Treatment failure and transition to next-line therapy in myelofibrosis: a modified Delphi panel approach

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Introduction

- Ruxolitinib (RUX) has been a first-line treatment option for intermediate- or high-risk myelofibrosis (MF) for many years, and improves splenomegaly and MF symptoms; however, patients experience loss of response and discontinuation rates are high (40%-70%)[1,2]
- With fedratinib now available and novel agents to come, guidance on how to transition to next lines of therapy in MF is needed
- There is no consensus on how to define RUX failure; clinical trials for second-line agents had varied criteria for RUX failure and were highly dependent on investigator judgement
- As current treatment guidelines[3] do not define all aspects related to RUX failure and transition to next-line therapy, addressing these underlying gaps may add to existing guidelines to improve the treatment of MF in patients progressing on RUX treatment

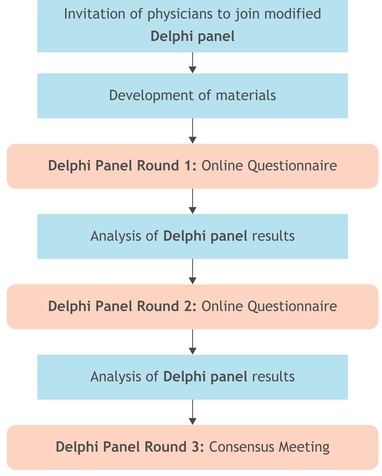
Objective

- To establish how RUX failure can be defined in real-world practice and develop parameters to guide appropriate transition to next-line therapy

Methods

- A 3-round modified Delphi panel was conducted with 14 hematologists-oncologists from across the US who were actively treating patients (management of > 15 patients per year) and who had been a principal investigator on ≥ 1 clinical trial or involved in developing National Comprehensive Cancer Network® (NCCN) myeloproliferative neoplasm (MPN) guidelines
- Physicians were recruited by a third party to avoid bias, conflict of interest, or compromising study integrity
- Online questionnaires had 2 survey rounds scored using 9-point Likert scales, followed by an online consensus meeting to resolve conflicting statements (**Figure 1**)

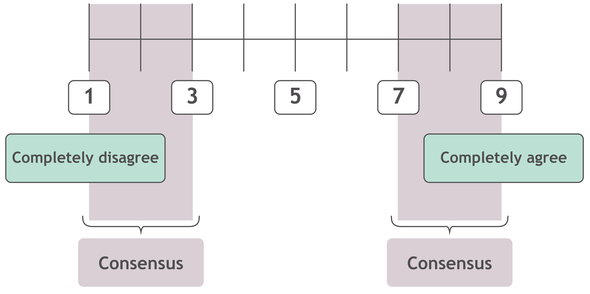
Figure 1. Overview of modified Delphi panel process



The modified Delphi panel uses a consensus meeting to allow for group discussion and clarification of uncertainties rather than multiple survey rounds until consensus is achieved.

- Following the first round, survey responses were analyzed and the second-round questionnaire was developed to include median scores of the group; statements that reached consensus in round 1 were excluded from the second round
- In the consensus meeting, wherever possible, statements were discussed until consensus was reached or there was agreement that consensus would not be reached
- Agreement was defined as ≥ 80% of respondents scoring between 7 and 9, and disagreement between 1 and 3 (**Figure 2**)[3,4]

Figure 2. Likert scale used to assess consensus



Results

Primary refractory

- Consensus was reached for primary refractory treatment failure (**Table 1**)
  - To support defining no spleen response based on no reduction in spleen length compared with baseline, imaging techniques can be used to assess response should palpation from the bedside be uncertain
  - No symptom response includes: night sweats, itching, abdominal discomfort, fevers, early satiety, and weight loss
  - Patient-reported symptoms including fatigue, lack of concentration, inactivity, and bone pain are too general to be linked with MF and should therefore only be considered when other specific MF symptoms are also present
- Suboptimal response can be defined by a patient responding to treatment at a lower rate than expected and should be classified as a different subcategory to treatment refractory

Table 1. Summary of consensus on primary refractive treatment failure

Category	Definition	Criteria	Measurement	Timeline
Primary refractory	Patients who fail to respond to RUX indicated by no response to treatment, assuming the patient is on a maximally tolerated dose	No spleen response	• No reduction in spleen length or volume compared with baseline (assuming ≥ 5 cm below LCM), measured by palpation, with imaging (MRI and ultrasound) as a supportive measure – The percentage reduction in spleen response can be defined as up to 20%	≥ 3 months
		No symptom response	• No symptom improvement compared with baseline based on MPN-SAF score – The percentage reduction in MPN-SAF score in intermediate to highly symptomatic patients can be defined as up to 20%[a] • No symptom improvement compared to baseline based on no meaningful improvement in symptoms or a symptom response that remains unacceptable to the patient	

[a]Intermediate to highly symptomatic includes baseline score of ≥ 10 or individual symptoms of ≥ 5.
LCM, left costal margin; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; MRI, magnetic resonance imaging.

