Health-Related Quality of Life (HRQOL) and Colorectal Cancer (CRC) Symptoms in Metastatic CRC: Panitumumab Plus Best Supportive Care (BSC) Versus BSC Alone by *KRAS* Tumor Status

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INTRODUCTION

- Panitumumab, a fully human anti-EGFR monoclonal antibody, is approved in Europe as monotherapy for metastatic colorectal cancer (mCRC) patients with wild-type (nonmutated) *KRAS* tumors.
- Phase 3, randomized, open-label, multicenter study.
- Subjects included chemorefractory mCRC patients who have progressed on prior fluoropyrimidine, irinotecan, and oxaliplatin therapy and had no prior anti-EGFR therapy.
- Study arms consisted of: (1) panitumumab (6 mg/kg every 2 weeks) plus BSC, or (2) BSC only.
- *KRAS* tumor status (mutant or wild-type) was determined in 92% of the randomized patients by a blinded central laboratory.
- Patient-reported disease-related symptoms and HRQOL were collected and analyzed as secondary endpoints.
- Patients in the BSC-only arm whose disease progressed were allowed to receive panitumumab in a separate study. Patient-reported outcomes (PROs) were not collected in this separate study.

OBJECTIVE

- To estimate the treatment effect of panitumumab on HRQOL and CRC symptoms using statistical methods that properly account for the large amount of missing PRO data

METHODS

- PRO assessments were obtained at baseline, every 2 weeks, or monthly during the treatment phase of the study and at the 30-day safety follow-up visit. Primary endpoints based on PROs included the following[1, 2]:
  - CRC symptoms were measured using the National Comprehensive Cancer Network (NCCN) Functional Assessment of Cancer Therapy (FACT) Colorectal Symptom Index (FCSI).
  - HRQOL was measured using the EuroQol–5 Dimensions (EQ 5D) index.

EQ-5D

- The EQ-5D index score is a generic preference-based measure of overall quality of life (QOL) assessed across five dimensions:
  1. Mobility
  2. Self-care
  3. Usual activities
  4. Pain/discomfort
  5. Anxiety/depression
- Scores range from -0.594 to 1, with 1 indicating perfect health (United Kingdom tariff model).

FCSI

- The FCSI is a brief 9-item symptom index comprising clinically relevant symptoms for assessing symptomatic response to treatment for CRC.
- Scores range from 0 to 100, with higher scores indicating less CRC symptomatology.

Analysis Methods

Linear Mixed Model

- Change from baseline PRO score was modeled using unstructured covariance, with fixed covariates for visit, treatment, baseline PRO scale score, study stratification variable, and baseline collection medium and a random effect for subject.

Sensitivity Analysis: Pattern-Mixture Model

- Step 1: Created dropout categories based on missing data patterns
- Step 2: Modeled change from baseline PRO score using a mixed-effects model, with unstructured covariance and fixed covariates for visit, treatment, and dropout pattern (and interactions) and a random effect for subject

Rationale

- Standard methods such as last value carried forward can be biased if data are not missing completely at random (MCAR). A linear mixed model is preferable in longitudinal clinical trials when the missing data can be assumed to be missing at random (MAR).[3] In this study, high drop-out rates also may indicate informative (i.e., not MAR) missing data, most likely due to declining health. Often used as a sensitivity analysis of linear mixed models, a pattern-mixture model does not require the MAR assumption because observations are grouped according to patterns of missing values, and these patterns are incorporated into the statistical model.[4, 5]

RESULTS

- Table 1 presents the number of patients in the *KRAS* PRO analysis set (used in all analyses) and the number completing the FCSI for each week until week 17. The amount of missing data is substantial, with less than 25% providing PROs by week 17 (results similar for EQ-5D).

Table 1. Analysis Set and Number of Patients Completing the FCSI

	Panitumumab Plus BSC		BSC Alone	
	Wild-Type *KRAS*	Mutant *KRAS*	Wild-Type *KRAS*	Mutant *KRAS*
KRAS PRO analysis set	112	76	96	79
Number completing FCSI subscale:				
Week 1 (baseline)	104	73	94	78
Week 3	102	65	78	61
Week 5	103	67	78	45
Week 7	96	56	62	29
Week 9	70	30	28	19
Week 13	63	17	9	4
Week 17	56	6	6	1

Linear Mixed Models

- The EQ-5D index score favors panitumumab plus BSC over BSC alone in the wild-type *KRAS* populations (Figure 1); estimate exceeds the minimal clinically important difference (MCID) of 0.08.[6]
- The FCSI treatment difference favors panitumumab plus BSC over BSC alone for the wild-type *KRAS* population (Figure 2). Estimate exceeds the estimated MCID of 4.0.[6]

No significant differences between treatments were seen in the mutant *KRAS* population (Table 2).

