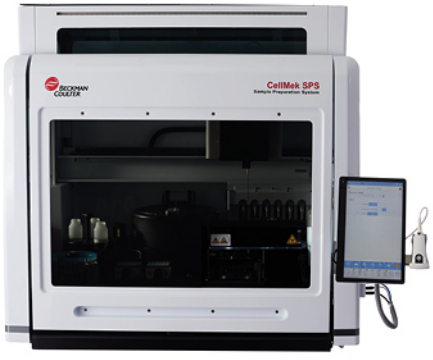


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RESEARCH ARTICLE

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# Treosulfan compared with reduced-intensity busulfan improves allogeneic hematopoietic cell transplantation outcomes of older acute myeloid leukemia and myelodysplastic syndrome patients: Final analysis of a prospective randomized trial

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## Abstract

The phase III study was designed to compare event-free survival (EFS) after treosulfan-based conditioning with a widely applied reduced-intensity conditioning (RIC) busulfan regimen in older or comorbid patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) undergoing allogeneic hematopoietic cell transplantation (HCT). A previously reported confirmatory interim analysis of the randomized clinical study including 476 patients demonstrated statistically significant noninferiority for treosulfan with clinically meaningful improvement in EFS. Here, the final study results and pre-specified subgroup analyses of all 570 randomized patients with completed longer-term follow-up are presented. Patients presenting HCT-specific comorbidity index >2 or aged ≥50 years were randomly assigned (1:1) to intravenous (IV) fludarabine with either treosulfan (30 g/m$^2$ IV) or busulfan (6.4 mg/kg IV) after stratification by disease risk group, donor type, and participating institution. The primary endpoint was EFS with disease recurrence, graft failure, or death from any cause as events. EFS of patients (median age 60 years) was superior after treosulfan compared to RIC busulfan: 36-months-EFS rate 59.5% (95% CI, 52.2–66.1) vs. 49.7% (95% CI, 43.3–55.7) with a hazard ratio (HR) of 0.64 (95% CI, 0.49–0.84), $p = 0.0006$. Likewise, overall survival (OS) with treosulfan was superior compared to busulfan: 36-month-OS rate 66.8% vs. 56.3%; HR 0.64 (95% CI, 0.48–0.87), $p = 0.0037$. Post hoc analyses revealed that these differences were consistent with the confirmatory interim analysis, and thereby the treosulfan regimen appears particularly suitable for older AML and MDS patients.

## 1 | INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment option for many adult patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). This particularly applies to older AML and MDS patients due to an age-dependent increase of disease prevalence and unfavorable disease prognosis with sole conventional treatment.[1–3] Application of myeloablative conditioning (MAC) regimens is largely restricted to younger and fit patients due to excess regimen-related morbidity and mortality observed in older and comorbid patients. The development of reduced-intensity conditioning (RIC) regimens has paved the way for a broader application of allogeneic

HCT in these patients due to a substantial reduction of otherwise limiting procedural toxicities.[4] However, the improved tolerability of RIC regimens is partially counterbalanced by an increased risk of disease recurrence after allogeneic HCT. Therefore, further improvement of preparative regimens for allogeneic HCT is an unmet medical need particularly for the growing number of older or comorbid AML and MDS transplantation candidates.

A dose-reduced busulfan regimen combined with the purine analog fludarabine is a widely applied RIC regimen for patients with AML or MDS. At present, two prospective randomized studies directly compared this RIC regimen with MAC regimens and both studies demonstrated significantly reduced nonrelapse mortality (NRM) after this RIC regimen.[5,6] This beneficial effect, however, was outweighed by an increased relapse incidence in one study.[5]

Several phase II studies demonstrated that treosulfan, a water-soluble bifunctional alkylating agent, combined with fludarabine has a particularly favorable acute organ toxicity profile and allows rapid donor cell engraftment with complete and sustained donor hematopoietic chimerism after allogeneic HCT.[7–10] Due to these properties, the combination of treosulfan with fludarabine is referred to as a myeloablative, but toxicity-reduced regimen.[7]

To investigate, whether the treosulfan regimen is at least noninferior compared with the RIC busulfan regimen, we performed a multicenter prospective, group-sequential randomized phase III study (study acronym: MC-FludT.14/L) in AML and MDS patients, who were considered ineligible for MAC regimens due to patient age between 50 and 70 years, HCT-specific comorbidity index of at least 3, or both.[11,12] Primary endpoint of this study was event-free survival (EFS) after allogeneic HCT with disease recurrence, graft failure, or death from any cause as events. Results of the second pre-specified interim analysis after enrollment of 476 evaluable patients into this study prompted the independent data monitoring committee (DMC) to recommend stopping further patient recruitment, because EFS met the criteria for noninferiority with a clinically meaningful EFS advantage of treosulfan over RIC busulfan (hazard ratio [HR] 0.65 [95% CI, 0.47–0.90]).[13]

At the time of the DMC recommendation, a total of 570 patients had already been randomized and data collection continued for patients remaining on study.

Therefore, the objective of this report is to present results of the final pre-specified analysis of efficacy and safety outcomes for all 570 randomized patients of the MC-FludT.14/L study and for relevant pre-specified subgroups including all pre-specified follow-up and post-surveillance visits.

