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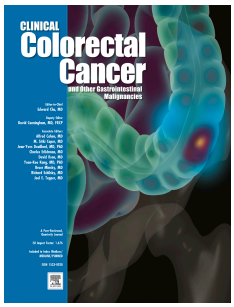

Cetuximab alone or with irinotecan for resistant *KRAS-, NRAS-, BRAF-* and *PIK3CA*-wild-type metastatic colorectal cancer: the AGITG randomised phase II ICECREAM study

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Title: Cetuximab alone or with irinotecan for resistant *KRAS-, NRAS-, BRAF-* and *PIK3CA*-wild-type metastatic colorectal cancer: the AGITG randomised phase II ICECREAM study

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Key words

Cetuximab, irinotecan, RAS, metatastic colorectal cancer

Conflict of Interest

JDS has received travel support from Amgen and Merck Serono. ST has received travel support from Roche. CU has received research funding from Ignyta, Atrium, AbbVie, Boehringer Ingelheim, Boston Biomedical, Regeneron, Bristol-Myers Squibb, Medivation and travel support from Astellas. CK has been paid for a consulting or advisory role with Merk Serono and Amgen. LC has been paid for an advisory role and received travel support has from Amgen. NP has been paid for a consulting or advisory role with Merk Serono. NT has been paid for a consulting or advisory role with Roche, Amgen, Merck Serono and received funding support from Roche and Amgen. TP has been paid for an advisory role with Amgen and Merck Serono. MK has been paid for a consulting or advisory role with AbbVie, Bristol-Myers Squibb, Eli Lilly, Sirtex, Pfizer and received research funding from EMD Serono, Bristol-Myers Squibb, AbbVie. GvH has been paid for a consulting or advisory role with Roche, Merck Serono, Sirtex and has received research and travel funding from Sirtex and is part of Sirtex's Speakers Bureau. PW has employment with Dorevitch Pathology, Roche, Melbourne Pathology and has been paid for a consulting or advisory role with AstraZeneca, Pfizer, Novartis, Amgen and has stock holdings in Roche and Novartis. ST has been paid for an advisory role and has received research and travel funding with Merck Serono is part of Merck Serono's Speakers Bureau. JS institution received funding Merck Serono for ICECREAM Study. VG has been paid for a consulting role and travel funding from Sirtex. JD has been paid for a consulting or advisory role with Bionomics, Novartis, Novartis, Amgen, Roche, Eli Lilly and has received research funding from Roche, Bionomics, Novartis. ES has been paid for an advisory role with Merck Serono, Ipsen and has received travel support from Roche and been paid a speakers fee by Shire.

All remaining authors have declared no conflicts of interest.

Microabstract

Most unresectable metastatic colon cancer remains incurable, with a median survival of less than three years. Molecularly targeted therapies have recently been developed; in particular, monoclonal antibodies against the EGFR receptor, which are efficacious in 40–60% of chemotherapy-resistant patients with wild-type *KRAS*. This study shows that cetuximab plus irinotecan, compared with cetuximab alone, increases the response rate and delays progression in irinotecan-resistant *RAS* wild-type colorectal cancer.

Abstract

Background

The ICECREAM study assessed the efficacy of cetuximab monotherapy compared with cetuximab combined with chemotherapy for quadruple wild-type (*KRAS, NRAS, BRAF,* or *P13KCA* exon 20) metastatic colorectal cancer.

Patients and methods

Patients were enrolled in an open-label, multicentre, phase II trial and randomly assigned to cetuximab 400 mg/m^2, then 250 mg/m^2 cetuximab weekly, with or without irinotecan 180 mg/m^2 every 2 weeks. The primary end point was 6-month progression-free survival; secondary end points were response rate, overall survival, toxicity and quality of life.

