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Zipalertinib Plus Chemotherapy for 1st Line NSCLC With *EGFR* Exon 20 Insertions: Results From the Phase 3 Trial (REZILIENT 3)

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Disclosures

- Consultant: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, DKSH, GlaxoSmithKline, Merck, Novartis, Pfizer, Roche, Beigene, Zymeworks, Genmab, Astellas, and Takeda
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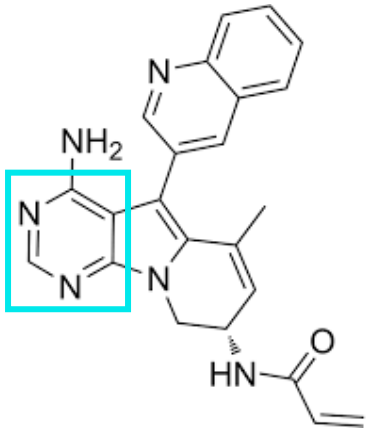
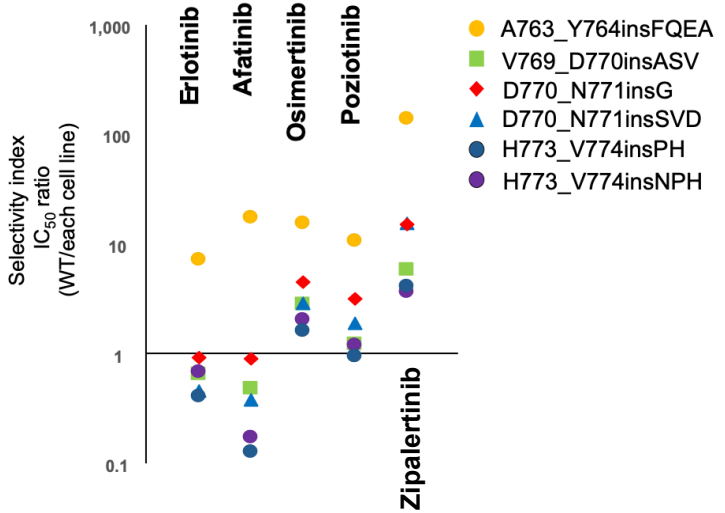
- Advisor/Stock options: PRISM.AI and T-Knife Therapeutics
- Board/Directorship: HutchMed and Epoch Biosciences

Background

- **NSCLC with *EGFR* exon 20 insertions (ex20ins)** comprise 5–10% of *EGFR* mutations and represents a heterogeneous molecular subgroup with variable responses to EGFR-directed therapies[1]
- Amivantamab (1L in combination with platinum-based chemotherapy) and sunvozertinib have shown improved PFS vs chemotherapy in randomized trials[2,3]
- **Zipalertinib (TAS6417, CLN-081) is a TKI with high selectivity to EGFR with ex20ins** compared with wild-type EGFR



- ➢ Unique pyrrolopyrimidine scaffold
- ➢ Irreversible covalent bond with C797
- ➢ High selectivity over wild type
- ➢ In phase I/II studies, demonstrated clinical activity (including CNS and post-amivantamab)[4]



1L, first-line; CNS, central nervous system; EGFR, epidermal growth factor receptor; IC_{50}, half maximal inhibitory concentration; NSCLC, non–small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; WT, wild-type.

1. Lau ELY, et al. *Drugs*. 2026;86:1075–90. 2. Zhou C, et al. *N Engl J Med*. 2023;389:2039–51. 3. Zhou C, et al. *N Engl J Med*. 2026;395:765–75.
4. Piotrowska Z, et al. *J Clin Oncol*. 2025;43:2387–97.

