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The Effect of Lenalidomide on Health-Related Quality of Life in Patients With Lower-Risk non-del(5q) Myelodysplastic Syndromes: Results From the MDS-005 Study

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Disclosure of conflict of interest

VS: Celgene Corporation – research funding, honoraria; Janssen – honoraria; Novartis – honoraria; Astex – honoraria; Amgen – honoraria. A Almeida: Celgene Corporation – consultancy, speakers bureau. AG: Celgene Corporation – consultancy, honoraria, board of directors or advisory committees. UP: Celgene Corporation – honoraria; RB: Celgene Corporation – consultancy, research funding, honoraria; Novartis – consultancy, honoraria. CLB and CW: Celgene Corporation – employment, equity ownership. SG and A Altincatal: Evidera – employment. PF: Celgene Corporation – research funding; Janssen – research funding; Novartis – research funding.

Authorship

VS, A Almeida, AG, UP, RB, and PF contributed to the collection of data. SG, A Altincatal and CW performed the statistical analyses. All authors were involved in the analysis and interpretation of the data, review and revision of the work and approval of the final version of the manuscript.

MicroAbstract

HRQoL was evaluated among RBC-TD patients with lower-risk non-del(5q) MDS treated with lenalidomide (*n* = 160) or placebo (*n* = 79) in the phase 3 MDS-005 study. Lenalidomide did not worsen HRQoL; response to lenalidomide was associated with significant HRQoL improvement. Lenalidomide represents a treatment option for patients with lower-risk non-del(5q) MDS who are ineligible for or refractory to ESAs.

Abstract

Background: The phase 3 MDS-005 study compared lenalidomide versus placebo in red blood cell transfusion-dependent (RBC-TD) patients with lower-risk non-del(5q) myelodysplastic syndromes (MDS), ineligible/refractory to erythropoiesis-stimulating agents. Lenalidomide-treated patients were more likely to achieve transfusion independence (TI) ≥ 8 weeks (26.9% vs 2.5%; *P* < 0.001) and haemoglobin increase ≥ 1.5 g/dL (19.4% vs 2.5%) versus placebo.

Patients and Methods: Patients were randomized 2:1 to oral lenalidomide 10 mg once daily or placebo once daily (both on 28-day cycles). Patients with creatinine clearance 40–60 mL/min were given lenalidomide 5 mg once daily. Health-related quality of life (HRQoL), a predefined secondary endpoint, was assessed using the EORTC QLQ-C30 questionnaire at baseline, week 12, week 24, every 12 weeks thereafter and at discontinuation.

Results: At week 24, lenalidomide was associated with benefit versus placebo across all 5 preselected questionnaire scales (Fatigue, Dyspnoea, Global Quality of Life, Physical Functioning, and Emotional Functioning). After adjustment for baseline scores, only Emotional Functioning achieved significance (*P* = 0.047). Further improvement versus baseline was observed for patients continuing lenalidomide after week 24. In post hoc analyses, achievement of TI ≥ 8 weeks was associated with significant improvements across all scales (*P* < 0.01); increase in haemoglobin level correlated with significant improvements in all scales at week 24, except Emotional Functioning (*P* < 0.05).

Conclusion: Lenalidomide did not adversely affect HRQoL in RBC-TD patients with lower-risk non-del(5q) MDS and response to lenalidomide was associated with significant improvements in HRQoL.

Keywords: Clinical trial, response, transfusion independence, haemoglobin, anaemia

Introduction

Anaemia is present in most patients with myelodysplastic syndromes (MDS) and contributes substantially to the clinical symptoms and burden of the disease.[1] Red blood cell (RBC) transfusions may help to alleviate the symptoms of anaemia,[2] but prolonged transfusion dependence is associated with increased morbidity,[3] shorter survival,[4,5] higher health-care costs,[6,7] and poor health-related quality of life (HRQoL).[8-10] Consequently, reducing transfusion dependence and anaemia-related symptoms is the main therapeutic goal in patients with transfusion-dependent lower-risk MDS.

Lenalidomide treatment results in RBC transfusion independence (RBC-TI) in more than half of patients with lower-risk MDS and del(5q),[11,12] and corresponding improvements in HRQoL have been observed.[13,14] For patients without del(5q), erythropoiesis-stimulating agents (ESAs) are the first-choice treatment for anaemia, and response to ESAs has been associated with improved HRQoL.[15-18] However, treatment options after failure of ESAs are limited,[2] which frequently leaves anaemic patients dependent on RBC transfusions. Recently, a phase 3 study (MDS-005) evaluated lenalidomide in transfusion-dependent patients with International Prognostic Scoring System (IPSS) Low- or Intermediate-1-risk MDS without del(5q) who were ineligible for or refractory to ESAs.[19] In this study, the proportion of patients who achieved RBC-TI ≥ 8 weeks was significantly higher in the lenalidomide group than in the placebo group (26.9% vs 2.5%; $P < 0.001$), with the majority responding within 16 weeks of treatment. A higher proportion of patients in the lenalidomide group achieved a haemoglobin increase of ≥ 1.5 g/dL compared with the placebo group (19.4% vs 2.5%).

HRQoL was a prespecified secondary endpoint of the MDS-005 study.[19] This report presents detailed results of the primary and additional post hoc analyses of patient-reported outcomes

data collected from the MDS-005 study to assess the impact of lenalidomide treatment on HRQoL in lower-risk non-del(5q) MDS patients.

Patients and Methods

The MDS-005 trial was a randomized, placebo-controlled, double-blind phase 3 study evaluating the efficacy and safety of lenalidomide in patients with IPSS Low- or Intermediate-1-risk MDS without del(5q) who were ineligible for or refractory to ESA treatment. Full details of the study supporting the efficacy, safety, and selected HRQoL findings have been published previously.[19] The study was approved by individual Institutional Review Boards of participating centres and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients before enrolment. The trial was registered as NCT01029262 at https://clinicaltrials.gov.

Study design

Eligible patients were aged ≥ 18 years, had transfusion-dependent anaemia (transfusion dependence was defined as an average transfusion requirement of ≥ 2 units packed RBCs every 28 days and no 8 consecutive weeks without RBC transfusions in the 16 weeks before randomization) due to IPSS Low- or Intermediate-1-risk MDS, had non-del(5q) karyotype and were ineligible for or refractory to ESAs (defined as [1] RBC transfusion dependence despite ESA treatment of ≥ 40,000 units/week recombinant human erythropoietin or equivalent dose of darbepoetin for 8 weeks, or [2] serum erythropoietin level >500 mU/mL in patients not previously treated with ESAs).

Patients were randomized 2:1 to oral lenalidomide 10 mg once daily or placebo once daily (both on 28-day cycles). Patients with creatinine clearance 40–60 mL/min were given lenalidomide 5 mg once daily. Patients with RBC-TI ≥ 8 weeks or erythroid response by week 24 continued

double-blind treatment until erythroid relapse, disease progression, unacceptable toxicity, or consent withdrawal.

Clinical endpoints

The primary clinical endpoint of the trial was the proportion of patients who achieved RBC-TI for ≥ 8 consecutive weeks. Secondary clinical endpoints included RBC-TI ≥ 24 weeks, progression to acute myeloid leukaemia, overall survival, HRQoL, and safety.

HRQoL assessment

A schematic overview of the methodology used in the MDS-005 study for the assessment of HRQoL is presented in Figure S1. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30)[20] at baseline, week 12, week 24, every 12 weeks thereafter and at discontinuation. The QLQ-C30 is a well-validated and commonly used questionnaire in MDS research.[21] It consists of 30 items, including 5 multi-item functional scales (Physical, Role, Emotional, Social, and Cognitive), 3 multi-item symptom scales (Fatigue, Nausea/Vomiting, and Pain), a Global Health Status/QoL scale and 6 single-item symptom scales (Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea, and Financial Difficulties). The standardized scores for this questionnaire range from 0 to 100, with higher scores indicating greater levels of functioning or more severe symptoms. Data were collected electronically using tablet computers. All HRQoL scales of the QLQ-C30 were analysed; however, the analysis focused on 5 preselected and clinically relevant scales[22-25]: Fatigue, Dyspnoea, Global Quality of Life, Physical Functioning, and Emotional Functioning.

Statistical analyses

Analyses of HRQoL were based on patients in the intent-to-treat (ITT) population who completed the baseline HRQoL assessment and had ≥ 1 post-baseline assessment available (i.e. the HRQoL-evaluable ITT population). The statistical methods are described in further detail in the Supplementary material.

Results

Patients

From February 2010 to June 2013, 239 patients were enrolled at 72 treatment centres and randomized to lenalidomide (*n* = 160) or placebo (*n* = 79), constituting the ITT population. Baseline characteristics were comparable between the 2 treatment groups; overall, median age was 71 years (range 43–87); 67.8% were male; median time from diagnosis was 2.6 years (range 0.1–29.6); and 49.4% had an Eastern Cooperative Oncology Group (ECOG) score of 1 or 2. Patients had received a median of 3.0 packed RBC units/28 days (range 1.5–9.8), and 83.7% had received prior therapy, 78.7% of whom received ESAs. Overall, 122 of 160 (76.3%) patients in the lenalidomide group and 56 of 79 (70.9%) patients in the placebo group completed a baseline HRQoL assessment and had ≥ 1 follow-up assessment available, thus constituting the HRQoL-evaluable ITT population.

Questionnaire compliance

HRQoL questionnaire response compliance rates were high and did not differ significantly between treatment groups across all assessment visits ($P > 0.05$; Table 1). Compliance rates for the combined lenalidomide and placebo groups were 89.5%, 82.0%, 83.9%, 82.2%, and 70.6% at baseline and weeks 12, 24, 36, and 48, respectively. No significant differences were seen in key baseline characteristics between compliant and noncompliant patients within each treatment group ($P > 0.05$) (data not shown).

