Illuminating novel biological aspects and potential new therapeutic approaches for chronic myeloproliferative malignancies

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Abstract

This review reflects the presentations and discussion at the 14th post-American Society of Hematology (ASH) International Workshop on Chronic Myeloproliferative Malignancies, which took place on the December 10 and 11, 2019, immediately after the 61st ASH Annual Meeting in Orlando, Florida. Rather than present a resume of the proceedings, we address some of the topical translational science research and clinically relevant topics in detail. We consider how

recent studies using single-cell genomics and other molecular methods reveal novel aspects of hematopoiesis which in turn raise the possibility of new therapeutic approaches for patients with myeloproliferative neoplasms (MPNs). We discuss how alternative therapies could benefit patients with chronic myeloid leukemia who develop *BCR-ABL*1 mutant subclones following *ABL*1-tyrosine kinase inhibitor therapy. In MPNs, we focus on efforts beyond JAK-STAT and the merits of integrating activin receptor ligand traps, interferon-α, and allografting in the current treatment algorithm for patients with myelofibrosis.

1 | INTRODUCTION

Despite the development of significant genomic insights and the availability of successful treatment options, chronic myeloproliferative malignancies, with the exception of chronic myeloid leukemia (CML), remain enigmatic.[1] For patients with CML, we now have five licensed *ABL1* tyrosine kinase inhibitors (TKIs) that can durably reduce the number of CML cells, and the life expectancy of most patients now approaches that of the normal population; for patients with higher-risk myelofibrosis (MF), the most serious and life-threatening of the myeloproliferative neoplasms (MPNs), there are two licensed JAK inhibitors (JAKi) that accord rapid and substantial clinical benefits in terms of constitutional symptoms and splenomegaly but few molecular complete remissions and no significant impact on the risk of transformation to acute myeloid leukemia.[2] Indeed, there is a paucity of disease-modifying drugs for MF and the disease remains incurable with a median survival of 4 to 5 years. This is similar to the historical scenario that existed when cytotoxic chemotherapy was used to treat newly diagnosed patients with CML who benefitted from a transient control of their leukocytosis and splenomegaly but awaited the inevitable leukemic transformation with equanimity.

Compared with CML, the Ph-negative MPNs and particularly MF demonstrate substantial genetic and bone marrow microenvironment complexity, which impacts upon disease biology and treatment. In this regard, the significant insights into the biochemical and biological consequences of the well-characterized driver mutations found in about 90% of MF patients and the corresponding clinical implications is raising the possibility of new therapeutic approaches. This review, based on the presentations at the 14th post-ASH International Workshop on Chronic Myeloproliferative Malignancies, which took place on the December 10 and 11, 2019, immediately after the 61st American Society of Hematology Annual Meeting in Orlando, Florida presents the important aspects of the biological and therapeutic advances as well as the recent progress made in treating disease-related complications. To illustrate, we address how symptomatic anemia related to MF can be alleviated by targeting transforming growth factor beta (TGF-β) by an activin receptor ligand, luspatercept. We also discuss the emerging role of single cell technologies in MPNs and tools to personalize the management of MF.

2 | USING SINGLE CELL TECHNOLOGIES TO IDENTIFY NOVEL TARGETS IN MPNS

Since the first studies performing whole transcriptome analysis in individual cells, termed single cell RNA-sequencing (scRNAseq) a decade ago, there has been an explosion of technological advances in single cell methods, resulting in advanced platforms for high-throughput and/or multiomic approaches to study molecular biology at single cell resolution.[3] Indeed, single cell sequencing was selected as "Method of the Year" by *Nature Methods* in 2013, and single cell multimodal omics as "Method of the Year" in 2019.[4] In hematology, these approaches have been applied to gain insight into normal and aberrant hematopoiesis, and more recently the bone marrow niche.[5–12]

Technological and computational challenges and high cost have prohibited widespread application in clinical diagnostics or monitoring pipelines. So what is the future potential for clinical application of single cell omics in MPNs? First, it provides the necessary resolution to detect and characterize rare cellular populations such as leukemic stem cells. In addition to understanding disease biology and mechanisms of relapse or treatment resistance, this technology may identify novel leukemia stem cell-specific drug targets. Second, dissection of tumor heterogeneity will enable step changes in personalized medicine, identifying tumors most likely to respond to a given treatment approach, informing the selection of treatment combinations that are most likely to be effective in any given cancer at a particular stage in the disease course. Thirdly, unlike genomic (or proteomic) analyses of cells studied in "bulk," single cell studies provide information on specific combinations or genes or proteins expressed by cellular subtypes. For example, identification of unique combinations of cell surface proteins may enable selective targeting of cancers were specific individual markers have not been found. Finally, comprehensive characterization of bone marrow cells in MPNs may be applied to simultaneously study the MPN clone together with associated immune or nonclonal cells as well as the tissue stroma, leading to key insights into the cell-cell interactions that are important for disease evolution.

