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# Quality of life, compliance, safety and effectiveness in fit older metastatic colorectal patients with cancer treated in first-line with chemotherapy plus cetuximab: A restrospective analysis from the ObservEr study

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ABSTRACT

*Objectives:* The influence of age (<70 years and ≥70 years) was retrospectively studied on the quality of life (QoL), incidence of side effects (including skin reactions) and efficacy of chemotherapy plus cetuximab in patients with *KRAS* wild type (WT) metastatic colorectal cancer (mCRC).
*Methods:* 225 patients of the Observed study (PS 0-1) were retrieved based on age (< 70 and ≥70 years) and evaluated through EORTC QLQ-C30 and DLQI questionnaires.
*Results:* The two patient groups (141 < 70 and 84 ≥ 70 years, respectively) were balanced with no differences in any of the clinical and pathological characteristics considered. Both groups underwent similar type of first-line chemotherapy plus cetuximab, treatment duration and compliance. Cetuximab therapy caused similar incidence of side effects and impact on QoL in older and younger patients. No difference was observed in progression free survival (PFS) and in disease control rates between the two patient populations. Median overall survival (OS) was higher in patients <70 (27 months, 95% CI: 22.7–31.27) than in patients ≥70 (19 months, 95% CI: 14.65–23.35) ($p = 0.002$), which is likely due to higher proportions of metastatic resection (27.0% vs 8.3%; $p = 0.001$) and utilization of second-line therapy in younger group (58.9% vs 42.9%; $p = 0.028$).
*Conclusion:* The current data suggest that fit older patients with mCRC can be safely treated with a cetuximab-based therapy, as QoL and safety profile do not seem to be affected by age. In addition, age did not impact the choice of chemotherapy to be associated to cetuximab and treatment compliance.


## 1. Introduction

In >40% of the cases, a colorectal cancer is diagnosed in patients older than 70 years [1]. In these patients often the choice of treatment is guided by data obtained in non-elderly or mixed population studies, which might compromise the quality of care in this age group [2,3]. Indeed, older patients with cancer are generally underrepresented in clinical trials; in fact, those >70 years old constitute <15% of most study cohorts [2], making the extrapolation of the results to this specific population difficult. Lower rates of chemotherapy and surgery in olderpatients with colon cancer across all stages of disease have been reported [4–7] and more frequently this subset of patients is more likely to be offered monotherapy than combination chemotherapy, even if the latter would probably be more efficacious [5].

Cetuximab is a monoclonal antibody specifically targeting the Epidermal Growth Factor Receptor (EGFR receptor) [8]. It has been

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granted approval for the treatment of patients with RAS WT mCRC [9]. The clinical use of cetuximab is associated with a wide range of EGFR specific side-effects, mainly skin reactions, which could impact QoL as well as treatment compliance [1,10]. There are several reports that suggest that skin reaction is a surrogate of drug efficacy, as its severity has been shown to correlate with cetuximab clinical activity [11,12].

The very few data available on the use of anti-EGFR therapy, including cetuximab, in older patients with mCRC have been recently reviewed [13,14]. However, no data exist on the QoL of this patient population treated with cetuximab in the first-line setting. Recently, the results of considering the cetuximab-related skin reactions on patients's QoL in first-line routine setting have been reported by the ObservEr study, a observational, multicentre, prospective study aiming at investigating the QoL, safety and efficacy of first-line chemotherapy in combination with cetuximab in patients with *KRAS* WT mCRC [15]. The data suggested that cetuximab plus chemotherapy did not have a negative impact on QoL in mCRC patients in this real life clinical setting; in addition, a correlation between OS time and skin reactions severity was also observed, further corroborating the reported activity in clinical trials [11–13]. The score change on the EORTC QLQ-C30 QoL result was not associated with age in the multivariate analysis and the incidence of cetuximab related skin reactions showed no significant relationship to age [15].

The primary aim of this retrospective analysis was to study the influence of age (<70 years and ≥70 years) on the QoL through the incidence of skin reactions and other side effects as well as the efficacy of first-line chemotherapy in combination with cetuximab in patients with *KRAS* WT mCRC.

