POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Difetti acquisiti della coagulazione

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Disclosures of Alberto Tosetto

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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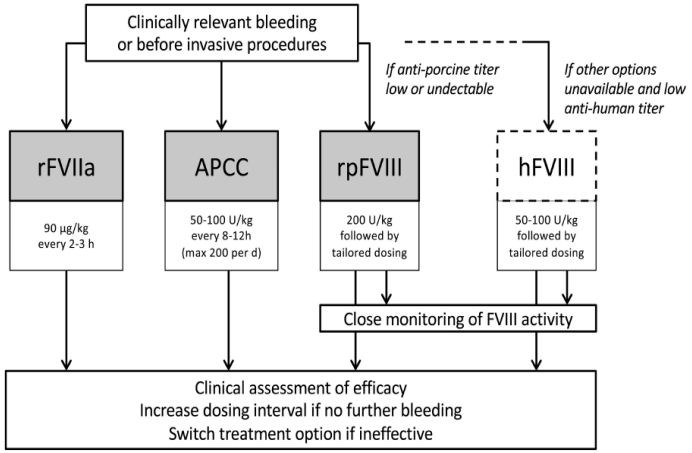
Novo-Nordisk						√	

Difetti acquisiti della coagulazione

- Emofilia acquisita
- Sicurezza delle terapie antitrombotiche
- HHT

Background: Acquired Hemophilia A Therapeutic approach

Bleeding control



Immunosuppression

FVIII ≥1 IU/dL & low-titer inhibitor (≤20 BU; *Low-risk AHA*):

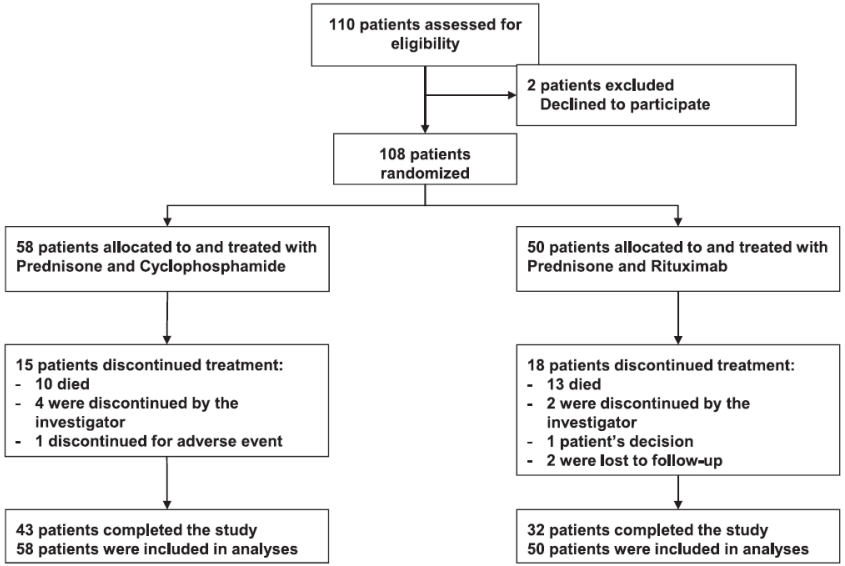
- Oral prednisone 1 mg/kg or Prednisolone e.v. 0.8 mg/kg) for three weeks

FVIII <1 IU/dL, or high-titer inhibitor or refractoriness *(High-risk AHA)*:

- Rituximab 375 mg/m^2 weekly *or*
- Cyclophosphamide 1.5–2 mg/kg/day PO, for six weeks

Tiede, et al., Haematologica, 2020

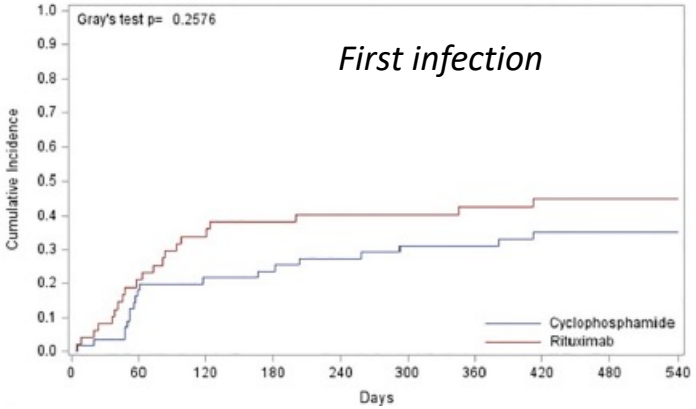
Background: Immunosuppression in AHA



108 patients randomized to PDN+R vs PDN+EDX

Study endpoints	PDN+EDX (n=58)	PDN+R (n=50)
CR at 3 month	41 (70.7)	34 (68.0)
High-risk pts	21 (75.0) **	13 (52.0)
Time to CR (days)	46	48

*** p<0.05*



Lévesque et al. Thrombosis Research, 2024

First-Line Immunosuppression in Acquired Hemophilia A (Cusano et al., Oral 554)

A Canadian multicenter study, 2020-2022. AHA diagnosis: inhibitor titre >0.60 BU/mL and FVIII:C <50 IU/dL

	Entire cohort	Prednisone	Rituximab	EDX	R+EDX	p
Patients	126	33 (26.2)	19 (15.1)	63 (50.0)	11 (8.7)	
Age, median	71	71	76	68	71	0.03
High-risk*	72 (57.1)	11 (33.3)	17 (89.5)	37 (58.7)	7 (63.6)	0.001

* High-risk profile: FVIII:C <1IU/dL OR inhibitor titer >20 BU/mL

Outcomes (I)

	Entire cohort	Prednisone	Rituximab	EDX	R+EDX	p
Mean number of bleeds	2.1	2.2	2.1	2.1	1.8	0.90
Major bleed, n	122 (47.1)	31 (43.1)	16 (40.0)	64 (50.4)	11 (55)	0.24
Mean Dose*						0.29
rFVIIa (mg)	144	96	92	163	253	
FEIBA (kIU)	79	71	44	93	140	
Hospitalization Days	16.8	14.0	13.4	25.1	7.4	0.52

