Classical Hematology: Managing Disorders of Bleeding and Clotting

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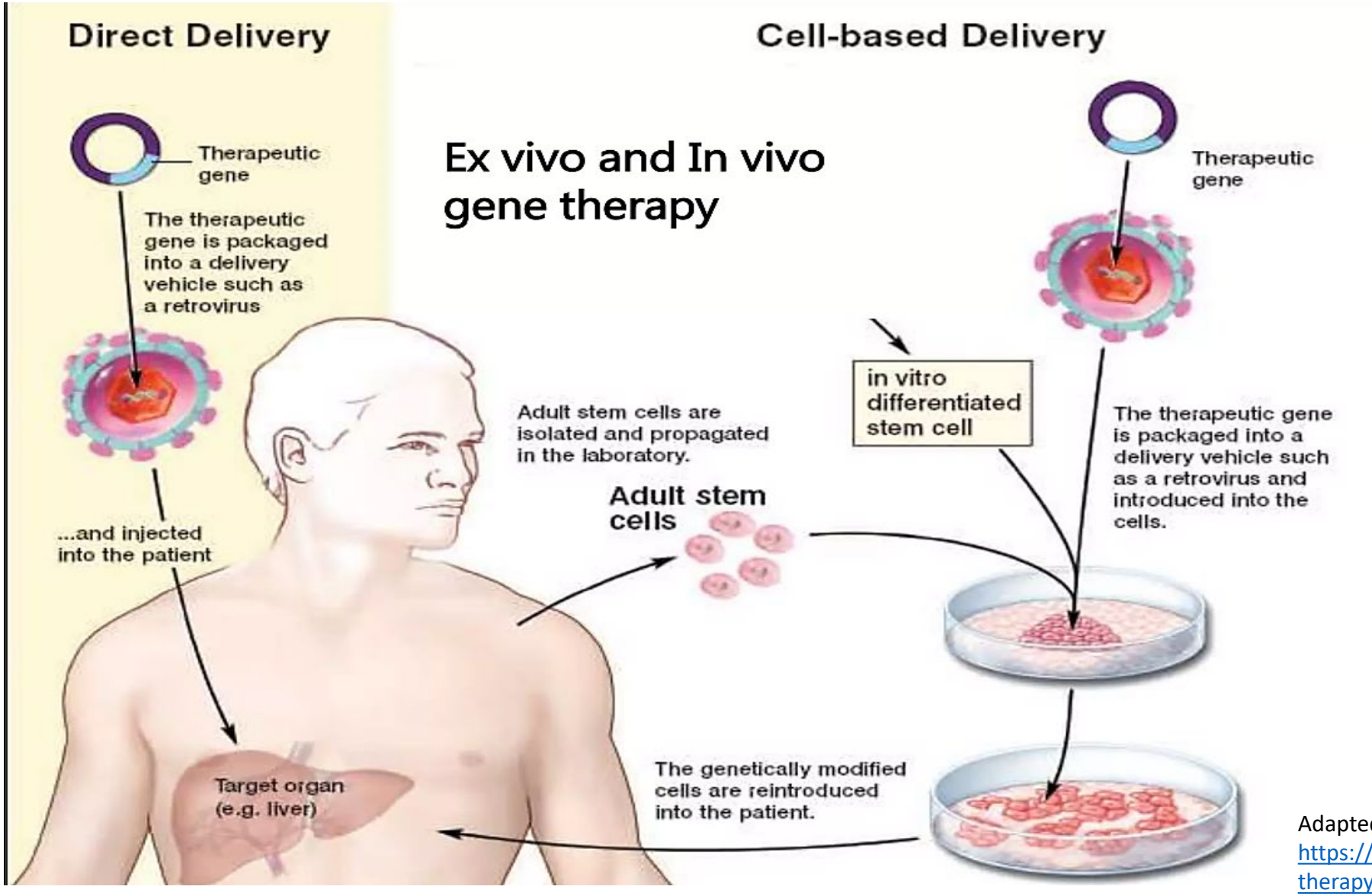
Disclosures

- Research- Bayer, Genentech/Roche, Octapharma, Incyte, Stago
- Advisory Boards- Bayer, Biogen, BioMarin, CSL-Behring, Genentech/Roche, NovoNordisk, Novartis, Octapharma, Pfizer, Rigel, Takeda
- DSMB- NIH, Bayer, Octapharma
- Stock- Not applicable
- Employment – Not applicable
- Speakers’ Bureau – Not applicable