HRQoL outcomes at baseline and follow-up

At baseline, mean scores for each scale of the QLQ-C30 did not differ significantly between treatment groups (Table S1). Compared with HRQoL data reported for the general population,[26] baseline HRQoL scores for patients in the MDS-005 study were worse, particularly for Global Quality of Life, Physical Functioning, Role Functioning, Fatigue, Dyspnoea, and Constipation (Table S1). At week 12, mean changes in HRQoL scores from baseline were not significantly different between treatment groups across the 5 preselected HRQoL scales (Figure 1). At week 24, lenalidomide was associated with significantly less Fatigue (P = 0.046) and better Emotional Functioning (P = 0.035) compared with placebo (Figure 1). After week 24, an improving trend was observed across all preselected scales in patients continuing treatment with lenalidomide; the number of patients in the placebo group was too small to show a trend, as most had discontinued study drug by this time point (Figure 1). No significant difference in mean change from baseline between treatment groups was observed for the remaining unselected scales, except for a significant improvement in Insomnia at week 24 in the lenalidomide group compared with placebo (P = 0.038; data not shown).

After adjusting for baseline scores, changes in HRQoL from baseline were not significantly different between treatment groups at week 12 (Figure 2). At week 24, only change in Emotional Functioning was statistically significant (+0.8 with lenalidomide vs −7.1 with placebo; P = 0.047) in the preselected scales; however, no adjustment for multiplicity was performed. In the remaining unselected scales, lenalidomide was associated with a significant improvement in Insomnia (P = 0.004) and a significant worsening in Diarrhoea (P = 0.050) at week 24 compared with placebo (data not shown).

Differences in predicted least-squares mean changes in HRQoL scores at week 24 for the preselected scales are shown in Figure 3. Lenalidomide was associated with better HRQoL scores versus placebo across all preselected scales, particularly Fatigue, Dyspnoea, and Emotional Functioning. None of the scales reached statistical significance, possibly due to small sample size. The analyses were not adjusted for the imputation of missing data; however, our analyses were consistent with results of analyses using complete cases, last observation carried forward and pattern mixture approaches to imputing missing data.

The proportion of patients in the lenalidomide and placebo groups categorized as having clinically meaningful improvement or worsening in preselected HRQoL scales at week 24 is shown in Figure 4. For each scale, the lenalidomide group had a larger proportion of patients with clinically meaningful improvement and a smaller proportion with clinically meaningful worsening as compared with placebo, although the difference between groups was not statistically significant for any of the scales.

Relationship between achievement of RBC-TI ≥ 8 weeks response and changes in HRQoL outcomes

In a post hoc analysis based on HRQoL-evaluable patients who completed a baseline HRQoL assessment and ≥ 1 post-baseline assessment (lenalidomide, *n* = 134; placebo, *n* = 62), achievement of RBC-TI ≥ 8 weeks (*n* = 41) was associated with a significant improvement ($P < 0.01$) in HRQoL across all preselected scales (Figure 5). The benefit associated with RBC-TI ≥ 8 weeks exceeded the prespecified score difference of ≥ 10 points versus baseline for clinically meaningful improvement in all 5 scales.

In another post hoc analysis, changes in HRQoL from baseline for the 5 preselected scales were not significantly different between lenalidomide nonresponders (i.e. lenalidomide-treated

patients who did not achieve RBC-TI ≥ 8 weeks) and placebo patients, suggesting that lenalidomide treatment even in the absence of a response had no significant negative impact on HRQoL. However, lenalidomide responders (i.e. those who achieved RBC-TI ≥ 8 weeks) did show improvements in all 5 scales compared with lenalidomide nonresponders or placebo patients. This suggests that patients responding to lenalidomide therapy not only benefitted in terms of becoming RBC-TI, but also experienced a significant alleviation of patient-reported symptoms (Figure S2**)**. The incidence of common grade 3/4 adverse events was comparable between RBC-TI ≥ 8 weeks responders and nonresponders (Table S2).

Relationship between change in haemoglobin level and changes in HRQoL outcomes

In a post hoc analysis of the lenalidomide and placebo groups combined, change in haemoglobin level from baseline correlated significantly ($P < 0.05$) with changes in HRQoL across all scales and time points, except for Emotional Functioning at weeks 12 and 24 and Dyspnoea at week 12 (Table 2). Haemoglobin level correlated positively with functional scales and negatively with symptom scales. The strength of the correlation increased from week 12 to week 24.

Discussion

This study provides the first detailed analysis of HRQoL from a randomized, placebo-controlled phase 3 study of lenalidomide in RBC transfusion-dependent patients with lower-risk, non-del(5q) MDS who were ineligible for or refractory to ESAs. Overall, treatment with lenalidomide did not worsen HRQoL compared with placebo, and clinically meaningful improvements were observed at week 24 in a proportion of patients, with a trend toward sustained improvements when lenalidomide treatment was extended beyond 24 weeks. Notably, response to lenalidomide was associated with significant improvements in HRQoL.

Anaemia is the most common cause of symptoms in patients with lower-risk MDS,[1] and anaemia-related fatigue can negatively affect HRQoL.[27,28] Dependence on RBC transfusions is also associated with worse HRQoL[8,9] and significantly shorter survival.[4,5] In addition, self-reported fatigue severity strongly correlates with patient-perceived symptom severity[29] and may provide prognostic information for overall survival independent of standard risk assessment in patients with higher-risk MDS.[30] Achievement of RBC-TI during lenalidomide therapy was associated with significant improvements in HRQoL. Our findings showed that an increase in haemoglobin level positively affected HRQoL, and the effect appeared to increase over time. These observations are consistent with previous reports on the impact of haemoglobin level and RBC transfusion dependence on HRQoL in MDS.[8,9,31]

Other studies of lenalidomide in lower-risk MDS have also reported positive effects on HRQoL.[13,14,32] In a phase 3 study of lower-risk MDS patients with del(5q), scores for the Functional Assessment of Cancer Therapy–Anemia (FACT-An) scale improved significantly from baseline in patients treated with lenalidomide 5 mg and 10 mg (+5.7 and +5.7, respectively) versus placebo (−2.8) (both $P < 0.05$).[13] Improvements were significantly greater in patients who achieved transfusion independence. The HRQoL benefit was apparent after 12 weeks in this patient population with del(5q) MDS. Continued treatment with lenalidomide was associated with further benefits. Similarly, a single-arm phase 2 trial of patients with anaemia and lower-risk del(5q) MDS reported that erythroid response with lenalidomide was associated with significant improvements in several scales of the MDS-specific QOL-E questionnaire compared with nonresponders.[32] Recent findings further suggest that transfusion-independent patients with lower-risk del(5q) MDS and moderate levels of anaemia may also benefit from early treatment with lenalidomide in terms of better physical functioning.[14] Our study has found that the HRQoL benefits of lenalidomide in lower-risk MDS are not just restricted to patients with the del(5q) karyotype.

The observed improvements in HRQoL are consistent with the known biological and clinical effects of lenalidomide in lower-risk MDS.[11,12,19,33-35] In a phase 2 study of transfusion-dependent patients with del(5q), 67% of patients treated with lenalidomide achieved RBC-TI ≥ 8 weeks, with a median peak increase in haemoglobin level of 5.4 g/dL.[11] In a subsequent phase 3 study, significantly more patients treated with lenalidomide 5 mg and 10 mg achieved RBC-TI ≥ 26 weeks compared with placebo (42.6% and 56.1%, respectively, vs 5.9%; both $P < 0.001$).[12] In the MDS-005 phase 3 study of non-del(5q) lower-risk patients, lenalidomide resulted in RBC-TI ≥ 8 weeks in 26.9% of patients,[19] which was consistent with the response rate observed in the initial phase 2 MDS-002 trial.[33] Myelosuppression is a common adverse event observed in patients treated with lenalidomide: in MDS-005, the incidence of grade 3/4 neutropenia and thrombocytopenia was 62% and 36%, respectively.[19] The incidence of common grade 3/4 adverse events was comparable between responders and nonresponders. In contrast to previous findings in patients with del(5q) from the MDS-003 study,[36] lenalidomide-induced myelosuppression occurring early during treatment did not predict response to lenalidomide in patients with non-del(5q) MDS in the present study (data not shown). In our analysis, achievement of RBC-TI ≥ 8 weeks was nevertheless associated with improved HRQoL. This suggests that, overall, in terms of HRQoL, the positive effects of achieving transfusion independence may outweigh the negative effects of adverse events associated with treatment.

Whereas improvements in HRQoL were observed after 12 weeks of lenalidomide treatment in patients with del(5q),[13] our analysis of a non-del(5q) population showed that the HRQoL benefit was delayed until week 24 of treatment. This observation is consistent with the longer median time to onset of RBC-TI in non-del(5q) patients compared with del(5q) patients.[12,19] The reported HRQoL benefits we observed, together with the possibility of selecting patients more likely to respond to lenalidomide based on endogenous erythropoietin level,[19] is encouraging in this

ESA-refractory or -ineligible group with otherwise very limited treatment options. Furthermore, the combination of lenalidomide and erythropoietin[37] has been added to the updated National Comprehensive Cancer Network (NCCN) guidelines as a treatment option for patients with lower-risk non-del(5q) MDS who fail to respond or stop responding to ESAs.[38]

A potential limitation of the current study is that only patients who achieved RBC-TI ≥ 8 weeks or erythroid response were allowed to continue treatment after week 24. The small number of patients in this group precludes comparisons of HRQoL between treatment groups beyond week 24. However, the available data after week 24 (in responding patients) suggest continued positive effects of long-term treatment with lenalidomide in terms of HRQoL. Questionnaire-based studies are subject to selection bias due to study dropout and patient-related factors, such as older age and higher level of comorbidity.[39] However, despite the elderly patient population and electronic method of data collection, compliance rates in this study were high and similar between treatment groups at all assessment visits. Baseline characteristics of compliant and noncompliant patients were comparable, suggesting that the data are representative of all patients in the MDS-005 study and the results are unlikely to be affected by dropouts. Notably, imputation using different methods and missing-data assumptions produced consistent results, indicating that bias due to missing data is unlikely. Our results add to the existing evidence demonstrating the utility of the QLQ-C30 in patients with MDS.[29,40,41]

Conclusion

In conclusion, treatment with lenalidomide did not worsen HRQoL overall compared with placebo in patients with lower-risk non-del(5q) MDS, regardless of responder status. Achievement of RBC-TI ≥ 8 weeks during lenalidomide therapy was associated with significant improvements in HRQoL. Continued lenalidomide treatment appeared to maintain or increase improvements in HRQoL. Based on these findings and the results of the MDS-005 trial,

lenalidomide represents a treatment option for patients with lower-risk non-del(5q) MDS who are ineligible for or refractory to ESAs, and optimal benefit may be attained when treatment is maintained after achievement of RBC-TI.