## 2 | METHODS

### 2.1 | Study design

MC-FludT.14/L, an open-label, multicenter, Phase III, randomized parallel study was performed in 31 clinical institutions across five European countries and enrolled 570 patients between June 2013 and December 2016. The study protocol (online only; EudraCT-No: 2008–002356-18, ClinicalTrials.gov Identifier: NCT00822393) was approved by the responsible ethics committees and competent regulatory authorities in the participating countries. The protocol prespecified three interim analyses and a final analysis. An independent DMC supervised the study conduct, safety, and preplanned interim analyses. Patients were randomly assigned to the reference and study arm by a computer-generated, 1:1 randomization using a permuted block technique with stratification by donor type (matched-related or matched-unrelated donor), participating institution, and disease risk group. Disease risk group stratification was based on two groups (definition given below). The study was performed in accordance with applicable laws and guidelines, including the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, Guideline for Good Clinical Practice (E6). All patients gave written informed consent in accordance with the Declaration of Helsinki and applicable legislation. Their identities were kept confidential. Details of the entire study conduct have been previously published.[13]

### 2.2 | Patients

Eligible patients were between 18 and 70 years old, had AML in first or consecutive hematologic complete remission (CR) or MDS according to WHO 2008 and were indicated for allogeneic HCT, but were considered ineligible for MAC regimens due to patient age between 50 and 70 years, HCT-specific comorbidity index of at least 3, or both.[11,14] Further details of eligibility criteria, including donors, histocompatibility matching, and graft sources as well as exclusion criteria for study entry have been previously published.[13] Assignment to disease risk group II included all patients with genetically adverse risk AML according to European Leukemia Network (ELN) recommendations 2010 in first CR or high- and very high-risk MDS according to the Revised International Prognostic Scoring System (IPSS-R) for MDS.[15,16] Patients with AML beyond first CR were also assigned to disease risk group II. All other patients were assigned to disease risk group I.

### 2.3 | Study conduct

The study conduct and protocol amendments until the preplanned confirmatory second interim analysis, which included 476 patients enrolled until May 3rd, 2016, have been previously outlined in detail.[13] Patient enrollment continued until the independent DMC recommended on December 7th, 2016 to stop further patient recruitment, because the primary study objective had been accomplished. At the time of DMC recommendation, a total of 570 patients had already been randomized. Therefore, data collection continued for patients remaining on study. According to protocol patients were to be followed-up for at most 2 years after transplantation. In addition, post-surveillance with respect to overall survival (OS) and EFS was planned 1 year after transplantation of the last randomized patient.

The last date of contact and termination of the study was January 25th, 2018.

## 2.4 | Conditioning regimens and additional treatment

Patients randomly assigned to RIC busulfan received 0.8 mg/kg busulfan applied as 2-hour infusion every 6 hours on Days −4 and − 3 (total dose 6.4 mg/kg) (Day 0 designates the day of HCT). Patients assigned to the treosulfan arm received 10 g/m$^2$ treosulfan applied as 2-hour infusion on days −4, −3, and −2 (total dose 30 g/m$^2$). All patients additionally received 30 mg/m$^2$ fludarabine on days −6 to −2 applied as 0.5-hour infusion (total dose 150 mg/m$^2$). The administration of busulfan followed the instructions given in the European Summary of Product Characteristics (Busilvex®, manufactured by Pierre Fabre Médicament, France). For the prevention of seizures, either phenytoin or benzodiazepine was daily administered to all patients in the busulfan arm between days −5 and −2.

Prophylaxis of graft-versus-host-disease (GvHD) was standardized in both arms and was based on ciclosporin starting on Day −1 (5 mg/kg daily initially, and through blood-level adapted thereafter) and short-course methotrexate (15 mg/m$^2$ on Day +1, and 10 mg/m$^2$ on Days +3 and +6). All matched unrelated donor transplantation recipients additionally received anti-T-lymphocyte immune globulin (either ATG Fresenius® or Grafalon® [Neovii] at a dose of 10 mg/kg on days −4, −3, and −1 or Thymoglobulin® [Sanofi Genzyme] at a dose of 2.5 mg/kg on days −2 and −1). Supportive care measures were at the discretion of the clinical study investigators at the participating institutions.

## 2.5 | Outcomes

The primary endpoint was EFS after HCT as defined by the time interval between day 0 to the day of disease recurrence or progression (based on common morphological, cytogenetic, or molecular criteria; Appendix 2.1; online only), graft failure (durable decline of blood neutrophil counts below 0.5 × 10$^9$ cells/L and biopsy-confirmed marrow aplasia), or death (whichever occurred first). Secondary endpoints were OS, cumulative incidence of relapse or progression (CIR), cumulative incidence of graft-failure, and NRM. As for EFS, all additionally available post-surveillance information was included in the analysis of these secondary outcome endpoints. For the calculation of CIR, cumulative incidence of graft-failure, and NRM their respective competing events were considered. Details of the evaluation of endpoints are outlined in Data S1). Additional explorative evaluation of the impact of Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) score at study entry on NRM was performed.[11] For this purpose, organ-specific weighted comorbidities included in the HCT-CI were aggregated into three categories: arrhythmia, cardiac, and heart valve disease, mild and moderate to severe hepatic, and moderate to severe pulmonary disease. In addition, diabetes mellitus and prior solid tumor were considered as single comorbidities, which all occurred in at least 10% of all patients.

Acute and chronic GvHD were graded according to Glucksberg's and the modified Seattle criteria.[17,18] Chronic GvHD was evaluated until 24 months after HCT. Adverse events (AEs) were continuously assessed and graded with Common Terminology Criteria for Adverse Events version 4.03 between Days −6 and +28. The conditional cumulative incidence of recovery of leukocytes >1.0 × 10$^9$/L, neutrophils >0.5 × 10$^9$/L, and self-sustaining platelets >20.0 × 10$^9$/L on day +28 and the incidence of complete (>95%) donor cell chimerism on days +28 and +100 were determined as previously described.[13] Furthermore, the composite endpoints of GvHD-free and relapse- or progression-free survival (GRFS) as well as chronic GvHD-free and relapse- or progression-free survival (CRFS) were included in Data S1.[19]

## 2.6 | Statistical analysis

Safety was assessed in the Safety Analysis Set; this set included all randomized patients who were treated at least one time with study medication. Efficacy was assessed according to the Intention-to-Treat Principle in the Full Analysis Set (FAS). The FAS included all randomized patients of the Safety Analysis Set with at least one efficacy parameter documented after baseline.

