Overview

Saturday, March 23rd

Module 1: 7:30 AM – 9:10 AM — Hodgkin and Non-Hodgkin Lymphoma

Module 2: 9:30 AM – 10:20 AM — Gynecologic Cancers

Module 3: 10:20 AM – 11:10 AM — Localized Breast Cancer; SABCS 2023 Review

Module 4: 11:10 AM – 12:00 PM — Metastatic HER2-Positive and Triple-Negative Breast Cancer; SABCS 2023 Review

Module 5: 12:30 PM – 1:20 PM — Prostate Cancer

Module 6: 1:20 PM – 2:10 PM — Urothelial Bladder Cancer

Module 7: 2:10 PM – 3:00 PM — Renal Cell Carcinoma

Module 8: 3:20 PM – 4:10 PM — Targeted Therapy for Non-Small Cell Lung Cancer

Module 9: 4:10 PM – 5:00 PM — Nontargeted Treatments for Lung Cancer

Third Annual National General Medical Oncology Summit

Agenda

Module 1: Management of Non-Small Cell Lung Cancer with an EGFR Mutation — Dr Yu

Module 2: Care of Individuals with other Targetable Genomic Abnormalities — Dr Dagogo-Jack

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Module 1: Management of Non-Small Cell Lung Cancer with an EGFR Mutation — Dr Yu

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Memorial Sloan Kettering Cancer Center

Management of Non-Small Cell Lung Cancer (NSCLC) with an EGFR mutation

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

Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Blueprint Medicines, C4 Therapeutics, Cullinan Oncology, Daiichi Sankyo Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc
Data and Safety Monitoring Board /Committee	Janssen Biotech Inc
Research Funding to My Institution	AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Blueprint Medicines, Cullinan Oncology, Daiichi Sankyo Inc, Erasca, Janssen Biotech Inc, Novartis, Pfizer Inc

Outline

EGFR-mutant lung cancers

- Osimertinib in early-stage disease
- Osimertinib + chemotherapy for metastatic disease
- Role for amivantamab in 1L and 2L treatment
- Role for HER3 antibody drug conjugates

EGFR exon 20 pos lung cancers

- Role for amivantamab in 1L and 2L treatment

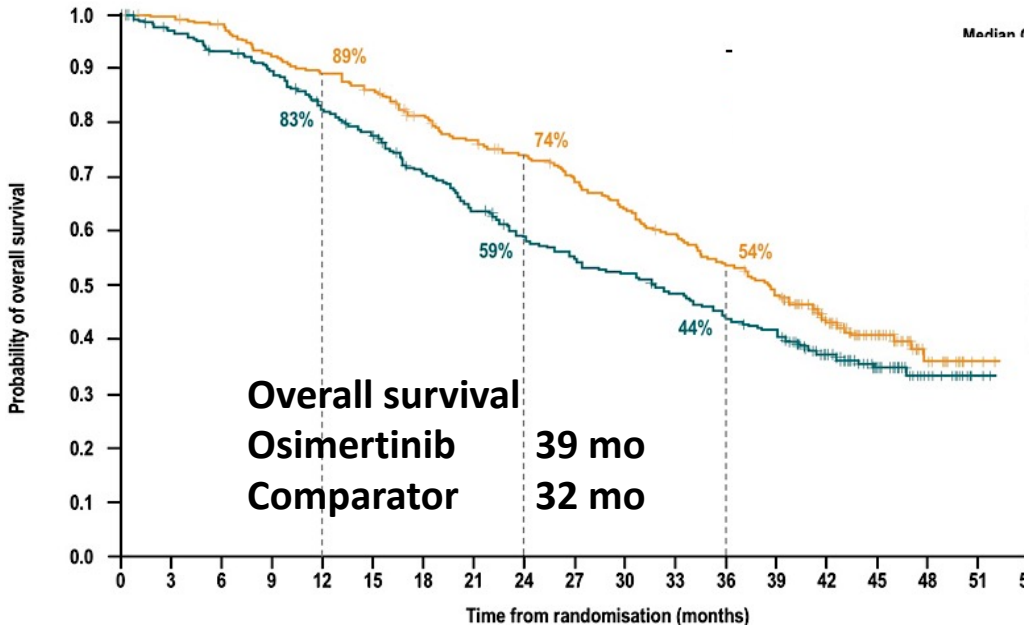
Case

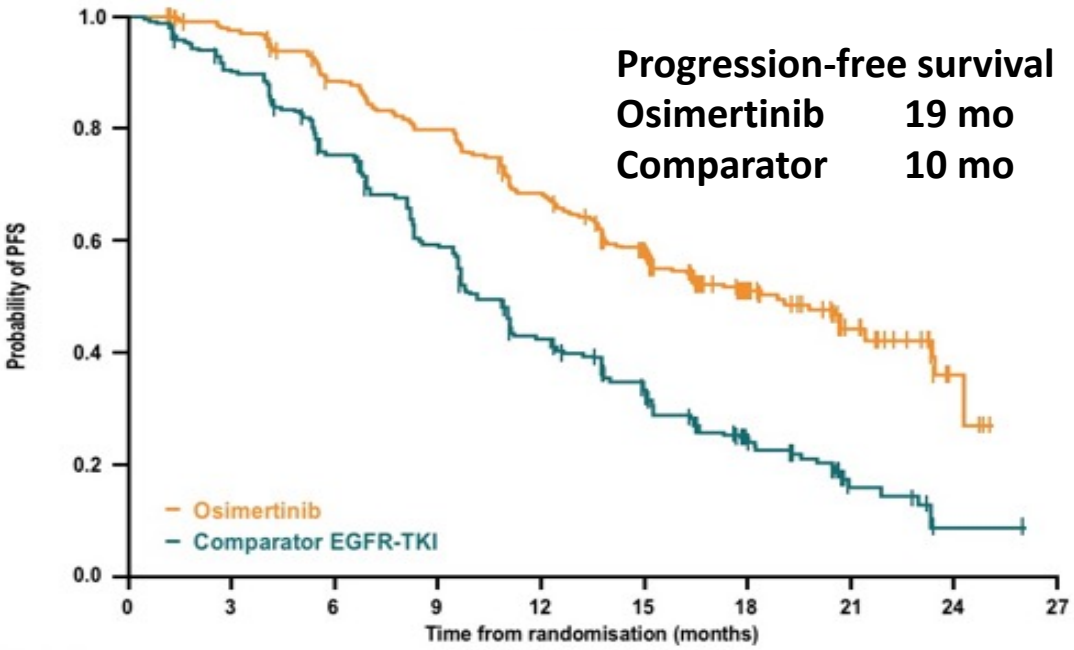
A 50-year-old never smoker patient presents with metastatic lung adenocarcinoma with a large pleural effusion, bone metastases, and liver metastases. She is symptomatic with shortness of breath. Her molecular testing shows an EGFR exon 20 p.S768_V769delins. What is the optimal first-line approach?

A. Start osimertinib orally daily
B. Start mobocertinib orally daily
C. Start carboplatin, pemetrexed and amivantamab
D. Start carboplatin, pemetrexed and pembrolizumab

Soria JC et al. *N Engl J Med*. 2018;378(2):113-125. Ramalingam SS et al. 2019 ESMO Congress. Abstract 567.

Osimertinib as Best-in-Class EGFR TKI





- Osimertinib is a third-generation, irreversible, mutant-specific EGFR TKI
- Osimertinib initially approved for use after earlier generation EGFR TKIs with acquisition of EGFR T790M
- Improved PFS and OS compared to earlier generation EGFR TKIs
- Even so, PFS and OS still relatively short with acquired resistance a certainty

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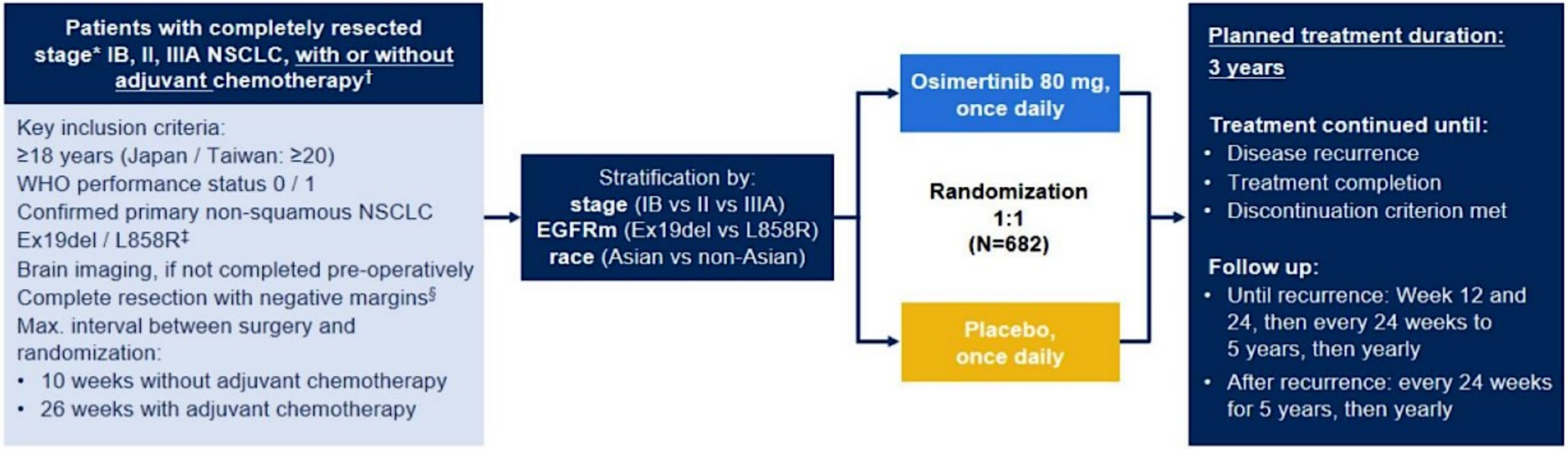
Soria JC et al. *N Engl J Med*. 2018;378(2):113-125. Ramalingam SS et al. 2019 ESMO Congress. Abstract 567.

Osimertinib after surgery – ADAURA study



Endpoints

- **Primary endpoint:** DFS by investigator assessment in stage II / IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

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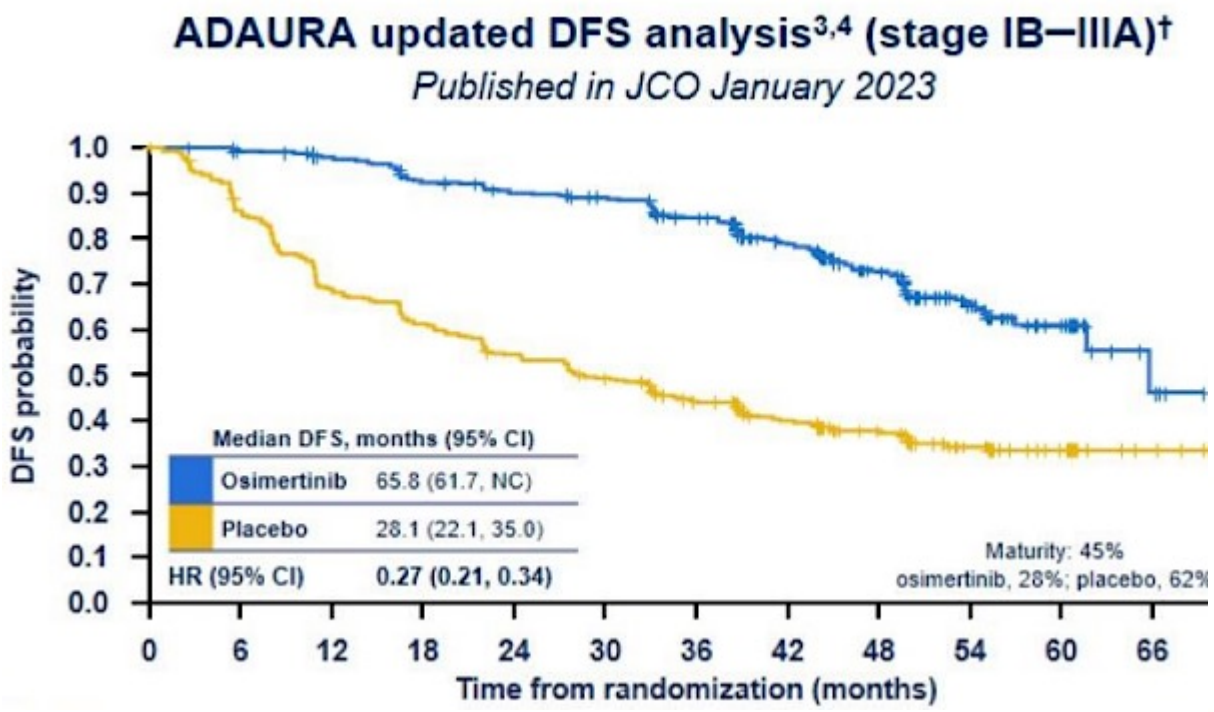
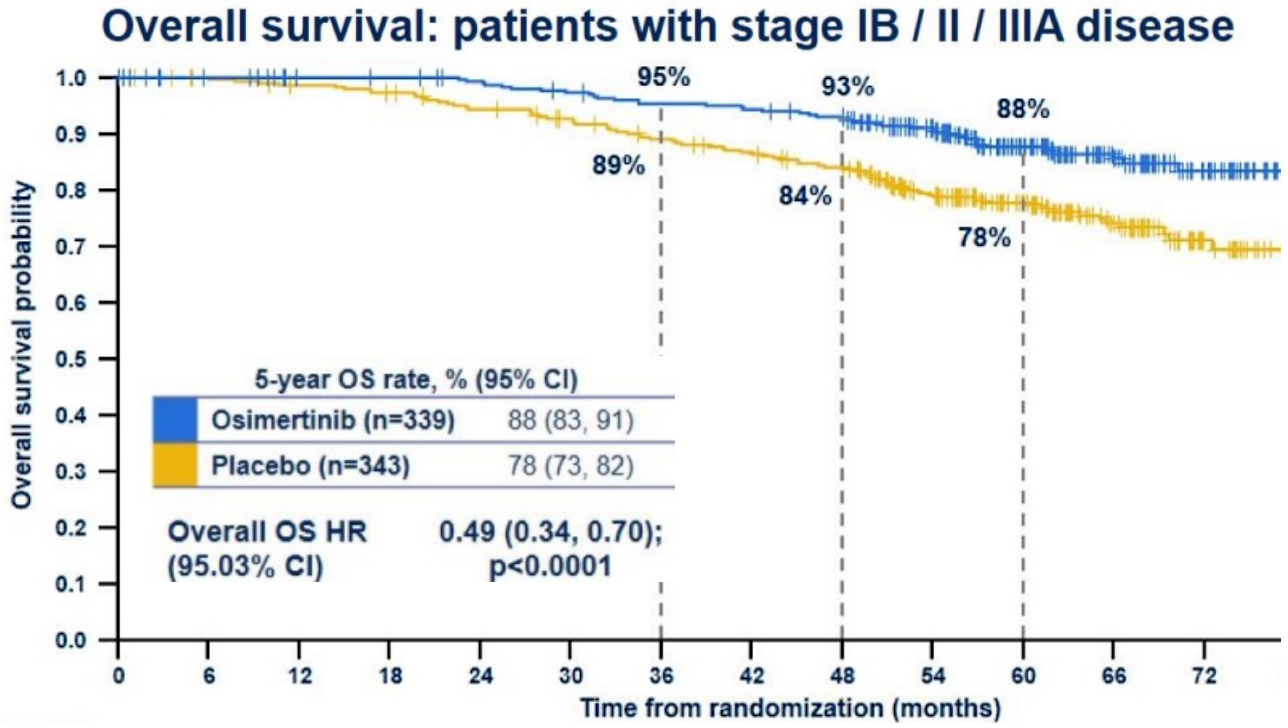
Amin et al JTO 2023

Osimertinib after surgery – ADAURA study





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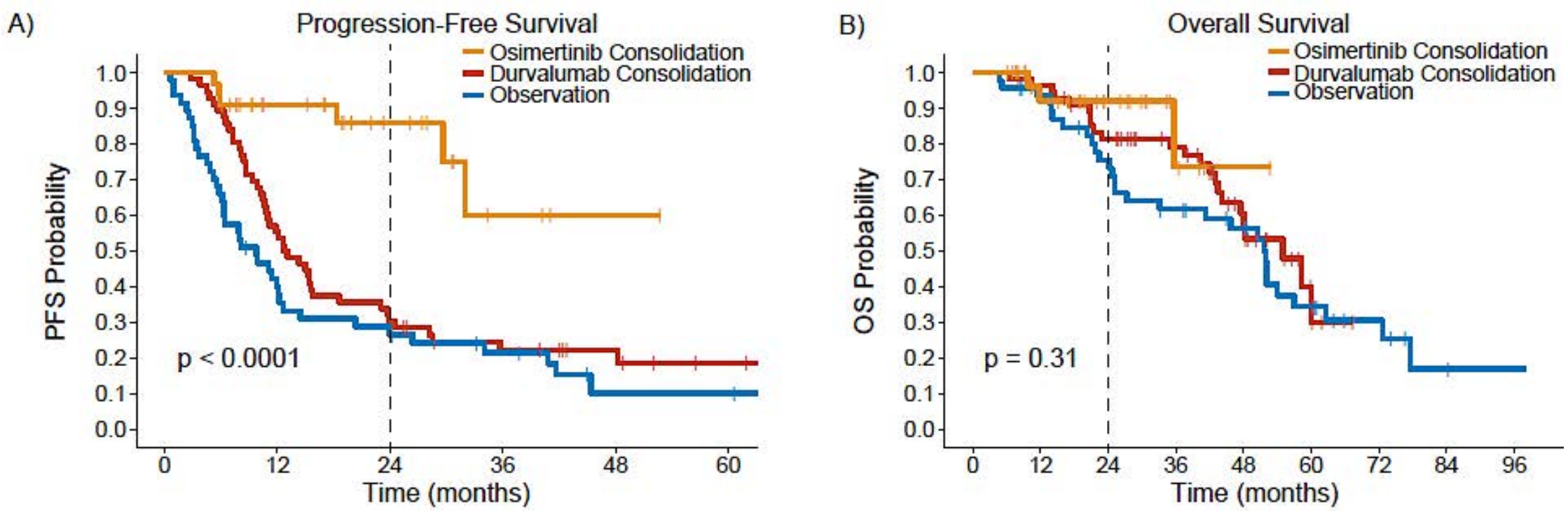
Herbst et al JCO 2020, Herbst ASCO 2023

Osimertinib after RT

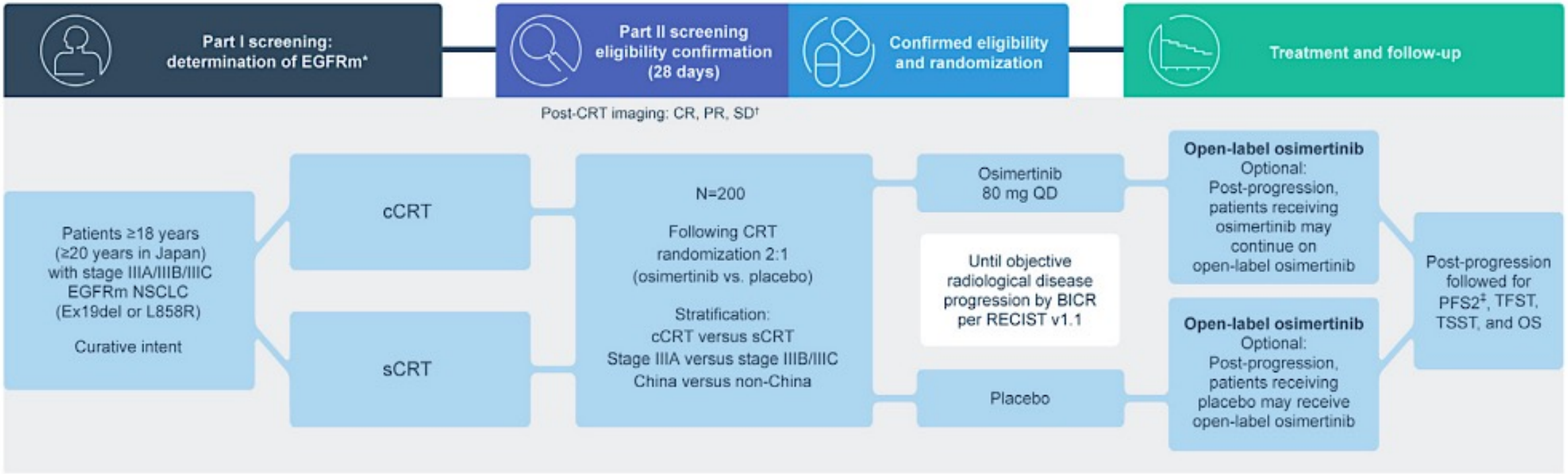


- Multi-center retrospective review of consolidation durvalumab, osimertinib or observation after concurrent chemoradiation
- 24mo rwPFS was 86% with osimertinib, 30% with durvalumab and 27% with observation

Memorial Sloan Kettering Cancer Center

Amin et al JTO 2023

Osimertinib after RT – LAURA study



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

PUBLISHED
19 February 2024

Heterogeneity of outcomes

76 yo, EGFR ex19 deletion only
Asymptomatic
Oligometastatic disease
Thoracic only disease
Slow growing
ctDNA neg
On osimertinib x 4 years

Median PFS on 1L osimertinib

19 months

52yo, EGFR G719A, TP53, RB1
High symptom burden
Diffuse mets including brain, liver, bone
Large tumor burden
ctDNA pos at 3 weeks
Progression within 4 mo on osimertinib

Should we treat these patients the same? Right now, we do.
What factors can we use to risk-adapt treatment?
How can we escalate treatment?
At what timepoint should we escalate?

Osimertinib + Chemotherapy – FLAURA2

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

Patients with untreated locally advanced / metastatic EGFRm NSCLC

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

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

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

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

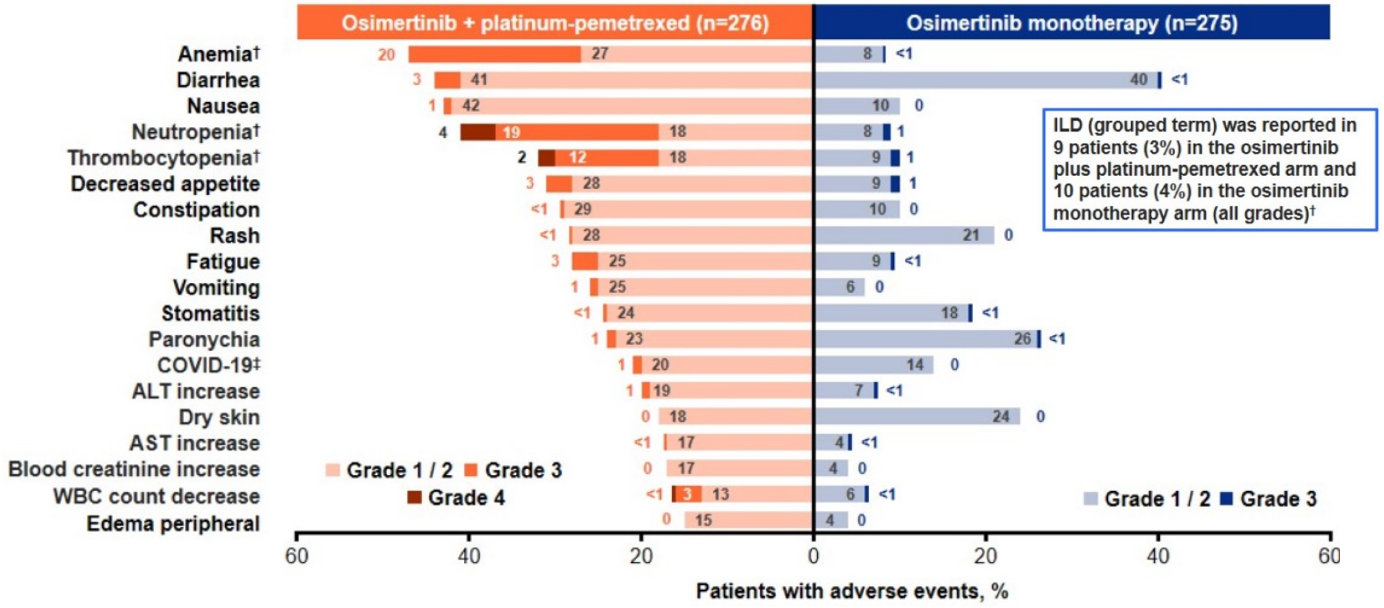
Randomization 1:1 (N=557)

Osimertinib 80 mg (QD)

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

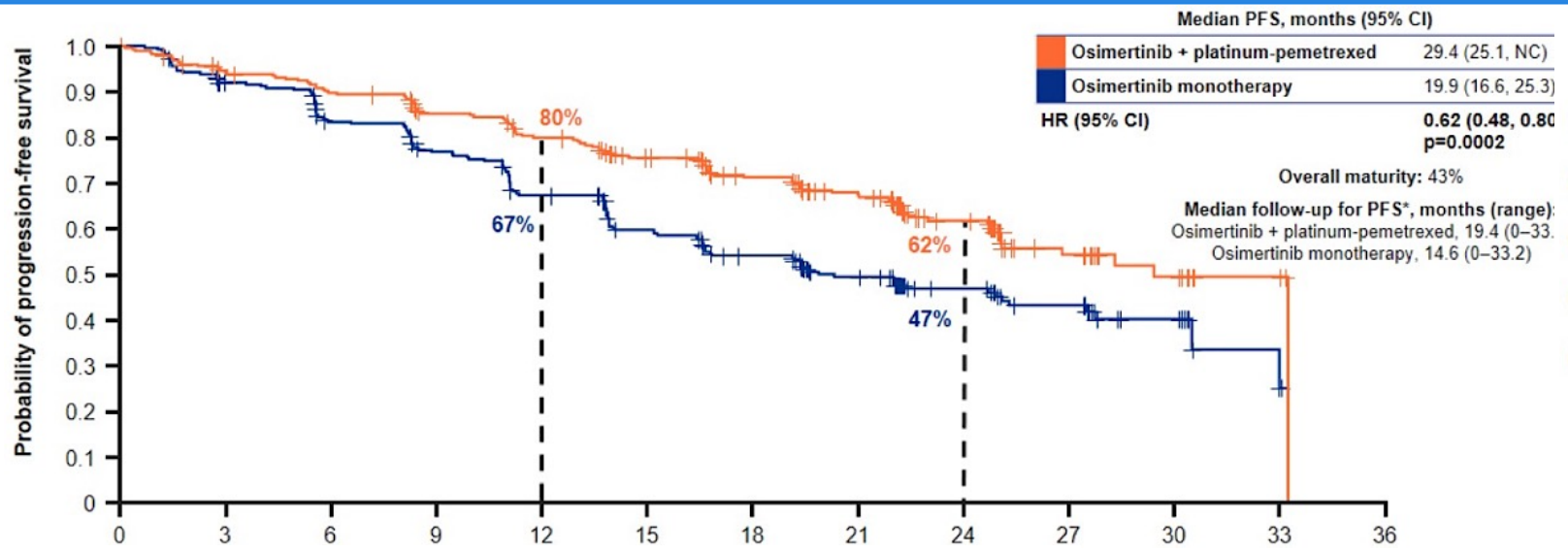
- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

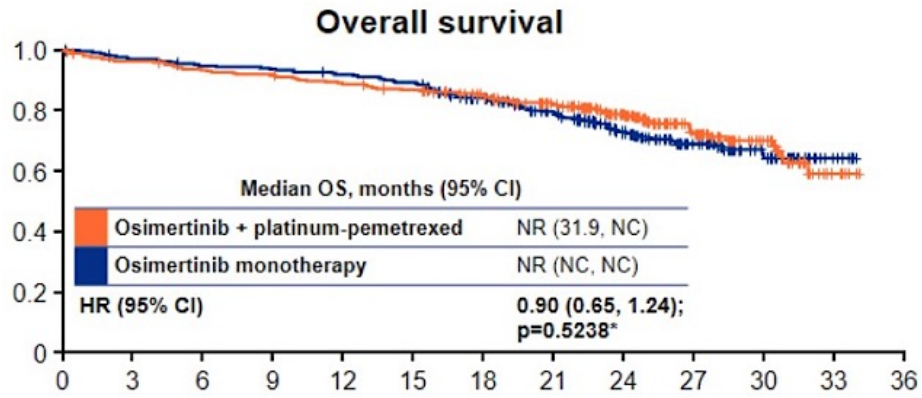
Characteristics, %*	Osimertinib + platinum-pemetrexed (n=279)†	Osimertinib monotherapy (n=278)†
Sex: male / female	38 / 62	39 / 61
Age: median (range), years	61 (26–83)	62 (30–85)
Race: Chinese Asian / non-Chinese Asian / non-Asian / missing	25 / 39 / 35 / <1	25 / 38 / 36 / 1
WHO PS: 0 / 1‡	37 / 62	37 / 63
Smoking status: never / current / former	67 / 1 / 31	65 / 1 / 33
Histology: adenocarcinoma / adenosquamous / other	99 / 1 / 1	99 / 0 / 1
EGFR mutation at randomization§: Ex19del / L858R	61 / 38	60 / 38
Locally advanced / metastatic	5 / 95	3 / 97
Extra-thoracic metastases‖	53	54
CNS metastases	42	40
Baseline tumor size, mean (SD) / median (range), mm	65 (42) / 57 (10–284)	64 (39) / 57 (11–221)

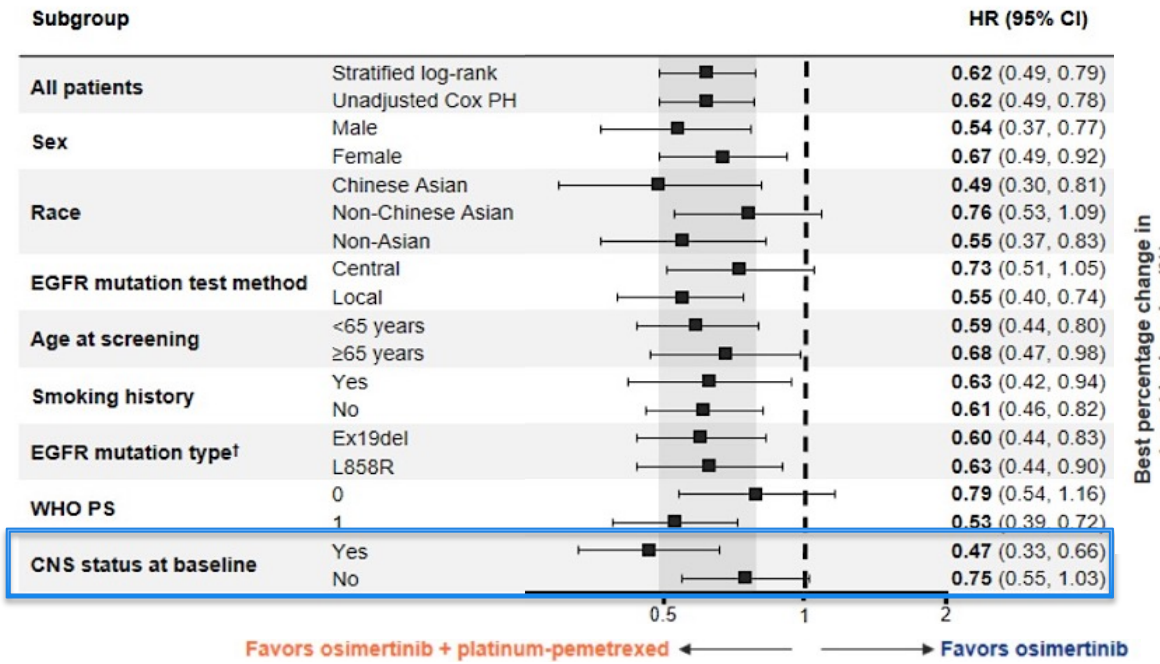


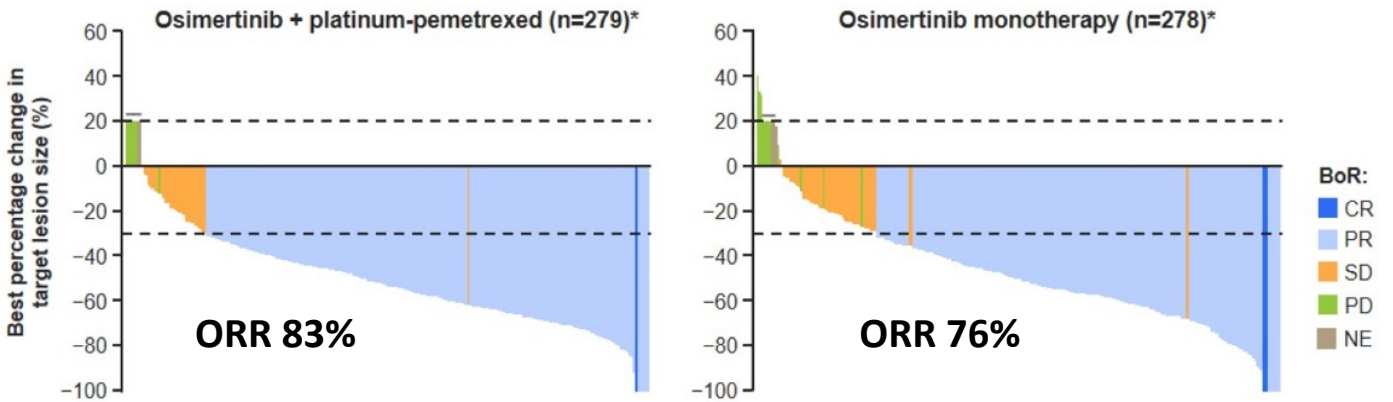
Janne PA et al. WCLC 2023;Abstract PL03.13

Osimertinib + Chemotherapy – FLAURA2









Janne PA et al. WCLC 2023;Abstract PL03.13

1L Amivantamab and lazertinib- MARIPOSA

Serial brain MRIs were required for all patients[a]

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)

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

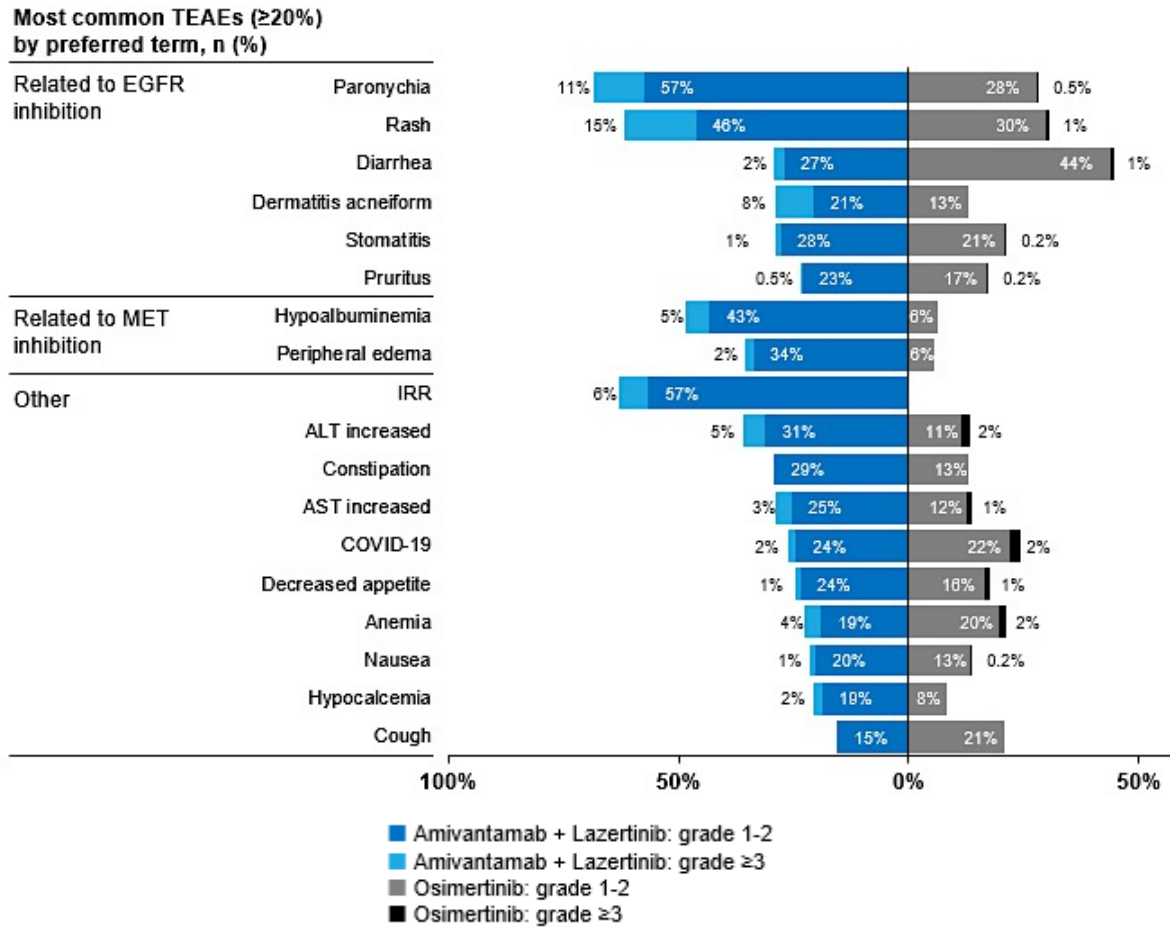
Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks **Lazertinib:** 240 mg daily
Osimertinib: 80 mg daily

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

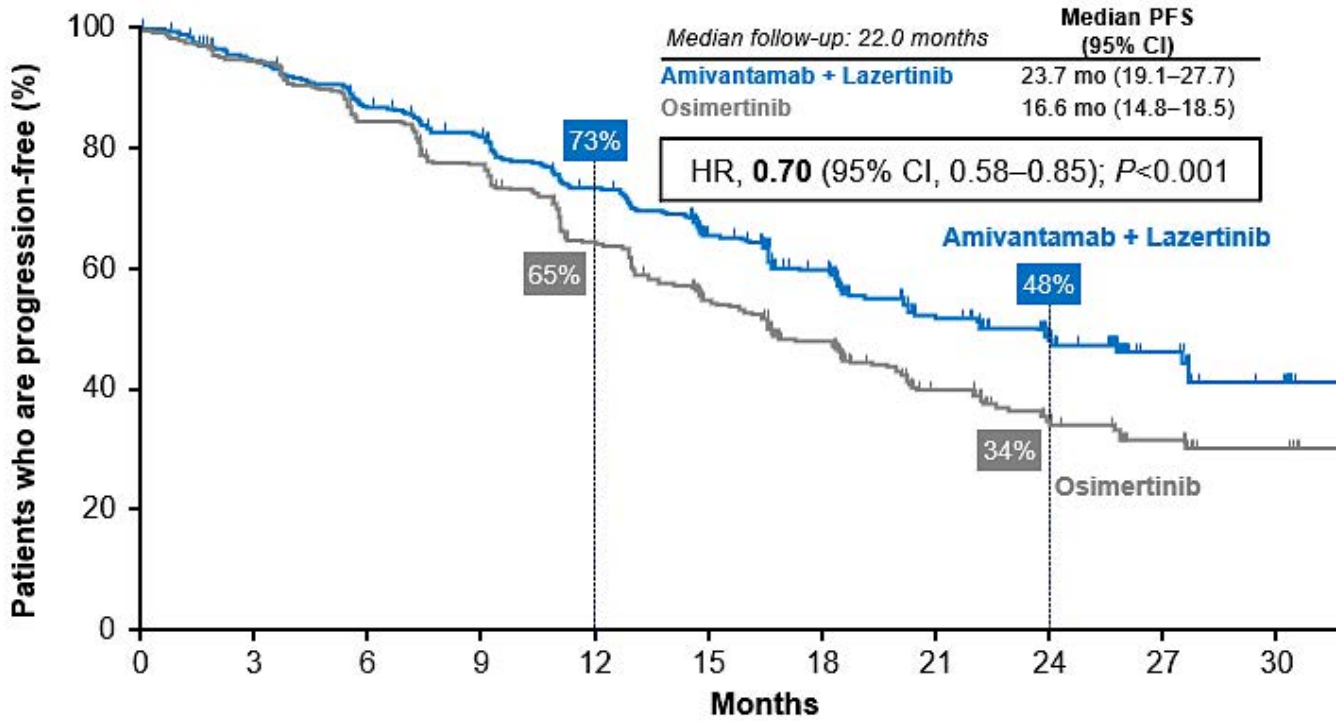
Characteristic, n (%)	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)	Lazertinib (n=216)
Median age, years (range)	64 (25-88)	63 (28-88)	63 (31-87)
Female	275 (64)	251 (59)	136 (63)
Race			
Asian	250 (58)	251 (59)	128 (59)
White	164 (38)	165 (38)	79 (37)
History of brain metastases	178 (41)	172 (40)	86 (40)
EGFR mutation type[b]			
Ex19del	258 (60)	257 (60)	131 (61)
L858R	172 (40)	172 (40)	85 (39)



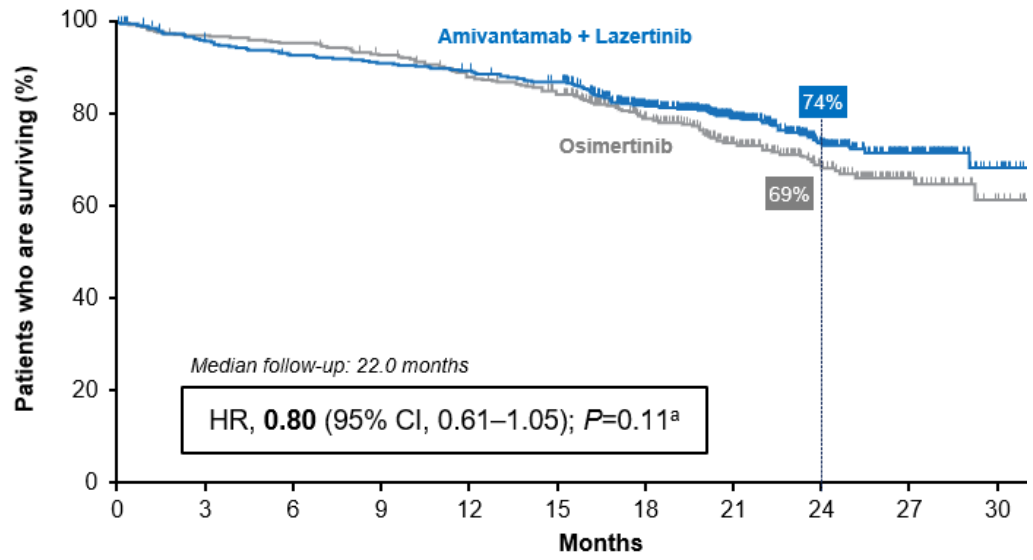
Cho BC et al. ESMO 2023;Abstract LBA14.

