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REVIEW

Perspective: Pivotal translational hematology and therapeutic insights in chronic myeloid hematopoietic stem cell malignancies

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Abstract

Despite much of the past 2 years being engulfed by the devastating consequences of the SAR-CoV-2 pandemic, significant progress, even breathtaking, occurred in the field of chronic myeloid malignancies. Some of this was show-cased at the 15th Post-American Society of Hematology (ASH) and the 25th John Goldman workshops on myeloproliferative neoplasms (MPN) held on 9th-10th December 2020 and 7th-

10th October 2021, respectively. The inaugural Post-ASH MPN workshop was set out in 2006 by John Goldman (deceased) and Tariq Mughal to answer emerging translational hematology and therapeutics of patients with these malignancies. Rather than present a resume of the discussions, this perspective focuses on some of the pivotal translational hematology and therapeutic insights in these diseases.

KEYWORDS
chronic myeloid leukemia, clinical, Myelofibrosis, systemic mastocytosis, thrombosis, translational

1 | INTRODUCTION

The introduction in 1998 of imatinib mesylate and in 2008 of ruxolitinib revolutionized management of patients with chronic myeloid leukemia (CML) and myelofibrosis (MF), an advanced form of myeloproliferative neoplasm (MPN), respectively, and the second and subsequent generation of these molecules may well prove superior.[1–3] The translational and therapeutic spectrum of these and related diseases is still unfolding. Indeed, the introduction of techniques for confirming the diagnosis, risk stratification, monitoring the response to therapy, and new therapies have evolved at such a rapid pace that any recommendations made should be considered provisional and will require revision as new evidence emerges. Although some uncertainty with regards to the precise initial genetic event remains, CML is generally recognized as a distinct form of MPN characterized by a consistent cytogenetic abnormality, the Philadelphia (Ph) chromosome and the exclusive presence of the *BCR-ABL1* fusion gene; in contrast, the BCR-ABL1 negative MPN are initiated by the acquisition of gene mutation (s) in a hematopoietic stem cell, typically occurring in the genes encoding *JAK2* (*JAK2*^{V617F}), calreticulin (*CALR*) or the thrombopoietin receptor, *MPL*.[4–7] The underlying pathogenesis is complex and incompletely understood, with regards to the contribution of clonal expansion, clonal evolution, and effects of cancer therapy on clonal hematopoiesis.[8,9] Recent astute observations suggestive of an in utero and childhood germline origin of MPN arising in adults add much to the remarkable biological complexity and clinical implications of these disorders.[10] As new evidence emerges, there is palpable enthusiasm for novel cancer drug discovery and drug development in these cancers. These workshops provide a platform for leaders in the field to deliberate the translational and clinical scenario and sum up well where we are now. Herein, we summarize some of these topics.

1.1 | Targeting immune dysfunction in myelofibrosis

Recent data supports the notion of targeting the underlying immune dysfunction in MF with immunotherapy.[11] MF is associated with significant changes to the bone marrow (BM) stroma that underscores the importance of targeting the MPN clone by innate and adaptive immune mechanisms. Ruxolitinib, the first-in-class type I JAK2 inhibitor accords substantial clinical benefit, reduction in splenomegaly and a modest survival improvement.[12,13] The drug, however, is not a panacea. Clonal evolution to acute myeloid leukemia (AML) is not impacted and in most patients the allelic mutational burden remains unchanged. It can be associated with cytopenias, in particular anemia and thrombocytopenia. Fedratinib, a type I JAK2 and a FLT3 inhibitor, was approved in 2019 and is being tested in patients in ruxolitinib treated patients who lose response.[14] Preclinical studies, however, suggest cross-resistance among type I JAK2 inhibitors. Momelitinib and pacritinib, also type I JAK2 inhibitors, are in late stage development and anticipated to be licensed soon, in particular for patients with anemia and thrombocytopenia.[15,16] Indeed, pacritinib was licensed on 28th February 2022 by the US Food and Drug Administration (FDA) for the treatment of adult patients diagnosed with intermediate or high-risk MF with baseline platelets (50×10^9/L). Momelitinib mitigates anemia by inhibiting the activin A receptor and decreasing hepcidin production; pacritinib has a nonmyelosuppressive profile and appears suitable for thrombocytopenic patients, in which the drug is currently being tested in a randomized, controlled, phase 3 study (PACIFICA).[17]

A principal focus of current research is to develop disease-modifying therapies for MF. In this regard there is considerable interest in assessing the opportunities for immunotherapy and new targets supported by pre-clinical data. Recent observations, such as the vulnerability to SAR-CoV-2 infection in MPN, underscores the importance of targeting immune dysfunction and targeting the MPN clone with therapeutic antibodies is attractive.[18] One such target is CD123, the receptor for IL-3, that has been identified as a therapeutic target in diverse CD123-positive hematologic malignancies. Preclinical evaluation of tagraxofusp (SL-401), a rationally designed targeted therapy directed to CD123 that consists of recombinant IL-3 fused to a truncated diphtheria toxin, observed activity in primary patient samples, including those in accelerated phase and with high molecular risk profiles. alone and in combination with ruxolitinib.[19] Following the FDA approval in blastic plasmacytoid dendritic cell neoplasm in 2018, a Phase I/II study of tagraxofusp in patients with relapsed/refractory MF demonstrated clinical efficacy with manageable toxicity, and a combination study is now planned.[20,21] Other targeted immunomodulatory approaches include those informed by the demonstration of increased expression of the immune checkpoint receptor PD-1 and CTLA-4 on CD4+ and CD8+ T cells in MPN, and the notion of *JAK2*^{V617F} and *CALR* mutants

enhancing PD-L1 expression.[22,23] Vaccines and adoptive cell therapy are in early-stage development. The safety and efficacy of vaccination with *mut*CALR has been tested in a small cohort of patients with MF and essential thrombocythemia (ET).[24] There is also interest in targeting CD47, which is overexpressed in MPN, for activating the innate immune pathways.[25] And, since *TP53* is an important driver of leukemic transformation, CD47 represents an attractive target in myeloid malignancies (discussed below).

