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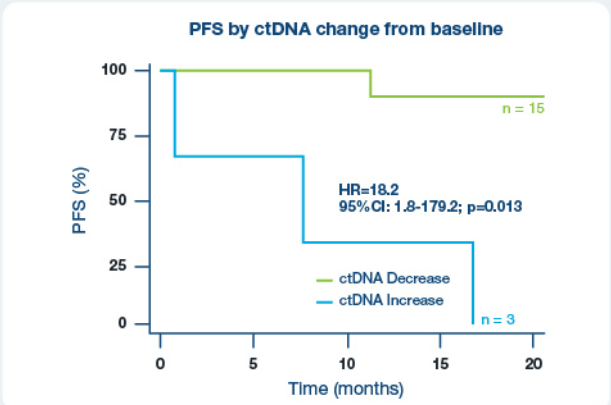
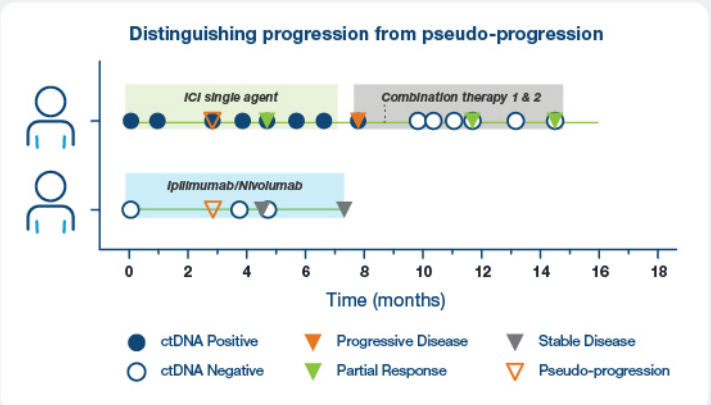
METASTATIC MELANOMA

Use Signatera™ ctDNA dynamics to inform earlier treatment decisions in metastatic melanoma patients

Early on-treatment ctDNA dynamics were predictive of PFS in metastatic melanoma patients receiving 1st line ICI treatment[1]

At week 6, Signatera™ identified that patients with increasing ctDNA had a 18x higher risk of progression than ctDNA-negative patients

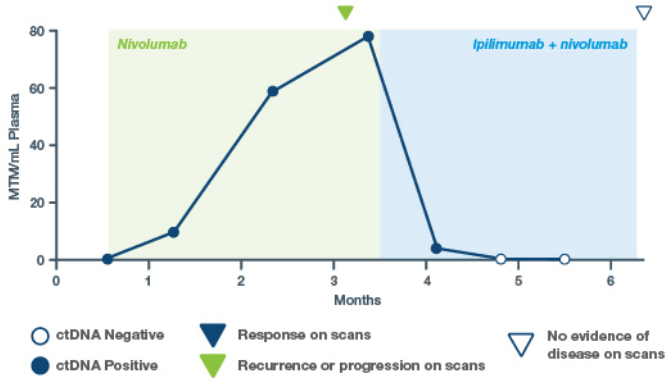




- Patients with any increase in ctDNA levels from baseline by week 6 of 1st Line ICI treatment (monotherapy and combination ICIs) had a significantly shorter PFS (HR: 18; p=0.013).
- Signatera™ was able to help distinguish between true vs pseudo-progression

Should treatment be changed or escalated?

Early rise in ctDNA can help inform treatment escalation or change



60-year-old stage IV metastatic melanoma patient[2]

Adapted from a real-world Signatera™ patient case. Case features modified to protect patient confidentiality. No treatment recommendations are made or should be implied.

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PFS = Progression-free survival

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Received: 24 January 2023 | Revised: 21 March 2023 | Accepted: 23 March 2023

DOI: 10.1002/cncr.34822

ORIGINAL ARTICLE

International validation of two EORTC questionnaires for assessment of health-related quality of life for patients with high-grade non-Hodgkin lymphoma (QLQ-NHL-HG29) and low-grade non-Hodgkin lymphoma (QLQ-NHL-LG20)

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Funding information
EORTC Quality of Life Group, Grant/Award Number: 004-2016

Abstract

Background: Health-related quality of life (HRQOL) is a critical aspect to consider when making treatment decisions for patients with non-Hodgkin-lymphoma (NHL). This international study by the European Organisation for Research and Treatment of Cancer (EORTC) tested the psychometric properties of two newly developed measures for patients with high-grade (HG)- and low-grade (LG)-NHL: the EORTC QLQ-NHL-HG29 and the EORTC QLQ-NHL-LG20 to supplement the core questionnaire (EORTC QLQ-C30).

Methods: Overall, 768 patients with HG-NHL ($N = 423$) and LG-NHL ($N = 345$) from 12 countries completed the QLQ-C30, QLQ-NHL-HG29/QLQ-NHL-LG20 and a debriefing questionnaire at baseline, and a subset at follow-up for either retest ($N = 125/124$) or responsiveness to change (RCA; $N = 98/49$).

Results: Confirmatory factor analysis showed an acceptable to good fit of the 29 items of the QLQ-NHL-HG29 on its five scales (symptom burden [SB], neuropathy,

physical condition/fatigue [PF], emotional impact [EI], and worries about health/functioning [WH]), and of the 20 items of the QLQ-NHL-LG20 on its four scales (SB, PF, EI, and WH). Completion took on average 10 minutes. Test–retest reliability, convergent validity, known-group comparisons, and RCA find satisfactory results of both measures. A total of 31%–78% of patients with HG-NHL and 22%–73% of patients with LG-NHL reported symptoms and/or worries (e.g., tingling in hands/feet, lack of energy, and worries about recurrence). Patients reporting symptoms/worries had substantially lower HRQOL compared to those without.

Discussion: The use of the EORTC QLQ-NHL-HG29 and QLQ-NHL-LG20 questionnaires in clinical research and practice will provide clinically relevant data to better inform treatment decision-making.

Plain language summary

- The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group developed two questionnaires.
- These questionnaires measure health-related quality of life.
- The questionnaires are for patients with high-grade or low-grade non-Hodgkin lymphoma.
- They are called the EORTC QLQ-NHL-HG29 and QLQ-NHL-LG20.
- The questionnaires are now internationally validated.
- This study demonstrates that the questionnaires are reliably and valid, which are important aspects of a questionnaire.
- The questionnaires can now be used in clinical trials and practice.
- With the information gathered from the questionnaires, patients and clinicians can better evaluate treatments and discuss the best choice for a patient.

