New Developments in EGFR and K-RAS Therapies in NSCLC

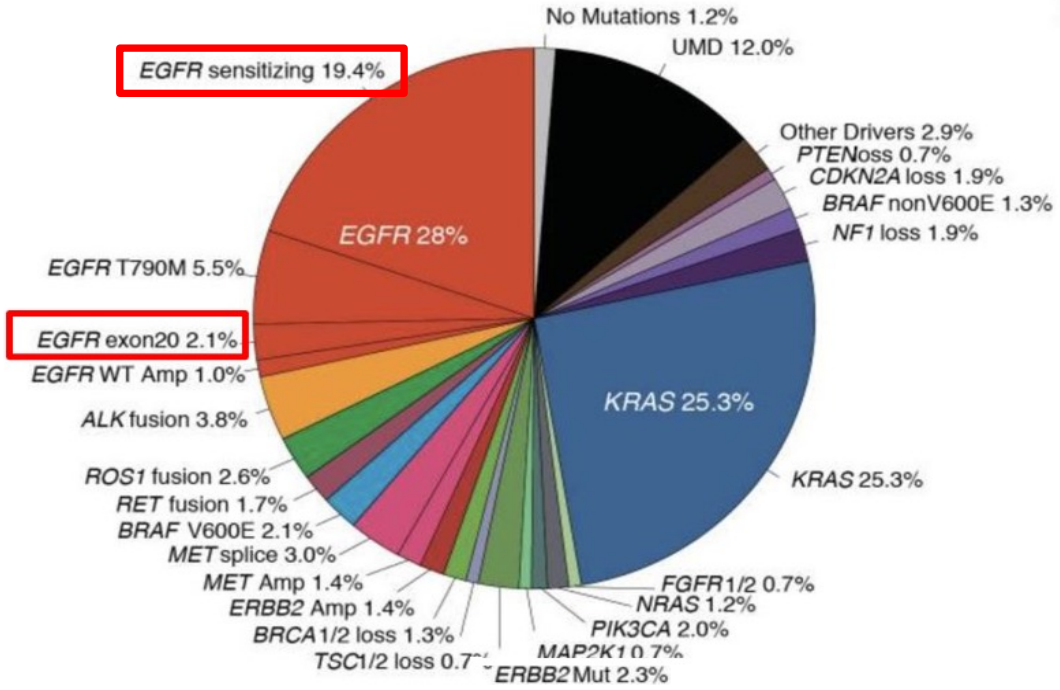
Edgardo S. Santos, MD, FACP
Medical Director- Broward County, Florida
The Oncology Institute (TOI) of Hope and Innovation
Clinical Associate Professor
Charles E. Schmidt School of Medicine/Florida Atlantic University
Treasurer, FLASCO
President, FLASCO Foundation

December 2, 2023

FLORIDA ATLANTIC UNIVERSITY

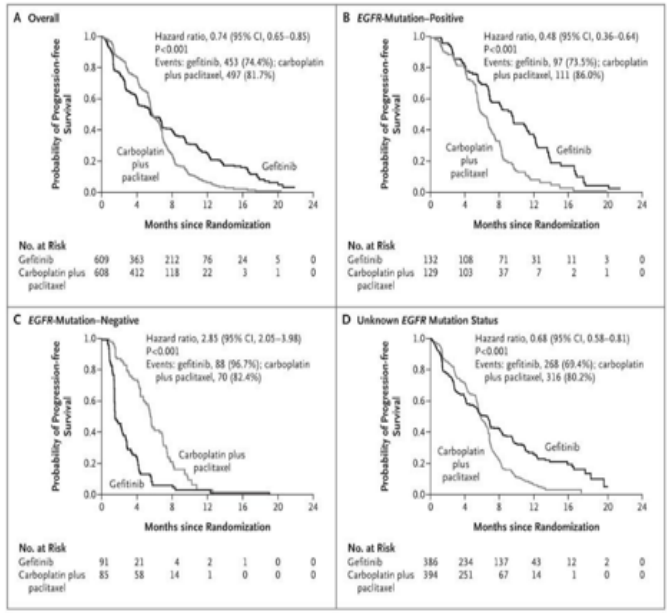
The Oncology Institute of Hope & Innovation

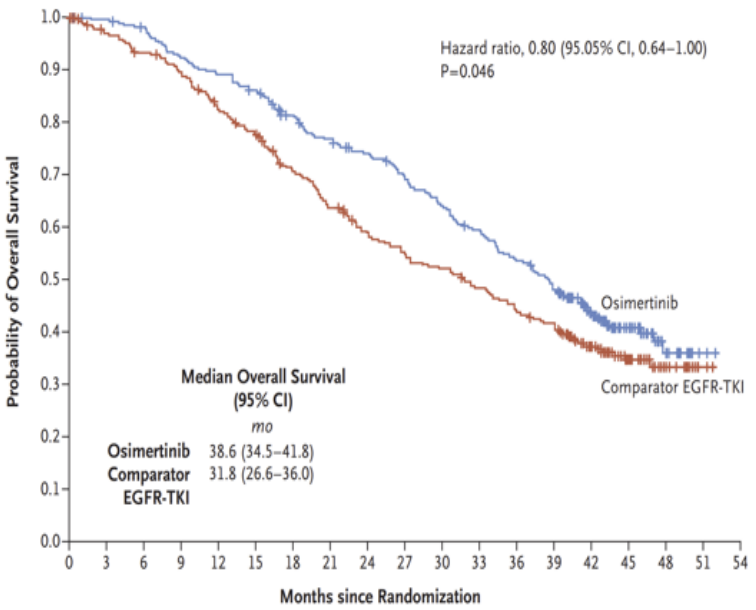
EGFRex19del, L858R (ex21) & EGFRex20ins



FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Where are we going?...





1L Treatment of EGFRm NSCLC November 2023

+ Chemo

FLAURA2: Osimertinib + Chemotherapy > Osimertinib

+ EGFR/MET mAb

MARIPOSA: Amivantamab + Lazertinib > Osimertinib, Lazertinib

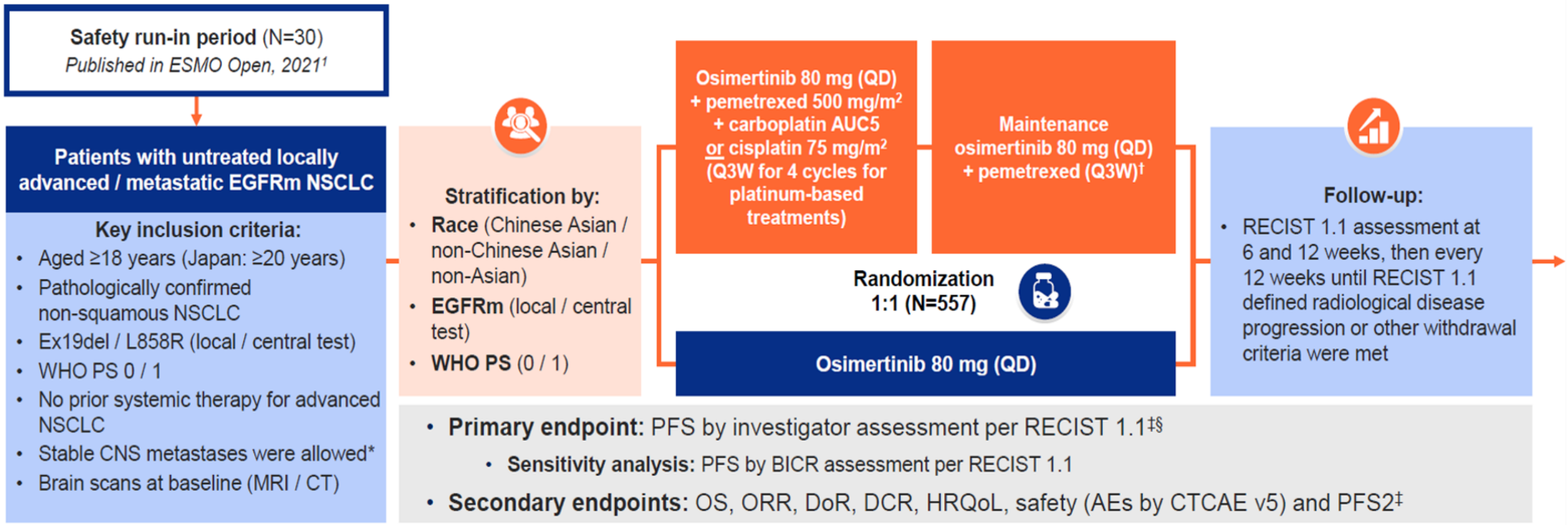
IPASS 2009 | **FLAURA 2018** | **2023**

IPASS Mok TS et all NEJM 2009; FLAURA Soria JC et al NEJM 2018; FLAURA2 Janne P et al NEJM 2023; MARIPOSA Cho et al ESMO 2023

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

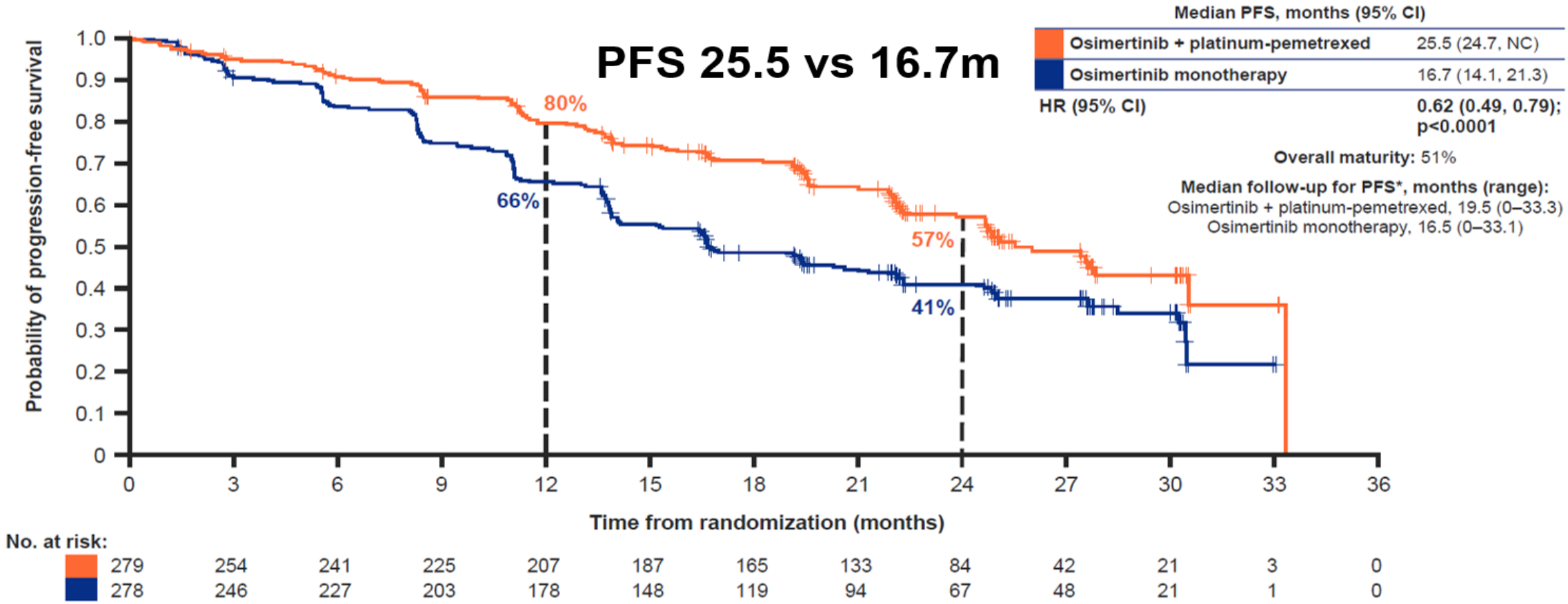
FLAURA2: 1L Osimertinib + Chemotherapy vs Osimertinib



Presented by P. Janne, IASLC WCLC 2023, PL03.13

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

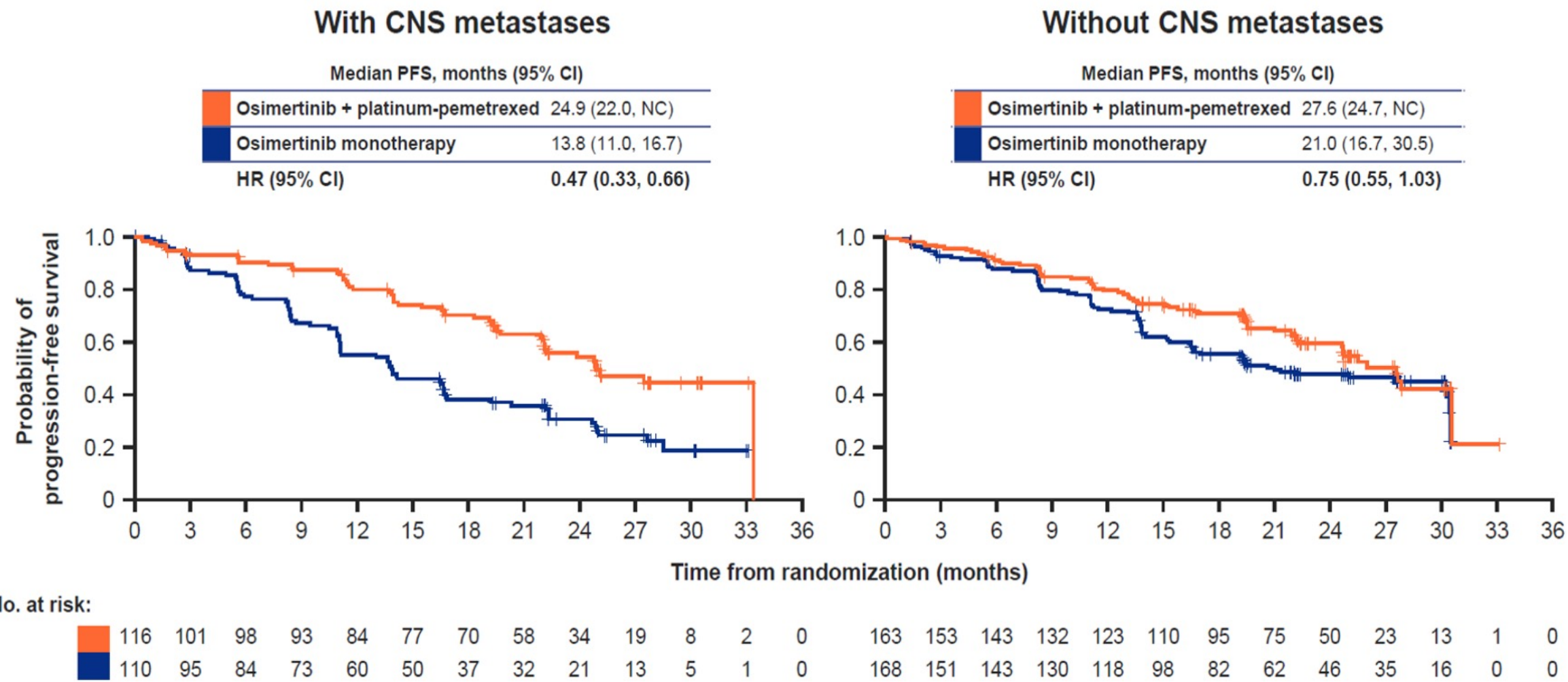
FLAURA2: PFS per investigator



Presented by P. Janne, IASLC WCLC 2023, PL03.13

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

FLAURA2: PFS per investigator by CNS Metastases

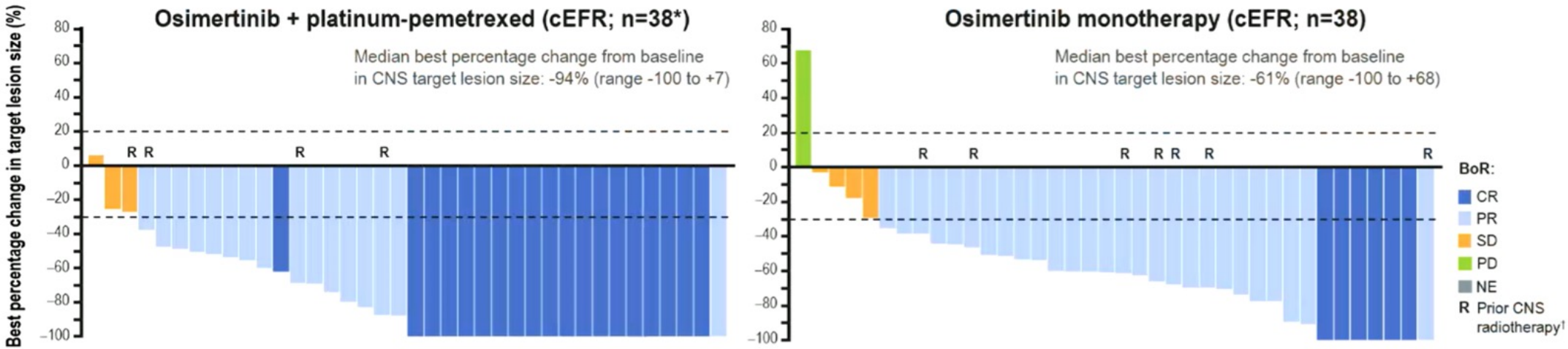


Presented by P. Janne, IASLC WCLC 2023, PL03.13

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

FLAURA2: Updated CNS Data ESMO 2023

OSIMERTINIB WITH THE ADDITION OF CTx DEMONSTRATED A HIGH PROPORTION OF COMPLETE RESPONSES IN THE CNS BY CNS BICR



	cFAS (n=222) Measurable + non-measurable BM		cEFR (n=78) Measurable BM	
CNS response‡	**Osi + CTx (n=118)**	**Osi mono (n=104)**	**Osi + CTx (n=40)**	**Osi mono (n=38)**
CNS ORR, % (95% CI)	**73 (64 to 81)**	**69 (59 to 78)**	**88 (73 to 96)**	**87 (72 to 96)**
Complete response, n (%)	70 (59)	45 (43)	19 (48)	6 (16)
Partial response, n (%)	16 (14)	27 (26)	16 (40)	27 (71)
CNS DCR, % (95% CI)	91 (84 to 95)	93 (87 to 97)	95 (83 to 99)	97 (86 to 100)
Median DoR, months (95% CI)§	**NR (23.8, NC)**	**26.2 (19.4, NC)**	**NR (21.6, NC)**	**20.9 (12.6, NC)**

*Two pts had ≥1 measurable CNS lesion at baseline by CNS BICR but died before the follow-up CNS BICR scan; †In the cEFR, 4/40 pts (10%) in the osimertinib + platinum-pemetrexed arm and 7/38 pts (18%) in the osimertinib arm had received prior CNS radiotherapy; stable neurological status for ≥2 weeks after completion of definitive treatment and steroids was required before study entry, if received; ‡Responses did not require confirmation, per RECIST guidance on randomized studies; §Kaplan–Meier estimates.