REZILIENT 3: 1L Zipalertinib + Chemotherapy vs Chemotherapy

REZILIENT :**Re**searching **Zi**pa**l**ertinib **i**n ***E****GFR*mt **N**on–Small Cell Lung Cancer **T**umors

Eligibility criteria:

- 1L metastatic NSCLC
- **Local testing** of *EGFR*mt ex20ins for eligibility
- ECOG PS 0 or 1
- Stable brain metastases permitted
- Archival tissue available

Safety Lead-in
(N=6)

Zipalertinib (100 mg BID)
+
Pemetrexed/Platinum
(Carboplatin or cisplatin)

Safety lead-in completed:
Combination safe to proceed as assessed by IDMC

Randomized Phase 3 Study (NCT05973773)
(N=280)

R

- **Zipalertinib + Pemetrexed/Platinum** (Carboplatin or cisplatin)
- **Pemetrexed/Platinum** (Carboplatin or cisplatin) → Optional Cross-over → **Zipalertinib**

Stratification factors:

- ECOG PS
- Brain metastases (Yes/No)
- Region (Asia/Non-Asia)

Primary:

- **PFS by BICR**

Secondary

- OS
- PFS (investigator)
- ORR
- DoR
- Safety
- PROs

- 122 clinical sites globally
- Study overseen by IDMC

Primary analysis: at 162 PFS events to detect HR 0.60, 2-sided α: 0.05, 90% power

Pre-specified interim analysis:

- At 122 PFS events (data cutoff date May 29, 2026)
- If one-sided P<0.0098, superiority to be claimed

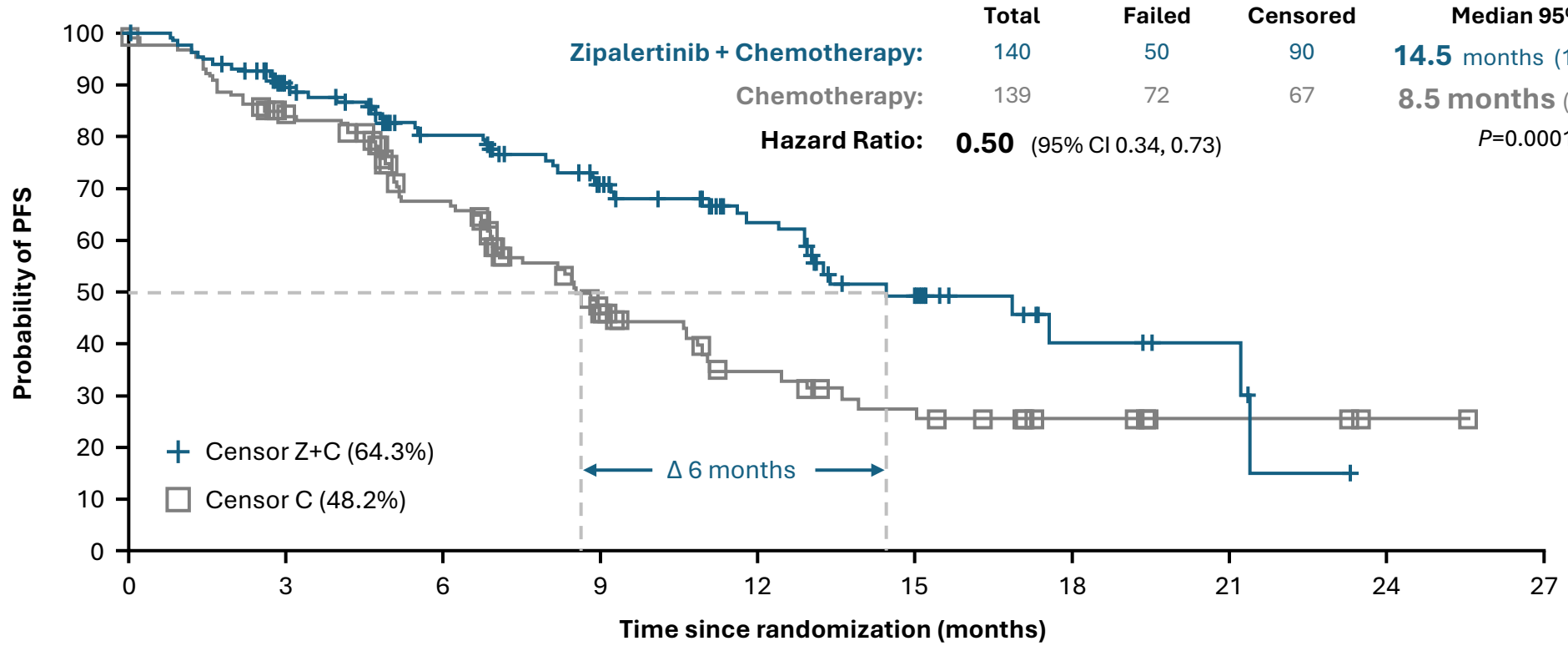
1L, first line; BICR, blinded independent central review; BID, twice daily; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*mt, epidermal growth factor receptor mutant; ex20ins, exon 20 insertions; HR, hazard ratio; IDMC, Independent Data Monitoring Committee; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcome; R, randomization.

