

**Comprehensive Pharmacogenetic Profiling of the Epidermal
 Growth Factor Receptor Pathway for Biomarkers of
 Response to, and Toxicity from, Cetuximab**

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4 Factor Receptor Pathway for Biomarkers of Response to, and Toxicity
5 from, Cetuximab
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ABSTRACT

Background

Somatic mutations in the epidermal growth factor receptor (EGFR) intracellular signalling pathways predict non-response to cetuximab in the treatment of advanced colorectal cancer (aCRC). We hypothesized that common germline variants within these pathways may also play similar roles.

Methods

We analysed 54 potentially functional, common, inherited EGFR pathway variants in 815 aCRC patients treated with oxaliplatin-fluoropyrimidine chemotherapy +cetuximab. Primary endpoints were response and skin rash (SR). We had >85% power to detect ORs=1.6 for variants with minor allele frequencies >20%.

Results

We identified five potential biomarkers for response and four for SR, although none remained significant after correction for multiple testing. Our initial data supported a role for Ser313Pro in *PIK3R2* in modulating response to cetuximab - in patients with *KRAS* wild type CRCs, 36.4% of patients with one allele encoding proline responded, as compared to 71.2% of patients homozygous for alleles encoding serine (OR 0.23, 95% CI 0.09-0.56, $P=0.0014$) and this association was predictive for cetuximab ($P_{interaction}=0.017$); however, independent replication failed to validate this association. No previously proposed predictive biomarkers were validated.

Conclusions

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3 Our study highlights the need to validate potential pharmacogenetic biomarkers. We
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5 did not find strong evidence for common germline biomarkers of cetuximab response
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7 and toxicity.
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11 **Key Words:** Pharmacogenetics, colorectal cancer, cetuximab, biomarkers.
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INTRODUCTION

The treatment of colorectal cancer (CRC) is improving with average survival for advanced CRC (aCRC) increasing from ~6 months with best supportive care alone, through 10-12 months with fluoropyrimidine-based regimens [1] and up to 16-21 months with oxaliplatin or irinotecan and a fluoropyrimidine.[2, 3] In addition, monoclonal antibodies (McAbs) against the epidermal growth factor receptor (EGFR) improve overall survival (OS) in patients with aCRC in whom other treatments have failed [4] and, in combination with first line therapy, in those with *RAS* wild type tumours.[5] EGFR acts as a gate-way for the Ras-Raf-MAP and PI3K-PTEN-Akt intracellular signalling pathways. The efficacy of cetuximab and panitumumab (anti-EGFR McAbs) is dependent upon an absence of somatic mutations in members of this signalling cascade such as *KRAS* [6] and *NRAS*,[5] and these predictive biomarkers help guide the treatment of aCRC.[7]

Inherited factors are also likely to affect response to, and side effects from, chemotherapy and biological therapy. Pro241 in *CCND1*,[8] 61A>G in *EGF*,[8, 9] His131Arg in *FCGR2A*,[10] Val158Phe in *FCGR3A*,[10, 11] 765G>C and +8473T>C in *PTGS2*,[12] and, Arg521Lys [13] and a (CA)_n repeat [11, 14] in *EGFR* have all been suggested to predict response to cetuximab.

The United Kingdom MRC COIN trial (NCT00182715), which consists of 2445 aCRC patients treated with oxaliplatin-fluoropyrimidine chemotherapy ±cetuximab, serves as an important resource for the discovery of new, and validation of existing, genetic biomarkers.[15, 16] We used this resource, together with patients from the allied COIN-B trial of oxaliplatin-fluoropyrimidine chemotherapy +cetuximab

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3 (NCT00640081) [17] to investigate the role of 54 potentially functional, common,
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5 inherited EGFR-related variants in predicting response to, and side effects from,
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7 cetuximab.
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10 11 **METHODS**

12 13 **Patients and treatments**

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15 All patients had metastatic or locally advanced colorectal adenocarcinoma and
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17 received no previous chemotherapy for advanced disease. All patients gave fully
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19 informed consent for this study (approved by REC [04/MRE06/60]). COIN patients
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21 were randomised 1:1:1 to receive continuous oxaliplatin and fluoropyrimidine
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23 chemotherapy (Arm A), continuous chemotherapy +cetuximab (Arm B), or
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25 intermittent chemotherapy (Arm C).[15, 16] COIN-B patients were randomised 1:1 to
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27 receive intermittent chemotherapy and cetuximab (Arm D) or intermittent
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29 chemotherapy and continuous cetuximab (Arm E) (Supplementary Figure).[17]
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36 37 **Selection and genotyping of potential pharmacogenetic variants**

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39 Potentially functional inherited variants were sought in 146 genes identified from
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41 literature reviews as likely to play a role in the EGFR signalling pathways. Variants
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43 were considered potentially functional if there was previous clinical or biological
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45 evidence for an effect on response or side effects, if they were nonsynonymous, or if
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47 they occurred in the promoter region. Variants were mined from dbSNP (v.129,
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49 <http://www.ncbi.nlm.nih.gov/SNP/>) and from exome re-sequencing germline data,
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51 and those with a minor allele frequency (MAF) >5% (Caucasian population) were
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53 considered for genotyping. Genotyping was carried out using a custom Illumina
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55 GoldenGate assay or by in-house assays (Supplementary Information).
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Independent analysis of Ser313Pro in *PIK3R2*

We obtained germline DNA samples together with response data for 309 unrelated patients with *KRAS* wild-type CRCs that were treated with cetuximab alone or in combination with chemotherapy. These were previously collected as part of an international consortium study.[18] We carried out PCR amplification using the primers 5'-GGGCCGTAAATACTGATCCCT-3' and 5'-TCCAACATTGGGACTGCCGA-3' and directly sequenced the purified products. In total, 81.9% (n=253) of samples were successfully amplified and genotyped.

Clinical parameters assessed

The primary endpoints were: (i) 12-week response, defined as complete response or partial response *versus* stable disease or progressive disease at 12-weeks; and, (ii) grade ≥ 2 skin rash (SR) or cetuximab dose reduction or delay due to SR *versus* grade < 2 SR with no cetuximab dose modification. Response was assessed using RECIST criteria and SR toxicity was graded using NCI Common Terminology Criteria version 3.0.[19] Secondary efficacy endpoints were OS and overall response rate (ORR), and secondary toxicity endpoints were grade ≥ 2 at any point *versus* grade < 2 for lethargy, nausea or vomiting, diarrhoea, stomatitis, Hand-Foot Syndrome (HFS), hypomagnesaemia and nail changes.

Sample size and power considerations

Patients from COIN Arm B and COIN-B (those treated with cetuximab) had similar efficacy and toxicity outcomes at 12-weeks, so were combined to increase power, as were patients from COIN Arms A and C (no cetuximab). A total of 2183 patients

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3 were genotyped, of which 815 received cetuximab (676 had a response outcome
4 and 730 had a SR outcome) and 1368 did not receive cetuximab (1169 had a
5 response outcome). Based on 676 patients (received cetuximab, genotyped and with
6 data on response), we had >85% power ($P<0.05$) to detect an OR of 1.6, equating to
7 a 12% difference in response or SR (45% responded or had SR) for a variant with a
8 MAF>20%, and an OR of 2.3, corresponding to a 20% difference in response or SR,
9 for a variant with a MAF>5%.
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20 21 **Statistical analyses**

22 Genotypes were tested for deviation from the Hardy Weinberg Equilibrium (HWE)
23 using a chi-squared test with $P<9.3\times 10^{-4}$ (multiple testing for $n=54$ variants).
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26 Pharmacogenetic analyses were carried out using Stata 12.1 with a co-dominant
27 model, and tested using the likelihood-ratio chi-squared statistic. For significant
28 associations ($P<0.05$), subsequent analyses were carried out using logistic
29 regression under the best-fitting allele model and adjusted for the type of
30 fluoropyrimidine. Correction for multiple testing was by Bonferroni.
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40 41 **RESULTS**

