Table 1. Patients with grade 2-5 CTCAE toxicities at 12 weeks and detectable odds ratios at 70% power

Toxicity	Frequency		Detectable odds ratio	
	XELOX ± cetuximab n (%)	FOLFOX ± cetuximab n (%)	XELOX ± cetuximab	FOLFOX ± cetuximab
Diarrhoea	288 (27)	187 (25)	2	3
Neutropenic sepsis	6 (1)	63 (8)	NA	4
Peripheral neuropathy	154 (15)	73 (10)	2	3
Hand-foot syndrome	109 (10)	65 (9)	3	4
Neutropenia	42 (4)	209 (28)	4	2
Lethargy	361 (34)	256 (34)	2	2
Stomatitis	61 (6)	150 (20)	4	3
Nausea	210 (20)	88 (12)	2	3
Vomiting	122 (12)	59 (8)	3	4
Rash	177 (17)	201 (27)	2	2

Percentage of patients in parentheses. NA - for neutropenic sepsis in patients treated with XELOX ± cetuximab we had insufficient power to perform the genome-wide association study. Patients with hand-foot syndrome were graded 2-3.

Table 2. Relationship between hand-foot syndrome (HFS) and patient outcome in COIN and COIN-B

Model	Grade of HFS (n)	Response at 12 weeks				Overall survival			
		% Responders	OR	95% CI	*P* (multivariate)	Median survival (days)	HR	95% CI	*P* (multivariate)
Grouped	0-1 (1626)	58	1.6	1.1-2.2	$1.4x10^{-2}$ ($2.0x10^{-2}$)	503	0.81	0.67-0.97	$2.4x10^{-2}$ (0.15)
	2-3 (174)	68				596			
Linear	0 (1264)	56	1.3	1.2-1.6	$1.4x10^{-4}$ ($2.0x10^{-4}$)	499	0.90	0.83-0.97	$5.8x10^{-3}$ ($4.6x10^{-2}$)
	1 (362)	66				514			
	2 (144)	68				596			
	3 (30)	67				687			

Response was defined as complete or partial response using RECIST 1.0 guidelines and no response was defined as stable or progressive disease. 1,800 patients had data on overall survival and 1,590 had data on response at 12 weeks. Covariates included

in the multivariate analysis were age, sex, disease site, World Health Organisation performance status, primary tumour resection status, white blood cell count, chemotherapy regimen and cetuximab status.

Table 3. Relationship between rs6783836 and hand-foot syndrome (HFS) in patients from COIN and COIN-B treated with XELOX ± cetuximab.

Treatment groups analysed	Total patients	Patients G0-1 HFS			Patients G2-3 HFS			OR	95% CI	*P*-value
		wild type	heterozygous	homozygous	wild type	heterozygous	homozygous			
Meta-analysis	1,042	734	190	10	58	48	2	3.1	2.1-4.6	$4.3x10^{-8}$
Subgroups:										
XELOX	699	520	121	5	30	21	2	3.3	1.9-5.7	$2.7x10^{-5}$
XELOX + cetuximab	343	214	69	5	28	27	0	2.9	1.6-5.1	$3.0x10^{-4}$

Reference allele = T, OR = Odds ratio, CI = Confidence intervals.