Indeed, there is an abundance of new therapies in clinical development for MF, including "add-on" drugs that improve efficacy of ruxolitinib, novel JAK inhibitors that are more selective for JAK2 and new targets such as PI3K, BCL-xL, LSD1, telomerase and TGF-β.[26] Table 1 depicts some of the current phase III ongoing studies. Many of these agents, such as bromodomain and extra-terminal motif (BET) oral inhibitor, pelabresib (CPI-0610), have robust anti-inflammatory activity and clinical activity in phase II studies have been noted.[27] Updated Phase II study results of the combination of pelabresib with ruxolitinib as front-line therapy (MANIFEST) observed better clinical activity with higher spleen volume reduction of >35% and total symptom burden reduction, both at week 24 compared with historical ruxolitinib phase 3 studies. Anemia, thrombocytopenia, and diarrhea were the principal side-effects and correlative studies observed pelabresib to decrease inflammatory cytokines, improving BM fibrosis and clinical responses to be independent of mutation status.[28] A randomized Phase III clinical trial of ruxolitinib with or without pelabresib (MANIFEST-2) for newly diagnosed MF patients is currently ongoing. Navitoclax (BCL-xL inhibitor) and parsaclisib (PI3Kδ inhibitor) have been tested as an add-on strategy with ruxolitinib in "suboptimal" ruxolitinib responders, with improvements in spleen and symptom responses in phase II studies.[29,30] Updates from alternative JAK2 inhibition studies, such as the telomerase inhibitor, imetelstat, also demonstrate efficacy and in a closely matched real world trial (MYF2001) of JAK2 inhibitor failure, a longer overall survival (OS) compared to best available therapy (30 vs. 12 months).[31]

1.2 | Novel approaches to treat *BCR-ABL1*-mutation induced resistance and improve TFR rates in CML

The CML success story unfolded over a relatively short period of time and treatment involves a choice of four first-line oral administered tyrosine-kinase-inhibitors (TKIs) that bind and inhibit the ABL1-kinase.[8] However, none of these drugs are perfect; only approximately 60% of patients remain on the standard doses of imatinib after 6 years due either lack of drug tolerance or drug resistance. To address intolerance or resistance, novel approaches to target BCR-ABL1-mutation-induced resistance are needed. Furthermore, at present only about 50% of patients who have maintained deep molecular responses can safely discontinue treatment without molecular relapse, referred to as "treatment-free remission" (TFR).[32] TFR is now a major goal of CML treatment and novel approaches will be needed to improve this. Currently, despite

TABLE 1 Selected investigational drugs in phase 3 clinical trials for MF

Investigational agent	Mechanism of action	Ongoing phase 3 clinical trials	Evaluated MF patients	Comparator agent	Clinical setting
Momelotinib	ACVR1/ALK2 JAK1/2 inhibitor	MOMENTUM (NCT04173494)	Symptomatic (TSS>10) Hb <10g/dl	Danazol	Second-line
Navitoclax (+ruxolitinib)	BCL-XL inhibitor	TRANSFORM-1 (NCT04472598)	Previously untreated with JAK2 inhibitors	Placebo (+ruxolitinib)	First-line
Navitoclax (+ruxolitinib)	BCL-XL inhibitor	TRANSFORM-2 (NCT04468984)	Refractory/resistant to JAK2 inhibitors	BAT*	Second-line
Pelabresib (+ruxolitinib)	BET inhibitor	MANIFEST-2 (NCT04603495)	Previously untreated with JAK2 inhibitors	Placebo (+ruxolitinib)	First-line
Luspatercept	Activin receptor ligand trap	INDEPENDENCE (NCT04717414)	Patients on stable dose of ruxolitinib who require transfusion for anemia	Placebo	Add-on to ruxolitinib
Parsaclisib	PI3Kδ inhibitor	LIMBER-304 (NCT04551053)	Patients with suboptimal response to ruxolitinib	Placebo	Add-on to ruxolitinib
Parsaclisib (+ruxolitinib)	PI3Kδ inhibitor	LIMBER-313 (NCT04551066)	Previously untreated with JAK2 inhibitors	Placebo (+ruxolitinib)	First-line
KRT-232	HDM2 inhibitor	BOREAS (NCT03662126)	Refractory/resistant to JAK2 inhibitors	BAT	Second-line
Imetelstat	Telomerase	IMpactMF (NCT04576156)	Refractory/resistant to JAK2 inhibitors	BAT	Second-line

Note: *BAT = best available therapy (may be specified in selected studies).

Source: Adapted, with permission, Chifotides HT, Verstovsek S. Clin Lymp Myeloma & Leukemia, SOHO 2021, Suppl, p S130.

dasatinib and nilotinib achieving deeper and faster molecular responses than imatinib, the rates of TFR are similar and there appears to be no OS benefit.[33–36]

One potential drug to address the twin challenges of TFR and intolerance/resistance is asciminib (previously ABL001). It is an allosteric inhibitor that binds to the N-terminal myristoyl binding site of ABL1 and was tested in a phase I study in CML patients after TKI failure.[37] The drug has now been explored in a randomized phase III study versus bosutinib in CML after 2 or more prior TKI and included patients with T315I mutated CML.[38] The cumulative incidence of major molecular response by week 24, the primary endpoint, was 25% with asciminib compared with 12% ($p = 0.029$) for bosutinib, and asciminib showed a rather favorable side-effect profile; the responses following asciminib treatment were not dissimilar to those observed in the phase I study. Asciminib was approved by the FDA on 29 October 2021 for patients with CML who have failed two or more previous TKIs.[38] As BCR-ABL1-dependent TKI resistance is often induced by mutations within the gene-fragment encoding for the ABL1 kinase domain, binding the myristoyl pocket located at a different site on the BCR-ABL1 protein, resulting in a conformational change that inhibits downstream signaling, is attractive. The drug is now being tested to assess if its earlier use might improve the kinetics and rate of deep responses and eventually, even more successful TFR rates with perhaps, less toxicity.