Key challenges for the field include reducing the high cost and practical challenges to enable single cell omics to be delivered in the context of routine clinical practice and clinical trials. In addition, further advances in spatial single cell omics are required to enable study of myeloid neoplasms in their native context, without losing key information contained within the tissue architecture as occurs when cells are studied "in suspension." Moreover, just as hematology has led the way in other areas of precision oncology, the application of single cell technologies in MPNs is also highly relevant for other cancer types.

Recently, single cell omics has been applied to study abnormal hematopoiesis in MF. A dramatic bias toward megakaryocyte (Mk) differentiation was identified from early stem cells, present across clinical and molecular MF subgroups.[13] Mk progenitors were heterogeneous, with distinct expression of inflammatory mediators and unique populations present in MF. Aberrant cell surface expression of G6B expression on MF stem and progenitors was identified, which could allow selective immunotherapeutic targeting of the MF clone.

3 | TARGETING SPECIFIC BCR-ABL1 MUTANT SUBCLONES BY ALTERNATIVE TREATMENT APPROACHES

Although the introduction of ABL1-TKIs has revolutionized the treatment of BCR-ABL1-positive leukemias, including CML and Philadelphia (Ph)-positive acute lymphoblastic leukemia (ALL), they are not panacea. Outgrowth of leukemic clones harboring resistant point mutations in the BCR-ABL1 tyrosine kinase domain (TKD) poses a serious clinical problem. These mutant subclones are believed to expand due to disruption of the TKI/TKD interaction. However, due to the positioning of resistant mutations at functional key positions of the BCR-ABL1 TKD, Lion and colleagues hypothesized that these mutations have a biological effect on BCR-ABL1 downstream signaling and oncogenic gene expression. They generated over 50 Ba/F3 cell lines expressing BCR-ABL1 with various single and compound mutations (CMs) at levels comparable to patient-derived cells.[14] These cell lines were tested against a panel of TKIs, with a particular focus on CMs and their in vitro responsiveness to ponatinib. Their findings identified three categories of CMs displaying either high, intermediate, or low sensitivity to ponatinib. While the intermediate category of CMs was shown to respond to higher, yet clinically achievable concentrations of ponatinib, the inhibitory concentrations required for growth suppression of the least sensitive category of CMs were too high for clinical applicability.[15] The latter category comprised particularly CMs including the gatekeeper mutation T315I in combination with a variety of other TKD mutations, and these CMs were shown to be unresponsive even to the most potent TKI available at present, thus presenting a great clinical challenge. Investigation of the effect of individual CMs on intracellular downstream signaling identified altered patterns in comparison to cells carrying wild-type BCR-ABL1. These findings provided the basis for identifying potentially druggable vulnerabilities, implicating various compounds not directly targeting the kinase activity of BCR-ABL1, such as cell cycle progression inhibitors, proteasome inhibitors, and others. Interestingly, in contrast to native BCR-ABL1 and several mutant subclones, CMs including the T315I mutation was very sensitive in vitro to treatment with hydroxyurea (HU), and molecular analyses provided a biological basis for the intriguing effect of this compound. The observation that, unlike cells with native BCR-ABL1, CMs including the T315I mutation display highly upregulated cyclin-dependent kinase 6 (CDK6), thus raising the possibility that specific inhibitors of the enzyme might be effective in these instances. Indeed, in vitro testing revealed great efficacy of palbociclib and ribociclib at concentrations readily achievable in the clinical setting. Moreover, synergistic effects of ponatinib in combination with HU or ciclibs against cells carrying highly resistant CMs including the T315I mutation have been demonstrated.[16] It appears therefore that the upregulation of CDK6 documented in BCR-ABL1-positive cells displaying the T315I mutation alone or as part of a CM, provides a therapeutically exploitable vulnerability of the mutant cells. If these observations can be confirmed in the clinical setting, the therapeutic armamentarium would facilitate control of mutant BCR-ABL1 subclones resistant to all presently approved ABL1 TKIs. The observations so far demonstrate that the impact of acquiring TKI-resistant mutations may go far beyond hindering the TKI/TKD interaction. Studying the differential downstream signaling in mutant *BCR-ABL*1 subclones should facilitate the understanding of their biological behavior and help establish their druggable

vulnerabilities, as a basis for the development of novel effective treatment options in patients resistant to currently available TKI-based therapies.

