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Article

ARTICLE

A Randomized Phase II/III Study of Dalotuzumab in Combination With Cetuximab and Irinotecan in Chemorefractory, *KRAS* Wild-Type, Metastatic Colorectal Cancer

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Abstract

Background: Insulin-like growth factor type 1 receptor (IGF-1R) mediates resistance to epidermal growth factor receptor (EGFR) inhibition and may represent a therapeutic target. We conducted a multicenter, randomized, double blind, phase II/III trial of dalotuzumab, an anti-IGF-1R monoclonal antibody, with standard therapy in chemo-refractory, *KRAS* wild-type metastatic colorectal cancer.

Methods: Eligible patients were randomly assigned to dalotuzumab 10 mg/kg weekly (arm A), dalotuzumab 7.5 mg/kg every alternate week (arm B), or placebo (arm C) in combination with cetuximab and irinotecan. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints included exploratory biomarker analyses. All statistical tests were two-sided.

Results: The trial was prematurely discontinued for futility after 344 eligible *KRAS* wild-type patients were included in the primary efficacy population (arm A = 116, arm B = 117, arm C = 111). Median PFS was 3.9 months in arm A (hazard ratio [HR] = 1.33, 95% confidence interval [CI] = 0.98 to 1.83, $P = .07$) and 5.4 months in arm B (HR = 1.13, 95% CI = 0.83 to 1.55, $P = .44$) compared with 5.6 months in arm C. Median OS was 10.8 months in arm A (HR = 1.41, 95% CI = 0.99 to 2.00, $P = .06$) and 11.6 months in arm B (HR = 1.26, 95% CI = 0.89 to 1.79, $P = .18$) compared with 14.0 months in arm C. Grade 3 or higher asthenia and hyperglycaemia occurred more frequently with dalotuzumab compared with placebo. In exploratory biomarker analyses, patients with high IGF-1 mRNA tumors in arm A had numerically better PFS (5.6 vs 3.6 months, HR = 0.59, 95% CI = 0.28 to 1.23, $P = .16$) and OS (17.9 vs 9.4 months, HR = 0.67, 95% CI = 0.31 to 1.45, $P = .31$) compared with

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those with high IGF-1 mRNA tumors in arm C. In contrast, in arm C high IGF-1 mRNA expression predicted lower response rate (17.6% vs 37.3%, $P = .04$), shorter PFS (3.6 vs 6.6 months, HR = 2.15, 95% CI = 1.15 to 4.02, $P = .02$), and shorter OS (9.4 vs 15.5 months, HR = 2.42, 95% CI = 1.21 to 4.82, $P = .01$).

Conclusions: Adding dalotuzumab to irinotecan and cetuximab was feasible but did not improve survival outcome. IGF-1R ligands are promising biomarkers for differential response to anti-EGFR and anti-IGF-1R therapies.

Cetuximab is a monoclonal antibody that targets the epidermal growth factor receptor (EGFR) and inhibits tumor proliferation, invasion, and angiogenesis (1). Cetuximab gained both US Food and Drug Administration and European Medicines Agency approval for the treatment of chemo-refractory, metastatic colorectal cancer (mCRC) in 2004 (2).

Since its introduction into routine practice, mechanisms of resistance have been elucidated. The identification of *KRAS* and *NRAS* mutations as predictors of resistance to anti-EGFR agents resulted in revision of the drug label in 2009 and, more recently, in 2013 (3,4). However, even within the *RAS* wild-type population, response rates are modest and response durations short lasting. Additional mediators of anti-EGFR activity have been described such as *EGFR* amplification/mutation, EGFR ligand expression, downstream mutations (*BRAF*), and alternative growth factor receptor pathway activation, including mesenchymal-epithelial transition factor gene (MET), EGFR-3 (HER-3), and insulin-like growth factor type 1 receptor (IGF-1R) (5–9).

Signaling through IGF-1R mediates proliferation and resistance to apoptosis (10). The interplay between the EGFR and IGF-1R pathways has long been recognized (11). EGFR and IGF-1R share downstream effectors (MAP-K, PI3K) and signalling through IGR-1R leads to activation of EGFR and resistance to cetuximab (12,13). Preclinical data indicate that concurrent inhibition of IGF-1R and EGFR results in reduced phosphorylation of ERK1/2 and AKT, inhibition of tumor proliferation, and increased apoptosis compared with inhibition of either receptor alone. These synergistic antitumor effects support a role for IGF-1R as a mediator of resistance to anti-EGFR agents and a potential therapeutic target (14).

Dalotuzumab (MK-0646) is a humanized IgG1 monoclonal antibody directed to the ectodomain of IGF-1R and does not cross-react with the insulin receptor (15). Dalotuzumab inhibits ligand (IGF-1, IGF-2) binding and induces receptor internalization and degradation with inhibition of downstream pathway activation (16). In a phase I study, dalotuzumab was well tolerated, with only 6% of patients experiencing grade 3 or higher adverse events, and no maximum tolerated dose was identified. Pharmacodynamic analyses showed downregulation of several markers including IGF-1R, EGFR, and pMAP-K in post-treatment tumor specimens. Also preliminary activity was observed with 8% of heavily pretreated patients achieving disease stabilization and 4% having a metabolic response (17).

We report the clinical results and biomarker findings from a multicenter, double-blind, randomized, phase II/III trial of cetuximab and irinotecan plus or minus dalotuzumab in chemo-refractory, *KRAS* exon 2 wild-type mCRC.

Methods

Patients

Eligibility was restricted to patients with histologically confirmed diagnosis of measurable mCRC who had failed (as verified by local investigators) irinotecan- and oxaliplatin-containing regimens and had progressed on or within three months of last line of therapy (as verified by central review). Oxaliplatin failure included failure because of toxicities. Key eligibility criteria included: age 18 years or older, ECOG performance status of 1 or less, no prior exposure to IGF-1R or EGFR inhibitors, and adequate bone marrow, renal, and hepatic function. Archival tumor tissue was required. In 2009, the study protocol was amended and further recruitment was restricted to patients with *KRAS* exon 2 wild-type tumors. The study protocol and its amendments were approved by an independent ethics committee or institutional review board at each site. All patients provided written informed consent.

