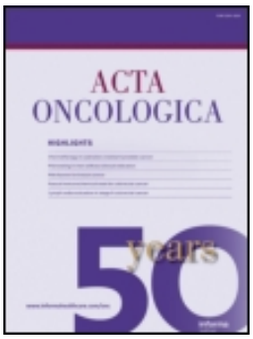

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ORIGINAL ARTICLE

The relationship between rash, tumour KRAS mutation status and clinical and quality of life outcomes in patients with advanced colorectal cancer treated with cetuximab in the NCIC CTG/AGITG CO.17

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ABSTRACT

Background. The NCIC CTG/AGITG CO.17 trial demonstrated that cetuximab monotherapy improved overall and progression-free survival (OS and PFS) in patients previously treated for advanced colorectal cancer. A strong relationship was observed between benefit from cetuximab and development of rash. In this analysis, the association of rash and benefit from cetuximab is explored and presented by KRAS mutation status.

Material and methods. Rash was graded by NCI CTC 2.0 criteria. Landmark analysis was performed by excluding patients who died or dropped out within 28 days and then grouping by worst grade of rash experienced by day 28. Multivariate Cox models were conducted separately for patients with KRAS wild-type (WT) tumours and KRAS mutated (MUT) tumours. CO.17 primary outcome was OS.

Results. Development of grade 2 + rash on cetuximab was associated with a trend towards increased OS (HR 0.61 with 95% CI 0.36–1.02 and $p = 0.06$) and PFS (HR 0.68 with 95% CI 0.45–1.03 and $p = 0.07$) as compared to grade 0/1 rash in patients with WT tumours. In patients with WT tumours on cetuximab both grade 0/1 and grade 2 + rash were associated with increased PFS (HR 0.57 95% CI 0.38–0.86; $p = 0.008$; and HR 0.32 95% CI 0.21–0.49; $p < 0.0001$) respectively, in comparison with best supportive care (BSC). Only development of grade 2 + rash on cetuximab was associated with increased OS (HR 0.52 with 95% CI 0.34–0.80 and $p = 0.003$) in comparison with BSC. No significant difference was found in OS or PFS among patients on cetuximab with MUT tumours with either rash grade as compared to BSC. No consistent trend was observed for the association of severity of rash and quality of life (QoL).

Conclusion. As all patients with WT tumours benefitted to some extent from cetuximab regardless of the grade of rash, grade of rash was not a useful predictive marker.

Adding specific target agents to standard cytotoxic chemotherapy has led to improved outcomes in patients with metastatic colorectal cancer. Cetuximab, a monoclonal antibody inhibitor of the epidermal growth factor receptor (EGFR), improves outcomes in combination with first- or second-line chemotherapy [1–5] and as a single agent when other treatments have failed [6].

Cetuximab is only effective in patients who have tumours with wild-type (WT), or non-mutated

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(MUT) KRAS genes [1,5,7]. However, other biomarkers of efficacy are needed, as 40% of patients with WT tumours do not derive any apparent benefit from treatment with cetuximab [1]. A more accurate method of selecting those who might benefit from cetuximab is crucial, to spare patients ineffective treatment and possible toxicity.

Skin rash is one of the most significant side effects of inhibition of EGFR, a growth factor receptor for normal epidermis development [8]. Severe rash is associated with improved response and survival in patients with colorectal cancer treated with EGFR inhibitors [3,6,7,9,10]. So far, this association has not been confirmed in patients with chemotherapy-refractory metastatic colorectal cancer with known KRAS mutation status on cetuximab monotherapy.

In the NCIC CTG/AGITG CO.17 trial, patients with advanced colorectal cancer in whom all other treatments had failed were randomised to cetuximab alone or best supportive care (BSC) [6]. Included in the published results was a brief summary of a landmark type analysis grouping patients by worst rash severity at any time, which showed that the grade of the rash was associated with survival [6]. The current paper provides a detailed analysis of the relationship between tumour KRAS mutation status, rash, treatment efficacy and quality of life (QoL) outcomes. By doing this study we hope to better identify patients who benefit from cetuximab treatment and avoid futile treatment with its associated toxicities in those who do not.

Material and methods

Patients

Included patients had advanced, pretreated, histologically proven colorectal cancer, for which no other standard anticancer therapies were available. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Additional eligibility criteria have been reported previously [6].