## 2. Experimental Methods

### 2.1. Patients and Treatment

The recently published ObservEr study [15] was an observational, multicentre, prospective study of QoL (primary endpoint), safety and efficacy of first-line chemotherapy in combination with cetuximab in patients with *KRAS* WT mCRC. Briefly, patients, prospectively enrolled in the study, with a measurable *KRAS* WT mCRC were eligible to receive cetuximab plus chemotherapy. In each center, all consecutive eligible patients were prospectively enrolled in the study with the exception of Performance Status 2 (PS2) or higher patients as per inclusion criteria (PS 0–1). Cetuximab was administered weekly with chemotherapy until disease progression or unacceptable toxicity, according to clinical practice at the center.

All patients who were eligible for participation provided written informed consent with all applicable governing regulations fulfilled before undergoing any study procedure. The study was performed in accordance with the Declaration of Helsinki.

### 2.2. Endpoints and Measurements

As cetuximab-related skin reactions generally develop within the first three weeks of therapy [16], QoL, the primary endpoint, was assessed within the first eight–twelve weeks of therapy to allow the assessment of the impact of skin reactions. Patient-reported outcomes were evaluated in all treated patients who had completed the baseline assessment and at least one post baseline assessment including the Dermatology Life Quality Index (DLQI) [17] and EORTC Quality of Life Questionnaire (QLQ) C30 version 3.0 (EORTC DataCenter, Brussels). Patients completed the DLQI questionnaire at baseline and weekly during the first 8 weeks, then at every evaluation visit scheduled per local clinical practice until disease progression. EORTC QLQ-C30 questionnaires were completed at baseline, at week eight–twelve (first post baseline evaluation), and every subsequent evaluation visit. DLQI total scores ranging from 0 to 1 were interpreted as no effect on dermatology-related QoL, from 2 to 5 as a small effect, 6 to 10 as a moderate effect, 11 to 20 as a very large effect, and 21 to 30 as an extremely large effect [17] In EORTC QLQ-C30 a ten-unit difference in the change in scores was considered clinically important or relevant [18,19].

Secondary endpoints evaluated were: incidence of cetuximab-related skin reaction and any serious adverse events (SAE), which were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version4.03; OS was defined as months from first cetuximab dose to death or last contact when a death had not been registered and the proportion of patients still alive at two years; PFS was calculated as the time from start of therapy to evidence of clinical/radiologic progression; and overall response rate (ORR) was defined as the percentage of complete responses (CR) and partial responses (PR) according to RECIST v1.1 (Revised RECIST guidelines version 1.1).

Treatment compliance (%) was calculated at total doses received/total planned doses ×100.

### 2.3. Statistical Methods

Descriptive summary statistics for continuous variables comprised number of non-missing observations, mean, standard deviation (SD), median, lower and upper quartiles, minimum, and maximum, where appropriate. Frequencies and percentages were provided for categorical variables. The Chi-square test was used to detect statistical differences between the frequencies in the two age groups. Changes in DLQI and EORTC-QLQ-C30 scores from baseline to first post-baseline visit were evaluated with mixed-design ANOVA. OS and PFS were analysed using the Kaplan–Meier method. *P*-values are reported and statistical significance declared for $p < 0.05$, without correction for multiplicity. All the analyses were carried out with the software Statistical Package for Social Science (SPSS) version 24.

## 3. Results

Between May 2011 and November 2012, 225 patients with *KRAS* WT mCRC entered the ObservEr study protocol to receive first-line treatment with cetuximab plus chemotherapy. The patients were stratified based on their age: <70 year ($n = 141$) (mean age 59.08 ± 0.58) and ≥70 ($n = 84$) (mean age 74.33 ± 0.30). Table 1 reports their main socio-demographics and baseline characteristics. The two groups were similar with no significant differences in all the variables considered.

