



## The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

## 631. CHRONIC MYELOID LEUKEMIA: BIOLOGY AND PATHOPHYSIOLOGY, EXCLUDING THERAPY

## ELN Criteria for Cytoreduction Start Identify Patients with Polycythemia Vera at Higher Thrombotic Risk

Francesca Palandri, MD<sup>1</sup>, Giulia Benevolo, MD<sup>2</sup>, Elena Maria Elli, MD<sup>3</sup>, Roberto Latagliata<sup>4</sup>, Giuseppe Auteri, MD<sup>5,6</sup>, Filippo Branzanti, MSc<sup>1</sup>, Mario Tiribelli, MD<sup>7</sup>, Francesco Cavazzini, MD<sup>8</sup>, Alessia Tieghi, MD<sup>9</sup>, Nicola Polverelli, MD<sup>10</sup>, Alessandra D'Addio, MD<sup>11</sup>, Elisabetta Abruzzese, MD<sup>12</sup>, Federica Colombo, MD<sup>13</sup>, Marta Venturi<sup>1,5</sup>, Francesco Ramundo<sup>14,15</sup>, Rikard Mullai, MD<sup>16</sup>, Antonio Cuneo, MD<sup>17</sup>, Benedetto Bruno, MD PhD<sup>18</sup>, Michele Cavo, MD<sup>19,5</sup>, Giuseppe Alberto Palumbo, MD<sup>20</sup>, Florian H Heidel, MD<sup>21</sup>, Massimo Breccia<sup>22</sup>, Valerio De Stefano, MD<sup>15,23</sup>

<sup>1</sup>IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy, Bologna, Italy

<sup>2</sup>University Hematology Division, Città della Salute e della Scienza Hospital, Torino, Italy, Torino, Italy

<sup>3</sup>Fondazione IRCCS, San Gerardo dei Tintori, Monza, Monza, Italy

<sup>4</sup>Hematology Unit, Ospedale Belcolle, Viterbo, Italy, Rome, ITA

<sup>5</sup>Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy, Bologna, Italy

<sup>6</sup>IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy, Bologna, ITA

<sup>7</sup>Division of Hematology and BMT, Department of Medical Area, University of Udine, Udine, Italy

<sup>8</sup>Division of Hematology, University of Ferrara, Ferrara, Ferrara, ITA

<sup>9</sup>Department of Hematology, Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Reggio Emilia, ITA

<sup>10</sup>Unit of Blood Diseases and Stem Cells Transplantation, Department of Clinical and Experimental Sciences, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Brescia, Italy

<sup>11</sup>Division of Hematology, Onco-hematologic Department, AUSL della Romagna, Ravenna, Ravenna, ITA

<sup>12</sup>Division of Hematology, Ospedale S. Eugenio, Roma, Roma, Italy

<sup>13</sup>Hematology Department, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy

<sup>14</sup>Hematology Division, Sapienza University, Policlinico Umberto I, Rome, Roma, Italy

<sup>15</sup>Institute of Hematology, Catholic University School of Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Roma, Italy

<sup>16</sup>Division of Hematology and BMT, Department of Medical Area, University of Udine, Udine, Udine, Italy

<sup>17</sup>Division of Hematology, University of Ferrara, Ferrara, Ferrara, Italy

<sup>18</sup>Division of Hematology and Stem Cell Transplant Unit, University Hospital AOU Città della Salute e della Scienza, Torino, Italy

<sup>19</sup>Dipartimento di Scienze Mediche e Chirurgiche, University of Bologna, Bologna, Italy

<sup>20</sup>Department of Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia", University of Catania, Catania, Catania, Italy

<sup>21</sup>Internal Medicine II, Hematology and Oncology, Friedrich-Schiller-University Medical Center, Jena, Germany, Greifswald, Germany

<sup>22</sup>Division of Cellular Biotechnologies and Hematology, University Sapienza, Roma, Roma, Italy

