Prognostic value of CPSS cytogenetic risk classification in patients with CMML after allogeneic hematopoietic cell transplantation: a retrospective multicenter study of the Chronic Malignancies Working Party of the EBMT.

C. Koenecke, D. J. Eikema, S. Hazelaar, T. Schroeder, V. Potter, N. Kröger, M. Bornhäuser, J. Finke, U. Platzbecker, A. Radujkovic, et al.

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TO THE EDITOR:

The only curative treatment approach for patients with chronic myelomonocytic leukemia (CMML) is allogeneic hematopoietic cell transplantation (allo-HCT), but disease relapse after transplantation is a major concern [1]. Predictors for disease outcome after transplant are limited. However, beside other risk factors (ASXL1 mutations, monocytosis, cytopenias and circulating immature myeloid cells), cytogenetic abnormalities have been shown to serve as predictors for outcome in CMML patients [2–5]. Cytogenetic abnormalities are frequently seen in 20–30% of patients [6, 7]. According to the CMML-specific prognostic scoring system (CPSS) patients can be categorized into three risk groups (high risk: trisomy 8, chromosome 7 abnormalities, or complex karyotype; low risk: normal karyotype and -Y; intermediate risk: all other chromosomal abnormalities) [8]. There is evidence, that adverse cytogenetics are also a risk factor for worse outcome after allo-HCT [9]. However, cytogenetic information according to CPSS was not evaluated in the setting of allo-HCT to date. Therefore, the aim of this large multicentric, international study was to retrospectively determine the impact of CPSS-cytogenetic on outcome after allo-HSCT.

Adult patients (age > = 18years) who had received a first allo-HCT for the treatment of CMML between 2000 and 2015 were selected from the European Society of Bone and Marrow Transplantation (EBMT) database. 233 centers participated into this study. In total, 1347 patients were included. Impact of CPSS-cytogenetic classification was analysed regarding overall survival (OS), progression free survival (PFS) and cumulative incidence of relapse and non-relapse mortality (NRM) after transplant. OS and PFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the Log-Rank test. Median follow-up was determined using the reverse Kaplan-Meier method. The cumulative incidence of relapse (RI) and NRM were analysed together in a competing risks framework. Subgroup differences in cumulative incidences were assessed using Gray's test. Multivariable Cox regression was applied to investigate the simultaneous impact of multiple covariates on OS and PFS. Included covariates were: CPSS (intermediate, high versus low), stage at transplant (no CR, untreated versus CR), disease (transformed to AML versus other), age at transplant (in decades) and year of allo-HCT. Continuous variables are presented in the text as median and interquartile range (IQR) or range and categorical variables as percentages. All survival estimates and hazard ratios are reported with corresponding 95% confidence intervals in parentheses. All *p*-values are two-sided and $p < 0.05$ is considered significant. Statistical analyses were performed in R version 3.6.0 (R Development Core Team, Vienna, Austria), using packages 'survival', 'prodlim' and 'cmprsk'.

436 female (32.4%) and 909 male (67.6%) patients were included into the study. Median age at HSCT was 58.1 years (range 20–75.4). At time of HCT, 383 (68.6%) patients were diagnosed with CMML-I, 175 (31.4%) with CMML-II, 412 (74.9%) with dysplastic and 138 (25.1%) with proliferative CMML. Only 392 (30.6%) patients were in complete remission, whereas 668 (52.2%) had not reached CR and 220 (17.2%) had not received chemotherapy before allo-HCT. 212 (35.0%) patients received conventional chemotherapy and 119 (19.6%) hypomethylating agents before transplantation. Matched related donor allo-HCT was performed in 35.6% of the patients, matched unrelated donor in 7.4%, unrelated donor (complete HLA unavailable) in 51.6%, mismatched related in 2.8% and mismatched unrelated in 2.6%. Bone marrow (10.2%), peripheral blood (87.3%), or both (0.2%) served as the stem cell graft. Cord blood was used in 2.3%. Myeloablative conditioning regimens were used in 187 patients (13.9%), and less intensive regimens were given to 1156 patients (86.1%). Median follow-up of patients was 51.4 (47.8–56.8) months.