No differences between the two age groups were observed in the type of administered first-line chemotherapy (irinotecan, oxaliplatin and other fluoropyrimidine-based) (Table 2) and in the percentage of patients treated with 5-fluorouracil/capecitabine plus cetuximab ($p = 0.095$). Table 2 also reports the main reasons for treatment discontinuation.

There was a trend of a longer duration of cetuximab treatment in patients <70 as compared to those ≥70 (157 days and 126 days, respectively). However, this difference did not reach a statistical significance ($p = 0.086$). Treatment compliance was similar in the two patient groups. In fact, a treatment compliance of >90% was observed in 91.5% and 94%, and was between 70 and 69% in 7.1% and 6% respectively in patients <70 and in those ≥70 ($p = 0.554$).

### 3.1. QoL

In both cases the changes in QoL were not different between the two age groups ($p = 0.132$ and $p = 0.405$, respectively), suggesting that cetuximab therapy had no detrimental effect on patient's QoL. Of note, a 16.7% deterioration of the Global Health status (GHS) was observed in the overall patient population enrolled in the ObservEr study. Similar GHS values were found when considering the two different patient age groups (Fig. 1A). When considering the different subscales of the EORTC-QLQ-C30 questionnaire, a decrease in mean values was observed, indicative of a slight worsening from baseline; however, again no significant differences between the two age groups were found (Fig. 1A). However, when the individual symptoms were considered,

**Table 1**
Demographic and baseline characteristics of the patients under study.

| Characteristics | Age < 70 | Age ≥ 70 | p |
|---|---|---|---|
| Gender, n (%) | 141 | 84 | |
| Female | 43 (30.5) | 33 (39.3) | 0.178 |
| Male | 98 (69.5) | 51 (60.7) | |
| Ethnicity, n (%) | | | |
| Caucasian | 139 (98.6) | 84 (100) | 0.584 |
| Asian | 1 (0.7) | 0 (0) | |
| Other | 1 (0.7) | 0 (0) | |
| ECOG performance status, n (%) | | | |
| 0 | 113 (80.1) | 62 (73,8) | 0.269 |
| 1 | 28 (19.9) | 22 (26.2) | |
| Symptoms at baseline | | | |
| No, a little | 20 (14.2) | 11 (13.1) | 0.875 |
| No, at all | 105 (74.5) | 66 (76.6) | |
| Yes, quite a bit | 13 (9.2) | 6 (7.1) | |
| Yes, very much | 3 (2.1) | 1 (1.2) | |
| Primary tumor surgery, n (%) | | | |
| No | 44 (31.3) | 19 (22.6) | 0.165 |
| Yes | 97 (68.8) | 65 (77.4) | |
| Prior adjuvant chemotherapy, n (%) | | | |
| No | 88 (62.4) | 57 (67.9) | 0.409 |
| Yes | 53 (37.6) | 27 (32.1) | |
| Number of metastatic sites, n (%) | | | |
| 1 | 89 (63.1) | 52 (61.9) | 0.865 |
| >1 | 52 (36.9) | 32 (38.1) | |
| Sites of metastases, n (%) | | | |
| Liver | 103 (73.0) | 55 (65.5) | 0.23 |
| Only liver | 64 (45.4) | 33 (39.3) | 0.371 |
| Lung | 28 (19.9) | 25 (29.8) | 0.09 |
| Bone | 3 (2.1) | 1 (1.2) | 0.607 |
| Lymph node | 44 (31.2) | 20 (23.8) | 0.234 |

ECOG: Eastern Cooperative Oncology Group.

patients ≥70 reported a significant worsening of diarrhoea as compared to patients <70 (Fig. 1B), and these data are reflected in a trend of higher incidence of gastrointestinal side effects ($p = 0.228$; Table 3).

