

Dalotuzumab in chemorefractory *KRAS* exon 2 mutant colorectal cancer: results from a randomised phase II/III trial

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Abbreviations: CRC: colorectal cancer; IGF-1: insulin-like growth factor 1; IGF-2: insulin-like growth factor 2; IGF-1R: insulin-like growth factor type 1 receptor; IGFBP-3: insulin-like growth factor binding protein 3; IR: insulin receptor; EGFR: epidermal growth factor receptor; RNA: ribonucleic acid; mRNA: messenger ribonucleid acid; ECOG: Eastern Cooperative Oncology Group; RECIST: Response Evaluation Criteria in Solid Tumors; CT: computed tomography; MRI: magnetic resonance imaging; qRT-PCR: quantitative real-time polymerase chain reaction; PFS: progression-free survival; OS overall survival; HR: hazard ratio; CI: confidence intervals; Ct: cycle threshold; IQR: interquartile range;

What's new

We have shown that combining cetuximab-based therapy with an anti-IGF-1R monoclonal antibody (dalotuzumab) did not improve the outcome of chemorefractory, *KRAS* exon 2 mutant, metastatic colorectal cancer patients. By using a large prospective dataset we have also found that family members of the IGF signalling pathway were more expressed in *KRAS* wild-type compared to *KRAS* exon 2 mutant colorectal cancers while IGF-1 expression was higher in rectal compared to colon tumours.

Abstract

Limited data are available on the efficacy of anti-IGF-1R agents in *KRAS* mutant colorectal cancer (CRC). We analysed outcome of 69 chemorefractory, *KRAS* exon 2 mutant CRC patients who were enrolled in a double-blind, randomised, phase II/III study of irinotecan and cetuximab plus dalotuzumab 10 mg/kg once weekly (arm A), dalotuzumab 7.5 mg/kg every second week (arm B) or placebo (arm C). Objective response rate (5.6% vs. 3.1% vs. 4.8%), median progression-free survival (2.7 vs. 2.6 vs. 1.4 months) and overall survival (7.8 vs. 10.3 vs. 7.8 months) were not statistically significantly different between treatment groups. Most common grade ≥ 3 treatment-related toxicities included neutropenia, diarrhoea, hyperglycaemia, fatigue and dermatitis acneiform. Expression of IGF-1R, IGF-1, IGF-2 and EREG by quantitative real-time polymerase chain reaction was assessed in 351 patients from the same study with available data on *KRAS* exon 2 mutational status. Median cycle threshold values for all biomarkers were significantly lower (i.e., higher expression, $p < 0.05$) among patients with *KRAS* wild-type compared to those with *KRAS* exon 2 mutant tumours. No significant changes were found according to location of the primary tumour with only a trend towards lower expression of IGF-1 in colon compared to rectal cancers ($p = 0.06$). Albeit limited by the small sample size, this study does not appear to support a potential role for anti-IGF-1R agents in *KRAS* exon 2 mutant CRC. Data on IGF-1R, IGF-1 and IGF-2 expression here reported may be useful for patient stratification in future trials with inhibitors of the IGF pathway.

Introduction

The insulin receptor (IR) and the type I insulin-like growth factor receptor (IGF-1R) are membrane tyrosine kinase receptors that are expressed in both normal tissues and cancer cells.¹ While in the former they regulate physiological processes such as glucose homeostasis, in the latter they are thought to be involved in the promotion of carcinogenesis and tumour proliferation.^{1,2} Oncogenic signaling through this family of receptors is mediated by three main ligands (i.e., insulin, IGF-1 and IGF-2) through endocrine, autocrine and paracrine mechanisms and largely converges towards the RAS-RAF-MEK-ERK and PI3K-AKT pathways.³ Based on this biological rationale and supportive evidence from preclinical experiments with IR/IGF-1R inhibitors, targeting this signaling pathway has been considered an attractive option in the development of novel anti-cancer therapeutics.^{4,5} However, clinical studies have failed to confirm the pre-clinical promise with IR/IGF-1R targeted agents showing no benefit in a number of tumour types including colorectal cancer (CRC).⁶⁻²⁰

Suboptimal patient selection is one of the hypotheses to explain failure of IGF-1R inhibitors in the clinical setting. So far studies have been largely conducted in unselected patient populations and preclinical data as well as retrospective analyses of prospective trials suggest that enrichment strategies using circulating or tissue biomarkers may be key to the success of such agents.^{20,22-24} Indeed, the relative influence of the IGF signalling axis on the mechanisms of tumour growth and progression may vary according to a number of tumour-related factors, either clinical or molecular.^{20,25,26}

KRAS is a downstream effector of both epidermal growth factor receptor (EGFR) and IGF-1R and is mutated in approximately 35-40% of CRC patients.²⁷ Whilst mutation of *KRAS* is now a well-established predictive marker of resistance to anti-EGFR monoclonal antibodies²⁸, preclinical studies suggest that the anti-tumour activity of anti-IGF-1R agents, either alone or

in combination with inhibitors of the RAS-RAF-MEK-ERK pathway, is independent of *KRAS* status.^{25,26} Furthermore, the functional relevance of the IGF-1R/PI3K signalling axis as well as the therapeutic potential of its inhibition have been reported to be higher in *KRAS* mutant compared to *KRAS* wild-type cells.^{25,26} To our knowledge, only one study has selectively reported on the outcome of patients treated with anti-IGF-1R-based regimens in *KRAS* mutated metastatic CRC.¹⁸ Also, data on the expression of members of the IGF-1R pathway by *KRAS* status in large CRC patient series are lacking.

