NSCLC TARGETED THERAPIES

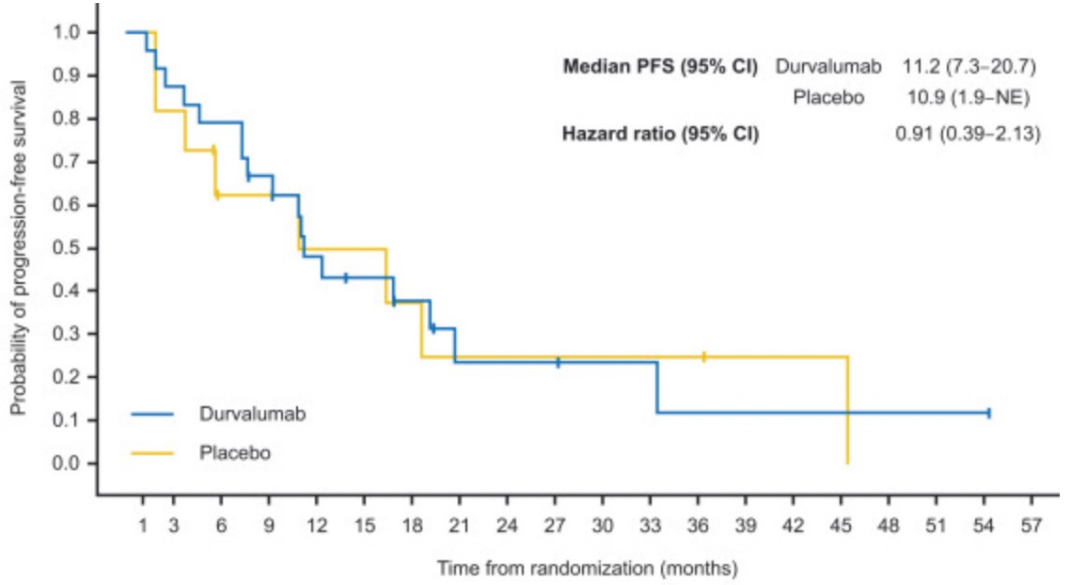
ASCO 2024 UPDATES

JASON PORTER, MD

WEST CANCER CENTER

OUTLINE

- EGFR:
  - LAURA (OSIMERTINIB POST CHEMO-XRT)
  - HARMONI-A (IVONESCIMAB + CHEMO POST EGFR-TKI)
- ALK:
  - CROWN (LORLATIINIB VS CRIZOTINIB)
- KRAS G12C:
  - KRYSTAL 12 (ADAGRASIB VS DOCETAXEL IN PRETREATED ADVANVED/METASTATIC NSCLC)



PACIFIC TRIAL: EGFR-M POST-HOC PFS

- TREATMENT OF STAGE III EGFR-MUTATED NSCLC PATIENTS WITH CONSOLIDATIVE DURVALUMAB DOES NOT SHOW CLEAR BENEFIT
- THIS IS AN AREA OF UNMET NEED, CALLING FOR EFFECTIVE APPROACHES IN THIS DISEASE STATE

https://www.sciencedirect.com/science/article/pii/S1556086423001375

LAURA TRIAL DESIGN

Patients with locally advanced, unresectable stage III EGFRm non-small cell lung cancer with no progression during/following definitive concurrent chemo radiation therapy

Key inclusion criteria:

- Age ≥ 18 years (Japan ≥ 20 years)
- WHO PS 0/1
- Confirmed locally advanced Stage III NSCLC
- Ex 19 Del / L858R
- Maximum interval between last dose CRT and randomization: 6 weeks

Osimertinib 80 mg, once daily

Randomization
2:1
(N=216)
Statification by:
Concurrent vs sequential CRT
Stage IIIA vs Stage IIIB/IIIC
China vs non-China

Placebo, Once daily

Treatment duration until BICR-assessed progression (per RECIST v 1.1), toxicity or other discontinuation criteria

Open-label Osimertinib after BICR-confirmed progression offered in both treatment arms

Tumor assessments:

Chest CT / MRI and brain MRI

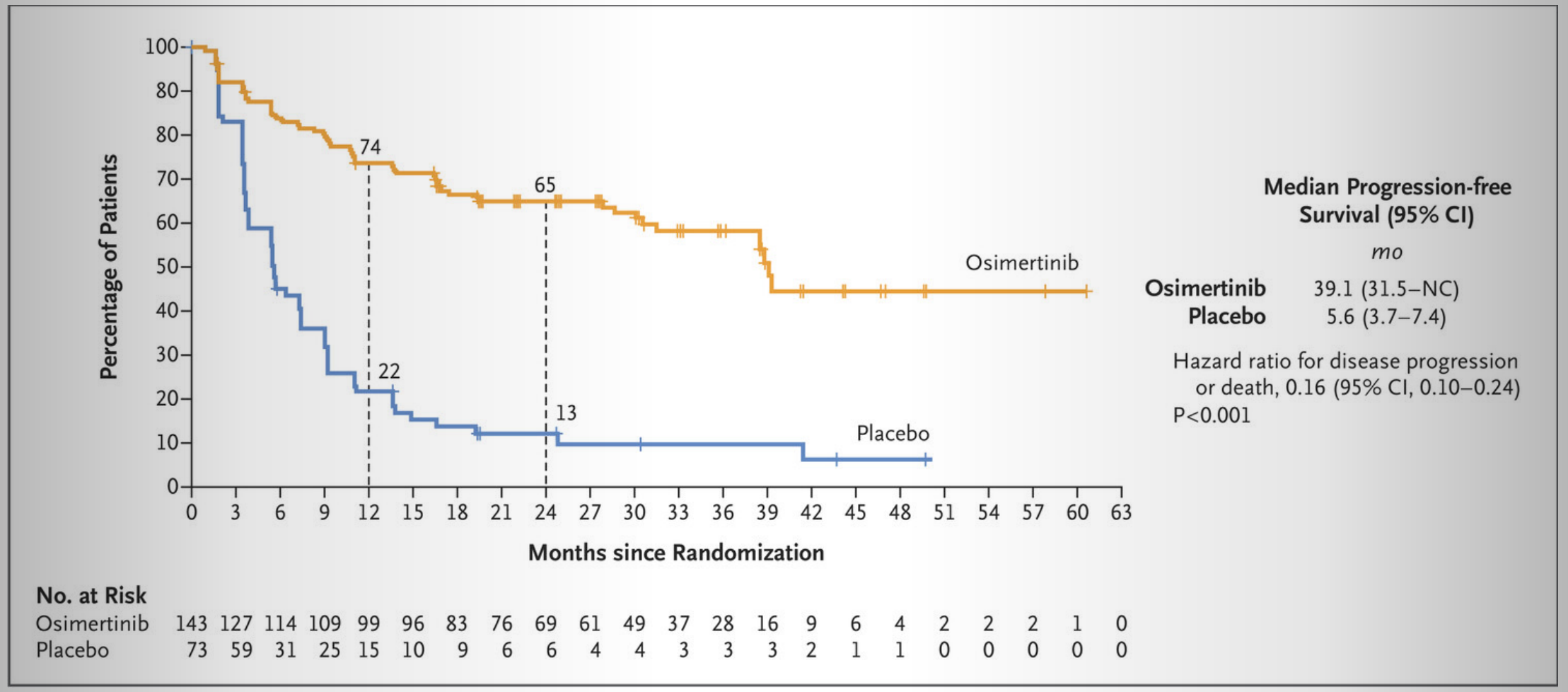
At baseline, every 8 weeks to week 48, and then every 12 weeks until BICR-assessed progression

Endpoints

- **Primary Endpoint: PFS by BICR per RECIST v 1.1 (sensitivity analysis: PFR by investigator**
- **Secondary Endpoints: OS, CNS PFS, Safety**

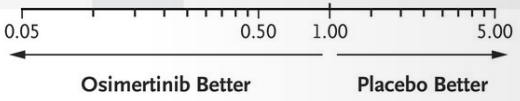
Characteristic	Osimertinib (N=143)	Placebo (N=73)
Sex — no. (%)		
Male	53 (37)	31 (42)
Female	90 (63)	42 (58)
Age — yr		
Median	62	64
Range	36 to 84	37 to 83
Smoking status — no. (%)		
Current	4 (3)	1 (1)
Former	37 (26)	23 (32)
Never	102 (71)	49 (67)
Race — no. (%)†		
Asian	116 (81)	62 (85)
Non-Asian	27 (19)	11 (15)
WHO performance-status score — no. (%)‡		
0	80 (56)	31 (42)
1	63 (44)	42 (58)
AJCC–UICC disease stage — no. (%)§		
IIIA	52 (36)	24 (33)
IIIB	67 (47)	38 (52)
IIIC	24 (17)	11 (15)
Histologic type — no. (%)		
Adenocarcinoma	139 (97)	69 (95)
Squamous-cell carcinoma	3 (2)	2 (3)
Other¶	1 (1)	2 (3)
EGFR mutation type at screening — no. (%)‖		
Exon 19 deletion	74 (52)	43 (59)
L858R mutation	68 (48)	30 (41)
Type of chemoradiotherapy — no. (%)**		
Concurrent	131 (92)	62 (85)
Sequential	12 (8)	11 (15)
Best overall response to chemoradiotherapy — no. (%)††		
Complete response	4 (3)	3 (4)
Partial response	67 (47)	27 (37)
Stable disease	61 (43)	37 (51)
Not evaluable‡‡	11 (8)	6 (8)
Target-lesion size — mm§§	33±18	36±17

https://www.nejm.org/doi/full/10.1056/NEJMoa2402614?logout=true#t1



https://www.nejm.org/doi/full/10.1056/NEJMoa2402614

Subgroup	Osimertinib	Placebo	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
Overall			
Stratified log-rank analysis	57/143	63/73	0.16 (0.10–0.24)
Unadjusted Cox proportional-hazards analysis	57/143	63/73	0.23 (0.16–0.33)
Sex			
Male	23/53	27/31	0.26 (0.15–0.46)
Female	34/90	36/42	0.21 (0.13–0.34)
Age			
<65 yr	31/81	36/39	0.16 (0.10–0.26)
≥65 yr	26/62	27/34	0.33 (0.19–0.57)
Smoking history			
Current or former	20/41	22/24	0.26 (0.14–0.48)
Never	37/102	41/49	0.22 (0.14–0.34)
Race or national group			
Chinese	7/27	11/13	NC (NC–NC)
Non-Chinese	50/116	52/60	0.26 (0.17–0.39)
Asian	43/116	55/62	0.20 (0.13–0.29)
Non-Asian	14/27	8/11	0.48 (0.20–1.19)
Stage			
IIIA	22/52	20/24	0.28 (0.15–0.52)
IIIB or IIIC	35/91	43/49	0.21 (0.13–0.33)
EGFR mutation			
Exon 19 deletion	26/74	39/43	0.17 (0.10–0.29)
L858R mutation	31/68	24/30	0.32 (0.19–0.56)
Chemoradiotherapy			
Concurrent	53/131	54/62	0.25 (0.17–0.36)
Sequential	4/12	9/11	NC (NC–NC)
Response to previous CRT			
Complete response	1/4	2/3	NC (NC–NC)
Partial response	28/67	25/27	0.20 (0.11–0.34)
Stable disease	24/61	34/37	0.18 (0.10–0.30)
Not evaluable	4/11	2/6	NC (NC–NC)



https://www.nejm.org/doi/full/10.1056/NEJMoa2402614?logout=true#t1

ADVERSE EVENTS OF INTEREST

- THE MOST COMMON AE IN BOTH ARMS WAS RADIATION PNEUMONITIS
- INTERSTITIAL LUNG DISEASE REPORTED IN 8% OF PATIENTS IN THE OSIMERTINIB ARM
- MOST ILD CASES WERE GRADE ½ (GRADE 5 = 1)

Table 3. Most Common Adverse Events of Any Cause in >5% of Patients in Either Group.*

