Second Opinion: Investigators Discuss How They Apply Available Clinical Research in the Care of Patients with Non-Small Cell Lung Cancer with an EGFR Mutation

Friday, May 31, 2024

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Jonathan W Goldman, MD
Corey J Langer, MD
Joel W Neal, MD, PhD
Zofia Piotrowska, MD, MHS
Joshua K Sabari, MD

Moderator

Helena Yu, MD

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Faculty

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Friday May 31	**Hepatobiliary Cancers** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Non-Small Cell Lung Cancer with an EGFR Mutation 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday June 1	**Antibody-Drug Conjugates in the Treatment of Lung Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 2	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 3	**Colorectal Cancer (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 4	**Bispecific Antibodies in the Management of Lymphoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

Hepatobiliary Cancers

Friday, May 31, 2024

11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)

Faculty

Robin K (Katie) Kelley, MD
Edward Kim, MD
Arndt Vogel, MD, PhD

Antibody-Drug Conjugates in Lung Cancer

Saturday, June 1, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rebecca S Heist, MD, MPH
Luis Paz-Ares, MD, PhD
Jacob Sands, MD

Non-Small Cell Lung Cancer with an EGFR Mutation

Friday, May 31, 2024

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Jonathan W Goldman, MD
Corey J Langer, MD
Joel W Neal, MD, PhD
Zofia Piotrowska, MD, MHS
Joshua K Sabari, MD
Helena Yu, MD

Prostate Cancer

Saturday, June 1, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Neeraj Agarwal, MD, FASCO
Emmanuel S Antonarakis, MD
Andrew J Armstrong, MD, ScM
Tanya B Dorff, MD
Matthew R Smith, MD, PhD

Exciting CME Events in Chicago You Do Not Want to Miss

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Multiple Myeloma

Sunday, June 2, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rafael Fonseca, MD
María-Victoria Mateos, MD, PhD
Elizabeth O'Donnell, MD

LIVE WEBCAST

Colorectal Cancer

Monday, June 3, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Scott Kopetz, MD, PhD
John Strickler, MD

Ovarian and Endometrial Cancer

Sunday, June 2, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Floor J Backes, MD
Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Angeles Alvarez Secord, MD, MHSc
Brian M Slomovitz, MD

Metastatic Breast Cancer

Monday, June 3, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Aditya Bardia, MD, MPH
Harold J Burstein, MD, PhD
Professor Giuseppe Curigliano, MD, PhD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Exciting CME Events in Chicago You Do Not Want to Miss

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LIVE WEBCAST

Bispecific Antibodies in Lymphoma

Tuesday, June 4, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

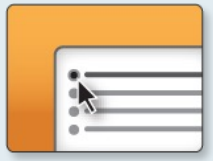
Faculty

Joshua Brody, MD
Ian W Flinn, MD, PhD
Tycel Phillips, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Clinicians Attending via Zoom

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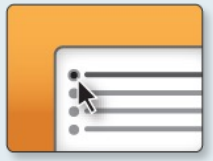

Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
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Second Opinion: Investigators Discuss How They Apply Available Clinical Research in the Care of Patients with Non-Small Cell Lung Cancer with an EGFR Mutation

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Joshua K Sabari, MD

Moderator

Helena Yu, MD

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Roy S Herbst, MD, PhD
Yale Cancer Center
New Haven, Connecticut

John V Heymach, MD, PhD
The University of Texas
MD Anderson Cancer Center
Houston, Texas

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Agenda

Module 1: Contemporary Care for Patients with Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) with an EGFR Mutation — Dr Langer

Module 2: Evolving First-Line Treatment for Metastatic NSCLC with an EGFR Mutation — Dr Goldman

Module 3: Biological Rationale for and Emerging Role of Antibody-Drug Conjugates in the Management of NSCLC with an EGFR Mutation — Dr Yu

Module 4: Other Emerging Strategies for Relapsed Metastatic NSCLC with an EGFR Mutation — Dr Sabari

Module 5: Current and Future Management of NSCLC with an EGFR Exon 20 Insertion Mutation — Dr Piotrowska

Module 6: Management of Toxicities Associated with Available and Emerging Therapies for NSCLC with an EGFR Mutation — Dr Neal

Agenda

Module 1: Contemporary Care for Patients with Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) with an EGFR Mutation — Dr Langer

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Module 5: Current and Future Management of NSCLC with an EGFR Exon 20 Insertion Mutation — Dr Piotrowska

Module 6: Management of Toxicities Associated with Available and Emerging Therapies for NSCLC with an EGFR Mutation — Dr Neal

Consulting Faculty Comments

ADAURA and LAURA trials: Integration of adjuvant osimertinib

Dr Roy S Herbst
(New Haven, Connecticut)

Dr John V Heymach
(Houston, Texas)

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QUESTIONS FOR THE FACULTY

Are there any circumstances in which you would use adjuvant osimertinib for a patient with Stage IA disease with an EGFR mutation outside of a clinical trial today?

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Consulting Faculty Comments

Initial treatment approach for localized disease with an EGFR mutation

Dr John V Heymach (Houston, Texas)

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QUESTIONS FOR THE FACULTY

Are there patients for whom you would currently offer osimertinib in lieu of adjuvant chemotherapy?

Among patients with Stage IB, II and III disease in ADAURA, was there a notable difference in 5-year overall survival between individuals who did and did not receive chemotherapy?

QUESTIONS FOR THE FACULTY

Has osimertinib replaced durvalumab as consolidation therapy for all patients with Stage III disease with an EGFR mutation?

Are there any situations in which you would still consider durvalumab?

Consulting Faculty Comments

Potential role of ctDNA assays in the adjuvant setting

Dr Roy S Herbst (New Haven, Connecticut)

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QUESTIONS FOR THE FACULTY

What, if any, is the future role of ctDNA assays for localized or locally advanced lung cancer?

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Penn Medicine
Abramson Cancer Center

Division of Hematology & Oncology

Contemporary Care for Pts with Nonmetastatic EGFR-Mt (+) NSCLC
State-of-the-Art - 2024

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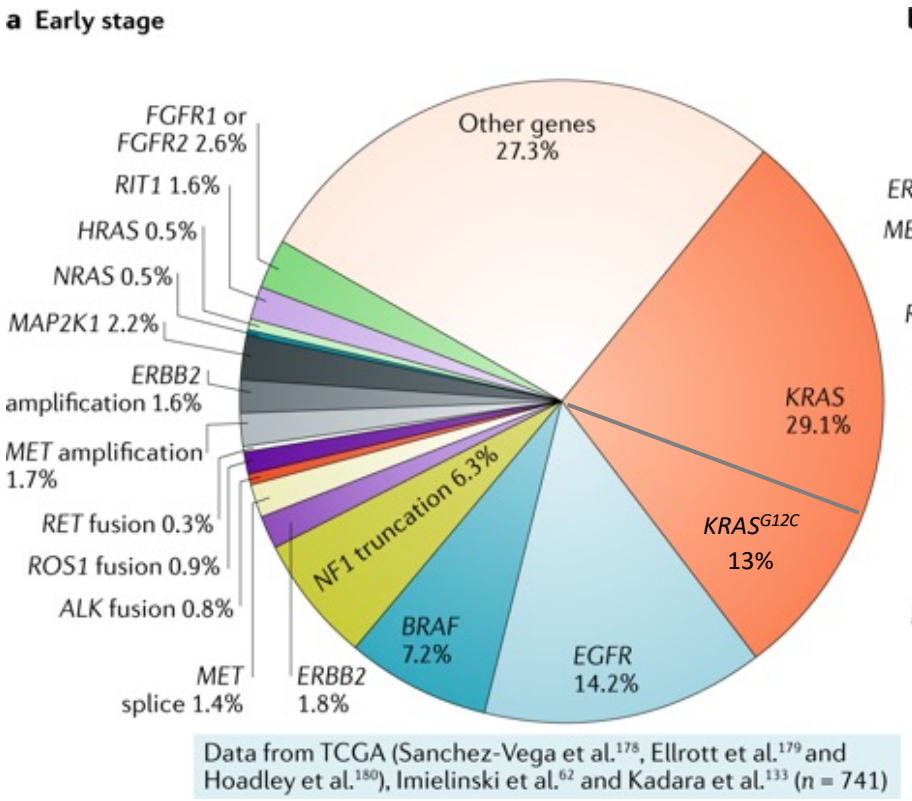
May 2024: RTP, FL

Synopsis

1. Incidence of targetable EGFR mutations in localized, locally advanced and metastatic NSCLC; optimal timing of and method for EGFR testing
2. Long-term data, including overall survival (OS) outcomes and rates of CNS disease recurrence, from the Phase III ADAURA trial evaluating adjuvant osimertinib for patients with completely resected Stage IB to IIIA EGFR mutation-positive NSCLC
3. Ongoing efforts (eg, NeoADAURA, ADAURA2, PACIFIC-4, TARGET) seeking to further define the role of osimertinib in localized NSCLC
4. Emerging positive data from the Phase III LAURA trial assessing osimertinib after chemoradiation therapy for patients with unresectable, Stage III EGFR-mutated NSCLC **(plenary paper at ASCO 2024)**

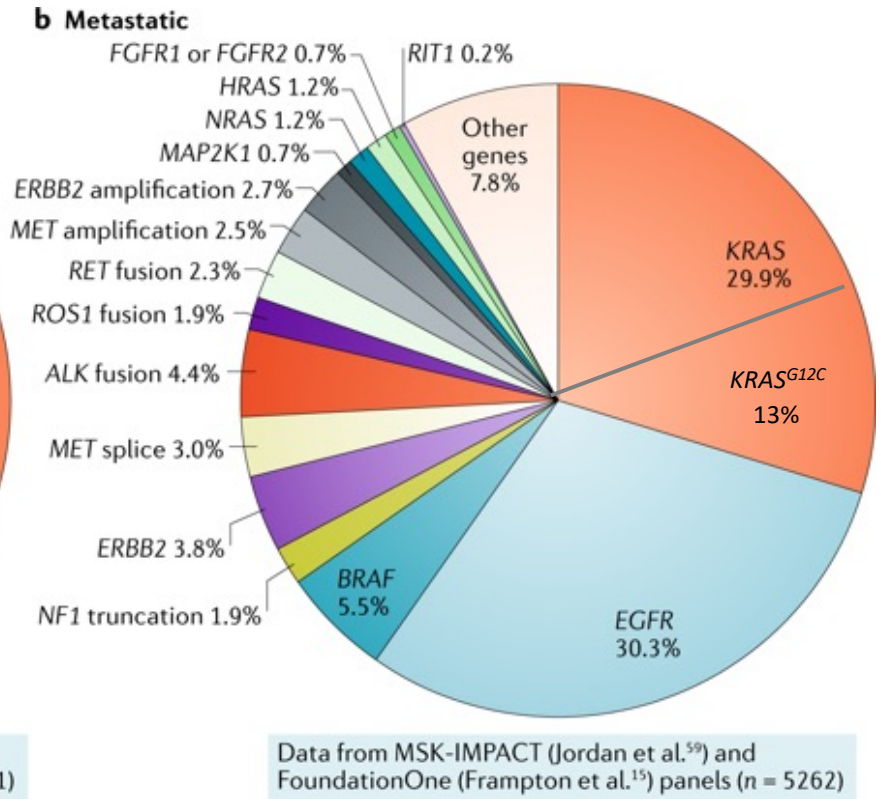
More than 50% of pts with non-squamous NSCLC have oncogenic drivers that potentially drive treatment choices

Early Stage



Data from TCGA (Sanchez-Vega et al.[178], Ellrott et al.[179] and Hoadley et al.[180]), Imielinski et al.[62] and Kadara et al.[133] (n = 741)

Metastatic Stage



Data from MSK-IMPACT (Jordan et al.[59]) and FoundationOne (Frampton et al.[15]) panels (n = 5262)

- Skoulidis F, et al. *Nat Rev Cancer*. 2019;19(9):495-509.

Penn Medicine
Abramson Cancer Center

Phase III studies of adjuvant (first gen) EGFR TKIs vs chemotherapy in resected *EGFR* mutation positive NSCLC

	ADJUVANT/ CTONG 1104	EVIDENCE	IMPACT	
Design	**Gefitinib** 2 years v Chemotherapy Phase 3, n=222	**Icotinib** 2 years v Chemotherapy Phase 3, n=322	**Gefitinib** 2 years v Chemotherapy Phase 3, n=232	
Disease Free Survival	mDFS: 28.7 v 18.0 mo (HR, 0.60; p=0.0054) ✓	mDFS 47 v 22 mo (HR 0.36, p<0.01) ✓	mDFS: 35.9 vs 25.1 mo (HR, 0.92; p=0.63) ✗	
Overall Survival	mOS: 75.5 vs 62.8 mo (HR 0.92; p=0.674) ✗	NR ?	mOS: NR vs NR (HR, 1.03; p=0.89) ✗	✗

Zhong Lancet Oncology 2018; Zhong JCO 2021; He Lancet Respir Med 2021;Tada JCO 2022

ADAURA: Positive for primary endpoint Disease Free Survival – initial analysis (2020)

Patients with completely resected stage* IB, II, IIIA NSCLC with EGFR mutations (L858R or Exon 19 del), with or without adjuvant chemotherapy†

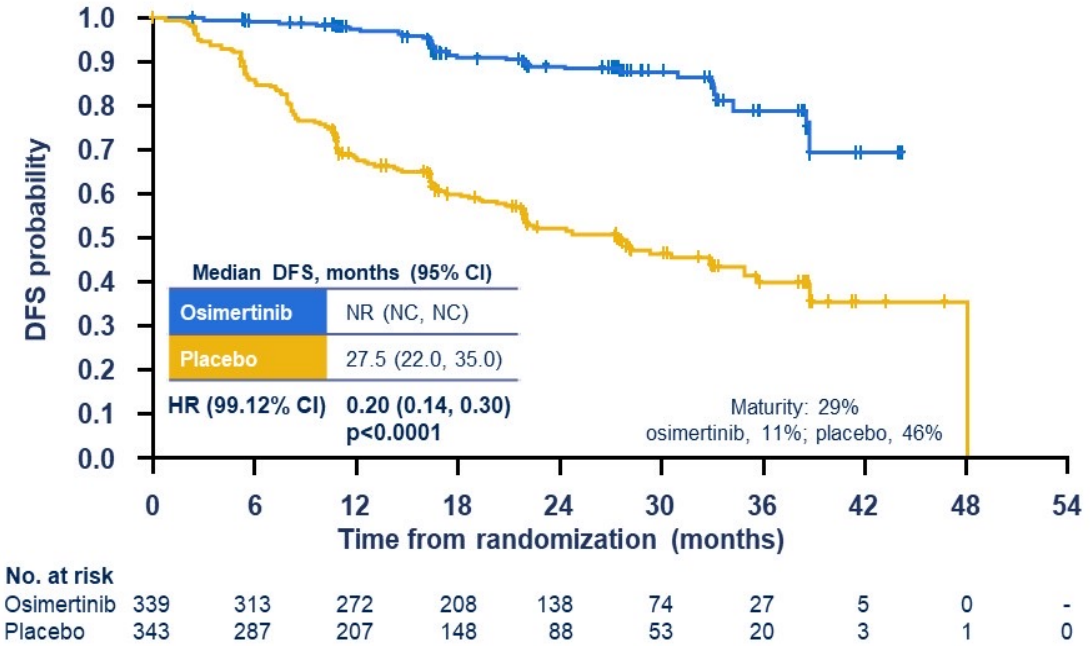
→ Osimertinib 80 mg, once daily For 3 years

Randomization 1:1 (N=682)

→ Placebo, once daily

ADAURA primary DFS analysis (stage IB–IIIA)*

*Study reported early on recommendation of IDMC



FDA approval December 2020

Regulatory approval in 98 additional countries
(not always with accompanying reimbursement)

Herbst LBA5, ASCO Plenary session 2020 (Virtual); Wu et al. NEJM 2020

Adjuvant osimertinib has significantly improved CNS DFS

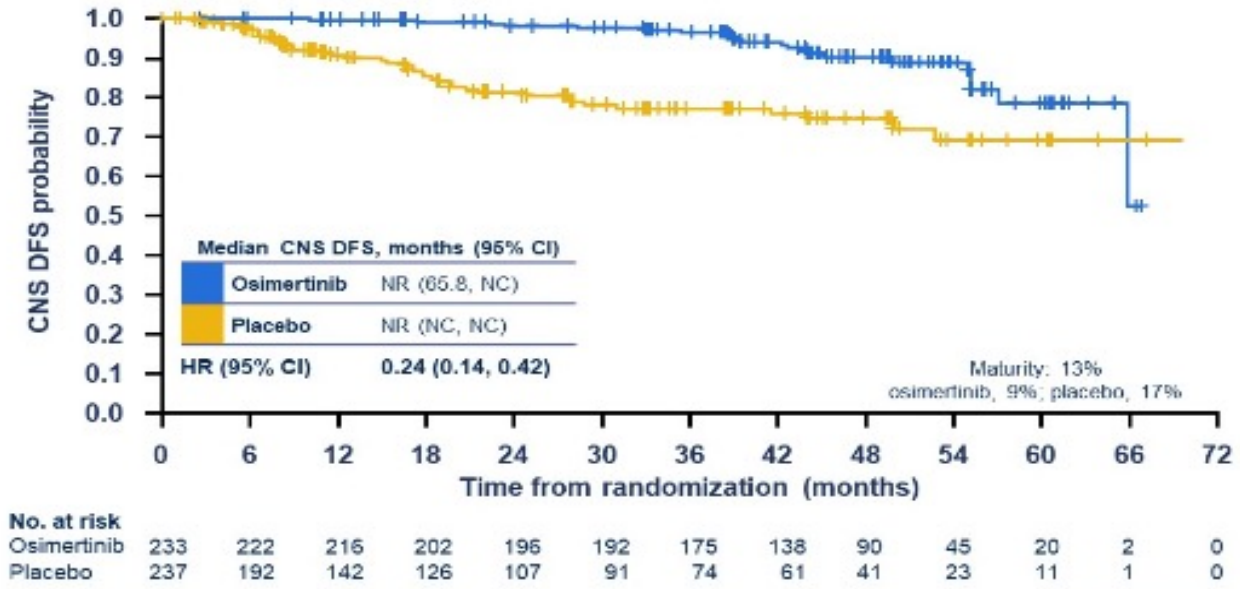
- CNS metastases are a poor prognostic factor among patients with NSCLC, and are associated with deterioration in quality of life[1]

Improved CNS efficacy with osimertinib treatment

- Osimertinib has shown greater penetration of the blood-brain barrier and higher exposure in the brain compared with other EGFR-TKIs[2–4]
- Adjuvant osimertinib demonstrated CNS DFS* benefit vs placebo in both the stage II–IIIA and IB–IIIA populations[5,6]

ADAURA updated CNS DFS analysis[5,6] (stage II–IIIA)

JCO January 2023



No. at risk													
Osimertinib	233	222	216	202	196	192	175	138	90	45	20	2	0
Placebo	237	192	142	126	107	91	74	61	41	23	11	1	0

Data cut-off: April 11, 2022.

*CNS DFS events were defined as CNS disease recurrence or death by any cause.

1. Peters et al. Cancer Treat Rev 2016;45:139–162. 2. Colclough et al. Eur J Cancer 2015;69:S28. 3. Ballard et al. Clin Cancer Res 2015;22:5130–5140. 4. Vishwanathan et al. Cancer Res 2018; 78:CT013. 5. Herbst et al. J Clin Oncol 2023;41:1830–1840. 6. Tsuboi et al. Ann Oncol 2022;33(Suppl 7): abstract/ oral LBA47.

CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, EGFR mutated; EGFR-TKI, EGFR-tyrosine kinase inhibitor; HR, hazard ratio; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer.

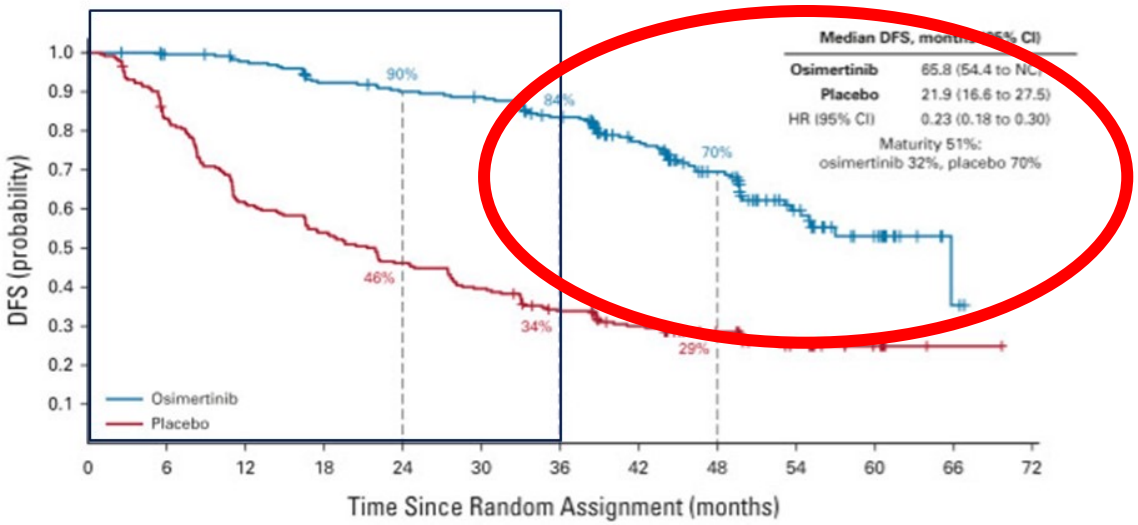
Herbst RS et al. ASCO 2023;Abstract LBA3.

Updated/Final DFS analysis (2022)

- Updated DFS curves at protocol specified maturity ~ 50% showed HR 0.23 (stage II/IIIA); HR 0.27 (stage IB-IIIA)
- Reduced risk of CNS recurrence (HR 0.24)

Does the improvement in DFS translate to improved Overall Survival?

ADAURA updated DFS analysis (stage II/IIIA)
Data cut off: April 2022



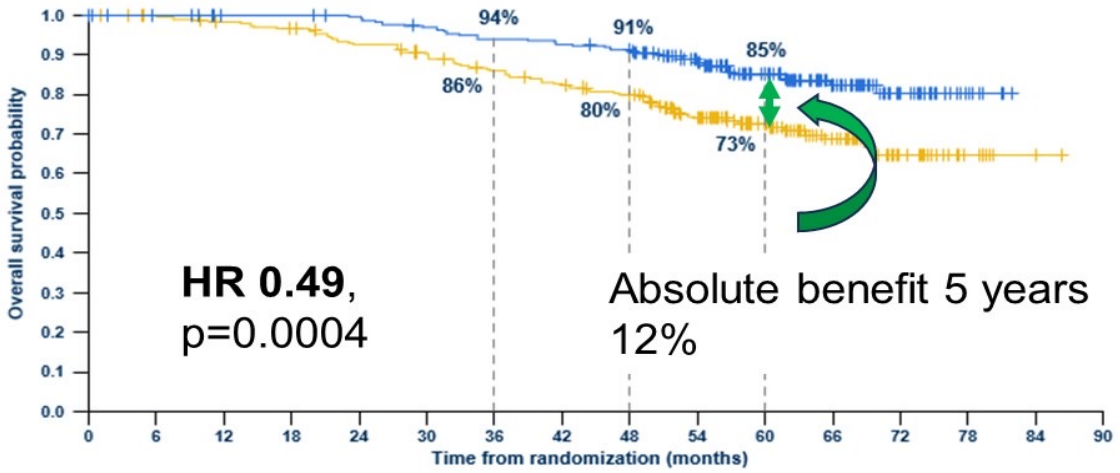
Duration of Osimertinib treatment

Herbst, Wu et al. JCO 2023

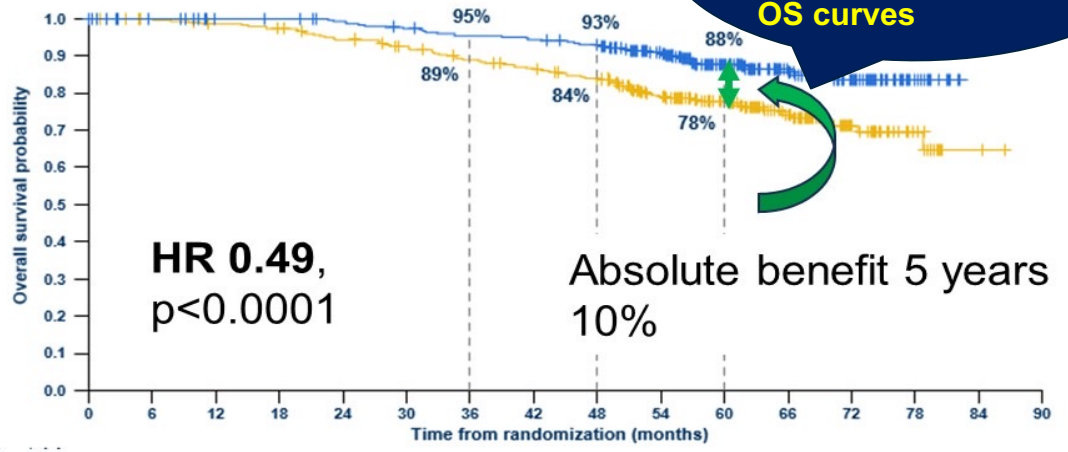
Solomon BJ et al. ASCO 2023;Abstract LBA3.

Osimertinib improves Overall Survival in resected *EGFR* mutation positive NSCLC

Stage II/IIIA



Stage IB/II/IIIA



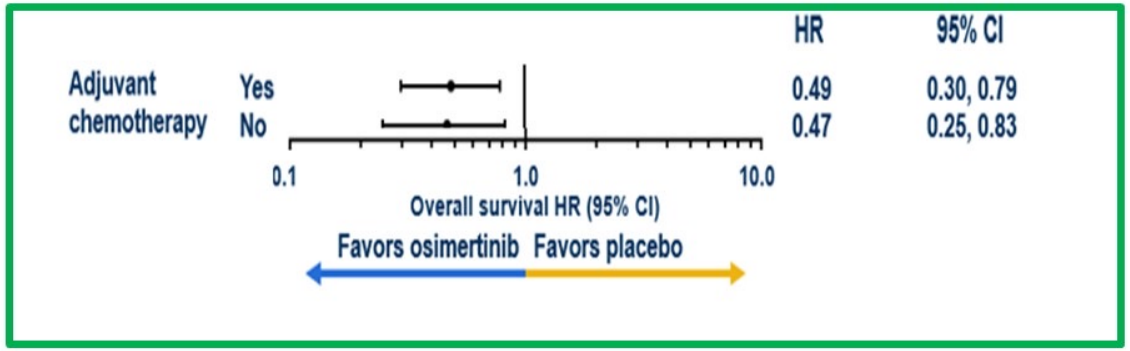
Fish tail OS curves as opposed to "banana" shaped OS curves

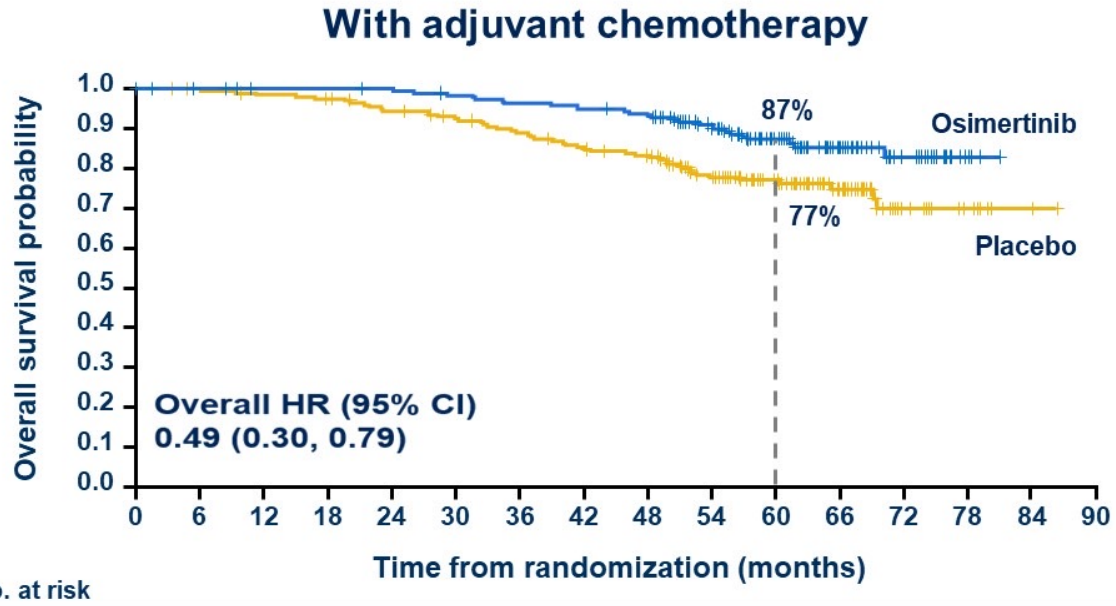
- **Early but protocol pre-specified final analysis** with 21% maturity and ~60 months median follow up

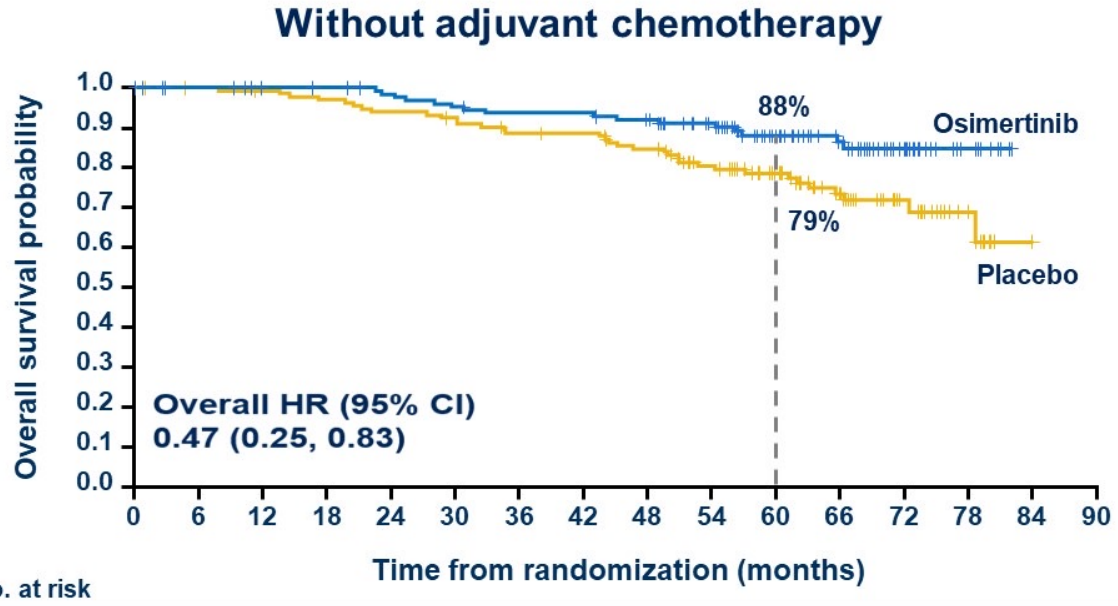
- **Subsequent treatment:** More patients in placebo arm received EGFR TKIs (88% vs 76%)

Solomon BJ et al. ASCO 2023;Abstract LBA3.

Benefit regardless of adjuvant chemotherapy







Solomon BJ et al. ASCO 2023;Abstract LBA3.

ADAURA Conclusions

ADAURA is the first phase 3 study of a targeted therapy in the adjuvant setting for NSCLC to demonstrate an overall survival benefit

→ firmly establishes adjuvant osimertinib as the standard of care for resected *EGFR* mutation positive NSCLC and mandates *EGFR* mutation testing in early-stage NSCLC

ADAURA is a groundbreaking trial in lung cancer moving targeted therapies from advanced disease to the early-stage setting – opening a new chapter for precision medicine with targeted therapy for early-stage NSCLC

Solomon BJ et al. ASCO 2023;Abstract LBA3.

ADAURA Conclusions

ADAURA is the first phase 3 stud… …g for NSCLC to demonstrate…

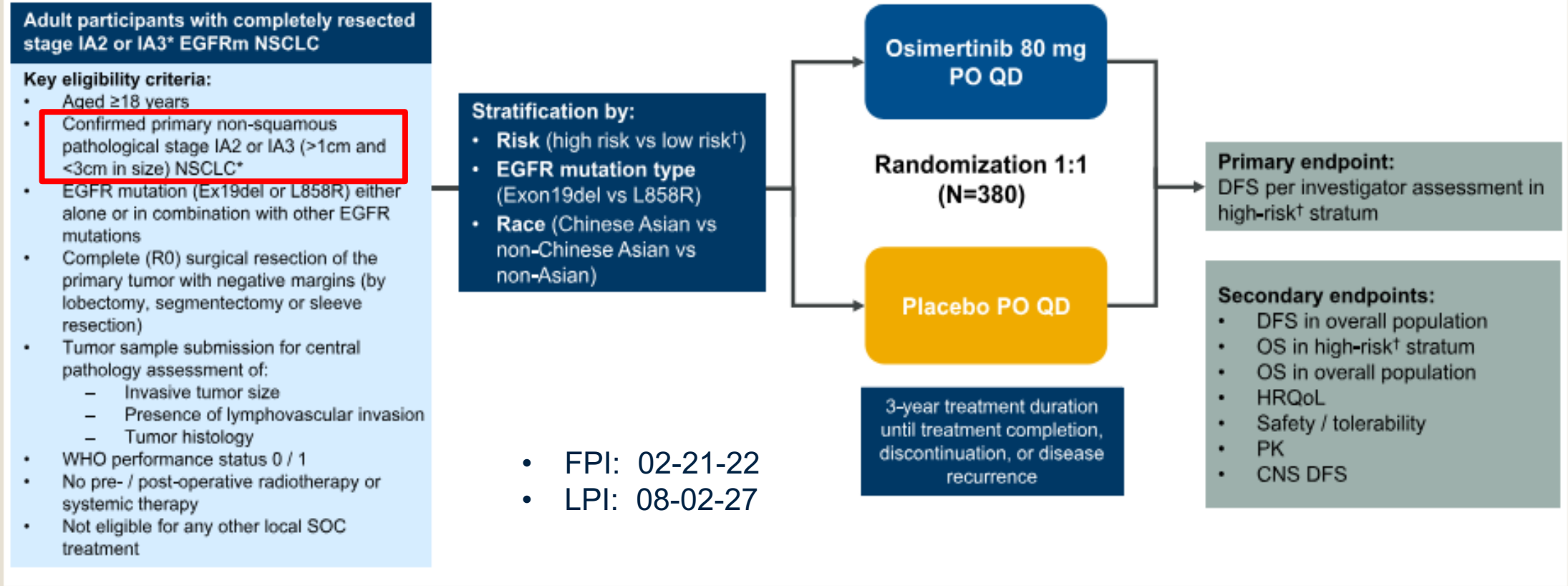
→ firs… *EGFR*… stage …

ADAUR… advance… medicine… …ples from …apter for precision

- Major criticism – only 38.5% of those with PD on the control arm crossed over to osimertinib
- Ongoing Questions
  - Duration of Tx – 3 yrs was empiric
  - Role in atypical sensitizing EGFR mt (+) or earlier stage, resected NSCLC
- Underscores need to obtain routine molecular testing in early stage NSCLC

Solomon BJ et al. ASCO 2023;Abstract LBA3.

ADAURA2: Study Design



- FPI: 02-21-22
- LPI: 08-02-27

PIs: Jonathan Goldman, UCLA; Yauhiro Tsutani, Japan

Tsutani Y et al. *Clin Lung Cancer*. 2023;24(4):376-380.

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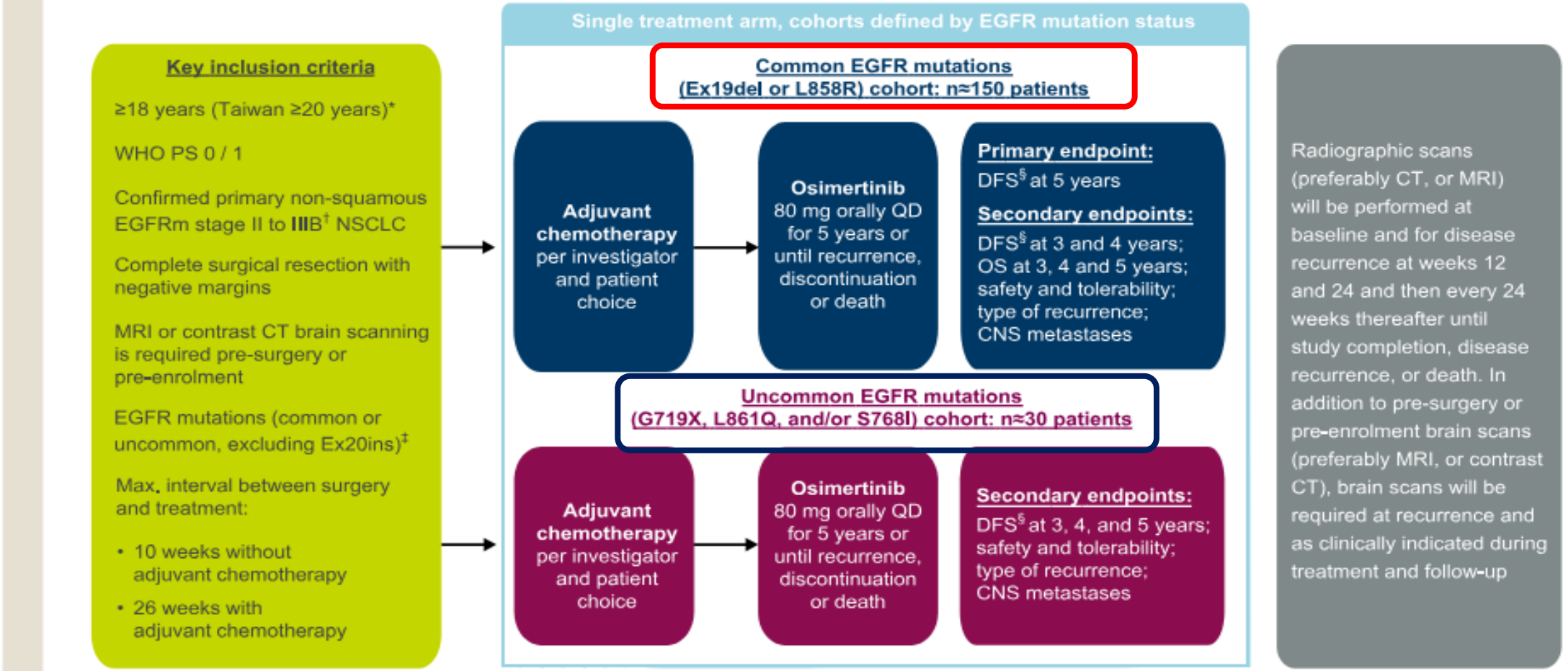
TARGET Trial:
Phase II in sensitizing and atypical EGFR mt (+) IB-IIIA



Soo RA et al. *Clin Lung Cancer*. 2024;25(1):80-84.

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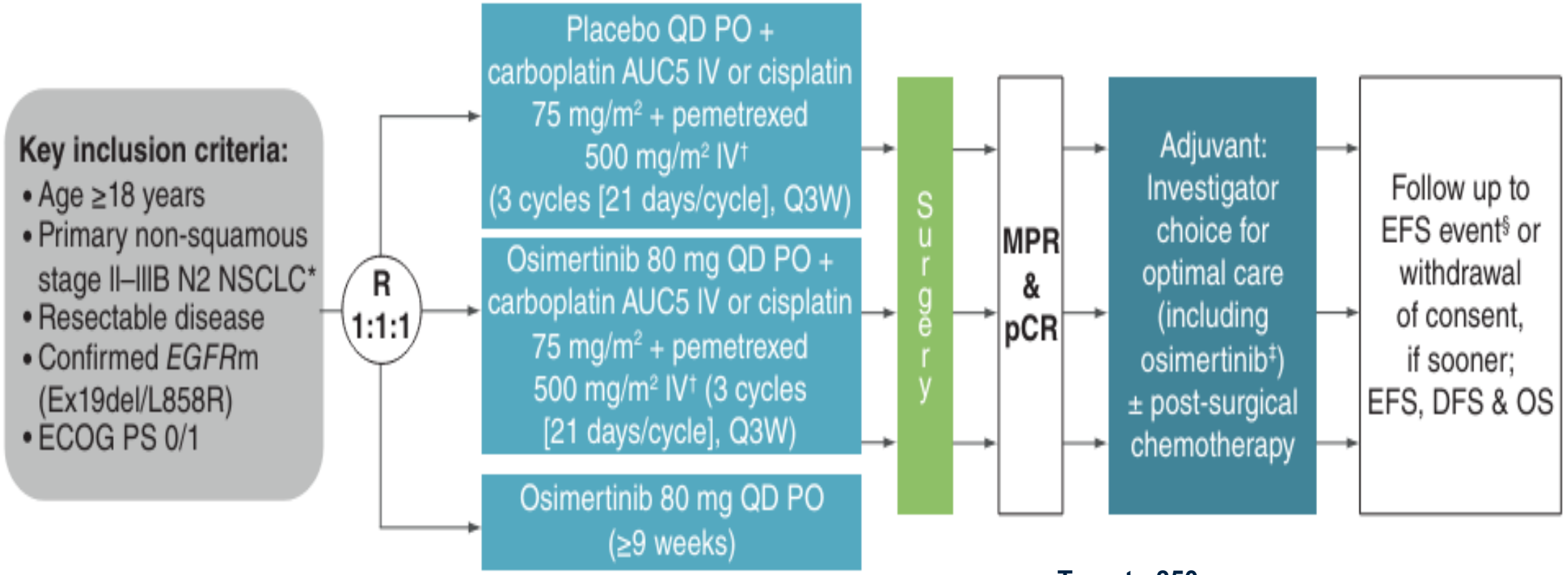
NeoADAURA



- **Target: 350**
- **FPI: 12-16-20**
- **LPI: 07-05-24**

- PIs: Tsuboi, ...Chaft, J Frontiers Oncology 2021

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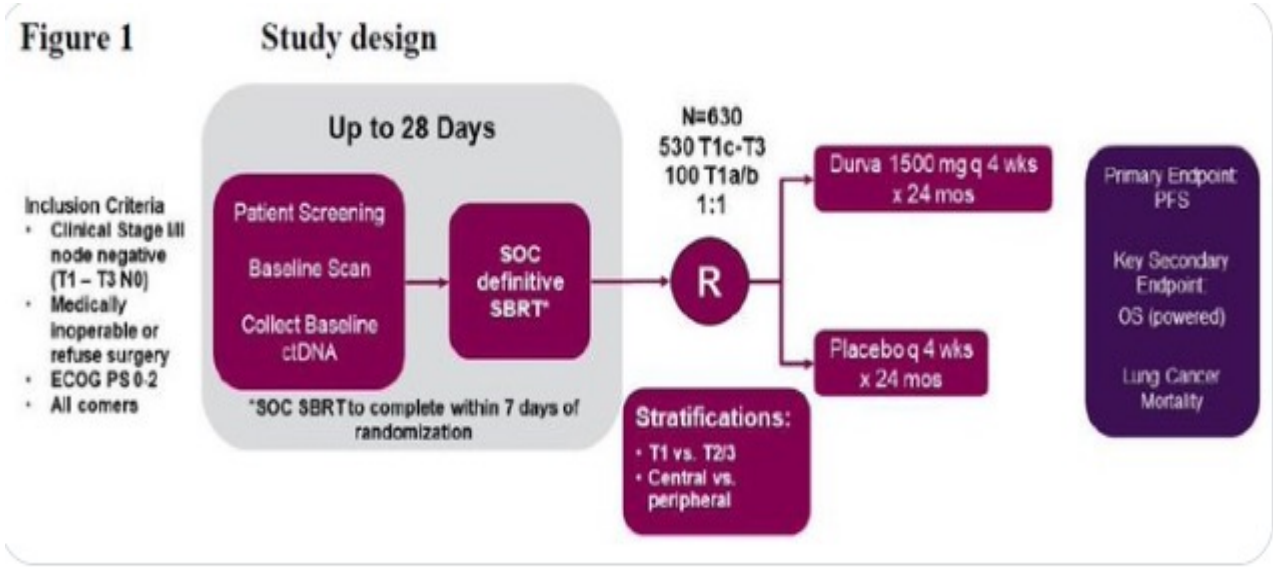
PACIFIC-4 post SBRT

Phase III, randomized, placebo-controlled, double-blind multi-center study assessing the efficacy and safety of durvalumab versus placebo following SoC SBRT in pts with unresected clinical stage I/II LN (-) (T-T3N0M0) NSCLC



- Study opening: 03-06-19
- Projected closure: 03-31-26

- Later amended to have a 2nd EGFR mt (+), phase II cohort, assigned to Osimertinib after completion of SBRT
- N = 60

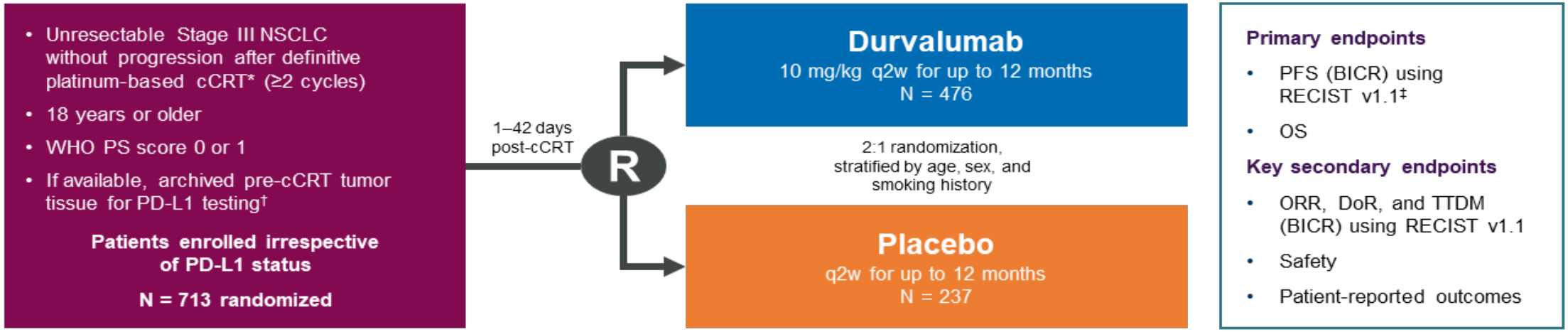
- Primary objective: PFS by BICR for Durva vs Placebo in Stage T1c – T3NOMO iNSCLC
- Secondary objectives: OS, LCSM, PKs, immunogenicity, Sx and health-related QoL
- Tertiary: Assess PFS in EGF mt (+) cohort

Robinson CR et al. ASCO 2023;Abstract TPS8607.

