RANDOMIZED PHASE 3 STUDY OF FIRST-LINE AZD3759 (ZORIFERTINIB) VERSUS GEFITINIB OR ERLOTINIB IN EGFR-MUTANT (EGFRm+) NON-SMALL CELL LUNG CANCER (NSCLC) WITH CENTRAL NERVOUS SYSTEM (CNS) METASTASIS

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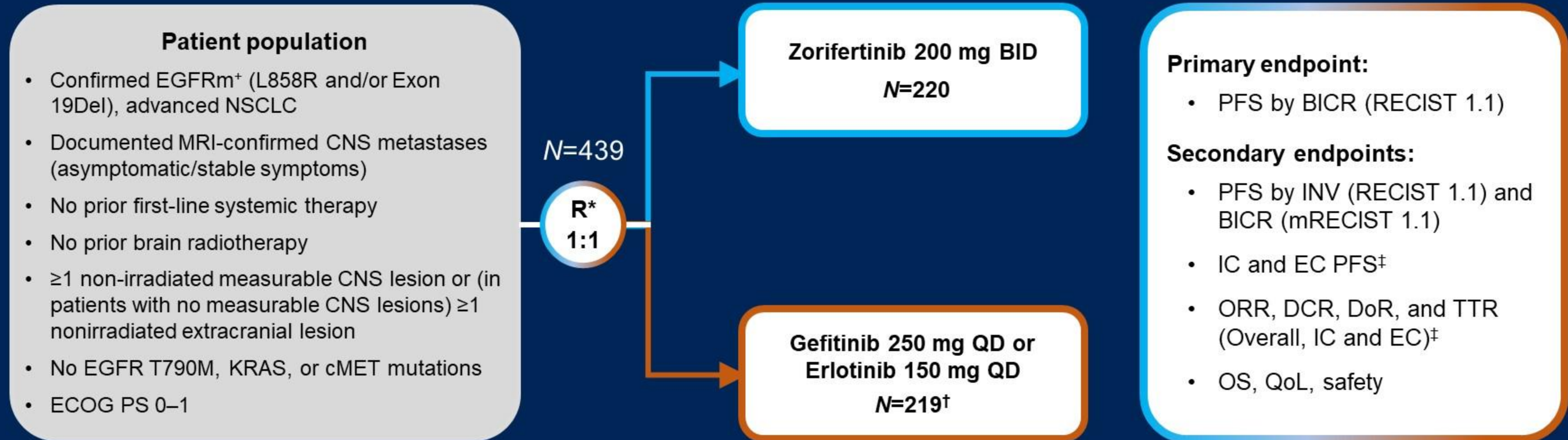KNOWLEDGE CONQUERS CANCER

Background and Rationale

- **More than 50%** of patients with NSCLC and activating epidermal growth factor receptor gene mutations (EGFRm[+]) develop CNS metastases during their lifetime, with a consequently poor prognosis[1]

- **There is** **a critical need to develop a brain-active EGFR-TKI**

  - Approved EGFR-TKIs show variable penetration across the blood–brain barrier (BBB), with $K_{puu,CSF}$ values (ratio of CSF concentration to free plasma concentration) ranging from 0.066 to 0.29[1]

  - Some EGFR-TKIs have shown promising intracranial (IC) antitumor activity, with the supporting evidence largely limited to subgroup analyses,[2,3,4] single-arm studies,[5] or retrospective analyses[6]

- Zorifertinib (AZD3759), a potent, oral EGFR-TKI, was **specially designed to have high BBB penetration** ($K_{puu,CSF}$ 1.11), [1,7] and has shown promising systemic and IC antitumor activity in phase 1 and 2 studies[1,8,9]

- Phase 3 AZD3759-003 (EVEREST) was **the first randomized, controlled, open-label, multinational study** aiming to compare the efficacy and safety of up-front zorifertinib versus first-generation EGFR-TKIs **exclusively in patients with advanced EGFRm[+] NSCLC and untreated CNS metastases**

1. Ahn MY, et al. *Lancet Respir Med.* 2017;5:891–902; 2. Shi Y, et al. *J Thorac Oncol.* 2022;17:1297–1305; 3. Lu S, et al. *J Clin Oncol.* 2022;40(Suppl 16):9096; 4. Reungwetwattana T, et al. J Clin Oncol. 2018 Aug 28:JCO2018783118; 5. Yamaguchi H, et al. *J Thorac Oncol.* 2021;16:2121-2132; 6. Xie L, et al. *Oncologist.* 2019;24:836-843. 7. Zeng Q, et al. *J Med Chem.* 2015;58:8200-8215; 8. Liu S-YM, et al. *J Thorac Oncol.* 2023;18(4):S52; 9. Data on file; Alpha Biopharma (Jiangsu) Co., Ltd. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor

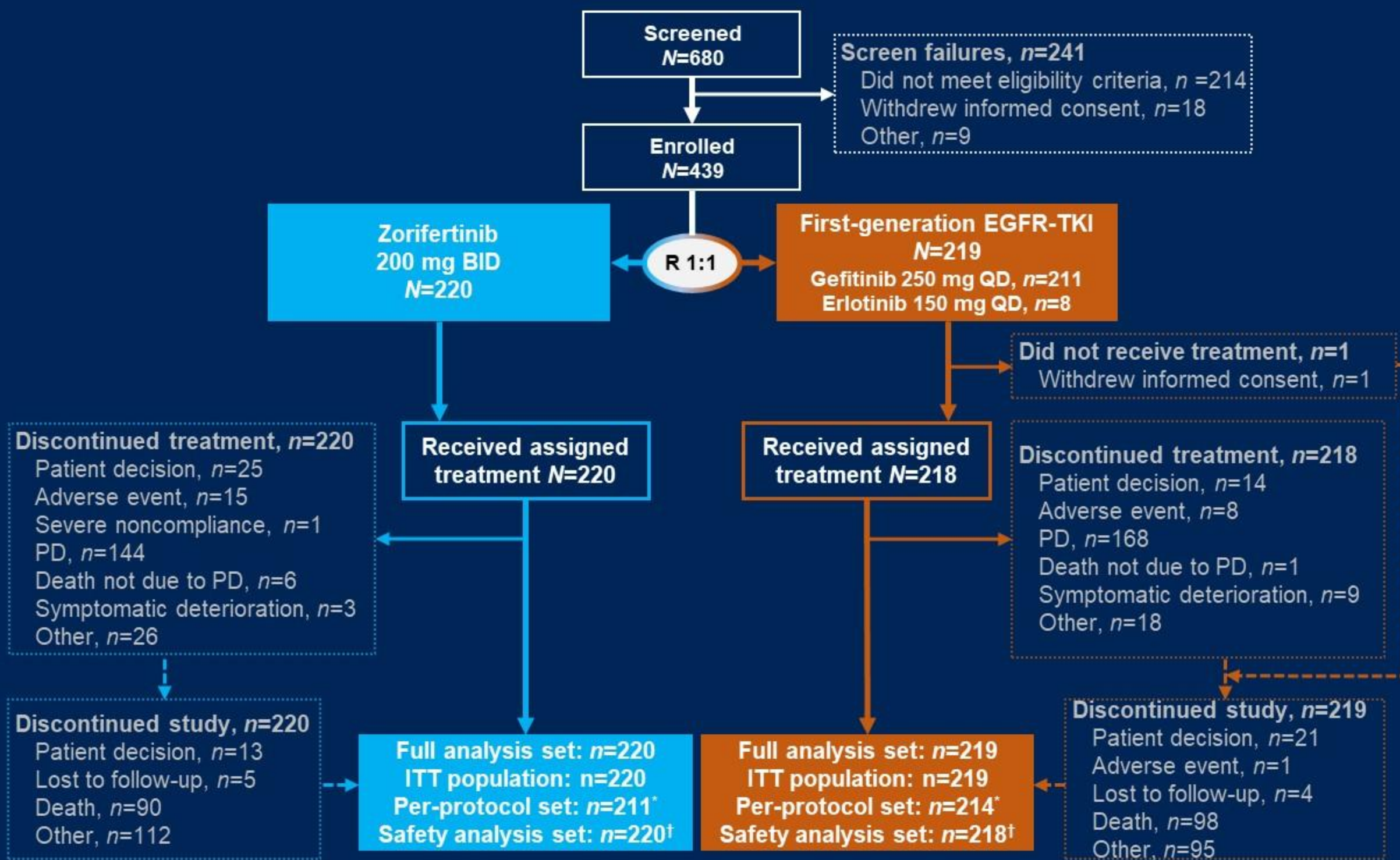# Study Design: Randomized, Controlled, Open-label, Phase 3

Patient population

- Confirmed EGFRm[+] (L858R and/or Exon 19Del), advanced NSCLC
- Documented MRI-confirmed CNS metastases (asymptomatic/stable symptoms)
- No prior first-line systemic therapy
- No prior brain radiotherapy
- ≥1 non-irradiated measurable CNS lesion or (in patients with no measurable CNS lesions) ≥1 nonirradiated extracranial lesion
- No EGFR T790M, KRAS, or cMET mutations
- ECOG PS 0–1

N=439

R* 1:1

Zorifertinib 200 mg BID
N=220

Gefitinib 250 mg QD or Erlotinib 150 mg QD
N=219[†]

Primary endpoint:

- PFS by BICR (RECIST 1.1)

Secondary endpoints:

- PFS by INV (RECIST 1.1) and BICR (mRECIST 1.1)
- IC and EC PFS[‡]
- ORR, DCR, DoR, and TTR (Overall, IC and EC)[‡]
- OS, QoL, safety

This trial is registered at ClinicalTrials.gov: NCT03653546

*Randomization was stratified according to sex (male vs female), smoking status (current vs former), and ECOG PS (0 vs 1). [†]Gefitinib was administered in mainland China and South Korea; erlotinib was administered in Taiwan China and Singapore. [‡]Assessed by INV (per RECIST 1.1 and [for IC disease only] RANO-BM) and BICR (per RECIST 1.1 and mRECIST 1.1). BICR, blinded independent central review; BID, twice daily; DCR, disease control rate; DoR, duration of response; EC, extracranial; ECOG PS, Eastern Cooperative Oncology Group performance status; IC: intracranial; INV, investigator; (m)RECIST 1.1, (modified) Response Evaluation Criteria in Solid Tumors version 1.1; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; QoL, quality of life; R, randomized; RANO-BM, Response Assessment in Neuro-Oncology – Brain Metastases criteria; TTR, time to response

Study Conduct and Disposition

4

Screened N=680

Screen failures, n=241
 Did not meet eligibility criteria, n =214
 Withdrew informed consent, n=18
 Other, n=9

Enrolled N=439

R 1:1

Zorifertinib 200 mg BID N=220

First-generation EGFR-TKI N=219
Gefitinib 250 mg QD, n=211
Erlotinib 150 mg QD, n=8

Did not receive treatment, n=1
 Withdrew informed consent, n=1

Received assigned treatment N=220

Received assigned treatment N=218

Discontinued treatment, n=220
 Patient decision, n=25
 Adverse event, n=15
 Severe noncompliance, n=1
 PD, n=144
 Death not due to PD, n=6
 Symptomatic deterioration, n=3
 Other, n=26

Discontinued treatment, n=218
 Patient decision, n=14
 Adverse event, n=8
 PD, n=168
 Death not due to PD, n=1
 Symptomatic deterioration, n=9
 Other, n=18

Discontinued study, n=220
 Patient decision, n=13
 Lost to follow-up, n=5
 Death, n=90
 Other, n=112

Full analysis set: n=220
ITT population: n=220
Per-protocol set: n=211[*]
Safety analysis set: n=220[†]

Full analysis set: n=219
ITT population: n=219
Per-protocol set: n=214[*]
Safety analysis set: n=218[†]

Discontinued study, n=219
 Patient decision, n=21
 Adverse event, n=1
 Lost to follow-up, n=4
 Death, n=98
 Other, n=95

Enrollment: Feb 1, 2019, to Jan 12, 2021

58 sites: 41 in mainland China, 12 in South Korea, 4 in Taiwan China, 1 in Singapore

Analysis data cutoff date: July 12, 2022

Median follow-up duration: 20.4 months

*Fourteen patients in the intention-to-treat population were excluded from the per-protocol set: nine from the zorifertinib arm and five from the control arm. †One patient who did not receive control treatment (gefitinib) after randomization was excluded from the safety analysis set. ITT, intention-to-treat; PD, disease progression

