Original Study

Improvements in Patient-Reported Outcomes in Relapsed or Refractory Large B-Cell Lymphoma Patients Treated With Epcoritamab

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Abstract

The impact of cancer therapies on health-related quality of life is an important consideration in treatment decision-making. Patient-reported outcomes were evaluated in a clinical trial of patients with relapsed/refractory large B-cell lymphoma treated with epcoritamab monotherapy (N = 157). Patients reported consistent, marked improvements in lymphoma symptoms, health-related quality of life, and satisfaction with epcoritamab, complementing its favorable clinical efficacy and safety.

Background: Patient-reported outcomes were evaluated in EPCORE NHL-1 in patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) treated with epcoritamab monotherapy (NCT03625037). **Materials and Methods:** Adults with R/R CD20$^+$ LBCL and ≥2 prior systemic antilymphoma therapies, including anti-CD20, completed the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) and EQ-5D-3L. A subgroup of patients provided additional feedback in one-on-one qualitative interviews. FACT-Lym and EQ-5D-3L score changes from baseline (CFB) to cycle 9 or end of treatment were interpreted using published minimally important differences (MID). **Results:** In total, 157 patients (88.5% with diffuse LBCL) were treated (median age, 64 years). In total, 70.7% had ≥3 prior treatments, 61.1% had primary refractory disease, and 82.8% were refractory to last systemic therapy. FACT-Lym scores exceeded MID thresholds: mean (SD) CFB were 4.4 (15.2), MID 3.0 to 7.0 (FACT-General); 5.9 (7.6), MID 2.9 to 5.4 (FACT-Lymphoma subscale); 8.4 (15.2), MID 5.5 to 11.0 (FACT-Trial Outcome Index); 10.3 (20.2), MID 6.5 to 11.2 (FACT-Lym total score). EQ-5D-3L index scores, 0.09 (0.20), MID 0.08, and EQ-VAS scores, 16.6 (22.8), MID 7.0, improved. In 20 qualitative interviews, 88.2% reported symptom improvements; 80.0% were "very satisfied" or "satisfied" with epcoritamab. **Conclusions:** R/R LBCL patients reported consistent, clinically meaningful improvements in symptoms and HRQoL and satisfaction with epcoritamab.

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Keywords: Bispecific antibodies, EQ-5D-3L, FACT-Lym, Health-related quality of life, Qualitative data

Introduction

Large B-cell lymphoma (LBCL) is a non-Hodgkin lymphoma (NHL) subset composed of several subtypes, including diffuse LBCL (DLBCL, not otherwise specified [NOS], including transformed DLBCL), follicular lymphoma (FL) grade 3B, high-grade B-cell lymphoma (HGBL), and primary mediastinal B-cell lymphoma (PMBCL).[1,2] DLBCL is the most common subtype, accounting for 30% of all NHL cases.[2] The estimated annual number of new DLBCL cases in the United States is 5.6 per 100,000,[3] and the estimated national prevalence is 63 883 to 142 889 cases.[4] DLBCL is an aggressive lymphoma,[5] and patients with relapsed or refractory (R/R) DLBCL often experience poor health-related quality of life (HRQoL), owing to both disease symptoms and treatment.[6,7]

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Unfortunately, there is no clearly defined standard of care in later-line (3L+) treatment settings, although several options exist.[8] Patients who progress after or fail ≥2 lines of therapy (LOTs) may benefit from treatments recently approved by the US Food and Drug Administration (FDA), such as CD3xCD20 bispecific antibodies, chimeric antigen receptor T-cell (CAR T), loncastuximab tesirine, polatuzumab vedotin, selinexor, or tafasitamab plus lenalidomide.[9-15] Other options include investigational treatments, chemoimmunotherapy regimens, palliative radiation therapy, or best supportive care.[8]

Epcoritamab is a readily available subcutaneous (SC) T-cell–engaging CD3xCD20 bispecific antibody that has received regulatory approvals in the United States, Europe, and Japan; in the United States, epcoritamab is approved for the treatment of DLBCL, NOS, including DLBCL arising from indolent lymphoma, and HGBL, after ≥2 lines of systemic therapy.[15-18] The pivotal, single-arm, phase II EPCORE NHL-1 study (NCT03625037) demonstrated deep and durable responses and favorable long-term outcomes including survival in a challenging-to-treat population of patients with 3L+ (D)LBCL.[19] In this study, adults with R/R CD20$^+$ LBCL received epcoritamab as 1-mL SC injections once weekly in 28-day cycles for cycles 1 to 3, once every 2 weeks in cycles 4 to 9, and once every 4 weeks in cycles 10 and beyond, until disease progression or unacceptable toxicity.[19,20] As of January 31, 2022, 157 patients were enrolled and treated. At a median follow-up of 10.7 months, the overall response rate was 63.1% (95% CI, 55.0-70.6) and the complete response (CR) rate was 38.9% (95% CI, 31.2-46.9).[20] At a median follow-up of 20 months, median duration of CR was 20.8 months, median overall survival for patients who experienced CR was not reached; and 91% were still in CR at 9 months.[21] The trial demonstrated that epcoritamab has a manageable safety profile, with few discontinuations due to adverse events. Cytokine release syndrome, which is an expected class effect, was predominantly low-grade and had a predictable onset.[20]

HRQoL, which has been shown to worsen with increasing number of prior LOTs, is an important consideration in treatment decision-making.[7,22,23] With more treatments becoming available for patients with R/R LBCL, patients and clinicians face challenging, complex choices regarding treatment selection.[23] Patient-reported outcomes (PROs) and HRQoL provide a unique patient-centric perspective on the impact of cancer therapies and have been identified as key components of improved healthcare delivery.[23] The value and increasing importance of PROs in determining treatment benefit in cancer research has also been endorsed by regulatory bodies, including the FDA and the European Medicines Agency.[23] Therefore, in addition to clinical safety and efficacy, EPCORE NHL-1 explored the impact of epcoritamab on PROs, patients' well-being, and HRQoL.

The objective of this study was to evaluate PROs related to lymphoma symptoms, well-being, and overall HRQoL based on Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) and 3-level EQ-5D (EQ-5D-3L) changes among patients treated with epcoritamab in the EPCORE NHL-1 study. A subgroup of patients also participated in qualitative interviews to provide detailed feedback on their experience with epcoritamab.

