Microangiopatie trombotiche: novità da ASH Orlando 2025

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European Reference Network | Hematological Diseases (ERN EuroBloodNet)

Disclosures

- Speaker at educational meetings oganized by Sanofi

Outline

1) Diagnosi e stratificazione prognostica della TTP immunomediata (iTTP)

2) Trattamento della iTTP in fase acuta

3) Trattamento della iTTP durante la remissione clinica

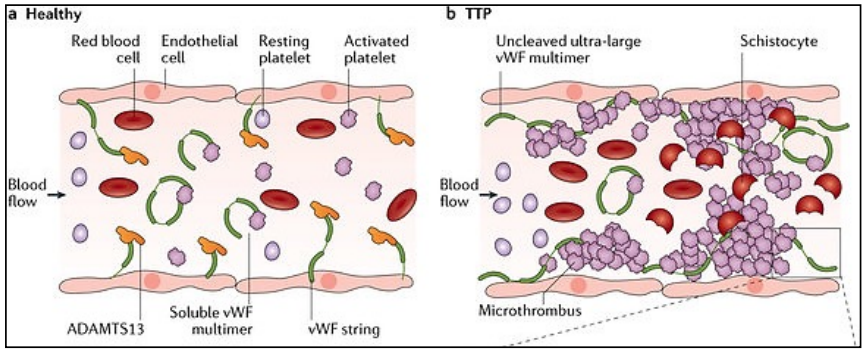
4) Trattamento della TTP congenita (cTTP)

TTP: a life-threatening disease

Rare thrombotic microangiopathy:

- Platelet consumption → **severe thrombocytopenia**
- Red blood cell fragmentation → **Coombs-negative hemolytic anemia**
- Formation of platelet-rich thrombi in the microcirculation → **tissue ischemia** (**brain,** kidney, heart)
- **90% lethal** if not promptly treated

A microvessel in a healthy individual vs a patient with TTP



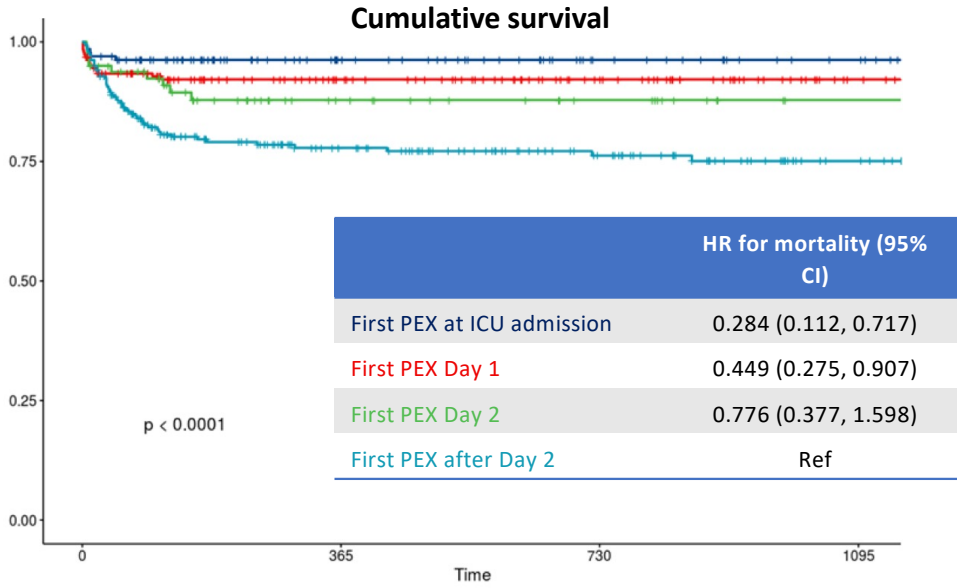
Caused by ADAMTS13 severe deficiency (activity <10% of normal)

- ADAMTS13 gene mutation [**congenital** TTP (**cTTP**)] **5%**
- Autoantibodies [acquired **immune-mediated** TTP (**iTTP**)] **95%**

Bhandari S, et al. N Engl J Med. 2019; Zheng XL, et al. J Thromb Haemost. 2020

Diagnosi e stratificazione prognostica della iTTP - premessa

- Nella TTP «time is life»



	HR for mortality (95% CI)
First PEX at ICU admission	0.284 (0.112, 0.717)
First PEX Day 1	0.449 (0.275, 0.907)
First PEX Day 2	0.776 (0.377, 1.598)
First PEX after Day 2	Ref

- La decisione di iniziare terapia si basa sul **PLASMIC score**, non sull'esito di ADAMTS13 *(ISTH guidelines)*

PLASMIC ≥6 → alto

Platelet count <30 x 10^9/L	**No 0**	Yes +1
Hemolysis Reticulocyte count >2.5%, haptoglobin undetectable, or indirect bilirubin >2.0 mg/dL (34.2 µmol/L)	**No 0**	Yes +1
Active cancer Treated for cancer within the past year	No +1	Yes 0
History of solid-organ or stem-cell transplant	No +1	Yes 0
MCV <9.0 x 10^{-14} L (<90 fL)	**No 0**	Yes +1
INR <1.5	**No 0**	Yes +1
Creatinine <2.0 mg/dL (176.8 µmol/L)	**No 0**	Yes +1

Zheng XL, et al. J Thromb Haemost. 2020; Van de Louw A, et al. PLoS One. 2021

Diagnosi e stratificazione prognostica della iTTP - novità da ASH

1) Ridurre le barriere al test ADAMTS13

Oral

901. Health Services and Quality Improvement: Non-Malignant Conditions Excluding Hemoglobinopathies

FAST4TMA: A national rapid ADAMTS13 testing initiative for TMA patients — 2025 update

Clare Martin [1], Ara Metjian [2]

- FAST4TMA operates across the United States, coordinating testing via a **centralized high-throughput reference lab**
- In- and out-patients (48% prelievi domiciliari)
- **Cost-effective** → saved approximately $4.34 million in downstream care costs (unnecessary PEX, admissions)
- **Patient benefit** → early recognition of ADAMTS13 relapse

