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MYELOPROLIFERATIVE NEOPLASMS (B STEIN, SECTION EDITOR)

Novel Therapies in Myeloproliferative Neoplasms (MPN): Beyond JAK Inhibitors

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Abstract

Purpose of Review With increased understanding of the pathobiology of myeloproliferative neoplasms (MPNs), multiple new agents are now being investigated. We aim to cover some of the current treatment options for MPNs and discuss new agents in development.

Recent Findings The introduction of ruxolitinib improved the treatment of many patients with intermediate and higher risk myelofibrosis. However, ruxolitinib monotherapy does not benefit all patients, and not all patients can receive this therapy due to limiting cytopenias. The unraveling of new molecular abnormalities and cellular pathways led to the development of several novel targeted agents that are currently under investigation in clinical trials. These agents have different mechanisms of action and are being used either alone or in combination with ruxolitinib.

Summary Novel targets include inhibition of apoptosis, the tumor microenvironment, telomerase enzyme action, immunotherapy, and fibrosis with associated cytokines. We comprehensively review and summarize the available preclinical and clinical trials with novel agents for MPNs.

Keywords Ruxolitinib · Myeloproliferative neoplasms · Novel therapies · JAK inhibitors · Novel drugs

Introduction

The myeloproliferative neoplasms (MPNs) primary myelofibrosis (MF), essential thrombocythemia (ET), polycythemia vera (PV), and chronic myeloid leukemia (CML) were first recognized at the end of the nineteenth century. Dr. William Dameshek was the first one to interconnect these disorders identifying them as variable manifestations of proliferative activity of the bone marrow cells [1]. Landmark genetic aberrations identified in the clonal proliferation of elements of the myeloid lineage were later introduced and helped classify these disorders as MPNs. These aberrations include the BCR-ABL1 gene rearrangement in Philadelphia chromosome-positive CML and JAK2 and later MPL and CALR mutations in Philadelphia chromosome-negative MPNs [2–8]. These driver mutations in turn lead to increased JAK2 signaling and thus an overactive JAK-STAT pathway resulting in uncontrolled myeloproliferation and excessively high levels of pro-inflammatory cytokines. [9]

As a result, JAK inhibiting strategies emerged as a promising concept soon after the discovery of JAK2 V617F point mutation in 2005. The first JAK1/2 pathway inhibitor is ruxolitinib which was approved for patients with MF in 2011 and hydroxyurea-resistant or intolerant PV in 2014 based on the results of phase 3 trials [10–12]. Despite the reduction of MPN-associated symptoms and splenomegaly with ruxolitinib, there is still question regarding if this agent is truly disease modifying [13]. Another area of debate is whether ruxolitinib should be used earlier in the treatment course of other MPNs (such as in frontline PV) and what the role of this medication is in adolescents and young adults, who

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are typically underrepresented in the majority of our studies in the MPN field [14, 15]. Finally, JAK inhibitors are currently being rationally combined with other targeted agents on the basis of potential synergism.

In this paper, we will review the current therapies, those under investigation and the role of medications beyond JAK2 inhibitors in the treatment of MPNs. We will primarily focus on patients with MF.

JAK Inhibition Targeted Therapy

MF

The JAK1/JAK2 inhibitor ruxolitinib was the first targeted FDA-approved medication for MF. It was evaluated in the COMFORT-I and COMFORT-II studies and showed significant improvement in symptom burden including reduction in spleen size [10, 16]. In some cases, long-term therapy with ruxolitinib may lead to decrease of bone marrow fibrosis and may gradually decrease mutant allele burden [13, 17]. Treatment success and durability can be affected by the presence of adverse prognostic mutations at presentation [18].

Treatment initiation is based on risk stratification. For patients with high and intermediate risk disease, ruxolitinib can be initiated [19–21]. The optimal timing of ruxolitinib initiation has yet to be identified, and most of the data come from retrospective studies. Lower treatment response rates were reported in a large retrospective cohort of patients with high-risk disease and delay in ruxolitinib initiation [22]. This could suggest starting ruxolitinib earlier in the disease course, as conveyed by the National Comprehensive Cancer Network guidelines that advocate for the use of ruxolitinib in low-risk MF patients with troublesome symptoms [23]. Prospective studies of earlier ruxolitinib use are currently underway [19, 21].

