

Phase 1/2 Study of Vebreltinib (APL-101) in Combination with Osimertinib in Patients with EGFR-mutant Metastatic Non–Small Cell Lung Cancer (NSCLC)

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INTRODUCTION

Patients on front-line osimertinib for metastatic EGFR-mutant NSCLC often develop disease resistance through activation of the MET signaling pathway. Vebreltinib (APL-101) is a potent, selective, oral MET inhibitor with clinical activity. We hypothesize that the addition of vebreltinib to osimertinib will induce more durable responses in the frontline setting. This phase 1/2 study evaluates the safety, tolerability, and preliminary efficacy of vebreltinib combined with osimertinib in patients with previously untreated EGFR-mutant metastatic NSCLC.

Combined MET and EGFR inhibition has shown encouraging activity in EGFR-mutant NSCLC with MET-driven resistance, including vebreltinib plus an EGFR-TKI in a phase Ib/II study conducted in China.³

STUDY DESIGN

Key Inclusion Criteria

- Metastatic NSCLC with TKI-Sensitive EGFR mutation
- Measurable disease by RECIST 1.1
- Planning to initiate therapy with osimertinib

Key Exclusion Criteria

- Prior osimertinib
- Prior IO in metastatic setting
- Symptomatic or Unstable CNS disease

Osimertinib
Lead-In
8-16 weeks

Osimertinib +
Vebreltinib

Disease assessment of SD or better prior to starting combination ctDNA and biopsy (when feasible) at baseline, and on study. Primary Objectives: Safety (Phase I) and PFS (Phase II)

Dose Level	Vebreltinib (APL-101) Dose	Osimertinib Dose
Level –1	200 mg PO (100 mg AM; 100 mg PM)	40 mg or 80 mg PO
Level 1 (Starting Dose = RP2D)	300 mg PO (100 mg AM; 200 mg PM; asymmetric dosing)	QD (if dose reduction was required during initial 8–16 weeks)
Level 2	400 mg PO (200 mg AM; 200 mg PM)	

RESULTS

- 22 patients** enrolled January 2022–March 2026 started combination therapy: dose escalation MTD/DL1 (n=6) and MTD/DL2 (n=7); expansion at the RP2D (n=9).
- 15 patients** treated at the RP2D (MTD/DL1 + expansion) were evaluable for efficacy; safety assessed in all 22 patients.

RESULTS

Table 1. Baseline demographic and disease characteristics

Characteristic	All Patients (N=22)	RP2D (N=15)
Median age (range) — yr	70 (56–85)	70 (59–82)
Sex — no. (%)		
Female	17 (77)	12 (80)
Male	5 (23)	3 (20)
Race — no. (%)		
White	17 (77)	11 (73)
Asian	4 (18)	3 (20)
Black or African American	1 (5)	1 (7)
Ethnic group — no. (%)		
Non-Hispanic	21 (95)	14 (93)
Unknown	1 (5)	1 (7)
ECOG performance status — no. (%)		
0	2 (9)	2 (13)
1	20 (91)	13 (87)
EGFR mutation — no. (%)		
Exon 19 deletion	12 (55)	10 (67)
L858R	7 (32)	4 (27)
L861Q	2 (9)	1 (7)
G719A	1 (5)	0
TP53 co-mutation — no. (%)		
Yes	15 (68)	9 (60)
No	6 (27)	5 (33)
Unknown	1 (5)	1 (7)
Brain metastases — no. (%)	8 (36)	5 (33)
Liver metastases — no. (%)	3 (14)	1 (7)