<sup>23</sup>Hematology Division, Sapienza University, Policlinico Umberto I, Rome, Roma, Italy

## Introduction

Recently, the European Leukemia Net (ELN) recommended cytoreduction in patients (pts) with Polycythemia Vera (PV) at low risk (LR) (age <60 yrs & no previous thromboses) but carrying additional criteria for therapy start (CTS) (Marchetti M et al, *Lancet Haematol* 2022). Little is known about: 1] efficacy of hydroxyurea (HU) in LR pts, high risk due to age >60 yrs (HR-AGE) or high risk due to previous thrombosis regardless of age (HR-THRO); 2] impact of CTS on thrombotic risk.

## Aims

In a large cohort of HU-treated PV pts, we investigated if thrombotic risk was influenced by: 1] conventional risk factors for thrombosis; 2] ELN-defined complete response (CR) at 12 mos; 3] presence of CTS.

## Methods

After IRB approval, data of 961 WHO2016-defined PV pts were retrospectively collected by 21 Hematology Centers. In April 2023, an update was performed in 10 participating Centers with specific focus on CTS at diagnosis and HU start; 504 HU-treated pts resulted eligible for this analysis. Therapy was at discretion of the treating hematologist. Pts were followed until death or data cut-off date.

CTS evaluated for association with thrombosis included: persistent/progressive leukocytosis (100% increase if white blood cells (WBC)  $<10 \times 10^9/L$  or 50% increase if WBC  $>10$  or WBC  $>15$  at diagnosis and HU start); extreme persistent thrombocytosis ( $>1000 \times 10^9/L$  platelets (PLT) at diagnosis and HU start); progressive splenomegaly (increase of  $>5$  cm from diagnosis); inadequate hematocrit (Hct) control ( $>6$  PHL/yr; HCT  $>53\%$  at diagnosis and HU start; PHL intolerance); uncontrolled cardiovascular risk factors (CVRF). Symptoms were present as the only ELN criterion in 40 patients, of whom none had thrombosis; therefore, they were not included in the analysis.

#### Results

504 pts received HU: 81 pts were at LR and 423 (83.9%) were at HR (HR-AGE, no. 290, 57.5%; HR-THRO, no. 133, 26.4%). Median time on HU was 11.6 yrs (0.1-23.1).

During HU, 53 pts had 69 thromboses (35 arterial) for an incidence rate of thrombosis (IR-thro) of 1.5 %p-y, comparably in LR and HR (Table 1). Notably, IR-thro was equal in LR and HR-AGE ( $p=0.94$ ), but significantly higher in HR-THRO pts ( $p=0.005$  vs LR and  $p=0.009$  vs HR-AGE).

At 12 months, CR was achieved by 8.2%, 23% and 25% of LR, HR-AGE and HR-THRO pts, respectively (LR vs HR-AGE and HR-THRO,  $p<0.001$  and  $p=0.003$ ).

Thrombosis-free survival (TFS) by landmark analysis at 12 months was significantly better in CR pts ( $p=0.01$ ). Specifically, best TFS was observed in LR and HR-AGE pts with CR, while HR-THRO pts without CR had the worst TFR ( $p=0.009$ ).

CTS were observed in 255 (50.6%) pts: 48 LR (59.3%), 139 HR-AGE (47.9%) and 68 HR-THRO (51.1%). In the remaining LR pts, HU was triggered by mild thrombocytosis ( $<1000 \times 10^9/L$ ) and/or mild leukocytosis ( $<15 \times 10^9/L$ ) and/or mild splenomegaly ( $<5$  cm from costal margin) and/or persistent systemic symptoms.

