Lung Cancer: 2024 Year In Review

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knowledge changing life

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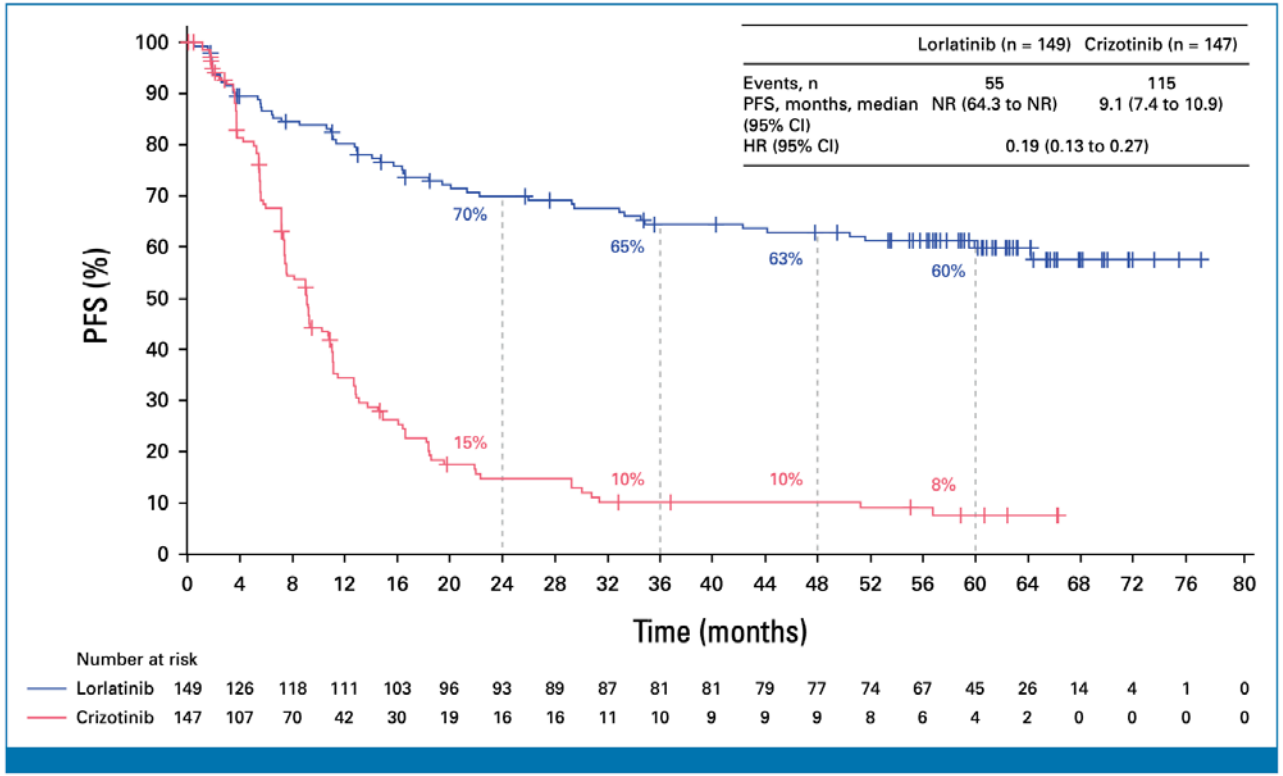
Objectives

- Review Practice Changing Data for Treatment of Lung Cancer
  - Non-small cell lung cancer
    - Lorlatinib for front-line metastatic ALK+ NSCLC
    - Consolidative Osimertinib for Unresectable EGFR-mutated NSCLC
  - Small Cell Lung Cancer
    - Consolidative Durvalumab for Limited Stage SCLC
    - Tarlatamab for relapsed Extensive Stage SCLC
- Discuss Modern Controversies in Lung Cancer
  - Perioperative systemic therapy for resectable NSCLC
  - Combination therapies for metastatic, EGFR-mutated NSCLC
    - Chemotherapy + Osimertinib or Amivantamab + Lazertinib for 1L metastatic, EGFR-mutated NSCLC
    - Chemotherapy + Amivantamab for 2nd line metastatic, EGFR-mutated NSCLC

New Standards of Care

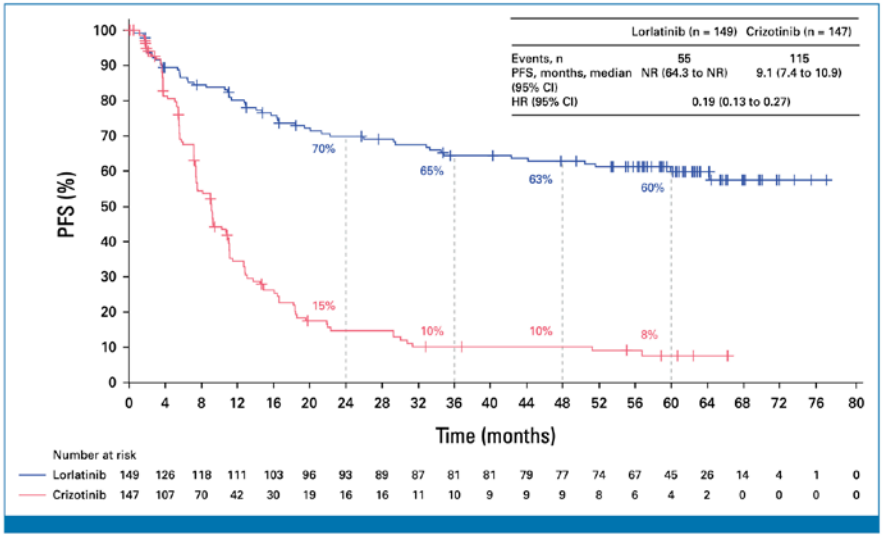
First-line lorlatinib for metastatic ALK+ NSCLC

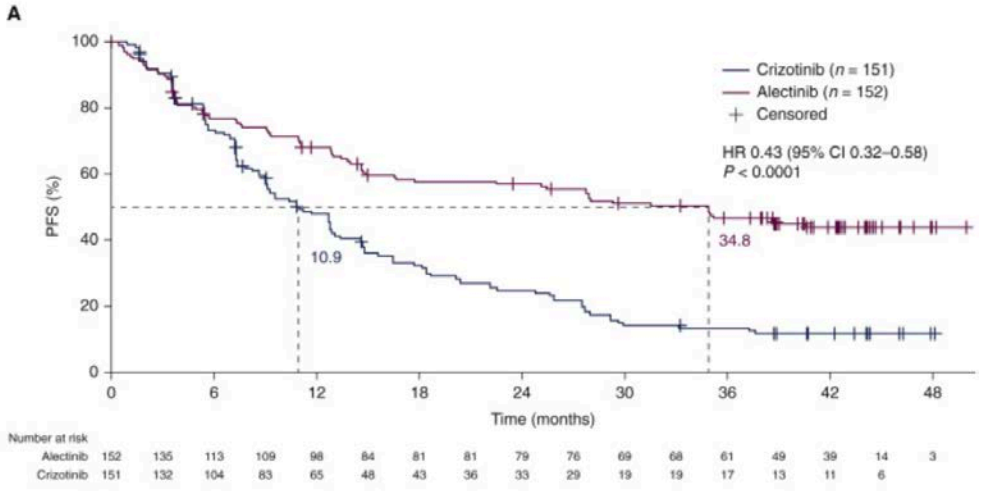
Lorlatinib for treatment naïve, metastatic, ALK+ NSCLC (CROWN)



Solomon et al, J Clin Oncol 2024;42:3400-3409.

Lorlatinib vs Alectinib (CROWN vs ALEX) – Lorlatinib PFS numerically better

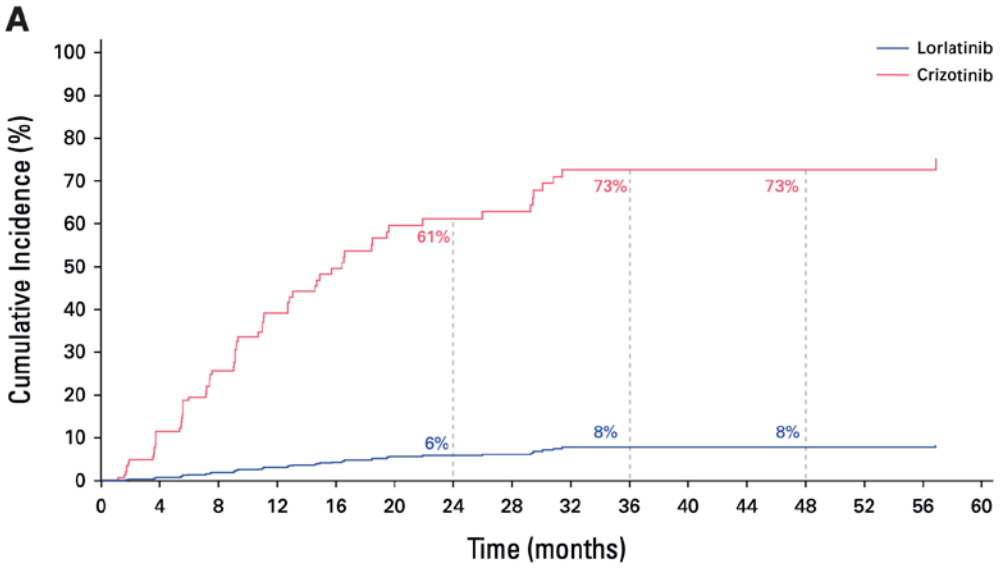




Solomon et al, J Clin Oncol 2024;42:3400-3409.
Mok et al, Ann Oncol 2020;31:1056-1064.

Lorlatinib has excellent CNS activity

	Lorlatinib	Crizotinib
Patients with measurable and/or nonmeasurable baseline brain metastases, No.	35	38
Confirmed intracranial ORR, % (95% CI)	60 (42 to 76)	11 (3 to 25)
Best overall response, No. (%)		
Complete response	17 (49)	2 (5)
Partial response	4 (11)	2 (5)
Stable disease	0	4 (11)
Noncomplete response or nonprogressive disease	13 (37)	22 (58)
Progressive disease	1 (3)	5 (13)
Not evaluable	0	3 (8)
ORR for lorlatinib *v* crizotinib, OR (95% CI)	12.02 (3.23 to 54.92)	
Duration of intracranial response, months, median (95% CI)	NR (NR to NR)	12.8 (7.5 to NR)
Duration of intracranial response ≥2 years, n/N (%)	17/21 (81)	0



Solomon et al, J Clin Oncol 2024;42:3400-3409.

Lorlatinib has unique side effect profile

TABLE 2. Summary of AEs

Safety Population	Lorlatinib (n = 149)	Crizotinib (n = 142)
All-causality AEs, No. (%)		
Any grade	149 (100)	140 (99)
Grade 3/4	115 (77)	81 (57)
Grade 5	14 (9)	7 (5)
Serious	65 (44)	45 (32)
Leading to temporary drug discontinuation	92 (62)	68 (48)
Leading to dose reduction	34 (23)	21 (15)
Leading to permanent drug discontinuation	16 (11)	15 (11)
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)

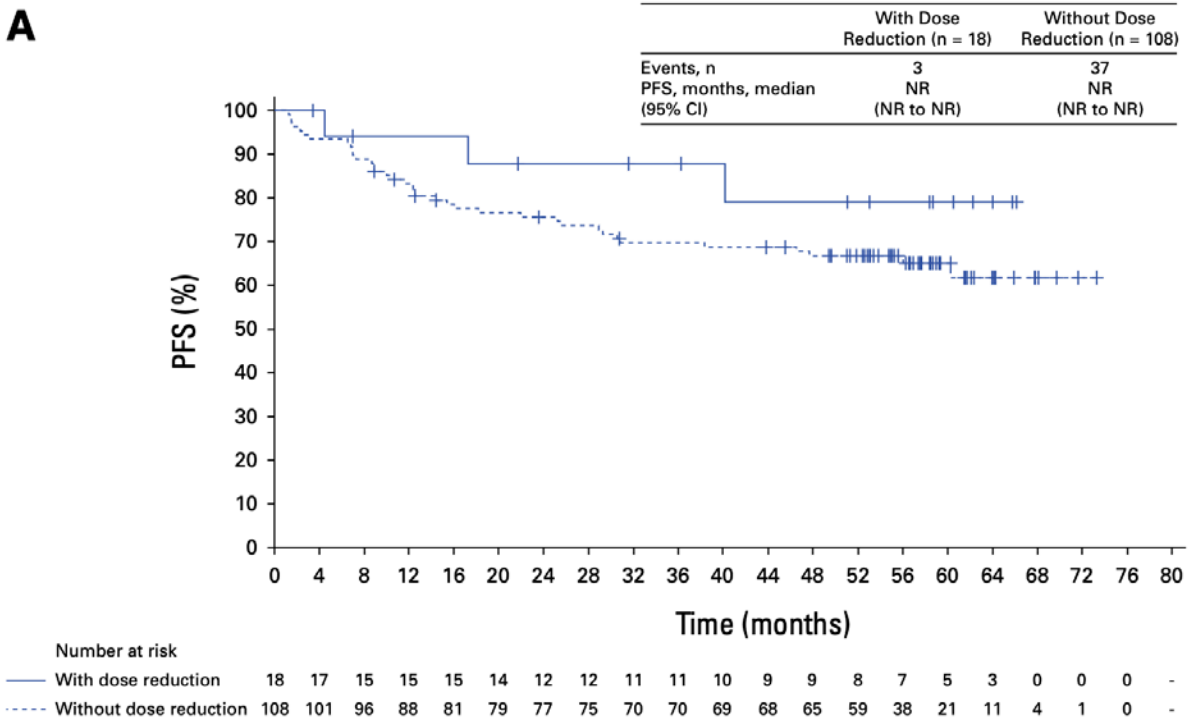
Abbreviation: AE, adverse event.

TABLE A4. Summary of CNS AEs in the Lorlatinib Group

	Lorlatinib (n = 149)				
Cluster Term	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AEs, No. (%)	63 (42)	36 (24)	18 (12)	8 (5)	1 (1)
Cognitive effects[a]	41 (28)	25 (17)	11 (7)	5 (3)	0
Mood effects[b]	31 (21)	17 (11)	12 (8)	2 (1)	0
Speech effects[c]	9 (6)	6 (4)	2 (1)	1 (1)	0
Psychotic effects[d]	8 (5)	5 (3)	1 (1)	1 (1)	1 (1)

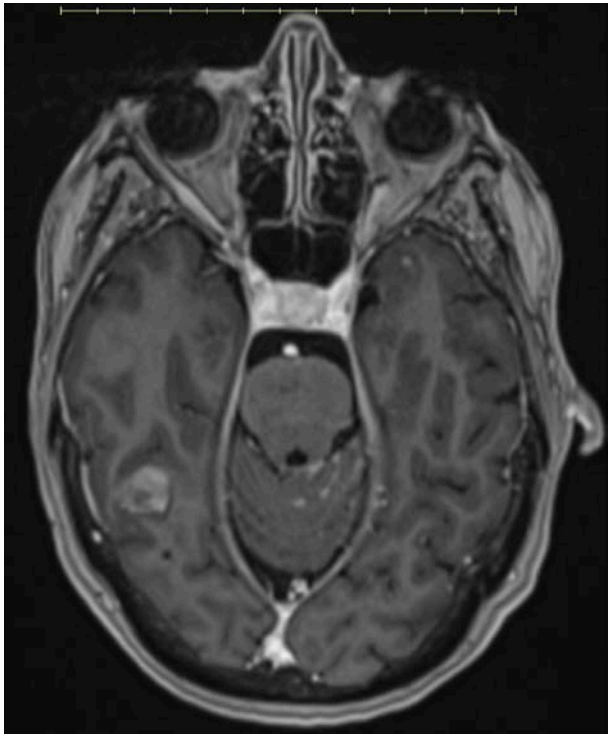
Solomon et al, J Clin Oncol 2024;42:3400-3409.

