PERSPECTIVE ARTICLE

Moving forward from spleen response as an endpoint in randomized controlled trials in myelofibrosis

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Abstract

Anticancer drugs should make patients live longer and/or feel better. Ideally, endpoints of cancer randomized controlled trials (RCT) should demonstrate that a drug leads to an increase in overall survival and/or improvement in quality of life. With the aim of including smaller numbers of patients, running shorter trials and thus getting new drugs to patients faster, cancer RCT are increasingly using (putative) surrogate endpoints. However, changes in surrogate endpoints often do not reliably predict improvements in overall survival and/or quality of life. Furthermore, especially in later lines of cancer treatments or in cancer patients with a short life expectancy, use of surrogates hardly speeds up the availability of novel therapies but does increase the advent of costly toxic drugs with uncertain benefit, thereby harming both patients and society. In myelofibrosis, spleen response has extensively been used as a surrogate for clinical outcome. In this review we argue that there is no convincing evidence for the use of spleen response or other surrogate endpoints in myelofibrosis, and that the use of surrogate endpoints in RCT in myelofibrosis should be avoided altogether.

Introduction

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm characterized by clonal trilineage myeloid proliferation with megakaryocyte atypia and progressive bone marrow fibrosis, resulting in extramedullary hematopoiesis, splenomegaly and constitutional symptoms. Ultimately, these MF-related symptoms impair quality of life (QOL), and survival of patients with this cancer is limited.[1,2] For transplant-ineligible patients, JAK-inhibitors are the mainstay of symptomatic treatment, but there remains an unmet medical need for disease-modifying treatments that prolong life. Spleen response is still the most frequently used putative surrogate endpoint in randomized controlled trials (RCT) investigating new MF therapies. Recent papers have discussed methodological challenges for new MF trials.[3,4]

New cancer drugs should lead to longer and/or better lives for patients. Randomized clinical trials comparing new cancer therapies to the existing standard of care are therefore ideally designed with clinical primary endpoints, such as overall survival (OS) and/or patient-reported QOL. In order to get new drugs to patients faster, surrogate endpoints are increasingly used as primary outcome measures in cancer RCT, as fewer patients are needed, making the duration of these trials shorter.[5] However, limitations of putative surrogate endpoints are increasingly recognized and addressed, with an emphasis on the fact that they often do not reliably predict OS and/or QOL.[6] Furthermore, especially in later lines of cancer treatments or in cancer patients with a short life expectancy, use of surrogates hardly speeds up the availability of novel therapies but does increase the advent of costly toxic drugs of uncertain benefit.[7,8] In MF, spleen response has extensively been used as a surrogate for clinical outcome in RCT. We argue that there is no convincing evidence for the use of spleen response as a surrogate for clinical outcome in MF and that use of surrogate endpoints in RCT for MF should be avoided altogether.

Background on spleen response in myelofibrosis

Myelofibrosis arises in a primary state or following polycythemia vera or essential thrombocytosis. The disease is classified within the World Health Organization (WHO) 2022 entity *BCR::ABL1*-negative chronic myeloproliferative

neoplasms.[9] Both the WHO and International Consensus Classification (ICC) of myeloid neoplasms recognize a pre-fibrotic/early MF and overt fibrotic MF stage.[9,10] Throughout its history, splenomegaly has been a cardinal sign of the disease – a characteristic accordingly reflected in current diagnostic criteria. Palpable splenomegaly is a minor diagnostic criterion for both overt fibrotic and pre-fibrotic MF. Although a hallmark of disease progression in MF patients, spleen enlargement in itself is not a prognostic marker for OS in the clinically used risk assessment scores, neither in non-transplant[11,12] nor in transplant settings.[13] The primary use of contemporary prognostication in clinical practice is selecting patients for potential transplant. Allogeneic hematopoietic stem cell transplantation remains the only disease-modifying and curative treatment option. Current guidelines recommend consideration for transplant in patients with Dynamic International Prognostic Scoring System Plus (DIPSS Plus) intermediate-2 and high-risk and Mutation-enhanced International Prognostic Scoring System Plus (MIPSS70 Plus version 2.0) high and very high-risk disease.[14] No treatment is indicated for asymptomatic and low-risk MF. Transplant-ineligible or intermediate-risk patients are treated for MF-related symptoms, anemia or symptomatic splenomegaly. Both in clinical practice and in interventional trials, spleen response continues to be the cornerstone treatment goal and primary endpoint, and it is a recognized response criterion according to the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT).[15,16]

