Linking the European Organisation for Research and Treatment of Cancer Item Library to the Common Terminology Criteria for Adverse Events

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abstract

PURPOSE The European Organisation for Research and Treatment of Cancer (EORTC) Item Library is an interactive online platform currently composed of 950 unique items (questions) derived from 67 patient-reported outcome (PRO) questionnaires. PROs complement clinician adverse event (AE) reporting classifications like the Common Terminology Criteria for Adverse Events (CTCAE). This work aims to create a standardized framework using the CTCAE to systematically classify symptomatic AEs from the EORTC Item Library through linking individual items to corresponding AEs.

METHODS The EORTC Item Library items were searched for within the CTCAE (v5.0) and linked to an AE if they were described within the AE’s title, description, or grading. Symptoms described in EORTC items but not located in the CTCAE were coded as missing symptoms. Other nonsymptom EORTC items, not described within the CTCAE were assigned a non-CTCAE descriptive classification. Further descriptive codes (eg, multiple issues) were allocated to enable descriptive analysis. Two raters independently coded 26.2% (n = 249) of the items. The remaining 701 items were coded by one rater and verified by the second, followed by discussion with two additional raters to reach consensus.

RESULTS Overall, 625 (65.8%) EORTC items were linked to 208 different AEs. Three hundred sixty-nine items provide information about non-CTCAE cancer–related issues and were categorized into seven descriptive classifications, including body image; emotional impact of a symptom, diagnosis, or treatment; global health and quality of life; and impact on life and daily activities. Inter-rater agreement for independent coding was 79.1%. Bowel urgency and tenesmus were identified as missing symptoms in CTCAE v5.0.

CONCLUSION The EORTC Item Library provides considerable coverage of CTCAE toxicities, along with other complementary issues important to patients with cancer. Using the CTCAE clinical framework to classify symptomatic PRO items may facilitate PRO selection and use in clinical trials and routine care.

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BACKGROUND Regulatory authorities are increasingly aware of the need to develop and advance novel cancer therapies with a patient-centered approach.1 The complexity of novel cancer treatment, including prolonged treatment duration and multimodal therapies, while improving overall survival, has led to the need to consider the burden of long-term adverse events (AEs) and impact on quality of life (QOL).2

The gold standard for AE reporting in cancer clinical trials is the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).3 This descriptive terminology catalog of 838 different AEs is a clinician-developed instrument, maintained and regularly revised by the US National Cancer Institute. It measures symptomatic AEs (eg, pain), observable AEs (eg, rash), and laboratory and radiographic findings. Clinicians interpret, diagnose, and grade AEs using a scale from 1-5 over the duration of the trial. However, increasingly, regulators, including the US Food and Drug Administration and the European Medicines Agency, have recognized the importance of inclusion of patient-reported outcomes (PROs), alongside other clinical outcome assessments, to support decisions around safety, tolerability, and efficacy within trials.2,4

By providing unique insights into domains that are difficult to assess through biomedical outcomes and clinician ratings alone (eg., fatigue and pain), PROs provide a more complete, patient-centered picture of the impact of disease and treatment.5

PROs are included in cancer clinical trials to complement clinician reporting and to capture the patient perspective, including the measurement of symptomatic AEs, function, and QOL. The European Organisation
for Research and Treatment of Cancer (EORTC) Quality of Life questionnaires (QLQ) are some of the most commonly used PROs in cancer clinical trials.6 Since the initial development of the core questionnaire (QLQ-C30) in 1993, the EORTC Quality of Life Group (QLG) has published 66 different PROs measures tailored to different disease types, treatments, and populations, with more than 110 different language versions available for some questionnaires.7 The development of each questionnaire follows a rigorous, well-defined process designed to capture patient experience across a disease and treatment spectrum, using the literature, along with patient and health care provider interviews to generate issues before psychometric testing.8 One of the most recent additions to the QLQ measurement system is the release of the EORTC Item Library.9 This online, interactive platform is currently composed of 950 unique items from the EORTC QLG’s portfolio of questionnaires.10,11 It enables more flexible usage of the static questionnaires by allowing users to create customized item lists, thereby increasing flexibility to cover different disease and treatment contexts.12 The PRO-CTCAE and FACIT Searchable Library provide similar approaches.13,14

Given that both the EORTC Item Library and CTCAE v5.0 are extensive measurement systems (with nearly 2,000 different items or AEs together), it is important to create a comprehensive framework linking the Item Library with the CTCAE. This research aims to map the EORTC Item Library, one of the most widely used PRO systems in cancer clinical trials, onto the clinician-reported CTCAE to facilitate the identification of items and provide a common clinical framework. Such a framework may support the integration, analysis, and application of PROs within future clinical trials by harmonizing the selection of additional items between trials when specific AEs or issues associated with novel treatments or techniques are not present within the validated questionnaires.12 This framework will be integrated into the Item Library searchable database to provide researchers and clinicians with information on which PRO items are most relevant for specific AEs as classified by the CTCAE system.12,15,16

METHODS

A descriptive mapping exercise was undertaken with the primary aim of comparing and contrasting the EORTC Item Library content (accessed July 2020) with the current CTCAE framework (v5.0).3,9 A typical EORTC symptom item may capture the presence of a symptom (eg, “Did you have pain?”) and the impact of a symptom (eg, “Did pain interfere with your daily activities?”) and sometimes capture several aspects of a symptom in one item (“Have you had skin problems [eg, itchy, dry?]”). The EORTC Item Library also contains items covering the impact of cancer and treatment on QOL and function (eg, physical, emotional, and social aspects) and, for example, satisfaction with care. Generally, EORTC item responses are graded by presence/severity (not at all/a little/quite a bit/very much). The CTCAE framework is organized by System Organ Class (SOC; eg, GI disorders), the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) terminology hierarchy, and further subcategorized by AE (eg, diarrhea), a MedDRA lowest level term, and accompanied by a definition. Ascribed to each AE is a severity grade description ranging from 1 (mild symptoms) to 5 (death; Tables 1 and 2). All 950 items from the EORTC Item Library were exported into a database (QLQ-C30/modules/standalone questionnaires/computerized adaptive testing item banks).30,11 Some items are used in multiple questionnaires, and some domains are measured by several different items (eg, QLQ-C30 and corresponding computerized adaptive testing item banks).