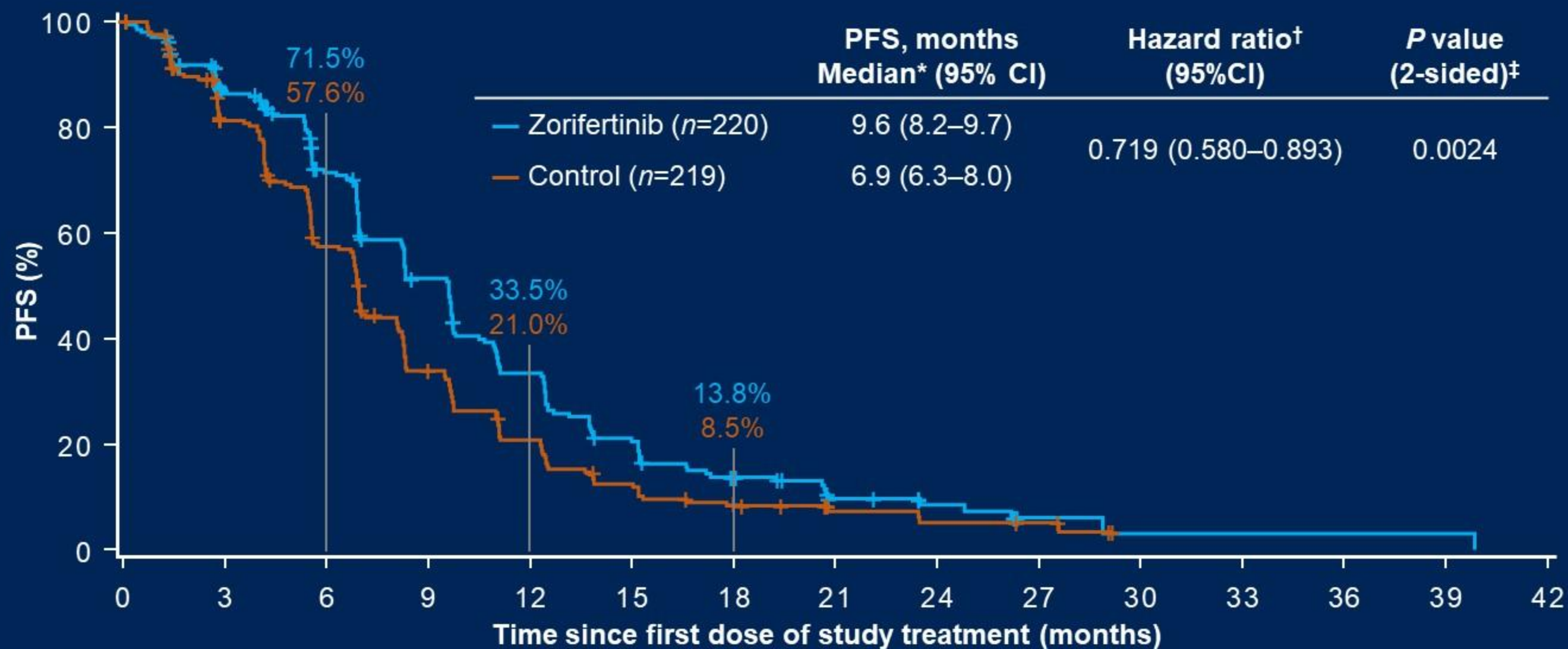Professor Yi-Long Wu

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Patient Baseline Characteristics

Data are *n* (%) unless stated otherwise		Zorifertinib N=220		Control N=219	
Age (years)	Median (range)	58.0	(34–84)	59.0	(33–82)
Sex	Male	80	(36.4)	78	(35.6)
	Female	140	(63.6)	141	(64.4)
Smoking status	Current/former	64	(29.1)	63	(28.8)
	Never	156	(70.9)	156	(71.2)
ECOG PS	0	49	(22.3)	50	(22.8)
	1	171	(77.7)	169	(77.2)
Geographic location	Mainland China	199	(90.5)	200	(91.3)
	Taiwan China	7	(3.2)	8	(3.7)
	South Korea	13	(5.9)	11	(5.0)
	Singapore	1	(0.5)	0	
Tumor histopathology	Adenocarcinoma	218	(99.1)	209	(95.4)
	Squamous cell carcinoma	1	(0.5)	1	(0.5)
	Adenosquamous cell carcinoma	1	(0.5)	5	(2.3)
	Others*	0		4	(1.8)
EGFR mutation	Exon 19Del	101	(46.0)	98	(44.7)
	L858R	118	(53.6)	120	(54.8)
	Co-mutations of Exon 19Del and L858R	1	0.5	1	0.5
No. of IC lesions#	0	3	(1.4)	1	(0.5)
	1	51	(23.2)	49	(22.4)
	2-3	44	(20.0)	55	(25.1)
	>3	122	(55.5)	114	(52.1)
Patients with LM#		18	(8.2)	18	(8.2)
Patients with IC target lesion#		144	(65.5)	137	(62.6)

*The histopathologic classification for 4 patients was NSCLC (*n*=2), adenocarcinoma or adenosquamous cell carcinoma (*n*=1), and poorly differentiated cancer (NSCLC; *n*=1).
#Assessed by BICR. LM, leptomeningeal metastases; IC: intracranial; IQR, interquartile ratio