Many questions, however, remain and a current research focus is to assess the molecular heterogeneity and novel pathways that may affect CML stem cell maintenance and progression to leukemic transformation to identify novel and potentially targetable mechanisms. Studies are also exploring the impact of the immune system and BM microenvironment on TFR. There is preliminary evidence that CML stem cell-resistance is affected by proinflammatory cytokines, such as TNF, IL1 or IL6, and composition of specific cell types, for example, NK-cells, and IFNα may improve TFR maintenance.[39–42] Indeed, a phase I trial incorporating natural killer (K-NK003) cells for patients with CML and MRD after TKI therapy is currently ongoing.[43] Research is also assessing different TKIs being used sequentially or in combination with other drugs such as ruxoltinib or venetoclax (VEN), to target CML stem cells.[44–46] Additionally, activation of BTK has been shown to depend on the expression of the ITIM receptor Fc-γ receptor IIb (FcγRIIb, CD32b) and dual BCR-ABL1/BTK-targeting significantly enhanced apoptosis in TKI resistant non-proliferating CML stem cells[47] (Figure 1).

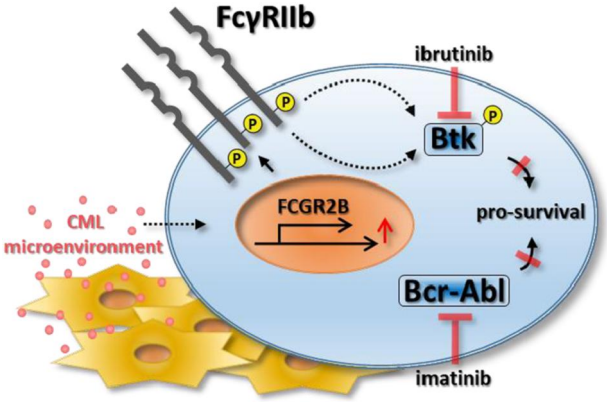

FIGURE 1 Elevated FcγRIIb expression in malignant cells persists despite BCR-ABL1 inhibition and this could be mediated via the proleukemic microenvironment. FcγRIIb-activity results in increased BTK expression and phosphorylation and dual targeting of BCR-ABL1 and BTK activity induces apoptosis in non-proliferating LSCs

1.3 | Artificial intelligence for the diagnosis and classification of MPN

Accurate diagnosis of the MPN and appropriate classification is crucial for optimal management, as treatment targets and the risk of progression differ among the MPN disorders. Diagnosis depends upon careful integration of clinical, genetic, and histological features and is enshrined in the revised 2016 World Health Organization classification scheme of myeloid malignancies.[48] Despite significant advances over recent years in genomic technologies relevant to diagnosis and disease monitoring in MPN, the key elements of morphological assessment remain largely unchanged.[49,50] Indeed, key morphologic features relating to marrow cellularity, megakaryocyte pleomorphism/atypia, and fibrosis are firmly embedded in current MPN classification schemes but remain subjective and largely qualitative. Inconsistencies in the interpretation of key morphologic features may lead to inaccurate diagnosis and disease classification, with multiple studies suggesting significant intra- and inter-observer variability among pathologists. Although this appears to be partly attributable to experience and training, the subjective and qualitative nature of routine BM biopsy reporting remains a fundamental limiting factor in any classification scheme incorporating morphology-based assessment of marrow tissue.

In response, several investigators demonstrate the utility of an automated machine-learning image analysis pipeline that uses image analysis/machine learning techniques to extract and interrogate important cytomorphological and topographic features of megakaryocytes from digitized images of BM biopsies (Figure 2).[50,51] This allowed them to differentiate reactive samples from common MPN subtypes and assisted in disease classification. Using the machine-learned features from extracted megakaryocytes we identified discrete cellular subtypes beyond the sensitivity of detection by specialist pathologists. These cellular subtypes were found to correlate with the underlying MPN driver mutation status. When combined with topographic assessment incorporating patterns of megakaryocyte distribution throughout the BM and cell clustering, the extracted features could be merged to produce a multidimensional representation of an individual sample well beyond conventional microscopic assessment. Critically, the rapid automated analysis of scanned and digitalized samples allowed index cases of MPN or reactive marrows to be reviewed and contextualized against libraries of previously analyzed samples. This approach enables the tracking of morphologic features over time, corresponding to either stable disease or progression. This work highlights the potential of image analysis, driven by