Methods

Study Design

EPCORE NHL-1 is a global, single-arm, open-label, phase II study of SC epcoritamab in patients with R/R LBCL, registered on ClinicalTrials.gov (NCT03625037).[16,19] Full study details and patient eligibility criteria are described elsewhere.[16] In brief, eligible patients were age ≥18 years with pathologically confirmed CD20$^+$ mature B-cell non-Hodgkin lymphoma—including patients with de novo or transformed DLBCL (including double/triple-hit), HGBL, PMBCL, or FL grade 3B. Patients were required to have measurable disease and previous treatment with ≥2 systemic therapies, including an anti-CD20 monoclonal antibody–containing regimen, and had either failed or were ineligible for autologous stem cell transplant (ASCT). Patients with prior CAR T were eligible if ≥30 days had elapsed since last treatment.[16,20,24] Patients were excluded if they had primary central nervous system lymphoma or central nervous system involvement, or if they were eligible for curative intensive salvage therapy followed by high-dose chemotherapy with ASCT.[24] Patients were treated until disease progression or unacceptable toxicity.[20] EPCORE NHL-1 was conducted in accordance with the guidelines on good clinical practice put forth by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki. Site-specific institutional review board or institutional ethics committee approval was obtained before study initiation.[16]

Data Collection and PRO Assessments

Patients enrolled in EPCORE NHL-1 who received ≥1 dose of epcoritamab completed the FACT-Lym and EQ-5D-3L assessments at baseline, on day 1 of cycles 3, 5, 7, and 9, and at the end of treatment (time of drug discontinuation).

FACT-Lym captures clinically relevant, disease-specific symptomatic burden and well-being in lymphoma, including DLBCL.[25] Components of this assessment include the Lymphoma subscale (Lym S), FACT-General (FACT-G), FACT-Trial Outcome Index (FACT-TOI), and FACT-Lym total score (FACT-Lym TS).[25] The Lym S has a single domain consisting of 15 items specific to lymphoma burden. This domain assesses disease and treatment-related symptoms, including fatigue, fever, insomnia, itching, loss of appetite, night sweats, swelling, weight loss, and pain, with a score ranging from 0 to 60.[26] FACT-G has 4 well-being domains, physical (7 items), social/family (7), emotional (6), and functional (7), with scores ranging from 0 to 108.[25] FACT-TOI combines FACT-G's physical and functional domains with Lym S, with scores ranging from 0 to 116. Last, FACT-Lym TS combines FACT-G with Lym S, with scores ranging from 0 to 168.[25,26] For FACT-Lym and its components, higher scores indicate better HRQoL.[25]

EQ-5D-3L, a widely used measure of general HRQoL, has been validated for use in general populations and can be used in specific diseases to estimate the value of different health states. EQ-5D-3L has 5 dimensions: anxiety/depression, mobility, pain/discomfort, self-care, and usual activities. In the 3L version, each dimension has 3 response levels: 1, no problems; 2, some problems; 3, extreme problems. On this measure, patients indicate their health state by selecting the most appropriate response level for each dimension. A

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patient's responses yield a combination of 5 levels of overall health state at the time. Value sets for the UK general population are then used to generate the derived health state. EQ-5D-3L also includes the EQ visual analog scale (EQ-VAS), which patients use to score their health from *worst health imaginable* (0) to *best health imaginable* (100).[27]

Qualitative Interviews

Clinical trial participants at a subset of sites were invited to take part in a voluntary in-depth, qualitative telephone interview scheduled to occur approximately 14 days after the cycle 10 visit or end of treatment, whichever came first. The objective of the qualitative interviews was to understand any patient-reported symptom improvements that occurred with epcoritamab from baseline, as well as treatment impacts and patient satisfaction with treatment. The interviews, which followed a semistructured interview guide, began with general, open-ended questions about the patient's treatment experiences. Patients were then asked about the study treatment benefits, negative impacts, and outcomes, including any improvements observed. The impacts of treatment with epcoritamab included those related to patients' daily activities (eg, work, household chores, errands), physical functioning (eg, ability to move around, exercise), social functioning (eg, friend/family relationships, activities), and emotional functioning (eg, fear, worry, anxiety, stress, depression). Interviews lasted approximately 60 minutes and were audio-recorded.

Statistical Analysis

Patient compliance to completing PRO instruments was defined as the proportion of patients who provided a PRO response at each time point during treatment. Mean changes in FACT-Lym, EQ-5D-3L index, and EQ-VAS scores were calculated from baseline through cycle 9 day 1 and/or end of treatment (for patients whose disease later progressed or who discontinued treatment). For the calculation of PRO scores, missing items within an available PRO instrument were handled according to the guidelines defined by the authors of the instruments. Data analysis was performed with SAS software version 9.4 (SAS Institute, Cary, NC).

Qualitative interview data were analyzed with a thematic qualitative data analysis approach. Coding and analysis were performed with Microsoft Excel.

Minimally Important Differences. Changes in patients' PRO assessment scores were interpreted according to published ranges of minimally important difference (MID) thresholds. MID represents the minimum instrument score needed to indicate a perceived therapeutic benefit.[28] The literature identifies MID ranges of 2.9 to 5.4 for Lym S, 3.0 to 7.0 for FACT-G, 5.5 to 11.0 for FACT-TOI, and 6.5 to 11.2 for FACT-Lym TS.[26] For EQ-5D-3L and EQ-VAS, respectively, thresholds of 0.08 and 7.0 were considered MID.[29,30]

Results

Patient Characteristics

As of January 31, 2022, a total of 157 patients with LBCL (DLBCL, 88.5%; HGBL, 5.7%; FL grade 3B, 3.2%; PMBCL, 2.5%) were enrolled in EPCORE NHL-1 and treated with ≥1 dose of epcoritamab. Table 1 lists patients' baseline characteristics. Median (range) age was 64 (20-83) years; 49.0% of patients were age ≥65 years, and 18.5% were age ≥75 years. Patients' median number (range) of prior LOTs was 3 (2-11): 70.7% had ≥3 prior LOTs, 61.1% were primary refractory, 82.8% were refractory to most recent systemic therapy, and 75.8% were refractory to ≥2 consecutive LOTs. Approximately 39% of patients received CAR T therapy previously; of these patients, 75% were refractory to CAR T.