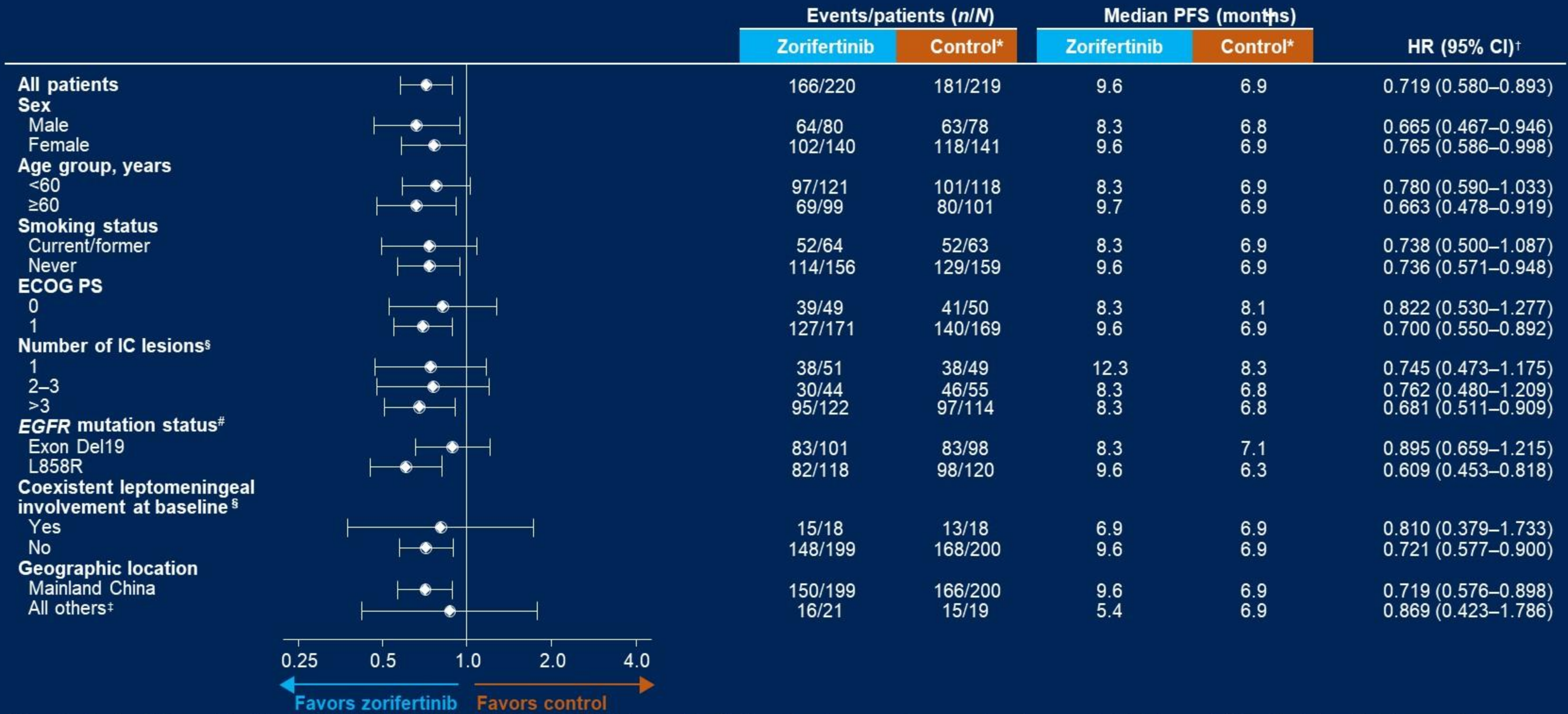# Primary Endpoint: PFS Assessed by BICR per RECIST 1.1 (ITT)

	PFS, months Median* (95% CI)	Hazard ratio[†] (95%CI)	P value (2-sided)[‡]
Zorifertinib (n=220)	9.6 (8.2–9.7)	0.719 (0.580–0.893)	0.0024
Control (n=219)	6.9 (6.3–8.0)		

71.5%
57.6%

33.5%
21.0%

13.8%
8.5%

PFS (%) axis: 100, 80, 60, 40, 20, 0

Time since first dose of study treatment (months) axis: 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42

No. at risk (no. censored)

Zorifertinib	220 (0)	169 (23)	130 (34)	90 (38)	57 (40)	34 (41)	20 (44)	10 (49)	7 (51)	2 (54)	1 (54)	1 (54)	1 (54)	1 (54)	0 (54)
Control	219 (0)	162 (18)	112 (21)	63 (25)	38 (26)	22 (27)	13 (29)	7 (34)	5 (34)	4 (35)	0 (38)	0 (38)	0 (38)	0 (38)	0 (38)

*Based on Kaplan–Meier analysis. †Based on stratified Cox model. ‡Based on stratified log-rank test. BICR, blinded independent central review. ITT, Intention to Treat
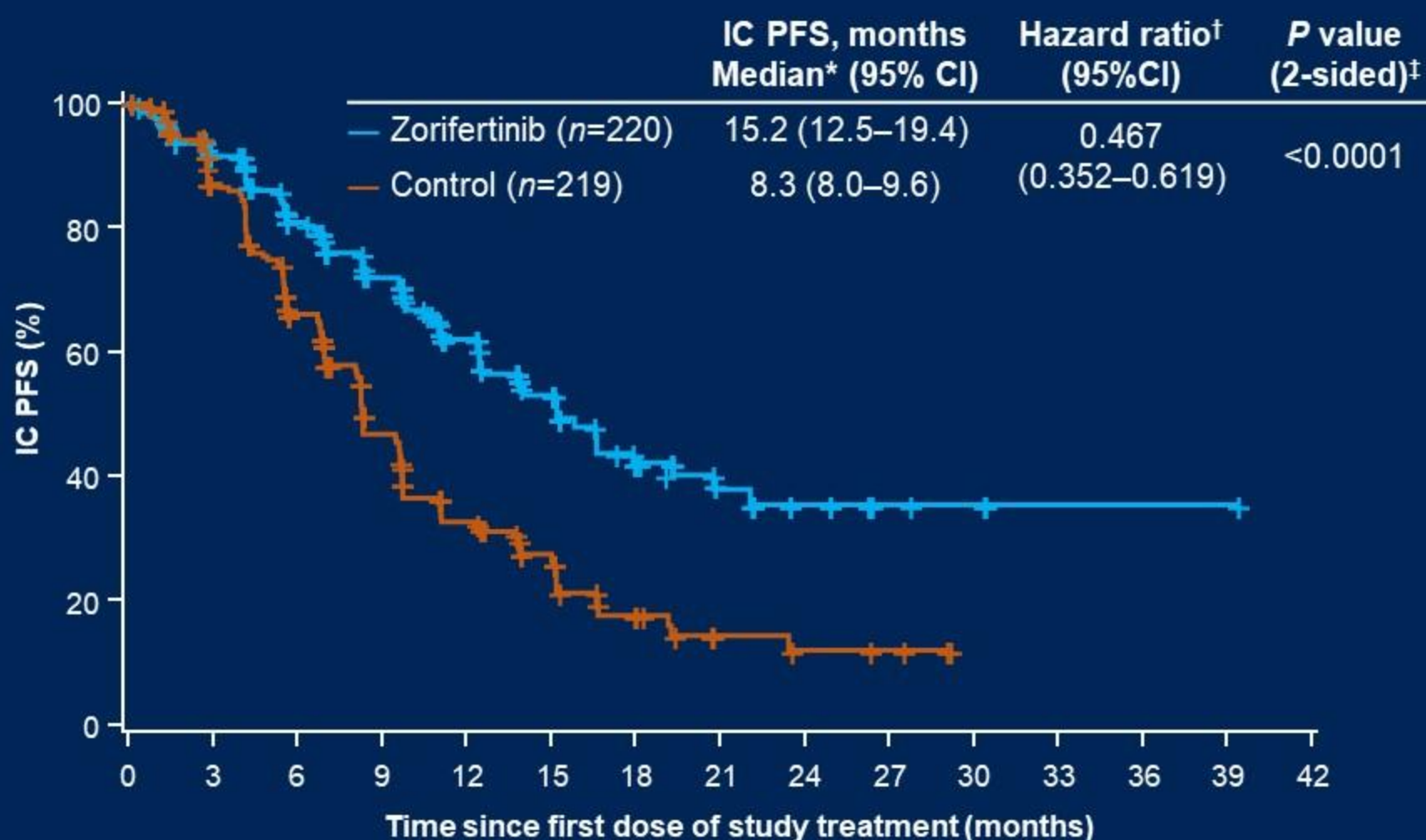
Subgroup Analyses of PFS