KEYWORDS
EORTC, non-Hodgkin lymphoma, PRO, psychometric properties, quality of life, questionnaire, symptoms

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy.[1] Worldwide, an estimated 545,000 people were diagnosed with NHL in 2020.[2] It encompasses many subtypes and ranges from low-grade (LG; e.g., follicular lymphoma) to high-grade (HG) lymphomas (e.g., diffuse large B-cell lymphoma).[3] Patients with LG-NHL are typically considered incurable, and their disease is characterized by a chronic course with repeated relapses, treatment, and progression.[3] Patients with HG-NHL typically have acute and more rapid progression and can be cured with intensive chemo-immunotherapy.

Advances in treatment for NHL have led to improved survival rates and/or remission duration in the past decades.[1] With improved survival, there has been increased attention to the health-related quality of life (HRQOL) of patients and survivors with NHL, albeit still to a limited extent. Literature shows that both patients with HG- and LG-NHL report a variety of problems such as functional, neurosensory and cardiopulmonary impairments, fatigue, anxiety, sleeping problems, and worries about new symptoms and recurrence of disease that negatively impact their HRQOL.[4–8]

In 2018, an international expert panel on hematological malignancies has voiced concern about the limited amount of data in this area and advocated for urgent efforts to raise standards of patient-reported outcomes (PROs) in research and practice.[9] International recommendations for various hematologic diseases are now increasingly focusing on the assessment of HRQOL.[10,11] Assessment of PROs, including functional aspects or symptom burden, can provide unique information that may help to facilitate clinical decision-making in the setting of hematologic malignancies.[12]

Although the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)[13] is the most frequently used PRO measure in the context of cancer randomized controlled trials, this questionnaire does not include symptoms and functional health issues relevant for patients with NHL. Therefore, the EORTC Quality of Life Group previously developed the EORTC QLQ Non-Hodgkin Lymphoma High Grade 29 (QLQ-NHL-HG29) and the EORTC QLQ Non- Hodgkin Lymphoma Low

Grade 20 (QLQ-NHL-LG20) to capture disease-specific symptoms for patients with HG- or LG-NHL, respectively.[14]

The aim of this study was to validate the QLQ-NHL-HG29 and QLQ-NHL-LG20 by testing their scale structure and to evaluate their acceptability and reliability, in an international sample of patients with HG- and LG-NHL, respectively.

MATERIALS AND METHODS

This study was performed according to the EORTC Quality of Life Group (QLG) guidelines for module development.[15] In brief, this module development process consists of four phases: Phase I: generation of relevant quality of life issues; Phase II: conversion of the quality of life issues into a set of items; Phase III: pretesting the item list or preliminary module questionnaire; and Phase IV: large-scale international field testing. Phases I–III have been published previously[14] (Figure 1). This article presents the Phase IV results.

Patients

Patients were eligible for inclusion if they were ≥18 years old at diagnosis, had a confirmed diagnosis of either HG- or LG-NHL,[16] and were sufficiently proficient in the local language. Patients with severe psychiatric disorders or major cognitive dysfunctions on record were excluded.

Recruitment

Patients were recruited in 12 countries. Ethical approval from each participating center was obtained and all patients provided written informed consent. The protocol was approved by the EORTC QLG. The study was coordinated from the Netherlands and collaborators met at the biannual meeting of the EORTC QLG to discuss the project.

Questionnaires and data collection

Patients completed the EORTC QLQ-C30 (version 3.0),[13] EORTC QLQ-NHL-HG29,[14] or QLQ-NHL-LG20[14] and a debriefing questionnaire. The questionnaire was completed at any time from diagnosis onward, including after treatment, this was defined as the baseline questionnaire. A subset of patients who were clinically stable (i.e., those who were at least 3 months after completion of treatment and had no change in clinical status in the 2 weeks after the completion of the first questionnaire) completed the questionnaire 2 weeks later for a second time (test–retest analysis). For responsiveness to change analysis (RCA), another subset of patients, who were expected to experience a change in clinical status (e.g., on vs. after treatment) completed the questionnaires again between 3 and 5 months after termination of treatment. EORTC translation guidelines were used to produce questionnaires in the EORTC standard language and all relevant languages for participating countries.[17] The Computer-based Health Evaluation Software (CHES[18]) was used for data collection. Patients had the possibility to complete questionnaires using paper-based versions or electronically at the hospital or using a remote patient portal configured for this study.

EORTC QLQ-NHL-HG29 and EORTC QLQ-NHL-LG20

The QLQ-HG-NHL29 consists of 29 items, contributing to five multi-item subscales and three conditional items: symptom burden due to disease and/or treatment (seven items), neuropathy (two items), physical condition/fatigue (five items), emotional impacts (four items) and worries about health and functioning (eight items). The three conditional items, which patients complete only if relevant to them, are about having problems at work/education, worries about work/education and concerns about the ability to have children.

The QLQ-LG-NHL20 consists of 20 items, contributing to four multi-item subscales and two conditional items: symptom burden due to disease and/or treatment (four items), physical condition/fatigue (four items), emotional impacts (four items), and worries about health and functioning (six items). The two conditional items are about problems at work/education and worries about work/education.

For both questionnaires, items are rated using a four-point response scale ("not at all," "a little," "quite a bit," and "very much") and the reference time frame for all items is the past week.[14] The scoring approach for the QLQ-HG-NHL29 and QLQ-LG-NHL20 is identical to that of the EORTC QLQ-C30, i.e., calculating the mean of the items of a specific multi-item scale or using the single conditional item score and then converting it into a standardized scale ranging from 0 to 100. A higher score for all the multi-item scales and items represent a higher level of symptomatology or problems.

EORTC QLQ-C30

The EORTC QLQ-C30 comprises 30 items of five functional scales (physical, role, cognitive, emotional, and social), seven symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), one item assessing financial impact, and two items to rate overall health and quality of life.[13] For the functioning and the overall health and quality of life scales, a higher score indicates better health. For the symptom scales, a higher score indicates a higher level of symptom burden.[13]

Debriefing questionnaire

The EORTC QLG Phase IV debriefing questionnaire was used to assess how much time patients took to complete the QLQ-NHL-HG29 or QLQ-NHL-LG20 questionnaire, whether they needed help to complete it, whether any of the items were confusing or difficult to