JAK Inhibitors in Combination Therapies

There has been long-lasting interest in using JAK inhibitors in combination with conventional agents. Given some of the clinical limitations of initiating ruxolitinib or maintaining response, finding the optimal drug combination has been a sought after approach. This is especially true in patients with MF where survival can be short and several combination trials are currently underway. These trials are depicted in Table 1.

Novel Therapies in MPNs: Moving Beyond JAK2

Outcomes in patients with relapsed/refractory MF after ruxolitinib are generally poor with survival approximately 14 months [24, 25]. In addition, for patients with intermediate-2 or high-risk MF no standard therapy exists after JAK inhibitor (JAKi) failure. In the setting of thrombocytopenia, it is, in many cases, contraindicated to administer JAKi and low platelet number is a poor prognostic factor. Multiple new agents have recently come in the picture trying to address these needs. These agents have different mechanisms of action and are in differing stages of development. Table 2 depicts new agents that are being studied as monotherapy in MPNs.

Promotion of Apoptosis

An emerging concept in MPN pathobiology is the finding of increased levels of tumor necrosis factor alpha (TNFα) [26]. TNFα is increased in MF and promotes survival of malignant over normal cells [27, 28]. Second mitochondria-derived activator of caspases (SMAC) mimetics or inhibitors of apoptosis (IAP) antagonists lead to increased apoptotic cancer cell death especially in tumor models with high TNFα expression [29, 30]. Antagonism of IAP proteins by SMAC occurs via binding of the N-terminal tetrapeptide (AVPI) of SMAC to selected domains of the IAPs. Small molecule compounds that mimic the AVPI motif of SMAC have been designed to overcome IAP-mediated apoptosis resistance of cancer cells [31].

Targeting of the IAP family has been investigated previously in AML [32]. In this study, the authors tested an X-chromosome–linked inhibitor of apoptosis (XIAP) antisense oligonucleotide (AEG35156), in combination with idarubicin for relapsed/refractory AML. At highest doses, AEG35156 knocked down XIAP and 47% of patients (15/32) achieved complete remission. Another compound from the same family has been tested in MDS: birinapant which is an IV SMAC mimetic and was added to azacitidine in patients with MDS (NCT02147873).

LCL-161 is a small oral molecule SMAC mimetic that inhibits multiple IAP family proteins by binding to several proteins and triggering caspase and cytokine-mediated apoptotic cell death [33]. This agent is currently being studied in a phase II study from our group in patients with primary, post-PV or post-ET MF (NCT02098161). Primary outcome is to determine the efficacy and objective response rate (ORR) of LCL-161 monotherapy in these patients. Secondary objectives include safety, time to response, response duration, and symptom burden. Preliminary results from 44 patients enrolled show approximately 30% ORR defined as complete remission (CR) + partial remission (PR) + clinical improvement. Median overall survival has not yet been reached. Most common adverse events were nausea (77%), fatigue (52%), and dizziness/vertigo (32%). Seventeen patients (39%) had dose reductions, and the most common cause of dose reduction was grade 2 fatigue [34••].

Another class of agents that works by inhibiting apoptosis, is the BCL-xL inhibitors. Navitoclax is a high-affinity small molecule that is orally available and inhibits the anti-apoptotic activity of BCL-X_L [35]. As listed in Table 1, navitoclax is