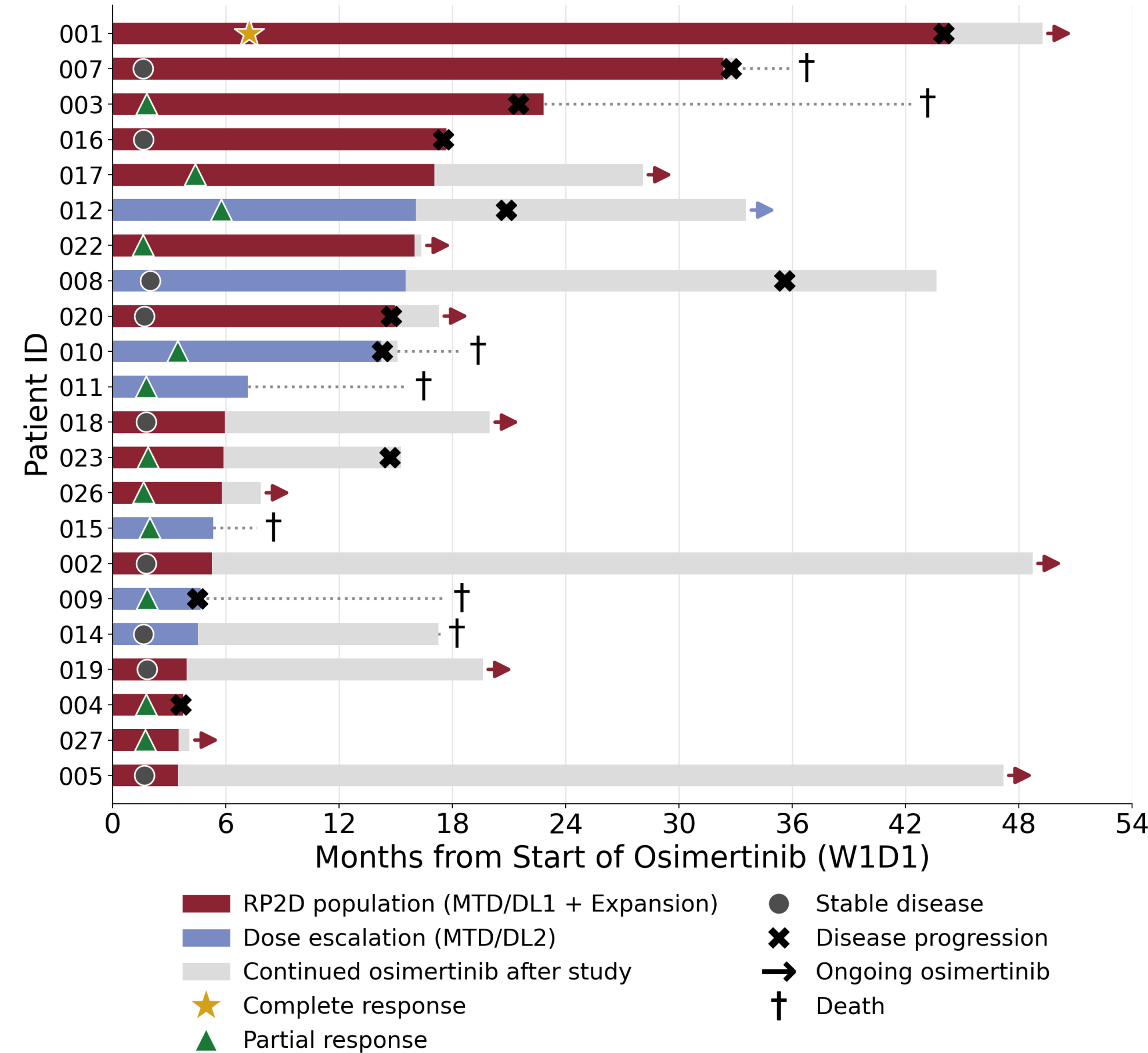


Figure 1. Time on study and total time on osimertinib (N=22)