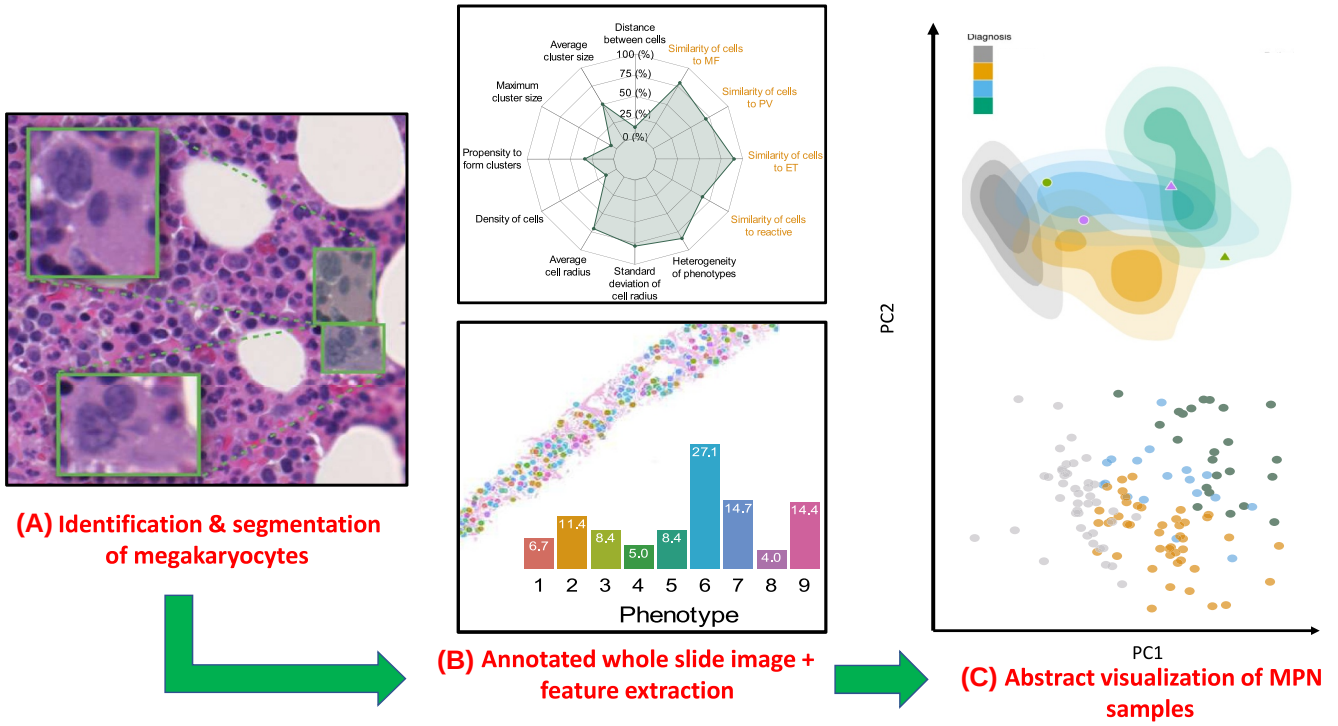

FIGURE 2 Overview of how digital pathology approaches were used to analyze megakaryocyte morphology and topography in myeloproliferative neoplasms (MPN). (A) An annotated megakaryocyte library of 37,284 validated (by a hematologist) reactive and MPN samples was established. (B) Clustering analysis identified megakaryocyte phenotypic and topographical profile. (C) The profile was used to create abstract representations in 2-dimensional space with new samples indexed to annotated disease cohorts

advanced machine learning approaches, to augment integrated diagnosis in MPN and correlate BM morphologic features with standard mutational and clinical data collected during the routine investigation of patients with MPN. Importantly, the automated extraction of objective quantitative data from routinely prepared hematoxylin & eosin-stained slides is ideally suited to future integration with the results of whole-tissue immunolabeling studies, advanced single-cell genomic analysis, and the outputs from high-resolution multiplexed tissue imaging performed in the research setting.

The importance and value of developing advanced, analytical strategies for capturing the complexity of marrow tissue architecture in MPN extends beyond the potential for improving diagnosis and classification using current diagnostic criteria. As the disrupted relationships between clonal and nonclonal hematopoietic cells and components of the BM stem cell niche are gradually unraveled, novel therapeutic strategies targeting the mediators of tumor cell survival and proliferation are beginning to emerge. Translating these findings to the clinic and validating novel therapies will require a concerted effort to move from the subjective and laborious description of tissue morphologic features by pathologists to more objective, quantitative descriptions of the BM environment. In addition to such promising future applications, these machine learning approaches offer more immediate potential benefits over current routine histological analysis. Indeed, a fully automated pipeline has the potential to provide a rapid initial diagnostic assessment of specimens in advance of formal specialized pathology reporting. This is of value where access to such expertise is restricted, particularly in low-resource health care systems where conventional pathology infrastructure is often lacking. In this regard, a November 2021 resume from Haferlach and colleagues, illustrates how artificial intelligence and machine learning algorithms are impacting hematopathology in general.[52] Their study demonstrated how neural networks outperform feature-based approach to BM cell classification in a data set comprising >170,000 microscopic images from almost 1000 patients.

1.4 | *TP53* mutations as molecular biomarkers in MPN

The *TP53* gene, often described as the "guardian of the genome", is the most frequently mutated gene in all cancers with variable implications in different tumor types.[53] In myeloid malignancies, *TP53* mutations are present in 5%–15% of cases and are almost universally adverse.[54,55] Despite being one of the first genes known to be somatically mutated in myeloid disorders, we only now have a more nuanced understanding of its pathologic mechanisms and clinical implications, including novel ways to target it. *TP53* mutations are associated with several adverse clinical features across myeloid disorders including highly disordered complex and monosomal karyotypes. In myelodysplastic syndromes (MDS), for example, mutant patients have increased BM blast counts and greater cytopenias compared to TP53-intact patients.[56] However, these adverse

features underestimate disease risk in *TP53* mutant patients as their outcomes are even poorer than their clinical prognosis would suggest. Cells with *TP53* mutations are relatively resistant to chemotherapy and often emerge as resistant clones in patients treated with novel agents including lenalidomide and venetoclax (VEN).[57] *TP53* mutant clones are also enriched in patients previously exposed to chemotherapeutic agents and increase the risk of developing therapy-related myeloid neoplasms.[58,59]

The pathogenic effects of *TP53* mutations in myeloid diseases are characterized by chromosomal genomic instability with increased likelihood of chromothripsis as well certain recurrent lesions including del(5q).[60] Patients do not appear to have a hypermutator phenotype and typically will have fewer somatically co-mutated genes than comparable TP53-intact patients.[56] These shared cytogenetic and point-mutation phenotypes, together with their clinical features, poor outcomes, and resistance to treatment, suggest that TP53-mutant myeloid disorders constitute a unique disease subtype.

However, not all who harbor a *TP53* mutation have poor outcomes. *TP53* mutations can occur in normal persons with clonal hematopoiesis of indeterminate potential as well as in diverse cancer patients who may have received cytotoxic therapies.[56,58,61] In these cases, *TP53* mutant clones are often of low abundance and can remain stable for many years without evidence of clonal or clinical progression. Bernard et al. examined a large MDS cohort of 3300 patients, identifying 394 with disruptions of *TP53* or its locus.[56] The study confirmed the dismal prognosis associated with *TP53* mutations in general. Yet, 125 patients were noted to have a single *TP53* mutation and no other abnormality affecting the *TP53* chromosomal locus on 17p (i.e., they retained a normal *TP53* allele) while the other *TP53* mutant patients either had a second *TP53* mutation or deletion of the remaining allele, or copy-number neutral loss of heterozygosity of the *TP53* locus, all of which result in no intact *TP53* allele remaining. Patients with multi-hit *TP53* abnormalities drove the poor prognosis of the group while those with a retained unmutated allele had an overall survival identical to that of *TP53* unmutated MDS patients. Biallelic disruption of *TP53* is similarly associated with blastic progression in MPNs.[62] However, the emergence of heterozygous *TP53* mutant clones is not necessarily adverse or associated with progression even when observed to expand in response to targeted therapy with MDM2 inhibiting nutlins.[63]