Two-year and five-year PFS were 39% (36–42%) and 29% (26–32%), respectively. Two- and 5-year relapse incidence were 35% (33–38%) and 41% (38–44%) respectively, with a relapse observed in 474 patients at any time during follow-up. The median time to relapse in the patients who relapsed was 4.9 months (IQR 2.7–11.7). Two- and 5-year NRM were 26% (23–28%) and 30% (27–33%), respectively. Two- and 5-year OS were 46% (43–49%) and 33% (30–36%).

570 patients had sufficient cytogenetic information according to CPSS (777 missing). 132 (23.2%) patients could be categorized into CPSS-high, 76 (13.3%) into intermediate and 362 (63.5%) into low-risk cytogenetics, respectively. In univariate analysis CPSS cytogenetic information was found to be strongly associated with OS ($p < 0.001$; low 35% (29–41%), intermediate 39% (27–51%), high 24% (15–32%)) at 5 years. A higher cumulative incidence of relapse ($p = 0.015$; low 42% (37–48%), intermediate 43% (30–56%), high 51% (42–60%)) was detected. In line, cytogenetic status was associated with PFS ($p < 0.001$; low 30% (25–36%), intermediate 30% (18–42%), high 21% (13–28%). However, NRM

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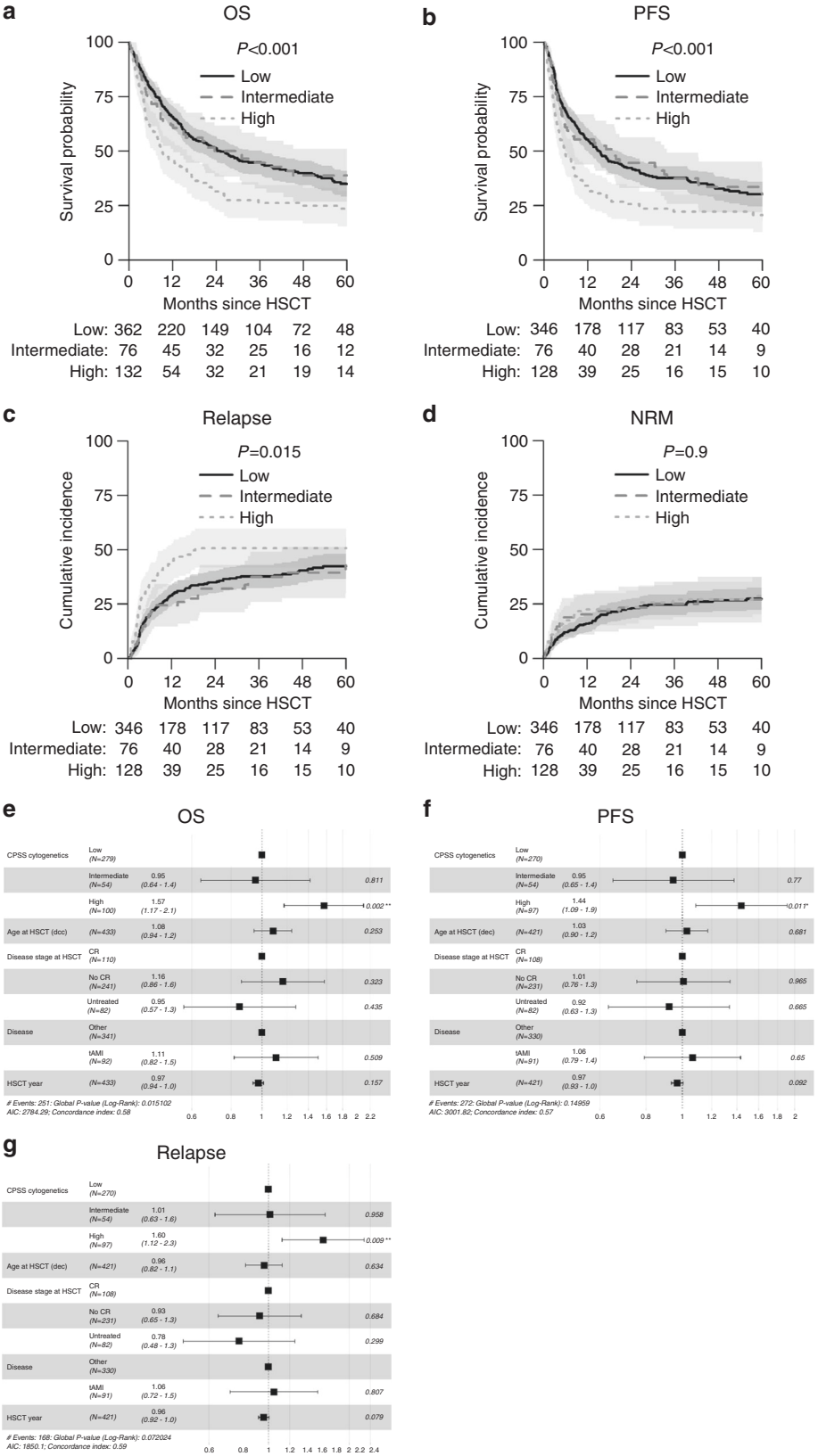