* Mean dose of FVIIIa or FEIBA

Cusano et al., Oral 554

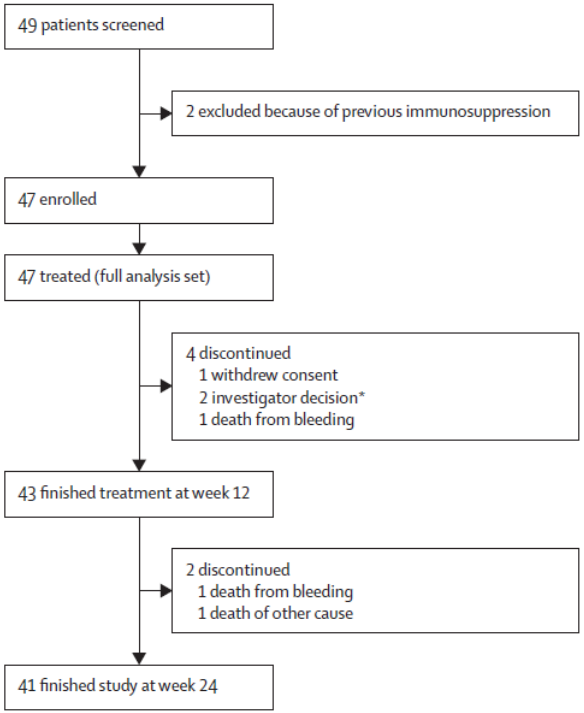
Outcomes (II)

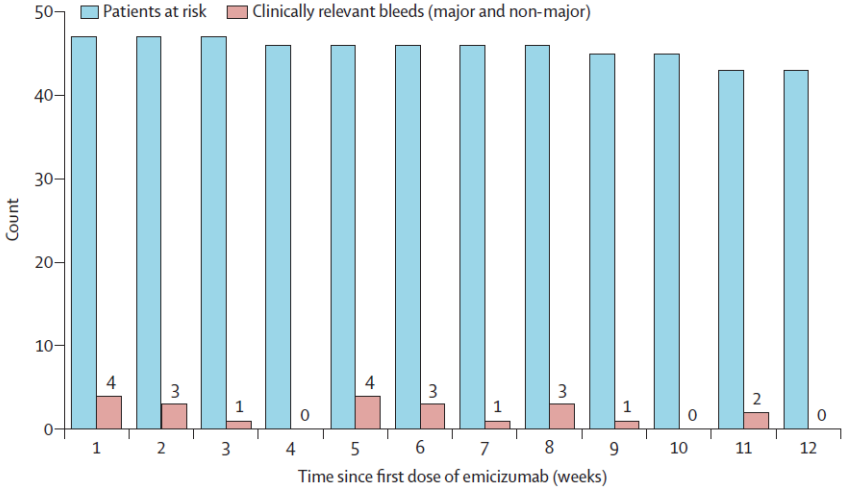
	Entire cohort	Prednisone	Rituximab	EDX	R+EDX	p
Pancytopenia/ Neutropenia	30 (26.5)	2 (8.3)	9 (47.4)	17 (30.4)	2 (14.3)	0.02
Infection	54 (14.9)	14 (12.6)	9 (12.7)	22 (15.5)	9 (23.7)	0.37
Response						
CR	97 (77)	23 (69.7)	15 (78.9)	48 (76.2)	13 (100)	0.56
Time to response months	3.3	3.0	3.1	3.4	4.4	0.26
Mean cost ($)	34,703	30,032	26,456	51,115	15,979	0.64

* Mean dose of rFVIIa or FEIBA

Cusano et al., Oral 554

Background: Emicizumab prophylaxis in patients with AHA





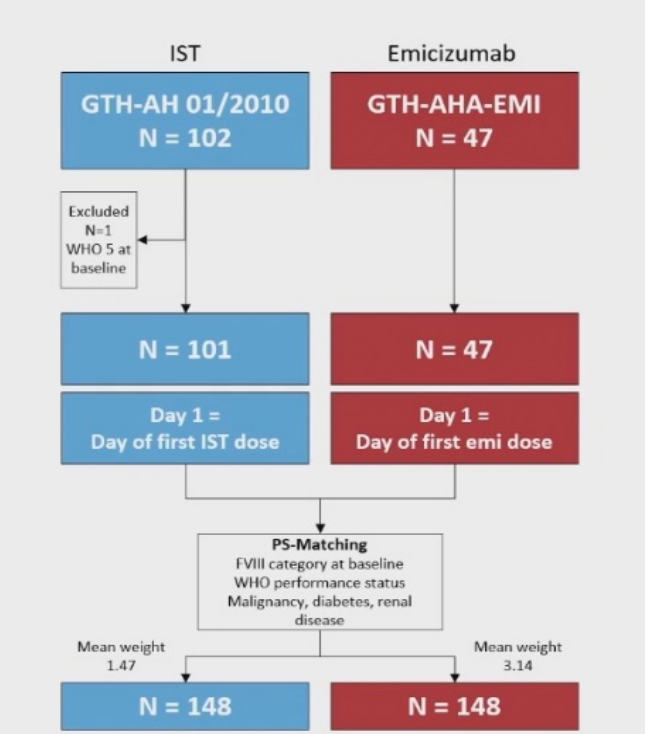
The mean bleeding rate was 0.04 bleeds per patient-week, significantly below 0.15, meeting the predefined one-sample efficacy criterion ($p<0{\cdot}001$).

