Original Research

Health-related quality of life in patients with RAS wild-type metastatic colorectal cancer treated with panitumumab-based first-line treatment strategy: A pre-specified secondary analysis of the Valentino study

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Background: Quality of life (QoL) patient-reported outcomes (PROs) data from pivotal first-line trials in metastatic colorectal cancer (mCRC) are poor. The Valentino study showed that de-escalation to single-agent panitumumab after 4-month induction with panitumumab-FOLFOX is inferior to panitumumab-5-FU/LV in patients with RAS wild-type mCRC, although slightly reducing toxicity. We report QoL, a secondary end-point.

Methods: PROs were assessed by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire — Core 30 (QLQ-C30), EORTC QLQ-CR29, EuroQol EQ-5D questionnaires, at baseline and every 8 weeks until disease progression. First two evaluations correspond to induction treatment (identical in both arms), while subsequent to maintenance. To describe QoL changes over time, mean changes from baseline at each time point were calculated in overall population. To compare maintenance between two arms, mean changes and proportion of improved/stable/worse patients versus baseline were compared for each item.

Results: In arm A/B, 91.5%/92.0% of enrolled patients completed questionnaires at baseline. No significant differences in the two arms were reported in compliance, baseline scores and mean changes versus baseline for the three questionnaires during maintenance (24/32/40 weeks). Overall, mean changes versus baseline showed an early deterioration during induction with partial recovering during maintenance for global QoL, functional scales and several symptoms/items of QLQ-C30 (fatigue, nausea/vomiting, appetite loss, diarrhoea) and QLQ-CR29 (body image, dry mouth, hair loss, taste, faecal incontinence, sore skin), and EQ-5D Visual Analogue Scale (VAS) score.

Conclusion: In patients with RAS wild-type mCRC, induction with oxaliplatin-containing chemotherapy plus anti-EGFRs induces a transient significant QoL deterioration. After induction phase, treatment deintensification determines an overall recovery of health-related QoL, besides the expected prevention of oxaliplatin-related neurotoxicity.

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inferior progression-free survival (PFS) compared with panitumumab plus 5-FU/LV in patients with \textit{RAS} wild-type mCRC, although slightly reducing the toxicity burden \cite{8}. In the Valentino study, the analysis of QoL assessed through PROs was a pre-specified secondary end-point. Here we report the results of the QoL analysis.

2. Materials and methods

2.1. Study design and trial population

The Valentino study (NCT02476045) was a multicenter, randomized, open-label phase II trial designed to evaluate the non-inferiority in terms of PFS of maintenance with single-agent panitumumab (arm B) versus panitumumab plus 5-FU/LV (arm A) \cite{8}. Randomization was performed before the start of induction treatment, and this allowed us to describe the changes in QoL during both induction and maintenance phases, in the whole study population and in the two treatment arms separately.

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice. Institutional review board and ethics committee approval was obtained from all participating Centres. All patients provided written informed consent before any study-related procedures.

2.2. QoL analysis

PROs were assessed by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire — Core 30 (QLQ-C30) \cite{13}, and the colorectal cancer-specific module (EORTC QLQ-CR29) \cite{14}, EuroQol — 5D (EQ-5D) \cite{15} questionnaires.

For each domain or symptom of EORTC QLQ-C30 and QLQ-CR29, mean changes from baseline to each of the planned time points were reported. A positive value represents an improvement for global health status and functional scales, and a worsening for symptom scales. For comparison between treatment arms at each time point, differences from baseline scores were compared by a multivariable linear regression model, using baseline values as covariates. The first 2 assessments (after 8 and 16 weeks) were not formally compared because induction treatment was in principle the same in both arms, and differences could be attributed to chance. Subsequent time points (24, 32, 40 weeks, and treatment discontinuation due to progressive disease) were formally compared. In the whole study population, comparison of EQ-5D VAS at each time point versus baseline was performed by T test for paired data.

For comparison of EQ-5D Visual Analogue Scale (VAS) between treatment arms at each time point, differences from baseline scores were compared by a multivariable linear regression model, using baseline values as covariates. In the whole study population, comparison of EQ-5D VAS at each time point versus baseline was performed by T test for paired data.

Because of the exploratory nature of the QoL analysis, adjustment for multiple item comparisons was not performed and \( P < 0.05 \) was considered statistically significant. Additional details are described in Supplementary Methods.

3. Results

3.1. Compliance analysis

Of the 229 patients enrolled and randomized in the trial, a total number of 210 patients completed the QLQ-C30, QLQ-CR29 and EQ-5D questionnaires at baseline and were considered for the PROs analyses, 107/117 in arm A and 103/112 in arm B (Supplementary Fig. 1). Therefore, the compliance at baseline was 91.5% and 92.0% in arm A and B, respectively. The rate of patients completing the assessments at designated time points over the total number of randomized patients progressively decreased at the following time points (Fig. 1A).

