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Health Solutions

May 2017

Estimating the effects of patient-reported outcome (PRO) diarrhea and pain measures on PRO fatigue: data analysis from a phase 2 study of abemaciclib monotherapy, a CDK4 and CDK6 inhibitor, in patients with HR+/HER2- breast cancer, after chemotherapy for metastatic disease: MONARCH 1

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Draft Poster Content

Background

- Breast cancer is the most common cancer among women in the US. [1]
- In 2017, an estimated 252,710 new invasive breast cancer cases will be diagnosed and an estimated 40,610 will die from breast cancer. [1]
- Disease-related symptoms of pain and fatigue are common.
- Previous research has shown that the relationship between symptom burden and health-related quality of life (HRQoL) can be mediated through fatigue. [2, 3]
- Treatment-related symptoms or treatment-emergent adverse effects (TEAEs) are also common. If a clinical trial is adequately instrumented, at least some of these should be captured by both patient-reported outcome measures (PROMs) and investigator-reported TEAEs. This multi-method approach is intended to support the validity of these assessments.
  - Treatment-related or treatment-emergent diarrhea, pain, and fatigue —the focus of this research— are captured by both PROMs and TEAEs.
  - Investigators reported Grade 1-3 TEAEs of diarrhea, fatigue, and abdominal pain in 90, 65, and 39% of patients, respectively.
  - Although it is well-known that both diarrhea and pain can be associated with fatigue, their relative contribution to fatigue in this setting has not been previously studied.

Objective

- This study sought to model the relative associations of pain and diarrhea with fatigue, using both cross-sectional and longitudinal patient-level clinical trial PROM data.

Methods

- Data arose from a single-arm, multi-national, open-label study of previously-treated (3rd-line or greater) patients with metastatic breast cancer (mBC) (MONARCH1).
- Recruited patients numbered 132.
- PROMs used to measure fatigue, diarrhea, pain, and pain interference were:
  - The EORTC QLQ-C30 fatigue scale (3 items) and single item measures of pain, pain interference, and diarrhea.
  - The modified Brief Pain Inventory short form (mBPI-sf) pain interference scale (7 items).
- Using data from Cycle 2 (following 28 days of abemaciclib treatment), a structural equation model (SEM) was built to estimate the direct and indirect effects of pain and diarrhea on fatigue.
- Longitudinal patient-level data were analyzed using all available data from screening through to Cycle 8.
  - Extended pattern mixture modeling (ePMM) [4] was separately conducted for pain, diarrhea, and fatigue to assess subgroup heterogeneity in change over time.
  - Thereafter, pain and diarrhea subgroup identifiers were added as predictors of the fatigue subgroup identifier in the fatigue ePMM, using 3-step regression approach.[5]
    - This was done to evaluate the extent that changes in pain and diarrhea classification predicted changes in fatigue classification.

Structural Equation Model

- SEM was used to simultaneously examine the hypothesized relationships among multiple manifest (observed) and latent (unobserved) mBPI-sf and the EORTC QLQ-C30 variables. A complete description and modeling results have been disclosed as part of a larger project. [2]
- The interpretive focus was on the overall fit of the hypothesized SEM model to the data, the strength of individual SEM estimates between variables, and the magnitude of SEM direct and indirect effects.
- Here, we focus on the particular results for fatigue, pain, and diarrhea at Cycle 2, using available data from 116 patients.

Extended Pattern Mixture Model

- ePMM is a form of growth modeling that allows the measurement of individual-level change across time using data from all available time points of interest, while simultaneously examining the effect of dropout (i.e. missing) data.
- For every individual in the trial, two latent (i.e., unobserved) variables were measured: the intercept (a value for the starting point of the curve) and a slope (the trajectory of change).
- Dummy variables were created for every post-screening assessment point which mark whether the data were present (a value of 1) or missing (a value of 0).
- The ePMM identified subgroups of individuals (latent classes) who have similar intercepts and slopes of change, which are different from that of other identified subgroups.
  - In this way, data-driven subgroups of differential symptom burden were found.
- The latent class subgroup identifier was regressed on the missing data dummy variables, to allow the explicit modeling of missing data.
  - With oncology patients, the inclusion of missing data modeling was a critical step because patient dropout is commonly indicative of greater disease burden.

