The Implications of Recent Datasets for the Current and Future Management of Lung Cancer — A Review of Information from ESMO Congress 2024 and Other Conferences

A CME/MOC-Accredited Live Webinar

Tuesday, October 29, 2024
5:00 PM – 6:00 PM ET

Faculty

Suresh S Ramalingam, MD
Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

Faculty

Suresh S Ramalingam, MD
Executive Director, Winship Cancer Insitute
Roberto C Goizueta Chair for Cancer Research
Emory University School of Medicine
Atlanta, Georgia

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Gregory J Riely, MD, PhD
Ning Zhao and Ge Li Chair in Lung Cancer Research
Vice Chair of Clinical Research, Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

Commercial Support

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Dr Love — Disclosures

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Dr Ramalingam — Disclosures

No relevant conflicts of interest to disclose

Dr Riely — Disclosures

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Data and Safety Monitoring Board/Committee	Novartis

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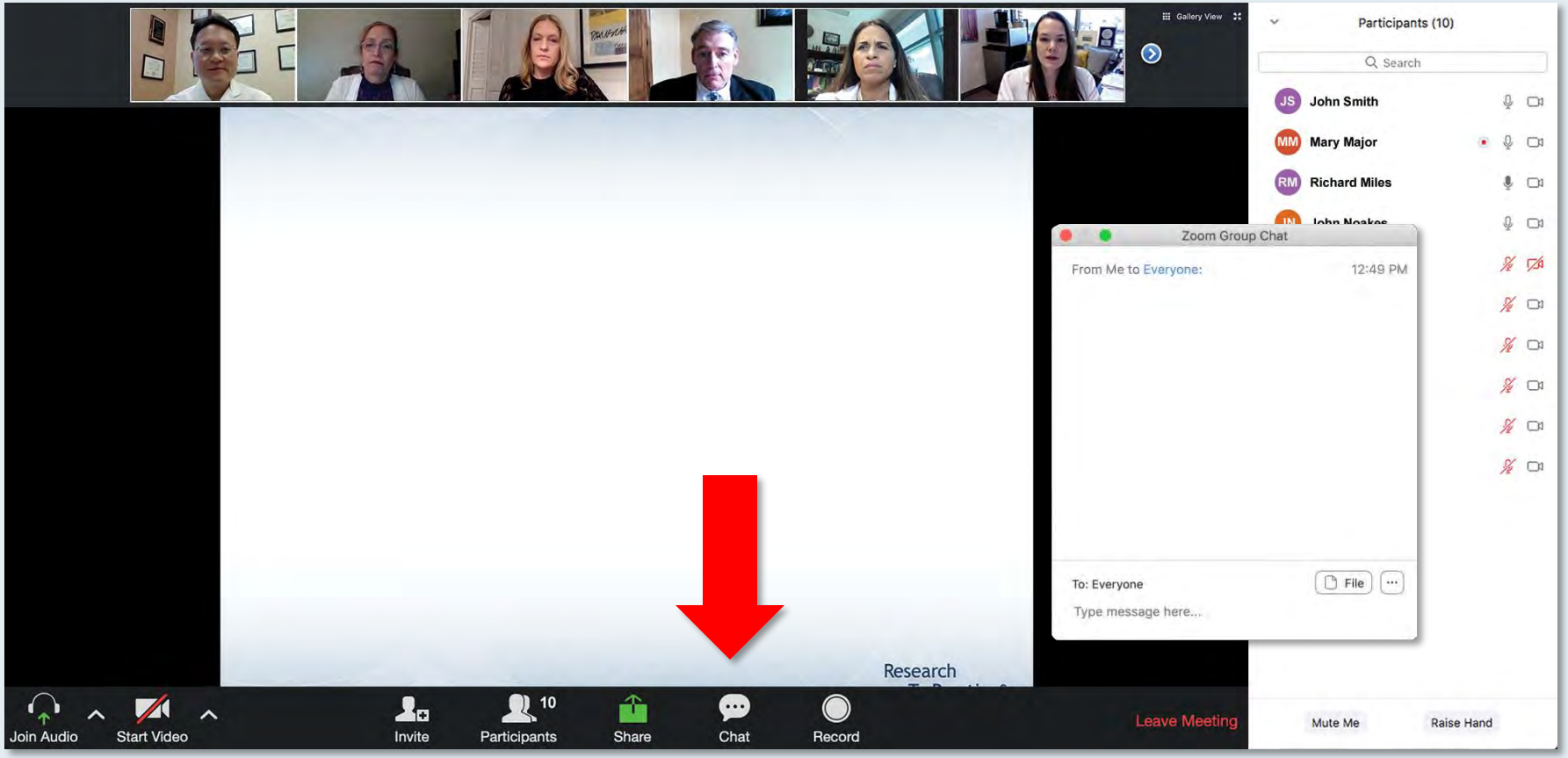

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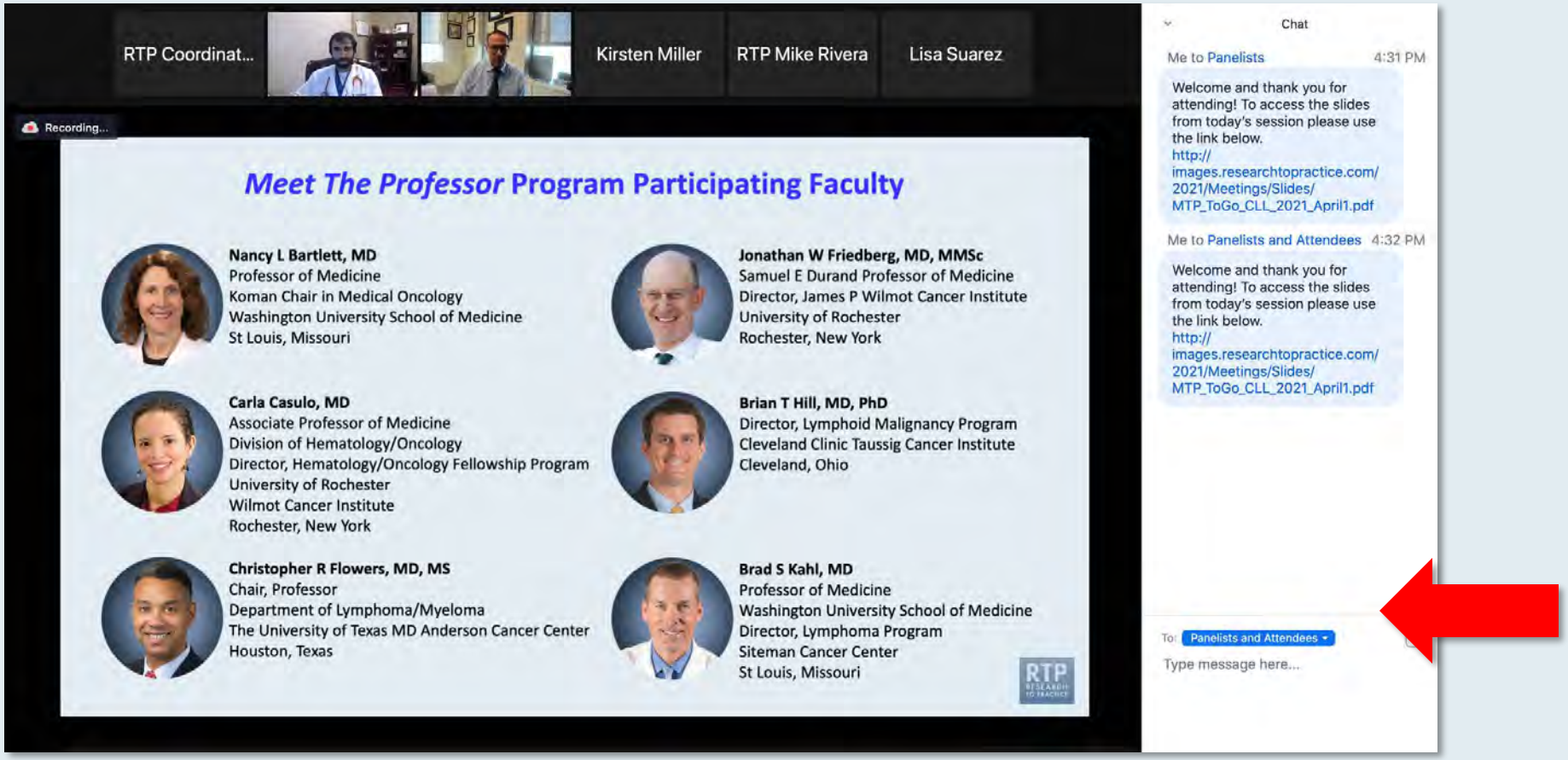

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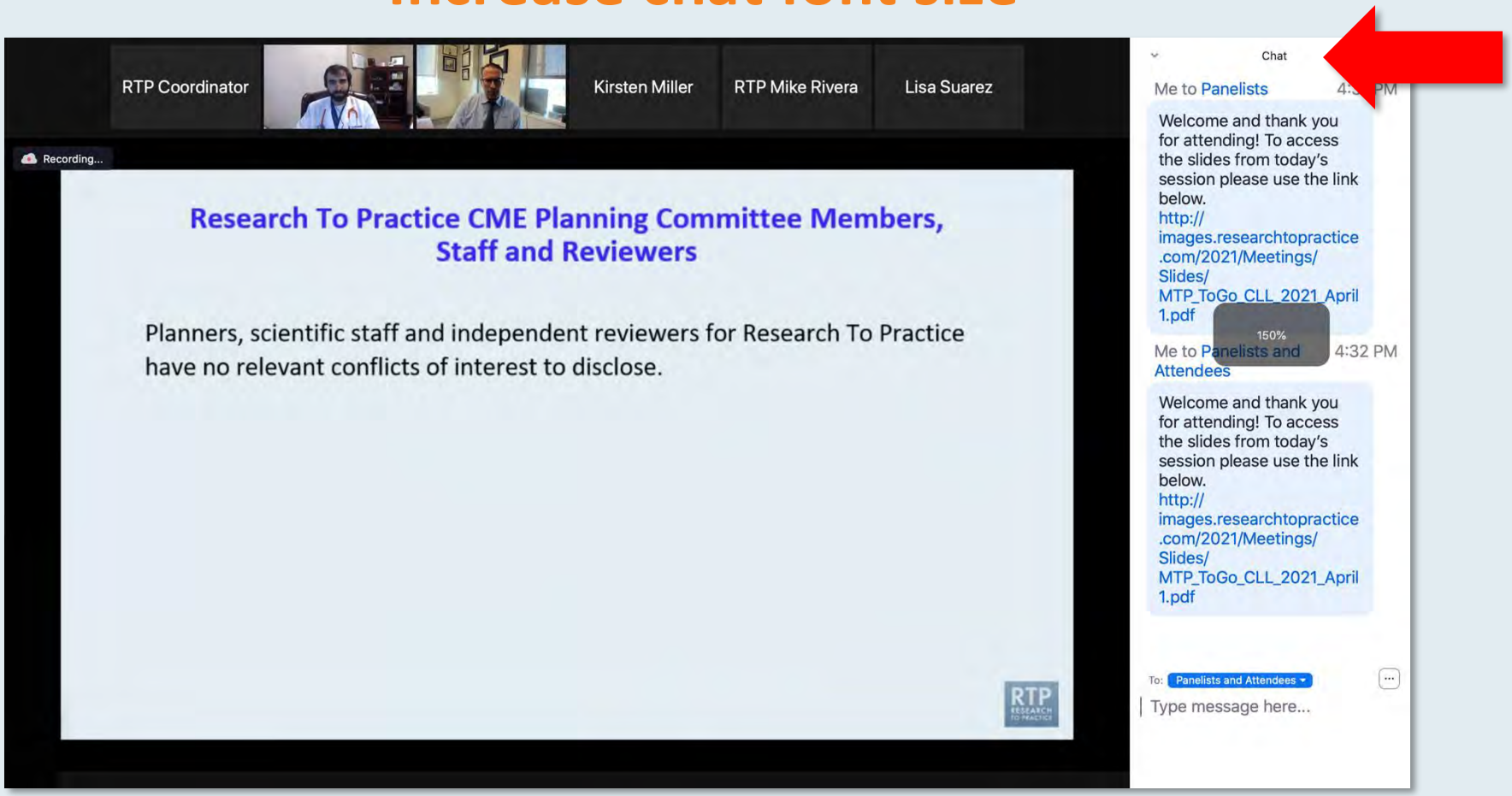

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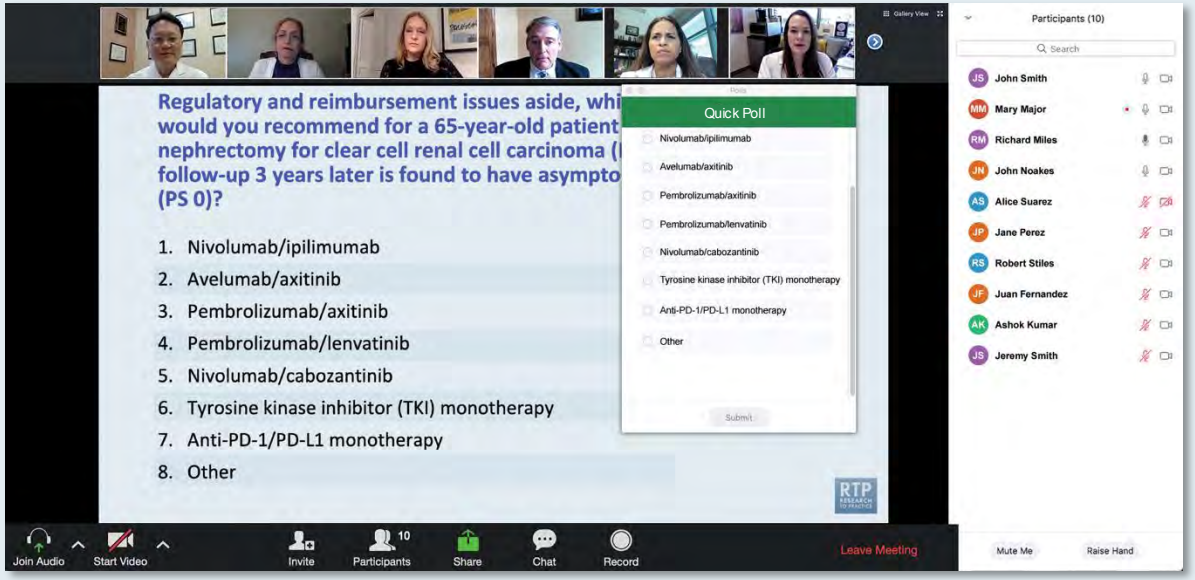

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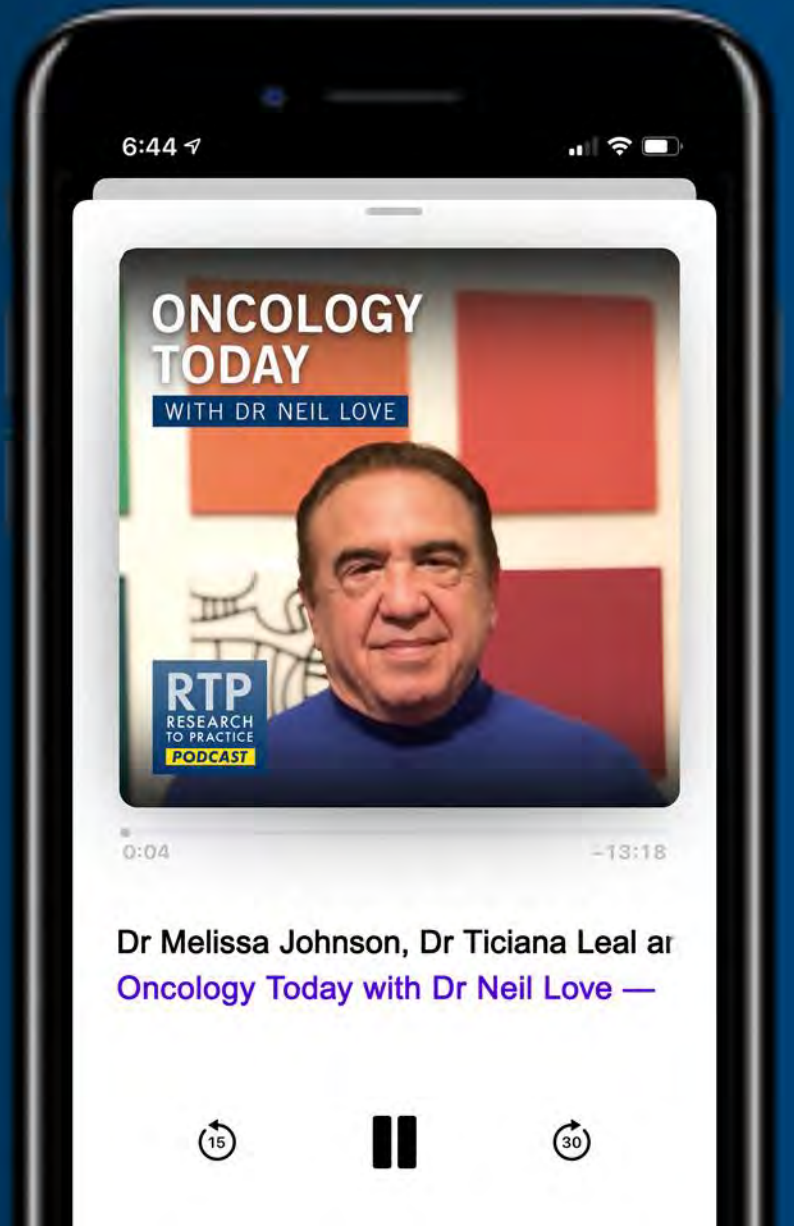

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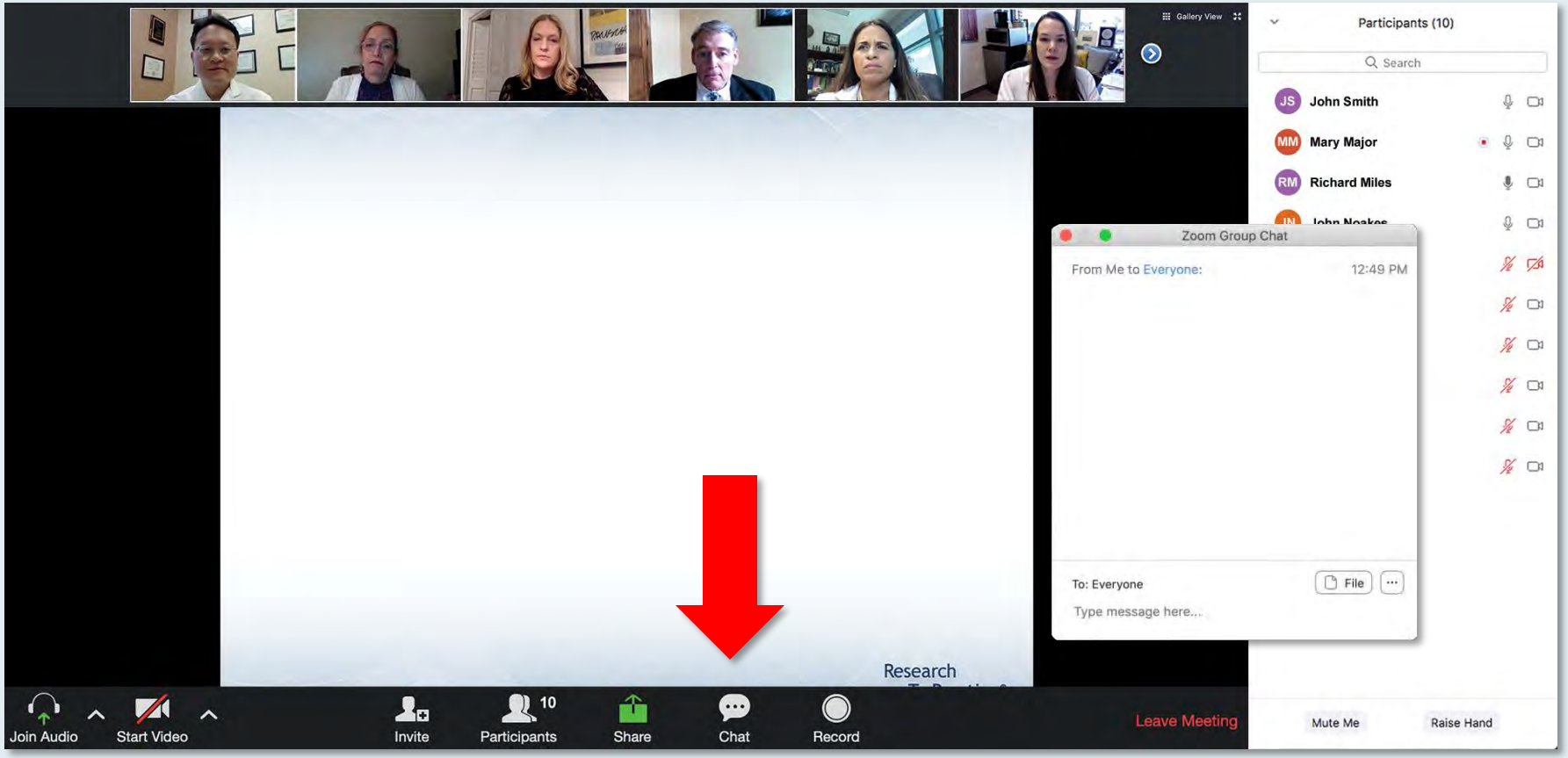

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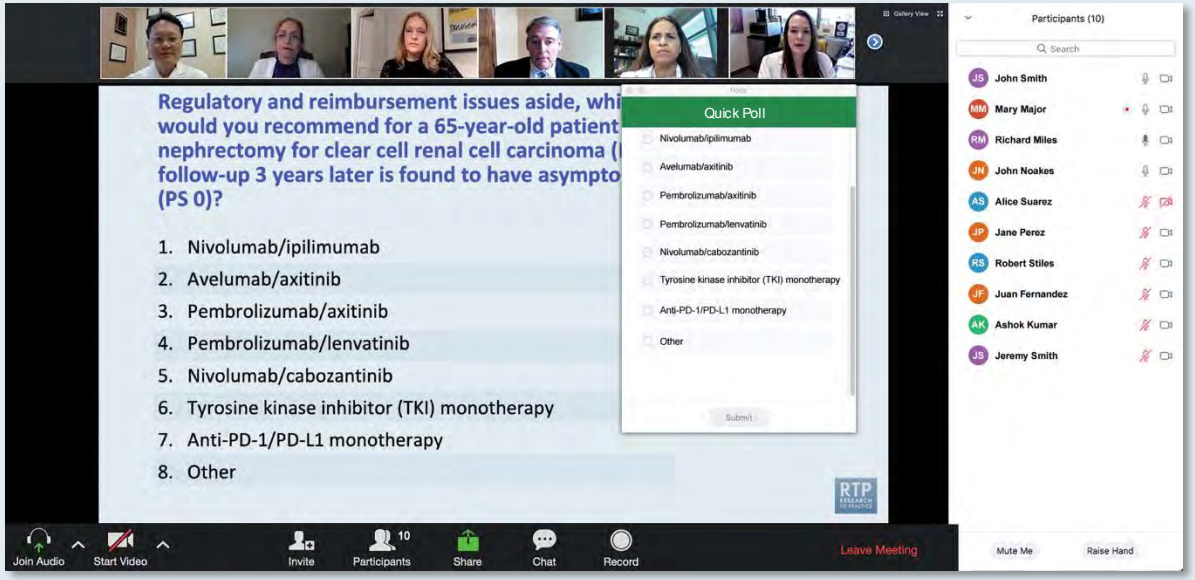

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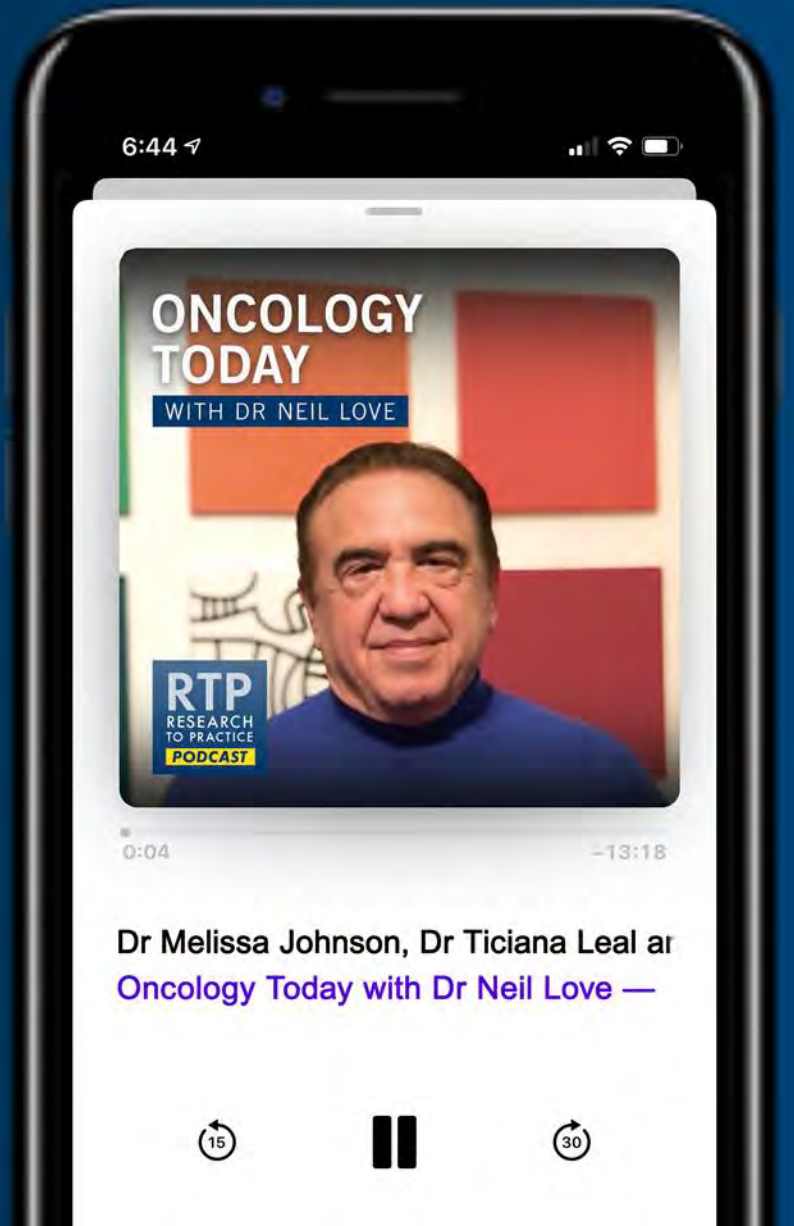

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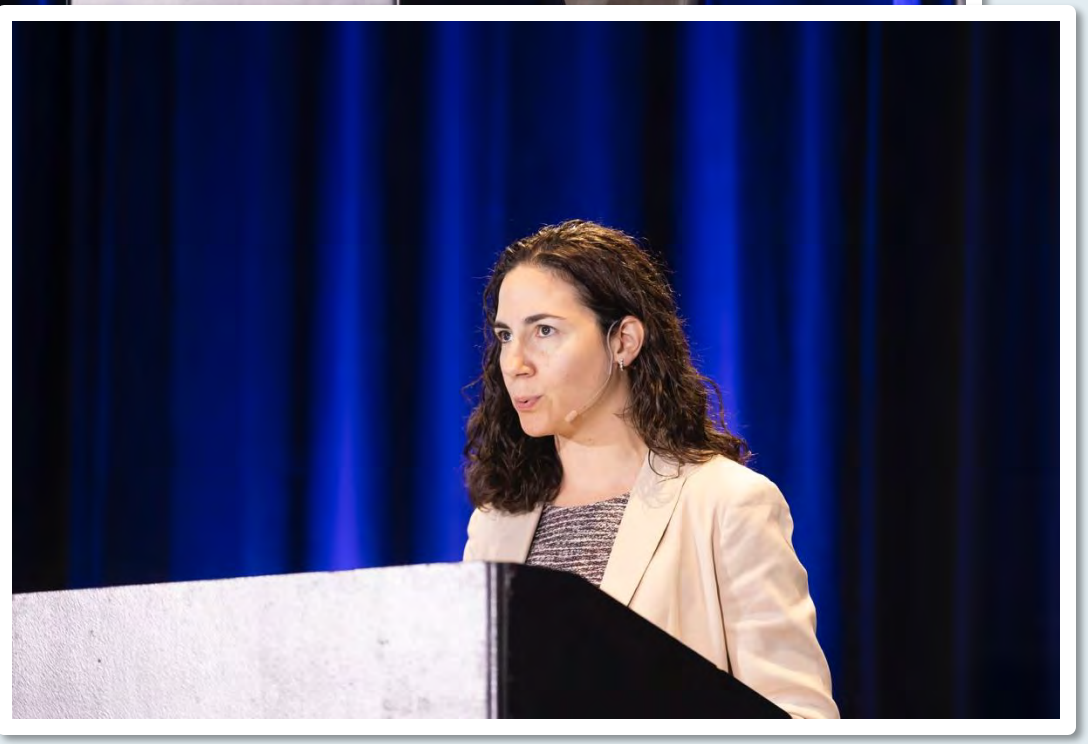

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Introduction: Tumor Treating Fields

Module 1: Nontargeted Therapy for Lung Cancer — Dr Ramalingam

Module 2: Targeted Therapy for Non-Small Cell Lung Cancer — Dr Riely

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FDA Approves Tumor Treating Fields (TTFields) for the Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

Press Release: October 15, 2024

The FDA has approved TTFields for concurrent use with PD-1/PD-L1 inhibitors or docetaxel in the treatment of metastatic NSCLC for adult patients who have experienced disease progression on or after a platinum-based regimen.

Approval was based on results of the Phase III LUNAR trial that compared TTFields concurrent with PD-1/PD-L1 inhibitors or docetaxel (experimental arm) to PD-1/PD-L1 inhibitors or docetaxel alone (control arm) for patients with metastatic NSCLC whose disease progressed during or after platinum-based therapy.