4 | ACTIVIN RECEPTOR LIGAND TRAPS FOR THE TREATMENT OF ANEMIA ASSOCIATED WITH CHRONIC MYELOPROLIFERATIVE MALIGNANCIES

Anemia is not only common in patients with MF (and is a WHO minor diagnostic criterion), but contributes adversely to the quality of life, morbidity and mortality, and increased symptom burden. The activin receptor ligand traps sotatercept (ACE-011) and luspatercept belong to a novel class of fusion proteins that are capable of alleviating anemia resulting from a range of benign and malignant conditions.[17,18] These drugs consist of the extracellular domain of the activin receptor (A in the case of sotatercept; B in the case of luspatercept) fused to the Fc domain of human IgG1 and improve anemia by sequestering ligands belonging to the TGF-β superfamily that suppress terminal erythropoiesis.[19] Mechanistically, growth and differentiation factor 11 (GDF11) has been considered to be an important TGF-β superfamily ligand trapped by such agents that ameliorate anemia resulting from diverse causes.[20] Indeed, luspatercept was approved in November 2019 for the treatment of anemia in patients with β-thalassemia and patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or MDS/MPN with RS and thrombocytosis (MDS/MPN-RS-T) in April 2020.[21]

An important distinguishing feature of this class of drugs that sets them apart from erythropoietin and its analogs is that they act on late-stage erythroid precursors (Figure 1). Based on preclinical studies suggesting anemia benefit secondary to its ability to sequester ligands secreted by the MF bone marrow stroma that inhibit erythropoiesis via Smad signaling, sotatercept was studied in an ongoing clinical trial.[22] Eligible patients had to be anemic or transfusion-dependent (TD) per International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria.[23] Sotatercept was studied both as monotherapy and in patients on a stable dose of ruxolitinib.[24] The response rate, a combination of transfusion independent (TI) by IWG-MRT criteria and anemia response by Gale criteria, was 35% in patients treated with sotatercept alone and 12.5% in patients treated with the combination of sotatercept and ruxoloitinib.[25] Grade 3 treatment-emergent adverse events (TEAEs) were limited to hypertension and limb pain. These findings initiated a phase 2 study of luspatercept alone or in combination with ruxolitinib in 76 anemic patients with MF, either alone (cohorts 1 and 2) or in combination with ruxolitinib (cohorts 3A and 3B).[26] Patients in cohorts 1 (n = 22) and 3A (n = 14) could not have been receiving any transfusions, while patients in cohorts 2 (n = 21) and 3B (n = 19) had to be TD per IWG-MRT criteria. By intention-to-treat analysis, the anemia response rates (by Gale criteria) in cohorts 1 and 3A were 14% and 21%, respectively, while the RBC TI rates in cohorts 2 and 3B were 10% and 32%, respectively. The proportions of patients who achieved a mean increase in hemoglobin of 1.5 g/dL and who achieved a 50% reduction in the number of units transfused also favored the ruxolitinib cohorts, a pattern of response not well understood at this time. The most frequent TEAEs included hypertension (12%), bone pain (9%), and diarrhea (5%). Noteworthy, the activin receptor ligand traps discussed above

do not target TGF-β per se, a candidate therapeutic target in MF, and discussed in the next section. This cytokine is secreted at high levels, primarily by Mks in the MF bone marrow milieu, and is implicated in both the fibrotic process and in promoting clonal dominance in the classic MPNs.[27]

5 | CURRENT AND INVESTIGATIONAL THERAPIES FOR MF

The introduction into clinical practice in 2011 of the original type I JAKi ruxolitinib was an important therapeutic advance, as with this agent most MF patients achieve substantial spleen volume reduction (SVR) and improvement in total symptom score (TSS), and some may expect prolongation of survival compared with earlier methods of treatment.[28,29] Ruxolitinib, an oral JAK1 and JAK2 inhibitor, targets the ATP-binding site of the JAKs under the active conformation of the kinase domain. The median duration of response to ruxolitinib is about 2 to 3 years, and the prognosis of patients who relapse, or are refractory or resistant, or have clonal evolution, have a median survival of 14 months.[30,31] Patients with monocytosis, accelerated phase, or high-risk genetic features also have a poor prognosis.[32,33]

Second-line therapies comprise of an alternative type I JAKi, or agents that target mechanisms beyond JAK/STAT signaling, either alone or in combination with JAKi. Many of these JAKis have had their clinical development discontinued due to the emergence of serious toxicity. Fedratinib, a JAK2/FLT3 inhibitor, demonstrated efficacy in both first and second-line, but a clinical hold was placed in 2013 by the FDA due to concerns over increased risk for Wernicke encephalopathy.[34,35] This was subsequently revised and the drug licensed.[36,37] Pacritinib, a JAK2/FLT3/IRAK1/CFS1R inhibitor, and momelotinib, a JAK1/2 inhibitor, remain investigational. Pacritinib is being tested in MF patients with thrombocytopenia at a revised dose in a randomized phase III trial (PACIFICA).[38] The drug was previously found to be effective in phase III trials in reducing splenomegaly and symptom control, but there were concerns about cardiotoxicity and hemorrhage.[39,40] Momelotinib can improve anemia by improving functional iron availability by decreasing hepcidin production through the ACVR1 pathway. The drug was noninferior to ruxolitinib for SVR but not TSS response in first-line and in second-line setting, there were improvements in TI and TSS, but inadequate SVR.[41,42] There was concern for emergent peripheral neuropathy and further studies are underway to assess the drug's candidacy for second-line anemic/TD patients (MOMENTUM).

