Supplementary Table 1 Demographic and clinical characteristics between patients in subsequent line anti- epidermal growth factor receptor (EGFR) approaches who received and never received anti-EGFR therapy

Characteristics	All (N=219)	Never received anti-EGFR (N = 71)	Received anti-EGFR (N =148)	P-value
Age at diagnosis				
Median (range), years	60 (30-92)	61(30-88)	59.5 (30-92)	
≥ 65 years, n (%)	71 (32.4)	30 (42.3)	41 (27.7)	0.031
Sex, n (%)				
Male	138 (63)	43 (60.6)	95 (64.2)	0.603
Female	81 (37)	28 (39.4)	53 (35.8)	
ECOG, n (%)				0.04
0	30 (13.7)	4 (5.6)	26 (17.6)	
1	183 (83.6)	65 (91.5)	118 (79.7)	
2	5 (2.3)	1 (1.4)	4 (2.7)	
3	1 (0.5)	1 (1.4)	0	
Underlying disease, n (%)	114 (52.1)	30 (42.3)	84 (56.8)	0.044
Yes	83 (37.9)	24 (33.8)	59 (39.9)	0.387
Hypertension	43 (19.6)	12 (16.9)	31 (20.9)	0.481
Diabetes	48 (21.6)	17 (23)	31 (20.9)	0.729
Dyslipidemia	7 (3.2)	2 (2.8)	5 (3.4)	0.825

Cerebrovascular disease	9 (4.1)	5 (7.0)	4 (2.7)	0.130
Ischemic heart disease	5 (2.3)	3 (4.2)	2 (1.4)	0.183
Other cancers				
Tumor location,n (%)				0.006
Splenic flexure	6 (2.7)	0	6 (4.1)	
Descending colon	19 (8.7)	7 (9.9)	12 (8.1)	
Sigmoid colon	104 (47.5)	27 (38)	77 (52)	
Rectosigmoid	33 (15.1)	19 (26.8)	14 (9.5)	
Rectum	57 (26)	18 (25.4)	39 (26.4)	
Histologic subtype, n (%)				0.750
Mucinous adenocarcinoma	2 (0.9)	1 (1.4)	1 (0.7)	
Signet ring cell carcinoma	2 (0.9)	1 (1.4)	1 (0.7)	
Tumor grade, n (%)				0.021
Well differentiate	71 (37.0)	30 (46.2)	41 (32.3)	
Moderates differentiate	103 (53.6)	26 (40.0)	77 (60.6)	
Poorly differentiate	18 (9.4)	9 (13.8)	9 (7.1)	
Metastatic type, n (%)				0.701
Synchronous	182 (83.1)	60 (84.5)	122 (82.4)	
Metachronous	37 (16.9)	11 (15.5)	26 (17.6)	
Number of metastatic sites, n (%)				0.788
1	121 (55.3)	41 (57.7)	80 (54.1)	
2	73 (33.3)	24 (33.8)	49 (33.1)	

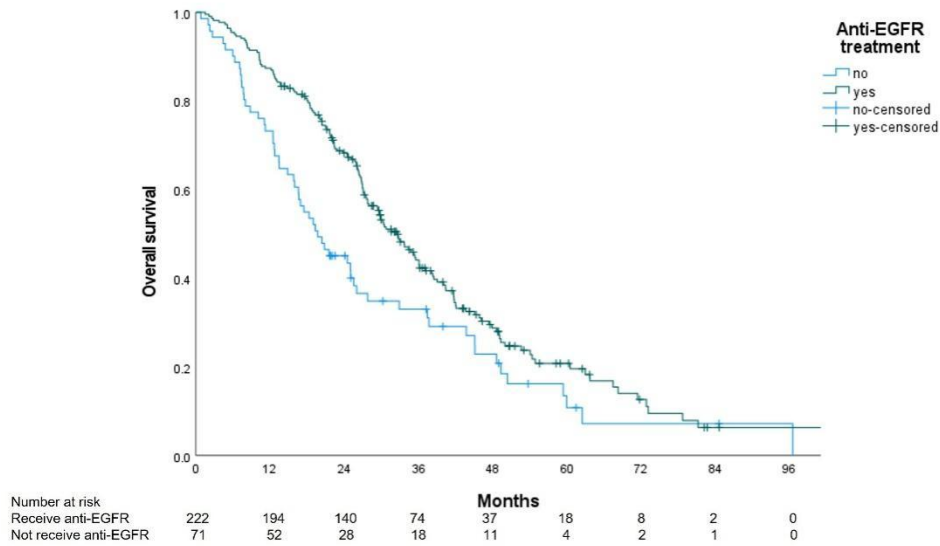|				
3	15 (6.8)	4 (5.6)	11 (7.4)	
≥4	10 (4.6)	2 (2.8)	8 (5.4)	
Site of metastasis, n (%)				
==Liver-limited metastasis==	79 (36.1)	28 (39.4)	51 (34.5)	0.473
Liver	162 (74)	53 (74.6)	109 (73.6)	0.875
Lung	73 (33.3)	21 (29.6)	52 (35.1)	0.414
Peritoneal	54 (24.7)	18 (25.4)	36 (24.3)	0.869
Distant lymph nodes	32 (14.6)	8 (11.3)	24 (16.2)	0.332
Any lines of Bevacizumab, n (%)	134 (61.2)	24 (33.8)	110 (74.3)	< 0.001
Regimen chemotherapy at first line, n (%)				0.011
5FU/Capecitabine	7 (3.2)	2 (2.8)	5 (3.4)	
FOLFOX/CAPEOX	176 (80.4)	64 (90.1)	112 (75.7)	
FOLFIRI/CAPIRI	30 (13.7)	2 (2.8)	28 (18.9)	
FOLFOXIRI/mFOLFORINOX	6 (2.7)	3 (4.2)	3 (2)	
Line number of systemic treatments, n (%)				
Median (range)	3 (1-8)	2 (1-5)	4 (2-8)	< 0.001
1	24 (11)	24 (33.8)	-	
2	45 (20.5)	27 (38)	18 (12.2)	
3	56 (25.6)	12 (16.9)	44 (29.7)	
4	53 (24.2)	7 (9.9)	46 (31.1)	
≥ 5	41 (18.7)	1 (1.4)	40 (27)	