The primary endpoint of the study was achieved demonstrating a statistically significant and clinically meaningful 3.3-month (p = 0.04) extension in median overall survival (OS) for patients who received TTFields concurrently with a PD-1/PD-L1 inhibitor or docetaxel (n = 145). The group treated with TTFields concurrently with a PD-1/PD-L1 inhibitor or docetaxel had a median OS of 13.2 months (95% CI, 10.3 to 15.5 months) compared to a median OS of 9.9 months (95% CI, 8.2 to 12.2 months) in the group who received a PD-1/PD-L1 inhibitor or docetaxel (n = 146).

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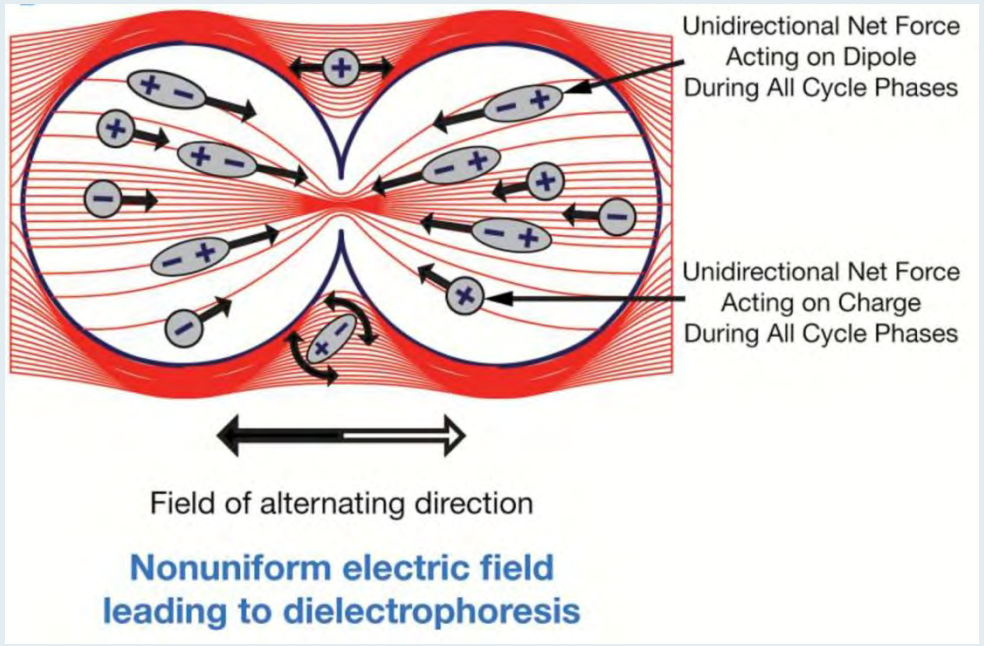
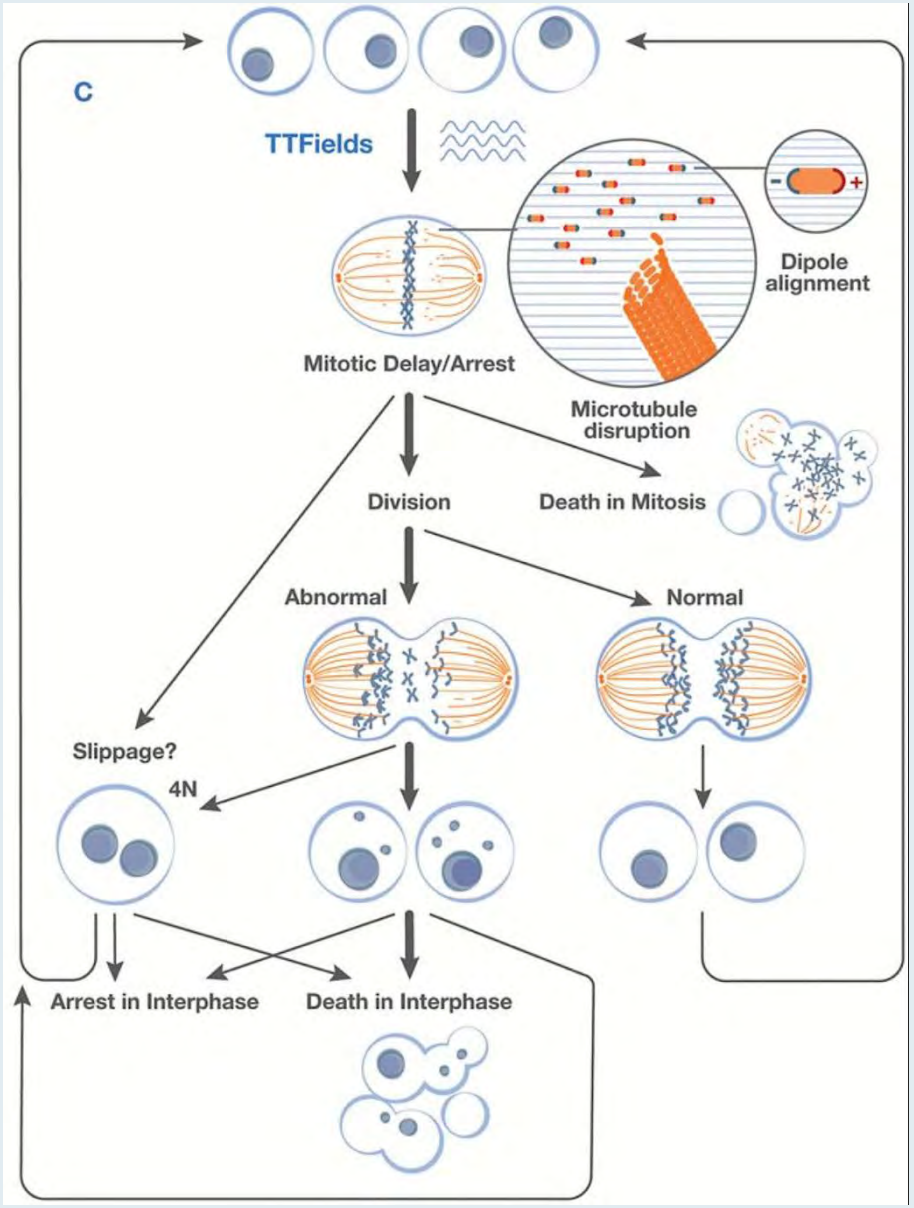
https://www.novocure.com/fda-approves-novocures-optune-lua-for-the-treatment-of-metastatic-non-small-cell-lung-cancer/

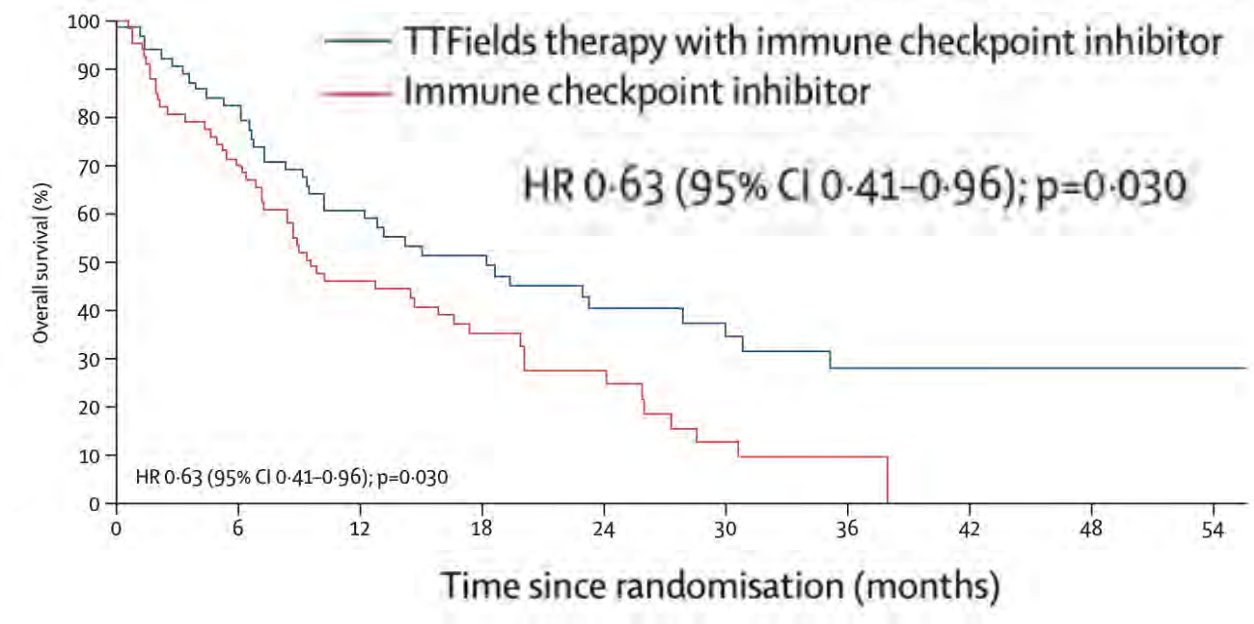
TTFields Mechanism of Action

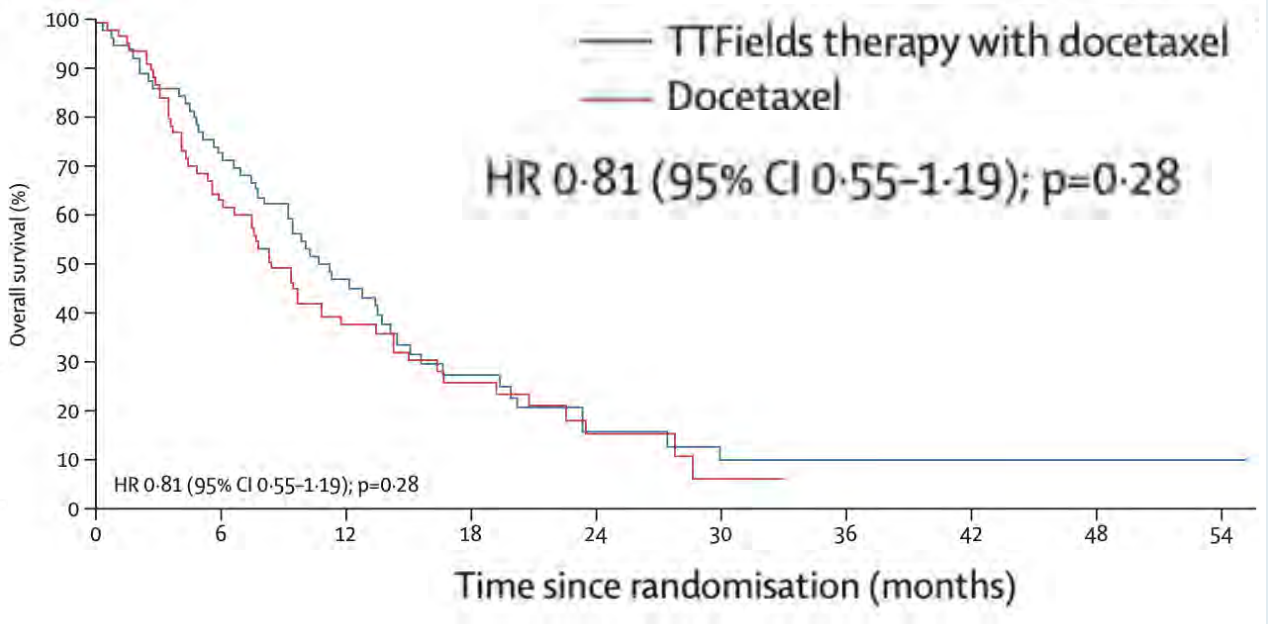




Hottinger AF et al. *Neuro Oncol* 2016;18(10):1338-49.

LUNAR: TTFields with ICI vs TTFields with Docetaxel – OS Outcomes





Leal T et al. ASCO 2023;Abstract LBA9005. Leal T et al. *Lancet Oncol* 2023;24(9):1002-17.

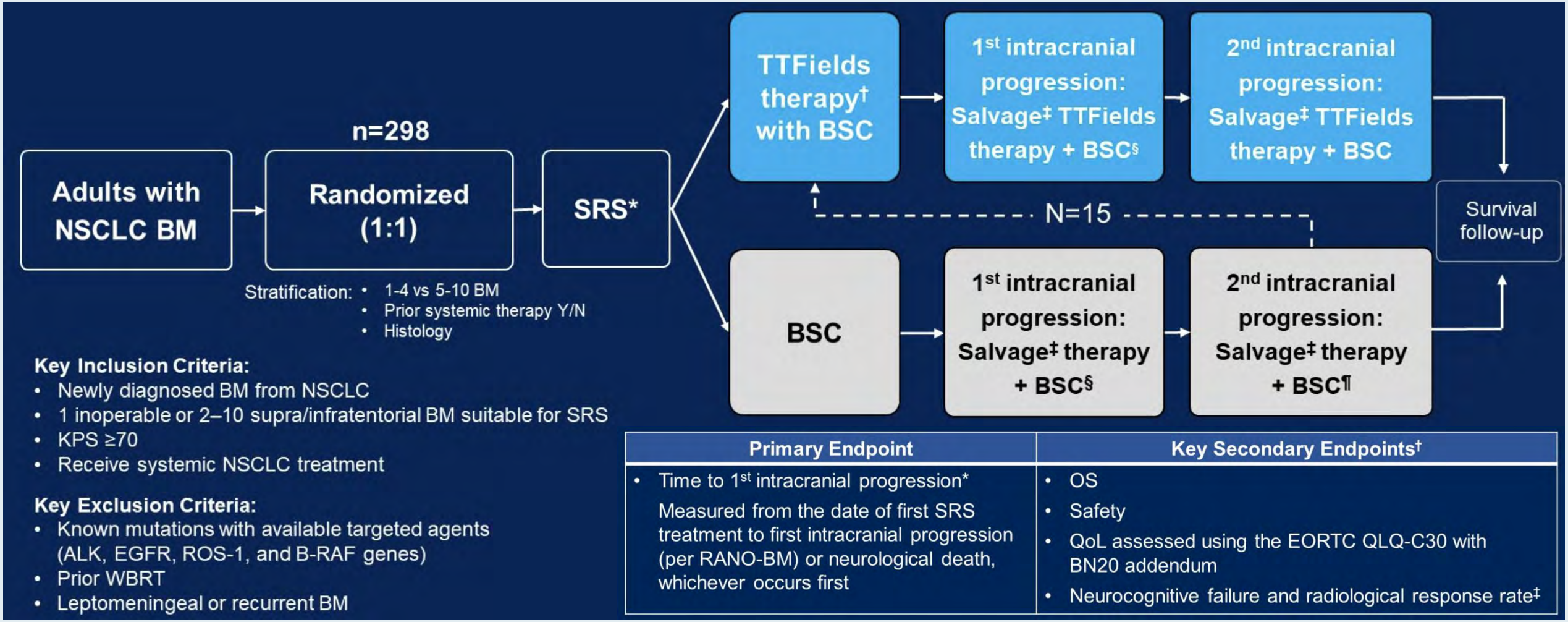
LUNAR: Safety Outcomes

	TTFields + SOC (n=133)		SOC (n=134)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE*	97%	59%	91%	56%
Most frequent AEs				
Dermatitis	**43%**	**2%**	**2%**	**0%**
Fatigue	28%	4%	37%	8%
Musculoskeletal pain	36%	3%	27%	4%
Dyspnea	20%	7%	25%	3%
Anemia	23%	8%	22%	8%
Diarrhea	19%	2%	19%	0%
Cough	18%	0%	19%	1%
Nausea	19%	0%	16%	1%
Leukopenia	17%	14%	18%	14%
Pneumonia	15%	11%	17%	11%
Alopecia	10%	0%	17%	1%
Respiratory tract infection	15%	3%	16%	0%
Localized edema	15%	1%	16%	2%
Any serious AE	53%		38%	
Any AE leading to discontinuation	36%		20%	
Any AE leading to death	10%		8%	

AE = adverse event

Leal T et al. ASCO 2023;Abstract LBA9005. Leal T et al. *Lancet Oncol* 2023;24(9):1002-17.

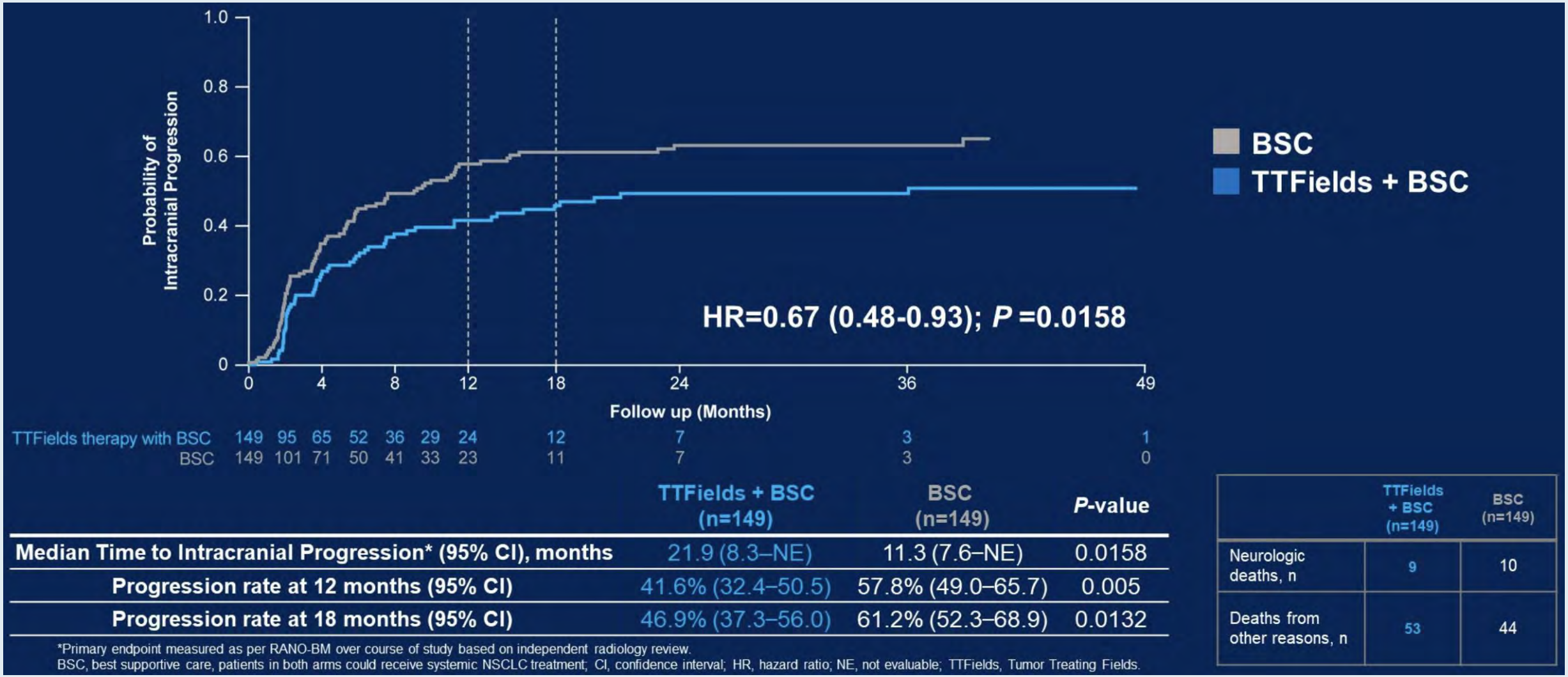
METIS: An International, Multicenter Phase III Randomized Study of TTFields for NSCLC with Brain Metastases



SRS = stereotactic radiosurgery; BSC = best supportive care; BM = brain metastases; WBRT = whole brain radiotherapy; QoL = quality of life

Mehta MP et al. ASCO 2024;Abstract 2008.

METIS: Primary Endpoint of Time to First Intracranial Progression or Neurologic Death



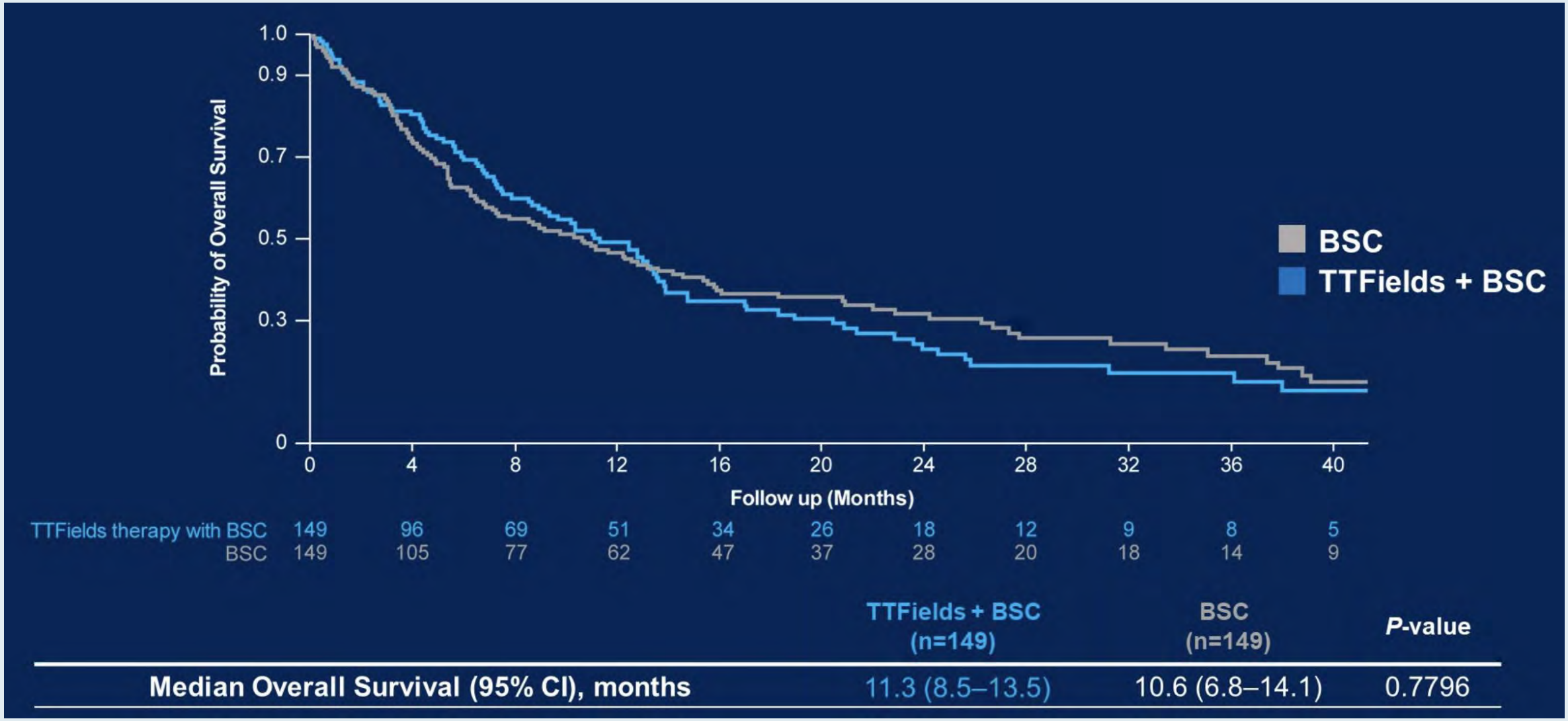
	TTFields + BSC (n=149)	BSC (n=149)	*P*-value
Median Time to Intracranial Progression* (95% CI), months	21.9 (8.3–NE)	11.3 (7.6–NE)	0.0158
Progression rate at 12 months (95% CI)	41.6% (32.4–50.5)	57.8% (49.0–65.7)	0.005
Progression rate at 18 months (95% CI)	46.9% (37.3–56.0)	61.2% (52.3–68.9)	0.0132

*Primary endpoint measured as per RANO-BM over course of study based on independent radiology review.
BSC, best supportive care, patients in both arms could receive systemic NSCLC treatment; CI, confidence interval; HR, hazard ratio; NE, not evaluable; TTFields, Tumor Treating Fields.

	TTFields + BSC (n=149)	BSC (n=149)
Neurologic deaths, n	9	10
Deaths from other reasons, n	53	44

Mehta MP et al. ASCO 2024;Abstract 2008.

METIS: Overall Survival Outcomes

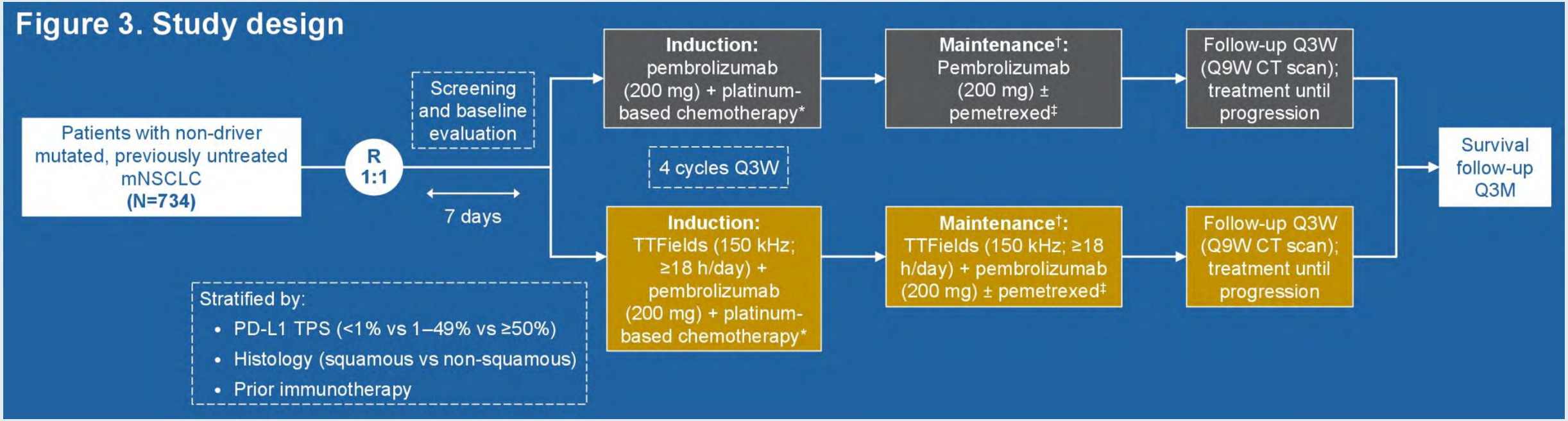


	TTFields + BSC (n=149)	BSC (n=149)	*P*-value
Median Overall Survival (95% CI), months	11.3 (8.5–13.5)	10.6 (6.8–14.1)	0.7796

Mehta MP et al. ASCO 2024;Abstract 2008.

LUNAR-2 Trial: Front-Line TTFields with an Immune Checkpoint Inhibitor and Chemotherapy for mNSCLC

Figure 3. Study design



Inclusion criteria

- Histologically/cytologically confirmed stage IV NSCLC
- No prior systemic treatment for mNSCLC
- Evaluable (measurable or non-measurable) disease in the thorax per RECIST v1.1
- ≥18 years old (≥22 years in the US)
- ECOG PS 0–1

Endpoints

Primary*	• OS and PFS per RECIST v1.1 as assessed by a BICR
Secondary	• OS and PFS (by histology and PD-L1 TPS) per RECIST v1.1 as assessed by BICR • ORR, DoR, and DCR (all per RECIST v1.1 as assessed by BICR and by investigator) • PFS rates at 6, 12, 24 and 36 months per RECIST v1.1 as assessed by BICR • 1-, 2-, and 3-year survival rates • Safety profile
Exploratory	• PFS and OS according to in-field or out-of-field location of the disease

TPS = tumor proportion score; OS = overall survival; PFS = progression-free survival; BICR = blinded independent central review; ORR = objective response rate; DoR = duration of response; DCR = disease control rate

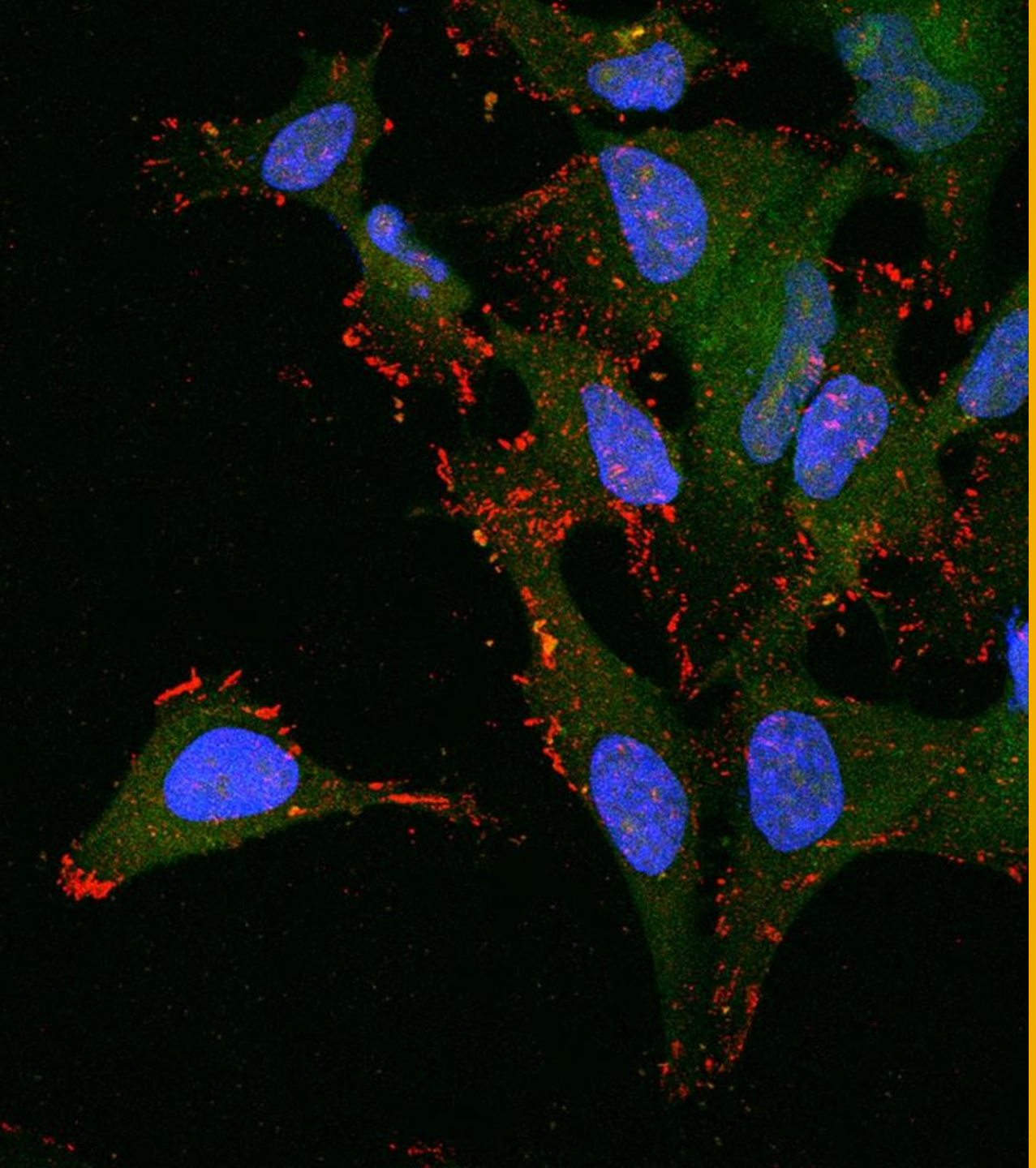
Eaton M et al. ASCO 2024;Abstract TPS8665.