Table 1 Patient Baseline Demographic and Clinical Characteristics

Characteristic	Patients (N = 157)
Age, y, median (range)	64 (20-83)
Age ≥65 y, %	49.0
Age ≥75 y, %	18.5
Years from initial diagnosis, median	1.6
ECOG performance status 0/1, %	96.8
Disease type at trial entry, %	
DLBCL	88.5
HGBL	5.7
FL grade 3B	3.2
PMBCL	2.5
Double/triple hits in *c-MYC/BCL2/BCL6* genes, % (n/N)	13.1 (13/99)
Prior ASCT, %	19.7
Progressed ≤12 mo after ASCT, %	58.1
Prior CAR T, %	38.9
Progressed ≤6 mo after CAR T, %	75
Prior lines of therapy, median (range)	3 (2–11)
Prior lines of therapy, %	
2 lines	29.3
3 lines	31.8
≥4 lines	38.9
Primary refractory, %	61.1
Refractory to last-line systemic antineoplastic therapy, %	82.8
Refractory to ≥2 consecutive lines of prior antilymphoma therapy, %	75.8
Relapsed after last-line systemic antineoplastic therapy, %	17.2

Abbreviations: ASCT = autologous stem cell transplant; CAR T = chimeric antigen receptor T-cell; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; HGBL = high-grade B-cell lymphoma; PMBCL = primary mediastinal B-cell lymphoma.

Compliance

From baseline through cycle 9, compliance rates were ≥81.8% (FACT-Lym) and ≥90.8% (EQ-5D-3L), apart from cycle 3 (FACT-Lym, 35.8%, 39/109 patients; EQ-5D-3L, 37.6%, 41/109 patients) (Table 2). The lower cycle 3 compliance rate is attributable to PRO collection not being required at this time point in an older version of the protocol (it was added in a protocol amendment).

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Table 2 Patient Compliance to PRO Assessments Throughout Study

Time point, n/N (%)	FACT-Lym (N = 157)	EQ-5D-3L (N = 157)
Baseline/C1D1	140/157 (89.2)	146/157 (93.0)
C3D1[a]	39/109 (35.8)	41/109 (37.6)
C5D1	72/84 (85.7)	78/84 (92.9)
C7D1	56/65 (86.2)	59/65 (90.8)
C9D1	45/55 (81.8)	50/55 (90.9)
End of treatment	50/92 (54.3)	55/92 (59.8)

Note: Percentage calculations based on number of eligible patients at each time point.
Abbreviations: C = cycle; D = day; EQ-5D-3L = 3-level EQ-5D; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; PRO = patient-reported outcome.
[a] PRO response collection was omitted for cycle 3 in a protocol version and reinstated upon protocol amendment.

Table 3 FACT-Lym and EQ-5D-3L MIDs and Assessment Scores

FACT-Lym Assessment	MID[26,29]	Baseline Score, Mean (SD), All Patients N = 140	C9D1 Score, Mean (SD), All Patients N = 45	EOT Score, Mean (SD), Patients Who Progressed or Discontinued Treatment N = 50	Change From Baseline to C9D1, Mean (SD), All Patients
N	—	140	45	50	41
Lym S	2.9-5.4	42.2 (10.0)	51.1 (6.4)	43.7 (9.8)	5.9 (7.6)
FACT-G	3.0-7.0	76.2 (16.9)	85.1 (15.1)	74.4 (16.9)	4.4 (15.2)
FACT-TOI	5.5-11.0	79.5 (19.9)	94.0 (13.8)	80.4 (19.6)	8.4 (15.2)
FACT-Lym TS	6.5-11.2	118.4 (25.5)	136.2 (19.4)	118.1 (25.5)	10.3 (20.2)
N	—	129	50	55	48
EQ-5D-3L index score	0.08	0.73 (0.28)	0.87 (0.17)	0.65 (0.34)	0.09 (0.20)
EQ-VAS	7.0	62.4 (22.6)	81.4 (15.0)	63.0 (22.0)	16.6 (22.8)

Abbreviations: C9D1 = cycle 9 day 1; EOT = end of treatment; EQ-5D-3L = 3-level EQ-5D; EQ-VAS = EQ visual analog scale; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; G = General; Lym S = Lymphoma subscale; Lym TS = Lymphoma total score; MID = minimally important difference; SD = standard deviation; TOI = Trial Outcome Index.

FACT-Lym

Mean FACT-Lym scores improved from baseline to cycle 9 day 1, with all score changes at cycle 9 day 1 exceeding the lower MID bounds (Table 3). LymS scores also exceeded upper MID bounds. Among patients who later progressed and/or discontinued treatment, mean FACT-Lym scores at the end of treatment remained comparable to those at baseline. Figure 1 shows mean FACT-Lym score changes from baseline to each time point for all patients with LBCL or DLBCL. For both groups, starting at cycle 3 day 1, all improvements in Lym S, FACT-G, and FACT-Lym TS scores were clinically meaningful, as they exceeded the lower bounds of published MID ranges. This was also true for FACT-TOI, starting at cycle 5 day 1.

EQ-5D-3L

Mean EQ-5D-3L index scores improved from baseline to cycle 9 day 1, exceeding the MID at cycle 9 day 1 (Table 3). Improvements in mean EQ-VAS scores were more pronounced at cycle 9 day 1 and also exceeded the MID. Among patients who later progressed and/or discontinued treatment, mean EQ-5D-3L index scores and EQ-VAS scores at the end of treatment remained comparable to those at baseline. Figure 2 illustrates the mean changes from baseline in EQ-5D-3L index scores and EQ-VAS scores at each time point for all patients with LBCL and all those with DLBCL. For both groups, there was a trend of improvement in EQ-5D-3L index scores, with changes exceeding the MID only at cycle 9 day 1. For EQ-VAS scores, however, all improvements were clinically meaningful, starting from cycle 3 day 1, in that they exceeded the MID.

Qualitative Interviews

A total of 20 patients completed qualitative interviews, of which 14 (70%) completed cycle 10 and 6 (30%) terminated earlier. The interview sample was evenly split between males and females. Mean (range) age was 66 (21-84) years.