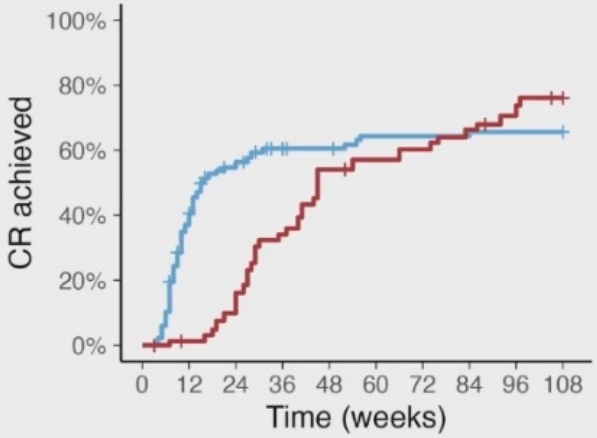
Open-label, single-arm, multicentre, phase 2 study

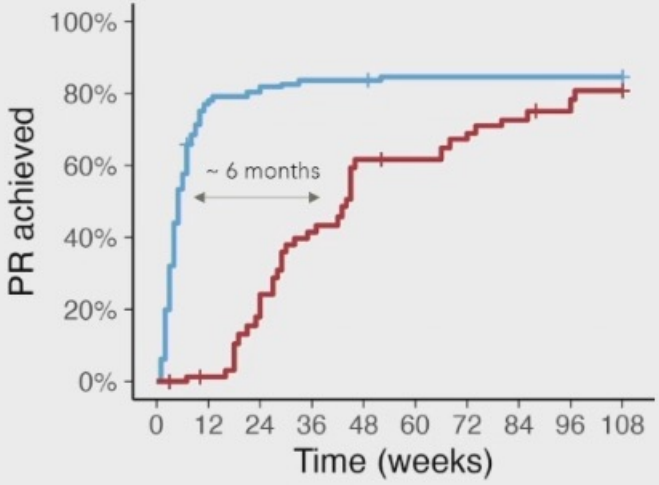
Tiede et al. The Lancet Haematology, 2023

Emicizumab Prophylaxis Instead of Immunosuppression during Early Management of Acquired Hemophilia (Schimansky et al., Oral 555)

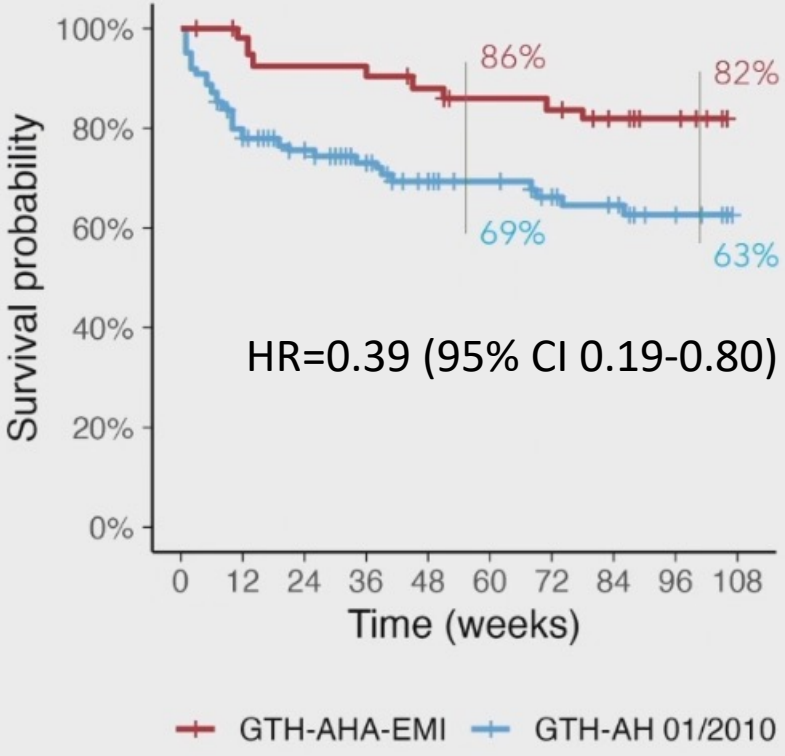
- Long-term outcomes of emicizumab treatment compared with propensity-score-matched patients receiving traditional IST immediately after diagnosis
- 2-year individual patient data from the GTH-AHA-EMI study (n=47, emicizumab weeks 1 to 12, delayed IST after week 12), and the historic GTH-AH 01/2010 study (n=101, immediate IST week 1 to 10 plus on-demand bypassing)







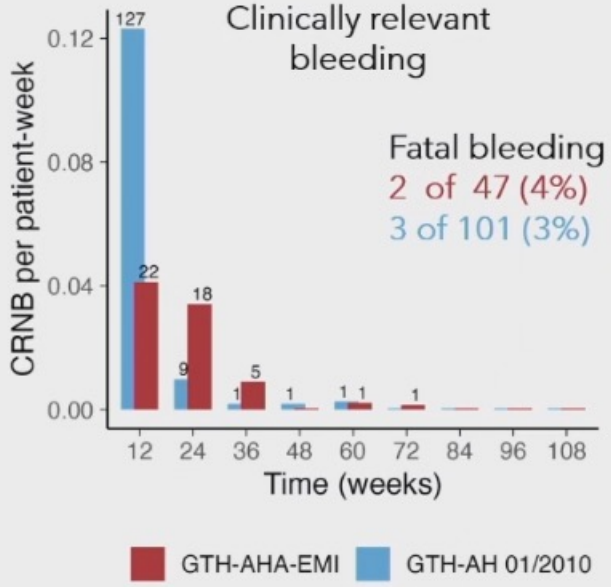
Overall survival

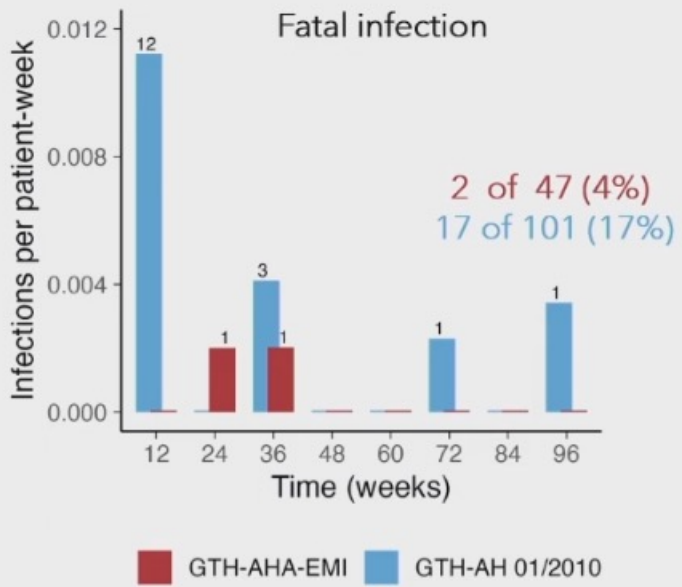


HR=0.39 (95% CI 0.19-0.80)