We have recently reported the results of a large randomised, placebo-controlled, three-arm, phase II/III study (n=344) where two schedules of the anti-IGF-1R humanised IgG1 monoclonal antibody dalotuzumab were assessed in combination with irinotecan and cetuximab in chemorefractory *KRAS* exon 2 wild-type metastatic CRC.²⁰ Neither investigational arm was found to be superior to standard therapy and an unexpected detrimental effect of weekly dalotuzumab on patients' outcome observed; therefore recruitment was terminated after a pre-planned interim analysis. This study commenced recruitment prior to the introduction of *KRAS* characterisation and included a cohort of patients with *KRAS* exon 2 mutated CRC.

In this article we report efficacy and safety data from patients with *KRAS* mutated metastatic CRC who were enrolled in this study before a protocol amendment restricted eligibility to patients with *KRAS* wild-type tumours. Moreover, we report on tumour expression of IGF-1R, IGF-1, IGF-2 and epiregulin (EREG) as assessed in the whole study population.

Materials and methods

Eligibility criteria

Eligibility criteria have been previously reported in detail.²⁰ In short, patients were deemed eligible for this study if they were ≥ 18 years old, had histologically confirmed diagnosis of measurable metastatic CRC, failed prior irinotecan- and oxaliplatin-containing regimens, had progressed on or within three months of last line of therapy, had no previous exposure to IGF-1R or EGFR inhibitors and their Eastern Cooperative Oncology Group (ECOG) performance status was ≤ 1 . Although availability of archival tumour tissue was mandatory, assessment of *KRAS* status was not part of the study screening procedures until 2009 when recruitment was restricted to patients with *KRAS* exon 2 wild-type tumours.

Study design

Study design and procedures have been previously reported in detail.²⁰ In summary, this was an international, multicentre, double-blind, randomised, phase II/III study with a short safety run-in conducted in 55 sites across four continents. Eligible patients were randomised in a 1:1:1 ratio to receive irinotecan and cetuximab plus dalotuzumab 10 mg/kg once weekly (arm A), irinotecan and cetuximab plus dalotuzumab 15 mg/kg loading dose and then 7.5 mg/kg every second week (arm B) or irinotecan and cetuximab plus placebo (arm C). Cetuximab was administered at a dose of 250 mg/m² once weekly (loading dose of 400 mg/m²) while the same dose and schedule as had been previously given during the patient's pre-study therapy was used for irinotecan. Treatment was administered until disease progression, unbearable toxicity, or consent withdrawal. Response Evaluation Criteria in Solid Tumors (RECIST) v1.0²⁹ was used to assess tumour response (central independent review) with computed tomography (CT) or magnetic resonance imaging (MRI) scans performed every 6 weeks for the first 48 weeks and every 3 months thereafter. The study was approved by an independent ethics committee or

institutional review board at each site. All patients provided written informed consent. This study was registered at ClinicalTrials.gov (NCT00614393).

KRAS testing and exploratory biomarker analyses

Throughout the study, *KRAS* exon 2 mutations were screened for in a central laboratory using the TheraScreen *KRAS* test (Qiagen, Manchester, UK). In post-hoc exploratory analyses IGF-1R, IGF-1, IGF-2 and EREG expression were assessed by quantitative real-time polymerase chain reaction (qRT-PCR) (Almac Diagnostics, Craigavon, UK) using RNA extracted from formalin-fixed, paraffin-embedded tissue.²⁰

Statistical design

The statistical design of the main study has been previously reported in detail.²⁰ The dual primary endpoints in *KRAS* mutant patients were progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from randomisation to the first documented disease progression (as per independent review), or death due to any cause, whichever occurred first. OS was defined as the time from randomisation to death due to any cause. Patients without a documented event were censored at the date of the last follow-up. PFS and OS were analysed using Kaplan Meier methods and comparison between groups used Cox regression analysis. Chi squared test was used for comparison of objective response rates between treatment groups. IGF-1, IGF-2, IGF-1R and EREG expression according to *KRAS* status and site of tumour was assessed by Wilcoxon rank sum test. Also, a pairwise correlation analysis of biomarker expression in individual patients was performed (a correlation coefficient of 0.00, ≥ 0.30 , ≥ 0.50 , ≥ 0.70 and 1.00 indicated no linear relationship, weak positive linear relationship, moderate positive linear relationship, strong positive linear relationship and perfect positive linear relationship, respectively).