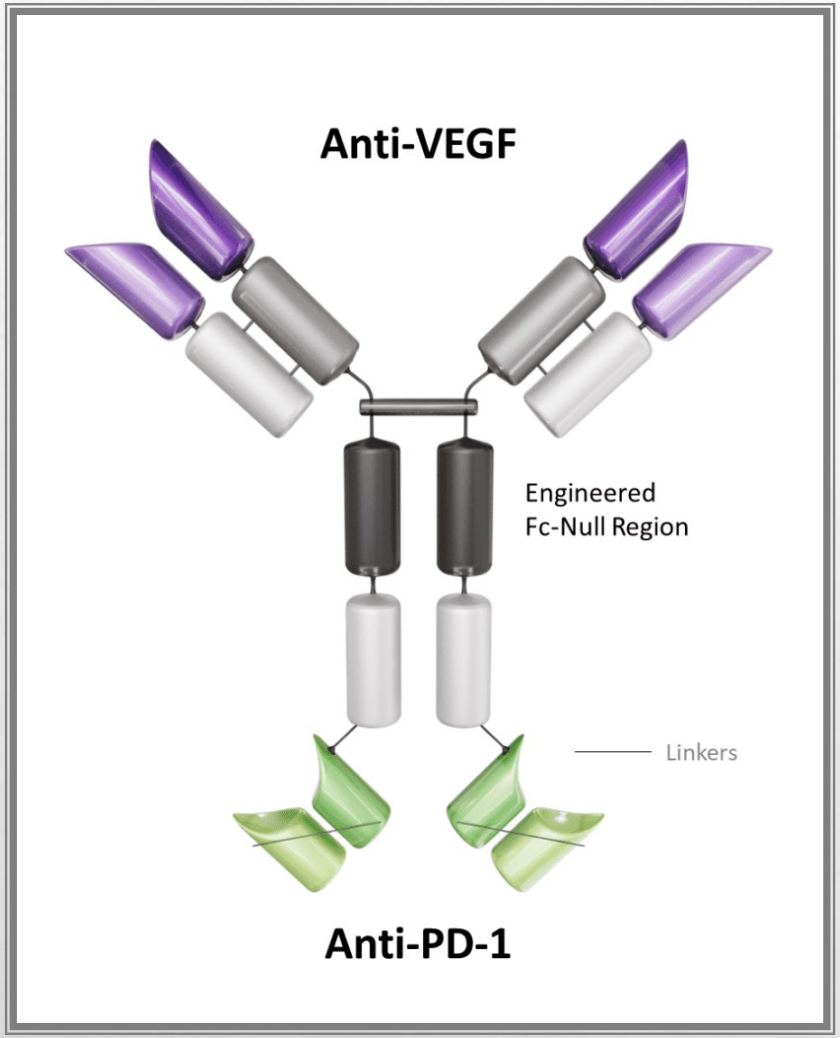
Adverse Event	Osimertinib (N=143)					Placebo (N=73)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	140 (98)	16 (11)	74 (52)	42 (29)	5 (3)	64 (88)	23 (32)	32 (44)	6 (8)	1 (1)
Radiation pneumonitis	68 (48)	21 (15)	44 (31)	3 (2)	0	28 (38)	14 (19)	14 (19)	0	0
Diarrhea	51 (36)	45 (31)	3 (2)	3 (2)	0	10 (14)	6 (8)	4 (5)	0	0
Rash	34 (24)	28 (20)	6 (4)	0	0	10 (14)	10 (14)	0	0	0
Coronavirus 2019	29 (20)	4 (3)	24 (17)	1 (1)	0	6 (8)	4 (5)	2 (3)	0	0
Paronychia	24 (17)	16 (11)	8 (6)	0	0	1 (1)	0	1 (1)	0	0
Cough	23 (16)	11 (8)	12 (8)	0	0	7 (10)	5 (7)	2 (3)	0	0
Decreased appetite	21 (15)	11 (8)	9 (6)	1 (1)	0	4 (5)	3 (4)	1 (1)	0	0
Dry skin	18 (13)	15 (10)	2 (1)	1 (1)	0	4 (5)	4 (5)	0	0	0
Pruritus	18 (13)	17 (12)	1 (1)	0	0	5 (7)	5 (7)	0	0	0
Stomatitis	17 (12)	11 (8)	6 (4)	0	0	2 (3)	2 (3)	0	0	0
Decreased white-cell count	17 (12)	6 (4)	10 (7)	1 (1)	0	2 (3)	0	2 (3)	0	0
Pneumonia	16 (11)	3 (2)	9 (6)	3 (2)	0	6 (8)	1 (1)	2 (3)	3 (4)	0
Anemia	14 (10)	6 (4)	7 (5)	1 (1)	0	3 (4)	1 (1)	2 (3)	0	0
Herpes zoster	13 (9)	3 (2)	10 (7)	0	0	2 (3)	1 (1)	1 (1)	0	0
Urinary tract infection	11 (8)	2 (1)	8 (6)	1 (1)	0	2 (3)	1 (1)	1 (1)	0	0
Increased ALT level	10 (7)	7 (5)	2 (1)	1 (1)	0	2 (3)	2 (3)	0	0	0
Arthralgia	10 (7)	5 (3)	4 (3)	1 (1)	0	6 (8)	4 (5)	2 (3)	0	0
Upper respiratory tract infection	10 (7)	3 (2)	7 (5)	0	0	1 (1)	1 (1)	0	0	0
Acneiform dermatitis	9 (6)	9 (6)	0	0	0	2 (3)	2 (3)	0	0	0
Decreased platelet count	8 (6)	7 (5)	1 (1)	0	0	0	0	0	0	0
Dyspnea	8 (6)	7 (5)	1 (1)	0	0	5 (7)	4 (5)	1 (1)	0	0
Increased AST level	8 (6)	7 (5)	1 (1)	0	0	1 (1)	1 (1)	0	0	0
Nasopharyngitis	8 (6)	2 (1)	6 (4)	0	0	0	0	0	0	0
Pneumonitis	8 (6)	2 (1)	4 (3)	1 (1)	0	1 (1)	1 (1)	0	0	0
Sinus tachycardia	8 (6)	3 (2)	5 (3)	0	0	1 (1)	1 (1)	0	0	0
Productive cough	7 (5)	3 (2)	4 (3)	0	0	4 (5)	4 (5)	0	0	0
Musculoskeletal chest pain	5 (3)	3 (2)	2 (1)	0	0	9 (12)	8 (11)	1 (1)	0	0
Myalgia	5 (3)	4 (3)	1 (1)	0	0	6 (8)	6 (8)	0	0	0
Headache	2 (1)	2 (1)	0	0	0	4 (5)	4 (5)	0	0	0

* Safety analyses included all the patients who had undergone randomization and received at least one dose of osimertinib or placebo. Data reported in the table include adverse events with an onset date on or after the date of the first trial dose and up to and including 28 days after the date of the last trial dose and on or before the start of a subsequent anticancer treatment. Patients reporting multiple events for the same preferred term were counted only once for that preferred term. Each patient could have had more than one adverse event. Grade 5 adverse events of any cause occurred in 3 patients (2%) in the osimertinib group (pneumonitis, pneumonia, and a road traffic accident in 1 patient each [1%]) and 2 patients (3%) in the placebo group (myocardial infarction and aortic aneurism rupture in 1 patient each [1%]). ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

https://www.nejm.org/doi/full/10.1056/NEJMoa2402614?logout=true#t1

LIKELY NEW STANDARD OF CARE

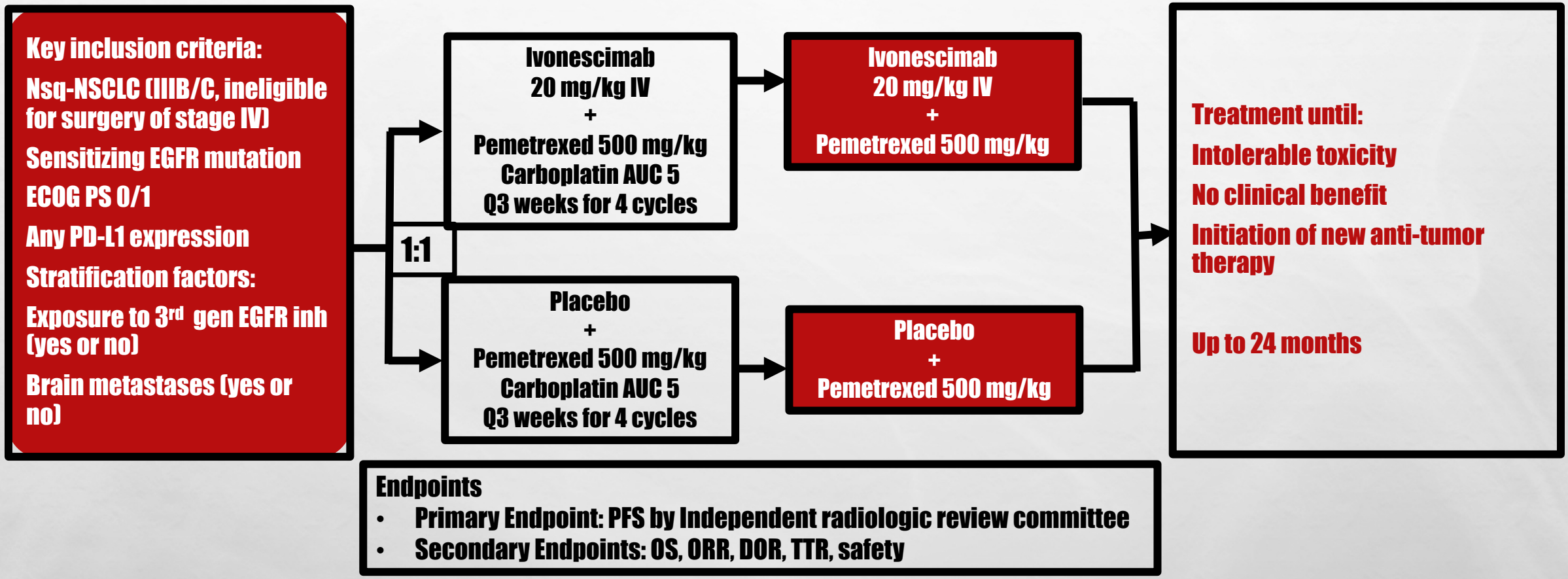
- OSIMERTINIB RESULTED IN CLINICALLY MEANINGFUL IMPROVEMENT IN PFS VS PLACEBO IN STAGE III EGFR-MUTATED NSCLC FOLLOWING DEFINITIVE CHEMORADIATION
  - 39.1 MOS (95% CI 31.5, NC) VS 5.6 MOS (95% CI 3.7, 7.4)
  - HR 0.16 (95% CI 0.10, 0.24), P < 0.001
- EVEN WITH 81% CROSSOVER, INTERIM OS DATA SHOWED A POSITIVE TREND IN FAVOR OF OSIMERTINIB
- POST-CHEMORADIOTHERAPY SAFETY PROFILE WAS AS EXPECTED AND MANAGEABLE
- MOLECULAR PROFILING FOR EGFR IS ESSENTIAL FOR STAGE III PATIENTS TO ENSURE APPROPRIATE AND OPTIMAL THERAPY
- MECHANISMS OF RESISTANCE TO HOPEFULLY GUIDE FURTHER THERAPY AND RESEARCH



IVONESCIMAB

- BI-SPECIFIC ANTIBODY TARGETING:
  - PD-1 AND VEGF
- POTENTIAL EFFICACY IN EGFR MUTATED NSCLC PROGRESSING ON TKI IN PHASE I AND II TRIALS

HARNONI-A TRIAL DESIGN

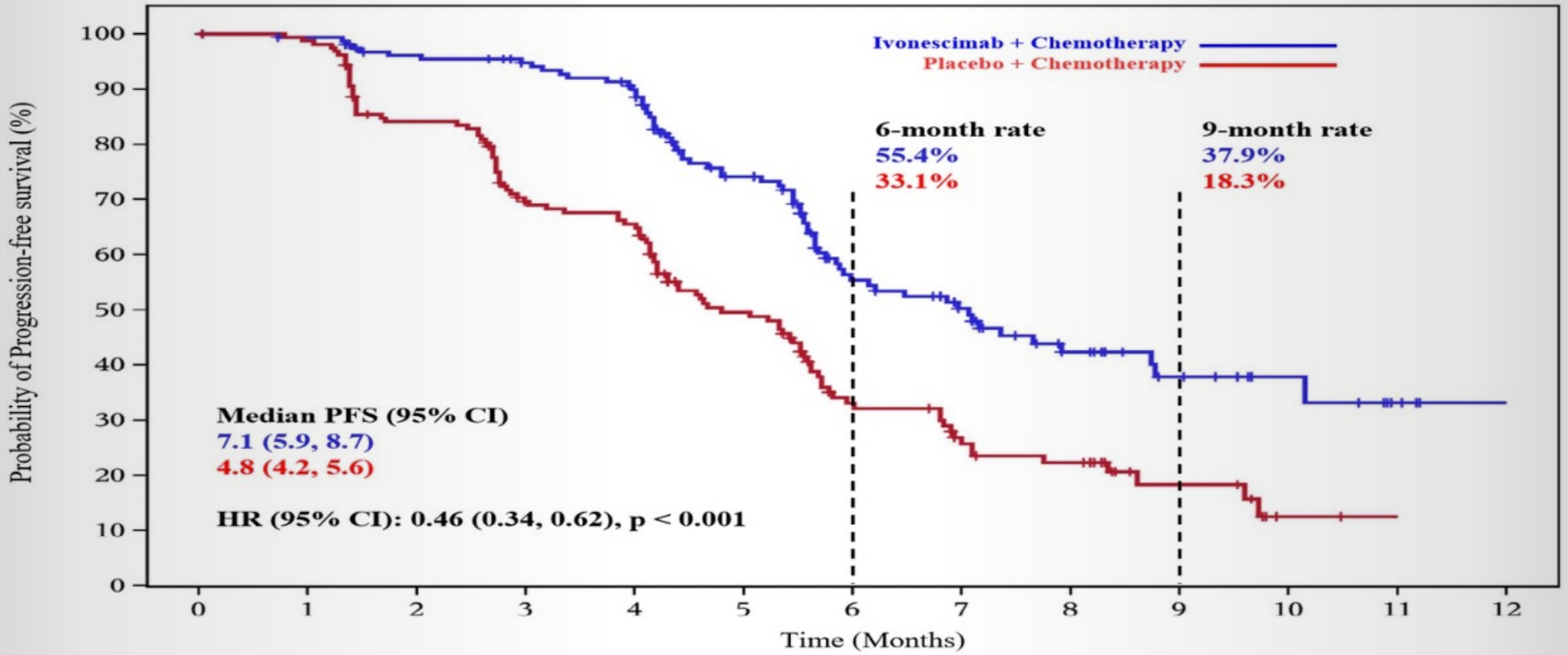


Endpoints

- **Primary Endpoint: PFS by Independent radiologic review committee**
- **Secondary Endpoints: OS, ORR, DOR, TTR, safety**

