Estimating Meaningful Change Thresholds for EORTC Scales in a Phase 3 Trial in Participants with Inoperable or Metastatic Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer

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Objective

- To estimate meaningful change thresholds (MCTs) for selected European Organisation for Research and Treatment of Cancer (EORTC) scales of the EORTC QLQ-C30 and the EORTC IL116 (breast and arm symptoms from the breast cancer module 45 items) from the TROPION-Breast01 trial of advanced breast cancer (NCT05104866)

Conclusions

- MCTs were derived for the selected EORTC scales and will support the analysis and interpretation of patient-reported outcome (PRO) endpoints in this trial
- This work can aid PRO interpretation in both clinical trials and routine care to better understand the significance of longitudinal change

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Disclosures

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Introduction

- Interpretation of clinical study data is limited without defined MCTs for assessing within-participant change and between-group difference of study endpoints
- Traditionally, an MCT of 10 points has been used as a threshold to define deterioration or improvement in EORTC scores[1,2]
- Such thresholds may often differ across groups of patients characterized by various diseases, underlying comorbidities, and levels of severity[1,2]
- Thus, an MCT of 10 points may not be appropriate to use for all subscales in all studies
- The FDA draft guidance on the "Core PRO in Cancer Clinical Trials" (June 2021) emphasized the importance of providing a pre-specified plan for the analysis of PRO data, including the threshold for and interpretation of a meaningful change in scores[3]
- Different threshold scores may be needed for within-participant change over time and between-group difference, as well as the direction of the change, i.e., deterioration or improvement

Methods

Study design and data source

- The data were obtained from TROPION-Breast01[4], a phase 3 trial of Datopotamab deruxtecan (Dato-DXd) vs investigator's choice of standard-of-care chemotherapy in inoperable or metastatic hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer
- Pre-specified analyses were performed to define MCTs for selected EORTC scales, including Global Health Status/Quality of Life (GHS/QoL), functioning (physical, role, emotional, cognitive, social), pain, fatigue, arm, and breast symptoms using pooled blinded data from baseline, Week 6, and Week 12 prior to database lock

Study analysis

- Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) were used as anchors (a measure that generally reflects the patient's point of view on the the health status assessed and is used to interpret a change in PRO)
- For assessing PGIC, patients were asked to rate the change in their health status since starting this study as much better, moderately better, a little better, about the same, a little worse, moderately worse, or much worse
- For assessing PGIS, patients were asked to select the response that best describes the severity of their overall cancer symptoms over the past 7 days as none, mild, moderate, or severe
- Anchor appropriateness was assessed via Spearman correlations, with values ≥0.371 considered adequate[5]
- Distribution-based approaches included the one-half standard deviation of baseline scores, the standard error of measurement (SEM) and the minimum detectable change (MDC)
- SEM=SD_baseline*√(1-r), wherein 'r' is the reliability (test-retest reliability coefficient or internal consistency reliability coefficient) of each PRO scale score at baseline, and MDC=1.96*√2*SEM=2.77*SEM
- Thresholds were estimated via distribution-based approaches: for each scale, the lower bound of the range was based on the maximum value of 0.5 SD and SEMs estimates, and the upper bound was based on the minimum value of MDCs estimates
- The within-participant MCT estimates were further evaluated against the possible amount of change observable on the 0–100 transformed scale

Results and interpretation

- The number of participants who provided evaluable scores at baseline, Week 6, and Week 12 are summarized in Table 1

Table 1. Study population

Instrument	Baseline	Week 6	Week 12
EORTC QLQ-C30	530	495	392
EORTC IL116*	513	486	384

*Includes breast and arm symptoms from the breast cancer module 45 items
EORTC IL116, European Organization for the Research and Treatment of Cancer Item Library 116; **EORTC QLQ-C30**, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, 30-item instrument

- Anchor correlations were <0.371 for most scales (Table 2), thus, anchor-based estimates were given limited consideration

Table 2. Anchor evaluation: Correlations between change from baseline in EORTC QLQ-C30 and EORTC IL116 scores with PGIS change and PGIC at Weeks 6 and 12