Symptom Improvements. Three (15%) of the 20 patients reported they did not have any cancer symptoms before starting epcoritamab (at baseline) (Table 4). Of the 17 patients (85%) with ≥1 symptom at baseline, 15 (88.2%) reported seeing improvements in ≥1 symptom with epcoritamab; the other 2 patients (11.8%), who terminated the study early, did not. Of the 15 patients who reported improvements, 12 (80%) experienced improvements in ≥2 symptoms. With respect to symptom severity, all patients who reported improvements stated their current (improved) symptom severity level was either mild or no symptoms at all (Supplemental Table 1).

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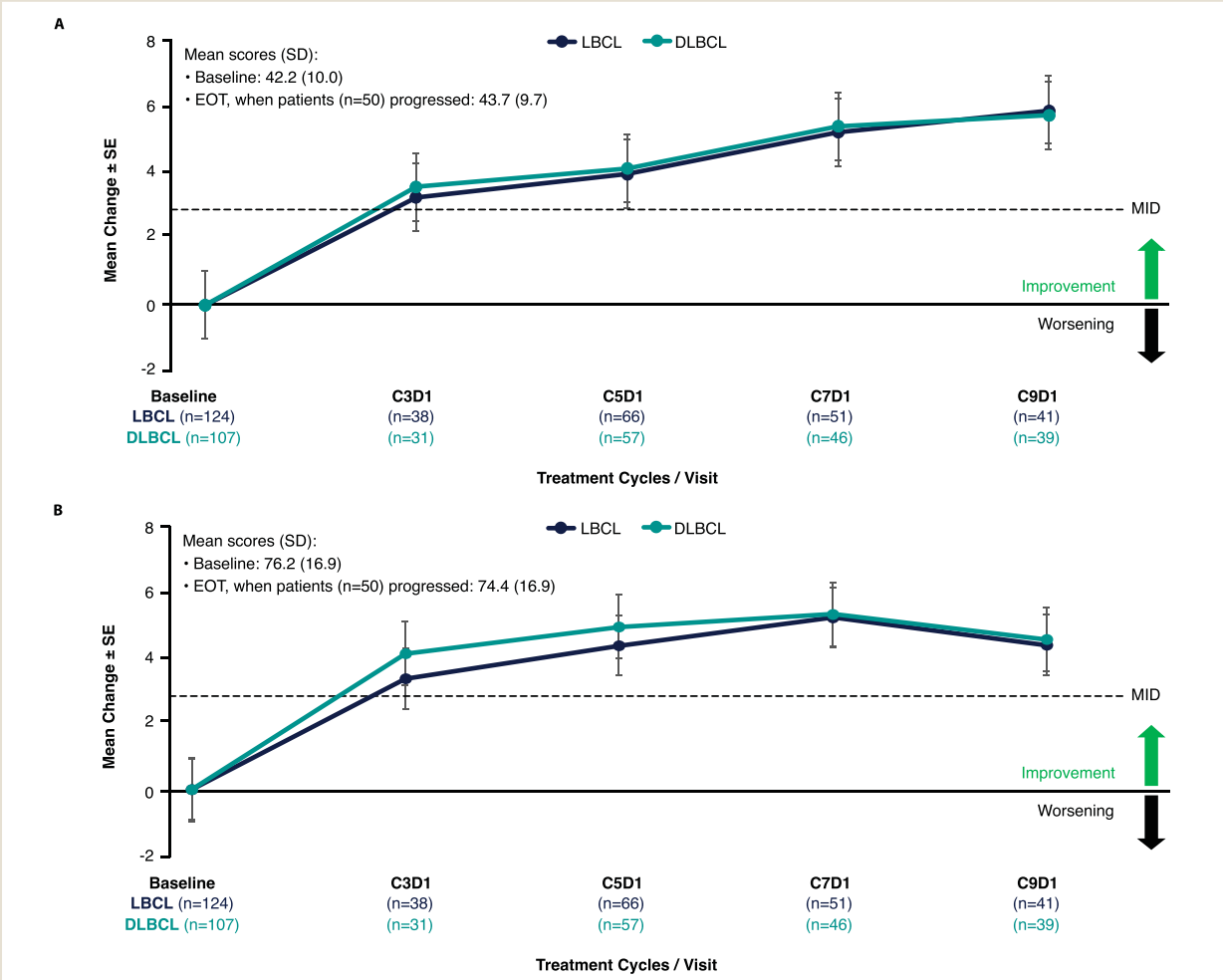
Figure 1 Mean change from baseline in (A) Lym S, (B) FACT-G, (C) FACT-TOI, and (D) FACT-Lym TS. MID line for each figure represents the lower bounds of previously published MIDs for the FACT-Lym.
Abbreviations: C = cycle; D = day; DLBCL = diffuse large B-cell lymphoma; EOT = end of treatment; FACT-G = Functional Assessment of Cancer Therapy–General; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; FACT-Lym TS = Functional Assessment of Cancer Therapy–Lymphoma total score; FACT-TOI = Functional Assessment of Cancer Therapy–Trial Outcome Index; LBCL = large B-cell lymphoma; Lym S = Lymphoma subscale; MID = minimally important difference; SD = standard deviation; SE = standard error.



Impact of treatment. At least 18 of the 20 patients (90%) provided feedback on treatment impacts (Supplemental Table 2 for participant quotes). With respect to daily activities (n = 18), 61.1% of patients reported positive impacts and 38.9% reported no change with epcoritamab. For physical functioning (n = 16), patients reported positive impacts (7, 43.8%), no change (7, 43.8%), or negative impacts (2, 12.5%). For emotional functioning (n = 18), patients reported positive impacts (7, 38.9%), no change (10, 55.6%), or negative impacts (1, 5.6%). For social functioning (n = 17), patients reported positive impacts (7, 41.2%) or no change (10, 58.8%).

Satisfaction With Treatment. Sixteen patients reported being either very satisfied (11, 55.0%) or satisfied (5, 25.0%) with epcoritamab treatment (this group included 3 patients who terminated the study early) (Supplemental Table 2 for participant quotes). Of the remaining 4 patients, 2 (10.0%) reported being dissatisfied (1 terminated early), 1 (5.0%) reported being neither satisfied nor dissatisfied with treatment (this patient terminated early), and 1 (5.0%) terminated early and was unable to provide a response.

