Applications for Community Oncology

Lung Cancer Data Review

May 2, 2024

cornerstone specialty network™

Key Studies

Perioperative NSCLC	EGFR Mutated Metastatic NSCLC	Metastatic and Actionable Mutated NSCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • KEYNOTE 789 • HERTHENA-Lung01	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

KEYNOTE-671

Does perioperative pembrolizumab benefit patients with early-stage NSCLC?

On October 16, 2023, the US FDA granted pembrolizumab approval for the treatment of resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery

KEYNOTE-671

Study Design: Randomized, double-blinded phase III

Stratified by: Disease stage (II vs III), PD-L1 TPS (<50% vs ≥50%), Histology (squamous vs non-squamous), Geographic region (east Asia vs not east Asia)

Key Eligibility Criteria
- Pathologically confirmed, resectable stage II, IIIA, or IIIB (N2) NSCLC per AJCC v8
- No prior therapy
- Able to undergo surgery
- Provision of tumor sample for PD-L1 evaluation[a]
- ECOG PS 0 or 1

(N = 786)

R 1:1

Pembrolizumab 200 mg IV Q3W + Cisplatin and Gemcitabine[b] or Cisplatin and Pemetrexed[c] for up to 4 cycle

Placebo IV Q3W + Cisplatin and Gemcitabine[b] or Cisplatin and Pemetrexed[c] for up to 4 cycles

SURGERY

Pembrolizumab 200 mg IV Q3W for up to 13 cycle

Placebo IV Q3W for up to 13 cycles

[a]Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx

Dual primary endpoints: EFS per investigator review and OS
Key secondary endpoints: mPR and pCR per blinded, independent pathology review and safety

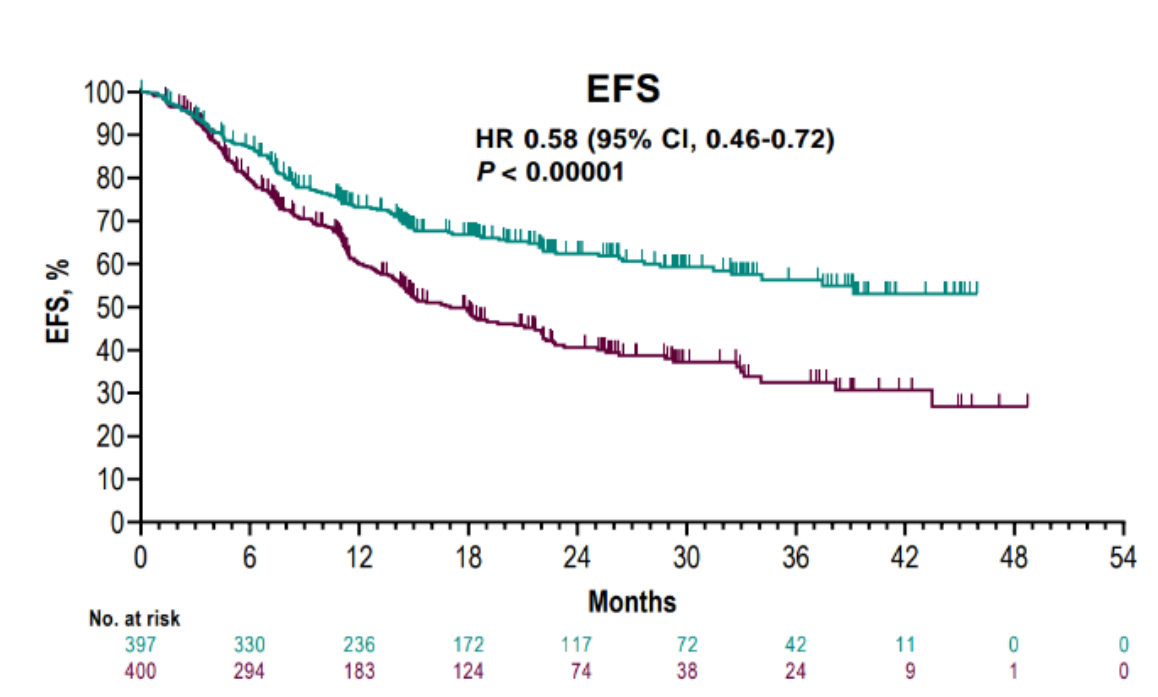
Interim analysis 2 (IA2)
– Prespecified to occur after ~416 EFS events observed
– Final analysis of EFS
– Interim analysis of OS (significance boundary, one-sided P = 0.00543)
– Data cutoff date: July 10, 2023

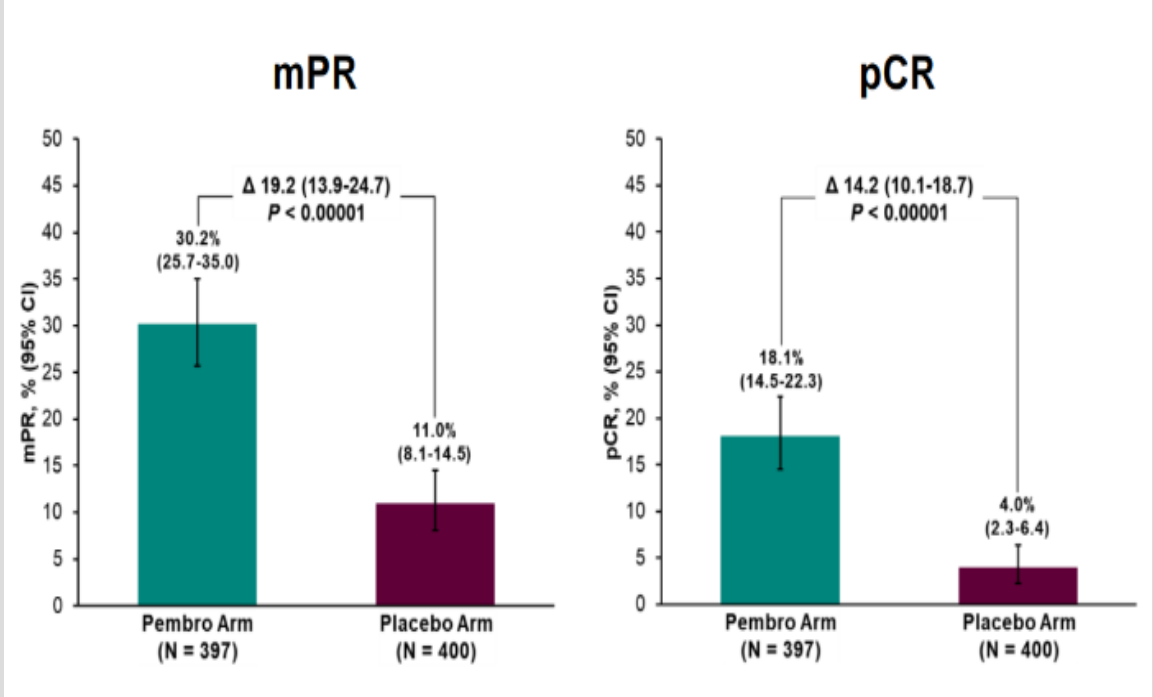
b Cisplatin 75 mg/m2 IV Q3W + gemcitabine 1000 mg/m2 IV on days 1 and 8 Q3W was permitted for squamous histology only.
c Cisplatin 75 mg/m2 IV Q3W + pemetrexed 500 mg/m2 IV Q3W was permitted for nonsquamous histology only.
d Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease.

KEYNOTE-671

Interim Analysis 1 (previously reported)

Data cutoff: July 29, 2022





- Neoadjuvant pembrolizumab + chemotherapy followed by surgery and adjuvant pembrolizumab significantly improved EFS, mPR, and pCR compared with neoadjuvant chemotherapy and surgery alone
- AE profile was as expected based on the known profiles of the individual treatment components

Wakelee H et al. N Engl J Med 2023;389:491-503.

Note - mPR: major pathological response; pCR pathological complete response

KEYNOTE-671

Baseline Characteristics

Characteristic	Pembrolizumab Arm (n = 397)	Placebo Arm (n = 400)
Male, n (%)	279 (70.3%)	284 (71.0%)
Median age, yr (range)	63 (26-83)	64 (35-81)
Race		
• American Indian or Alaska Native	1 (0.3%)	0
• Asian	124 (31.2%)	125 (31.3%)
• Black or African American	6 (1.5%)	10 (2.5%)
• Multiple	3 (0.8%)	10 (2.5%)
• White	250 (63.0%)	239 (59.8%)
• Missing data	13 (3.3%)	16 (4.0%)
Geographic Region		
• East Asia	123 (31.0%)	121 (30.3%)
• Not East Asia	274 (69.0%)	279 (69.8%)
ECOG PS		
• 0	253 (63.7%)	246 (61.5%)
• 1	144 (36.3%)	154 (38.5%)
Histology		
• Non-squamous	226 (59.6%)	227 (56.8%)
• Squamous	171 (43.1%)	173 (43.3%)

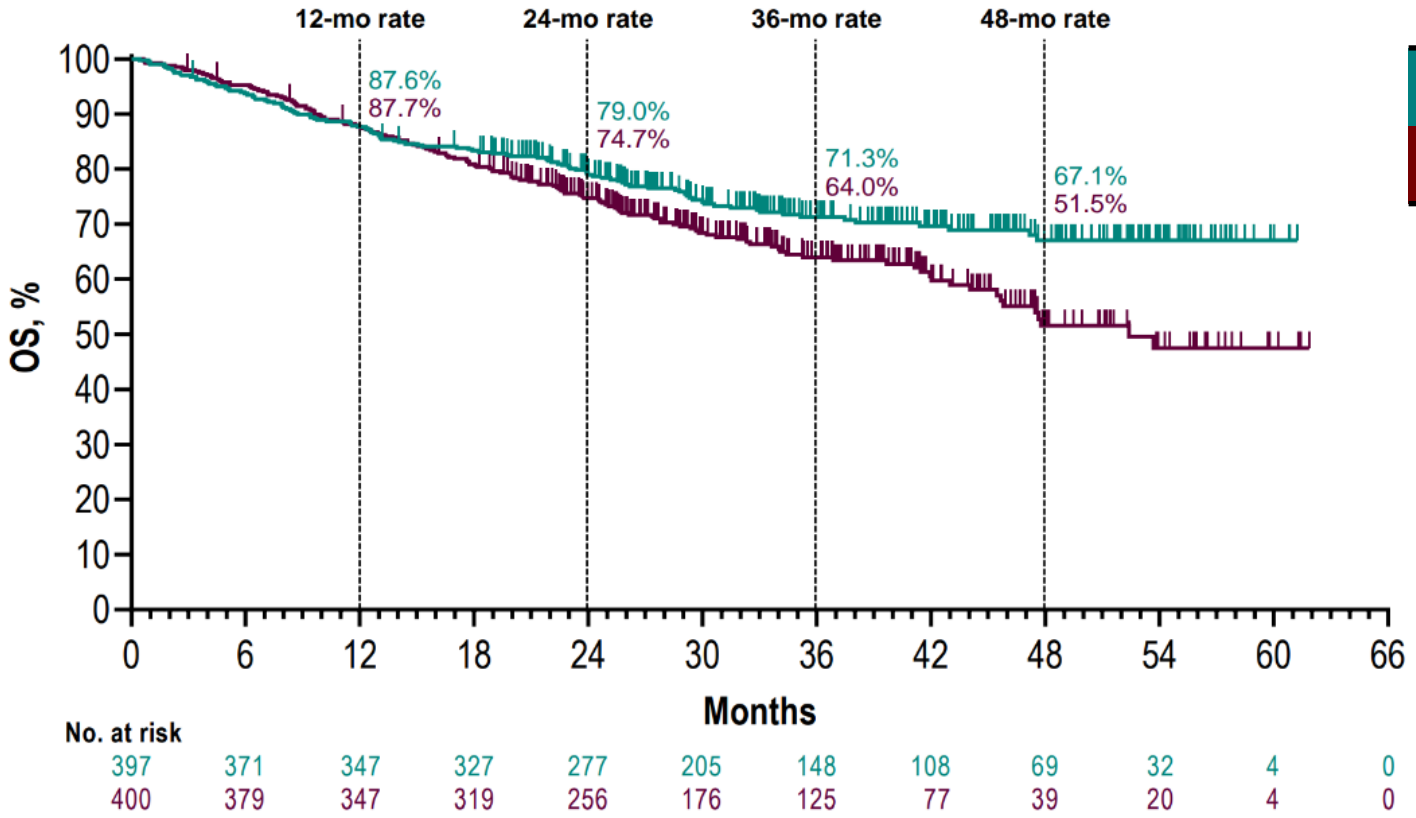
Characteristic, %	Pembrolizumab Arm (n = 397)	Placebo Arm (n = 400)
Smoking Status		
• Current	96 (24.2%)	103 (25.8%)
• Former	247 (62.2%)	250 (62.5%)
• Never	54 (13.6%)	47 (11.8%)
Clinical Stage		
• II	118 (29.7%)	121 (30.3%)
• IIIA	217 (54.7%)	224 (56.0%)
• IIIB	62 (15.6%)	55 (13.8%)
N Status		
• cN0	148 (37.3%)	142 (35.5%)
• cN1	81 (20.4%)	71 (17.8%)
• cN2	168 (42.3%)	187 (46.8%)
PD-L1 TPS		
• ≥50%	132 (33.2%)	134 (33.5%)
• 1-49%	127 (32.0%)	115 (28.8%)
• <1%	138 (34.8%)	151 (37.8%)
Known EGFR mutation	14 (3.5%)	19 (4.8%)
Known ALK translocation	12 (3.0%)	9 (2.3%)

EGFR mutation and ALK translocation status were tested locally per investigator discretion. EGFR status was unknown in 272 (68.5%) participants in the pembro arm and 257 (64.3%) in the placebo arm; ALK status was unknown in 281 (70.8%) and 259 (64.8%), respectively.

Data cutoff date for IA2: July 10, 2023.

KEYNOTE-671

Overall Survival: Interim Analysis 2



	Pts with Event	Median (95% CI), months
Pembro Arm	27.7%	NR (NR – NR)
Placebo Arm	36.0%	52.4 (45.7 – NR)

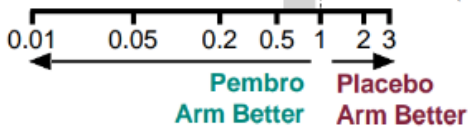
HR 0.72 (95% CI, 0.56-0.93)
one-sided P = 0.00517[a]

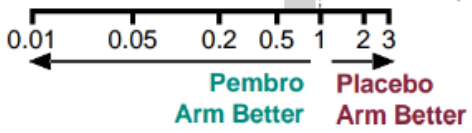
OS defined as time from randomization to death from any cause. a Significance boundary at IA2, one-sided P = 0.00543.
Data cutoff date for IA2: July 10, 2023.
Median Follow-Up: 36.6 months (range, 18.8-62.0)

KEYNOTE-671

Overall Survival in Subgroups: Interim Analysis 2

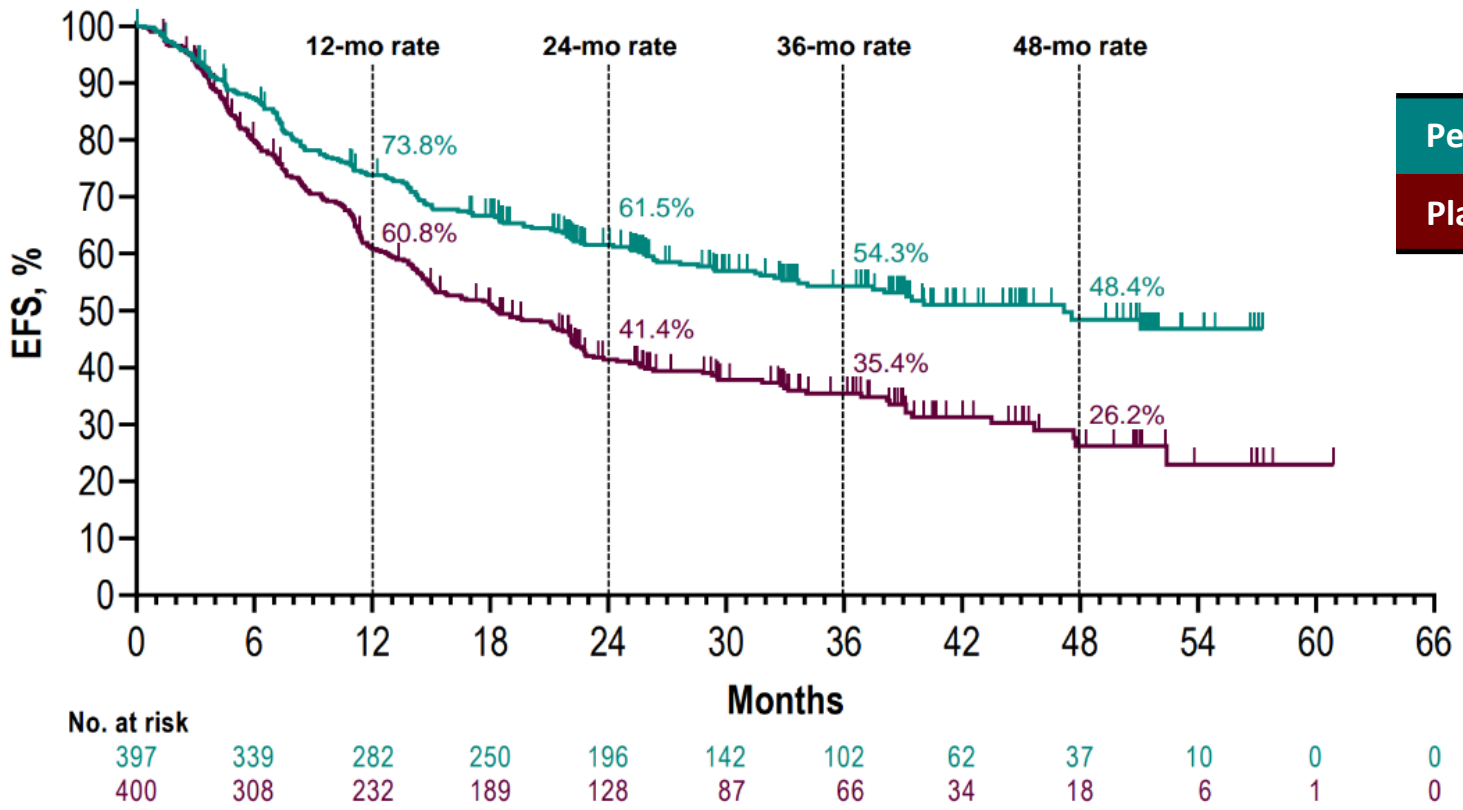
Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	110/397	144/400	0.72 (0.56-0.93)
Age			
<65 y	54/221	82/214	0.57 (0.40-0.80)
≥65 y	56/176	62/186	0.96 (0.67-1.38)
Sex			
Female	21/118	30/116	0.69 (0.39-1.20)
Male	89/279	114/284	0.73 (0.55-0.96)
Race			
White	73/250	97/239	0.66 (0.49-0.90)
All others	34/134	39/145	0.93 (0.59-1.48)
Geographic region			
East Asia	32/123	30/121	1.05 (0.64-1.73)
Not east Asia	78/274	114/279	0.63 (0.48-0.85)
Smoking status			
Current	31/96	48/103	0.59 (0.38-0.93)
Former	69/247	87/250	0.76 (0.56-1.05)
Never	10/54	9/47	1.00 (0.41-2.46)
Histology			
Nonsquamous	49/226	64/227	0.73 (0.50-1.06)
Squamous	61/171	80/173	0.71 (0.51-0.99)
Clinical stage			
II	26/118	39/121	0.67 (0.41-1.10)
IIIA	62/217	79/224	0.74 (0.53-1.03)
IIIB	22/62	26/55	0.69 (0.39-1.22)
N status			
cN0	40/148	52/142	0.70 (0.46-1.06)
cN1	21/81	24/71	0.74 (0.41-1.33)
cN2	49/168	68/187	0.74 (0.52-1.07)
PD-L1 TPS			
≥50%	23/132	39/134	0.55 (0.33-0.92)
1-49%	35/127	44/115	0.69 (0.44-1.07)
<1%	52/138	61/151	0.91 (0.63-1.32)
***EGFR* mutation**			
No	20/111	33/124	0.64 (0.37-1.11)
Yes	1/14	5/19	0.24 (0.03-2.03)
Unknown	89/272	106/257	0.75 (0.56-0.99)
***ALK* translocation**			
No	22/104	38/132	0.70 (0.41-1.18)
Unknown	87/281	105/259	0.72 (0.54-0.96)





KEYNOTE-671

Event-Free Survival: Interim Analysis 2



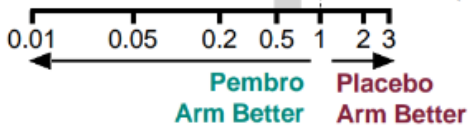
	Pts with Event	Median (95% CI), months
Pembro Arm	43.8%	47.2 (32.9 – NR)
Placebo Arm	62.0%	18.3 (14.8 – 22.1)

HR 0.59 (95% CI, 0.48-0.72)

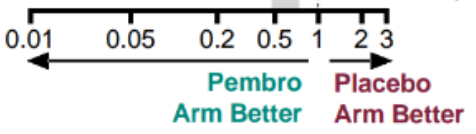
KEYNOTE-671

Event-Free Survival in Subgroups: Interim Analysis 2

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)



KEYNOTE-671

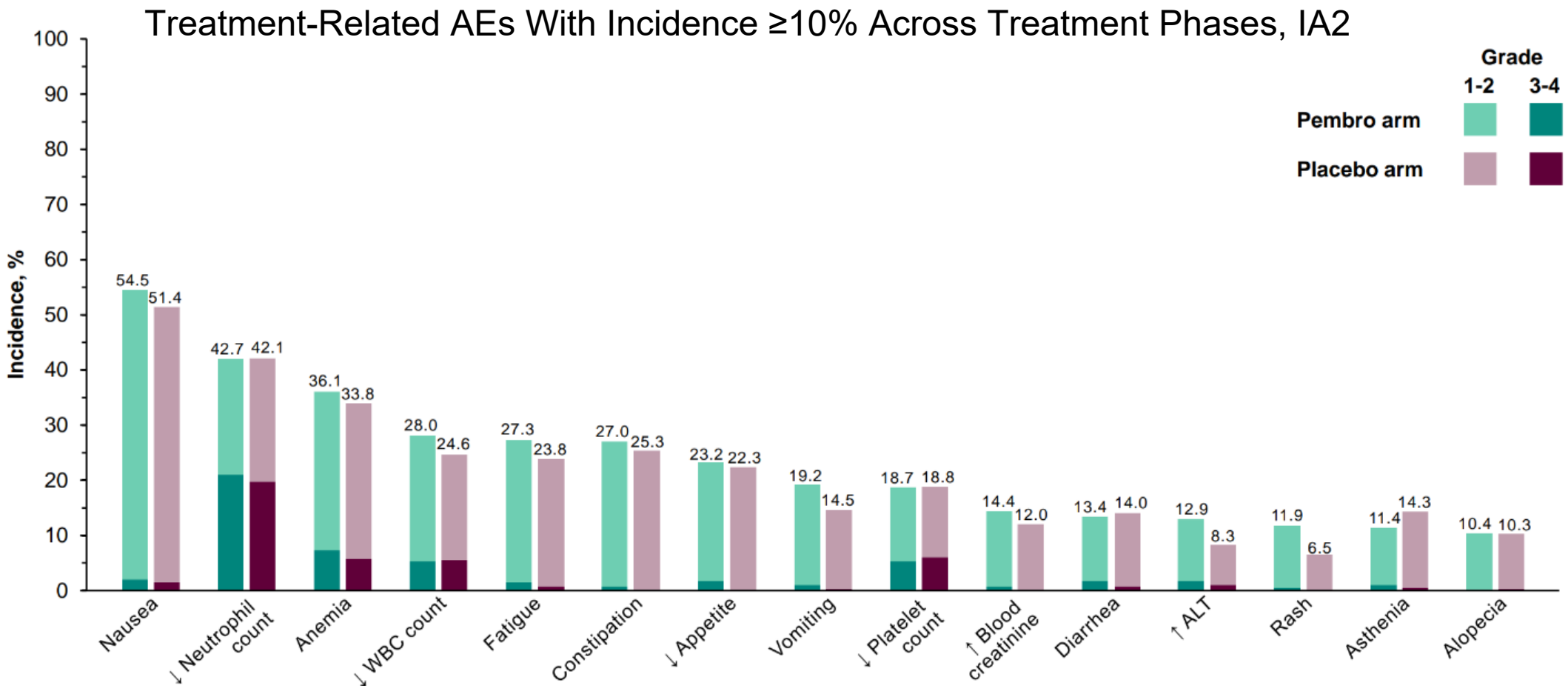
Safety: Interim Analysis 2

	Pembrolizumab Arm (n = 396)	Placebo Arm (n = 399)
Exposure		
• Study days on pembro or placebo, median (range)	375.5 days (1-728)	337.0 days (1-644)
• No. pembro or placebo administrations, median (range)	15 (1-17)	12 (1-17)
Treatment Related AEs[a]	383 (96.7%)	381 (95.5%)
• Grade 3 – 5	179 (45.2%)	151 (37.8%)
• Serious	73 (18.4%)	58 (14.5%)
• Led to death	4 (1.0%)[b]	3 (0.8%)[c]
• Led to discontinuation of all study treatment	54 (13.6%)	21 (5.3%)
Immune-mediated AEs and infusion reactions	103 (26.0%)	36 (9.0%)
• Grade 3 – 5	26 (6.6%)	6 (1.5%)
• Serious	24 (6.1%)	6 (1.5%)
• Led to death	1 (0.3%)[d]	0
• Led to discontinuation of all study treatment	23 (5.8%)	3 (0.8%)

a Considered by the investigator to be related to chemotherapy, pembrolizumab, and placebo.
b AEs leading to death (n = 1 each): atrial fibrillation, immune-mediated lung disease, pneumonia, and sudden cardiac death (no new treatment-related deaths vs IA1).
c AEs leading to death (n = 1 each): acute coronary syndrome, pneumonia, and pulmonary hemorrhage (no new treatment-related deaths vs IA1).
d AE leading to death: pneumonitis (recorded in the database as immune-mediated lung disease; no new immune-mediated deaths vs IA1).

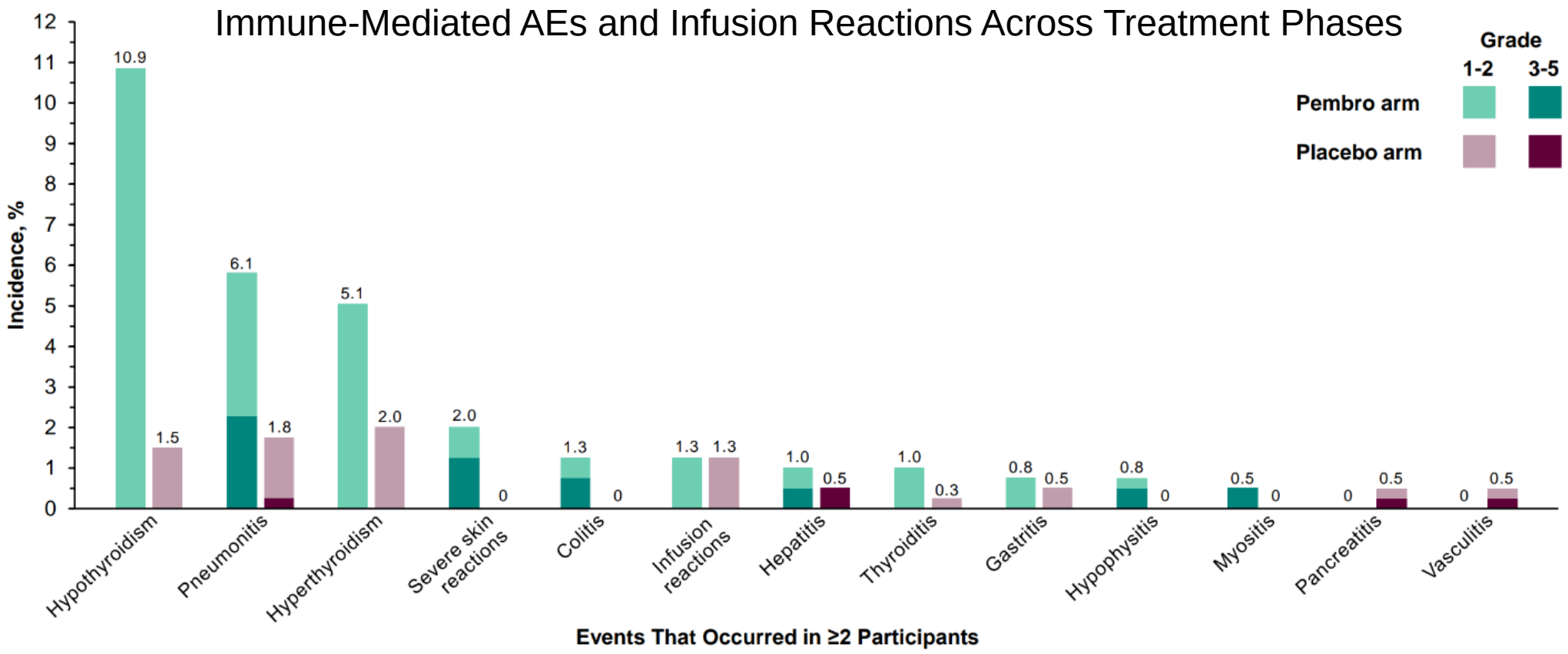
KEYNOTE-671

Safety: Interim Analysis 2



KEYNOTE-671

Safety: Interim Analysis 2



SUMMAY

KEYNOTE-671

- At Interim analysis 2 there was a significant improvement in overall survival for neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab versus neoadjuvant chemotherapy and surgery alone
  - HR was 0.72 (95% CI, 0.56-0.93)

- EFS benefit observed at Interim Analysis 1 was maintained at Interim Analysis 2

- No new safety signals observed

Note: Molecular testing was not mandated in KEYNOTE-671, and very few patients with EGFR mutations or ALK translocations in their tumors were identified, limiting any insights in these subgroups.

ESMO 2023, Abstr LBA56

KEYNOTE-671

Perioperative pembrolizumab (with neoadjuvant chemotherapy) should be considered as a potential standard of care approach for early-stage NSCLC

Key Studies

Neoadjuvant, Perioperative, Adjuvant NSCLC	Metastatic and Actionable EGFR Mutated NSCLC	Metastatic and Actionable Mutated NSCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • KEYNOTE 789 • HERTHENA-Lung01	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

AEGEAN

Does perioperative durvalumab benefit patients with early-stage NSCLC?

KEY DATA

AEGEAN

Study Design: International randomized, double-blinded phase III

- Patients with previously untreated resectable NSCLC (stage IIA-IIIB per AJCC 8th ed)
- Planned lobectomy, sleeve resection, or bilobectomy
- Confirmed PD-L1 status*
- No documented EGFR/ALK mutations
- ECOG PS 0/1

(N = 802)

Stratified 1:1 by disease stage (II vs III), PD-L1 expression (<1% vs ≥1%)

R 1:1

Durvalumab 1500 mg IV + Platinum-based CT† Q3W x 4

(n = 366)

Placebo IV Q3W + Platinum-based CT† Q3W x 4

(n = 374)

SURGERY‡

Durvalumab 1500 mg IV Q4W x 12

Placebo IV Q4W x 12

Primary endpoints: pCR by central lab, EFS by BICR (RECIST v1.1)
Secondary endpoints: MPR by central lab, DFS by BICR (RECIST v1.1), OS

*Per Ventana PD-L1 (SP263) IHC.
†Based on histology and investigator decision: nonsquamous, cisplatin + pemetrexed or carboplatin + pemetrexed; squamous, carboplatin + paclitaxel, cisplatin + gemcitabine, or carboplatin + gemcitabine if comorbidities present and/or unlikely to tolerate cisplatin.
‡Postoperative RT permitted per local guidance.

Mitsudomi. WCLC 2023. Abstr OA12.05. Heymach. AACR 2023. Abstr CT005. N Engl J Med 2023;389:1672-84.