42 We extracted DNA from peripheral blood samples from 2183 unrelated patients with
43 aCRC from the UK national trials COIN (2070 of the 2445 randomised) and COIN-B
44 (113 of the 226 randomised). All patients received oxaliplatin and fluoropyrimidine
45 chemotherapy \pm cetuximab as continuous or intermittent regimens. For the first 12-
46 weeks, at which point the primary pharmacogenetic analyses were carried out,
47 treatments were identical in all patients apart from the choice of fluoropyrimidine
48 (n=834, 38% received OxMdG and n=1349, 62% received Xelox) together with the
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3 randomisation of ±cetuximab (n=815, 37% received cetuximab) (Supplementary
4 Figure, Supplementary Table S1). Here, we focussed on the analysis of the 815
5 patients treated with cetuximab, to identify predictive biomarkers for this biological
6 therapy (Figure).
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14 Eighty potentially functional, common (MAFs >5%), inherited, coding and promoter-
15 region variants were identified in the EGFR pathway. Of these, 71 passed *in silico*
16 locus conversion on the GoldenGate platform and 51 were successfully assayed.
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18 Four variants were assayed 'in house' of which three were successfully genotyped.
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20 No genotypes deviated from the HWE. Therefore, in total, 54 variants were
21 considered for the analyses of response to, and side effects from, cetuximab
22 (Supplementary Table S2, Figure).
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32 **Primary analyses for response**

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34 Five variants were associated with response ($P<0.05$), the most significant being a
35 nonsynonymous variant (Ser313Pro) in the phosphatidylinositol 3-kinase regulatory
36 (PIK3R) subunit 2 (Table, Supplementary Table S3); 40.3% of patients with an allele
37 encoding proline responded as compared to 60.4% of patients homozygous for
38 alleles encoding serine (OR=0.44, 95% CI 0.26-0.75, $P=0.002$). We stratified by
39 *KRAS* status and found that this association was only significant in patients with
40 *KRAS* wild type CRCs (36.4% of patients with an allele encoding proline responded
41 as compared to 71.2% of patients homozygous for alleles encoding serine, OR 0.23,
42 95% CI 0.09-0.56, $P=0.0014$; [as compared to 40.0% and 50.5% of patients with
43 *KRAS* mutant CRCs respectively, OR 0.65 95% CI 0.30-1.43, $P=0.29$];
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3 $P_{interaction}=0.076$], Supplementary Table S4). No associations remained significant
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5 after correction for multiple testing.
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10 We analysed Ser313Pro in *PIK3R2* in *KRAS* wild-type patients who did not receive
11 cetuximab (from Arms A and C of COIN), and observed a predictive effect for
12 response to cetuximab ($P_{interaction}=0.017$, Supplementary Table S4).
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18 We sought independent evidence for a predictive role of Ser313Pro by analysing
19 germline DNA samples from 309 unrelated patients with *KRAS* wild-type CRCs that
20 were treated with cetuximab. We had >90% power to observe an OR 0.23 equating
21 to a 35% difference in response (found in COIN). We did not find any effect on
22 objective response, with an allelic trend in the opposite direction: 45.8% (11/24) of
23 patients with one allele encoding proline had a response, as compared to 32.2%
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60 (68/211) of patients homozygous for alleles encoding serine ($P=0.18$).

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2 **Table - Variants with $P < 0.05$ for the primary endpoints**
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Endpoint	rs no.	Gene	Variant	Endpoint +/-	AA	AB	BB	χ^2 (df) P-value ^a	OR (95% CI) P-value ^b	Predictive for cetuximab (YES/NO) OR (95% CI) & P-value for no cetuximab ^c P interaction			
										Any KRAS status		KRAS wild type	
12-week response	rs1011320	PIK3R2	Ser313Pro	+	0	25	371	9.42 (1)	0.44 (0.26, 0.75)	NO	YES		
				-	0	37	243	0.002	0.002 (d)	0.73 (0.50, 1.07), 0.11 P interaction = 0.13	0.82 (0.47, 1.45), 0.51 P interaction = 0.017		
	rs17537869	PLCG2	Arg268Trp	+	1	61	336	8.13 (2)	1.66 (1.03, 2.67)	YES	NO		
				-	3	25	253	0.017	0.037 (d)	0.64 (0.45, 0.89), 0.009 P interaction = 0.001	0.68 (0.41, 1.11), 0.12 P interaction = 0.052		
	rs4444903	EGF	c.1-382 A>G	+	135	218	45	7.54 (2)	0.56 (0.36, 0.86)	NO	NO		
				-	94	135	52	0.023	0.008 (r)	0.91 (0.67, 1.25), 0.56 P interaction = 0.070	0.73 (0.47, 1.14), 0.17 P interaction = 0.17		
	rs78803121	EREG	Cys141Phe	+	1	34	363	7.44 (2)	0.57 (0.37, 0.89)	NO	NO		
				-	5	35	251	0.024	0.013 (a)	0.85 (0.60, 1.21), 0.38 P interaction = 0.16	0.83 (0.50, 1.39), 0.49 P interaction = 0.15		
	rs5275	PTGS2	c.1812+430 T>C	+	142	196	60	6.95 (2)	1.51 (1.10, 2.06)	YES	NO		
				-	128	114	39	0.031	0.010 (d)	1.02 (0.80, 1.28), 0.90 P interaction = 0.046	1.09 (0.78, 1.53), 0.60 P interaction = 0.21		
rs785467	PIK3R3	Asn283Lys	+	160	182	34	9.55 (2)	1.56 (1.17, 2.10)	YES	n/a			
			-	190	133	31	0.009	0.003 (d)	0.43 (0.16, 1.17), 0.099 P interaction = 0.014				
rs16858808	IL8RA	Arg335Cys	+	0	23	353	5.29 (1)	2.36 (1.10, 5.04)	NO	n/a			
			-	0	10	343	0.022	0.027 (d)	1.85 (0.42, 8.24), 0.42 P interaction = 0.81				
SR	rs41292521	EPS15	Ser438Leu	+	0	25	351	5.17 (1)	2.26 (1.09, 4.68)	NO	n/a		
				-	0	11	342	0.023	0.028 (d)	1.24 (0.16, 9.47), 0.84 P interaction = 0.58			
rs602990	VAV2	Met584Val	+	83	163	130	6.85 (2)	n/a (od)	NO	n/a			
			-	61	187	106	0.033		χ^2 (df) = 0.33 (2), 0.85 P interaction = 0.91				

35 Results shown using a co-dominant model^a and, odds ratios and 95% confidence intervals using the best model that fitted the data^b [models for (d) = dominant allele, (r) = recessive
36 allele, (a) = additive allele, (od) = over-dominant allele]. ^cPatients not treated with cetuximab were from Arms A and C of COIN. For endpoints, + = patients that responded or had SR, -
37 patients that did not respond or have SR. A and B alleles were assigned by Illumina; the common allele encodes the wild type amino acid, so for Ser313Pro the B allele encodes Ser
38 and for Asn283Lys the A allele encodes Asn. n/a, not applicable for over-dominant model and SR is unlikely to be related to the tumours molecular profile. No associations were
39 significant after correction for multiple testing.