J Clin Oncol 42, 2024 (suppl 16; abstr 8508)

Study Met Primary Endpoint of PFS per IRRC



At risk (events)

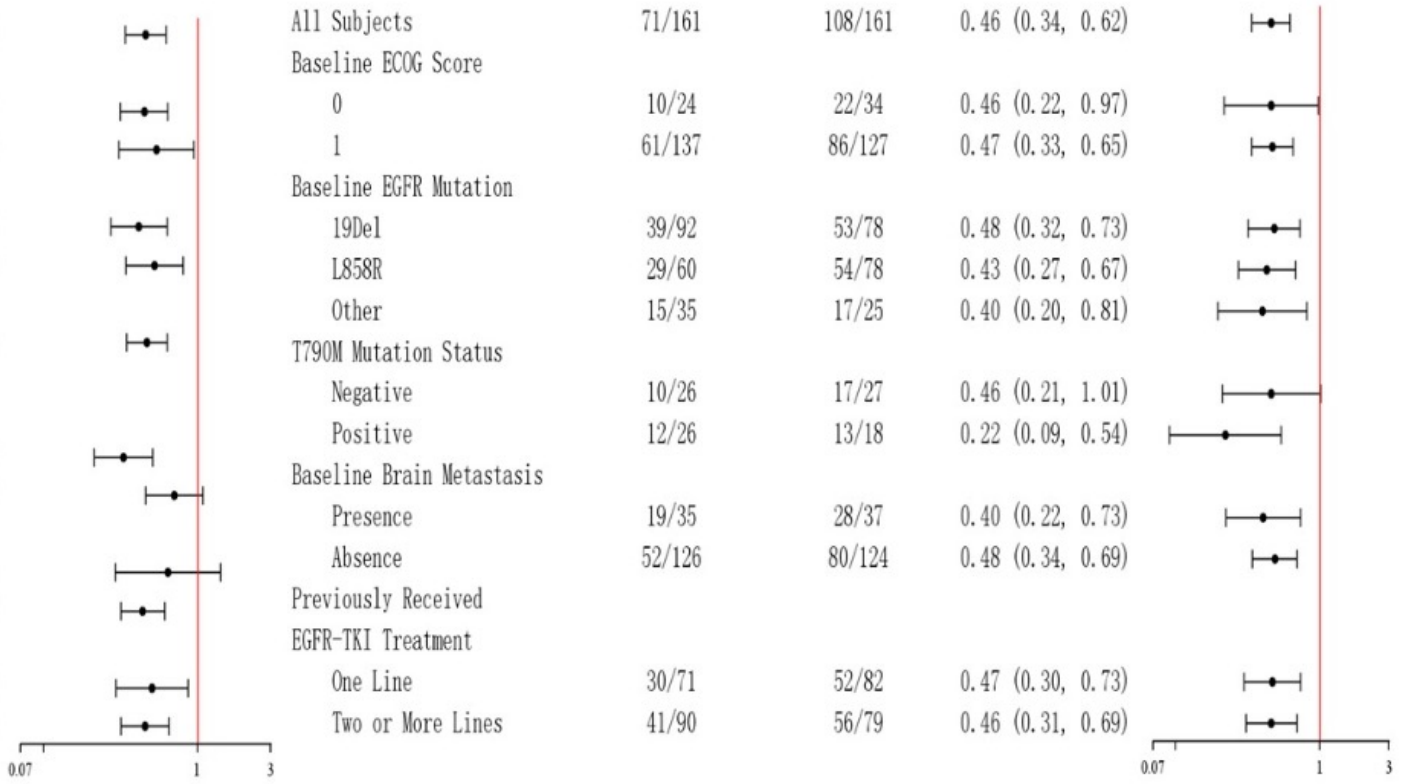
Ivonescimab + Chemo	161 (0)	155 (1)	144 (6)	138 (8)	129 (15)	92 (36)	56 (57)	44 (62)	27 (68)	16 (70)	8 (70)	3 (71)	0 (71)
Placebo + Chemo	161 (0)	157 (2)	130 (25)	102 (47)	96 (53)	63 (75)	33 (94)	23 (101)	19 (104)	8 (106)	1 (108)	0 (108)	

HR and P-value were stratified by previous 3rd Gen EGFR-TKI ues (yes vs. no) and presence of brain metastases (yes vs. no), and were calculated with stratified Cox model and log rank test. The two-sided P-value boundary is 0.024 as calculated using Lan-Demets spending function with O'Brien-Fleming approximation.
HR, hazard ratio; CI, confidence interval; IRRC, independent radiology review committee.

J Clin Oncol 42, 2024 (suppl 16; abstr 8508)

Subgroup Analysis of PFS per IRRC

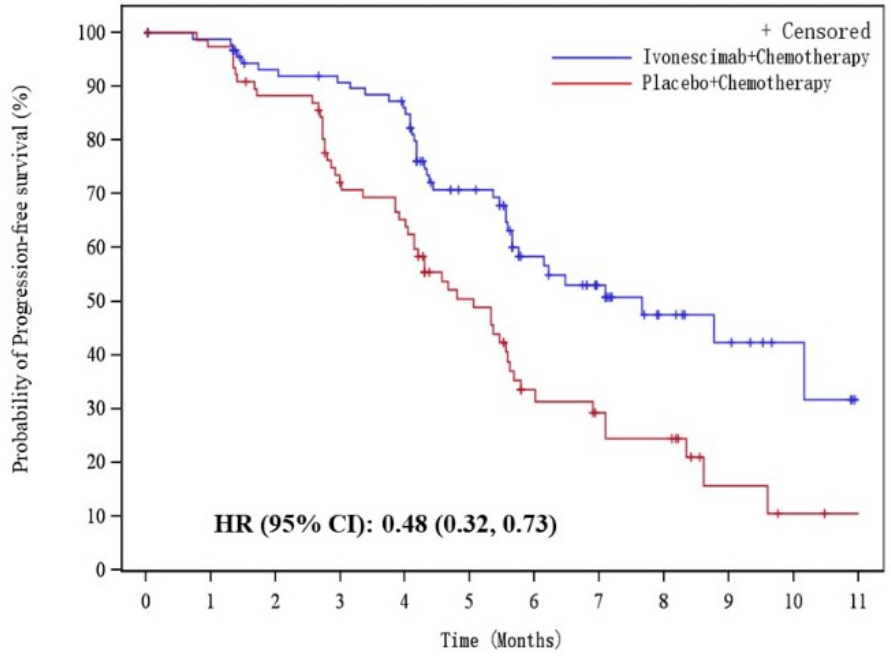
	No. of events/No. of patients		HR (95% CI)
	Ivonescimab + Chemo	Placebo + Chemo	
All Subjects	71/161	108/161	0.46 (0.34, 0.62)
Age			
<65 years	51/111	75/110	0.45 (0.31, 0.64)
>=65 years	20/50	33/51	0.54 (0.31, 0.95)
Sex			
Male	34/77	57/79	0.41 (0.27, 0.64)
Female	37/84	51/82	0.52 (0.34, 0.80)
Clinical Stage at Study Entry			
IV	69/158	105/156	0.47 (0.34, 0.63)
Number of Distant Metastasis Sites at Baseline			
<3	30/87	64/93	0.33 (0.21, 0.51)
>=3	41/74	44/68	0.70 (0.46, 1.08)
Liver Metastasis			
Presence	13/21	12/17	0.64 (0.29, 1.41)
Absence	58/140	96/144	0.44 (0.32, 0.61)
Smoking History			
Yes	23/49	31/46	0.50 (0.29, 0.87)
No	48/112	77/115	0.45 (0.32, 0.65)
All Subjects	71/161	108/161	0.46 (0.34, 0.62)
Baseline ECOG Score			
0	10/24	22/34	0.46 (0.22, 0.97)
1	61/137	86/127	0.47 (0.33, 0.65)
Baseline EGFR Mutation			
19Del	39/92	53/78	0.48 (0.32, 0.73)
L858R	29/60	54/78	0.43 (0.27, 0.67)
Other	15/35	17/25	0.40 (0.20, 0.81)
T790M Mutation Status			
Negative	10/26	17/27	0.46 (0.21, 1.01)
Positive	12/26	13/18	0.22 (0.09, 0.54)
Baseline Brain Metastasis			
Presence	19/35	28/37	0.40 (0.22, 0.73)
Absence	52/126	80/124	0.48 (0.34, 0.69)
Previously Received EGFR-TKI Treatment			
One Line	30/71	52/82	0.47 (0.30, 0.73)
Two or More Lines	41/90	56/79	0.46 (0.31, 0.69)



J Clin Oncol 42, 2024 (suppl 16; abstr 8508)

PFS of 19del and L858R

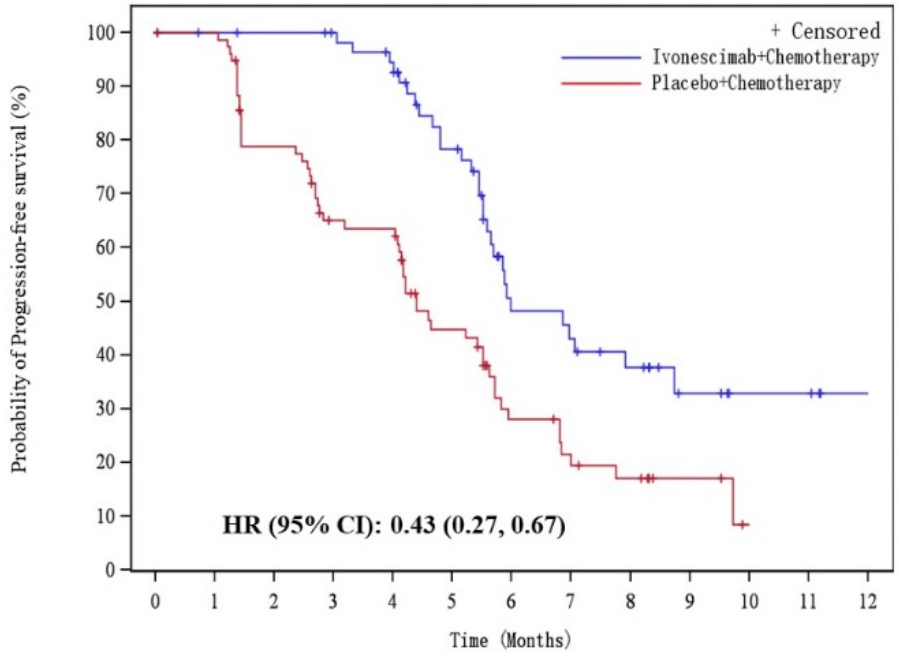
PFS Kaplan Meier Curve Evaluated by IRRC
with 19del



Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	92 (0)	89 (1)	79 (6)	76 (8)	71 (12)	50 (24)	33 (32)	23 (35)	12 (37)	8 (38)	4 (38)	0 (39)
Placebo+Chemotherapy	78 (0)	75 (2)	67 (9)	52 (21)	47 (26)	31 (36)	16 (46)	12 (48)	10 (50)	3 (52)	1 (53)	0 (53)

PFS Kaplan Meier Curve Evaluated by IRRC
with L858R



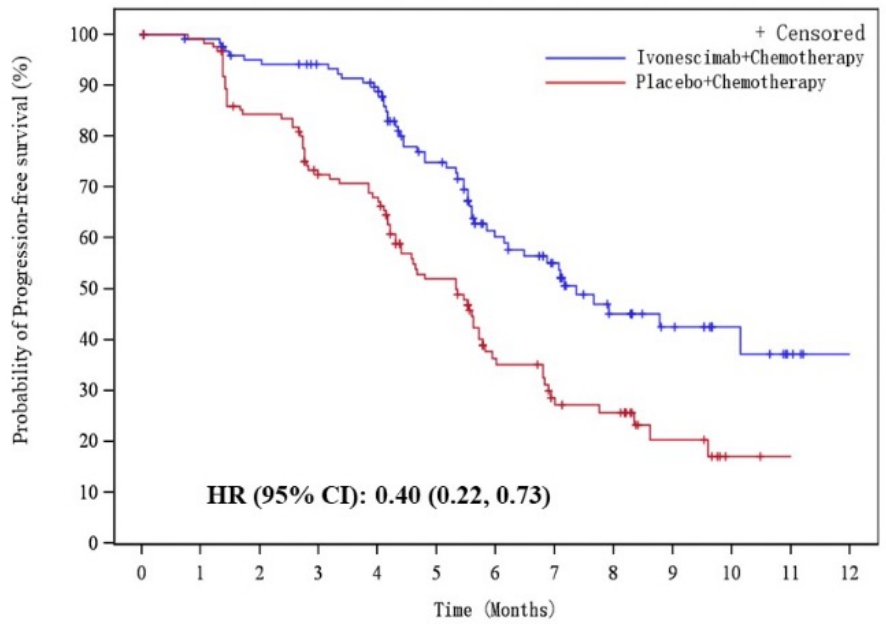
Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	60 (0)	58 (0)	57 (0)	55 (0)	51 (3)	38 (11)	19 (24)	17 (26)	13 (28)	6 (29)	3 (29)	3 (29)	0 (29)
Placebo+Chemotherapy	78 (0)	77 (0)	58 (16)	45 (26)	44 (27)	27 (39)	14 (48)	9 (52)	7 (53)	3 (53)	0 (54)		

