# New Therapeutic Directions in Lung Cancer

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**25th Annual**
Advances in Oncology

[Lung cancer biomarker here]

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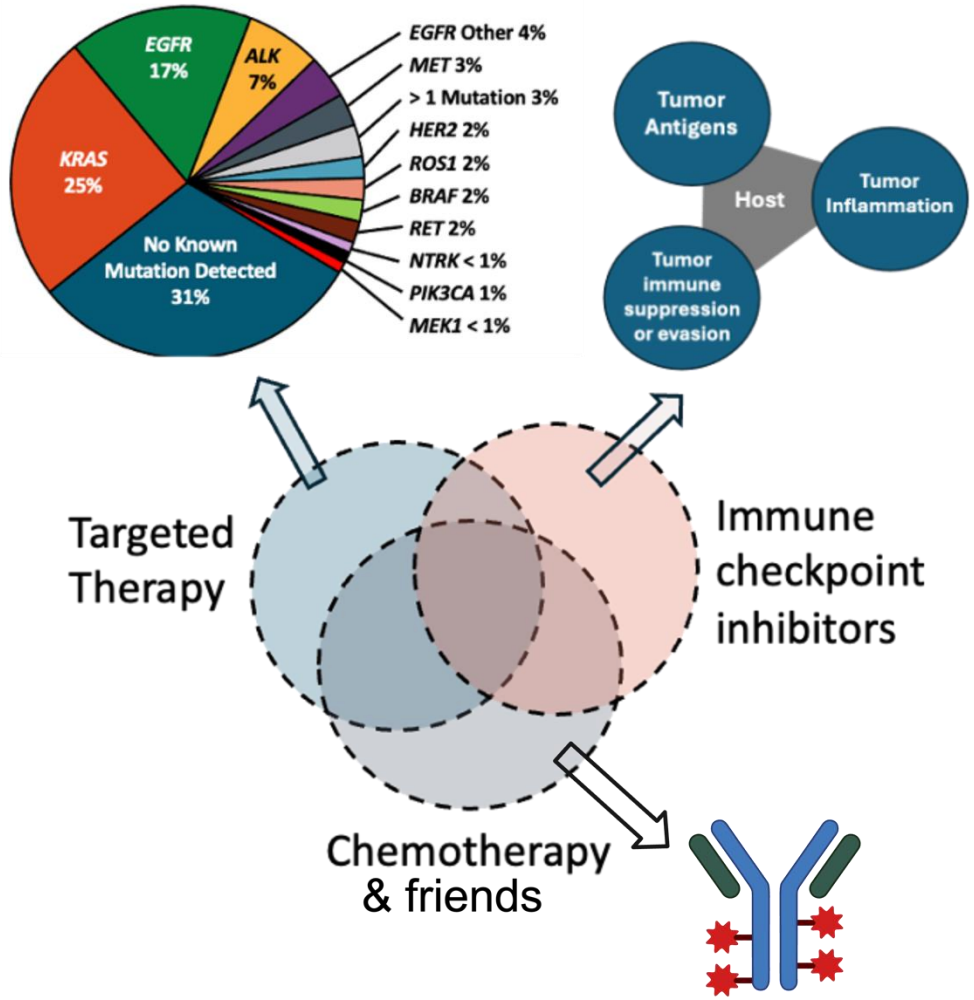
# Lung Cancer in 2024

**Current Era = Precision Medicine**




2024 ASCO ANNUAL MEETING

BARCELONA 2024 ESMO congress

CELEBRATING 50 YEARS IASLC 1974–2024

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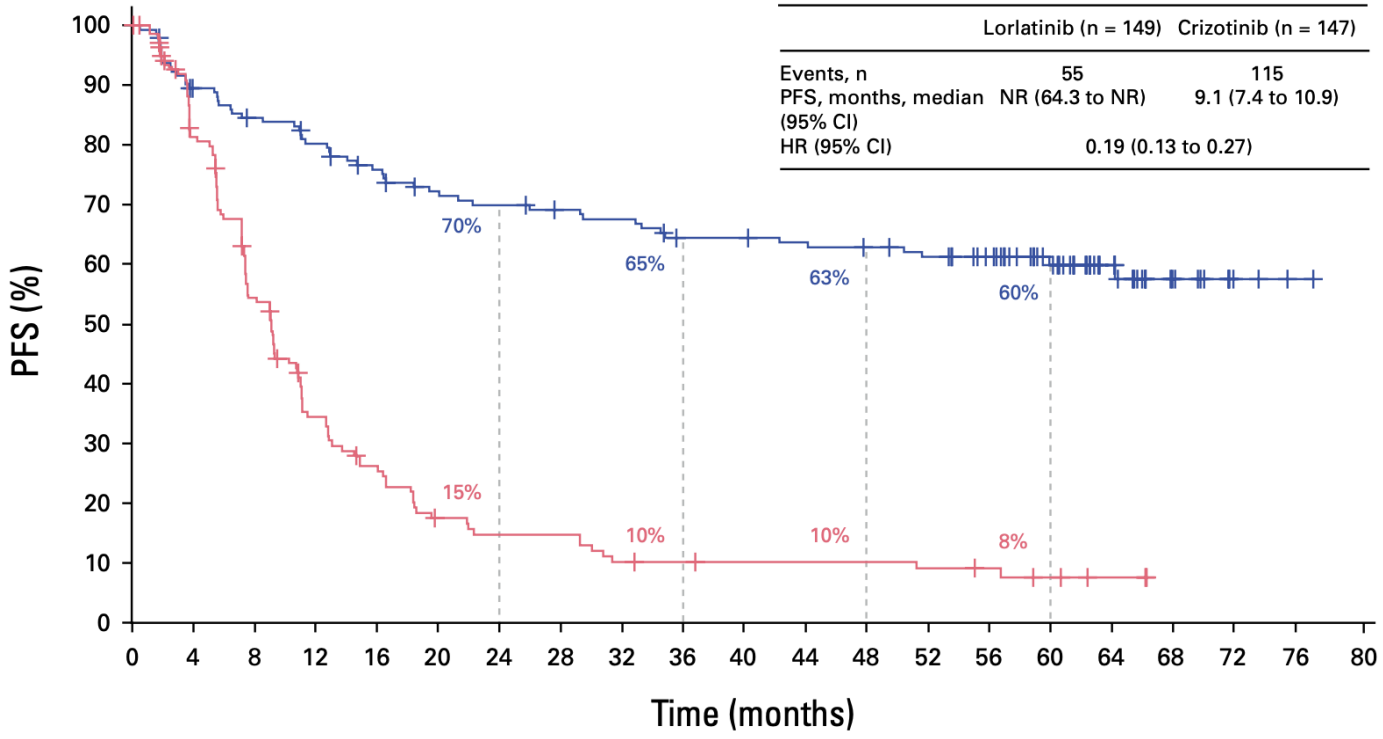
# Why the CROWN Trial Earned Big Applause

Patient Power

## Very impressive HR of lorlatinib versus crizotinib




## Cumulative Incidence Brain Metastases Progression in Patients with Baseline Brain Mets

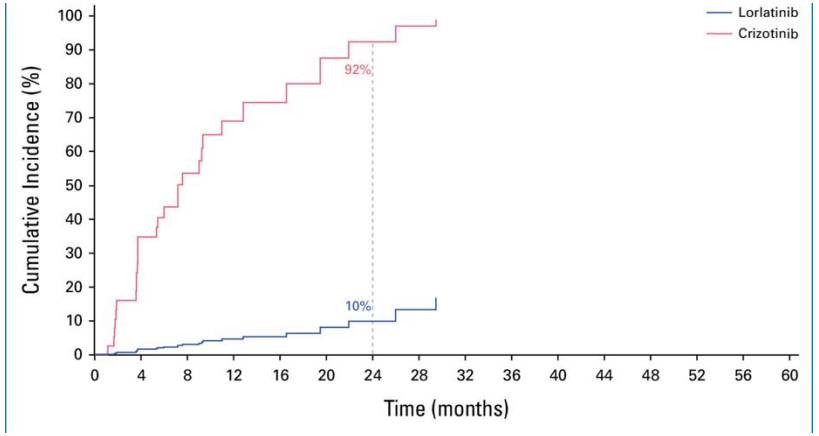



**TABLE 2.** Summary of AEs

| Safety Population | Lorlatinib (n = 149) | Crizotinib (n = 142) |
|---|---|---|
| Treatment-related AEs, No. (%) | | |
| Any grade | 145 (97) | 133 (94) |
| Grade 3/4 | 99 (66) | 55 (39) |
| Grade 5 | 2 (1) | 0 |
| Serious | 14 (9) | 9 (6) |
| Leading to temporary drug discontinuation | 58 (39) | 51 (36) |
| Leading to dose reduction | 31 (21) | 19 (13) |
| Leading to permanent drug discontinuation | 8 (5) | 8 (6) |

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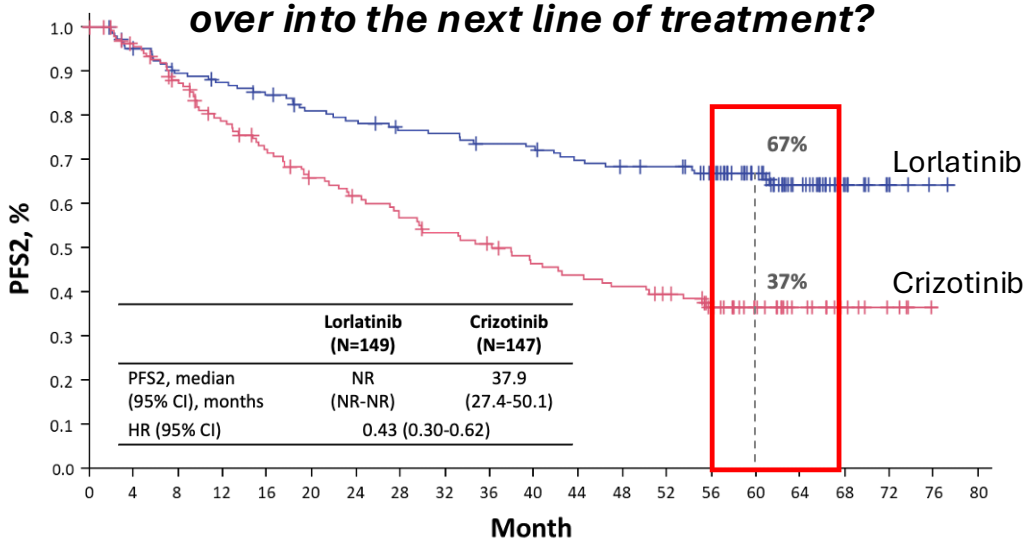
# The Rich (treated with 1L lorlatinib) Get Richer

***PFS2: Does the benefit of the 1L treatment carry over into the next line of treatment?***




**Most patients with progression on crizotinib received 2L alectinib, not lorlatinib**

| First subsequent systemic anticancer therapy, n (%) | Lorlatinib (n=38) | Crizotinib (n=109) |
|---|---|---|
| ALK TKI | 23 (61) | 101 (93) |
| Alectinib | 12 (52) | 68 (67) |
| Crizotinib | 4 (17) | 5 (5) |
| Ceritinib | 3 (13) | 3 (3) |
| Lorlatinib | 3 (13) | 4 (4) |
| Brigatinib | 1 (4) | 21 (21) |
| Chemotherapy ± anti-angiogenic | 13 (34) | 4 (4) |

**NVL-655 Is a Selective and Brain-Penetrant Inhibitor of Diverse ALK-Mutant Oncoproteins, Including Lorlatinib-Resistant Compound Mutations**

Any prior ALK TKI +/- chemotherapy: **ORR 38%**
≥3 prior ALK TKI, including 2G and lorlatinib: **ORR 37%**
G1202R ALK mutation: **ORR 76%**
Compound (≥ 2 mutations): **ORR 58%**

**Treatment-Related Adverse Events (TRAEs) in ≥ 10% of Patients**
**All Treated (N = 133)**

| Preferred Term | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) | Any Grade n (%) |
|---|---|---|---|---|---|
| ALT increased | 21 (16%) | 6 (5%) | 17 (13%) | 1 (1%) | 45 (34%) |
| AST increased | 21 (16%) | 7 (5%) | 12 (9%) | - | 40 (30%) |
| Constipation | 15 (11%) | 6 (5%) | - | - | 21 (16%) |
| Dysgeusia | 15 (11%) | 2 (2%) | - | - | 17 (13%) |
| Nausea | 15 (11%) | 1 (1%) | - | - | 16 (12%) |

**2% discontinued due to TRAE**

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# Phase 1/2 ARROS-1 study of NVL-520