We used an item-level content analysis approach adapted from previous work.17,20 Primary fields included item wording and a numeric identifier assigned to each unique EORTC
item. In the initial phases of coding (phase I and II), the EORTC source questionnaires (eg, QLQ-C30) from which each item originated were deliberately not included to blind the coders. This blinded approach had the secondary aim of assessing the face validity and potential versatility of items for use outside of the setting that it was developed for. The coding took place in several phases (Fig 1 and Table 1). Items were deductively searched for within the CTCAE (v5.0) and coded with a CTCAE AE code if they were described within the CTCAE term, definition, or grade description of an AE. Not all items from the CTCAE could be considered as appropriate for symptomatic item coding.21 Many items (approximately n = 85) are analytic AEs (eg, laboratory findings), and many others (approximately n = 547) are diagnostic AEs (eg, mitral valve disease), which limited the total number of AEs from the CTCAE relevant to this exercise. However, the use of a deductive searching technique enabled laboratory findings and diagnostic AE codes to be used if they were deemed sufficiently descriptive (Table 2, examples 4/5). Once an appropriate AE was identified, the raters assigned an SOC and AE code to each item. During phase I, both raters independently assigned codes to 249 items, derived from a set of randomly selected questionnaires (C30/BM22/BN20/BR23/CR29/CX24/EN24/G1.NET21/HCC18/H&N35/LC13/LMC21/MY20/OG25/OV28/PR25/PR23/STO22), aiming for a coverage of approximately 25% of the Item Library content. Following phase I, the coding framework (Table 1) underwent minor modifications to clarify the decision rules and reduce future discrepancies. In phase II, the remaining 701 items were coded by one rater (C.P.) and reviewed by the second (A.G.) to reach agreement, highlighting ambiguous items for further review. In phase III, all 950 items were unblinded (revealing the source questionnaire(s) and scale structure) and reaffirmed by both raters (A.G./C.P.) and a third rater (G.V.) to discuss areas of coding ambiguity. In phase IV, final coding decisions were taken including a fourth rater (M.G.) to reach final consensus and finalize the decision rules. The coding framework is shown in Table 1 with examples in Table 2.

### Abbreviations
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; SOC, System Organ Class.

### Table 1. Decision Rules (adapted from the study by Cieza et al17)

| No. | Rule                                                                 | Example                                                                 |
|-----|----------------------------------------------------------------------|------------------------------------------------------------------------|
| 1   | Each item of the PRO should be linked to the single most precise CTCAE category | eg, “Were you short of breath?” coded with a single symptomatic CTCAE AE code dyspnea and SOC respiratory, thoracic, and mediastinal disorders. More than one option exists, the most accurate single CTCAE AE code is selected |
| 2   | If a single item encompasses different constructs, the information in each construct should be linked to all relevant AEs and items may qualify for several AEs from the same or different SOCs | eg, “Have you had skin problems (eg, itchy, dry)" coded with two CTCAE AE codes dry skin and pruritus from SOC skin and subcutaneous tissue disorders |
| 3   | All constructs of the item to be linked have to be highlighted (ie, multiple distinct issues) | eg, “Have you had other problems with your nose, like smell, runny or blocked nose, sneezing, sore or dry nose?" was coded as being linked to multiple issues and CTCAE AE sneezing and allergic rhinitis and SOC respiratory, thoracic, and mediastinal disorders |
| 4   | If the content of an item is not explicitly named an AE but could be described using an CTCAE diagnostic AE, this was linked | eg, “Have you had yellow (jaundiced)?” coded with CTCAE AE blood bilirubin increased and SOC investigations, accepting the limitation that although a PRO assessment would not provide sufficient information to perform a diagnosis, it could be informative |
| 5   | Items not found in the CTCAE are classified as either missing symptoms or not covered by CTCAE (non-CTCAE) | Symptomatic toxicity items captured within the EORTC Item Library and not located within the CTCAE v5.0 coded as missing symptoms, with the specific symptom described. Items not captured in the CTCAE and not linked to specific symptoms are assigned a non-CTCAE classification, eg, impact on life and daily activities |
| 6   | Item content not adequately described by a single CTCAE code should have a non-CTCAE code added (dual coding) | eg, “Did you take any medicine for pain?” was coded as a pain AE and a non-CTCAE code medication/medical device use |
| 7   | After unblinding to source questionnaire, CTCAE secondary AE codes should be linked | eg, “Have you had pain in your genital area?” is from the vulval cancer module (VU34). When blind to the source questionnaire, genitalia is not ascribed to sex. After unblinding, the primary AE is coded as vaginal pain and the secondary AE codes are coded as penile pain, scrotal pain, and testicular pain, all from SOC reproductive system and breast disorders |
they were sufficiently described within the CTCAE v5.0 (Table 2; examples 1 and 2). Items were linked to all relevant AEs, therefore some qualified for several AEs from the same or different SOCs (examples 3, 5, and 6). For some items, multiple potential AE diagnoses were included (example 5). If an item was clearly linked to several different underlying issues (eg, used in different source questionnaires to evaluate different issues, or the item itself included multiple distinct issues) it was coded as linked to multiple issues (example 3). Items linked to a CTCAE diagnosis only code were coded as such, accepting the limitation that although a PRO assessment would not provide sufficient information to carry out a diagnosis, it could be informative (eg, jaundice; example 4). Items that were linked to both a diagnostic AE and a symptomatic toxicity were coded as diagnostic + symptomatic toxicity items (example 9). Symptomatic toxicity items captured within the EORTC Item Library but not located within the CTCAE v5.0 were coded as missing symptoms, with the specific symptom described. After unblinding the source questionnaires, the scale structure could be reviewed, which provided additional insight into the underlying issues that the items were developed to capture, to improve coding quality. If an alternative clinical application for an item was recognized (pending testing), a secondary AE code was ascribed (example 6).22 Items not captured in the CTCAE and that could not be linked to a specific symptomatic AE were inductively assigned a non-CTCAE classification (eg, body image, example 7; medication/medical device use, example 8), defined using a bottom-up approach. During phase I, one rater (A.G.) devised a provisional list of non-CTCAE classification codes, which was later agreed upon with all raters (Table 3). These codes were also used in addition to an AE code if the content of an item was not sufficiently captured within the CTCAE grading (non-CTCAE + AE code; example 8).

In total, the coding database underwent 17 different iterations (Appendix Table A1, online only). Descriptive analyses were performed on the full group of items (n = 950) to evaluate the full number and range of CTCAE SOCs and AEs captured by EORTC items, the number of non-CTCAE classification codes, missing symptoms, multiple issue, diagnosis only, and diagnosis plus symptomatic AE codes. Results were also stratified by CTCAE SOC to highlight the items and linked AEs within each SOC. The resulting framework will be made available as part of the Item Library online search strategy.

RESULTS

For phase I, independent coding of the initial 249 items led to a 79.1% agreement rate between raters; 145 items had at least one overlapping AE, and 52 items were considered not suitable for CTCAE coding by both raters. For the 52 items where there was disagreement, this was mainly due to one rater deeming the item to be ineligible for CTCAE coding and the other assigning a CTCAE AE code (59.2%; Table 2; example 10—non-CTCAE item codes were agreed after phase I leading to this discrepancy), items describing a complex movement pattern involving different anatomic areas (12.2%, example 9), items where the item content led to ambiguity in coding (8.2%, examples 6 and 9), and simple disagreements related to CTCAE AE codes assigned (20.4%). These issues were resolved through minor modifications to the coding framework before phase II, unblinding of items to reveal the source questionnaire(s), and consensus discussion. Ascribing coding for items that were not simply symptomatic AEs or non-CTCAE issues encouraged significant debate, and additional raters (G.V./M.G.) were consulted to reach consensus.

For phase IV, 625 items (65.8%) were linked to 208 different AEs from 20 different SOCs (Table 4; Appendix Table A2, online only). The majority of linked PRO items were associated with one (65.6%) or two (23.5%) different CTCAE AE codes, with a smaller proportion associated with three or more (10.9%; range 3-7 AEs; Table 5). Fatigue was the most commonly linked AE, representing 4.9% of all linked AEs followed by general disorders and administration site conditions, other specify (used to describe AEs affecting activities of daily living; 4.1%), pain (4.1%), and dyspnea (3.8%; Appendix Table A3, online only). SOC GI disorders had the largest number of different AEs coded (n = 37; 17.8%) followed by nervous system disorders (n = 23; 11.1%) and reproductive system and breast disorders (n = 21; 10.1%; Table 4).