Spleen response in transplant-ineligible myelofibrosis patients

Since the first description of chronic myeloproliferative neoplasms in 1951,[17] splenomegaly has been recognized as a hallmark of disease in MF. The therapeutic success of early palliative treatment options, such as busulfan, hydroxyurea and splenic irradiation, was mainly based on their ability to control disease-related symptoms and induce spleen responses. The degree of evidence for treatments that predate the JAK-inhibitor era is low and mainly based on retrospective cohort analyses (Table 1).[18-46] More comprehensive data, but no RCT, are available for survival outcomes after splenectomy in drug-refractory patients with splenomegaly (Table 1).[30-33] Hydroxyurea still has a limited place as a symptomatic treatment in current MF guidelines: as first-line in symptomatic splenomegaly or cytosis without anemia[18] or first-line for cytoreduction.[19] No properly designed RCT are available that have shown an impact of achieving spleen responses with these palliative treatments on an OS primary endpoint. In 2013, the European LeukemiaNET (ELN) and IWG-MRT proposed, alongside molecular and morphological criteria, response criteria that also captured drug benefit in terms of MF-associated symptom burden, such as spleen response, constitutional symptom response and red cell transfusion independency – all clinically relevant therapeutic objectives in palliative treatment.[15] The threshold for spleen response with magnetic resonance imaging or ultrasound was set at 35% (spleen volume reduction of 35%; SVR35), given that this benchmark corresponds, somewhat arbitrarily, with a reproducible 50% decrease in palpable splenomegaly (spleen reduction of 50%; SR50).[47] Following the discovery of molecular drivers of MF pathophysiology, *JAK2* V617F, *CALR* and later *MPL* mutations, and a resulting interest in targeted therapies and molecular response criteria, the ELN and IWG-MRT later offered a more specific framework for clinical endpoints for drug treatment trials.[16] Key recommendations included the need for time-to-event endpoints such as OS and progression-free survival (PFS) in phase III trials with potential disease-modifying therapies. None of the putative surrogate endpoints, such as molecular or pathological response, patient-reported outcomes, or spleen response, was adequately validated to be used in phase III trials for the development of new drugs.[4]

JAK-inhibitors exert their clinical activity through inhibition of the JAK-STAT signaling pathway, central in MF pathophysiology, and through suppression of an inflammatory cytokine response, both in *JAK2* wild-type and mutated MF. Based on preclinical and early phase I-II data showing potential activity, these molecules were developed with their disease-modifying potential in mind.[47,48] Contrary to ELN and IWG-MRT recommendations to use time-to-event clinical endpoints, the ensuing RCT, COMFORT-1 and COMFORT-2, introduced SVR35 at 24 weeks and 48 weeks as the primary endpoints (Table 1).[36,37] In 2011, the US Food and Drug Administration (FDA) approved ruxolitinib based on these results. Current guidelines place ruxolitinib as first line for symptomatic splenomegaly in intermediate-1 or -2 or high-risk disease, or second-line after hydroxyurea failure.[18,19] Pivotal RCT with newer generation JAK-inhibitors, such as fedratinib, pacritinib and momelotinib, all proved efficacy and superiority over placebo or best available therapy based on spleen and symptom responses (Table 1). At later follow-up of the initial registration trials, only COMFORT-1 (ruxolitinib *vs*. placebo) and PERSIST-2 (pacritinib *vs*. best available therapy) demonstrated a statistically significant OS benefit as a secondary endpoint, the latter for a prespecified group of thrombocytopenic patients with platelet counts ≤100×10^9/L.[49,50] Both studies allowed cross-over to the experimental arm, were not powered to evaluate a potential survival benefit as a primary endpoint, and no further data on post-protocol treatment are available. In part due to protocol-allowed cross-over after 24 weeks and the resulting confoundment of long-term comparison between arms, no convincing survival benefit has been shown in COMFORT-2,[51] PERSIST-1,[42] MOMENTUM,[52] SIMPLIFY-1 or SIMPLIFY-2.[53] For FREEDOM-2, OS analysis is still pending. Multiple *post-hoc* and pooled analyses, with their inherent limitations most recently summarized by Barosi and colleagues,[3,54] further show contradictory data on a possible correlation between spleen response and OS. Given that these registration studies were not designed with