## Preliminary Activity: Radiographic Tumor Response Across Previously Treated Patients with ROS1+ NSCLC

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

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

**NVL-520 induced intracranial responses following prior treatment with brain-penetrant ROS1 TKIs**


**No TRAEs led to discontinuation**

**Treatment-Related Adverse Events (TRAEs) in ≥ 10% of Patients**
**All Treated (N = 104)**

| Preferred Term | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Any Grade n (%) |
|---|---|---|---|---|
| Oedema peripheral | 15 (14%) | 5 (5%) | - | 20 (19%) |
| ALT increased | 11 (11%) | - | - | 11 (11%) |
| AST increased | 11 (11%) | - | - | 11 (11%) |
| Weight increased | 7 (7%) | 3 (3%) | 1 (1%) | 11 (11%) |

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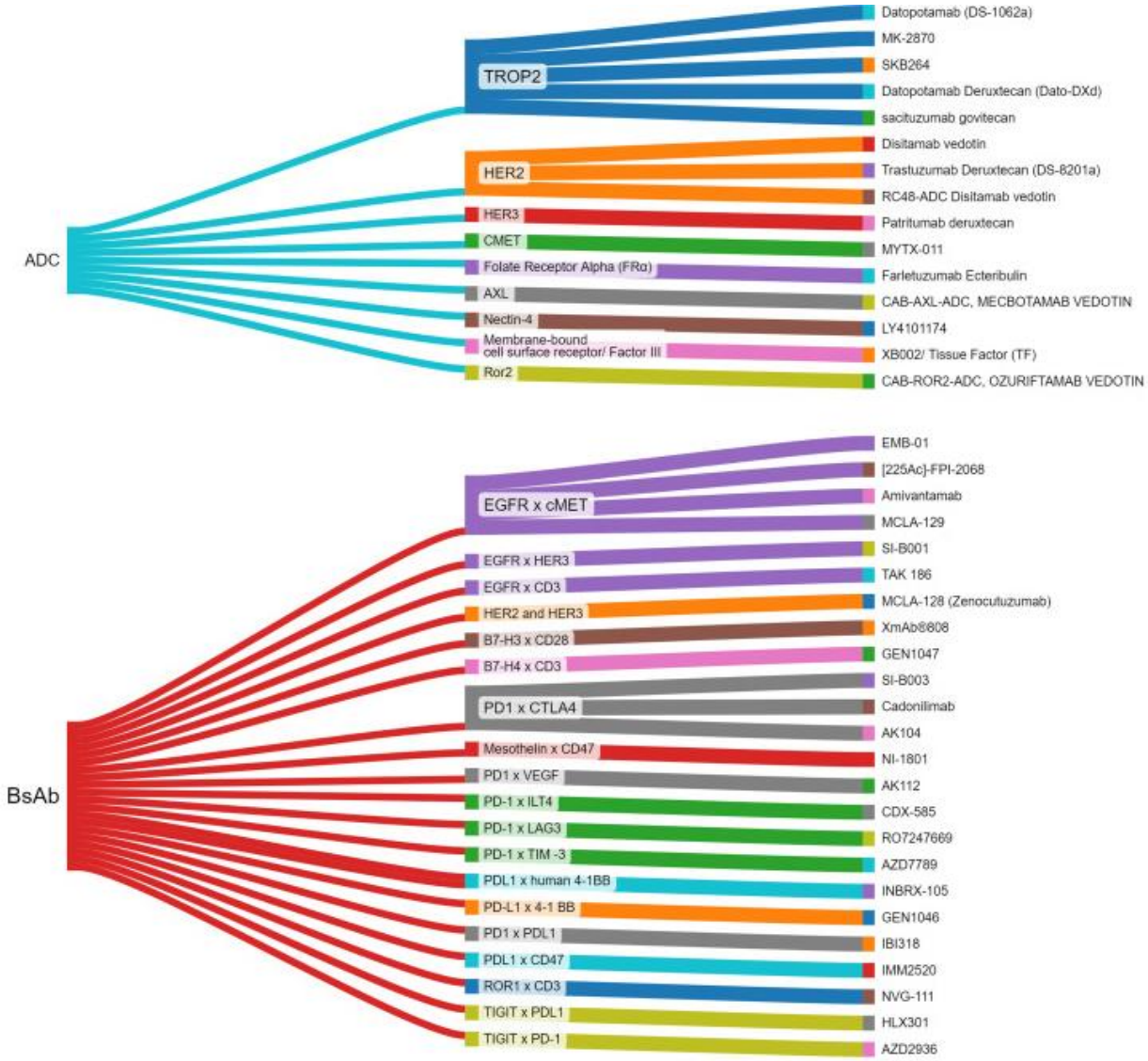
# Antibody Drug Conjugates and Bispecific Antibodies




**ADCs**:

Trastuzumab deruxetecan: advanced NSCLC with **HER2** driver mutations

Datopotamab deruxetecan: TROP2 ADC

Sacituzumab govitecan: TROP2 ADC

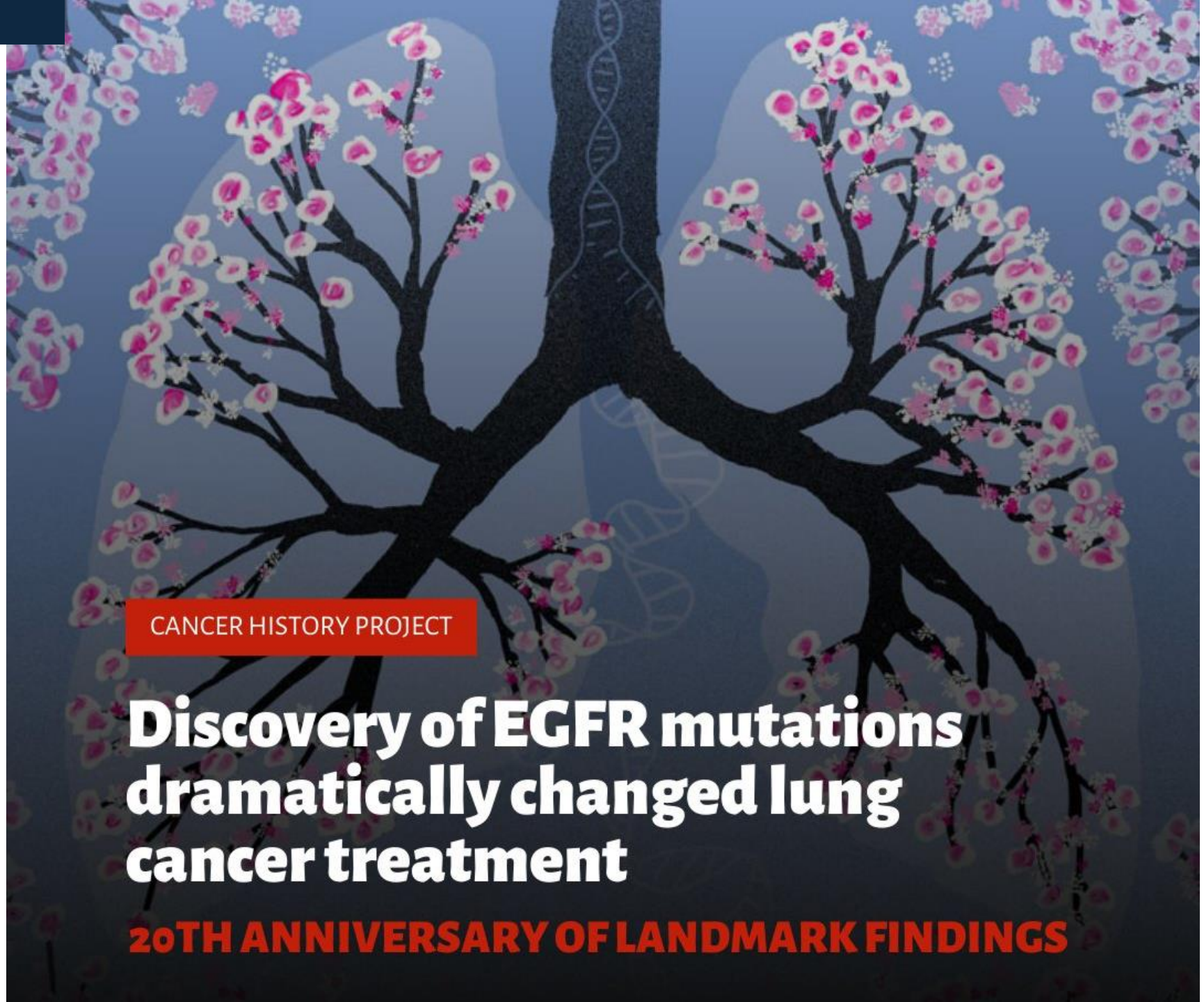
**Bispecifics**:

Amivantamab: **EGFR** and MET

Ivonescimab: VEGF and PD-1

**… much more to come**

Kumar et al., Clinical Lung Cancer, 2024


CANCER HISTORY PROJECT
Discovery of EGFR mutations dramatically changed lung cancer treatment
20TH ANNIVERSARY OF LANDMARK FINDINGS

# FLAURA2 – 1L Stage IV EGFR

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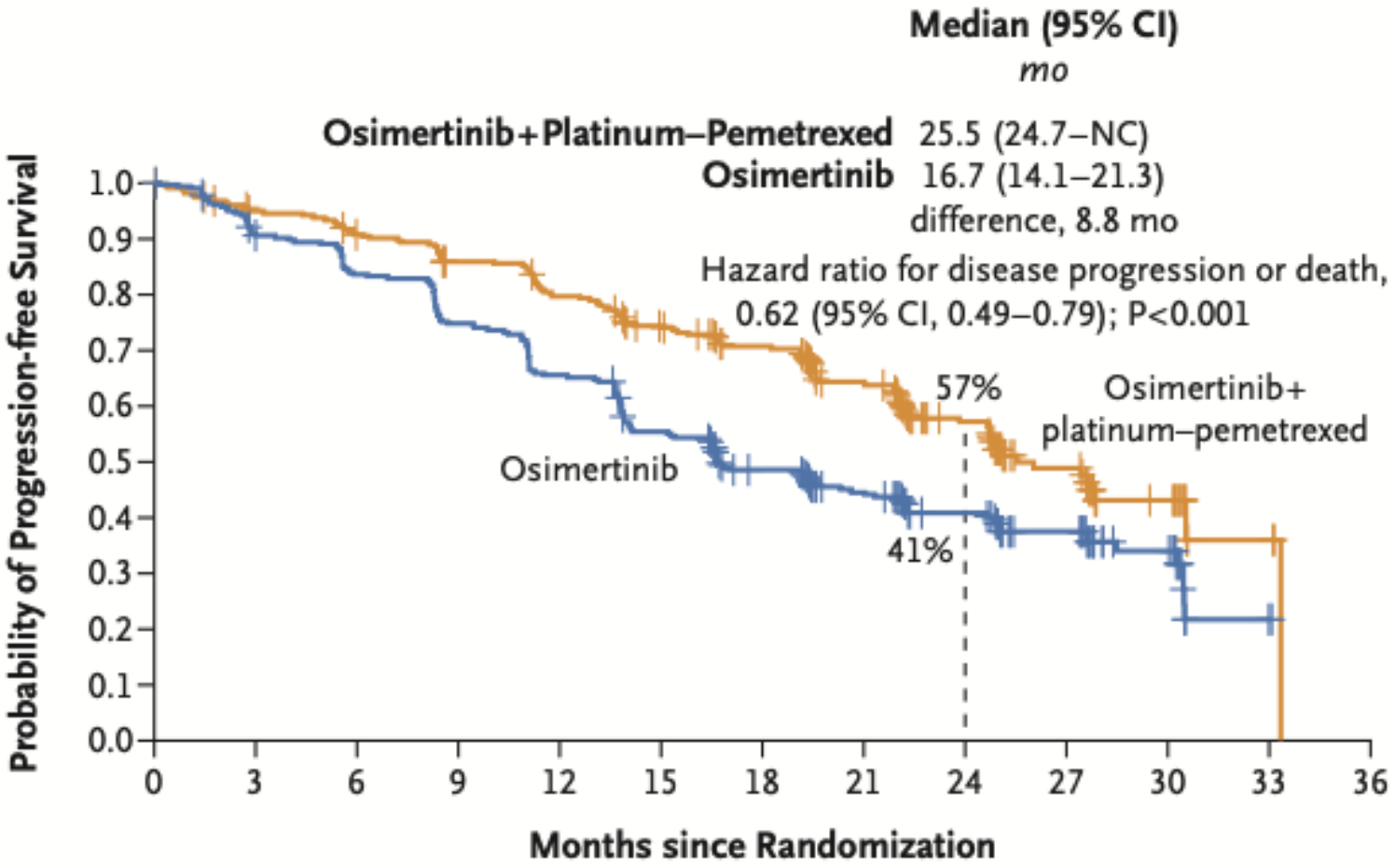
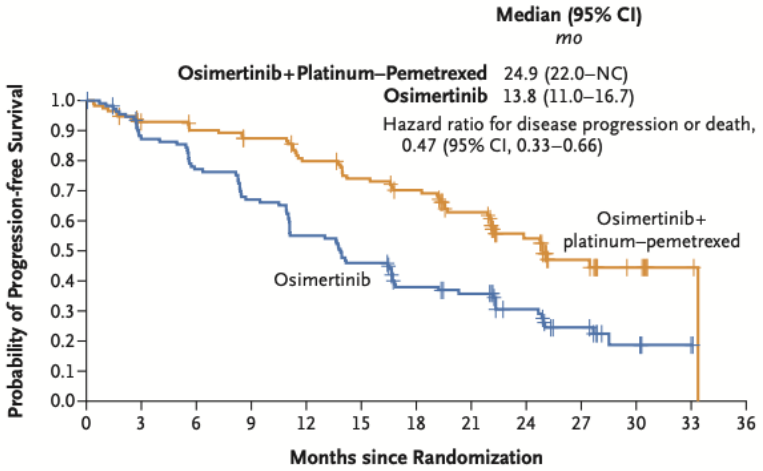
## Addition of platinum chemotherapy to osimertinib improves PFS

