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Safety and Antitumor Activity of Zipalertinib in NSCLC Patients With EGFR Exon 20 Insertion Mutations Who Received Prior Amivantamab

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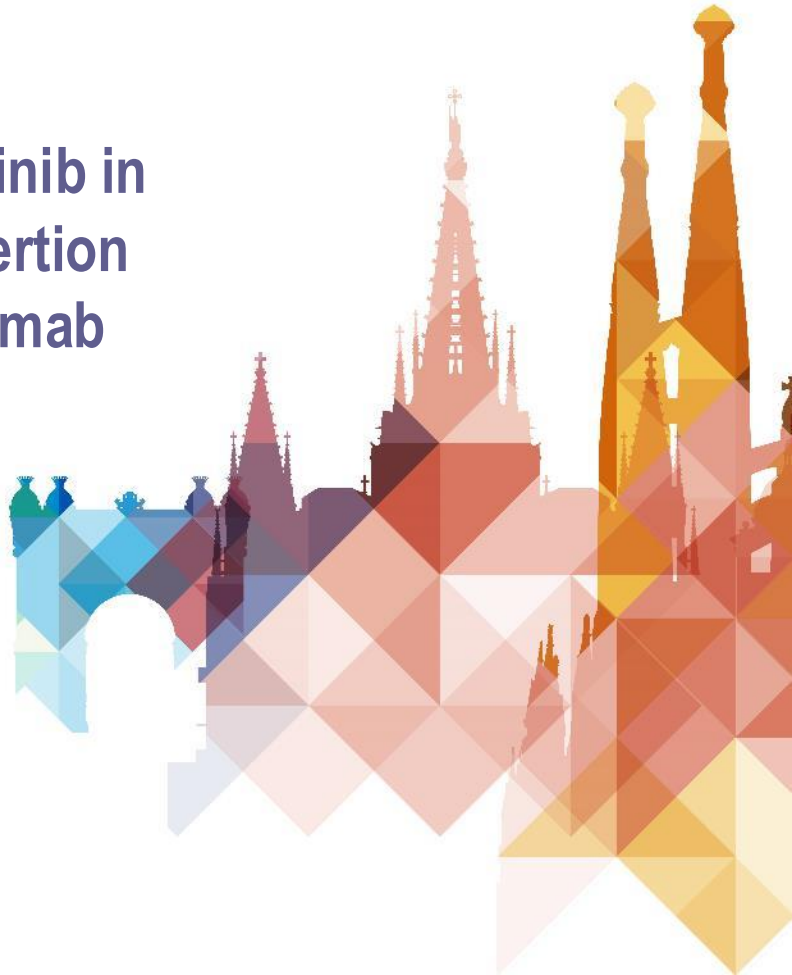


DECLARATION OF INTERESTS

Antonio Passaro, MD, PhD

- **Consultant/Advisory role:** AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Janssen/Johnson & Johnson, Gilead, GSK, Merck Sharp & Dohme, Mundipharma, Novartis, Pfizer, Roche/Genentech
- **Talk in a company's organized public event supported by**: AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, ecancer, Medscape, Takeda, Janssen/Johnson & Johnson, Merck Sharp & Dohme, PeerView, PeerVoice, touchONCOLOGY
- **Receipt of grants/research supports:** (Sub)investigator in trials (institutional financial support for clinical trials) sponsored by ArriVent, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cullinan Therapeutics, Daiichi Sankyo, Eli Lilly, Janssen/Johnson & Johnson, Merck Serono, Merck Sharp & Dohme, Mirati, MRC, Pfizer, Roche/Genentech, Summit Therapeutics
- **Non-financial interests:** ESMO Council Member as Communication Committee Chair and ESMO Faculty for Lung and Other Thoracic Tumours

REZILIENT1 Phase 2b Module C: Study Rationale and Design

- Zipalertinib, a novel irreversible and selective EGFR ex20ins TKI, has been granted Breakthrough Therapy Designation by the US FDA after demonstrating promising efficacy and favorable safety profile in a Phase 1/2a study (*JCO* 2023)
- Module C of this Phase 2b study investigates the efficacy and safety of zipalertinib in patients who progressed on or after amivantamab, a significant emerging unmet medical need (NCT04036682)