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3 Arg268Trp in *PLCG2* was also associated with response in COIN/COIN-B (OR=1.66,
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5 95% CI 1.03-2.67, $P=0.037$) and was predictive for cetuximab ($P_{interaction}=0.001$,
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7 Table); however, this effect was only significant in the *KRAS* mutant subset
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9 ($P_{interaction}=0.034$, Supplementary Table S5) and was not significant after correction
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11 for multiple testing.
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14 15 16 **Primary analyses for SR**

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18 Four variants were associated with SR ($P<0.05$), the most significant being
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20 Asn283Lys in *PIK3R3* (Table, Supplementary Table S3); 56.8% of patients with at
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22 least one allele encoding lysine had severe SR as compared to 45.7% of patients
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24 homozygous for alleles encoding asparagine (OR 1.56, 95% CI 1.17-2.10, $P=0.003$).
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26 This association was predictive for cetuximab ($P_{interaction}=0.014$, Table); however, no
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28 associations remained significant after correction for multiple testing. There was no
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30 interaction with the type of fluoropyrimidine used ($P=0.66$).
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36 **Previously proposed predictive biomarkers**

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38 Numerous germline variants in the EGFR pathway have been suggested to be
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40 predictive biomarkers for cetuximab response.[8-14] These were tested as part of
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42 our study and only c.1-382A>G (61A>G) in *EGF* and c.1812+430T>C in *PTGS2*
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44 were significantly associated with response ($P=0.008$ and 0.010, respectively), and
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46 trended towards ($P_{interaction}=0.07$), or had a significant ($P_{interaction}=0.046$), predictive
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48 effect for cetuximab (irrespective of *KRAS* status), respectively (Table). However,
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50 neither were predictive in the *KRAS* wild type subset ($P_{interaction} = 0.17$ and 0.21,
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52 respectively; Table).
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Secondary analyses

Ser313Pro in *PIK3R2* was associated with OS and ORR, Cys141Phe in *EREG* with ORR and Asp784Val in *EGF* with OS (Supplementary Table S6). Val906Ile in *MAP3K1* was associated with lethargy, His321Arg in *RASAL1* and Arg574Pro in *MMP9* with nausea/vomiting, Lys344Thr in *RPS6KA1* and Val906Ile in *MAP3K1* with diarrhoea, Arg298His in *PTGES2*, Met322Thr in *TSC1*, Phe212Val in *FCGR3A* and c.1-1671insA in *MMP3* with stomatitis, c.1-382 A>G in *EGF*, Pro1170Ala in *ERBB2*, Cys141Phe in *EREG* and Asp806Asn in *MAP3K1* with HFS, Tyr187His in *DUSP1* with hypomagnesaemia and Arg335Cys in *IL8RA*, Glu920Val in *EGF* and Lys220Arg in *PLAUR* with nail changes (Supplementary Table S7). None of the associations remained significant after correction for multiple testing.

DISCUSSION

In total, we analysed 54 inherited variants from genes in the EGFR-related pathways for a potential role in response to, or side effects from, cetuximab in the treatment of aCRC. Given the size of our cohort, we had considerable power to detect common alleles of small effects. Although, we identified five potential biomarkers for response and four for SR in our primary analyses, none remained significant after adjusting for multiple testing. Numerous common inherited biomarkers for cetuximab response have been proposed by others;[8-14] however, many of these have been derived from studies using small cohorts of patients and, consequently, the majority have failed,[14] or have been inconsistent upon independent replication.[12, 14, 18, 20] In our study, we analysed these variants and had limited evidence for c.1-382A>G (61A>G) in *EGF* and c.1812+430T>C (+8473T>C) in *PTGS2* in predicting response to cetuximab. However, neither effect was found in the important *KRAS* wild-type

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3 subset (which had the potential to respond), and, our data did not support the
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5 proposed direction of allelic effect for c.1-382A>G.[12, 14] Therefore, we have no
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7 strong evidence for a predictive role for any of these variants.
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13 Our study clearly highlights the need to validate potential pharmacogenetic
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15 biomarkers. Initial data from our study strongly supported a role for Ser313Pro in
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17 *PIK3R2* in modulating response to cetuximab and this association was only
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19 significant in those patients with CRCs that were wild type for *KRAS*, so had the
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21 potential to respond, and was not found in patients that did not receive cetuximab,
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23 regardless of their *KRAS* status, so was unlikely to be a prognostic effect. However,
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25 we carried out a well-powered independent analysis of unrelated patients and failed
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27 to validate our initial observations, suggesting that this was a chance event.
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35 In conclusion, we have carried out a comprehensive, well-designed study to identify
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37 common germline biomarkers for cetuximab-related outcomes, but failed to establish
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39 strong evidence for their existence.
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51
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57 **COMPETING INTEREST**

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4
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8 9 **AUTHOR CONTRIBUTIONS**

10 JP Cheadle and TSM obtained funding for this study. The study was designed by JP
11
12 Cheadle, AM, TSM, DF and RSK, and was carried out under the direction of JP
13
14 Cheadle. AM carried out the literature searches and identified the variants for
15
16 genotyping. TSM was CI of COIN, HW was CI of COIN-B and, RAA and AM were
17
18 COIN trial fellows; all provided clinical advice and assistance, and supported the
19
20 translational research. AMM and RSK managed the COIN and COIN-B trials and
21
22 facilitated access to the clinical data. ST and BVdB provided samples and clinical
23
24 data for the validation analyses. SI extracted the COIN and COIN-B blood DNA
25
26 samples and, with RH, prepared them for genotyping at Illumina. VH and JM
27
28 undertook the in-house genotyping under the direction of JP Colley. DF undertook all
29
30 of the statistical analyses. AM and JP Cheadle interpreted the data with input from
31
32 DF, RAA and TSM. JP Cheadle and AM wrote the paper with input from DF, and all
33
34 authors provided comments.
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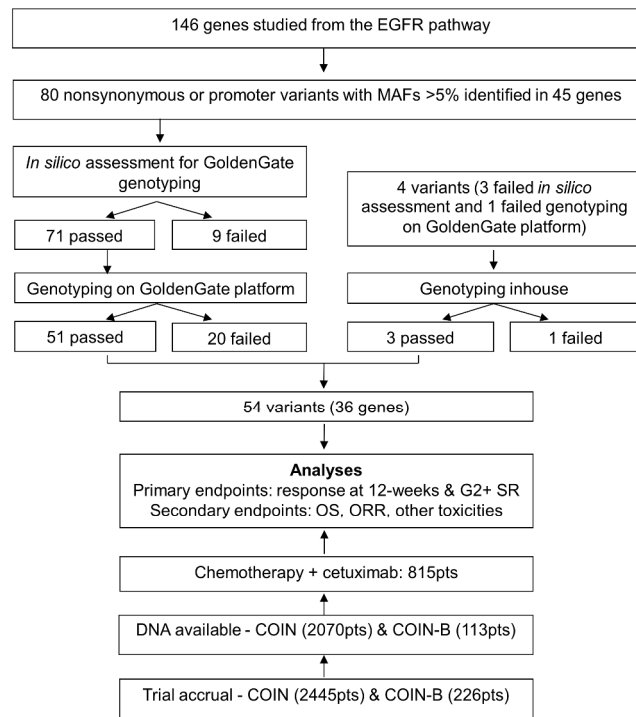
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LEGEND TO FIGURE

Figure. CONSORT diagram of the study design and analyses. Shown are the numbers of variants analysed, together with the numbers of patients studied, and the primary and secondary endpoints. MAF, minor allele frequency; pts, patients; SR, skin rash; OS, overall survival; ORR, overall response rate.

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CONSORT diagram of the study design and analyses. Shown are the numbers of variants analysed, together with the numbers of patients studied, and the primary and secondary endpoints. MAF, minor allele frequency; pts, patients; SR, skin rash; OS, overall survival; ORR, overall response rate.