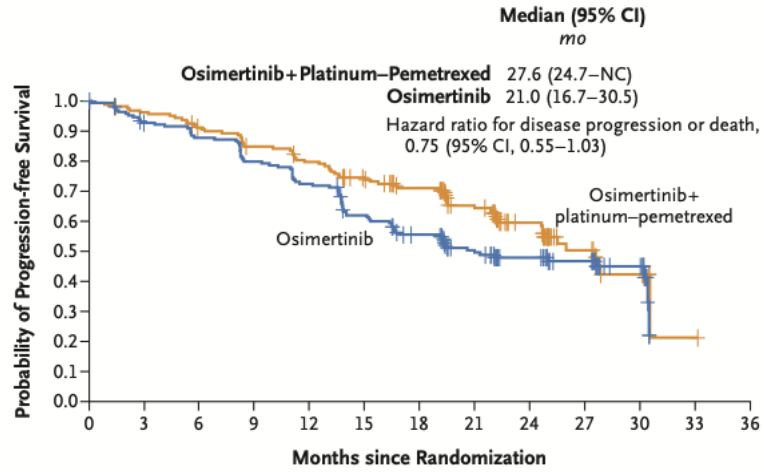



## Greatest benefit for those with baseline CNS metastases

### Baseline CNS metastases




### Without Baseline CNS metastases



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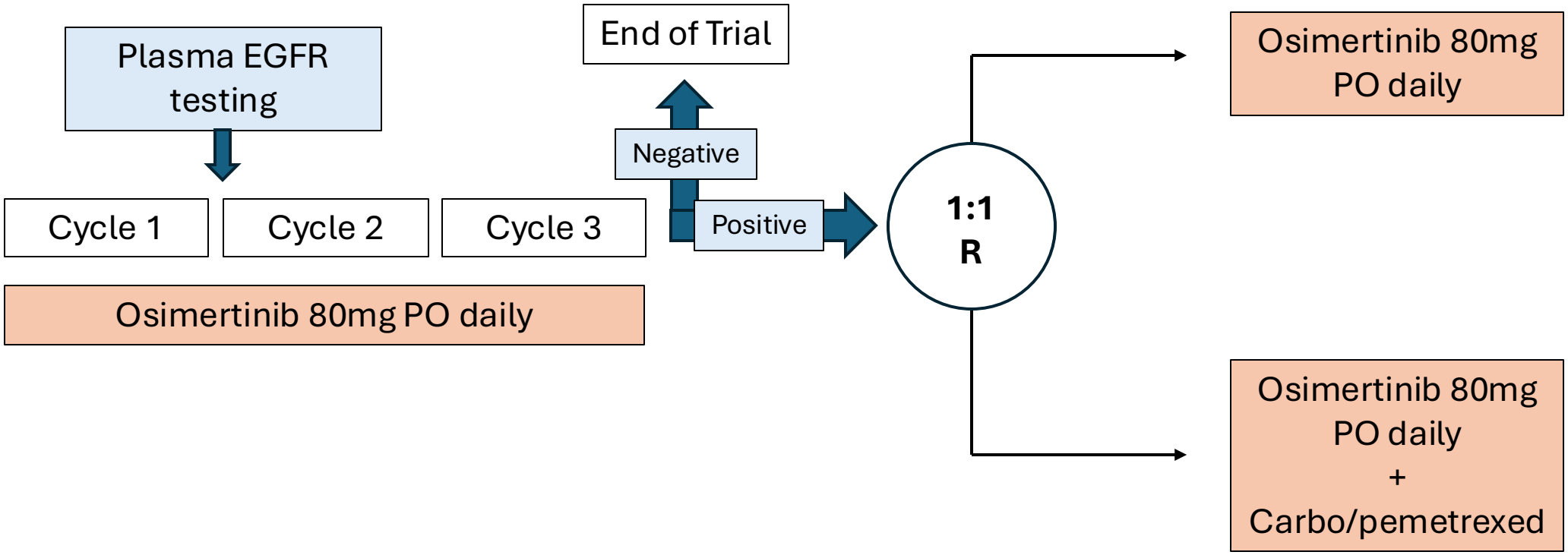
# Can we use cfDNA to identify who would benefit from treatment intensification with chemotherapy?

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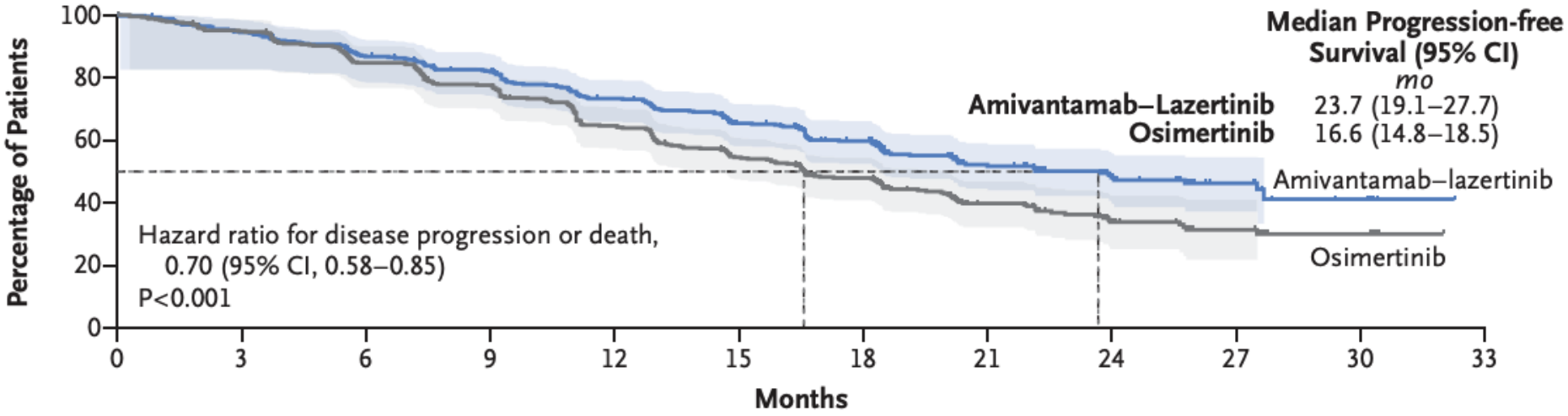
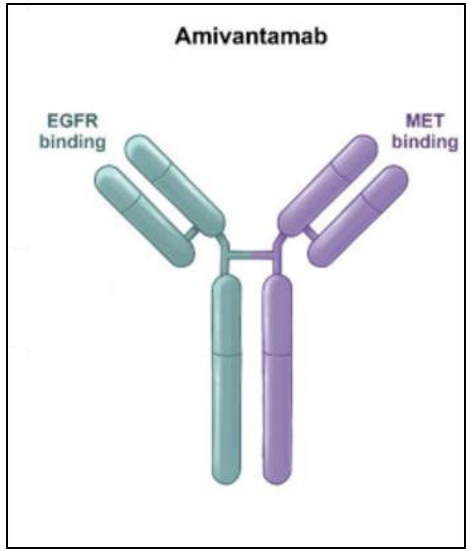
# MARIPOSA – 1L Stage IV EGFR

## Amivantamab-Lazertinib improves PFS compared to osimertinib




## Overall survival data are immature

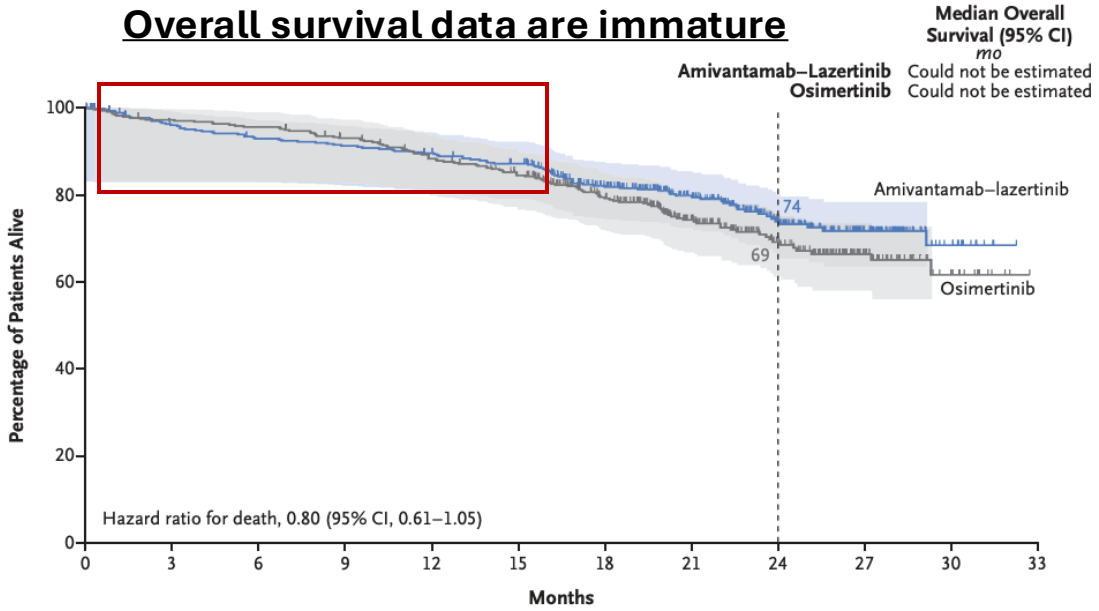



**Table 3. Adverse Events.***

| Event | Amivantamab–Lazertinib (N=421) | | Osimertinib (N=428) | |
|---|---|---|---|---|
| | All | Grade ≥3 | All | Grade ≥3 |
| | *number of patients (percent)* | | | |
| Any event | 421 (100) | 316 (75) | 425 (99) | 183 (43) |
| Any serious event | 205 (49) | | 143 (33) | |
| Any event resulting in death | | 34 (8) | | 31 (7) |
| Event leading to interruption of any trial agent | 350 (83) | | 165 (39) | |
| Event leading to dose reduction of any trial agent | 249 (59) | | 23 (5) | |
| Event leading to discontinuation of any trial agent | 147 (35) | | 58 (14) | |

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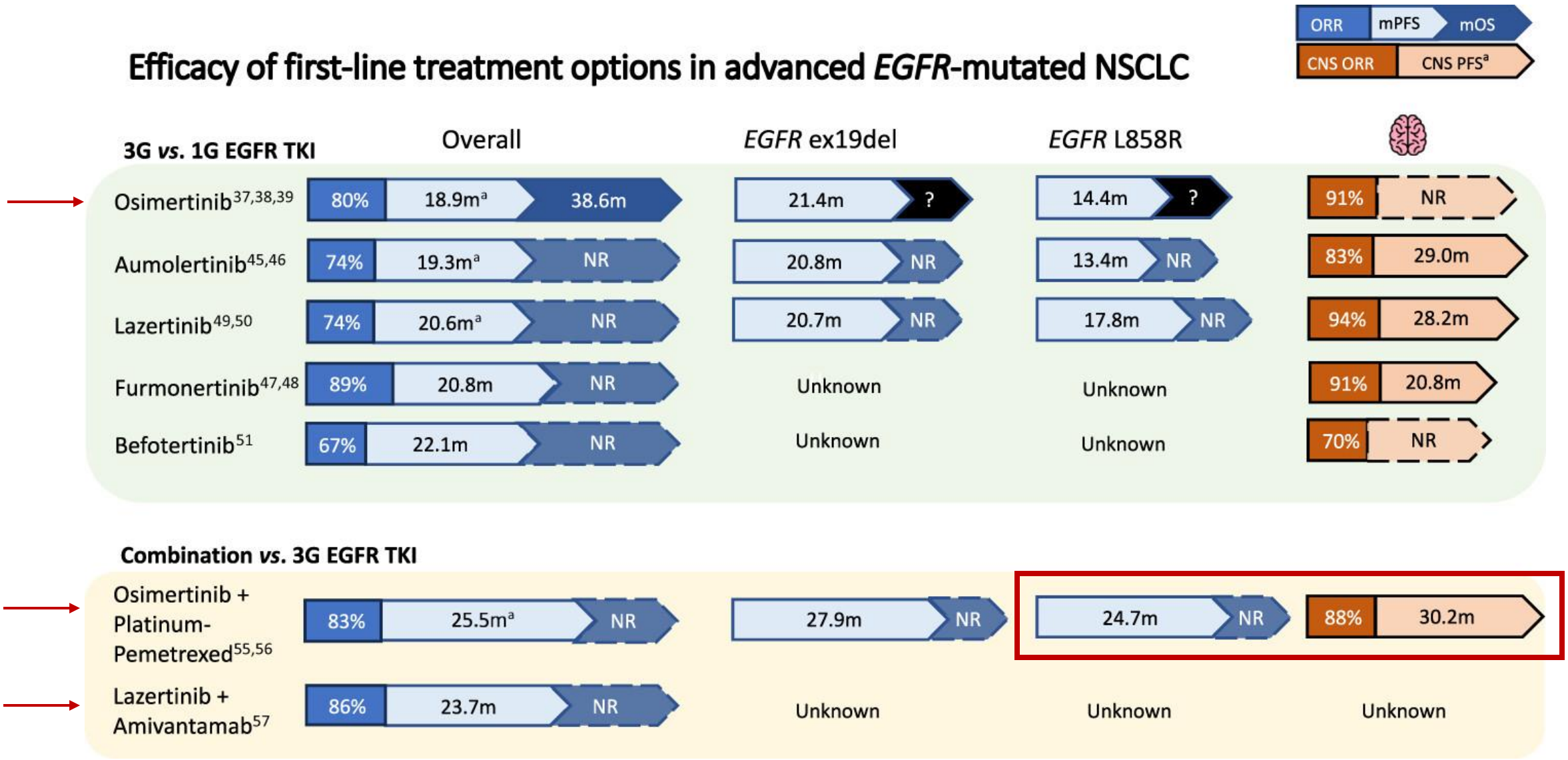
# Stage IV Classical EGFR Mutations, 1L