For the 625 items linked to a CTCAE code, 19 items (3.0%) were coded as being linked to multiple issues (Table 2, examples 3, 6, and 9), 42 (6.7%) were linked to both a CTCAE symptomatic AE and a diagnosis code, and an additional 42 (6.7%) were linked to a CTCAE diagnosis alone (Table 2, example 4; Table 5). Twelve items (1.9%) were eligible for a secondary AE code, denoting a PRO item developed for a particular (sub)population, whose content meant that it could be relevant in a different patient (sub)population if validated (Table 2, example 6). Only two symptoms, linked to six different EORTC items, were coded as missing symptoms not captured within the CTCAE: tenesmus and bowel urgency (Table 3).

Although the majority of items (73.9%) have only one source questionnaire (eg, QLQ-C30), a smaller proportion of PRO items appear in multiple different questionnaires: two (12.4%), three (4.8%), and four or more (8.9%; Table 2, example 9; Table 4). The item included in the greatest number of different questionnaires is “Were you worried about your health in the future?” included in 24 modules.

For the items not eligible for CTCAE classification, seven non-CTCAE codes were developed: body image; emotional impact of a symptom, diagnosis, or treatment; global health and QOL; impact on life and daily activities; information/
| No. | Item                                                                 | Non-CTCAE Classification | Primary CTCAE Codes | Secondary CTCAE Codes | Multiple Issues Only CTCAE Code | Diagnosis + Symptomatic Toxicity Code | Rationale                                                                                       |
|-----|----------------------------------------------------------------------|----------------------------|---------------------|-----------------------|---------------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------|
| 1   | Were you short of breath?                                           | NA                         | Respiratory, thoracic, and mediastinal disorders | Dyspnea               | NA                              | No                                    | Simple PRO item to AE match                                                        |
| 2   | Have you had tingling in your fingers or toes?                      | NA                         | Nervous system disorders | Paresthesia           | NA                              | No                                    | Additional diagnostic code peripheral sensory neuropathy omitted since the symptomatic toxicity code paresthesia adequately describes the issue |
| 3   | Have you had skin problems (eg, itchy, dry)?                        | NA                         | Skin and subcutaneous tissue disorders | Dry skin              | Pruritus                        | Yes                                   | Wording of item captures two distinct issues                                       |
| 4   | Have your skin or eyes been yellow (jaundiced)?                     | NA                         | Investigations        | Blood bilirubin increased | NA                      | Yes                                   | The only relevant code for this item is diagnostic                                |
| 5   | Have you had blood in your stools (motions)?                        | NA                         | GI disorders          | Colitis, Proctitis, Anal hemorrhage, Rectal hemorrhage | NA                         | Yes                                   | Multiple relevant diagnostic codes to describe per rectal bleeding symptom         |
| 6   | Have you had pain in your genital area?                             | NA                         | Reproductive system and breast disorders | Vaginal pain           | Reproductive system and breast disorders, Penile Pain, Scrotal pain, Testicular pain | No                                    | Primary code assigned is vaginal pain as this item was developed and tested to measure genital pain in vulvar cancer, but the item (pending testing) could also be applied to other types of genital pain and hence the secondary codes |
| 7   | Have you felt less feminine as a result of your disease or treatment? | Body image                 | NA                   | NA                    | NA                              | No                                    | This item is not eligible for a CTCAE code as it covers a broader QOL issue (body image) not captured within the scope of the CTCAE |
| 8   | Did you frequently have to change your urostomy bag?                | Medication/medical device use | Renal and urinary disorders | Urinary frequency | NA                              | No                                    | Given that the urinary frequency code in the CTCAE does not capture the use of a urinary stoma, the additional non-CTCAE classification is also used |
| No. | Item | Non-CTCAE Classification | Primary CTCAE Codes | Secondary CTCAE Codes | Diagnosis Only CTCAE Code | Diagnosis + Symptomatic Toxicity Code | Rationale |
|-----|------|--------------------------|---------------------|-----------------------|---------------------------|--------------------------------------|-----------|
| 9   | Have you had trouble with eating? | NA | GI disorders | Mucositis oral | Oral pain | Dysphagia | Sore throat | Gastrointestinal pain | NA | NA | NA | NA | Yes | No | Yes | Unblinding to source questionnaires (H&N43, H&N35, BIL21, LMC21, OES18, GI.NET21, and OG25) increased the number of AE codes allocated—reflecting the AE arising from different underlying issues, both anatomical (eg, because of oral, throat, or bowel problems) and toxicity/disease-related (eg, inflammatory, anorexia, or because of a stricture); mucositis oral is a diagnosis, whereas the other codes are symptomatic toxicities and hence the diagnostic code.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; NA, not available; PRO, patient-reported outcome; QLQ, Quality of Life questionnaires; QOL, quality of life; SOC, System Organ Class.
satisfaction with care; medication/medical device use; and screening items (eg, “Do you have a stoma bag [colostomy/ileostomy]?”). Three hundred twenty items were coded with a non-CTCAE code only, with an additional 49 coded with both CTCAE and non-CTCAE codes (Table 2, example 8). The majority of descriptive classifications were assigned for items related to the emotional impact of symptom, diagnosis, or treatment (n = 124; 33.6%), followed by information/satisfaction with care (n = 117; 31.7%) and impact on life and daily activities (n = 84; 22.8%; Table 3).

**DISCUSSION**

To our knowledge, this is the first comprehensive analysis and mapping of EORTC-QLQ items to the CTCAE. This work was performed to provide a framework to systematically classify symptomatic AEs from the EORTC Item Library using the CTCAE and will be made available as part of a planned update of the Item Library online search strategy. Both within clinical trials and routine care, the selection of appropriate additional EORTC item(s) to supplement an existing questionnaire is crucial for the assessment of the impact of cancer and its treatment from the patient perspective. This is particularly relevant when the selected questionnaires may not adequately cover all relevant toxicities from novel treatments or their impact on a patient’s QOL and function. This work aimed to develop a framework to harmonize the selection of additional items for use within clinical trials and practice. The analysis...
shows considerable overlap between the two systems, with the EORTC Item Library providing coverage of 208 different AEs from the CTCAE (v.5.0), noting that not all CTCAE AEs are relevant for patient-reporting. Of the 950 EORTC Item Library items, 625 items were mapped to a CTCAE AE code. In addition, 369 EORTC-QLQ items provide information on issues not specifically related to AEs alone, in particular regarding the impact of disease, symptoms, and treatment on patients’ function (n = 84) and emotional well-being (n = 124). The analysis also revealed two missing symptoms from the CTCAE: bowel urgency and tenesmus. Bowel urgency, specifically, has been highlighted as missing in previous work. MedDRA terms for these missing symptoms (defecation urgency and rectal tenesmus) and other issues (eg, body image) can be found.

