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Role of allo-HCT in 'non-classical' MPNs and MDS/MPNs: recommendations from the PH&G Committee and the CMWP of the EBMT

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Abstract:
'Non-classical' Myeloproliferative Neoplasms (MPNs) and Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPNs) represent a heterogeneous group of malignancies characterized by a wide range of clinical manifestations. Unlike classical MPNs, there is no standardized management approach for these conditions, particularly concerning the indications for and management of allogeneic hematopoietic cell transplantation (HCT). To address this gap, the EBMT Practice Harmonization and Guidelines (PH&G) Committee and the Chronic Malignancies Working Party (CMWP) have collaborated to develop shared guidelines aimed at optimizing the selection and management of patients with these rare forms of neoplasms. A comprehensive review of the literature from the publication of the revised 4th edition of the (2016) WHO classification onward was conducted. A multidisciplinary group of experts in the field convened to produce this document, which was developed through multiple rounds of draft circulation. Key recommendations include the early identification of potential transplant candidates, particularly in cases of chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL) / CEL, not otherwise specified (CEL-NOS), myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusions (MLN-TK) with FGFR1, JAK2, ABL1, and FLT3 rearrangements, MDS/MPN with neutrophilia / atypical chronic myeloid leukemia (aCML), and MDS/MPN, NOS. For patients with MPN, NOS / MPN unclassifiable, standard recommendations for myelofibrosis (MF) should be applied. Similarly, in MDS/MPN with thrombocytosis, transplantation is recommended based on established MDS guidelines. Given the current lack of robust evidence, this document will serve as a valuable resource to guide future research activities, providing a framework for addressing critical unanswered questions and advancing the field.

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COI notes: JG: was included in the Response adjudication Committee for FIGHT-203 Trial (Pemigatinib in FGFR1-Rearranged MLN). NG: received fees for advisory Board for DISC Medicine and Agios; YC: has received institutional consulting fees for advisory board from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, Astra-Zeneca, Servier, Takeda, Pierre Fabre, Medac; Travel support from MSD, Roche, Novartis, Pfizer, BMS, Gilead, Amgen, Incyte, Abbvie, Janssen, Astra-Zeneca, Jazz, Pierre Fabre, Sanofi all via the institution. The other authors declare no financial conflict of interest

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Role of allo-HCT in 'non-classical' MPNs and MDS/MPNs: recommendations from the PH&G Committee and the CMWP of the EBMT

Best practice recommendations from the Practice Harmonization and Guidelines Committee and the Chronic Malignancy Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

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Summary

'Non-classical' Myeloproliferative Neoplasms (MPNs) and Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPNs) represent a heterogeneous group of malignancies characterized by a wide range of clinical manifestations. Unlike classical MPNs, there is no standardized management approach for these conditions, particularly concerning the indications for and management of allogeneic hematopoietic cell transplantation (HCT). To address this gap, the EBMT Practice Harmonization and Guidelines (PH&G) Committee and the Chronic Malignancies Working Party (CMWP) have collaborated to develop shared guidelines aimed at optimizing the selection and management of patients with these rare forms of neoplasms. A comprehensive review of the literature from the publication of the revised 4th edition of the (2016) WHO classification onward was conducted. A multidisciplinary group of experts in the field convened to produce this document, which was developed through multiple rounds of draft circulation. Key recommendations include the early identification of potential transplant candidates, particularly in cases of chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL) / CEL, not otherwise specified (CEL-NOS), myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusions (MLN-TK) with *FGFR1*, *JAK2*, *ABL1*, and *FLT3* rearrangements, MDS/MPN with neutrophilia / atypical chronic myeloid leukemia (aCML), and MDS/MPN, NOS. For patients with MPN, NOS / MPN unclassifiable, standard recommendations for myelofibrosis (MF) should be applied. Similarly, in MDS/MPN with thrombocytosis, transplantation is recommended based on established MDS guidelines. Given the current lack of robust evidence, this document will serve as a valuable resource to guide future research activities, providing a framework for addressing critical unanswered questions and advancing the field.

Introduction

Myeloproliferative neoplasms (MPNs) and myelodysplastic/myeloproliferative neoplasms (MDS/MPNs) represent a heterogeneous and complex group of hematological malignancies. Recent refinements introduced by the World Health Organization (WHO) classification of tumors and International Consensus Classification (ICC) have enhanced our understanding and categorization of these conditions.[1,2] These entities frequently display a broad spectrum of clinical manifestations and can present significant challenges to accurate diagnosis, prognostication, and treatment. Among 'classical' MPNs, chronic myeloid leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF) are the most frequently recognized. Several recent publications have addressed the primary treatment goals and the role of transplant in these conditions.[3-5] Similarly, chronic myelomonocytic leukemia (CMML) is the most common form of MDS/MPN, and contemporary management has been thoroughly discussed in the recent literature.[6] By contrast, due to their relative rarity and hence limited cumulative evidence base, adult 'non-classical' forms of MPNs and MDS/MPNs remain an area with significant unmet need in terms of both diagnosis and clinical management. These uncommon disorders include chronic neutrophilic leukemia (CNL) [WHO/ICC], chronic eosinophilic leukemia (CEL) [WHO] / CEL, not otherwise specified (NOS)[ICC], myeloid/lymphoid neoplasms (MLN) with eosinophilia and tyrosine kinase (TK) gene fusions (MLN-TK), NOS [WHO] and MPN, NOS [WHO] / MPN-unclassifiable (U) [ICC] among the MPNs. In addition, MDS/MPN with neutrophilia [WHO] / atypical CML (aCML) [ICC], MDS/MPN with *SF3B1* mutation and thrombocytosis [WHO] / MDS/MPN with thrombocytosis and *SF3B1* mutation [ICC], MDS/MPN with ring sideroblasts and thrombocytosis, NOS (recognized only by ICC), and MDS/MPN, NOS [WHO/ICC] are included under the spectrum of MDS/MPN diseases.[1,2]

