

Tiragolumab plus atezolizumab and bevacizumab in immunotherapy-refractory, PD-L1-positive, advanced NSCLC

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Background

- Treatments for checkpoint inhibitor immunotherapy (CPI)-refractory advanced non-small cell lung cancer (NSCLC) are limited.
- Vascular endothelial growth factor (VEGF) inhibition has shown synergy with PD(L)1-blockade in CPI-naïve and -refractory NSCLC.^{1,2}
- Blockade of T-cell immunoglobulin and ITIM domain (TIGIT) has shown synergy with anti-PD(L)1 CPI.³
- Translational data suggest immune inhibitory cells commonly found in CPI-refractory NSCLC (Tregs, macrophages) are important in anti-TIGIT CPI efficacy.⁴
- Here we present data from a multi-cohort single-arm phase 2 trial of tiragolumab (anti-TIGIT) plus atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) in CPI-refractory, PD-L1+, advanced non-squamous NSCLC (NCT04958811).**

Methods

- Key eligibility criteria, treatment schedule, and endpoints are shown below (Fig 1).
- Primary endpoint: objective response rate (ORR) per RECIST v1.1.
- Design: Simon 2-stage with null ORR 4% tested against one-sided alternative ORR 20%.
- Sample size of 21 patients provides 80% power with one-sided type 1 error rate of 5%.
- ≥1 response needed in stage 1 to proceed to stage 2.
- Pre/on-treatment tissue/blood collected for translational analyses.