REZILIENT 3: Baseline Characteristics

Characteristics	Zipalertinib + Chemotherapy (n=140)	Chemotherapy (n=139)
Median Age (min–max)	66.5 (30–89)	64.0 (27–82)
Female, n (%)	92 (65.7)	88 (63.3)
Never Smoker	83 (59.3)	85 (61.2)
Region per IVRS, n (%)		
Asia	56 (40.0)	56 (40.3)
Rest of world	84 (60.0)	83 (59.7)
ECOG PS, n (%)		
0/1	58 (41.4)/82 (58.5)	56 (40.3)/83 (57.6)
Histology, n (%)		
Adenocarcinoma	136 (97.1)	135 (97.1)
Other/non-squamous	4 (2.9)	4 (2.9)
Baseline Brain Metastasis, n (%)	44 (31.4)	44 (31.7)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; IVRS, interactive voice response system.

REZILIENT 3: Primary Endpoint PFS by BICR

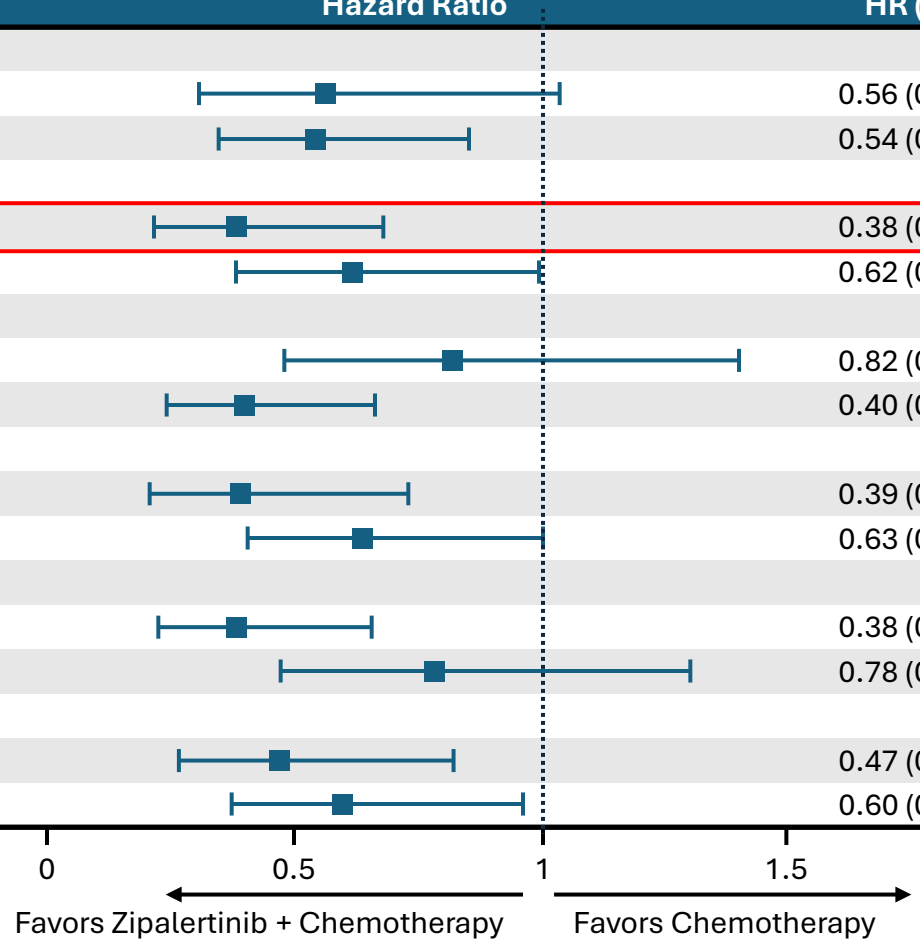


Number at risk										
Zipalertinib + chemotherapy	140	109	81	59	40	22	7	4	0	
Chemotherapy	139	102	73	36	20	14	6	3	1	0

BICR, blinded independent central review; C, chemotherapy; CI, confidence interval; NE, not estimable; PFS, progression-free survival; Z+C, zipalertinib + chemotherapy.

REZILIENT 3: BICR PFS by Subgroups

Subgroup	Zipalertinib + Chemotherapy Event n/N (%)	Chemotherapy Event n/N (%)	HR (95% CI)
Baseline ECOG PS			
0	18/58 (31.0)	24/56 (42.9)	0.56 (0.30, 1.04)
1	32/82 (39.0)	48/83 (57.8)	0.54 (0.34, 0.85)
Brain Metastases			
Yes	21/44 (47.7)	30/44 (68.2)	0.38 (0.21, 0.67)
No	29/96 (30.2)	42/95 (44.2)	0.62 (0.38, 0.99)
Region			
Asia	26/56 (46.4)	29/56 (51.8)	0.82 (0.48, 1.40)
ROW	24/84 (28.6)	43/83 (51.8)	0.40 (0.24, 0.66)
Sex			
Male	17/48 (35.4)	29/51 (56.9)	0.39 (0.21, 0.73)
Female	33/92 (35.9)	43/88 (48.9)	0.63 (0.40, 1.00)
Age			
<65	20/63 (31.7)	42/71 (59.2)	0.38 (0.22, 0.65)
≥65	30/77 (39.0)	30/68 (44.1)	0.78 (0.47, 1.30)
Smoking History			
Yes	21/57 (36.8)	30/54 (55.6)	0.47 (0.27, 0.82)
No	29/83 (34.9)	42/85 (49.4)	0.60 (0.37, 0.96)



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; ROW, rest of world.