Lorlatinib dose reduction does not impact efficacy



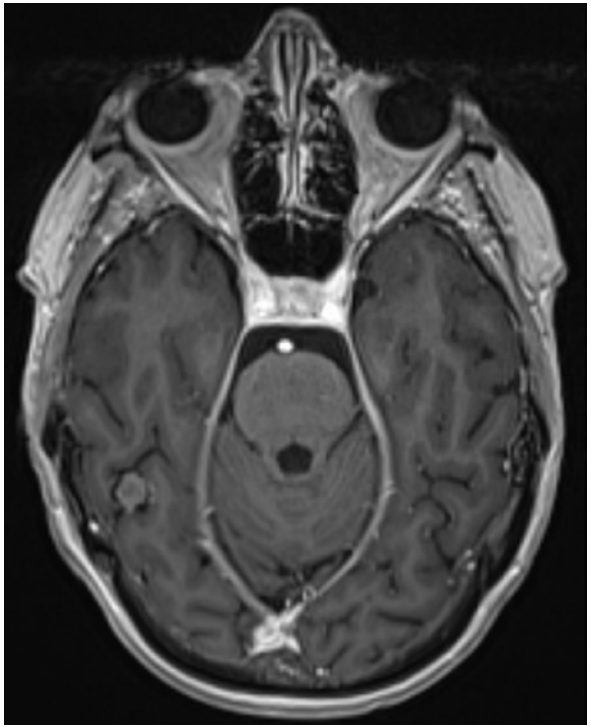
Solomon et al, J Clin Oncol 2024;42:3400-3409.

Lorlatinib Case



Before lorlatinib

70 yo F with ALK+ NSCLC and multiple brain metastases and leptomeningeal disease



2 months after starting lorlatinib

Take Aways - Lorlatinib

- Lorlatinib in treatment naïve, metastatic, ALK+ NSCLC provides historically long PFS and should be considered the new standard of care in this setting

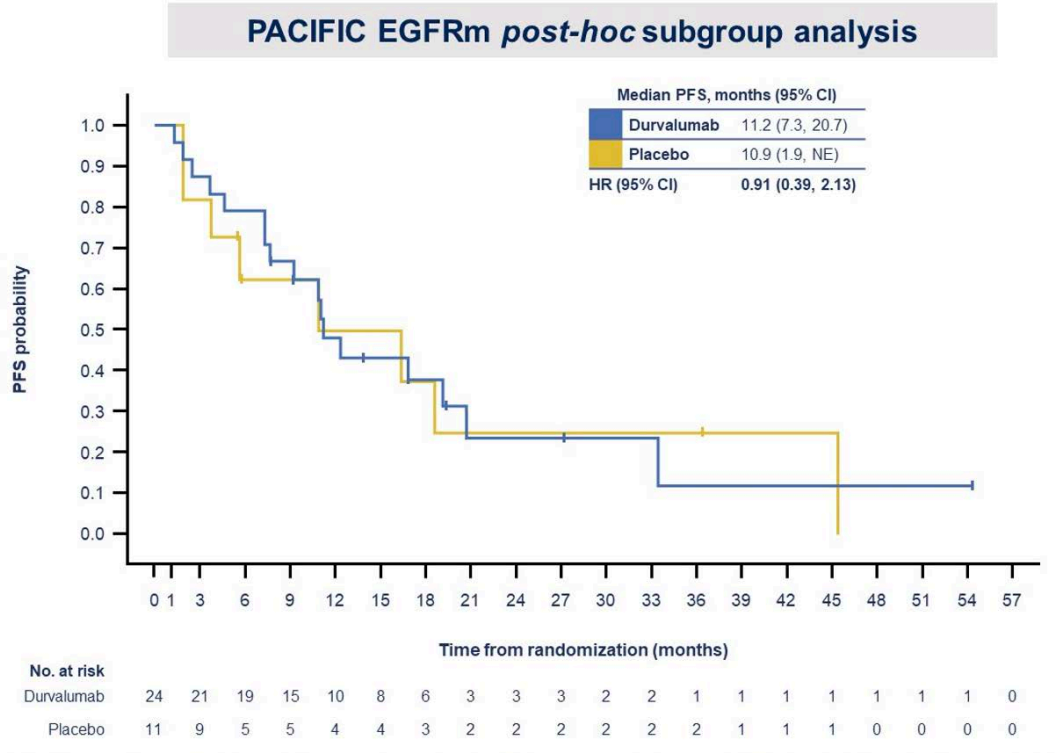
- Side effect profile can be challenging, but manageable with dose reduction.

- Dose reduction does not appear to impact efficacy

Osimertinib consolidation after chemoradiation for unresectable, EGFR-mutated NSCLC (LAURA)

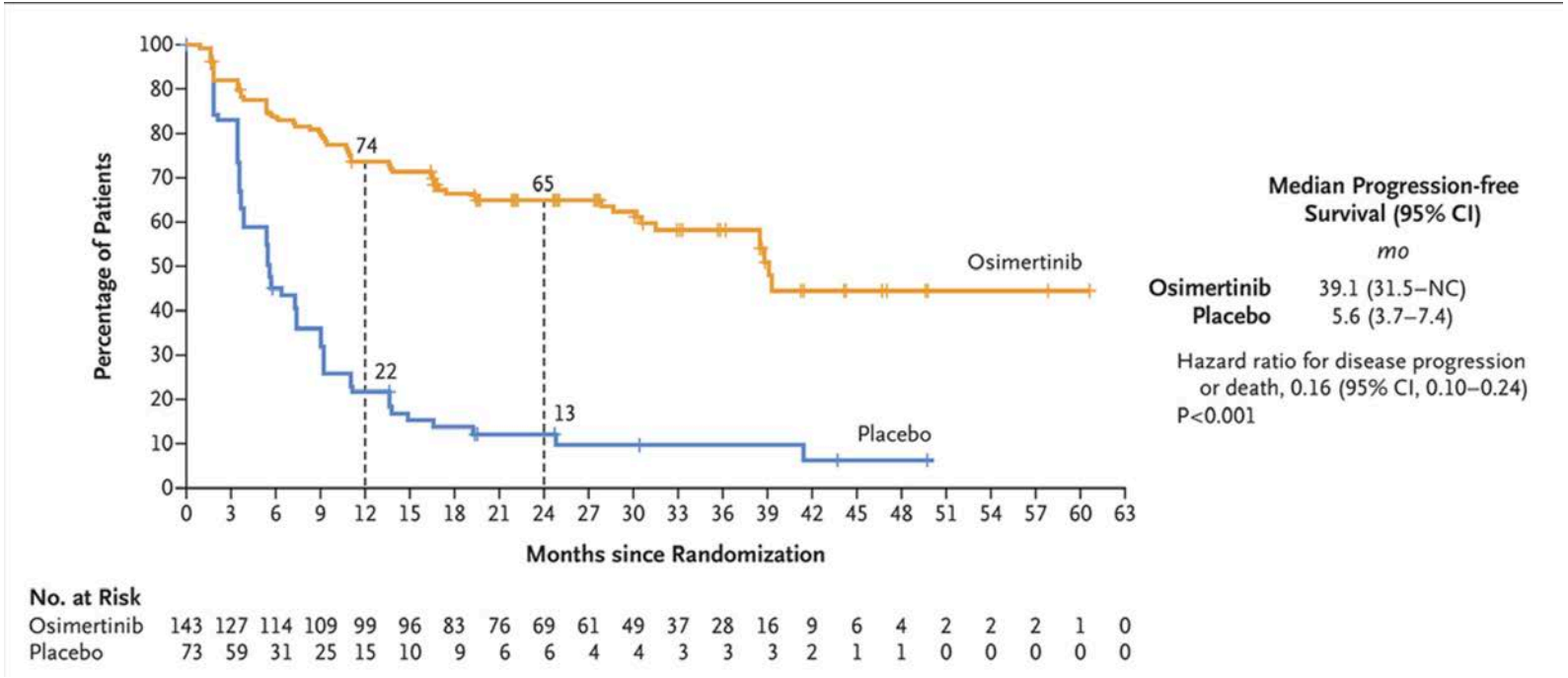
LAURA- Background

- Immune checkpoint inhibitors are ineffective for EGFR-mutated NSCLC
- Post-hoc analysis of PACIFIC showed no benefit from Durvalumab for EGFR-mutated patients



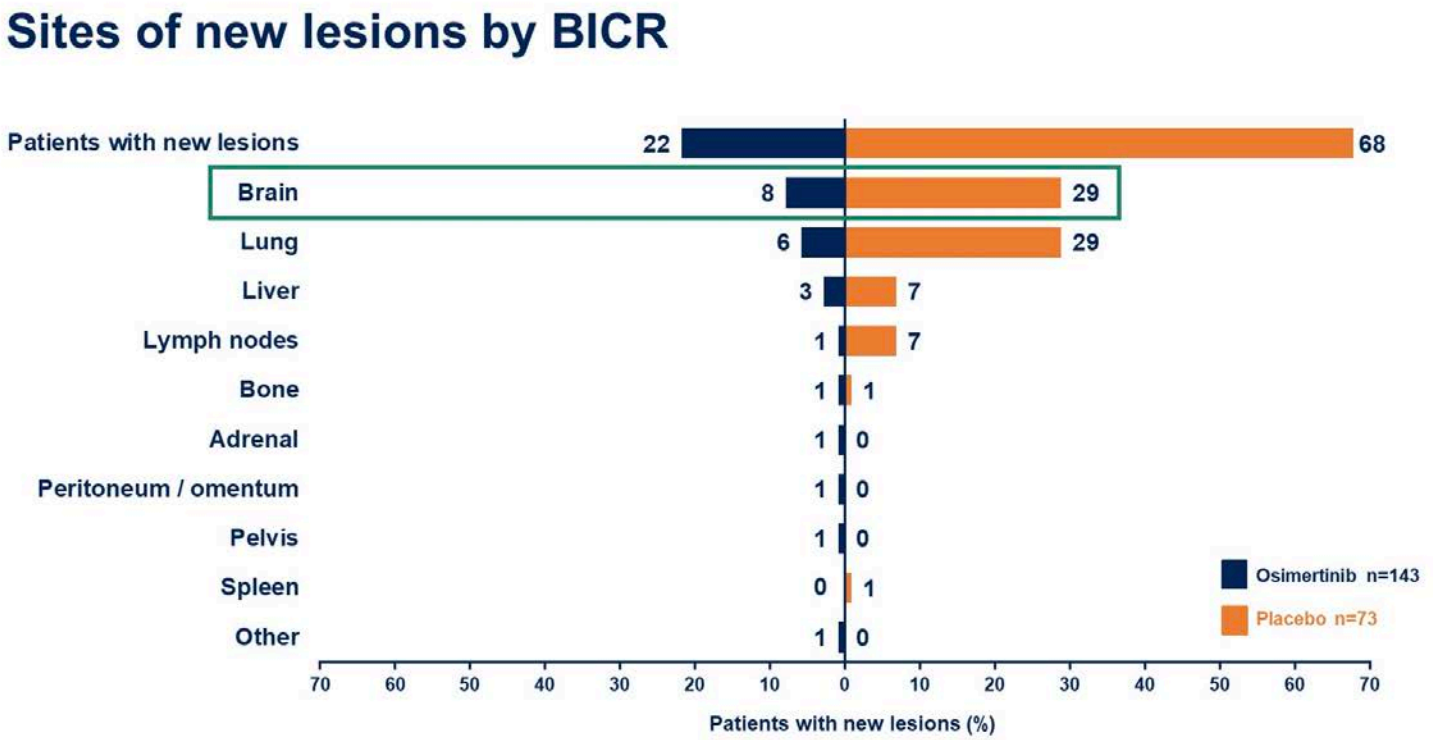
Naidoo et al., J Thorac Oncol, 2023;657-663.

Osimertinib prolongs PFS after chemoradiation



Lu et al, N Engl J Med 2024;391:585-597.

Osimertinib reduces risk of brain metastases



Percentages based on number of patients in each treatment arm. Patients can have more than one new lesion site. Based on BICR assessments according to RECIST v1.1 and includes all new lesions at any time (including those whose RECIST progression event had been censored).

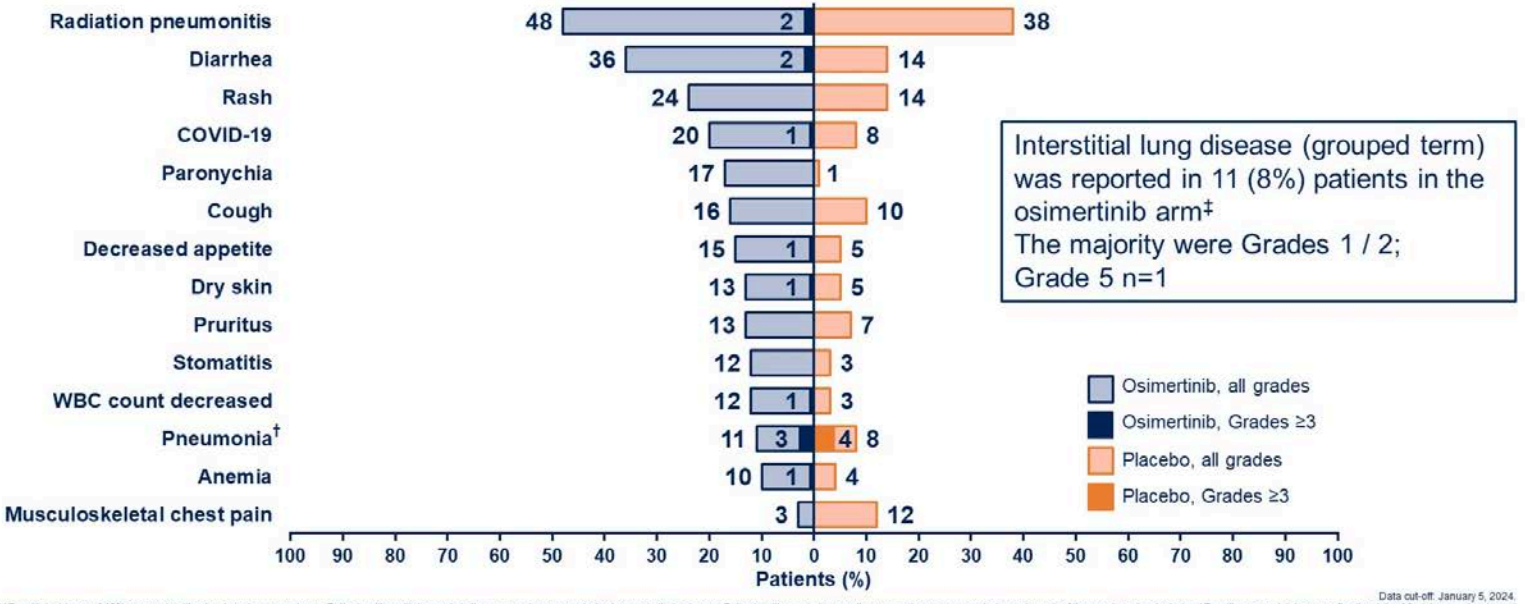
Data cut-off: January 5, 2024.

BICR, blinded independent central review

Osimertinib increases pneumonitis risk

All-causality adverse events (≥10%)*

- The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2; Grade 5 n=1

*AEs with incidence of 10% or more in either treatment arm are shown. Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy; †One grade 5 AE of pneumonia was reported in the osimertinib arm; ‡Interstitial lung disease (grouped term) was reported in 1 patient (1%) in placebo arm; AE was pneumonitis, Grade 1.

Data cut-off: January 5, 2024.

AE, adverse event; WBC, white blood cells

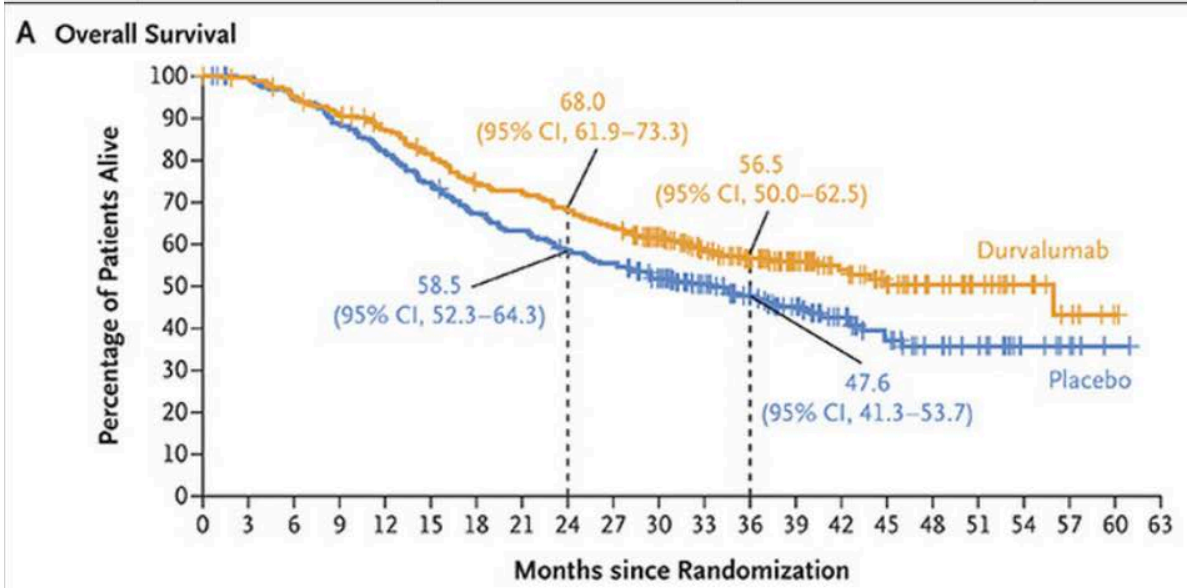
LAURA Take Home Points

- Osimertinib significantly improves PFS in unresectable, EGFR-mutated NSCLC following chemoradiation and is the new standard of care in this population.

