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Running head: MSC therapy in pediatric patients with refractory aGvHD

Author contributions:

KV, PB, EO, MT, ML-W and HB were responsible for writing, reviewing and editing this manuscript. MT was responsible for data analysis. Patients were treated by FZ, MM, CK, JE, JG, BM-K, OB, PS, AJ, MW, J-HD, PL, AvS and PB. All authors have read and approved the published version of the manuscript.

Data availability statement:

Data supporting the findings of this real-world study are not publicly available due to privacy restrictions related to the small and potentially identifiable patient population. De-identified data may be made available from the corresponding author upon reasonable request and subject to appropriate approvals.

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ABSTRACT

Patients with acute graft-versus-host disease (aGvHD) not responding to steroids or further-line treatment, including ruxolitinib, face a poor prognosis. We conducted a multi-center, retrospective analysis of real-world data from 140 treatment episodes in 139 pediatric patients with steroid- or treatment-refractory aGvHD receiving the random-donor mesenchymal stromal cell (MSC) preparation tomostrocel. Most patients received 4–6 infusions of 1–2 million MSCs/kg body weight after a median of 3.5 prior therapies, including ruxolitinib in 76 patients. At baseline, over two-thirds had grade III/IV aGvHD, mostly with lower gastrointestinal involvement. At day 28, overall response (OR) rate was 62.9% (74.1%, 75.0% and 53.2% for grade II, III and IV aGvHD, respectively). OR was similar with versus without ruxolitinib pre-treatment. Organ stage with skin, liver, lower gastrointestinal and upper gastrointestinal involvement improved at day 28 in 69.4%, 57.5%, 58.6% and 39.5% of patients, respectively. Most responses were sustained. Six-month overall survival was 64.1%. Favorable survival factors were younger age, lower grade aGvHD and OR at day 28. The favorable safety profile of tomostrocel was consistent with prior MSC reports. Treatment with tomostrocel resulted in good responses with a favorable safety profile in heavily pre-treated pediatric patients, including those pre-treated with ruxolitinib.

Introduction

Acute graft-versus-host disease (aGvHD) remains a major complication in pediatric patients following allogeneic hematopoietic stem cell transplantation (HSCT) [1]. It is a leading cause of morbidity and mortality, resulting from both the disease itself and complications associated with intensive immunosuppressive therapy [2,3].

Risk of aGvHD can be mitigated by carefully tailoring conditioning regimens, donor selection and prophylactic therapies [4,5]. Despite this, aGvHD of grade II–IV still affects approximately 20–52% of pediatric patients undergoing HSCT [6,7].

High-dose systemic corticosteroids remain the established first-line therapy. However, up to 50% of patients have an inadequate or lack of response, defining steroid-dependent or steroid-refractory aGvHD (SR-aGvHD) [7,8]. This group is associated with a substantially worse prognosis, rapid disease progression, increased rates of hospitalization, prolonged immunosuppressive therapy, higher risk of severe infections and greater risk of morbidity [9]. Response to corticosteroids is particularly poor with grade III–IV aGvHD, which can account for up to 84% of the SR-aGvHD group [7]. Grade III–IV disease is generally associated with higher risk for mortality [9].

Supported by the prospective REACH 2 and 4 studies, ruxolitinib was approved by the FDA in 2019 and by EMA in 2021 as the first authorized drug to treat SR-aGvHD in adults and adolescents, and most recently also in children [10,11]. Recommendations from the European Society for Blood and Marrow Transplantation endorse ruxolitinib as first-line therapy for SR-aGvHD [12]. However, approximately 50% of patients do not derive a long-lasting benefit and a

relevant proportion of patients discontinue treatment due to therapy-related toxicity [13–15]. Consequently, a great medical need for improved treatment for these patients remains.

Potential further lines of therapy include conventional immunosuppressive agents such as mycophenolate mofetil, methotrexate and sirolimus; monoclonal antibodies such as basiliximab; non-pharmacological treatments such as extracorporeal photopheresis; and cellular therapies such as mesenchymal stromal cell (MSC) therapy [16,17]. Most of these treatments are associated with limited efficacy, unfavorable safety profiles and a high incidence of treatment-related complications, including severe infections, delayed immune reconstitution and organ toxicity, cumulatively leading to markedly increased transplant-related morbidity [17,18].

MSCs have emerged as a promising therapeutic option, with a very favorable safety profile [19,20]. These third-party cells are expanded and cultured *in vitro* and exhibit both immunomodulatory and regenerative properties [21]. Since its first reported clinical application in aGvHD in 2004, MSC therapy has been tested and implemented in numerous centers worldwide [22,23] . While several studies have reported encouraging outcomes, others have shown limited or inconsistent efficacy. This variability is likely attributable to differences in MSC source, inter-donor variability, manufacturing process and differences in study design [19].

A notable advancement is tomostrocel (also known as MSC-FFM, Obnitix® or MC0518). Tomostrocel is a standardized, Good Manufacturing Practice (GMP)-compliant MSC product designed to minimize inter-donor variability in MSC products and to ensure consistent potency and safety across batches [24,25].

The product was developed in an academic setting and is currently manufactured under standardized GMP conditions within a controlled multi-site manufacturing framework by the Blood Donation Service Baden-Württemberg-Hessen. medac GmbH (Wedel, Germany) acts as license holder and distributes tomostrocel via Hospital Exemption in Germany (under the name Obnitix$^{\rightarrow}$) according to §4b of the German Medicinal Products Act and Named Patient Use elsewhere. A mandatory requirement for Hospital Exemption is the continuous collection of patient data within a designated data surveillance program.

Early clinical experience with tomostrocel demonstrated promising clinical outcomes with a favorable safety profile in children and adults with SR-aGvHD [26].

This analysis provides additional real-world data from heavily pre-treated pediatric patients with aGvHD, evaluating the effectiveness and safety of tomostrocel in this particularly high-risk group.

Methods

Data collection

This multi-center retrospective analysis evaluated pseudonymized safety and efficacy data for pediatric patients receiving tomostrocel. Data were actively collected from the license holder to support the legally required annual report to the German national regulatory authority, the Paul-Ehrlich-Institute in Langen, Germany. As this report is a legal requirement, all ethical rules were appropriately considered. Consent procedures and the follow-up schedule are described in the Supplementary Methods S1.

Cell product characterization and patient treatment

The pre-clinical product development of the proprietary MSC preparation tomostrocel has been previously reported [24,27]. In brief, these are cryopreserved MSCs manufactured following stringent current GMP protocols from pooled bone marrow-derived mononuclear cells from 8 donors. Each donor pool constitutes a cell bank from which several hundred product batches are manufactured. Further information about MSC preparation, batch and bank release, including product supply and administration, are described in the Supplementary Methods S2.

Tomostrocel is dosed at 1–2 million cells/kg body weight once weekly for 4 consecutive weeks. Additional doses may be given at the clinician's discretion in responding patients with residual aGvHD.