CTS were associated to significantly increased of IR-thro in the overall cohort ( $p<0.001$ ), in LR pts ( $p=0.04$ ), in HR-AGE pts ( $p=0.02$ ) and in HR-THRO pts ( $p=0.03$ ) (Table 1). The impact of CTS was confirmed in the overall cohort both for arterial (1.30 vs 0.44 %p-y,  $p=0.01$ ) and venous thrombosis (1.37 vs 0.44 %p-y,  $p=0.007$ ).

TFS at 5 yrs was 87% and 95% in pts with or without CTS ( $p<0.001$ ) (Fig. 1a). In presence of CTS, TFS of LR and HR-AGE pts were comparable to HR-THRO pts without CTS (Fig. 1b).

In multivariate Cox analysis considering age  $>60$  yrs, previous thrombosis, CTS, and CR to HU at 12 months, CTS and previous thrombosis remained associated with thrombotic risk (HR: 2.7, 95% CI: 1.4-5,  $p=0.002$ ; HR: 2.4, 95% CI: 1.4-4.2,  $p=0.001$ ).

Finally, in 59 additional LR pts untreated with HU, IR-thro was 0.78 in absence of CTS, and 1.57 %p-y in presence of such criteria.

#### Conclusions

Albeit retrospective, this study shows for the first time that ELN criteria for therapy start including splenomegaly, leukocytosis, thrombocytosis, uncontrolled Hct and CVRF, identified an increased risk phenotype either in LR and HR pts treated with HU. This was confirmed also in HU-untreated pts.

Also, lack of CR at 12 months was detrimental on TFS particularly in HR-THRO pts, and less significantly than CTS.

These findings, that complement data from the Majic-PV trial (Harrison CN et al, J Clin Oncol 2023), dictate better management of HU therapy, and call for greater attention to CTS and their integration into prognostic models that go beyond the two categories related only to age and thrombotic history.

**Disclosures Palandri:** Novartis, BMS, Celgene, GSK, Amgen, AbbVie, Karyopharm, AOP, Sierra Oncology, Janssen: Consultancy, Honoraria. **Elli:** Novartis: Membership on an entity's Board of Directors or advisory committees; BMS: Membership on an entity's Board of Directors or advisory committees. **Latagliata:** Janssen: Honoraria; Novartis: Honoraria; BMS: Honoraria; Celgene: Honoraria. **Cavazzini:** Novartis: Honoraria; Pfizer: Honoraria; Incyte: Honoraria. **Polverelli:** Abbvie: Honoraria; GSK: Honoraria; BMS: Honoraria; Novartis: Honoraria. **Abruzzese:** Takeda: Consultancy; Novartis: Consultancy, Membership on an entity's Board of Directors or advisory committees; Pfizer: Consultancy; Incyte: Consultancy, Membership on an entity's Board of Directors or advisory committees; BMS: Consultancy, Membership on an entity's Board of Directors or advisory committees. **Cavo:** GlaxoSmithKline: Honoraria; Adaptive: Honoraria; Janssen: Consultancy, Honoraria, Speakers Bureau; Celgene/Bristol Myers Squibb: Consultancy, Honoraria, Speakers Bureau; Sanofi: Consultancy, Honoraria; Takeda: Honoraria; AbbVie: Consultancy, Honoraria; Amgen: Honoraria; Roche: Honoraria. **Palumbo:** Incyte: Speakers Bureau; GSK: Membership on an entity's Board of Directors or advisory committees; Morphosys: Membership on an entity's Board of Directors or advisory committees; BeiGene: Honoraria; Janssen: Honoraria; Abbvie: Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; AstraZeneca: Membership on an entity's Board of Directors or advisory committees; AOP: Membership on an entity's Board of Directors or advisory committees; BMS: Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Novartis: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Heidel:** Amgen: Consultancy, Honoraria; Abbvie: Consultancy, Honoraria; AOP: Consultancy, Honoraria; Novartis: Consultancy, Honoraria, Research Funding; CTI: Consultancy, Honoraria, Research Funding; Kartos: Consultancy, Honoraria; Celgene/BMS: Consultancy, Honoraria, Research Funding. **Breccia:** BMS: Honoraria; Pfizer: Honoraria; Incyte: Honoraria; AOP: Honoraria; AbbVie: Honoraria; Novartis: Honoraria. **De Stefano:** Alexion: Consultancy, Honoraria; AOP: Consultancy, Honoraria; Amgen: Consultancy, Honoraria; Celgene: Consultancy, Honoraria; Grifols: Consultancy, Hon-