2) Migliorare gli score diagnostici…

Oral

331. Thrombotic Microangiopathies/Thrombocytopenias: Clinical and Epidemiological

External validation of TTP-14: A novel machine learning model that improves rapid diagnosis of immune TTP

Mouhamed Yazan Abou-Ismail [1], Meera Sridharan [2], Chong Zhang [3], Peter Kouides [4], Ming Lim [1]

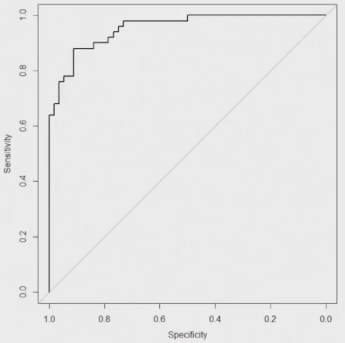
- PLASMIC score (7 items) ha basse specificità (58%) e PPV (51%)
- **TTP-14** usa **14 items** (4 clinici + 10 lab)

TTP-14 outperformed PLASMIC in the external validation cohort

- External validation cohort included 50 iTTP patients, 56 controls

Among patients without missing PLASMIC variables (n=93):

- TTP-14 achieved an **AUC of 0.96 (95% CI: 0.93–0.99)**
- It outperformed PLASMIC's **AUC of 0.90 (95% CI: 0.83–0.96)**
- TTP-14's AUC in this cohort also exceeded its own previously reported cross-validated AUC of **0.91 (95% CI: 0.90–0.92)** from the development cohort



- TTP-14 mantiene accuratezza diagnostica in **pazienti over60** (AUC 0.98) e in caso di **mancanza di variabili di laboratorio**

3) … ma gli score prognostici ?

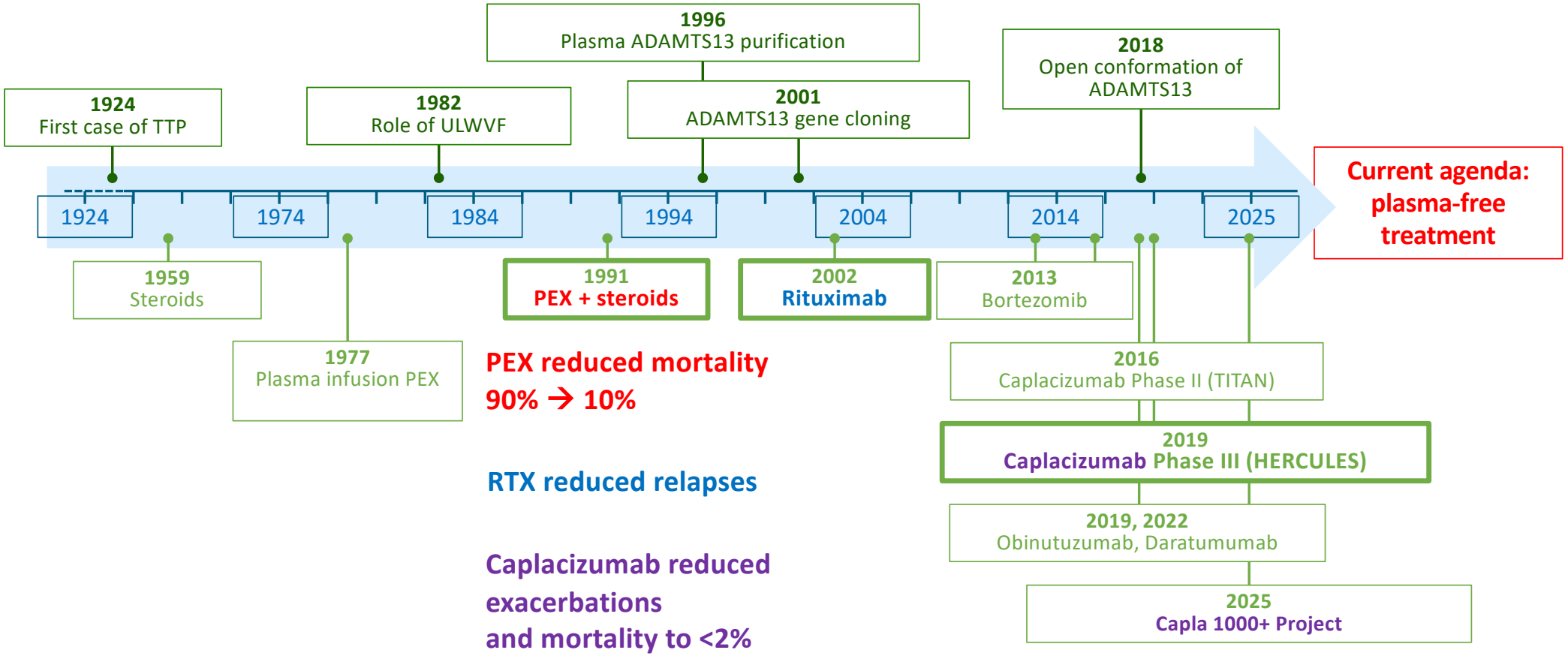
Poster

331. Thrombotic Microangiopathies/Thrombocytopenias: Clinical and Epidemiological

Mortality in immune TTP remains unpredictable: Shortcomings of prediction models despite machine learning advances

Mouhamed Yazan Abou-Ismail [1], Meera Sridharan [2], Sanjana Kashinath [3], Mukul Singal [4], Rishabh Singh [5], Simon Bechara [6], Ashley Khouri [7], Cecilia Peterson [7], Ho Jun Lee [8], Carley Mitchell [9], Manasa Kandula [6], Chong Zhang [10], Peter Kouides [11], Lalitha Nayak [5], Marshall Mazepa [12], Ming Lim [1], USTMA Investigators [13]

