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Clinical end points for drug treatment trials in BCR-ABL1-negative classic myeloproliferative neoplasms: consensus statements from European LeukemiaNET (ELN) and Internation Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT)

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AUTHOR CONTRIBUTIONS

GB, AT and TB designed the project; GB wrote a preliminary version of the paper; AT, TB, CB, G Birgegard, FC, GF, HG, MG, CH, RH, SH, JJK, NK, RM, MCM, AP, FP, JS, AMV, AR, RTS, SV and GT discussed the preliminary version of the paper and contributed to write the final version of the manuscript.

CONFLICT OF INTEREST

SH, CH, JJK, RM, AR, JS and MFMM received honoraria and had consulting role in Novartis; JJK, CH had a speakers' bureau in Novartis; JJK, RH and CB received research funds from Novartis; G Birgegard had a consulting/advisory role in Shire; RM received research funding from Incyte, Gilead, Celgene, Genentech and NS Pharma; and SV received research funding from: Incyte Corporation, Astrazeneca, Lilly Oncology, Roche, Geron, NS Pharma, Bristol Myers Squibb, Novartis, Celgene, Infinity Pharmaceuticals, YM Biosciences, Seattle Genetics, Promedior, and Cell Therapeutics Inc. The remaining authors declare no conflict of interest.

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Abstract

The discovery of somatic mutations, primarily *JAK2*V617F and *CALR*, in classic *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs) has generated interest in the development of molecularly targeted therapies, whose accurate assessment requires a standardized framework. A working group, comprised of members from European LeukemiaNet (ELN) and International Working Group for MPN Research and Treatment (IWG-MRT), prepared consensus-based recommendations regarding trial design, patient selection and definition of relevant end points. Accordingly, a response able to capture the long-term effect of the drug should be selected as the end point of phase II trials aimed at developing new drugs for MPNs. A time-to-event, such as overall survival, or progression-free survival or both, as co-primary end points, should measure efficacy in phase III studies. New drugs should be tested for preventing disease progression in myelofibrosis patients with early disease in randomized studies, and a time to event, such as progression-free or event-free survival should be the primary end point. Phase III trials aimed at preventing vascular events in polycythemia vera and essential thrombocythemia should be based on a selection of the target population based on new prognostic factors, including *JAK2* mutation. In conclusion, we recommended a format for clinical trials in MPNs that facilitates communication between academic investigators, regulatory agencies and drug companies.

INTRODUCTION

The classic BCR-ABL1-negative myeloproliferative neoplasms (MPNs) are the most common variants of MPNs, with a crude incidence in Europe of 1.8 cases per 100 000

person-years.[1] They encompass essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis (MF),[2] that is, primary myelofibrosis (PMF), post-PV and post-ET MF. The identification of the *JAK2*V617F mutation present in about 95% of patients with PV and approximately 60% of those with ET and PMF has promoted the understanding of the pathogenesis of MPNs.[3–6] The discovery of other somatic mutations (*JAK2* exon 12, *CALR*, *MPL*, *TET*2, *CBL*, *ASXL-1*, *IDH1/IDH2*, *LNK*, *EZH2*, *SF3B1* and *SRSF2*) involving different cellular signaling pathways has heralded a new dimension in the diagnosis and treatment of MPNs.[7–10] There are now agents targeting the different MPN molecular mechanisms, such as Janus-activated kinase (JAK)–signal transducer and activator of transcription factor,[11] mammalian target of rapamycin,[12,13] or phosphatidylinositol 3′-kinase/AKT signaling,[14] and immunomodulators,[15] histone deacetylase inhibitors,[16–18] hypomethylating[19] and anti-telomerase drugs,[20] which have the potential to change the natural history of the disorders. Moreover, evidence that interferon may reduce the *JAK2*V617F allele burden in PV[21,22] has provided a proof of concept that molecularly targeted therapies could abolish the malignant clone sustaining the disorders.