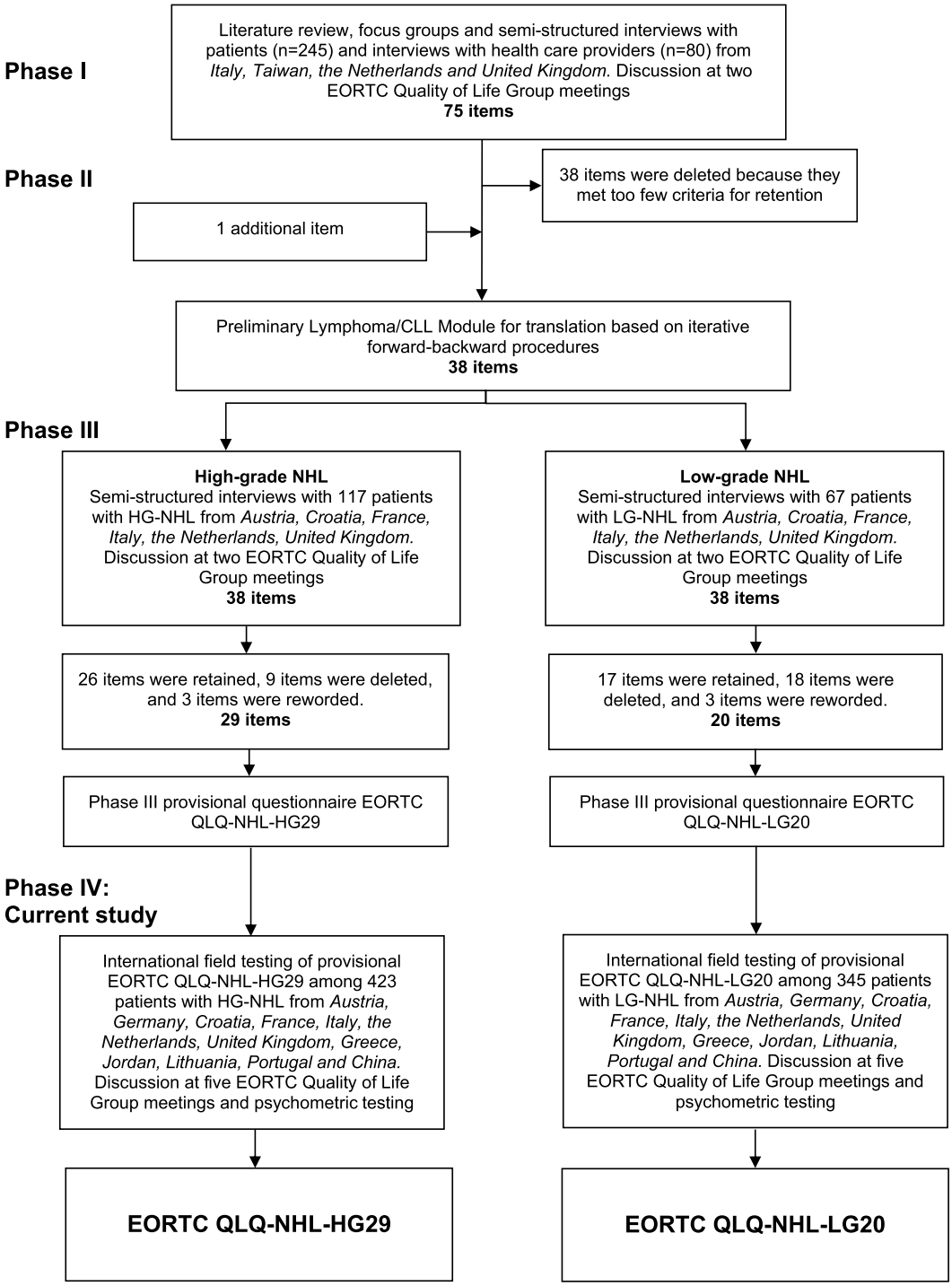

FIGURE 1 Summary of EORTC QLQ-NHL-HG29 and EORTC QLQ-NHL-LG20 module development.

answer or upsetting, and whether patients had any further comments or suggestions.[15]

Sociodemographic and clinical data

Sociodemographic (age, sex) and clinical (NHL type, treatment type, treatment line, time since last treatment, time since diagnosis, stage of disease, and international prognostic index) data were collected at time of a patients first questionnaire completion and again at the second assessment for patients completing RCA assessment. A modified version of the Charlson comorbidity index (with the addition of high blood pressure)[19,20] and the Eastern Cooperative Oncology group (ECOG) performance status[21] were also collected. These data were retrieved from patients medical records by the hospital staff (i.e., clinician, nurse, or research coordinator). Data on living arrangement, educational level and employment status were provided by the patients themselves.

Statistical analyses

Analyses were performed using R[22] version 4.0.5 and SAS version 9.4 (SAS Institute, Cary, North Carolina). A p value <.05 was considered statistically significant. Effect sizes (ES) were calculated using Cohen's d statistic, where an ES of 0.2 is considered small, 0.5 is considered moderate, and 0.8 is considered large.[23] Psychometric analyses were performed, i.e., confirmatory factor analyses, Cronbach's α calculations, test–retest reliability, convergent and divergent validity, known-groups validity, and responsiveness to change. The details of the performed analyses are described in Supplement S1.

Analyses of covariance were performed to compare the mean QLQ-C30 scales for functioning and global health status/HRQOL between patients with or without six selected key symptoms/worries adjusted for sex and age. The percentage of patients who reported symptoms and worries on the QLQ-NHL-HG29 and QLQ-NHL-LG20 was based on the number of patients who answered, "a little," "quite a bit," or "very much" on a certain item.[24] The evidence-based guideline for interpretation of the QLQ-C30 was used to determine clinically relevant differences between groups.[25]

RESULTS

Patients

In the years 2018–2021, a prospective sample of 768 patients was enrolled, of whom 423 diagnosed with HG-NHL and 345 diagnosed with LG-NHL. Patients were recruited from 12 countries. Mean age of patient with HG-NHL was 58 years, 55% was male, 51% was on treatment during baseline questionnaire completion, and mean time since diagnosis was 2.6 years. The mean age of the patients with LG-NHL was 62 years, 59% were male, 39% were on treatment during baseline questionnaire completion, and the mean time since diagnosis was 4.4 years. Additional patients' characteristics by NHL subtype are reported in Table 1. With respect to RCA and test–retest, respectively 94 and 125 patients were recruited with HG-NHL and, respectively, 49 and 124 with LG-NHL.

Compliance rates and debriefing results

HG-NHL

A total of 376 patients (89%) completed the QLQ-NHL-HG29 without missing any item. Item 7 ("Have you felt ill or unwell?") had the most missing data (N = 16, 4%).

The three conditional questions (items 27, 28, and 29) were completed by 72% (n = 304), 71% (n = 300), and 66% (n = 279), respectively.