Results

From 2012 to 2016, 48 patients were recruited. Two were ineligible and two were not evaluable for response. Characteristics were balanced, except sex (male, 62% versus 72%) and primary sidedness (left, 95% versus 68%). For cetuximab compared with cetuximab-irinotecan, progression-free survival was 14% versus 41% (hazard ratio (HR), 0.39, 95% CI 0.20–0.78; *P*=0.008); response rate 10% (two partial responses) versus 38% (one complete, eight partial); *P*=0.04. Grade 3–4 toxicities were less with cetuximab monotherapy (23% versus 50%); global and specific quality-of-life scores did not differ.

Conclusion

In comparison to cetuximab alone, cetuximab plus irinotecan increases the response rate and delays progression in irinotecan-resistant RAS wild-type colorectal cancer. This echoes data from molecularly unselected patients.

Introduction

Colorectal cancer is globally the fourth leading cause of cancer mortality.[1] Unresectable, metastatic colorectal cancer is treated with systemic cytotoxic therapy and biological agents. Despite stepwise advances over the last 20 years, most disease remains incurable, with median survival less than 3 years and few patients surviving longer than 5 years.[2,3]

Identification of prognostic and predictive molecular biomarkers has allowed therapy to be tailored, in particular by using a class of monoclonal antibodies that target the epidermal growth factor receptor (EGFR). Multiple retrospective series determined that their efficacy is restricted to patients with tumours that are wild-type (no mutations) for exon 2 of the *KRAS* gene.[4-7] Subsequently, benefit was found to be further restricted to tumours also wild-type for *KRAS* exons 3 and 4 and *NRAS* exons 2, 3, and 4.[8-11] The EGFR monoclonal antibodies were initially used in patients with chemotherapy-resistant disease; the landmark CO-17 trial of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)–Australasian Gastro-Intestinal Trials Group (AGITG) demonstrated that cetuximab, compared with best supportive care, in patients with wild-type *KRAS* (exon 2 only), improves progression-free survival (PFS) and also overall survival (OS) to a median of 9.5 months versus (v) 4.8 months (hazard ratio (HR) 0.55; 95% confidence interval (CI), 0.41 to 0.74; $P<0.001$).[7] Extended *RAS* mutation testing is now routinely performed to select the 40% of metastatic colorectal tumours that are all-*RAS* wild-type, and so suitable for the two currently available EGFR monoclonal antibodies (cetuximab and panitumumab).[12]

Even among patients with all-*RAS* wild-type, chemotherapy-resistant disease, only 40–60% respond to EGFR antibody treatment,[13] prompting interest in the predictive value of additional biomarkers downstream of the target in the MAP kinase and PI3 kinase pathways. Retrospective consortium analyses and systematic reviews have demonstrated that *BRAF* and *PIK3CA* mutations and nonfunctional *PTEN* mutations or loss of protein expression may predict resistance to EGFR therapy, concluding that “biomarker analyses beyond *KRAS* exon 2 should be implemented”.[14-16] However, this remains clinically controversial, and

practice varies as to whether patients with tumours harboring these other mutations are offered such therapy. At the time of devising the current study, standard practice was to exclude only patients with *KRAS* exon 2 tumour mutations. The AGITG Irinotecan Cetuximab Evaluation and Cetuximab Response Evaluation (ICECREAM) trial (ACTRN12612000901808) aimed to prospectively evaluate the efficacy of cetuximab in a highly molecularly selected population—a quadruple wild-type genotype (no mutations in *KRAS, NRAS, BRAF,* or *P13KCA* exon 20). The other part of the trial, evaluating cetuximab in 51 patients whose tumours harbored a G13D mutation in *KRAS* exon 2, has been published.[17]

A further question of interest in the molecularly selected population is whether cetuximab might be more efficacious in combination with chemotherapy than as monotherapy. Efficacy of cetuximab was first demonstrated in unselected chemotherapy-resistant metastatic colorectal cancers in the Bowel Oncology with Cetuximab Antibody (BOND) study.[18] Patients who had documented disease progression on irinotecan-based therapy were randomised to cetuximab alone or in combination with irinotecan. Those who received cetuximab and irinotecan had higher response rates and delayed disease progression. Despite this, after *KRAS* was identified as a biomarker for response to EGFR antibody treatment, several large phase III trials elected to use these drugs as monotherapy for resistant disease.[19-21] The ICECREAM trial assessed the efficacy of monotherapy compared to combination with chemotherapy in the molecularly selected quadruple wild-type population.