Trattamento della iTTP in fase acuta - premessa



Cataland SR, et al. Blood. 2024
Coppo P, et al. EClinicalMedicine. 2025

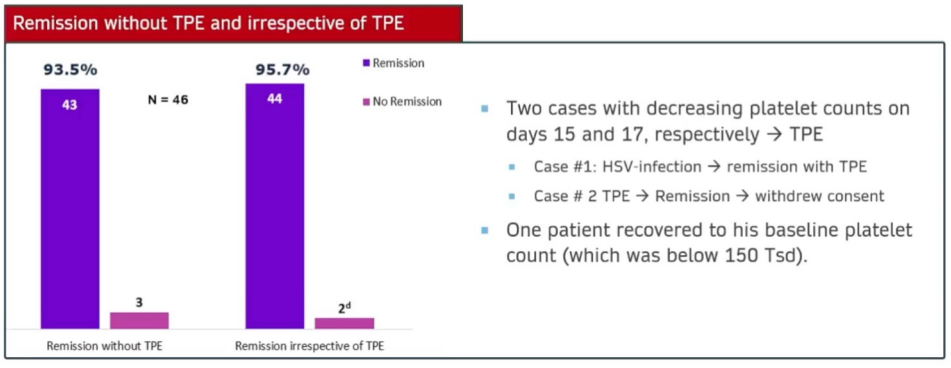
Trattamento della iTTP in fase acuta - nuovi paradigmi PEX-free … e unmet needs

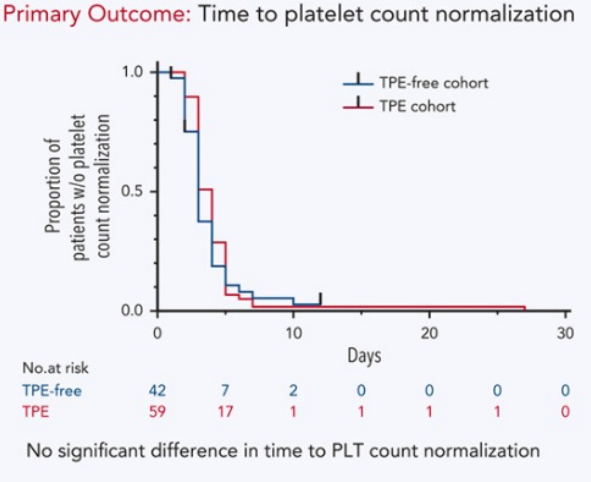
CHANGES IN iTTP THERAPY PARADIGMS

	Historical paradigm	Novel paradigm
Plasma Exchange	Frontline until platelets > 150 x 10E9/L + 2 days	Few or none
Caplacizumab initiation	Rescue medication (exacerbation, refractory)	Frontline
Caplacizumab duration	Platelet guided or fixed scheme (30 + 28)	ADAMTS13-guided

- **Stroke** nel 30-40% dei pazienti **all'esordio**
- Stroke overt e silenti nel 50% dei survivors **durante follow-up**

MAYARI - PRIMARY AND SECONDARY ENDPOINTS





Warnings about PEX-free approach

- Solo in centri TTP-expert
- Disponibilità PEX 24/7
- Dosaggio ADAMTS13 24/7 entro poche ORE

Truma A, et al. Thromb Res. 2024; Volker L. ASH 2025 educational; Sukumar S. ASH 2025 educational

Trattamento della iTTP in fase acuta - novità da ASH 2025 1/2

Rationale: the initial thrombus burden at the time of iTTP diagnosis remains unresolved → prolonged ischemic organ damage