The primary objective of this study was to demonstrate, as a minimum, noninferiority of treosulfan as an alternative conditioning agent to busulfan with respect to EFS after allogeneic HCT. The noninferiority margin on the HR scale was pre-specified as 1.3. The pre-specified, hierarchical multiplicity strategy to preserve the Type 1 error rate was implemented to allow both noninferiority and superiority testing of EFS. For the last analysis of 570 patients with 234 observed events presented in this report, the nominal one-sided significance level for testing of noninferiority of EFS was 0.001262 based on O'Brien-Fleming type stopping boundaries. Therefore, one-sided *p*-values are reported for the primary endpoint analysis; all other *p*-values are two-sided.

Kaplan–Meier estimates were calculated for EFS and OS. Cox regression models with donor type as factor and disease risk group and participating center as strata were fitted for the confirmatory analysis. Cumulative incidences of relapse/progression and NRM were estimated by a Fine and Gray model with donor type as factor and disease risk group as stratum.

Homogeneity of the treatment effects across pre-specified subgroups were investigated using graphical methods. In addition, statistical tests for the presence of a treatment-by-subgroup interaction were performed for the primary endpoint EFS. If the associated *p*-value was less than 10%, this was taken as evidence of heterogeneity of the treatment effects across subgroups. Detailed methods of statistical analysis for comparisons of outcomes are delineated in the Data S1. Further details of the statistical analysis plan have been published previously.[13]

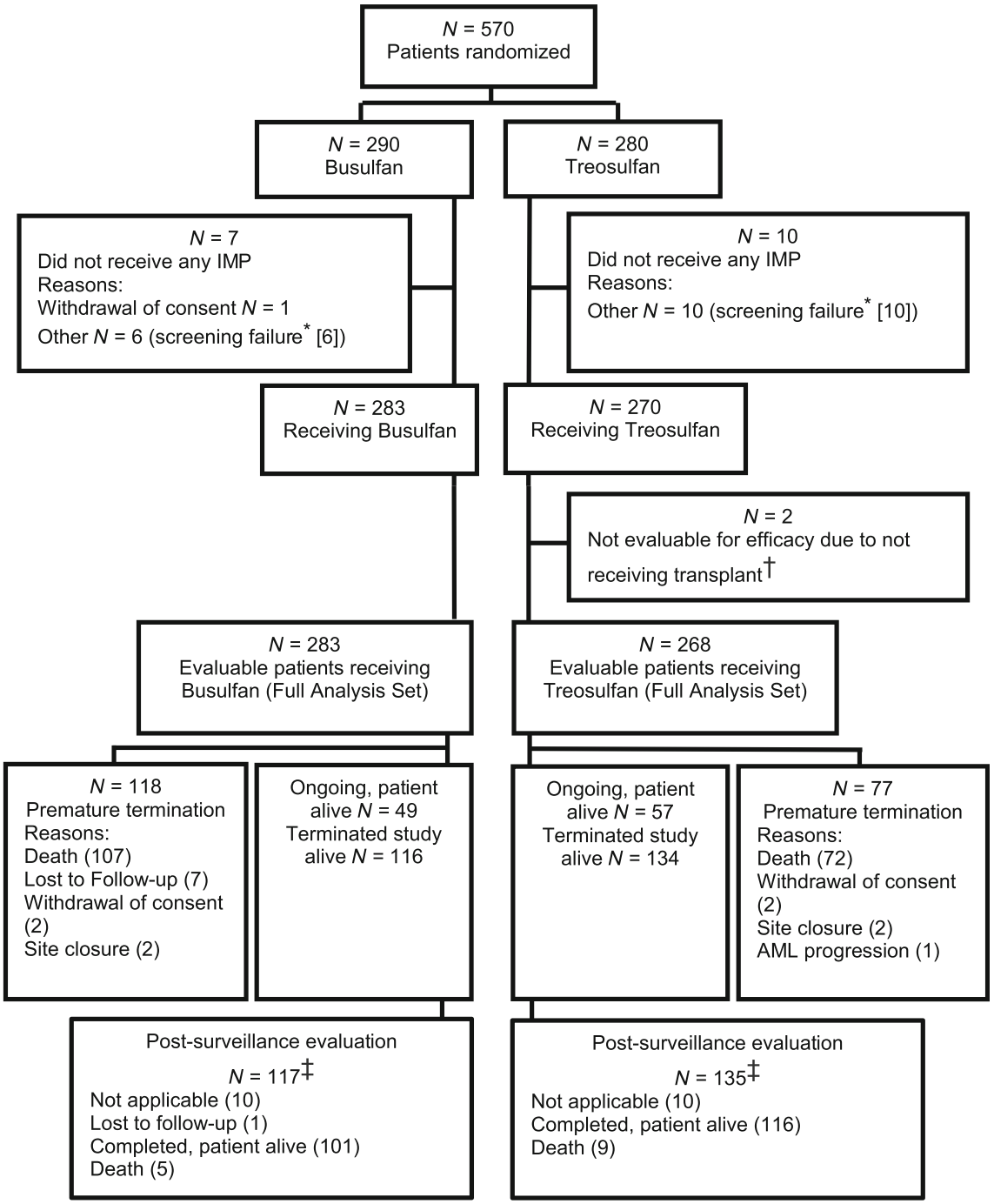


**FIGURE 1** CONSORT diagram. Study Profile and Disposition of Patients. *After randomization, but before conditioning treatment, Investigator became aware of new information leading to patients no longer meeting the inclusion/exclusion criteria. †Cancellation of donor's clearance after start of conditioning treatment, no transplantation took place (1 patient); withdrew consent before hematopoietic stem cell transplantation (1 patient). ‡For 1 patient in each treatment group post-surveillance was filled in, although the structured visit at 24 months visit was not performed. AML, acute myeloid leukemia; IMP, investigational medicinal product, *N*, number of patients.

