

Health-Related Quality of Life in Adults With B-Cell Precursor Acute Lymphoblastic Leukemia and Minimal Residual Disease Treated with Blinatumomab

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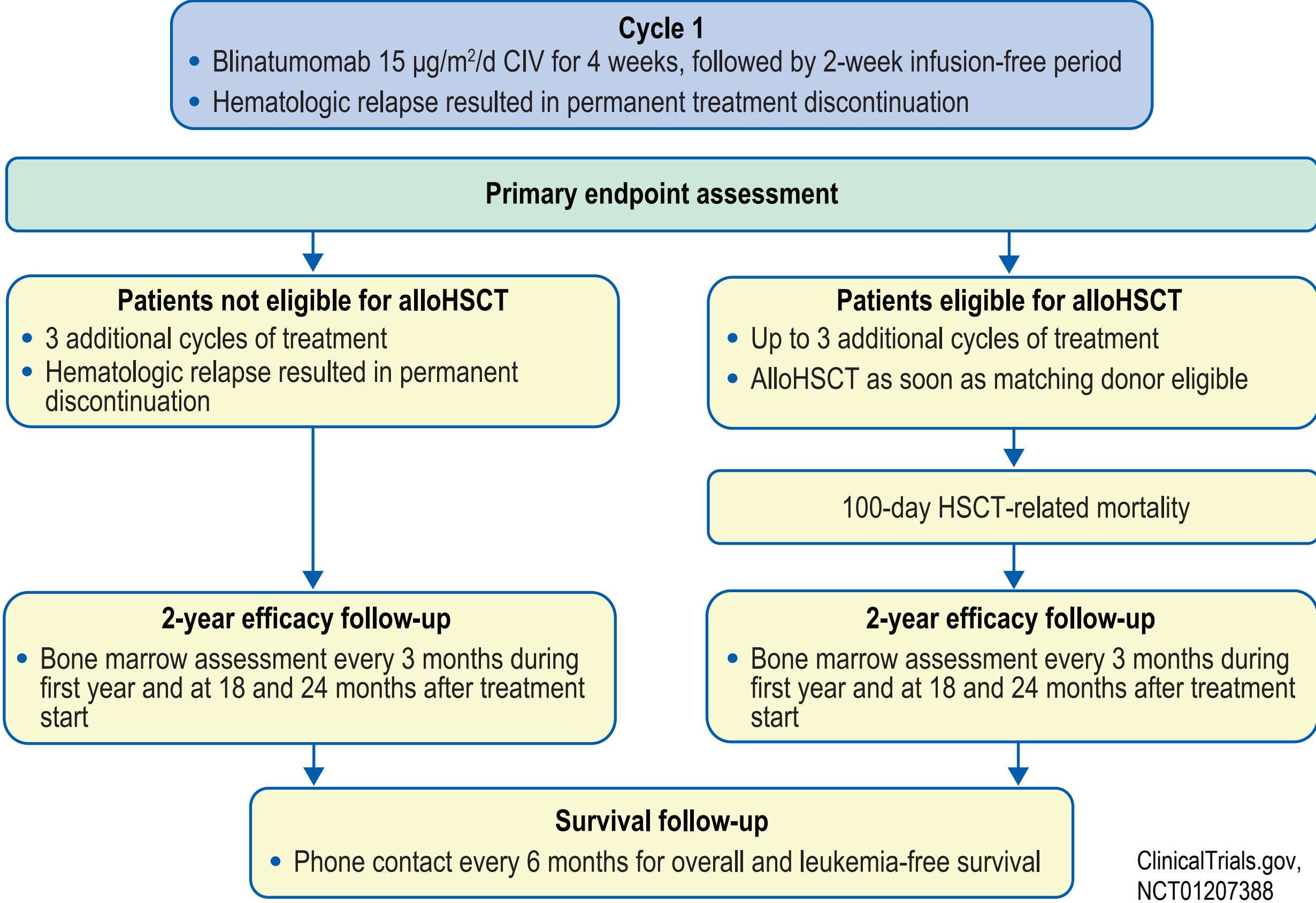
INTRODUCTION

- Minimal residual disease (MRD) is an established prognostic factor for hematologic relapse, negative allogeneic hematopoietic stem cell transplantation (aHSCT) outcome, and mortality in adults with B-cell precursor acute lymphoblastic leukemia (ALL)¹
- Blinatumomab is a bispecific T-cell engager (BiTE®) immunotherapy that redirects cytotoxic T cells to CD19-positive blast cells
 - In the open-label, single-arm phase 2 BLAST study (N = 116; ClinicalTrials.gov, NCT01207388) of adults with ALL in complete remission (CR) and with MRD, treatment with blinatumomab led to complete MRD response in 88 of 113 (78%) patients after cycle 1; 2 more patients had complete MRD response after cycle 2²
 - Median overall survival was 36.5 months²; median overall survival was not reached in complete MRD responders at a median follow-up of 53.1 months²
 - Among patients with Philadelphia chromosome–negative B-cell ALL in complete MRD remission, relapse-free survival was 54% at 18 months²
- The health-related quality of life (HRQoL) in patients with B-cell precursor ALL and MRD treated with blinatumomab has not been assessed

STUDY OBJECTIVE

- To assess the HRQoL measured by EORTC QLQ-C30 during and after treatment with blinatumomab in patients in the BLAST study

Open-label Phase 2 Study



METHODS

Key Inclusion Criteria

- Aged ≥ 18 years with B-cell precursor ALL in first or later hematologic CR and with persistent or recurrent MRD ≥ 10⁻³ after ≥ 3 blocks of intensive chemotherapy
- For MRD assessment, patients had ≥ 1 molecular marker based on individual rearrangements of immunoglobulin or TCR genes or a flow cytometric profile evaluated by a national or local reference laboratory
- ANC ≥ 1000/µL; platelets ≥ 5000/µL (transfusion allowed); hemoglobin ≥ 9 g/dL (transfusion permitted); AST, ALT, and AP < 2 × ULN; total bilirubin < 1.5 × ULN; creatinine clearance ≥ 50 mL/min

Key Exclusion Criteria

- Circulating blasts or extra-medullary involvement by ALL
- Prior or current CNS pathology or infiltration of cerebrospinal fluid by ALL
- Prior alloHSCT or blinatumomab
- Systemic therapy within 2 weeks or radiotherapy or monoclonal antibodies within 4 weeks before study

Study Endpoints

- Primary
 - Rate of complete MRD response after cycle 1 of blinatumomab
- Secondary
 - Hematologic relapse-free survival rate at 18 months following initiation of blinatumomab
 - Overall survival
 - Mortality rate within 100 days of alloHSCT
 - Time to hematologic relapse
 - Duration of complete MRD response
 - Effect on MRD level
 - Incidence and severity of adverse events (AEs)
 - HRQoL
 - Resource utilization