1L Amivantamab and lazertinib- MARIPOSA

Primary Endpoint: Progression-free survival by BICR



Interim Overall Survival



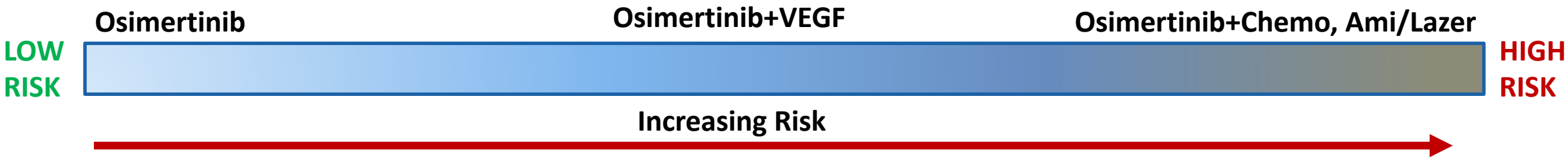
Overall response rate

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)

	Median DoR[c] (95% CI)
Amivantamab + Lazertinib	25.8 mo (20.1–NE)
Osimertinib	16.8 mo (14.8–18.5)

Cho BC et al. ESMO 2023;Abstract LBA14.

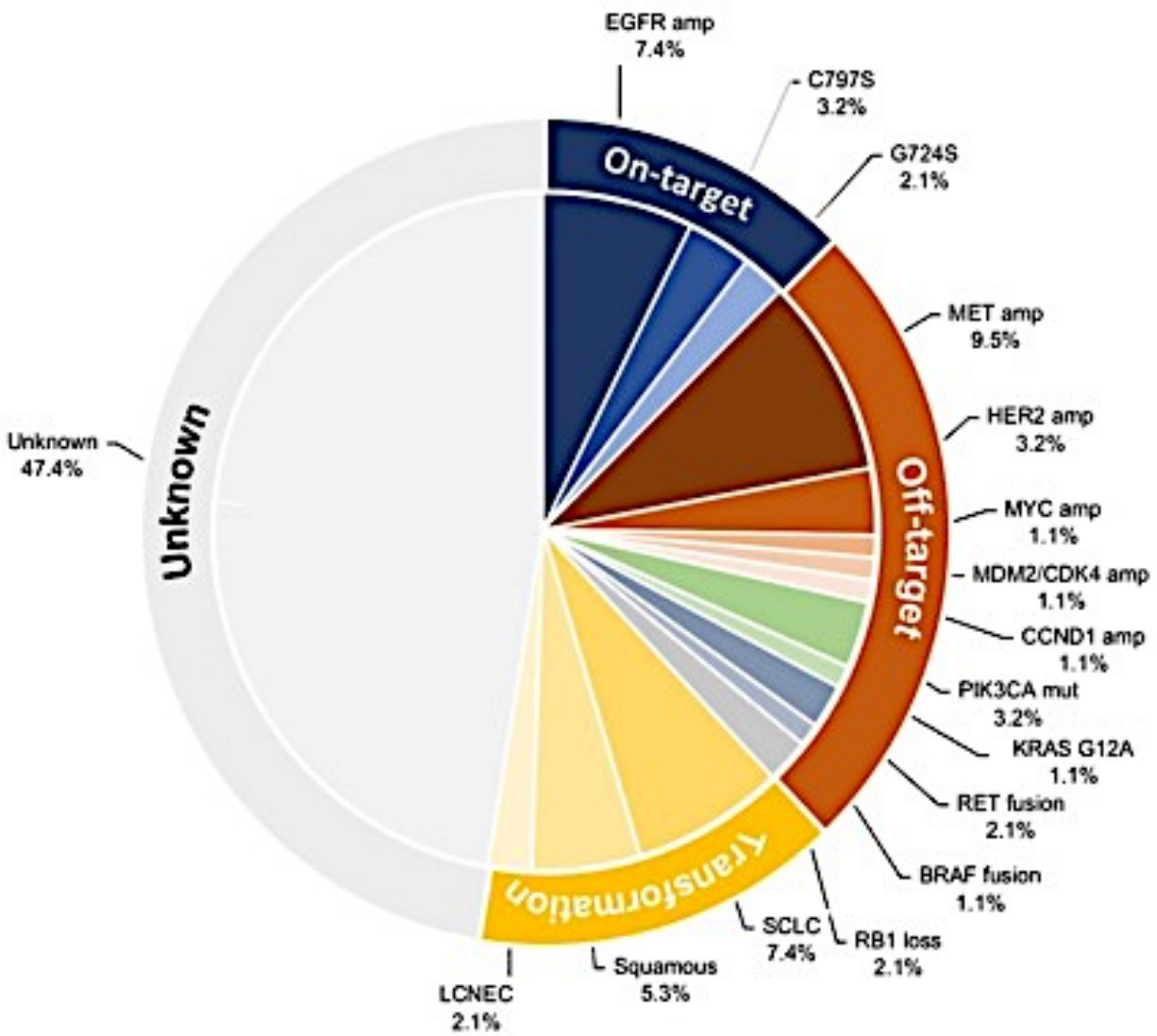
Osimertinib First-Line Combinations



EGFR ex19 deletion Asymptomatic Oligometastatic disease Thoracic only disease Slow growing ctDNA neg at baseline Younger age	EGFR L858R Moderate tumor burden ctDNA pos at baseline	EGFR atypical mutation (exon 18) High symptom burden Diffuse mets including brain, liver, bone Large tumor burden Fast growing ctDNA pos at 3 weeks Older age

- **Awaiting mature PFS and OS benefit from combination studies**
- **Ideally will have prospective data to determine whether high-risk subgroups benefit from treatment escalation**
- **Will always be a discussion between provider and patient**

Mechanisms of Resistance to First-Line Osimertinib



- Mechanisms of resistance to first-line osimertinib are diverse, with no dominant mechanism so upfront combinations to prevent resistance not appropriate without a biomarker
- With development of better EGFR inhibitors, there is more off target resistance seen
- High incidence of lineage plasticity including both small cell and squamous transformation
- Frequent acquired gene alterations such as gene fusions which are rare de novo
- There will be a role for non-biomarker selected therapies that focus on enhanced EGFR on-target inhibition or address general tumor biology

Yu H. Submitted Paper.

Treatments Post Osimertinib: Amivantamab + chemotherapy

Key Eligibility Criteria

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

Stratification Factors

- Osimertinib line of therapy (1st vs 2nd)
- Asian race (yes or no)
- History of brain metastases (yes or no)

Serial brain MRIs were required for all patients[a]

2:2:1 Randomization (N=657)

- **Amivantamab-Lazertinib-Chemotherapy (n=263)**
- **Chemotherapy (n=263)**
- **Amivantamab-Chemotherapy (n=131)**

Dosing (in 21-day cycles)

Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at Cycle 3 (week 7)

Lazertinib: 240 mg daily starting after completion of carboplatin[b]

Chemotherapy administered at the beginning of every cycle:

- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² 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

Characteristic, n (%)	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Median age, years (range)	62 (31–85)	62 (36–84)	61 (23–83)
Female	157 (60)	81 (62)	168 (64)
Asian	127 (48)	63 (48)	125 (48)
White	123 (47)	60 (46)	129 (49)
History of brain metastases	120 (46)	58 (44)	120 (46)
Osimertinib line of therapy[b]			
First	181 (69)	97 (74)	185 (70)
Second	82 (31)	34 (26)	77 (29)
EGFR mutation type			
Ex19del	183 (70)	89 (68)	165 (63)
L858R	79 (30)	42 (32)	98 (37)

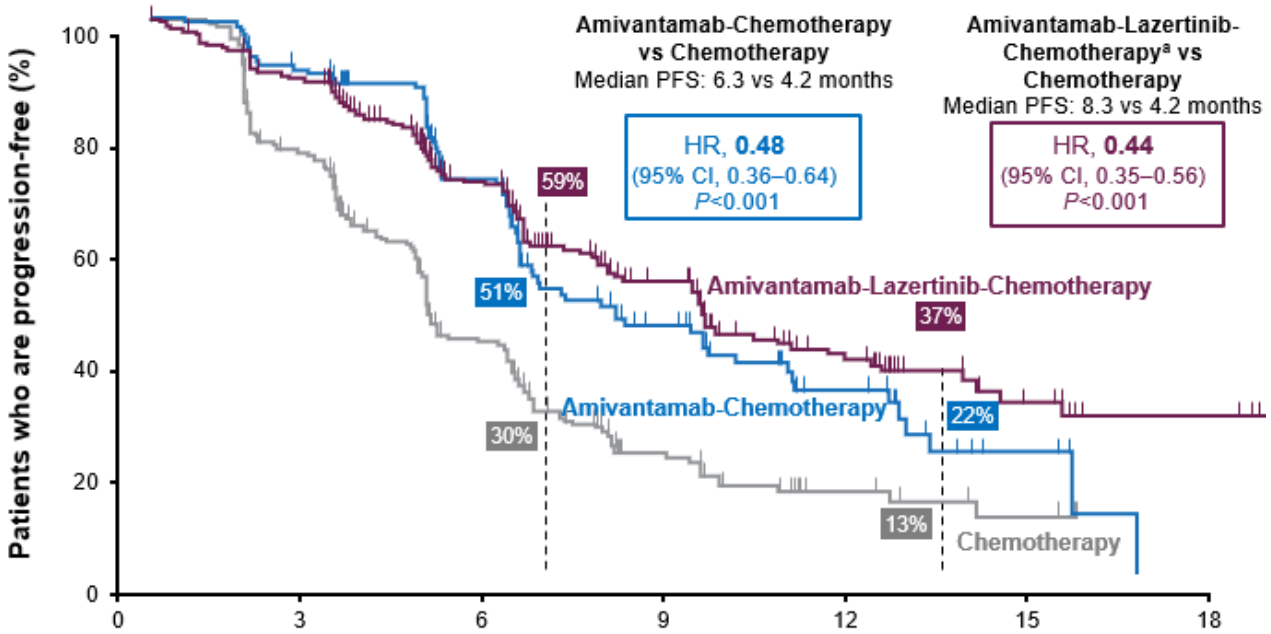
TEAE, n (%)	Chemo (n=243)	Ami-Chemo (n=130)	Ami-Laz-Chemo (n=263)
Any AEs	227 (93)	130 (100)	263 (100)
Grade ≥3 AEs	117 (48)	94 (72)	242 (92)
Serious AEs	49 (20)	42 (32)	137 (52)
AEs leading to death	3 (1)	3 (2)	14 (5)
Any AE leading to treatment:			
Interruptions of any agent	81 (33)	84 (65)	202 (77)
Reductions of any agent	37 (15)	53 (41)	171 (65)
D/C of any agent	9 (4)	24 (18)	90 (34)

Most common TEAEs (≥25%) by preferred term, n (%)	Chemotherapy (n=243)		Ami-Chemo (n=130)	
	All	Grade ≥3	All	Grade ≥3
Associated with EGFR				
Paronychia	1 (0.4)	0	48 (37)	3 (2)
Rash	12 (5)	0	56 (43)	8 (6)
Stomatitis	21 (9)	0	41 (32)	1 (1)
Associated with MET				
Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)
Peripheral edema	15 (6)	0	42 (32)	2 (2)
Associated with Chemo				
Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)
Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)
Anemia	97 (40)	23 (9)	51 (39)	15 (12)
Leukopenia	68 (28)	23 (9)	37 (28)	26 (20)
Other				
Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)
Nausea	90 (37)	2 (1)	58 (45)	1 (1)
Constipation	72 (30)	0	50 (38)	1 (1)
Decreased appetite	51 (21)	3 (1)	40 (31)	0
Vomiting	42 (17)	1 (0.4)	32 (25)	1 (1)
Fatigue	47 (19)	4 (2)	36 (28)	4 (3)
VTE[c]	11 (5)	7 (3)	13 (10)	3 (2)
ILD	0	0	2 (2)	1 (1)

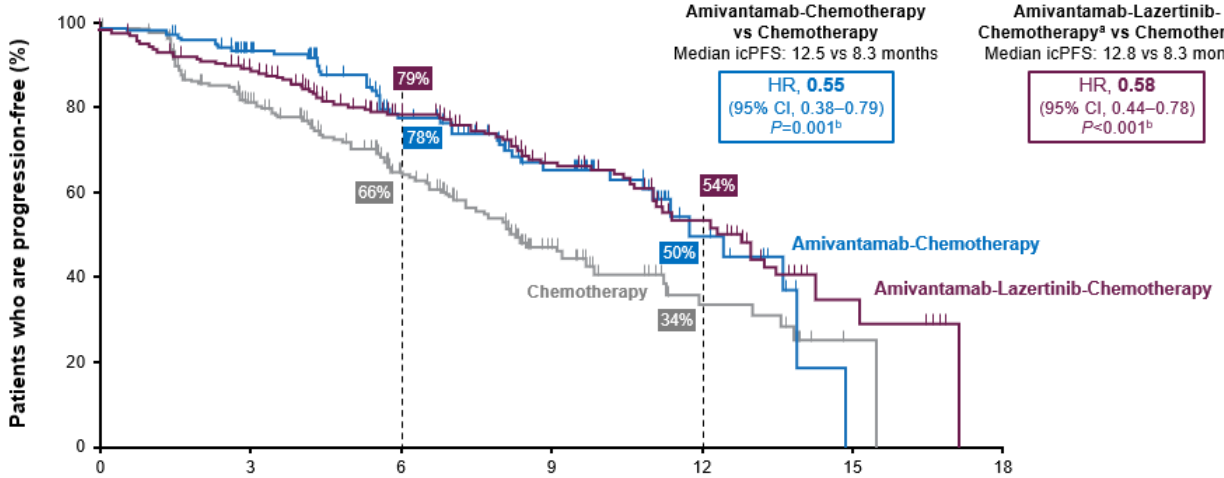
Passaro A et al. ESMO 2023;Abstract LBA15.

Treatments Post Osimertinib: Amivantamab + chemotherapy

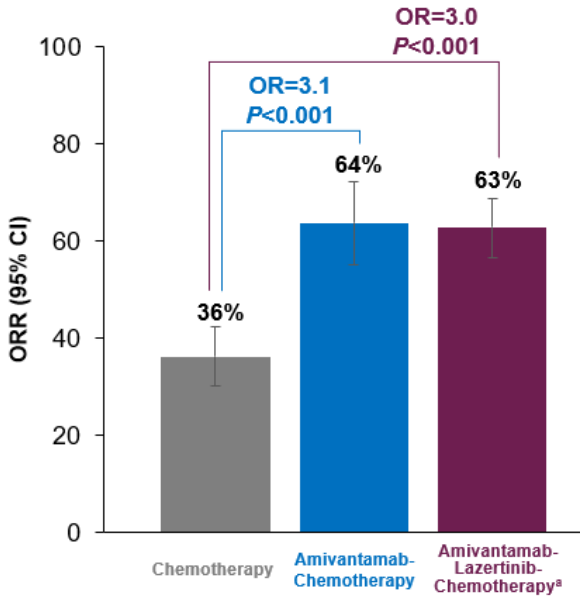
Primary Endpoint: Progression-free survival by BICR



Intracranial PFS by BICR



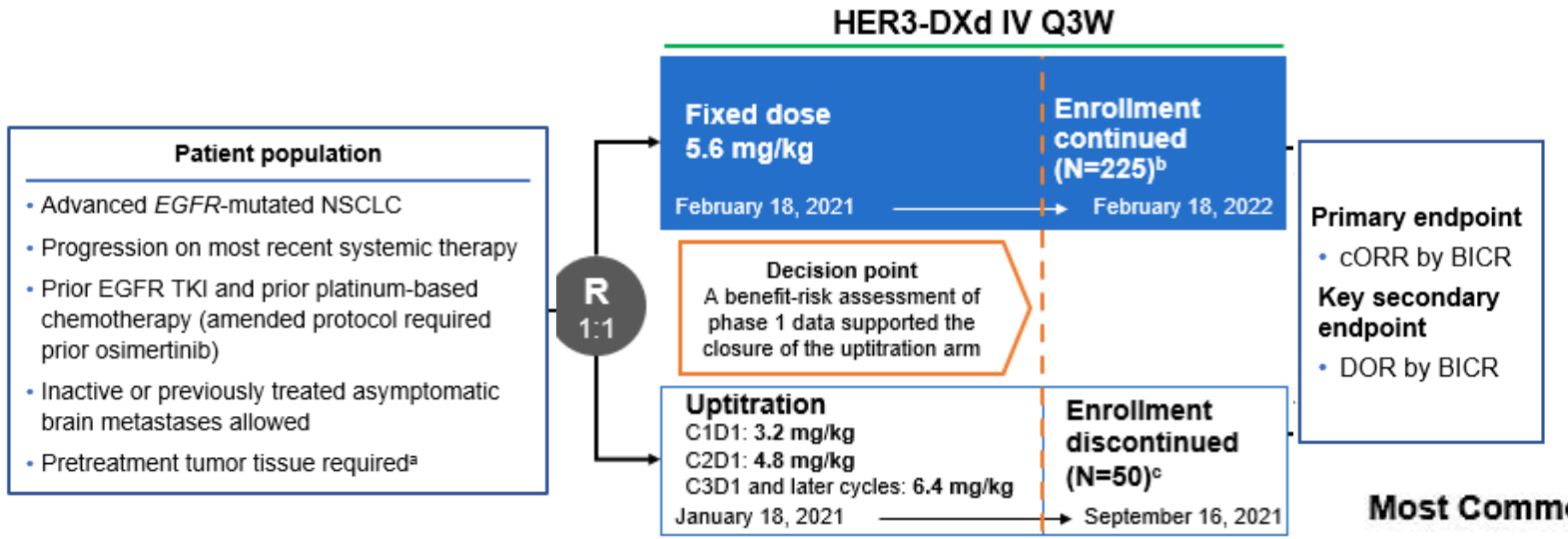
Overall response rate



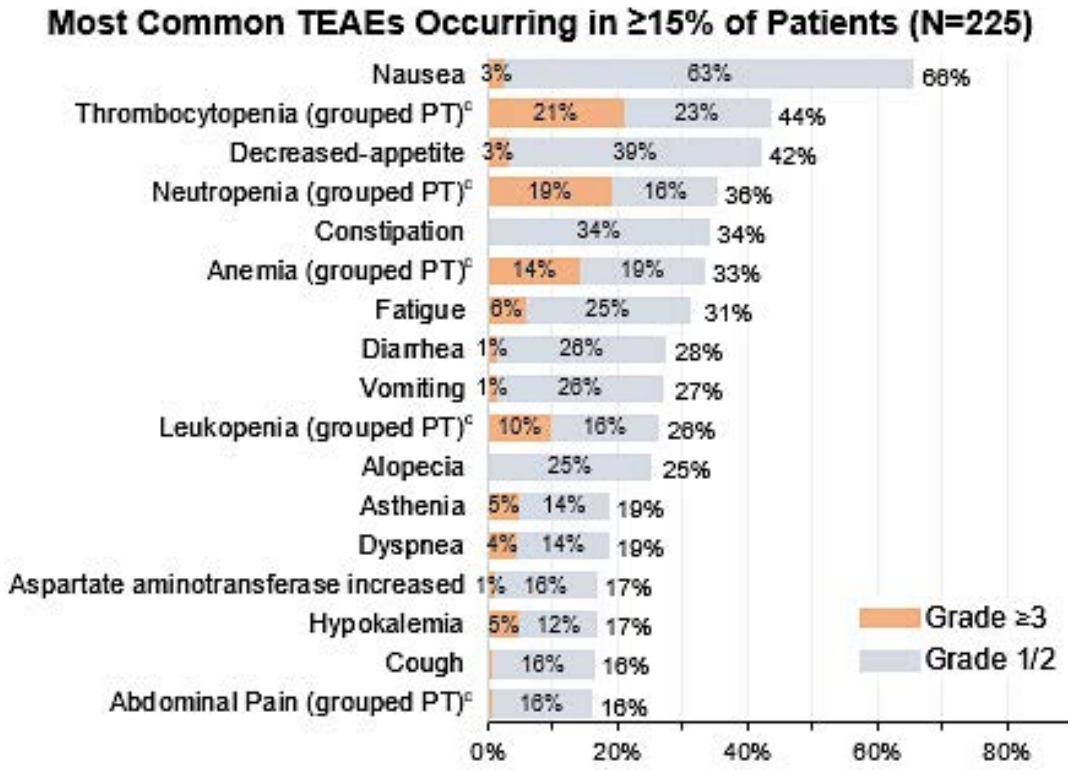
Passaro A et al. ESMO 2023;Abstract LBA15.

Treatments Post Osimertinib: Patritumab Deruxtecan

Yu HA et al. *JCO.* 2023



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 chemo	225 (100)
	Prior immunotherapy	90 (40)



Treatments Post Osimertinib: Patritumab Deruxtecan

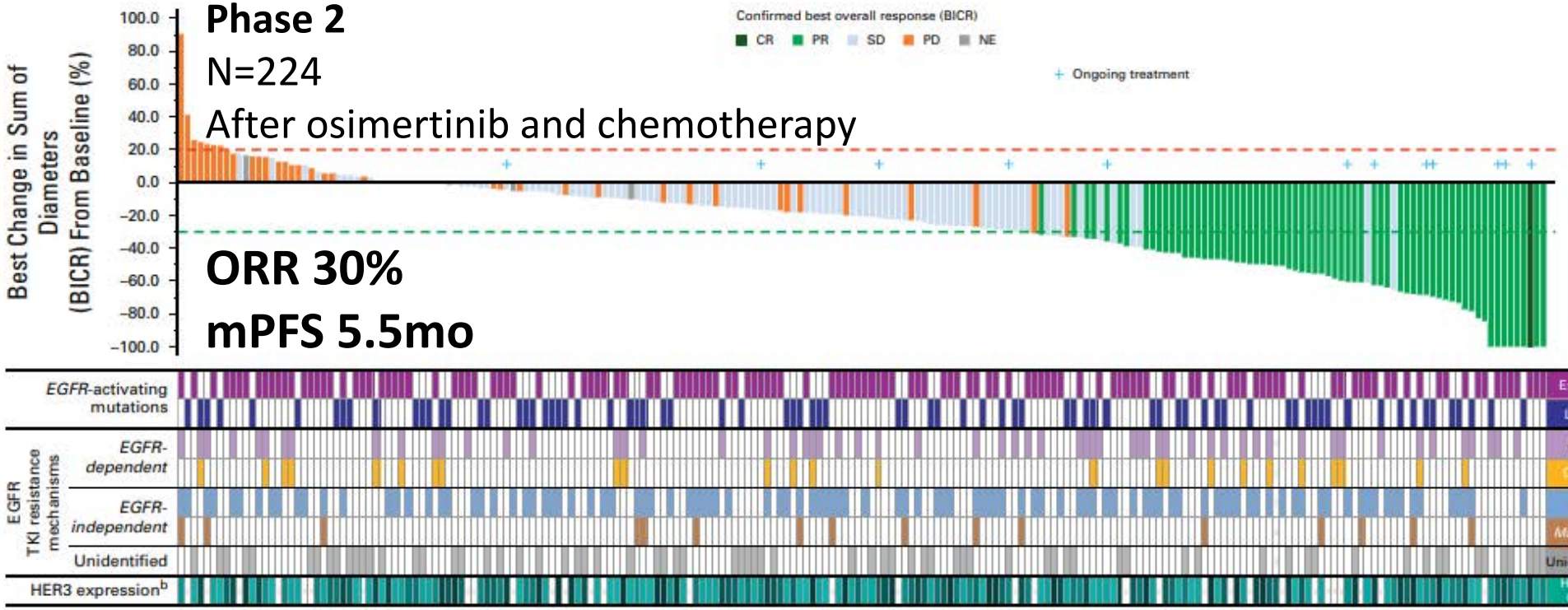
Phase 2

N=224

After osimertinib and chemotherapy

ORR 30%

mPFS 5.5mo

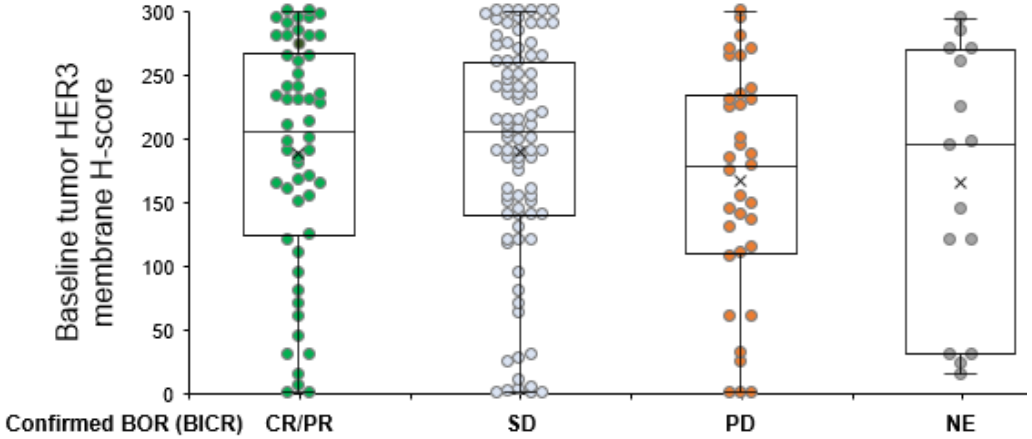


B

Result	Patients with brain metastasis at baseline (n = 30)
cORR, No. (%) (95% CI)[a]	10 (33.3) (17.3-52.8)
CR, No. (%)	9 (30.0)[b]
PR, No. (%)	1 (3.3)
SD or non-CR/non-PD, No. (%)	13 (43.3)
PD, No. (%)	4 (13.3)
NE, No. (%)	3 (10.0)
Duration of response, months, median (95% CI)	8.4 (5.8-9.2)

	Type of EGFR TKI resistance mechanism			
	EGFR-dependent, only (n=34)	*EGFR*-independent, only (n=81)	Both *EGFR*-dependent and -independent (n=32)	None identified (n=77)
Confirmed ORR (95% CI), %	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)

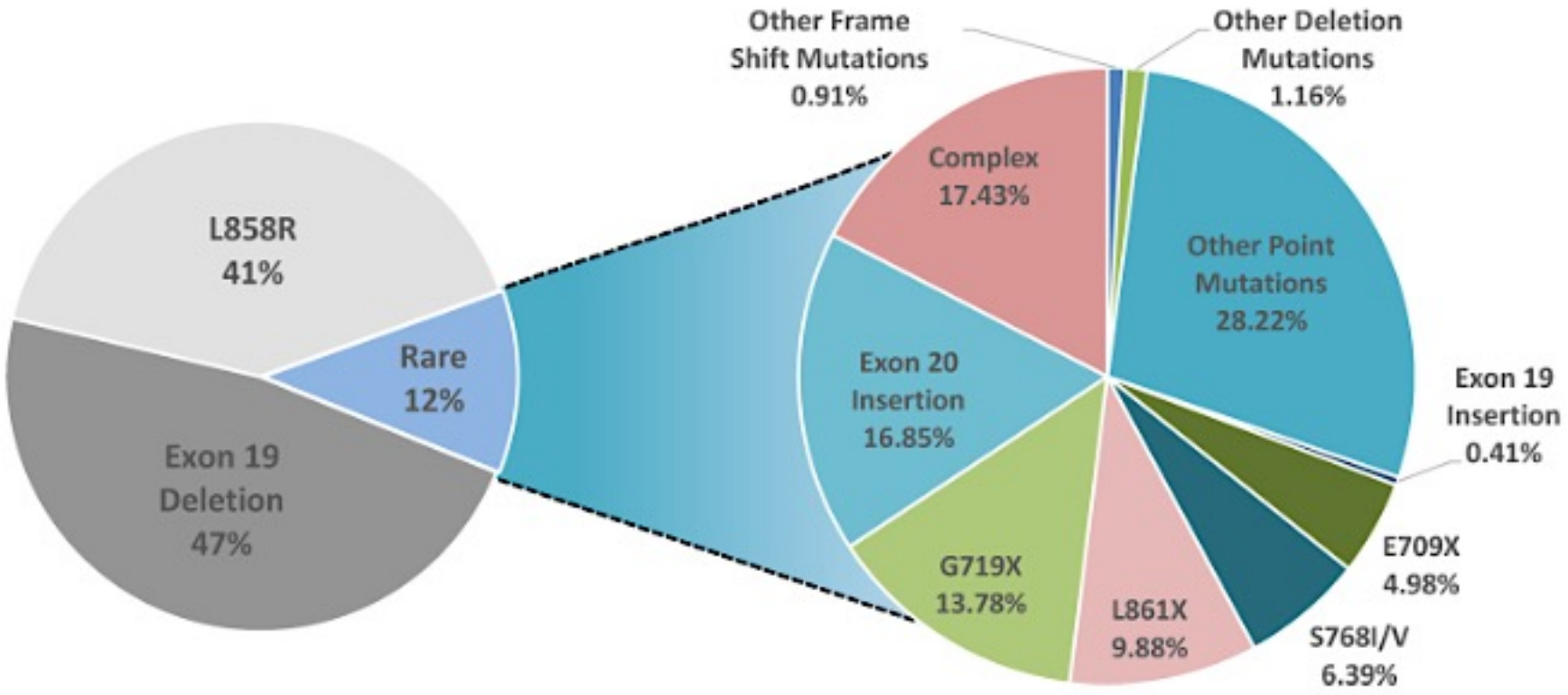
HER3 expression does not correlate with response



Memorial Sloan Kettering Cancer Center

Yu HA et al. *JCO.* 2023

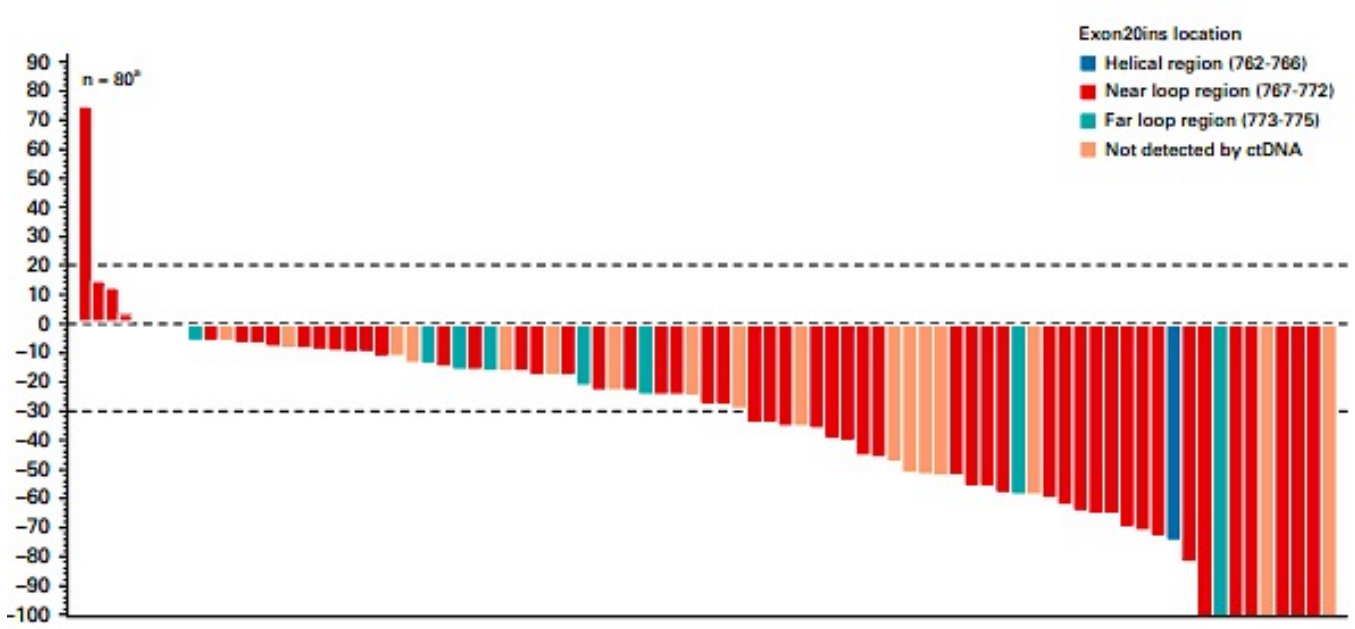
EGFR Exon 20 Insertions



- Subset of EGFR mutations that are activating but not sensitizing to traditional EGFR TKIs (erlotinib, osimertinib)
- Recent first approvals for targeted therapies for these lung cancers

Harrison PT et al. *Sem Cancer Biol*. 2019;61:167-179.

Amivantamab

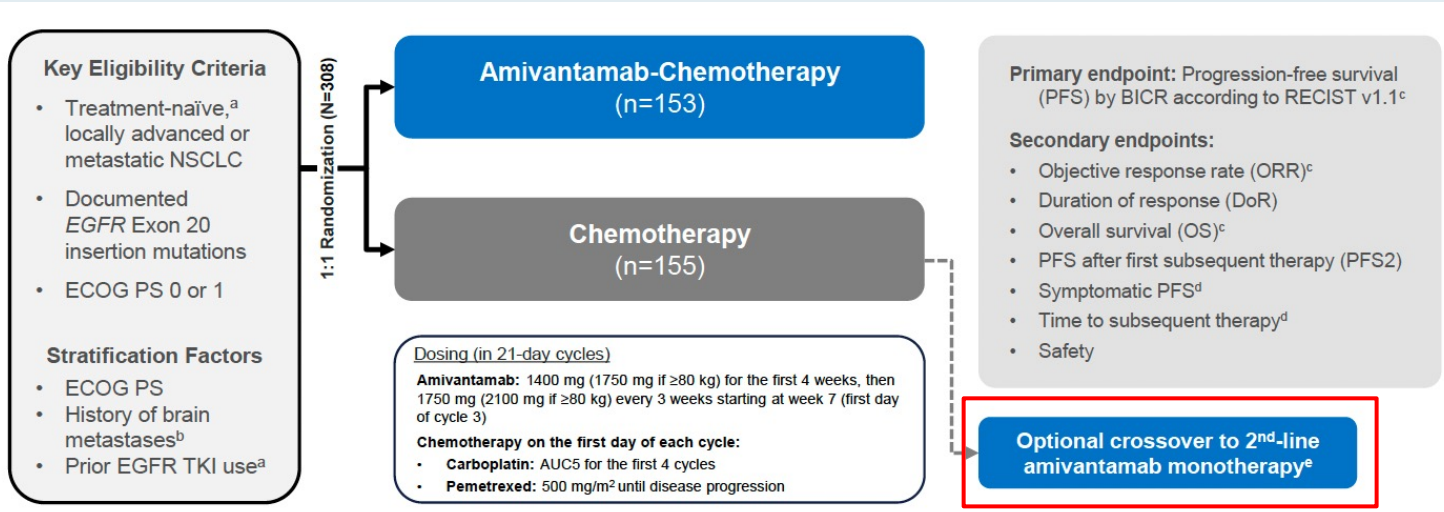


AE (≥15% of Treatment-emergent AEs), n (%)	Safety Population (N=114)			
	Treatment-emergent AE		Treatment-related AE	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Rash[a]	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0
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)

- Bispecific EGFR/MET antibody that is given intravenously
- ORR 40%, DoR 11.1mo, mPFS 8.3mo, mOS 22.8mo
- Also being assessed in sensitizing EGFR mutations

Park K et al. *J Clin Oncol*. 2021;39(30):3391-3402.

PAPILLON: First-Line Amivantamab and Chemotherapy for EGFR Exon 20 Insertions



Treatment-emergent AEs, n (%)	Amivantamab-Chemotherapy (n=151)	Chemotherapy (n=155)
Any AEs	151 (100)	152 (98)
Grade ≥3 AEs	114 (75)	83 (54)
Serious AEs	56 (37)	48 (31)
AEs leading to death	7 (5)	4 (3)
Any AE leading to treatment:		
Interruptions of any agent	104 (69)	56 (36)
Related interruptions of amivantamab	63 (42)	–
Reductions of any agent	73 (48)	35 (23)
Related reductions of amivantamab	54 (36)	–
Discontinuations of any agent	36 (24)	16 (10)
Related discontinuations of amivantamab	10 (7)	–
Discontinuations of all study agents due to AEs	12 (8)	12 (8)

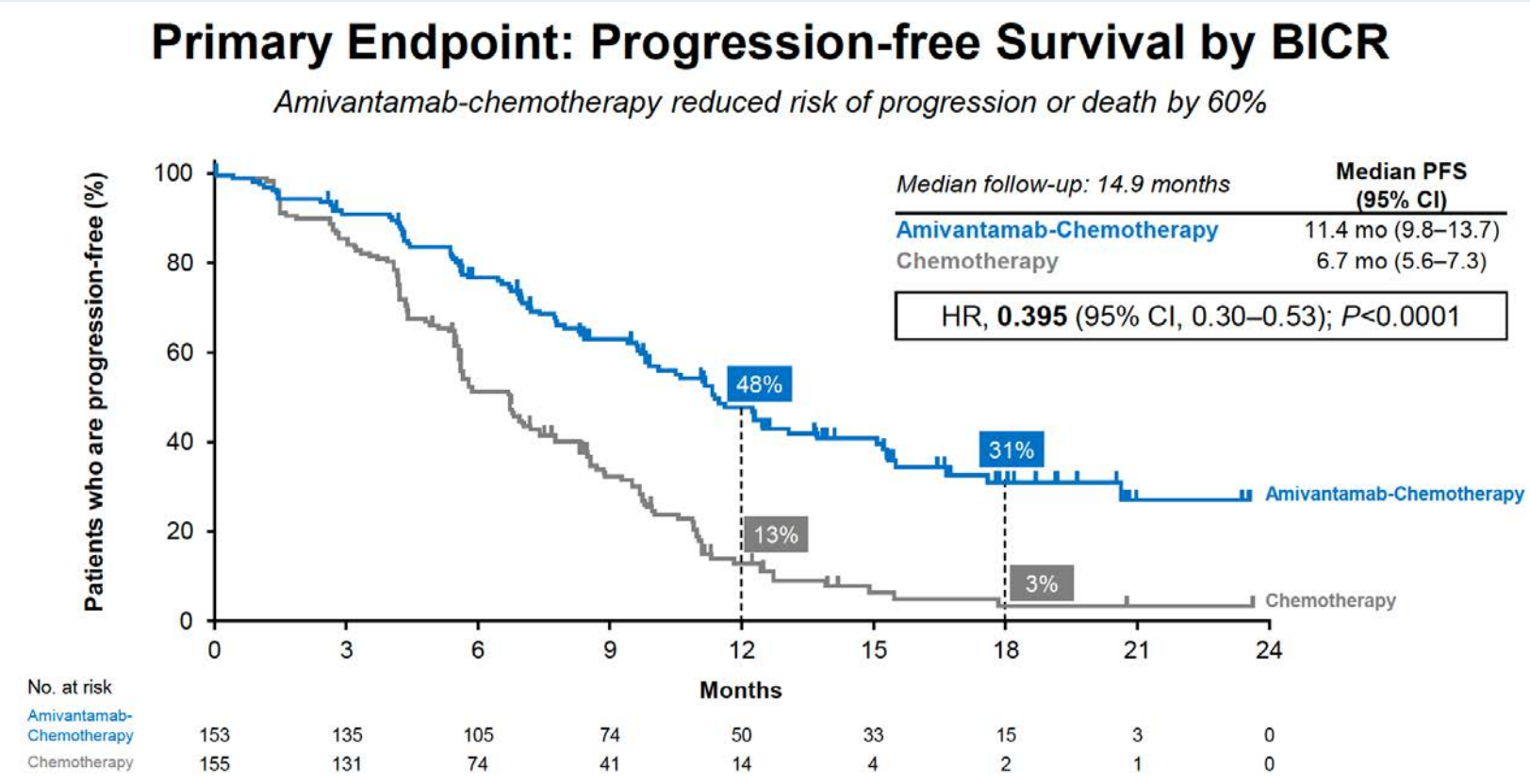
BICR-assessed response[b]	Amivantamab-Chemotherapy (n=153)	Chemotherapy (n=155)
Mean percent change of SoD	-53%[c]	-34%
ORR	73% (95% CI, 65–80)	47% (95% CI, 39–56)
Odds ratio	3.0 (95% CI, 1.8–4.8); *P*<0.0001	
Best response, n (%)		
Complete response	6 (4)	1 (1)
Partial response	105 (69)	71 (47)
Stable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

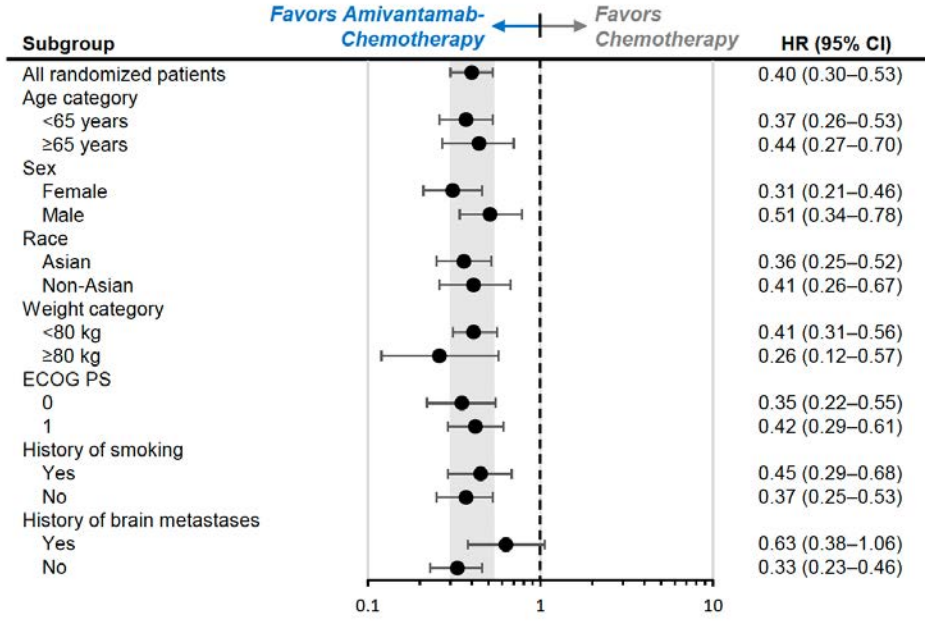
Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Stomatitis	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

Girard N et al. ESMO 2023;Abstract LBA5.