This work addresses one of the past criticisms of the EORTC-QLQ measurement system, which has been the inflexibility of the static measures to accurately measure symptomatic toxicities associated with novel agents, used in combination and alone, in a clinical trial setting. Providing a framework to cover novel AEs and patient issues not covered by the existing questionnaires is essential in a fast-changing clinical world and to allow comparison between trials. Although the flexible use of the EORTC-QLQ items has long been practiced in trial settings where a disease-specific module was not available, the lack of a platform with a well-developed classification system describing the scope of the items has limited wider application. Other commonly used PRO systems in cancer clinical trials have addressed the issue of flexible symptomatic toxicity measurement. The National Cancer Institute (NCI) PRO-CTCAE was developed from the CTCAE through a process of mapping symptomatic toxicities onto PRO items for self-report. The PRO-CTCAE covers 78 symptomatic toxicities in 124 items. These items may be selected to create a trial-specific questionnaire. In comparison, the approach described by the FACIT Organization is similar to the EORTC Item Library. The FACIT Searchable Library contains more than 700 items taken from the Functional Assessment of Cancer Therapy (FACT) static questionnaires and may be searched to find coverage of symptomatic AEs. The FACIT website reports that 55 of the 78 systematic AEs covered by the NCI PRO-CTCAE are included. The results of our analysis suggest that the EORTC-QLQ system has excellent symptomatic AE coverage. Further work is needed to address the

| Non-CTCAE Classification                  | EORTC Items | CTCAE Code(s), No. (%) |
|-------------------------------------------|-------------|------------------------|
| Descriptive/general                        | Total, No. (%) | CTCAE Code(s), No. (%) |
| Body image                                | 22 (6.0)   | —                      |
| Screening item                            | 4 (1.1)    | —                      |
| Emotional impact of symptom, diagnosis, or treatment | 124 (33.6) | 6 (12.2)  |
| Global health and QOL                      | 2 (0.5)    | —                      |
| Impact on life and daily activities        | 84 (22.8)  | 39 (79.6)  |
| Information/satisfaction with care         | 117 (31.7) | —                      |
| Medication/medical device use              | 16 (4.3)   | 4 (8.2)    |
| Total                                     | 369 (100)  | 49 (100)   |

| Missing symptoms                          | Total, No. (%) |
|-------------------------------------------|----------------|
| Bowel urgency                              | 4 (66.7)       |
| Tenesmus                                   | 2 (33.3)       |
| Total                                     | 6 (100)        |

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; QOL, quality of life.

*Items that were eligible for both non-CTCAE classification and CTCAE code(s).
This work provides a framework mapping the EORTC Item Library, containing all validated EORTC QLG questionnaires (accessed July 2020), onto the current version of the CTCAE (v5.0). These results will be integrated into the EORTC Item Library platform to facilitate identification of items using the CTCAE framework. The strengths of the methodological approach used include the following: independent researcher coding followed by code verification and consensus discussions; inclusion of multiple raters from different clinical, research, and language backgrounds; and blinding of the source questionnaires to enable decontextualized initial coding of the items. Regarding the limitations, the methodology used limits the ability to establish if there are CTCAE symptomatic toxicity items that are not covered by the EORTC Item Library insofar as the mapping used the Item Library as the initial framework, rather than vice versa. Although the process of PRO development used by the EORTC QLG aims to develop items that are relevant to capturing patient experience (including symptomatic AEs), future work mapping symptomatic AEs from the CTCAE onto the EORTC Item Library is necessary. This will ensure that the EORTC Item Library has comprehensive coverage of all symptomatic AEs. However, this work has identified that potentially, there are more symptomatic AEs than the 78 AEs identified by the NCI PRO-CTCAE team, which could be suitable for patient self-report. Future work will compare the EORTC-QLQ system with other PRO systems, as well as MedDRA and WHO-ICF. The analysis also did not seek to select the best PRO item(s) to use for a specific AE; future work will aim to hone the specificity of this mapping, taking into account multiple issues such as content validity, cultural adaptability, translatability, psychometric properties, statistical performance, clinical relevance, and frequency of use within existing questionnaires, to improve the selection process, develop new items where needed, and potentially adapt or remove problematic items. The authors also acknowledge the limitation around the need to better understand the similarities and differences between clinician and patient-reported systems regarding AE severity grading. This complex issue, which requires a multiple methods approach, is an area of future work.

The primary focus of this article is on improving the searchability and item selection for relevant symptomatic toxicities from the EORTC Item Library to assess in a trial from the patient perspective. However, this research has highlighted a need for future stakeholder work, including the regulatory perspective, to establish agreement on key issues related to PRO implementation within clinical trials, including (1) how to optimize use of PROs reporting within a trial AE database; (2) how to manage discrepancies and duplication of AE reporting to minimize clinician and patient burden (ie, are some AEs better reported with a PRO or vice versa); (3) how to manage PRO AE reporting, which may trigger clinical assessment, leading to hospitalization or modification of

### TABLE 5. Summarized Results of EORTC QLQ to CTCAE Mapping

| QLQ Frequency | EORTC Item, No. (%) |
|---------------|---------------------|
| Total No. of source questionnaires for an EORTC item | |
| 1 | 702 (73.9) |
| 2 | 118 (12.4) |
| 3 | 46 (4.8) |
| 4 | 33 (3.5) |
| 5 | 18 (1.9) |
| 6 | 9 (0.9) |
| 7 | 8 (0.8) |
| 8 | 2 (0.2) |
| 9 | 3 (0.3) |
| 10 | 3 (0.3) |
| 11 | 2 (0.2) |
| 12 | 2 (0.2) |
| 13 | 1 (0.1) |
| 15 | 1 (0.1) |
| 21 | 1 (0.1) |
| 24 | 1 (0.1) |
| Total items | 950 (100) |

| AE Frequency | EORTC Item, No. (%) |
|--------------|---------------------|
| Total No. of AEs linked to an EORTC item | |
| 1 | 410 (65.6) |
| 2 | 147 (23.5) |
| 3 | 48 (7.7) |
| 4 | 15 (2.4) |
| 5 | 3 (0.5) |
| 6 | 1 (0.2) |
| 7 | 1 (0.2) |
| Total items | 625 (100) |

| Proportions Calculated on the Basis of Total Linked Items (n = 625) | EORTC Item, No. (%) |
|---------------------------------------------------------------|---------------------|
| Total No. of AEs assigned to EORTC items | 913 (100) |
| 24 (100) |
| Single EORTC items linked to multiple underlying AEs | 19 (3.0) |
| Single EORTC items linked only to diagnostic AEs | 42 (6.7) |
| Single EORTC items linked to both diagnostic and symptomatic AEs | 42 (6.7) |

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; QLQ, Quality of Life questionnaires.
In summary, this extensive descriptive analysis provides a comprehensive, clinical framework to facilitate selection of additional symptomatic AEs and cancer-related issues from the EORTC Item Library for use in clinical trials and practice. Future research will involve working with stakeholders to address issues around optimal PRO selection and application of the Item Library framework in clinical trials.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Linking the European Organisation for Research and Treatment of Cancer Item Library to the Common Terminology Criteria for Adverse Events