Clinical Assessments

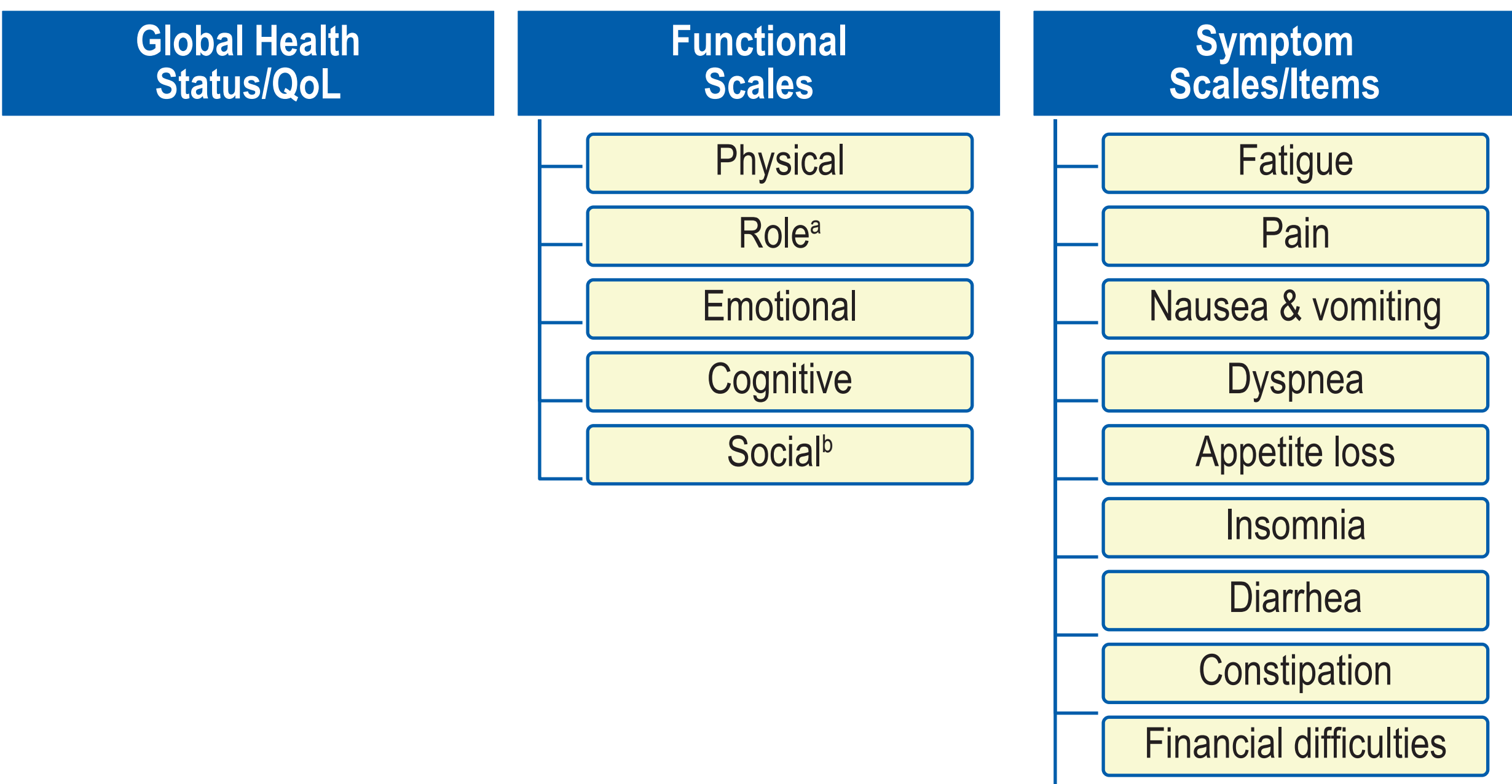
- All AEs were recorded and graded using NCI-CTCAE, version 4.0
- MRD was assessed based on PCR of bone marrow at completion of the first cycle of treatment; complete MRD response was reached if no PCR amplification of immunoglobulin or TCR genes was detected by the clone-specific PCR

METHODS (Continued)

HRQoL Assessment

- HRQoL was assessed using the EORTC QLQ-C30 Questionnaire (recall period: 1 week) at baseline, on day 29 of each treatment cycle, at the safety follow-up visit (30 days after end of treatment), and at the efficacy follow-up visits (3, 6, 9, 12, 18, and 24 months after treatment start; Figure 1).
- For global health status/QoL and functional scales, a higher score indicated better HRQoL; for symptom scales and items, lower scores indicated better HRQoL
- A 10-point change is often viewed as the minimum clinically important difference (MID) within patient in EORTC QLQ-C30³
- For the global health status/QoL and functional scales, response was defined as ≥ 10-point change from baseline, and deterioration was defined as a ≥ 10-point decrease from baseline. For symptom scales, deterioration was defined as a ≥ 10-point increase from baseline⁵

Figure 1. EORTC QLQ-C30 Questionnaire³



Assessment Schedule²

Baseline	Cycles 1–4	Safety Follow-up	Efficacy Follow-up
Day –21 to –1	Day 29 treatment	30 Days after end of after treatment start	3, 6, 9, 12, 18, 24 months

²Based on the extent to which a patient was limited in doing work or other daily activities, and pursuing hobbies or other leisure time activities.
³Based on the extent to which a patient's physical condition or medical treatment interfered with family life or social activities.
⁵Patients who underwent HSCT or had hematological relapse would enter follow-up and HRQoL assessments were no longer conducted.

Statistical Analysis

- Patients with a non-missing baseline and non-missing cycle 1, day 29 score for any scale or item were included
- Mean (SD) HRQoL scores for each scale or item was summarized at each scheduled assessment during and after blinatumomab treatment
- In addition, mean (SD) change from baseline to end of cycle 1 was also summarized for each scale or item

RESULTS

Global Health Status and Functional Scales

- 89 patients were evaluable for HRQoL. The percentage of form level missing was small at each assessment points.
- Compared with patients with relapsed or refractory B-cell precursor ALL from TOWER trial (blinatumomab arm), the baseline HRQoL was generally better in almost all scales/items for patients from BLAST trial (Table 1).
- Patient-reported global health status was stable over time during and after blinatumomab treatment with a trend suggesting modest improvement (Figure 2)
- Similarly, patient-reported physical, role, emotional, cognitive, and social functioning were stable or slightly improving over time during and after blinatumomab treatment (Figure 2)