Agenda

Introduction: Tumor Treating Fields

Module 1: Nontargeted Therapy for Lung Cancer — Dr Ramalingam

Module 2: Targeted Therapy for Non-Small Cell Lung Cancer — Dr Riely



NONTARGETED THERAPY FOR LUNG CANCER

Suresh S. Ramalingam, MD, FASCO

Executive Director

Winship Cancer Institute of Emory University

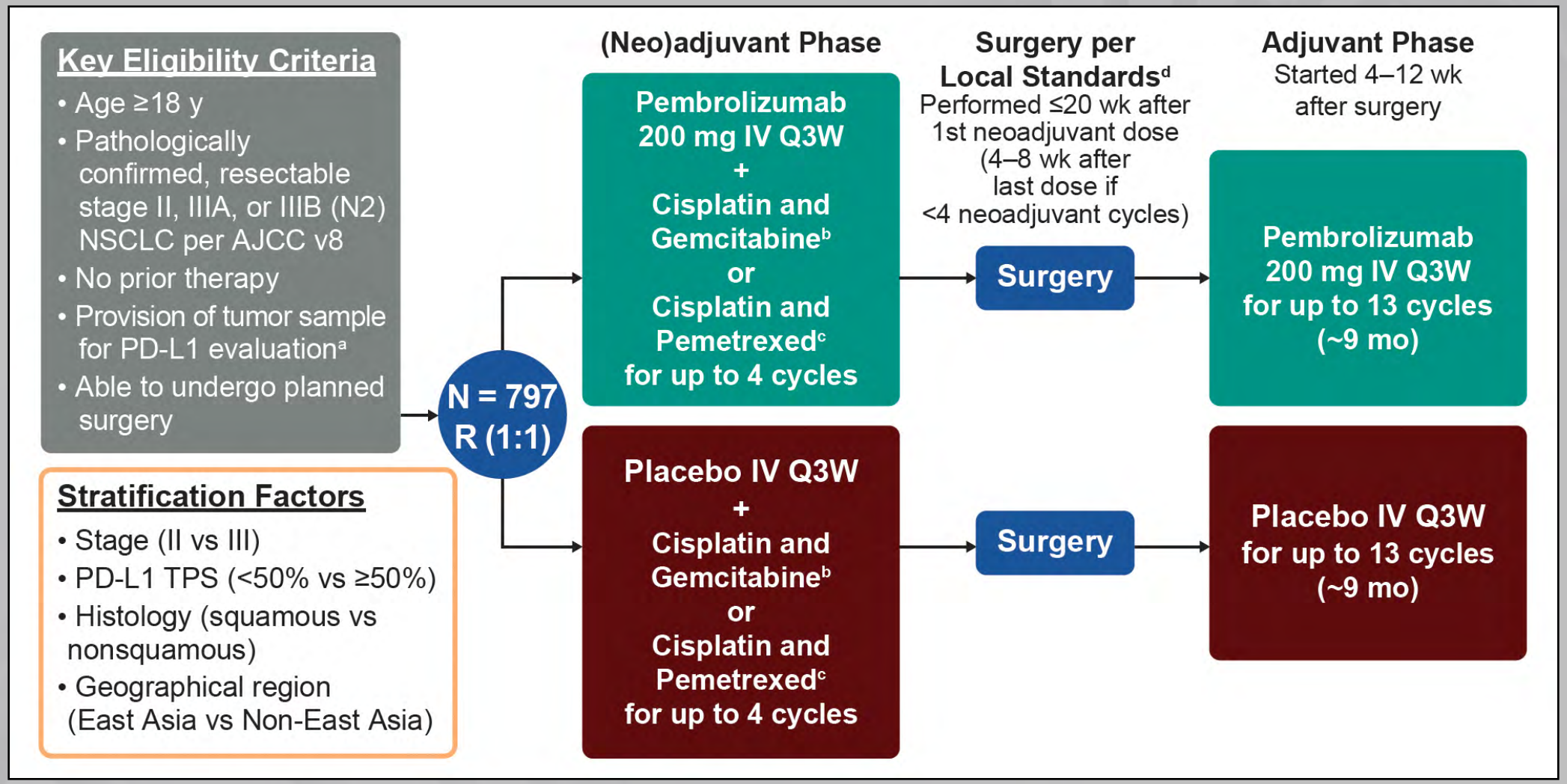
EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

OUTLINE

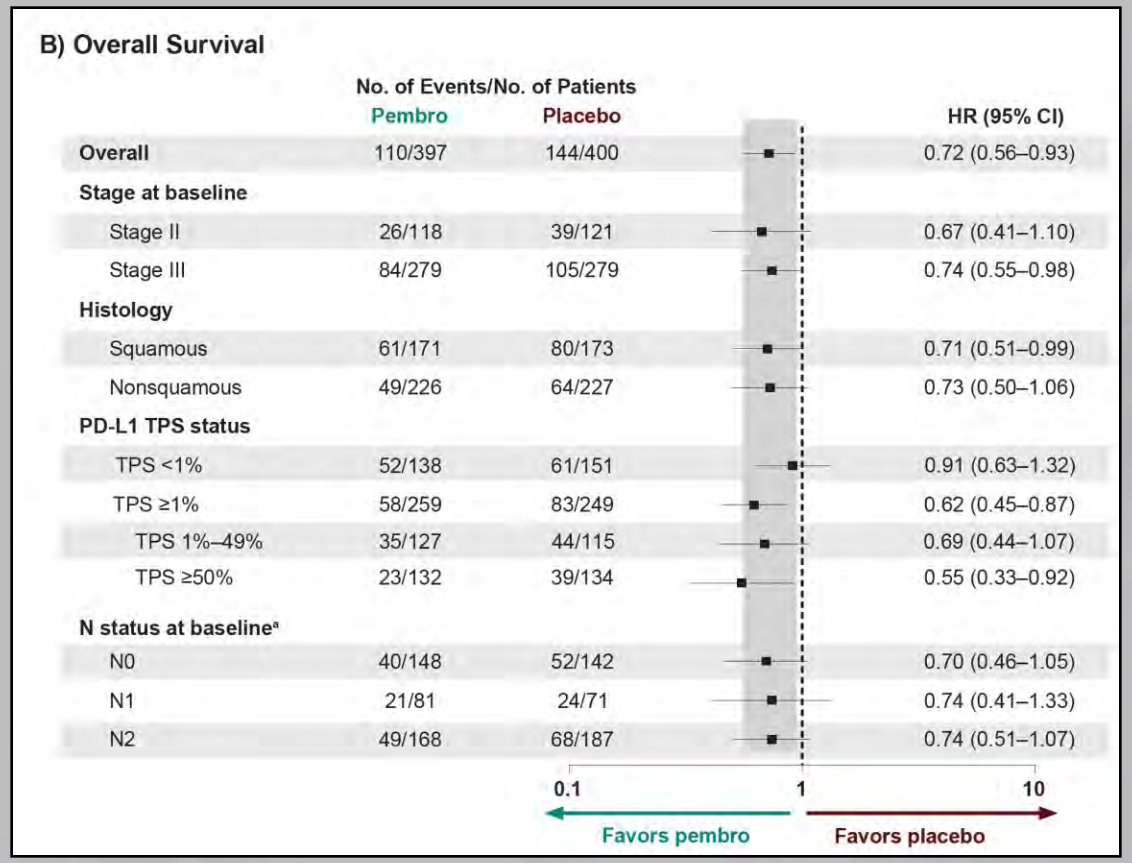
- Neo-adjuvant and adjuvant immunotherapy
- First-line immunotherapy for metastatic NSCLC
- ADC as salvage therapy
- Advances in small cell lung cancer

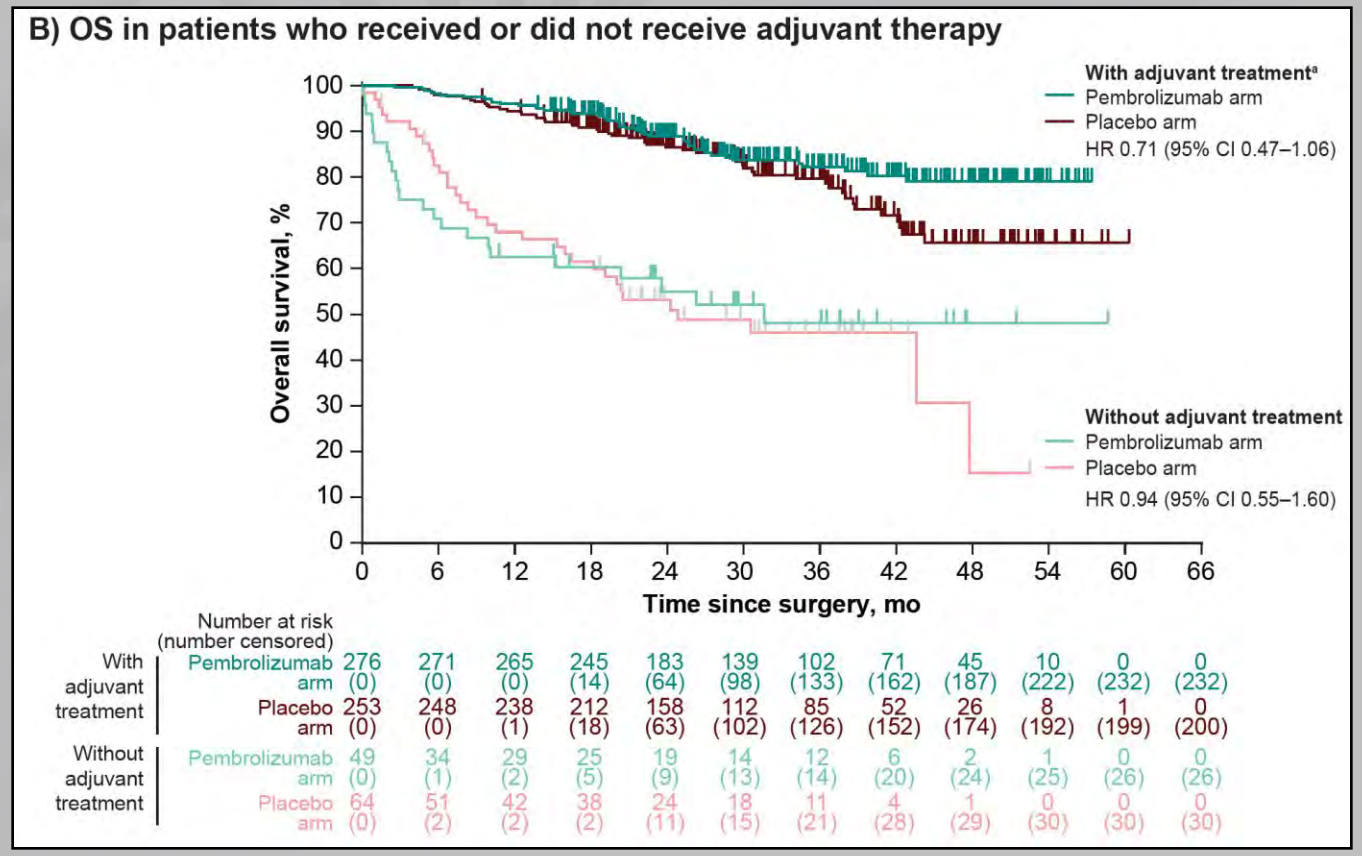
KN-671 TRIAL: PEMBROLIZUMAB IN EARLY STAGE NSCLC



Garassino M et al, ESMO 2024.

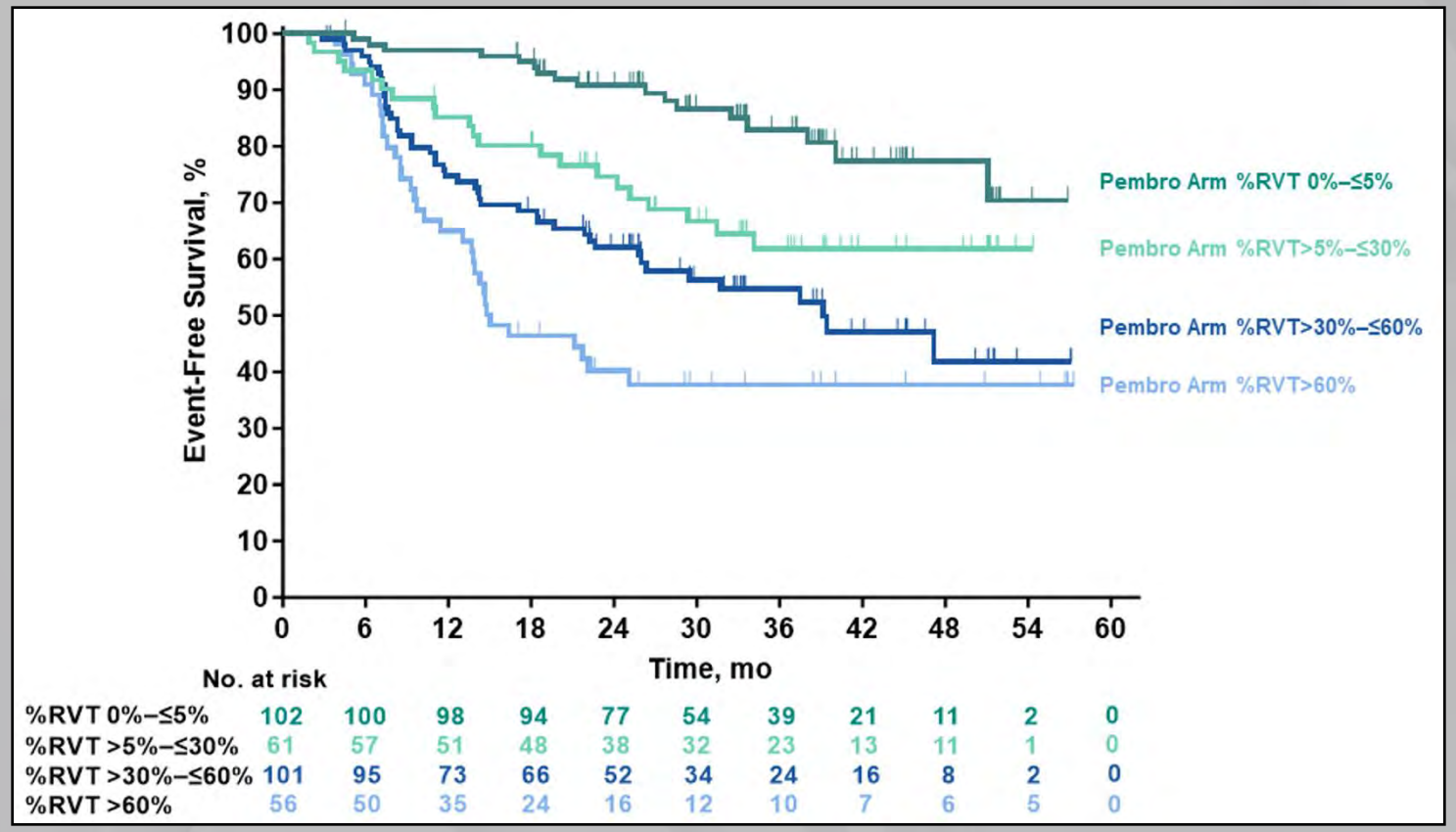
SURVIVAL OUTCOMES IN KN-671

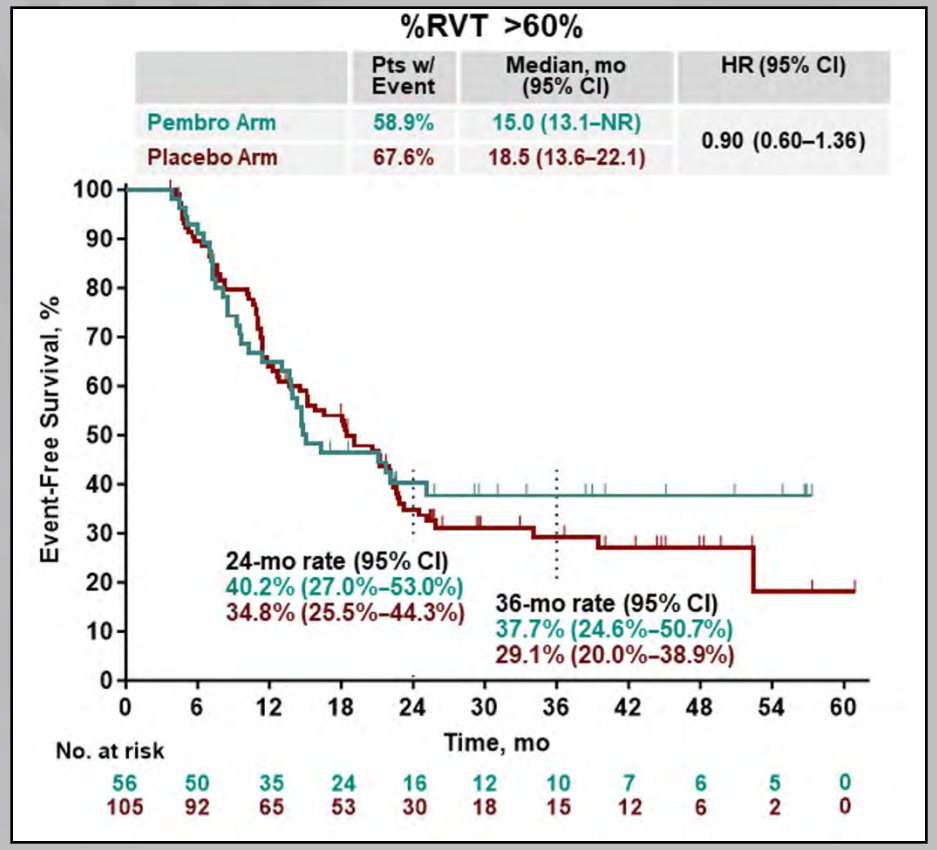




Garassino M et al, ESMO 2024.

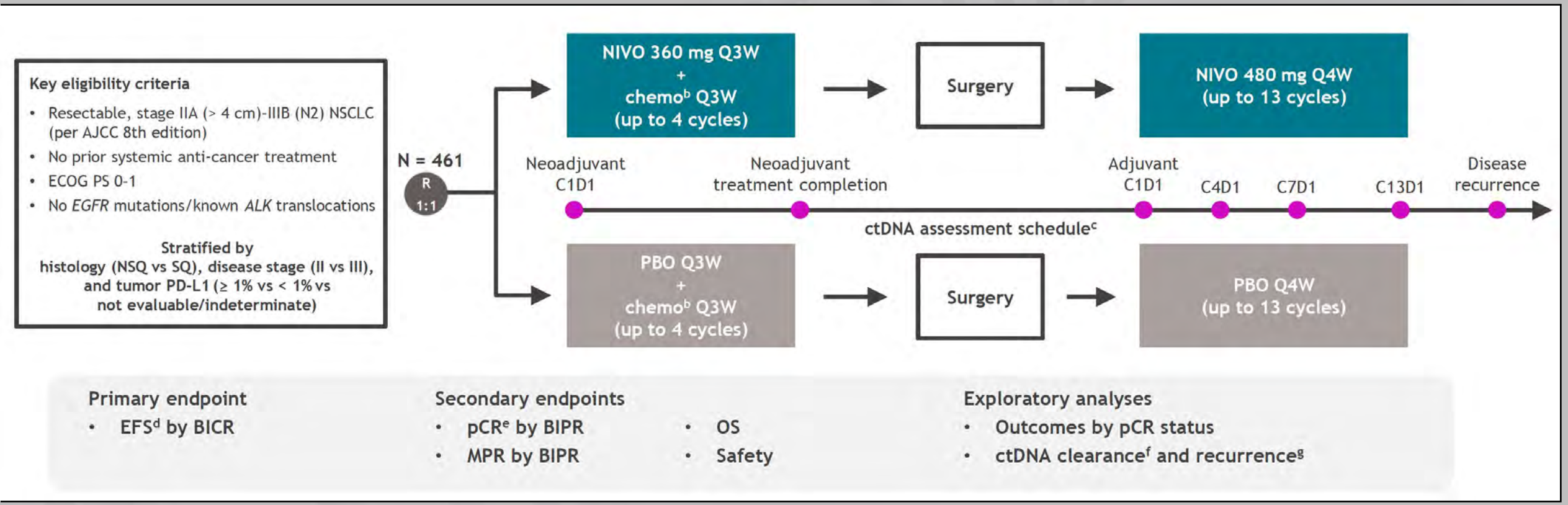
KN-671: OUTCOMES BASED ON RESIDUAL VIABLE TUMOR





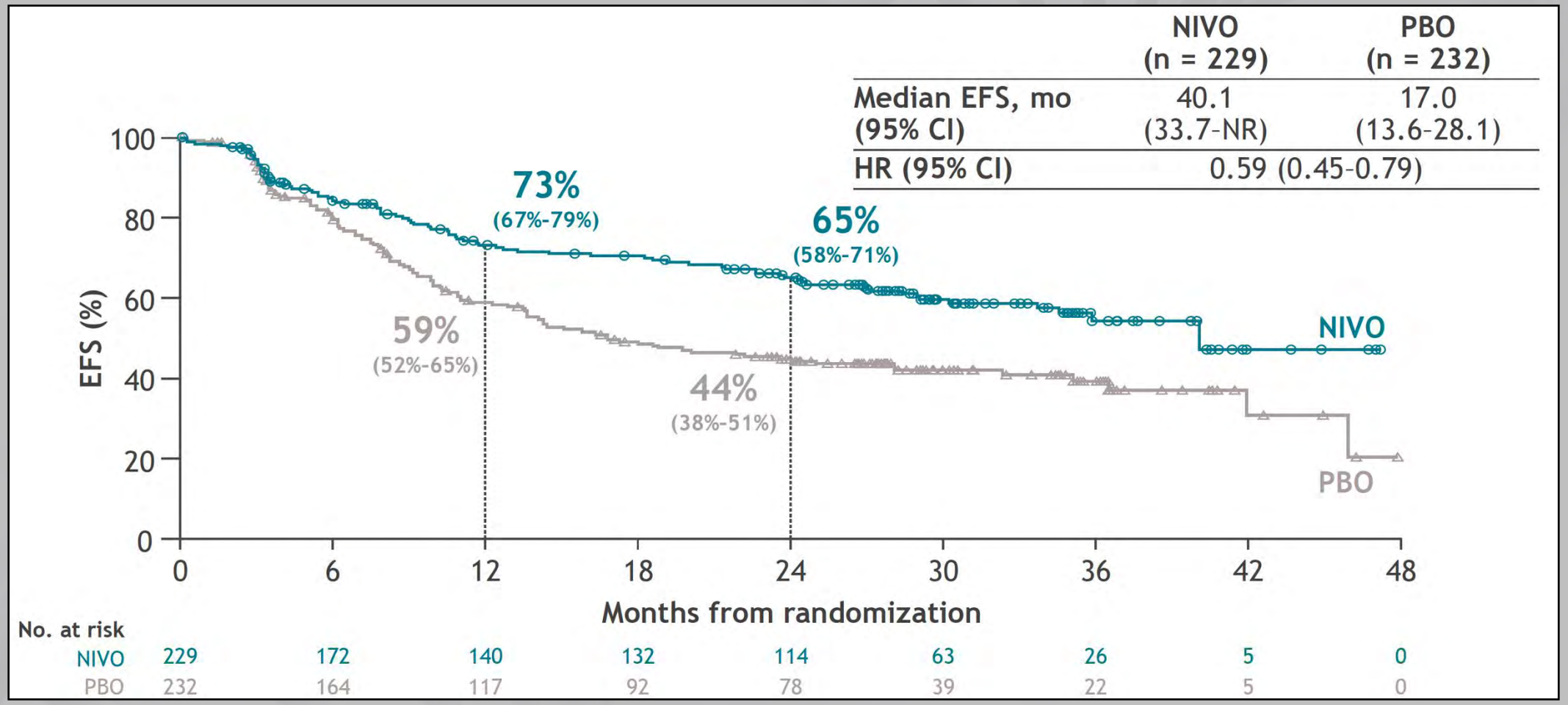
Jones DR et al, WCLC, 2024.

CHECKMATE 77T: PERI-OPERATIVE NIVOLUMAB



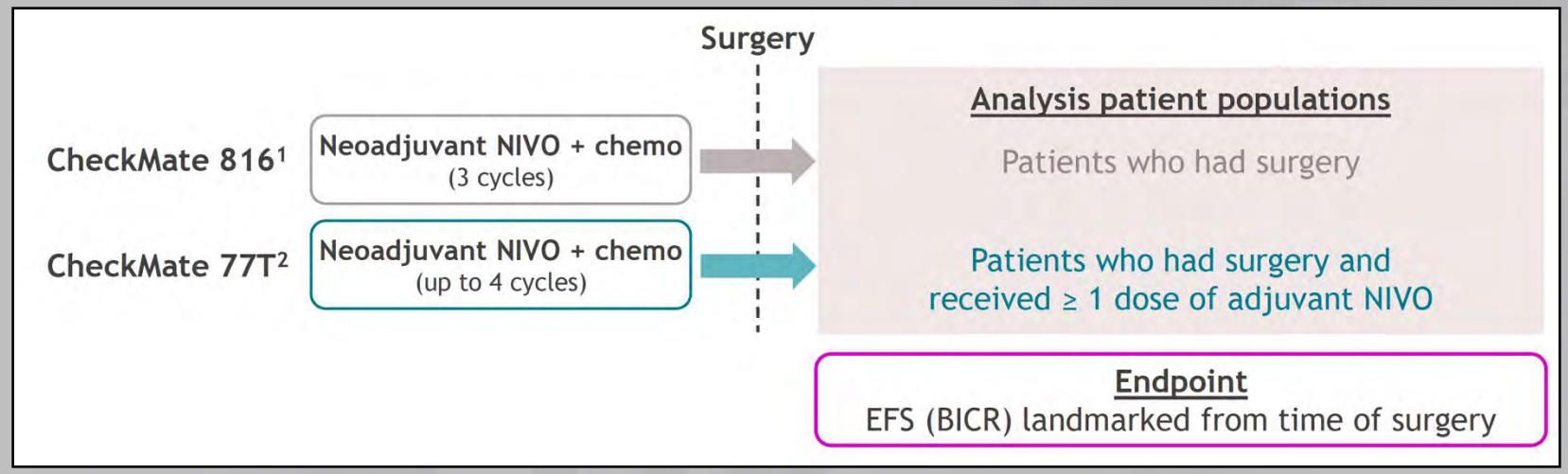
Spicer J et al, ESMO, 2024.

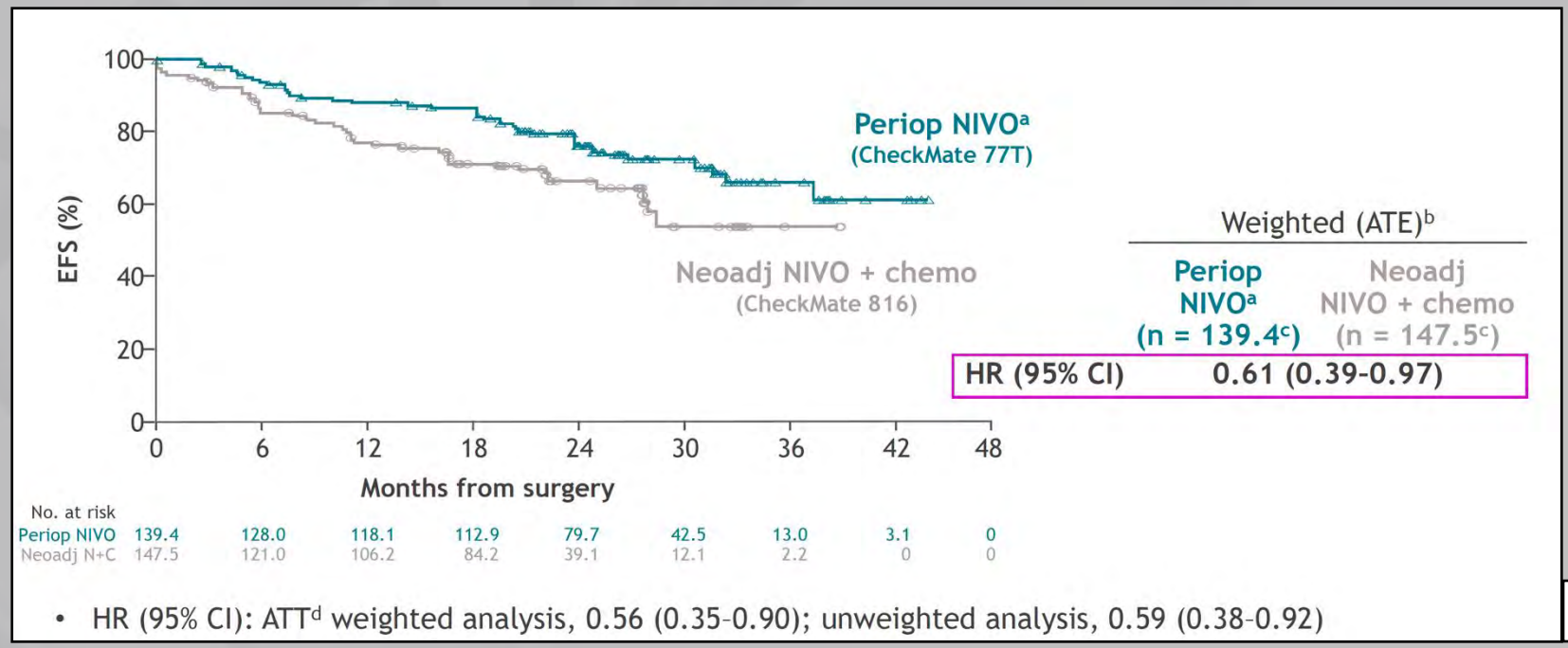
EVENT-FREE SURVIVAL BY BICR



Spicer J et al, ESMO, 2024.