## 3 | RESULTS

### 3.1 | Enrollment

Between June 2013 and December 2016, a total of 570 study patients were enrolled, of which 280 patients were randomly assigned to treosulfan and 290 patients to reference RIC busulfan (Figure 1). The assigned study treatment could not be initiated in 17 randomized patients because of violations of inclusion or exclusion criteria noted after randomization in 16 patients and withdrawal of informed consent in one patient. Two further patients, in whom the assigned treosulfan treatment was initiated, did not proceed to HCT due to

**TABLE 1** Patient, disease and transplantation characteristics by random assignment

| | Busulfan | Treosulfan |
|---|---|---|
| All patients | *N* = 283 | *N* = 268 |
| Sex | | |
| Male, *n* (%) | 173 (61.1) | 162 (60.4) |
| Female, *n* (%) | 110 (38.9) | 106 (39.6) |
| Age | | |
| Median age, years (Q1, Q3) | 60.0 (57, 64) | 60.0 (55, 65) |
| ≥50 years, *n* (%) | 271 (95.8) | 252 (94.0) |
| ≥60 years, *n* (%) | 161 (56.9) | 140 (52.2) |
| Comorbidity | | |
| Median HCT-CI score (Q1, Q3) | 3.0 (1.0, 4.0) | 3.0 (1.0, 4.0) |
| HCT-CI score ≥3, *n* (%) | 167 (59.0) | 156 (58.2) |
| Donor type and graft source, *n* (%) | | |
| MRD | 68 (24.0) | 62 (23.1) |
| MUD | 215 (76.0) | 206 (76.9) |
| Graft source peripheral blood | 276 (97.5) | 260 (96.3) |
| Graft source bone marrow | 7 (2.5) | 8 (3.0) |
| Diagnosis, *n* (%) | | |
| AML | 168(59.4) | 184 (68.7) |
| MDS | 115 (40.6) | 84 (31.3) |
| **Patients with AML** | ***N* = 168** | ***N* = 184** |
| Median time between diagnosis and HCT, months (Q1, Q3) | 5.0 (3.6, 8.2) | 5.3 (3.8, 8.6) |
| CR1/>CR1 | 144 (85.7)/24 (14.3) | 159 (86.4)/25 (13.6) |
| Disease risk group stratification | | |
| Risk group I | 94 (33.2) | 87 (32.5) |
| Risk group II | 74 (26.1) | 97 (36.2) |
| Disease risk group, ELN | | |
| Low risk | 18 (10.7) | 19 (10.3) |
| Intermediate risk | 76 (45.2) | 68 (37.0) |
| High risk | 50 (29.8) | 72 (39.1) |
| NA if > CR1 | 24 (14.3) | 25 (12.6) |
| **Patients with MDS** | ***N* = 115** | ***N* = 84** |
| Median time between diagnosis and HCT, months | 7. 9 (4.9, 16.1) | 6.4 (4.1, 16.2) |
| Etiology: De novo / therapy-related MDS | 93 (80.9)/22 (19.1) | 66 (78.6)/16 (19.0) |
| Untreated/treated MDS | 47 (40.9)/68 (59.1) | 42 (50.0)/42 (50.0) |
| Disease risk group stratification | | |
| Risk group I | 55 (19.4) | 38 (14.2) |
| Risk group II | 60 (21.2) | 46 (17.2) |
| Disease risk group, IPSS-R | | |
| Very low risk | 1 (0.9) | 5 (6.0) |
| Low risk | 19 (16.5) | 15 (17.9) |
| Intermediate risk | 35 (30.4) | 18 (21.4) |
| High risk | 28 (24.3) | 22 (26.2) |
| Very high risk | 32 (27.8) | 24 (28.6) |

*Note*: Data are *n* (%) or median (IQR).
Abbreviations: AML, acute myeloid leukemia; CR, complete remission; ELN, European Leukemia Network; HCT-CI, Hematopoietic Cell Transplantation-specific Comorbidity Index; IPSS-R, Revised International Prognostic Scoring System; IQR, interquartile ranges, MDS, myelodysplastic syndrome; MRD, matched-related donor; MUD, matched unrelated donor; *N*, number of patients; *n*, number of patients in category; NA, not applicable; PBSCT, peripheral blood stem cell transplantation; Q, quartile.

sudden cancellation of donor clearance and delayed withdrawal of informed consent for HCT, respectively. Thereby, 551 of 570 (93%) study patients (treosulfan arm: 268 patients, busulfan arm: 283 patients) represent the FAS. Patient, disease and HCT characteristics of randomly assigned patients included in the FAS are summarized in Table 1. The distribution of patient age, HCT-CI, graft source, and donor type was well balanced between the randomly assigned treatment arms. The proportion of AML patients was higher in the treosulfan arm, while a higher proportion of MDS patients was assigned to the busulfan arm. Disease risk categories applied as stratum for randomization, however, was comparable between both arms. Frequencies of aggregated HCT-CI categories (occurring in at least 10% of patients) are summarized in Table S1 and were equally distributed between the two treatment arms. The median follow-up was 2.5 years for all patients and nearly identical in both arms (Table 2).

## 3.2 | Primary outcome

At the last analysis, the 36-month EFS was 59.5% (95% CI, 52.2–66.1) for patients in the treosulfan arm and 49.7% (95% CI, 43.3–55.7) for patients assigned to busulfan (Table 2). EFS with treosulfan met the defined significance level for noninferiority. Applying the pre-defined hierarchical testing strategy EFS of treosulfan was shown to be significantly superior compared to RIC busulfan ($p = 0.0005787$; Figure 2A) with a clinically meaningful benefit (HR 0.64 [95% CI, 0.49–0.84]).

The favorable effect of treosulfan on 36-month EFS was notable irrespective of categorized patient subsets (risk group of disease, underlying disease, age group of patients, and HCT-CI; *p*-value >0.10 for all interaction tests, data not shown) (Figure 2B). It was most pronounced in the prevailing subset of patients, who underwent HCT from MUD. Contrarily, no apparent effect of the assigned treatment on 36-month EFS was detectable for the smaller subset of patients after MRD transplantation.

