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Decitabine in Older Patients with AML: Quality of Life Results of the EORTC-GIMEMA-GMDS-SG Randomized Phase III Trial

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Abstract:
We hypothesized that fit older patients with acute myeloid leukemia (AML) treated with decitabine (DEC) would report better health-related quality of life (HRQoL) outcomes compared to those receiving intensive chemotherapy (IC). We conducted a phase 3 randomized trial to compare DEC (10-day schedule) to IC (3+7) in older fit AML patients. HRQoL was a secondary endpoint, and it was assessed with the EORTC QLQ-C30 and the QLQ-ELD14. The following scales were a priori selected for defining the primary endpoint: physical and role functioning, fatigue, pain, and burden of illness. HRQoL was assessed at baseline, at regeneration from cycle 2, and at 6 and 12 months after randomization, and also prior to allo-HSCT and 100 days after transplantation. Overall, 606 patients underwent randomization. At 2 months, the risk of HRQoL deterioration was lower in the DEC arm than in the 3+7 arm (76% [95% CI, 69 to 82] v 88% [95% CI, 82 to 93]; odds ratio, 0.43 [95% CI, 0.24 to 0.76], P=.003). No statistically significant HRQoL differences were observed between treatment arms at the long-term evaluation combining assessments at 6 and 12 months. HRQoL deteriorations between baseline and post-allo-HSCT were observed in both arms. However, these deteriorations were not clinically meaningful in patients randomized to DEC, while this was the case for those in the 3+7 arm, in four out of the five primary HRQoL scales. Our HRQoL findings suggest that lower-intensity treatment with DEC, may be preferable to current standard IC (3+7), in fit older AML patients. ClinicalTrials.gov (NCT02172872).

Conflict of interest: COI declared - see note

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Clinical trial registration information (if any): ClinicalTrials.gov (NCT02172872).

Decitabine in Older Patients with AML: Quality of Life Results of the EORTC-GIMEMA-GMDS-SG Randomized Phase III Trial

Running Title: Quality of Life in Older Patients with AML

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*GH and ML contributed equally to this paper

Key Points

- Little data is available on Quality of Life (QoL) of patients with AML treated with decitabine.
- Current QoL findings support the use of lower intensity decitabine, compared to the current standard of care in fit older patients with AML.

ABSTRACT

We hypothesized that fit older patients with acute myeloid leukemia (AML) treated with decitabine (DEC) would report better health-related quality of life (HRQoL) outcomes compared to those receiving intensive chemotherapy (IC). We conducted a phase 3 randomized trial to compare DEC (10-day schedule) to IC (3+7) in older fit AML patients. HRQoL was a secondary endpoint, and it was assessed with the EORTC QLQ-C30 and the QLQ-ELD14. The following scales were *a priori* selected for defining the primary endpoint: physical and role functioning, fatigue, pain, and burden of illness. HRQoL was assessed at baseline, at regeneration from cycle 2, and at 6 and 12 months after randomization, and also prior to allo-HSCT and 100 days after transplantation. Overall, 606 patients underwent randomization. At 2 months, the risk of HRQoL deterioration was lower in the DEC arm than in the 3+7 arm (76% [95% CI, 69 to 82] *v* 88% [95% CI, 82 to 93]; odds ratio, 0.43 [95% CI, 0.24 to 0.76], *P*=.003). No statistically significant HRQoL differences were observed between treatment arms at the long-term evaluation combining assessments at 6 and 12 months. HRQoL deteriorations between baseline and post-allo-HSCT were observed in both arms. However, these deteriorations were not clinically meaningful in patients randomized to DEC, while this was the case for those in the 3+7 arm, in four out of the five primary HRQoL scales. Our HRQoL findings suggest that lower-intensity treatment with DEC, may be preferable to current standard IC (3+7), in fit older AML patients. ClinicalTrials.gov (NCT02172872).

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Key words: Quality of Life; Patient-Reported Outcomes; Acute Myeloid Leukemia; Decitabine; Randomized controlled trial; Chemotherapy; Elderly Cancer.

INTRODUCTION

Acute myeloid leukemia (AML) is a disease that typically affects older persons, with a median age of 68 years at the time of diagnosis.[1] Although major advances have been made in the treatment of younger patients with AML over the last decades[2], the 5-year survival rates for those aged ≥ 65 years remain poor.[3]

Treatment options for older patients with AML have historically been very limited until the introduction of low-intensity doses and schedules of the hypomethylating agents (HMAs) decitabine (DEC) and azacitidine (AZA).[4,5] In more recent years, further advances have been observed for elderly patients who are unfit for intensive chemotherapy (IC). Based on findings from two pivotal randomized controlled trials (RCTs),[6,7] the Food and Drug Administration approved venetoclax in combination with HMAs or low-dose cytarabine, thereby defining a new standard of care for this population. The inclusion of health-related quality of life (HRQoL) as secondary endpoints in these RCTs has been critical to demonstrate a longer preservation of functioning and overall health status in patients treated with this novel regimen.[8]

Further, clinical decision-making for older patients with AML who are considered fit for IC at clinical presentation remains a major challenge[9], and these patients have poor survival unless they are consolidated with an allogeneic hematopoietic stem cell transplantation (allo-HSCT).[10] The current standard bridging approach to allo-HSCT is IC, which may not be well-tolerated by many patients who are then forced to discontinue therapy, hence limiting the option of the potentially curative value of allo-HSCT.

Therefore, an international phase 3 RCT in fit older patients with AML was performed to compare IC (3+7) *v* DEC followed by allo-HSCT, which revealed similar survival and

comparable allo-HSCT rates between treatment groups.[11] Briefly, the hazard ratio for death was 1.04 (95% confidence interval [CI], 0.86 to 1.26; *P*=0.68). The remission rates achieved as a part of the protocol treatment were 48% (95% CI, 42 to 54%) for DEC and 61% (95% CI, 56 to 67%) for 3+7. Overall remission rates including response to post-protocol treatments prior to allografting were 60% (95% CI, 55 to 66%) in the DEC and 67% (95% CI, 61 to 72%) in the 3+7 arm and hospital stays were shorter in the DEC than in the 3+7 arm.[11] Given the importance of relying on evidence-based HRQoL information to optimize patient-centred care in the AML setting[3], and cognizant of the high value placed on HRQoL by patients with AML[12], we included it as a secondary endpoint in the study protocol of this RCT.[11]

We aimed to generate patient-reported outcome (PRO) data that could better inform risk-benefit assessment in this setting and hypothesized that patients receiving DEC would experience better HRQoL outcomes owing to the lower intensity regimens of HMAs compared to 3+7.