The prognosis for patients with such 'non-classical' MPNs and MDS/MPNs varies widely based on the specific subtype, molecular landscape and individual patient factors. While some patients experience a relatively indolent disease course, others may display an aggressive disease course with significant rates of morbidity and a markedly reduced life expectancy. Thus, allogeneic hematopoietic stem cell

transplantation (HCT) remains a viable option for eligible patients, despite inherent risks in terms of both morbidities and non-relapse mortality (NRM). The rarity, heterogeneity, and complexity characteristics to the management of these disorders underscore the need for standardized best practice recommendations, particularly in the context of HCT. These recommendations are key to address critical issues such as ideal patient selection, pretransplant treatment strategies, optimal timing for HCT and comprehensive transplant policies. Given these challenges, the European Society for Blood and Marrow Transplantation (EBMT) Practice Harmonization and Guidelines (PH&G) Committee has prioritized the development of best practice recommendations for the management of adult patients with non-classical MPNs and MDS/MPNs undergoing HCT. These recommendations aim to provide a cohesive framework to improve patient outcomes and harmonize clinical practices across treatment centers internationally.

Methodology

This workshop was conducted according to the methodology published by the EBMT Practice Harmonization and Guidelines (PH&G) Committee.[7] The Chronic Malignancies Working Party (CMWP) of the EBMT proposed the development of practice recommendations for 'non classical' MPNs and MDS/MPNs. To comprehensively assess the scope of the issue, the EBMT registry was analyzed, collecting data on transplant procedures for each indication starting from 2016, following the release of the 4th edition of the WHO classification (**Table 1**). Despite the limited number of cases, transplant procedures have shown a consistent upward trend in recent years, suggesting a growing awareness of such diseases.

A list of global experts and key opinion leaders in the field, including hematologists, hematopathologists, molecular biology specialists, and transplant physicians, was compiled based on their professional experience, prior research, and relevant scientific contributions. Key clinical questions and areas of unmet clinical needs were identified to guide consensus development, organized into three distinct sections (**supplemental material**).

During the initial meeting in June 2024, experts formed specific subgroups to focus on individual topics. A comprehensive literature search of PubMed/MedLine until September 2024 was conducted for each key question, identifying indexed papers. In accordance with the EBMT practice recommendation methodology, and due to the lack of prospective studies, the evidence was derived from retrospective studies, reviews, and expert opinions, without formal evidence grading.

A task force was established to draft panel positions addressing the identified key questions. These drafts underwent multiple iterations within respective subgroups. A hybrid face-to-face and virtual meeting with EBMT members was held on September 30 and October 1, 2024, in Lille, France, to finalize the recommendations.

The primary goal of the meeting was to develop a comprehensive draft consensus paper, which was subsequently reviewed by all authors to finalize these agreed-upon best practice recommendations with a focus on the identification and pre- and post-transplant management of 'non-classical' MPN and MDS/MPN patients, where relevant literature was available. All recommendations were considered valid if an agreement of over 80% was reached. **Table 2** presents a list of the key publications in the field of transplantation for these entities.

Section 1: Current state of the art approaches

1.1 Molecular landscape of non-classical MPNs and MDS/MPNs

The application of next generation sequencing (NGS) technology to large cohorts of patients with non-classical MPNs and MDS/MPNs has unveiled molecular features characterizing, but not defining, the individual nosological disease types, now recognized in the most recent diagnostic classifications (see below section 1.2).[1,2] Particularly, studies focusing on the molecular architecture of these disorders identified specific co-mutational patterns underpinning the multi-step pathogenesis linked to the clinical heterogeneity of these non-classical MPNs and MDS/MPNs.

Non-classical MPNs are frequently diagnosed based on prominent clinical features (e.g. eosinophilia, splenomegaly, leukocytosis etc.), and absence of criteria fulfilling the diagnosis of classical MPNs. Some but not all are characterized by specific molecular patterns:

i) CNL is strongly, but not exclusively, associated with pathogenetic *CSF3R* mutations.

ii) CEL is a diagnosis of exclusion with no indicative molecular features

iii) MLN-TK have disease-defining gene alterations: *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *FLT3* and *ETV6::ABL1* and other tyrosine-kinase alterations

iv) Cases with MPN, NOS/U typically have *JAK2*, *CALR* or *MPL* mutations but do not meet the hematological and histopathological criteria for classical MPN.

Within the MDS/MPN entities, conventional cytogenetics can identify clonality/aberrations in 15-35% of cases, most typically in MDS/MPN with neutrophilia / aCML,[8] while NGS panels show recurrent myeloid gene mutations in approximately 90% of cases.[9] Mutations in epigenetic regulators (*ASXL1, TET2, DNMT3A*), splicing (*SF3B1, SRSF2, U2AF1*), the JAK-STAT pathway (*JAK2, CALR, MPL*) and the RAS pathway (*NRAS, KRAS, CBL*) genes are the most recurrent alterations.[8] In general, the combination and order of acquisition of such lesions dictate the clinicopathological presentation. The current classification is not

strictly segregated according to molecular lesions, such that mutations may occur promiscuously across these entities. However, several studies have highlighted that patients with MDS/MPN could be broadly characterized by their genomic make-up:[8,10,11]

i) MDS/MPN with neutrophilia / aCML frequently carry *SETBP1* and/or *ASXL1* mutations

ii) "MDS/MPN with ring sideroblasts and thrombocytosis" cases are dominated by *SF3B1* and often *JAK2* mutations or, at a low frequency *CALR* or *MPL* mutations

iii) Especially in MDS/MPN, NOS, molecular mutations can be useful for further disease stratification. Genotypically "CMML-like" MDS/MPN, NOS patients show enrichment for *TET2*, as well as *SRSF2*, *ASXL1*, *RUNX1*, and *RAS* pathway alterations

iv) Phenotypically "MDS/MPN with neutrophilia-like" MDS/MPN, NOS patients show enrichment for *ASXL1*, *SETBP1*, *ETNK1*, *RUNX1*, *TET2* and *RAS* pathway gene mutations.