Results

From 2008 through 2009 (before study recruitment was limited to patients with *KRAS* exon 2 wild-type tumours), 242 patients were enrolled in the trial. Of these, 71 were found to have tumours harbouring a mutation within exon 2 of the *KRAS* gene. Eighteen were randomised to arm A, 32 to arm B and 21 to arm C. Baseline demographics and clinical characteristics of these patients are presented in Table 1 including 2 patients who were found to be ineligible and not included in the primary efficacy analysis.

Dalotuzumab/placebo was administered for a median of 11.9 weeks (range 1.0 – 53.3), 8.0 weeks (range 1.0 – 53.3) in arm A, 10.0 weeks (range 3.0 – 48.0) in arm B and 11.4 weeks (range 1.0 – 40.0) in arm C. In the eligible population, objective responses as assessed by independent radiological review were observed in 3 patients, 1 for each arm (response rate: 5.6% in arm A, 3.1% in arm B, 4.8% in arm C). At the time of this analysis, 55 events were recorded for PFS and 54 for OS. Median PFS in the control arm was 1.4 months compared with 2.7 months [HR 0.75 (95% CI: 0.35 – 1.58); p=0.45] and 2.6 months [HR 1.08 (95% CI: 0.56 – 2.09); p=0.56] in arm A and B, respectively (Figure 1). In the same treatment groups, median OS was 7.8, 7.8 and 10.3 months. At 1 year, 25% of patients in the control arm were alive compared to 50.0% [HR 0.88 (95% CI: 0.42 – 1.84); p=0.73] and 22.6% [HR 0.96 (95% CI: 0.49 – 1.90); p=0.92] in arm A and B, respectively. Results were not different when the outcome of all dalotuzumab-treated patients (arm A + arm B, n=49) was compared with that of arm C patients (n=20). In the former group median PFS and OS were 2.6 and 10.3 months, respectively, compared with 1.4 [HR 0.94 (95% CI: 0.51 – 1.74); p=0.84] and 7.8 months [HR 0.93 (95% CI: 0.49 – 1.74); p=0.82], respectively, in the latter group (Supplementary Figure 1).

Grade ≥ 3 toxicity was observed in 72.2% of patients in arm A, 53.1% in arm B, and 52.4% in arm C. Most common grade ≥ 3 treatment-related adverse events by study arm are reported in Table 2 and included neutropenia, diarrhoea, hyperglycaemia, fatigue and dermatitis acneiform. In only one case, treatment was discontinued as a result of a drug-related adverse event.

IGF-1R, IGF-1 and IGF-2 expression

Expression of IGF-1R, IGF-1 and IGF-2 by qRT-PCR was assessed in 357, 354 and 354 eligible patients who were randomised in the study (either before or after study protocol amendment in 2009), respectively. Of these, 351 were tested for *KRAS* exon 2 mutation [285 (81.2%) *KRAS* wild-type and 66 (18.8%) *KRAS* mutant] while 353 had available information regarding the site of the primary tumour (216 (61.2%) colon and 137 (38.8%) rectum).

Expression of IGF-1R, IGF-1 and IGF-2 by tumour site and/or *KRAS* status is presented in Figure 2-4. Median cycle threshold (Ct) values are inverse to the amount of mRNA, therefore lower values indicate high amounts of mRNA while higher values indicate lower amounts of mRNA. No difference between colon and rectal cancers were observed with regards to the level of IGF-1R [Ct values: 5.3 (interquartile range (IQR): 4.4 – 6.5) and 5.4 (IQR: 4.3 – 6.4), respectively, $p=0.71$] and IGF-2 [Ct values: 1.7 (IQR: 0.5 – 2.6) and 1.4 (IQR: 0.04 – 2.3), respectively, $p=0.18$]. IGF-1 expression appeared to be higher in rectal cancers [Ct value: 3.2 (IQR: 2.1 – 4.7)] than in colon cancers [Ct value: 3.6 (IQR: 2.4 – 5.0)] and this difference approached statistical significance ($p=0.06$). The analysis by *KRAS* status showed that all members of the IGF pathway were significantly more expressed in *KRAS* wild-type tumours [Ct values: IGF-1R: 5.0 (IQR: 4.2 – 6.0); IGF-1: 3.2 (IQR: 2.0 – 4.5); IGF-2: 1.4 (IQR: 0.3 – 2.3)] compared to *KRAS* exon 2 mutated tumours [Ct values: IGF-1R: 6.6 (IQR: 5.9 – 7.8);

