Prima Giornata Fiorentina dedicata ai pazienti con malattie mieloproliferative croniche

Venerdì 15 aprile 2011

I nuovi farmaci per la mielofibrosi

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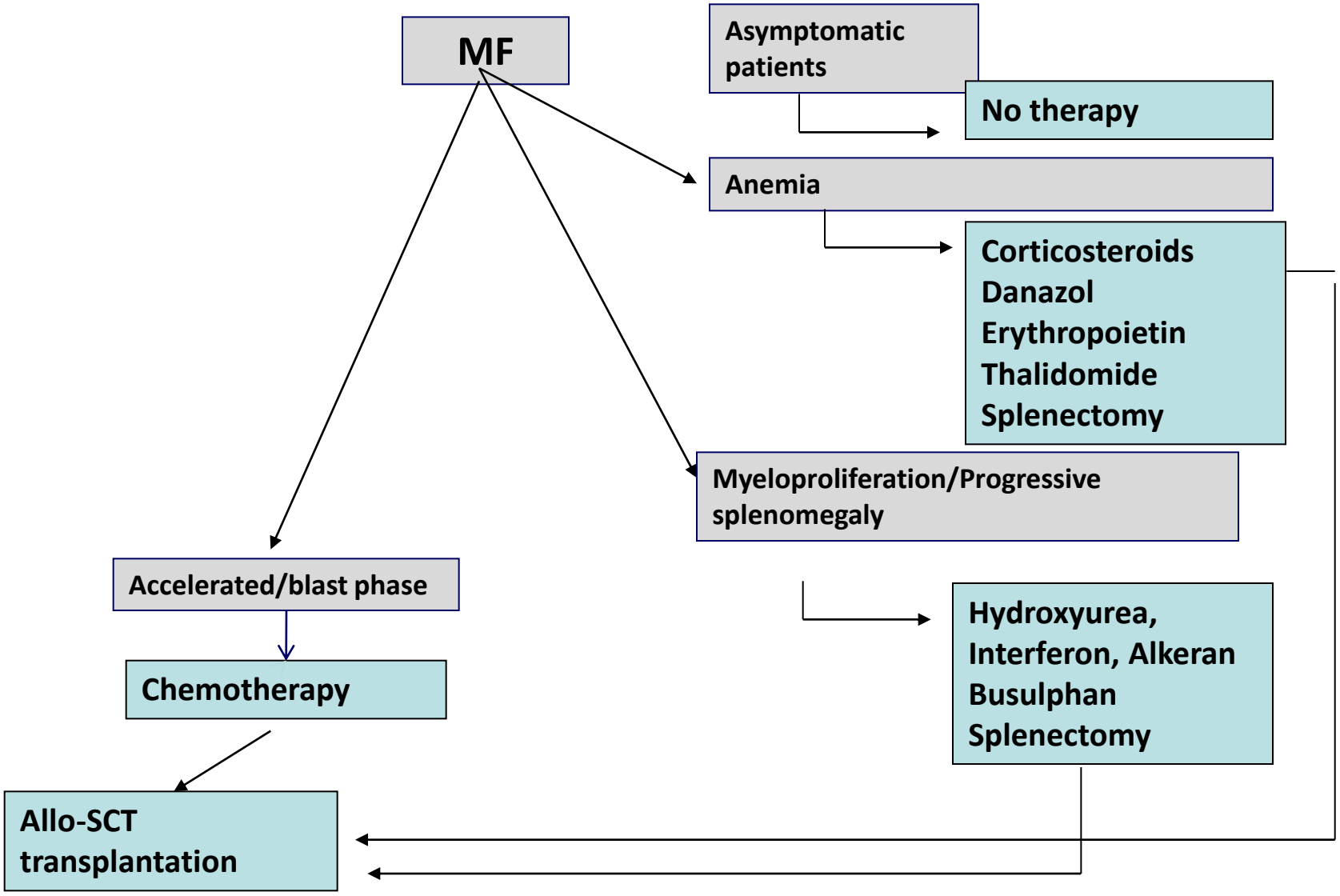
