Supplementary Table 1

		Munich	Regensburg
Patients - no.		25	53
Mean age at HSCT - yr		57.4 ± 8.6	54.2 ± 12.2
Male/Female Sex - no. (%)		14 (56)/11 (44)	31 (58)/22 (42)
Diagnosis - no. (%)	Acute leukaemia	10 (40)	28 (53)
	MDS/MPN	9 (36)	15 (28)
	NHL	4 (16)	7 (13)
	other	2 (8)	3 (6)
Donor type - no. (%)	Unrelated	18 (72)	39 (74)
	Sibling	2 (8)	7 (13)
	Haploidentical	5 (20)	7 (13)
Conditioning - no. (%)	Ablative	3 (12)	7 (13)
	Reduced intensity	22 (88)	46 (87)
Stem cell source - no. (%)	PBSC	24 (96)	40 (75)
	BM	1 (4)	13 (25)
GI-GvHD - no. (%)	none	11 (44)	25 (47)
	mild	3 (12)	18 (34)
	severe	11 (44)	10 (19)
	steroid refractory	13 (52)	11 (21)
2 year relapse cumulative incidence % (% SE)		20 (8)	21 (6)
2 year TRM cumulative incidence % (% SE)		28 (9)	15 (5)
2 year survival - % (% SE)		52 (10)	70 (7)

Patient characteristics according to transplantation center. A total of 68% of the patients in the overall study population were enrolled at University Medical Center, Regensburg and 32% at University Hospital Rechts der Isar, Munich. HSCT denotes hematopoietic stem cell transplantation, MDS myelodysplastic syndrome,

MPN myeloproliferative neoplasia, NHL Non-Hodgkin lymphoma, PBSC peripheral-blood stem cell, BM bone marrow, GI-GvHD acute gastrointestinal graft-vs-host disease, SE standard error, and TRM transplantation-related mortality. Diseases categorized as “other” include aplastic anemia, chronic active Epstein-Barr virus infection, blastic plasmacytoid dendritic cell neoplasm and myelosarcoma.

Supplementary Table 2

	Munich	Regensburg
Intestinal decontamination	-	Rifaximin
Prophylaxis of hepatic complications	Ursodeoxycholic acid 250 mg p.o. 3x daily from start of conditioning until discontinuation of immunosuppression	Ursodeoxycholic acid 250 mg p.o. 3x daily if patient develops elevation of liver enzymes and/or bilirubin
Pneumocystis jirovecii prophylaxis	Trimethoprim/ Sulfamethoxazole	Trimethoprim/ Sulfamethoxazole
Antifungal prophylaxis	Micafungin; after regeneration: Posaconazole	Fluconazole; in GvHD/other risk factors: Posaconazole
Cytomegalovirus prophylaxis	Letermovir	Letermovir
Herpesvirus prophylaxis	Valacyclovir	Acyclovir
Antibiotics - 1st line	Piperacillin/Tazobactam ± Vancomycin/Teicoplanin	Piperacillin/Tazobactam ± Vancomycin/Teicoplanin
Antibiotics - 2nd line	Meropenem ± Vancomycin/Linezolid	Meropenem ± Vancomycin/Teicoplanin
Antimycotics	liposomal Amphotericin B, Caspofungin, Isavuconazol	liposomal Amphotericin B, Caspofungin, Isavuconazol
Virostatics	Foscavir, Ganciclovir, Valganciclovir	Foscavir, Ganciclovir, Valganciclovir

Antibiotic, antimycotic and antiviral treatment and prophylaxis standards in Munich and Regensburg.