Table 1 Current clinical trials involving ruxolitinib combinations

Agent	Mechanism of action	Eligible patients	Phase	NCT	Primary outcome
Azacitidine	Antimetabolite	MDS/MPN regardless of prior treatment	II	NCT01787487	Best ORR
PU-H71	HSP-90i	MF receiving ruxolitinib for more than 3 months		NCT03935555	Safety, tolerability
Navitoclax	BCL-X_Li	MF patients who have received ruxolitinib for at least 12 weeks	II	NCT03222609	Change in spleen volume
TGR-1202	PI3Kδi	MF. Either previously treated or naïve	I	NCT02493530	Safety
Parsaclisib	PI3Kδi	MF, spleen > 10 cm	II	NCT02718300	Safety
Pomalidomide	Immunomodulator	MPN, spleen > 11 cm and/or leukoerythroblastosis	Ib/II	NCT01644110	Best ORR
Thalidomide	Immunomodulator	Intermediate/high risk if untreated, or previously treated MF	II	NCT03069326	Best ORR
Panobinostat	HDACi	MF, spleen > 5 cm. Either previously treated or naive	Ib	NCT01433445	Safety
PIM447	CDK4/6i	JAK2V617F positive MF	Ib	NCT02370706	Safety
Itacitinib	JAKi	MF, spleen > 5 cm, on ruxolitinib less than 20 mg (cohort A), with progression in the spleen (cohort B)	II	NCT03144687	Change in spleen volume
Pevonedistat	NAEi	Intermediate/high-risk MF, on treatment with ruxolitinib > 3 months	I	NCT03386214	Safety
Sotatercept	TGFβi	MPN-associated MF, anemic patient	II	NCT01712308	Anemia response
Luspatercept	TGFβi	MPN-associated MF, anemic patient	II	NCT03194542	Anemia response
Peg-interferon alpha-2a	–	Intermediate/high risk MF, need for active therapy	I/II	NCT02742324	Efficacy/safety

BCL-X_Li B cell lymphoma extra-large inhibitor, *CDK4/6* cyclin-dependent kinase 4/6, *HDACi* histone deacetylase inhibitor, *HSP-90i* heat shock protein 90 inhibitor, *JAKi* janus kinase inhibitor, *NAEi* NEDD8-activating enzyme inhibitor, *ORR* objective response rate, *PI3Kδi* phosphatidylinositol 3-kinase δ inhibitor, *TGFβi* transcription growth factor β inhibitor

Table 2 Active clinical trials involving new agents being used as monotherapy in MPNs

Agent	Mechanism of action	Eligible patients	Phase	NCT	Primary outcome
LCL-161	SMAC mimetic/IAPi	Intermediate-1 risk or higher, spleen > 5 cm	II	NCT02098161	ORR
SL-401	CD123 inhibitor	High-risk MPN	I/II	NCT03222609	MTD, safety
IMG-7289	LSD1 inhibitor	Intermediate-2 risk or higher MF	IIb	NCT03136185	Safety
Selinexor	XPO1 inhibitor	MF or ET intolerant to JAKi	II	NCT03627403	Reduction in spleen volume
Idasanutlin	MDM2 inhibitor	HU resistant/intolerant PV	II	NCT03287245	Hematocrit control
Idasanutlin	MDM2 inhibitor	HU resistant/intolerant ET and MF without prior JAK2i	I	NCT02407080	DLT
KRT-232	MDM2 inhibitor	Phlebotomy-dependent PV	II	NCT03669965	Reduction in spleen volume + phlebotomy independence
KRT-232	MDM2 inhibitor	MF with JAK2i failure	II	NCT03662126	Spleen response
PRM-151	Pentraxin-2 inhibitor	MF with grade 2 marrow fibrosis, not candidates for RUX	II	NCT01981850	Bone marrow response rate
Alisertib	Aurora Kinase A inhibitor	MF or R/R AML	II	NCT02530619	Safety
Sotatercept	TGF-β inhibitor	MPN-associated MF with anemia	II	NCT01712308	Anemia response
Luspatercept	TGF-β inhibitor	MPN-associated MF with anemia	II	NCT03194542	Anemia response
AVID200	TGF-β inhibitor	Intermediate-2 risk or higher MF	I/Ib	NCT03895112	MTD
Imetelstat	Telomerase inhibitor	Intermediate-2 or higher risk MF, previously JAKi	II	NCT02426086	Spleen volume reduction, total symptom score
CPI-0610	BET protein inhibitor	Intermediate-1 risk or higher MF	II	NCT02158858	Spleen reduction, rbc transfusion independence

allo-SCT allogeneic stem cell transplantation, *BET* bromodomain and extraterminal; *CTLA4* cytotoxic T lymphocyte-associated protein 4, *DLT* dose-limiting toxicity, *HU* hydroxyurea, *IAP* inhibition of apoptosis antagonists, *JAK2i* janus kinase 2 inhibitor, *LSD1* lysine-specific demethylase 1, *MPN*, myeloproliferative neoplasms, *MTD* maximum tolerated dose, *PS* performance status, *RBC* red blood cells, *RUX* ruxolitinib, *SMAC* Second mitochondria-derived activator of caspases; *TGF-β* transforming growth factor-beta, *XPO1* exportin 1

currently being evaluated in a phase II trial in combination with ruxolitinib for patients with MF (NCT03222609). Primary outcome will include the reduction of splenic volume from baseline.