Penn Medicine Abramson Cancer Center

Segueing EGFR TKIs into LA-NSCLC

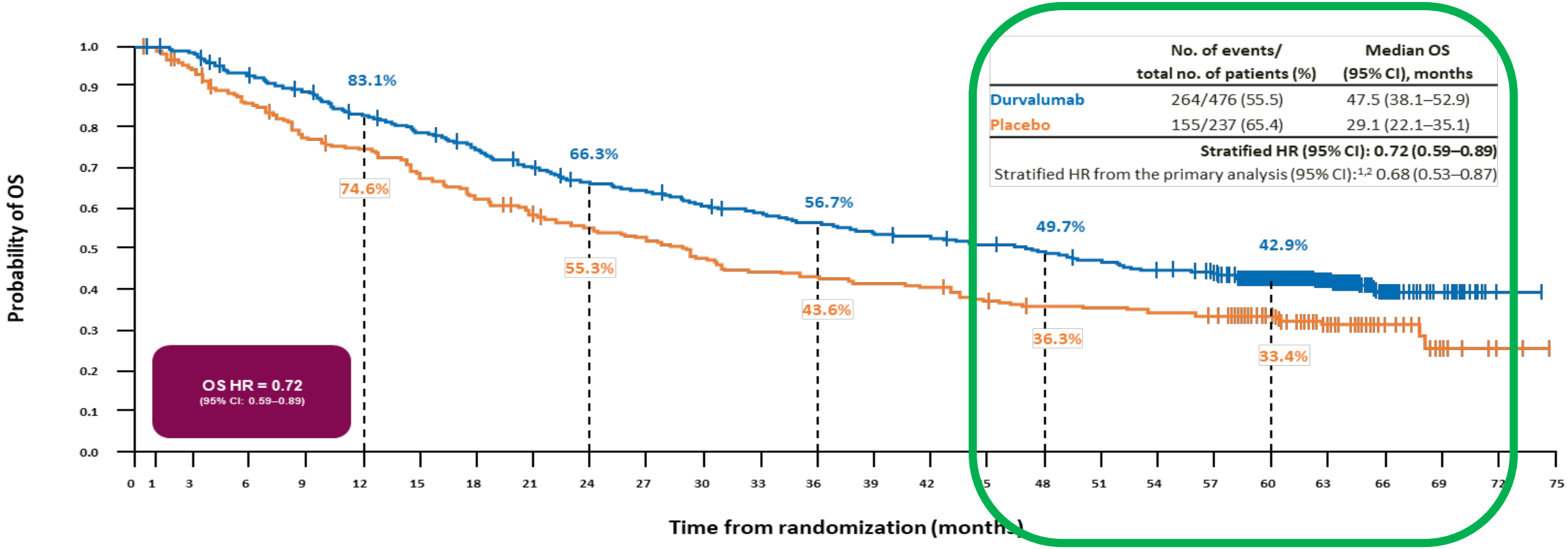
PACIFIC: Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Trial



- Updated analyses of OS and PFS, assessed ~5 years after the last patient was randomized (data cutoff: 11 January 2021; exploratory, post-hoc analysis)
  - Treatment effects were estimated using stratified log-rank tests in the ITT population
  - Medians and yearly landmark rates were estimated using the Kaplan–Meier method

Spigel et al., JCO 2022

Updated OS (ITT)



	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	264/476 (55.5)	47.5 (38.1–52.9)
Placebo	155/237 (65.4)	29.1 (22.1–35.1)
	Stratified HR (95% CI): 0.72 (0.59–0.89)	
Stratified HR from the primary analysis (95% CI):[1,2] 0.68 (0.53–0.87)		

No. at risk

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

Spigel et al., JCO 2022

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Abstract 8541 ASCO 2022:
Durvalumab (durva) after chemoradiotherapy (CRT) in unresectable, stage III, EGFR mutation-positive (EGFRm) NSCLC: Post hoc subgroup analysis from PACIFIC.

PACIFIC

- 713 pts enrolled, 35 had EGFR mutations (2/3 exon 19/21, 1/3 “other”)
- For all pts – OS HR 0.68, PFS HR 0.52
- Of 35 EGFR mutation+ pts, 24 rec’d durva, 11 pbo

	Placebo	Durvalumab
Male, %	73	54
IIIA, %	64	46
PS 0, %	64	54
Ind Rx, %	36	8
Asian, %	55	63
PD-L1 <25%	36	67
Med PFS, mo	10.9	11.2*
Med OS, mo	43.0	46.8**
ORR, %	18.2	26.1

* HR 0.91 (0.39, 2.13)
** HR 1.02 (0.39, 2.63)

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Rationale for Consolidation Tx with Targeted Tx in Oncogenic-Driven LA-NSCLC

- Their empiric use, either as consolidation or concurrently with chemoradiation, in absence of clear cut oncogenic drivers, has failed to yield an OS benefit
  - SWOG-0023 and RTOG-0617 are examples
- Similarly, Durvalumab in the EGFR mt (+) population in PACIFIC has not resulted in any PFS or OS advantage
- In retrospective analysis, pts with EGFR mt (+) LA-NSCLC receiving an “appropriate” TKI fared better than those receiving CPI or undergoing observation

Consolidation EGFR-Tyrosine Kinase Inhibitor vs. Durvalumab vs. Observation in Unresectable *EGFR*-Mutant Stage III NSCLC

A.H. Nassar[#], E. Adib[#], D. Kaldas, J. Feng, T. AbuAli, J. Aredo, B. Fitzgerald, J. Bar, R. Thummalapalli, K. Parikh, R. Whitaker, L. Chen, J. Harris, A. Ayanambakkam, S. Farid, D. Owen, J. Sharp, A.I. Velazquez, M. Ragavan, A. D'aiello, H. Cheng, Z. Piotrowska, M. Wilgucki, J.E. Reuss, T. Patil, Y. Nie, J. Baena Espinar, H. Luders, C. Grohe, K. Sankar, M. Nagasaka, Y.P. Ashara, D.J. Kwiatkowski, R. Mak, A. Amini, A. Lobachov, J.J. Lin, T. Marron, H. Yu, J.W. Neal, H.A. Wakelee, F.A. Shepherd, T.J. Dilling, J.E. Gray, A.R. Naqash*, S.B. Goldberg*, S.Y. Kim*

[#] Co-first authors
*Co-senior authors

Amin Nassar
Yale University
United States

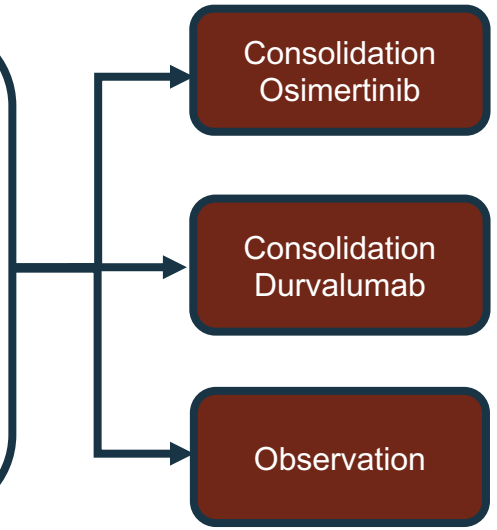
Penn Medicine
Abramson Cancer Center

STUDY DESIGN & PATIENT DEMOGRAPHICS

Multi-institutional retrospective analysis including 24 institutions

Inclusion Criteria:

(1) ≥ age 18 treated years 2015 or later
(2) Stage III, locally advanced, unresectable NSCLC with *EGFR*-sensitizing mutation
(3) Received ≥2 cycles of platinum-based concurrent chemoradiation
(4) No disease progression at time of initiation of consolidation treatments



Co-primary endpoints: Disease-free survival (DFS) and overall survival (OS)[#]

Secondary endpoints: Consolidation treatment-related adverse events (trAE), central nervous system disease-free survival (CNS DFS)

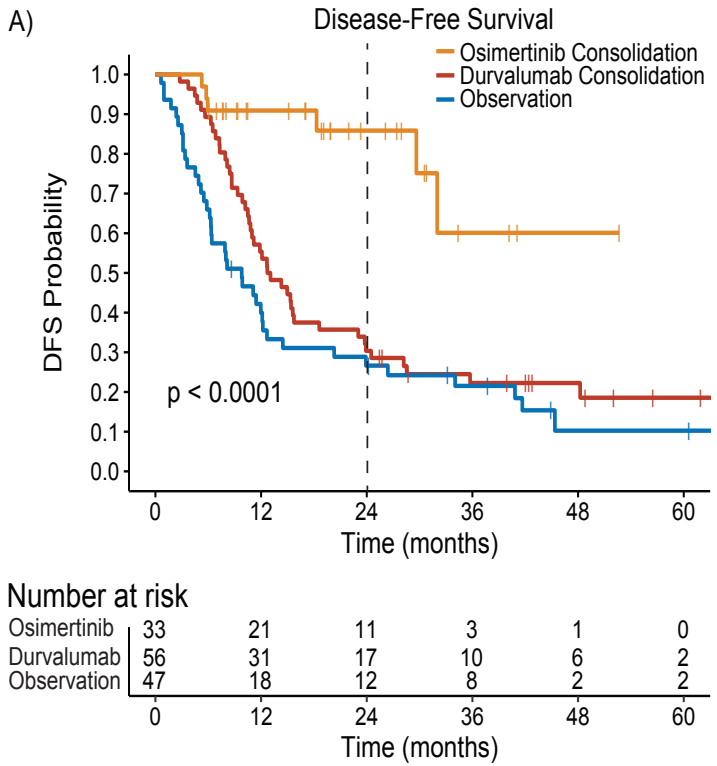
[#]multivariable including nodal status (N stage), stage III A/B/C AJCC 8th, and age

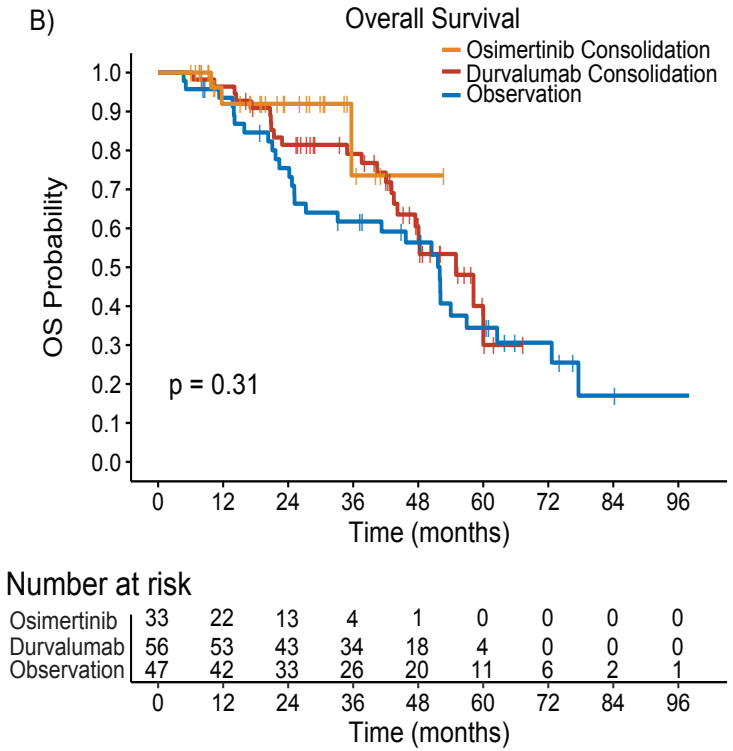
Baseline characteristics

	Total (N=136)	Osimertinib (N=33)	Durvalumab (N=56)	Observation (N=47)	P-value
Age – Median (IQR)	66 [57, 72]	65 [60, 72]	67 [56, 71]	64 [57, 72]	0.8
Sex – Female	88 (64.7%)	22 (66.7%)	34 (60.7%)	32 (68.1%)	0.7
Race					0.2
White	88 (64.7%)	22 (66.7%)	33 (58.9%)	33 (70.2%)	
Asian	36 (26.5%)	9 (27.3%)	20 (35.7%)	7 (14.9%)	
Black	6 (4.4%)	1 (3.0%)	2 (3.6%)	3 (6.4%)	
Smoking					0.06
Former/Current	55 (40.4%)	10 (30%)	32 (1.8%)	27 (57.4%)	
Never	81 (59.6%)	23 (69.7%)	38 (67.9%)	20 (42.6%)	
PD-L1 TPS*					0.4
<1%	35 (37.2%)	10 (40%)	15 (31.3%)	10 (47.6%)	
≥1%	59 (62.8%)	15 (60%)	33 (68.8%)	11 (52.4%)	
Stage					0.31
IIIA	52 (38.2%)	11 (33.3%)	20 (35.7%)	21 (44.7%)	
IIIB	68 (50.0%)	15 (45.5%)	30 (53.6%)	23 (48.9%)	
IIIC	16 (11.8%)	7 (21.2%)	6 (10.7%)	3 (6.4%)	

*Tumor proportion score

DISEASE-FREE AND OVERALL SURVIVAL





Subsequent systemic therapy after consolidation treatment or observation

Subsequent systemic therapy

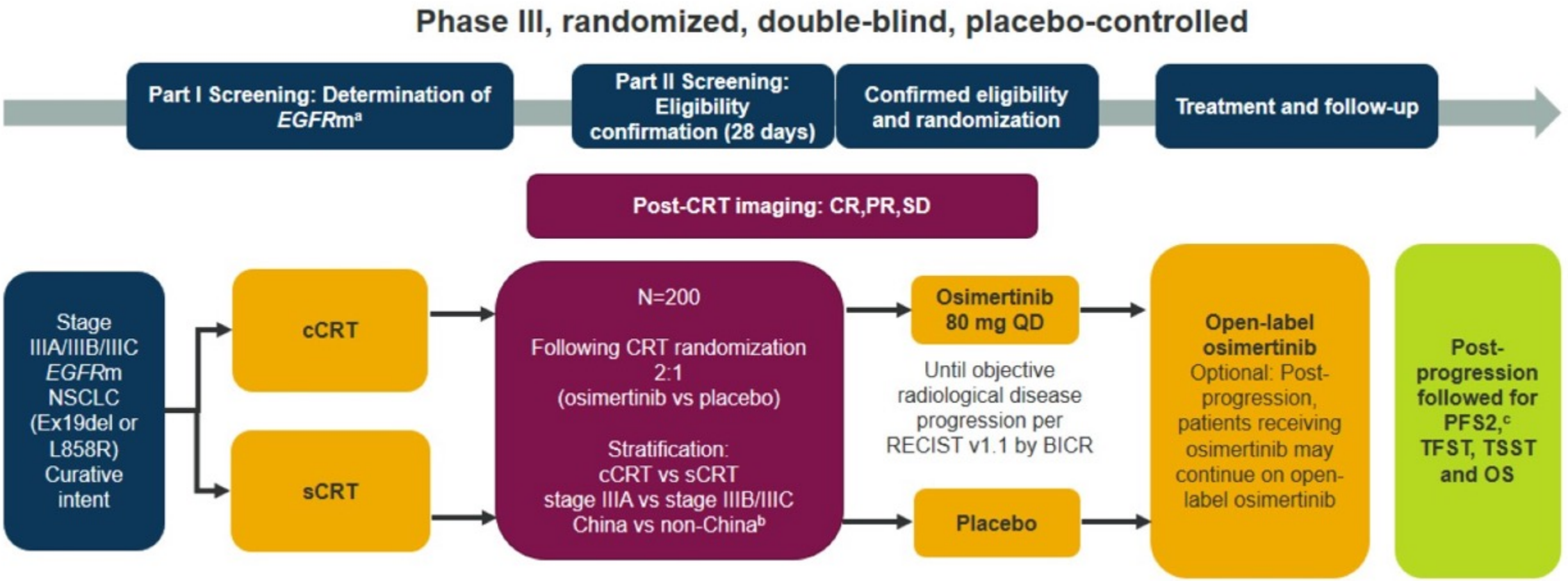
Arm	EGFR TKI	IO	Other	Total
Osimertinib	1 (3%)	1 (3%)	1 (3%)	3 (3.7%)
Durvalumab	37 (66%)	1 (1.8%)	3 (5.4%)	41 (51%)
Observation	35 (74%)	1 (2.2%)	1 (2.2%)	37 (46%)
Total	73 (90%)	3 (3.7%)	5 (6.2%)	81

24-month CNS Relapse: Osimertinib: 6.7% (95% CI, 1.7-32); Durvalumab: 17% (95% CI, 8.1-30); Observation: 11% (95% CI, 3.8-25)

Rationale for Consolidation Tx with Targeted Tx in Oncogenic-Driven LA-NSCLC

- Their empiric use, either as consolidation or concurrently with chemoradiation, in absence of clear cut oncogenic drivers, has failed to yield an OS benefit
  - SWOG-0023 and RTOG-0617 are examples
- Similarly, Durvalumab in the EGFR mt (+) population in PACIFIC has not resulted in any PFS or OS advantage
- In retrospective analysis, pts with EGFR mt (+) LA-NSCLC receiving an "appropriate" TKI fared better than those receiving CPI or undergoing observation
- Outcome data from ADAURA in resectable EGFR mt (+) NSCLC and ALINA in resectable ALK (+) NSCLC would suggest that a similar approach in LA-NSCLC is worthwhile

LAURA: Study Design



LAURA Trial (NCT03521154)

- Osimertinib Maintenance After Definitive Chemoradiation in Unresectable EGFR Mutation+ Stage III NSCLC
- Primary Endpoint- BICR- confirmed PFS
- Secondary Endpoints- CNS PFS, OS, PFS by mutation status, safety
- 1st pt- July 2018
- Expected results- late 2022

ASCO – plenary 2024

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Conclusions: LA-NSCLC

- PACIFIC remains the SOC
- Optimal approach in PD-L1 0% is uncertain; “default” for now remains Durvalumab post CT-XRT
- **Strongly suspect pts with oncogenic driven tumors will benefit from “appropriate” bio-marker specific TKIs**

Osimertinib demonstrated overwhelming efficacy benefit for patients with unresectable, Stage III EGFR-mutated lung cancer in LAURA Phase III trial

PUBLISHED 19 February 2024

First EGFR inhibitor and targeted treatment to demonstrate progression-free survival benefit in Stage III setting

Positive high-level results from the LAURA Phase III trial showed osimertinib **demonstrated a statistically significant and highly clinically meaningful improvement in progression-free survival (PFS) for patients with unresectable**, Stage III epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) after chemoradiotherapy (CRT) compared to placebo after CRT.

Overall survival (OS) data showed a favorable trend for osimertinib, although data were not mature at the time of this analysis. The trial will continue to assess OS as a secondary endpoint.

Each year an estimated 2.4 million people are diagnosed with lung cancer globally with 80-85% of patients diagnosed with NSCLC, the most common form of lung cancer.[1-3] Approximately 10-15% of NSCLC patients in the US and Europe, and 30-40% of patients in Asia, have EGFR mutations.[4-7] More than one in six patients with NSCLC are diagnosed with unresectable Stage III disease (15%).[8]

Suresh Ramalingam, MD, Executive Director of Winship Cancer Institute of Emory University, Atlanta, US, and principal investigator in the trial, said: ***"These results represent a major advance for patients with Stage III EGFR-mutated lung cancer who have a high propensity for early progression and spread to the brain, and where no targeted therapy is available. LAURA shows osimertinib can provide impactful clinical benefit and could become the first targeted treatment option for patients with Stage III disease."***

The safety and tolerability of osimertinib in the LAURA trial was consistent with its established profile and no new safety concerns were reported with osimertinib maintenance treatment following CRT.

Agenda

Module 1: Contemporary Care for Patients with Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) with an EGFR Mutation — Dr Langer

Module 2: Evolving First-Line Treatment for Metastatic NSCLC with an EGFR Mutation — Dr Goldman

Module 3: Biological Rationale for and Emerging Role of Antibody-Drug Conjugates in the Management of NSCLC with an EGFR Mutation — Dr Yu

Module 4: Other Emerging Strategies for Relapsed Metastatic NSCLC with an EGFR Mutation — Dr Sabari

Module 5: Current and Future Management of NSCLC with an EGFR Exon 20 Insertion Mutation — Dr Piotrowska

Module 6: Management of Toxicities Associated with Available and Emerging Therapies for NSCLC with an EGFR Mutation — Dr Neal

Consulting Faculty Comments

Choosing optimal first-line therapy for metastatic disease with an EGFR mutation; role of amivantamab

Dr Roy S Herbst
(New Haven, Connecticut)

Dr John V Heymach
(Houston, Texas)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What is your current first-line therapy for a younger patient with NCSLC with an EGFR mutation and CNS metastases?

QUESTIONS FOR THE FACULTY

What is your current first-line therapy for a patient who experiences disease progression while receiving adjuvant osimertinib?

Does this change at all for someone who completed 3 years of osimertinib before disease progression?

QUESTIONS FOR THE FACULTY

If amivantamab/lazertinib are approved as first-line treatment, for which types of patients will you prioritize this regimen?

RTP
RESEARCH
TO PRACTICE

The Evolving First-Line Treatment Options for Metastatic EGFR Mutation-Positive NSCLC

Jonathan W. Goldman, MD
Associate Professor, UCLA Hematology & Oncology
Director of Clinical Trials in Thoracic Oncology
Associate Director of Drug Development

First-Line EGFRm NSCLC

Landmark Studies

- FLAURA: PFS and OS benefit with up-front osimertinib monotherapy
- FLAURA2: Osimertinib combined with chemotherapy versus osimertinib alone
- MARIPOSA: Amivantamab and lazertinib versus osimertinib

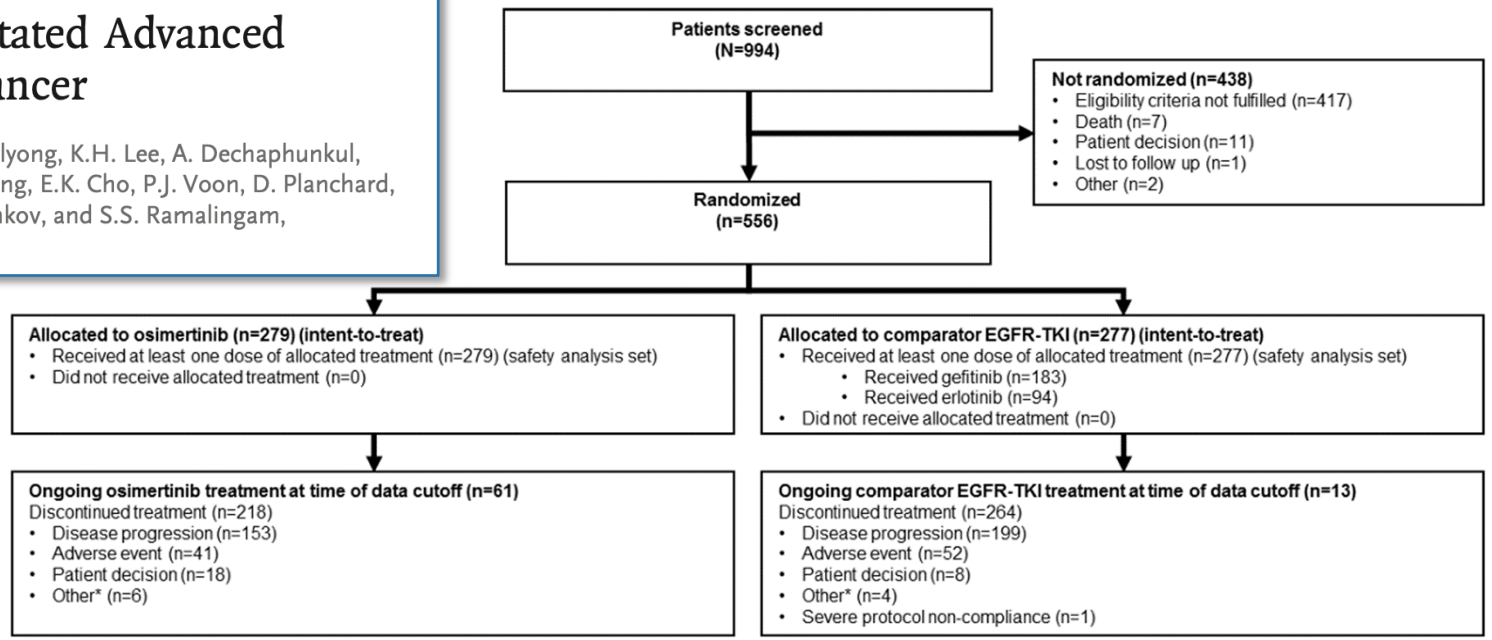
FLAURA Trial: osimertinib vs 1st Gen TKI

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*



*Any reason not specifically recorded; for example, subject died.

EGFR denotes epidermal growth factor receptor, TKI tyrosine kinase inhibitor.

Soria JC, Ohe Y, Vansteenkiste J, et al. NEJM 2018;378:113-125.
Ramalingam SS, Vansteenkiste J, Planchard D, et al. NEJM 2020 0;382:41-50.

FLAURA: Landmark survival rates and the number of patients continuing to receive the first-line trial drug were consistently higher in the osimertinib group.

Table 1. Overall Survival and Continuation of First-Line Trial Drug.*

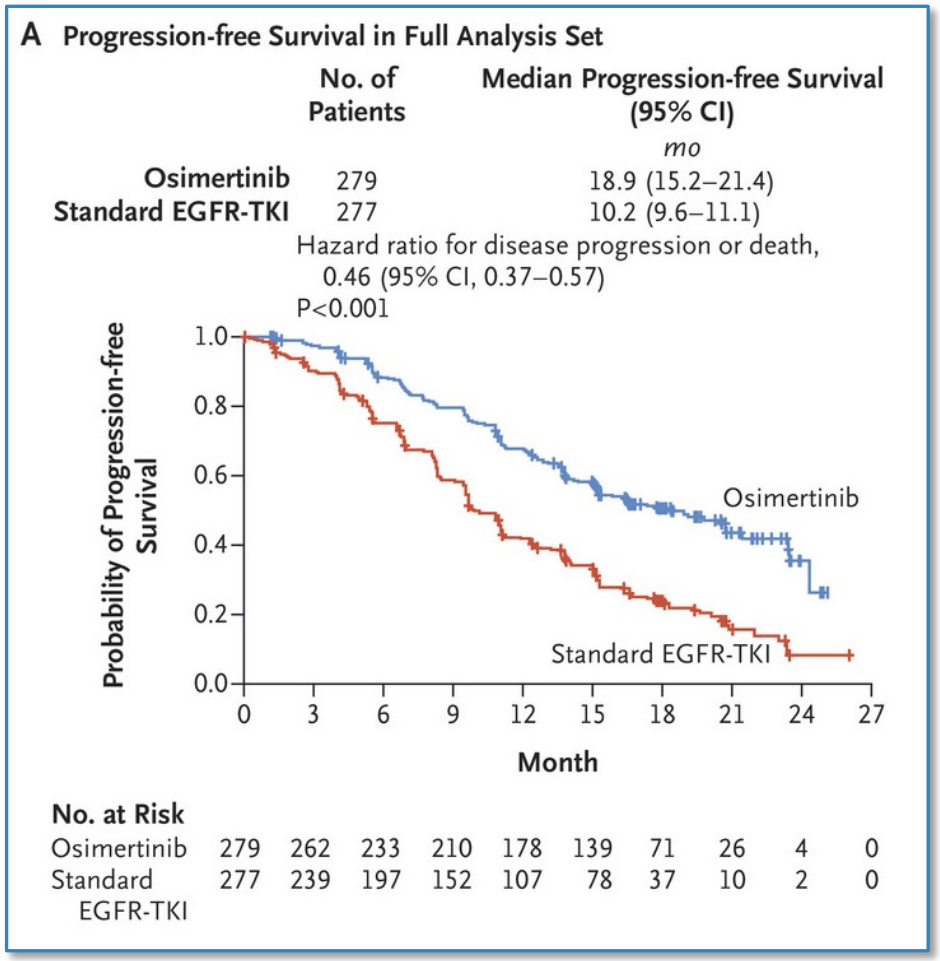
Variable	Osimertinib (N=279)	Comparator EGFR-TKI (N=277)
Overall survival — % (95% CI)		
At 12 mo	89 (85–92)	83 (77–87)
At 24 mo	74 (69–79)	59 (53–65)
At 36 mo	54 (48–60)	44 (38–50)
Patients continuing to receive first-line trial drug — no. (%)		
At 12 mo	194 (70)	131 (47)
At 24 mo	118 (42)	45 (16)
At 36 mo	78 (28)	26 (9)

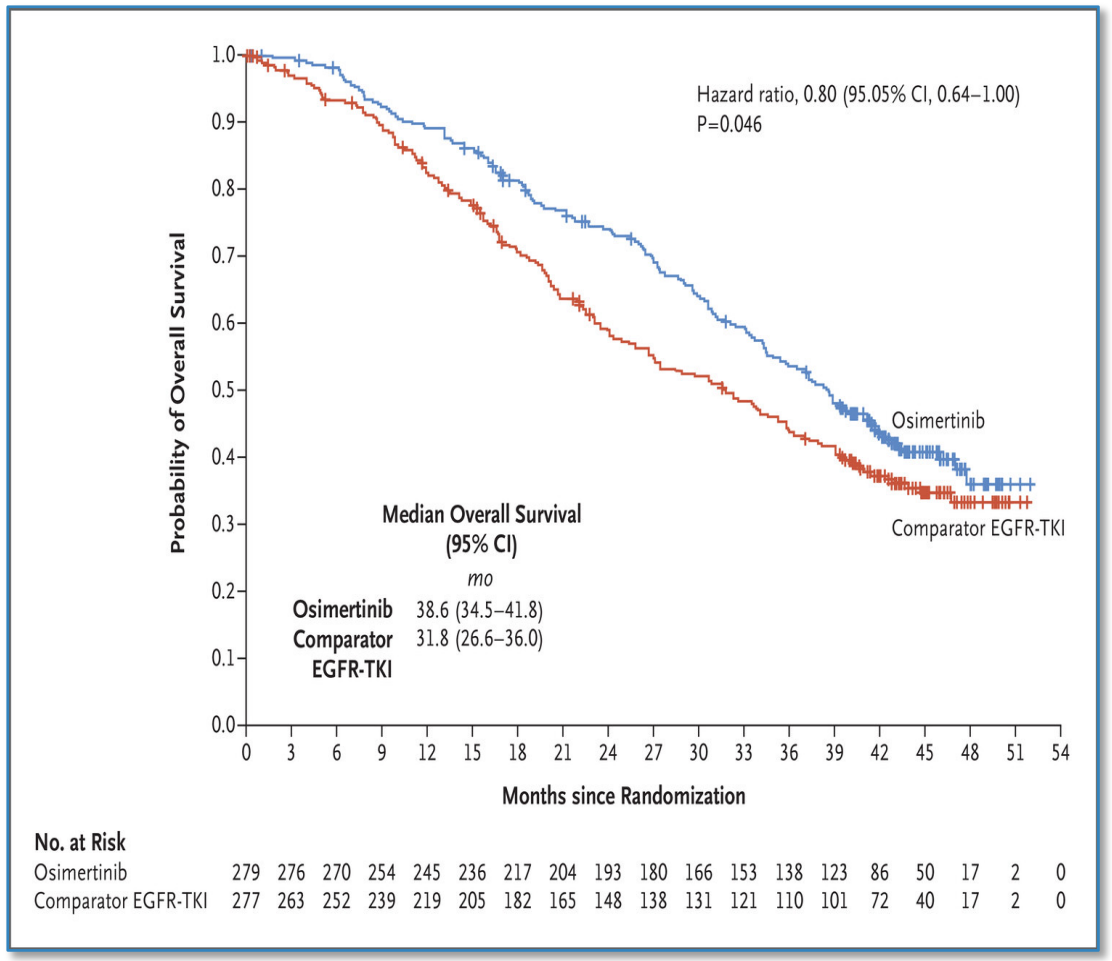
* In the comparator group, patients received one of two tyrosine kinase inhibitors of epidermal growth factor receptor (EGFR-TKI): gefitinib or erlotinib.

Grade 3 AE rate also favored osimertinib: 42% vs 47%.

Ramalingam SS, Vansteenkiste J, Planchard D, et al. NEJM 2020 0;382:41-50.

FLAURA: PFS and OS Benefit





- *Osimertinib group:* 38.6 m (95% CI, 34.5 – 41.8)
- *Placebo group:* 31.8 m (95% CI, 26.6 – 36.0)

Soria JC, Ohe Y, Vansteenkiste J, et al. NEJM 2018;378:113-125.
Ramalingam SS, Vansteenkiste J, Planchard D, et al. NEJM 2020;382:41-50.

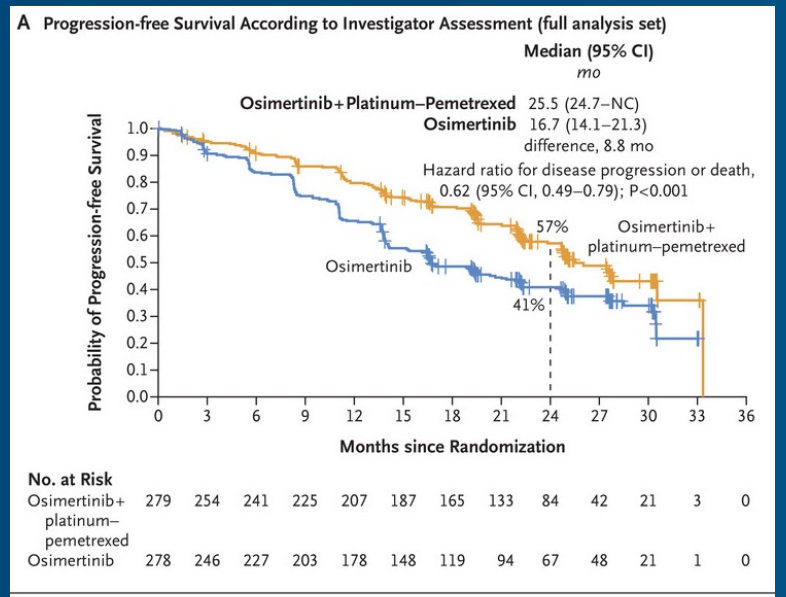
FLAURA2: osimertinib with chemo vs osimertinib

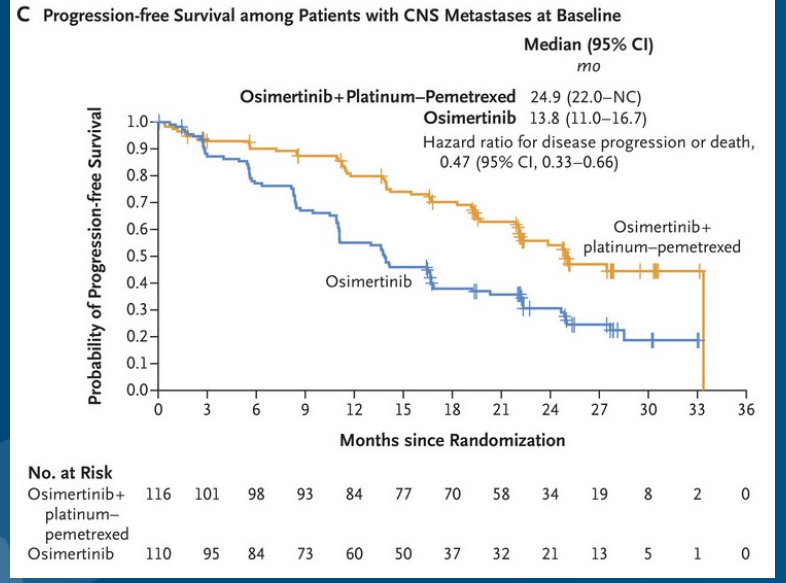
- Addition of platinum and pemetrexed improved:
  - **ORR from 76 to 83%**
  - **Duration of Response from 15.3 to 24.0 m**
  - **mPFS from 16.7 to 25.5 months (HR 0.62)**

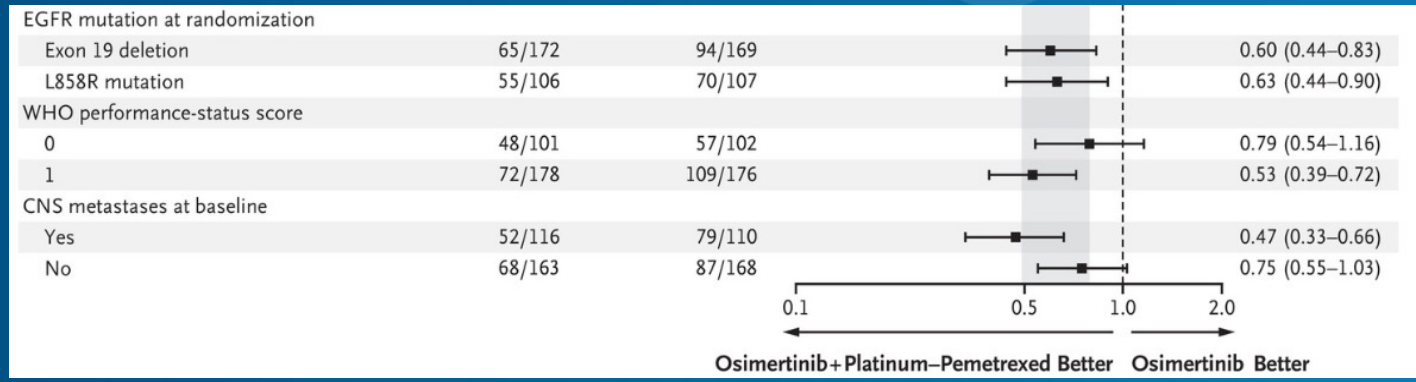
End Point	Analysis According to the Investigator	
	Osimertinib+ Platinum–Pemetrexed (N=279)	Osimertinib Monotherapy (N=278)
Median progression-free survival (95% CI) — mo	25.5 (24.7–NC)	16.7 (14.1–21.3)
Hazard ratio for disease progression or death (95% CI)	0.62 (0.49–0.79)†	—
Progression-free survival (95% CI) — %		
At 12 mo	80 (74–84)	66 (60–71)
At 18 mo	71 (65–76)	49 (42–54)
At 24 mo	57 (50–63)	41 (35–47)
Objective response (95% CI) — %	83 (78–87)	76 (70–80)
Best objective response — no. (%)‡		
Complete response	1 (<1)	2 (1)
Partial response	231 (83)	208 (75)
Stable disease for ≥35 days§	34 (12)	51 (18)
Disease progression	1 (<1)	9 (3)
Death¶	6 (2)	3 (1)
Could not be evaluated	6 (2)	5 (2)
Disease control (95% CI) — %‖	95 (92–98)	94 (90–96)
Median duration of response (95% CI) — mo**	24.0 (20.9–27.8)	15.3 (12.7–19.4)
Continued response (95% CI) — %		
At 12 mo	80 (74–84)	64 (57–70)
At 18 mo	69 (62–75)	44 (37–51)
At 24 mo	49 (41–57)	35 (27–42)

Planchard D, Jänne P, Cheng Y, et al. NEJM 2023;389:1935-1948.

FLAURA2: benefits



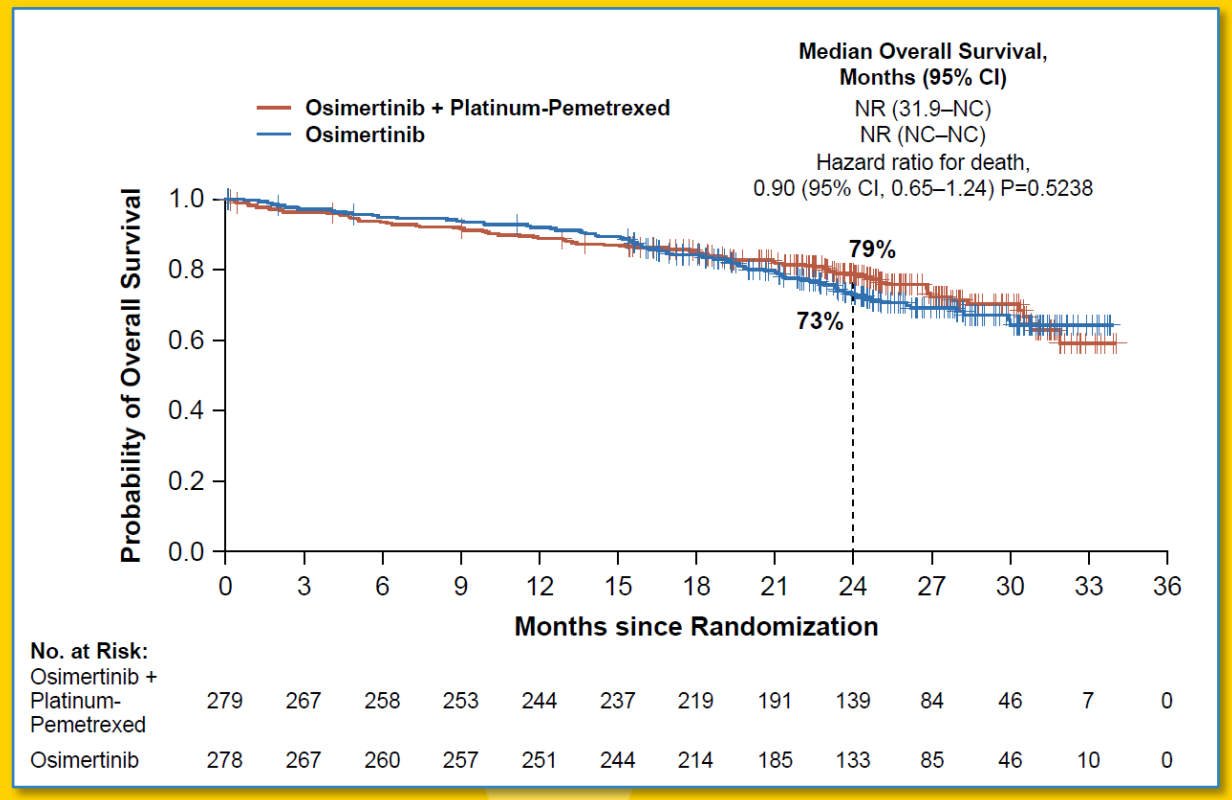


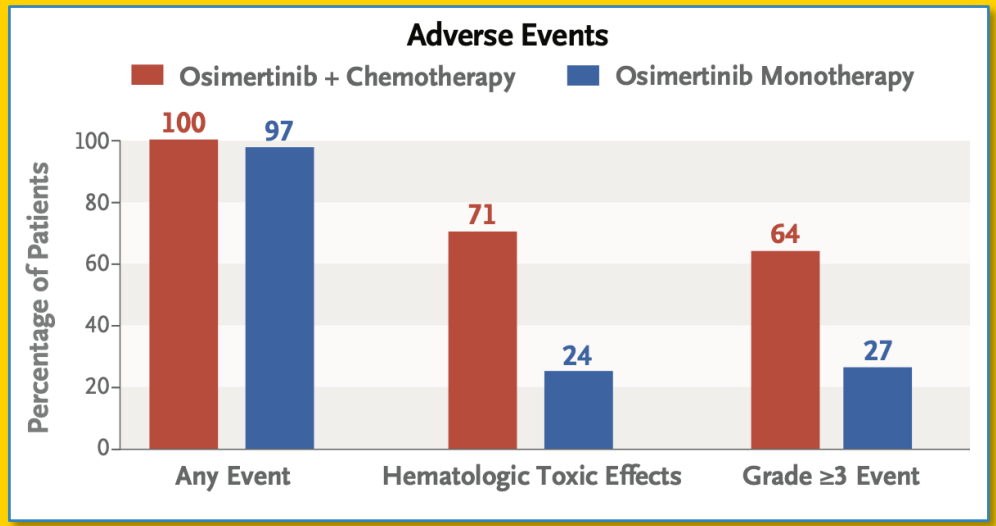


Efficacy Parameter	CNS Measurable Lesions	
	Osimertinib with pemetrexed and platinum-based chemotherapy (N=40)	Osimertinib (N=38)
CNS Tumor Response Assessment[*,†]		
CNS ORR, % (95% CI)	80 (64, 91)	76 (60, 89)
Complete response, %	48	16
Partial response, %	33	61
CNS Duration of Response[†,‡]		
Number of responders	32	29
Response Duration ≥6 months, %	75	50
Response Duration ≥12 months, %	65	34

Planchard D, Jänne P, Cheng Y, et al. NEJM 2023;389:1935-1948.
Osimertinib package insert, released 4/29/24, accessdata.fda.gov.

FLAURA2: outstanding questions





First interim OS analysis at 27% data maturity.

Second interim OS Analysis: at 41% data maturity, the OS interim results NR (38-NC) vs 36.7 m (33.2-NC)(HR 0.75; 95% confidence interval [CI] 0.57-0.97), not significant.

Planchard D, Jänne P, Cheng Y, et al. NEJM 2023;389:1935-1948.
Planchard, et al, NEJM Research Summary. DOI: 10.1056/NEJMoa2306434
AstraZeneca, https://www.astrazeneca.com/media-centre/press-releases/2024/, 3/21/2024.