IGF-1: 4.9 (IQR: 3.7 – 5.9); IGF-2: 2.0 (IQR: 0.9 – 3.0)] (p values: <0.001, <0.001 and 0.02, respectively). This association remained evident when the analysis was restricted to the group of patients with colon cancers [Ct values: IGF-1R: 5.0 (IQR: 4.2 – 6.1) vs. 6.8 (IQR: 5.9 – 8.0), p<0.001; IGF-1: 3.4 (IQR: 2.2 – 4.6) vs. 5.2 (IQR: 4.2 – 6.3), p<0.001; IGF-2: 1.5 (IQR: 0.4 – 2.5) vs. 2.3 (IQR: 1.7 – 3.1), p=0.02]. However, in the group of patients with rectal cancers, this association was observed only for IGF-1R [Ct values: 4.8 (IQR: 4.1 – 5.8) vs. 6.5 (IQR: 5.8 – 7.7), p<0.001] and IGF-1 [Ct values: 3.0 (IQR: 1.8 – 3.9) vs. 4.8 (IQR: 3.2 – 5.6), p<0.001] but not for IGF-2 [Ct values: 1.4 (IQR: 0.0 – 2.2) vs. 1.6 (IQR: 0.1 – 2.9), p=0.33].

EREG expression

Expression of EREG by qRT-PCR was assessed in 354 eligible patients. Of these, 351 were tested for *KRAS* exon 2 mutation [285 (81.2%) *KRAS* wild-type and 66 (18.8%) *KRAS* mutant] while 353 had available information regarding the site of the primary tumour (216 (61.2%) colon and 137 (38.8%) rectum).

Expression of EREG by tumour site and/or *KRAS* status is presented in Supplementary Figure 2. Higher levels of EREG were found in *KRAS* wild-type compared to *KRAS* mutant tumours [Ct values: 1.4 (IQR: 0.3 – 3.0) vs. 3.3 (IQR: 2.5 – 5.1), p<0.001]. This association remained evident when the analysis was restricted to the group of patients with either colon cancer [Ct values: 1.6 (IQR: 0.3 – 3.2) vs. 3.1 (IQR: 2.5 – 5.6), p<0.001] or rectal cancer [Ct values 1.3 (IQR: 0.1 – 2.6) vs. 3.4 (IQR: 2.1 – 4.6), p<0.001]. In contrast, no difference in EREG expression was found by tumour site in *KRAS* unselected patients [Ct values: 2.0 (IQR: 0.7 – 3.5) for colon and 1.8 (IQR: 0.4 – 3.4) for rectum, p=0.41].

Pairwise correlation analysis

The results of the pairwise correlation analysis of IGF-1R, IGF-1, IGF-2 and EREG in individual patients are reported in Supplementary Table 1. In the overall study population a weak positive linear relationship was observed between IGF-1R and IGF-1 (correlation coefficient: 0.4318). This was maintained both in the group of patients with *KRAS* wild-type (correlation coefficient: 0.3918) and *KRAS* mutant tumours (correlation coefficient: 0.3347). Also, a similar relationship was found between IGF-1R and EREG in the overall population (correlation coefficient: 0.3132) and between IGF-1 and IGF-2 in patients with *KRAS* mutant tumours (correlation coefficient: 0.3329).

Discussion

The functional link between *KRAS* and the IGF signalling axis has long been reported, initial studies in murine fibroblasts showing the potential of IGF-1 to induce *KRAS* mRNA expression and *KRAS* mediated-progression through the late G1 phase of the cell cycle.^{30,31} More recently, preclinical data has indicated that the activity of IGF-1 pathway inhibitors may be independent of *KRAS* mutational status.²⁶ In lung cancer cell lines and genetically engineered mouse models dependence on IGF signalling as well as sensitivity to its inhibition was shown to be higher in *KRAS* mutated compared to *KRAS* wild-type tumours.²⁵ Similarly, in *KRAS* mutated gastrointestinal cancers, the anti-IGF-1R monoclonal antibody figitumumab was found to induce suppression of tumour proliferation when given as monotherapy or in combination with chemotherapy.³²

Despite these preclinical data, most of the available data on the activity of anti-IGF-1R monoclonal antibodies in CRC are from studies conducted in populations with unselected^{17,33} or *KRAS* wild-type tumours.^{17,19,20} In a randomised phase II study (n=44) of IMC-A12 with or without cetuximab in patients who had previously received standard chemotherapy and an anti-

EGFR agent, only 1 out of 21 patients (5%) had partial response in the combination arm while no objective tumour response was reported in the monotherapy arm.¹⁷ Of note, no antitumour activity of the combination treatment was observed in an additional, non-randomised study arm restricted to patients with *KRAS* exon 2 wild-type tumours (n=20). In another randomised, placebo-controlled, phase II study, combining ganitumab with panitumumab in *KRAS* wild-type chemorefractory patients did not improve response rate (22% vs. 21%), median progression-free survival (PFS) (5.3 vs. 3.7 months) or overall survival (OS) (10.6 vs. 11.6 months) compared to standard therapy.¹⁹ Only the study by Cohn et al investigated IGF-1R inhibition in selected patients with *KRAS* mutated CRC.¹⁸ In this randomised, double-blind, phase II trial (n=104) the addition of ganitumab to FOLFIRI in patients who had progressed after first-line oxaliplatin-based chemotherapy failed to show superiority over standard therapy in terms of response rate (8% vs. 2%), median PFS (4.5 vs. 4.6 months) and OS (12.4 vs. 12.0 months).

