

Supplemental Materials for

**Response to anti-EGFR therapy in patients with BRAF non-V600 mutant metastatic colorectal cancer**

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Supplementary Table S1. Classification of BRAF variants identified in this study

<b>Class2</b>			<b>Class 3</b>			<b>Unknown</b>		
Mutation	N (%)	RAS mt	Mutation	N (%)	RAS mt	Mutation	N (%)	RAS mt
	32 (27)	2		72 (61)	18		13 (11)	11
G464V	1	1	G466E	5	3	T241M	1	1
G469A	11	1	G466V	2	1	R271H	1	1
G469V	3	0	G466R	1	1	P277Hfs*2	1	1
L485F	1	0	G469E	2	1	Q285Tfs*3	1	0
L525R	1	0	Q524L	1	0	F294L	1	1
L597R	2	0	N581I	2	1	P403Lfs*8	1	1
K601E	7	0	N581S	2	0	A404Cfs*9	1	1
Fusion	3	0	N581T	1	0	Y472S	1	1
T599_V600TinsT	1	0	N581Y	1	1	Y472dup	1	1
T599dup	2	0	D594G	38	6	E501K	1	1
			D594N	8	1	H574Y	1	1
			D594A	1	1	F583C	1	0
			D594E	1	1	S602Y	1	1
			D594V	1	1			
			F595L	2	0	<b>No Effect on ERK signal (N.E)</b>		
			G596R	1	0	A33T	1	0
			F247L	2	0			
			R558Q	1	0			

Supplementary Table S2. Patient characteristics based on *BRAF* classification

		Class 2 n = 32	Class 3 n = 72	Unknown or no effect on ERK signal n = 14	Total n = 118 (%)	<i>P</i> Class 2 vs 3
Mean age, years [range]		58 [35-83]	59 [27-79]	50 [30-75]	58 (27-83)	
Sex	Male	19	43	7	69 (58.5)	1.00
	Female	13	29	7	49 (41.5)	
Primary site	Right-sided colon	13	19	6	38 (32.2)	0.12
	Left-sided colon	12	22	6	40 (33.9)	
	Rectum	7	30	2	39 (33.1)	
	Unknown	0	1	0	1 (0.8)	
Mucinous histology	Yes	1	7	3	11 (9.3)	0.43
	No	29	60	7	96 (81.4)	
	Unknown	2	5	4	11 (9.3)	
Stage at diagnosis	1	2	2	0	4 (3.4)	0.41
	2	1	8	2	11 (9.3)	
	3	4	13	4	21 (17.8)	
	4	22	46	8	76 (64.4)	
	Unknown	3	3	0	6 (5.1)	
Adjuvant chemotherapy	Yes	6	17	6	29 (24.6)	0.80
	No	26	55	8	89 (75.4)	
RAS	Wild-type	29	53	3	85 (72.0)	0.03
	Mutant	2	18	11	31 (26.3)	
	Missing	1	1	0	2 (1.7)	
MSI (MMR)	MSI-H (dMMR)	1	0	2	3 (2.5)	0.31
	MSS (pMMR)	18	43	12	73 (61.9)	
	Missing	13	29	0	42 (35.6)	

MSI-H identified in patients with BRAF G469A (n=1), A33T (n=1), and P403Lfs\*8 (n=1).