- Pneumonitis risk increases slightly with Osimertinib after chemoradiation and careful monitoring is necessary.

Durvalumab consolidation after chemoradiation for Limited Stage Small Cell Lung Caner (ADRIATIC)

Durvalumab consolidation after chemoradiation improves OS for LS-SCLC



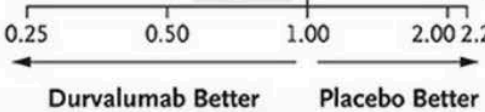
	No. of Deaths/ Total No. (%)	Median Overall Survival (95% CI)
		mo
Durvalumab	115/264 (43.6)	55.9 (37.3–NR)
Placebo	146/266 (54.9)	33.4 (25.5–39.9)

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

Cheng et al, N Engl J Med 2024;391:1313-1327.

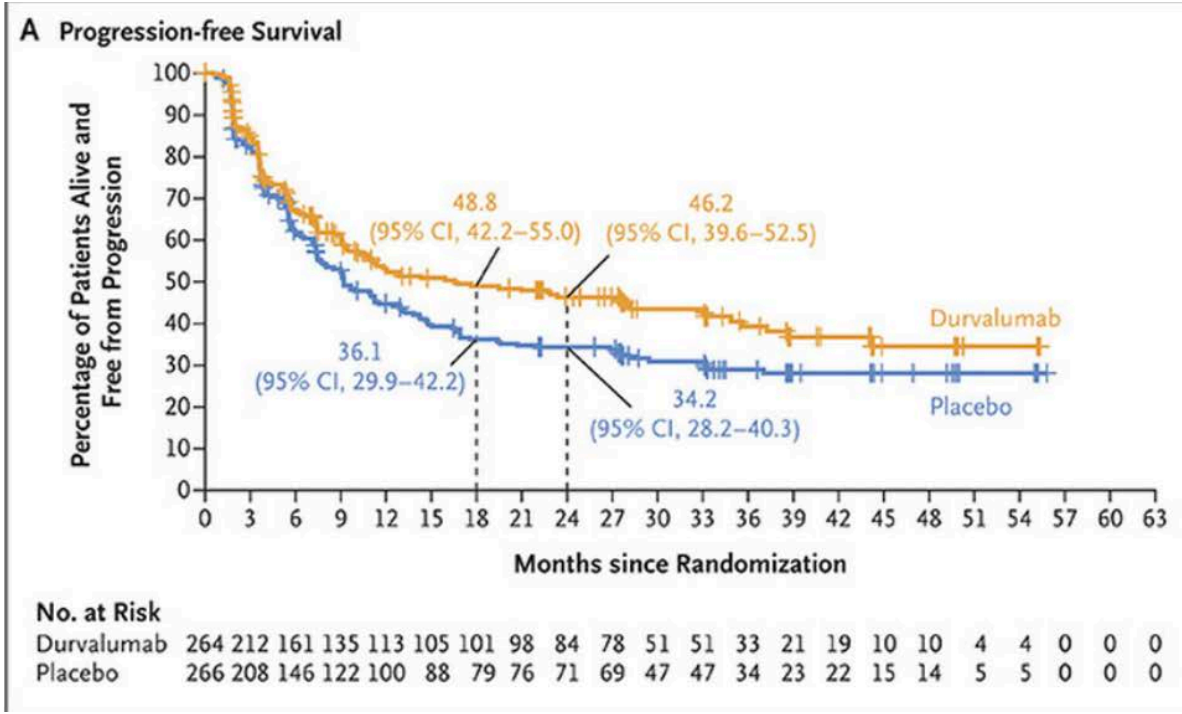
Durvalumab consolidation after chemoradiation improves OS for LS-SCLC

Previous chemotherapy			
Carboplatin–etoposide	31/91 (34)	46/88 (52)	0.56 (0.35–0.89)
Cisplatin–etoposide	84/173 (48.6)	100/178 (56.2)	0.82 (0.61–1.10)
Previous radiotherapy schedule			
Once daily	92/195 (47.2)	107/187 (57.2)	0.72 (0.55–0.95)
Twice daily	23/69 (33)	39/79 (49)	0.68 (0.40–1.14)
Best response to concurrent CRT			
Complete response	12/31 (39)	15/34 (44)	0.90 (0.41–1.92)
Partial response	88/191 (46.1)	116/200 (58.0)	0.76 (0.57–1.00)
Stable disease	15/42 (36)	15/32 (47)	0.54 (0.25–1.13)
Time from end of concurrent CRT to randomization			
<14 days	14/32 (44)	24/32 (75)	0.47 (0.24–0.91)
14 to <28 days	37/79 (47)	51/80 (64)	0.59 (0.38–0.90)
≥28 days	64/153 (41.8)	71/154 (46.1)	0.90 (0.64–1.27)
Receipt of prophylactic cranial irradiation			
Yes	53/142 (37.3)	67/143 (46.9)	0.75 (0.52–1.07)
No	62/122 (50.8)	79/123 (64.2)	0.71 (0.51–0.99)



Cheng et al, N Engl J Med 2024;391:1313-1327.

Durvalumab consolidation after chemoradiation improves PFS for LS-SCLC



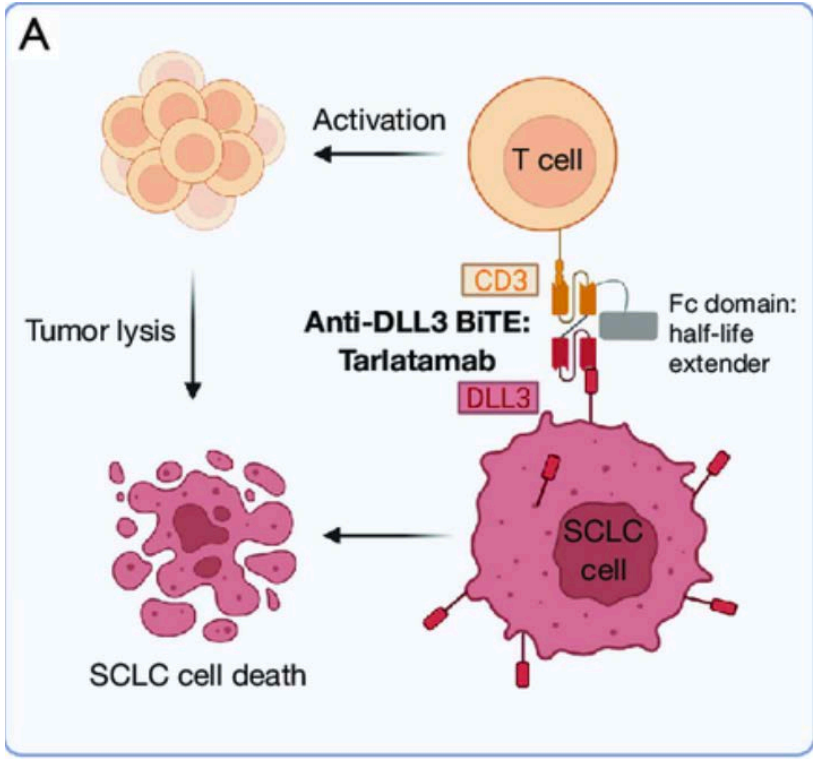
	No. of Events/ Total No. (%)	Median Progression-free Survival (95% CI)
		mo
Durvalumab	139/264 (52.7)	16.6 (10.2–28.2)
Placebo	169/266 (63.5)	9.2 (7.4–12.9)

Stratified hazard ratio for disease progression or death, 0.76
(99.816% CI, 0.53–1.08)
(97.195% CI, 0.59–0.98)
P=0.02

Cheng et al, N Engl J Med 2024;391:1313-1327.

Tarlatamab for previously treated Extensive Stage SCLC

Tarlatamab – Mechanism of Action



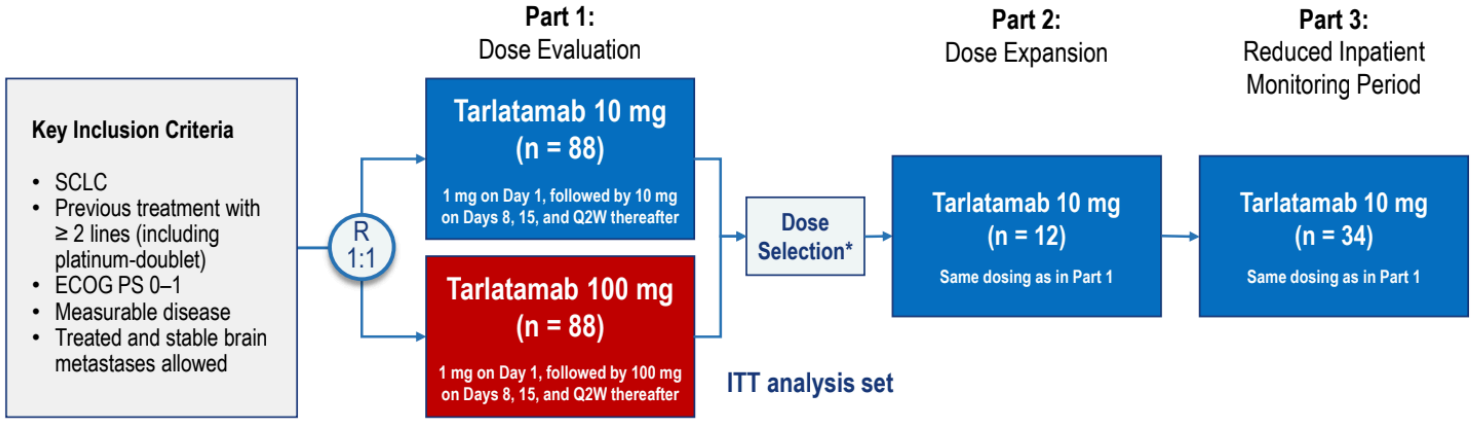
Anpaydin and Sage, Transl Lung Cancer Res 2023.

Tarlatamab – DeLLphi-301

DeLLphi 301

DeLLphi-301 Study Design

- Phase 2, open-label study (NCT05060016)



Primary Endpoint: ORR per RECIST 1.1 by BICR
Secondary Endpoints Included: DOR, DCR, PFS per RECIST 1.1 by BICR, OS, TEAEs, tarlatamab serum concentrations

Sands et al, WCLC 2024.

Tarlatamab – DeLLphi-301 – Response Rates

DeLLphi 301

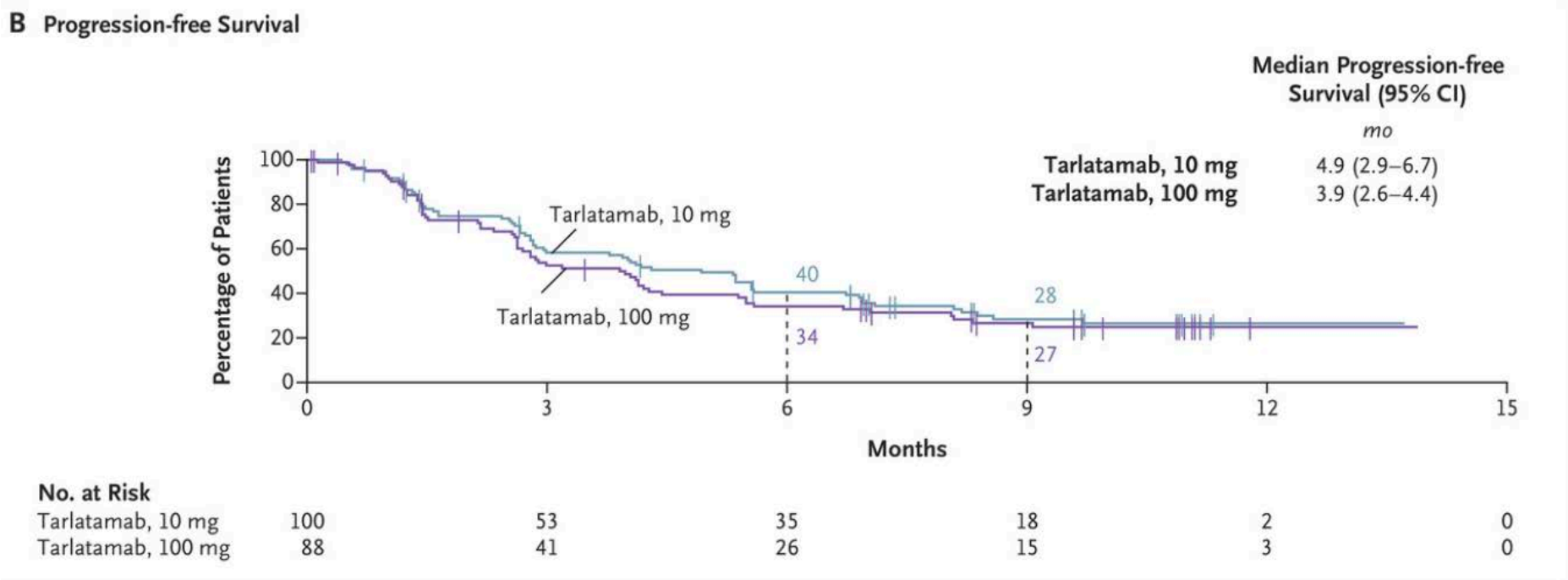
Tarlatamab Anti-Cancer Activity

Outcome	Part 1 + 2 Tarlatamab 10 mg (N = 100)
Objective response rate, n (%) (95% CI for %)	40 (40) (30.3–50.3)
Complete response	3 (3)
Partial response	37 (37)
Stable disease	30 (30)
Progressive disease	20 (20)
Not evaluable / no post-baseline scan*	10 (10)
Disease control rate, n (%) (95% CI for %)	70 (70) (60.0–78.8)

Tarlatamab 10 mg demonstrated anti-cancer activity in heavily pretreated SCLC, with an ORR of 40%

Sands et al, WCLC 2024.

Tarlatamab – DeLLphi-301 – PFS



Ahn et al, N Engl J Med 2023;389:2063-2075.