Lysin-specific demethylase 1A (LSD1) is a demethylase that was identified in 2004 [36] and works by removing methyl groups from histone 3 protein and thereby increasing transcriptional activation. LSD1 has been implicated in the promotion of several cancers including breast, prostate, and AML [37–39]. IMG-7289 is a first-in-class orally available irreversible inhibitor of LSD1 that enhances methylation of histone 3 protein and increases the expression of tumor suppression genes. IMG-7289 will be studied in a phase II study in patients with MF (NCT03136185).

Finally, exportin 1 (XPO1) is a protein responsible for the nuclear export of tumor suppressor proteins (TSPs) [40]. In many cancers, XPO1 is overexpressed, which leads to increased transport of TSPs outside of the nucleus and thus allowing cancer cells to evade genome surveillance and cell-cycle regulation [41, 42]. Selinexor is the first in class XPO1 inhibitor that forces nuclear retention and functional activation of TSPs. Selinexor is currently being studied in patients with MF or ET who are intolerant to JAK inhibitors (NCT03627403).

Targeting Hematopoietic Stem Cell/Micro-environment

CD123 or interleukin-3 receptor is a membrane biomarker that is frequently expressed by various cellular components of hematologic malignancies including leukemias, MPNs, and MDS [43]. In MF, monocytosis is associated with an accelerated disease phase and poor prognosis [44]. Monocytes share a common precursor with plasmacytoid dendritic cells (high expresser of CD123) and express CD123 themselves. Monocytosis in MF is similar to that seen in chronic myelomonocytic leukemia (CMML) but does not lead to disease reclassification. In some cases, morphological and molecular (e.g., ASXL1, TET2, SRSF2 mutations) characteristics overlapping MF and CMML are observed. Such cases most likely represent primary MF with monocytosis, dysplasia, and secondary (non-driver) mutations at presentation. As such, innovative therapeutic approaches may be required in this poor-prognosis patient subset. SL-401 (tagraxofusp) is a novel targeted therapy that is comprised of recombinant IL-3 genetically fused to a truncated diphtheria toxin payload, directed to CD123 [45]. Tagraxofusp was recently approved by FDA for patients with another hematologic malignancy, blastic plasmacytoid dendritic neoplasm, a disease which is noted to have particularly high expression of CD123 [46]. This agent is being studied in a multicenter phase I/II study as monotherapy for patients with high-risk MPNs including myelofibrosis and CMML (NCT02268253). Primary outcome of the Ph I/safety portion of the study is the maximum tolerated dose, and for the Ph II portion (ongoing) is efficacy. Preliminary results from 19 patients showed that this agent was fairly well tolerated with primary adverse events being headache and hypoalbuminemia (22% each). All of the patients thus far (100%) with monocytosis at baseline and spleen size > 5 cm had reduction in baseline splenomegaly [47].

Heat shock protein-90 (Hsp90) is a chaperone protein that stabilizes other proteins against heat stress and aids in protein degradation [48]. Hsp90 is found both in normal and cancer cells but thought to be more important in cancer cells [49]. PU-H71 is an Hsp90 inhibitor that is new trial is assessing the safety and tolerability of oral PU-H71 in patients already taking ruxolitinib (NCT03935555).

Histone deacetylase inhibitors (HDACi) have been implicated in MPNs due to the downregulation of JAK2. This is possible through interference with the chaperone function of HSP90 (through acetylation) [50]. As shown in Table 1, there are ongoing trials evaluating ruxolitinib in combination with HDACi. These trials are based on the demonstration of synergism between the 2 drug classes [51].