	Events/patients (n/N)		Median PFS (months)		HR (95% CI)†
	Zorifertinib	Control*	Zorifertinib	Control*	
All patients	166/220	181/219	9.6	6.9	0.719 (0.580–0.893)
Sex					
Male	64/80	63/78	8.3	6.8	0.665 (0.467–0.946)
Female	102/140	118/141	9.6	6.9	0.765 (0.586–0.998)
Age group, years					
<60	97/121	101/118	8.3	6.9	0.780 (0.590–1.033)
≥60	69/99	80/101	9.7	6.9	0.663 (0.478–0.919)
Smoking status					
Current/former	52/64	52/63	8.3	6.9	0.738 (0.500–1.087)
Never	114/156	129/159	9.6	6.9	0.736 (0.571–0.948)
ECOG PS					
0	39/49	41/50	8.3	8.1	0.822 (0.530–1.277)
1	127/171	140/169	9.6	6.9	0.700 (0.550–0.892)
Number of IC lesions§					
1	38/51	38/49	12.3	8.3	0.745 (0.473–1.175)
2–3	30/44	46/55	8.3	6.8	0.762 (0.480–1.209)
>3	95/122	97/114	8.3	6.8	0.681 (0.511–0.909)
EGFR mutation status#					
Exon Del19	83/101	83/98	8.3	7.1	0.895 (0.659–1.215)
L858R	82/118	98/120	9.6	6.3	0.609 (0.453–0.818)
Coexistent leptomeningeal involvement at baseline §					
Yes	15/18	13/18	6.9	6.9	0.810 (0.379–1.733)
No	148/199	168/200	9.6	6.9	0.721 (0.577–0.900)
Geographic location					
Mainland China	150/199	166/200	9.6	6.9	0.719 (0.576–0.898)
All others‡	16/21	15/19	5.4	6.9	0.869 (0.423–1.786)

0.25 0.5 1.0 2.0 4.0

← Favors zorifertinib   Favors control →

*Based on Kaplan–Meier analysis. †Hazard ratio for all patients was based on a stratified Cox model, while those for subgroup analyses were based on an unstratified Cox model. §3 patients in zorifertinib arm and 1 patient in control arm had no IC lesions assessed by BICR. #One patient in each of the treatment arms harbored co-mutations of Exon 19Del and L858R, HR was not evaluable; PFS of the patient with zorifertinib was 17.2months, PFS of the patient with control was censored and it was 8.9months to the time of censor. ‡Zorifertinib: 13 patients from South Korea, 7 from Taiwan China, and 1 from Singapore; control: 11 patients from South Korea and 8 from Taiwan China. IC: intracranial.

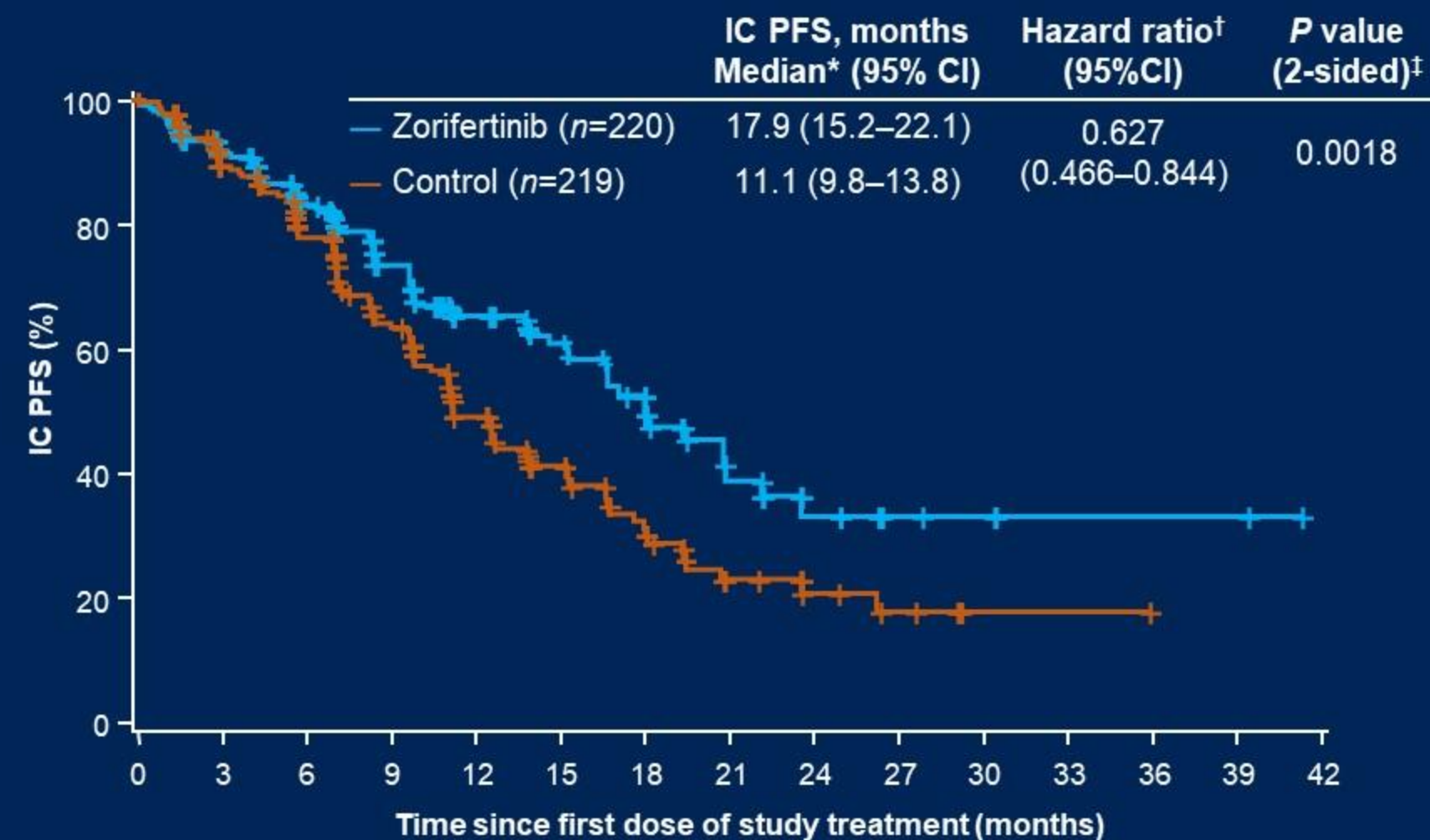# Intracranial PFS: Significantly Longer with Zorifertinib vs Control