### 3.2. Toxicity

81.6% and 72.6%, 66% and 56% of patients <70 and ≥70 years of age, respectively, reported any Grade (G)1 and G2 skin reactions respectively. Similar incidences of severe skin reactions (G3 only) were reported in both groups (14.2% vs 14.3% in <70 and ≥70 respectively; Chi square test $p = 0.983$); no grade 4 or 5 were recorded in any age group. As regards serious adverse events (SAEs), their prevalence was 56/141 patients (39,7%) vs 44/84 (52,4%) in <70 and ≥70, respectively ($p = 0.0872$); a slightly higher incidence of gastrointestinal events were reported in older patients (9.2% vs 15.5% in <70 and ≥70 respectively, $p = 0.228$) (Table 3). No cetuximab-related deaths were reported in any of the age groups.

**Table 2**
First-line therapy administered in two patient groups and reasons for treatment discontinuation.

| | Age < 70 | Age ≥ 70 |
|---|---|---|
| | n (%) | n (%) |
| First line chemotherapy | | |
| Irinotecan based | 90 (63.8) | 55 (65.5) |
| Oxaliplatin based | 43 (30.5) | 24 (28.6) |
| Fluoropyrimidines monotherapy | 8 (5.7) | 5 (6) |
| Main reason of discontinuation | | |
| Progression | 65 (46) | 38 (45) |
| Lost to follow up/other | 6 (4.2) | 0 (0) |
| Resection | 12 (8.5) | 4 (4.8) |
| Clinical deterioration without documented progression | 11 (7.8) | 12 (14.3) |
| Treatment toxicity (any grade) | 9 (6.3) | 10 (11.9) |
| Patient non compliance | 4 (2.8) | 4 (4.8) |
| Death | 5 (3.5) | 6 (7.1) |

### 3.3. Second-line Therapies

Differences were observed in the percentage of patients receiving second-line chemotherapy (Table 4); in fact, only 36 of the 84 patients (42.9%) aged ≥70 received second-line therapy as compared to the 58.9% (83 out of the 141) of patients aged <70 year patients ($p = 0.028$).

### 3.4. Response, PFS and OS

Overall response (complete and partial) rates (53.9% vs 35.7%, $p = 0.012$) were observed in patients <70 and in patients ≥70, respectively, while the disease control rate was similar in the two patient populations (75.2% vs 69%, $p = 0.398$). Patients aged ≥70 were less likely to undergo metastasis resection than patients <70 (rates were 8.3 vs 27%, Chi-square test: $p = 0.001$).

Fig. 2, left panel, shows the OS in the two groups; a longer median survival of 27 months (95% CI: 22.7–31.27) was observed in patients <70 (blue curve) than in patients ≥70 (green curve) who showed a median OS of 19 months (95% CI: 14.65-23.35) ($p = 0.002$). In both patient groups, most deaths were tumor-related. When considering the PFS, however, no difference was observed between patients under and greater or equal 70 years ($p = 0.781$) (Fig. 2, right panel).

## 4. Discussion

Life expectancy is increasing in Western countries and the median age of onset of colon carncer is 71 years at present [20]. A better knownledge of the impact of chemotherapy and targeted therapy in older patients as compared to younger patients will help in a better implementation of tailored therapies, also considering that older patients generally have several comorbidities [21].

The ObservEr study is an observational study on QoL, safety and effectiveness of first-line cetuximab plus chemotherapy in *KRAS* WT mCRC patients [15]. Considering that 40% of the patients enrolled in the ObservEr study were older than 70, a retrospective analysis was conducted to evaluate QoL, incidence of skin reactions, severe side effects and the efficacy of first-line chemotherapy in combination with cetuximab according to the patients' age. The two age groups (<70 and ≥70 years) were well balanced with no significant differences in any of the clinical and pathological characteristics considered. Both patient groups underwent similar first-line chemotherapy. No relevant differences in the duration of cetuximab treatment and treatment compliance were observed, suggesting that age is not a factor that seems to influence the choice of a cetuximab combination therapy nor affects cetuximab combined treatment compliance. In this analysis, the age did not affect the QoL outcomes and the safety profile of cetuximab. Indeed, the incidences of skin reactions and severe side effects were quite similar in the two patient groups except for a higher incidence of gastrointestinal disorders in the older. These tolerability data reflect the results obtained with the DLQI and EORTC QLQ-C30 questionnaires, suggesting that age did not compromise QoL, although worse outcomes were observed in patients ≥70 with the EORTC QLQ-C30 diarrhoea subscale. These findings on QoL and safety data are important as they support the good safety profile of cetuximab in the elderly and agree with previous reports in the same population [11,12] and recently reviewed [13,14].