AEGEAN

Baseline Characteristics

Characteristic, %		Durvalumab + CT (n = 366)	Pbo + CT (n = 374)
Median age, yr (range)		65.0 (30-88)	65.0 (39-85)
Age ≥75 yr		12.0	9.6
Male		68.9	74.3
ECOG PS 1		31.4	31.8
Race	• Asian • White • Other	39.1 56.3 4.6	43.9 51.1 5.1
Region	• Asia • Europe • N America • S America	38.8 38.5 11.7 10.9	43.6 37.4 11.5 7.5
Smoking status	• Current • Former • Never	26.0 60.1 13.9	25.4 59.6 15.0
Planned neoadjuvant Chemotherapy	• Cisplatin • Carboplatin	27.3 72.7	25.7 74.3

Characteristic, %		Durvalumab + CT (n = 366)	Pbo + CT (n = 374)
Disease stage (AJCC 8th ed)	• II • IIIA • IIIB	28.4 47.3 24.0	29.4 44.1 26.2
Histology	• Squamous • Non-squamous	46.2 53.6	51.1 47.9
PD-L1 expression	• TC <1% • TC 1%-49% • TC ≥50%	33.3 36.9 29.8	33.4 38.0 28.6
Primary tumor	• T1 • T2 • T3 • T4	12.0 26.5 35.0 26.5	11.5 28.9 34.5 25.1
Regional LNs	• N0 • N1 • N2 • Single station • Multistation	30.1 20.5 49.5 38.5 9.3	27.3 23.3 49.5 35.3 10.7

KEY DATA

AEGEAN

Neoadjuvant Treatment and Surgery Summary in mITT* Population

Outcome	Durvalumab + CT (n = 366)	Placebo + CT (n = 374)
Received neoadjuvant tx, n (%)	366 (100)	371 (99.2)
Completed 4 cycles of plt doublet, n (%)	310 (84.7)	326 (87.2)
Completed 4 cycles of durva or placebo, n (%)	318 (86.9)	331 (88.5)
Underwent surgery, n (%)	**295 (80.6)**	**302 (80.7)**
• Stage II/III, %	84.3/79.2	88.9/77.4
Did not undergo surgery, n (%)	**71 (19.4)**	**72 (19.3)**
• PD, %	6.8	7.8
• Patient decision, %	3.3	4.5
• Unfit for surgery, %	4.1	2.7
• Death, %	2.5	0.5
• AEs, %	1.4	1.1
• Other, %	1.4	2.7
Completed surgery, n (%)	**284 (77.6)**	**287 (76.7)**
• Stage II/III, %	83.3/75.4	86.1/72.9
Did not complete surgery, n (%)	**11 (3.0)**	**15 (4.0)**
• PD, %	1.4	2.1
• Unfit to complete surgery, %	0.3	0.3
• Other, %	1.4	1.6

Outcome	Durvalumab + CT	Placebo + CT
	(n = 295)	**(n = 302)**
Median duration from last neoadjuvant tx dose to surgery, days (range)	34.0 (12-91)	34.0 (13-103)
• Stage II	34.0 (14-90)	34.0 (14-103)
• Stage III	34.0 (12-91)	34.0 (13-96)
Median duration from surgery to first adjuvant tx dose, days (range)	50.0 (22-136)	52.0 (21-141)
• Stage II	49.0 (26-97)	49.0 (21-112)
• Stage III	51.0 (22-136)	55.0 (22-141)
Adjuvant Phase, ongoing	**(n = 366)**	**(n = 374)**
• Started durvalumab or placebo	241 (65.8)	237 (63.4)
• Completed durvalumab or placebo	88 (24.0)	79 (21.1)
• Discontinued durvalumab or placebo	68 (18.6)	70 (18.7)
• Ongoing durvalumab or placebo	85 (23.2)	88 (23.5)

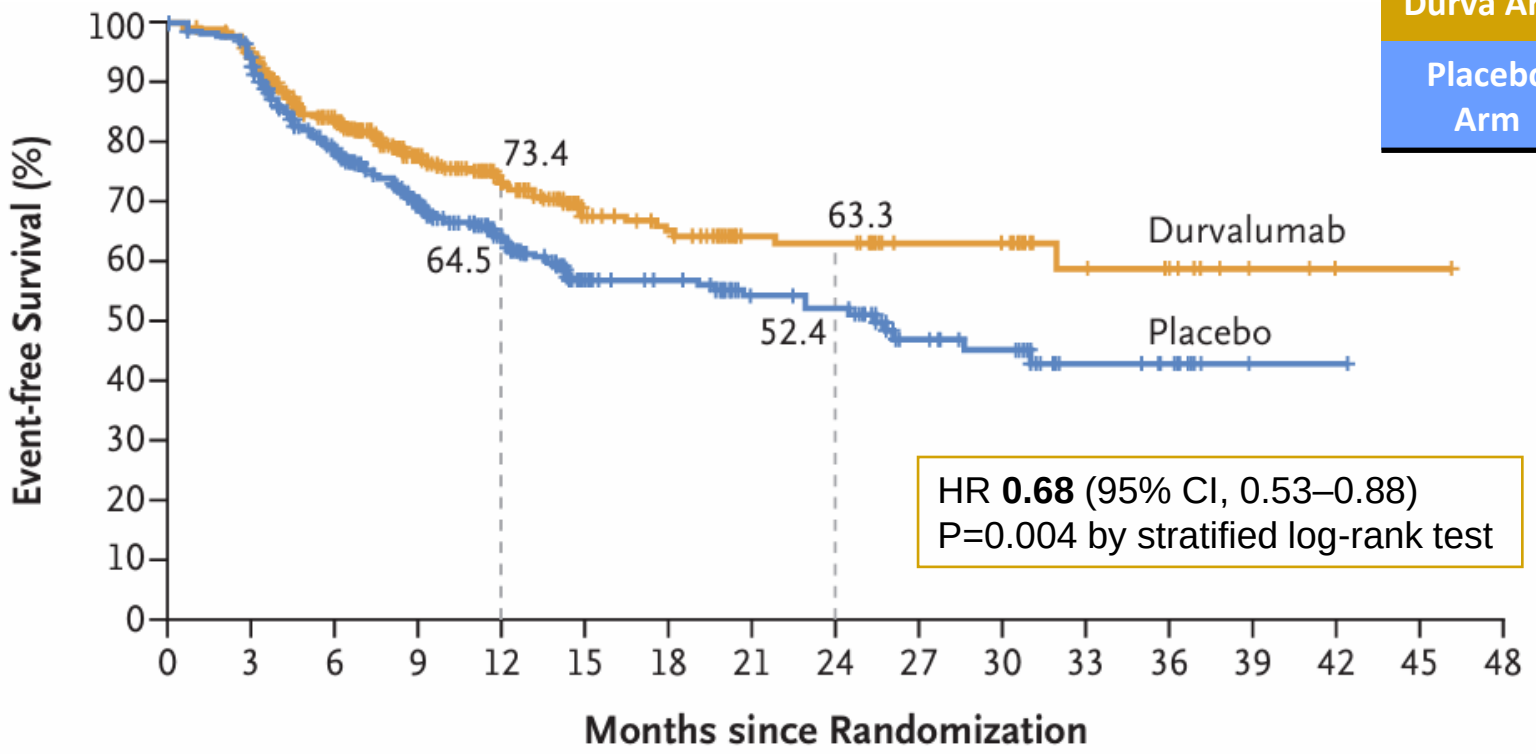
*Pts with documented EGFR/ALK aberrations were excluded for efficacy analyses in the modified intent-to-treat (mITT) population

WCLC 2023. Abstr OA12.05.

AEGEAN

Event-Free Survival in mITT Population

	No. of Events/No. of Pts	Median EFS (95% CI), months
Durva Arm	98/366 (26.8%)	NR (31.9–NR)
Placebo Arm	138/374 (36.9%)	25.9 (18.9–NR)



No. at Risk

Durvalumab	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
Placebo	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

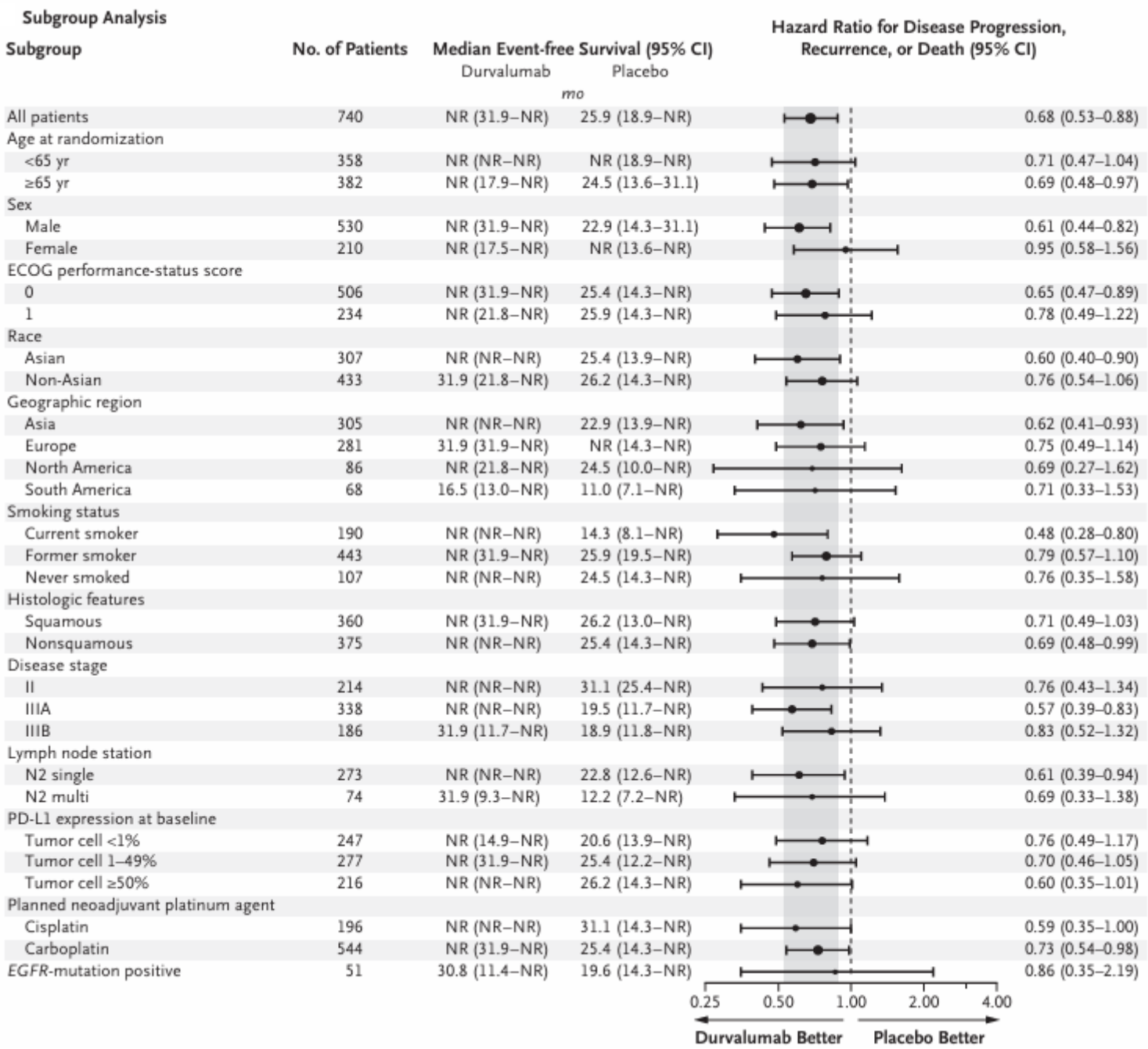
Note: analyses of data from 740 patients as of the data cutoff of November 10, 2022

N Engl J Med 2023;389:1672-84.

KEY DATA

AEGEAN

Event-Free Survival Subgroup Analysis



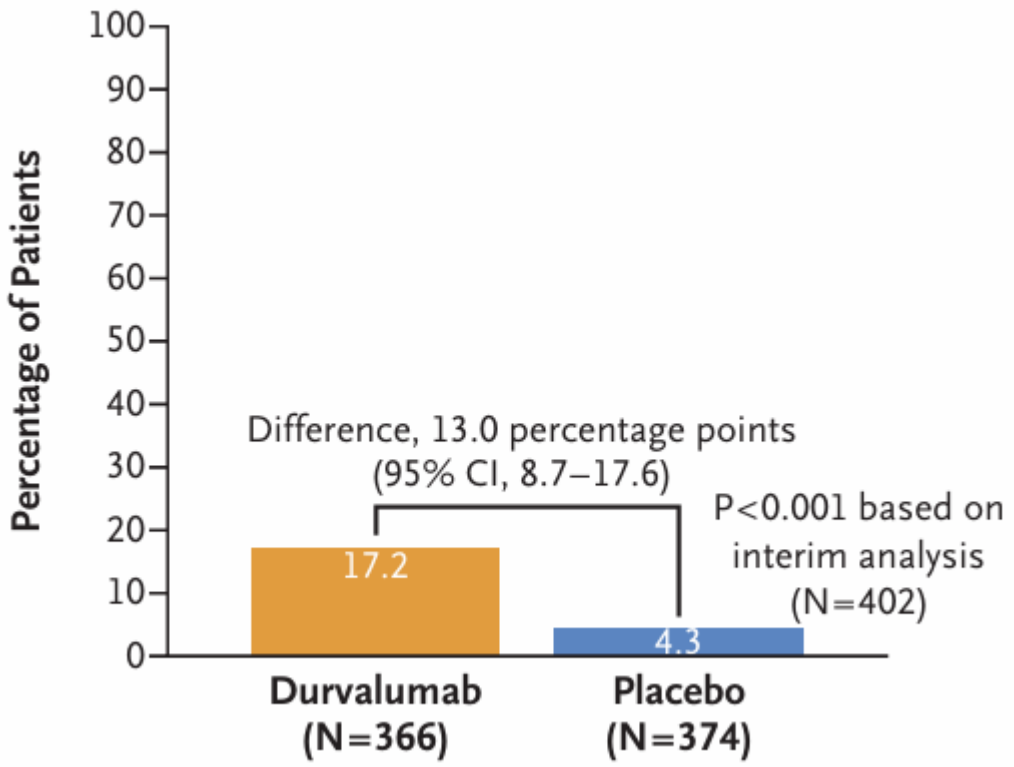
Note: The size of the data point is proportional to the number of events in each subgroup.
Shading indicates the hazard ratio and 95% confidence interval for the modified intention-to-treat population.
NR, not reached

N Engl J Med 2023;389:1672-84.

KEY DATA

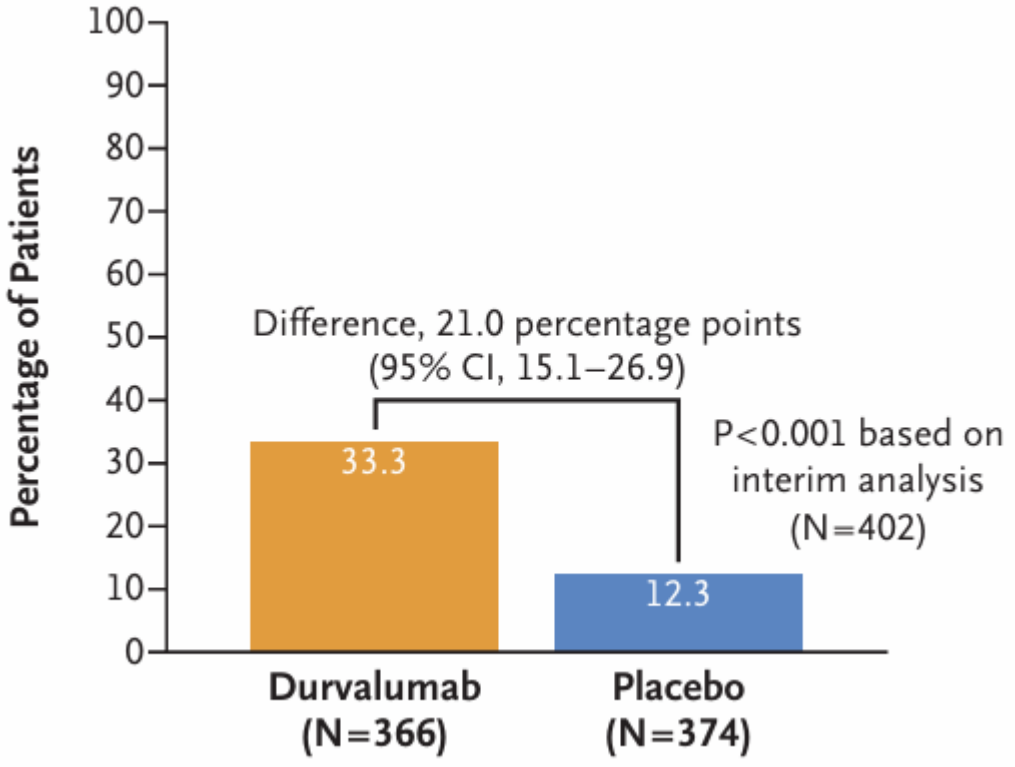
AEGEAN

Pathological Complete Response



Pathological complete response was defined as a lack of viable tumor cells after complete evaluation of the resected lung-cancer specimen and all sampled regional lymph nodes.

Major Pathological Response



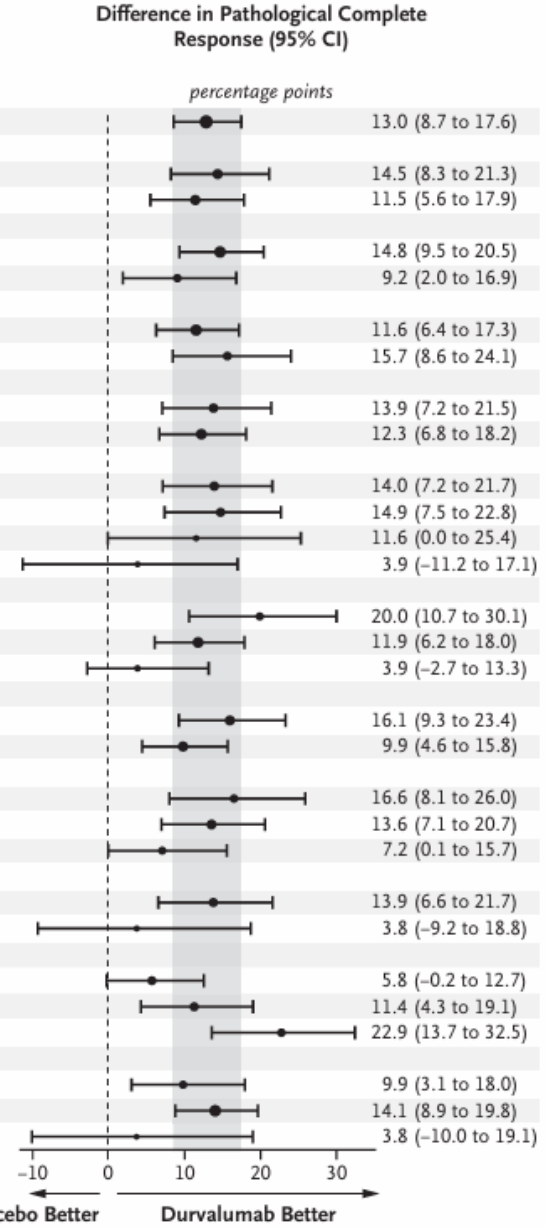
Major pathological response was defined as 10% or less of viable tumor cells in the lung primary tumor after complete evaluation of the resected lung-cancer specimen.

N Engl J Med 2023;389:1672-84.

AEGEAN

Subgroup Analysis for Pathological Complete Response

Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Difference in Pathological Complete Response (95% CI)
		Durvalumab	Placebo	
		percent		*percentage points*
All patients	740	17.2 (13.5 to 21.5)	4.3 (2.5 to 6.9)	13.0 (8.7 to 17.6)
Age at randomization				
<65 yr	358	18.3 (12.9 to 24.8)	3.8 (1.6 to 7.7)	14.5 (8.3 to 21.3)
≥65 yr	382	16.2 (11.3 to 22.2)	4.7 (2.2 to 8.8)	11.5 (5.6 to 17.9)
Sex				
Male	530	19.4 (14.7 to 24.9)	4.7 (2.5 to 7.9)	14.8 (9.5 to 20.5)
Female	210	12.3 (6.9 to 19.7)	3.1 (0.6 to 8.9)	9.2 (2.0 to 16.9)
ECOG performance-status score				
0	506	16.7 (12.3 to 21.9)	5.1 (2.7 to 8.6)	11.6 (6.4 to 17.3)
1	234	18.3 (11.7 to 26.5)	2.5 (0.5 to 7.2)	15.7 (8.6 to 24.1)
Race				
Asian	307	18.2 (12.2 to 25.5)	4.3 (1.7 to 8.6)	13.9 (7.2 to 21.5)
Non-Asian	433	16.6 (12.0 to 22.1)	4.3 (2.0 to 8.0)	12.3 (6.8 to 18.2)
Geographic region				
Asia	305	18.3 (12.3 to 25.7)	4.3 (1.7 to 8.6)	14.0 (7.2 to 21.7)
Europe	281	19.9 (13.6 to 27.4)	5.0 (2.0 to 10.0)	14.9 (7.5 to 22.8)
North America	86	14.0 (5.3 to 27.9)	2.3 (0.1 to 12.3)	11.6 (0.0 to 25.4)
South America	68	7.5 (1.6 to 20.4)	3.6 (0.1 to 18.3)	3.9 (−11.2 to 17.1)
Smoking status				
Current smoker	190	24.2 (16.0 to 34.1)	4.2 (1.2 to 10.4)	20.0 (10.7 to 30.1)
Former smoker	443	17.3 (12.5 to 22.9)	5.4 (2.8 to 9.2)	11.9 (6.2 to 18.0)
Never smoked	107	3.9 (0.5 to 13.5)	0.0 (0.0 to 6.4)	3.9 (−2.7 to 13.3)
Histology				
Squamous	360	21.3 (15.4 to 28.3)	5.2 (2.5 to 9.4)	16.1 (9.3 to 23.4)
Nonsquamous	375	13.3 (8.9 to 18.8)	3.4 (1.2 to 7.2)	9.9 (4.6 to 15.8)
Disease stage				
II	214	21.2 (13.8 to 30.3)	4.5 (1.5 to 10.3)	16.6 (8.1 to 26.0)
IIIA	338	18.5 (13.0 to 25.1)	4.8 (2.1 to 9.3)	13.6 (7.1 to 20.7)
IIIB	186	10.2 (4.8 to 18.5)	3.1 (0.6 to 8.7)	7.2 (0.1 to 15.7)
Lymph node station				
N2 single	273	18.4 (12.4 to 25.8)	4.5 (1.7 to 9.6)	13.9 (6.6 to 21.7)
N2 multi	74	8.8 (1.9 to 23.7)	5.0 (0.6 to 16.9)	3.8 (−9.2 to 18.8)
PD-L1 expression at baseline				
Tumor cell <1%	247	9.0 (4.6 to 15.6)	3.2 (0.9 to 8.0)	5.8 (−0.2 to 12.7)
Tumor cell 1–49%	277	16.3 (10.5 to 23.6)	4.9 (2.0 to 9.9)	11.4 (4.3 to 19.1)
Tumor cell ≥50%	216	27.5 (19.4 to 36.9)	4.7 (1.5 to 10.6)	22.9 (13.7 to 32.5)
Planned neoadjuvant platinum agent				
Cisplatin	196	12.0 (6.4 to 20.0)	2.1 (0.3 to 7.3)	9.9 (3.1 to 18.0)
Carboplatin	544	19.2 (14.6 to 24.4)	5.0 (2.8 to 8.3)	14.1 (8.9 to 19.8)
EGFR-mutation positive	51	3.8 (0.1 to 19.6)	0.0 (0.0 to 13.7)	3.8 (−10.0 to 19.1)



Note: The size of the data point is proportional to the number of events in each subgroup.
Shading indicates the hazard ratio and 95% confidence interval for the modified intention-to-treat population.

N Engl J Med 2023;389:1672-84.

KEY DATA

AEGEAN

Safety

Event, n (%)	Durvalumab Group (N = 401)	Placebo Group (N = 398)
Adverse events of any grade and any cause	**387 (96.5)**	**377 (94.7)**
• Maximum grade 3 or 4	170 (42.4)	172 (43.2)
• Serious adverse events	151 (37.7)	125 (31.4)
• Events leading to death	23 (5.7)	15 (3.8)
• Leading to discontinuation of durvalumab or placebo	48 (12.0)	24 (6.0)
• Leading to cancellation of surgery	7 (1.7)	4 (1.0)
Adverse events of any grade possibly related to durvalumab, placebo, or chemotherapy	**348 (86.8)**	**321 (80.7)**
• Maximum grade 3 or 4	130 (32.4)	131 (32.9)
• Events leading to death	7 (1.7)	2 (0.5)

Note: Adverse events with an outcome of death included deaths assessed by the investigator as possibly related to any systemic trial treatment and include interstitial lung disease (in two patients) and immune-mediated lung disease, pneumonitis, hemoptysis, myocarditis, and decreased appetite (one patient each) in the durvalumab group and pneumonia and infection (one patient each) in the placebo group.

Immune-mediated adverse events of any grade were reported in 23.7% of patients who received durvalumab and 9.3% of patients who received placebo; most were grade 1 or 2 adverse events, with grade 3 or 4 immune mediated adverse events reported in 4.2% and 2.5%, respectively, in the two groups.

Immune mediated pneumonitis of any grade was report ed in 3.7% of patients in the durvalumab group and 1.8% of those in the placebo group; grade 3 or 4 immune-mediated pneumonitis was reported in 1.2% and 1.0%, respectively.

N Engl J Med 2023;389:1672-84.

SUMMAY

AEGEAN

- Neoadjuvant durvalumab plus chemotherapy followed by adjuvant durvalumab resulted in significantly better event-free survival and pathological complete response compared to neoadjuvant chemotherapy alone
  - EFS HR 0.68 (p = 0.004)
  - pCR 13 % points difference (p<0.001)

- Benefits were observed across subgroups, including PD-L1 although benefit was greater in patients with PD-L1 expression of at least 50%

- No new safety signals observed

Note: the AEGEAN trial was designed and began enrollment prior to the approval for adjuvant osimertinib for patients with EGFR-mutated resectable NSCLC. No clear benefit was observed in the small subgroup before the protocol was amended.

N Engl J Med 2023;389:1672-84.

AEGEAN

Perioperative durvalumab (with neoadjuvant chemotherapy) should be considered as a potential standard of care approach for early-stage NSCLC

Key Studies

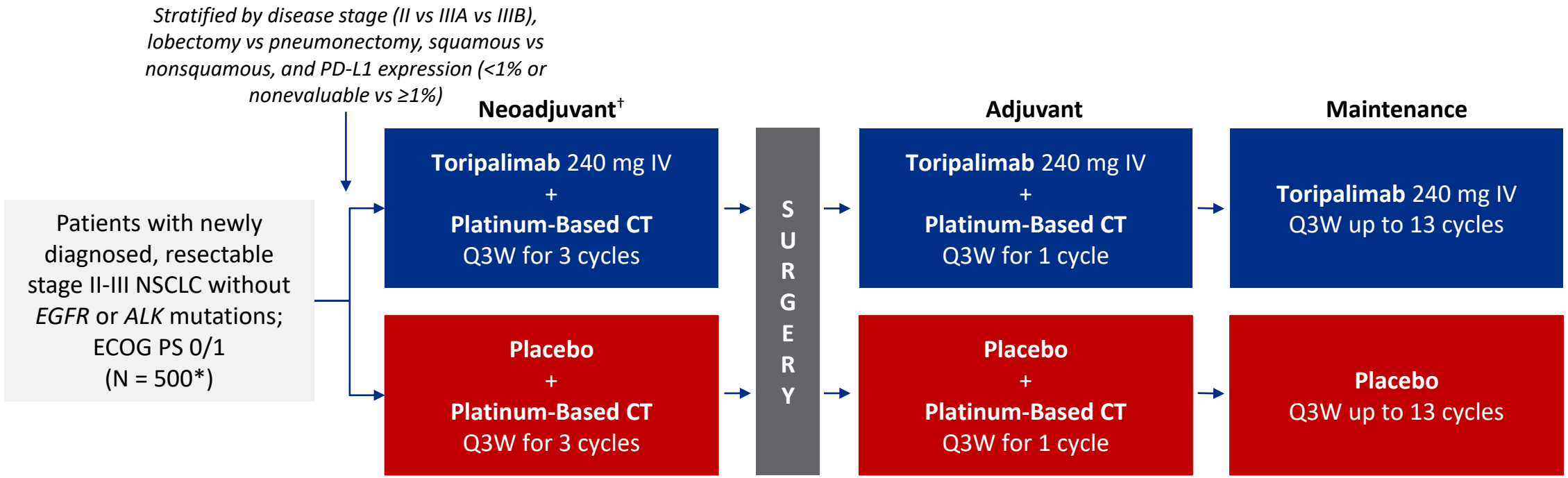
Neoadjuvant, Perioperative, Adjuvant NSCLC	Metastatic and Actionable EGFR Mutated NSCLC	Metastatic and Actionable Mutated NSCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • KEYNOTE 789 • HERTHENA-Lung01	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

NEOTORCH

Does perioperative toripalimab benefit patients with early-stage NSCLC?

NEOTORCH

Study Design: Randomized, double-blind, placebo-controlled, multicenter phase III trial



*Planned enrollment: ~400 stage III; ~100 stage II.

†Trial required 3 cycles of neoadjuvant CT, with total of 4 cycles of perioperative CT, allowing surgeon's choice of surgery timing.

Primary endpoints: EFS by investigator (stage III and stage II-III), MPR rate by BIPR (stage III and stage II-III)

Secondary endpoints: OS, pCR by BIPR (stage III and stage II-III), EFS by IRC (stage III and stage II-III), DFS, safety

Lu. ASCO 2023. Abstr 8501.
JAMA. 2024 Jan 16;331(3):201-211

NEOTORCH

Baseline Characteristics

Characteristic, n (%)	Toripalimab + CT (n = 202)	Placebo + CT (n = 202)
Median age, yr (range)	62 (31-70)	61 (29-70)
Age <65 yr	140 (69.3)	138 (68.3)
Male	181 (89.6)	189 (93.6)
Smoking status		
• Nonsmoker	28 (13.9)	21 (10.4)
• Smoker	30 (14.9)	23 (11.4)
• Former	144 (71.3)	158 (78.2)
ECOG PS		
• 0	70 (34.7)	73 (36.1)
• 1	132 (65.3)	129 (63.9)
Histology		
• Nonsquamous	45 (22.3)	45 (22.3)
• Squamous	157 (77.7)	157 (77.7)

Characteristic, n (%)	Toripalimab + CT (n = 202)	Placebo + CT (n = 202)
PD-L1 expression		
• TC ≥1%	133 (65.8)	132 (65.3)
• TC <1% or NE	69 (34.2)	70 (34.7)
Clinical stage*		
• IIIA	136 (67.3)	136 (67.3)
• IIIB	65 (32.2)	64 (31.7)
N stage†		
• N0	17 (8.4)	18 (8.9)
• N1	46 (22.8)	39 (19.3)
• N2	138 (68.3)	145 (71.8)

*In major protocol deviation, 1 patient with stage IIIC (toripalimab arm) and 2 patients with stage IV (placebo arm) were enrolled but were excluded from per-protocol analysis and did not receive surgery.
†1 patient with N3 disease was enrolled in toripalimab arm.

Although this trial did enroll patients with stage II and III disease, only data from stage III were reported at this first interim analysis

NEOTORCH

Treatment Summary

Surgery, n (%)	Toripalimab + CT (n = 202)	Placebo + CT (n = 202)
No surgery performed	36 (17.8)	54 (26.7)
• PD	5 (2.5)	31 (15.3)
• Patient refusal	18 (8.9)	13 (6.4)
• AE	6 (3.0)*	0
• Other	7 (3.5)†	10 (5.0)‡
Surgery performed	166 (82.2)	148 (73.3)
• R0 resection (% of surgery performed)	159 (95.8)	137 (92.6)
Type of surgery (% of surgery performed)		
• Lobectomy	134 (80.7)	123 (83.1)
• Sleeve lobectomy	15 (9.0)	11 (7.5)
• Pneumonectomy	15 (9.0)	14 (9.5)
• Other	2 (1.2)§	0

Systemic Treatment, n (%)	Toripalimab + CT (n = 202)	Placebo + CT (n = 202)
Neoadjuvant treatment	202 (100)	202 (100)
• Received 3 cycles	176 (87.1)	185 (91.6)
• Received 4 cycles	14 (6.9)	7 (2.5)
• Cisplatin based	37 (18.3)‖	31 (15.3)‖
• Carboplatin based	166 (82.2)‖	170 (84.2)¶
Adjuvant treatment	144 (71.3)	131 (64.9)
Maintenance treatment	145 (71.8)	130 (64.4)
• Ongoing	25 (12.4)	20 (9.9)
• Discontinued	120 (59.4)	110 (54.5)
• Completed 13 cycles	88 (43.6)	66 (32.7)

‖1 patient received both cisplatin and carboplatin treatment.
¶1 patient received neither cisplatin nor carboplatin due to allergy.

*3 judged related to toripalimab; 3 judged not related.
†Unresectable at baseline (n = 3); unresectable during intraoperative exploration, poor lung function, tumor-enclosing blood vessels, unremarkable shrinkage (n = 1 each).
‡Unresectable at baseline (n = 5); unresectable during intraoperative exploration (n = 2); intolerant to anesthetic, lower limb edema and ventricular pressure, lost to follow-up (n = 1 each).
§R2 resection; underwent regional lymph node dissection.

NEOTORCH

Primary Endpoints

Primary Endpoints	Toripalimab + CT (n = 202)	Placebo + CT (n = 202)
Median EFS by investigator, mo	NE	15.1
HR (95% CI)	**0.40** (0.277-0.565; P <.0001)	
• 12-mo EFS, %	84.4	57.0
• 24-mo EFS, %	64.7	38.7
MPR by BIPR, %	48.5	8.4
Difference, % (95% CI)	40.2 (32.2-48.1; P <.0001)	

Lu. ASCO 2023. Abstr 8501.