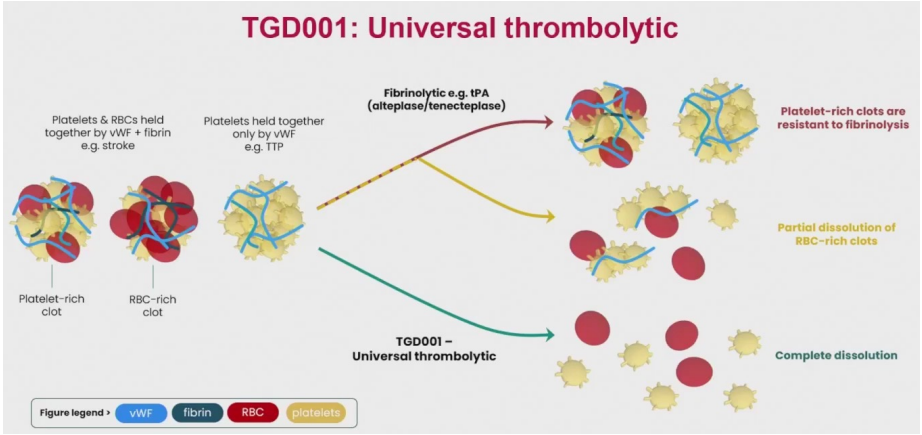
1) TGD001 in murine models

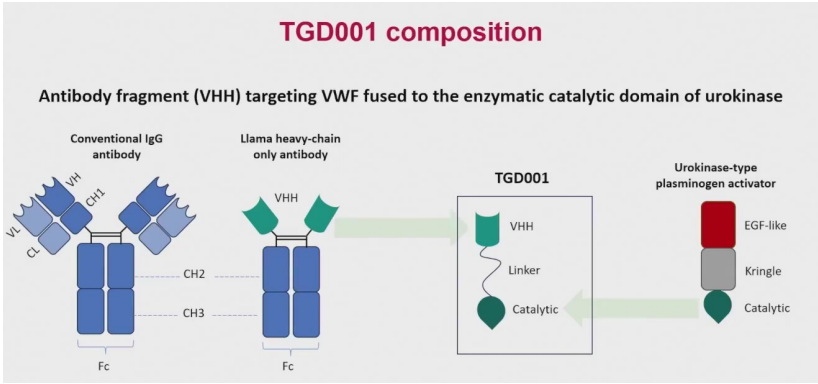
Oral

330. Vascular Biology, Thrombosis, and Thrombotic Microangiopathies: Basic and Translational

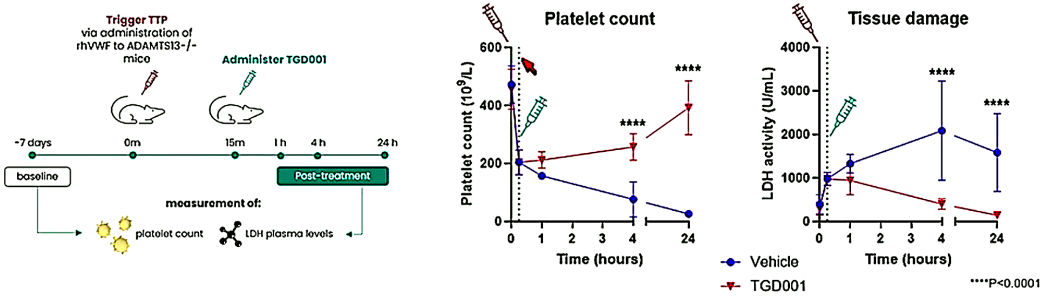
Novel von willebrand factor targeting thrombolytic TGD001 is effective in diverse thrombotic models, demonstrating its potential as a universal thrombolytic

Volker Laux [1], Claudia Tersteeg [2], Sarah Vandelanotte [3], Sarah Mc Fie [1], Danielle Versluis [1], Filio Petsini [1], Anne-Sophie Delmote [2], Kristof Vercruysse [1], Simon de Meyer [3], Karen Vanhoorelbeke [2], Steven de Maat [1]





TGD001 restores platelet count and reduces tissue damage in TTP



Modelli murini di TTP (VWF-rich) e diabete (fibrin-rich)

- TGD001 riduce la perdita di tessuto neuronale
- TDG001 agisce in maniera proporzionale al contenuto di VWF

Trattamento della iTTP in fase acuta - novità da ASH 2025 2/2

2) TGD001 in healthy volunteers

Oral

331. Thrombotic Microangiopathies/Thrombocytopenias: Clinical and Epidemiological

Novel von willebrand factor targeting thrombolytic TGD001 is safe and well tolerated in a phase 1 first-in-human trial

Marie Scully [1 2], Spero Cataland [3], Paul Coppo [4 5], Paul Knoebl [6], Paul Brinkkoetter [7], Javier de la Rubia [8 9], Marielle Klein Hesselink [10], Josefin-Beate Holz [10], Flora Peyvandi [11 12]

Phase 1 Study

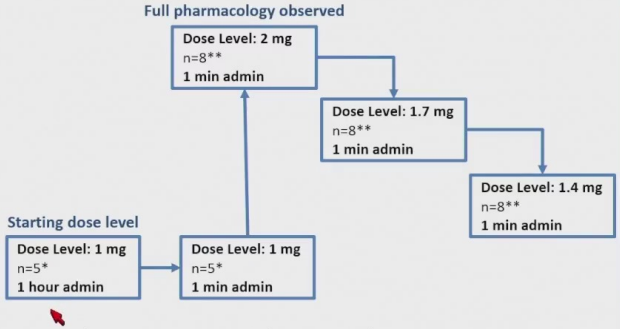
Study design
Randomized, double-blind, placebo-controlled single-ascending dose study

Primary objective
Safety and tolerability of a single ascending IV administration of TGD001

Study population
Healthy male participants:

	TGD001 (n=24)	Placebo (n=10)
Age (years)	38.8 ± 10.1	35.3 ± 8.6
Race: White (n)	22	10
Asian (n)	2	0
Weight (kg)	81.1 ± 8.9	76.0 ± 13.8

Data are mean ± SD



*Two sentinels randomized 1:1 (TGD001: Placebo); subsequent participants 2:1
**Two sentinels randomized 1:1 (TGD001: Placebo); subsequent participants 5:1

Trial conducted by TargED Biopharmaceuticals with Scirent Cardiovascular Clinical Research Organization, & Charité Research Organisation, Berlin

Safety: TGD001 was well tolerated with no dose-limiting toxicities

All treatment-emergent adverse events (TEAEs) were transient, and no spontaneous bleedings occurred

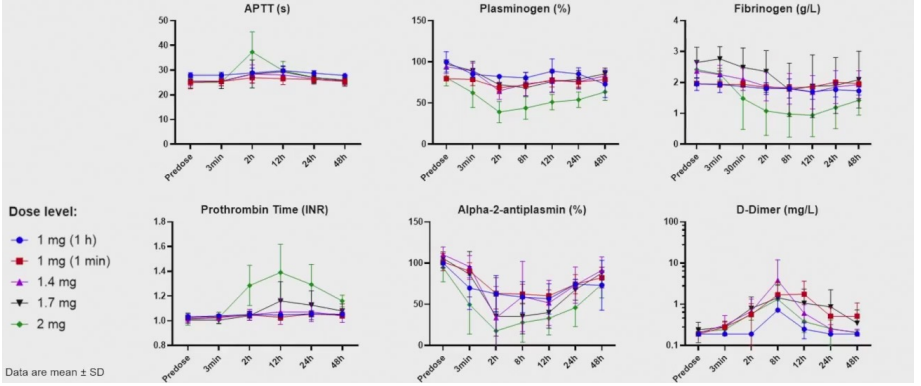
	1 mg (1 h) n=3	1 mg (1 min) n=3	1.4 mg n=6	1.7 mg n=6	2 mg n=6	Placebo n=10
Any TEAE	0	0	1	4	4	5
TEAE related to study treatment	0	0	0	3**	2*	1**
TEAE leading to interruption/withdrawal of study treatment	0	0	0	0	0	0
Any SAE	0	0	0	0	0	0

* Two incision-site hemorrhages (CTCAE: grade 2);
** Four incision-site hematomas (CTCAE: grade 1): three in the 1.7 mg dose group and one in the placebo group

Immunogenicity: No treatment emergent anti-drug antibodies detected

$t_{1/2}$ = 2 - 8 hours

Pharmacodynamics:
Dose-related thrombolytic activity shown across PD markers



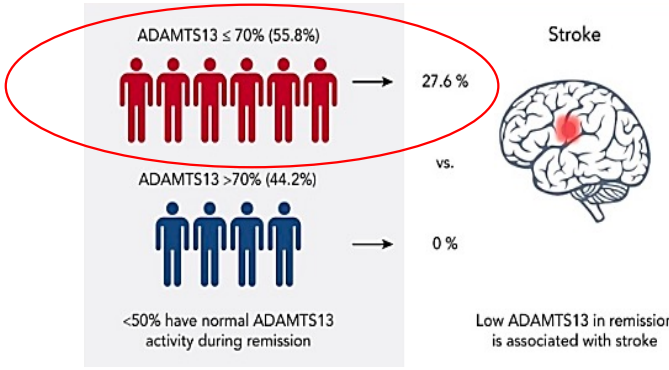
Data are mean ± SD

Trattamento della iTTP durante la remissione clinica - the more the ADAMTS13 the better?