Study Design, Dosing, and Assessment

This was a multicenter, double-blind, randomized, phase II/III study. This study was registered at ClinicalTrials.gov (NCT00614393). All eligible patients received irinotecan and cetuximab and were randomly assigned to weekly dalotuzumab (Arm A), two-weekly dalotuzumab (Arm B), or placebo (Arm C). Prior to commencing the randomized part of the study, a safety run-in was undertaken to determine the safety of the investigational combination treatment (18). Subsequent random assignment was in a 1:1:1 ratio.

Cetuximab was administered weekly at a dose of 250 mg/m^2 (loading dose 400 mg/m^2). Irinotecan was delivered according to the same dose and schedule as had been previously received during the patient's prestudy therapy. Permissible schedules included 125 mg/m^2 once every week for four weeks followed by two weeks' rest, 180 mg/m^2 once every two weeks, or 350 mg/m^2 once every three weeks. Prior dose reductions were maintained, and there were no on-study dose escalations.

Patients received the addition of IV dalotuzumab or placebo as follows: arm A: dalotuzumab 10 mg/kg once weekly; arm B: dalotuzumab 15 mg/kg loading dose followed by 7.5 mg/kg every second week, with normal saline (placebo) delivered on alternate weeks; arm C: normal saline (placebo) once weekly. Dalotuzumab/placebo infusions commenced in the second week of treatment.

Treatment continued until disease progression, intolerable toxicity, or consent withdrawal. Tumor response was assessed by computer tomography scans or magnetic resonance imaging every six weeks for the first 48 weeks and every three months thereafter. Assessment of response was conducted locally and independently reviewed centrally using RECIST criteria v1.0 (19).

KRAS Testing and Biomarker Analyses

KRAS exon 2 mutations were screened for centrally by the TheraScreen *KRAS* test (Qiagen, Manchester, UK) for purposes of identifying the primary efficacy analysis population. Following the protocol amendment in 2009, mutational tests performed

locally could be used, if available at the time of screening, for purposes of defining study eligibility (Figure 1).

Prespecified biomarker analyses evaluated treatment effect by IGF-1R and epiregulin (EREG) expression. Post hoc biomarker analyses evaluated treatment effect by IGF-1 and IGF-2 expression.

IGF-1R expression was assessed by immunohistochemistry (Ventana, AZ) (detailed methods available in the Supplementary Materials, available online) and measured by an independent core laboratory pathologist according to the following scale: 0 = no staining; 1+ = weak staining; 2+ = moderate staining; 3+ = strong staining. A membrane stain score of 1+ or more was considered as positive regardless of the proportion of positive tumor cells (≥1%). Moreover, in a predefined exploratory analysis, IGF-1R expression was quantitated using the H-score, a composite score of the percentage of cells at each staining intensity level summed across all possible staining intensities.

Following RNA extraction from formalin-fixed, paraffin-embedded tissue (detailed methods available in the Supplementary Materials, available online) EREG, IGF-1, and IGF-2 expression were assessed by quantitative real-time polymerase chain reaction (Almac Diagnostics, Craigavon, UK). Based on a different pattern and distribution of mRNA expression between IGF-1 and IGF-2, as observed in an independent colorectal gene expression profiling dataset available for analysis (Supplementary Figure 1, available online), different cutoff points were used for these biomarkers: top 25% and 15% levels were considered positive for IGF-1 and IGF-2, respectively. In accordance with previous studies, the median signal intensity was used as the cutoff point to define high vs low EREG expression (5). All the cutoff points were prespecified.

Statistical Analysis

The dual primary endpoints were progression-free survival (PFS) and overall survival (OS) in patients with *KRAS* exon 2 wild-type tumors. It was estimated that 1156 *KRAS* wild-type patients had to be randomly assigned to achieve 700 deaths in any arm-wise comparison between placebo and one of the two dalotuzumab arms to detect a 20% reduction in hazard rate for OS with 77% power and a type I error of 0.02 (one-sided). PFS was defined as the time from random assignment to the first documented disease progression (as per independent review), or death because of any cause, whichever occurs first. OS was defined as the time from random assignment to death because of any cause. Patients without a documented event were censored at the date of the last follow-up. PFS and OS were analyzed using Kaplan Meier methods, and comparison between groups used Cox regression analysis.

Secondary endpoints included overall response rate, toxicity, and quality of life. Two-sided Miettinen and Nurminen's method for stratified data was used for comparison of objective response rates and grade 3 or higher toxicities between treatment groups