In exploiting the clinical research with drug treatments, the MPN community is facing the issue of testing a high number of new agents with studies whose design and methodology should be clearly agreed and outcomes should measure clinically relevant benefits for the patients. Thus there is an increasing pressure to rethink drug development in a new framework for clinical research. This is a challenging task as several factors contribute to the difficulties in designing clinical trials in MPNs. In fact, there is a lack of consensus regarding how to select patient populations who should enter clinical trials, and the advent of molecular targeted therapies must be integrated into the use of conventional end points (for example, hematological response rate) in phase III trials. Finally, the need for phase III clinical trials has made urgent the choice of the best comparator. Standardization of these issues would facilitate approval of effective new treatments by expediting protocol development, comparison and consolidation of data on a given therapy collected at multiple sites and comparison of efficacy results of various therapeutic agents for MPNs evaluated in different clinical trials.

Given these unmet needs, a group of experts was convened by the European Leukemia Net (ELN) Consortium and the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) to participate in a consensus projects to review distinct aspects of MPNs that impact trial design and to formulate recommendations relevant to the conduct of clinical research in these disorders.

THE END POINTS PROJECT

An Expert Panel (hereafter referred to as the Panel) of 24 experts was selected for their expertise in research and clinical practice of management of MPNs. During an initial meeting held in San Diego, CA, USA, December 2011, the outline of the project was discussed, and the topics forming the structure of this document were established. The key therapeutic questions were selected through a series of questionnaires, whose results were considered by three panelists delegated to draft a document addressing the patient populations and end points for the identified key therapeutic questions. Through

questionnaires, the remaining panelists scored their agreement with the proposed statements and provided suggestions for the final consensus.

NATURAL HISTORY OF MPNS

In ET, representatives from international centers of excellence for MPNs reported 10-year and 15-year survival rates of 89% and 80%, respectively, leukemic transformation rates of 0.7% and 2.1%, respectively, and rates of progression to overt MF of 0.8% and 9.3%, respectively.[23] The death, leukemia and overt MF incidence rates per 100 patient-years were 1.3, 0.1 and 0.5%, respectively. Survival was similar to the sex- and age-standardized European population. Thrombosis is the most frequent complication in ET. In prospective studies, the rate of fatal and non-fatal thrombotic events ranged between 2% and 4% patient-years[24,25] and the incidence of arterial events was two to three times higher than that of venous events.[24–26]

The natural history of PV has been delineated in 1545 patients with Worrld Health Organization (WHO)-defined PV.[27] Median survival (14.1 years) was significantly worse than that of the age- and sex-matched US population. Evolution to myelodysplastic syndrome and leukemic transformation was the main cause of death in the very long term in a randomized phase III study with conventional therapies (hydroxyurea and pipobroman).[28] Cumulative hazard of leukemic transformation, with death as a competing risk, was 2.3% at 10 years and 5.5% at 15 years.[27] In the largest epidemiological study in PV (European Collaboration on Low-dose Aspirin), cardiovascular mortality accounted for 41% of all deaths (1.5 deaths per 100 persons per year).[29] The cumulative rate of non-fatal thrombosis was 3.8 events per 100 persons per year, without difference between arterial and venous thrombosis.[29]

The natural history of MF is characterized by the evolution towards the appearance or worsening of anemia, splenomegaly and disease-related symptoms. Moreover, MF patients frequently develop complications and acute myeloid leukemia. Median survival in MF is estimated at 6 years, but it can range from months to many years.[30] Taking into account the WHO classification tha includes prefibrotic MF,[2] the number of patients with an early stage of the disease and better prognosis is higher than traditionally reported. The best actual outcome reported in patients with prefibrotic MF is 76% survival at 10 years.[31] The overall cumulative rate of cardiovascular death and non-fatal thrombotic complications are 2.2 events per 100 persons per year without significant difference between non-fatal venous and arterial thrombosis.[32]

PROGNOSTIC CLASSIFICATION IN MPNS

The risk stratification of ET and PV is traditionally targeted at the provision of vascular events by advanced age (>60 years of age) and history of thrombosis.[33] From these prognostic factors, a two-tiered model was devised with patients classified at high- or low-risk. The perceived need for a better risk stratification of patients with ET and PV has recently produced revised prognostic models that include novel risk factors for death in PV[27] and for thrombosis in ET, such as the *JAK2*V617F mutation.[34]