J Clin Oncol 42, 2024 (suppl 16; abstr 8508)

PFS by Presence of Brain Metastases

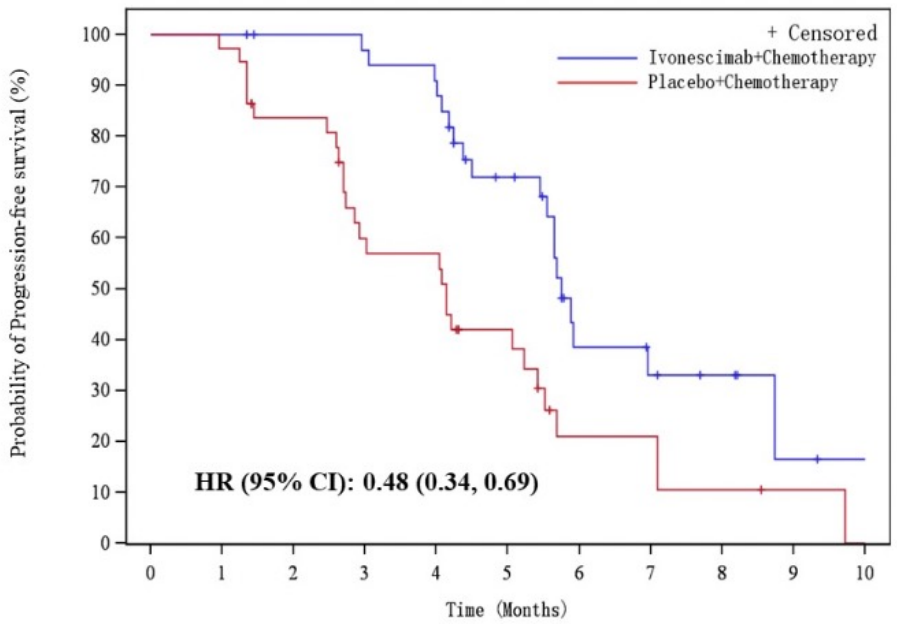
PFS Kaplan Meier Curve Evaluated by IRRC
without Brain Metastasis



Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	126 (0)	120 (1)	111 (6)	106 (7)	99 (12)	72 (27)	48 (40)	38 (44)	23 (50)	15 (51)	8 (51)	3 (52)	0 (52)
Placebo+Chemotherapy	124 (0)	121 (1)	101 (19)	82 (33)	77 (38)	52 (55)	29 (69)	19 (76)	17 (77)	7 (79)	1 (80)	0 (80)	

PFS Kaplan Meier Curve Evaluated by IRRC
with Brain Metastasis

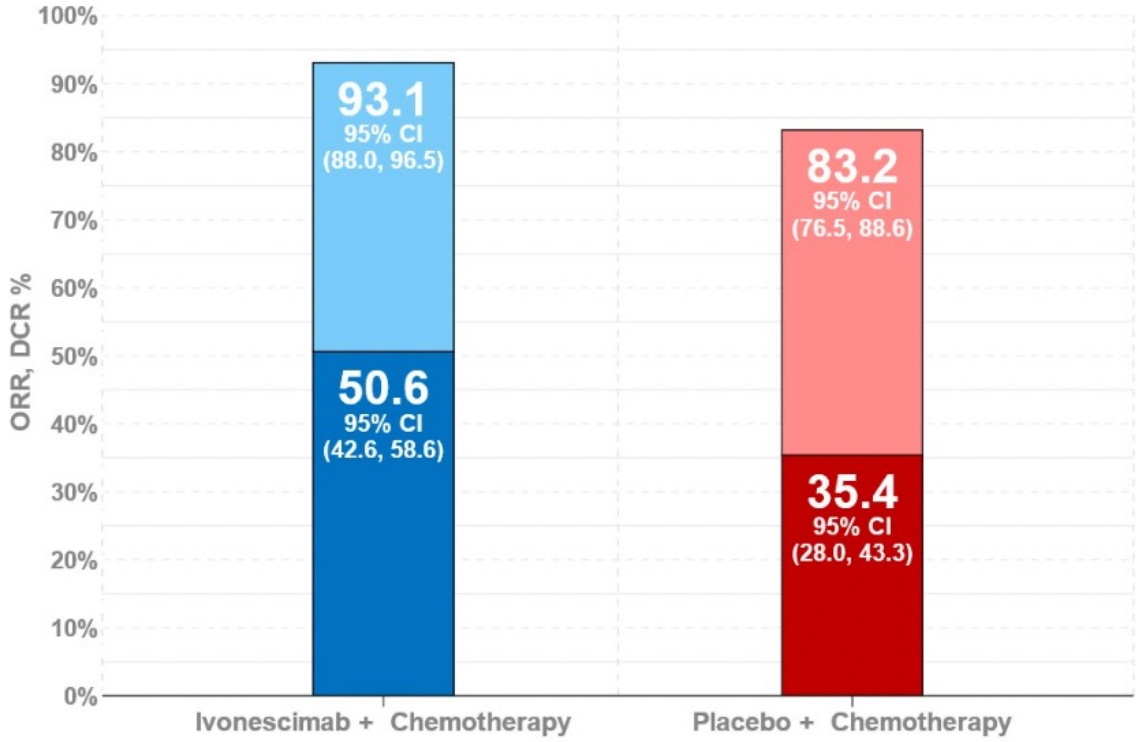


Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	35 (0)	35 (0)	33 (0)	32 (1)	30 (3)	20 (9)	8 (17)	6 (18)	4 (18)	1 (19)	0 (19)
Placebo+Chemotherapy	37 (0)	36 (1)	29 (6)	20 (14)	19 (15)	11 (20)	4 (25)	4 (25)	2 (27)	1 (27)	0 (28)

J Clin Oncol 42, 2024 (suppl 16; abstr 8508)

ORR, DCR and DoR per IRRC

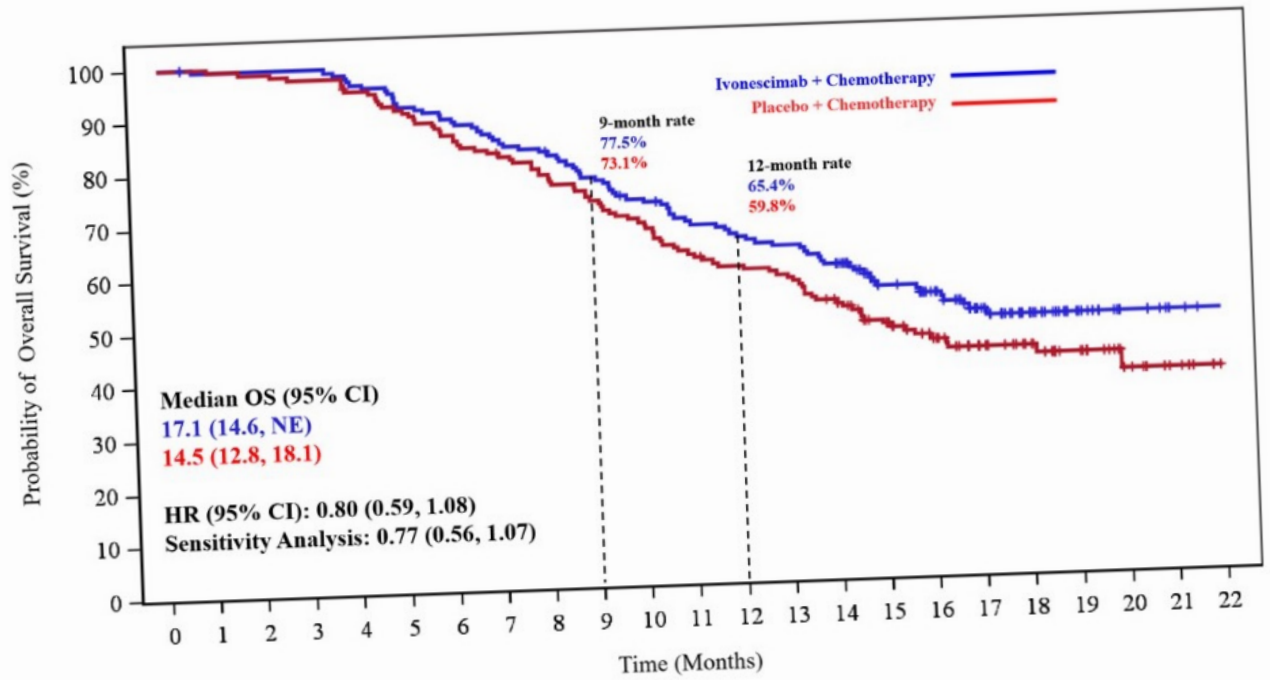


	Ivonescimab + Chemo	Placebo + Chemo
ORR, % (95% CI)	**50.6** (42.6, 58.6)	**35.4** (28.0, 43.3)
DCR, % (95% CI)	**93.1** (88.0, 96.5)	**83.2** (76.5, 88.6)
Median DoR, month (95% CI)	**6.6** (4.3, 7.6)	**4.2** (3.0, 4.7)

RD, rate difference; CI, confidence interval.
RD and CI were calculated using Miettinen-Nurminen method stratified by exposure to 3rd generation EGFR-TKI before (yes vs.no) and brain metastases (yes vs. no)

J Clin Oncol 42, 2024 (suppl 16; abstr 8508)

Overall Survival (at 52% of Data Maturity)



HR: 0.80 (0.59, 1.08) after 52% of data maturity

OS is consistent for both analysis

Data cutoff date: December 2023
(median follow-up of 17.6 months)

HR, hazard ratio; CI, confidence interval.

J Clin Oncol 42, 2024 (suppl 16; abstr 8508)

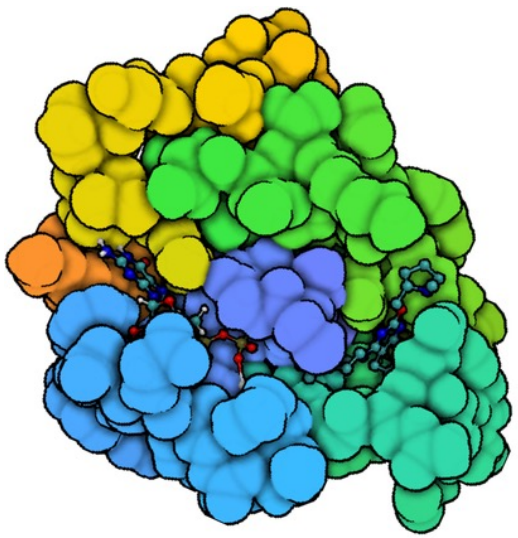
Adverse Events of Special Interest (AESI)

Categories	Ivonescimab + Chemotherapy (N=161)		Placebo + Chemotherapy (N=161)	
Preferred Term, n(%)	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
AESI	48 (29.8)	5 (3.1)	25 (15.5)	4 (2.5)
Proteinuria	28 (17.4)	1 (0.6)	13 (8.1)	0
Haemorrhage	11 (6.8)	0	8 (5.0)	0
Urinary occult blood positive	4 (2.5)	0	3 (1.9)	0
Haemoptysis	2 (1.2)	0	0	0
Epistaxis	3 (1.9)	0	1 (0.6)	0
Mouth haemorrhage	1 (0.6)	0	0	0
Gastrointestinal haemorrhage	0	0	1 (0.6)	0
Gingival bleeding	1 (0.6)	0	0	0
Eye haemorrhage	1 (0.6)	0	2 (1.2)	0
Vaginal haemorrhage	0	0	1 (0.6)	0
Occult blood positive	0	0	1 (0.6)	0
Hypertension	13 (8.1)	3 (1.9)	5 (3.1)	3 (1.9)
Arterial thromboembolism	1 (0.6)	0	1 (0.6)	1 (0.6)
Cardiac failure congestive	1 (0.6)	1 (0.6)	0	0

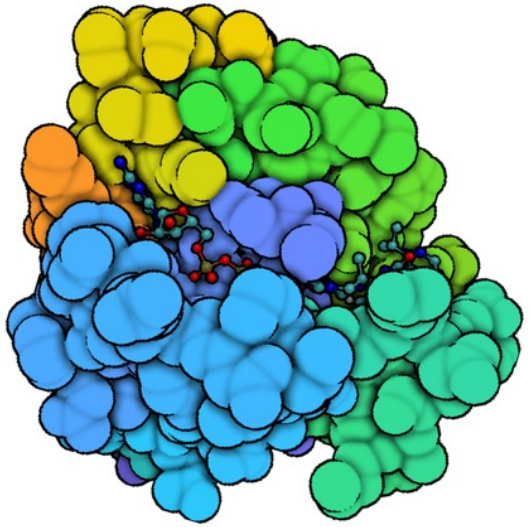
J Clin Oncol 42, 2024 (suppl 16; abstr 8508)