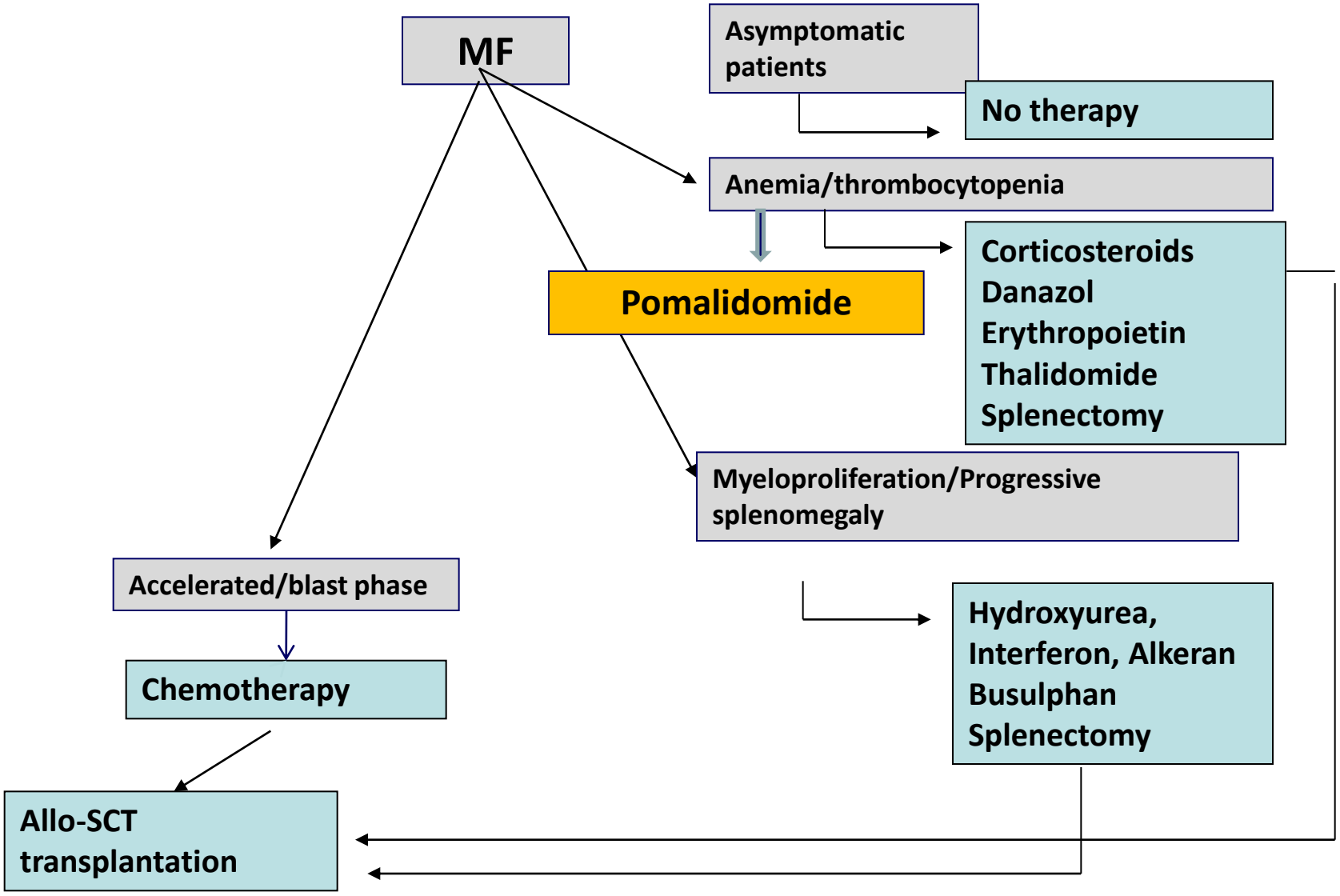
I problemi clinici rilevanti della mielofibrosi

1. Anemia
2. Splenomegalia progressiva e sintomatica
3. Accellerazione della malattia (aumento dele cellule immature nel sangue, deterioramento delle condizioni fisiche)