CM 816 & CM 77T: A PATIENT-LEVEL ANALYSIS





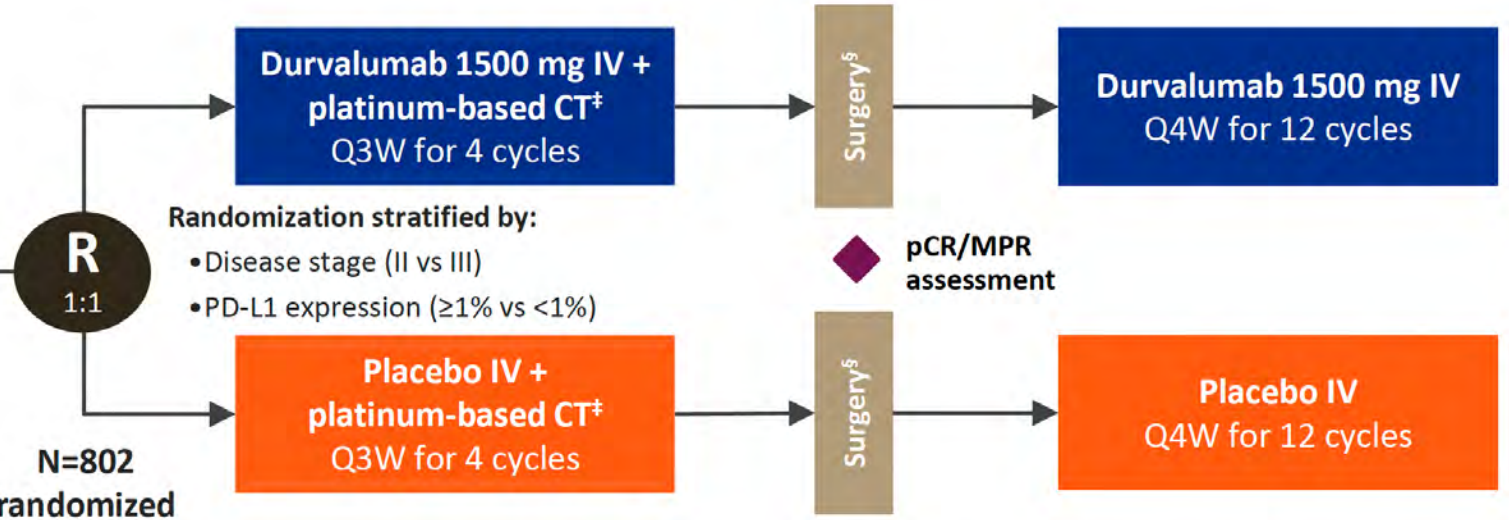
- HR (95% CI): ATT[d] weighted analysis, 0.56 (0.35-0.90); unweighted analysis, 0.59 (0.38-0.92)

Forde P et al, WCLC 2024.

PERI-OPERATIVE DURVALUMAB: AEGEAN STUDY

Study population

- Resectable NSCLC* (stage IIA–IIIB[N2]; AJCC 8th ed)
- Treatment-naïve
- ECOG PS 0 or 1
- Lobectomy, sleeve resection, or bilobectomy as planned surgery*
- Confirmed PD-L1 status†
- No documented *EGFR/ALK* aberrations*



Efficacy analyses were performed in the mITT population (or its resected subpopulation), which excluded patients with documented EGFR/ALK *aberrations*¶

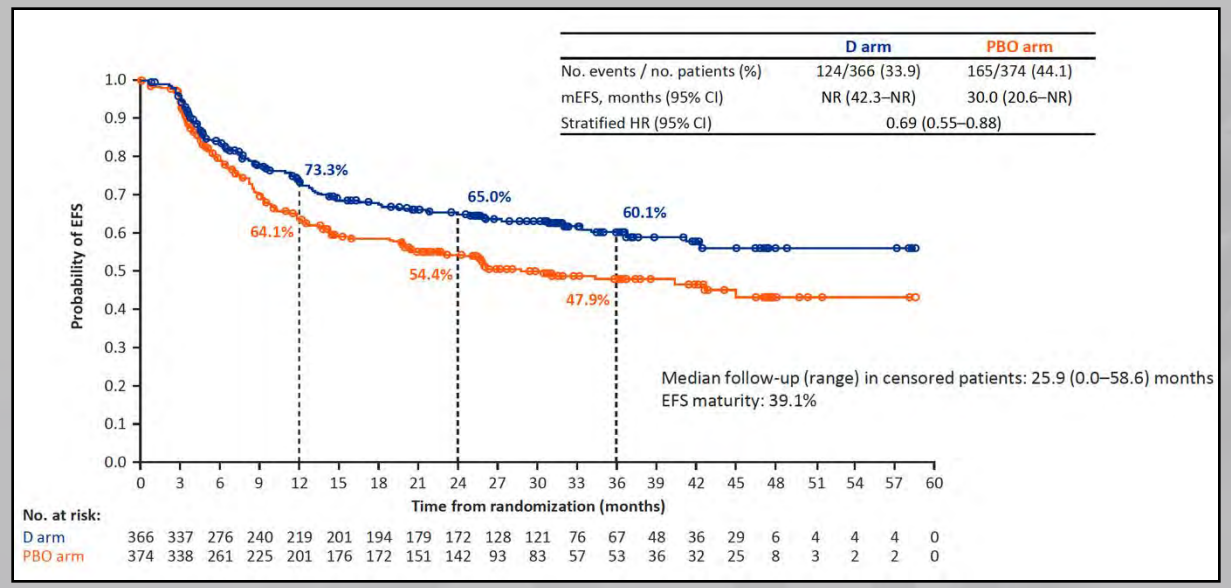
Primary endpoints: pCR, evaluated centrally (IASLC 2020[1]), and EFS per BICR (RECIST v1.1)

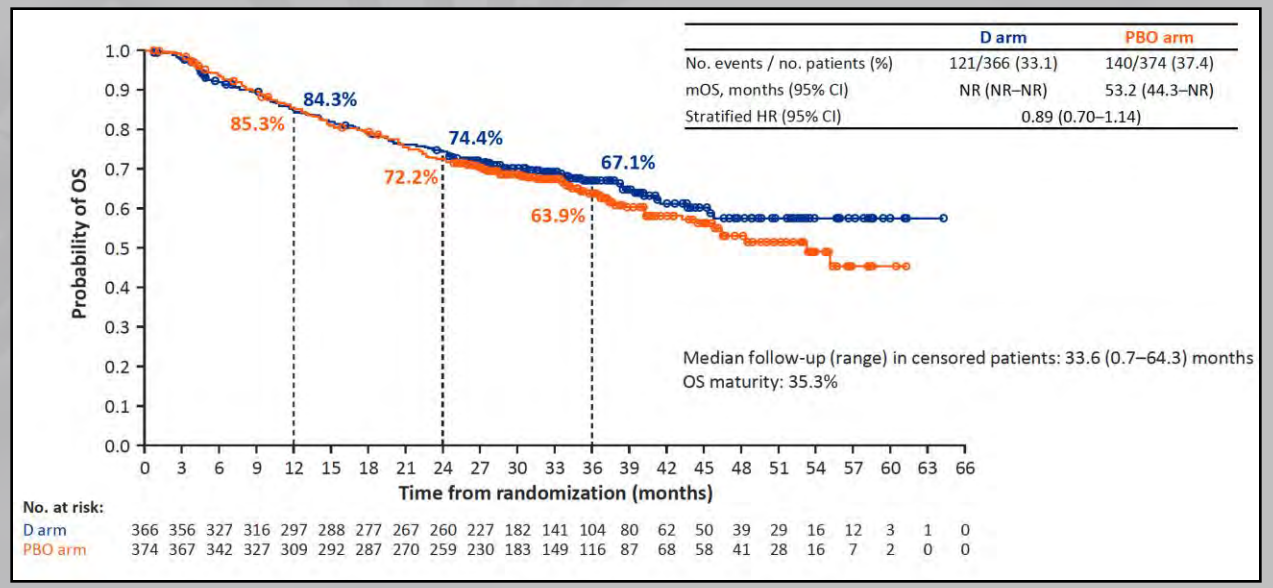
Key secondary endpoints: MPR, evaluated centrally (IASLC 2020[1]), DFS per BICR (RECIST v1.1) in the resected subpopulation, and OS

	EFS interim analysis #1	EFS interim analysis #2 (reported here)
Data cutoff	November 10, 2022	May 10, 2024
Median EFS follow-up	11.7 months (censored patients)	25.9 months (censored patients)
Data maturity	31.9%	39.1%

Heymach J et al, WCLC, 2024.

AEGEAN OUTCOMES: EFS & PRELIMINARY OS





Other observations

EFS was better for patients who received cisplatin versus carboplatin

Benefit with durvalumab was noted regardless of pCR status

Exploratory analysis suggested benefit with adjuvant durvalumab

Heymach J et al, WCLC, 2024.

Questions?

METASTATIC NSCLC

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NCI
Designated
Comprehensive
Cancer Center

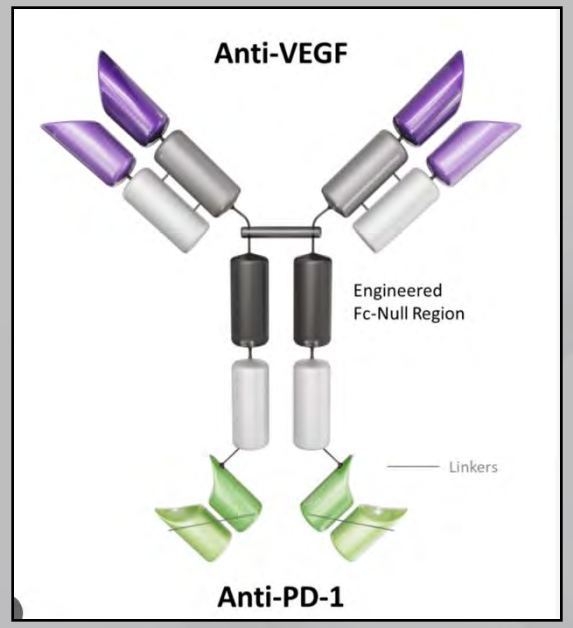
SINGLE AGENT IO FOR PD-L1 HIGH DISEASE

	Pembrolizumab (KEYNOTE-024)	Atezolizumab (IMpower110)	Cemiplimab (EMPOWER-Lung 1)
PD-L1 def	TPS ≥ 50%	TC 3 or IC 3	TPS ≥ 50%
OS median (mo)	26.3 (HR-0.62)	20.2 (HR-0.59)	26.1(HR-0.57)
PFS median (mo)	7.7 (HR-0.5)	8.1 (HR-0.63)	8.2 (HR-0.54)
ORR	46%	38%	39%
5-year survival	31.9%	NR	NR

Options for patients with PD-L1 < 50%
Chemotherapy + IO
Chemotherapy + Ipilimumab + Nivolumab
Ipilimumab + Nivolumab
Chemotherapy + Durvalumab + Tremelimumab

Reck M et al JCO 2021, Herbst R et al NEJM 2020, Sezer A Ann Oncol 2020 LBA52,

HARMONI-2 TRIAL: IVONESCIMAB VERSUS PEMBROLIZUMAB



Patient Population

- Stage IIIB-IV aNSCLC
- No prior systemic therapy
- No *EGFR* mutations or *ALK* rearrangements
- ECOG PS 0 or 1
- PD-L1 TPS ≥1%

R
1:1

N=398

Ivonescimab
20 mg/kg Q3W (N=198)

Pembrolizumab
200 mg Q3W (N=200)

Treatment until no clinical benefit, unacceptable toxicity or up to 24 months

Stratification

- Clinical stage (IIIB/C vs. IV)
- Histology (SQ vs. non-SQ)
- PD-L1 TPS (≥50% vs. 1-49%)

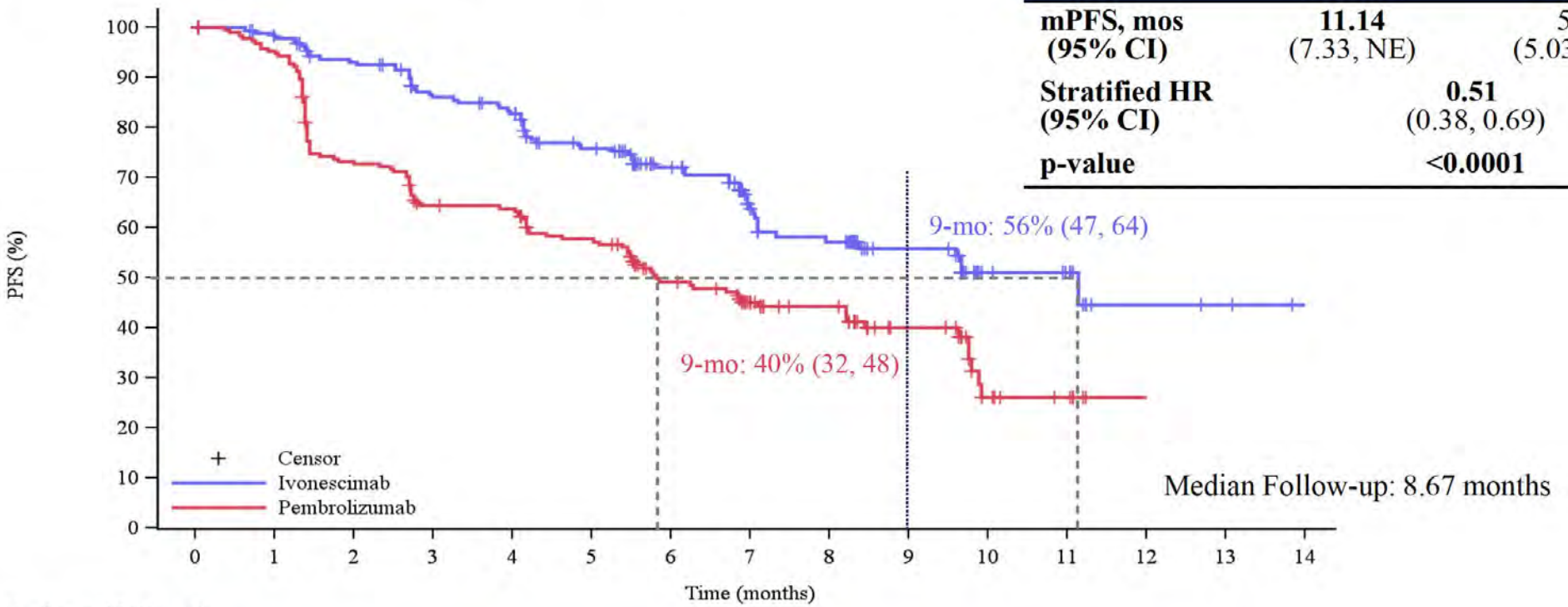
Endpoints

Primary: PFS by blind IRRC per RECIST v1.1
Secondary: OS, PFS assessed by INVs, ORR, DoR, TTR and safety
Exploratory: QoL

Zhou C et al, WCLC 2024.

Primary endpoint: PFS per IRRC

	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	**11.14** (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	**0.51** (0.38, 0.69)	
p-value	**<0.0001**	



Number at risk (Events)

Ivonescimab	198(0)	189(3)	175(13)	156(26)	148(32)	128(44)	99(50)	68(60)	59(67)	38(68)	14(71)	11(71)	3(72)	2(72)	0(72)
Pembrolizumab	200(0)	187(9)	141(52)	121(69)	119(70)	103(81)	74(95)	53(101)	45(102)	25(106)	9(112)	5(112)	0(112)		

Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 month improvement in mPFS.

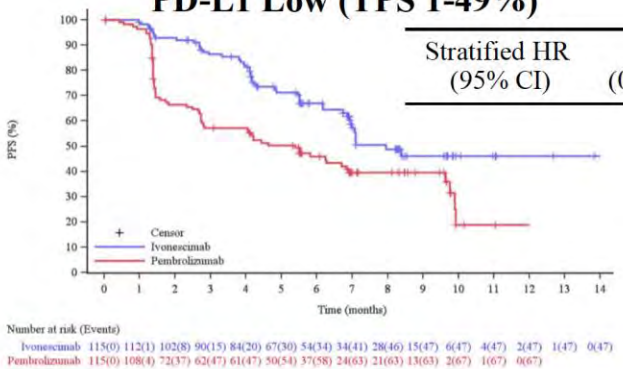
Zhou C et al, WCLC 2024.

HARMONI-2 TRIAL

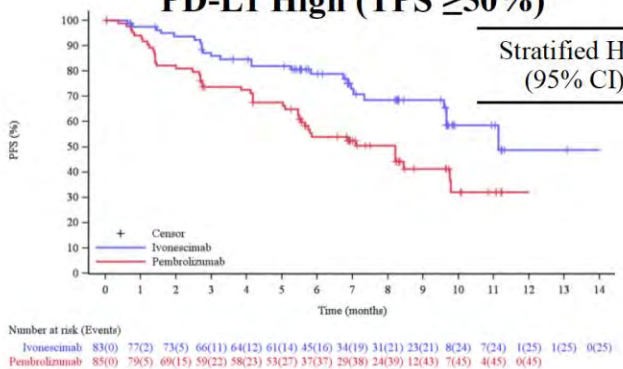
Key PFS Subgroup Analyses

PD-L1 expression

PD-L1 Low (TPS 1-49%)

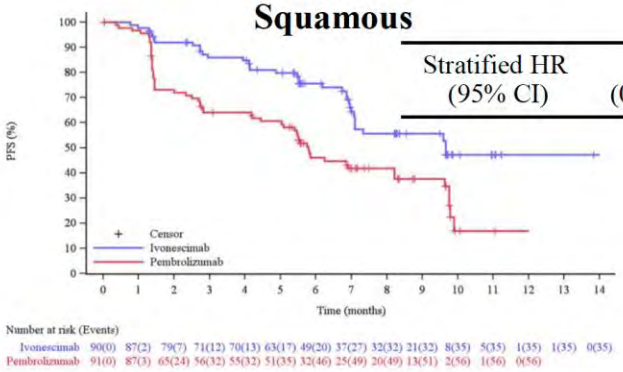


PD-L1 High (TPS ≥50%)

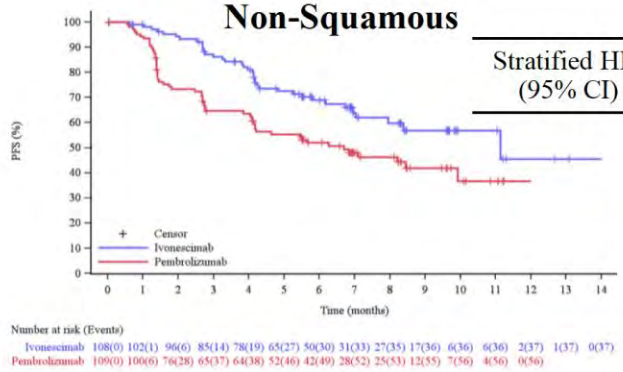


NSCLC Histology

Squamous



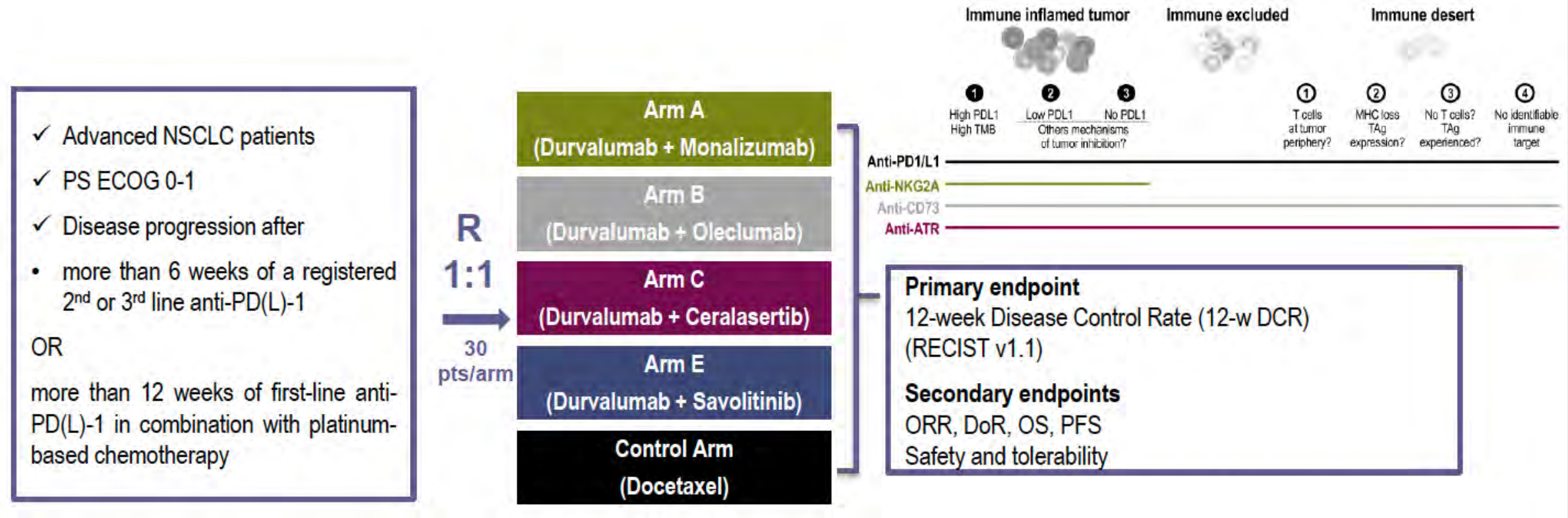
Non-Squamous



Ivonescimab showed meaningful improvement in PFS vs. pembrolizumab in patients with both low and high PD-L1, with squamous or non-squamous advanced NSCLC.

Zhou C et al, WCLC 2024.

PIONeeR Study Design and Outcomes



	D + monalizumab (n = 28)	D + oleclumab (n = 3)	D + ceralasertib (n = 32)	D + savolitinib (n = 20)	Docetaxel (n = 31)
Mean estimated 12-week DCR (Primary endpoint)	24.1%	0	50.0%	13.6%	54.5%
Common Grade ≥ 2 AEs	Arthralgia		Fatigue, anemia, neutropenia, lymphopenia, thrombocytopenia, pancytopenia	Fatigue, dyspnea, nausea, vomiting, decreased appetite, hypoalbuminemia	Fatigue, diarrhea, alopecia, neutropenia, anemia

ORR = overall response rate; DoR = duration of response; OS - overall survival; PFS = progression-free survival; AEs = adverse events

Tomasini P et al. ESMO 2024;Abstract LBA8.

TROPION-LUNG01

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Key eligibility criteria

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

Without actionable genomic alterations

- One to two prior lines, including platinum-based 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*
- One to two prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

1:1

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

Docetaxel
75 mg/m^2 Q3W
(N=305)

Dual primary endpoints

- PFS by BICR[a]
- OS

Secondary endpoints

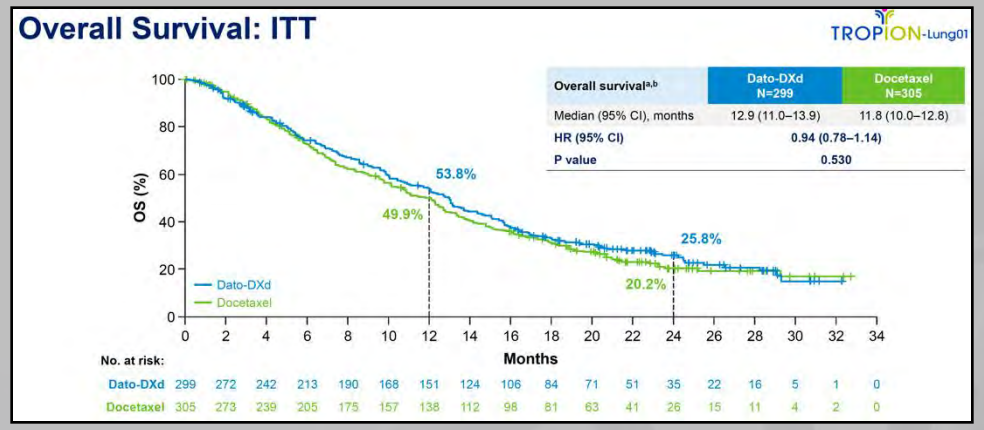
- ORR[a]
- DOR[a]
- Safety and tolerability

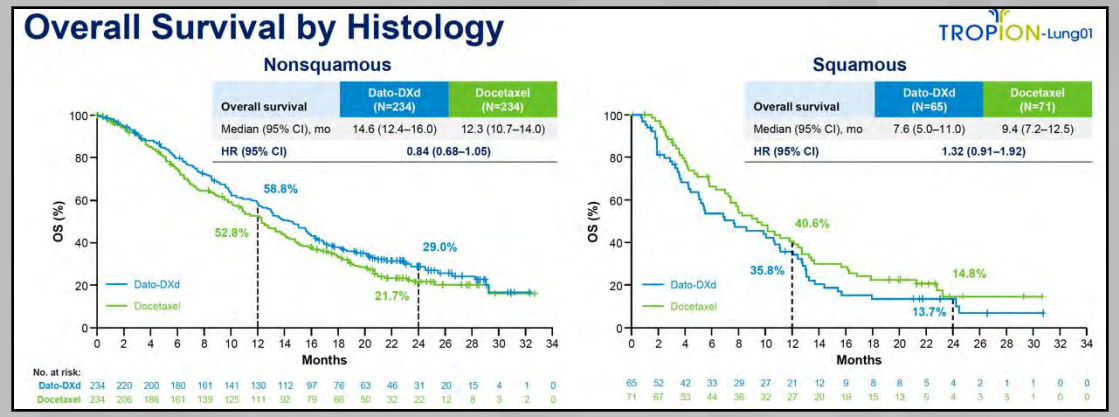
Stratified by histology (nonsquamous vs squamous), actionable genomic alteration status,[b] anti–PD-(L)1 mAb included in most recent prior therapy, and geography[c]

Statistical considerations: Study deemed positive if either of the dual primary endpoints (PFS by BICR or OS) were statistically significant; the pre-specified P-value boundary for the OS analysis was α=0.045

Sands J et al, WCLC, 2024.

TROPION-LUNG01

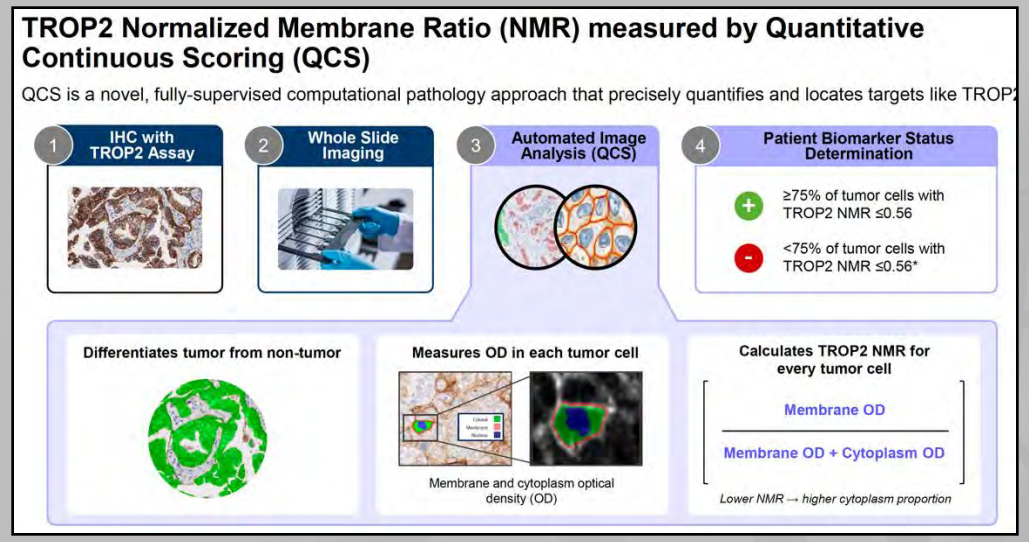




TRAEs,[a] n (%)	Dato-DXd (N=297)		Docetaxel (N=290)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Stomatitis	141 (47)[b]	20 (7)	45 (16)	3 (1)
Nausea	101 (34)	7 (2)	48 (17)	3 (1)
Alopecia	95 (32)	0	101 (35)	1 (<1)[c]
Decreased appetite	68 (23)	1 (<1)	46 (16)	1 (<1)
Asthenia	56 (19)	8 (3)	56 (19)	5 (2)
Anemia[d]	44 (15)	12 (4)	60 (21)	12 (4)
Diarrhea	30 (10)	1 (<1)	55 (19)	4 (1)
Neutropenia[e]	14 (5)	2 (1)	76 (26)	68 (23)
Leukopenia[f]	9 (3)	0	45 (16)	38 (13)
Adjudicated drug-related ILD or pneumonitis	26 (9)[g]	11 (4)	12 (4)	4 (1)

Sands J et al, WCLC, 2024.