oraria; Novartis: Consultancy, Honoraria; Sanofi: Consultancy, Honoraria; SOBI: Consultancy, Honoraria; Takeda: Consultancy, Honoraria; Novartis: Research Funding.

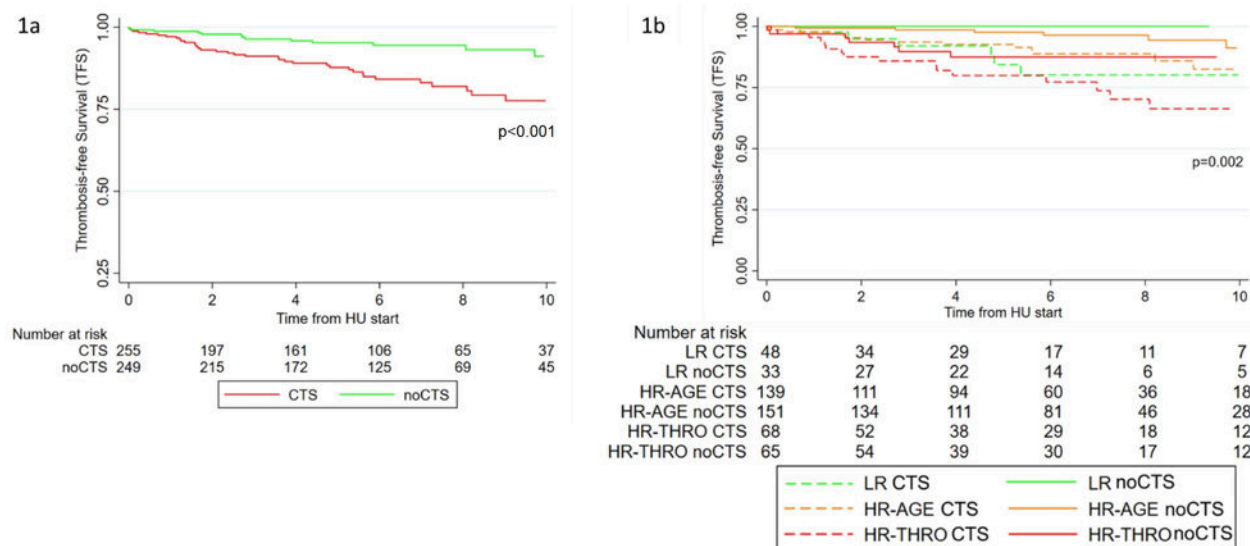
**Table 1: Incidence rate of thrombosis per 100 pt-years in the different risk categories.**

In LR pts, thromboses were censored at the age of 60.

	Overall	CTS (no.255)	noCTS (no.249)	p
HR-THRO (no. 133)	2.97	4.36	1.67	0.03
HR-THRO only (no.30)	1.90	6.03	0	0.01
HR-THRO & AGE (no. 103)	3.35	4.02	2.56	0.34
HR-AGE (no. 290)	1.30	1.98	0.72	0.02
LOW RISK (no. 81)	1.32	2.28	0	0.04
All pts (no. 504)	1.5	2.67	0.89	<0.001

**Fig.1. Thrombosis-free survival.**

TFS was evaluated according to presence of ELN criteria for therapy start (CTS) at HU start (*fig.1a*, in the overall cohort; *fig.1b*, in the different thrombotic risk categories)



**Figure 1**

<https://doi.org/10.1182/blood-2023-181553>