Figure 1. Least Square Mean Differences in EQ-5D Scores Between Panitumumab Plus BSC Versus BSC Alone by Analysis Week (Wild-Type KRAS Population)

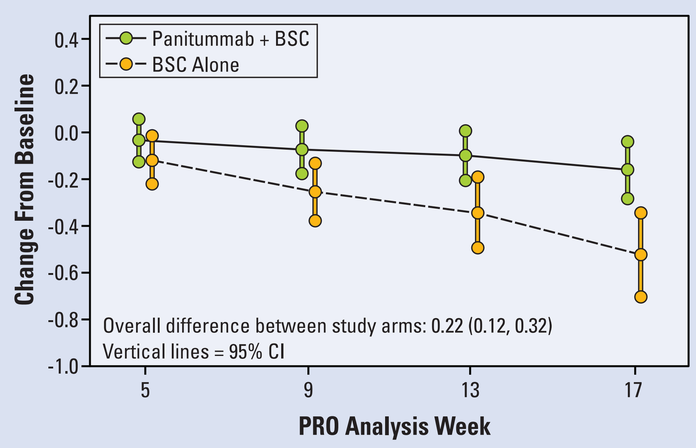


Figure 2. Least Square Mean Differences in FCSI Scores Between Panitumumab Plus BSC Versus BSC Alone by Analysis Week (Wild-Type KRAS Population)

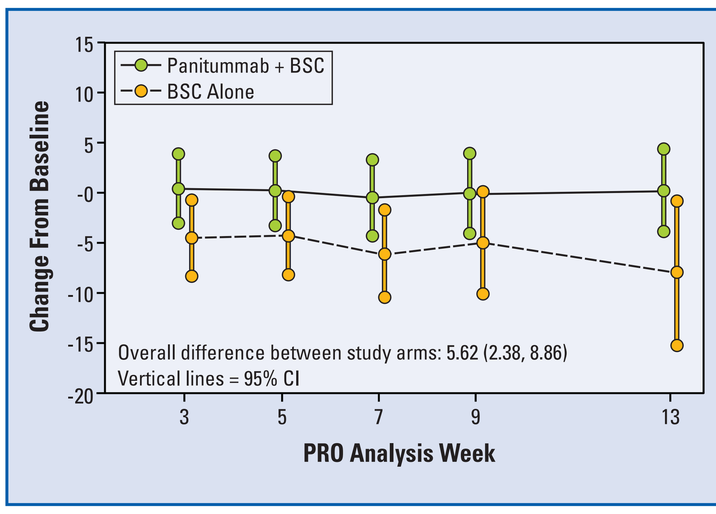


Table 2. Least Square Mean Differences Between Panitumumab Plus BSC Versus BSC Alone[a]

Pro	Wild-Type *KRAS* (95% CI)	Mutant *KRAS* (95% CI)
EQ-5D index	0.22[b] (0.12, 0.32)	0.08 (-0.04, 0.19)
FCSI	5.62[b] (2.38, 8.86)	-1.41 (-6.41, 3.59)

[a] Least square adjusted means are the difference in change from baseline PRO score between study arms through week 17 for EQ-5D and week 13 for FCSI, where a positive difference favors the panitumumab-plus-BSC group.
[b] $P \leq 0.05$.

Pattern-Mixture Models

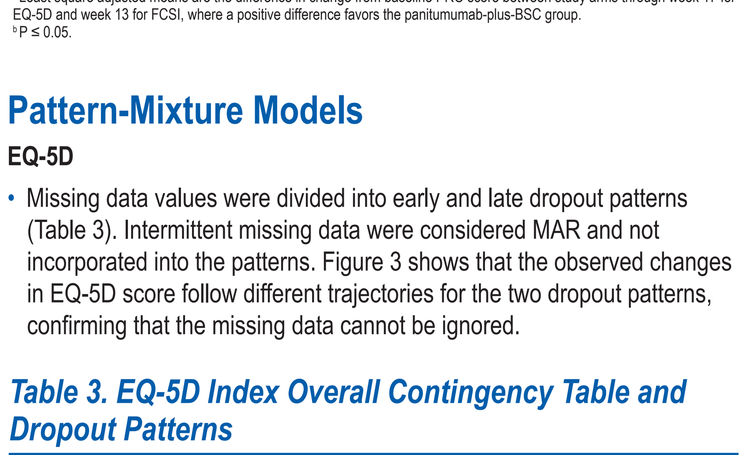
EQ-5D

- Missing data values were divided into early and late dropout patterns (Table 3). Intermittent missing data were considered MAR and not incorporated into the patterns. Figure 3 shows that the observed changes in EQ-5D score follow different trajectories for the two dropout patterns, confirming that the missing data cannot be ignored.

Table 3. EQ-5D Index Overall Contingency Table and Dropout Patterns

Dropout Pattern	Week 5	Week 9	Week 13	Week 17	Frequency
Early	X	Missing	Missing	Missing	94
Early	X	X	Missing	Missing	70
Late	X	X	X	Missing	56
Late	X	X	X	X	96

Figure 3. Average Change From Baseline EQ-5D Score, by Week of PRO Assessment and Dropout Pattern[a]



[a] Missing data excluded.