Schimansky et al., Oral 555

Propensity-matched event rates Emicizumab vs IST+bypassing therapy (historic historic GTH-AH 01/2010)

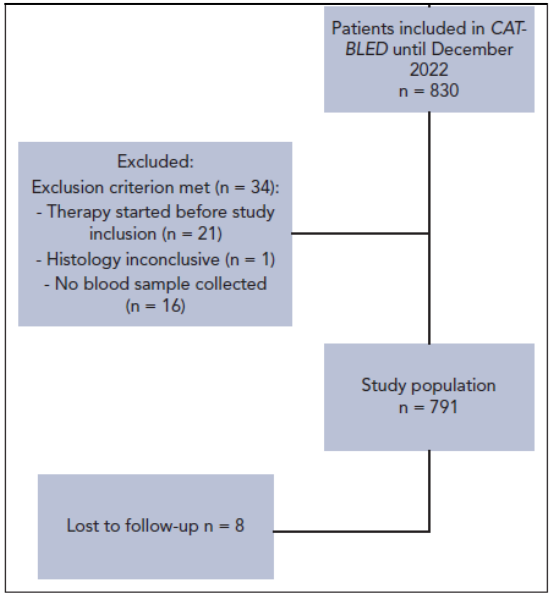


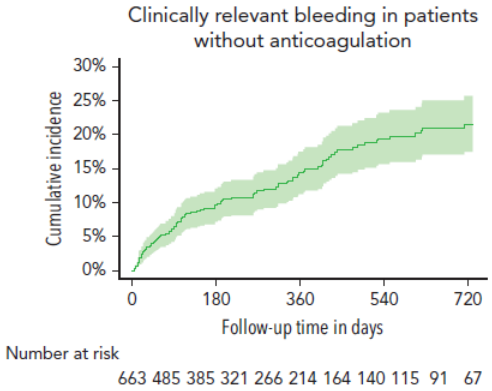


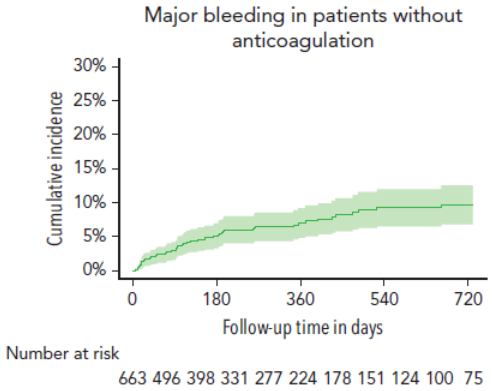
PR: FVIII >50% of normal, no bleeding, no hemostatic medication
CR: PR plus inhibitor negative, GC <15 mg prednisolone per day and other IST stopped