Saw et al., ASCO Educational Book, 2024

# EGFR Exon 20 Insertions, 1L

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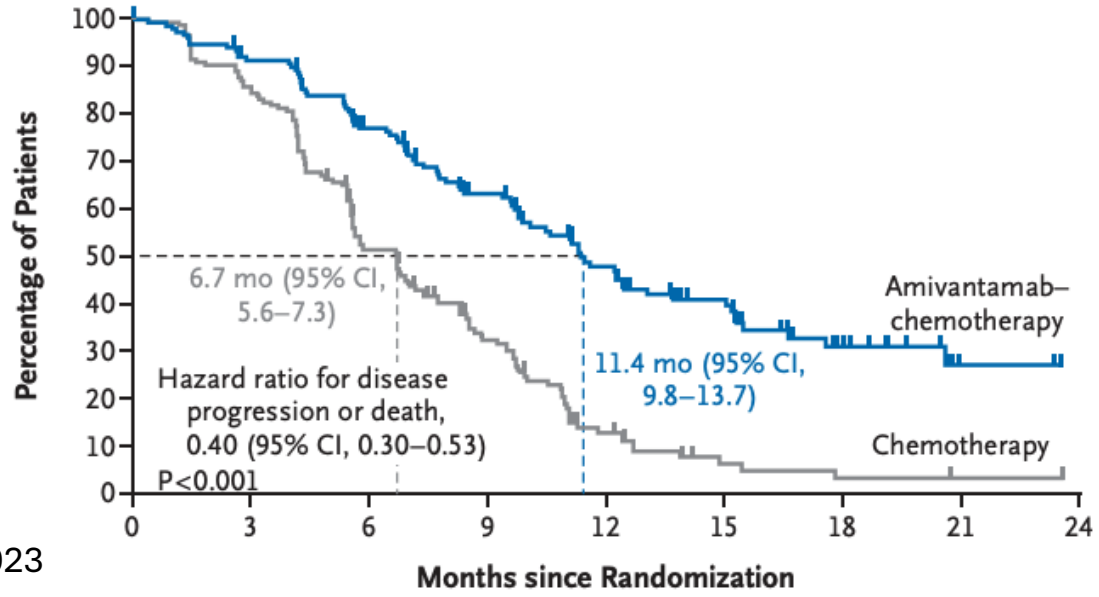
**PAPILLON:**
**Amivantamab + chemotherapy**

**PFS**

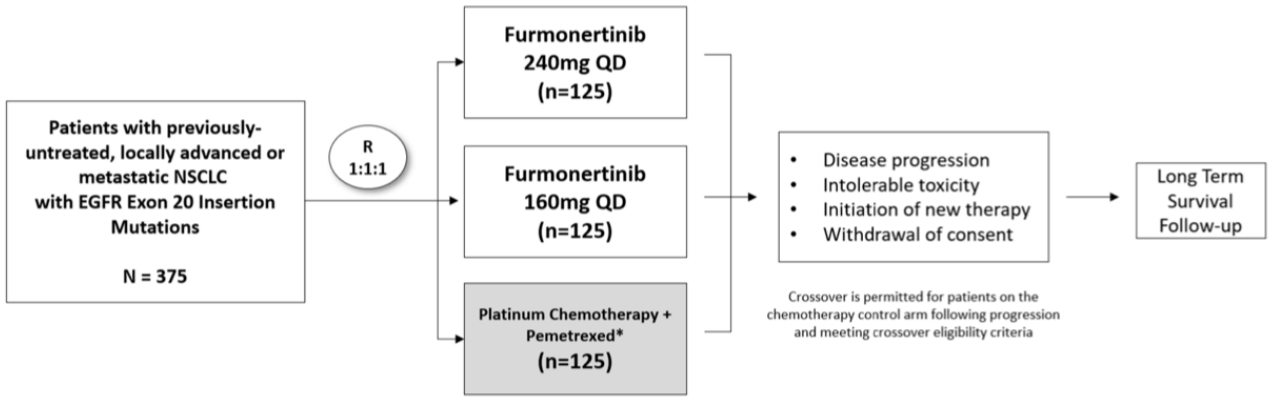



Zhou et al., NEJM, 2023

**Table 3. Adverse Events.***

| Adverse Events | Amivantamab–Chemotherapy (N=151) | | Chemotherapy (N=155) | |
|---|---|---|---|---|
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| | *number of patients (percent)* | | | |
| Any event | 151 (100) | 114 (75) | 152 (98) | 83 (54) |
| Any serious event | 56 (37) | | 48 (31) | |
| Any event resulting in death | 7 (5) | | 4 (3) | |
| Any event leading to interruption of any agent | 104 (69) | | 56 (36) | |
| Interruption in dose of amivantamab | | | | |
| Any | 97 (64) | | | |
| Related to amivantamab† | 63 (42) | | | |
| Any event leading to reduction of any agent | 73 (48) | | 35 (23) | |
| Reduction in dose of amivantamab | | | | |
| Any | 54 (36) | | | |
| Related to amivantamab† | 54 (36) | | | |
| Any event leading to discontinuation of any agent | 36 (24) | | 16 (10) | |
| Discontinuation of amivantamab | | | | |
| Any | 17 (11) | | | |
| Related to amivantamab† | 10 (7) | | | |
| Discontinuation of all agents because of adverse events‡ | 12 (8) | | 12 (8) | |

**FURMO-004:**
**Furmonertinib versus chemotherapy**




***Global, Phase 3 trial is ongoing***

# Stage IV Classical EGFR Mutations, 2L+

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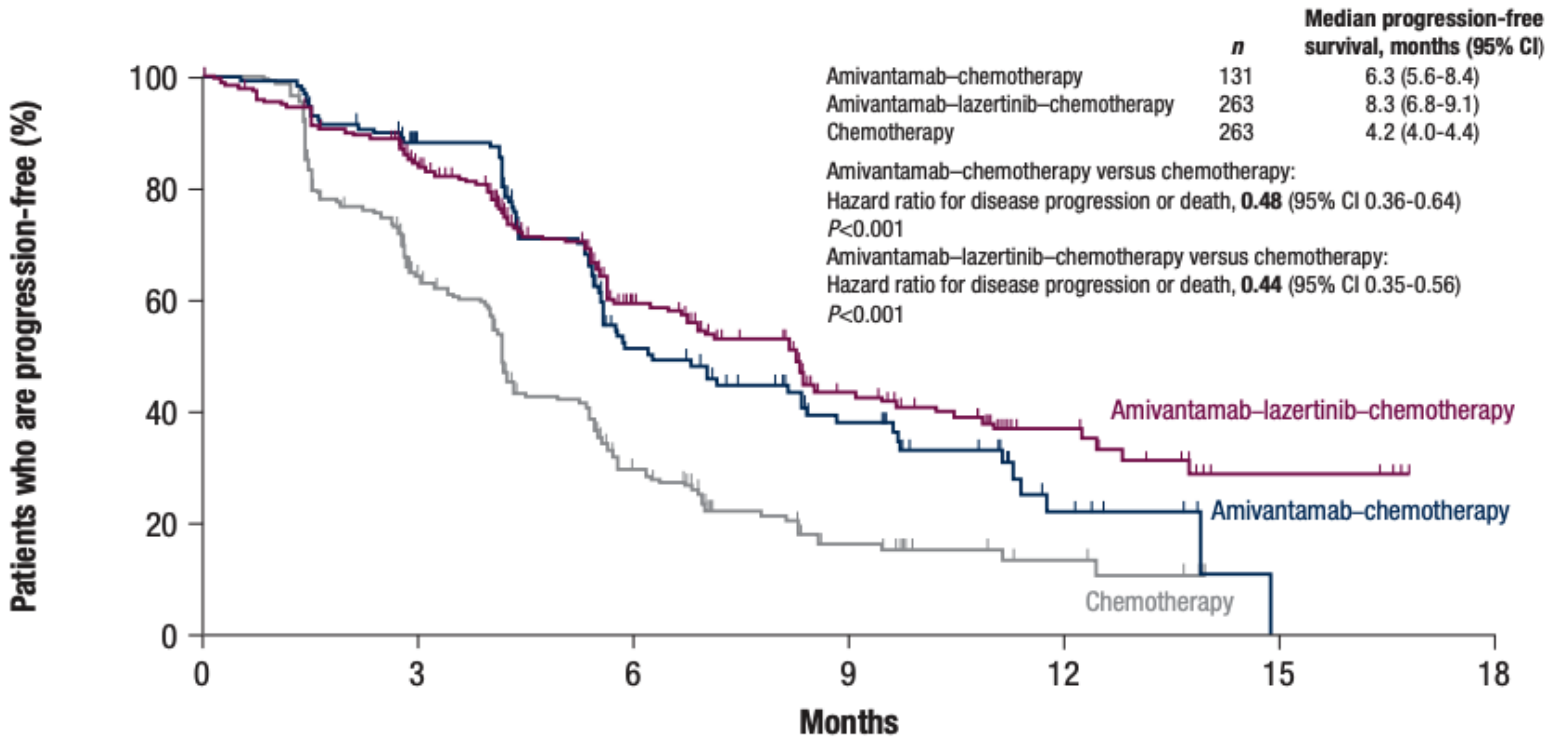
**MARIPOSA-2:**
**Amivantamab + chemotherapy**

**ESMO 2024 Median OS from IA2**
**Ami-chemo: 17.7 months**
**Chemo: 15.3 months**
Numerically improved with ami-chemo, did not yet meet prespecified significance




**Amivantamab + chemotherapy very promising in the 2L+ setting.**

**Too much toxicity when Lazertinib is added to the amivantamab + chemotherapy**

**Table 3. Treatment-emergent adverse events**

| Event, *n* (%) | Chemotherapy (*n* = 243) | Amivantamab–chemotherapy (*n* = 130) | Amivantamab–lazertinib–chemotherapy (*n* = 263) |
|---|---|---|---|
| Any event | 227 (93) | 130 (100) | 263 (100) |
| Grade ≥3 | 117 (48) | 94 (72) | 242 (92) |
| Any serious event | 49 (20) | 42 (32) | 137 (52) |
| Any event resulting in death | 3 (1) | 3 (2) | 14 (5) |
| Any event leading to: | | | |
| Interruptions of any study agent | 81 (33) | 84 (65) | 202 (77) |
| Reductions of any study agent | 37 (15) | 53 (41) | 171 (65) |
| Discontinuations of any study agent | 9 (4) | 24 (18) | 90 (34) |

Passaro et al., Annals of Oncology, 2024

# Stage IV Classical EGFR Mutations, 2L+

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**HARMONI-A:**
**Ivonescimab + chemotherapy**

**Locally advanced or metastatic non-squamous NSCLC:**

- → Positive sensitive EGFR mutation
- → Progressed on 1st/2nd generation EGFR-TKI with negative T790, or on 3rd generation EGFR-TKI
- → ECOG = 0 or 1
- → Regardless of PD-L1 expression

Randomization (N~420)

**Group A**
Ivonescimab 20 mg/kg Q3W
+Pemetrexed 500 mg/m² Q3W
+Carboplatin AUC 5 Q3W
4 cycles (3 weeks/cycle)

→ **Group A**
Ivonescimab 20 mg/kg Q3W
+Pemetrexed 500 mg/m² Q3W
Maintenance Period