PATIENTS METHODS

Study design and patients

We conducted a prospective**,** multinational open-label, phase 3 randomized trial. Eligibility criteria and full treatment procedures are reported elsewhere.[11] In brief, patients with confirmed newly diagnosed AML aged ≥60 years, considered eligible for standard IC were randomized to DEC at a dose of 20 mg/m^2 x 10 days *v* IC, i.e., conventional induction chemotherapy, daunorubicin 60 mg/m^2 x 3 days and cytarabine 200 mg/m^2 x 7 days ("3+7"), followed by 1-3 additional chemotherapy cycles. All patients, irrespective

of their genetic risk profile, having an HLA-matched donor and attaining at least disease stabilization after ≥1 treatment cycle, were encouraged to undergo an allo-HSCT. Overall survival was the primary study endpoint and HRQoL a secondary endpoint.

This study involved 54 centres, across 9 European countries, from 3 groups: European Organisation for Research and Treatment of Cancer (EORTC), Gruppo Italiano Malattie EMatologiche dell Adulto (GIMEMA) and German Myelodysplastic Syndromes Study Group (GMDS-SG). The study was approved by all Ethics Committees of each participating centres. The trial was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonization. All patients provided written informed consent. The trial was sponsored by the EORTC and was designed by the academic authors. The study is registered at ClinicalTrials.gov (NCT02172872).

Randomization

Registration was done centrally at the EORTC headquarters (Brussels, Belgium). Eligible patients were randomly assigned (1:1) to receive DEC or 3+7. The randomization, based on a minimisation technique, was stratified by AML type (de novo *v* secondary), age (60-64 *v* 65-69 *v* ≥70 years) and site. The study was open label.

Procedures for HRQoL assessment and reporting of study results

The EORTC Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (version 3)[13] in conjunction with its elderly module (EORTC QLQ-ELD14)[14] was used to assess HRQoL.

The EORTC QLQ-C30 consists of five functioning scales: physical, role, emotional, cognitive and social; nine symptom scales: fatigue, nausea/ vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial difficulties; and the global health status/QoL scale. The items were scaled and scored using the recommended EORTC procedures.[15] Standardized scores range from 0 to 100 with higher scores representing a higher level of functioning and health status/QoL or higher level of symptoms. This questionnaire is one of the most frequently used HRQoL measures in cancer RCTs in general[16] and also specifically in AML studies.[17] The QLQ-ELD14 was selected having being developed in an international setting to cover key HRQoL aspects relevant for older patients with cancer.[14] It consists of the following two functional scales: maintaining purpose and family support; it also has five symptom scales: mobility, worries about others, future worries, burden of illness, and joint stiffness. Standardized scores range from 0 to 100 with higher scores on the functional scales indicating better functioning and higher scores on the symptom scales indicating more severe problems.

The following five scales were *a priori* selected for defining the primary HRQoL endpoint: physical and role functioning, fatigue, pain (EORTC QLQ-C30) and burden of illness (QLQ-ELD14). This selection was based on clinical relevance for our study population.

Questionnaires were completed by patients (paper version) at the hospital when patients came for a scheduled visit according to the EORTC Guidelines for administration of questionnaires.[18] Baseline questionnaires were filled before start of protocol treatment. Subsequent questionnaires were filled out at regeneration cycles 2-3 (in between end of cycle 2 and start of cycle 3) and at 6 and 12 months after randomization. For those who received an allo-HSCT, HRQoL was also assessed prior to starting the conditioning and at

day +100 after transplantation. HRQoL data were collected regardless of the patient's progression status. The HRQoL findings of this study are reported in accordance with the CONSORT-PRO Extension guidelines.[19]

Outcomes

The main endpoint was HRQoL deterioration, defined as the occurrence of any of the following events: 1) deterioration (of at least 10 points) in fatigue, pain, burden of illness, physical functioning or role functioning relative to baseline, 2) death prior to the HRQoL evaluation, and 3) disease progression prior to the HRQoL evaluation. For the purpose of this study, a difference of at least 10 points in any HRQoL scale was considered as clinically meaningful.[20] Two versions of this endpoint used in the analysis were short-term and long-term HRQoL deterioration. The short-term HRQoL deterioration was based on the HRQoL evaluation approximately 2 months after the randomization. The long-term HRQoL deterioration was defined as HRQoL deterioration either at 6 months or at 12 months after randomization.

Statistical methods

The study was initially planned to define the primary endpoint HRQoL deterioration as a deterioration at any of the 5 evaluation time points (regeneration from cycle 2, at 6 months, at 12 months, prior to allo-HSCT, and 100 days after allo-HSCT). However, since only a proportion of patients underwent allo-HSCT and since not all patients proceeded to cycle 2, compliance checks revealed a prohibitively low compliance for many of the 5 evaluation time points. Therefore, the evaluations at 6 and 12 months were analysed

separately, as an indicator of the long-term HRQoL. The evaluation at 2 months was analysed separately as well as an indicator of the HRQoL during the treatment and it used questionnaires administered after cycle 2 and prior to allo-HSCT. Finally, the time points prior to and 100 days after an allo-HSCT were analysed separately in the cohort of transplanted patients. The time windows for all evaluation time points used in the analyses are available in Supplementary Table 1.

The exact test was used to compare short-term and long-term HRQoL deterioration between the treatment arms. A logistic regression model without covariates was used to estimate the odds ratio (OR). Exact CIs were used for proportions. CIs based on the t-distribution of group means and differences in group means were used. The variance of the difference in group means was estimated using the Satterthwaite method. Patients without a baseline questionnaire were excluded from all analyses. In the main analysis of HRQoL deterioration, alive and progression-free patients at the time of the HRQoL evaluation and without a HRQoL questionnaire for the time points of interest were excluded.