Extended Pattern Mixture Model (*continued*)

- Separate ePMMs were conducted on the following EORTC QLQ-C30 data, measured from screening through to Cycle 8:
  - Fatigue (scored 0-100, with higher scores indicating greater fatigue),
  - Pain (scored 0-100, with higher scores indicating greater pain),
  - Diarrhea (transformed score 0-100, with higher scores indicating greater likelihood of occurrence).
- Once the models that best fit the data were identified, the subgroup identifier variables from both the pain and diarrhea models were built in to the fatigue model as predictor variables.
  - This allowed an assessment of whether greater/lesser pain/diarrhea experience predicted greater/lesser fatigue experience.

Results

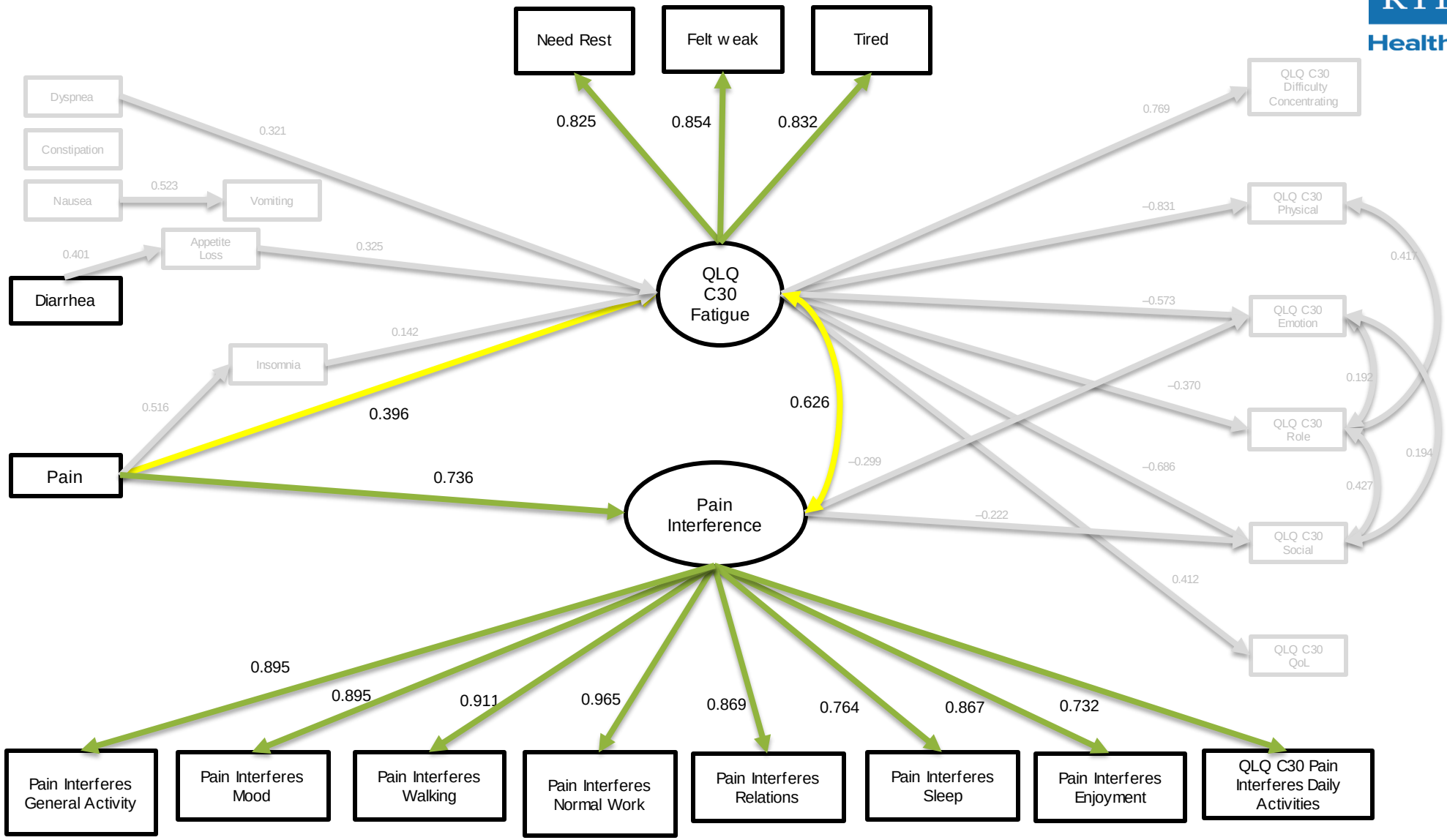
Structural Equation Model

- We evaluated several preliminary models until we obtained a conceptually cohesive and adequately fitting model.
- A statistically acceptable and parsimonious model that logically represented the mBC disease process was achieved based on:
  - Magnitude and statistical significance of the factor loadings and path coefficients, and
  - Suggestions from modification indices.

