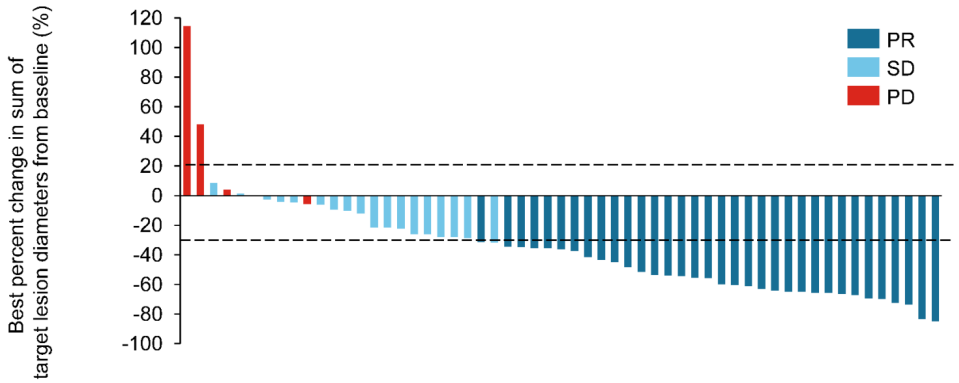
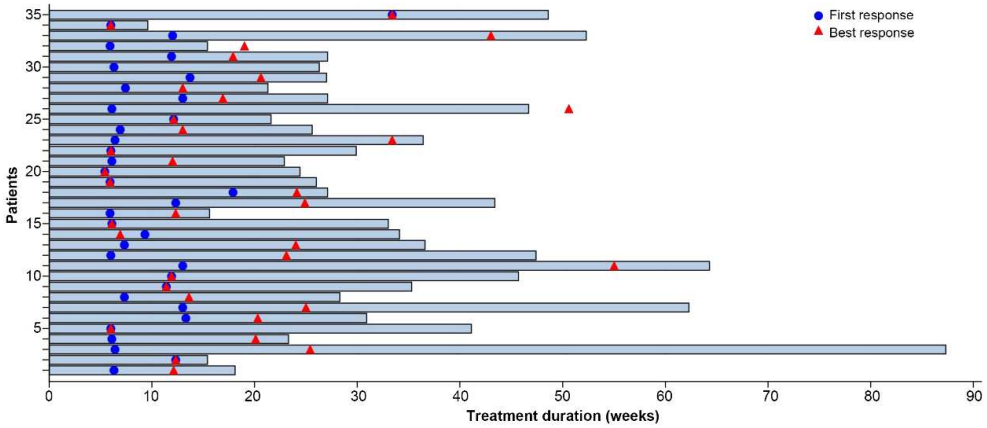
Supplementary materials

Supplementary Figure S1. Maximum tumor reduction in EAS (n=62)



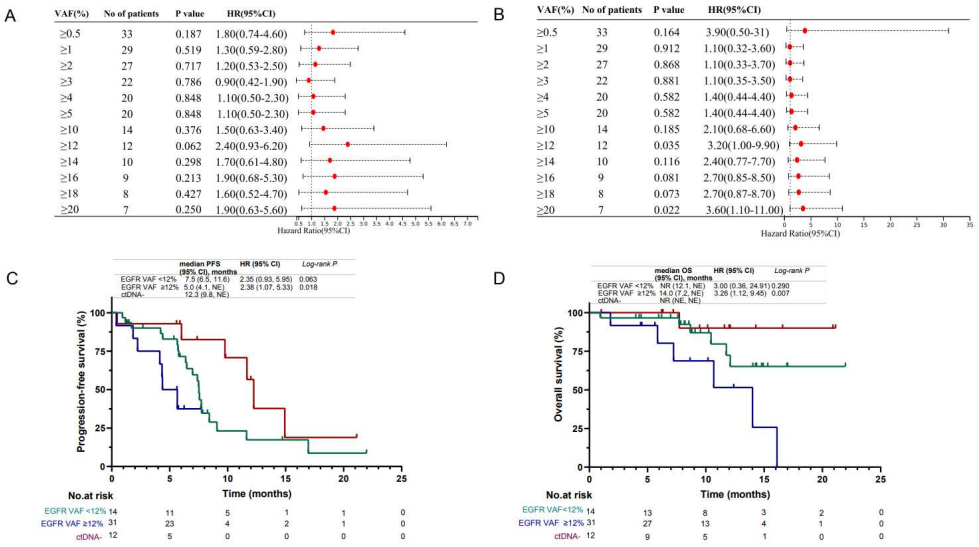
Abbreviations: EAS, efficacy analysis set; PR, partial response; SD, stable disease; PD, progressive disease.