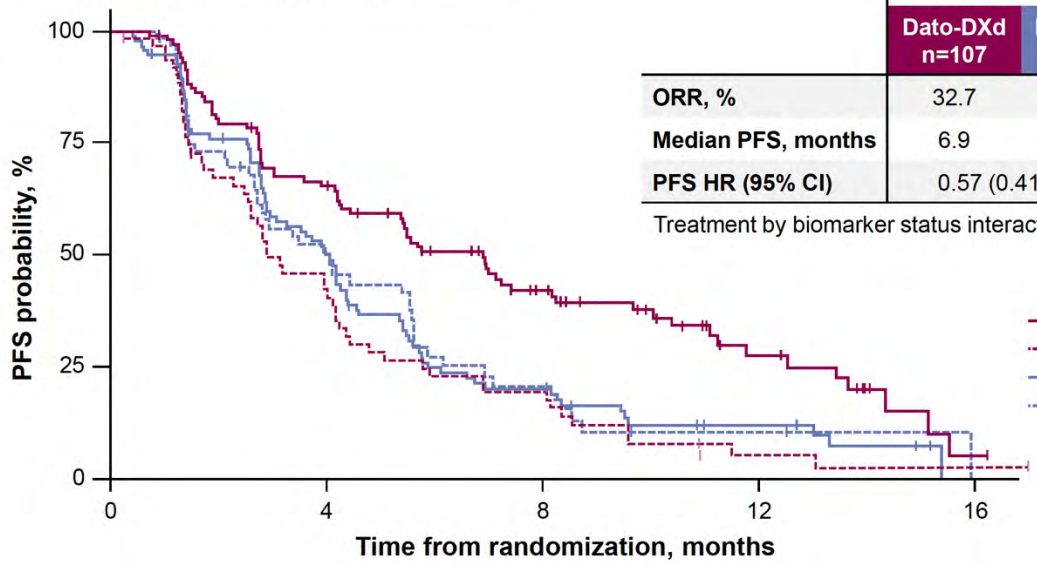
TROPION-LUNG01: BIOMARKER DEVELOPMENT



Overall BEP: Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the biomarker-evaluable population

Biomarker-evaluable population, n=352



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

Garassino M et al, WCLC, 2024.

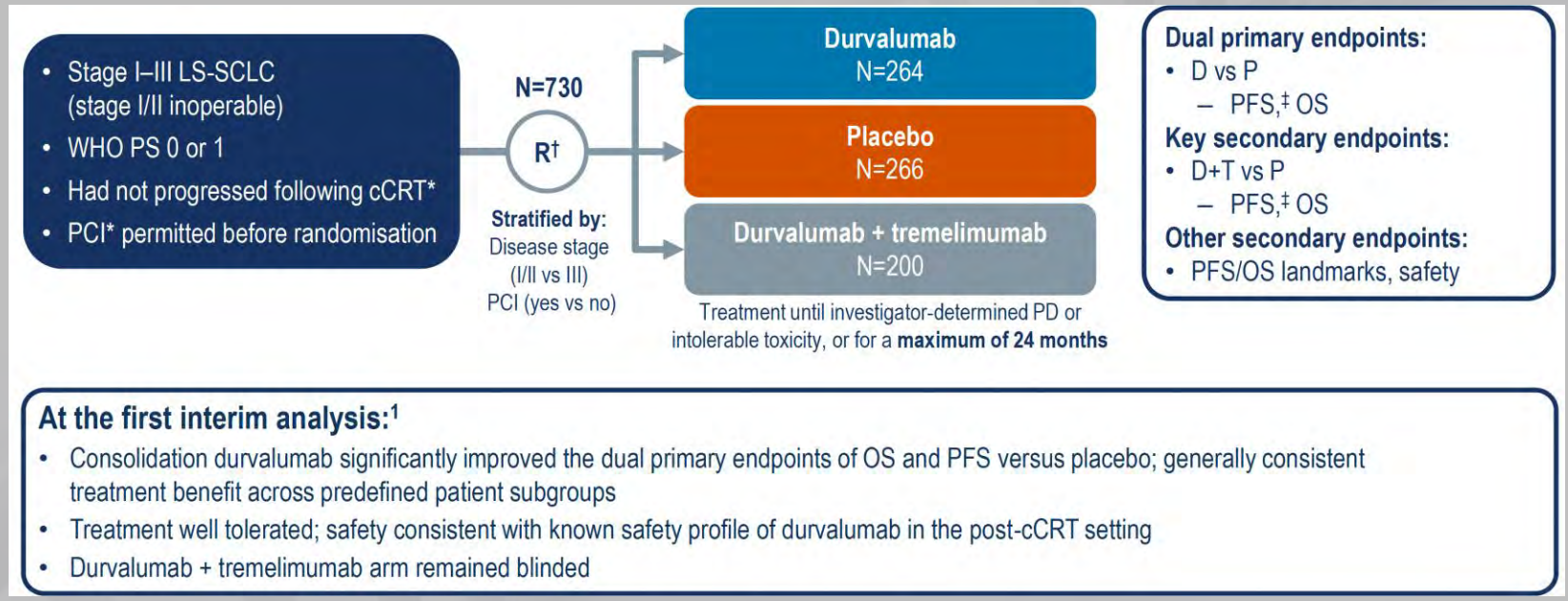
Questions?

SMALL CELL LUNG CANCER

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI
Designated Comprehensive Cancer Center

ADRIATIC STUDY: IMPACT OF PCI



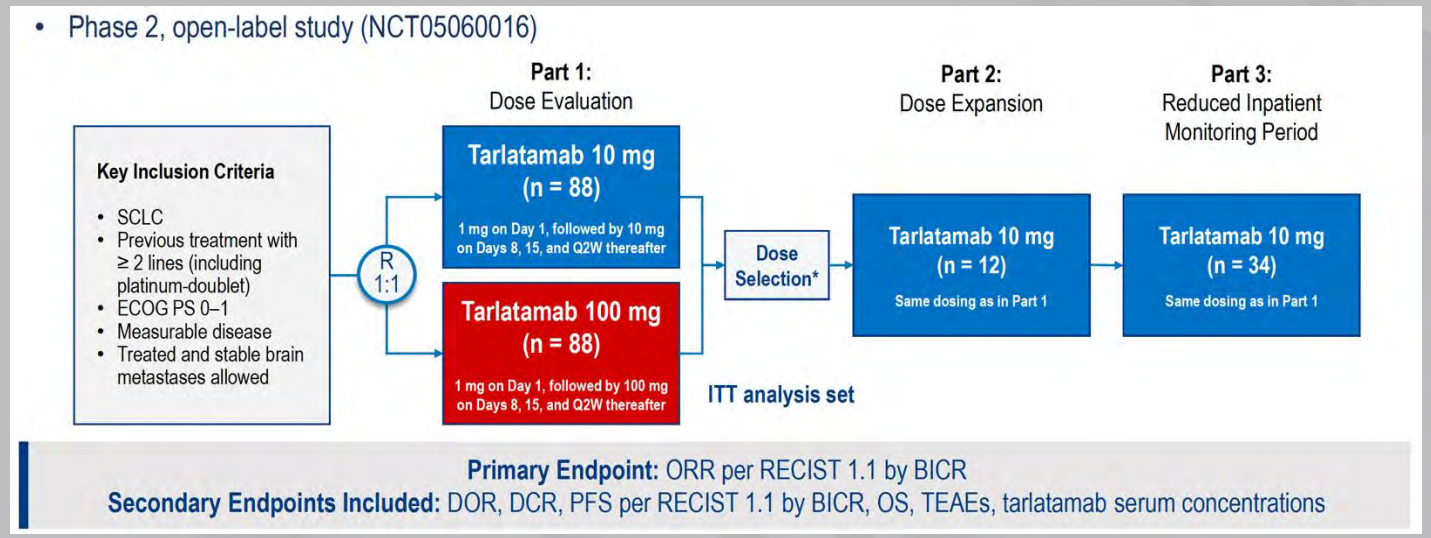
At the first interim analysis:[1]

- Consolidation durvalumab significantly improved the dual primary endpoints of OS and PFS versus placebo; generally consistent treatment benefit across predefined patient subgroups
- Treatment well tolerated; safety consistent with known safety profile of durvalumab in the post-cCRT setting
- Durvalumab + tremelimumab arm remained blinded

	PCI-yes		PCI-no	
	D (n = 142)	P (n = 143)	D (n = 122)	P (n = 123)
Median OS (95% CI), months	NR (43.9–NE)	42.5 (33.4–NE)	37.3 (24.3–NE)	24.1 (18.8–31.1)
3-year OS, %	62.1	56.5	50.2	37.3
HR (95% CI)	0.75 (0.52–1.07)*		0.71 (0.51–0.99)*	
Multivariable HR (95% CI)	0.72 (0.50–1.03)‡		0.73 (0.52–1.02)‡	

Senan S et al, ESMO 2024.

TARLATAMAB IN SCLC



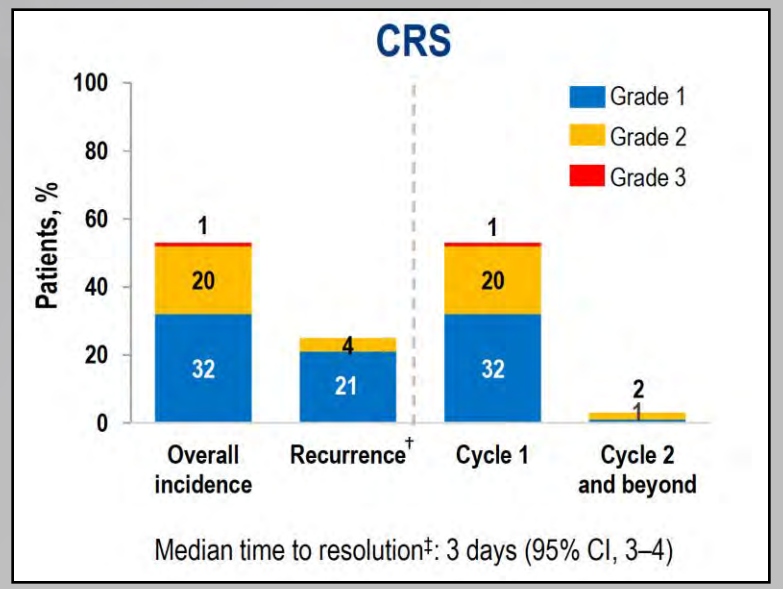
Efficacy Summary

Response rate: 40%

mPFS: 4.3 m

mOS: 15.2m

mDOR: 9.7m



Sands J et al, WCLC 2024.

OTHER NOVEL AGENTS FOR SCLC

Agent	MK-6070	Ifinatamab Deruxtecan (I-DXd)
MoA	DLL3 targeting T cell engager	ADC targeting B7H3
ORR	36%	55%
mPFS	NR*	5.5m
mOS	NR*	11.8m
Intracranial activity	25%	38%
Salient AE	CRS, ICANS	Nausea, anorexia, fatigue, anemia, neutropenia

*Not reported

Choudhury NJ et al, WCLC, 2024; Rudin CM et al, WCLC, 2024; Johnson ML et al, ESMO, 2024.

Questions?

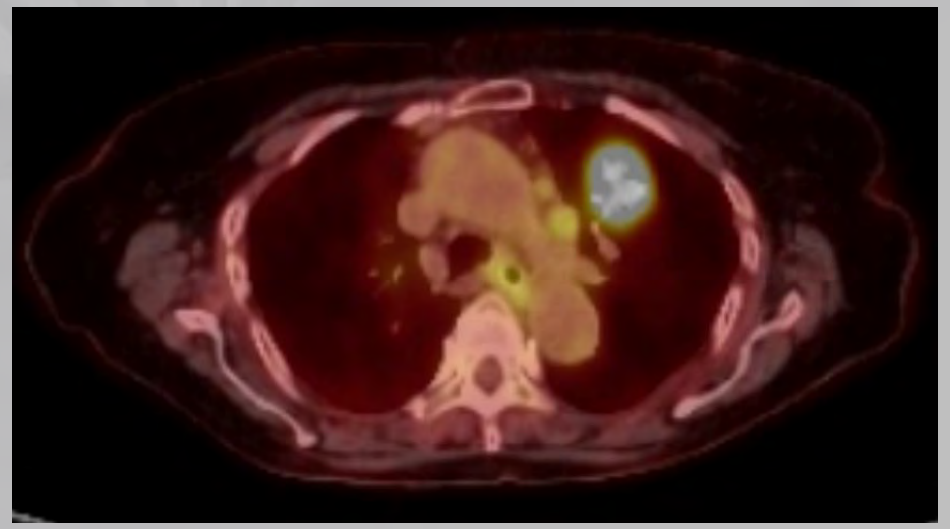
CASES

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI
Designated Comprehensive Cancer Center

CASE PRESENTATION: DR RAMALINGAM — 77-YEAR-OLD WOMAN WITH EARLY-STAGE NSCLC

- 77 year old female
- Sustained a fall and evaluated at the ED
- CXR revealed left lung mass
- CT- 4X 3.6 cm mass in left upper lobe of lung
- PET-CT: 4.2 cm mass in left upper lobe, SUV 29; enlarged AP window and left hilar nodes with elevated SUV; no distant metastasis
- Biopsy of lung mass and left hilar node: squamous cell carcinoma
- PD-L1 negative



CASE PRESENTATION: DR RAMALINGAM — 59-YEAR-OLD WOMAN WITH PROGRESSIVE SCLC

- 59 yr old woman
- Diagnosed with SCLC in Sept 2022
  - 8.8 cm right suprahilar mass, SVC obstruction
  - Cisplatin and etoposide with radiotherapy completed in Dec 2022
  - PCI completed in Jan 2023
  - Progression of disease in Jan 2024
  - 6 cycles of lurbinectedin completed in June 2024
  - PD following Tarlatamab X 2 cycles
- ECOG PS 1
- PET- CT shows lung and liver lesions
- Next step?

Agenda

Introduction: Tumor Treating Fields

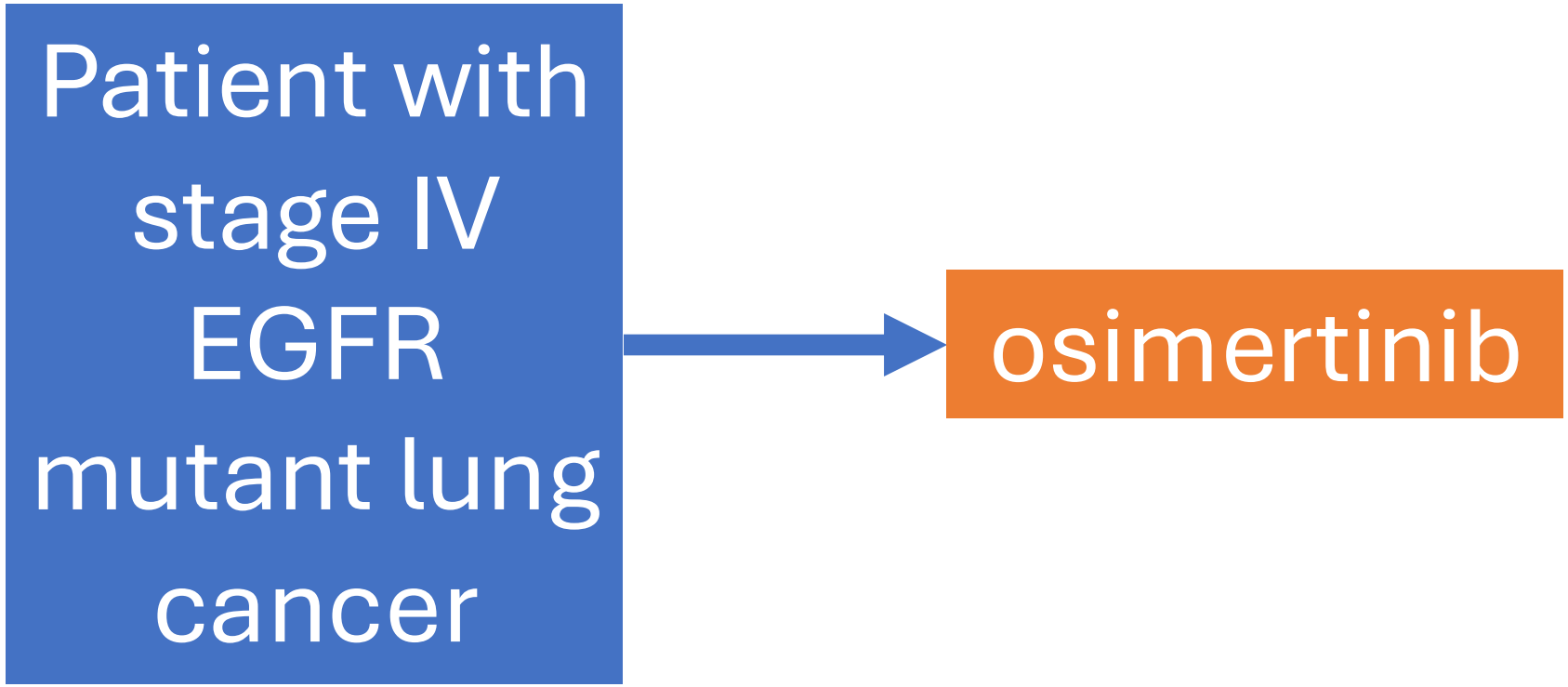
Module 1: Nontargeted Therapy for Lung Cancer — Dr Ramalingam

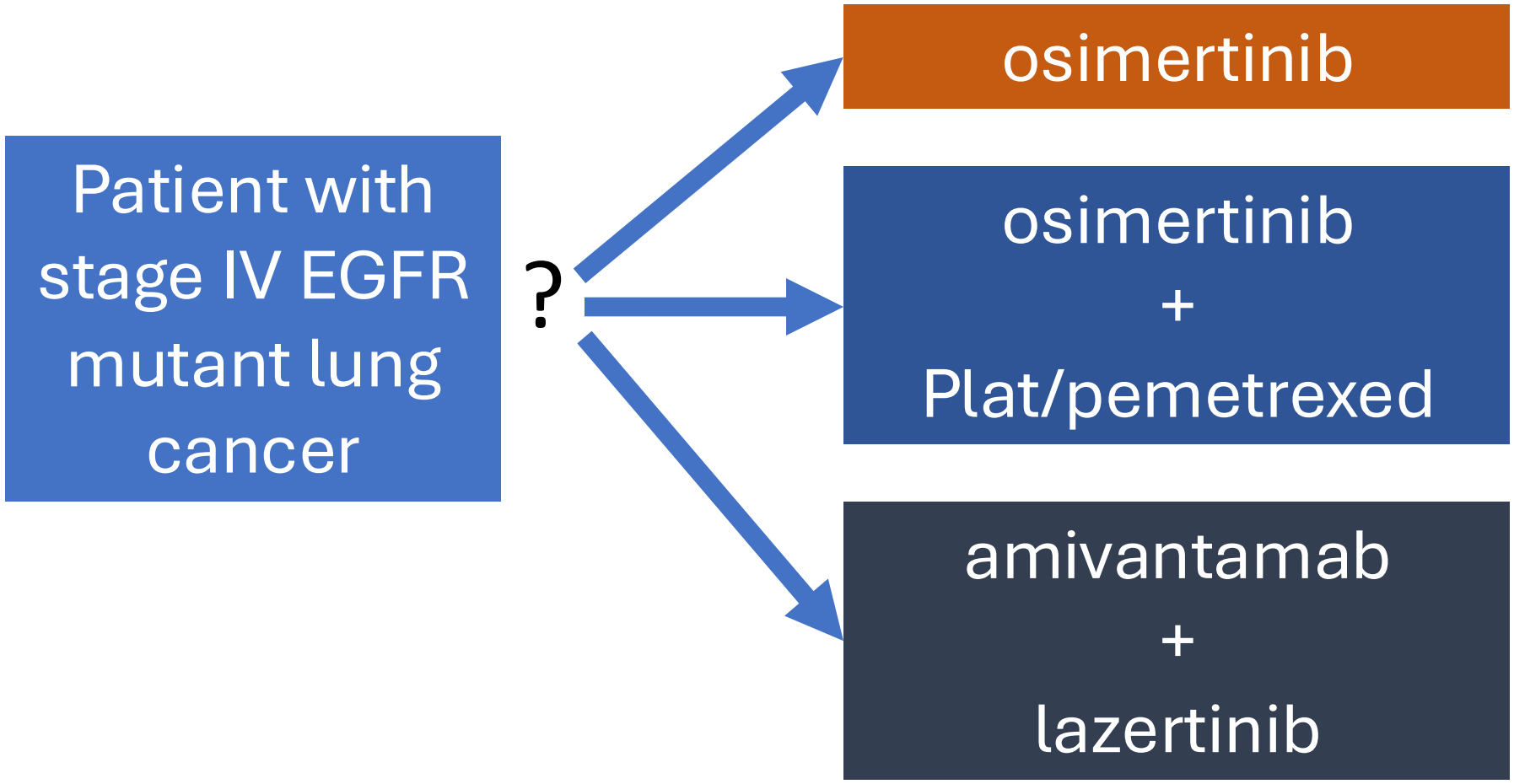
Module 2: Targeted Therapy for Non-Small Cell Lung Cancer — Dr Riely

Targeted Therapy Updates from WCLC and ESMO 2024

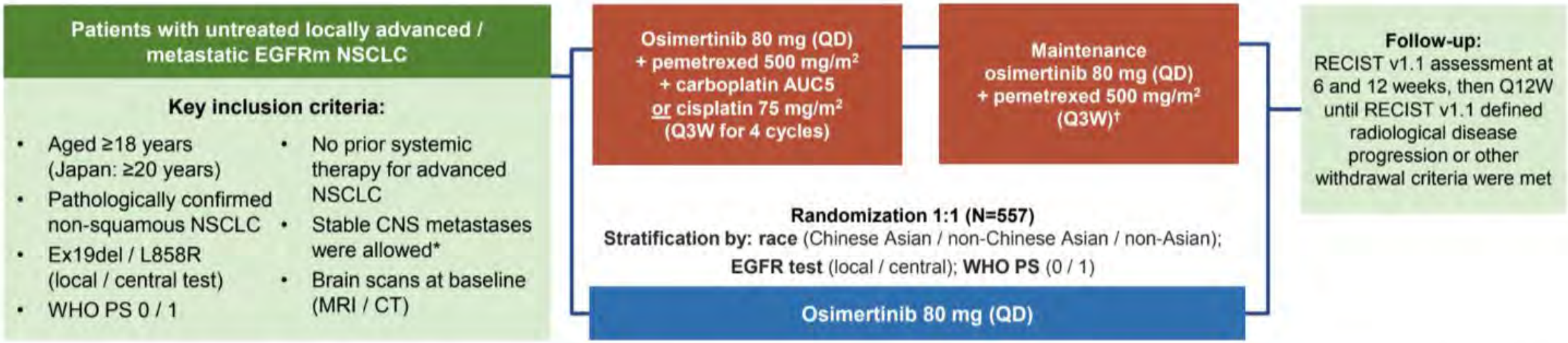
Gregory J Riely, MD, PhD
Memorial Sloan Kettering Cancer Center
New York, New York

Remember when it was simpler?




Patient with stage IV EGFR mutant lung cancer
?
osimertinib
osimertinib + Plat/pemetrexed
amivantamab + lazertinib

Osimertinib +/- Chemotherapy for EGFR mut NSCLC



- **Primary endpoint:** PFS by investigator assessment per RECIST v1.1‡§
- **Secondary endpoints include:** OS, ORR, DoR, DCR, HRQoL and safety (AEs by CTCAE v5) and PFS2‡

Post-hoc analysis of PFS by tumor burden categories

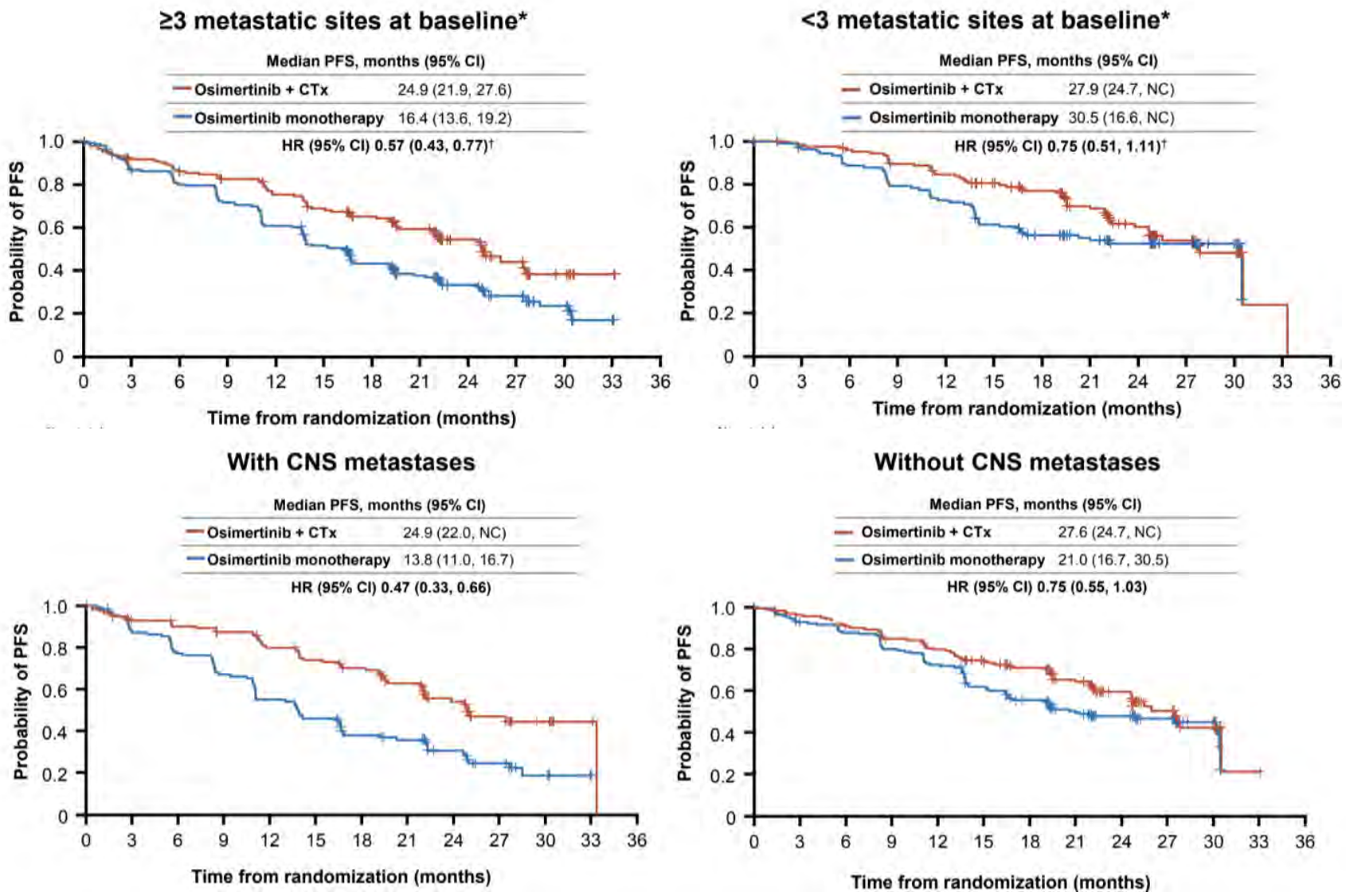
Number of metastatic anatomical sites at baseline¶[1–4]
Each anatomical site counted as one metastatic site regardless of the number of lesions present

→ **≥3 (high tumor burden)**

→ **<3 (low tumor burden)**

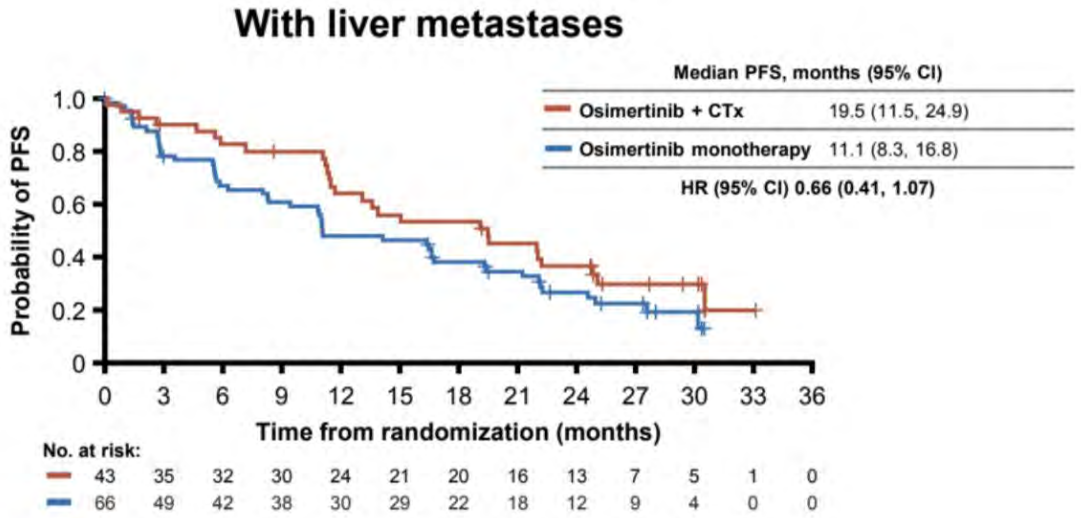
Valdiviezo et al, WCLC 2024

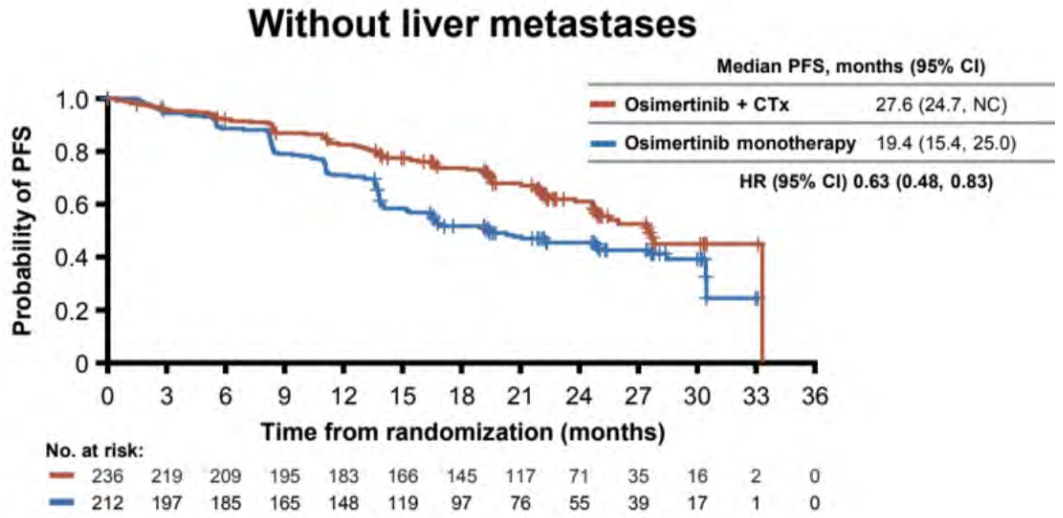
Osimertinib +/- Chemotherapy for EGFR mut NSCLC