Since myeloid malignancy patients with *TP53* mutations have such poor outcomes, they represent a population in great need of novel effective therapies. Complex karyotype MDS and AML patients with *TP53* mutations may have high complete remission rates in response to hypomethylating agents. A study of a 10-day decitabine regimen had an impressive 100% response rate in two different patient cohorts.[64] While these patients relapsed quickly and had no overall survival advantage, they demonstrated transient clearance of their *TP53* mutant clone after 4 cycles of therapy. A strategy that quickly moves patients with mutation clearance into allogeneic stem cell transplantation might delay relapse and improve outcomes for these patients. Novel agents that target TP53 include eprenetapopt (APR-246), a small molecule that covalently binds cysteines in the TP53 core domain, thus stabilizing the active conformation of mutant TP53.[65] A phase Ib/II trial of this agent in combination with azacitidine in 55 patients with AML, MDS, and MDS/MPN demonstrated a 71% response rate with 44% achieving a complete remission (CR).[66,67] More than a third of patients went on to allogeneic transplantation with a median overall survival of over 14.7 months. However, a randomized phase 3 study of azacitidine +/− eprenetapopt was less impressive, achieving only a 30% CR rate compared to 20% in the control arm, falling short of the study's primary objective. Magrolimab, a monoclonal antibody directed against CD47, has also shown impressive activity in *TP53* mutant MDS and AML when combined with azacytidine.[68,69] In a Phase 1b study of this combination, overall response rates in the AML patients reached 64% with a complete remission/complete remission with incomplete hematologic recovery (CR/CRi) rate of 56%. In 12 patients with *TP53* mutant AML, the CR/CRi rate was 75%, indicating similar outcomes in this often refractory population. While magrolimab targets innate immune pathways, *TP53* mutant myeloid malignancies may be ideal targets for adaptive immunotherapy.[70] *TP53* mutant clones are not enriched in response to immunologic stress, potentially making them less resistant to immune attack.[71] Approaches that target neoantigens with adoptive T-cell transfer or dendritic cell vaccines, chimeric-antigen-receptor T-cells, and bispecific T-cell engagers are all in clinical studies and may prove to have greater benefit in this population with few therapeutic options and extremely poor outcomes. Figure 3 depicts a summary of *TP53* gene and potential treatment options.

1.5 | Clonal architecture and prognostic value of additional mutations in MPN

In *BCR-ABL1*-negative MPN, many genes involved in different cellular pathways can be mutated in addition to one of the three driver genes that are *JAK2*, *CALR* and *MPL*. In some MPN sub-types, such as those with splanchnic vein thrombosis, the presence of additional mutations, in particular the so-called “high risk mutations”, increase the risk of transformation to MF and affects OS.[72] They are now included in the prognostic scoring systems.[55] Marcault and colleagues recently demonstrated the impact of *NFE2* and *SF3B1* on the risk of leukemic transformation in a clinical cohort of 1250 MPN patients. *NFE2* is a key transcription factor for erythroid and megakaryocytic maturation and differentiation that is rarely found mutated in MPN patients.[73] In transgenic murine models, mutated or overexpressed *NFE2* is associated with an MPN phenotype. Importantly, mutant *NFE2* mice often acquired additional genetic abnormalities (trisomy 8, 5q deletions and TP53 mutations), favoring subsequent leukemic transformation.[74,75] The prognostic impact *SF3B1* was found to be similar, in particular risk of MF transformation.[76] An important clinical question raised by these observations is how these findings might influence future management of MPNs.

As illustration, IFNα has been tested in 383 adult MPN patients and following a median follow-up of 72 months, IFNα therapy could be safely stopped in those who achieved complete hematological

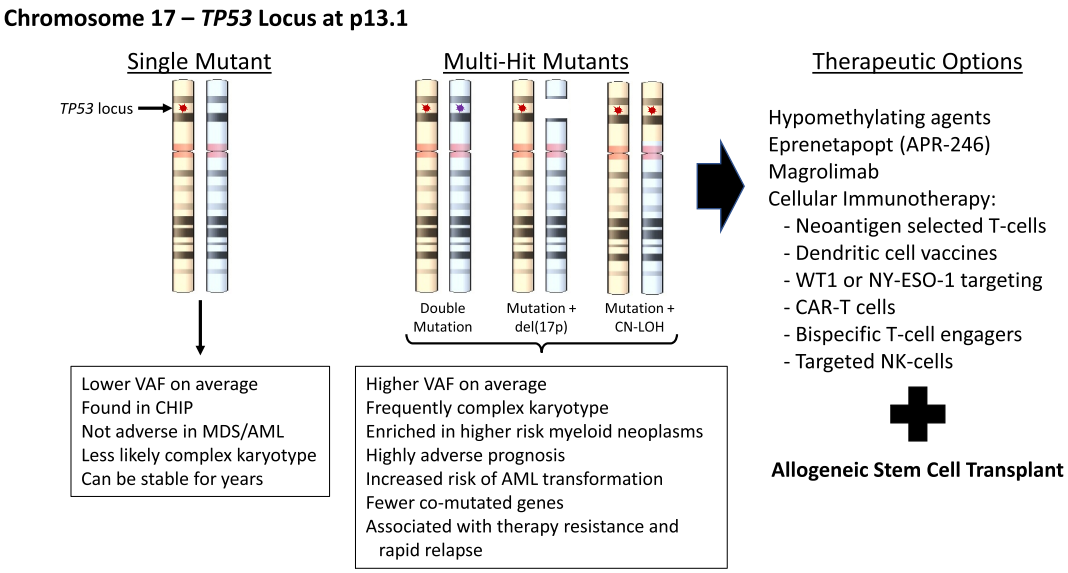

FIGURE 3 *TP53* Locus at p13.1 on chromosome 17 and potential therapeutic options

remission (CHR), without risk of vascular events or transformation to MF when the mutant allele burden was reduced below 10%.[77] In addition, these patients had approximately 50% chance of maintaining CHR without re-introduction of cytoreductive therapy, a proportion strikingly like that found in patients with CML in deep molecular response after TKI discontinuation. This is the first evidence showing a reduction of the mutant allele burden to 10% in BCR-ABL1-negative MPNs has a beneficial impact on the clinical evolution of the disease. In addition, these patients had approximately 50% chance of maintaining hematological complete response without re-introduction of any cytoreductive therapy. IFNα therapy has also been explored in childhood MPN and there is preliminary evidence confirming safety and efficacy, supporting the and provides clear rationale for further well-designed studies.[78,79]