Clinical Practice Points

- Transfusion dependent MDS is associated with poor HRQoL due to anaemia-related fatigue and the burden of undergoing chronic transfusions
- In the MDS-005 phase 3 study of patients with non-del(5q) lower-risk MDS, 26.9% of patients achieved RBC-TI ≥ 8 weeks with lenalidomide treatment. Until this analysis, however, the impact of lenalidomide on patient HRQoL in this setting was relatively unclear
- Our study shows that HRQoL did not worsen during lenalidomide treatment, and patients who responded to lenalidomide reported significant improvements in HRQoL. Continued lenalidomide treatment appeared to maintain or increase improvements in HRQoL
- Firstly, these findings highlight the importance of achieving RBC-TI in patients with lower-risk MDS, as this was associated with a significant improvement in patient HRQoL. Achievement of TI should therefore remain an important goal of therapy for these patients
- Secondly, our findings further support the use of lenalidomide in patients with lower-risk non-del(5q) MDS who are refractory to ESAs. Given the limited treatment options currently available for these patients, the use of lenalidomide in selected patients may help improve patient outcomes, including HRQoL

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Table 1 EORTC QLQ-C30 Response Compliance Rates

Scheduled Visit, *n*/*N* (%)	Lenalidomide	Placebo	*P* Value
Baseline	144/160 (90.0)	70/79 (88.6)	0.823
Week 12	134/160 (83.8)	62/79 (78.5)	0.371
Week 24*	91/106 (85.8)	50/62 (80.6)	0.391
Week 36	33/41 (80.5)	4/4 (100)	1.000
Week 48	23/32 (71.9)	1/2 (50.0)	0.508

***Only patients with RBC-TI ≥ 8 weeks or erythroid response by week 24 continued double-blind treatment.

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; RBC-TI = red blood cell transfusion independence.

Table 2 Relationship Between Change From Baseline in Haemoglobin Level and Changes in HRQoL Outcomes for the Combined Lenalidomide and Placebo Groups in Patients With Available Haemoglobin and HRQoL Data at Weeks 12 and 24

Scale of EORTC QLQ-C30	Scheduled Visit	*n*	Correlation Coefficient	*P* Value
Symptom Scales				
Fatigue	Week 12	131	−0.24042	0.0057
	Week 24	92	−0.45423	< 0.0001
Dyspnoea	Week 12	131	−0.13084	0.1363
	Week 24	92	−0.21807	0.0368
Functional Scales				
Global Quality of Life	Week 12	131	0.21277	0.0147
	Week 24	92	0.32566	0.0015
Physical Functioning	Week 12	131	0.19409	0.0263
	Week 24	92	0.55735	< 0.0001
Emotional Functioning	Week 12	131	0.09999	0.2558
	Week 24	92	0.20479	0.0502

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL = health-related quality of life.

Figure legends

Figure 1 Mean Change from Baseline in HRQoL Scores Without Adjusting for Baseline Scores for Preselected EORTC QLQ-C30 Scales (A: Fatigue, B: Dyspnoea, C: Global Quality of Life, D: Physical Functioning, E: Emotional Functioning) by Randomized Treatment Group

*Indicates significant difference ($P < 0.05$) between treatment groups. †Data for placebo group at week 48 not shown due to low patient number.

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL = health-related quality of life; SE = standard error.

Figure 2 Mean Change from Baseline in HRQoL Scores After Adjusting for Baseline Scores for Preselected EORTC QLQ-C30 Scales by Randomized Treatment Group

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL = health-related quality of life.

Figure 3 Difference in Predicted Least-Squares Mean Changes for Preselected EORTC QLQ-C30 HRQoL Scales Between Lenalidomide Versus Placebo at Week 24. The Model Included the Following Covariates: Treatment Group, Time (in Weeks), Baseline Score and a Treatment Group × Time Interaction Term, with Intercept and Time as Random Effects

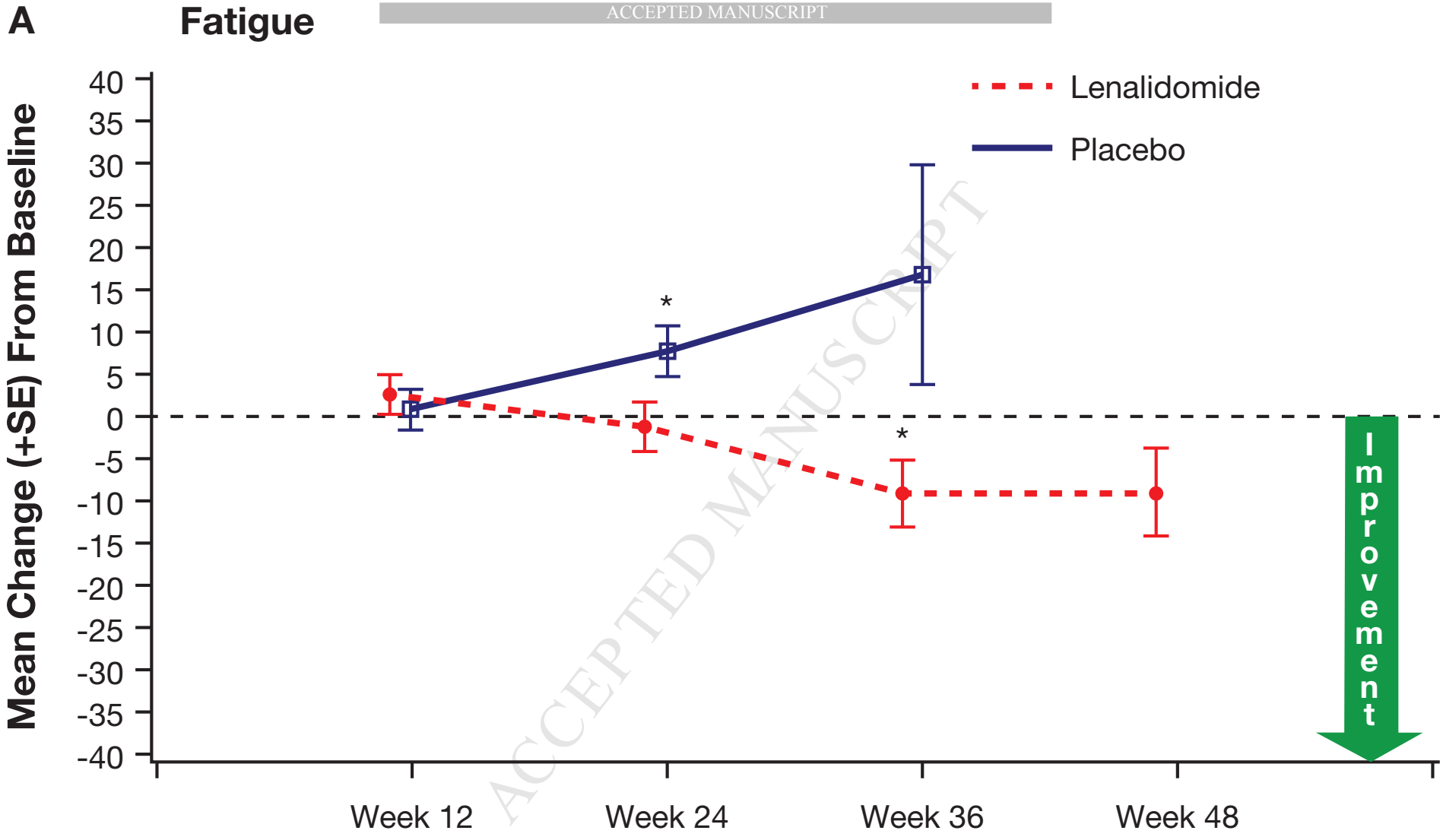
Abbreviations: CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL = health-related quality of life.

Figure 4 Proportion of Patients With Clinically Meaningful Improvement or Worsening in Scores for Preselected EORTC QLQ-C30 HRQoL Scales at Week 24. A Clinically Meaningful Change was Defined as a Change of ≥ 10 Points from Baseline

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL = health-related quality of life.

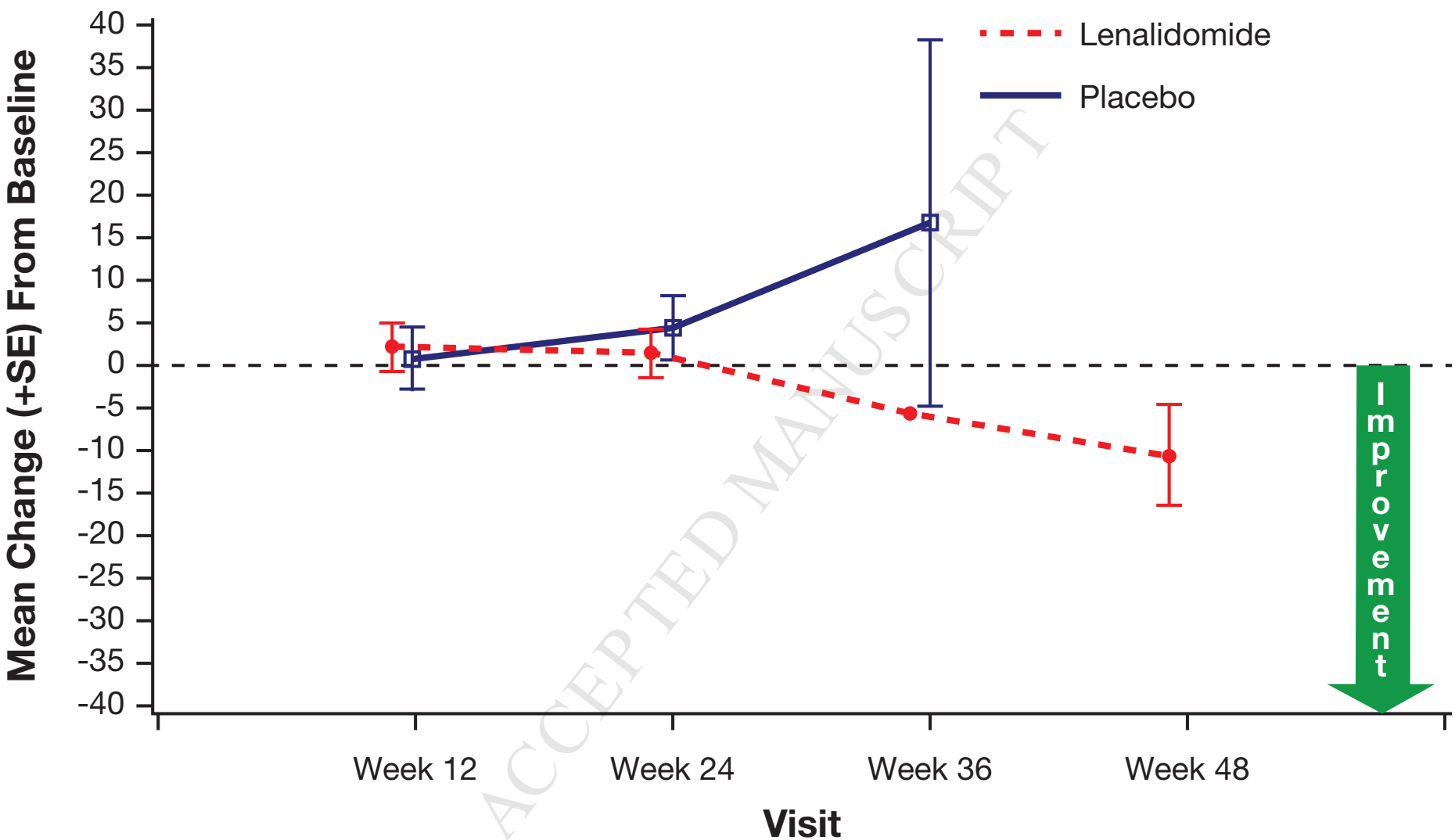
Figure 5 Relationship Between Achievement of RBC-TI ≥ 8 Weeks and Change in HRQoL. For Each EORTC QLQ-C30 Scale, the Effect of RBC-TI ≥ 8 Weeks Achievement on HRQoL was Adjusted for Other Relevant Covariates, Including Baseline Score, Time (Visits) and Treatment Group

