

Il trattamento della mielofibrosi dopo il fallimento del ruxolitinib

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The clinical relevance

Effective therapies for those patients with MF who have failed ruxolitinib is an area of **great unmet need** given that until very recently there was **no currently approved therapy** and the overall **prognosis is often poor**

Prognosis after ruxolitinib failure

- ✓ Patients receiving ruxolitinib = 145
- ✓ Died while on treatment = 23
- ✓ Failed treatment = 64
- ✓ **Median overall survival (OS) after ruxo discontinuation = 13 months.**

*Kuykendall AT, et al. Ann Hematol.
2018 Mar;97(3):435-441.*

- ✓ MF patients enrolled in a phase 1/2 study = 107
- ✓ Died while on treatment = 30
- ✓ Failed treatment = 56
- ✓ **Median overall survival (OS) after ruxo discontinuation = 14 months**

*Newberry KJ et al. Blood.
2017 Aug 31;130(9):1125-1131*

Critical issue (I)

1. Currently, there is no consensus on what specific criteria define failure to ruxolitinib treatment in MF.

Criteria of ruxolitinib failure used for clinical trials*

Relapse/refractory:

- ✓ Ruxolitinib therapy \geq 3 months
- ✓ with an initial response followed by either spleen regrowth
- ✓ or suboptimal response (defined as $<$ 10% spleen volume reduction or $<$ 30% decrease in spleen size from baseline).

Intolerant:

- ✓ Ruxolitinib treatment for \geq 28 days
- ✓ complicated by development of RBC transfusion requirement (\geq 2 units per month for 2 months)
- ✓ or grade \geq 3 thrombocytopenia, anemia, hematoma and /or hemorrhage while receiving ruxolitinib

**JAKARTA 2 updated analysis of an ITT cohort (n=97) (Harrison, C et al. Clin Myel Lymph Leuk 2019; 19:S356)*

Criteria of ruxolitinib failure used in clinical practice (real world)

Drug discontinuation for lack of a clinically significant response, unacceptable toxicity or disease progression

Barosi G, et al. Leukemia. 2016 Aug;30(8):1772-5.

Critical issue (II)

1. Currently, there is no consensus on what specific criteria define failure versus suboptimal response to ruxolitinib treatment in MF
2. Currently, there is no consensus on what specific criteria define **disease progression** during ruxolitinib treatment.

Disease progression

IWG-MRT/ELN*:

- $\geq 25\%$ increase in spleen volume from baseline.

COMFORT II:**

- An increase in spleen volume of $\geq 25\%$ from the on-study nadir (including baseline)
- splenic irradiation or splenectomy
- leukemic transformation defined by an increase in peripheral - blood blast percentage to $\geq 20\%$ that was sustained for ≥ 8 weeks or bone marrow blast count $\geq 20\%$
- Death

Our definition (unpublished)

- A progressive increase of PB blasts (or CD34+ cells) up to alarming values (3% of blasts or $350 \times 10^6/L$ CD34+ cells)

*Tefferi A, IWG-MRT/ELN. *Blood*. 2013 Aug 22;122(8):1395-8.

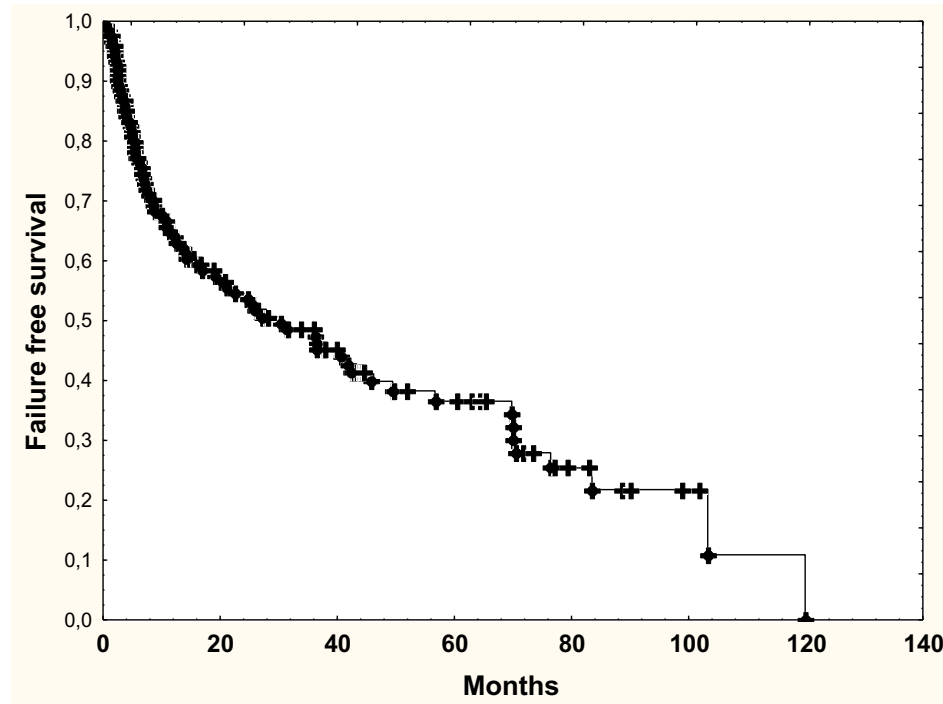
**Harrison C, et al. *N Engl J Med*. 2012 Mar 1;366(9):787-98