The International Prognostic Scoring System (IPSS) or Dynamic IPSS (DIPSS) classification has emerged during recent years as the standard classification that is used for trial design and clinical management of patients with MF.[30,35] DIPSS was recently modified into DIPSS-plus by incorporating three additional DIPSS-independent risk factors: platelet count $<100 \times 10^9$/l,, red cell transfusion need and unfavorable karyotype; median survival for the low, intermediate-1, intermediate-2 and high-risk categories were 15.4, 6.5, 2.9 and 1.3 years.[36] No established clinically applicable biological or genetic markers associated with clinical outcomes have been identified to classify patients with MPNs. The recent evidence that the MPNs genetic basis, and particularly CALR mutations, are independent predictors of outcomes [37,38] has generated the hypothesis that they dictate distinct clinical outcomes and could challenge the traditional prognostic models.

STANDARD TREATMENT FOR MPNS

The selection of therapy for MPNs is conventionally based on the patient risk category, age and presenting disease manifestations. In PV and ET, the recommendations on treatment are shaped according to the thrombosis risk categories, so that only patients at high risk are deemed to need cytoreductive treatment.[33] This recommendation is based on the evidence that the application of cytoreductive therapies in high-risk patients significantly reduces the incidence of vascular events.[24,39,40] In patients with MF and lower risk, the key is to avoid overtreatment, while for patients with high risk of progression, systematic therapies are targeted to managing anemia, splenomegaly and improving quality of life.[33] Strategies to cure the disease with high-intensity therapies and stem cell transplantation are generally reserved for patients with intermediate-2 or high-risk disease.[33]

ASSESSMENT OF RESPONSE

The complexity of clinical manifestations of MPNs has produced response definitions based on different dimensions of disease, ranging from decrease of blood cells in peripheral blood, decrease of clinically significant organomegaly, disappearance of disease-related symptoms, improvement of histological bone marrow features and reduction or disappearance of the molecular signature of the disease.[41,42] In 2013, the ELN and IWG-MRT published new response criteria for MPNs aiming at providing a standard for response in investigator-initiated and registration clinical trials.[43,44] The new recommendations are based on the emerging concept that definition of response should be able to capture the long-term effects of new drugs. The use of Symptom Assessment Form (MF-SAF), a recently validated inventory to measure the symptom burden in MPNs,[45] has covered the need to include a patient-oriented dimension of response. Moreover, the inclusion of changes in bone marrow morphology has accounted for a biologically relevant measure of disease modification.

THERAPEUTIC KEY ISSUES

The panel selected a series of key therapeutic issues relevant to clinical research in MPNs (Table 1).

Developing new drug therapies in MPNs

The drug development process is based on the selection of patients most likely to benefit from the therapy in well-designed clinical trials with the most informative end points.

Phase I trials.—Ethical conduct of phase I trials is based on the concept that the trial should be addressed to patients who have exhausted all reasonable and standard therapeutic options and at the same time are not so fragile that they would incur a high rate of toxicity.[46] The main selection criteria of patients in most phase I MPN trials are based on prognostic factors (Supplementary Table S1). The prognostic categories in MPN[27,29,34,36] were deemed appropriate to portray disease severity and to adequately represent patients to enroll in phase I clinical trials. The Panel recommended that predicting potential toxicity from preclinical data should be informative for exclusion criteria of patients from study, thus minimizing the risk of toxicity and early trial attrition.