Local treatment at metastatic sites, n (%)	95 (43.4)	24 (33.8)	71 (48)	0.048
Metastectomy at liver, n (%)	41 (18.7)	6 (8.5)	35 (23.6)	0.007
Patient status at last follow-up, n (%)				0.473
No evidence of disease	2 (0.9)	0	2 (1.4)	
Alive with disease	46 (21)	13 (18.3)	33 (22.3)	
Death	171 (78.1)	58 (81.7)	113 (76.4)	

Supplementary Table 2 All systemic treatments during any lines of therapy

Type of treatment n (%)	Frontline anti-EGFR (N = 74)	Subsequent line anti-EGFR	
		Received anti-EGFR (N =148)	Never received anti-EGFR (N = 71)
5FU/Capecitabine	73 (98.6)	148 (100)	71 (100)
Oxaliplatin	68 (91.9)	139 (93.9)	68 (95.8)
Irinotecan	51 (68.9)	148 (100)	47 (66.2)
Anti-EGFR	74 (100)	148 (100)	0
Bevacizumab	33 (44.6)	110 (74.3)	24 (33.8)
Ramucirumab	1 (1.4)	0	1 (1.4)
Regorafenib	12 (16.2)	42 (28.4)	2 (2.8)
Trifluridine/tipiracil hydrochloride	8 (10.8)	18 (12.2)	1 (1.4)
Pembrolizumab	1 (1.4)	0	0
Nivolumab	0	1 (0.7)	0
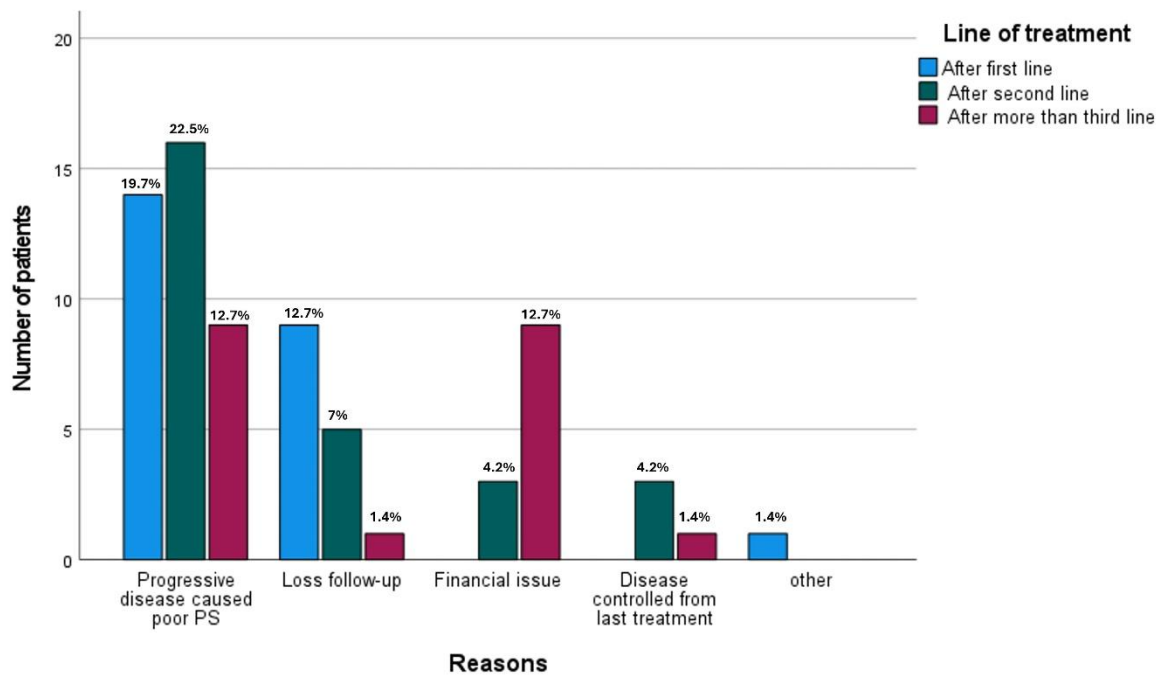
Supplementary Figure 1 Reasons for not receiving subsequent line treatment among patients who never received anti- epidermal growth factor receptor therapy.

Number at risk

Receive anti-EGFR	222	194	140	74	37	18	8	2	0
Not receive anti-EGFR	71	52	28	18	11	4	2	1	0

Supplementary Figure 2 Comparison of overall survival between patients who received and never received anti- epidermal growth factor receptor treatment in all patient populations. Kaplan-Meier survival analysis with long-rank test of overall survival by receiving or not receiving anti-EGFR treatment in all patients. Median overall survival in patients who received anti-EGFR was 32.50 months (95% CI 28.64-36.36). Median overall survival in patients who never received anti-EGFR was 19.70 months (95% CI 12.87-26.53). Log rank test = HR 0.65, P-value = 0.005.