Abbreviations: CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL = health-related quality of life; RBC-TI = red blood cell transfusion independence. [Copyright permission JCO pending[19]]



No. of patients				
Lenalidomide	122	83	29	22
Placebo	56	47	4	1†

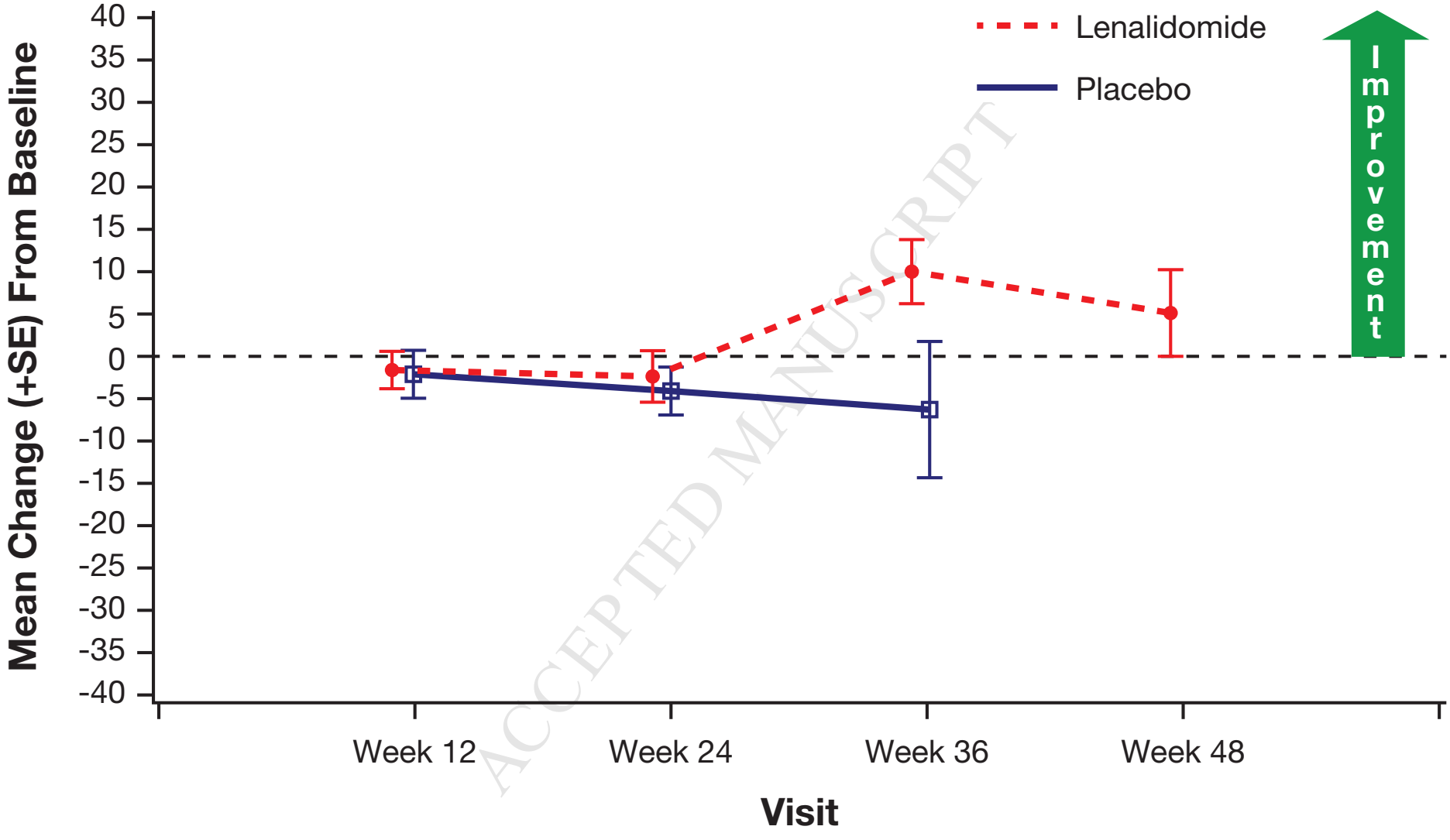
B **Dyspnoea**



No. of patients				