The current WHO/ICC classifications incorporate only *SF3B1* as a disease-defining lesion in the MDS/MPN and thrombocytosis category.

Apart from these recurrent genomic profiles, some less frequent mutations may identify cases with specific clinical trajectories and outcomes (e.g., *TP53*, *CBL*).[12] Genomic information may help to establish an accurate diagnosis, enhance prognostication, and even support reclassification of ambiguous cases into currently-defined disease entities, supplementing pathomorphological and clinical criteria.[13]

1.2 Comparison of WHO/ICC classifications

The 5th edition of the WHO classification[2] and the ICC of myeloid and lymphoid neoplasms[1] are built on the revised 4th edition of the (2016) WHO classification.[14] For entities included in this manuscript, the definitions and diagnostic criteria in the WHO 5th edition and ICC are similar, with some key differences as summarized in **Table 3**.

Regarding MPN classification, the definition of CNL remained unchanged in the WHO 5th edition, whereas the ICC reduced the threshold of required neutrophilia (>13x10^9/L) in the presence of a *CSF3R* mutation. The ICC defines both accelerated and blast phases. These definitions may enable therapeutic interventions and interpretations of outcomes in future trials. CEL continues to be recognized in the WHO 5th edition and ICC as an MPN characterized by persistent eosinophilia, clonality and abnormal/dysplastic bone marrow morphology that does not fulfil the diagnostic criteria of MLN with eosinophilia and TK fusions (MLN-TK) or other defined myeloid neoplasms that may present with eosinophilia. Although both classifications regard CEL as a diagnosis of exclusion in patients with sustained eosinophilia, they differ in minor aspects.

In the category of MDS/MPNs, the WHO 5th edition renamed atypical chronic myeloid leukemia (aCML) as MDS/MPN with neutrophilia but kept diagnostic parameters the same. The ICC maintained the name of atypical CML adding mutational status (*SETBP1* and/or *ASXL1*) as supportive of the diagnosis. Both classifications split MDS/MPN with ring sideroblasts and thrombocytosis into *SF3B1* mutated and unmutated. The ICC explicitly defined MDS/MPN with *SF3B1* and thrombocytosis to exclude therapy-related and other cytogenetic and genetic anomalies. The WHO 5th edition additionally recognizes that any MDS/MPN entity may arise after exposure to cytotoxic therapy. Both the WHO 5th edition and the ICC have renamed MDS/MPN, U as MDS/MPN, NOS.

Disease specific HCT indications

Chronic neutrophilic leukemia (CNL) [WHO/ICC]

CNL is a rare disorder presenting with leukocytosis and frequently splenomegaly. It has a variable clinical course but is ultimately associated with a poor prognosis, with a median survival of less than 2 years. Disease progression remains the primary cause of death.[15,16] Conventional treatment strategies are highly variable, ranging from cytoreduction with hydroxycarbamide and interferon to use of targeted kinase inhibitors such as ruxolitinib or dasatinib, albeit responses are commonly short lived.[17] 'Acute myeloid

leukemia (AML)-style' induction approaches may be considered in accelerated/blast-phase disease as a potential bridge to HCT in eligible patients but the regimen of choice remains undetermined.[18]

Features of progression include debilitating splenomegaly, treatment refractoriness and progressive neutrophilia, acquisition of transfusion dependency and increasing genomic complexity.[15,19] The presence/acquisition of pathogenetic mutations in *ASXL1*, *CBL*, *CEBPA*, *EZH2*, *NRAS*, *TET2*, and/or *U2AF1* are associated with poor overall prognosis.[15,19]

Given the poor prognosis associated with conventional therapy, all CNL patients should be assessed early after diagnosis for potential transplant eligibility. However, data addressing the HCT outcomes in this disease group are limited. The largest cohort published to date was a retrospective evaluation of 29 patients who underwent transplantation between 2000 and 2018 performed on behalf of the Center for International Blood and Marrow Transplant Research (CIBMTR) and the EBMT.[20] Blast phase patients were excluded. Stem cell source was predominantly peripheral blood (PB), with myeloablative conditioning (MAC) accounting for approximately 50% while NMA/RIC was used in the other 50%. -Overall survival after transplantation exceeded 50% at 4 years, with limited NRM but relapse rate of 35% at 4 years (**Table 2**), underscoring the importance of rigorous post-transplant monitoring to detect early signs of disease recurrence. No specific studies are available on the use of pre-transplant treatments as a bridge to HCT. However, given the limited disease modulation, pre-transplant cytoreductive or TKI therapy should be considered to enhance disease control (reduce white cell count; improve splenomegaly) and optimize the patient's physical condition in preparation for HCT, balancing the risks and benefits while considering the potential use of such treatments (e.g., infectious risk, disease progression, etc.).[15] Development of dynamic post-transplant measurable residual disease (MRD) analyses when a molecular marker is detected (e.g. *CSF3R*) needs to be further investigated in this setting but is encouraged by the panel to collate such data where possible.[21] The use of maintenance therapy after transplant with agents such as ruxolitinib or dasatinib remains investigational. Panel recommendations for CNL are summarized in **table 4**.