Loss of response

- Loss of response following initial response to RUX can define treatment failure (**Table 2**)
  - Loss of spleen response can be confirmed by imaging techniques or a physical examination via palpation
  - For defining loss of symptom response, a longer timeframe of ≥ 3 months should be used due to a high level of clinical heterogeneity (eg, variability in number of and severity of symptoms) between patients; however, this may be adjusted by the treating physician for highly symptomatic patients (**Table 2**)

Table 2. Summary of consensus on loss of response

Category	Definition	Criteria	Measurement	Timeline
Loss of response	Patients who lose initial response to treatment, assuming the patient is on a maximally tolerated dose of RUX	Loss of spleen response	• An initial spleen response to treatment followed by any regrowth or return to baseline • An increase in spleen length compared with best achieved response • An increase in spleen length compared with baseline – The percentage increase in spleen length or volume can be defined as ≥ 25%	≥ 1 month
		Loss of symptom response	• An initial response to treatment followed by any return of symptoms or increase in symptoms from baseline • Increase in symptoms compared with baseline based on MPN-SAF score – The percentage increase in MPN-SAF score can be defined as ≥ 30% • Increase in symptoms based on MPN-SAF score compared with best achieved response – The percentage increase in MPN-SAF score in intermediate to highly symptomatic patients can be defined as ≥ 50% • An initial response and return of symptoms unacceptable to the patient	≥ 3 months

Progressive disease

- Progression of MF during treatment with RUX can indicate treatment failure (**Table 3**)
- Appearance of new palpable splenomegaly can define treatment failure with RUX (**Table 3**)
- Disease progression to an accelerated phase, blast phase, or leukemic transformation during treatment with RUX can define progressive disease (**Table 3**)

Table 3. Summary of consensus on progressive disease

Category	Definition	Criteria	Measurement	Timeline
Progression	Progression of MF during treatment, assuming the patient is on a maximally tolerated dose of RUX	Appearance of a new palpable splenomegaly	• Compared with no palpable splenomegaly at treatment initiation – The size of new palpable splenomegaly below the LCM of 5 cm	≥ 3 months
		Accelerated phase	• 10%-19% blast cells in the bone marrow or blood	At any point
		Blast phase	• ≥ 20% blast cells in the bone marrow or blood	
		Leukemic transformation	• Bone marrow blast count of > 20% or peripheral blood blast content of ≥ 20% associated with an absolute blast count of > 1 × 10^9/L for ≥ 2 weeks	

Intolerance

- Development of intolerance can also indicate RUX failure (**Table 4**)
- Treatment-emergent toxicities should be addressed per the prescribing information, alongside discussions between the patient and physician
  - For grade 4 toxicities, dose adjustment per prescribing information should be considered

Table 4. Summary of consensus on intolerance

Category	Definition	Criteria	Measurement	Timeline
Intolerance	Development of an intolerance with RUX	Treatment-emergent toxicity	• Any treatment-emergent toxicity deemed unacceptable to the patient	≥ 4 weeks

Transition to next-line therapy

- Following RUX failure, consensus recommendations for next-line treatment suggest that treatment should be guided by patient characteristics to mitigate risk of withdrawal, such as current dose and symptoms, and started as soon as clinically appropriate (**Table 5**)
- Tapering before RUX discontinuation should be based on current RUX dose, disease status, and comorbidities (**Table 5**)
- RUX discontinuation syndrome[5] should be considered a concern when discontinuing RUX

Table 5. Criteria and consensus recommendations for transition to next-line therapy

Category	Criteria	Recommendations	Timeline
Appropriate transition from RUX to next-line therapy	Following treatment failure with RUX, alternative treatment options should be considered	The following options may be considered to support transition to alternative therapy options, while mitigating risk of withdrawal based on patient characteristics in the absence of evidence-based recommendations and lack of biomarkers: • Tapering of RUX • Tapering of RUX overlapped with the introduction of a second-line treatment • Introducing steroids at the first sign of RDS • When clinically appropriate, a second-line drug treatment can be started immediately after stopping RUX treatment	≥ 2 weeks (tapering only)

RDS, ruxolitinib discontinuation syndrome.

Limitations

- Although these findings can contribute to the definition of treatment failure with RUX and guide appropriate transition to next-line therapy in patients with MF, the statements derived offer a lower level of evidence than randomized controlled trials[3,6]

Conclusions

- This research provides expert consensus on further defining RUX failure in those with no treatment response or progression, based on spleen and symptom control and intolerance
- These definitions can be utilized to add further guidance to future clinical guidelines/pathways to assist providers in recognizing RUX failure in real-world practice, thus improving patients' outcomes with the utilization of new therapies
- Although consensus was reached on all statements, there are still gaps in the evidence; further clinical and real-world research is needed to ensure patients receive the best possible treatment option leading to an optimal response in MF

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