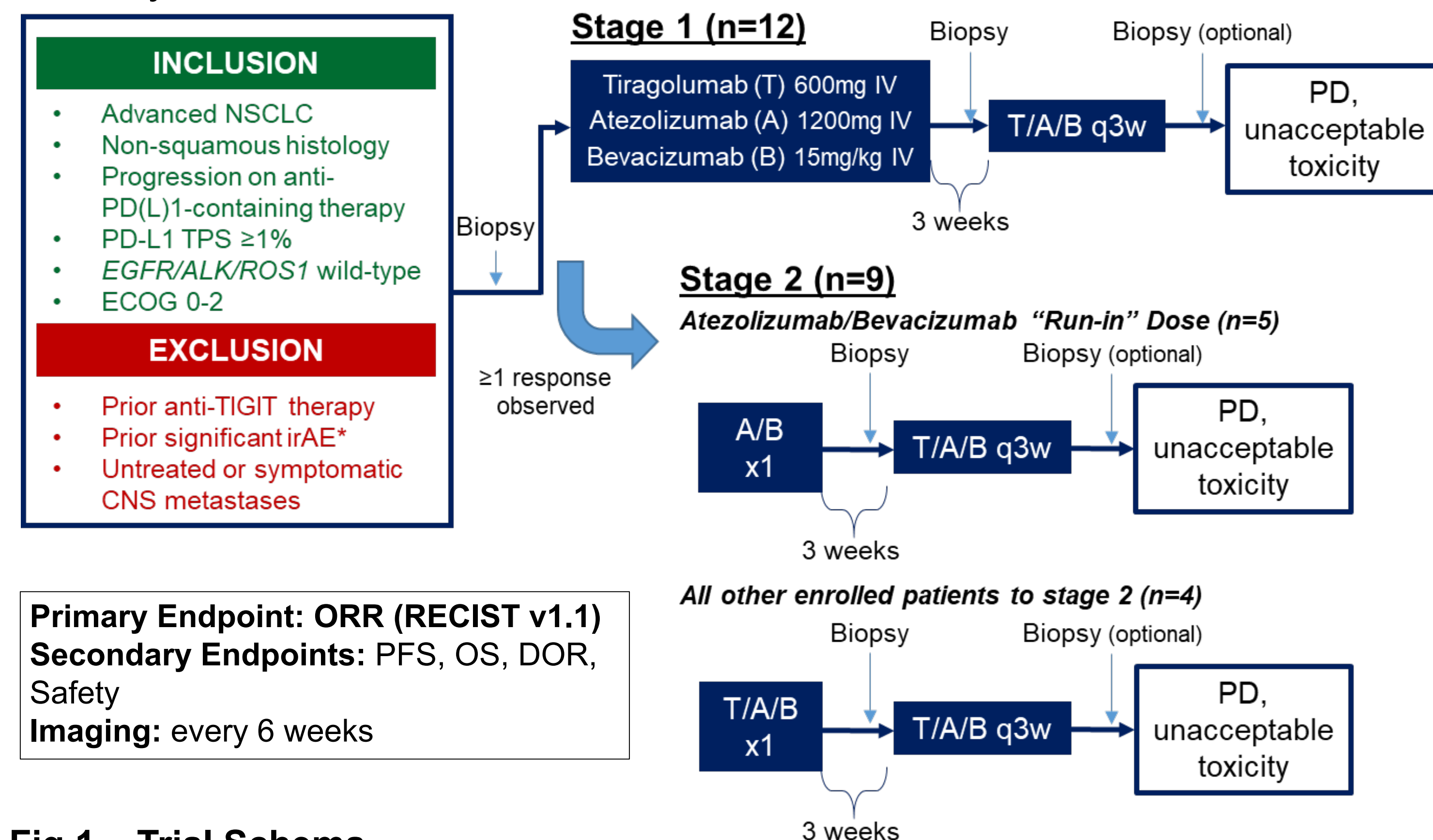


Fig 1 – Trial Schema.

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; irAE, immune-related adverse event; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; RECIST, response evaluation criteria in solid tumors; T/A/B, tiragolumab/atezolizumab/bevacizumab; TPS, tumor proportion score.

*Significant irAE denotes any irAE resulting in permanent discontinuation of CPI.

Results

Table 1 – Baseline Characteristics

Characteristics	N=20
Age	
Median (IQR)	64.5 (59.00, 75.00)
Sex, n (%)	
Male	10 (50)
Female	10 (50)
Race, n (%)	
White	9 (45)
African American	9 (45)
Unknown	2 (10)
Smoking Status, n (%)	
Never Smoker	4 (20)
Ever Smoker	16 (80)
PD-L1 Status, n (%)	
≥50%	10 (50)
1-49%	10 (50)
Concurrent KRAS, STK11, KEAP1 and/or SMARCA4, n (%)	
Yes	14(70)
No	6(30)
Prior Therapy, n (%)	
Median (IQR)	1 (1, 2)
1	14 (70)
2	3 (15)
3	2 (10)
≥4	1 (5)

Table 2 – Treatment-emergent adverse events occurring in >10% of study population (n, %)

Adverse event	Grade 1	Grade 2	Grade 3*	Grade 4	Grade 5*	Total
Fatigue	10 (50%)	1 (5%)	0	0	0	11 (55%)
Anorexia	3 (15%)	3 (15%)	0	0	0	6 (30%)
Proteinuria	2 (10%)	3 (15%)	0	0	0	5 (25%)
AST increased	5 (25%)	0	0	0	0	5 (25%)
Arthralgia	4 (20%)	1 (5%)	0	0	0	5 (25%)
Hypertension	0	2 (10%)	2 (10%)	0	0	4 (20%)
Weight loss	2 (10%)	2 (10%)	0	0	0	4 (20%)
ALT increased	3 (15%)	0	0	0	0	3 (15%)
AKI	3 (15%)	0	0	0	0	3 (15%)
Nausea	2 (10%)	1 (5%)	0	0	0	3 (15%)
Limb edema	3 (15%)	0	0	0	0	3 (15%)
Hyponatremia	1 (5%)	1 (5%)	1 (5%)	0	0	3 (15%)
Pneumothorax^	0	0	3 (15%)	0	0	3 (15%)

Eleven patients (55%) experienced a grade 3 treatment-related adverse event (no G4/5) including hypertension (2 patients, 17%), colonic perforation (1 patient, 5%), and memory impairment (1 patient, 5%).

*One event each of aspiration, colonic perforation, constipation, dyspnea, lung infection, memory impairment, peritoneal infection, thromboembolism.

^One event, ventricular fibrillation, related to illicit drug overdose, unrelated to treatment.

AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

^occurred spontaneously in setting of bullous emphysema, unrelated to treatment.

