Azienda Ospedaliero Universitaria Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

VIII Giornata Fiorentina dedicata ai pazienti con malattie mieloproliferative croniche

Sabato 28 aprile 2018

Le Linee Guida ELN 2018

Giovanni Barosi

IRCCS Policlinico San Matteo
Pavia

CRIMM
Centro di Ricerca e Innovazione
per le Malattie Mieloproliferative

Linee guida- definizione

Systematically *developed statements to assist practitioner and patient decisions about* ***appropriate*** *health care for specific clinical circumstances* (Institue of Medicine, 1990)

VOLUME 29 · NUMBER 6 · FEBRUARY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Philadelphia-Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations From European LeukemiaNet

Tiziano Barbui, Giovanni Barosi, Gunnar Birgegard, Francisco Cervantes, Guido Finazzi, Martin Griesshammer, Claire Harrison, Hans Carl Hasselbalch, Rudiger Hehlmann, Ronald Hoffman, Jean-Jacques Kiladjian, Nicolaus Kröger, Ruben Mesa, Mary F. McMullin, Animesh Pardanani, Francesco Passamonti, Alessandro M. Vannucchi, Andreas Reiter, Richard T. Silver, Srdan Verstovsek, and Ayalew Tefferi

Domains: diagnosis; patient comunication; risk classification; management; special issues in MPN.

Methods : Delphi technique, consensus conference.

Barbui et al. JCO, 2011;29:761

REVIEW ARTICLE

Chronic myeloproliferative neoplasms

Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet

Tiziano Barbui[1] · Ayalew Tefferi[2] · Alessandro M. Vannucchi[3] · Francesco Passamonti[4] · Richard T. Silver[5] · Ronald Hoffman[6] · Srdan Verstovsek[7] · Ruben Mesa[8] · Jean-Jacques Kiladjian[9] · Rüdiger Hehlmann[10] · Andreas Reiter[10] · Francisco Cervantes[11] · Claire Harrison[12] · Mary Frances Mc Mullin[13] · Hans Carl Hasselbalch[14] · Steffen Koschmieder[15] · Monia Marchetti[16] · Andrea Bacigalupo[17] · Guido Finazzi[1] · Nicolaus Kroeger[18] · Martin Griesshammer[19] · Gunnar Birgegard[20] · Giovanni Barosi[21]

Barbui et al. Leukemia 2018, Feb. 27

Objective: to revise the 2011 ELN recommendations
Domains: diagnosis, risk prediction, therapy
Methods: Delphi technique; trials with a comparison group were critically appraised to rate confidence in estimates of effect (GRADE).

Le linee guida usano l’evidenza derivata dai trials clinici per risolvere l’incertezza delle decisioni

Domanda:
Quale è il livello di ematocrito ottimale per i pazienti con policitemia vera?

THERAPY - PV

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events and Intensity of Treatment in Polycythemia Vera