	Week 6		Week 12	
Change from baseline	**Change from baseline in PGIS**	**PGIC**	**Change from baseline in PGIS**	**PGIC**
EORTC QLQ-C30				
Global health status/QoL	−0.323	−0.320	−0.303	−0.323
Physical functioning	−0.337	−0.279	−0.279	−0.178
Role functioning	−0.290	−0.313	−0.286	−0.174
Emotional functioning	−0.281	−0.215	−0.128	−0.232
Cognitive functioning	−0.191	−0.116	−0.117	−0.188
Social functioning	−0.286	−0.274	−0.268	−0.169
Fatigue	0.391	0.304	0.323	0.279
Pain	0.410	0.328	0.281	0.249
EORTC IL116				
Arm symptoms	0.240	0.139	0.138	0.169
Breast symptoms	0.219	0.157	0.148	0.172

PGIC, Patient Global Impression of Change (patients were asked to rate the change in their health status since starting this study as much better, moderately better, a little better, about the same, a little worse, moderately worse, or much worse); **PGIS**, Patient Global Impression of Severity (patients were asked to select the response that best describes the severity of their overall cancer symptoms over the past 7 days as none, mild, moderate, or severe); **QoL**, quality of life

- Thresholds were estimated via distribution-based approaches, supported by adequate reliability for most scales (Table 3)

Table 3. Meaningful change distribution-based approach

		SEM		MDC	
Scale	**0.5 SD at Baseline**	**Test-retest reliability**	**Internal consistency reliability**	**Test-retest reliability**	**Internal consistency reliability**
EORTC QLQ-C30					
Global health status/QoL	10.1	10.6	6.6	29.3	18.4
Physical functioning	9.4	6.9	8.3	19.0	23.1
Role functioning	13.1	12.2	9.9	33.7	27.4
Emotional functioning	10.3	9.6	8.4	26.5	23.3
Cognitive functioning	8.9	8.7	11.7	24.0	32.3
Social functioning	12.6	13.1	10.8	36.2	30.0
Fatigue	11.3	9.3	8.8	25.8	24.5
Pain	13.8	15.6	9.9	43.1	27.3
EORTC IL116					
Arm symptoms	10.1	10.8	10.6	29.8	29.3
Breast symptoms	9.7	8.3	7.4	23.0	20.6

MDC, minimum detectable change; **SD**, standard deviation; **SEM**, standard error of measurement

- The within-participant threshold for deterioration/improvement ranged from 11.1 to 33.3 (Table 4)
- Time to deterioration (TTD) in global health status/QoL, physical functioning, and pain were used as secondary endpoints in this trial, where the lower bound of identified MCT range for the within-participant change (Table 4) was used to define the deterioration
- The between-group difference MCT range was 6.6–15.6 (Table 4)

Table 4. MCT for within-participant change and between-group difference*

Instrument/Scale	Minimum change value observed for the scale	MCT for the within-participant change	MCT for the between-group difference
EORTC QLQ-C30			
Global health status/QoL	8.3	[16.6, 25.0]	[6.6, 10.6]
Physical functioning	6.7	[13.3, 20.0]	[6.9, 9.4]
Role functioning	16.7	[16.6, 33.3]	[9.9, 13.1]
Emotional functioning	8.3	[16.6, 25.0]	[8.4, 10.3]
Cognitive functioning	16.7	[16.6, 33.3]	[8.7, 11.7]
Social functioning	16.7	[16.6, 33.3]	[10.8, 13.1]
Fatigue	11.1	[11.1, 33.3]	[8.8, 11.3]
Pain	16.7	[16.6, 33.3]	[9.9, 15.6]
EORTC IL116			
Arm symptoms	11.1	[11.1, 33.3]	[10.1, 10.6]
Breast symptoms	8.3	[16.6, 25.0]	[7.4, 9.7]

*The MCTs presented in this table apply to both deterioration and improvement
MCT, meaningful change threshold