BICR, blinded independent central review; BM, brain metastases; BoR, best overall response; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; CI, confidence interval; CNS, central nervous system; CR, complete response; CTx, chemotherapy; DCR, disease control rate; DoR, duration of response; mono, monotherapy; NC, not calculable; NE, not evaluable; NR, not reached; ORR, objective response rate; osi, osimertinib; PD, progressive disease; PR, partial response; pts, patients; SD, stable disease

Data cut-off: 03 April 2023.

MADRID 2023 ESMO congress

Measurable CNS lesions: CR rate 16% vs 48%

Presented Planchard et al. ESMO 2023 Abstract LBA68

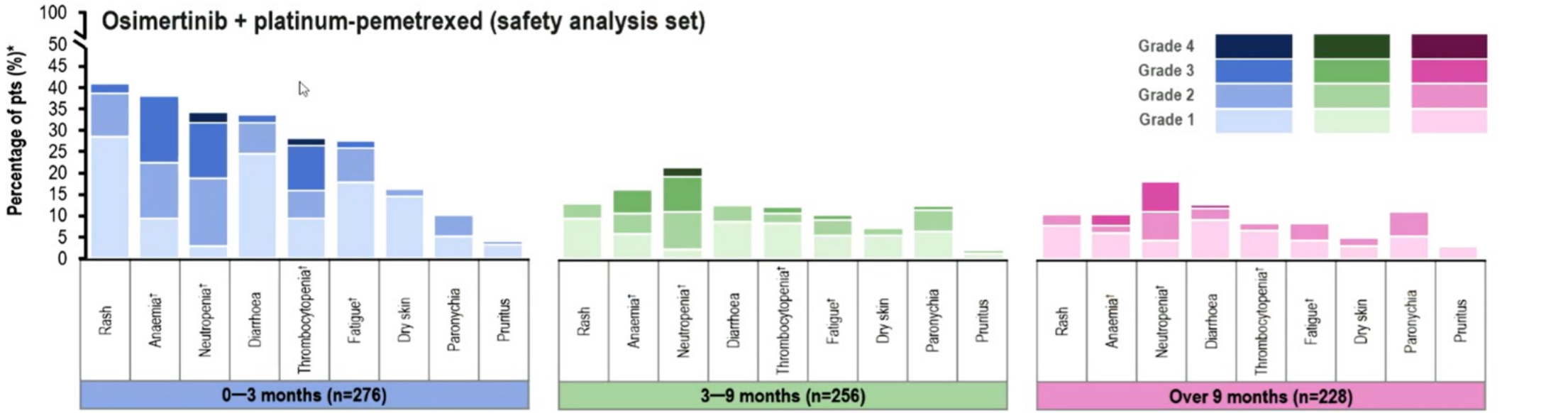
FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

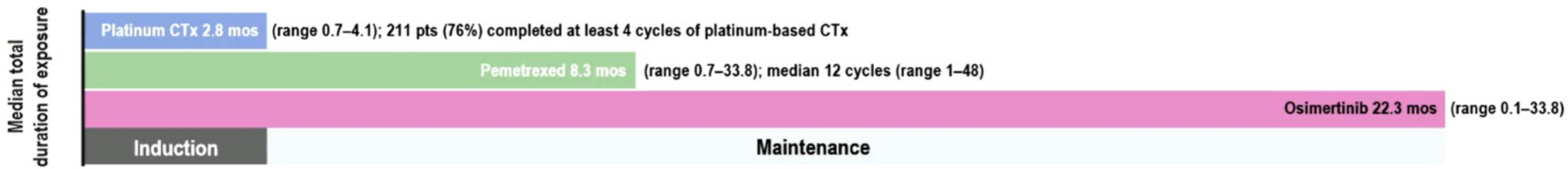
The Oncology Institute of Hope & Innovation

What about toxicity?

AE ONSET FREQUENCY AND SEVERITY WERE HIGHEST DURING THE INDUCTION PERIOD, AND GRADUALLY REDUCED OVER TIME

- In the osi + CTx arm, the onset of ≥Grade 3 AEs reduced by ~50% between 0–3 mos (n=135; 49%) and 3–9 mos (n=62; 24%)





Presented Planchard et al. ESMO 2023 Abstract LBA68

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

FLAURA2: Unanswered Questions

- Overall Survival?

- Is benefit of addition of chemotherapy to Osimertinib worth the risk/increased toxicity?
  - ✓ Subgroups: CNS mets, EGFR L8585R, co-mutations (e.g., TP53)

- Is benefit of addition of chemotherapy to Osimertinib better than other combination strategies?
  - ✓ 4th Generation EGFR TKI
  - ✓ MET targeting agents (TKI, bispecifics)
  - ✓ ADCs (e.g. patritumab deruxtecan)

- Resistance mechanisms and persister cell populations
  - ✓ Helena Yu Shedder Study Ongoing

Joshua Sabari, MD. Masters in Thoracic Oncology Summit (MATOS) 2023.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

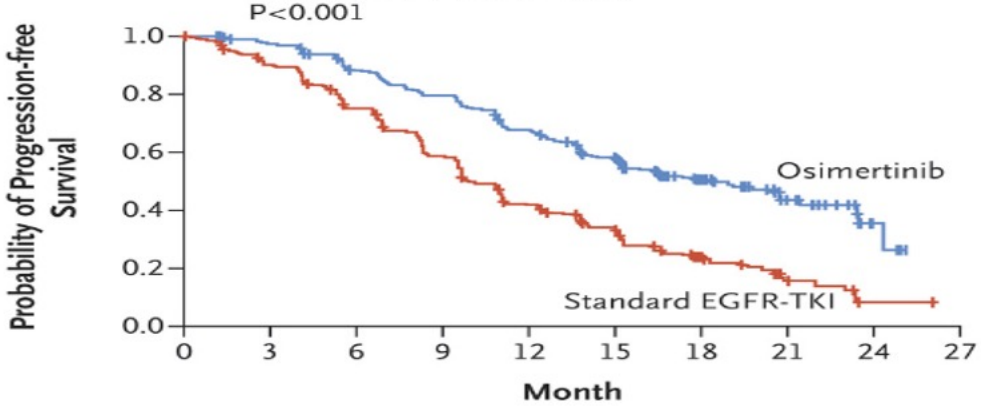
Just to Remember…..

FLAURA vs FLAURA2

A Progression-free Survival in Full Analysis Set

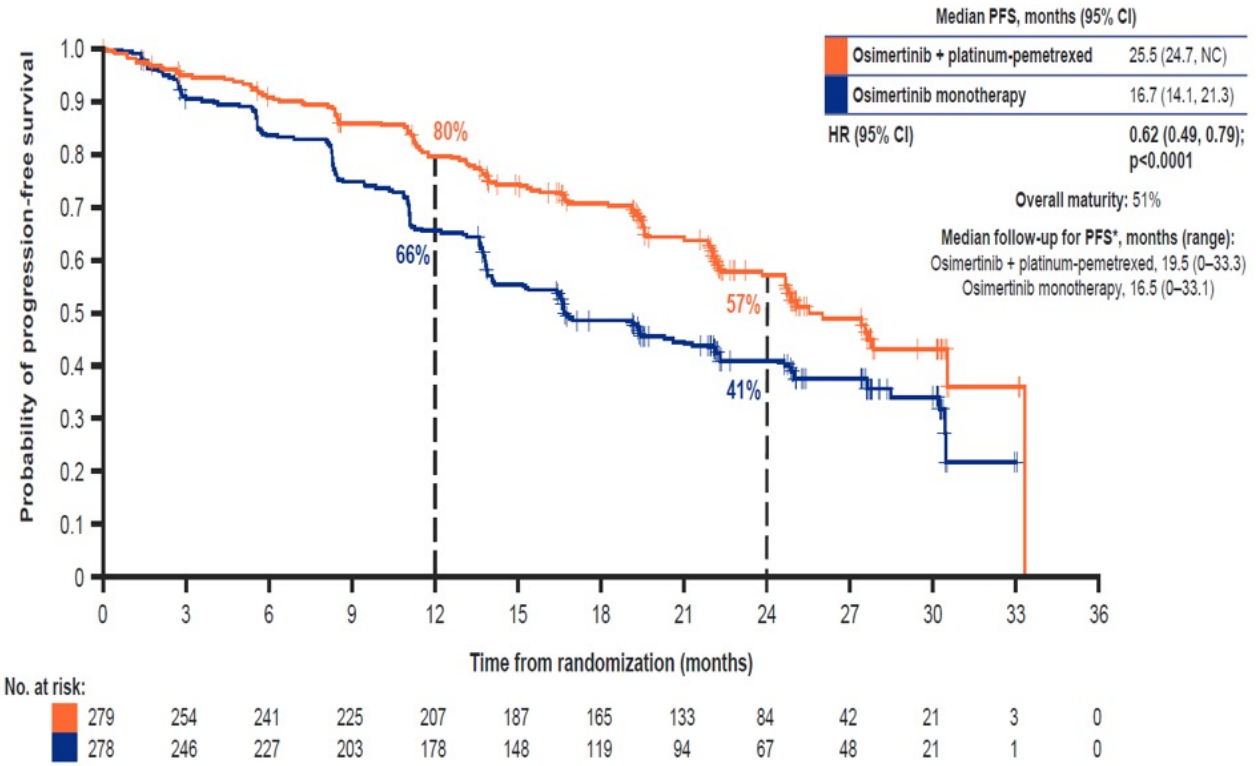
	No. of Patients	Median Progression-free Survival (95% CI) mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



No. at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0



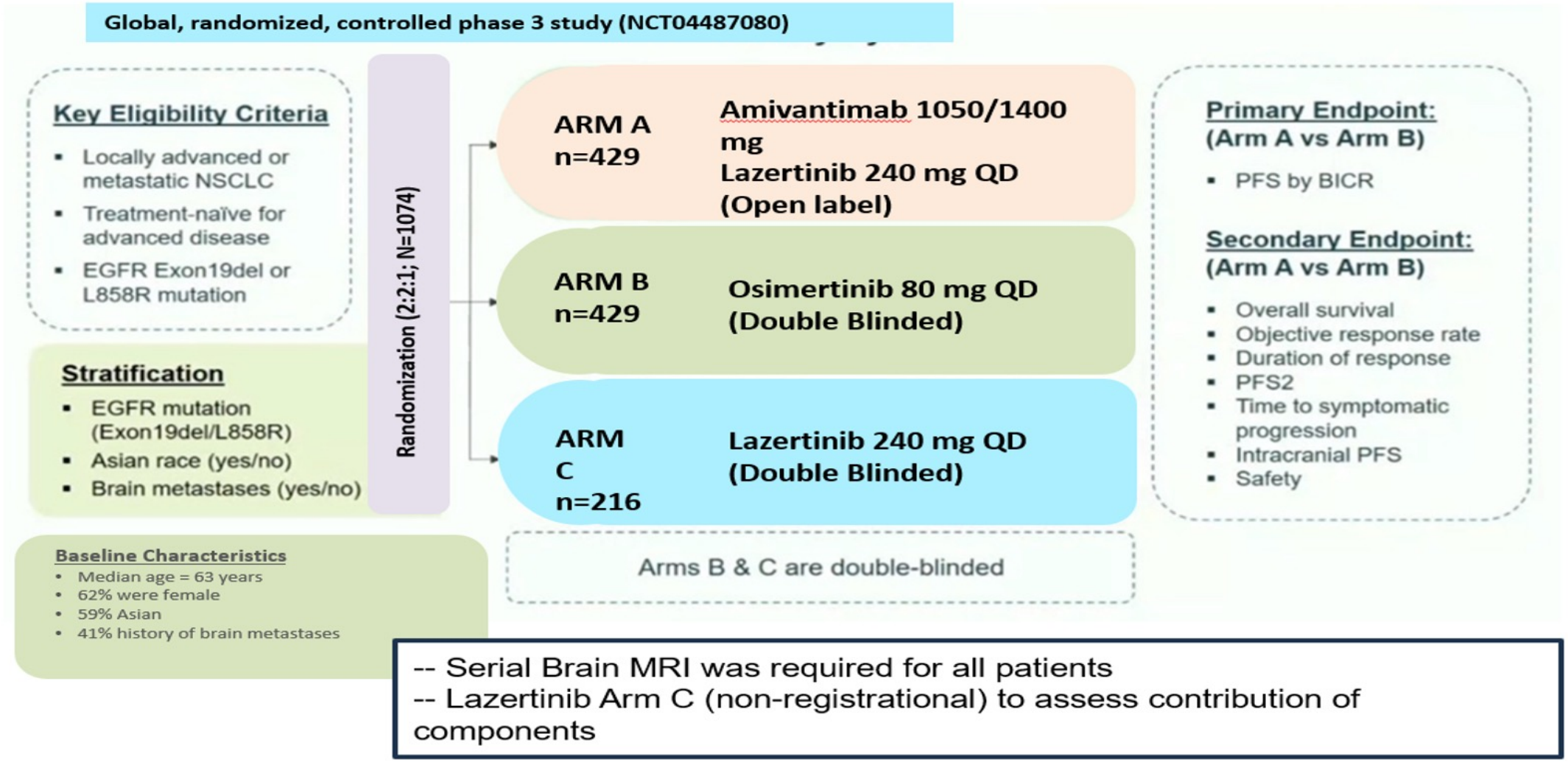
FLAURA mPFS: 18.9 months
mOS 38.6 months

FLAURA2 mPFS: 25.5 months
mOS not mature

Edgardo Santos, MD. 2023 Updates in Cancer Therapies.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

MARIPOSA: 1L Amivantamab + Lazertinib



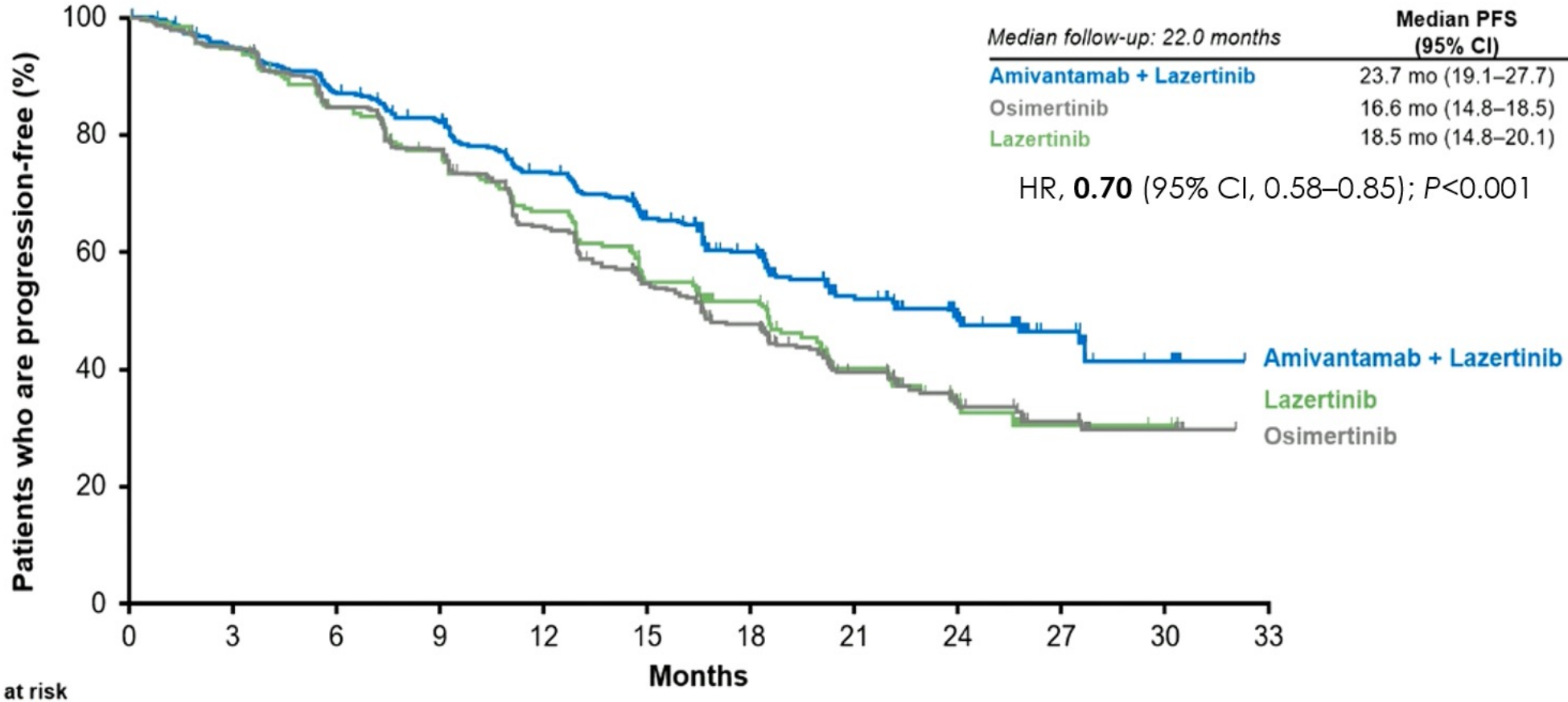
-- Serial Brain MRI was required for all patients
-- Lazertinib Arm C (non-registrational) to assess contribution of components