Marchioli et al, NEJM 2013;368:22-33

CYTO-PV TRIAL

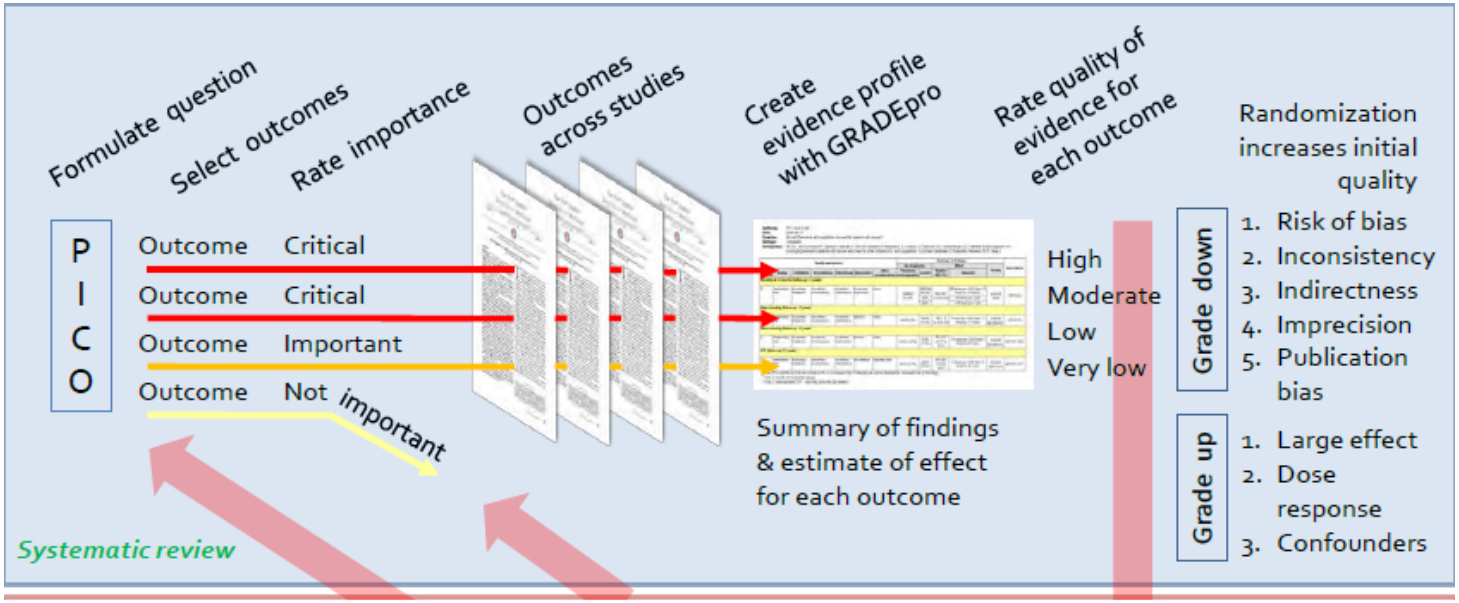
PV patients in need of phlebotomy (N= 365)

random

- Phlebotomy/HU - Target hematocrit < 45%
- Phlebotomy/HU - Target hematocrit, 45 to 50%

Results: Time until death from cardiovascular cause or major thrombotic events was recorded in 2.7% patients in the low-hematocrit group and in 9.8% patients in the high-hematocrit group (HR in the high-hematocrit group, 3.91; 95% confidence interval (CI) = 1.45 to 10.53).

GRADE SYSTEM – A method for grading the evidence



GRADE SYSTEM – A method for guideline development

THERAPY - PV

Recommendations

The Panel strongly recommended that all patients with PV should be managed with phlebotomy to maintain the hematocrit below 45%....

Domanda:

E’ ruxolitinib (JAKAVI) la scelta terapeutica migliore per i pazienti con PV che si sono dimostrati refrattari o intolleranti all’Oncocarbide?

THERAPY – 2° LINE IN PV

Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

Vannucchi et al. NEJM 2015;372:426-435

Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study

Passamonti et al. Lancet Oncology 2017;18:88-99

RESPONSE & RESPONSE- 2 TRIALS

Inadequletely controlled PV patients with splenomegaly (N=222) /without splenomegaly (N= 173)

random

ruxolitinib

BAT

THERAPY – 2nd LINE IN PV

Results

RESPONSE trial: Hematocrit control was achieved in 60% of patients receiving ruxolitinib and 20% of those receiving standard therapy;

***RESPONSE-2 trial*:** Hematocrit control was achieved in 62% of ruxolitinib-treated patients versus 19% who received best available therapy (odds ratio 7·28 [95% CI 3·43-15·45]; p<0·0001).

THERAPY – 2nd LINE IN PV

Recommendations

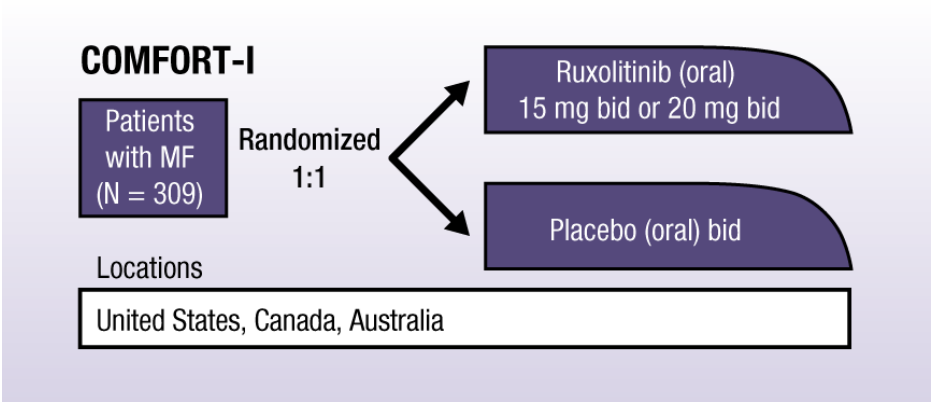
The Panel agreed that both rINFα and ruxolitinib are appropriate second-line drug therapies for PV patients who are intolerant or have inadequate response to hydroxyurea.