Our analysis of the efficacy of dalotuzumab in patients with *KRAS* exon 2 mutated tumours is largely exploratory and limited by the small sample size. However, the results presented here are in keeping with those reported in the larger study by Cohn et al and provide additional data to suggest that IGF-1R/IR pathway inhibition is not of therapeutic value in *KRAS* mutated CRC. Although the lack of an extended *RAS* analysis has to be considered as a limitation of both studies, it is unlikely that selecting for patients with all *RAS* wild-type tumours would significantly change the overall findings. In this regard, it is interesting to note that in cell line studies the effect of *KRAS* mutation appeared to be heterogeneous, with *KRAS*^{G13D} mutation, but not codon 12 mutations, conferring CRC resistance to IGF-1R/IR inhibition.²⁶ Similar to the efficacy data, the safety profile of dalotuzumab did not appear to be influenced by the

tumours *KRAS* status and toxicity data in this population were comparable to those we have previously reported in patients with *KRAS* wild-type tumours.²⁰

In line with the importance of the IGF signalling axis in the mechanisms of CRC carcinogenesis and progression³⁴, expression of the IGF family members has been found to be higher in tumour tissue compared to adjacent normal mucosa.³⁵⁻³⁸ Furthermore, a gradual increase of the levels of the components of this oncogenic pathway has been reported along the length of the bowel, with IGF-1, IGF-2, IGF-1R, and IGF binding protein 3 (IGFBP-3) showing higher expression in rectal mucosa compared to mucosa of the ascending colon.³⁹ To our knowledge, no large clinical studies have investigated possible differences in the expression of the IGF family members according to the anatomical site or molecular characteristics of the primary tumour. By analysing all assessable patients enrolled in the MK-0646-025 trial, we have shown that IGF-1 is significantly more expressed in rectal cancers compared to colon cancers, while all IGF family members investigated, with the only exception of IGF-2 in rectal cancer, are significantly more expressed in *KRAS* wild-type tumours compared to those harbouring a mutation in exon 2 of the *KRAS* gene. The main value of this analysis is in contributing further information on the relative biological relevance of the IGF pathway in metastatic CRC and in providing useful data that can be used for patient stratification/selection in future clinical trials with IGF-1R inhibitors. Our results could also be of clinical relevance if we consider that in this setting IGF-1 may serve as a biomarker to predict benefit from anti-IGF-1R agents and resistance to anti-EGFR monoclonal antibodies.^{20,40,41} As previously highlighted, however, it should be considered that the lack of information on the source of tumour tissue used for the analysis (primary tumour versus metastasis), the potential influence of pelvic radiotherapy on the biomarker expression values for rectal tumours and contamination by adjacent normal tissue may have had a potential significant impact on the overall results.^{20,42} Similar

considerations apply to the analysis of EREG in this study. It is interesting to note, however, that our results suggesting an association between the expression of this EGFR ligand and the *KRAS* mutational status are in line with previous studies.⁴³

Clinical and molecular data reported in this article have the merit of augmenting the existing body of knowledge regarding the role of the IGF system as oncogenic signalling pathways and potential therapeutic target in advanced CRC. Although the assumption that IGF-1R could be a useful target in CRC therapy has been significantly challenged by the number of negative studies conducted in this setting, it still remains uncertain whether refinement of patient selection has the potential to revert this unfavourable trend. Specific studies aiming to further investigate the role of the IGF axis in the mechanisms of CRC growth, progression and response to treatment as well as the functional relevance of feedback activation of alternative oncogenic signalling pathways are desirable and likely to shed light into the next development of this class of agents.

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Table 1. Baseline patient demographics and clinical characteristics (*KRAS* mutant cohort)

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	ARM A N=18 (%)	ARM B N=32 (%)	ARM C N=21 (%)	TOTAL N=71 (%)
Gender				
Male	11 (61.1)	19 (59.4)	8 (38.1)	38 (53.5)
Female	7 (38.9)	13 (40.6)	13 (61.9)	33 (46.5)
Age (years)				
median	65	57.5	62	59
range	49 - 79	39 - 78	36 - 72	36 - 79
Race				
Caucasian	6 (33.3)	12 (37.5)	9 (42.9)	27 (38.0)
Asian	12 (66.7)	20 (62.5)	12 (57.1)	44 (62.0)
ECOG PS				
0	5 (27.8)	15 (46.9)	8 (38.1)	28 (39.4)
1	13 (72.2)	17 (53.1)	13 (61.9)	43 (60.6)
Tumour site				
Colon	9 (50.0)	15 (46.9)	16 (76.2)	40 (56.3)
Rectum	9 (50.0)	17 (53.1)	5 (23.8)	31 (43.7)
No. of previous lines of therapy				
median	2.5	2.5	3.0	3
range	2 - 4	2 - 4	2 - 5	2 - 5