Results

Structural Equation Model

- Figure 1 presents the overall model. Fatigue, pain, and diarrhea relationships, the focus of this SEM investigation, are highlighted.
- Table 1 shows the total, direct, and indirect effects of pain and diarrhea on fatigue.
- The effects of these two symptoms on fatigue were as follows:
  - **Pain was a significant, direct predictor of fatigue** (β=0.40; P<0.001), and
  - **Diarrhea was not a significant, direct predictor of fatigue** (β=0.08; P=0.07).



Note: Only significant pathways (P < 0.05) are presented. The figure highlights only the pathways of interest within this model for this presentation. Green arrows represent a strong relationship (ß ≥ 0.7); yellow arrows represent a moderate relationship (ß > 0.3 and < 0.7)..

Table 1: Decomposition table: Total Effects, Direct Effects, and Total Indirect Effects of Pain and Diarrhea on Fatigue

Dependent Variable	Explanatory Variable	Total Effects	Direct Effects	Total Indirect Effects
Fatigue	Pain	0.444***	0.396***	0.048 ns
Fatigue	Diarrhea	0.211**	0.080 ns	0.130***

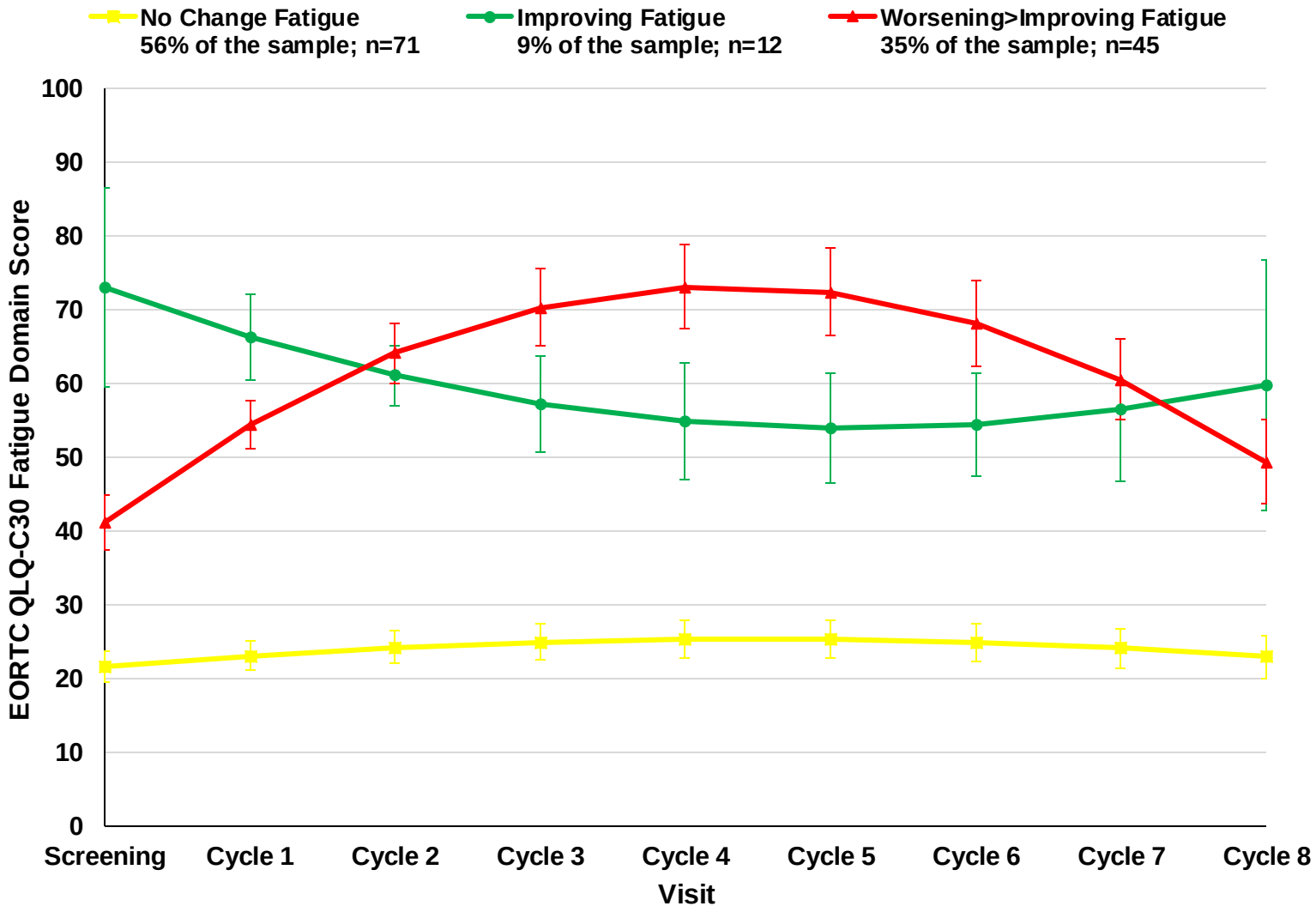
** P ≤ 0.01; *** P ≤ 0.001

Results

Extended Pattern Mixture Model

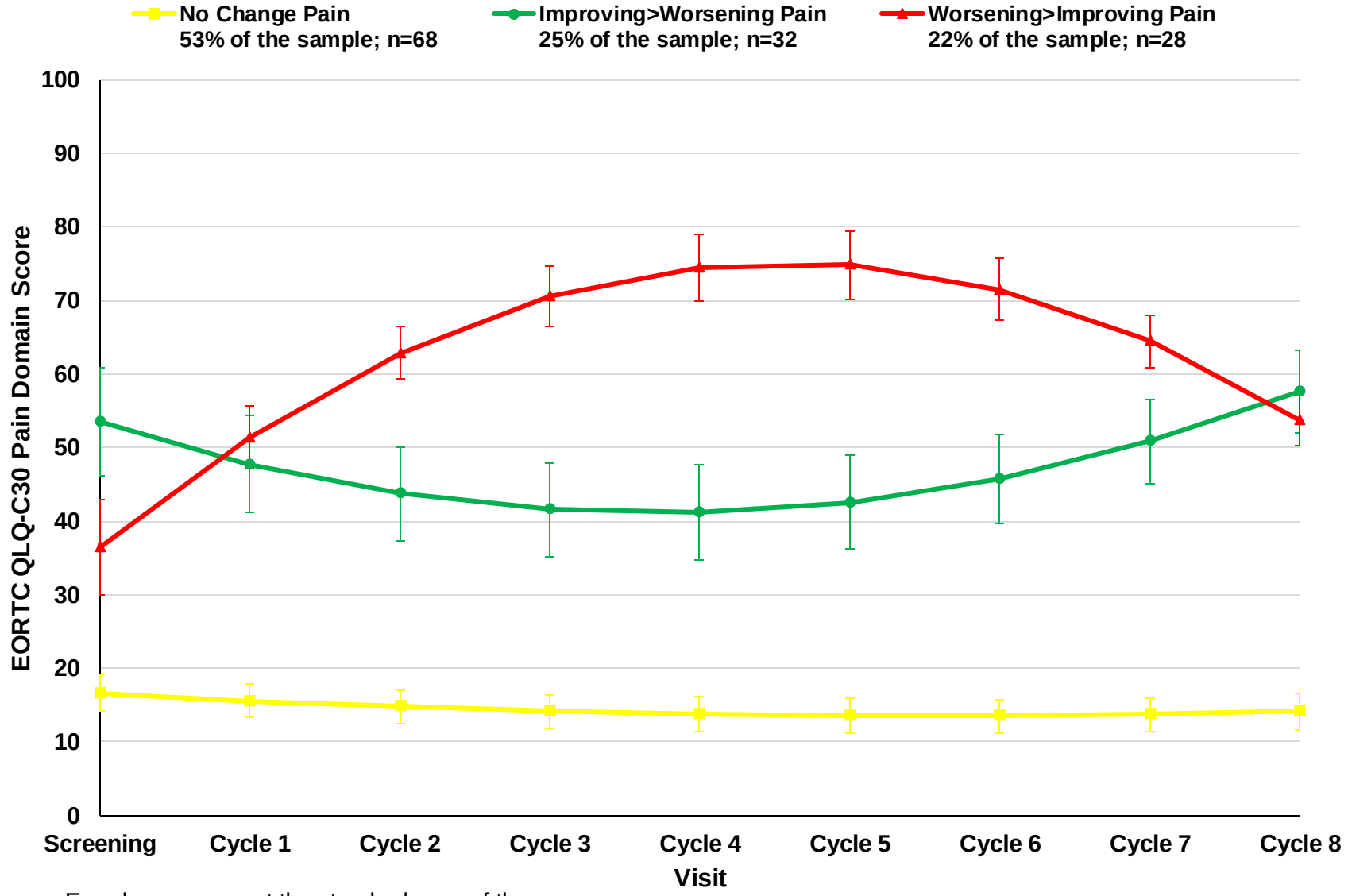
- For fatigue, pain, and diarrhea, the model that best fit the data was a quadratic model identifying three distinct subgroups of respondents.
- Figure 3 shows the results for each ePMM (3a–fatigue, 3b-pain, 3c-diarrhea).