Modulation of TP53 Pathway

The p53 tumor suppressor is a principal mediator of growth arrest and apoptosis in response to multiple cellular insults [52]. In normal cells, p53 is an unstable protein due to continuous degradation mediated by MDM2 [52]. During stress and oncogene activation, p53 stabilizes via block of its degradation. During the past 20 years, MDM2 has emerged as a principal cellular antagonist of p53 by limiting the p53 tumor suppressor function [53]. Idasanutlin is an MDM2 antagonist that has shown clinical activity in acute leukemias [54]. Idasanutlin is being studied as monotherapy in phase II, single-arm study in patients with hydoxyurea-resistant/intolerant PV (NCT03287245). It also being studied for patients with PV and ET in phase I study (NCT02407080). Preliminary results from 13 patients showed that the overall response rate was 78% (7 out of 9 evaluable patients). It was well tolerated with no dose-limiting toxicity yet identified. Another MDM2-targeted agent (KRT-232) is being compared in phase II study to ruxolitinib in patients with phlebotomy-dependent PV (NCT03669965). Primary outcome of this study will be to the proportion of patients with splenomegaly who achieve both phlebotomy independence and reduction in spleen volume at week 32. Finally, KRT-232 is being studied in patients with MF who have previously failed a JAK inhibitor (NCT03662126). This phase II study will have a primary outcome to determine the spleen response.

Targeting Fibrosis and Associated Cytokines

A defining feature of MF is progressive bone marrow fibrosis and higher-grade marrow fibrosis is associated with poor

prognosis [55, 56]. Treatment with JAKi usually does not reverse marrow fibrosis or reverse the disease [57]. Bone marrow fibrosis in MF is thought to be reactive, secondary to growth factor production by clonal megakaryocytes [58]. Treatment with the fibrocyte inhibitor serum amyloid P (SAP; pentraxin-2) significantly prolonged survival and slowed the development of marrow fibrosis in mice models [59].

Pentraxin-2 is an endogenous human protein that acts at sites of tissue damage, including macrophage differentiation to prevent and reverse fibrosis [60]. PRM-151 is a recombinant form of SAP (pentraxin-2) that is currently being evaluated in a phase II trial in patients with MF (NCT01981850). Primary outcome of this study will be the bone marrow response rate defined as the reduction in bone marrow fibrosis score by at least one grade according to WHO criteria. Preliminary results showed that PRM-151 had durable safety and efficacy at 72 weeks. Of 13, patients evaluated, 7 (53%) had morphologic bone marrow response. Most common adverse events included fatigue (31%), nausea, and fever (23% each).

Anemia in MF

Anemia is very common in MPN-associated MF and is frequently worsened by ruxolitinib therapy. Transcription growth factor-beta (TGF-β) has been implicated in the fibrotic phase of MF [61]. Sotatercept is a first-in-class, activin receptor IIA ligand trap that improves anemia by sequestering TGF-β ligands secreted by bone marrow stromal cells (especially GDF11) and improving erythroid differentiation [62, 63]. Sotatercept improves erythropoiesis in preclinical models of β-thalassemia, Diamond Blackfan anemia and in hepcidin transgenic mice [64–66]. There is an ongoing study of sotatercept in patients with MPN-associated MF and anemia (NCT01712308). Primary outcome of this phase II study will be the anemia response. Interim results showed anemia response n 36% of evaluable patients (5/14). Luspatercept is another investigational erythroid maturation agent that works by neutralizing select TGF-β superfamily ligands and enhance late-stage erythropoiesis in MDS models [67]. In a phase II study of patients with low-risk MDS, luspatercept yielded a high frequency of transfusion reduction and was well tolerated [68]. There is an ongoing phase II multicenter clinical trial investigating luspatercept in patients with MPN-associated MF who have anemia (NCT03194542). Primary outcome will be anemia response as defined by increase in hemoglobin and decrease in red blood cell transfusion requirement. In patients with MDS with ring sideroblasts, luspatercept was found to increase the duration of red blood cell transfusion-independence in a phase III trial when compared with placebo [69•].

Finally, AVID200 is an engineered TGF-β inhibitor that is hypothesized to decrease the fibrogenic stimuli leading to MF. It is being studied in phase I/Ib study in patients with intermediate-2 risk or higher MF (NCT03895112).

Aurora Kinase Inhibition

Finally, the selective aurora kinase-alpha inhibitor, alisertib has disease-modifying activity in murine models of myelofibrosis by eradicating atypical megakaryocytes and thus resulting in reduction of marrow fibrosis [70]. Alisertib was recently studied in phase II clinical trial for patients with MF or relapsed/refractory acute megakaryoblastic leukemia [71]. Alisertib was well tolerated and reduced splenomegaly and symptom burden in 29% and 32% of patients respectively. In addition, it normalized megakaryocytes and reduced fibrosis in 5 of 7 patients for whom sequential marrows were available [71].

