# SUPPLEMENTARY ONLINE APPENDIX – QUALITY OF LIFE

## Methods

### *Quality-of-Life Measures*

Quality of life (QoL), a secondary trial endpoint, was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ)-C30 (version 3.0) and breast module QLQ-BR23 (version 1.0) at baseline, 6 weeks, 3, 6, 12, 18, and 24 months, or until disease progression/initiation of other antitumor treatment. The principal prespecified outcome was overall QoL expressed as change from baseline in Global Health Status (GHS)/QoL measured on a scale from 0 (worse) to 100 (best).

### *Statistical Analysis*

Two populations were considered for the QoL analysis. The cross-sectional population for descriptive analysis was defined at each QoL data collection time point and included any patient who was surviving in the study at day 1 of the cycle relevant to that data collection time point. For longitudinal analysis, the population was defined for each QoL collection period from baseline to each cycle for analysis and included any patient who survived in the study from baseline to day 1 of any cycle or treatment discontinuation.

Longitudinal analyses were carried out using linear-mixed model and pattern-mixture model techniques. Linear-mixed models assume that missing data are missing at random, which indicates that missing data are related to the observed values of the outcome and possibly other covariates, but not to unobserved values of the outcome. Pattern-mixture models stratify

incomplete data by the pattern of missing values and formulate distinct models within each stratum that best fit the data.[1] To test for differences between treatment arms, best-fitting models were tested for effects of treatment on QoL profile within strata, with tests then combined across strata.

Clinical interpretation of the GHS/QoL was evaluated using a proportion analysis comparing patients' change at each post-baseline assessment. Patients were categorized as improved, worsened or stable at each time points depending on a change score threshold of 10 points on the GHS/QoL; a change generally considered clinically meaningful.

## Results

Almost all (>95%) QoL data were available at baseline for both eribulin and capecitabine; completion rates over time decreased similarly in both arms (Table 1). GHS/QoL scores were low at baseline for both eribulin and capecitabine (mean [standard deviation], 56.3 [22.2] and 54.7 [21.7], respectively).

Table 1 also shows mean GHS/QoL scores, and changes in mean GHS/QoL scores from baseline, at each time point. Figure 1 represents the proportion of patients in each arm reporting an improved, worsened or stable overall QoL, as measured by changes in GHS/QoL scores. Analysis of the data at discrete time points shows similar improvements over time in mean GHS/QoL scores, and similar proportions of patients with clinically significant QoL improvement or deterioration, in both arms with time. Longitudinal analyses using the linear-mixed model and pattern-mixture model showed no significant difference between the treatment groups (Table 2).

## Discussion

When attrition rates are high, pattern-mixture modelling offers a robust mechanism for assessing differences between treatments. In our study, this analysis of our data demonstrated no evidence of a significant difference between the treatment groups in change in overall QoL. However, analysis of the various domains in the QoL questionnaires may reveal specific QoL benefits.

## References

1. Little RJ, Wang Y. Pattern-mixture models for multivariate incomplete data with covariates. Biometrics 52:98-111, 1996

**Table 1.** GHS/QoL scores at discrete time points

| | | Baseline | 6 weeks | 3 months | 6 months | 12 months | 18 months | 24 months |
|---|---|---|---|---|---|---|---|---|
| No. of completed QoL forms* (%) | E | 536/554 (96.8) | 450/494 (91.1) | 329/369 (89.2) | 167/191 (87.4) | 56/65 (86.2) | 22/30 (73.3) | 13/17 (76.5) |
| | C | 526/548 (96.0) | 419/484 (86.6) | 299/341 (87.7) | 170/194 (87.6) | 63/72 (87.5) | 24/29 (82.8) | 15/20 (75.0) |
| Mean GHS/QoL score (SD) | E | 56.3 (22.2) | 57.3 (20.9) | 59.9 (20.4) | 59.6 (20.2) | 61.8 (20.5) | 68.9 (23.7) | 72.4 (24.9) |
| | C | 54.7 (21.7) | 57.7 (22.4) | 60.5 (21.3) | 61.1 (21.4) | 60.2 (22.0) | 69.6 (17.7) | 71.1 (14.7) |
| Change in mean GHS/QoL from baseline (SD)† | E | – | 0.1 (19.2) | 1.1 (22.1) | -0.1 (21.4) | -2.1 (28.0) | 8.7 (29.7) | 13.5 (36.3) |
| | C | – | 1.7 (20.7) | 4.1 (21.3) | 2.8 (22.2) | 3.9 (19.0) | 9.8 (16.0) | 8.3 (15.7) |

E, eribulin; C, capecitabine; GSH/QoL, Global Health Status/quality of life; SD, standard deviation.

*Number of patients completing at least one question in the EORTC questionnaire among those who completed a baseline questionnaire; percentage is of those who were scheduled to complete questionnaire at visit time.

†Score at each time point minus baseline for that patient; the mean score of individual change and SD is presented.

**Table 2.** Estimated treatment effect on QoL over time (up to 24 months)

| | Linear-mixed model | | | Pattern-mixture model* | | |
|---|---|---|---|---|---|---|
| | **Coefficient** | **SE** | ***P* value** | **Coefficient** | **SE** | ***P* value** |
| GHS/QOL eribulin vs. capecitabine | –0.068 | 1.293 | 0.958 | 0.082 | 1.283 | 0.949 |

*Adjusted for completers, deaths and discontinuations; SE = standard error