Figure

254x190mm (300 x 300 DPI)

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3 Supplementary Information for “Comprehensive Pharmacogenetic Profiling of the
4 Epidermal Growth Factor Receptor Pathway for Biomarkers of Response to, and
5 Toxicity from, Cetuximab”
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10 11 12 13 **Supplementary Methods**

14 15 **Genotyping**

16
17 Most variants were single nucleotide polymorphisms (SNPs) genotyped using a
18 custom Illumina GoldenGate assay. The Assay Design Tool (Illumina) was used to
19 anticipate genotyping success. This was based on the designability rank and
20 validation class for a given SNP. When two or more SNPs occurred within 60bp of
21 one another, the SNP selected for submission was chosen based on its designability
22 score, MAF and likelihood of being functional using *in silico* analyses (PolyPhen or
23 align-GVGD). For the 51 SNPs successfully genotyped on the GoldenGate platform,
24 the mean GC score was 0.83 (range 0.49-0.96), genotype success rate was 99.9%
25 (41522/41565) and there was 100% concordance between duplicate samples.
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41 Four variants were assayed ‘in house’ because they were not suitable for (n=3), or
42 failed (n=1), GoldenGate genotyping. The (CA)_n repeat in intron 1 of *EGFR*
43 (rs11568315) was assayed using the primers 5'-GGCTCACAGCAAACCTTCTCC-3'
44 and 5'-TATGGTCGGTAGTCACGAAGC-3' and the c.1-1671 insertion A in the *MMP3*
45 promoter (rs35068180) was assayed using the primers 5'-
46 AGCTGCCACAGCTTCTACAC-3' and 5'-GTATTCTATGGTTCTCCATTC-3'. One of
47 the primers for each pair was fluorescently labelled and PCR products were
48 analysed on an ABI3100 using the GeneScan Analysis Software (ABI). Phe212Val in
49 *FCGR3A* (rs396991) was assayed using a Taqman real time quantitative PCR assay
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(ABI). The -216 G>T variant in the *EGFR* promoter (rs17288945) was analysed using a Taqman assay, allele-specific amplification and by direct sequencing without success.

Supplementary Figure: Treatment schedules for patients in COIN and COIN-B.

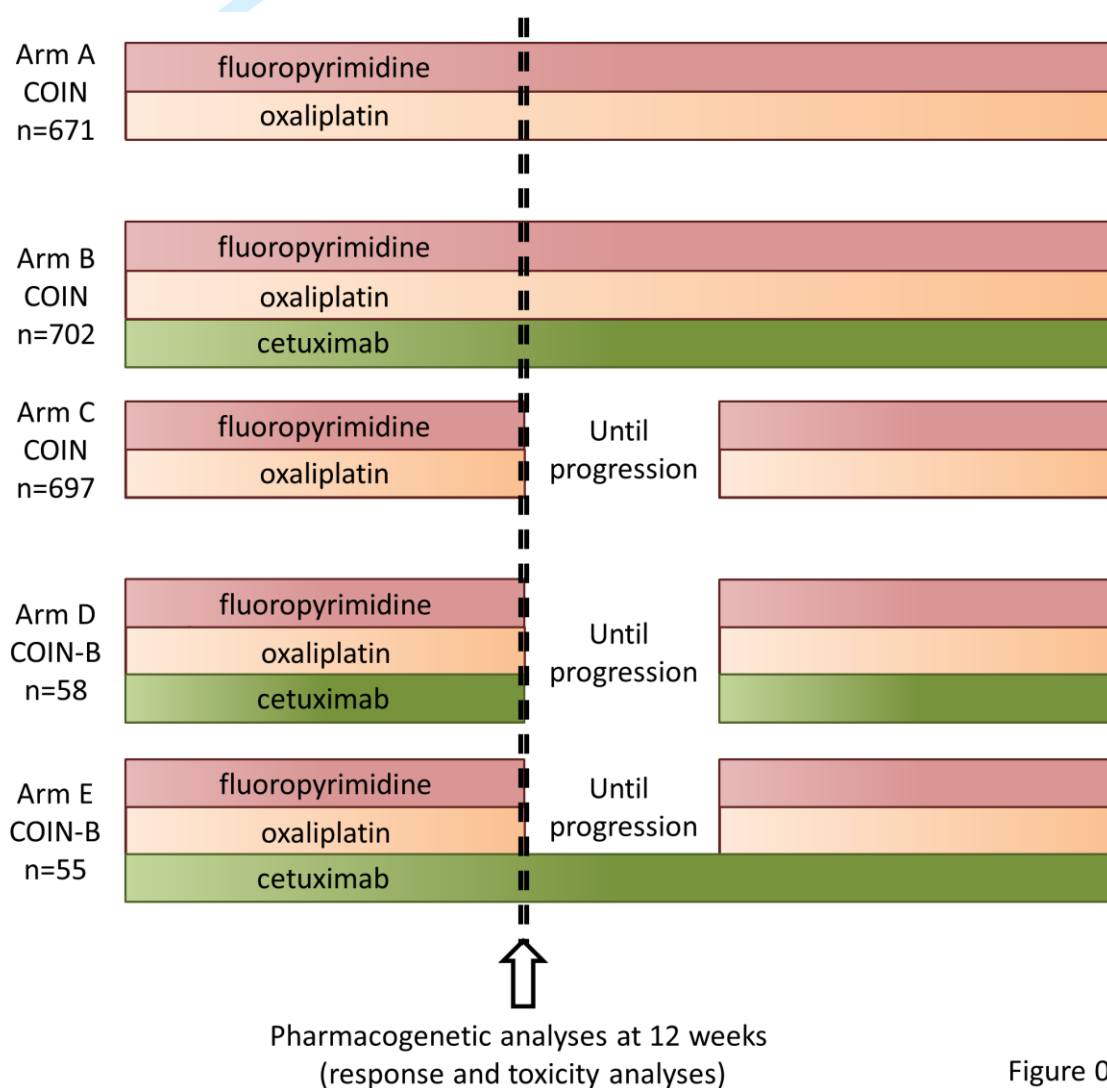


Figure 01

Patients received continuous oxaliplatin and fluoropyrimidine chemotherapy (Arm A), continuous chemotherapy +cetuximab (Arm B), intermittent chemotherapy (Arm C), intermittent chemotherapy with cetuximab (Arm D) and intermittent chemotherapy

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2
3 with continuous cetuximab (Arm E). In all patients, treatment was identical for the
4
5 first 12-weeks apart from the choice of fluoropyrimidine together with the
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7 randomisation of \pm cetuximab. Primary pharmacogenetic analyses were carried out at
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9 12-weeks. For arms with intermittent therapy, treatment was stopped from 12-weeks
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11 (apart from cetuximab in Arm E) if there was complete response, partial response or
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13 stable disease and re-initiated upon disease progression.
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Supplementary Tables:

Supplementary Table S1 - Clinicopathological data for patients in COIN and COIN-B, and heterogeneity across analysis groups and their arms (genotyped patients)