TABLE 1 Sociodemographic and clinical characteristics of phase IV participating patients with high-grade and low-grade non-Hodgkin lymphoma.

	HG-NHL, N = 423 No. (%)	LG-NHL, N = 345 No. (%)
Country (language)		
Austria (German)	17 (4)	13 (4)
China (Chinese)	25 (6)	10 (3)
Croatia (Croatian)	48 (11)	24 (7)
France (French)	28 (7)	17 (5)
Germany (German)	13 (3)	10 (3)
Greece (Greek)	1 (0.2)	3 (1)
Italy (Italian)	26 (6)	23 (7)
Jordan (Jordanian Arabic)	50 (12)	45 (13)
Lithuania (Lithuanian)	30 (7)	5 (1)
Netherlands (Dutch)	70 (17)	75 (22)
Portugal (Portuguese)	54 (13)	51 (15)
United Kingdom (English)	61 (14)	69 (20)
Sociodemographic information		
Age (years), mean (SD), median, range	58.2 (16.1), 61, 18–99	62.0 (14.5), 63, 19–95
Sex		
Male	233 (55)	204 (59)
Female	190 (45)	140 (41)
Living arrangement		
Living with partner/family	355 (84)	274 (80)
Living with others	9 (2)	9 (3)
Living alone	49 (12)	57 (17)
Missing		5
Education		
No or primary school	36 (9)	32 (10)
Secondary education	165 (39)	146 (44)
Pre-university training, university	212 (50)	157 (47)
Missing		10
Employment		
Yes	166 (39)	123 (36)
No (incl. retired, homemaker)	255 (60)	217 (64)
Missing		5
Disease-related information		
Most common type of HG or LG-NHL		
DLBCL	312 (74)	–
FL	–	264 (77)

(Continues)

TABLE 1 (Continued)

	HG-NHL, *N* = 423 No. (%)	LG-NHL, *N* = 345 No. (%)
Treatment received		
Systemic therapy (chemo and/or immunotherapy)	409 (97)	264 (77)
Radiotherapy	105 (32)	46 (13)
Watchful waiting	—	54 (16)
Stem cell transplantation		
Other		3
Treatment line		
First	272 (64)	239 (69)
Subsequent	52 (12)	74 (21)
Unknown	99 (23)	32 (9)
On active treatment at time of baseline questionnaire		
Yes	215 (51)	134 (39)
No	197 (47)	211 (61)
Time since start last active treatment		
<3 months	215 (51)	66 (23)
3 months–1 year	61 (14)	70 (24)
>1 year	143 (34)	143 (49)
Missing		12 (4)
Not applicable (watchful waiting)		54
Time since diagnosis in years: mean (SD), median	2.6 (3.4), 1.2	4.4 (4.4), 3.2
<1 year	193 (46)	84 (24)
1–3 years	115 (27)	76 (22)
3–5 years	61 (14)	65 (19)
>5 years	54 (13)	113 (33)
Missing		7 (2)
Stage of disease (Ann Arbor)		
I	72 (17)	38 (11)
II	72 (17)	38 (11)
III	66 (16)	58 (17)
IV	188 (44)	152 (44)
Missing/not determined	25 (6)	59 (17)
IPI score		
Low risk (0–1 points)	143 (34)	—
Low-intermediate risk (2 points)	96 (23)	—
High-intermediate risk (3 points)	110 (26)	—
High-risk (4–5 points)	39 (9)	—
Missing	35 (8)	—

TABLE 1 (Continued)

	HG-NHL, *N* = 423 No. (%)	LG-NHL, *N* = 345 No. (%)
FLIPI score		
Low risk (0–1 points)	—	105 (30)
Intermediate risk (2 points)	—	69 (20)
High-risk (≥3 points)	—	75 (22)
Missing	—	96 (28)
Comorbidity		
No	136 (32)	119 (34)
1	131 (31)	92 (27)
2 or more	156 (37)	126 (37)
Unknown		7 (2)
Most common comorbidities		
Diabetes	51 (12)	28 (8)
Arthritis	24 (6)	34 (10)
Lung condition	34 (8)	31 (9)
High blood pressure	124 (29)	90 (26)
Heart condition	63 (15)	42 (12)
ECOG		
0	209 (49)	190 (55)
1	143 (34)	96 (28)
2	36 (9)	13 (4)
3	8 (2)	2 (1)
Missing	27 (7)	44 (13)

Note: Educational level was categorized as low (i.e., no/primary school), medium (i.e., lower general secondary education/vocational training), and high (i.e., pre-university education/high vocational training/university).

Abbreviations: DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular lymphoma international prognostic index; HG, high-grade; IPI, international prognostic index; LG, low-grade; NHL, non-Hodgkin lymphoma.

LG-NHL

A total of 338 patients (98%) completed the QLQ-NHL-LG20 without missing any item. Items 17 ("Have you worried about getting another type of cancer?") and 18 ("Have you worried about your treatment causing future health problems?") had the most missing data (*N* = 7, 2%). The two conditional questions (items 19 and 20) were completed by 68% and 67%, respectively.

The debriefing questionnaire was completed by 392 patients (93%) with HG-NHL and 319 patients (92%) with LG-NHL. Completion of the QLQ-NHL-HG29/QLQ-NHL-LG20 took on average 10/9 minutes and 84%/88% completed it in ≤15 minutes. Assistance was

provided to 20% of the patients (n = 81/n = 65), primarily with reading and/or writing. Patients needing assistance were mostly over 70 years of age and/or receiving treatment at time of questionnaire completion.

With respect to the QLQ-NHL-HG29, 25–28 patients (6%–7%) found at least one of the items confusing or upsetting. This primarily involved the items on worrying, recurrence, ability to work, and fertility. With respect to the QLQ-NHL-LG20, 20 patients (6%) found at least one of the questions confusing, and eight patients (2.5%) found at least one question upsetting. This primarily involved the items on worrying on future health, becoming dependent on others, and on recurrence.

Scale structure and reliability

Standardized factor loadings for the original 5-factor model for the QLQ-NHL-HG29 and 4-factor model for the QLQ-NHL-LG20 were all statistically significant and greater than 0.4 (Supplement S2). The models showed acceptable to good fit, and correlations between the factors ranged between 0.33–0.93, with the highest correlations between the symptom burden and physical condition/fatigue factors (both questionnaires). Cronbach's α was acceptable to good for all scales of the QLQ-NHL-HG29/QLQ-NHL-LG20 (Supplement S2).

Test–retest reliability

Test–retest reliability revealed no significant differences in responses over time. The ICCs were good to excellent for all scales and single conditional items of the QLQ-NHL-HG29 and QLQ-NHL-LG20 scales (Table 2).