Patients were randomly assigned to receive cetuximab (400 mg/m^2 initial dose followed by a weekly dose of 250 mg/m^2) plus BSC (n = 287) or BSC alone (n = 285). Treatment was continued until death, unacceptable adverse events, tumour progression, worsening symptoms of cancer or request for discontinuation by the patient. The primary analysis has been reported, demonstrating that cetuximab improved overall and progression-free survival (OS, PFS), objective tumour response rate and better-preserved QoL compared with BSC alone [6,11].

Rash development

Rash was graded weekly by NCI CTC2.0 criteria: grade 0, no rash; grade 1, rash without associated symptoms; grade 2, rash with associated symptoms covering < 50% of body surface; grade 3, symptomatic rash covering 50% of body surface area; grade 4, generalised rash. Due to small numbers for patients with grade 0 or 3 rash (Figure 1), rash severity in patients with MUT and WT tumours

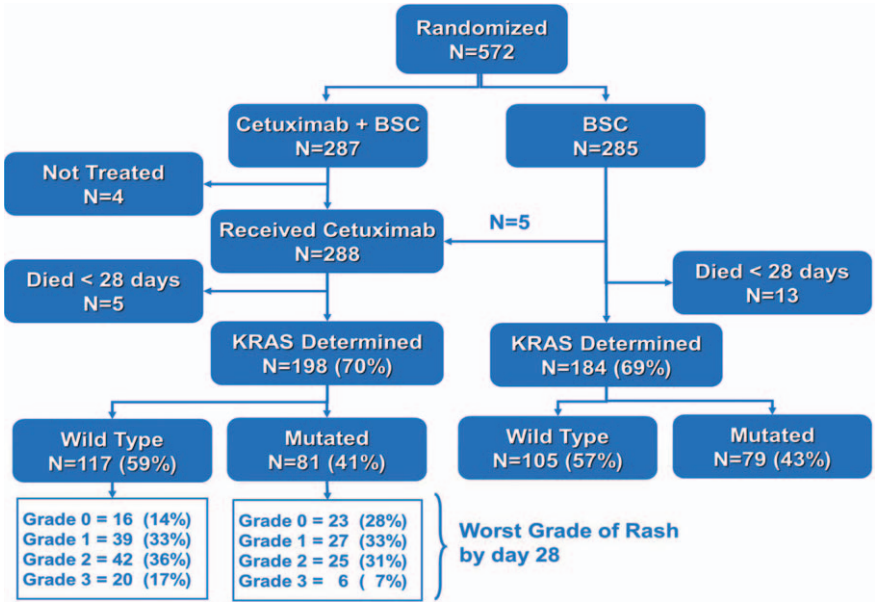

Figure 1. Disposition of patients included in rash analyses.

was grouped in: grade 0/1 versus grade 2 or higher. All cases of rash which occurred on or before day 28 of the study were included in the analyses regardless of causation.

Health-related quality of life assessment

QoL was assessed using the European Organisation for Research and Treatment of Cancer C30 (EORTC-C30) self-administered, cancer-specific, questionnaire which includes five scales (physical, role, cognitive, emotional and social), a two-item global health status scale, three symptom scale (fatigue, pain, nausea and vomiting) and six single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, and financial impact). The questionnaire was to be completed at baseline and at 4, 8, 16 and 24 weeks post random assignment unless the patient had deteriorated to a PS of 4 or was hospitalised for end of life care.

Statistical considerations

All patients who received at least one dose of cetuximab, regardless of arm of randomisation, were included in the cetuximab arm.

To assess relationships between rash and risk of subsequent events, a landmark analysis (LTA) was performed excluding patients who died or dropped out study within 28 days of randomisation [12]. Patients were classified by severity of rash [grade 0 or 1 vs. grade 2 or worse (grade 2+)] based on worst grade of rash observed on or before day 28 of the study. Day 28 was chosen because this coincided with the first formal assessment of the patients. More than 90% of patients had developed rash at day 28.