At present, a major focus of drug development in MF is identifying new therapeutic targets beyond JAK-STAT inhibition (Figure 2). As illustration, to mention a few, encouraging preliminary results have been noted in trials investigating AURKA inhibitors, HDAC inhibitors, PARP inhibitors, PRMT5 inhibitors, HDM2 inhibitors, hedgehog pathway inhibitors, TGF-β inhibitors, telomerase inhibitors, and immunomodulatory drugs.[43,44] Novel immunological therapeutic approaches are also being tested, and include CD123 targeted antibody, mutant CALR blocking antibodies, and peptide vaccination. Preclinical models have also studied type II JAKis, such as NVP-BBT594 and NVPCHZ868, and found them to be effective.[45] Table 1 depicts some of the agents that have shown safety

and efficacy in second line use either as monotherapy or in combination with ruxolitinib ("add-on"/"add-back").[46]

A focus on apoptosis is illustrated by an ongoing phase II study of the BCL-XL inhibitor, navitoclax, combined with ruxolitinib.[47] In this small study, 29% of the patients achieved an SVR 35% and a 20% improvement in TSS; 42% patients had SVR 35% at any time on study; 25% patients had bone marrow fibrosis improvement; and 42% patients were observed to have major molecular responses. Grade 3/4 TEAE included thrombocytopenia (44%) and anemia (24%). A three-arm phase II trial (MANIFEST), assessing epigenetic modification by a bromodomain and extraterminal inhibitor, CPI-0610, observed 80% of patients to achieve SVR 35 at week 12, 50% of patients to achieve TSS response, 43% TD patients became TI and some improvements in bone marrow fibrosis were noted in first-line setting with CPI-060 plus ruxolitinib.[48] The most common TEAEs were thrombocytopenia (23%). Updated results of a phase II trial of ruxolitinib with either thalidomide or pomalidomide, confirmed earlier positive results demonstrating improvements in cytopenias, in particular thrombocytopenia and other clinical benefits.[49,50]

Other studies of note included a phase 1 study of an Mk-targeting therapy, alisertib, a specific inhibitor of aurora kinase (AURKA) demonstrated clinical benefits in a third of patients by reducing splenomegaly and symptom burden.[53] Importantly, alisertib reduces bone marrow fibrosis, mutant allele burden and restores normal morphology in atypical MF Mks in some cases. The most common grade 3/4 TEAEs were neutropenia (42%), thrombocytopenia (29%), and anemia (21%). Another novel approach is tagraxofusp, a CD123-directed antibody, composed of human IL-3 and truncated diptheria toxin, licensed in 2018 for children and adults with blastic plasmacytoid neoplasm.[55] Tagraxofusp has been tested in a preclinical model either alone or in combination with ruxolitinib and noted to have activity in primary MF (PMF).[56] Interim clinical results from a phase 2 study of tagraxofusp in patients with relapsed/refractory MF with thrombocytopenia observed spleen responses in 20% and symptom reduction in half of the patients.[51] The most common TEAE was abnormal liver function tests and the most serious was a single patient experiencing grade 4 capillary leak syndrome. The final results of a phase 2 study assessing apoptosis induced by a SMAC mimetic (IAP antagonists) agent in high-risk thrombocytopenic MF patients observed an overall response rate of 32%, a modest anemia response and a median overall survival that has not been reached with median follow-up of about 2 years.[57] The most common TEAEs were nausea/vomiting (60%); fatigue syndrome (49%); grade 3/4 thrombocytopenia occurred in 3 pts (6%) and correlative studies confirmed target-inhibition (cIAP1). Results from a small phase I/II study of epigenetic modification by means of a lysine specific demethylase1 inhibitor, bomedemstat, showed 75% to have a modest decrease in SVR and symptom burden, and bone marrow fibrosis improvement.[52] A small repurposing effort with a biguanide, metformin, to target bone marrow fibrosis revealed a progressive reduction in bone marrow collagen fibers from 26.9% at baseline to 3.8% at 3 months and 0.84% at 6 months posttherapy.[58] Finally, AVID200, a TGF-β ligand trap, has shown promise in preclinical studies and is now in a clinical trial in patients with MF.[54]