**Group B**
Placebo Q3W
+Pemetrexed 500 mg/m² Q3W
+Carboplatin AUC 5 Q3W
4 cycles (3 weeks/cycle)

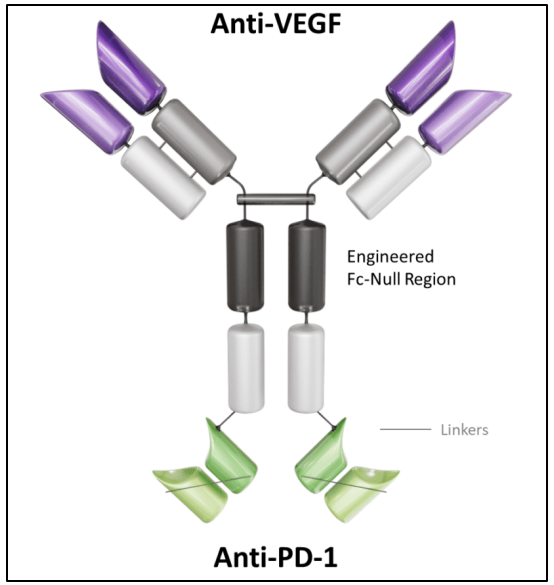
→ **Group B**
Placebo Q3W
+Pemetrexed 500 mg/m² Q3W
Maintenance Period

**Treatment Until**
- → Intolerable toxicity
- → No clinical benefit (Investigator assessment)
- → Initiation of a new anti-tumor therapy
- → Complete 24 months of treatment

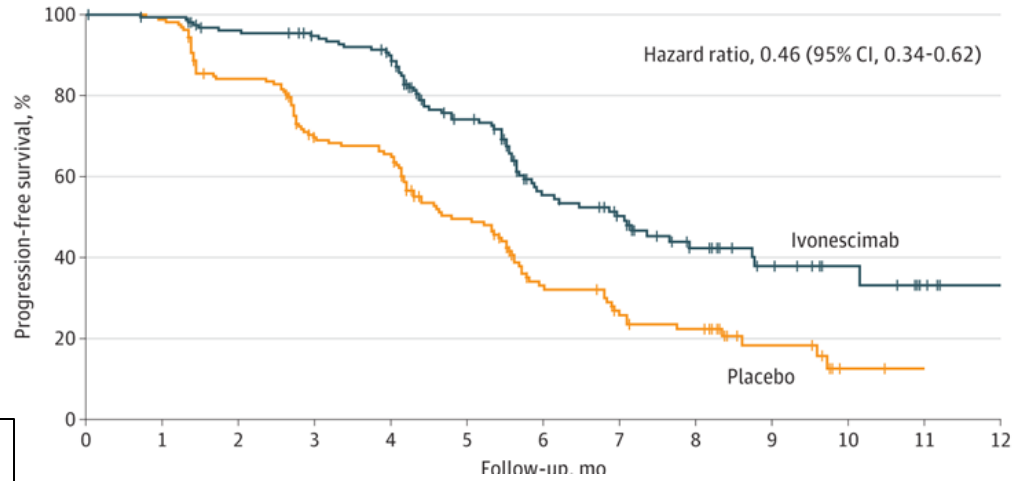
**Endpoints:**

**Primary**
- OS, PFS assessed by irRC

**Secondary**
- ORR by irRC, DoR, safety and tolerability




**Progression Free Survival**




**Promising results with ivonescimab in the 2L+ setting in China.**
**U.S. –based study is ongoing**

Fang et al., JAMA, 2024

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# HARMONi-2: Ivonescimab in NSCLC *without* EGFR or ALK, 1L

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

R 1:1

N=398

**Ivonescimab**
20 mg/kg Q3W (N=198)

**Pembrolizumab**
200 mg Q3W (N=200)

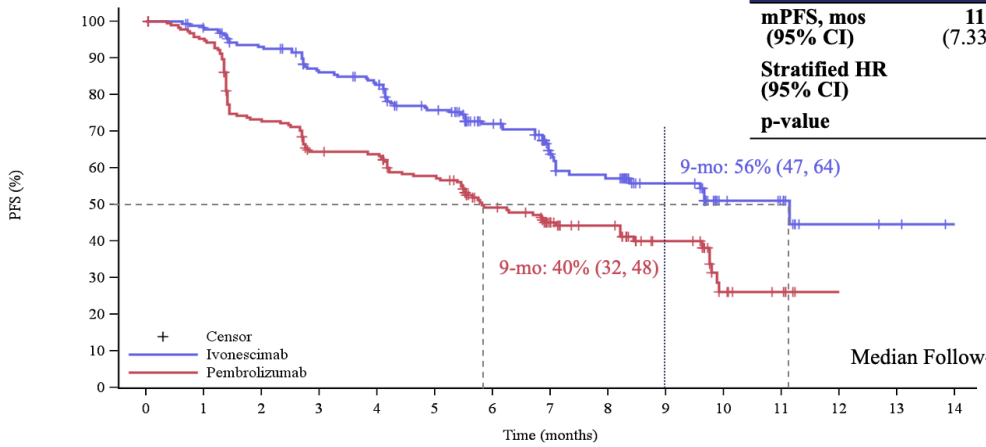
Treatment until no clinical benefit, unacceptable toxicity or up to 24 months

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

**Endpoints**

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

## Primary endpoint: PFS per IRRC



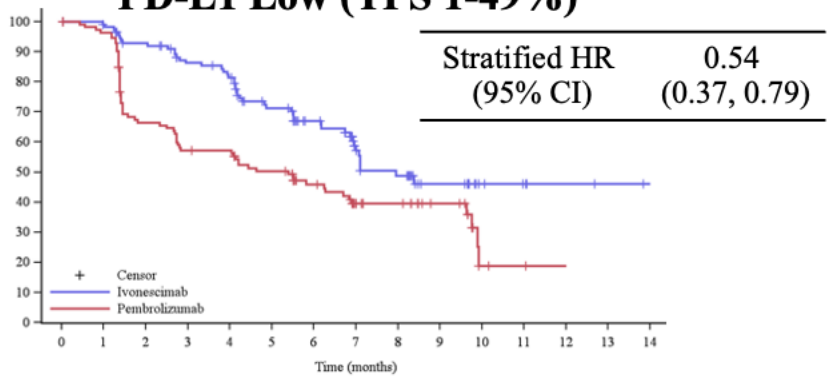

| | Ivonescimab (n = 198) | Pembrolizumab (n = 200) |
|---|---|---|
| **mPFS, mos (95% CI)** | **11.14** (7.33, NE) | 5.82 (5.03, 8.21) |
| **Stratified HR (95% CI)** | **0.51** (0.38, 0.69) | |
| **p-value** | **<0.0001** | |

Median Follow-up: 8.67 months

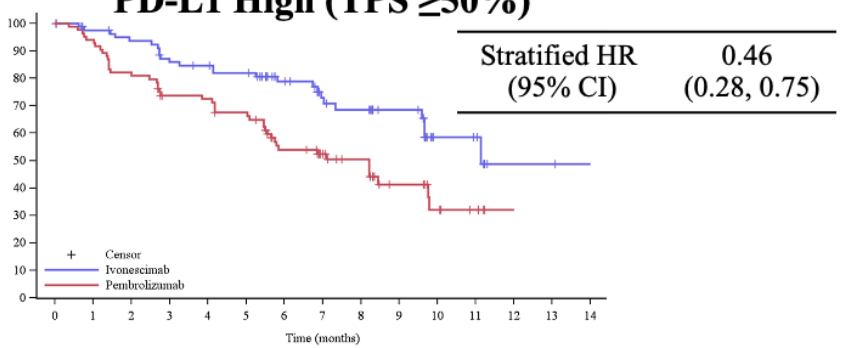
Comparator arm was pembrolizumab alone (no chemotherapy)

## PFS Benefit Observed Across PD-L1 Subgroups

### PD-L1 Low (TPS 1-49%)




### PD-L1 High (TPS ≥50%)




Zhou et al., World Lung, 2024

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# HARMONi-3: Ivonescimab + chemotherapy in squamous NSCLC, 1L

**All PD-L1 subgroups included**

- Untreated metastatic squamous NSCLC
- ECOG 0 or 1

Stratification factors
- Sex (female vs male)
- Age (<65 vs ≥65 years)
- Geographic region: East Asia vs Rest of World
- Liver or brain metastases at study entry (present vs absent)

**Study Endpoints**
Primary endpoints: OS
Secondary endpoints: PFS, ORR, safety and tolerability

(N=400)

R 1:1

**Group A**
Ivonescimab + carboplatin + paclitaxel (or nab-paclitaxel) q3w
(4 cycles: 3 weeks/cycle)

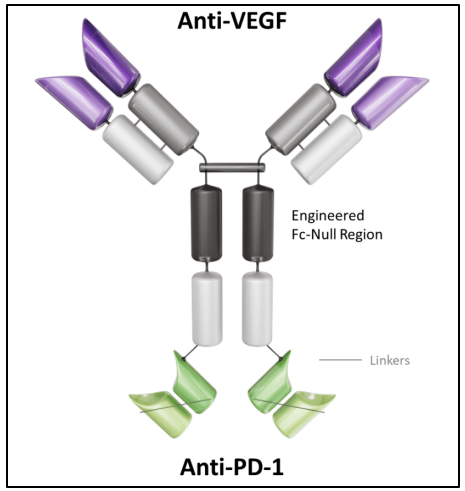
**Group A**
Ivonescimab q3w
(Maintenance up to 24 months)

**Group B**
Pembrolizumab + carboplatin + paclitaxel (or nab-paclitaxel) q3w
(4 cycles: 3 weeks/cycle)

**Group B**
Pembrolizumab q3w
(Maintenance up to 24 months)

**Treatment until:**
- Intolerable toxicity, or
- No clinical benefit, or
- Initiation of a new anti-tumor therapy, or
- 24 months of treatment

Safety and Survival Follow up




**Randomization is 1:1 compared to chemotherapy + pembrolizumab**

***Phase 3 clinical trial is ongoing***

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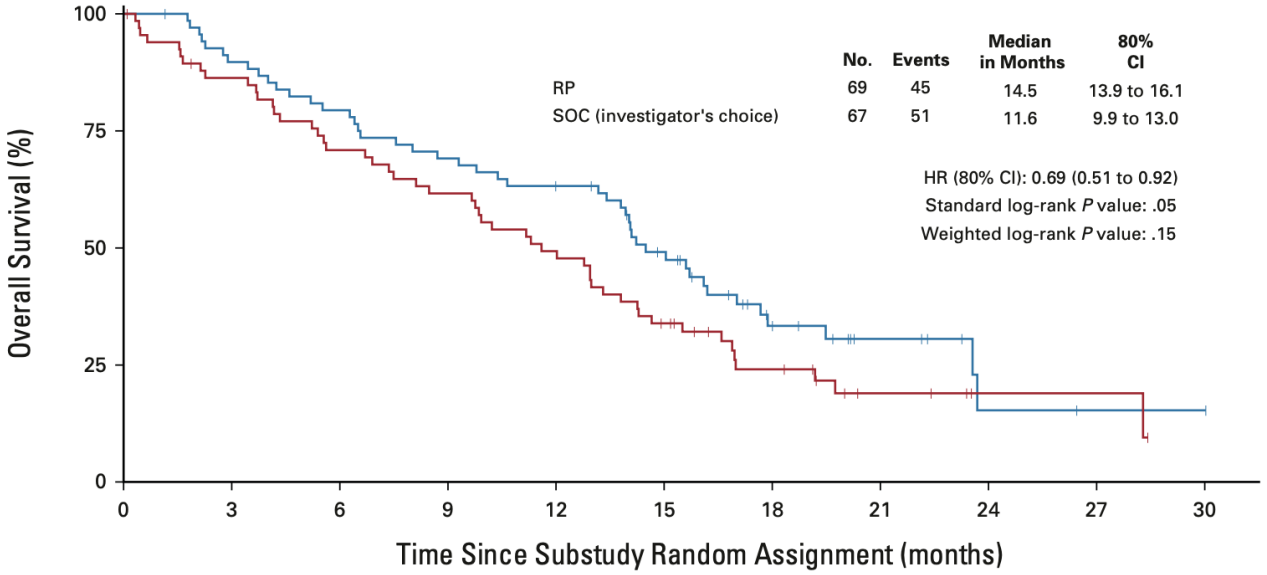
# PRAGMATICA: A New Approach to Clinical Trials

## S1800A: Combination of anti-VEGF (ramucirumab) + PD-1 inhibitor (pembrolizumab) improves OS among patients previously treated with PD-(L)1 inhibitors