Schimansky et al., Oral 555

Background: Bleeding is still a significant complication in cancer patients

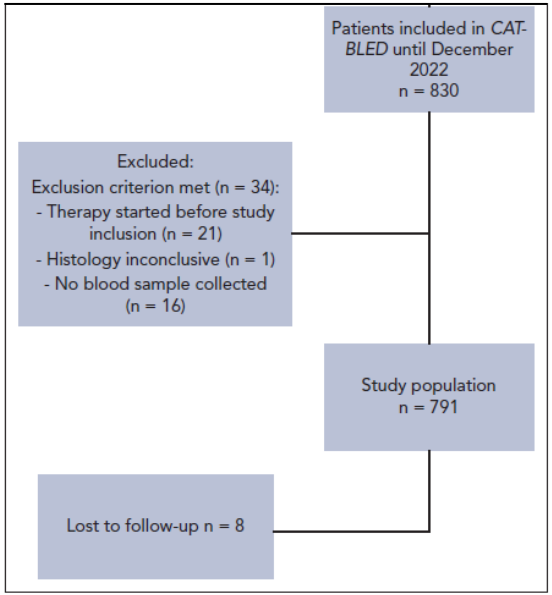


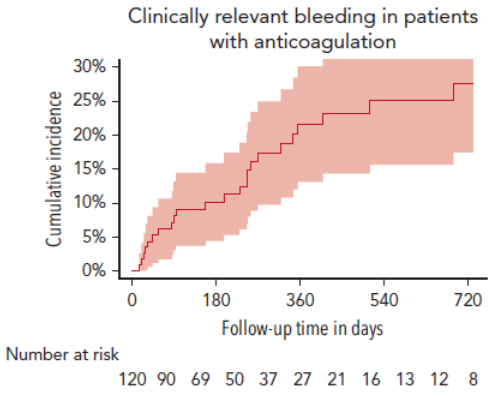


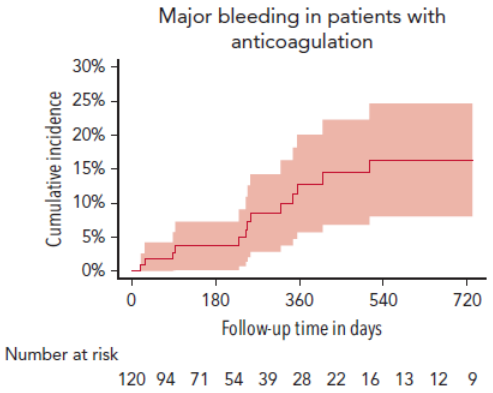


Englisch et al. Blood, 2024

Background: Bleeding is still a significant complication in cancer patients





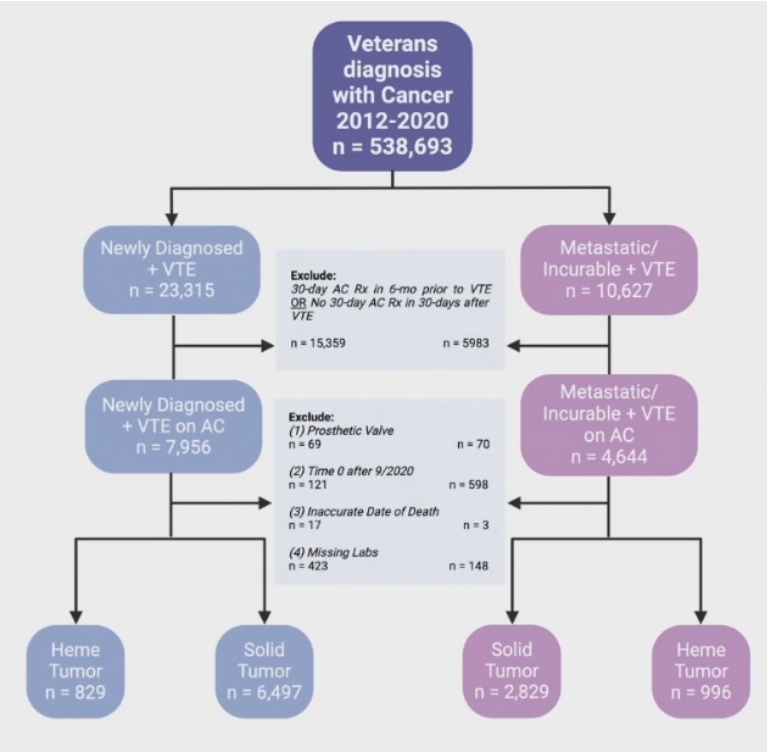


Englisch et al. Blood, 2024

Elimination of Modifiable Risk Factors for Anticoagulant-Related Bleeding in Patients with Cancer

(Sanfilippo et al., Oral 814)

- Cohort of 11,731 patients with cancer-associated VTE identified between 2012 and 2020 in the US Veterans Administration healthcare system
- LMWH 47.7%, DOACs 26.8%, VKA 24.5%, and fondaparinux 1%
- Cumulative incidence function (CIF) to account for the competing event of non-bleeding associated mortality



Elimination of Modifiable Risk Factors for Anticoagulant-Related Bleeding in Patients with Cancer (Sanfilippo et al., Oral 814)

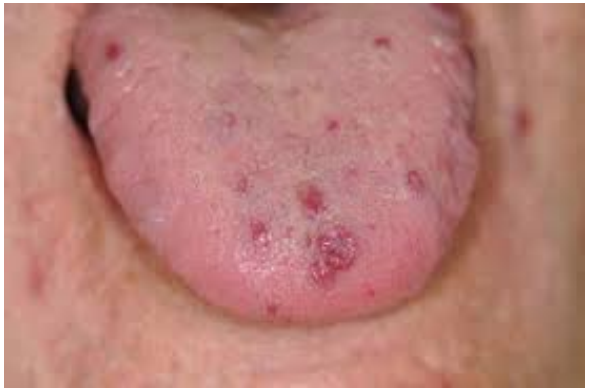
Risk factor	HR	PAF
Anemia	1.27	12.2%
Uncontrolled hypertension	1.19	7.8%
Alcohol abuse	1.30	2.0%
Antiplatelet therapy	1.16	2.7%
All four risk factors		22.7%

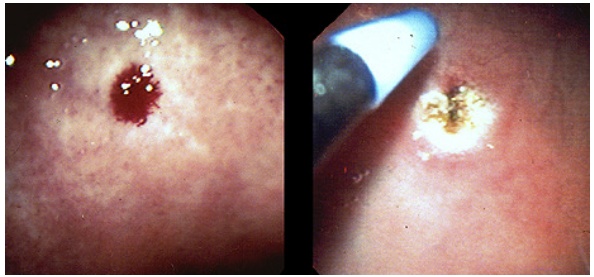
12 months incidence of bleeding: 8.5 % pt-year

Sanfilippo et al., Oral 814

Background: Hereditary Hemorrhagic Telangiectasia (HHT; Osler-Weber-Rendu syndrome)

- An autosomal dominant vascular disorder
- Associated with mucocutaneous telangiectasia, epistaxis, gastrointestinal bleeding, and iron deficiency anemia
- Arteriovenous malformations (AVMs) commonly occur in the pulmonary, hepatic, and cerebral circulation
- Estimated prevalence 1:4-5000 (*most prevalent bleeding disorder after VWD*)
- No approved therapy worldwide