Chronic eosinophilic leukemia (CEL) [WHO] / CEL, NOS [ICC])

CEL [WHO] / CEL, NOS [ICC] is a rare, debilitating and aggressive MPN with an augmented risk of organ-failure (especially cardiac failure) due to eosinophilic infiltration and high rates of transformation to acute leukemia. Median survival is poor, often estimated at < 2 years from time of diagnosis.[22,23]

Therapeutic options range from supportive care approaches including steroids or hydroxycarbamide/interferon to 'AML-like' induction therapy and HCT; most cases frequently display limited response to therapy.[22,23]

Data on the outcomes of HCT in CEL is limited to a single report by the EBMT on 30 patients transplanted between 2000 and 2018.[24] Median age was 46 years (Interquartile range, 39-59), with a male predominance. Stem cell source was PB-derived in 67%, MAC utilized in 61%, unrelated donor (URD) used in 67%, and *in-vivo* T-cell depletion in 52% of cases. The 1- and 3-year OS estimates were 46% and 34%, respectively; however, for patients with matched sibling donor (MSD), OS was 65% at 3-years. Transplant failure was attributable to high rates of NRM (38% at 1 year), particularly following use of an URD. It is important to note that this analysis was conducted prior to the widespread use of post-transplant cyclophosphamide (PTCy), which suggests that outcomes for unrelated donor transplants may have improved in recent years.

Panel recommendations for CEL [WHO] / CEL, NOS [ICC] are summarized in **table 5**.

Myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusions (MLN-TK) [WHO/ICC]

According to both the ICC and WHO 2022 classifications, several MLN associated with rearrangements of *PDGFRA, PDGFRB, FGFR1, JAK2, ABL1* or *FLT3* tyrosine kinase genes (MLN-TK) fall within this categorization. These are rare malignancies with a frequently aggressive clinical course that can present as a MPN with a high tendency to blast phase transformation, or directly as AML, T or B lymphoblastic leukemia (ALL)/lymphoma or mixed phenotype acute leukemia (MPAL), with or without a concomitant MPN component. Cardiac eosinophilic infiltration is particularly prominent in MLN-TK-*PDGFRA* patients.[25,26]

Recently, comprehensive response criteria have been proposed to address the heterogeneous clinical presentation of MLN-TK.[27]

Treatment with TKI, primarily imatinib, is very effective in most patients with MLN harboring *PDGFRA* [28] or *PDGFRB*[29] fusion genes, even in the blast phase.[30] This treatment can induce durable complete molecular remissions akin to those achieved in CML.[31] In the German registry, only 16 out of 104 (15%) patients with *PDGFRA/B* fusion genes had died after a median follow-up of 9.2 years.[32] Acquired resistance to imatinib due to mutations has been reported in a few patients with primarily blast phase disease,[33,34] though some of them may respond to alternative TKI (e.g., ponatinib for T674I mutations or avapritinib for D842V mutations).[35,36]

In contrast, patients with *FGFR1*, *JAK2*, *ABL1* or *FLT3* fusion genes have less favorable responses to TKIs, often ultimately progressing to blast phase, with a median survival of about 5 years in the German registry.[32,37] However, exceptions may include patients with chronic phase MLN-*FGFR1* or MLN-*ETV6*::*ABL1*, who can achieve molecular responses to pemigatinib[38] or nilotinib/dasatinib,[37] respectively.

Nevertheless, the durability of these responses remains uncertain, and HCT constitutes the only treatment with demonstrated long-term disease control in these conditions. A recent retrospective study by the EBMT, including 22 patients with MLN-*FGFR1* undergoing HCT, reported rates of 5-year OS, progression-free survival, NRM and relapse incidence of 74%, 63%, 14% and 23%, respectively, underscoring the curative potential of HCT in this aggressive disease.[39] Among 12 patients with MLN-*FLT3* from several US institutions, 6 underwent HCT, with four still alive at the last follow-up.[40] HCTHCT

Based on these data, early referral to HCT is recommended for most eligible patients with *FGFR1, JAK2, ABL1* or *FLT3* fusion genes in chronic phase, since TKI treatment typically does not yield durable remissions, and the disease can rapidly progress to blast phase.[26,38] Patients with MLN-*FGFR1* or MLN-*ETV6::ABL1* who achieve deep responses to TKIs (pemigatinib for *FGFR1* or nilotinib/dasatinib for *ABL1*) might delay transplant if predicted to be at high risk for NRM, with close monitoring of their TKI response and reconsideration if warning signals arise. In general, bridging therapy with a specific TKI with or without

chemotherapy should be considered. Patients ineligible for HCT should be considered for clinical trials. Finally, the role of TKI maintenance after HCT deserves investigation in a standardized fashion. **Table 6** summarizes the panel recommendations for MLN-TK.

MPN, NOS [WHO]/ MPN-U [ICC]

MPN, NOS / MPN-U encompasses a heterogeneous group of MPN which fail to meet stringent diagnostic criteria of other MPN entities within the WHO or ICC classification systems.[1,2] True incidence remains unknown, but it is estimated to represent 5% of all MPNs if strict diagnostic criteria are applied.[41] Dynamic reassessment is warranted, as over time the characteristics may meet the diagnostic criteria of other MPN entities. Clinical phenotype is markedly heterogeneous– ranging from those with an indolent disease course to those with aggressive disease associated with significant splenomegaly and symptom burden and inherent risk of leukemic transformation.[42,43] Of note, a large series from a UK tertiary center, with median follow up of > 7 years, suggested thrombotic complications in around 20% of patients and transformation rates of approximately 9%, highlighting the need for close vigilance.[42] Median Event Free Survival (EFS) was 11-years. Recently, a retrospective study by Crane and colleagues comprising 94 patients reported a median OS of 54 months.[44] Interestingly, the Dynamic International Prognostic Scoring System (DIPSS)-plus model and high-risk molecular profile retained prognostic relevance, suggesting that MF-derived prognostic scores may be used to inform prognosis also in this context.