Reckamp et al., JCO, 2022

## PRAGMATICA Clinical Trial

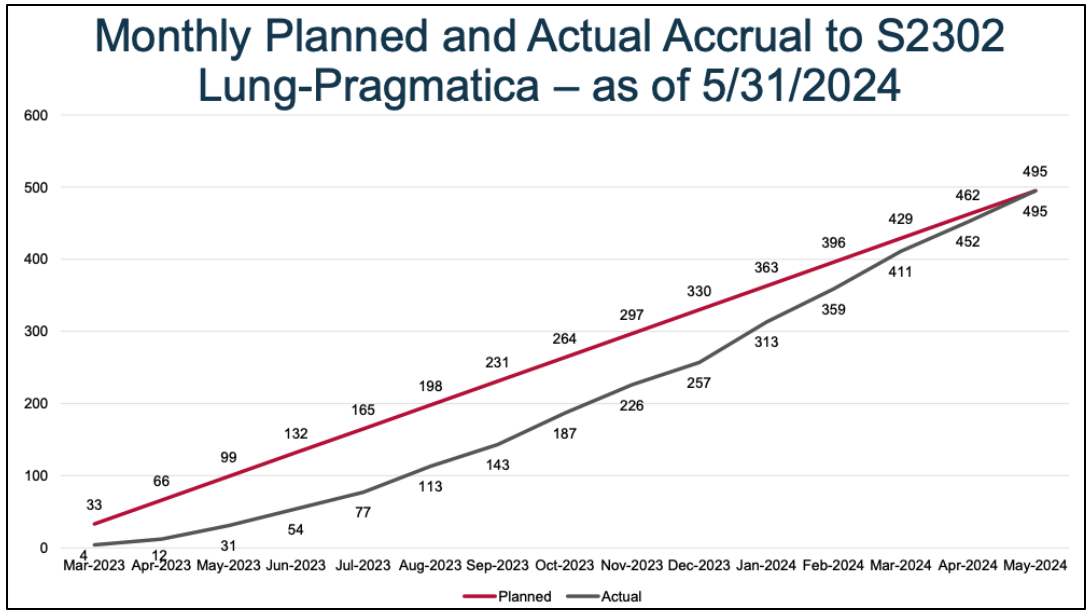
Patients with Stage IV or recurrent non-small cell lung cancer

Randomization

Arm A: Investigator's Choice of Standard of Care [A]

Arm B: Ramucirumab + Pembrolizumab

Primary outcome: OS
All imaging assessments per investigator



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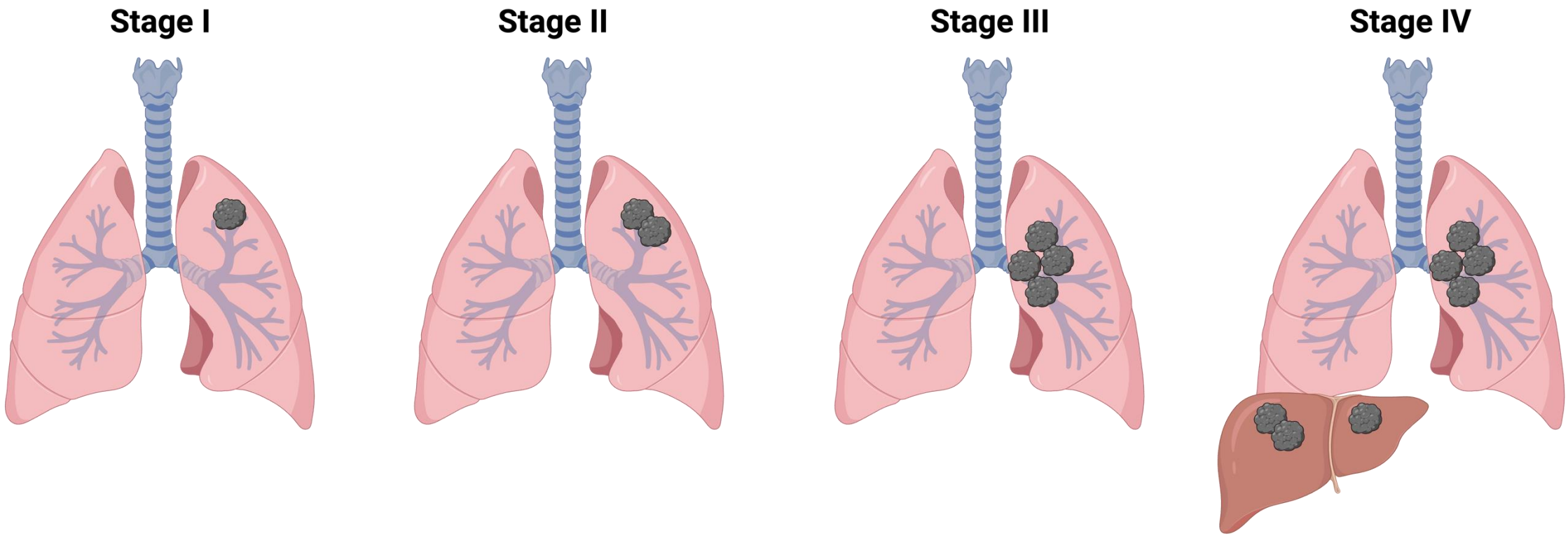


**Bringing therapeutic advances to earlier stages to potentially increase chances of providing a cure.**

# LAURA Clinical Trial

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## Osimertinib after chemoRT for unresectable, locally advanced NSCLC

### LAURA Phase 3 double-blind study design (NCT03521154)

**Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT†**

**Key inclusion criteria:**
- ≥18 years old (Japan: ≥20 years)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Max 6 weeks from last dose of CRT to randomization
- **Patients with asymptomatic radiation pneumonitis / pneumonitis post-CRT were eligible**

**Osimertinib 80 mg, QD**

**Randomization 2:1 (N=216)**

**Stratification by:**
**cCRT vs sCRT**
**Stage IIIA vs stage IIIB / IIIC**
**China vs non-China**

**Placebo, QD**

Treatment until BICR-assessed PD (per RECIST v1.1), toxicity, or other discontinuation criteria met

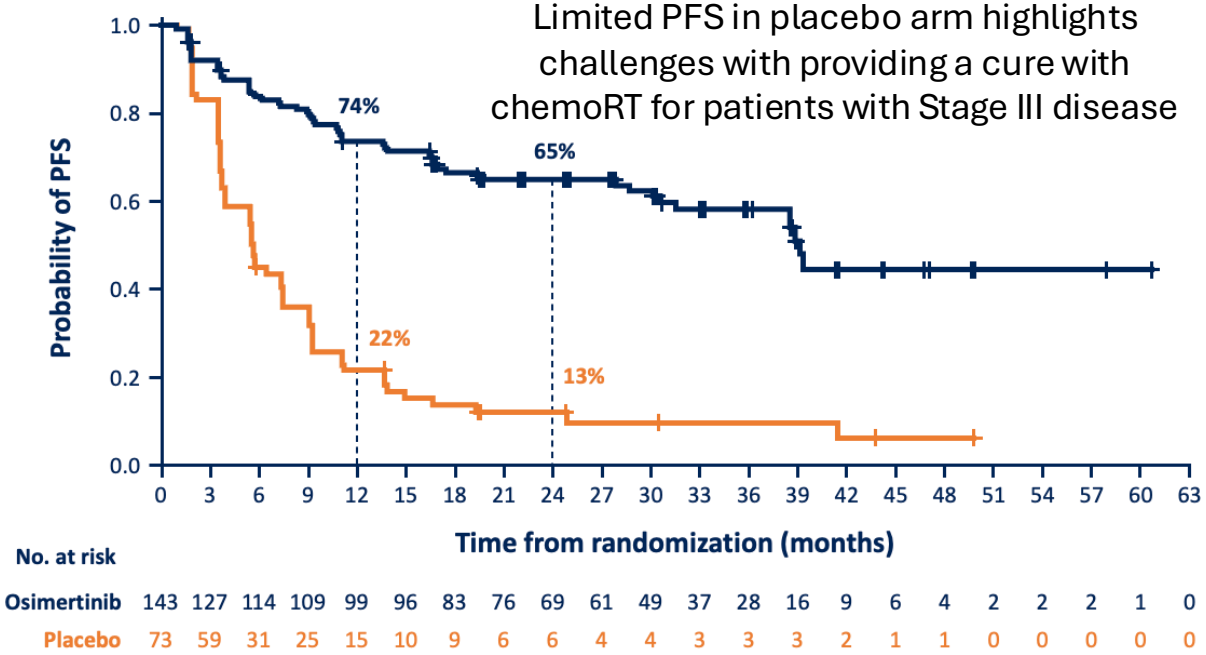
**Open-label osimertinib offered to both treatment arms after BICR-confirmed PD§**

**Tumor assessments**
- Chest CT / MRI and brain MRI
- Baseline, Q8W to Week 48, then Q12W until BICR-assessed progression

**Safety assessments**
- Baseline, Weeks 2, 4 and Q4W to Week 24, Q8W to Week 48, then Q12W until treatment discontinuation
  - Reporting of AEs and causality were investigator-assessed
- All AEs, SAEs and AESIs reported from screening to 28-day follow-up post-discontinuation

**Endpoints**
- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1
- **Secondary endpoints included:** OS, CNS PFS, **safety**

### LAURA primary analysis




- Also, trend for improved OS with osimertinib, but data not mature
- Incidence of Grade ≥3 adverse events: 35% osimertinib versus 12% in placebo group

Lu et al., NEJM 2024

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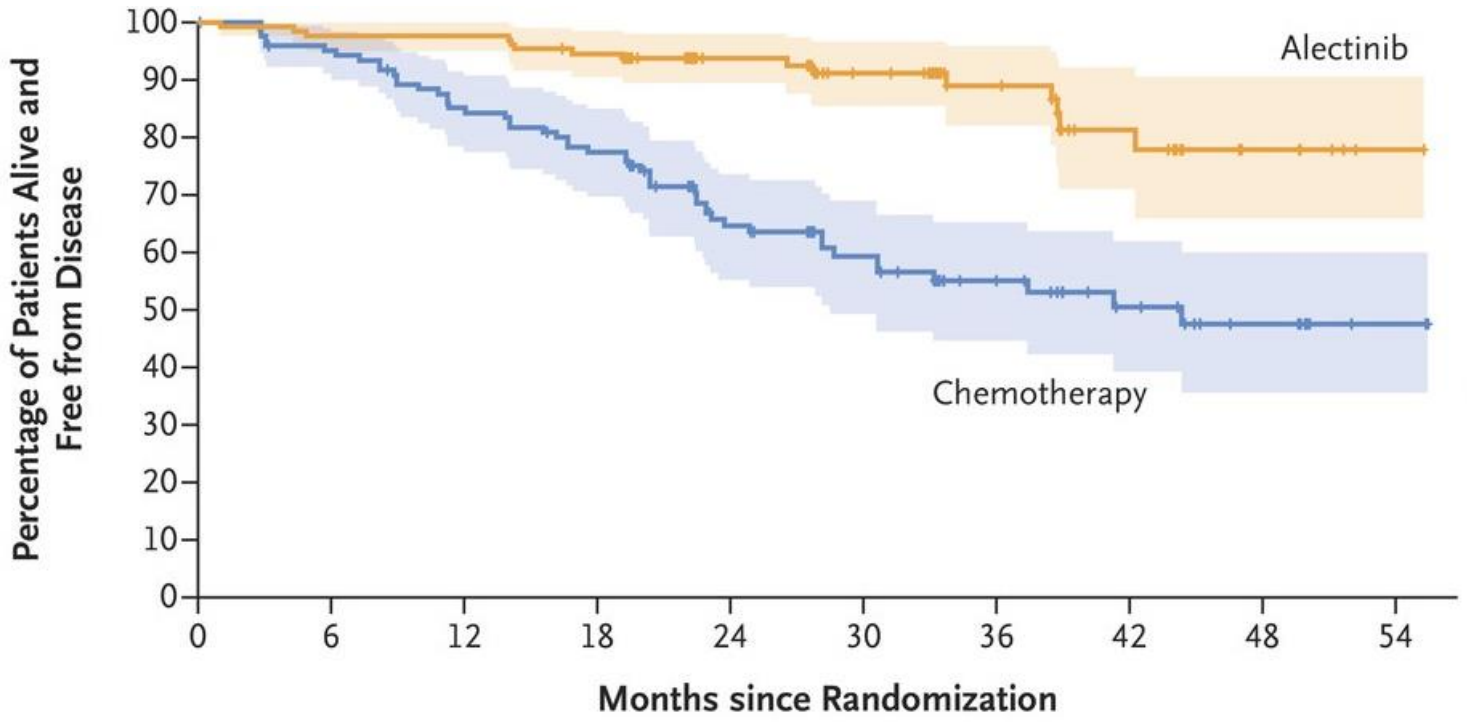
# This was a big year for EGFR...

| | Classical EGFR Mutations | EGFR Exon 20 Insertion |
|---|---|---|
| **Stage III** | • Indefinite osimertinib after chemoradiation | |
| **Stage IV 1L Setting** | • Osimertinib<br>• Osimertinib + chemotherapy<br>• Osimertinib + chemo based on cfDNA*<br>• Amivantamab + Lazertinib | • Amivantamab + chemotherapy<br>• Furmonertinib* |
| **Stage IV 2L + Setting** | • Amivantamab + chemotherapy<br>• Ivonescimab + chemotherapy* | • Zipalertinib* |