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## APPENDIX

### TABLE A1. Coding Examples

| Code | Wording                                                                 | Source Questionnaire(s) | Total Source Questionnaires | Non-CTCAE Classification 1 Total SOC | Total AE 1 | Secondary AE(s) | Diagnosis-Only CTCAE Code | Diagnosis + Symptomatic Toxicity Codes | SOC 1 | AE 1 | AE 2 | AE 3 | AE 4 | AE 5 |
|------|------------------------------------------------------------------------|-------------------------|-----------------------------|---------------------------------------|------------|-----------------|--------------------------|----------------------------------------|-------|-----|-----|-----|-----|-----|
| Q1   | Have you felt less masculine as a result of your disease or treatment? | PR25 SHQ-C22 TC26       | 3                           | Body image                            |            |                 |                          |                                        |       |     |     |     |     |     |
| Q10  | Were you limited in pursuing your hobbies or other leisure time activities? | C30 CAT Role Functioning | 2                           | Impact on life and daily activities   |            |                 |                          |                                        |       |     |     |     |     |     |
| Q100 | Have you been satisfied with your level of intimacy?                   | SHQ-C22                 | 1                           | Emotional impact of symptom, diagnosis, or treatment |            |                 |                          |                                        |       |     |     |     |     |     |
| Q101 | Have you had problems eating in front of other people?                 | H&N43 H&N35 OE318       | 5                           | Emotional impact of symptom, diagnosis, or treatment |            |                 |                          |                                        |       |     |     |     |     |     |
| Q102 | Have you felt insecure regarding your ability to satisfy your partner? | SHQ-C22                 | 1                           | Emotional impact of symptom, diagnosis, or treatment |            |                 |                          |                                        |       |     |     |     |     |     |
| Q103 | Have you had problems enjoying your meals?                             | H&N43 H&N35 OE318       | 5                           | Impact on life and daily activities    |            |                 |                          |                                        |       |     |     |     |     |     |
| Q104 | Have you been satisfied with your sex life?                            | SHQ-C22                 | 1                           | Emotional impact of symptom, diagnosis, or treatment |            |                 |                          |                                        |       |     |     |     |     |     |
| Q105 | To what extent did you feel sexual enjoyment?                          | SHQ-C22                 | 1                           | 1                                      | 2          | Psychiatric disorders Anorgasmia Delayed orgasm |                          |                                        |       |     |     |     |     |     |
| Q106 | Have you had problems talking to other people?                         | H&N43 H&N35             | 2                           | 1                                      | 3          | Nervous system disorders Dysarthria Dysphasia Aphonia |                          |                                        |       |     |     |     |     |     |

(continued on following page)
| Code | Wording | Source Questionnaire(s) | Total Source Questionnaires | Non-CTCAE Classification 1 | Missing Symptom (not in CTCAE) | Total SOCs | Total AEs | Secondary AEs | Diagnosis-Only CTCAE Code | Diagnosis + Symptomatic Toxicity Codes | SOC 1 | AE 1 | AE 2 | AE 3 | AE 4 | AE 5 |
|------|---------|-------------------------|-----------------------------|----------------------------|-------------------------------|------------|----------|-------------|-------------------------|------------------------------------------|--------|------|------|------|------|------|
| Q107 | Were you confident about obtaining and maintaining an erection when you had sex? | SHQ-C22 | 1 | 1 | 1 | | | | | | Reproductive system and breast disorders | Erectile dysfunction | | | | | |
| Q109 | Have you been feeling less feminine as a result of your disease or treatment? | BR45 | BR23 | CO24 | 6 | Body image | | | | | | | | | | | |
| Q11  | Were you short of breath? | CB0 | CAT Dyspnea | C-PAL15 | 4 | | 1 | 1 | | Respiratory, thoracic, and mediastinal disorders | Dyspnea | | | | | |
| Q110 | Have you had problems talking on the telephone? | H&N43 | H&N35 | | 2 | | 1 | 3 | | Nervous system disorders | Dyssarthria | Dysphasia | Aphonia | | |
| Q111 | Have you had trouble having social contact with your family? | H&N35 | | | 1 | Impact on life and daily activities | | | | | | | | | |
| Q112 | Have you had trouble having social contact with friends? | H&N35 | LMC21 | | 2 | Impact on life and daily activities | | | | | | | | | |
| Q113 | Have you had problems going out in public? | H&N43 | H&N35 | | 2 | Impact on life and daily activities | | | | | | | | | |
| Q114 | Did food and drink taste different than usual? | CAQ24 | SBQ74 | BR45 | 11 | | 1 | 1 | | Nervous system disorders | Dygeusia | | | | | |
| Q115 | Were your eyes painful, irritated, or watery? | BR45 | BR23 | | 2 | | 1 | 2 | | Eye disorders | Eye pain | Watering eyes | | | |

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SOC, System Organ Class.
| Wording                                                                 | Source Questionnaire(s) | SOC 1                                                                 | AE 1          |
|------------------------------------------------------------------------|-------------------------|----------------------------------------------------------------------|---------------|
| Have you felt slowed down?                                              | CAT Fatigue FA12        | General disorders and administration site conditions                | Fatigue       |
| Have you lacked energy?                                                | CAT Fatigue FA12        | General disorders and administration site conditions                | Fatigue       |
| Did you have trouble getting things started?                           | FA12                    | General disorders and administration site conditions                | Fatigue       |
| Have you found it difficult to finish things you started?              | HCC18                   | General disorders and administration site conditions                | Fatigue       |
| Have you felt mentally exhausted?                                      | THY34                   | General disorders and administration site conditions                | Fatigue       |
| Did you need to rest?                                                  | C30 CAT Fatigue         | General disorders and administration site conditions                | Fatigue       |
| Were you tired?                                                        | C30 CAT Fatigue C-PAL15 | General disorders and administration site conditions                | Fatigue       |
| Did you feel drowsy during the daytime?                                | BN20                    | General disorders and administration site conditions                | Fatigue       |
| Have you been too tired to eat?                                        | CAT Fatigue CAX24       | General disorders and administration site conditions                | Fatigue       |
| Have you felt exhausted?                                               | CAT Fatigue FA12        | General disorders and administration site conditions                | Fatigue       |
| Did tiredness interfere with your daily activities?                    | FA12                    | General disorders and administration site conditions                | Fatigue       |
| Have you been so tired it was difficult keeping your eyes open during daytime? | CAT Fatigue             | General disorders and administration site conditions                | Fatigue       |
| Have you woken up with a feeling of exhaustion?                        | CAT Fatigue             | General disorders and administration site conditions                | Fatigue       |
| Have you lacked the energy to do things?                               | CAT Fatigue             | General disorders and administration site conditions                | Fatigue       |
| Have you been too tired to do your usual activities?                   | CAT Fatigue             | General disorders and administration site conditions                | Fatigue       |
| Have you felt drained?                                                 | CAT Fatigue             | General disorders and administration site conditions                | Fatigue       |
| Have you been so exhausted it felt almost impossible to move your body? | CAT Fatigue             | General disorders and administration site conditions                | Fatigue       |
| Have you had trouble starting things because you were tired?           | CAT Fatigue             | General disorders and administration site conditions                | Fatigue       |

