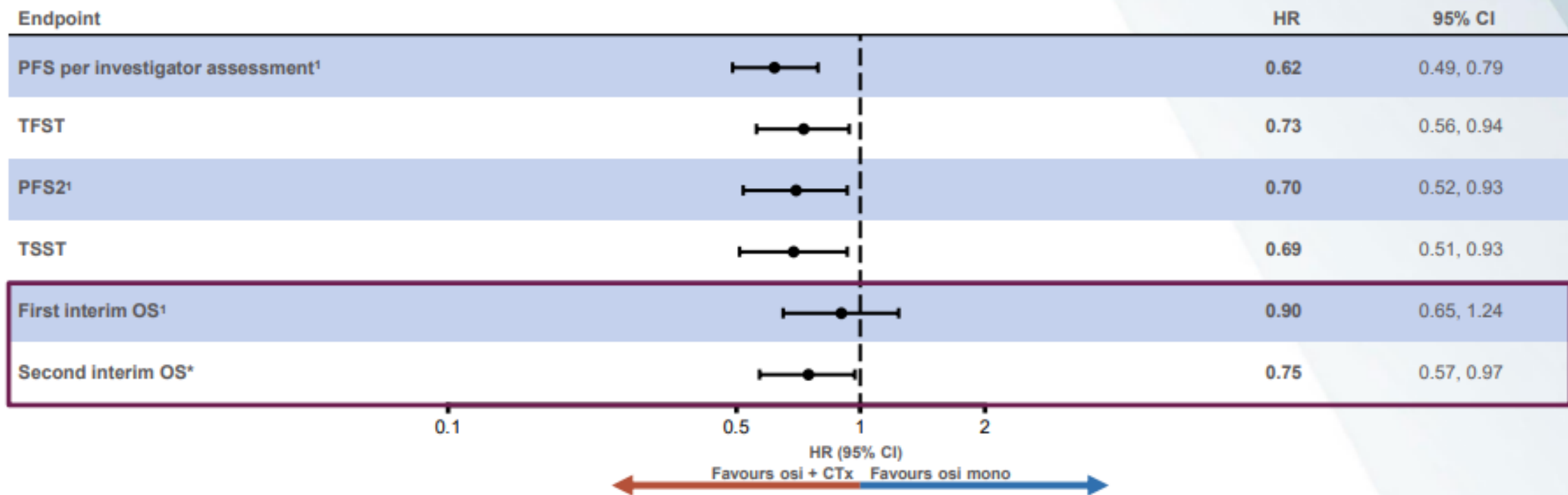
Planchard D et al. N Engl J Med 2023;389:1935-1948.