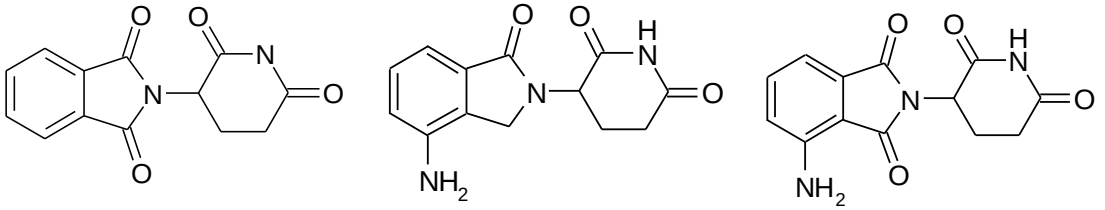
Terapia della mielofibrosi



Nuove terapie nella mielofibrosi. Pomalidomide



IMiDs In-vitro Pharmacology



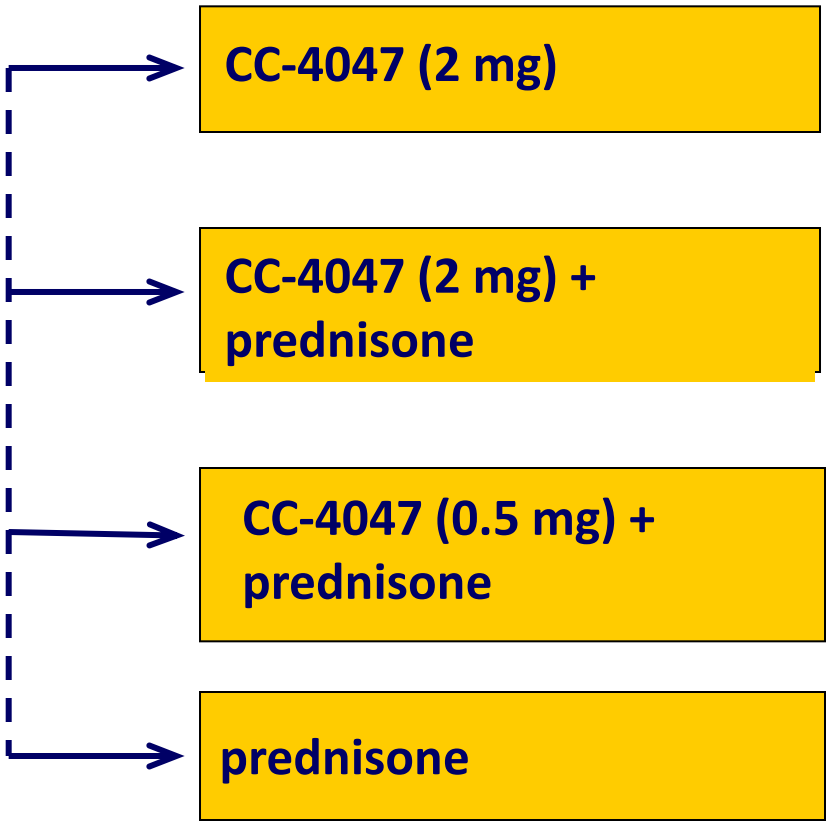
	Thalidomide	Lenalidomide	Pomalidomide
• Anti-angiogenic activity • (human explant model)	++++	+++	++++
• Anti-inflammatory activity	+	++++	+++++
• T cell/NK cell costimulation	+	++++	+++++
• Anti-proliferative activity	-	+/++	+++
• Pro-erythroid activity	-	+++	+++++

Gli studi fatti

Pomalidomide in MF (CC4047-001)

- **Background:** Pomalidomide (CC-4047, Actimid, *Celgene*) is a second generation antiangiogenic, immunomodulatory thalidomide analog with a superior toxicity and activity profile

- **Design:** Phase-2 Randomized, Multicenter, Double-blind, Active-control, Parallel-group Study
- **Sites:** USA, Europe
- **Start of enrollment**: January 07
- **End of enrollement**: May 08
- **Enrolled patients**: 84