Convergent validity

For both the QLQ-NHL-HG29 and QLQ-NHL-LG20, the scales predicted to be conceptually related, correlated substantially with one another (r > 0.4; Supplement S3). Furthermore, although not hypothesized a priori, the worries about health and functioning scale of the QLQ-NHL-HG29/QLQ-NHL-LG20 correlated substantially (r > 0.4) with social functioning and fatigue (QLQ-C30).

Known-group comparisons

Patients with an ECOG score ≥1 had statistically significant higher mean scores on the symptom burden (p < .01; ES = 0.81), neuropathy (p < .01; ES = 0.39), physical condition/fatigue (p < .01; ES = 0.90), and emotional impact (p < .01; ES = 0.71) scales of the QLQ-NHL-HG29 compared to patients with an ECOG score of 0. Similar results were observed for the QLQ-NHL-LG20 (Table 3).

TABLE 2 Test–retest validity of the scales and single items of the EORTC QLQ-NHL-HG29 and EORTC QLQ-NHL-LG20.

EORTC	ICC	95% CI, lower bound	95% CI, upper bound
QLQ-NHL-HG29 (N = 125)			
Scales			
SB	0.90	0.85	0.93
NP	0.88	0.83	0.92
PC	0.91	0.87	0.94
EI	0.90	0.86	0.93
WH	0.90	0.86	0.93
Single items (conditional)			
PW	0.85	0.77	0.90
WW	0.87	0.80	0.91
CC	0.93	0.89	0.96
QLQ-NHL-LG20 (N = 124)			
Scales			
SB	0.93	0.90	0.95
PC	0.91	0.88	0.94
EI	0.90	0.86	0.93
WH	0.92	0.88	0.94
Single items (conditional)			
PW	0.79	0.66	0.87
WW	0.88	0.80	0.93

Abbreviations: CC, concern about ability to have children; CI, confidence interval; EI, emotional impact; EORTC, European Organisation for Research and Treatment of Cancer; ICC, Intraclass correlation coefficient; NP, neuropathy; PC, physical condition/fatigue; PW, problems at work/place of study; QLQ-NHL-HG29, Quality of Life Questionnaire non-Hodgkin Lymphoma High-Grade 29; QLQ-NHL-LG20, Quality of Life Questionnaire non-Hodgkin Lymphoma Low-Grade 20; SB, symptom burden; WH, worries about health and functioning; WW, worries about work/study.

Furthermore, patients who were on treatment during completion of the baseline questionnaire had statistically significant higher mean scores on the symptom burden (p < .01; ES = 0.64), physical condition/fatigue (p < .01; ES = 0.51), and emotional impact scale (p < .01; ES = 0.35) and on the single conditional item concerning about the ability to have children (p = .03; ES = 0.27) of the QLQ-NHL-HG29 compared to those after/not on treatment. With respect to the QLQ-NHL-LG20, patients under watchful waiting had statistically significantly lower mean scores on the physical condition/fatigue (p < .01; ES = 0.48), emotional impact (p = .01; ES = 0.41) and worries about health and functioning (p = .02; ES = 0.37) scales and on the single conditional item regarding problems at work (p = .03; ES = 0.45) compared to those who received active treatment.

TABLE 3 Known-group comparisons of the scales and single items of the EORTC QLQ-NHL-HG29 and EORTC QLQ-NHL-LG20.

	ECOG performance status						On versus after treatment at baseline					
EORTC QLQ-NHL-HG29	Score = 0 *N* = 206, mean (SD)	Score = ≥1 *N* = 186, mean (SD)	*F* statistic	*p*	Difference between means	Cohen's *d* ES	On treatment *N* = 215, mean (SD)	After treatment *N* = 197, mean (SD)	*F* statistic	*p*	Difference between means	Cohen's *d* ES
Scales												
SB	17.6 (17.5)	32.9 (20.1)	23.0	<.01	15.3	0.81	30.5 (21.0)	18.2 (17.1)	41.1	<.01	12.6	0.64
NP	18.8 (26.7)	30.6 (33.6)	6.88	<.01	11.8	0.39	26.4 (31.8)	20.9 (28.0)	3.44	.06	5.5	0.18
PC	18.0 (20.9)	38.2 (24.0)	12.7	<.01	14.0	0.90	33.6 (25.1)	21.5 (22.3)	26.2	<.01	12.1	0.51
EI	19.4 (20.6)	36.5 (27.3)	27.9	<.01	17.1	0.71	32.4 (26.7)	23.6 (24.0)	12.2	<.01	8.8	0.35
WH	34.0 (25.9)	40.0 (26.4)	2.35	.07	6.0	0.23	38.6 (26.5)	35.3 (26.2)	1.56	.21	3.3	0.13
Single items (conditional)												
PW	16.7 (32.3)	22.2 (36.1)	2.03	.11	5.5	0.16	22.3 (36.6)	17.9 (31.8)	1.21	.27	4.4	0.13
WW	21.1 (21.5)	31.7 (39.1)	2.11	.09	10.6	0.33	28.4 (37.8)	25.6 (35.3)	0.41	.52	2.8	0.08
CC	15.2 (29.9)	13.1 (28.8)	2.02	.11	−2.1	0.07	10.6 (25.6)	18.4 (32.7)	4.73	.03	7.8	0.27

	ECOG performance status						Watchful waiting versus on or after active treatment					
EORTC QLQ-NHL-LG20	Score = 0 *N* = 190, mean (SD)	Score ≥1 *N* = 111, mean (SD)	*F* statistic	*p*	Difference between means	Cohen's *d* ES	Watchful waiting *N* = 54, mean (SD)	On/after active treatment *N* = 291, mean (SD)	*F* statistic	*p*	Difference between means	Cohen's *d* ES
Scales												
SB	17.8 (21.6)	30.5 (24.0)	8.46	<.01	12.7	0.56	17.6 (20.3)	22.7 (23.7)	2.22	.14	5.1	0.23
PC	18.9 (21.9)	34.5 (25.5)	12.7	<.01	15.6	0.66	15.4 (20.1)	26.1 (24.6)	9.01	<.01	10.7	0.48
EI	18.5 (23.3)	28.2 (26.7)	3.77	.01	9.7	0.39	13.5 (19.8)	22.8 (25.4)	6.50	.01	9.3	0.41
WH	34.7 (28.6)	34.6 (26.1)	0.14	.94	0.3	0.003	24.9 (23.5)	34.3 (27.8)	5.37	.02	9.4	0.37
Single items (conditional)												
PW	11.8 (26.0)	15.2 (30.2)	0.57	.63	3.4	0.12	4.3 (13.6)	14.6 (29.0)	4.74	.03	10.3	0.45
WW	22.8 (34.6)	18.4 (32.5)	0.39	.76	4.4	0.13	18.8 (31.3)	20.4 (33.1)	0.08	.78	1.6	0.05

Abbreviations: CC, concern about ability to have children; ECOG, Eastern Cooperative Oncology Group; EI, emotional impact; ES, effect size (an ES of 0.2 is considered small, 0.5 is considered moderate, and 0.8 is considered large); NP, neuropathy; PC, physical condition/fatigue; PW, problems at work/place of study; QLQ-NHL-HG29, quality of life questionnaire non-Hodgkin lymphoma high-grade 29; QLQ-NHL-LG20, quality of life questionnaire non-Hodgkin lymphoma low-grade 20; SB, symptom burden; WH, worries about health and functioning; WW, worries about work/study.