- EQ-5D results significantly favor panitumumab plus BSC over BSC alone in the late dropout group for the wild-type *KRAS* tumor status group. Estimates exceed the MCID and are consistent with findings from the linear model. This treatment advantage was not evident for patients in the early dropout pattern group (Table 4).

Table 4. Least Square Mean Differences Between Panitumumab Plus BSC Versus BSC Alone in EQ-5D Index Scores, KRAS-PRO Analysis Set[a]

Dropout Pattern	Wild-Type *KRAS* (95% CI)	Mutant *KRAS* (95% CI)
Early dropout	-0.19 (-0.38, 0.01)	-0.02 (-0.19, 0.15)
Late dropout	0.32[b] (0.18, 0.45)	0.13 (-0.03, 0.29)

[a] Least square adjusted means are the difference in change from baseline PRO score between study arms through week 17, where a positive difference favors the panitumumab-plus-BSC group.
[b] $P \leq 0.05$.

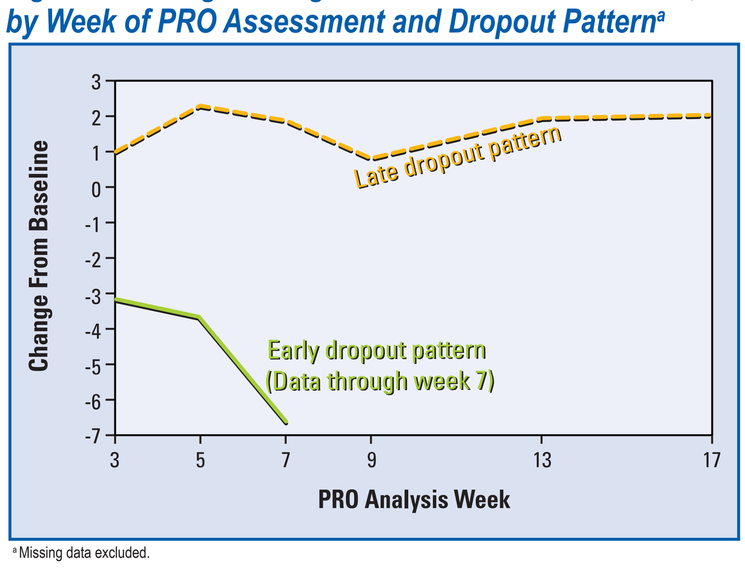
FSCI

- FCSI was collected at additional timepoints and dropout patterns were redefined to account for increased number of assessments (Table 5). Figure 4 also confirms that the missing data cannot be ignored.

Table 5. FCSI Overall Contingency Table and Dropout Patterns

Dropout Pattern	Week 3	Week 5	Week 7	Week 9	Week 13	Week 17	Frequency
Early	X	Missing	Missing	Missing	Missing	Missing	36
Early	X	X	Missing	Missing	Missing	Missing	49
Early	X	X	X	Missing	Missing	Missing	97
Late	X	X	X	X	Missing	Missing	58
Late	X	X	X	X	X	Missing	26
Late	X	X	X	X	X	X	65

Figure 4. Average Change From Baseline FCSI Score, by Week of PRO Assessment and Dropout Pattern[a]



[a] Missing data excluded.

- FCSI results significantly favor panitumumab plus BSC over BSC alone in the late dropout group for the wild-type *KRAS* tumor status group. The estimate exceeds the MCID and is consistent with findings from the linear model. This treatment advantage was not evident for patients in the early dropout pattern group (Table 6).

Table 6. Least Square Mean Differences Between Panitumumab Plus BSC Versus BSC Alone[a]

Dropout Pattern	Wild-Type *KRAS* (95% CI)	Mutant *KRAS* (95% CI)
Early dropout	-2.21 (-7.16, 2.75)	4.27 (-1.33, 9.88)
Late dropout	5.75[b] (1.45, 10.04)	-0.66 (-7.27, 5.95)

[a] Least square adjusted means are the difference in change from baseline PRO score between study arms through week 13, where a positive difference favors the panitumumab-plus-BSC group.
[b] $P \leq 0.05$.

Conclusion

- Standard imputation methods (e.g., last value carried forward) may provide biased results in longitudinal clinical trials when missing data assumptions are not met (most notably, MCAR).
- Our results show that missing PRO data in this study were not MCAR and followed distinct patterns based on dropout status. Therefore, it was important to use statistical methods that properly accounted for the missing PRO data (linear mixed model and pattern-mixture models).
- Our results indicate that panitumumab patients with wild-type *KRAS* showed significantly better HRQOL and CRC symptoms compared to BSC alone. A sensitivity analysis using pattern-mixture models suggested that the treatment improvement was particular to those subjects who did not stop treatment early.

References

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