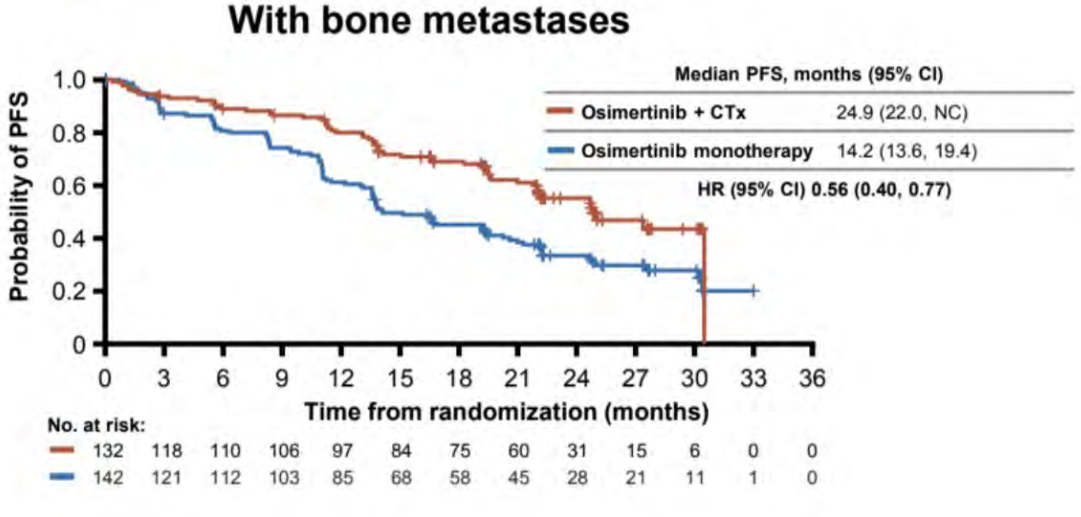


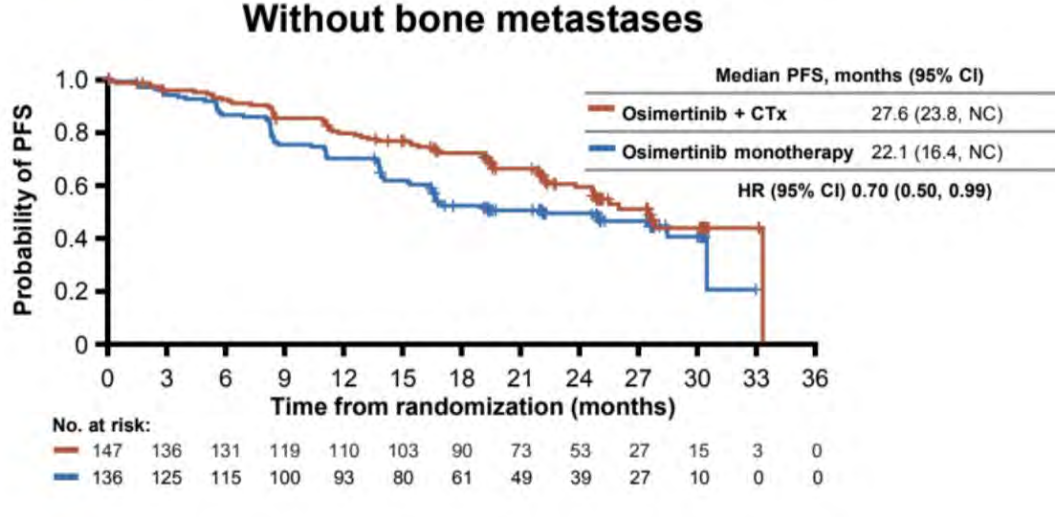
Valdiviezo et al, WCLC 2024

Osimertinib +/- Chemotherapy for EGFR mut NSCLC





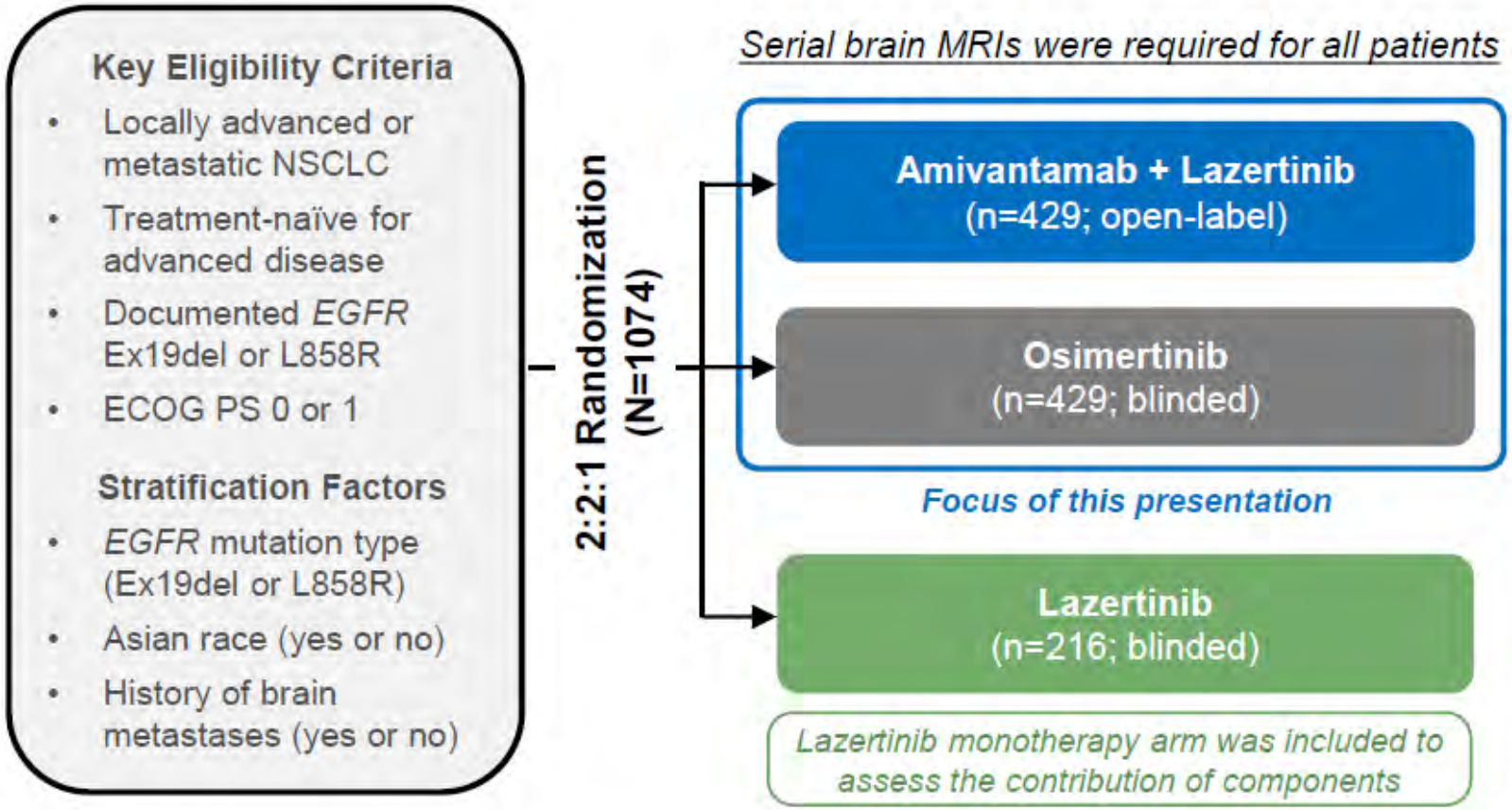




Valdiviezo et al, WCLC 2024

Amivantamab + lazertinib vs osimertinib for EGFR mut NSCLC

(EGFR/MET bispecific Ab + 3rd generation EGFR TKI)

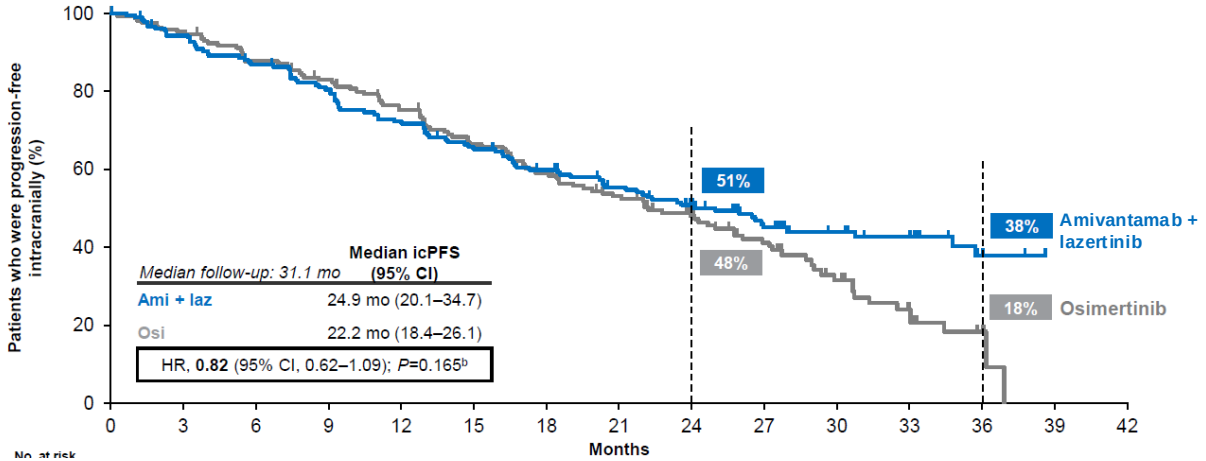


Gadgeel et al, WCLC 2024

Amivantamab + lazertinib vs osimertinib for EGFR mut NSCLC

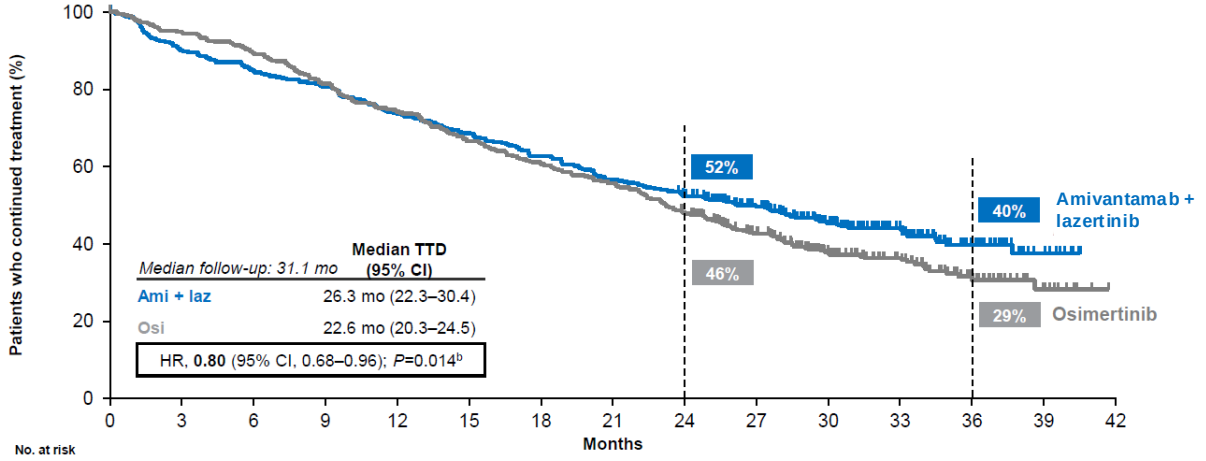
Intracranial PFS[a]

MARIPOSA required serial brain imaging for all patients, which provides robust evaluation of CNS outcomes
Amivantamab + lazertinib showed a favorable trend in icPFS with sustained and durable CNS control at 3 years



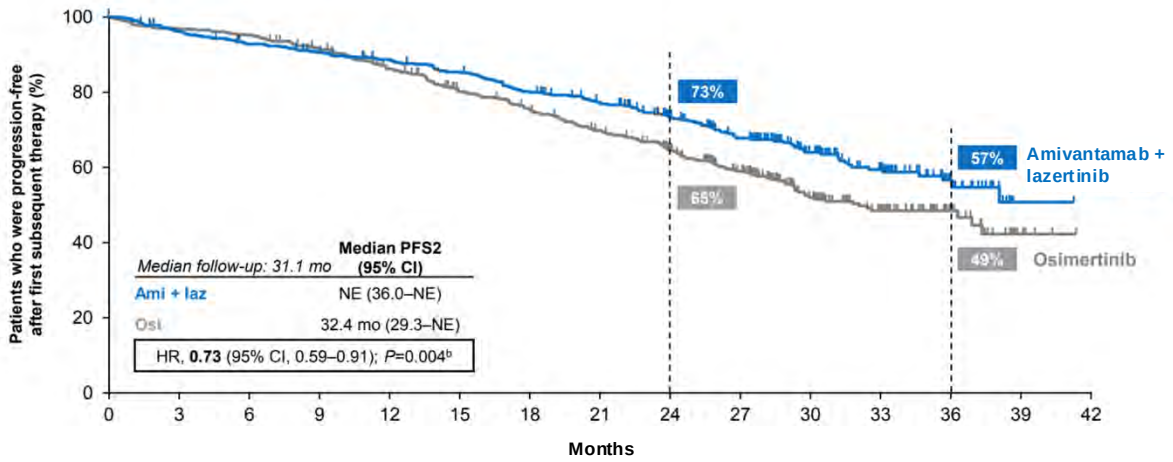
Time to Treatment Discontinuation[a]

Amivantamab + lazertinib demonstrated significantly longer TTD vs osimertinib



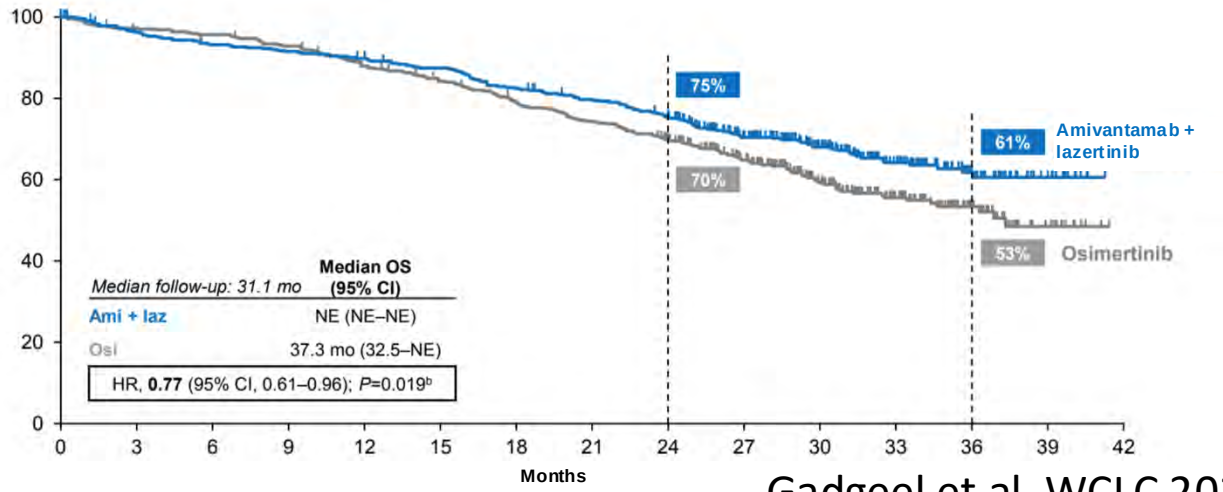
PFS2: PFS After First Subsequent Therapy[a]

Amivantamab + lazertinib significantly reduced the risk of 2nd disease progression or death by 27%



Updated Overall Survival Analysis[a]

A strong OS trend favoring amivantamab + lazertinib was observed

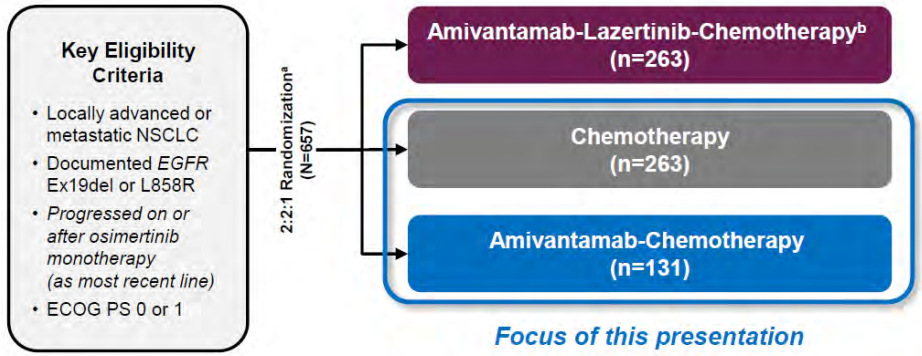


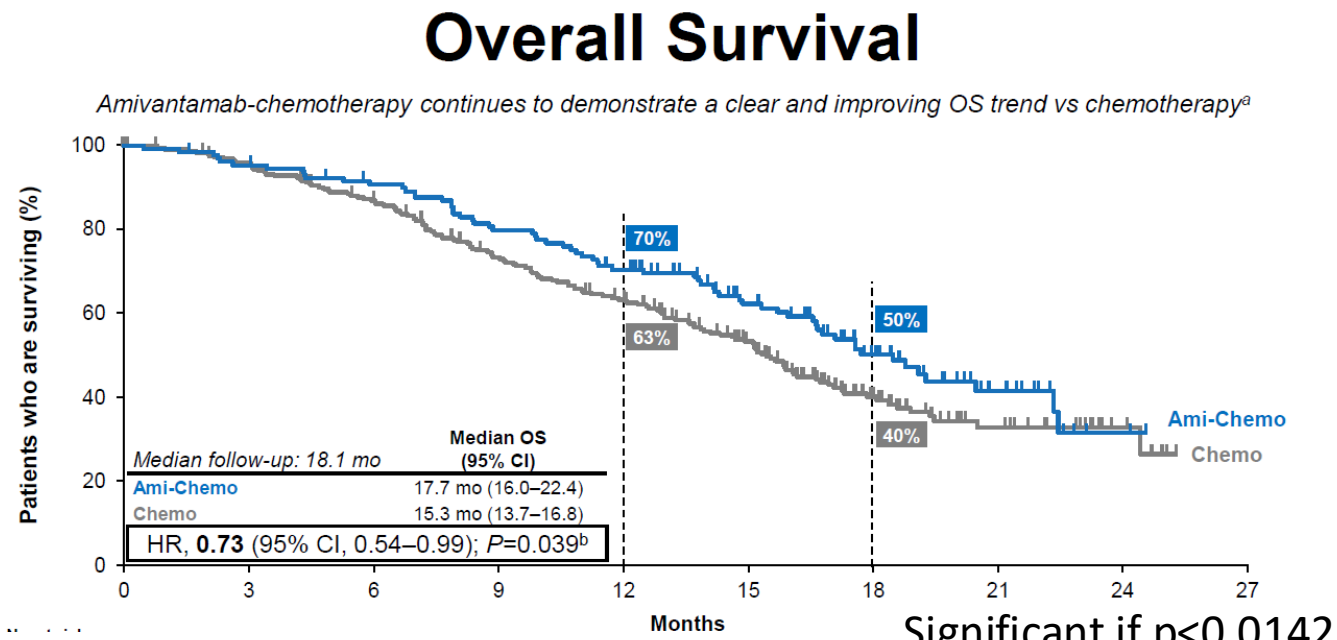
Significant if p<0.00001

Gadgeel et al, WCLC 2024

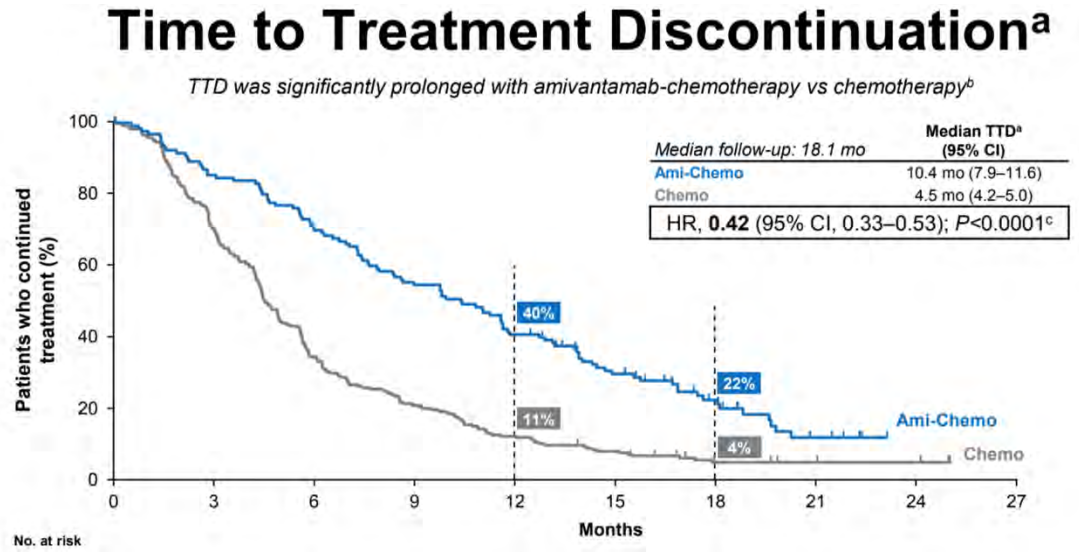

Patient with stage IV EGFR mutant lung cancer
osimertinib
?

Amivantamab + chemotherapy in EGFR mut NSCLC after osimertinib



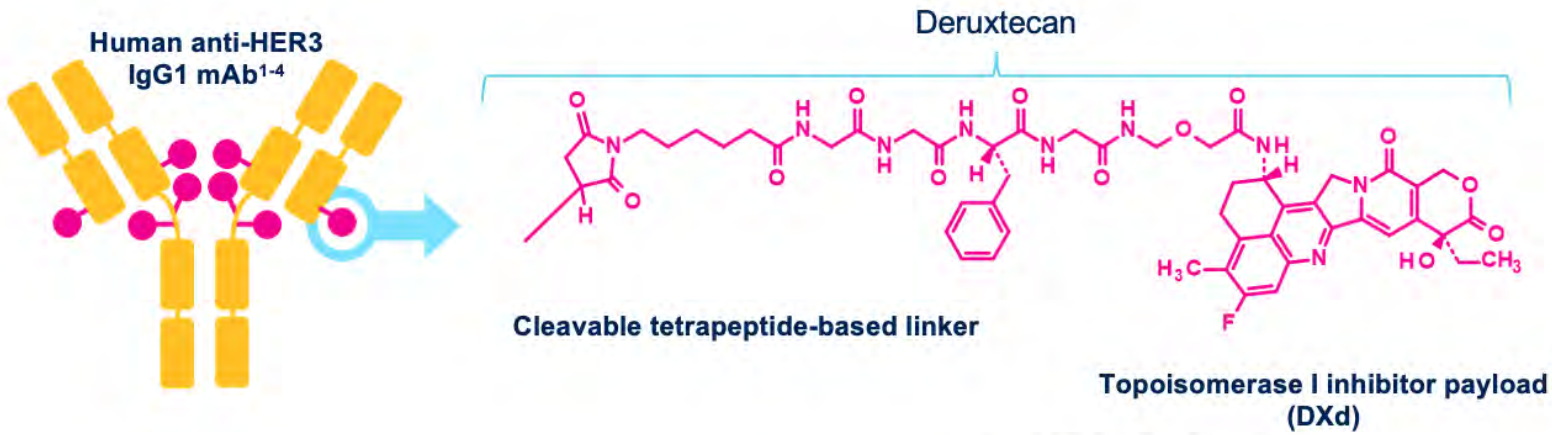


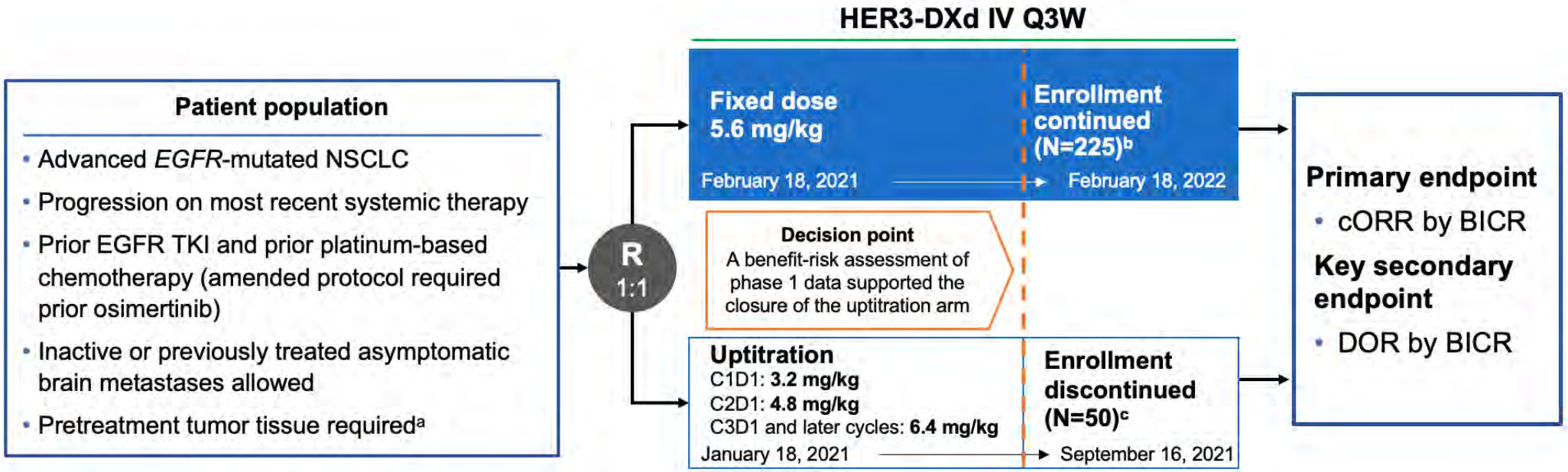
Significant if p<0.0142



Popat et al, ESMO 2024

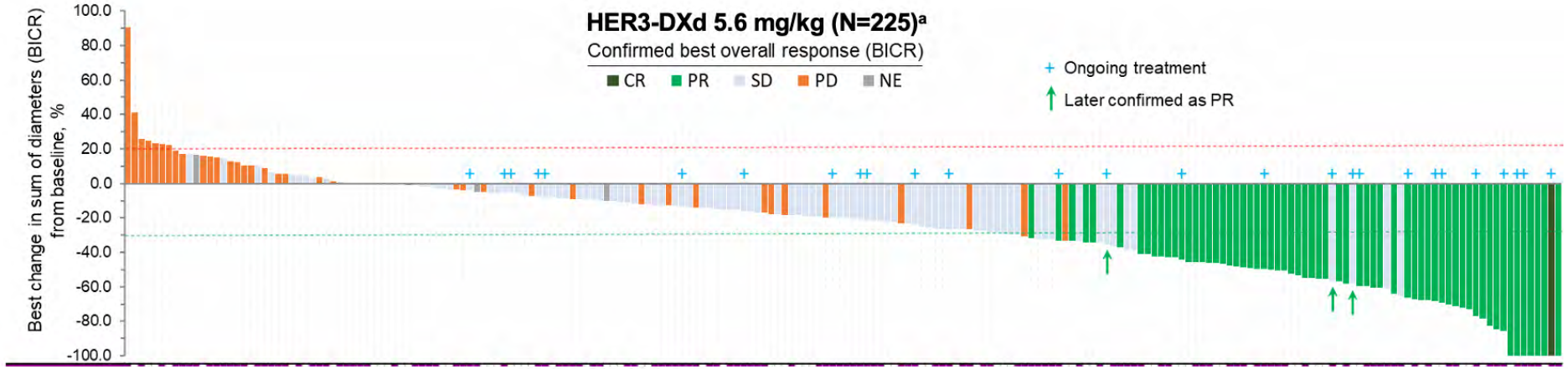
Patritumab Deruxtecan





Yu et al, WCLC 2023

Patritumab Deruxtecan after osimertinib and chemotherapy



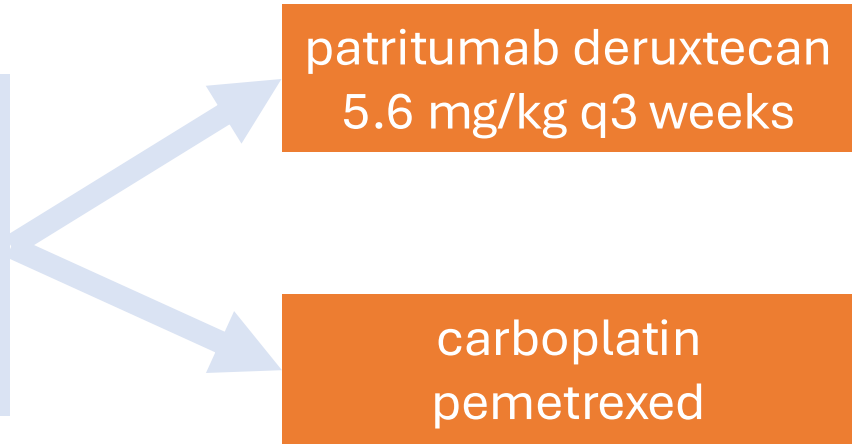
Confirmed responses and survival		Prior EGFR TKI (any) and PBC (N=225)	Subset with prior 3G EGFR TKI and PBC (n=209)
cORR (95% CI), %		**28.4 (22.6-34.8)**	**28.2 (22.2-34.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	63 (28.0)	58 (27.8)
	SD[a]	102 (45.3)	93 (44.5)
	PD	43 (19.1)	41 (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		6.0 (4.4-7.2)	6.4 (4.4-7.2)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.8 (11.2-12.6)	11.8 (10.9-12.6)