6 | GENOMIC RISK SCORES FOR ALLOGENEIC STEM CELL TRANSPLANTATION IN MF

At present, allografting remains the only potentially curative treatment for patients with MF but is confounded by therapy-related morbidity and nonrelapse mortality, due at least in part, to the older age and the general poor condition of many patients at diagnosis.[59] Transplant outcomes have improved further with advances in transplant technology which has increased donor availability, reduced transplant toxicity and the introduction of reduced-intensity conditioning.[60] Furthermore, the potential use of JAKi therapy, pretransplant to reduce splenomegaly and improve constitutional symptoms, peritransplant to reduce graft vs host disease and posttransplant to improve long-term outcomes appears attractive but requires confirmation.[61]

Until recently, there were no suitable risk stratification methodology to optimize the decision-making process for treating MF patients with transplantation. The best-studied method was the Lille score, first introduced in 1996, for nontransplant treatment of patients with PMF.[62] Since then, multiple new risk assessment methods have been introduced for PMF and extrapolated into the treatment-decision-making process for all MF patients, including post-ET/PV MF who comprise about 60% of MF, and adapted with modest success for transplant selection criteria (Figure 3). These have included the International Prognostic Scoring System (IPSS), based on age >65 years, hemoglobin <10 g/L, leucocyte count >25 × 10^9/L, the presence of circulating peripheral blasts and constitutional symptoms; the Dynamic IPSS (DIPSS), which assesses prognosis during the course of the disease and is based on the prognostic variables as IPSS but ranks anemia as a higher risk factor; and the DIPSS-plus, which added transfusion-dependence, platelet count <100 × 10^9/L and unfavorable karyotype to the DIPSS model.[63–65] Current risk scores have improved prognostic ability compared with IPSS and have incorporated genomic information to optimize risk stratification. These include the updated Mutation-Enhanced Prognostic Score (MIPSS-70 version 2.0), which includes CALR type I mutation, the presence of *ASXL1*, *EZH2*, *SRSF2*, *U2AF1*, or *IDH*1/2 mutations and a three-tiered cytogenetic risk classification, myelofibrosis secondary to PV and ET (MYSEC-PM) score, which includes the presence of constitutional symptoms, platelets <150 × 10^9/L, hemoglobin <11 g/dL, circulating blasts >3% and a CALR-unmutated genotype, and a simpler genetic risk score, the genetically inspired scoring system.[66–68] These risk models are clearly useful in the nontransplant setting but are not optimal for transplant purposes, possibly due to the omission of transplant- and patient-specific factors that influence clinical outcomes following a transplant.[69,70]

In 2019, a risk score, the myelofibrosis transplant scoring system (MTSS), was developed specifically for all MF patients to predict outcomes after transplantation.[71] MTSS was formulated at diagnosis in a cohort of 361 patients (PMF = 260; post-ET MF = 101; post-PV MF = 46) and excluded patients who had progressed to acute leukemia. It is based on multivariable analysis which identified age (57 years), Karnofsky performance status (<90%), pretransplant thrombocytopenia, leucocyte count (>25 × 10^9/L), HLA-mismatched unrelated donor, *ASXL1* mutation and triple-negative, and non-*CALR/MPL* or *JAK2* driver

mutation as independent prognostic factors for posttransplant survival. A comparison of the MTSS with some of the nontransplant risk-scoring systems, including those (such as MPISS-70 or MYSEC-PM) incorporating genetic information that now considered an integral facet, suggests an improvement in the patient selection for transplantation for all MF patients with respect to posttransplant outcomes.[72] Figure 4 depicts a potential treatment algorithm incorporating transplantation for patients with MF. It is of interest that neither constitutional symptoms, nor clinical variables such as transfusion dependence, appear to influence outcome after transplantation. Clearly, the MTSS will require additional validation prior to wider clinical use, but represents conceivably an important step forward in precision cancer medicine for patients with MF.