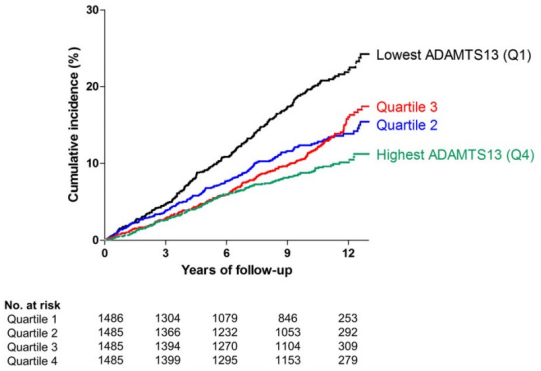
- 30-50% of iTTP patients eventually **relapse**
- Low ADAMTS13 activity during remission is the strongest predictor of clinical relapse

- iTTP survivors can develop **long-term cerebro/cardiovascular complications**
- Low ADAMTS13 activity during remission <u>appear to</u> increase the risk of vascular disease…

… in iTTP survivors



… and the general population!



Oral

332. Thrombosis and Anticoagulation: Clinical and Epidemiological

VWF:ADAMTS13 ratio is associated with white matter hyperintensity (WMH)

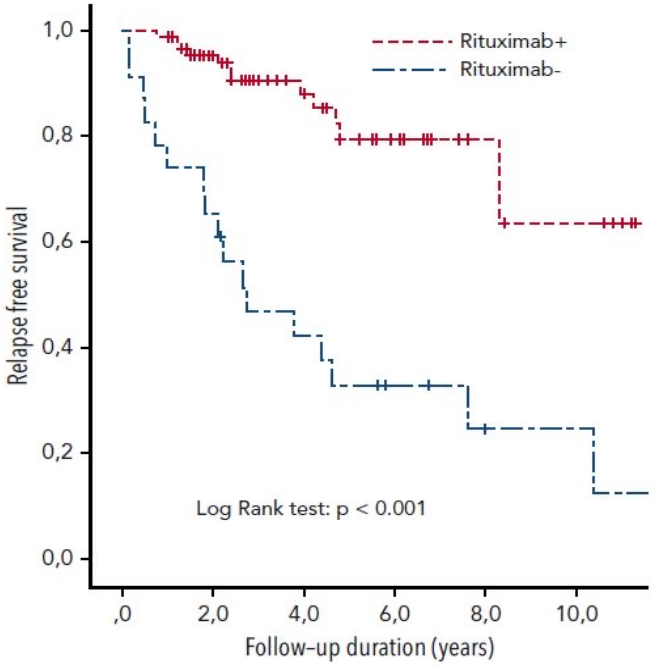
Charlotte Story [1], Lisa Yanek [2], Ivo Francischetti [3], Dhananjay Vaidya [2], Jenna Brown [1], Paul Nyquist [4], Shruti Chaturvedi [1]

- 287 healthy relatives of probands with early-onset cardiovascular disease
- the **vWF:ADAMTS13 ratio** was higher in those with WMH vs those without WMH
- higher in those with large WMH
- significantly associated with large WMH in a model <u>adjusted for all cardiovascular risk factors</u>

Sonneveld MAH, et al. Blood. 2015; Upreti H, et al. Blood. 2019

Trattamento della iTTP durante la remissione clinica - l'armamentario a nostra disposizione

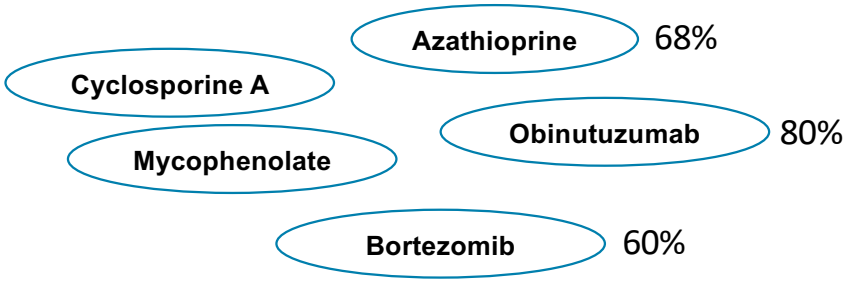
- In case of ADAMTS13 relapse (activity <20%) during remission, **rituximab** prevents clinical relapses
- Median duration of response: 17.5 months



BUT…

- **10-15%** of patients do not respond to rituximab (> Black people)
- **ADAMTS13 relapse-free survival** may progressively **shorten**

- The efficacy of other immunosuppressive drugs relies on limited evidence (non-controlled studies)



Jestin M, et al. Blood. 2018; Bichard C, et al. Blood Adv. 2022; Weisinger J, et al. Am J Hematol. 2025; Fatola A, et al. Blood Adv. 2025; Giannotta JA, et al. J Thromb Haemost. 2025

Trattamento della iTTP durante la remissione clinica - novità da ASH 2025 1/3

Quale dose di rituximab ?

Abstract Title : Rituximab dosing to prevent clinical relapse in immune thrombotic thrombocytopaenic purpura.