- IVONESCIMAB PLUS CHEMOTHERAPY SIGNIFICANTLY IMPROVED PFS IN PATIENTS WHO PROGRESSED ON EGFR-TKI THERAPY:
  - HR 0.46 (95% CI 0.34, 0.62) P < 0.001
- BENEFIT OF IVONESCIMAB PLUS CHEMOTHERAPY VS CHEMOTHERAPY WAS OBSERVED ACROSS ALL PRESPECIFIED SUBGROUPS
- ADVERSE REACTIONS WERE AS EXPECTED GIVEN THE COMPONENTS OF THE THERAPEUTIC REGIMEN AND MANAGEABLE
- THE STUDY IS NOW ENROLLING PATIENTS IN THE US AND EUROPE FOR FURTHER VALIDATION

J Clin Oncol 42, 2024 (suppl 16; abstr 8508)



MRTX849 (Adagrasib) Bound to KRASG12C



AMG510 (Sotorasib) bound to KRASG12C

KRAS G12C: THE ELUSIVE TARGET

- SMALL BINDING POCKET INHIBITS DRUG BINDING
- HIGH AFFINITY FOR GTP (ON-STATE)
- INCREASED PROTEIN EXPRESSION IN PRESENCE OF INHIBITOR
- OFTEN NOT A STANDALONE DRIVER IN MALIGNANCY (PRESENCE OF CO-MUTATIONS)

KRYSTAL-12[a] study design

Key eligibility criteria

- Locally advanced or metastatic NSCLC with *KRAS*^{G12C} mutation[b]
- Prior treatment with platinum-based chemotherapy and anti-PD-(L)1 therapy[c]
- ECOG PS 0-1
- Stable brain metastases allowed

Stratified by:

- **Region (non-Asia-Pacific vs Asia-Pacific)**
- **Prior treatment (sequential vs concurrent chemotherapy and immunotherapy)**

N = 453

R

2:1

ADA 600 mg BID PO[d]

DOCE 75 mg/m^2 Q3W IV

Crossover from DOCE to ADA was allowed in cases where disease progression per RECIST v1.1 was confirmed by real-time BICR[e]

Primary endpoint

- PFS by BICR (RECIST v1.1)

Secondary endpoints

- ORR by BICR (RECIST v1.1)
- DOR
- OS
- Safety
- Patient-reported outcomes

Database lock: March 19, 2024. Data cut-off: December 31, 2023.

[a]NCT04685135. [b]Detected in tumor tissue using sponsor-approved local or central testing. [c]No washout period was required between prior therapy and study treatment. [d]Tablet formulation, except for four patients who initially received the capsule formulation. [e]Other crossover criteria: ECOG PS 0-2, recovery from DOCE-related AEs to grade 1 or baseline (except peripheral neuropathy and alopecia for which grade 2 is acceptable).

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8509)

Baseline patient characteristics

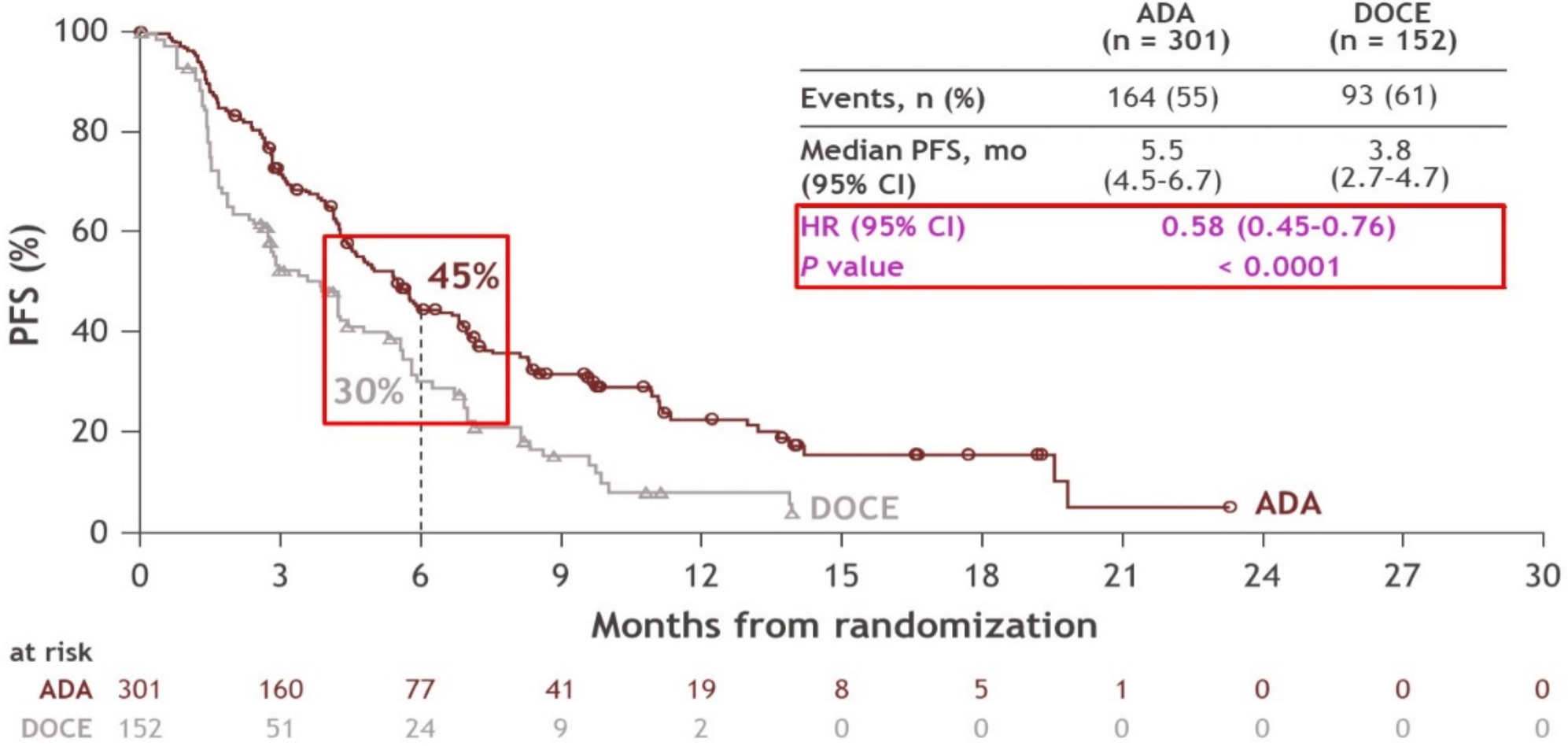
	ADA (n = 301)	DOCE (n = 152)
Median age, years (range)	64 (34-83)	65 (45-80)
Age category, %		
< 65 years	53	49
≥ 65 years	47	51
Male, %	64	72
Region, %		
Non-Asia-Pacific	74	74
Asia-Pacific	26	26
ECOG PS, %[a]		
0	32	31
1	68	68
Disease stage, %		
Locally advanced	6	5
Metastatic	94	95
Histology, %		
Adenocarcinoma	94	97
Other[b]	6	3

	ADA (n = 301)	DOCE (n = 152)
Smoking status, %[a]		
Current	19	20
Former	76	74
Never	6	6
Metastases at baseline, %[c]		
Brain	17	18
Liver	15	12
Bone	23	26
Tumor PD-L1 expression, %		
< 1%	20	22
1-49%	42	45
≥ 50%	24	19
Not evaluated	14	13
Prior chemo-immunotherapy, %		
Sequential	27	27
Concurrent	73	73

Percentages may not total 100 due to rounding. [a]Data missing for 1 patient in DOCE arm. [b]Other histologies in ADA/DOCE arms, respectively, were large-cell (n = 4/n = 1), unclassified or undifferentiated (n = 6/n = 1), squamous (n = 6/n = 0) and other (n = 2/n = 3). [c]In accordance with RECIST v1.1 per BICR.

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8509)

Primary endpoint: PFS[a] per BICR



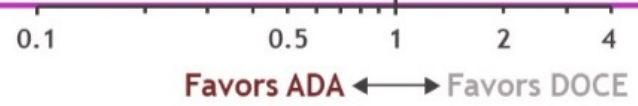
	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

Median follow-up: 7.2 months.

[a]Time from randomization to the date of disease progression per BICR or death due to any cause, whichever occurs first. For patients who started a subsequent anticancer therapy prior to disease progression or death, PFS was censored at the date of the last tumor assessment prior to the start of the new therapy.

PFS subgroup analysis per BICR

	Median PFS, mo		Unstratified HR (95% CI)	Unstratified HR
	ADA (n = 301)	DOCE (n = 152)		
Overall (N = 453)	5.5	3.8		0.58
< 65 years (n = 234)	5.4	2.9		0.56
≥ 65 years (n = 219)	5.9	4.2		0.60
Male (n = 303)	5.4	2.9		0.55
Female (n = 150)	5.6	5.6		0.64
Non-Asia-Pacific (n = 335)	5.7	3.4		0.55
Asia-Pacific (n = 118)	5.4	3.9		0.66
ECOG PS 0 (n = 143)	11.1	5.8		0.44
ECOG PS 1 (n = 309)	4.6	2.8		0.61
Current smoker (n = 86)	4.2	4.4		0.89
Former smoker (n = 340)	5.8	3.6		0.51
Never smoker (n = 26)	5.5	6.2		0.70
Brain metastases at baseline (n = 80)[a]	4.1	4.2		0.71
No brain metastases at baseline (n = 373)[a]	5.8	3.6		0.55
Liver metastases at baseline (n = 64)[a]	4.5	1.4		0.43
No liver metastases at baseline (n = 389)[a]	5.6	4.2		0.59
Bone metastases at baseline (n = 107)[a]	4.4	2.8		0.56
No bone metastases at baseline (n = 346)[a]	5.8	4.2		0.58
PD-L1 < 1% (n = 95)	5.8	2.8		0.44
PD-L1 1-49% (n = 195)	5.9	3.6		0.56
PD-L1 ≥ 50% (n = 100)	5.0	3.9		0.62
Sequential chemo-immunotherapy (n = 121)	5.8	2.9		0.53
Concurrent chemo-immunotherapy (n = 332)	5.4	3.9		0.60

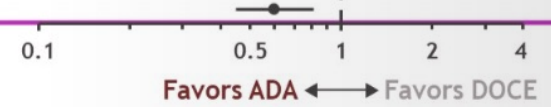


Median follow-up: 7.2 months

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8509)

PFS subgroup analysis per BICR

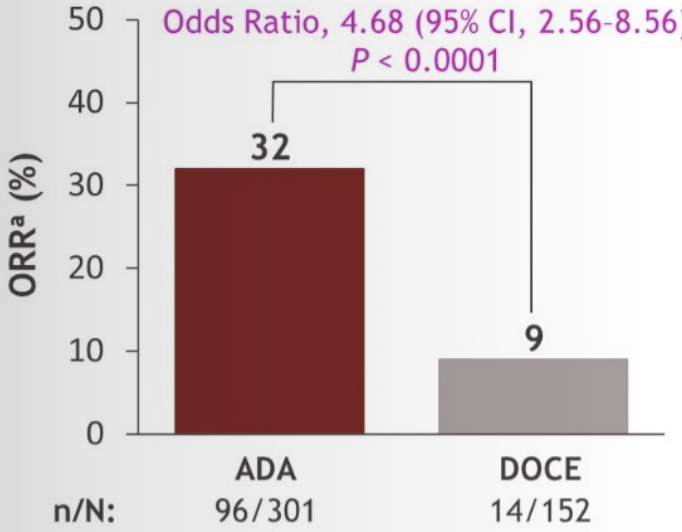
	Median PFS, mo		Unstratified HR (95% CI)	Unstratified HR
	ADA (n = 301)	DOCE (n = 152)		
Overall (N = 453)	5.5	3.8		0.58
< 65 years (n = 234)	5.4	2.9		0.56
≥ 65 years (n = 219)	5.9	4.2		0.60
Male (n = 303)	5.4	2.9		0.55
Female (n = 150)	5.6	5.6		0.64
Non-Asia-Pacific (n = 335)	5.7	3.4		0.55
Asia-Pacific (n = 118)	5.4	3.9		0.66
ECOG PS 0 (n = 143)	11.1	5.8		0.44
ECOG PS 1 (n = 309)	4.6	2.8		0.61
Current smoker (n = 86)	4.2	4.4		0.89
Former smoker (n = 340)	5.8	3.6		0.51
Never smoker (n = 26)	5.5	6.2		0.70
Brain metastases at baseline (n = 80)[a]	4.1	4.2		0.71
No brain metastases at baseline (n = 373)[a]	5.8	3.6		0.55
Liver metastases at baseline (n = 64)[a]	4.5	1.4		0.43
No liver metastases at baseline (n = 389)[a]	5.6	4.2		0.59
Bone metastases at baseline (n = 107)[a]	4.4	2.8		0.56
No bone metastases at baseline (n = 346)[a]	5.8	4.2		0.58
PD-L1 < 1% (n = 95)	5.8	2.8		0.44
PD-L1 1-49% (n = 195)	5.9	3.6		0.56
PD-L1 ≥ 50% (n = 100)	5.0	3.9		0.62
Sequential chemo-immunotherapy (n = 121)	5.8	2.9		0.53
Concurrent chemo-immunotherapy (n = 332)	5.4	3.9		0.60