1.6 | Paradigm shift in the treatment of advanced systemic mastocytosis

Systemic mastocytosis (SM) is a rare hematopoietic stem cell malignancy of mast cells, driven by activating *KIT* mutations, typically D816V, associated with infiltration of the BM and other organs with mast cells.[80] Whilst most patients with SM have an indolent course, patients with advanced SM (advSM), a term which comprises of variant aggressive SM, SM with an associated hematological disorder and mast cell leukemia, have poor prognosis with a decreased OS.[81] The introduction of the KIT inhibitors, midostaurin and avapritinib has improved the survival for patients with advSM.[82] A principal challenge has been the development of an agreeable treatment response criteria which captures the remarkable biological and clinical heterogeneity of the disease, including measures of mast cell burden (percentage of BM mast cells and serum tryptase level) and mast cell-related organ damage (referred to as C findings).[83] In this regard, work done by Valent, Gotlib and others, over the past two decades helped define the 2013 International Working Group-Myeloproliferative Neoplasms Research (IWG-MRT) and European Competence Network on Mastocytosis (IWG-MRT-ECNM) response criteria (Table 2).[84–86] More recently, to improve surrogate markers for OS, a "pure pathologic response (PPR)" criterion has been proposed.[87] PPR rely solely on measures of mast cell burden and exclude consideration of organ damage findings. This concept was tested in the recent avapritinib trials and discussed below. Patients with advSM often tend to be older, and have high mast cell burden, leukocytosis, anemia, thrombocytopenia, and the presence of high molecular risk mutations, such as *SRSF2*, *ASXL1*, *RUNX1*. The presence of ≥2 of these mutations have been found to be associated with inferior OS and the inclusion of molecular response in future response criteria.[88]

The multi-kinase inhibitor midostaurin was approved in 2017 by the FDA for the treatment of advSM based on phase II single arm study demonstrating an overall response rate (ORR) 60% and a median OS of 28.7 months.[89] Avapritinib (BLU-285), a selective inhibitor of *KIT* ^{D816V} and *PDGFRA* ^{D842V} was approved by the FDA on 16 June 2021 for the treatment of advSM.[90,91] This was based upon the ORR of 75%, by the "modified" IWG-MRT-ECNM criteria, and a robust reduction of mast cell and disease burden (serum tryptase, BM mast cells, *KIT* ^{D816V} allele fraction) in 53 efficacy-evaluable patients with mutant KIT advSM. The ORR was 83% in midostaurin-naïve and 59% in midostaurin-exposed patients and comprised of 36% CR/CR with partial hematologic recovery (CRh), 34% partial responses and 6% clinical improvement (Table 2). The median OS was 46.9 months, and the principal adverse events include periorbital edema, anemia, diarrhea, cognitive impairment, and fatigue; non-traumatic intracranial hemorrhage was also reported, particularly in patients with baseline platelets $<50 \times 10^9$/L. This study also supports the need for response criteria revisions aligned with precision medicine era. Indeed, when the PPR definition was adopted to analyze the phase I (EXPLORER) trial, the ORR was

TABLE 2 Definitions of response according to the modified IWG-MRT-ECNM criteria

Complete response with full (CR) or partial (CRh) hematologic recovery
• Bone marrow mast cell aggregates eliminated
• Serum tryptase <20 ng/ml
• Resolution of palpable hepatosplenomegaly
• Full (CR) or partial (CRh) hematologic recovery
• Full resolution of evaluable C findings
Partial response (PR)
• 50% reduction in bone marrow mast cells, serum tryptase
• Full resolution of >1 evaluable findings
Clinical Improvement (CI)
• Full resolution of >1 evaluable findings
Stable disease (SD)
• Not in a CR, CRh, PR, CI or PD
Progressive disease (PD)
• Worsening of evaluable C findings, or
• Progression to acute myeloid leukemia

Abbreviations: PD, Progressive disease; PR, Partial response, SD, Stable disease.

similar (77%), but the rate of CR/CRh improved from 36% to 47% (n = 53).[92] Importantly, an additional 11 patients were found to be evaluable by PPR criteria. Furthermore, landmark analyses starting after cycle 6 showed that PPR correlated significantly with survival, while the same could not be said of modified IWG-MRT-ECNM responses. The concept of PPR should help adjudicate responses in future clinical trials.[87]

1.7 | Novel insights into mechanisms of acquired treatment resistance in myeloid malignancies

In myeloid leukemias, including CML, chronic myelomonocytic leukemia (CMML), mast cell leukemia (MCL), and AML, leukemia stem cell (LSC) exhibit multiple forms of drug resistance, including primary stem cell resistance, niche-mediated LSC resistance, acquired (secondary) resistance and immune checkpoint-mediated resistance.[93] These forms of resistance act together to protect LSC from drug effects which is a major clinical challenge. In fact, overriding one form of LSC resistance alone may not be sufficient to develop curative (LSC-eradicating) treatment concepts. Therefore, current research is seeking novel broadly operative, multi-functional targets and target pathways that contribute to two or more form of LSC resistance. One of these pathways may be the BET-MYC axis.[94] In fact, MYC appears to be a BET-dependent, essential, trigger of LSC resistance in various leukemia models. Correspondingly, BET inhibitors can counteract niche-mediated resistance as well as acquired resistance in LSC in most myeloid neoplasms.[95] Moreover, BET inhibitors counteract IFN-γ and TNFα-mediated expression of the key checkpoint antigen PD-L1. However, LSC may also develop resistance against BET-targeting drugs, which is mostly due to re-activation of MYC expression through a Wnt-signaling pathway.[96] This form of resistance is difficult to break. However, recent data suggest that novel BET degraders, such as dBET6, are capable of suppressing growth of LSC and expression of PD-L1 independent of Wnt and other resistance mechanisms.[97] Another approach to overcome multiple forms of LSC resistance in myeloid leukemias, including LSC quiescence, is to apply targeted antibody-based drugs or CAR-T or CAR-NK cells.[98] Candidate targets expressed in excess on LSC over normal stem cells in most myeloid malignancies include, among others, CD25, CD33, CD123, CLL-1 and IL-1RAP. In CML and FLT3 ITD-mutated AML, LSC also express CD26 in an aberrant manner. However, most of these surface targets, including CD33 and CD123 are also displayed by normal stem cells thereby keeping the therapeutic window very small. Furthermore, the LSC fraction of a leukemia represents highly heterogeneous populations of cells, including subclones that may lack one or more of these target antigens. As a result, resistance may develop in subclones. Therefore, even antibody-based LSC-targeting therapies need to be combined with other anti-leukemic therapies such as stem cell transplantation, to achieve long-lasting remissions in patients.