Patients and Methods

Patients were recruited at 13 hospitals in Australia. The study was performed in accordance with the Declaration of Helsinki. Central or institutional ethics and local research governance approval was required. All patients provided written informed consent. The protocol has been published.[22] Key eligibility criteria were: unresectable, chemotherapy-resistant metastatic colorectal cancer; age over 18 years; Eastern Cooperative Oncology Group performance status 0–2; quadruple wild-type genotype from primary or metastasis;

measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST v1.1);[23] and adequate marrow, hepatic, and renal function. Patients were required to have disease progression after standard therapy with (unless intolerant of) oxaliplatin and fluoropyrimidines. All patients were required to have documented progression within 6 months of receiving an irinotecan-containing regimen, but deemed still fit enough to receive further irinotecan.

Mutation status

Quadruple wild-type status (no activating mutations in *KRAS, NRAS, BRAF, or PI3KCA* exon 20) was centrally confirmed at the Centre for Translational Pathology, University of Melbourne, Australia. DNA was derived from archival formalin-fixed, paraffin-embedded (FFPE) tumour from the primary colorectal cancer or any metastatic site. Next-generation sequencing analysis targeted regions of interest from exon 15 of the *BRAF* gene, exons 9 and 20 of the *PIK3CA* gene, and exons 2, 3, and 4 of both *KRAS* and *NRAS* genes. The assay limit of detection was 5%, as published.[22]

Study design and treatment

Treatment assignment was stratified by hospital and was not blinded. Patients were centrally randomised 1:1 to receive an intravenous (IV) loading dose of 400 mg/m^2 cetuximab, then 250 mg/m^2 IV weekly, with or without 180 mg/m^2 irinotecan IV every 2 weeks. Treatment continued until disease progression, unmanageable toxicity, or a decision by the patient or clinician to stop. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[24] If toxicity was attributable to one particular drug, the other drug could be continued on schedule. Either drug could be delayed for maximum of 28 days; if an adverse event (excluding skin toxicity and alopecia) had not then returned to grade 0, study treatment was permanently discontinued. An independent data and safety monitoring committee regularly assessed patient safety and trial progress.

End points

The primary end point was the proportion of patients remaining free from progression, defined as the Kaplan-Meier estimate of patients without progressive disease at 6 months after random assignment (6-month PFS). Response was measured according to RECIST v1.1 criteria on the basis of 6-weekly computed tomography scans. Patients were censored on the date of last follow-up or at the start of non-protocol anticancer treatment. Secondary end points were: response rate, defined as the proportion of evaluable patients with a complete response or partial response; OS, measured from the date of random assignment to the date of death from any cause (patients still alive were censored at the date of last follow-up); quality of life, defined by scores on the global scale of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C)[25] assessed at baseline and every 4 weeks until disease progression, the skin-specific Dermatology Life Quality Index[26] and Functional Assessment of Cancer Therapy Epidermal Growth Factor Receptor Inhibitor 18 (FACT-EGFRI-18) questionnaires,[27] assessed at baseline then weekly for 12 weeks or until disease progression; and toxicity.

Statistical assumptions used Simon's two-stage design[28] to establish that 25 patients would provide 80% power to rule out 30% 6-month PFS for cetuximab monotherapy, in favor of a clinically relevant rate of at least 58% for cetuximab plus irinotecan, at α level 0.05. As this study was comparing treatments that are considered standard of care, a formal futility analysis was considered unnecessary, and the protocol was amended to reflect this. Exploratory analyses comparing treatment groups for PFS and OS were described using HRs, and their associated 95% CIs were estimated by using Cox proportional-hazards models. Waterfall plots were constructed by using the biggest decrease from baseline in the sum of the target lesion measurements. Patients with a decreased sum of target lesions but with new nontarget lesions were set to a zero change but coded as having progressive disease. Response rates were compared using a chi-sqaured test. Quality-of-life changes

over time were modeled by using generalised estimating equations. Analyses used SAS software v9.3 (SAS Institute, Cary, NC).