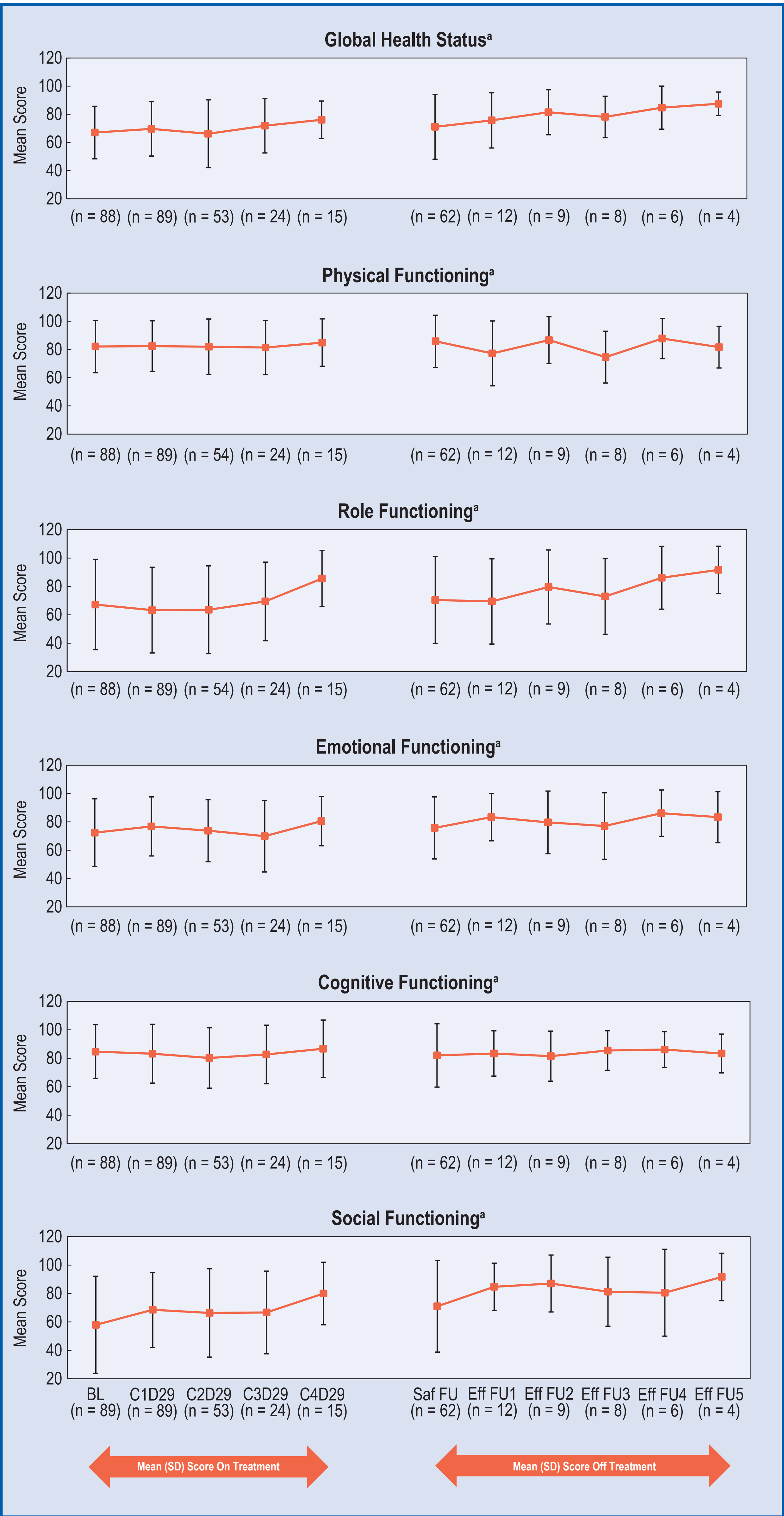
Table 1. Baseline HRQoL of the Patients from BLAST vs TOWER Blinatumomab Arm

	BLAST	TOWER Blinatumomab Arm
Global health status	67.1	54.2
Physical functioning	82.1	70.0
Role functioning	67.2	56.2
Emotional functioning	72.4	70.8
Cognitive functioning	84.7	85.5
Social functioning	58.0	56.7
Fatigue	32.5	43.0
Nausea and vomiting	4.7	10.7
Pain	16.5	27.9
Dyspnea	15.0	21.8
Insomnia	22.1	29.4
Appetite loss	13.9	21.3
Constipation	4.2	15.8
Diarrhea	8.3	9.0
Financial difficulties	26.8	33.2

Notes: For global health status and functional scales, a higher score indicated better HRQoL. For symptoms and single item scales, a lower score indicated better HRQoL

RESULTS (Continued)

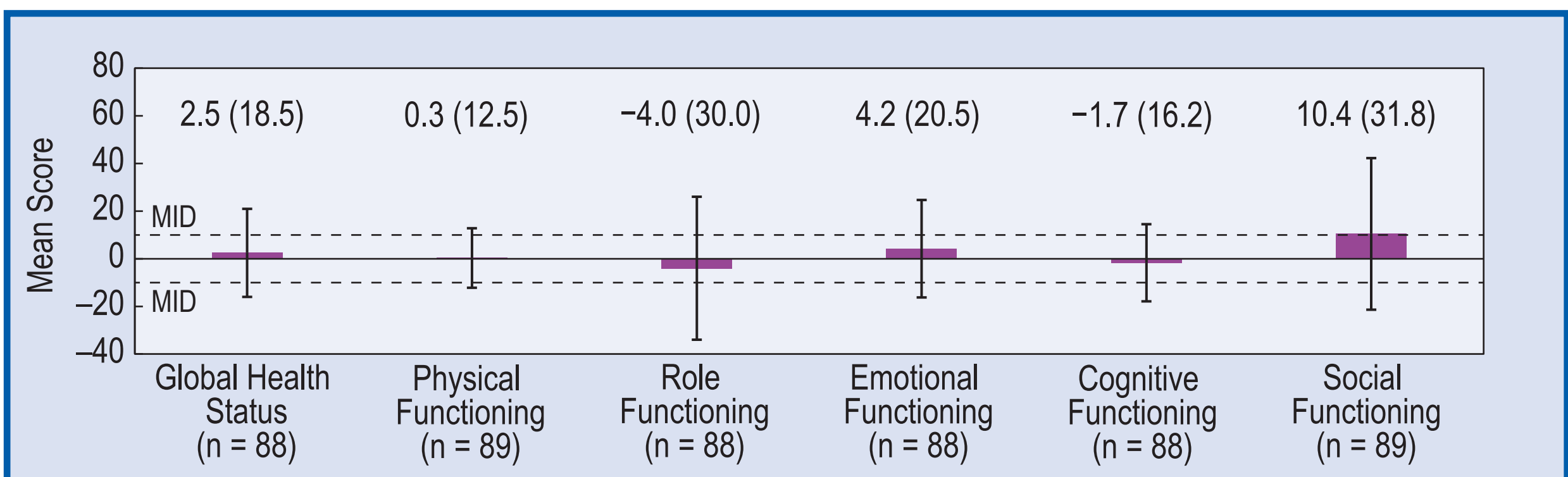
Figure 2. Mean (SD) Global Health Status and Functional Scale Scores



BL, baseline; C, cycle; D, day; Eff, efficacy; FU, follow-up
²For global health status and functional scales, a higher score indicated better HRQoL.