Table 1. Evidence for spleen-directed treatment in patients with transplant-ineligible myelofibrosis.

Spleen-directed treatment	Place in current American guidelines[18]	Place in current ELN guidelines[19]	RCT	Source of evidence	Key endpoints or reported outcomes	Ref
Therapies other than JAK-inhibitors						
Hydroxyurea	First line in symptomatic splenomegaly or cytosis without anemia	First line for cytoreduction	NA	Retrospective cohort (N=10)	Control of disease-related symptoms and signs, including spleen response and blood counts.	20
				Retrospective cohort (N=10)	Control of disease-related symptoms and signs, including spleen response and blood counts.	21
				Retrospective cohort (N=40)	Response according to EUMNET criteria, including spleen response.	22
Interferon α	Limited value	No place	NA	Phase II (N=11)	Pathological response (reticulin fibrosis or osteosclerosis).	23
Pegylated interferon α-2a	Under investigation	No place	NA	Retrospective cohort (N=18)	Response according to EUMNET criteria, including spleen response and blood counts.	24
				Retrospective cohort (N=62)	Response according to IWG-MRT criteria, including spleen response and blood counts.	25, 26
				Phase I/II (N=37); combination with ruxolitinib	Dose-limiting toxicities. SR50 at 24w. Molecular response. OS.	27
Busulfan	No place	No place	NA	Retrospective cohort (N=7)	Control of disease-related symptoms and signs, including spleen response and blood counts.	28
Melphalan	No place	No place	NA	Retrospective cohort (N=104)	Control of disease-related symptoms and signs, including spleen response and blood counts.	29
Splenectomy	Drug-refractory and symptomatic splenomegaly; pretransplant	Drug-refractory and symptomatic splenomegaly	NA	Retrospective cohort (N=223)	Post-splenectomy survival. Operative morbidity and mortality. Response in cytopenia.	30
				Retrospective cohort (N=549)	Cumulative incidence of blast transformation.	31
				Retrospective cohort (N=314)	Peri-operative outcomes. Long-term complications. OS.	32
				Retrospective cohort (N=94)	Response according to IWG-MRT criteria, including spleen response and blood counts.	33
Splenic irradiation	Less certain palliative need	No place	NA	Retrospective cohort (N=23)	Control of disease-related symptoms and signs, including spleen response.	34
				Retrospective cohort (N=14)	Control of disease-related symptoms and signs, including spleen response.	35
JAK-inhibitors						
Ruxolitinib (RUX)	Symptomatic splenomegaly or cytosis without anemia, after hydroxyurea failure	First line for symptomatic splenomegaly in intermediate-1 or -2 or high risk disease; symptomatic splenomegaly after hydroxyurea failure	COMFORT-1	RCT; RUX *vs.* PLAC (N=309); double-blind	SVR35 at 24w. TSS50 at 24w. OS.	36
			COMFORT-2	RCT; RUX *vs.* BAT (N=219); open-label	SVR35 at 48w. QLQ-C30/FACT-Lym. OS.	37