McLornan and colleagues reported an EBMT-registry based evaluation of outcomes following HCT in 70 patients with a verified diagnosis of MPN, NOS/MPN-U, representing the largest transplant cohort reported to date.[45] Regarding conditioning intensity, 31 patients underwent MAC and 39 patients reduced intensity conditioning (RIC). There was a non-significant trend towards delayed engraftment with RIC protocols. The 1- and 5-year OS estimates were 77% and 42% (MAC) and 59% and 41% (RIC). NRM rates at 1- and 3 -years were considerable at 19% and 29% for MAC and 28% and 28% for RIC. Cumulative incidences of relapse at 1- and 3-years were 10% and 23% (MAC) and 28% and 36% (RIC), respectively. Risk of relapse tended to be

higher in those MPN-NOS patients who had an abnormal karyotype at time of HCT. Regarding donor type, univariate analysis suggested worse OS and NRM rates with use of an URD compared to MSD.

Given the rarity of the disease group, any recommendations for HCT are solely translated from experience with other MPNs, predominantly MF. Pragmatically, as it has been previously suggested, consideration to HCT in transplant-eligible individuals with MPN,NOS/ MPN-U who have a suitable donor may include those ascertained as having higher risk disease i.e. those with increasing peripheral blood/ marrow blasts, acquisition of cytogenetic or mutational profiles predicted to be associated with a worse prognosis (transcribed from MF data as no sufficient evidence in MPN, NOS / MPN-U), progressive debilitating splenomegaly despite optimized medical therapy or those who become transfusion dependent.[3,4,42,43,46,47] From a practical stance, in our opinion, approaches taken to optimize outcomes in HCT for MF could be applied to those with MPN, NOS / MPN-U given a lack of contemporary data to guide best practice.[3] The recommendations for MPN, NOS / MPN-U are included in **table 7**.

MDS/MPN with neutrophilia [WHO] / atypical CML [ICC]

Life expectancy of patients with MDS/MPN with neutrophilia / aCML is, in general, quite short, with a sizable proportion (up to 40%) transforming into AML within 12–18 months from diagnosis and a median OS reported in the 12-24 months range.[48,49] Despite the advent of novel targeted therapies and drug combinations currently under active investigation, HCT remains the only curative option. Factors reported as associated with inferior survival by retrospective analyses of a limited-size patient series include age > 65 years, presence of cytopenias (anemia and thrombocytopenia), leukocytosis, elevated LDH level, and/or higher marrow blast percentage, presence of pathogenetic *TET2* mutations, with several models proposed to stratify patients at diagnosis according to the risk of disease-associated death.[49-52] However, median survival remained extremely poor, even in the lower risk groups (< 2 years median OS).

An EBMT registry-based retrospective study of 42 patients reported that half of patients were alive after 6 years after transplant.[53] A smaller Japanese experience with shorter follow-up demonstrated comparable results.[54] The MD Anderson group reported on 65 patients, 7 of whom underwent transplant. Median

survival for the non-transplant cohort was 24.6 months and not reached in the transplant cohort.[49] There are no robust data on whether pre-transplant treatment influences outcomes after transplantation. Leukocytosis is typically managed with cytoreductive agents like hydroxyurea or immunomodulation with interferon. Hypomethylating agents (HMAs) and/or chemotherapy-based induction regimens are usually favored when there is a high blast count in advanced stages of the disease, particularly in the context of AML transformation. **Table 8** lists the panel's recommendations for this entity.

MDS/MPN with SF3B1 mutation and thrombocytosis [WHO] / MDS/MPN with thrombocytosis and SF3B1 mutation [ICC]

This entity, affecting often elderly individuals, generally presents a good prognosis, with a low risk of leukemic transformation and a median survival exceeding 5 years.[55] The presence of abnormal karyotype, *ASXL1/SETBP1* mutations, and/or moderate to severe anemia (hemoglobin <10 g/dl) at diagnosis or at follow-up were reported to be associated with worse prognosis, with expected median OS shorter than 1 year.[56] No well-molecularly annotated cohorts of transplanted MDS/MPN with *SF3B1* mutation have been reported to date, with only a few case series or report available.[57-60]

MDS/MPN with ring sideroblasts and thrombocytosis, NOS [ICC only]

The absence of the canonical *SF3B1* mutation characterizes 10-30% of MDS/MPN with ring sideroblasts and thrombocytosis cases.[61] However, discordant prognostic significance has been documented according to *SF3B1*-mutational status, with some recent reports showing no impact on OS and progression-free survival.[56] In analogy to patients with *SF3B1* mutation, no specific data are available in the literature regarding the role of transplantation. As shown in **Table 1**, only 10 patients with MDS/MPN with thrombocytosis with or without *SF3B1* mutation have been reported in the EBMT registry as having undergone a transplant for this indication. Standard recommendations for HCT in MDS should hence be applied.[62]

Table 9 summarizes the recommendations for both MDS/MPN with *SF3B1* mutation and thrombocytosis [WHO] / MDS/MPN with thrombocytosis and *SF3B1* mutation [ICC] and MDS/MPN with ring sideroblasts and thrombocytosis, NOS [ICC only].