Phase I studies are intended to optimize drug dosage by using end points, such as dose-limiting toxicity, maximum tolerated dose, pharmacokinetic and pharmacodynamic profile. To allow better selection of a potentially effective dose, phase I trials increasingly are designed to test efficacy besides evaluating safety and toxicity. The use of ‘seamless’ designs, in which a phase I protocol defines an expansion to phase II *a priori* (phase I/II trials), are designed to detect antitumor activity over a relatively short period (4–6 months) by the use of maximum tolerated dose as established in phase I. The expansion phase ordinarily uses effectiveness measures that reflect relevant biological processes (biomarkers or hematological parameters). The Panel agreed that there are many reasons to discourage the use of such phase I/II design in MPNs. The maximum tolerated dose does not necessarily provide the most promising outlook for efficacy as it is not necessarily the maximum effective dose. Thus, with the extension phase, information on dose/effectiveness could be misleading. Moreover, in the absence of predictive molecular biomarkers reflecting tumor and host biology, the efficacy results may be misleading for the planning of subsequent studies. New adaptive phase I/II method that takes into account both toxicity and efficacy,[47] or separate phase II trial with dose randomization or titration, seems the best way to overcome the limits of traditional phase/II studies.

Phase II trials.—The great majority of phase II trials investigating new agents aimed at contrasting the myeloproliferative mechanisms in MPNs have enrolled patients according to the criterion of ‘need of therapy’ (Supplementary Table S2). The Panel claimed this criterion as appropriate for ET and PV patients. However, the criterion was judged too general for MF where treatment is addressed to a variety of disease manifestations, such as anemia, splenomegaly, thrombocytopenia, systemic symptoms, accelerated disease, blast transformation or other disease complications, that are not feasible targets for the time horizon of phase II trials. For this reason, selection of the MF patients population in phase II trials should focus on contrasting major disease manifestations, excluding rare or life-threatening complications.

The great majority of the phase II studies have been designed to measure efficacy of new treatments with dosing strategies defined as the highest tolerated dose. However, phase II

trials with pomalidomide or vorinostat in MF are illustrative examples that the relationship between high drug exposure and high efficacy has not been established convincingly in all clinical trials in MPNs.[48,49] At the present time, it seems rational to design phase II trials that include mechanisms of optimization of drug exposure. The Panel stressed the importance that dose titrations or dose randomization designs should be included in the phase II studies, with the expectation to allow the administration of doses lower than maximum tolerated dose while increasing efficacy.[50]

The great majority of phase II studies in MPNs have ‘disease response’ as the primary end point (Supplementary Table S3). However, there were trials that adjudicated response on the basis of reduction of splenomegaly[51] or of *JAK2*V617F allele burden alone.[21] Under the assumption that in phase II trials the primary end point should act as a surrogate for a clinically relevant time-to-event end point, panelists critically appraised the acceptability of surrogate end points that represented a limited response. They convened that the use of ‘overall response’ (complete plus partial remission), even though not validated for its surrogacy for a time-to-event end point, was the only adequate end point for phase II trials. As a matter of fact, in the revised response definitions of the three MPNs,[43,45] the metrics of benefit was precisely addressed, response definition incorporated validated patient-reported outcome instruments and histological measurement, and they considered detainment of disease progression and vascular complications.

To allow the full effect of the drug being exploited, the time at which response is measured in phase II trials should be sufficiently long. The great majority of the phase II studies measured response after 6–12 months. The Panel recommended that the time at which the response should be measured should not be shorter than 12 months. Phase II studies should also report ‘duration of response’, that is, duration from the first observation of any response to the time of disease progression.

Phase III trials.—Phase III trials with agents having the potential of modifying the natural history of the disease are not experimentally affordable in PV and ET, where the measurable outcomes occur in a time range of decades. Testing a novel agent for MF should include all patients in need of therapy for the disease, that is, presenting disease symptoms, manifestations or complications. Patients with intermediate or high-risk disease or low-risk disease but with a significant degree of splenomegaly are appropriate target populations. The Panel identified as an unmet clinical need a more focused population that could be selected when molecular biomarkers would allow stratification of patients for molecular risk or molecular pathogenesis.

For phase III trials in MF, the primary end point should be a time-to-event end point that is relevant to the patients, such as overall survival or progression free survival. Analysis of time-to-event typically requires a large sample size and long follow-up time in order to identify statistically significant as well as clinically meaningful differences between treatment arms. For this reason, the Panel discussed and weighted in the context of MF patients the shortcomings of using surrogate end points to reduce the cost and shorten the duration of phase III trials. None of the candidate surrogate end points, molecular response,

pathological response, patient-reported outcomes or overall response was deemed to have adequate validation to be used in phase III trials for new drugs' development.