- The mean change in HRQoL from baseline to end of cycle 1 was minimal for global health status and physical, role, emotional, cognitive functioning. The improvement in social functioning was larger than MID (Figure 3)

Figure 3. Mean (SD) Change From Baseline to End of Cycle 1 in Global Health Status and Functional Scale Scores

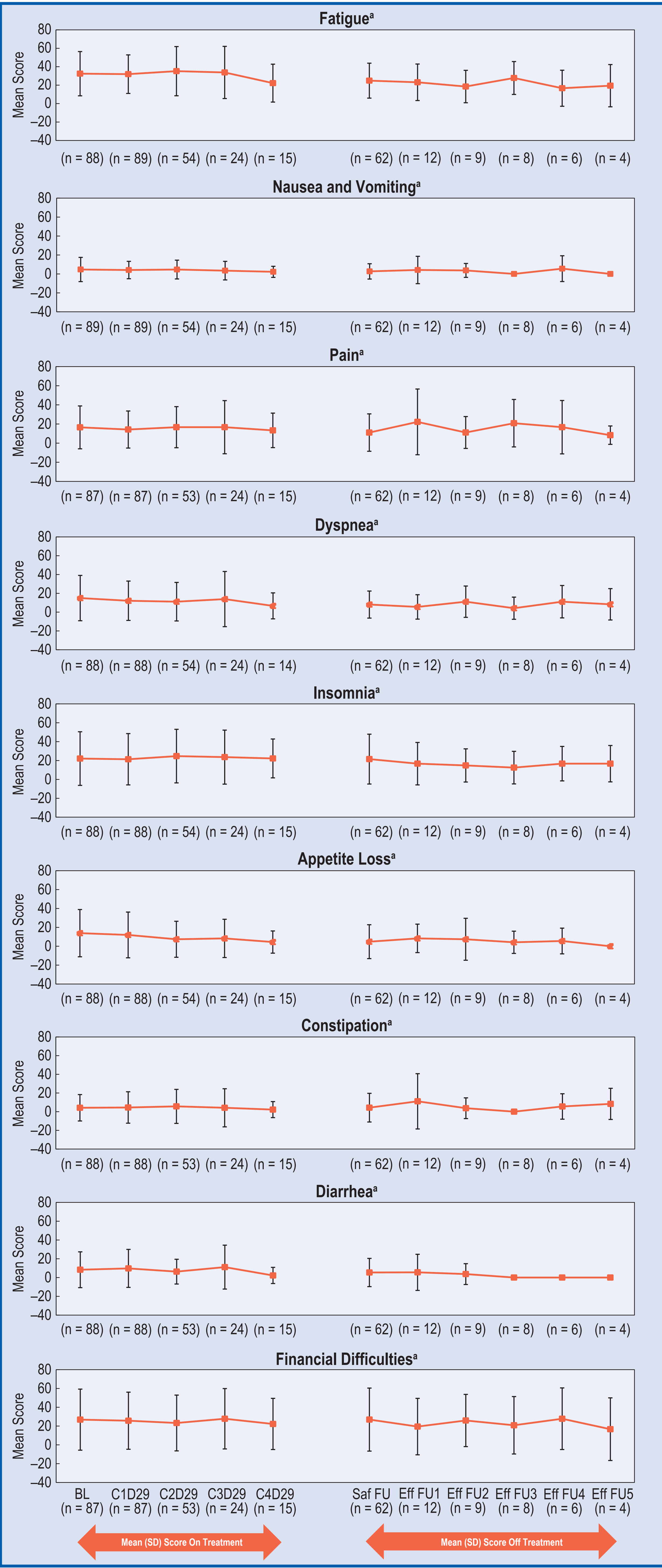


MID, minimum clinically important difference.

Symptom Scales and Single Items

- Patient-reported fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties were stable over time during and after blinatumomab treatment (Figure 4)

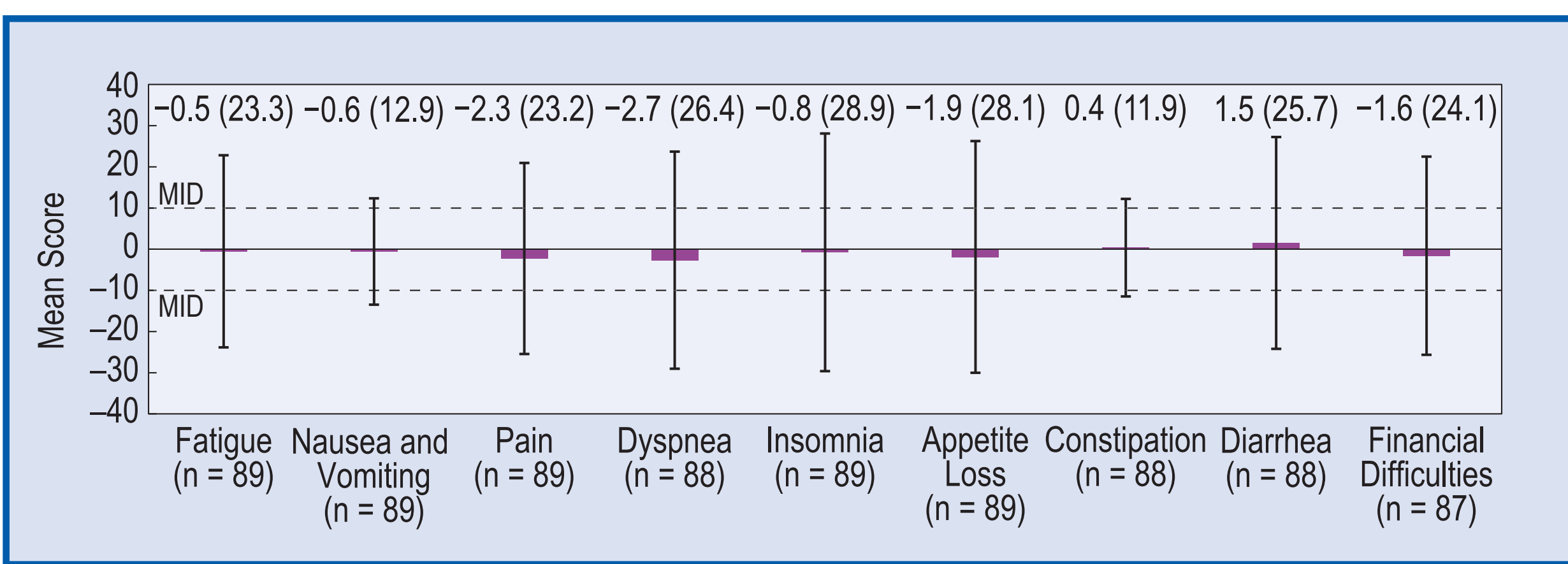
Figure 4. Mean (SD) Symptom Scale and Single Item Scores



BL, baseline; C, cycle; D, day; Eff, efficacy; FU, follow-up
²For symptoms and single item scales, a lower score indicates better HRQoL

- The mean change in HRQoL from baseline to end of cycle 1 was minimal for fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties

Figure 5. Mean (SD) Change From Baseline to End of Cycle 1 in Symptom Scale and Single Item Scores



MID, minimum clinically important difference.

CONCLUSIONS

- Patients with MRD positive B-cell ALL had a trend toward better HRQoL at baseline compared with R/R ALL
- In patients with B-cell precursor ALL and MRD treated with blinatumomab, HRQoL was maintained during and after treatment
 - This is a noteworthy observation considering the potential HRQoL impact of standard chemotherapy⁷
- The results were consistent across all EORTC QLQ-C30 scales/items, namely global health status, functional scales, symptom scales, and single symptom items and were stable throughout treatment
- After 1 cycle of treatment with blinatumomab, there was clinically meaningful improvement in social functioning, and no clinically meaningful deterioration in any scales/items
- Limitations
 - Due to many patients receiving alloHSCT, after which HRQoL data were not collected, the results should be interpreted with caution, as the sample size decreased substantially after month 3

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- This study was funded by Amgen Inc.
- Medical writing assistance in the development of the poster was provided by Ben Scott (Scott Medical Communications, LLC) and was funded by Amgen Inc.