Kaplan-Meier methods and log rank testing were used to analyse OS and PFS. Multivariate Cox models, adjusting for ECOG performance status, gender, age, site of primary cancer, baseline grades of LDH, alkaline phosphatase, and haemoglobin, number of organ sites, number of previous chemo drug classes, and presence of liver and lung metastases, were used to compare the OS and PFS between cetuximab-treated patients with grade 0/1 rash, cetuximab-treated patients with grade 2 + rash, and BSC patients separately for patients with WT and MUT tumours.

Clinically important deterioration of QoL as measured with the EORTC QLQ-C30 was defined a priori as a change score from baseline of at least −10 points in Physical Functioning and/or Global Health Status Scales at 8 and/or 16 weeks. The Wilcoxon test was used to compare mean QoL changes and Fisher's exact test was used to compare the proportions of patients experiencing QoL deterioration between three groups of patients (cetuximab-treated patients with grade 0/1 rash, cetuximab-treated patients with grade 2 + rash, and BSC patients) separately for patients with WT and MUT tumours.

Results

Patients characteristics

In total 572 patients were randomly assigned to receive cetuximab (n = 287) or BSC (n = 285). Tumour KRAS mutation status was available in 394 patients (69%). Among them, 164 (42%) had MUT tumours. A total of 382 patients with known KRAS mutation status and alive after 28 days after randomisation were included in this analysis (Figure 1). The baseline characteristics of these patients are presented in Table I. For cetuximab-treated patients with WT tumours, those who developed grade 2 + were more likely to be male, have ECOG performance status 0 or 1 (p = 0.04) and have 2 or less organ sites involved (p = 0.04), compared to those with less rash.

Rash development

The number of patients by worst grade of rash experienced by day 28 is presented in Figure 1. Among cetuximab-treated patients, 86% with WT tumours developed rash of any grade by day 28 as compared to 72% of patients with MUT tumours. More grade 2 + rash was observed in the WT tumour patients (53%) as compared to MUT tumour group (38%; p = 0.04). Median time to onset of rash was 9 and 10 days, respectively for those with WT and MUT tumours.

Rash and clinical outcomes in patients with WT tumours

Figure 2A presents OS by severity of rash and treatment arm among WT status patient. Cetuximab-treated patients with grade 2 + rash had a marginally longer median OS (9.8 months (95% CI 8.0–11.6 months) than patients with grade 0/1 rash [median 8.0 months (95% CI 6.2–10.3); adjusted hazard ratio (HR) 0.61 (95% CI 0.36 –1.02), p = 0.06]. The OS in patients treated with BSC [median 5.0 months, (95% CI 4.5–5.7)] was not different from that of cetuximab-treated patients with grade 0/1 rash [adjusted HR 1.18 (95% CI 0.76–1.79), p = 0.46]. The OS in patients with BSC was significantly shorter compared to cetuximab-treated patients with grade 2 + rash [adjusted HR 1.92 (95% CI 1.25–2.94), p = 0.003].

Table I. Baseline characteristics of patients included in the analysis.

(1) Patients with Wild-type Kras.

Characteristic	BSC (N = 105)	Cetuximab Grade 0 or 1 (N = 55)	Cetuximab Grade 2+ (N = 62)	p-value*
Age (year)				0.20
< 65	53 (50.5%)	36 (65.5%)	36 (58.1%)	
≥ 65	52 (49.5%)	19 (34.5%)	26 (41.9%)	
Gender				0.02
Female	34 (32.4%)	24 (43.6%)	12 (19.4%)	
Male	71 (67.6%)	154 (56.4%)	50 (80.6%)	
ECOG performance status				0.04
0 or 1	83 (79.0%)	40 (72.7%)	56 (90.3%)	
2	22 (21.0%)	15 (27.3%)	6 (9.7%)	
Site of primary cancer				0.30
Colon only	57 (54.3%)	35 (63.6%)	38 (61.3%)	
Rectum only	30 (28.6%)	9 (16.4%)	10 (16.1%)	
Both colon and rectum	18 (17.1%)	11 (20.0%)	14 (22.6%)	
Number of organ sites				0.04
≤ 2	39 (37.1%)	28 (50.9%)	35 (56.5%)	
> 2	66 (62.9%)	27 (49.1%)	27 (43.5%)	
Presence of liver and lung metastases				0.22
Yes	89 (84.8%)	41 (74.5%)	53 (85.5%)	
No	16 (15.2%)	14 (25.5%)	9 (14.5%)	

(2) Patients with mutated Kras.