The Panel argued that, in some circumstances, using a single time-to-event end point in phase III trials for MF may not provide a comprehensive picture of all the benefits of a new treatment over the disease manifestations and safety. Recently, pharmaceutical drug development has indicated the challenge of multiple co-primary end points, and regulators have recommended multiple co-primary end points for assessing the response of new drugs in an array of chronic and disabling disorders.[52,53] As the natural history of MF is described by elements of different origin, related to the progression of the disease or to therapies or unrelated to both, the Panel indicated that the combination of overall survival and progression free survival may better capture the effect of new agents on disease course. A clear and comprehensive definition of disease progression is necessary to make the end point clinically worthwhile. According to the ELN/IWG-MRT criteria,[44] progression of MF is documented if there is progression in splenomegaly and the number of blasts in the marrow or peripheral blood (Table 2). However, the appearance of one or more new disease manifestations, such as disease-associated anemia, thrombocytopenia or systemic symptoms, should also be included in the definition of progression.

The Panel recommended that an objective of phase III clinical trials in MF should be the proof of concept that individualized tailoring of therapy with new agents according to the prediction of treatment effect by molecular characteristics and biological biomarkers could enhance treatment efficacy and safety. This objective should be met by the use of trials' data to develop multivariable prediction models able to provide an estimate of absolute treatment effect for individual patients based on their specific characteristics according to the paradigm of individualized medicine.

Preventing disease progression in MF patients with early disease The era of molecularly targeted agents in MPNs has brought forth the new rationale of reducing or abolishing the mutated clone or its malignant activity, thus abrogating or preventing disease progression.[54,55] Ethical considerations preclude PV and ET patients from an upfront disease-abrogating treatment trial due to the minimal chance of progression and a long life expectancy of the patients.

The definition of the MF target population who deserve testing with early treatment is challenging. Silver *et al.*[56] included in a prospective study patients with WHO criteria-defined MF grade 0–1 bone marrow fibrosis according to EUMNET criteria,[57] with a residual erythropoietic activity occupying ⩾ 30% of marrow biopsy. However, the Panel agreed that the target population of MF patients should be more precisely defined. Previously untreated patients with grade 0 prognostic score (low-risk disease) according to IPSS classification were identified as the target population.

Documentation of slowing down of disease progression requires a controlled clinical trial comparing the experimental agent with the best supportive therapy. The Panel suggested using progression free survival or event-free survival or both as co-primary end points. Event-free survival is to be measured from the time from study entry

to any treatment failure, including disease progressionor discontinuation of treatment for any reason (for example, disease progression, toxicity, patient preference, initiation of new treatment without documented progression or death). Event-free survival end point is generally not encouraged by regulatory agencies, because it combines efficacy, toxicity and patient withdrawal. However, it is useful in the evaluation of some therapies such as those that provide new and unexpected toxicities. In cancer trials, the Food and Drug Administration and other regulatory authorities require a blinded independent central review for both side effects and progression (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf and http://www.fda.gov/downloads/ Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590). The Panel recommended that a central review for estimates of the event-free survival treatment effects should be planned.

Testing new drugs for the relief of MF-associated symptoms

Even though aimed at modifying the natural history of the disease, molecularly targeted agents may be used in patients who need relief of disease-associated symptoms. In this case, the trial should be designed according to the primary end point of symptom improvement.

The panel identified two categories of symptoms associated with MPNs that may be targeted by novel therapies in experimental studies.

Symptomatic splenomegaly.—To allow the transfer into clinical practice of the results of trials addressed at the relief of splenomegaly, a stringent definition of the population needing therapy of splenomegaly is necessary, and this definition should inform the selection of patients to be enrolled in the study (Table 3).