Presented by B. Cho. ESMO 2023. LBA14

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

MARIPOSA: 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)
Lazertinib	18.5 mo (14.8–20.1)

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
Lazertinib	216	200	174	157	134	103	83	41	19	6	2	0

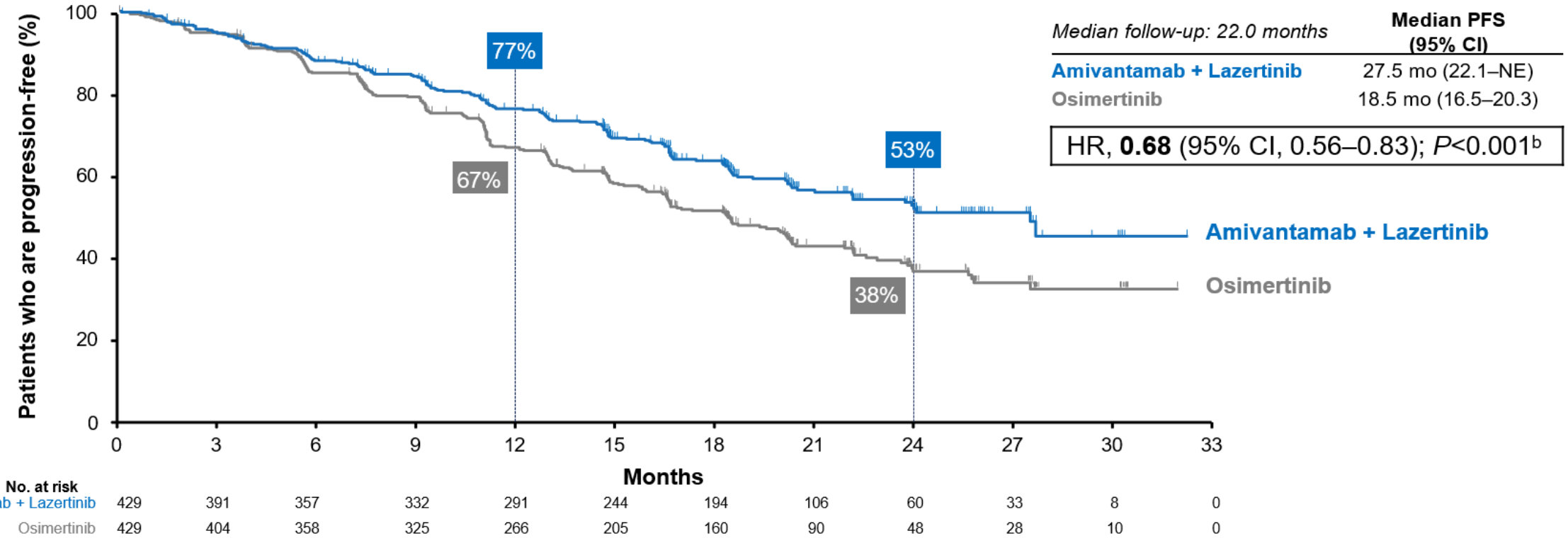
Presented by B. Cho. ESMO 2023. LBA14

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Extracranial Progression-free Survival by BICR[a]

Amivantamab + lazertinib reduced the risk of extracranial progression or death by **32%** and improved median PFS by 9 months

MARIPOSA conducted serial brain MRIs on all patients, which is not routinely done in *EGFR*-mutant NSCLC trials
Both median PFS estimates increase if CNS-only first progressions are censored but a consistent benefit is observed



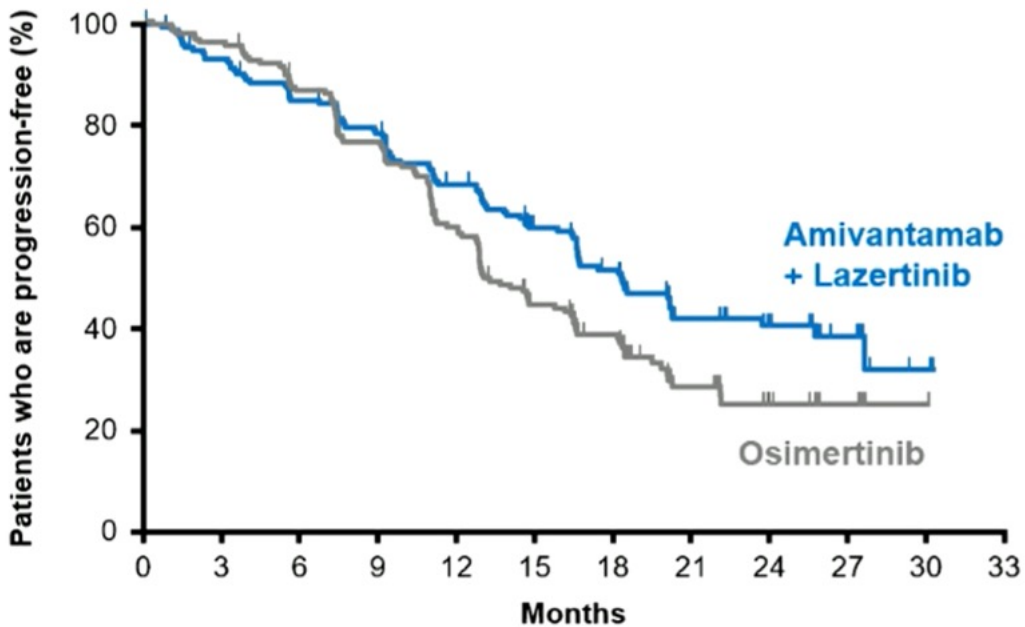
[a]Extracranial PFS was defined as time from randomization to disease progression (detected by extracranial scans) or death. If first progression was solely detected by CNS, these patients were censored at the time of CNS disease progression.
[b]Nominal *P*-value; endpoint was exploratory and not part of hierarchical hypothesis testing.
BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; mo, months; NE, not estimable; PFS, progression-free survival.

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

MARIPOSA: PFS by CNS Metastases

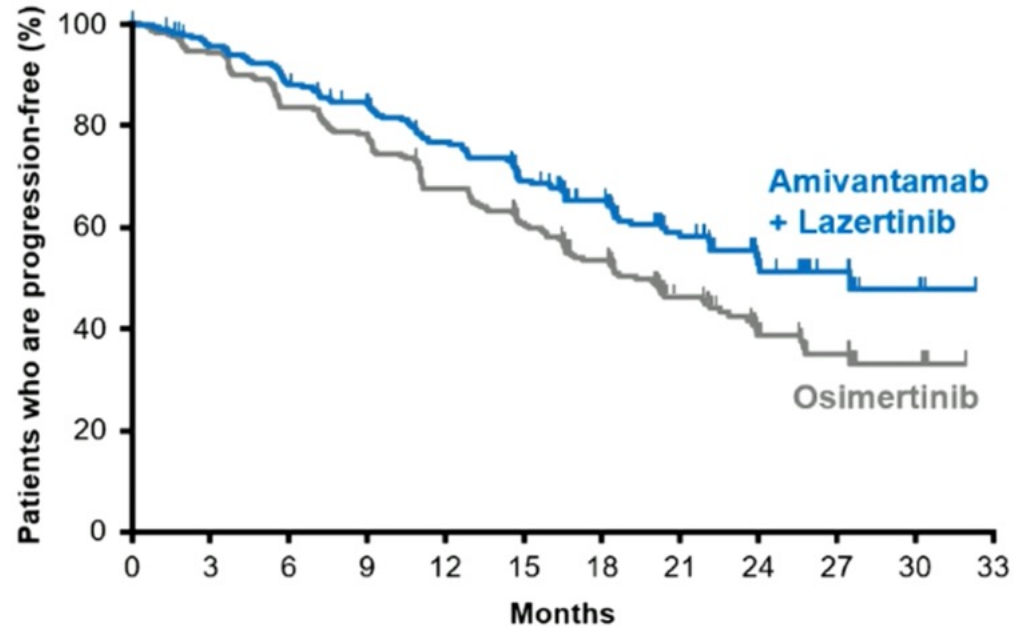
With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

HR, **0.69** (95% CI, 0.53–0.92)



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)

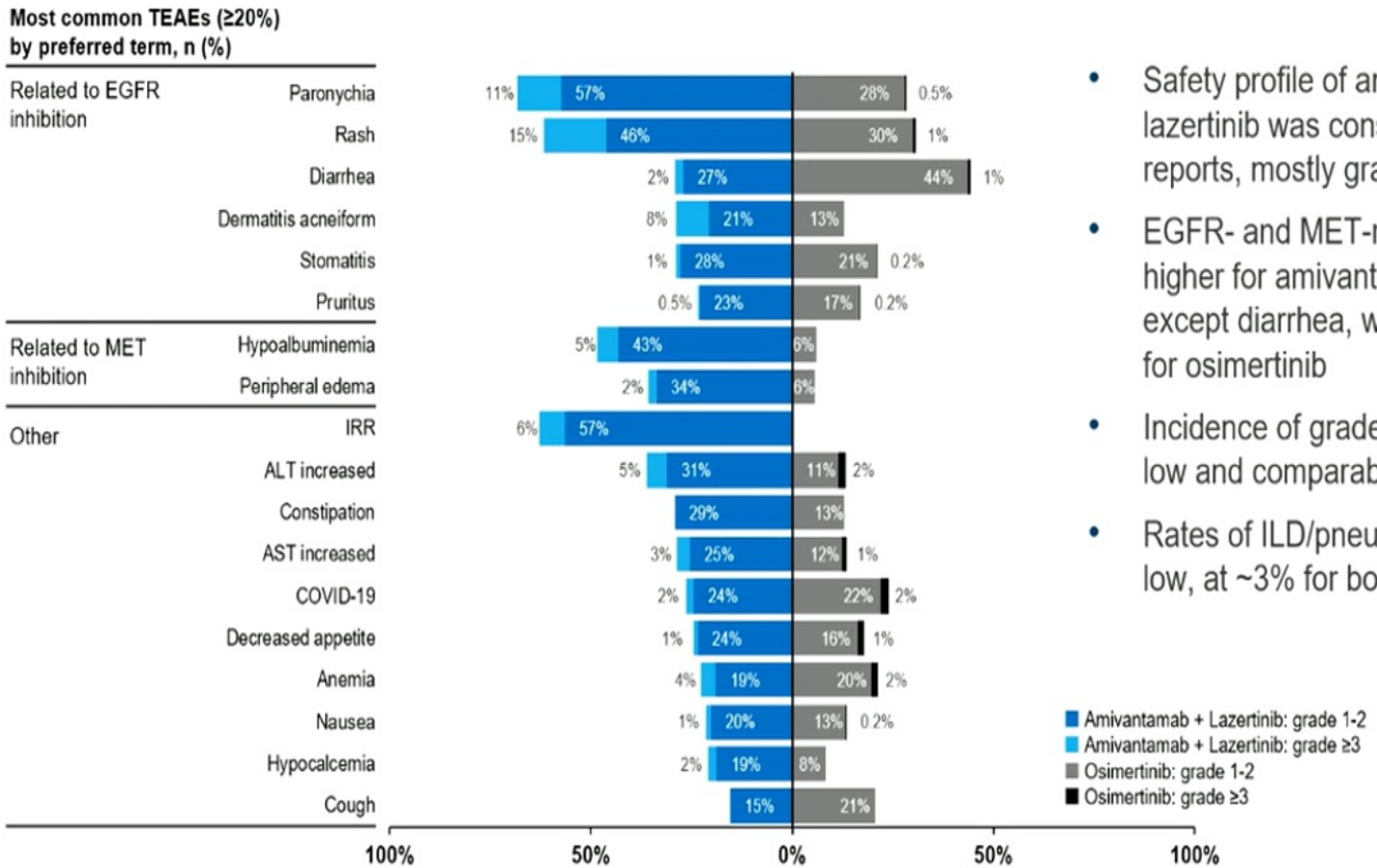
HR, **0.69** (95% CI, 0.53–0.89)



Presented by B. Cho. ESMO 2023. LBA14

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

What about toxicity?



- Safety profile of amivantamab + lazertinib was consistent with prior reports, mostly grades 1-2
- EGFR- and MET-related AEs were higher for amivantamab + lazertinib except diarrhea, which was higher for osimertinib
- Incidence of grade 4-5 AEs was low and comparable between arms
- Rates of ILD/pneumonitis remained low, at ~3% for both arms

Toxicity
Ami/Laz vs Osimertinib

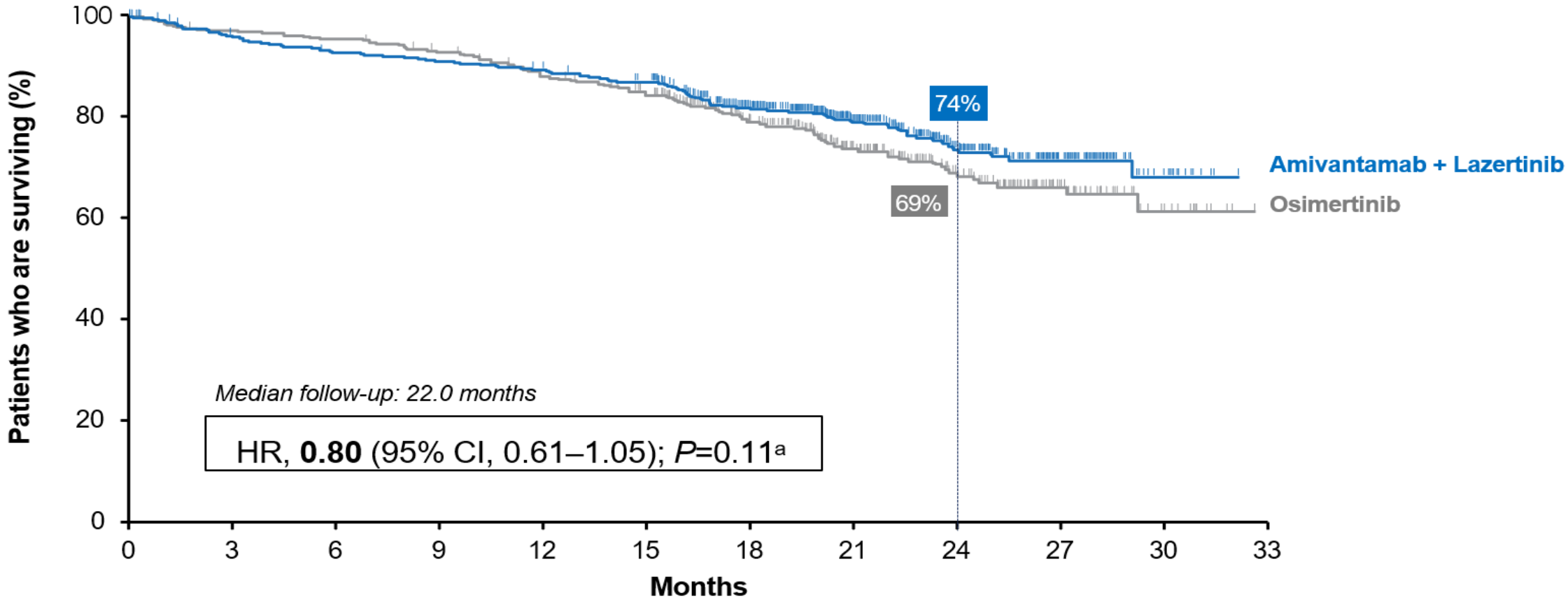
- IRR: 63% vs 0%
- VTE: 37% vs 9%
- Rash: 61% vs 31%
- Diarrhea: 29% vs 45%
- ILD: 3% vs 3%

Presented by B. Cho. ESMO 2023. LBA14

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Interim Overall Survival

Early survival data show a trend favoring amivantamab + lazertinib vs osimertinib



No. at risk												
Amivantamab + Lazertinib	429	403	389	382	374	360	293	201	122	58	14	0
Osimertinib	429	416	409	395	372	349	280	186	110	54	13	0

[a]There were a total of 214 deaths in the amivantamab + lazertinib and osimertinib arms at time of the prespecified interim OS analysis, which represents 25% of all randomized patients and 55% of the ~390 projected deaths for the final OS analysis. Medians at this time are not estimable.

CI, confidence interval; HR, hazard ratio; OS, overall survival.

MARIPOSA: Unanswered Questions

- Overall Survival?