RTP RESEARCH TO PRACTICE

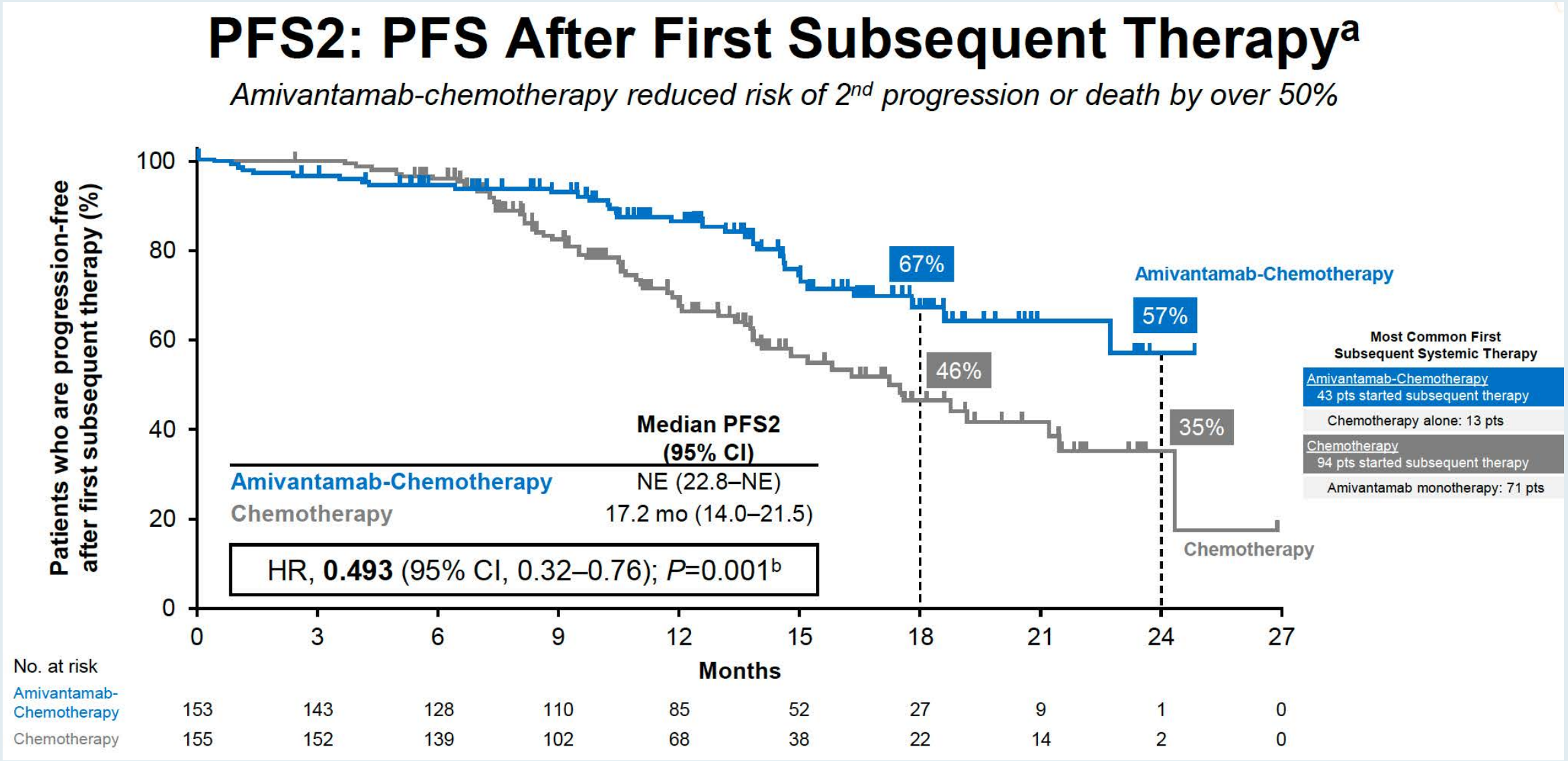
PAPILLON: First-Line Amivantamab and Chemotherapy for EGFR Exon 20 Insertions — PFS Outcomes





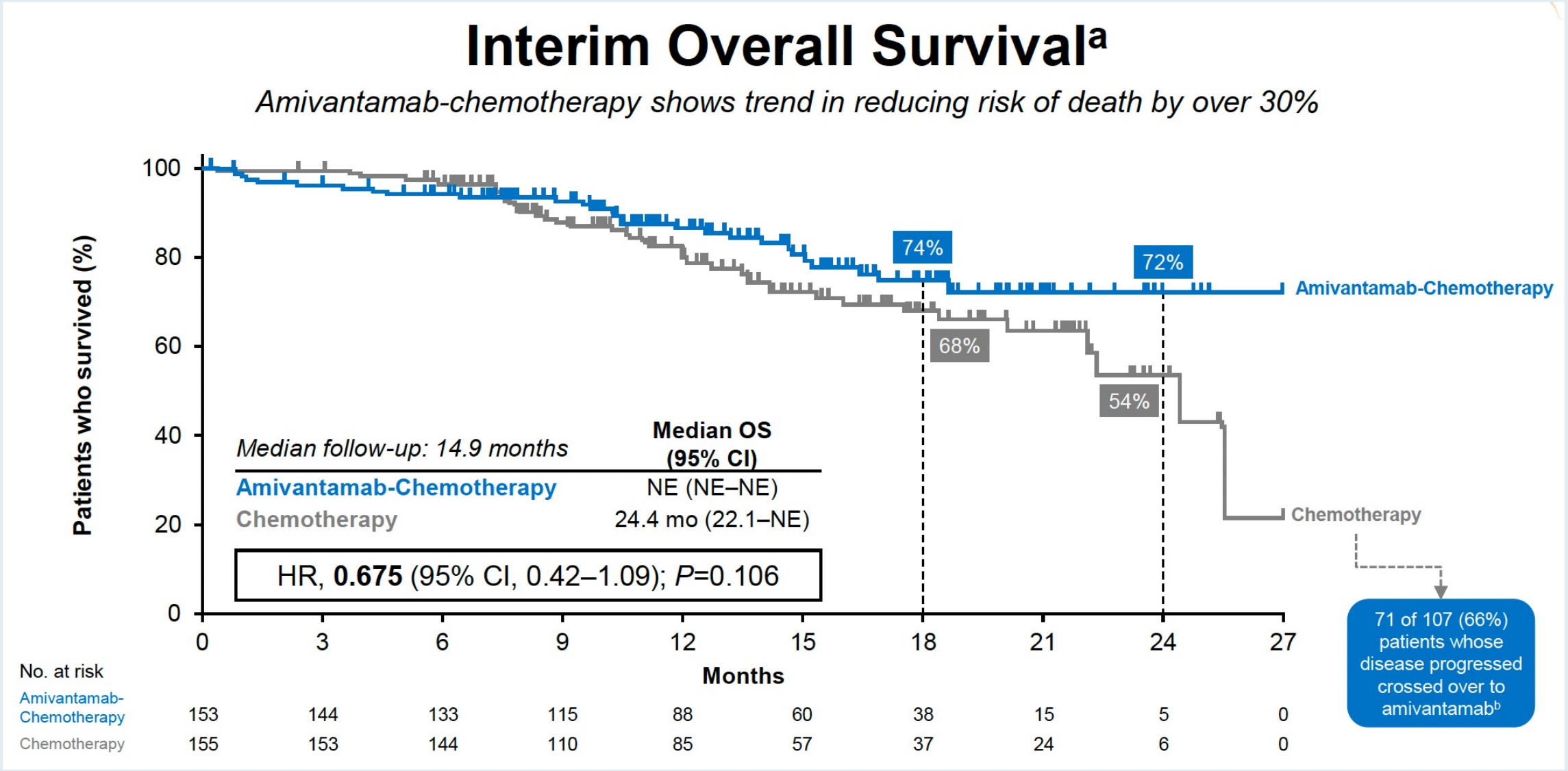
Girard N et al. ESMO 2023;Abstract LBA5.

PAPILLON: First-Line Amivantamab and Chemotherapy for EGFR Exon 20 Insertions — PFS2 Outcomes



Girard N et al. ESMO 2023;Abstract LBA5.

PAPILLON: First-Line Amivantamab and Chemotherapy for EGFR Exon 20 Insertions — OS Outcomes



Girard N et al. ESMO 2023;Abstract LBA5.

Summary

- Osimertinib is the first line monotherapy standard of care for EGFR-mutant lung cancer
- Osimertinib is also approved after surgery as adjuvant therapy for early-stage disease, and there are upcoming data suggesting a role for osimertinib after definitive radiation for early-stage disease as well.
- New combinations have shown added PFS benefit over osimertinib as first-line therapy including chemotherapy plus osimertinib and amivantamab with lazertinib.
- Currently there are no targeted therapies approved after osimertinib. Both patritumab deruxtecan and chemotherapy with amivantamab show activity in this setting.
- For EGFR exon 20 insertion positive lung cancer, chemotherapy and amivantamab is a newly approved possibility to use in the first-line setting. Amivantamab monotherapy can still be used after chemotherapy.

Agenda

Module 1: Management of Non-Small Cell Lung Cancer with an EGFR Mutation — Dr Yu

Module 2: Care of Individuals with other Targetable Genomic Abnormalities — Dr Dagogo-Jack

Targeted Therapies for NSCLC
GMO Summit 2024

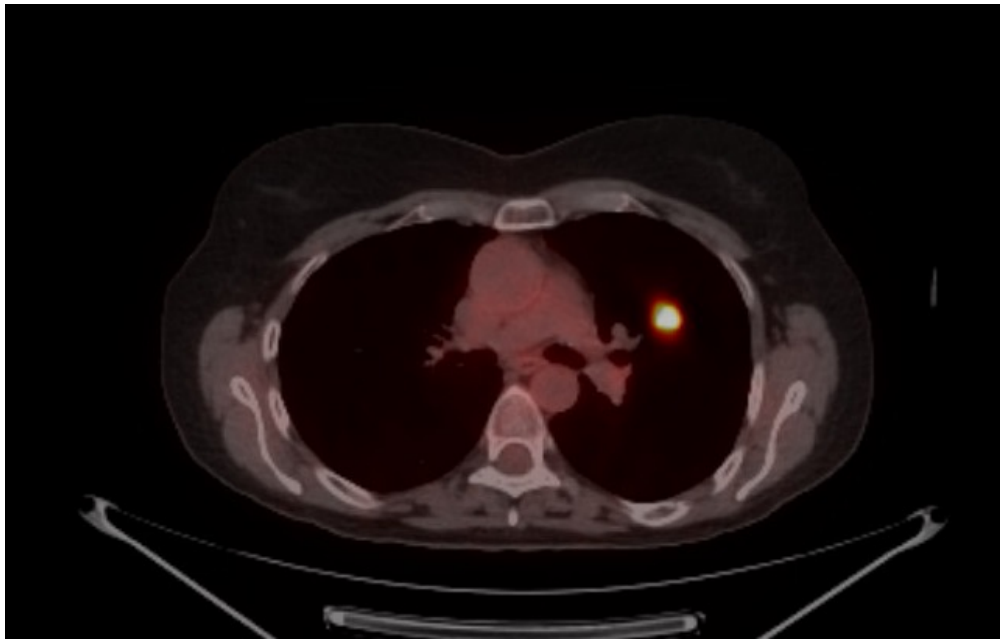
Ibiayi Dagogo-Jack, MD
Assistant Professor of Medicine
Massachusetts General Hospital Cancer Center
Harvard Medical School

Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BostonGene, Bristol Myers Squibb, Foundation Medicine, Genentech, a member of the Roche Group, Merus BV, Novocure Inc, Pfizer Inc, Roche Laboratories Inc, Sanofi, Thermo Fisher Scientific Inc
Contracted Research	Genentech, a member of the Roche Group, Novartis, Pfizer Inc
Data and Safety Monitoring Board/Committee	Vivace Therapeutics, Inc

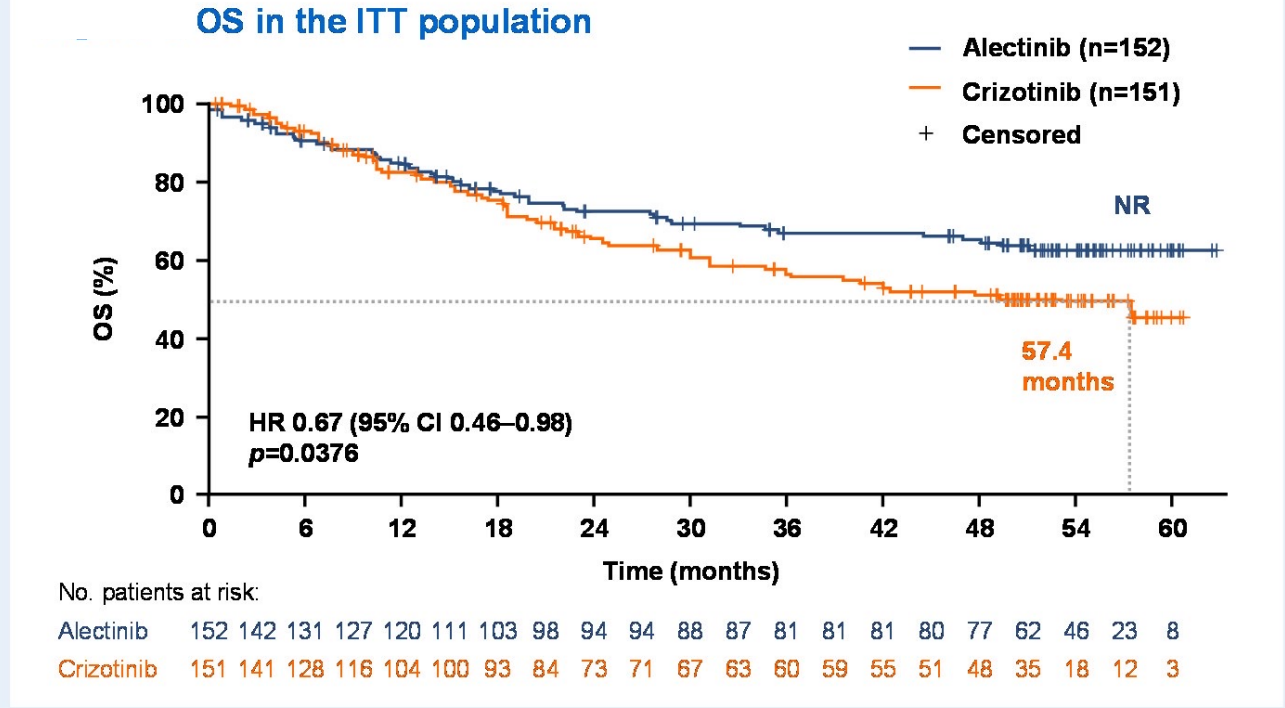
Patient Case: Stage II ALK+ NSCLC

- **In 2019**, a 55 year old woman without a smoking history is incidentally noted to have a 1 cm L upper lobe lung nodule on imaging obtained to evaluate dysphagia.
- Medical history is notable for hyperlipidemia, hypertension, and Gilbert's syndrome
- PET scan confirms uptake in the LUL nodule without uptake elsewhere. Brain MRI is negative.
- Left upper lobectomy performed with mediastinal nodal dissection. Pathology consistent with a 1.6 cm **adenocarcinoma** involving the 10L node. Overall, **stage IIB (pT1bN1).**
- Molecular testing reveals an ***EML4-ALK* fusion**. She is referred to my clinic to discuss adjuvant strategies.



Management of Stage IV ALK-Rearranged NSCLC

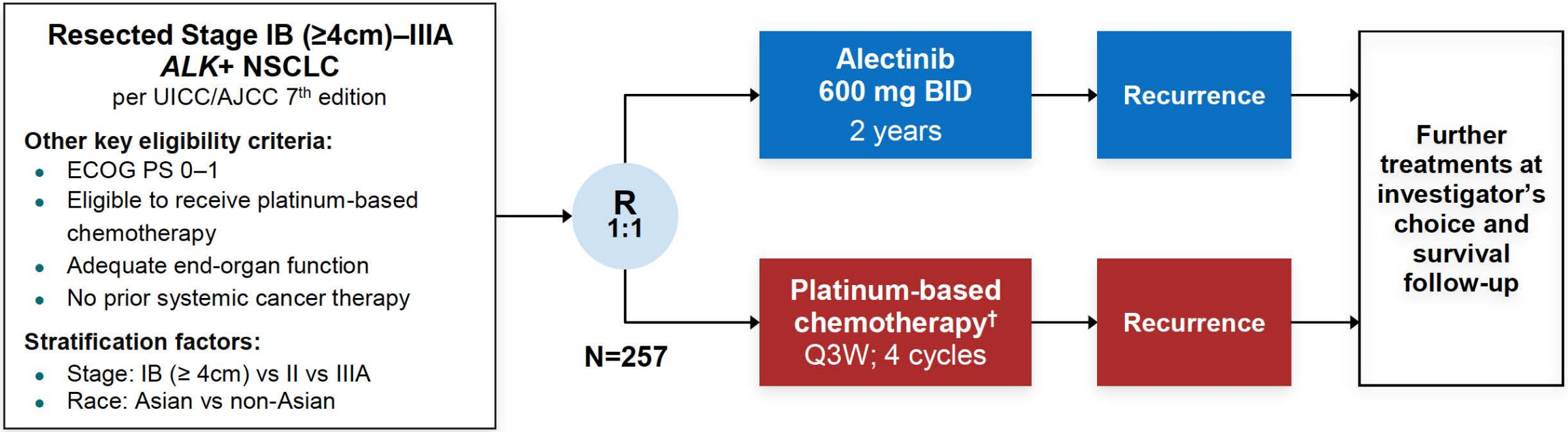
ALK TKI	ORR (%) *Investigator Assessed	Median PFS
Alectinib vs Crizotinib ALEX	*82.9 vs 75.5	25.7 vs 10.4
Brigatinib vs Crizotinib ALTA-1L	74 vs 62	24.0 vs 11.1
Lorlatinib vs Crizotinib CROWN[3]	76 vs 58	NR vs 9.3 (HR 0.27)



Mok Ann of Onc 2020, Camidge JTO 2021, Shaw NEJM 2020, Solomon Lancet Resp Med 2022

Role of Adjuvant ALK Inhibitor: ALINA

- Global randomized phase III study comparing adjuvant chemotherapy to adjuvant alectinib
- 76% crossover in control group



Primary endpoint

- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

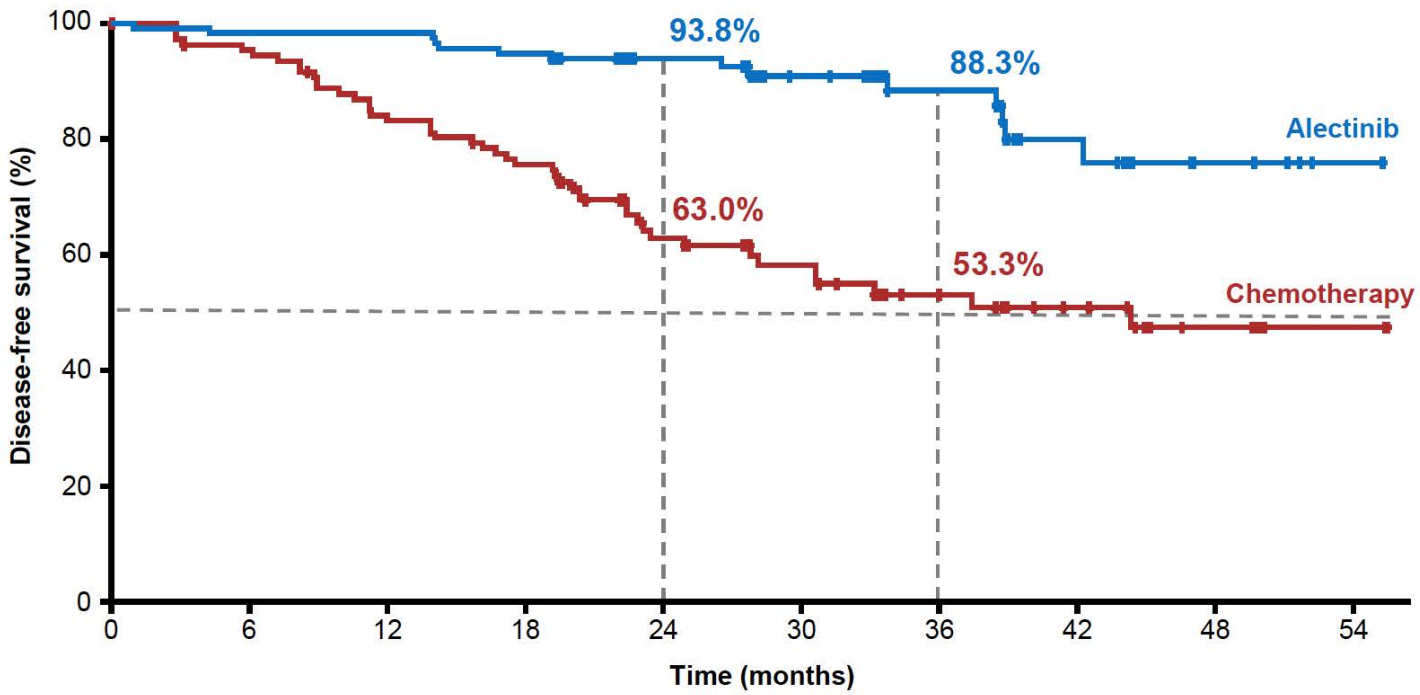
Other endpoints

- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

Solomon ESMO 2023

ALINA: Disease-Free Survival in Stage II-III (AJCC v7)



No. at risk

Alectinib	116	111	111	107	67	49	35	21	10	3
Chemo	115	102	88	79	48	35	23	17	10	2

	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

MADRID 2023 ESMO congress

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months
*Per UICC/AJCC 7th edition; †Stratified log rank; DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

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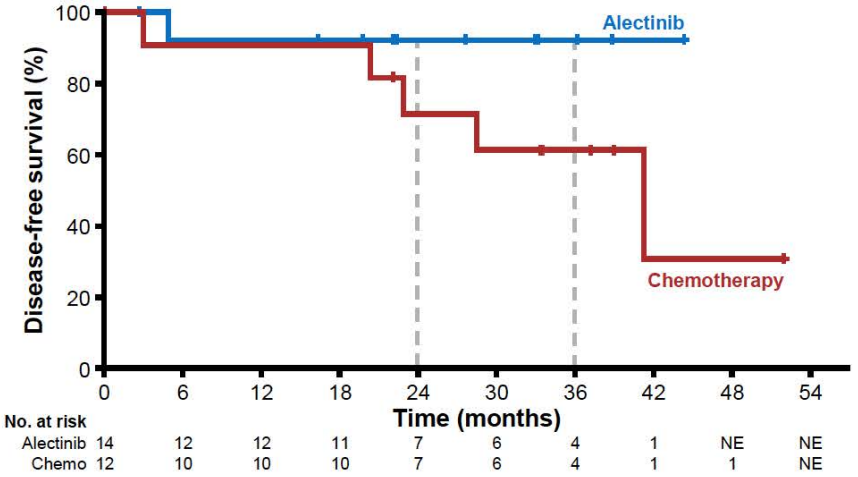
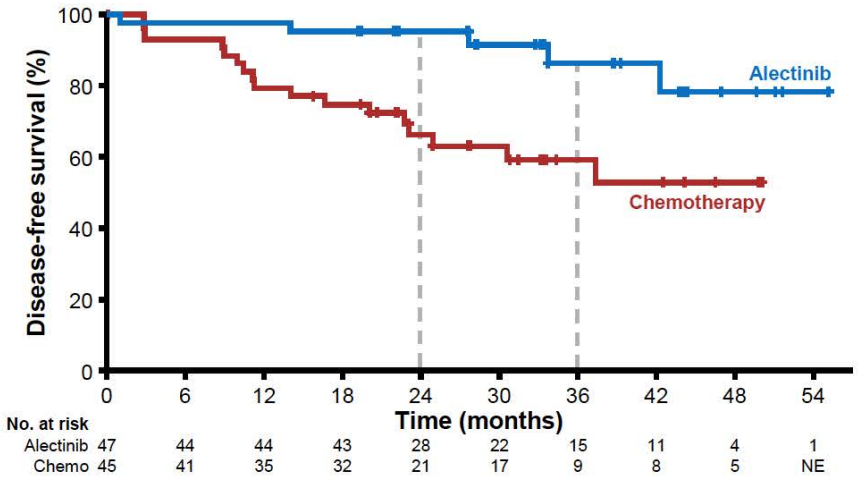
ALINA: Disease-Free Survival by Stage

Stage IB

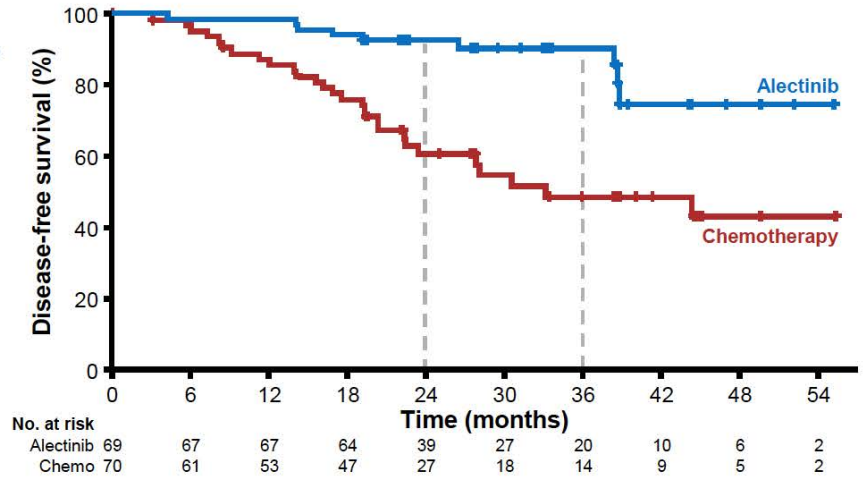


2-year DFS rate, % (95% CI)	Stage IB (n=26)	Stage II (n=92)	Stage IIIA (n=139)
Alectinib	92.3 (77.8, 100.0)	95.6 (89.5, 100.0)	92.7 (86.4, 98.9)
Chemotherapy	71.6 (44.2, 99.0)	66.3 (51.7, 81.0)	60.7 (47.9, 73.5)
HR† (95% CI)	0.21 (0.02, 1.84)	0.24 (0.09, 0.65)	0.25 (0.12, 0.53)

Stage II



Stage IIIA



Data cut-off: 26 June 2023

*Per UICC/AJCC 7th edition; †Unstratified analysis

MADRID 2023 ESMO congress

Solomon ESMO 2023

ALINA: Safety of Adjuvant Alectinib and Outstanding Questions

	Alectinib (n=128)	Chemotherapy (n=120)
Median treatment duration	**23.9 months**	**2.1 months**
Patients with any AEs, %	**98**	**93**
Grade 3/4 AEs	30	31
Grade 5 AEs	0	0
Serious AEs	13	8
Treatment-related serious AEs	2	7
AEs leading to dose reduction	26	10
AEs leading to dose interruption	27	18
AEs leading to treatment withdrawal	5	13

Remaining Questions

- Will improved DFS translate to improved Overall Survival?
- Are we increasing the cure rate? If not, are 2 years of therapy sufficient?
- Do we feel comfortable omitting chemotherapy, particularly for stage II-III?
- What about someone who has completed chemoradiation for unresectable stage III (HORIZON-01)?

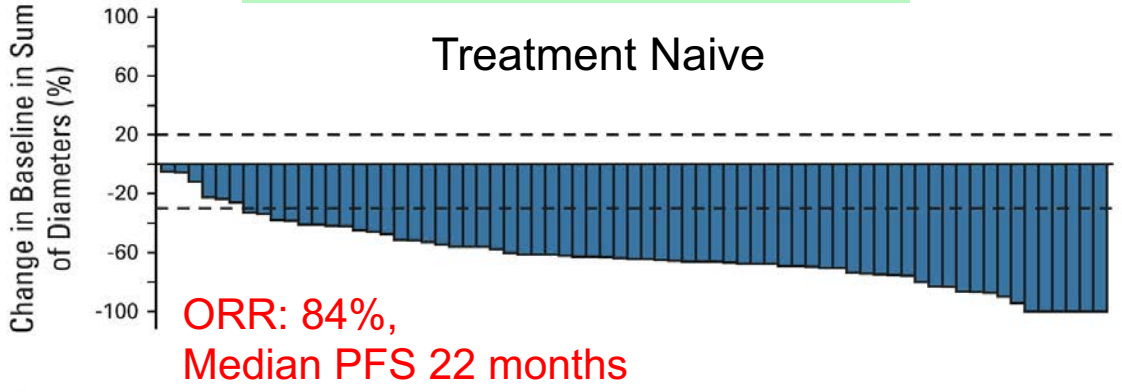
Solomon ESMO 2023

RET-Rearranged NSCLC: Current Management

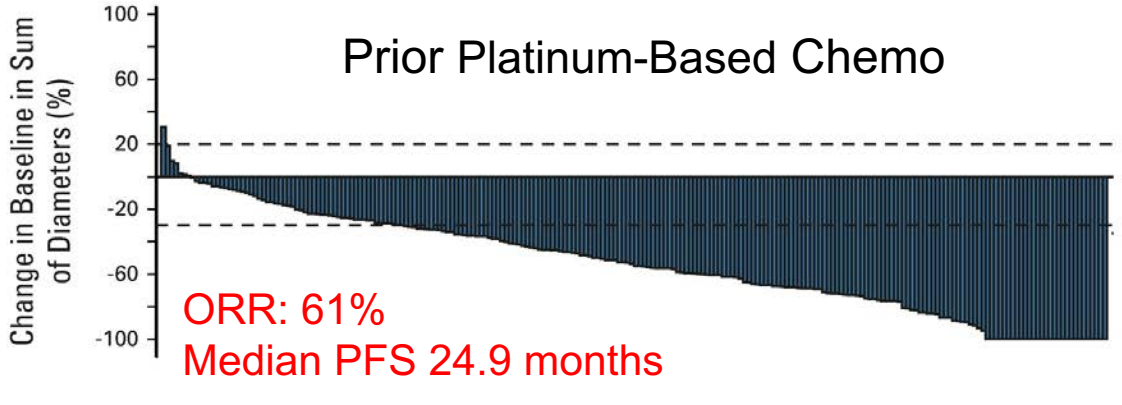
Selpercatinib and Pralsetinib are both FDA-approved for treatment of *RET*-rearranged NSCLC.

Selpercatinib

Treatment Naive

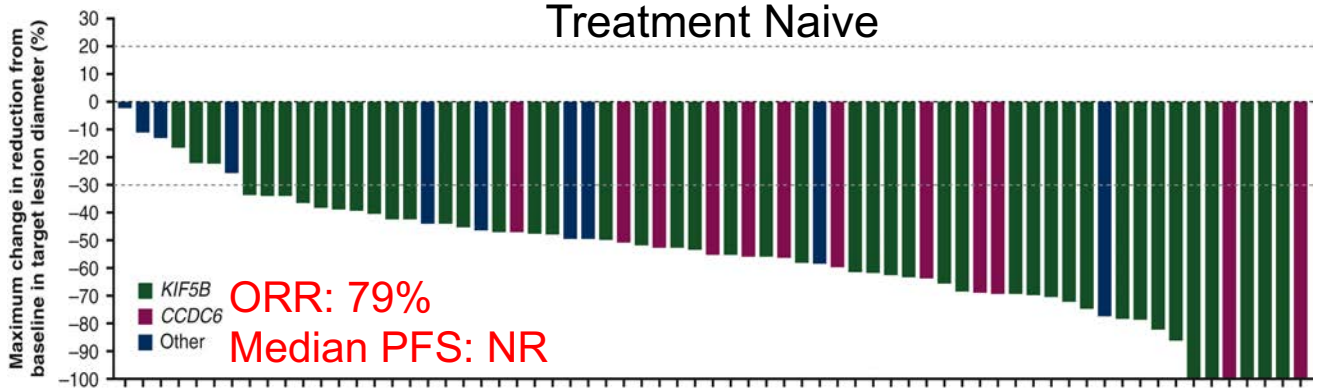


Prior Platinum-Based Chemo

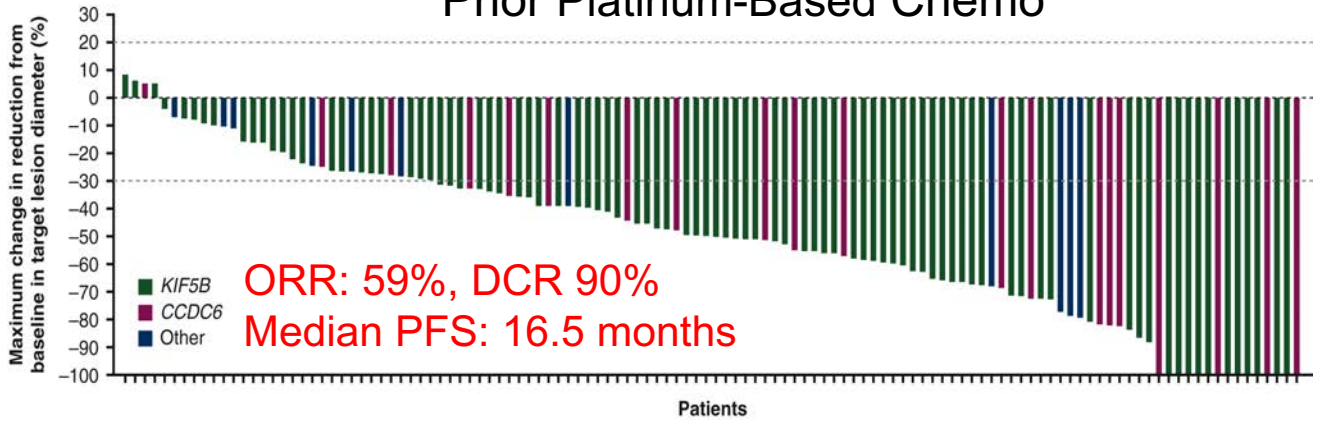


Pralsetinib

Treatment Naive



Prior Platinum-Based Chemo



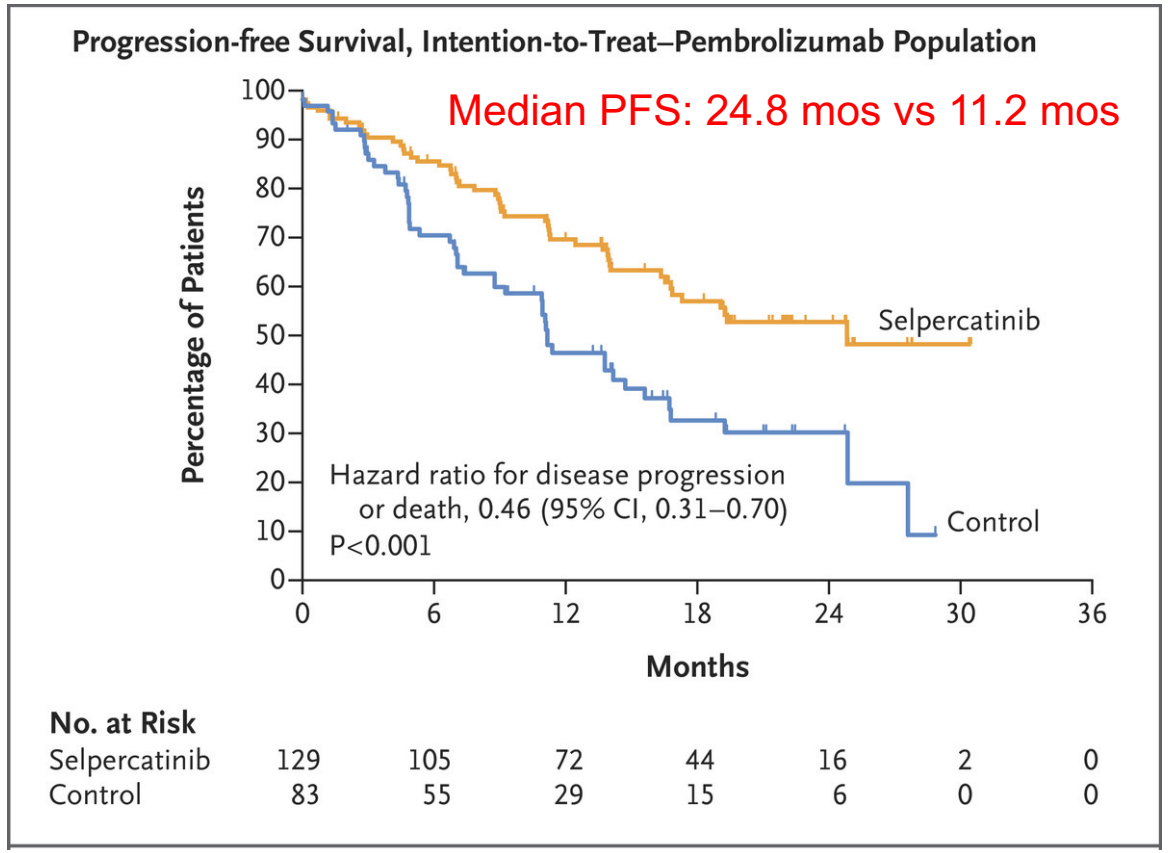
Drilon JCO 2023, Greisinger Annals of Oncology 2022

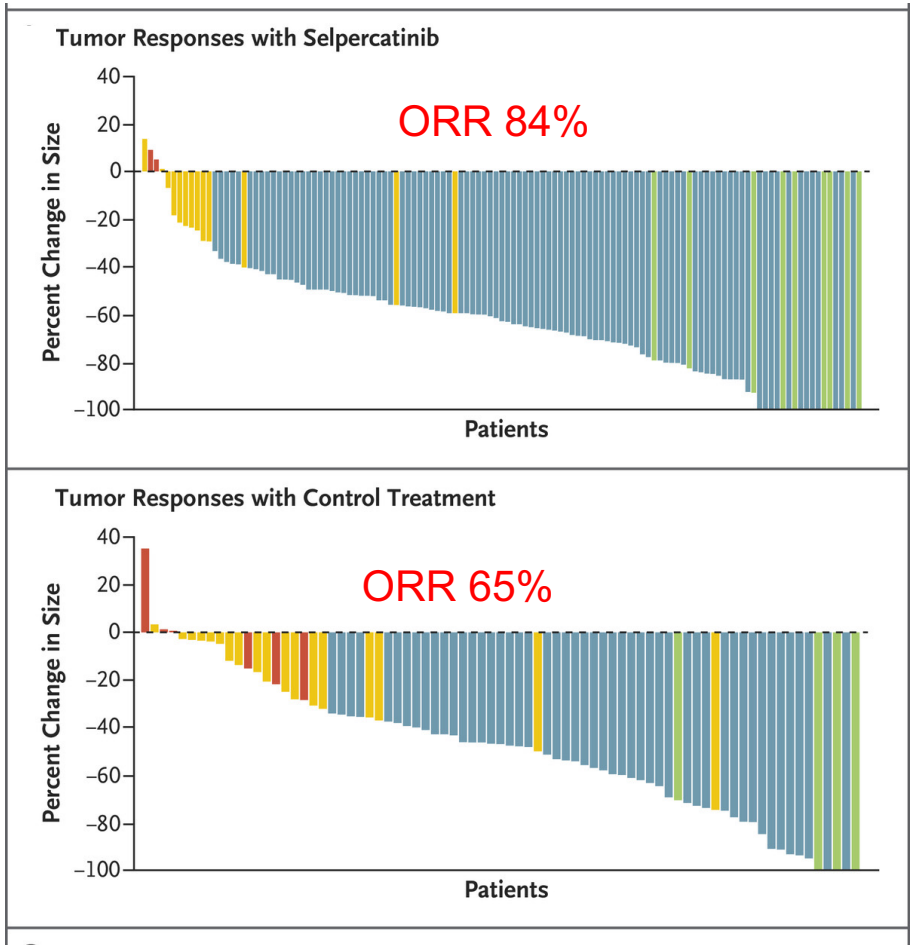
1st Line Selpercatinib: LIBRETTO-431

Global randomized phase III study comparing Selpercatinib to chemo +/- immunotherapy in 1st line

Was the study necessary? Initially 1:1 randomization, ultimately 2:1 (overall 1.6:1).

Crossover occurred in 60% of pts in control arm + additional 15% of pts received a RET TKI outside of study





CNS ORR
82%

CNS ORR
58%

Zhou NEJM 2023

Efficacy of MET TKIs in NSCLC Harboring MET Exon 14 Skipping Alterations

- Tepotinib and Capmatinib are both approved in a line-agnostic fashion.
- I prioritize TKI therapy in the 1st line over immunotherapy +/- chemotherapy due to better efficacy in the 1st line and the potential toxicity of the reverse sequence.