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Spleen-directed treatment	Place in current American guidelines[18]	Place in current ELN guidelines[19]	RCT	Source of evidence	Key endpoints or reported outcomes	Ref
JAK-inhibitors						
Fedratinib (FED)	Symptomatic splenomegaly after RUX failure.	Not available at time of last ELN guideline	JAKARTA	RCT; FED *vs.* PLAC (N=289); double-blind	SVR35 at 24w. TSS50 at 24w.	38
			JAKARTA-2	Phase II, single arm FED after RUX (N=97)	SVR35 at 24w. TSS50 at 24w. Safety.	39
			FREEDOM-1	Phase IIIb, single arm FED after RUX (N=38)	SVR35 at 24w. TSS50 at 24w. Safety.	40
			FREEDOM-2	RCT; FED *vs.* BAT (incl RUX) after RUX (N=201); open-label	SVR35 at 24w. TSS50 at 24w. OS.	41
Pacritinib (PAC)	Thrombocytopenia with splenomegaly or symptoms in first line or after RUX failure	Not available at time of last ELN guideline	PERSIST-1	RCT; PAC *vs.* BAT (no RUX) (N=327); open-label	SVR35 at 24w. TSS50 at 24w. OS.	42
			PERSIST-2	RCT; PAC *vs.* BAT incl RUX (N=311); open-label	SVR35 at 24w. TSS50 at 24w. OS.	43
Momelotinib (MMB)	Anemia with splenomegaly or symptoms in first line or after RUX failure; anemia without splenomegaly second line	Not available at time of last ELN guideline	MOMENTUM	RCT; MMB *vs.* DAN (N=195); double-blind	TSS50 at 24w. SVR35 at 24w. Transfusion independence. OS.	44
			SIMPLIFY-1	RCT; MMB *vs.* RUX (N=432); double-blind	SVR35 at 24w. TSS50 at 24w. Transfusion independence.	45
			SIMPLIFY-2	RCT; MMB *vs.* BAT after RUX (N=156); open-label	SVR35 at 24w. TSS50 at 24w. Transfusion independence.	46

ELN: European LeukemiaNet; RCT: randomized controlled trial; Ref: reference; NA: not available; EUMNET: European Myelofibrosis Network; IWG-MRT: International Working Group Myelofibrosis Research and Treatment; SR50 at 24w: spleen response of 50% by palpation at 24 weeks; OS: overall survival; PLAC: placebo; SVR35 at 24w: spleen response of 35% by imaging at 24 weeks; TSS50 at 24w: reduction in Total Symptom Score of 50% at 24 weeks; BAT: best available therapy; QLQ-C30/FACT-Lym: European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire core model (QLQ-C30) and the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) scale; DAN: danazol.

an OS primary endpoint, *post-hoc* analyses are often underpowered to detect significant differences in survival outcome. Barosi and colleagues have stated that a randomized controlled trial, investigating JAK-inhibitor treatment *versus* conventional therapy, is needed, specifically designed and powered to evaluate OS, and that this would not contradict the notion of equipoise. To this day, no trial-level analysis is available supporting spleen response on JAK-inhibitors as a validated surrogate for OS.

Spleen response in transplant-eligible myelofibrosis patients

The rationale for spleen-directed treatment is different for high-risk, transplant-eligible patients: physicians aim for a reduction of spleen size to improve post-transplant outcomes. Despite the bias inherent to retrospective cohort analyses, the European Society for Blood and Marrow Transplantation (EBMT) showed an impact of palpable spleen length ≥15 cm on post-transplant survival,[55] making it a possible prognostic marker at the patient level. The hypothesis behind this observation is that MF patients with splenomegaly and a pro-inflammatory marrow niche have a potentially higher incidence of non-relapse mortality due to poor graft function and graft failure.[56] However, the most recent Myelofibrosis Transplant Scoring System (MTSS) does not incorporate splenomegaly as a prognos-

tic marker,[13] and post-transplant outcomes are mainly dependent on three factors: donor type (increased mortality in HLA-mismatched unrelated donor or cord blood), Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI; increased mortality with HCT-CI ≥3) and the use of post-transplant cyclophosphamide (improved survival associated with its use). Despite the lack of definitive evidence on clinical outcome, physicians aim to reduce spleen size prior to transplant. As a pre-transplant spleen-directed treatment option, splenectomy is decreasingly used.[55] Given the ubiquitous use of JAK-inhibitors in MF, preliminary phase II data and retrospective analyses have suggested better transplant outcomes in MF patients with ongoing ruxolitinib spleen response at the moment of transplant as compared to non-responders and refractory patients.[57-59] Current EBMT guidelines recommend pre-transplant spleen-directed management with JAK-inhibitors as first-line treatment, especially for MF patients with spleen sizes ≥15 cm below the costal margin.[14,60] Importantly, transplant-eligible patients were excluded from all registration trials with JAK-inhibitors. There is an unmet need for prospective data in this setting, especially for newer JAK-inhibitors. To this day, no trial-level analysis is available supporting spleen response prior to transplant as a validated surrogate for OS.