## 3.3 | Secondary outcomes

The 36-month OS essentially reflects the results of the primary endpoint and was 66.8% (95% CI, 59.9–72.9) for patients assigned to

treosulfan compared with 56.3% (95% CI, 49.6–62.6) for patients in the busulfan arm (HR 0.64 [95% CI, 0.48–0.87] adjusted Cox regression $p$-value = 0.0037) (Table 2; Figure 2C). Accordingly, a consistent favorable effect of treosulfan was notable among the aforementioned patient subsets and appeared in the same order of magnitude as shown in the analysis of the primary endpoint (Figure 2D). Notably, OS of patients with AML and MDS exceeded 60% at 3 years in the treosulfan arm. At the end of the post-surveillance period, 70.0% of patients assigned to treosulfan and 60.4% of patients in the busulfan arm were alive and median OS has not been reached in either study

**TABLE 2** Event-free survival and secondary outcomes (full analysis set)

| | BusulfanN = 283 | TreosulfanN = 268 | p-value |
|---|---|---|---|
| Median follow-up of those surviving[a], months (range) | 29.4 (3.0, 54.3) | 29.7 (3.0, 52.1) | |
| Event-free survival | | | |
| Patients with event, *n* (%) | 137 (48.4) | 97 (36.2) | |
| Death[b], *n* (%) | 56 (19.8) | 35 (13.1) | |
| Relapse/progression[b], *n* (%) | 72 (25.4) | 61 (22.8) | |
| Primary graft failure[b], *n* (%) | 1 (0.4) | 1 (0.4) | |
| Secondary graft failure[b], *n* (%) | 8 (2.8) | 0 (0.0) | |
| Event-free survival at 24 months[c], % (95% CI) | 51.2 (45.0, 57.0) | 65.7 (59.5, 71.2) | |
| Event-free survival at 36 months[c], % (95% CI) | 49.7 (43.3, 55.7) | 59.5 (52.2, 66.1) | .0000001*,** .0005787*,*** |
| Overall survival | | | |
| Patients with event, *n* (%) | 112 (39.6) | 81 (30.2) | |
| Overall survival at 24 months[c], % (95% CI) | 60.2 (54.0, 65.8) | 72.7 (66.8, 77.8) | |
| Overall survival at 36 months[c], % (95% CI) | 56.3 (49.6, 62.6) | 66.8 (59.9, 72.9) | .0037* |
| Relapse/progression | | | |
| Patients with event, *n* (%) | 72 (25.4) | 61 (22.8) | |
| Cumulative relapse/progression incidence at 24 months, % (95% CI) | 25.2 (20.0, 30.3) | 22.0 (16.9, 27.1) | |
| Cumulative relapse/progression incidence at 36 months, % (95% CI) | 26.0 (20.6, 31.4) | 25.9 (19.8, 32.1) | .2631† |
| Nonrelapse mortality | | | |
| Patients with event, *n* (%) | 56 (19.8) | 35 (13.1) | |
| Cumulative nonrelapse mortality incidence at 24 months, % (95% CI) | 20.4 (15.5, 25.2) | 12.0 (8.0, 15.9) | |
| Cumulative nonrelapse mortality incidence at 36 months, % (95% CI) | 21.0 (16.1, 26.0) | 14.2 (9.5, 18.9) | .0343† |
| Recovery of Neutrophils, >0.5 × $10^9$/L | | | |
| Patients with event, *n* (%) | 279 (98.6) | 263 (98.1) | |
| Conditional cumulative incidence of neutrophil engraftment at 28 days, % (95% CI) | 96.8 (94.6, 99.1) | 96.2 (93.4, 99.1) | .4235† |
| Recovery of leukocytes, >1.0 × $10^9$/L | | | |
| Patients with event, *n* (%) | 280 (98.9) | 263 (98.1) | |
| Conditional cumulative incidence of leukocyte engraftment at 28 days, % (95% CI) | 98.5 (96.1, 100.0) | 97.2 (95.2, 99.1) | .2307† |
| Recovery of platelets (>20 × $10^9$/L) | | | |
| Patients with event, *n* (%) | 274 (96.8) | 260 (97.0) | |
| Conditional cumulative incidence of platelet engraftment at 28 days, % (95% CI) | 97.8% (96.3, 99.4) | 94.7% (92.0, 97.4) | .0038† |
| Mean duration of neutropenia, <0.5 × $10^9$/L | | | |
| Patients with event, *n* (%) | 280 (98.9) | 268 (100.0) | |
| Duration, Days (SD) | 13.8 (7.3) | 16.2 (6.4) | .0001† |
| Incidence of complete donor chimerism, *n* (%) | | | |
| Day +28 | 235 (83.3) | 245 (93.2) | .0159†† |

(Continues)

**TABLE 2** (Continued)

| | BusulfanN = 283 | TreosulfanN = 268 | p-value |
|---|---|---|---|
| Day +100 | 211 (80.2) | 217 (86.1) | .0381[††] |
| Graft failure, (95% CI) | | | |
| Patients with event, *n* (%) | 9 (3.2) | 1 (0.4) | |
| Cumulative incidence at 36 months, % (95% CI) | 3.2 (1.1, 5.3) | 0.4 (0.0, 1.1) | .0392[†] |

*Note*: Data are *n* (%) or median (IQR) unless otherwise specified.
Abbreviations: CI, confidence interval; IQR, interquartile ranges; *N*, number of patients; *n*, number of patients in category.
[a]Based on reverse Kaplan–Meier estimates for overall survival.
[b]Only if this event occurred first.
[c]Based on Kaplan–Meier estimates.
*Adjusted for donor type as factor, and disease risk group and center as strata using Cox regression model.
**p-Value for testing non-inferiority of treosulfan compared to busulfan.
***p-Value for testing superiority of treosulfan compared to busulfan.
[†]Adjusted for donor type as factor and risk group as stratum using Fine and Gray model.
[††]Stratified Cochran–Mantel–Haenszel test adjusted for donor type and risk group.[†] Based on the Wilcoxon–Mann–Whitney test.

arm (Figure 2B). Causes of death in the two study arms are displayed in Table S2.