Tarlatamab – DeLLphi-301 – durable responses

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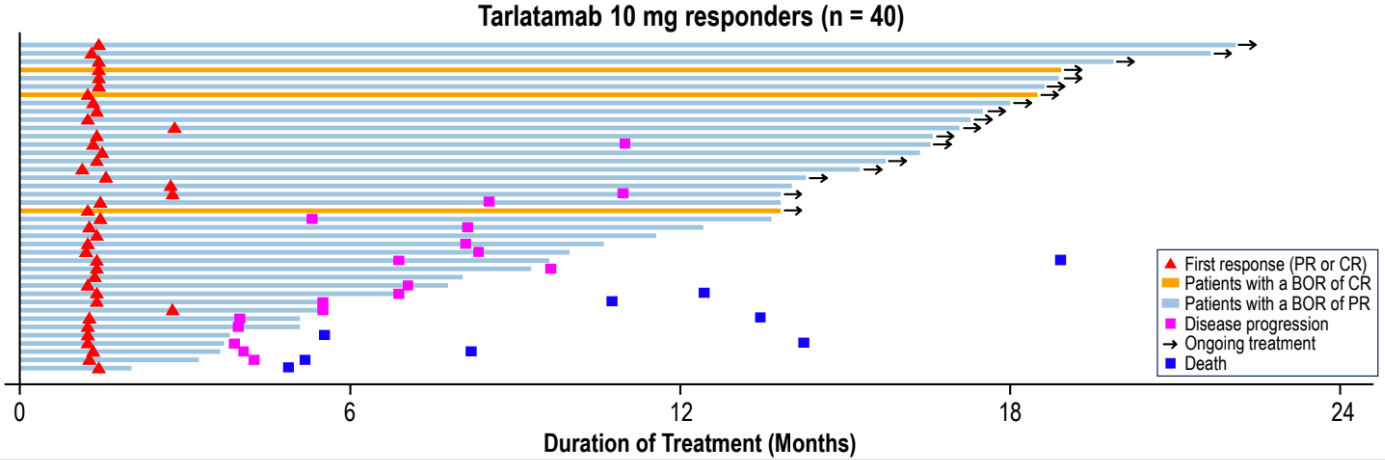
DeLLphi 301

Duration of Response and Time on Treatment



- Median time to response was 1.4 months (IQR, 1.3–1.4)
- Median DOR was 9.7 months (95% CI, 6.9–NE) with 17/40 (43%) of responses ongoing at data cutoff

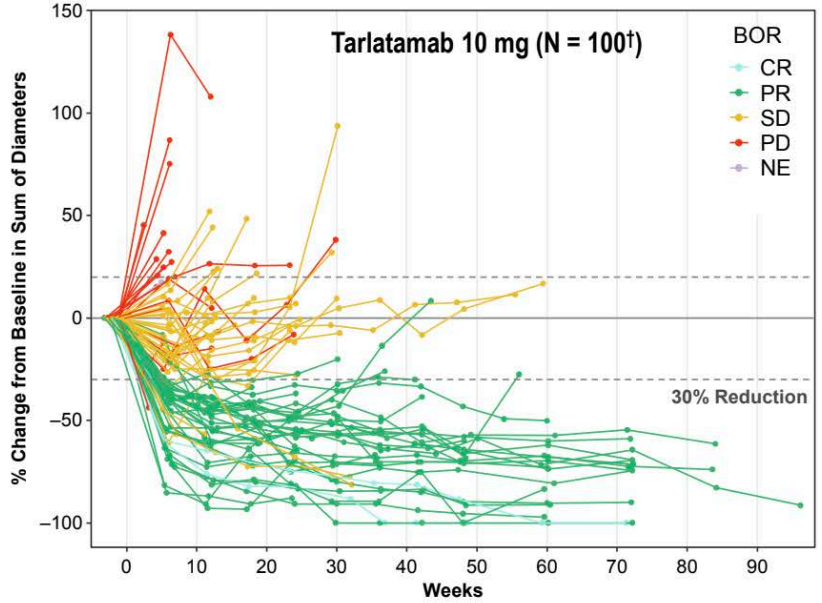
Data cutoff was January 12, 2024. Median follow up for DOR was 15.1 months. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 100). One patient did not receive tarlatamab 10 mg but was included in the ITT analysis. Part 3 was a safety sub-study and was not included in this response analysis. **BOR,** best overall response; **CR,** complete response; **DOR**, duration of response; **ITT,** intention-to-treat; **IQR**, interquartile range; **NE**, not estimable; **PR**, partial response.

Sands et al, WCLC 2024.

Tarlatamab – DeLLphi-301 – durable control

DeLLphi 301

Sustained Disease Control*



- Tumor shrinkage was seen in 72% of patients
- The median duration of disease control was 6.9 months (95% CI, 5.4–8.6)

26 patients (26%; 3 CR, 20 PR, 3 SD) had sustained disease control* ≥ 52 weeks

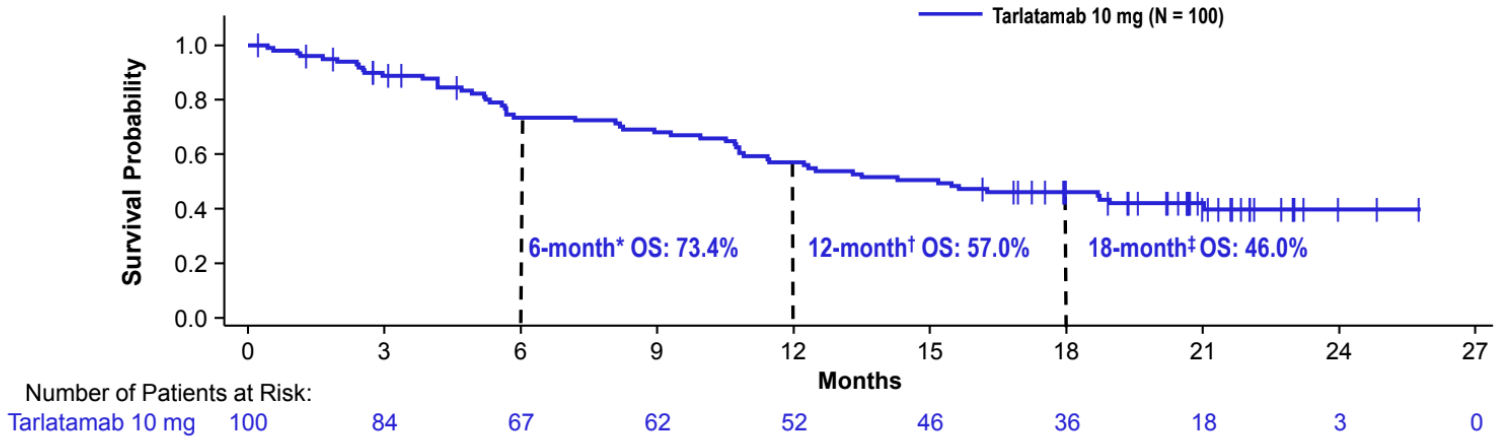
Data cutoff, January 12, 2024. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 100). One patient did not receive tarlatamab 10 mg but was included in the ITT analysis. Part 3 was a safety substudy and was not included in this response analysis.
*Sustained disease control was defined as disease control (CR, PR, or SD) with time on treatment ≥ 52 weeks.
†Seven patients did not have a postbaseline scan.
BOR, best overall response; **CR,** complete response; **ITT,** intention-to-treat; **NE,** not evaluable; **PD,** progressive disease; **PR,** partial response; **SD,** stable disease.

Sands et al, WCLC 2024.

Historically long OS for heavily treated population

DeLLphi 301

Overall Survival



Median OS was 15.2 months (95% CI, 10.8–NE)

Sands et al, WCLC 2024.

No OS difference between chemosensitive and chemoresistant SCLC

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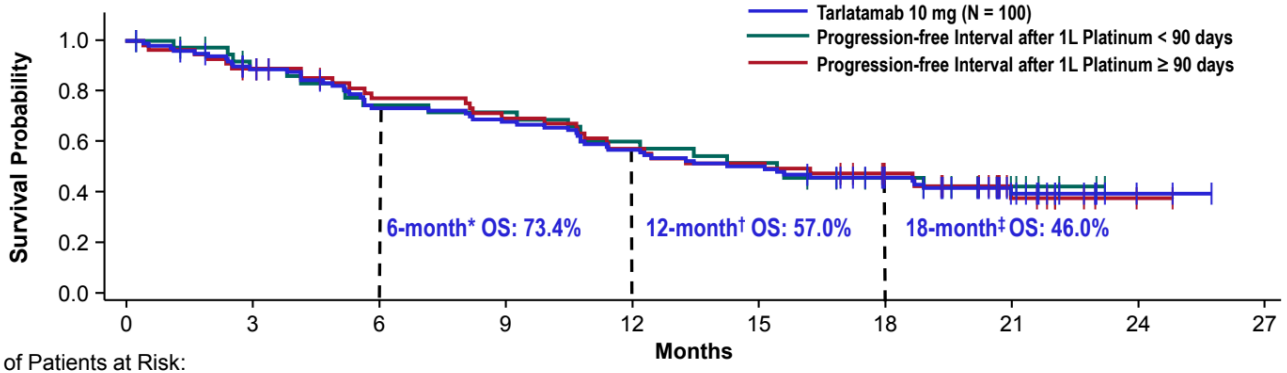
DeLLphi 301

Overall Survival



Number of Patients at Risk:

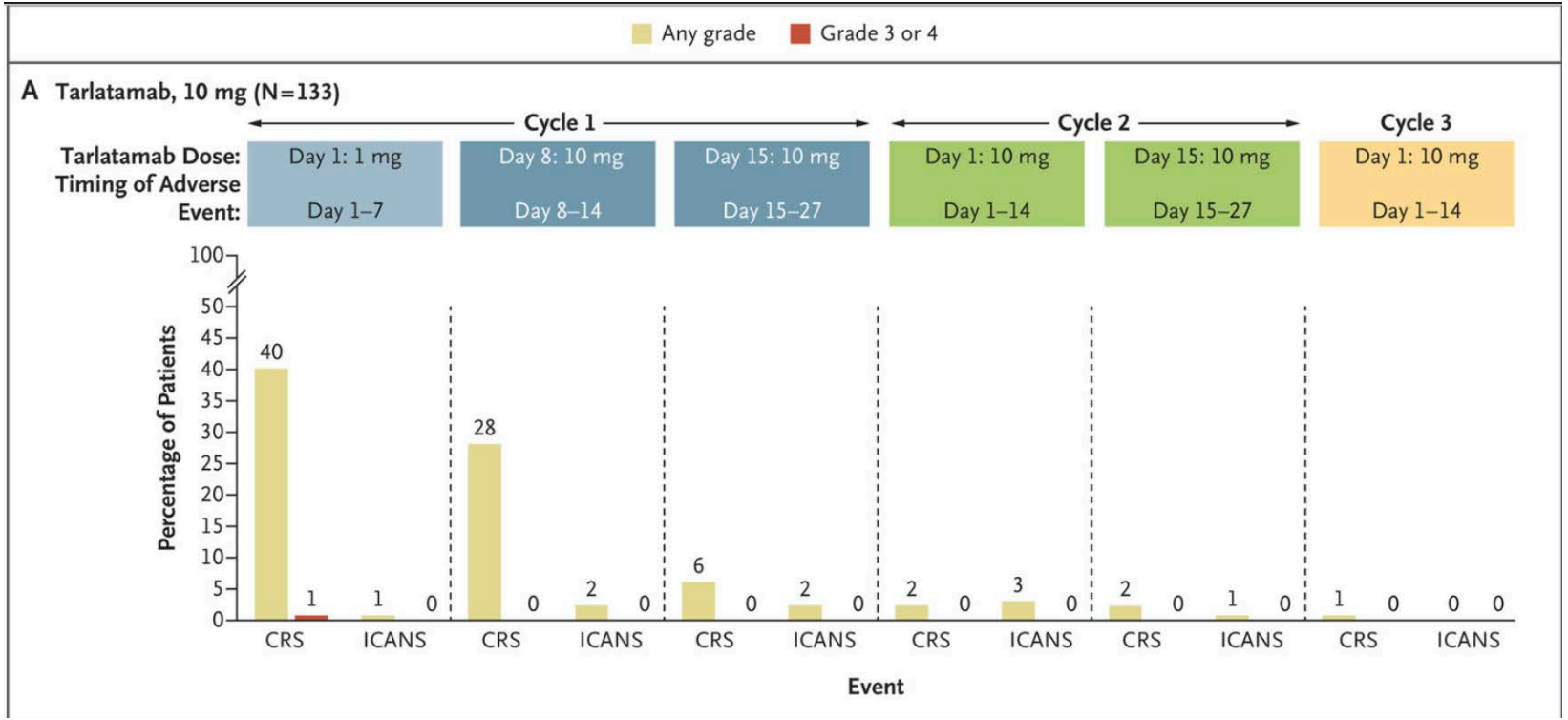
Tarlatamab 10 mg	100	84	67	62	52	46	36	18	3	0
< 90 days	39	31	26	25	21	18	13	7	0	
≥ 90 days	55	48	39	35	29	26	21	9	2	0

OS was similar regardless of progression-free interval after 1L platinum treatment (< 90 d vs ≥ 90 d)

Median follow-up for OS was 20.7 months. Data cutoff, May 16, 2024. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 100). One patient did not receive tarlatamab 10 mg but was included in ITT analysis. Part 3 was a safety substudy and was not included in this response analysis. *95% CI, 63.2–81.2. †95% CI, 46.3–66.3. ‡95% CI, 35.6–55.8. Progression-free interval after first line platinum treatment is defined as days from the last first line platinum treatment to disease progression or start of second line treatment, whichever is earlier. **ITT**, intention-to-treat; **NE**, not estimable; **OS**, overall survival.

Sands et al, WCLC 2024.

Tarlatamab – DeLLphi-301 – CRS/ICANS

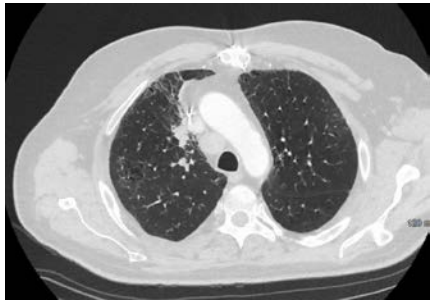


Ahn et al, N Engl J Med 2023;389:2063-2075.

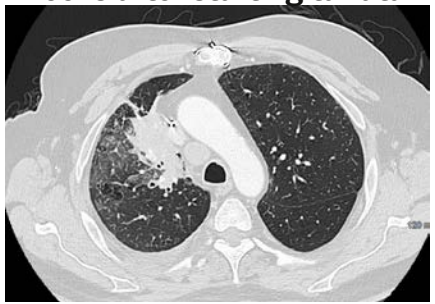
Tarlatamab Case Study

- 66 yo M with ES-SCLC, progression on CT after 4 cycles of chemoimmunotherapy
- Grade 1 CRS with C1D1 tarlatamab (persisted for 72 hours).
  - Received one dose of dexamethasone on day 4 with resolution of fevers.
- Grade 1 CRS with C1D8. No tx needed, new hypoxia prompts CT chest which shows disease progression.
- No further CRS with C1D15 or C2D1
- CT A/P shows disease response after C1D15, feeling very well and hypoxia resolved

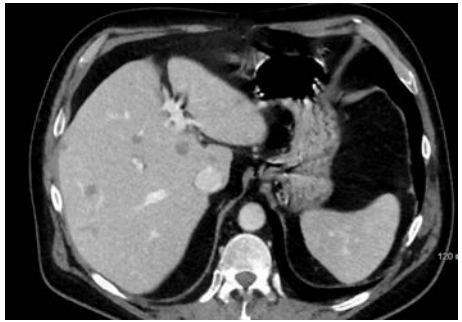
Baseline



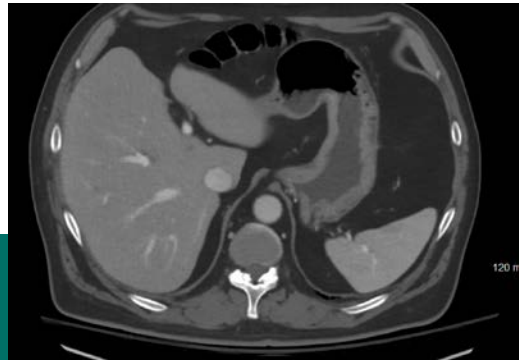
2 weeks after starting tarlatamab



Baseline



4 weeks after starting tarlatamab



Tarlatamab Take Aways

- Provides unprecedented duration of response and overall survival in heavily pretreated ES-SCLC
  - Even chemorefractory patients can benefit
- CRS occurs frequently in 1st cycle, but is manageable and rarely severe
  - Inconvenience and unique toxicities can be barriers to treatment
- Unclear CNS activity/safety for patients with untreated brain metastases
- Promising treatment but may not be appropriate for all

Controversies

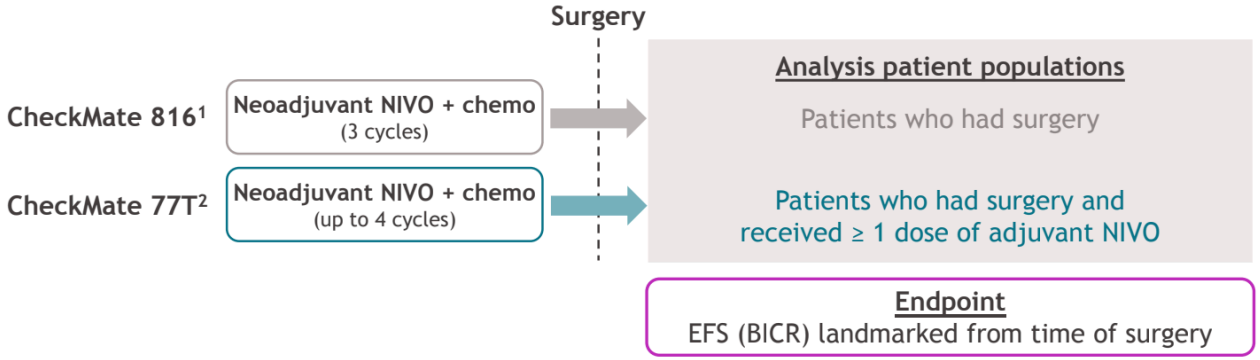
Neoadjuvant vs Perioperative Chemoimmunotherapy for resectable NSCLC