Table 3 – Characteristics of patients with response or durable stable disease (PFS ≥6 mo)

Age	Sex	Smoking Hx	PD-L1	Molecular Profile	Best Response	PFS (mo)
63	Male	Current, 40py	5%	KRAS L19F, STK11 S216F, ARID1A E1886fs, TP53 E294*	PR	13.1+
63	Male	Former, 22.5py	5%	KRAS G12V	PR	16.0
69	Female	Former, 40py	70%	KEAP1, TP53	PR	4.0
79	Female	Former, 25py	10%	KEAP1, PIK3CA, TP53, DNMT3A, SMARCA4, TET2	PR	18.0
59	Female	Former, 3py	60%	KRAS G12V, ARID1A	SD	9.1
59	Male	Former, 20py	80%	TP53, NF1, TERT, RET(VUS), ATM(VUS)	SD	8.1
57	Male	Former, 4py	50%	KRAS G12V, BRAF G469V, FBXW7, SETD2, TP53	SD	11.6
63	Female	Former, 11.5py	1%	TP53, EGFRamp	SD	7.3

+ treatment ongoing without PFS event

Conclusions

- Accrual was halted early following discontinuation of tiragolumab development.
- Data analysis demonstrated modest clinical efficacy, and it is unclear whether tiragolumab provides additional benefit beyond PD-(L)1/VEGF blockade in immunotherapy-refractory NSCLC.
- Responses in patients with KEAP1/STK11-mutated NSCLC suggest there may be a patient subset that benefits from this approach.

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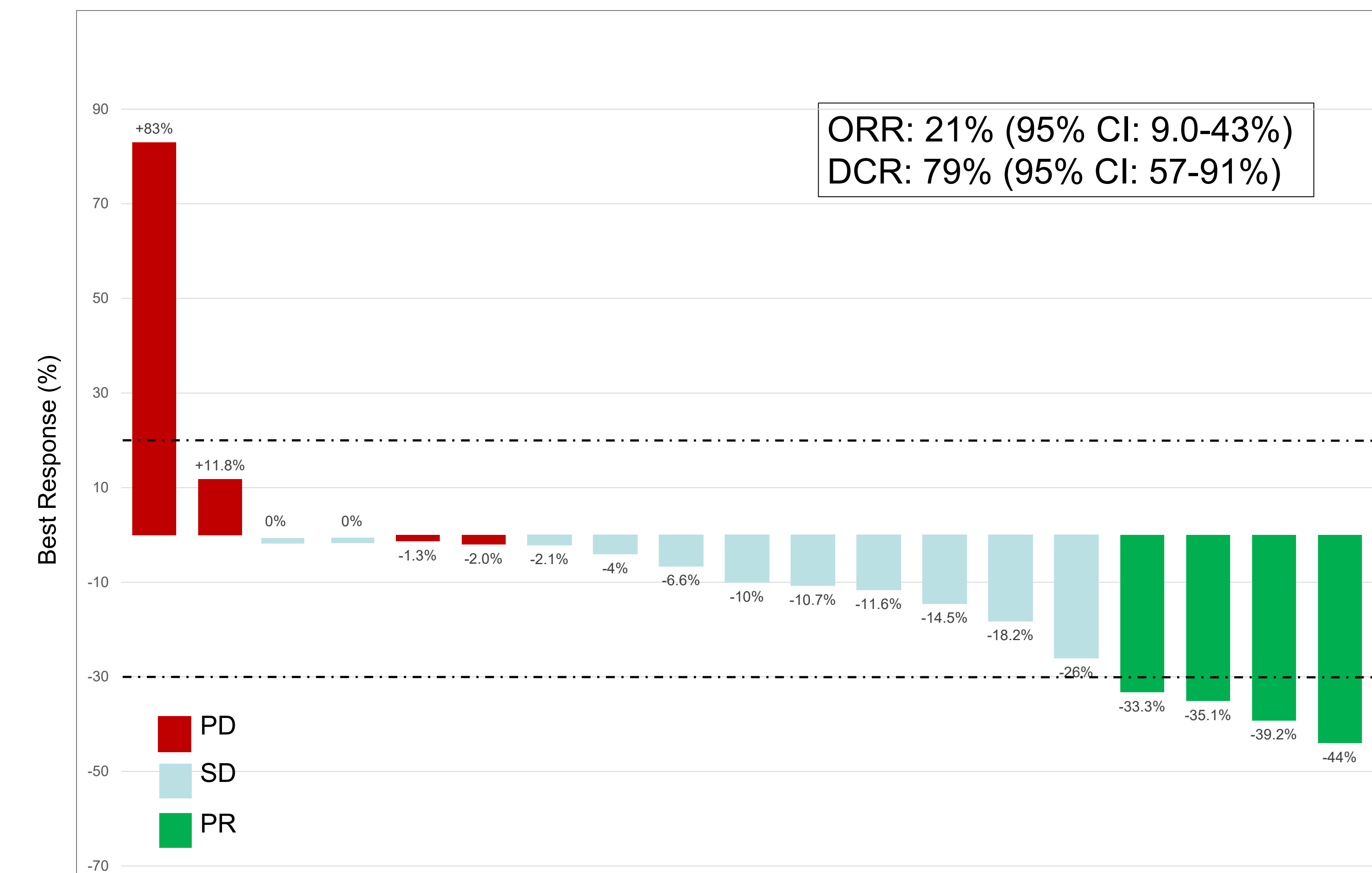