Fig. 1 CPSS cytogenetic information predict outcome after allogeneic transplantation in CMML patients. a–d Probability of overall survival (OS), progression free survival (PFS), relapse incidence and non relapse mortality (NRM) of CMML patients with low, intermediate or high risk cytogentic. **e–g** Forest plots on overall survival (OS), progression free survival (PFS) and relapse incidence.

Table 1. Multivariate analysis overall (OS), progression free survival (PFS) and relapse incidence (RI).

		OS			PFS			RI		
		N	HR (95% CI)	*p*	*N*	HR (95% CI)	*p*	*N*	HR (95% CI)	*P*
	Total	433			421			421		
CPSS	Low	279			270			270		
	Intermediate	54	0.95 (0.64–1.42)	0.8	54	0.95 (0.65–1.37)	0.8	54	1.01 (0.63–1.62)	>0.99
	High	100	1.57 (1.17–2.1)	0.002	97	1.44 (1.09–1.91)	0.01	97	1.6 (1.12–2.27)	0.009
Stage at transplant	CR	110			108			108		
	no CR	241	1.16 (0.86–1.58)	0.3	231	1.01 (0.76–1.34)	0.9	231	0.93 (0.65–1.33)	0.7
	Untreated	82	0.85 (0.57–1.28)	0.4	82	0.92 (0.63–1.34)	0.7	82	0.78 (0.48–1.25)	0.3
Disease	Other	341			330			330		
	tAML	92	1.11 (0.82–1.5)	0.5	91	1.06 (0.79–1.43)	0.7	91	1.05 (0.72–1.52)	0.8
Age (decades)		433	1.08 (0.94–1.24)	0.3	421	1.03 (0.9–1.17)	0.7	421	0.96 (0.82–1.13)	0.6
Tx year		433	0.97 (0.94–1.01)	0.16	421	0.97 (0.93–1.01)	0.09	421	0.96 (0.92–1)	0.08

($p = 0.87$; low 27% (22–33%), intermediate 27% (16–38%), high 29% (20–37%)) at 60 months was not affected by cytogenetic status at time of transplantation (Fig. 1).

In multivariable analysis (MVA), including only patients with available data on included covariates, CPSS-high risk cytogenetics was associated with shorter overall survival after allogeneic transplantation compared to intermediate and low risk cytogenetics (hazard ratio (HR), 1.57 (1.17–2.1)). This finding was also present in MVA for PFS (HR 1.44 (1.09–1.91)) and RI (HR 1.6 (1.12–2.27)). Patients' age, year of transplant, and status of the disease at transplant were not associated with a reduced OS, PFS and RI (Table 1). In another study by this working group, status of the disease before transplantation was associated with survival [10].

