Supplementary Online Content

Han B, Li K, Wang Q, et al. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non–small cell lung cancer: the ALTER 0303 phase 3 clinical trial. *JAMA Oncol.* 2018;4(12): e183039. doi:10.1001/jamaoncol.2018.3039

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Inclusion and Exclusion Criteria of Patients

Inclusion criteria

1) patients voluntarily participate in this study, signed informed consent

2) patients pathologically diagnosed as late (IIIB / IV) non-small cell lung cancer, with measurable lesions

3) patients who have received at least three or more treatment regimens or are unable to tolerate treatment

4) Detection of genotypes by providing detectable specimens (tissue or cancerous pleural effusion) prior to enrollment: including patients with EGFR mutation, or ALK rearrangement negative test results or patients with positive test results and resistance to targeted drug after treatment or cannot tolerate the treatment[a]

5) patients aged between 18 -75 years; with ECOG PS Scoring: 0~1 point; with expected survival time>3 months

6) patients with normal organ function within 7 days prior to treatment, the following criteria are met

a) blood routine examination criteria (without blood transfusion in 14 days)

i) hemoglobin (HB) ≥90g/L

iii) neutrophil absolute (ANC) $\geq 1.5\times10^9$/L

iv) platelet (PLT) $\geq 80\times10^9$/L

b) biochemical tests meet the following criteria

i) total bilirubin (TBIL) ≤1.5 times of upper limit of normal (ULN)

ii) alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 ULN, if liver metastasis occurred, ALT and AST ≤5 ULN

iii) serum creatinine (Cr) ≤1.5 ULN or creatinine clearance (CCr) ≥60mL/min

c) Doppler ultrasound evaluation: left ventricular ejection fraction (LVEF) ≥50%

7) female patients of childbearing age agree that contraceptive measures (such as intrauterine devices, birth control pills or condoms) must be used within the study period and within 6 months after the end of the study drug treatment. The serum or urine test indicates unpregnancy within 7 days prior to the study, and must be non-lactating patients. Male patients agree to have contraceptive use during the study period and within 6 months after the end of the study period

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Exclusion criteria

1) patients who had previously used anlotinib hydrochloride capsules

2) patients with small cell lung cancer (including small cell carcinoma and non-small cell carcinoma mixed lung cancer)

3) patients who were tested positive for EGFR mutation or ALK rearrangement but did not use the relevant targeted drug

4) patients with central, empty lung squamous cell carcinoma, or non-small cell lung cancer with hemoptysis (>50 mL/day)

5) patients had other malignancies in the past 5 years or currently, except cured cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumor (Ta [non-invasive tumor], Tis [carcinoma in situ] and T1 [tumor infiltrating basement membrane])

6) patients who planned to receive systemic anti-tumor therapy within 4 weeks prior to allocation or during the course of this study, including cytotoxic therapy, signal transduction inhibitors, immunotherapy (or receiving the Mitomycin C 6 weeks prior to medication). Extra-field radiotherapy (EF-RT) was performed 4 weeks prior to allocation or restricted radiotherapy for assessing tumor lesions within 2 weeks prior to allocation

7) patients with more than common terminology criteria for adverse events (CTC AE) level 1 unmitigated toxicity due to any previous treatment, not including hair loss and ≤ 2 level neurotoxicity caused by oxaliplatin

8) patients have a variety of factors that affect oral medication (such as cannot swallow, chronic diarrhea and intestinal obstruction, etc.)

9) with pleural effusion or ascites, causing respiratory syndrome (≥ CTC AE level 2 dyspnea)

10) patients with brain metastases have symptoms or controlled symptoms less than 2 months

11) patients with any severe and/or uncontrolled disease, including:

a) blood pressure control is not ideal (systolic blood pressure ≥ 150 mmHg, diastolic blood pressure ≥ 100 mmHg)

b) Myocardial ischemic or myocardial infarction, arrhythmia (including QTc ≥480 ms) and ≥ 2 levels of congestive heart failure (NYHA classification)

c) active or uncontrollable serious infection (≥CTC AE Level 2 infection)

d) liver cirrhosis, decompensated liver disease, active hepatitis or chronic hepatitis need to be treated with antiretroviral therapy

e) renal failure requires hemodialysis or peritoneal dialysis

f) history of immunodeficiency, including HIV-positive or other acquired, congenital immunodeficiency disease, or history of organ transplantation

g) poor control of diabetes (fasting blood glucose [FBG]> 10 mmol/L)

h) urine routine test protein ≥++, and confirmed 24 hours urine protein> 1.0 g

i) patients with a seizure and need treatment

12) received a major surgical treatment within 28 days prior to allocation, with a biopsy or a significant traumatic injury