- Is benefit of addition of Amivantamab to Lazertinib worth the risk/increased toxicity?
  - ✓ Subgroups: CNS mets benefited in both groups, L858R, co-mutations
  - ✓ Toxicity: IRR; VTE, Rash

- Is benefit of addition of Amivantamab to Lazertinib better than other combination strategies?
  - ✓ 3rd generation EGFR TKI + Chemotherapy (e.g., FLAURA2)
  - ✓ MET targeting agents (TKI)
  - ✓ ADCs (e.g., patritumab deruxtecan)
  - ✓ MARIPOSA2

- Resistance mechanisms
  - ✓ MET expression de novo vs post 3G TKI

Joshua Sabari, MD. Masters in Thoracic Oncology Summit (MATOS) 2023.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

MADRID 2023 ESMO congress

TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer with actionable genomic alterations

Luis Paz-Ares,[1] Myung-Ju Ahn,[2] Aaron Lisberg,[3] Satoru Kitazono,[4] Byoung Chul Cho,[5] George Blumenschein Jr,[6] Elaine Shum,[7] Elvire Pons Tostivint,[8] Yasushi Goto,[9] Kiyotaka Yoh,[10] Rebecca Heist,[11] Paul Baas,[12] David Planchard,[13] Maurice Pérol,[14] Enriqueta Felip,[15] Wu-Chou Su,[16] Hong Zebger-Gong,[17] Lan Lan,[18] Chelsea Liu,[18] Jacob Sands[19]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Samsung Medical Center, Seoul, South Korea; [3]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [4]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [5]Severance Hospital, Seoul, South Korea; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]NYU Langone Health Perlmutter Cancer Center, New York, NY, USA; [8]University Hospital of Nantes, Nantes, France; [9]National Cancer Center Hospital, Tokyo, Japan; [10]National Cancer Center Hospital East, Kashiwa, Japan; [11]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [12]The Netherlands Cancer Institute, Amsterdam, the Netherlands; [13]Gustave Roussy, Villejuif, France; [14]Centre Léon Bérard, Lyon, France; [15]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [16]National Cheng Kung University Hospital, Tainan, Taiwan; [17]Daiichi Sankyo Europe GmbH, Munich, Germany; [18]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [19]Dana-Farber Cancer Institute, Boston, MA, USA

Introduction and Study Design

- **Dato-DXd** is a TROP2-directed ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- In the **phase 1 TROPION-PanTumor01** study, Dato-DXd showed promising efficacy in patients with actionable genomic alterations[2]
- **TROPION-Lung05** (NCT04484142) is a **phase 2**, single-arm study evaluating Dato-DXd in patients with **advanced or metastatic NSCLC with actionable genomic alterations** that progressed on or after targeted therapy and platinum-based chemotherapy

Screening

Key inclusion criteria

- Stage IIIB, IIIC, or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS of 0 or 1
- ≥1 line of targeted therapy
- 1 or 2 prior cytotoxic agent–containing therapies including platinum-based therapy in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

Dato-DXd
6 mg/kg
Q3W

Endpoints[a]

Primary: ORR by BICR

Secondary:

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

ADC, antibody-drug conjugate; BICR, blinded independent central review; CBR, clinical benefit rate; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG1, immunoglobulin G1; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; TROP2, trophoblast cell-surface antigen 2; TTR, time to response.

[a]The primary completion date will occur when all patients have had either a minimum of 9 months of follow-up after the start of study treatment or have discontinued from the study.

1. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329-2340. **2.** Shimizu T, et al. *J Clin Oncol*. Published online June 16, 2023.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

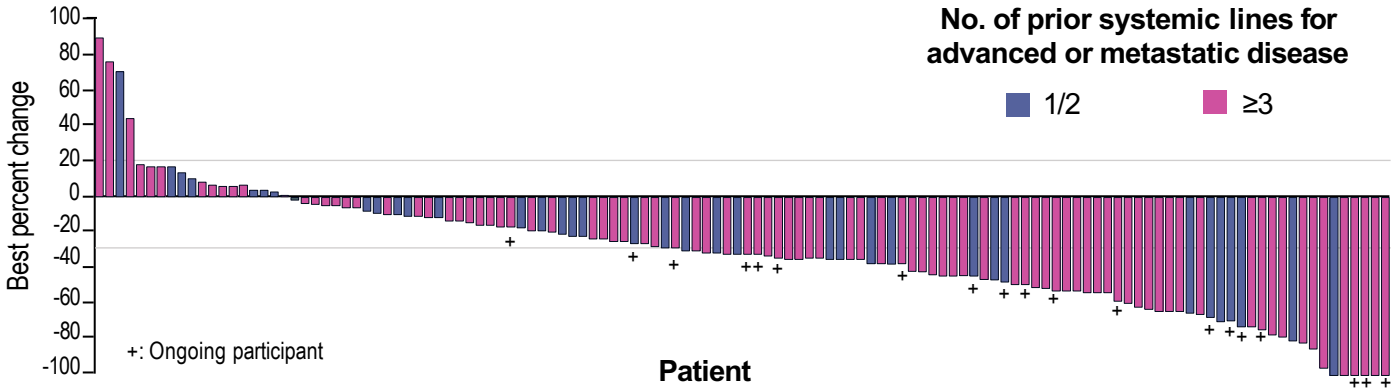
Efficacy Summary

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

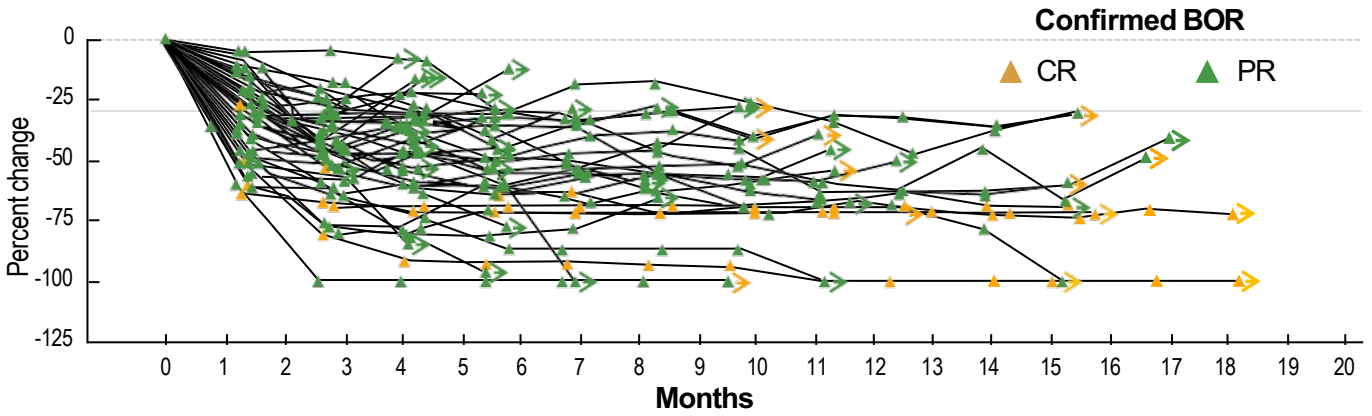
BOR: In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR

***EGFR* subset:** Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

Best Percent Change From Baseline in Sum of Diameters of Target Lesions



Percent Change From Baseline in Sum of Diameters of Target Lesions in Patients With Confirmed CR/PR[c]



BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

[a]The 2-sided 95% CIs are based on the Clopper-Pearson exact binomial method. [b]Median PFS and PFS probabilities are based on the Kaplan-Meier method. [c]Per BICR.

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

Targeting Mechanisms of Resistance

- *MET* amplification (15 - 25%)
  - Add MET inhibitor (INSIGHT 2) vs platinum doublet +/- IO (Phase III SAFFRON)

- SCLC transformation (13%)
  - Platinum etoposide plus osimertinib or immunotherapy (ECOG)

- *EGFR C797S* (5 – 10%)
  - Add 1st Gen EGFR TKI (i.e. gefitinib) vs platinum doublet +/- IO

- Acquired targetable oncogenic mutations (< 5%)
  - Add relevant targeted therapy (*BRAF* V600E, *RET* fusion, etc.)

Tan DSW, et al. INSIGHT-2. ASCO 2023
Ramalingam SS, et al. Targeting osimertinib resistance. WCLC 2022; JTO 16(3): e15-20. OA03.05
Rotow J, et al. Osimertinib + selpercatinib in EGFR mutant and RET fusion NSCLC. CCR 2023.
Wei XW, et al. Treatment for EGFR mutant NSCLC with concomitant BRAF mutations. JTO CRR 2022.

Osi Resistance: Without Mechanism Identified.

- Carboplatin plus pemetrexed
  - +/- osimertinib (continuation)
  - +/- immunotherapy (IMPower-150; ATTLAS)
  - +/- bevacizumab
- Patritumab deruxtecan (HERTHENA-Lung01)
- Amivantamab + Lazertinib (CHRYSALIS-2)
- Amivantamab + chemotherapy +/- Lazertinib (MARIPOSA-2)
- Datopotamab deruxtecan (TROPION-Lung05)
- Other antibody drug conjugates (e.g., CEACAM5 expression [Tusatumimab]; MET overexpression [Telisotuzumab]; another TROP2 [Sacituzumab, EVOKE-01 and EVOKE-02])

Patel JD. J Clin Oncol 2023; Socinski MA. J Thorac Oncol 2021; Ahn M-J et al., 2023 ESMO Congress; Yu H, et al. HERTHENA-Lung01, JCO 2023; Shu CA et al., 2022 ASCO Congress; Passaro A, 2023 ESMO Congress; Paz-Ares L et al., 2023 ESMO Congress; Ricordel C et al., 2022 ASCO Congress; Goldman J et al., 2022 ASCO Congress; BC Cho et al. 2023 WCLC Singapore.

MADRID 2023 ESMO congress

Amivantamab Plus Chemotherapy vs Chemotherapy as First-line Treatment in *EGFR* Exon 20 Insertion–mutated Advanced Non-small Cell Lung Cancer (NSCLC)

Primary Results From PAPILLON, a Randomized Phase 3 Global Study

Nicolas Girard,[1] Keunchil Park,[2,*] Ke-Jing Tang,[3] Byoung Chul Cho,[4] Luis Paz-Ares,[5] Susanna Cheng,[6] Satoru Kitazono,[7] Muthukkumaran Thiagarajan,[8] Jonathan W. Goldman,[9] Joshua K. Sabari,[10] Rachel E. Sanborn,[11] Aaron S. Mansfield,[12] Jen-Yu Hung,[13] Sanjay Popat,[14] Josiane Mourão,[15] Archan Bhattacharya,[16] Trishala Agrawal,[17] S. Martin Shreeve,[18] Roland E. Knoblauch,[17] Caicun Zhou[19]

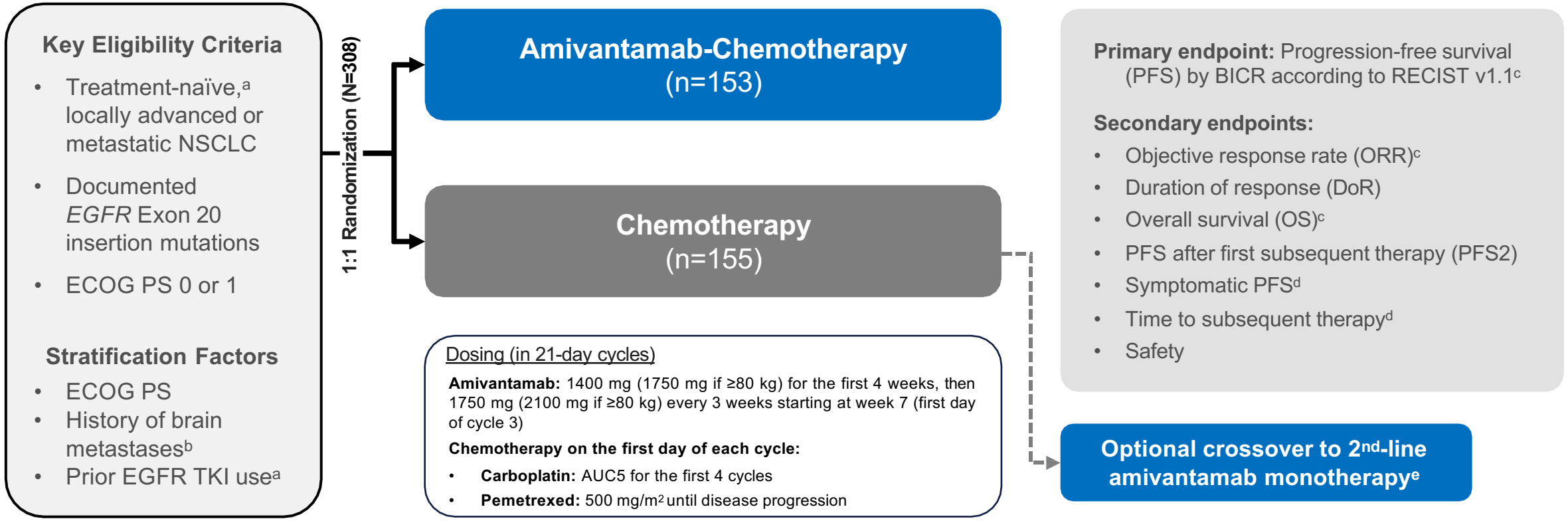
[1]Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France and Paris Saclay University, UVSQ, Versailles, France; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [4]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [5]Hospital Universitario 12 de Octubre, Madrid, Spain; [6]Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; [7]Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [8]General Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [9]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA; [10]NYU Langone Health, New York, NY, USA; [11]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [12]Mayo Clinic, Rochester, MN, USA; [13]Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [14]Royal Marsden Hospital NHS Foundation Trust, London, UK and The Institute of Cancer Research, London, UK; [15]Barretos Cancer Hospital, Barretos, Brazil; [16]Janssen R&D, High Wycombe, UK; [17]Janssen R&D, Spring House, PA, USA; [18]Janssen R&D, San Diego, CA USA; [19]Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China.

*Current Affiliation: MD Anderson Cancer Center, Houston, TX, USA.

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

PAPILLON: Phase 3 Study Design



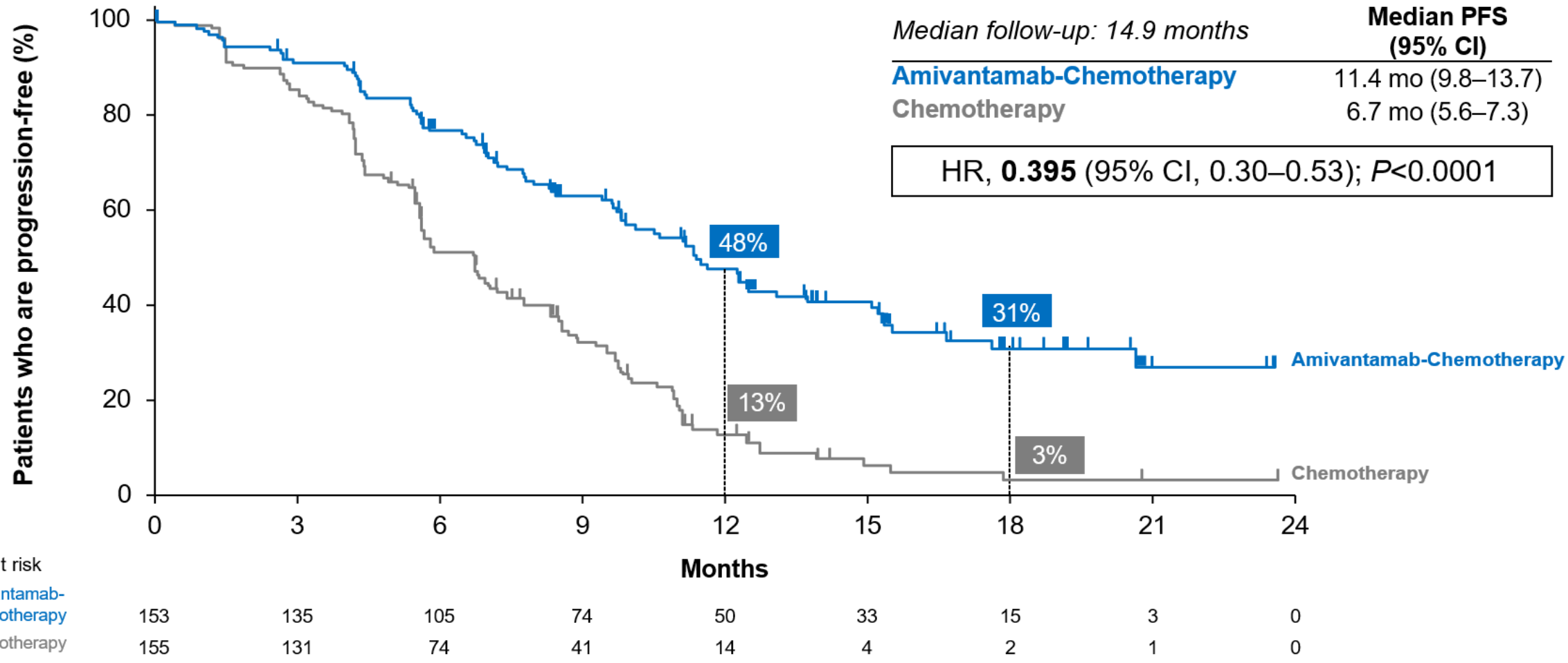
PAPILLON (ClinicalTrials.gov Identifier: NCT04538664) enrollment period: December 2020 to November 2022; data cut-off: 3-May-2023.

[a]Removed as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented).
[b]Patients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomization.
[c]Key statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing.
[d]These secondary endpoints (time to subsequent therapy and symptomatic progression-free survival) will be presented at a future congress.
[e]Crossover was only allowed after BICR confirmation of disease progression; amivantamab monotherapy on Q3W dosing per main study.