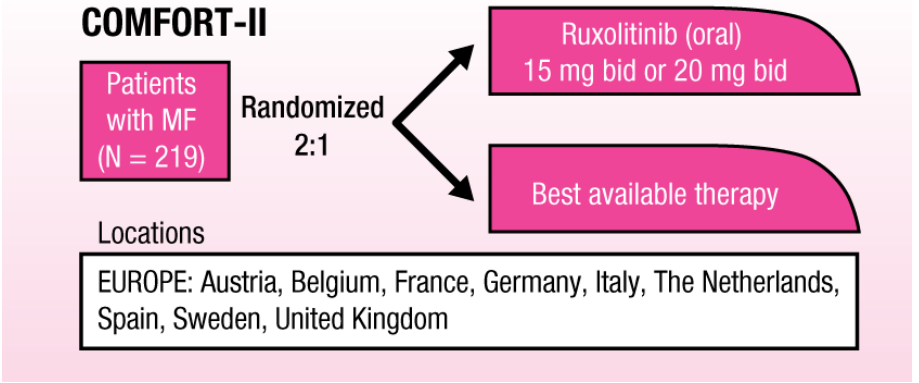
In this setting, the recommendation of use of ruxolitinib was judged by the Panel as strong, even though the confidence in the outcome measures was moderate.

Domanda:

E’ ruxolitinib (JAKAVI) la prima terapia «diretta verso la malattia» (non sintomatica) nella mielofibrosi?

THERAPY - MF





Primary endpoint: Proportion of patients achieving a ≥ 35% reduction in spleen volume at Week 24

Secondary endpoints included
- Proportion of patients who had a ≥50% reduction from baseline at Week 24 in Total Symptom Score (TSS) as measured by the modified MFSAF v2.0 diary
- Change from baseline to Week 24 in TSS as measured by the modified MSFAF v2.0 diary
- Duration of maintenance of a ≥35% reduction in spleen volume

Primary endpoint: Proportion of patients achieving a ≥ 35% reduction in spleen volume at Week 48

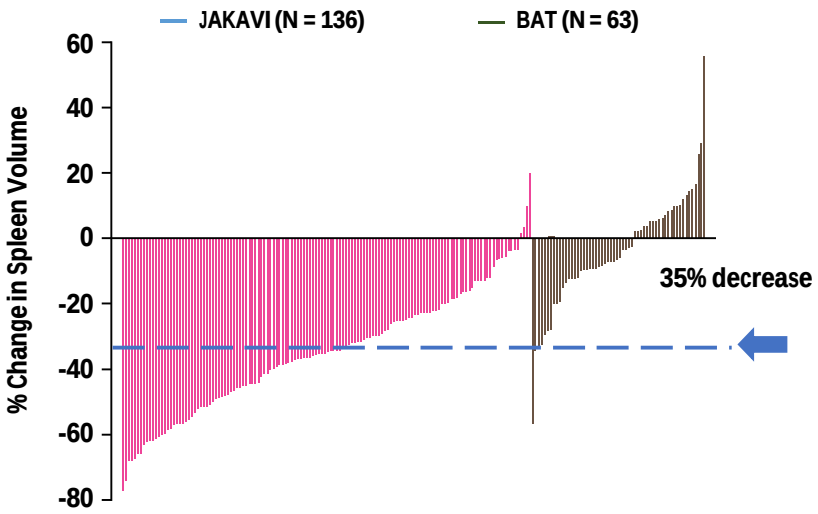
Secondary endpoints included
- Proportion of patients achieving a ≥35% reduction in spleen volume at Week 24
- Duration of maintenance of a ≥35% reduction from baseline in spleen volume

Verstovsek S, et al. N Engl J Med. 2012;366(9):799-807.
Harrison C, et al. N Engl J Med. 2012;366(9):787-798.