In the registration trials with ruxolitinib for MF,[58,59] physical examination alone has been judged as an unreliable method for determining the size of spleen. Therefore, nuclear magnetic resonance or computed tomography imaging has been recommended. Alhough ultrasound would seem a desirable method to evaluate splenomegaly, given that bi-dimensional measurements are possible without ionizing radiation, unfortunately there is a lack of consistent repetitive measurements based on the variability in imaging planes. Moreover, the examination cannot be reproduced for independent review at a later time point. With nuclear magnetic resonance or computed tomography imaging, the proposed thresholds for defining ‘significant’ spleen response was >35% decrease in spleen volume. This has been advocated to correspond to a >50% decrease in palpable splenomegaly. In non-registration trials, as with everolimus[12] or givinostat,[18] change in splenomegaly was assessed by clinical examination. The Panel agreed that the definition of response provided by ELN may be consistently used as response in clinical trials (Table 4).[44]

Randomized controlled trials offer the best value for efficacy, and the best comparator should be the standard therapy for splenomegaly, that is, hydroxycarbamide.

Severe anemia.—Unlike splenomegaly, the presence of anemia (hemoglobin o100 g/l) has been identified as one of the five independent predictors for inferior survival in MF.[30] Furthermore, transfusion dependency at the time of diagnosis, or its acquisition within a

year of diagnosis, has been shown to be an IPSS-independent adverse prognostic factor for survival in MF.[36]

Two different response definitions have been provided both based on increased of hemoglobin level after a defined interval of time or reduction/abolishment of transfusion need (Table 5).[44,60] The Panel agreed that the definition of response given by the IWG-MRT[44] should be consistently used in clinical trials.

In the absence of a standard therapy for anemia in MF, any new drug for relieving anemia in MF should be compared with the best available therapy (androgens, danazol, erythropoiesis-stimulating agents, low-dose thalidomide plus corticosteroids). Maintenance of response should also be evaluated in the long range of time. In this setting, the overall response of the disease remains a secondary end point.

Preventing vascular events in PV and ET

On the basis of the evidence that the application of cytoreductive therapies in high-risk patients with PV or ET significantly reduces the incidence of vascular events,[24,39,40] patients classified at high risk of thrombosis are deemed to need treatment. Nevertheless, the current recommendations for treatment leave PV patients at low risk of thrombosis untreated, even though their risk is double than that of normal population.[29] The risk classification currently used for therapy planning in ET does not consider predictors of thrombosis, such as the presence of *JAK2*V617F mutation or constitutional vascular risk factors.[34] Whether the higher than normal risk of thrombosis in the so called low-risk ET and PV patients should lead to modifying the treatment recommendations is uncertain. In fact, the risk/effectiveness of the use of cytoreductive agents has never been experimentally tested in low-risk patients. The Panel agreed that a controlled trial that compares drug treatment with no-drug treatment is the best strategy for solving the uncertainty.

The frequency/incidence rate of vascular event has been the primary end point in phase III trials testing the objective of reducing vascular events.[24,39,40] The Panel argued that surrogate end points with the potential to correlate with the true clinical outcome of thrombosis prevention, as the attainment of molecular response, normalization of blood levels of inflammatory cytokines, or reactive proteins, such as reactive C protein, failed to receive adequate validation.

To secure the potency of the study and to reach an adequate sample size, an international multicenter trial should be outlined. To provide the expected numbers of subjects, an articulate strategy would consist of a multicenter network of clinicians. Ethical considerations are against the use of potentially leukemogenic drugs, such as chemotherapeutic agents. JAK2 inhibitors, histone deacetylase inhibitors, mammalian target of rapamycin inhibitors, anti-telomerase drugs or interferon are the candidate experimental drugs in this setting.

CONCLUSIONS

In this paper, we used group discussion methods for outlining a forward-looking framework for clinical research in MPNs. The main aim of this endeavor was to provide rules that should facilitate comparability of trials' results among researchers and expedited approval of the trials by the regulatory authorities.