AUC, area under the curve; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

Primary Endpoint: Progression-free Survival by BICR

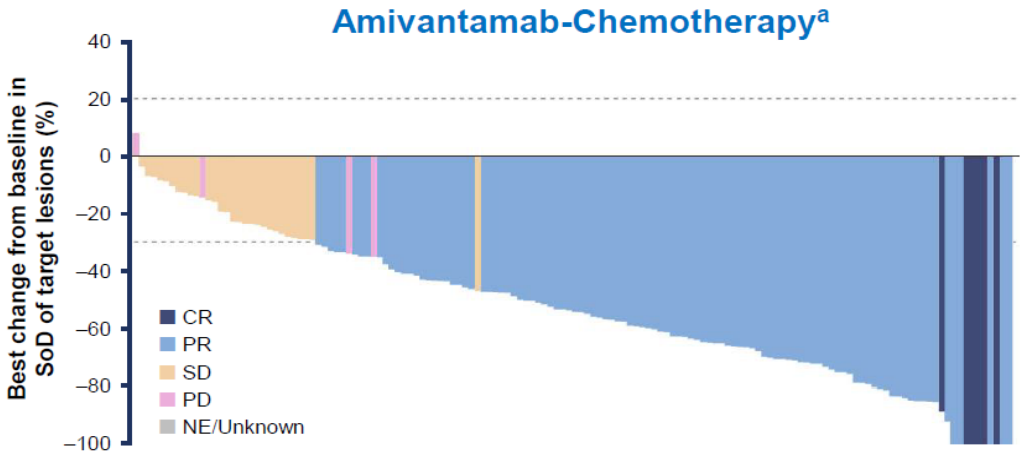
Amivantamab-chemotherapy reduced risk of progression or death by 60%

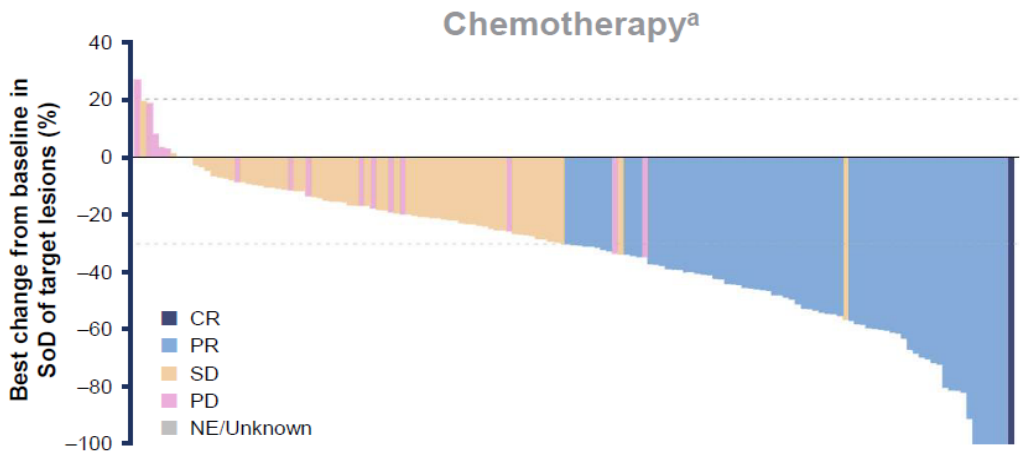


Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001[a])

[a]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Best Response and ORR by BICR





BICR-assessed response[b]	Amivantamab-Chemotherapy (n=153)	Chemotherapy (n=155)
Mean percent change of SoD	-53%[c]	-34%
ORR	73% (95% CI, 65–80)	47% (95% CI, 39–56)
Odds ratio	3.0 (95% CI, 1.8–4.8); *P*<0.0001	
Best response, n (%)		
Complete response	6 (4)	1 (1)
Partial response	105 (69)	71 (47)
Stable disease	29 (19)	62 (41)
Progressive disease	4 (3)	16 (11)
NE/Unknown	8 (5)	2 (1)
Median time to response	6.7 wk (range, 5.1–72.5)	11.4 wk (range, 5.1–60.2)

Consistent results with investigator assessment: ORR of 66% vs 43% (OR, 2.6; *P*<0.0001)

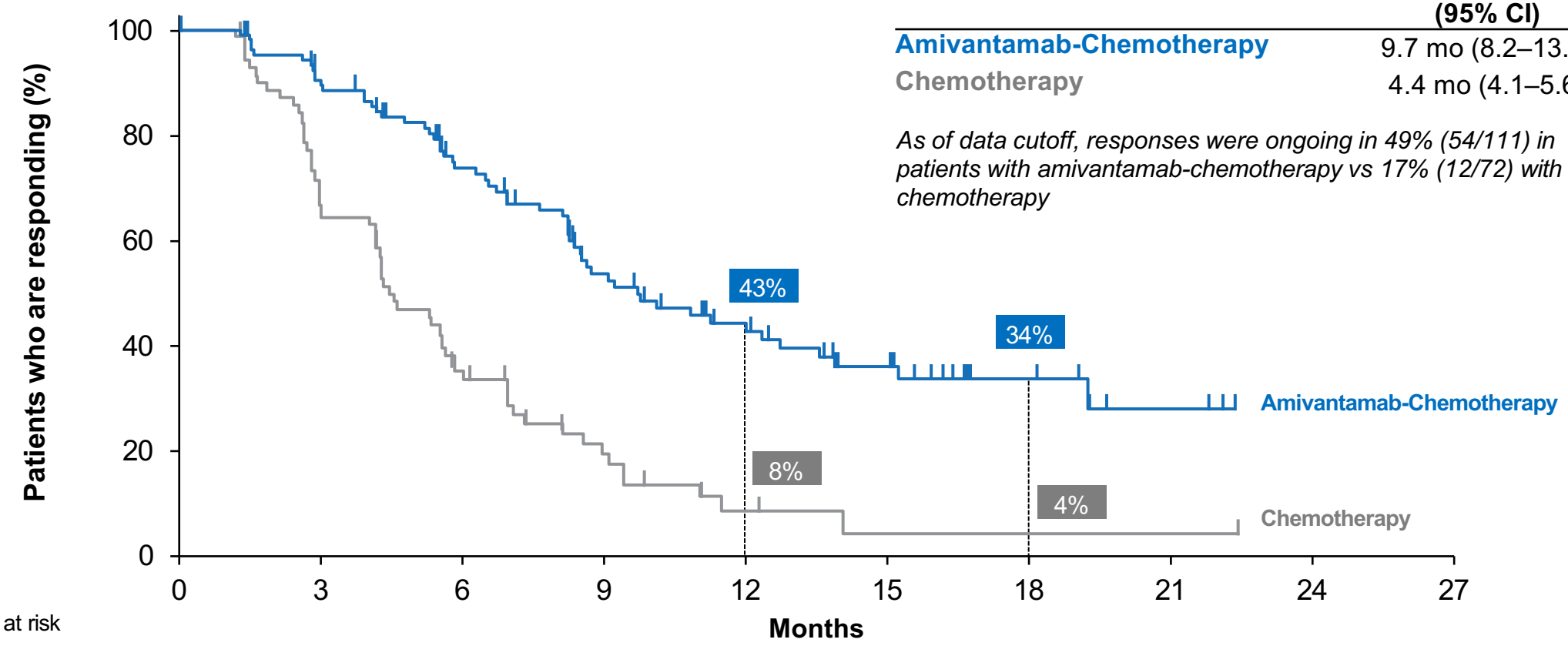
[a]Patients without postbaseline tumor assessment were not included in this plot. [b]No. of patients with measurable disease at baseline by BICR was 152 in both arms; response data presented among all responders. [c]Nominal *P*<0.001; endpoint not part of hierarchical testing.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; mo, month; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response;

Duration of Response (DoR) by BICR

	Median DoR[a] (95% CI)
Amivantamab-Chemotherapy	9.7 mo (8.2–13.5)
Chemotherapy	4.4 mo (4.1–5.6)

As of data cutoff, responses were ongoing in 49% (54/111) in patients with amivantamab-chemotherapy vs 17% (12/72) with chemotherapy



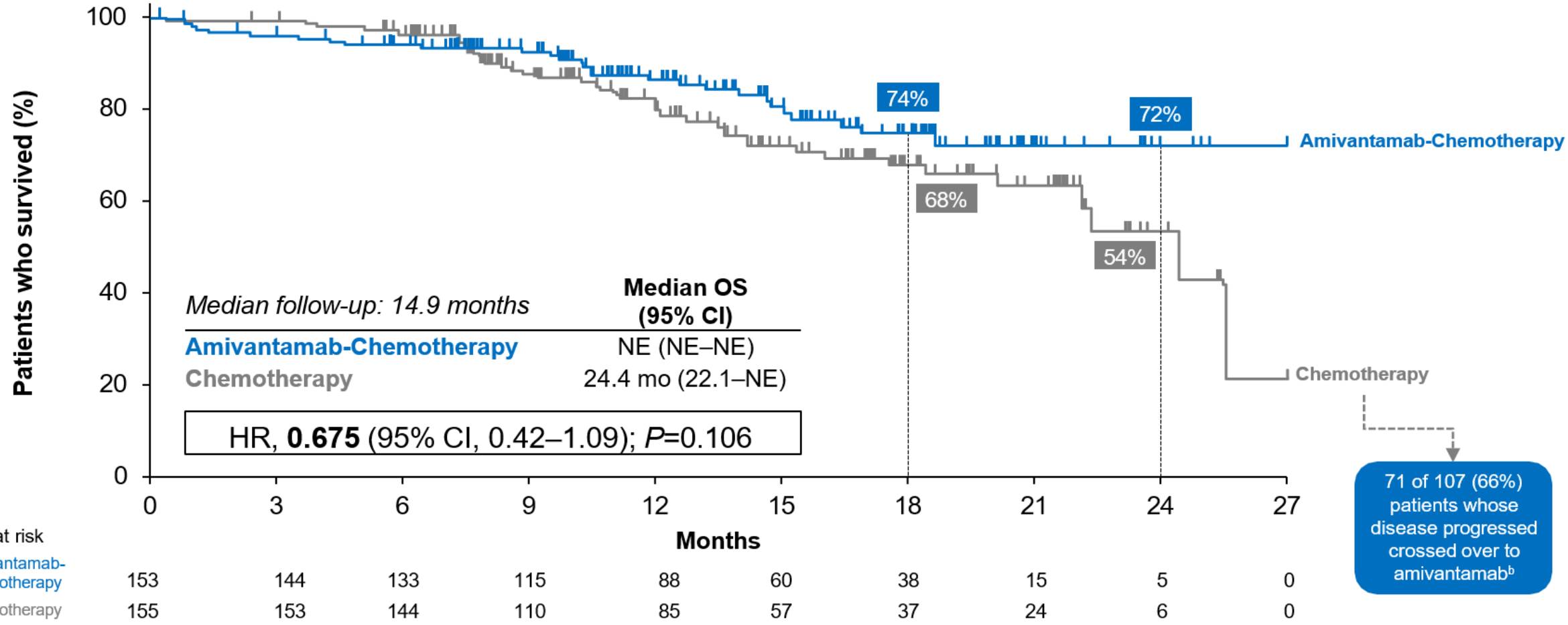
No. at risk									
Amivantamab-Chemotherapy	111	91	66	42	28	18	8	3	0
Chemotherapy	72	45	23	10	3	1	1	1	0

Consistent DoR benefit was seen with investigator assessment: 13.5 vs 6.8 mo

[a]Among all responders. BICR, blinded independent central review; CI, confidence interval; mo, months.

Interim Overall Survival[a]

Amivantamab-chemotherapy shows trend in reducing risk of death by over 30%



[a]There were 70 deaths in the study at the time of the prespecified interim OS analysis, which represents 23% of all randomized patients and 33% of the ~210 projected deaths for the final OS analysis.
[b]A total of 71 patients (65 patients as part of the crossover arm plus an additional 6 patients off-protocol) received second-line amivantamab monotherapy out of 107 chemotherapy-randomized patients with disease progression.

CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; OS, overall survival.

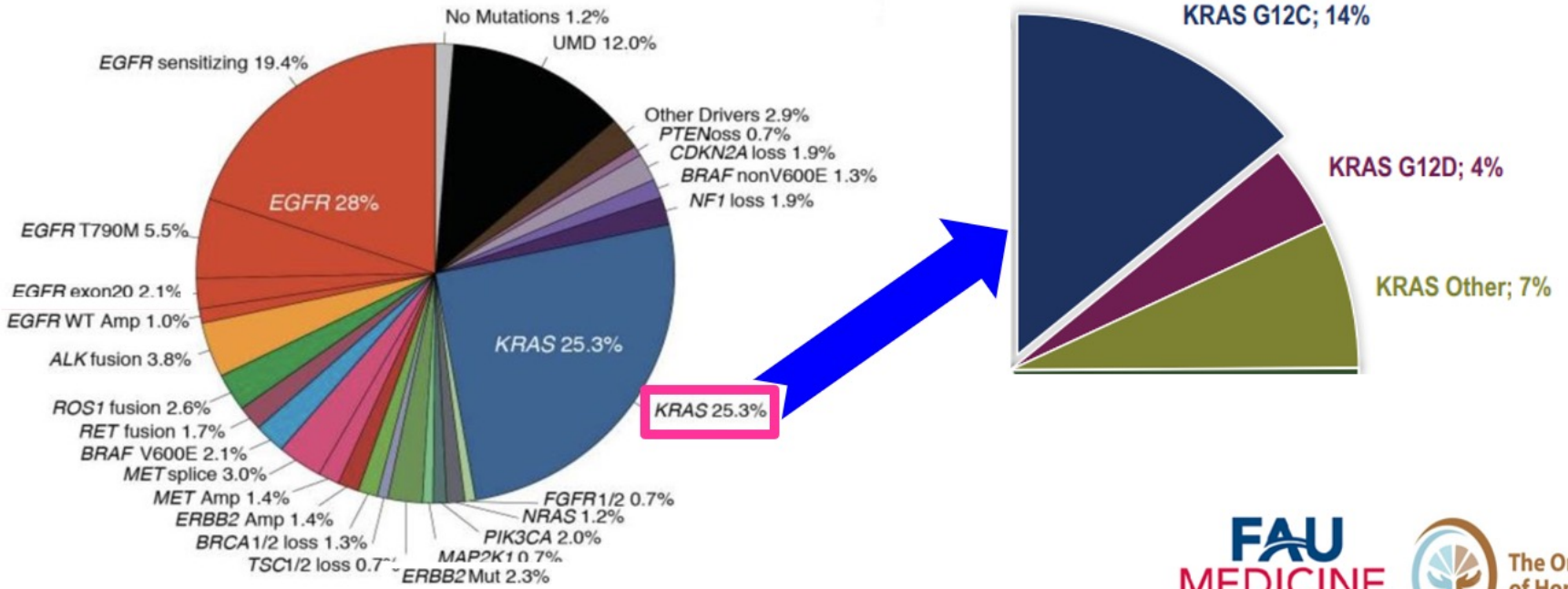
Safety Profile

Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Peripheral edema	45 (30)	2 (1)	16 (10)	0
Other				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Alanine aminotransferase increased	50 (33)	6 (4)	56 (36)	2 (1)
Aspartate aminotransferase increased	47 (31)	1 (1)	51 (33)	1 (1)
COVID-19	36 (24)	3 (2)	21 (14)	1 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)

- EGFR- and MET-related AEs were increased with amivantamab-chemotherapy, primarily grade 1-2
- Chemotherapy-associated hematologic and GI toxicities were comparable except for neutropenia
- Neutropenia was transient; majority of events were not serious, with low rates of discontinuations
- Pneumonitis was reported in 4 (3%) patients in the amivantamab-chemotherapy arm
- Treatment-related discontinuations of amivantamab were low (7%).

AE, adverse event; EGFR, epidermal growth factor receptor; GI, gastrointestinal.

KRAS^{G12C} Pathway

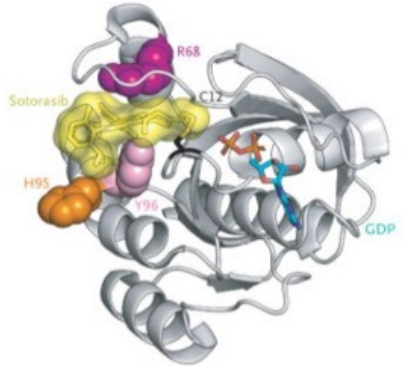


Background→ 2L Standard of Care.

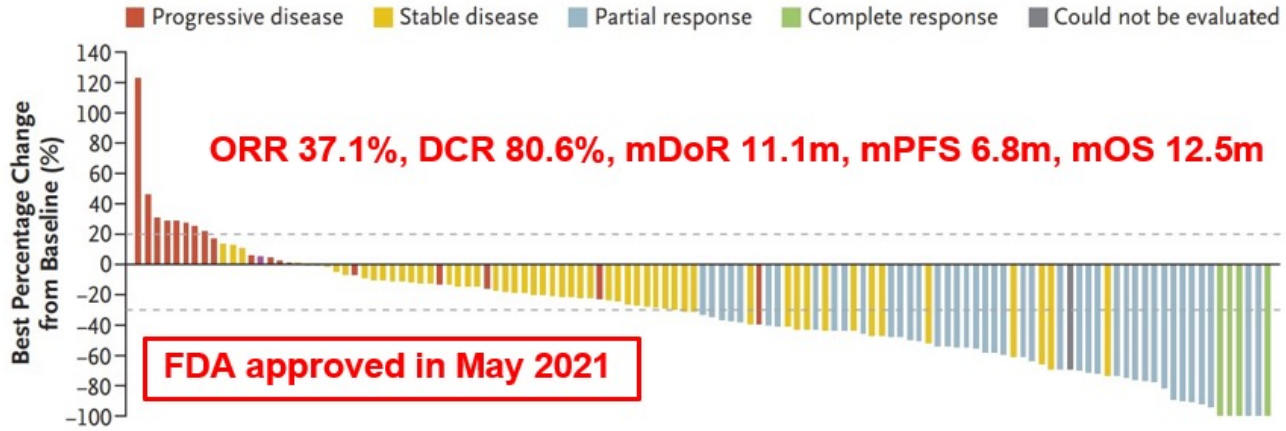
Covalent *KRAS*^{G12C} Inhibitors

A.