THERAPY - MF

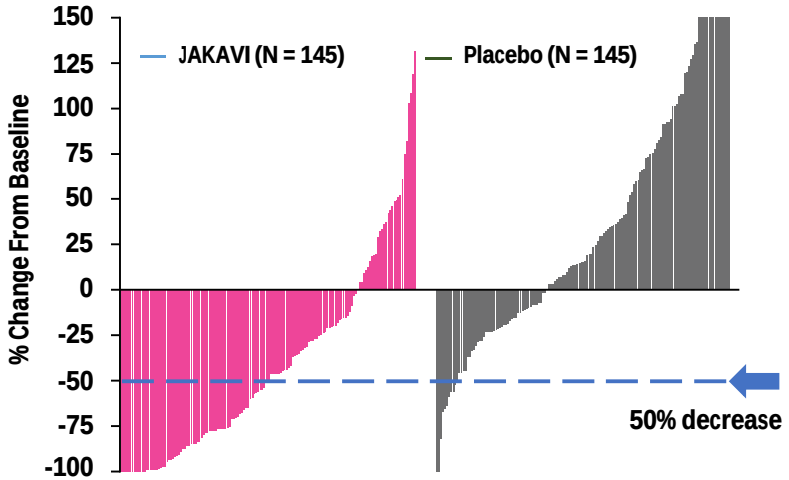
Splenomegaly Response in COMFORT-II

Best Percentage Change in Splenomegaly From Baseline by Week 48[1]



Symptom Response in COMFORT-I

Percent Change From Baseline in TSS in Individual Patients at Week 24[2]



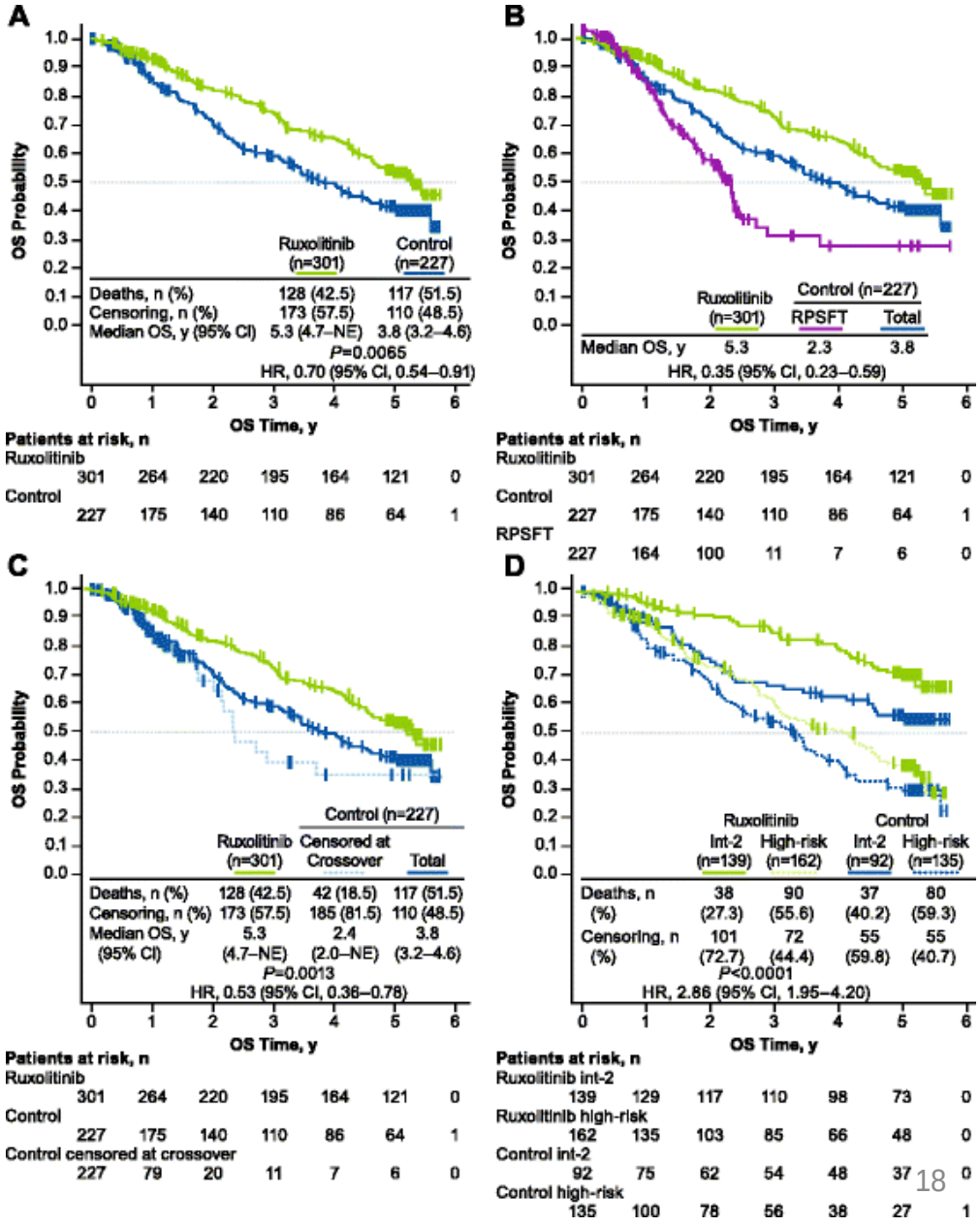
Harrison C, et al. N Engl J Med. 2012;366(9):787-798.
Verstovsek S, et al. N Engl J Med. 2012;366(9):799-807.