	Not A Formal Comparison			
Response & Toxicity	Capmatinib Tx Naive n = 28	Capmatinib Prior Tx n=69	Tepotinib Tx Naive n = 69	Tepotinib Prior Tx n= 83
Confirmed ORR, %	67.9*	40.6	57.3	45.0
Disease Control Rate, %	96	78	78.7	73.8
Median PFS, months	12.4	5.4	12.6**	11.0
Median OS, months	20.8	13.6	21.3**	19.3
CNS ORR, %	54 (n=13)		66.7 (n=15)	

***Real world Capmatinib:** ORR 91% in 1st line and 62% in 2nd line. CNS ORR 85% in 1st line (Paik Future Oncology 2023)
****Real world Tepotinib**: Median PFS 15.9 months and median OS 29.7 months (Christopoulos, ESMO, TOGETHER study)

Wolf NEJM 2020, Mazieres JAMA Onc 2023

Safety Data: Capmatinib and Tepotinib

Adverse Event	Not A Formal Comparison Capmatinib| Grade ≥3	Tepotinib| Grade ≥3
Peripheral Edema	**43%| 8%**	**67%| 11%**
Increased AST	6%| 3%	6%| 1%
Increased ALT	9%| 6%	14%| 2%
Fatigue	14%| 3%	7%| 0.4%
Nausea	34%| 2%	23%| 0.6%
Creatinine Increase (Pseudo-AKI, check cystatin C)	18%| 0%	22%| 1%
Dose Reduction	**23%**	**34%**
Discontinuation	11%	15%

Key Toxicity Considerations

- Peripheral edema (reversible) is a common toxicity with MET targeted therapy
- Management strategies include diuretics, elevation, compression stockings, exercise, dietary changes, lymphedema therapy. **In my opinion, dose reduction and interruption are the most effective strategies.**

Wolf NEJM 2020; Mazieres JAMA Oncology. 2023, Wolf ASCO 2021

Trastuzumab Deruxtecan in HER2-Mutant NSCLC

- Trastuzumab deruxtecan is approved for NSCLC with a *HER2* mutation (not amplification)
- Randomized two cohort noncomparative phase 2 study to optimize safety (i.e., ILD risk)
- FDA-approved dose is 5.4 mg/kg

DESTINY-Lung02	Not Powered to Compare the 2 Arms	
Response Assessment	**T-DXd 5.4 mg/kg n = 102**	**T-DXd 6.4 mg/kg n = 50**
Confirmed Objective Response Rate, n (%)	50 (49.0)	28 (56.0)
Best overall response, n (%) Complete Response Partial Response Stable Disease Progressive Disease	 1 (1.0) 49 (48.0) 45 (44.1) 4 (3.9)	 2 (4.0) 26 (52.0) 148 (36.0) 2 (4.0)
Disease Control Rate, n (%)	95 (93.1)	46 (92.0)
Median PFS, Months	9.9	15.4
Median OS, Months	19.5	NR
Interstitial Lung Disease (Prior ICI/No Prior ICI), %	**12.9 (14.9/7.4)**	**28.0 (28.2/27.3)**
Dose Reduction/Drug Discontinuation, %	16.8/13.9	32/20

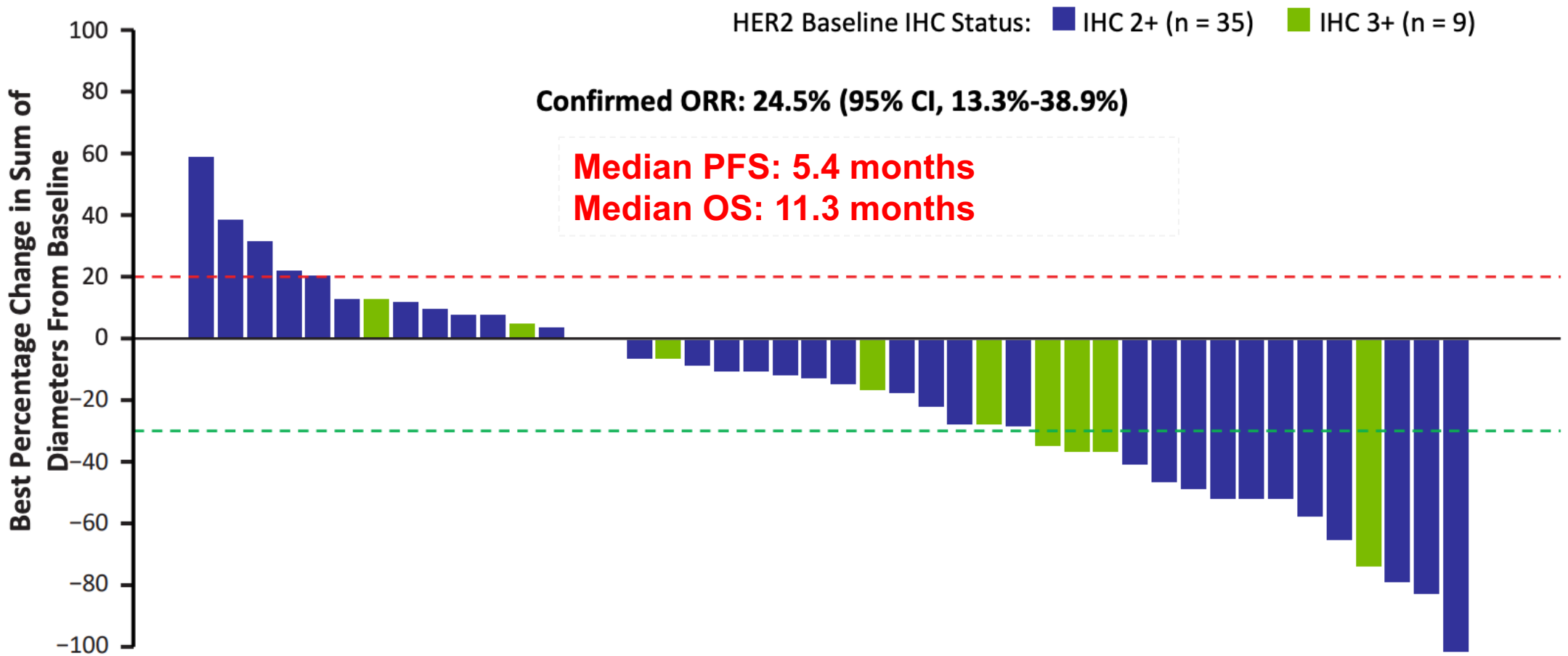
Should We Use T-DXd in the 1st Line?
- DESTINY-Lung04

Median Onset of ILD
- 88 days

CNS ORR and DOR
- 50% with 5.4 mg/kg
- 9.5 months with 5.4 mg/kg

Goto JCO 2023

Trastuzumab Deruxtecan in HER2 Expressing NSCLC: DESTINY-Lung01 (6.4 mg/kg)



Nakagawa WCLC 2020

Trastuzumab Deruxtecan in HER2 Expressing NSCLC: DESTINY-Lung01 (6.4 mg/kg)

Response Assessment by ICR	IHC 3+ (n = 10)	IHC 2+ (n = 39)	Overall (N = 49)
Confirmed ORR, n (95% CI)	**20.0%** 2 (2.5-55.6)	**25.6%%** 10 (13.0-42.1)	**24.5%** 12 (13.3-38.9)
CR, n (%)	0	1 (2.6%)	1 (2.0%)
PR, n (%)	2 (20.0%)	9 (23.1%)	11 (22.4%)
SD, n (%)	6 (60.0%)	16 (41.0%)	22 (44.9%)
PD, n (%)	1 (10.0%)	10 (25.6%)	11 (22.4%)
Not evaluable, n (%)	1 (10.0%)	3 (7.7%)	4 (8.2%)
DCR, n (95% CI)	**80.0%** 8 (44.4-97.5)	**66.7%** 26 (49.8-80.9)	**69.4%** 34 (54.6-81.8)
Median DOR, months (95% CI)	**6.0 (NE-NE)**	**5.8 (3.2-NE)**	**6.0 (3.2-NE)**

Nakagawa WCLC 2020

Overview

Saturday, March 23rd

Module 1: 7:30 AM – 9:10 AM — Hodgkin and Non-Hodgkin Lymphoma

Module 2: 9:30 AM – 10:20 AM — Gynecologic Cancers

Module 3: 10:20 AM – 11:10 AM — Localized Breast Cancer; SABCS 2023 Review

Module 4: 11:10 AM – 12:00 PM — Metastatic HER2-Positive and Triple-Negative Breast Cancer; SABCS 2023 Review

Module 5: 12:30 PM – 1:20 PM — Prostate Cancer

Module 6: 1:20 PM – 2:10 PM — Urothelial Bladder Cancer

Module 7: 2:10 PM – 3:00 PM — Renal Cell Carcinoma

Module 8: 3:20 PM – 4:10 PM — Targeted Therapy for Non-Small Cell Lung Cancer

Module 9: 4:10 PM – 5:00 PM — Nontargeted Treatments for Lung Cancer

Agenda

Module 1: Role of Immune Checkpoint Inhibitors in Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Langer

Module 2: Immune Checkpoint Inhibitors and Other Emerging Therapeutic Approaches for Metastatic NSCLC without a Targetable Tumor Mutation — Dr Garon

Agenda

Module 1: Role of Immune Checkpoint Inhibitors in Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Langer

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Penn Medicine
Abramson Cancer Center

Division of Hematology & Oncology

Immunotherapy in Resectable and Locally Advanced NSCLC: State-of-the-Art - 2024

Corey J. Langer, MD, FACP
Director of Thoracic Oncology
Abramson Cancer Center
Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA 19104
Corey.langer@uphs.upenn.edu
CP: 215-806-6152

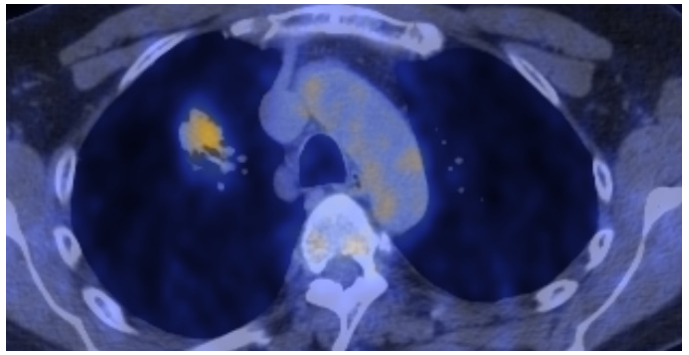
March 2024: RTP, FL

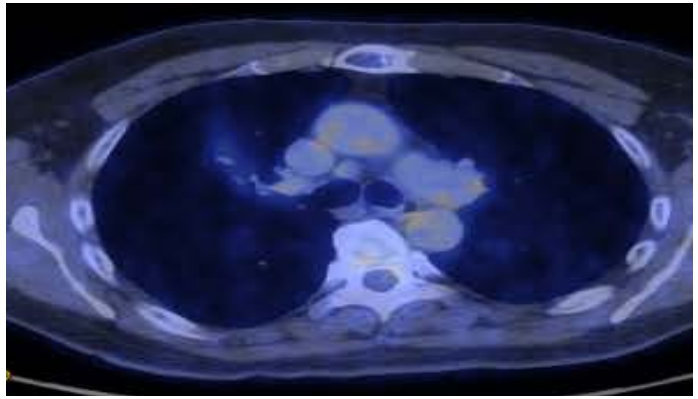
Disclosures

- **Consulting Fees**:
  - AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Heat Biologics, Merck, Mirati Therapeutics Inc, Novocure Inc, Pfizer Inc, Regeneron Pharmaceuticals Inc, Sanofi, Takeda Pharmaceuticals USA Inc
- **Data Safety Monitoring Board or Advisory Board (Co-Chair):**
  - Amgen Inc, Oncocyte
- **Medical Writing:**
  - Novartis
- **Research Funding:**
  - AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Inovio Pharmaceuticals Inc, Lilly, Merck, Oncocyte, Takeda Pharmaceuticals USA Inc, Trizell
- **Nonrelevant Financial Relationship:**
  - US Department of Veterans Affairs

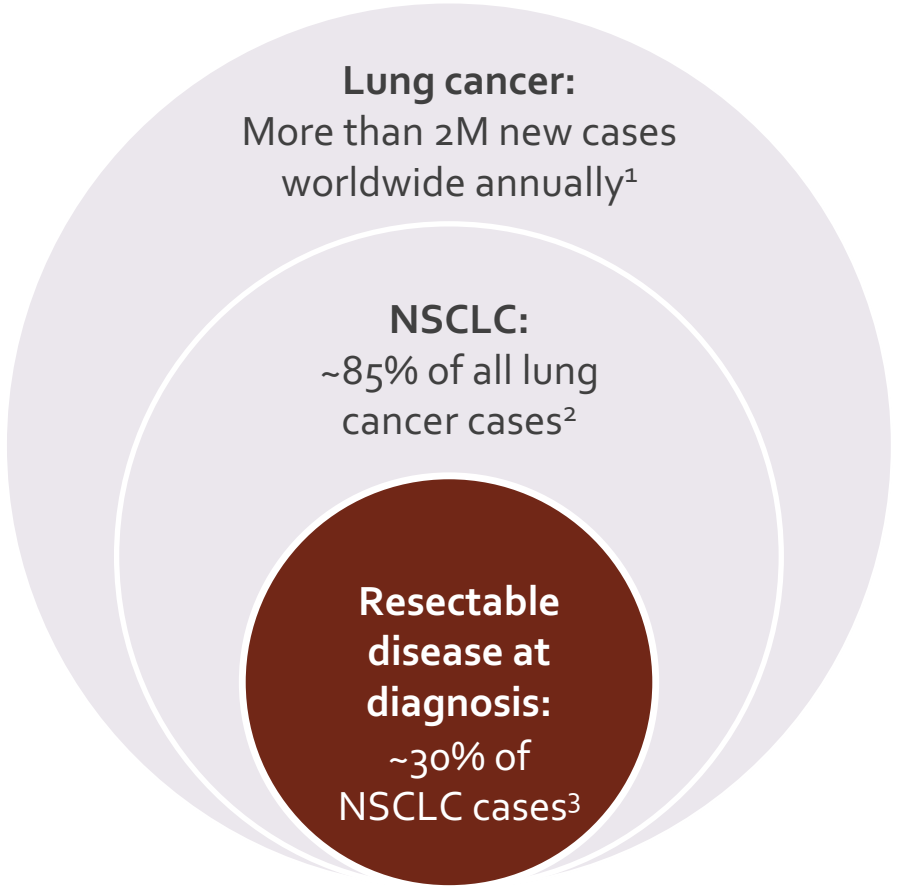
Case Scenario: Stage IIIA NSCLC

- 68 yo WM with 30 pk-yr smoking hx presents with cough, minor wheezing
- CXR shows RUL nodule
- Subsequent CT and PET show
  - 2.8 x 3.2 cm RUL mass (SUV 4.7)
  - Pre-carinal node 1.2 cm (SUV 2.5)
- PET (-) extrathoracic metastatic disease or other FDG avid adenopathy
- Brain MRI (-)
- CT guided core needle bx of RUL mass (+) adenocarcinoma, TTF1 (+)
- FOB/EBUS confirms pd adenoca in precarinal LN, all other LNs are (-)
- PDL1 is (+) at 50%; EGFR and ALK are (-)
- What is standard of care for this patient?
  1. Surgical resection, followed by adj Pem/DDP x 4, followed by CPI (Atezo or Pembro)
  2. Chemo/RT → CPI (Durvalumab)
  3. Induction Chemo/IO x 3-4 cycles, followed by Surgery → CPI if < pCR
  4. Induction Chemo/IO x 3-4 cycles, followed by Chemo/RT → CPI
  5. 1, 2, and 3
  6. All of the above

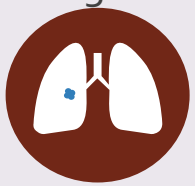




Outcomes in Resectable NSCLC Need to be Improved



Disease recurrence/death rates increases with advancing disease stage[4]

Early stage	Regional / locally advanced disease	
Stage IB	Stage II	Stage III
		
45% chance of recurrence or death	**62%** chance of recurrence or death	**76%** chance of recurrence or death

Adjuvant cytotoxic chemotherapy delivers a moderate survival benefit[4]

5.4%

5-year absolute OS benefit[4]

1. World Health Organization. Cancer Fact Sheet. Available at: https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed August 2021;
2. Cancer.org. Lung Cancer Statistics. Available at: https://www.cancer.org/content/dam/CRC/PDF/Public/8703.00.pdf. Accessed August 2021;
3. Cagle PT, et al. Arch Pathol Lab Med 2013;137:1191–8; 4. Pignon JP, et al. J Clin Oncol 2008;26:3552–9

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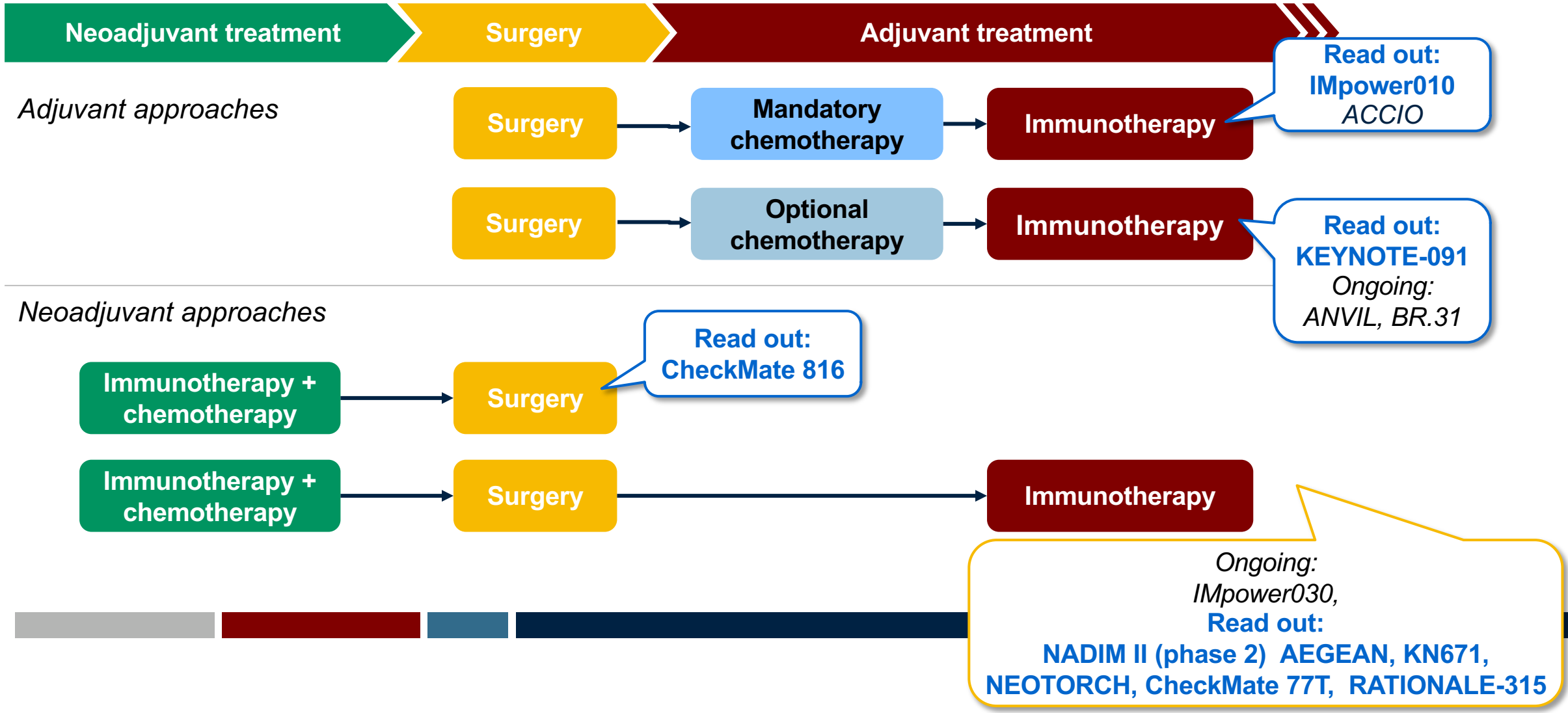
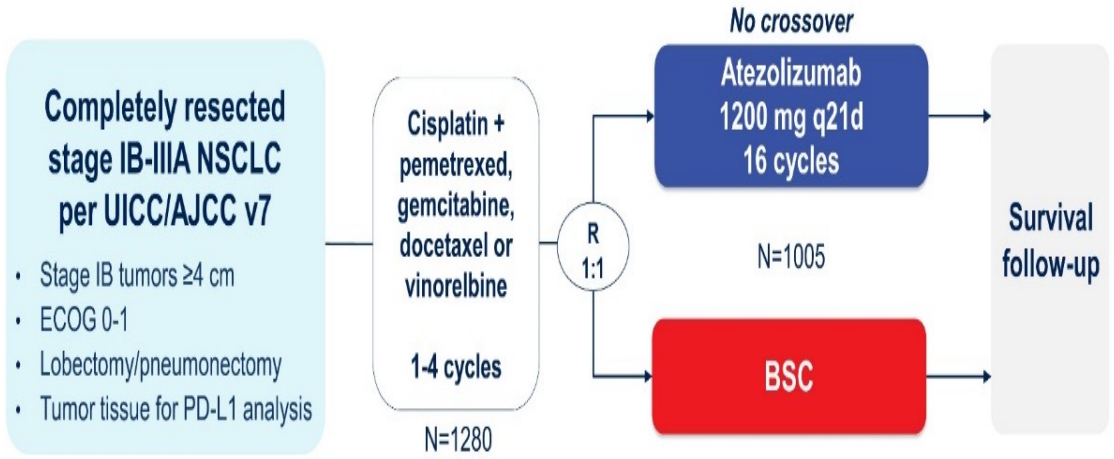
Phase III studies with immunotherapy in resectable NSCLC are taking different approaches



1st Adjuvant IO Phase III randomized trial to report: IMpower010



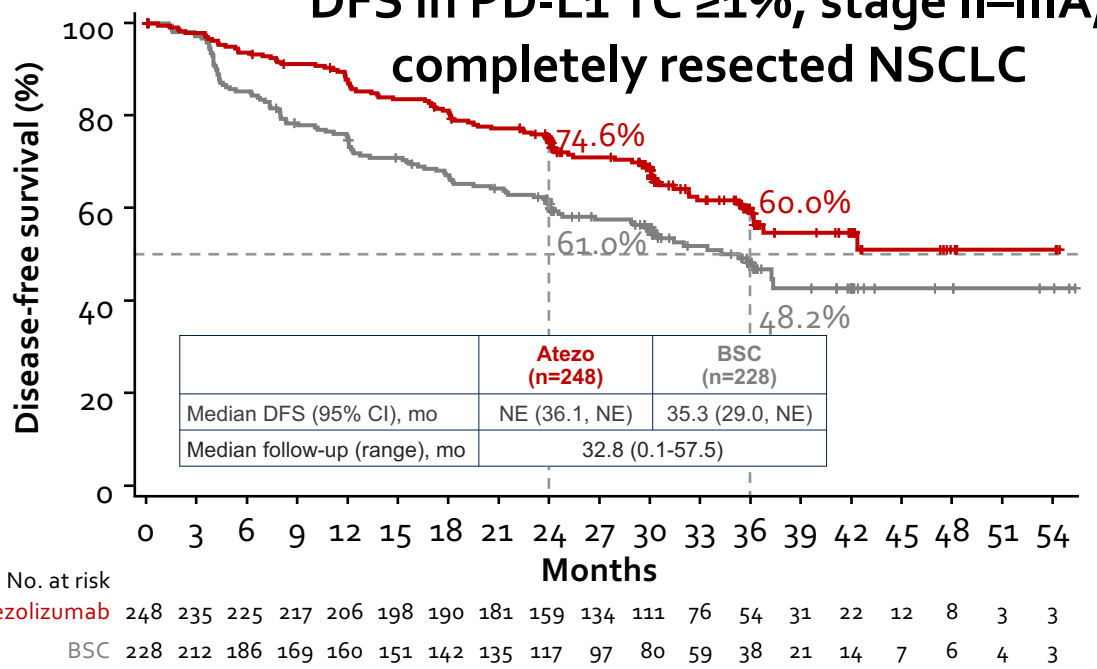
Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a] TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

*Per TNM 7th edition (select stage II–IIIB per TNM 8th edition)

DFS in PD-L1 TC ≥1%, stage II–IIIA, completely resected NSCLC



Population analysed for DFS	n	HR (95% CI)§
PD-L1 TC ≥1%, stage II–IIIA	476	0.66 (0.50, 0.88)
All randomised, stage II–IIIA	882	0.79 (0.64, 0.96)
ITT (all randomised, stage IB–IIIA)	1005	0.81 (0.67, 0.99)

Primary analysis populations

Endpoint was met at DFS IA

Endpoint was not met at DFS IA, and follow-up is ongoing

Wakelee, et al. ASCO 2021 (Abs 8500); Felip, et al. Lancet 2021

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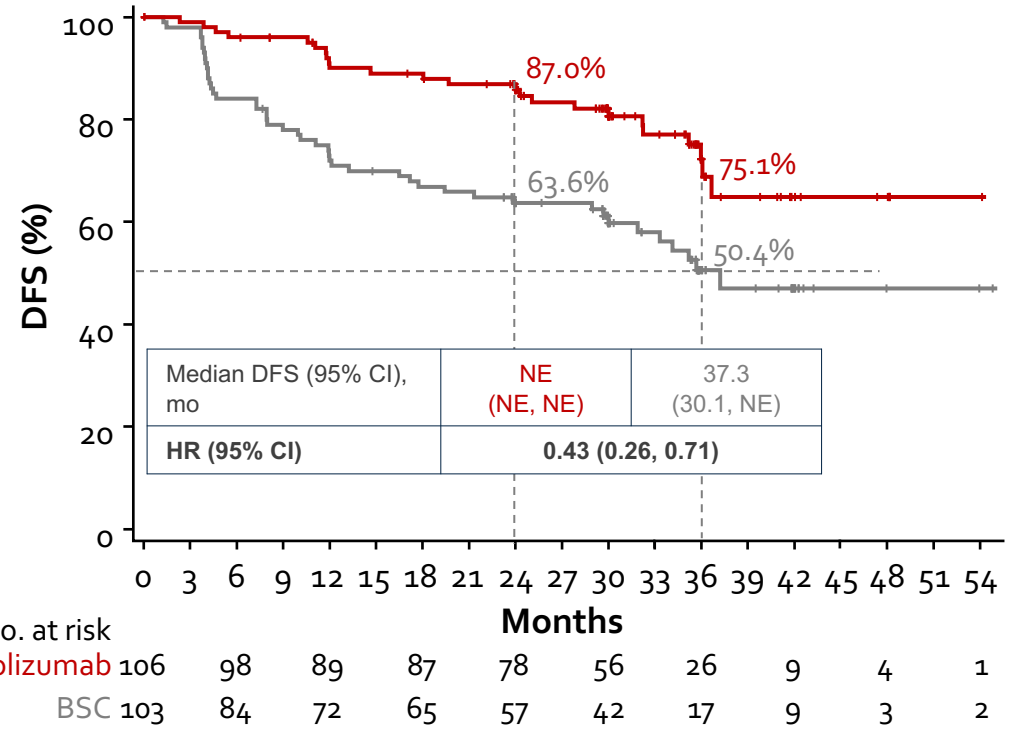
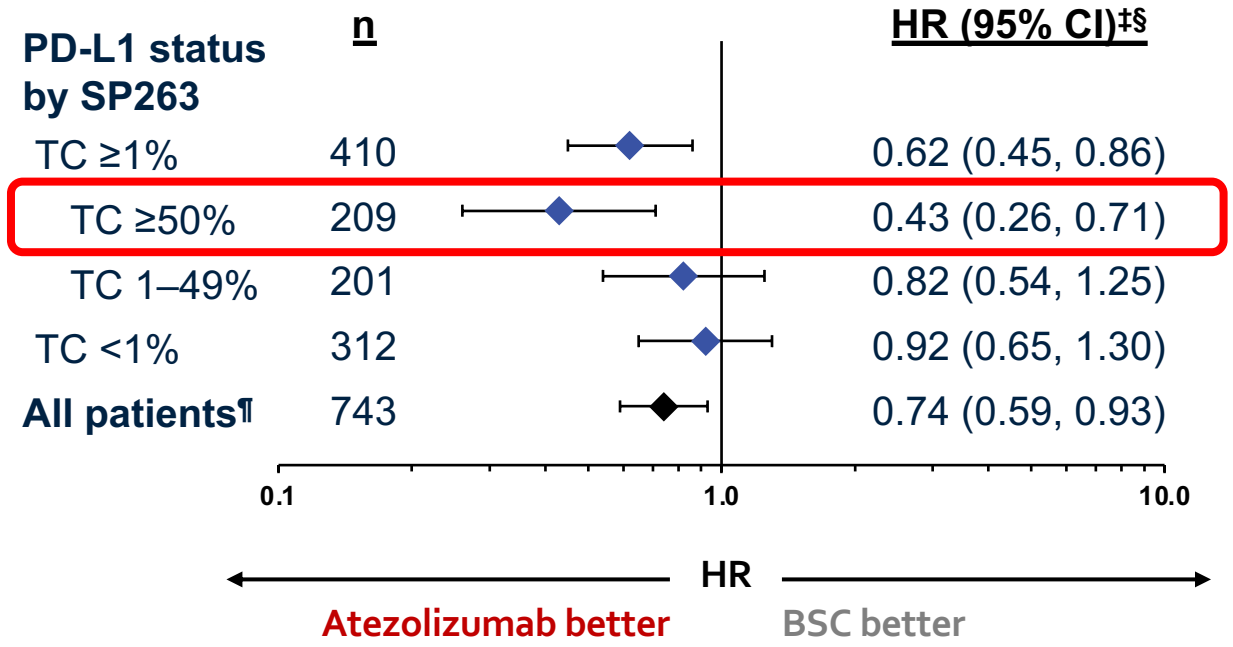
Greatest magnitude of DFS benefit with adjuvant atezolizumab over BSC was in PD-L1 TC ≥50%, stage II–III NSCLC

DFS in PD-L1 TC ≥50%, stage II–IIIA population (excluding *EGFR*+/*ALK*+ NSCLC)[1]



DFS by PD-L1 status in the all-randomised, stage II–IIIA population (excluding *EGFR*+/*ALK*+ NSCLC)[2]



OS data are not yet mature

Clinical cut-off: 21 January 2021

*Unstratified HR; ‡Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups; §DFS analyses in the PD-L1 TC <1% and TC 1–49% subgroups were exploratory; ¶23 patients had unknown PD-L1 status as assessed by SP263

1. Felip, et al. ELCC 2022 (Abs 8oO)
2. Felip, et al. ESMO 2021 (Abs LBA9)

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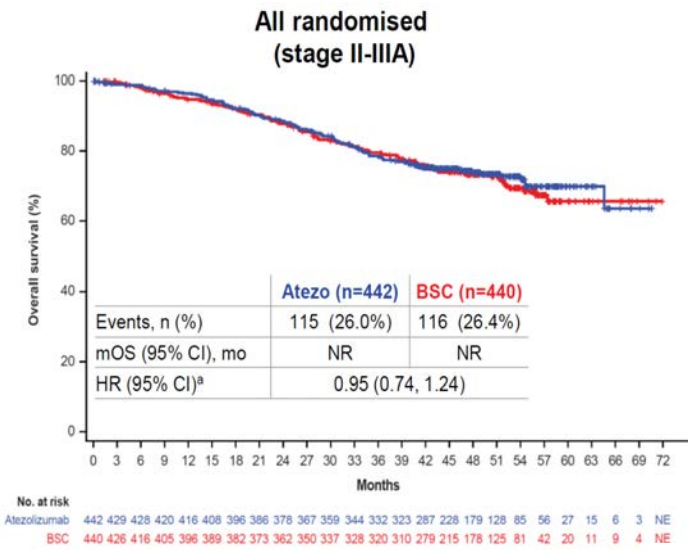
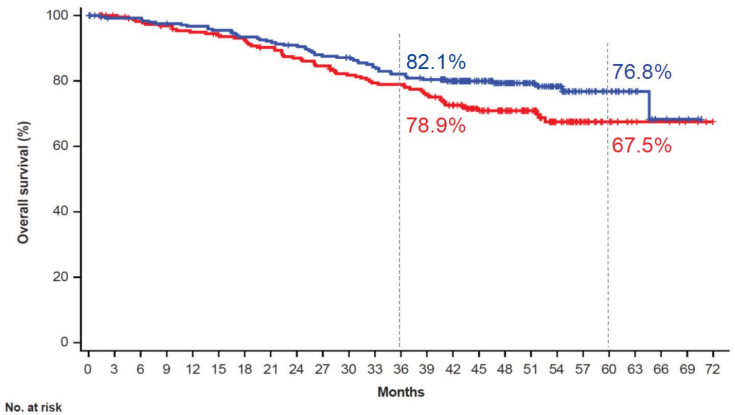
IMpower010: OS trend of atezolizumab in PD-L1 ≥1% Stage II–IIIA (interim OS analysis)

No OS benefit in the all-randomised Stage II–IIIA



	Atezo (n=442)	BSC (n=440)
Events, n (%)	115 (26.0%)	116 (26.4%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.95 (0.74, 1.24)	

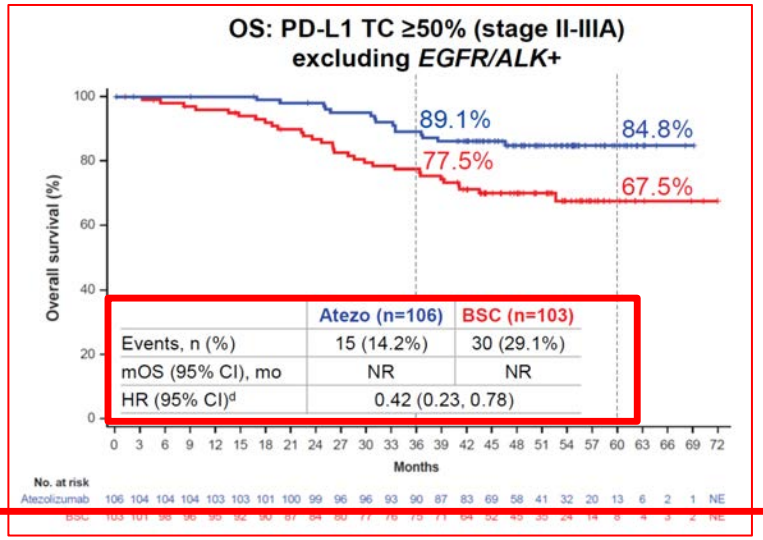
OS interim analysis in PD-L1 TC ≥1% (Stage II–IIIA)



mOS, median overall survival; NR, not reached. [a]By SP263 assay. [b]Stratified.

	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[b]	0.71 (0.49, 1.03)	

Clinically meaningful OS trend in PD-L1 ≥50%



	Atezo (n=106)	BSC (n=103)
Events, n (%)	15 (14.2%)	30 (29.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[d]	0.42 (0.23, 0.78)	

Felip E, Altorki N, Zhou C, et al. *Ann Oncol*. 2023;34(10):907-919.

Adjuvant Pembro post resection stage IB – IIIA:
PEARLS/KEYNOTE-091

Eligibility for Registration
- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomization
- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R 1:1

- Pembrolizumab 200 mg Q3W for ≤18 administrations (~1 yr)
- Placebo Q3W for ≤18 administrations (~1 yr)

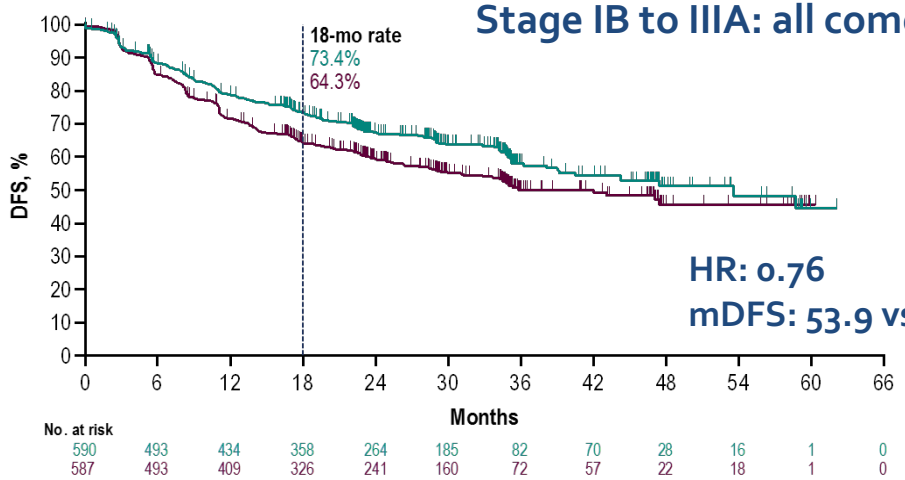
Stratification Factors
- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

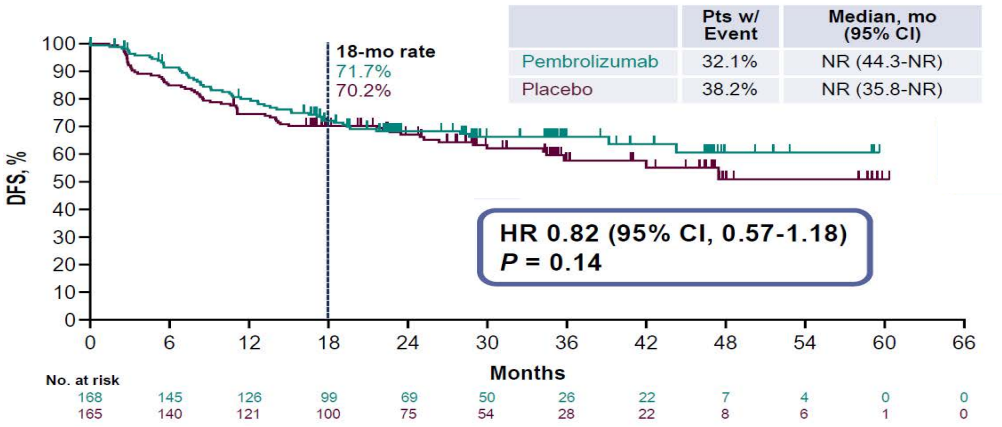
OS data are not yet mature

Stage IB to IIIA: all comers



HR: 0.76
mDFS: 53.9 vs 42 months

DFS in PD-L1 TPS ≥50%, stage IB–III, completely resected NSCLC*



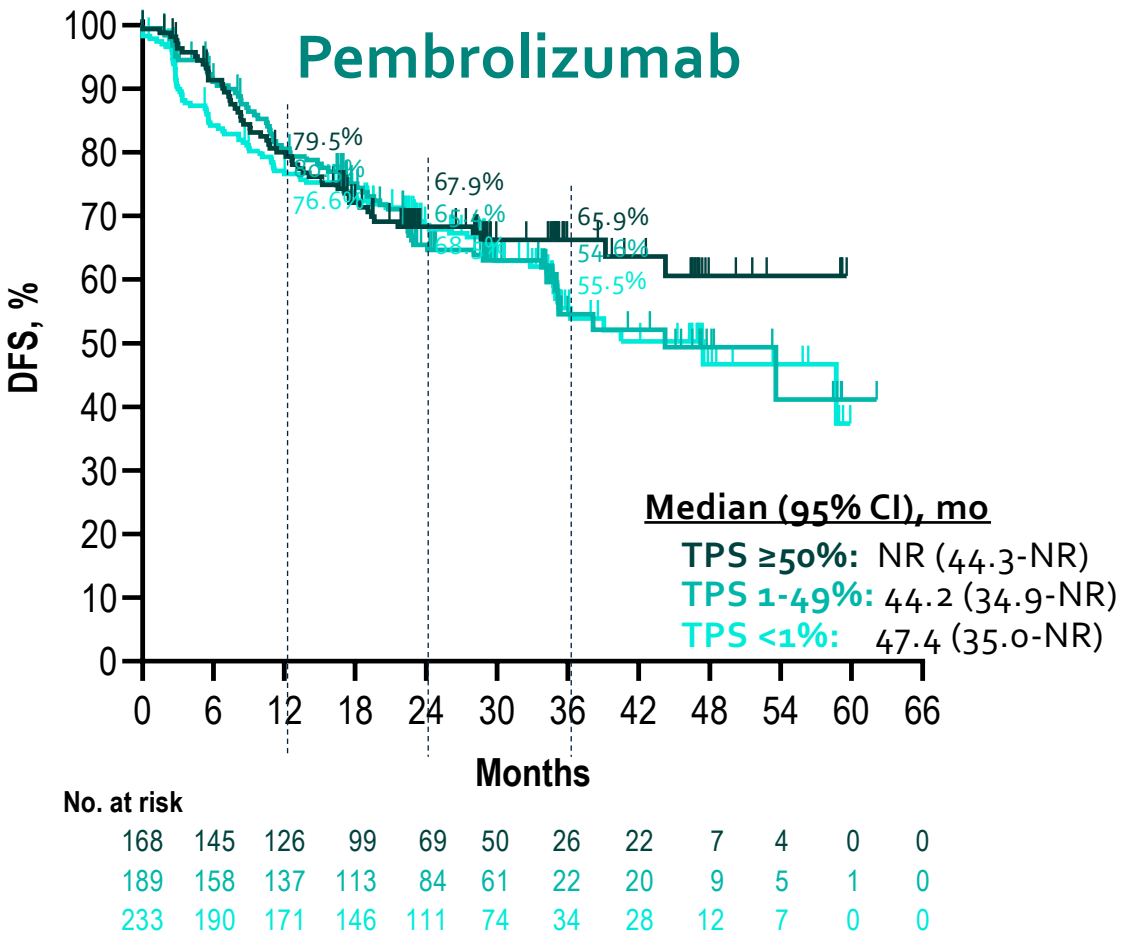
	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)

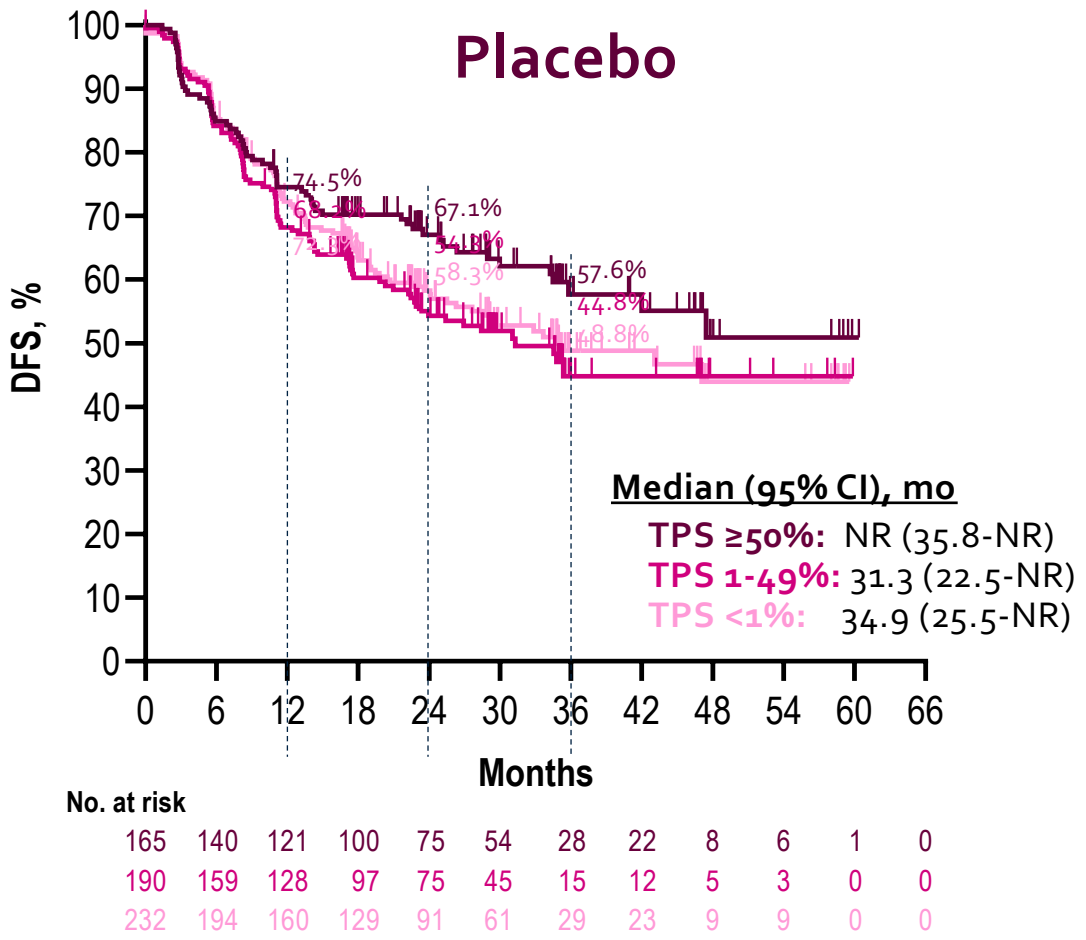
HR 0.82 (95% CI, 0.57-1.18)
***P* = 0.14**

Paz-Ares L, et al. Presented at ESMO Congress 2022 (Abstract VP3-2022)

DFS: Overperformance of high PD-L1 in placebo arm

(no imbalance in baseline characteristics or toxicity)





Paz-Ares L, et al. Presented at ESMO Congress 2022 (Abstract VP3-2022)

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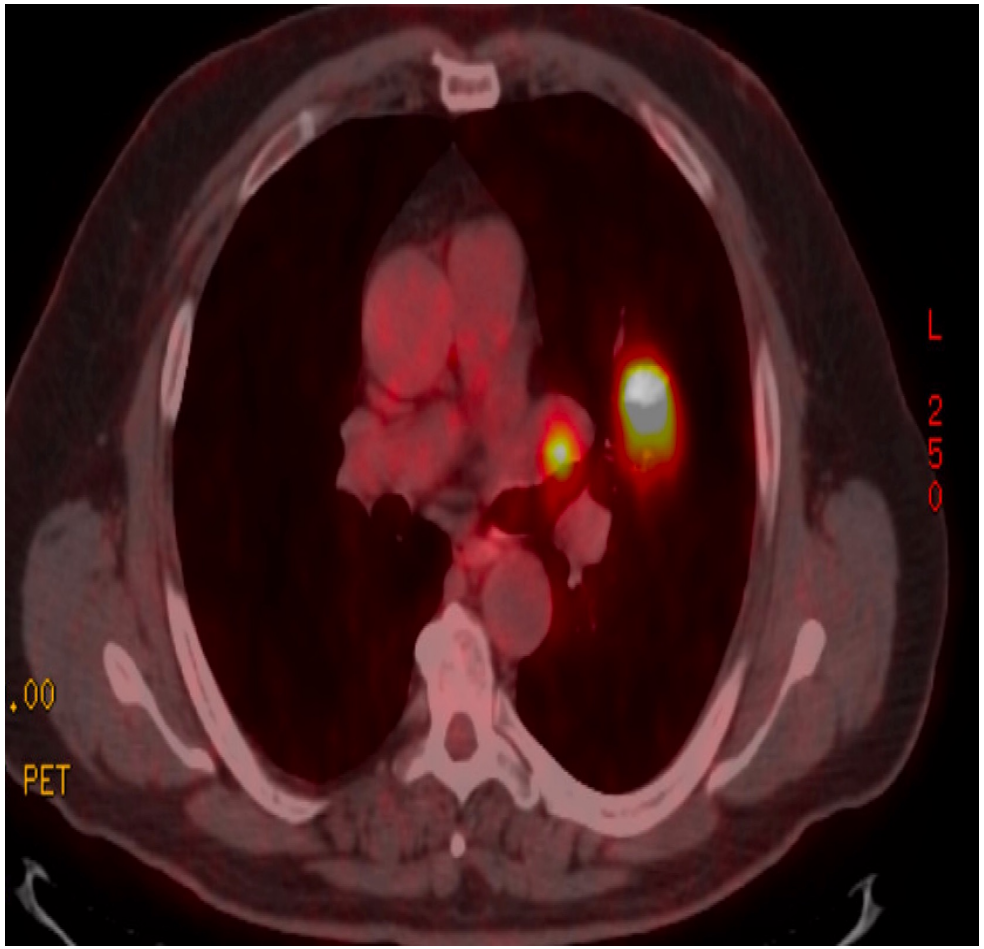
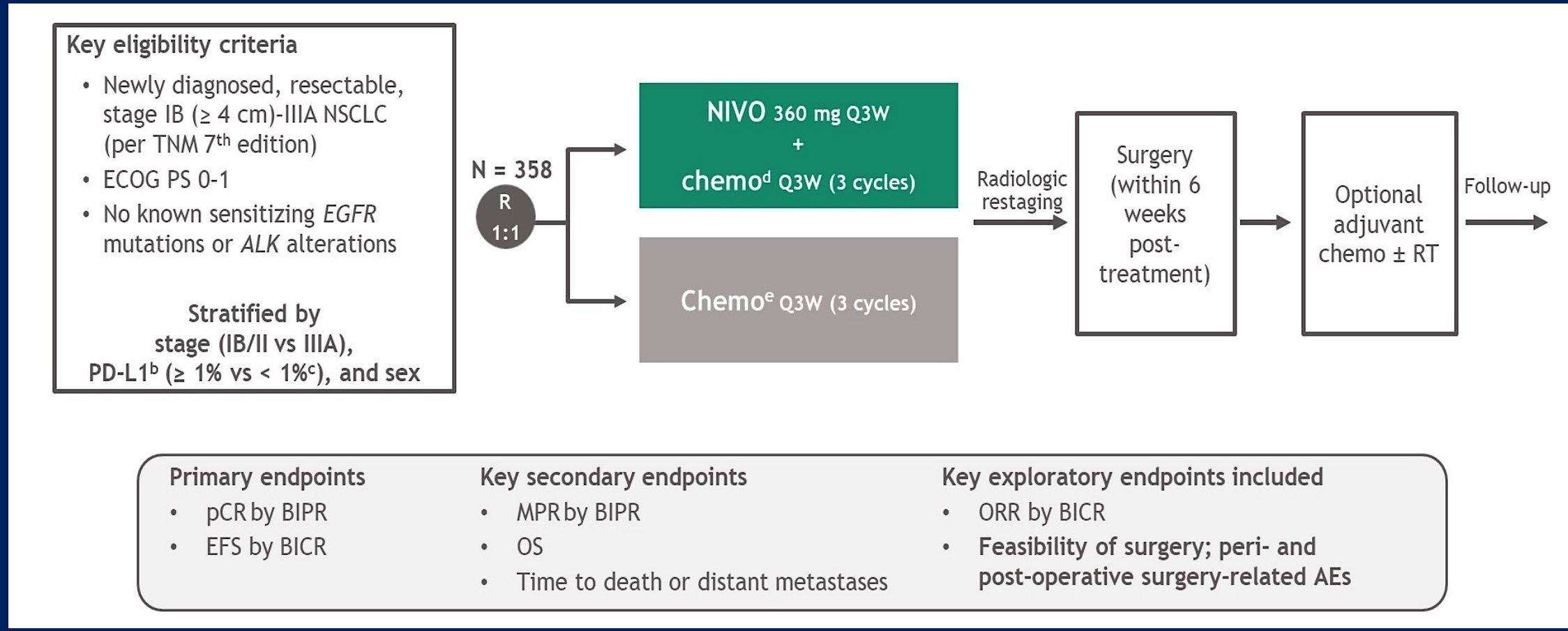
What About Neoadjuvant or Periadjuvant Tx in NSCLC?