Telomerase Inhibition

Telomerase is a ribonuclear protein complex that is transiently activated in stem and progenitor cells but inactive in mature somatic cells. It has been shown to be activated in most cancer cells regardless of tumor type [72]. Imetelstat is a first-in-class potent competitive inhibitor of telomerase with a long half-life that binds the RNA component of telomerase. It inhibits proliferation and induces apoptosis of cancer stem cells. It has been studied in multiple settings including solid and hematologic malignancies [73, 74]. Although it was found to have modest clinical activity, phase II studies showed that imetelstat can produce molecular responses in patients with ET who are intolerant to prior therapies [75]. In addition, there were complete remissions noted with imetelstat in a pilot study in patients with MF [76]. Based on the above, it is hypothesized that imetelstat has disease-modifying activity and is currently being evaluated in phase II study for patients with intermediate-2 or higher risk MF that were previously treated with JAKi (NCT02426086). Primary outcome of the study is reduction in spleen volume and reduction in total symptom score. Preliminary results show that median survival was 19.9 months with 4.7 mg/kg dose and 29.9 months with 9.4 mg/kg dose.

Bromodomain and Extraterminal Protein Inhibition

BET (bromodomain and extraterminal) family of proteins are chromatin reader proteins [77]. One of their purported mechanisms of action includes that ability to recruit chromatin-modifying enzymes and to stimulate the mRNA transcript elongation of promoters of oncogenes, especially c-Myc, BCL-xL, PIM1, and CDK4/6 [78–81]. Several BET protein inhibitors have been developed, including OTX015 and GSK525762 [82, 83]. BET protein inhibitors are hypothesized to inhibit in vivo and in vitro growth of primary AML cells [84, 85]. Recently, it was also shown that in patients who develop secondary AML post-MPN, BET protein inhibitor combinations may be active in pre-clinical models [86]. Co-treatment with BET inhibitor and HSP90 inhibitor was synergistically lethal against ruxolitinib-persistent secondary AML

cells [86]. Finally, co-treatment of BET protein inhibitor and the BCL2 inhibitor venetoclax was significantly more effective in reducing AML cell-burden compared with either treatment alone in patients with AML [87•]. The BET protein inhibitor CPI-0610 is currently being studied with and without ruxolitinib in patients with MF (NCT02158858). In this phase II study, primary endpoints will include spleen size response and red blood cell transfusion independence rate.

Future Directions

The improved understanding over time of the molecular pathobiology of MPNs has led to the development of multiple investigational targeted therapies in the past several years. With the increasing availability of reliable biological profiling techniques, we might be able to identify specific sub-groups of patients that might benefit from targeted therapies.

There is a growing body of evidence suggesting that clinicians should focus, in addition to reducing burden of splenomegaly and bone marrow disease, on the quality of life and fatigue, amelioration of anemia in MF, and possibly decreasing thrombotic risk, in our patients with MPNs. It is notable, as is commonly seen in many rare diseases, that there is a striking mismatch between physician perception and patient's priority for management in a recent landmark study [88]. Patient care can thus be improved with improved patient-physician communication, and possibly through the development of novel therapies, either as monotherapy or in combination with JAK inhibitors that may focus on differing aspects of MPN disease burden, separate from the JAK inhibitor class of therapies.

Ruxolitinib was the first targeted therapy approved for treatment of patients with MPNs and has revolutionized the management of our patients. Notably, some of the patients present with thrombocytopenia and are not candidates for ruxolitinib treatment. Newer medications with different mechanism of action outside of the JAK/STAT pathway are therefore needed. To this end, multiple agents have been introduced into clinical trials at various stages of clinical development.

Despite all of the challenges, there has been some progress in the investigation and development of novel therapies beyond JAK inhibition in the MPN field. The clinical heterogeneity of MPNs necessitates a deeper understanding of the molecular features of the disease in order to individualize treatment and improve outcomes.

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Compliance with Ethical Standards

Conflict of Interest Minas P. Economides declares no conflict of interest.

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- • Of importance
- •• Of major importance

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