Lenalidomide	122	83	29	22
Placebo	56	47	4	1†

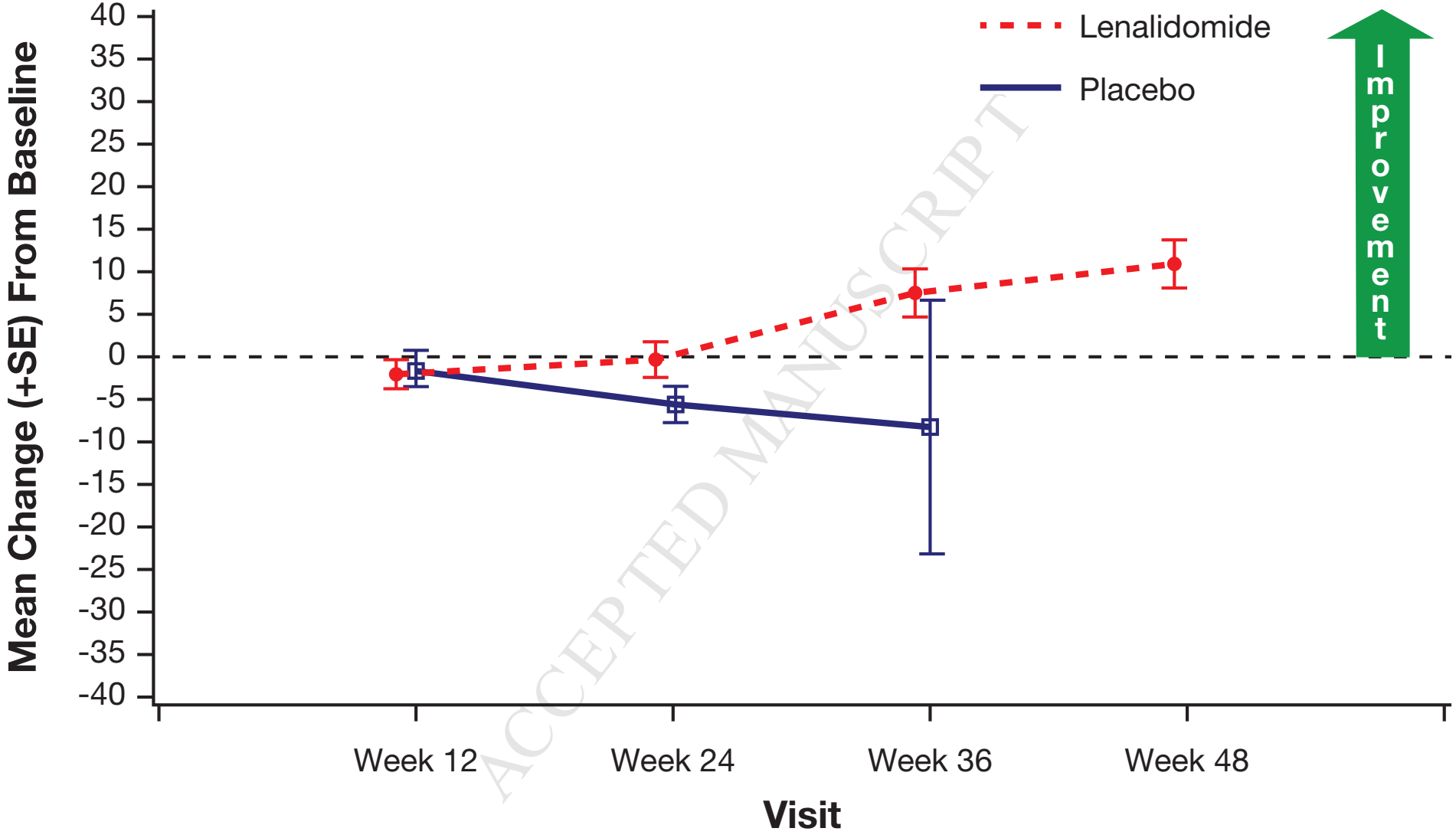
C

Global Quality of Life



No. of patients				
Lenalidomide	122	83	29	22
Placebo	56	47	4	1†

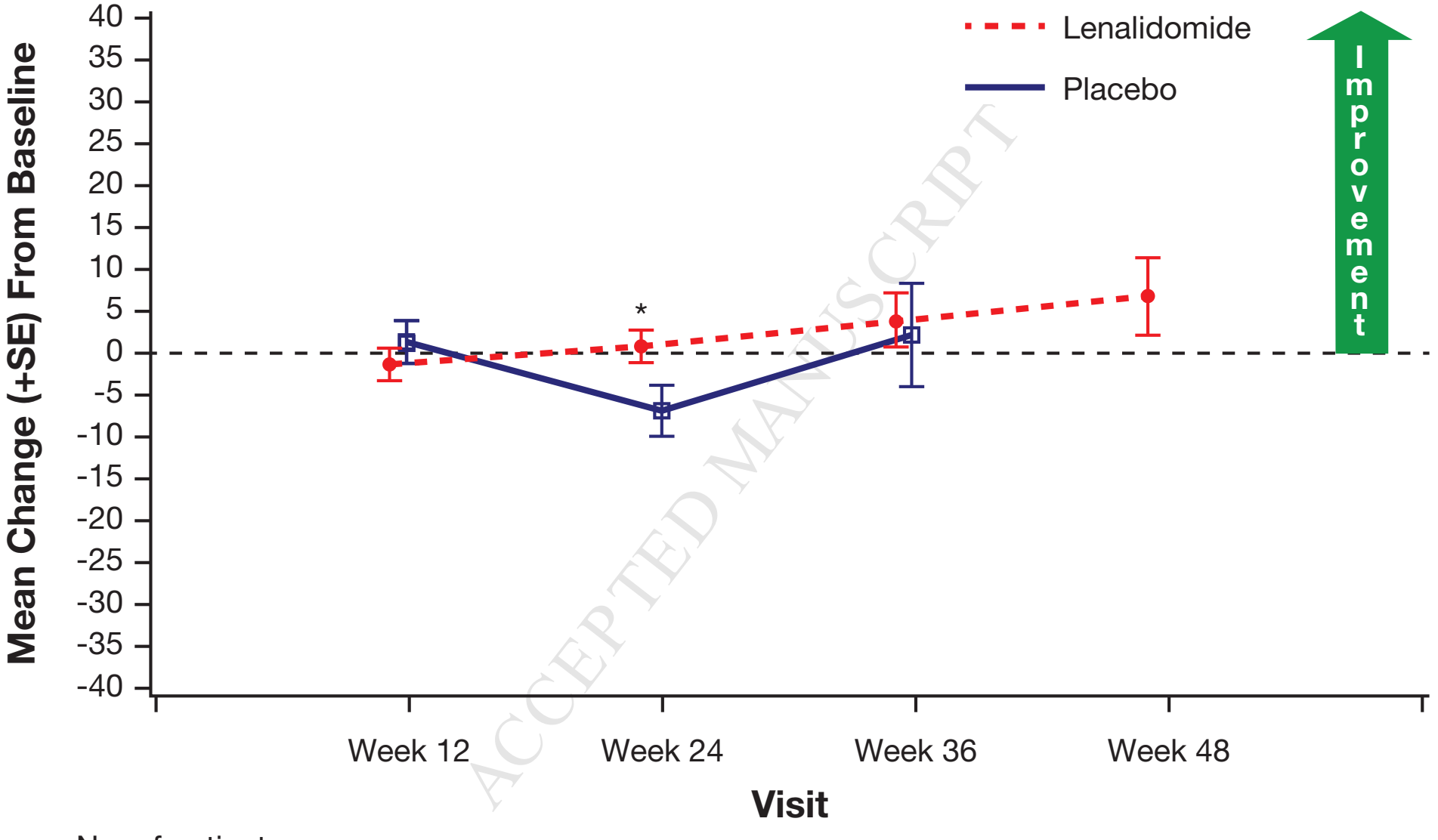
D **Physical Functioning**



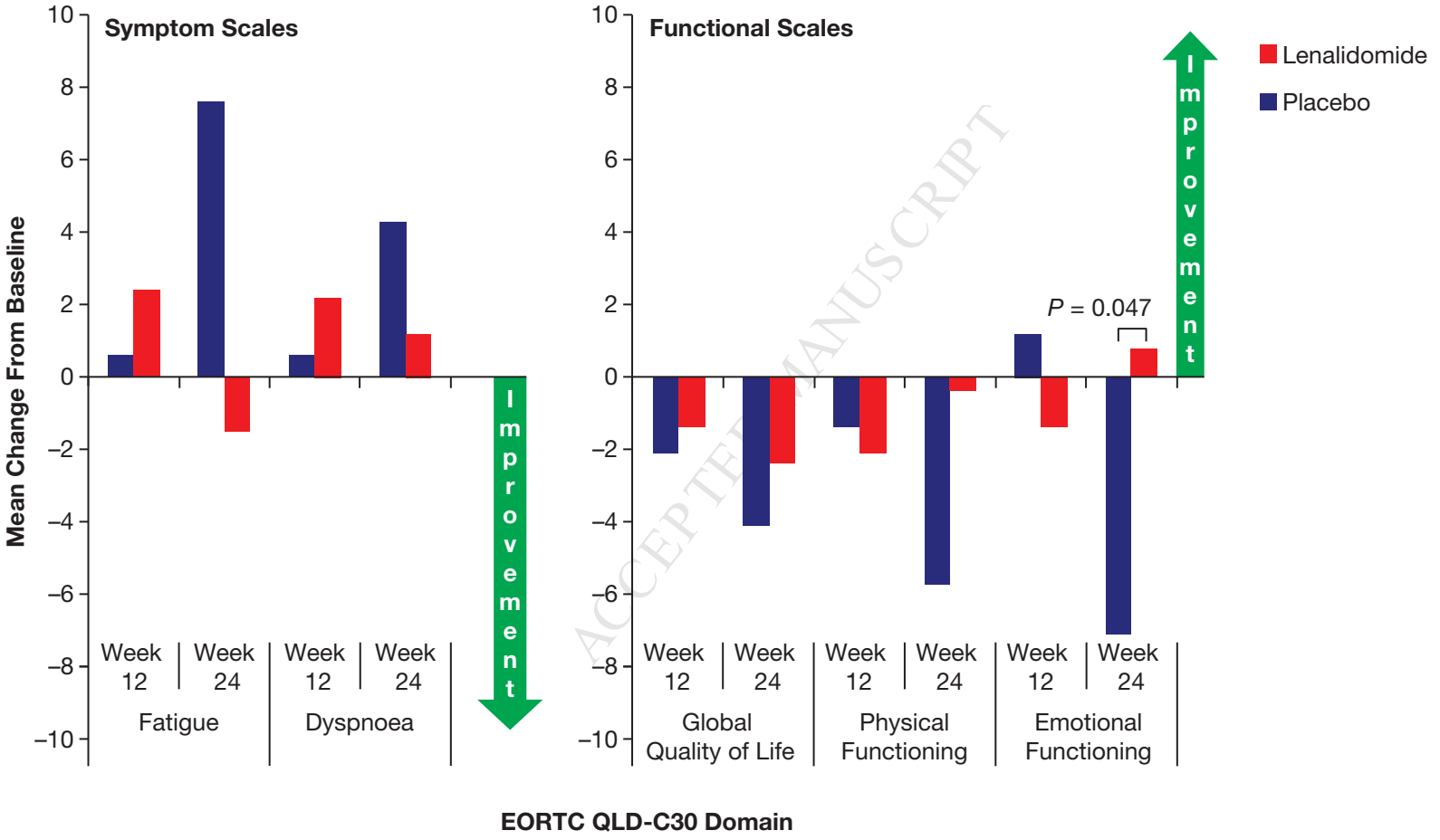
No. of patients				
Lenalidomide	122	83	29	22
Placebo	56	47	4	1†