Data availability

ICECREAM trial data are not automatically available to other researchers. Proposals for analyses of these data or collaborative studies by other researchers are welcome. The ICECREAM dataset is held by the National Health and Medical Research Council Clinical Trials Centre, University of Sydney.

Results

Between November 2012 and June 2016, 48 patients with quadruple wild-type tumours were randomly assigned to cetuximab monotherapy or cetuximab plus irinotecan (Figure 1). Two participants were later found to be ineligible; one was not irinotecan-resistant according to definition and one was found to have a *BRAF* mutation. Two of the 46 patients available for efficacy were not evaluable for response as they did not receive any study treatment. Baseline characteristics (Table 1) were balanced between the treatment arms, with the exception of sex (male 62% versus 72%) and primary disease site (left 95% versus 68%).

The median time on treatment for cetuximab monotherapy was 4.3 months compared with 5.9 months for cetuximab plus irinotecan (Table 2). A median of 9 (cetuximab) versus 12.5 (cetuximab plus irinotecan) cycles of cetuximab was administered.

Primary end point

The 6-month PFS rate was 14% (95% CI, 4%–32%) in the cetuximab arm and 41% (95% CI, 22%–60%) in the combination arm (HR 0.39; 95% CI, 0.20–0.78; *P*=0.008) (Figure 2). In a sensitivity analysis including the two ineligible patients, HR was 0.37 (95% CI, 0.19-0.73; *P*=0.004). The result of an analysis including only eligible patients and adjusting for the baseline imbalances of sex and sidedness was similar (HR 0.37; 95% CI, 0.19–0.75; *P*=0.006).

Secondary end points

Objective responses were achieved in 2 of 20 (10%) evaluable patients who received cetuximab and in 9 of 24 (38%) who received cetuximab plus irinotecan, including one complete response (difference in response rates 28%; 95% CI, 4%–51%; *P*=0.04). In patients who received cetuximab, the best response was stable disease in 14 (70%), while 4 (20%) had progressive disease. In those treated with the combination, 11 (46%) had stable disease and 4 (17%) had progressive disease. The best responses by treatment arm are shown in Figure 3.

At the time of data cut-off, four patients were still alive. The 6-month OS rates were 62% versus 76% (HR 0.66; 95% CI, 0.35–1.23, *P*=0.19) (Figure 4).

No new or unexpected toxicities were encountered (Table 2). Less toxicity was observed with monotherapy: 23% versus 50% experienced at least one grade 3 or 4 adverse event and 14% versus 42% had at least one serious adverse event. Most patients in the cetuximab arm ceased the study due to disease progression, while more patients in the combination arm ceased because of patient or clinician preference. No significant differences in quality of life were observed between treatment arms (Figure 5).

Discussion

This phase II trial demonstrates a significant response and PFS benefit for the addition of irinotecan to cetuximab in a highly molecularly selected population of patients with resistant colorectal cancer, echoing the BOND data generated in 2004 in an unselected population.[18] The importance of this finding relates to the widespread clinical practice of abandoning the addition of irinotecan to cetuximab since the identification of *KRAS* as a biomarker of response to EGFR monoclonal antibody therapy. Cetuximab monotherapy was used as the control arm in international phase III clinical trials such as the CO.17 and CO.20 studies.[19,21] Trials with panitumumab in the resistant setting also used monotherapy as the standard arm.[20] On the other hand, combination therapy had been uniformly adopted for earlier lines

of treatment. Until the ICECREAM trial, the contention that EGFR antibody efficacy would not be enhanced by concurrent irinotecan in chemotherapy-resistant, *RAS* wild-type tumours had not been tested in a biomarker selected, metastatic colorectal cancer population.