THERAPY - MF

COMFORT I-II pooled analysis (5-year data)

The risk of death was reduced by 30% among patients randomized to ruxolitinib compared with patients in the control group (HR = 0.70; 95% CI = 0.54-0.91)

Verstovsek, J Hematol Oncol 2017;10:156.



Therapy - MF

Recommendations

The Panel agreed that moving to a disease-oriented therapeutic strategy with ruxolitinib for MF is not justified, and the revised recommendations were issued across the different phenotypes/problems of the disease

Domanda

Quando dovrebbe essere usato ruxolitinib per il trattamento della splenomegalia della mielofibrosi?

MF therapy - splenomegaly

Recommendations

Ruxolitinib is recommended as first-line approach for MF-associated splenomegaly in patients with intermediate-2 or high-risk disease.

In patients with intermediate-1 risk disease and highly symptomatic splenomegaly, first-line therapy is ruxolitinib.

In other patients with intermediate-1 risk disease, and in those with low-risk disease, hydroxyurea is recommended as first-line therapy.

Le linee-guida rendono esplicita la incertezza

Domanda:
Siamo pronti per una terapia individulizzata della Mielofibrosi basata sulla classificazione prognostica molecolare?

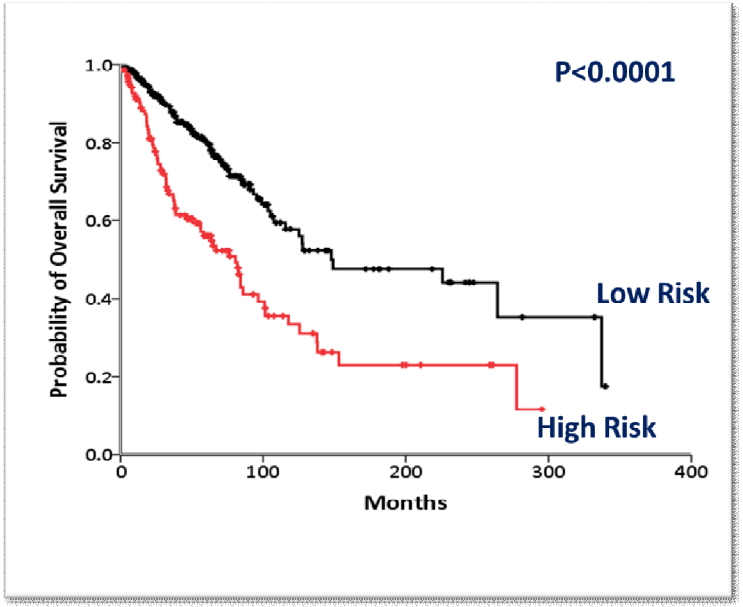
PROGNOSTIC FACTORS - MF

Gene	Chromosome location	MF (%)
TET2	4q24	7-17
IDH1/2	2q33.3 / 15q26.1	4
DNMT3A	2p23	2-15
EZH2	7q36.1	7-13
ASXL1	20q11.1	13-32
SRSF2	17q25.1	≈15%
SF3B1	2q33.1	7%
CBL	11q23.3	6%
TP53	17p13.1	4%
U2AF1	21q22.3	16%