Sotorasib (AMG 510)



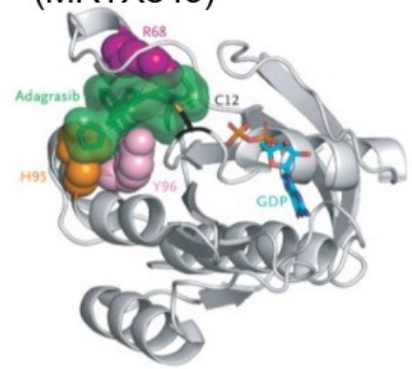
Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393



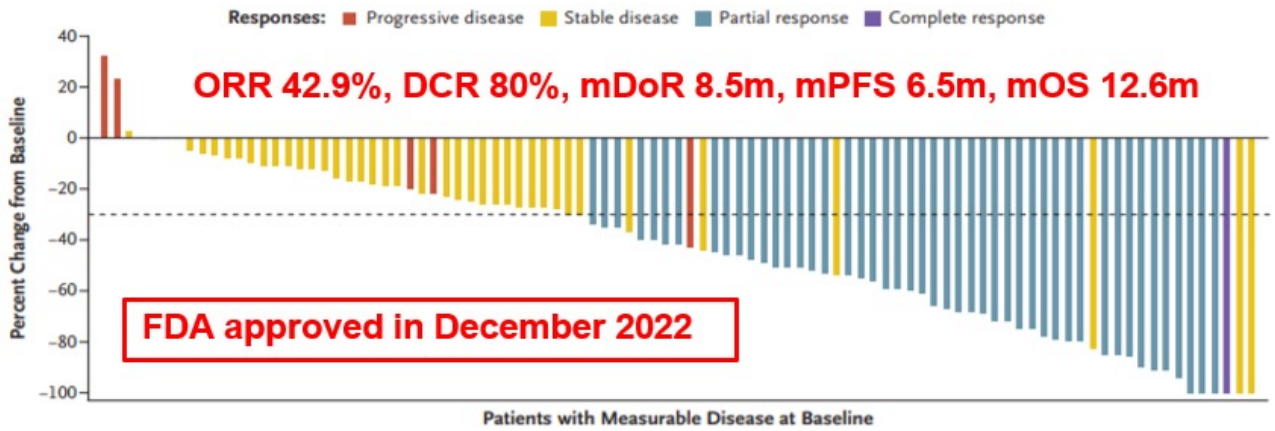
Skoulidis F et al. *N Engl J Med* 2021 Jun 24;384(25):2371-2381

B.

Adagrasib (MRTX849)



Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393



Jänne PA al. *N Engl J Med* 2022 Jul 14;387(2):120-131 (Epub 2022 June 3)

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

2023 ASCO® ANNUAL MEETING

KontRASt-01 update: Safety and efficacy of JDQ443 in *KRAS G12C*-mutated solid tumors including non-small cell lung cancer (NSCLC)

Philippe A Cassier,[1] Christophe Dooms,[2] Anas Gazzah,[3] Enriqueta Felip,[4] Neeltje Steeghs,[5] Kristoffer Staal Rohrberg,[6] Filippo De Braud,[7] Benjamin Solomon,[8] Martin Schuler,[9] Daniel SW Tan,[10] Noboru Yamamoto,[11] Herbert HF Loong,[12] Byoung Chul Cho,[13] Jürgen Wolf,[14] Chia-Chi Lin,[15] Marcelo V Negrao,[16] Lillian Werner,[17] Xiaoming Cui,[18] Anna F Farago,[17] **María de Miguel**[19]

1. Centre Léon Bérard, Lyon, France; 2. University Hospitals Leuven, Leuven, Belgium; 3. Gustave Roussy, Villejuif, France; 4. Vall d'Hebron University Hospital, Barcelona, Spain; 5. The Netherlands Cancer Institute, Amsterdam, the Netherlands; 6. Department of Oncology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; 7. Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; 8. Peter MacCallum Cancer Centre, Melbourne, Australia; 9. West German Cancer Center, University Hospital Essen, Essen, Germany; 10. National Cancer Centre Singapore, Singapore; 11. National Cancer Center Hospital, Tokyo, Japan; 12. Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong; 13. Yonsei University College of Medicine, Seoul, Republic of Korea; 14. Department I of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany; 15. National Taiwan University Hospital, Taipei, Taiwan; 16. MD Anderson Cancer Center, Houston, TX, USA; 17. Novartis Institutes for BioMedical Research, Cambridge, MA, USA; 18. Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 19. START-CIOCC Hospital Universitario HM Sanchinarro, Madrid, Spain.

Dr. María de Miguel

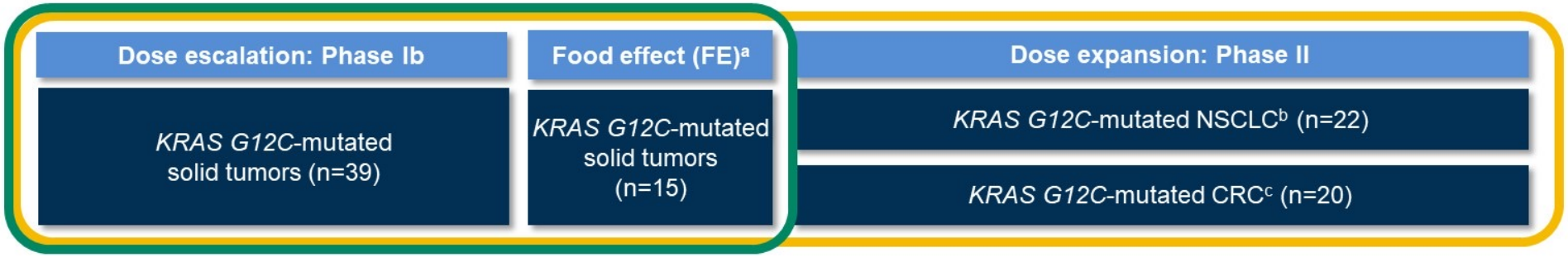
Scan to obtain presentation

https://bit.ly/CassierP9007

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

KontRASt-01: JDQ443 monotherapy



Safety data set: All patients (N=96) across dose escalation, FE and dose expansion cohorts

Efficacy data set: Patients with NSCLC (N=27) from dose escalation and FE cohorts

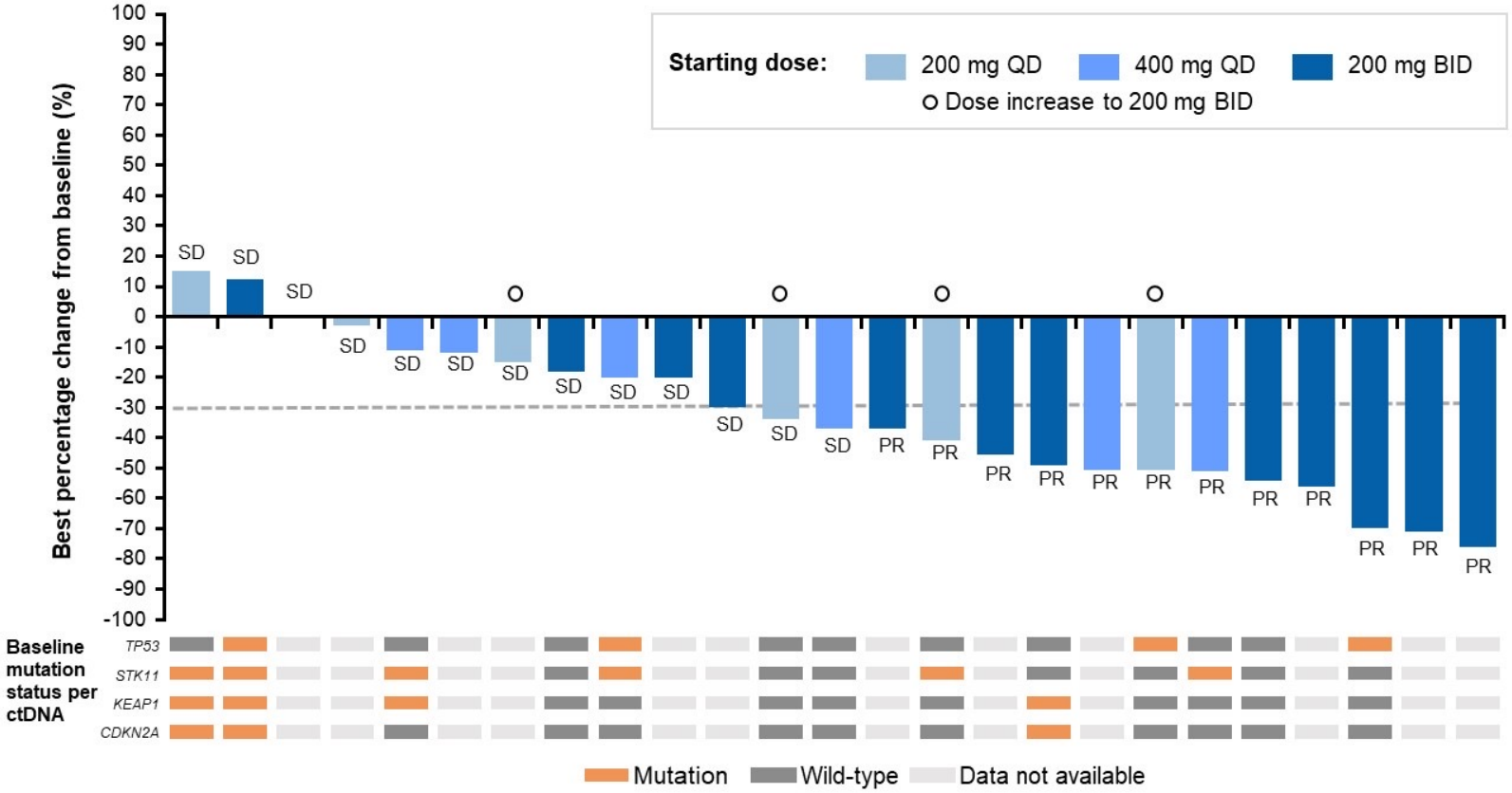
Pre-planned analyses in the Phase II NSCLC expansion group will be the subject of future presentations.

Key objectives for dose escalation	Key objectives for dose expansion
Primary: Assess the safety and tolerability of JDQ443 and identify the MTD and/or RD and regimen for future studies **Secondary:** Evaluate the antitumor activity and characterize the PK of JDQ443	**Primary:** Evaluate the antitumor activity of JDQ443 monotherapy **Secondary:** Assess the safety and tolerability and characterize the PK of JDQ443
Key eligibility criteria	
Patients with advanced, *KRAS G12C*-mutated solid tumors who have received standard-of-care therapy or who are intolerant of or ineligible for approved therapies; ECOG PS 0–1; no prior treatment with a $KRAS^{G12C}$ inhibitor	

Data presented are from a cut-off date of February 1, 2023. [a]Patients in the FE cohort received treatment on an empty stomach, at least 1 hour before and 2 hours after a meal, from Day 1 to Day 7. Following a washout period with no treatment on Day 8, patients commenced standard treatment cycles at the same dose and schedule, receiving JDQ443 with food. For dose escalation and dose expansion, JDQ443 was dosed with food at all time points; [b]All patients with NSCLC must have been previously treated with a platinum-based chemotherapy regimen and an immune checkpoint inhibitor, either in combination or in sequence, unless ineligible to receive such therapy; [c]Patients with CRC must have previously received standard-of-care therapy, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, unless ineligible to receive such therapy.
BID, twice daily; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; FE, food effect; KRAS, Kirsten rat sarcoma viral oncogene homolog; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; PS, performance status; QD, once daily; RD, recommended dose.

Maria de Miguel et al. 2023 ASCO Annual Meeting.

NSCLC: Best overall response



	JDQ443 200 mg BID (n=14)	JDQ443 All dose levels, pooled (n=27)
Confirmed ORR	**57.1%**	44.4%
DCR	**92.9%**	92.6%
BOR[a], n (%)		
PR	8 (57.1)	12 (44.4)
SD	5 (35.7)	13 (48.1)
PD	0	0
Unknown	1 (7.1)	2 (7.4)

Data presented with a cut-off date of February 1, 2023. Waterfall plot: 25 (92.6%) patients with NSCLC with available change from baseline tumor assessments; data are plotted out of n=27 patients with NSCLC who received JDQ443 single-agent. Patients were enrolled in dose escalation and food effect cohorts. [a]Best overall response per RECIST 1.1 based on investigator's assessment. Intra-patient dose escalation, per protocol, occurred in four patients from 200 mg QD to 200 mg BID. Mutation detection: plasma ctDNA at baseline; assay validated to 0.5% allele frequency. 95% CI for ORR: 28.9–82.3 for 200 mg BID; 25.5–64.7 for all dose levels.
BID, twice daily; CI, confidence interval; ctDNA, circulating tumor DNA; DCR, disease control rate; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Maria de Miguel et al. 2023 ASCO Annual Meeting.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Summary

- JDQ443 is a structurally unique KRAS^{G12C} inhibitor that exhibits antitumor activity in NSCLC
  - Preliminary ORR: 57.1% (8/14) at recommended dose for expansion of 200 mg BID
- JDQ443 is well tolerated and has an acceptable safety profile
  - TRAEs were low-frequency, low-grade events
    - No Grade 4–5 TRAEs
    - No nausea, vomiting, or diarrhea higher than Grade 2
    - ALT/AST Grade 2–3 elevation events were rare and of limited duration
  - Safety/tolerability profile supports potential for combination strategies
- Actively enrolling: JDQ443 doublet combinations in KontRASt-01 have completed dose escalation and are now in Phase II dose expansion
  - JDQ443 + tislelizumab (anti–PD-1)
  - JDQ443 + TNO155 (SHP2 inhibitor)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; KRAS, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-1, programmed cell death protein-1; SHP2, Src homology-2 domain–containing protein tyrosine phosphatase-2; TRAE, treatment-related adverse event.

Maria de Miguel et al. 2023 ASCO Annual Meeting.

2023 ASCO ANNUAL MEETING

The primary endpoint analysis of SCARLET study:

A single-arm, phase II study of Sotorasib plus CARbopLatin-pemETrexed in advanced non-squamous, non-small cell lung cancer patients with KRAS G12C mutation: WJOG14821L

Shinya Sakata[1], Hiroaki Akamatsu[2], Koichi Azuma[3], Takehiro Uemura[4], Yuko Tsuchiya-Kawano[5], Hiroshige Yoshioka[6], Mitsuo Osuga[2], Yasuhiro Koh[2], Satoshi Morita[7], Nobuyuki Yamamoto[2]

[1]Kumamoto University Hospital, [2]Wakayama Medical University, [3]Kurume University School of Medicine, [4]Nagoya City University Graduate School of Medical Sciences, [5]Kitakyushu Municipal Medical Center, [6]Kansai Medical University, [7]Kyoto University Graduate School of Medicine, JPN

Presented by Hiroaki Akamatsu. 2023 ASCO Annual Meeting.

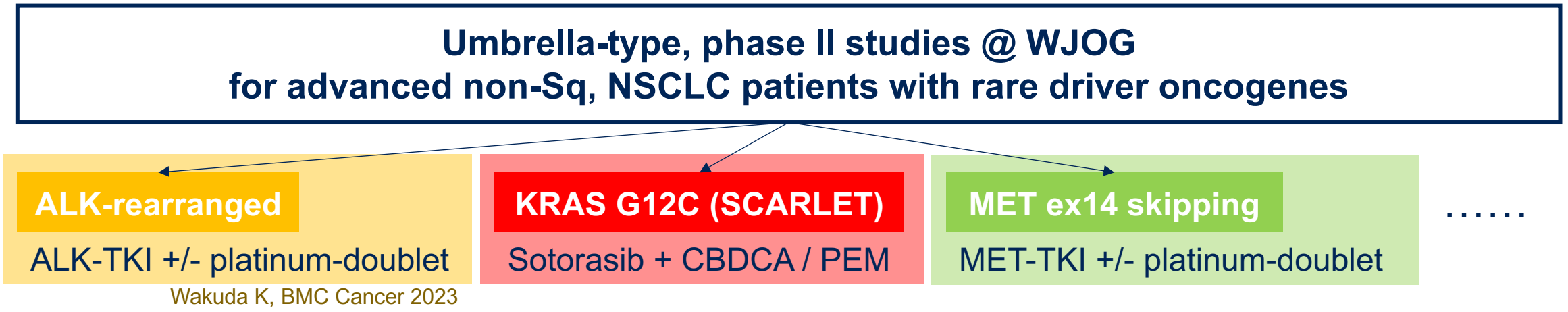
FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

Background

- Molecular-targeted drugs have a critical role in advanced non-squamous, non-small cell lung cancer (non-Sq, NSCLC) patients with oncogenic driver alterations
- In EGFR-mutated tumor, phase III trials showed the benefit of adding cytotoxic chemotherapy on gefitinib

Hosomi Y, JCO 2019. Miyauchi E, JCO 2022. Noronha V, JCO 2020. Hou X, JAMA Network Open 2023.