NEOTORCH

EFS by Subgroups

	PD-L1 <1% or NE		PD-L1 1%-49%		PD-L1 ≥50%	
	Toripalimab + CT (n = 69)	Placebo + CT (n = 70)	Toripalimab + CT (n = 69)	Placebo + CT (n = 68)	Toripalimab + CT (n = 64)	Placebo + CT (n = 64)
Median EFS, mo	NE	15.3	24.6	12.7	NE	15.5
HR (95% CI)	0.59 (0.327-1.034)		0.31 (0.176-0.554)		0.31 (0.152-0.618)	

	Nonsquamous NSCLC		Squamous NSCLC	
	Toripalimab + CT (n = 45)	Placebo + CT (n = 45)	Toripalimab + CT (n = 157)	Placebo + CT (n = 157)
Median EFS, mo	NE	21.9	NE	12.9
HR (95% CI)	0.54 (0.265-1.096; P = .0827)		0.35 (0.236-0.528; P <.0001)	

NEOTORCH

Secondary Endpoints

Key Secondary Endpoints	Toripalimab + CT (n = 202)	Placebo + CT (n = 202)
pCR by BIPR, %	24.8	1.0
Difference, % (95% CI)	23.7 (17.6-29.8; P <.0001)	
Median EFS by IRC, mo	NE	15.5
HR (95% CI)	0.40 (0.271-0.572; P <.0001)	
Median OS,* mo (95% CI)	NE (NE-NE)	30.4 (29.2-NE)
HR (95% CI)	0.62 (0.38-0.999; P = .0502)	
1-yr OS rate, %	94.4	89.6
2-yr OS rate, %	81.2	74.3

*Median follow-up: 18.25 mo.

Lu. ASCO 2023. Abstr 8501.

NEOTORCH

Safety

AE Category, n (%)	Toripalimab + CT (n = 202)	Placebo + CT (n = 202)
Any TEAEs	201 (99.5)	199 (98.5)
Any TEAEs grade ≥3	128 (63.4)	109 (54.0)
Any serious AEs	82 (40.6)	57 (28.2)
TEAEs leading to death	6 (3.0)	4 (2.0)
Treatment related	1 (0.5)	0
TEAEs leading to:		
• Interruption	57 (28.2)	29 (14.4)
• Discontinuation	19 (19.4)	15 (7.4)
Immune-related AEs*		
• Any grade	85 (42.1)	46 (22.8)
• Grade ≥3	24 (11.9)	6 (3.0)
Infusion-related reaction	7 (3.5)	13 (6.4)

Surgery-Related Postoperative AEs, n (%)	Toripalimab + CT (n = 166)	Placebo + CT (n = 148)
Any AEs	124 (74.4)	104 (70.3)
AEs grade ≥3	36 (21.7)	30 (20.3)
Any AEs leading to:		
• Interruption	11 (6.6)	2 (1.4)
• Discontinuation	3 (1.8)	4 (2.7)
AEs leading to death	0	2 (1.4)

*Determined by investigator.

SUMMARY

NEOTORCH

- Interim analysis of the phase III NEOTORCH trial of patients with stage III NSCLC found that the addition of toripalimab to chemotherapy resulted in significant improvement compared to chemotherapy alone
  - EFS (NE vs 15.1 mo; HR: 0.40; *P* <.0001)
  - MPR (48.5% vs 8.4%)
  - pCR (24.8% vs 1.0%) rates
- EFS improvement was consistent across key subgroups
  - PD-L1: <1% (HR: 0.59), 1%-49% (HR: 0.31), and ≥50% (HR: 0.31)
  - Squamous (HR: 0.35) and nonsquamous (HR: 0.54) subtypes

Lu. ASCO 2023. Abstr 8501.

NEOTORCH

Perioperative toripalimab (with neoadjuvant chemotherapy) supports the standard of care approach of perioperative immunotherapy with chemotherapy for early-stage NSCLC

PERIOPERATIVE SYSTEMIC THERAPY

- **Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors, see below.**
- **Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors**
- **Adjuvant Chemotherapy**
- **Systemic Therapy Following Surgical Resection**

Neoadjuvant Systemic Therapy

- **All patients should be evaluated for preoperative therapy, with strong consideration for nivolumab or pembrolizumab + chemotherapy for those patients with tumors ≥4 cm or node positive and no contraindications to immune checkpoint inhibitors.[a] Otherwise refer to the Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors.**
- **Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]). PD-L1 status can be incorporated with other clinical factors to determine patients who may benefit from induction chemotherapy and immunotherapy. Principles of Molecular and Biomarker Analysis (NSCL-H).**
- **Clinical trials for neoadjuvant nivolumab + chemotherapy excluded patients harboring *EGFR* mutations and *ALK* rearrangements. Thus, exclusion of these biomarkers, at a minimum, is recommended prior to consideration for neoadjuvant nivolumab + chemotherapy.**
- **After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction systemic therapy as an alternative.**

Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors

- **Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[1]**
  - **Platinum-doublet chemotherapy options include:**
    - **Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)**
    - **Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)**
    - **Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)**
    - **Cisplatin 75 mg/m² day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)**
  - **Chemotherapy regimens for patients who are not candidates for cisplatin-based therapy**
    - **Carboplatin AUC 5 or AUC 6 day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)**
    - **Carboplatin AUC 5 or AUC 6 day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)**
- **Pembrolizumab 200 mg and cisplatin-based doublet therapy every 3 weeks for 4 cycles and then continued as single-agent pembrolizumab as adjuvant treatment after surgery (category 1); Systemic Therapy Following Surgical Resection[2]**
  - **Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² days 1 and 8 (squamous histology)**
  - **Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)**

[a] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR* exon 19 deletion or exon 21 L858R, *ALK* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

QUESTION

Is perioperative immunotherapy (with neoadjuvant chemotherapy) the new standard of care?

	KEYNOTE-671 (pembrolizumab)		AEGEAN (durvalumab)		NEOTORCH (toripalimab)		CHECKMATE-77T (nivolumab)	
Current Indication/FDA approval	***Approved October 16, 2023***: for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery		***Not approved for resectable NSCLC (perioperative setting)*** For the treatment of adult patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy		***Not approved***		***Not approved for resectable NSCLC (perioperative setting)*** For resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy	
Treatment Arms	**Pembrolizumab** + Chemotherapy	Chemotherapy	**Durvalumab** + Chemotherapy	Chemotherapy	**Toripalimab** + Chemotherapy	Chemotherapy	Nivolumab + Chemotherapy	Chemotherapy
N	397	400	366	374	202	202	229	232
Median EFS, overall population HR (95% CI)	**47.2** (32.9 – NR)	**18.3** (14.8 – 22.1)	**NR** (31.9–NR)	**25.9** (18.9–NR)	**NE**	**15.1**	**NR** (28.9 – NR)	**18.4** (13.6 – 28.1)
	HR 0.59 (95% CI, 0.48-0.72)		**HR 0.68** (95% CI, 0.53–0.88) P=0.004		**HR 0.40** (95%CI 0.277-0.565) P <.0001		**HR 0.58** (95%CI 0.42 – 0.81) P =0.00025	
Median EFS by PD-L1 expression								
<1%	**HR 0.75** (0.56 – 1.01)		**HR 0.76** (0.49 – 1.17)		**HR 0.59** (0.327-1.034)		**HR 0.73**(0.47-1.15)	
1-49%	**HR 0.52** (0.36 – 0.75)		**HR 0.70** (0.46 – 1.05)		**HR 0.31** (0.176-0.554)		**HR 0.76** (0.46-1.25)	
≥50%	**HR 0.48** (0.33 – 0.71)		**HR 0.60** (0.35 – 1.01)		**HR 0.31** (0.152-0.618)		**HR 0.26** (0.12-0.55)	
pCR	**18.1%** (14.5 – 22.3%)	**4.0%** (2.3 – 6.4%)	**17.2%**	**4.3%**	**24.8%**	**1.0%**	**25.3%**	**4.7%**
			P<0.001 based on interim analysis		**HR 23.7** (17.6-29.8; P <.0001)		**Odds Ratio 6.64** (3.40 – 12.97)	
Overall Survival HR (95% CI)	**NR** (NR – NR)	52.4 (45.7 – NR)	---		NE (NE-NE)	30.4 (29.2-NE)	---	
	HR 0.72 (95% CI, 0.56-0.93) one-sided P = 0.00517				**HR 0.62** (0.38-0.999; P = 0.0502)			
Reference	ESMO 2023, Abstr LBA56		N Engl J Med 2023;389:1672-84.		ASCO 2023. Abstr 8501.		ESMO 2023. Abstr LBA1	

QUESTION

Is perioperative immunotherapy (with neoadjuvant chemotherapy) superior to neoadjuvant chemoimmunotherapy for early-stage non-small cell lung cancer?

	CheckMate-816 (Nivolumab)	NADIM II (Nivolumab)
Indication/FDA approval	Nivolumab with platinum-doublet chemotherapy for adult patients with resectable NSCLC in the **neoadjuvant** setting	
Treatment Arms	**Nivolumab + chemo** vs chemo (R 1:1) No known EGFR/ALK alterations Optional adjuvant CT ± RT post surgery	**Nivolumab + chemo** vs chemo (R 2:1) No known EGFR/ALK alterations If RO resection: Adjuvant Nivo post surgery)
N	358	86
Median EFS, overall population **HR (95% CI)**	31.6 vs 20.8 months HR 0.63 (97.38% CI: 0.43 - 0.91; p=0.0052)	---
Median EFS by PD-L1 expression **<1%** **≥1%** **1-49%** **≥50%**	 25.1 vs 18.4; HR 0.85 (0.54-1.32) (n=155) NR vs 21.2; HR 0.41 (0.24-0.70) (n=178) NR vs 26.7; HR 0.58 (0.30-1.12) (n=98) NR vs 19.6; HR 0.24 (0.10-0.61) (n=80)	PDL1 expression (≥1%) significantly identified patients with improved PFS HR: 0.26 (95%CI: 0.08-0.77; P = 0.015)
pCR; Odds ratio And by PD-L1 expression **<1%** **≥1%** **1-49%** **≥50%**	24% vs 2.2%; 13.94 (99% CI: 3.49 –55.75;P<0.001) 16.7% vs 2.6% 32.6% vs 2.2% 23.5% vs 0% 44.7% vs 4.8%	36.8% vs 6.9% ; P = 0.0068 ---
Overall Survival HR (95% CI)	Not reached vs Not reached HR 0.57 (99.67% CI, 0.30 – 1.07; P=0.008)	OS at 24 months: 84.7% vs 63.4% HR 0.40 (0.17 – 0.93; P=0.034)
Reference	N Engl J Med. 2022 May 26;386(21):1973-1985.	2022 World Conference on Lung Cancer. Abstract PL03.12

	PEARLS/KEYNOTE-091 (Pembrolizumab)	IMpower010 (Atezolizumab)
Indication/FDA approval	For **adjuvant** treatment following resection and platinum-based chemotherapy in patients with **stage IB (T2a ≥4 cm), II, or IIIA** NSCLC	For **adjuvant** treatment following resection and platinum-based chemotherapy in patients with **Stage II to IIIA** NSCLC whose tumors have **PD-L1 expression on ≥ 1%** of tumor cells, as determined by an FDA-approved test
Treatment Arms	**Pembrolizumab** vs placebo (R 1:1)	**Atezolizumab** vs best supportive care (R 1:1)
N	1,177	1,280
Median DFS, overall population **HR (95% CI)**	53.6 vs 42.0 months HR 0.76 (95% CI: 0.63 – 0.91; P=0.0014)	Not reached vs 35.3 months HR 0.66 (95% CI: 0.50 – 0.88; P=0.004)
Median DFS by PD-L1 expression **<1%** **≥1%** **1-49%** **≥50%**	 HR 0.78 (0.58 – 1.03) (n=465) --- HR 0.67 (0.48 – 0.92) (n=337) NR vs NR; HR 0.82 (0.57 – 1.18.; P=0.14) (n=333)	 --- NR vs 35.3; HR 0.66 (n=476) 32.8 vs 31.4; HR 0.87 (n=247) NR vs 35.7; HR 0. 43 (0.27 – 0.68) (n=229)
Median OS by PD-L1 expression **≥1%** **1-49%** **≥50%**	Overall survival results were not mature with only 42% of pre-specified OS events in the overall population	 HR 0.71 (0.49 – 1.03) HR 0.95 (0.59 – 1.54) HR 0.43 (0.24 – 0.78)
Overall Survival HR (95% CI)	Not reached vs Not reached HR 0.87 (0.67 – 1.15.; P=0.17)	Not reached vs Not reached HR 0.71 (0.49 – 1.03)
Reference	ESMO Virtual Plenary 2022: Abstr VP3-2022; ASCO 2022 Abstr 8512 The Lancet 2022, vol 23 (10): 1274-1286	WCLC2022 Absrt PL03.09 (Plenary 3: Presidential Symposium) The Lancet 2021, vol 398 (10308): 1344-1357

Key Studies

Perioperative NSCLC	EGFR Mutated Metastatic NSCLC	Metastatic and Actionable Mutated NSCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • HERTHENA-Lung01 • KEYNOTE 789	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

FLAURA2

Does osimertinib with chemotherapy benefit patients with treatment naïve EGFR-mutated advanced NSCLC?

On February 16, 2024, the Food and Drug Administration approved osimertinib (Tagrisso, AstraZeneca Pharmaceuticals LP) with platinum-based chemotherapy for patients with locally advanced or metastatic non-small cell lung cancer (la/mNSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

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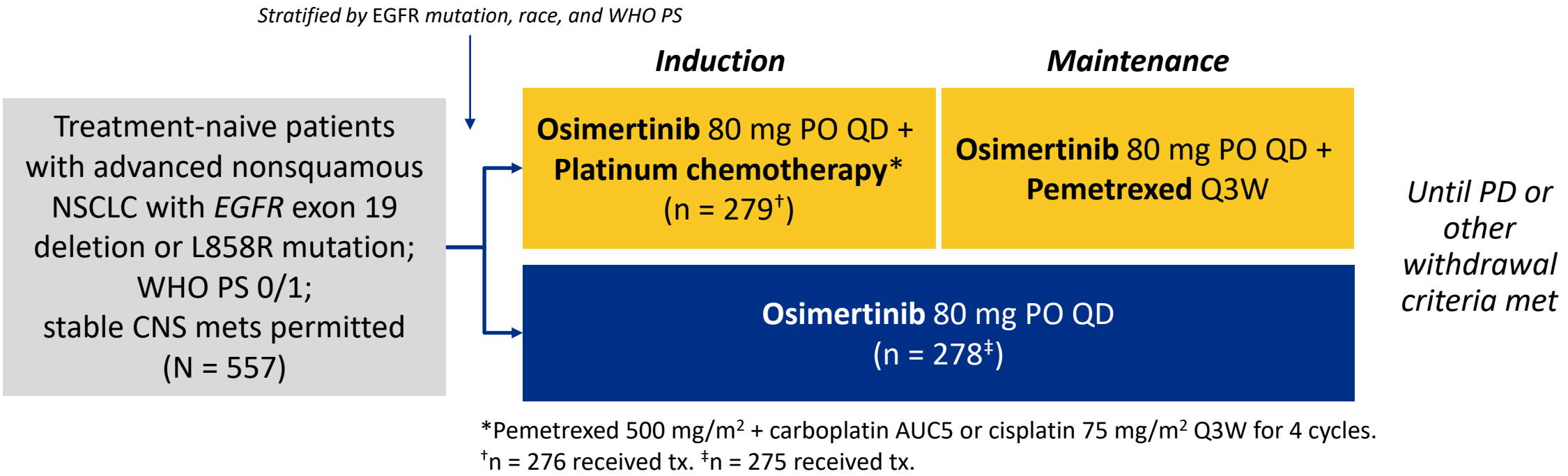
FLAURA2

Study Design: Global, randomized, open-label phase III study



*Pemetrexed 500 mg/m^2 + carboplatin AUC5 or cisplatin 75 mg/m^2 Q3W for 4 cycles.
†n = 276 received tx. ‡n = 275 received tx.

Primary endpoint: investigator-assessed PFS (RECIST v1.1)

Key secondary endpoints: ORR, DoR, DCR, OS, PFS2, HRQoL, safety

Data cutoff: April 3, 2023

WCLC 2023. Abstr PL03.13
N Engl J Med 2023;389:1935-48.

KEY DATA

FLAURA2

Baseline Characteristics

Characteristic	Osimertinib + Platinum CT (n = 279)	Osimertinib Monotherapy (n = 278)
Median age, yr (range)	61 (26-83)	62 (30-85)
Female, %	62	61
Race, %		
• Chinese Asian	25	25
• Non-Chinese Asian	39	38
• Non-Asian	35	36
• Missing	<1	1
WHO PS 0/1, %	37/62	37/63
Smoking status, %		
• Never	67	65
• Current	1	1
• Former	31	33

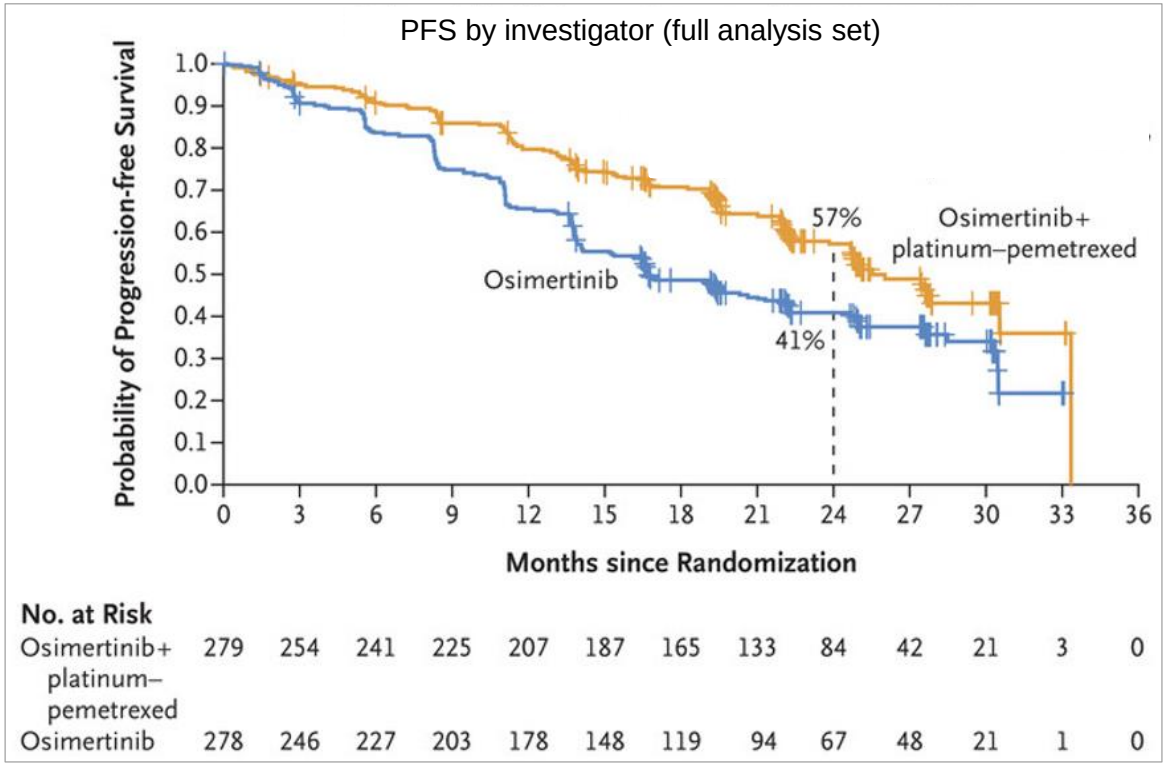
Characteristic	Osimertinib + Platinum CT (n = 279)	Osimertinib Monotherapy (n = 278)
Histology, %		
• Adenocarcinoma	99	99
• Adenosquamous	1	0
• Other	1	1
EGFR mutation, %		
• Ex19del	61	60
• L858R	38	38
Metastatic disease, %	95	97
• Extrathoracic metastases	53	54
• CNS metastases	42	40
Median tumor size at BL, mm (range)	57 (10-284)	57 (11-221)

WCLC 2023. Abstr PL03.13
N Engl J Med 2023;389:1935-48.

KEY DATA

FLAURA2

Primary Endpoint: PFS



Median PFS	Osimertinib + Platinum CT (n = 279*)	Osimertinib Monotherapy (n = 278*)	HR (95% CI)	P Value
Per investigator (primary endpoint), mo	**25.5**	**16.7**	**0.62 (0.49-0.79)**	**< 0.0001**
Per BICR, mo	29.4	19.9	0.62 (0.48-0.80)	0.0002
Per investigator by CNS mets at BL, mo (n/N)				
• With CNS mets	24.9 (52/116)	13.8 (79/110)	0.47 (0.33-0.66)	--
• Without CNS mets	27.6 (68/163)	21.0 (87/168)	0.75 (0.55-1.03)	--
Per investigator by EGFR mut at BL, mo (n/N)				
• ex19del	27.9 (65/172)	19.4 (94/169)	0.60 (0.44-0.83)	--
• L858R	24.7 (55/106)	13.9 (70/107)	0.63 (0.44-0.90)	--

*n = 3 in each arm did not receive tx.

- PFS data per investigator currently 51% mature
- Median follow-up 19.5 mo in osimertinib + chemotherapy arm, 16.5 mo in osimertinib monotherapy arm
- PFS benefit with addition of chemotherapy to osimertinib observed across all predefined subgroups

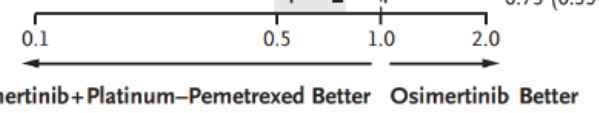
WCLC 2023. Abstr PL03.13
N Engl J Med 2023;389:1935-48.

KEY DATA

FLAURA2

PFS by Subgroup

Subgroup	Osimertinib+ Platinum–Pemetrexed	Osimertinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
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)



WCLC 2023. Abstr PL03.13
N Engl J Med 2023;389:1935-48.

FLAURA2

Secondary Endpoints

Response Outcome	Osimertinib + Platinum CT (n = 279*)	Osimertinib Monotherapy (n = 278*)	Adjusted OR (95% CI)
ORR, n (%)	**231 (83)**	**209 (76)**	1.61 (1.06-2.44)
• CR	1 (<1)	2 (1)	
• PR	231 (83)	208 (75)	
• SD ≥35 days	34 (12)	51 (18)	
• PD	3	4	
Median best change in target lesion size, % (range)	-52.6 (-100 to 20.0)	-50.0 (-100 to 40.4)	
Median DoR, mo (95% CI)	24.0 (20.9-27.8)	15.3 (12.7-19.4)	

Survival Outcome, Mo	Osimertinib + Platinum CT (n = 279)	Osimertinib Monotherapy (n = 278)	HR (95% CI)	P Value
Median PFS2	30.6	27.8	0.70 (0.52-0.93)	.0132
Median OS	Not reached	Not reached	0.90 (0.65-1.24)	.5238

PFS2, second progression-free survival

- PFS2 and OS data 34% and 27% mature, respectively
- 46% of patients in osimertinib + CT arm and 60% of patients in osimertinib monotherapy arm received subsequent anticancer treatment, typically cytotoxic chemotherapy (33% and 54%, respectively)

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N Engl J Med 2023;389:1935-48.

FLAURA2

Safety

Safety Outcome	Osimertinib + Platinum CT (n = 276)	Osimertinib Monotherapy (n = 275)
Median osimertinib exposure, mo (range)	22.3 (0.1-33.8)	19.3 (0.1-33.8)
Completed 4 cycles platinum-based chemotherapy, %	76	--
Any AE, n (%)	**276 (100)**	**268 (97)**
• Grade ≥3	176 (64)	75 (27)
• Serious	104 (38)	53 (19)
• Leading to death	18 (7)	8 (3)
• Leading to discontinuation	132 (48)	17 (6)
– Discontinuation of osimertinib | platinum | pemetrexed	30 (11) | 46 (17) | 119 (43)	17 (6) | --|--
Any possibly treatment-related AE, n (%)	**269 (97)**	**241 (88)**
• Grade ≥3	146 (53)	29 (11)
– Related to osimertinib| platinum|pemetrexed	81 (29) |104 (38) | 130 (47)	29 (11) |--|--
• Serious	52 (19)	15 (5)
• Leading to death	5 (2)	1 (< 1)
– Related to osimertinib|platinum|pemetrexed	3 (1) |2 (1) |3 (1)	1 (< 1) |--|--

WCLC 2023. Abstr PL03.13
N Engl J Med 2023;389:1935-48.

FLAURA2

Safety

Most Common AEs (Overall Incidence ≥15% in Either Arm), %	Osimertinib + Platinum CT (n = 276)		Osimertinib Monotherapy (n = 275)	
	Grade 1/2	Grade 3/4*	Grade 1/2	Grade 3/4†
Anemia	27	20	8	<1
Diarrhea	41	3	40	<1
Nausea	42	1	10	0
Neutropenia	18	23	8	1
Thrombocytopenia	18	14	9	1
Decreased appetite	28	3	9	1
Constipation	29	<1	10	0
Rash	28	<1	21	0
Fatigue	25	3	9	<1
Vomiting	25	1	6	0
Stomatitis	24	<1	18	<1
Paronychia	23	1	26	<1

*All common (≥15%) grade 4 AEs in combination arm were hematologic associated with CT. †No common grade 4 events in osimertinib monotherapy arm.

WCLC 2023. Abstr PL03.13
N Engl J Med 2023;389:1935-48.

SUMMARY

FLAURA2

- Primary results of phase III FLAURA2 trial show that combined treatment with osimertinib and platinum-based chemotherapy significantly improves PFS vs osimertinib alone in treatment-naive patients with *EGFR*-mutated advanced NSCLC
  - Investigator-assessed median PFS: 25.5 vs 16.7 mo
  - PFS benefit was observed across all predefined subgroups
  - Mature PFS2 and OS data to come
- No new safety concerns

WCLC 2023. Abstr PL03.13
N Engl J Med 2023;389:1935-48.

FLAURA2

Osimertinib with platinum-based chemotherapy is a new standard of care option for patients with newly diagnosed EGFR-mutated advanced NSCLC

Key Studies

Neoadjuvant, Perioperative, Adjuvant NSCLC	Metastatic and Actionable EGFR Mutated NSCLC	Metastatic and Actionable Mutated NSCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • HERTHENA-Lung01 • KEYNOTE 789	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

PAPILLION

Does amivantamab with chemotherapy benefit patients with treatment naïve EGFR-mutated advanced NSCLC?

On March 1, 2024, the Food and Drug Administration approved amivantamab-vmjw (Rybrevant, Janssen Biotech, Inc.) with carboplatin and pemetrexed for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test.

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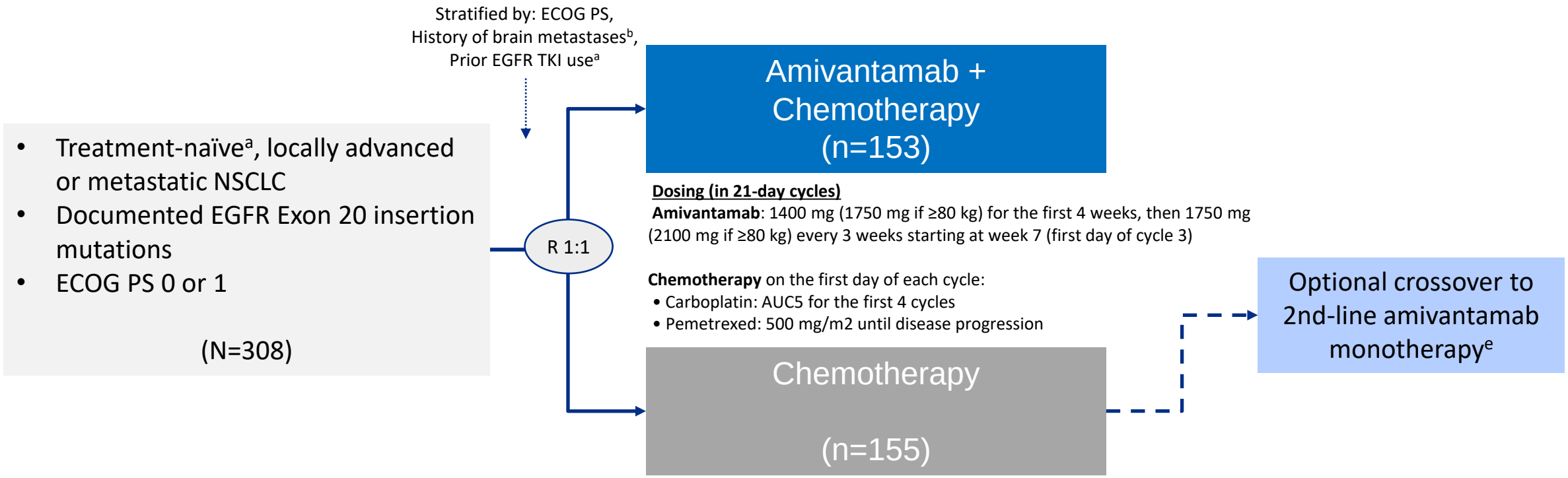
PAPILLION

Study Design: Global, randomized Phase 3 study



Primary endpoint: Progression-free survival (PFS) by BICR according to RECIST v1.1[c]

Secondary endpoints: Objective response rate (ORR)[c], Duration of response (DoR)[c], Overall survival (OS), PFS after first subsequent therapy (PFS2), Symptomatic PFS[d], Time to subsequent therapy[d], Safety

aRemoved as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented).
bPatients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomization.
cKey statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing.
dThese secondary endpoints (time to subsequent therapy and symptomatic progression-free survival) will be presented at a future congress.
eCrossover was only allowed after BICR confirmation of disease progression; amivantamab monotherapy on Q3W dosing per main study.

Data cut-off: 3-May-2023

PAPILLION

Baseline Characteristics

Characteristic, n (%)	Amivantamab-Chemotherapy (n=153)	Chemotherapy (n=155)
Median age, years (range)	61 (27–86)	62 (30–92)
Female / male	85 (56) / 68 (44)	93 (60) / 62 (40)
Race[a]		
Asian	97 (64)	89 (59)
White	49 (32)	60 (39)
Other[b]	5 (3)	3 (2)
ECOG PS 0 / 1	54 (35) / 99 (65)	55 (35) / 100 (65)
History of smoking: yes / no	65 (42) / 88 (58)	64 (41) / 91 (59)
History of brain metastases: yes / no	35 (23) / 118 (77)	36 (23) / 119 (77)
Prior EGFR TKI use: yes[c] / no	1 (1) / 152 (99)	3 (2) / 152 (98)
Histology: adenocarcinoma subtype / other[d]	151 (99) / 2 (1)	153 (99) / 2 (1)

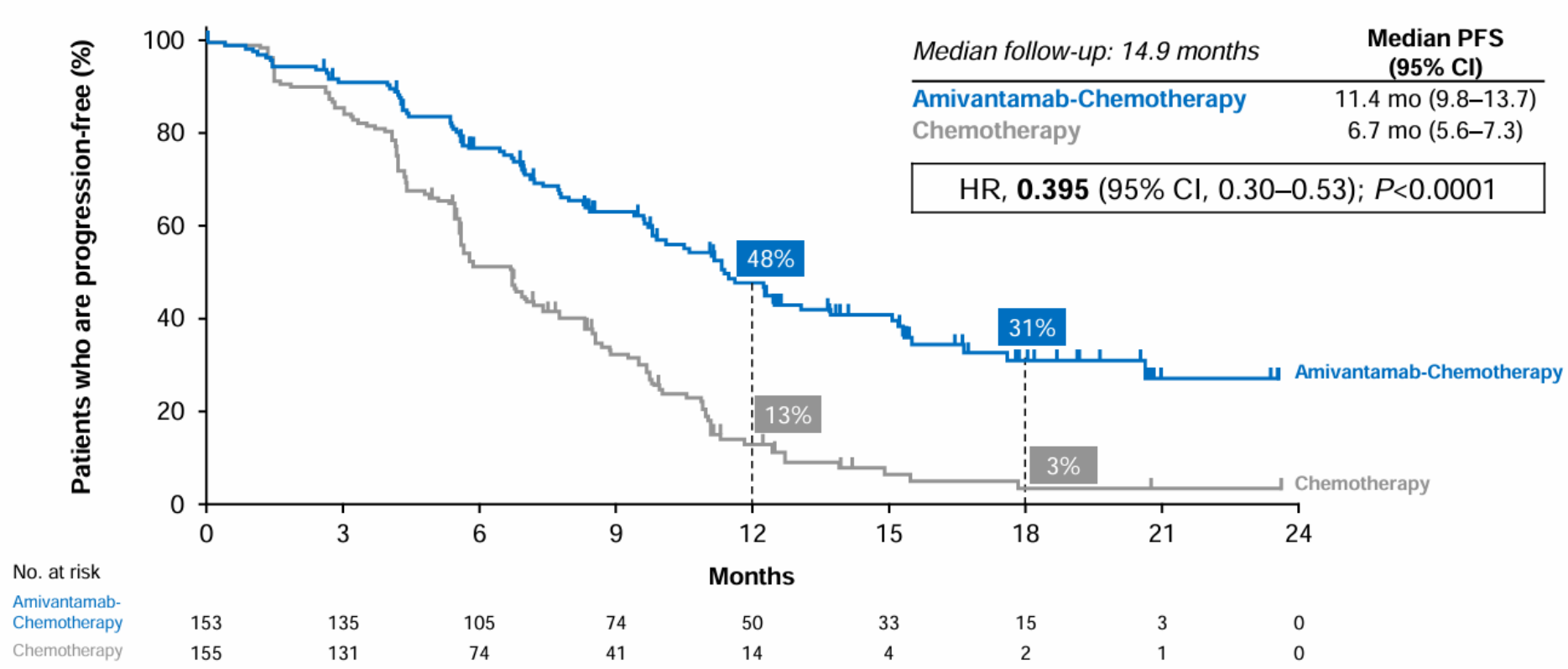
A total of 308 patients from 24 countries were randomized in the PAPILLON study

Note: percentages may not sum to 100 due to rounding.
a In some regions, the reporting of race was not required (amivantamab-chemotherapy, n=151; chemotherapy alone, n=152).
b Other includes American Indian or Alaska Native, Black or African American, multiple, and unknown.
c Transient monotherapy with common EGFR TKIs was allowed if lack of response was documented.
d Other includes large cell carcinoma, squamous cell carcinoma, and other.