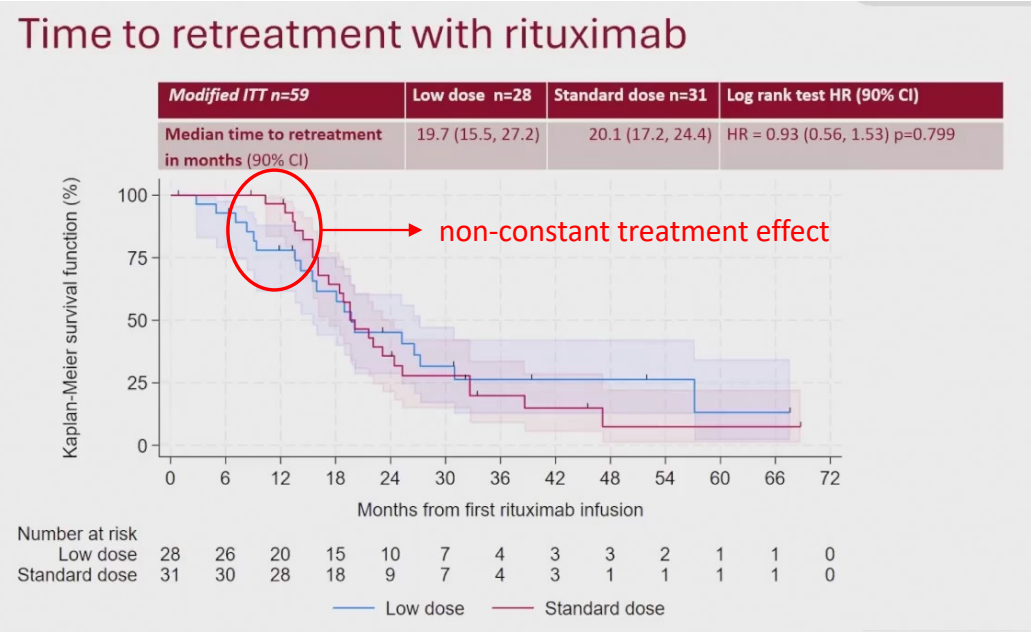
Category: 300s - Hemostasis, Thrombosis and Vascular Wall Biology

Review Category: 331. Thrombotic Microangiopathies/Thrombocytopenias: Clinical and Epidemiological

Authors

Mari Thomas[1], Maryam Subhan[1], Amanda Clark[2], Tina Dutt[3], Kate Talks[4], Lara Howells[1], Victoria Stables[5], Sabina McCann[6], Louisa Keogh[1], Emily Greenlay[7], Marie Scully[1]

- Randomised, UK multicentre, non-inferiority trial
- 70 patients in clinical remission but ADAMTS13 relapse
- N=35 **RTX 375 mg/mq** x4 weeks (standard) **vs**
  N=35 **RTX 200 mg** x4 weeks (low dose)



SAFETY: similar rates of infusion reactions and delayed AEs

No difference in median time to retreatment after low dose RTX compared to standard dose

But more re-treatments in the first 12 months with low dose

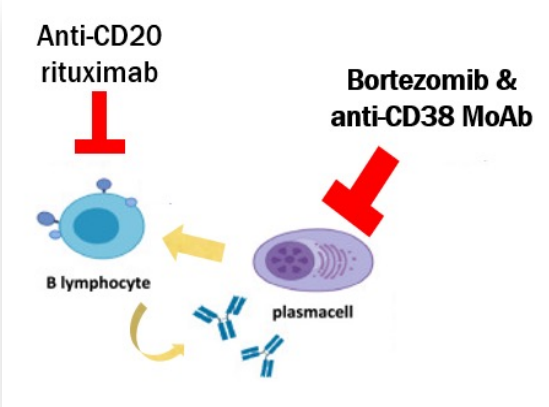
Trattamento della iTTP durante la remissione clinica - novità da ASH 2025 2/3

Poster

331. Thrombotic Microangiopathies/Thrombocytopenias: Clinical and Epidemiological

Daratumumab for immune-mediated thrombotic thrombocytopenic purpura (iTTP): Results from the international, multicenter darttp study

Juri Alessandro Giannotta [1], Raïda Bouzid [2], Monica Carpenedo [3], Syna Miri [1], Ilaria Mancini [1], Faustino García-Candel [4], Fabrizia Colasante [5], Prassede Salutari [5], A.J. Gerard Jansen [6], Dorothea Evers [7], Andrea Artoni [1], Addolorata Truma [1], Giorgia Mancini [8], Pasquale Agosti [9], Paul Coppo [2], Flora Peyvandi [9]



First data cut-off: *31 July 2025*

- N = **20 patients**
- 7 Centers (Italy, France, Spain, The Netherlands)

- Median 3 previous treatments

(Final data analysis: ongoing on 31 patients, 14 Centers)

75% **overall response**

66% sustained response (> 6 months)

15 / 20 patients
- 11 ADAMTS13 complete remissions
- 4 ADAMTS13 partial remissions

- Median time to response: 26 days
- Median duration of ADAMTS13 remission: 11 months
- 8 immediate infusion reactions (6/8 mild), IV > subcu
- 1 zoster infection (non prophylaxed patient)