Characteristic	BSC (N = 79)	Cetuximab Grade 0 or 1 (N = 50)	Cetuximab Grade 2+ (N = 31)	p-value*
Age (year)				0.58
< 65	49 (62.0%)	28 (56.0%)	21 (67.7%)	
≥ 65	30 (38.0%)	22 (44.0%)	10 (32.3%)	
Gender				0.07
Female	27 (34.2%)	26 (52.0%)	9 (29.0%)	
Male	52 (65.8%)	24 (48.0%)	22 (71.0%)	
ECOG performance status				0.60
0 or 1	63 (79.7%)	37 (74.0%)	26 (83.9%)	
2	16 (20.3%)	13 (26.0%)	5 (16.1%)	
Site of primary cancer				0.20
Colon only	50 (63.3%)	38 (76.0%)	17 (54.8%)	
Rectum only	18 (22.8%)	5 (10.0%)	9 (29.0%)	
Both colon and rectum	11 (13.9%)	7 (14.0%)	5 (16.1%)	
Number of organ sites				0.04
≤ 2	39 (49.4%)	15 (30.0%)	17 (54.8%)	
> 2	40 (50.6%)	35 (70.0%)	14 (45.2%)	
Presence of liver and lung metastases				0.68
Yes	63 (79.7%)	41 (82.0%)	23 (74.2%)	
No	16 (20.3%)	9 (18.0%)	8 (25.8%)	

Figure 2B presents PFS by severity of rash and treatment arm among WT status patient. The median PFS was 1.9 (95% CI 1.8–2.0), 2.2 (95% CI 1.8–3.9), and 5.1 months (95% CI 3.6–5.5) for patients treated with BSC, cetuximab with grade 0/1 rash, and cetuximab with grade 2 + rash, respectively. The PFS of patients treated with BSC was significantly shorter than cetuximab-treated patients with grade 0/1 rash [adjusted HR 1.75 (95% CI 1.16–2.63), p = 0.008] and also than those with grade 2 + rash [adjusted HR 3.13 (95% CI 2.04–4.76), p < 0.0001]. The difference in PFS between cetuximab-treated patients with grade 2 + rash and with grade 0/1 rash was only marginal and borderline statistically significant [adjusted HR 0.68 (95% CI 0.45–1.03), p = 0.07].

Rash and clinical outcomes in patients with MUT tumours

In patients with MUT tumours, patients treated with cetuximab with grade 2 + rash had significantly better OS than patients treated with cetuximab with grade 0/1 rash [adjusted HR 0.49 (95% CI 0.27 to

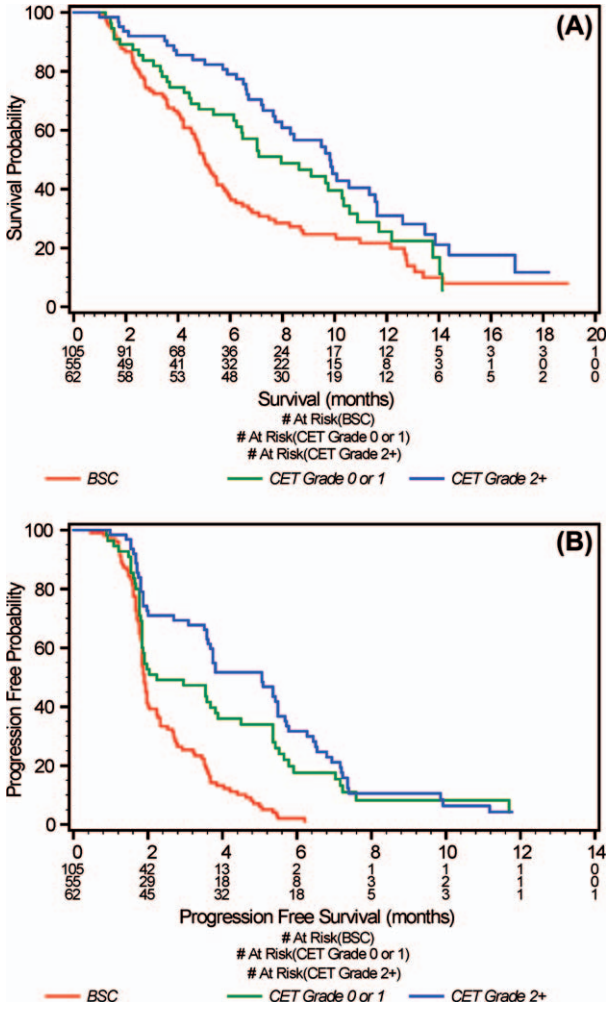

Figure 2. (A) OS for patients with wild-type Kras. (B) PFS for patients with wild-type Kras.