KEY DATA

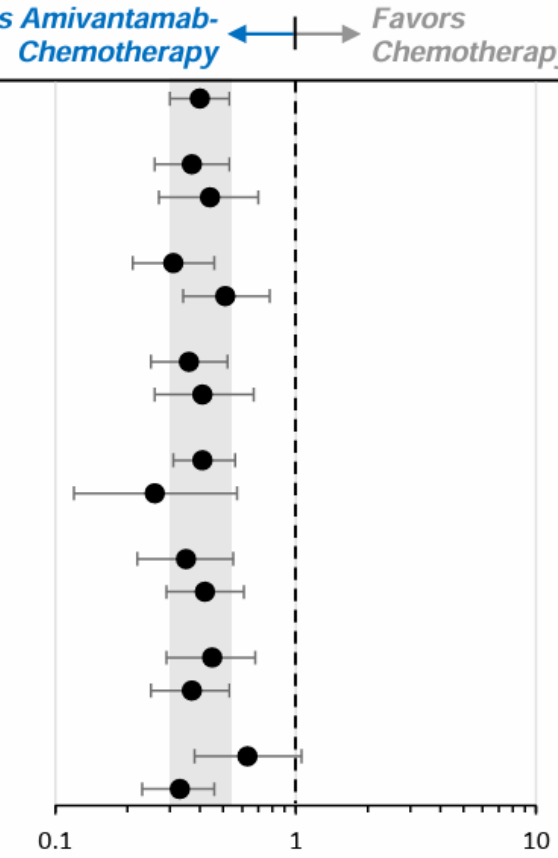
PAPILLION

Primary Endpoint: PFS by BICR



PAPILLION

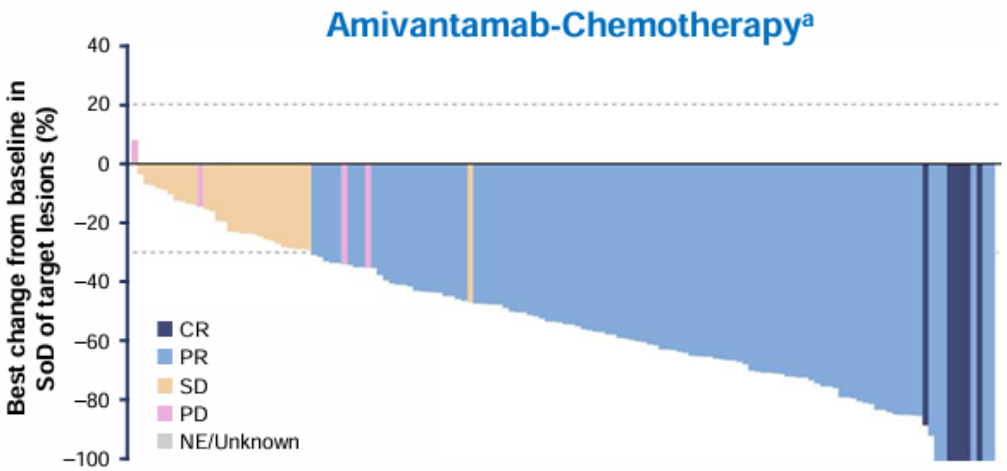
PFS by BICR across Subgroups

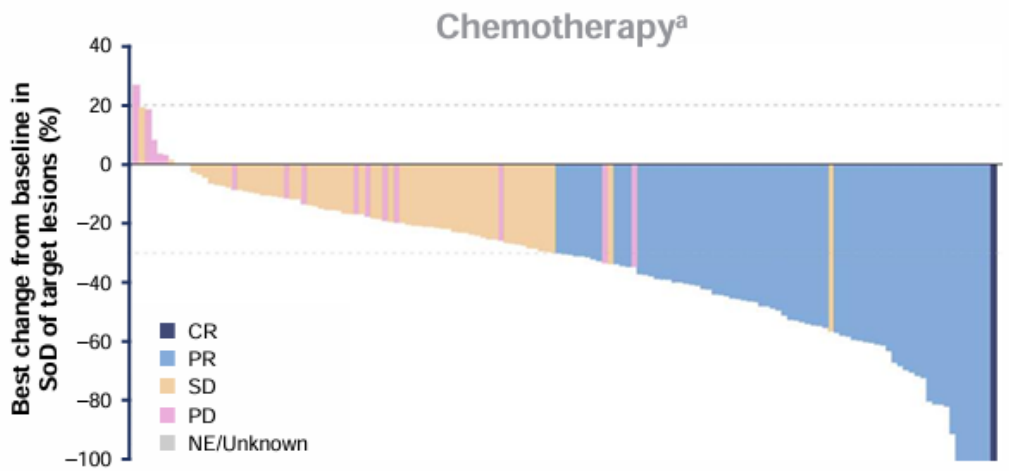


Subgroup	HR (95% CI)	Events/N: Amivantamab-Chemotherapy	Events/N: Chemotherapy
All randomized patients	0.40 (0.30–0.53)	84/153	132/155
Age category			
<65 years	0.37 (0.26–0.53)	56/97	77/92
≥65 years	0.44 (0.27–0.70)	28/56	55/63
Sex			
Female	0.31 (0.21–0.46)	41/85	81/93
Male	0.51 (0.34–0.78)	43/68	51/62
Race			
Asian	0.36 (0.25–0.52)	55/97	77/89
Non-Asian	0.41 (0.26–0.67)	27/53	51/62
Weight category			
<80 kg	0.41 (0.31–0.56)	74/132	108/128
≥80 kg	0.26 (0.12–0.57)	10/21	24/27
ECOG PS			
0	0.35 (0.22–0.55)	31/59	51/58
1	0.42 (0.29–0.61)	53/94	81/97
History of smoking			
Yes	0.45 (0.29–0.68)	37/65	57/64
No	0.37 (0.25–0.53)	47/88	75/91
History of brain metastases			
Yes	0.63 (0.38–1.06)	28/36	34/38
No	0.33 (0.23–0.46)	56/117	98/117

PAPILLION

Best Response and ORR by BICR

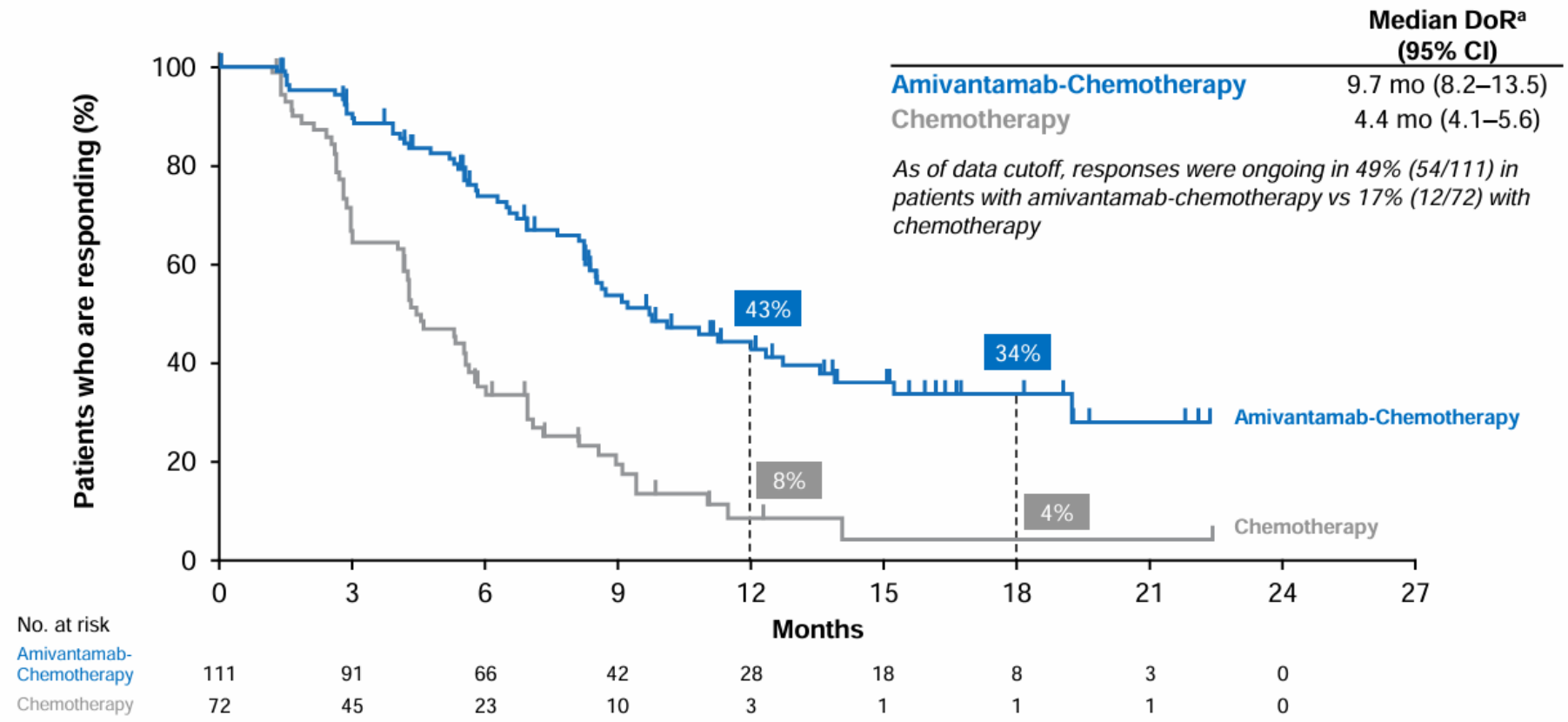




BICR-assessed response[b]	Amivantamab-Chemotherapy (n=153)	Chemotherapy (n=155)
Mean percent change of SoD	-53%[c]	-34%
ORR	73% (95% CI, 65–80)	47% (95% CI, 39–56)
Odds ratio	3.0 (95% CI, 1.8–4.8); *P*<0.0001	
Best response, n (%)		
Complete response	6 (4)	1 (1)
Partial response	105 (69)	71 (47)
Stable 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)

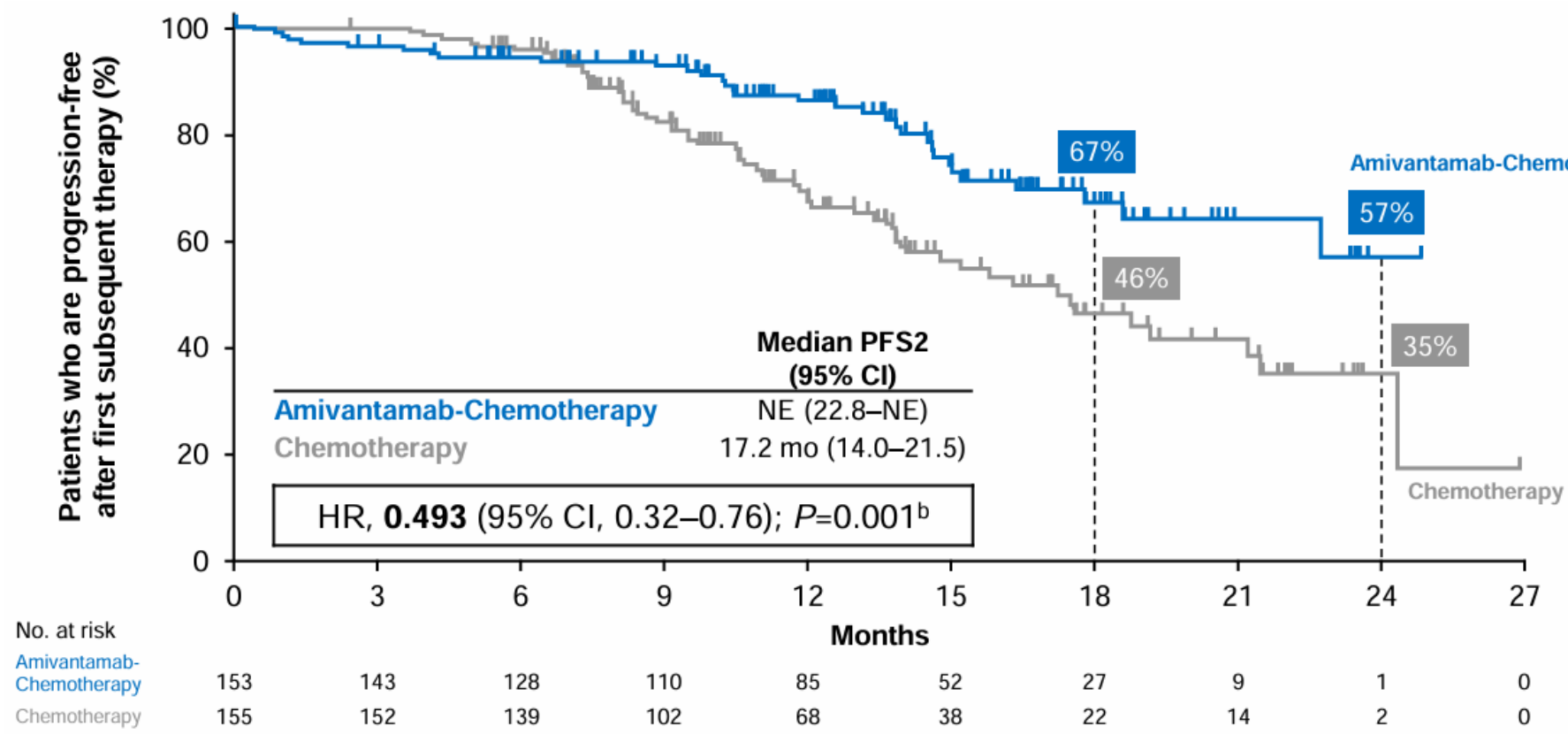
PAPILLION

Duration of Response by BICR



PAPILLION

PFS2: PFS After First Subsequent Therapy



Most common first subsequent therapy:

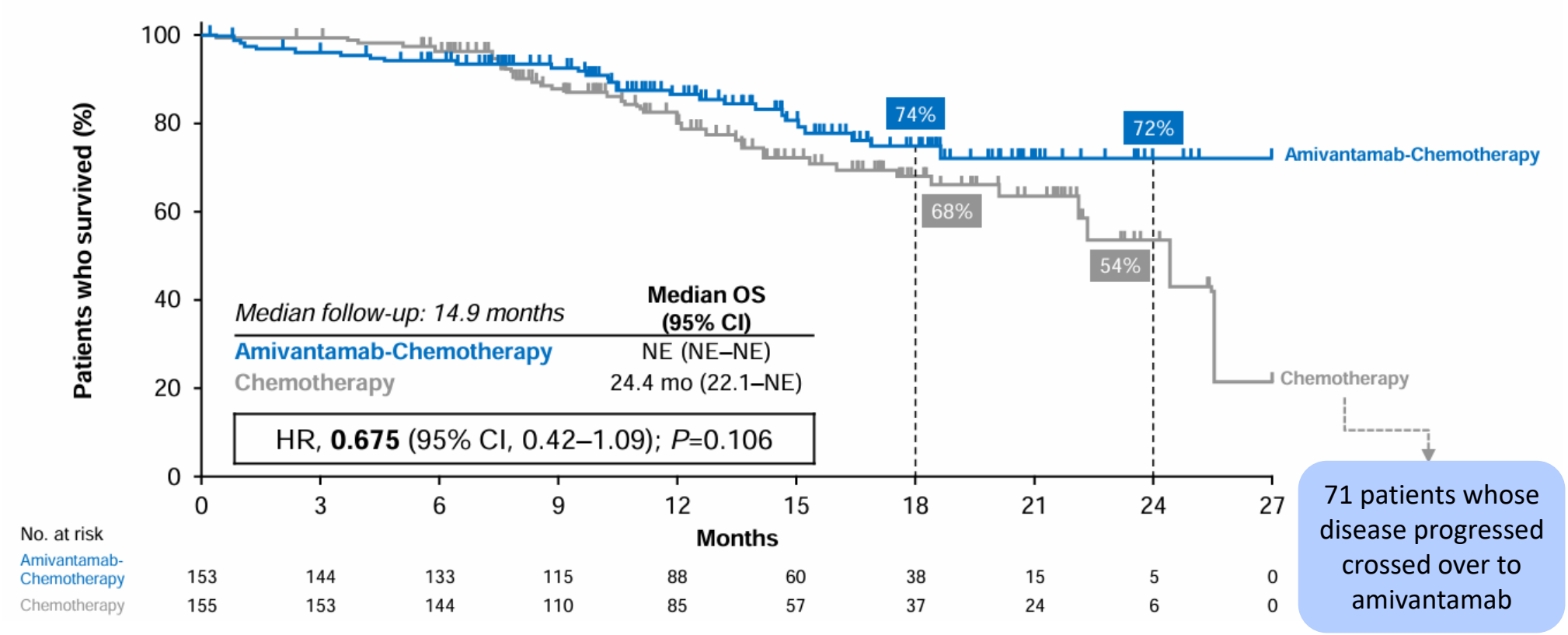
Of pts on Ami + Chemo:
43 pts started subsequent therapy
→ 13 pts received chemotherapy alone

Of pts on Chemotherapy:
94 pts started subsequent therapy
→ 71 pts received amivantamab alone

KEY DATA

PAPILLION

Interim Overall Survival



PAPILLION

Safety

	Amivantamab-Chemotherapy (n=151)	Chemotherapy (n=155)
Median treatment duration, months (range)	9.7 (0.1–26.9)	6.7 (0–25.3)
No. of chemotherapy cycles, median (range)		
Carboplatin	4 (1–4)	4 (1–5)
Pemetrexed	13 (1–34)	10 (1–37)

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)

Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Peripheral edema	45 (30)	2 (1)	16 (10)	0
Other				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Alanine aminotransferase increased	50 (33)	6 (4)	56 (36)	2 (1)
Aspartate aminotransferase increased	47 (31)	1 (1)	51 (33)	1 (1)
COVID-19	36 (24)	3 (2)	21 (14)	1 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)

SUMMAY

PAPILLION

- Amivantamab plus chemotherapy significantly improved PFS vs chemotherapy alone in first-line EGFR Ex20ins advanced NSCLC
  - PFS: HR 0.395; P<0.0001
  - Consistent PFS benefit was observed across all subgroups
  - Significantly higher ORR, longer DoR, and deeper mean reduction in tumor size
  - Longer PFS2, supporting the first-line use of amivantamab-chemotherapy
- Favorable interim OS trend (HR 0.675; P=0.106)
- The safety profile of amivantamab-chemotherapy was consistent with individual agents
- Low rates of treatment-related discontinuations with amivantamab (7%)

PAPILLION

Amivantamab with platinum-based chemotherapy is a new standard of care option for patients with newly diagnosed EGFR-mutated advanced NSCLC

Key Studies

Neoadjuvant, Perioperative, Adjuvant NSCLC	Metastatic and Actionable EGFR Mutated NSCLC	Metastatic and Actionable Mutated NSCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • HERTHENA-Lung01 • KEYNOTE 789	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

CLINICAL QUESTION

HERTHENA-Lung01

Does patritumab deruxtecan (HER3-DXd) benefit patients with metastatic or locally advanced NSCLC with EGFR-activating mutations (exon 19 deletion or L858R) whose disease has progressed on or after osimertinib?

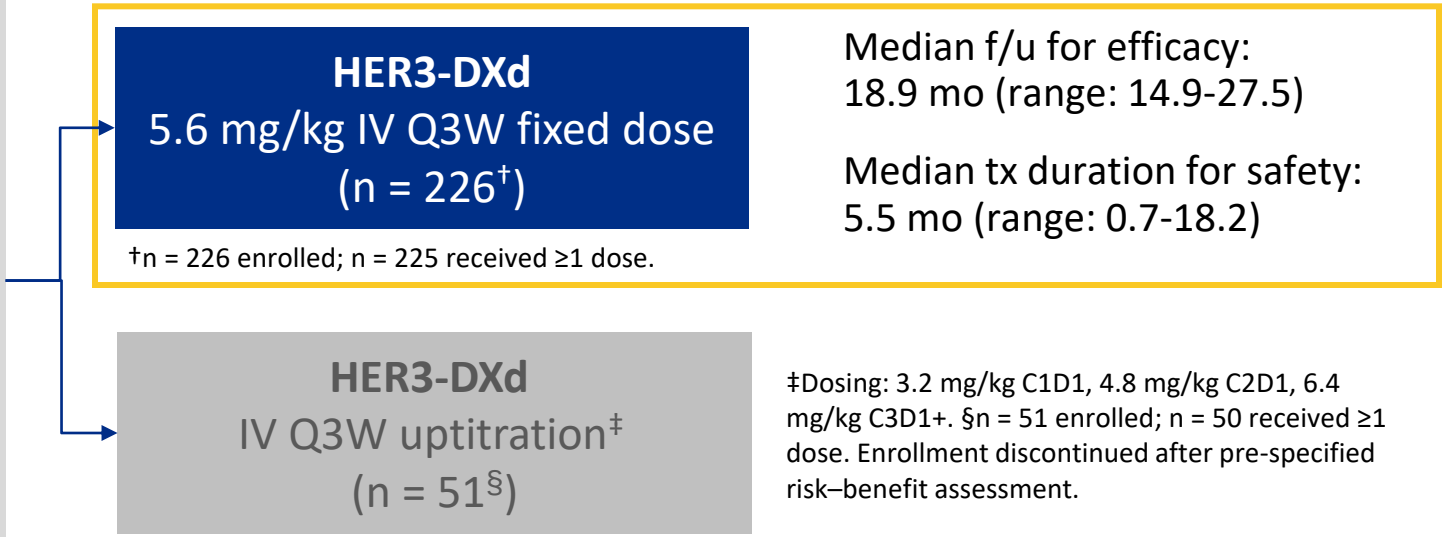
KEY DATA

HERTHENA-Lung01

Study Design: Multicenter, randomized, open-label, two-arm phase II trial

- Patients with advanced *EGFR*-mutated (ex19del or L858R) NSCLC progressing on most recent systemic therapy
- Prior treatment with EGFR TKI* and platinum-based chemotherapy
- Inactive or previously treated asymptomatic brain mets allowed
- Pretreatment tissue biopsy required but not selected for by HER3 expression
- ECOG PS 0 or 1

(N = 277)



*Protocol amended to require prior osimertinib

Primary endpoint: confirmed ORR by BICR

Key secondary endpoint: DoR by BICR, ORR and DoR by investigator, PFS, disease control rate, time to response, best % change from baseline, OS, safety, correlation of baseline HER3 expression with efficacy measures

Exploratory analysis: confirmed objective response of intracranial tumors by BICR using CNS

HER3 immunohistochemistry (IHC) was performed centrally on formalin-fixed, paraffin-embedded tissue using anti-HER3 clone SP438 (investigational use only), a rabbit monoclonal antibody developed by Ventana Medical Systems, Inc. HER3 membrane expression on tumor cells was quantified by H-scores. H-score (range, 0-300) was defined as the sum of the percentage of IHC 1+ (weak staining) plus two times the percentage of IHC 2+ (moderate staining) plus three times the percentage of IHC 3+ (strong staining).

J Clin Oncol. 2023 Dec 10; 41(35): 5363–5375; Yu. Future Oncol. 2023;19:1319.
Yu. WCLC 2023. Abstr OA05.03; Yu. JCO. 2023; JCO2301476.
ESMO 2023. Abstr 1319MO

KEY DATA

HERTHENA-Lung01

Baseline Characteristics

Characteristic	HER3-DXd 5.6 mg/kg (N = 225)
Median age, yr (range)	64 (37-82)
Female, n (%)	132 (59)
Asian, n (%)	105 (47)
ECOG PS 0/1/2,* n (%)	73 (32)/149 (66)/3 (1)
Median time since initial diagnosis, mo (range)	41.0 (9.1-224.7)
Median sum of target lesion diameters at baseline (BICR), mm (range)	68 (11-248)
History of CNS metastasis, n (%)	115 (51)
Brain metastasis at Baseline (BICR), n (%)	72 (32)
Liver metastasis at BL (BICR), n (%)	75 (33)

- 122 locations in North America, Europe, East Asia, Southeast Asia, and Australia

Characteristic	HER3-DXd 5.6 mg/kg (N = 225)
EGFR activating mutation,† n (%)	
• Ex19del	142 (63)
• L858R	82 (36)
Median prior lines of systemic therapy, n (range)	**3 (1-11)‡**
• 2 prior lines, n (%)	58 (26)
• >2 prior lines, n (%)	165 (73)
Prior anticancer regimens, n (%)	
• EGFR TKI	225 (100)
• Third-generation EGFR TKI	**209 (93)**
• Platinum-based CT	225 (100)
• Immunotherapy	90 (40)

*Those with ECOG PS 2 were 0 or 1 at screening.
†n = 1 with Ex19del and L858R mutations. ‡n = 2 with 1 prior line of therapy.

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WCLC 2023. Abstr OA05.03; Yu. JCO. 2023; JCO2301476.
ESMO 2023. Abstr 1319MO

KEY DATA

HERTHENA-Lung01

Responses

Efficacy Outcome	Patients		All Patients: History of Brain Metastases	
	All Patients (N = 225)	**Prior 3G EGFR TKI (n = 209)**	**Yes (n=115)**	**No (n=110)**
Confirmed ORR, % (95% CI)	29.8 (23.9-36.2)	29.2 (23.1-35.9)	28.7 (20.6 – 37.9)	30.9 (22.4 – 40.4)
Best overall response, n (%)				
• CR	1 (0.4)	1 (0.5)	0	1 (0.9)
• PR	66 (29.3)	60 (28.7)	33 (28.7)	33 (30.0)
• SD	99 (44.0)	91 (43.5)	48 (41.7)	51 (46.4)
• PD	43 (19.1)	41 (19.6)	26 (22.6)	17 (15.5)
• NE	16 (7.1)	16 (7.7)	8 (7.0)	8 (7.3)
DCR, % (95% CI)	73.8 (67.5-79.4)	72.7 (66.2-78.6)	70.4 (61.2 – 78.6)	77.3 (68.3 – 84.7)
Median DoR, mo (95% CI)	6.4 (4.9-7.8)	6.4 (5.2-7.8)	5.5 (4.2 – 7.8)	6.9 (4.4 -10.6)
• Pts with DOR ≥6 months, %	43.3%	45.9%	36.4%	50.0%
Median PFS, mo (95% CI)	5.5 (5.1-5.9)	5.5 (5.1-6.4)	4.3 (4.0 – 5.5)	6.2 (5.5 – 8.1)
Median OS, mo (95% CI)	11.9 (11.2-13.1)	11.9 (10.9-13.1)	11.6 (10.0 – 12.6)	12.9 (10.6 – 14.7)

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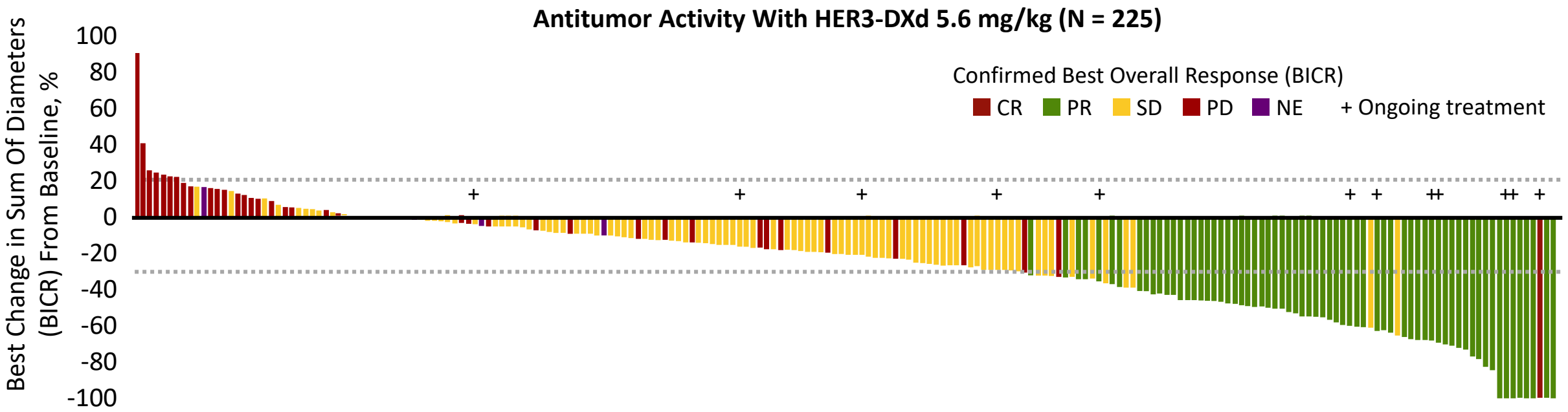
ESMO 2023. Abstr 1319MO

HERTHENA-Lung01

Antitumor Activity Across EGFR TKI Resistance Mechanisms



	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)

J Clin Oncol. 2023 Dec 10; 41(35): 5363–5375; Yu. Future Oncol. 2023;19:1319.
Yu. WCLC 2023. Abstr OA05.03; Yu. JCO. 2023; JCO2301476.
ESMO 2023. Abstr 1319MO

HERTHENA-Lung01

Intracranial Response

Outcomes by CNS BICR in patients with brain metastases at baseline with no previous radiotherapy

Intracranial Response (BICR) per CNS RECIST	Patients With Brain Metastasis at Baseline and No Prior Radiotherapy (n = 30)*
Confirmed ORR, % (95% CI)	33.3 (17.3-52.8)
Best overall response, n (%)	
• CR	9 (30.0)†
• PR	1 (3.3)
• SD	13 (43.3)
• PD	4 (13.3)
• NE	3 (10.0)
DCR, % (95% CI)	76.7 (57.7-90.1)
Median DoR, mo (95% CI)	8.4 (5.8-9.2)

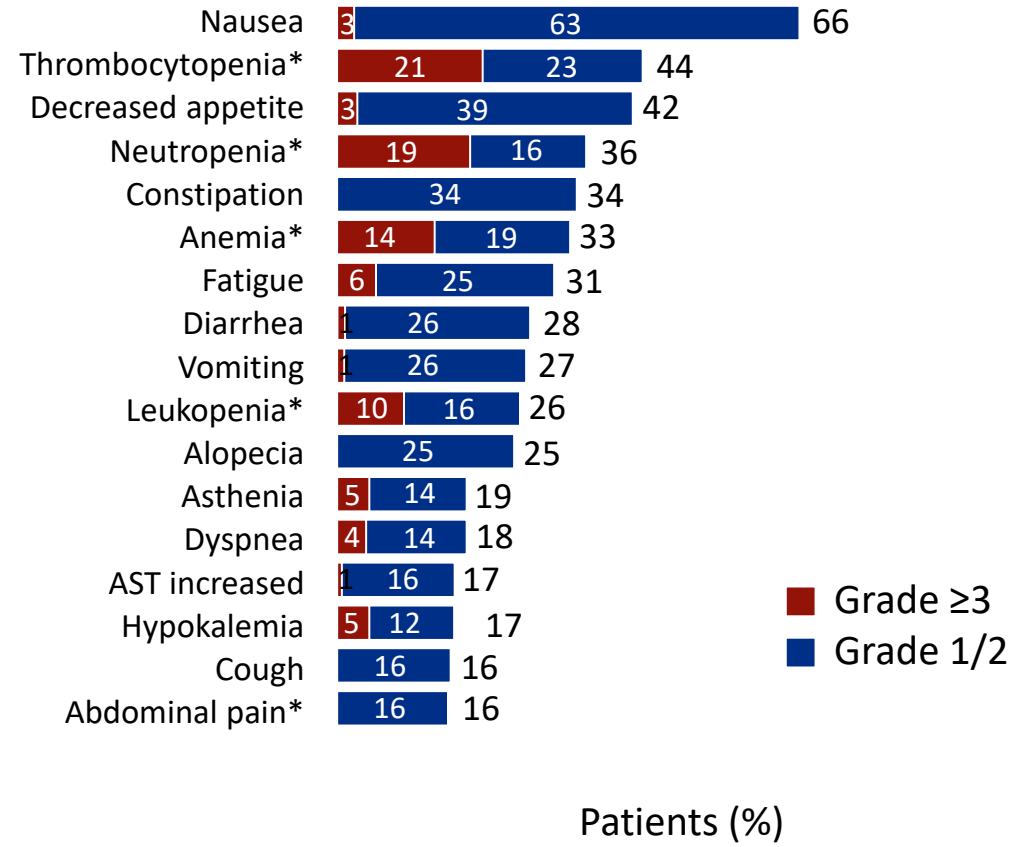
J Clin Oncol. 2023 Dec 10; 41(35): 5363–5375; Yu. Future Oncol. 2023;19:1319.
Yu. WCLC 2023. Abstr OA05.03; Yu. JCO. 2023; JCO2301476.
ESMO 2023. Abstr 1319MO

HERTHENA-Lung01

Safety Summary

Safety Outcome, n (%)	HER3-DXd 5.6 mg/kg (N = 225)
Any TEAE	224 (99.6)
• **Associated with treatment d/c**	**16 (7.1)**
• Associated with dose reduction	48 (21.3)
• Associated with dose interruption	91 (40.4)
TEAE grade ≥3	146 (64.9)
Treatment-related TEAE	215 (95.6)
• Grade ≥3	102 (45.3)
• Serious TEAE	34 (15.1)
• Associated with death	4 (1.8)
Adjudicated ILD (as treatment related)	**12 (5.3)**
• Grade 1	1 (0.4)
• Grade 2	8 (3.6)
• Grade 3	2 (0.9)
• Grade 4	0
• Grade 5	1 (0.4)
Median time to onset, days (range)	53 (9-230)

Most Common TEAEs Occurring in ≥15% of Patients (N = 225)



*Grouped preferred terms.