BICR-assessed per mRECIST 1.1

	IC PFS, months Median* (95% CI)	Hazard ratio[†] (95%CI)	P value (2-sided)[‡]
— Zorifertinib (n=220)	15.2 (12.5–19.4)	0.467 (0.352–0.619)	<0.0001
— Control (n=219)	8.3 (8.0–9.6)		

No. at risk (no. censored)

Zorifertinib 220 (0) 172 (31) 137 (47) 102 (68) 70 (87) 44 (104) 26 (114) 15 (123) 9 (128) 4 (133) 3 (134) 1 (136) 1 (136) 1 (136) 0 (137)

Control 219 (0) 165 (28) 115 (39) 70 (53) 42 (61) 28 (69) 13 (75) 6 (80) 4 (81) 3 (82) 0 (85) 0 (85) 0 (85) 0 (85) 0 (85)

INV-assessed per RANO-BM

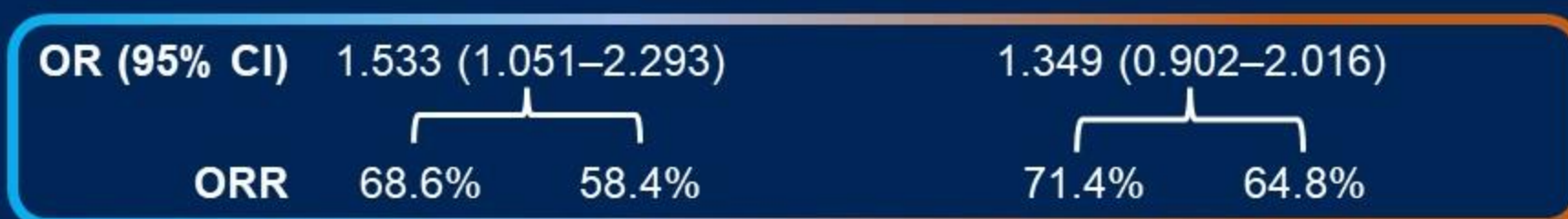|	IC PFS, months Median* (95% CI)	Hazard ratio[†] (95%CI)	P value (2-sided)[‡]
— Zorifertinib (n=220)	17.9 (15.2–22.1)	0.627 (0.466–0.844)	0.0018
— Control (n=219)	11.1 (9.8–13.8)		

No. at risk (no. censored)

Zorifertinib 220 (0) 174 (29) 143 (45) 104 (69) 71 (91) 50 (108) 27 (122) 17 (128) 10 (133) 5 (138) 4 (139) 2 (141) 2 (141) 2 (141) 0 (143)

Control 219 (0) 171 (27) 134 (43) 96 (58) 61 (73) 41 (84) 24 (91) 13 (97) 8 (101) 5 (103) 1 (107) 1 (107) 0 (108) 0 (108) 0 (108)

*Based on Kaplan–Meier analysis. [†]Based on the stratified Cox model. [‡]Based on stratified log-rank test. BICR, blinded independent central review; IC, intracranial; INV, investigator; mRECIST 1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; RANO-BM, Response Assessment in Neuro-Oncology – Brain Metastases criteria.

# Confirmed Overall ORR and DoR by BICR and INV per RECIST 1.1

OR (95% CI)	1.533 (1.051–2.293)		1.349 (0.902–2.016)	
ORR	68.6%	58.4%	71.4%	64.8%

Proportion (%): 80, 70, 60, 50, 40, 30, 20, 10, 0

n=1

Zorifertinib n=150, Control n=128 — BICR per RECIST 1.1
Zorifertinib n=157, Control n=142 — INV per mRECIST 1.1