The impetus for ICECREAM arose from the real-life observation that, in Australia, there was an approximate 50/50 split between antibody monotherapy and combination treatment for resistant disease. A superselected group of likely responders to EGFR antibodies seemed to be an ideal setting in which to test the contribution of irinotecan to response in patients with resistant colorectal cancer. At the time of the trial conception in 2011, only *KRAS exon 2* was used as a biomarker of response, although retrospective evidence was emerging of similar selectivity with extended *KRAS* testing (exons 3 and 4), as well as *NRAS*. Data on the predictive value of *BRAF* was less certain at the time and remains controversial, but overall, patients with tumours with BRAF mutations appear to derive less benefit from EGFR antibody treatment. To maximise recruitment, our study permitted the enrolment of patients whose disease had progressed within 6 months of irinotecan chemotherapy, whereas the BOND study required progression within 3 months of irinotecan.[18] Although EGFR antibodies were not publicly funded in Australia for earlier lines of therapy until near the end of the study, availability through clinical trials and access schemes posed a recruitment challenge. Nevertheless, the results of both trials are remarkably similar. In the BOND trial, 6-month PFS was 8% for monotherapy, improved to 30% with combination therapy; in ICECREAM this was 14%, improved to 41%. For response rate, the BOND study reported 11% versus 23%; we report here 10% versus 38%. The small numbers enrolled in our trial likely underplayed the benefit of superselection, as mutations in extended *RAS* testing are relatively infrequent.

For the *KRAS* G13D–mutant arm of the ICECREAM study we reported a similar improvement in 6-month PFS with the addition of irinotecan to cetuximab.[17] Coupled with the quadruple wild-type data, it appears that true synergy between irinotecan and cetuximab is likely, although we cannot exclude the notion that part of the observed irinotecan benefit

derives from response of chemosensitive clones within a heterogeneous tumour. The HR of 0.66 for OS was at a clinically meaningful level, with the small sample size contributing to the survival difference not being statistically significant. The apparent extra benefit from the chemotherapy needs to be weighed against toxicity, although importantly, our study did not observe a difference in quality of life. In summary, data from this focused and strategic trial should be sufficient to inform practice, given its consistency with previous data and the reality that further examination in a phase III study is unlikely.

Conclusion

The AGITG ICECREAM trial confirms significant benefit for the addition of irinotecan to cetuximab, with improved PFS and increased response rate in patients with quadruple wild-type metastatic colorectal cancer. This echoes data in molecularly unselected patients and suggests that cetuximab is optimally used in combination with irinotecan for resistant colorectal tumours.

Clinical Practice Points

- Monoclonal antibodies against the EGFR receptor have been shown to be efficacious in 40–60% of chemotherapy-resistant colon cancer patients with wild-type *RAS*. Whether these antibodies should be used as a monotherapy or in combination with a chemotherapeutic agent in these patients remains an open question.

- This study shows that cetuximab plus irinotecan, compared with cetuximab alone, offers signicant benefit in this selected patient group, increasing the response rate and delaying progression in chemotherapy-resistant quadruple wild-type *RAS* colorectal cancer.

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Manuscript writing: All authors

Final approval of manuscript: All authors

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Table 1: Baseline characteristics of patients eligible for efficacy analysis

Characteristic	Cetuximab (*n*=21)	Cetuximab + Irinotecan (*n*=25)
Median age, years (range)	67 (41–75)	65 (38–76)
Male sex	13 (62%)	18 (72%)
ECOG status		
0	7 (33%)	7 (28%)
1	14 (67%)	17 (68%)
2		1 (4%)
Location of primary tumour*		
Left	20 (95%)	17 (68%)
Right	1 (5%)	8 (32%)
Sites of disease		
More than one site or organ	14 (67%)	18 (72%)
Primary tumour in situ	5 (24%)	8 (32%)
Liver	15 (71%)	18 (72%)
Lung	13 (62%)	11 (44%)
Lymph nodes	5 (24%)	10 (40%)
Peritoneal/omental	2 (10%)	6 (24%)
Bone	2 (10%)	2 (8%)
Median number of prior systemic therapies for metastatic disease (range)	3 (1–4)	2 (1–4)
Irinotecan in most recent regimen before study	17 (81%)	21 (84%)
Median irinotecan-free interval, months (range)	1.8 (0.4–10.1)	1.8 (0.1–18.3)
Median time since metastatic disease diagnosis, months (range)	22.7 (12.7–76.9)	23.7 (7.6–91.3)

* Left includes the descending and sigmoid colon and rectum. Right includes the cecum, ascending and transverse colon.