Fig 2 – Best change in tumor size from baseline (per RECIST). One patient was not evaluable for response. Hashed line indicates cutoff required for response/progression. DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; 95% CI, 95% confidence interval.

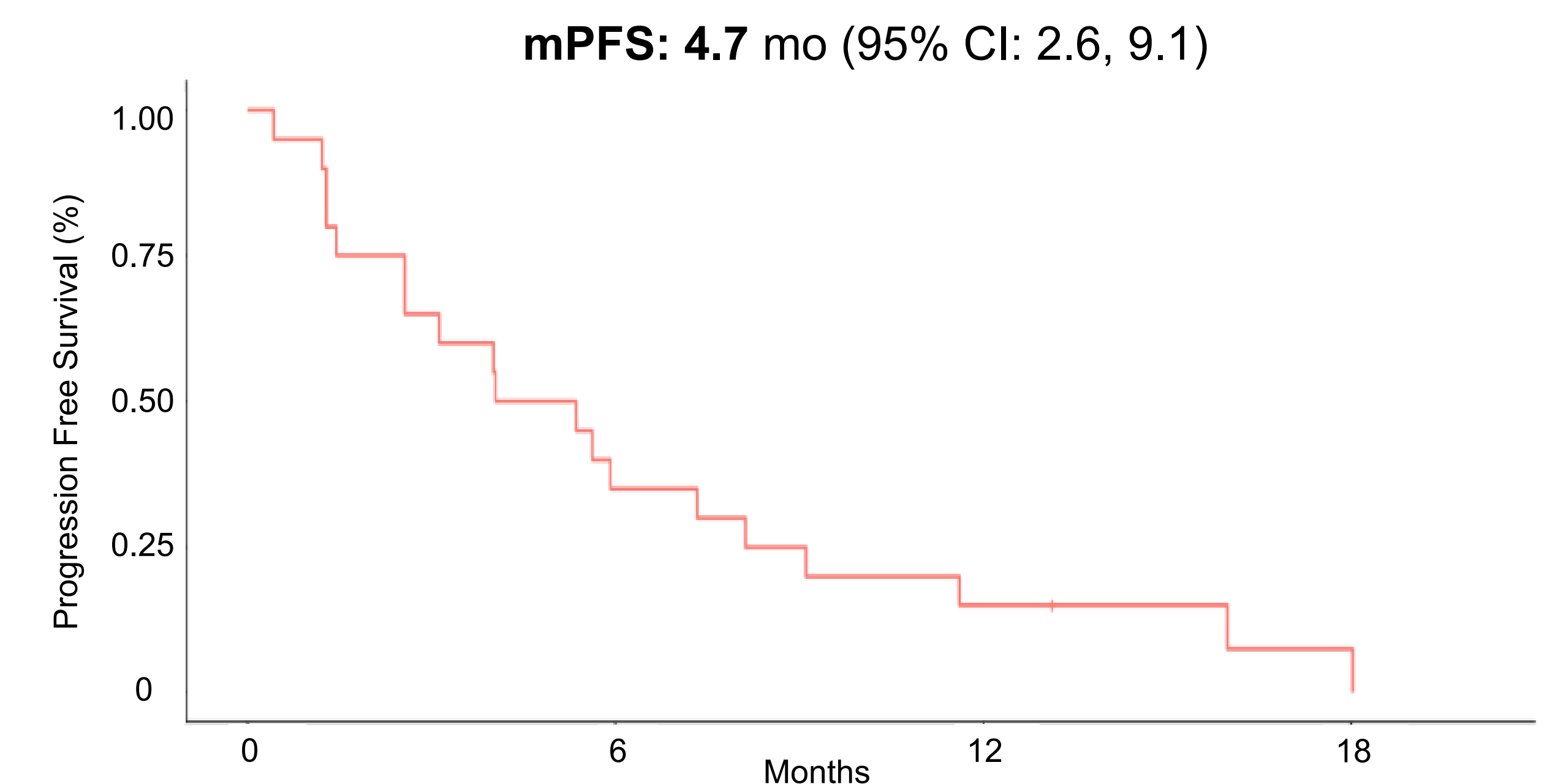


Fig 3 – Progression-free Survival. CI, confidence interval; mo, months; mPFS, median progression-free survival.