Patients and disease scoring

Patients were under 18 years old. Treatment with tomostrocel is intended for patients with steroid- or treatment-refractory aGvHD following HSCT. Definitions of steroid-refractory [28] and treatment-refractory aGvHD are given in the Supplementary Methods S3.

aGvHD grade was assessed using the internationally accepted Mount Sinai Acute GvHD International Consortium criteria, and treatment response was subsequently determined based on this evaluation [28]. Complete response (CR) was defined as the absence of any signs of aGvHD. Partial response (PR) was defined as a minimum improvement of one stage in at least one organ system without worsening in another. CR and PR were collectively summarized as overall response (OR). Non-response (NR) was defined as the absence of OR

or death. Patients who died before day 28 were classified as NR. Missing values were conservatively considered NR.

Adverse drug reactions were reported if there was a plausible association with MSC administration.

Data analysis

The percentage of patients for each response category was reported. Overall survival (OS) probability was estimated and graphically displayed using Kaplan–Meier methodology. Survival was the time from first tomostrocel infusion to death from any cause or to the date of last follow-up for patients who remained alive (censored patients). To compare OS between responders and non-responders, a day-28 landmark analysis was performed, including only patients alive at day 28 to account for immortal time bias. Non-relapse mortality (NRM) was the time from first MSC infusion to death from any cause in the absence of prior relapse or progression of underlying disease. Cumulative incidence functions were applied to estimate NRM, accounting for relapse/progression as a competing risk.

Given the limited sample size in certain subgroups, statistical analyses are considered exploratory. Corresponding p-values for subgroup analyses were reported to support interpretation but should be interpreted with caution. Overall response probabilities were compared using Fisher's exact test, Kaplan–Meier curves with log-rank tests, and cumulative incidence functions using Gray's test.

Results

Patient characteristics

Between 2017–2025, data were collected on 140 treatment episodes in 139 pediatric patients who received tomostrocel treatment at 34 centers in 10 countries (Table 1). Treating centers are shown in Supplementary Table S1.

Most patients (60.0%) had undergone allogeneic HSCT for malignant hematopoietic disease, predominantly acute lymphoblastic leukemia (25.7%) or acute myeloid leukemia (14.3%) (Table 1). Overall, 75.7% of patients had grade III–IV aGvHD, with the skin and lower gastrointestinal (GI) tract most commonly affected (Table 2). aGvHD grade at baseline, i.e. prior to the first tomostrocel infusion, was similarly distributed across the different age groups.

Most patients were treatment refractory (118; 84.3%), including 76 with prior ruxolitinib exposure. A further 17 patients (12.1%) were steroid-refractory; 1 patient received a single non-steroid therapy, and no prior aGvHD therapy was documented for 5 patients (3.6%) before tomostrocel administration. This latter group may reflect documentation-related errors. The median number of prior aGvHD therapies was 3.5 (range: 0–11).

The median duration from last HSCT to first tomostrocel administration was 80.5 days (range: 15–483 days). Most patients (72.9%) received 1–2 million MSCs/kg body weight per infusion and 67.1% received 4–6 infusions of tomostrocel (Table 1).

Response

At day 28, the OR rate was 62.9%, consisting of 22.1% CR and 40.7% PR. OR by aGvHD severity was 74.1% for grade II, 75.0% for grade III, and 53.2% for grade IV aGvHD, with CR being 48.1%, 25.0%, and 8.1%, respectively.

By day 60, OR had increased for all-grade aGvHD to 66.9% (CR: 44.9%, PR: 22.1%). CR at day 60 was 80.0% for grade II, 40.9% for grade III, and 32.8% for grade IV aGvHD. Patients pre-treated with ruxolitinib (n=76) had an OR at day 28 of 64.5% and at day 60 of 64.9%. Improvement in CR in the ruxolitinib pre-treated group was particularly pronounced, increasing from 18.4% to 40.5% from day 28 to day 60.

The organ stage in patients with skin, liver, lower GI and upper GI improved from baseline to day 28 in 69.4%, 57.5%, 58.6% and 39.5% of patients, respectively. Clinical worsening of aGvHD under tomostrocel treatment was infrequent (Table 2).

Patients with non-malignant disease showed better OR at day 28 compared with patients with malignant underlying disease (74.1% vs 56.0%, p=0.0463). Analysis by age showed numerically higher OR rates in infants (71.4%, p=0.4217) and children (69.3%, p=0.0245) compared with adolescents (48.9%). Due to the small number of infants (n=7), results in this subgroup should be interpreted with caution. CR was comparable between children and adolescents (23.9% vs. 20.0%; Table 3).

Data on day 60 response for the total cohort, patients with ruxolitinib pre-treatment and according to baseline aGvHD grade are shown in Supplementary Table S2.

Survival

OS was 64.1%, 55.1% and 50.6% at 6, 12 and 24 months, respectively (Figure 1a). OS probability correlated with OR at day 28, being 72.9% and 64.3% in responders and 55.5% and 46.7% in non-responders at 6 and 12 months, respectively (p=0.0231, Figure 1b). Survival probability at 6 months was higher for patients with lower grade aGvHD prior to first MSC infusion (p=0.0002, Figure 2a) and patients of lower age (p=0.0680, Figure 2b). Patients with non-malignant underlying disease had numerically higher survival probability at 6 months than those with malignant underlying disease (p=0.2363, Figure 3a). Cumulative incidence of NRM was comparable (p=0.6862, Figure 3b). Relapse-related mortality was 4.3%.

Safety

Overall, tomostrocel was well tolerated. There were 4 adverse drug reactions reported in 3 patients (3 serious, 1 non-serious). These were hepatic encephalopathy with hyperammonemia, autoimmune hemolytic anemia, mild expiratory stridor (non-serious), and adenovirus sepsis. The mild expiratory stridor was reported in a patient with a concurrent pulmonary infection. After full recovery, this patient developed adenovirus sepsis with fatal outcome. Infections were reported in 39.3% of patients. None of these infections was considered related to tomostrocel administration. Detailed information on infection etiologies are reported in Supplementary Table S3.

Deaths

By the end of the observation period, 43.2% of patients had died, with a median time to death of 83.5 days after first tomostrocel infusion (range: 4–716 days). Patients who

responded by day 28 had a markedly lower mortality rate than non-responders (34.5% vs. 54.1%, respectively). Among those achieving CR at day 28, mortality was 19.4%.

The most frequently reported causes of death were related to GvHD (20.9%) and infections (18.0%). Details on infection-related deaths according to infectious etiology are presented in Supplementary Table S4. Numerically higher rates of both GvHD-related and infection-related mortality were observed among patients who had previously received ruxolitinib compared with those who had not (GvHD-related: 26.3 % vs. 14.3%, respectively, p=0.0961; infection-related: 21.1% vs. 14.3%, respectively, p=0.3769).