MDS/MPN, NOS [WHO/ICC]

MDS/MPN, NOS remains an exceedingly rare disease entity with no established consensus on optimal therapy and a dismal prognosis. A two-center report on 135 patients highlighted a median leukemia-free survival of 24 months.[12] Evaluation of a cohort of 85 patients from the MD Anderson center, followed from 1987 to 2013, reported a worse life expectancy, approaching 1 year.[63] Additionally, the presence of *TP53* mutations confer higher risk of progression.[64] Regarding treatment approaches, in the above-mentioned experience, 59 out of 135 received HMAs but overall had poor responses (only 1 patient achieving a CR). Eight (6%) patients underwent HCT, of whom 5 (63%) were alive and disease free at the last follow-up.[12] The largest transplant series to date comes from the Japanese Society for Hematopoietic Cell Transplantation,[65] which included a cohort of 86 MDS/MPN, NOS patients transplanted between 2001 and 2017 using a heterogeneous range of transplant platforms. Disease status (stable/responsive versus progressive) and advanced age were significant prognostic factors for transplant outcomes, with overall long-term survival approaching 50%. Recently, the North American cooperative group reported on a cohort of 120 MDS/MPN patients, including 48 NOS/U cases, who underwent haploidentical transplantation, primarily with RIC and non-myeloablative conditioning regimens. Interestingly, transplant outcomes were comparable to those observed in CMML and other MDS/MPN overlap syndromes, with younger age (<65 years) and absence of splenomegaly identified as independent favorable factors for survival after transplant.[66] All these data support the potential application of CMML-like transplant strategies even in the context of MDS/MPN, NOS.[6] Cytoreductive agents like hydroxyurea or immunomodulation with interferon are typically used to manage increased leukocyte proliferation, while HMAs may be considered for patients with predominant cytopenias and/or increased blast count. JAK inhibitors, alone or combined with HMAs,

have also been investigated.[67] For younger patients progressing to AML, induction treatment is employed as a bridge to HCT. **Table 10** provides the panel's recommendations for this entity.

Chimerism and Measurable Residual Disease Assessment

The panel agreed that chimerism and MRD monitoring should be performed in the post HCT period, where relevant. This will facilitate data collection in an area where there is a major lack of robust evidence. A range of techniques to assess lineage specific chimerism are available, most commonly assessed via the Polymerase Chain Reaction (PCR) analysis of short tandem repeats (STRs) to define host and donor populations.[68] The role of CD34+ specific chimerism requires evaluation. MRD assessment for these disease entities remains experimental but if assessed, sensitive laboratory techniques are preferred, ideally with a sensitivity of 0.01-1%, and consideration to use of digital PCR or quantitative PCR. These recommendations are as per recently suggested by the EBMT group for MRD assessment in MF as no specific guidelines exist for the specific diseases covered in these guidelines.[69] The panel agreed that use of extended NGS panels for MRD assessment remains a research tool at present. Timing of assessment is as per individual institutional policies.

Unanswered questions and future research areas

Several critical questions remain unanswered in the field of 'non-classical' MPN and MDS/MPN. First, a better understanding of disease prognostication is essential, and ongoing efforts such as the IWG registry are expected to provide valuable insights. Additionally, pretransplant treatment strategies across the range of disorders need to be optimized to improve outcomes, as current protocols vary significantly between institutions. A relevant issue will be the determination of transplant eligibility, which remains poorly defined. Given the older age of many patients, frailty screening to assess physical function and capacity is an area of paramount importance. This screening could also incorporate tools to more specifically evaluate cognitive function, comorbidities, social status, anxiety, and nutrition, ensuring a thorough assessment of

the patient's overall health and eligibility for transplantation.[70] In this regard, a strict age limit should not be imposed. Instead, it seems reasonable to extend transplant evaluation up to 70 years and, in selected fit patients, even up to 75.

Furthermore, donor matching is a crucial factor in weighing the risks and benefits of transplantation, although this aspect has not been extensively addressed in this particular setting. All these considerations are fundamental when discussing transplant indications and must be carefully balanced against the intrinsic risk of the disease, which remains largely undefined in many scenarios. Given the available evidence, it is not possible to recommend a one-size-fits-all timing for every case and transplant center. However, it seems reasonable to initiate the search for a donor (preferably a related donor, or an unrelated/alternative donor when necessary) early in all patients affected by diseases with an expected survival of less than 5 years, taking into account comorbidities, transplant risks, and patient preferences.

Another important aspect is identifying the optimal transplantation platform, including the choice of donor, the intensity of the conditioning regimen, and the approach to GVHD prophylaxis, to achieve superior long-term outcomes across various patient population. Disease monitoring, especially in cases where molecular markers are available, requires standardization to ensure consistent and reliable assessments across different centers. Furthermore, the role of donor lymphocyte infusion (DLI) and maintenance therapy, particularly when TKIs are available, remains an area of active investigation. Finally, there is an urgent need for international prospective trials with harmonized protocols to establish universally accepted treatment guidelines and improve patient outcomes across diverse healthcare settings. In this context, this document will be useful in guiding future research activities, providing a framework for addressing these critical unanswered questions and driving advancements in the field.

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Authorship contribution

NPo and DM proposed the topic for practice recommendations and led the literature review. CG, KR, JCHB, FO, NPo, and DM identified key clinical questions and areas of unmet clinical needs to guide consensus development.

CG and KR organized the task force for the “Current State of the Art” section, JCHB and DM focused on non-classical MPNs, while NPo and FO addressed non-classical MDS/MPNs.

DAA, NC, PG, CH, JDK, JK, LM, RM, EP, FPal, MMP, AO, DRa, AR, and DHW drafted the “Current State of the Art” section. GB, FC, TC, VF, NGag, NGan, JG, FPas, NPe, and IYA contributed to the “Non-classical MPN” section, while LA, FDB, YC, JDS, GH, NK, MM, MR, DR, KS, AT, and AMV worked on the “Non-classical MDS/MPN” section.

The preliminary draft was thoroughly reviewed by NPol, KR, MK, MR, JDS, TC, JCHB, FO, IYA, and DM, who prepared the final draft. All authors reviewed the manuscript and approved its final version.