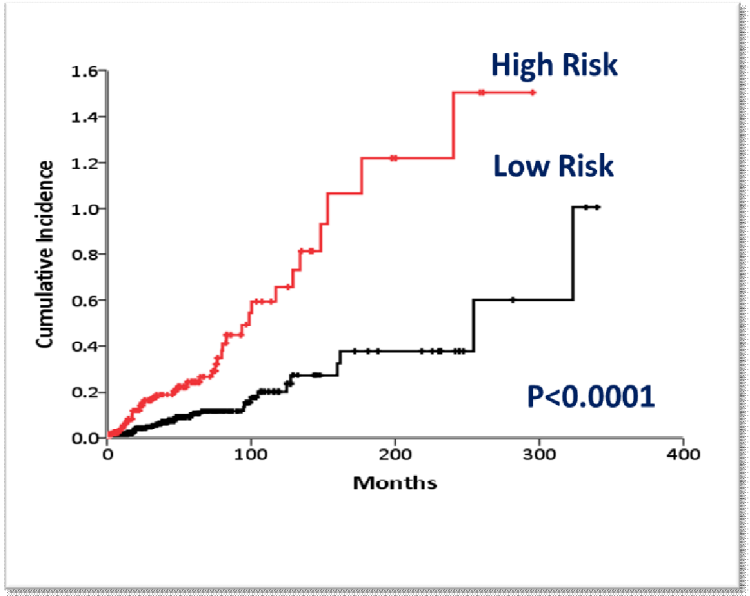
Vainchenker W et al, Blood. 2011; 18;118(7):1723-35;
Vannucchi AM et al, Leukemia 2013; 27:1861-9.

PROGNOSTIC FACTORS - MF

Overall Survival



Blast Transformation



Harboring ≥1 mutation in any one of ***ASXL1, EZH2, SRSF2, IDH1/2.*** A HMR status is associated with reduced OS and increased risk of blast transformation in PMF patients independent of IPSS/DIPPS-plus

Vannucchi AM, et al. Leukemia. 2013;27:1861-9

PROGNOSTIC FACTORS - MF

Recommendations

There is increasing evidence that integration of IPSS with additional genetic information, ... allows a more detailed individualized prognostic classification.

For this reason, cytogenetic studies, classification of CALR mutations into type 1/like and type 2/like, and screening for non-driver additional mutations including at least ASXL1 and SRSF2, has become current practice in research centers.

The Panel agreed that a complete genetic assessment should be encouraged in all patients for the prognostic assessment at diagnosis.

PROGNOSTIC FACTORS - MF

Recommendations

However, the Panel also claimed that failure to perform a full genetic characterization at the time of diagnosis is acceptable in clinical practice.

Molecular assessment during the course of the disease (at least ASXL1 mutation) is recommended for therapeutic decisions in selected MF patients, such as to decide a transplant in those who have an intermediate-1 risk category according to the DIPSS/DIPSS-plus score.

Philadelphia Chromosome-Negative Classical Myeloproliferative Neoplasms: Revised Management Recommendations from European LeukemiaNet

Barbui T
Tefferi A
Vannucchi AM
Passamonti F
Silver RA
Hoffman R
Verstovsek S
Mesa R
Kiladjian J-J
Hehlmann R
Reiter A
Cervantes F
Harrison C
McMullin MF
Hasselbalch HC
Kischmieder S
Marchetti M
Bacigalupo A
Finazzi G
Kreoger N
Griesshammer M
Birgegard G
Barosi G.

CRITICAL APPRAISAL OF CYTO-PV TRIAL

Risk of bias (internal validity):	The trial was not blinded: however, frequencies of subjects stopping or changing the assigned treatment was minimal (2·2 and 2·7%) in the two arms, suggesting lack of attrition bias.
External validity	The low confidence interval boundary of the HR of primary endpoint closest to no effect (HR=1) provided only 0·45-fold greater rate of cardiovascular events in patients with higher-hematocrit target (HR in the high-hematocrit group, 3.91; 95% confidence interval (CI) = 1.45 to 10.53). Thus, the **precision** of benefit was deemed to be moderate. Moreover, it is impossible to discern the relative merits of more stringent hematocrit control from those of a lower leukocyte count (**indirectness of the therapy).**
Confidence rate	The core quality of evidence of the trial was deemed moderate.