Our results show that CPSS cytogenetics is a strong predictor of relapse and overall survival after allo-HCT. Adverse cytogenetic alterations lead to a disease biology which is more likely to be resistant to an allograft. This observation has been made in a variety of myeloid malignant diseases, such as MDS and AML [11]. Currently, molecular diagnostics are becoming more and more standard in patients with CMML. We were not able to include such information into this retrospective study. It might be that even more distinct risk-groups can be identified using that diagnostic tool [5].

In this international, multicentric analysis we show that CMML patients with high-risk cytogenetics had significantly worse overall and progression-free survival after allo-HCT than patients with intermediate or low risk cytogenetics according to CPSS. New therapeutic strategies to prevent relapse after allo-HCT in CMML patients with high-risk cytogenetics are needed.

Christian Koenecke[1]✉, Dirk-Jan Eikema[2], Sheree Hazelaar[3], Thomas Schroeder[4], Victoria Potter[5], Nicolaus Kröger[6], Martin Bornhäuser[7], Jürgen Finke[8], Uwe Platzbecker[9], Aleksandar Radujkovic[10], Arnold Ganser[1], Urpu Salmenniem[11], Didier Blaise[12], Guido Kobbe[13], Ellen Meijer[14], Lone Friis[15], Johan Maertens[16], Dolores Caballero[17], Jan J. Cornelissen[18], Attilio Olivieri[19], Ozet Gulsum[20], Patrick J. Hayden[21], Francesco Onida[22], Marie Robin[23] and Ibrahim Yakoub-Agha[24]

[1]Hannover Medical School, Hannover, Germany. [2]EBMT statistical Unit, Leiden, The Netherlands. [3]EBMT data office Leiden, Leiden, The Netherlands. [4]Universitätsklinikum Essen, Essen, Germany. [5]GKT School of Medicine, London, UK. [6]University Hospital Eppendorf, Hamburg, Germany. [7]University Hospital TU Dresden, Dresden, Germany. [8]University of Freiburg, Freiburg, Germany. [9]University Hospital Leipzig, Leipzig, Germany. [10]University of Heidelberg, Heidelberg, Germany. [11]HUCH Comprehensive Cancer Center, Helsinki, Finland. [12]Institut Paoli-Calmettes, Marseille, France. [13]Heinrich Heine Universitaet, Duesseldorf, Germany. [14]Vrije Universiteit Medical center, Amsterdam, The Netherlands. [15]Rigshospitalet, Copenhagen, Denmark. [16]University Hospital Gasthuisberg, Leuven, Belgium. [17]Hospital Clinico, Salamanca, Spain. [18]Erasmus MC Cancer Institute, Rotterdam, The Netherlands. [19]Azienda Ospedali Riuniti di Ancona, Ancona, Italy. [20]Ankara Sehir Hastanesi, Ankara, Turkey. [21]Trinity College Dublin, St. James's Hospital, Dublin, Ireland. [22]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico-University of Milan, Milan, Italy. [23]Hopital St. Louis, Paris, France. [24]CHU de Lille, INSERM U1286, Infinite, Université de Lille, 59000 Lille, France.
✉email: koenecke.christian@mh-hannover.de

DATA AVAILABILITY

CK, DJE, and IYA had full access to all study data (available upon data-specific request).