*Denotes approaches currently in clinical trials

# ALINA Clinical Trial

**Marked PFS benefit with adjuvant alectinib compared to chemotherapy after resection of Stage IB-IIIA NSCLC**




| | Median Disease-free Survival (95% CI) *mo* |
|---|---|
| Alectinib | Not reached |
| Chemotherapy | 41.3 (28.5–NE) |

Hazard ratio for disease recurrence or death, 0.24 (95% CI, 0.13–0.43)
P<0.001

| | ALINA | ADAURA |
|---|---|---|
| Disease | Resected stage IB-IIIA ALK rearranged NSCLC | Resected Stage IB-IIIA EGFR mutated NSCLC |
| Treatment | Alectinib (2 years) without chemotherapy | Osimertinib (3 years); 60% received chemotherapy |

***Should we be giving adjuvant chemotherapy before alectinib?***

Wu et al., NEJM 2024

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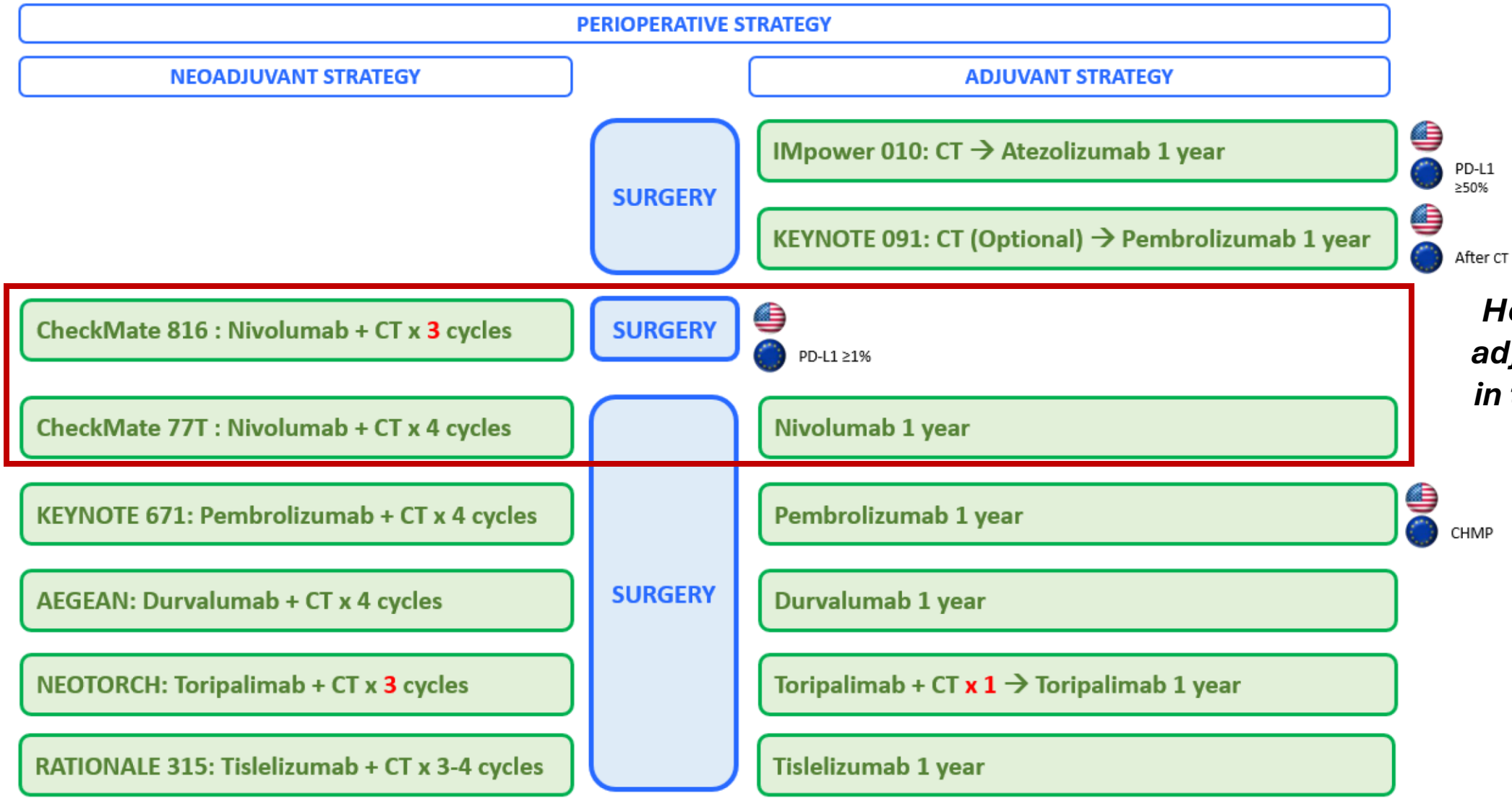
# Neoadjuvant versus Perioperative




***How critical is this adjuvant nivolumab in the perioperative approach?***

Lavaud et al., Cancers 2024

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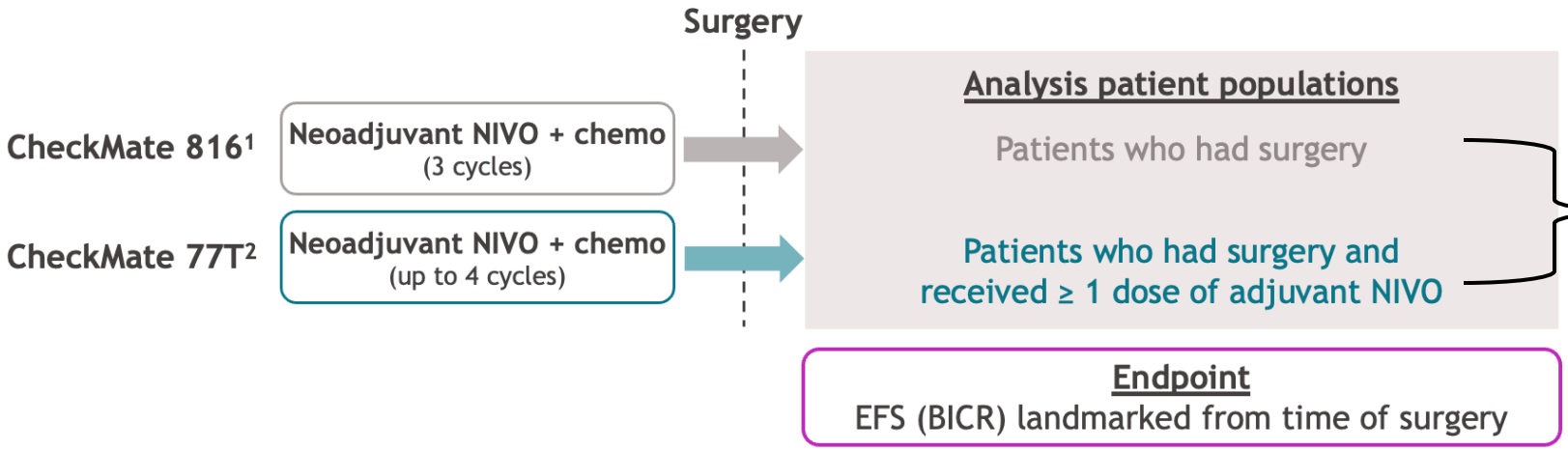
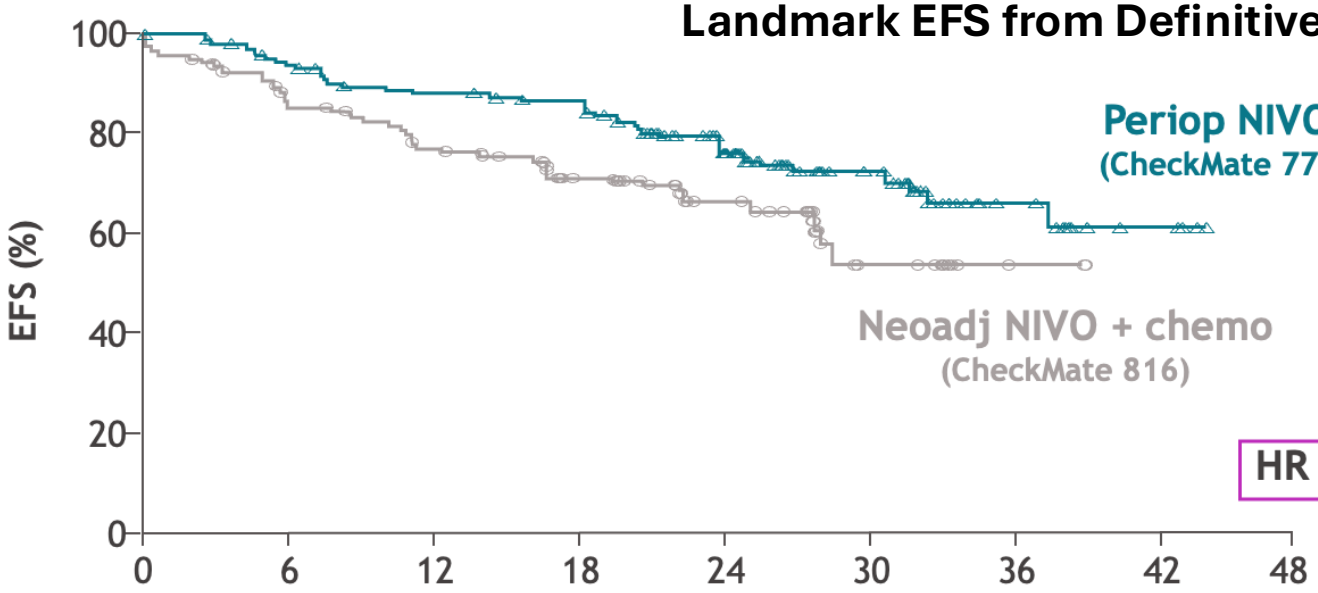
# Perioperative versus neoadjuvant nivolumab




**These are different populations – patients who received 1 dose of adjuvant nivolumab were well enough after surgery to receive treatment**

## Landmark EFS from Definitive Surgery




| | Weighted (ATE)[b] | |
|---|---|---|
| | Periop NIVO[a] (n = 139.4[c]) | Neoadj NIVO + chemo (n = 147.5[c]) |
| HR (95% CI) | 0.61 (0.39-0.97) | |