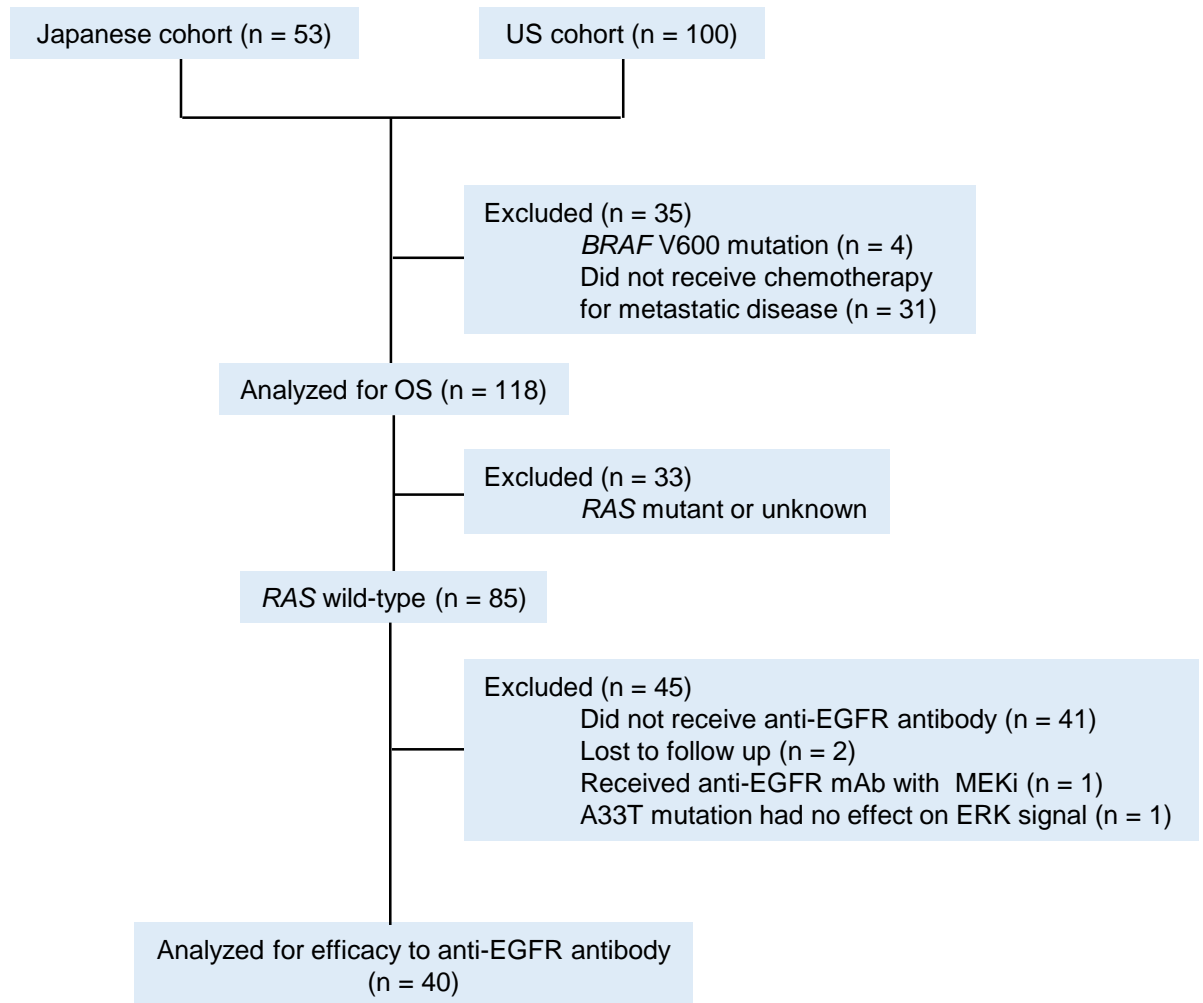
Supplementary Table S3. Characteristics of patients treated with anti-EGFR antibody therapy

		Class 2 n=12	Class 3 n=28	Total N=40	<i>P</i> (class 2 vs. 3)
Median age, years [range]		56 [35-70]	56 [29-77]	56 [29-77]	
Sex	Male	5	15	20 (50.0)	0.73
	Female	7	13	20 (50.0)	
Primary site	Right-sided colon	3	7	10 (25.0)	0.40
	Left-sided colon	5	6	11 (27.5)	
	Rectum	4	14	18 (45.0)	
	Unknown	0	1	1 (2.5)	
Mucinous histology	Yes	0	1	1 (2.5)	1.00
	No	12	25	37 (92.5)	
	Unknown	0	2	2 (5.0)	
Stage at diagnosis	1	0	1	1 (2.5)	0.21
	2	0	2	2 (5.0)	
	3	1	4	5 (12.5)	
	4	8	18	26 (65.0)	
	Unknown	3	3	6 (15.0)	
Adjuvant chemotherapy	Yes	4	8	12 (30.0)	1.00
	No	8	20	28 (70.0)	
MSI (MMR)	MSI-H (dMMR)	0	0	0 (0.0)	1.00
	MSS (pMMR)	6	12	18 (45.0)	
	Missing	6	16	22 (55.0)	

Supplementary Table S4. Response to anti-EGFR antibody therapy based on BRAF classification and the sidedness of the tumor