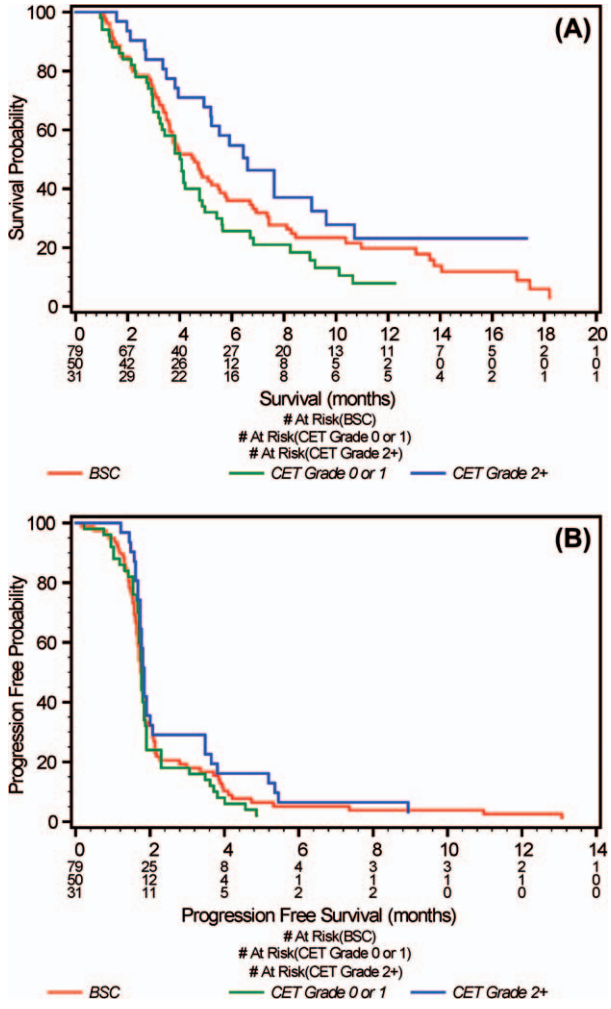

Figure 3. (A) OS for patients with mutated Kras. (B) PFS for patients with mutated Kras.

0.90), p = 0.02] but with no significant difference from the patients treated by BSC [adjusted HR 0.82 (95% CI 0.47–1.41), p = 0.46] (Figure 3A). There was a trend that the OS of the cetuximab-treated patients with grade 0/1 rash was worse than BSC patients [adjusted HR 1.47 (95% CI 0.95–2.27), p = 0.08]. There was, however, not any difference among these three groups with respect to PFS, as seen in Figure 3B.

Rash and dose delivery

Cetuximab dose intensity, dose omissions and dose reductions by worst grade of rash experienced by day 28 are presented in Table II. The dose intensity was significantly higher in patients with WT tumours and grade 0/1 rash as compared to patients with WT tumours and grade 2 + rash (p = 0.001).

For the patients with MUT tumours, the dose intensity of cetuximab during the study was also significantly higher in patients with grade 0/1 rash as compared to patients with grade 2 + rash (p = 0.01).

Rash and changes in quality of life

Changes in global health status and physical function QoL scales in patients with WT tumours are presented in Table III. Changes in global health status from baseline to week 8 and 16 did not differ between patients with grade 0/1 rash and grade 2 + treated with cetuximab. Changes in global health status were significantly different between patients treated with cetuximab with either grade of rash and patients treated with BSC at 8 weeks (p = 0.008 both for patients treated with cetuximab with grade 0/1 and grade 2 + rash vs. BSC) and 16 weeks (p = 0.004 for patients treated with cetuximab with grade 0/1 rash vs. BSC and p = 0.002 for patients treated with cetuximab with grade 2 + rash vs. BSC).