We used a number of strategies to deal with the problem of missing values. First, since patients with a disease progression were expected to have a low HRQoL and a low compliance to HRQoL evaluations potentially introducing a bias in the analysis, progressions were treated as indicating a deterioration in the main endpoint HRQoL deterioration. Two sensitivity analyses were performed by modifying the definition of the endpoint HRQoL deterioration. First, the definition was modified by counting patients who discontinued the treatment as having a deterioration, which was expected to significantly reduce the number of patients with a missing value. Second, the definition of

deterioration used in the primary analysis was changed by not counting patients who had a disease progression as having a deterioration. In addition, we also performed sensitivity analyses using multiple imputation, in which we imputed missing values using HRQoL at remaining timepoints, treatment arm, age, sex, performance status at the time of evaluation and remission status at the time of evaluation (details are described in the supplementary material). Since these covariates were expected to represent most important predictors of HRQoL in the trial, the analysis using multiple imputation was expected to significantly reduce the risk of bias due to missing values. The analysis was performed in SAS version 9.4 (SAS Institute, Inc, Cary, NC).

The study was approved by all Ethics Committees of each participating centres.

RESULTS

Between December 2014 and August 2019, 606 patients were randomized (303 in the DEC arm and 303 in the 3+7 arm). The flowchart of patients included in the HRQoL analysis is reported in Figure 1.

Compliance at baseline was, overall, 91% (n=549), and 92% (n=279) and 89% (n=270) in the DEC and 3+7 arm, respectively. Baseline demographics and clinical characteristics of patients included in the HRQoL analysis were well balanced between the two arms (Table 1). Baseline characteristics of patients with (n=549) and without (n=57) baseline HRQoL questionnaires were similar (supplementary Table 2). Baseline scores of the HRQoL primary scales were well balanced between groups (Table 2), as were the scores for all other scales (supplementary Table 3). Among patients with baseline HRQoL data available, the median (range) time on protocol treatment was 90 days (2-1287) in the DEC and 64 days (1-307) in the 3+7 arm. In the same group of patients, the median (range) number of cycles was 3 (1-41) in the DEC and 2 (1-4) in the 3+7 arm.

Overall compliance was 57% (311/550), 57% (272/475) and 64% (229/360) at 2, 6 and 12 months, respectively. At 2 months, a significantly higher compliance rate was observed in the DEC arm (63%, 175/279) than in the 3+7 arm (50%, 136/271) (supplementary Table 4).

Insert Figure 1 and Table 1 and Table 2

Primary HRQoL analysis in the overall population

At 2 months, patients from the DEC arm had a statistically significant lower risk of HRQoL deterioration compared to those from the 3+7 arm (76% [95% CI, 69 to 82] *v* 88% [95% CI, 82 to 93]; OR, 0.43 [95% CI, 0.24 to 0.76]; *P*=.003). The risk of HRQoL deterioration at long-term was not significantly different between arms. Sensitivity analyses counting treatment discontinuation prior to HRQoL assessment as an event or excluding disease progression confirmed the findings, and are reported in Figure 2. A distribution of the endpoints composing deterioration is available in supplementary Table 5 (at 2 months) and Table 6 (long-term).

Insert Figure 2

Additional HRQoL analyses in the overall population

Investigation of average changes from baseline to subsequent assessments showed a lower burden of illness in the DEC arm as compared to the 3+7 arm (difference [Δ]=-11.0 [95% CI, -17.9 to -4.0]; *P*=.004) at 2 months. No statistically significant differences were observed between arms in other primary HRQoL scales (supplementary Table 7). Mean changes from baseline at 2, 6 and 12 months for the five primary scales are depicted in Figure 3. In both arms, there appeared to be a HRQoL deterioration at 2 and 6 months and a resumption to baseline levels at 12 months. At 6 months, deterioration in the 3+7 arm was clinically meaningful for physical and role functioning and burden of illness. Deterioration in the DEC arm was not clinically meaningful at any time point. Mean changes from baseline of all other HRQoL scales are reported in Figure 4.

Insert Figure 3 and Figure 4

Descriptive HRQoL analyses among patients who received allo-HSCT

Overall, 240 patients received an allo-HSCT as a part of the study protocol, 122 in the DEC and 118 in the 3+7 arm. Two-hundred eighteen (91%) of these 240 patients had a baseline HRQoL assessment and compliance pre- and post-allo-HSCT was 68% (163/240) and 65% (138/211), respectively. There were no significant differences in HRQoL compliance rates between the two arms at any time point (supplementary Table 8). Socio-demographic and clinical characteristics of transplanted patients, before the procedure (supplementary Table 9) and donor and conditioning regimen characteristics were well-balanced between the treatment arms (supplementary Table 10). Graft-versus-host disease was reported for 80 (70%) patients from the DEC and 65 (63%) patients from the 3+7 arm among those with available baseline HRQoL assessment.

Baseline scores of the HRQoL primary scales were also well balanced between the treatment arms (Table 2). Patients from the 3+7 arm reported a clinically meaningful deterioration post allo-HSCT, relative to baseline, regarding physical functioning (Δ=-13.5 [95% CI, -20.5 to -6.5]), role functioning (Δ=-19.4 [95% CI, -29.5 to -9.2]), fatigue (Δ=12.0 [95% CI, 2.7 to 21.2]), and burden of illness (Δ=13.2 [95% CI, 3.9 to 22.5]). However, among patients from the DEC arm, no clinically meaningful deteriorations post-allo-HSCT were observed for any of the five primary HRQoL scales (Figure 5).

Insert Figure 5

Missingness mechanism and supportive analyses

Inspection of reasons for missing HRQoL data indicated that this information was mainly not documented (596 [53%] of 1129) or was due to administrative failure (456 [40%]). Investigation of missingness mechanism indicated an association with poorer performance and remission status. However, it was independent of age, sex and ELN risk stratification. In the subgroup of transplanted patients, more frequent missing data were associated with a poorer performance status. Sensitivity analyses in the overall group and in the subgroup of transplanted patients using multiple imputations yielded similar results to the main analyses, confirming robustness of the findings (*data not shown*).

Adjusting for ELN risk group, the effect of treatment arm on the risk of HRQoL deterioration at 2 months was similar as in the unadjusted analysis (OR, 0.45 [95% CI, 0.25 to 0.83]; *P*=.011).

DISCUSSION

In this large international RCT we observed, at 2 months, a significantly lower risk of HRQoL deterioration in patients from the DEC arm, but no difference in the long-term. This short-term benefit finding has major implications, as it suggests that the induction with DEC may be preferrable to standard IC in fit older patients with AML. Together with the clinical efficacy and safety findings of this RCT[11], our HRQoL results provide novel information that will help both physicians and older patients with AML to make more informed decisions when considering treatment options. Of note, out of the primary HRQoL scales of the study, the burden of illness from the QLQ-ELD14 (a dedicated questionnaire for elderly patients) was the key one by indicating a statistically significant difference between arms in the short-term. This may also suggest the importance of this specific scale in future AML trials with older patients.