Immunotherapy for Resectable NSCLC

Trial Name	Regimen	DFS/EFS	pCR
Impower 010	**Adjuvant** atezolizumab x 1 year	HR **0.66** (0.50-0.88; p=0.0039) for PD-L1+	N/A
Keynote 91	**Adjuvant** Pembrolizumab x 1 year	HR **0.76 (0.63-0.91; p=0.0014)**	N/A
CheckMate 816	**Neoadjuvant** chemo+nivolumab x 3 cycles	HR **0.63** (0.43-0.91; p=0.005)	24%
Keynote 671	**Perioperative** Neoadjuvant chemo+pembrolizumab x 4 and adjuvant pembrolizumab q 3 weeks x 13 cycles	HR **0.58** (0.46-0.72; p<0.001)	18.1%
AEGEAN	**Perioperative** Neoadjuvant chemo+durvalumab x 4 and adjuvant durvalumab q4wk x12 cycles	HR **0.*68*** *(0.53-0.88; p=0.004)*	17.2%
Checkmate 77T	**Perioperative** Neoadjuvant chemo+nivolumab x 4 and adjuvant nivolumab q 4 wk x 1 year	HR **0.58** (0.42-0.81; p<0.001)	25.3%

Neoadjuvant vs Perioperative chemoIO

Methods: perioperative NIVO vs neoadjuvant NIVO + chemo



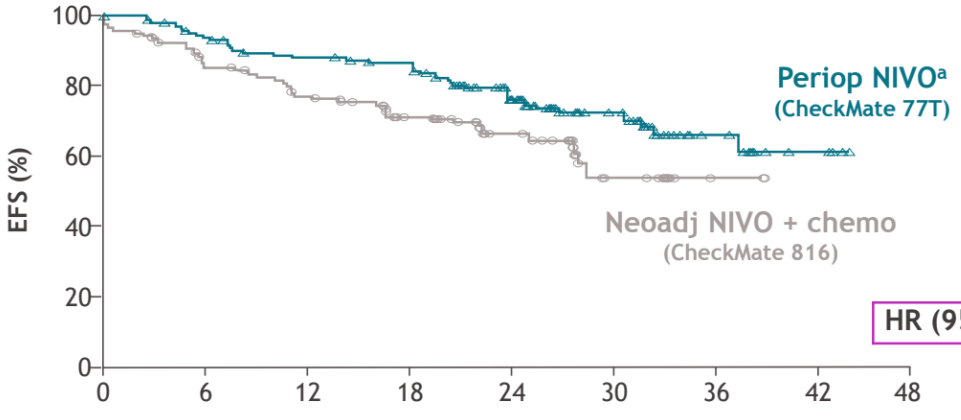
- In lieu of a head-to-head trial, exploratory propensity score weighting analyses (ATT[a] and ATE[b]) were performed to allow simplified reproduction of a randomized trial by adjusting for clinically relevant baseline demographics and disease characteristics[c] between study populations and reducing the confounding effects of these factors
  - Subgroup analyses were not weighted due to smaller sample sizes
- Median duration of follow-up[d]: 29.5 months (CheckMate 816) and 33.3 months (CheckMate 77T)

Forde et al, WCLC 2024.

Neoadjuvant vs Perioperative chemoIO

Perioperative vs neoadjuvant NIVO: Patient-level analy

Landmark EFS (BICR) from definitive surgery



No. at risk

Periop NIVO	139.4	128.0	118.1	112.9	79.7	42.5	13.0	3.1	0
Neoadj N+C	147.5	121.0	106.2	84.2	39.1	12.1	2.2	0	0

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)	

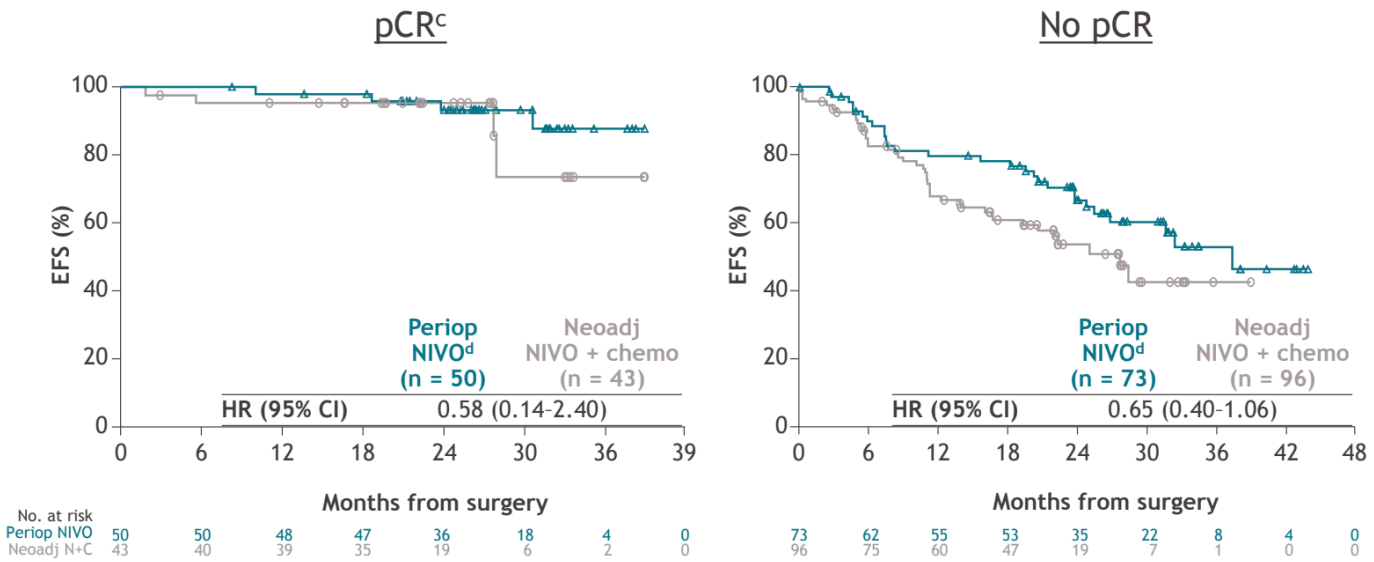
- HR (95% CI): ATT[d] weighted analysis, 0.56 (0.35-0.90); unweighted analysis, 0.59 (0.38-0.92)

Forde et al, WCLC 2024.

Patients without pCR may benefit more from more IO

Perioperative vs neoadjuvant NIVO: Patient-level analysis

Landmark EFS[a] (analysis population) by pCR status[a,b]



Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Patients with non-evaluable pCR status were excluded. [b]Unweighted analyses.
[c]pCR rates in this analysis population: perioperative NIVO, 40.7%; neoadjuvant NIVO + chemo, 30.5%. [d]Includes only patients who received ≥ 1 dose of adjuvant NIVO.

Forde et al, WCLC 2024.

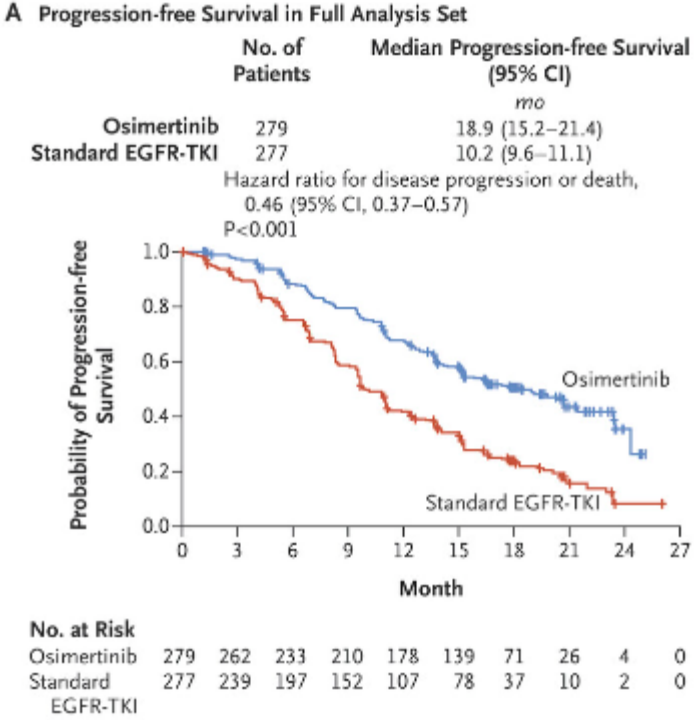
Immunotherapy for Resectable NSCLC Take Aways

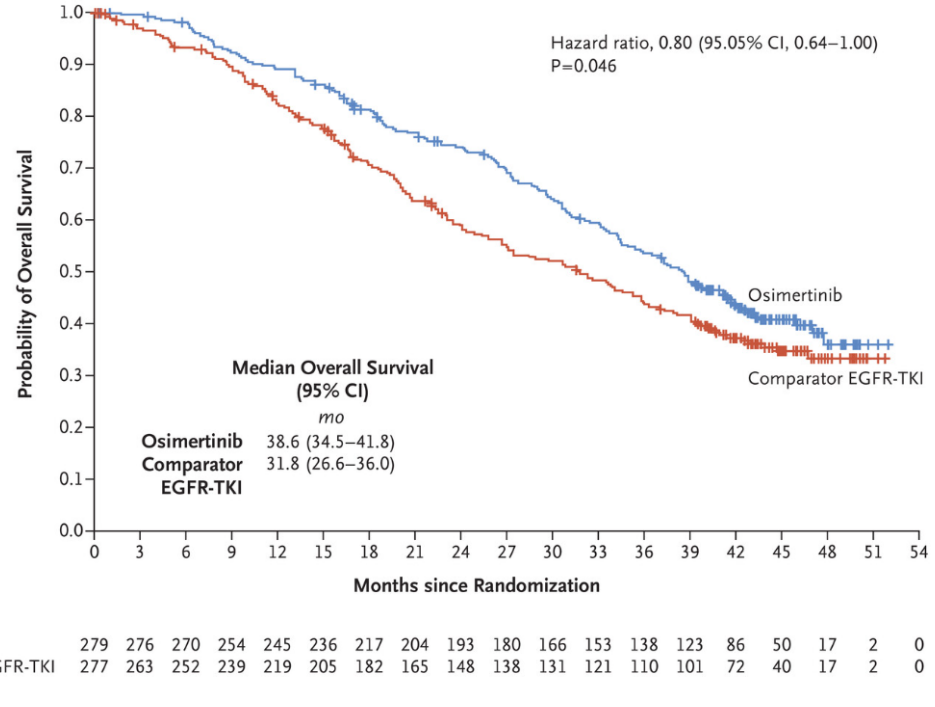
- Nuanced discussion with patient, no universal strategy currently
  - Randomized phase III trials being designed to try to identify best strategy

- We favor neoadjuvant chemoimmunotherapy for node positive disease (particularly stage 3)
  - Consider additional adjuvant immunotherapy if no pathologic CR

New treatment options for 1L, metastatic, EGFR-mutated NSCLC

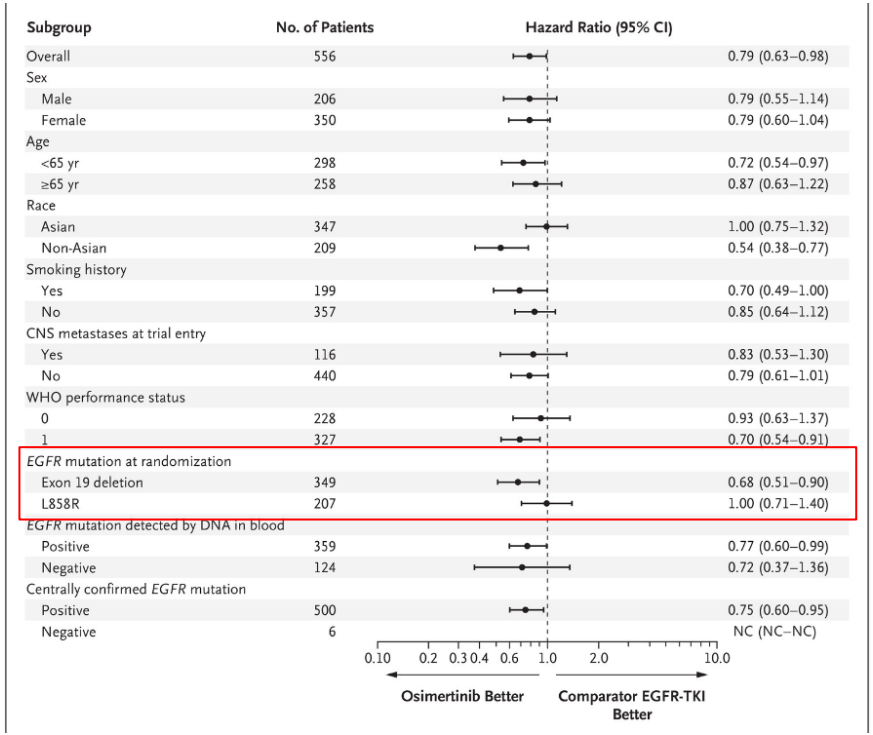
The “Old” Days: FLAURA





Ramalingam et al, N Engl J Med 2020;382:41-50.

The “Old” Days: FLAURA



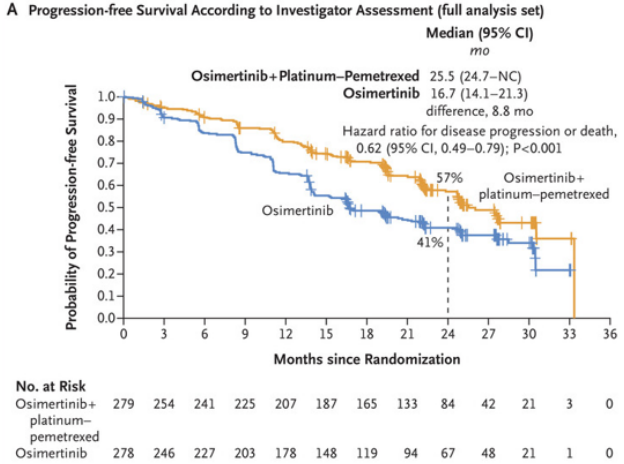
Subgroup	No. of Patients	Hazard Ratio (95% CI)
Overall	556	0.79 (0.63–0.98)
Sex		
Male	206	0.79 (0.55–1.14)
Female	350	0.79 (0.60–1.04)
Age		
<65 yr	298	0.72 (0.54–0.97)
≥65 yr	258	0.87 (0.63–1.22)
Race		
Asian	347	1.00 (0.75–1.32)
Non-Asian	209	0.54 (0.38–0.77)
Smoking history		
Yes	199	0.70 (0.49–1.00)
No	357	0.85 (0.64–1.12)
CNS metastases at trial entry		
Yes	116	0.83 (0.53–1.30)
No	440	0.79 (0.61–1.01)
WHO performance status		
0	228	0.93 (0.63–1.37)
1	327	0.70 (0.54–0.91)
EGFR mutation at randomization		
Exon 19 deletion	349	0.68 (0.51–0.90)
L858R	207	1.00 (0.71–1.40)
EGFR mutation detected by DNA in blood		
Positive	359	0.77 (0.60–0.99)
Negative	124	0.72 (0.37–1.36)
Centrally confirmed *EGFR* mutation		
Positive	500	0.75 (0.60–0.95)
Negative	6	NC (NC–NC)

Ramalingam et al, N Engl J Med 2020;382:41-50.