At week 8 the change in physical function did not differ between patients treated with cetuximab with

Table II. Dose intensity, omissions and reductions of cetuximab by worst rash grade by day 28.

(1) Patients with Wild-type Kras.

	Cetuximab Grade 0 or 1 (N = 55)	Cetuximab Grade 2+ (N = 62)
Dose intensity (mg/m^2)		
Median	249	238
Range	174–262	117–256
Proportion receiving ≥ 90% of planned dose	90%	62%
Proportion experiencing dose reduction due to rash	0%	8%
Proportion experiencing dose omission duo to rash	4%	32%

(2) Patients with mutated Kras.

	Cetuximab Grade 0 or 1 (N = 50)	Cetuximab Grade 2+ (N = 32)
Dose intensity (mg/m^2)		
Median	249	236
Range	150–258	141–261
Proportion receiving ≥ 90% of planned dose	87%	68%
Proportion experiencing dose reduction due to rash	0%	6%
Proportion experiencing dose omission due to rash	2%	25%

grade 0/1 or grade 2 + rash and patients on BSC ($p = 0.19$). At week 16 patients on BSC had a significantly larger decrease in physical function compared to patients treated with cetuximab with either grade 0/1 ($p = 0.02$) or grade 2 + rash ($p = 0.02$), respectively. No statistically significant differences were found in the above comparisons repeated for patients with MUT tumours.

Rash and important deterioration in QoL

The proportion of patients with WT tumours experiencing clinically important deterioration (> 10 points) in global health status and physical function at week 8 and week 16 is presented in Table IV. Again, the proportions in either scale did not significantly differ between patients treated with cetuximab with grade 0/1 or grade 2 + rash at either time point of the assessment. The proportion of patients with deterioration on BSC was significantly greater as compared to the two rash subgroups in global health at both assessment times (at week 8: $p = 0.03$ for patients treated with cetuximab with grade 0/1 rash and $p = 0.01$ for patients treated with cetuximab with grade 2 + rash; at week 16: $p = 0.04$ for patients treated with cetuximab with either grade 0/1 or grade 2 + rash). Deterioration in physical domain was only significantly greater in patients treated with BSC as compared to patients treated with cetuximab at week 16 and those with grade 0/1 rash ($p = 0.04$).

Again, no statistically significant differences were found in any of the above comparisons repeated for patients with MUT tumours.

Discussion

Based on the large randomised CO.17 trial in patients treated with cetuximab monotherapy or BSC for chemotherapy refractory CRC, our findings

Table III. Mean change scores from baseline for physical function and global health status with wild-type Kras.

	BSC		Cetuximab Grade 0 or 1		Cetuximab Grade 2+	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Week 8						
Physical function	62	−7.3 (20.3)	40	0.5 (15.7)	50	−1.6 (11.7)
Global health	63	−7.7 (21.3)	37	4.7 (22.5)	51	2.1 (17.4)
Week 16						
Physical function	36	−13.8 (21.5)	26	−2.3 (23.4)	43	−4.1 (13.9)
Global health	36	−18.1 (27.6)	26	1.9 (26.6)	44	−1.5 (17.5)

Table IV. Proportion of patients experiencing deterioration from baseline scores for physical function and global health status in patients with wild-type Kras.

	BSC		Cetuximab Grade 0 or 1		Cetuximab Grade 2+	
	Total	Deteriorated (%)	Total	Deteriorated (%)	Total	Deteriorated (%)
Week 8						
Physical function	62	16 (25.8)	40	7 (17.5)	50	9 (18.0)
Global health	63	23 (36.5)	37	7 (18.9)	51	7 (13.7)
Week 16						
Physical function	36	17 (47.2)	26	5 (19.2)	43	10 (23.3)
Global health	36	21 (58.3)	26	7 (26.9)	44	13 (29.6)

demonstrated that the development of severe (grade 2+) rash in patients with WT tumours and treated by cetuximab was associated with marginally longer OS as compared to patients with grade 0/1 rash. Importantly, the design of this trial, comparing cetuximab versus BSC, allowed us to assess the absolute predictive effect of the development of grade 2 + and grade 0/1 rash, showing that patients with WT tumours who received cetuximab and developed either grade 0/1 or grade2 + rash had significantly longer PFS as compared to patients with WT tumours on BSC. In addition, the difference in median OS between patients with WT tumours who received cetuximab with grade 0/1 versus grade 2 + rash was only 1.8 months. These data suggest that all patients with WT tumours with either grade 0/1 and grade 2 + rash derived benefit from cetuximab therapy to some extent such that patients who only develop a grade 0/1 rash should not be advised to discontinue cetuximab.

