

eTable 3: Outcome according to high vs. low unnormalized AREG expression in all patients and subgroups											
Parameter				Overall survival				Progression-free survival			
	AREG threshold value*	n AREG high	n AREG low	Median AREG high [months]	Median AREG low [months]	HR [95% CI]	p value	Median AREG high [months]	Median AREG low [months]	HR [95% CI]	p value
All patients (n = 675)	Median	340	335	25.7	21.5	0.82 [0.70 – 0.97]	0.019	10.0	8.2	0.75 [0.65 – 0.88]	0.000
RAS WT treated with cetuximab (n = 187)	Median	99	88	36.6	23.5	0.59 [0.42 – 0.81]	0.001	10.6	8.1	0.72 [0.53 – 0.97]	0.029
RAS WT treated with bevacizumab (n = 134)	Median	64	70	27.5	24.7	1.09 [0.76 – 1.56]	0.65	11.1	10.3	1.03 [0.72 – 1.46]	0.89
RAS WT treated with chemotherapy (n = 94)	Median	45	49	23.2	21.6	0.65 [0.41 – 1.04]	0.07	8.7	7.6	0.69 [0.45 – 1.08]	0.10
RAS/BRAF/PIK3CA WT & EGFR positive treated with cetuximab (n = 25)	Median	15	10	36.0	11.3	0.57 [0.21 – 1.52]	0.26	9.6	4.3	0.32 [0.12 – 0.86]	0.023
RAS/BRAF/PIK3CA WT & EGFR negative treated with cetuximab (n = 13)	Median	7	6	40.4	18.0	0.35 [0.09 – 1.26]	0.11	11.8	5.9	0.23 [0.06 – 0.95]	0.042
RAS/BRAF/PIK3CA WT & right sided tumor treated with cetuximab (n = 26)	Median	10	16	24.5	16.1	0.32 [0.11 – 0.87]	0.026	8.5	4.3	0.47 [0.21 – 1.09]	0.08
RAS/BRAF/PIK3CA WT & left sided tumor treated with cetuximab (n = 96)	Median	54	42	38.7	26.9	0.75 [0.47 – 1.20]	0.23	10.6	8.8	0.73 [0.47 – 1.11]	0.14
All patients (n = 675)	3rd quartile	171	504	27.5	23.0	0.80 [0.66 – 0.97]	0.02	10.5	8.9	0.81 [0.67 – 0.97]	0.019
RAS WT treated with cetuximab (n = 187)	3rd quartile	61	126	36.6	25.5	0.64 [0.44 – 0.91]	0.012	10.7	8.6	0.81 [0.59 – 1.11]	0.19
RAS WT treated with bevacizumab (n = 134)	3rd quartile	33	101	28.2	24.1	0.96 [0.64 – 1.43]	0.84	11.5	10.7	1.05 [0.70 – 1.56]	0.83
RAS WT treated with chemotherapy (n = 94)	3rd quartile	27	67	23.2	21.8	0.78 [0.48 – 1.28]	0.33	7.5	8.1	0.81 [0.50 – 1.32]	0.40
RAS/BRAF/PIK3CA WT & EGFR positive treated with cetuximab (n = 25)	3rd quartile	9	16	39.9	14.6	0.45 [0.16 – 1.29]	0.14	11.2	4.4	0.50 [0.21 – 1.19]	0.12
RAS/BRAF/PIK3CA WT & EGFR negative treated with cetuximab (n = 13)	3rd quartile	5	8	31.6	20.5	0.53 [0.14 – 2.06]	0.36	11.8	6.5	0.44 [0.13 – 1.50]	0.19
RAS/BRAF/PIK3CA WT & right sided tumor treated with cetuximab (n = 26)	3rd quartile	8	18	24.5	16.1	0.35 [0.12 – 1.05]	0.06	8.5	4.3	0.52 [0.22 – 1.25]	0.14
RAS/BRAF/PIK3CA WT & left sided tumor treated with cetuximab (n = 96)	3rd quartile	36	60	38.3	33.1	0.71 [0.44 – 1.15]	0.16	10.7	8.9	0.82 [0.53 – 1.26]	0.36

Legend: AREG = amphiregulin; HR = hazard ratio; 95% CI = 95% confidence interval. P values were calculated by Cox regression analyses. P values < 0.05 are considered significant and displayed bold. *For each trial, trial-specific median and 3rd quartile of AREG expression was used to dichotomize high and low expression without normalization. Patients exceeding the trial-specific threshold values were pooled as group "AREG high" and patients deceeding the trial-specific threshold value were pooled as group "AREG low".