Estimating meaningful change thresholds (MCTs) for European Organisation for Research and Treatment of Cancer (EORTC) scales in a phase 3 trial for patients with locally recurrent inoperable or metastatic triple-negative breast cancer

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Objective

- This study aimed to estimate the MCTs for selected EORTC scales used in participants of the TROPION-Breast02 trial (NCT05374512).

Conclusions

- MCTs were derived for the selected EORTC scales (see table on meaningful thresholds). These thresholds support the analysis and interpretation of change in the time-to-event PRO endpoints in TROPION-Breast02.
- This work can aid PRO interpretation in both clinical trials and routine care to better understand the clinical relevance of longitudinal change in PRO outcomes.

Plain language summary

Why did we perform this research?

This research looked at how much symptoms or daily well-being need to worsen before patients feel the change truly matters, using information from the TROPION-Breast02 study in participants with advanced triple-negative breast cancer.

How did we perform this research?

This study used questionnaire data from patients in the TROPION-Breast02 study. Researchers tracked changes in patients' symptoms and daily well-being over time to identify when any worsening became clearly noticeable.

What were the findings of this research?

This study identified specific amounts of change in questionnaire scores that reflect a meaningful worsening from the patient's point of view. These amounts were different depending on the symptom or aspect of daily life being measured.

What are the implications of this research?

The results allow researchers to interpret whether improvements in symptoms, functioning, and quality of life are clinically relevant to this patient population.

Where can I find more information?

More information about the TROPION-Breast02 study is available on clinicaltrials.gov (study number NCT05374512).

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Introduction

- TROPION-Breast02 is a phase 3 study evaluating datopotamab deruxtecan (Dato-DXd) versus standard chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer not eligible for programmed cell death protein 1/programmed cell death-ligand 1 inhibitors (NCT05374512).
- The study includes secondary patient-reported outcome (PRO) endpoints assessing pain, physical functioning, and global health status/quality of life (GHS/QoL) using EORTC IL146 (subset of EORTC QLQ-C30), and breast and arm symptoms using IL116 (subset of EORTC QLQ-BR45).
- MCTs represent the smallest change possible that could be of clinical significance to patients.
  - MCTs are critical for interpreting clinical benefit because they define the magnitude of change at the individual patient level that reflects a meaningful improvement or deterioration (i.e., clinically meaningful benefit as experienced by patients).[1]

Methods

Analysis population

- PRO analyses were performed on all randomised trial patients, including those who were randomised but did not subsequently receive treatment.
- Data was extracted on January 1, 2025 before database lock and analyses were conducted using blinded pool arms.

Analysis of meaningful change

- Pooled blinded data were analyzed to determine MCTs for within-participant deterioration from baseline to Week 12 on selected EORTC IL146 and IL116 scales, using anchor-based methods and empirical cumulative distribution function curves.
- Distribution-based estimates (half a standard deviation [SD] at baseline and one standard error of measurement [SEM]) ensured that anchor-based estimates were above the natural variability of the change scores.
- In determining meaningful change, 1–3 anchors per scale were considered, with Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) as primary anchors.
- Anchor appropriateness was assessed via polyserial correlations, with values ≥0.371 considered adequate.[2]
- In case none of them showed enough correlation, an anchor showing a correlation of ≥0.30 was considered.[3]
- The within-participant MCT estimates were further evaluated against the possible amount of change observable on the 0–100 transformed scale.

Anchor	Recall period	Possible values
PGIS–Overall cancer symptoms	Past week	None (1), Mild (2), Moderate (3), and Severe (4)
PGIC–Overall change in health status	Since the start of study treatment	Much better (1), Moderately better (2), A little better (3), About the same (4), A little worse (5), Moderately worse (6), and Much worse (7)
EORTC IL146 Item 28–Overall health	Past week	Very poor (1) to Excellent (7)
EQ-5D-5L (Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression)	Past week (i.e., 7 days)	No problems, Slight problems, Moderate problems, Severe problems, and Extreme problems or Unable to perform activity
PRO-Common Terminology Criteria for Adverse Events (CTCAE)		
Pain severity item (Item 12b) – pain at its worst	Past week	Branched logic: if participants experienced the symptom (Item 12a), they scored: None (1), Mild (2), Moderate (3), Severe (4), and Very severe (5); Otherwise: imputed to None (1)
Fatigue severity item (Item 13a) – fatigue, tiredness, or lack of energy at its worst	Past week	None (1), Mild (2), Moderate (3), Severe (4), and Very severe (5)

Results

Number of participants and PRO completion

- Overall, the number of participants with evaluable scores for both EORTC IL146 and EORTC IL116 instruments was sufficient for the performed analyses.