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Documented *EGFR* exon 20 insertion
- *Progressed on or after amivantamab*
- ECOG PS 0 or 1
- Stable/asymptomatic brain metastases allowed

→ **Zipalertinib**
100 mg BID oral[a]

[a]Zipalertinib may be taken with or without food

Primary endpoint:

- ORR and DOR per RECIST v1.1

Secondary endpoints:

- Safety
- PFS
- DCR

- At data cutoff on March 29, 2024, 45 patients were enrolled
- 30 patients were response evaluable (≥2 on-treatment tumor assessments or had disease progression/death)

BID, twice daily; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; US FDA, United States Food and Drug Administration.

Demographic and Baseline Disease Characteristics

Characteristics, n (%)	Ami only[a] (n=28)	Ami + other ex20ins[b] (n=17)	Total (N=45)
Median age, y (range)	62 (36–85)	63 (33–77)	62 (33–85)
Female	20 (71)	14 (82)	34 (76)
Race			
Asian	13 (46)	7 (41)	20 (44)
White	13 (46)	9 (53)	22 (49)
ECOG PS 1	19 (68)	12 (71)	31 (67)
Median prior systemic regimens, n (range)	2 (1–6)	4 (3–6)	3 (1–6)
Prior chemotherapy	26 (93)	17 (100)	43 (96)
Prior anti–PD-1/L1	9 (32)	11 (65)	20 (44)
Prior target therapy (non-ex20ins)	9 (32)	5 (30)	14 (31)
Prior amivantamab	28 (100)	17 (100)	45 (100)
Prior investigational ex20ins	0	17 (100)	17 (38)
History of brain metastases	15 (54)	7 (41)	22 (49)

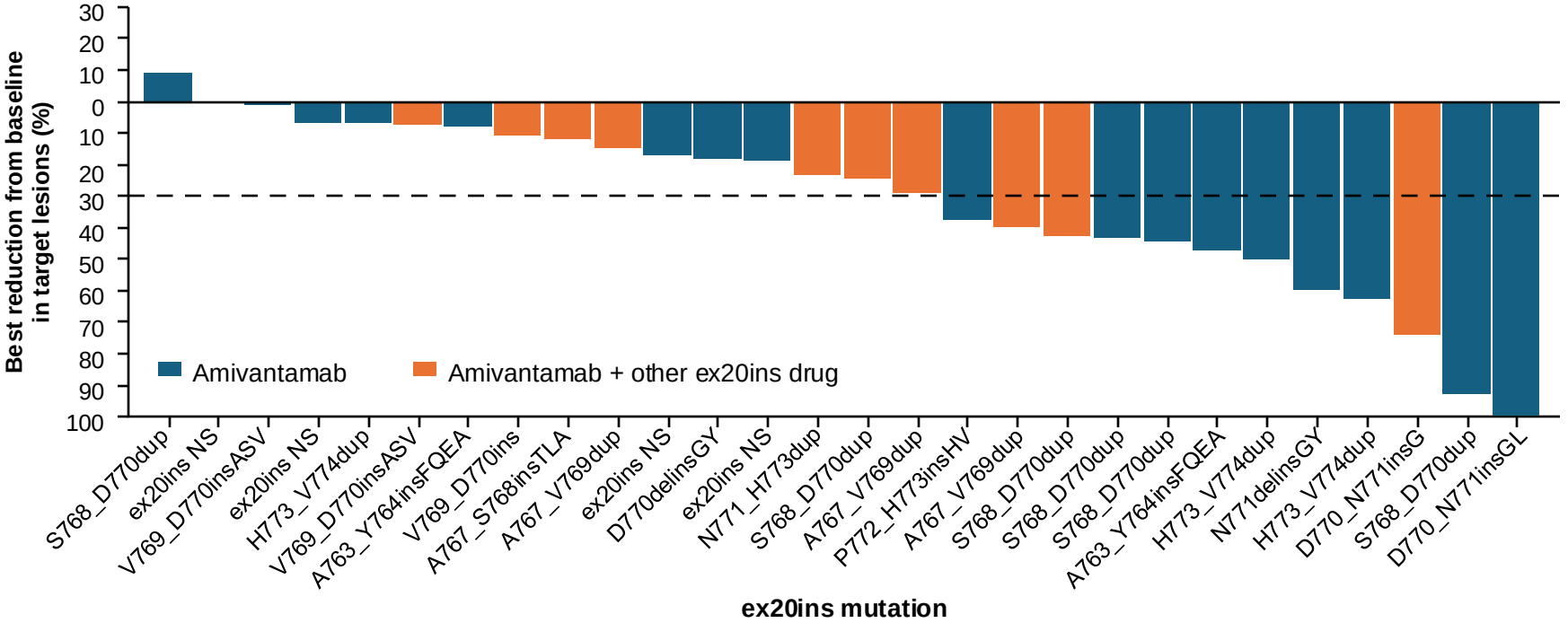
[a]Ami only: patients had amivantamab for ex20ins mutation–targeted treatment. [b]Ami + other ex20ins: patients had both amivantamab and other investigational ex20ins: mobocertinib, BLU-451, or poziotinib.