ECOG, Eastern Cooperative Oncology Group

Table 2: Treatment and toxicity

Treatment	Cetuximab	Cetuximab + Irinotecan
Number of eligible patients who received treatment	20	24
Median months on treatment (range)	4.3 (0.4–9.8)	5.9 (0.9–14.2)
Median number of cetuximab cycles (range)	9 (1–22)	12.5 (1–25)
Median number of irinotecan cycles (range)	–	10 (1–24)
Patients with at least one omitted drug in a cycle	6 (29%)	19 (76%)
Patients with at least one delay	6 (29%)	17 (68%)
Patients with at least one dose reduction	1 (5%)	2 (8%)
Reasons for cessation of study*		
Adverse event	1 (4%)	1 (4%)
Progression	20 (87%)	19 (76%)
Clinician preference	0	2 (8%)
Patient preference	1 (4%)	3 (12%)
Death	1 (4%)	0
Toxicity†		
Patients with at least one adverse event grade 3 or higher	5 (23%)	12 (50%)
Patients with at least one skin adverse event grade 3 or higher	1 (5%)	1 (4%)
Patients with at least one serious adverse event	3 (14%)	10 (42%)
Number of serious adverse events	3	19

* Cetuximab, *n*=23; cetuximab + irinotecan, *n*=25

† Cetuximab, *n*=22; cetuximab + irinotecan, *n*=24; included all patients who received treatment, including ineligible patients

Figure Legends

Figure 1

CONSORT diagram.

Figure 2

Progression-free survival in patients treated with cetuximab versus cetuximab plus irinotecan.

Figure 3

Waterfall plots showing the largest decrease in the sum of the target lesion measurements from baseline, coloured by best response. Dashed lines denote a 30% reduction from baseline.

Patients with no change in tumour measurements are displayed with a zero bar. Four patients were unable to be included in the plots (three cetuximab, one cetuximab plus irinotecan). For cetuximab: one patient did not receive study treatment, so was not evaluable, one died before completing the first cycle, and one patient had no target lesions. For cetuximab plus irinotecan, one patient did not receive study treatment, so was not evaluable.

Figure 4

Overall survival in patients treated with cetuximab versus cetuximab plus irinotecan.

Figure 5

Absolute change in Functional Assessment of Cancer Therapy-Colorectal (FACT-C) from baseline, by treatment. Positive scores indicate improved quality of life from baseline, and scores range from 0 to 28 points.