Discussion

In a group of patients with heavily pretreated R/R LBCL in EPCORE NHL-1, treatment with SC epcoritamab not only provided clinical benefit but also consistent and clinically meaningful improvements in lymphoma symptoms and HRQoL based on FACT-Lym and EQ-VAS. In both the overall patient group and the DLBCL subgroup, these improvements exceeded published MIDs throughout the study. Of note, this study population included challenging-to-treat patients with highly refractory disease.[19] In

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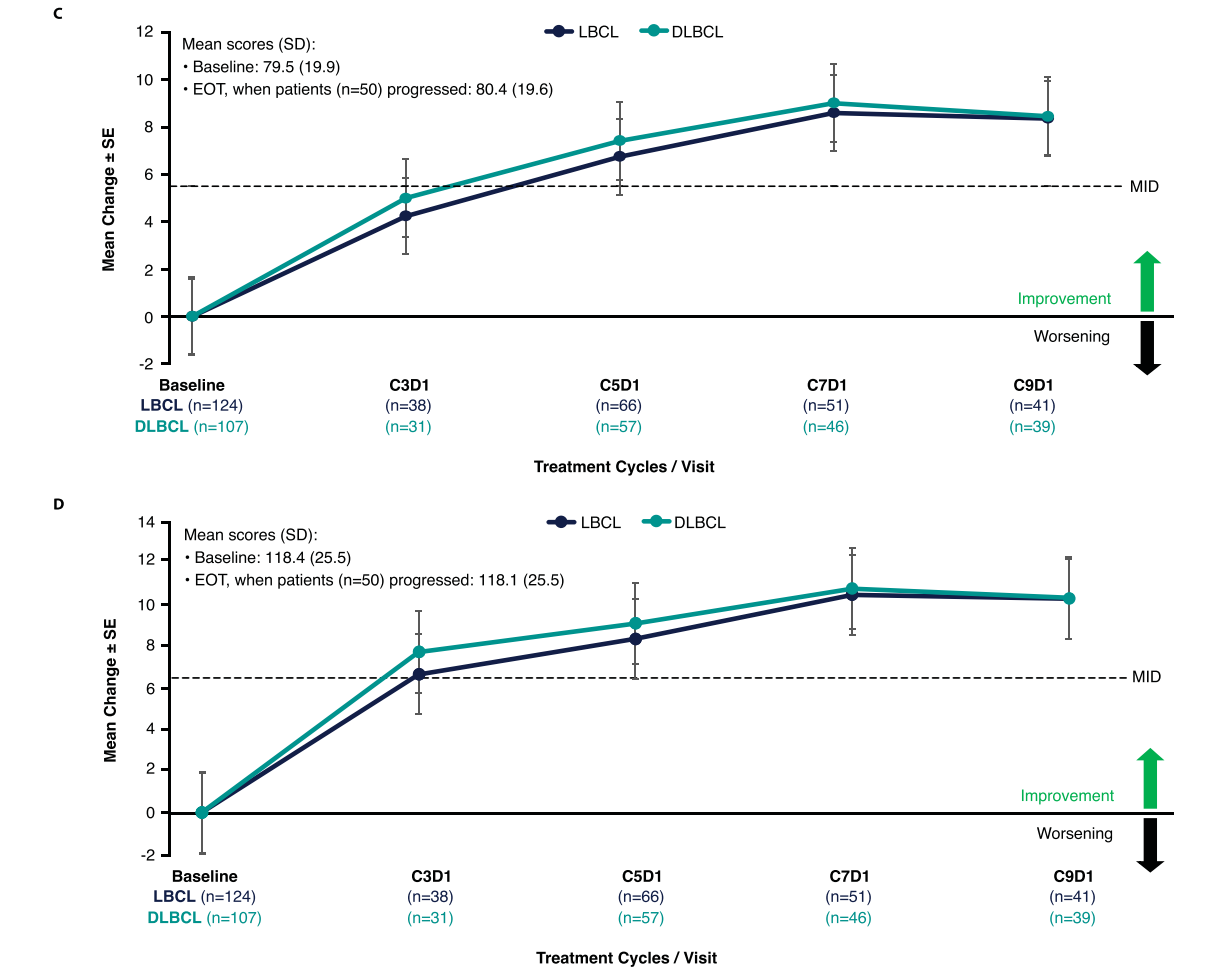
Figure 1 Continued



addition, in qualitative interviews, the vast majority (88.2%) of interviewed patients who presented with symptoms at baseline reported improvements after treatment with epcoritamab. Nearly two-thirds (61.1%) of interviewed patients reported epcoritamab had a positive impact on daily activities, and most (80.0%) of these patients (including 3 who terminated the study early) reported being either "very satisfied" or "satisfied" with the study medication.

PROs recently investigated in clinical trials of several other novel R/R DLBCL treatments have shown clinically meaningful deterioration or improvement, no meaningful change, or deterioration in HRQoL.[26,30-32] In the phase IIb, open-label, single-arm SADAL trial, the HRQoL of patients with R/R DLBCL treated with single-agent selinexor was assessed using FACT-Lym (n = 101) and the 5-level EQ-5D (EQ-5D-5L; n = 89).[31] Patients were transplant-ineligible (ASCT or CAR T) or had relapsed after ASCT, and had received ≥2 prior systemic therapies. Patients with DLBCL (de novo or transformed from indolent lymphoma) were included, and patients with PMBCL excluded. Scores on FACT-Lym, its components, and EQ-5D-5L decreased between baseline and end of treatment. The deterioration of HRQoL and reduction of FACT-Lym and its subscale scores surpassed published MIDs at all time points.