The clinical prevalence (from trials)

Trial	N	Treatment arm	Median follow-up	Ruxolitinib discontinuation rate
COMFORT-I	155	Ruxolitinib	5.15 yrs	72%
COMFORT-II	146	Ruxolitinib	4.7 yrs	73%

The clinical prevalence (from real world)

Response rate (IWG criteria)= 49/123 (39.8%)

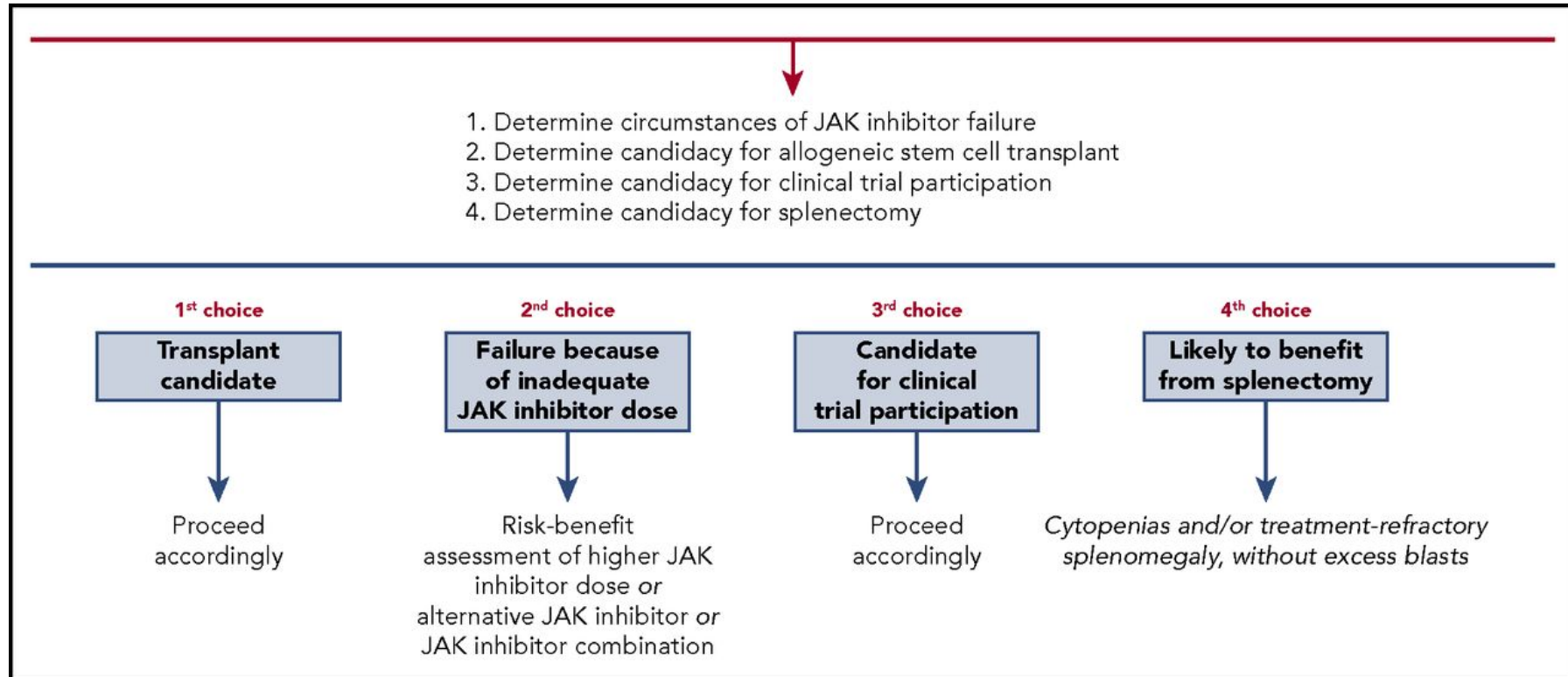


- ✓ 50% discontinuation rate at 24 months (2 years)
- ✓ 80% discontinuation rate at 80 months (6.6 years)

Causes of failure:

- ✓ Failure to respond = 26/123 (21%)
- ✓ Hematologic toxicity = 14 /123 (11%)
- ✓ Non-hematologic toxicity = 14/123 (11%)
- ✓ Disease progression = 21/123 (18%)

How I treat myelofibrosis after failure of JAK inhibitors



Animesh Pardhanani, Ayalew Tefferi, How I treat myelofibrosis after failure of JAK inhibitors, *Blood*, 2018,

New available agent: Fedratinib

Cpiare I ounti del lavro su fedratinib

Treatment principles for myelofibrosis patients failing ruxolitinib

- 1. In any case, re-consider the candidacy for allogeneic stem cell transplantation patient had before the initiation of ruxolitinib therapy*
- 2. Determine candidacy for allogeneic stem cell transplantation at ruxolitinib failure*

Transplant candidate



Proceeds accordingly (+/- splenectomy)

Treatment principles for myelofibrosis patients failing ruxolitinib

3. In non-transplant candidate with disease progression



- ✓ High dose hydroxyurea
- ✓ Thioguanine
- ✓ Azacytidine
- ✓ Experimental ruxo combinations

Treatment principles for myelofibrosis patients failing ruxolitinib

4. In non-transplant candidate failing for resistance or intolerance



- ✓ Second line JAK inhibitors (fedratinib),
- ✓ Clinical trials