MARIPOSA: Amivantamab Plus Lazertinib Versus Osimertinib as First-line Treatment in EGFR-mutated Advanced NSCLC

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)

2:2:1 Randomization (N=1074)

Serial brain MRIs were required for all patients[a]

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**

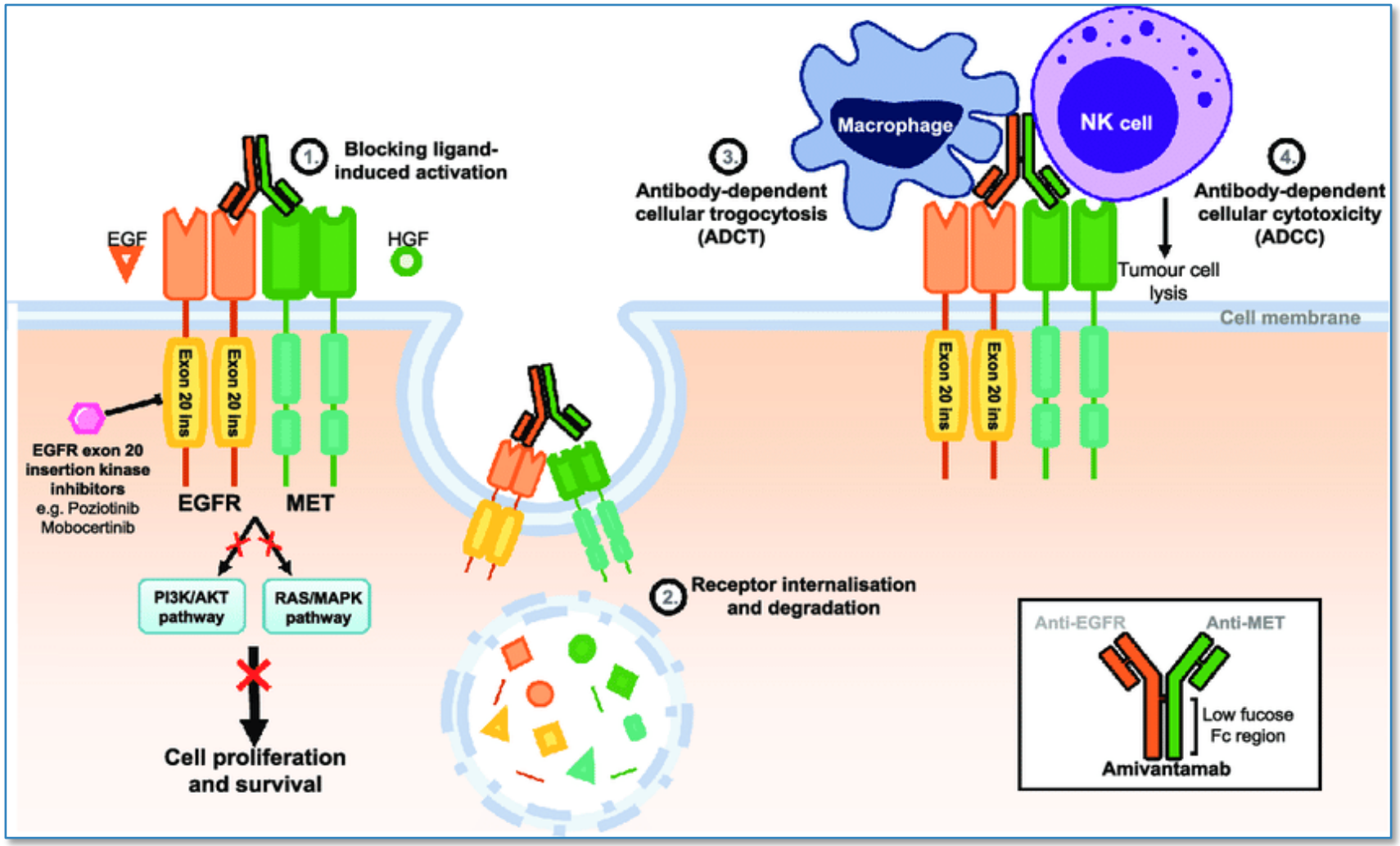
Secondary endpoints of amivantamab + lazertinib vs osimertinib:

- 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

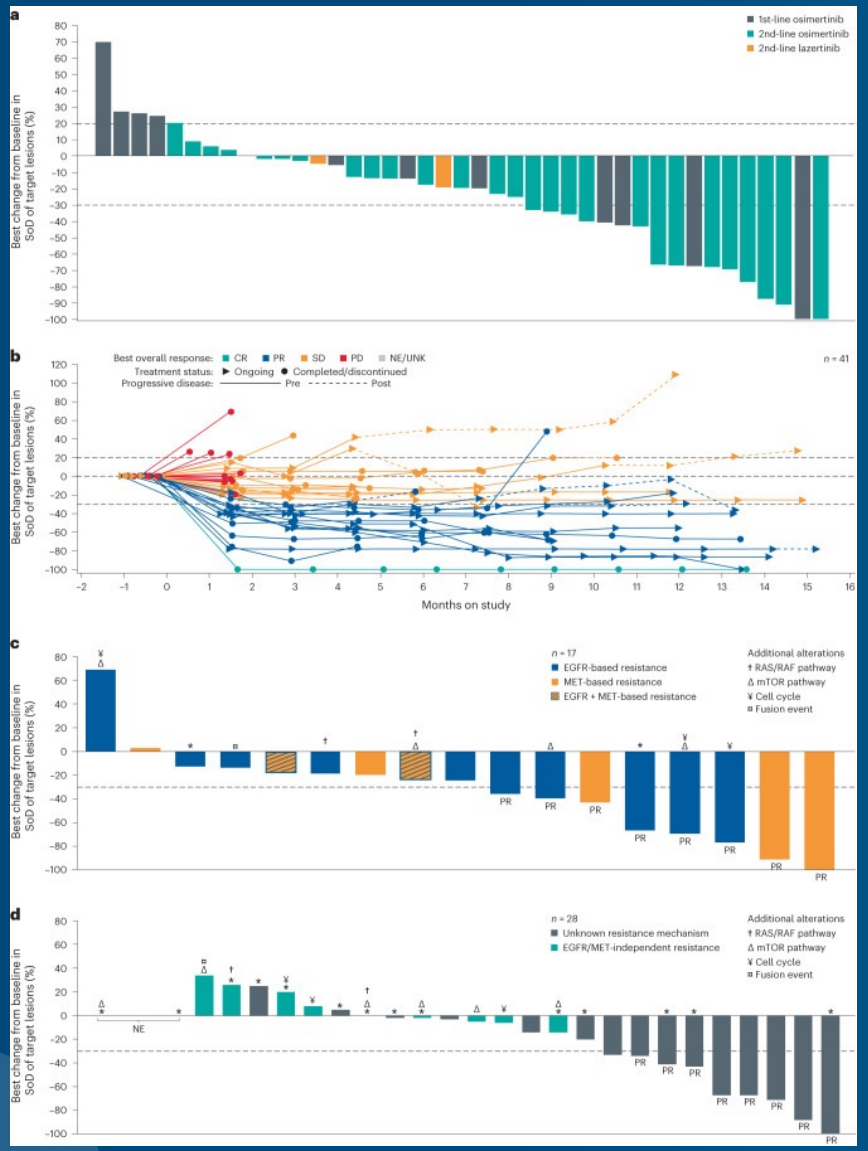
Cho BC, Felip E, Spira A. ESMO Congress, Madrid 2023.

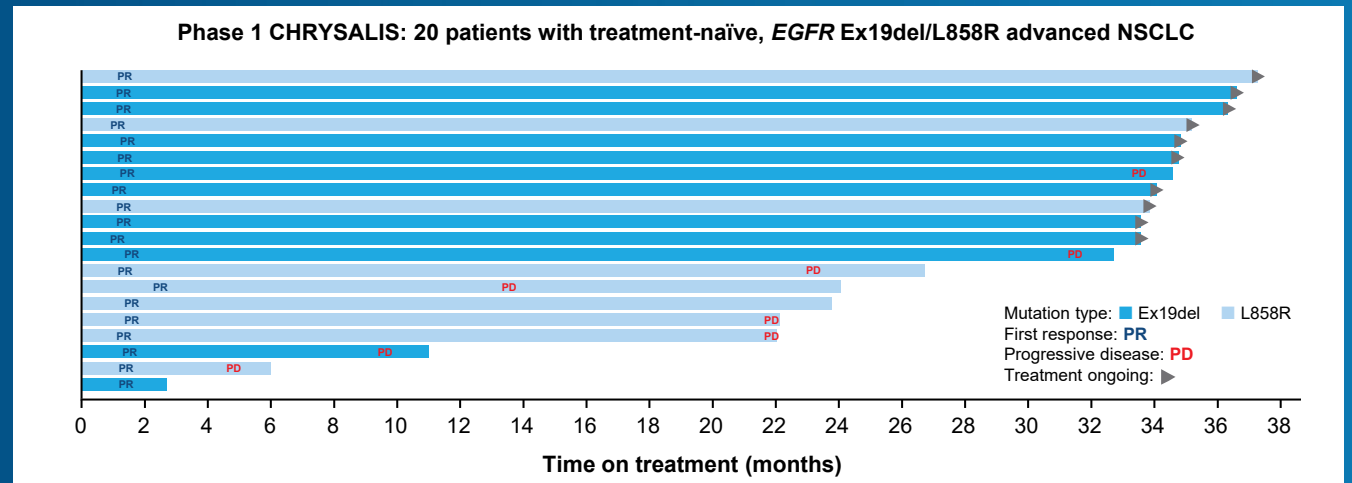
Amivantamab: Mechanism of Action



Vyse A, et al. *Expert Rev Vaccines*. 2021;20(10):1311-1325.

Anti-tumor activity of amivantamab + lazertinib combination in CHRYSALIS trial (part 2 expansion cohort E):



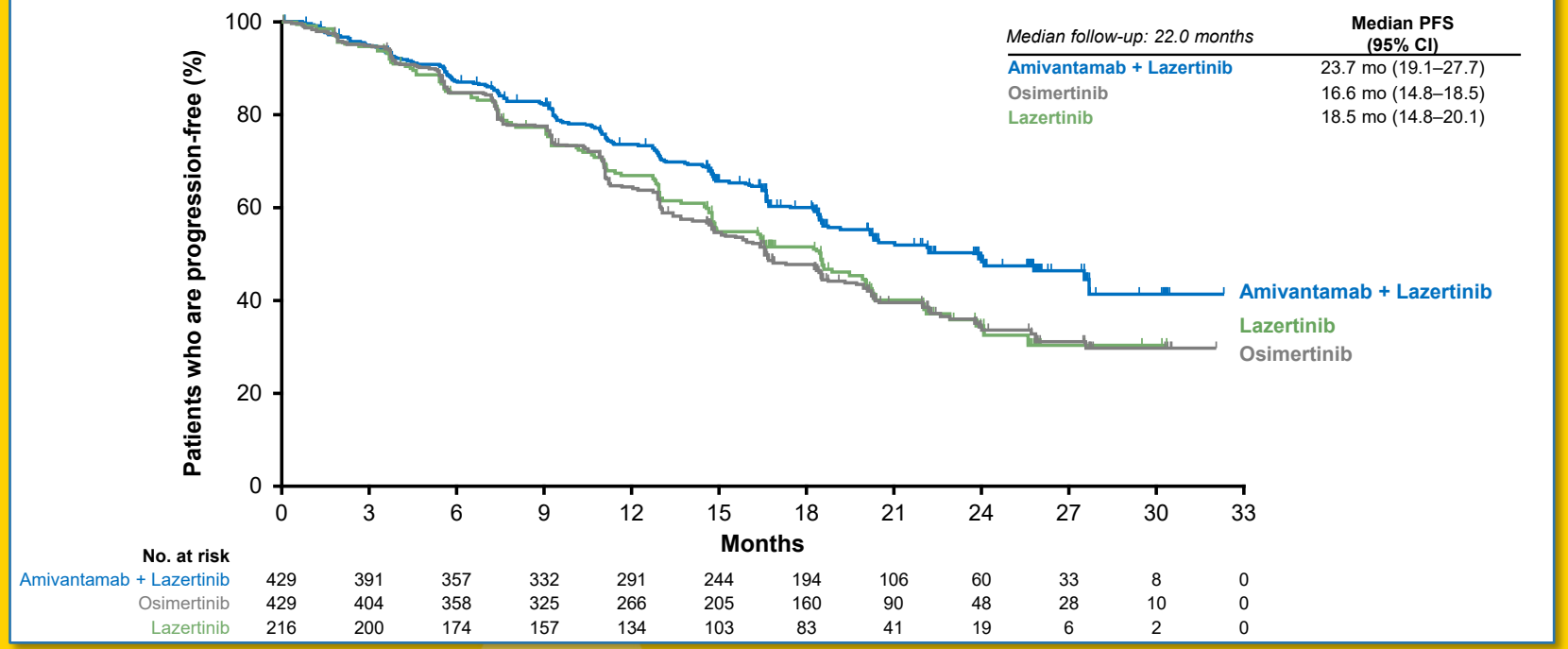


- All 20 patients responded to amivantamab + lazertinib and demonstrated durable responses[1]
- At a median follow-up of 33.6 months, 10 of 20 patients were receiving ongoing treatment[2]

Cho, B.C., Kim, DW., Spira, A.I. *et al.* 2023 *Nat Med* 29, 2577–2585. Cho BC, Felip E, Spira A. ESMO Congress, Madrid 2023.

MARIPOSA: PFS Benefit

Lazertinib Monotherapy Demonstrates Meaningful Clinical Activity



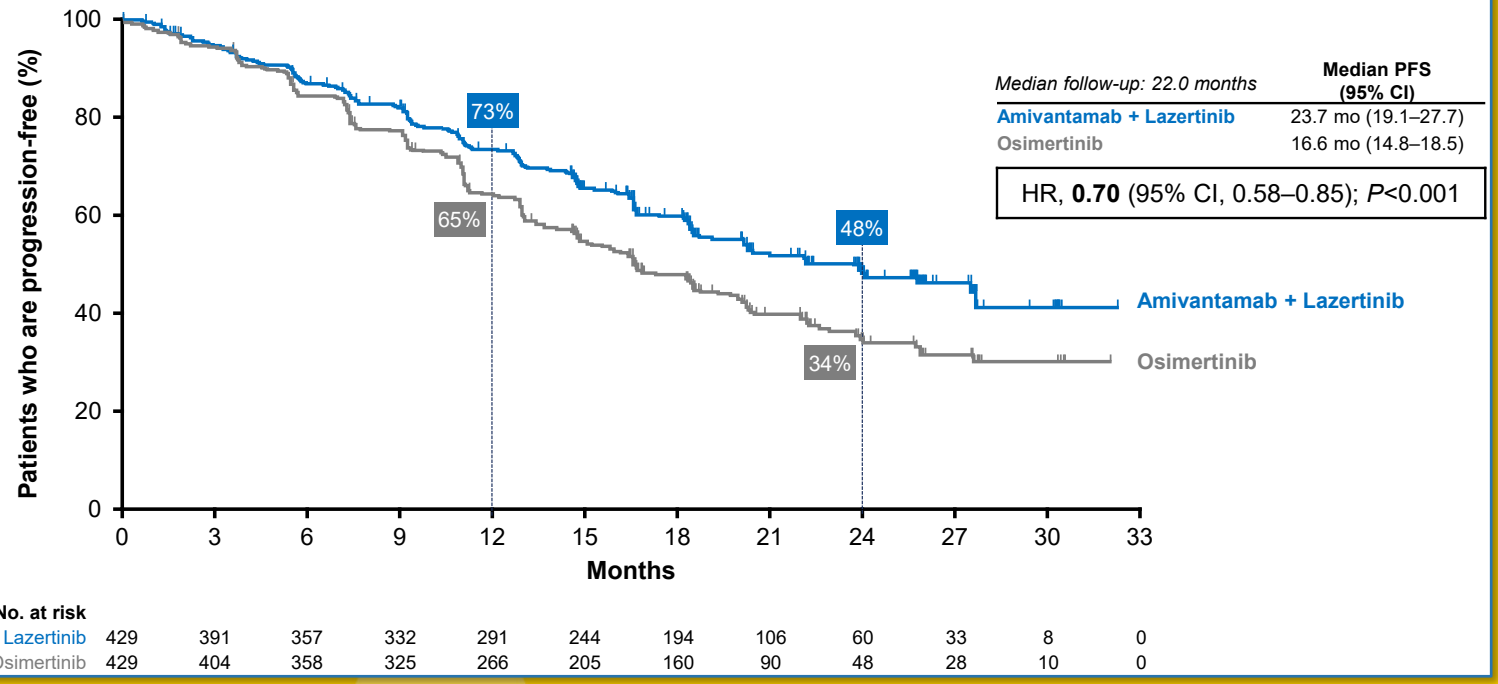
For a contribution of components analysis, lazertinib performed similarly to osimertinib.

Cho BC, Felip E, Spira A. ESMO Congress, Madrid 2023.

MARIPOSA: PFS Benefit

Primary Endpoint: Progression-free Survival by BICR[a]

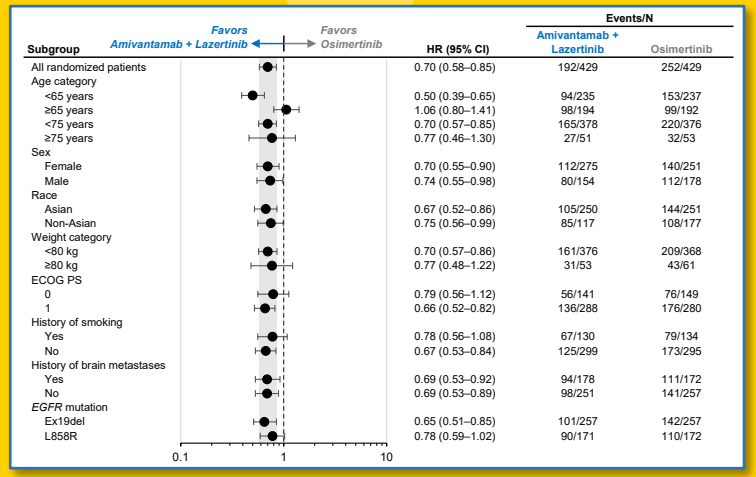
Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



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

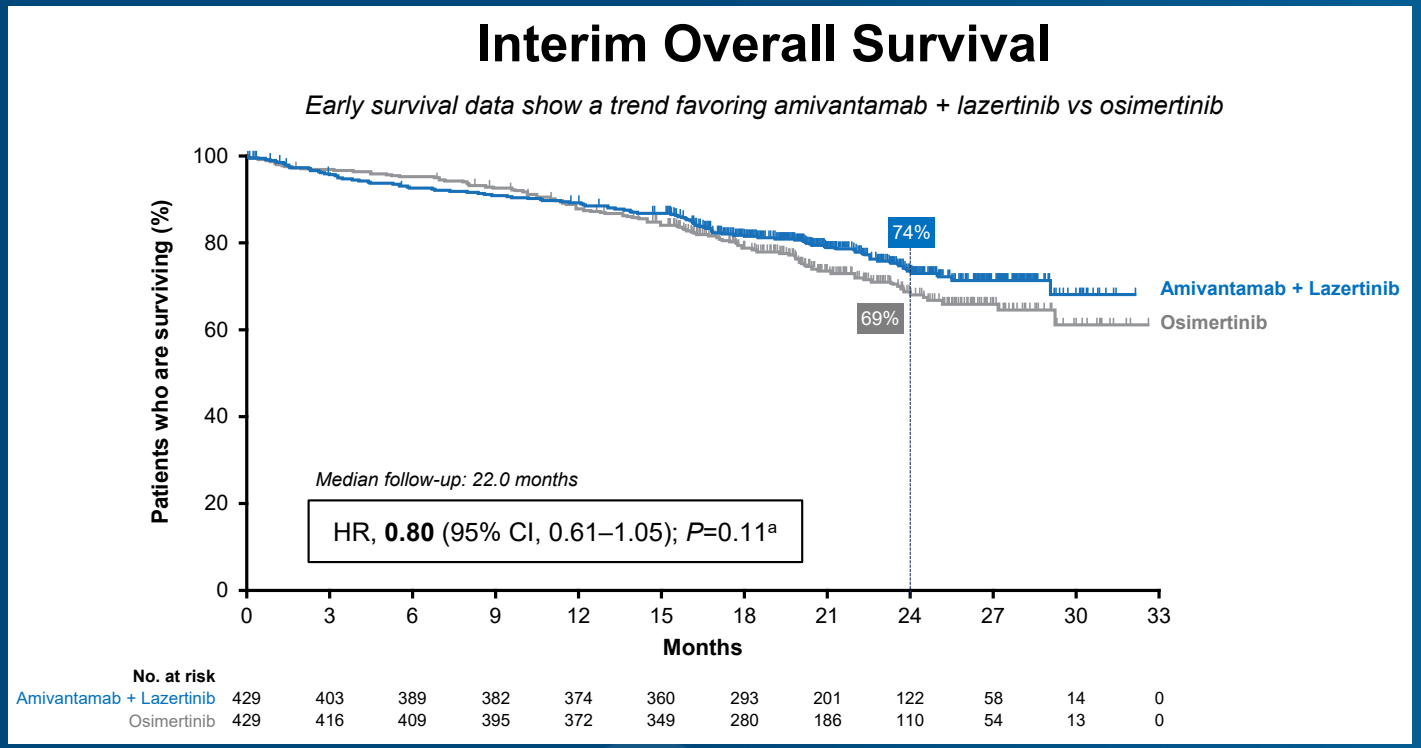


BICR-assessed response, n (%)[a]	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)
ORR		
All responders	86% (95% CI, 83–89)	85% (95% CI, 81–88)
Confirmed responders	80% (95% CI, 76–84)	76% (95% CI, 71–80)
Best response[b]		
CR	29 (7)	15 (4)
PR	334 (79)	335 (81)
SD	30 (7)	42 (10)
PD	7 (2)	11 (3)
NE/UNK	21 (5)	11 (3)
Ongoing responses	209 of 336 (62%)	151 of 314 (48%)

Primary endpoint: amivantamab + lazertinib vs osimertinib

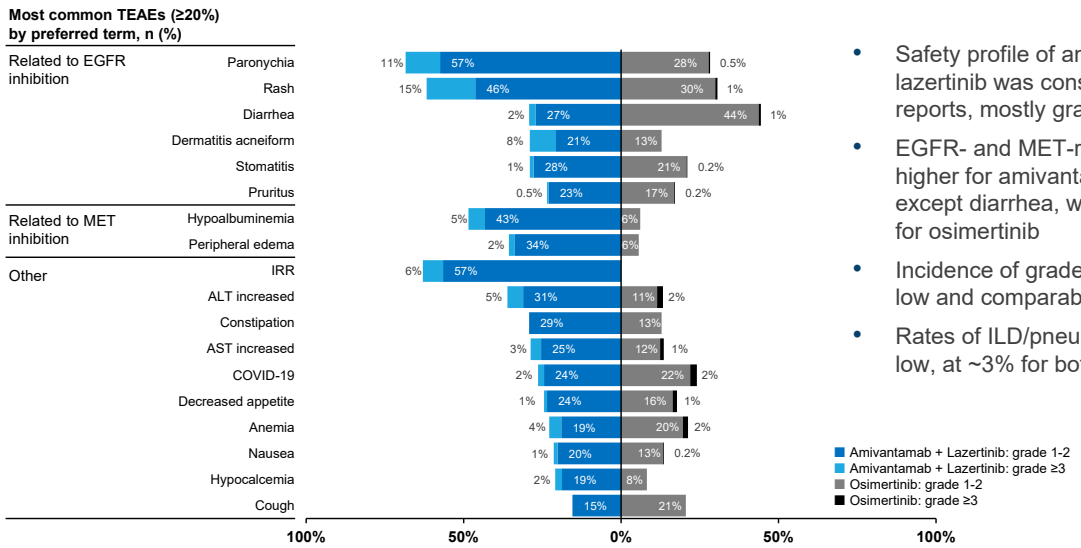
Cho BC, Felip E, Spira A. ESMO Congress, Madrid 2023.

MARIPOSA: outstanding questions



Cho BC, Felip E, Spira A. ESMO Congress, Madrid 2023.

MARIPOSA: outstanding questions



- 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

Adverse Event of Special Interest: VTE[a]

	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	157 (37)	39 (9)
Grade 1	5 (1)	0
Grade 2	105 (25)	24 (6)
Grade 3	43 (10)	12 (3)
Grade 4	2 (0.5)	1 (0.2)
Grade 5	2 (0.5)	2 (0.5)
Any VTE leading to death, n (%)	2 (0.5)	2 (0.5)
Any VTE leading to any discontinuation, n (%)	12 (3)	2 (0.5)
Anticoagulant use at time of first VTE, n (%)		
On anticoagulants	5 (1)	0
Not on anticoagulants	152 (36)	39 (9)
Median onset to first VTE	84 days	194 days
Within first 4 months, n (%)	97 of 157 (62)	13 of 39 (33)

- VTE rates were higher for amivantamab + lazertinib
  - Most common preferred terms were pulmonary embolism and deep vein thrombosis
  - Most VTEs were grade 1-2
  - Incidence of grade 4-5 VTEs was low (<1%) and comparable between arms
- Rates of discontinuations due to VTE were low and comparable between arms
- At time of first VTE:
  - Most patients were not on anticoagulants
  - Majority in the amivantamab + lazertinib arm occurred within the first 4 months
- Prophylactic dose anticoagulation is now recommended for the first 4 months of treatment in ongoing trials of amivantamab + lazertinib

Toxicities and QOL may determine if the benefit is “worth it.”

Cho BC, Felip E, Spira A. ESMO Congress, Madrid 2023.

Amivantamab plus lazertinib vs osimertinib in first-line *EGFR*-mutant advanced non-small cell lung cancer (NSCLC) with biomarkers of high-risk disease: A secondary analysis from the phase 3 MARIPOSA study

2024 ASCO Annual Meeting; Abstract 8504

Friday, May 31st; 3:57PM CDT

UCLA David Geffen School of Medicine

Agenda

Module 1: Contemporary Care for Patients with Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) with an EGFR Mutation — Dr Langer

Module 2: Evolving First-Line Treatment for Metastatic NSCLC with an EGFR Mutation — Dr Goldman

Module 3: Biological Rationale for and Emerging Role of Antibody-Drug Conjugates in the Management of NSCLC with an EGFR Mutation — Dr Yu

Module 4: Other Emerging Strategies for Relapsed Metastatic NSCLC with an EGFR Mutation — Dr Sabari

Module 5: Current and Future Management of NSCLC with an EGFR Exon 20 Insertion Mutation — Dr Piotrowska

Module 6: Management of Toxicities Associated with Available and Emerging Therapies for NSCLC with an EGFR Mutation — Dr Neal

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Comments

Novel HER3-targeted antibody-drug conjugate patritumab deruxtecan for NSCLC with an EGFR mutation

Dr Roy S Herbst (New Haven, Connecticut)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Should all patients experiencing disease progression on first-line osimertinib undergo repeat biomarker testing to identify potentially targetable mechanisms of resistance?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Assuming you had access to amivantamab/chemotherapy and patritumab deruxtecan, how would you likely sequence them for a patient experiencing disease progression on osimertinib?

In which line of therapy would you likely use them?

Consulting Faculty Comments

Management of transformed small cell lung cancer (SCLC); FDA approval of the bispecific T-cell engager tarlatamab for previously treated extensive-stage SCLC

Dr John V Heymach (Houston, Texas)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What do you see as the future role, if any, of bispecific antibodies in small cell lung cancer?

Memorial Sloan Kettering Cancer Center

Biologic rationale for and emerging role of antibody drug conjugates in management of EGFR-mutant NSCLC

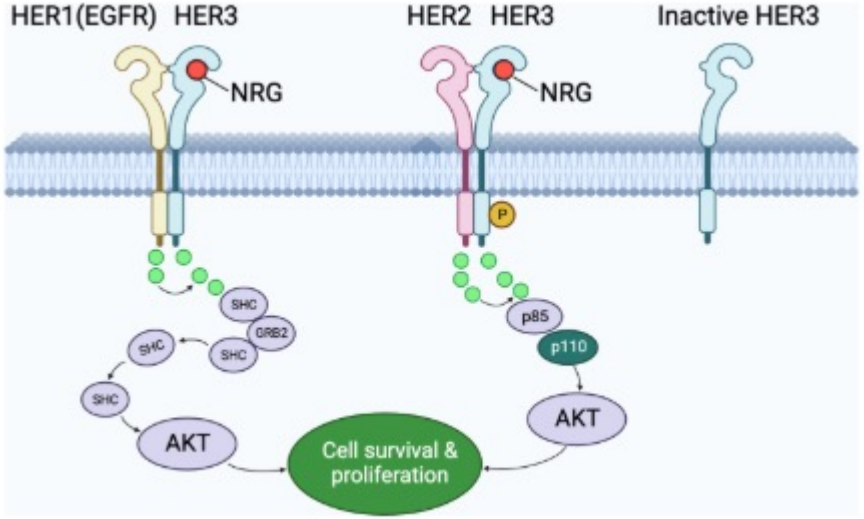
Helena Yu, MD
Associate Attending
Research Director, Thoracic Oncology Service
Memorial Sloan Kettering Cancer Center
May 31st, 2024

Outline

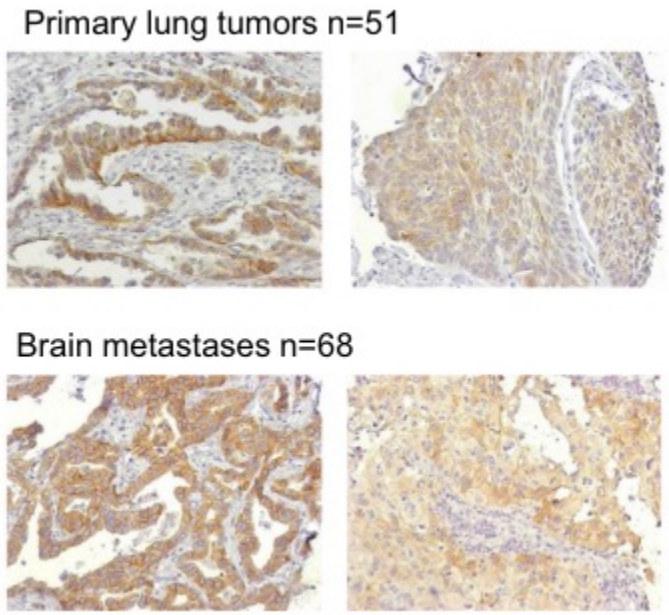
- HER3 as a target in EGFR-mutant lung cancer
- ADC structure and patritumab deruxtecan (HER3-DXd)
- Phase 2 study of HER3-DXd (HERTHENA-Lung01)
- Phase 3 study of HER3-DXd (HERTHENA-Lung02)
- Datopotamab deruxtecan in EGFR+ NSCLC (TROPION-Lung05)

HER3 as a therapeutic target

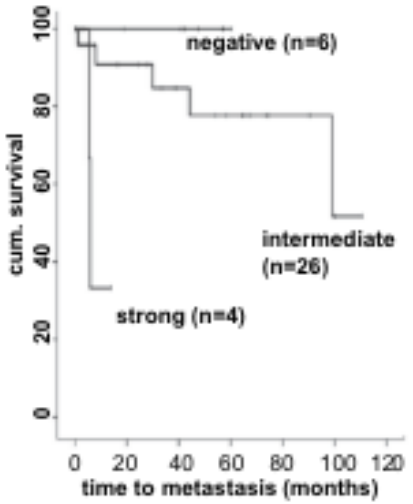
EGFR/HER3 heterodimerization

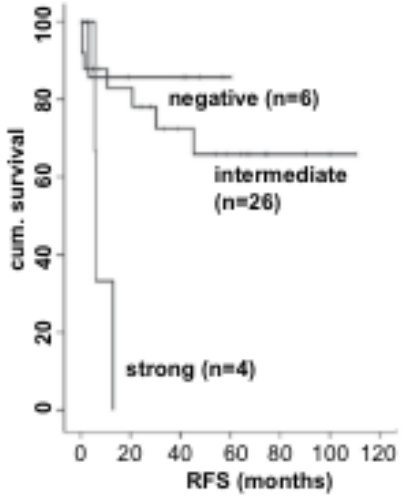


HER3 expression in NSCLC



HER3 poor prognostic biomarker





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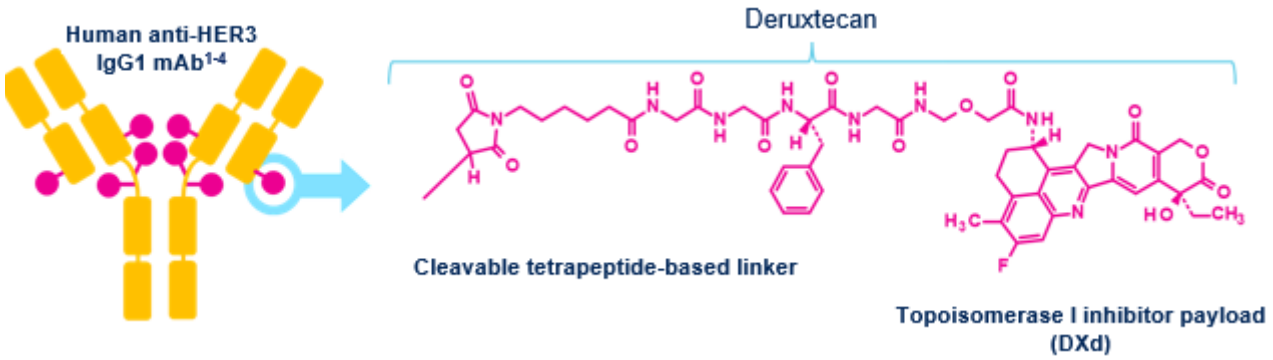
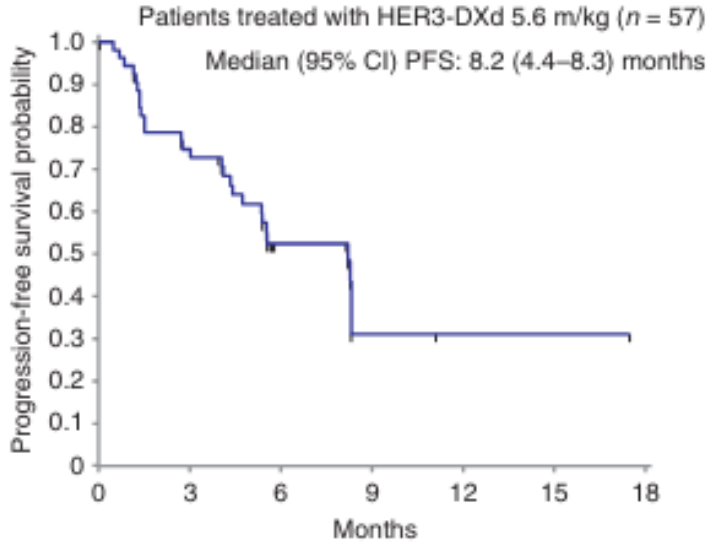
Chen Frontiers 2024
Scharpenseel Sci Rep 2019

Patritumab deruxtecan – HER3 Antibody drug conjugate





ORR 39%
PFS 8.2mo
DOR 6.9mo

HER3-DXd Dose Escalation[a]

Patritumab deruxtecan IV Q3W

Recommended dose for expansion: HER3-DXd 5.6 mg/kg IV Q3W

Locally advanced/metastatic NSCLC with *EGFR* mutations

Progression with prior EGFR TKI treatment

- 6.4 mg/kg (n=5)
- **5.6 mg/kg (n=12)**
- 4.8 mg/kg (n=15)
- 3.2 mg/kg (n=4)

Guided by the modified continual reassessment method using escalation with overdose control.

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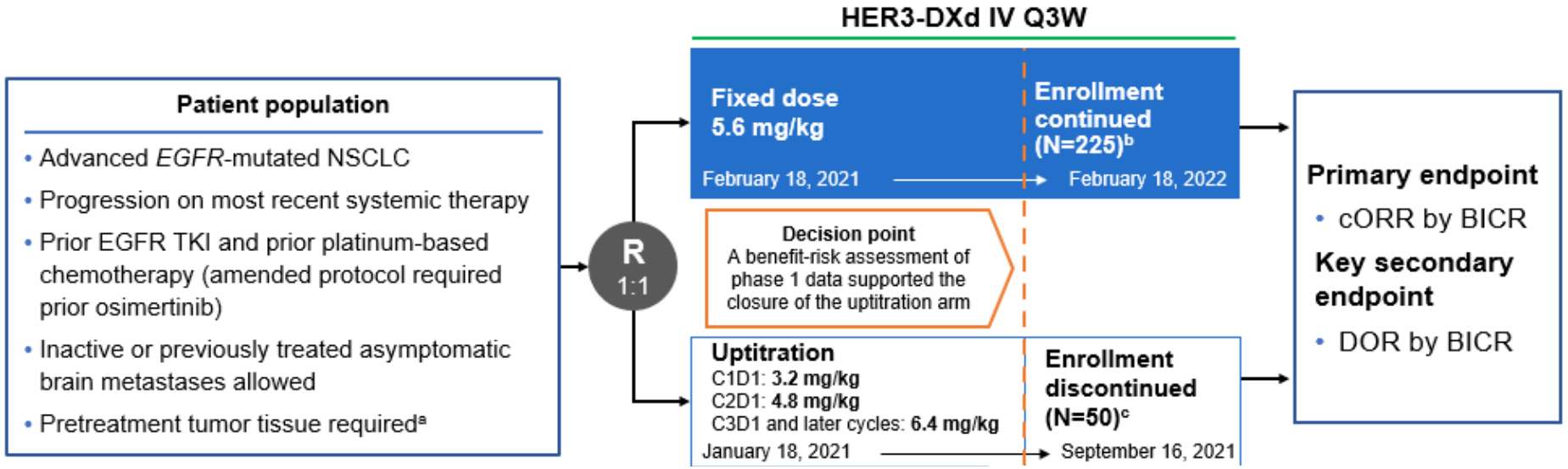
Janne Canc Disc 2022

Phase 2- HERTHENA-Lung01



Baseline characteristics		HER3-DXd 5.6 mg/kg (N=225)
Age, median (range), years		64 (37-82)
Female, n (%)		132 (59)
Asian, n (%)		105 (47)
Time since initial NSCLC diagnosis, median (range), months		41.0 (9.1-224.7)
ECOG performance status, n (%)	0/1	73 (32)/149 (66)
	2[a]	3 (1)
Sum of target lesion diameters at baseline (BICR), median (range), mm		68 (11-248)
History of CNS metastasis, n (%)		115 (51)
Brain metastasis at baseline (BICR), n (%)		72 (32)
Liver metastasis at baseline (BICR), n (%)		75 (33)
EGFR-activating mutations, n (%)[b]	Ex19del	142 (63)
	L858R	82 (36)
No. of prior lines of systemic therapy (locally advanced/metastatic)	Median (range)	3 (1-11)[c]
	2 prior lines, n (%)	58 (26)
	>2 prior lines, n (%)	165 (73)
Prior cancer regimens, n (%)	Prior EGFR TKI therapy	225 (100)
	Prior third-generation EGFR TKI	209 (93)
	Prior platinum-based chemotherapy	225 (100)

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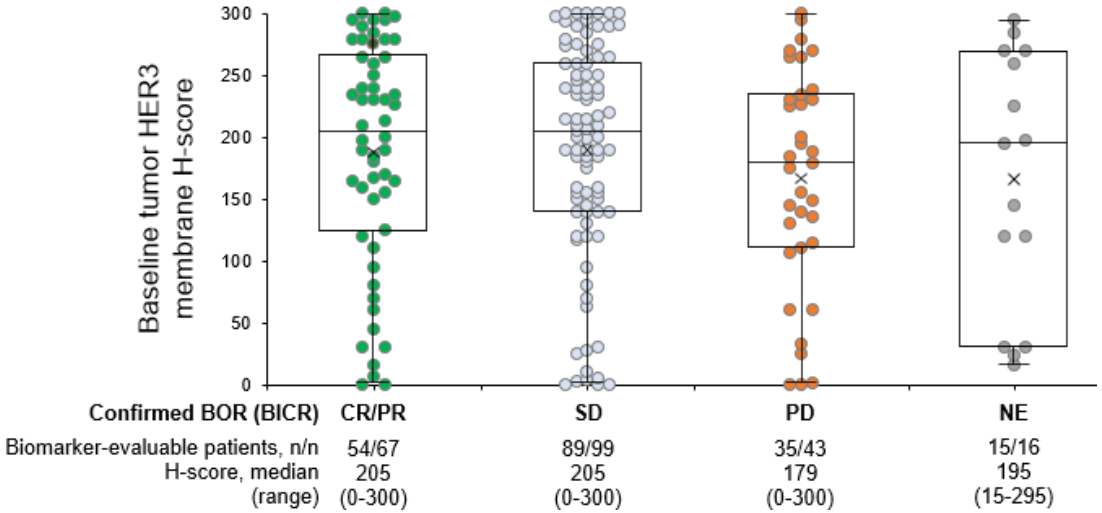
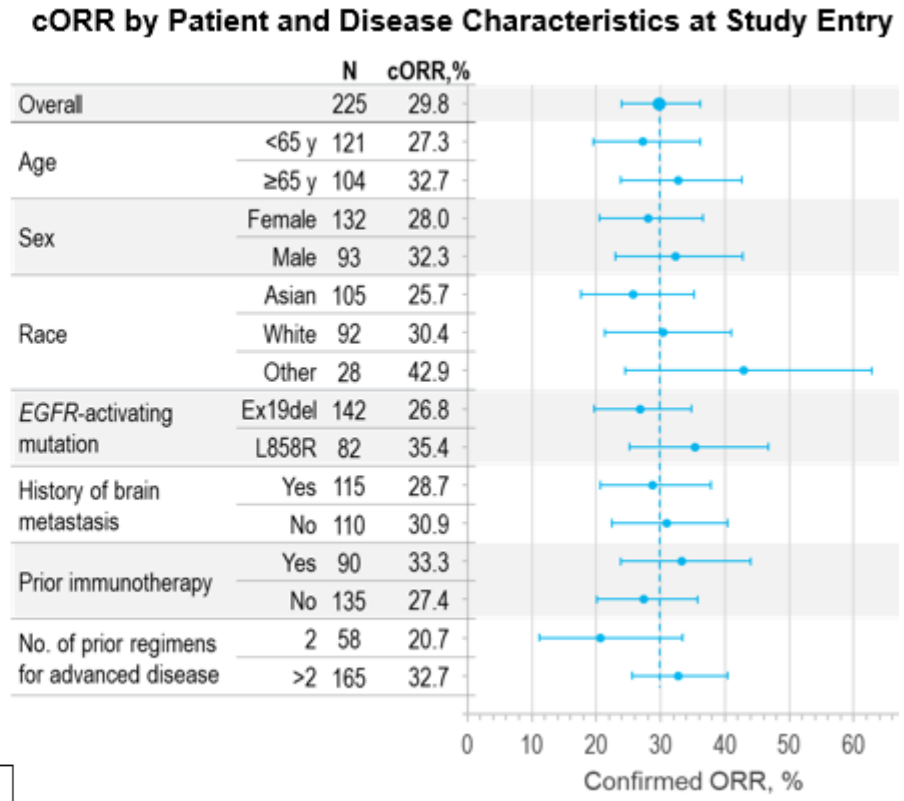
Yu WCLC 2023

Phase 2- HERTHENA-Lung01

Confirmed responses and survival		Prior EGFR TKI (any) and PBC (N=225)	Subset with prior 3G EGFR TKI and PBC (n=209)
cORR (95% CI), %		**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)





-Efficacy was seen across clinical subgroups
-No association between tumor membrane HER3 expression and response to HER3- DXd

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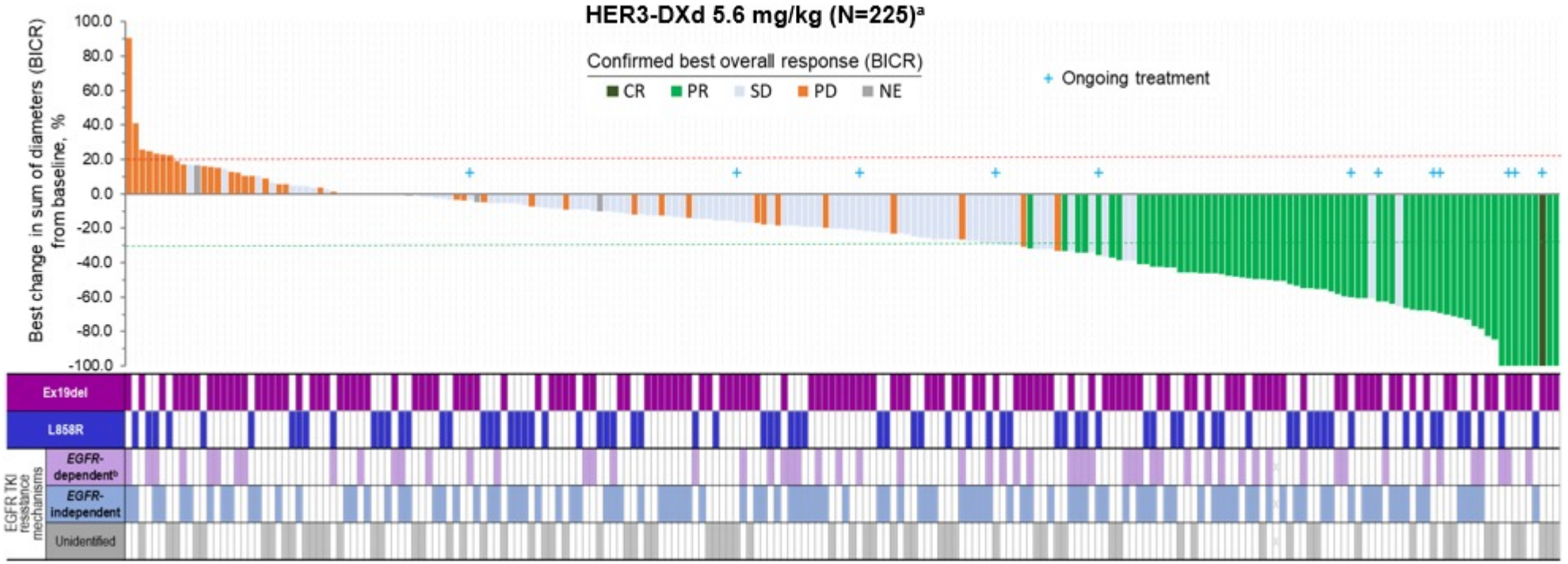
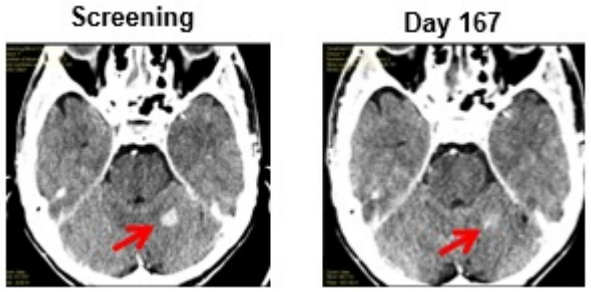
Phase 2- HERTHENA-Lung01