The HRQoL impact of the CAR T therapy lisocabtagene maraleucel was assessed with EQ-5D-5L (N = 186) and other questionnaires in the phase I, open-label, single-arm TRANSCEND trial.[32] Enrolled patients had received ≥2 prior systemic therapies and could have had disease progression after ASCT. The study included patients with DLBCL (de novo or transformed from indolent lymphoma), HGBL (including double/triple-hit), FL grade 3B, and PMBCL. At 12 and 18 months, EQ-5D-5L index score changes were not clinically meaningful. In the phase II, open-label, single-arm JULIET trial, HRQoL outcomes with tisagenlecleucel, another CAR T therapy, were investigated with FACT-Lym and other questionnaires.[26] Enrolled patients were ASCT-ineligible or had relapsed after ASCT, and had received ≥2 prior systemic therapies. The study included patients with DLBCL, transformed FL, and HGBL (including double/triple-hit); patients with PMBCL were excluded. In JULIET, most PRO assessments were completed by responders (patients who had CR or partial response); these

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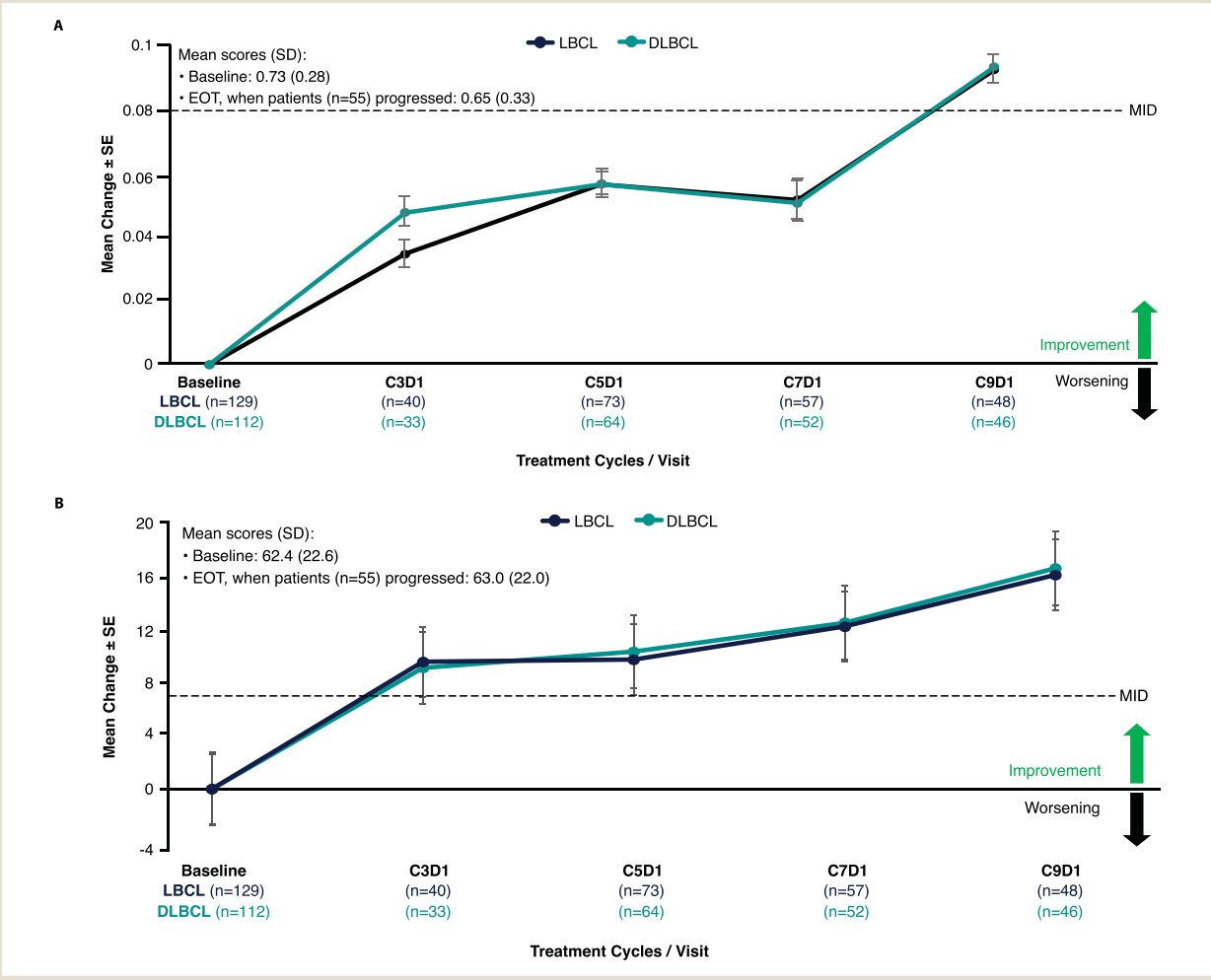
Figure 2 Mean change from baseline in (A) EQ-5D-3L index scores and (B) EQ-VAS scores.
Abbreviations: C = cycle; D = day; DLBCL = diffuse large B-cell lymphoma; EOT = end of treatment; EQ-5D-3L = 3-level EQ-5D; EQ-VAS = EQ visual analog scale; LBCL = large B-cell lymphoma; MID = minimally important difference; SD = standard deviation; SE = standard error.



patients had clinically meaningful improvements in HRQoL, as assessed by FACT-Lym subscales, through 18 months.

Finally, HRQoL with loncastuximab tesirine was evaluated in the phase II, open-label, single-arm LOTIS-2 trial with FACT-Lym and EQ-VAS.[33] Enrolled patients had received ≥2 prior systemic therapies and could have disease progression after ASCT or CAR T. LOTIS-2 included patients with DLBCL (de novo or transformed from indolent lymphoma), HGBL (including double/triple-hit), and PMBCL, and excluded patients with bulky disease. When adjusted for baseline scores, changes from baseline in FACT-Lym or its components were not clinically meaningful. Similarly, mean changes from baseline in EQ-VAS scores showed a trend of improvement throughout the study but were not clinically meaningful.