Topics

- Gene Therapy Beyond Sickle Cell Disease- Have we “cured” hemophilia?
- Guidelines for treatment of chemotherapy induced thrombocytopenia
- Novel therapies in autoimmune thrombocytopenic purpura
- Treatment of thrombotic complications of cirrhotic liver disease
- Issues in cancer associated thrombosis
- New strategies for thrombotic thrombocytopenic purpura

Techniques for gene transfer in gene therapy



Viral Vectors

Retrovirus Lentivirus	**integrates into host genome**
Adenovirus AAV	**episomal**

Non-viral vectors

Lipid and polymer based nanoparticles to deliver DNA, siRNA, or miRNA

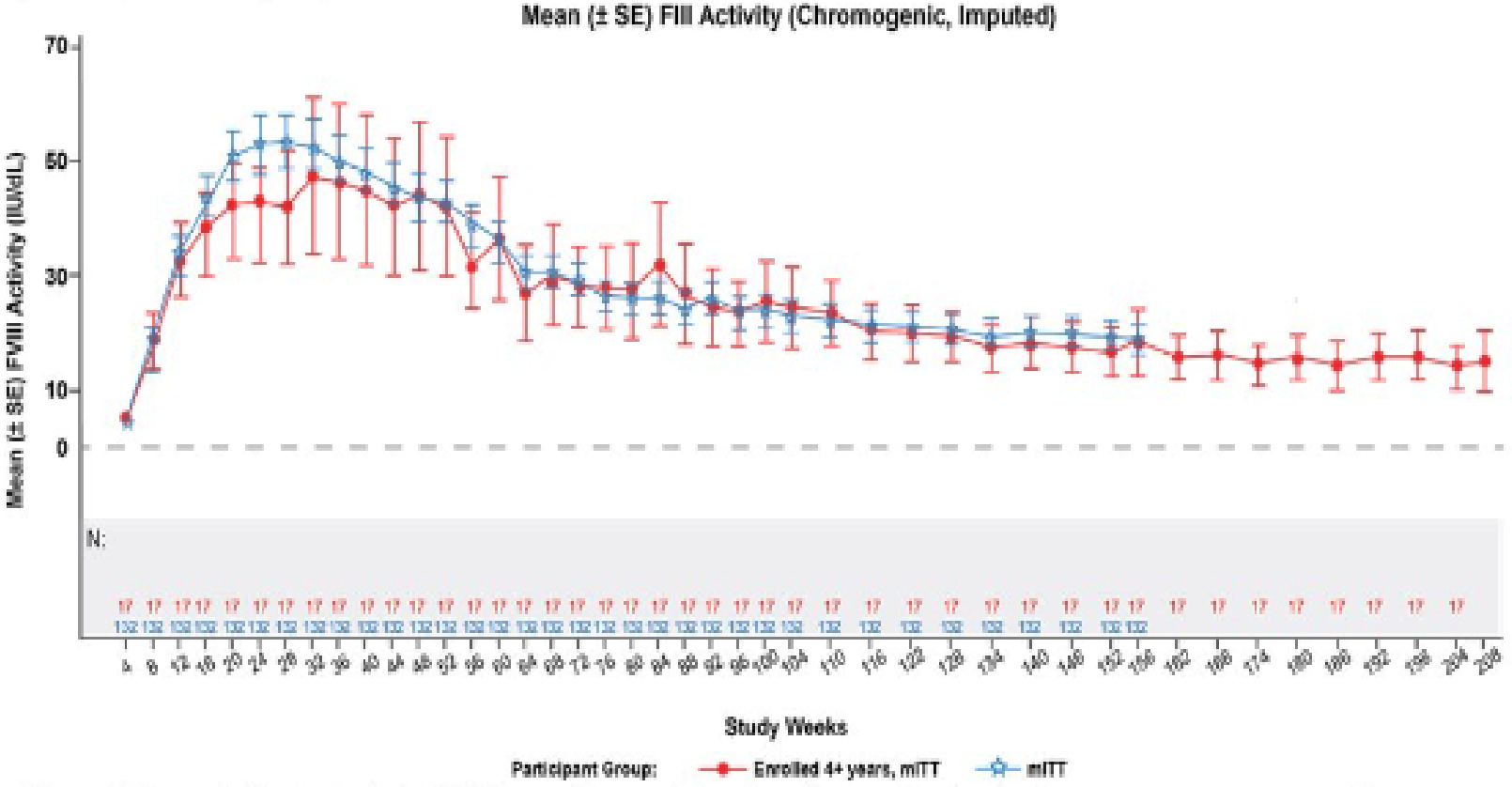
Adapted from: https://www.slideshare.net/anniemirza14/gene-therapy-58257727; downloaded 2/5/2023