Intracranial response by CNS BICR per CNS RECIST	Pts with BrM at baseline and no prior RT (N=30)
Confirmed ORR (95% CI), %	33.3 (17.3-52.8)
CR, n (%)	9 (30.0)[b]
PR, n (%)	1 (3.3)
SD, n (%)[c]	13 (43.3)
PD, n (%)	4 (13.3)
DCR (95% CI), %	76.7 (57.7-90.1)
DOR, median (95% CI), mo	8.4 (5.8-9.2)

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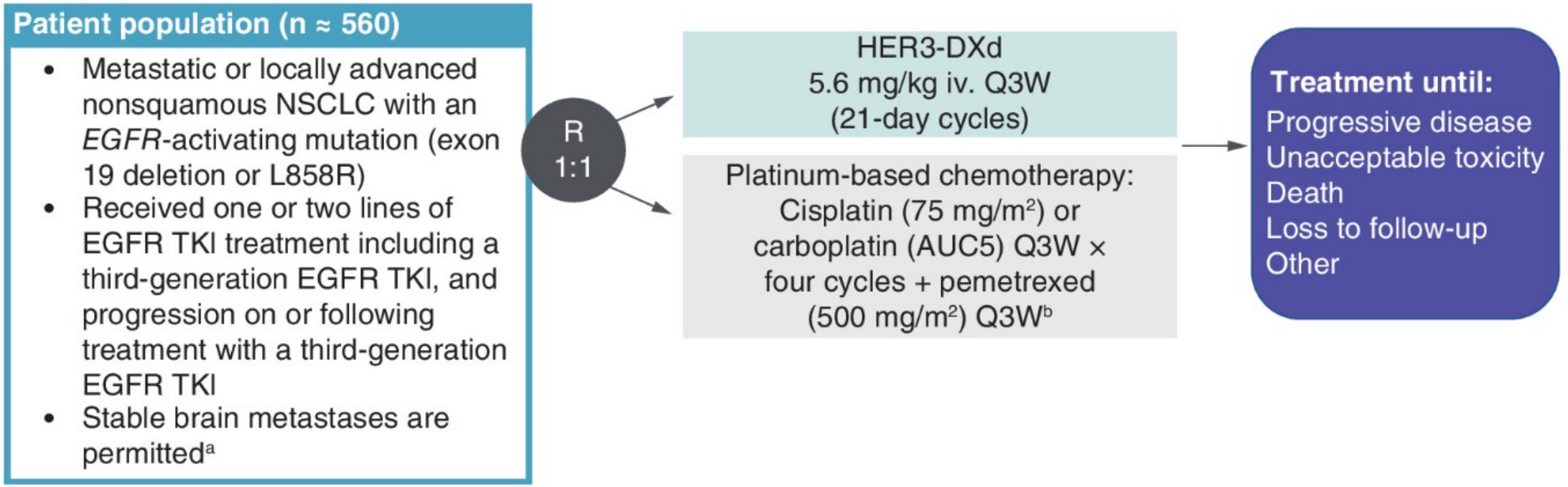
Phase 3- HERTHENA-Lung02

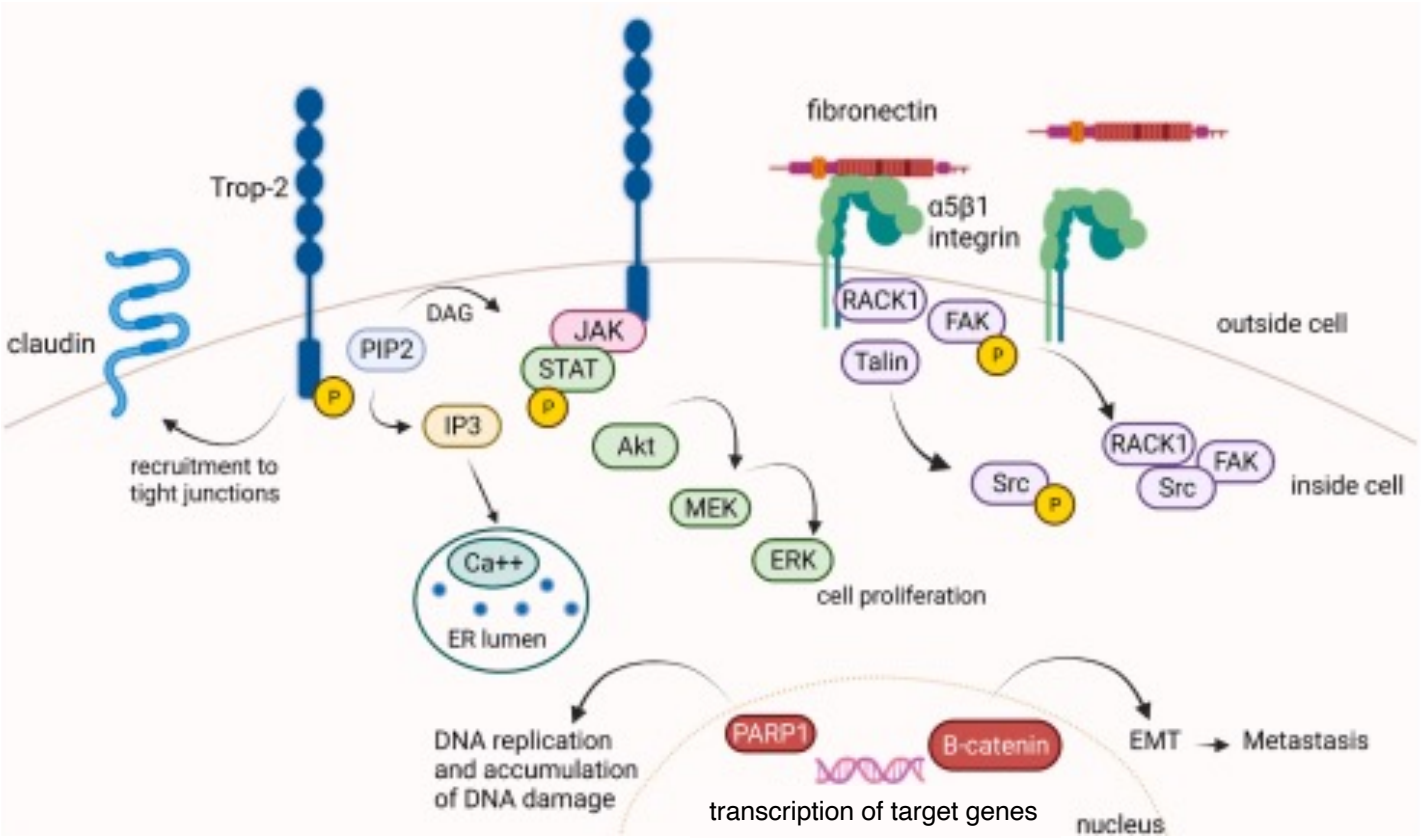


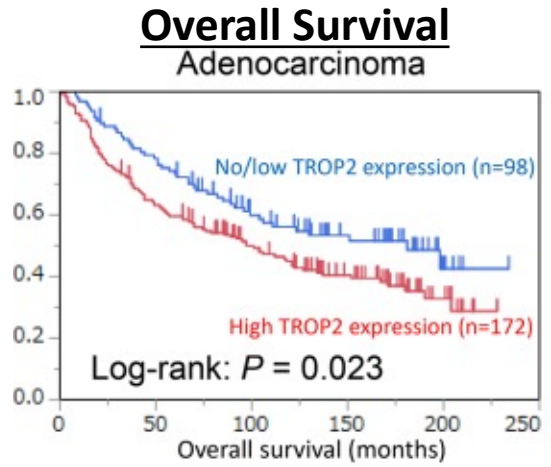
Primary endpoint: Progression-free survival by BICR
Secondary endpoints: Overall survival by inv, objective response rate, duration of response, clinical benefit rate, disease control rate, time to response, safety, biomarkers

Enrollment began August 2022, study is closed to enrollment
179 clinical sites from 21 countries globally

Mok Fut Med 2023

TROP2 as a therapeutic target





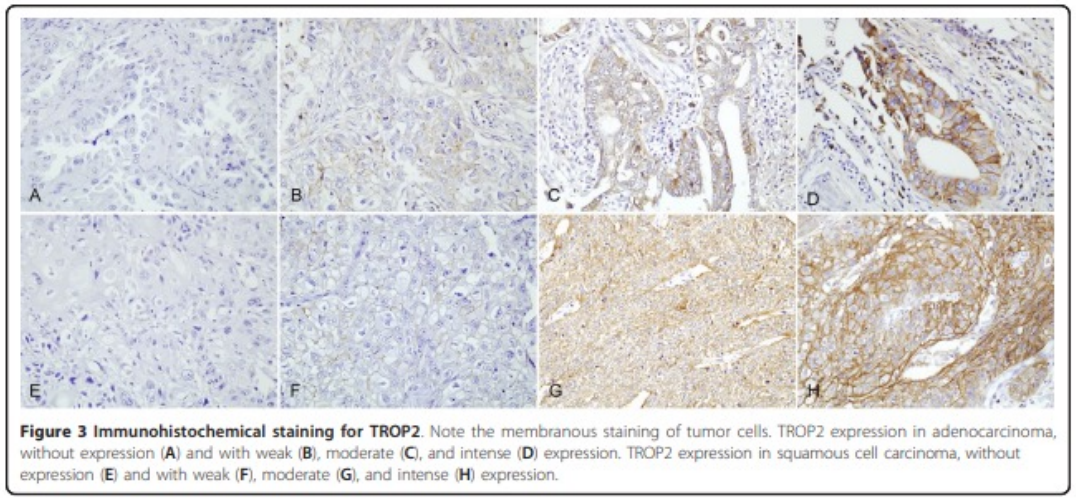


Figure 3 Immunohistochemical staining for TROP2. Note the membranous staining of tumor cells. TROP2 expression in adenocarcinoma, without expression (**A**) and with weak (**B**), moderate (**C**), and intense (**D**) expression. TROP2 expression in squamous cell carcinoma, without expression (**E**) and with weak (**F**), moderate (**G**), and intense (**H**) expression.

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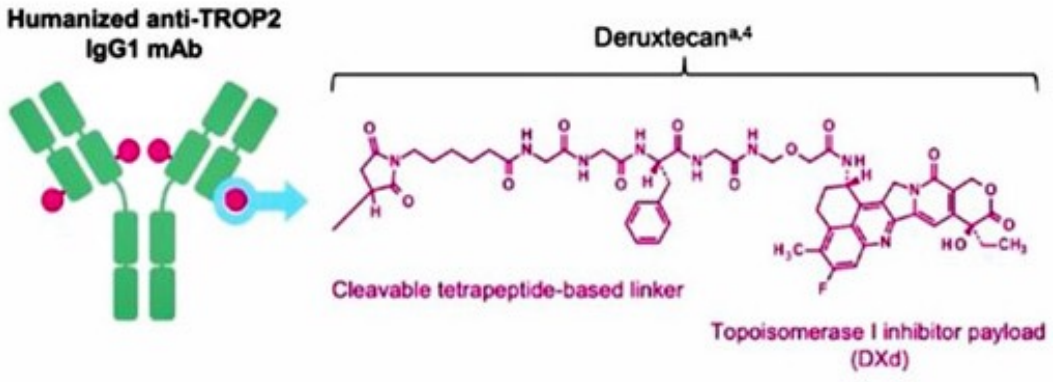
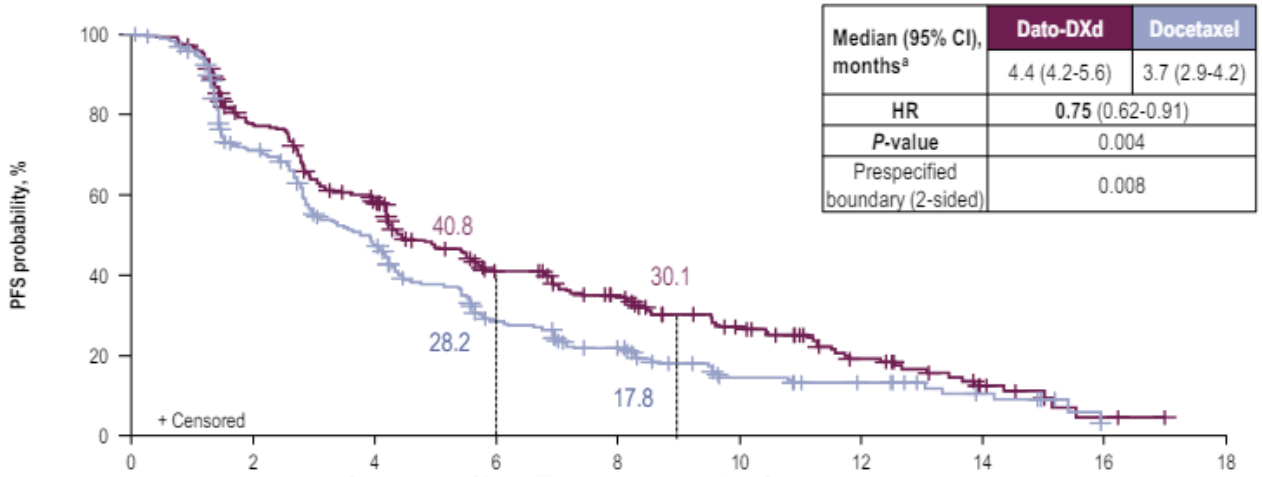
Parisi C Trtmt Rev 2023
Pak W J Surg Onc 2012
Inamura Oncotarget 2017

Datopotamab deruxtecan

Datopotamab Deruxtecan





Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations[a]
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

Dato-DXd
6 mg/kg Q3W
(N=299)

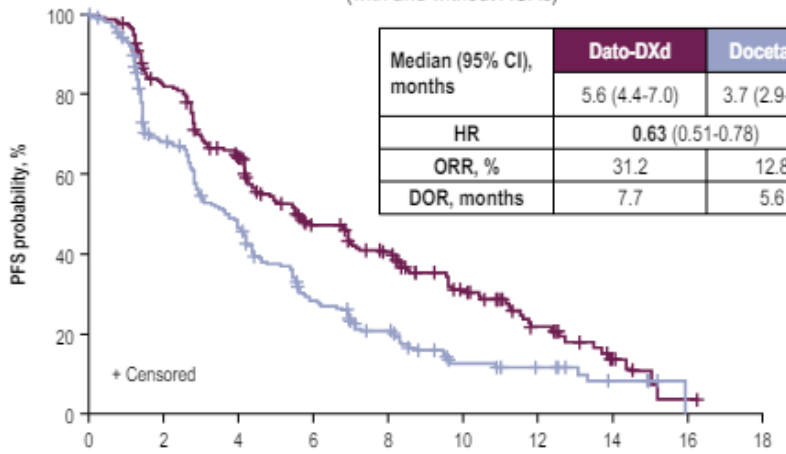
Docetaxel
75 mg/m² Q3W
(N=305)

Dual Primary Endpoints
- PFS by BICR
- OS

Secondary Endpoints
- ORR by BICR
- DOR by BICR
- Safety

	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

Non-squamous
(with and without AGAs)



Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

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Lisberg ESMO 2023

Phase 2- TROPION-Lung05

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

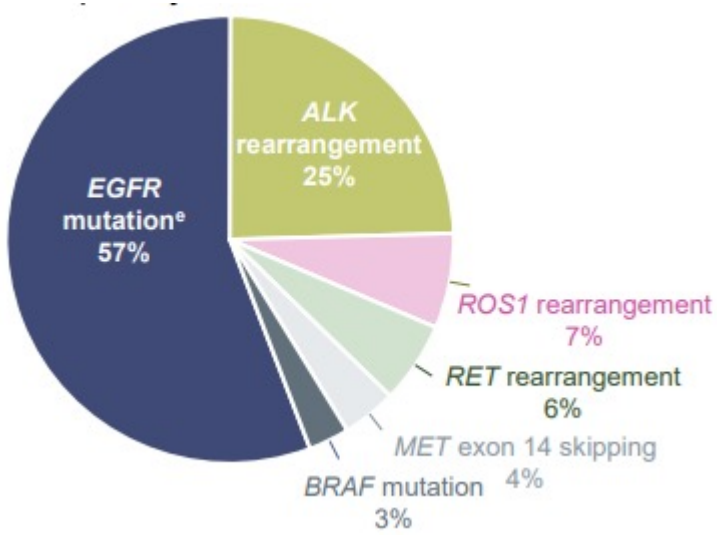
Treatment

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



Demographic characteristics	Dato-DXd (N=137)
Median age (range), years	60 (29-79)
Female, n (%)	83 (61)
Histology, n (%)	
Adenocarcinoma	130 (95)
History of brain metastasis, n (%)[a]	70 (51)
Median prior lines of therapy for adv/met disease	3
Prior lines of therapy, n (%)	137 (100)
≥3 prior lines of therapy for adv/met disease	98 (72)
Prior platinum chemotherapy	137 (100)
Prior anti–PD-1/anti–PD-L1 immunotherapy	49 (36)
≥2 prior lines of targeted therapies for indicated genomic alteration	82 (60)

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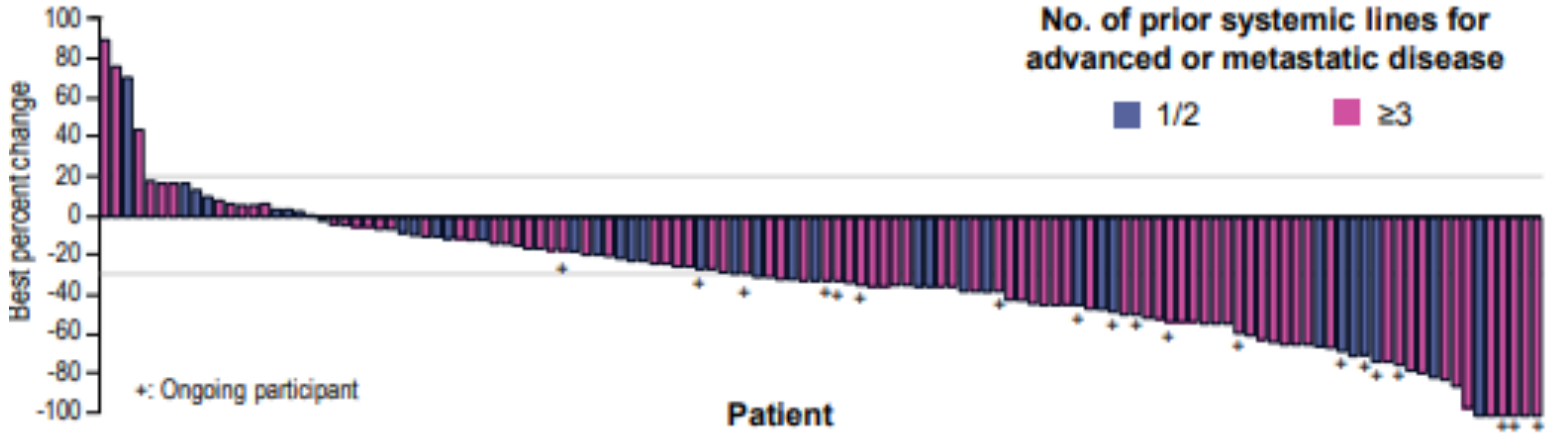
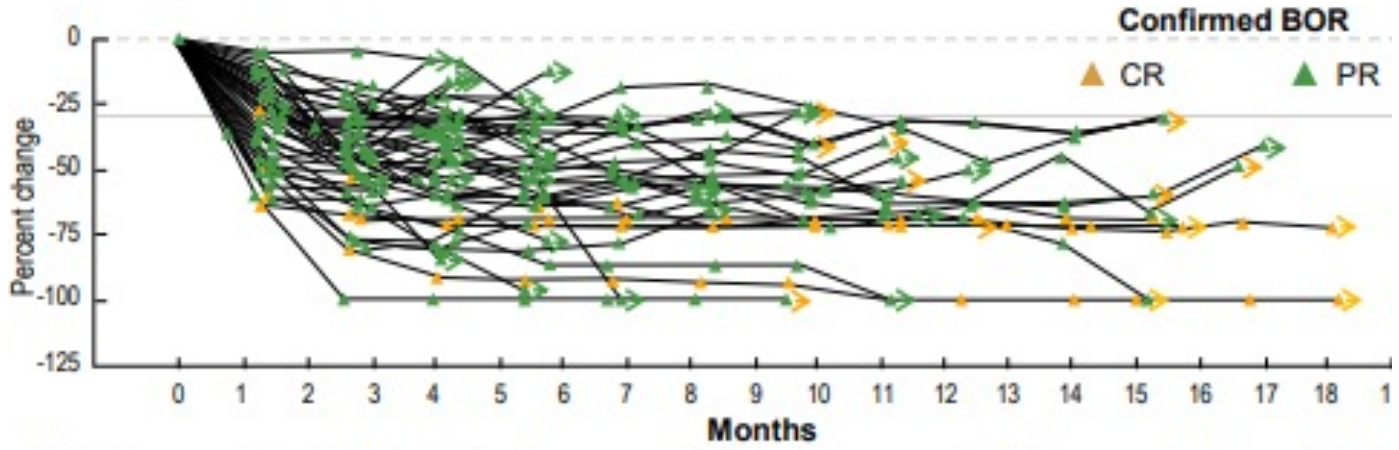
Phase 2- TROPION-Lung05

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)

<u>EGFR subset</u>: sensitizing EGFR mutation, previous treatment with osimertinib, ORR was 49.1%





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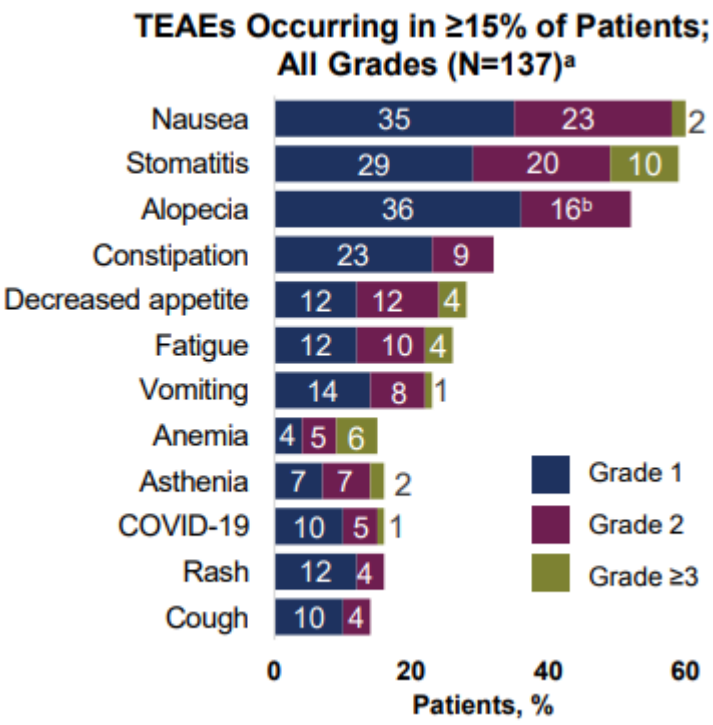
ADC Toxicity

Dato-DXd



- 137 (100%) had TEAEs (grade ≥3, 47%)
  - 129 (94%) had treatment-related TEAEs (grade ≥3, 29%)
- 30 (22%), 13 (10%), 2 (2%) had TEAEs associated with dose reduction, discontinuation, death

AESI Incidence by Grade[d]

n (%)	Total	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis	90 (66)	45 (33)	30 (22)	15 (11)
Ocular surface toxicity[e]	36 (26)	26 (19)	7 (5)	3 (2)[f]
IRR	22 (16)	15 (11)	7 (5)	0
Adjudicated drug-related ILD	5 (4)	1 (1)	3 (2)	1 (1)[g]

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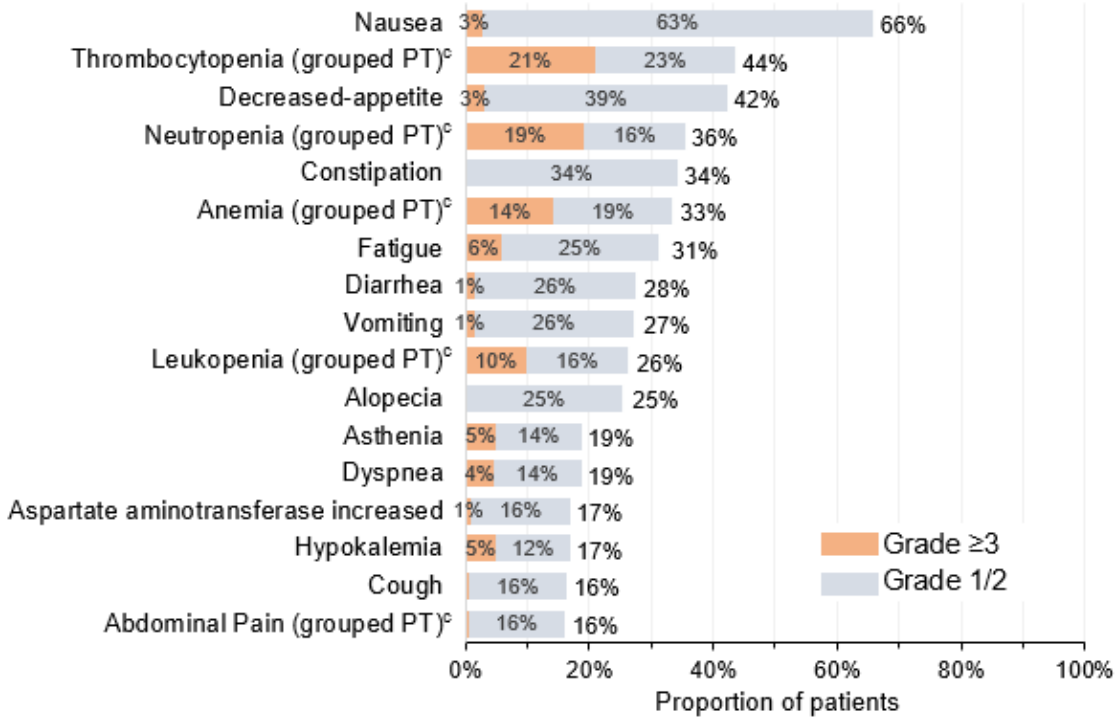
Paz Ares ESMO 2023
Yu WCLC 2023

HER3-DXd



Safety summary	HER3-DXd 5.6 mg/kg
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation[a]	16 (7.1)
Associated with treatment dose reduction	48 (21.3)
Associated with treatment dose interruption	91 (40.4)
Treatment-related TEAE, n (%)	215 (95.6)
Grade ≥3	102 (45.3)
Adjudicated interstitial lung disease, n (%) [All were adjudicated as treatment-related]	12 (5.3)
Grade 1/2	9 (4.0)
Grade 3/4	2 (0.9)/0
Grade 5	1 (0.4)

Summary

- Antibody drug conjugates are being assessed in all lines of therapy, in particular after progression on 1L treatment
- HER3 is expressed widely in EGFR+ NSCLC, has poor prognostic significance and is associated with acquired resistance to EGFR TKIs
- HER3-DXd is active in patients with EGFR+ NSCLC after EGFR TKI and chemotherapy and is effective across all mechanisms of resistance
- TROP2 is expressed in NSCLC, and Dato-DXd is an active ADC targeted TROP2
- Dato-DXd is active in adenocarcinoma after progression on initial therapy and appears to be especially active in EGFR+ NSCLC

Agenda

Module 1: Contemporary Care for Patients with Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) with an EGFR Mutation — Dr Langer

Module 2: Evolving First-Line Treatment for Metastatic NSCLC with an EGFR Mutation — Dr Goldman

Module 3: Biological Rationale for and Emerging Role of Antibody-Drug Conjugates in the Management of NSCLC with an EGFR Mutation — Dr Yu

Module 4: Other Emerging Strategies for Relapsed Metastatic NSCLC with an EGFR Mutation — Dr Sabari

Module 5: Current and Future Management of NSCLC with an EGFR Exon 20 Insertion Mutation — Dr Piotrowska

Module 6: Management of Toxicities Associated with Available and Emerging Therapies for NSCLC with an EGFR Mutation — Dr Neal

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Comments

Repeat genetic testing after disease progression on osimertinib; treatment options for osimertinib-resistant NSCLC

Dr John V Heymach
(Houston, Texas)

Dr Roy S Herbst
(New Haven, Connecticut)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

For a patient who receives first-line osimertinib/chemotherapy and experiences disease progression after 3 years, what second-line therapy do you typically consider?

Will you rechallenge with platinum/pemetrexed?

Do you think your approach will change if/when patritumab deruxtecan is approved?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Given they both rely on a deruxtecan payload, do you have any concerns about potentially utilizing datopotamab deruxtecan for a patient with NSCLC with an EGFR mutation who has previously received patritumab deruxtecan?

Emerging Strategies for Relapsed Metastatic EGFRm NSCLC

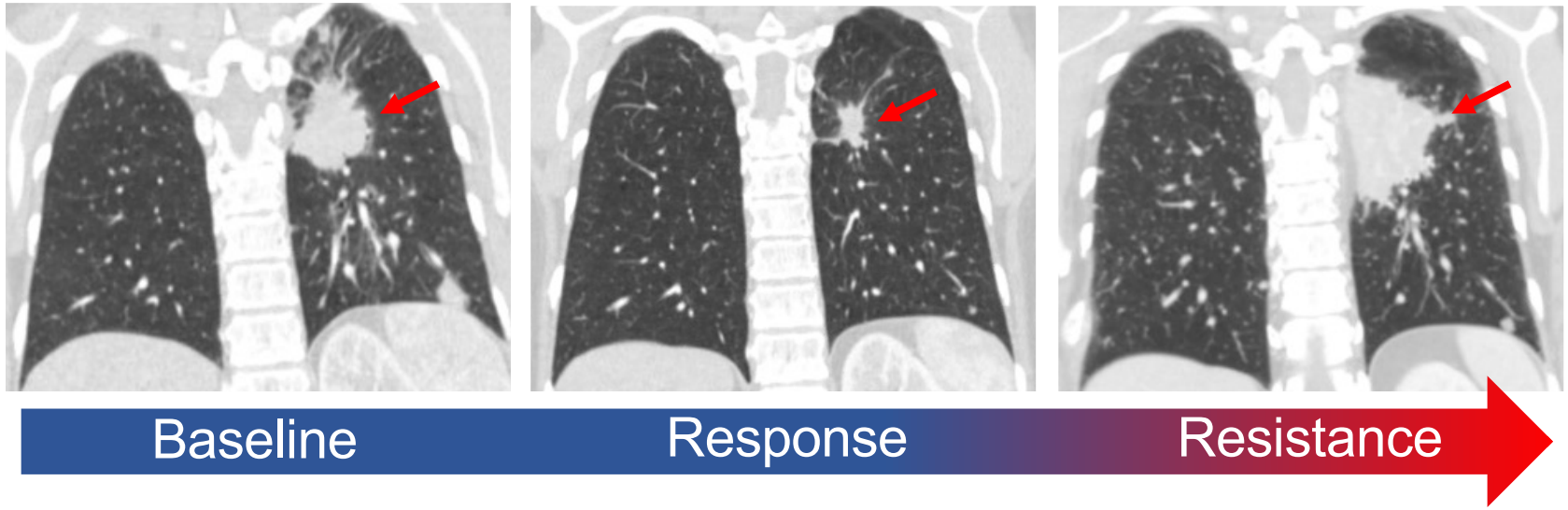
Joshua Sabari, MD
Assistant Professor of Medicine
NYU Langone Health
Perlmutter Cancer Center

Outline

- Biology of acquired resistance
- On-target vs Off-target mechanism of resistance
- MARIPOSA-2: Amivantamab + Chemotherapy 2L
- Role for Immunotherapy in EGFR mutant NSCLC

Acquired Resistance

EGFR mutant NSCLC



Acquired Resistance

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
EGFR exon 19 deletion (L747_A750>P)	Gefitinib Osimertinib Erlotinib

OTHER SHORT VARIANTS AND SELECT REARRANGEMENTS AND COPY NUMBER ALTERATIONS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product.
See *professional services* section for information on the alterations listed in this section as well as any additional detected copy number alterations, gene rearrangements, or biomarkers.

OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

CHEK2 E308fs*12 #
CTNNB1 S33F
EGFR C797S

Acquired Resistance

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
EGFR exon 19 deletion (L747_A750>P)	Gefitinib Osimertinib Erlotinib

OTHER SHORT VARIANTS AND SELECT REARRANGEMENTS AND COPY NUMBER ALTERATIONS IDENTIFIED

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OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

CHEK2 E308fs*12 #
CTNNB1 S33F
EGFR C797S

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
EGFR L858R	Afatinib Gefitinib Osimertinib Erlotinib Dacomitinib

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported. See Appendix: About FoundationOne CDx for details. This report, or some of the results within, is qualified due to sample insufficiency or sample quality. Please contact FMI Client Services for more information and, if within 30 days of the report date, to discuss potential options for retesting the patient at no charge.

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status Cannot Be Determined α §
Tumor Mutational Burden Cannot Be Determined §
FANCC splice site 166-2A>G
MET amplification §
NFKBIA amplification §
NKX2-1 amplification §

POTENTIAL RESISTANCE

Individual patient response to listed therapies may vary based on genomic profile and other factors. See *professional services* section for additional information including alteration association with potential resistance.

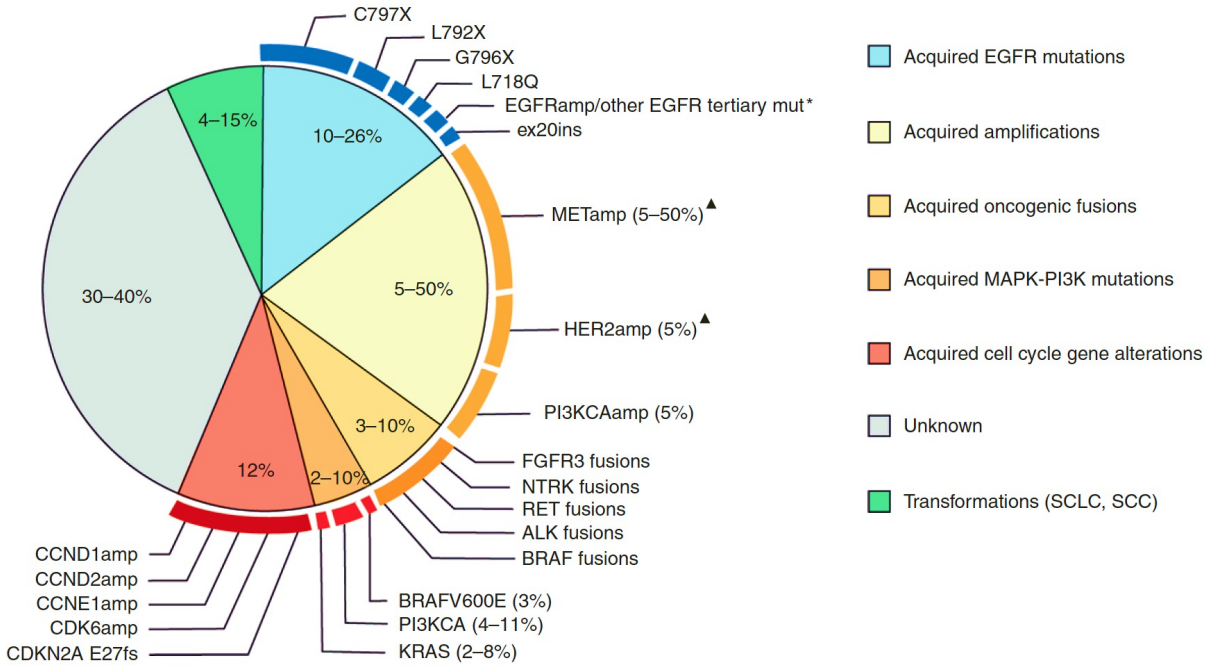
α Microsatellite status was reported as Cannot Be Determined as the MSI score could not be determined as QC requirements were not met. Patients with this result should consider re-testing with FoundationOne CDx or an orthogonal (alternative) method, if clinically appropriate.

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

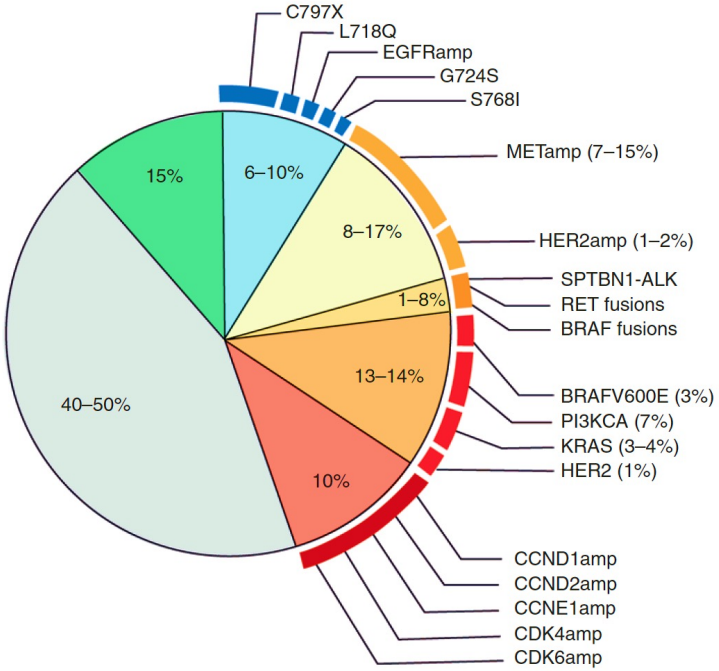
Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Resistance Mechanisms to EGFR TKI

Resistance mechanisms to second-line osimertinib



Resistance mechanisms to first-line osimertinib

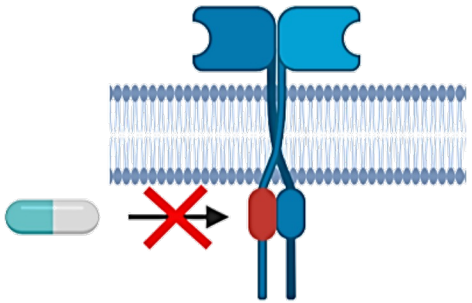


- ***EGFR* T790M is** the predominant mechanism with 1st and 2nd generation TKIs
- Acquired *EGFR* or *HER2* mutations, and *EGFR, HER2*, or *MET* amplification are common with first-line osimertinib
  - ✓ Other mechanisms include acquired cell cycle gene alterations, MAPK-PIK3CA alterations (*BRAF V600E, KRAS*), and acquired oncogenic fusions (*ALK, RET*)

Westover D, et al. *Ann Oncol*. 2018;29(Supp 1):i10–i19; Leonetti A, et al. *Br J Cancer*. 2019;121:725–737.