REZILIENT 3: Tumor Response by BICR

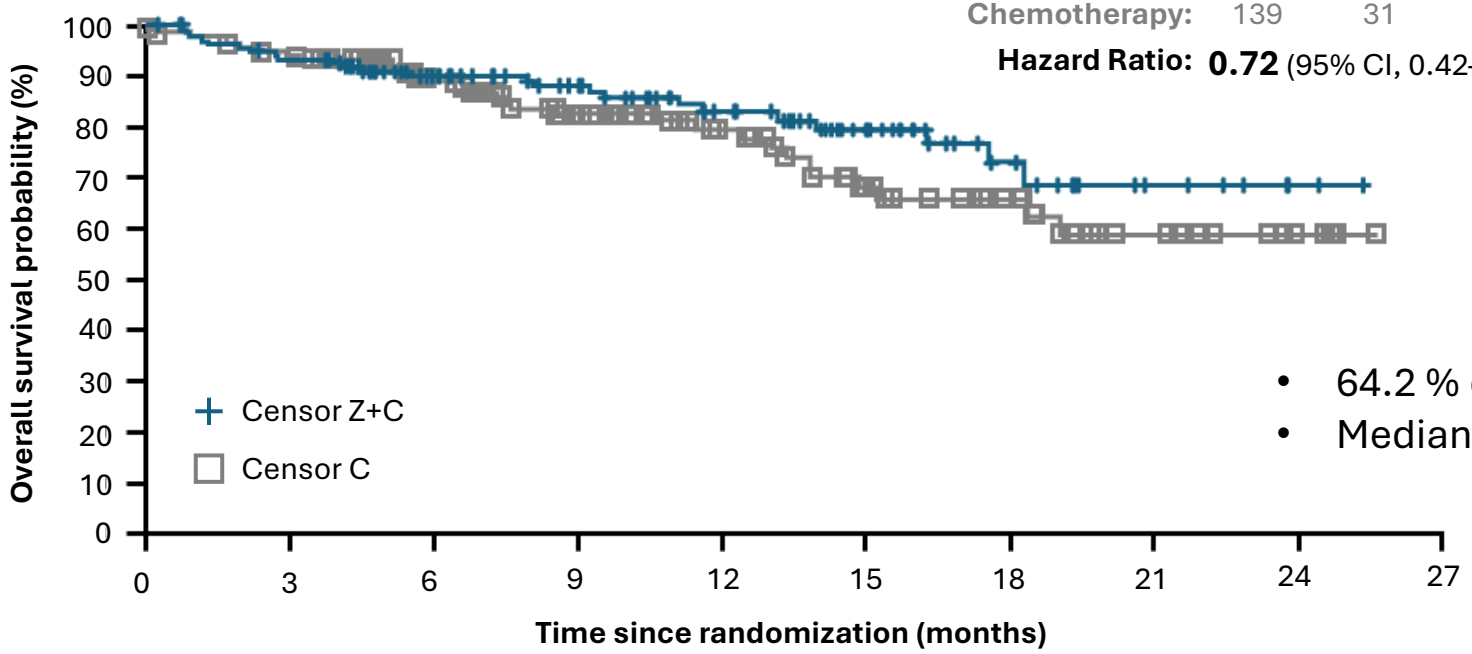
Response (RECIST v1.1)	**Zipalertinib + Chemotherapy** (n=140)	**Chemotherapy** (n=139)
Best Overall Response, n (%)		
Complete response	9 (6.4)	3 (2.2)
Partial response	82 (58.6)	53 (38.1)
Stable disease	29 (20.7)	55 (39.6)
Progressive disease	4 (2.9)	12 (8.6)
Objective Response Rate, % (95% CI)	**65.0** (56.49, 72.86)[a]	**40.3** (32.06, 48.94)
Disease Control Rate, % (95% CI)	**89.3** (82.94, 93.88)	**81.3** (73.81, 87.40)
Duration of Response	**Zipalertinib + Chemotherapy** (n=91)	**Chemotherapy** (n=56)
Duration of Response, median in months (95% CI)	**14.2** (10.51, NE)	**9.9** (6.80, NE)
Time to Response, median in months	1.4	2.6

[a]*P*-value <0.0001 vs chemotherapy alone.
BICR, blinded independent central review; CI, confidence interval; NE, not estimable; RECIST, response evaluation criteria in solid tumors.

REZILIENT 3: Overall Survival

	Total	Failed	Censored	Median 95% CI
Zipalertinib + chemotherapy:	140	24	116	NE (NE, NE)
Chemotherapy:	139	31	108	NE (18.4, NE)

Hazard Ratio: **0.72** (95% CI, 0.42–1.23) *P*=0.11082



- 64.2 % crossover to zipalertinib[a]
- Median follow-up 10.9 months

Number at risk

Zipalertinib + Chemotherapy	140	127	98	79	56	38	19	8	3	0
Chemotherapy	139	126	97	67	47	31	22	11	4	0

[a]Based on 53 patients with progressive disease, of whom 34 crossed over.
C, chemotherapy; NE, not estimable; Z+C, zipalertinib + chemotherapy.