Additional frequent causes of death included pulmonary toxicity (10.1%), multi-organ failure (10.8%), renal failure (11.5%) and hemorrhage (8.6%). Death related to the underlying primary disease occurred in 8.6% of patients.

Discussion

These real-world data suggest that tomostrocel has clinically meaningful efficacy in heavily pre-treated pediatric patients with severe steroid- and treatment-refractory aGvHD, a population with very limited treatment options and high risk of NRM.

Most patients had severe SR-aGvHD (75.7% grade III–IV) after multiple prior lines of therapy (median 3.5) – including ruxolitinib in more than half of patients – underscoring the refractory nature of aGvHD and difficulty treating this population. The robust rates of OR to tomostrocel (62.9% at day 28 and 66.9% at day 60 across all aGvHD grades) align with previous data on MSCs in pediatric SR-aGvHD, including other MSC products [29–32] and earlier

reports on tomostrocel [24,26,33,34]. Furthermore, they exceed the reported day 28 OR of 34% reported by Rashidi et al.[35] for pediatric patients treated with anti-thymocyte globulin, etanercept or mycophenolate mofetil, suggesting MSC efficacy.

Ruxolitinib failure or intolerability has been frequently reported both in pediatric and adult patients [14,36,37]. At least in adult patients, failure to respond to ruxolitinib has been associated with very poor outcomes [38]. It is noteworthy that patients in our cohort who were pre-treated with ruxolitinib still achieved an OR rate of 64.5%, underscoring that tomostrocel can serve as a valuable treatment option.

Our data also provide insights into organ-specific efficacy. The pattern and extent of organ involvement can critically affect prognosis and treatment response, with multi-organ disease and advanced lower GI or hepatic involvement previously found to be particularly frequent in SR-aGvHD as well as consistently associated with poorer outcomes [7,35,39]. Many second-line therapies show limited efficacy. While skin usually responds best, the GI tract responds only moderately and with higher risk of persistent disease and mortality, while liver involvement shows the lowest response rates and poorest outcomes [40–43]. Our cohort represented a high-risk group: lower GI involvement at baseline was frequent (79.3%) and almost one-third of patients had liver involvement, presumably negatively selected by several earlier treatment lines to which the lower-risk patients may have responded. The impression of clinically meaningful organ-specific activity of tomostrocel was observed in all organ classes. Our findings are comparable to (and in part more favorable than) reported organ responses to other MSC products, particularly with regard to liver involvement. They confirm that

responses in patients with high-risk organ manifestations are achievable with MSC therapy [20,44–46].

Clinical improvement after tomostrocel translated into favorable survival benefits. Overall, 6-month OS was 64.1%, being 83.9%, 76.1% and 49.3% for grade II, III and IV aGvHD, respectively (p=0.0002). Consistent with previous findings [29,30,32], achieving a response by day 28 was a strong predictor of OS. Accordingly, patients with aGvHD of grade II or III exhibited higher OR rates at day 28 and better OS compared with patients with grade IV aGvHD. This suggests that improved survival is mediated by better treatment response, probably due to lower disease severity at treatment initiation, and highlights the importance of initiating MSC therapy as early as possible. Even the subgroup of patients with grade IV disease – typically associated with poorer prognosis – showed encouraging OS under tomostrocel treatment.

In our cohort, younger age was associated with favorable OS, mirroring previous studies. Verbeek et al. (2022)[7] reported a direct association between older age and increased mortality in pediatric SR-aGvHD. In adult cohorts, age has repeatedly been identified as a prognostic factor for both OS and NRM [4,35,47]. NRM remains high in pediatric SR-aGvHD, mostly caused by the aggressive disease course of aGvHD as well as treatment-related complications, such as infections [7,9,35,39].

Overall, tomostrocel therapy was well tolerated in our cohort. These findings are in line with other studies demonstrating the favorable safety profile of MSC therapy in pediatric patients with SR-aGvHD [48], including with long-term use[49].

Our analysis has several limitations inherent to real-world observational data. Concomitant therapies used before, during or after tomostrocel may have contributed to clinical improvement. Treatment allocation may have been influenced by patient characteristics or physician preference. The cohort may not reflect the full spectrum of aGvHD severity, as the most critically ill patients may have died before tomostrocel administration, while milder cases may have received and responded to alternative treatments. Another short-coming is that some data are missing, particularly from the early phase of the data surveillance program, mainly due to limited center responsiveness despite repeated follow-up efforts. Given the real-world setting, no further data retrieval was feasible. However, the proportion of missing data was small relative to the overall dataset and is therefore unlikely to have materially affected the interpretation of the results. Moreover, whenever response data were missing, the least favorable response, i.e. non-response, was assumed, so that our reported data may even underestimate the potential of tomostrocel. Data for chronic GvHD were not collected within the Data Surveillance Program.

This work was restricted to a specific and unique bone marrow-derived MSC preparation designed for scalable manufacturing while meeting stringent pharmaceutical quality standards. We do not claim superiority of this product over other MSC preparations, since no such comparison was sought. Rather, tomostrocel demonstrably represents a distinct therapeutic entity and our findings support its potential in the treatment of severe, refractory pediatric aGvHD. We further encourage continued research into optimized MSC preparations, whether derived from bone marrow or alternative tissue sources, as well as innovative manufacturing approaches, including MSC pooling strategies.

Nevertheless, our dataset has important strengths. The large sample size collected over a long study period enables robust and temporally stable analyses. Moreover, the inclusion of 34 treatment centers reduces potential center-specific limitations and increases the external validity of the results.

To investigate the clinical efficacy and safety of tomostrocel in the second line, i.e. after determination of steroid-refractoriness according to the MAGIC definition, the prospective, randomized controlled phase II BALDER (NCT06075706) and phase III IDUNN (NCT04629833) trials in pediatric and adult patients were initiated [50]. At the time of writing, recruitment into BALDER was complete and the patients were in follow-up for the assessment of long-term survival, while the recruitment for the IDUNN trial was ongoing.

Conclusion

Overall, these real-world data demonstrate good responses to tomostrocel and a favorable safety profile in heavily pre-treated pediatric patients with steroid- and treatment-refractory aGvHD, including those previously exposed to ruxolitinib. In light of the inherent limitations of real-world data, the results of the BALDER and IDUNN clinical trials are eagerly awaited.