ABS OC 20.1: Bleeding, FVIII activity, and safety 3 years after gene transfer with valoctocogene roxaparvovec: Results from GENEr8-1

(ISTH 2023, Mahlangu J et al.) drive rank score=1

Valoctocogene Roxaparvovec in vivo Liver Directed AAV5 Gene Therapy for Hemophilia A

Figure. FVIII activity over 3 years post-treatment with valoctocogene roxaparvovec in the mITT population (N=132) and a subgroup of the mITT dosed ≥4 years (N=17)



HIV, FVIII inhib, AAV5 AB negative

Mean ABR for all bleeds = 1.3

During yr 3: 61.6% had no bleeds

At wk156: mean and median FVIII were 18.8 and 8.4 IU/dL

11.4% of pts with FVIII ≥40 IU/dL; **32.6% of pts < 5 IU/dL**

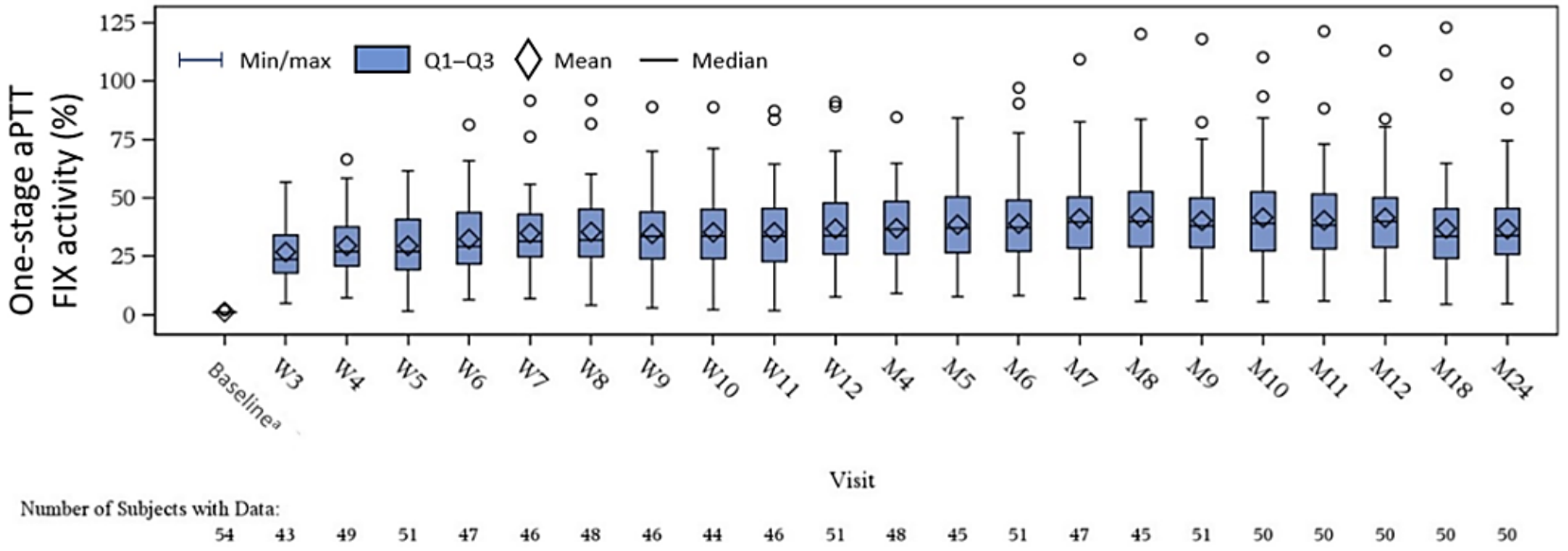
79.1% used corticosteroids for ↑ALT for median 33 wks

ABS 1055: Long-Term Bleeding Protection, Sustained FIX Activity, Reduction of FIX Consumption and Safety of Hemophilia B Gene Therapy: Results from the HOPE-B Trial 3 Years after Administration of a Single Dose of Etranacogene Dezaparvovec in Adult Patients with Severe or Moderately Severe Hemophilia B (ASH 2023, Pipe S et al)

drive rank score=1

Etranacogene Dezaparvovec in the HOPE-B Phase 3 Clinical Trial for Mod/Severe Hemophilia B Now FDA approved

Figure 2. FIX activity level over time



AAV5 vector, containing a codon-optimized, highly active factor IX (FIX) Padua R338L transgene (ABS 2141: ASH 2022, Pipe SW et al.)