		+ cetuximab		- cetuximab	<i>P</i> ¹	<i>P</i>	<i>P</i>
		COIN	COIN-B	COIN		D vs E	A vs C
		Arm B	Arms D+E	Arms A+C			
n =		702	113	1368			
	Mean (S.D.)	62.9 (9.8)	61.9 (10.5)	62.4 (9.8)	0.39	0.82	0.20
	<20	0 (0.0)	0 (0.0)	1 (0.1)	0.69	0.32	0.30
Age at randomisation	20-49	74 (10.5)	12 (10.6)	133 (9.7)			
	50-59	147 (20.9)	25 (22.1)	329 (24.1)			
	60-69	289 (42.2)	50 (44.3)	563 (41.2)			
	70-79	186 (26.5)	24 (21.4)	335 (24.5)			
	80-89	6 (0.9)	2 (1.8)	7 (0.5)			
Sex	Female	231 (32.9)	48 (42.5)	465 (34.0)	0.14	0.77	0.92
	Male	471 (67.1)	65 (57.5)	903 (66.0)			
WHO-PS	0	330 (47.0)	58 (51.3)	639 (46.7)	0.76	0.89	0.99
	1	325 (46.3)	46 (40.7)	623 (45.5)			
	2	47 (6.7)	9 (8.0)	106 (7.8)			
Primary Site	Colon	377 (53.7)	69 (61.1)	739 (54.0)	0.85	0.009 ²	0.21
	Rectum	229 (32.6)	32 (28.3)	424 (31.0)			
	RSJ	95 (13.5)	12 (10.6)	202 (14.8)			
	Other	1 (0.1)	0 (0.0)	2 (0.2)			
	Missing	0 (0.0)	0 (0.0)	1 (0.1)			
Number of metastatic sites	0	5 (0.7)	1 (0.9)	9 (0.7)	0.37	0.41	0.99
	1	267 (38.0)	43 (38.1)	469 (34.2)			
	2	265 (37.8)	50 (44.3)	548 (40.1)			
	≥3	165 (23.5)	19 (16.8)	342 (25.0)			
Metastatic sites	Liver only	168 (23.9)	24 (21.2)	290 (21.2)	0.47	0.85	0.94
	Liver + others	356 (50.7)	56 (49.6)	738 (54.0)			
	No Liver	178 (25.4)	33 (29.2)	340 (24.9)			
Treatment details	Continuous OxFp	0 (0.0)	0 (0.0)	671 (49.1)	N/A	N/A	N/A
	Continuous OxFp+C	702 (100.0)	0 (0.0)	0 (0.0)			
	Intermittent OxFp	0 (0.0)	0 (0.0)	697 (50.9)			
	Intermittent OxFp C	0 (0.0)	58 (51.3)	0 (0.0)			
	Int. OxFp+maint C	0 (0.0)	55 (48.7)	0 (0.0)			
Fluoropyrimidine partner	Xelox	462 (65.8)	0 (0.0)	887 (64.8)	0.66 ³	N/A	0.88
	OxMdG	240 (34.2)	113 (100.0)	481 (35.2)			

<i>KRAS</i> result	Wild-type	319 (55.1)	60 (61.2)	671 (59.5)	0.17	0.083	0.35
	Mutated	260 (44.9)	38 (38.8)	456 (40.5)			
<i>NRAS</i> result	Wild-type	551 (95.2)	53 (93.0)	1087 (97.1)	N/A	N/A	N/A
	Mutated	28 (4.8)	4 (7.0) ⁴	33 (2.9)			
<i>BRAF</i> result	Wild-type	545 (93.8)	44 (80.0)	1006 (89.7)	N/A	N/A	N/A
	Mutated	36 (6.2)	11 (20.0) ⁴	116 (10.3)			

¹Comparing patients treated with cetuximab to those without. ²Not significant after correction for multiple testing. ³Excluding COIN-B (i.e. comparing COIN cetuximab vs non-cetuximab).

⁴In COIN-B, only carried out on *KRAS* wild-type CRCs. N/A – not applicable. RSJ – Rectosigmoid junction. Percentages in parentheses, unless otherwise stated.

Supplementary Table S2 - Coding region and promoter variants and their associated genes analysed in this study

rs no.	Gene	Variant	MAF
rs3740199	<i>ADAM12</i>	Gly48Arg	0.45
rs459552	<i>APC</i>	Val1822Asp	0.22
rs11938093	<i>BTC</i>	Leu124Met	0.26
rs9344	<i>CCND1</i>	Pro241	0.43
rs2230804	<i>CHUK</i>	Val268Ile	0.47
rs34471628	<i>DUSP1</i>	Tyr187His	0.04
rs770087	<i>DUSP6</i>	Ser144Ala	0.20
rs4444903	<i>EGF</i>	promoter c.1-382 A>G	0.40
rs11568943	<i>EGF</i>	Arg431Lys	0.06
rs2237051	<i>EGF</i>	Ile708Met	0.38
rs11569017	<i>EGF</i>	Asp784Val	0.05
rs4698803	<i>EGF</i>	Glu920Val	0.21
rs2227983	<i>EGFR</i>	Arg521Lys	0.26
rs11568315	<i>EGFR</i>	intron 1 (CA) _n repeat	0.45
rs17567	<i>EPS15</i>	Ile822Met	0.23
rs41292521	<i>EPS15</i>	Ser438Leu	0.02
rs1058808	<i>ERBB2</i>	Pro1170Ala	0.31
rs78803121	<i>EREG</i>	Cys141Phe	0.06
rs1801274	<i>FCGR2A</i>	His166Arg	0.48
rs396991	<i>FCGR3A</i>	Phe212Val	0.34
rs4073	<i>IL8</i>	promoter c.1-352 T>A	0.46
rs16858808	<i>IL8RA</i>	Arg335Cys	0.03
rs1870377	<i>KDR</i>	Gln472His	0.23
rs2305948	<i>KDR</i>	Val297Ile	0.11
rs702689	<i>MAP3K1</i>	Asp806Asn	0.28
rs832582	<i>MAP3K1</i>	Val906Ile	0.17
rs243865	<i>MMP2</i>	promoter c.1-2206 C>T	0.25
rs679620	<i>MMP3</i>	Lys45Glu	0.48
rs35068180	<i>MMP3</i>	promoter c.1-1671insA	0.48
rs17576	<i>MMP9</i>	Gln279Arg	0.35
rs2274756	<i>MMP9</i>	Arg668Gln	0.14
rs2250889	<i>MMP9</i>	Arg574Pro	0.04
rs41427445	<i>MMP9</i>	Asn38Ser	0.01
rs3729680	<i>PIK3CA</i>	Ile391Met	0.07
rs3730089	<i>PIK3R1</i>	Met326Ile	0.16
rs1011320	<i>PIK3R2</i>	Ser313Pro	0.05
rs785467	<i>PIK3R3</i>	Asn283Lys	0.30
rs2302524	<i>PLAUR</i>	Lys220Arg	0.16
rs4760	<i>PLAUR</i>	Leu317Pro	0.16
rs2228246	<i>PLCG1</i>	Ser279Gly	0.16
rs753381	<i>PLCG1</i>	Ile813Thr	0.46
rs17537869	<i>PLCG2</i>	Arg268Trp	0.07
rs13283456	<i>PTGES2</i>	Arg298His	0.20
rs1236913	<i>PTGS1</i>	Trp8Arg	0.7

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3	rs5789	<i>PTGS1</i>	Leu237Met	0.03
4			promoter	
5	rs20417	<i>PTGS2</i>	c.1-899 C>G	0.16
6			3'UTR	
7	rs5275	<i>PTGS2</i>	c.1812+430 A>G	0.35
8				
9	rs751019	<i>PTK2B</i>	Lys838Thr	0.45
10	rs1284879	<i>RASAL1</i>	His321Arg	0.22
11	rs2229712	<i>RPS6KA1</i>	Lys344Thr	0.22
12	rs61755579	<i>SOS2</i>	Ala208Thr	0.03
13	rs1073123	<i>TSC1</i>	Met322Thr	0.13
14	rs602990	<i>VAV2</i>	Met584Val	0.47
15	rs61751477	<i>VAV2</i>	Ile779Met	0.01
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MAF – Minor allele frequencies in patients from COIN and COIN-B.