CONFLICTS OF INTEREST

- Ralf C. Bargou: consultant/advisor for Amgen Inc., Gemoab, Cellex, and Novartis; patents and royalties from Amgen Inc. Gerhard Zugmaier: employment by and stock ownership in Amgen Research (Munich) GmbH; patents and royalties from Amgen Inc. Massimiliano Bonifacio, Carlos Graux, Christoph Faul: no disclosures. Max S. Topp: honoraria, advisory committee, and travel and research funding from Amgen Inc.; research funding from Boehringer Ingelheim; honoraria and research funding from Regeneron Pharmaceuticals, Inc. Qui Tran, Xinke Zhang: employment by and stock ownership in Amgen Inc. Nicola Gökbüget: consultancy, travel support, and research funding from Amgen Inc., Pfizer, and Novartis; consultancy for Celgene and Kite/Gilead.

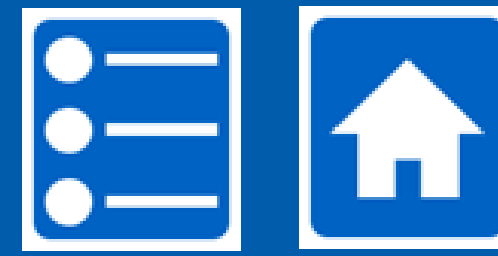


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Health-Related Quality of Life of Blinatumomab Versus Chemotherapy in Patients with Relapsed or Refractory Philadelphia Chromosome–Negative B-cell Precursor Acute Lymphoblastic Leukemia in a Randomized, Open-Label Phase 3 Study (TOWER: Disease Burden Subgroup Analysis)



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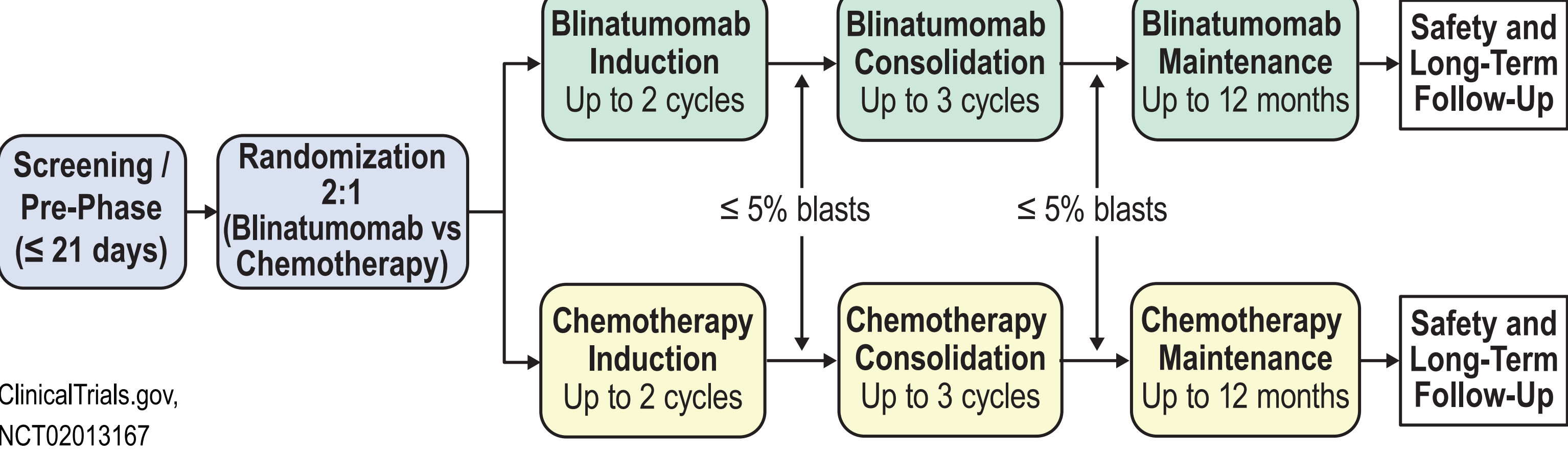
INTRODUCTION

- Historically, outcomes are poor for patients with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL) treated with chemotherapy: median overall survival (OS) was between 3 to 6 months with 5-year survival < 10%¹⁻⁵
- Adults with ALL have poor health-related quality of life (HRQoL) because the disease is severe and treatment is aggressive with prolonged hospitalization and with side effects that further compromise physical, emotional, and social functioning, and that severely curtail activities of daily living^{6,7}
- Blinatumomab is a bispecific T-cell engager (BiTE®) immunotherapy that redirects T cells and triggers cytotoxicity of CD19-positive blast cells
- The phase 3 TOWER study assessed blinatumomab versus standard salvage chemotherapy in adult patients with R/R Philadelphia chromosome–negative (Ph–) B-cell precursor (BCP) ALL⁸
 - Patients who received blinatumomab had significantly improved OS (median, 7.7 vs 4.0 months; *P* = 0.01;) and better health-related quality of life (HRQoL) outcomes versus chemotherapy
- The treatment benefits of blinatumomab with respect to OS and complete remission (CR) rate were consistent across key subgroups, including varying levels of disease burden measured by baseline bone marrow blasts level^{8,9}
- Disease burden is one of the most important prognostic factors for outcomes; however, the impact of blinatumomab on HRQoL in patients with R/R Ph– BCP ALL by baseline blasts level has not been assessed

STUDY OBJECTIVE

- To assess the HRQoL in patients with low or high disease burden who received blinatumomab or chemotherapy in TOWER

Study Design



METHODS

Key Inclusion Criteria

- Aged ≥ 18 years with Ph– BCP ALL
 - Refractory to primary induction or salvage therapy or
 - Untreated first relapse with first remission duration < 12 months or
 - Untreated second or greater relapse or
 - Relapse after allogeneic hematopoietic stem cell transplant (HSCT)
- Intensive combination therapy for initial treatment or subsequent salvage therapy
- > 5% bone marrow blasts, ECOG performance status ≤ 2

Key Exclusion Criteria

- Malignancy within the previous 5 years except treated with curative intent; adequately treated non-melanoma skin cancer, lentigo maligna, cervical or breast ductal carcinoma in situ without evidence of disease; and prostatic neoplasia without evidence of cancer
- Extra-medullary involvement by ALL
- Prior or current central nervous system (CNS) pathology or infiltration of cerebrospinal fluid by ALL
- Autologous or allogeneic HSCT within 6 or 12 weeks, respectively, of study
- Chemotherapy or radiotherapy within 2 weeks of study or immunotherapy within 4 weeks before treatment initiation
- Prior CD19-directed therapy

Study Endpoints

- Primary
 - Overall survival
- Secondary
 - CR within 12 weeks of treatment initiation
 - CR with full, partial, or incomplete hematologic recovery (CR/CRh/CRi) within 12 weeks of treatment initiation
 - Event free survival
 - Duration of CR
 - Duration of CR/CRh/CRi
 - MRD remission
 - Time to a 10-point decrease from baseline in global health status and HRQoL
 - Allogeneic HSCT
 - Incidence and severity of adverse events
 - 100-day mortality after allogeneic HSCT
 - Incidence of anti-blinatumomab antibody formation
 - Changes in vital signs and laboratory parameter