Trattamento della iTTP durante la remissione clinica - novità da ASH 2025 3/3

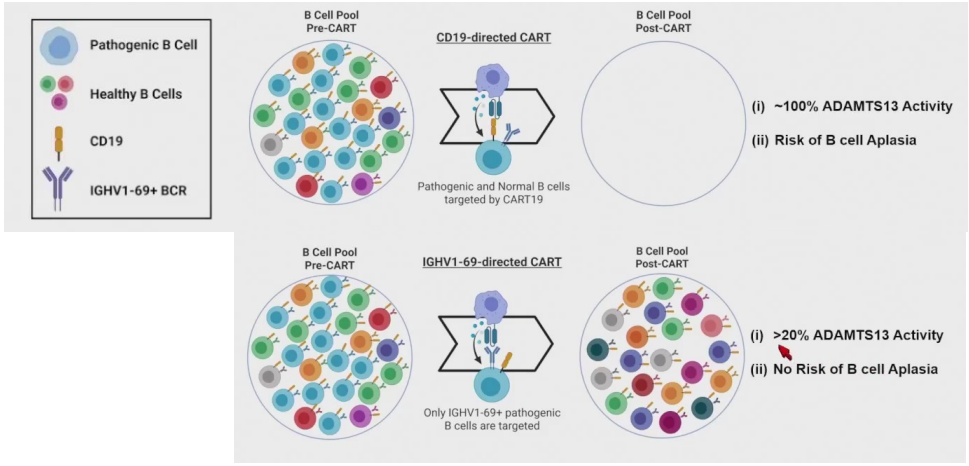
Oral

330. Vascular Biology, Thrombosis, and Thrombotic Microangiopathies: Basic and Translational

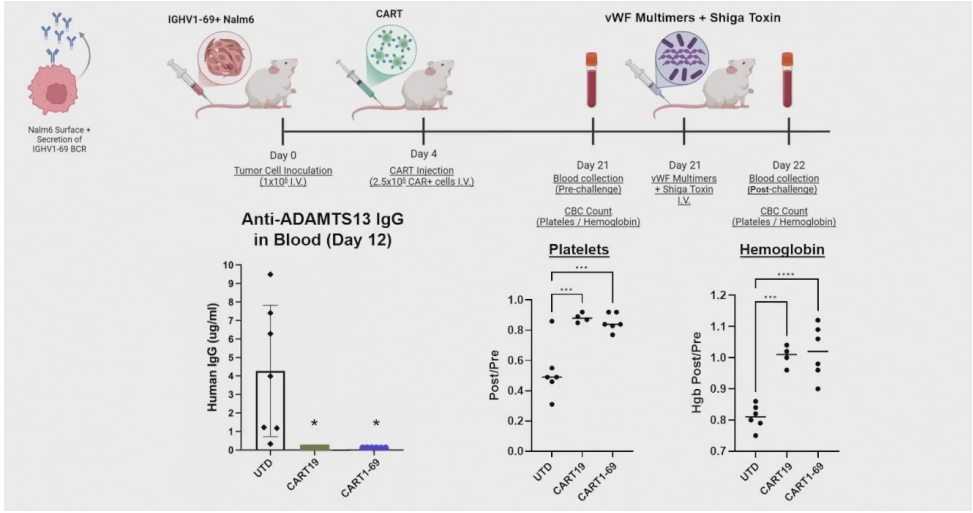
Precision targeting of autoantibody-producing IGHV1-69+ B cells in immune-mediated thrombotic thrombocytopenic purpura (iTTP) using chimeric antigen receptor T cells

Ivan Cohen [1], Roman Khadka [1], Jean Lemoine [1], Audrey Bochi-Layec [1], Seul Jung [1], Ki Hyun Kim [1], Huiwu Zhao [1], Morgan Hresko [1], Don Siegel [1], Paolo Ghia [2], Kostas Stamatopoulos [3], Stephen Schuster [1], Vijay Bhoj [1], Marco Ruella [1]

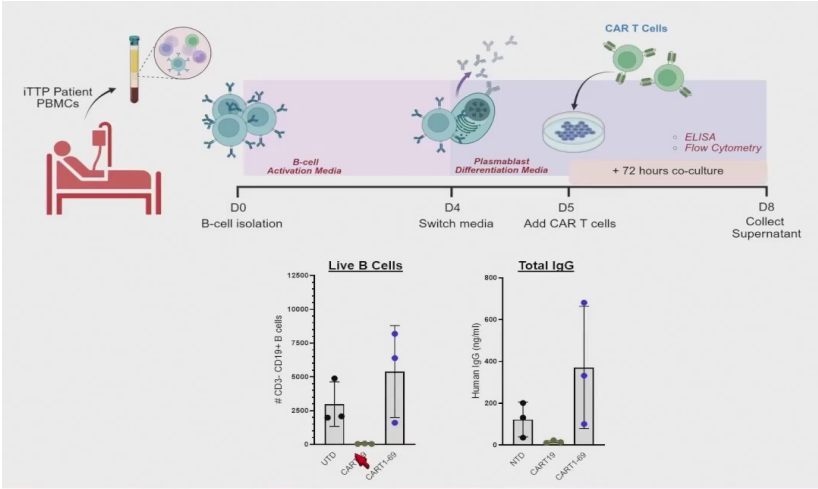
iTTP patients often carry the region IGHV1-69 (anti-ADAMTS13 antibodies)



1) CART1-69 effectively prevents TTP in a mouse model



2) CART1-69 do not eliminate normal B cells in iTTP patient samples



Trattamento della TTP congenita (cTTP) - premessa

Epidemiology

- Incidence: 2-6 people per 1,000,000 per year
- 38% childhood onset (1/3 neonatal, infections) / **62% adult onset** (2/3 pregnancy, infections, immunization)
- Only **50%** diagnosed at first episode (**misdiagnosis**: ITP, Evans syndrome, aHUS)

Treatment goals

- Reduce acute episodes
- Reduce end-organ damage (ischemic stroke, renal impairment)
- Reduce symptom burden (headache, depression/anxiety, abdominal pain, fatigue)

Who should receive prophylaxis

- Recurrent episodes of overt TTP
- During pregnancy
- … maybe all patients ? → 50% of non-overt cTTP patients aged >40y have had an arterial event

Which prophylaxis?