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AUTHOR CONTRIBUTIONS

CK assembled and analyzed data and wrote the paper. CK, MR, FO, and IYA designed the study, supervised research and analyzed data. DJE and SH assembled the data, performed statistical analysis, and commented on the paper. All other co-authors collected data, recruited patients, and helped with writing the paper. All authors approved submission of the paper for publication. Aymen Bushra Ahmed, Haukeland University Hospital, Bergen, Norway; Carmen Albo López, Hospital Álvaro Cunqueiro—Complejo Hospitalario Universitario de Vigo, Vigo, Spain; Adrián Alegre Amor, Hospital de la Princesa, Madrid, Spain; Mahmoud Aljurf, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia; Achilles Anagnostopoulos, George Papanicolaou General Hospital, Thessaloniki, Greece; Emanuele Angelucci, Ospedale San Martino, Genova, Italy; Jane Apperley, Imperial College, London, UK; William Arcese, ¨Tor Vergata¨ University of Rome, Rome, Italy; Grzegorz Basak, Central Clinical Hospital, Warsaw, Poland; Jacques-Olivier Bay, CHU ESTAING, Clermont_Ferr, France; Yves Beguin, University of Liege, Liege, Belgium; Fabio Benedetti, Policlinico G.B. Rossi, Verona, Italy; Arancha Bermúdez Rodríguez, Hospital U. Marqués de Valdecilla, Santander, Spain; Wolfgang Bethge, Universitaet Tuebingen, Tuebingen, Germany; Igor Wolfgang Blau, Medizinische Klinik m. S. Hämatologie, Onkologie und Tumorimmunologie, Berlin, Germany; Adrian Bloor, Christie NHS Trust Hospital, Manchester, UK; Francesca Bonifazi, Bologna University, S.Orsola-Malpighi Hospital, Bologna, Italy; Jean Henri Bourhis, Gustave Roussy Cancer Campus, Villejuif, France; Peter Brossart, Universitaet Bonn, Bonn, Germany; Gesine Bug, Goethe-Universitaet, Frankfurt_Main, Germany; Claude Eric Bulabois, CHU Grenoble Alpes - Université Grenoble Alpes, Grenoble, France; Alessandro Busca, S.S.C.V.D Trapianto di Cellule Staminali, Torino, Italy; Jenny Byrne, Nottingham University, Nottingham, UK; Jörg Cammenga, University Hospital, Linkoeping, Sweden; Antonio Campos, Inst. Português de Oncologia do Porto, Porto, Portugal; Angelo Michele Carella, IRCCS, Casa Sollievo della Sofferenza, SGiovanni_Rot, Italy; Kristina Carlson, University Hospital, Uppsala, Sweden; Ben Carpenter, University College London Hospital, London, UK; Marco Casini, Hospital San Maurizio, Bolzano, Italy; Jochen Casper, Klinikum Oldenburg, Oldenburg, Germany; Luca Castagna, U.O.D Trapianti di midollo osseo, Palermo, Italy; Yves Chalandon, Département d'Oncologie, Service d'Hématologie, Geneva, Switzerland; Amandine Charbonnier, University of Amiens: CHU Amiens, Amiens, France; Patrice Chevallier, CHU Nantes, Nantes, France; Fabio Ciceri, Ospedale San Raffaele s.r.l., Milano, Italy; Andrew Clark, Bone Marrow Transplant Unit, Glasgow, UK; Johannes Clausen, Elisabethinen-Hospital, Linz, Austria; Thomas