REZILIENT 3: Safety Summary

	Zipalertinib + Chemotherapy (n=140), n (%)	Chemotherapy (n=136), n (%)
Treatment-Related Adverse Events	138 (98.6)	120 (88.2)
Grade ≥3 treatment-related adverse events	113 (80.7)	55 (40.4)
Serious Adverse Events	71 (50.7)	45 (33.1)
Treatment-related serious adverse events	53 (37.9)	17 (12.5)

	Zipalertinib	Pemetrexed	Carbo/ cisplatin	Pemetrexed	Carbo/ cisplatin
AE Leading to Treatment Interruption	116 (82.9)	104 (74.3)	70 (50)	60 (44.1)	40 (29.4)
AE Leading to Dose Reductions	61 (43.6)	68 (48.6)	46 (32.9)	29 (21.3)	21 (15.4)
AE Leading to Drug Discontinuation[a]	24 (17.1)	44 (31.4)	22 (15.7)	16 (11.8)	7 (5.1)
Adverse Events With Outcome of Death[b]	13 (9.3)			4 (2.9)	
TRAE with outcome of death	3 (2.1)			0	
Sepsis/septic shock	3 (2.1)			0	
Chemotherapy Administration					
Platinum choice: Carboplatin/cisplatin	138/4[c]			123/14[c]	
Pemetrexed number of cycles (median , range)	7 (1-35)			8 (1-36)	

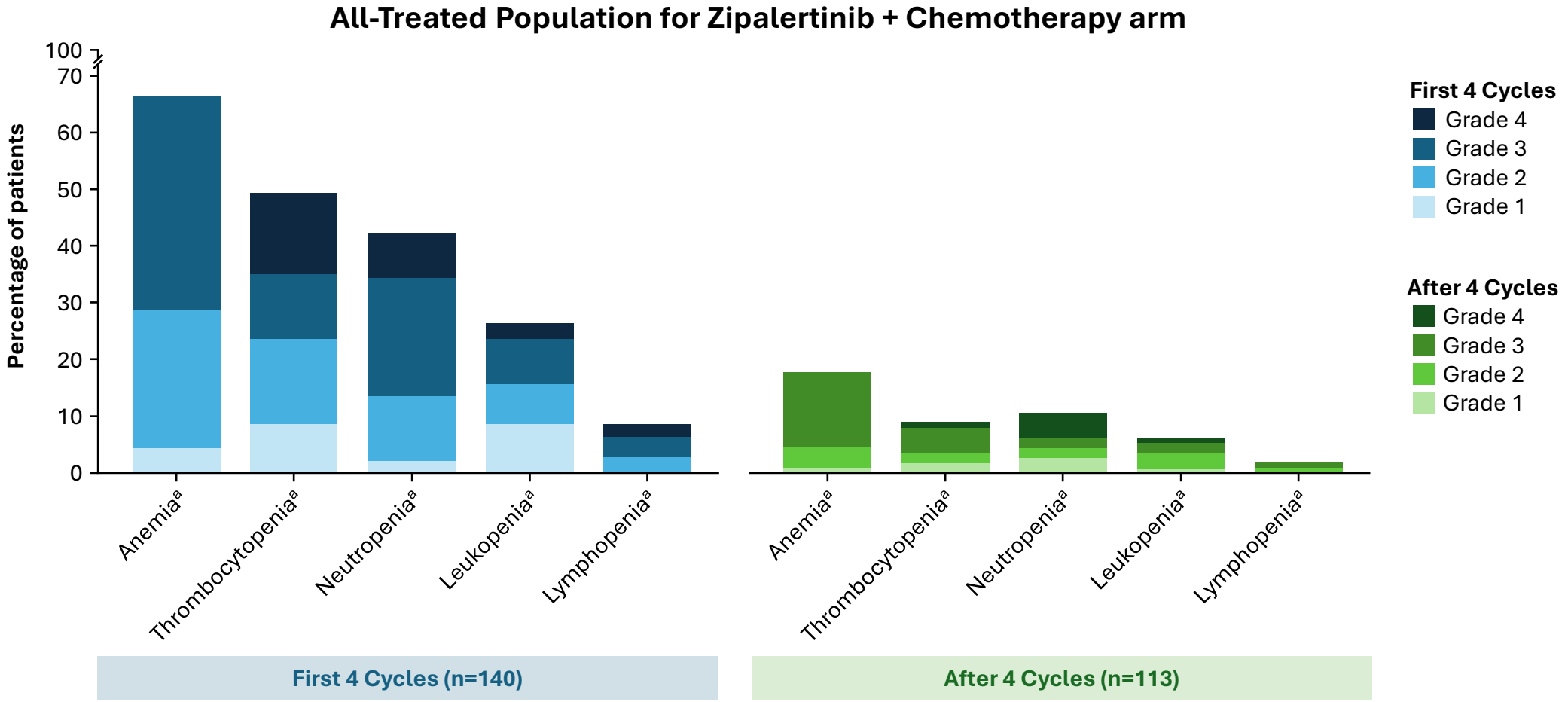
[a]Refers to the regimen where a component was the primary reason for treatment discontinuation.
[b]Death events were: Z+C: sepsis (3), pneumonia (1), respiratory tract infection (1), septic shock (1), acute respiratory failure (1), dyspnea (1), hemoptysis (1), respiratory failure (1), death (1), sudden death (1), diabetic ketoacidosis (1). C: sepsis (1), pneumonia (1), acute respiratory failure (1), cerebrovascular accident (1).
[c]Reflects some patients received both agents.
AE, adverse event; C, chemotherapy; Carbo, carboplatin; TRAE, treatment-related adverse event; Z+C, zipalertinib + chemotherapy.