Supplementary Table 3

Comparison	Status	Cumulative Incidence (Gray) p-value	Hazard ratio (Fine and Gray)	95% Confidence interval	Log Rank p-value	Hazard ratio (Cox Regression)	95% Confidence interval
IMM-RI	TRM	0.052	5.980	0.730-49.020	0.040	6.528	0.826-51.594
	Relapse	0.044	6.260	0.826-47.619	0.006	56.761	0.251-12818.351
	GvHD	0.054	1.020	0.513-2.049	0.848	1.074	0.486-2.372
	Death	0.122	2.580	0.543-12.210	0.006	6.164	1.415-26.854
Bacterial diversity	TRM	0.001	9.460	1.174-76.336	<0.001	0.072	0.009-0.554
	Relapse	0.452	0.885	0.164-4.776	0.814	1.136	0.392-3.291
	GvHD	0.001	1.604	0.699-3.676	0.015	0.459	0.232-0.907
	Death	0.992	not converged	not defined	0.002	0.261	0.103-0.661
Fungal diversity	TRM	0.555	0.774	0.245-2.445	0.481	0.664	0.210-2.093
	Relapse	0.757	2.067	0.413-10.341	0.819	1.136	0.381-3.381
	GvHD	0.487	0.743	0.313-1.761	0.772	1.095	0.568-2.107
	Death	0.782	not converged	not defined	0.514	0.757	0.327-1.754
Viral diversity	TRM	0.256	0.290	0.033-2.591	0.269	3.329	0.346-32.014
	Relapse	0.620	1.570	0.284-8.621	0.690	0.696	0.116-4.167
	GvHD	0.220	0.939	0.391-2.257	0.688	1.198	0.448-3.203
	Death	0.584	not converged	not defined	0.867	1.125	0.281-4.501
Factor1	Death	not defined	not defined	not defined	<0.001	0.262	0.120-0.573
Factor3	Death	not defined	not defined	not defined	<0.001	0.253	0.106-0.607
Factor4	Death	not defined	not defined	not defined	0.011	3.290	1.237-8.749

Outcome analyses, statistics. IMM-RI denotes immune-modulatory metabolites risk index, TRM transplantation related mortality, GvHD graft-versus-host disease.

Supplementary Table 4

Metabolite (median, IQR)	Alive (0)	Deceased (1)	p-value (MWU)
Acetic acid	90.11 (144.65)	27.81 (99.21)	0.157
Propionic acid	18.90 (39.27)	0.55 (8.89)	0.037
Isobutyric acid	1.33 (2.70)	0.37 (1.23)	0.057
Butyric acid	2.30 (10.15)	0.12 (4.06)	0.137
Methylbutyric acid	0.81 (1.54)	0.10 (0.74)	0.071
Isovaleric acid	1.23 (2.32)	0.03 (0.99)	0.013
Valeric acid	0.12 (0.94)	0.02 (0.22)	0.086
Desaminotyrosine	0.02 (0.10)	0.00 (0.01)	0.018
Indolecarboxyaldehyde	0.02 (0.06)	0.00 (0.02)	0.056
Lithocholic acid	14.56 (0.00)	14.56 (0.00)	0.717
Deoxycholic acid	67.18 (2340.61)	96.56 (1399.38)	0.808
Cholic acid	2106.99 (5001.94)	2321.15 (8567.47)	0.919
Chenodeoxycholic acid	453.87 (1809.12)	35.79 (1320.19)	0.488
Tauroursodeoxycholic acid	24.39 (2006.57)	47.35 (2813.83)	0.195
Ursodeoxycholic acid	789.80 (3882.05)	764.78 (2259.80)	0.903
Dehydrolithocholic acid	1.06 (132.33)	7.62 (104.57)	0.983
Total primary bile acids	10442.49 (20156.44)	3133.39 (16590.48)	0.800
Total secondary bile acids	7803.66 (10910.42)	7119.79 (4354.19)	0.420

Metabolites stratified by overall survival. IQR denotes interquartile range, MWU Mann-Whitney-U Test.

Supplementary Table 5

Pathways	MetaCyc
4-amino-2-methyl-5-diphosphomethylpyrimidine biosynthesis II	PWY-7282
Acetyl-CoA fermentation to butyric acid	PWY-5676
Adenosine degradation II	SALVADEHYPOX-PWY
anaerobic energy metabolism	PWY-7383
biosynthesis of thiamine diphosphate	PWY-7282
degradation of 4-aminobutanoate to butyric acid	PWY-5022
Guanosine degradation II	PWY-6606
Guanosine degradation III	PWY-6608
L-arginine biosynthesis III	PWY-5154
L-arginine biosynthesis IV	PWY-7400
L-histidine degradation I	HISDEG-PWY
L-histidine degradation III	PWY-5030
L-methionine biosynthesis IV	PWY-7977
starch degradation III	PWY-6731
the degradation of N-acetylneuraminate to acetic acid or ethanol	P441-PWY
Superclass	
acetate_pathways	PWY0_1312,PWY_5535,PWY_8328, PWY_5536,P161_PWY,P124_PWY, PWY_804,P461_PWY,P162_PWY, P163_PWY,PROPFERM_PWY
butanoate_pathways	PWY_5022,PWY_5676,P162_PWY, GLUDEG_II_PWY,PWY_8190,P163_PWY, CENTFERM_PWY,PWY_5677
fermentation_superclass	ANAEROFRUCAT_PWY,CENTFERM_PWY, FERMENTATION_PWY,P108_PWY, P122_PWY,PWY_5676,PWY_5677, PWY_6588,PWY_6590,PWY_7111, PWY_7383,PWY_7385,PWY_7396, PWY4LZ_257
propanoate_pathways	PWY_8086,PWY_7013,PWY_8188, PWY_5088,PWY_8377,PROPFERM_PWY
SCFA_superclass	acetate_pathways, butanoate_pathways, propanoate_pathways
Superclass of thiamine biosynthesis	THISYN_PWY,"PWY_6895", "THISYNARA_PWY"