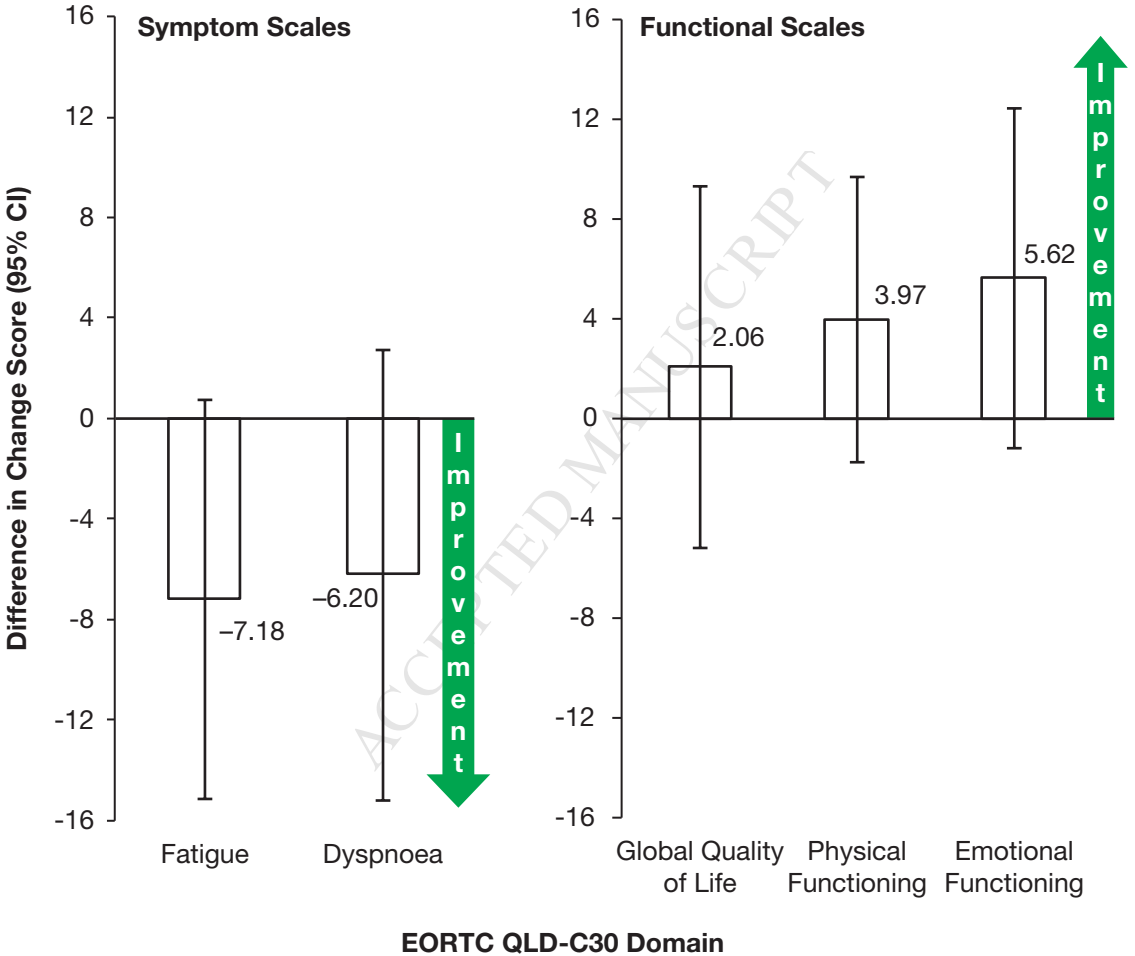
E

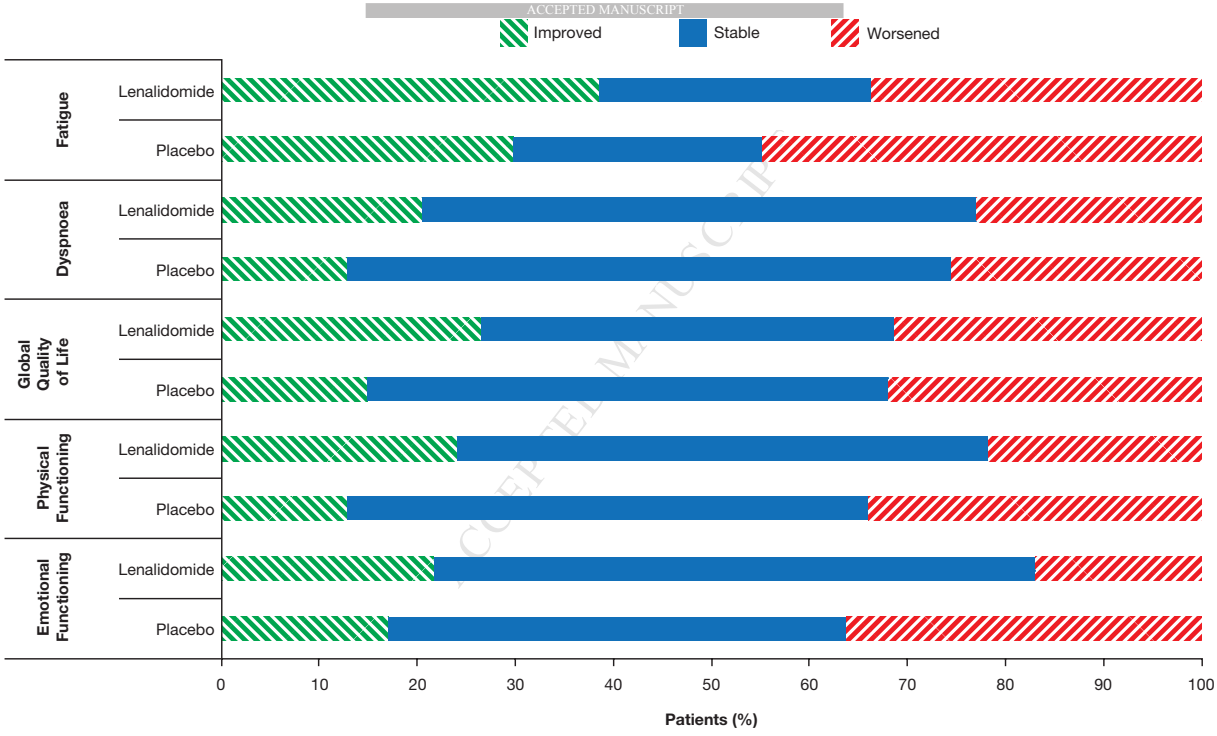
Emotional Functioning

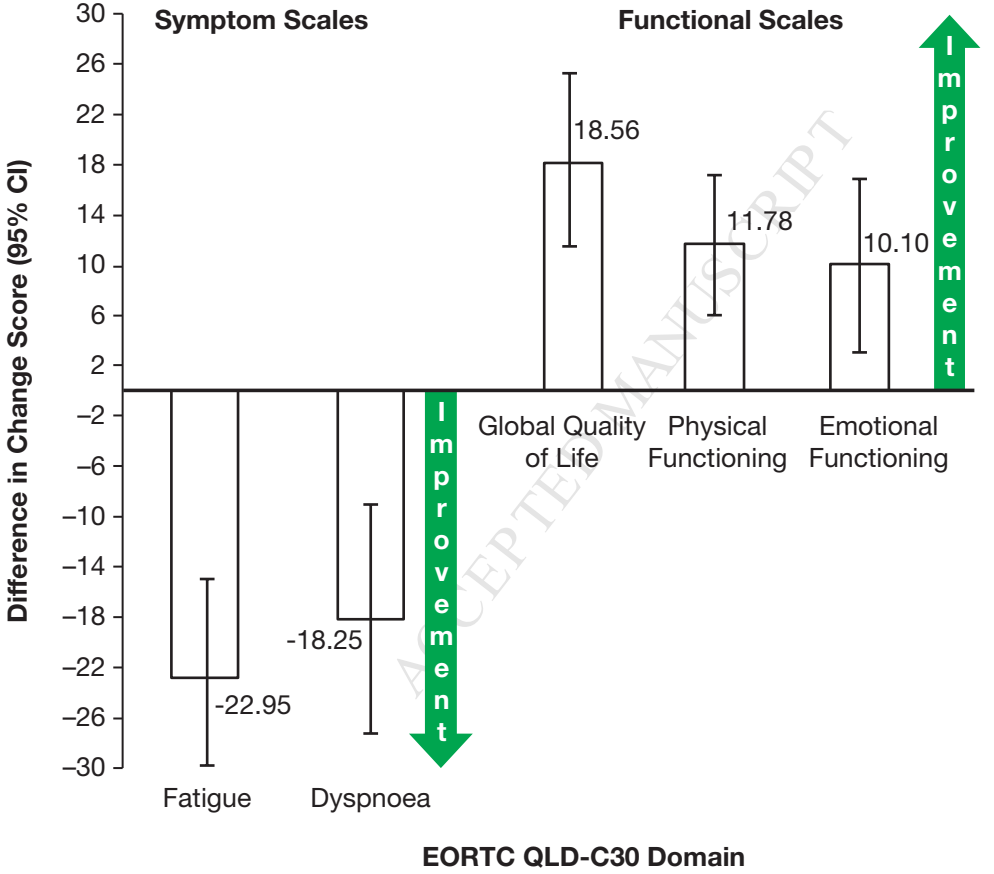


No. of patients				
Lenalidomide	122	83	29	22
Placebo	56	47	4	1†









Supplementary Material for "The Effect of Lenalidomide on Health-Related Quality of Life in Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes: Results From the MDS-005 Study" (Santini *et al*)

Additional Methods: Statistical Analyses

The proportion of patients completing the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) was calculated at each assessment visit. A patient was considered compliant at a particular visit if ≥ 15 of 30 questionnaire items were completed. The denominator for each visit was calculated based on the number of patients who were still on the study drug at that time point. The two-sided Fisher exact test was used to compare the proportion of compliant patients at each assessment visit between treatment groups. Key baseline characteristics between compliant and noncompliant patients were compared between treatment groups using the two-sided Fisher exact test for categorical variables and the two-sample *t*-test for continuous variables.

For each scale of the QLQ-C30, descriptive statistics of observed scores and change from baseline scores were calculated for each visit. A pooled, two-sample, two-sided *t*-test was used to determine differences in mean changes from baseline between treatment groups. Between-group comparisons were limited to weeks 12 and 24 due to low patient numbers after 24 weeks. To account for differences in baseline scores between treatment groups, analysis of variance was also performed on change from baseline scores in preselected health-related quality of life (HRQoL) scales between treatment groups. Sensitivity analyses using last observation carried forward, complete-case analysis and pattern mixture model were performed to assess the impact of missing data on the primary analyses.

To estimate the effect of treatment on each scale of the QLQ-C30 over time and assess differences between treatment groups, a linear mixed-effects repeated-measures analysis model with random intercept/slope was used, using a restricted maximum-likelihood estimation

method. The following covariates were included: treatment group, time (in weeks), baseline score and a treatment group × time interaction term, with intercept and time as random effects. Results were summarized using the least-squares means for change from baseline to week 24 within each treatment group and the difference in least-squares means between treatment groups.

Clinically meaningful changes in HRQoL scale scores were prespecified as a score difference of ≥ 10 points versus baseline.[1] Patients were accordingly grouped into categories of improvement, no change, or worsening. The two-sided Fisher exact test was used to compare the proportions of patients within these categories at each post-baseline visit between treatment groups.

A post hoc analysis was performed to assess the impact of red blood cell transfusion independence (RBC-TI), as a time-varying covariate while controlling for other significant factors, on preselected HRQoL scales using a linear mixed-effects regression model to estimate the difference in scores between RBC-TI ≥ 8 weeks responders and nonresponders. The incidence of grade 3/4 adverse events was analysed according to RBC-TI ≥ 8 weeks response in lenalidomide-treated patients. Adverse events were coded as in the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3·0). In addition, a post hoc analysis was conducted to assess the relationship between change in haemoglobin level and changes in HRQoL outcomes at weeks 12 and 24 across all 5 preselected scales. The post-baseline haemoglobin collection dates were matched with the HRQoL assessments to obtain haemoglobin data on the same day as the HRQoL visit. The association between variables was analysed using the Pearson correlation coefficient.

The data cutoff date for inclusion in this analysis was 17 March 2014.