The problem with spleen response as a primary endpoint for new investigational therapies in myelofibrosis

The treatment of MF is advancing to disease-modifying therapies that aim to prolong life by changing the natural course of disease, especially for patients not eligible for a transplant. In recent years, multiple clinical trials have shown a shift away from JAK-inhibitors towards new molecules, investigated as single agents or as add-on to ruxolitinib (Table 2).[61-65] These include pelabresib, with recent phase III data from the MANIFEST-2 trial,[62] awaited phase III results for navitoclax, navtemadlin, imetelstat, selinexor, and ongoing phase II trials for, among others, bomedemstat, paraclisib and tasquinimod (Table 2). Despite the abovementioned shortcomings of spleen response as a surrogate for clinical outcome, the majority of these trials still implement spleen or symptom responses as a primary endpoint for evaluation of efficacy (Table 2). Only one, the phase III IMpactMF study with the telomerase inhibitor imetelstat, uses OS as a time-to-event primary endpoint (NCT04576156). Preliminary data are presented as potentially disease-modifying, supported by responses in biomarkers, such as reduction in variant allele frequency of molecular drivers, cytokines or marrow fibrosis, which have no trial-level validity as surrogates for OS.[15] The authors of the phase II MANIFEST trial claimed potential disease modification based on such biomarker findings,[61] but the subsequent phase III study with the same regimen in JAK-inhibitor-naïve patients was designed with spleen volume reduction as the primary endpoint.[62] The TRANSFORM-1 trial with the new molecule navitoclax added to ruxolitinib in treatment-naïve patients was closed early due to a failure in achieving the total symptom score (TSS) endpoint (treatment-emergent toxicity is probably captured in the TSS), even though these data supported a doubling of spleen response on navitoclax-ruxolitinib as compared to placebo-ruxolitinib (SVR35 at 24 weeks of 63.2% *vs*. 31.5%, respectively), proving a dissociation between the two endpoints. The phase II REFINE trial (navitoclax plus ruxolitinib in refractory patients) had shown a SVR35 of 26.5% and TSS50 of 30% both at 24 weeks.[63] No data are available for the phase III TRANSFORM-2 trial of the combination in refractory patients. Only clear OS data capture relapse mortality and potential treatment-related non-relapse mortality.

Framework for surrogate endpoints and the way forward in myelofibrosis

Trial-level validated surrogate endpoints should only be used to predict clinical outcome when this results in shorter and smaller trials and possibly faster drug approval.[66] Improvement in a valid surrogate endpoint reflects a proportionate improvement in OS and/or QOL.[6,67] At trial-level correlation, the change in the surrogate endpoint is correlated against the change in the clinical endpoint in all RCT performed for the specific drug class in the specific treatment line. The German Institute for Quality and Efficiency in Health Care (IQWIG) dictates that a surrogate is validated at the trial level when a correlation coefficient R≥0.85 (lower limit of the 95% confidence interval) is achieved, with R≤0.7 (upper limit of the 95% confidence interval) indicating the putative surrogate unsuitable, and values in between indicating it uncertain.[68]

Whereas an improvement in a validated surrogate informs on a treatment effect of an intervention, an individual level association of a studied surrogate endpoint with clinical outcome is predictive of outcome irrespective of treatment received.[69] For example, patients achieving a pathological complete response (pCR) after neo-adjuvant chemotherapy in breast cancer, *irrespective of treatment provided*, have a longer OS as compared to patients not achieving pCR. At trial-level correlation, however, the change in the fraction of patients achieving pCR does not predict an improvement in OS.[70] Those extra patients achieving pCR due to addition of a new drug in an RCT do not fare as well as those patients who achieved a pCR anyway. Simply put, achieving pCR predicts better outcome for a patient, but pCR is of no use as a surrogate endpoint to approve

Table 2. Ongoing phase II and phase III trials with new investigational therapies in myelofibrosis.