Supplementary Table S3 - Analyses of 12-week response and skin rash (SR) (primary endpoints)

rs no.	Response		SR	
	X ² (df)	P-value	X ² (df)	P-value
rs9344	0.18 (2)	0.91	1.35 (2)	0.51
rs1801274	2.41 (2)	0.30	0.08 (2)	0.96
rs396991	1.97 (2)	0.37	0.94 (2)	0.63
rs20417	0.87 (2)	0.65	2.72 (2)	0.26
rs5275	6.95 (2)	0.031	5.24 (2)	0.073
rs2227983	2.73 (2)	0.26	2.62 (2)	0.27
rs11568315	0.40 (2)	0.82	1.37 (2)	0.50
rs4444903	7.54 (2)	0.023	1.36 (2)	0.51
rs11568943	1.43 (2)	0.23	1.86 (2)	0.39
rs2237051	5.73 (2)	0.057	1.93 (2)	0.38
rs11569017	2.96 (2)	0.086	1.12 (1)	0.29
rs4698803	4.87 (2)	0.088	2.83 (2)	0.24
rs11938093	2.26 (2)	0.32	0.48 (2)	0.79
rs3729680	0.51 (2)	0.77	3.87 (2)	0.14
rs78803121	7.44 (2)	0.024	4.59 (2)	0.10
rs1011320	9.42 (1)	0.0021	3.59 (1)	0.058
rs17537869	8.13 (2)	0.017	1.85 (2)	0.40
rs2228246	1.99 (2)	0.37	2.27 (2)	0.32
rs2302524	1.06 (2)	0.59	1.37 (2)	0.50
rs4760	0.66 (2)	0.72	0.37 (2)	0.83
rs679620	1.76 (2)	0.41	0.10 (2)	0.95
rs751019	3.83 (2)	0.15	2.82 (2)	0.24
rs753381	3.16 (2)	0.21	1.15 (2)	0.56
rs13283456	0.99 (2)	0.61	0.56 (2)	0.76
rs1870377	5.02 (2)	0.081	0.66 (2)	0.72
rs2230804	0.13 (2)	0.94	1.50 (2)	0.47
rs2305948	0.52 (2)	0.77	0.91 (2)	0.63
rs4073	0.00 (2)	0.99	0.28 (2)	0.87
rs602990	1.27 (2)	0.53	6.85 (2)	0.033
rs702689	0.14 (2)	0.93	0.42 (2)	0.81
rs785467	0.37 (2)	0.83	9.55 (2)	0.0085
rs832582	0.92 (2)	0.63	0.77 (2)	0.68
rs1073123	1.56 (2)	0.46	2.89 (2)	0.24
rs1236913	0.32 (1)	0.57	0.22 (1)	0.64
rs1284879	0.09 (2)	0.96	0.72 (2)	0.70
rs17576	0.28 (2)	0.87	0.26 (2)	0.88
rs2274756	0.31 (2)	0.86	1.86 (2)	0.40
rs243865	2.74 (2)	0.25	2.54 (2)	0.28
rs3740199	3.48 (2)	0.18	3.33 (2)	0.19
rs459552	5.88 (2)	0.053	1.43 (2)	0.49
rs770087	1.07 (2)	0.59	4.28 (2)	0.12
rs1058808	2.28 (2)	0.32	3.30 (2)	0.19
rs2229712	0.64 (2)	0.73	1.73 (2)	0.42
rs16858808	0.60 (1)	0.44	5.29 (1)	0.022
rs17567	3.41 (2)	0.18	0.76 (2)	0.68
rs2250889	2.80 (1)	0.095	0.19 (1)	0.66
rs34471628	1.11 (1)	0.29	1.54 (1)	0.21
rs41427445	0.36 (1)	0.55	0.56 (1)	0.45
rs5789	0.12 (1)	0.73	1.23 (1)	0.27

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3	rs41292521	1.00 (1)	0.32	5.17 (1)	0.023
4	rs61755579	0.07 (1)	0.79	0.13 (1)	0.72
5	rs61751477	0.63 (1)	0.43	0.20 (1)	0.65
6	rs3730089	0.32 (2)	0.85	1.93 (2)	0.38
7	rs35068180	2.01 (2)	0.37	0.10 (2)	0.95
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Supplementary Table S4 - Association of Ser313Pro in *PIK3R2* with response to cetuximab

Cetuximab	All patients		<i>KRAS</i> mutant		<i>KRAS</i> wild type ¹	
	+	-	+	-	+	-
≥1 allele encoding proline	25/62 (40.3%)	58/117 (49.6%)	12/30 (40.0%)	17/40 (42.5%)	8/22 (36.4%)	31/55 (56.4%)
homozygous for alleles encoding serine	371/614 (60.4%)	602/1050 (57.3%)	110/218 (50.5%)	191/353 (54.1%)	210/295 (71.2%)	317/521 (60.8%)
OR (95% CI)	0.44 (0.26, 0.75)	0.73 (0.50, 1.07)	0.65 (0.30, 1.43)	0.63 (0.32, 1.22)	0.23 (0.09, 0.56)	0.82 (0.47, 1.45)
P-value	0.002	0.11	0.29	0.17	0.001	0.51
Predictive for cetuximab?	NO <i>P</i> interaction=0.13		NO <i>P</i> interaction=0.94		YES <i>P</i> interaction=0.017	

Numbers represent patients with that genotype that responded to treatment over all patients for whom we had data on response, with percentages in parentheses. ¹On a *RAS* (*KRAS* and *NRAS*) wild-type background, 38.1% (8/21) of patients treated with cetuximab and with ≥1 allele encoding proline responded as compared to 74.0% (202/273) of patients homozygous for alleles encoding serine (OR 0.21, 95% CI 0.08-0.52, *P*=0.001 unadjusted; OR 0.22, 95% CI 0.09-0.58, *P*=0.002 adjusted for *BRAF* status). This was significantly predictive for cetuximab, *P*_{interaction}=0.027 unadjusted and 0.026 adjusted (OR_{no cetuximab} 0.73, 95% CI 0.40-1.32, *P*=0.30 unadjusted, OR 0.80, 95% CI 0.44-1.46, *P*=0.46 adjusted). No associations were significant after correction for multiple testing.

Supplementary Table S5 - Association of Arg268Trp in *PLCG2* with response to cetuximab

cetuximab	All patients		<i>KRAS</i> mutant		<i>KRAS</i> wild type	
	+	-	+	-	+	-
≥1 allele encoding tryptophan homozygous for alleles encoding arginine	62/90 (69.9%)	72/154 (46.7%)	22/34 (64.7%)	24/52 (46.2%)	32/41 (78.1%)	38/73 (52.1%)
OR (95% CI)	1.66 (1.03, 2.67)	0.64 (0.45, 0.89)	2.05 (0.96, 4.40)	0.73 (0.41, 1.31)	1.70 (0.78, 3.73)	0.68 (0.41, 1.11)
P-value	0.037	0.009	0.064	0.29	0.18	0.12
Predictive for cetuximab?	YES <i>P</i> interaction=0.001		YES <i>P</i> interaction=0.034		NO <i>P</i> interaction=0.052	

Numbers represent patients with that genotype that responded to treatment over all patients for whom we had data on response, with percentages in parentheses.

Supplementary Table S6 - Analyses of overall survival (OS) and overall response rate (ORR) (secondary endpoints)