REZILIENT 3: Summary of Adverse Events

	Zipalertinib + Chemotherapy (n=140)		Chemotherapy (n=136)	
Adverse Event in ≥25%[a], %	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Anemia[a]	80.7	**48.6**	50.0	**12.5**
Neutropenia[b]	50.7	**33.6**	40.4	**22.1**
Thrombocytopenia[c]	56.4	**30.0**	19.9	**8.1**
Rash	45.7	10.7	6.6	0
Nausea	44.3	3.6	41.9	0.7
Constipation	32.1	0	30.9	0
Paronychia	31.4	1.4	0	0
Stomatitis	28.6	5.0	7.4	0.7
Diarrhea	27.1	1.4	8.8	0
Pneumonitis[d]	5.7	2.1	2.2	1.5

[a]Includes anemia and/or reduced red blood cells. [b]Includes neutropenia and/or decreased neutrophils. [c]Includes thrombocytopenia and/or platelets decreased.
[d]Includes those with ≥25% and/or EGFR-associated toxicity. Pneumonits included as an EGFR-associated AE of interest though reported <25%.

REZILIENT 3: Cytopenias Observed With Combination



[a]Adverse events represent grouped terms (either blood term or lab term decreased).

Conclusions

- **REZILIENT-3 met its primary endpoint, with Zipalertinib and chemotherapy demonstrating statistically significant improvement in PFS compared to chemotherapy alone**
  - 6-month improvement in median PFS (**14.5 months vs 8.5 months**, HR of 0.5, *P*=0.00015)
  - Increased ORR (**65% vs 40.3%**, *P*<0.0001) with improved duration of response (14.2 m vs 9.9 m)

- **Although the combination resulted in more Grade 3 adverse events, these were largely related to cytopenias and associated sequelae**
  - Particularly observed in first 4 cycles during combination with platinum doublet;
  - Patient selection, dose modifications and supportive care measures

- **Zipalertinib in combination with platinum-based chemotherapy is a new highly efficacious option for frontline treatment of metastatic *EGFR* ex20ins-mut NSCLC**
  - Study ongoing to further characterize the AE profile and OS benefit
  - REZILENT 4 (NCT 07128199) Phase 3 study for adjuvant zipalertinib in early stage resected NSCLC with uncommon *EGFR*mt

AE, adverse event; EGFR, epidermal growth factor receptor; *EGFR*mt, epidermal growth factor receptor mutant; HR, hazard ratio; m, months; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Acknowledgments

- Trial participants, their families, and caregivers
- Investigators, team members and site staff (represents 122 sites across 24 countries in Asia, North America, South America, and Europe)
- Steering committee

Thank You.