Objective Response Rate by Investigators

Statistics, n (%) [95% CI]	Ami only (n=18)	Ami + other ex20ins (n=12)	Total (N=30)
Confirmed ORR	9 (50.0) [26.0–74.0]	3 (25.0) [5.5–57.2]	12 (40.0) [22.7–59.4]
CR	1 (5.6) [0.1–27.3]	0	1 (3.3) [0.1–17.2]
PR	8 (44.4) [21.5–69.2]	3 (25.0) [5.5–57.2]	11 (36.7) [19.9–56.1]
SD	7 (38.9) [17.3–64.3]	8 (66.7) [34.9–90.1]	15 (50.0) [31.3–68.7]
DCR (CR+PR+SD)	16 (88.9) [65.3–98.6]	11 (91.7) [61.5–99.8]	27 (90.0) [73.5–97.9]

- Duration of response was NE (not estimable) at data cutoff
- Median PFS: 9.7 months (90% CI: 4.1–NE)
- Data on efficacy of brain metastases are not available at this data cutoff

Best Percentage Change From Baseline in Target Lesions and Confirmed Response by Investigators



Two patients died.
ex20ins NS: ex20ins mutation not specified.

Summary of Treatment-Related Adverse Events

TRAE ≥10%, n (%)	Ami only (n=28)	Ami + other ex20ins (n=17)	Total (N=45)
Rash	12 (43)	5 (29)	17 (38)
Paronychia	11 (39)	5 (29)	16 (36)
Anemia	6 (21)	5 (29)	11 (24)
Dry skin	5 (18)	4 (24)	9 (20)
Dermatitis acneiform	3 (11)	4 (24)	7 (16)
Nausea	4 (14)	3 (18)	7 (16)
Stomatitis	2 (7)	3 (18)	5 (11)

TRAE Grade ≥3 (≥2 patients), n (%)	Ami only (n=28)	Ami + other ex20ins (n=17)	Total (N=45)
Anemia	2 (7)	2 (12)	4 (9)
Rash	2 (7)	1 (6)	3 (7)
Pneumonitis/ILD	3 (11)	0	3 (7)
Dose reduction[a]	2 (7)	1 (6)	3 (7)
Dose discontinuation[b]	3 (11)	0	3 (7)

[a]Platelet count decrease, anemia, anemia/rash. [b]Pneumonitis/ILD.
ILD: interstitial lung disease; TRAE: treatment-related adverse event.

Antonio Passaro, MD, PhD

Conclusions

- This is the first presentation to systematically characterize the anti-tumor activity of zipalertinib, a new irreversible and selective EGFR ex20ins TKI, in heavily treated patients with NSCLC harboring *EGFR* ex20ins mutations who have received prior amivantamab
- Zipalertinib demonstrated promising efficacy in patients progressed on or after amivantamab:
  - ORR: 40%
  - PFS: 9.7 months
- Zipalertinib is well tolerated and demonstrated a manageable safety profile in patients who progressed on or after amivantamab. No new safety signals have been identified

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