The CIR at 36 months of patients assigned to treosulfan (25.9% [95% CI, 19.8–32.1] and busulfan (26.0% [95% CI, 20.6–31.4]) was nearly identical (Table 2; Figure 2E).

In contrast, the 36-month NRM for patients in the treosulfan arm (14.2% [95% CI, 9.5–18.9]) was lower than for patients in the busulfan arm (21.0% [95% CI, 16.1–26.0]) corresponding to a significantly reduced HR (HR 0.63 [95% CI, 0.41–0.97] adjusted Fine and Gray-model *p*-value = 0.0343) (Table 2; Figure 2F). No adverse influence of increasing numbers of aggregated HCT-CI categories compared with absence of any comorbidity on NRM was detectable by multivariate analysis (Table S3). Thus, comorbidities apparently did not impact NRM or its difference between study arms.

The proportion of patients with recovery of neutrophils, leukocytes, and platelets by day 28 after HCT was not different between the two treatment arms (Table 2). The prolonged duration of neutropenia below $0.5 \times 10^9$/L in patients assigned to treosulfan resulted from a faster and steeper decline of neutrophil counts after initiation of treatment compared with those of patients in the busulfan arm (Table 2). A higher proportion of patients in the treosulfan arm achieved complete donor cell chimerism at days +28 and +100 after HCT. Accordingly, the cumulative incidence of graft failure was lower for patients assigned to treosulfan (Table 2). The single patient in the treosulfan arm and 5 of the 9 patients in the busulfan arm deceased after graft failure.

The cumulative incidence of the categorized grades of severity of acute GvHD was similar in the treosulfan and busulfan arm. Furthermore, the cumulative incidence of overall chronic GvHD at 2 years was nearly identical (Table S4).

Exploratory analysis of GRFS and CRFS until 2 years after HCT confirmed a superior outcome of patients assigned to treosulfan (Figure S1).

Frequencies of treatment-emergent AEs of all grades and serious AEs were equally distributed between the study arms (Table S4). Furthermore, frequencies of patients with treatment-emergent serious AEs categorized by organ class and term were comparably low and no unknown safety risks were identified (Table S5).

## 4 | DISCUSSION

The present updated and extended final analysis of the prospective randomized MC-FludT.14/L study confirms the published results of the interim analysis and additionally demonstrates clinically relevant superiority of treosulfan over RIC busulfan with regard to the primary endpoint EFS.[13]

This difference was mainly attributable to lower NRM of patients assigned to treosulfan and also translated into improved OS compared with patients who received the RIC busulfan regimen. The 36-month NRM estimate obtained with the reference regimen in this study is in line with most previous results of retrospective registry studies and prospective randomized studies, which evaluated RIC busulfan or similar RIC regimens in adult patients with AML and MDS.[6,20–22] As an example, one recently published prospective randomized study performed in a largely consistent cohort of AML and MDS patients compared an augmented RIC regimen with conventional fludarabine-based RIC treatments, which predominantly consisted of the RIC busulfan regimen as employed in the reference arm of the present study.[23] In this study, the NRM rate and OS estimate for patients assigned to the control arm was 21% and 58.8% after 2 years, respectively, which appears in accordance with the results of these endpoints in the present study (20% and 60%, respectively).[13] Notwithstanding the limited comparability between similar treatment arms from different prospective studies, this comparison, as well as previous comparisons of the RIC busulfan regimen with other preparative regimens, support that the results obtained with the reference arm in the present study are contemporary and representative for older and comorbid patients with AML or MDS undergoing allogeneic HCT.

Implementation of more patients and a longer follow-up period in the present final study analysis has consolidated the results obtained by the second preplanned interim analysis with improvement of EFS and