Supplementary Figure S2. Swimmer plot of patients achieving partial response (n=35)



Supplementary Figure S3. The association between *EGFR* VAF and patient outcome

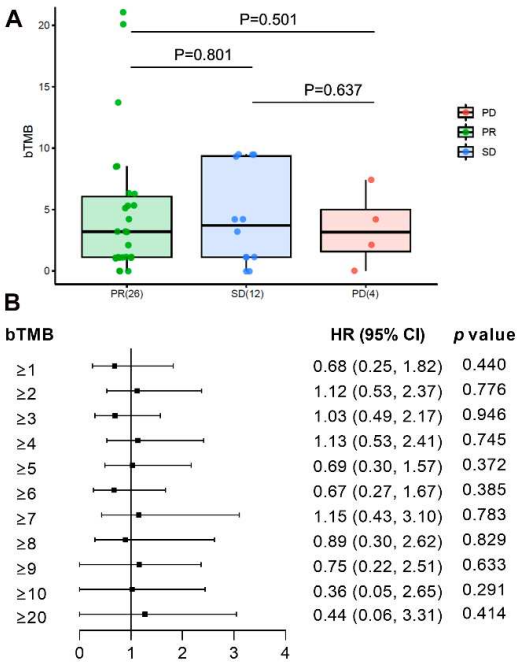
(A) The association between EGFR VAF and PFS as per different cut-points; (B) The association between EGFR VAF and OS as per different cut-points; (C) PFS and (D) OS in patients with high EGFR VAF, low EGFR VAF and negative ctDNA.



Abbreviations: VAF, variant allele frequency; PFS, progression-free survival; OS, Overall survival; HR, hazard ratio; CI, confidence interval.

Supplementary Figure S4. The association between bTMB and clinical outcomes

(A) bTMB levels as per tumor response; (B) The association between bTMB and PFS as per different cut-points.



Abbreviations: bTMB, blood tumor mutational burden; PD, disease progression; PR, partial response; SD, stable disease; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval. *P values were corrected for multiple hypotheses testing using the false discovery rate (FDR) adjustment method.

Supplementary Table S1. Treatment response

Group	EAS (n=62)	Prior systematic chemo.		Prior anti-angiogenesis treatment		Prior EGFR-TKI treatment			EGFR mutation type		EGFR T790M mutation	
		Yes (n=11)	No (n=51)	Yes (n=18)	No (n=44)	1st/2nd (n=23)	Only 3rd (n=7)	1st/2nd/3rd (n=32)	L858R (n=26)	19DEL (n=35)	Positive (n=18)	Negative/unknown (n=44)
BOR, % (n)												
PR	56.5 (35)	45.5 (5)	58.8 (30)	61.1 (11)	54.5 (24)	69.6 (16)	57.1 (4)	46.9 (15)	46.2 (12)	62.9 (22)	66.7 (12)	52.3 (23)
SD	30.6 (19)	27.3 (3)	31.4 (16)	16.7 (3)	36.4 (16)	26.1 (6)	28.6 (2)	34.4 (11)	34.6 (9)	28.6 (10)	33.3 (6)	29.5 (13)
PD	11.3 (7)	27.3 (3)	7.8 (4)	16.7 (3)	9.1 (4)	0	14.3 (1)	18.8 (6)	15.4 (4)	8.6 (3)	0	15.9 (7)
NA	1.6 (1)	0	2.0 (1)	5.6 (1)	0	4.3 (1)	0	0	3.8 (1)	0	0	2.3 (1)
DCR, %	87.1	72.7	90.2	77.8	90.9	95.7	85.7	81.3	80.8	91.4	100	81.8
Confirmed ORR, %	50.0	36.4	52.9	50.0	50.0	56.5	57.1	43.8	46.2	51.4	61.1	45.5

Abbreviations: EAS, efficacy analysis set; BOR, best overall response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; ORR, objective response rate.