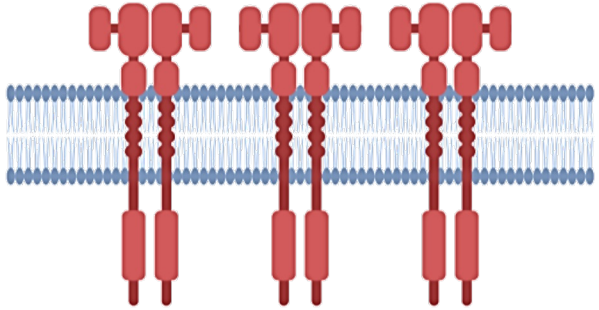
Mechanisms of Resistance to TKI

Mutations in the Drug Target



Impact drug binding

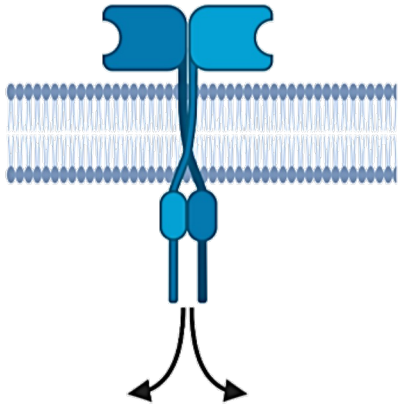
Bypass Signaling

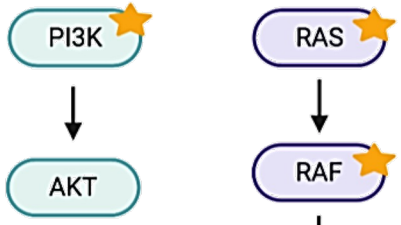


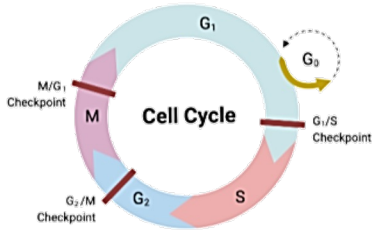
Oncogene Amplification

Oncogene Rearrangement

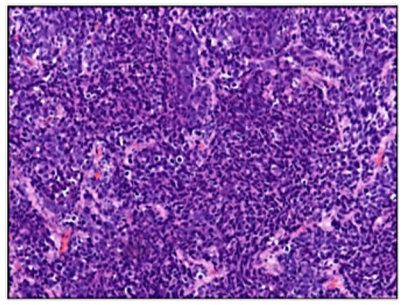
Mutations in Downstream Effectors







State Transformation



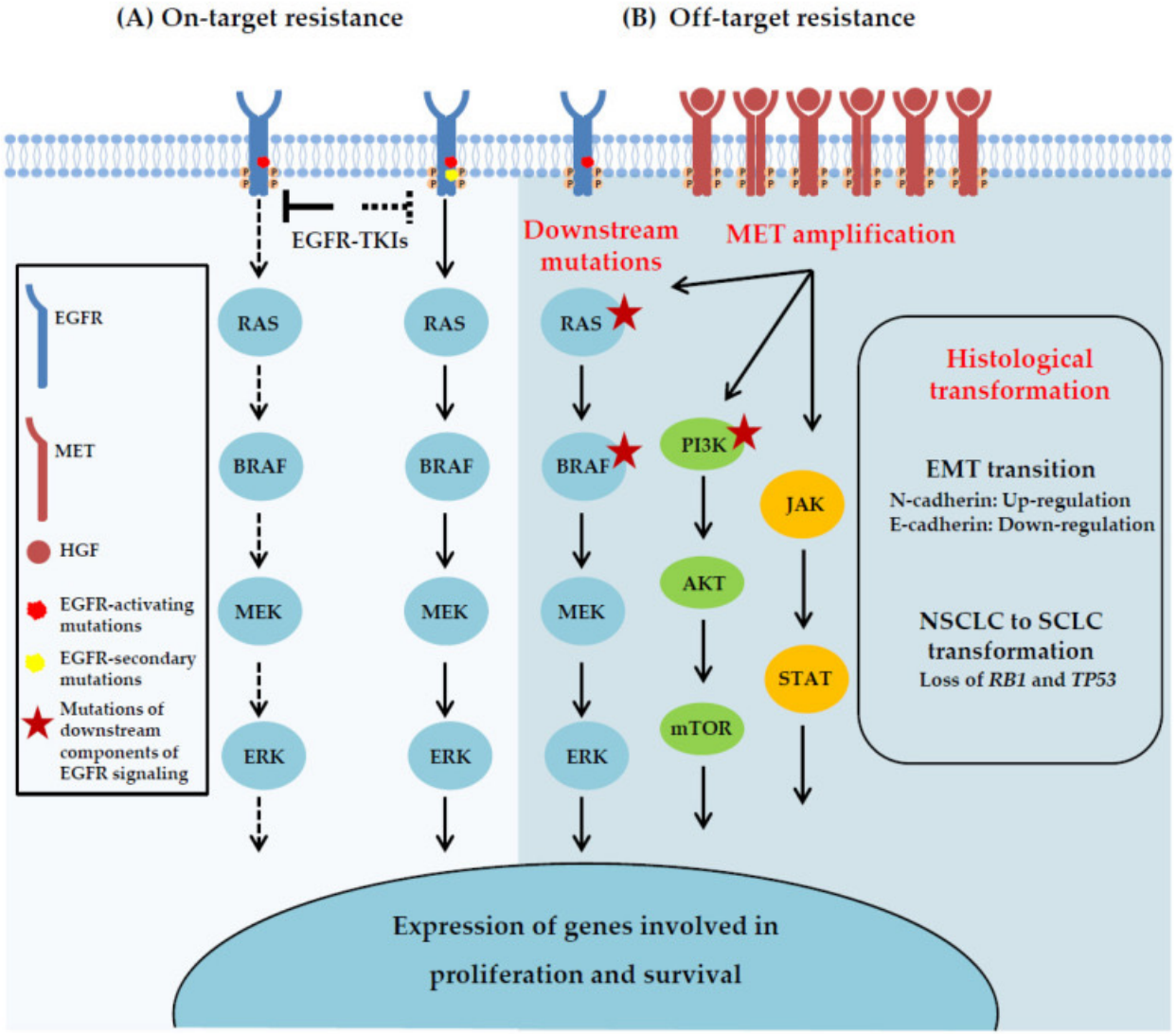
Small cell lung cancer
Squamous cell lung cancer

Overcoming Resistance – Combination Strategies

- Selective (On-target resistance)
  - EGFR T790M, C797S, G724S
    - Acquired vs de novo
  - 3rd and 4th generation EGFR TKI

- Non-selective (Off-target resistance)
  - MET / BRAF / RET / ALK / HER2 / PI3K
  - EMT State transformation

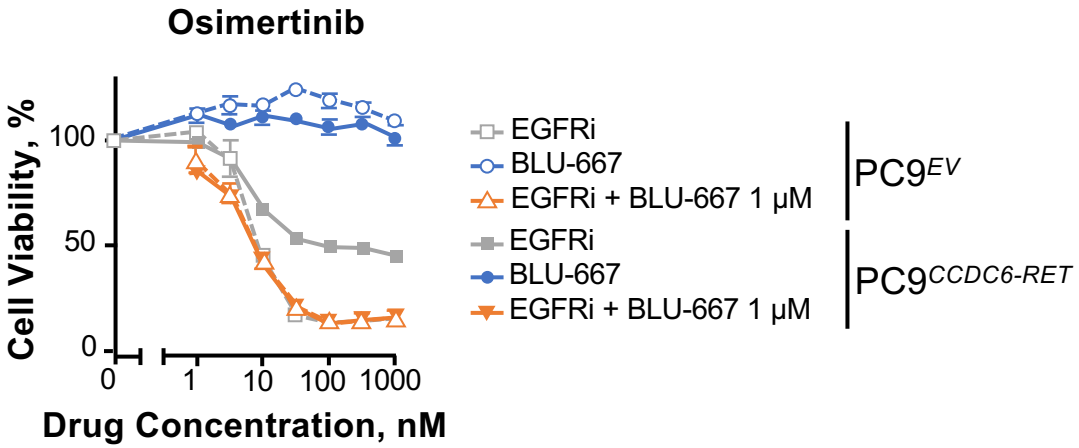
  - **Novel MOA**
    - Bispecifics
    - T-cell engagers
    - Antibody drug conjugates
    - Conventional chemotherapy combinations

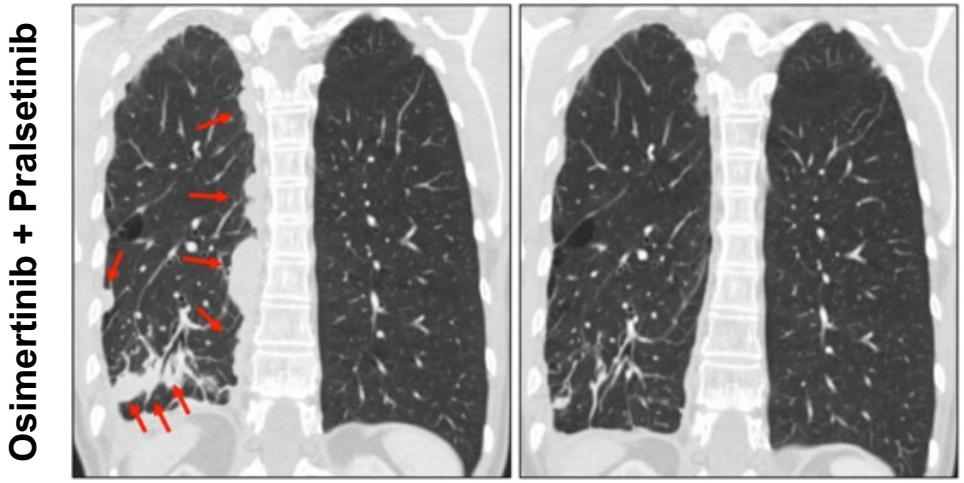


Houssein C. et al Cancer 2023

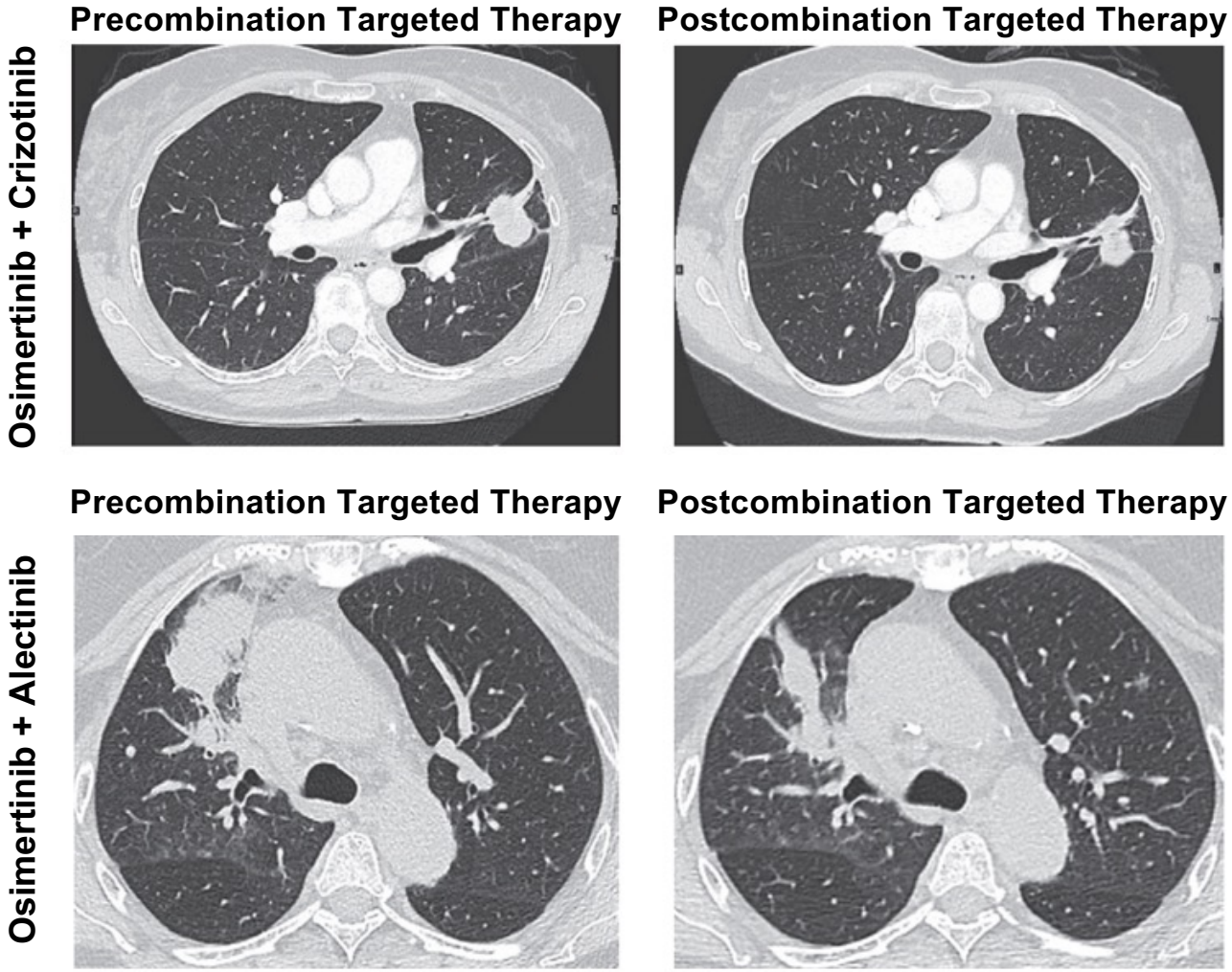
Targeting Acquired *RET*, *ALK*, and Other Fusions

Acquired *RET* Fusions





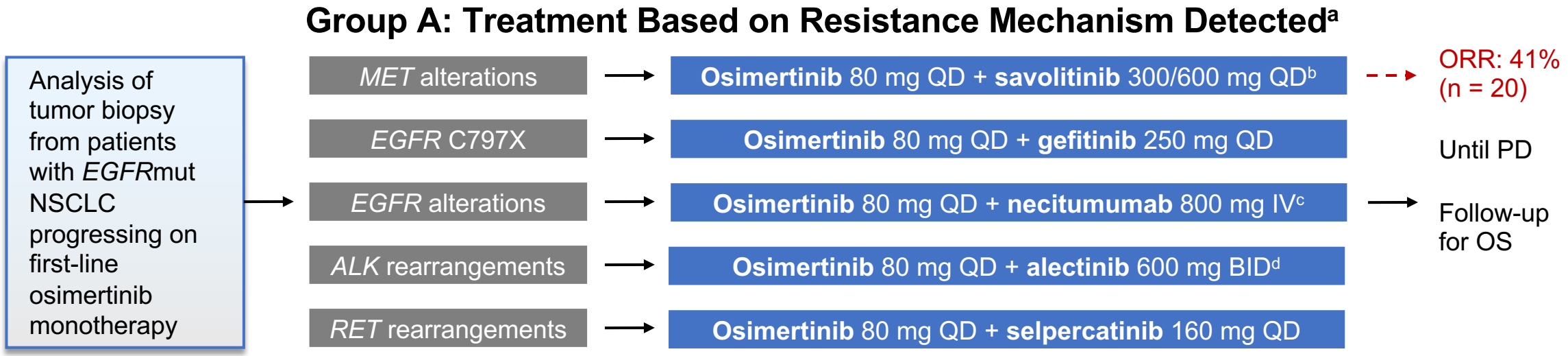
Acquired *ALK* Fusions



1. Piotrowska Z et al. *Cancer Discov*. 2018;8:1529-1539. 2. Offin M et al. *JCO Precis Oncol*. 2018;2:PO.18.00126.

ORCHARD: Biomarker-Directed Study in Advanced *EGFR*mut NSCLC Progressing on 1L Osimertinib

- Open-label, multicenter, multidrug, biomarker-directed phase 2 platform trial



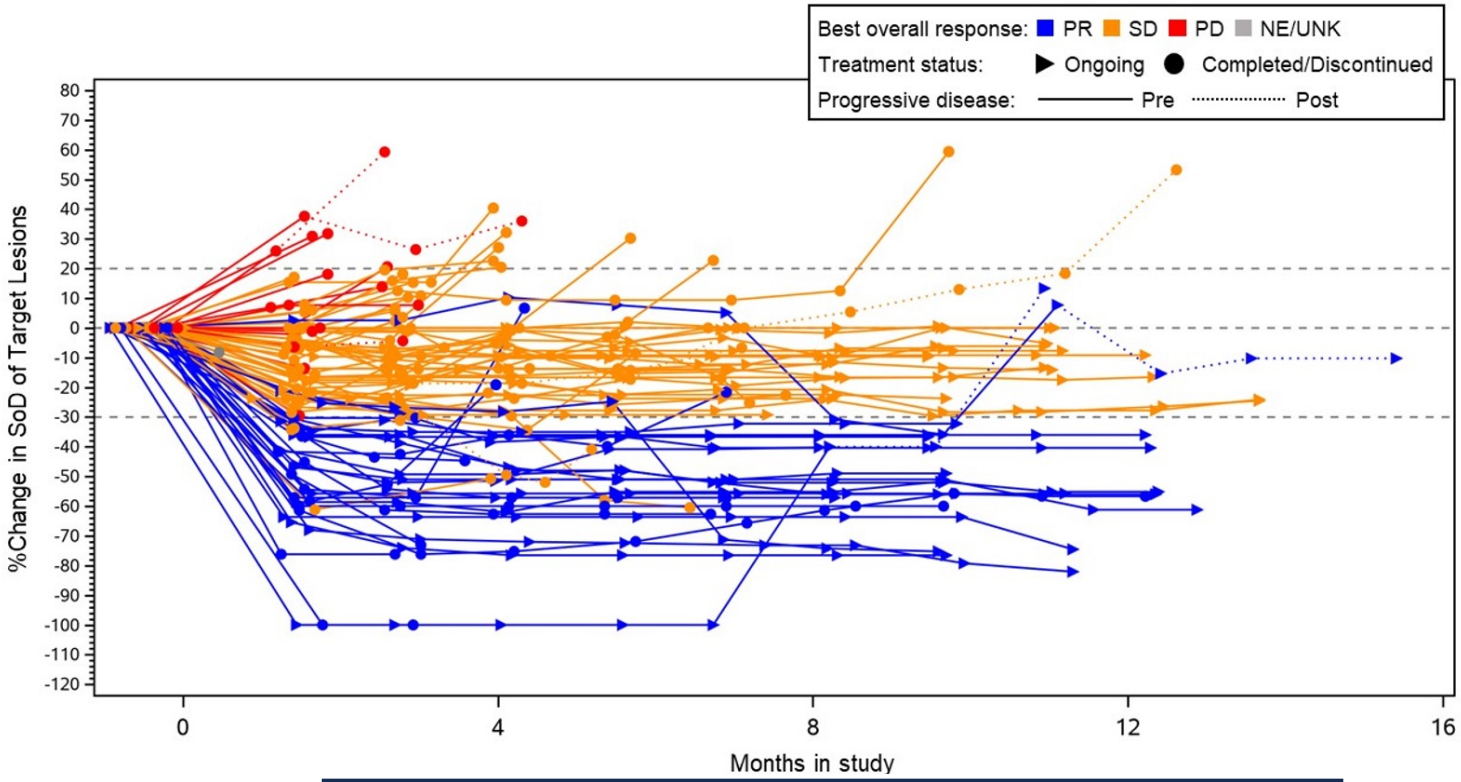
- **Group B**: Nonmatched arm for patients without a detectable resistance mechanism will sequentially be assigned to durvalumab + chemotherapy > osimertinib + necitumumab > others
- **Group C**: Observational arm for patients whose optimal treatment falls outside of group A or B (eg, transformation to SCLC)
- Patients with failed baseline NGS results go directly to follow-up

[a] Future arms may be added. [b] Savolitinib dose 300 mg QD for all new patients. [c] Day 1 and 8 of 3 week cycle. [d] 300 mg BID in Japan.

1. Cho BC et al. *J Thorac Oncol*. 2021;16:S598. 2. Yu H et al. *Clin Lung Cancer*. 2021;22:601. 3. Yu H et al. ESMO 2021. Abstract 1239P.

CHRYSALIS-2: 2L Amivantamab + Lazertinib post progression on Osimertinib

	n=101
ORR	30% (95% CI, 21–40)
Median DOR	10.8 months (95% CI, 5.5–NE)
CBR[b]	69% (95% CI, 59–78)
Median PFS	5.7 months (95% CI, 4.0–8.2)
Median OS	Not estimable



ORR overall:	30%
ORR MET IHC+	61%
ORR MET IHC-	14%

Besse B et al. CHRYSALIS-2 ASCO 2023 Abstract 9013

Phase III MARIPOSA-2: Study Design

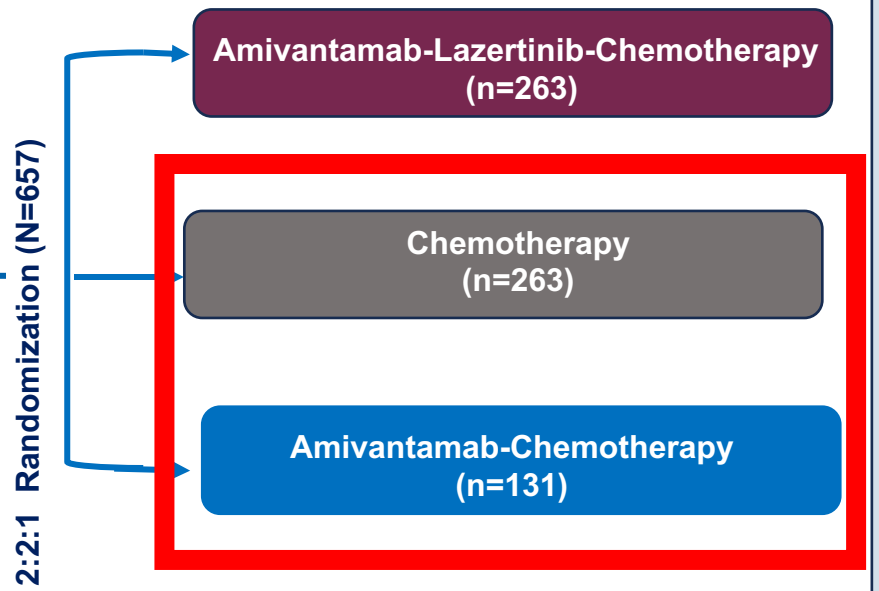
Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Documented EGFR Ex19del or L858R
- Progressed on or after osimertinib monotherapy, as most recent line of therapy
- ECOG PS 0 or 1
- Stable brain metastases were allowed:
  - Radiation or definitive therapy was not required (untreated)

Stratification Factors

- Osimertinib line of therapy (first vs second)
- Asian race (yes or no)
- History of brain metastases (yes or no)

Serial Brain MRIs Were Required for All Patients[a]



Dosing (in 21–Day Cycles)
Amivantamab: 1400 mg (1750 mg if ≥80 kg) x first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) Q3W starting at Cycle 3 (Week 7)
Lazertinib: 240 mg QD starting after completion of carboplatin[b]
Chemotherapy Administered at the Beginning of Every Cycle
- **Carboplatin: AUC5 for the First 4 Cycles**
- **Pemetrexed: 500 mg/m^2 Until Disease Progression**

Dual Primary Endpoint of PFS[c] by BICR per RECIST v1.1

Amivantamab-Lazertinib-Chemotherapy vs Chemotherapy
Amivantamab-Chemotherapy vs Chemotherapy

Secondary Endpoints:

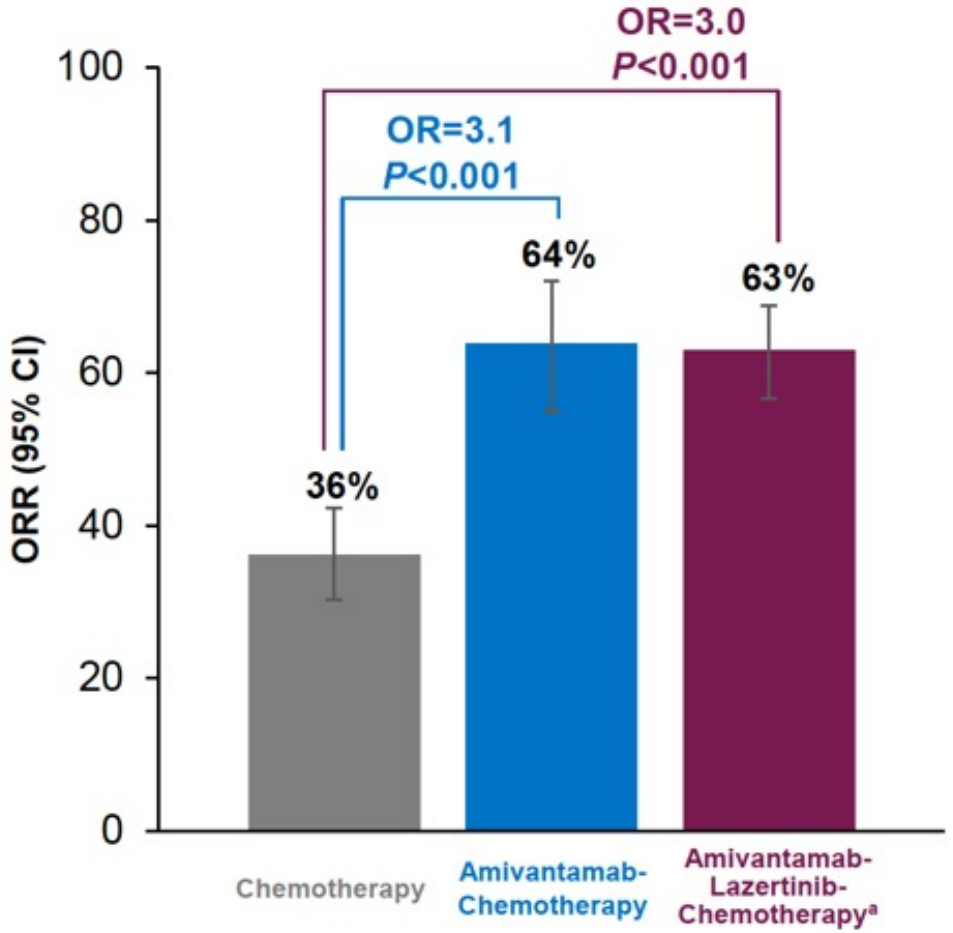
- Objective Response Rate (ORR)[c]
- Duration of Response (DoR)
- Overall Survival (OS)[c]
- Intracranial PFS
- Time to Subsequent Therapy[d]
- PFS After First Subsequent Therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

[a]Patients who could not have MRI were allowed to have CT scans.
[b]All patients randomized before November 7, 2022, initiated lazertinib on the first day of Cycle 1
[c]Key statistical assumptions: 600 patients with 350 events across all 3 arms would provide approximately 83% and 93% power for amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy, respectively, vs chemotherapy to detect a HR of 0.65 using a log-rank test, with an overall two-sided alpha of 0.05

NCT: 04988295

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

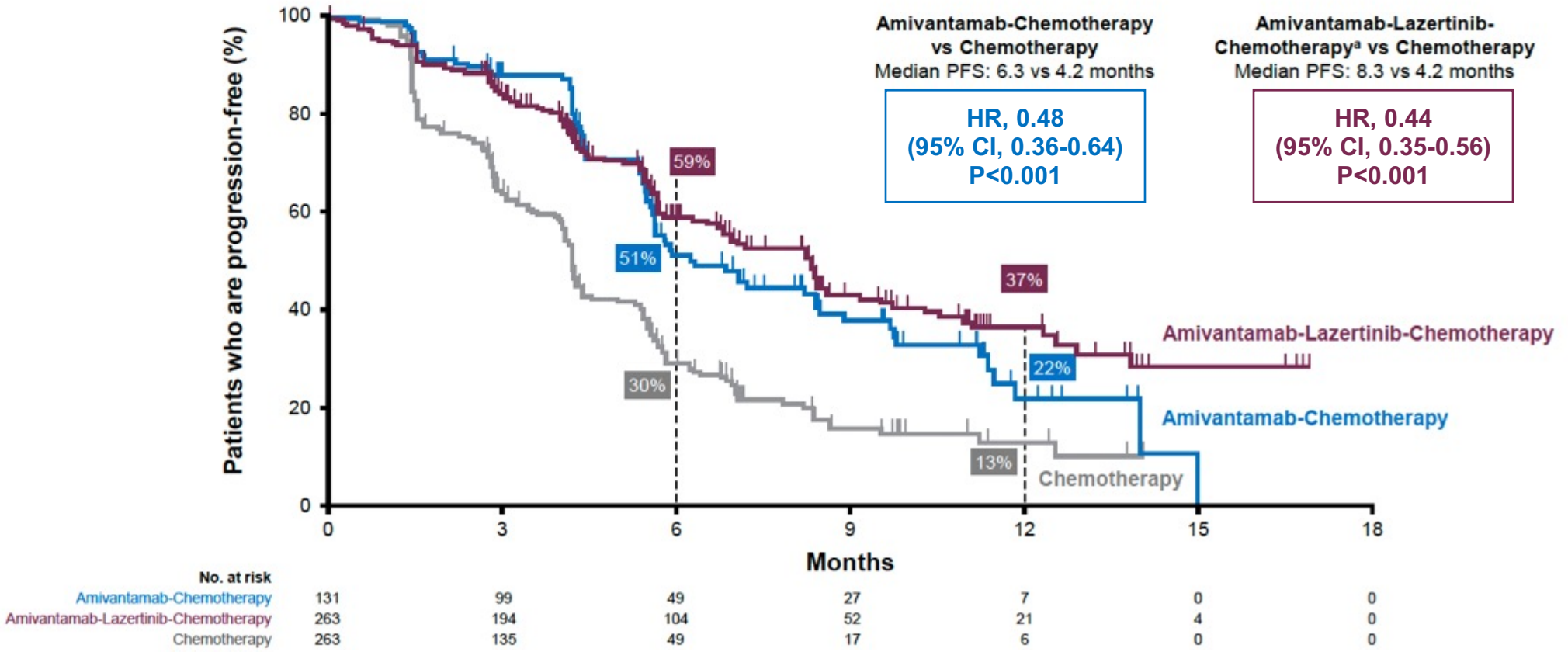
MARIPOSA-2: Objective Response Rate and Duration of Response by BICR



BICR-assessed Response, n (%)[b]	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Best Response			
CR	1 (0.4)	2 (2)	6 (2)
PR	93 (36)	81 (62)	157 (61)
SD	82 (32)	30 (23)	61 (24)
PD	52 (20)	10 (8)	14 (5)
NE/UNK	32 (12)	7 (5)	21 (8)
Median DoR[c]	5.6 mo (95% CI, 4.2–9.6)	6.9 mo (95% CI, 5.5–NE)	9.4 mo (95% CI, 6.9–NE)

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

MARIPOSA-2: Progression-Free Survival by BICR



[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received.
[b]Normal P-value: endpoint not part of hierarchal hypothesis testing.

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

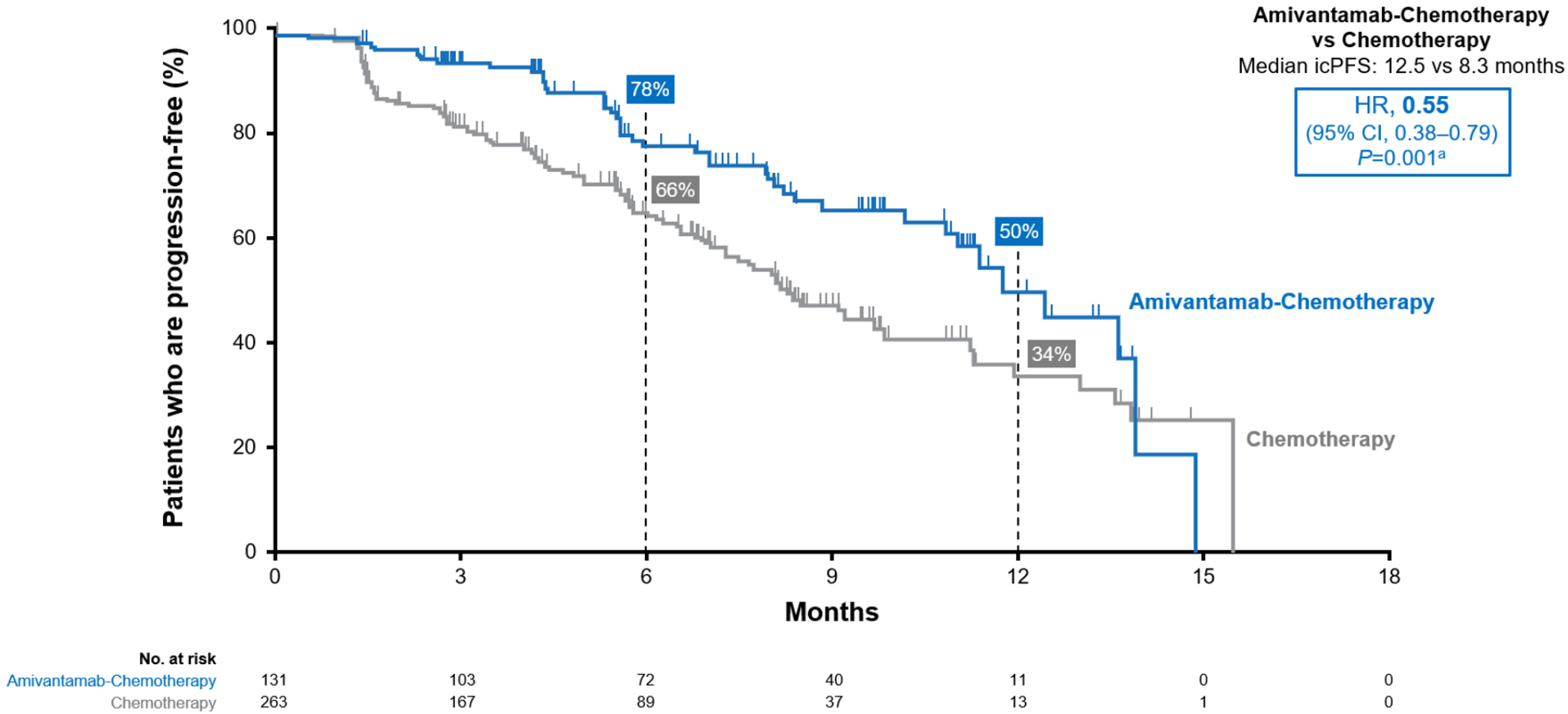
Consistent PFS Benefit by Investigator:
HR, 0.41 (8.2 vs 4.2 months; P<0.001[b])
HR, 0.38 (8.3 vs 4.2 months; P<0.001[b])

Median follow-up: 8.7 months..

Passaro A, et al. Presented at the European Society for Medical Oncology 2023 Meeting. 20-24 October 2023. Madrid, Spain. Abstract LBA15.

MARIPOSA-2: Intracranial PFS

Amivantamab + chemotherapy reduced the risk of intracranial progression or death by 45%

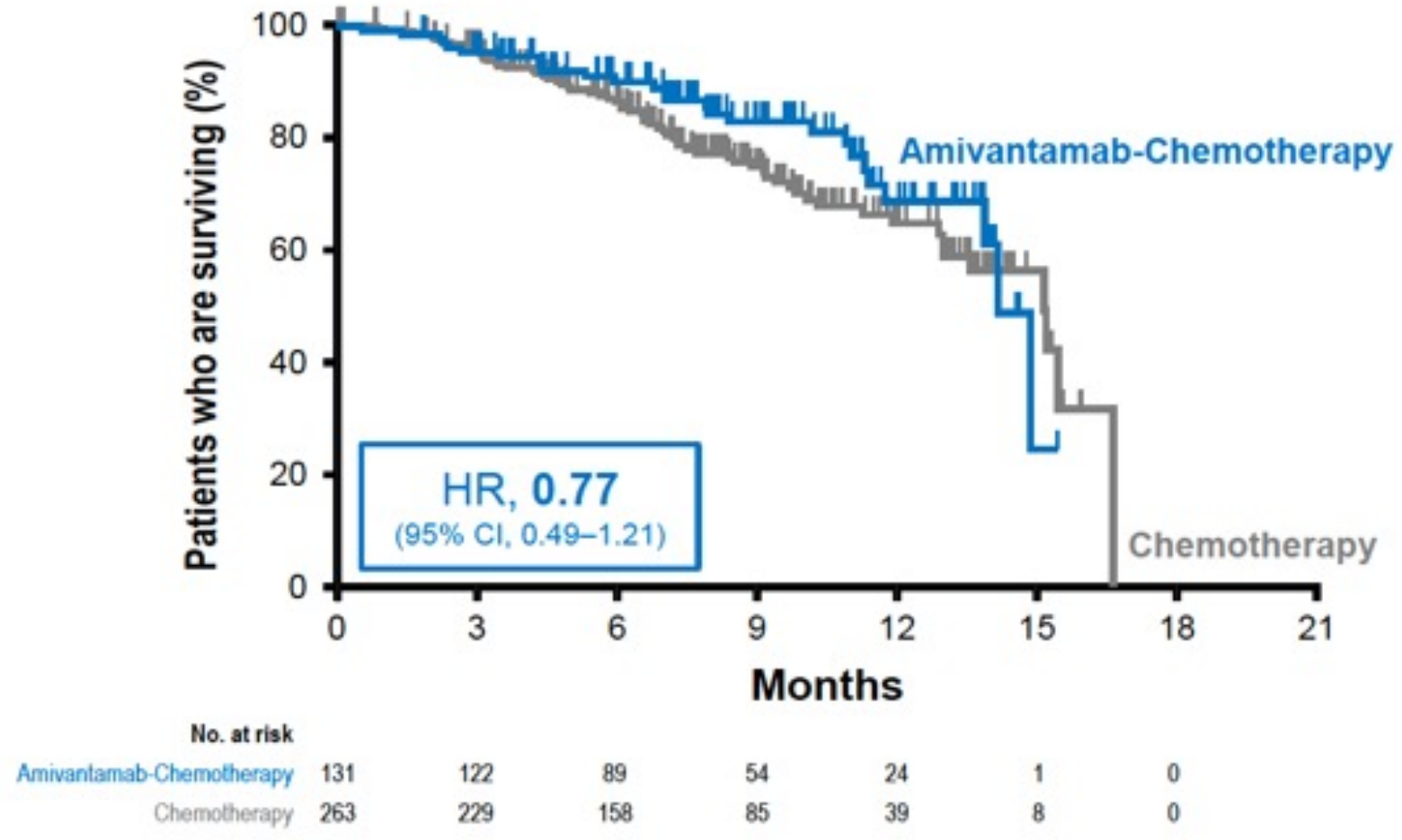


Median follow-up: 8.7 months.

Passaro A, et al. Presented at the European Society for Medical Oncology 2023 Meeting. 20-24 October 2023. Madrid, Spain. Abstract LBA15.

MARIPOSA-2: Overall Survival

At time of data cut off median follow up was 8.7 months; 40% maturity



Passaro A, et al. Presented at the European Society for Medical Oncology 2023 Meeting. 20-24 October 2023. Madrid, Spain. Abstract LBA15.

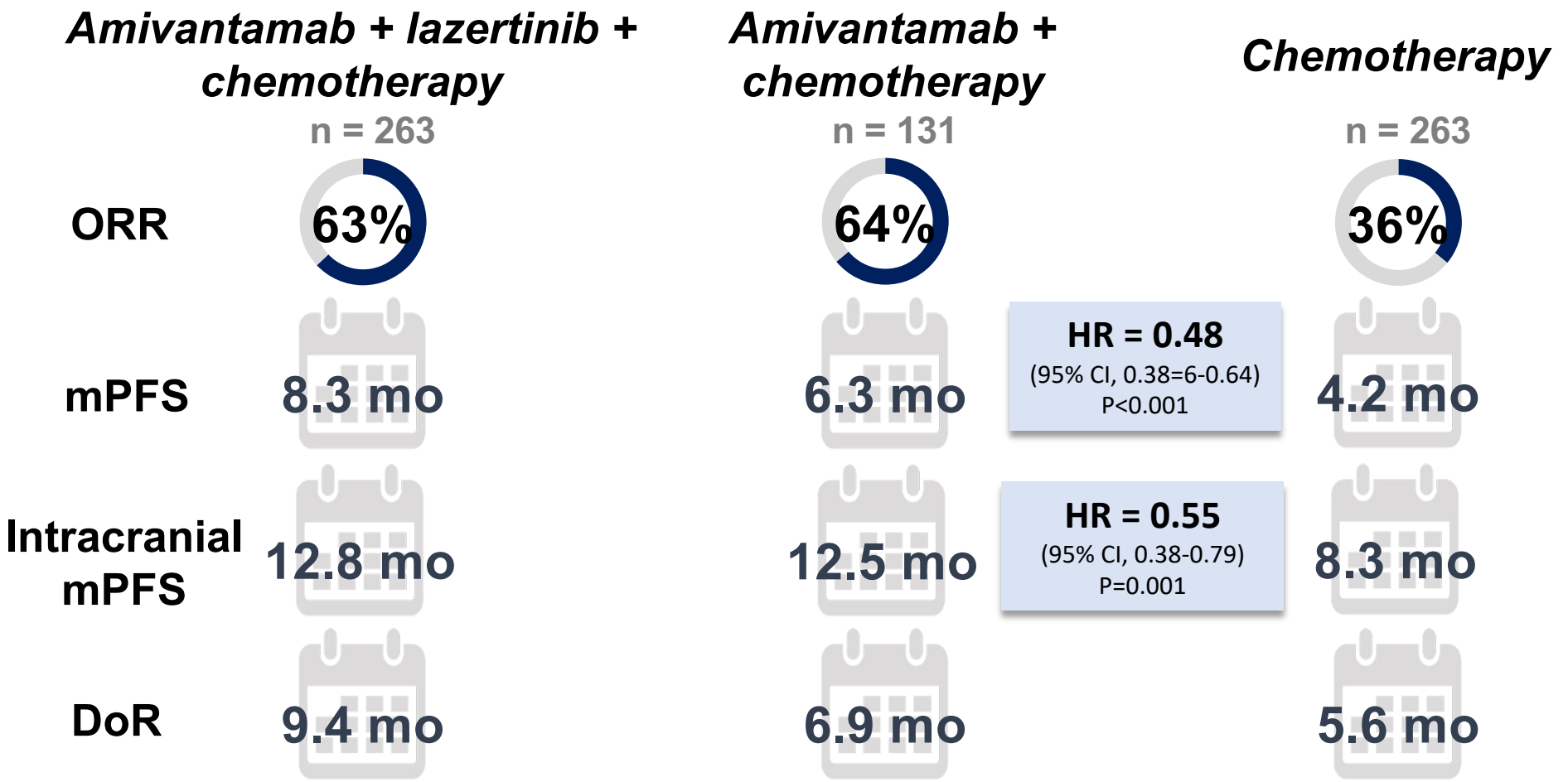
MARIPOSA-2: Summary of Adverse Events

	Amivantamab + Chemotherapy (n=130)	Chemotherapy (n=243)
Treatment duration, median (range)	6.3 months (0-14.7)	3.7 months (0-15.9)
No. of chemotherapy cycles, median (range)		
Carboplatin	4 (1-4)	4 (1-5)
Pemetrexed	9 (1-22)	6 (1-23)

TEAE, n (%)	Amivantamab + Chemotherapy (n=130)	Chemotherapy (n=243)
Any AEs	130 (100)	227 (93)
Grade ≥3 AEs	94 (72)	117 (48)
Serious AEs	42 (32)	49 (20)
AEs leading to death	3 (2)	3 (1)
Any AE leading to treatment:		
Interruption of any agent	84 (65)	81 (33)
Reductions of any agent	53 (41)	37 (15)
Discontinuations of any agent	24 (18)	9 (4)
Discontinuations of all agents due to AE	14 (11)	10 (4)

Passaro A, et al. Presented at the European Society for Medical Oncology 2023 Meeting. 20-24 October 2023. Madrid, Spain. Abstract LBA15.

MARIPOSA-2: Trial Summary



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

Utility of PD1/PD-L1 inhibitors in EGFRm NSCLC

- Phase III IMpower150: Carboplatin, Paclitaxel, Bevacizumab and Atezolizumab; Subset Analysis of EGFR/ALK mutated NSCLC

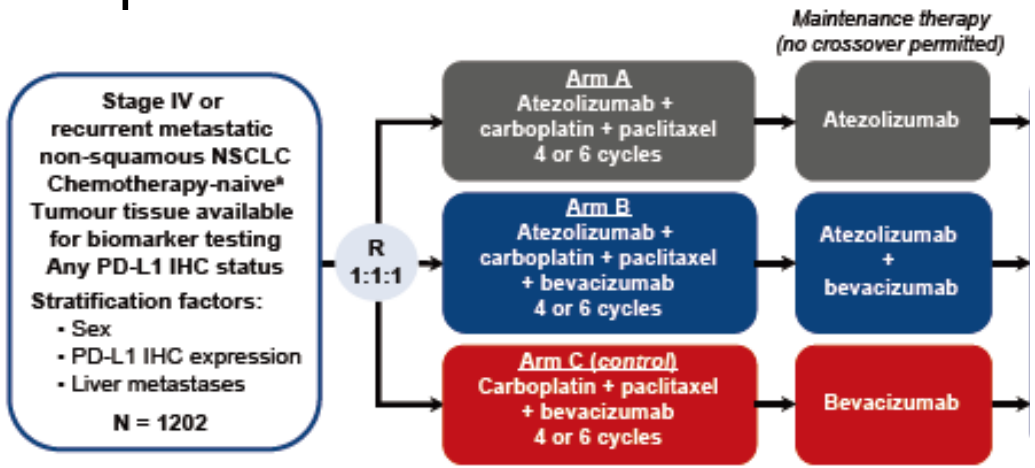
- Phase III ORIENT-31: Sintilimab plus chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer with disease progression after EGFR tyrosine-kinase inhibitor therapy

- Phase III CheckMate 722: Nivolumab + Pemetrexed/Platinum Chemotherapy in TKI-Resistant, EGFR-Mutated, Metastatic NSCLC

- Phase III KEYNOTE-789: Pembrolizumab + Pemetrexed/Platinum Chemotherapy in TKI-Resistant, EGFR-Mutated, Metastatic NSCLC

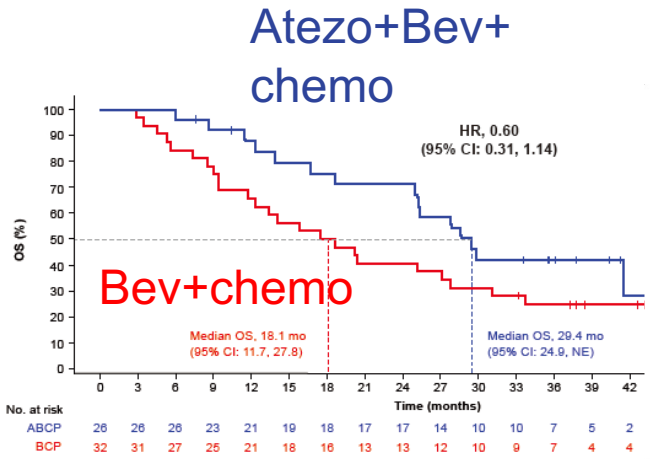
EGFR Mutant NSCLC Post TKI May Benefit from PD1 + Chemotherapy + VEGFi

IMpower150

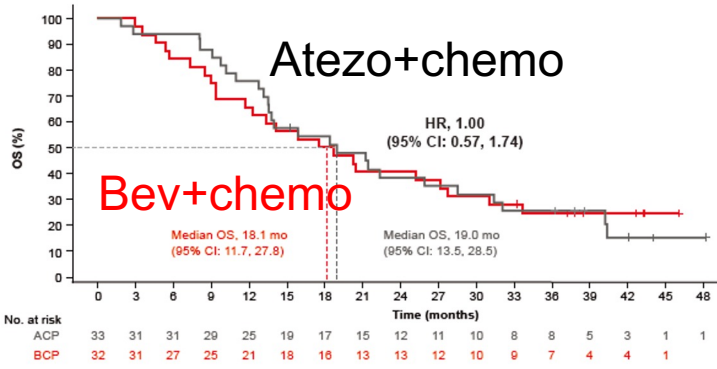


Nogami et al., JTO, 2021

EGFR mutant patients



HR0.60 (0.31-1.14)

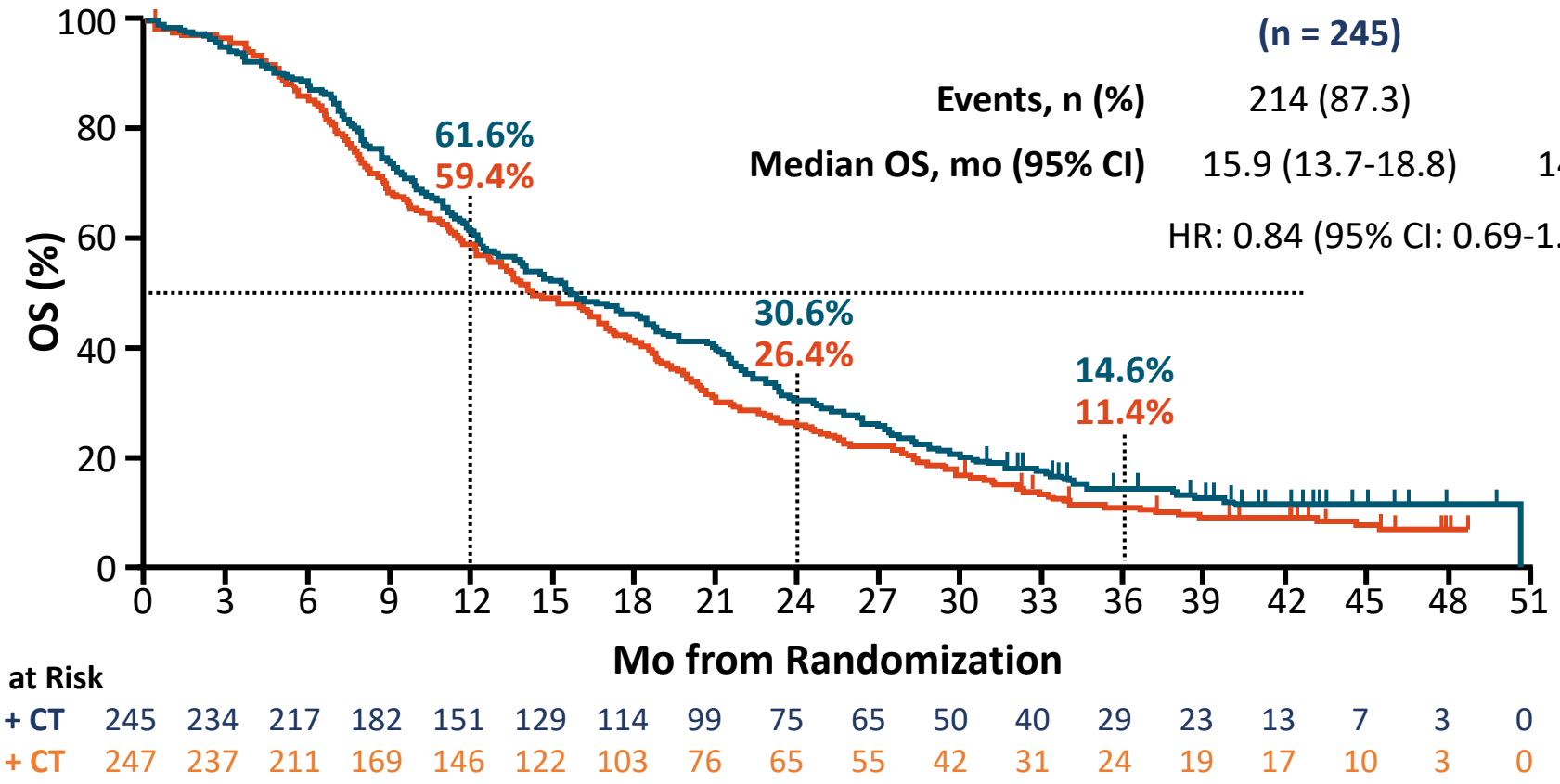


HR1.00 (0.57-1.74)

Subset Analysis; not pre-specified

West et al., Lancet Oncol, 2019

OS: KEYNOTE-789: Chemotherapy ± Pembrolizumab in TKI-Resistant, *EGFR*-Mutated, Metastatic NSCLC



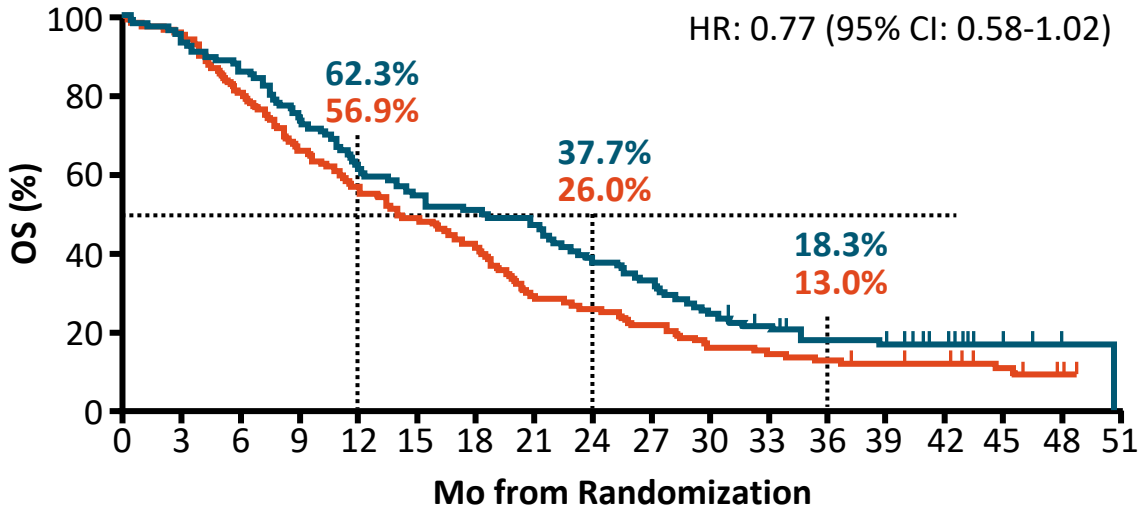
Yang. ASCO 2023. Abstr LBA9000.