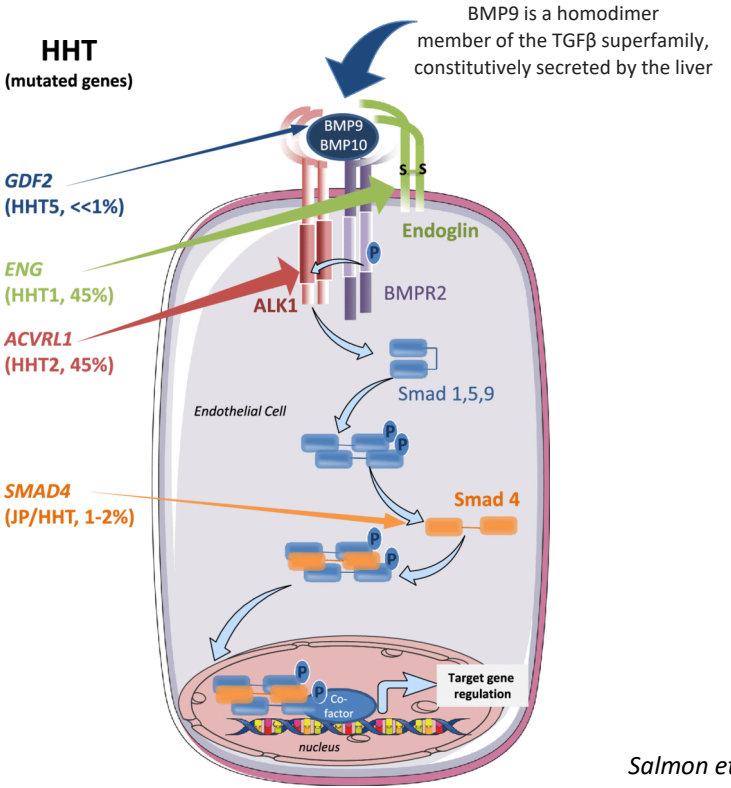
Zhang et al. Blood Advances, 2024

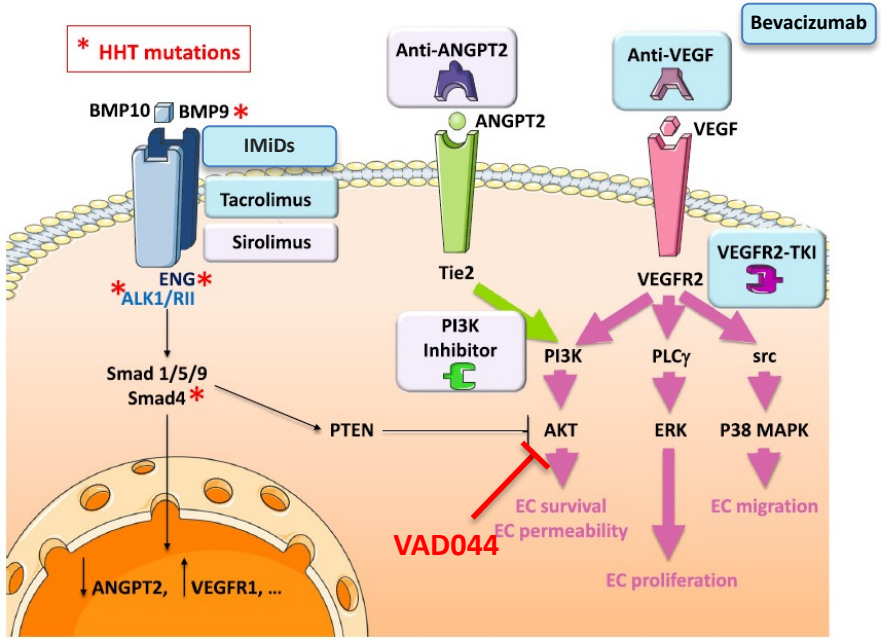
Background: Treatment options in HHT

Phase	Intervention	Comparator	Outcomes	Ref
III crossover	Tranexamic acid	Placebo	17.3% (15.7 min) in the duration of epistaxis per month	*Gaillard et al. J Thromb Haemost, 2014*
II	Thalidomide up to 200 mg/d	None	3/31 complete response (no bleedings) 28/31 partial response	*Invernizzi et al. Lancet Haematol, 2015*
IIb	Bevacizumab 5mg/kg every 14days	Placebo	7/11 (63%) in the bevacizumab group vs 4/12 (33.3%) n the placebo group decreased the number of RBC transfusions by at least 50%	*Dupuis-Girod et al. J Intern Med, 2023*
Retrospective cohort	Bevacizumab 5mg/kg every 14days	Pre-treatment	238 HHT patients. Increase of mean Hb by 3.2 g/dL and decrease of the epistaxis severity score (ESS) by 3.4 points	*Al-Samkari et al. Haematologica, 2021*

Al-Samkari H et al., Haematologica 106 (8):2161-2169, 2021. Dupuis-Girod S et al. Journal of internal medicine 294 (6):761-774., 2023
Gaillard S et al. J Thromb Haemost 12 (9):1494-1502, 2014. Invernizzi R et al., The Lancet Haematology 2 (11):e465-473, 2015

AKT (protein kinase B) is a central druggable target in HHT



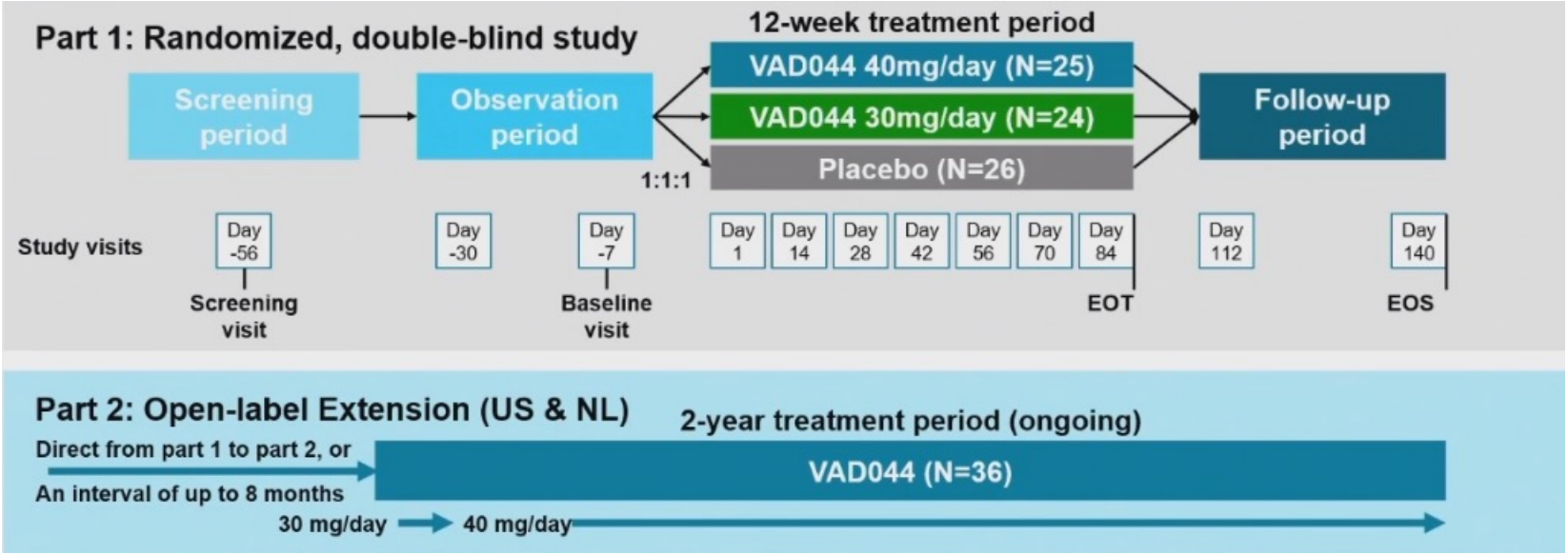


Salmon et al. Nat Commun, 2020; Robert et al. Orphanet Journal of Rare Diseases, 2020 (modified)