Given the paucity of RCTs including older patients with AML in the setting of transplantation[21], it is difficult to compare our findings with those of other studies, and this is particularly true when considering HRQoL data of patients receiving DEC. With regard to HMAs, in general, we note that HRQoL was assessed in a previous RCT of newly diagnosed patients (≥65 years) with AML comparing AZA vs conventional care regimens, and authors observed that HRQoL domains generally improved over the 9 treatment cycles in both arms[5]. However, it is difficult to compare it with our findings given the few details provided about the HRQoL assessment methodology and the descriptive nature of the analysis.

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The differences between the treatment arms regarding HRQoL at a long-term follow-up were not statistically significant. At 12 months, there were negligible HRQoL differences relative to their baseline values in each arm. This finding may suggest that, once off-treatment, patients treated with 3+7 recover well, which is partly in line with the sparse evidence in this area. A recent review[22] summarizing HRQoL findings of studies comparing intensive *v* lower intensity therapies in older adults with AML, noted that HRQoL may initially worsen with IC, but then improve to the levels of lower intensity therapies.

Another finding, from our descriptive analysis was that patients treated with DEC did not experience a clinically meaningful deterioration in any of the five prespecified primary HRQoL scales post-allo-HSCT, while this was the case for patients treated with 3+7. Relative to their baseline HRQoL, patients in this arm reported clinically relevant worse scores for physical and role functioning, as well as fatigue and burden of illness. A possible explanation is that this may reflect the higher cumulative burden of therapy experienced by patients treated with 3+7 prior to allo-HSCT since no large differences between the treatment arms were apparent regarding the characteristics of patients at the time of allografting, conditioning regimen use, donor characteristics, or graft-versus-host disease rates. The number of patients who are consolidated with an allo-HSCT in patients aged ≥60 years with hematologic malignancies has increased over the past decade.[23] Therefore, the HRQoL trajectories post-allo-HSCT by type of bridging therapy observed in our study provide novel insights on expected outcomes after transplantation.

Our study has limitations. Although the baseline HRQoL compliance was optimal, we observed a decline over time which necessitated a change in analysis approach. Missing

HRQoL data is a known challenge in international cancer trials[24], and this is particularly true when involving vulnerable patients with an acute disease as the ones included in this RCT. In order to deal with this limitation, the definition of the primary endpoint included disease progression, since patients with disease progression were expected to have a poor HRQoL and a poor compliance to HRQoL evaluations. Moreover, we performed several sensitivity analyses dealing with missing values, which showed results similar to the main analyses. Also, we cannot rule out the possibility that a specific HRQoL measure developed for AML patients[25] could have provided further insights on top of the data we reported. However, our selection was driven by the international nature of the study (i.e., requiring linguistically validated questionnaires for all participating centres) and the need to describe specific aspects relevant to elderly cancer patients, which are comprehensively covered by the well validated EORTC QLQ-ELD14 questionnaire.[14]

This study also has notable strengths. To the best of our knowledge, this is the first international RCT reporting comparative HRQoL data in fit older patients with AML treated with either 3+7 or HMAs. Second, the large sample including more than 600 patients from several countries, lends further credit to the generalizability of our findings. Third, considering the importance of moving towards a more patient-centred drug development process in oncology[26] and the historical lack of HRQoL data from AML clinical trials[27-29], our findings bridge an important gap in this area of research. Indeed, owing to the number of novel drugs approved since 2017[2], HRQoL data should become even more critical to thoroughly inform clinical decisions. Recent guidelines by the American Society of Hematology have also pointed to the importance of patient-reported outcome research in the setting of newly diagnosed AML in older adults.[30] Finally, our

results were reported in accordance with the highest quality standards for PRO reporting from clinical trials.[19]

In summary, together with the efficacy results of this RCT[11] our HRQoL findings suggest that use of lower intensity DEC may be preferable to the current standard of care in the frontline setting of fit older patients with AML.

Data sharing

EORTC supports developing greater knowledge to improve diagnostics, treatments, survival, and quality of life. Data requestors are invited to submit a research proposal, according to the EORTC data sharing policy by using the online form. For details, see https://eortc.org.

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Author Contributions

Conception and design: Fabio Efficace, Michael Lübbert, Gerwin Huls, Michal Kicinski, Corneel Coens, Stefan Suciu.

Manuscript writing: All authors.

Final approval of manuscript: All authors.

Accountable for all aspects of the work: All authors

Conflict of Interest

M Lü received research support to his institution from Janssen and European Organisation for Research and Treatment of Cancer (EORTC); is on the advisory boards for AbbVie, Astex, Janssen-Cilag, Otsuka, and Syros; and is currently working in an ongoing trial with a study drug provided by Cheplapharm. MK received research funding from Merck, Bristol Myers Squibb (BMS), Pierre Fabre, Janssen, and Immunocore.
SF received personal funding by BMS and Celgene. AG received a grant for study conduct, and drug supply for Dacogen from Janssen Pharma Educational. JHJ received support for molecular analysis from Janssen and EORTC. FE had consultancy or advisory role for AbbVie, Incyte, Syros, Novartis, and JAZZ Pharmaceuticals outside the submitted work. RW received consulting fees from Amgen, BMS, Celgene, Janssen, Kite, Gilead, Novartis, Pfizer, and Sanofi; payment from AbbVie, Amgen, BMS, Celgene, Janssen, Kite, Gilead, Pfizer, and Sanofi; and support for attending meetings or travel from Janssen. UD received personal honoraria for participation in a data safety monitoring board from Avencell Europe and data safety monitoring board for an acute myeloid leukaemia CAR-T cell trial from Avencell Europe. FB received payments to his institution from Incyte Biosciences, Takeda, ExCellThera, and MaaT Pharma. SS received funding to his institution from Janssen Pharmaceuticals. All other authors declare no competing interests. AC reports honoraria (consultancy, advisory role, or travel support) from AbbVie, Astellas, Janssen, Jazz, Celgene, Gilead, Pfizer, Incyte, and Amgen, outside the submitted work. ML received consulting fees from Jazz Pharma, Incyte, Grifols, Abbvie, Roche, Novartis. RF speakers bureau for Amgen, Novartis, Incyte, AbbVie, outside the submitted work. AV research funding from Jazz Pharmaceuticals; consultancy for Servier, AstraZeneca, Pfizer, Kyte-Gilead, Abbvie, J&J, Astellas, Astex, Otzuka, Stemline

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Table 1.