METHODS (Continued)

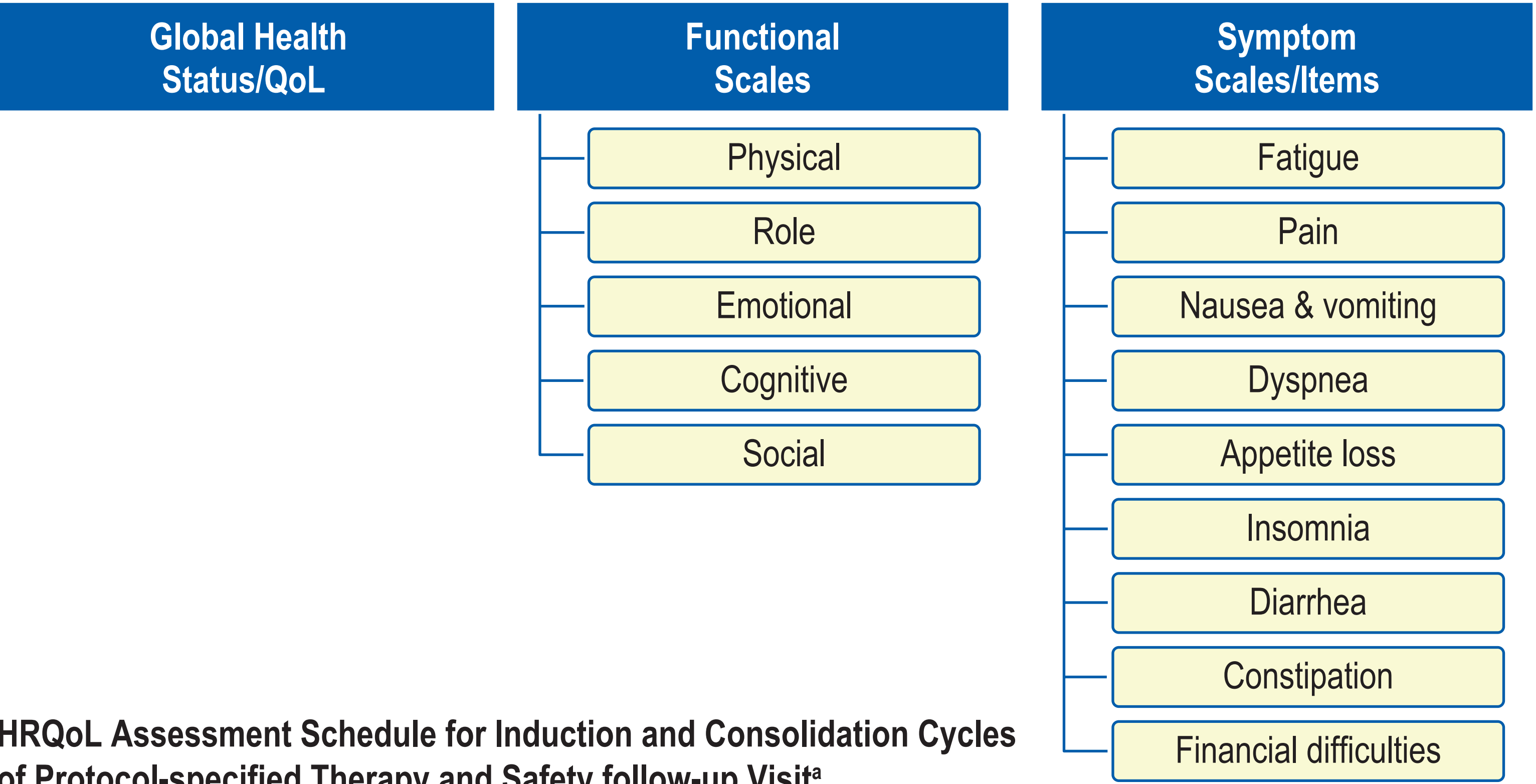
HRQoL Assessment

- HRQoL was assessed using the EORTC QLQ-C30 Questionnaire (recall period, 1 week; Figure 1)
- For global health status and functional scales, higher scores indicate better HRQoL; for symptom scales and single items, lower scores indicate better HRQoL
- A 10-point change is often viewed as the minimum clinically important difference (MID) within a patient on the EORTC QLQ-C30.¹⁰ For the global health status/QoL and functional scales, response was defined as ≥10-point change from baseline, deterioration was defined as a ≥10-point decrease from baseline; for symptom subscales, deterioration was defined as a ≥10-point increase from baseline⁹
- HRQoL was assessed in patient subgroups by screening the bone marrow aspirates for low blast levels (< 50% blasts) versus high blast levels (≥ 50% blasts)

Statistical Analysis

- Analyses included patients with baseline and at least 1 postbaseline result of any multi-item scale or single-item measure
- Mean (SD) change from baseline in the scores of each scale or item was summarized at each scheduled assessment point in cycle 1
- Time to deterioration analyses assessed the treatment effect based on timing from the initiation of treatment to a 10-point deterioration in each scale or item from baseline

Figure 1. EORTC QLQ-C30 Questionnaire¹¹



HRQoL Assessment Schedule for Induction and Consolidation Cycles of Protocol-specified Therapy and Safety follow-up Visit*

Day 1	Day 8	Day 15	Day 29 ± 8 days	Safety follow-up visit (30 ± 3 days)
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*EORTC QLQ C30 was completed on days 1, 8, 15, and 29 during cycle 1; days 1, 15, and 29 during each consolidation cycle, and at the safety follow-up visit. EORTC QLQ C30 was not collected during the maintenance period (cycles 6–9) or in the long-term follow-up period. A safety follow-up visit was required 30 days after the last dose of protocol-specified therapy; a safety follow-up visit must have occurred before HSCT or any non-protocol-specified anticancer therapy. In the case of treatment interruptions that did not result in the initiation of a new cycle (ie, < 7 days), all assessments were completed according to the number of active days on treatment.