Intracranial response by CNS BICR per CNS RECIST	Patients with brain metastasis at baseline and no prior radiotherapy (N=30)[a]
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)
NE, n (%)	3 (10.0)
DOR, median (95% CI), mo	8.4 (5.8-NE)

Yu et al, WCLC 2023

Patients with:
- EGFR mutant NSCLC
- Progressed after prior osimertinib

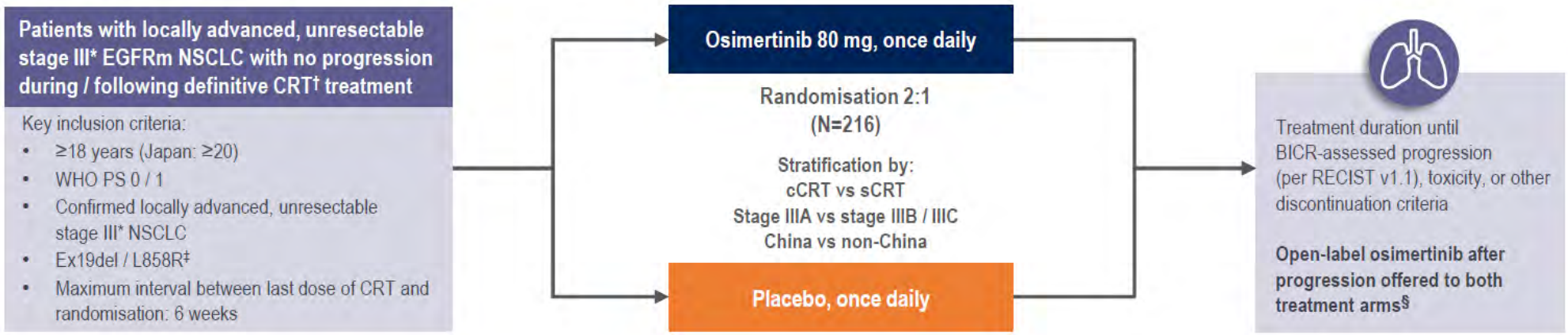
AND platinum-doublet chemotherapy
n=586

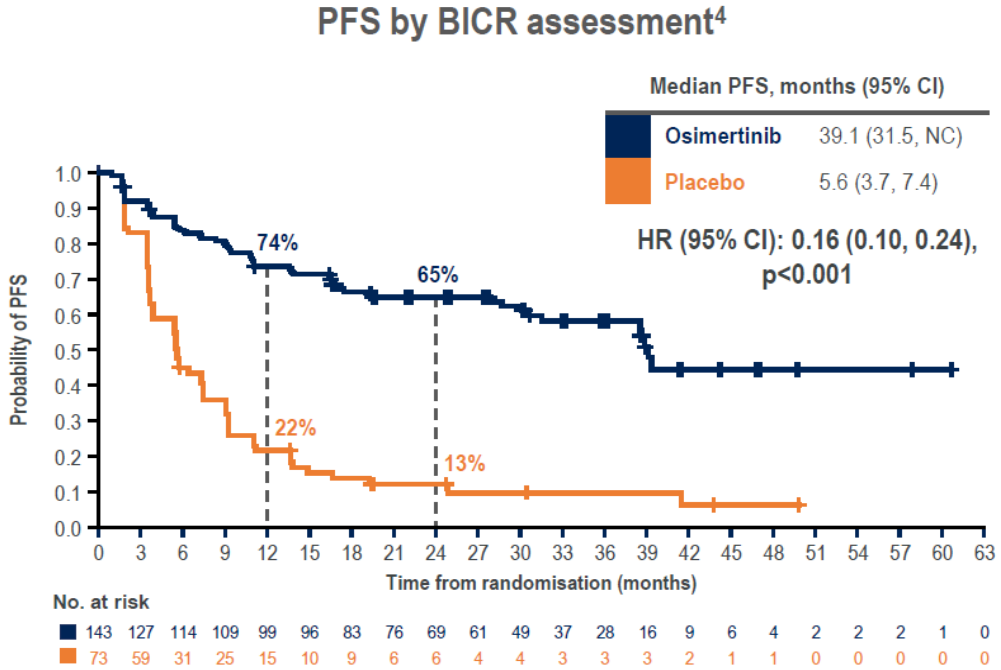


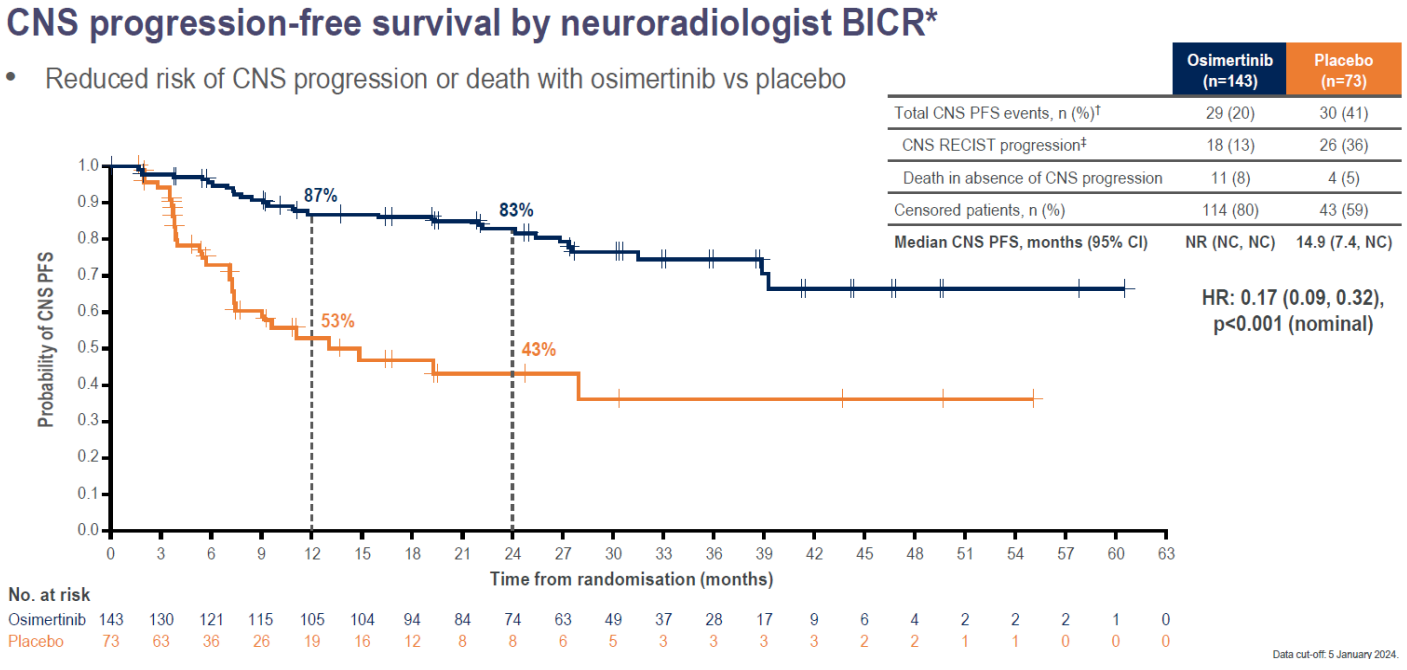
Patritumab Deruxtecan Demonstrated Statistically Significant Improvement in Progression-Free Survival Versus Doublet Chemotherapy in Patients with Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer in HERTHENA-Lung02 Phase 3 Trial

-press release 9/17/24

Osimertinib in locally advanced NSCLC

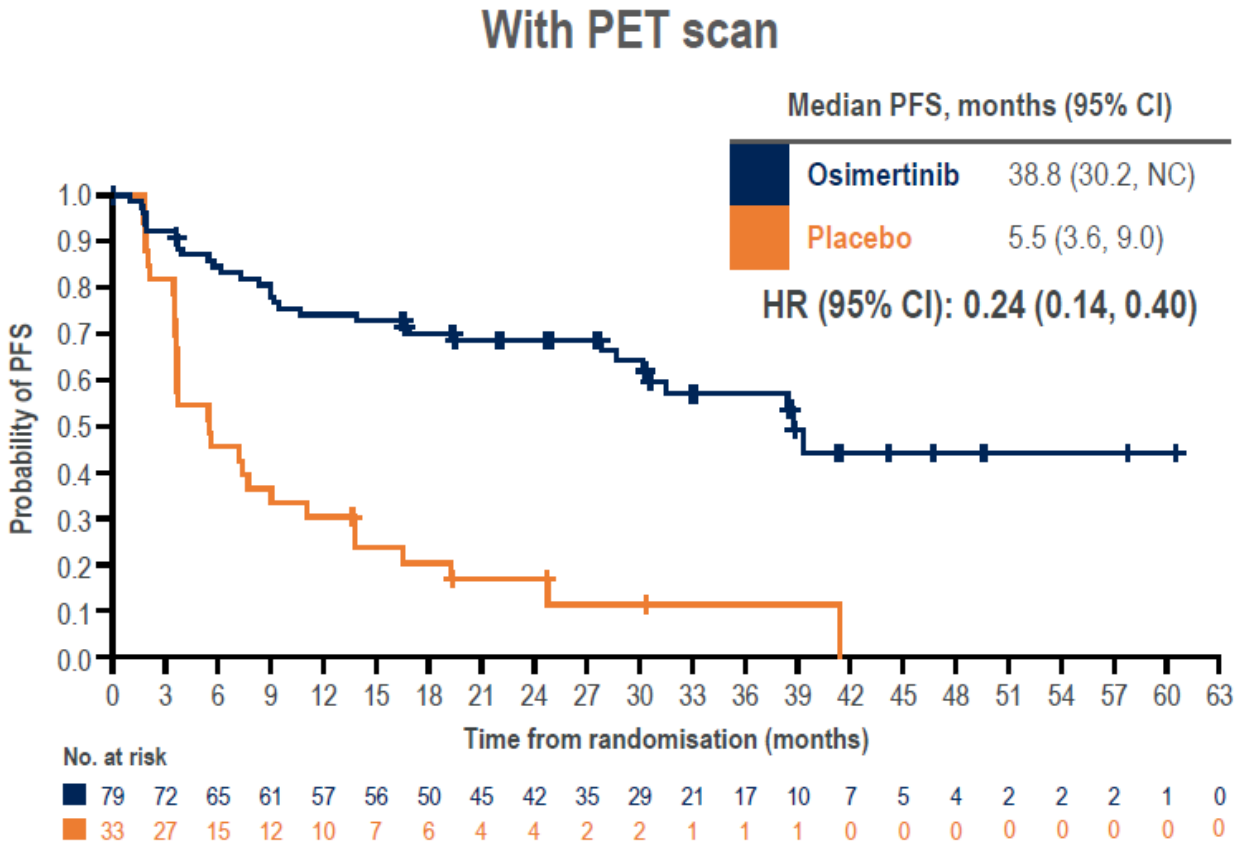


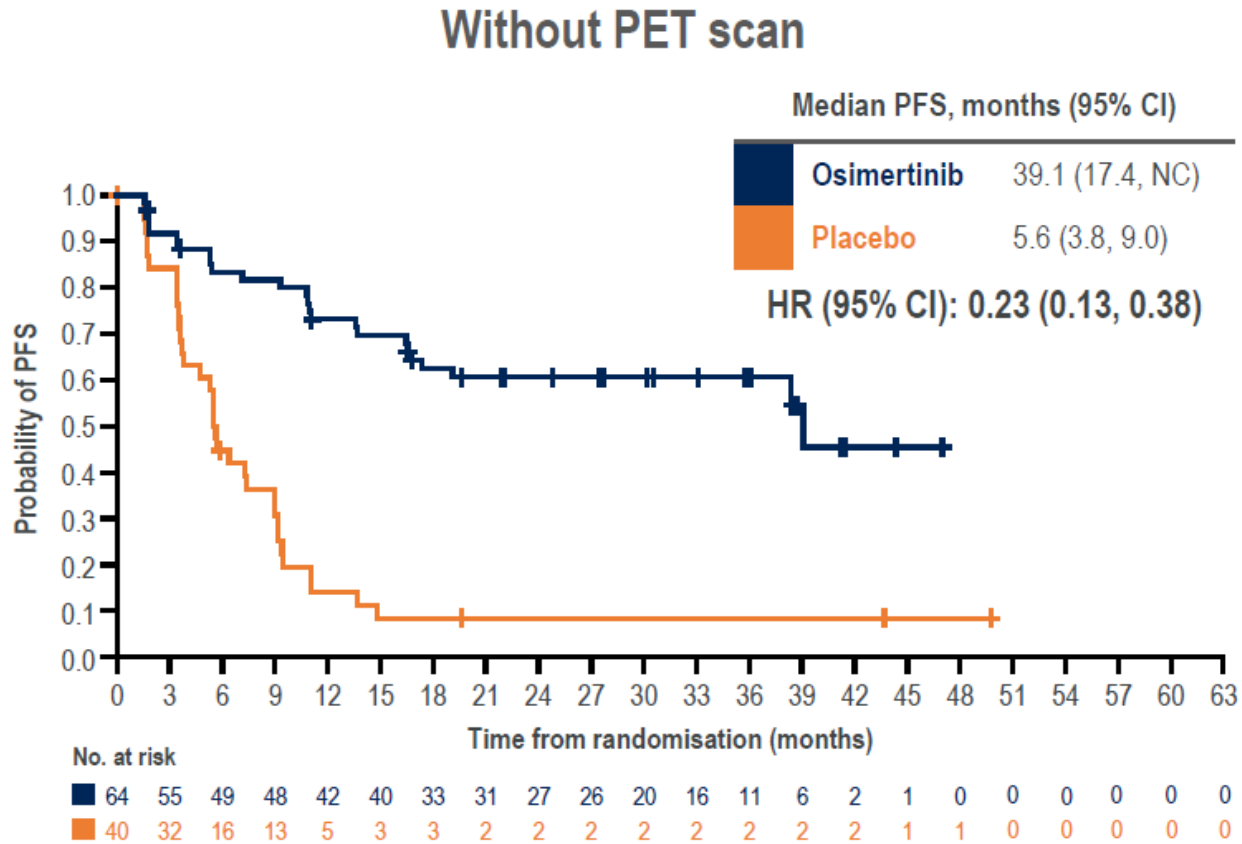




Lu et al, ESMO 2024

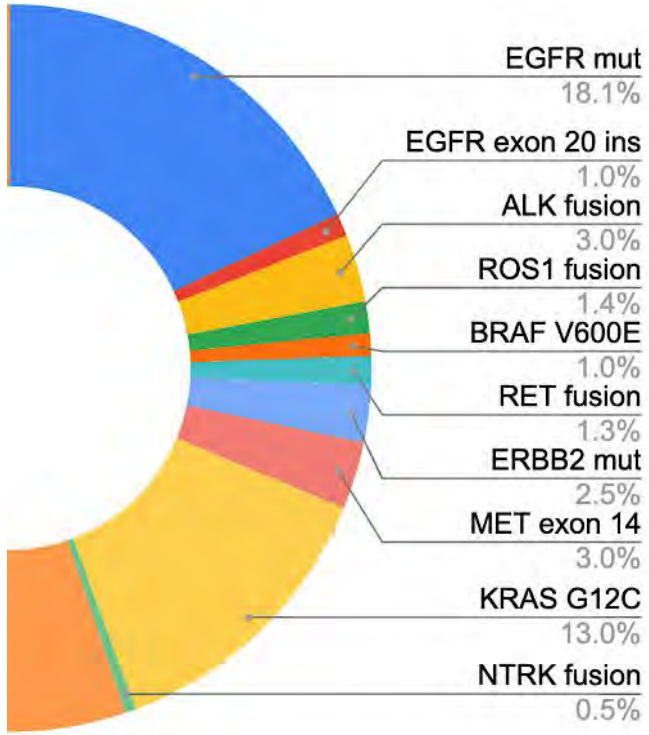
Osimertinib benefits were consistent +/-prior PET

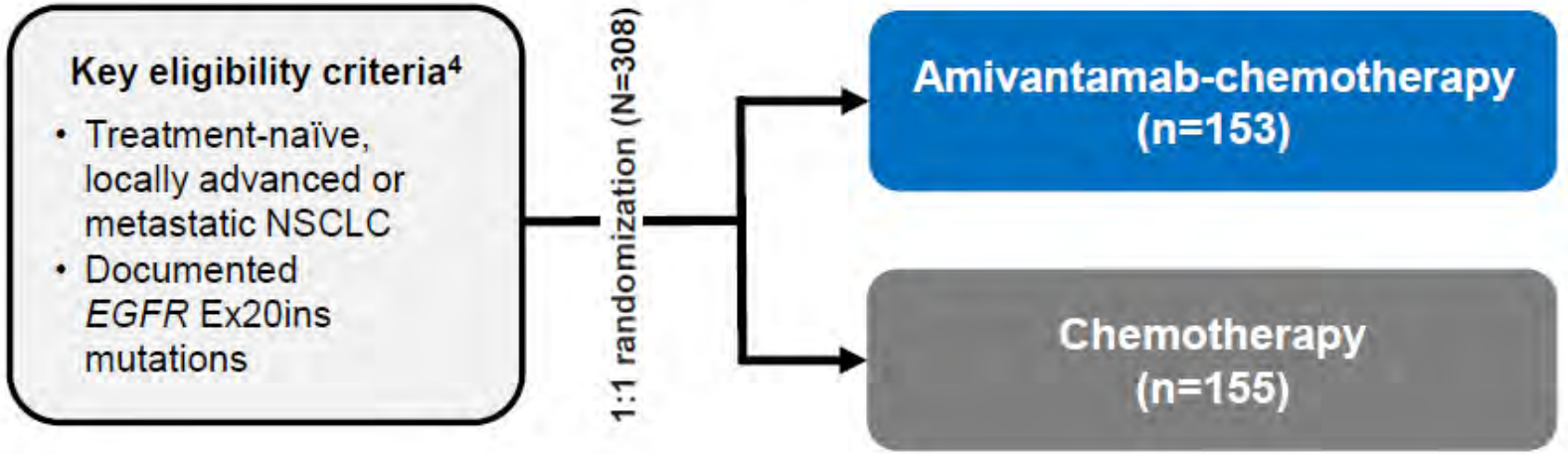




Lu et al, ESMO 2024

Chemotherapy +/- Amivantamab for EGFR exon 20 insertion NSCLC

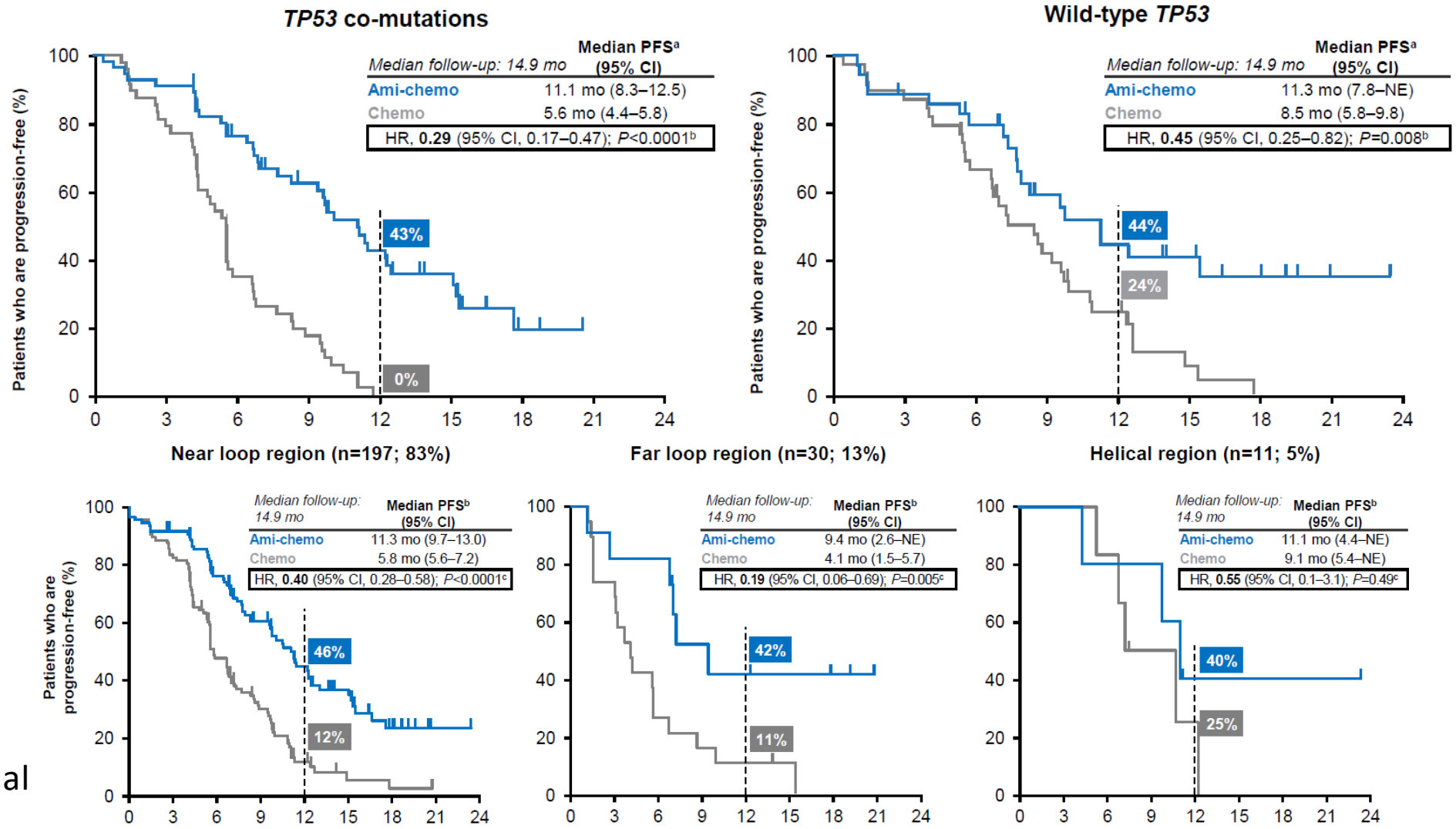




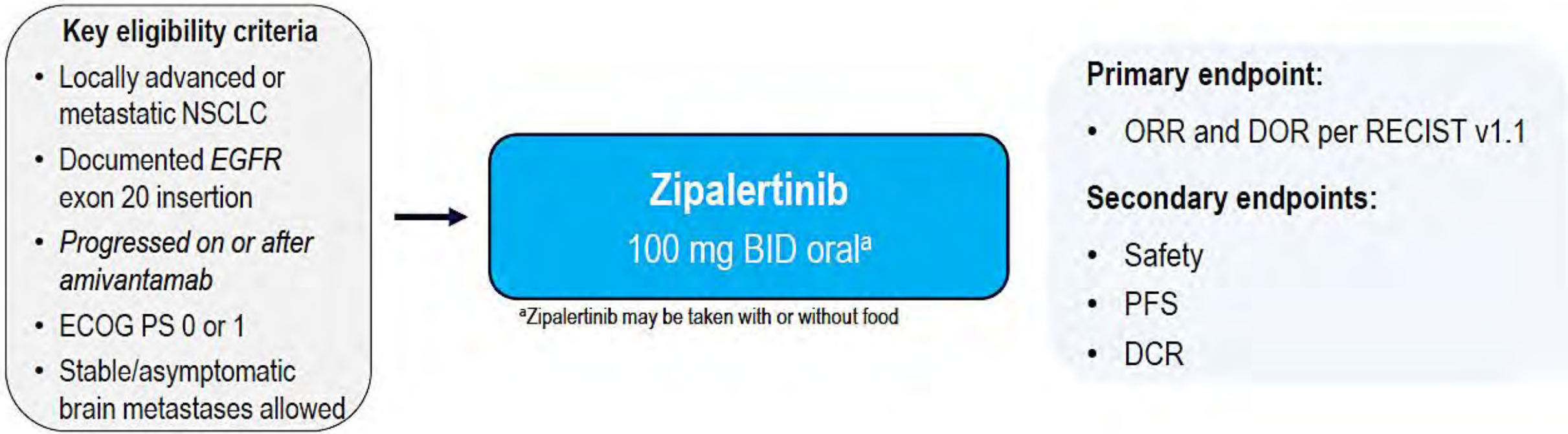
AACR GENIE BPC lung,
Data freely available at
https://genie.cbioportal.org/

Goldman et al, WCLC 2024

Chemotherapy +/- Amivantamab for EGFR exon 20 insertion NSCLC

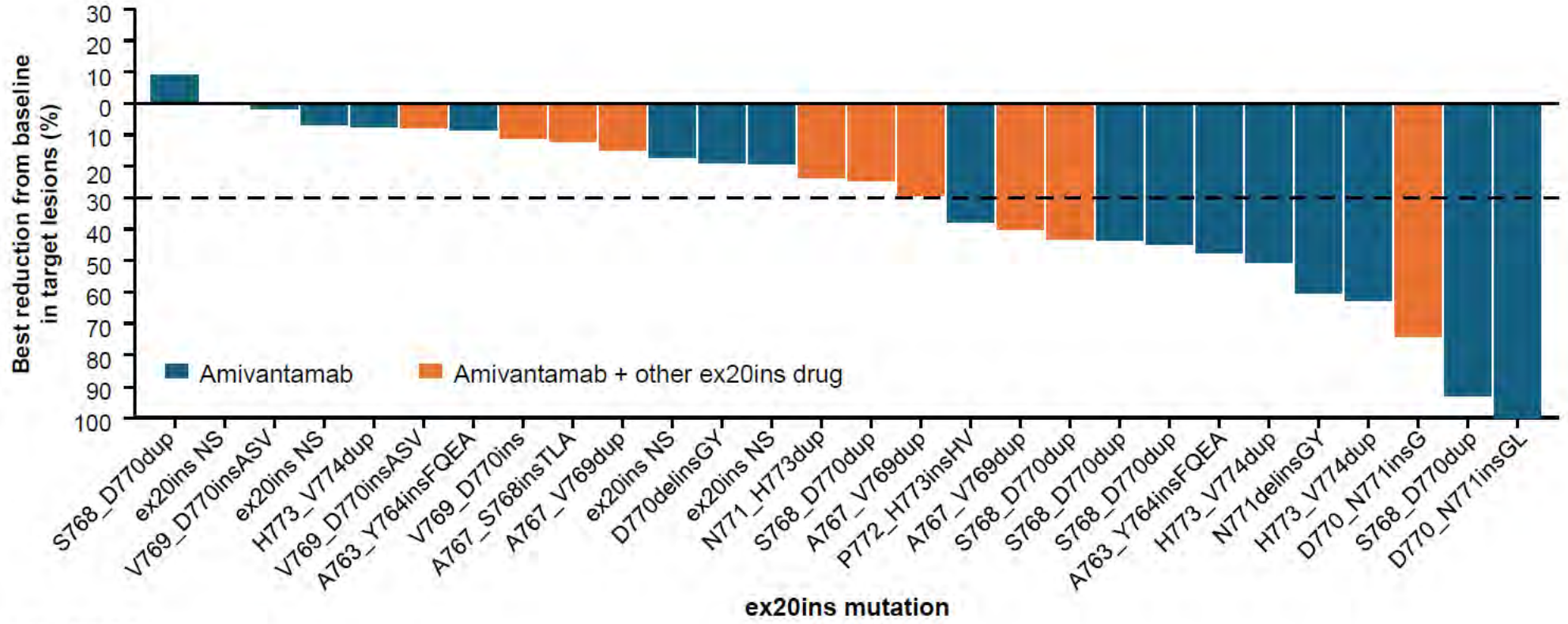


Goldman et al
WCLC 2024



Passaro et al, ESMO 2024

Zipalertinib in EGFR exon 20 with prior amivantamab



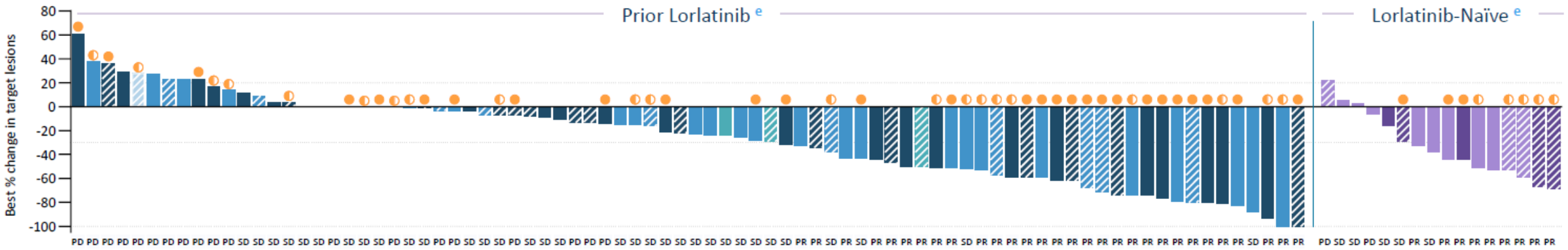
Statistics, n (%) [95% CI]	Ami only (n=18)	Ami + other ex20ins (n=12)	Total (N=30)
Confirmed ORR	9 (50.0) [26.0–74.0]	3 (25.0) [5.5–57.2]	12 (40.0) [22.7–59.4]

Passaro et al, ESMO 2024

Questions?