COMFORT trials -outcome: survival: Critical appraisal

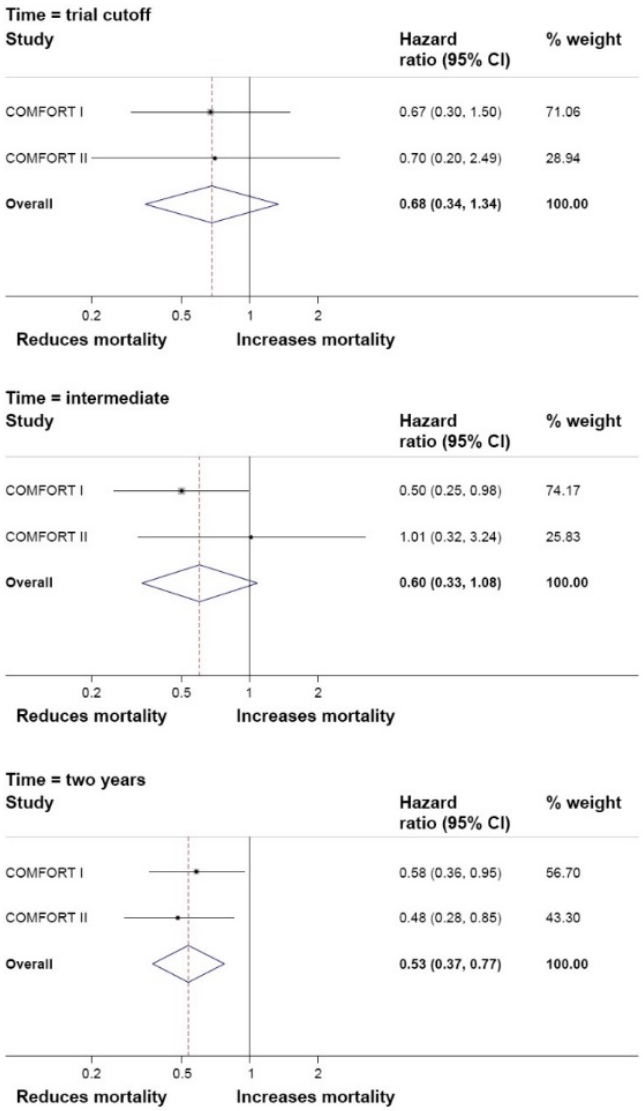


Figure 1 Forest plot of hazard ratios with their 95% CIs for survival among patients taking ruxolitinib vs controls.
Notes: Upper panel: at data cutoff. Middle panel: at a median follow-up of 55 weeks (COMFORT I) and 61.1 weeks (COMFORT II). Lower panel: at a median follow-up of 2 years (COMFORT I) and 3 years (COMFORT II).
Abbreviation: CI, confidence interval.

We applied criteria of **optimal information size** (OIS). Because meta-analysis fails to meet OIS criteria, we down-graded confidence in the estimates of survival advantage of ruxolitinib for **imprecision** (too few events).

Barosi et al. Onco Targets Ther. 2015;8:1091-102

COMFORT trials -outcome: survival. Critical appraisal

«**The original COMFORT trials were largely underpowered** to provide a precise estimation of the effect of treatment on survival, due to the short follow-up and the small number of events at the time of the cut-off analysis.
Reports of follow-up updates are richer in events.
Nevertheless, because of the high rate of cross-over to the new therapy in both trials, **the measures of the differential survival based on ITT should be regarded as imprecise estimates of the true treatment effect**.»

Cervates & Pereira. Blood. 2017;129:832-837

MF THERAPY - Outcome: Splenomegaly. Critical appraisal

Risk of bias (internal validity):	The trial was not blinded. Evidence of attrition bias.
External validity	Indirectness of the comparator (BAT) Indirectness of the outcome measurement (response in splenomegaly) High level of precision of the outcome
Confidence rate	The core quality of evidence of the effect of ruxolitinib on splenomegaly was deemed moderate.