(continued on following page)
| Wording                                                                 | Source Questionnaire(s) | SOC 1 | AE 1               |
|------------------------------------------------------------------------|-------------------------|-------|-------------------|
| Have you been too tired to do even simple things?                      | CAT Fatigue             |       | Fatigue           |
| Have you found shopping and doing errands exhausting?                  | CAT Fatigue             |       | Fatigue           |
| Have you felt physically exhausted?                                     | CAT Fatigue THY34       |       | Fatigue           |
| Have you found leisure and recreational activities exhausting?         | CAT Fatigue             |       | Fatigue           |
| Have you had to sleep for long periods during daytime?                 | CAT Fatigue             |       | Fatigue           |
| Have you become easily tired?                                           | CAT Fatigue             |       | Fatigue           |
| Have you had trouble sitting up because you were tired?                | CAT Fatigue             |       | Fatigue           |
| Have you felt worn out?                                                | CAT Fatigue             |       | Fatigue           |
| Have you had a feeling of overwhelming and prolonged lack of energy?   | CAT Fatigue             |       | Fatigue           |
| Have you had trouble finishing things because you were tired?          | CAT Fatigue             |       | Fatigue           |
| Have you become tired from walking upstairs?                           | CAT Fatigue             |       | Fatigue           |
| Have you required frequent or long periods of rest?                    | CAT Fatigue             |       | Fatigue           |
| Have you become tired from carrying out your duties and responsibilities?| CAT Fatigue             |       | Fatigue           |
| Have you had an extreme need for rest?                                 | CAT Fatigue             |       | Fatigue           |
| Have you become exhausted from dressing?                               | CAT Fatigue             |       | Fatigue           |
| Have you felt tired for a long time after physical activity like taking a long walk? | CAT Fatigue             |       | Fatigue           |
| Have you become exhausted from taking a shower?                        | CAT Fatigue             |       | Fatigue           |
| Has fatigue or a lack of energy affected your sex life?                | SHQ-C22                 |       | Fatigue           |

Abbreviations: AE, adverse event; SOC, System Organ Class.
| SOC                        | AE                          | Primary Classification, No. (%) | Secondary Classification, No. (%) | Total, No. (%) |
|---------------------------|-----------------------------|---------------------------------|-----------------------------------|----------------|
| Cardiac disorders         | Chest pain—cardiac          | 1 (0.1)                         | 1 (4.2)                           | 2 (0.2)        |
|                           | Palpitations                | 2 (0.2)                         | —                                 | 2 (0.2)        |
| Ear and labyrinth disorders | Hearing impaired            | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Vertigo                     | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Vestibular disorder         | 1 (0.1)                         | —                                 | 1 (0.1)        |
| Endocrine disorders       | Hyperthyroidism             | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Hypothyroidism              | 1 (0.1)                         | —                                 | 1 (0.1)        |
| Eye disorders             | Blurred vision              | 4 (0.4)                         | —                                 | 4 (0.4)        |
|                           | Conjunctivitis              | 3 (0.3)                         | —                                 | 3 (0.3)        |
|                           | Dry eye                     | 7 (0.8)                         | —                                 | 7 (0.7)        |
|                           | Extraocular muscle paresis  | 3 (0.3)                         | —                                 | 3 (0.3)        |
|                           | Eye pain                    | 6 (0.7)                         | —                                 | 6 (0.6)        |
|                           | Flashing lights             | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Floaters                    | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Night blindness             | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Periorbital edema           | 2 (0.2)                         | —                                 | 2 (0.2)        |
|                           | Photophobia                 | 2 (0.2)                         | —                                 | 2 (0.2)        |
|                           | Retinal tear                | 2 (0.2)                         | —                                 | 2 (0.2)        |
|                           | Uveitis                     | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Watering eyes               | 4 (0.4)                         | —                                 | 4 (0.4)        |
| Eye disorders—others, specify |                      | 13 (1.4)                        | —                                 | 13 (1.4)       |
| GI disorders              | Abdominal distension        | 2 (0.2)                         | —                                 | 2 (0.2)        |
|                           | Abdominal pain              | 8 (0.9)                         | —                                 | 8 (0.9)        |
|                           | Anal hemorrhage             | 2 (0.2)                         | —                                 | 2 (0.2)        |
|                           | Anal pain                   | 3 (0.3)                         | —                                 | 3 (0.3)        |
|                           | Bloating                    | 2 (0.2)                         | —                                 | 2 (0.2)        |
|                           | Cecal hemorrhage            | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Cheilitis                   | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Colitis                     | 4 (0.4)                         | —                                 | 4 (0.4)        |
|                           | Colonic hemorrhage          | 1 (0.1)                         | —                                 | 1 (0.1)        |
|                           | Constipation                | 10 (1.1)                        | —                                 | 10 (1.1)       |
|                           | Dental caries               | 2 (0.2)                         | —                                 | 2 (0.2)        |
|                           | Diarrhea                    | 18 (2.0)                        | —                                 | 18 (1.9)       |
|                           | Dry mouth                   | 3 (0.3)                         | —                                 | 3 (0.3)        |
|                           | Dyspepsia                   | 5 (0.5)                         | —                                 | 5 (0.5)        |
|                           | Dysphagia                   | 13 (1.4)                        | —                                 | 13 (1.4)       |
|                           | Enterocolitis               | 2 (0.2)                         | —                                 | 2 (0.2)        |
|                           | Fecal incontinence          | 11 (1.2)                        | —                                 | 11 (1.2)       |
|                           | Flatulence                  | 6 (0.7)                         | —                                 | 6 (0.6)        |
|                           | Gastroesophageal reflux disease | 1 (0.1)                        | —                                 | 1 (0.1)        |
|                           | GI pain                     | 10 (1.1)                        | —                                 | 10 (1.1)       |
|                           | Gastroparesis               | 1 (0.1)                         | —                                 | 1 (0.1)        |

(continued on following page)
| SOC                                      | CTCAE                  | EORTC Items | Primary Classification, No. (%) | Secondary Classification, No. (%) | Total, No. (%) |
|------------------------------------------|------------------------|-------------|---------------------------------|-----------------------------------|---------------|
| Gingival pain                            | 1 (0.1)                |             | 1 (0.1)                         |                                   |               |
| Lip pain                                 | 1 (0.1)                |             | 1 (0.1)                         |                                   |               |
| Mucositis oral                           | 11 (1.2)               |             | 11 (1.2)                        |                                   |               |
| Nausea                                   | 18 (2.0)               |             | 18 (1.9)                        |                                   |               |
| Oral dysesthesia                         | 1 (0.1)                |             | 1 (0.1)                         |                                   |               |
| Oral hemorrhage                          | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Oral pain                                | 8 (0.9)                |             | 8 (0.9)                         |                                   |               |
| Periodontal disease                      | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Proctitis                                | 4 (0.4)                |             | 4 (0.4)                         |                                   |               |
| Rectal hemorrhage                        | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Rectal pain                              | 3 (0.3)                |             | 3 (0.3)                         |                                   |               |
| Salivary duct inflammation               | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Stomach pain                             | 8 (0.9)                |             | 8 (0.9)                         |                                   |               |
| Toothache                                | 1 (0.1)                |             | 1 (0.1)                         |                                   |               |
| Vomiting                                 | 18 (2.0)               |             | 18 (1.9)                        |                                   |               |
| GI disorders—others, specify             | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Chills                                    | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Edema face                               | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Edema limbs                              | 6 (0.7)                |             | 6 (0.6)                         |                                   |               |
| Edema trunk                              | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Fatigue                                  | 46 (5.0)               |             | 46 (4.9)                        |                                   |               |
| Fever                                    | 3 (0.3)                |             | 3 (0.3)                         |                                   |               |
| Gait disturbance                         | 13 (1.4)               | 2 (8.3)     | 15 (1.6)                        |                                   |               |
| Generalized edema                        | 1 (0.1)                |             | 1 (0.1)                         |                                   |               |
| Injection site reaction                  | 4 (0.4)                |             | 4 (0.4)                         |                                   |               |
| Localized edema                          | 8 (0.9)                |             | 8 (0.9)                         |                                   |               |
| Malaise                                  | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Neck edema                               | 1 (0.1)                |             | 1 (0.1)                         |                                   |               |
| Noncardiac chest pain                    | 2 (0.2)                |             | 2 (0.2)                         |                                   |               |
| Pain                                     | 37 (4.1)               | 1 (4.2)     | 38 (4.1)                        |                                   |               |
| General disorders and administration site conditions—others, specify | 36 (3.9)               | 2 (8.3)     | 38 (4.1)                        |                                   |               |

