EUROPEAN RCT IN MPDs

A. Multicenter, Multinational
- EORTC
- ECLAP
- ANHIDRET

B. Multicenter, National
- French PV RCTs
- Italian ET RCT
- PT-1 RCTs

C. European Leukemia NET studies

D. Future: JAK-2 inhibitor drugs

EORTC RCT

Outcome	^{32}P (n=146)	Busulfan (n=147)	P
10-year survival	55%	70%	0.02
Vascular deaths	18%	5%	
Acute leukemia	1.5%	2%	n.s.
Myeloid splenomegaly	4%	5%	n.s.

Median follow-up: 8 yrs

EORTC, BR J Cancer 1981; 44:75

ECLAP

European Collaboration on Low-dose Aspirin in Polycythaemia vera

A randomised, parallel, double-blind, placebo-controlled trial

The study has been conceived, conducted, analyzed, interpreted, and (will be) published independently under the direct responsibility of the ECLAP Steering Committee.

Bayer AG partially supported the study and furnished the study drug.

BIOMED 2 Program, Contract No. ERBBMH4CT961433

EUROPEAN COLLABORATION ON LOW-DOSE ASPIRIN IN PV

Research Network

Participating Countries 12

Haematological Centres 94

Countries	Centres	No. of Pts *1,638*
Austria	**5**	**133**
France	**1**	**37**
Germany	**2**	**6**
Greece	**2**	**12**
Ireland	**2**	**7**
Israel	**4**	**59**
Italy	**40**	**1043**
Netherlands	**2**	**21**
Spain	**8**	**62**
Sweden	**19**	**201**
Switzerland	**3**	**6**
United Kingdom	**6**	**51**

FRENCH POLYCYTHEMIA STUDY GROUP

RCT IN PTS < 65 yrs

Outcomes	HU (n=150)	Pipobroman* (n=142)	P
Survival, at 14 yrs	70%	70%	
Thrombosis	=	=	
Leukemia/MDS	10%	10%	
Myelofibrosis	17%	2.1%	0.03

Max. follow-up: 16 yrs

* A piperazine derivative with an alkylating mechanism of action

(Najean, Blood 1997; 90:3370)