Responsiveness to change

Patients with HG-NHL who had a change in their clinical status (i.e., from "on treatment" to "after treatment ≥3 months") showed statistically significantly lower scores on the symptom burden ($p < .01$; ES = 0.46) and physical condition/fatigue ($p < .01$; ES = 0.37) of scales the QLQ-NHL-HG29. Scores on neuropathy, emotional impacts, and worries about health and functioning scales and on the three conditional single items remained relatively stable (Table 4).

Patients with LG-NHL who had a change in their clinical status showed statistically significantly lower scores on the physical condition/fatigue ($p < .01$; ES = 0.33) and emotional impact ($p = .01$; ES = 0.26) scales and on the conditional single item regarding worries about work or study ($p = .02$; ES = 0.43) of the QLQ-NHL-LG20. There was a trend toward lower scores on symptom burden ($p = .09$; ES = 0.19) whereas worries about health and functioning remained relatively stable.

Prevalence of symptoms and worries and their impact on HRQOL

The percentage of patients with HG-NHL who reported at least some symptoms and/or worries on items of the QLQ-NHL-HG29 ranged from 30% to 66% (Table 5) and from 22% to 73% for LG-NHL.

TABLE 4 Responsiveness to change of the scales and single items of the EORTC QLQ-NHL-HG29 ($N = 94$) and EORTC QLQ-NHL-LG20 ($N = 49$).

EORTC QLQ-NHL-HG29	T1 on treatment $N = 94$, mean (SD)	T2 ≥3 months after treatment $N = 94$, mean (SD)	t value	*p*	Difference between means	Cohen's *d* ES
Scales						
Symptom burden	30.1 (21.5)	22.1 (16.6)	4.46	<.001	8.0	0.46
Neuropathy	25.9 (31.1)	25.6 (31.8)	0.22	.83	0.3	0.01
Physical condition/fatigue	30.4 (24.2)	22.1 (20.0)	4.00	<.001	8.3	0.37
Emotional impacts	29.8 (25.9)	26.6 (25.8)	1.54	.13	3.2	0.16
Worries about health and functioning	35.3 (24.9)	31.5 (26.0)	1.84	.07	3.8	0.15
Single items (conditional)						
Problems at work/place of study	23.3 (37.0)	15.5 (31.3)	1.37	.18	7.8	0.23
Worries about work/study	25.6 (36.7)	24.9 (34.1)	0.43	.67	0.7	0.02
Concern about ability to have children	11.0 (24.3)	10.6 (26.3)	0.60	.55	0.4	0.02
EORTC QLQ-NHL-LG20	**T1 on treatment $N = 49$, mean (SD)**	**T2 ≥3 months after treatment $N = 49$, mean (SD)**	**t value**	***p***	**Difference between means**	**Cohen's *d* ES**
Scales						
Symptom burden	26.2 (27.1)	21.1 (26.0)	1.72	.09	5.1	0.19
Physical condition/fatigue	30.3 (26.9)	21.9 (23.7)	2.77	<.01	8.4	0.33
Emotional impacts	26.0 (29.4)	18.9 (25.8)	2.67	.01	7.1	0.26
Worries about health and functioning	39.2 (29.0)	37.9 (32.8)	0.47	.64	1.3	0.04
Single items (conditional)						
Problems at work/place of study	16.7 (32.9)	9.3 (26.0)	1.07	.29	7.4	0.25
Worries about work/study	28.6 (35.7)	14.9 (27.6)	2.56	.02	13.7	0.43

Abbreviations: ES, effect size (an ES of 0.2 is considered small, 0.5 is considered moderate, and 0.8 is considered large); QLQ-NHL-HG29, Quality of Life Questionnaire non-Hodgkin Lymphoma High-Grade 29; QLQ-NHL-LG20, Quality of Life Questionnaire non-Hodgkin Lymphoma Low-Grade 20.

Patient with HG-NHL who reported symptoms and worries had statistically significantly and clinically relevantly lower functioning and HRQOL compared to those without symptoms and worries (Figure 2). Similar results were observed for patients with LG-NHL (data not shown).

DISCUSSION

This study presents the final validation phase of the EORTC module development process and examined the psychometric properties of the QLQ-NHL-HG29 and QLQ-NHL-LG20 questionnaires in a large international cohort. Results showed that the questionnaires were well understood, easy to complete and perceived as relevant by patients with HG- or LG-NHL. The originally hypothesized factor models exhibited acceptable to good model–data fit. Furthermore, test–retest reliability, convergent validity, known-group comparisons, and responsiveness to change were demonstrated.

The highest (i.e., worst) scores of the QLQ-NHL-HG29/LG20 were observed on the worries about health and functioning scale, for both patients with HG- and LG-NHL. Emerging literature shows that worrying about the course and recurrence of the disease is a problematic (long-term) effect for lymphoma survivors. It impacts their HRQOL and functioning negatively and increases use of health services.[26-28] Importantly, the HG- and LG-NHL survivors who had completed treatment more than 3 months ago and patients with LG-NHL who were not actively treated reported worries about health and functioning, which has been observed previously in patients with CLL, another indolent lymphoid cancer.[24] These findings have important implications for patient-tailored care, encouraging health care providers to actively address and deal with patients worries and fears. For patients with severe worries, referral to psycho-oncology staff for supportive care has been shown to be effective.[29]

With respect to scores over time, most scale scores improved for both patients with HG- and LG-NHL, with better scores at ≥3 months after treatment compared with scores during treatment for symptom burden (although not statistically significant for LG-NHL), physical

TABLE 5 Prevalence of symptoms and worries of the EORTC QLQ-NHL-HG29 or EORTC QLQ-NHL-LG20.