It is important to note that these cited clinical trials enrolled heterogenous patient populations, which may influence both treatment outcomes and HRQoL and may pose limitations on the comparison. For example, there were 3 times as many patients with primary refractory disease in EPCORE NHL-1 (61.1%) than in LOTIS-2 (20.0%).[19,33] The vast majority of patients (82.8%) in EPCORE NHL-1 were refractory to their last systemic therapy and 38.9% had prior CAR T, whereas 54% and 57.9% of patients were refractory to their last therapy in JULIET and LOTIS-2, respectively, and 9% had previous CAR T in LOTIS-2.[26,33] In addition, while the EPCORE NHL-1 LBCL cohort included ~39% of patients with prior CAR T exposure, JULIET and TRANSCEND had no prior CAR T-exposed patients.[20,32,34] These baseline characteristics are noteworthy, as a recent real-world COTA database analysis of patients with R/R DLBCL showed that primary refractoriness, refractoriness to last LOT, and prior CAR T exposure were associated with increased likelihood of poor outcomes, as was treatment with multiple prior LOTs.[35] Therefore, given the highly refrac-

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Table 4 Qualitative Interviews: Patient-Reported Symptoms at Baseline and Improvements With Epcoritamab Treatment

Symptom, n	Patients Who Completed Cycle 10 (N = 14)		Patients Who Terminated Early (N = 6)		All Patients (N = 20)	
	Baseline Symptom	Improvement	Baseline Symptom	Improvement	Baseline Symptom	Improvement
Fatigue/lack of energy	10	9	4	1[a]	14	10
Tumors that could be seen or felt	5	5	2	0	7	5
Body pain	3	3	4	2[a]	7	5
Weight loss	3	2	1	0	4	2
Night sweats	3	3	0	0	3	3
Sleep difficulties[b]	2	2	1	1	3	3
Lack of appetite[b]	2	2	0	0	2	2
Breathlessness[b]	2	2	0	0	2	2
Fever	1	1	0	0	1	1
Nausea[b]	1	1	0	0	1	1
Weakness[b]	1	1	0	0	1	1
No symptoms	2	NA	1	NA	3	NA

Abbreviation: NA = not applicable.
[a] One patient noticed improvement until cycle 3; then symptom worsened/returned; participant eventually terminated study early.
[b] Symptom was not systematically probed during interviews; instead, patient(s) spontaneously reported the symptom(s).

tory nature of these patients' disease, the positive HRQoL results in EPCORE NHL-1 are even more notable and compelling.

Strengths and Limitations

This study described the impact of treatment with epcoritamab on patients' HRQoL and provided findings relevant to patients, caregivers, and clinicians. In addition, through qualitative interviews, the study elicited patients' detailed reports regarding their experiences with epcoritamab treatment. Because EPCORE NHL-1 was an uncontrolled study, this presented constraints on any extensive assessment of whether there were other drivers of HRQoL changes. Nevertheless, the patient-reported improvements in HRQoL and lymphoma symptoms are potentially related to responses to therapy, as patients may be more likely to report improvements in PROs if they benefit from treatment.

Conclusion

During the 9-cycle observation period, patients with R/R LBCL treated with SC epcoritamab, including highly refractory, heavily pretreated, and hard-to-treat patients, reported consistent and marked improvements in lymphoma symptoms and overall HRQoL. These quantitative PRO improvements, measured with FACT-Lym and EQ-VAS, were clinically meaningful, exceeded published MID thresholds, and were supported by findings from one-on-one qualitative interviews in which most patients reported being "very satisfied" or "satisfied" with epcoritamab treatment. These HRQoL benefits nicely complement the previously reported favorable clinical efficacy and safety of SC epcoritamab[20] and support the clinical use of epcoritamab as a novel treatment option for patients with R/R LBCL.

Clinical Practice Points

- What is already known about this subject?
  DLBCL is an aggressive lymphoma, and patients with R/R DLBCL often experience poor HRQoL, owing to both disease symptoms and treatment. Epcoritamab is a subcutaneous T-cell–engaging CD3xCD20 bispecific antibody recently approved in the United States, Japan, and the European Union for the treatment of R/R DLBCL, based on the clinical safety and efficacy demonstrated in the phase 2 EPCORE NHL-1 trial.
- What are the new findings?
  In a group of patients with heavily pretreated R/R LBCL in EPCORE NHL-1, treatment with epcoritamab provided clinical benefit but also consistent and clinically meaningful improvements in lymphoma symptoms and HRQoL based on the FACT-Lym and EQ-VAS. In both the overall patient group and the DLBCL subgroup, the observed improvements exceeded published MIDs throughout the study. These positive impacts were corroborated in qualitative interviews with a subset of patients.
- How might it impact on clinical practice in the foreseeable future?
  Patients enrolled in EPCORE NHL-1 were highly refractory, heavily pretreated, and had hard-to-treat disease, with approximately 60% having primary refractory disease, 80% refractory to their last systemic therapy, and 40% previously treated with CAR T. Given the highly refractory nature of these patients' disease, the positive HRQoL results in EPCORE NHL-1 are notable and compelling. These findings also complement the previously reported favorable clinical efficacy and safety of SC epcoritamab. Together, the positive PROs, safety, and efficacy of epcoritamab support its clinical use as a novel treatment option for patients with R/R LBCL.

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Medical Writing, Editorial, and Other Assistance

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Author Contributions

TP was responsible for leading the investigation, enrolling patients, and collecting and assembling the data; PL was responsible for leading the investigation, enrolling patients, and collecting and assembling the data; AK was responsible for designing the study and collecting, assembling, and analyzing the data; AM was responsible for collecting, assembling, and analyzing the data and preparing the manuscript; AW was responsible for collecting, assembling, and analyzing the data; JB was responsible for designing the study and analyzing the data; KK was responsible for designing the study and collecting, assembling, and analyzing the interview data; SM was responsible for designing the study and collecting, assembling, and analyzing the interview data; MS was responsible for designing the study and collecting, assembling, and analyzing the data; NK was responsible for designing the study and collecting, assembling, and analyzing the data; CT was responsible for leading the investigation, enrolling patients, and collecting and assembling the data. All the authors were responsible for interpreting the data, reviewing and revising the manuscript, and giving final approval of the manuscript.

Data Sharing Statement

Deidentified individual participant data collected during the trial will not be available upon request for further analyses by external independent researchers. Aggregated clinical trial data from the trial is provided via publicly accessible study registries/databases as required by law. For more information, please contact ClinicalTrials@genmab.com.