The rate of patients completing the three questionnaires at each pre-specified time point, was 91.5% and 92.0% in arm A and B, respectively. The rate of patients completing the assessments at designated time points over the total number of randomized patients progressively decreased at the following time points (Fig. 1B). The compliance, reported with the three modalities, was similar between the two arms at any time point, as illustrated in Fig. 1.

3.2. Patients and disease characteristics

Overall, in the final PROs data set, median age was 63.5 (Interquartile range (IQR): 55.4—69.8) years and baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0 and 1 in 65.7% and 34.3% of
cases, respectively. Overall, patients with 1 and > 1 metastatic site accounted for 55.7% and 44.3%, respectively, patients with liver-limited disease were 35.2% and those with peritoneal localizations were 22.9%. The global rate of presence of \textit{BRAF} mutation was 3.8% and of right-sidedness 15.7% (Supplementary Table 1).

3.3. QoL analysis in patients stratified in the two treatment arms

3.3.1. Quality of Life Questionnaire – Core 30

There were no significant differences between the two arms in baseline scores for global QoL, functional scales and symptoms. In details, in arm A versus B, mean score (standard deviation) at baseline was 65.19 (18.94) versus 67.48 (21.15) for global QoL. Further details are shown in (Table 1).

During the maintenance phase, at the pre-defined time points of 24, 32 and 40 weeks, no significant differences were found between the two arms in terms of mean changes versus baseline of global QoL (−2.6/−1.75, \(P = 0.74\); −1.55/0, \(P = 0.58\); +0.29/0, \(P = 0.80\) at 24, 32, 40 weeks in arm A and B, respectively), functional scales and all the individual symptoms (Fig. 2A).

Regarding the best response versus baseline analysis, no significant differences between the two treatment arms were reported in the proportion of improved, stable and worse patients considering the best response
overall (including the global variation in mean scores in the three time points, 24, 32 and 40 weeks) for global QoL ($P = 0.88$), physical ($P = 0.90$), role ($P = 0.95$), emotional ($P = 0.09$), cognitive ($P = 0.97$) and social functioning ($P = 0.99$), and individual symptoms (Supplementary Table 2).

### 3.3.2. Quality of Life Questionnaire – CR29

In QLQ-CR29, the mean scores at baseline for all the items did not show statistically significant differences between patients in arm A and B, as illustrated in Supplementary Table 3. Consistently, no significant differences were reported in mean changes versus baseline between the two treatment arms, for all the individual items of the questionnaire (Supplementary Fig. 2).

### 3.3.3. EQ-5D

Accordingly, for what regards the VAS of the questionnaire EQ-5D, no significant differences between arm A and B were reported, at 24 ($P = 0.68$), 32 ($P = 0.28$) and 40 ($P = 0.80$) weeks, respectively (Fig. 2B).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline scores of EORTC QLQ-C30 questionnaire.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm A</td>
</tr>
<tr>
<td></td>
<td>panitumumab</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Global QoL</td>
<td>65.19 (18.94)</td>
</tr>
<tr>
<td>Functional scales</td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>82.37 (17.09)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>77.73 (24.76)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>80.06 (19.25)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>90.97 (14.71)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>83.80 (21.65)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>28.76 (22.43)</td>
</tr>
<tr>
<td>Nausea-vomiting</td>
<td>5.14 (10.59)</td>
</tr>
<tr>
<td>Sleeping disturbance</td>
<td>21.18 (26.85)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>13.40 (21.41)</td>
</tr>
<tr>
<td>Constipation</td>
<td>16.82 (26.45)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9.97 (20.07)</td>
</tr>
<tr>
<td>Financial</td>
<td>11.21 (22.87)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>10.59 (19.21)</td>
</tr>
</tbody>
</table>

5-FU/LV, 5-fluorouracil/leucovorin; SD, standard deviation; EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire — Core 30.

Fig. 2. Mean changes from baseline for EORTC QLQ-C30 and EQ-5D VAS in the two treatment arms. In this figure the mean changes from baseline scores for EORTC QLQ-C30 questionnaire (panels A) and EQ-5D VAS (panel B) in the study population stratified per treatment arm (A versus B, in blue and red, respectively) are depicted. For each bar, the 95% confidence interval is reported. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.) EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire — Core 30; VAS, Visual Analogue Scale.
3.4. QoL analysis in the overall population

3.4.1. Quality of Life Questionnaire — Core 30
In the overall study population, mean changes versus baseline showed a significant early deterioration of global QoL during the induction treatment phase (−4.25, \( P = 0.004 \) at 8 weeks and −2.84, \( P = 0.11 \) at 16 weeks), but a progressive recovering in the maintenance phase (−2.27, −0.94, +0.18 at 24, 32, 40 weeks, respectively, although not statistically significant). Similarly, all the five functional scales and several symptoms (specifically fatigue, nausea/vomiting, appetite loss, diarrhoea) significantly worsened during induction, with partial recovering during maintenance, as depicted in Fig. 3A.