KEYNOTE-789 Final Analysis: OS by PD-L1 TPS

PD-L1 TPS ≥1%

	Pembro + CT (n = 106)	Placebo + CT (n = 123)
Events, n (%)	88 (83.0)	110 (89.4)
mOS, mo (95% CI)	18.6 (12.5-22.9)	14.1 (11.4-18.1)

HR: 0.77 (95% CI: 0.58-1.02)

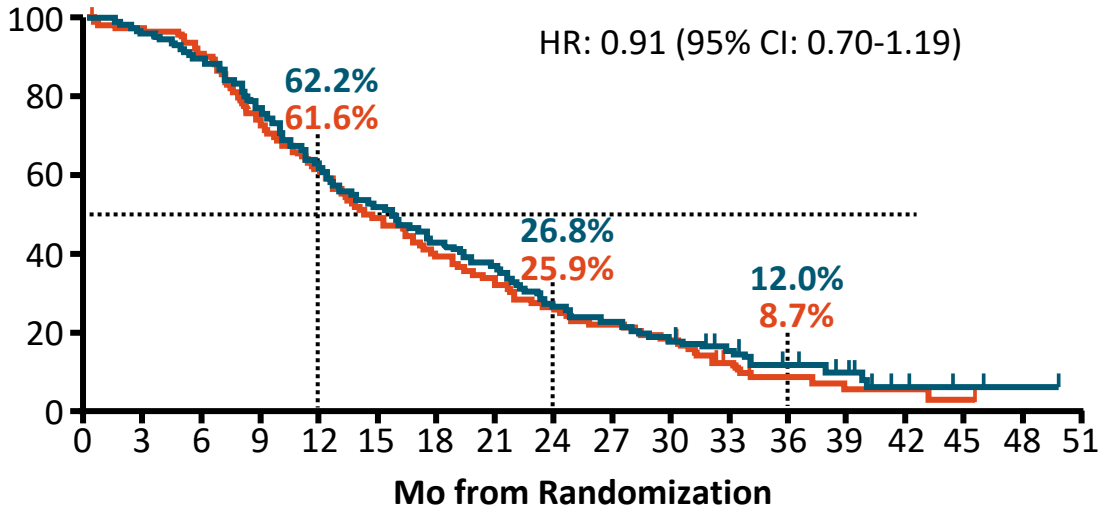


Pembro + CT	106	101	92	80	66	58	54	50	40	35	26	21	16	15	10	5	2	0
Placebo + CT	123	118	99	81	70	60	52	36	32	27	20	18	16	14	13	9	3	0

PD-L1 TPS <1%

	Pembro + CT (n = 127)	Placebo + CT (n = 113)
Events, n (%)	115 (90.6)	104 (92.0)
mOS, mo (95% CI)	15.7 (12.4-18.8)	14.7 (12.2-17.3)

HR: 0.91 (95% CI: 0.70-1.19)



Pembro + CT	127	122	114	96	79	66	55	47	34	29	23	18	12	8	3	2	1	0
Placebo + CT	113	108	102	81	69	55	44	36	29	25	20	11	6	4	3	1	0	0

Yang. ASCO 2023. Abstr LBA9000.

Use of immunotherapy in driver population

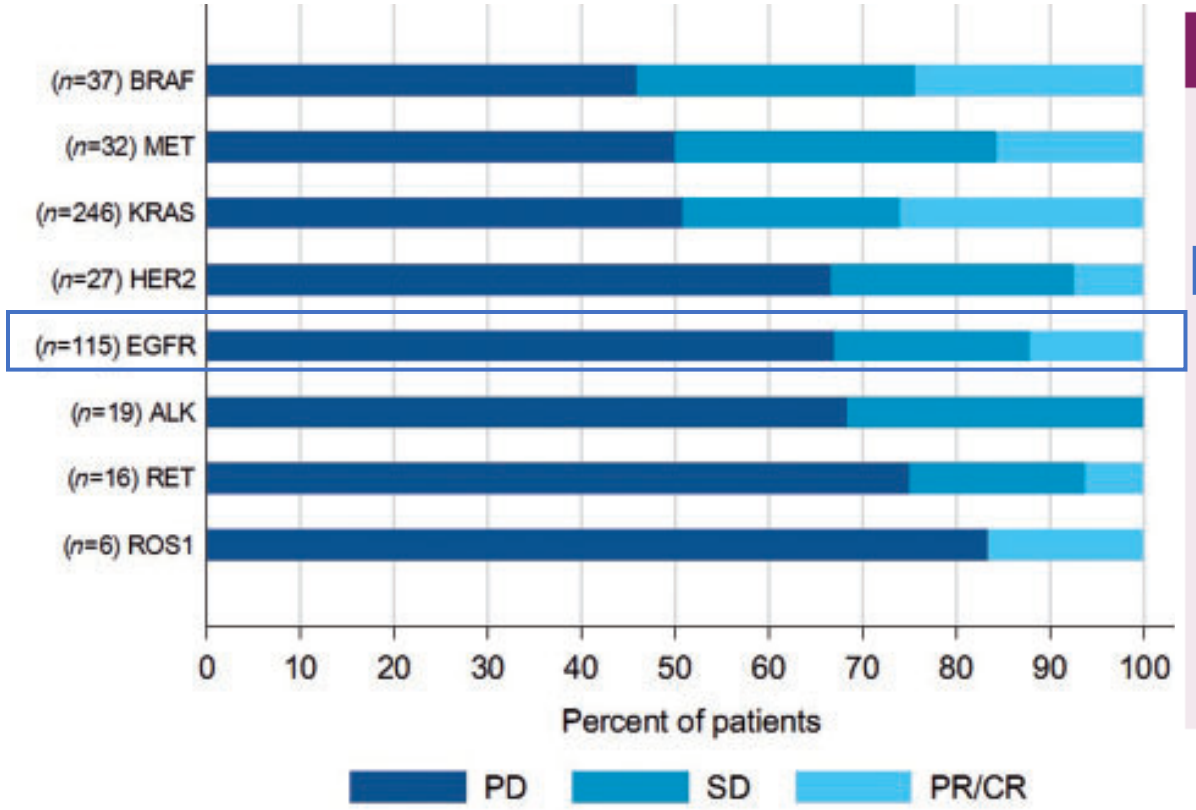


Table 2. PFS according to primary oncogenic driver from initiation of ICI

	EVT/*N*	Median PFS [95% CI] (months)
KRAS	208/271	3.2 [2.7; 4.5]
EGFR	117/125	2.1 [1.8; 2.7]
BRAF	34/43	3.1 [1.8; 4.6]
HER2	23/29	2.5 [1.8; 3.5]
MET	26/36	3.4 [1.7; 6.2]
ALK	21/23	2.5 [1.5; 3.7]
ROS1	–	–
RET	15/16	2.1 [1.3; 4.7]

EVT, event; *N*, number.

Mazieres et al Immunotarget Ann Oncol 2018

Immune Related Adverse Events

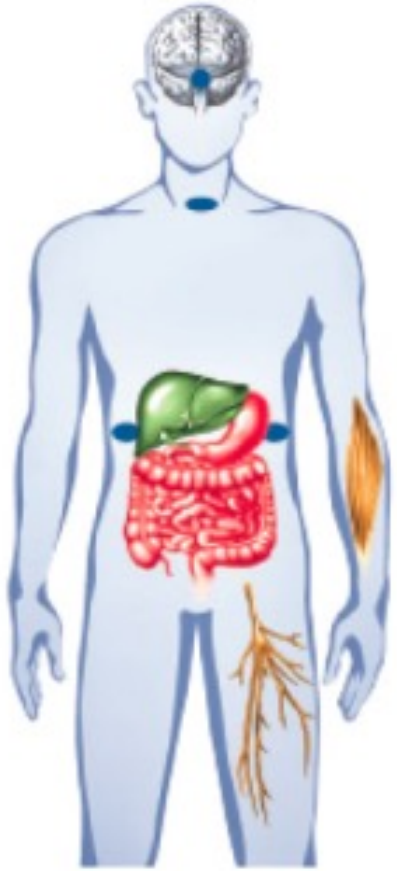
Hypophysitis

Thyroiditis

Adrenal insufficiency

Enterocolitis

Dermatitis



Pneumonitis

Hepatitis

Pancreatitis

Motor and sensory neuropathies

Arthritis

Immune Related Adverse Events

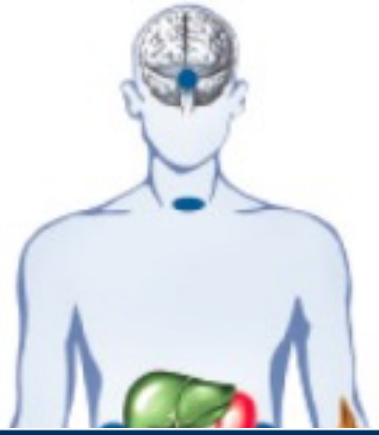
Hypophysitis

Thyroiditis

Adrenal insufficiency

Enterocolitis

Dermatitis



Pneumonitis

Hepatitis

Pancreatitis

ANNALS OF ONCOLOGY driving innovation in oncology

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ORIGINAL ARTICLES THORACIC TUMORS | VOLUME 30, ISSUE 5, P839-844, MAY 01, 2019

Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib

A.J. Schoenfeld • K.C. Arbour • H. Rizvi • ... G.J. Riely • H.A. Yu † • M.D. Hellmann † •

Show all authors • Show footnotes

Open Archive • DOI: https://doi.org/10.1093/annonc/mdz077

Agenda

Module 1: Contemporary Care for Patients with Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) with an EGFR Mutation — Dr Langer

Module 2: Evolving First-Line Treatment for Metastatic NSCLC with an EGFR Mutation — Dr Goldman

Module 3: Biological Rationale for and Emerging Role of Antibody-Drug Conjugates in the Management of NSCLC with an EGFR Mutation — Dr Yu

Module 4: Other Emerging Strategies for Relapsed Metastatic NSCLC with an EGFR Mutation — Dr Sabari

Module 5: Current and Future Management of NSCLC with an EGFR Exon 20 Insertion Mutation — Dr Piotrowska

Module 6: Management of Toxicities Associated with Available and Emerging Therapies for NSCLC with an EGFR Mutation — Dr Neal

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Comments

Second-line treatment of metastatic NSCLC with EGFR exon 20 insertion mutations

Dr John V Heymach (Houston, Texas)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What is your usual first-line therapy for a patient with NSCLC with an EGFR exon 20 insertion mutation?

QUESTIONS FOR THE FACULTY

Which novel agents do you believe are the most promising for patients with progressive NSCLC with an EGFR exon 20 mutation?

Would you like to have access to any of these therapies at the current time?

Current and Future Management of EGFR Exon 20 Mutation-Positive NSCLC

Zosia Piotrowska, MD, MHS

Massachusetts General Hospital

May 31, 2024

Distinguishing between *EGFR* mutations in NSCLC

SENSITIZING

Common EGFR Mutations

Exon 19 Deletions (~45%)

Most commonly between AA E746 and A750:
E746_A750del, L747_P753insS, L747_T751del, L747_A750insP, E746-S752insV, etc.

L858R point mutation (exon 21), (~40%)

Atypical EGFR Mutations

L861Q, G719X, S768I, etc

Others (TKI sensitivity varies)

RESISTANT to standard EGFR TKIs

Exon 20 Insertions (AA 761-775)

A767_V769dup

S768_D770dupSVD

V769_D770insASV

D770_N771ins…

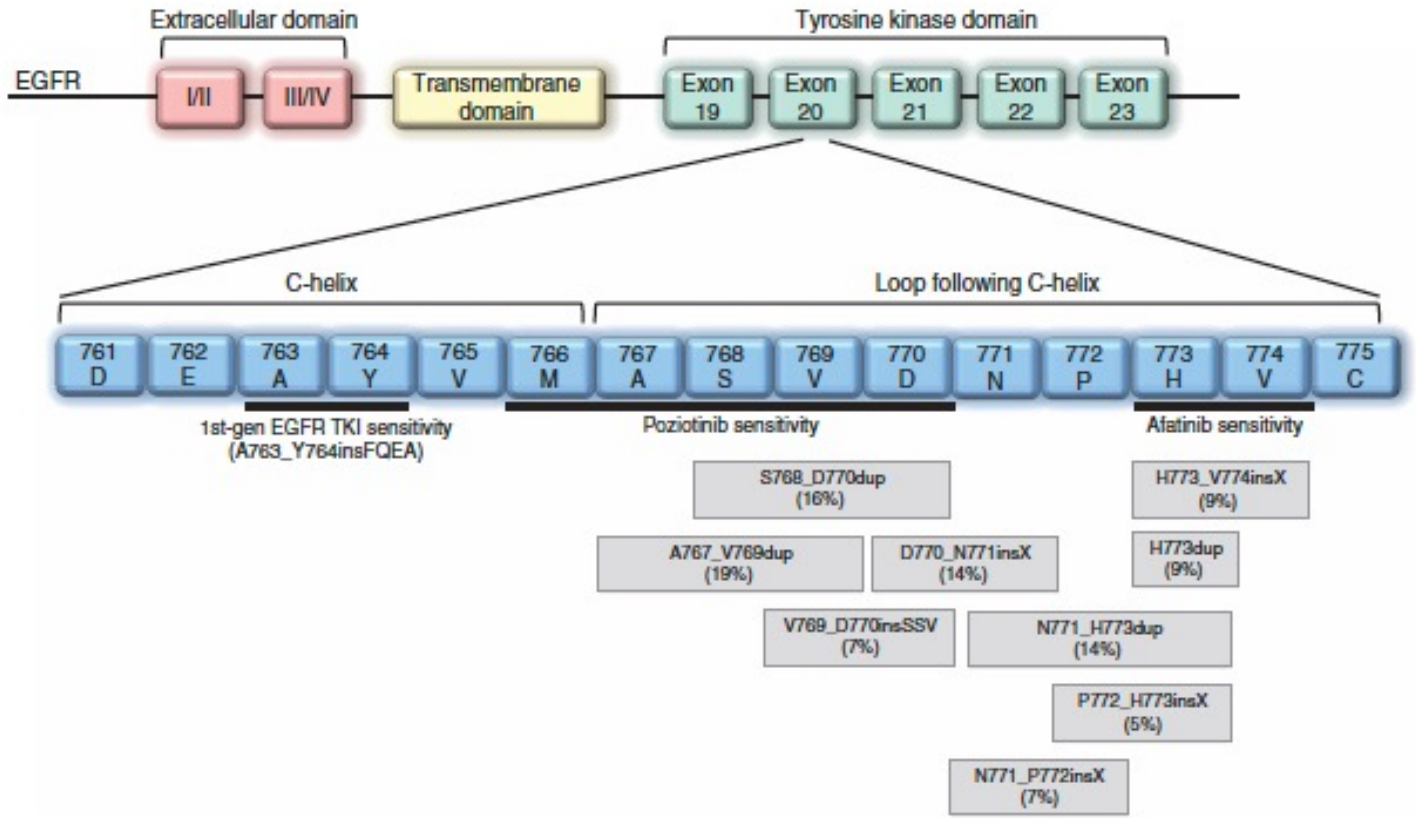
D770_P772dup

N771_H773dup

N771_P772ins…

P772_H773dupPH

V774ins

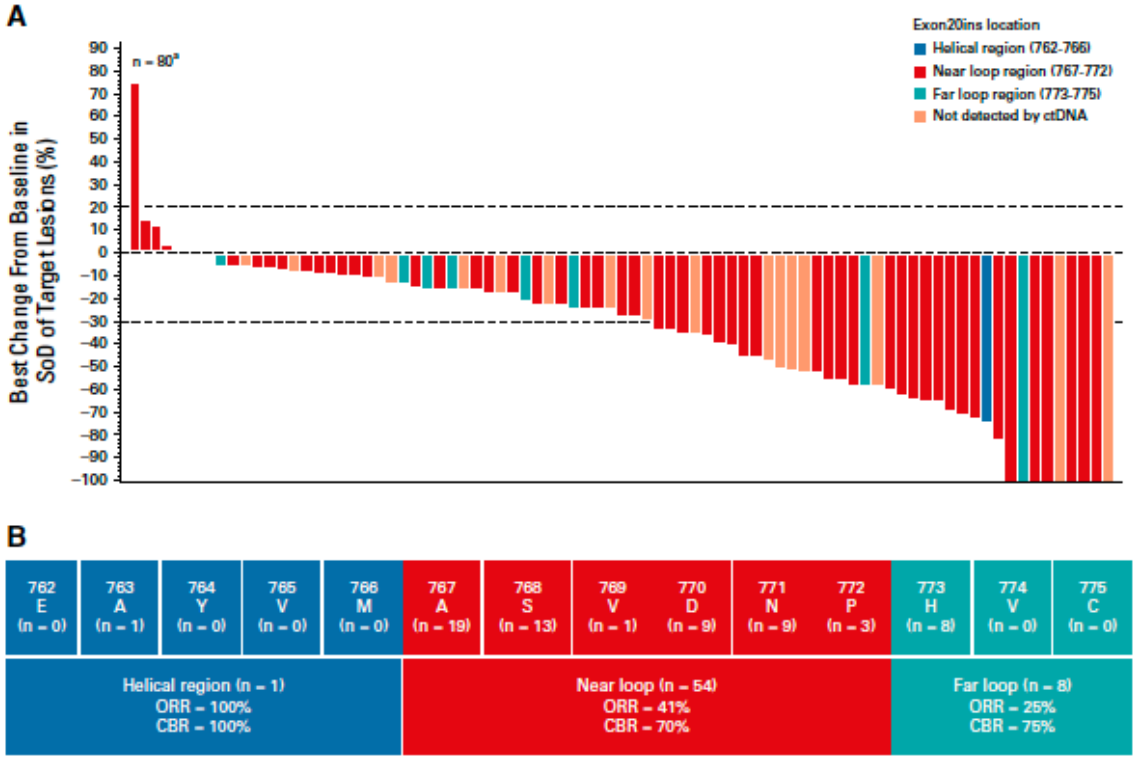


Meador CB et al. *Cancer Disc.* 2021;11:2145-2157.

Amivantamab for EGFR Exon 20 Insertions

Amivantamab

- EGFR and MET bispecific antibody
- Initially received accelerated FDA approval (2021) for patients with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

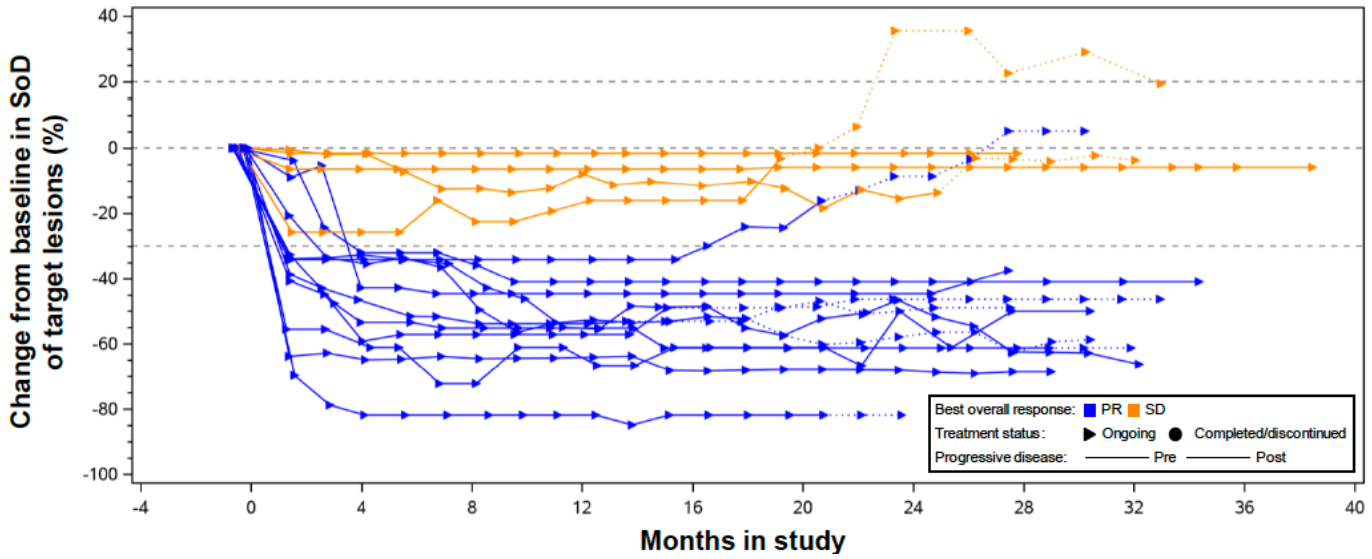


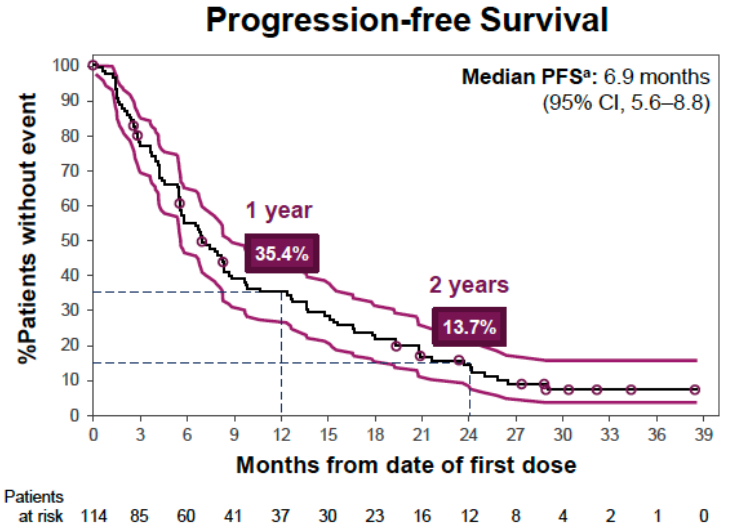
CHRYSALIS (Phase 1) Trial:
Efficacy population: 81 patients
Confirmed ORR 40% (95% CI, 29-51)
mDOR 11.1 (95% CI, 6.9-NR)
mPFS 8.3 mos (95% CI, 6.5-10.9)

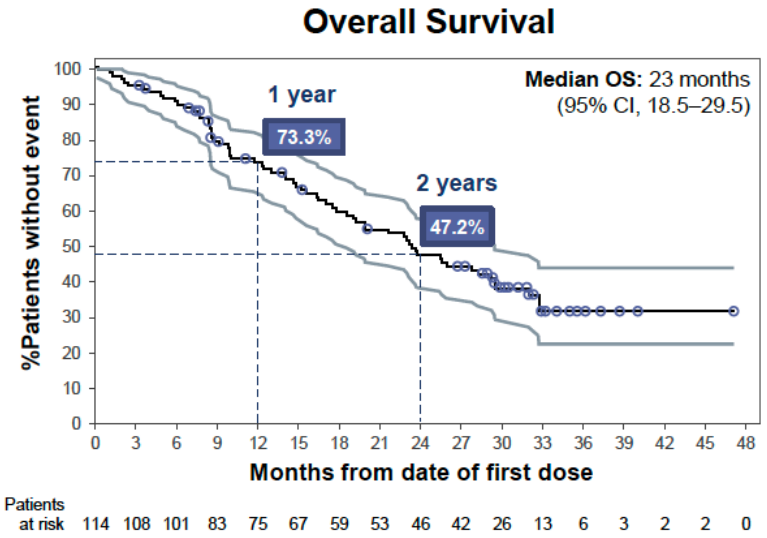
Park K et al. *J Clin Oncol.* 2021;39:3391-3402.

Amivantamab for EGFR Exon 20 Insertions

With longer follow up of 114 EGFR exon 20 ins+ patients who received amivantamab monotherapy on the CHRYSALIS trial, 42% had sustained clinical benefit (≥ 12 cycles)





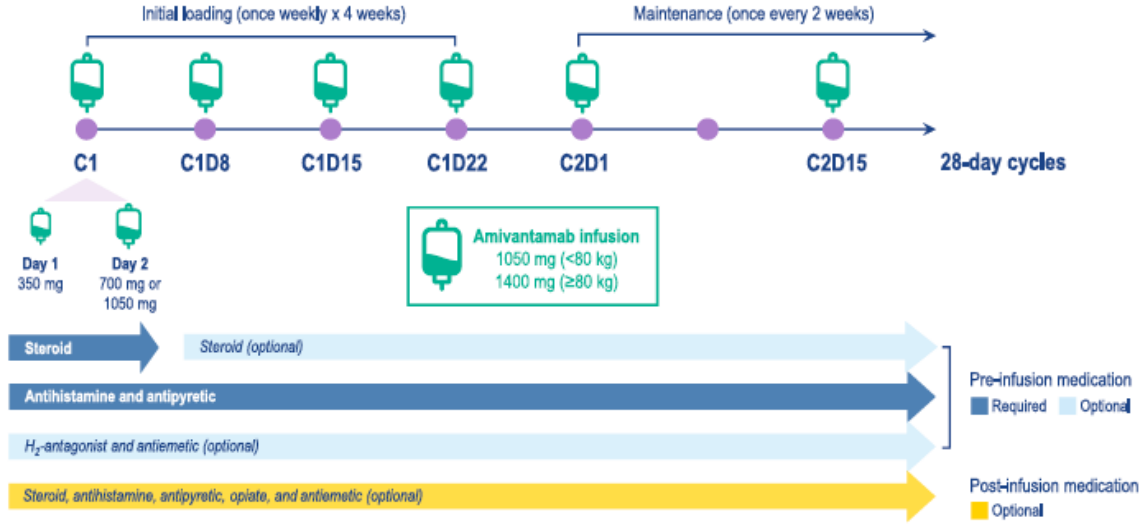


Garrido-Lopez P, ELCC 2023

Amivantamab Toxicities

AE (≥15% of Treatment-emergent AEs), n (%)	Safety Population (N=114)			
	Treatment-emergent AE		Treatment-related AE	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Rash[a]	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0
MET-related				
Hypoalbuminemia	31 (27)	3 (3)	17 (15)	2 (2)
Peripheral edema	21 (18)	0	11 (10)	0
Other				
Infusion related reaction	75 (66)	3 (3)	75 (66)	3 (3)
Constipation	27 (24)	0	7 (6)	0
Nausea	22 (19)	0	13 (11)	0
Dyspnea	22 (19)	2 (2)	6 (5)	0
Fatigue	21 (18)	2 (2)	14 (12)	1 (1)
Increased ALT	17 (15)	1 (1)	14 (12)	1 (1)

IRRs

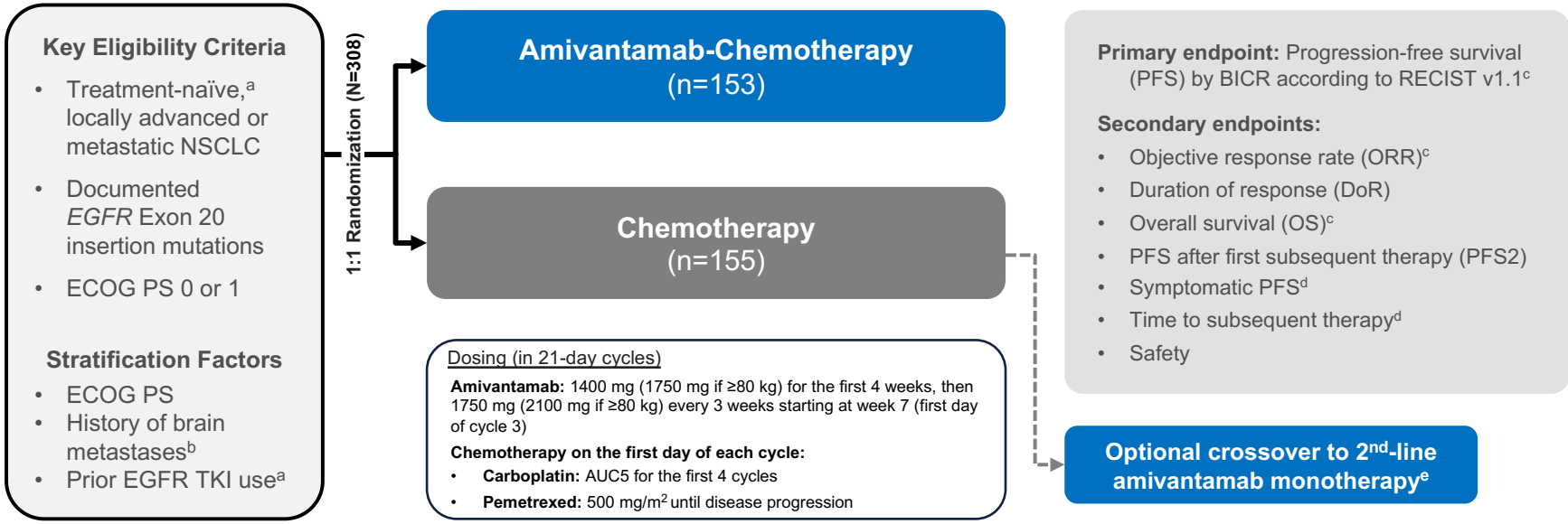


Infusion reactions occur with 1st infusion in ~2/3 of patients, but are **mitigated by the new subcutaneous formulation of amivantamab.**

Park K, Lung Cancer 2023.
Haura EB et al. ASCO 2019. Abstract 9009.

PAPILLON: First-line Amivantamab + Chemotherapy

PAPILLON: Phase 3 Study Design



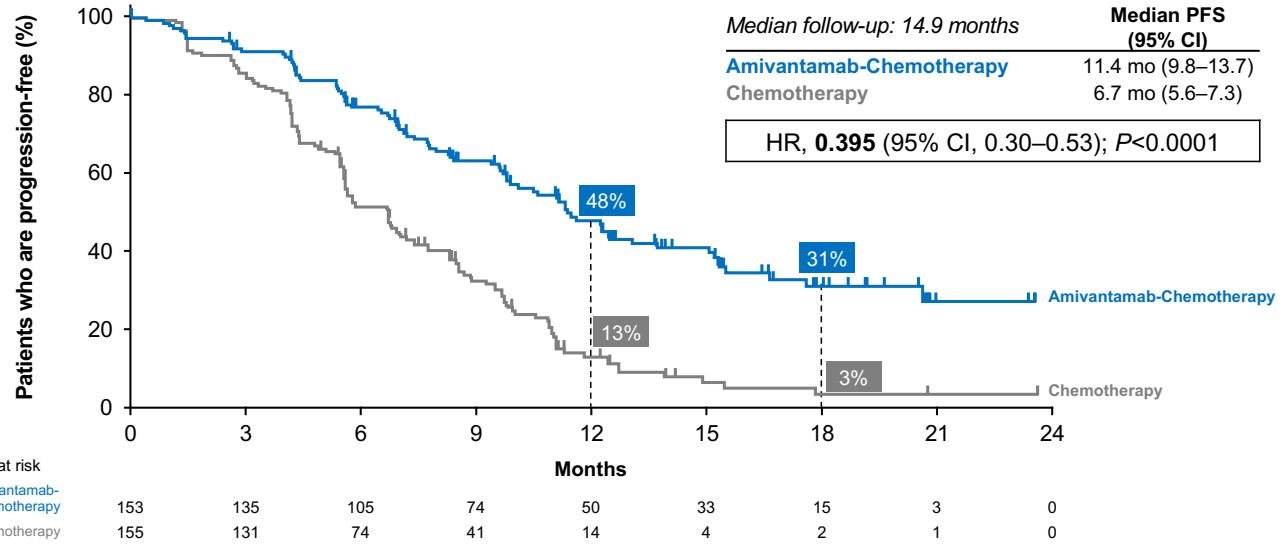
*Amivantamab given weekly for 4 weeks, then every 3 weeks starting at week 7

Girard N, ESMO 2023
Zhou C, NEJM 2023

PAPILLON: First-line Amivantamab + Chemotherapy

Primary Endpoint: Progression-free Survival by BICR

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



	Amivantamab-Chemo	Chemo	
ORR	73% (95% CI, 65-80)	47% (95% CI, 39-56)	
mPFS	11.4 mo (9.8-13.7)	6.7 (95% CI, 5.6-7.3)	HR 0.395 (95% CI, 0.30-0.53)
[OS (interim)*	*NE*	*24.4 mo (95% CI, 22.1-NE)*	*HR 0.675 (95% CI, 0.42-1.09)]*

OS data are immature (~33% maturity), 66% of patients who progressed crossed over to amivantamab.

Girard N, ESMO 2023
Zhou C, NEJM 2023

PAPILLON: Safety

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)

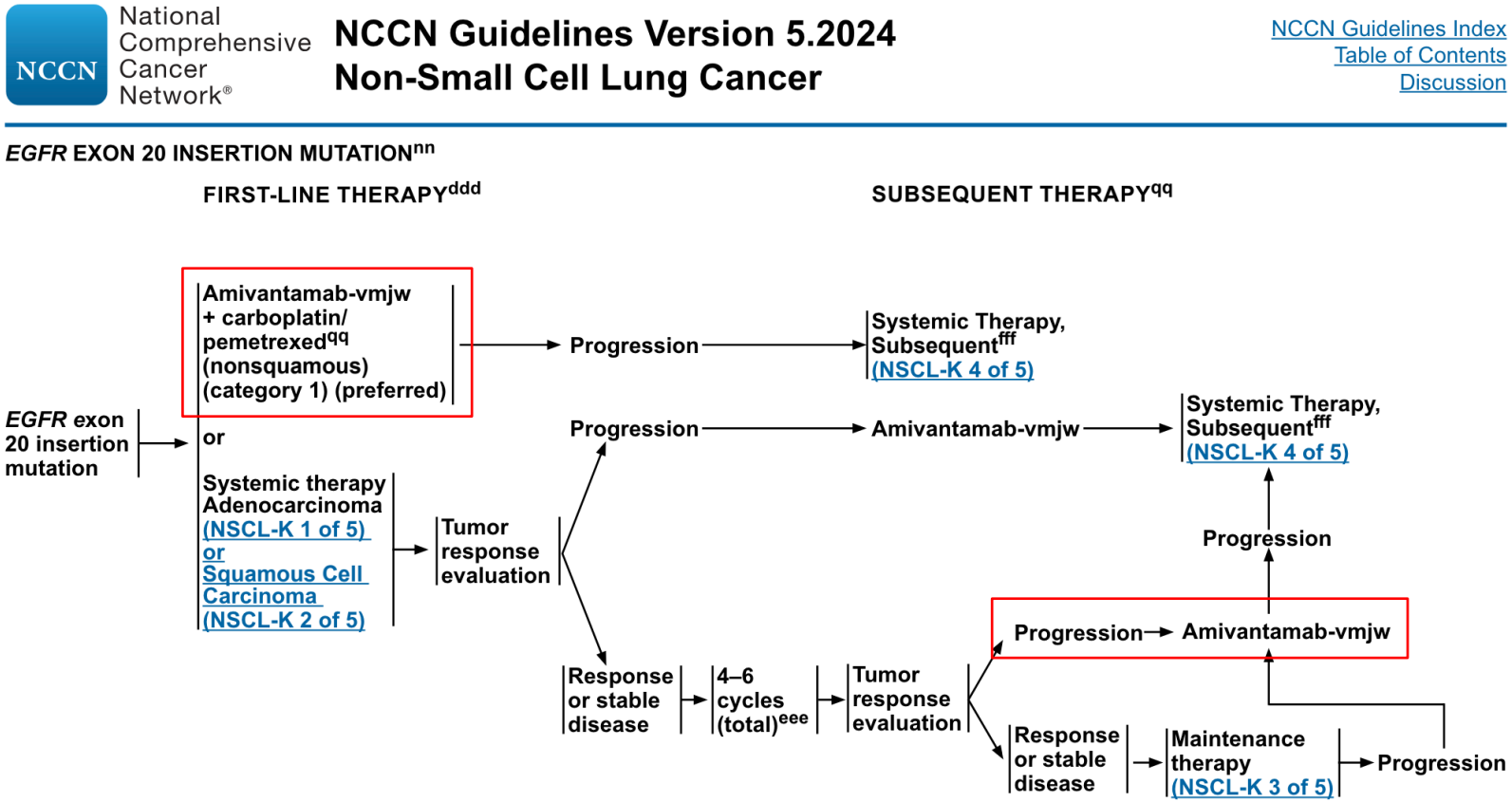
<u>Ami + Chemo Safety:</u>

- Toxicities of Ami (IRR, paronychia, rash, edema) appear to be additive with chemo (hematologic toxicities)
- Neutropenia was slightly higher in combination
- Pneumonitis: 3% in Ami-Chemo

- Dose reductions:
  - Any agent; 48% vs. 23% (36% reduced amivantamab)
- Discontinuation:
  - Any agent; 24% vs 10% (7% discontinued Ami)

Girard N, ESMO 2023 and Zhou C, NEJM 2023

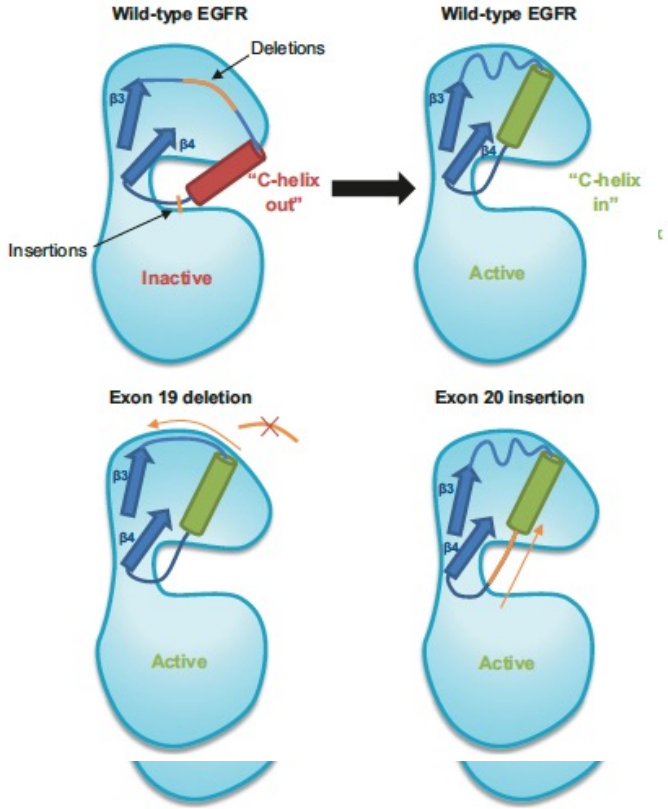
Amivantamab + chemo is now the SOC in the front-line



* For frail patients where the toxicities of amivantamab + chemotherapy are a concern, consider sequential use of carboplatin/pemetrexed followed by amivantamab.

Oral drugs in development for EGFR exon 20 insertions

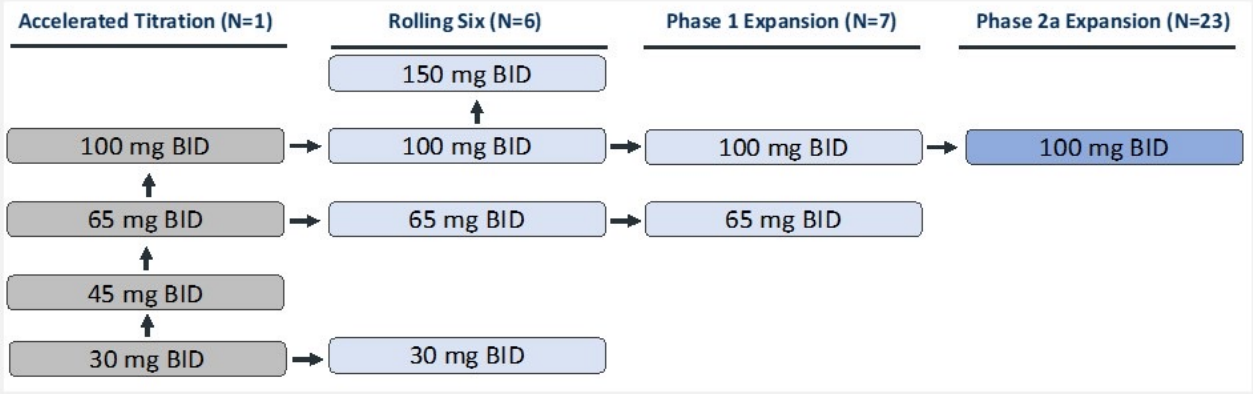
- In contrast to exon 19 deletions, exon 20 insertions shift the C-helix P-loop of the EGFR protein into the binding pocket, resulting in a **steric hindrance** which is structurally unique from other types of EGFR mutations.
- Traditional (first, second and third generation) EGFR TKIs have limited binding and limited clinical activity.
- Novel, fourth generation, EGFR TKIs have been developed specifically to overcome EGFR exon 20 insertions.



Vyse S, Huang PH. Signal Transduct Target Ther. 2019

Zipalertinib (CLN-081) – Phase 1/2a Study Design (NCT04036682)

STUDY SCHEMA



- Dose escalation used both an accelerated titration and rolling-six design
- Phase 1 and Phase 2a dose expansion cohorts enrolled additional patients at dose levels meeting pre-defined thresholds for efficacy and tolerability

KEY ELIGIBILITY

- Confirmed recurrent or metastatic NSCLC with documented EGFR ex20ins mutation demonstrated by local laboratory
- Prior treatment in the recurrent/metastatic setting including a platinum-based chemotherapy regimen unless declined
- Prior treatment with an EGFR exon20in-targeting drug was allowed only in dose-escalation cohorts
- Patients with CNS metastases stable for ≥4 weeks prior to C1D1 were eligible

TREATMENT PLAN

- Patients receive CLN-081 twice daily and may continue to receive treatment until disease progression, unacceptable toxicity or withdrawal of consent
- Tumor response was assessed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) at 6 weeks and every 9 weeks thereafter

Yu H, et al. ASCO 2022;Abstract 9007.