J Clin Oncol. 2023 Dec 10; 41(35): 5363–5375; Yu. Future Oncol. 2023;19:1319.
Yu. WCLC 2023. Abstr OA05.03; Yu. JCO. 2023; JCO2301476.
ESMO 2023. Abstr 1319MO

SUMMARY

HERTHENA-Lung01

- HER3-DXd demonstrated durable antitumor activity in patients with EGFR-mutated advanced NSCLC following prior EGFR TKI and platinum-based chemotherapy
  - Confirmed ORR: 29.8%;
  - DCR: 73.8%; median
  - DoR: 6.4 mo
- Intracranial antitumor activity was observed in patients with untreated brain metastases, with intracranial confirmed ORR of 33.3% and intracranial DCR of 76.7%
- HER3-DXd safety profile was manageable and tolerable
  - Monitor for ILD

J Clin Oncol. 2023 Dec 10; 41(35): 5363–5375; Yu. Future Oncol. 2023;19:1319.
Yu. WCLC 2023. Abstr OA05.03; Yu. JCO. 2023; JCO2301476.
ESMO 2023. Abstr 1319MO

HERTHENA-Lung01

Patritumab deruxtecan (HER3-DXd) provides benefit for patients with previously treated EGFR-mutated NSCLC and is a potential new treatment option

PDUFA date: June 26, 2024

Key Studies

Neoadjuvant, Perioperative, Adjuvant NSCLC	Metastatic and Actionable EGFR Mutated NSCLC	Metastatic and Actionable Mutated NSCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • HERTHENA-Lung01 • KEYNOTE 789	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

KEYNOTE-789

Does pembrolizumab benefit patients with TKI-resistant, EGFR-mutant, metastatic non-squamous NSCLC?

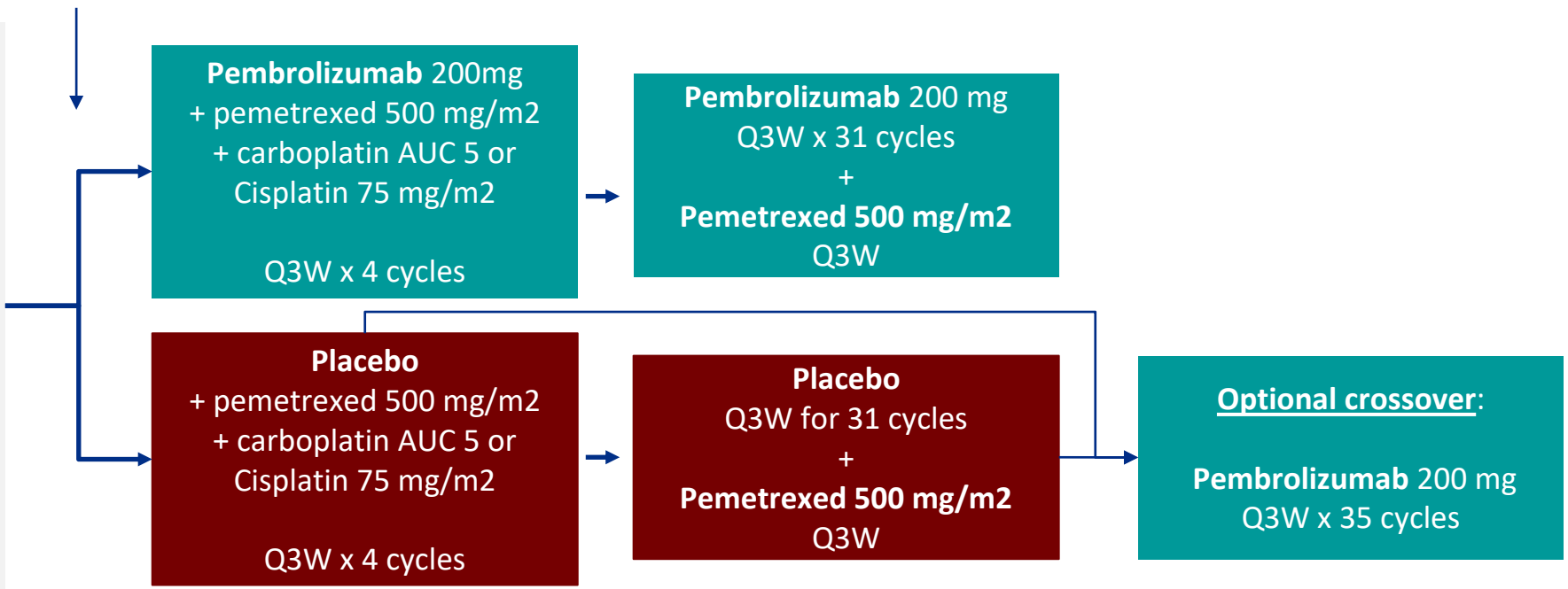
KEY DATA

KEYNOTE-789

Study Design: Randomized phase III trial

Stratified byPD-L1 TPS (<50% vs ≥50%), treatment history (with or without osimertinib), geographic region (East Asia vs not East Asia)

- Confirmed stage IV non squamous NSCLC
- EGFR Del19 or L858R
- ECOG PS 0 or 1
- PD Per RECIST v1.1
  - After 1st or 2nd gen EGFR TKI without T790M mutation
  - After 1st or 2nd EGFR TKI with T790M mutation and osimertinib failure
  - Osimertinib failure as a 1st-line therapy regardless of T790M status



Dual Primary endpoints: PFS per RECIST v1.1 by BICR and OS

Secondary endpoints: ORR and DOR per RECIST v1.1 by BICR, safety, and patient-reported outcomes

KEYNOTE-789

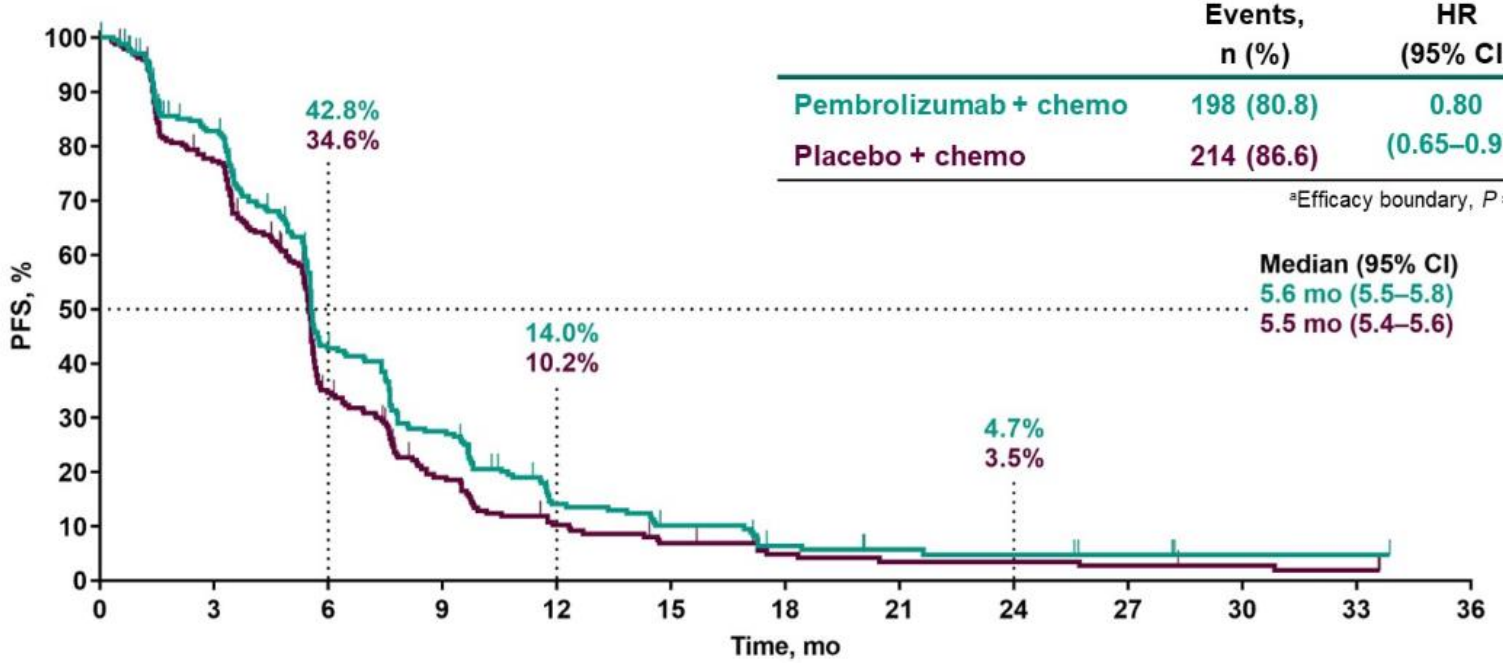
Baseline Characteristics

Characteristic	Pembrolizumab Plus Chemotherapy n = 245	Placebo Plus Chemotherapy n = 247
Age, median (range), y	62 (34–87)	64 (34–84)
Women	152 (62.0)	151 (61.1)
Enrolled in East Asia	150 (61.2)	150 (60.7)
ECOG performance status 1	174 (71.0)	155 (62.8)
Current or former smoker	84 (34.3)	83 (33.6)
Adenocarcinoma histology	239 (97.6)	243 (98.4)
PD-L1 TPS ≥50%	52 (21.2)	51 (20.6)
Chemotherapy received		
Cisplatin/pemetrexed	37 (15.1)	43 (17.4)
Carboplatin/pemetrexed	208 (84.9)	203 (82.2)
Prior therapy		
Neoadjuvant therapy	1 (0.4)	4 (1.6)
Adjuvant therapy	13 (5.3)	12 (4.9)
Radiation	81 (33.1)	92 (37.2)

Characteristic	Pembrolizumab Plus Chemotherapy n = 245	Placebo Plus Chemotherapy n = 247
Brain metastasis at baseline	51 (20.8)	47 (19.0)
EGFR-activating mutation[a]		
L858R	103 (42.0)	102 (41.3)
DEL19	139 (56.7)	142 (57.5)
L858R and *DEL19*	2 (0.8)	2 (0.8)
EGFR T790M mutation		
Positive	95 (38.8)	87 (35.2)
Negative	129 (52.7)	140 (56.7)
Not done	21 (8.6)	20 (8.1)
Previous use of TKI		
Treated with TKI except for osimertinib	128 (52.2)	126 (51.0)
Treated with first-line osimertinib	28 (11.4)	33 (13.4)
Treated with second-line osimertinib	88 (35.9)	88 (35.6)
Other	1 (0.4)	0

KEYNOTE-789

PFS at Interim Analysis 2

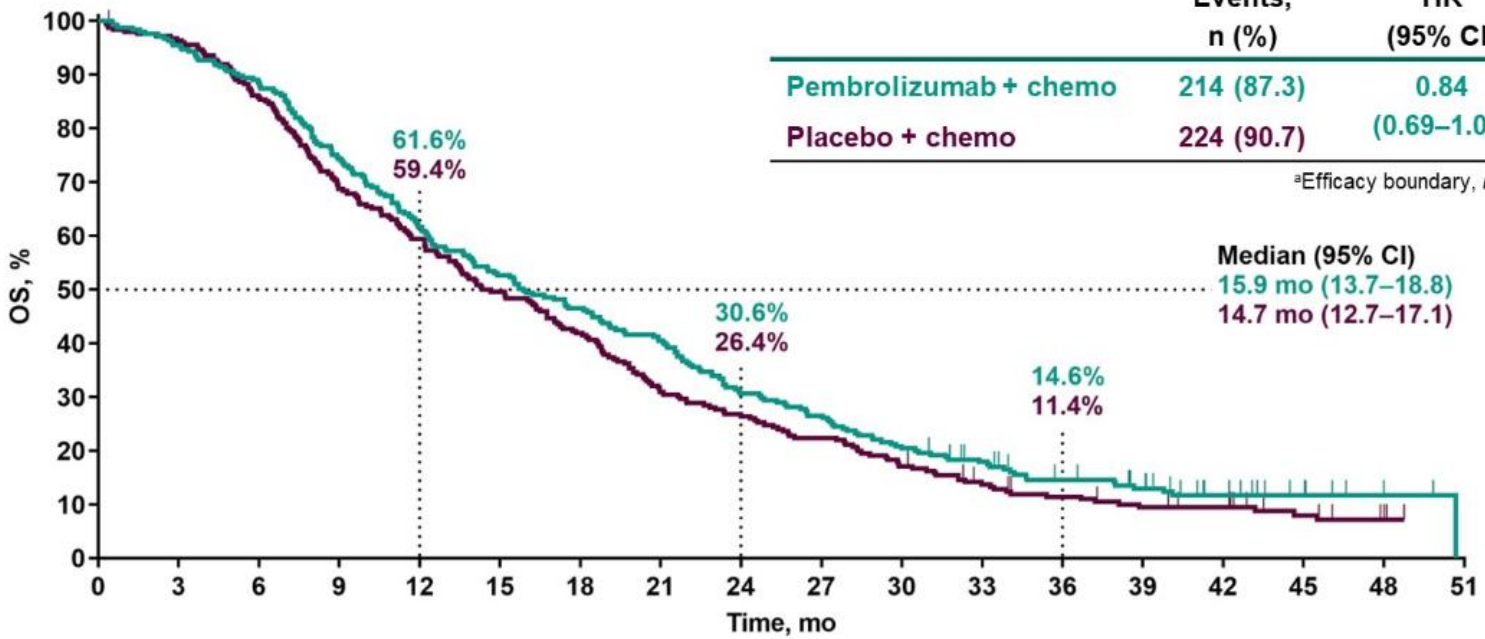


	Events, n (%)	HR (95% CI)	*P* value[a]
Pembrolizumab + chemo	198 (80.8)	0.80 (0.65–0.97)	0.0122
Placebo + chemo	214 (86.6)		

[a]Efficacy boundary, $P = 0.0117$ for PFS (IA2).

KEYNOTE-789

OS at Final Analysis

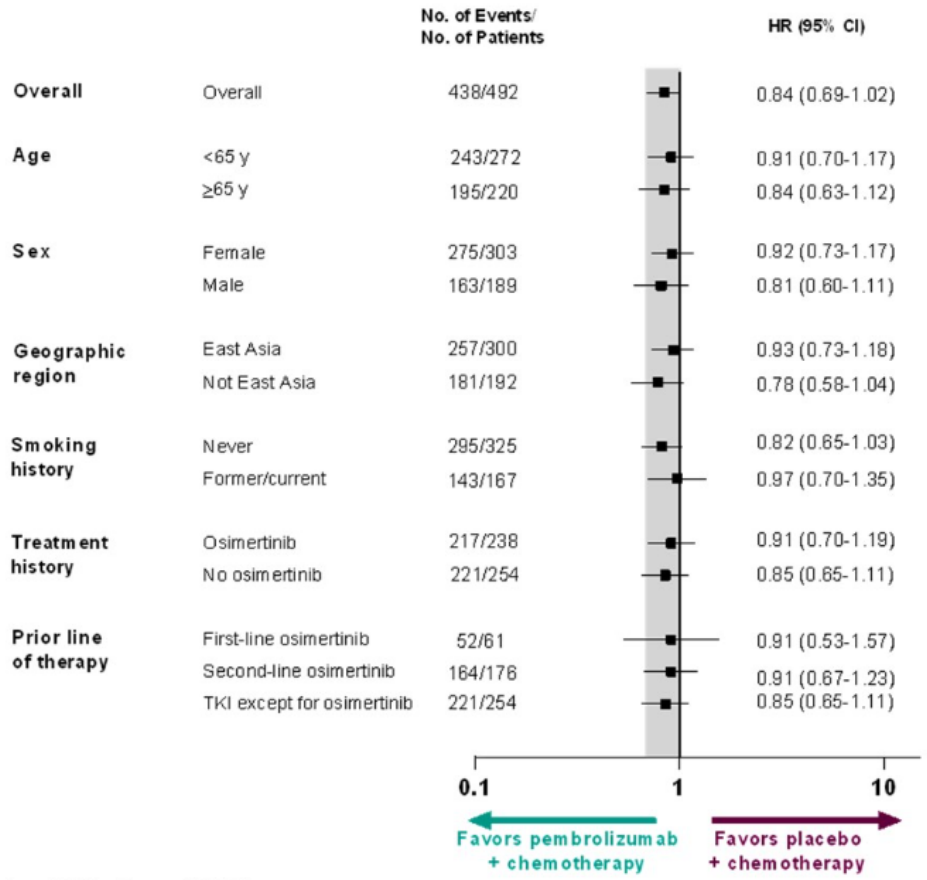


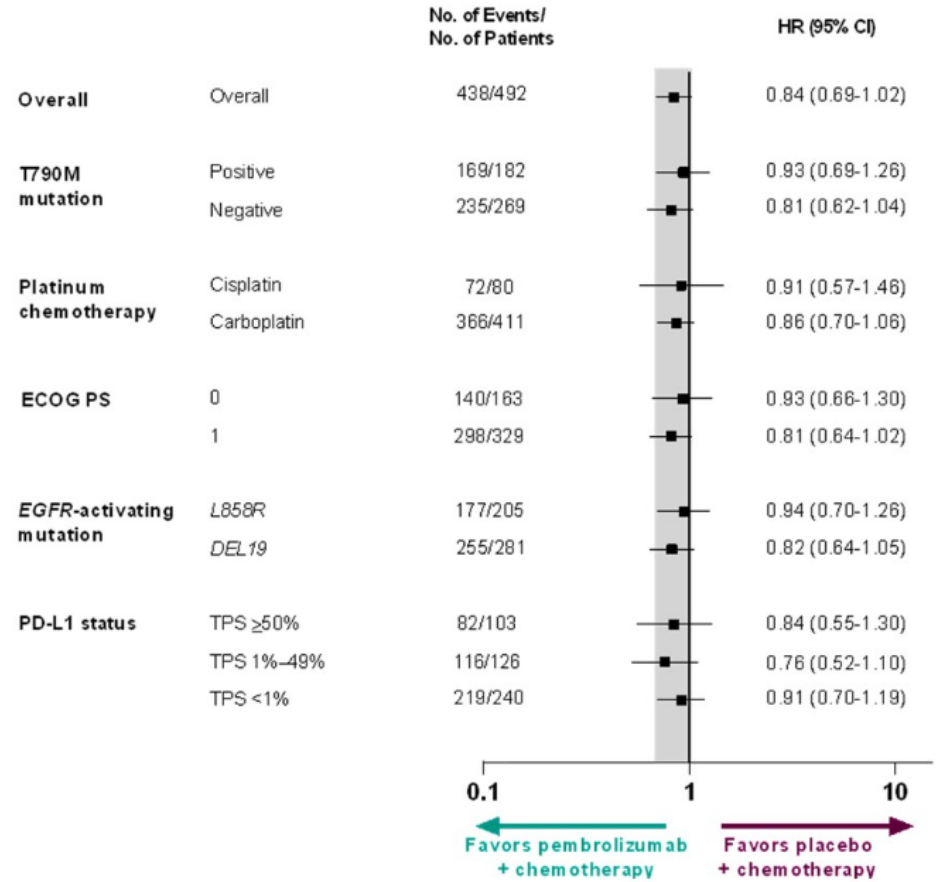
	Events, n (%)	HR (95% CI)	*P* value[a]
Pembrolizumab + chemo	214 (87.3)	0.84 (0.69–1.02)	0.0362
Placebo + chemo	224 (90.7)		

[a]Efficacy boundary, $P = 0.0117$ for OS (FA).

KEYNOTE-789

OS by Subgroup at Final Analysis

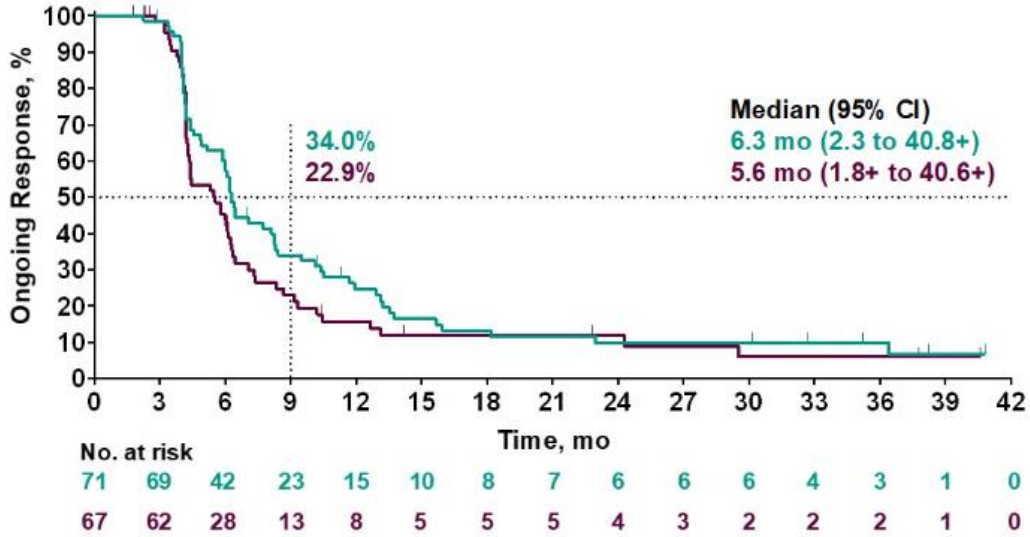




KEYNOTE-789

Antitumor activity and Duration of Response at Final Analysis

	Pembrolizumab Plus Chemotherapy n = 245	Placebo Plus Chemotherapy n = 247
ORR (95% CI), %	**29.0 (23.4–35.1)**	**27.1 (21.7–33.1)**
Best overall response		
Complete response	5 (2.0)	3 (1.2)
Partial response	66 (26.9)	64 (25.9)
Stable disease[a]	121 (49.4)	117 (47.4)
Progressive disease	37 (15.1)	52 (21.1)
Not evaluable[b]	8 (3.3)	5 (2.0)
No assessment[c]	8 (3.3)	6 (2.4)



KEYNOTE-789

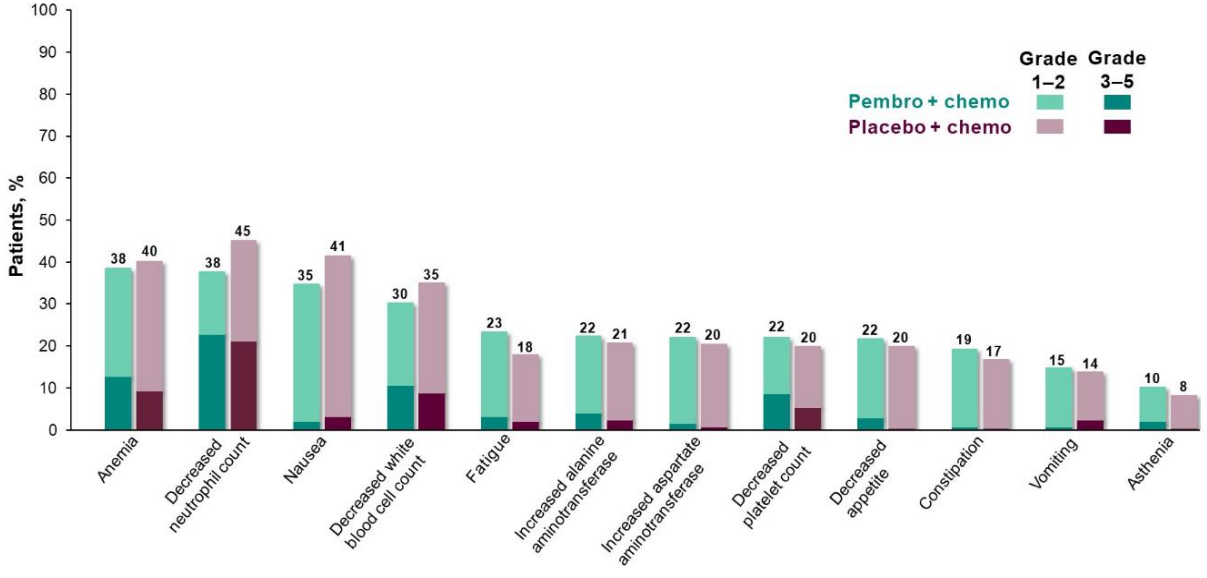
Safety

Patients With AE, n (%)	Pembrolizumab Plus Chemotherapy n = 245	Placebo Plus Chemotherapy n = 246
Any AE (all-cause)	239 (97.6)	241 (98.0)
Grade 3–5	137 (55.9)	143 (58.1)
Led to death	5 (2.0)	12 (4.9)
Treatment related	220 (89.8)	212 (86.2)
Grade 3–5[a]	107 (43.7)	95 (38.6)
Led to discontinuation of any treatment component	40 (16.3)	29 (11.8)
Led to discontinuation of pembrolizumab or placebo	24 (9.8)	11 (4.5)
Led to discontinuation of any chemotherapy	31 (12.7)	29 (11.8)
Led to discontinuation of all treatment components	7 (2.9)	5 (2.0)
Immune-mediated AEs and infusion reactions	49 (20.0)	20 (8.1)
Grade 3–5	11 (4.5)	5 (2.0)

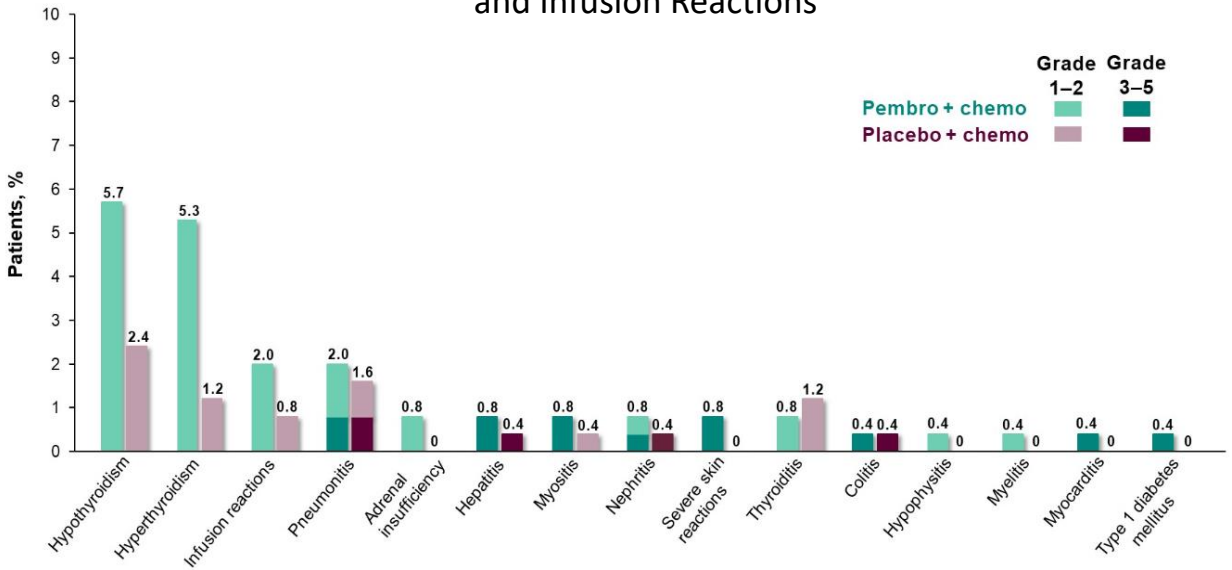
KEYNOTE-789

Safety

Treatment-Related AEs
Incidence ≥10% in any treatment group



Immune-mediated AEs
and Infusion Reactions



KEYNOTE-789

Pembrolizumab does not provide additional benefit for patients with TKI-resistant, EGFR-mutant metastatic NSCLC

Key Studies

Perioperative NSCLC	EGFR Mutated Metastatic NSCLC	Metastatic and Actionable Mutated NSCLC and SCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • HERTHENA-Lung01 • KEYNOTE 789	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

FDA APPROVAL

DESTINY-Lung01

*On **April 5, 2024**, the Food and Drug Administration granted accelerated approval to **fam-trastuzumab deruxtecan-nxki** (Enhertu, Daiichi Sankyo, Inc.) for adult patients with **unresectable or metastatic HER2-positive (IHC 3+) solid tumors** who have received prior systemic treatment and have no satisfactory alternative treatment options based on DESTINY-PanTumor02, **DESTINY-Lung01**, and DESTINY-CRC02.*

- The recommended fam-trastuzumab deruxtecan-nxki dosage for this indication is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

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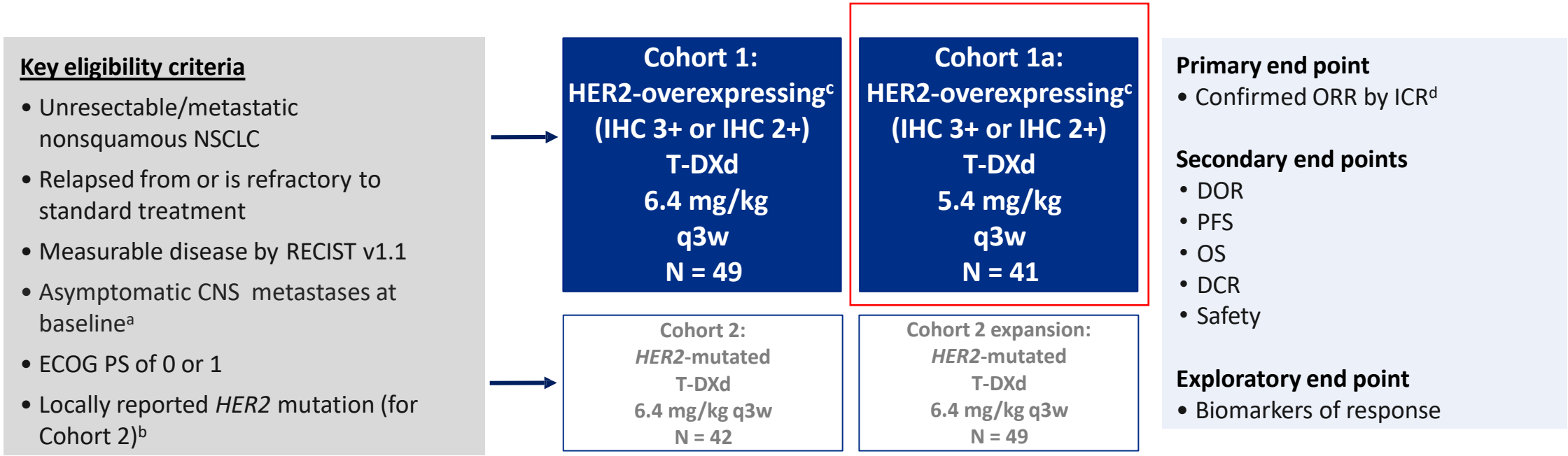
KEY DATA

DESTINY-Lung01

Study Design: Multicenter, international, open-label, 2-cohort phase 2 trial

DESTINY-Lung01 included 17 patients with previously treated, unresectable, or metastatic, centrally confirmed HER2-positive (IHC 3+) NSCLC



Data cutoff: Dec 3, 2021

ESMO Congress 2021; Abstract LBA45; NEJM 2022; 386:241-251

KEY DATA

DESTINY-Lung01

- In DESTINY-Lung01, patients with centrally confirmed HER2-positive (IHC 3+) non-small cell lung cancer (NSCLC) treated with ENHERTU showed a confirmed **ORR of 52.9%** (95% CI: 27.8-77.0) and median DoR of **6.9 months** (range: 4.0-11.7+)

	DESTINY-PanTumor02 N=111	DESTINY-Lung01 (Cohort 1a) N=17	DESTINY-CRC02 N=64
Confirmed ORR (95% CI)	51.4% (41.7 – 61.0)	52.9% (27.8 – 77.0)	46.9% (34.3 – 59.8)
• **CR**	2.7%	5.9%	0%
• **PR**	48.6%	47.1%	46.9%
Duration of Response			
Median, months (range)	19.4 (1.3 – 27.9+)	6.9 (4.1 – 11.7+)	5.5 (1.3+ - 9.7+)

Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial. Smit et al., The Lancet, April 2024

PDUFA DATE

TROPION-Lung01

February 19, 2024 *– Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) Biologics License Application (BLA) for datopotamab deruxtecan (Dato-DXd) has been accepted in the U.S. for the treatment of adult patients with locally advanced or metastatic* ***nonsquamous*** *non-small cell lung cancer (NSCLC) who have received prior systemic therapy. Datopotamab deruxtecan is a specifically engineered TROP2 directed DXd antibody drug conjugate (ADC) being jointly developed by Daiichi Sankyo and AstraZeneca.*

The Prescription Drug User Fee Act (PDUFA) date, the U.S. Food and Drug Administration (FDA) action date for its regulatory decision, is December 20, 2024.