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Table 1. Baseline patient characteristics, including aGvHD grade and prior therapies, and details of treatment with tomostrocel.[a]

Sex, n (%)	
Male	96 (68.6%)
Female	43 (30.7%)
Data missing	1 (0.7%)
Age, years	
Mean (SD)	8.4 (4.7)
Median (Q1, Q3)	8.0 (4.5, 12.0)
Min, max	0, 17
ICH age group, n (%)	
Infants and toddlers (28 days to 23 months)	7 (5.0%)
Children (2 to 11 years)	88 (62.9%)
Adolescents (12 to 17 years)	45 (32.1%)
Indication for HSCT, n (%)	
Malignant hematopoietic disease	84 (60%)
Non-malignant disease	54 (38.6%)
Data missing	2 (1.4%)
Overall aGvHD grade, n (%)	
I	1 (0.7%)
II	27 (19.3%)
III	44 (31.4%)
IV	62 (44.3%)
Data missing	6 (4.3%)
Number of prior aGvHD therapies, n (%)	
0 or none reported	5 (3.6%)
1	17 (12.1%)
2	22 (15.7%)
3	26 (18.6%)
>3	70 (50.0%)
Median	3.5
Min, max	0, 11
Duration from last HSCT to first MSC administration, days	
Mean (SD)	112.7 (94.4)
Median (Q1, Q3)	80.5 (48.0, 149.5)
Min, max	15, 483
Data missing	4
Mean MSC dose per infusion, n (%)	
<1 000 000/kg BW	4 (2.9%)
1 000 000 to 2 000 000/kg BW	102 (72.9%)
>2 000 000/kg BW	29 (20.7%)
Data missing	5 (3.6%)
Number of MSC administrations, n (%)	
<4	35 (25.0%)
4 to 6	94 (67.1%)
>6	11 (7.9%)

aGvHD acute graft-versus-host disease, *BW* body weight, *HSCT* hematopoietic stem cell transplantation, *ICH* International Council for Harmonisation, *Max* maximum, *Min* minimum, *MSC* mesenchymal stromal cell, *n* number of patients, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation.

[a]One patient is included twice in this table due to 2 treatment episodes.

Table 2. aGvHD organ stage at baseline and change from baseline at day 28 (N=140).[a]

	Skin	**Liver**	**Lower GI tract**	**Upper GI tract**
Prior to tomostrocel, n %				
Stage 0	39 (27.9%)	95 (67.9%)	27 (19.3%)	92 (65.7%)
Stage 1	16 (11.4%)	16 (11.4%)	12 (8.6%)	43 (30.7%)
Stage 2	21 (15.0%)	7 (5.0%)	13 (9.3%)	NA
Stage 3	46 (32.9%)	11 (7.9%)	36 (25.7%)	NA
Stage 4	15 (10.7%)	6 (4.3%)	50 (35.7%)	NA
Data missing	3 (2.1%)	5 (3.6%)	2 (1.4%)	5 (3.6%)
Change from baseline to day 28[b]				
	n=98	**n=40**	**n=111**	**n=43**
Improved	68 (69.4%)	23 (57.5%)	65 (58.6%)	17 (39.5%)
No change	18 (18.4%)	10 (25.0%)	30 (27.0%)	21 (48.8%)
Worsened	2 (2.0%)	4 (10.0%)	4 (3.6%)	0 (0.0%)
Data missing	10 (10.2%)	3 (7.5%)	12 (10.8%)	5 (11.6%)

aGvHD acute graft-versus-host disease, *GI* gastrointestinal, *n* number of patients.

[a]One patient is included twice in this table due to 2 treatment episodes.

[b]Change from baseline is given for patients who had stage 1–4 disease at baseline in the specified organ.

		Response, n, (%)			
	n	**Overall response**	**Complete response**	**Partial response**	**No response**
Total cohort	140	88 (62.9%)	31 (22.1%)	57 (40.7%)	52 (37.1%)
Patients with ruxolitinib pre-treatment	76	49 (64.5%)	14 (18.4%)	35 (46.1%)	27 (35.5%)
aGvHD grade prior to tomostrocel infusion					
Grade I	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Grade II	27	20 (74.1%)	13 (48.1%)	7 (25.9%)	7 (25.9%)
Grade III	44	33 (75.0%)	11 (25.0%)	22 (50.0%)	11 (25.0%)
Grade IV	62	33 (53.2%)	5 (8.1%)	28 (45.2%)	29 (46.8%)
Data missing	6	2 (33.3%)	2 (33.3%)	0 (0.0%)	4 (66.7%)
ICH age group					
Infants and toddlers (28 days to 23 months)	7	5 (71.4%)	1 (14.3%)	4 (57.1%)	2 (28.6%)
Children (2 to 11 years)	88	61 (69.3%)	21 (23.9%)	40 (45.5%)	27 (30.7%)
Adolescents (12 to 17 years)	45	22 (48.9%)	9 (20.0%)	13 (28.9%)	23 (51.1%)
Indication for HSCT					
Malignant disease	84	47 (56.0%)	16 (19.0%)	31 (36.9%)	37 (44.0%)
Non-malignant disease	54	40 (74.1%)	15 (27.8%)	25 (46.3%)	14 (25.9%)

Table 3. Response to tomostrocel at day 28 in the total cohort and according to baseline aGvHD grade, ICH age group and indication for HSCT.[a]
aGvHD acute graft-versus-host disease, *HSCT* hematopoietic stem cell transplantation, *ICH* International Council for Harmonisation, *n* number of patients.
[a]One patient is included twice in this table due to 2 treatment episodes.

Figure legends

Figure 1. Overall survival after first tomostrocel infusion for all patients and according to treatment response. **a** Overall survival for all patients[a] and **b** Landmark analysis of overall survival according to response to tomostrocel at day 28[a].

NR non-response, *OR* overall response, *R6m* rate at 6 months.

[a]One patient with two treatment episodes is included only once in this display.

Figure 2. Overall survival after first tomostrocel infusion according to baseline patient characteristics. Overall survival stratified by **a** aGvHD grade[a] at baseline and **b** ICH age group[a] at baseline.

aGvHD acute graft-versus-host disease, *ICH* International Council for Harmonisation, *R6m* rate at 6 months, *<2* patients <2 years old, *2-11* patients 2–11 years old, *12-17* patients 12–17 years old, *I/II* aGvHD grade I/II, *III* aGvHD grade III, *IV* aGvHD grade IV.