Table 2. Most common grade ≥ 3 drug-related toxicities and adverse event summary

	Arm A N=18 (%)	Arm B N=32 (%)	Arm C N=21 (%)	Difference Arm A vs. Arm C p-value (exact test)	Difference Arm B vs. Arm C p-value (exact test)
Neutropenia	6 (33.3)	5 (15.6)	4 (19.0)	0.465	1.00
Diarrhoea	9 (50.0)	1 (3.1)	1 (4.8)	0.002	1.00
Hyperglycaemia	2 (11.1)	3 (9.4)	1 (4.8)	0.586	1.00
Dermatitis acneiform	0 (0)	3 (9.4)	2 (9.5)	0.490	1.00
Rash	2 (11.1)	1 (3.1)	0 (0)	0.206	1.00
Fatigue	3 (16.7)	2 (6.3)	0 (0)	0.089	0.512
Asthenia	1 (5.6)	2 (6.3)	1 (4.8)	1.00	1.00
Hypokalaemia	2 (11.1)	1 (3.1)	0 (0)	0.206	1.00
Patients with ≥ 1 toxicities	13 (72.2)	17 (53.1)	11 (52.4)	0.323	1.00
Patients with SAE	13 (72.2)	14 (43.8)	10 (47.6)	0.192	1.00
Drug-related SAE [†]	7 (38.9)	2 (6.3)	2 (9.5)	0.055	1.00
Discontinuation [‡] due to AE	7 (38.9)	1 (3.1)	7 (33.3)	0.750	0.003
Discontinuation [‡] due to drug-related AE	1 (5.6)	0 (0)	0 (0)	0.462	-
Discontinuation [‡] due to SAE	5 (27.8)	1 (3.1)	6 (28.6)	1.00	0.012
Discontinuation [‡] due to drug-related SAE	0 (0)	0 (0)	0 (0)	-	-
Death within 60 days of trial entry	0 (0)	0 (0)	4 (19.0)	0.110	0.020

[†] Determined by the investigator to be related to the drug.

[‡] Study medication withdrawn.

Abbreviations: AE, adverse event; SAE, serious adverse event.

Figures

Figure 1. Progression-free survival (a) and overall survival (b) by treatment group

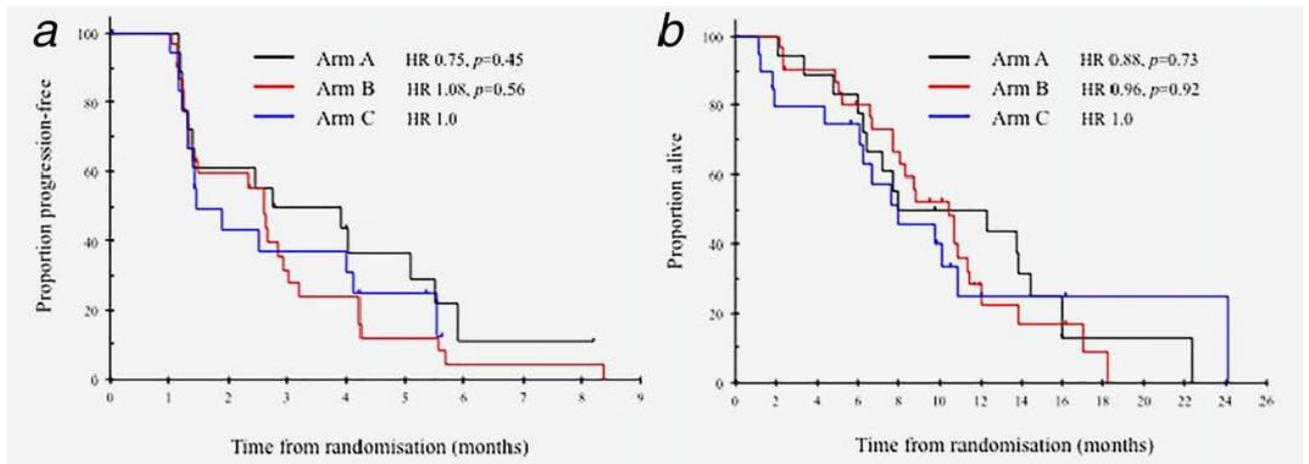


Figure 2. Box plots for IGF-1R expression according to location of primary tumour (*a*), *KRAS* status (*b*) or both (*c*)

The y axis show median cycle threshold (Ct) values (log transformation). Ct values are inverse to the amount of mRNA, therefore lower values indicate high amounts of mRNA while higher values indicate lower amounts of mRNA.