- It is better tolerated
- Predictive biomarker data can be obtained pre-treatment
- IOs may be more effective with the tumor *in situ* rather than post resection
- No time for clonal evolution – more homogenous tumors
- Opportunity for a lesser lung resection
- Abbreviated Tx: 3 cycles (9 wks) vs 1+ year of Tx
- Capacity to assess efficacy of Tx
- Pathologic data can help predict prognosis and potentially guide post-op treatment

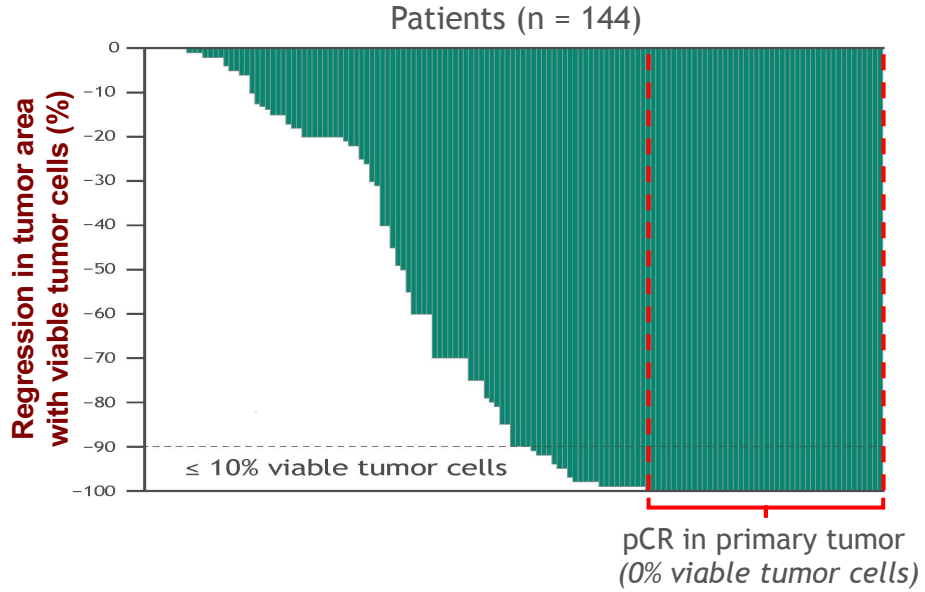
CheckMate 816: Neoadjuvant Chemo +/- Nivo

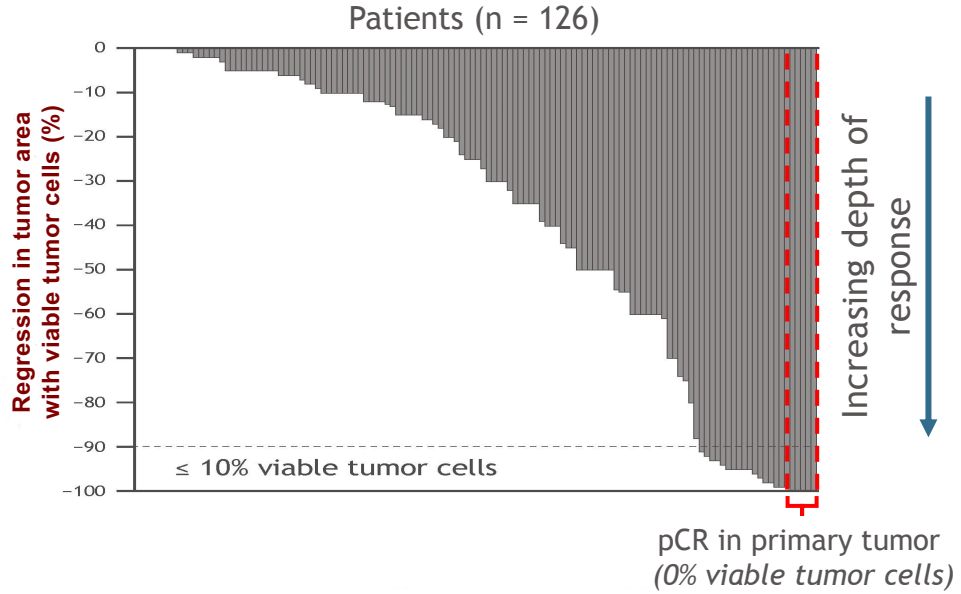


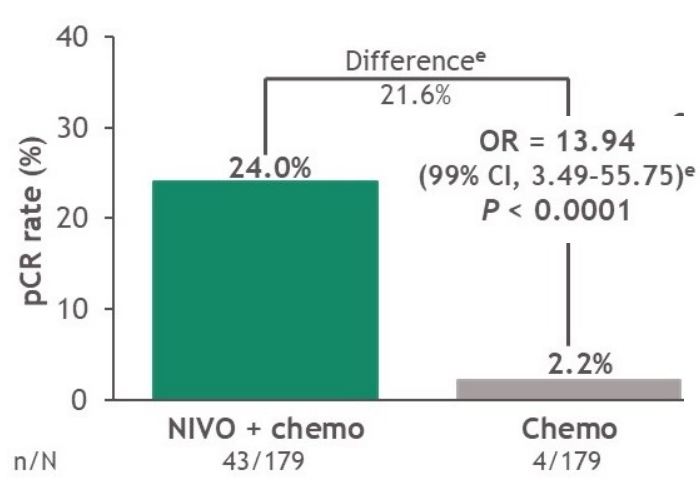
BIPR = blinded independent pathological review; BICR = blind independent central review; AEs = adverse events.

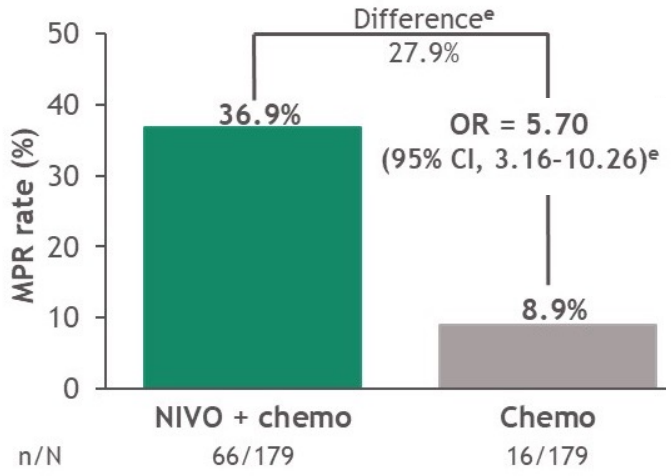
Spicer J, et al. *J Clin Oncol*. 2021;39(15_suppl):8503.

CheckMate 816 Path Response Data









Spicer J, et al. *J Clin Oncol*. 2021;39(15_suppl):8503.

- Adapted from Spicer J, et al. ASCO Annual Meeting. Abstract 8503.

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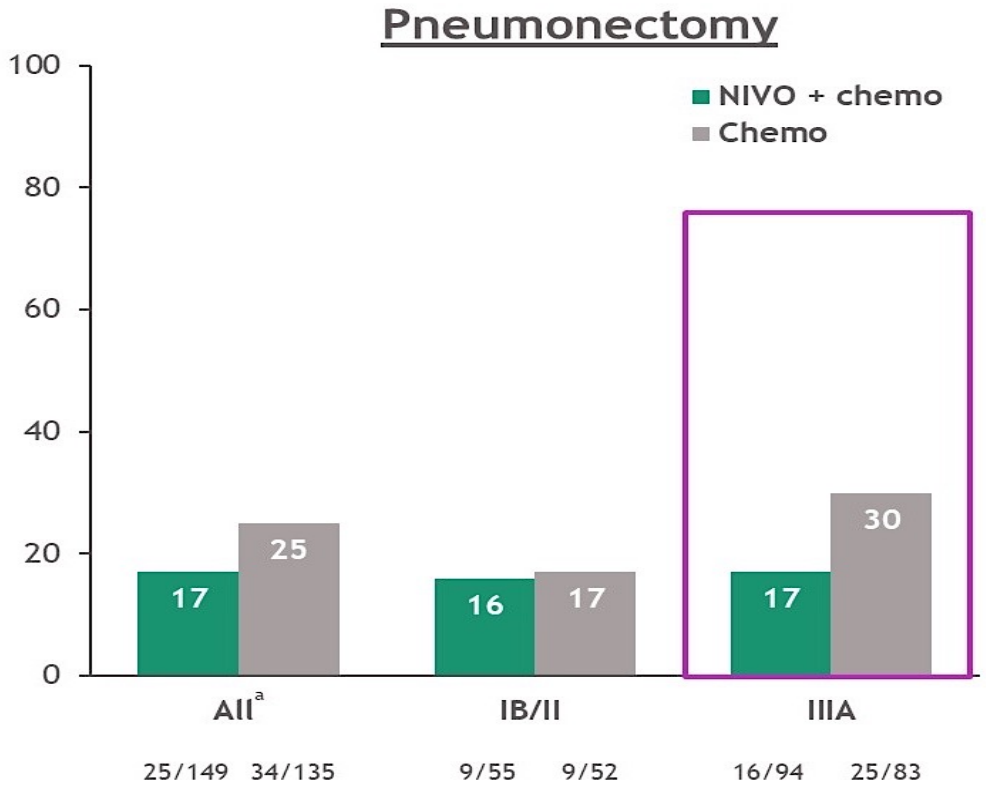
More Complete Resections, Fewer Pneumonectomies



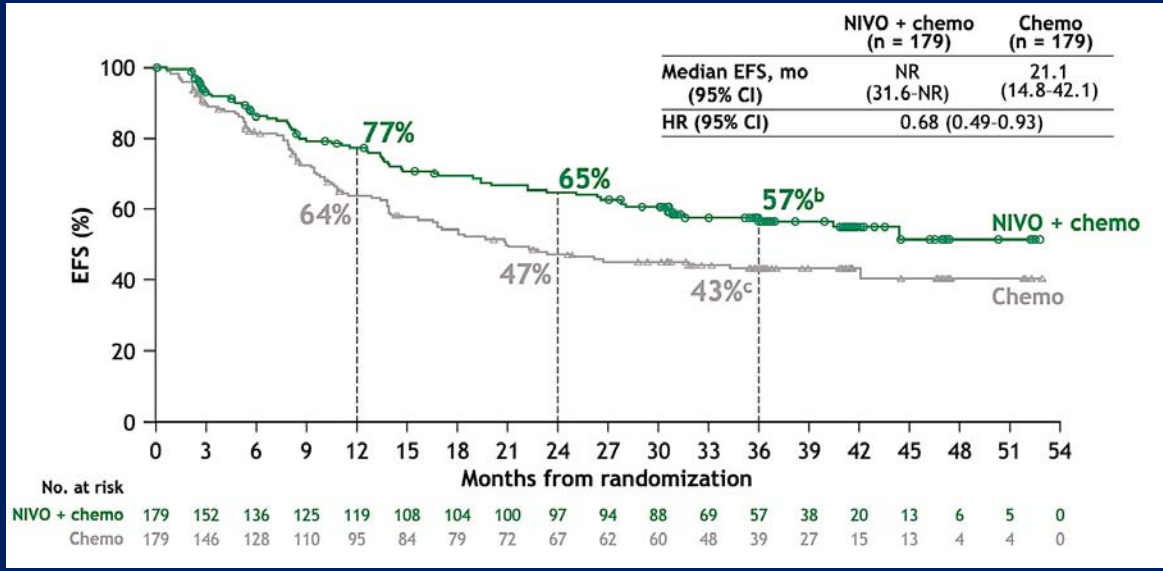
Adding anti-PD-1 to Neoadjuvant Chemo:

- More tumor kill
- Greater complete resection rate
- More lung sparing resections/Fewer pneumonectomies

Spicer J, et al. *J Clin Oncol*. 2021;39(15_suppl):8503.

- Adapted from Spicer J, et al. ASCO Annual Meeting. Abstract 8503.

CheckMate 816 Event-free Survival



	Median EFS, mo		Unstratified HR[a] (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	NR	21.0		0.66
< 65 years (n = 176)	NR	22.4		0.61
≥ 65 years (n = 182)	40.4	20.9		0.72
Male (n = 255)	44.4	18.0		0.69
Female (n = 103)	NR	NR		0.59
North America (n = 91)	NR	42.1		0.83
Europe (n = 66)	NR	21.1		0.69
Asia (n = 177)	NR	16.5		0.53
ECOG PS 0 (n = 241)	NR	31.8		0.69
ECOG PS 1 (n = 117)	NR	14.0		0.64
Stage IB-II (n = 126)	NR	NR		0.94
Stage IIIA (n = 229)	NR	16.9		0.57
Squamous (n = 182)	40.4	22.9		0.82
Nonsquamous (n = 176)	NR	20.8		0.52
Current/former smoker (n = 318)	NR	23.3		0.71
Never smoker (n = 39)	44.4	10.4		0.34
PD-L1 < 1% (n = 155)	26.4	20.8		0.87
PD-L1 ≥ 1% (n = 178)	NR	26.7		0.46
PD-L1 1%-49% (n = 98)	NR	31.8		0.63
PD-L1 ≥ 50% (n = 80)	NR	19.7		0.29
TMB < 12.3 mut/Mb (n = 102)	44.4	31.8		0.82
TMB ≥ 12.3 mut/Mb (n = 76)	NR	NR		0.67
Cisplatin (n = 258)	44.4	21.1		0.72
Carboplatin (n = 72)	NR	10.6		0.45

0.125 0.25 0.5 1 2 4

Favors NIVO + chemo ⟷ Favors chemo

Minimum/median follow-up: 32.9/41.4 months.

- Forde PM, et al. ELCC 2023; Abstract 840.

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Neoadjuvant or perioperative chemo/IO : available R data

CheckMate 816

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB/II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex

N = 358, R 1:1

- NIVO 360 mg Q3W + chemo[d] Q3W (3 cycles)
- Chemo[e] Q3W (3 cycles)

→ Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT → Follow-up

Primary endpoints:
- pCR Central
- EFS by BICR

CheckMate 77T

Key eligibility criteria

- Resectable, stage IIA (> 4 cm)-IIIB (N2) NSCLC (per AJCC 8th edition)
- No prior systemic anti-cancer treatment
- ECOG PS 0-1
- No *EGFR* mutation/known *ALK* alterations[b]

Stratified by histology (NSQ vs SQ) disease stage (II vs III), and tumor PD-L1[c] (≥ 1% vs < 1% vs not evaluable/indeterminate)

N = 461, R 1:1

- NIVO 360 mg Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → NIVO 480 mg Q4W (1 year)
- PBO Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → PBO Q4W (1 year)

→ Follow-up

Primary endpoint:
- EFS by BICR

Forde PM, et al. *N Engl J Med* 2022;386:1973-1985; Cascone T, et al. ESMO 2023

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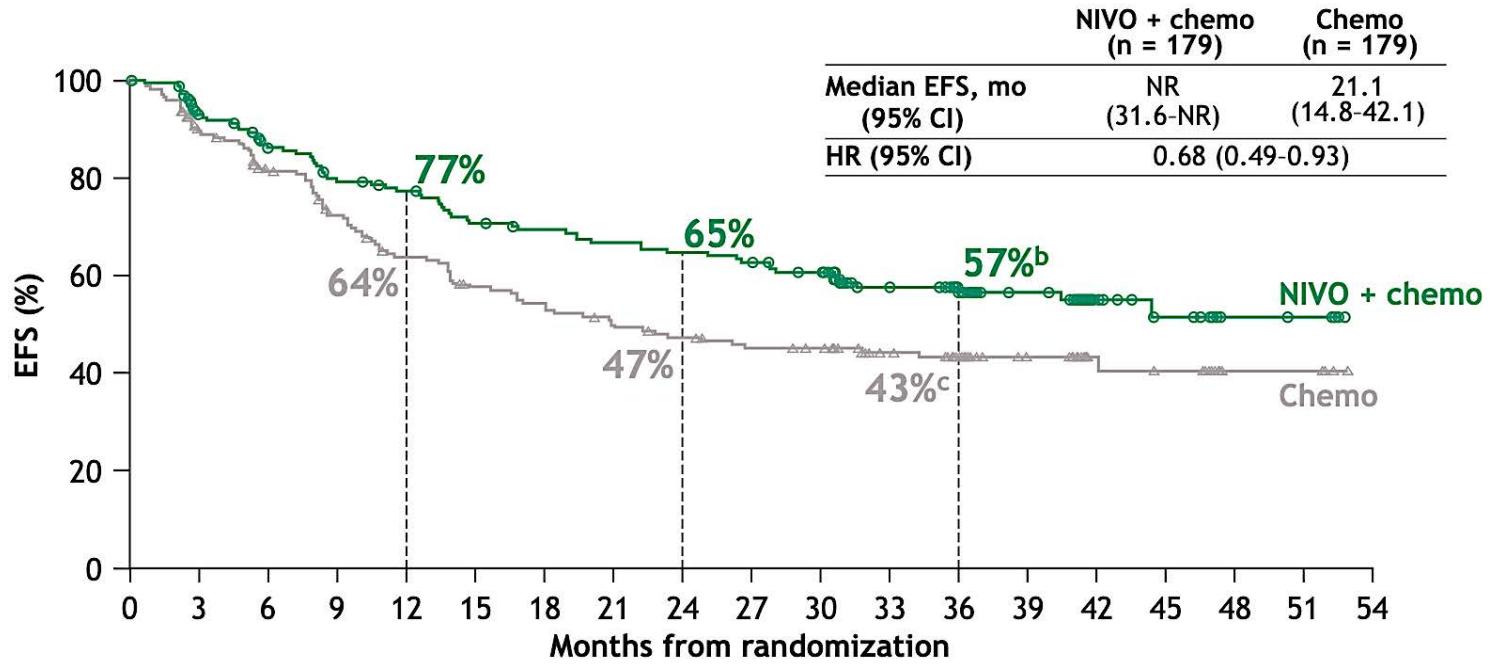
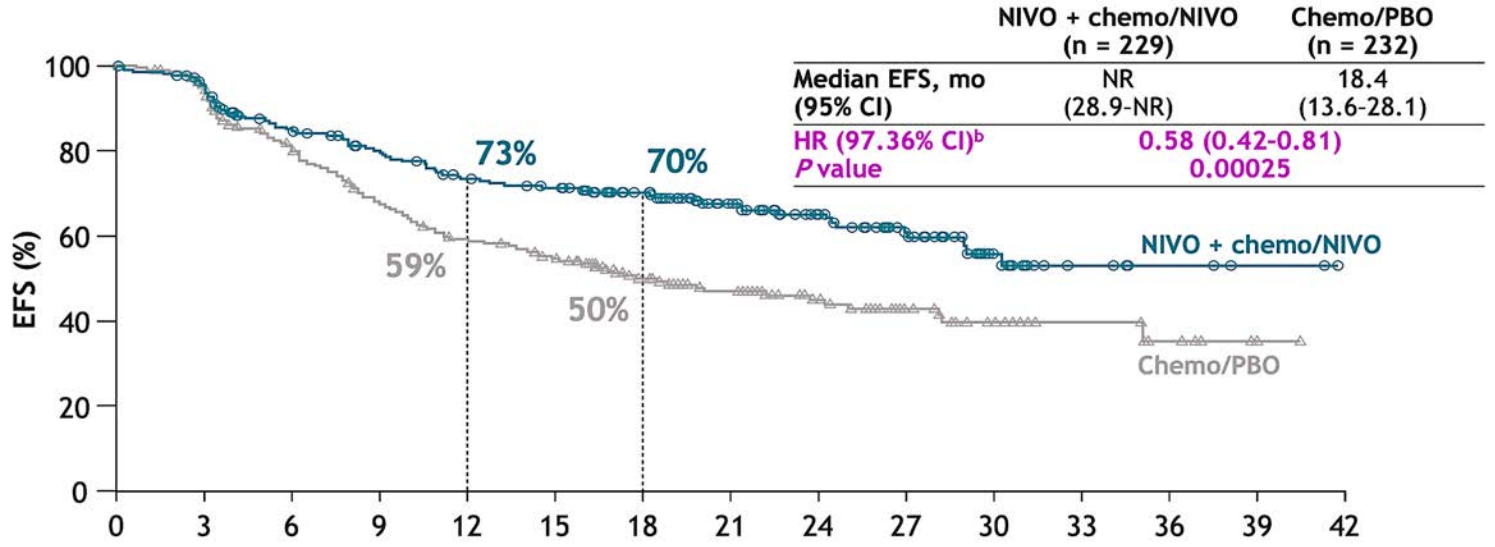
Neoadjuvant or perioperative chemo/IO: available R data

CheckMate 816



PCR 2% ->25%

CheckMate 77T



PCR 5% ->25%

Forde PM, et al. ELCC 2023; Abstract 840. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985; Cascone T, et al. ESMO 2023

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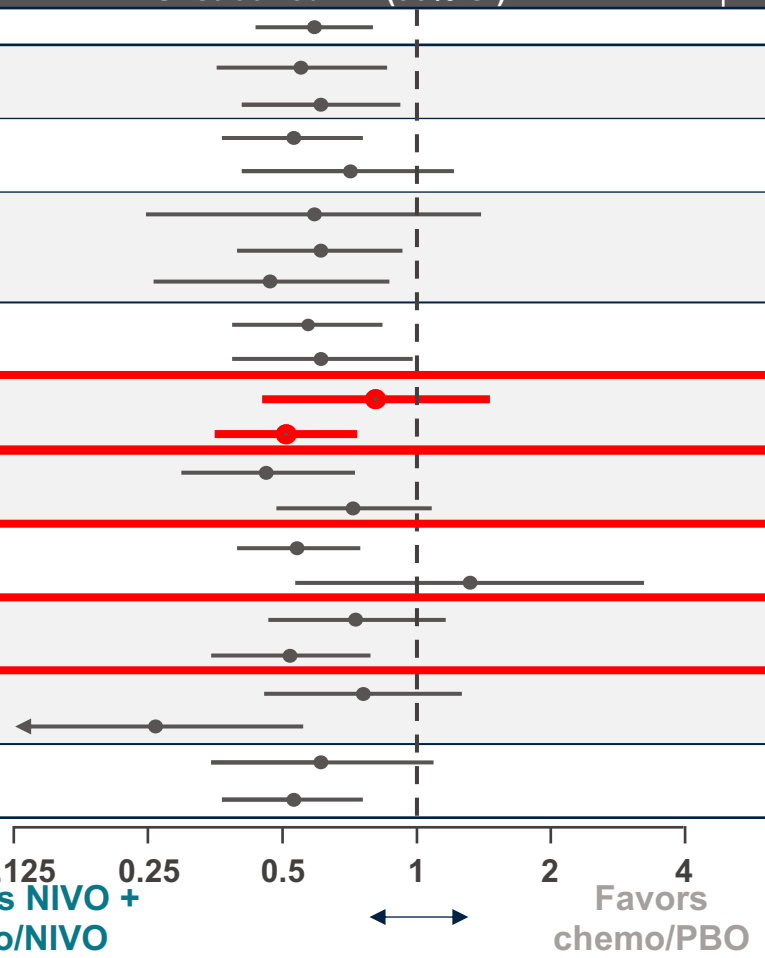
CheckMate 77T: EFS subgroup analysis

	Median EFS,[a] mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)		
Overall (N = 461)	NR	18.4		0.59
< 65 years (n = 202)	NR	16.7		0.55
≥ 65 years (n = 259)	NR	20.1		0.61
Male (n = 327)	NR	16.7		0.53
Female (n = 134)	30.2	18.8		0.71
North America (n = 44)	30.2	9.4		0.59
Europe (n = 250)	NR	23.7		0.61
Asia (n = 115)	NR	13.9		0.47
ECOG PS 0 (n = 288)	NR	20.1		0.57
ECOG PS 1 (n = 173)	29.0	17.3		0.61
Stage II (n = 162)	NR	NR		0.81
Stage III (n = 297)	30.2	13.4		0.51
Squamous (n = 234)	NR	17.0		0.46
Non-squamous (n = 227)	28.9	18.4		0.72
Current/former smoker (n = 417)	NR	17.0		0.54
Never smoker (n = 44)	19.7	25.0		1.32
PD-L1 < 1% (n = 186)[b]	29.0	19.8		0.73
PD-L1 ≥ 1% (n = 256)[b]	NR	15.8		0.52
PD-L1 1–49% (n = 159)[b]	30.2	28.1		0.76
PD-L1 ≥ 50% (n = 97)[b]	NR	8.0		0.26
Cisplatin (n = 97)	27.0	15.8		0.61
Carboplatin (n = 347)	NR	17.3		0.53



Median follow-up (range): 25.4 months (15.7–44.2).

[a]Per BICR. [b]Tumor PD-L1 expression was not evaluable/indeterminate in 19 patients.

Cascone, T et al ESMO 2023

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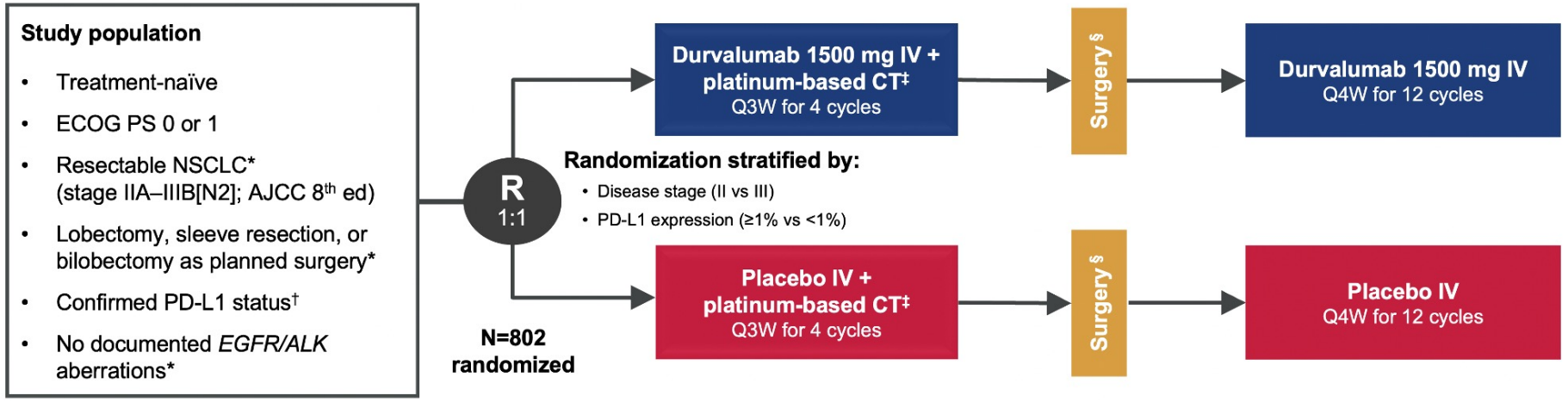
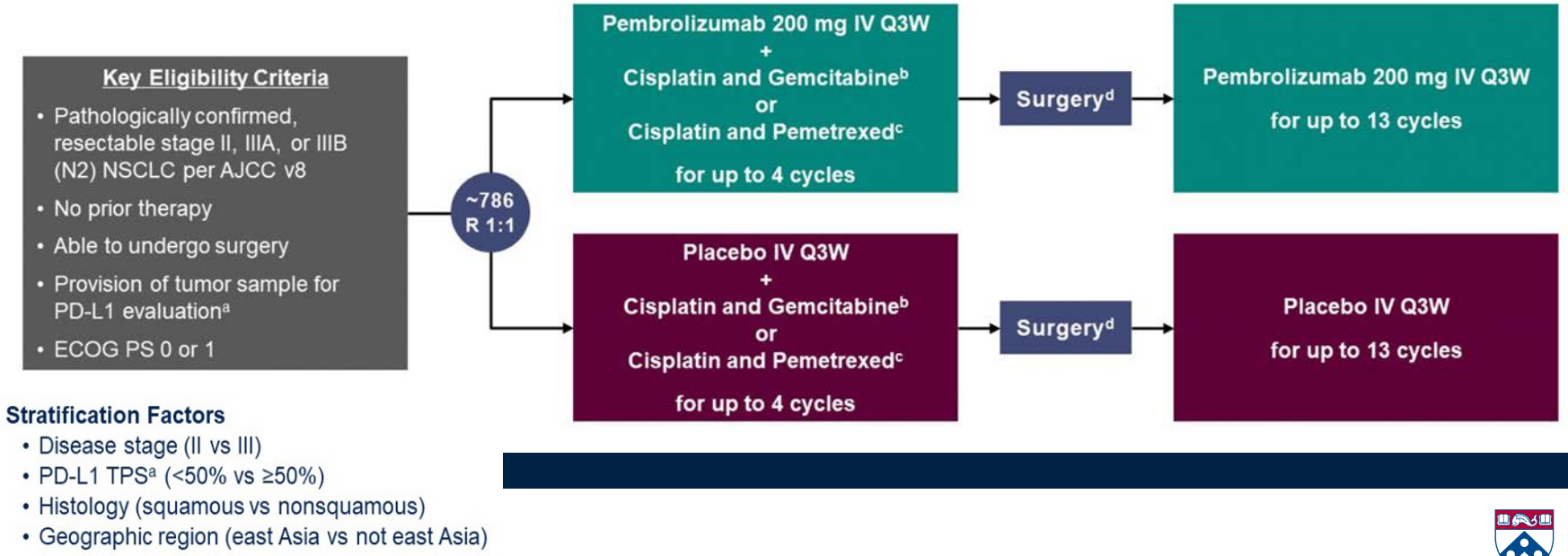
Neoadjuvant or perioperative chemo/IO: available R data

AEGEAN



Primary endpoints:
- pCR Central
- EFS by BICR

KEYNOTE-671

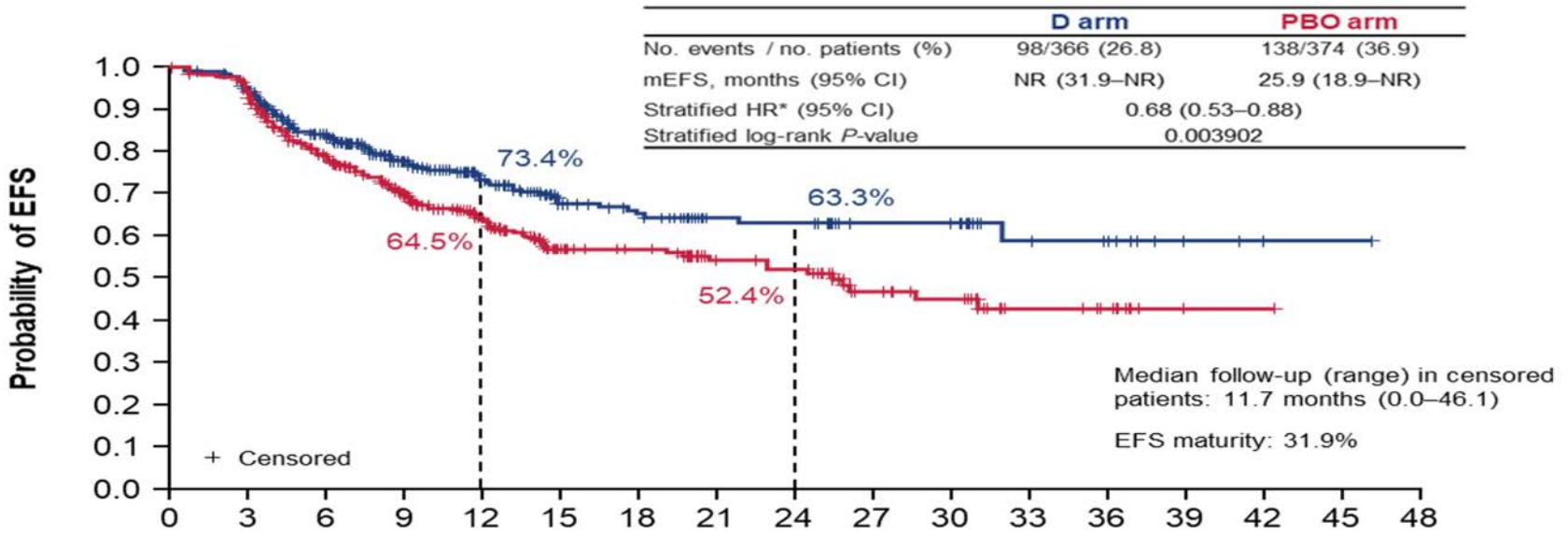


Primary endpoints:
- pCR
- EFS by BIRC

Heymach JV, et al, AACR Annual Meeting 2023; Wakelee H, et al, ASCO Annual Meeting, 2023; Spicer J, et al. ESMO 2023

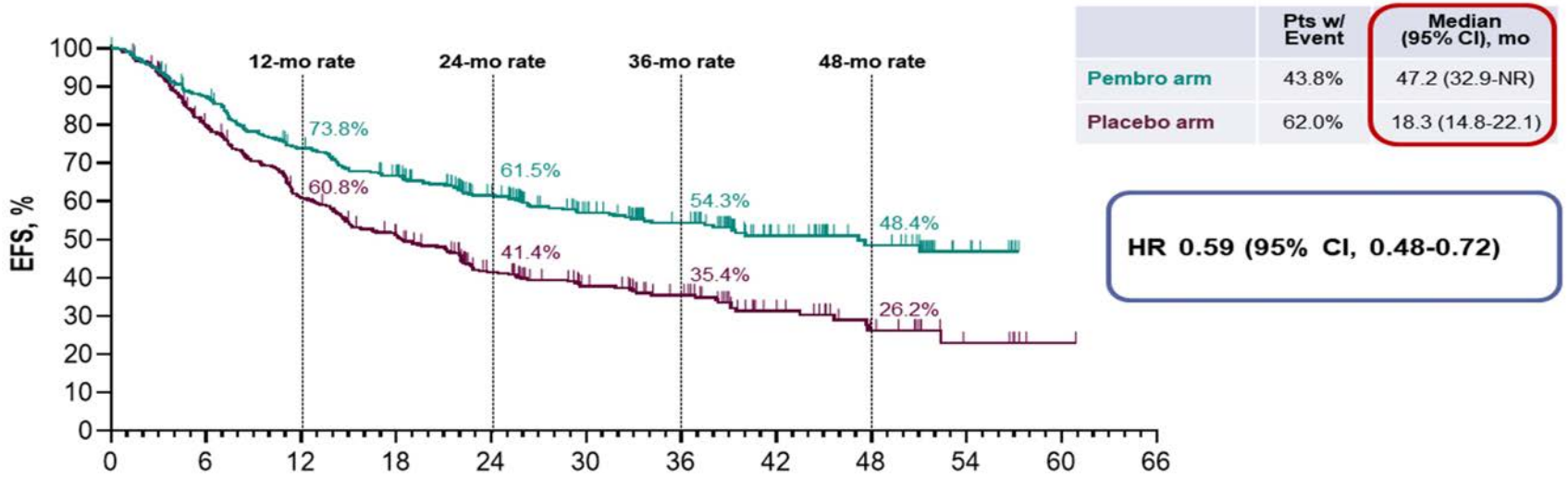
Neoadjuvant or perioperative chemo/IO : available R data

AEGEAN



pCR 4% ->17%

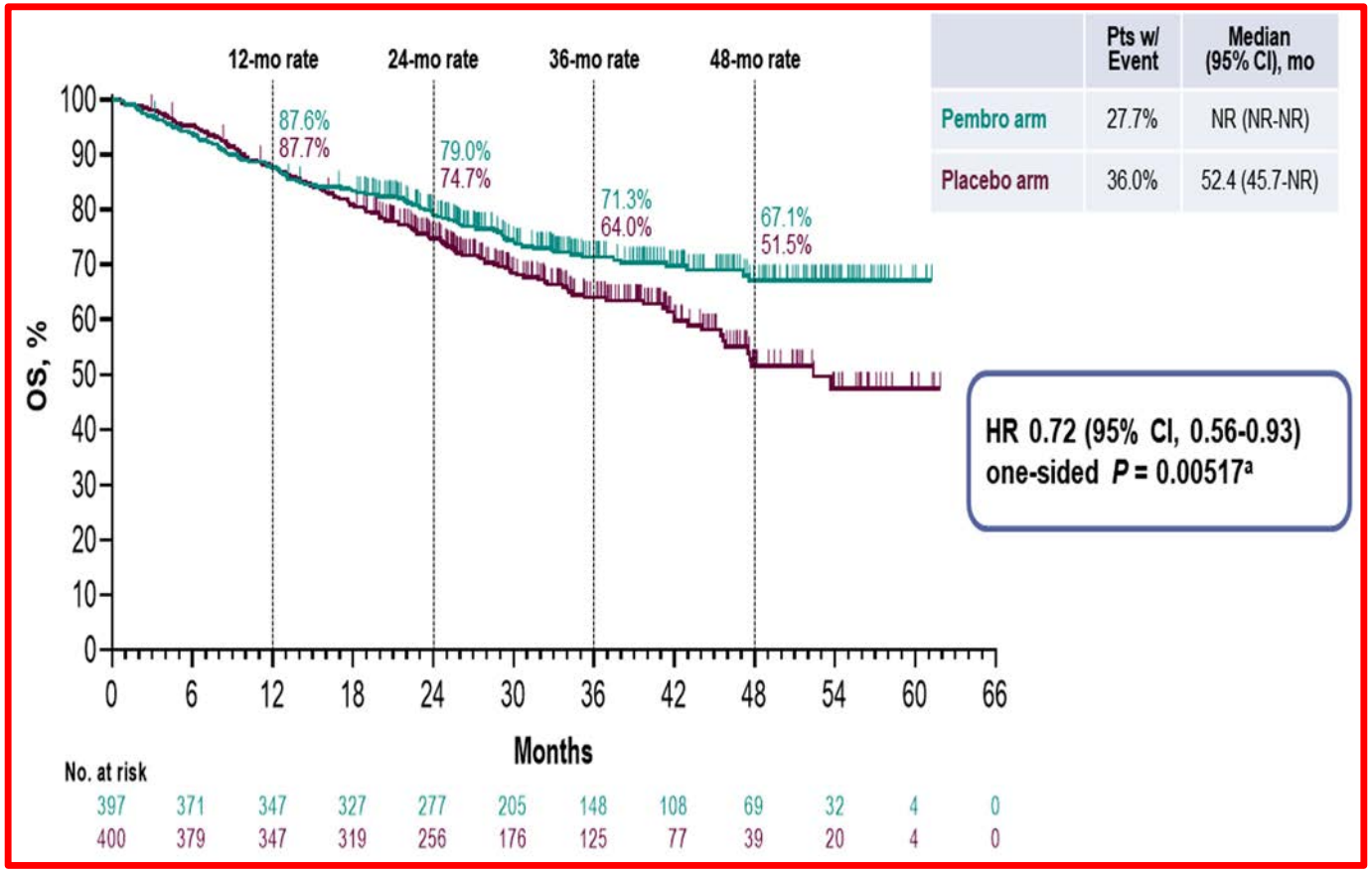
KEYNOTE-671



pCR 4% ->18%

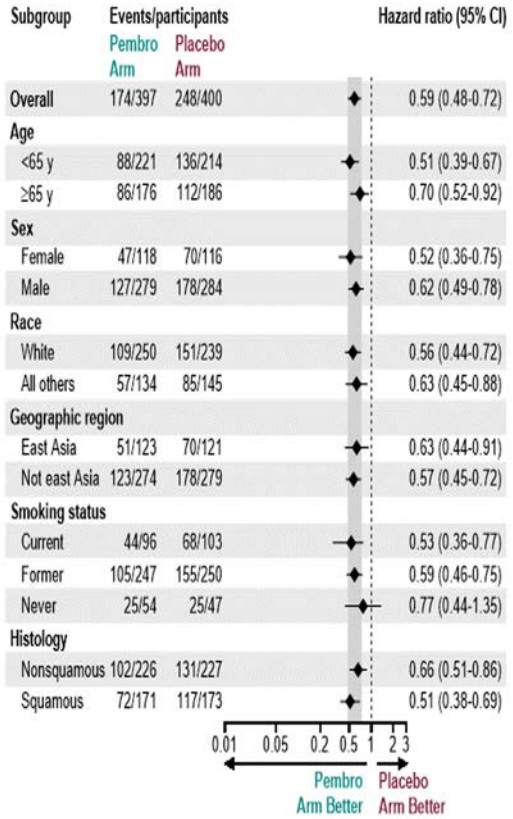
Heymach JV, et al. *N Engl J Med*. 2023;389(18):1672-1684. Heymach JV, et al. AACR Annual Meeting 2023; Wakelee H, et al. *N Engl J Med*. 2023;389(6):491-503. Wakelee H, et al. ASCO Annual Meeting, 2023; Spicer J, et al. ESMO 2023