The best response versus baseline analysis in the overall population was performed for global QoL and a trend towards an increase in the improved versus stable/worsened categories from the treatment start to week 40th was evidenced, as illustrated in Fig. 4.

3.4.2. Quality of Life Questionnaire — CR29
Consistently with QLQ-C30, in QLQ-CR29 analysis for mean changes versus baseline, a number of symptoms or items related to social functioning (body image, dry mouth, hair loss, taste, faecal incontinence, sore skin) significantly worsened during induction, and partially recovered during maintenance (Supplementary Fig. 3).

3.4.3. EQ-5D
The VAS score of EQ-5D showed, in the mean changes versus baseline analysis in the overall trial population, a significant deterioration during the induction phase, with a partial recovering in the maintenance phase (−3.97, \( P = 0.001 \) at 8 weeks; −4.19, \( P = 0.007 \) at 16 weeks; −4.71, \( P = 0.02 \) at 24 weeks; −3.77, \( P = 0.06 \) at 32 weeks and −1.45, \( P = 0.62 \) at 40 weeks), with a further significant deterioration at the time of disease progression (−4.38, \( P = 0.015 \) ) (Fig. 3B).

We compared changes in global QoL between patients who experienced any type of severe toxicity (grade III or higher in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03) versus patients who did not. The analysis did not show significant differences between the two groups (data not shown).

3.5. QoL analysis and primary tumour sidedness
In patients stratified in accordance with primary tumour sidedness, no significant differences were found in terms

![Fig. 3. Mean changes from baseline for EORTC QLQ-C30 and EQ-5D VAS in the overall population.](image-url)
Global QoL

Fig. 4. Best response for global Quality of Life overall. In this figure, the best response for global Quality of Life score of EORTC QLQ-C30 questionnaire in the overall study population is reported, stratifying patients in accordance with the three pre-specified categories (improved, stable and worse). EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire — Core 30.

4. Discussion

In this pre-specified secondary end-point analysis of the Valentino study, we investigated health-related QoL assessed through PROs in patients with previously untreated RAS wild-type mCRC receiving a 4-month induction with panitumumab plus FOLFOX followed by panitumumab-based maintenance treatment.

In the overall trial population, we observed a QoL deterioration during induction treatment, followed by a relevant recovery in the maintenance phase. Such trends were observed for global QoL, all the five functional scales, and some individual symptoms (fatigue, nausea/vomiting, appetite loss, diarrhoea) in QLQ-C30, a number of symptoms or items related to social functioning in QLQ-CR29 and VAS in EQ-5D. Our results were internally consistent and reinforce the rationale for deintensification strategies to improve QoL, besides decreasing the dose-cumulative toxicities, such as oxaliplatin-related neurotoxicity. Because we did not observe a significant association between severe treatment-related adverse events and QoL changes, we emphasize that QoL should not be regarded as the direct and unique consequence of treatment toxicity, but it should be interpreted in light of the complex balance of many treatment-, patient- and tumour-related factors.

These results are peculiarly relevant in light of the characteristics of the trial population, which included patients with good ECOG PS (0/1), RAS wild-type tumours with a negligible proportion of BRAF mutations and low frequency (15%) of right-sided primary tumours, and limited disease burden with single-metastatic site in more than half of cases. In this population with more favourable prognostic outcomes and potentially lower disease-related symptoms at baseline, the treatment toxicity may be more often associated with an evident, though slight, deterioration of QoL [1]. However, the relative improvement of QoL during the maintenance phase and its limited worsening at the time of disease progression could be explained not only by the better tolerability of the deintensified maintenance therapy, but also by the high percentage of study patients with long-term disease control and the potential lack of severe progression-related symptoms thanks to the efficacy of this treatment strategy. Pivotal trials in mCRC provided evidence that de-escalation strategies significantly reduce the drug-related toxicity burden, without jeopardizing the survival outcomes [5]. However, QoL data were not widely reported from trials investigating maintenance strategies, and most of them are derived from bevacizumab-based maintenance trials. In details, in the CAIRO3 study, maintenance therapy with metronomic capecitabine plus bevacizumab did not impair patients’ QoL assessed by the mean QoL score of...
QLQ-C30 compared with observation [6]. Consistently, in the AIO 0207 trial, maintenance treatment with bevacizumab alone or plus 5-FU/LV was not associated with a detrimental effect on QoL, assessed with QLQ-C30 and QLQ-CR29, compared with observation, and no significant differences were reported between the two maintenance arms [17]. However, because patients enrolled in both trials were randomized after the induction treatment, the impact of induction therapy on patients’ QoL could not be evaluated. Moreover, treatment-related toxicities may have a relatively worse impact in patients who do not achieve disease control after the induction phase and may undergo a more rapid PS deterioration, being ineligible for maintenance trials.