Investigational product	Mode of action	Trial methodology	Trial	Trial status	JAK-inhibitor	Primary endpoint	Key secondary endpoints	Reference
Pelabresib (CPI-0610)	BET inhibitor	Add-on ruxolitinib Open-label	Phase II MANIFEST *NCT02158858*	Completed	Naïve	SVR35 at 24w	TSS50 at 24w. Anemia response. Change in marrow fibrosis and *JAK2*V617F-mutant allele fraction.	61
		Add-on ruxolitinib Double-blind	Phase III MANIFEST-II *NCT04603495*	Active	Naïve	SVR35 at 24w	TSS50 at 24w. OS. Anemia response. Change in marrow fibrosis.	62
Navitoclax (ABT-263)	BCL2/BCLxl inhibitor	Add-on ruxolitinib Open-label	Phase II REFINE *NCT03222609*	Completed	R/R	SVR35 at 24w	TSS50 at 24w. Anemia response. Change in marrow fibrosis.	63
		Add-on ruxolitinib Double-blind	Phase III TRANSFORM-I *NCT04472598*	Terminated	Naïve	SVR35 at 24w	TSS50 at 24w. OS. Anemia response. Change in marrow fibrosis.	Preliminary results at ASH 2023
		Add-on ruxolitinib Open-label	Phase III TRANSFORM-II *NCT04468984*	Active	R/R	SVR35 at 24w	TSS50 at 24w. OS. Anemia response. Change in marrow fibrosis.	No data published
Navtemadlin (KRT-232)	MDM2 inhibitor	Single agent Open-label	Phase II BOREAS *NCT03662126*	Completed	R/R	SVR35 at 24w	TSS50 at 24w.	Preliminary results at EHA 2020
		Single agent Open-label	Phase III BOREAS *NCT03662126*	Active	R/R	SVR35 at 24w	TSS50 at 24w. OS. Anemia response.	Preliminary results at ASH 2024
		Add-on ruxolitinib Double-blind	Phase III POIESIS *NCT06479135*	Active	R/R	SVR35 at 24w TSS50 at 24w	OS.	No data published
Imetelstat (GRN163L)	Telomerase inhibitor	Single agent Single-blind	Phase II IMBark *NCT02426086*	Completed	R/R	SVR35 at 24w TSS50 at 24w	OS. Response rate per IWG-MRT criteria.	64
		Single agent Open-label	Phase III IMpactMF *NCT04576156*	Active	R/R	OS	SVR35 at 24w. TSS50 at 24w. Change in marrow fibrosis. Response rate per IWG-MRT criteria.	No data published
Selinexor (KPT-330)	XPO1 inhibitor	Single agent Open-label	Phase II ESSENTIAL *NCT03627403*	Active	R/R	SVR35 at 24w	TSS50 at 24w.	Preliminary results at ASH 2021
		Single agent Open-label	Phase II SENTRY-2 *NCT05980806*	Active	Naïve	SVR35 at 24w	TSS50 at 24w. OS. Anemia response.	No data published
		Add-on ruxolitinib Double-blind	Phase III SENTRY *NCT04562389*	Active	Naïve	SVR35 at 24w TSS50 at 24w	OS. Anemia response.	No data published