New Kids on the Block

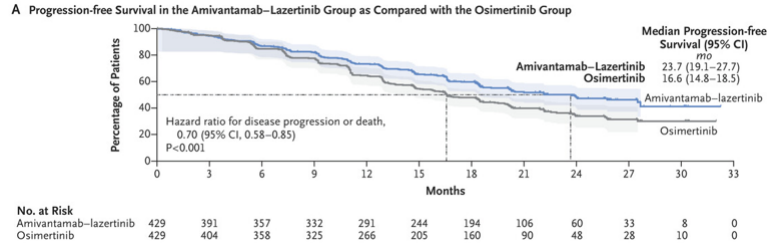
FLAURA2:

Chemotherapy + Osimertinib



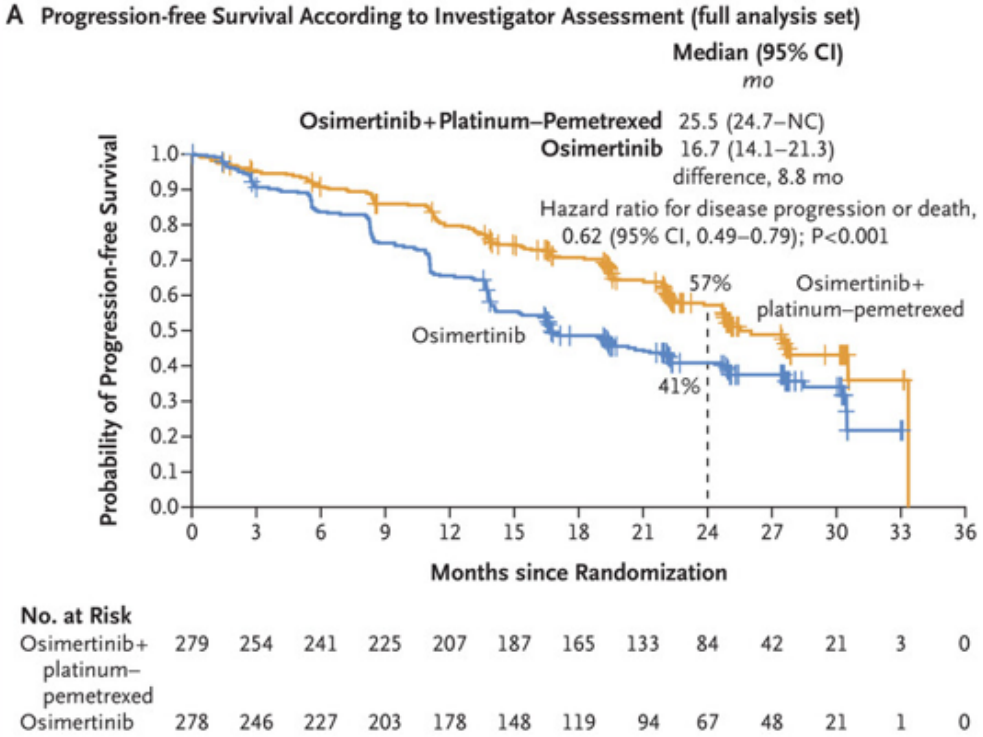
Mariposa:

Amivantamab + Lazertinib



Planchard et al, N Engl J Med 2023;389:1935-1948.
Cho et al, N Engl J Med 2024.

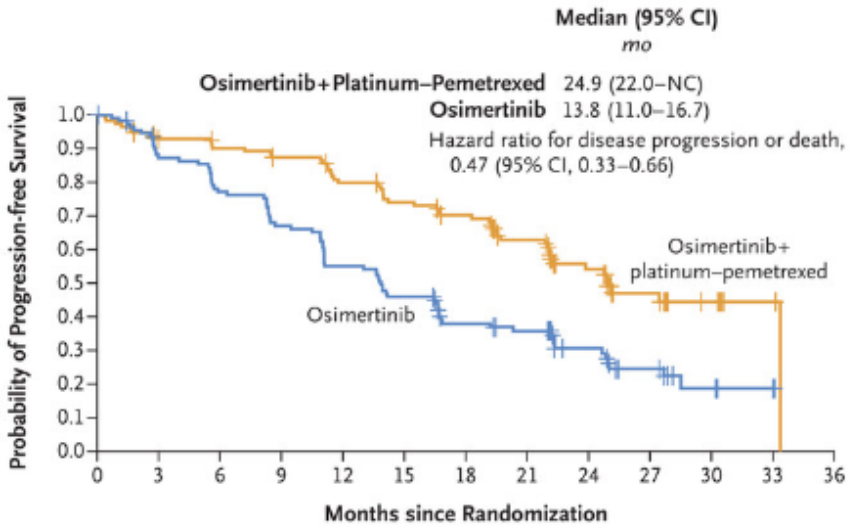
FLAURA2



Planchard et al, N Engl J Med 2023;389:1935-1948

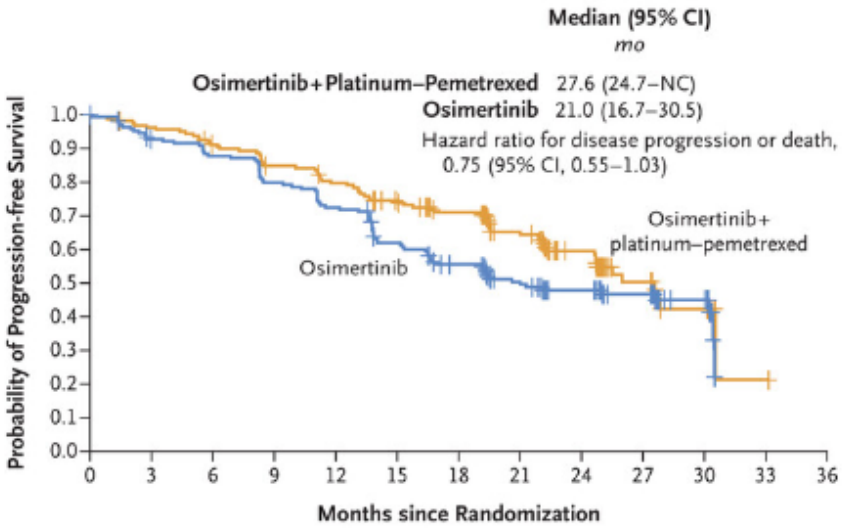
FLAURA2

C Progression-free Survival among Patients with CNS Metastases at Baseline



No. at Risk													
Osimertinib+ platinum–pemetrexed	116	101	98	93	84	77	70	58	34	19	8	2	0
Osimertinib	110	95	84	73	60	50	37	32	21	13	5	1	0

D Progression-free Survival among Patients without CNS Metastases at Baseline

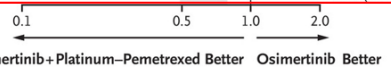


No. at Risk													
Osimertinib+ platinum–pemetrexed	163	153	143	132	123	110	95	75	50	23	13	1	0
Osimertinib	168	151	143	130	118	98	82	62	46	35	16	0	0

Planchard et al, N Engl J Med 2023;389:1935-1948

FLAURA2

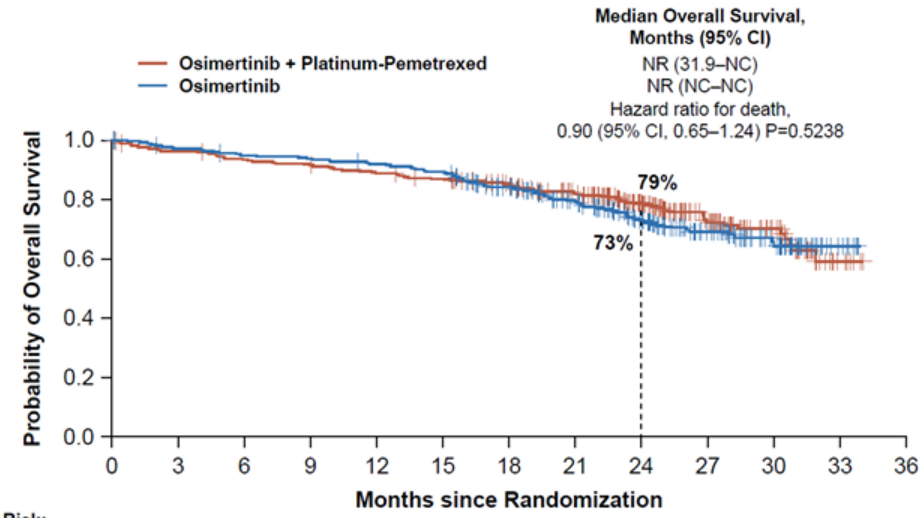
Subgroup	Osimertinib+ Platinum–Pemetrexed (no. of events/no. of patients)	Osimertinib (no. of events/no. of patients)	Hazard Ratio for Disease Progression or Death (95% CI)
Overall			
Stratified log-rank analysis	120/279	166/278	0.62 (0.49–0.79)
Unadjusted Cox proportional-hazards analysis	120/279	166/278	0.62 (0.49–0.78)
Sex			
Male	51/106	73/109	0.54 (0.37–0.77)
Female	69/173	93/169	0.67 (0.49–0.92)
Race			
Asian Chinese	26/71	43/69	0.49 (0.30–0.81)
Asian non-Chinese	54/107	65/107	0.76 (0.53–1.09)
Non-Asian	40/101	58/102	0.55 (0.37–0.83)
Method used for tissue testing			
Central	52/121	67/119	0.73 (0.51–1.05)
Local	68/158	99/159	0.55 (0.40–0.74)
Age at screening			
<65 yr	73/174	97/166	0.59 (0.44–0.80)
≥65 yr	47/105	69/112	0.68 (0.47–0.98)
History of smoking			
Yes	43/91	57/97	0.63 (0.42–0.94)
No	77/188	109/181	0.61 (0.46–0.82)
EGFR mutation at randomization			
Exon 19 deletion	65/172	94/169	0.60 (0.44–0.83)
L858R mutation	55/106	70/107	0.63 (0.44–0.90)
WHO performance-status score			
0	48/101	57/102	0.79 (0.54–1.16)
1	72/178	109/176	0.53 (0.39–0.72)
CNS metastases at baseline			
Yes	52/116	79/110	0.47 (0.33–0.66)
No	68/163	87/168	0.75 (0.55–1.03)



Planchard et al, N Engl J Med 2023;389:1935-1948

FLAURA2

Figure S6. Overall Survival Interim Analysis.



No. at Risk:													
Osimertinib + Platinum-Pemetrexed	279	267	258	253	244	237	219	191	139	84	46	7	0
Osimertinib	278	267	260	257	251	244	214	185	133	85	46	10	0

Planchard et al, N Engl J Med 2023;389:1935-1948

FLAURA2

Table 3. Adverse Events.*

Event	Osimertinib + Platinum–Pemetrexed (N=276)					Osimertinib Monotherapy (N=275)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	128 (46)	30 (11)	43 (16)	55 (20)	0	22 (8)	15 (5)	6 (2)	1 (<1)	0
Diarrhea	120 (43)	83 (30)	29 (11)	8 (3)	0	112 (41)	89 (32)	22 (8)	1 (<1)	0
Nausea	119 (43)	81 (29)	34 (12)	4 (1)	0	28 (10)	22 (8)	6 (2)	0	0
Decreased appetite	85 (31)	49 (18)	28 (10)	8 (3)	0	26 (9)	18 (7)	6 (2)	2 (1)	0
Constipation	81 (29)	60 (22)	20 (7)	1 (<1)	0	28 (10)	23 (8)	5 (2)	0	0
Rash	77 (28)	55 (20)	21 (8)	1 (<1)	0	57 (21)	46 (17)	11 (4)	0	0
Fatigue	76 (28)	45 (16)	23 (8)	8 (3)	0	26 (9)	24 (9)	1 (<1)	1 (<1)	0
Vomiting	73 (26)	50 (18)	20 (7)	3 (1)	0	17 (6)	13 (5)	4 (1)	0	0
Stomatitis	68 (25)	40 (14)	27 (10)	1 (<1)	0	50 (18)	32 (12)	17 (6)	1 (<1)	0
Neutropenia	68 (25)	4 (1)	27 (10)	30 (11)	7 (3)	9 (3)	3 (1)	4 (1)	2 (1)	0
Paronychia	65 (24)	28 (10)	35 (13)	2 (1)	0	73 (27)	37 (13)	35 (13)	1 (<1)	0
Neutrophil count decrease	62 (22)	5 (2)	26 (9)	25 (9)	6 (2)	16 (6)	6 (2)	8 (3)	2 (1)	0
Covid-19†	57 (21)	23 (8)	31 (11)	2 (1)	0	39 (14)	18 (7)	21 (8)	0	0
ALT increase	56 (20)	36 (13)	16 (6)	4 (1)	0	21 (8)	17 (6)	3 (1)	1 (<1)	0
Platelet count decrease	51 (18)	19 (7)	11 (4)	18 (7)	3 (1)	19 (7)	18 (7)	1 (<1)	0	0
Thrombocytopenia	51 (18)	19 (7)	13 (5)	16 (6)	3 (1)	12 (4)	6 (2)	3 (1)	3 (1)	0
Dry skin	50 (18)	43 (16)	7 (3)	0	0	66 (24)	62 (23)	4 (1)	0	0
AST increase	48 (17)	42 (15)	5 (2)	1 (<1)	0	13 (5)	12 (4)	0	1 (<1)	0
Blood creatinine increase	46 (17)	33 (12)	13 (5)	0	0	12 (4)	10 (4)	2 (1)	0	0
White-cell count decrease	44 (16)	7 (3)	28 (10)	8 (3)	1 (<1)	18 (7)	9 (3)	8 (3)	1 (<1)	0
Peripheral edema	42 (15)	33 (12)	9 (3)	0	0	12 (4)	9 (3)	3 (1)	0	0

Planchard et al, N Engl J Med 2023;389:1935-1948.

FLAURA2

- Adverse events leading to discontinuation of osimertinib
  - 11% in chemo + osimertinib group
  - 6% in osimertinib group
- Dose interruptions of osimertinib
  - 43% in chemo + osi
  - 19% in osi
- Osimertinib dose reductions
  - 10% chemo + osi
  - 3% osi
- Chemotherapy discontinuation
  - 76% received the 4 planned cycles of platinum + pemetrexed
  - 17% discontinued platinum and 43% discontinued pemetrexed due to AEs.

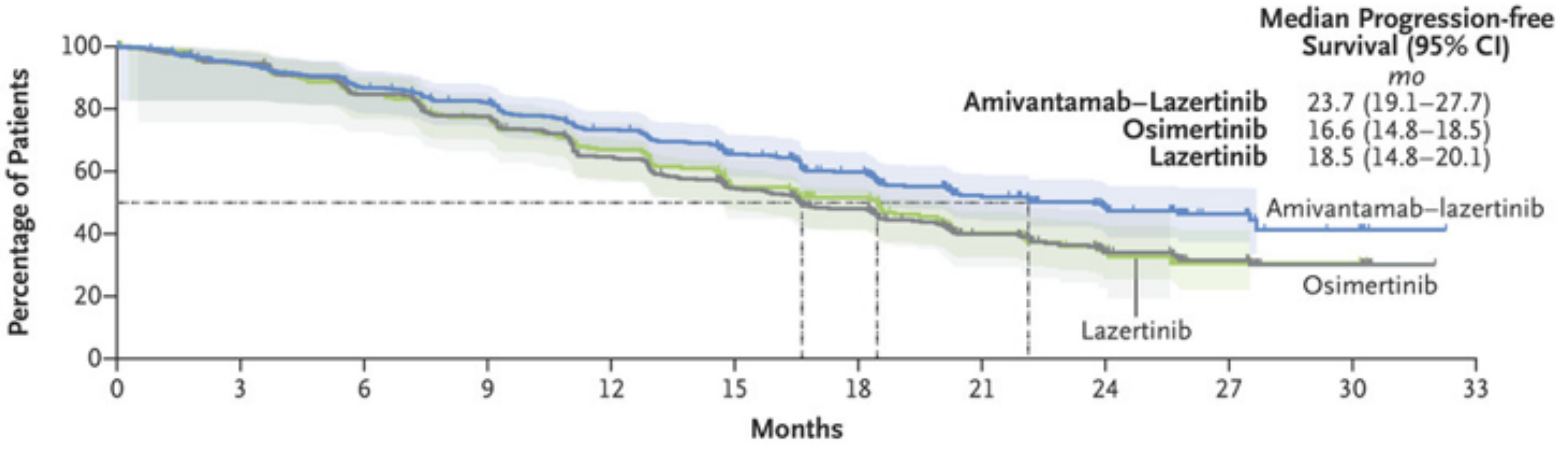
Planchard et al, N Engl J Med 2023;389:1935-1948.

FLAURA2

- Pros
  - Significant gains in PFS with combination therapy
    - Particularly in L858R and pts with underlying brain metastases
- Cons
  - Significantly increases toxicity (mainly cytopenias)
  - Unclear if combination impacts overall survival

Mariposa

B Progression-free Survival in Amivantamab–Lazertinib Group as Compared with the Osimertinib and the Lazertinib Monotherapy Groups



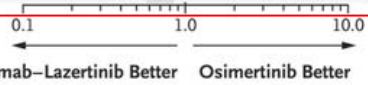
No. at Risk												
Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0
Lazertinib	216	200	174	157	134	103	83	41	19	6	2	0

Cho et al, N Engl J Med 2024.