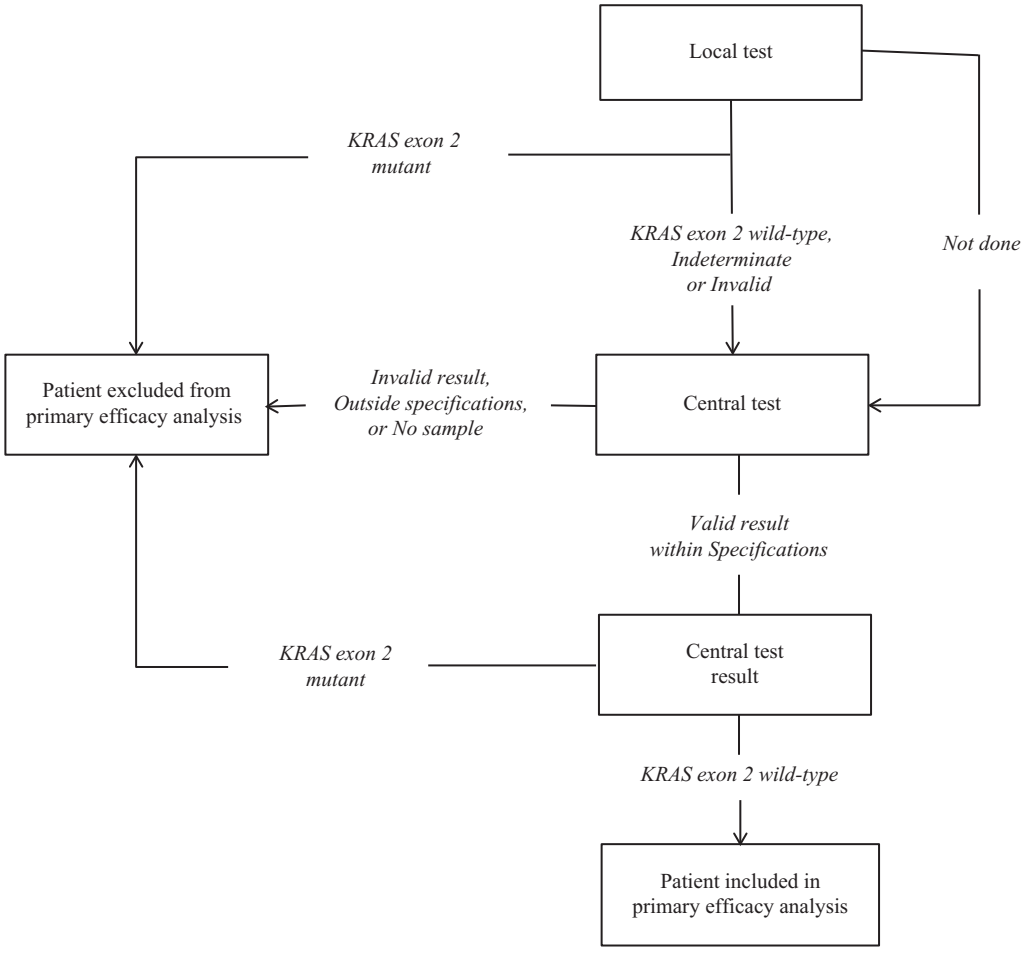

Figure 1. Overview of determining patient inclusion/exclusion from the primary efficacy analysis population.

(20). Toxicity was graded according to the National Cancer Institute CTCAE v3.0 and evaluated in the eligible population. Prespecified biomarker analyses included evaluation of treatment effect (PFS) by IGF-1R and EREG expression as assessed by Cox-regression. To assess possible interaction between treatment and biomarker, an interaction term between treatment and biomarkers was included in the Cox regression.

There were three planned interim analyses. The first was planned when 296 patients were enrolled and 162 PFS events observed. The PFS endpoint at this interim analysis was to be tested with an overall one-sided α of 0.15, which equated to an α 0.08870 for each pair-wise test of dalotuzumab vs placebo. This equated to continuing the trial if the estimated hazard rate reduction was greater than 23.0%. If proof-of-concept was achieved, one dalotuzumab arm (based on activity and safety) would move forward to phase III. If neither experimental arm achieved proof-of-concept criteria, the study would be terminated. All statistical analyses were based on the intent-to-treat, *KRAS* exon 2 wild-type (as per centralized test) eligible population (primary efficacy population). A *P* value of less than .05 was considered statistically significant.

Results

Study recruitment started in January 2008. After the first interim analysis (data cutoff September 2010), the trial was discontinued, as neither dalotuzumab dosing regimen met the predefined criteria for continuation. At the time of this analysis, 538 patients were enrolled from 55 international centers, 38 in Europe, nine in Asia, five in Australia, and three in South America. Of these, 242 were enrolled before the protocol amendment. A total of 353 patients were deemed eligible based on the *KRAS* exon 2 wild-type status of the tumor (as assessed locally or centrally), and 344 were included in the primary efficacy population, 116 in arm A, 117 in arm B, and 111 in arm C (Figure 2). Baseline characteristics were well balanced between the treatment groups (Table 1). The majority of patients had received three or more prior lines of therapy (55.5% in arm A, 56.3% in arm B, and 58.6% in arm C), with bevacizumab administered in less than one third of cases (26.1% in arm A, 31.9% in arm B, and 27.6% in arm C).

Eligible patients received dalotuzumab/placebo for a median of 12.0 weeks (range = 0.0–99.0) in arm A, 20.9 weeks (range = 0.0–83.0) in arm B, and 23.0 weeks (range = 0.0–97.1) in arm C. Radiological response as assessed by independent central review is summarized in Table 2. Objective responses were observed in 21.6%, 23.9%, and 26.1% of patients in arms A, B, and C, respectively, with no statistically significant differences between the investigational treatments and standard therapy. However, disease control in arm A was statistically significantly lower compared with the control arm (42.3% vs 65.7%, *P* = .01).

Eligible patients remained on study for a median of 13.0 weeks (range = 0.0–113.1) in arm A, 21.9 weeks (range = 0.0–125.1) in arm B, and 26.0 weeks (range = 0.0–115.0) in arm C. Median PFS in the control arm was 5.6 months, compared with 3.9 months (hazard ratio [HR] = 1.33, 95% confidence interval [CI] = 0.98 to 1.83, *P* = .07)