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Investigational product	Mode of action	Trial methodology	Trial	Trial status	JAK-inhibitor	Primary endpoint	Key secondary endpoints	Reference
Bomedemstat (IMG-7289)	LSD1 inhibitor	Add-on ruxolitinib Open-label	Phase II *NCT05569538*	Active	Naïve	Adverse events	SVR35 at 24w. TSS50 at 24w.	Preliminary results at ASH 2023
Parsaclisib (INCB-050465)	PI3Kδ inhibitor	Add-on ruxolitinib Open-label	Phase II *NCT02718300*	Terminated	R/R	SVR at 12w Dose-limiting toxicities	SVR at 24w. TSS at 24w.	65
		Add-on ruxolitinib Double-blind	Phase III LIMBER-313 *NCT04551066*	Terminated	Naïve	SVR35 at 24w	TSS50 at 24w. OS.	No data published
		Add-on ruxolitinib Double-blind	Phase III LIMBER-304 *NCT04551053*	Terminated	R/R	SVR25 at 24w	TSS50 at 24w. OS.	No data published
Roginolisib (IOA-244)	PI3Kδ inhibitor	Add-on ruxolitinib Open-label	Phase I/II HEMA-MED *NCT06887803*	Active	R/R	Adverse events	SVR35 at 24w. TSS50 at 24w. Anemia response.	No data published
Tasquinimod (ABR-215050)	Quinoline-3-carboxamide immune-modulatory agent	Single agent and add-on ruxolitinib Open-label	Phase II *NCT06327100*	Active	R/R	Adverse events	/	No data published
		Single agent Open-label	Phase Ib/II TasqForce HO172 *NCT06605586*	Active	R/R	SVR35 at 24w Dose-limiting toxicities	SR50 at 24w. Change in marrow fibrosis. Anemia response.	No data published
Canakinumab (ACZ-885)	IL-1β monoclonal antibody	Single agent Open-label	Phase II *NCT05467800*	Active	R/R	Response rate per IWG-MRT criteria	Adverse events. SVR at 24w.	No data published
Reparixin (DF-1681Y)	CXCR1/2 inihbitor	Single agent Open-label	Phase II *NCT05835466*	Active	R/R	Response rate per IWG-MRT criteria	SVR at 24w. Change in marrow fibrosis.	No data published

NCT-number corresponds to a ClinicalTrials.gov identifier. BET: bromodomain and extraterminal domain; SVR35 at 24w: spleen response of 35% by imaging at 24 weeks; TSS50 at 24w: reduction in Total Symptom Score of 50% at 24 weeks; OS: overall survival; BCL2/BCLxl: B-cell lymphoma 2 protein B-cell lymphoma extra-large protein; R/R: relapsed/refractory; ASH: American Society of Hematology Conference; MDM2: mouse double minute 2; EHA: European Hematology Association Conference; IWG-MRT: International Working Group Myeloproliferative Neoplasms Research and Treatment; XPO1: exportin 1; LSD1: lysine-specific demethylase 1; PI3Kδ: phosphoinositide 3-kinase delta; SR50: spleen response of 50% by palpation; IL-1β: interleukin-1 beta; CXCR: C-X-C motif chemokine receptor.

drugs. If the correlation between a change in a putative surrogate endpoint and the change in clinical endpoint is not highly significant, it cannot predict clinical benefit of a drug and therefore should not be used for approving drugs. As detailed above, spleen response is a widely used endpoint in MF and it reflects drug activity. It is intuitive that MF patients achieving spleen response feel better and are likely to have an improved QOL. As such, in clinical practice, it remains a useful parameter as part of an overall assessment of impact on meaningful health outcome. However, as trial-level validation justifying spleen response as a surrogate for both QOL and OS is lacking, it is not suitable as a surrogate endpoint in RCT evaluating drug efficacy. Furthermore, given the different pathophysiological targets of newer therapies (Table 2), a biological rationale for spleen response as an endpoint is not supported.

When using QOL endpoints, clinicians should be aware that subjective outcome measures such as patient-reported outcomes are known to be biased to the experimental group in open-label studies.[71] Five out of nine JAK-inhibitor registration RCT were open label (Table 1), as are three out of nine RCT with new investigational therapies measuring QOL (Table 2). As the FDA allows drug approvals based on symptom reduction in the absence of an OS benefit, we would argue that RCT that measure QOL must be double-blinded and use validated tools for directly measuring QOL, instead of a putative surrogate. The myeloproliferative neoplasm symptom assessment form (MPN-SAF) TSS is such a validated tool for MPN.[72]