CR
PR
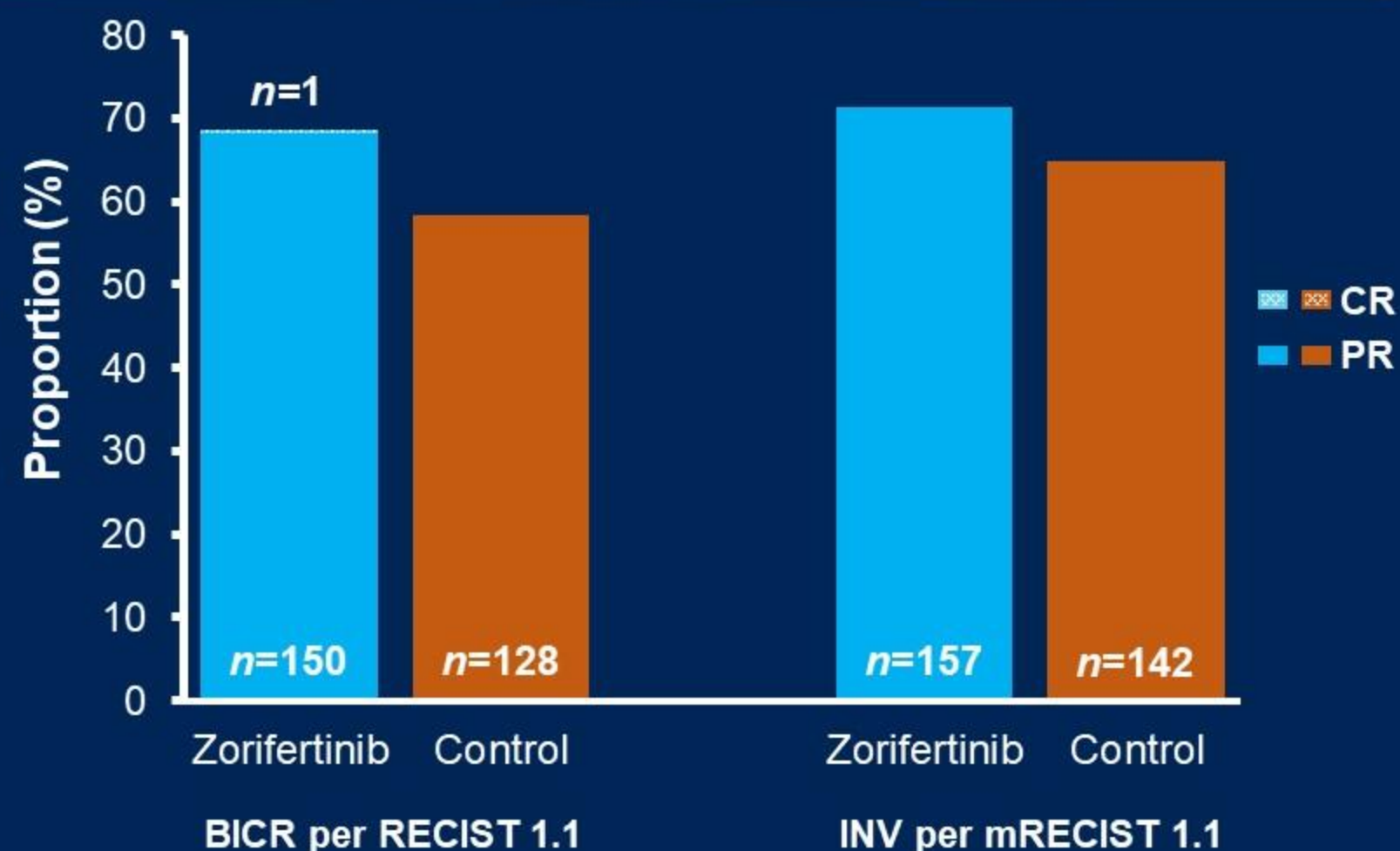
	BICR per RECIST 1.1		INV per RECIST 1.1	
	Zorifertinib (N=220)	Control (N=219)	Zorifertinib (N=220)	Control (N=219)
Median DoR (95% CI), months	8.2 (6.9–8.3)	6.8 (5.6–7.0)	9.7 (8.5–12.4)	8.4 (7.6–9.7)
Hazard ratio (95% CI)	0.801 (0.613–1.047)		0.817 (0.628–1.602)	
P value (2-sided)	0.0997		0.1276	

BICR, blinded independent central review; CI, confidence interval; INV, investigator; OR, odds ratio; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Confirmed Intracranial ORR and DoR Assessed by INV per RANO-BM and by BICR per mRECIST 1.1*

OR (95% CI)	1.904 (1.098–3.302)		1.658 (0.993–2.768)	
ORR	75.6%	62.3%	75.0%	64.2%

Legend: CR, PR
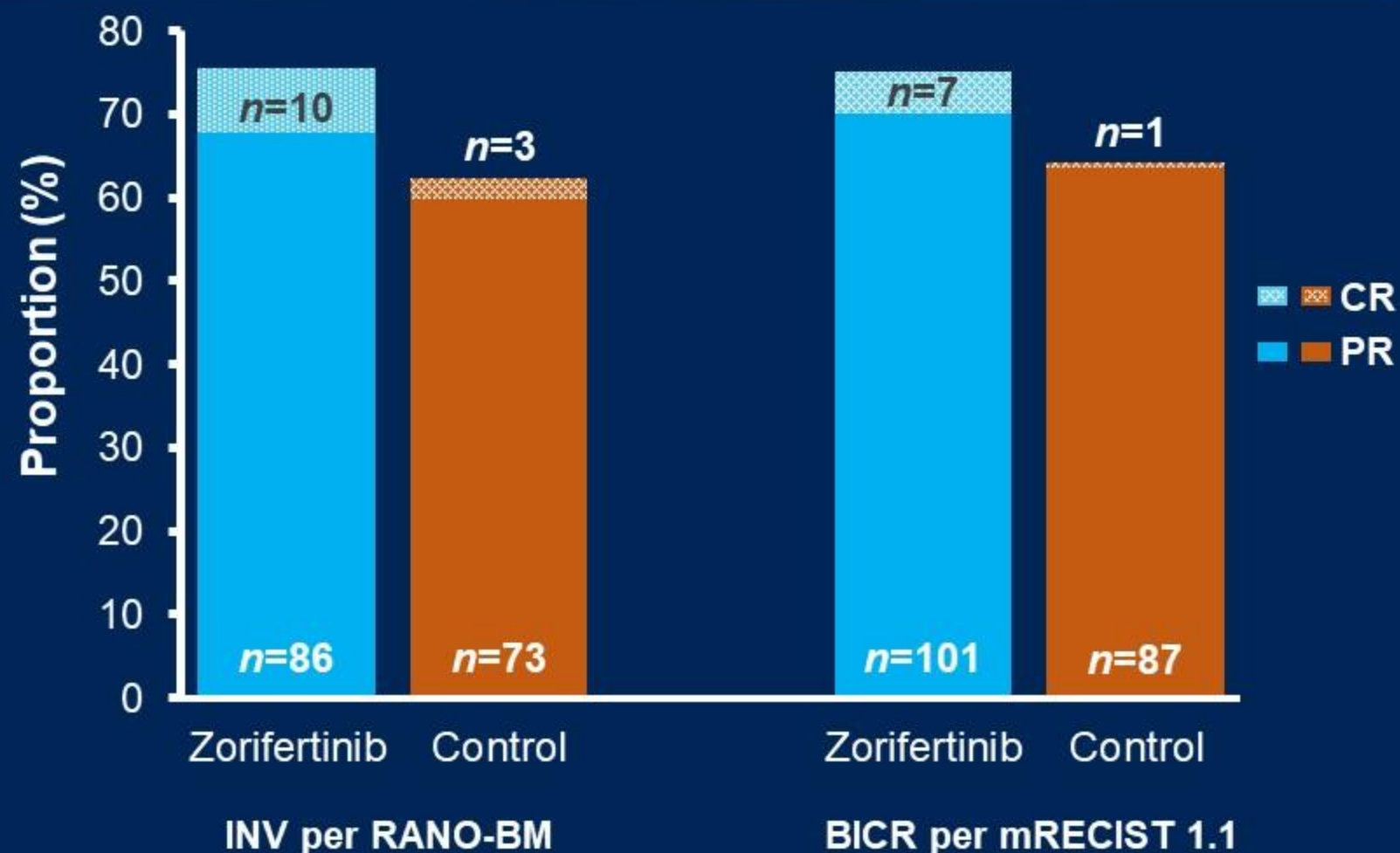
	INV per RANO-BM		BICR per mRECIST 1.1	
	Zorifertinib (*N*=220)	Control (*N*=219)	Zorifertinib (*N*=220)	Control (*N*=219)
Median DoR (95% CI), months	13.8 (8.5–22.1)	11.1 (8.3–14.0)	12.4 (9.6–19.4)	7.0 (6.9–9.7)
Hazard ratio (95% CI)	0.789 (0.501–1.244)		0.521 (0.352–0.773)	
P value (2-sided)	0.3037		0.0009	

*IC lesions were evaluated separately per RECIST 1.1. BICR, blinded independent central review; CI, confidence interval; INV, investigator; mRECIST 1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; OR, odds ratio; RANO-BM, Response Assessment in Neuro-Oncology – Brain Metastases criteria.