Patients with HG-NHL, *N* = 423			Patients with LG-NHL, *N* = 345	
Yes, No. (%)	Item no. QLQ-NHL-HG29	Items of the EORTC QLQ-NHL-HG29 and EORTC QLQ-NHL-LG20	Item no. QLQ-NHL-LG20	Yes, No. (%)
222 (53)	1.	Muscle weakness	1.	151 (44)
240 (58)	2.	Aches or pains in your muscles or joints	2.	186 (54)
166 (40)	3.	Aches or pain in your bones		
126 (31)	4.	Dry cough		
226 (54)	5.	Dry mouth	3.	161 (47)
159 (38)	6.	Problems with sense of taste	4.	76 (22)
210 (52)	7.	Felt ill or unwell		
180 (44)	8.	Tingling hands or feet		
180 (44)	9.	Numbness fingers or toes		
197 (47)	10.	Shortness of breath on exertion	5.	145 (42)
196 (48)	11.	Setbacks in physical condition		
281 (67)	12.	Lack of energy	6.	214 (62)
210 (50)	13.	Felt drowsy	7.	153 (44)
218 (52)	14.	Sudden tiredness	8.	149 (43)
211 (51)	15.	Mood changes		
216 (52)	16.	Lack of confidence body	9.	130 (38)
		Restless or agitated	10.	143 (42)
232 (56)	17.	Dissatisfied how body functioning	11.	164 (48)
221 (53)	18.	Difficulty accepting disease	12.	134 (39)
258 (62)	19.	Worried about picking up an infection	13.	192 (56)
325 (78)	20.	Worried about your health in the future	14.	249 (73)
318 (77)	21.	Worried about recurrence of your disease	15.	225 (66)
250 (61)	22.	Worried about becoming chronically ill		
266 (64)	23.	Worried about becoming dependent on others	16.	184 (54)
237 (57)	24.	Worried about getting another type of cancer	17.	165 (49)
256 (62)	25.	Worried about your treatment causing future health problems	18.	180 (53)
214 (52)	26.	Worried about damage to your heart and blood vessels		
91 (30)	27.	If applicable: problems at your work or place of study	19.	52 (22)
128 (43)	28.	If applicable: worried about not being able to continue working or your education	20.	78 (34)
63 (23)	29.	If applicable: concerned about ability to have children		

Note: Percentage "Yes" was categorized when patients answered, "a little," "quite a bit," or "very much" on a certain item.

Abbreviations: HG, high-grade; LG, low-grade; NHL, non-Hodgkin lymphoma; QLQ-NHL-HG29, quality of life questionnaire non-Hodgkin lymphoma high-grade 29; QLQ-NHL-LG20, quality of life questionnaire non-Hodgkin lymphoma low-grade 20.

condition/fatigue and emotional impact (although not statistically significant for HG-NHL). Regarding LG-NHL, a smaller sample was available for RCA, because of relatively few changes in clinical status in LG-NHL due to long-term treatment. This could have hampered the evaluation of the responsiveness of the questionnaire in observing statistically significant differences.

In contrast to the reported improvements in symptom burden and physical condition/fatigue, worries about health and functioning and neuropathy (HG-NHL only) did not improve over time. Chemotherapy-induced peripheral neuropathy (CIPN) is a common side-effect of specific lymphoma chemotherapies such as vincristine.[30] Currently, there are no evidence-based preventive strategies

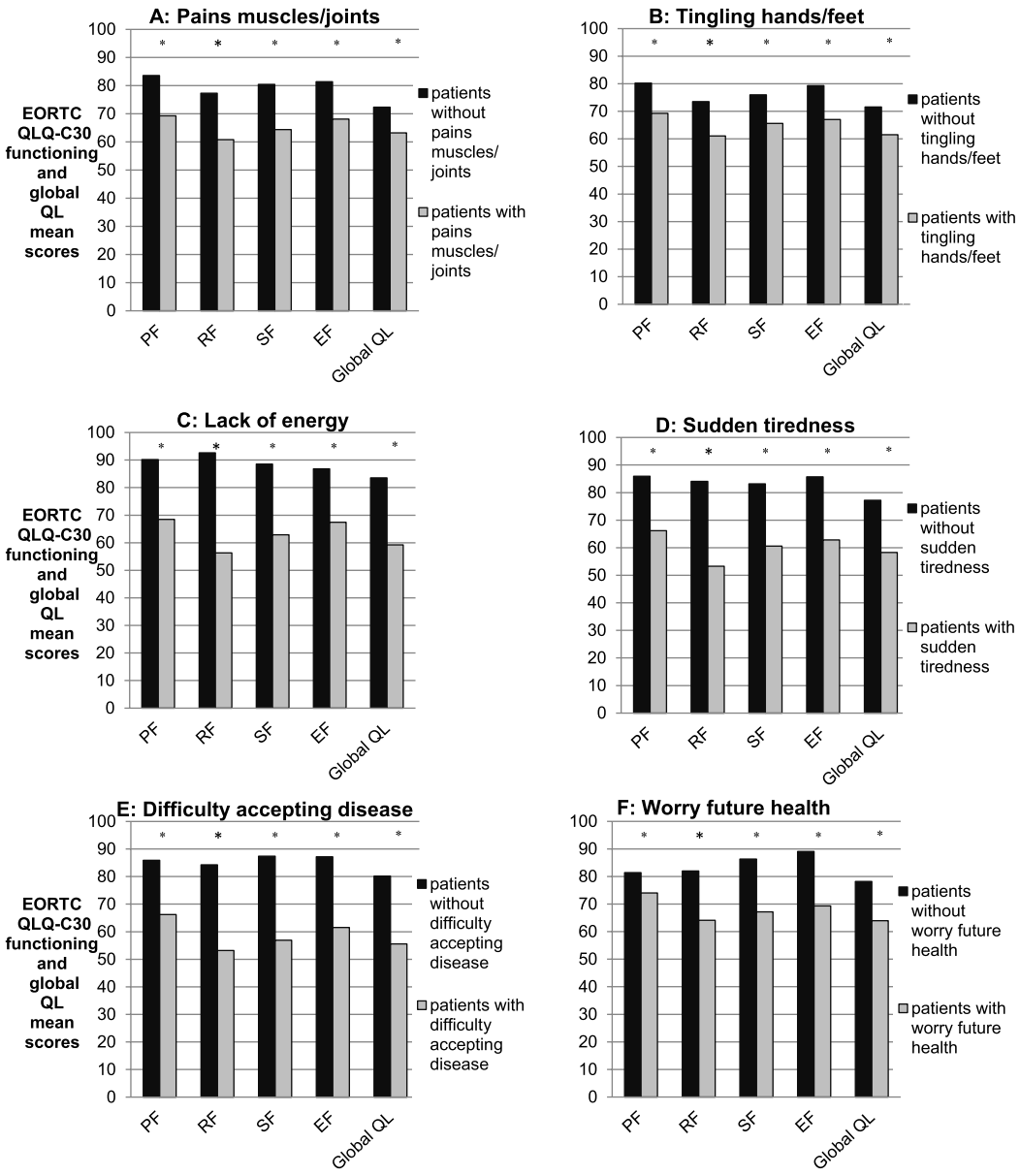

FIGURE 2 EORTC QLQ-C30 functioning and global QL scores of HG-NHL patients with and without symptoms and/or worries.