Changes in biomarkers, such as marrow fibrosis, cytokine signatures or molecular driver variant allele frequency are important to monitor disease-modifying activity, especially in phase II studies.[4] To this day, however, they lack trial-level validation as surrogates for clinical outcome. Minimal residual disease has no accepted place outside of transplant practice in MF. Attempts to validate such biomarkers as surrogates for an unvalidated surrogate such as spleen response is both of little relevance for use in clinical trials and in clinical practice, and should therefore not be pursued. As an example, minimal residual disease was recently validated as a surrogate for PFS in multiple myeloma even though PFS in itself is no reliable surrogate for OS at the trial level.[73] The FDA approval of minimal residual disease as a surrogate used for drug approval in the myeloma frontline setting has appropriately raised concern.[74]

How to move forward? Ross and colleagues have argued that, for trials with potential disease-modifying therapies, it is impractical to wait for demonstration of prolonged survival.[4] We disagree: in the absence of a validated surrogate, an OS primary endpoint is essential for such trials. The median survival of transplant-ineligible MF patients with DIPSS Plus intermediate-2 and high-risk disease ranges from 2.9 to 1.3 years, respectively.[11] Survival of JAK-inhibitor-refractory or -intolerant patients ranges from 11 to 13 months.[75,76] Patients with high-risk myelodysplastic syndrome (MDS) ineligible for transplant have a comparable prognosis.[77] In contrast to the situation in MF, recent phase III clinical trials studying new MDS treatments are designed with OS as primary endpoints. Examples include venetoclax in the VERONA trial (NCT04401748), magrolimab in the ENHANCE trial (NCT0431388; although recently terminated) and MBG453 in the STIMULUS-MDS2 trial (NCT04266301). Clearly, in the groups of MF patients detailed above, RCT with OS as a primary endpoint are feasible. This will give unequivocal results on clinical outcome and avert exposing patients to interventions with uncertain clinical benefit.

In the absence of validated surrogate endpoints, the tradeoff between introducing greater uncertainty of drug efficacy by using unvalidated surrogate endpoints and the longer time needed to perform RCT directly measuring OS, is especially relevant in studying lower-risk MF. Survival of these patients is considerably longer and hence, RCT studying drug efficacy will take longer, require larger numbers of patients and be costlier. For these lower-risk patients, RCT measuring alternative endpoints such as transfusion independency, are more defensible, as long as we acknowledge that such parameters are not proven trial-level surrogates for OS and/or QOL. Trial practices in low-risk MDS are comparable to this, with studies often focusing on hemoglobin improvement, red cell transfusion independency or time to next treatment. Ultimately, throughout phase I to III trials, in all stages of malignant disease, patient-reported QOL remains a valid and clinically relevant endpoint. Phase II clinical trials allow for more leniency. As they investigate feasibility of potential new disease-modifying therapies, phase II trials in higher-risk MF can focus on toxicity and the measurement of biomarkers of biological activity, with clinical endpoints as secondary outcomes. When moving drugs with demonstrated activity to phase III RCT to assess efficacy, clinical outcomes as primary endpoints are key: OS and QOL.

Conclusion

Historically, MF treatment has been focused on symptom relief, with spleen response a ubiquitously used, though not adequately validated endpoint for the evaluation of efficacy of JAK-inhibitors in RCT. RCT investigating new molecules with potential disease-modifying activity should move on from spleen response as an endpoint. New surrogate endpoints should have trial-level validation per different treatment entity and per specific treatment line. We argue against the use of unvalidated surrogates for regulatory decisions and accelerated approval of these often costly cancer treatments. Although they might be prognostic on an individual patient level, such surrogates

are not validated to predict a change in outcome of clinically relevant endpoints. Consequently, even though these putative surrogates indicate drug activity, they cannot be used for evaluation of treatment efficacy. In the absence of validated surrogates, and still in accordance with the IWG-MRT guidelines,[15] proving an impact on quantity- or quality-of-life can be, and therefore should be, the gold standard for clinical trials in MF.

Disclosures

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Contributions

All authors contributed to the design and writing of the manuscript.

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