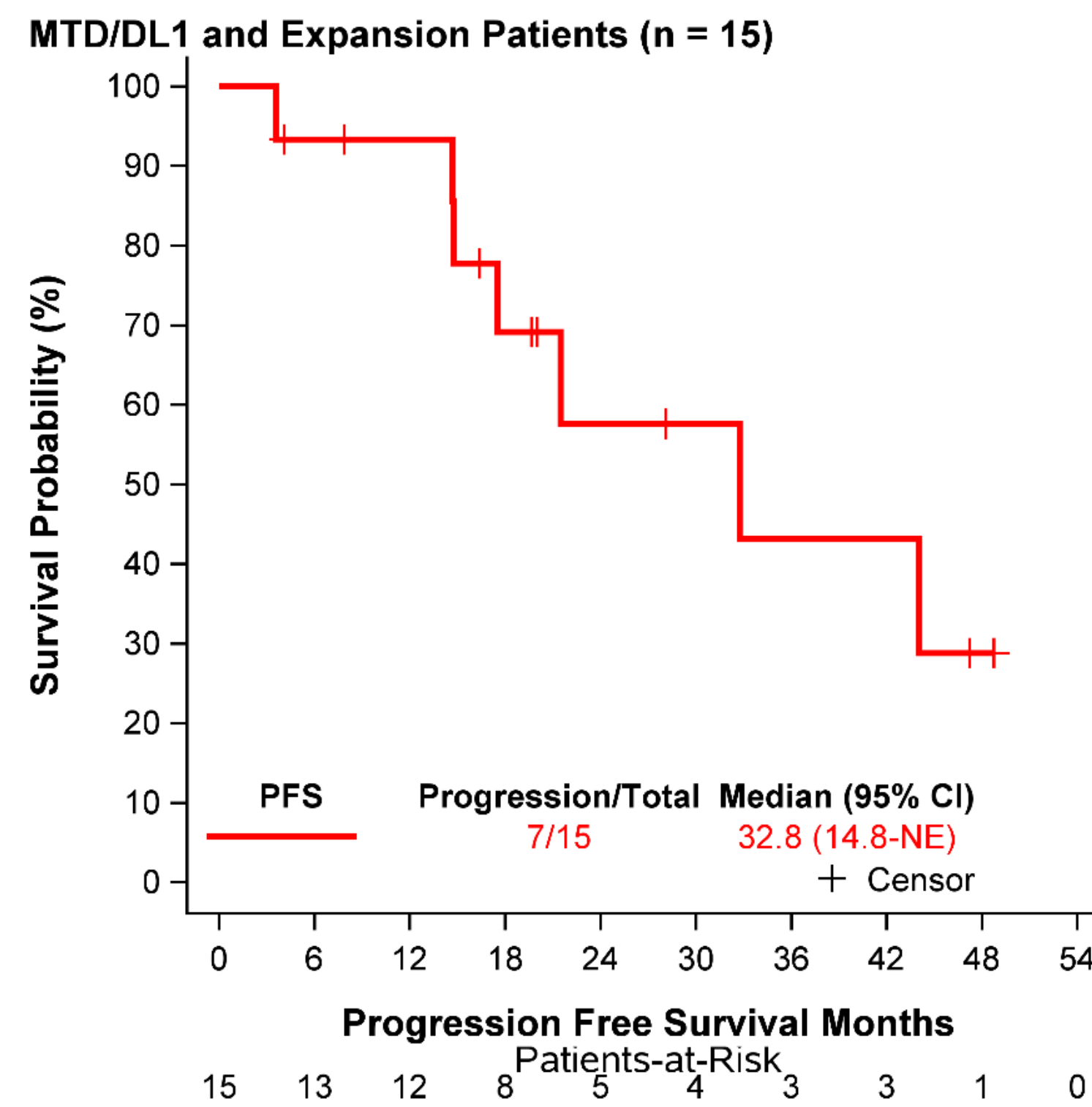


Figure 2. Progression-free survival (n=15)