Disclosure

Tycel Phillips: Seattle Genetics, Pharmacyclics, Incyte, Genentech, Bayer, Gilead Sciences, Curis, Kite/Gilead, Celgene, Genmab, TG Therapeutics, ADC Therapeutics: Consulting or Advisory Role; Seattle Genetics, Lymphoma & Myeloma Connect: Honoraria; AbbVie, Pharmacyclics/Janssen, Bayer: Research Funding; The Leukemia & Lymphoma Society: Scholar in Clinical Research; *Pieternella Lugtenburg*: Takeda, Servier: Research Grants; Celgene, Roche, Takeda, Genmab, AbbVie, Incyte, Regeneron: Advisory Honoraria. Y-mAbs Therapeutics: Consultancy Honoraria; Lilly: Speakers Bureau; *Anupama Kalsekar*: Employee of Genmab; *Alex Mutebi*: Employee of Genmab; *Anthony Wang*: Employee of AbbVie; *Julie Blaedel*: Employee of Genmab; *Katherine Kosa*: Employee of RTI Health Solutions who received funding from Genmab for the design, conduct, and analysis of the qualitative interviews; *Susan Martin*: Employee of RTI Health Solutions who received funding from Genmab for the design, conduct, and analysis of the qualitative interviews; *Mariana Sacchi*: Employee of Genmab; *Nurgul Kilavuz*: Employee of Genmab; *Catherine Thieblemont*: BMS/Celgene, Hospira, Roche: Research Funding; AbbVie, Amgen, BMS/Celgene, Cellectis, Gilead Sciences, Kite, Novartis, Roche: Consultancy; AbbVie, Amgen, Bayer, Cellectis, Gilead Sciences, Incyte, Janssen, Kite, Novartis, Takeda: Honoraria; AbbVie, Amgen, BMS/Celgene, Cellectis, Gilead Sciences, Incyte, Janssen, Kite, Novartis, Roche, Takeda: Membership on an Entity's Board of Directors or Advisory Committees; AbbVie, Amgen, BMS/Celgene, Cellectis, Gilead Sciences, Kite, Novartis, Roche: Travel, Accommodations, Expenses.

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Supplemental Appendix

Supplemental Table 1, Supplemental Table 2

Table S1 Degree of Symptom Improvements Before and After Treatment (N=15)

Symptom	Patient IDI#	Before treatment	After treatment
Fatigue/lack of energy (n=9)[a]	1	Mild	None
	4	Moderate	Mild
	6[b]	Not asked	Not asked
	9	Severe	Mild
	11	Moderate	None
	15	Severe	Mild
	17	Severe	Mild
	18	Moderate	Mild
	19	Mild	None
Size of tumors that could be seen or felt (n=5)[a]	3	Severe	Mild
	5	Severe	Mild
	12	Severe	None
	16	Moderate	Mild
	17	Moderate	None
Body pain (n=5)[a,c]	6[b]	Not asked	Not asked
	11	Mild	None
	12	Moderate	Mild
	16	Moderate	Mild
	20	Severe	None
Weight loss (n=2)[a]	3	Severe	None
	4	Severe	None
Night sweats (n=3)[a]	3	Severe	Mild
	11	Moderate	None
	12	Moderate	None
Fever (n=1)[a]	11	Moderate	None
	2	Not asked	Not asked
Sleep difficulties (n=3)[a,d]	18	Severe	Mild
	19	Mild	None
Lack of appetite (n=2)[a,d]	3	Severe	None
	17	Severe	None
Breathlessness (n=2)[a,d]	15	Severe	Mild
	16	Severe	Mild
Nausea (n=1)[a,d]	17	Severe	None
Weakness (n=1)[a,d]	9	Severe	Mild

[a] Number of patients who reported symptom improvement with treatment.
[b] One patient noticed improvement until cycle 3; then symptom worsened/returned; patient eventually terminated study early.
[c] Patients generally reported pain in the region of the lymphoma (eg, abdomen, underarm, groin, back).
[d] Symptom was not systematically probed during interviews; instead, patient(s) spontaneously reported symptom(s).
Note: Before and after treatment, patients rated their symptoms on a scale with 4 response options: none, mild, moderate, severe.
Abbreviation: IDI#, in-depth interview number.

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Table S2 Impact of Epcoritamab Treatment on Patient-Reported Lymphoma Symptoms and Health-Related Quality of Life as Described by Participants in Qualitative Interviews

	Participant ID	Quote
Impacts of treatment	IDI 3	"Oh boy. I'm happy about all of [the improvement in symptoms] but probably getting the weight back, that made me feel a lot better. I can taste food, and it tastes good, so I eat."
	IDI 4	"I'm no longer depressed as I was during the initial phases, so I'd say that the whole process is a success."
	IDI 9	"Getting strong, stronger, I think, probably, if I had to say one thing. Well, still I've got to take care, [but] the strength in the limbs is still gradually getting stronger…it's taking a bit of time but I'm convinced it will [continue to improve]."
	IDI 11	"…it's like we're back to where we were before. I do the cleaning at home for the whole day, I cook…I was very tired before, and now I can do anything…I used to be a very dynamic woman, and the fact that I can cook for my little family, take care of my grandchildren, go anywhere and do anything…"
	IDI 12	"No, I am less stressed out. Because as I said, the disease was there. Now, since it's reduced, I am necessarily less stressed out."
	IDI 17	"Yes, I can move about. I can go for a walk. Before that, I couldn't…I didn't feel like it."
Satisfaction with treatment	IDI 2	"I was absolutely thrilled with the treatment. It worked. [Plus], this [treatment] left my immune system intact, and I was able to go to church. I was able to do a few things when the plague wasn't raging. I'm thrilled with it. As I said, last year, I went through 5 different treatments, [and] 2 of them put me in bed…some of them…did nothing. I feel like I wasted time. I wasted some of my health and energy, and [after] one of them, I got the scan back, and my tumors had tripled."
	IDI 12	"The injection takes 5 minutes. When you have 7 hours of chemo, it doesn't compare."
	IDI 15	"Yes, but with this one, I was less tired. I didn't have any nausea. I had no side effects, and…there's been a remission from March until now, and I hope that it'll continue on." "I am very satisfied with the treatment…because there is a complete remission now. We'll check that each month, but for now I am very satisfied."
	IDI 16	"I am satisfied because right now I am experiencing a complete remission, because it gives me hope for the future, because there are hardly any side effects, and the very few side effects I've experienced, we manage to make them disappear and because I can go on with my life normally."

Abbreviation: IDI#, in-depth interview number.

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