| Immune system disorders                  |                        |             |                                |                                   |               |
| Allergic reaction                        | 1 (0.1)                |             | 1 (0.1)                        |                                   |               |

| Infections and infestations              |                        |             |                                |                                   |               |
| Lip infection                            | 1 (0.1)                |             | 1 (0.1)                        |                                   |               |
| Stoma site infection                     | 2 (0.2)                |             | 2 (0.2)                        |                                   |               |
| Tooth infection                          | 1 (0.1)                |             | 1 (0.1)                        |                                   |               |
| Upper respiratory infection              | 1 (0.1)                |             | 1 (0.1)                        |                                   |               |
| Infections and infestations—others, specify | 2 (0.2)                |             | 2 (0.2)                        |                                   |               |

(continued on following page)
### TABLE A3. CTCAE SOCs and AEs Covered by EORTC Items (continued)

| SOC                                    | CTCAE                      | EORTC Items                      | Primary Classification, No. (%) | Secondary Classification, No. (%) | Total, No. (%) |
|----------------------------------------|----------------------------|----------------------------------|---------------------------------|-----------------------------------|----------------|
| Injury, poisoning, and procedural complications | **Bruising** 2 (0.2)       | —                                | 2 (0.2)                         |                                   |                |
|                                        | **Dermatitis radiation** 4 (0.4) | —                                | 4 (0.4)                         |                                   |                |
|                                        | **Intestinal stoma leak** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Postoperative thoracic procedure complication** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Urostomy leak** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Wound complication** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Injury, poisoning, and procedural complications—others, specify** 2 (0.2) | —                                | 2 (0.2)                         |                                   |                |
| Investigations                         | **Blood bilirubin increased** 3 (0.3) | —                                | 3 (0.3)                         |                                   |                |
|                                        | **Weight gain** 3 (0.3) | 1 (4.2)                          | 4 (0.4)                         |                                   |                |
|                                        | **Weight loss** 10 (1.1) | —                                | 10 (1.1)                        |                                   |                |
| Metabolism and nutrition disorders     | **Anorexia** 9 (1.0) | —                                | 9 (1.0)                         |                                   |                |
| Musculoskeletal and connective tissue disorders | **Arthralgia** 6 (0.7) | —                                | 6 (0.6)                         |                                   |                |
|                                        | **Arthritis** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Back pain** 4 (0.4) | —                                | 4 (0.4)                         |                                   |                |
|                                        | **Bone pain** 3 (0.3) | —                                | 3 (0.3)                         |                                   |                |
|                                        | **Buttock pain** 2 (0.2) | —                                | 2 (0.2)                         |                                   |                |
|                                        | **Generalized muscle weakness** 4 (0.4) | —                                | 4 (0.4)                         |                                   |                |
|                                        | **Joint range of motion decreased** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Joint range of motion decreased lumbar spine** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Muscle weakness, left-sided** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Muscle weakness, lower limb** 6 (0.7) | 1 (4.2)                          | 7 (0.7)                         |                                   |                |
|                                        | **Muscle weakness, right-sided** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Muscle weakness, upper limb** 6 (0.7) | 1 (4.2)                          | 7 (0.7)                         |                                   |                |
|                                        | **Myalgia** 6 (0.7) | 2 (8.3)                          | 8 (0.9)                         |                                   |                |
|                                        | **Neck pain** 1 (0.1) | —                                | 1 (0.1)                         |                                   |                |
|                                        | **Pain in extremity** 2 (0.2) | —                                | 2 (0.2)                         |                                   |                |
|                                        | **Superficial soft tissue fibrosis** 3 (0.3) | —                                | 3 (0.3)                         |                                   |                |
|                                        | **Trismus** 2 (0.2) | —                                | 2 (0.2)                         |                                   |                |

(continued on following page)
| SOC                            | CTCAE                | EORTC Items                                                                 |
|-------------------------------|----------------------|-----------------------------------------------------------------------------|
| Nervous system disorders      |                      |                                                                            |
| Akathisia                     | 1 (0.1)              | 1 (0.1)                                                                     |
| Amnesia                       | 1 (0.1)              | 1 (0.1)                                                                     |
| Aphonia                       | 4 (0.4)              | 1 (4.2) 5 (0.5)                                                            |
| Ataxia                        | 1 (0.1)              | 1 (0.1)                                                                     |
| Brachial plexopathy           | 1 (0.1)              | 1 (0.1)                                                                     |
| Cognitive disturbance         | 4 (0.4)              | 4 (0.4)                                                                     |
| Concentration impairment      | 13 (1.4)             | 13 (1.4)                                                                    |
| Dizziness                     | 3 (0.3)              | 3 (0.3)                                                                     |
| Dysarthria                    | 5 (0.5)              | 1 (4.2) 6 (0.6)                                                            |
| Dysgeusia                     | 5 (0.5)              | 5 (0.5)                                                                     |
| Dysphasia                     | 6 (0.7)              | 1 (4.2) 7 (0.7)                                                            |
| Headache                      | 1 (0.1)              | 1 (0.1)                                                                     |
| Hypersomnia                   | 7 (0.8)              | 7 (0.7)                                                                     |
| Lethargy                      | 33 (3.6)             | 33 (3.5)                                                                    |
| Memory impairment             | 24 (2.6)             | 24 (2.6)                                                                    |
| Oculomotor nerve disorder     | 3 (0.3)              | 3 (0.3)                                                                     |
| Paresthesia                   | 16 (1.8)             | 1 (4.2) 17 (1.8)                                                            |
| Peripheral motor neuropathy   | 9 (1.0)              | 1 (4.2) 10 (1.1)                                                            |
| Peripheral sensory neuropathy | 8 (0.9)              | 1 (4.2) 9 (1.0)                                                            |
| Seizure                       | 1 (0.1)              | 1 (0.1)                                                                     |
| Somnolence                    | 11 (1.2)             | 11 (1.2)                                                                    |
| Stroke                        | 1 (0.1)              | 1 (0.1)                                                                     |
| Syncope                       | 1 (0.1)              | 1 (0.1)                                                                     |
| Psychiatric disorders         |                      |                                                                            |
| Agitation                     | 5 (0.5)              | 5 (0.5)                                                                     |
| Anorgasmia                    | 4 (0.4)              | 4 (0.4)                                                                     |
| Anxiety                       | 6 (0.7)              | 6 (0.6)                                                                     |
| Confusion                     | 1 (0.1)              | 1 (0.1)                                                                     |
| Delayed orgasm                | 3 (0.3)              | 3 (0.3)                                                                     |
| Depression                    | 16 (1.8)             | 16 (1.7)                                                                    |
| Insomnia                      | 12 (1.3)             | 12 (1.3)                                                                    |
| Irritability                  | 1 (0.1)              | 1 (0.1)                                                                     |
| Libido decreased              | 4 (0.4)              | 4 (0.4)                                                                     |
| Libido increased              | 1 (0.1)              | 1 (0.1)                                                                     |
| Restlessness                  | 2 (0.2)              | 2 (0.2)                                                                     |
| Psychiatric disorders—others, | 5 (0.5)              | 5 (0.5)                                                                     |
| specify                       |                      |                                                                            |