Table S1 Mean Scores of EORTC QLQ-C30 Scales at Baseline Among HRQoL-Evaluable Patients From the MDS-005 Study (Lenalidomide and Placebo Columns) and the General Population.[2] A Clinically Meaningful Change was Defined as a Change of ≥ 10 Points From Baseline

EORTC QLQ-C30 Scale, Mean Score (SD)	Lenalidomide (n = 131)	Placebo (n = 58)	General Population (N = 7802)
Global Quality of Life	57.1 (21.96)	59.9 (17.27)	71.2 (22.4)
Physical Functioning	69.6 (20.95)	73.1 (17.35)	89.8 (16.2)
Role Functioning	68.8 (30.48)	74.7 (25.02)	84.7 (25.4)
Emotional Functioning	76.8 (21.27)	78.7 (20.72)	76.3 (22.8)
Cognitive Functioning	83.5 (19.99)	88.2 (14.65)	86.1 (20.0)
Social Functioning	80.0 (23.79)	82.5 (21.04)	87.5 (22.9)
Fatigue	42.8 (26.23)	37.5 (20.37)	24.1 (24.0)
Nausea/Vomiting	4.1 (10.36)	5.7 (12.70)	3.7 (11.7)
Pain	21.9 (29.89)	21.3 (26.27)	20.9 (27.6)
Dyspnoea	30.3 (30.51)	31.6 (29.57)	11.8 (22.8)
Insomnia	27.7 (30.7)	27.0 (31.50)	21.8 (29.7)
Appetite Loss	15.5 (27.21)	8.6 (15.99)	6.7 (18.3)
Constipation	17.0 (26.59)	15.5 (23.54)	6.7 (18.4)
Diarrhoea	9.7 (21.28)	80.(18.00)	7.0 (18.0)
Financial Difficulties	13.2 (25.38)	15.5 (24.36)	9.5 (23.2)

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL = health-related quality of life; SD = standard deviation.

Table S2 Grade 3/4 TEAEs in Lenalidomide-Treated Patients According to RBC-TI ≥ 8 Weeks Response

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Patients with ≥ 1 grade 3/4 TEAE	39 (90.7)	99 (84.6)	1 (50.0)	34 (44.2)
Blood and Lymphatic System Disorders	37 (86.0)	81 (69.2)	1 (50.0)	16 (20.8)
Neutropenia	35 (81.4)	64 (54.7)	0	9 (11.7)
Thrombocytopenia	15 (34.9)	42 (35.9)	0	3 (3.9)
Leukopenia	10 (23.3)	8 (6.8)	0	1 (1.3)
Anaemia	2 (4.7)	7 (6.0)	0	4 (5.2)
Bone marrow reticulin fibrosis	0	1 (0.9)		
Coagulopathy	0	1 (0.9)		
Haemolysis	0	1 (0.9)		
Pancytopenia	0	1 (0.9)		
Febrile neutropenia	1 (2.3)	0	1 (50.0)	0
Lymphopenia	1 (2.3)	0		

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Infections and Infestations	4 (9.3)	19 (16.2)	0	3 (3.9)
Pneumonia	3 (7.0)	6 (5.1)	0	2 (2.6)
Neutropenic sepsis	0	3 (2.6)		
Urinary tract infection	0	2 (1.7)	0	1 (1.3)
Atypical pneumonia	0	1 (0.9)		
Bronchitis	0	1 (0.9)		
Bronchopneumonia	0	1 (0.9)		
Cellulitis	0	1 (0.9)		
Escherichia sepsis	0	1 (0.9)		
Folliculitis	0	1 (0.9)		
Parotitis	0	1 (0.9)		
Peritonitis bacterial	0	1 (0.9)		
Pneumonia viral	0	1 (0.9)		
Staphylococcal infection	0	1 (0.9)		

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Tooth abscess	0	1 (0.9)		
Lobar pneumonia	1 (2.3)	0		
Influenza			0	1 (1.3)
General Disorders and Administration-Site Conditions	4 (9.3)	11 (9.4)	0	2 (2.6)
Asthenia	1 (2.3)	5 (4.3)	0	1 (1.3)
Fatigue	1 (2.3)	4 (3.4)	0	1 (1.3)
Face oedema	0	1 (0.9)		
Oedema peripheral	0	1 (0.9)		
General physical health deterioration	1 (2.3)	0		
Malaise	1 (2.3)	0		
Investigations	4 (9.3)	10 (8.5)	0	4 (5.2)
Liver function test abnormal	0	2 (1.7)		
Alanine aminotransferase increased	2 (4.7)	1 (0.9)	0	1 (1.3)

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Blood bilirubin increased	0	1 (0.9)		
Blood creatinine increased	0	1 (0.9)		
Blood glucose increased	0	1 (0.9)		
C-reactive protein increased	0	1 (0.9)		
HLA marker study positive	0	1 (0.9)		
Mycobacterium test positive	0	1 (0.9)		
Oxygen saturation decreased	0	1 (0.9)		
Troponin increased	0	1 (0.9)	0	1 (1.3)
Aspartate aminotransferase increased	1 (2.3)	0		
Weight decreased	1 (2.3)	0	0	1 (1·3)
Gamma-glutamyltransferase increased			0	1 (1.3)
Serum ferritin increased			0	1 (1.3)
Metabolism and Nutrition Disorders	2 (4.7)	10 (8.5)	0	5 (6.5)
Hypokalaemia	1 (2.3)	6 (5.1)		

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Decreased appetite	0	1 (0.9)		
Hyperglycaemia	0	1 (0.9)		
Hyperkalaemia	0	1 (0.9)		
Hypocalcaemia	0	1 (0.9)		
Iron overload	1 (2.3)	1 (0.9)	0	2 (2.6)
Fluid overload			0	1 (1.3)
Hyperuricaemia			0	1 (1.3)
Hypoglycaemia			0	1 (1.3)
Gastrointestinal Disorders	1 (2.3)	8 (6.8)	0	4 (5.2)
Diarrhoea	0	4 (3.4)		
Abdominal pain	0	1 (0.9)	0	1 (1.3)
Ascites	0	1 (0.9)		
Gastrointestinal necrosis	0	1 (0.9)		
Haematemesis	0	1 (0.9)		

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Nausea	0	1 (0.9)		
Inguinal hernia, obstructive	1 (2.3)	0		
Constipation			0	2 (2.6)
Diverticulum			0	1 (1.3)
Pancreatitis			0	1 (1.3)
Pancreatitis necrotizing			0	1 (1.3)
Skin and Subcutaneous Tissue Disorders	3 (7.0)	8 (6.8)	0	2 (2.6)
Drug eruption	0	1 (0.9)		
Dry skin	0	1 (0.9)		
Exfoliative rash	0	1 (0.9)		
Neurodermatitis	0	1 (0.9)		
Pruritus	2 (4.7)	1 (0.9)	0	2 (2.6)
Rash erythematous	0	1 (0.9)		

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Rash pruritic	0	1 (0.9)		
Skin ulcer	1 (2.3)	1 (0.9)		
Urticaria	0	1 (0.9)		
Rash	1 (2.3)	0		
Respiratory, Thoracic, and Mediastinal Disorders	1 (2.3)	7 (6.0)	0	3 (3.9)
Dyspnoea	0	3 (2.6)	0	3 (3.9)
Pleural effusion	0	2 (1.7)		
Acute respiratory distress syndrome	0	1 (0.9)		
Epistaxis	0	1 (0.9)		
Hypoxia	0	1 (0.9)		
Lung disorder	0	1 (0.9)		
Asthma	1 (2.3)	0		
Cardiac Disorders	0	6 (5.1)	0	5 (6.5)

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Cardiac failure	0	2 (1.7)	0	1 (1.3)
Myocardial infarction	0	2 (1.7)	0	1 (1.3)
Atrial fibrillation	0	1 (0.9)	0	3 (3.9)
Cardiac failure congestive	0	1 (0.9)		
Atrial flutter			0	1 (1.3)
Ventricular arrhythmia			0	1 (1.3)
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	1 (2.3)	4 (3.4)	0	5 (6.5)
Myelodysplastic syndromes	0	2 (1.7)		
Adenocarcinoma of colon	0	1 (0.9)		
Lung squamous cell carcinoma stage IV	0	1 (0.9)		
Invasive ductal breast carcinoma	1 (2.3)	0		

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Acute myeloid leukaemia			0	2 (2.6)
Chronic myelomonocytic leukaemia			0	1 (1.3)
Prostate cancer			0	1 (1.3)
Squamous cell carcinoma of lung			0	1 (1.3)
Musculoskeletal and Connective	0	3 (2.6)	0	1 (1.3)
Tissue Disorder				
Intervertebral disc protrusion	0	1 (0.9)		
Osteoarthritis	0	1 (0.9)		
Pain in jaw	0	1 (0.9)		
Rhabdomyolysis			0	1 (1.3)
Nervous System Disorders	0	3 (2.6)		
Headache	0	1 (0.9)		
Lethargy	0	1 (0.9)		
Syncope	0	1 (0.9)		