Scale	Recall period	Possible values
EORTC IL146	GHS/QoL and Fatigue: n=422 Other scales: n=423	GHS/QoL: n=329 Other scales: n=338
EORTC IL116	All scales: n=428	Arm symptoms: n=340 Breast symptoms: n=339

Anchor adequacy

- All scales showed appropriate correlations with ≥1 anchor, except Cognitive functioning (≥0.30 but <0.371).
- For each scale, ≥1 anchor was adequate for estimating within-participant MCTs.

Table notes:

- SEM is calculated based on internal consistency reliability (i.e., Cronbach alpha for scales with ≥3 items and Spearman–Brown for scales with 2 items).
- The change from baseline scores is based on the difference between all non-missing scores minus the scores at baseline.
- Higher scores on EORTC IL146 symptom scales indicate greater symptom burden, while higher scores on GHS/QoL and functioning scales indicate better health status/functioning.
  - A negative change score on EORTC IL146 symptom scales indicates improvement, while a negative change score on GHS/QoL and functioning scales indicates greater symptom burden.
- Higher scores on EORTC IL116 symptom scales indicate greater symptom burden.
  - A negative change score on symptom scales indicates improvement.
- The polyserial correlation coefficients (r) are shown. Only selected anchors considered adequate for each scale are presented.

Distribution-based approach and estimated within-participant clinically meaningful thresholds of deterioration for EORTC IL146 and EORTC IL116

Scale	Anchor selected for threshold estimation (r)	Minimum change values observed for the scale	Distribution-based estimates		Derived MCT for within participant change
			0.5 SD at baseline	SEM	
EORTC IL146					
GHS/QoL	PGIS (−0.43) PGIC (−0.47) EQ-5D-5L Usual activities (−0.51)	8.33	11.30	5.60	−16.66 (−16.66 to −33.33)
Physical functioning	PGIS (−0.47) EQ-5D-5L Mobility (−0.53) EQ-5D-5L Usual activities (−0.59)	6.67	11.00	8.48	−13.33
Role functioning	PGIS (−0.39) EQ-5D-5L Usual activities (−0.66)	16.66	14.08	9.09	−16.66 (−16.66 to −33.33)
Emotional functioning	PGIS (−0.34) EQ-5D-5L Anxiety/depression (−0.54)	8.33	12.16	8.65	−16.66
Cognitive functioning	EORTC IL146 item 28 (0.32)	16.66	9.59	12.07	−16.66
Social functioning	PGIS (−0.42) EQ-5D-5L Usual activities (−0.52)	16.66	12.53	11.18	−16.66
Fatigue	PGIS (0.50) PRO-CTCAE fatigue (0.73)	11.11	12.74	9.26	22.22
Pain	PGIS (0.56) EQ-5D-5L Pain/discomfort (0.68) PRO-CTCAE pain (0.70)	16.66	15.44	11.08	16.66
EORTC IL116					
Arm symptoms	PGIS (0.35) EQ-5D-5L Pain/discomfort (0.46)	11.11	11.98	11.53	22.22
Breast symptoms	PGIS (0.50) EQ-5D-5L Pain/discomfort (0.55)	8.33	13.08	9.87	16.66

Abbreviations

EORTC IL116/IL146, European Organisation for Research and Treatment of Cancer Item Library 116/Item Library 146; **EORTC QLQ-C30/-BR45**, European Organisation for Research and Treatment of Cancer Quality of Life–Core 30-item/Breast Cancer 45-item; **EQ-5D-5L**, EuroQoL 5-dimension, 5-Level; **GHS/QoL**, global health status/quality of life; **MCT**, meaningful change threshold; **PGIC**, Patient Global Impression of Change; **PGIS**, Patient Global Impression of Severity; **PRO**, patient-reported outcome; **PRO-CTCAE**, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; **SD**, standard deviation; **SEM**, standard error of measurement.

References

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