There remain several challenges in the advancement of clinical research in MPNs. First, it should be established whether disease biomarkers, molecular (gene mutations), inflammatory (cytokines) or patient-reported outcomes, meet the surrogacy principle for survival so that they could be used as primary end points. Biomarker validation is a subtle process that may deserve specific clinical trials or may be achieved in clinical trials as the secondary end points. Second, a more precise molecular classification of MPNs might become clinically practical and substitute for the clinico-pathological classification in the near future, and this might improve trial design. Specific molecular studies with the techniques of next-generation sequencing and wide genome screening may meet clinical needs in the future.

The spirit of the recommendations issued in this paper is that the continued dialogue between the regulatory authorities and scientific societies will no doubt strengthen the expansion of guidance to better serve the development of new therapeutic agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Recommendations for appropriateness of patient populations and primary end points in clinical trials in Ph-neg MPNs according to the therapy key questions

Key question: Developing new drug therapies in MPNs
Phase I trials should enroll patients with high-risk prognostic categories. Dose-limiting toxicity, maximum tolerated dose, pharmacokinetic and pharmacodynamic profile are the most appropriate primary end points
Phase II trials in PV or ET should enroll patients in need of therapy for the disease. Phase II trials in MF should enroll patients in need of therapy for contrasting the major disease manifestations, excluding rare or life-threatening complications. Overall response rate and duration of response are the most appropriate primary end points
Phase III trials should enroll patients in need of therapy for the disease. Overall survival or progression-free survival are the most appropriate primary end points
Key question: Preventing disease progression in MF patients with early disease
Trials should enroll previously untreated patients with IPSS score 0 (low-risk disease). Progression-free survival or event-free survival are the most appropriate primary end points
Key question: Testing new drugs for the relief of MF-associated symptoms
Trials aimed at evaluating drugs efficacy on splenomegaly should enroll patients in need of therapy for splenomegaly. The efficacy end point should be response on splenomegaly according to the IWG-MRT/ELN criteria
Trials aimed at evaluating the drugs efficacy on anemia should enroll patients in need of therapy for anemia. The efficacy end point should be response on anemia according to the IWG-MRT/ELN criteria
Key question: Preventing vascular events in PV and ET
Trials aimed at preventing vascular events in PV and ET should enroll patients with high risk of thrombosis. The efficacy end point should be time to vascular event

Abbrevations: ELN, European LeukemiaNet; ET, essential thrombocythemia; IPSS, International Prognostic Scoring System; IWG-MRT, International Working Group for MPN Research and Treatment; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera.

Table 2.

Definition of disease progression in myelofibrosis44

Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM, or
A ⩾ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5–10 cm, or
A 50% increase in palpable distance, below LCM, for baseline splenomegaly of 410 cm, or
Leukemic transformation confirmed by a bone marrow blast count of ⩾ 20%, or
A peripheral blood blast count of ⩾ 20% that lasts for at least 2 weeks

Abbreviation: LCM, left costal margin

Table 3.

Definition of patients in need of therapy for splenomegaly in myelofibrosis

Having a spleen 410 cm from the costal margin, or Having a progressive splenomegaly, that is, an increase of at least 3 cm in the past year and symptoms of compression

Table 4.

Criteria for assessment of response on splenomegaly (A baseline splenomegaly that is palpable at o5 cm, below the LCM, is not eligible for spleen response) 44

A baseline splenomegaly that is palpable at 5–10 cm, below the LCM, becomes not palpable, or A baseline splenomegaly that is palpable at 410 cm, below the LCM, decreases by ⩾ 50%

Abbreviation: LCM, left costal margin.

Table 5.

Criteria for assessment of response on anemia

Clinical improvement in anemia (International Working group (IWG) consensus criteria for treatment response in myelofibrosis)44	**Delphi expert-consensus panel definition of RBC-transfusion dependence and independence (applicable only for patients with baseline hemoglobin level of <100 g/l)**
A minimum 20 g/l increase in hemoglobin level, or becoming transfusion independent for at least 8-week duration* *Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the past month	Becoming transfusion independent for at least 3-month duration* *Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions every month for at least 3 months (for a hemoglobin level of o85 g/l that was not associated with clinically overt bleeding