Despite higher ORR observed in patients <70 than in patients ≥70, disease control rates and PFS time were similar. Younger patients showed a median OS of 27 months as compared to nineteen months in patients ≥70 years. The shorter OS in older patients is most likely influenced by the decreased percentage of older patients undergoing metastasis resections (8.3% in patients ≥70 vs 27% in patients <70) and second-line chemotherapies (42.9% patients ≥70 vs 58.9% of patients <70) compared to younger patients.

There are a number of limitations of the present manuscript that could potentially impact the results. The limited sample size (only 84


**Fig. 1.** Results from the EORTC QLQ-C30 questionnaire for patients with baseline and post-baseline assessment in the two patient population age groups <70 (blank) and ≥70 (grey) and in all the patients enrolled in the ObservEr study (black). A.) Mean change from baseline in Global Health Status and Function at the first post-baseline visit (8–12 weeks). B) Mean change from baseline for individual symptoms at the first post-baseline visit (8–12 weeks). SD standard deviation. A 10 unit difference in the change score is considered clinically important or relevant [18].

patients over 70 years old) and the sampling methods, which include PS 0–1 patients, could indeed limit the generalizability to the older adult population at large. In addition, due to the retrospective nature of the study, very limited information on geriatric specific factors or geriatric assessment (impact of functional status, cognition, nutrition and comorbidities) were not available and this could potentially impact the outcomes. Lastly, the fact that the ObservEr study's recruitment took place from May 2011 until Nov 2012 [15], when only KRAS testing was necessary for cetuximab administration without information on NRAS and BRAF status, is another study limitation.

Nevertheless, we think that our data suggest that fit (EGOG 0–1) older patients with mCRC can be safely treated with a cetuximab-based therapy, as QoL and safety profile do not seem to be affected by age. We observed a lower median OS in older patients likely to be due the fact that these patients less often underwent both metastatic resection and second-line therapies. Age, even in the absence of clear data,

**Table 3**
Frequencies of severe adverse events in the two different patient groups.

| Type of severe adverse event | Age < 70 | Age ≥ 70 |
|---|---|---|
| | n (%) | n (%) |
| Blood and lymphatic system disorders | 4 (2.8) | 2 (2.4) |
| Cardiac disorders | 3 (2.1) | 2 (1.2) |
| Gastrointestinal disorders | 13 (9.2) | 13 (15.5) |
| General disorders and administration site conditions | 8 (5.7) | 5 (5.9) |
| Hepatobiliar disorders | 2 (1.4) | 1 (1.2) |
| Infections and infestations | 4 (2.8) | 2 (2.4) |
| Injury, poisoning and procedural complication | 2 (1.4) | 2 (2.4) |
| Metabolism and nutrition disorders | 5 (3.5) | 5 (5.9) |
| Musculoskeletal and connective tissue disorders | 3 (2.1) | 2 (2.4) |
| Nervous system disorders | 1 (0.1) | 1 (1.2) |
| Renal and urinary disorders | 3 (2.1) | 2 (1.2) |
| Respiratory, thoracic and mediastinal disorders | 3 (2.1) | 3 (3.9) |
| Skin and subcutaneous tissue disorders | 4 (2.8) | 5 (5.9) |
| Vascular disorders | 1 (0.7) | 1 (1.2) |