for CIPN and only limited options for treatment.[31] Because CIPN has a negative impact on functioning and HRQOL, routine monitoring of neuropathy symptoms and evaluation of their severity with patients during treatment is therefore of utmost importance.

A limitation of the study was, although the total sample was large, the samples per countries were too small to perform country-specific psychometric evaluation (e.g., DIF analyses). This could be explored in more detail in future research. With respect to LG-NHL, a part of patients will follow a watchful waiting policy whereas others will undergo chemoimmunotherapy or targeted therapies. The questionnaire was developed for all patients with LG-NHL and some treatment specific symptoms such as neuropathy are not included. To account for these or possible (future) treatment-related symptoms the QLQ-NHL-LG20 can be complemented with for example items on bone pains and neuropathy from the EORTC Item Library when applicable to the specific treatment. The Item Library is a repository of over 950 unique items and available in many languages and was developed to facilitate flexible and timely measurement of symptoms.[32] In the context of clinical trials and comparative studies, selection of key items from this library may be particularly helpful.

A key strength of this study was the generalizability of our results as a large and cultural heterogeneous sample of lymphoma patients was included from a high number of international participating countries. The recruited sample was representative for the LG- and HG-NHL population with respect to sociodemographic and clinical characteristics. Furthermore, the QLQ-NHL-HG29 and the QLQ-NHL-LG20 were developed for all patients with HG- or LG-NHL,

respectively, in the modern treatment landscape of current NHL therapies. This has greatly increased their accuracy in capturing the most relevant HRQOL aspects for NHL patients currently seen in routine practice. These PRO measures can therefore be used in clinical trials to evaluate treatments' effects on HRQOL and in daily clinical practice to help clinicians identify specific HG- or LG-NHL symptoms that require further examination and discussion with the patient. The scoring algorithm for generating the QLQ-NHL-HG29 and QLQ-NHL-LG20 scale scores is available via the EORTC Quality of Life Group's website (http://groups.eortc.be/qol). Separate items may be used to calculate the frequency of issues, although use of the multi-item scales enlarges the reliability.

In conclusion, this large-scale international study supports the validity and clinical utility of two newly developed PRO measures for patients with HG-NHL (EORTC QLQ-NHL-HG29) and for patients with LG-NHL (EORTC QLQ-NHL-LG20). The use of these disease-specific questionnaires, in conjunction with the EORTC QLQ-C30, makes it feasible to assess most relevant aspects of the well-being of patients with NHL, and to respond to new issues resulting from the ongoing development of new therapies for these patients. Implementation of these specific NHL questionnaires in research and practice is expected to further increase quality of PRO research and to generate clinically relevant data that can be used to better inform treatment decision-making.

AUTHOR CONTRIBUTIONS

Simone Oerlemans: Research study design, included patients, performed research, analyzed data, and wrote the manuscript. **Fabio Efficace:** Research study design, included patients, and performed research. **Charalampia Kyriakou:** Research study design, included patients, and performed research. **Ana Carolina Freitas:** Included patients and performed research. **Omar Shamieh:** Included patients and performed research. **Carien L. Creutzberg:** Research study design, included patients, and performed research. **Jens Lehmann:** Included patients and performed research. **Duska Petranovic:** Research study design, included patients, and performed research. **Eva Nagele:** Included patients and performed research. **Anne Bredart:** Research study design, included patients, and performed research. **Dong Dong:** Included patients and performed research. **Christian W. Scholz:** Included patients and performed research. **Giovanni Caocci:** Included patients and performed research. **Stefano Molica:** Included patients and performed research. **Laimonas Griskevicius:** Included patients and performed research. **Aliki Xochelli:** Included patients and performed research. **Jacobien M. Kieffer:** Analyzed data. **Joost A. Agelink van Rentergem:** Included patients, performed research, and analyzed data. **Anja Mueller:** Included patients and performed research. **Maria Gomes Da Silva:** Included patients and performed research. **Filipa Alves da Costa:** Included patients and performed research. **Sandra Malak:** Included patients and performed research. **Kim Cocks:** Research study design. **Lonneke V. van de Poll-Franse:** Research study design. All authors critically revised the article and approved the submitted and final version of the manuscript.

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ACKNOWLEDGMENTS

The following are additional members of the EORTC Quality of Life Group: Bayan Inserat (King Hussein Cancer Center, Amman, Jordan) Corine M. H. de Jong (Leiden University Medical Center, Leiden, the Netherlands), Monika Sztankay (University Hospital of Psychiatry II, Medical University of Innsbruck, Innsbruck, Austria), Lucia Neppl

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CONFLICT OF INTEREST STATEMENT

Filipa Alves da Costa reports consulting fees from the Instituto Português de Oncologia de Lisboa. Fabio Efficace reports consulting fees from AbbVie, Incyte Corporation, Janssen Pharmaceuticals, Inc, Novartis, and Syros. Maria Gomes da Silva reports fees from the Portuguese Association Against Leukemia and the Portuguese Society of Hematology. Jens Lehmann reports consulting fees from Evaluation Software Development. Sandra Malak reports fees from Marie Curie Cancer Care. Christian W. Scholz reports fees from AbbVie Deutschland, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hozmann-La Roche, Fondation Sanofi Espoir, Incyte Corporation, Merck Sharp and Dohme, Novartis, and Takeda Oncology; and travel fees from BeiGene, Ltd.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Oerlemans S, Efficace F, Kyriakou C, et al. International validation of two EORTC questionnaires for assessment of health-related quality of life for patients with high-grade non-Hodgkin lymphoma (QLQ-NHL-HG29) and low-grade non-Hodgkin lymphoma (QLQ-NHL-LG20). *Cancer*. 2023;129(17):2727-2740. doi:10.1002/cncr.34822