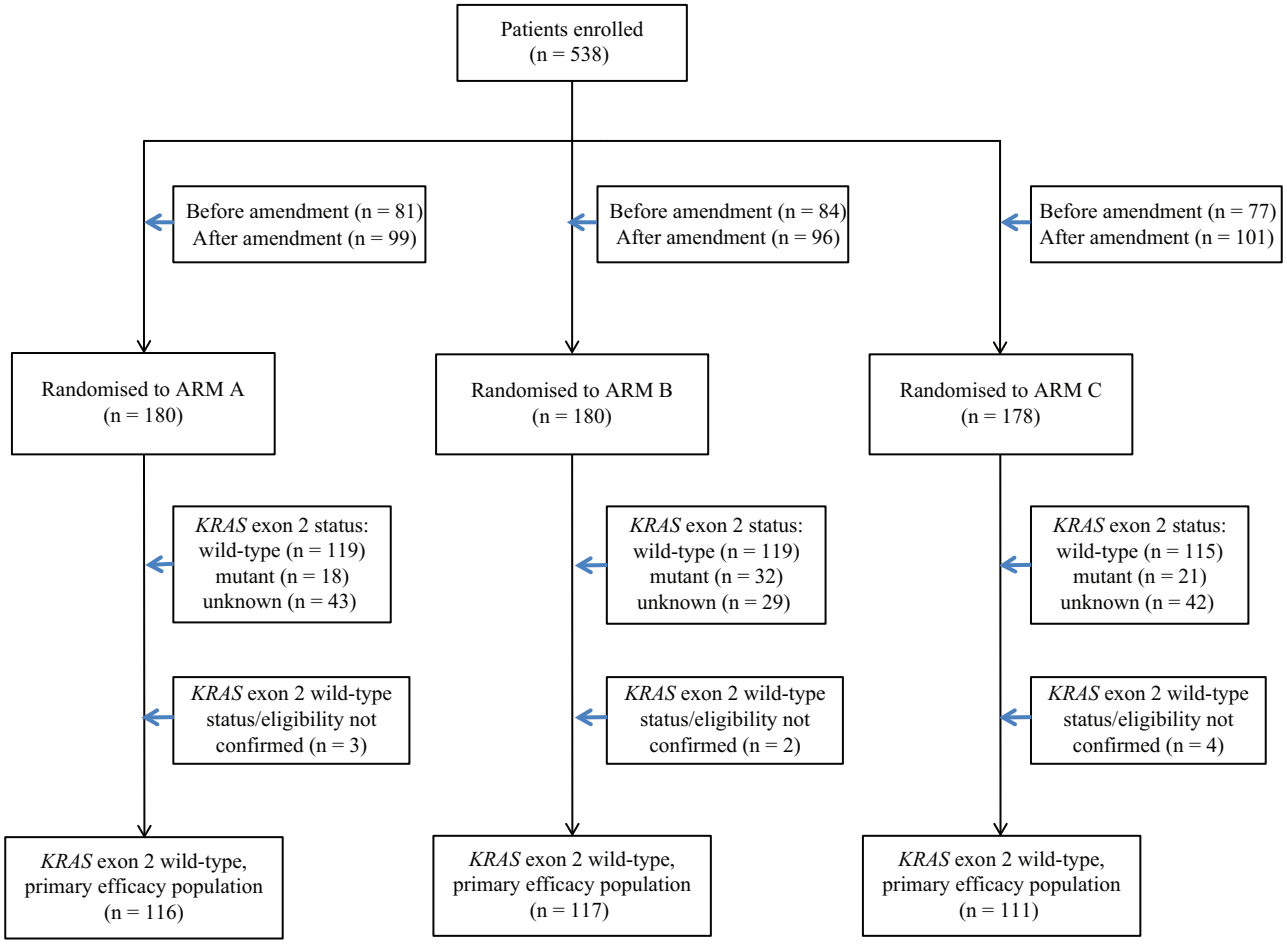

Figure 2. CONSORT diagram.

Table 1. Baseline patient demographics and clinical characteristics in the eligible study population

Demographic/characteristic	Arm A (n = 119) No. (%)	Arm B (n = 119) No. (%)	Arm C (n = 116) No. (%)
Sex			
Male	86 (72.3)	75 (63.0)	82 (70.7)
Female	33 (27.7)	44 (37.0)	34 (29.3)
Age, y			
<65	79 (66.4)	68 (57.1)	73 (62.9)
≥65	40 (33.6)	51 (42.9)	43 (37.1)
Race			
Caucasian	62 (52.1)	55 (46.2)	60 (51.7)
Asian	54 (45.4)	59 (49.6)	49 (42.2)
Other	3 (2.5)	5 (4.2)	7 (6.1)
ECOG PS			
0	53 (44.5)	48 (40.3)	45 (38.8)
1	66 (55.5)	70 (58.8)	71 (61.2)
Unknown	0 (0.0)	1 (0.9)	0 (0.0)
Tumor site			
Colon	69 (58.0)	71 (59.7)	75 (64.7)
Rectum	50 (42.0)	47 (39.5)	41 (35.3)
Colon/rectum	0 (0.0)	1 (0.8)	0 (0.0)
No. of previous lines of therapy			
≤2	53 (44.5)	52 (43.7)	48 (41.4)
≥3	66 (55.5)	67 (56.3)	68 (58.6)
Last failed line of therapy			
Oxaliplatin	26 (21.8)	23 (19.3)	17 (14.6)
Irinotecan	81 (68.1)	77 (64.7)	75 (64.7)
Neither	12 (10.1)	19 (16.0)	24 (20.7)
Previous bevacizumab			
No	88 (73.9)	81 (68.1)	84 (72.4)
Yes	31 (26.1)	38 (31.9)	32 (27.6)
Liver metastases			
No	24 (20.2)	31 (26.1)	28 (24.1)
Yes	95 (79.8)	88 (73.9)	88 (75.9)
Lung metastases			
No	49 (41.2)	46 (38.7)	47 (40.5)
Yes	70 (58.8)	73 (61.3)	69 (59.5)

Table 2. Overall response rate by RECIST criteria version 1.0 based on Independent Radiology Review

RECIST Response % (confirmed)	Arm A (n = 116) No. (%)	Arm B (n = 117) No. (%)	Arm C (n = 111) No. (%)	P* Arm A vs Arm C	P* Arm B vs Arm C
Complete response	0	0	0	-	-
Partial response	25 (21.6)	28 (23.9)	29 (26.1)	.82	.87
Stable disease	24 (20.7)	33 (28.2)	44 (39.6)	-	-
Disease control	49 (42.3)	61 (52.1)	73 (65.7)	.01	.06
Progressive disease	40 (34.5)	37 (31.6)	25 (22.5)	-	-
Not assessable	27 (23.3)	19 (16.2)	13 (11.7)	-	-

* Two-sided, stratified Miettinen and Nurminen's method.

and 5.4 months (HR = 1.13, 95% CI = 0.83 to 1.55, P = .44) in arms A and B, respectively (Table 3). At the time of this analysis, 201 patients in the primary efficacy population had died, 70 in arm A, 74 in arm B, and 57 in arm C. Median OS in the control arm was 14.0 months, compared with 10.8 months (HR = 1.41, 95% CI = 0.99 to 2.00, P = .06) and 11.6 months (HR = 1.26, 95% CI = 0.89 to 1.79, P = .18) in arms A and B, respectively (Table 3 and Figure 3).

Safety

Overall rates of treatment-related (investigator attributed) grade 3 or higher toxicity were comparable between treatment arms (Table 4). Grade 3 or higher hyperglycaemia was more frequently observed in arm A (21.0%, P < .01) and B (17.6%, P < .01) vs in arm C (5.2%), and a higher number of patients in arm B experienced grade 3 or higher asthenia (9.2%) compared with the control arm (1.5%, P = .02).