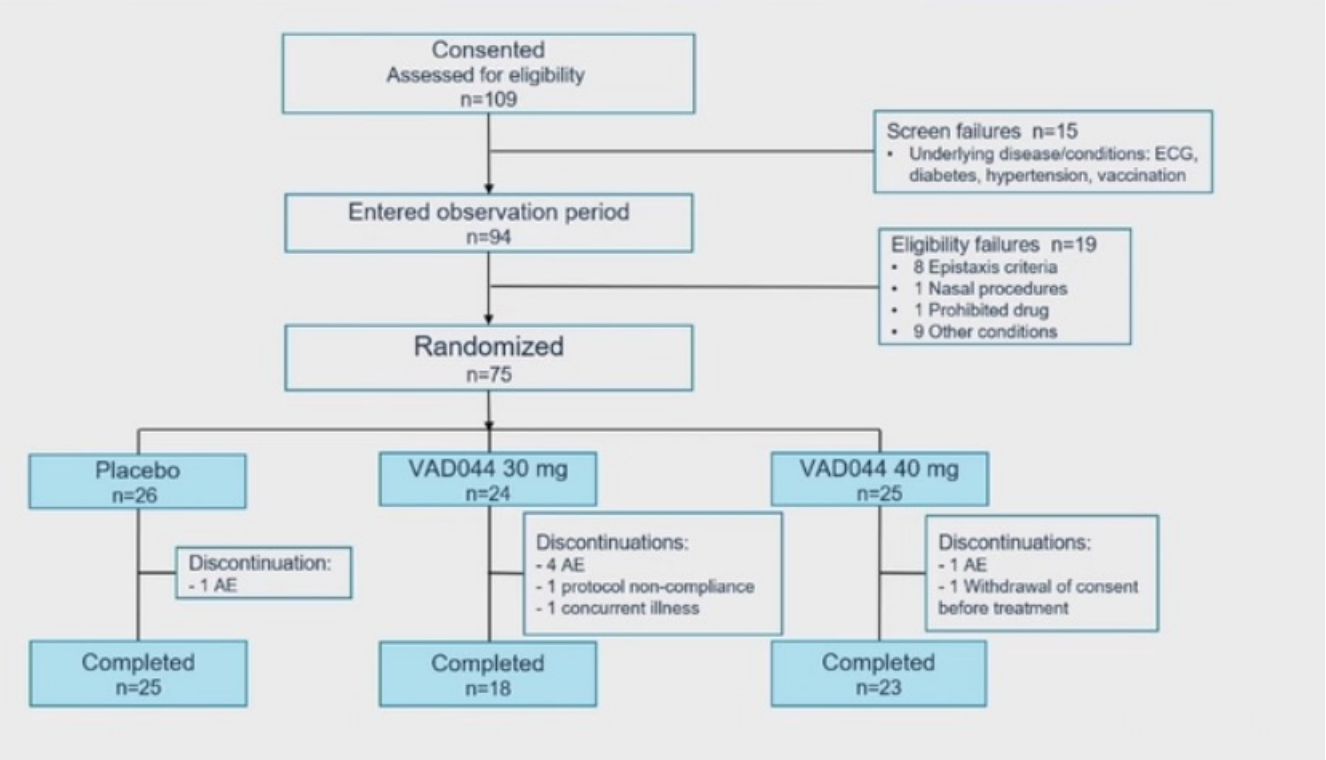
VAD044 in Adults with HHT, a phase I-II study
(Al-Samkari et al., Oral 553)

- A Randomized, Placebo-Controlled, Multicenter Proof-of-Concept (POC) Study to Assess the Safety and Efficacy of the Novel Allosteric AKT Inhibitor, VAD044
- Primary objective: safety and tolerability of 30 or 40mg doses of VAD044 administered daily for 12 weeks
- Secondary objective: effect on epistaxis, QoL, hemoglobin

VAD044 in Adults with HHT, a phase I-II study
(Al-Samkari et al., Oral 553)



Al-Samkari et al., Oral 553

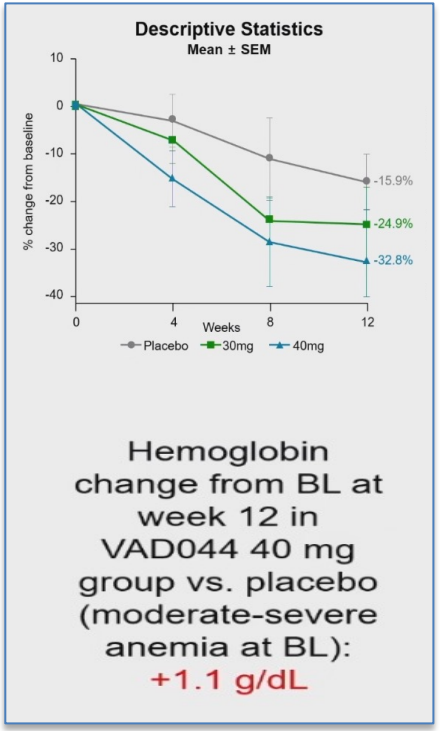


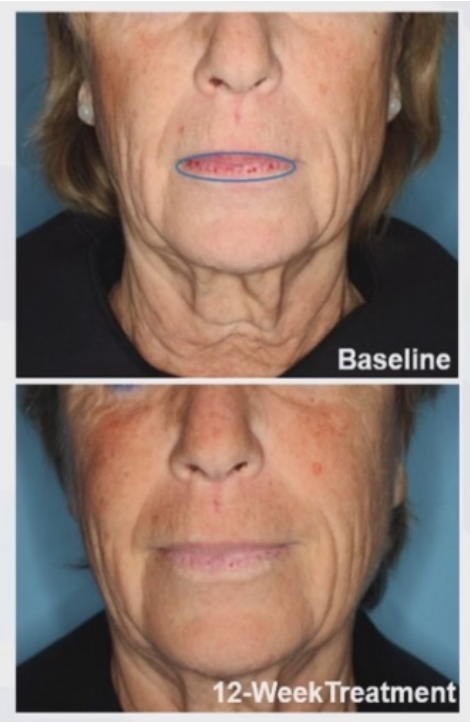
Al-Samkari et al., Oral 553

VAD044 in Adults with HHT, a phase I-II study
(Al-Samkari et al., Oral 553)