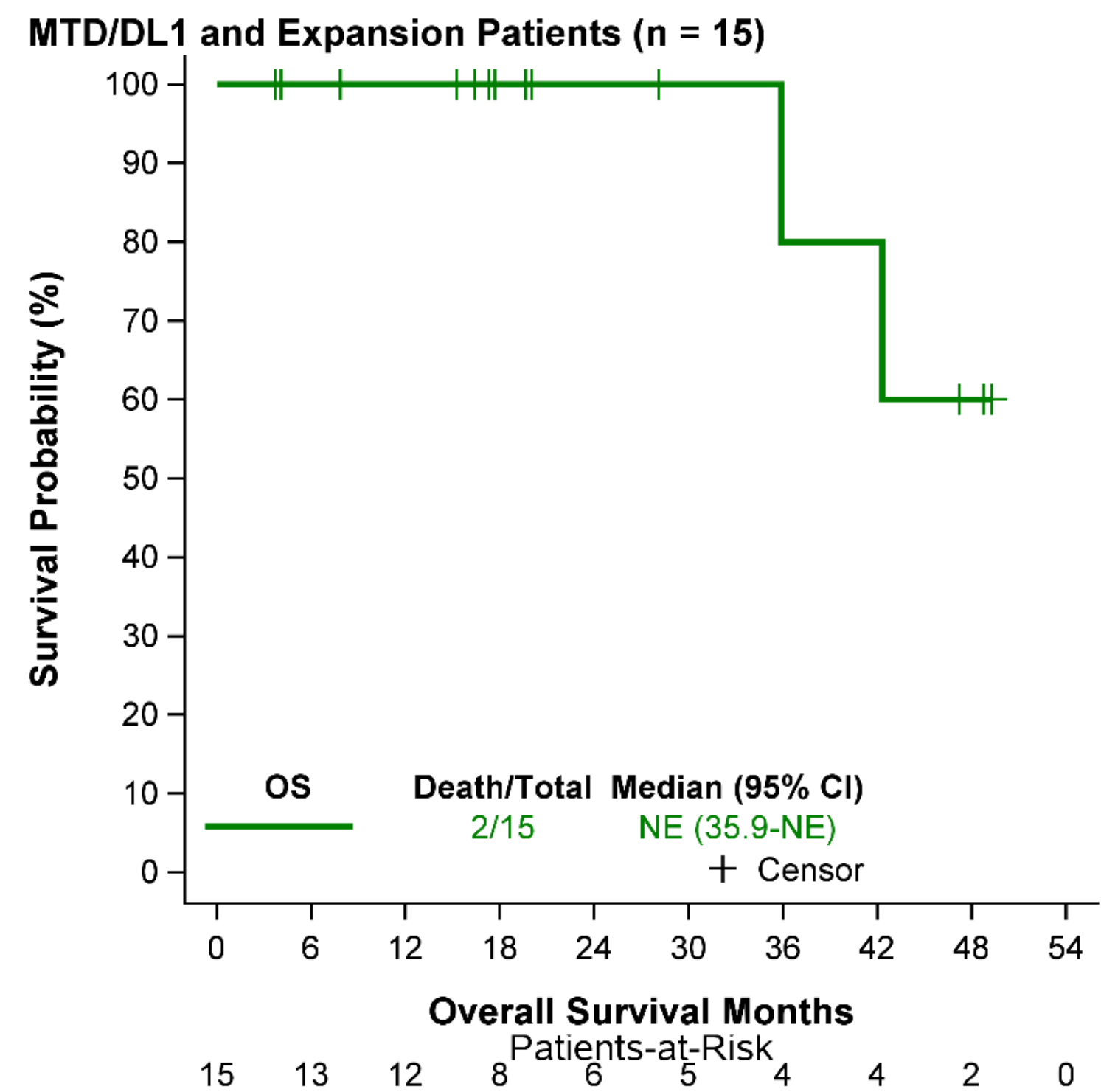


Figure 3. Overall survival (n=15)

Table 2. Grade 3 or higher treatment-related adverse events

Event	Grade 3-4 No (%) n=22
Edema limbs/trunk	2 (9)
Aspartate aminotransferase increased	2 (9)
GGT increased	2 (9)
Fatigue	1 (5)
Heart failure	1 (5)
Middle ear inflammation	1 (5)
Mucositis oral	1 (5)
Nausea	1 (5)
Pneumonitis	1 (5)
Skin infection	1 (5)
Neutrophil count decreased	1 (5)
White blood cell decreased	1 (5)

RESULTS

Table 3. Efficacy in the RP2D population (n=15)

Endpoint	RP2D Population (n=15)
Confirmed ORR — % (95% CI)	53.3 (26.6–78.7)
Complete response	1 (7)
Partial response	7 (47)
Stable disease	7 (47)
Disease control rate — %	100
Median DoR (95% CI) — mo	19.7 (1.8–NE)
Median PFS (95% CI) — mo	32.8 (14.8–NE)
Median OS (95% CI) — mo	NE (35.9–NE)

DISCUSSION AND CONCLUSION

Conclusions

- Vebreltinib + full-dose frontline osimertinib is feasible; RP2D: vebreltinib **100 mg qAM + 200 mg qPM**.
- Toxicity was manageable: grade ≥3 events in 36% (8/22); most common grade 3/4 treatment-related AEs were hepatotoxicity (n=4) and edema (n=2).
- Median PFS of **32.8 months** is longer than historical control with osimertinib monotherapy; median OS was not reached.
- Confirmed ORR 53.3% (1 CR, 7 PR); disease control 100%; median DoR 19.7 months.

Future Direction for Research

- These results support further evaluation of this fully oral, chemotherapy-free frontline combination in a larger randomized study.
- Ongoing ctDNA and paired-biopsy analyses will characterize MET pathway activation and mechanisms of resistance.

REFERENCES & ACKNOWLEDGEMENTS

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Acknowledgements

We thank the patients and their families, the clinical and data coordination teams, and the Siteman Cancer Center clinical trials office. Study funding and vebreltinib (APL-101) was provided by Apollomics.

Clinical trial information: NCT04743505.

AI Use Disclosure: Claude (Anthropic) was used to assist with table/figure preparation, and poster layout. All content was reviewed and verified by the authors.