Response rate (IWG-RT)

Treatment arm	Response on anemia among all 84 patients	Response on anemia among 62 patients who completed 3 cycles of treatment
Pomalidomide (2 mg/day) + placebo	23% (5 of 22)	38% (5 of 13)
Pomalidomide (2 mg/day) + prednisone	16% (3 of 19)	23% (3 of 13)
Pomalidomide (0.5 mg/day)	36% (8 of 22)	40% (8 of 20)
Prednisone	19% (4 of 21)	25% (4 of 16)

Tefferi A et al.: JCO, 2010

Grade 3-4 toxicities

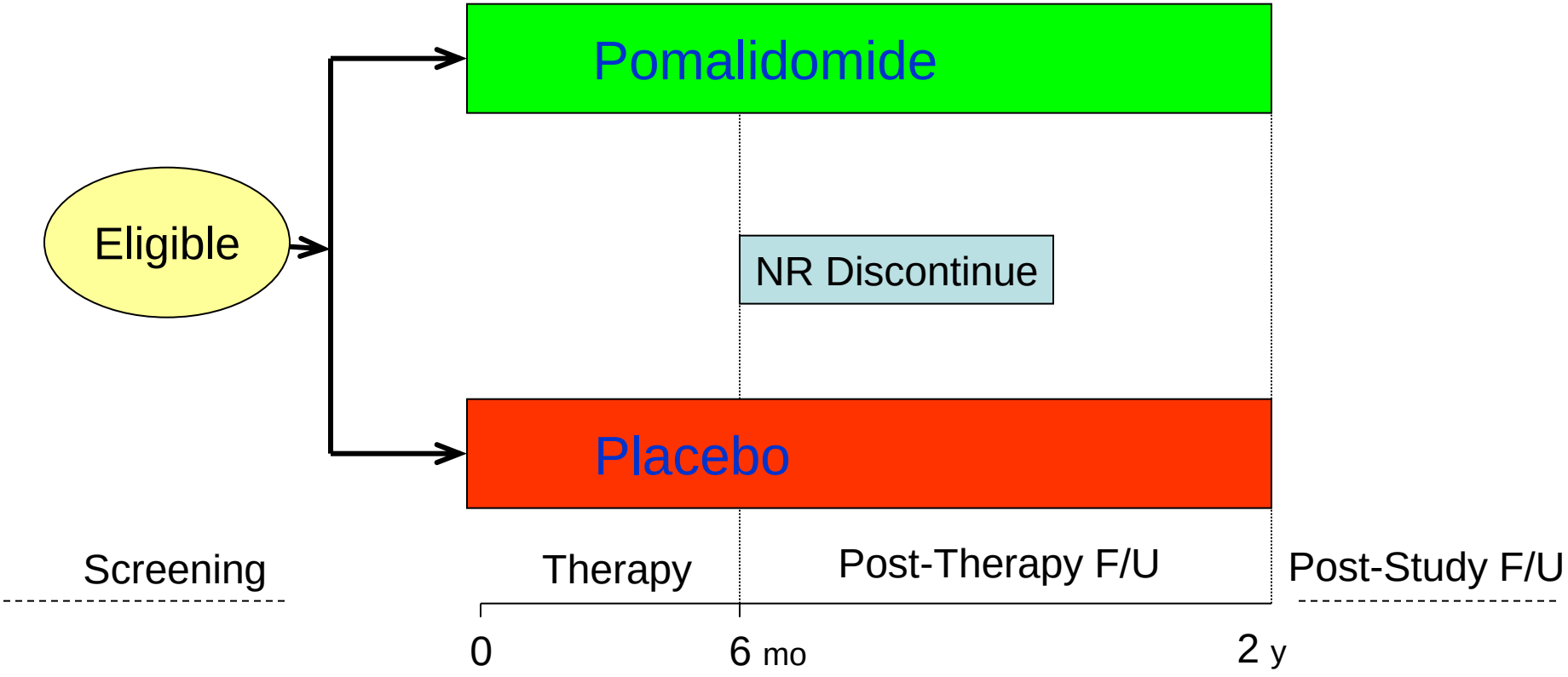
Treatment arm	Neutropenia	Thrombocytopenia	Thrombosis
Pomalidomide (2 mg/day) + placebo	9%	14%	9%
Pomalidomide (2 mg/day) + prednisone	16%	16%	5%
Pomalidomide (0.5 mg/day)	5%	9%	0%
Prednisone	5%	5%	0%