Another area of interest of high clinical relevance is the resistance mechanisms that arise during treatment with VEN, a BCL2 inhibitor.[99] Treatment outcomes in adults with newly diagnosed AML who are not fit intensive chemotherapy have been transformed by the advent of VEN combination therapy.[100] Nonetheless, a substantial proportion of patients treated develop drug resistance. Molecular studies suggest the presence of FLT3, biallelic silencing TP53 and upregulation of MCL-1 to play a role in developing primary or acquired resistance to VEN.[101–103] Ex vivo drug screening and multivariate analysis of risk factors for resistance to VEN has revealed VEN resistance to leukemia cells with increased monocytic differentiation.[104] Out of 100 newly diagnosed AML patients who received VEN + azacitidine, 8/13 (62%) with increased monocytes [AML French-American British (FAB) subtype M5] were refractory, compared to 7/87 (8%) of non-FAB M5 patients.[105] In addition, this work showed that select patients who responded and then relapsed did so with enrichment in the monocytic population, present at diagnosis but expanded at relapse. The mechanism for VEN resistance in FAB M5 AML is of high interest. BCL-2 dependence in AML with monocytic differentiation is significantly lower than more primitive AML subsets; interestingly, in AML with monocytic differentiation, MCL-1 expression is higher, providing a potential therapeutic target for these patients. In addition, it has been shown that leukemic stem cells rely on amino-acid driven oxidative phosphorylation as their preferred metabolic fuel source, and that VEN with azacitidine specifically impairs this type of metabolism.[106,107] However, patients who are resistant to VEN may have a stem cell population that has more metabolic flexibility, and can for instance preferentially metabolize fatty acids to evade VEN-based regimens.[108] To the extent that this mechanism contributes to monocytic

AML's resistance to VEN, exploitation of this vulnerability may be a way to target this AML population. There is also interest in examining the potential synergistic effects of statins, such as pitivastatin, in combination with VEN in leukemias and leveraging the metabolic changes to help circumvent VEN resistance.[109]

1.8 | PARP1 inhibitor-induced synthetic lethality in myeloid malignancies

Oncogenic tyrosine kinases are found in diverse tumors including hematopoietic malignancies.[110] Skorski and colleagues have previously reported that OTK-positive malignant cells accumulate spontaneous and drug-induced DNA double-strand breaks (DSBs), but they survive because of enhanced/altered DNA repair activities.[111–114] Therefore, survival of OTK–positive cells depends on efficient DSB repair. Double-strand breaks, the most lethal DNA lesions, are repaired by two major mechanisms, homologous recombination (HR; major proteins: BRCA1, BRCA2, PALB2, RAD51B, RAD51C, RAD51D, XRCC2, XRCC3, RAD54, RAD51) and DNA-PK –mediated non-homologous end-joining (D-NHEJ; major proteins: DNA-PKcs, Ku70, Ku80, NHEJ1, Artemis, LIG4, XRCC4).[115] HR and D-NHEJ repair DSBs in proliferating cells, D-NHEJ plays a major role in quiescent cells, and PARP1 –dependent back-up NHEJ (B-NHEJ; major proteins: PARP1, LIG3) serves as back-up in both proliferating and quiescent cells.[116,117]

The success of the poly(ADP-ribose) PARP1 inhibitors in BRCA1/2-deficient breast and ovarian cancers established a proof-of-concept for personalized cancer therapy utilizing synthetic lethality and PARPi are now being tested in myeloid malignancies.[118,119] Skorski and colleagues have previously reported that inhibition of DNA repair mechanisms, which are essential for leukemia cell survival but expendable in normal cells, can trigger synthetic lethality selectively eliminating LSCs and leukemia progenitor cells (LPCs) while sparing normal cells.[120–123] Although BRCA1/2 mutations are rare in hematological malignancies, they discovered that OTKi-mediated inhibition of *FLT3*$^{ITD/TKD}$, *JAK2*^{V617F} and *BCR-ABL*1 induced BRCA/DNA-PK-deficiency [downregulation of key HR (BRCA1, BRCA2, PALB2 and/or RAD51) and D-NHEJ (LIG4) proteins associated with inhibition of HR and D-NHEJ activities] and sensitized proliferating and quiescent LSCs/LPCs to synthetic lethality triggered by PARPi.[124] However, their recent observations suggest that "additional" mutations accompanying the "driver" mutations can dramatically change the sensitivity of AML/MPN cells to OTKi + PARPi.[125] In addition, they observed that BM microenvironment (BMM) conditions provided significant protection for leukemia cells against synthetic lethal effect of OTKi + PARPi[126] (Figure 4). This effect depends on hypoxia-induced overexpression of transforming growth factor beta receptor (TGF-βR) kinase on malignant cells, which is activated by BM stromal cells - derived transforming growth factor beta 1 (TGF-β1). Inhibition of the TGF-βR kinase resulted in restoration of sensitivity of malignant cells to PARPi in BMM conditions and prolonged survival of leukemia-bearing mice. They speculate a therapeutic application of TGF-βR inhibitor in patients receiving PARP inhibitors.