There are growing data to suggest that patients who develop moderate or severe rash have a greater chance of benefit from cetuximab than patients who do not. This was confirmed by a recent meta-analysis by Petrelli et al. who by combining data from studies with cetuximab or panitumumab showed that the occurrence of severe skin rash was significantly associated with reduced risk of death in patients with metastatic CRC [13]. However, the majority of large trials on cetuximab included in that analysis did not provide data on KRAS mutation status [3,6]. One of the trials that had data on KRAS mutation status was the study from Stintzing et al. [9]. They evaluated the correlation between skin rash and the treatment efficacy of cetuximab in 149 patients on first line treatment for metastatic CRC randomised to cetuximab plus capecitabine/irinotecan or cetuximab plus capecitabine/oxaliplatin. They observed a trend towards different OS (HR 0.75 95% CI 0.50–1.12, p = 0.161) and PFS (HR 0.78 95% CI 0.55–1.10, p = 0.154) within the total group of patients when patients with or without severe rash were compared. In the subgroup of patients with WT tumours no association between rash and longer OS was observed. Several phase II trials and series of patients showed that rash is a prognostic factor associated with OS and PFS in patients after at least first line chemotherapy, but in majority of cases without information of KRAS status [7,10,13,14]. Since mutation status information is essential as only patients with WT tumours are currently treated with cetuximab, the strength of the present data is that we were able to show that development of severe rash in a large subgroup of patients with WT tumours was associated with only marginally improved OS and PFS.

Dose intensity of cetuximab during the study was significantly lower in patients who developed grade 2 + rash as compared to patients with grade 0/1 rash. Not surprisingly, patients with severe skin rash had significantly more dose reductions because of skin toxicity than patients without severe skin toxicity. In the current trial, conducted from 2003 to 2005, it was not standard of care to recommend prophylactic skin therapy. Possibly, patients who are able to receive higher doses of cetuximab if upfront skin therapy is prescribed might have improved outcomes, but this is unknown. In the EVEREST trial Van Cutsem et al. studied the effect of cetuximab dose escalation in patients with irinotecan-refractory metastatic colorectal cancer who developed no or mild skin toxicity after 21 days of treatment [15]. As expected, they found that dose escalation increased the number of patients with a grade 2 + rash and improved response rates, but OS did not differ between dose escalation and control group. The larger EVEREST 2 study, currently underway will hopefully elucidate whether dose escalation of cetuximab as first line treatment of mCRC guided by development of rash is of benefit and should become the standard of care (http://jco.ascopubs.org.ezproxy2.library.usyd.edu.au/external-ref?link_type = CLINTRIALGOV&access_num = NCT01251536).

Surprisingly, development of rash was not significantly adversely associated with global QoL and

physical function in the CO.17 trial, although it is known that development of rash is associated with significant physical and psychosocial discomfort [8,16]. It could be that the impact of skin toxicity was not captured by using the global health-related QoL EORTC QLQ30 questionnaire. Differences in skin toxicity related issues might have been detected had a specific skin QoL questionnaire been used [16]. In addition the numbers of patients with QoL outcomes and severe rash were small, making it hard to draw conclusions from the available data.

In conclusion, this study adds to the evidence that the development of grade 2 or greater rash during treatment with cetuximab is associated with improvements in OS and PFS, not only in the whole study population but to a lesser extent in those patients who have WT tumours. While the additional benefit of development of grade 2 rash was marginal among patients with WT tumours, there was no disadvantage in terms of poorer QoL. Importantly this study showed that WT patients with grade 0/1 rash also benefit from cetuximab with an increased PFS as compared to patients on BSC. It appears that the development of grade 2 + rash could be used to select patients with a greater likelihood of clinical benefit, but that the development of grade 0/1 rash is not able to predict lack of benefit. More studies that include information on KRAS mutation status are necessary to further unravel the predictive value of rash in patients treated with cetuximab.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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