Survival data KEYNOTE-671

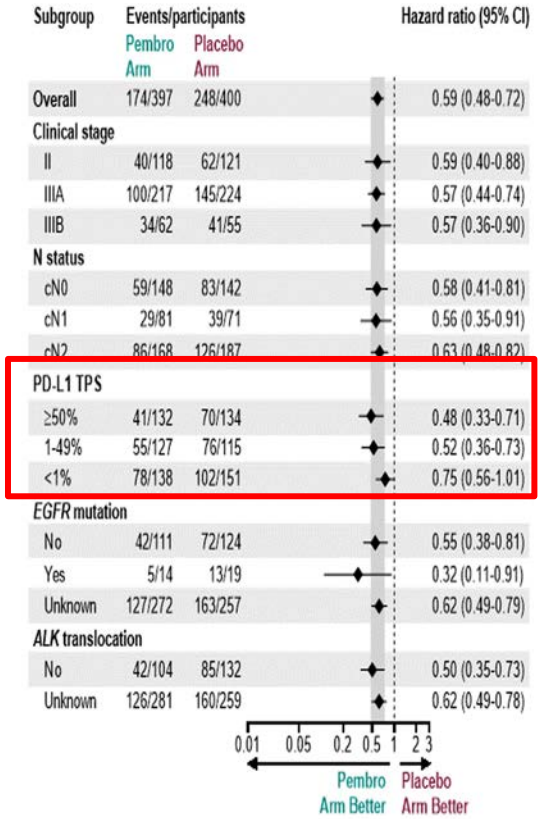


	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

HR 0.72 (95% CI, 0.56-0.93)
one-sided *P* = 0.00517[a]



Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	174/397	248/400	0.59 (0.48-0.72)
Age			
<65 y	88/221	136/214	0.51 (0.39-0.67)
≥65 y	86/176	112/186	0.70 (0.52-0.92)
Sex			
Female	47/118	70/116	0.52 (0.36-0.75)
Male	127/279	178/284	0.62 (0.49-0.78)
Race			
White	109/250	151/239	0.56 (0.44-0.72)
All others	57/134	85/145	0.63 (0.45-0.88)
Geographic region			
East Asia	51/123	70/121	0.63 (0.44-0.91)
Not east Asia	123/274	178/279	0.57 (0.45-0.72)
Smoking status			
Current	44/96	68/103	0.53 (0.36-0.77)
Former	105/247	155/250	0.59 (0.46-0.75)
Never	25/54	25/47	0.77 (0.44-1.35)
Histology			
Nonsquamous	102/226	131/227	0.66 (0.51-0.86)
Squamous	72/171	117/173	0.51 (0.38-0.69)



Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	174/397	248/400	0.59 (0.48-0.72)
Clinical stage			
II	40/118	62/121	0.59 (0.40-0.88)
IIIA	100/217	145/224	0.57 (0.44-0.74)
IIIB	34/62	41/55	0.57 (0.36-0.90)
N status			
cN0	59/148	83/142	0.58 (0.41-0.81)
cN1	29/81	39/71	0.56 (0.35-0.91)
cN2	86/168	126/187	0.63 (0.48-0.82)
PD-L1 TPS			
≥50%	41/132	70/134	0.48 (0.33-0.71)
1-49%	55/127	76/115	0.52 (0.36-0.73)
<1%	78/138	102/151	0.75 (0.56-1.01)
EGFR mutation			
No	42/111	72/124	0.55 (0.38-0.81)
Yes	5/14	13/19	0.32 (0.11-0.91)
Unknown	127/272	163/257	0.62 (0.49-0.79)
ALK translocation			
No	42/104	85/132	0.50 (0.35-0.73)
Unknown	126/281	160/259	0.62 (0.49-0.78)

Wakelee H, et al. *N Engl J Med*. 2023;389(6):491-503; Wakelee H, et al. ASCO Annual Meeting, 2023; Spicer J, et al. ESMO 2023

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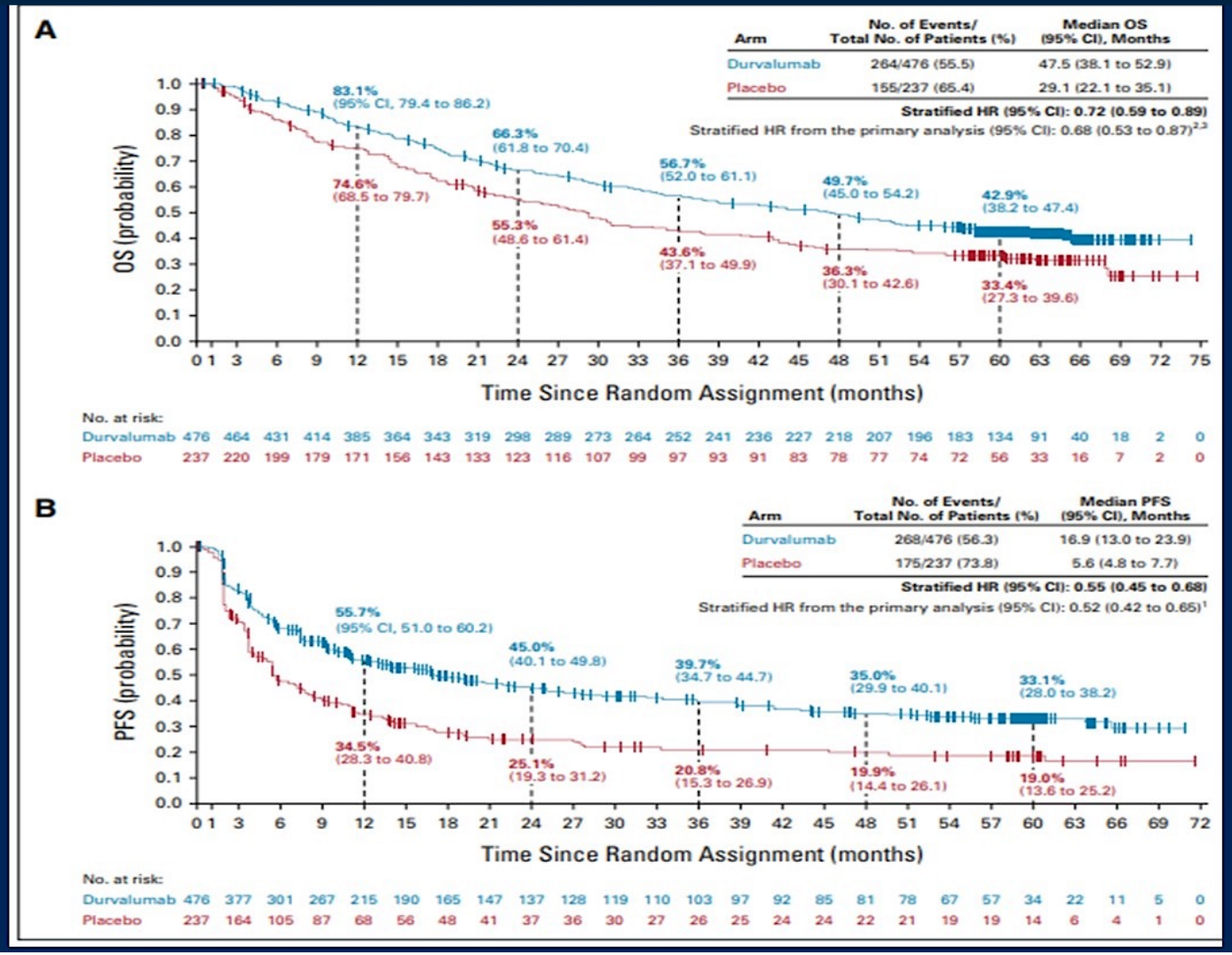
General Conclusions:
Adjuvant, Neo- and Peri-adjuvant Therapy in Early Stage NSCLC

- **Adjuvant atezolizumab confers a clear PFS advantage in stage II/IIIA PDL1 (+) NSCLC post resection and adjuvant chemotherapy**
  - **PDL1 > 50% may realize an OS advantage**
- **Adjuvant Pembrolizumab yields similar PFS benefits, independent of PDL1 status and stage (IB-IIIA); approved as of 2023**
- **Neoadjvuant and periadjuvant therapy with chemo-IO confer a clear and striking pCR, MPR, and EFS advantage**
- **Peri-adj Pembro with Cisplatin-based chemo has also yielded an OS benefit; other, similar studies of chemo-IO induction +/- IO post resection are exhibiting the same trends**
- **We will need de-escalation studies in pts with pCR and intensification trials in those with < pCR**

PACIFIC TRIAL post CRT for Unresectable LA-NSCLC



HR = 0.72 OS
Median 47.5 vs 29.1mn

HR = 0.55 PFS
Median 16.9 vs 5.6 mn

Entry Criteria

- No progression during the course of CHEMO/RT
- No unresolved > Grade 2 toxicities
- No Grade ≥ 2 Pneumonitis

[1]Antonia et al. NEJM. 2018

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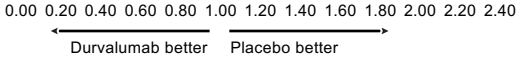
Overall Survival by Subgroup (ITT)

		Durvalumab	Placebo	Unstratified HR*
		No. of events / No. of patients (%)		(95% CI)
	All patients	183/476 (38.4)	116/237 (48.9)	0.68 (0.54–0.86)
Sex	Male	141/334 (42.2)	80/166 (48.2)	0.78 (0.59–1.03)
	Female	42/142 (29.6)	36/71 (50.7)	0.46 (0.30–0.73)
Age at randomization	<65 years	89/261 (34.1)	58/130 (44.6)	0.62 (0.44–0.86)
	≥65 years	94/215 (43.7)	58/107 (54.2)	0.76 (0.55–1.06)
Smoking status	Smoker	169/433 (39.0)	103/216 (47.7)	0.72 (0.56–0.92)
	Non-smoker	14/43 (32.6)	13/21 (61.9)	0.35 (0.16–0.76)
Disease stage	Stage IIIA	101/252 (40.1)	70/125 (56.0)	0.63 (0.46–0.85)
	Stage IIIB	79/212 (37.3)	44/107 (41.1)	0.77 (0.53–1.11)
Tumor histologic type	Squamous	103/224 (46.0)	56/102 (54.9)	0.72 (0.52–0.99)
	Non-squamous	80/252 (31.7)	60/135 (44.4)	0.61 (0.44–0.86)
Best response to prior treatment	CR	2/9 (22.2)	3/7 (42.9)	–
	PR	83/237 (35.0)	50/112 (44.6)	0.69 (0.49–0.99)
	SD	93/223 (41.7)	61/115 (53.0)	0.66 (0.48–0.91)
PD-L1 status	≥25%	37/115 (32.2)	23/44 (52.3)	0.46 (0.27–0.78)
	<25%	74/187 (39.6)	41/105 (39.0)	0.92 (0.63–1.34)
	Unknown	72/174 (41.4)	52/88 (59.1)	0.62 (0.43–0.89)
	≥1%†	70/212 (33.0)	45/91 (49.5)	0.53 (0.36–0.77)
	1–24%†	33/97 (34.0)	22/47 (46.8)	0.60 (0.35–1.03)
	<1%†	**41/90 (45.6)**	**19/58 (32.8)**	**1.36 (0.79–2.34)**
***EGFR* status**	Positive	10/29 (34.5)	6/14 (42.9)	–
	Negative	117/317 (36.9)	80/165 (48.5)	0.64 (0.48–0.86)
	Unknown	56/130 (43.1)	30/58 (51.7)	0.77 (0.49–1.20)



*Not calculated if the subgroup has less than 20 events
†Assessed as part of exploratory post-hoc analyses

[1]Antonia et al. NEJM. 2018

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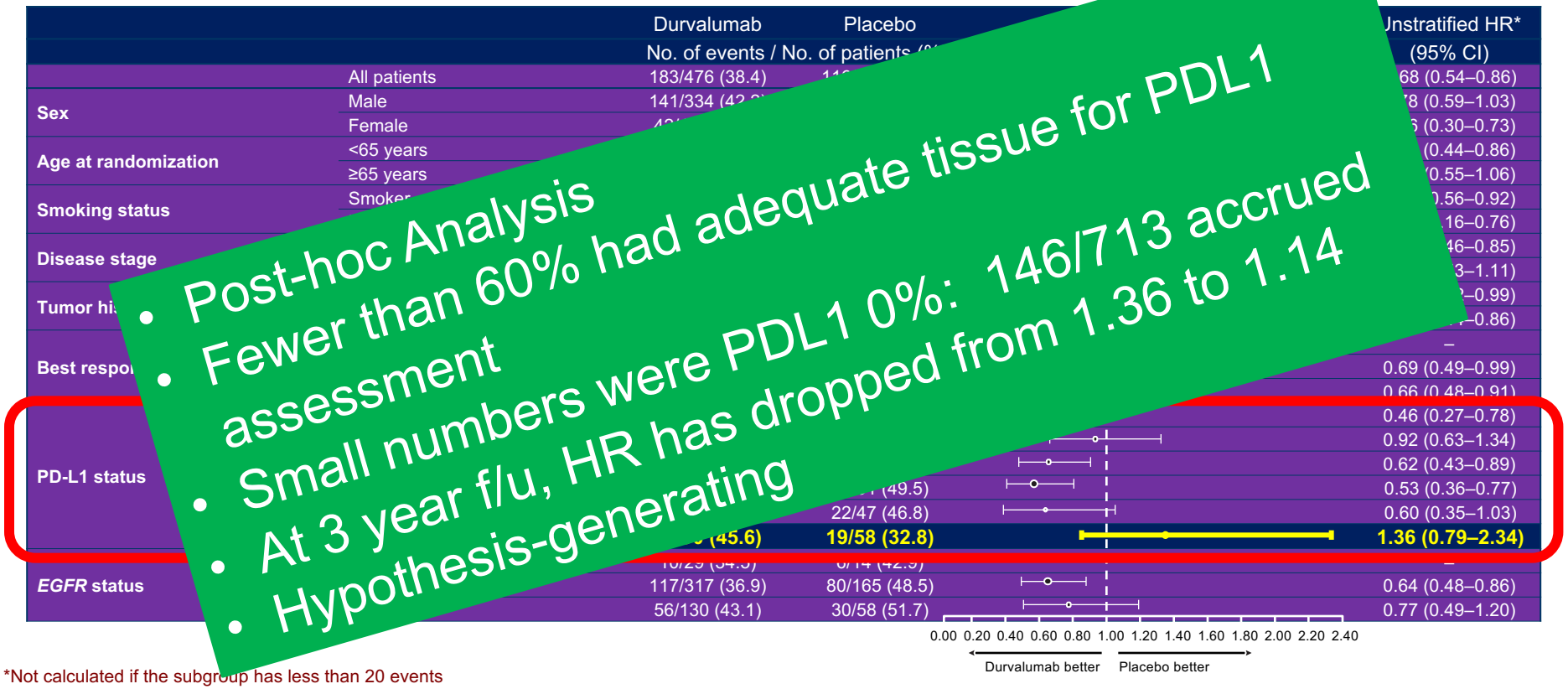
Overall Survival by Subgroup (ITT)



- Post-hoc Analysis
- Fewer than 60% had adequate tissue for PDL1 assessment
- Small numbers were PDL1 0%: 146/713 accrued
- At 3 year f/u, HR has dropped from 1.36 to 1.14
- Hypothesis-generating

*Not calculated if the subgroup has less than 20 events
†Assessed as part of exploratory post-hoc analyses

Antonia et al. NEJM. 2018; Spigel DR, *J Clin Oncol*. 2022;40(12):1301-1311.

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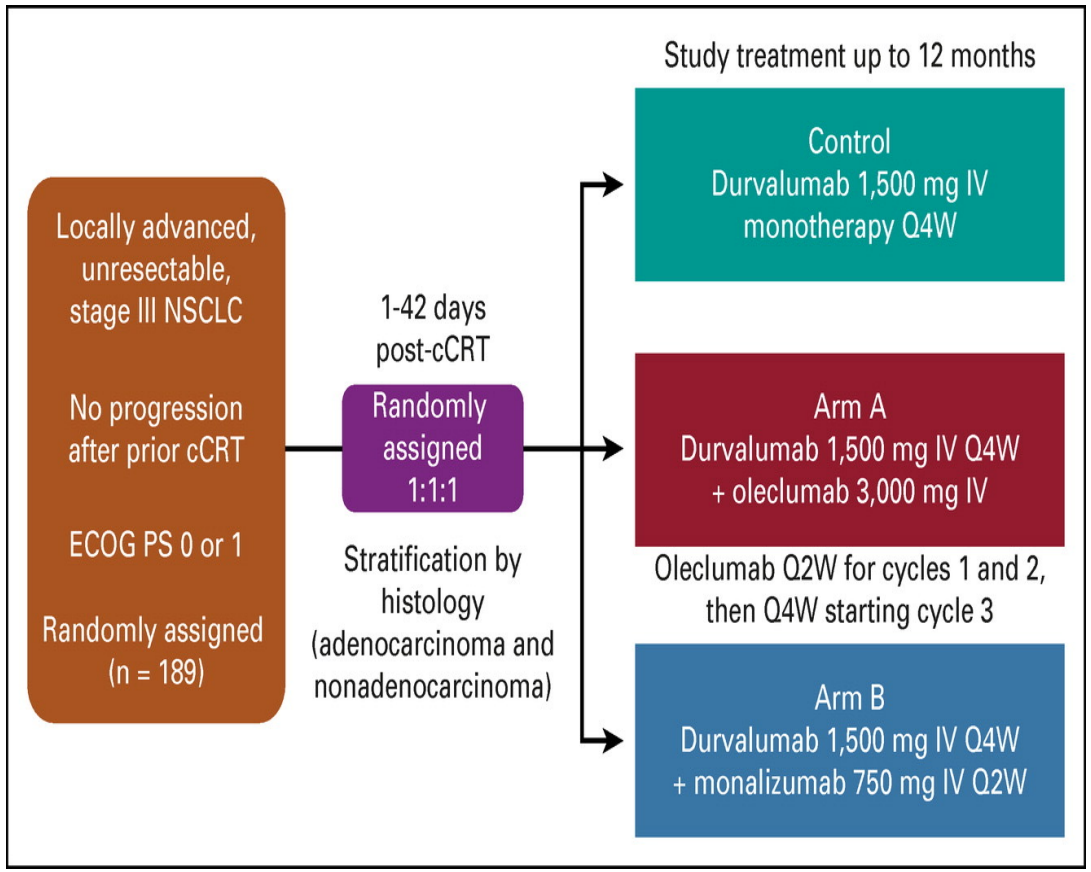
COAST - Ph II trial – 1^0 Endpoint - ORR

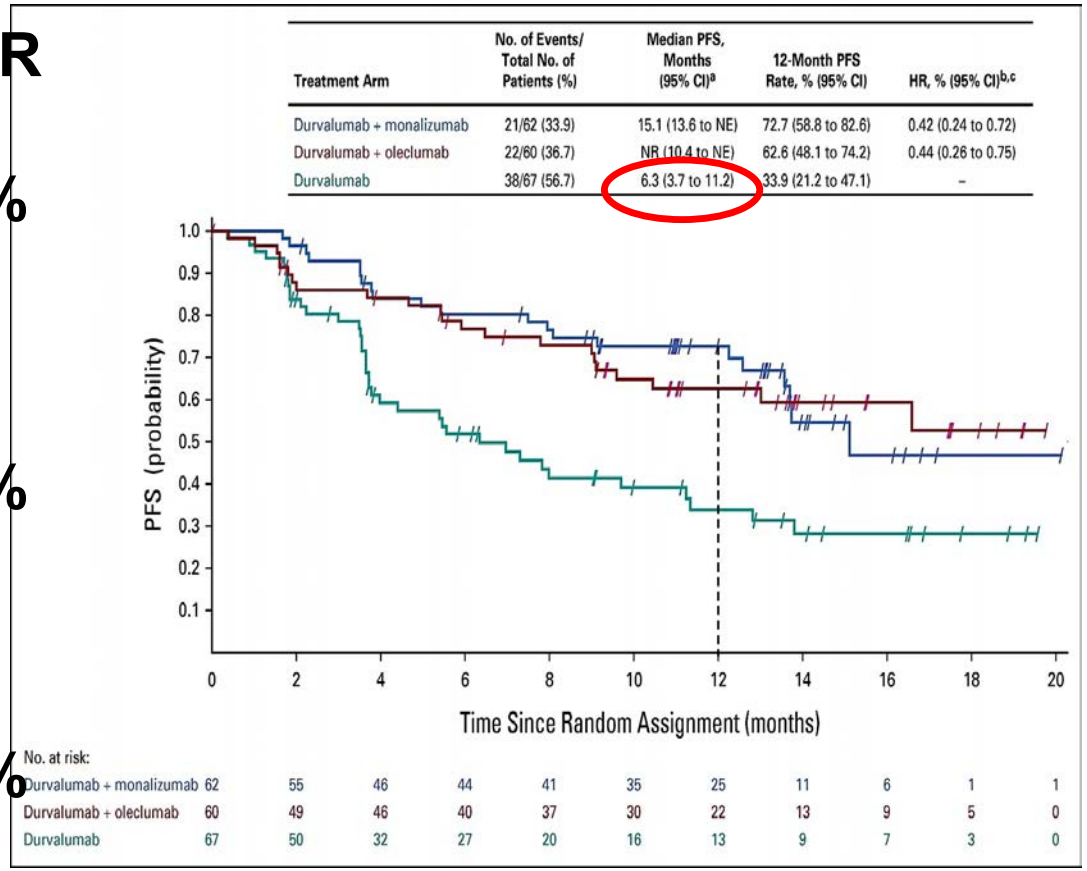


ORR

18%

36%

30%



Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–

Oleclumab – inhibits CD73 (adenosine pathway); Monalizumab – blocks NKG2A
Herbst et al. J Clin Oncol 2022

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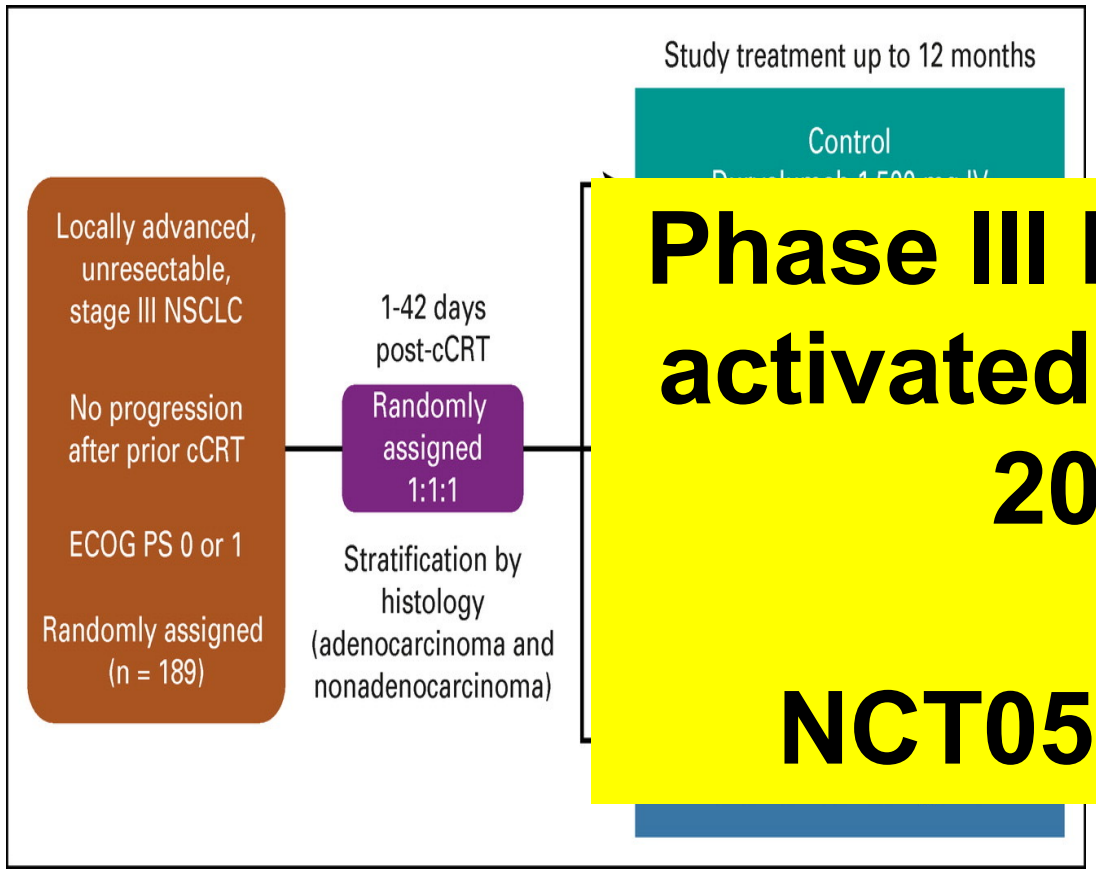
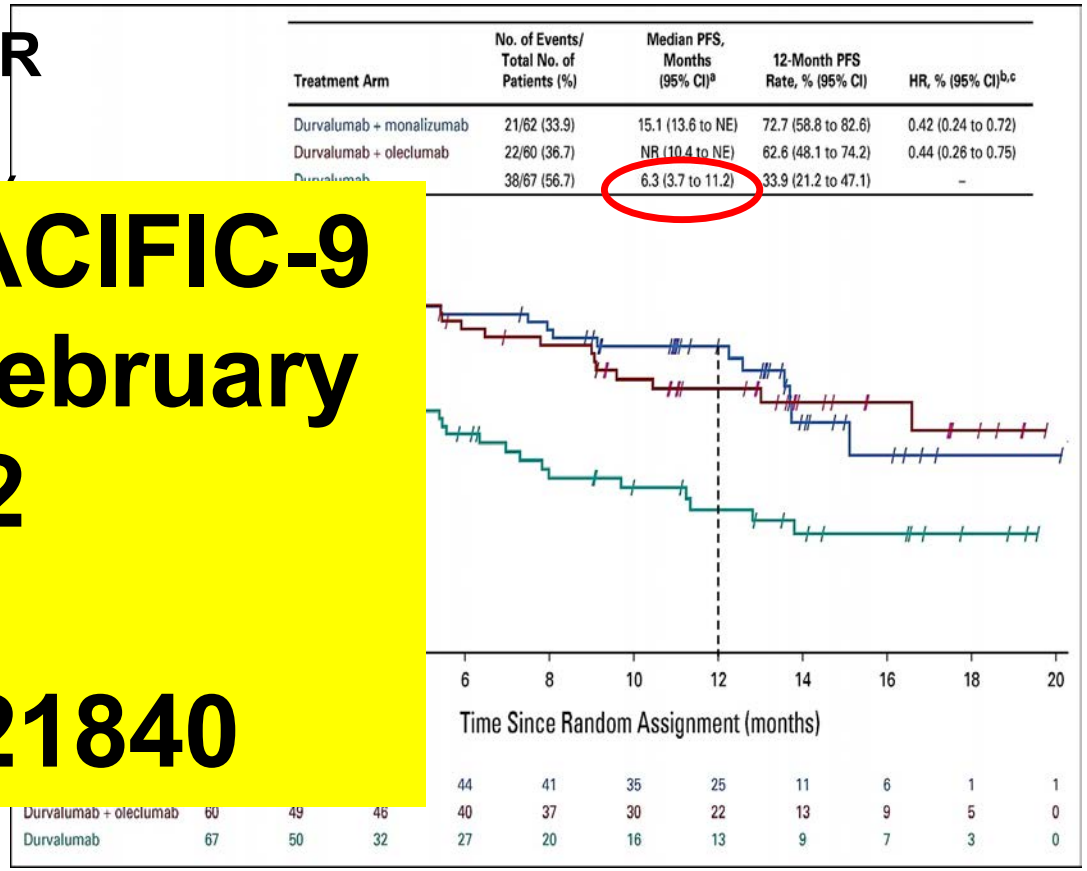
COAST - Ph II trial – 1^0 Endpoint - ORR



ORR

Phase III PACIFIC-9 activated February 2022

NCT05221840



Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
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Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–

Oleclumab – inhibits CD73 (adenosine pathway); Monalizumab – blocks NKG2A
Herbst et al. J Clin Oncol 2022

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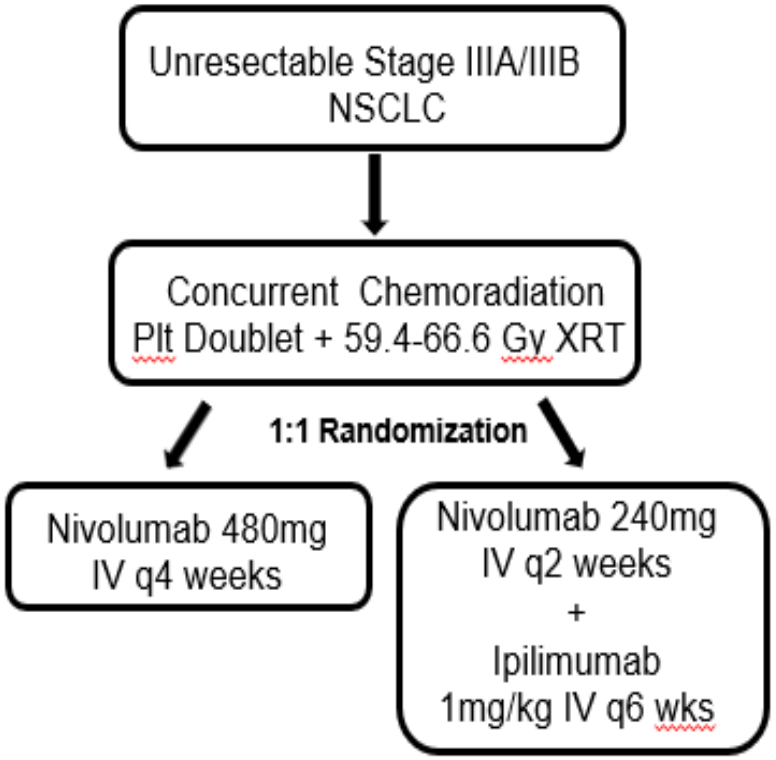
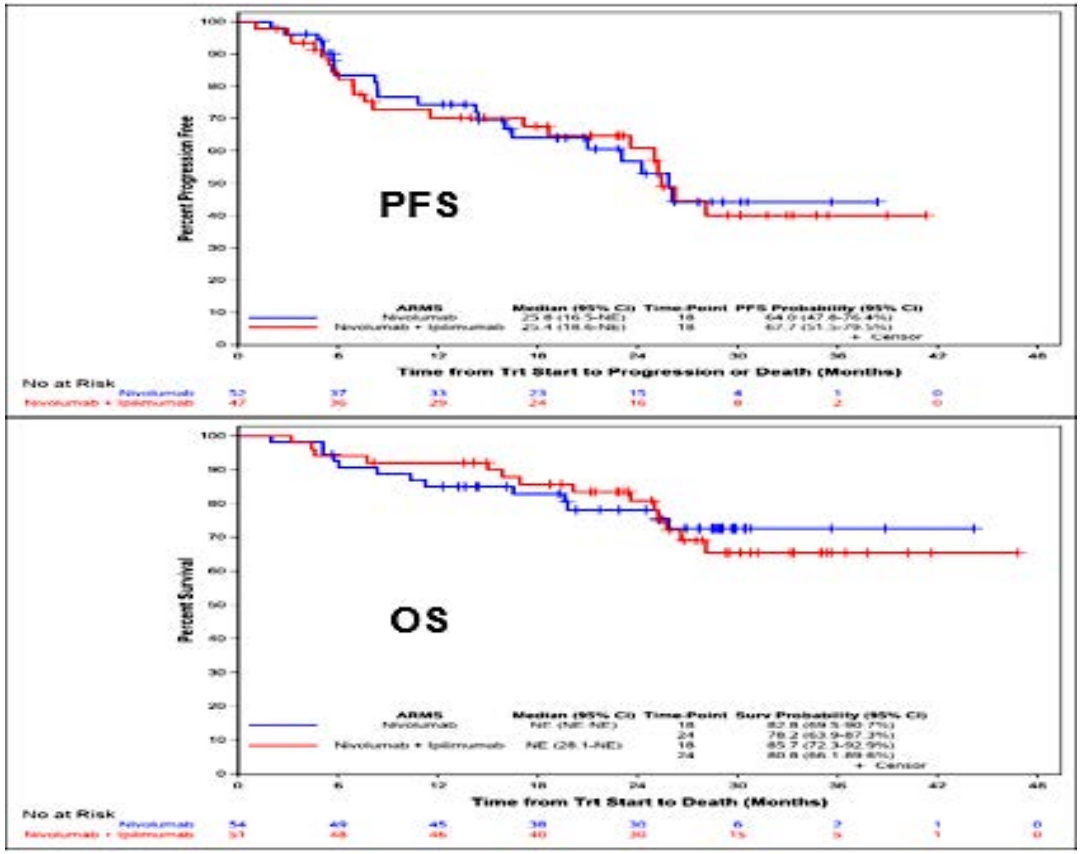
Consolidation PD-1 or CTLA-4/PD-1



- Multi-center, open label randomized phase II trial
- Pts enrolled following completion of CCRT
- Duration of immunotherapy was 6 months in both arms
- Nivo arm compared to historical control of CCRT alone, Nivo/Ipi arm compared to historical control of CCRT -> Durvalumab



N	Regimen	ORR (%)	PFS, med (mos)	Pneumontis G3+ (%)	trAEs Gr ≥ 3 (%)
54	Chemo-RT → Nivo	**NR**	**25.8**	**9.3**	**38.5**
51	Chemo-RT → Nivo/Ipi	**NR**	**25.4**	**15.7**	**52.9**

Conclusion: Ipi yields no further Tx benefit, just heightened toxicity

Durm et al WCLC 2022

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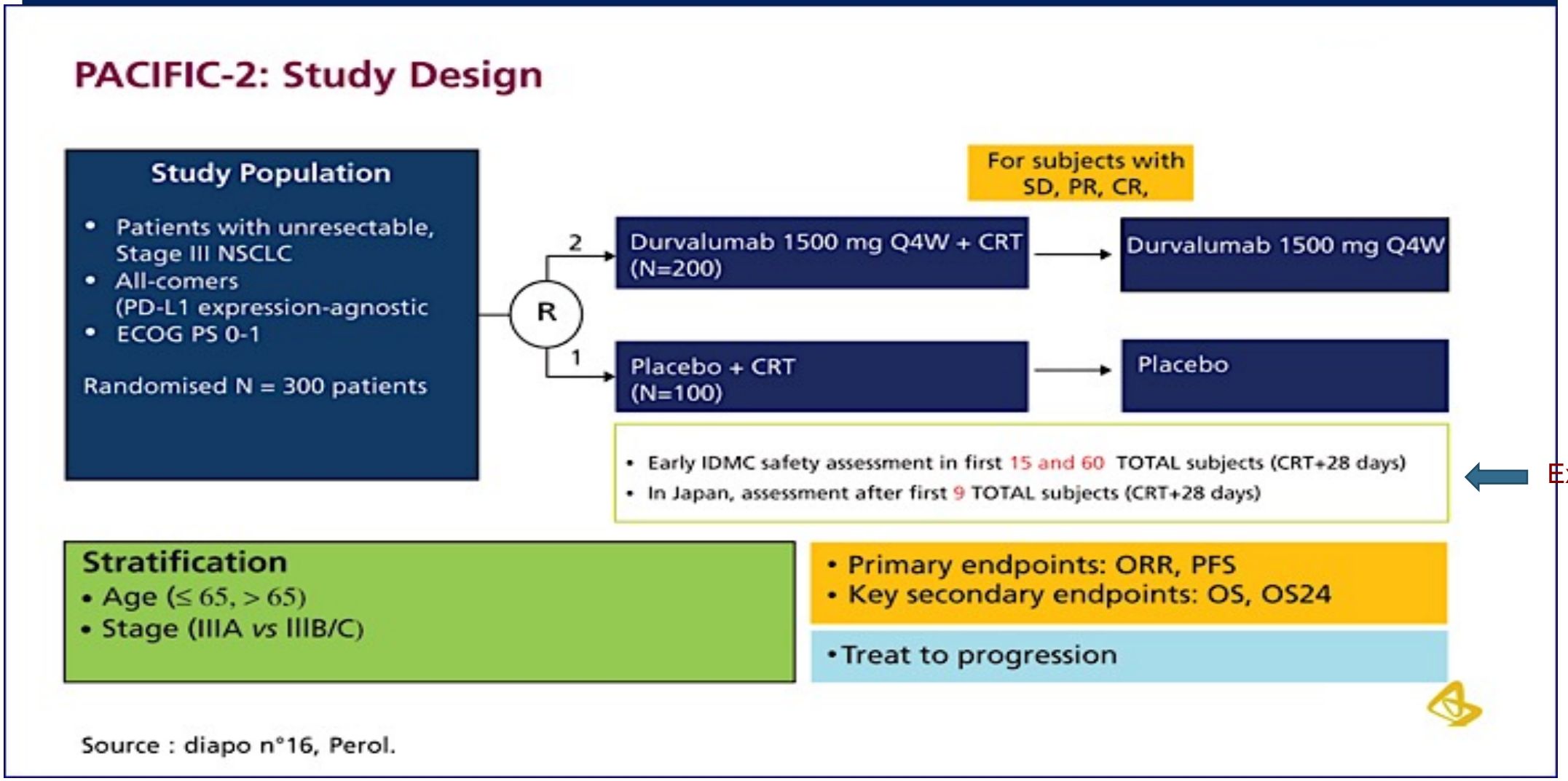
PACIFIC-2: testing both concurrent and consolidation



Baldini and Vuagnat, Innov Therap Onc 2019

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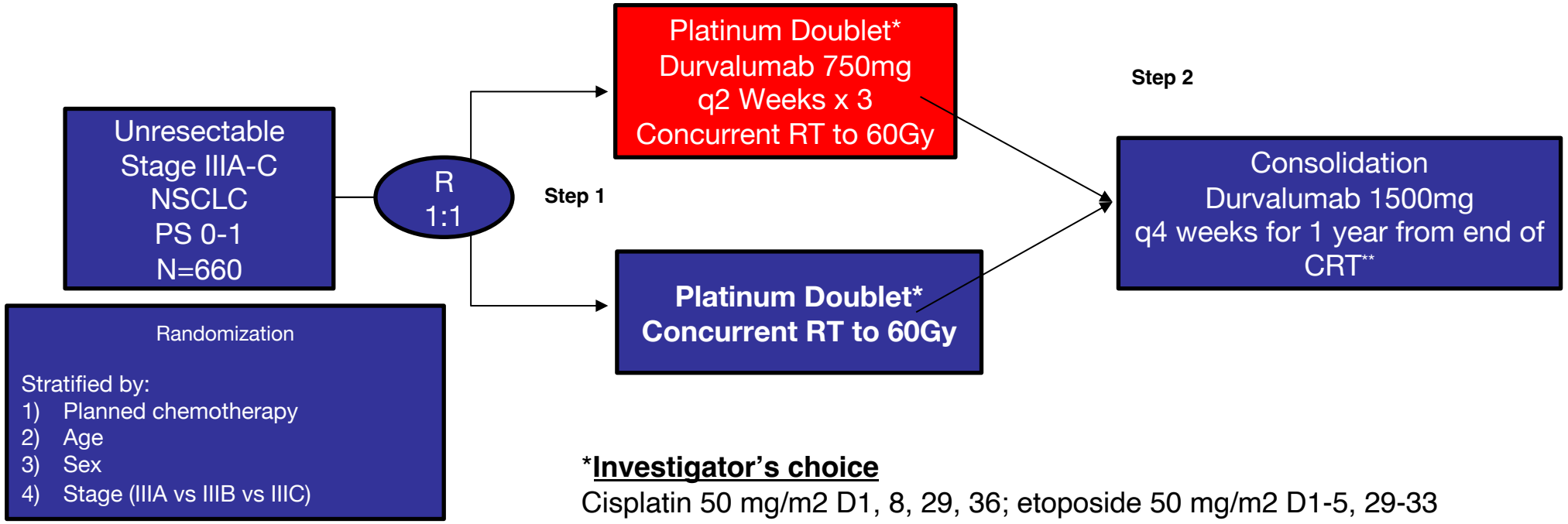
PACIFIC-2 Press Release Jan 2024

"The PACIFIC-2 Phase III trial for durvalumab concurrently administered with chemoradiotherapy (CRT) **did not achieve statistical significance for the primary endpoint of progression-free survival** (PFS) versus CRT alone for the treatment of patients with unresectable, Stage III non-small cell lung cancer (NSCLC)."