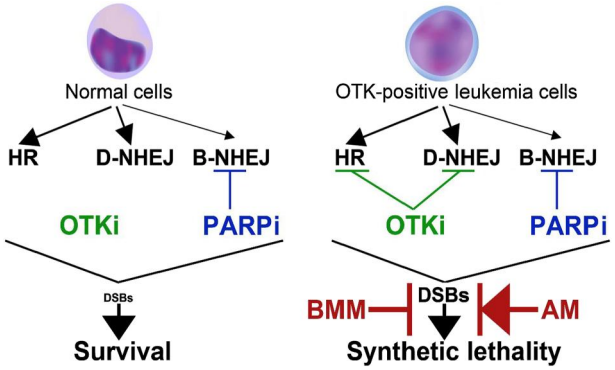

FIGURE 4 Conceptual principles of OTKi + PARPi mediated synthetic lethality

1.9 | Hypoxia inducible factors (HIF), thrombosis, and phlebotomies in PV and ET

Arterial and venous thromboses are the major causes of morbidity and mortality in polycythemia vera (PV) and ET. However, the molecular mechanism of thrombosis in MPN is largely unknown. In multivariate analyses, the leukocyte count independently correlates with the risk of thrombosis.[127] The earlier work of Prchal's laboratory demonstrated that HIF-1 and HIF-2, which are upregulated in both granulocytes and platelets in PV and ET, promote the transcription of prothrombotic and proinflammatory genes.[128] Leukocytes are the only source of tissue factor (TF) in the blood, and PV neutrophils constitutively express TF activity[129]

In Chuvash erythrocytosis/polycythemia (CE), a congenital disorder associated with increased HIF-1 and HIF-2 due to a hypomorphic R200W mutation of the Von Hippel-Lindau gene, the incidence of thrombosis is higher than in PV and phlebotomy did not prevent thrombosis but instead facilitated it.[130] Repeated phlebotomies induced iron deficiency (ID) which further increased the level of HIF-1 and HIF-2 by inhibiting the negative regulator of HIFs, prolyl hydroxylase domain 2 enzyme, which requires iron as a co-factor. Therefore, these authors hypothesized that the up-regulation of Hypoxia inducible factors (HIF) signaling in granulocytes and platelets, perhaps with an additional contribution of augmented inflammation, plays a central role in the development of thrombosis in PV and ET. In a pivotal study, Prchal and colleagues quantitated mRNA of these HIF-regulated prothrombotic genes: *THBS1*, *SERPINE1*, *ITGA2B*, *PTGS2*, *SELP*, *PDGFA*, and *ITGB3*.[131,132] They analyzed granulocytes from 16 CE subjects (8 iron deficient) and platelets from 12 CE subjects (7 iron deficient). In platelets, *THBS1*, *SELP*, *SERPINE1*, and *PDGFA* mRNA levels were higher in iron deficient CE subjects than those with normal ferritin ($p = 0.015$-0.088). In all CE subjects, the mRNA levels of these four genes correlated inversely with ferritin. *PTGS2* (known to be down regulated in thrombosis) was down regulated in iron deficient CE patients and its expression showed a positive correlation with ferritin. *ITGB3* and *ITGA2B* mRNA levels were not different between the two groups. In granulocytes, *SELP* mRNA was augmented in CE patients with ID and both *SELP* and *ITGB3* mRNA levels correlated inversely with ferritin.

They then tested the hypothesis of augmentation of thrombosis risk by ID in granulocytes from 50 PV and ET patients (9 with ID) and in platelets from 41 patients (5 with ID). *THBS1*, *SELP*, and *IRAK1* mRNA levels were higher in patients with ID, and *IRAK1*, *THBS1*, and *SERPINE1* mRNA levels correlated inversely with ferritin. In platelets, *THBS1*, and *SERPINE1* mRNA were higher in patients with ID and *SELP*, *THBS1*, and *SERPINE1* mRNA levels correlated inversely with ferritin. *JAK2*^{V617F} allele burden also correlated inversely with ferritin. In sum, the study demonstrates that ID is associated with increased expression of HIF-regulated prothrombotic genes in CE platelets and granulocytes in a pattern that differs between these two cell types. The study also observed an increased expression of prothrombotic genes in PV and ET patients with ID. Collectively, these results underline the potential peril of phlebotomies in attempts to control high hematocrit and caution against indiscriminate use of therapeutic phlebotomies for treatment of patients with PV and other forms of erythrocytosis.[133]

2 | SUMMARY

The lessons learned from recent advances in the biology and treatment of patients with MPN pays tribute to the vital insights of the work of those who went before us. We still need to understand how best to selectively ablate the MPN clone, in both BCR-ABL1-positive and negative MPN. The clinical outcomes for patients with CML have undoubtedly improved since the development of oral TKI targeting the ATP binding site of the BCR-ABL1 oncoprotein. The majority of CML patients achieve durable major molecular response with a lifespan approaching that of the general population. The recent approval of asciminib, a small molecule which binds to the myristoyl pocket located at a different site on the BCR-ABL1 protein, looks to improve the outlook further by improving TFR with less toxicity. Ascertaining how best to harness the immune system and develop effective immunotherapies in tandem with better JAK inhibitors and other novel agents, holds promise for a personalized treatment approach for childhood and adult MPN. For patients with AdvSM, the recent approval of avapritinib augments current therapeutic choices. These advances underscore the increasing utility of single cell methodologies and modern DNA sequencing methods not only to help identify new potential targets, but also for improvement in diagnosis, prognosis, and applications in disease monitoring. In this regard the recent insights into the mutant *TP53* and *NFE2* story, the modulation of PARP inhibitor-induced synthetic lethality, and the cautionary recommendations against indiscriminate use of therapeutic phlebotomies in PV are important. Finally, as artificial intelligence-based morphological tools for assessing disease in MPN are entering the clinics apace and we need to support these efforts in low-resource health care systems.

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AUTHOR CONTRIBUTIONS

Tariq I. Mughal, Giuseppe Saglio and Richard A. van Etten designed the outline strategy of the manuscript, analyzed and interpreted data, wrote the draft version without any writing assistance provided by a third party. All authors participated in writing significant sections of the paper and all approved the final version of the manuscript.

CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

All references in Google Scholar.

PEER REVIEW

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