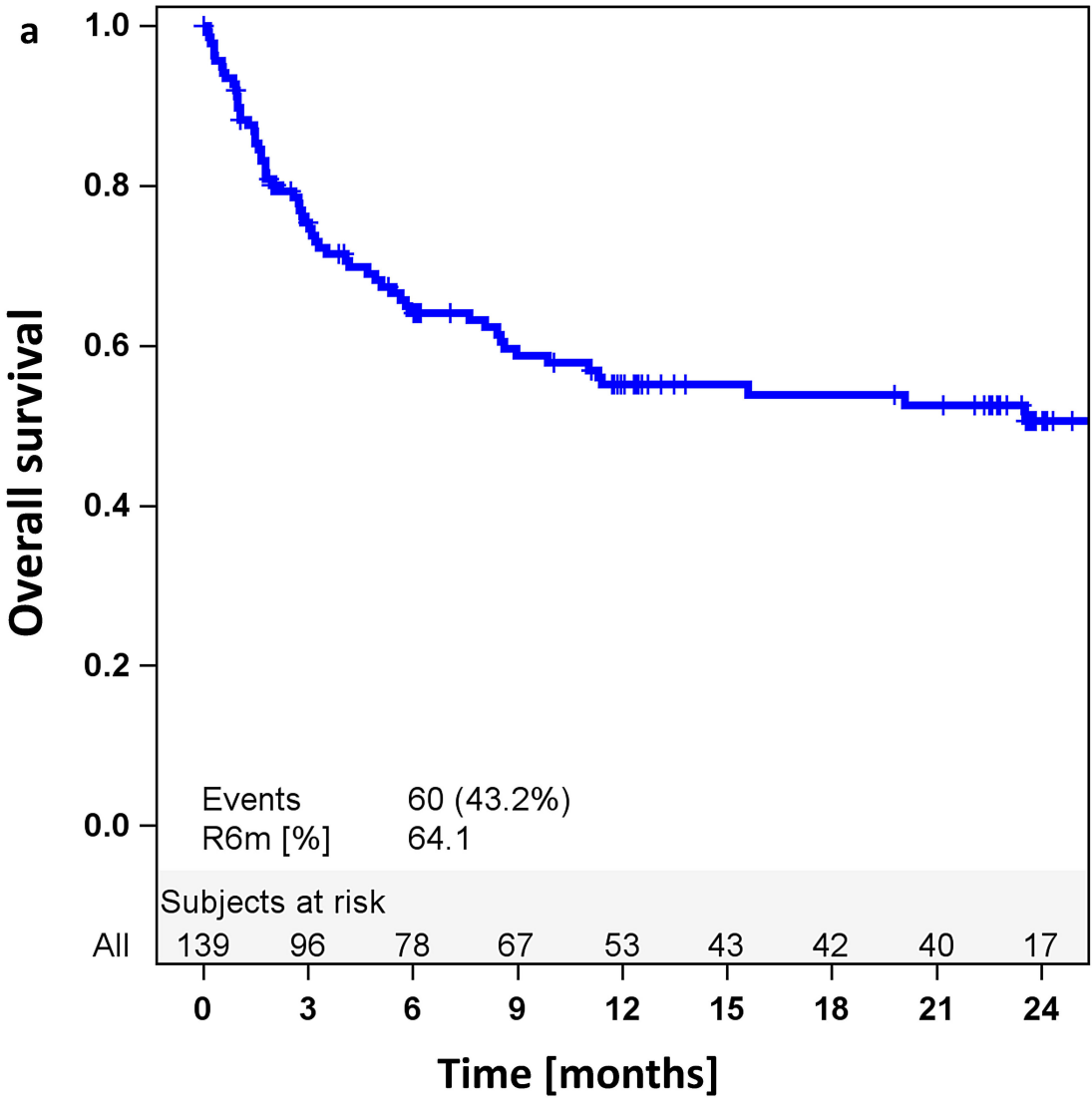
[a]One patient with two treatment episodes is included only once in this display.

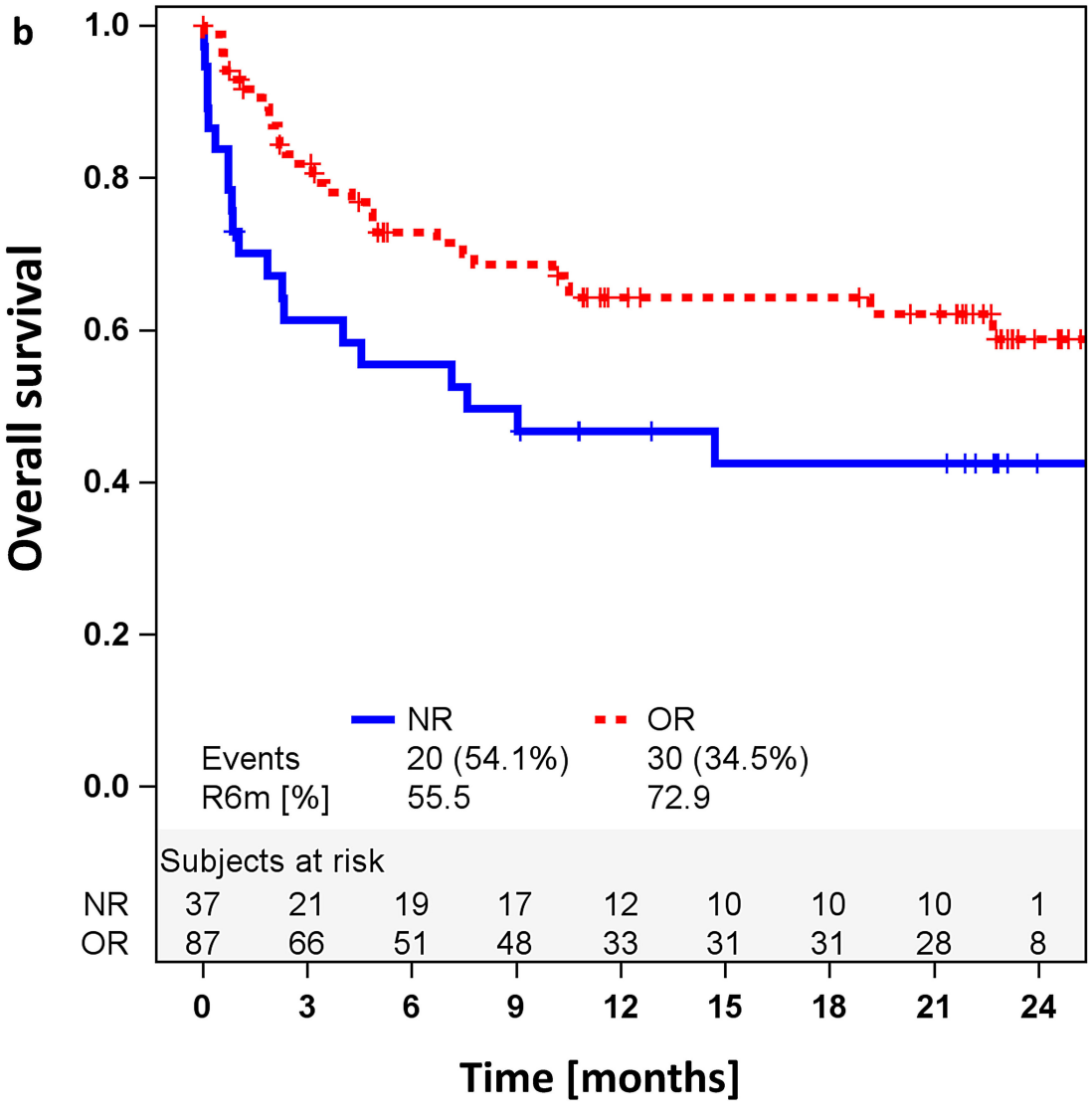
Figure 3. Overall survival and cumulative incidence of NRM by indication for HSCT after first tomostrocel infusion. **a** Overall survival[a,b], **b** cumulative incidence of NRM[a,b].