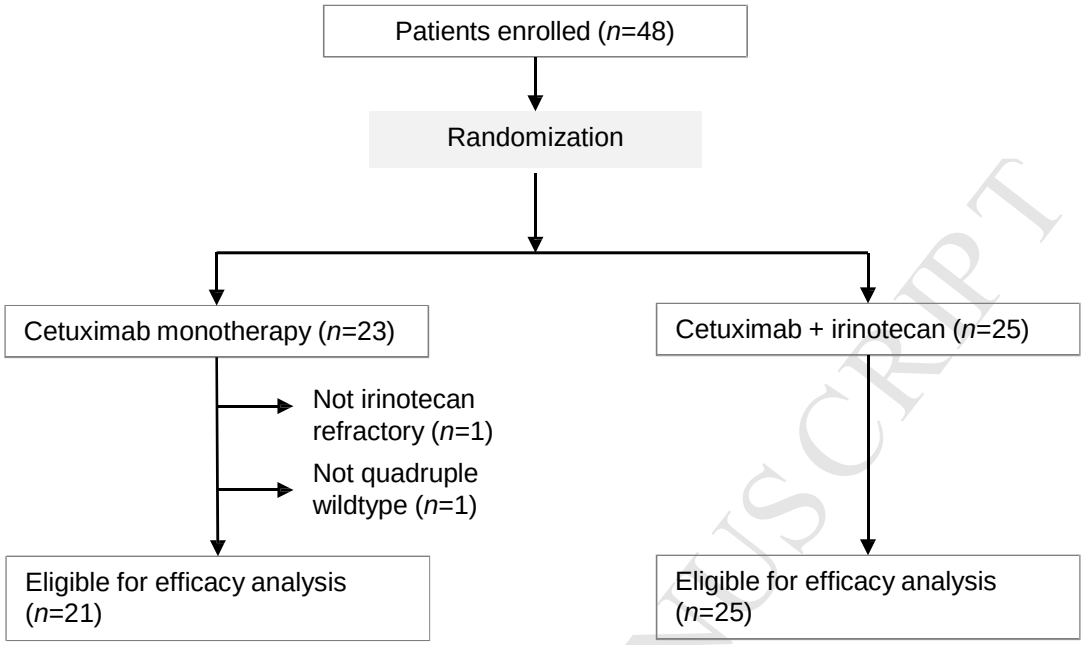
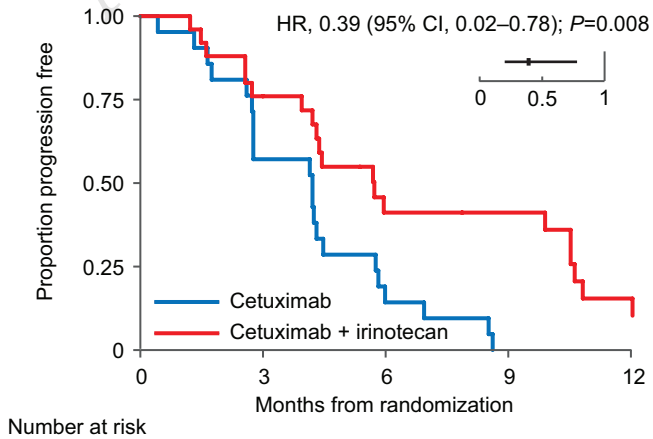


Figure 2 26 Feb 2018



Number at risk					
Cetuximab	21	12	3	0	0
Cetuximab + irinotecan	25	18	9	8	3

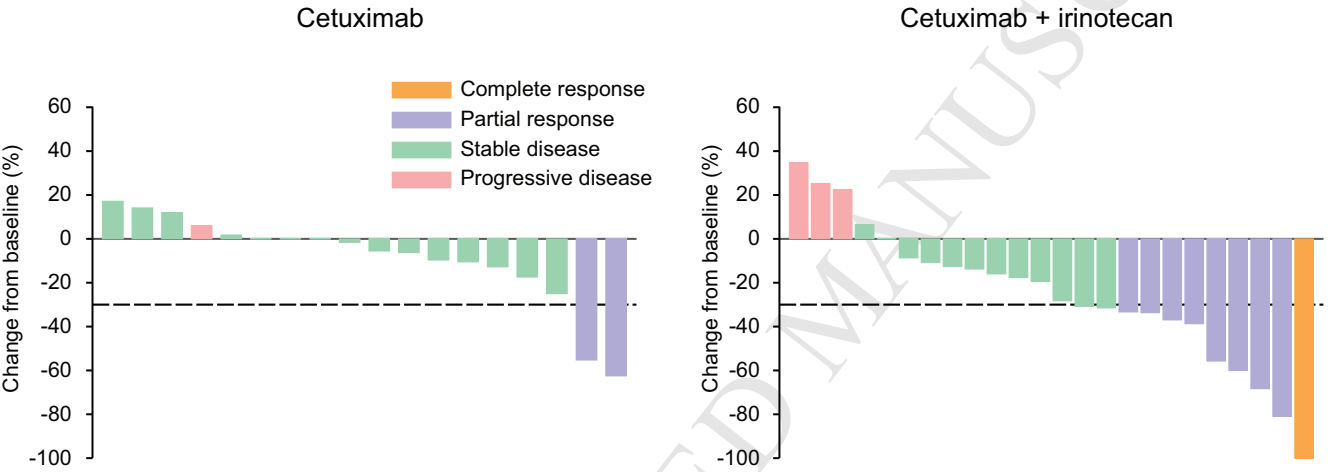
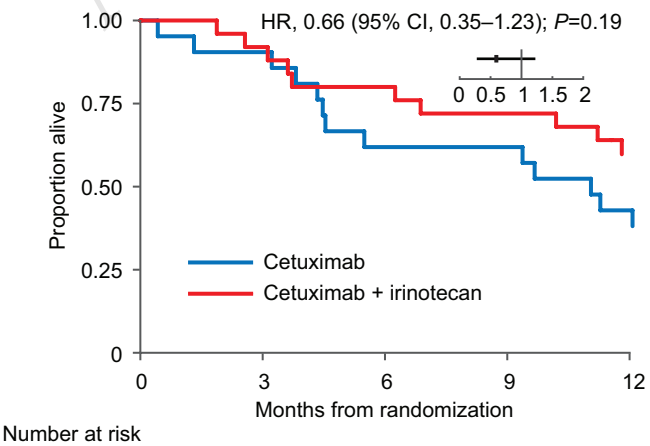