RESULTS

Low and High Blast Patient Subgroups

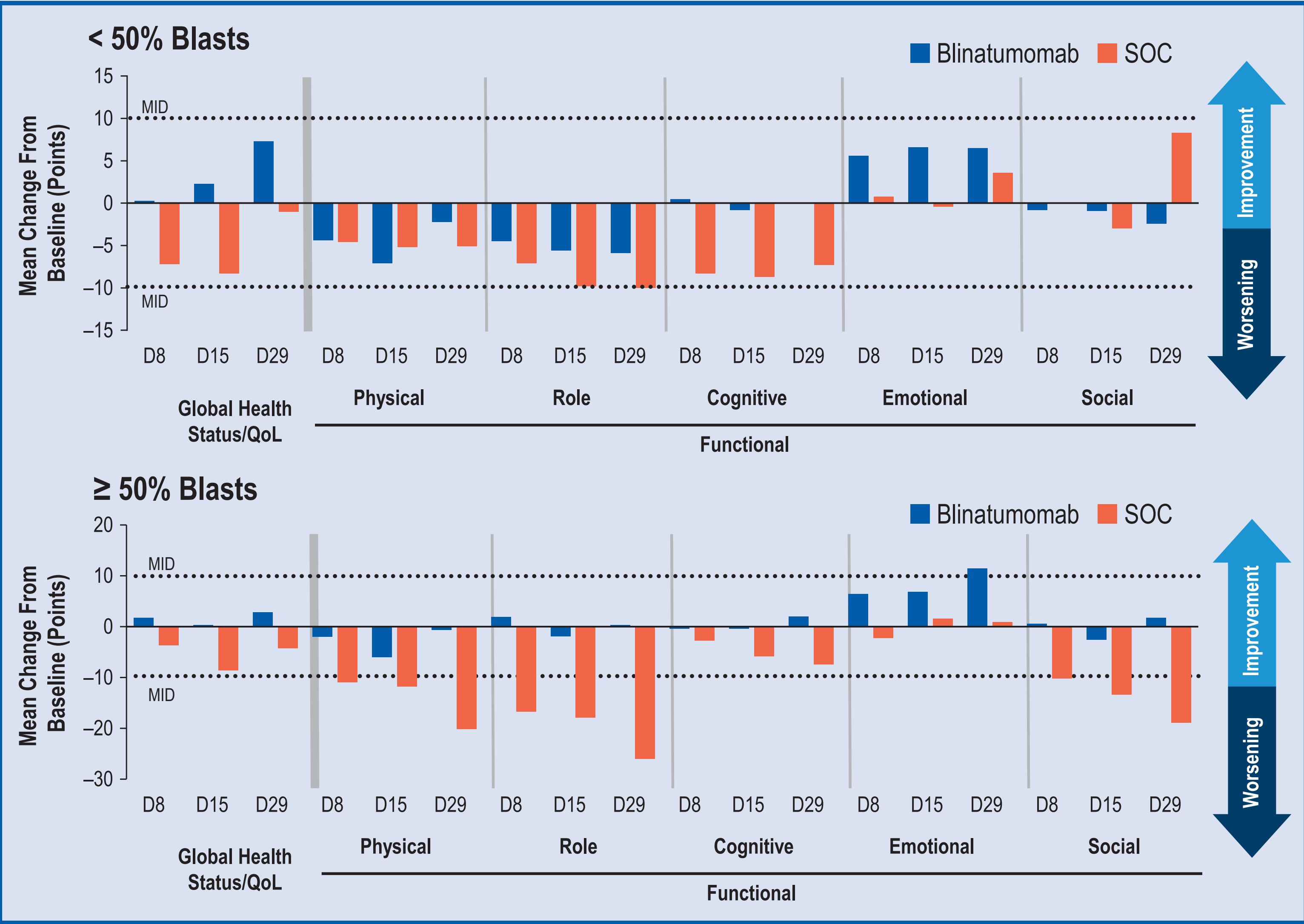
- 342 patients (blinatumomab, n = 247; SOC, n = 95) were evaluable for HRQoL
 - Low blasts, n = 87 (blinatumomab, n = 64; SOC, n = 23)
 - High blasts, n = 255 (blinatumomab, n = 183; SOC, n = 72)

Change From Baseline in Cycle 1 in Global Health Status and Functional Scale Scores in Low and High Blasts Subgroups

- Global health status improved in the blinatumomab arm but worsened in the chemotherapy arm, regardless of baseline blast level
- Functional scale scores tended to stay the same or worsen with both blinatumomab and chemotherapy regardless of blast level, except emotional scores, which improved with blinatumomab, regardless of blast level
- When functional scores worsened, the extent of worsening was almost always smaller for blinatumomab versus chemotherapy, especially in the high blasts group, for which the change in blinatumomab arm was minimal

RESULTS (Continued)

Figure 2. Mean (SD) Change From Baseline in Cycle 1 in Global Health Status and Functional Scales in Low and High Blast Subgroups

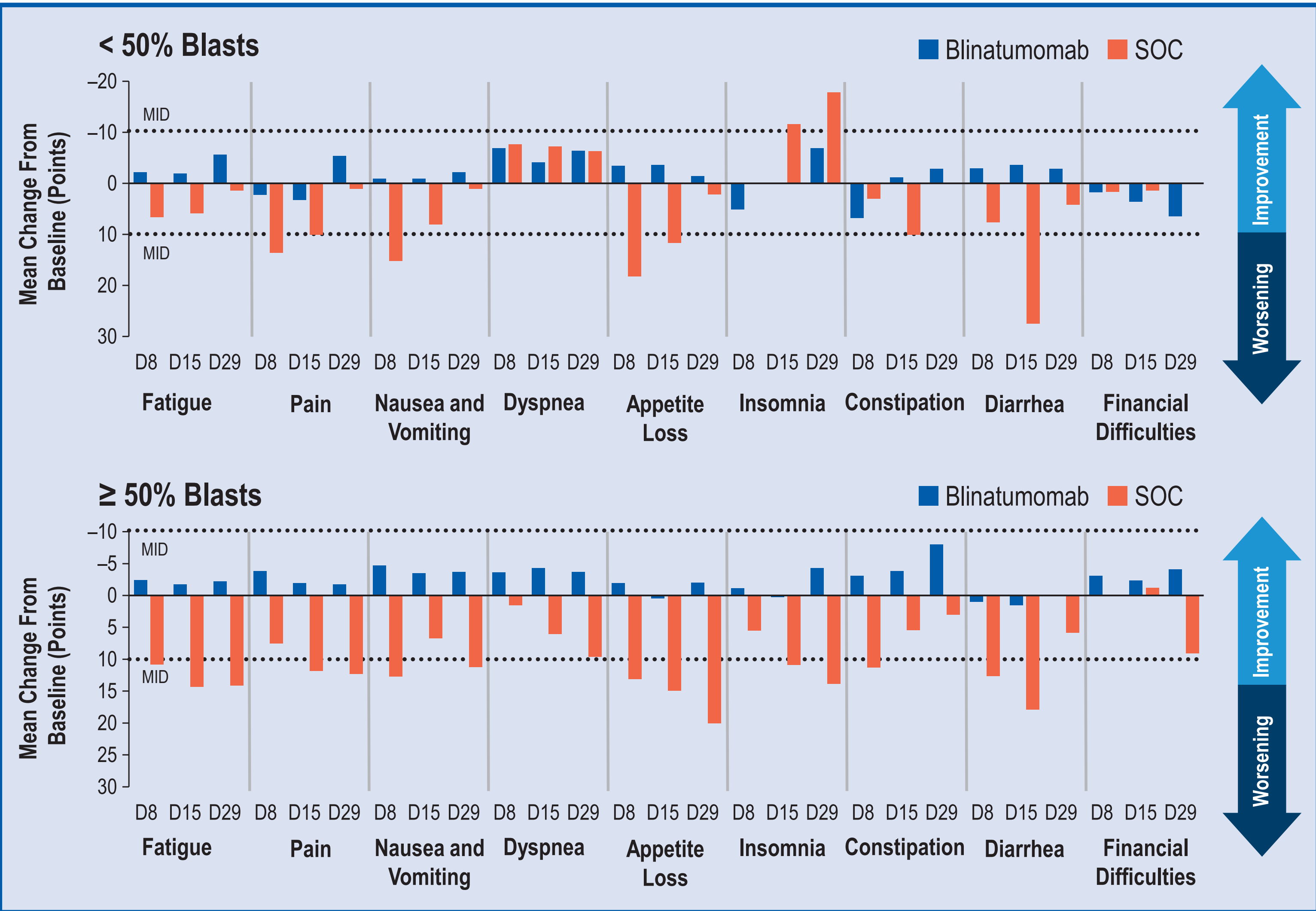


D, day; MID, minimal clinically important difference.