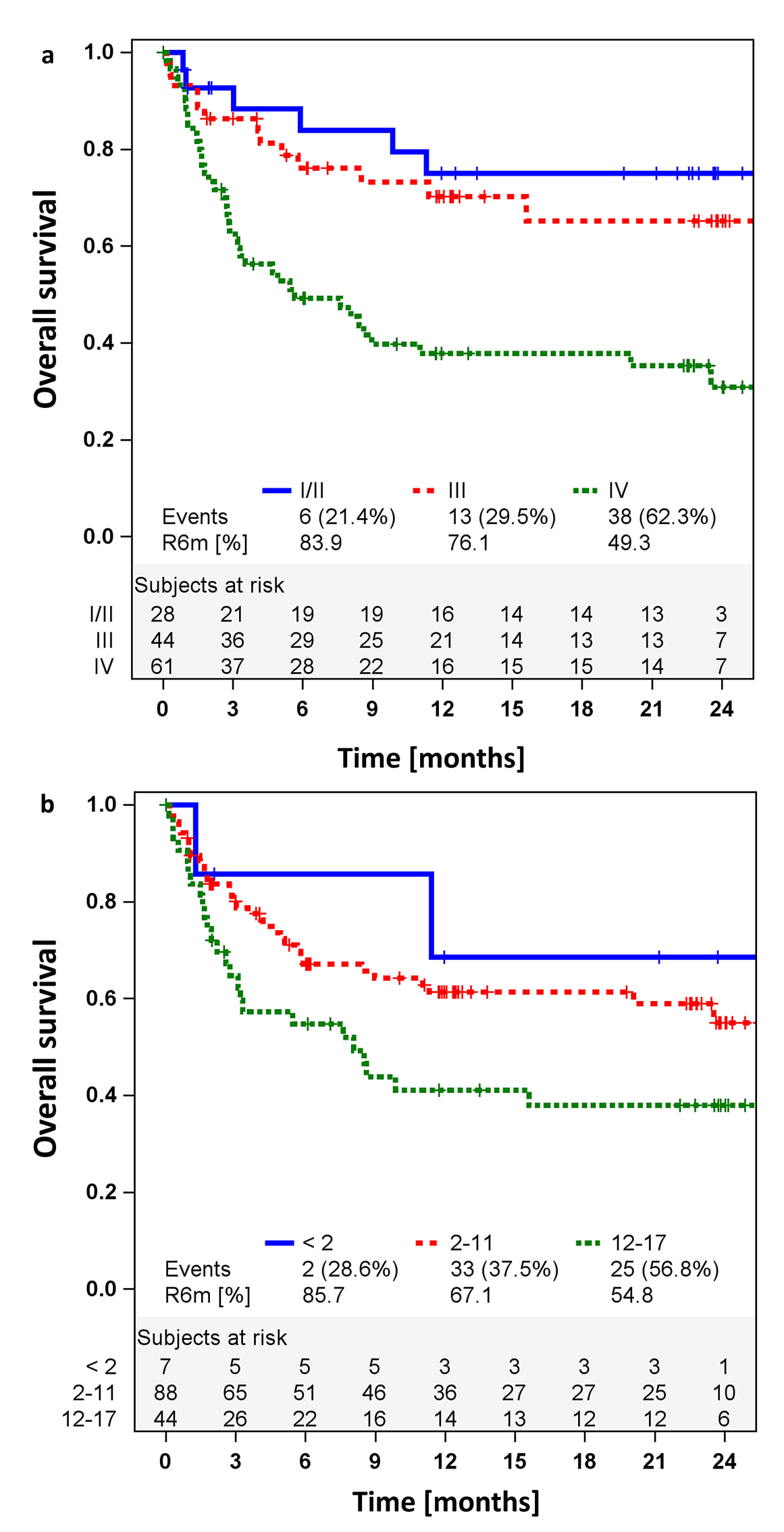
HSCT Hematopoietic stem cell transplantation, *Mal.* malignant, *Non-mal.* non-malignant, *NRM* non-relapse mortality, *R6m* rate at 6 months.

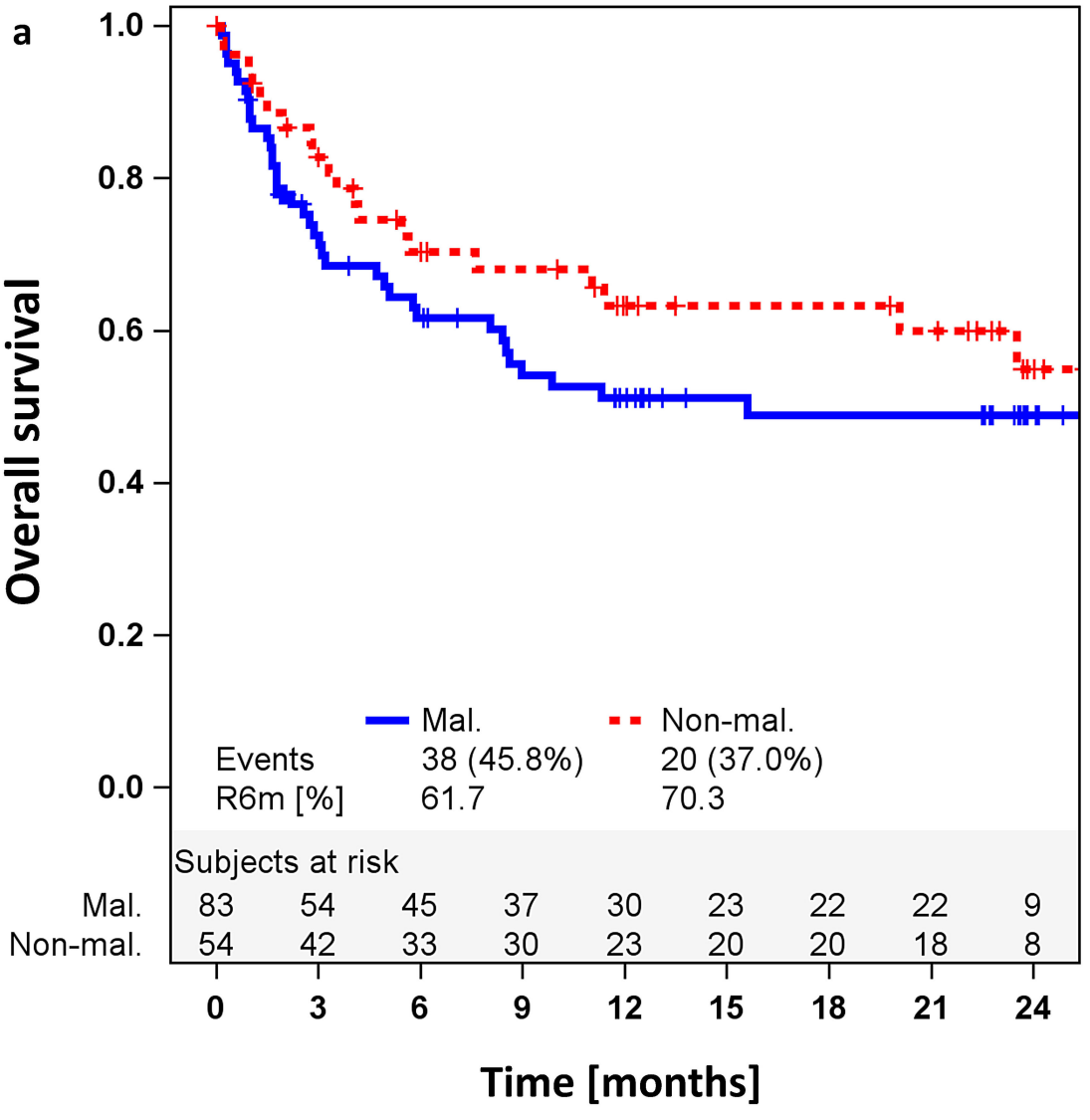
[a]One patient with two treatment episodes is included only once in this display.