rs no.	OS		ORR	
	X ² (df)	P-value	X ² (df)	P-value
rs9344	0.72 (2)	0.70	0.74 (2)	0.69
rs1801274	1.27 (2)	0.53	1.57 (2)	0.46
rs396991	0.63 (2)	0.73	1.91 (2)	0.39
rs20417	0.69 (2)	0.71	1.58 (2)	0.45
rs5275	1.26 (2)	0.53	5.04 (2)	0.080
rs2227983	1.00 (2)	0.61	3.48 (2)	0.18
rs11568315	0.41 (2)	0.81	0.35 (2)	0.84
rs4444903	3.33 (2)	0.19	5.08 (2)	0.079
rs11568943	2.73 (2)	0.26	0.46 (1)	0.50
rs2237051	1.87 (2)	0.39	4.34 (2)	0.11
rs11569017	3.91 (2)	0.048	3.03 (1)	0.082
rs4698803	1.46 (2)	0.48	1.42 (2)	0.49
rs11938093	4.68 (2)	0.096	0.68 (2)	0.71
rs3729680	0.75 (2)	0.69	0.85 (2)	0.65
rs78803121	0.77 (2)	0.68	6.71 (2)	0.035
rs1011320	7.34 (1)	0.0067	10.3 (1)	0.0014
rs17537869	2.09 (2)	0.35	5.11 (2)	0.078
rs2228246	2.23 (2)	0.33	2.31 (2)	0.31
rs2302524	3.02 (2)	0.22	1.41 (2)	0.49
rs4760	2.14 (2)	0.34	1.41 (2)	0.49
rs679620	0.82 (2)	0.66	1.06 (2)	0.59
rs751019	0.31 (2)	0.85	5.41 (2)	0.067
rs753381	2.03 (2)	0.36	2.49 (2)	0.29
rs13283456	1.42 (2)	0.49	2.98 (2)	0.23
rs1870377	1.25 (2)	0.54	1.77 (2)	0.41
rs2230804	0.34 (2)	0.84	0.46 (2)	0.79
rs2305948	0.41 (2)	0.82	0.39 (2)	0.82
rs4073	5.25 (2)	0.072	1.34 (2)	0.51
rs602990	1.21 (2)	0.55	0.98 (2)	0.61
rs702689	1.64 (2)	0.44	0.43 (2)	0.80
rs785467	0.83 (2)	0.66	0.31 (2)	0.85
rs832582	1.51 (2)	0.47	0.25 (2)	0.88
rs1073123	2.26 (2)	0.32	1.40 (2)	0.50
rs1236913	1.41 (1)	0.24	0.52 (1)	0.47
rs1284879	2.78 (2)	0.25	0.98 (2)	0.61
rs17576	2.32 (2)	0.31	0.39 (2)	0.82
rs2274756	0.88 (2)	0.64	0.32 (2)	0.85
rs243865	0.95 (2)	0.62	2.86 (2)	0.24
rs3740199	0.30 (2)	0.86	3.50 (2)	0.17
rs459552	0.17 (2)	0.92	5.24 (2)	0.073
rs770087	1.32 (2)	0.52	1.45 (2)	0.49
rs1058808	1.07 (2)	0.59	1.81 (2)	0.41
rs2229712	5.86 (2)	0.054	3.46 (2)	0.18
rs16858808	0.47 (1)	0.49	0.15 (1)	0.70
rs17567	2.45 (2)	0.29	0.13 (2)	0.94
rs2250889	1.96 (1)	0.16	2.90 (1)	0.089
rs34471628	0.42 (1)	0.52	1.48 (1)	0.22
rs41427445	0.30 (1)	0.58	1.62 (1)	0.20
rs5789	0.24 (1)	0.62	0.40 (1)	0.53

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4	rs41292521	0.32 (1)	0.57	0.84 (1)	0.36
5	rs61755579	0.34 (1)	0.56	0.01 (1)	0.94
6	rs61751477	3.53 (2)	0.17	0.95 (1)	0.33
7	rs3730089	0.50 (2)	0.78	0.29 (2)	0.86
8	rs35068180	0.23 (2)	0.89	1.06 (2)	0.59
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Supplementary Table S7 – Analyses of individual toxicities (secondary endpoints)

rs no.	Lethargy		Nausea/vomiting		Diarrhoea		Stomatitis		HFS		Hypomagnesaemia		Nail changes	
	χ^2 (df)	P-value	χ^2 (df)	P-value	χ^2 (df)	P-value	χ^2 (df)	P-value	χ^2 (df)	P-value	χ^2 (df)	P-value	χ^2 (df)	P-value
rs9344	1.36 (2)	0.51	4.83 (2)	0.089	0.29 (2)	0.87	0.12 (2)	0.94	1.01 (2)	0.60	0.32 (2)	0.85	0.21 (1)	0.64
rs1801274	2.13 (2)	0.34	2.52 (2)	0.28	5.40 (2)	0.067	2.84 (2)	0.24	4.84 (2)	0.089	2.24 (2)	0.33	4.62 (2)	0.099
rs396991	0.32 (2)	0.85	2.42 (2)	0.30	3.14 (2)	0.21	7.18 (2)	0.028	1.16 (2)	0.56	0.52 (2)	0.77	0.40 (1)	0.53
rs20417	0.20 (2)	0.91	1.01 (2)	0.60	2.36 (2)	0.31	0.35 (2)	0.84	0.10 (2)	0.95	0.91 (1)	0.34	0.31 (1)	0.58
rs5275	3.48 (2)	0.18	2.73 (2)	0.26	1.87 (2)	0.39	1.57 (2)	0.46	0.30 (2)	0.86	0.37 (1)	0.54	2.97 (2)	0.23
rs2227983	1.01 (2)	0.60	3.26 (2)	0.20	0.05 (2)	0.98	0.99 (2)	0.61	3.86 (2)	0.15	0.48 (1)	0.49	2.93 (1)	0.087
rs11568315	0.27 (2)	0.87	1.67 (2)	0.43	0.03 (2)	0.98	2.55 (2)	0.28	0.05 (2)	0.98	0.02 (1)	0.88	0.75 (2)	0.69
rs4444903	0.98 (2)	0.61	1.37 (2)	0.51	2.03 (2)	0.36	1.75 (2)	0.42	9.42 (2)	0.0090	0.86 (2)	0.65	0.65 (2)	0.72
rs11568943	0.01 (2)	0.99	0.82 (2)	0.66	0.18 (1)	0.67	0.79 (2)	0.67	0.23 (1)	0.63	0.06 (1)	0.81	0.11 (1)	0.74
rs2237051	1.05 (2)	0.59	2.14 (2)	0.34	3.76 (2)	0.15	3.23 (2)	0.20	3.94 (2)	0.14	1.14 (2)	0.56	1.10 (2)	0.58
rs11569017	0.01 (1)	0.94	0.08 (1)	0.78	0.56 (1)	0.45	1.45 (1)	0.23	0.11 (1)	0.74	0.21 (1)	0.64	0.00 (1)	0.97
rs4698803	1.03 (2)	0.60	1.01 (2)	0.60	1.44 (2)	0.49	2.65 (2)	0.27	2.81 (2)	0.25	0.18 (1)	0.67	10.6 (2)	0.0049
rs11938093	1.08 (2)	0.58	1.21 (2)	0.55	2.25 (2)	0.32	0.72 (2)	0.70	0.79 (2)	0.67	0.53 (2)	0.77	0.91 (2)	0.64
rs3729680	0.39 (2)	0.82	0.57 (1)	0.45	0.27 (1)	0.61	1.52 (1)	0.22	0.48 (2)	0.79	0.00 (1)	0.99	Cannot be fitted	
rs78803121	0.41 (2)	0.82	0.79 (2)	0.67	0.95 (2)	0.62	0.06 (2)	0.97	4.08 (1)	0.043	0.10 (1)	0.76	Cannot be fitted	
rs1011320	0.46 (1)	0.50	0.00 (1)	0.98	0.25 (1)	0.62	0.73 (1)	0.39	0.25 (1)	0.62	Cannot be fitted		0.68 (1)	0.41
rs17537869	1.69 (2)	0.43	2.39 (1)	0.12	4.09 (2)	0.13	0.14 (2)	0.93	2.29 (2)	0.32	1.02 (1)	0.31	0.27 (1)	0.60
rs2228246	0.84 (2)	0.66	0.55 (2)	0.76	2.19 (2)	0.34	0.79 (2)	0.67	1.10 (2)	0.58	Cannot be fitted		1.90 (1)	0.17
rs2302524	1.54 (2)	0.46	3.19 (2)	0.20	2.01 (2)	0.37	3.04 (2)	0.23	2.13 (2)	0.35	2.02 (1)	0.16	6.50 (2)	0.039
rs4760	1.84 (2)	0.40	1.37 (2)	0.50	0.30 (2)	0.86	1.06 (2)	0.59	0.97 (2)	0.62	0.47 (1)	0.49	1.60 (2)	0.45
rs679620	1.33 (2)	0.51	0.43 (2)	0.81	0.05 (2)	0.97	0.16 (2)	0.92	0.57 (2)	0.75	1.36 (2)	0.51	2.59 (2)	0.27
rs751019	2.23 (2)	0.33	0.62 (2)	0.73	0.38 (2)	0.83	0.42 (2)	0.81	3.79 (2)	0.15	2.00 (2)	0.37	2.89 (2)	0.24
rs753381	0.46 (2)	0.80	1.87 (2)	0.39	0.50 (2)	0.78	0.58 (2)	0.75	4.87 (2)	0.088	4.13 (2)	0.13	4.63 (2)	0.099
rs13283456	0.90 (2)	0.64	2.45 (2)	0.29	2.01 (2)	0.37	8.05 (2)	0.018	4.83 (2)	0.089	0.52 (1)	0.47	0.28 (1)	0.60
rs1870377	5.61 (2)	0.061	1.18 (2)	0.56	0.10 (2)	0.95	0.59 (2)	0.74	1.34 (2)	0.51	0.32 (1)	0.57	0.48 (1)	0.49
rs2230804	3.50 (2)	0.17	2.04 (2)	0.36	0.70 (2)	0.70	0.50 (2)	0.78	1.31 (2)	0.52	0.74 (2)	0.69	2.03 (1)	0.15
rs2305948	0.10 (2)	0.95	1.79 (2)	0.41	1.30 (2)	0.52	3.45 (2)	0.18	0.08 (1)	0.78	0.10 (1)	0.75	0.93 (1)	0.36
rs4073	2.20 (2)	0.33	0.92 (2)	0.63	1.50 (2)	0.47	0.43 (2)	0.81	0.88 (2)	0.64	0.29 (2)	0.86	3.20 (2)	0.20
rs602990	2.86 (2)	0.24	0.18 (2)	0.91	1.71 (2)	0.43	2.45 (2)	0.29	0.11 (2)	0.95	2.00 (2)	0.37	2.91 (2)	0.23
rs702689	3.76 (2)	0.15	1.37 (2)	0.50	5.58 (2)	0.061	1.59 (2)	0.45	6.08 (2)	0.048	0.33 (1)	0.57	0.01 (1)	0.93