Supplementary Table S2. Overall summary of adverse events

	SAS (N=69)
Any grade TEAEs	65 (94.2)
Treatment-related	65 (94.2)
Grade 3-4 TEAEs	28 (40.6)
Treatment-related	27 (39.1)
TEAE leading to dose modification/delay of any study treatment	20 (29.0)
TEAE leading to discontinuation of any study treatment	4 (5.8)
SAEs	13 (18.8)
Treatment-related	11 (15.9)
irAEs	19 (27.5)
Grade 3-4 irAEs	5 (7.2)

Data are n (%). Abbreviations: TEAEs, treatment-emergent adverse events; SAEs, serious adverse events; irAEs, immune-related adverse events.

Supplementary Table S3. Adverse events during induction phase and maintenance phase

	Induction phase		Maintenance phase		Overall	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
TRAEs						
Any TRAEs	63 (91.3)	20 (29.0)	42 (60.9)	13 (18.8)	65 (94.2)	27 (39.1)
Anaemia	34 (49.3)	6 (8.7)	19 (27.5)	1 (1.4)	42 (60.9)	7 (10.1)
Decreased white blood cell count	30 (43.5)	6 (8.7)	20 (29)	1 (1.4)	36 (52.2)	6 (8.7)
Decreased neutrophil count	25 (36.2)	10 (14.5)	17 (24.6)	6 (8.7)	31 (44.9)	12 (17.4)
Decreased platelet count	25 (36.2)	5 (7.2)	11 (15.9)	3 (4.3)	28 (40.6)	7 (10.1)
Alopecia	23 (33.3)	0	0	0	23 (33.3)	0
Increased aspartate aminotransferase	11 (15.9)	0	12 (17.4)	0	20 (29.0)	0
Nausea	16 (23.2)	0	3 (4.3)	0	17 (24.6)	0

Hypoesthesia	14 (20.3)	0	1 (1.4)	0	15 (21.7)	0
Increased alanine aminotransferase	9 (13)	0	7 (10.1)	1 (1.4)	14 (20.3)	1 (1.4)
Rash	11 (15.9)	1 (1.4)	3 (4.3)	0	14 (20.3)	1 (1.4)
Hypercholesterolemia	8 (11.6)	0	10 (14.5)	0	13 (18.8)	0
Decreased lymphocyte count	11 (15.9)	4 (5.8)	5 (7.2)	2 (2.9)	13 (18.8)	4 (5.8)
Decreased hemoglobin	11 (15.9)	2 (2.9)	1 (1.4)	0	12 (17.4)	2 (2.9)
Constipation	9 (13)	0	1 (1.4)	0	10 (14.5)	0
Decreased appetite	9 (13)	0	3 (4.3)	0	10 (14.5)	0
Asthenia	7 (10.1)	0	2 (2.9)	0	9 (13.0)	0
Hypokalemia	5 (7.2)	1 (1.4)	4 (5.8)	0	8 (11.6)	1 (1.4)
Hyponatremia	3 (4.3)	0	6 (8.7)	0	8 (11.6)	0
Hypertriglyceridaemia	5 (7.2)	0	6 (8.7)	0	8 (11.6)	0
Increased blood lactate dehydrogenase	4 (5.8)	0	6 (8.7)	0	7 (10.1)	0
irAEs						
Any irAEs	14 (20.3)	4 (5.8)	9 (13)	2 (2.9)	19 (27.5)	5 (7.2)
Rash	6 (8.7)	1 (1.4)	2 (2.9)	0	8 (11.6)	1 (1.4)
Decreased platelet count	2 (2.9)	2 (2.9)	0	0	2 (2.9)	2 (2.9)
Immune-mediated pulmonary disease	1 (1.4)	0	1 (1.4)	0	2 (2.9)	0
Decreased free thyroxine	0	0	2 (2.9)	0	2 (2.9)	0

Supplementary Table S4. The association between gene alterations and PFS

	HR (95% CI)	P value	FDR adjusted P value*
TP53	1.24 (0.59-2.63)	0.574	0.861
LRP1B	0.52 (0.07-3.85)	0.514	0.861
PIK3CA	6.12 (1.54-24.4)	0.004	0.018
PTEN	1.8 (0.54-6.06)	0.335	0.861
RB1	1.07 (0.37-3.13)	0.896	0.906
BRCA2	0.88 (0.12-6.75)	0.906	0.906
CTNNB1	5.87 (1.56-22)	0.004	0.018
KRAS	1.43 (0.42-4.86)	0.565	0.861
MTOR	0.77 (0.10-5.86)	0.799	0.906

Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.