No statistically significant differences between the treatment arms were observed in the incidence of drug-related serious adverse events (SAEs). The proportion of patients in each group who discontinued study medication because of a drug-related AE was comparable as was the 60-day all-cause mortality. AEs resulting in death during the study period occurred in three patients in arm B (one pneumonia, one renal failure, and

Table 3. Survival outcomes by treatment arm in the primary efficacy population*

Treatment arm	PFS events	Median PFS, mo	HR (95% CI)	P*
A (n = 116)	79	3.9 (2.7 – 5.4)	1.33 (0.98 to 1.83)	.07
B (n = 117)	77	5.4 (3.9 – 6.7)	1.13 (0.83 to 1.55)	.44
C (n = 111)	78	5.6 (4.1 – 6.7)	-	(.19)
	OS events	Median OS, mo		
A (n = 116)	70	10.8 (7.9 – 12.9)	1.41 (0.99 to 2.00)	.06
B (n = 117)	74	11.6 (9.6 – 14.3)	1.26 (0.89 to 1.79)	.18
C (n = 111)	57	14.0 (10.7 – 16.1)	-	(.15)

* Two-sided Cox regression analysis. CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

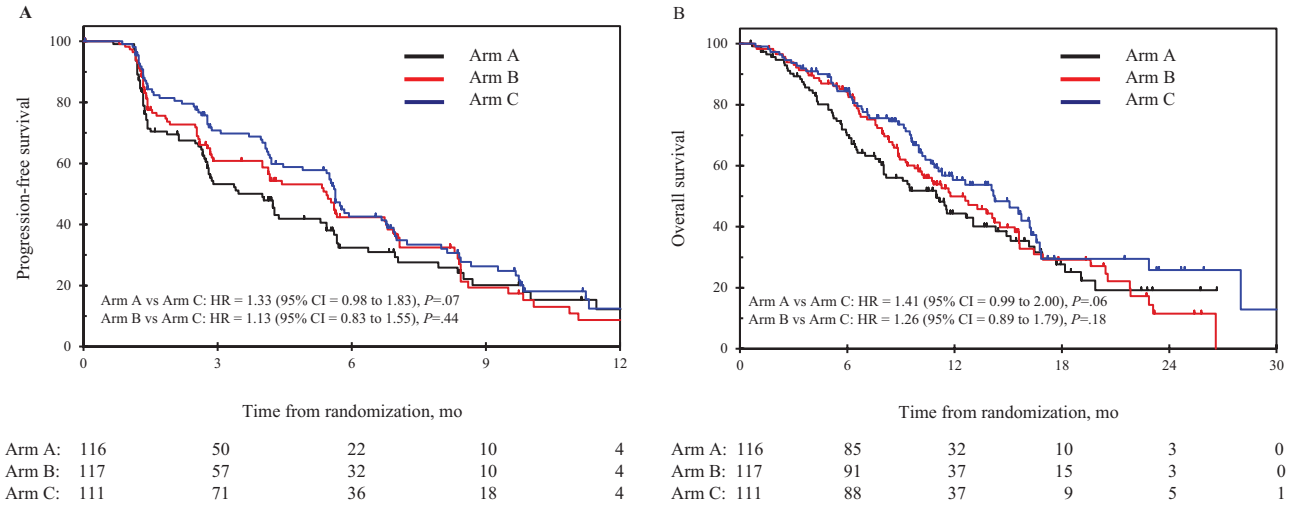

Figure 3. Kaplan-Meier curves for progression-free survival **(A)** and overall survival **(B)** in the primary efficacy population. Treatment groups were compared using a two-sided Cox regression analysis. CI = confidence interval; HR = hazard ratio.

one general physical health deterioration), and four patients in arm C (one cardiac failure, one pneumonia, one hypoglycaemia, and one unknown).

Biomarker Analyses

IGF-1R overexpression (n = 187) was observed in 45.1% and 51.5% of patients treated with dalotuzumab and placebo, respectively. In the same groups, high levels of EREG mRNA (n = 288) were found in 50.0% and 49.5% of patients. An association between either IGF-1R or EREG and PFS was not found (Supplementary Table 1, available online).

In a post hoc biomarker analysis, IGF-1R ligands expression was assessed in 287 patients (histograms representing EREG, IGF-1, and IGF-2 expression are available in Supplementary Figure 2, available online). In the control arm, high IGF-1 (n = 17) was associated with lower response rate (17.6% vs 37.3%, P = .04), shorter PFS (3.6 vs 6.6 months, HR = 2.15, 95% CI = 1.15 to 4.02, P = .02), and shorter OS (9.4 vs 15.5 months, HR = 2.42, 95% CI = 1.21 to 4.82, P = .01) (Figure 4; Supplementary Table 2, available online).

Thirty-one of 92 (33.6%) patients in arm A had IGF-1–overexpressing tumors. In this subgroup, numerically better PFS (5.6 vs 3.6 months, HR = 0.59, 95% CI = 0.28 to 1.23, P = .16) and OS (17.9 vs 9.4 months, HR = 0.67, 95% CI = 0.31 to 1.45, P = .31) were observed when compared with patients with IGF-1–overexpressing tumors in arm C (17/94, 18.1%). In contrast, in the group of patients with low IGF-1 tumors (n = 138, 61 in arm A and 77 in arm C), a statistically significant detrimental effect of dalotuzumab was observed both in terms of PFS (3.9 months in arm A vs 6.6 months in arm C, HR = 1.56, 95% CI = 1.05 to 2.33, P = .03) and OS (11.3 months in arm A vs 15.5 months in arm C, HR = 1.59, 95% CI = 1.01 to 2.52, P = .047 [data not shown]). The test for interaction revealed an interaction between IGF-1 expression and treatment effect (arm A vs arm C) for PFS (P = .02). A similar interaction was found for OS (P = .06). Although the numbers of patients with IGF-2–overexpressing tumors in these treatment groups were small (arm A, n = 15; arm C, n = 10), worse outcomes were observed in those allocated to arm A compared with those treated in arm C (response rate: 26.6% vs 40%, P = .26; PFS: 2.6 vs 8.3 months, HR = 3.13, 95% CI = 1.16 to 8.48, P = .02; OS: 7.8 months vs not reached, HR = 3.45, 95% CI = 0.96 to 12.4, P = .06).

When the effect of study treatment was further evaluated by both IGF-1 expression and tumor site, the risk of progression and death with dalotuzumab was lower in IGF-1 positive tumors compared with IGF-1 negative tumors, rectal cancers compared with colon cancers, and IGF-1 positive rectal cancers compared with IGF-1 positive colon cancers (Table 5).

Discussion

We showed that adding dalotuzumab to cetuximab and irinotecan in chemo-refractory, *KRAS* exon 2 wild-type, mCRC patients was associated with an acceptable safety profile. However, no benefit over standard therapy was observed.