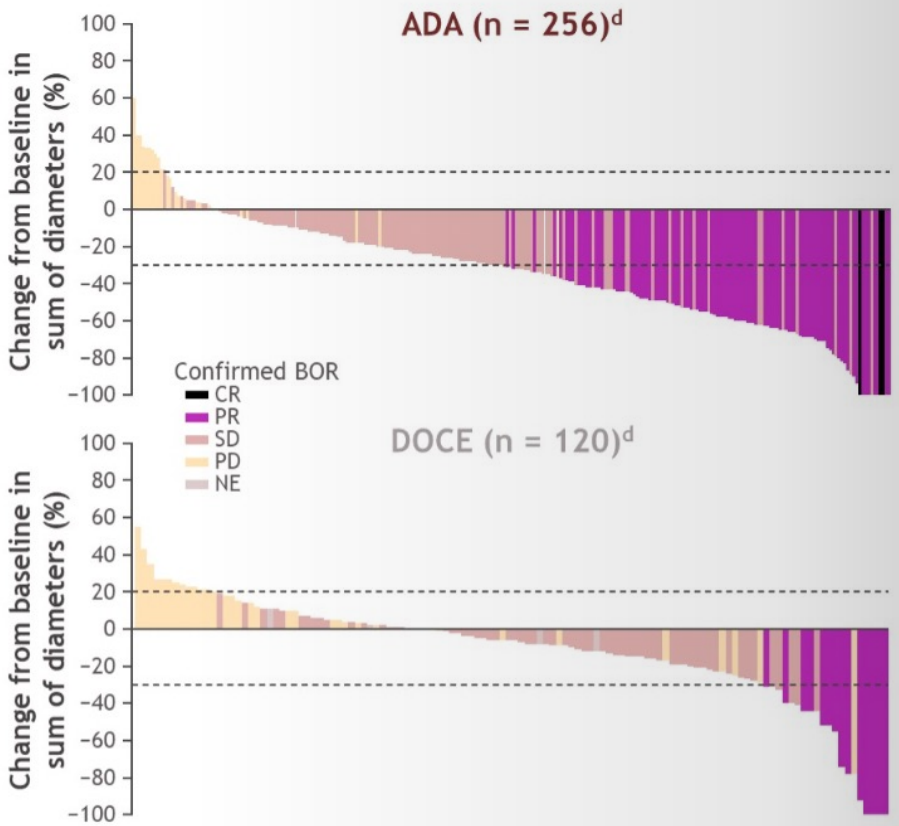
Median follow-up: 7.2 months.
Bold text indicates stratification factors. [a]In accordance with RECIST v1.1 per BICR.

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8509)

Tumor response per BICR



Tumor response	ADA (n = 301)	DOCE (n = 152)
DCR,[b] n (%)	236 (78)	89 (59)
Median DOR,[c] mo (95% CI)	8.3 (6.1-10.4)	5.4 (2.9-8.5)
Remaining in response at 6 mo, %	64	39

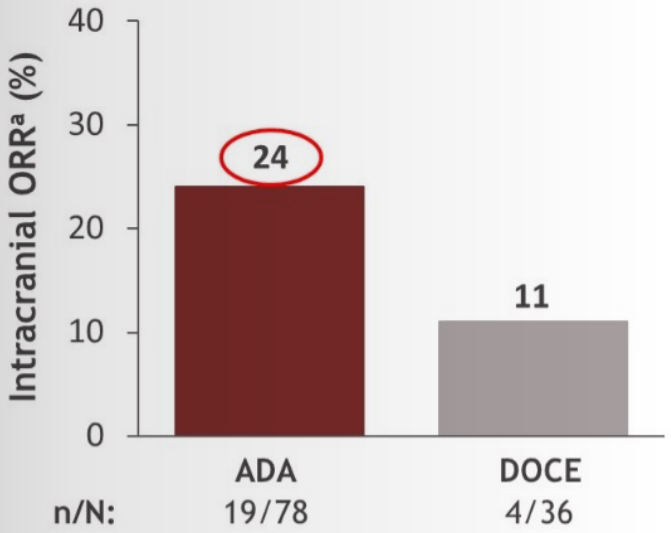


[a]ORR is defined as the percent of patients documented to have a confirmed CR/PR by BICR (per RECIST v1.1). [b]Disease control rate (DCR) is defined as the percent of patients documented to have a confirmed CR/PR/SD by BICR (per RECIST v1.1). [c]DOR is defined as the time from the date of first documentation of CR/PR to the first documentation of PD or death due to any cause in the absence of documented PD. DOR is only calculated for patients with confirmed CR/PR. [d]Waterfall plots include patients with at least one target lesion at baseline and at least one post-baseline tumor assessment.

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8509)

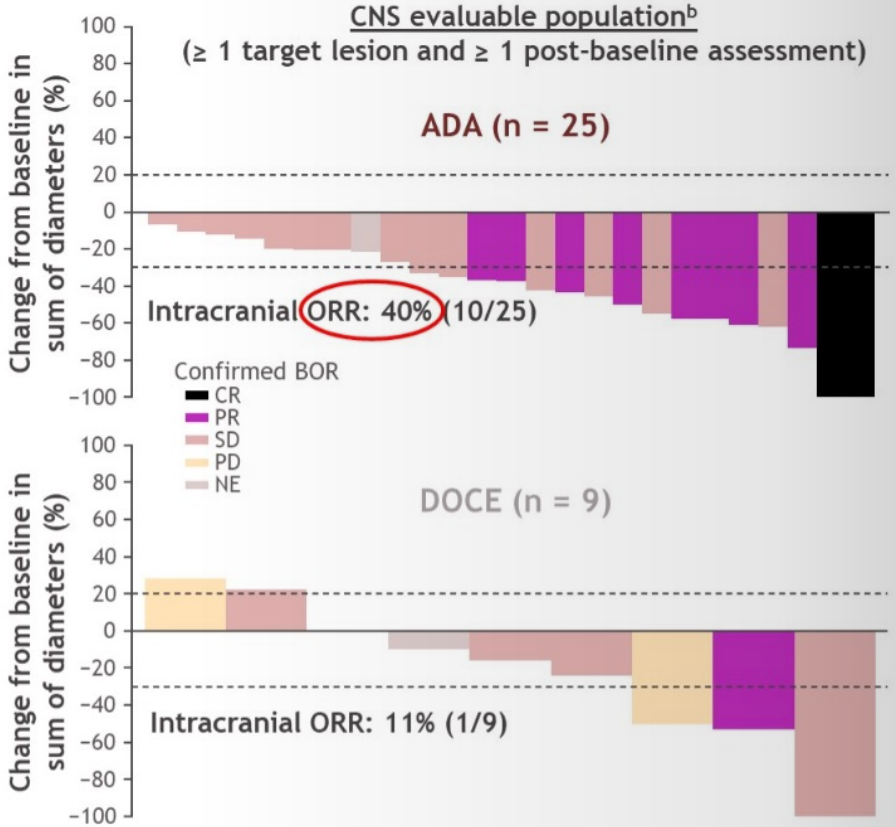
Intracranial response per BICR[a]

All patients with baseline CNS metastases[a]



Intracranial response[a]	ADA (n = 78)	DOCE (n = 36)
Intracranial DCR, n (%)	64 (82)	20 (56)

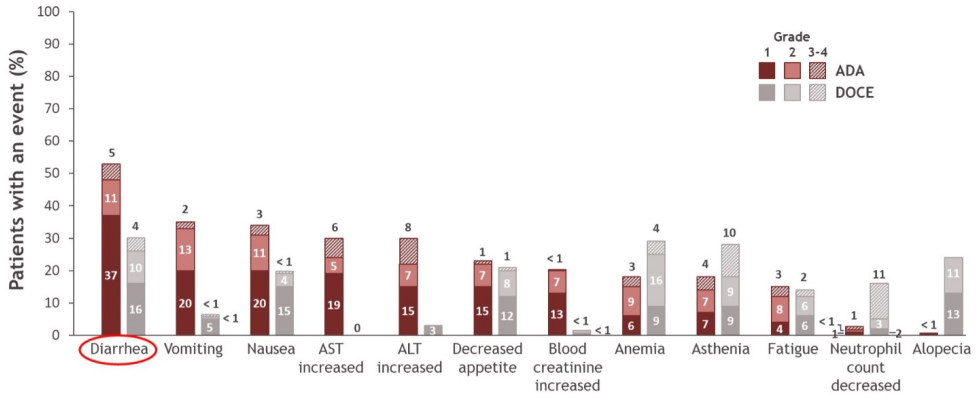
CNS evaluable population[b]
(≥ 1 target lesion and ≥ 1 post-baseline assessment)



[a]In accordance with CNS-adapted RECIST v1.1. CNS RECIST data (including identification of patients with baseline CNS metastases) were based on a separate CNS imaging charter and neuroradiologist review. [b]Waterfall plots show CNS evaluable population including patients with at least one CNS target lesion at baseline and at least one post-baseline CNS tumor assessment. For lesions to be considered target lesions, they must have been measurable and either not previously treated with CNS-directed therapy or must have progressed after prior CNS-directed therapy.

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8509)

Most frequent TRAEs (> 15% in either treatment arm[a])



[a]For each TRAE, patients are included only once at the maximum severity.

KRYSTAL-12: ADA in previously treated KRAS^{G12C} NSCLC

Safety summary[a]

Patients, %	ADA (n = 298)	DOCE (n = 140)
TRAEs	94	86
Grade ≥ 3 TRAEs	47	46
TRAEs leading to discontinuation[b]	8	14
TRAEs leading to dose reduction	48	24
TRAEs leading to dose interruption	59	19
Treatment-related SAEs	21	16
Treatment-related deaths[c]	1	< 1

[a]AEs per CTCAE v5.0 and MedDRA v26.0. Includes events reported between the first dose and 28 days after the last dose, and prior to the initiation of subsequent anticancer therapy. For each category, patients are included only once, even if they experienced multiple events in that category. [b]Most common TRAEs leading to treatment discontinuation were ALT increased (n = 3), neutropenia, diarrhea, and pneumonitis (n = 2 each) with ADA, and asthenia, fatigue, and peripheral neuropathy (n = 3 each) with DOCE. [c]Treatment-related deaths were due to epilepsy, hepatic failure, hepatic ischemia, and unknown cause with ADA, and sepsis with DOCE (n = 1 each).

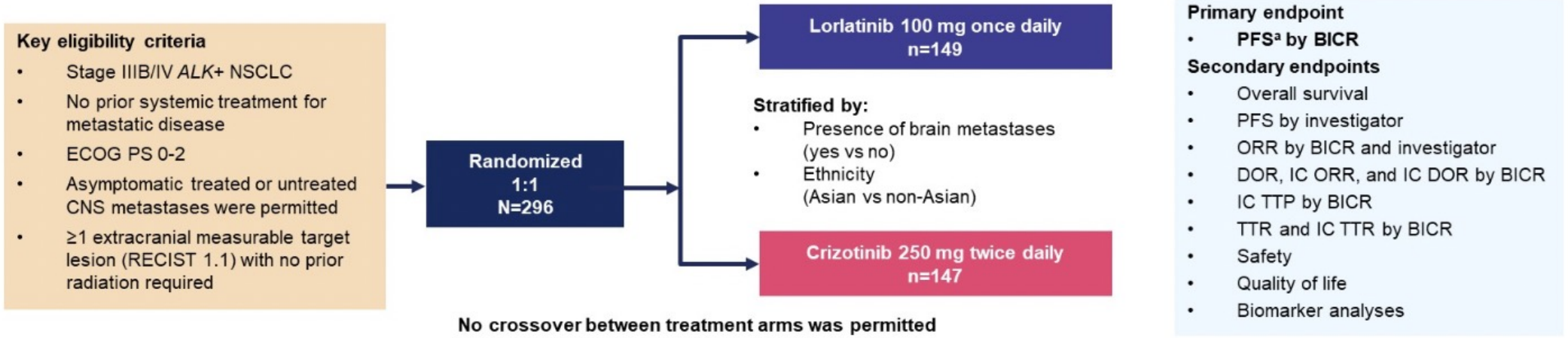
J Clin Oncol 42, 2024 (suppl 17; abstr LBA8509)

- IN THE PHASE 3 KRYSTAL-12 TRIAL, ADA DEMONSTRATED A STATISTICALLY SIGNIFICANT AND MEANINGFUL IMPROVEMENT IN PFS OVER DOCE IN PATIENTS WITH PREVIOUSLY TREATED KRASG12C-MUTATED NSCLC (MEDIAN PFS, 5.5 VS 3.8 MO, RESPECTIVELY; HR, 0.58; $P < 0.0001$)
- PFS BENEFIT WAS OBSERVED ACROSS KEY SUBGROUPS
- ORR WAS ALSO SIGNIFICANTLY HIGHER WITH ADA VS DOCE (32% VS 9%; ODDS RATIO, 4.68; $P < 0.0001$); OVERALL, THE RESPONSES WERE DEEP AND APPEAR TO BE DURABLE
- ADA SHOWED INTRACRANIAL EFFICACY AMONG PATIENTS WITH BRAIN METASTASES AT BASELINE, WITH A RESPONSE RATE THAT WAS MORE THAN DOUBLE THAT OBSERVED WITH DOCE (INTRACRANIAL ORR, 24% VS 11%)
- THE SAFETY PROFILES OF ADA AND DOCE WERE CONSISTENT WITH PREVIOUS REPORTS, WITH NO NEW SAFETY SIGNALS
- THESE RESULTS REINFORCE ADA AS AN EFFICACIOUS TREATMENT OPTION FOR PATIENTS WITH KRASG12C-MUTATED NSCLC AFTER DISEASE PROGRESSION ON PRIOR CHEMOTHERAPY AND IMMUNOTHERAPY
- A PHASE 3 TRIAL COMPARING FIRST-LINE ADA PLUS PEMBROLIZUMAB VS PEMBROLIZUMAB ALONE IS CURRENTLY ENROLLING