7 | A FIVE DECADE ODYSSEY OF INTERFERON-α IN CHRONIC MYELOPROLIFERATIVE LEUKEMIAS

Interferon-α (IFNα) is a member of a large family of glycoproteins of biologic origin with antiviral and antiproliferative properties. Studies in the early 1980s showed that IFNα was active in CML and able to induce major cytogenetic remissions in 5% to 15% of patients with restoration of Ph-negative (putatively normal) hematopoiesis and a survival advantage. IFNα, in particular the long-acting form, has since been tested in MPNs in phase 2 studies, including the MPD-RC 111 trial in which recombinant IFNα−2a was observed to reverse all hematological features of PV in 22% of the 50 HU refractory/intolerant patients.[73–75] More recently, ropeginterferon-α−2b was compared to HU in a prospective randomized controlled phase 3 trial (PROUD-CONTINUATION) in patients with PV.[76] The 4-year follow-up of this study demonstrated sustained complete hematological responses in 61% of patients treated with IFNα vs 43% in the HU group ($P = .02$), with a similar efficacy for reducing thromboembolic events to very low rates (0.0%, 0.0%, and 1.1% of patients treated with IFNα in the second, third, and fourth years).[77] Of particular interest was the observation that 67% of IFNα-treated patients achieved reduction in the *JAK2*V617F allele burden compared with 26% of the HU-treated cohort (RR: 2.5 [95% CI: 1.7–3.7; $P < .0001$]). Serial measurements of the allele burden in the IFNα-treated patients confirmed 14% complete molecular remissions and 36% major molecular response at month 48. This raises the important question of whether these "molecular responders" would have their life prolonged by treatment with IFNα compared with HU. Furthermore, the majority of the "molecular responders" also achieved complete hematological remissions, suggesting that treatment discontinuation could be possible. Toxicity after 4 years was generally mild and reversible, and was similar between the two groups of patients: 28% (IFNα) vs 22.9% (HU); four cases of secondary malignancies have been reported in the HU patients so far. Collectively, these observations signal the need to consider the merits of IFNα replacing HU as the primary treatment for PV and randomized controlled studies to test it against ruxolitinib, the latter of which was approved as a second-line therapy for PV in 2014.[78]

8 | CONCLUSION

MPNs are clonal stem cell neoplasms with heterogenous clinical phenotypes and complex genetic architecture, which currently remain incurable. Treatment with a choice of two

first-line orally administered JAKis, ruxolitinib, and fedratinib, for patients with MF has led to substantial symptomatic improvement, improvement in quality of life, but no sustained disease modification or long-term remissions. It seems crucial, therefore, to improve our understanding of the various JAKi resistance mechanisms and develop new treatment approaches beyond JAK-STAT inhibition. Moreover, new MPN biological and clinical entities, such as those associated with the novel *JAK2*ex13InDel mutation and linked with eosinophilia and erythrocytosis, add to the heterogeneity and underline the need for reconciliation within the treatment algorithm.[79] The improved molecular technologies, such as single-cell transcriptome approaches tracking somatic mutations and characterizing cellular and molecular features are informing on clonal dynamics and architecture in MF and allowing insights into disease progression and treatment. scRNAseq demonstrates a Mk-biased differentiation in MF stem and progenitors that are associated with specific molecular signatures and suitable for Mk-targeted therapies. In contrast to MF, most patients with CML have an overall survival similar to that of the general population, following treatment with any of the *ABL*1 TKIs licensed for first-line therapy. Resistance, however, from mutant *BCR-ABL1* subclones arising from the likely disruption of the TKI/TKD interaction, is increasingly being recognized as a serious problem due to the biological effect on *BCR-ABL1* downstream signaling and oncogenic gene expression. These mutant clones display highly upregulated CDK6 and raise the possibility of new therapeutic approaches. Last but not least, the long-term data from the randomized PROUD-CONTINUATION study in patients with PV raises the prospect of IFNα replacing HU as the primary treatment for this MPN.

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CONFLICTS OF INTEREST

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(a)

Structure of Luspatercept and Sotatercept

(ACE-536) Luspatercept	(ACE-011) Sotatercept
Modified Extracellular Domain of **ActRIIB** Fc Domain of human IgG₁ Antibody	Extracellular Domain of **ActRIIA** Fc Domain of human IgG₁ Antibody

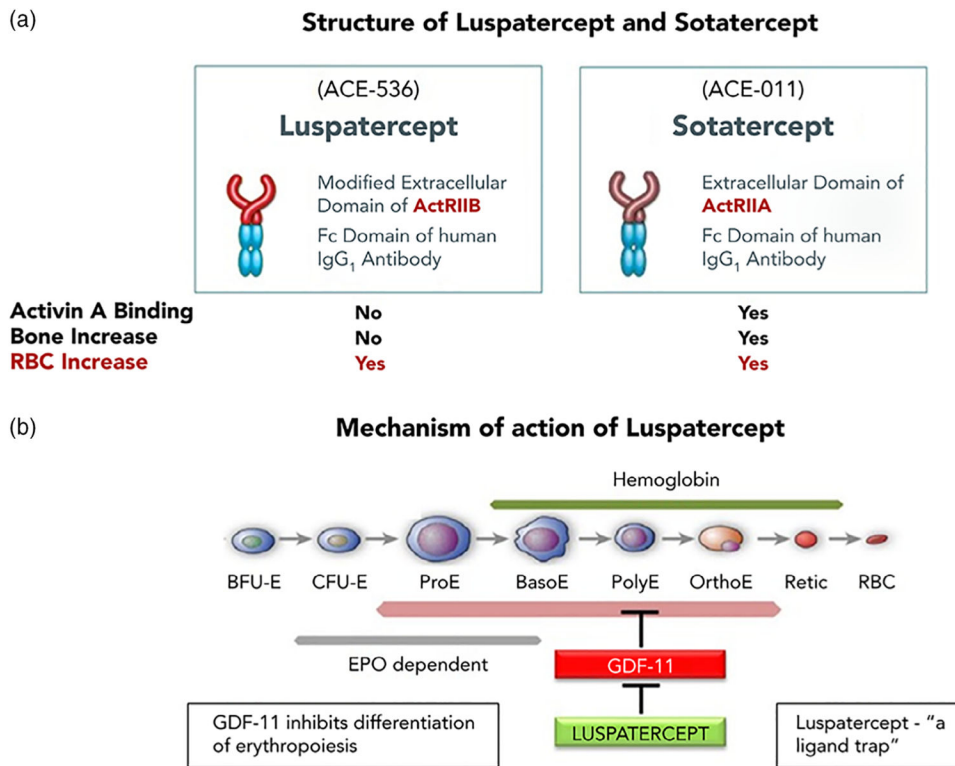|		
Activin A Binding	No	Yes
Bone Increase	No	Yes
RBC Increase	Yes	Yes