Change From Baseline in Cycle 1 in Symptom Scale/Item Scores

- Symptom scores generally improved with blinatumomab but not with SOC, particularly in patients with high blasts

Figure 3. Mean (SD) Change From Baseline in Cycle 1 in Symptom Scales/Items in Low and High Blast Subgroups



D, day; MID, minimal clinically important difference.

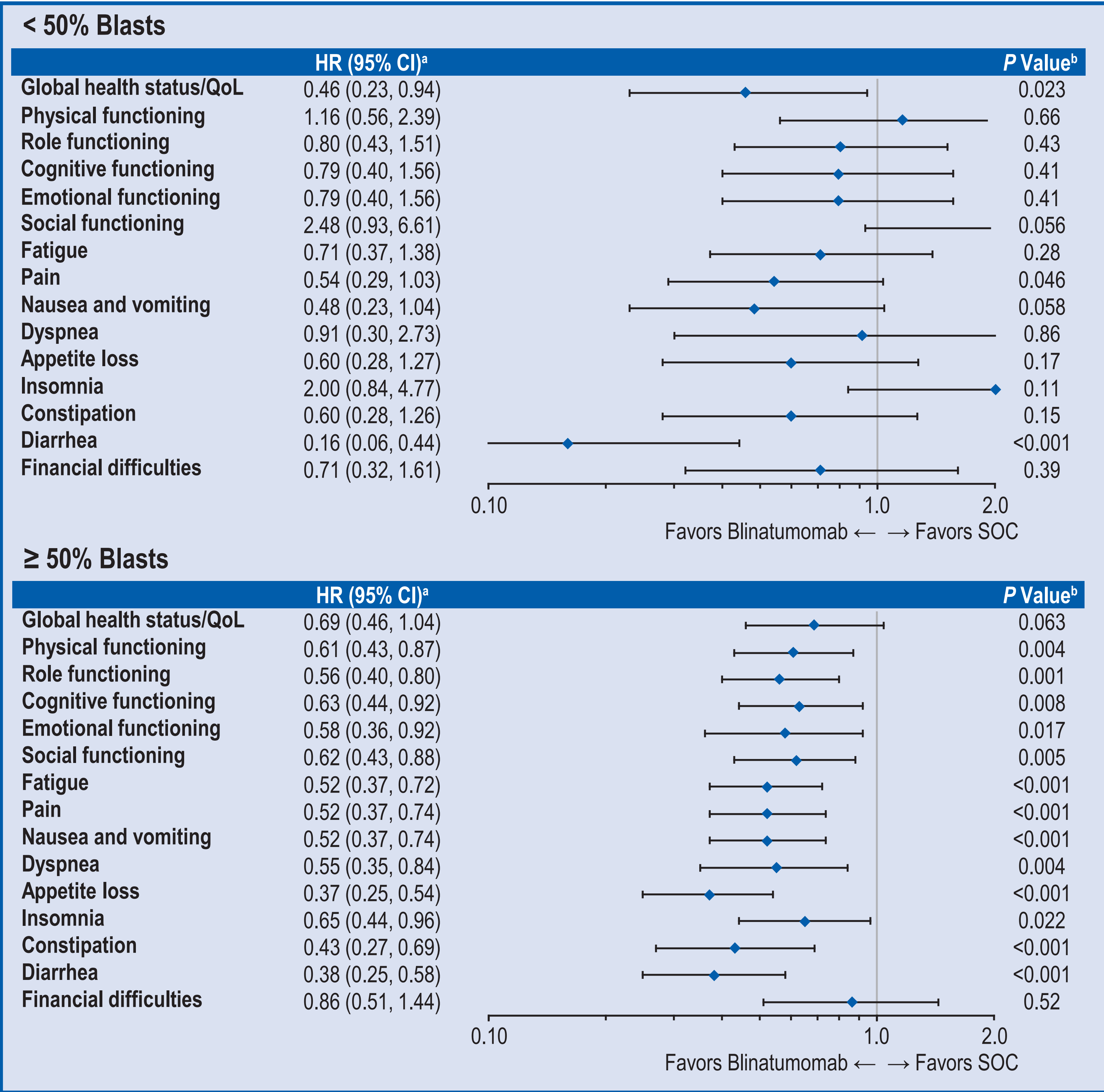
DISCLOSURES

- Anthony S. Stein:** speakers' bureau for Amgen Inc. and Cellgene. **Hervé Dombret:** consultancy, honoraria, travel expenses, research funding, and speaker's bureau for Amgen Inc an Ariad (Incyte); consultancy, honoraria, research funding, and speakers' bureau for Pfizer; consultancy, honoraria, and research funding from Jazz Pharma, Kite Pharma, and Novartis; consultancy and honoraria from Agios, Sunesis, Ambit (Daiichi Sankyo), Karyopharm, Menarini, Astellas, Janssen, Servier, Seattle Genetics, Immunogen, Shire-Baxalta, Abbvie, and Otsuka; travel expenses from Cellectis; travel expenses and speakers' bureau from Celgene. **Max S. Topp:** honoraria, board/advisory committee, travel and research funding from Angen Inc.; research funding from Boehringer Ingelheim; honoraria and research funding from Regeneron Pharmaceuticals, Inc.; board/advisory committee for F. Hoffmann–La Roche Ltd. **Zachary F. Zimmerman, Janet Franklin, Ze Cong, and Xinke Zhang:** employment by and stock ownership in Amgen Inc. **Andre Schuh:** consultancy for Amgen Inc., Celgene, Shire, Teva, Novartis, Otsuka, Jazz, and Pfizer. **Paul Cannell, Johan Maertens, and Yan Li:** no disclosures.

Time to Deterioration Analyses

- Compared with salvage chemotherapy, blinatumomab delayed time to deterioration, particularly in patients with high blasts

Figure 4. Time to Deterioration Analysis in Low and High Blast Subgroups



^a Stratified hazard ratio for EORTC for treatment difference.

^b Stratified log rank test for EORTC for treatment difference.

CONCLUSIONS

- In the HRQoL subgroup analysis, HRQoL was maintained or improved for patients treated with blinatumomab versus chemotherapy, even more so for patients with high disease burden
- Blinatumomab delayed time to HRQoL deterioration compared with chemotherapy, and the treatment effects were particularly larger among patients with high disease burden

Limitations

- Bone marrow blasts percentage was not a stratification factor, and thus, groups may have been imbalanced. However, baseline HRQoL scores were broadly similar between the blinatumomab and chemotherapy arms for each subgroup.
- Because the TOWER study was not designed to formally test HRQoL end points and because there was no adjustment in this analysis for multiple comparisons, all results are descriptive. As the sample size was small due to discontinuation or death, and was further reduced after restricting to subgroups, these analyses were not powered to conduct formal statistical significance tests.

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