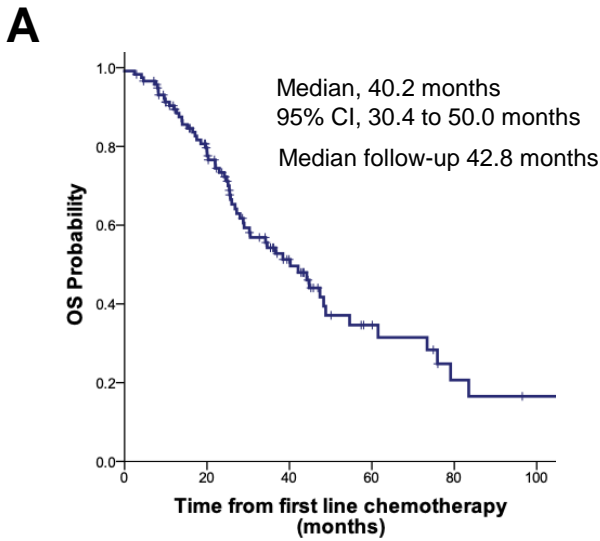
	Class 2		Class 3		<i>P</i>
	No. of patients	No. Responded (%)	No. of patients	No. Responded (%)	
<b>Right-sided</b>	3	0 (0)	7	2 (29)	0.47
<b>Left-sided</b>	9	1 (12)	20	12 (60)	0.02
<b>Total</b>	12	1 (8)	27*	14 (52)	0.01

\* Sidedness was unknown in one patient with class 3 BRAF mutation.



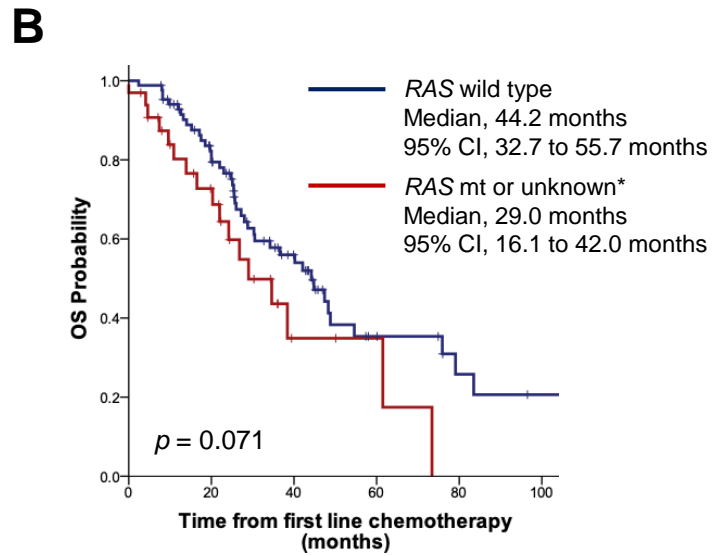
Supplementary Fig. S1. CONSORT diagram.





No. at risk:

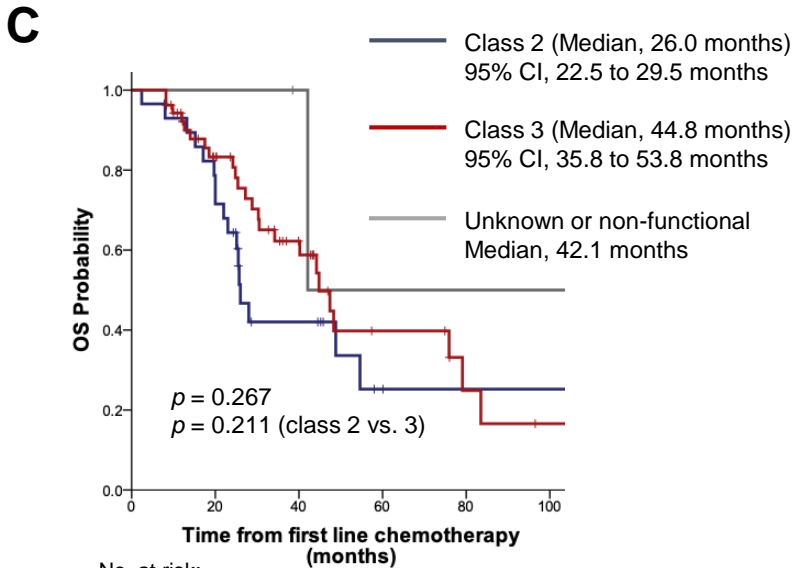
118 78 31 12 5 3



No. at risk:

RAS wt	85	60	28	10	5	3
RAS mt or unknown	33	18	3	2	0	0

\*RAS status was unknown in two patients



No. at risk:

Class 2	29	22	8	2	1	1
Class 3	53	35	18	7	3	1

Unknown or no effect on ERK signal	3	3	2	1	1	1
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Supplementary Fig. S3. OS in all patients with *BRAF* non-V600 mutation (A) and stratified by *RAS* mutation (B), or stratified by *BRAF* classification in patients with *RAS* wild-type tumors (C).