Figure 3 Waterfall 5 Oct 17

Figure 4 26 Feb 2018



Number at risk

Cetuximab	21	19	13	13	9
Cetuximab + irinotecan	25	23	20	18	15

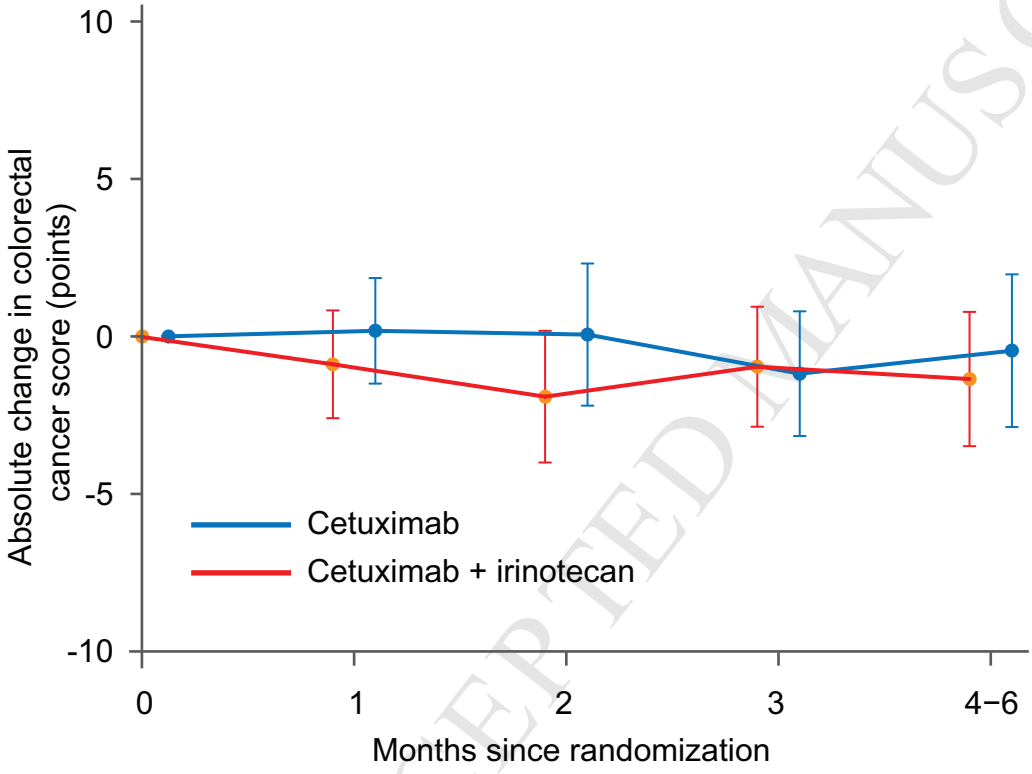


Figure 5 26 Feb 2018