Patient characteristics by treatment arm among those with a baseline health-related quality of life evaluation

	Treatment arm		
	DEC (N=279)	**3+7 (N=270)**	**Total (N=549)**
	N (%)	**N (%)**	**N (%)**
Age, years			
N	279 (100.0)	270 (100.0)	549 (100.0)
60-64	66 (23.7)	65 (24.1)	131 (23.9)
65-69	119 (42.7)	112 (41.5)	231 (42.1)
≥70	94 (33.7)	93 (34.4)	187 (34.1)
Sex			
N	278 (99.6)	269 (99.6)	547 (99.6)
Male	149 (53.6)	169 (62.8)	318 (58.1)
Female	129 (46.4)	100 (37.2)	229 (41.9)
ECOG performance status			
N	279 (100.0)	270 (100.0)	549 (100.0)
0	144 (51.6)	146 (54.1)	290 (52.8)
1	112 (40.1)	103 (38.1)	215 (39.2)
2	23 (8.2)	21 (7.8)	44 (8.0)
Baseline HSCT–Comorbidity index			
N	277 (99.3)	267 (98.9)	544 (99.1)
0-1	154 (55.6)	157 (58.8)	311 (57.2)
2	35 (12.6)	28 (10.5)	63 (11.6)
≥3	88 (31.8)	82 (30.7)	170 (31.3)
AML type at baseline			
N	278 (99.6)	268 (99.3)	546 (99.5)
De novo AML	196 (70.5)	196 (73.1)	392 (71.8)
Secondary AML	82 (29.5)	72 (26.9)	154 (28.2)
ELN 2017 risk group			
N	248 (88.9)	247 (91.5)	495 (90.2)
Favorable	64 (25.8)	42 (17.0)	106 (21.4)
Intermediate	112 (45.2)	119 (48.2)	231 (46.7)
Adverse	72 (29.0)	86 (34.8)	158 (31.9)

Abbreviations: AML, acute myeloid leukemia; DEC, decitabine; ECOG, Eastern Cooperative Oncology Group; ELN, European Leukemia Net; HSCT, Hematopoietic stem cell transplantation; N: number of patients.

Table 2.
Baseline scores of primary health-related quality of life scales in all patients (left side) and in transplanted patients (right side) by treatment arm.

	Treatment arm		Treatment arm	
	DEC (N=279)	**3+7 (N=270)**	**DEC (N=115)**	**3+7 (N=103)**
EORTC QLQ-C30				
Physical Functioning				
N	278	267	114	101
Mean (SD)	75.38 (23.86)	78.61 (21.98)	77.38 (22.91)	78.89 (23.27)
Role Functioning				
N	276	268	112	103
Mean (SD)	65.34 (33.58)	69.34 (31.51)	68.75 (32.89)	68.93 (32.84)
Fatigue				
N	277	269	113	103
Mean (SD)	41.86 (30.31)	39.45 (28.87)	38.84 (31.81)	38.46 (29.79)
Pain				
N	278	270	114	103
Mean (SD)	17.99 (25.93)	17.65 (26.79)	15.06 (25.47)	17.64 (27.10)
EORTC QLQ-ELD14				
Burden of illness				
N	245	242	100	97
Mean (SD)	54.90 (26.59)	54.06 (28.78)	55.00 (26.11)	54.98 (29.38)

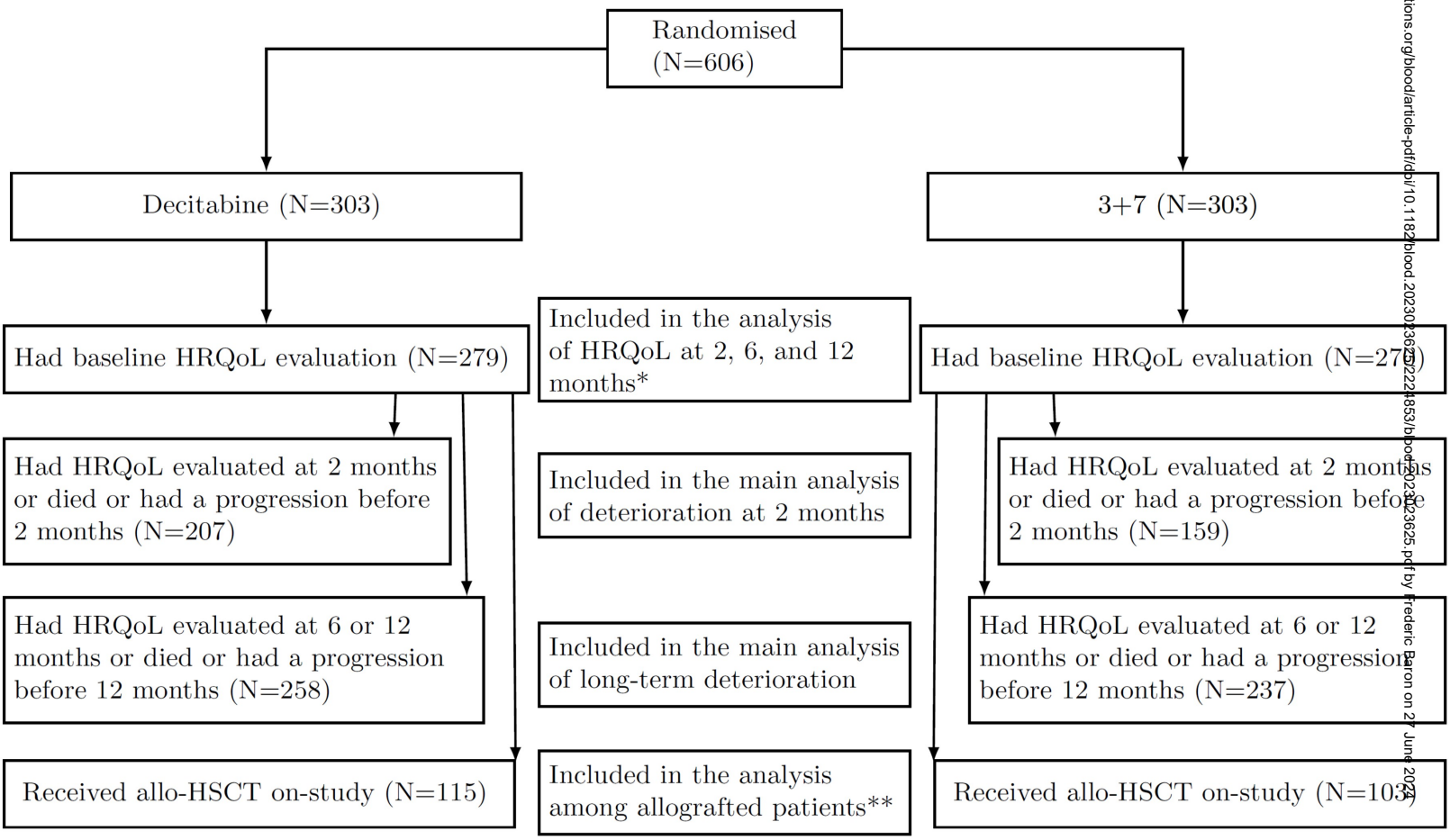
Abbreviations: DEC, decitabine; N, number of patients; SD, standard deviation