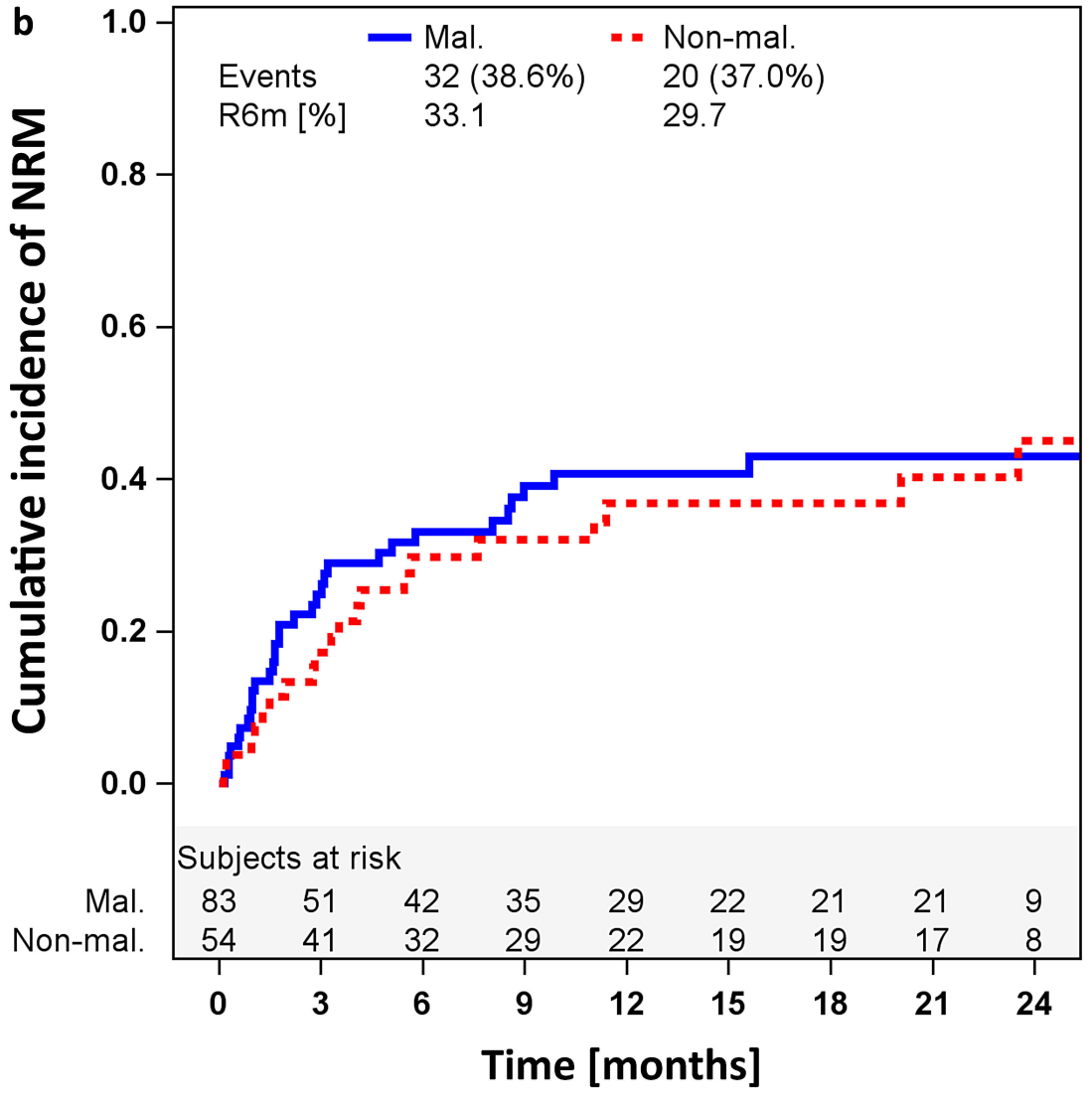
[b]Two patients with missing primary diagnosis group excluded.


a
1.0
0.8
0.6
0.4
0.2
0.0
Overall survival
Events 60 (43.2%)
R6m [%] 64.1
Subjects at risk
All 139 96 78 67 53 43 42 40 17
0 3 6 9 12 15 18 21 24
Time [months]


b
1.0
0.8
0.6
0.4
0.2
0.0
Overall survival
NR
OR
Events 20 (54.1%) 30 (34.5%)
R6m [%] 55.5 72.9
Subjects at risk
NR 37 21 19 17 12 10 10 10 1
OR 87 66 51 48 33 31 31 28 8
0 3 6 9 12 15 18 21 24
Time [months]


a
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
I/II
III
IV
Events
6 (21.4%)
13 (29.5%)
38 (62.3%)
R6m [%]
83.9
76.1
49.3
Subjects at risk
I/II 28 21 19 19 16 14 14 13 3
III 44 36 29 25 21 14 13 13 7
IV 61 37 28 22 16 15 15 14 7
0 3 6 9 12 15 18 21 24
Time [months]
b
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
< 2
2-11
12-17
Events
2 (28.6%)
33 (37.5%)
25 (56.8%)
R6m [%]
85.7
67.1
54.8
Subjects at risk
< 2 7 5 5 5 3 3 3 3 1
2-11 88 65 51 46 36 27 27 25 10
12-17 44 26 22 16 14 13 12 12 6
0 3 6 9 12 15 18 21 24
Time [months]


a
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
Mal.
Non-mal.
Events
38 (45.8%)
20 (37.0%)
R6m [%]
61.7
70.3
Subjects at risk
Mal. 83 54 45 37 30 23 22 22 9
Non-mal. 54 42 33 30 23 20 20 18 8
0 3 6 9 12 15 18 21 24
Time [months]


b
Cumulative incidence of NRM
1.0
0.8
0.6
0.4
0.2
0.0
Mal.
Non-mal.
Events
32 (38.6%)
20 (37.0%)
R6m [%]
33.1
29.7
Subjects at risk
Mal. 83 51 42 35 29 22 21 21 9
Non-mal. 54 41 32 29 22 19 19 17 8
0 3 6 9 12 15 18 21 24
Time [months]

Supplementary materials

Supplementary Methods S1. Data collection

The treating physician obtained written informed consent for both treatment with tomostrocel and data documentation for scientific and regulatory requirements from the patient and/or legal guardian. Treating physicians and, where necessary, flying study nurses (providing project support across multiple centers), documented data in an electronic or paper case report form. Baseline characteristics were documented before the first infusion of tomostrocel. Patients were followed up on days 28, 60 and 180 as well as 1 and 2 years after the first administration of tomostrocel.