PATIENTS WITH ET AT HIGH RISK OF THROMBOSIS

HIGH RISK **(randomized clinical trial)****

114 patients

56
Hydroxyurea

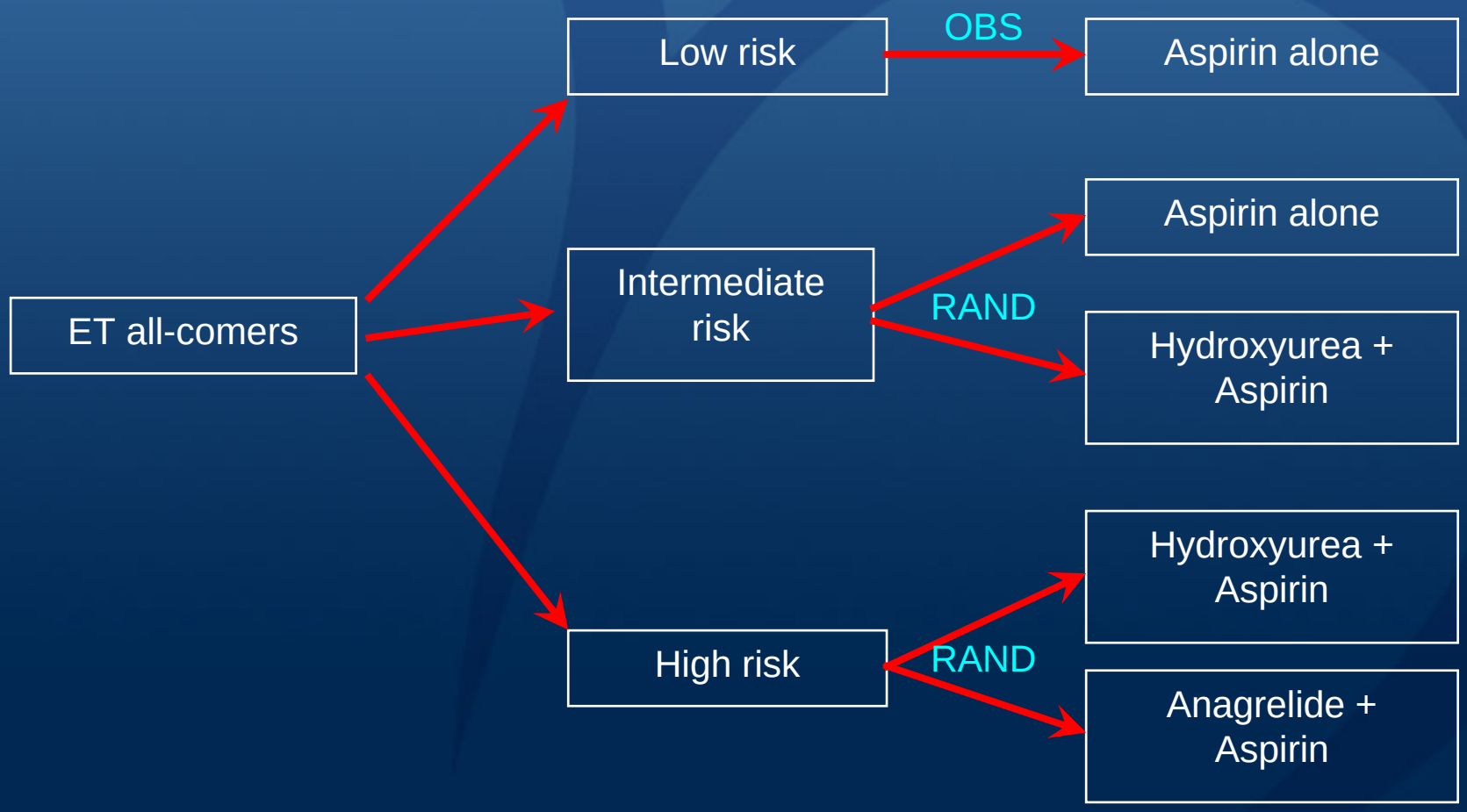
58
No cytoreduction

Median follow-up: 73 months

*** > 60 years old; previous thrombosis**
**** NEJM, 1995**

ECLAP

The PT-1 trials



NEJM 2005; 353: 33-45

EUROPEAN LEUKEMIA NET
CLINICAL TRIALS IN MPDs

WP-9

1. Registration study of high risk ET patients
   treated with Anagrelide(multicenter,multinational)
   Shire sponsored

2. Phase II study with Imatinimib in PV patients:
   completed (Germany)

3. Phase II clinical study of Velcade in Myelofibrosis:
   completed(Italy)

4. CYTO-PV RCT exploring two different HCT targets
   in PV (Italy)

ECLAP

IS PROTEASOME INHIBITION VALUABLE FOR MYELOFIBROSIS?

Giovanni Barosi
European Leukemia Net

ECLAP

Proteasome Inhibition Impairs Myelofibrosis and Osteosclerosis in TPO Mice

- Lethal murine model of myelofibrosis induced by TPO overexpression
- Bortezomib was able to inhibit TPO-induced NF-kB activation leading to deceased IL-1 alpha plasma levels
- Bortezomib decreased TGF-beta1 levels in marrow fluids and impaired marrow and spleen fibrosis development
- Bortezomib impaired osteosclerosis development through osteoprotegerin inihibition
- Bortezomib improved TPO^{high} mouse survival

Wagner-Ballon O, et al. Blood 2007

ECLAP

Overall Study Design

Objectives:

Primary:

Phase 1:

To determine the maximum tolerated dose (MTD) based on dose-limiting toxicity (DLT) of single-agent therapy with bortezomib (VELCADE®) in subject with MF who require therapy.

Phase 2:

a) To determine the rate of complete or major clinico-hematological response from treatment with bortezomib (VELCADE®) in this subject population as measured by the EUMNET response criteria.

b) To determine the safety.

ECLAP

Overall Study Design

Objectives:

Secondary:

To examine the effect of treatment on the following markers of disease:

- Bone marrow fibrosis and cellularity as standardized by the EUMNET Working Group; bone marrow microvessel density by immunostaining with anti-CD34 antibody.
- *JAK2* V617F mutational status in peripheral blood granulocytes by quantitative RT PCR
- CD34+ cell count in peripheral blood measured by cytofluorimetry
- Plasma VEGF, TGF-ß, SDF-1 levels by commercial assays
- CXCR4 cytofluorimetric expression on circulating CD34+ cells

ECLAP

Maximum Tolerated Dose

Dose Cohort	Patients Enrolled	Dose Limiting Toxicity
1 (0.8 mg/m^2/twice weekly)	3	0
2 (1 mg/m^2/twice weekly)	3	0
3 (1.3 mg/m^2/twice weekly)	6	1
Total	12	1

The MTD resulted to be 1.3 mg/m2/twice weekly

ECLAP

Conclusions from the Phase I Study

- The MTD defined in our study was 1.3 mg/m^2 given in 4 doses every 21 days for 6 cycles
- The most frequently encountered toxicity was thrombocytopenia, occurring at all dose levels.
- Four grade 3 toxicities represented 30% of severe toxicities, that is the expected rate in patients not receiving steroid therapy.
- No evidence of biologic effect on hematologic parameters. None of the patients achieved a response by standard criteria.
- Increase in CD34+ cells seems to be a biological paradoxic effect of Bortezomib and deserves explanation.
- The phase II study is running

New drugs in MPDs

Name	Company	Target	Status
INCB018424	Incyte	JAK2	Phase I/II
AZ2848	Astra Zeneca	JAK2	Preclinical
XL019	Exelexis	JAK2	Preclinical
CEP701	Cephalon	JAK2	Phase I
TG101209 and 101348	TargeGen Inc.	JAK2	Phase I/II
Erlotinib	Roche	JAK2	Preclinical
ITF2357	Italfarmaco	H-DAC	Phase I/II
Velcade	Janssen-Cilag	Proteasome	Phase I/II
Avastin	Roche	VEGF	Phase I/II
Everolimus	Novartis	TOC	Phase I

ECLAP

Toxicity Summary - Phase I trial (N=12)

Event	All adverse events	Grade 3 events
Thrombocytopenia	3	1
Fatigue	2	0
Rush	2	0
Pyrexia	2	0
Dyspnoea with pulmonary distress syndrome	1	1
Dyspnoea with pulmonary hypertension	1	1
Cutaneous vasculitis	1	1
Peripheral neuropathy	1	0