NVL-655 efficacy in previously-treated ALK+ NSCLC

RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [b]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	38% (39/103)	52% (30/58)	69% (22/32) [d]	35% (30/85)	47% (23/49)	54% (15/28)	53% (9/17)	88% (7/8)
RP2D	38% (15/39)	55% (12/22)	71% (10/14)	35% (11/31)	50% (8/16)	64% (7/11)	57% (4/7)	80% (4/5)



Data cut-off: 15 June 2024. Response-evaluable patients with NSCLC. All responses were confirmed.

NSCLC, non-small cell lung cancer; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **RP2D**, Recommended Phase 2 dose (150 mg QD); **SD**, stable disease; **TKI**, tyrosine kinase inhibitor.

[a] Includes all patients with ≥1 identified ALK resistance mutation as per local or central testing of blood (ctDNA) or tissue. Responses observed in patients with ALK I1171N/S, V1180L, L1196Q, L1198F, D1203N, or E1210K mutations, including where multiple mutations co-occur, in addition to those with G1202R.

[b] Includes patients with G1202R single and compound (≥2) mutations.

[c] Cis-allelic configuration has not been confirmed for all patients with compound (≥2) ALK resistance mutations.

[d] ORR = 67% (20/30) for G1202R patients with prior lorlatinib, and ORR= 100% (2/2) for lorlatinib-naïve G1202R patients.

[e] Five response-evaluable patients (4 with no known ALK mutations and 1 with single ALK mutation) not shown due to incomplete or missing post-baseline tumor assessments in the setting of PD or symptomatic deterioration.

KEY: PATIENT DETAILS

Lorlatinib Pre-treated:
- ≥ 3 prior ALK TKIs
- 2 prior, 2G + lorlatinib
- 2 prior, 1G + lorlatinib
- 1 prior (lorlatinib only)

Lorlatinib-naïve:
- ≥ 2 prior ALK TKIs
- 1 prior, alectinib

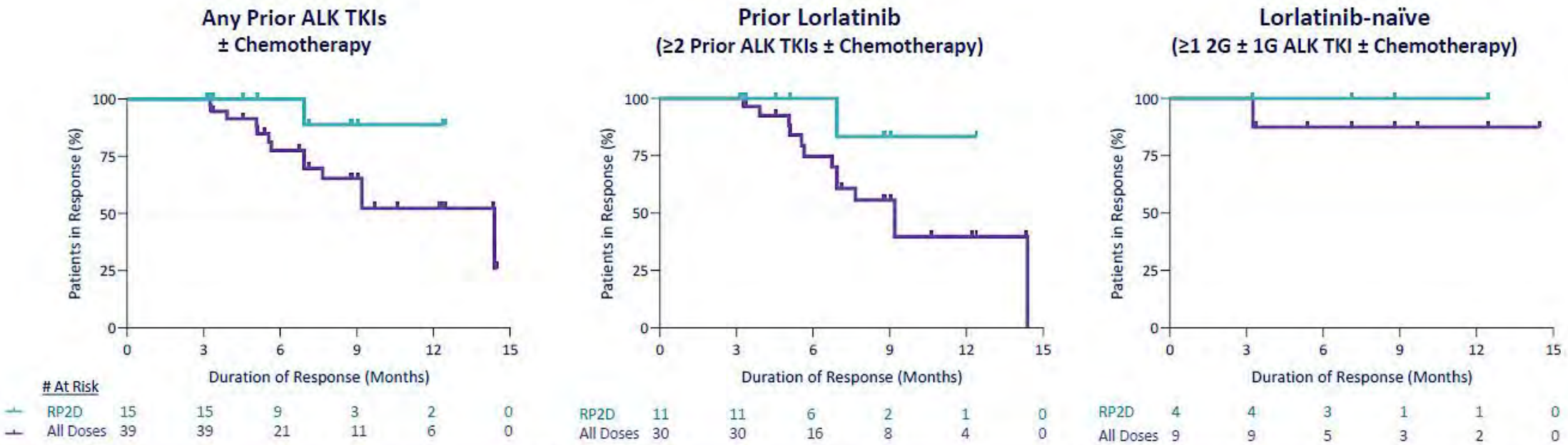
Patient treated at RP2D

ALK single resistance mutation

ALK compound (≥2) resistance mutation

Drilon et al, ESMO 2024

NVL-655 duration of response



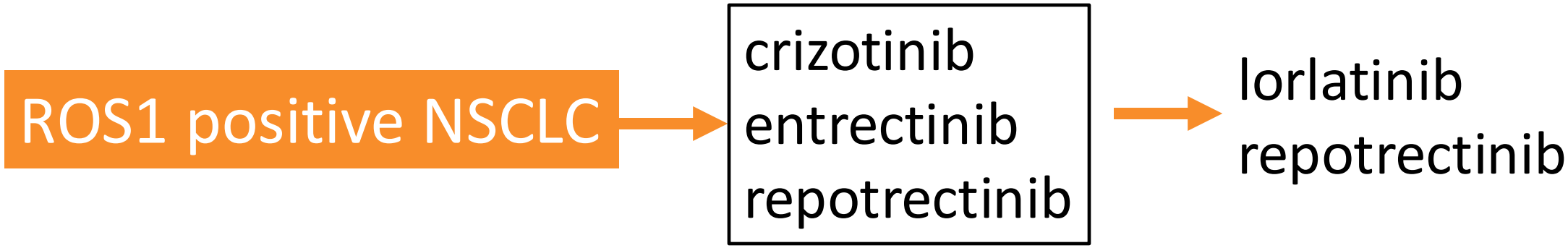
NSCLC Response-Evaluable	All Dose Levels	RP2D	All Dose Levels	RP2D	All Dose Levels	RP2D
Median DOR, m (95% CI)	**14.4** (6.9, NE)	**Not Reached** (6.9, NE)	**9.2** (6.9, NE)	**Not Reached** (6.9, NE)	**Not Reached** (3.3, NE)	**Not Reached** (NE, NE)
DOR ≥ 6 m [a] (95% CI)	**78%** (58, 89)	**100%** (100, 100)	**75%** (52, 88)	**100%** (100, 100)	**88%** (39, 98)	**100%** (100, 100)

Data-cut off: 15 June 2024. **1G**, 1st generation ALK TKI (i.e., crizotinib); **2G**, 2nd generation ALK TKI (i.e., ceritinib, alectinib, or brigatinib); **CI**, confidence interval; **DOR**, duration of response; **m**, months; **NE**, not evaluable; **NSCLC**, non-small cell lung cancer; **RP2D**, recommended phase 2 dose; **TKI**, tyrosine kinase inhibitor.

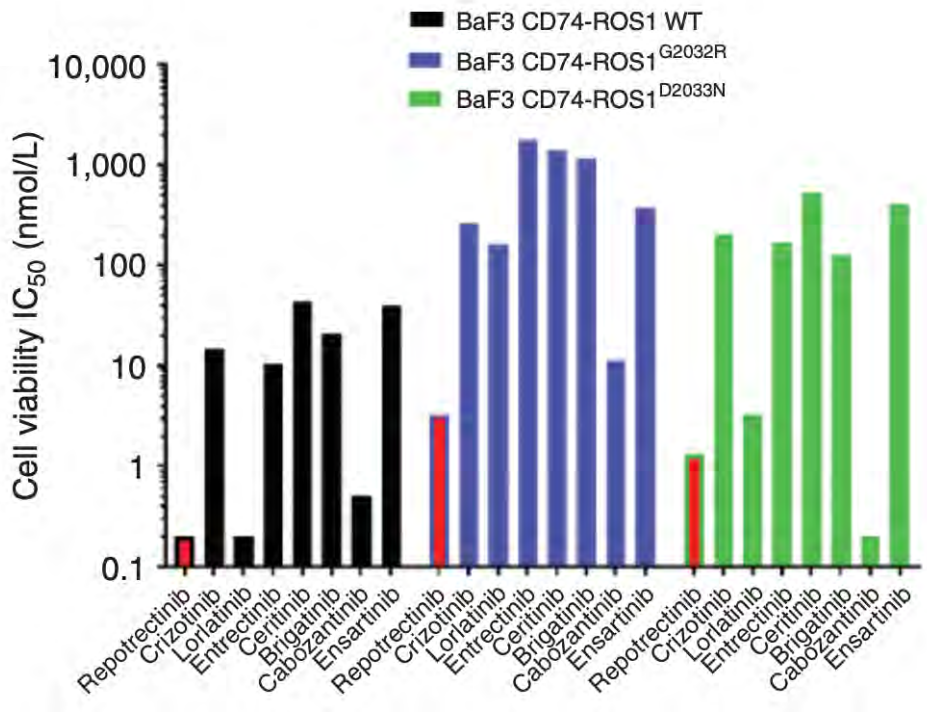
[a] Analyses of DOR based on Kaplan-Meier estimates.

Drilon et al, ESMO 2024

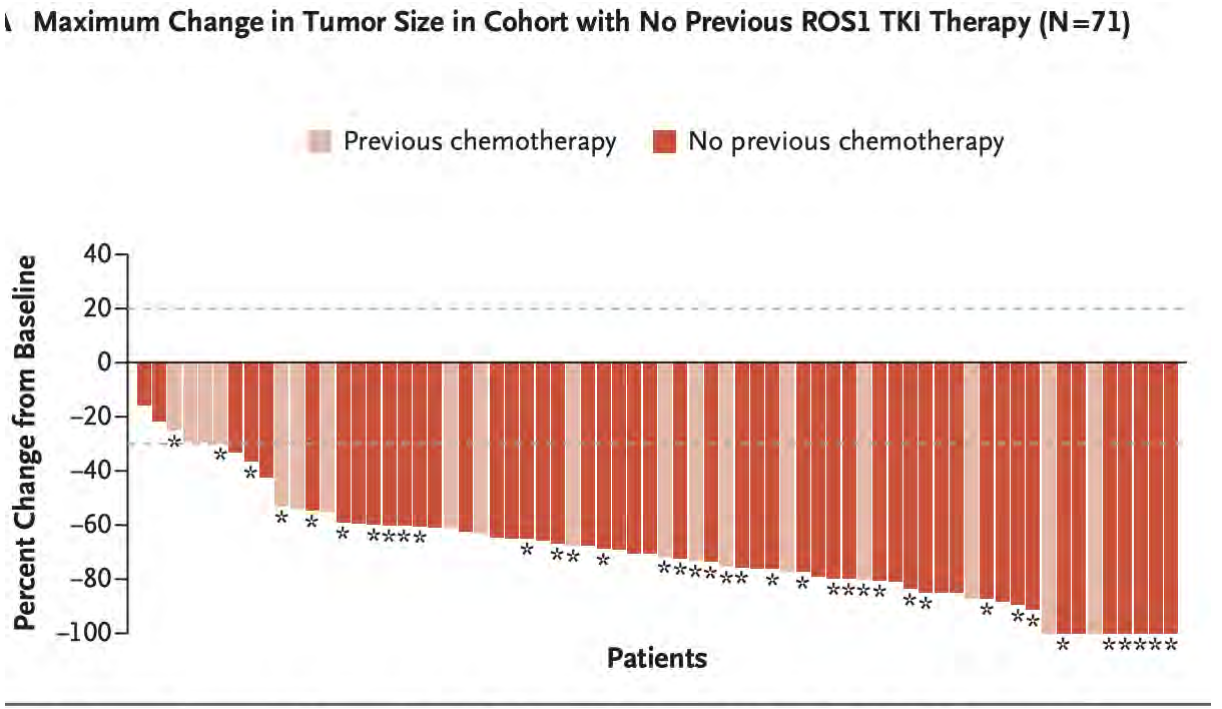
Today…

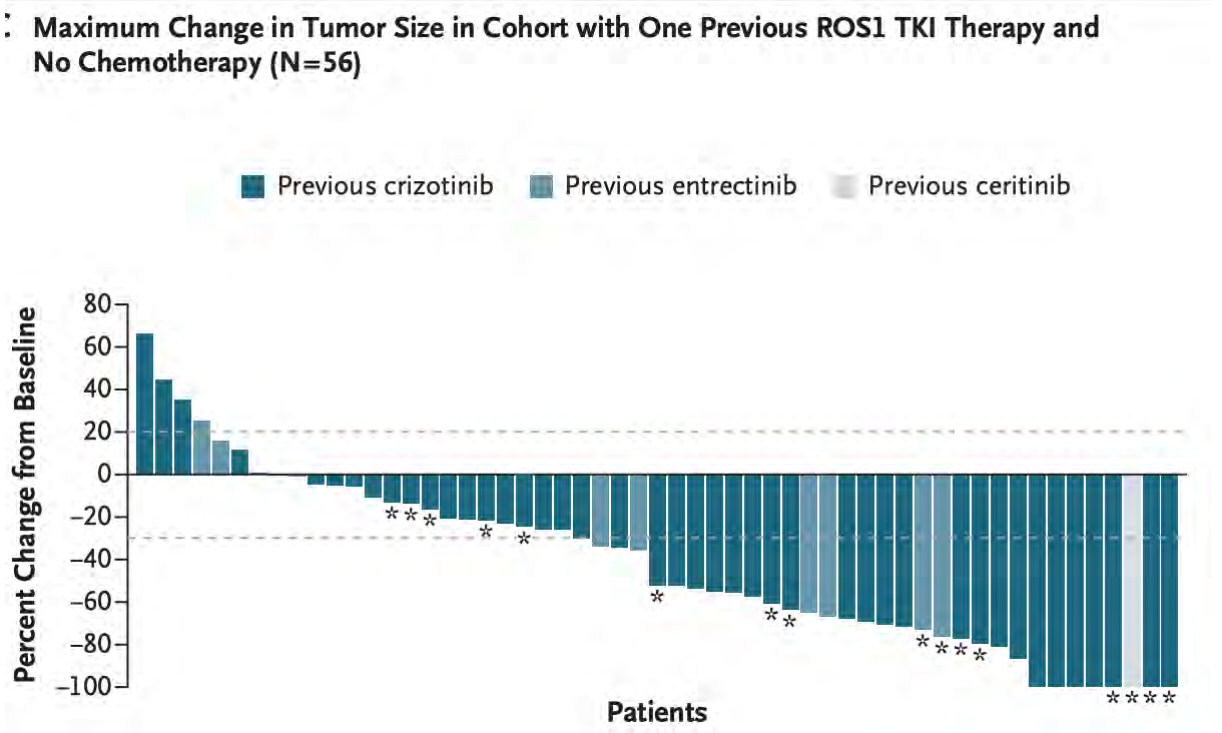

ROS1 positive NSCLC
crizotinib
entrectinib
repotrectinib
lorlatinib
repotrectinib

Repotrectinib



Drilon et al, Can Discovery 2018, Drilon et al NEJM 2024

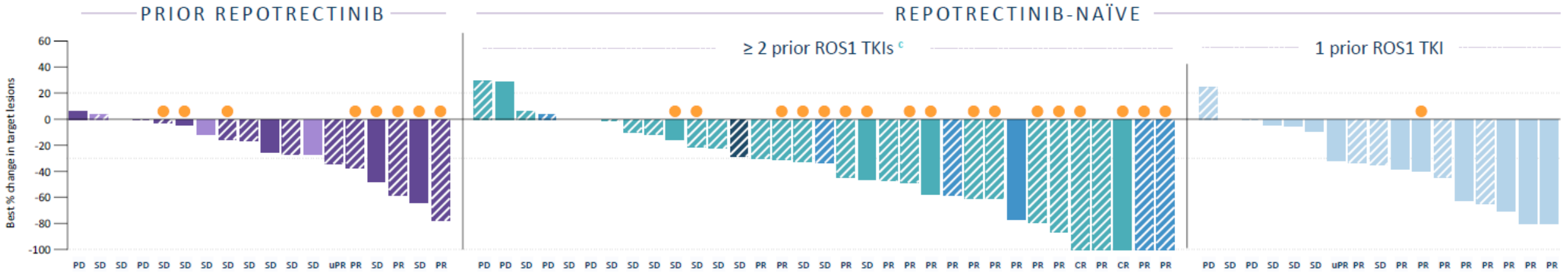




Zidesamtinib (NVL-520) Efficacy in ROS1+ NSCLC

All NSCLC Response Evaluable Patients *± chemotherapy*	Any Prior ROS1 TKI (range 1-4)				≥ 2 prior ROS1 TKIs			1 prior ROS1 TKI (crizotinib)
	All	Repotrectinib-naive	ROS1 G2032R Resistance Mutation [b]		All	Prior Lorlatinib	Repotrectinib-naive	
			Prior Repotrectinib	Repotrectinib-naive				
RECIST 1.1 ORR % (n/n) [a]	**44%** (31/71)	**51%** (27/53)	**38%** (3/8)	**72%** (13/18)	**41%** (21/51)	**44%** (17/39)	**47%** (17/36)	**73%** (8/11)
CR *	2	2	-	2	2	2	2	-

* 2 confirmed CRs ongoing with DOR 19.3+ and 26.3+ months. 5 additional CRs observed among patients without measurable disease (2 prior ROS1 TKIs [n=2], 1 prior ROS1 TKI (crizotinib [n=1], entrectinib [n=2])), all ongoing with DOR 3.6+, 3.7+, 13.8+, 13.9+, and 18.5+ months.



Data cut-off: 1 July 2024 . Response-evaluable patients with ROS1+ NSCLC.
CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; TKI, tyrosine kinase inhibitor; uPR, unconfirmed partial response.

[a] Includes two ongoing partial responses pending confirmation.

[b] ROS1 mutations as per local or central testing of blood (ctDNA) or tissue. Responses also observed in patients with ROS1 resistance mutations other than G2032R (S1986F, D2033N).

[c] Three response-evaluable patients not shown due to incomplete or missing post-baseline tumor assessments in the setting of symptomatic deterioration.

KEY: PATIENT DETAILS

Prior Repotrectinib: ≥ 2 prior ROS1 TKIs; 1 prior ROS1 TKI

Repotrectinib-naive: 4 prior ROS1 TKIs; 3 prior ROS1 TKIs; 2 prior ROS1 TKIs; 1 prior ROS1 TKI

+ chemotherapy

ROS1 G2032R mutation

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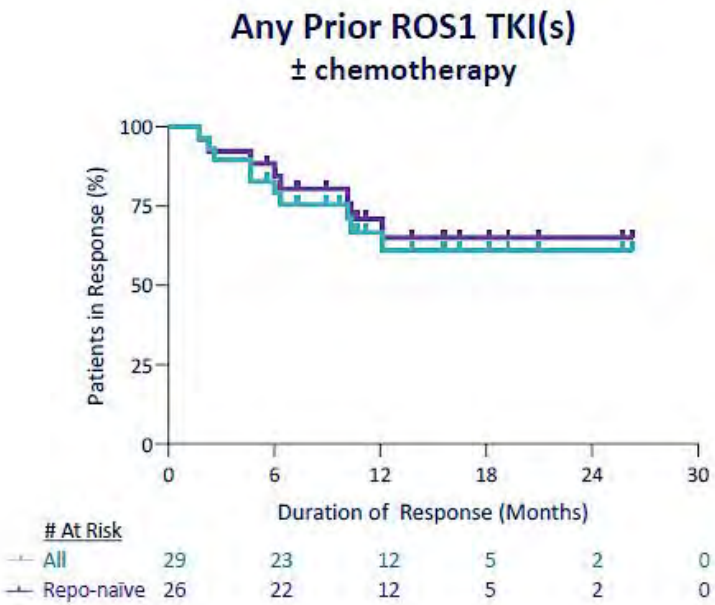
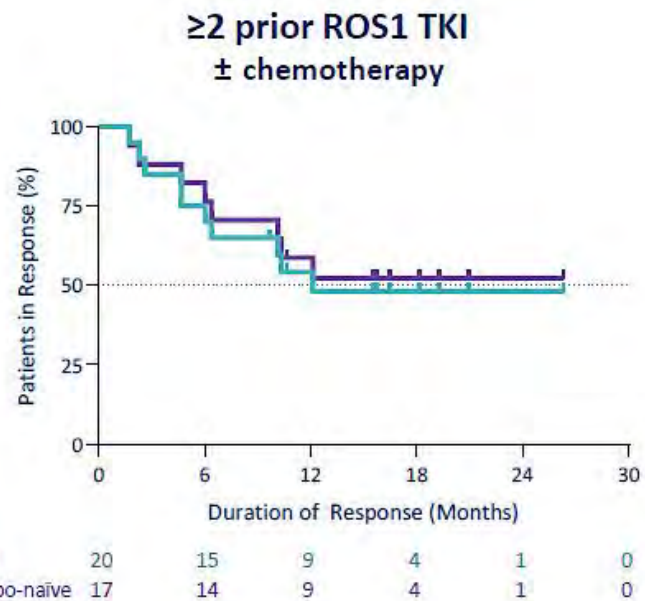
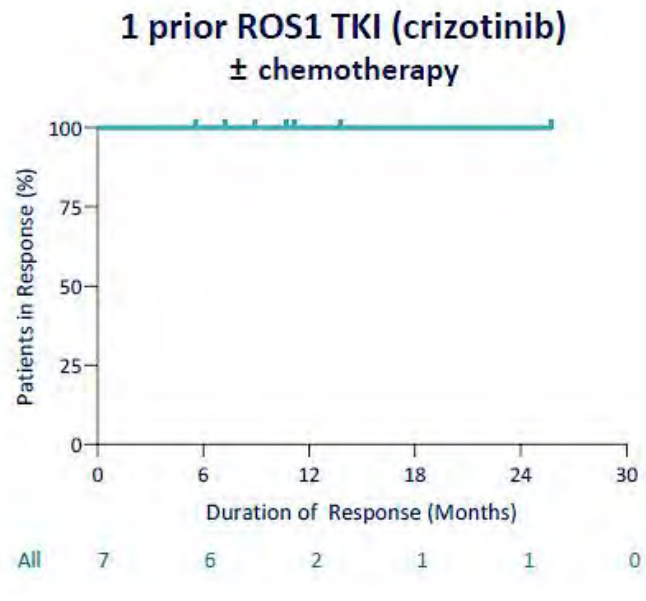
Zidesamtinib (NVL-520) duration of response in ROS1+ NSCLC







NSCLC Response-Evaluable, All Doses	All	Repotrectinib-naïve	All	Repotrectinib-naïve	All
Median DOR, months (95% CI)	**Not Reached** (10.3, NE)	**Not Reached** (10.3, NE)	**12.1** (4.7, NE)	**Not Reached** (6.0, NE)	**Not Reached** (NE, NE)
DOR ≥ 6 months [a] (95% CI)	**83%** (63, 92)	**88%** (68, 96)	**75%** (50, 89)	**82%** (55, 94)	**100%** (100, 100)
DOR ≥ 12 months [a] (95% CI)	**67%** (45, 81)	**71%** (48, 85)	**54%** (30, 73)	**59%** (33, 78)	**100%** (100, 100)

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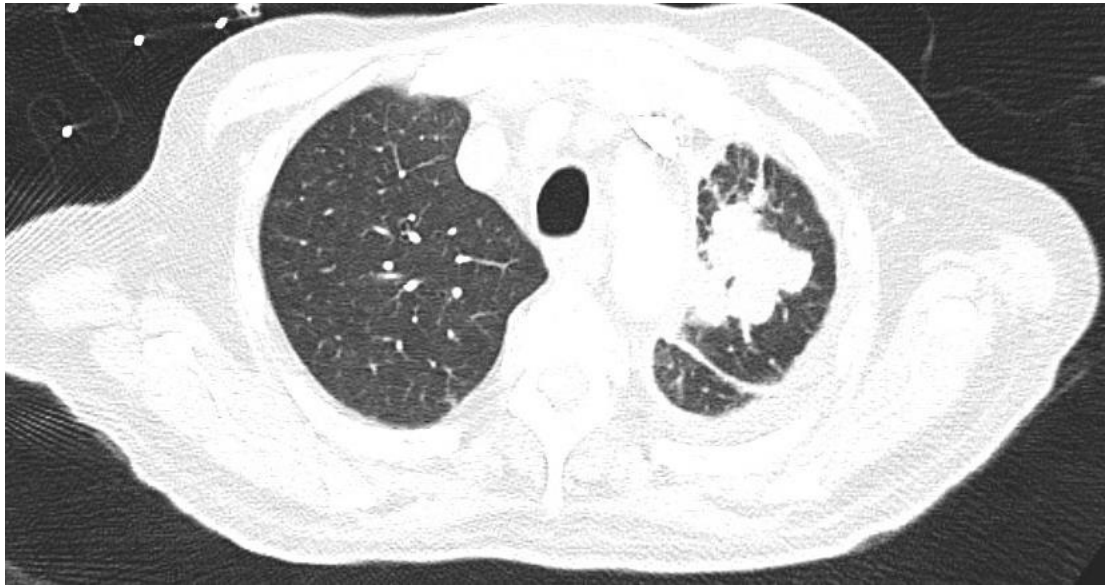
Questions?

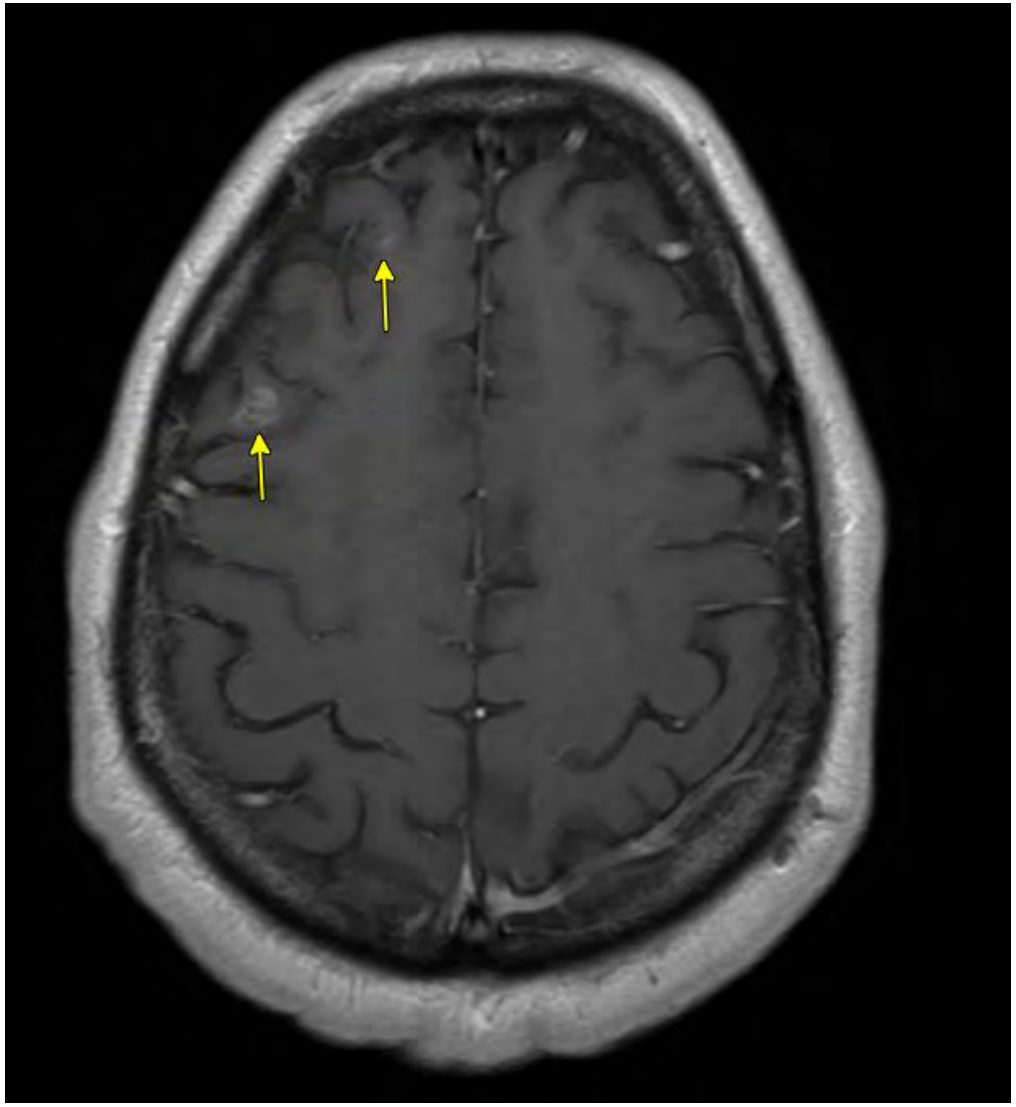
Dr Riely – Patient Case 1: 74-year-old woman

- 74 year old woman with history of metastatic lung cancer (involving lung and pleura).
- EGFR exon 19 deletion.
- Treated with initial osimertinib, with progression after two years.
- She was treated with carboplatin and pemetrexed for 4 cycles, and then maintenance pemetrexed for an additional 4 cycles.
- Most recent scan shows progression in adrenal gland as well as increase in four nodules in the right lung, with largest lesion measuring 4.6 cm



Dr Riely – Patient Case 2: 44-year-old man

- 44 year-old man initially presented with bilateral lung mass, pleural effusion. Molecular testing showed *EML4-ALK* fusion
- Patient had good response to alectinib with resolution of pleural effusion and complete response in the CNS.
- After three years of alectinib, patient had progression of disease with 2 new/recurrent lesions in the CNS. He was treated with Stereotactic Brain Radiation
- 3 months later, had further progression of disease in the CNS and progression in the lung
- Biopsy of the lung lesion showed *ALK* G1202R/L1196M



Optimizing Therapy for Patients with Hormone Receptor-Positive Metastatic Breast Cancer Harboring PI3K/AKT/PTEN Pathway Abnormalities

A CME/MOC-Accredited Live Webinar

Thursday, October 31, 2024
5:00 PM – 6:00 PM ET

Faculty

Komal Jhaveri, MD, FACP
Hope S Rugo, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

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