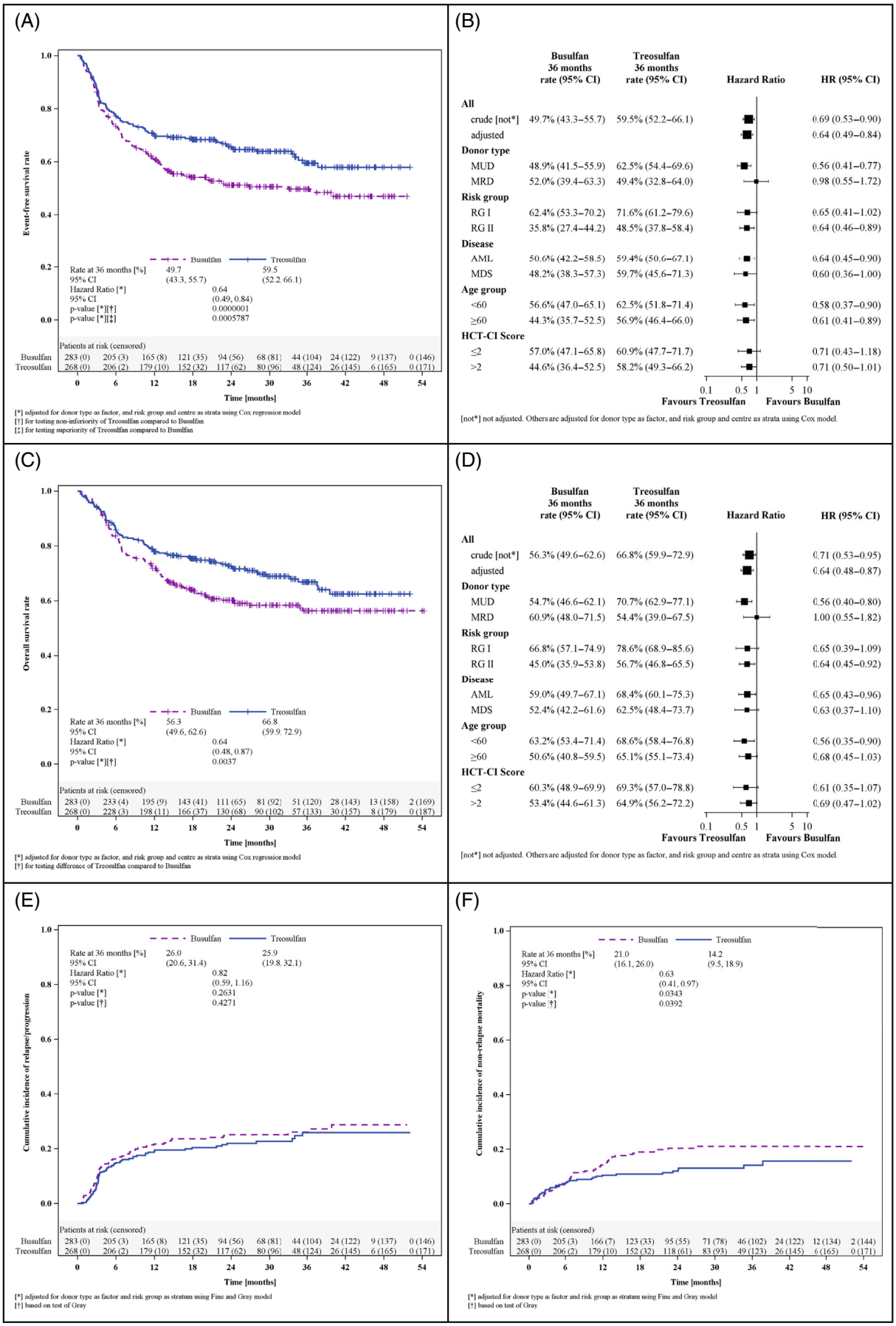


**FIGURE 2** Legend on next page.

OS by 10% and reduction of NRM by 7% at 36 months for patients enrolled in the treosulfan arm compared with those in the reference arm. The higher frequency of primary or secondary graft failure accounting for only 1 event (0.4%) after treosulfan and 9 events (3.2%) after RIC busulfan led to 1 and 5 fatal events, respectively. In conjunction with the higher cumulative incidence of complete donor cell chimerism attained by patients in the treosulfan arm, this observation underlines the stronger myeloablative properties of treosulfan as compared to RIC busulfan with otherwise well comparable nonhematologic toxicity profiles of both regimens in the present study. In opposite to previous retrospective investigations no apparent impact of the most frequent aggregated comorbidities on NRM was notable in this study.[24]

The incidence of disease recurrence or progression in both study arms was completely superimposable in the present study and appears well comparable to the CIR observed in two prospective randomized studies employing the RIC busulfan regimen in similar patient populations.[6,23] Only the BMT CTN 0901 study, in which the predominantly applied RIC busulfan regimen allowed oral or intravenous administration of busulfan, revealed a CIR of 48.3% at 18 months after HCT, which appears substantially higher than the 3-year CIR around 26% after both regimens in the present study.[5,25] The unexpectedly high CIR obtained with the RIC regimen in the BMT CTN 0901 study, which led to premature study termination, was accompanied by an exceptionally low TRM of 4.4% within 18 months. These figures raise the concern, whether inadequate exposure to RIC busulfan might have contributed to these singular study results. In the present study, the actual intravenously applied study drug dosages were almost identical with the dosages prescribed by the study protocol for patients in both study arms (data not shown). In further consideration of equal distributions of acute and chronic GvHD between both study arms, it appears justified to assume that the antileukemic efficacy of the experimental and reference regimen was identical and comparatively low in the present study.[18]

As previously outlined in detail, the present study has several limitations.[13] In brief, these include its open-label study design, missing implementation of minimal residual disease evaluation before and after HCT, as well as a common disease risk stratification for AML and MDS patients based on disease-specific risk categories, which were (and mostly still are) contemporary at the time of study design.[15,16,26–28] These limitations, however, appear compensated by comparatively comprehensive and well-balanced study arms, accomplishment of prespecified rigorous efficacy boundaries, and a meaningful follow-up period.

In conclusion, the final analysis of the MC-FludT.14/L study demonstrates that the treosulfan regimen leads to superior outcomes after allogeneic HCT compared with the reference RIC busulfan regimen and thereby appears particularly suitable for older AML and MDS transplantation candidates. Hence, this study provides a robust basis for future studies endeavored to further improve preparative regimens for the prevailing population of older AML and MDS patients, who are candidates for allogeneic HCT.

## AUTHOR CONTRIBUTIONS

Dietrich W. Beelen, Fabio Ciceri, Jochen Casper, Joachim Baumgart, and Uwe Pichlmeierconceived and designed the study.

Anja Kleinand Joachim Baumgart provided global project management.

Dietrich W. Beelen, Uwe Pichlmeieranalyzed the data.

Dietrich W. Beelen, Fabio Ciceri, Peter Dreger, Matthias Stelljes, Jochen Casper, Friedrich Stölzel, Joachim Baumgart, and Uwe Pichlmeierinterpreted the data.

Dietrich W. Beelen acted as coordinating principal investigator and corresponding author.

Miroslaw Markiewicz, Péter Reményi, Fabio Ciceri, and Hélène Labussiere-Walletacted as national coordinating investigators, respectively.

Dietrich W. Beelen, Matthias Stelljes, Péter Reményi, Eva-Maria Wagner-Drouet., Peter Dreger, Wolfgang Bethge, Fabio Ciceri, Friedrich Stölzel, Christian, Hélène Labussiere-Wallet, Kerstin Schaefer-Eckart, Goetz U. Grigoleit, Christof Scheid, Francesca Patriarca, Alessandro Rambaldi, Dietger Niederwieser, Inken Hilgendorf, Domenico Russo, Gérard Socié, Ernst Holler, Bertram Glassr, Jochen Casper, Gerald Wulf, Nadezda Basara, Maria Bieniaszewska, Gernot Stuhler, Mareike Verbeek, Ursula La Rocca, Juergen Finke, Fabio Benedetti, and Miroslaw Markiewicz actively admitted study patients and contributed clinical data from their site.