Mariposa

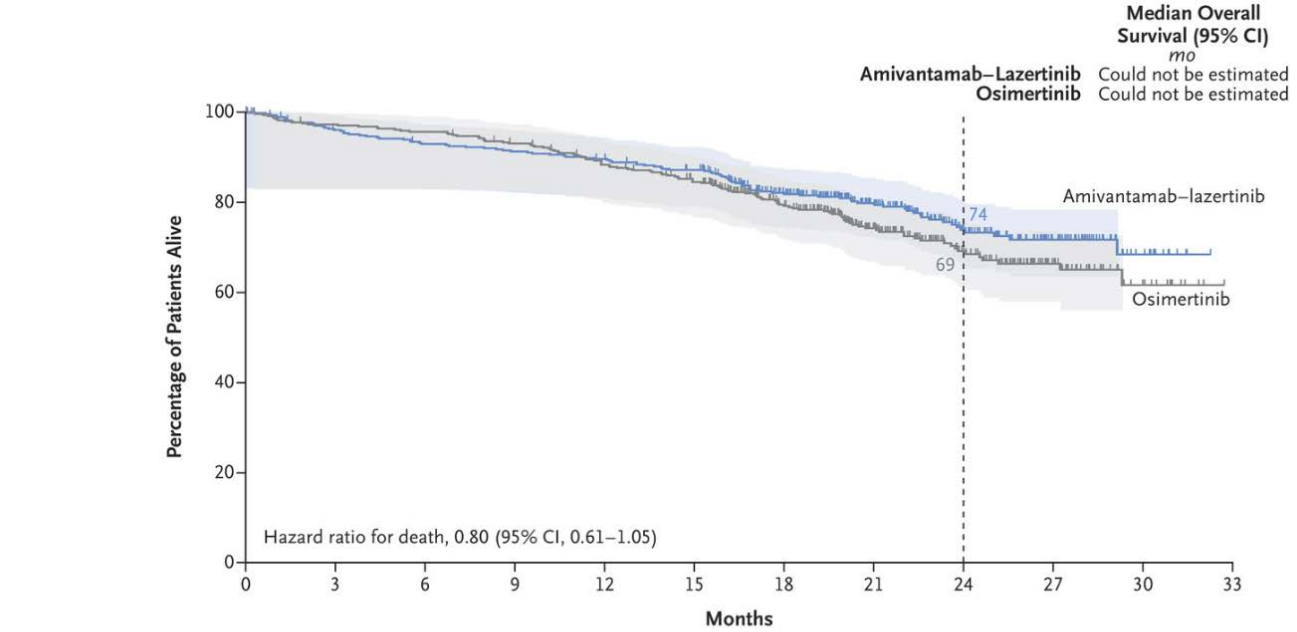
C Subgroup Analysis

Subgroup	Amivantamab–Lazertinib	Osimertinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. of patients		
All patients	192/429	252/429	0.70 (0.58–0.85)
Age			
<65 yr	94/235	153/237	0.50 (0.39–0.65)
≥65 yr	98/194	99/192	1.06 (0.80–1.41)
<75 yr	165/378	220/376	0.70 (0.57–0.85)
≥75 yr	27/51	32/53	0.77 (0.46–1.30)
Sex			
Male	112/275	140/251	0.70 (0.55–0.90)
Female	80/154	112/178	0.74 (0.55–0.98)
Race			
Asian	105/250	144/251	0.67 (0.52–0.86)
Non-Asian	85/177	108/177	0.75 (0.56–0.99)
Weight			
<80 kg	161/376	209/368	0.70 (0.57–0.86)
≥80 kg	31/53	43/61	0.77 (0.48–1.22)
ECOG performance-status score			
0	56/141	76/149	0.79 (0.56–1.12)
1	136/288	176/280	0.66 (0.52–0.82)
History of smoking			
Yes	67/130	79/134	0.78 (0.56–1.08)
No	125/299	173/295	0.67 (0.53–0.84)
History of brain metastases			
Yes	94/178	111/172	0.69 (0.53–0.92)
No	98/251	141/257	0.69 (0.53–0.89)
EGFR mutation			
Ex19del	101/257	142/257	0.65 (0.51–0.85)
L858R	90/171	110/172	0.78 (0.59–1.02)



Cho et al, N Engl J Med 2024.

Mariposa



Cho et al, N Engl J Med 2024.

Mariposa

Table 3. Adverse Events.*

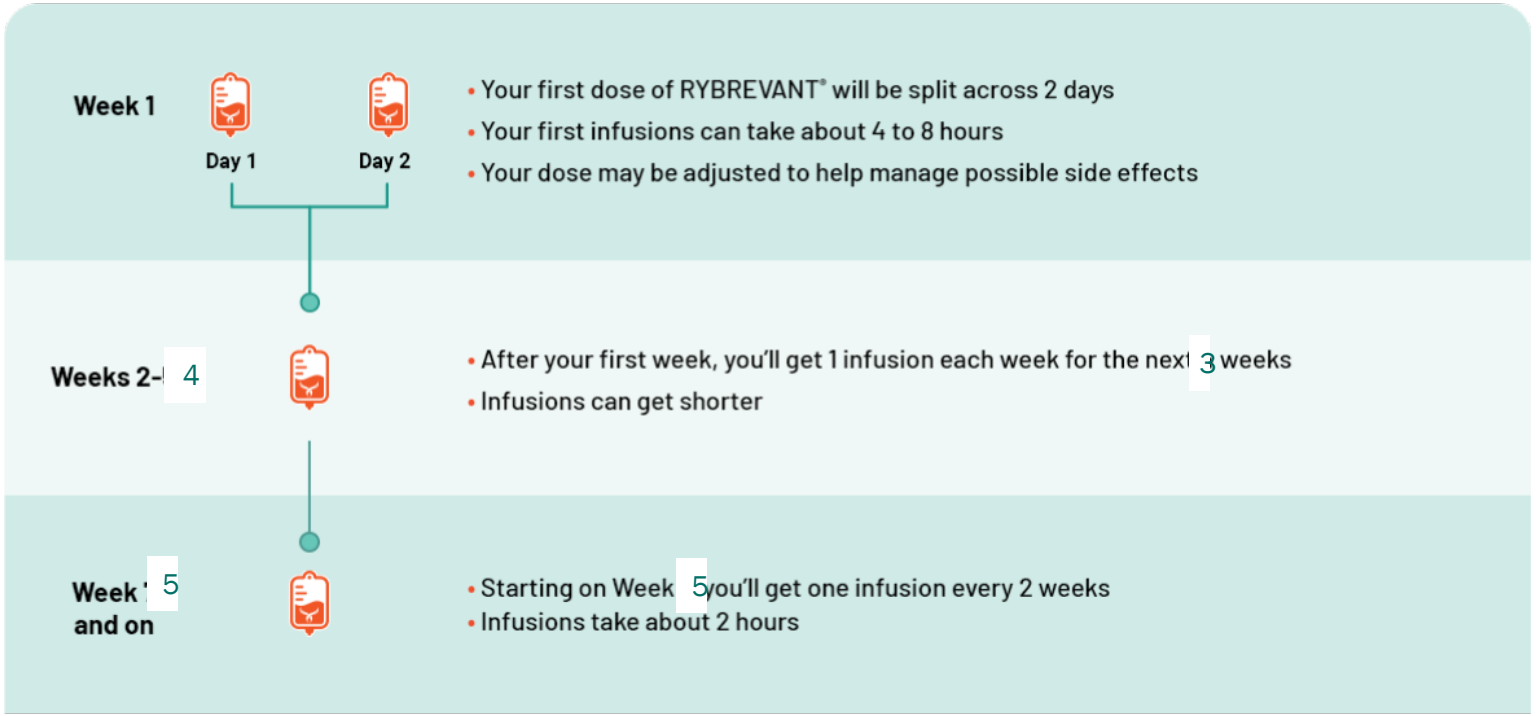
Event	Amivantamab–Lazertinib (N=421)		Osimertinib (N=428)	
	All	Grade ≥3	All	Grade ≥3
	number of patients (percent)			
Any event	421 (100)	316 (75)	425 (99)	183 (43)
Any serious event	205 (49)		143 (33)	
Any event resulting in death		34 (8)		31 (7)
Event leading to interruption of any trial agent	350 (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)	

Cho et al, N Engl J Med 2024.

Mariposa

Event	Amivantamab–Lazertinib (N=421)		Osimertinib (N=428)	
	All	Grade ≥3	All	Grade ≥3
Paronychia	288 (68)	46 (11)	121 (28)	2 (<1)
Infusion-related reaction	265 (63)	27 (6)	0	0
Rash	260 (62)	65 (15)	131 (31)	3 (1)
Hypoalbuminemia	204 (48)	22 (5)	26 (6)	0
Increased alanine aminotransferase	152 (36)	21 (5)	57 (13)	8 (2)
Peripheral edema	150 (36)	8 (2)	24 (6)	0
Constipation	123 (29)	0	55 (13)	0
Diarrhea	123 (29)	9 (2)	190 (44)	3 (1)
Dermatitis acneiform	122 (29)	35 (8)	55 (13)	0
Stomatitis	122 (29)	5 (1)	90 (21)	1 (<1)
Increased aspartate aminotransferase	121 (29)	14 (3)	58 (14)	5 (1)
Covid-19	111 (26)	8 (2)	103 (24)	9 (2)
Decreased appetite	103 (24)	4 (1)	76 (18)	6 (1)
Pruritus	99 (24)	2 (<1)	73 (17)	1 (<1)
Anemia	96 (23)	16 (4)	91 (21)	7 (2)
Nausea	90 (21)	5 (1)	58 (14)	1 (<1)
Hypocalcemia	88 (21)	9 (2)	35 (8)	0
Asthenia	78 (19)	12 (3)	46 (11)	4 (1)
Pulmonary embolism	73 (17)	35 (8)	20 (5)	10 (2)

Mariposa

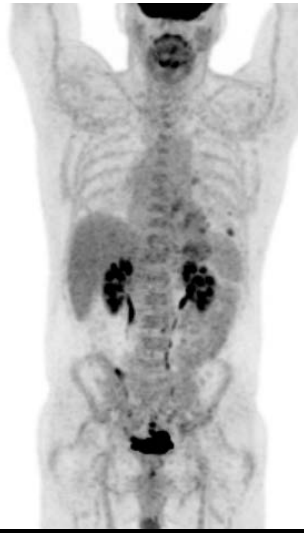


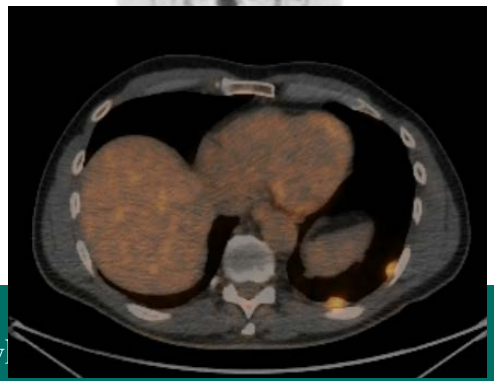
https://www.rybrevant.com/mariposa/what-to-expect/dosing-and-administration/

Mariposa

- Pros
  - Significant gains in PFS with combination therapy
- Cons
  - Substantial increase in challenging toxicities
  - Large time commitment
  - Overall survival data is immature

EGFR management is not “one size fits all”

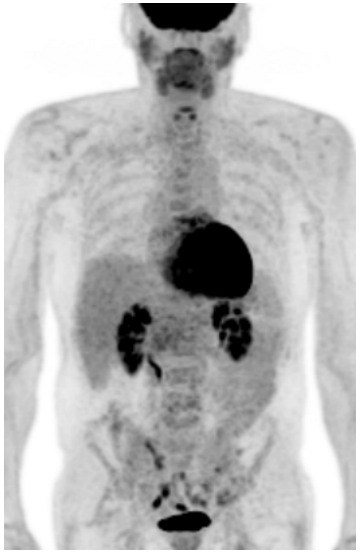


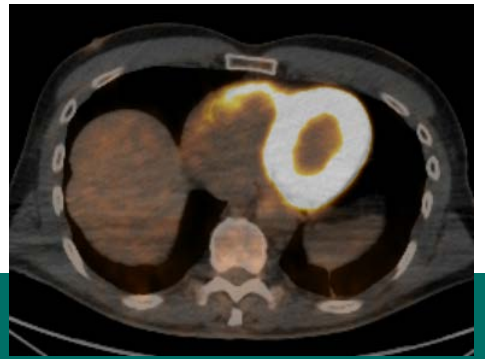


Before osimertinib

EGFR exon 19 del + TP53
3 pleural mets

NED after 4 years of
osimertinib

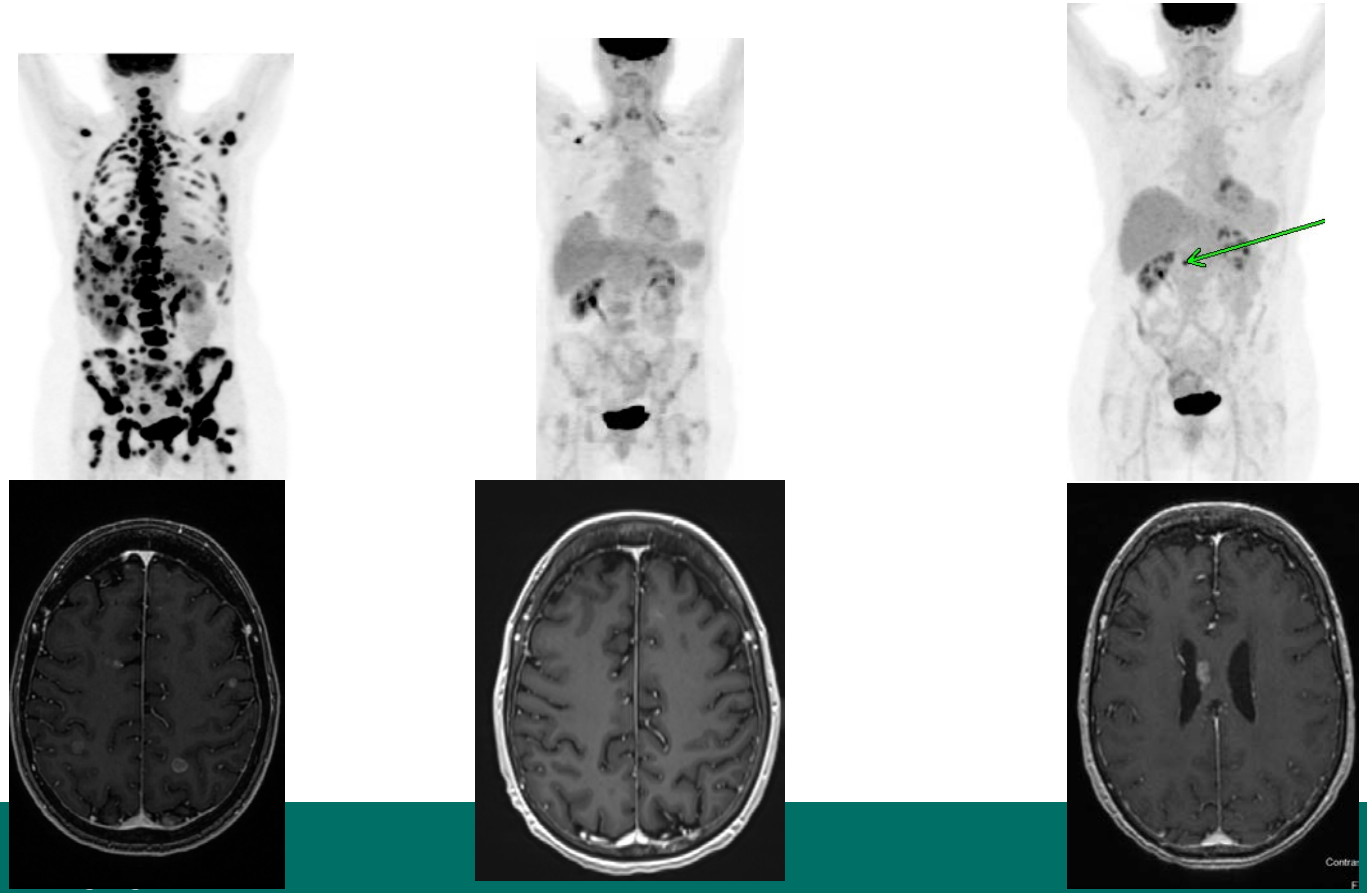




On osimertinib

EGFR management is not “one size fits all”