Zipalertinib (CLN-081) – Patient Demographics

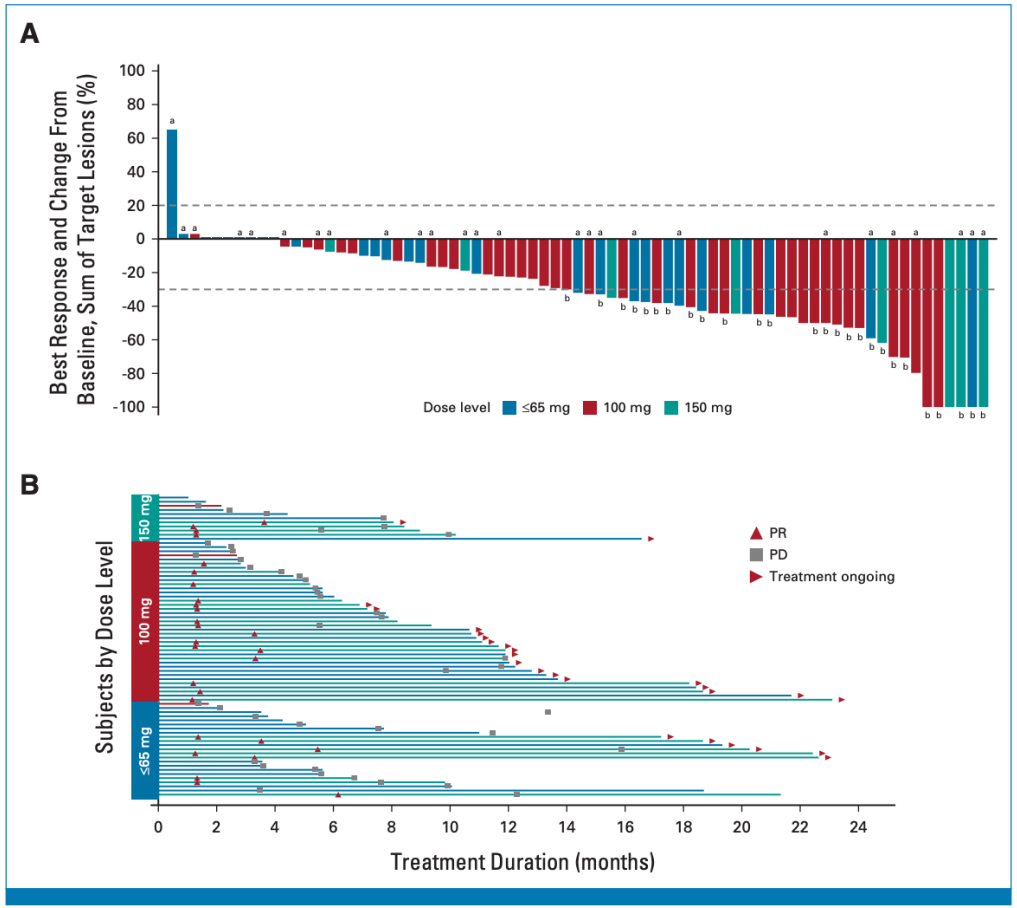
TABLE 1. Summary of Patient Demographics

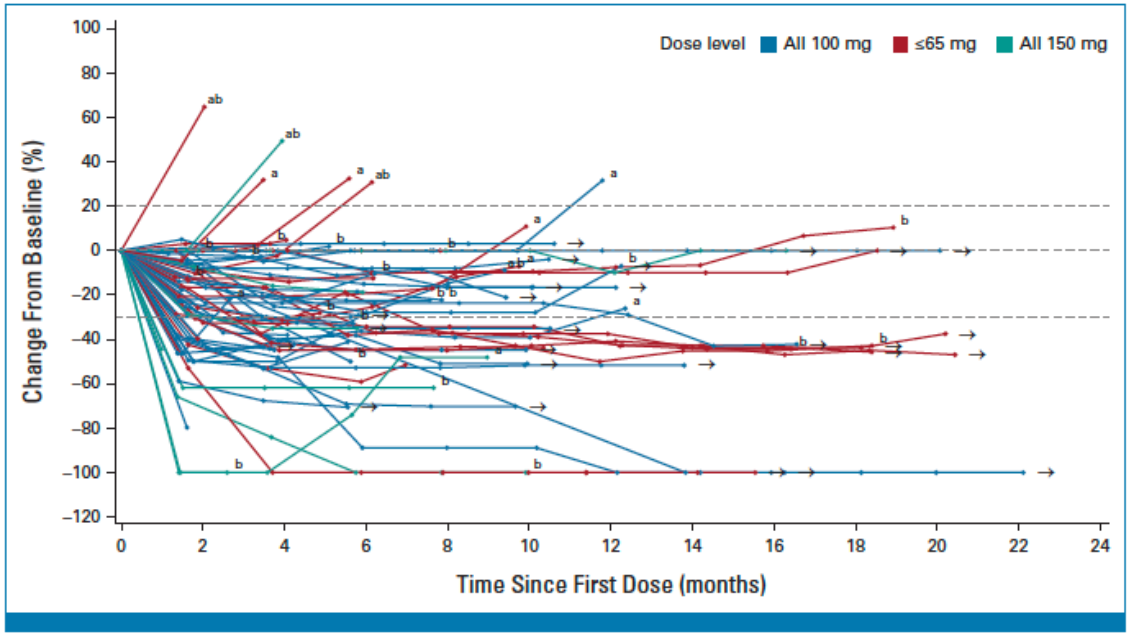
Characteristic	All Patients (N = 73)
Age, years, median (range)	64 (36-82)
Female, No. (%)	41 (56)
EGFR exon 20 insertion mutation, No. (%)	
Helical	2 (3)
Near-loop	52 (71)
Far-loop	9 (12)
Undetermined	10 (14)
ECOG performance status, No. (%)	
0	22 (30)
1	51 (70)
Previous systemic cancer regimens,[a] No. (%)	
0	3 (4)
1	22 (30)
2	32 (44)
3 or more	16 (22)
Median (range)	2 (1-9)
Previous EGFR TKIs (non-ex20ins), No. (%)	26 (36)
Previous afatinib or gefitinib	13 (18)
Previous osimertinib	13 (18)
Previous poziotinib and/or mobocertinib,[b] No. (%)	3 (4)
Previous PD-1/PD-L1 inhibitor, No (%)	40 (55)
History of CNS metastases, No. (%)	28 (38)

Piotrowska Z, et al. JCO 2023

Zipalertinib (CLN-081) – Efficacy Results

In a phase 1/2a study, **71 patients received zipalertinib** after prior platinum-based chemo (39 were treated at RP2D of 100mg BID).





	All Dose Levels (N=73)	100 mg BID (N=39)
Conf ORR	38.4%	41%
mDOR	10 mo (95% CI, 6-NC)	NR
mPFS	10 mo (95% CI, 6-12)	12 mo (95% CI, 5-13)

Piotrowska Z, et al. JCO 2023

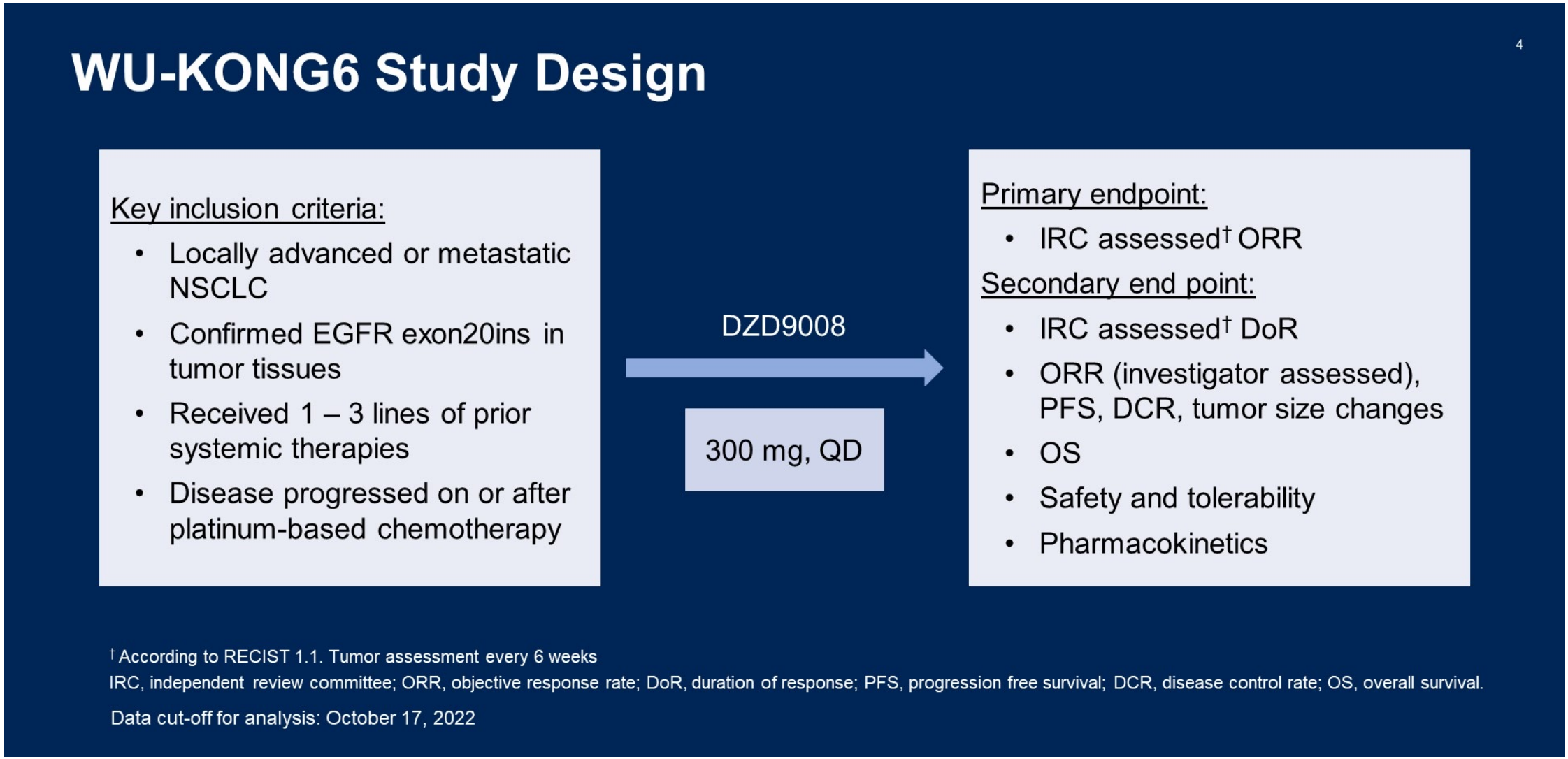
Zipalertinib (CLN-081) – Safety

Treatment-Related AEs Observed in ≥ 10% of Subjects

	100 mg BID (N=39)		Overall(N=73)	
AE	**All Grade**	**Grade ≥ 3**	**All Grade**	**Grade ≥ 3**
Rash	32 (82)	0	58 (80)	1 (1)
Paronychia	12 (31)	0	23 (32)	0
Diarrhea	14 (36)	0	22 (30)	2 (3)
Fatigue	8 (21)	0	15 (21)	0
Anemia	5 (13)	1 (2.6)	14 (19)	7 (10)
Dry skin	7 (18)	0	13 (18)	0
Nausea	4 (10)	0	12 (16)	0
Stomatitis	5 (13)	0	10 (14)	0
Alopecia	6 (15)	0	9 (12)	0
Dry eye	7 (18)	0	9 (12)	0
AST increase	3 (8)	1 (3)	8 (11)	3 (4)
Decreased appetite	4 (10)	0	8 (11)	0

Piotrowska Z, et al. JCO 2023

Sunvozertinib (DZD9008) – Phase II Study Design



Wang M, et al. ASCO 2023.

Sunvozertinib (DZD9008) – Patient Demographics

Demographics and Baseline Characteristics	N = 97
Median age, years (range)	58 (29, 79)
Male/Female, n (%)	39 (40.2)/58 (59.8)
History of smoking, Yes(%)/No(%)	32 (33)/65 (67)
Baseline brain metastasis, n (%)	31 (32.0)
Mutation subtypes, n (%)	
769_ASV	38 (39.2)
770_SVD	17 (17.5)
Others	42 (43.3)

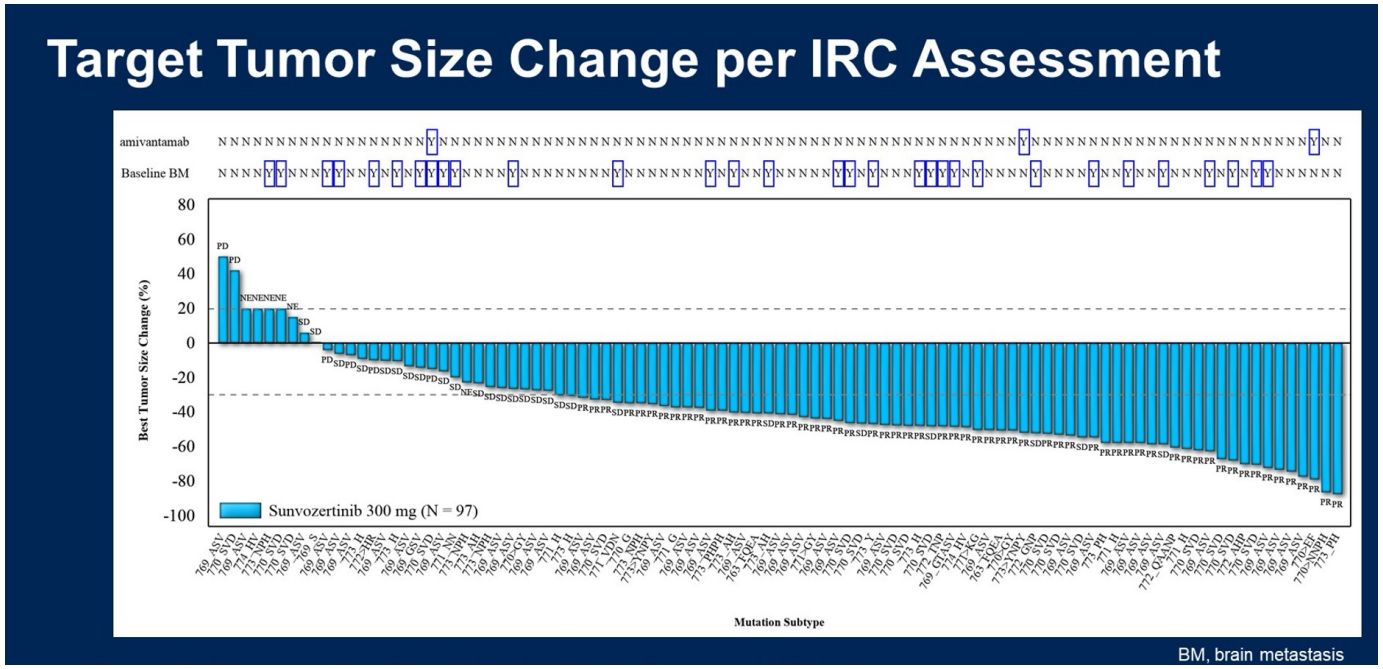
Patient Treatment History	N = 97
Median prior anti-cancer therapy, n (range)	2 (1, 3)
Prior anti-cancer therapy type, n (%)	
Chemotherapy	97 (100)
Platinum-based chemotherapy	97 (100)
EGFR TKI	26 (26.8)
PD-1/PD-L1	34 (35.1)
Anti-VEGF	58 (59.8)
Others	16 (16.5)

- As of October 17, 2022, a total of 104 subjects with over 30 EGFR Exon20ins subtypes were enrolled and the last subject has been followed up for 6 months. A total of 97 patients were included in the efficacy analysis set.

Wang M, et al. ASCO 2023.

Sunvozertinib (DZD9008) – Efficacy Results

In the WU-KONG6 trial, **97 patients were treated with sunvozertinib at the RP2D of 300mg QD** (all received prior platinum-based chemotherapy, 1-3 prior lines of therapy.)



Confirmed ORR, 59/97 (60.8%)

mDOR not reached (median follow up 5.6 mo, 64% pts still responding)

Common Treatment-Emergent Adverse Events (N=104 safety population)

AE	All Grade	Grade ≥ 3
Diarrhea	70 (67)	8 (8)
CPK Increase	60 (58)	18 (17)
Rash	56 (54)	1 (1)
Anemia	51 (49)	6 (6)
Creatinine Increase	39 (38)	0
Paronychia	34 (33)	2 (2)
Body weight decrease	30 (29)	1 (1)
WBC decrease	27 (26)	0
Lipase	27 (26)	2 (2)
Vomiting	25 (24)	1 (1)
Decreased appetite	25 (24)	2 (2)
Mouth ulceration	(24 (23)	0

Wang M, et al. ASCO 2023.

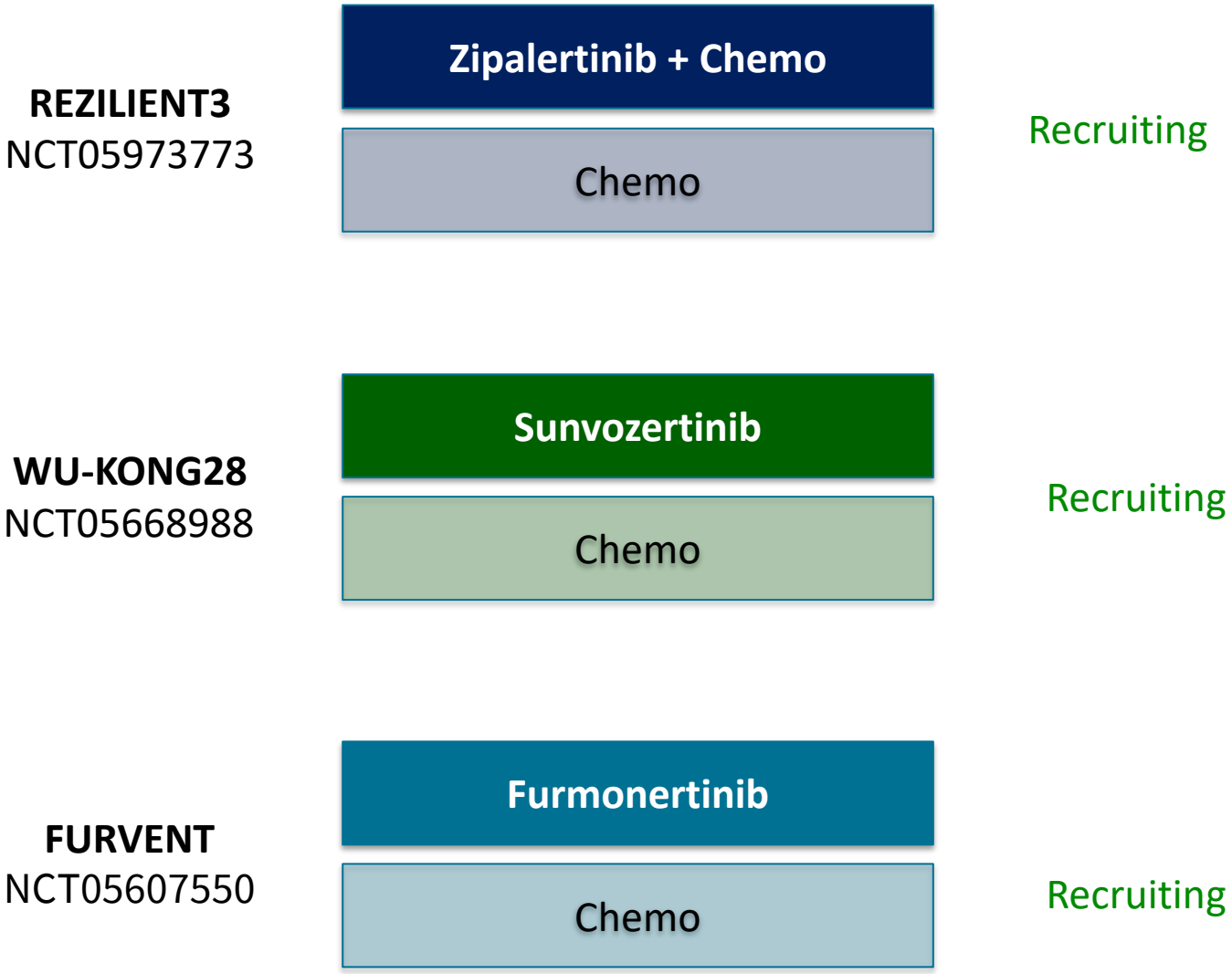
EGFR Exon 20 TKIs in Development

Drug	RP2D	n	ORR	mPFS mDOR	Major Toxicities Tox, % All Grade (% 3+)
Sunvozertinib[1] (DZD9008)	300 mg QD	97 (300mg QD)	60.8%	NR	Diarrhea, 67% (7.7%) Rash, 54% (1%) CPK Increase, 58% (17%)
Zipalertinib[2] (CLN-081)	100 mg BID	39 (100mg BID)	41%	12 mo NR	Diarrhea, 30% (3%) Rash, 80% (1%) Paronychia: 32% (0%)
Furmonertinib[3]	TBD	30 (Tx naïve)	69% (Tx Naïve)	mPFS 10.7 mo	Rash, dry skin, nail disorders, diarrhea, stomatitis, LFTs
ORIC114[4]	TBD	50	4/13 (EGFR exon 20)	NR	Rash 54%, Diarrhea 40%, Stomatitis 30%, Paronychia 28%
Osimertinib[5] 160mg		17	24%	9.6 mo NR	Diarrhea, 76% (0%) Fatigue, 67% (10%) Rash, 38% (0%)
Mobocertinib[6]	160mg QD	114 (PPP)	28% (BICR)	7.3 mo 17.5 mo	Diarrhea, 91% (21%) Rash, 45% (0%)
Poziotinib[7]	16 mg QD	115	15%	4.2 mo 7.4 mo	Diarrhea, 79% (25%) Rash, 60% (28%) Stomatitis, 52% (9%)
BDTX-189[8]	Clinical Development Halted				
BLU-451[9]	Clinical Development Halted				

No longer in development

1. Wang M, ASCO 2023; 2. Piotrowska Z, JCO 2023; 3. Han B, et al, WCLC 2023 OA03.04; 4. Murray BW, AACR 2022, NCT05315700; 5. Piotrowska Z et al., ASCO 2020, Abstract 9513; 6. Zhou C, et al. JAMA Oncol 2021; 7. Le X, AACR 2020; Socinski M, ESMO 2020; 8. Schram A, et al, ASCO 2021, Abstract 3028; 9 Spira A, et al, ASCO 2022

Ongoing First-Line EGFR Exon 20 TKI Trials



Conclusions

- EGFR exon 20 insertions are distinct from other EGFR mutations, and best identified using NGS testing.
- Chemo + amivantamab is now the preferred first-line regimen for fit patients, but requires careful toxicity management.
- Multiple new EGFR TKIs targeting EGFR exon 20 insertions are in development with improving efficacy and safety.
- First-line trials are testing novel EGFR TKIs with and without chemotherapy, and may change our front-line standard of care.

Agenda

Module 1: Contemporary Care for Patients with Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) with an EGFR Mutation — Dr Langer

Module 2: Evolving First-Line Treatment for Metastatic NSCLC with an EGFR Mutation — Dr Goldman

Module 3: Biological Rationale for and Emerging Role of Antibody-Drug Conjugates in the Management of NSCLC with an EGFR Mutation — Dr Yu

Module 4: Other Emerging Strategies for Relapsed Metastatic NSCLC with an EGFR Mutation — Dr Sabari

Module 5: Current and Future Management of NSCLC with an EGFR Exon 20 Insertion Mutation — Dr Piotrowska

Module 6: Management of Toxicities Associated with Available and Emerging Therapies for NSCLC with an EGFR Mutation — Dr Neal

RTP RESEARCH TO PRACTICE

Consulting Faculty Comments

Adverse events associated with EGFR-targeted therapies

Dr Roy S Herbst (New Haven, Connecticut)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Do you follow the same interstitial lung disease (ILD) monitoring and management protocols for patritumab deruxtecan as you do for trastuzumab deruxtecan?

What grade of ILD would prompt you to recommend treatment interruption? When would you permanently discontinue patritumab deruxtecan for patients with documented ILD?

QUESTIONS FOR THE FACULTY

What are the most common toxicities that have been noted with patritumab deruxtecan?

Which of these do you find most challenging to manage?

Which of these do you believe are most detrimental to patient quality of life?

Consulting Faculty Comments

Toxicity profile of amivantamab and management of associated side effects

Dr John V Heymach (Houston, Texas)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What are the most common toxicities reported with amivantamab?

Which of these do you find most challenging to manage?

Which of these do you believe are most detrimental to patient quality of life?

Management of Toxicities Associated with Available and Emerging Therapies for EGFR-Mutant NSCLC

Joel W. Neal, MD, PhD
Associate Professor, Stanford University

Management of Toxicities Associated with Available and Emerging Therapies for EGFR-Mutant NSCLC — Dr Neal

- Spectrum, frequency and severity of toxicities with third-generation EGFR TKIs (eg, osimertinib, lazertinib)
- Incidence of common (eg, dermatologic AEs, fatigue, musculoskeletal pain, stomatitis) and less frequently occurring (eg, ILD, ocular AEs) toxicities with amivantamab
- Available results with and ongoing evaluation of a subcutaneous formulation of amivantamab
- Spectrum of commonly occurring AEs (eg, GI toxicities, fatigue, myelosuppression) associated with patritumab deruxtecan
- Pathophysiology, rates, severity and timing of ILD in clinical trial experiences with patritumab deruxtecan; strategies to monitor for and manage ILD

Spectrum, frequency and severity of toxicities with third-generation EGFR TKIs (eg, osimertinib, lazertinib)

Lazertinib AEs (Phase 2 study)

Table 3. Treatment-Emergent Adverse Events (>10% of Patients)

	Lazertinib 240 mg (N = 78)			
Adverse Event	All Grades	Grade 3	Grade 4	Grade 5
Patient with at least one TEAE	76 (97.4)	21 (26.9)	3 (3.8)	3 (3.8)
Rash	29 (37.2)	1 (1.3)	0	0
Pruritus	27 (34.6)	0	0	0
Paresthesia	26 (33.3)	2 (2.6)	0	0
Headache	22 (28.2)	0	0	0
Muscle spasms	22 (28.2)	0	0	0
Diarrhea	21 (26.9)	1 (1.3)	0	0
Decreased appetite	20 (25.6)	0	0	0
Paronychia	16 (20.5)	1 (1.3)	0	0
Cough	16 (20.5)	0	0	0
Constipation	15 (19.2)	0	0	0
Nausea	13 (16.7)	0	0	0
Fatigue	12 (15.4)	0	0	0
Aspartate aminotransferase increased	11 (14.1)	0	0	0
Dizziness	10 (12.8)	0	0	0
Alanine aminotransferase increased	10 (12.8)	0	0	0
Myalgia	10 (12.8)	0	0	0
Dyspepsia	9 (11.5)	0	0	0
Stomatitis	9 (11.5)	0	0	0
Blood creatinine increased	9 (11.5)	0	0	0
Dry skin	8 (10.3)	0	0	0
Vomiting	8 (10.3)	1 (1.3)	0	0
Pulmonary embolism	8 (10.3)	1 (1.3)	1 (1.3)	1 (1.3)

Note: Data expressed as number of patients (%).

Cho JTO 2022

JWN NOTE: Lazertinib monotherapy safety data from MARIPOSA has not been presented

Osimertinib AEs (FLAURA2)

Table 3. Adverse Events.*

Event	Osimertinib Monotherapy (N=275)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	22 (8)	15 (5)	6 (2)	1 (<1)	0
Diarrhea	112 (41)	89 (32)	22 (8)	1 (<1)	0
Nausea	28 (10)	22 (8)	6 (2)	0	0
Decreased appetite	26 (9)	18 (7)	6 (2)	2 (1)	0
Constipation	28 (10)	23 (8)	5 (2)	0	0
Rash	57 (21)	46 (17)	11 (4)	0	0
Fatigue	26 (9)	24 (9)	1 (<1)	1 (<1)	0
Vomiting	17 (6)	13 (5)	4 (1)	0	0
Stomatitis	50 (18)	32 (12)	17 (6)	1 (<1)	0
Neutropenia	9 (3)	3 (1)	4 (1)	2 (1)	0
Paronychia	73 (27)	37 (13)	35 (13)	1 (<1)	0
Neutrophil count decrease	16 (6)	6 (2)	8 (3)	2 (1)	0
Covid-19†	39 (14)	18 (7)	21 (8)	0	0
ALT increase	21 (8)	17 (6)	3 (1)	1 (<1)	0
Platelet count decrease	19 (7)	18 (7)	1 (<1)	0	0
Thrombocytopenia	12 (4)	6 (2)	3 (1)	3 (1)	0
Dry skin	66 (24)	62 (23)	4 (1)	0	0
AST increase	13 (5)	12 (4)	0	1 (<1)	0
Blood creatinine increase	12 (4)	10 (4)	2 (1)	0	0
White-cell count decrease	18 (7)	9 (3)	8 (3)	1 (<1)	0
Peripheral edema	12 (4)	9 (3)	3 (1)	0	0

Planchard NEJM 2023

Amivantamab safety overview (1/2)

Incidence of common (eg, dermatologic AEs, fatigue, musculoskeletal pain, stomatitis) and less frequently occurring (eg, ILD, ocular AEs) toxicities with amivantamab

MARIPOSA[1]

First-line amivantamab + lazertinib vs osimertinib

Exon 19 del or Exon 21 L858R mutation

Most common TEAEs (≥25%) by preferred term, %	Amivantamab+ Lazertinib (N=421)		Osimertinib (n=428)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	68	11	28	0.5
Rash	61	15	30	1
Diarrhea	29	2	44	1
Dermatitis acneiform	29	8	13	0
Stomatitis	29	1	21	0.2
Pruritus	23.5	0.5	17	0.2
Associated with MET inhibition				
Hypoalbuminemia	48	6	6	0
Peripheral edema	36	2	6	0

MARIPOSA-2[2]

Second-line amivantamab + chemo +/- lazertinib vs chemo alone

Exon 19 del or Exon 21 L858R mutation

Most common TEAEs (≥25%) by preferred term, n (%)	Amivantamab-Chemotherapy (n=130)		Chemotherapy (n=243)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	48 (37)	3 (2)	1 (0.4)	0
Rash	56 (43)	8 (6)	12 (5)	0
Stomatitis	41 (32)	1 (1)	21 (9)	0
Diarrhea	18 (14)	1 (1)	16 (7)	1 (0.4)
Associated with MET inhibition				
Hypoalbuminemia	29 (22)	3 (2)	21 (9)	1 (0.4)
Peripheral edema	42 (32)	2 (2)	15 (6)	0
Associated with chemotherapy				
Neutropenia	74 (57)	59 (45)	101 (42)	52 (21)
Thrombocytopenia	57 (44)	19 (15)	72 (30)	22 (9)
Anemia	51 (39)	15 (12)	97 (40)	23 (9)
Leukopenia	37 (28)	26 (20)	68 (28)	23 (9)

PAPILLON[3]

First-line amivantamab + chemo vs chemo alone

EGFR Exon 20 insertion mutations

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

NOTE: Lazertinib monotherapy safety data from MARIPOSA has not been presented

AE, adverse event; chemo, chemotherapy; *EGFR*, epidermal growth factor receptor; MET, mesenchymal epithelial transition; TEAE, treatment-emergent adverse event.

1. Cho B, et al. ESMO 2023. Oral presentation #LBA14. 2. Passaro A, et al. *Ann Oncol.* 2024;35:77–90. 3. Zhou C, et al. *N Engl J Med.* 2023;389:2039–2051.

Amivantamab safety overview (2/2)

Incidence of common (eg, dermatologic AEs, fatigue, musculoskeletal pain, stomatitis) and less frequently occurring (eg, ILD, ocular AEs) **VTE** toxicities with amivantamab

MARIPOSA[1]

First-line amivantamab + lazertinib vs osimertinib

Exon 19 del or Exon 21 L858R mutation

Most common TEAEs (≥25%) by preferred term, %	Amivantamab+ Lazertinib (N=421)		Osimertinib (n=428)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Other				
Infusion-related reaction	63	6	0	0
Alanine aminotransferase increased	36	5	13	2
Constipation	29	0	13	0
Aspartate aminotransferase increased	28	3	13	1
COVID-19	26	2	24	2
Decreased appetite	25	1	17	1
Anemia	23	4	22	2
Nausea	21	1	13.2	0.2
Hypocalcemia	21	2	8	0
Cough	15	0	21	0
Any VTE	37	11	9	4

NOTE: Lazertinib monotherapy safety data from MARIPOSA has not been presented

MARIPOSA-2[2]

Second-line amivantamab + chemo +/- lazertinib vs chemo alone

Exon 19 del or Exon 21 L858R mutation

Most common TEAEs (≥25%) by preferred term, n (%)	Amivantamab-Chemotherapy (n=130)		Chemotherapy (n=243)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Other				
Infusion-related reaction	76 (58)	7 (5)	1 (0.4)	0
Nausea	58 (45)	1 (1)	90 (37)	2 (1)
Constipation	50 (38)	1 (1)	72 (30)	0
Decreased appetite	40 (31)	0	51 (21)	3 (1)
Vomiting	32 (25)	1 (1)	42 (17)	1 (0.4)
Fatigue	36 (28)	4 (3)	47 (19)	4 (2)
Asthenia	34 (26)	1 (1)	40 (16)	5 (2)
Alanine aminotransferase increased	26 (20)	7 (5)	67 (28)	10 (4)
AESIs by grouped term, n (%)				
Rash*	92 (71)	13 (10)	30 (12)	0
VTE†	13 (10)	3 (2)	11 (5)	7 (3)
ILD	2 (2)	1 (1)	0	0

PAPILLON[3]

First-line amivantamab + chemo vs chemo alone

EGFR Exon 20 insertion mutations

Most common AEs of any cause by preferred term (≥15%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
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)

*Grouping includes the following preferred terms: rash, dermatitis acneiform, rash maculo-papular, erythema, acne, rash pruritic, rash erythematous, rash macular, drug eruption, folliculitis, dermatitis, skin lesion, rash pustular, papule, rash follicular, exfoliative rash, pustule, rash papular, skin exfoliation. †Grouping includes the following preferred terms: pulmonary embolism, deep vein thrombosis, embolism, renal vein thrombosis, venous thrombosis limb, venous thrombosis, embolism venous, jugular vein thrombosis, superficial vein thrombosis, thrombophlebitis, thrombosis.

AE, adverse event; AESI, adverse event of special interest; chemo, chemotherapy; *EGFR*, epidermal growth factor receptor; ILD, interstitial lung disease; TEAE, treatment-emergent adverse event; VTE, venous thromboembolism.

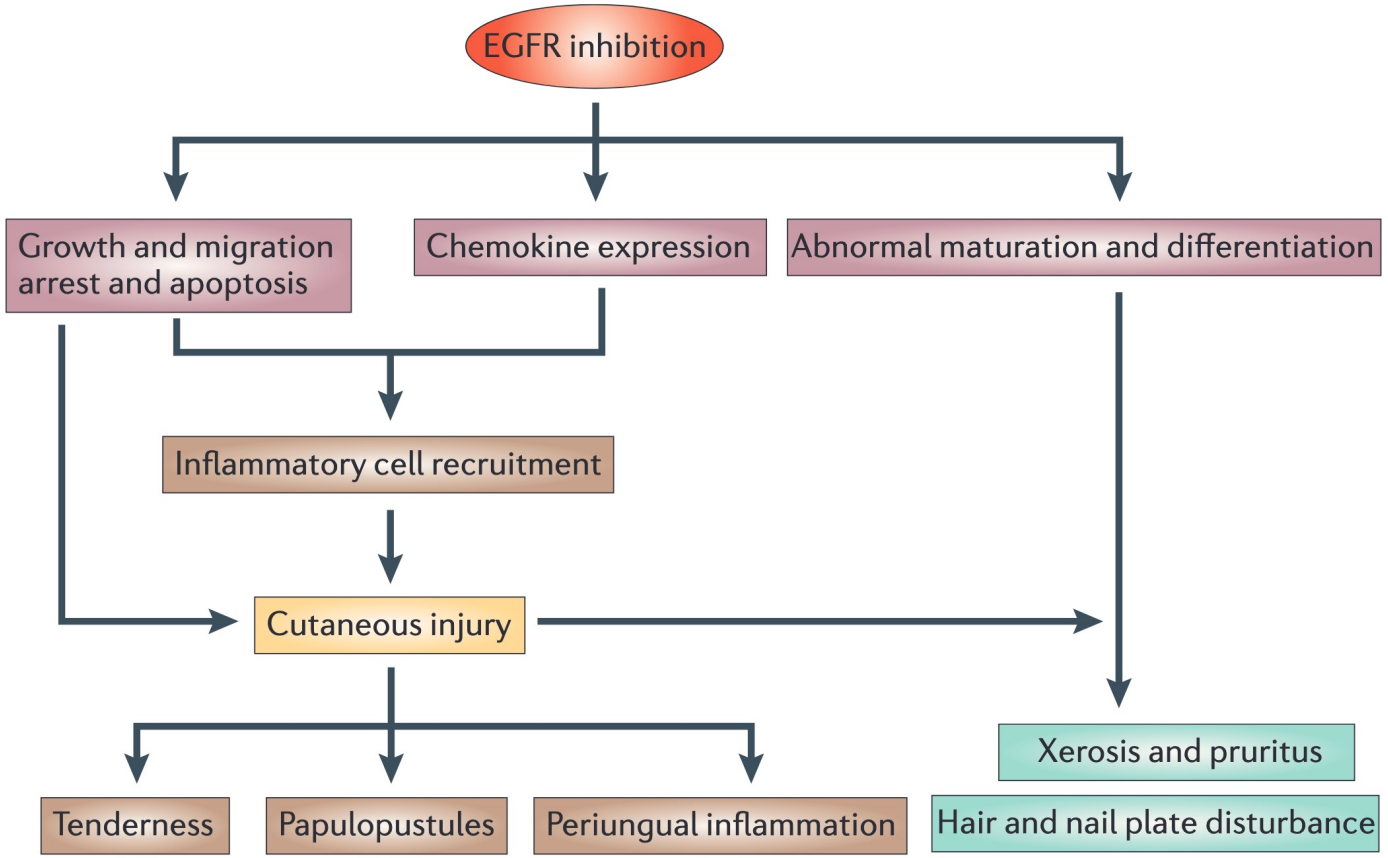
1. Cho B, et al. ESMO 2023. Oral presentation #LBA14. 2. Passaro A, et al. *Ann Oncol.* 2024;35:77–90. 3. Zhou C, et al. *N Engl J Med.* 2023;389:2039–2051.

Role of EGFR in Skin Physiology and Model of EGFR-Inhibitor-Induced Reactions

Box 1 | **Roles of EGFR in skin physiology**

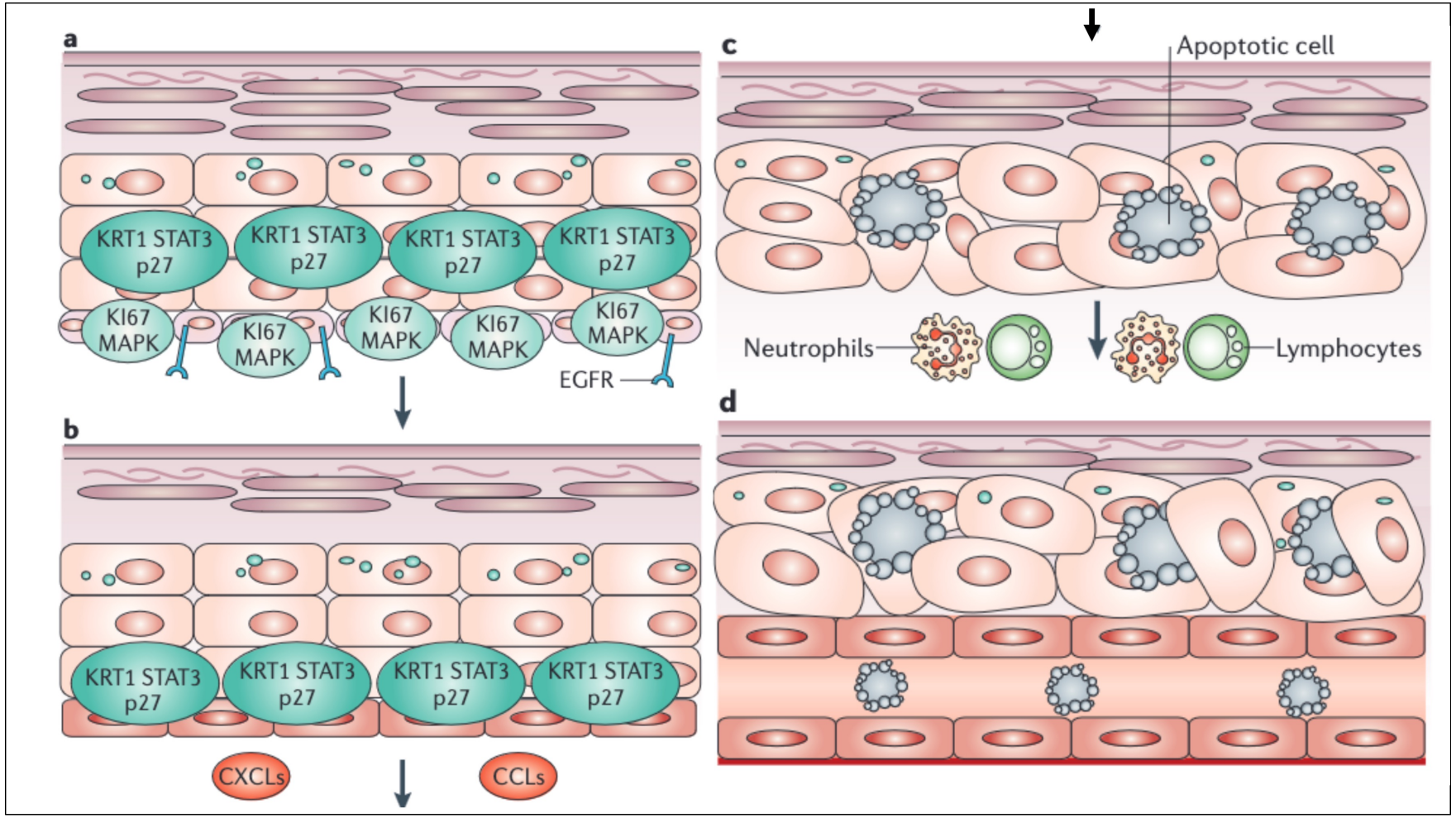
- Stimulation of epidermal growth
- Inhibition of differentiation
- Acceleration of wound healing
- Stimulation of keratinocyte migration through α2 integrins
- Activation of phosphatidylinositol turnover
- Activation of phospholipase A2 and, subsequently, arachidonic acid and prostaglandin E2
- Stimulation of vasoconstriction
- Diacylglycerol formation

EGFR, epidermal growth factor receptor.



Lacouture ME. *Nat Rev Cancer* 2006;6(10):803-12.

Effects of EGFR Inhibition in Skin



a. Normal expression of EGFR-dependent molecular markers.
b. During EGFR inhibitor therapy, pEGFR is abolished in all epidermal cells and MAPK expression is reduced. Inhibition of EGFR in basal keratinocytes leads to growth arrest and premature differentiation.
c. The release of inflammatory cell chemoattractants recruits leukocytes that release enzymes, causing apoptosis and tissue damage, with consequent apoptotic keratinocytes and dilated vessels.
d. Decreased epidermal thickness with a thin stratum corneum that lacks the characteristic basket-weave configuration, indicating abnormal differentiation.

Lacouture ME. *Nat Rev Cancer* 2006;6(10):803-12.

Management of EGFR Dermatologic Complications (not much has changed since 2015)

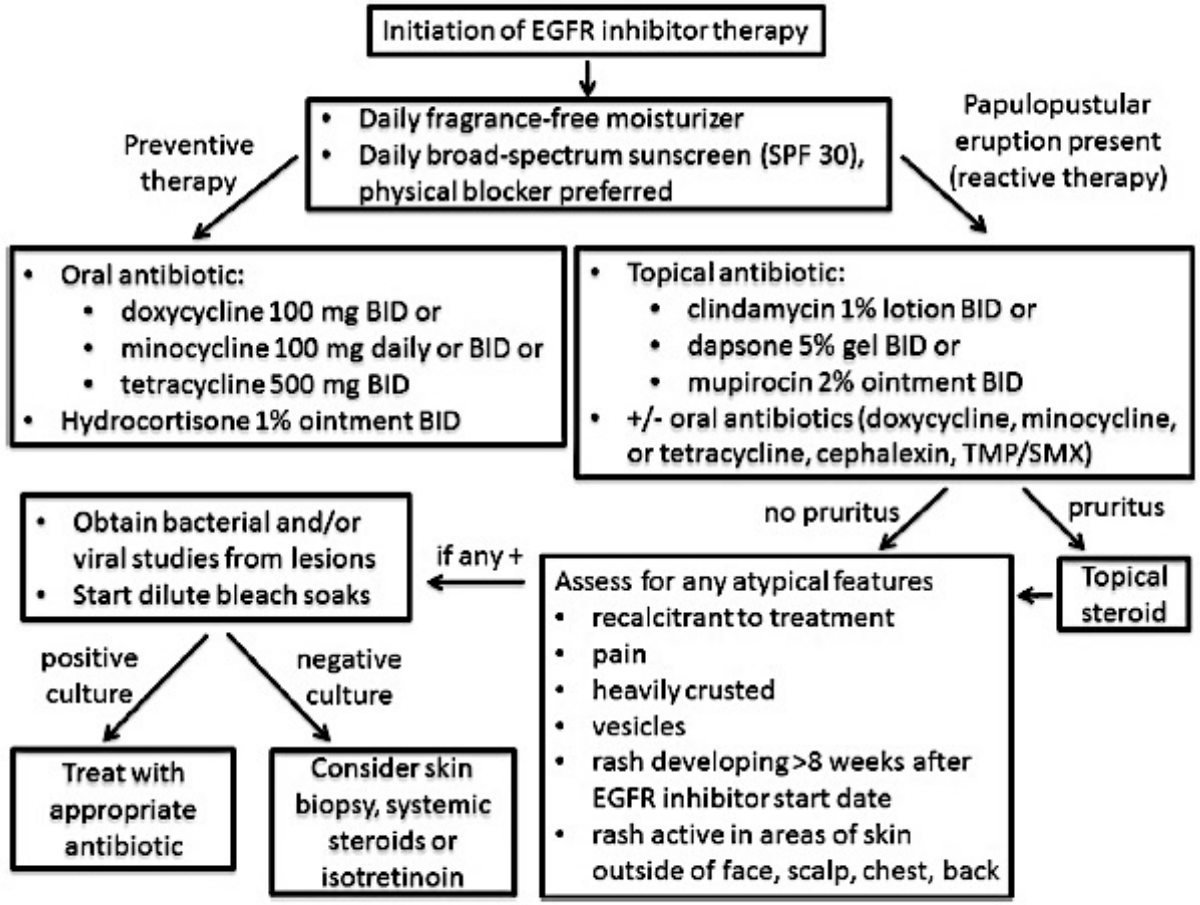
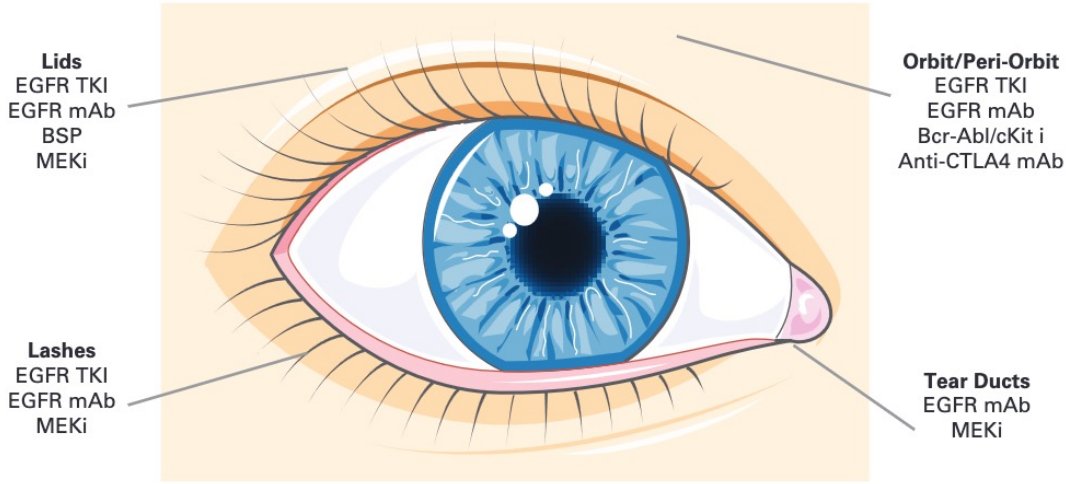
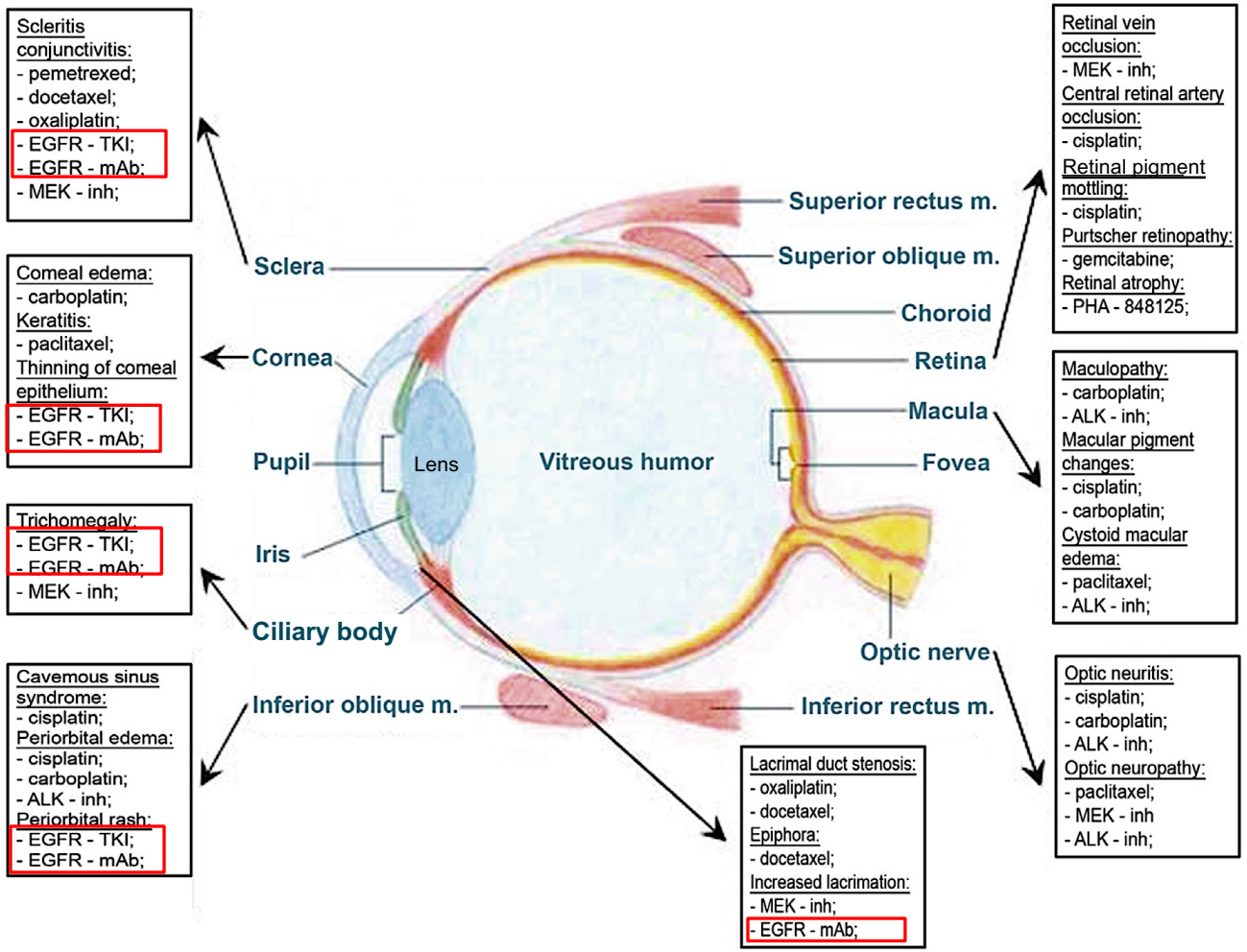


Fig. 2. Practical management of EGFR inhibitor-related papulopustular (acneiform) eruption.