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3	rs785467	3.79 (2)	0.15	1.03 (2)	0.60	0.41 (2)	0.81	2.37 (2)	0.31	3.10 (2)	0.21	0.15 (2)	0.93	1.02 (1)	0.31
4	rs832582	8.72 (2)	0.013	2.21 (2)	0.33	6.98 (2)	0.030	0.96 (2)	0.62	2.43 (2)	0.30	2.43 (1)	0.12	0.28 (1)	0.60
5	rs1073123	0.11 (2)	0.95	0.26 (2)	0.88	0.70 (2)	0.70	7.41 (2)	0.025	0.41 (2)	0.82	Cannot be fitted		0.05 (1)	0.82
6	rs1236913	0.19 (1)	0.67	1.36 (1)	0.24	0.39 (1)	0.53	0.59 (1)	0.44	0.73 (1)	0.39	0.00 (1)	0.98	1.43 (1)	0.23
7	rs1284879	4.72 (2)	0.094	7.71 (2)	0.021	3.73 (2)	0.16	2.61 (2)	0.27	3.08 (2)	0.21	0.90 (2)	0.64	0.53 (1)	0.47
8	rs17576	5.60 (2)	0.061	5.70 (2)	0.058	2.15 (2)	0.34	5.26 (2)	0.072	4.19 (2)	0.12	1.75 (2)	0.42	2.26 (2)	0.32
9	rs2274756	2.15 (2)	0.34	0.09 (1)	0.77	3.52 (2)	0.17	0.10 (1)	0.75	2.92 (2)	0.23	2.73 (1)	0.098	2.20 (1)	0.14
10	rs243865	0.03 (2)	0.99	0.60 (2)	0.74	1.77 (2)	0.41	1.54 (2)	0.46	0.24 (2)	0.89	0.95 (2)	0.62	0.00 (1)	0.97
11	rs3740199	4.76 (2)	0.093	0.78 (2)	0.68	0.08 (2)	0.96	0.54 (2)	0.76	3.37 (2)	0.19	0.51 (2)	0.77	0.16 (2)	0.92
12	rs459552	2.64 (2)	0.27	3.37 (2)	0.19	4.68 (2)	0.096	1.86 (2)	0.39	5.34 (2)	0.069	2.09 (2)	0.35	0.51 (1)	0.48
13	rs770087	0.25 (2)	0.88	0.26 (2)	0.88	1.90 (2)	0.39	0.38 (2)	0.83	0.90 (2)	0.64	1.16 (1)	0.28	0.42 (2)	0.81
14	rs1058808	5.90 (2)	0.053	1.61 (2)	0.45	0.33 (2)	0.85	0.77 (2)	0.68	8.77 (2)	0.013	0.18 (2)	0.91	0.02 (2)	0.99
15	rs2229712	1.09 (2)	0.58	0.91 (2)	0.63	8.05 (2)	0.018	0.65 (2)	0.72	1.11 (2)	0.58	0.21 (1)	0.65	0.18 (2)	0.91
16	rs16858808	0.55 (1)	0.46	0.00 (1)	0.95	0.30 (1)	0.59	0.39 (1)	0.53	0.97 (1)	0.32	Cannot be fitted		12.6 (1)	0.00039
17	rs17567	1.89 (2)	0.39	2.58 (2)	0.28	2.57 (2)	0.28	5.69 (2)	0.058	4.64 (2)	0.098	0.06 (1)	0.80	2.33 (2)	0.31
18	rs2250889	0.05 (1)	0.82	4.62 (1)	0.032	0.01 (1)	0.92	0.19 (1)	0.66	2.44 (1)	0.12	0.24 (1)	0.62	1.11 (1)	0.29
19	rs34471628	0.98 (1)	0.32	1.63 (1)	0.20	0.04 (1)	0.83	0.54 (1)	0.46	0.00 (1)	0.99	6.62 (1)	0.010	0.03 (1)	0.86
20	rs41427445	3.16 (1)	0.075	0.04 (1)	0.84	1.05 (1)	0.30	0.15 (1)	0.70	0.10 (1)	0.76	Cannot be fitted		Cannot be fitted	
21	rs5789	0.39 (1)	0.53	1.94 (1)	0.16	0.13 (1)	0.72	0.90 (1)	0.34	2.36 (1)	0.12	Cannot be fitted		Cannot be fitted	
22	rs41292521	1.86 (1)	0.17	2.00 (1)	0.16	1.92 (1)	0.17	0.03 (1)	0.86	0.01 (1)	0.91	Cannot be fitted		0.35 (1)	0.56
23	rs61755579	0.00 (1)	0.99	1.89 (1)	0.17	0.00 (1)	0.98	0.03 (1)	0.86	1.66 (1)	0.20	1.09 (1)	0.30	Cannot be fitted	
24	rs61751477	1.47 (1)	0.23	0.12 (1)	0.73	0.18 (1)	0.67	0.14 (1)	0.71	0.22 (1)	0.64	Cannot be fitted		Cannot be fitted	
25	rs3730089	1.61 (2)	0.45	0.69 (2)	0.71	3.52 (2)	0.17	0.52 (2)	0.77	1.09 (2)	0.58	1.66 (2)	0.44	0.23 (1)	0.63
26	rs35068180	0.32 (2)	0.85	2.37 (2)	0.31	3.14 (2)	0.21	7.18 (2)	0.028	1.16 (2)	0.56	0.52 (2)	0.77	0.40 (1)	0.53
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