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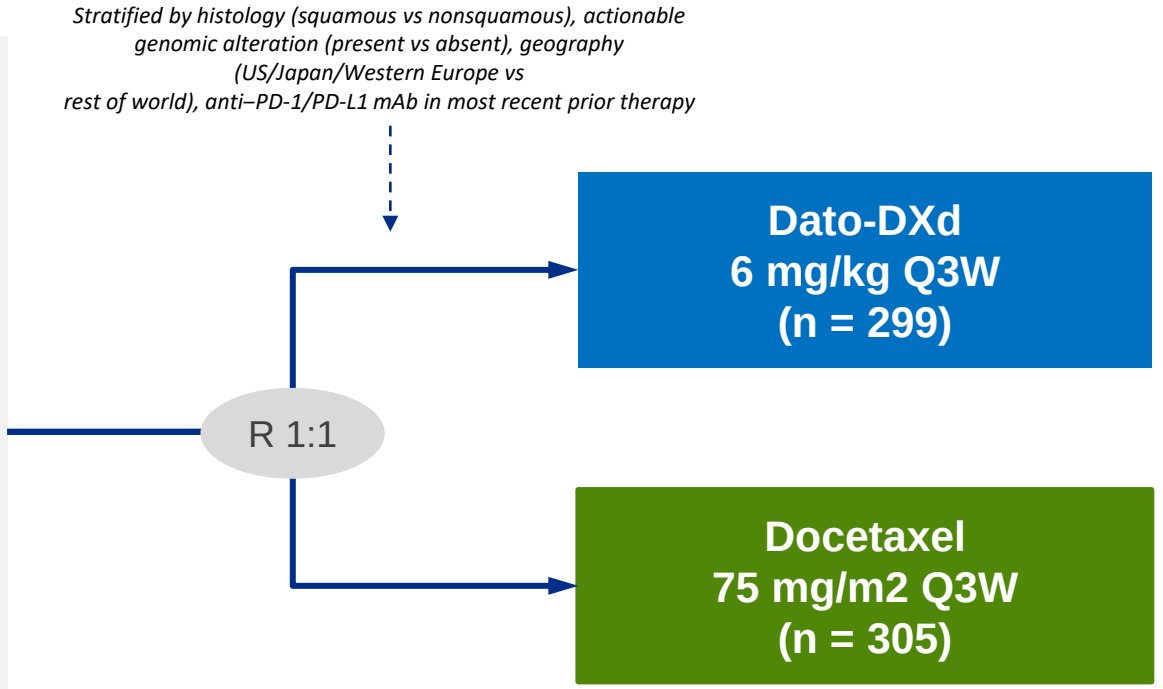
TROPION-Lung01

Study Design: Global, randomized, open-label phase III trial

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS 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

(N = 604)



[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.

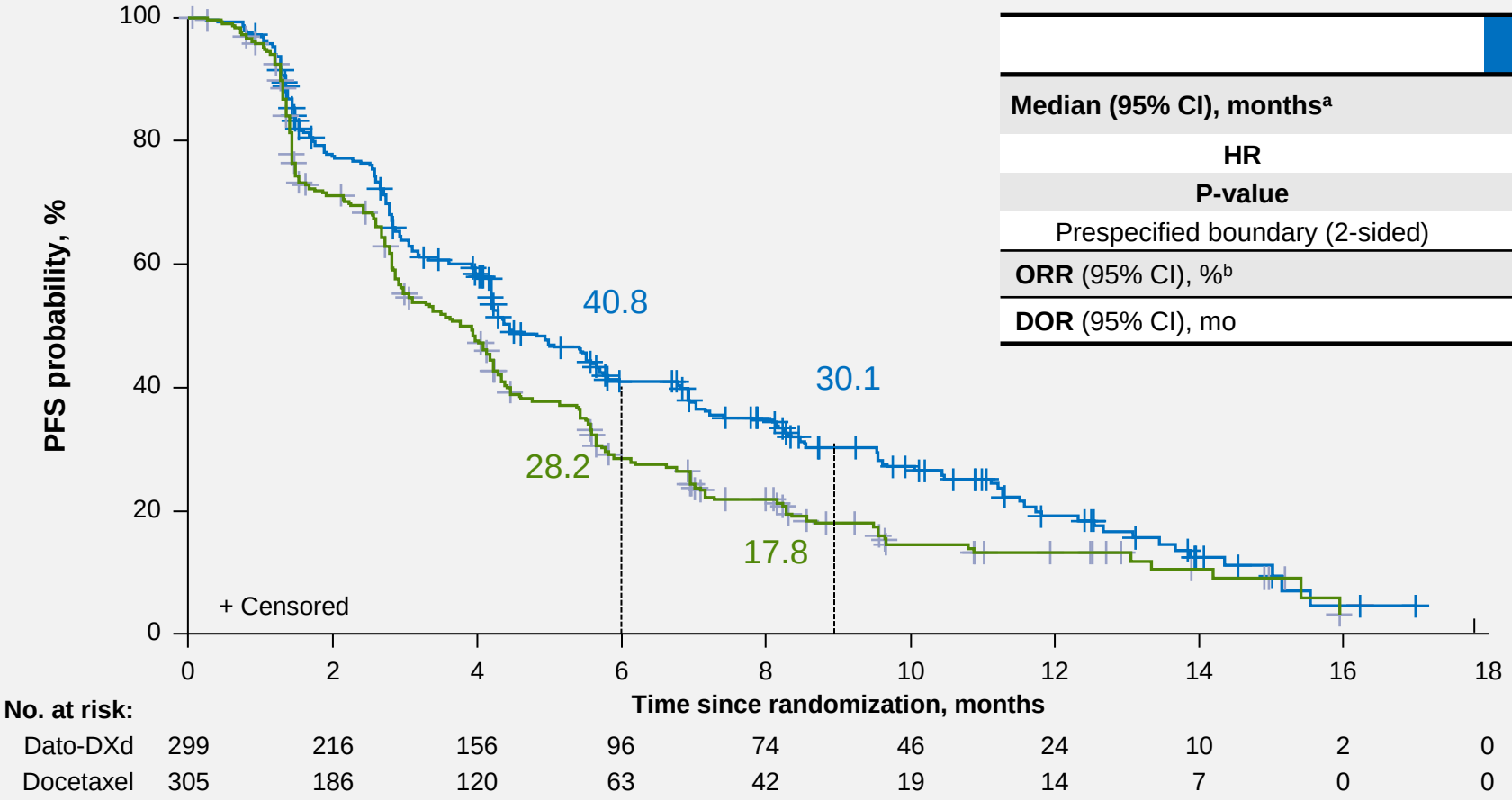
Primary endpoints: PFS by BICR and OS

Secondary endpoints: ORR (BICR), DoR (BICR), safety

KEY DATA

TROPION-Lung01

Primary Endpoint: PFS by BICR in ITT population (previously reported at ESMO 2023)



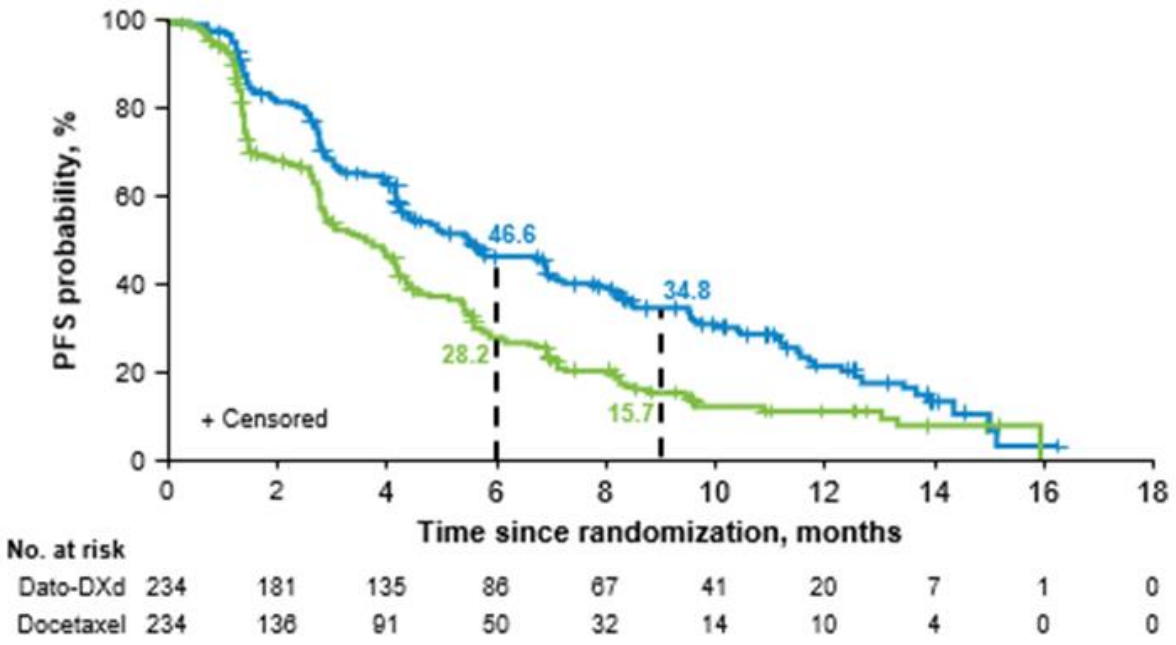
	Dato-DXd	Docetaxel
Median (95% CI), months[a]	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
P-value	**0.004**	
Prespecified boundary (2-sided)	0.008	
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

ESMO 2023. Abstr LBA12

KEY UPDATE

TROPION-Lung01

Dato-DXd in Non–Squamous 2L+ mNSCLC



Note: PFS HR for non–squamous without actionable genomic alterations (AGAs): 0.71

Note: PFS HR for Squamous: 1.38 with and without AGAs

With and without AGAs	**Dato-DXd n=234**	**Docetaxel n=234**
Median PFS (95% CI), months	5.5 (4.3 - 6.9)	3.6 (2.9 - 4.2)
• **HR**	**0.63** (0.51 - 0.79)	
Interim medium OS (95% CI), months	13.4 (12.1-16.4)	11.4 (10.1-13.8)
• **HR**	**0.79** (0.60-1.02)	
ORR, n (%)	**73 (31)**	**30 (13)**
• **CR**	4 (2)	0
• **PR**	69 (30)	30 (13)
DOR, (95% CI), mo	7.7 (5.6-11.1)	5.6 (5.4-6.0)

No new safety concerns:

- Stomatitis, nausea, and alopecia were the most frequent TRAEs seen with Dato-DXd. Stomatitis/oral mucositis events with Dato-DXd were predominantly grade 1 (28%) or 2 (22%) and associated with a low rate of discontinuation (1%)
- Lacrimation increased was the most common ocular event seen with Dato-DXd (8%), followed by dry eye (7%); all cases were grade ≤2
- 4 adjudicated drug-related grade 5 ILD events (2%) were seen with Dato-DXd; primary cause of death in 2/4 patients was attributed to disease progression by investigator
- IRRs were observed in 8% and 9% of patients treated with Dato-DXd and docetaxel, respectively; no grade ≥3 events in either arm were reported

Key Studies

Perioperative NSCLC	EGFR Mutated Metastatic NSCLC	Metastatic and Actionable Mutated NSCLC and SCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • HERTHENA-Lung01 • KEYNOTE 789	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

CLINICAL QUESTION

DESTINY-Lung02

Does trastuzumab deruxtecan (Enhertu, T-DXd) benefit patients with previously treated HER2-mutated metastatic NSCLC?

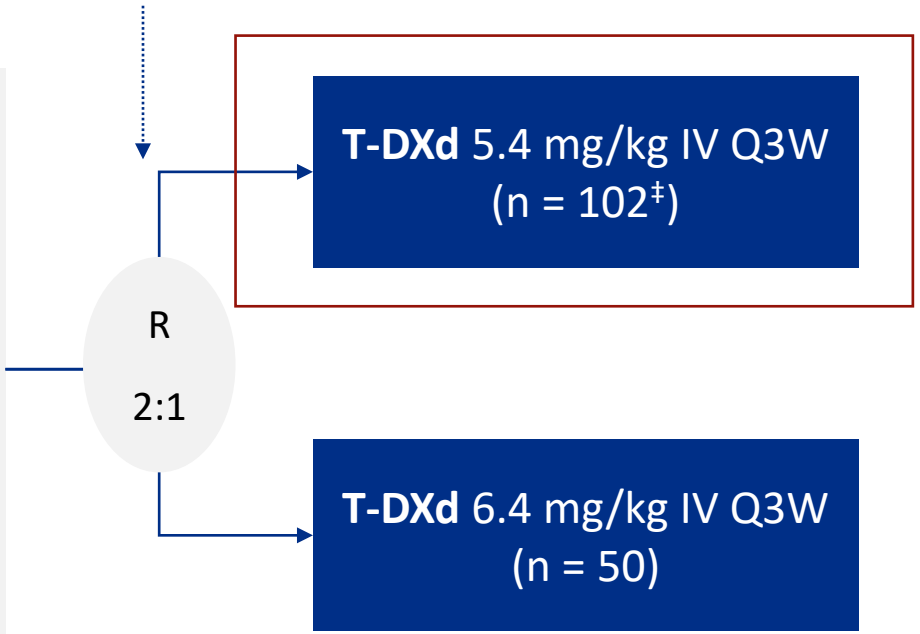
KEY DATA

DESTINY-Lung02

Study Design: international, randomized, double-blind, noncomparative phase II trial

- Metastatic ***HER2*-mutated*** NSCLC
- ≥1 previous anticancer treatment, including platinum-based chemotherapy
- Measurable disease by BICR (RECIST v1.1)
- Stable brain mets permitted at baseline†
- ECOG PS 0/1

(N = 152)



Primary endpoint:

- confirmed ORR by BICR¥

Secondary endpoints:

- ORR by inv; DoR, DCR, and PFS by BICR and inv; OS; safety

*Identified in fresh/archival tumor tissue. †Must be asymptomatic and not needing corticosteroids or anticonvulsants. ‡n = 1 did not receive treatment.

¥ Hypothesis tested by comparing lower limit of 95% CI for each T-DXd dose vs benchmark ORR of 26.4% (upper limit of ORR 95% CI observed with ramucirumab + docetaxel in REVEL trial)

Not statistically powered to compare between arm

WCLC 2023. Abstr MA13.10. 3
J Clin Oncol. 2023 Nov 1; 41(31): 4852–4863.

KEY DATA

DESTINY-Lung02

Response by BICR

Response	T-DXd 5.4 mg/kg (n = 102*)	T-DXd 6.4 mg/kg (n = 50)
Primary endpoint: confirmed ORR, n (%) [95% CI]	50 (49.0) [39.0-59.1]	28 (56.0) [41.3-70.0]
• CR, n (%)	1 (1.0)	2 (4.0)
• PR, n (%)	49 (48.0)	26 (52.0)
• SD, n (%)	45 (44.1)	18 (36.0)
• PD, n (%)	4 (3.9)	2 (4.0)
• NE, n (%)	3 (2.9)	2 (4.0)
DCR, n (%)	95 (93.1)	46 (92.0)
Median DoR, mo (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median time to initial response, mo (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, mo (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

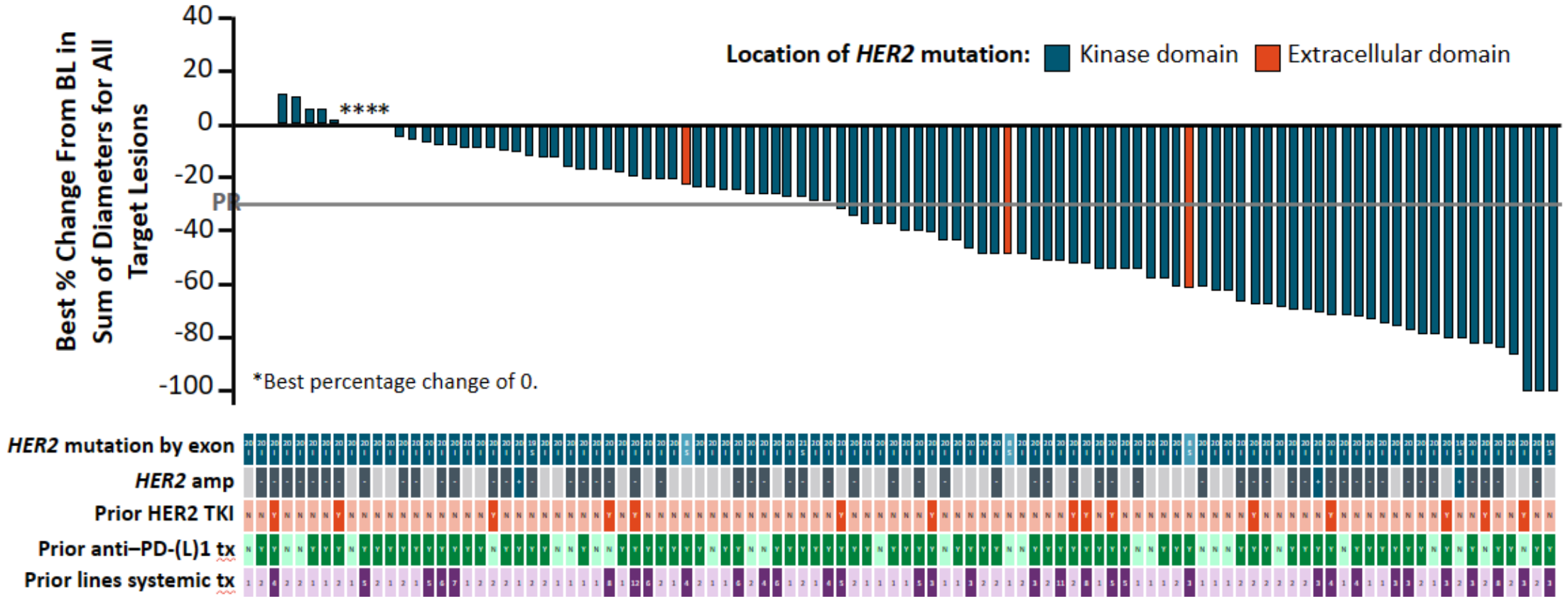
*n = 1 did not receive treatment.

WCLC 2023. Abstr MA13.10. 3
J Clin Oncol. 2023 Nov 1; 41(31): 4852–4863.

KEY DATA

DESTINY-Lung02

Antitumor Activity with T-DXd **5.4 mg/kg** Q3W



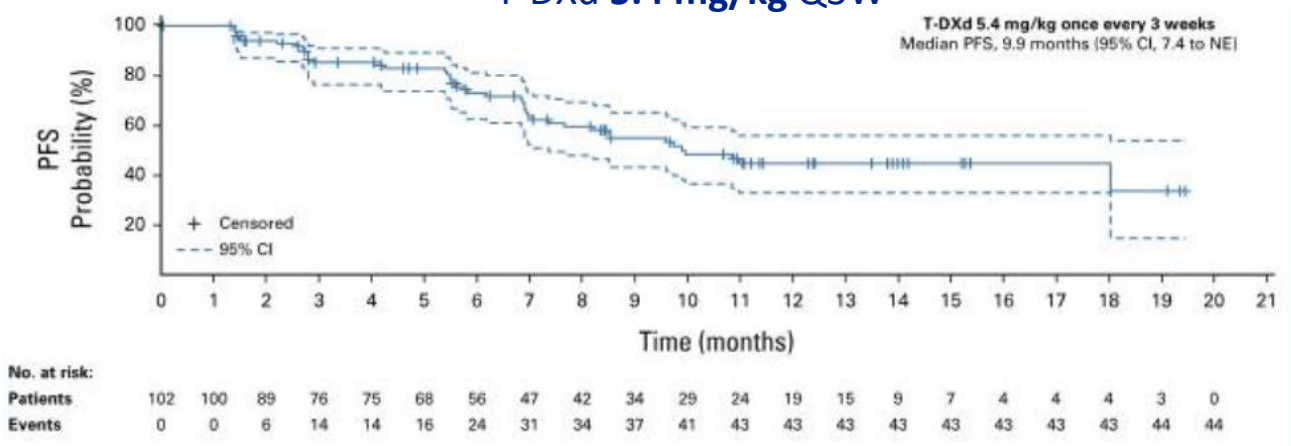
WCLC 2023. Abstr MA13.10. 3
J Clin Oncol. 2023 Nov 1; 41(31): 4852–4863.

KEY DATA

DESTINY-Lung02

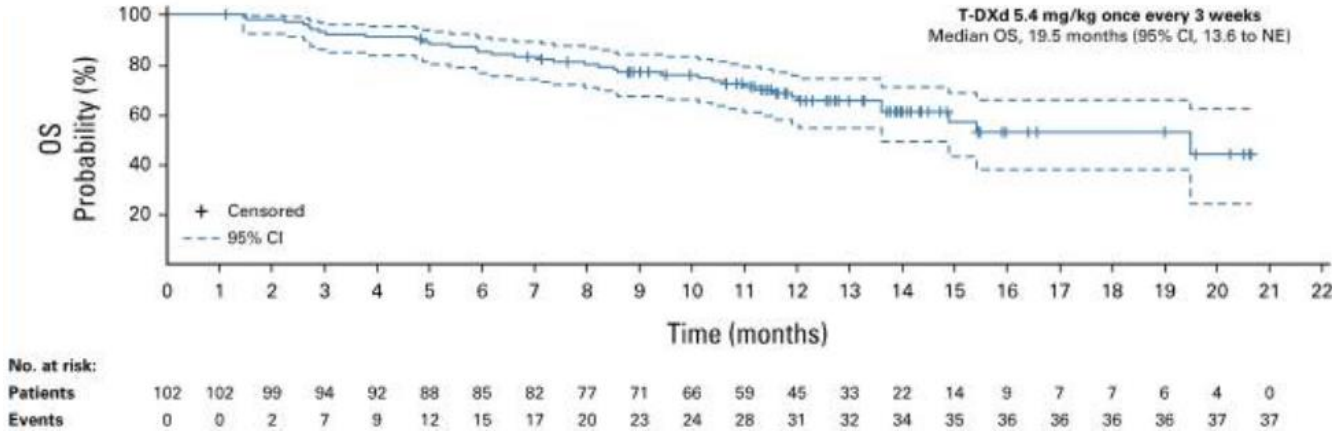
Progression Free Survival

T-DXd **5.4 mg/kg** Q3W



Overall Survival

T-DXd **5.4 mg/kg** Q3W



WCLC 2023. Abstr MA13.10. 3
J Clin Oncol. 2023 Nov 1; 41(31): 4852–4863.

DESTINY-Lung02

Safety

Drug-Related TEAE, n (%)	T-DXd 5.4 mg/kg (n = 101)		T-DXd 6.4 mg/kg (n = 50)	
Any grade	97 (96.0)		50 (100.0)	
Grade ≥3	39 (38.6)		29 (58.0)	
Serious	14 (13.9)		12 (24.0)	
Associated with drug discontinuation	14 (13.9)		10 (20.0)	
Associated with dose reduction	17 (16.8)		16 (32.0)	
Associated with drug interruption	27 (26.7)		24 (48.0)	
Associated with death	1 (1.0)		1 (2.0)	
Most Common TEAEs, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Nausea	68 (67.3)	4 (4.0)	41 (82.0)	3 (6.0)
Neutropenia	43 (42.6)	19 (18.8)	28 (56.0)	18 (36.0)
Fatigue	45 (44.6)	8 (7.9)	25 (50.0)	5 (10.0)
Decreased appetite	40 (39.6)	2 (2.0)	25 (50.0)	2 (4.0)
Anemia	37 (36.6)	11 (10.9)	26 (52.0)	8 (16.0)

WCLC 2023. Abstr MA13.10. 3
J Clin Oncol. 2023 Nov 1; 41(31): 4852–4863.

DESTINY-Lung02

Safety: Adjudicated Drug-Related ILD

Adjudicated Drug-Related ILD, n (%)	T-DXd 5.4 mg/kg (n = 101)	T-DXd 6.4 mg/kg (n = 50)
Any grade	13 (12.9)	14 (28.0)
• Grade 1	4 (4.0)	4 (8.0)
• Grade 2	7 (6.9)	9 (18.0)
• Grade 3	1 (1.0)	0
• Grade 4	0	0
• Grade 5	1 (1.0)	1 (2.0)
Median time to onset, d (range)	88.0 (40-421)	83.5 (36-386)
Case Outcomes, n (%)	**(n = 13)**	**(n = 14)**
Received steroid tx	11 (84.6)	10 (71.4)
Recovered by data cutoff	8 (61.5)	8 (57.1)
Grade 1 cases retreated with T-DXd, n/N	0/4	2/3

- No recurrence of ILD/pneumonitis observed in 2 patients with grade 1 events who were retreated with T-DXd

WCLC 2023. Abstr MA13.10. 3
J Clin Oncol. 2023 Nov 1; 41(31): 4852–4863.

SUMMARY

DESTINY-Lung02

- DESTINY-Lung02 met its primary endpoint of ORR
  - T-DXd 5.4 mg/kg: 49.0% (39.0%-59.1%)
    - *The recommended dosage of ENHERTU for HER2-mutant NSCLC is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.*
  - No new safety concerns

- *Pooled results from DESTINY-Lung01 and DESTINY-Lung02 for patients with HER2 (ERBB2) mutant metastatic NSCLC with treated and untreated brain metastases at baseline revealed that treatment with trastuzumab deruxtecan resulted in similar intracranial responses. Similar responses were also observed in patients with or without baseline brain metastases.*
  - *Small n size and lack of comparator arm*
  - *ESMO 2023. Abstract 1321MO:* Trastuzumab Deruxtecan in Patients With HER2 (ERBB2)-Mutant Metastatic Non–Small Cell Lung Cancer With and Without Brain Metastases: Exploratory Pooled Analyses From DESTINY-Lung01 and DESTINY-Lung02

WCLC 2023. Abstr MA13.10. 3
J Clin Oncol. 2023 Nov 1; 41(31): 4852–4863.

DESTINY-Lung02

T-DXd (5.4 mg/kg) benefits patients with previously treated HER2-mutated metastatic NSCLC and should be considered as a standard of care

Key Studies

Perioperative NSCLC	EGFR Mutated Metastatic NSCLC	Metastatic and Actionable Mutated NSCLC and SCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • HERTHENA-Lung01 • KEYNOTE 789	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

LIBRETTO-431

Does selpercatinib benefit patients with *RET* fusion positive NSCLC?

A protocol-specified interim analysis was conducted after 98 BICR PFS events were observed in the ITT-Pembrolizumab population.

LIBRETTO-431

Study Design: international, randomized, open-label phase II trial

- Unresectable stage IIIB, IIIC, or stage IV nonsquamous NSCLC
- *RET* fusion via NGS or PCR
- No prior systemic therapy for metastatic disease
- ECOG PS 0-2
- Symptomatic CNS mets excluded

(N = 261)

Stratified by geography (East Asia vs non–East Asia), brain metastasis (Y/N or unknown), choice of chemotherapy with pembrolizumab

R 2:1*

Selpercatinib 160 mg BID (n = 159)

Platinum-Based Chemotherapy† ± **Pembrolizumab** 200 mg (n = 102)

Optional crossover

Selpercatinib (upon BICR-confirmed PD)

*Randomization ratio was initially 1:1 but later amended to 2:1.

†Included investigator's choice of carboplatin AUC 5 or cisplatin 75 mg/m^2, plus pemetrexed 500 mg/m^2.

Gated primary endpoints: PFS by BICR in ITT-pembrolizumab and ITT populations

ITT-pembrolizumab = patients stratified by investigator intent to receive pembrolizumab with chemotherapy; had to comprise ≥80% of ITT population per protocol (n = 212 randomized)

Secondary endpoints: OS, ORR, DoR, CNS ORR, CNS DoR, CNS TTP, safety, PROs

Data cutoff date: 1 May 2023

Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

LIBRETTO-431

Baseline Characteristics

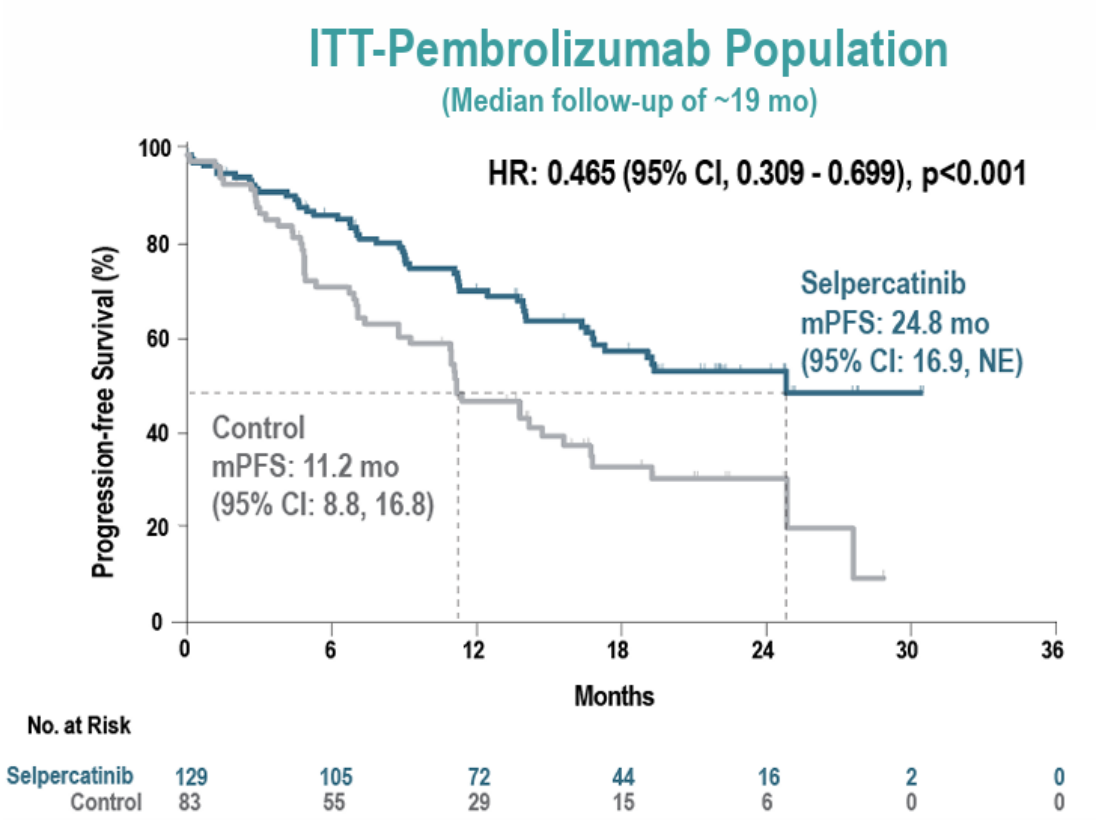
Baseline Characteristic	Selpercatinib (n = 129)	CT + Pembro (n = 83)
Median age, yr (range)	60 (31-84)	62 (31-83)
Female, n (%)	65 (50.4)	48 (57.8)
Smoking status, n (%)		
• Current/former smoker	44 (34.1)	24 (28.9)
• Never	85 (65.9)	59 (71.1)
Race, n (%)		
• Asian	76 (58.9)	41 (49.3)
• White	49 (38.0)	37 (44.6)
• Other	4 (3.2)	1 (1.3)
Enrollment in East Asia, n (%)	75 (58.1)	41 (49.4)
Stage IV disease, n (%)	122 (94.6)	76 (91.6)
ECOG PS, n (%)		
• 0	45 (34.9)	27 (32.5)
• 1	81 (62.8)	52 (62.7)
• 2	3 (2.3)	4 (4.8)

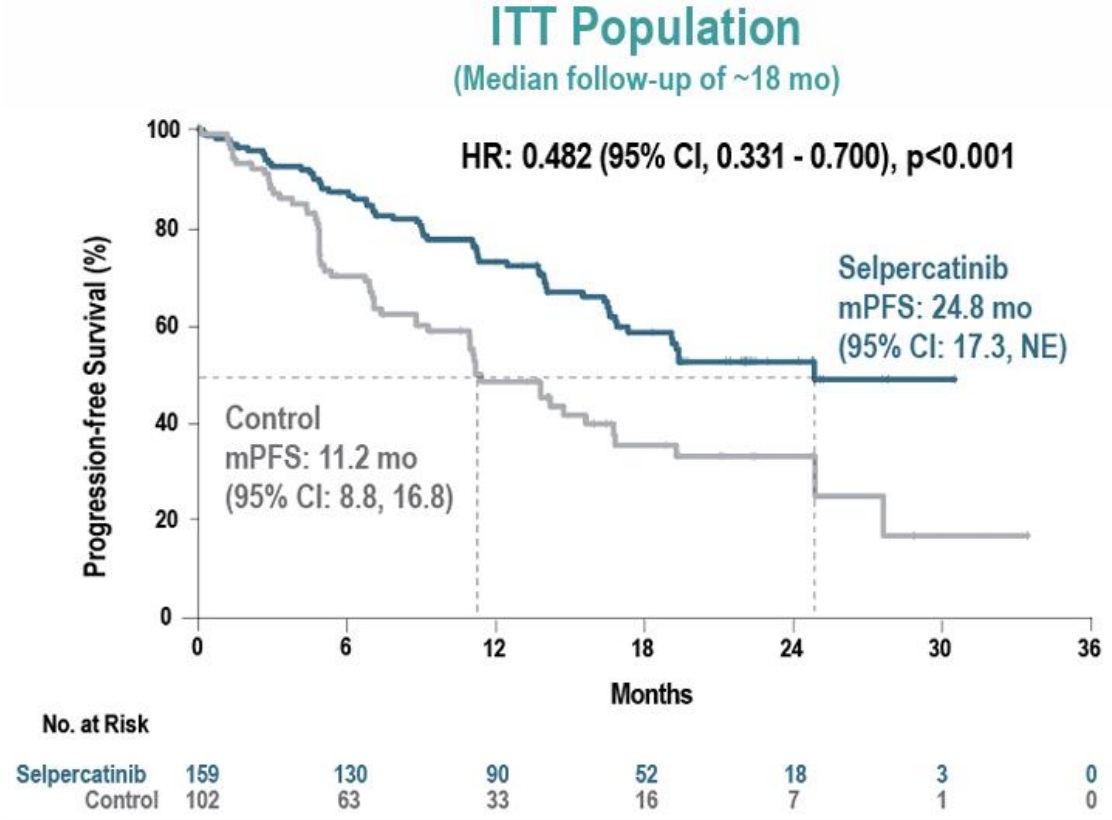
Baseline Characteristic	Selpercatinib (n = 129)	CT + Pembro (n = 83)
Brain metastasis, n (%)		
• Yes	25 (19.4)	18 (21.7)
• No/unknown	104 (80.6)	65 (78.3)
PD-L1 expression, n (%)		
• Negative	31 (24.0)	12 (14.5)
• Positive (≥1%)	55 (42.6)	39 (47.0)
• Missing	43 (33.3)	32 (38.6)
RET fusion partner, n (%)		
• KIF5B-RET	54 (41.9)	41 (49.4)
• CCDC6-RET	13 (10.1)	8 (9.6)
• Other	4 (3.1)	3 (3.6)
• Positive (partner undefined)	58 (45.0)	31 (37.3)

Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

LIBRETTO-431

Primary Endpoint: PFS by BICR

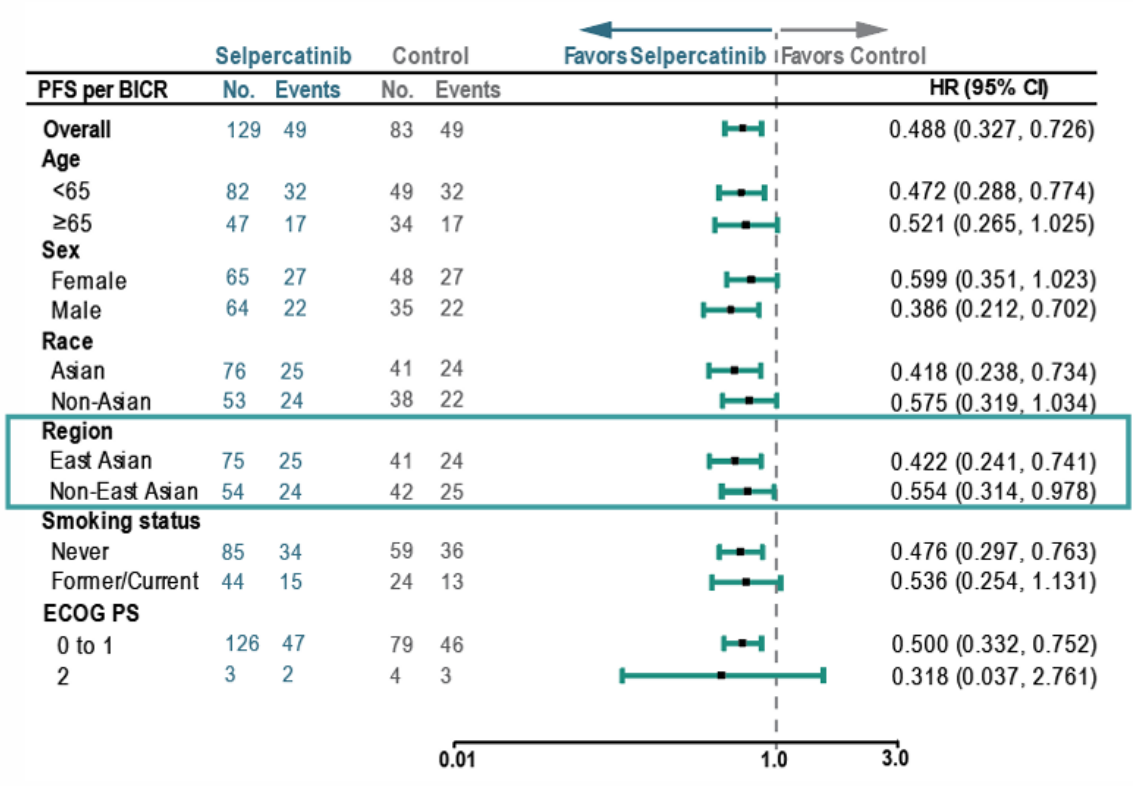


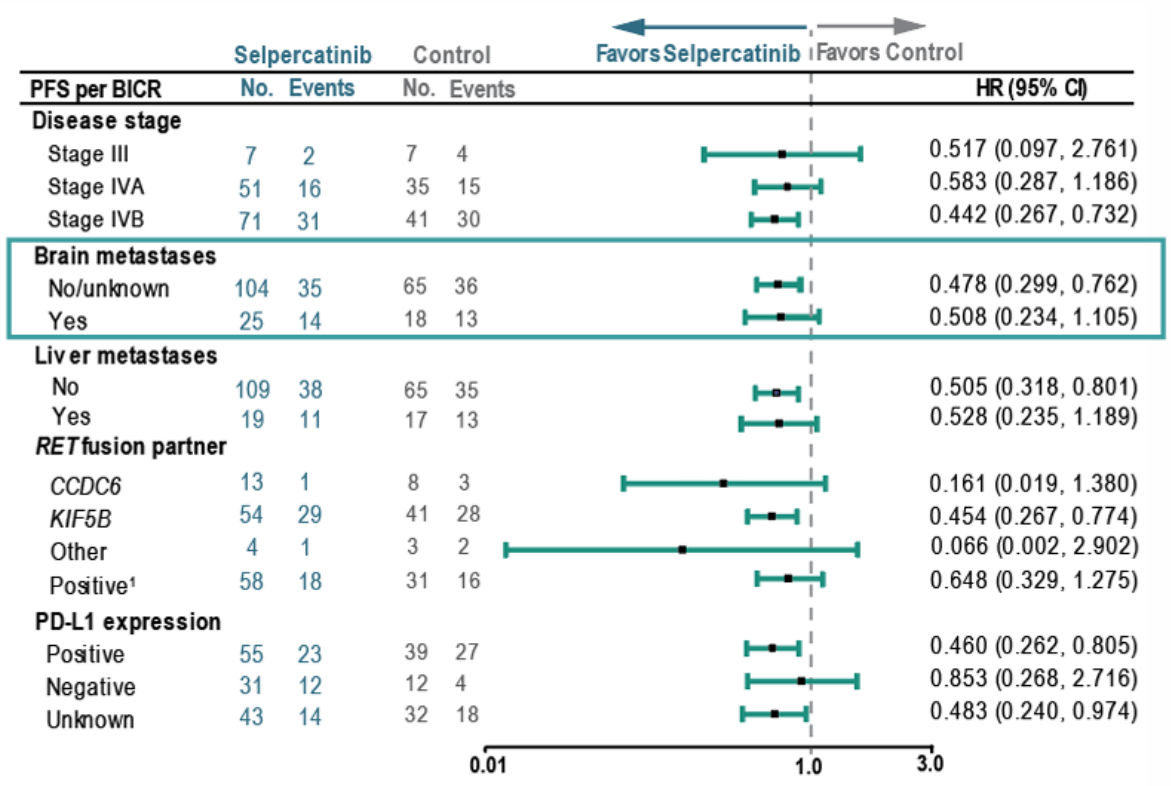


Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

LIBRETTO-431

PFS by BICR by Subgroup





Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

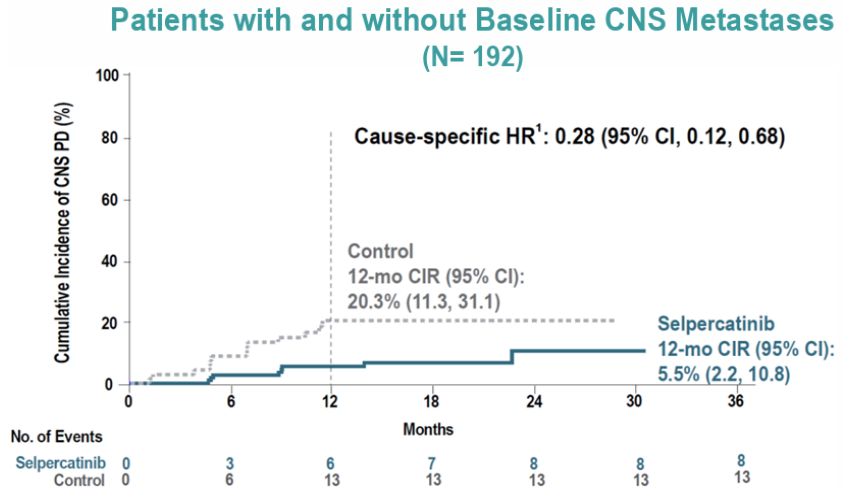
LIBRETTO-431

Response and CNS Progression

Efficacy Outcome	Selpercatinib	CT + Pembro
Systemic Outcomes	(n = 129)	(n = 83)
ORR, %	84	65
Median DoR, mo (95% CI)	24.2 (17.9-NE)	11.5 (9.7-23.3)

Intracranial Outcomes*	(n = 17)	(n = 12)
Intracranial ORR, % • Intracranial CR	82.4 35.3	58.3 16.7
12-mo intracranial DoR, % (95% CI)	76.0 (42.2-91.6)	62.5 (14.2-89.3)
Median intracranial PFS, mo (95% CI)	16.1 (8.8-NE)	10.4 (3.8-NE)

*Patients with CNS involvement at baseline.

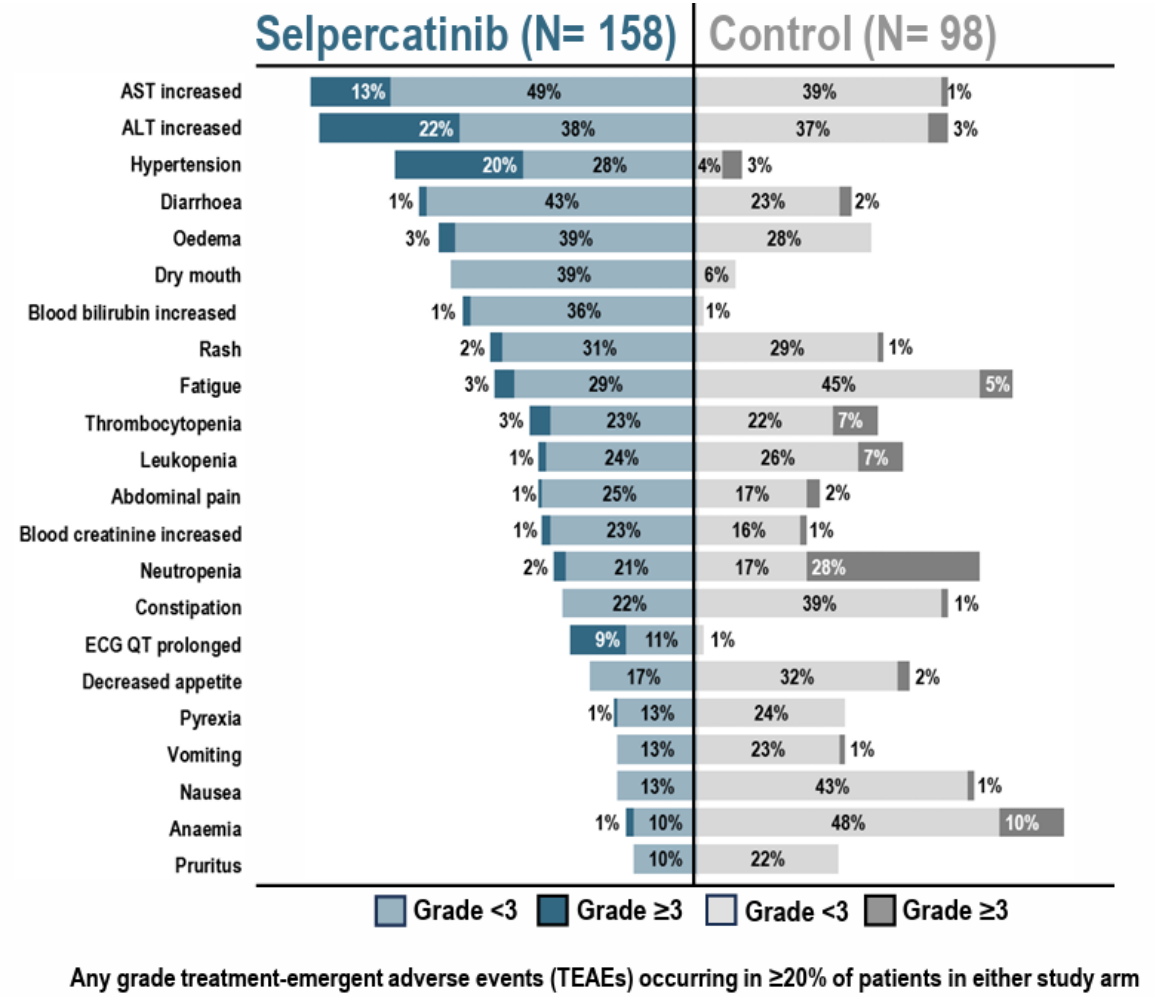


Time to CNS Progression	Selpercatinib	CT + Pembro
All Patients	(n = 120)	(n = 72)
12-mo CIR, % (95% CI)	5.5 (2.2-10.8)	20.3 (11.3-31.1)
Cause-specific HR (95% CI)	0.28 (0.12-0.68)	
Without CNS Mets at BL	(n = 99)	(n = 51)
12-mo CIR, % (95% CI)	1.1 (0.1-5.2)	14.7 (5.7-27.6)
Cause-specific HR (95% CI)	0.17 (0.04-0.69)	
With CNS Mets at BL	(n = 21)	(n = 21)
12-mo CIR, % (95% CI)	25.7 (8.8-46.7)	33.3 (14.3-53.8)
Cause-specific HR (95% CI)	0.61 (0.19-1.92)	

Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

LIBRETTO-431

Safety



Any grade treatment-emergent adverse events (TEAEs) occurring in ≥20% of patients in either study arm

Safety Outcome	Selpercatinib (n = 158)	CT + Pembro (n = 98)
Median time on tx, mo (SD)	16.7 (8.3)	9.8 (7.2)
Any AE, n (%)	158 (100)	97 (99.0)
Any grade ≥3 AE, n (%)	111 (70.3)	56 (57.1)
Death due to AE, n (%) • Related AE	7 (4.4) 2 (1.3)*	0 0
AEs leading to discontinuation, n (%)	16 (10.1)	2 (2.0)
AEs leading to dose adjustment, n (%)	123 (77.8)	74 (75.5)
AEs leading to dose reduction, n (%)	81 (51.3)	28 (28.6)

*Malnutrition (n = 1), sudden death (n = 1).

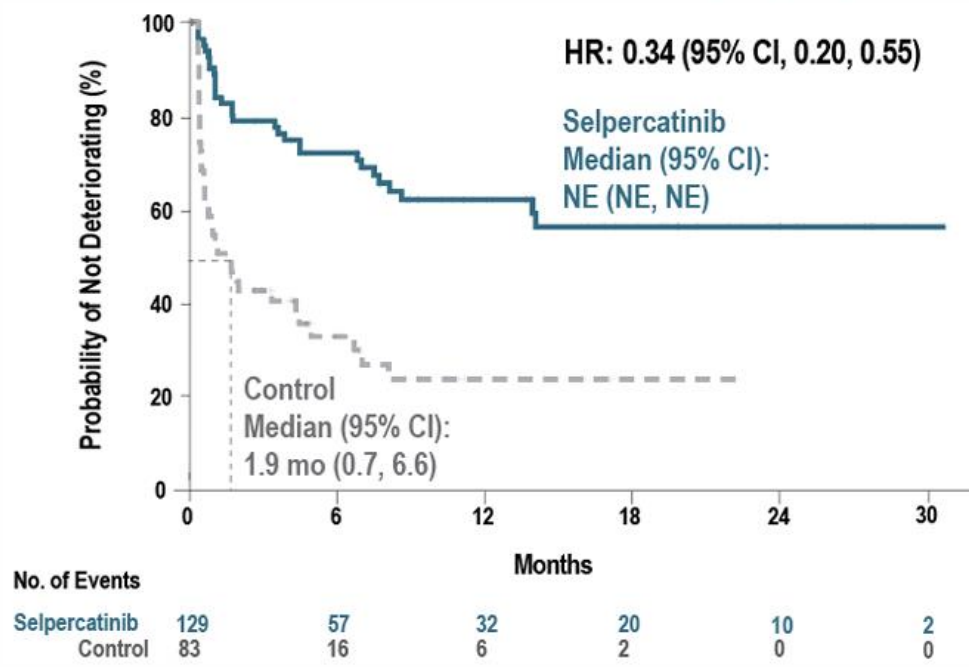
- Median time on tx ~70% longer with selpercatinib
- Selpercatinib TEAEs generally consistent with prior reports, largely managed with dose modification

Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

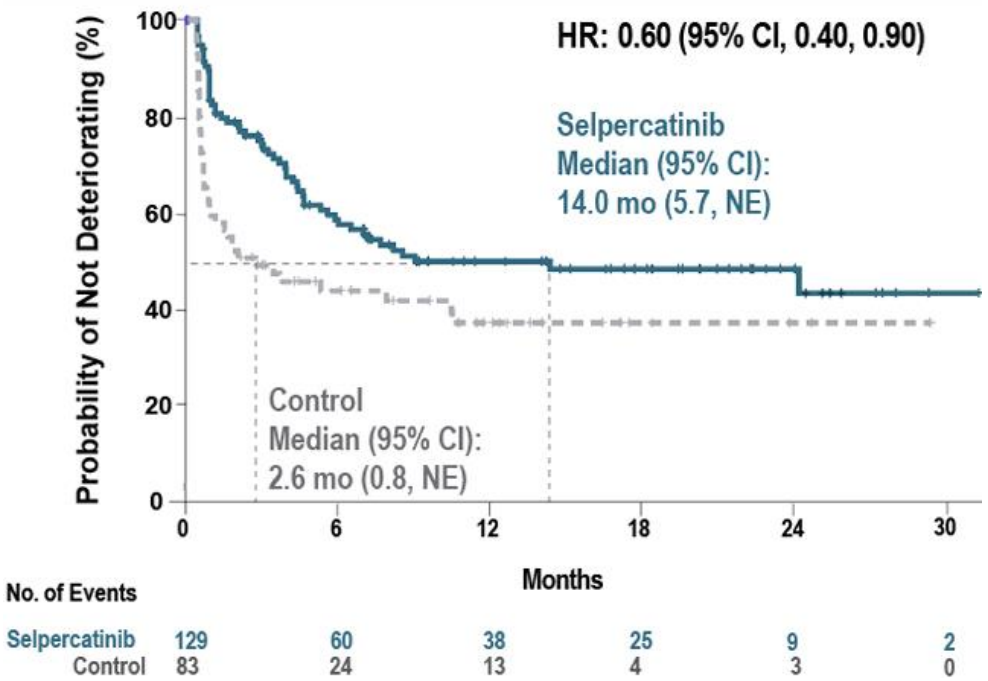
LIBRETTO-431

Patient Reported Outcomes

NSCLC-SAQ - Pulmonary Symptoms



EORTC QLQ-C30 - Physical Function



Selpercatinib delayed time to deterioration of pulmonary symptoms and overall physical function

Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

SUMMARY

LIBRETTO-431

- Selpercatinib showed greater efficacy versus chemotherapy with or without pembrolizumab in the 1L setting for patients with *RET* fusion-positive NSCLC
  - Selpercatinib significantly improved median PFS vs chemotherpy + pembrolizumab in ITT-pembrolizumab population, meeting primary endpoint: 24.8 vs 11.2 mo (HR: 0.46; 95% CI: 0.31-0.70; P <.001)
  - Selpercatinib improved intracranial response rate and delayed CNS progression vs chemotherapy + pembrolizumab
- No new safety concerns
  - Improved patient reported outcomes

Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

LIBRETTO-431

Selpercatinib should be considered as a 1L standard of care for patients with RET fusion-positive advanced NSCLC

Identification of eligible patients is critical at the time of diagnosis

Key Studies

Perioperative NSCLC	EGFR Mutated Metastatic NSCLC	Metastatic and Actionable Mutated NSCLC and SCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • HERTHENA-Lung01 • KEYNOTE 789	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

KRYSTAL-7

Does adagrasib plus pembrolizumab benefit patients with treatment-naïve, advanced NSCLC with a *KRAS* G12C mutation?

KEY DATA

KRYSTAL-7

Study Design: phase II trial

- Advanced, unresectable or metastatic NSCLC with
- KRASG12Cmutationa
- No prior systemic therapy for locally advanced/ metastatic disease
- Stable brain metastases allowed
- Known PD-L1 TPS score

(N = 261)

→

Cohort 1a and Cohort 2
Adagrasib 400 mg BID
+
Pembrolizumab 200mg Q3W
(n = 148)

- **Cohort 1a** had patients with PD-L1 expression of less than 1%
- **Cohort 1b** had a PD-L1 TPS <1% and received adagrasib monotherapy 600 mg twice daily
- **Cohort 2** had patients with PD-L1 expression of 1% or greater
  - 51 patients in Cohort 2 had high PD-L1 expression (PD-L1 TPS ≥ 50%)

Primary endpoints: ORR by RECIST v1.1 per investigator assessment
Secondary endpoints: OS, ORR, DoR, CNS ORR, CNS DoR, CNS TTP, safety, PROs

- Safety was reported in all treated patients (N=148) and efficacy in patients with PD-L1 TPS ≥50% (n=51d) from the KRYSTAL-7 study evaluating adagrasib + pembrolizumab (200 mg IV Q3W) in treatment-naïve patients with NSCLC harboring a KRASG12Cmutation

- Median follow-up for all treated patients was 8.7 months; PD-L1 TPS ≥50%, 10.1 months

aKRASG12Cmutation detected in tumor tissue and/or ctDNA by sponsor-approved local laboratory testing. BPrior systemic therapy or chemoradiation in the (neo)adjuvant setting were allowed if >1 year prior to the first dose of study treatment, and no TRAE of grade ≥2 while on (neo)adjuvant CPI (exceptions for clinically stable vitiligo and psoriasis regardless of grade, and hyper-or hypothyroidism that was adequately controlled). cCohort1a enrolled patients with PD-L1 TPS <1%; Cohort 2 enrolled patients with PD-L1 TPS ≥1%. Molecular testing for PD-L1 TPS was performed locally or centrally, with a sponsor-approved laboratory test (PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 28-8 pharmDx or Ventana PD-L1 [SP142] assay). An additional cohort (1b) is enrolling patients with PD-L1 TPS <1% to receive adagrasib monotherapy, 600 mg BID. DThree patients excluded due to protocol deviations, including one each of atrial fibrillation, stroke within 6 months of enrollment, and presence of KRASG13Cmutation. eKRYSTAL-7 was initiated using the capsule (fasted) form of adagrasib but switched to the tablet (fed or fasted) form during study conduct

ESMO 2023. Abstr LBA65.

KRYSTAL-7

Baseline Characteristics

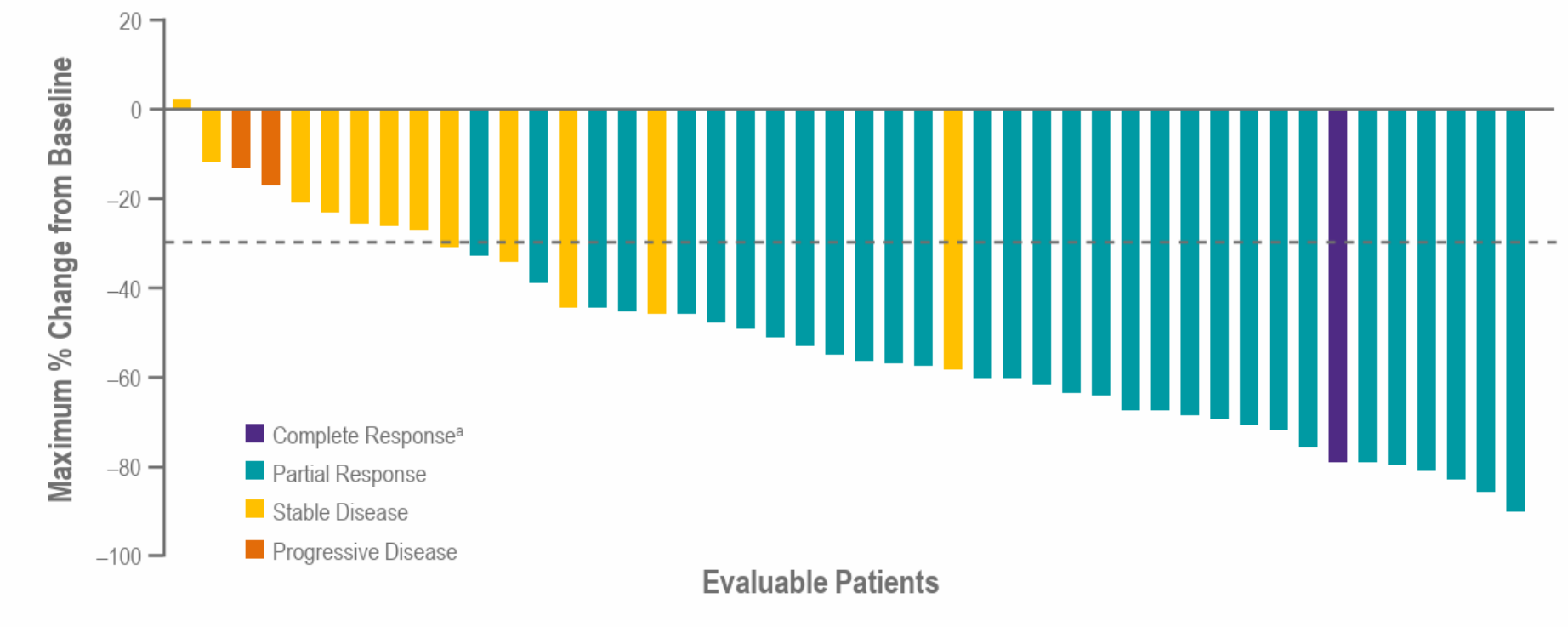
Concurrent 400 mg BID Adagrasib + Pembrolizumab	All Patients (N=148)	PD-L1 TPS ≥50% (n=54)
Median age (range), years	67 (40–90)	66 (40–80)
Female, n (%)	71 (48)	28 (52)
Race, n (%)		
• White	113 (76)	42 (78)
• Black or African American	5 (3)	3 (6)
• Asian / Other	26 (18)	9 (17)
ECOG PS, n (%)		
• 0	57 (39)	18 (33)
• 1	91 (61)	36 (67)
Smoking history, n (%)		
• Never smoker	2 (1)	0
• Current smoker	32 (22)	12 (22)
• Former smoker	114 (77)	42 (78)
Baseline metastases, n (%)		
• Bone	46 (31)	17 (31)
• CNS	21 (14)	9 (17)
• Adrenal	28 (19)	9 (17)
• Liver	24 (16)	10 (19)

ESMO 2023. Abstr LBA65.

KEY DATA

KRYSTAL-7

Primary Endpoint: ORR and Best Tumor Change from Baseline (with PD-L1 TPS ≥50%)



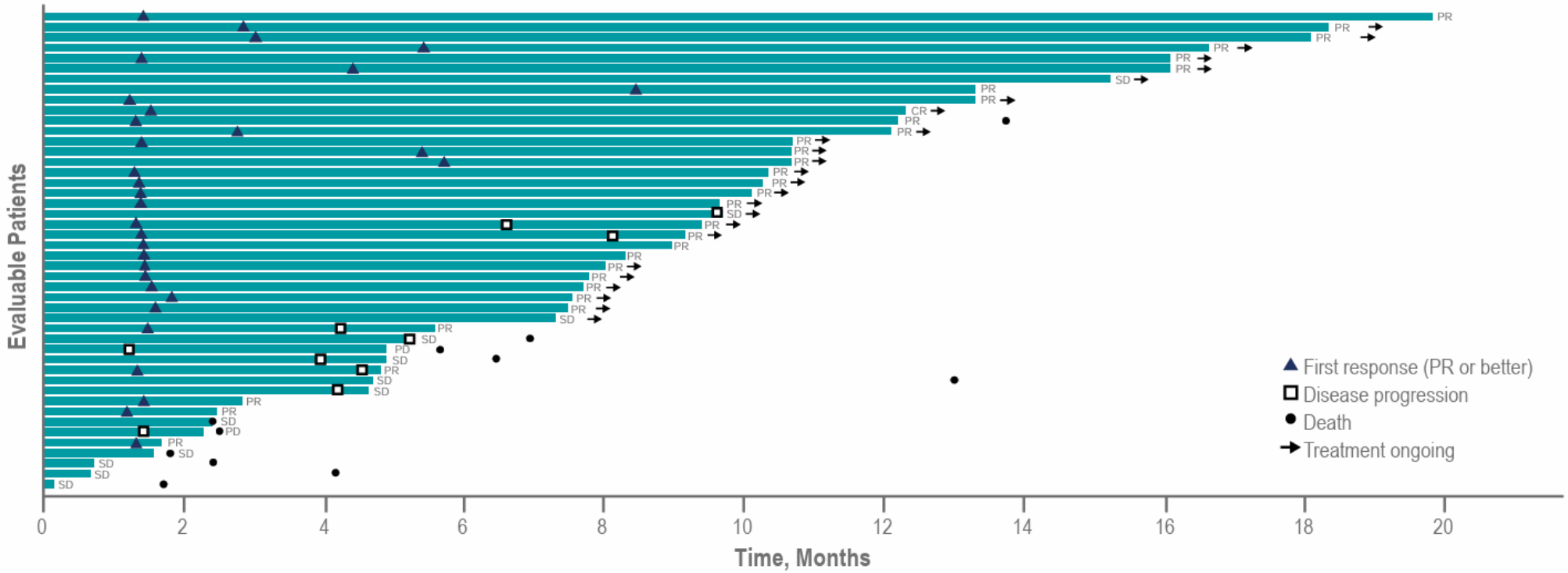
- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity, ORR was 70% (14/20; 95% CI, 46–88)

ESMO 2023. Abstr LBA65.

KRYSTAL-7

Duration of Treatment in patients with PD-L1 TPS ≥50%

- Median time to response was 1.4 months;
- Median duration of response was not reached (95% CI, 12.6–NE)

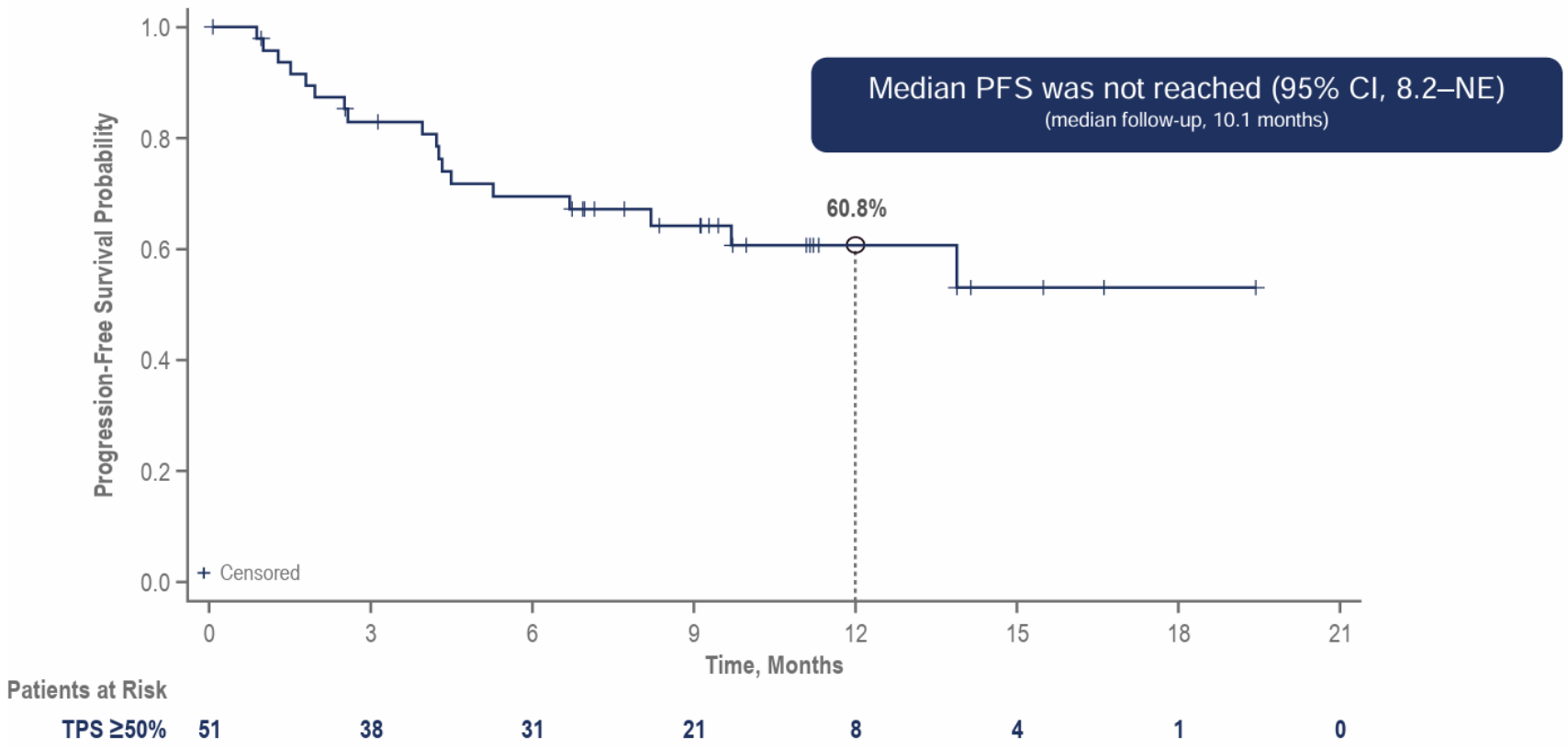


ESMO 2023. Abstr LBA65.