Table of figures

Figure 1

Figure 1.

Inclusion of patients in main analyses.



allo-HSCT, allogeneic hematopoietic stem cell transplantation; HRQoL, health-related quality of life; N, number of patients

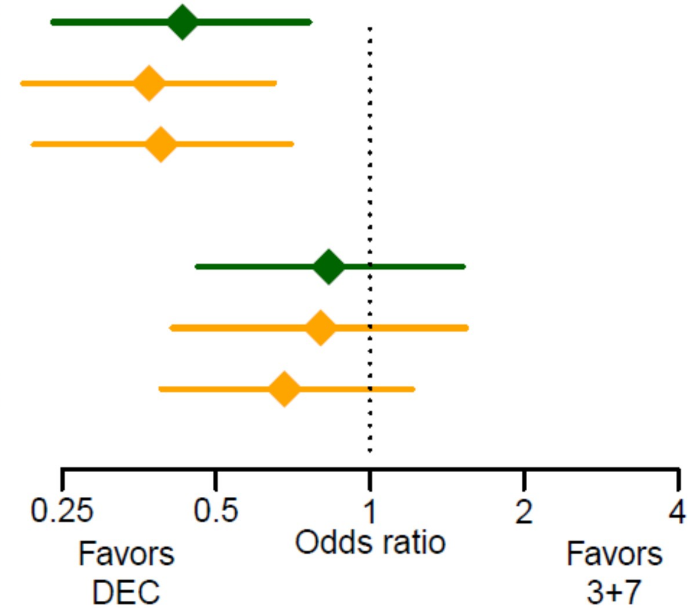
* The number of patients with a HRQoL evaluation at 2, 6, and 12 months is available in the supplement.

** The number of patients with a HRQoL evaluation prior to and post allo-HSCT is available in the supplement.

Figure 2.

Health-related quality of life deterioration by treatment arm.

	Decitabine		3+7		
Deterioration at 2 months	**N/Total**	**% (95% CI)**	**N/Total**	**% (95% CI)**	**OR (95% CI)**
Main analysis	157/207	76 (69−82)	140/159	88 (82−93)	0.43 (0.24, 0.76)
Including discontinuation	199/248	80 (75−85)	210/229	92 (87−95)	0.37 (0.21, 0.65)
Excluding progression	143/194	74 (67−80)	135/154	88 (81−92)	0.39 (0.22, 0.70)
Deterioration at long−term					
Main analysis	231/258	90 (85−93)	216/237	91 (87−94)	0.83 (0.46, 1.52)
Including discontinuation	252/274	92 (88−95)	244/261	93 (90−96)	0.80 (0.41, 1.54)
Excluding progression	212/245	87 (82−91)	207/229	90 (86−94)	0.68 (0.39, 1.21)