# FLAURA-2: PFS2

## CONSISTENT BENEFITS WERE SEEN FOR FLAURA2 POST-PROGRESSION OUTCOMES

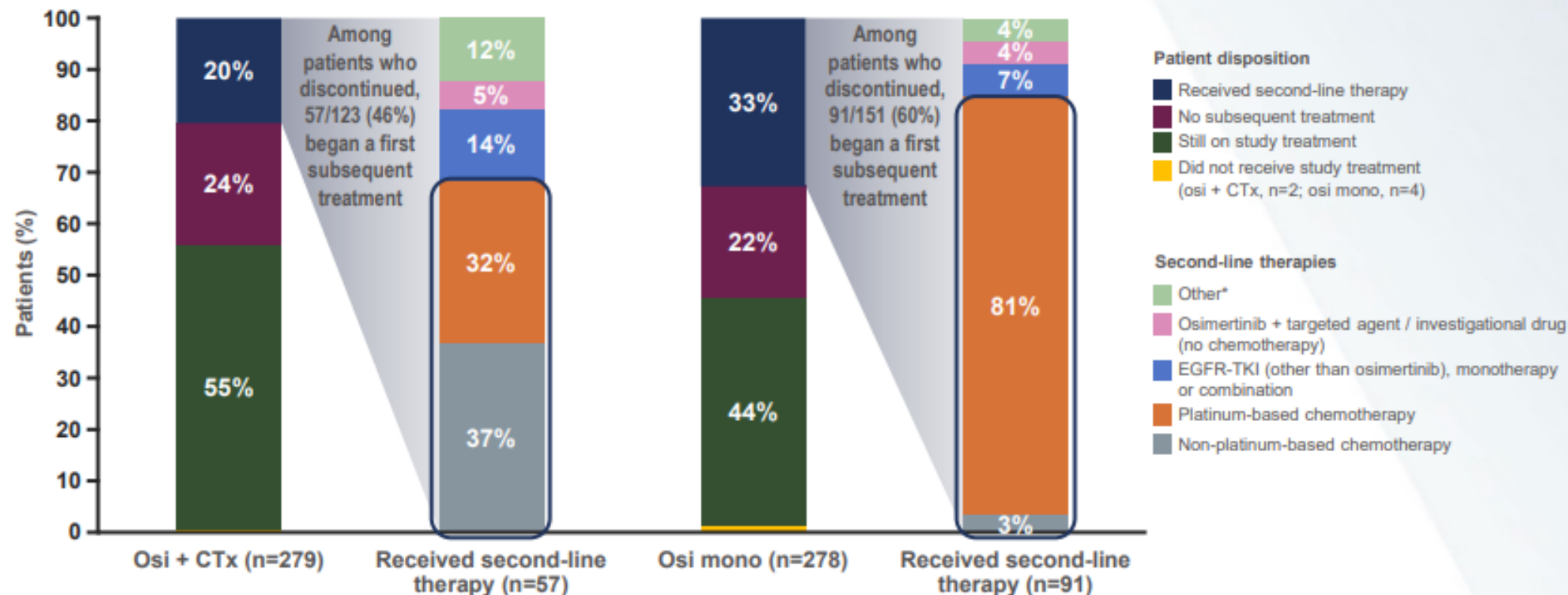


Valdiviezo N, et al, European Lung Cancer Congress 2024

# FLAURA-2: Post Progression

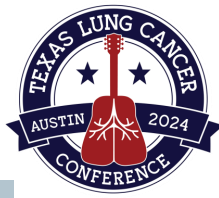


## CHEMOTHERAPY WAS THE MOST COMMON FIRST SUBSEQUENT TREATMENT

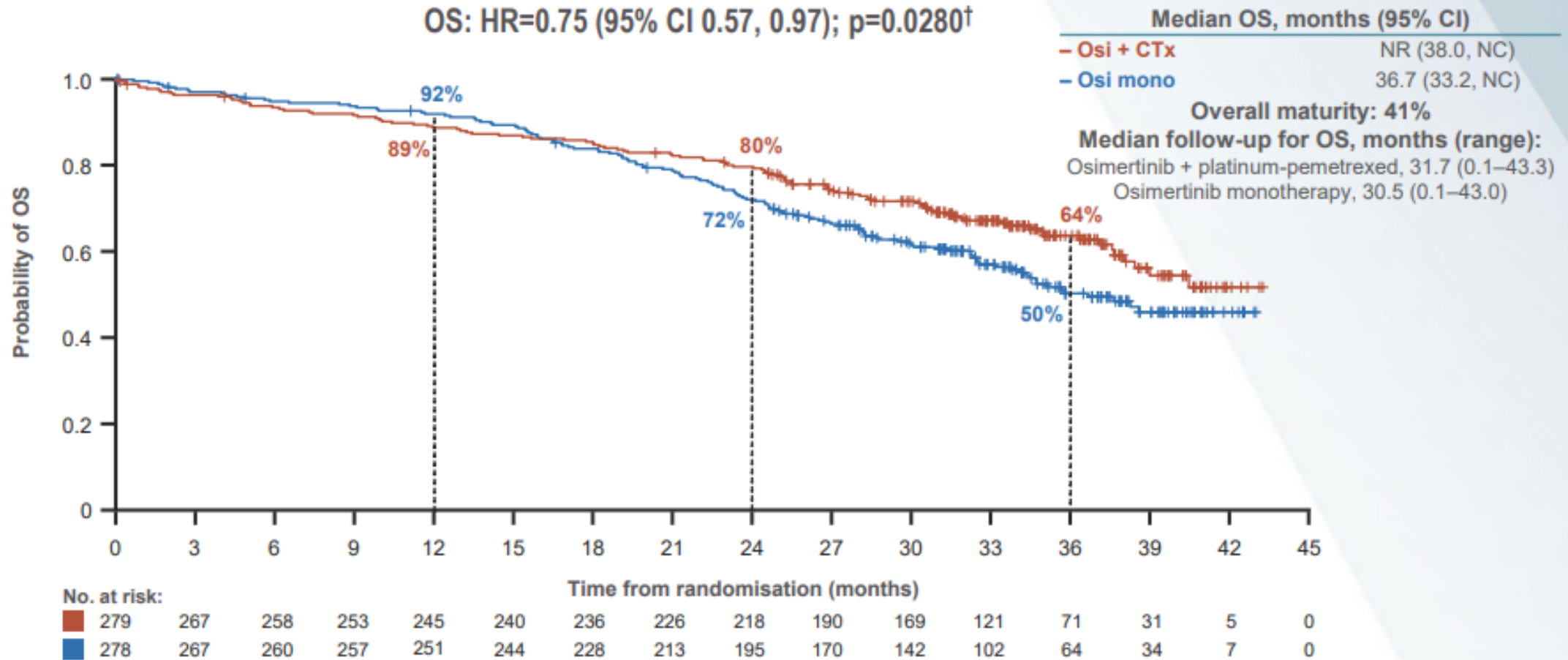