Figure 3a



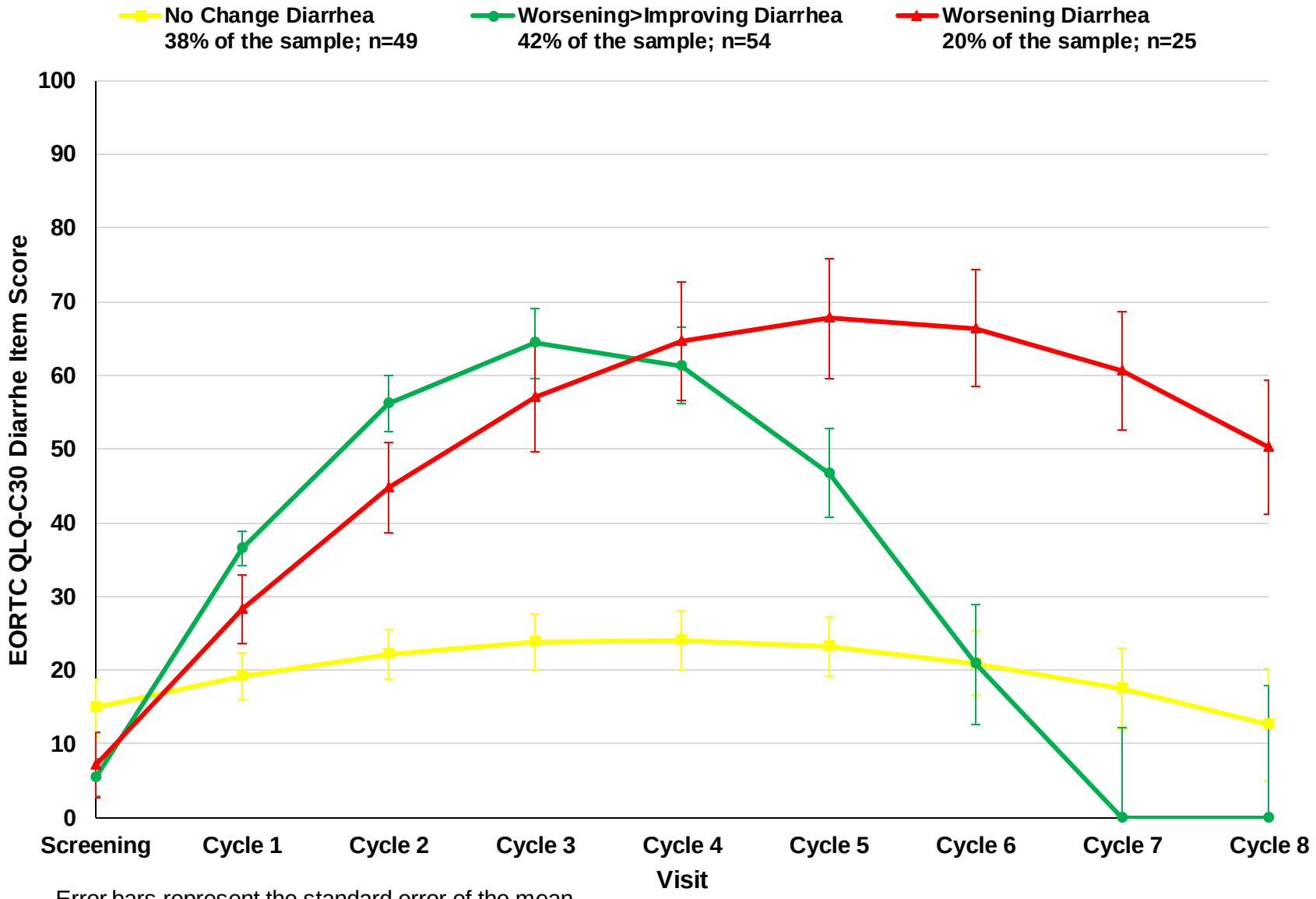
Error bars represent the standard error of the mean