KEY DATA

KRYSTAL-7

PFS in patients with PD-L1 TPS ≥50%



ESMO 2023. Abstr LBA65.

KRYSTAL-7

Safety

Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)

Most Frequent TRAEs[a], %	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	51	28	20	3	0
Diarrhea	44	33	7	3	0
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Vomiting	29	17	11	1	0
Fatigue	26	12	10	4	0
Decreased appetite	24	14	9	1	0
Lipase increased	24	3	9	10	1

a Any grade TRAEs occurring in ≥20% of patients.
b Includes all TRAEs of colitis, hepatitis, adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, nephritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and pneumonitis

Data as of 19 June 2023.
Median follow-up 8.7 months

- There were two Grade 5 TRAEs, one each of pneumonitis and pneumonia
- Immune-related TRAEs[b] of any grade occurred in 18% of patients (26/148) and grade ≥3 occurred in 5% (8/148)
- TRAEs led to adagrasib dose reduction in 46% of patients (68/148) and temporary dose interruption in 59% of patients (88/148)
- TRAEs led to permanent discontinuation of adagrasib only in 6% of patients (9/148) and pembrolizumab only in 11% of patients (16/148); 4% of patients (6/148) discontinued both drugs due to TRAEs

KRYSTAL-7

Safety: Liver Treatment Related Adverse Events

Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)

Most Frequent TRAEs, %	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Hepatitis	4	0	2	2	0
Hepatotoxicitya	1	0	1	1	0
Liver injury	1	0	1	0	0
Drug-induced liver injury	1	1	0	0	0
Hepatic failure	1	0	0	1	0
Acute hepatitis	1	0	1	0	0
Immune-mediated hepatitis	1	0	0	1	0

- No patient discontinued both adagrasib and pembrolizumab due to ALT/AST increase or hepatic TRAEs
- The median time to first resolution of increased ALT/AST was 22 days; resolution occurred in ~80% of cases

a Listed as preferred term.
b One patient discontinued adagrasib due to ALT increase and three discontinued pembrolizumab due to ALT/AST increase.
c Resolution rate at data cut-off; five patients remain on adagrasib treatment and ALT/AST increase may resolve with longer follow-up.
d Median time to any grade treatment-related increased ALT/AST onset was 40 and 42 days, respectively.
e Adagrasib was interrupted and resumed at a lower dose following resolution of grade ≥3 ALT/AST increase in 17/18 patients; pembrolizumab was interrupted and resumed at approved dosing following resolution of grade ≥3 ALT/AST increase. Five patients discontinued both drugs due to reasons other than ALT/AST increase and 18 resumed therapy

Data as of 19 June 2023. Median follow-up 8.7 months

SUMMARY

KRYSTAL-7

- Adagrasib in combination with pembrolizumab resulted in encouraging efficacy in patients with *KRAS* G12C-mutated NSCLC and PD-L1 ≥50%
  - In patients with PD-L1 ≥50%:
    - Objective Response Rate was 63% (32/51; 95% CI, 48–76)
    - Disease Control Rate was 84% (43/51; 95% CI, 71–93)
    - Median time to response was 1.4 months
    - Median duration of response was not reached (95% CI, 12.6–NE)
    - Median progression-free survival was not reached (95% CI, 8.2-NE) at the median follow-up of 10.1 months.
- Safety profile was as expected for both agents and manageable

The Phase 3 portion of the study compares the efficacy of adagrasib in combination with pembrolizumab versus pembrolizumab in patients with unresectable, locally advanced or metastatic nonsquamous NSCLC with KRAS G12C mutation and PD-L1 TPS >=50% and who are candidates for first line treatment

ESMO 2023. Abstr LBA65.

KRYSTAL-7

Adagrasib in combination with pembrolizumab may be a potential future treatment option for patients with KRAS G12C-mutated advanced NSCLC, especially those with high PD-L1 expression

Identification of eligible patients is critical at the time of diagnosis

More to come…

Key Studies

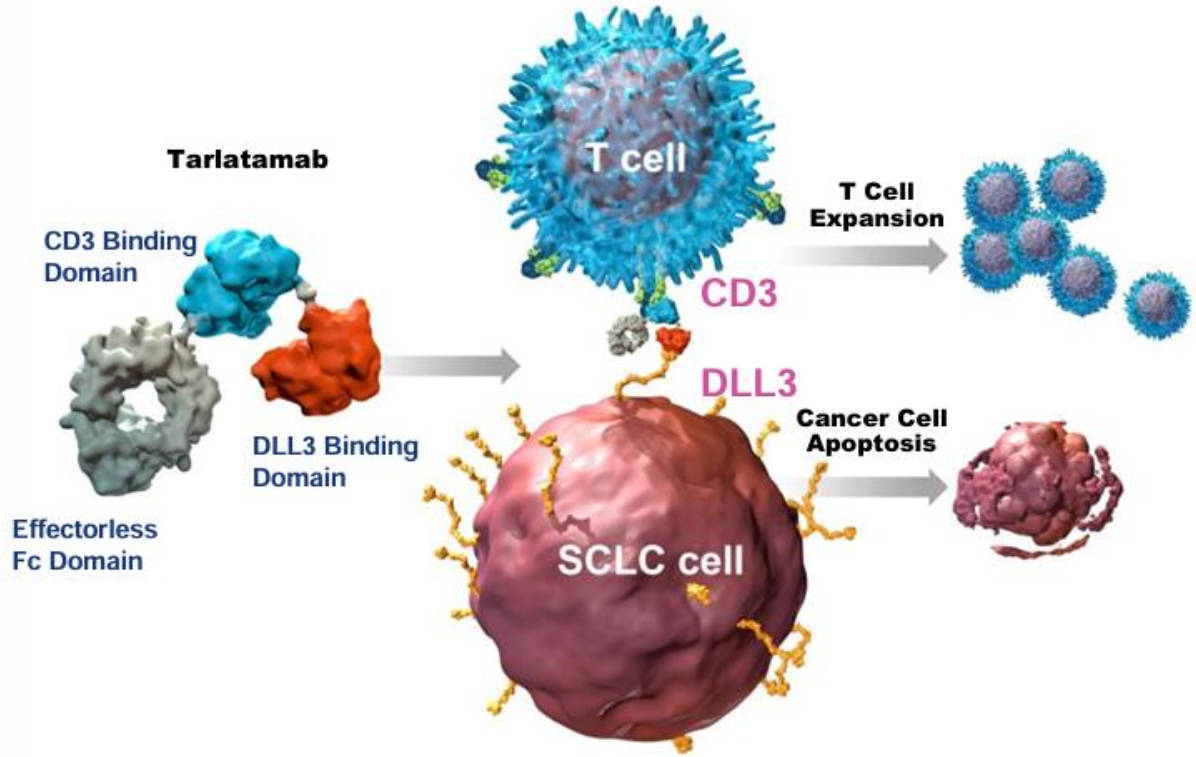
Perioperative NSCLC	EGFR Mutated Metastatic NSCLC	Metastatic and Actionable Mutated NSCLC and SCLC
• KEYNOTE-671 • AEGEAN • NEOTORCH	• FLAURA2 • PAPILLION • HERTHENA-Lung01 • KEYNOTE 789	• Key Updates • DESTINY-Lung02 • LIBRETTO-431 • KRYSTAL-7 • DeLLphi-301

DeLLphi-301

Does tarlatamab benefit patients with previously treated advanced SCLC?

December 13, 2023: The FDA accepted and granted Priority Review for the Company's Biologics License Application (BLA) for tarlatamab. Tarlatamab is a potential first-in-class, investigational delta-like ligand 3 (DLL3) targeting Bispecific T-cell Engager (BiTE®) therapy for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

Tarlatamab is a BiTE® (bispecific T-cell engager) immunotherapy that binds to both delta-like ligand 3 (DLL3) on SCLC cells and CD3 on T cells, leading to T cell-mediated cancer cell lysis



Tarlatamab activates T cells without relying on MHC-I

ESMO 2023 LBA92

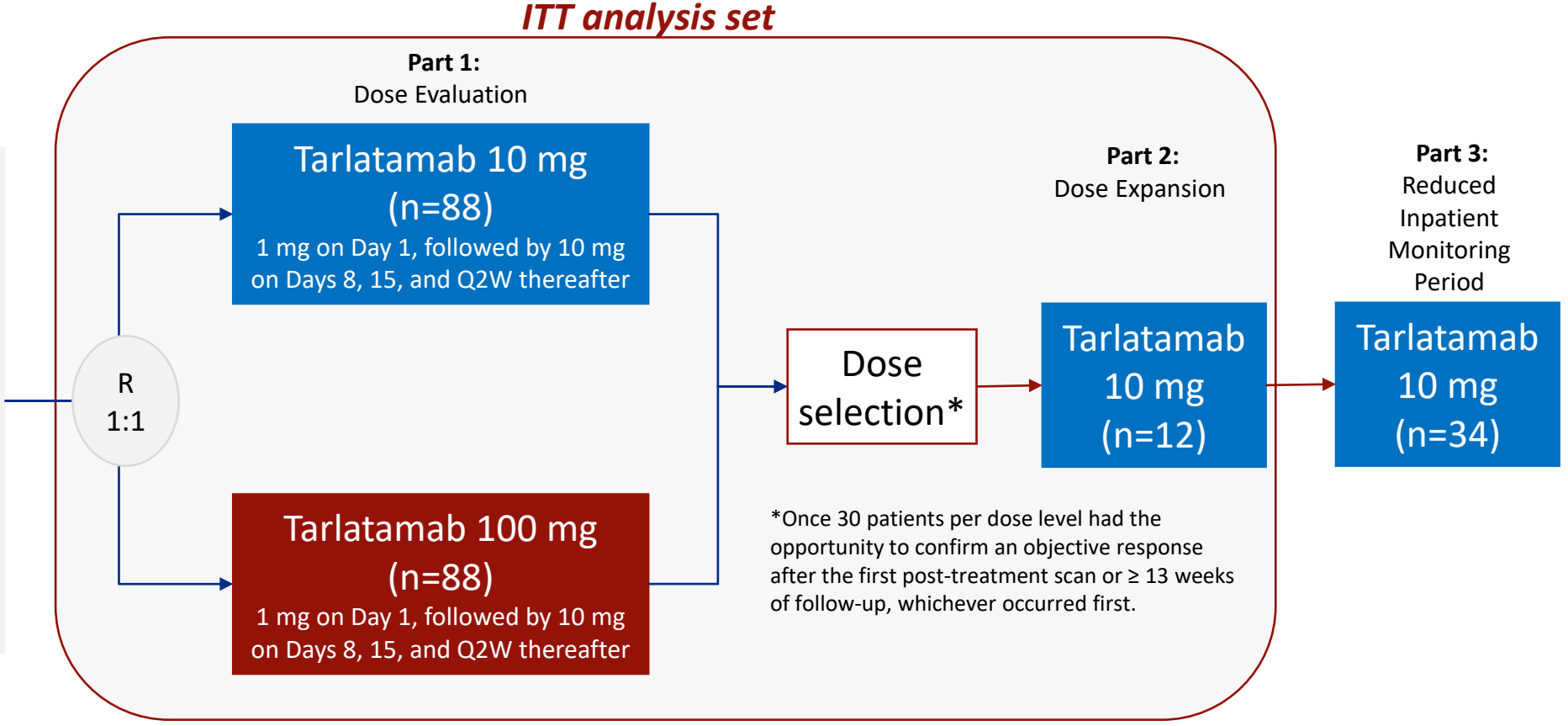
Ahn MJ, et al. N Engl J Med. 2023;389:2063-2075.

KEY DATA

DeLLphi-301

Study Design: open-label phase 2 study

- ES-SCLC
- Previous treatment with ≥ 2 lines (including platinum-doublet)
- ECOG PS 0–1
- Measurable disease Treated and stable brain metastases allowed



Primary Endpoint: ORR per RECIST v1.1 by BICR, TEAEs, tarlatamab serum concentrations
Secondary Endpoints: DOR, DCR, PFS per RECIST v1.1 by BICR, OS

Data cutoff, June 27, 2023.
Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg.

ESMO 2023 LBA92
Ahn MJ, et al. N Engl J Med. 2023;389:2063-2075.

DeLLphi-301

Baseline Characteristics

	Part 1 + 2 Tarlatamab 10 mg (n = 100)	Part 1 Tarlatamab 100 mg (n = 88)	Part 3 Tarlatamab 10 mg (n = 34)
Median age, years (range)	64 (35–82)	62 (34–80)	66 (49–80)
Male, %	72	70	71
Asian / Black or African American / White,* %	41 / 0 / 58	41 / 0 / 58	6 / 3 / 91
Ever smoker / non-smoker, %	92 / 8	94 / 6	97 / 3
ECOG performance status: 0 / 1, %	26 / 74	27 / 73	29 / 71
Prior lines of therapy, median (range)	2 (1–6)	2 (1–8)	2 (2–6)
2 prior lines of therapy, %	65	55	65
≥ 3 prior lines of therapy, %	33	43	35
Prior anti-PD-(L)1 treatment, %	73	70	82
< 90 days to progression after first-line platinum therapy,† %	28	20	21
Brain / liver metastases, %	23 / 39	36 / 34	12 / 35
DLL3 expression (> 0%), n/N evaluable (%)	80/83 (96)	71/74 (96)	N/A‡

*No patients of American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander race were enrolled.
†Platinum sensitivity was calculated as end of first-line platinum therapy to date of first progression.
‡DLL3 sample analysis from Part 3 in progress.
DLL3, delta-like ligand 3; ECOG, Eastern Cooperative Oncology Group; N/A, not available; PD-(L)1, programmed death 1 / ligand 1.

ESMO 2023 LBA92
Ahn MJ, et al. N Engl J Med. 2023;389:2063-2075.

KEY DATA

DeLLphi-301

Tarlatamab Anti-Tumor Activity

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Objective response rate, n (%) (97.5% CI)	40 (40) (29, 52)	28 (32) (21, 44)
Complete response	1 (1)	7 (8)
Partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable / no post-baseline scan*	10 (10)	20 (23)
Observed duration of response ≥ 6 months, n/N (%)	23/40 (58)	17/28 (61)
Disease control rate, n (%) (95% CI)	70 (70) (60, 79)	55 (63) (52, 73)

ESMO 2023 LBA92

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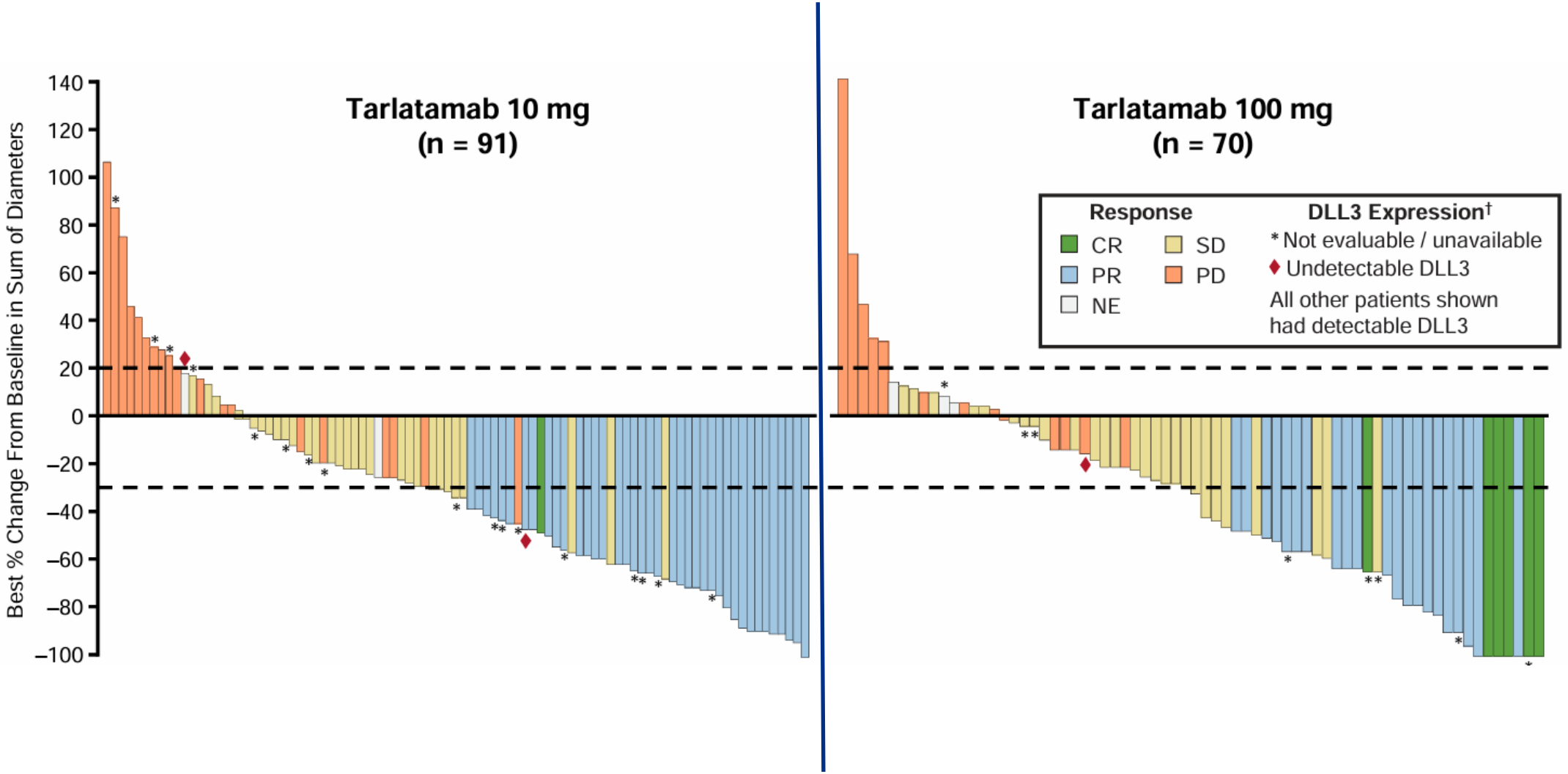
KEY DATA

DeLLphi-301

Tarlatamab Anti-Tumor Activity



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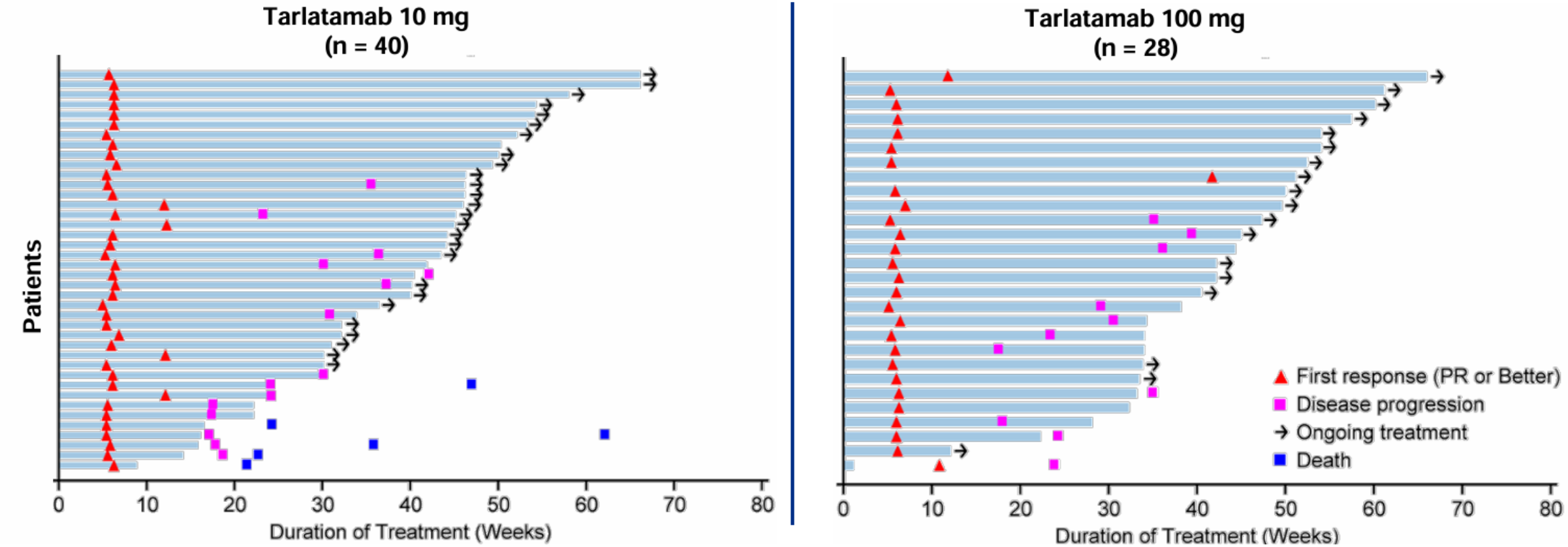
Ahn MJ, et al. N Engl J Med. 2023;389:2063-2075.

KEY DATA

DeLLphi-301

Duration of Response and Treatment



- Median time to objective response (TTR) was 1.4 months (range, 1.1–9.6 months), and median DOR was not reached
- Of the 68 responders, the DOR was ≥ 6 months in 40 patients (59%); Median follow-up time for DOR, 9.5 months (95% CI; 8.3, 9.7 months).
- 56% of the responses were ongoing at data cutoff

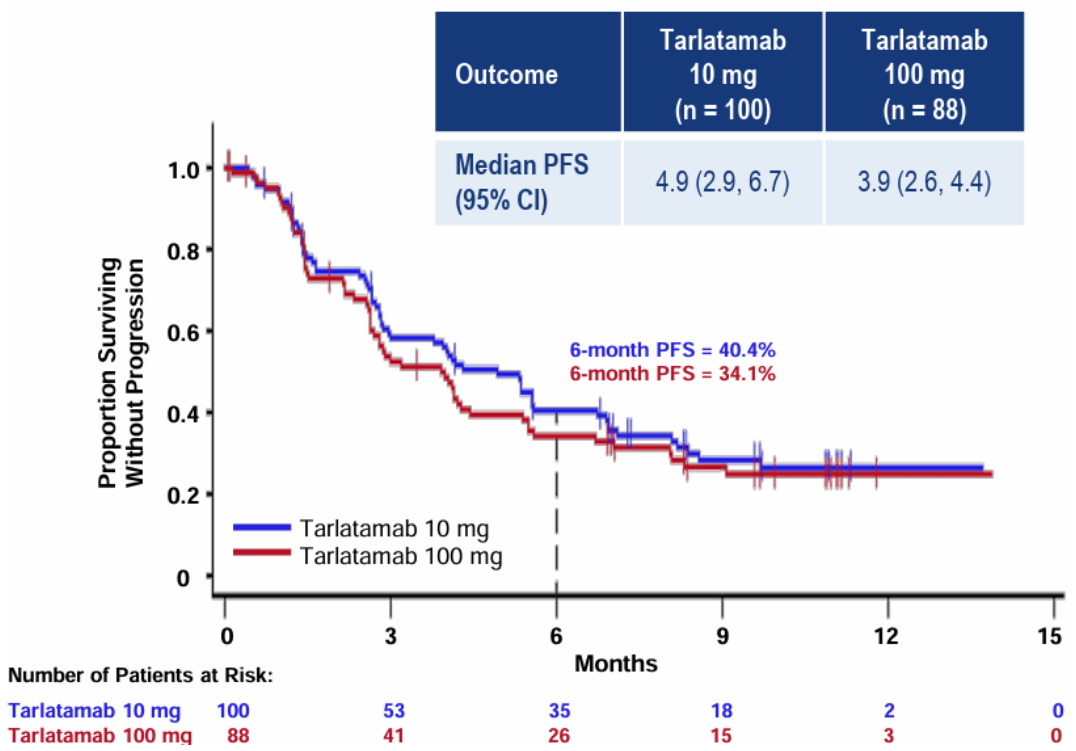
ESMO 2023 LBA92
Ahn MJ, et al. N Engl J Med. 2023;389:2063-2075.

KEY DATA

DeLLphi-301

Progression-Free Survival

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median PFS (95% CI)	4.9 (2.9, 6.7)	3.9 (2.6, 4.4)

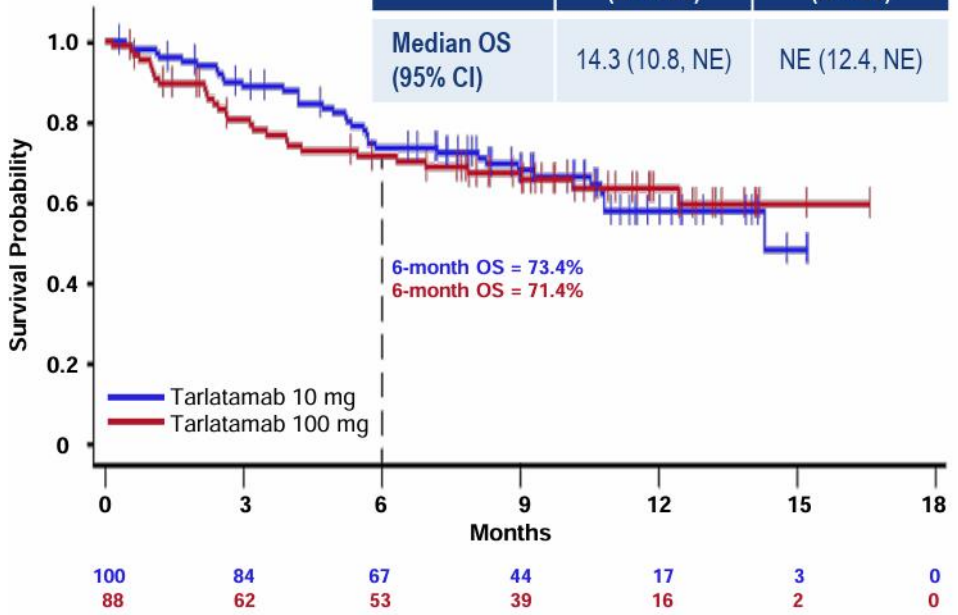


Number of Patients at Risk:

Tarlatamab 10 mg	100	53	35	18	2	0
Tarlatamab 100 mg	88	41	26	15	3	0

Overall Survival

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median OS (95% CI)	14.3 (10.8, NE)	NE (12.4, NE)



	100	84	67	44	17	3	0
	88	62	53	39	16	2	0

OS data is not yet mature; at the last follow-up, 57% of patients in the tarlatamab 10 mg group and 51% of patients in the tarlatamab 100 mg group were still alive

ESMO 2023 LBA92

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

KEY DATA

DeLLphi-301

Safety

TEAEs, n (%)	Part 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 100 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
Any grade	96 (97)	87 (100)	34 (100)
≥ Grade 3	57 (58)	56 (64)	22 (65)
Related to tarlatamab, any grade	89 (90)	81 (93)	29 (85)
≥ Grade 3	29 (29)	29 (33)	5 (15)
Fatal	0	0	1 (3)†
Leading to dose interruption/reduction	14 (14)	25 (29)	3 (9)
Leading to discontinuation	4 (4)	3 (3)	0

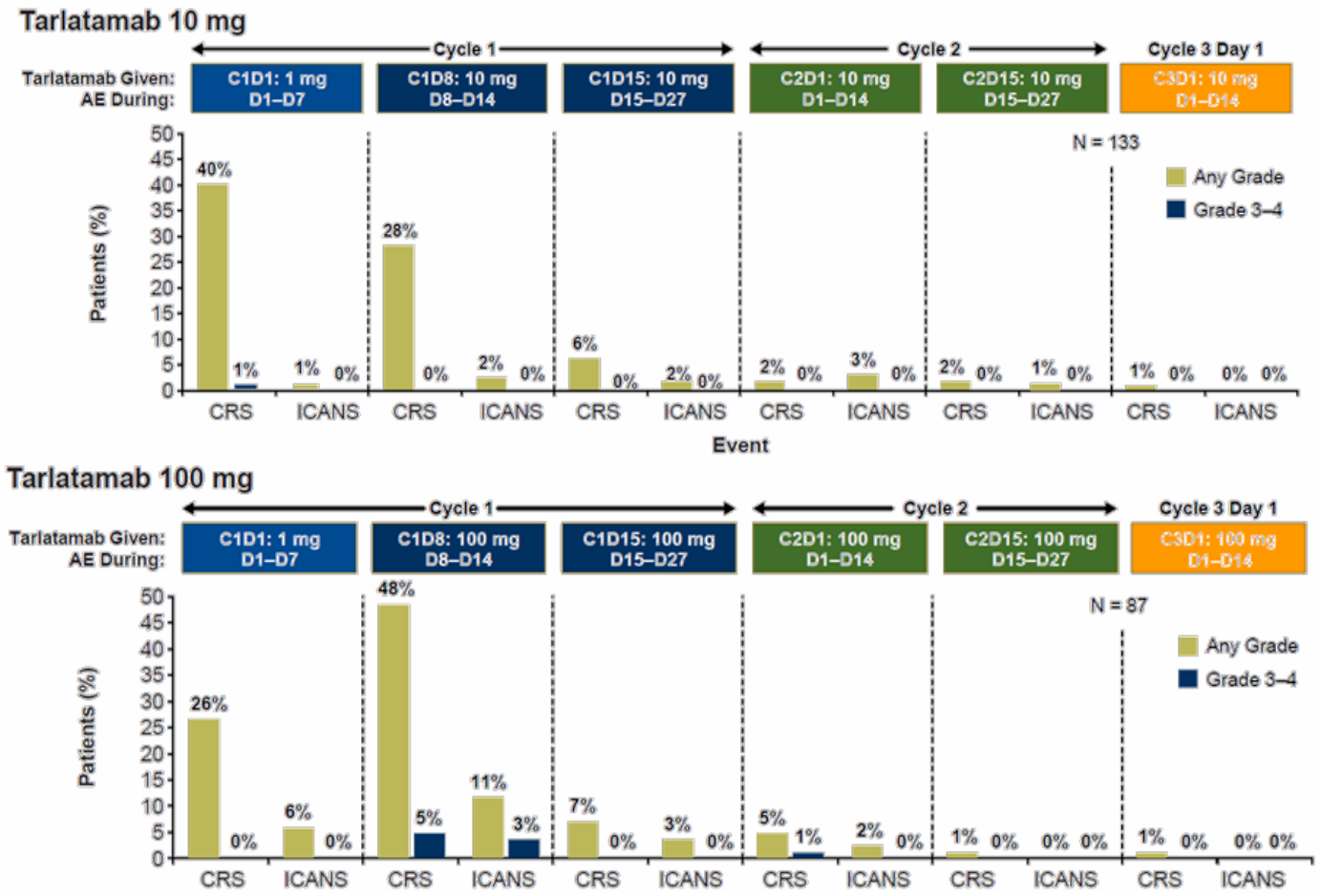
Most Common TEAEs in ≥ 20% of Patients, n (%)	Part 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 100 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
CRS	49 (49)	53 (61)	19 (56)
Grade 1–2	49 (49)	48 (55)	18 (53)
≥ Grade 3	0	5 (6)	1 (3)
Decreased appetite	25 (25)	38 (44)	13 (38)
Pyrexia	38 (38)	29 (33)	8 (24)
Constipation	28 (28)	22 (25)	8 (24)
Anemia	26 (26)	22 (25)	9 (26)
Asthenia	20 (20)	21 (24)	10 (29)
Dysgeusia	24 (24)	12 (14)	14 (41)
Fatigue	21 (21)	17 (20)	9 (26)

ESMO 2023 LBA92

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

DeLLphi-301

Safety: CRS and ICANS



- CRS was largely confined to the first or second dose (C1D1 or C1D8), primarily grade 1–2
- ICANS* occurred infrequently overall and was predominantly observed with tarlatamab 100 mg

CRS interventions:

Patients receiving tarlatamab, n (%)	10 mg (n = 133)	100 mg (n = 87)
Tocilizumab	7 (5)	9 (10)
Supplemental oxygen	11 (8)	8 (9)
Vasopressor support	1 (1)	1 (1)

ESMO 2023 LBA92
Ahn MJ, et al. N Engl J Med. 2023;389:2063-2075.

SUMMARY

DeLLphi-301

- Tarlatamab at 10 mg administered every 2 weeks improved outcomes for patients with previously treated SCLC
  - Objective response: **40%** (97.5% CI; 29 - 52) in the **10 mg** group
  - Objective response: **32%** (97.5% CI; 21 - 44) in the **100 mg** group
- Among patients with an objective response:
  - Duration of response was at least 6 months in 59% (40 of 68 patients)
- Median progression-free survival: 4.9 months (95% CI, 2.9 - 6.7) in the 10-mg group

  3.9 months (95% CI, 2.6 to 4.4) in the 100-mg group
- The most common adverse events were cytokine-release syndrome (during cycle 1, mostly Grade 1 or 2), decreased appetite, and pyrexia

The ongoing phase 3 DeLLphi-304 study will compare the efficacy and safety of tarlatamab (10 mg Q2W) with standard-of-care chemotherapy

ESMO 2023 LBA92
Ahn MJ, et al. N Engl J Med. 2023;389:2063-2075.

DeLLphi-301

Tarlatamab benefits patients with previously treated SCLC

The Prescription Drug User Fee Action (PDUFA) date for tarlatamab is June 12, 2024