Valdiviezo N, et al, European Lung Cancer Congress 2024

# FLAURA-2: 2<sup>nd</sup> Interim OS Analysis



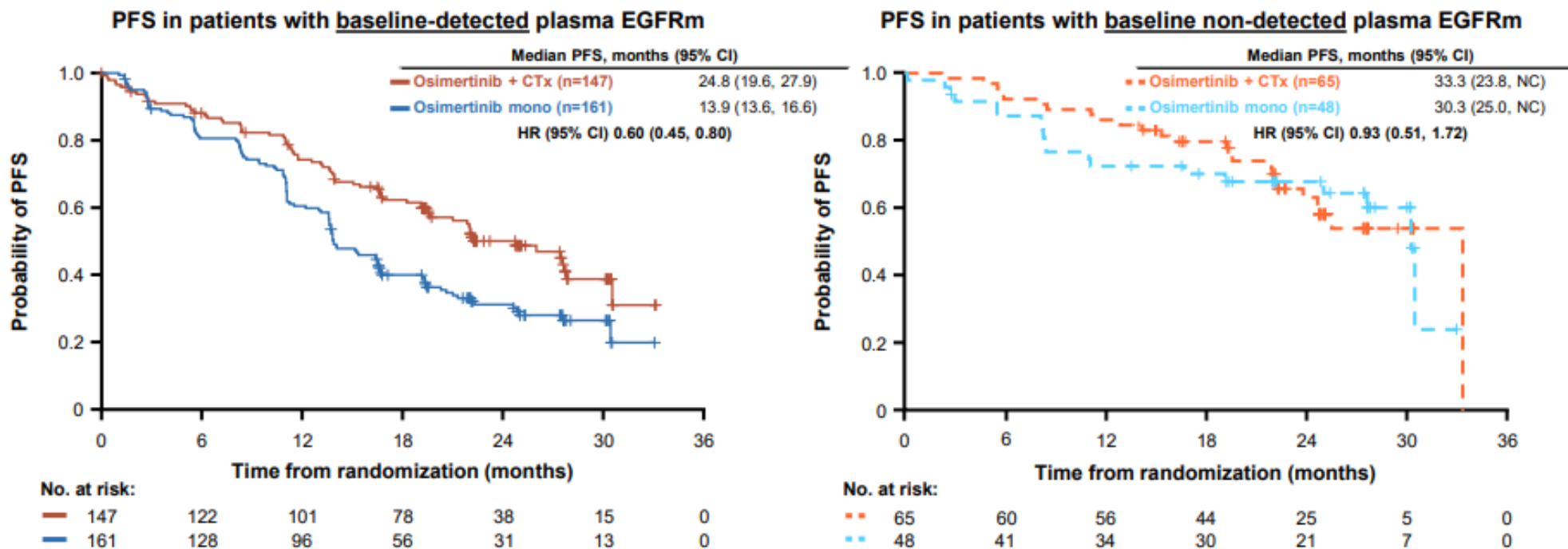
## SECOND INTERIM OVERALL SURVIVAL ANALYSIS



Valdiviezo N, et al, European Lung Cancer Congress 2024

# FLAURA-2: PFS and plasma EGFR

## PFS improved with osimertinib plus chemotherapy in patients with baseline-detected plasma EGFRm versus osimertinib alone