Cluzeau, CHU Nice - Hôpital de l'ARCHET I, Nice, France; Matthew Collin, Adult HSCT unit, Newcastle_Tyne, UK; Paolo Corradini, University of Milano, Milano, Italy; Charles Craddock, University Hospital Birmingham NHSTrust, Birmingham, UK; Charles Crawley, Addenbrookes Hospital, Cambridge, UK; Eric Deconinck, Hopital Jean Minjoz, Besancon, France; Dries Deeren, AZ Delta, Roeselare, Belgium; J.L. Diez-Martin, Hospital Gregorio Marañón, Madrid, Spain; Rafael Duarte, Clinica Puerta de Hierro, Madrid, Spain; Jaroslaw Dybko, DCTK, Wroclaw, Poland; Matthias Edinger, University Regensburg, Regensburg, Germany; Hermann Einsele, Universitaetsklinikum Wuerzburg, Wuerzburg, Germany; Ahmet Elmaagacli, Asklepios Klinik St. Georg, Hamburg, Germany; Edgar Faber, NADACE HAIMOM, Olomouc, Czech Rep; Franca Fagioli, Onco-Ematologia Pediatrica, Torino, Italy; Nathalie Fegueux, CHU Lapeyronie, Montpellier, France; Damian Finnegan, Belfast City Hospital, Belfast, UK; Catherine Flynn, Hope Directorate, Dublin, Ireland; Edouard Forcade, CHU Bordeaux, Pessac, France; Virginie Gandemer, Centre Hospitalier Universitaire de Rennes, Rennes, France; Tobias Gedde-Dahl, Oslo University Hospital, Rikshospitalet, Oslo, Norway; Lidia Gil, Poznan University of Medical Sciences, Poznan, Poland; Soledad González Muñiz, Hospital Universitario Central de Asturias, Oviedo, Spain; Sonia Gonzalez Pérez, Hospital Clinico Universitario, S_de_Compostela, Spain; Richard Greil, Gemeinnützige Salzburger, Salzburg, Austria; Hildegard Greinix, LKH - University Hospital Graz, Graz, Austria; John Gribben, St. Bartholomew's and The Royal London NHS Trust, London, UK; Laimonas Griskevicius, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; Zafer Gülbas, Anadolu Medical Center Hospital, Kocaeli, Turkey; Gunhan Gurman, Ankara University Faculty of Medicine, Ankara, Turkey; Denis Guyotat, Institut de Cancerologie Lucien Neuwirth, Saint_Etienne, France; Kazimierz Halaburda, Institute of Hematology and Transfusion Medicine, Warsaw, Poland; Rose-Marie Hamladji, Centre Pierre et Marie Curie, Alger, Algeria; Thomas Heinicke, Universitaetsklinium Magdeburg, Magdeburg, Germany; Grzegorz Helbig, Silesian Medical Academy, Katowice, Poland; Inmaculada Heras, Hospital Morales Meseguer, Murcia, Spain; Olivier Hermine, Hôpital Necker, Paris, France; Bernd Hertenstein, Klinikum Bremen-Mitte, Bremen, Germany; Inken Hilgendorf, Universitaetsklinikum Jena, Jena, Germany; Mathilde Hunault-Berger, CHRU, Angers, France; Anne Huynh, CHU - Institut Universitaire du Cancer Toulouse, Toulouse, France; Cecilia Isaksson, Umea University Hospital, Umea, Sweden; Maija Itäla-Remes, Turku University Hospital, Turku, Finland; Pavel Jindra, Charles University Hospital, Pilsen, Czech Rep; Jan-Erik Johansson, Sahlgrenska University Hospital, Goeteborg, Sweden; Peter R.E. Johnson, Western General