Fresh frozen plasma (FFP)
10-15 mL/kg

vs

Recombinant ADAMTS13
40 IU/kg

Taylor A and Scully M. ASH 2025 educational

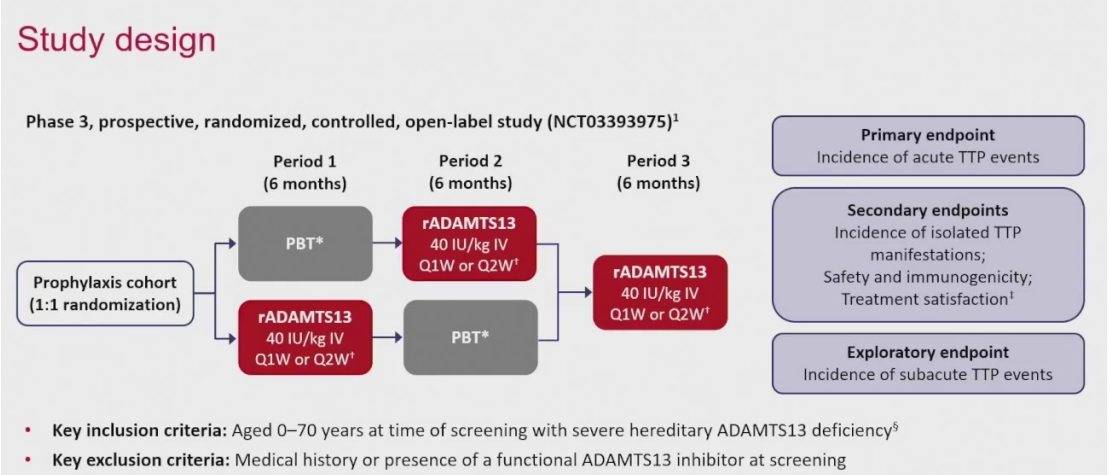
Trattamento della TTP congenita (cTTP) - novità da ASH 2025

Oral

331. Thrombotic Microangiopathies/Thrombocytopenias: Clinical and Epidemiological

Recombinant ADAMTS13 prophylaxis in patients with congenital thrombotic thrombocytopenic purpura: Final analysis from A phase 3 randomized, controlled study

Marie Scully [1], Paul Coppo [2], Masanori Matsumoto [3], Spero Cataland [4], Thomas Ortel [5], Jerzy Windyga [6], Paul Knoebl [7], Karim Kentouche [8], Ana Antun [9], Claire Dossier [10], Nathalie Biebuyck [11], Wolf-Achim Hassenpflug [12], Sami Ibrahimi [13], Masataka Ishimura [14], Indranil Bhattacharya [15], Shan Xiao [15], Kayode Badejo [15], Bjorn Mellgard [15], Dorothy Romanus [15], Linda Wang [15]...Tara Robinson [15]



N=48 patients randomized

Median age (range): 32.5 years (3-68)

- Acute TTP events: 0 in rADAMTS13 vs 1 in PBT
- Less isolated TTP manifestations with rADAMTS13:
  - Isolated thrombocytopenia (29% vs 47%)
  - Hemolytic anemia (18% vs 27%)
  - Less clear effect for neurological, renal and abdominal manifestations

- Serious AEs:
  0 rADAMTS13-related vs
  1 PBT-related
- Discontinuation/interruption
  0 rADAMTS13 vs 19 PBT
- No neutralizing antibodies

rADAMTS13 advantages vs PBT

- Peak levels: 70-100% (vs 20%)
- Volume: 10 mL (vs 0.5-1 L)
- Time of admin: 5 min (vs 2-3 h)

ISTH guidelines 2025 update: use of recombinant ADAMTS13 over fresh frozen plasma
(strong recommendation, moderate certainty evidence)

Conclusioni

1) Diagnosi e prognosi della iTTP

- Lo score TTP-14 potrebbe migliorare la specificità diagnostica rispetto al PLASMIC
- Non abbiamo ancora score prognostici validi → trattare rapidamente tutti i pazienti con tripletta (PEX+steroide+capla)

2) Trattamento della iTTP in fase acuta

- Con l'attuale standard of care la mortalità si è ridotta a <2%
- Ma il danno microangiopatico già occorso non è recuperabile → trombolitico TGD001 promettente per ridurlo

3) Trattamento della iTTP durante la remissione clinica

- E' possibile ottenere remissioni ADAMTS13 anche con dosaggi ridotti di rituximab (200 mg/week x 4 settimane)
- I pazienti rituximab-refrattari sono difficili da gestire, in mancanza di chiare evidenze prospettiche controllate (daratumumab? obinutuzumab? in futuro CAR-T cells dedicate?)

4) Trattamento della TTP congenita (cTTP)

- La profilassi con ADAMTS13 ricombinante offre benefici di efficacia e di sicurezza rispetto alla profilassi basata sull'infusione di plasma

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Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Sistema Socio Sanitario Regione Lombardia
CENTRO EMOFILIA E TROMBOSI ANGELO BIANCHI BONOMI
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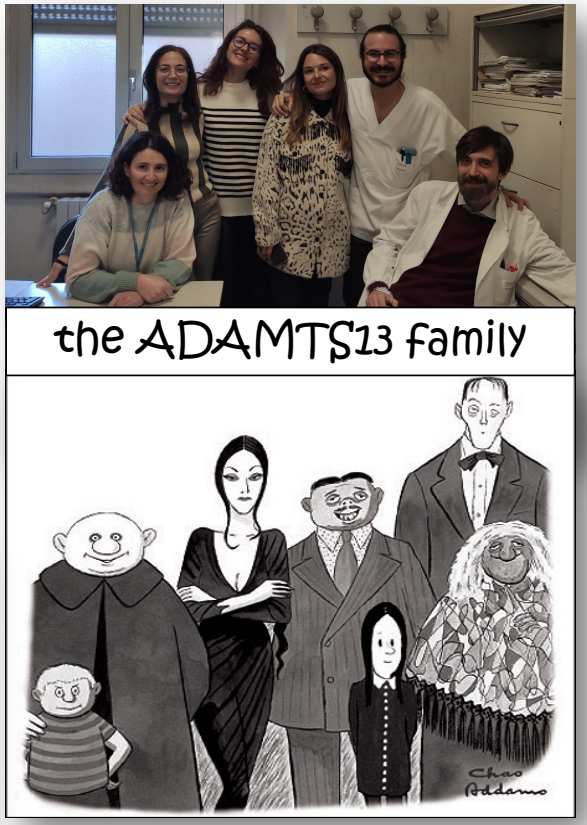

Thank you!

Flora Peyvandi

NO!

MILANO CORTINA 2026