Declaration of interests

JG: was included in the Response adjudication Committee for FIGHT-203 Trial (Pemigatinib in FGFR1-Rearranged MLN). NG: received fees for advisory Board for DISC Medicine and Agios; YC: has received institutional consulting fees for advisory board from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, Astra-Zeneca, Servier, Takeda, Pierre Fabre, Medac; Travel support from MSD, Roche, Novartis, Pfizer, BMS, Gilead, Amgen, Incyte, Abbvie, Janssen, Astra-Zeneca, Jazz, Pierre Fabre, Sanofi all via the institution. The other authors declare no financial conflict of interest

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Diagnosis	Year of HCT	2016	2017	2018	2019	2020	2021	2022	2023
		Frequency	**Frequency**	**Frequency**	**Frequency**	**Frequency**	**Frequency**	**Frequency**	**Frequency**
MPN	CNL [WHO/ICC]	4	7	11	9	13	8	10	10
	CEL [WHO]/ CEL, NOS [ICC]	1	1	4	-	2	1	3	4
	MLN-TK with *ABL1* rearrangement	-	-	-	-	-	-	-	-
	MLN-TK with *FGFR1* rearrangement	2	3	5	1	3	2	-	1
	MLN-TK with *FLT3* rearrangement	-	-	-	-	-	-	-	-
	MLN-TK with *JAK2* rearrangements	-	-	-	-	-	1	1	4
	MLN-TK with *PDGFRA/B* rearrangement	-	-	-	-	-	-	-	1
	MPN, NOS [WHO]/ MPN-U [ICC]	37	35	37	46	42	46	42	80
	Total 'non classical' MPN	***44***	***46***	***57***	***56***	***60***	***58***	***56***	***100***
MDS/MPN	MDS/MPN with neutrophilia [WHO]/ aCML [ICC]	37	32	40	44	36	40	38	40
	MDS/MPN with ring sideroblasts and thrombocytosis, NOS [ICC only]	-	-	-	-	-	1	2	7
	MDS/MPN with *SF3B1* mutation and thrombocytosis [WHO] / MDS/MPN with thrombocytosis and *SF3B1* Mutation [ICC]	-	-	-	-	-	-	-	-
	MDS/MPN, NOS [WHO/ICC]	59	84	98	91	107	99	112	86
	Total 'non classical' MDS/MPN	***96***	***116***	***138***	***135***	***143***	***140***	***152***	***133***

Table 1. Number of transplant procedures for 'non-classical' MPNs and MDS/MPNs performed in Europe from 2016 to 2023. HCT: allogeneic hematopoietic cell transplantation

Table 2. Main publications reporting on transplant cohorts of patients with 'non-classical' MPN and MDS/MPN.

Author (year)	MDS/MPN type	Pt N.	Tranplant period	Median age, y (range)	Donor	Conditioning	Stem cell source	NRM/relapse	Survival outcome
Dholaria (2022)	CNL	29	2000-2018	58 (33-72)	MRD 41% UD 56% MMRD 3%	MAC 48%	PB 93%	NRM 13.8% at 4y CIR 34.5% at 4y	OS 55.2% at 1y
McLornan (2022)	CEL / CEL, NOS	30	2000-2018	46 (IQR, 40-55)	MRD 30% UD 67% MMRD 3%	MAC 61%	PB 67%	NRM 45% at 3y CIR 20% at 3y	OS 34% at 3y
McLornan (2020)	MPN, NOS / MPN-U	70	2000-2015	NA (22-70)	MRD 39% UD 61%	MAC 44%	PB 91%	NRM 34% at 5y (MAC) CIR 27% at 5y (MAC)	OS 41% at 5y (MAC)
Metzgerod (2023)	MLN-TK	25	2003-2022	NA	NA	NA	NA	NR	10/12 alive at 3y (chronic phase) 7/13 alive at 4.7y (blast phase)
Hernandez-Boluda (2022)	MLN-TK with *FGFR1* rearrangement	22	1997-2018	51 (22-67)	MRD 23% UD 68% MMRD9%	MAC 55%	PB 86%	NRM 14% at 5y CIR 23% at 5y	OS 74% at 5y
Tang (2021)	MLN-TK with *FLT3* rearrangement	6	2005-2020	34 (2-43)	NA	NA	NA	NA	4/6 alive in CR at a median f-up of 41 months
Onida (2017)	MDS/MPN with neutrophilia / aCML	42	1997-2006	46 (25-67)	MRD 64% UD 36%	MAC 76%	PB 67%	NRM 24% at 5y CIR 40% at 5y	OS 51% at 5y
Itonaga (2018)	MDS/MPN with neutrophilia / aCML	14	2003-2014	45 (10-66)	MRD 36% UD 64%	MAC 86%	PB 14% BM 72% CB 14%	NRM 2 relapse/progression 4	8/14 alive at last follow-up
Kurusawa (2020)	MDS/MPN, NOS	86	2001-2017	57 (16-71)	MRD 28% UD 72%	MAC 62%	BM/PB 80% CB 20%	NRM 26% at 3y CIR 24% at 3y	OS 49% at 3y

Table 3. Differences and similarities among the WHO (5th edition) and ICC classifications.