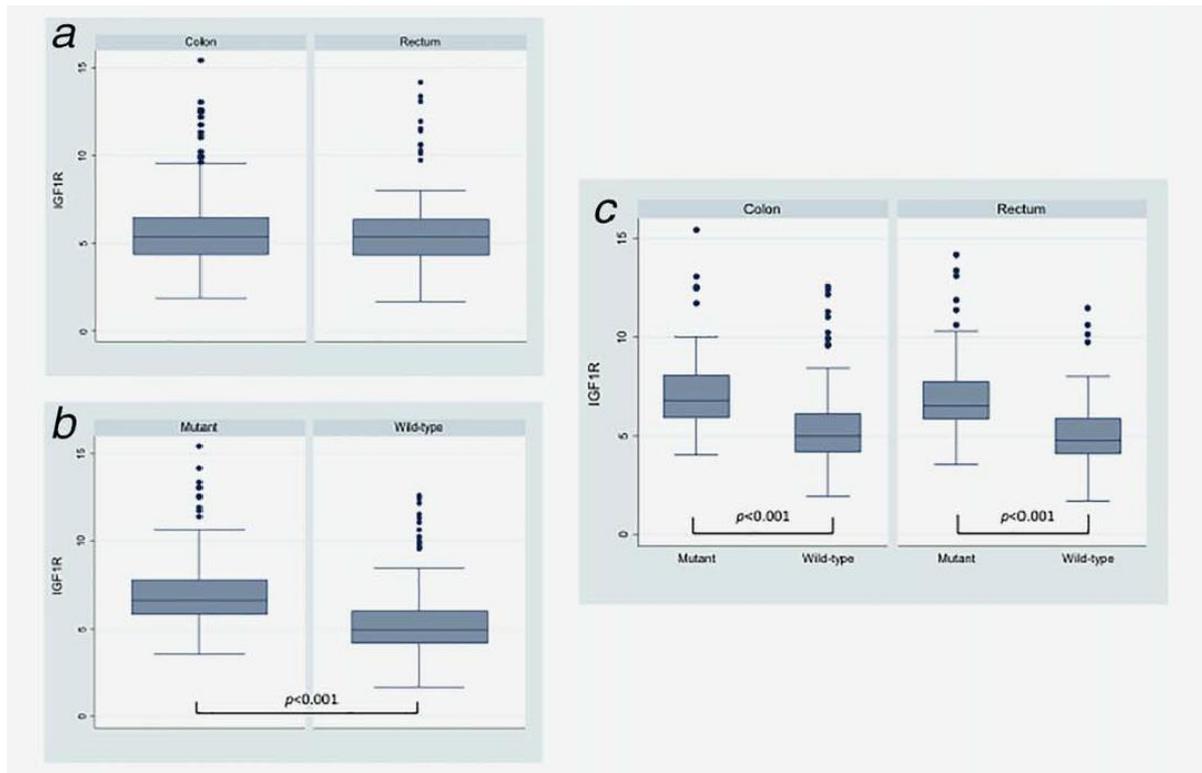


Figure 3. Box plots for IGF-1 expression according to location of primary tumour (*a*), *KRAS* status (*b*) or both (*c*)

The y axis show median cycle threshold (Ct) values (log transformation). Ct values are inverse to the amount of mRNA, therefore lower values indicate high amounts of mRNA while higher values indicate lower amounts of mRNA.