Tefferi A et al.: JCO, 2010

Gli studi in atto

CC4047-002

A phase-3, multi-center, randomized, double-blind, placebo-controlled, parallel group study to compare efficacy and safety of pomalidomide in subjects with MPN-associated MF and red blood cell-transfusion dependence



Eligibility-Criteria

- MPN-associated myelofibrosis
- Average ≥2 U RBC/28 days (prior 84 d)
- PMN ≥0.5 $x10^9$/L
- Platelets ≥25 $x10^9$/L
- Blasts <10%
- eGFR ≥30 ml/min
- Inappropriate: EPO, androgens, allotransplant
- No therapy within 30-86 d

Endpoints

1º

- RBC-transfusion-independence

2º

- Duration of RBC-transfusion-independence
- Time to RBC-transfusion-independence
- Survival
- Healthcare utilization
- Subject-reported outcomes

Centri Italiani

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Bergamo

Torino

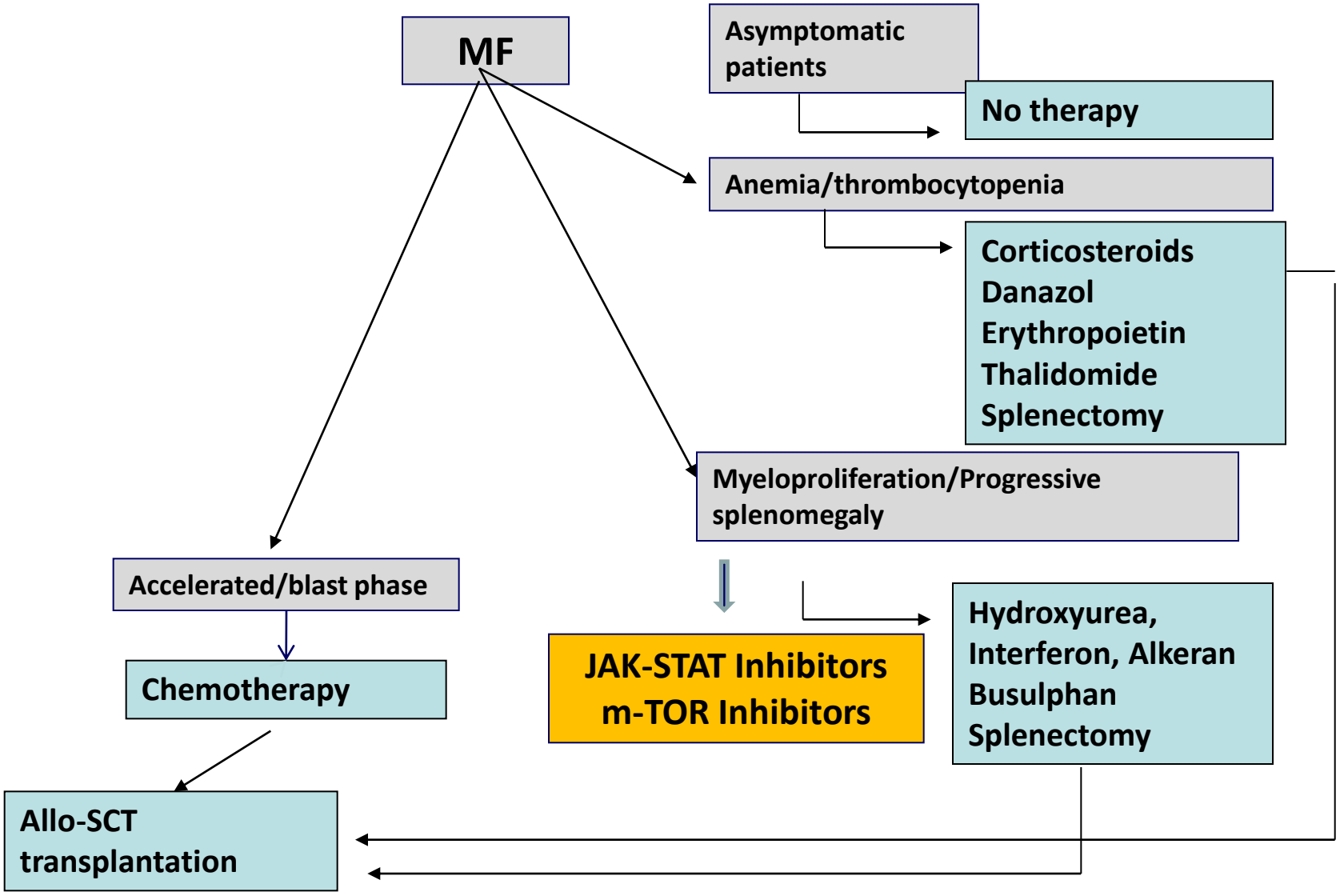
Firenze

Roma

Bari

Bologna

New Therapies in MF- Antiprolif. drugs



M-Tor Inhibitor
(Everolimus, RAD001)

STUDI FATTI

15th CONGRESS
JUNE 10 - 13, 2010
BARCELONA

EVIDENCE OF EFFICACY OF RAD001, AN INHIBITOR OF mTOR, IN A PHASE I/II STUDY IN PRIMARY MYELOFIBROSIS AND POST POLYCYTHEMIA VERA/ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS

AM Vannucchi, P Guglielmelli, L Lupo, MC Finazzi, L. Tozzi, F. Biamonte, E Antonioli, C Bogani, L Pieri, E Gattoni, A Masciulli, S Paratore, MC Susini, G Finazzi, R Marchioli, A Rambaldi, T Barbui, A Bosi, G Barosi

Division of Hematology, University of Florence; Centre for Myelofibrosis, IRCCS San Matteo, Pavia; Ospedali Riuniti di Bergamo; Mario Negri Sud Inst, Chieti; Italy