(b)

Mechanism of action of Luspatercept

FIGURE 1.
Luspatercept for the treatment of anemia in primary myelofibrosis
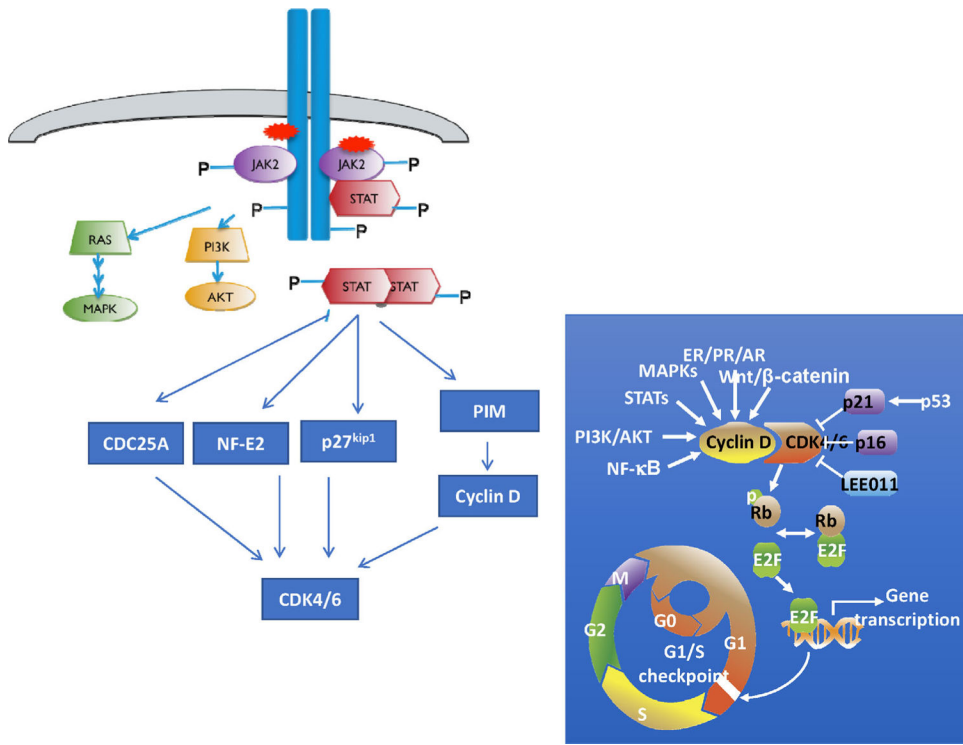
FIGURE 2.
Targeting cell signaling pathways beyond JAK/STAT

	Age	Hb (g/dL)	PLT (x10⁹/L)	WBC (x10⁹/L)	Blast (%)	P.S.	BM fibrosis	Driver mutation	Additional mutation	Donor
DIPSS	> 65 (1)	< 10 (2)	-	> 25 (1)	≥ 1% (1)	C.S. (1)		-	-	--
MIPSS-70 v2.0	-	< 10 (1)	< 100 (2)	> 25 (2)	≥ 2 (1)	C.S. (1)	≥ 2 (1)	Non CALR T1 (1)	HMR (1) >2 (2)	-
MYSEC-PM	Cont (0.15)	< 11 (2)	< 150 (1)	--	≥ 3 (2)	C.S. (1)		Non CALR (2)	-	-
MTSS	> 57 (1)	-	< 150 (1)	> 25 (1)	-	K. < 90% (1)	-	Non-CALR / MPL (2)	ASXL1 (1)	MMU (2)

Notes

DIPSS (Dynamic International Prognostic Scoring System); MIPSS-70 (Mutation-Enhanced International Prognostic Score System); MYSEC-PM (Myelofibrosis Secondary Prognostic model); MTSS (Myelofibrosis Transplant Scoring System). Hb: hemoglobin value; PLT: platelet count; WBC: white blood cell count; PS: performance status; BM: bone marrow; Cont: Continuous; CS: constitutional symptoms; K: Karnofsky; HMR: high molecular risk; MMU Mismatched unrelated