Drug-Resistance-Associated Biomarkers (Exploratory)*

- EGFR T790M mutation was the most common secondary resistance mutation

Data are n (%)	Zorifertinib (N=24)		Control (N=25)	
EGFR-T790M	8	(33.3)	3	(12.0)
EGFR-T790M with 19Del	5	(20.8)	0	
EGFR-T790M with L858R	3	(12.5)	0	
EGFR-T790M with exon 19 complex mutation	0		2	(8.0)
EGFR-T790M	0		1	(4.0)
EGFR exon 19 complex mutation	0		1	(4.0)

*Total population from the entire phase 2–3 study (NCT03653546).

Safety: TRAEs in ≥20% (Any Grade) or ≥2% (Grade ≥3) of Patients

TRAEs n (%)	Zorifertinib (N=220) Grade				Control (N=218) Grade			
	All	3	4	5	All	3	4	5
Any	215 (97.7)	139 (63.2)	5 (2.3)	1 (0.5)*	205 (94.0)	38 (17.4)	2 (0.9)	0
AST increased	152 (69.1)	14 (6.4)	1 (0.5)	0	121 (55.5)	16 (7.3)	0	0
ALT increased	145 (65.9)	23 (10.5)	1 (0.5)	0	123 (56.4)	22 (10.1)	1 (0.5)	0
Diarrhea	140 (63.6)	29 (13.2)	0	0	87 (39.9)	1 (0.5)	0	0
Rash	123 (55.9)	30 (13.6)	0	0	82 (37.6)	1 (0.5)	0	0
Decreased appetite	85 (38.6)	10 (4.5)	0	0	26 (11.9)	0	0	0
Blood bilirubin increased	80 (36.4)	4 (1.8)	0	0	37 (17.0)	1 (0.5)	0	0
Dermatitis acneiform	74 (33.6)	30 (13.6)	0	0	40 (18.3)	1 (0.5)	0	0
Paronychia	65 (29.5)	3 (1.4)	0	0	28 (12.8)	0	0	0
Proteinuria	56 (25.5)	0	0	0	19 (8.7)	0	0	0
Weight decreased	52 (23.6)	3 (1.4)	0	0	8 (3.7)	0	0	0
Alopecia	51 (23.2)	0	0	0	18 (8.3)	0	0	0
Stomatitis	48 (21.8)	9 (4.1)	0	0	11 (5.0)	0	0	0
Vomiting	44 (20.0)	4 (1.8)	0	0	13 (6.0)	0	0	0
γ-GT increased	42 (19.1)	12 (5.5)	2 (0.9)	0	27 (12.4)	5 (2.3)	0	0
Blood ALP increased	36 (16.4)	9 (4.1)	0	0	15 (6.9)	0	0	0
Hypokalemia	30 (13.6)	13 (5.9)	1 (0.5)	0	7 (3.2)	0	0	0
ECG QT prolonged	26 (11.8)	8 (3.6)	0	0	23 (10.6)	3 (1.4)	0	0

- All TRAEs were on-target:
  - Rates of rash and diarrhea were higher with zorifertinib vs control
  - Rates of AST and ALT increased were comparable between the two treatment arms

- No CNS-related safety signals

- AESIs:
  - Confirmed ILD: 0 (zorifertinib) vs 2 (control)
  - Hy's law: 1 (zorifertinib) vs 2 (control); all recovered

*One death was categorized as being related to zorifertinib because the investigator was unable to determine unequivocally the underlying reason. AESI, adverse event of special interest; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma glutamyltransferase; ILD, interstitial lung disease; TRAE, treatment-related adverse event.

Safety: Summary of Adverse Events Leading to Dose Discontinuation, and TRAEs Leading to Dose Modification in ≥5% of Patients

Adverse event summary, n (%)	Zorifertinib N=220		Control N=218	
Patients with any TEAE leading to permanent discontinuation of study treatment	16	(7.3)	8	(3.7)
Patients with any TRAE leading to permanent discontinuation of study treatment	13	(5.9)	5	(2.3)
Patients with any TEAE leading to dose modification of study treatment	160	(72.7)	42	(19.3)
Patients with any TRAE leading to dose modification of study treatment	155	(70.5)	38	(17.4)
TRAEs leading to dose modification of study treatment in ≥5% of patients				
Rash	39	(17.7)	1	(0.5)
Diarrhea	38	(17.3)	1	(0.5)
Dermatitis acneiform	33	(15.0)	3	(1.4)
ALT increased	31	(14.1)	26	(11.9)
AST increased	30	(13.6)	23	(10.6)
Decreased appetite	18	(8.2)	0	
Blood bilirubin increased	14	(6.4)	1	(0.5)

- Incidences of TRAEs leading to permanent discontinuation of study treatment were all <1%

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

- AZD3759-003 (EVEREST) is the first randomized, controlled, open-label, multinational study designed specifically to address an unmet medical need for patients with *EGFR*m$^+$ NSCLC and CNS metastases

- First-line zorifertinib demonstrated superior systemic and IC antitumor efficacy compared with first-generation EGFR-TKIs, significantly prolonging overall and IC PFS

- The PFS benefit with zorifertinib was consistent across all subgroups analyzed, including patients harboring *EGFR* L858R mutations and those with a higher IC tumor burden

- The safety profile of zorifertinib was as expected (most commonly rash, diarrhea, and abnormal liver function) and manageable; no new safety signals were identified

- Zorifertinib provides a novel, well-validated, first-line option for patients with *EGFR*m$^+$ NSCLC and CNS metastases

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