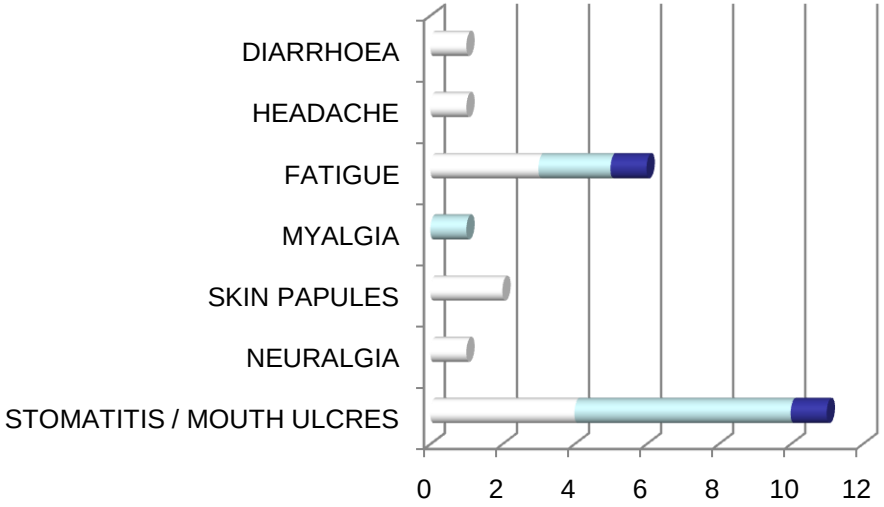
Trial information

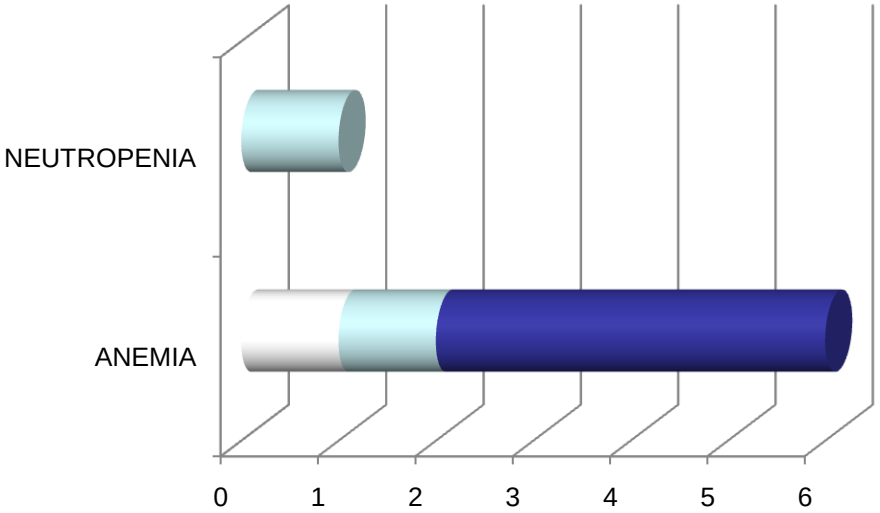
- A non-sponsored, investigator-initiated trial
- Non-randomized, open-label phase I/II study
- Phase II two-stage design according to Simon's
- Supported by Agenzia Italiana per il Farmaco (AIFA)
- Drug provided at no cost from Novartis

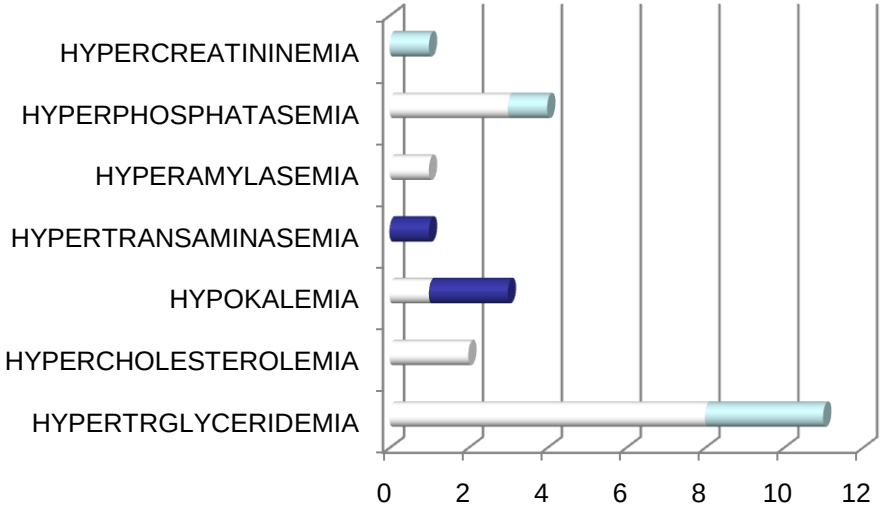
RAD001 (Everolimus): Results

- Evaluable patients (Intention to treat): 25
- Response on anemia: 25% (partial)
- Response on splenomegaly: 43% (complete and partial)
- Response on constitutional symptoms: 69%
- Response on pruritus: 80%
- EUMNET responders: 60% (27% major responses)
- No difference between JAK2 V617F mutated and non mutated patients

AE


DIARRHOEA
HEADACHE
FATIGUE
MYALGIA
SKIN PAPULES
NEURALGIA
STOMATITIS / MOUTH ULCRES
0
2
4
6
8
10
12


NEUTROPENIA
ANEMIA
0
1
2
3
4
5
6


HYPERCREATININEMIA
HYPERPHOSPHATASEMIA
HYPERAMYLASEMIA
HYPERTRANSAMINASEMIA
HYPOKALEMIA
HYPERCHOLESTEROLEMIA
HYPERTRGLYCERIDEMIA
0
2
4
6
8
10
12

Studi aperti

- Nessuno studio aperto
- Il farmaco è disponibile ad uso compassionevole da Novartis


Associazione
Mielofibrosi
Gianbattista
Mazzini