DIPSS categories: low (0); intermediate-1 (1-2), intermediate-2 (3-4), high risk (5-6)

MIPSS-70 categories: low (0-1); intermediate (2-4), high risk (≥5)

MYSEC-PM categories: low (<11); intermediate-1 (11-13), intermediate-2 (14-15), high risk (≥16). http://www.mysec-pm.eu

MTSS categories: low (0-2); intermediate (3-4), high (5), very high risk (6-9)

FIGURE 3.
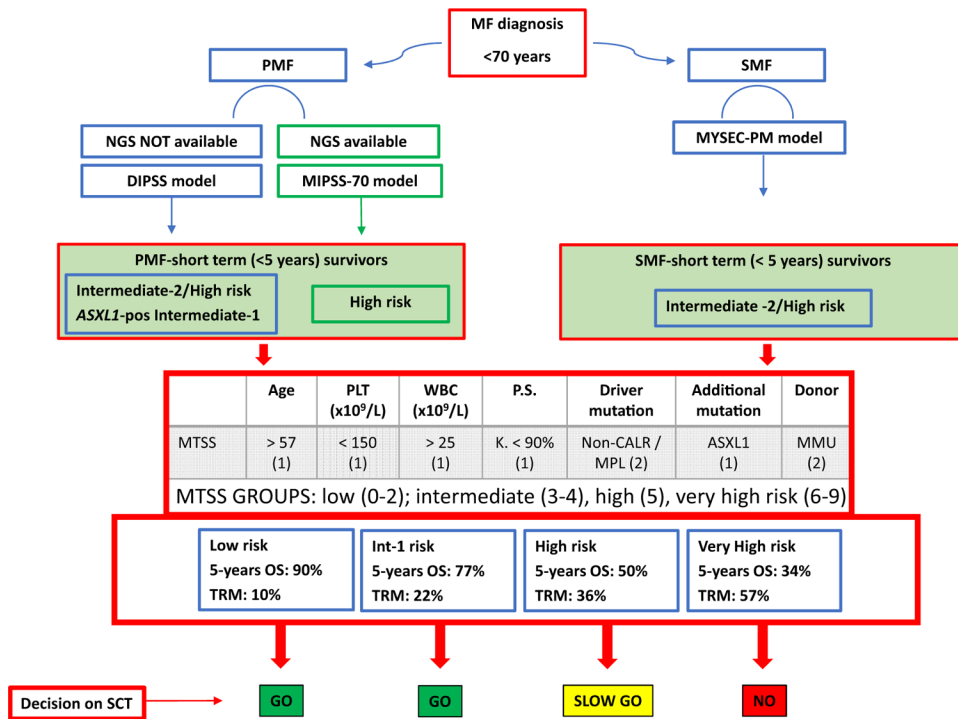Risk assessment methods for patients with myelofibrosis

FIGURE 4.

A potential treatment algorithm incorporating transplantation for patients with myelofibrosis (MF) (courtesy of Prof Francesco Passamonti)

TABLE 1

Myelofibrosis clinical drug development programs

Drug (class)	Comments	Reference
Momelotinib (JAK1/2 inhibitor)	Ongoing Phase 3 (NCT04173494)	[46,47]
Pacritinib (JAK2/ FLT 3 inhibitor)	Ongoing Phase 3 (NCT03165734)	[44,45]
Luspatercept ± ruxolitinib (receptor type IIb and IgG1Fc domain)	Ongoing phase 2 (NCT03194542)	[26]
CPI-0610 ± ruxolitinib (BET inhibitor)	Ongoing phase 2 (NCT02158858)	[48]
Navitoclax + ruxolitinib (Bcl-2 inhibitor)	Ongoing phase 2 (NCT03222609)	[47]
Pomalidomide + ruxolitinib (immunomodulatory)	Ongoing phase 2 (NCT01644110)	[49]
Thalidomide + ruxolitinib (immunomodulatory)	Ongoing phase 2 (NCT03069326)	[50]
Tagraxofusp (CD123 targeted antibody)	Ongoing phase 2 (NCT02268253)	[51]
Bomedemstat (LSD1 inhibitor)	Ongoing phase 2 (NCT03136185)	[52]
Alisertib (Aurora kinase inhibitor)	Ongoing phase 1/2 (NCT02530619)	[53]
Imetelstat (Telomerase inhibitor)	Completed phase 1/2 (NCT01731951)	[44]
AVID200 (TGF-β ligand trap)	Ongoing phase 1 (NCT03895112)	[54]

Abbreviations: BET, bromodomain and extraterminal; LSD1, lysine specific demethylase1; TGF-β, transforming growth factor beta.