Hospital, Edinburgh, UK; Manuel Jurado Chacón, Hospital Univ. Virgen de las Nieves, Granada, Spain; Wu Ka Lung, ZNA, Antwerp, Belgium; Ain Kaare, Tartu University Hospital, Tartu, Estonia; Dimitrios Karakasis, Evangelismos Hospital, Athens, Greece; Martin Kaufmann, Robert_Bosch_Krankenhaus, Stuttgart, Germany; Tessa Kerre, Ghent University Hospital, Gent, Belgium; Anjum Khan, Yorkshire Blood & Marrow Transplant Programme, Leeds, UK; Michael Kiehl, Klinikum Frankfurt (Oder) GmbH, Frankfurt_Oder, Germany; Matthias Klammer, St. George's Hospital, London, UK; Stefan Klein, Universitaetsmedizin Mannheim, Mannheim, Germany; Yener Koc, Medicana International Hospital Istanbul, Istanbul, Turkey; William Krüger, Klinik fuer Innere Medizin C, Greifswald, Germany; Jürgen Kuball, University Medical Centre, Utrecht, Netherlands; Aleksandr Kulagin, First State Pavlov Medical University of St. Petersburg, St_Petersburg, Russia; Giorgio La Nasa, Centro Trapianti Unico Di CSE Adulti e Pediatrico A. O Brotzu, Cagliari, Italy; Hélène Labussière-Wallet, Centre Hospitalier Lyon Sud, Lyon, France; Marco Ladetto, H SS. Antonio e Biagio, Alessandria, Italy; Véronique Leblond, Universite Paris IV, Hopital la Pitié-Salpêtrière, Paris, France; Xavier Leleu, Hopital La Miletrie, Poitiers, France; Stig Lenhoff, Skanes University Hospital, Lund, Sweden; Philippe Lewalle, Institut Jules Bordet, Brussels, Belgium; Bruno Lioure, Techniciens d'Etude Clinique suivi de patients greffes, Strasbourg, France; José Luis López Lorenzo, Fundación Jiménez Díaz, Madrid, Spain; Javier López-Jiménez, Hospital Ramón y Cajal, Madrid, Spain; David Marks, Bristol Royal Hospital for Children, Bristol, UK; Massimo Martino, Grande Ospedale Metropolitano Bianchi Melacrino Morelli - Centro Unico Trapianti A. Neri, Reggio_Calabria, Italy; Sebastien Maury, Hôpital Henri Mondor, Creteil, France; Patrizio Mazza, Ospedale Nord, Taranto, Italy; Patrick Medd, University Hospitals Plymouth NHS Trust, Plymouth, UK; Stephan Mielke, Karolinska University Hospital, Stockholm, Sweden; Nuno Miranda, Inst. Portugues Oncologia, Lisboa, Portugal; Mohamad Mohty, Hopital Saint Antoine, Paris, France; José Mª Moraleda, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; Ashrafsadat Mousavi, Shariati Hospital, Teheran, Iran; Lutz Peter Müller, Martin-Luther-Universitaet Halle-Wittenberg, Halle, Germany; Alberto Mussetti, ICO—Hospital Duran i Reynals, Barcelona, Spain; Maurizio Musso, Ospedale La Maddalena—Dpt. Oncologico, Palermo, Italy; Arnon Nagler, Chaim Sheba Medical Center, Tel_Hashomer, Israel; Andreas Neubauer, Philipps Universitaet Marburg, Marburg, Germany; Emma Nicholson, Royal Marsden Hospital, London, UK; Bendt Nielsen, University Department of Hematology, Aarhus, Denmark; Yana Novis, Hospital Sirio-Libanes, Sao_Paulo, Brazil; Kim Orchard, Southampton General Hospital, Southampton, UK; Zubeyde Nur Ozkurt, Gazi