(continued on following page)
| SOC                                | CTCAE AE                        | Primary Classification, No. (%) | Secondary Classification, No. (%) | Total, No. (%) |
|------------------------------------|---------------------------------|---------------------------------|-----------------------------------|----------------|
| Renal and urinary disorders        | Bladder spasm                   | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Cystitis noninfective           | 2 (0.2)                         |                                   | 2 (0.2)        |
|                                    | Urinary frequency               | 6 (0.7)                         |                                   | 6 (0.6)        |
|                                    | Urinary incontinence            | 3 (0.3)                         |                                   | 3 (0.3)        |
|                                    | Urinary retention               | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Urinary tract obstruction       | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Urinary tract pain              | 2 (0.2)                         |                                   | 2 (0.2)        |
|                                    | Urinary urgency                 | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Renal and urinary disorders—    |                                 |                                   |                |
|                                    | others, specify                 |                                 |                                   |                |
| Reproductive system and breast     | Breast atrophy                  | 4 (0.4)                         |                                   | 4 (0.4)        |
| disorders                           | Breast pain                     | 3 (0.3)                         |                                   | 3 (0.3)        |
|                                    | Dyspareunia                     | 5 (0.5)                         |                                   | 5 (0.5)        |
|                                    | Ejaculation disorder            | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Erectile dysfunction            | 2 (0.2)                         |                                   | 2 (0.2)        |
|                                    | Genital edema                   | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Gynecomastia                    | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Irregular menstruation          | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Menorrhagia                     | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Pelvic pain                     | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Penile pain                     | 2 (0.2)                         |                                   | 4 (0.4)        |
|                                    | Premature menopause             | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Scrotal pain                    | 2 (8.3)                         |                                   | 2 (0.2)        |
|                                    | Testicular pain                 | 2 (8.3)                         |                                   | 2 (0.2)        |
|                                    | Vaginal discharge               | 2 (0.2)                         |                                   | 2 (0.2)        |
|                                    | Vaginal dryness                 | 3 (0.3)                         |                                   | 3 (0.3)        |
|                                    | Vaginal hemorrhage              | 1 (0.1)                         |                                   | 1 (0.1)        |
|                                    | Vaginal inflammation            | 3 (0.3)                         |                                   | 3 (0.3)        |
|                                    | Vaginal pain                    | 6 (0.7)                         |                                   | 6 (0.6)        |
|                                    | Vaginal stricture               | 6 (0.7)                         |                                   | 6 (0.6)        |
|                                    | Reproductive system and breast  | 4 (0.4)                         |                                   | 4 (0.4)        |
|                                    | disorders—others, specify       |                                 |                                   |                |

(continued on following page)
| CTCAE EORTC Items | Primary Classification, No. (%) | Secondary Classification, No. (%) | Total, No. (%) |
|-------------------|---------------------------------|-----------------------------------|---------------|
| **Respiratory, thoracic, and mediastinal disorders** | | | |
| Allergic rhinitis | 1 (0.1) | — | 1 (0.1) |
| Aspiration | 1 (0.1) | — | 1 (0.1) |
| Bronchopulmonary hemorrhage | 1 (0.1) | — | 1 (0.1) |
| Cough | 3 (0.3) | — | 3 (0.3) |
| Dyspnea | 36 (3.9) | — | 36 (3.8) |
| Epistaxis | 1 (0.1) | — | 1 (0.1) |
| Hoarseness | 5 (0.5) | — | 5 (0.5) |
| Laryngeal hemorrhage | 1 (0.1) | — | 1 (0.1) |
| Laryngeal inflammation | 2 (0.2) | — | 2 (0.2) |
| Pharyngitis | 1 (0.1) | — | 1 (0.1) |
| Pleuritic pain | 1 (0.1) | 1 (4.2) | 2 (0.2) |
| Sneezing | 1 (0.1) | — | 1 (0.1) |
| Sore throat | 6 (0.7) | — | 6 (0.6) |
| Tracheal mucositis | 1 (0.1) | — | 1 (0.1) |
| Voice alteration | 3 (0.3) | — | 3 (0.3) |
| Wheezing | 3 (0.3) | — | 3 (0.3) |
| **Skin and subcutaneous tissue disorders** | | | |
| Alopecia | 5 (0.5) | — | 5 (0.5) |
| Dry skin | 4 (0.4) | — | 4 (0.4) |
| Erythroderma | 2 (0.2) | — | 2 (0.2) |
| Hair color changes | 1 (0.1) | — | 1 (0.1) |
| Hyperhidrosis | 1 (0.1) | — | 1 (0.1) |
| Nail loss | 2 (0.2) | — | 2 (0.2) |
| Nail ridging | 1 (0.1) | — | 1 (0.1) |
| Pain of skin | 10 (1.1) | — | 10 (1.1) |
| Palmar-plantar erythrodysesthesia syndrome | 2 (0.2) | — | 2 (0.2) |
| Photosensitivity | 1 (0.1) | — | 1 (0.1) |
| Pruritus | 7 (0.8) | — | 7 (0.7) |
| Skin hyperpigmentation | 1 (0.1) | — | 1 (0.1) |
| Skin hypopigmentation | 1 (0.1) | — | 1 (0.1) |
| Skin induration | 1 (0.1) | — | 1 (0.1) |
| Skin ulceration | 2 (0.2) | — | 2 (0.2) |
| Skin and subcutaneous tissue disorders—others, specify | 2 (0.2) | — | 2 (0.2) |
| **Surgical and medical procedures** | | | |
| Surgical and medical procedures—others, specify | 4 (0.4) | — | 4 (0.4) |
| **Vascular disorders** | | | |
| Flushing | 1 (0.1) | — | 1 (0.1) |
| Hot flashes | 4 (0.4) | — | 4 (0.4) |
| Peripheral ischemia | 1 (0.1) | — | 1 (0.1) |
| **Total AEs** | 913 (100) | 24 (100) | 937 (100) |

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; SOC, System Organ Class.