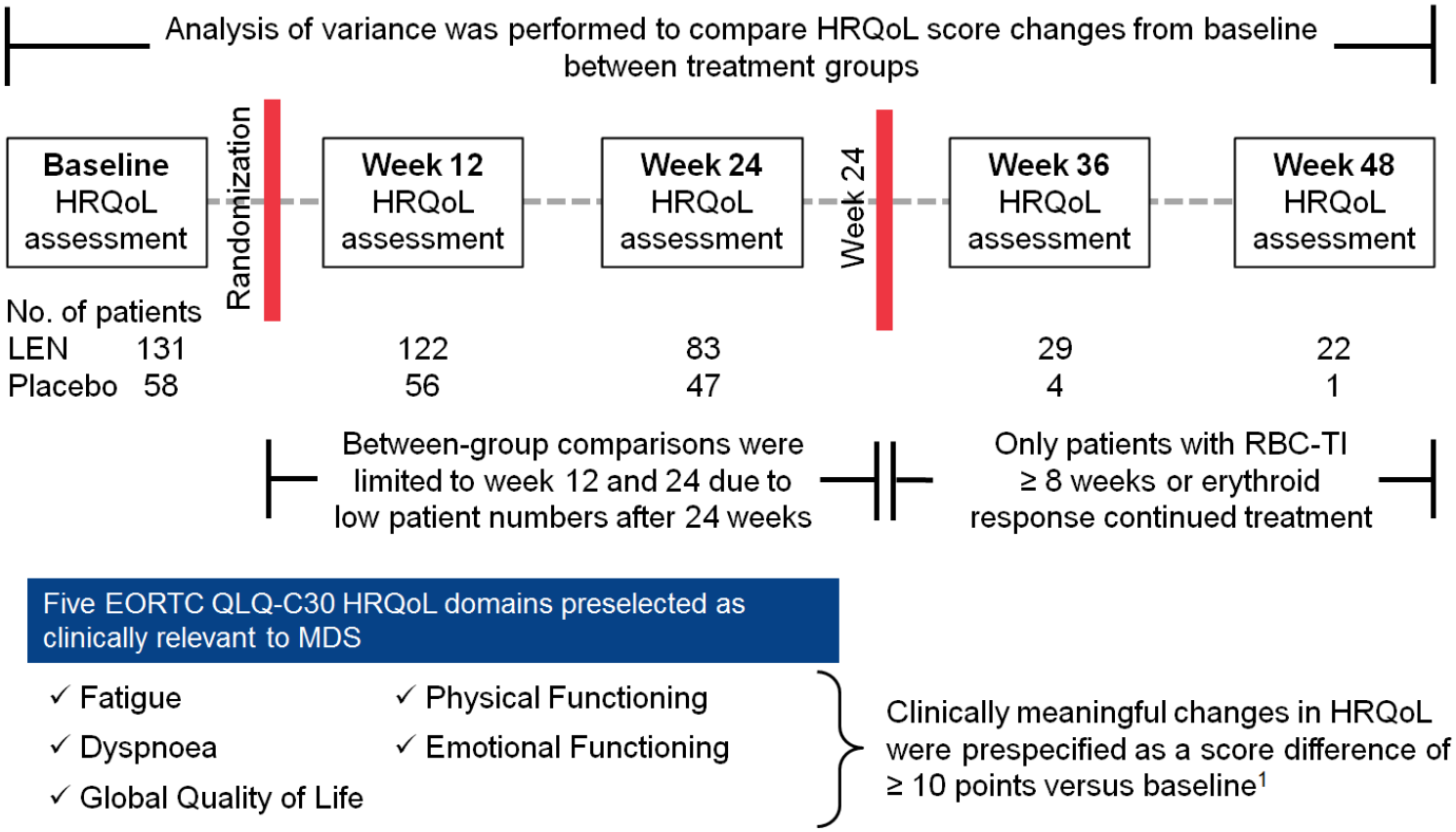
Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Vascular Disorders	2 (4.7)	3 (2.6)	0	1 (1.3)
Deep vein thrombosis	1 (2.3)	2 (1.7)		
Circulatory collapse	0	1 (0.9)	0	1 (1.3)
Hypotension	1 (2.3)	0		
Hepatobiliary Disorders	0	2 (1.7)	0	2 (2.6)
Hepatic cirrhosis	0	1 (0.9)	0	1 (1.3)
Hepatic failure	0	1 (0.9)		
Hyperbilirubinaemia	0	1 (0.9)	0	1 (1.3)
Jaundice	0	1 (0.9)		
Biliary colic			0	1 (1.3)
Injury, Poisoning, and Procedural Complications	4 (9.3)	2 (1.7)		
Femoral neck fracture	0	1 (0.9)		
Hip fracture	0	1 (0.9)		

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Femur fracture	2 (4.7)	0		
Lumbar vertebral fracture	1 (2.3)	0		
Thoracic vertebral fracture	1 (2.3)	0		
Traumatic intracranial haemorrhage	1 (2.3)	0		
Renal and Urinary Disorders	2 (4.7)	2 (1.7)		
Pollakiuria	0	1 (0.9)		
Renal failure acute	0	1 (0.9)		
Nephrolithiasis	1 (2.3)	0		
Renal colic	1 (2.3)	0		
Renal failure chronic	1 (2.3)	0		
Ear and Labyrinth Disorders	0	1 (0.9)		
Middle ear inflammation	0	1 (0.9)		
Psychiatric Disorders	2 (4.7)	0	0	2 (2.6)
Confusional state	1 (2.3)	0	0	1 (1.3)

Adverse Event, n (%)	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Insomnia	1 (2.3)	0		
Mental status changes	1 (2.3)	0		
Anxiety			0	1 (1.3)

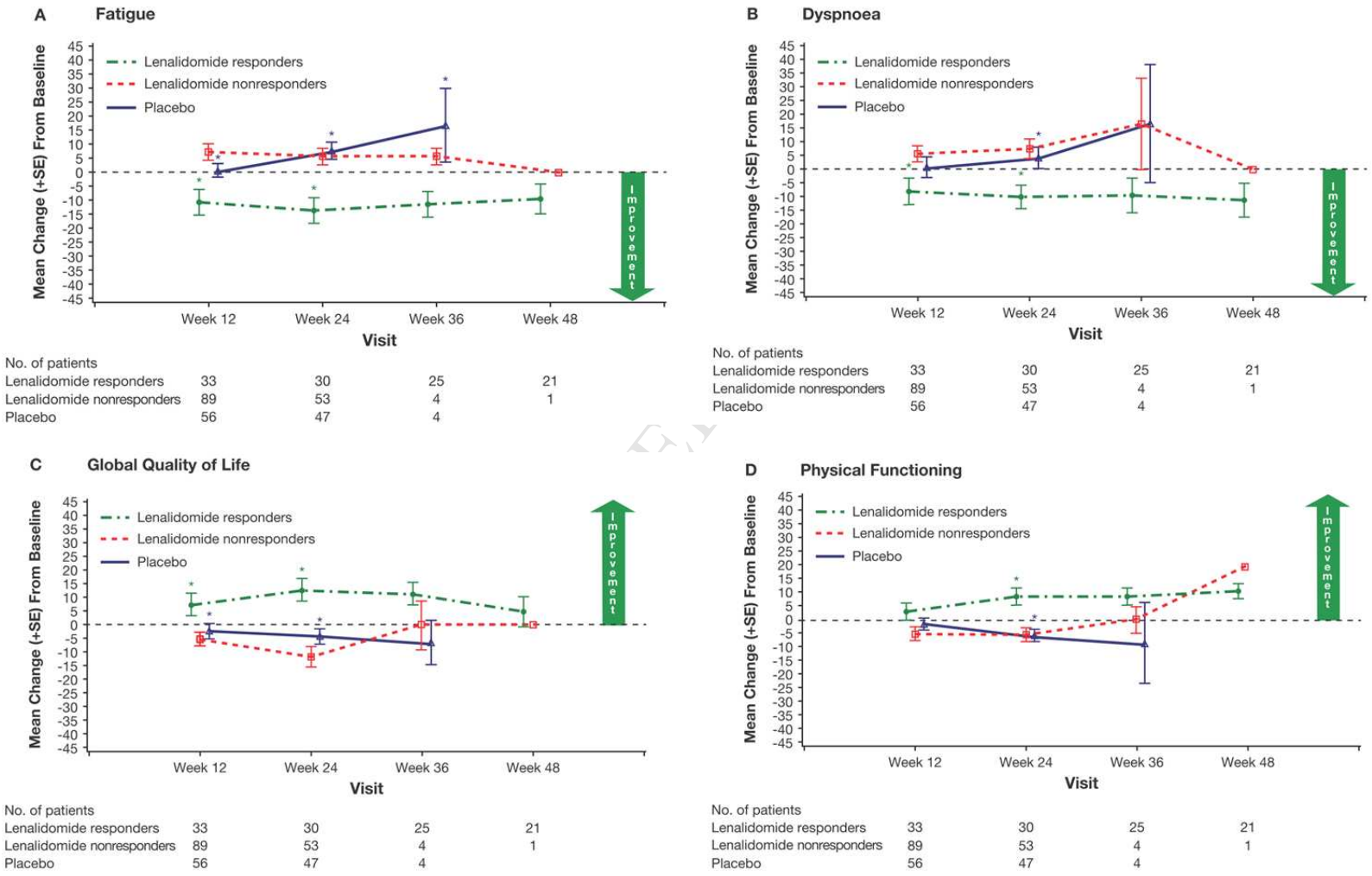
HLA = human leukocyte antigen; RBC-TI = red blood cell transfusion independence; TEAE = treatment-emergent adverse event.

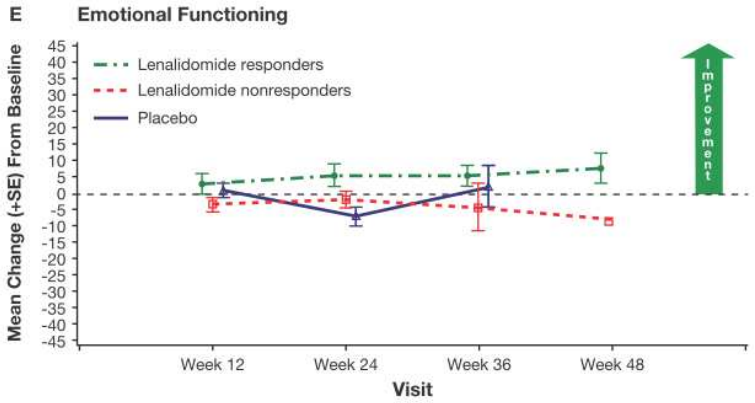
Figure S1 Assessment of HRQoL in the MDS-005 Study



Abbreviations: HRQoL = health-related quality of life; LEN = lenalidomide; MDS = myelodysplastic syndromes; RBC-TI = red blood cell transfusion independence.

Figure S2 Mean Change from Baseline in HRQoL Scores Without Adjusting for Baseline Scores for Preselected EORTC QLQ-C30 Scales (A: Fatigue, B: Dyspnoea, C: Global Quality of Life, D: Physical Functioning, E: Emotional Functioning) in Lenalidomide Responders, Lenalidomide Nonresponders, and Placebo Patients





No. of patients				
Lenalidomide responders	33	30	25	21
Lenalidomide nonresponders	89	53	4	1
Placebo	56	47	4	

*Denotes *P* < 0.05 for the comparison of lenalidomide responders vs lenalidomide nonresponders; lenalidomide nonresponders vs placebo; lenalidomide responders vs placebo.

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL = health-related quality of life; SE = standard error.

Supplementary reference list

1. Osoba D, Rodrigues G, Myles J, et al. (1998) Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol.*1998:16;39–144.

2. Scott NW, Fayers PM, Aaronson NK, et al. EORTC QLQ-C30 reference values. Brussels, Belgium: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group Publications; 2008. Available from: http://groups.eortc.be/qol/sites/default/files/img/newsletter/reference_values_manual2008.pdf. Accessed March 2017.