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8509)

CROWN: A Randomized Global Phase 3 Study

- Lorlatinib is a brain-penetrant, third-generation ALK TKI that has broader coverage of *ALK* resistance mutations than second-generation ALK TKIs[1,2]



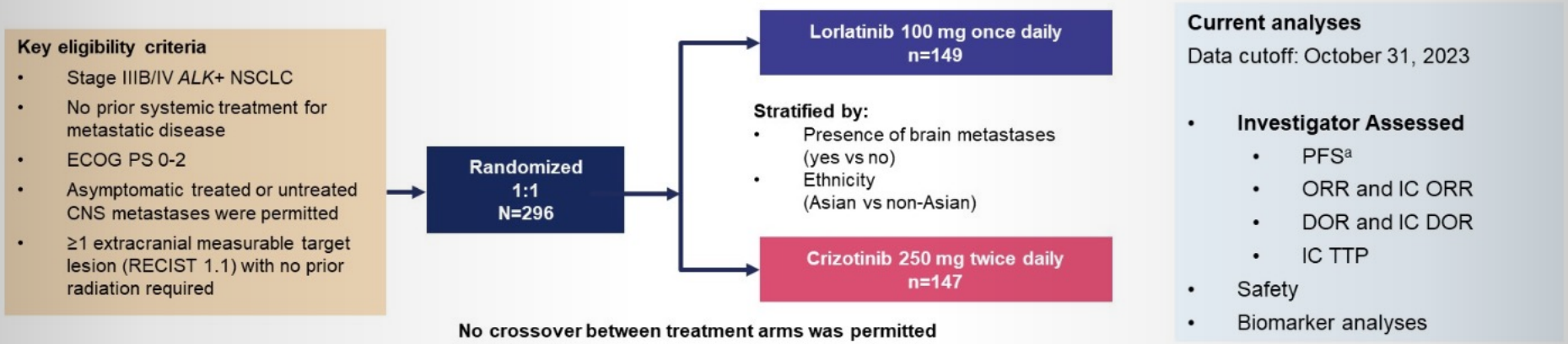
- At the planned interim analysis, at 18.3 months of median follow-up in the lorlatinib arm, median PFS by BICR was not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib, with an HR of 0.28 (95% CI, 0.19-0.41) and P<0.001[3]
- In a subsequent post hoc analysis, at 3 years of follow-up, median PFS by BICR was still not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (HR, 0.27; 95% CI, 0.18-0.39)[4]

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IC, intracranial; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TTP, time to tumor progression; TTR, time to tumor response.
[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.
1. Johnson TW, et al. *J Med Chem*. 2014;57:4720-4744. 2. Shaw AT, et al. *Lancet Oncol*. 2017;18:1590-1599. 3. Shaw AT, et al. *N Engl J Med*. 2020;383:2018-2029. 4. Solomon BJ, et al. *Lancet Respir Med*. 2023;11:354-366.

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8503)

Current Post Hoc Analyses at 5 Years

Endpoint evaluation by BICR stopped after the 3-year analysis

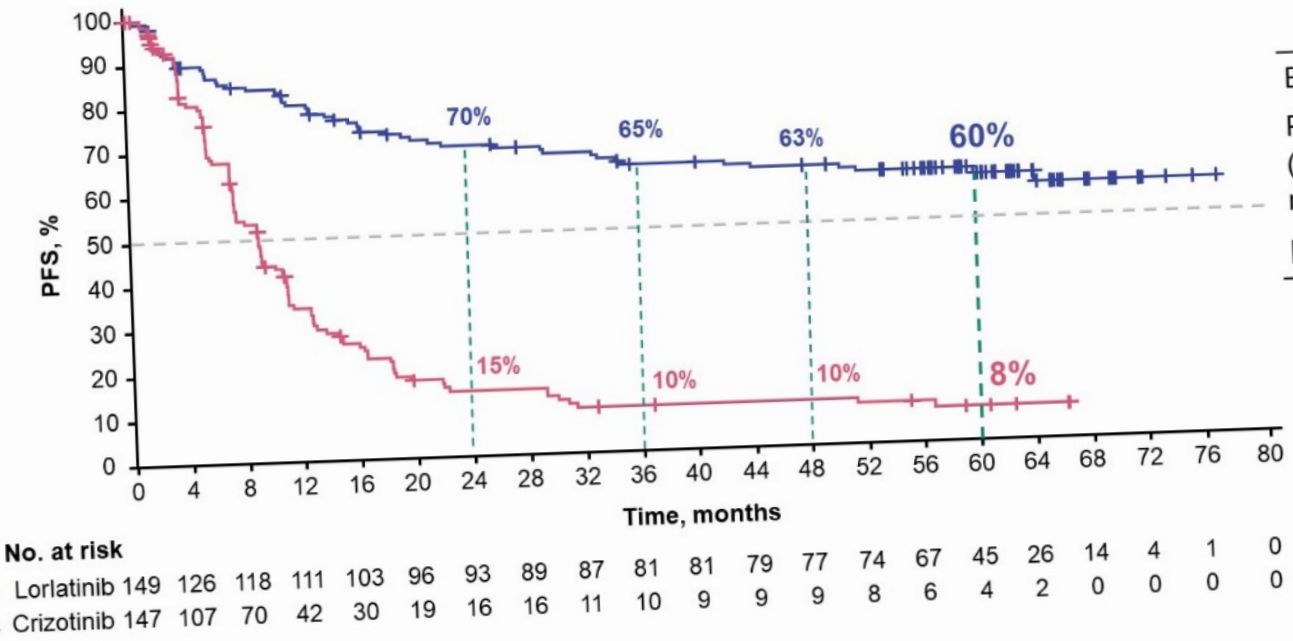


- The median duration of follow-up for PFS was 60.2 months (95% CI, 57.4-61.6) in the lorlatinib arm and 55.1 months (95% CI, 36.8-62.5) in the crizotinib arm

CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; ORR, objective response rate; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression.
[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8503)

At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

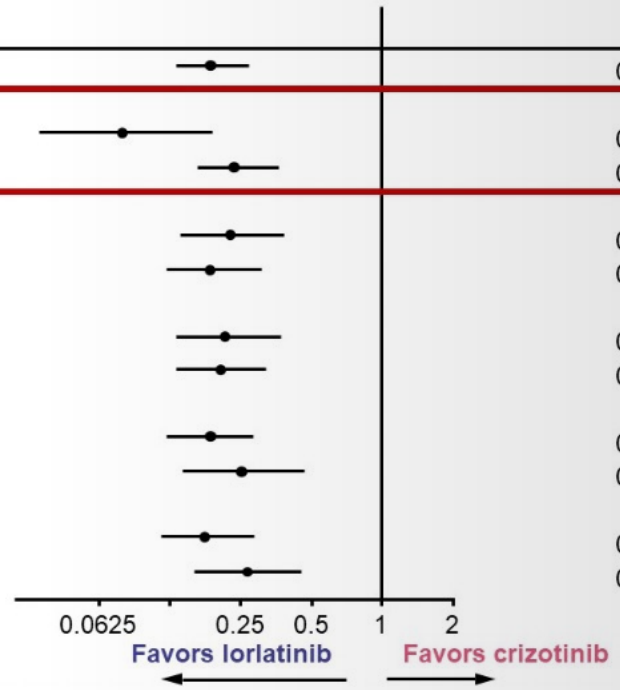
At the time of this analysis, the required number of OS events for a protocol-specified second interim analysis **has not been reached**. OS follow up is ongoing

HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8503)

PFS Benefit With Lorlatinib Was Observed Across Patient Subgroups

Subgroup	Patients, n (%)		Events, n		HR (95% CI)
	Lorlatinib	Crizotinib	Lorlatinib	Crizotinib	
All patients (stratified)	149 (100)	147 (100)	55	115	0.19 (0.13-0.27)
Presence of brain metastases					
Yes	35 (23)	38 (26)	16	34	0.08 (0.04-0.19)
No	114 (77)	109 (74)	39	81	0.24 (0.16-0.36)
Ethnic origin					
Asian	66 (44)	65 (44)	25	50	0.23 (0.14-0.38)
Non-Asian	83 (56)	82 (56)	30	65	0.19 (0.12-0.31)
Sex					
Male	65 (44)	56 (38)	24	48	0.22 (0.13-0.37)
Female	84 (56)	91 (62)	31	67	0.21 (0.13-0.32)
Age					
<65 years	96 (64)	110 (75)	33	88	0.19 (0.12-0.28)
≥65 years	53 (36)	37 (25)	22	27	0.26 (0.14-0.47)
Smoking status					
Never	81 (54)	94 (64)	30	75	0.18 (0.12-0.29)
Current/former	68 (46)	52 (35)	25	39	0.27 (0.16-0.45)



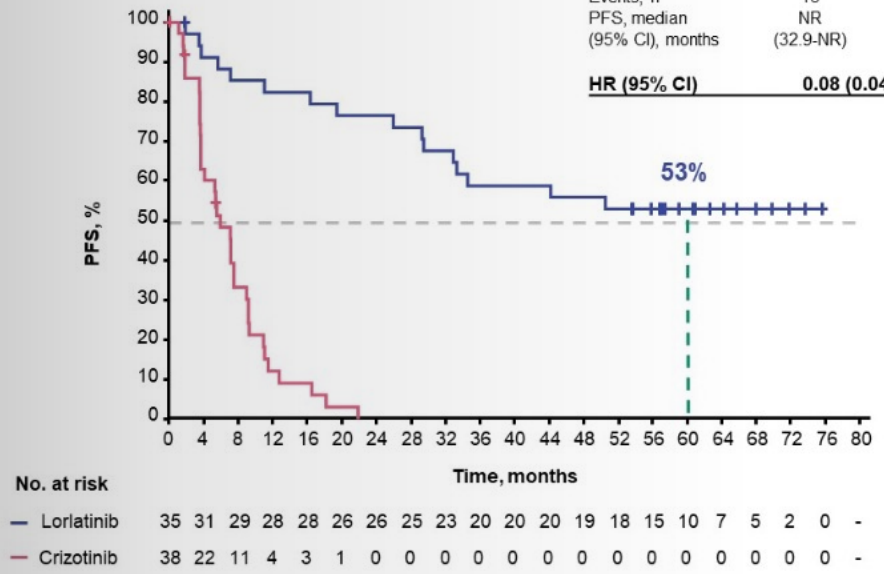
PFS, progression-free survival.

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8503)

Lorlatinib Showed Superior PFS Benefit Irrespective of Presence or Absence of Baseline Brain Metastases

With Baseline Brain Metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	16	34
PFS, median (95% CI), months	NR (32.9-NR)	6.0 (3.7-7.6)
HR (95% CI)	0.08 (0.04-0.19)	

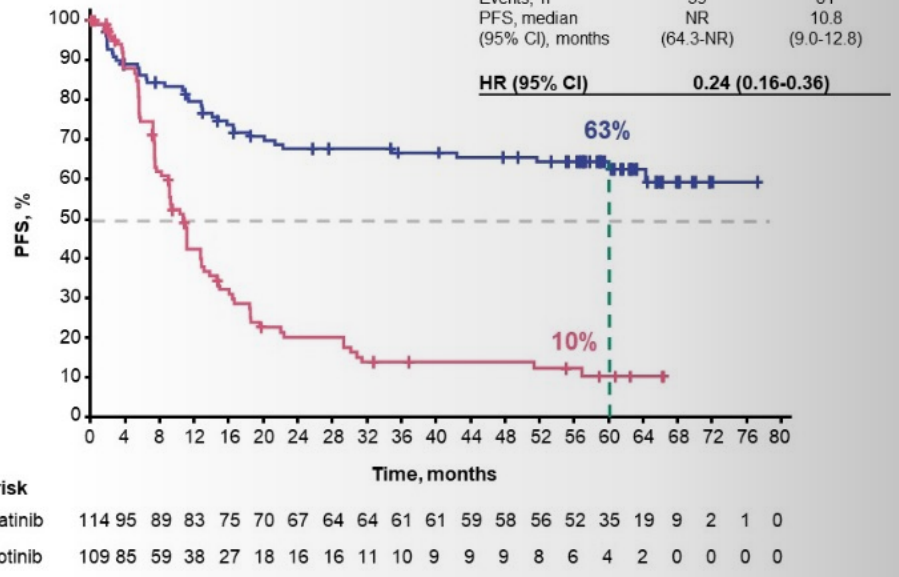


No. at risk

Lorlatinib	35	31	29	28	28	26	26	25	23	20	20	20	19	18	15	10	7	5	2	0	-
Crizotinib	38	22	11	4	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-

Without Baseline Brain Metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	39	81
PFS, median (95% CI), months	NR (64.3-NR)	10.8 (9.0-12.8)
HR (95% CI)	0.24 (0.16-0.36)	