**Baseline-detected plasma EGFRm was prognostic and may select for a higher degree of clinical benefit with osimertinib plus chemotherapy versus osimertinib alone**

Janne P, et al, European Lung Cancer Congress 2024





# Challenges: Higher Risk Populations

- Differences between mutations:

**L858R: Relatively shorter overall survival**

**FLAURA: OS Hazard Ratio 1.0 (vs 0.68 for Exon 19 del)**

**Real-World Analysis, Netherlands:**

**Median OS Exon 19 del: 28.4 mo;**

**Median OS L858R: 17.7 mo**

**( $p < 0.001$ )<sup>1</sup>**

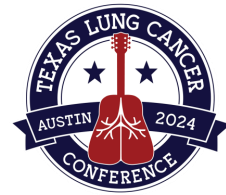
- **FLAURA2:**

**Median PFS for L858R with Chemotherapy + Osimertinib: 24.7 months**

**→ vs 13.9 months with osimertinib alone**

**(Exon 19 del: Median PFS 27.9 months vs 19.4 months)**

Ramalingam SS et al. N Engl J Med 2020; Gijtenbeek R GP, et al Lancet Regional Health 2023; Planchard D et al. N Engl J Med 2023



# Impact of Comutations: Or, What Selected Gene Testing Doesn't Tell You

- ***TP53* comutation**  
Associated with shorter PFS, OS on TKIs<sup>1</sup>  
Regardless of depth of initial radiographic response
- **Others associated with shorter duration of disease control**  
**MET alterations**  
**APC**  
**ERBB4**  
**KEAP1**  
**DNMT3A**

1. Vokes NI et al, J Thoracic Oncol 2022

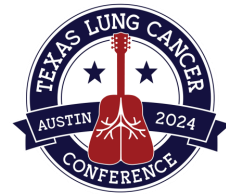


# Impact of Comutations: It Gets Worse--

- ***RB1* loss<sup>1</sup>**  
**Associated with small cell transformation**
- **Co-occurring *TP53* mutation and *RB1* loss<sup>1,2</sup>**  
**Shortest disease control**  
**High rates of small cell transformation**
- **Analysis from MSK-IMPACT, 863 patients:**

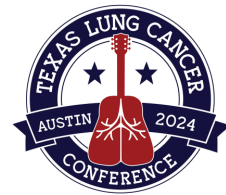
	<b>Time to TKI Discontinuation (Months)</b>	<b>Overall Survival (Months)</b>	<b>Small Cell Transformation</b>
<b>EGFR m</b>	<b>36.6</b>	<b>56.4</b>	
<b>EGFRm/TP53m</b>	<b>12.3</b>	<b>40.8</b>	
<b>EGFRm/TP53m/ RB1 loss</b>	<b>9.5</b>	<b>29.1</b>	<b>18%</b>

1. Vokes NI et al, J Thoracic Oncol 2022 2. Offin M, et al J Thoracic Oncol 2019



# Selecting the “Best Regimen”?

- **Efficacy**
  - **Toxicity**
  - **Quality of Life**
  - **Higher Risk Disease**
    - **Comutations**
    - **Patients with detectable ctDNA at baseline**
- No information about comutations in FLAURA2**



# Take Home Points

- **First-line therapy, advanced EGFR L858R or Exon 19 del:**

**FDA Approvals for both single-agent Osimertinib and Osimertinib with chemotherapy**

**Although improved PFS with Chemo/Osimertinib, Overall Survival data still pending**

- **Selection will be individualized**
- **Options will increase as further front-line combination studies mature:**
  - VEGF inhibition?**
  - Bispecific antibody combinations?**
  - Antibody drug conjugates?**