EGFR exon 19 del +

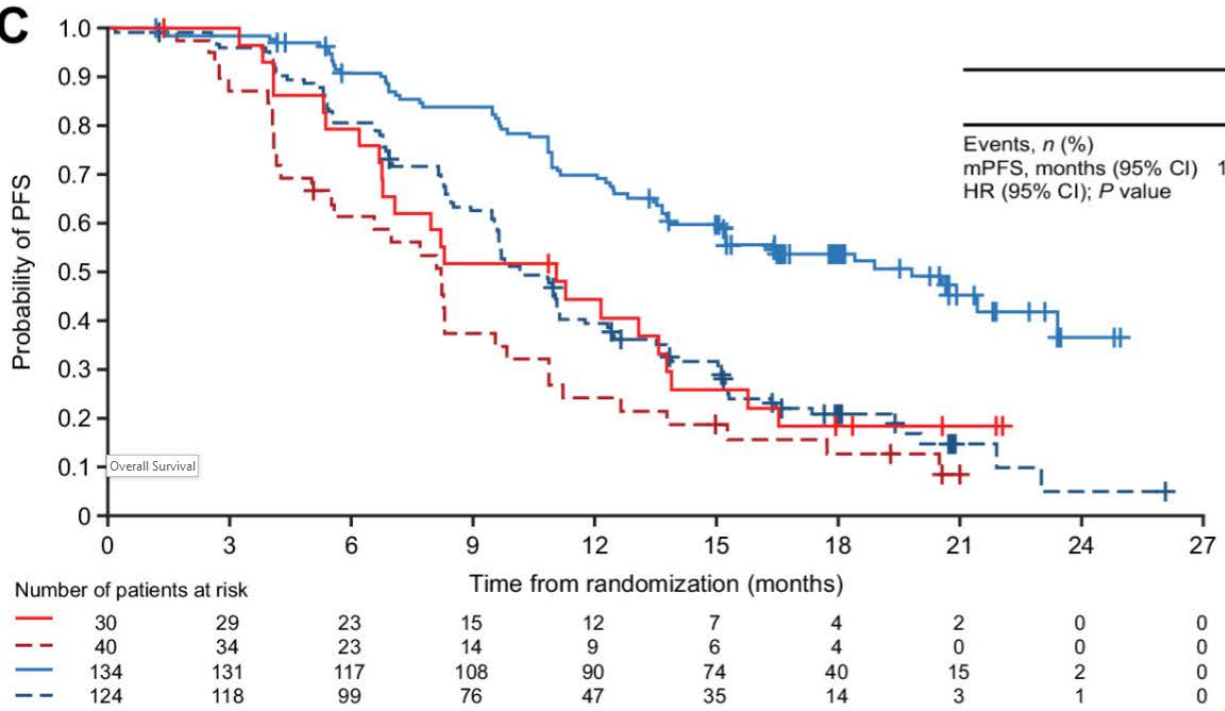


Before osimertinib

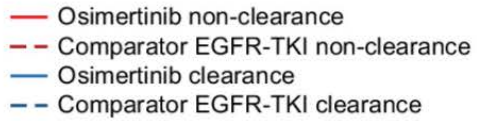
2 months after osimertinib

9 months after starting osimertinib

Can we use ctDNA to help stratify risk and adapt therapeutic approach?



	Week 6 non-clearance		Week 6 clearance	
	Osimertinib (*n* = 30)	Comparator EGFR-TKI (*n* = 40)	Osimertinib (*n* = 134)	Comparator EGFR-TKI (*n* = 124)
Events, *n* (%)	23 (77)	34 (85)	66 (49)	99 (80)
mPFS, months (95% CI)	11.1 (6.8–13.8)	8.2 (5.0–9.6)	19.8 (15.1–NC)	10.2 (9.5–11.1)
HR (95% CI); *P* value	0.69 (0.40–1.17); *P* = 0.164		0.40 (0.29–0.55); *P* < 0.0001	



NCT04410796: Randomized phase 2 trial evaluating osimertinib +/- chemotherapy after failure to clear ctDNA with osimertinib alone. Currently recruiting.

Gray et al, Clin Cancer Res 2023;29:3340-3351

How I treat metastatic EGFR-mutated NSCLC in 1L

- Individualized approach with shared decision making with ctDNA to help inform decision making

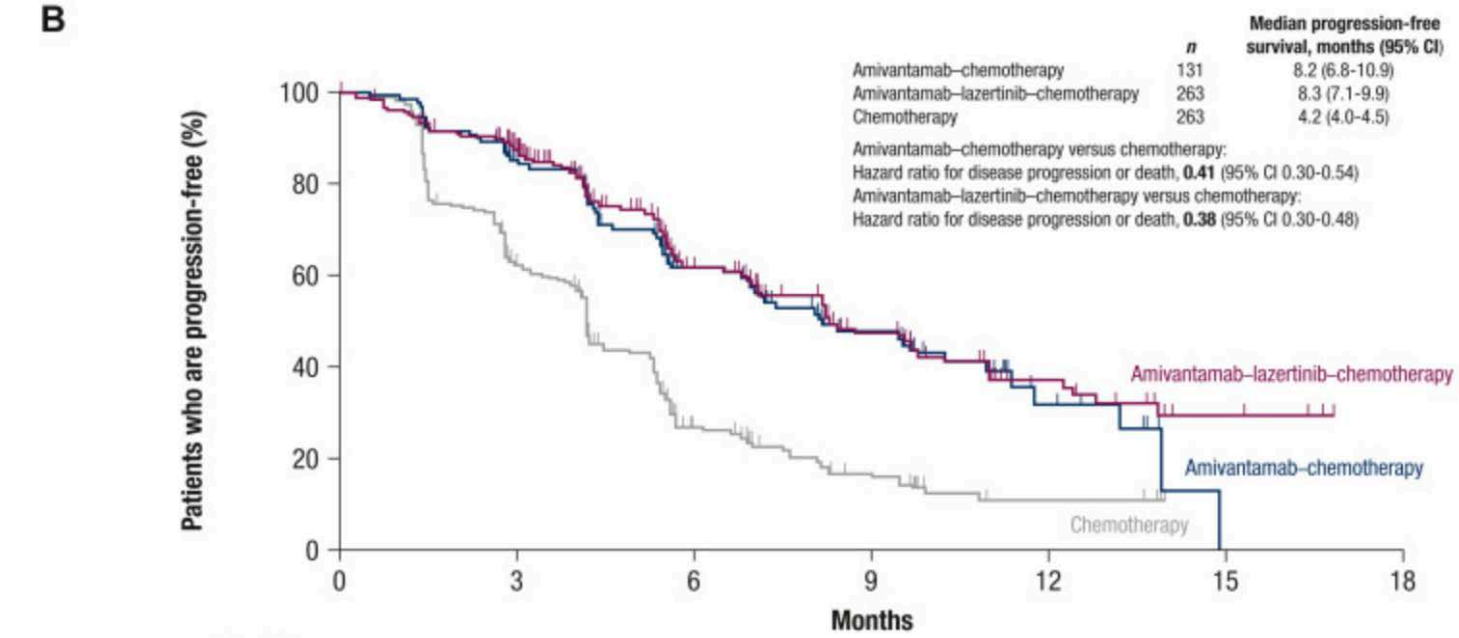
- Single-agent osimertinib remains very reasonable, particularly for:
  - Low burden of metastatic disease
  - No brain metastases
  - EGFR exon 19 deletion
  - Frail or elderly patients

- Consider chemotherapy and osimertinib for:
  - High-volume/symptomatic brain metastases
  - Heavy burden of disease with other poor prognostic markers (L858R, TP53)
  - Failure to clear ctDNA after 6 weeks of osimertinib

- Amivantamab + Lazertinib
  - Discuss this option, but toxicity and time burden is too much to recommend routinely
  - Subcutaneous Amivantamab and Lazertinib is more appealing but not yet approved
    - Equal efficacy
    - Dramatically decreased IRR, VTE risk, treatment time

Treatment after Osimertinib progression for metastatic, EGFR-mutated NSCLC

Mariposa-2: Chemotherapy + Amivantamab Prolongs PFS compared with chemo alone



Passaro et al, Ann Oncol 2024;35:77-90.

Mariposa-2: Chemotherapy + Amivantamab Prolongs intracranial PFS compared with chemo alone

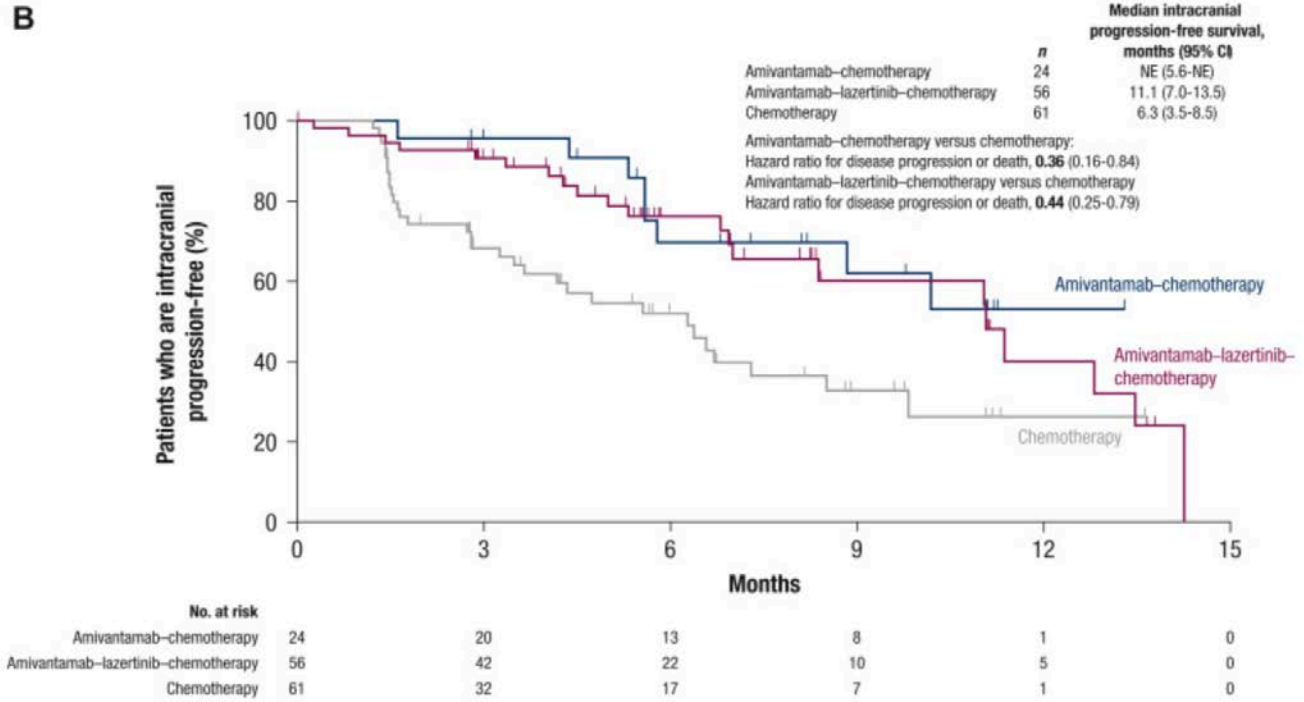
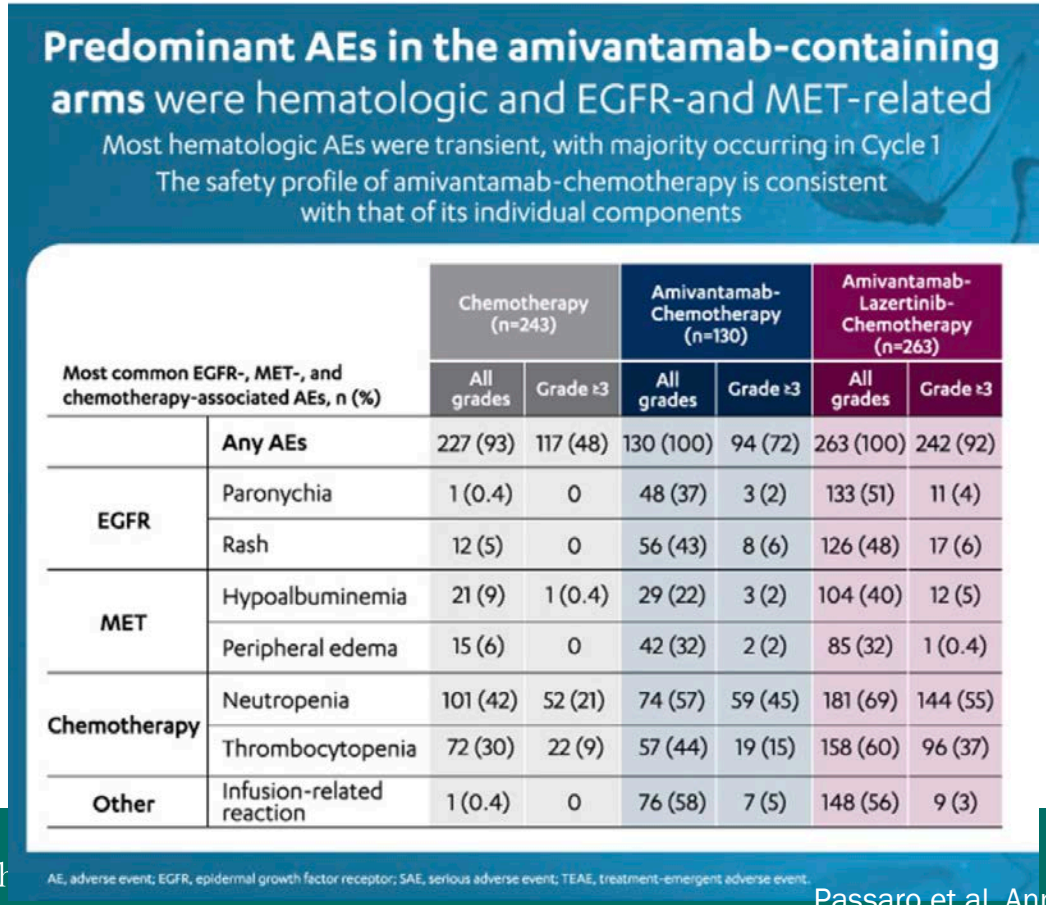


Figure 3 Intracranial progression-free survival.

Passaro et al, Ann Oncol 2024;35:77-90.

Adverse events increased with chemotherapy+amivantamab



Predominant AEs in the amivantamab-containing arms were hematologic and EGFR-and MET-related

Most hematologic AEs were transient, with majority occurring in Cycle 1

The safety profile of amivantamab-chemotherapy is consistent with that of its individual components

Most common EGFR-, MET-, and chemotherapy-associated AEs, n (%)		Chemotherapy (n=243)		Amivantamab-Chemotherapy (n=130)		Amivantamab-Lazertinib-Chemotherapy (n=263)	
		All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	Any AEs	227 (93)	117 (48)	130 (100)	94 (72)	263 (100)	242 (92)
EGFR	Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
	Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
MET	Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
	Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Chemotherapy	Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
	Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Other	Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)

AE, adverse event; EGFR, epidermal growth factor receptor; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Passaro et al, Ann Oncol 2024;35:77-90.

Chemotherapy + Amivantamab Take Aways

- Chemotherapy + Amivantamab prolongs PFS and intracranial PFS compared with chemo alone after Osimertinib progression
- Significantly increased toxicity with combination approach
- Consider for fit, highly motivated patients after Osimertinib progression
  - Particularly if high MET expression?

Summary

- New Standards of Care
  - Lorlatinib for treatment naïve, stage 4, ALK+ NSCLC
  - Osimertinib after chemoradiation for stage 3, unresectable, EGFR-mutated NSCLC
  - Durvalumab after chemoradiation for LS-SCLC
  - Tarlatamab for ES-SCLC after progression on at least 1 line of therapy

- Still controversial
  - Best Immunotherapy strategy for patients with resectable NSCLC
    - Consider additional immunotherapy if no pathologic CR to neoadjuvant chemoimmunotherapy
  - Chemotherapy + Osimertinib for ”high-risk,” treatment naïve, metastatic EGFR-mutated NSCLC
  - Chemotherapy + Amivantamab for metastatic, EGFR-mutated NSCLC after progression on osimertinib

Thank you