Supplementary Methods S2. Preparation, release, product supply and administration of tomostrocel

Tomostrocel is manufactured over a total culture period of 4 weeks under current GMP conditions. Previously frozen bone marrow-derived mononuclear cells from 8 donors are pooled and MSCs are generated and expanded in human platelet lysate-supplemented medium for an initial 2 weeks, after which a cell bank of several hundred MSC starter cultures is cryopreserved. Subsequently, MSCs are further expanded in 2D culture in human platelet-supplemented medium for an additional 2 weeks, including one intermediate passage, yielding batches of approximately 500–600 million MSCs. Final products are cryopreserved in bags containing 10, 30, 60 or 90 million cells. Quality control includes identity, purity, characterization of impurities, potency and biological safety using assays validated in accordance with applicable German and European standards.

Cell banks and individual batches that meet the stringent pre-defined quality specifications are eligible for release by a Qualified Person, with individual clearance of MSC banks by the Paul-Ehrlich-Institute, Langen, Germany. Four different MSC banks were used in this study.

Clinicians requested tomostrocel directly from medac GmbH on a Named Patient basis. Tomostrocel was provided to treating hospitals as frozen bags in liquid nitrogen dewars for slow intravenous infusion by gravity flow immediately after thawing using a conventional transfusion filter set.

Supplementary Methods S3. Definitions of steroid-refractory and treatment-refractory aGvHD

SR-aGvHD was defined as lack of response to corticosteroids within 3–5 days, the failure to improve within 5–7 days of treatment initiation, or incomplete response after more than 28 days of treatment [28]. Treatment-refractory aGvHD was defined as refractoriness to corticosteroids and at least one additional line of therapy.

Supplementary Table S1. Treating centers

Country	Center
Denmark	Rigshospitalet, University Hospital Copenhagen, Copenhagen
France	Robert Debré Hospital, Paris
	Rouen University Hospital-Charles Nicolle, Rouen
	Hautepierre Hospital – University Hospitals of Strasbourg, Strasbourg
	La Timone University Hospital, Marseille
	Necker-Enfants Malades University Hospital, Paris
	Clermont-Ferrand University Hospital, CHU Estaing, Clermont-Ferrand
	Léon Bérard Cancer Center, Lyon
Germany	University Hospital Essen, Essen
	University Hospital Regensburg, Regensburg
	University Hospital Tübingen, Tübingen
	University Hospital Erlangen, Erlangen
	University Hospital Gießen, Gießen
	Charité – Universitätsmedizin Berlin, Berlin
	University Hospital Jena, Jena
	University Hospital Heidelberg, Heidelberg
	University Hospital Greifswald, Greifswald
	University Hospital Leipzig, Leipzig
	Hannover Medical School, Hannover
	University Hospital Freiburg, Freiburg
	University Hospital Würzburg, Würzburg
	University Hospital Ulm, Ulm
	Klinikum Kassel, Kassel
	University Hospital Schleswig-Holstein, Campus Kiel, Kiel
	University Medical Center Hamburg-Eppendorf, Hamburg
	University Hospital Frankfurt, Frankfurt am Main
Great Britain	Royal Hospital for Children, Glasgow
Hungary	South-Pest Central Hospital, Budapest
Ireland	Children's Health Ireland at Crumlin, Dublin
Italy	Fondazione IRCCS Policlinico San Matteo, Pavia
Norway	Oslo University Hospital, Oslo
Sweden	Karolinska University Hospital, Stockholm
Switzerland	University Children's Hospital Zurich, Zurich
	University Hospital of Geneva, Geneva

Supplementary Table S2. Response to tomostrocel at day 60 in the total cohort and according to aGvHD grade.[a]

			Response, n (%)			
		n	**Overall response**	**Complete response**	**Partial response**	**No response**
Total cohort		136	91 (66.9%)	61 (44.9%)	30 (22.1%)	45 (33.1%)
Patients with ruxolitinib pre-treatment		74	48 (64.9%)	30 (40.5%)	18 (24.3%)	26 (35.1%)
aGvHD grade prior to first tomostrocel infusion						
	Grade I	1	1 (100.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
	Grade II	25	22 (88.0%)	20 (80.0%)	2 (8.0%)	3 (12.0%)
	Grade III	44	32 (72.7%)	18 (40.9%)	14 (31.8%)	12 (27.3%)
	Grade IV	61	34 (55.7%)	20 (32.8%)	14 (23.0%)	27 (44.3%)
	Data missing	5	2 (40.0%)	2 (40.0%)	0 (0.0%)	3 (60.0%)

aGvHD acute graft-versus-host disease, *n* number of patients.

[a]One patient is included twice in this table due to 2 treatment episodes.

Supplementary Table S3. Distribution of infectious etiologies of at least grade 3[a] in the overall cohort (N=140)[b] and relationship to tomostrocel administration

Subjects with infections	55 (39.3%)
Infectious etiologies[c], n (%)	
Bacterial	14 (10.0%)
Viral	44 (30.7%)
Fungal	8 (5.7%)
Parasitic	0 (0.0%)
Unspecified	2 (1.4%)
Related to tomostrocel[c], n (%)	
No	54 (38.6%)
Yes	0 (0.0%)
Missing	1 (0.7%)

[a]Grade 3 classification according to Common Terminology Criteria for Adverse Events (CTCAE).

[b]One patient is included twice in this table due to 2 treatment episodes.

[c]More than one type and relationship per patient possible.

Supplementary Table S4. Distribution of infectious etiologies among infection-related deaths in the overall cohort (N=139)

Subjects with infection-related deaths	25 (18%)
Infectious etiologies[a], n (%)	
Bacterial	9 (6.5%)
Viral	16 (11.5%)
Viral reactivation	6 (4.3%)
Fungal	9 (6.5%)
Parasitic	0 (0.0%)
Unspecified	1 (0.7%)

[a]Only infection-related deaths are included. Multiple causes of death could be selected for an individual patient. Causes of death reported as unknown were excluded.