Genes	
butyrate_kinase_ko	K00929
Bile salt hydrolase	K01442
7-alpha-hydroxysteroid dehydrogenase	K00076
Vancomycin resistance	ko01502
Antimicrobial resistance	ko01504

MetaCyc pathways, superclass and genes.

Supplementary Table 6

	Munich	Regensburg
AB therapy - no. (%)	25 (100)	50 (94)
AB timing - no. (%)		
Never	0 (0)	3 (6)
Early (during conditioning)	3 (12)	13 (25)
Regular (at/after transplantation)	22 (88)	37 (70)
AF therapy - no. (%)	13 (52)	22 (42)
AV therapy - no. (%)	0 (0)	8 (15)

AB denotes patients who received intravenous therapy with broad-spectrum antibiotics (including Piperacillin/Tazobactam, Meropenem, Ciprofloxacin, Ceftazidim), AF antifungal (including liposomal Amphotericin B, Isavuconazole, Caspofungin), AV antiviral (including Foscavir, Ganciclovir, Valganciclovir)

Supplementary Table 7

		IMM-RI low	IMM-RI high	p-value
N		19	31	
Mean Pt Age (95% CI)		53 (47-58)	58 (55-62)	0.040
male/female		9/10	17/14	0.608
ABX		17	31	0.065
Graft type	PBSC	18	24	0.134
	BM	1	7	
Donor type	Unrelated	15	21	0.401
	Sibling	2	2	
	Haplo	2	8	
Conditioning	Reduced intensity	16	26	0.975
	Myeloablative	3	5	
Diagnosis	Acute leukemia	11	12	0.457
	MDS/MPN	5	14	
	NHL	2	2	
	Other	1	1	
Stage	Early	10	14	0.835
	Intermediate	1	2	
	Advanced	1	4	
HCT-CI	Low	2	5	0.905
	Intermediate	5	6	
	High	5	9	
Compound median (IQR) [µmol/g dry feces]	Propionic acid	34.61 (27.11)	0.39 (1.56)	< 0.001
	Butyric acid	9.11 (18.25)	0.09 (0.11)	< 0.001
	Isovaleric acid	2.09 (1.72)	0.03 (0.21)	< 0.001
	Desaminotyrosine	0.08 (0.11)	0.00 (0.00)	< 0.001
	Indolecarboxyaldehyde	0.03 (0.12)	0.00 (0.01)	< 0.001

Patient characteristics and metabolic compounds in the Immuno-modulatory Index risk groups. IMM-RI denotes immune-modulatory metabolites risk index, Pt

patient, ABX patients who received broad-spectrum antibiotics before the samples have been collected (d7-21), PBSC peripheral blood stem cells, BM bone marrow, MDS myelodysplastic syndrome, MPN myeloproliferative neoplasm, NHL Non-Hodgkin's lymphoma, HCT-CI hematopoietic cell transplantation-comorbidity index, IQR interquartile range. For differences in metabolic compounds a two-sided Mann-Whitney U test was used.

Supplementary Table 8

Diet (Munich)	n=21 patients
Western	21 (100 %)
Vegetarian	0 (0%)
Pescetarian	0 (0%)
Vegan	0 (0%)

Diet in the Munich patient cohort. Animal-based Western diet: Total about 2000 kcal/day (carbohydrates 55%, protein 30%, fat 15%).

Supplementary Table 9

Compound	0 points	1 point
Propionic acid [µmol/g dry feces]	> 21.96	≤ 21.96
Butyric acid [µmol/g dry feces]	> 1.41	≤ 1.41
Isovaleric acid [µmol/g dry feces]	> 0.035	≤ 0.035
Desaminotyrosine [µmol/g dry feces]	> 0.005	≤ 0.005
Indolecarboxyaldehyde [µmol/g dry feces]	> 0.035	≤ 0.035

Metabolomic compounds of the Immuno-modulatory metabolite risk index. Variables were chosen upon biologic plausibility and optimized threshold values were defined according to Youden's Index (optimized sensitivity and specificity for binary outcome (alive/deceased)). Higher scores indicate microbiome dysfunction.