University Faculty of Medicine, Ankara, Turkey; Shankara Paneesha, Birmingham Heartlands Hospital, Birmingham, UK; Maria Jesús Pascual Cascon, Hospital Regional de Málaga, Malaga, Spain; Jakob Passweg, University Hospital, Basel, Switzerland; Andy Peniket, Department of Haematology, Oxford, UK; "Maria del Mar Perera Alvarez, Hospital de Gran Canaria 'Dr Negrin', Las_Palmas, Spain;" Jose Antonio Pérez-Simón, Hospital Universitario Virgen del Rocío, Sevilla, Spain; Mario Petrini, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; Pietro Pioltelli, Ospedale San Gerardo, Monza, Italy; Xavier Poiré, Cliniques Universitaires St. Luc, Brussels, Belgium; Mike Potter, The Trustee of London Clinic, London, UK; Werner Rabitsch, Medizinische Universitaet Wien, Vienna, Austria; Ron Ram, Tel Aviv Sourasky Medical Center, Tel_Aviv, Israel; Alessandro Rambaldi, ASST Papa Giovanni XXIII, Bergamo, Italy; Péter Reményi, Dél-pesti Centrumkórház—, Budapest, Hungary; Josep Maria Ribera Santasusana, ICO-Hospital Universitari Germans Trias i Pujol, Badalona, Spain; Mark Ringhoffer, Klinikum Karlsruhe gGmbH, Karlsruhe, Germany; Wolf Rösler, University Hospital Erlangen, Erlangen, Germany; Montserrat Rovira, Hospital Clinic, Barcelona, Spain; Marie Thérèse Rubio, CHRU Brabois, Vandœuvre-lès-Nancy, France; Piotr Rzepecki, Military Institute of Health Services BMT Unit, Warsaw, Poland; Riccardo Saccardi, Azienda Ospedaliera Universitaria Careggi, Firenze, Italy; Elisa Sala, Klinik fuer Innere Medzin III, Ulm, Germany; Antònia Sampol, Fundació Institut d'Investigació Sanitària Illes Balears—IdISBa, Palma_Mallorca, Spain; Stella Santarone, Ospedale Civile, Pescara, Italy; Jaime Sanz, University Hospital La Fe, Valencia, Spain; Valery Savchenko, National Research Center for Hematology, Moscow, Russia; Nicolaas Schaap, Nijmegen Medical Centre, Nijmegen, Netherlands; Kerstin Schäfer-Eckart, Klinikum Nuernberg, Nuernberg, Germany; Urs Schanz, University Hospital, Zurich, Switzerland; Christof Scheid, University of Cologne, Cologne, Germany; Christoph Schmid, Klinikum Augsburg, Augsburg, Germany; Roland Schroers, ZSIS Universitaetsklinikum Knappschaftskrankenhaus Bochum GmbH, Bochum, Germany; Wilfried Schroyens, Antwerp University Hospital (UZA), Antwerp_Edegem, Belgium; Dominik Selleslag, A.Z. Sint-Jan, Brugge, Belgium; Matjaz Sever, University Med. Center, Ljubljana, Slovenia; Jorge Sierra, Hospital Santa Creu i Sant Pau, Barcelona, Spain; Aleksander B. Skotnicki, Jagiellonian University, Krakow, Poland; John Snowden, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK; Gerard Socié, Hopital St. Louis, Paris, France; Alexandros Spyridonidis, Research Committee - University of Patras, Patras, Greece; Dragana Stamatovic, Clinic of Hematology, Belgrade, Serbia; Matthias Stelljes, University of Muenster, Muenster, Germany; Polina Stepensky, Hadassah University Hospital, Jerusalem, Israel; "Eleni Tholouli, Manchester Royal Infirmary, Manchester, UK;" Lorenz Thurner, University of Saarland, Homburg, Germany; Herve Tilly, Centre Henri Becquerel, Rouen, France; Johanna Tischer, Klinikum Grosshadern, Munich, Germany; Amos Toren, Edmond & Lily Safra Children's Hospital, Tel_Hashomer, Israel; Juan Pio Torres Carrete, Complejo Hospitalario de A Coruña, La_Coruna, Spain; Pascal Turlure, CHRU Limoges, Limoges, France; Ali Unal, Erciyes Medical School, Kayseri, Turkey; David Valcárcel, Hospital Vall d'Hebron, Barcelona, Spain; Thomas Valerius, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany; Carlos Vallejo Llamas, Hospital Universitario Donostia, San_Sebastian, Spain; Gwendolyn Van Gorkom, University Hospital Maastricht, Maastricht, Netherlands; David Veale, Royal Devon and Exeter Hospital, Exeter, UK; Joan Hendrik Veelken, Leiden University Hospital, Leiden, Netherlands; Mareike Verbeek, Klinikum Rechts der Isar, Munich, Germany; Giuseppe Visani, AORMN Hospital, Pesaro, Italy; Nikolas von Bubnoff, University Medical Center Schleswig-Holstein, Luebeck, Germany; Radovan Vrhovac, University Hospital Center Rebro, Zagreb, Croatia; Jan Vydra, Institute of Hematology and Blood Transfusion, Prague, Czech Rep; Eva Maria Wagner-Drouet, University Medical Center Mainz, Mainz, Germany; Keith M. O. Wilson, Department of Haematology, Cardiff, UK; Dominik Wolf, University Hospital Innsbruck, Innsbruck, Austria; Depei Wu, First Affiliated Hospital of Soochow University, Suzhou, China; Gerald. G. Wulf, Universitaetsklinikum Goettingen, Goettingen, Germany; Ipek Yonal-Hindilerden, Ýstanbul Tip Fakultesi, Istanbul, Turkey; Pavel Zák, Charles University Hospital, Hradec_Kralove, Czech Rep; Jan Zaucha, Medical University of Gdansk, Gdansk, Poland; Marco Zecca, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Tsila Zuckerman, Rambam Medical Center, Haifa, Israel; Teresa Zudaire, Unidad de Ensayos Clínicos de Hematología Pabellón A, bajo., Pamplona, Spain.

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Correspondence and requests for materials should be addressed to Christian Koenecke.

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