**Table 4**
Second-line therapy.

| | Age < 70 | Age ≥ 70 | |
|---|---|---|---|
| | n (%) | n (%) | p |
| Aflibercept + FOLFIRI | 1 (1.2) | 0 (0) | 0.43 |
| Bevacizumab + FOLFIRI | 4 (4.8) | 2 (5.6) | 0.83 |
| Bevacizumab + FOLFOX/XELOX | 14 (16.9) | 1 (2.8) | 0.023 |
| Bevacizumab + Fluoropirimidine (5FU/Capecitabine) | 7 (8.4) | 1 (2.8) | 0.26 |
| Bevacizumab monotherapy | 4 (4.8) | 2 (5.6) | 0.83 |
| Cetuximab + CT (Irinotecan or Oxaliplatin based) | 4 (4.8) | 0 (0) | 0.31 |
| Cetuximab + Irinotecan | 1 (1.2) | 0 (0) | 0.43 |
| Fluoropirimidine monotherapy (Capecitabine/5FU) | 6 (7.6) | 8 (22.2) | 0.19 |
| Irinotecan based CT (FOLFIRI/XELIRI/Irinotecan) | 20 (24.1) | 5 (13.9) | 0.092 |
| Other chemotherapy | 3 (3.6) | 2 (5.6) | 0.9 |
| Oxaliplatin based CT (FOLFOX/XELOX/Oxaliplatin) | 1 9(22.9) | 11 (30.6) | 0.93 |
| Panitumumab monotherapy | 0 (0) | 4 (11.1) | 0.036 |
| TOTAL | 83 (58.9) | 36 (42.9) | 0.028 |

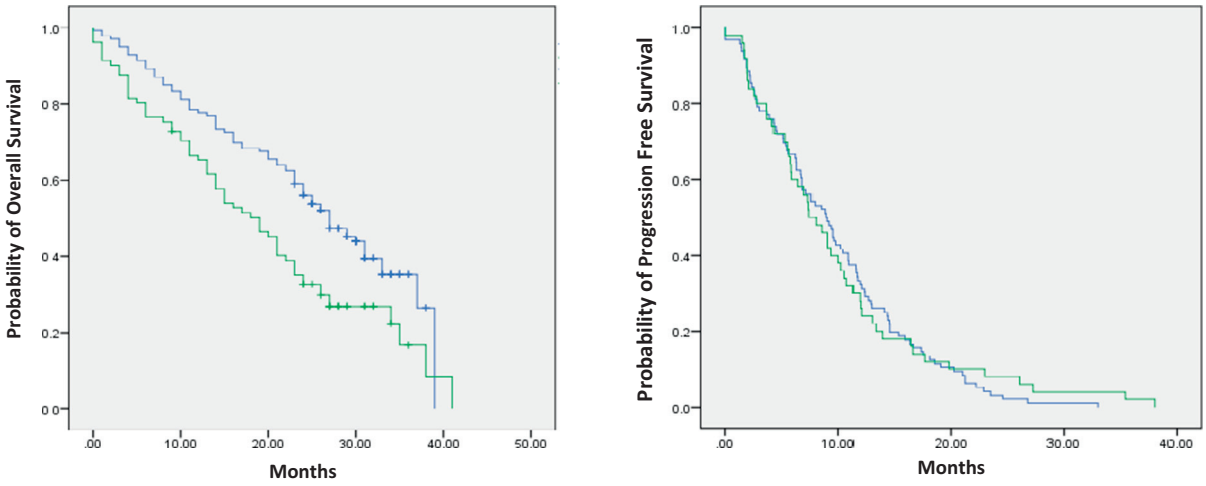


**Fig. 2.** Overall survival (left panel) and Progression Free Survival (right panel) in the two patient groups (blue line <70 years; green line ≥70 years). The median OS was 27 vs 19 months respectively in patient <70 and ≥70 years (Chi-Square p 0.002).

should not be a reason to deny, in first-line setting, the most effective therapeutic combination, according to patients' molecular profile [10,13,22,23]. Even if these data derived from a retrospective analysis and could likely suffer from selection bias, they suggest that in the real life clinical setting cetuximab based therapy is feasible and effective in mCRC fit older patients. Further research on older, more frail older patients with a more granular description of the study population is however warranted.

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## Conflict of Interest

The author declare no conflict of interest.

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