Table 4. Most common grade ≥3 drug-related toxicities and adverse event summary*

Adverse event	Arm A (n = 119) No. (%)	Arm B (n = 119) No. (%)	Arm C (n = 115) No. (%)	*P* Arm A vs Arm C	*P* Arm B vs Arm C
Neutropenia	27 (22.7)	41 (34.5)	34 (29.6)	0.24	0.57
Diarrhoea	22 (18.5)	22 (18.5)	23 (20.0)	0.87	0.77
Hyperglycaemia	25 (21.0)	21 (17.6)	6 (5.2)	<0.01	<0.01
Dermatitis acneiform	8 (6.7)	13 (10.9)	10 (8.7)	0.63	0.66
Rash	8 (6.7)	11 (9.2)	5 (4.3)	0.57	0.19
Fatigue	10 (8.4)	5 (4.2)	6 (5.2)	0.33	0.77
Asthenia	6 (5.0)	11 (9.2)	2 (1.5)	0.16	0.02
Leukopenia	4 (3.4)	8 (6.7)	6 (5.2)	0.48	0.78
Any toxicity grade ≥3	81 (68.1)	91 (76.5)	78 (67.8)	1.00	0.15
SAE	59 (49.6)	50 (42.0)	44 (38.3)	0.09	0.59
Drug-related SAE†	27 (22.7)	23 (19.3)	15 (13.0)	0.06	0.22
Discontinuation‡ because of AE	27 (22.7)	29 (24.4)	21 (18.3)	0.42	0.27
Discontinuation‡ because of drug-related AE	7 (5.9)	13 (10.9)	8 (7.0)	0.79	0.36
Discontinuation‡ because of SAE	22 (18.5)	16 (13.4)	18 (15.7)	0.60	0.71
Discontinuation‡ because of drug-related SAE	4 (3.4)	3 (2.5)	5 (4.3)	0.74	0.49
Death because of AE	17 (14.3)	19 (16.0)	15 (13.0)	0.78	0.58
60-day all cause mortality	6 (5.0)	4 (3.4)	3 (2.6)	0.50	1.00

* Two-sided, stratified Miettinen and Nurminen's method. AE = adverse event; SAE = serious adverse event.
† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

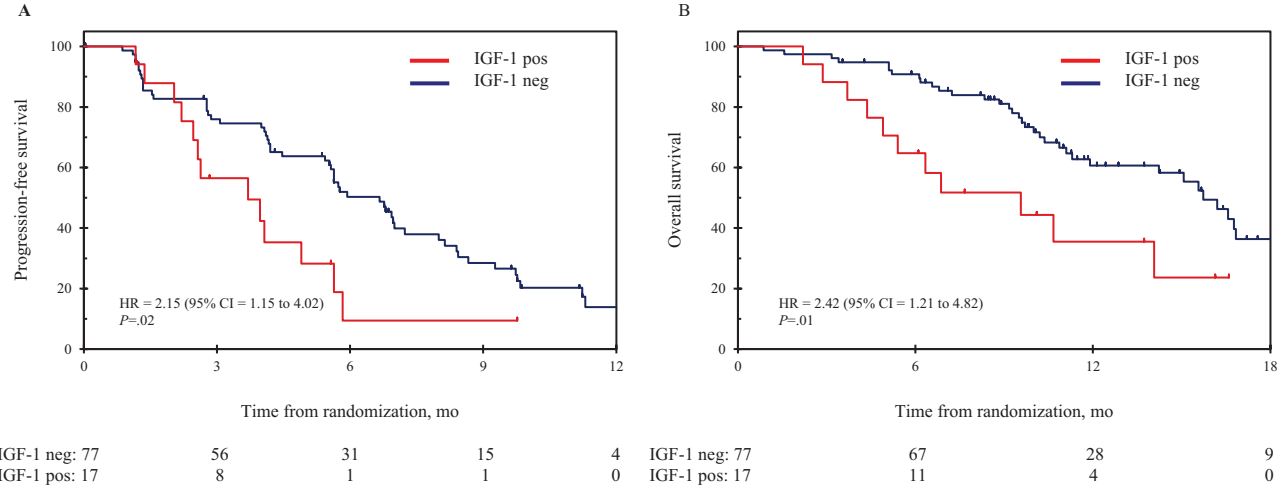

Figure 4. Kaplan-Meier curves for progression-free survival **(A)** and overall survival **(B)** according to IGF-1 expression in the control arm. Treatment groups were compared using a two-sided Cox regression analysis. CI = confidence interval; HR = hazard ratio.

Targeting the IGF signalling pathway has recently emerged as an attractive option in the development of novel anticancer therapeutics (21). However, despite a compelling biological rationale and promising preclinical data, studies have so far failed to provide definitive evidence that IGF-1R may represent a valid therapeutic target in solid tumors (22–26). In non–small cell lung cancer, a phase III study of carboplatin and paclitaxel plus or minus figitumumab was discontinued early when a preplanned analysis showed a survival benefit for chemotherapy alone and an increased rate of toxicities and early deaths in the experimental arm (22). Similar outcomes were observed in a phase II study investigating hormonal treatment with or without ganitumab in endocrine-resistant, postmenopausal, metastatic breast cancer patients (23). The scenario for IGF-1R inhibitors in mCRC does not appear to differ from other diseases. Reidy et al. reported limited clinical activity for IMC-A12 in chemo-refractory, anti-EGFR–pretreated mCRC patients, and no improvement in response rate was reported more recently with the addition of ganitumab to panitumumab in chemo-refractory, anti-EGFR–naïve patients (26,27).

In line with these data, in our study neither tumor response nor survival outcome was improved by using dalotuzumab in combination with standard therapy. Moreover, a detrimental effect on PFS and OS was observed when this agent was administered on a weekly schedule. It is worth noting that response rates and survival outcomes in the control arm were comparable with those reported in studies of single-agent cetuximab in chemo-refractory, *KRAS* exon 2 wild-type mCRC patients (3,28).