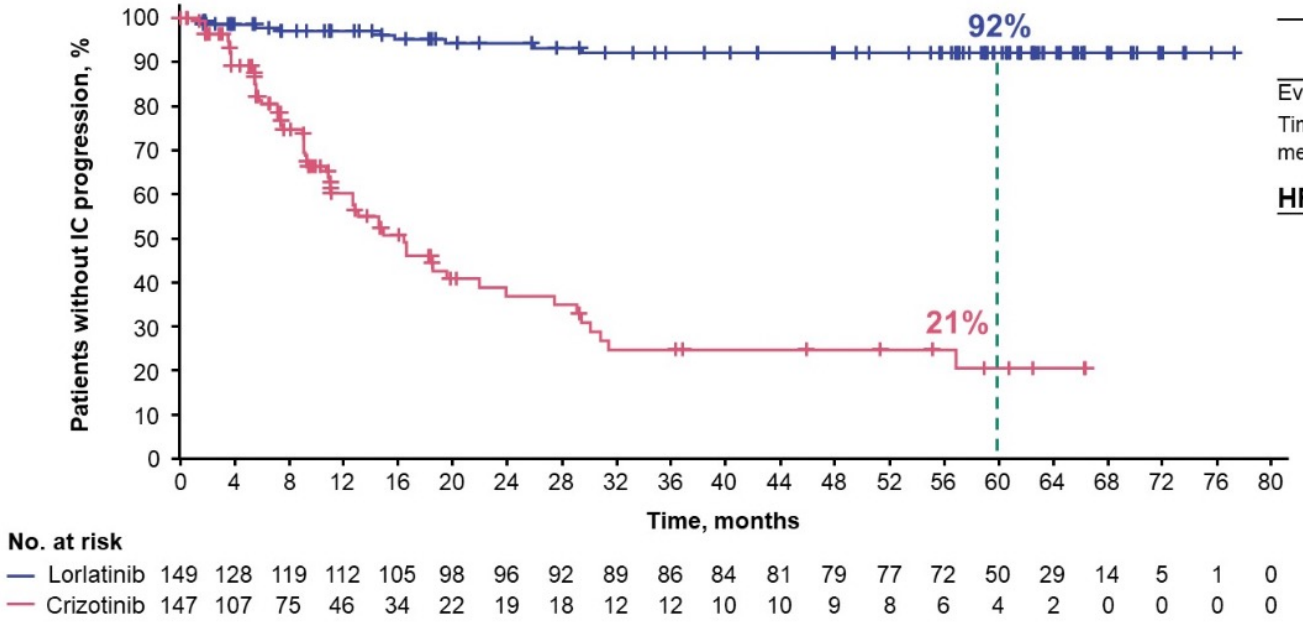
No. at risk

Lorlatinib	114	95	89	83	75	70	67	64	64	61	61	59	58	56	52	35	19	9	2	1	0
Crizotinib	109	85	59	38	27	18	16	16	11	10	9	9	9	8	6	4	2	0	0	0	0

HR, hazard ratio; NR, not reached; PFS, progression-free survival.

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8503)

Time to IC Progression by Investigator Assessment Was Longer With Lorlatinib (ITT Population)



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	**0.06 (0.03-0.12)**	

Tumor assessments, including brain MRI, have been performed every 8 weeks in all patients throughout the study

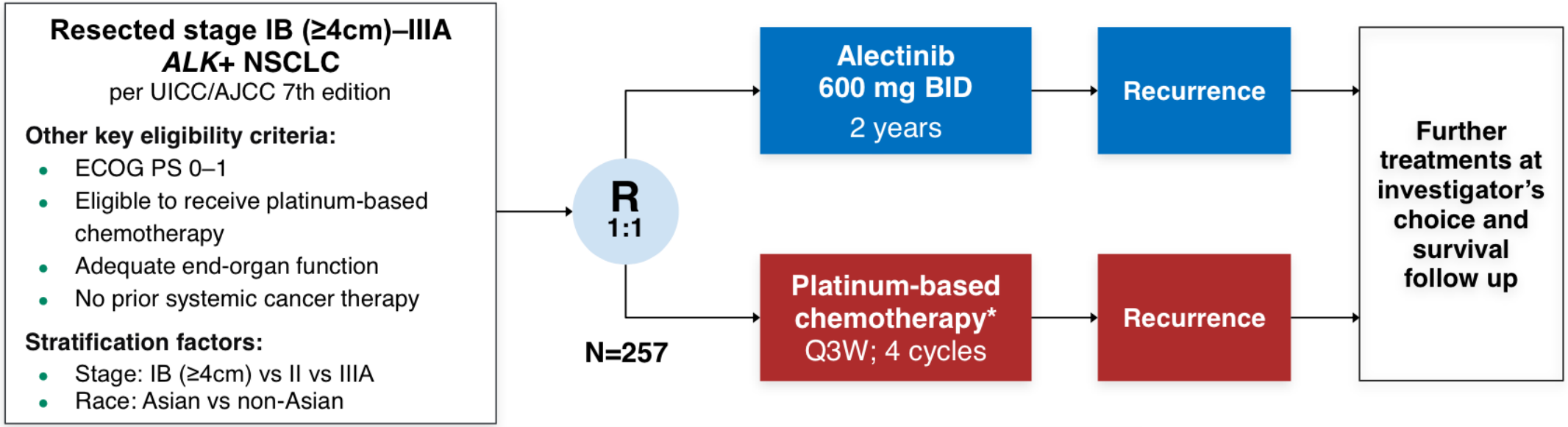
HR, hazard ratio; IC, intracranial; ITT, intention to treat; NR, not reached. MRI, magnetic resonance imaging

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8503)

- LORLATINIB BENEFITED PATIENTS WITH POOR PROGNOSTIC BIOMARKERS
  - EML4::ALK FUSION VARIANTS 1, 3
  - PRESENCE OF TP53 MUTATION
- EMERGING NEW ALK MUTATIONS WERE NOT DETECTED IN CT-DNA AT END OF LORLATINIB TREATMENT
- MEDIAN PFS NOT REACHED AT 5-YEAR FOLLOW UP = LONGEST PFS REPORTED IN ADVANCED NSCLC
- 92% PROBABILITY OF BEING FREE OF INTRACRANIAL DISEASE PROGRESSION
- NO NEW SAFETY SIGNALS

J Clin Oncol 42, 2024 (suppl 17; abstr LBA8503)

ALINA study design



Primary endpoint

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

Other endpoints

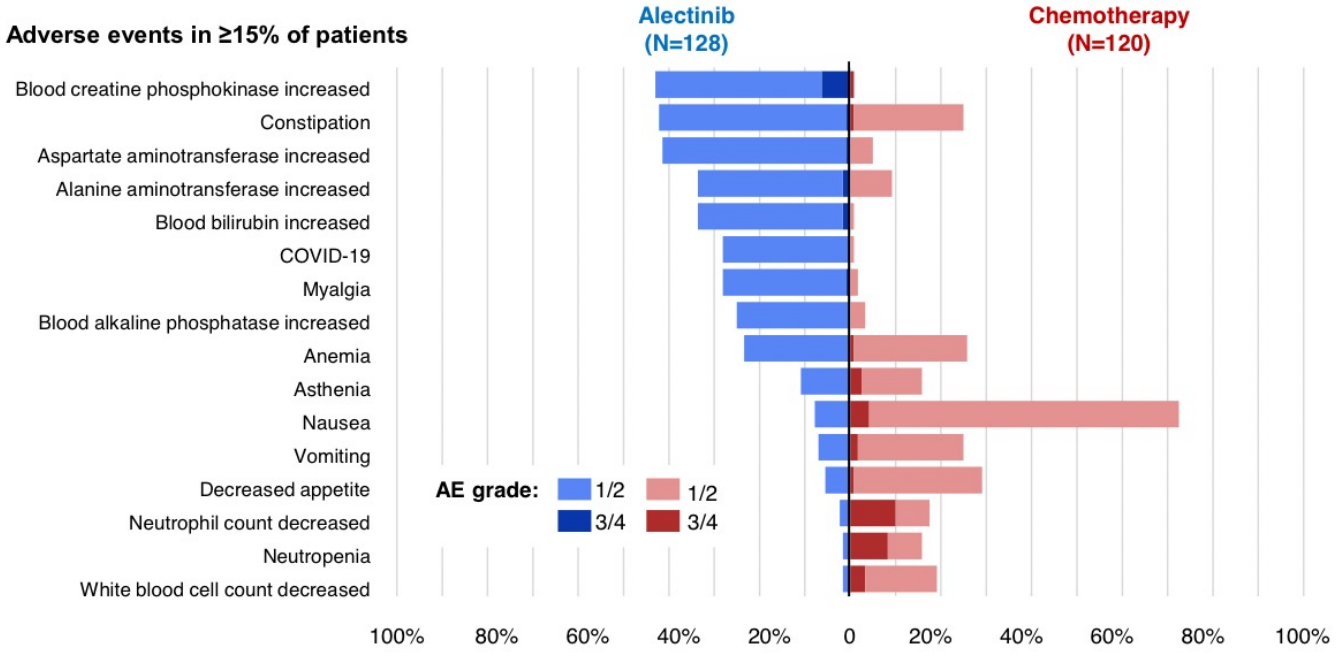
- CNS disease-free survival
- OS
- Safety
- Patient-reported outcomes

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

Data cut-off: June 26, 2023; BID, twice-daily; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat; Q3W, every three weeks; OS, overall survival; R, randomization; Crossover was not permitted prior to disease recurrence
*Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine, cisplatin could be switched to carboplatin in case of intolerability; †DFS defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; ‡Assessment by CT scan where MRI not available; **NCT03456076**

AEs occurring in ≥15% of patients

Adjuvant alectinib was tolerable, with a manageable safety profile which was in line with the known profile of alectinib[1,2]



AEs leading to:

- Dose reduction
  Alectinib: **26%** / Chemo: **10%**
- Dose interruption
  Alectinib: **27%** / Chemo: **18%**
- Treatment withdrawal
  Alectinib: **5%** / Chemo: **13%**

Median treatment duration

Alectinib: **23.9 months**
Chemo: **2.1 months**

AE, adverse event;
1. Solomon et al. ESMO 2023 (LBA2); 2. Wu et al. N Engl J Med 2024

Key points

- Health-related quality of life is an important clinical consideration for adjuvant treatment in **resected *ALK*+ NSCLC**
- This exploratory analysis of patient-reported outcomes from the phase III ALINA trial showed **mental and physical HRQoL improvement** from baseline with adjuvant alectinib, which was maintained over 2 years of treatment
- Together with the DFS benefit seen in ALINA, these HRQoL data support adjuvant alectinib as an **important new treatment strategy** for patients with resected *ALK*+ NSCLC

DFS, disease-free survival; HRQoL, health-related quality of life; **NCT03456076**

SUMMARY

- EGFR REMAINS A RELEVANT TARGET IN NSCLC, WITH A RAPIDLY EXPANDING REPERTOIRE OF AGENTS USEFUL AT NEARLY EVERY STAGE OF DISEASE
  - MOLECULAR PROFILING FOR EVERY LUNG CANCER PATIENT IS INEVITABLE
  - ADJUVANT OSIMERTINIB PROLONG PFS, WITH A TREND TOWARD IMPROVED OS, WHEN GIVEN AFTER CONCURRENT CHEMORADIOTHERAPY
  - IN PROGRESSIVE EGFR MUTATED NSCLC, MECHANISMS OF RESISTANCE ARE KEY TO CONTINUING TARGETED AND PRECISION APPROACHES (AGAIN DEPENDENT ON MOLECULAR PROFILING)
  - IVONESCIMAB WITH CHEMOTHERAPY IMPROVED PFS AND DCR, AS WELL AS PROLONGED DOR COMPARED TO CHEMOTHERAPY FOR PATIENTS PROGRESSING ON EGFR-TKI

SUMMARY

- KRAS G12C MUTATION POSITIVE DISEASE REPRESENTS NEARLY 13% OF NSQ-NSCLC
  - THE PROTEIN HAS BEEN CHALLENGING TO CONSISTENTLY TARGET
  - ADAGRASIB AND SOTORASIB ARE THE 2 G12C INHIBITORS CURRENTLY IN THE CLINIC
  - ADAGRASIB PROLONGED PFS COMPARED TO DOCETAXEL IN THE KRYSTAL-12 TRIAL
  - NEW GENERATION G12C INHIBITORS ARE ALREADY IN DEVELOPMENT AND MONOTHERAPY AND COMBINATION CLINICAL TRIALS ARE ONGOING

SUMMARY

- MANY ACTIVE ALK INHIBITORS ARE AVAILABLE FOR USE IN CLINICAL PRACTICE
- LORLATINIB HAS SHOWN THE LONGEST PFS IN NSCLC, WITH PFS STILL NOT REACHED AFTER 5 YEARS OF FOLLOW UP WHEN COMPARED TO CRIZOTINIB
- INTRACRANIAL ACTIVITY OF THE AGENT IS CONFIRMED IN THE CROWN INTRACRANIAL PFS DATA
- ALECTINIB, ALSO ACTIVE IN METASTATIC ALK+ NSCLC, IS NOW APPROVED AS AN ADJUVANT THERAPY IN EARLY STAGE, RESECTABLE ALK+

WEST
CANCER CENTER
& RESEARCH INSTITUTE

THANK YOU!