13) imaging shows that the tumor has been violated around important vascular or the researchers determine the tumor is likely to invade important blood vessels caused by fatal bleeding during the follow-up

14) regardless of the severity, patients with any signs or medical history of bleeding; within 4 weeks prior to allocation, patients with any bleeding events ≥ CTC AE level 3, unhealed wounds, ulcers or fractures

15) patients with artery/venous thrombotic occurred within 6 months before allocation, such as cerebrovascular accident (including temporary ischemic attack), deep vein thrombosis and pulmonary embolism

16) patients with a history of psychotropic medicine abuse and cannot quit or have mental disorders

17) patients participated in other anti-tumor drug clinical trials within four weeks

18) patients were diagnosed with disease which will severely endanger the security of patients or influence the completion of this research

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[a]EGFR-positive patients are required to use at least one of the following drugs and are resistant or intolerant: including erlotinib, alfortitine, gefitinib, iridinib, AZD9291, etc.; ALK rearrangement positive: at least one of the following drugs is used and resistant or intolerant: methazolidine, Ceritinib, etc.

eTable 2. Baseline Characteristics of the Study Population

	Anlotinib group (n=294)	**Placebo group (n=143)**
Age, years		
≤ 60	153 (52.0%)	90 (62.9%)
61-69	125 (42.5%)	41 (28.7%)
≥ 70	16 (5.4%)	12 (8.4%)
Sex		
Male	188 (64.0%)	97 (67.8%)
Female	106 (36.1%)	46 (32.2%)
Histology		
Adenocarcinoma	228 (77.6%)	108 (75.5%)
Squamous	53 (18.0%)	33 (23.1%)
Other[a]	13 (4.4%)	2 (1.4%)
Clinical stage		
IIIB	15 (5.1%)	7 (4.9%)
IV	277 (94.2%)	136 (95.1%)
Other[b]	2 (0.7%)	0
Number of sites of metastases		
≤ 3	171 (58.2%)	81 (56.6%)
> 3	123 (41.8%)	62 (43.4%)

EGFR mutation		
Mutant	93 (31.6%)	45 (31.5%)
Wild-type	201 (68.4%)	98 (68.5%)
ALK rearrangement		
Rearrangement	5 (1.7%)	2 (1.4%)
Wild-type	286 (98.3%)	140 (98.6%)
Missing data	3	1
Number of previous chemotherapy regimens		
1	4 (1.4%)	0
2	167 (56.8%)	78 (54.5%)
≥ 3	123 (41.8%)	65 (45.5%)
Previous Targeted treatment		
No	136 (46.3%)	74 (51.7%)
Yes	158 (53.7%)	69 (48.3%)
Radiotherapy history		
Yes	118 (40.1%)	65 (45.5%)
No	176 (59.9%)	78 (54.6%)
ECOG		
0	59 (20.1%)	22 (15.4%)
1	233 (79.3%)	120 (83.9%)
2[b]	2 (0.7%)	1 (0.7%)

Smoking history		
Once or now smoking	143 (48.6%)	77 (53.8%)
Non-smoker	151 (51.4%)	66 (46.2%)

[a]Patients with other classifications or cannot be classified.

[b]Two patients with Ib and IIb clinical stage and three patients with ECOG score of 2 were enrolled by mistake. According to the ITT principles and blind review, these patients were not excluded from FAS analysis.

eTable 3. Interaction Analysis Between Treatment and Subgroup Variables

Category and subgroup	Treatment	Events/Patients	Overall survival (months) Median (IQR)	Comparison between groups	Interaction between treatment and subgroup variables	Hazzard ratio (95%CI)
Age						
≤60	Placebo	66/90	6.2 (3.0, 14.5)	χ^2=8.31, *P*=.004	χ^2=2.13, *P*=.35	0.63 (0.46, 0.87)
	Anlotinib	97/153	10.1 (5.7, 18.9)			
60-70	Placebo	29/41	6.3 (4.0, 19.9)	χ^2=0.72,		0.83 (0.55, 1.27)

				P=.40		
	Anlotinib	84/125	7.9 (4.1, 17.5)			
≥70	Placebo	8/12	6.3 (3.3, 13.8)	χ^2=4.68,		0.34 (0.12, 0.94)
				P=.03		
	Anlotinib	8/16	14.5 (8.1, NA)			
Sex						
Male	Placebo	76/97	5.7 (3.0, 9.6)	χ^2=9.70,	χ^2=0.92,	0.64 (0.48, 0.85)
				P=.002	*P*=.34	
	Anlotinib	128/188	8.8 (4.1, 15.3)			
Female	Placebo	27/46	9.5 (3.5, NA)	χ^2=0.75,		0.82 (0.52, 1.29)
				P=.39		
	Anlotinib	61/106	11.4 (6.2, NA)			
Histology						

Adenocarcinoma	Placebo	77/108	6.9 (3.1, 14.5)	χ^2=7.86, *P*=.005	χ^2=0.03, *P*=.86	0.67 (0.51, 0.89)
	Anlotinib	142/228	9.6 (5.5, NA)			
Squamous and others	Placebo	26/35	6.3 (3.2, 11.0)	χ^2=1.70, *P*=.19		0.73 (0.45, 1.18)
	Anlotinib	47/66	9.2 (3.8, 15.6)			
Driver alterations						
No	Placebo	72/95	6.5 (3.2, 11.0)	χ^2=4.54, *P*=.03	χ^2=0.47, *P*=.49	0.73 (0.55, 0.98)
	Anlotinib	133/193	8.9 (4.7, 15.6)			
Yes	Placebo	30/47	6.3 (2.6, NA)	χ^2=4.71, *P*=.03		0.61 (0.39, 0.96)
	Anlotinib	54/98	11.1 (6.3, NA)			

EGFR mutation						
No	Placebo	74/98	6.5 (3.2, 11.3)	χ^2=4.81, *P*=.03	χ^2=0.59, *P*=.44	0.73 (0.55, 0.97)
	Anlotinib	138/201	8.9 (4.7, 15.6)			
Yes	Placebo	29/45	6.3 (3.0, NA)	χ^2=5.19, *P*=.02		0.59 (0.37, 0.93)
	Anlotinib	51/93	10.7 (6.3, NA)			
ALK rearrangement						
No	Placebo	101/140	6.5 (3.2, 14.5)	χ^2=9.51, *P*=.002	χ^2=0.19, *P*=.66	0.68 (0.54, 0.87)
	Anlotinib	184/286	9.6 (5.2, 18.9)			
Yes	Placebo	1/2	NA (0.9, NA)	χ^2=0.03,		1.23 (0.12, 13.02)

				P=.86		
	Anlotinib	3/5	15.4 (4.0, 15.4)			
Clinical stage						
ⅢB	Placebo	5/7	8.5 (3.0, NA)	χ^2=0.34,	χ^2=0.00,	0.72 (0.24, 2.17)
				P=.56	*P*=.94	
	Anlotinib	9/15	11.6 (7.9, NA)			
Ⅳ	Placebo	98/136	6.3 (3.2, 14.5)	χ^2=8.88,		0.69 (0.54, 0.88)
				P=.003		
	Anlotinib	179/277	9.3 (5.2, 18.9)			
Number of metastases						
≤3	Placebo	51/81	8.2 (3. 7, 19.9)	χ^2=5.42,	χ^2=0.01,	0.67 (0.47, 0.94)
				P=.02	*P*=.90	

	Anlotinib	92/171	11.6 (6.8, NA)			
>3	Placebo	52/62	4.8 (3.0, 8.6)	χ^2=4.48, *P*=.03		0.7 (0.50, 0.98)
	Anlotinib	97/123	7.1 (3.4, 12.9)			
ECOG						
0	Placebo	12/22	14.5 (3.8, 20.2)	χ^2=0.46, *P*=.50	χ^2=0.05, *P*=.82	0.79 (0.4, 1.56)
	Anlotinib	29/59	15.1 (6.8, NA)			
≥1	Placebo	91/121	6.3 (3.1, 11.0)	χ^2=8.16, *P*=.004		0.69 (0.53, 0.89)
	Anlotinib	160/235	8.8 (5.1, 16.2)			
Number of previous						

chemotherapy regimens						
2	Placebo	59/78	5.7 (3.0, 11.3)	χ^2=7.25, *P*=.007	χ^2=0.26, *P*=.61	0.65 (0.47, 0.89)
	Anlotinib	113/167	8.6 (4.7, 17.5)			
≥3	Placebo	44/65	7.7 (3.8, 20.2)	χ^2=2.91, *P*=.09		0.72 (0.5, 1.05)
	Anlotinib	74/123	10.1 (6.27, NA)			
Smoking history						
Non-smoker	Placebo	44/66	7.7 (3.2, 20.2)	χ^2=2.77, *P*=.10	χ^2=0.29, *P*=.59	0.74 (0.51, 1.06)
	Anlotinib	89/151	11.1 (6.3, NA)			
Once or now	Placebo	59/77	5.7 (3.0, 9.1)	χ^2=6.88,		0.65 (0.47, 0.9)

smoking				*P*=.009		
	Anlotinib	100/143	8.1 (4.1, 15.1)			
Previous target therapy						
No	Placebo	55/74	6.8 (3.6, 13.6)	χ^2=2.06, *P*=.19	χ^2=1.05, *P*=.30	0.78 (0.56, 1.09)
	Anlotinib	93/136	8.0 (4.6, 15.6)			
Yes	Placebo	48/69	6.2 (2.6, 20.2)	χ^2=7.89, *P*=.005		0.61 (0.43, 0.86)
	Anlotinib	96/158	10.2 (5.8, NA)			

Abbreviation: NA, not achieved.

eTable 4. Subsequent Treatment of Patients in Two Groups (FAS)

Index		Anlotib group	Placebo group	P value
Subsequent treatment (total subjects)	No.	294	143	
	no	151 (51.4%)	50 (35.0%)	.002
	yes	143 (48.6%)	93 (65.0%)	
Subsequent treatment (PD subjects)	No.	212	117	
	no	96 (45.3%)	43 (36.8%)	.16
	yes	116 (54.7%)	74 (63.3%)	
Type of treatment	Chemotherapy	66 (22.5%)	59 (41.3%)	< .0.001
	Targeting-drug therapy	84 (28.6%)	49 (34.3%)	.23

Radiotherapy	25 (8.5%)	21 (14.7%)	.07
TCM	32 (10.9%)	20 (14.0%)	.35
Surgery	7 (2.4%)	4 (2.8%)	.76
Others	3 (1.0%)	2 (1.4%)	.66

Abbreviations: FAS, Full analysis set; PD, progressive disease; TCM, traditional Chinese medicine.

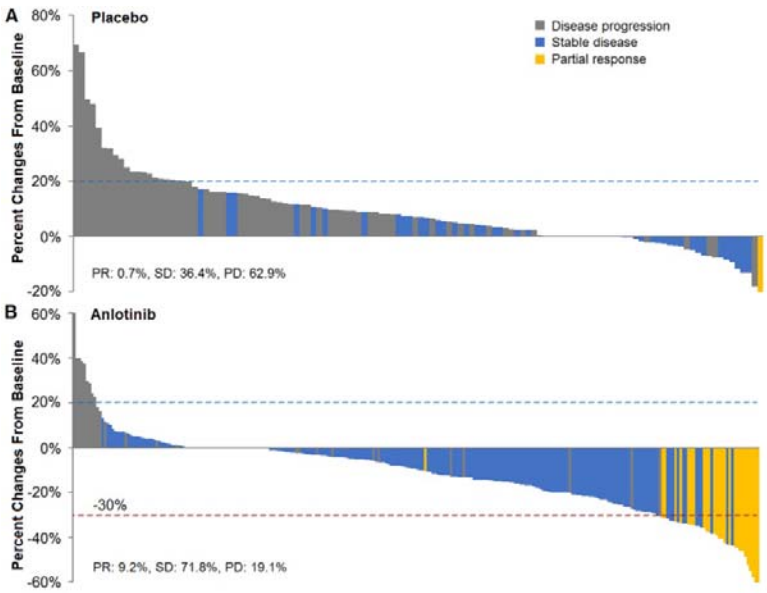
eTable 5. Adverse Events

Adverse events	Anlotinib group (n=294)		Placebo group (n=143)	
	All grades[a]	≥ Grade 3	All grades[a]	≥ Grade 3
Fatigue	153 (52.0%)	1 (0.3%)	41 (28.7%)	0
Anorexia	135 (45.9%)	3 (1%)	46 (32.2%)	3 (2.1%)
Weight loss	68 (23.1%)	0	12 (8.4%)	0
Headache	33 (11.2%)	0	5 (3.5%)	0
Diarrhoea	104 (35.4%)	3 (1.0%)	21 (14.7%)	0
Pharyngalgia	83 (28.2%)	2 (0.7%)	10 (7.0%)	0
Mucositis oral	68 (23.1%)	3 (1%)	4 (2.8%)	0
Hemoptysis	60 (20.4%)	9 (3.1%)	13 (9.1%)	2 (1.4%)
Fecal occult blood	26 (8.8%)	0	3 (2.1%)	0

Dysphonia	68 (23.1%)	3 (1%)	7 (4.9%)	1 (0.7%)
Cough	122 (41.5%)	3 (1%)	41 (28.7%)	1 (0.7%)
Arthralgia	22 (7.5%)	2 (0.7%)	2 (1.4%)	0
hand-foot syndrome	129 (43.9%)	11 (3.7%)	13 (9.1%)	0
Upper respiratory infection	37 (12.6%)	0	4 (2.8%)	0
Urinary tract infection	34 (11.6%)	0	6 (4.2%)	0
Hematuria	44 (15%)	0	8 (5.6%)	0
Proteinuria	85 (28.9%)	7 (2.4%)	19 (13.3%)	1 (0.7%)
Hypertension	199 (67.7%)	40 (13.6%)	24 (16.8%)	0
Thyroid-stimulating hormone elevation	137 (46.6%)	1 (0.3%)	12 (8.4%)	0
Hypertriglyceridemia	131 (44.6%)	9 (3.1%)	34 (23.8%)	0

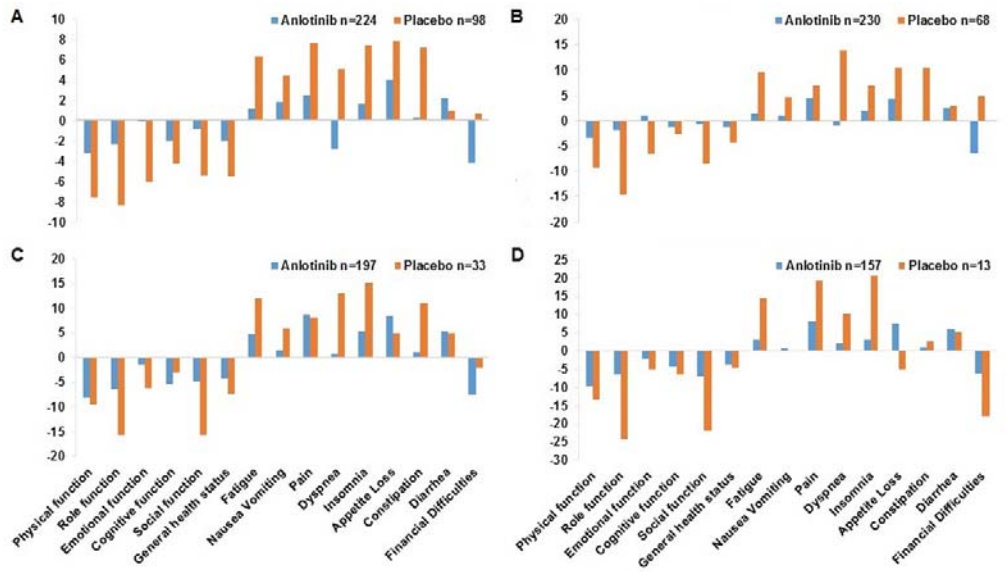
Hypercholesterolemia	123 (41.8%)	0	20 (14.0%)	0
Low density lipoprotein elevation	62 (21.1%)	2 (0.7%)	11 (7.7%)	0
γ-glutamyltransferase elevation	92 (31.3%)	16 (5.4%)	28 (19.6%)	10 (7%)
Blood bilirubin elevation	77 (26.2%)	5 (1.7%)	21 (14.7%)	2 (1.4%)
Hyponatremia	69 (23.5%)	24 (8.2%)	12 (8.4%)	5 (3.5%)
Hypochloridemia	22 (7.5%)	4 (1.4%)	1 (0.7%)	0
Decreased platelet count	31 (10.5%)	3 (1.0%)	6 (4.2%)	0

[a]Reported as adverse events of all grades occurring in at least 5% of patients and with statistical difference between the two groups.

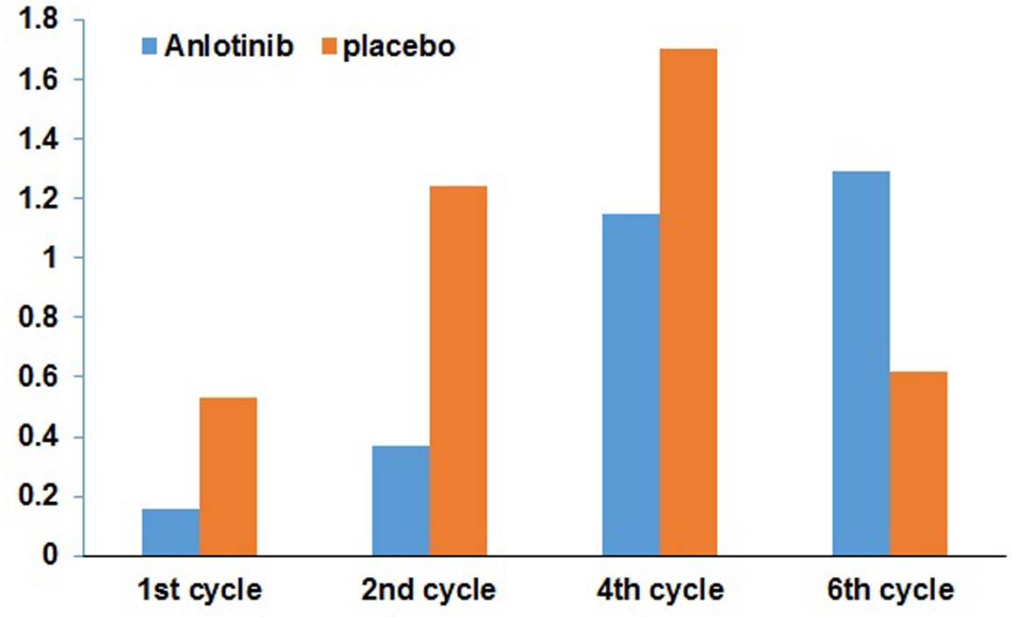


eFigure 1. Waterfall Plot of the Percentage Change From Baseline in the Sum of Longest Tumour Diameters

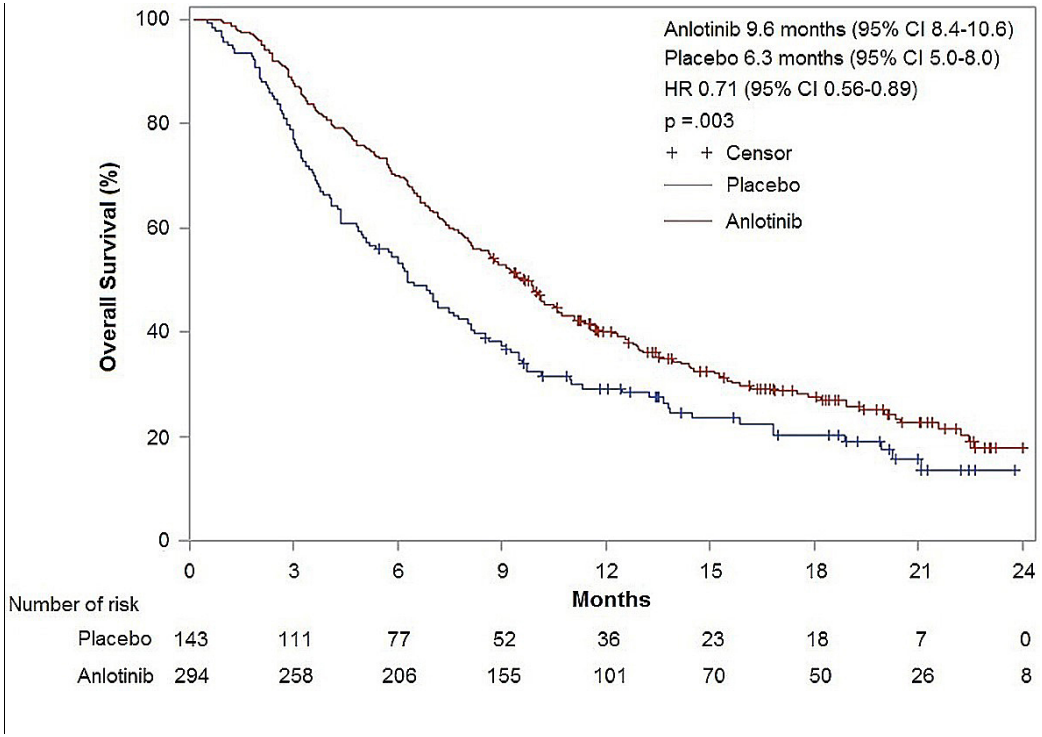
(A) Waterfall plot of tumor response in anlotinib. (B) Waterfall plot of tumor response in placebo. The blue dotted line represents a 20 percent increase in tumors. The red dotted line represents a 30 percent decrease in tumors.



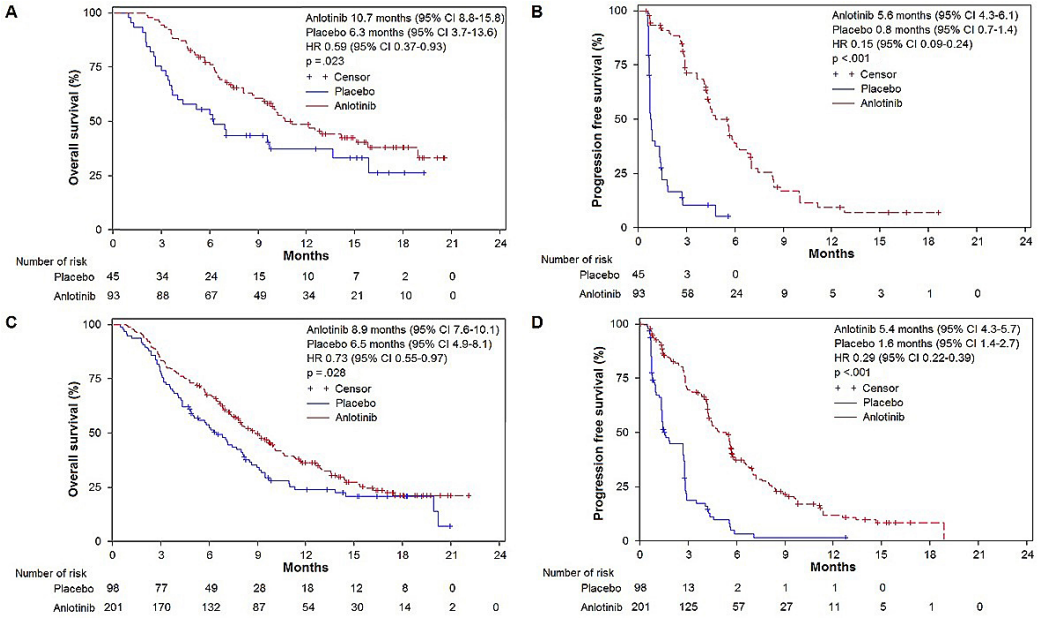
eFigure 2. Mean Changes of QLQ C-30 Score at the End of (A) 1st, (B) 2nd, (C) 4th and (D) 6th Treatment Cycle From Baseline



eFigure 3. Mean Changes of OLQ LC-13 Total Score at the End of Different Treatment Cycles From Baseline



eFigure 4. Kaplan-Meier Estimate of Overall Survival Until May 2017



eFigure 5. Kaplan-Meier Estimates of Overall Survival and Progression-Free Survival in Patients with EGFR+ and EGFR-

(A) Overall survival of patients with EGFR+. (B) progression-free survival of patients with EGFR+. (C) Overall survival of patients with EGFR-.

(D) progression-free survival of patients with EGFR-.