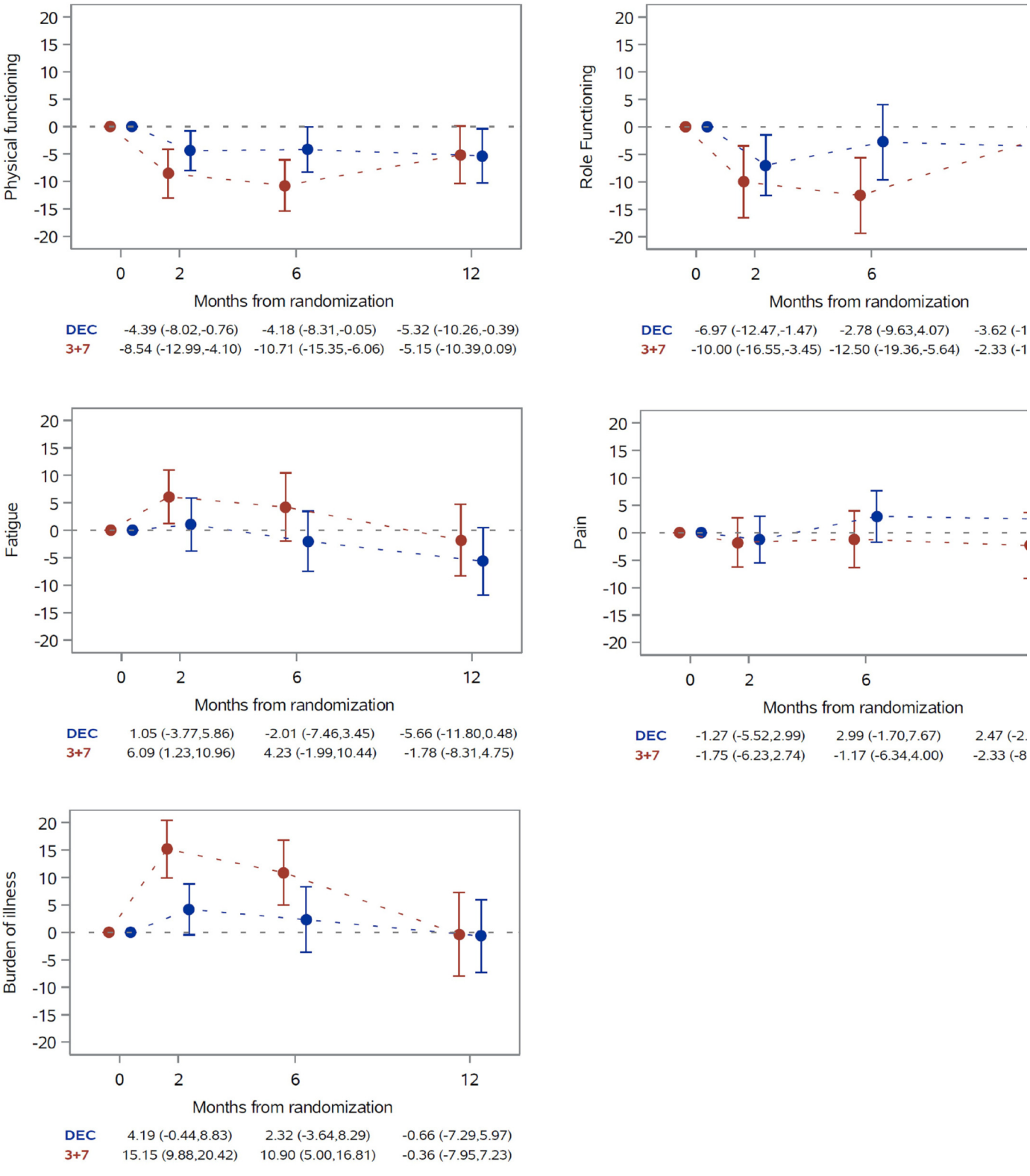


Abbreviations: CI, confidence interval; DEC, decitabine; N, number of patients with a deterioration; OR, odds ratio of a deterioration

Results of the main analyses are indicated in green on the plot. Results of the two sensitivity analyses, one modifying the definition of deterioration by counting patients who discontinued the treatment as having a deterioration and one modifying the definition of deterioration by not counting patients who had a disease progression as having a deterioration are indicated in orange.

Figure 3.

Mean change from baseline to 2, 6, and 12 months for the primary health-related quality of life scales by treatment arm.



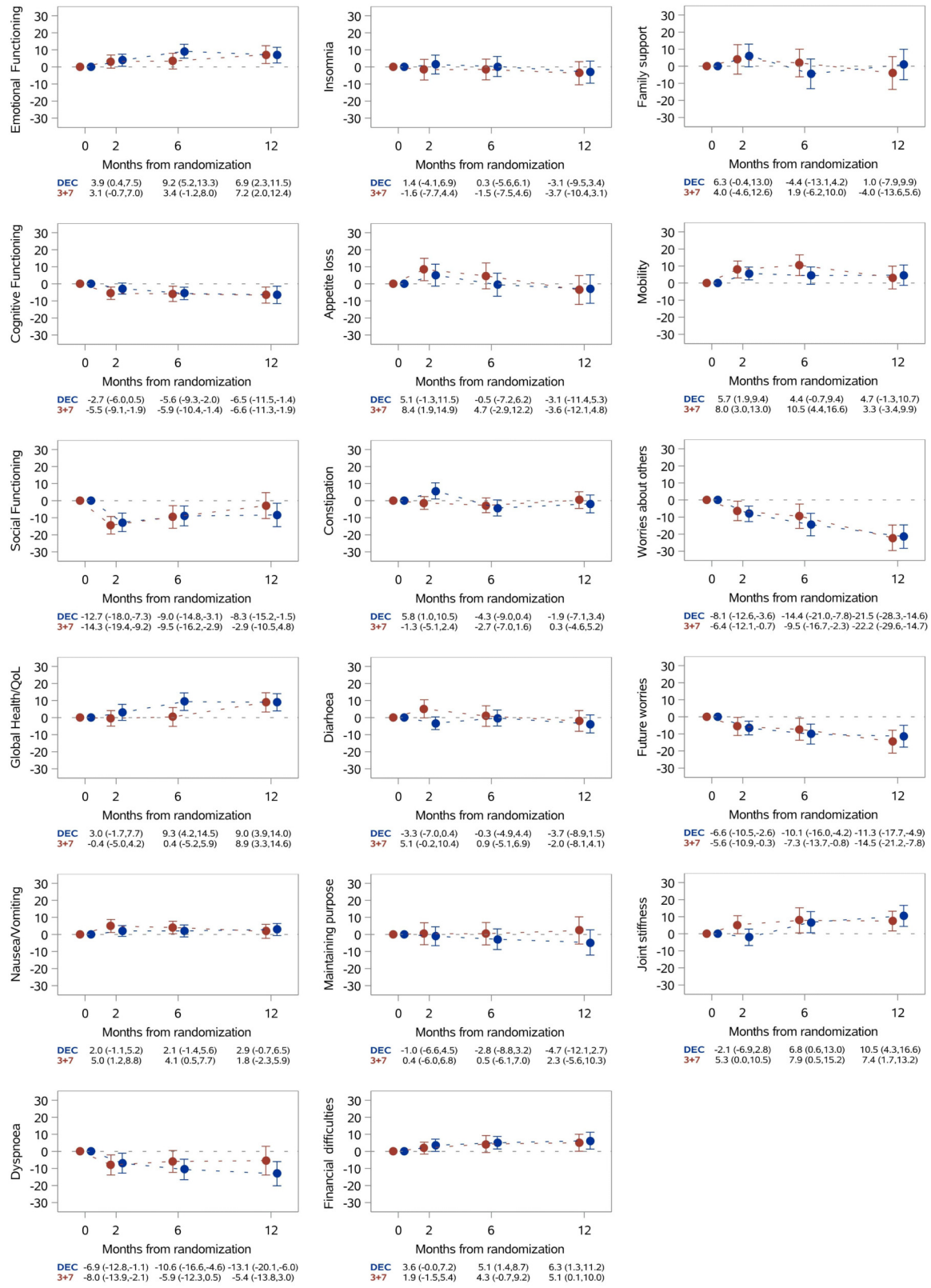
Abbreviation: DEC, decitabine

Mean change from baseline and 95% confidence intervals are displayed.

Higher scores in fatigue, pain and burden of illness scales indicate higher severity, while higher scores in physical and role functioning indicate better functioning.

Figure 4.

Mean change from baseline to 2, 6, and 12 months for secondary health-related quality of life scales by treatment arm.