The failure to replicate preclinical effects of IGF-1R inhibition in the clinical setting may be because of poor recapitulation of tumor conditions by explored preclinical models as well as suboptimal patient selection (29). Although the IGF system is largely present in most tumors, it is possible that only in a minority of cases IGF-1R is activated and plays a crucial role within the

Table 5. Hazard ratios for PFS and OS by site of primary tumor and IGF-1 expression*

	PFS		OS	
Patient subgroups	Arm A vs Arm C HR (95% CI)	Arm B vs Arm C HR (95% CI)	Arm A vs Arm C HR (95% CI)	Arm B vs Arm C HR (95% CI)
All patients (n = 344)	1.30 (0.95 to 1.78)	1.10 (0.80 to 1.51)	1.37 (0.96 to 1.95)	1.23 (0.87 to 1.74)
Rectal tumors (n = 133)	1.24 (0.72 to 2.14)	1.19 (0.69 to 2.04)	1.00 (0.57 to 1.77)	0.92 (0.52 to 1.60)
Colon tumors (n = 211)	1.40 (0.95 to 2.06)	1.08 (0.73 to 1.60)	1.69 (1.08 to 2.66)	1.49 (0.95 to 2.32)
IGF-1+ tumors (n = 73)	0.59 (0.28 to 1.24)	0.84 (0.40 to 1.76)	0.67 (0.31 to 1.45)	0.75 (0.34 to 1.64)
IGF-1+ rectal tumors (n = 33)	0.35 (0.10 to 1.19)	0.77 (0.24 to 2.43)	0.49 (0.15 to 1.56)	0.61 (0.19 to 1.92)
IGF-1+ colon tumors (n = 40)	0.84 (0.32 to 2.20)	0.94 (0.35 to 2.47)	0.89 (0.30 to 2.61)	0.91 (0.30 to 2.76)

* CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression free survival.

network of oncogenic signaling pathways (30). This hypothesis is supported by the results of our prespecified biomarker analysis where the expression of IGF-1R failed to predict increased sensitivity to the therapeutic blockade of IGF-1R.

The results of the exploratory post hoc analyses are of interest, albeit limited by the small samples size. IGF-1 and IGF-2 are the two principal IGF-1R ligands, which lead to deregulation of the IGF pathway through autocrine and paracrine mechanisms (10). When we analyzed the expression of these ligands, we identified subgroups of patients with differential response to cetuximab and dalotuzumab. We found that high IGF-1 expression was predictive of poor outcome in the control arm but marked a subset of patients who appeared to benefit from the addition of weekly dalotuzumab to standard therapy. These findings are in line with previous studies suggesting that IGF-1 may represent a predictive factor for resistance to cetuximab in *KRAS* wild-type mCRC (13,31) and high baseline circulating IGF-1 levels may predict response to IGF-1R inhibition (22,32). By contrast, overexpression of IGF-2 showed some association with lack of benefit from dalotuzumab, further supporting a potential role for this ligand in mediating activation of alternative downstream pathways through the insulin receptor (33).

The IGF system has been attributed an important role in the mechanisms of colorectal carcinogenesis and tumor progression (34). However, its functional relevance may vary according to the anatomical location of the primary tumor. Studies have reported an increased mRNA expression of several components of the IGF signaling pathway (including IGF-1, IGF-2, IGF-1R, and IGF binding protein-3) in normal rectal mucosa compared with normal mucosa from more proximal segments of the colon (35). In line with these findings, the effect of dalotuzumab in our study appeared stronger in patients with rectal cancers compared with those with colonic cancers, both in the unselected and IGF-1–positive population. Altogether, these data may suggest that the oncogenic activity of the IGF system is more prominent in rectal cancers and they would support the clinical relevance and potential therapeutic implications of the different molecular profiles observed in tumors arising along the length of the large bowel (36).

Unfortunately, at the time of this analysis, data on the source of tumor tissues were not available. We acknowledge that this is a potential weakness of our exploratory analyses. IGF-1 is largely produced by the liver, and contamination by normal liver tissue could have influenced the levels of mRNA expression in specimens derived from liver metastases. Moreover, the routine use of neoadjuvant treatment for locally advanced rectal cancers could have altered gene expression in the resected specimens.

In conclusion, we have demonstrated that, although combining an anti-IGF-1R with an anti-EGFR appears an attractive therapeutic strategy, dalotuzumab failed to improve the outcome of patients with chemo-refractory, *KRAS* exon 2 wild-type mCRC. The findings from this randomized prospective trial provide further insight into the pitfalls that have been encountered in the clinical development of anti-IGF-1R antibodies. In particular, they emphasise the need of using more sophisticated and reliable preclinical models to generate hypotheses that require validation in the clinical setting as well as the value of incorporating correlative biomarker studies in prospective clinical trials. Moreover, they highlight the key roles of companion diagnostics and patient enrichment in clinical drug development and the importance of early identification of robust molecular predictive factors for the success of clinical trials with targeted therapies.

Based on the results of our study and previous data, we believe that further investigation of IGF-1R inhibitors in unselected cancer populations is not recommended. However, investigation of IGF-1R targeted agents in molecularly selected patients in prospective, biomarker-driven studies is warranted. In this regard, although our biomarker analysis was limited by the retrospective design, the small numbers, and the absence of a full *RAS* mutational analysis, we showed that IGF-1 and IGF-2 may represent promising biomarkers predicting outcome with anti-IGF-1R- and anti-EGFR–targeted therapies. Further to this exploratory analysis, a randomized phase II trial of dalotuzumab in combination with irinotecan vs cetuximab and irinotecan for patients with high IGF-1/low IGF-2 metastatic rectal cancer was launched. Unfortunately, the study was prematurely discontinued because of slow recruitment. This underscores the challenges encountered when conducting trials in niche patient populations who are selected on the basis of tumor tissue biomarkers. However, it should not discourage the oncologic community from further investigating the relationship between the activity of anti-EGFR and anti-IGF-1R agents and the expression of IGF-1R ligands and pursuing the development of IGF-1R inhibitors in specific patient subgroups.