Pugilese, Neal and Kwong Current Treatment Options Oncology 2015

Ocular Toxicity with EGFR Inhibition





Renouf DJ et al. *J Clin Oncol* 2012;30(26):3277-86.
Agustoni F et al. *Cancer Treat Rev* 2014;40(1):197-203.

Available results with and ongoing evaluation of a subcutaneous formulation of amivantamab

elcc European Lung Cancer Congress 2024

Subcutaneous Amivantamab Administered Every 4 Weeks (Q4W) in Patients With Advanced Solid Malignancies: The Phase 1b PALOMA Study

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PALOMA

Background

- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[1-3]
- IV amivantamab[a] has an IRR rate of 67% (grade ≥3: 2%)[4]
  - To manage IRRs, the first dose is split over 2 days, with an average administration time of ~4 hours
- PALOMA (NCT04606381),[b] a phase 1b study, evaluated PK and safety of SC amivantamab[4,5]
  - Q2W and Q3W SC doses have been previously reported[c]
  - SC amivantamab has an IRR rate of 16% (grade ≥3: 0%)
  - First dose does not need to be split over 2 days with an average administration time of 4–7 minutes[d]

A Q4W dose for SC amivantamab was evaluated for PK and safety

Table 1: Demographics and Baseline Characteristics

Characteristic, n (%)	SC amivantamab Q4W (n=19)
Median age, years (range)	62 (39–84)
Male / female	9 (47) / 10 (53)
Body weight: <80 kg / ≥80 kg	16 (84) / 3 (16)
Race	
Asian	13 (68)
White	6 (32)
No. of prior systemic therapies	
1–3	10 (53)
≥4	9 (47)
Cancer type	
NSCLC	17 (89)
Adenocarcinoma	16 (94)
Squamous cell carcinoma	1 (6)
Other solid tumor[e]	2 (11)

[a]Q2W IV dose (1050 mg or 1400 mg if ≥80 kg); Q3W IV dose (1750 mg or 2100 mg if ≥80 kg). [b]Eligible patients were those who had advanced solid tumors and who may benefit from EGFR/MET–directed therapy. [c]The Q2W and Q3W SC amivantamab doses were identified to be 1600 mg (2240 mg if ≥80 kg) and 2400 mg (3360 mg if ≥80 kg), respectively. [d]The recommended administration rate was ~2 to 3 mL/min. [e]One patient had colorectal cancer and the other had renal cell cancer.

EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; IV, intravenous; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous.

1. Moores SL, et al. *Cancer Res.* 2016;76(13):3942–3953. 2. Vijayaraghavan S, et al. *Mol Cancer Ther.* 2020;19(10):2044–2056. 3. Yun J, et al. *Cancer Discov.* 2020;10(8):1194–1209. 4. Minchom A, et al. Presented at: American Society of Clinical Oncology (ASCO) 2023; 2–6 June 2023; Chicago, IL, USA. 5. RYBREVANT® (amivantamab-vmjw). Published 1 April 2021. Accessed 31 January 2024. https://www.rybrevant.com.

PALOMA

Safety Profile

TEAEs (≥15%) by preferred term, n (%)	SC amivantamab Q4W (n=19)[a]	
	All grades	Grade ≥3
Associated with EGFR inhibition		
Dermatitis acneiform	14 (74)	2 (11)
Paronychia	11 (58)	1 (5)
Stomatitis	6 (32)	0
Pruritus	4 (21)	0
Associated with MET inhibition		
Peripheral edema	5 (26)	0
Hypoalbuminemia	3 (16)	0
Other		
Myalgia	8 (42)	0
Fatigue	6 (32)	0
Nausea	6 (32)	1 (5)
Back pain	5 (26)	1 (5)
Pyrexia	4 (21)	0
Vomiting	4 (21)	1 (5)
Dyspnea	4 (21)	1 (5)
Headache	4 (21)	0
IRR	3 (16)	0
Constipation	3 (16)	0
Cough	3 (16)	0
Pleural effusion	3 (16)	1 (5)
Hypomagnesemia	3 (16)	0
ALT increased	3 (16)	0

- Most common TEAEs were EGFR- and MET-related, primarily of grade 1 to 2
  - Safety profile of SC amivantamab Q4W was consistent with previous amivantamab monotherapy safety data[1]
- Grade ≥3 TEAEs with SC amivantamab occurred in 9 (47%) patients
  - 3 events were reported to be related to treatment (2 dermatitis acneiform, 1 paronychia)
- Cumulative grouped rash[b] of all grades occurred in 15 (79%) patients
- Two patients discontinued SC amivantamab, due to TEAEs both unrelated to treatment

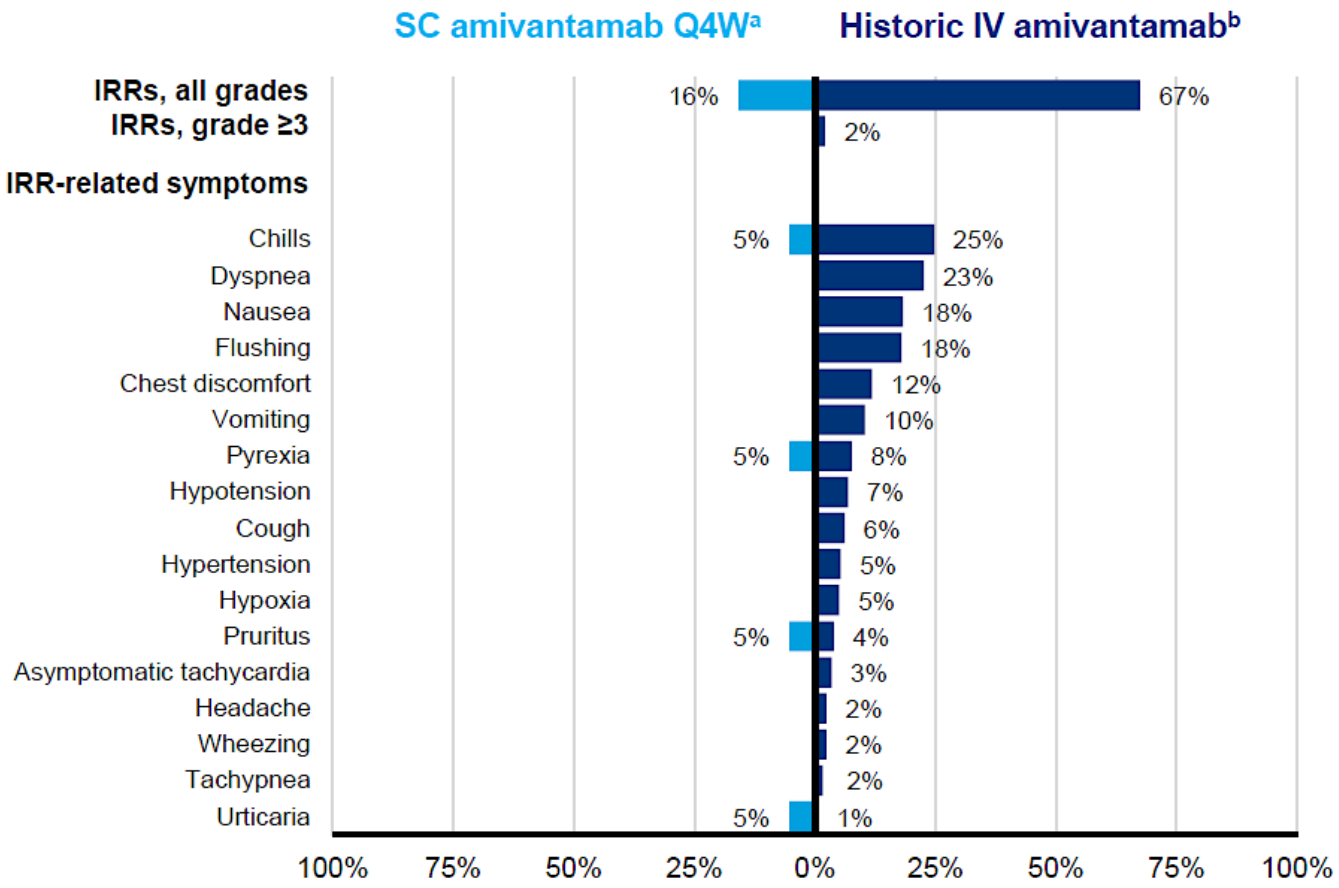
[a]Clinical cutoff: 18 December 2023. [b]Rash is defined by the following preferred terms: dermatitis, dermatitis acneiform, rash erythematous, and rash maculopapular.

ALT, alanine aminotransferase; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous; Q4W, every 4 weeks; TEAEs, treatment-emergent adverse events.

1. Minchom A, et al. Presented at: American Society of Clinical Oncology (ASCO) 2023; 2–6 June 2023; Chicago, IL, USA.

PALOMA

Incidence of IRRs and IRR-related Symptoms



- Three patients (16%) experienced IRRs with SC amivantamab Q4W; all were grade 1 to 2
  - IRR onset was 3, 11, and >24 hours following administration
- No patients required treatment for IRRs except for one patient who received diphenhydramine and clotrimazole for pruritus
- No recurrent IRRs were reported with consecutive administrations

[a]All IRR symptoms with SC administration are listed; clinical cut off: 18 December 2023.
[b]IRR symptoms in IV amivantamab are reported in all patients treated at the RP2D in the CHRYSALIS study based on a March 2021 data cutoff.
IRR, infusion-related reaction; IV, intravenous; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous.

Additional Subcutaneous Amivantamab Studies

PALOMA

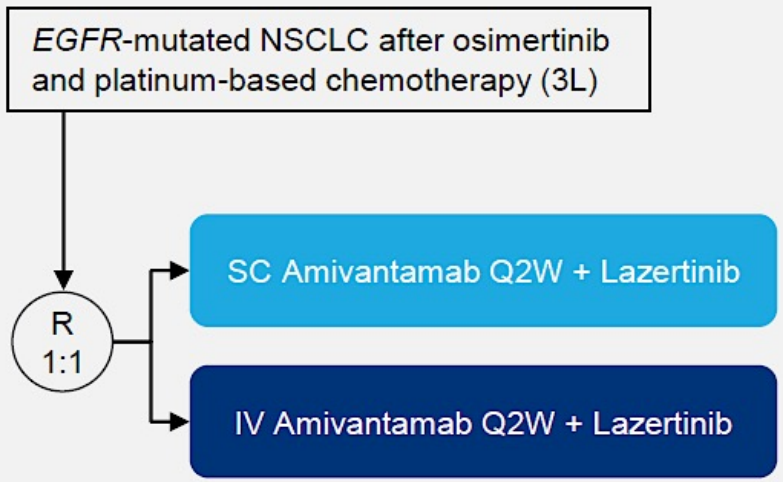
Phase 2 PALOMA-2

- SC Q2W and SC Q4W amivantamab + lazertinib in 1L *EGFR*-mutated NSCLC (**MARIPOSA** population)
- SC Q3W amivantamab + chemotherapy:
  - 1L *EGFR* Exon 20 insertion–mutated NSCLC (**PAPILLON** population)
  - *EGFR*-mutated NSCLC after progression on osimertinib (**MARIPOSA-2** population)

+ Additional cohorts

Primary endpoint: ORR per RECIST v1.1

Phase 3 PALOMA-3



Primary endpoint: PK non-inferiority[a]

[a]The co-primary PK non-inferiority endpoints were C_{trough} on Cycle 2 Day 1and $AUC_{D1\text{-}D15}$ of SC amivantamab versus IV amivantamab.

1L, first-line; 3L, third-line; AUC, area under the curve; C_{trough}, trough concentration; D, day; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; PK, pharmacokinetic; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomized; RECIST, Response evaluation criteria in solid tumors; SC, subcutaneous.

Subcutaneous amivantamab vs intravenous amivantamab, both in combination with lazertinib, in refractory EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Primary results, including overall survival (OS), from the global, phase 3, randomized controlled PALOMA-3 trial.

Leighl NB et al.

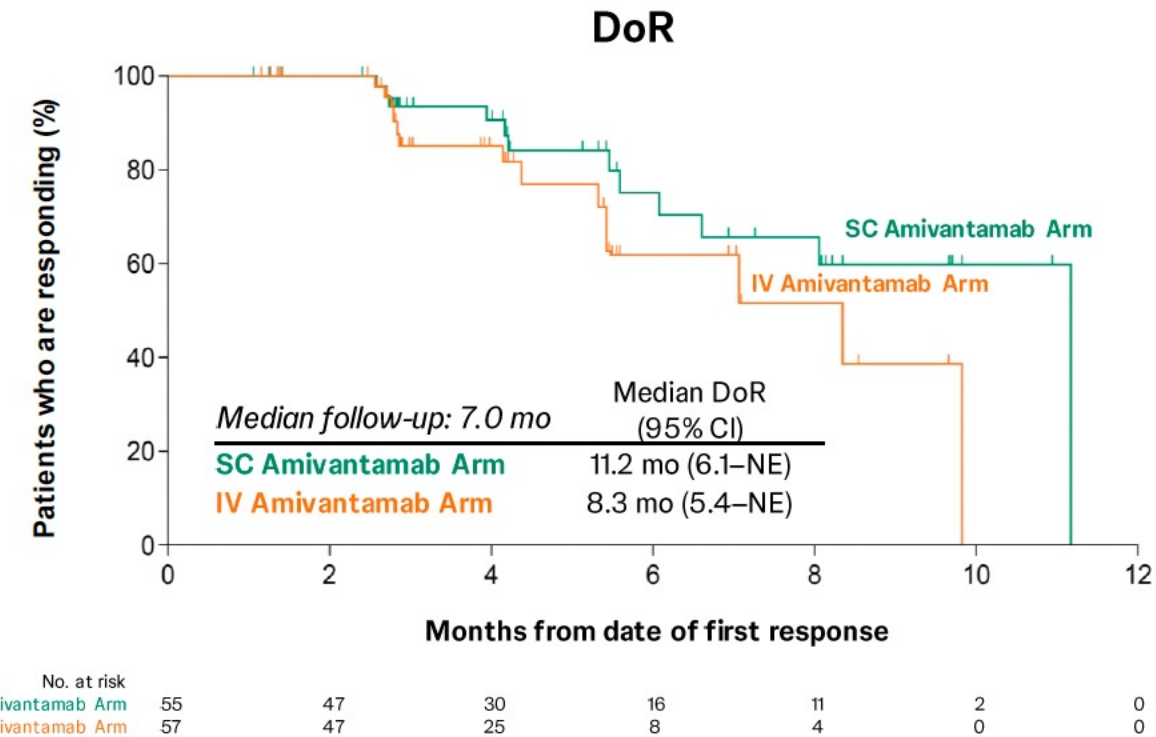
ASCO 2024; Abstract LBA8505

May 31, 2024 | 4:09 PM – 4:21 PM CDT

ORR and DoR

- ORR was noninferior between the SC and IV amivantamab arms
- DoR was 11.2 months in the SC arm vs 8.3 months in the IV arm, with twice as many patients, 29% in the SC arm vs 14% in the IV arm, having a response ≥6 months

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI)[a]		
All responders	30 (24–37)	33 (26–39)
	Relative risk, 0.92 (95% CI, 0.70–1.23); *P*=0.001	
Confirmed responders	27 (21–33)	27 (21–33)
	Relative risk, 0.99 (95% CI, 0.72–1.36); *P*<0.001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI)[b]	75 (69–81)	71 (64–77)
Median time to response (range), mo	1.5 (1.2–6.9)	1.5 (1.2–9.9)



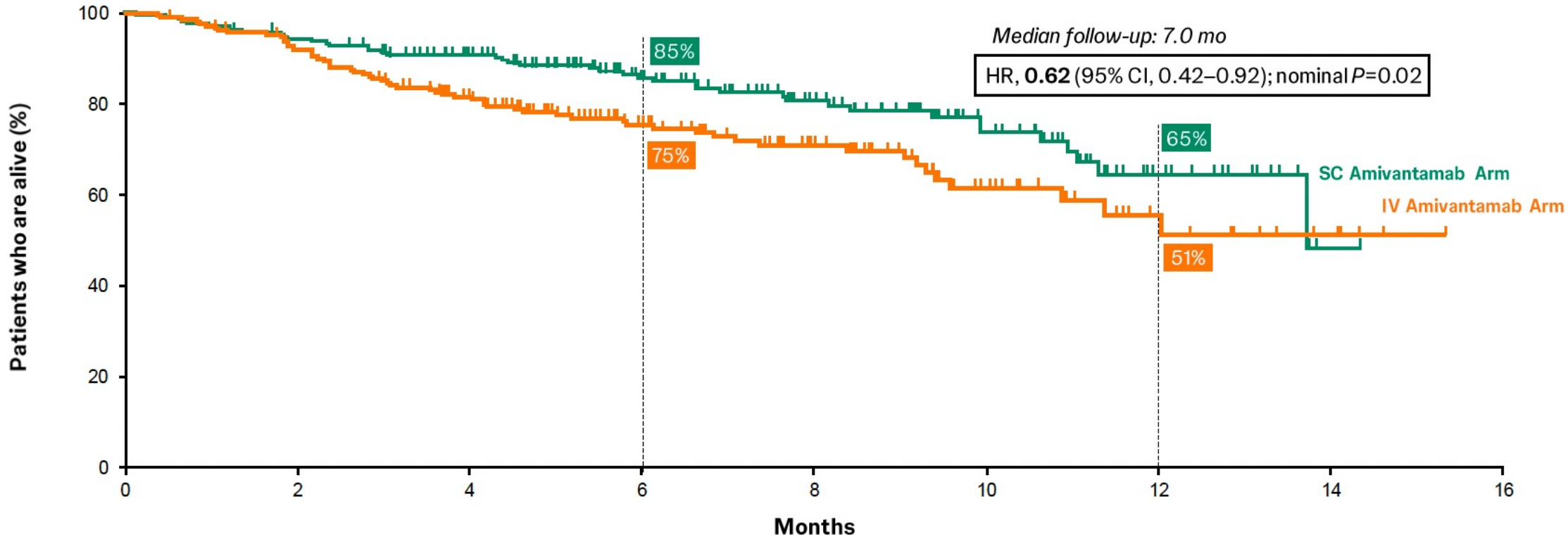
[a]The objective response (CR or PR) was assessed using RECIST v1.1 and analyzed using logistic regression. The lower bound of the 95% CI indicated ≥70% retention of ORR exceeding the predefined 60% retention assumed for determining noninferiority. [b]Not protocol specified.

CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD); DoR, duration of response; IV, intravenous; mo, months; NE, not estimable; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous; SD, stable disease.

Presented by NB Leighl at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Overall Survival

There was an OS benefit associated with SC amivantamab, with an HR of 0.62 compared to the IV amivantamab arm[a]



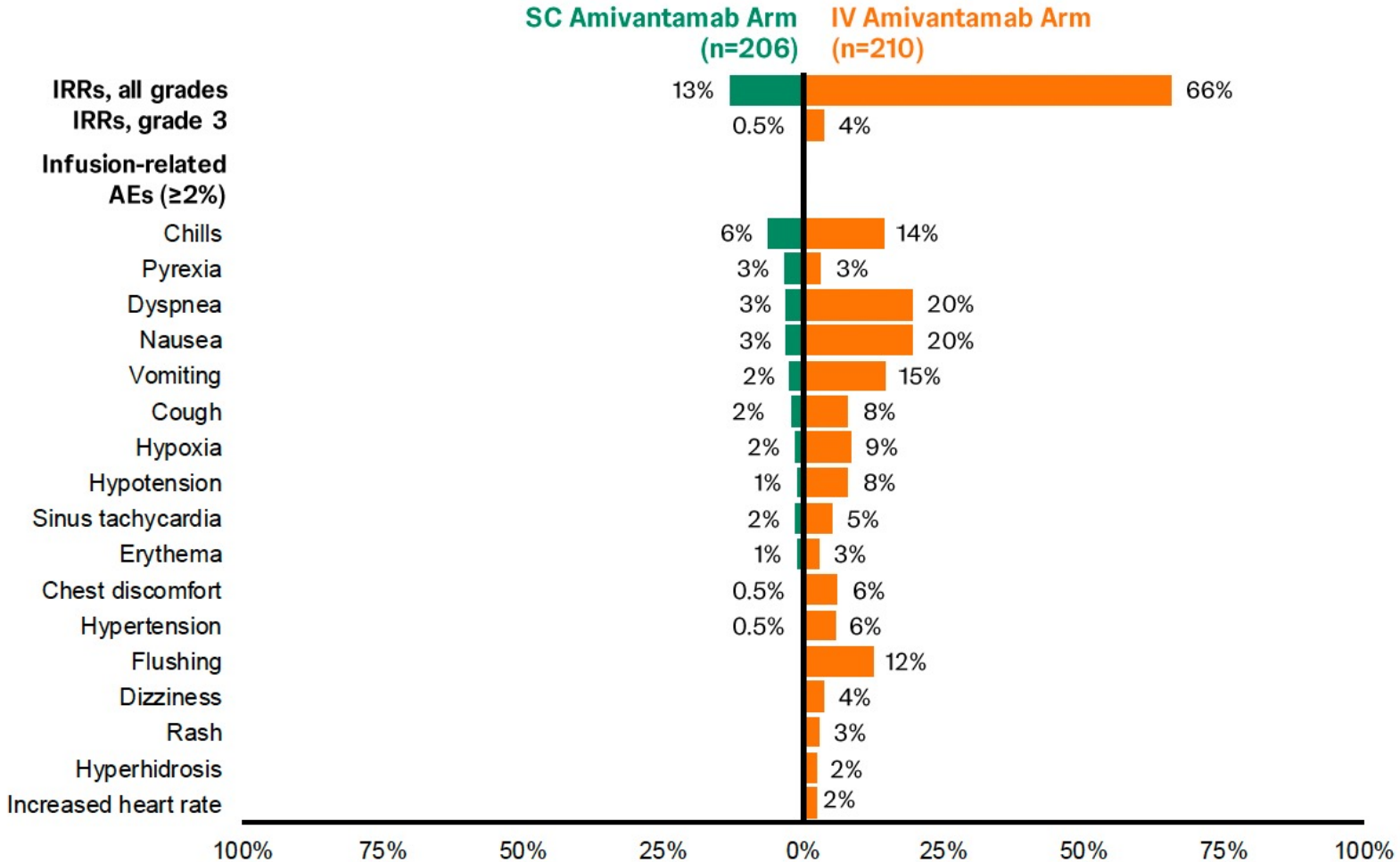
No. at risk									
SC Amivantamab Arm	206	192	163	109	71	36	10	0	0
IV Amivantamab Arm	212	191	144	92	51	24	10	1	0

Note: The efficacy population included all the patients who had undergone randomization. [a]There were 43 deaths in the SC amivantamab arm and 62 deaths in the IV amivantamab arm. Nominal *P* value was calculated from a log-rank test stratified by history of brain metastases, Asian race, *EGFR* mutation type (Ex19del or L858R), and last line of therapy (osimertinib or platinum-based therapy); the prespecified endpoint was exploratory and not part of hierarchical hypothesis testing.

CI, confidence interval; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; IV, intravenous; mo, months; OS, overall survival; SC, subcutaneous.

Presented by NB Leighl at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Incidence of IRR-related Symptoms



- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
  - There were no grade 4 or 5 IRRs
  - Most IRRs occurred during Cycle 1
- IRRs leading to hospitalization were not observed in the SC arm vs 2 events in the IV arm
- No IRR-related discontinuations occurred in the SC arm vs 4 events in the IV arm

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.

AE, adverse event; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous.

Presented by NB Leighl at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Spectrum of commonly occurring AEs (eg, GI toxicities, fatigue, myelosuppression) associated with patritumab deruxtecan

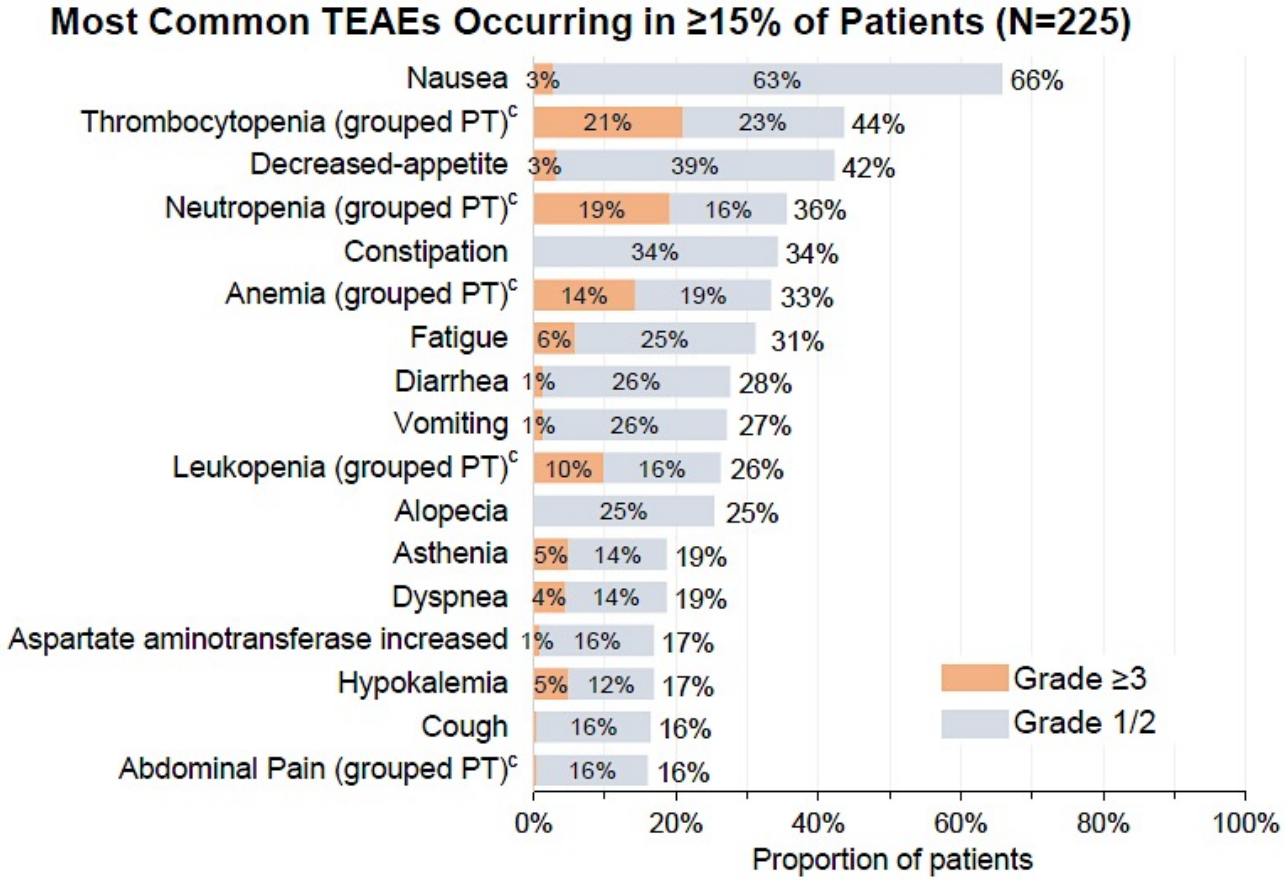
Patritumab Deruxtecan
HERTHENA-Lung01

The Safety Profile of HER3-DXd Was Manageable and Tolerable

- Median time to onset of adjudicated ILD was 53 (range, 9-230) days.

Safety summary	HER3-DXd 5.6 mg/kg (N=225)
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation[a]	16 (7.1)
Associated with treatment dose reduction	48 (21.3)
Associated with treatment dose interruption	91 (40.4)
Grade ≥3 TEAE, n (%)	146 (64.9)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[b]	4 (1.8)
Grade ≥3	102 (45.3)
Serious TEAE	34 (15.1)
Adjudicated interstitial lung disease, n (%) [All were adjudicated as treatment-related]	12 (5.3)
Grade 1	1 (0.4)
Grade 2	8 (3.6)
Grade 3	2 (0.9)
Grade 4	0
Grade 5	1 (0.4)

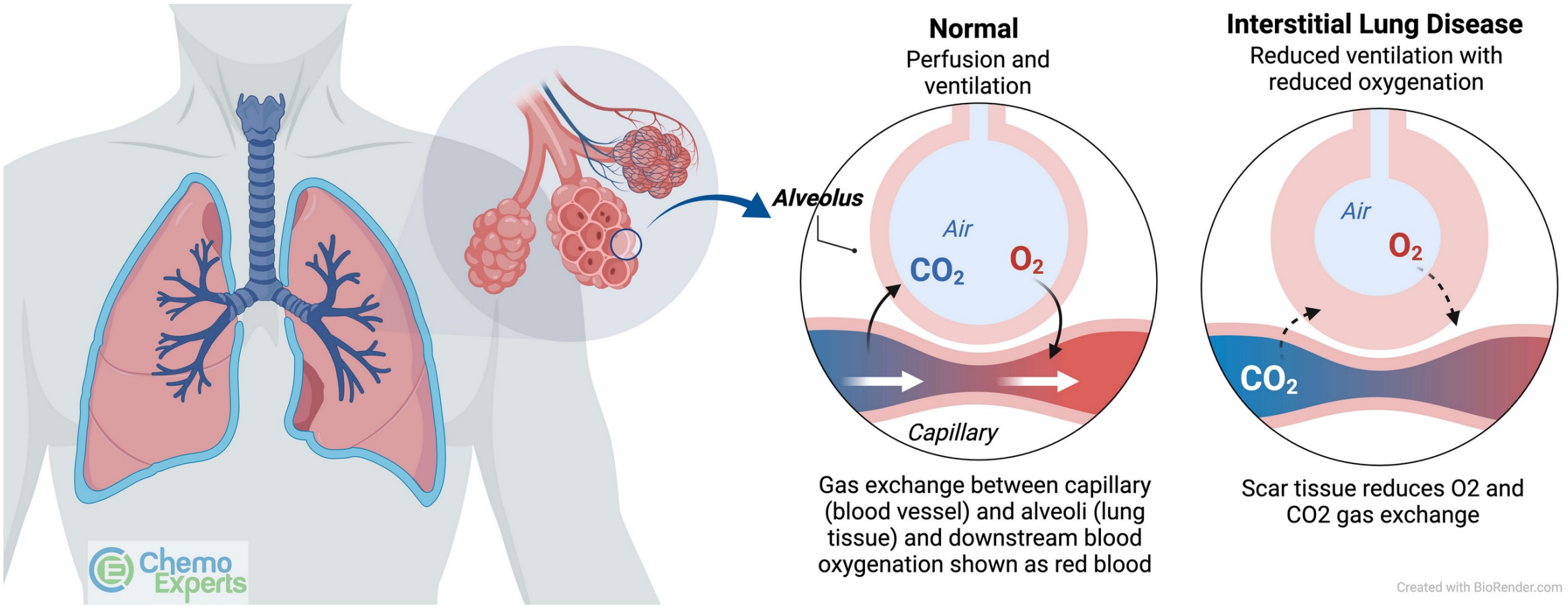
Primary data cutoff, 21 Nov 2022.
Median treatment duration: 5.5 (range, 0.7-18.2) months.



Any hematologic toxicities typically occurred early in treatment, were transient, and were not associated with clinical sequelae

Yu WCLC 2023

Pathophysiology of Interstitial Lung Disease (ILD)



https://www.chemoexperts.com/images/side-effects/Interstitial%20Lung%20Disease-%20ILD.jpeg

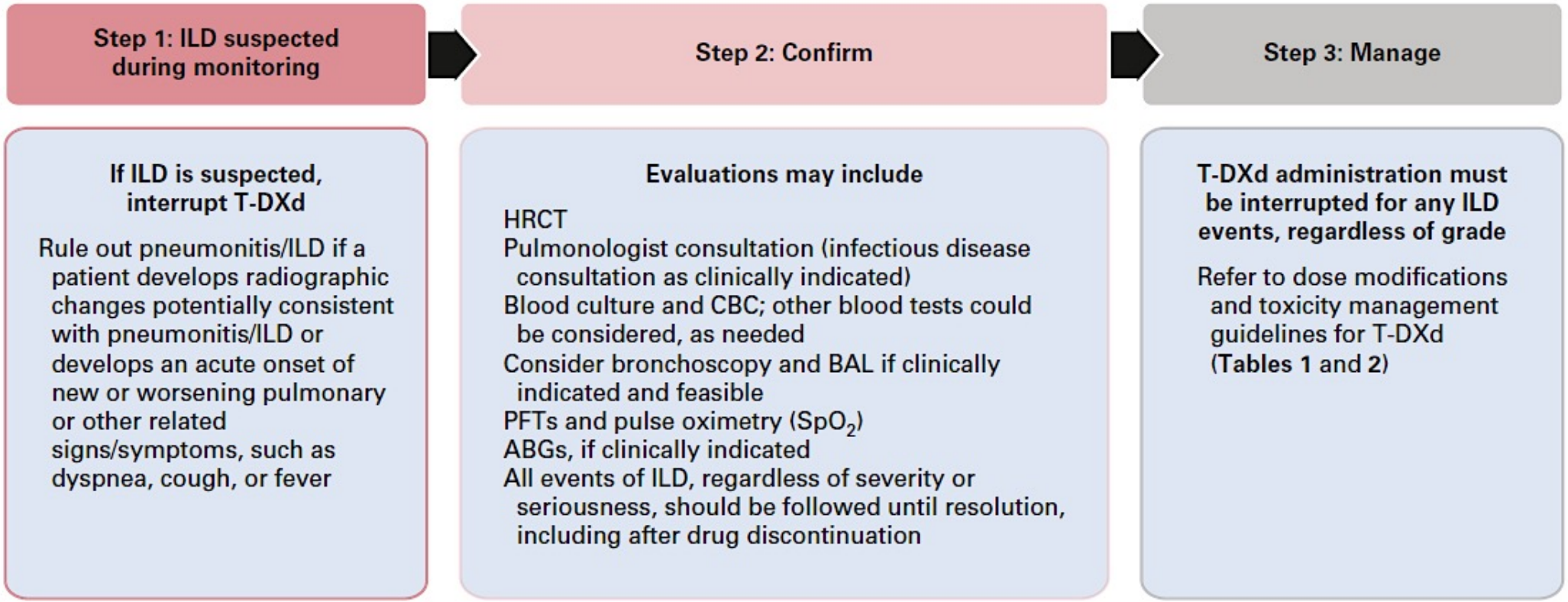
Pathophysiology, strategies to monitor for and manage ILD

Real-World Perspectives and Practices for Pneumonitis/ Interstitial Lung Disease Associated With Trastuzumab Deruxtecan Use in Human Epidermal Growth Factor Receptor 2–Expressing Metastatic Breast Cancer

Hope S. Rugo, MD[1]; Christine L. Crossno, PharmD[2]; Yaron B. Gesthalter, MD[3]; Kristen Kelley, MD[2]; Heather N. Moore, PharmD[4]; Mothaffar F. Rimawi, MD[5]; Kelly E. Westbrook, MD[4]; and Saundra S. Buys, MD[2]

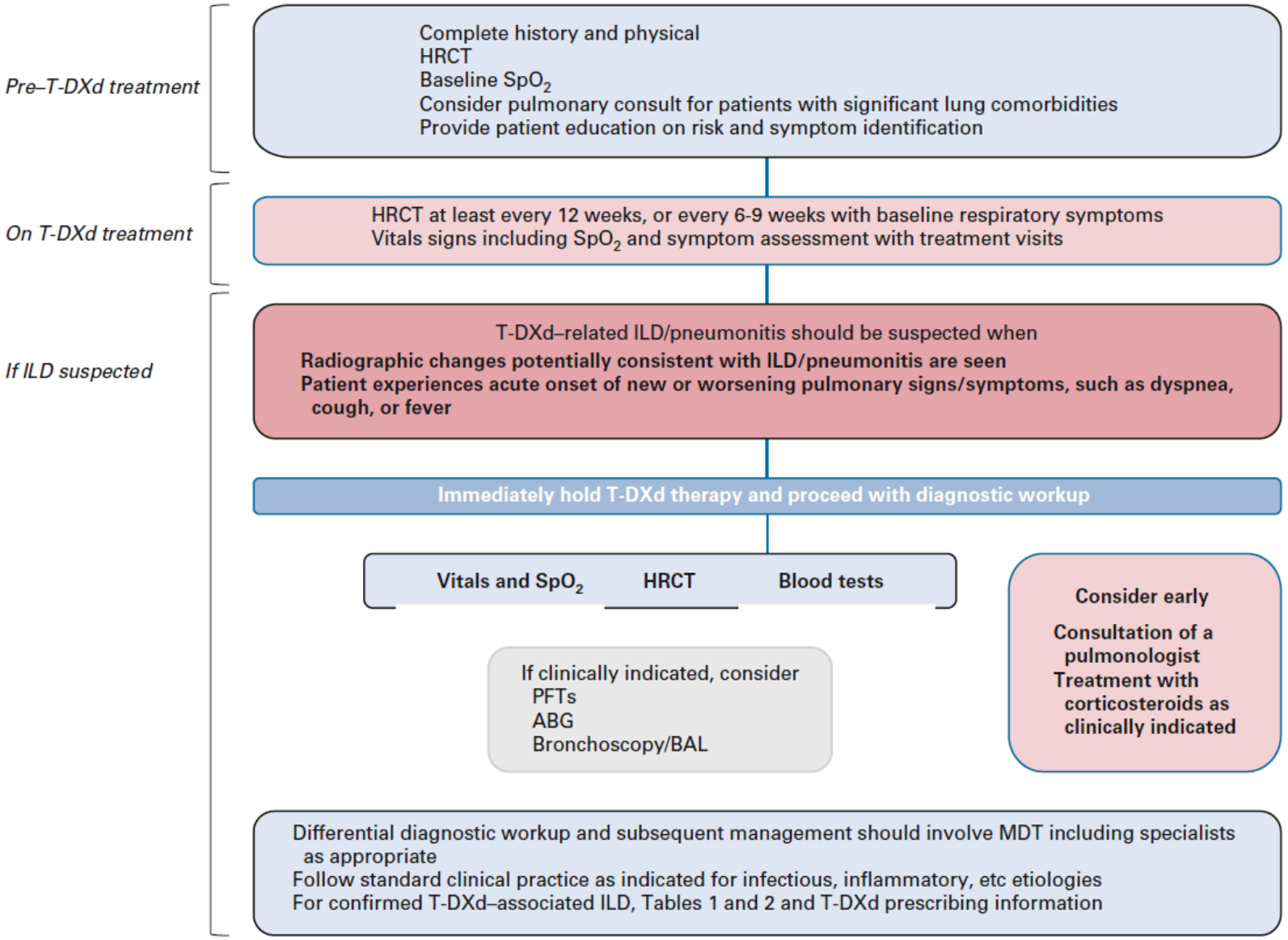
DOI https://doi.org/10.1200/OP.22.00480

"Multiple mechanisms of action play a role in pneumonitis/ILD related to various anticancer therapies (eg, radiation, cyclin-dependent kinase 4/6 inhibitors, and chemotherapy). Both cytotoxic and immune mechanisms of action may be involved. A recent study in cynomolgus monkeys suggested that alveolar macrophage update and redistribution of T-DXd could be involved in the development of pneumonitis/ILD. However, further research is still necessary to delineate the exact mechanism."



Rugo JCO Oncol Pract 2023

Strategies to monitor for and manage ILD



Rugo JCO Oncol Pract 2023

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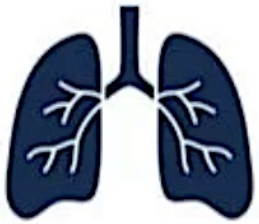				
Screen	**Scan**	**Synergy**	**Suspend Treatment**	**Steroids**
Careful patient selection is warranted before initiating therapies associated with ILD to optimize strategies based on baseline risk. **Screening continues during treatment with regular clinical**	**The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest. A baseline scan is recommended, with repeat scans to be performed every 6-**	**Minimizing the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected.**	**Therapy should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves.**	**The mainstay for treating drug-induced ILD remains corticosteroids, with dosing adapted to the toxicity grade.**

Adapted from Tarantino P and SM Tolaney. *JCO Oncol Pract* 2023;19:526-27.

Schedule Modification for ILD with HER3-DXd

Grade 1	Grade 2	Grade 3/4

The administration of HER3-DXd must be delayed. HER3-DXd can be restarted only if the event is fully resolved to grade 0:
• If resolved in ≤28 days from day of onset, maintain dose.
• If resolved in >28 days from day of onset, reduce dose 1 level.
Toxicity management:
• Monitor and closely follow up in 2 to 7 days for onset of clinical symptoms and pulse oximetry.
• Consider follow-up imaging in 1 to 2 weeks (or as clinically indicated).
• Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks.
• If diagnostic observations worsen despite initiation of corticosteroids, follow grade 2 guidelines (if patient is asymptomatic, then patient should still be considered as having toxicity grade 1 even if steroid treatment is given).
	Permanently discontinue patient from HER3-DXd.
	Toxicity management:
	• Promptly start systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT scan findings, followed by gradual taper over at least 4 weeks.
	• Monitor symptoms closely.
	• Reimage as clinically indicated.
	• If worsening or no improvement in clinical or diagnostic observations in 5 days,
	  ○ Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent); administration may be switched to IV (eg, methylprednisolone).
	  ○ Reconsider additional workup for alternative etiologies.
		○ Escalate care as clinically indicated.
		Permanently discontinue subject from HER3-DXd.
		Toxicity management:
		• Hospitalization required.
		• Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500 to 1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT findings, followed by gradual taper over at least 4 weeks.
		• Reimage as clinically indicated.
		• If still no improvement within 3 to 5 days,
		  • Reconsider additional workup for alternative etiologies.
		  • Consider other immunosuppressants and/or treat per local practice.

Worst toxicity grade NCI-CTCAE v5.0

Jänne PA et al. [Published correction appears in *Cancer Discov* 2022 June 2;12(6):1598]. *Cancer Discov* 2022;12(1):74-89.

Breakfast with the Investigators: Current and Emerging Role of Antibody-Drug Conjugates in the Treatment of Lung Cancer

A CME Symposium Held in Conjunction with the 2024 ASCO® Annual Meeting

Saturday, June 1, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rebecca S Heist, MD, MPH

Luis Paz-Ares, MD, PhD

Moderator

Jacob Sands, MD

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