"Initial analysis of the safety and tolerability for durvalumab and CRT in this patient population showed that the profiles were broadly consistent with the known profiles of these treatments, although there was an **increased rate of infection** observed during the concurrent treatment period in the experimental arm."

https://www.astrazeneca.com/media-centre/press-releases/2023/update-on-pacific-2-phase-iii-trial-for-imfinzi.html

EA5181: ("PACIFIC-2 vs. PACIFIC-1")



***Investigator's choice**

Cisplatin 50 mg/m2 D1, 8, 29, 36; etoposide 50 mg/m2 D1-5, 29-33
Cisplatin 75 mg/m2 D1, 22; pemetrexed 500 mg/m2 D1, 22 (nonsquamous only)
Carboplatin AUC 2 D1, 8, 15, 22, 29, 36; paclitaxel 45 mg/m2 D1, 8, 15, 22, 29, 36

**Starting within 14 days of CRT unless toxicity has not resolved to ≤ grade 2, but not later than 45 days post-CRT

LA-NSCLC: Conclusions

- Consolidation IO after standard CRT improves PFS and survival compared to CRT alone; benefits are most pronounced in PD-L1 (+) tumors
- Early trials of concurrent IO and CRT show the feasibility and safety of the approach, but at least one phase III trial testing both concurrent and consolidative IO with CRT has failed to yield an OS benefit vs CRT alone
- Ipilimumab in combination with Nivo in this setting appears no better than Nivo alone
- Other new IOs are being tested in LA-NSCLC

Agenda

Module 1: Role of Immune Checkpoint Inhibitors in Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Langer

Module 2: Immune Checkpoint Inhibitors and Other Emerging Therapeutic Approaches for Metastatic NSCLC without a Targetable Tumor Mutation — Dr Garon

Current Management of Metastatic NSCLC without a Targetable Tumor Mutation

Edward B. Garon, MD, MS

Professor

David Geffen School of Medicine at UCLA

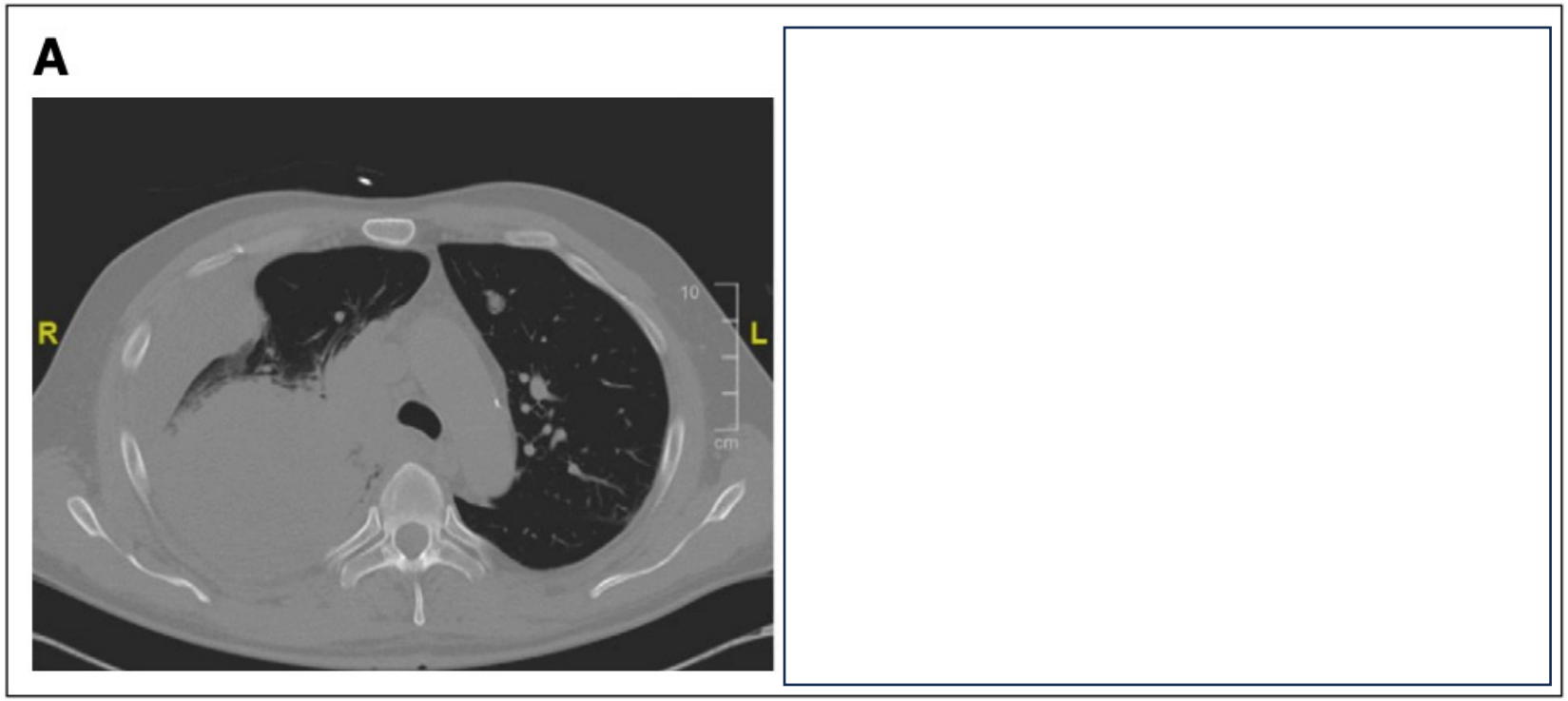
Los Angeles, CA

Disclosures

Advisory Committees	AbbVie Inc, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, Atreca, Bristol Myers Squibb, EMD Serono Inc, Gilead Sciences Inc, GSK, Hookipa Pharma Inc, LianBio, Lilly, Merck, Merus BV, Novartis, Personalis, QED Therapeutics, a BridgeBio company, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Sensei Biotherapeutics, Sumitomo Dainippon Pharma Oncology Inc, Summit Therapeutics, Synthekine, Xilio Therapeutics, Zymeworks Inc
Contracted Research	ABL Bio, ArriVent Biopharma, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Daiichi Sankyo Inc, EMD Serono Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Iovance Biotherapeutics, Lilly, Merck, Mirati Therapeutics Inc, Novartis, Prelude Therapeutics, Regeneron Pharmaceuticals Inc, Synthekine
Data and Safety Monitoring Board/Committee	Nuvalent
Sponsored Independent Medical Education	Daiichi Sankyo Inc, Ipsen Biopharmaceuticals Inc
Travel	A2 Bio, Novartis

Case 1

- 64 year old former smoker presented with chest pain, dyspnea, palpitations and hypoxia

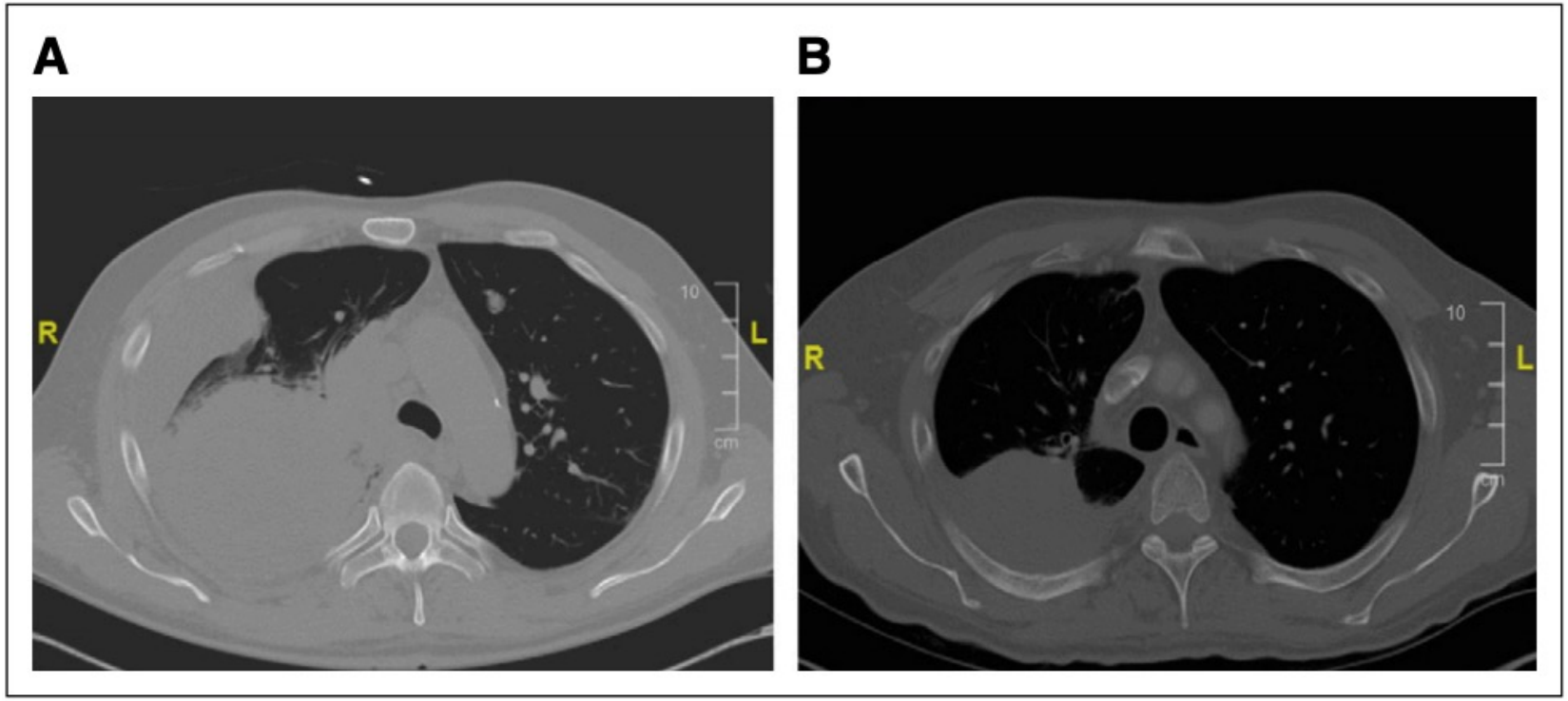


Case 1 Continued

- Admitted to ICU and chest tube placed
- PD-L1 per 22C3 is 90%
- No actionable genomic alterations
- Brain MRI showed no evidence of brain metastases
- Extensive metastases involving bone, liver, adrenal glands
- Patient was stabilized so that he could be discharged, and then initiated carboplatin, pemetrexed and pembrolizumab

Case 1 Update

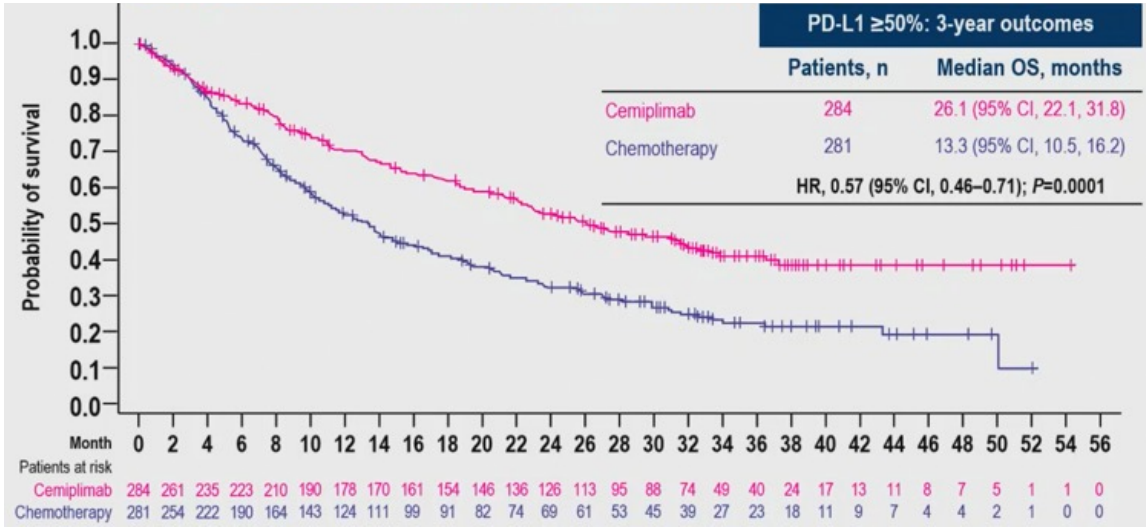
- Scans greatly improved after four cycles of therapy



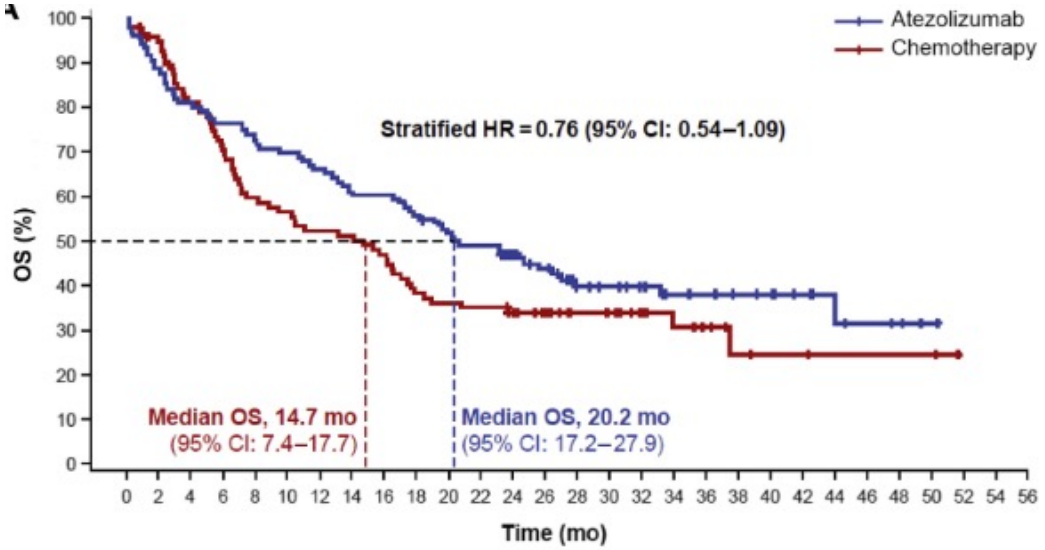
- Stopped all therapy during depths of the pandemic
- Subsequently resumed pembrolizumab but not pemetrexed

Long Term Update of Monotherapy Experience

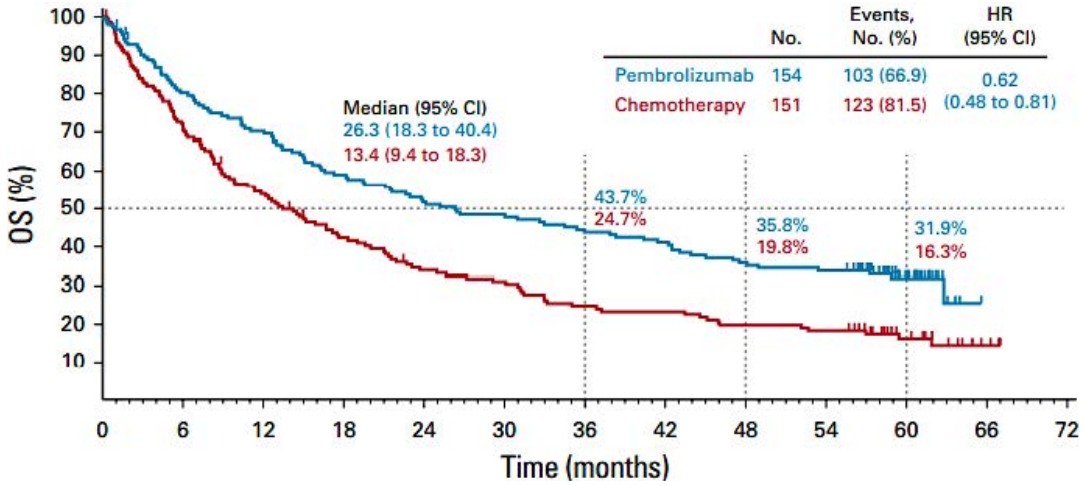
EMPOWER-1: 3 Years[a]



IMpower110: Updated Analysis[b]



KEYNOTE 024: 5 Years[c]



a. Ozguroglu M, et al. Presented at: European Society for Medical Oncology annual congress; September 9-13; 2022; Paris, France Abstract LBA54;

b. Jassem J, et al. J Thorac Oncol. 2021;16:1872-1882;

c. Reck M, et al. J Clin Oncol. 2021;39:2339-2349.

Overall Survival: TPS ≥1-49% (Exploratory Analysis[a])

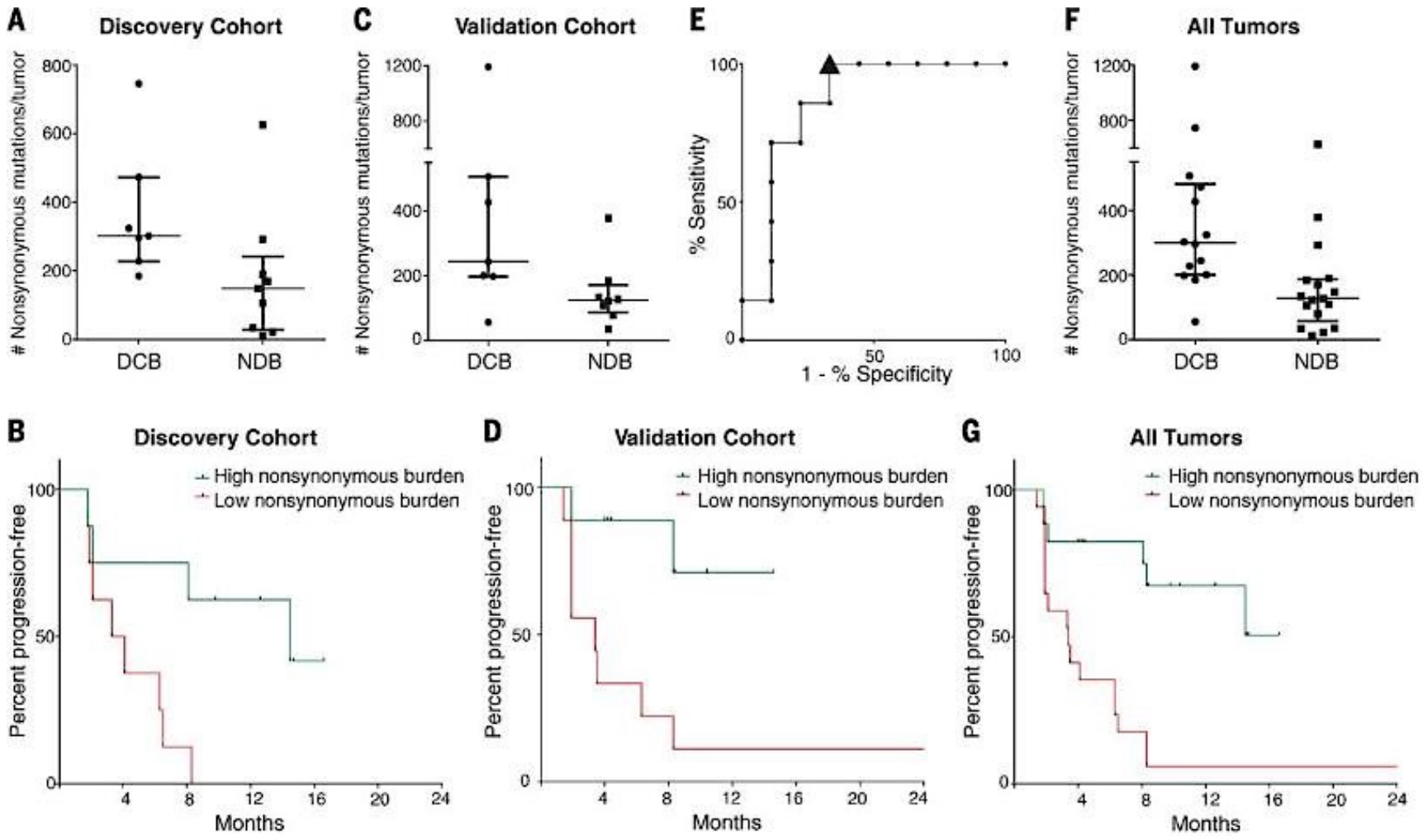
	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	

Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

[a]No alpha allocated to this comparison.

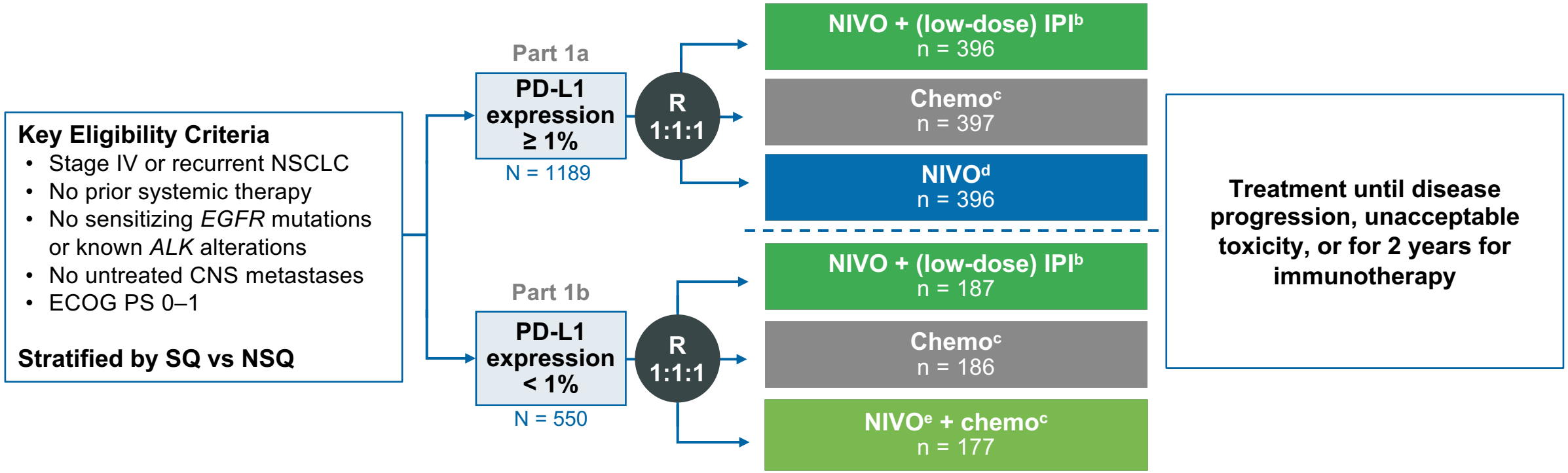
Data cutoff date: Feb 26, 2018.

Nonsynonymous mutation burden is associated with PFS benefit of anti–PD-1 therapy



Rizvi NA. *Science* 2015;348:124-128

CheckMate 227 Part 1 Study Design[a]



Independent co-primary endpoints: NIVO + IPI vs chemo

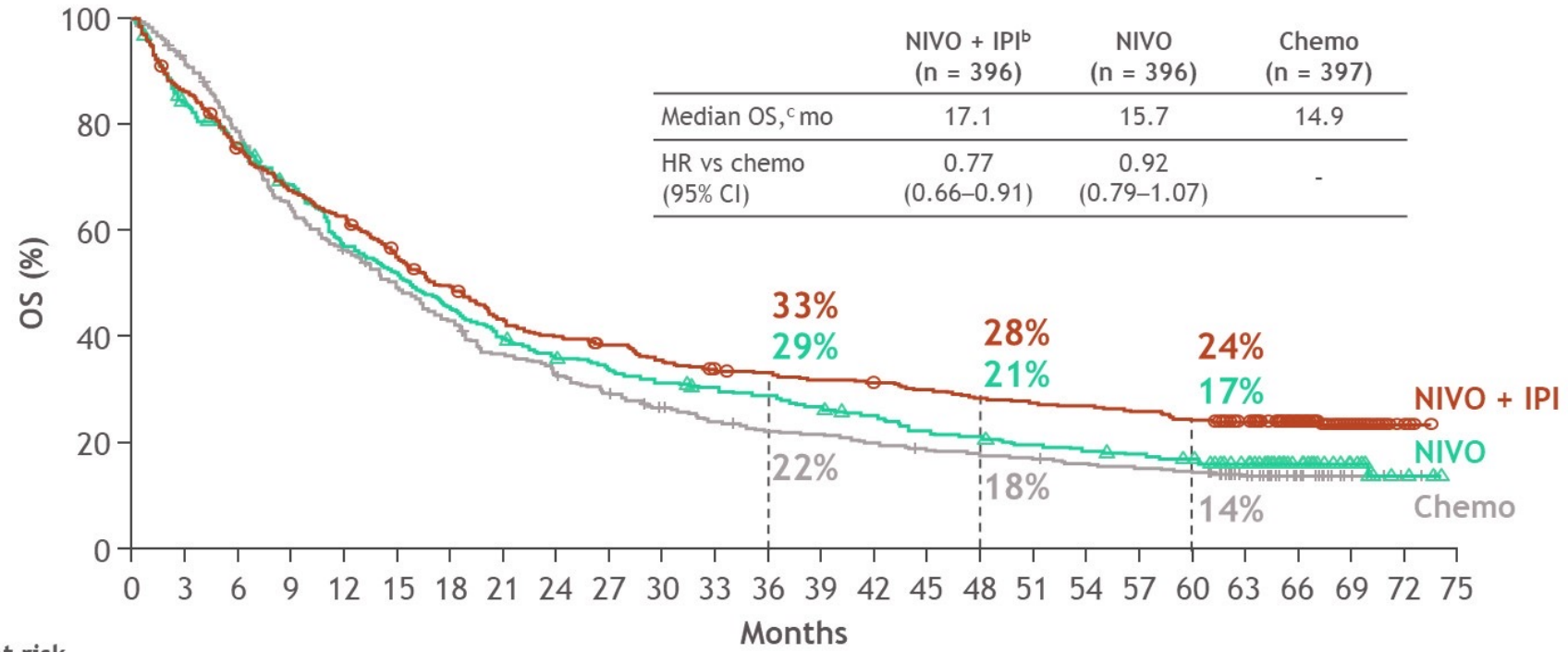
- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

Secondary endpoints (PD-L1 hierarchy):

- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

Peters S. ESMO 2019

5-year OS in patients with tumor PD-L1 ≥ 1%[a]



	NIVO + IPI[b] (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS,[c] mo	17.1	15.7	14.9
HR vs chemo (95% CI)	0.77 (0.66–0.91)	0.92 (0.79–1.07)	-

No. at risk																										
NIVO + IPI	396	341	296	265	246	214	192	166	154	146	134	126	123	118	115	110	104	101	99	95	89	74	47	20	3	0
NIVO	396	330	299	265	220	201	176	153	139	129	119	112	108	98	91	80	75	70	66	63	59	46	27	12	3	0
Chemo	397	358	306	250	218	190	166	141	126	112	98	87	80	78	72	66	63	60	56	53	50	37	18	5	2	0

Database lock: February 15, 2022; minimum/median follow-up for OS: 61.3/66.7 months.

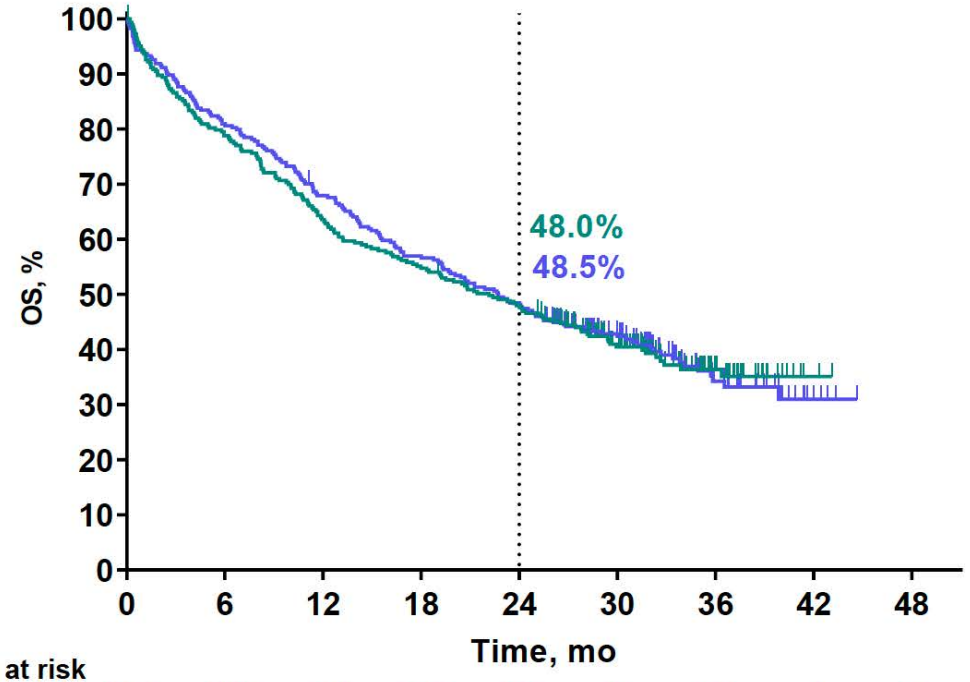
[a]In patients with PD-L1 ≥ 1% with a PFS event (per BICR), subsequent systemic therapy was received by 34% in the NIVO + IPI arm, 46% in the NIVO arm, and 48% in the chemo arm; subsequent immunotherapies by 7%, 9%, and 40%; subsequent chemo by 33%, 45%, and 25%, respectively. [b]NIVO + IPI vs NIVO HR was 0.84 (95% CI, 0.72–0.99). [c]Median OS 95% CI are 14.95–20.17 (NIVO + IPI), 13.27–18.14 (NIVO), and 12.71–16.72 (chemo).

BICR, blinded independent central review.

Brahmer et al. ASCO 2022; Abstract LBA9025.

Pembrolizumab ± Ipilimumab (3-year outcomes)

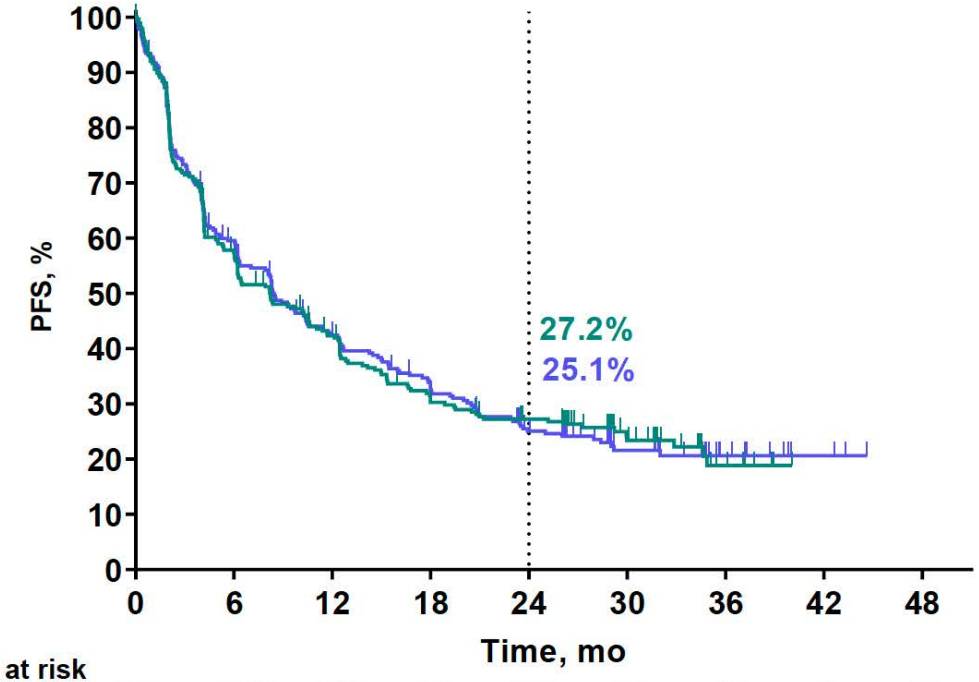
Overall Survival



No. at risk									
Pembo + Ipi	284	223	180	155	135	84	30	2	0
Pembro + Pbo	284	230	192	161	137	88	33	5	0

	Events, n (%)	Median (95% CI)	OS HR (95% CI)
Pembro + Ipi	173 (60.9)	22.1 (17.1–27.4)	**1.05 (0.85–1.29)**
Pembro + Pbo	176 (62.0)	22.7 (19.0–26.8)	

Progression-Free Survival[b]

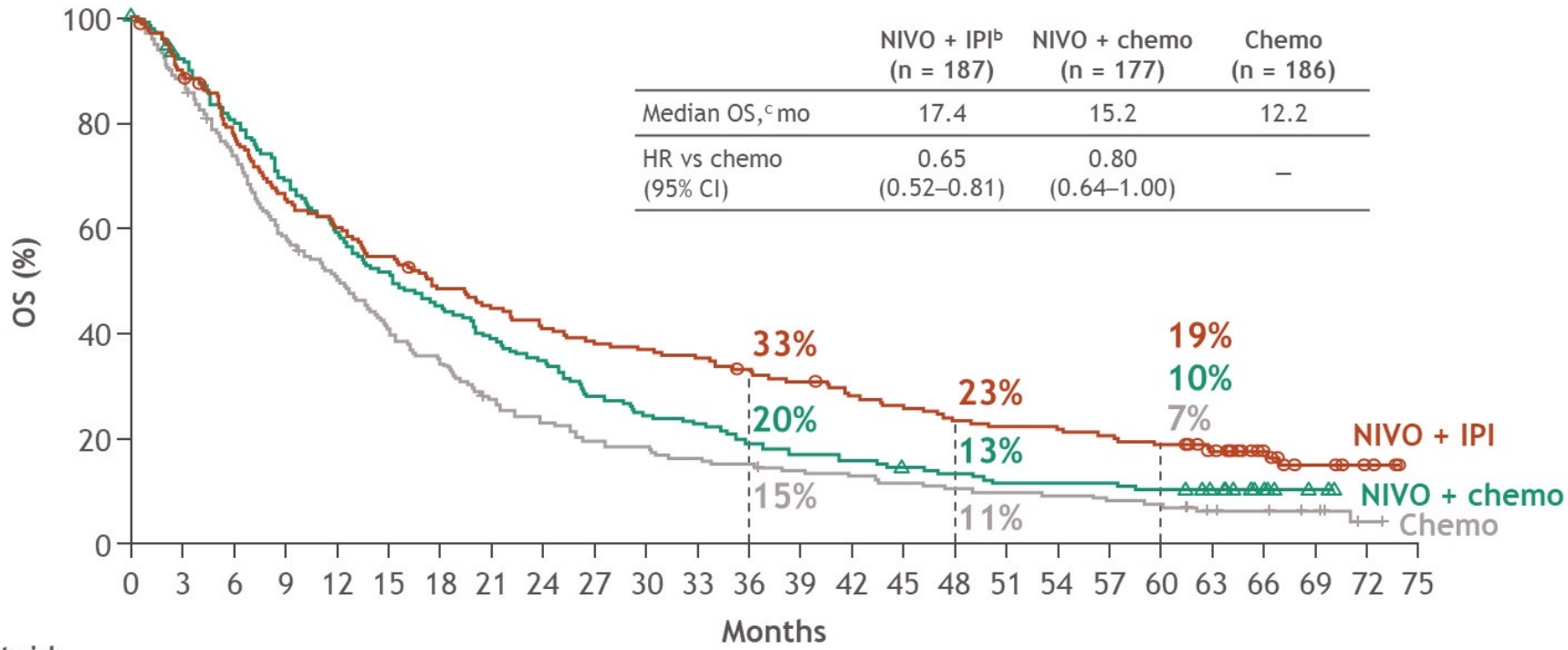


No. at risk									
Pembo + Ipi	284	148	103	71	60	30	8	0	0
Pembro + Pbo	284	157	105	79	55	30	11	3	0

	Events, n (%)	Median (95% CI)	PFS HR (95% CI)
Pembro + Ipi	198 (69.7)	8.2 (6.1–10.6)	**0.99 (0.81–1.21)**
Pembro + Pbo	203 (71.5)	8.4 (6.3–10.5)	

Rodríguez-Abreu et al. ESMO Lung 2022; Abstract 6MO.

5-year OS in patients with tumor PD-L1 < 1%[a]



	NIVO + IPI[b] (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS,[c] mo	17.4	15.2	12.2
HR vs chemo (95% CI)	0.65 (0.52–0.81)	0.80 (0.64–1.00)	–

No. at risk

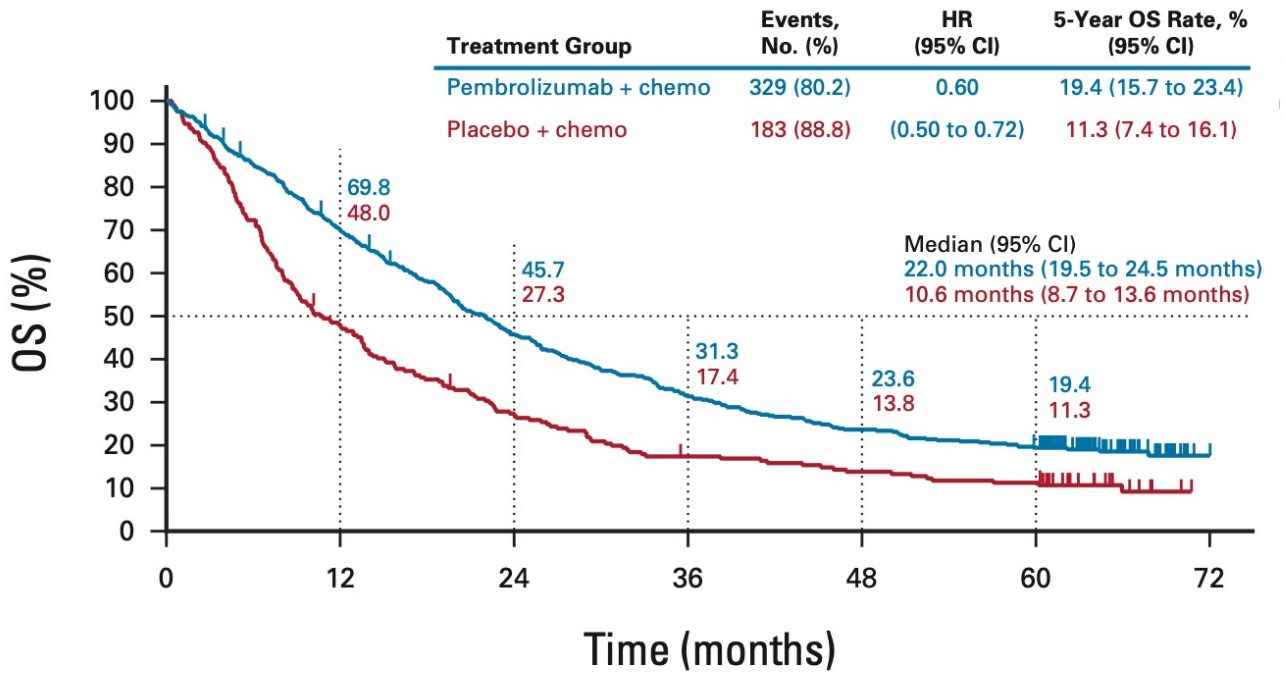
NIVO + IPI	187	165	142	120	110	100	88	81	74	69	67	64	59	55	49	45	41	39	38	36	33	27	15	8	3	0
NIVO + chemo	177	159	139	119	102	88	78	67	60	48	42	39	34	29	27	24	22	19	19	19	17	14	7	2	0	0
Chemo	186	164	135	107	92	74	62	49	41	35	33	29	27	24	22	20	18	17	16	14	12	8	7	5	1	0

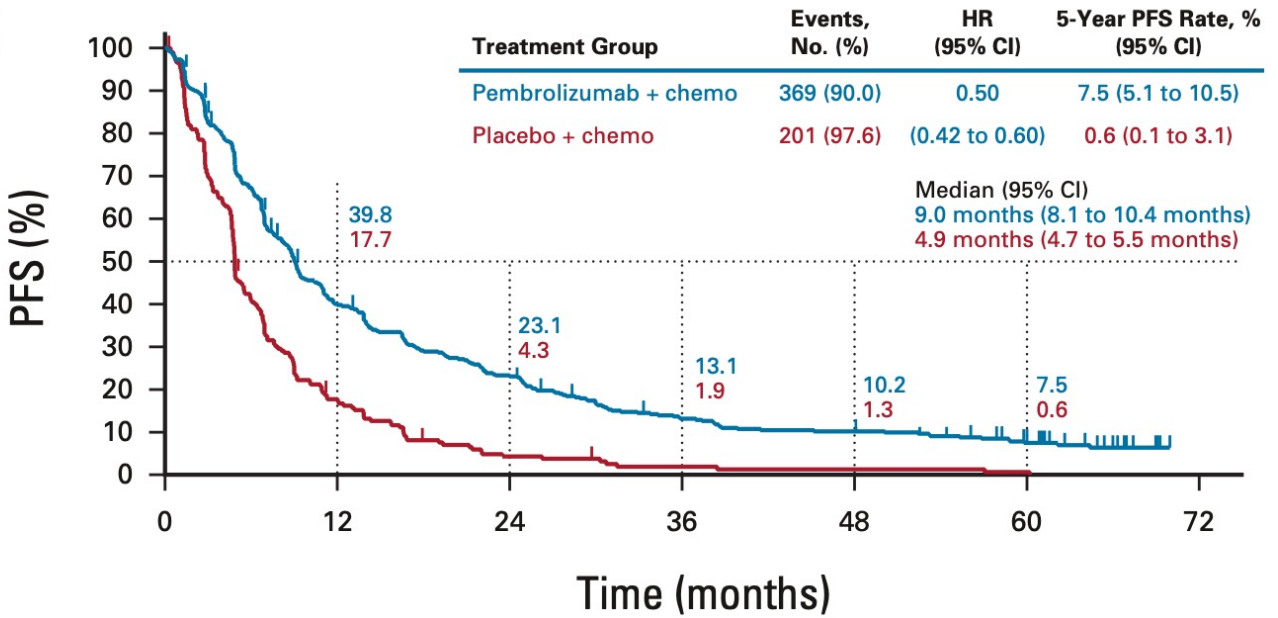
Database lock: February 15, 2022; minimum/median follow-up for OS: 61.3/66.7 months.

[a]In patients with PD-L1 < 1% with a PFS event (per BICR), subsequent systemic therapy was received by 44% in the NIVO + IPI arm, 39% in the NIVO + chemo arm, and 48% in the chemo arm; subsequent immunotherapies by 8%, 5%, and 33%; subsequent chemo by 43%, 37%, and 33%, respectively. [b]NIVO + IPI vs NIVO + chemo HR was 0.80 (95% CI, 0.63–1.00). [c]Median OS 95% CI are 13.21–22.05 (NIVO + IPI), 12.29–19.78 (NIVO + chemo), and 9.17–14.32 (chemo).

Brahmer et al. ASCO 2022; Abstract LBA9025.