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Notes

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References

1. Goldstein NI, Prewett M, Zuklys K, Rockwell P, Mendelsohn J. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. *Clin Cancer Res*. 1995;1(11):1311–1318.
2. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351(4):337–345.
3. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008;359(17):1757–1765.
4. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(10):1065–1075.
5. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol*. 2007;25(22):3230–3237.
6. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol*. 2010;11(8):753–762.
7. Scartozzi M, Giampieri R, Maccaroni E, et al. Analysis of HER-3, insulin growth factor-1, nuclear factor-kB and epidermal growth factor receptor gene copy number in the prediction of clinical outcome for K-RAS wild-type colorectal cancer patients receiving irinotecan-cetuximab. *Ann Oncol*. 2012;23(7):1706–1712.
8. Montagut C, Dalmases A, Bellosillo B, et al. Identification of a mutation in the extracellular domain of the Epidermal Growth Factor Receptor conferring cetuximab resistance in colorectal cancer. *Nat Med*. 2012;18(2):221–223.
9. Bardelli A, Corso S, Bertotti A, et al. Amplification of the MET receptor drives resistance to anti-EGFR therapies in colorectal cancer. *Cancer Discov*. 2013;3(6):658–673.
10. Pollack M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. *Nat Rev Cancer*. 2012;12(3):159–169.
11. Burgaud JL, Baserga R. Intracellular transactivation of the insulin-like growth factor I receptor by an epidermal growth factor receptor. *Exp Cell Res*. 1996;223(2):412–419.
12. Hu YP, Patil SB, Panasiewicz M, et al. Heterogeneity of receptor function in colon carcinoma cells determined by cross-talk between type I insulin-like growth factor receptor and epidermal growth factor receptor. *Cancer Res*. 2008;68(19):8004–8013.
13. Scartozzi M, Mandolesi A, Giampieri R, et al. Insulin-like growth factor 1 expression correlates with clinical outcome in K-RAS wild type colorectal cancer patients treated with cetuximab and irinotecan. *Int J Cancer*. 2010;127(8):1941–1947.
14. Kaulfuss S, Burfeind P, Gaedcke J, Scharf JG. Dual silencing of insulin-like growth factor-I receptor and epidermal growth factor receptor in colorectal cancer cells is associated with decreased proliferation and enhanced apoptosis. *Mol Cancer Ther*. 2009;8(4):821–833.
15. Scartozzi M, Bianconi M, Maccaroni E, Giampieri R, Berardi R, Cascinu S. Dalotuzumab, a recombinant humanized mAb targeted against IGFR1 for the treatment of cancer. *Curr Opin Mol Ther*. 2010;12(3):361–371.
16. Broussas M, Dupont J, Gonzalez A, et al. Molecular mechanisms involved in activity of h7C10, a humanized monoclonal antibody, to IGF-1 receptor. *Int J Cancer*. 2009;124(10):2281–2293.
17. Atzori F, Tabernero J, Cervantes A, et al. A phase I pharmacokinetic and pharmacodynamic study of dalotuzumab (MK-0646), an anti-insulin-like growth factor-1 receptor monoclonal antibody, in patients with advanced solid tumors. *Clin Cancer Res*. 2011;17(19):6304–6312.
18. Watkins DJ, Tabernero J, Schmoll HJ, et al. A phase II study of the anti-IGFR antibody MK-0646 in combination with cetuximab and irinotecan in the treatment of chemorefractory metastatic colorectal cancer. *Presented at the American Society of Clinical Oncology Annual Meeting*, Orlando, FL, May 29 - June 2, 2009.
19. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors (RECIST Guidelines). *J Natl Cancer Inst*. 2000;92(3):205–216.
20. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med*. 1985;4(2):213–226.
21. Sachdev D, Yee D. Disrupting insulin-like growth factor signaling as a potential cancer therapy. *Mol Cancer Ther*. 2007;6(1):1–12.
22. Langer CJ, Novello S, Park K, et al. Randomized, phase III trial of first-line figitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in patients with advanced non–small-cell lung cancer. *J Clin Oncol*. 2014;32(19):2059–2066.
23. Robertson JF, Ferrero JM, Bourgeois H, et al. Ganitumab with either exemestane or fulvestrant for postmenopausal women with advanced, hormone-receptor-positive breast cancer: a randomised, controlled, double-blind, phase 2 trial. *Lancet Oncol*. 2013;14(3):228–235.
24. Pappo AS, Patel SR, Crowley J, et al. R1507, a monoclonal antibody to the insulin-like growth factor 1 receptor, in patients with recurrent or refractory Ewing sarcoma family of tumors: results of a phase II Sarcoma Alliance for Research through Collaboration study. *J Clin Oncol*. 2011;29(34):4541–4547.
25. Ramalingam SS, Spigel DR, Chen D, et al. Randomized phase II study of erlotinib in combination with placebo or R1507, a monoclonal antibody to insulin-like growth factor-1 receptor, for advanced-stage non–small-cell lung cancer. *J Clin Oncol*. 2011;29(34):4574–4580.
26. Reidy DL, Vakiani E, Fakih MG, et al. Randomized, phase II study of the insulin-like growth factor-1 receptor inhibitor IMC-A12, with or without cetuximab, in patients with cetuximab- or panitumumab-refractory metastatic colorectal cancer. *J Clin Oncol*. 2010;28(27):4240–4246.
27. Van Cutsem E, Eng C, Nowara E, et al. Randomized phase Ib/II trial of rilotumumab or ganitumab with panitumumab versus panitumumab alone in patients with wild-type KRAS metastatic colorectal cancer. *Clin Cancer Res*. 2014;20(16):4240–4250.
28. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014;15(6):569–579.
29. Basu B, Olmos D, de Bono JS. Targeting IGF-1R: throwing out the baby with the bathwater? *Br J Cancer*. 2011;104(1):1–3.
30. Wilson S, Chia SK. IGF-1R inhibition: right direction, wrong pathway? *Lancet Oncol*. 2013;14(3):182–183.
31. Huang F, Xu L, Khambata-Ford S. Correlation between gene expression of IGF-1R pathway markers and cetuximab benefit in metastatic colorectal cancer. *Clin Cancer Res*. 2012;18(4):1156–1166.
32. Gualberto A, Hixon ML, Karp DD, et al. Pre-treatment levels of circulating free IGF-1 identify NSCLC patients who derive clinical benefit from figitumumab. *Br J Cancer*. 2011;104(1):68–74.
33. Buck E, Gokhale PC, Koujak S, et al. Compensatory insulin receptor (IR) activation on inhibition of insulin-like growth factor-1 receptor (IGF-1R): Rationale for cotargeting IGF-1R and IR in cancer. *Mol Cancer Ther*. 2010;9(10):2652–2664.
34. Donovan EA, Kummar S. Role of insulin-like growth factor-1R system in colorectal carcinogenesis. *Crit Rev Oncol Hematol*. 2008;66(2):91–98.
35. Vrieling A, Voskuil DW, Bosma A, et al. Expression of insulin-like growth factor system components in colorectal tissue and its relation with serum IGF levels. *Growth Horm IGF Res*. 2009;19(2):126–135.
36. Hong TS, Clark JW, Haigis KM. Cancers of the colon and rectum: identical or fraternal twins? *Cancer Discov*. 2012;2(2):117–121.