Wakuda K, BMC Cancer 2023

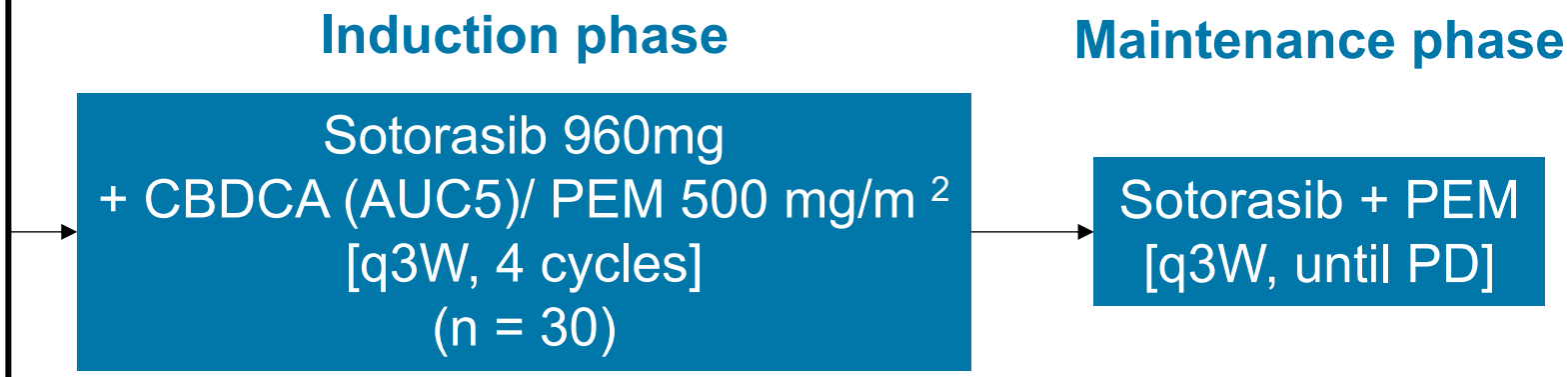
Presented by Hiroaki Akamatsu. 2023 ASCO Annual Meeting.

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

SCARLET: study schema

Key inclusion criteria

- Advanced non-Sq, NSCLC
- With KRAS G12C
- Naïve for Cytotoxic chemotherapy and KRAS inhibitor
- With measurable lesion
- ECOG PS 0-1
- Asymptomatic CNS mets allowed



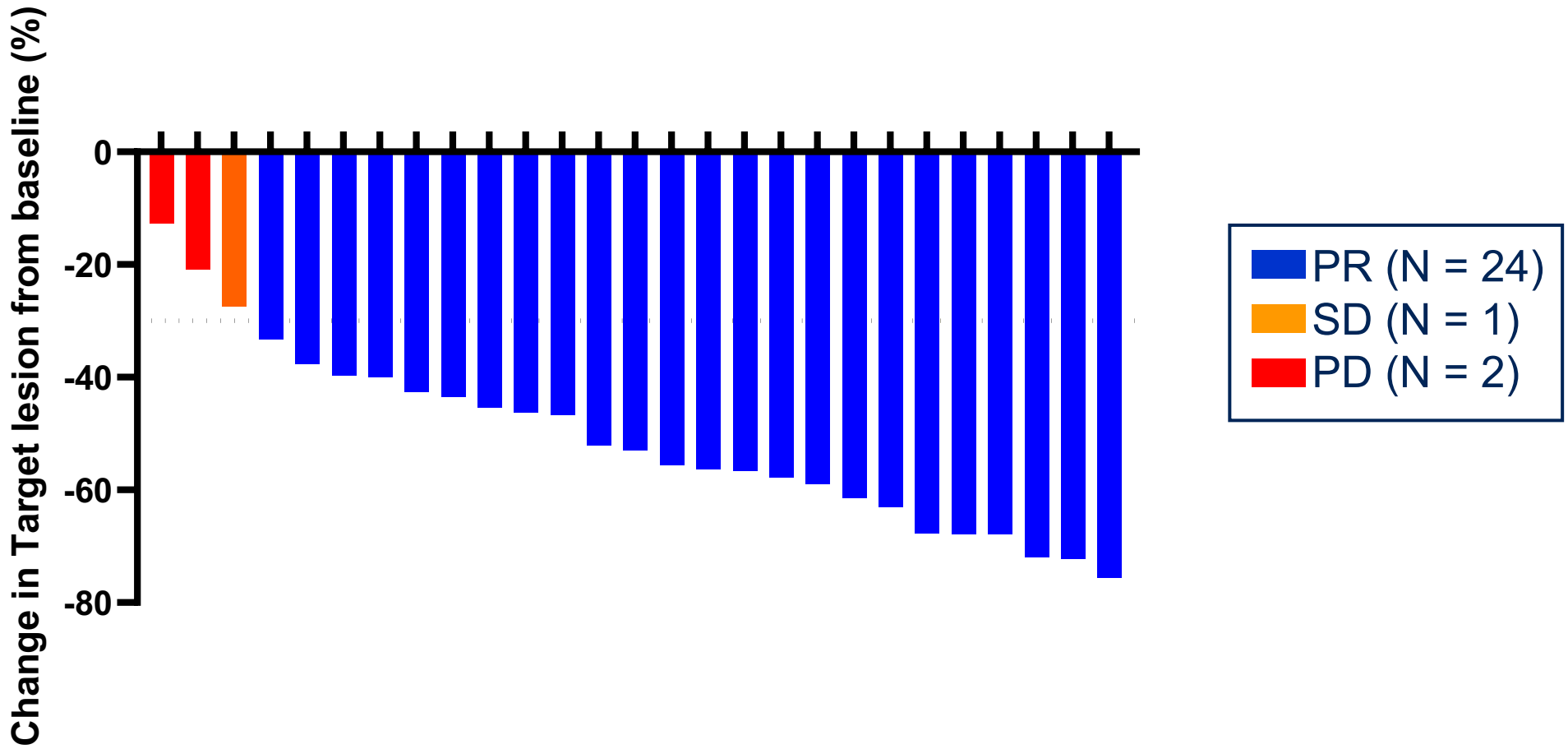
- Primary endpoint; ORR by blinded independent central review (BICR)
- Secondary endpoints; DCR, PFS, DOR, OS and AEs
- Translational research; NGS analysis (tissue and plasma [at baseline, 3 wks, and PD])

Trial identifier: jRCT2051210086

Presented by Hiroaki Akamatsu. 2023 ASCO Annual Meeting.

Primary endpoint: ORR by BICR

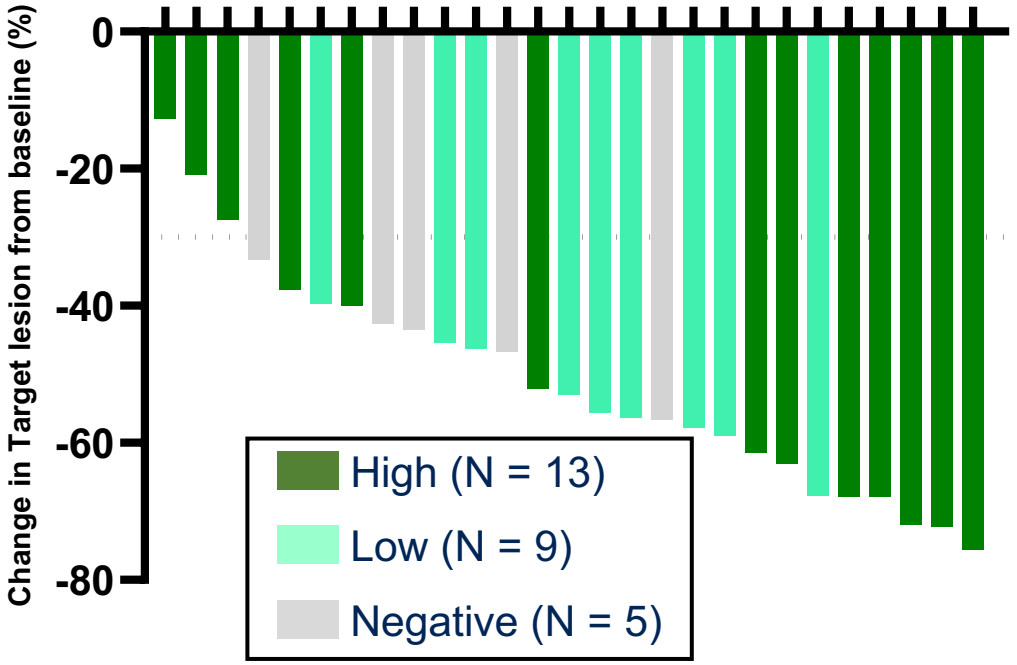
ORR 88.9% (80%CI 76.9-95.8%, 95%CI 70.8-97.6%)

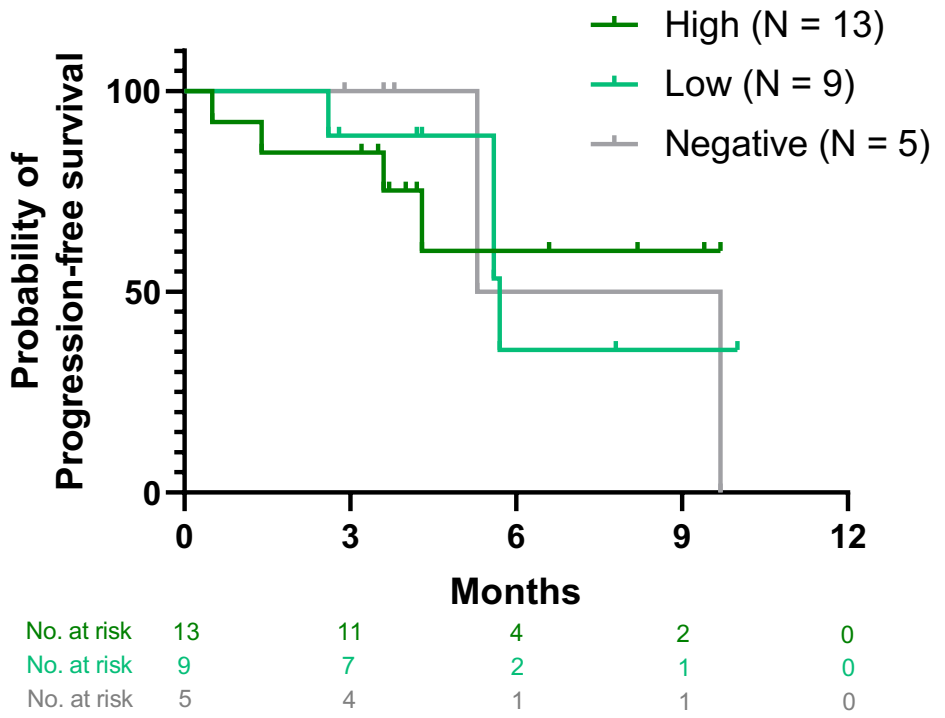


Presented by Hiroaki Akamatsu. 2023 ASCO Annual Meeting.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Efficacy by PD-L1 expression level





PD-L1 expression level	N	ORR	Median PFS (mo)
High (≥50%)	13	76.9% (95%CI 46.2-95.0%)	Not reached
Low (1-49%)	9	100% (95%CI 66.4-100%)	5.7
Negative (<1%)	5	100% (95%CI 47.8-100%)	7.5

Presented by Hiroaki Akamatsu. 2023 ASCO Annual Meeting.

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Treatment-related AEs (≥ 15% or any severe cases)

	Any Grade		>=Grade 3		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any adverse event	29	100.0	21	72.4	1	3.4	7	24.1	14	48.3	6	20.7	1	3.4
Anaemia	21	72.4	11	37.9	2	6.9	8	27.6	10	34.5	1	3.4	0	0.0
PLT decreased	13	44.8	7	24.1	4	13.8	2	6.9	5	17.2	2	6.9	0	0.0
Neutrophil decreased	12	41.4	7	24.1	0	0.0	5	17.2	4	13.8	3	10.3	0	0.0
Decreased appetite	10	34.5	0	0.0	4	13.8	6	20.7	0	0.0	0	0.0	0	0.0
Nausea	10	34.5	0	0.0	3	10.3	7	24.1	0	0.0	0	0.0	0	0.0
WBC decreased	10	34.5	6	20.7	1	3.4	3	10.3	4	13.8	2	6.9	0	0.0
Malaise	8	27.6	0	0.0	5	17.2	3	10.3	0	0.0	0	0.0	0	0.0
Constipation	7	24.1	0	0.0	4	13.8	3	10.3	0	0.0	0	0.0	0	0.0
Diarrhoea	7	24.1	2	6.9	3	10.3	2	6.9	2	6.9	0	0.0	0	0.0
γ-GTP increased	6	20.7	1	3.4	4	13.8	1	3.4	1	3.4	0	0.0	0	0.0
Neutropenia	5	17.2	3	10.3	0	0.0	2	6.9	3	10.3	0	0.0	0	0.0
Hiccups	5	17.2	0	0.0	4	13.8	1	3.4	0	0.0	0	0.0	0	0.0
ALT increased	5	17.2	1	3.4	2	6.9	2	6.9	0	0.0	1	3.4	0	0.0
Blood Cre increased	5	17.2	0	0.0	4	13.8	1	3.4	0	0.0	0	0.0	0	0.0
AST increased	4	13.8	2	6.9	2	6.9	0	0.0	2	6.9	0	0.0	0	0.0
Hyperkalaemia	3	10.3	1	3.4	0	0.0	2	6.9	1	3.4	0	0.0	0	0.0
Lymph decreased	3	10.3	1	3.4	1	3.4	1	3.4	1	3.4	0	0.0	0	0.0
Cellulitis	2	6.9	1	3.4	0	0.0	1	3.4	1	3.4	0	0.0	0	0.0
Pneumonia	2	6.9	1	3.4	0	0.0	1	3.4	0	0.0	0	0.0	1	3.4
Thrombocytopenia	2	6.9	1	3.4	0	0.0	1	3.4	0	0.0	1	3.4	0	0.0
Anaphylactic reaction	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0
Gastritis	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0
Cholecystitis	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0

Presented by Hiroaki Akamatsu. 2023 ASCO Annual Meeting.

Conclusion

- Sotorasib in combination with CBDCA/PEM demonstrated favorable ORR and tolerability in advanced non-Sq, NSCLC patients with KRAS G12C mutation.

Presented by Hiroaki Akamatsu. 2023 ASCO Annual Meeting.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

What do we do for K-RAS^{G12C} patients in 1L?

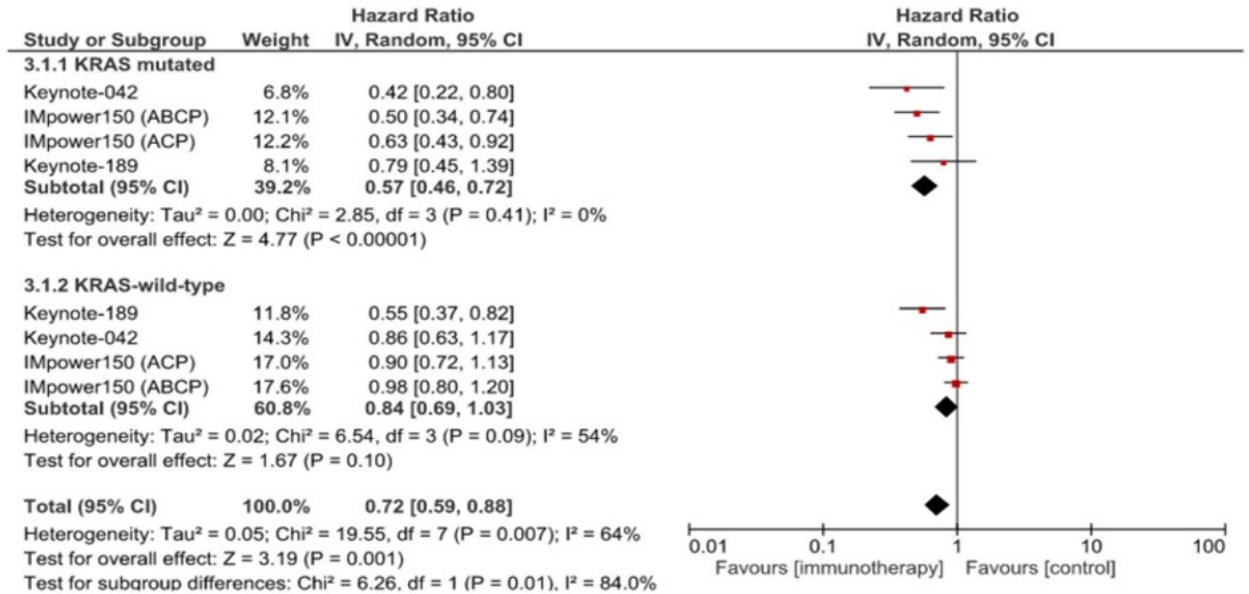
Some Facts→

1st Line trials included KRAS(+) patients

Keynote-042	Pembrolizumab	1,274
Keynote-189	Pembrolizumab +ChT	616
IMpower-150	Atezoli-zumab+ChT+bev-	1,200

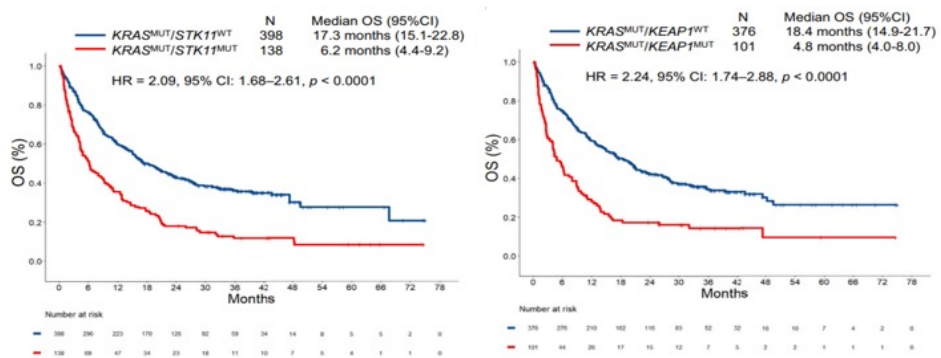
Landre Cancer Immunology, Immunotherapy (2022) 71:719–26.

KRAS mutated vs KRAS non-mutated- 1L Therapy



K-RAS and Co-mutations Tx w IO

Two independent academic based cohorts that received PDL1/PD1 IO and had KRAS with comprehensive genomic profiling



Riciutti B JTO 2022

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

Potential rescue with CTLA-4 + PDL-1 + platinum doublet "Quadruplet"

- POSEIDON trial: chemo+ tremelimumab + durvalumab vs chemo + durvalumab vs chemotherapy.