Primary study end points

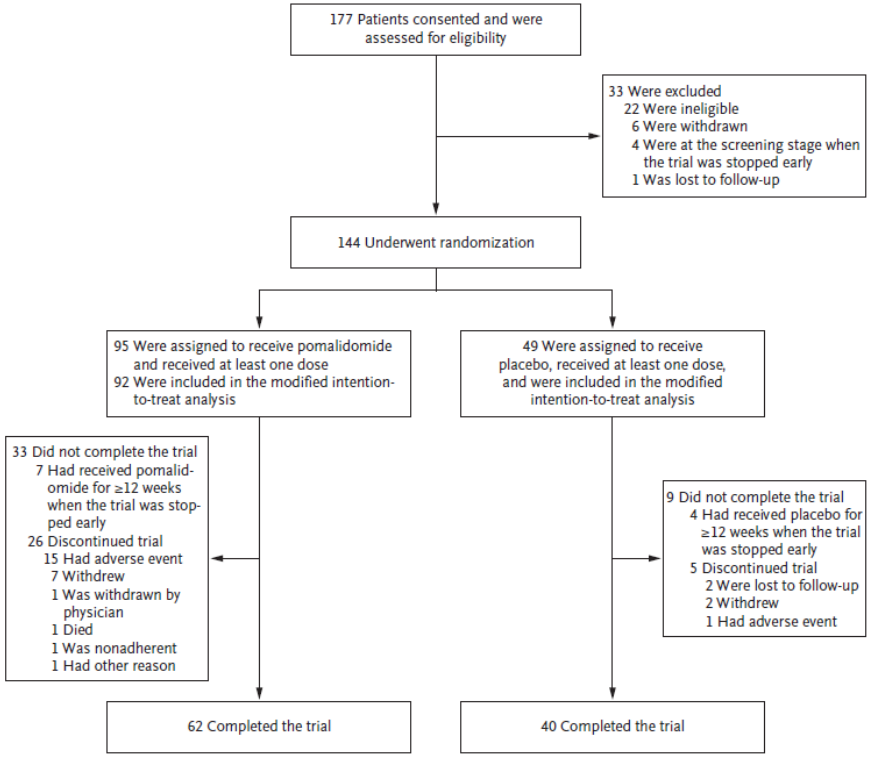
TAE	Placebo (n=25)	30 mg (n=18)	40 mg (n=23)
Diarrhea	1 (3.8)	3 (12.5)	2 (8.3)
Rash	2 (7.7)	6 (25)	11 (45.8)
Headache	4 (15.4)	7 (29.2)	1 (4.2)
Hyperglycemia	0	0	3 (12.5)

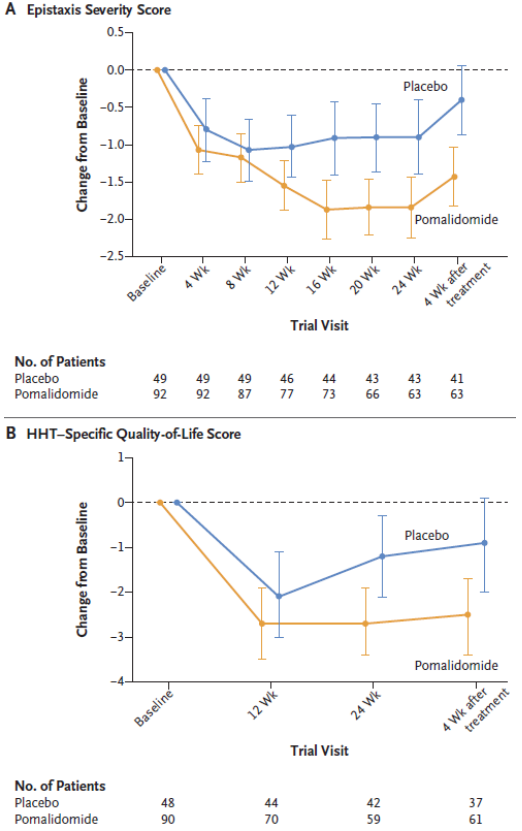




Al-Samkari et al., Oral 553

Background: Pomalidomide in HHT (PATH-HHT)





Al-Samkari et al. N Engl J Med, 2024

Long-Term Safety and Effectiveness of Pomalidomide in HHT (Zhang et al., Oral 558)

- Observational study of patients with HHT treated with pomalidomide initially enrolled on PATH-HHT who continued POM via a post-study POM access program.
- Primary study endpoint: durable epistaxis response
- 48 patients, POM 4 mg daily
- Mean treatment duration was 17.8 months; dose reduction due to treatment-emergent adverse events (TEAEs) to 3 or 2 mg daily occurred in 16 patients and did not appear to impact effectiveness.
- POM was discontinued in 15 patients: 8 due to TEAEs and 7 due to ineffectiveness. 4 patients died during the observation period due to HHT complications unrelated to POM.

Long-Term Safety and Effectiveness of Pomalidomide in HHT (Zhang et al., Oral 558)

Outcomes

- DER was achieved in 84%
- 2 (8%) discontinued due to loss of response.
- POM was less effective for GI bleeding: of 14 patients with HS-dependent active chronic GI bleeding at treatment initiation, 4 achieved liberation from HS dependence; 7 discontinued POM; and 3 continued on POM despite ongoing HS dependence due to epistaxis improvement.

Safety

- 98% (N=47/48) of patients experienced ≥1 TEAE; most were grade 1 or 2.
- The most common TEAEs were neutropenia (56%), constipation (52%), rash (35%), and fatigue (35%).
- Venous thromboembolism occurred in 1 patient (2%); no arterial thromboses were observed.

Compared with IV bevacizumab, POM may be inferior for GI bleeding but appears comparable or better for epistaxis.

Zhang et al., Oral 558

Grazie!

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