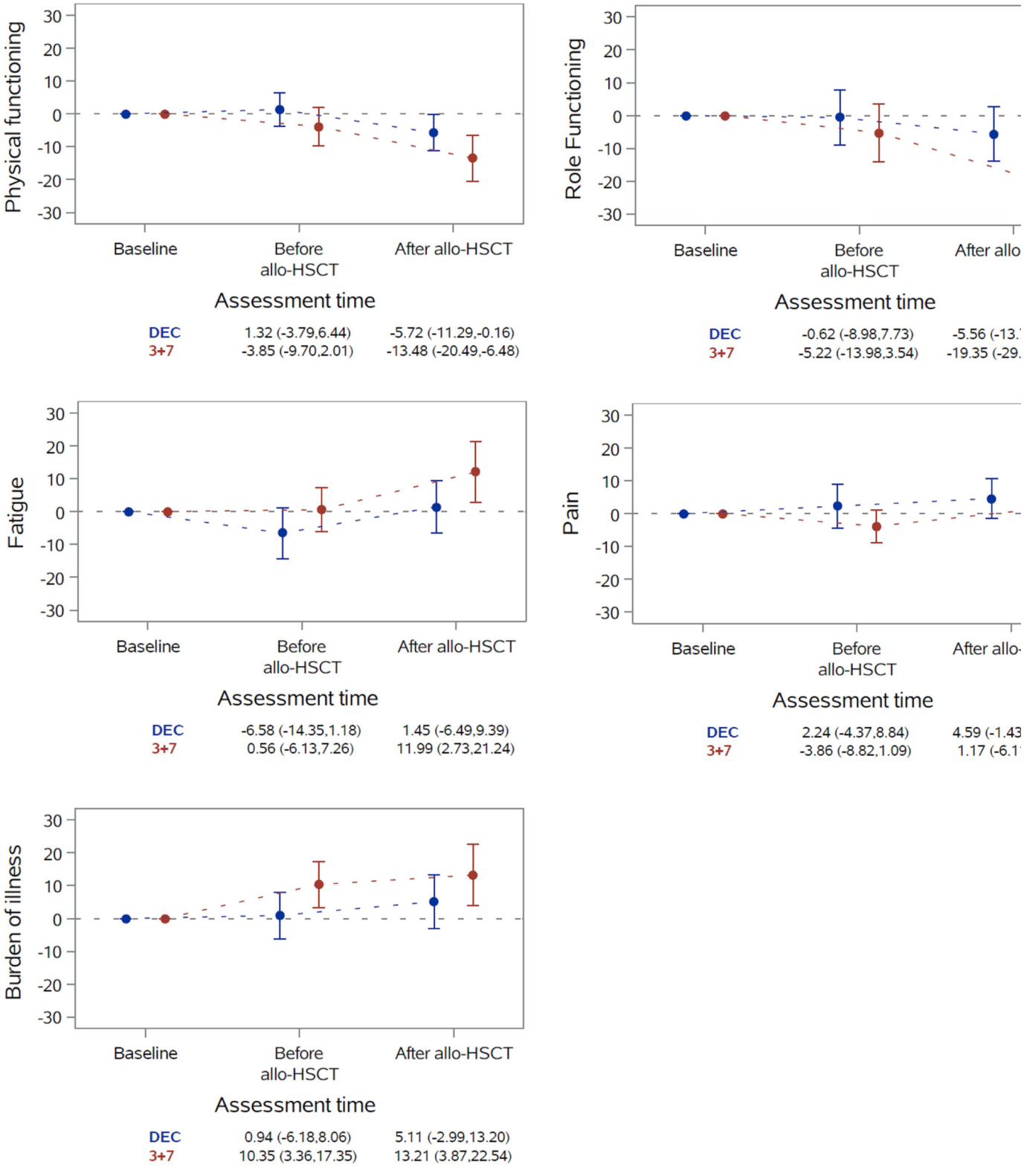
Abbreviation: DEC, decitabine

Mean change from baseline and 95% confidence intervals are displayed.

Higher scores in emotional, cognitive and social functioning, global health/quality of life, maintaining purpose, and family support indicate better functioning/quality of life. Higher scores in fatigue, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties, mobility, worries about others, future worries, and joint stiffness indicate higher severity of symptoms/problems.

Figure 5.

Mean change from baseline to scores prior to and post allo-HSCT for primary health-related quality of life scales by treatment arm.



Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; DEC, decitabine.

Mean change from baseline and 95% confidence intervals are displayed.

Higher scores in fatigue, pain and burden of illness scales indicate higher severity, while higher scores in physical and role functioning indicate better functioning.

Decitabine in Older Patients with Acute Myeloid Leukemia (AML): Quality of Life Results of the EORTC-GIMEMA-GMDS-SG Randomized Phase III Trial

ClinicalTrials.gov ID NCT02172872: 10-day decitabine versus conventional chemotherapy ("3+7") followed by allografting in AML patients ≥ 60 years

Between December 2014 and August 2019, 606 patients were randomized (303 in the DEC arm and 303 in the 3+7 arm)

Patient characteristics by treatment arm among those with a baseline health-related quality of life evaluation

	Treatment arm		
	DEC (N=279) N (%)	3+7 (N=270) N (%)	Total (N=549) N (%)
Age, years			
N	279 (100.0)	270 (100.0)	549 (100.0)
60-64	66 (23.7)	65 (24.1)	131 (23.9)
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Male	149 (53.6)	169 (62.8)	318 (58.1)
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Health-related quality of life (HRQoL) deterioration by treatment arm: decitabine vs intensive chemotherapy

	Decitabine		3+7		
Deterioration at 2 months	**N/Total**	**% (95% CI)**	**N/Total**	**% (95% CI)**	**OR (95% CI)**
Main analysis	157/207	76 (69–82)	140/159	88 (82–93)	0.43 (0.24, 0.76)
Including discontinuation	199/248	80 (75–85)	210/229	92 (87–95)	0.37 (0.21, 0.65)
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Main analysis	231/258	90 (85–93)	216/237	91 (87–94)	0.83 (0.46, 1.52)
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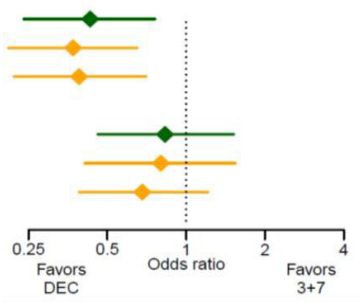

The results of the main analyses are indicated in green on the plot. The results of the two sensitivity analyses are indicated in orange

Conclusions: The current findings on HRQoL indicate that decitabine may be a preferable treatment option for fit older patients with AML compared to intensive chemotherapy.

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Blood Visual Abstract