Pembrolizumab + Chemo (5-year outcomes)

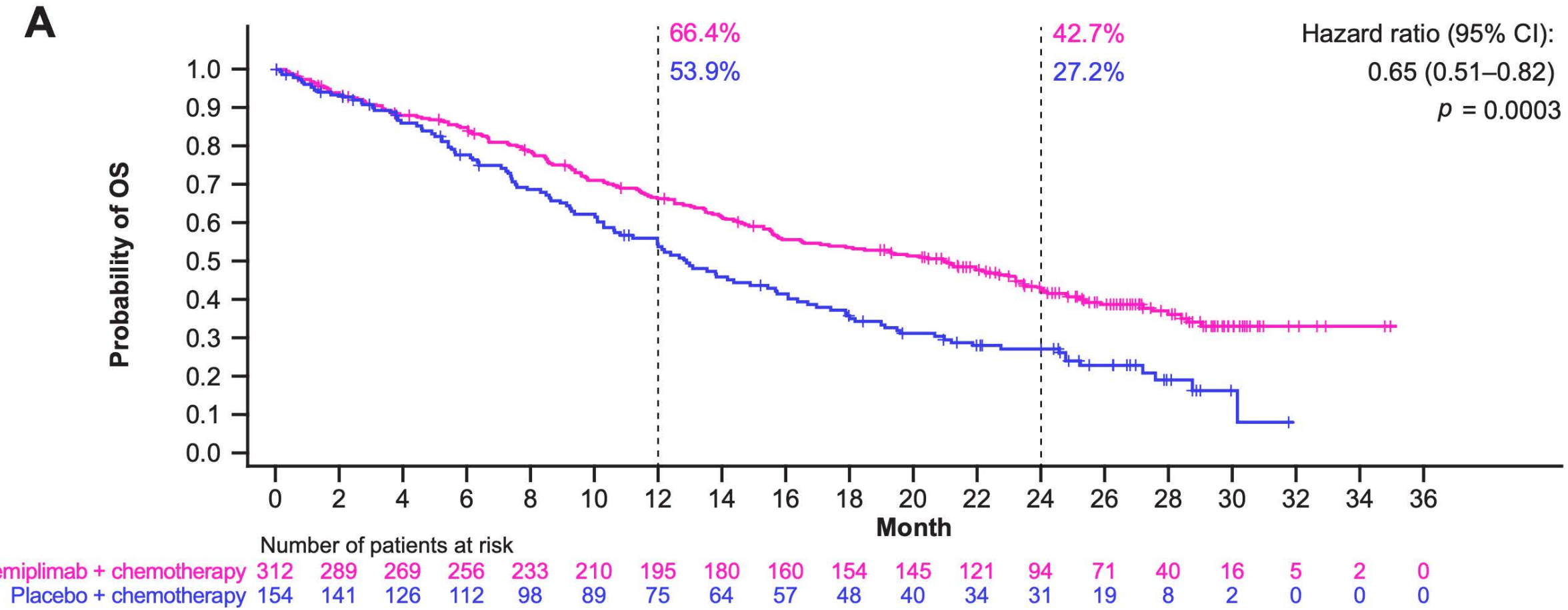




Garassino et al. *J Clin Oncol* 2023;41(11):1992-1998.

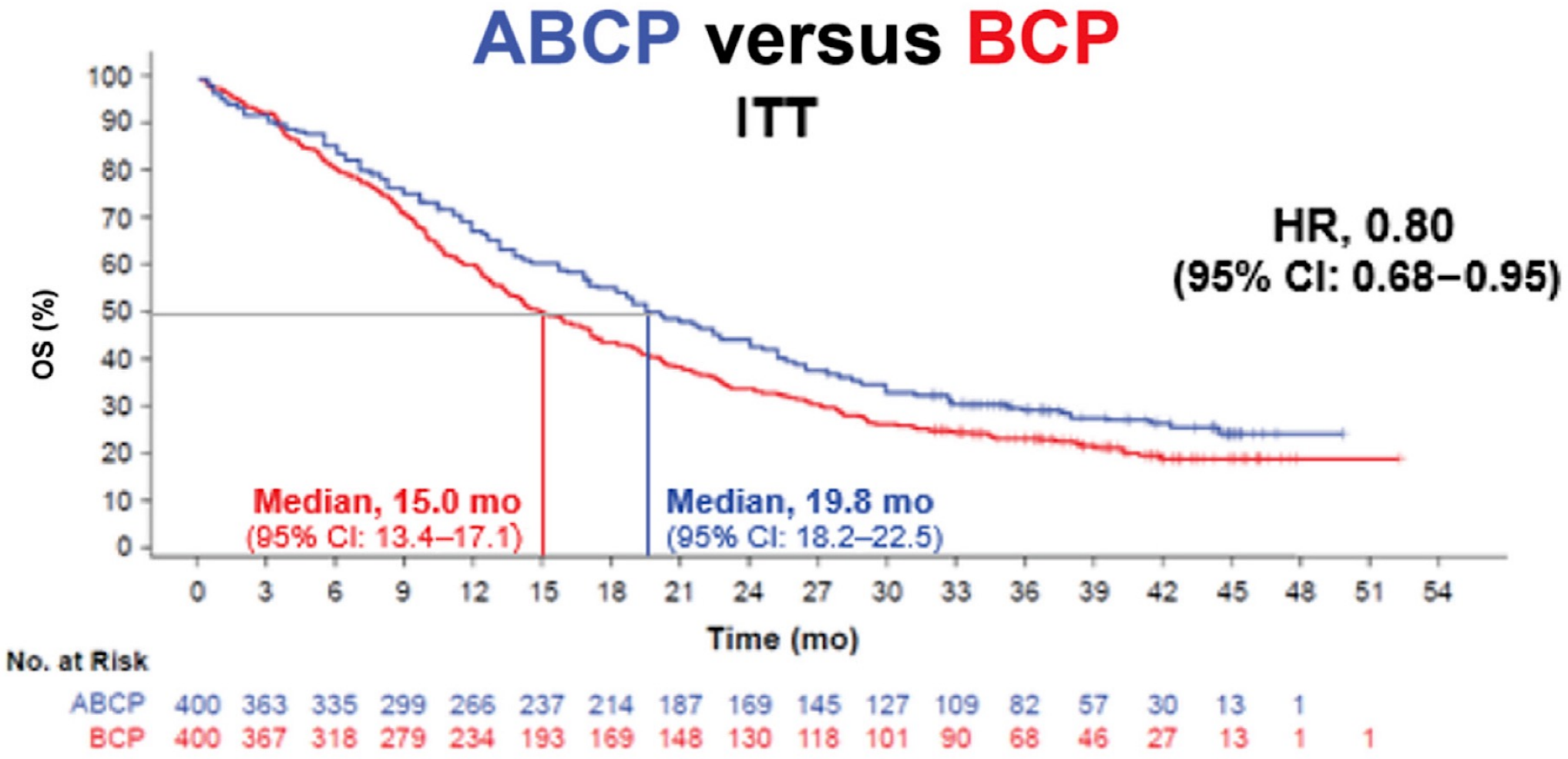
EMPOWER-Lung 3

	Median OS (95% CI)
Cemiplimab + chemo	21.1 months (15.9–23.5)
Placebo + chemo	12.9 months (10.6–15.7)



Makharadze et al. *J Thorac Oncol* 2023;18(6):755-768.

IMpower150 (atezolizumab/bevacizumab/carboplatin/paclitaxel)



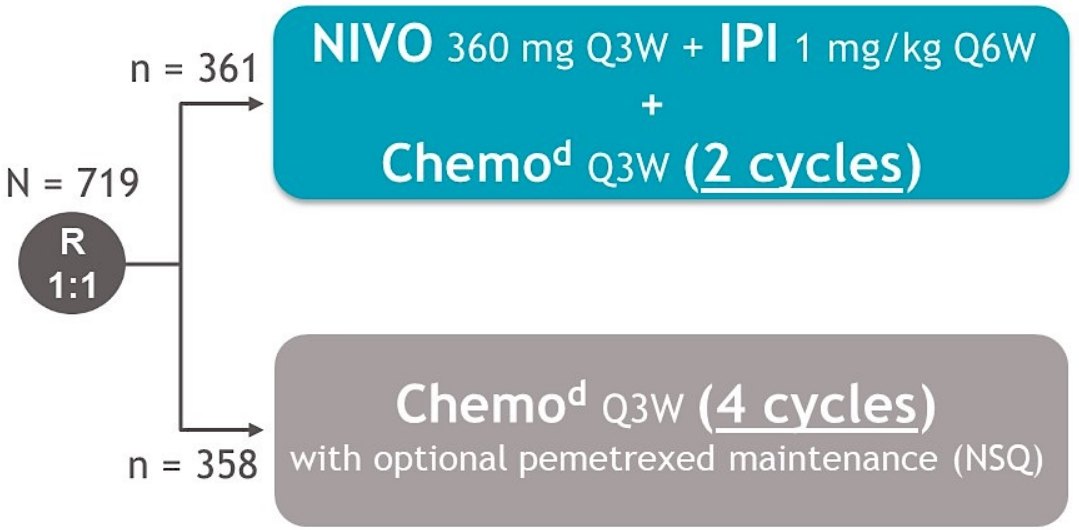
Socinski et al. *J Thorac Oncol* 2021;16(11):1909-1924.

CheckMate 9LA study design[a]

Key eligibility criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Exploratory endpoints
- Safety

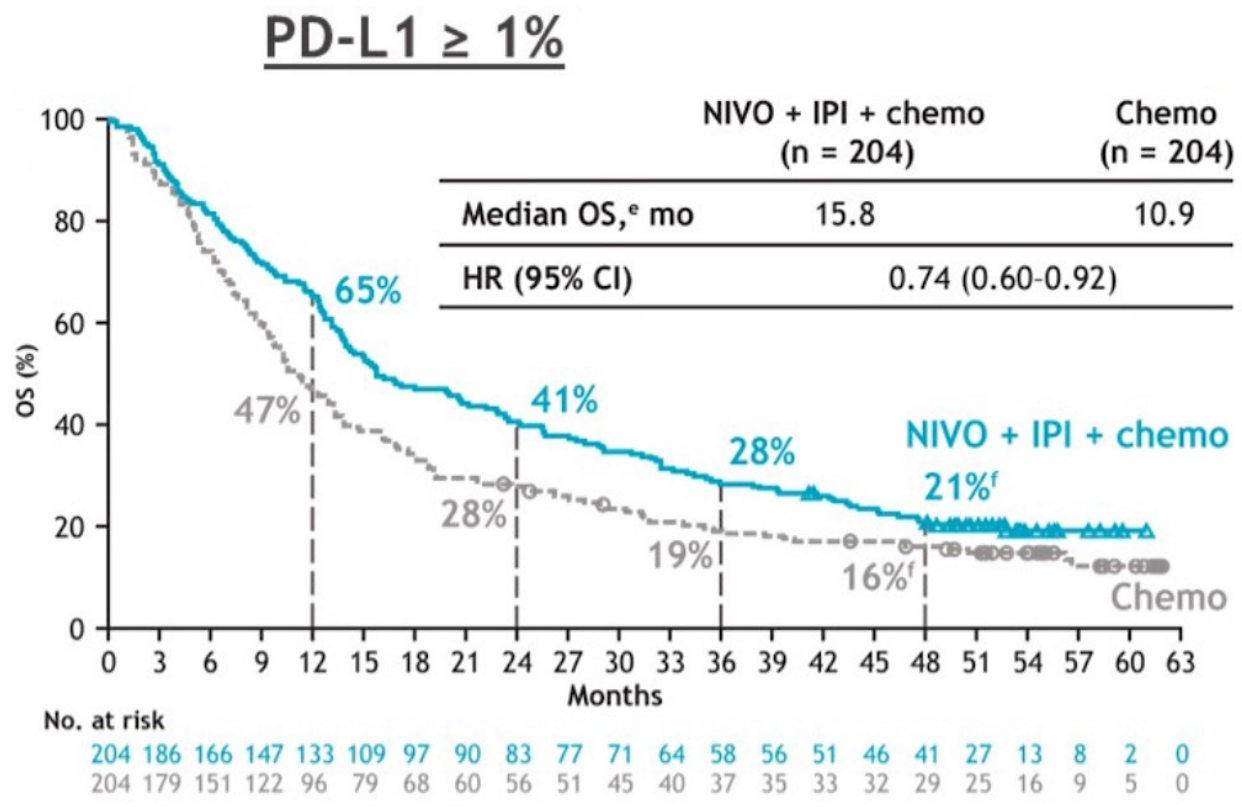
DBL: February 18, 2021; minimum / median follow-up for OS: 24.4 months / 30.7 months.

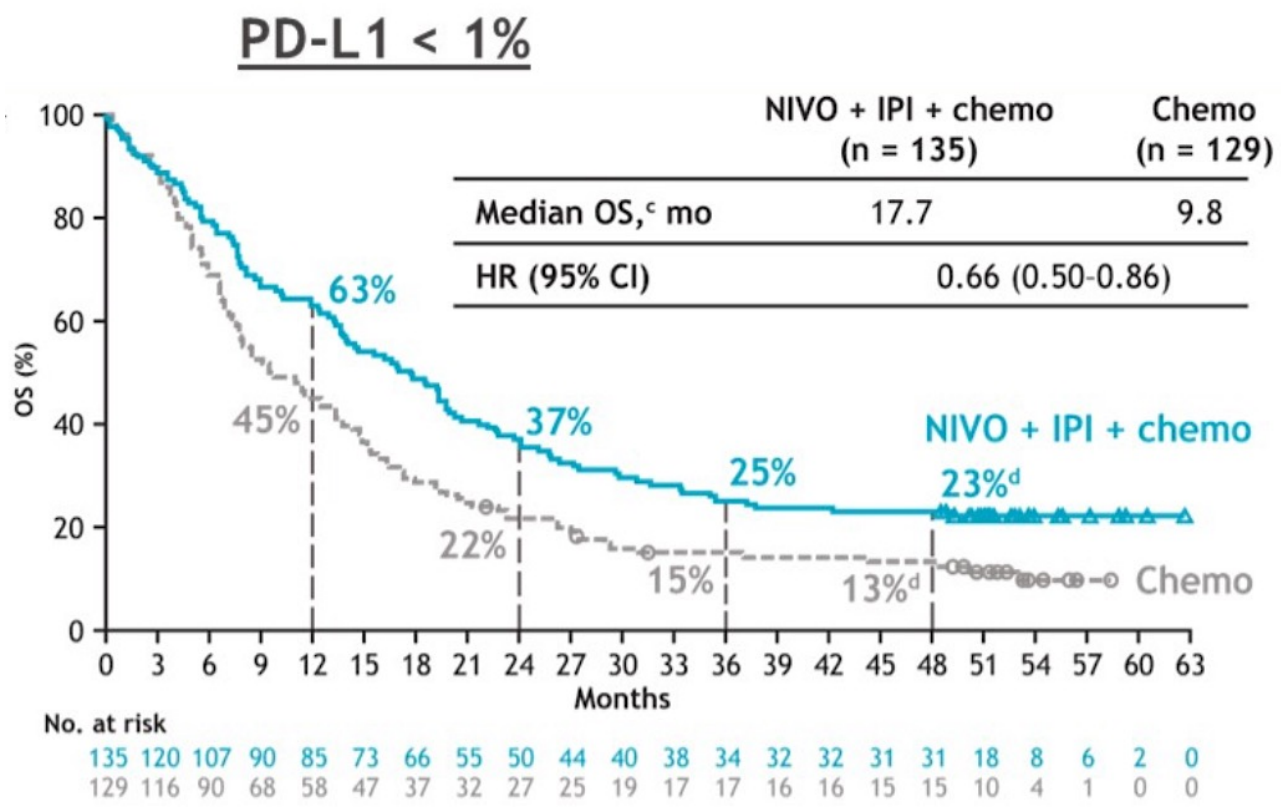
[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Reck M. ASCO 2021.

CheckMate 9LA: 4-Year Update

OS in subgroups by PD-L1 expression



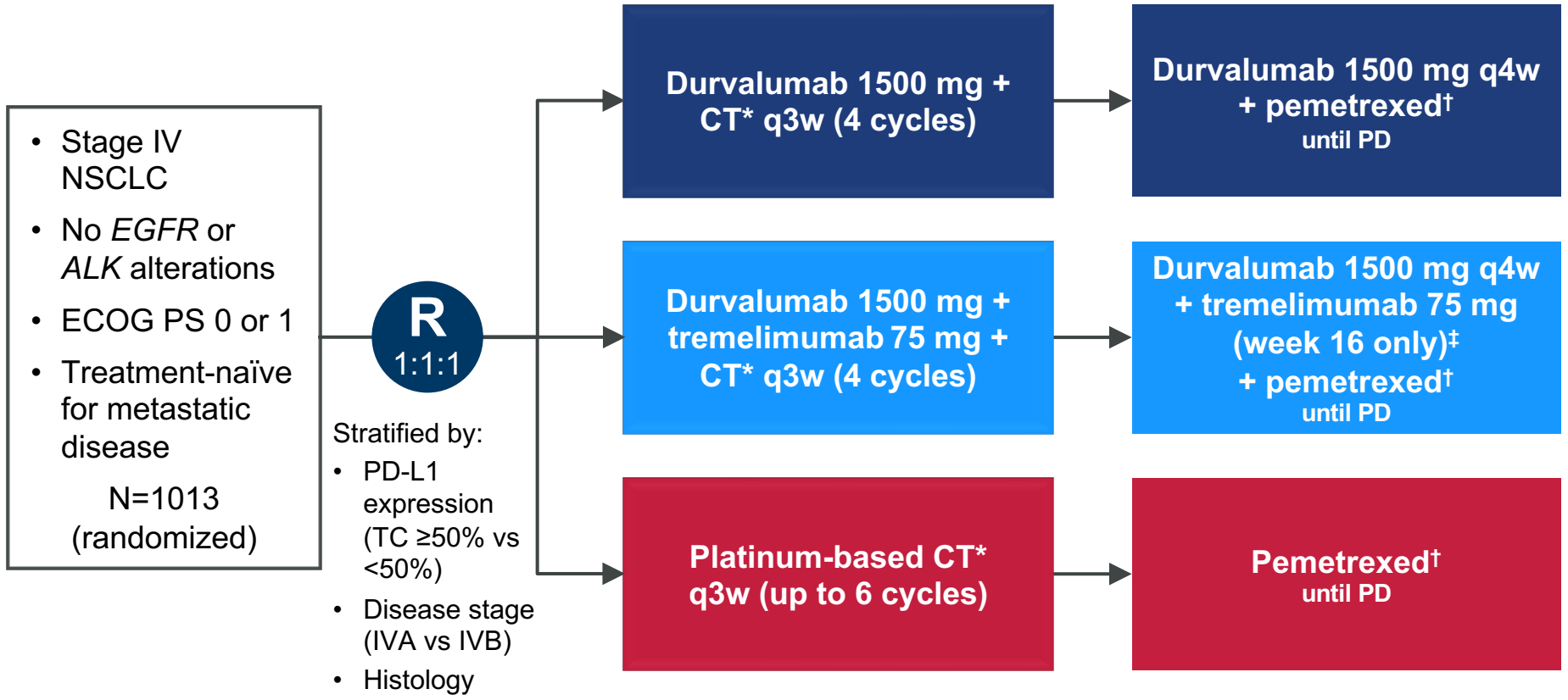


Carbone et al. ASCO 2023;Abstract LBA9023.

POSEIDON Study Design

Johnson ML et al. WCLC 2021.

Phase 3, global, randomized, open-label, multicenter study



Primary endpoints
- PFS by BICR (D+CT vs CT)
- OS (D+CT vs CT)

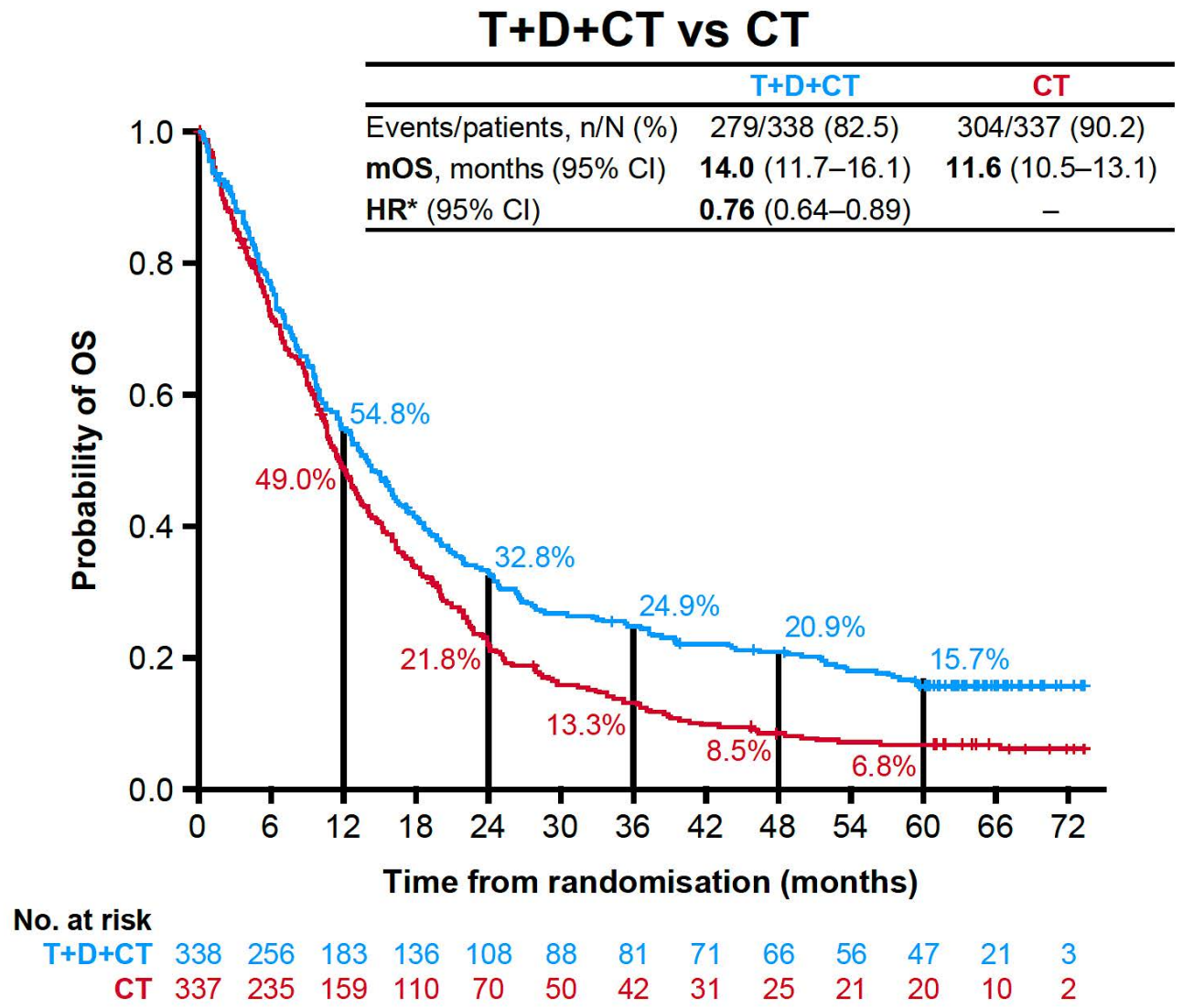
Key secondary endpoints
- PFS by BICR (D+T+CT vs CT)
- OS (D+T+CT vs CT)
- OS in patients with bTMB ≥20 mut/Mb (D+T+CT vs CT)

Additional secondary endpoints
- ORR, DoR, and BOR by BICR
- PFS at 12 months
- HRQoL
- Safety and tolerability

*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology);
†Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

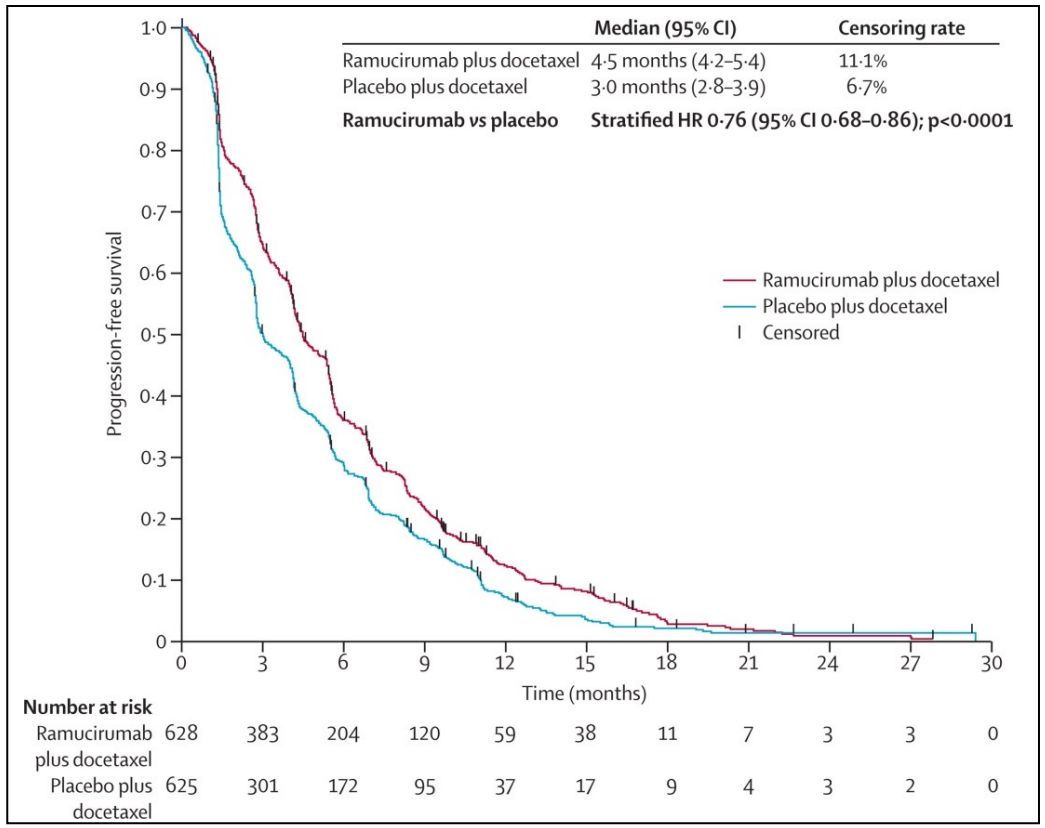
BICR, blinded independent central review; BOR, best objective response; bTMB, blood tumor mutational burden; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; Mb, megabase; mut, mutations; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumor cell

Durvalumab + Tremelimumab + CT vs CT: 5-year OS

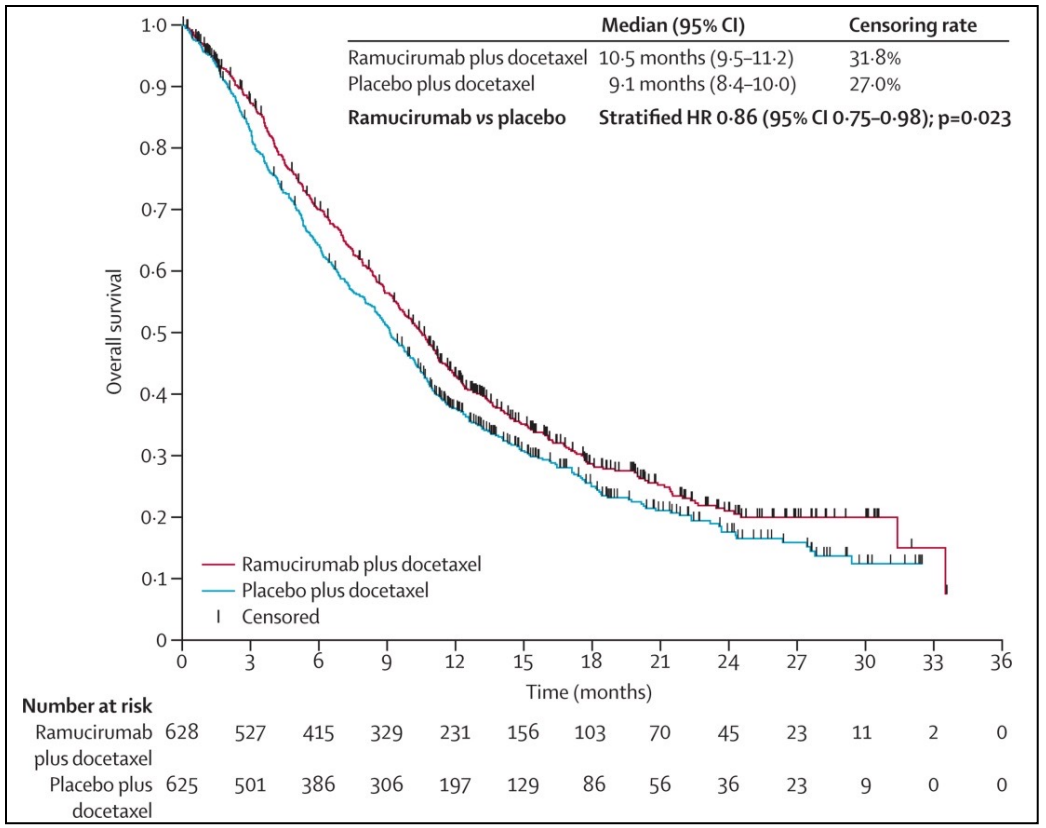


Peters et al. ESMO IO 2023;Abstract LBA3.

Ramucirumab: Survival Figures



Kaplan-Meier estimates of progression-free survival in the intention-to-treat population HR=hazard ratio.



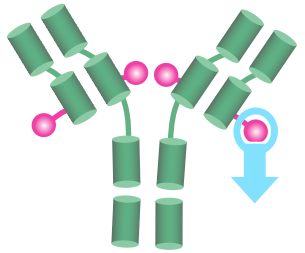
Kaplan-Meier estimates of overall survival in the intention-to-treat population HR=hazard ratio.

Garon EB et al. *Lancet*, 2014

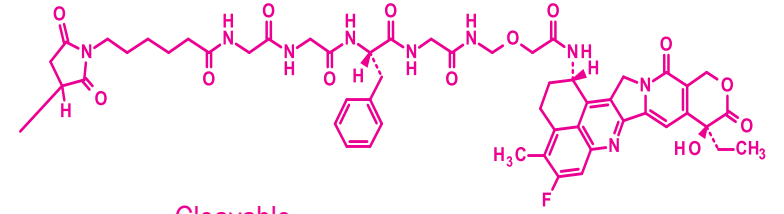
Background

- Standard-of-care, **second-line chemotherapy** for metastatic NSCLC is associated with a **modest benefit and substantial toxicity**
- **Dato-DXd** is a **TROP2-directed ADC** that selectively delivers a potent topoisomerase I inhibitor payload directly into tumor cells[1]
- **Promising antitumor activity** was seen with Dato-DXd in patients with adv/met NSCLC in the phase 1 TROPION-PanTumor01 trial (26% ORR)[1]

Dato-DXd: Humanized anti-TROP2 IgG1 mAb[2-5]



Deruxtecan



Cleavable tetrapeptide-based linker

Topo-I inhibitor payload (DXd)

Image is for illustrative purposes only; actual drug positions may vary.

ADC, antibody-drug conjugate; adv/met, advanced/metastatic; Dato-DXd, datopotamab deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; TROP2, trophoblast cell-surface antigen 2.

1. Shimizu T, et al. *J Clin Oncol.* 2023;41:4678-4687. 2. Okajima D, et al. *Mol Cancer Ther.* 2021;20:2329-2340. 3. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-185. 4. Ogitani Y, et al. Clin Cancer Res. 2016;22:5097-5108. 5. Ogitani Y, et al. *Cancer Sci.* 2016;107:1039-1046.

Ahn M et al. ESMO 2023;Abstract LBA12.

TROPION-Lung01 Study Design

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

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

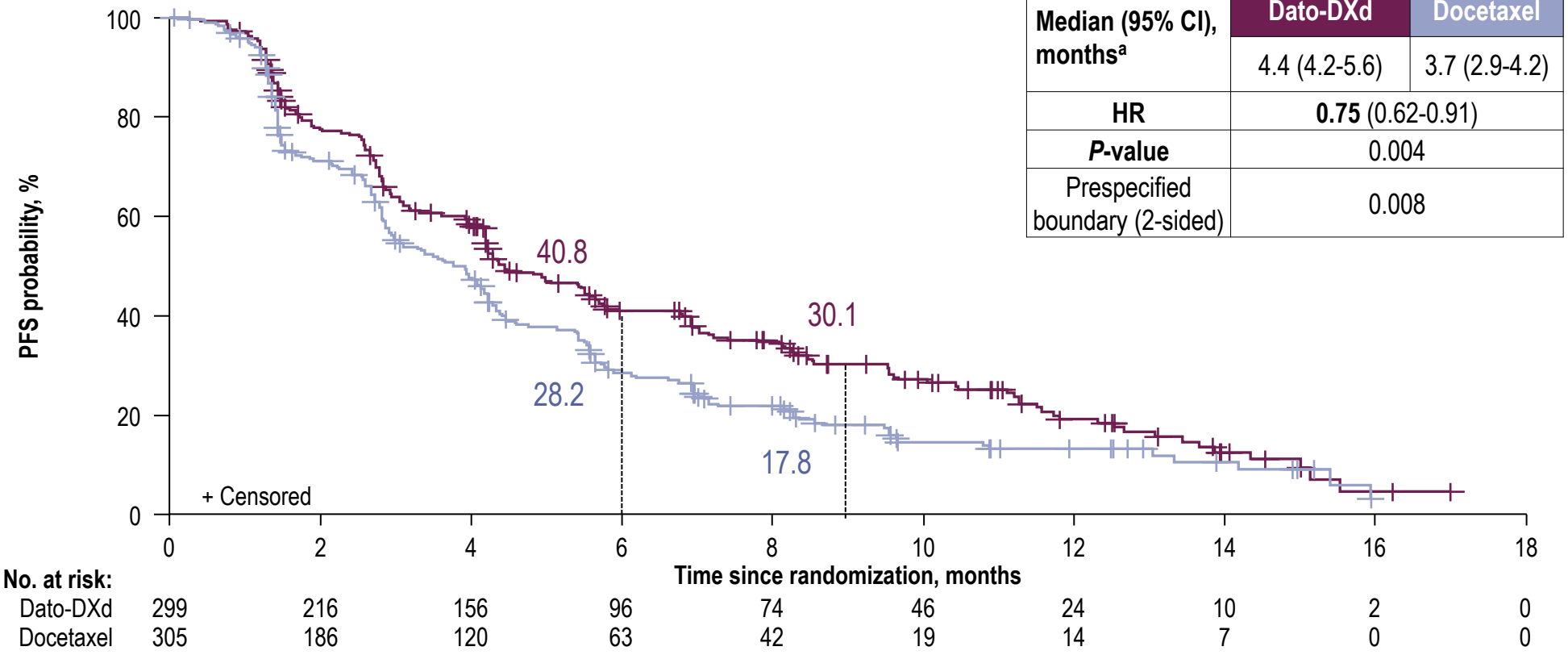
Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

Enrollment period: 19 February 2021 to 7 November 2022.
BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.
[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs non-squamous. [c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world.

Ahn M et al. ESMO 2023;Abstract LBA12.

Progression-Free Survival: ITT

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	



	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)

CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Median PFS follow-up was 10.9 (95% CI, 9.8-12.5) and 9.6 (95% CI, 8.2-11.9) months for Dato-DXd and docetaxel, respectively. [b]Included 4 CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.

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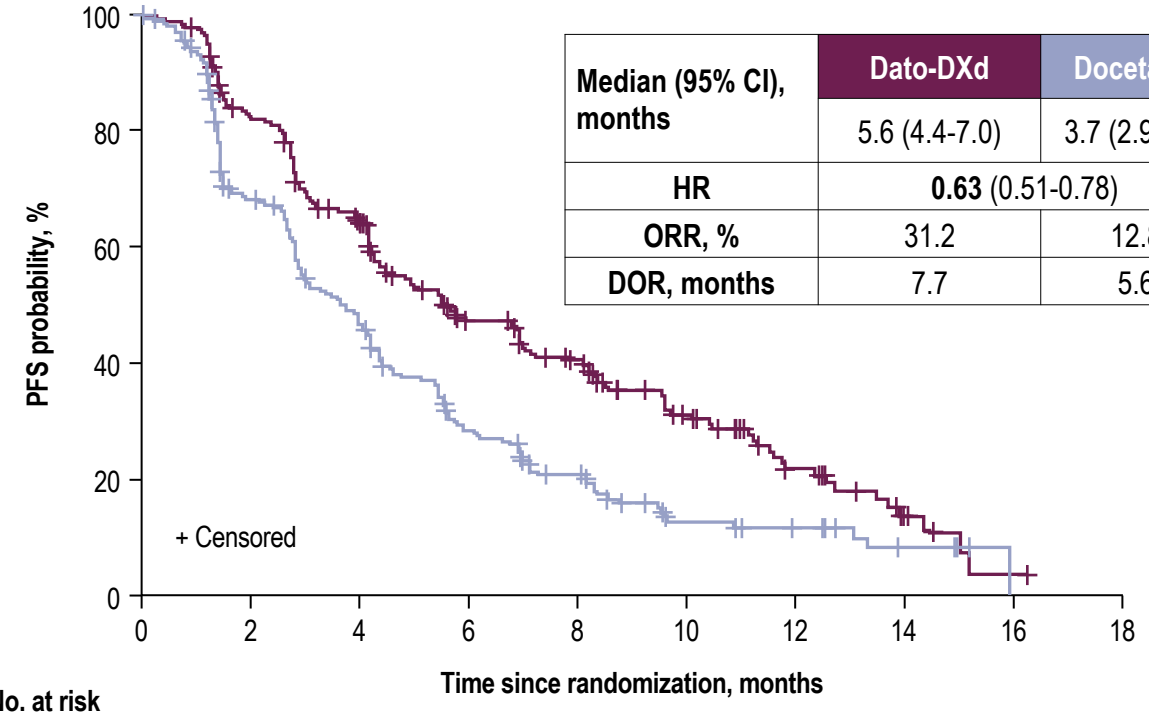
PFS by Histology

Non-squamous

(with and without AGAs)

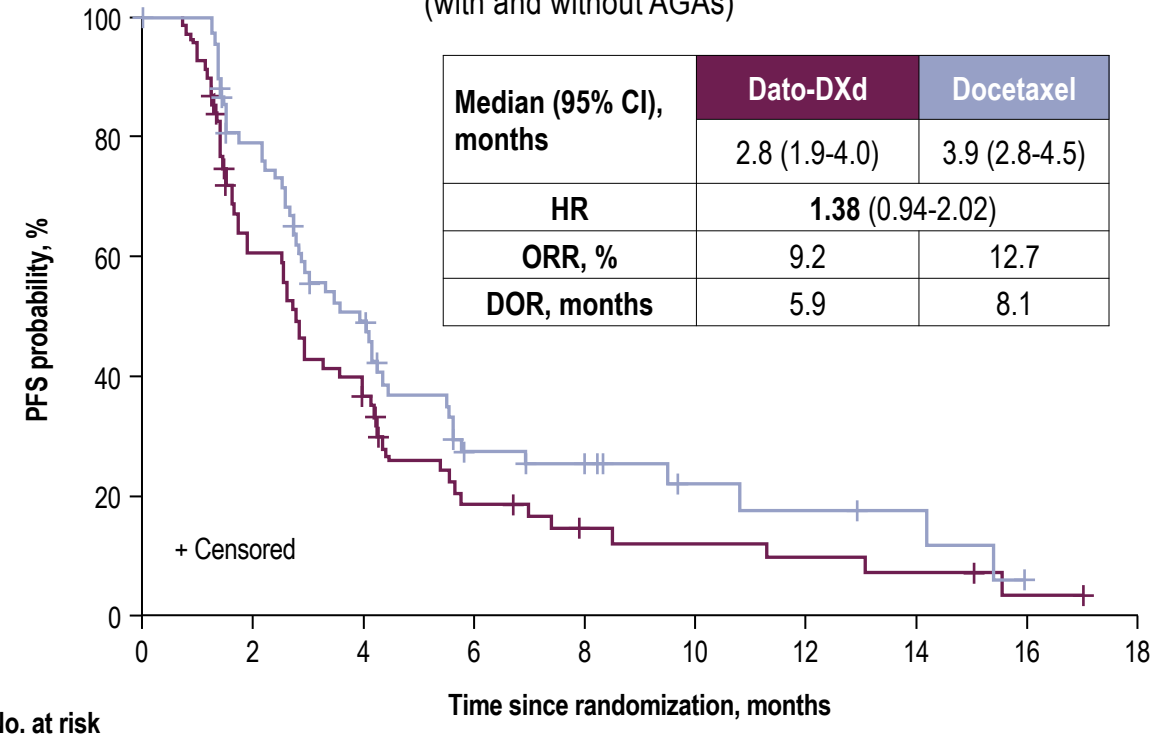


Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

No. at risk										
Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

Squamous

(with and without AGAs)



Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1

No. at risk										
Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)

AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response ratel PFS, progression-free survival.
Squamous subset included 3 patients with AGAs

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Safety Summary

System organ class Preferred term, n (%)	Dato-DXd N=297		Docetaxel N=290	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system				
Anemia	43 (15)	11 (4)	59 (20)	11 (4)
Neutropenia[a]	12 (4)	2 (1)	76 (26)	68 (23)
Gastrointestinal				
Stomatitis	140 (47)	19 (6)	45 (16)	3 (1)
Nausea	100 (34)	7 (2)	48 (17)	3 (1)
Vomiting	38 (13)	3 (1)	22 (8)	1 (0.3)
Constipation	29 (10)	0	30 (10)	0
Diarrhea	28 (9)	1 (0.3)	55 (19)	4 (1)
General				
Asthenia	55 (19)	8 (3)	55 (19)	5 (2)
Fatigue	34 (11)	2 (1)	40 (14)	6 (2)
Metabolism and nutrition				
Decreased appetite	68 (23)	1 (0.3)	45 (16)	1 (0.3)
Skin and subcutaneous				
Alopecia	95 (32)	0	101 (35)	1 (0.3)[b]
Rash	36 (12)	0	18 (6)	0
Pruritus	30 (10)	0	12 (4)	0

AESI, n (%)	Dato-DXd N=297	Docetaxel N=290
Stomatitis/oral mucositis[a]		
All grades	160 (54)	59 (20)
Grade ≥3	19 (6)	4 (1)
Ocular events[b]		
All grades	57 (19)	27 (9)
Grade ≥3	5 (2)[c]	0
Adjudicated drug-related ILD[d]		
All grades	25 (8)	12 (4)
Grade ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

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Conclusions

- Monotherapy options include
  - Pembrolizumab PD-L1 $\geq$ 1%
  - Cemiplimab PD-L1 $\geq$ 50%
  - Atezolizumab PD-L1 $\geq$ 50%, but weakening OS data over time
- Nivolumab ipilimumab approved in PD-L1 positive patients
- Chemotherapy plus PD-1 inhibitor options
  - Chemo plus pembrolizumab or cemiplimab
- Chemotherapy plus PD-(L)1 inhibitor plus CTLA-4 options
  - 2 chemo cycles plus nivolumab ipilimumab, durvalumab plus tremelimumab
- Docetaxel based therapy is standard of care at progression for now

The Annual
National General Medical Oncology Summit

Saturday, March 23, 2024

Moderator

Neil Love, MD

Faculty

Emmanuel S Antonarakis, MD
Ibiayi Dagogo-Jack, MD
Matthew D Galsky, MD
Edward B Garon, MD, MS
Erika Hamilton, MD
Eric Jonasch, MD
Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Matthew Lunning, DO
Kami Maddocks, MD
Rana R McKay, MD
Bradley J Monk, MD
David M O'Malley, MD
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