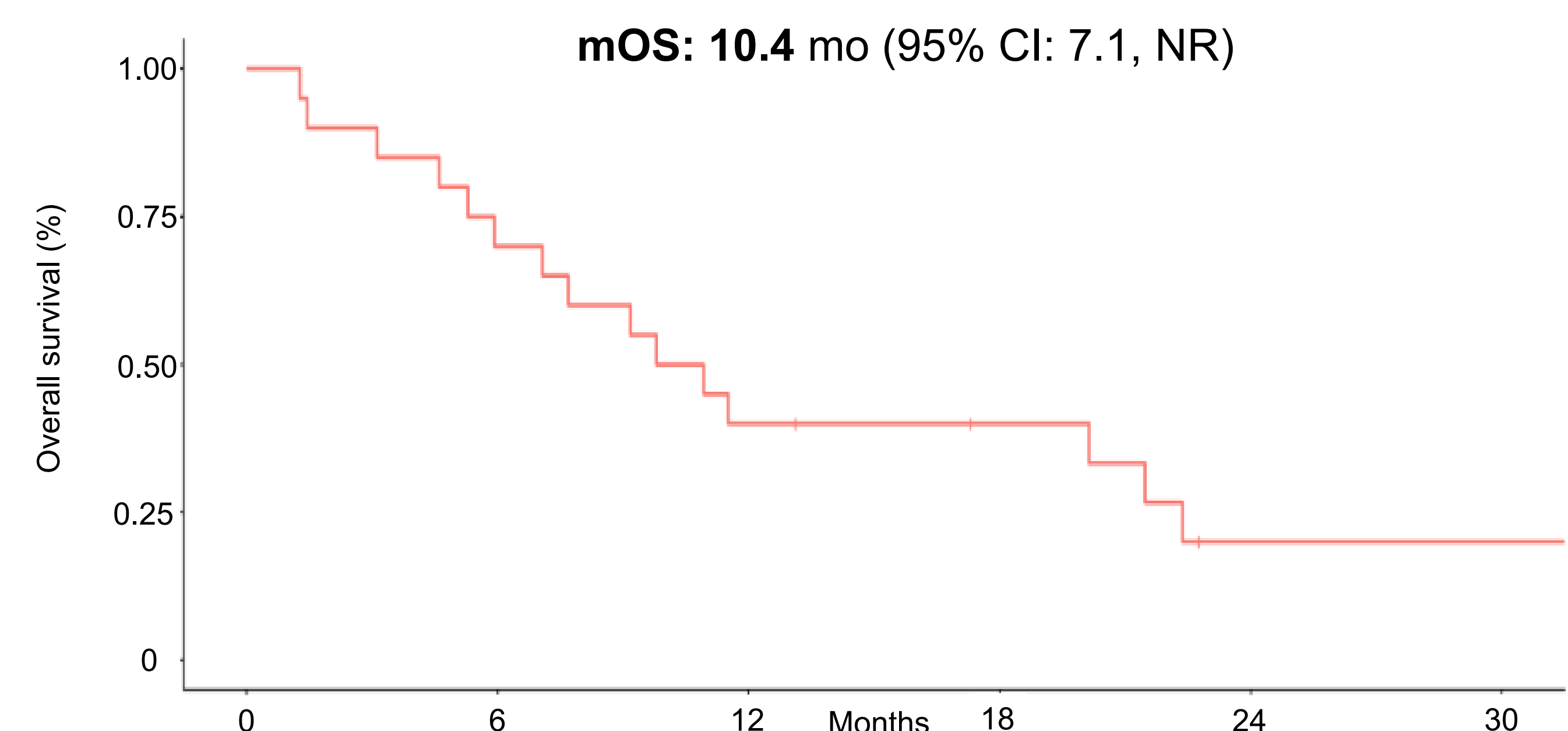


Fig 4 – Overall Survival. CI, confidence interval; mo, months; mOS, median overall survival; NR, not reached.