Figure 3b



Error bars represent the standard error of the mean

Figure 3c



Error bars represent the standard error of the mean

Results

- After obtaining these results, we then built a predictive model wherein the subgroup identifier for the pain and the diarrhea models was built into the fatigue model.
- Table 2 presents the predictive model results.
  - Belonging to a similar pain subgroup predicted belonging to the corresponding fatigue subgroup. Thus, **changes in pain predicted changes in fatigue**.
  - Belonging to a diarrhea subgroup did not predict belonging to a corresponding fatigue subgroup. Thus, **changes in diarrhea did not predict changes in fatigue**.
- Table 3 presents the proportions of individuals that belong to each Fatigue subgroup and also belong to each Pain/Diarrhea subgroup
  - Correspondence of fatigue subgroups with pain subgroups, and the correspondence of fatigue subgroups with diarrhea subgroups is indicated by a high proportion of individuals in the table diagonal cells.
    - Pain and fatigue subgroup proportions are very concentrated on the diagonal.
    - Diarrhea and fatigue subgroup proportions are not concentrated on the diagonal.

Table 2: Predicted fatigue subgroup classification: Results from adding pain and diarrhea subgroup identifiers as categorical predictors of the fatigue subgroup identifier in the fatigue ePMM regression model

	ß estimate	Standard Error	P-value
Fatigue Reference Class: No Change			
Improving Fatigue on Pain	4.747	1.574	**0.003**
Improving Fatigue on Diarrhea	0.422	0.544	0.438
Worsening>Improving Fatigue on Pain	9.112	3.016	**0.003**
Worsening>Improving Fatigue on Diarrhea	-0.057	0.821	0.945

The subgroup variables are coded such that:

1 = No Change Fatigue/No Change Pain/No Change Diarrhea

2 = Improving Fatigue/Improving>Worsening Pain/Worsening>Improving Diarrhea

3 = Worsening>Improving Fatigue/Worsening>Improving Pain/Worsening Diarrhea

Table 3: Proportions of patients within corresponding subgroups

		Fatigue		
		No Change	Improving	Worsening>Improving
Pain	No Change	**85.9%**	8.3%	13.3%
	Improving>Worsening	12.7%	**83.3%**	20.0%
	Worsening>Improving	1.4%	8.3%	**66.7%**
Diarrhea	No Change	**43.7%**	25.0%	33.3%
	Worsening>Improving	29.6%	**58.3%**	57.8%
	Worsening	26.8%	16.7%	**8.9%**

Discussion and Conclusions – your original with my one added discussion point

- These results suggest that for patients undergoing 3rd line or greater mBC treatment, pain is a significant predictor of fatigue.
  - This relationship was found early in the trial (treatment Cycle 2).
- When accounting for missing data, differential changes in pain predicted different changes in fatigue across the course of the trial.
- Diarrhea (a key TEAE in MONARCH1) had no effect on fatigue, and since fatigue was the key mediator between diarrhea and QoL outcomes, this demonstrates that diarrhea has no significant effect on QoL outcomes for these patients with mBC.
- These results have clinical applications; they suggest that reducing pain will result in lower fatigue.
  - Previous research has shown that fatigue is the key component affecting HRQL among patients with cancer [2]; thus, reducing fatigue should lead to an improvement in HRQL and a lower disease burden.
- Investigator-assessed Grade 1-3 TEAEs of diarrhea, fatigue, and pain are consistent with the salience of these symptoms to patients, providing evidence for the value of including PROM assessments of symptoms under investigation.
- A major challenge to these analyses was the relatively small sample size.
  - Further research using larger sample sizes is warranted and planned for currently ongoing mBC trials.

References

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