Forde et al., World Lung, 2024

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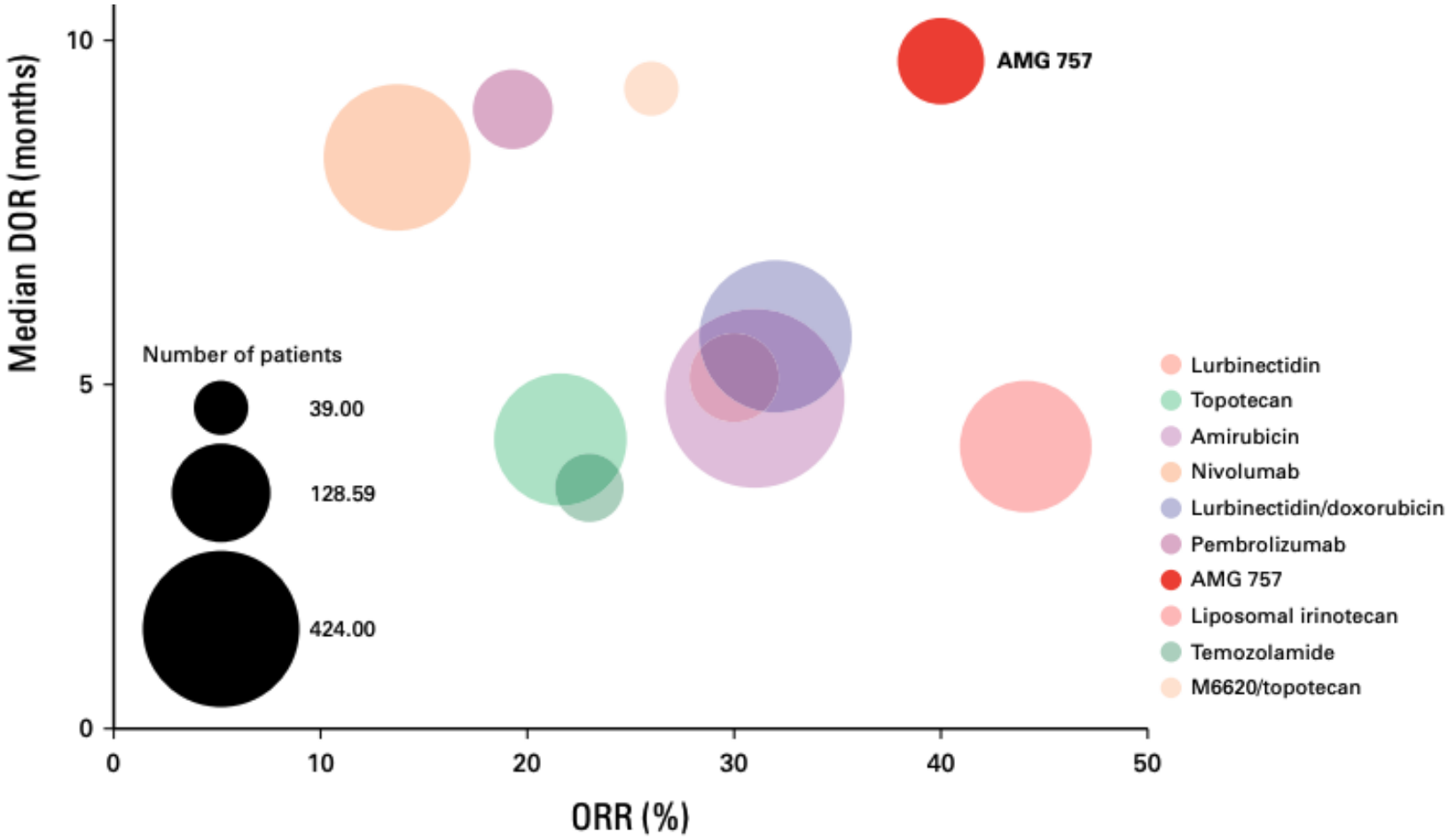
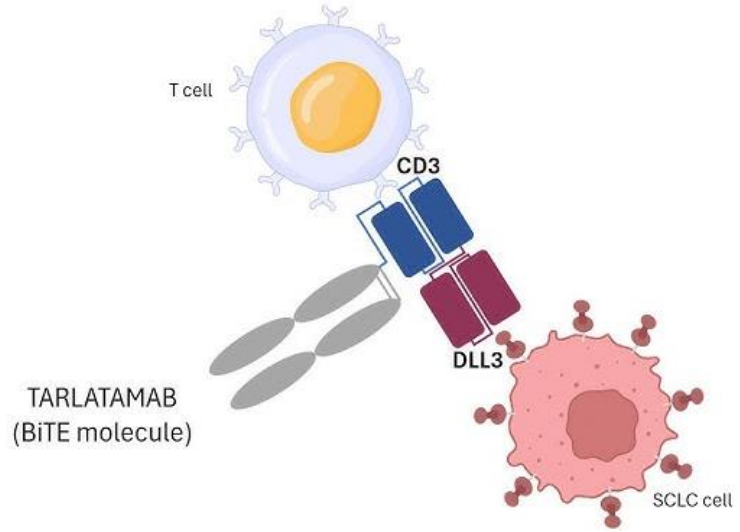
# Small Cell Lung Cancer: New Hope, New Challenges

## 2L+ SCLC Durations of Response Across Clinical Trials




## Tarlatamab (AMG 757) is a Bispecific T Cell Engager (BiTE)




Desai and Thomas, JCO Oncology Advances, 2024

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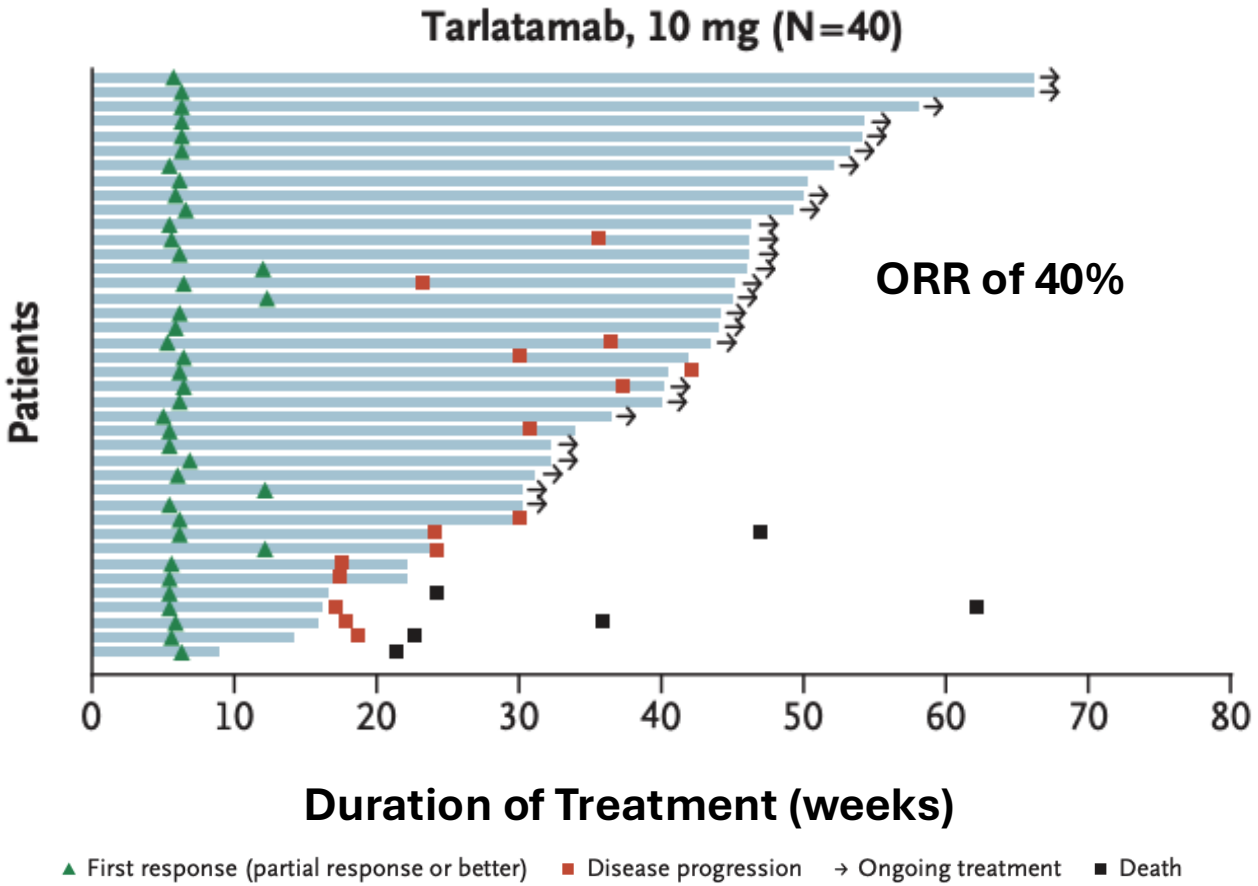
# FDA grants accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer




**ORR of 40%**

| | |
|---|---|
| Previous use of PD-L1 or PD-1 inhibitor — no. (%) | |
| Yes | 73 (73) |
| No | 27 (27) |
| Duration of sensitivity to platinum-based treatment — no. (%)§ | |
| <90 days | 28 (28) |
| 90 to <180 days | 22 (22) |
| ≥180 days | 20 (20) |
| Unknown | 30 (30) |
| DLL3 expression — no./total no. (%)¶ | 80/83 (96) |

**Table 3. Adverse Events (Safety Analysis Population).***

| Adverse Events | Tarlatamab, 10 mg | |
|---|---|---|
| | Parts 1 and 2 (N=99) | Part 3, Reduced Monitoring (N=34) |
| Cytokine-release syndrome† | | |
| Overall | 49 (49) | 19 (56) |
| Grade ≥3 severity | 0 | 1 (3) |
| Serious | 26 (26) | 5 (15) |
| Leading to tarlatamab discontinuation | 0 | 0 |
| Fatal | 0 | 0 |
| ICANS and associated neurologic events‡ | | |
| Overall | 7 (7) | 4 (12) |
| Grade ≥3 severity | 0 | 0 |
| Serious | 2 (2) | 2 (6) |
| Leading to tarlatamab discontinuation | 1 (1) | 0 |
| Fatal | 0 | 0 |

Ahn et al., NEJM, 2023

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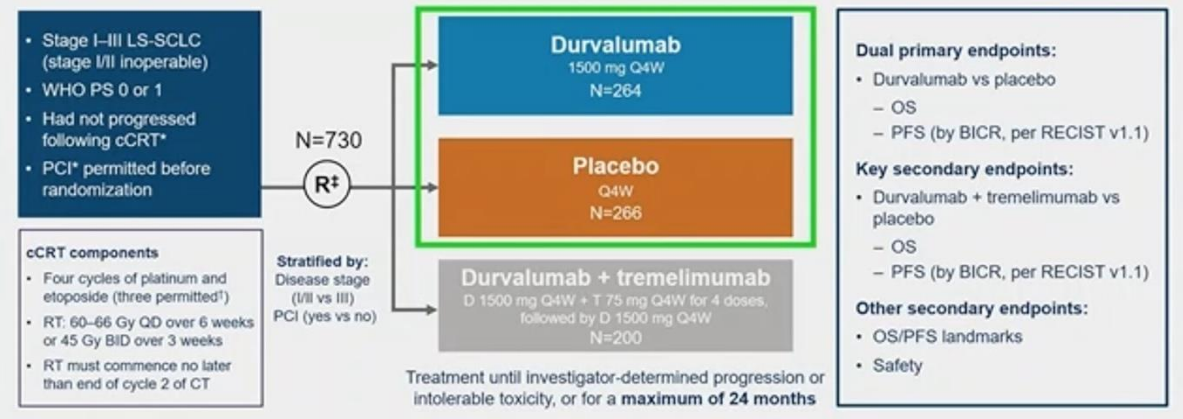
# Improved Overall Survival with Consolidative Durvalumab

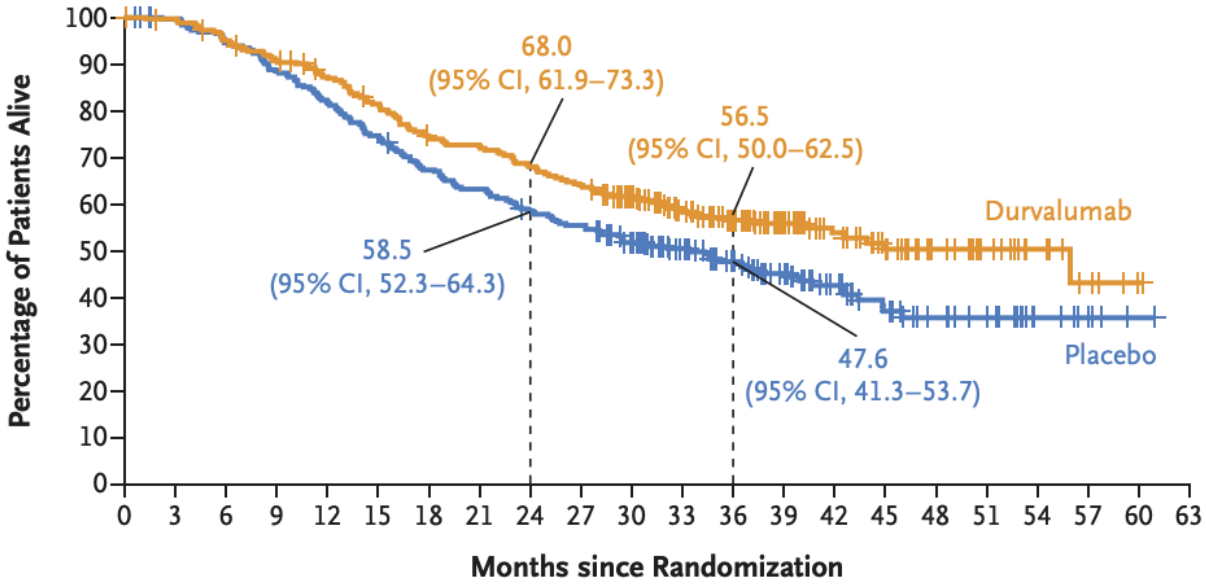
## ADRIATIC: Phase 3, randomized, double-blind RCT




| | No. of Deaths/ Total No. (%) | Median Overall Survival (95% CI) |
|---|---|---|
| | | *mo* |
| **Durvalumab** | 115/264 (43.6) | 55.9 (37.3–NR) |
| **Placebo** | 146/266 (54.9) | 33.4 (25.5–39.9) |

Stratified hazard ratio for death, 0.73 (98.321% CI, 0.54–0.98)
P=0.01

## 2 years of consolidative durvalumab associated with improved OS




Desai and Thomas, JCO Oncology Advances, 2024

# Key Practice Changes in Lung Cancer

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## This was a big year…

1L treatment of driver mutated, Stage IV NSCLC

- **Lorlatinib** for most people (ALK+)
- **Evolving 1L treatment options** other than osimertinib (classical EGFR+)
- **Amivantamab + chemo** (EGFR exon 20)

**Osimertinib indefinitely** after chemoradiation (EGFR+)

**Adjuvant alectinib** for 2 years after surgical resection (ALK+)

**Tarlatamab** 2L+ for SCLC

**Consolidative durvalumab** for 2 years after chemoRT (early-stage SCLC)

**These advances are only possible through clinical trials**