- Overall response rates in 4 drug regimen:
  - ✓ 45.2% for *STK11*-mutated subgroup
  - ✓ 45.5% for *KEAP1*-mutated subgroup
  - ✓ 55.0% for *KRAS*-mutated subgroup

- Median OS HR vs CT (95%):
  - ✓ HR of 0.56 (95% CI 0.30-1.03) for *STK11*-mutated non-squamous NSCLC
  - ✓ HR of 0.43 (95% CI 0.16-1.25) for *KEAP1*-mutated NSCLC
  - ✓ HR of 0.56 (95% CI 0.36-0.88) for KRAS-mutated non-squamous NSCLC.

Peters S 2022 World Conference on Lung Cancer. Abstract OA15.04

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Intracranial activity….

- Incidence of brain metastases about 40%.
- Delayed CNS with sotorasib compared with docetaxel, 9.6 months versus 5.4 months (HR 0.84 [95% CI: 0.32, 2.19], P=0.37).
- KRYSTAL-1 trial had 25 patients with untreated brain metastases:
  - ✓ icORR 42%
  - ✓ DCR 90%
  - ✓ PFS of 5.4 months

Cui W Lung Cancer 2020;146:310-7; Dingemans JCO.2023.41.17_suppl.LBA9016 Negrao JCO 2023

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Treatment-Related Adverse Events

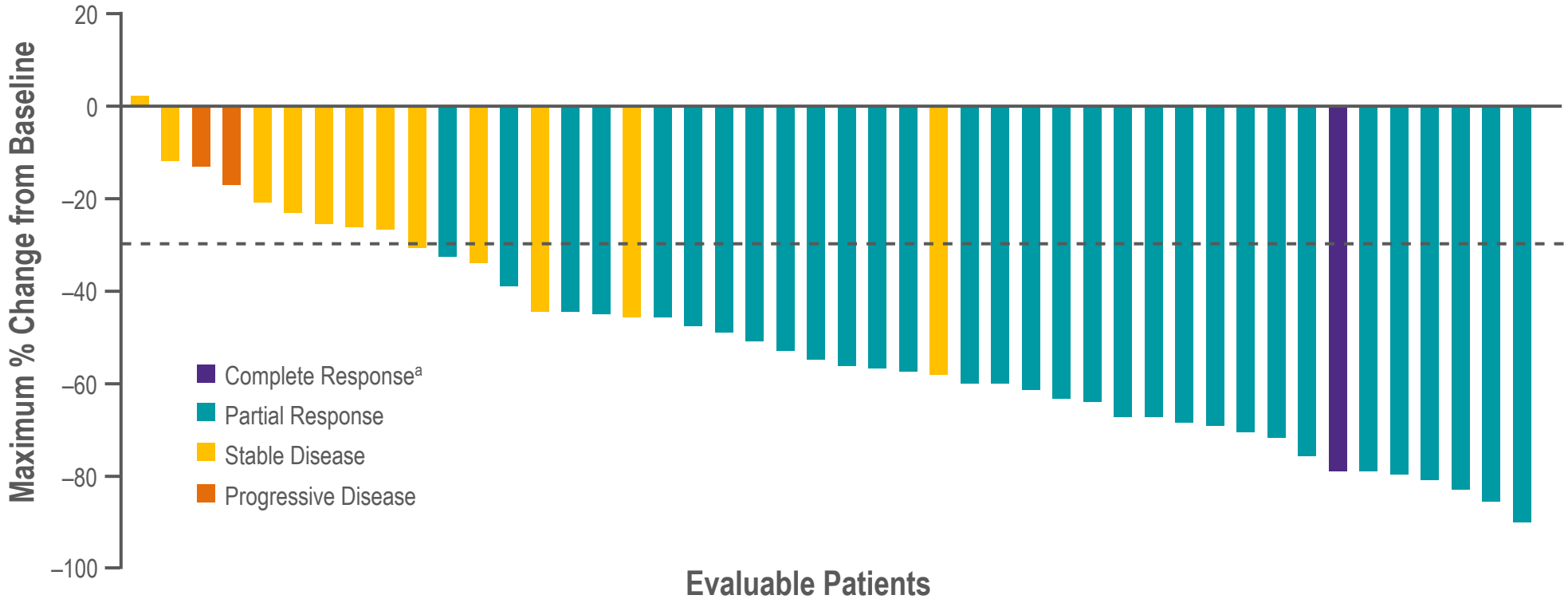
Most Frequent TRAEs[a], %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	51	28	20	3	0
Diarrhea	44	33	7	3	0
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Vomiting	29	17	11	1	0
Fatigue	26	12	10	4	0
Decreased appetite	24	14	9	1	0
Lipase increased	24	3	9	10	1

- There were two Grade 5 TRAEs, one each of pneumonitis and pneumonia
- Immune-related TRAEs[b] of any grade occurred in 18% of patients (26/148) and grade ≥3 occurred in 5% (8/148)
- TRAEs led to adagrasib dose reduction in 46% of patients (68/148) and temporary dose interruption in 59% of patients (88/148)
- TRAEs led to permanent discontinuation of adagrasib only in 6% of patients (9/148) and pembrolizumab only in 11% of patients (16/148); 4% of patients (6/148) discontinued both drugs due to TRAEs

- [a]Any grade TRAEs occurring in ≥20% of patients. [b]Includes all TRAEs of colitis, hepatitis, adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, nephritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and pneumonitis
- Data as of 19 June 2023. Median follow-up 8.7 months

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

ORR and Best Tumor Change from Baseline in Patients With PD-L1 TPS ≥50%



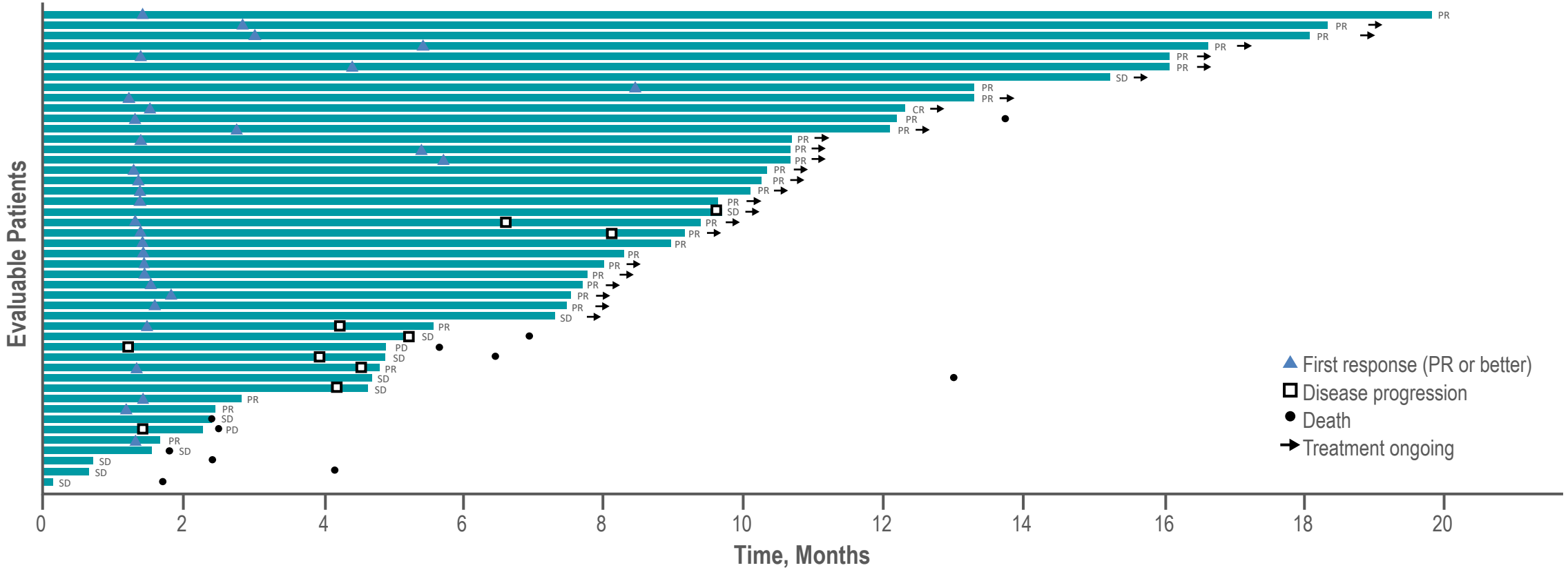
- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity[b], ORR was 70% (14/20; 95% CI, 46–88)

✓ Response per investigator assessment (n=51; modified full analysis set). Waterfall plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days). [a]One patient had CR without –100% change from baseline due to lymph node as target lesion. [b]Includes AST increase, ALT increase, mixed liver injury and liver function test increase; no grade 4 hepatotoxicity was observed in patients with PD-L1 TPS ≥50%

✓ Data as of 19 June 2023. Median follow-up 10.1 months

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Duration of Treatment in Patients With PD-L1 TPS ≥50%



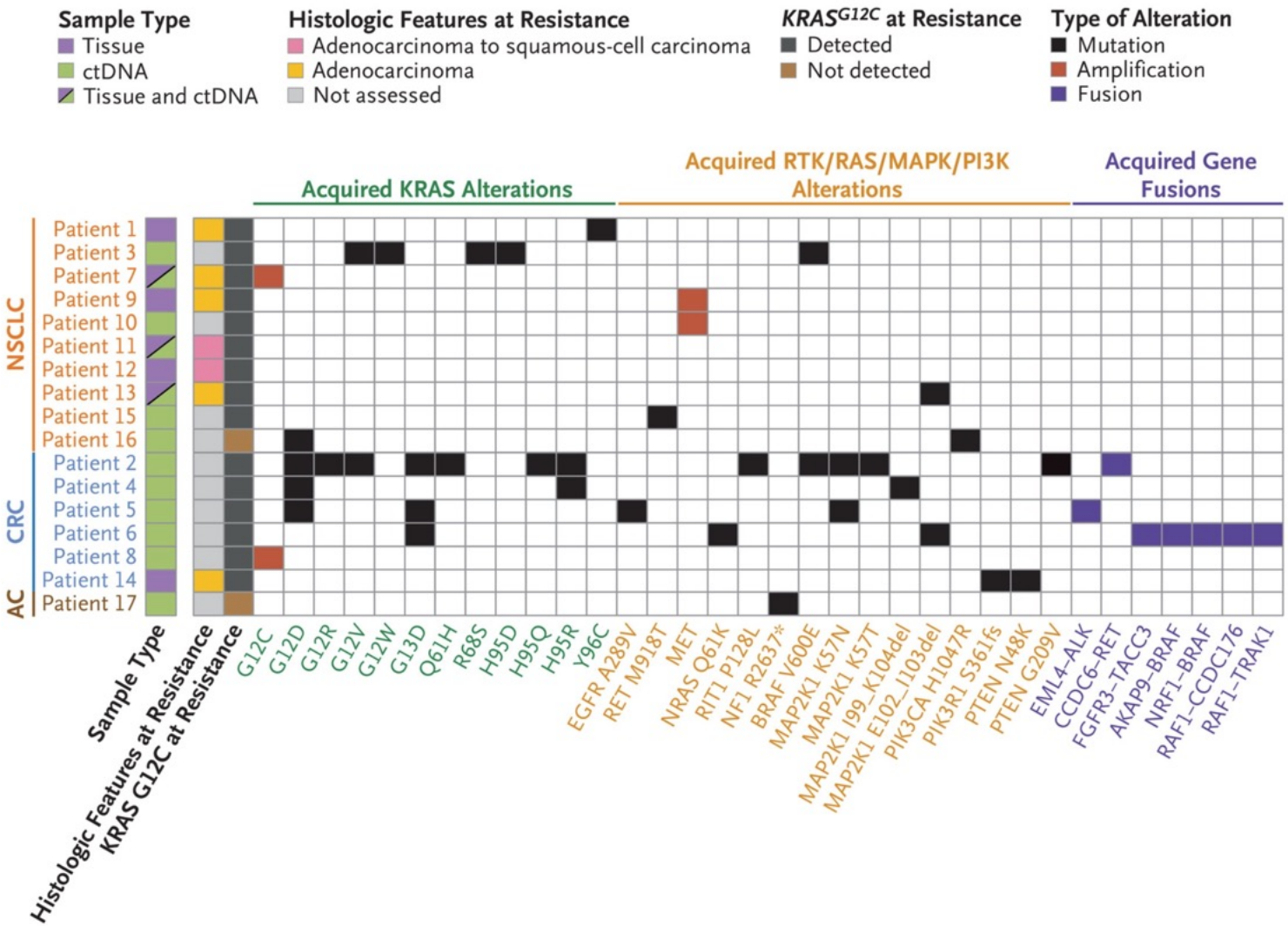
- Median time to response was 1.4 months; median duration of response was not reached (95% CI, 12.6–NE)

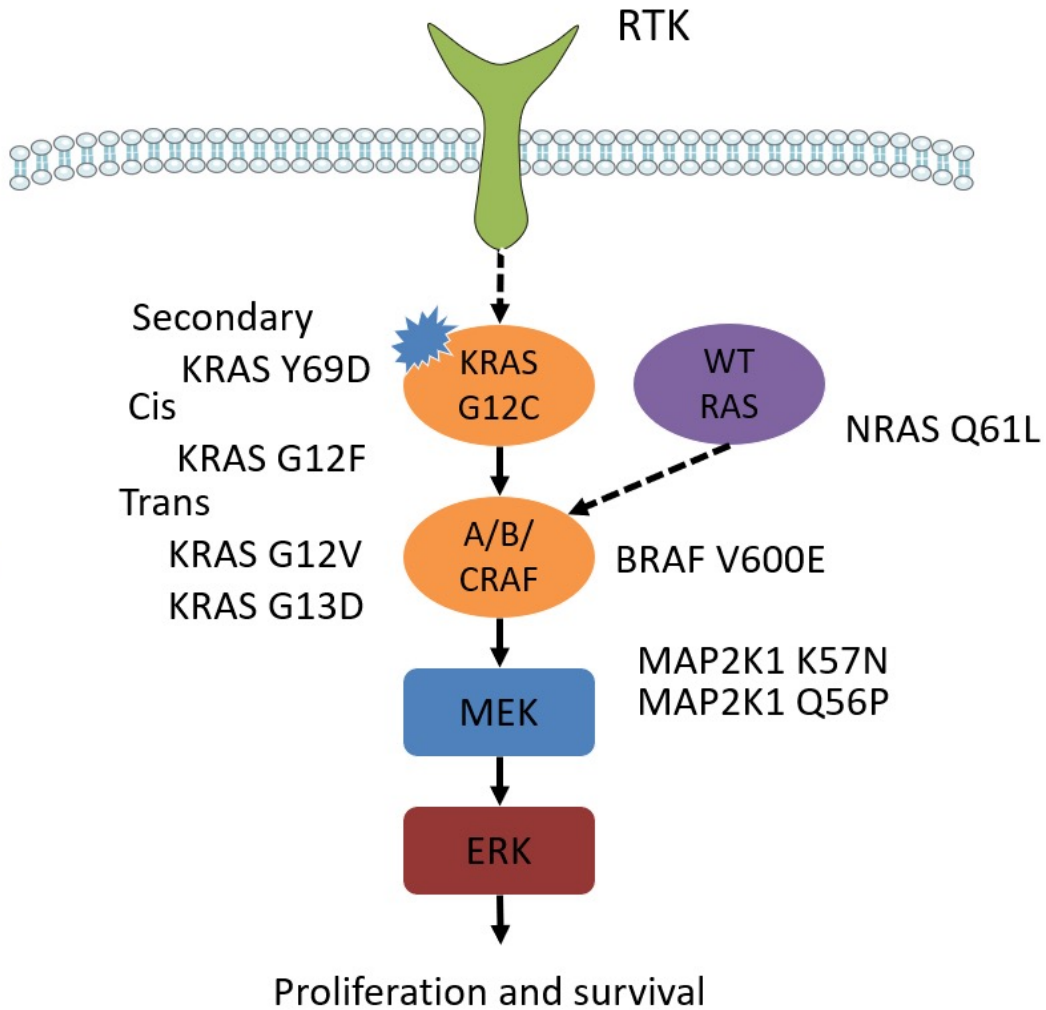
✓ Response per investigator assessment (n=51; modified full analysis set). Swimmer plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days)

✓ Data as of 19 June 2023. Median follow-up 10.1 months

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Acquired Resistance to *KRAS* G12C Inhibitors





Awad. NEJM. 2021;344:2382. Tanaka. Cancer Discov. 2021:11:1.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY
The Oncology Institute of Hope & Innovation

Conclusions

- FLAURA 2 and MARIPOSA trials results may challenge Osimertinib as sole 1st line therapy for patients with EGFRex19del or L858R mutations.
- For patients with CNS disease and L858R, Osi plus chemotherapy represents a better option than Osi alone (FLAURA 2).
- MARIPOSA study also showed that Ami/Chemo combination has CNS protectant effect.
- Amivantamab-chemotherapy is the new standard of care for EGFRex20in as it significantly improved PFS (HR, 0.395); OS trends in favor of Ami/Chemo despite high crossover (PAPILLON study).
- TROPION-Lung 05 showed encouraging antitumor activity with datopotomab deruxtecan in a heavily pretreated NSCLC population with actionable genomic alterations, including patients with *EGFR* mutations and *ALK* rearrangements.
- IO based therapy remains standard of care for first line treatment of KRAS mutations including $KRAS^{G12C}$.
- Unfavorable co-mutations (STK11/KEAP1) present with KRAS mutations portend to worse prognosis with IO therapy.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation