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Supplemental Tables for:
Anlotinib monotherapy for refractory metastatic colorectal cancer: A double-blinded, placebo controlled, randomized Phase III trial (ALTER0703)
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		Anlotinib (n=282)	Placebo (n=137)	P value
Subsequent systemic anti-tumor treatment	No	187(66.31%)	68(49.63%)	0.001
	Yes	95(33.69%)	69(50.36%)	
Type of treatment	Targeted therapy	48(17.02%)	31(22.63%)	0.1840
	Traditional Chinese medicine	55(19.50%)	29(21.17%)	0.6978
	Radiotherapy	21(7.45%)	14(10.22%)	0.3503
	Chemotherapy	77(27.30%)	49(35.77%)	0.0885
	Immunotherapy	8(2.84%)	2(1.46%)	0.5092
	Surgery	10(3.55%)	9(6.57%)	0.2096
	Standard chemotherapy (Oxaliplatin/5-Fu/Irinotecan)	37(13.12%)	28(20.44%)	0.0615
	Cetuximab	9(3.19%)	5(3.65%)	0.7787

Bevacizumab	19(6.74%)	5(3.65%)	0.2642
Apatinib / Regorafenib / Sunitinib / Sorafenib	24(8.51%)	22(16.06%)	0.0293

Supplementary table 1. Subsequent treatment of Anlotinib vs Placebo

Supplementary Table 2. Baseline characteristics (patients with or without subsequent systemic anti-tumor treatment subgroups) of Anlotinib vs Placebo

		Patients with Subsequent systemic anti-tumor treatment			Patients without Subsequent systemic anti-tumor treatment		
		Anlotinib (n=95)	Placebo (n=69)	P value	Anlotinib (n=187)	Placebo (n=68)	P value
Age n(%)	<65	73(76.8%)	58(84.1%)	0.2552	147(78.6%)	55(80.9%)	0.6925
	≥65	22(23.2%)	11(15.9%)		40(21.4%)	13(19.1%)	
Gender n(%)	Male	64(67.4%)	44(63.8%)	0.6312	113(60.4%)	47(69.1%)	0.2044
	Female	31(32.6%)	25(36.3%)		74(39.6%)	21(30.9%)	
ECOG n(%)	0	36(37.9%)	15(21.7%)	0.0273	49(26.2%)	17(25.0%)	0.8462
	1	59(62.1%)	54(78.3%)		138(73.8%)	51(75.0%)	
Primary site of disease n(%)	Colon	47(49.5%)	23(33.3%)	0.0480	95(50.8%)	32(47.1%)	0.3192
	Rectum	44(46.3%)	45(65.2%)		85(45.5%)	33(48.5%)	
	Both	4(4.2%)	1(1.5%)		7(3.7%)	3(4.4%)	

Left or right colon origin n(%)	Right	16(16.8%)	9(13.0%)	0.6610	23(12.3%)	11(16.2%)	0.3192
	Left	73(76.8%)	57(82.6%)		157(84.0%)	52(76.5%)	
	Unknown	6(6.4%)	3(4.4%)		7(3.7%)	5(7.3%)	
Liver metastasis n(%)	No	23(24.2%)	24(34.8%)	0.1394	43(23.0%)	17(25.0%)	0.7385
	Yes	72(75.8%)	45(65.2%)		144(77.0%)	51(75.0%)	
Colon cancer surgery n(%)	No	7(7.4%)	8(11.6%)	0.3540	28(15.0%)	13(19.1%)	0.4256
	Yes	88(92.6%)	61(88.4%)		159(85.0%)	55(80.9%)	
Time from diagnosis to	<18 months	83(87.4%)	57(82.6%)	0.3946	161(86.1%)	58(85.3%)	0.8708
metastases n(%)	≥18 months	12(12.6%)	12(17.4%)		26(13.9%)	10(14.7%)	
KRAS mutation n(%)	Yes (+)	40(42.1%)	36(52.2%)	0.0854	72(38.5%)	18(26.55)	0.1262
	No (-)	42(44.2%)	19(27.5%)		80(42.8%)	31(45.6%)	
	Unknown	13(13.7%)	14(20.3%)		35(18.7%)	19(27.9%)	
RAS/BRAF mutation n(%)	Yes (+)	45(47.4%)	37(53.6%)	0.1657	83(44.4%)	20(29.4%)	0.0866
	No (-)	36(37.9%)	17(24.7%)		67(35.8%)	29(42.7%)	
	Unknown	14(14.7%)	15(21.7%)		37(19.8%)	19(27.9%)	
Previous anti-VEGF treatment	No	55(57.9%)	43(62.3%)	0.5684	137(73.3%)	50(73.5%)	0.9659

n(%)[b]	Yes	40(42.1%)	26(37.7%)		50(26.7%)	18(26.5%)	
Previous chemotherapy n(%)	<3rd line	45(47.4%)	35(50.7%)	0.6712	97(51.9%)	34(50.0%)	0.7914
	≥3rd line	50(52.6%)	34(49.3%)		90(48.1%)	34(50.0%)	
Previous radiotherapy n(%)	No	61(64.2%)	43(62.3%)	0.8039	121(64.7%)		0.3892
	Yes	34(35.8%)	26(37.7%)		66(35.7%)		

Previous treatment included targeted agents in clinical trials' setting. a. Cetuximab, panitumumab, or nimotuzumab; b. Bevacizumab;

c. Regorafenib, fruquintinib, or apatinib

Supplementary Table 3. Results of Cox proportional hazards regression models for patients with subsequent systemic anti-tumor therapy

Factors		df	β	S.E.	χ^2	P	HR(95%CI)
Group	Anlotinib vs. Placebo	1	0.063	0.180	0.120	0.729	1.064(0.748-1.515)
ECOG PS	1 vs. 0	1	0.357	0.196	3.319	0.069	1.428(0.973-2.096)
Primary tumor site	Colon and Rectal vs. Colon	1	0.564	0.482	1.368	0.242	1.757(0.683-4.518)
	Rectal vs. Colon	1	-0.218	0.179	1.483	0.223	0.804(0.566-1.142)

Supplementary Table 4. Baseline characteristics (patients with or without subsequent chemotherapy subgroups) of Anlotinib vs Placebo

		Patients with Subsequent chemotherapy			Patients without Subsequent chemotherapy		
		Anlotinib (n=77)	Placebo (n=49)	P value	Anlotinib (n=205)	Placebo (n=88)	P value
Age n(%)	<65	62(80.5%)	43(87.8%)	0.2880	158(77.1%)	70(79.5%)	0.6406
	≥65	15(19.5%)	6(12.2%)		47(22.9%)	18(20.5%)	
Gender n(%)	Male	54(70.1%)	32(65.3%)	0.5707	123(60.0%)	59(67.0%)	0.2544
	Female	23(29.9%)	17(34.7%)		82(40.0%)	29(33.0%)	
ECOG n(%)	0	25(32.5%)	12(24.5%)	0.3378	60(29.3%)	20(22.7%)	0.2493
	1	52(67.5%)	37(75.5%)		145(70.7%)	68(77.3%)	
Primary site of disease n(%)	Colon	40(52.0%)	18(36.7%)	0.1508	102(49.8%)	37(42.1%)	0.4359
	Rectum	34(44.1%)	30(61.2%)		95(46.3%)	48(54.6%)	
	Both	3(3.9%)	1(2.1%)		8(3.5%)	3(3.4%)	
Left or right colon origin n(%)	Right	14(18.2%)	6(12.2%)	0.6893	25(12.2%)	14(15.9%)	0.5941

	Left	59(76.6%)	40(81.6%)		171(83.4%)	69(78.4%)	
	Unknown	4(5.2%)	3(6.2%)		9(4.4%)	5(5.7%)	
Liver metastasis n(%)	No	16(20.8%)	19(38.8%)	0.0279	50(24.4%)	22(25.0%)	0.9115
	Yes	61(79.2%)	30(61.2%)		155(75.6%)	66(75.0%)	
Colon cancer surgery n(%)	No	6(7.8%)	4(8.2%)	0.9999	29(14.1%)	17(19.3%)	0.2646
	Yes	71(92.2%)	45(91.8%)		176(85.9%)	71(80.7%)	
Time from diagnosis of metastases n(%)	<18 months	68(88.3%)	40(81.6%)	0.8885	176(85.9%)	75(85.2%)	0.8885
	≥18 months	9(11.7%)	9(18.4%)		29(14.1%)	13(14.8%)	
KRAS mutation n(%)	Yes (+)	31(40.3%)	25(51.0%)	0.0140	81(39.5%)	29(33.0%)	0.5137
	No (-)	36(46.7%)	11(22.5%)		86(42.0%)	39(44.3%)	
	Unknown	10(13.0%)	13(26.5%)		38(18.5%)	20(22.7%)	
RAS/BRAF mutation n(%)	Yes (+)	36(46.7%)	26(53.0%)	0.0244	92(44.9%)	31(35.2%)	0.3079
	No (-)	30(39.0%)	9(18.4%)		73(35.6%)	37(42.1%)	
	Unknown	11(14.3%)	14(28.6%)		40(19.5%)	20(22.7%)	
Previous anti-VEGF treatment	No	41(53.3%)	31(63.3%)	0.2679	151(73.7%)	62(70.5%)	0.5726

n(%)[b]							
	Yes	36(46.7%)	18(36.7%)		54(26.3%)	26(29.5%)	
Previous chemotherapy n(%)	<3rd line	36(46.8%)	27(55.1%)	0.3609	106(51.7%)	42(47.7%)	0.5322
	≥3rd line	41(53.2%)	22(44.9%)		99(48.3%)	46(52.3%)	
Previous radiotherapy n(%)	No	51(66.2%)	29(59.2%)	0.4230	131(63.9%)	54(61.4%)	0.6797
	Yes	26(33.8%)	20(40.8%)		74(36.1%)	34(38.6%)	

Previous treatment included targeted agents in clinical trials' setting. a. Cetuximab, panitumumab, or nimotuzumab; b. Bevacizumab;

c. Regorafenib, fruquintinib, or apatinib

Supplementary Table 5. Results of Cox proportional hazards regression models for patients with subsequent chemotherapy

Factors		df	β	S.E.	χ^2	P	HR(95%CI)
Group	Anlotinib vs. Placebo	1	0.310	0.245	1.591	0.207	1.363(0.842-2.205)
KRAS status	Mutated vs. Wild	1	0.209	0.529	0.156	0.693	1.232(0.437-3.473)
	Unknown vs. Wild	1	-0.418	0.754	0.307	0.580	0.659(0.150-2.886)
Ras status	Mutated vs. Wild	1	0.337	0.535	0.395	0.530	1.400(0.490-3.998)
	Unknown vs. Wild	1	0.898	0.743	1.460	0.227	2.454(0.572-10.531)

Supplementary Table 6. Tumor response of Anlotinib vs Placebo

Best response	Anlotinib (n=282)	Placebo (n=137)	P value
PR	12	1	
SD	202	41	
PD	47	73	
NE	0	1	
NA	21	21	
ORR,n(%)	12 (4.26%)	1 (0.73%)	0.0690
DCR,n(%)	214(75.89%)	42(30.66%)	<0.0001

ORR, objective response rate; DCR, disease control rate; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; NA, not available

Supplementary Table 7. Reasons for dose modification in Anlotinib and Placebo

Group	Patient no.	Cycles at adjustment	Dates at adjustment	Adjust dose to	Reason for adjustment	Cycles completed	Date of last dose
A	001	6	2015/4/2	10	III° diarrhea	8	2015/5/31
A	003	56	2018/3/14	10	II° pneumothorax	54	2018/3/2
A	014	10	2016/12/8	10	III° hypertension, II° oral mucositis, I° anorexia)	13	2016/3/9
A	019	1	2015/1/13	10	III° anemia	2	2015/1/26
A	044	3	2015/3/24	10	III° hand-foot skin reaction	6	2015/6/15
A	052	10	2015/8/29	10	III° hand-foot	12	2015/11/

Group	Patient no.	Cycles at adjustment	Dates at adjustment	Adjust dose to	Reason for adjustment	Cycles completed	Date of last dose
					skin reaction		20
A	061	6	2015/6/4	10	III° proteinuria	7	2015/7/20
A	066	Unscheduled visit after cycle 2	2015/3/25	10	II° proteinuria	4	2015/4/30
A	066	3	2015/3/25	10	II° proteinuria	4	2015/4/30
A	072	14	2016/4/26	10	II° fatigue、II° pain	28	2017/3/31
A	078	3	2016/4/24	10	III° hand-foot skin reaction	4	2016/5/28

Group	Patient no.	Cycles at adjustment	Dates at adjustment	Adjust dose to	Reason for adjustment	Cycles completed	Date of last dose
A	081	3	2015/3/31	10	II° lower GI bleeding	16	2016/3/11
A	091	4	2015/5/1	10	III° low platelet count	10	2015/9/29
A	095	2	2015/3/13	10	III° hand-foot skin reaction	2	2015/3/21
A	117	2	2015/9/8	10	III° hypertension with dizziness and headache	2	2015/9/21
A	118	5	2015/6/26	10	II° hand-foot skin reaction	6	2015/7/10
B	124	2	2016/4/22	10	III° hyperbilirubinemia	2	2016/5/5

Group	Patient no.	Cycles at adjustment	Dates at adjustment	Adjust dose to	Reason for adjustment	Cycles completed	Date of last dose
A	140	3	2015/6/26	10	III° low platelet count	3	2015/7/9
A	142	6	2015/9/1	10	III° tooth pain	12	2016/1/18
A	160	4	2015/10/15	10	III° hand-foot skin reaction	8	2016/2/11
A	163	2	2015/9/7	10	IV° malnutrition	6	2015/12/12
A	163	6	2015/12/11	8	Low body surface area	6	2015/12/12
A	168	7	2015/10/26	10	I° fatigue	15	2016/5/5
A	220	5	2015/8/6	10	III° hypertension	8	2015/11/17
A	237	7	2015/8/14	10	III° hand-foot	14	2016/1/2

Group	Patient no.	Cycles at adjustment	Dates at adjustment	Adjust dose to	Reason for adjustment	Cycles completed	Date of last dose
					skin reaction		1
A	240	5	2016/9/7	10	III° diarrhea	6	2015/10/11
A	251	2	2015/4/22	10	III° hyperbilirubinemia	4	2015/6/16
A	267	8	2015/12/23	10	III° GI bleeding	12	2016/4/11
A	275	3	2015/12/10	10	III° hand-foot skin reaction	4	2016/1/13
A	276	4	2016/01/09	10	II° anorexia	6	2016/03/07
A	290	2	2015/8/28	10	I° skin lesion	2	2015/9/12

Group	Patient no.	Cycles at adjustment	Dates at adjustment	Adjust dose to	Reason for adjustment	Cycles completed	Date of last dose
A	331	8	2016/3/22	10	III° hypertension、III° fatigue	8	2016/4/4
A	339	14	2016/10/19	10	III° hand-foot skin reaction	22	2017/5/10
A	357	3	2016/2/28	10	Hypertension, abdominal pain	4	2016/4/2
A	358	2	2015/10/30	10	III° bile duct obstruction, III° increased ALP	4	2015/12/24
A	364	6	2016/1/29	10	Proteinuria	6	2016/2/11
A	384	4	2015/12/7	10	III° hand-foot skin reaction, II°	10	2016/6/2

Group	Patient no.	Cycles at adjustment	Dates at adjustment	Adjust dose to	Reason for adjustment	Cycles completed	Date of last dose
					low platelet count		
A	421	3	2016/1/29	10	III° proteinuria	4	2016/3/3
A	422	13	2016/7/26	10	II° vomiting	22	2017/2/14
A	422	14	2016/8/23	8	II° vomiting	22	2017/2/14
A	424	7	2016/3/27	10	II° hematuria	8	2016/5/21
A	426	10	2016/8/4	10	III° diarrhea	11	2016/9/7
A	427	6	2016/3/16	10	II° diarrhea	14	2016/9/22
A	431	6	2016/3/24	10	II° hand-foot skin reaction 2°	8	2016/6/3
A	432	4	2016/1/14	10	III° hypertension	3	2016/1/2

Group	Patient no.	Cycles at adjustment	Dates at adjustment	Adjust dose to	Reason for adjustment	Cycles completed	Date of last dose
							7
A	433	9	2016/8/10	10	III° fatigue、III° anorexia	4	2016/4/21
A	441	4	2016/6/14	10	III° hand-foot skin reaction	6	2016/8/11
A	443	3	2015/12/31	10	II° hypertension	10	2016/6/4
A	454	6	2016/06/23	10	II° diarrhea	6	2016/07/06
A	461	3	2016/8/31	10	II° hypertension with headache	4	2016/10/4
A	469	4	2016/8/25	10	III° hand-foot skin reaction, III° aphthous stomatitis	8	2016/11/30

Group	Patient no.	Cycles at adjustment	Dates at adjustment	Adjust dose to	Reason for adjustment	Cycles completed	Date of last dose
A	471	5	2016/9/13	10	III° hypertension	18	2017/6/29
A	479	6	2016/7/28	10	II° proteinuria	16	2017/3/9
A	547	8	2016/10/21	10	II° anorexia, II° body weight loss	10	2016/12/15
A	553	6	2016/9/29	10	III° hand-foot skin reaction	8	2016/12/2
A	586	2	2016/7/27	10	III° low platelet count	2	2016/8/9

*56 dose adjustment happened in 53 patients during the trial; A: anlotinib group, B: placebo group