All authors approved the final version of the manuscript.

Dietrich W. Beelen, Peter Dreger, Joachim Baumgart, and Uwe Pichlmeierwere responsible for the preparation and writing of the manuscript. All authors reviewed and approved the final version of the manuscript.

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**FIGURE 2** Kaplan–Meier Estimate of Event-free Survival (A), Forest Plot for 36-month Event-free Survival by Prognostic Factors (B), Kaplan–Meier Estimate of Overall Survival (C), Forest Plot for 36-month Overall Survival by Prognostic Factors (D) as well as Cumulative Incidence of Relapse or Progression (E), and Non-relapse Mortality (F) (Full Analysis Set). *Adjusted for donor type as factor, and risk group and center as strata using Cox regression model (A,C). *Not adjusted. Other evaluations are adjusted for donor type as factor, and risk group and center as strata using Cox model (B,D). *Adjusted for donor type as factor and risk group as stratum using Fine and Gray model (E,F). †For testing non-inferiority of Treosulfan compared to Busulfan (A). †For testing difference of Treosulfan compared to Busulfan (C). ‡For testing superiority of Treosulfan compared to Busulfan (A). AML, acute myeloid leukemia; CI, confidence interval; HCT-CI, Hematopoietic Cell Transplantation-specific Comorbidity Index; MDS, myelodysplastic syndrome; MRD, matched-related donor; MUD, matched unrelated donor; *N*, number of patients; *n*, number of events; RG, risk group. [Color figure can be viewed at wileyonlinelibrary.com]

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## CONFLICT OF INTEREST

Péter Reményi, Fabio Ciceri, Christian, Hélène Labussiere-Wallet, Kerstin Schaefer-Eckart, Goetz U. Grigoleit, Domenico Russo, Nadezda Basara, Maria Bieniaszewska, G. Stuhler, Fabio Benedetti, Miroslaw Markiewicz declare no competing financial interests.

Dietrich W. Beelen and Matthias Stelljes have received honoraria from medac GmbH, have been paid to participate in a speakers' bureau by medac GmbH and received travel and accommodation expenses from medac GmbH; Eva-Maria Wagner-Drouet has been paid for a consulting or advisory role by Novartis, Kite Gilead, MSD and received travel, accommodation or expenses from medac GmbH, MSD; Peter Dreger obtained grants from medac GmbH; Wolfgang Bethge received honoraria from medac GmbH, has been paid for a consulting or advisory role by Gilead, Novartis, Celgene, BMS; Friedrich Stölzel received honoraria from medac GmbH, has been paid for a consulting or advisory role by medac GmbH, has been paid to participate in a speakers' bureau by Miltenyi and received travel, accommodation or expenses from medac GmbH, Celgene; Christof Scheid received honoraria from Amgen, BMS, GSK, Janssen, medac GmbH, MSD, Novartis, Pfizer, Roche, Sanofi, Takeda, has been paid for a consulting or advisory role by Amgen, BMS, GSK, Janssen, medac GmbH, MSD, Novartis, Pfizer, Roche, Takeda, obtained research funding from Janssen, Novartis, Takeda, received travel, accommodation or expenses from Amgen, BMS, GSK, Janssen, medac GmbH, MSD, Novartis, Pfizer, Takeda; Francesca Patriarca has been paid for a consulting or advisory role by Roche, Clinigen, Janssen Cilag, Amgen, Novartis and Glaxo; Alessandro Rambaldi received honoraria from Amgen, Pfizer, Novartis, Kite Gilead, Celgene BMS, Astellas, ABBVIE, Sanofi, Jazz and Omeros, has been paid for a consulting or advisory role by Amgen, Pfizer, Novartis, Kite Gilead, Celgene BMS, ABBVIE, Astellas, Sanofi and Omeros; Dietger Niederwieser received honoraria from Aichii; Novartis, Cellectis; Inken Hilgendorf received honoraria from Novartis, ABBVIE, has obtained travel, accommodation or expenses from medac GmbH, Janssen-Ciliag, Jazz Pharmaceuticals and Celgene; G.S. received honoraria from Novartis, Incyte, Elsalys, Xenikos, has been paid for a consulting or advisory role by Novartis, Incyte, Elsalys, Xenikos, received research funding from Alexion; Ernst Holler has been paid for a consulting or advisory role by Maat Pharma, Lyon, Novartis GmbH, medac GmbH (MSCs), Pharmabiome, Zurich has been paid to participate in a speakers' bureau by Maat Pharma, Neovii, received research funding from medac GmbH; Bertram Glassr has been employed by Helios Klinik Berlin, has been paid for a consulting or advisory role by Roche, Novartis, BMS, Kite, received research funding from Roche and Riemser; Jochen Casper received honoraria from Pfizer, Merck, Ipsen, Novartis, has been paid to participate in a speakers' bureau by Pfizer, Merck, Ipsen, received research funding from Takeda, medac GmbH, Ipsen, obtained travel, accommodation or expenses from Pfizer, Ipsen, medac GmbH, has been paid for a consulting or advisory role by Ipsen, Merck, Pfizer, medac GmbH; Gerald Wulf has been paid for a consulting or advisory role by Novartis, Kite Gilead, Clinigen and Takeda; Mareike Verbeek has received travel and accommodation expenses from medac GmbH; Ursula La Rocca has been paid for a consulting or advisory role by Novartis; Juergen Finke obtained grants from Novartis, medac GmbH, has been paid personal fees and other by Neovii and Riemser; Uwe Pichlmeier, Anja Klein, and Joachim Baumgart are employees of medac GmbH.

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## DATA AVAILABILITY STATEMENT

Research data are not shared

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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