On the other hand, for what concerns QoL analysis in pivotal first-line trials with anti-EGFR agents, few data are currently available [18]. In details, the addition of cetuximab to FOLFIRI did not significantly impair QoL assessed with QLQ-C30 in the CRYSTAL trial, even if such secondary analysis was conducted in KRAS exon 2 wild-type subgroup and not in all-RAS wild-type one [19]. A similar result was shown for panitumumab added to FOLFOX-4 in the RAS wild-type subgroup of the PRIME study, even if the QoL was evaluated only by means of the EQ-5D questionnaire, which is a less objective and standardizable scale [20].

At present, QoL data from trials investigating maintenance treatment strategies with anti-EGFRs are still lacking [21–24]. We did not observe significant differences between the two panitumumab-based maintenance arms for all the outcomes measured in the three questionnaires and the proportions of responders versus baseline in QLQ-C30 questionnaire did not significantly differ between the two arms, both at 24 weeks and at the combined analysis including the three analysed time points of the maintenance phase. Therefore, a maintenance strategy combining 5FU/LV monochemotherapy with panitumumab did not significantly impair patients’ QoL, although slightly increasing the toxicity burden as previously reported [5]. Our study has clear limitations. First, the reduction of the sample size over time could have biased the study results and forced us to limit our analysis to the 40-week time point. Moreover, our study involved an oxaliplatin-based induction treatment, and its results may not be generalized to irinotecan- and/or bevacizumab-based first-line therapies, which are not characterized by dose-cumulating adverse events. Finally, we decided to assess PROs using EORTC QLQ-C30, CR-29 and EQ-5D, based on the results of the previously reported studies conducted in this setting, but standard guidelines on the optimal tools and measures for QoL analysis are not currently available [11]. In addition, we did not use dermatological QoL measures, aimed at evaluating the psychological and social impact of the anti-EGFRs class-specific skin toxicity because these measures are poorly used in oncology but could help in better mirroring the real effect on patients’ QoL of these drugs [25].

In conclusion, induction treatment with panitumumab plus FOLFOX-4 may be associated with transient but non-negligible QoL deterioration in patients with RAS wild-type mCRC eligible for modern first-line trials. Treatment deintensification may lead to an overall recovery of health-related QoL, in addition to the expected prevention of oxaliplatin-related neurotoxicity. Thus, the choice of the optimal first-line regimen and its duration in patients with mCRC should be based on the balance between the efficacy, the toxicity and QoL data, as well as patient’s preferences. Further studies are needed on this topic both from clinical trials and real-world setting to collect robust evidence upon the impact of cancer treatments on patients’ QoL and to optimize the therapeutic decision-making algorithm in patients with mCRC.

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This was an academic study. A research grant and drug supply during panitumumab-based maintenance treatment was provided by Amgen.

Data presentation

This study was presented at the World Congress on Gastrointestinal Cancer 2019 in the Poster Discussion Session (PD-016): “Health-related quality of life in RAS wild-type metastatic colorectal cancer patients treated with panitumumab plus FOLFOX followed by panitumumab or panitumumab plus 5-FU/LV maintenance: the secondary endpoint of the Valentino study”.

Data sharing statement

All data included in this publication will be shared by the authors upon specific personal request.

Conflict of interest statement

F.P. reports receiving honoraria for speaker activities and participation in advisory boards from Sanofi SA, Amgen, Inc, Bayer AG, Merck-Serono, Roche, and Servier Laboratories. A.S.-B. reports participation in advisory boards for Amgen, Bayer and Sanofi. L.R. reports being related to this manuscript as a member of the advisory board and for panitumumab supply from Amgen; unrelated to this manuscript as consulting or advisory role from Lilly, Bayer, Baxter, Sirtex Medical, Italfarmaco, Sanofi, ArQule, Incyte, Ipsen, Exelixis, Celgene, Eisai, Hengrui, MSD; has also received lecture fees from AstraZeneca, AbbVie, Gilead, Roche; has received travel expenses from ArQule, Ipsen. A.Z. reports receiving honoraria for speaker activities and...
participation in advisory boards from Sanofi SA, Amgen, Inc, Bayer AG, Merck-Serono, and Roche. M.D.B. reports receiving honoraria for speaker activities and participation in advisory boards from Amgen, Inc, Roche, Eli Lilly and Company, Servier Laboratories. Incyte Corp, and Celgene Corporation. F.d.B. reports receiving honoraria for speaker activities and participation in advisory boards from Amgen, Inc, Roche, and Novartis International AG. No other disclosures were reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.04.048.

References