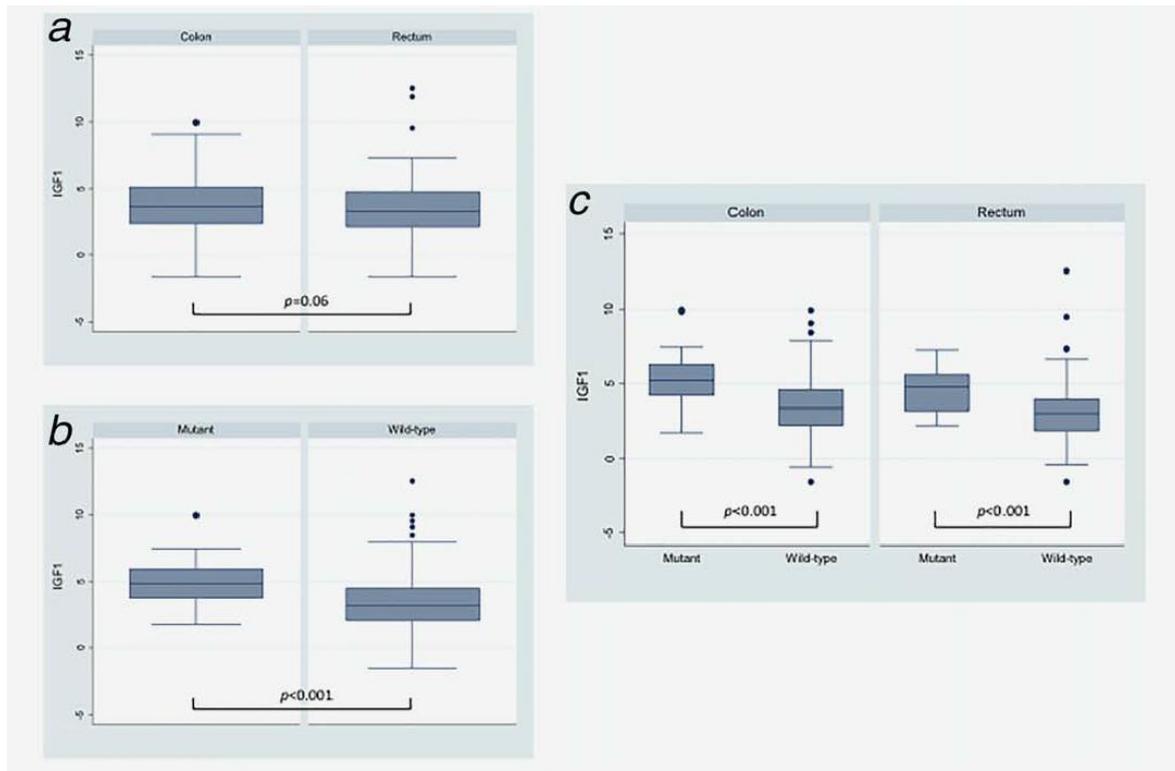
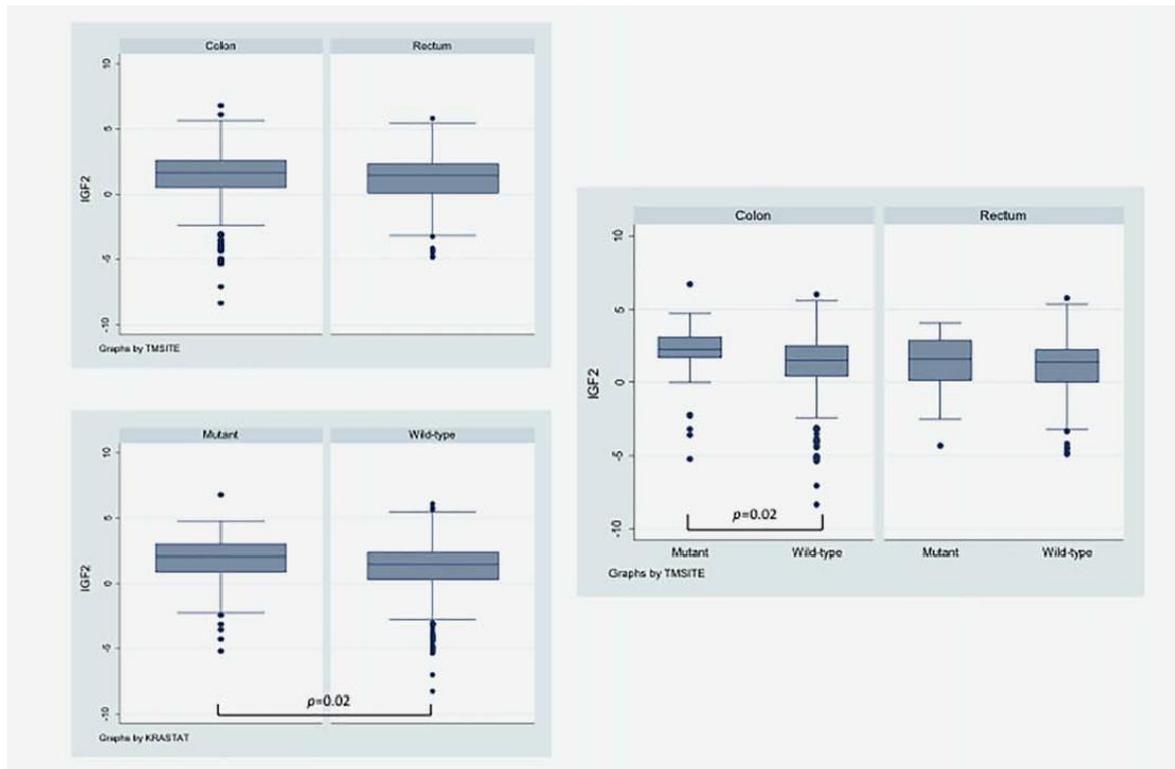


Figure 4. Box plots for IGF-2 expression according to location of primary tumour (a), *KRAS* status (b) or both (c)

The y axis show median cycle threshold (Ct) values (log transformation). Ct values are inverse to the amount of mRNA, therefore lower values indicate high amounts of mRNA while higher values indicate lower amounts of mRNA.



Key for box plots

		o	<- outside values
		o	
adjacent line	--+	-	<- upper adjacent value $(Q3+1.5(Q3-Q1))$
whiskers			
	-	+----+	<- 75th percentile (upper hinge) (Q3)
box		---	<- median (Q2)
	-	+----+	<- 25th percentile (lower hinge) (Q1)
whiskers			
adjacent line	--+	-	<- lower adjacent value $(Q1-1.5*(Q3-Q1))$
		o	<- outside value