WHO revised 4th edition	WHO 5th edition	ICC	Differences or similarities
CNL	**CNL** Unchanged from 2016	**CNL** Similar to WHO revised 4th edition except: Lowering of threshold PB WBC >13x10^9/L if accompanied by *CSF3R* mutation Defines Accelerated phase as circulating or BM blasts 10-19% with progressive splenomegaly or worsening thrombocytopenia Blast Phase as circulating or BM blasts ≥20%	In the presence of *CSF3R* mutation – lowering of the PB WBC threshold to >$13x10^9$/L for diagnosis in ICC Definition of accelerated and blasts phase add in ICC
CEL, NOS	**CEL**	**CEL, NOS**	Both exclude the growing number of tyrosine kinase gene fusions now categorized separately. WHO 5th edition drops the not otherwise specified (NOS) descriptor
Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement	**Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions**	**Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions**	Both add expanded categories involving *JAK2* and *FLT3* rearrangements and add *ETV6*::*ABL1* fusion
MPN, U	**MPN, NOS**	**MPN-U**	Remains unchanged, with only minor terminology adjustments in the

			WHO 5th edition
Atypical CML, *BCR-ABL1* negative	**MDS/MPN with neutrophilia** Same as revised 4th edition but name changed	**Atypical CML** Essentially unchanged from revised 4th edition except to delete reference to the lack of *BCR::ABL1* gene fusion in the name	Significant terminology changes in WHO 5th edition
MDS/MPN with ring sideroblasts and thrombocytosis	**MDS/MPN with *SF3B1* mutation and thrombocytosis**	**MDS/MPN with thrombocytosis and *SF3B1* mutation** **MDS/MPN with ring sideroblasts and thrombocytosis, NOS**	The ICC distinguishes forms carrying the *SF3B1* mutation from those without
MDS/MPN, U	**MDS/MPN, NOS**	**MDS/MPN, NOS**	Remains unchanged, with only minor terminology adjustments in the WHO 5th edition

Table 4. Panel recommendations for CNL

Disease	Panel recommendations
CNL [WHO/ICC]	- All CNL patients should be assessed early following diagnosis for potential transplant eligibility and donor search - Treatment aimed at optimizing disease control (control of leucocytosis, reduction in splenomegaly where relevant) is recommended as a 'bridge' prior to transplant, balancing the risks and benefits. - Given limited data, no recommendations can be made on optimal transplant conditioning regimens and post-transplant disease monitoring and maintenance. However, consideration needs to be given to considerable relapse rates and approaches tailored accordingly.

Table 5. Panel recommendations for CEL [WHO]/ CEL, NOS [ICC]

Disease	Panel recommendations
CEL [WHO]/ CEL, NOS [ICC]	- Given the poor prognosis of CEL / CEL, NOS and the risk of organ dysfunction all patients should be considered for HCT at diagnosis with a prompt donor search - Careful assessment of cardiac and pulmonary function is advised for transplant eligibility and then for tailoring transplant platform - Given the lack of disease-modifying agents, no recommendation can be made on pre-treatment strategies. - Transplant should not be delayed once a suitable donor is found

Table 6. Panel recommendations for *MLN-TK [WHO/ICC]*

Disease	Panel recommendations
MLN-TK [WHO/ICC]	- In patients with *PDGFRA/B*-rearranged MLN, both in chronic and blast phases, HCT is only considered after failure of TKI treatment. However, in young patients (<60 years) presenting with blast-phase disease, HCT could be considered upon achieving a response. - Careful assessment of cardiac and pulmonary function is advised for transplant eligibility and then for tailoring transplant platform - HCT, after bridging with an alternative TKI with or without chemotherapy, seems to be the preferred option for the rare cases of MLN-*PDGFRA/B* with secondary resistance to imatinib. - HCT with donor search should be considered early after diagnosis for most eligible patients with *FGFR1, JAK2, ABL1* and *FLT3*-rearranged MLN, given the low predictability and uncertain durability of responses to TKIs.- TKI treatment directed to the specific molecular abnormality is recommended to decrease disease burden pre-HCT. - A thorough evaluation of cardiac and pulmonary function is essential, given the possible organ impairment associated with prior/ongoing eosinophilic infiltration. - The HCT strategy should be tailored to the predominant clinical features of the disease (i.e. AML, ALL, MPN). - Monitoring of the underlying molecular abnormality using sensitive techniques is advised to inform treatment strategies to prevent overt disease relapse. - The role of TKI maintenance after HCT warrants investigation.

Table 7. Panel recommendations for *MPN, NOS [WHO]/ MPN, U [ICC]*

Disease	Panel recommendations
MPN, NOS [WHO]/ MPN-U [ICC]	- Given disease heterogeneity, therapeutic approaches to MPN, NOS should be discussed in centers with expertise in MPN management. - In transplant eligible MPN, NOS patients HCT can be considered for those patients at higher risk according to standard MF-derived prognostic systems - It is recommended that standard guidelines for MF pertaining to transplant are applied

Table 8. Panel recommendations for *MDS/MPN with neutrophilia [WHO] / atypical CML [ICC]*

Disease	Panel recommendations
MDS/MPN with neutrophilia [WHO]/ aCML [ICC]	- It is recommended that eligible patients are considered for transplant early after diagnosis with a prompt donor search - No recommendations can be made on optimal transplant conditioning and post-transplant disease monitoring and maintenance

Table 9. Panel recommendations for MDS/MPN with *SF3B1* mutation and thrombocytosis [WHO] / MDS/MPN with thrombocytosis and *SF3B1* Mutation [ICC] and MDS/MPN with ring sideroblasts and thrombocytosis, NOS [ICC only]

Disease	Panel recommendations
MDS/MPN with *SF3B1* mutation and thrombocytosis [WHO] / MDS/MPN with thrombocytosis and *SF3B1* Mutation [ICC] **&** **MDS/MPN with ring sideroblasts and thrombocytosis, NOS [ICC only]**	- Transplant should be considered in high risk eligible patients (e.g., refractory anemia, adverse cytogenetics, and/or presence of *ASXL1* or *SETBP1* mutations) in both MDS/MPN with thrombocytosis with or without *SF3B1* mutation, with a prompt donor search. - It is recommended that standard guidelines for MDS pertaining to transplant platform are applied

Table 10. Panel recommendations for *MDS/MPN, NOS*

Disease	Panel recommendations
MDS/MPN, NOS	- It is recommended that eligible patients are considered for transplant early after diagnosis, with a prompt donor search - It is recommended that standard guidelines for CMML pertaining to transplant platform are applied