- +/- preexisting AAV5 neutralizing Abs.
- Mean ABR for all bleeds ↓64% (ABR 1.52) vs 4.17; *P*=0.0004 in ≥.6 mos lead in period
- Mean FIX activity =41.5% at YR 1; 38.6% at YR 3 post-tx.
- At 3 yrs post-tx, 94% free of FIX prophy; 75% recvd no FIX
- Mean FIX use ↓ 96% at 3 yrs
- 1 case HCC; 16.7% recvd corticosteroids for a mean 81.4d (range: 51-130 d). No TEs

Treatment of Chemotherapy Induced Thrombocytopenia

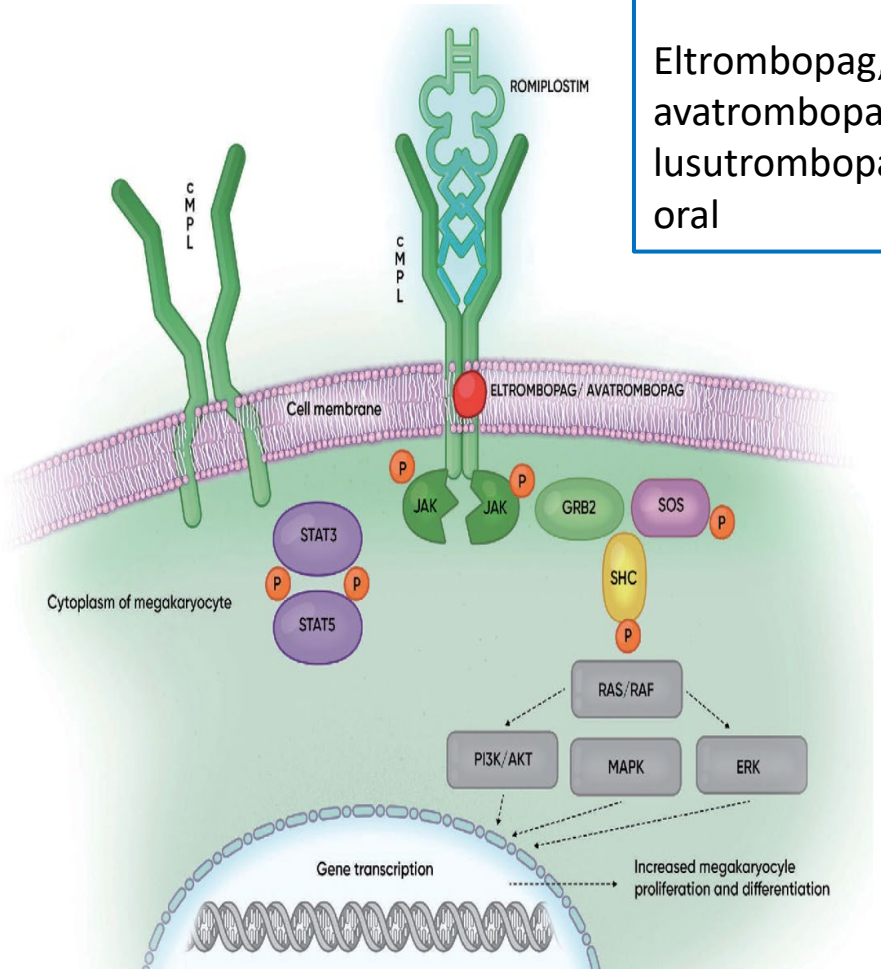
https://www.jthjournal.org/article/S1538-7836(23)00734-1/fulltext#%20

- Support for chemotherapy induced thrombocytopenia (CIT) remains an unmet need.
- Standard of care is for chemotherapy dose reduction or delay when the platelet count is < 100×10^9/L.
- Platelet transfusion is costly and provides only a short duration of support.
- Reduced chemotherapy dose intensity may adversely impact progression-free survival (PFS) and overall survival (OS) in patients with cancer.

NONE OF THE TPO-RAs HAS BEEN APPROVED FOR TREATMENT OF CIT BY THE FDA

Romiplostim-SQ

Eltrombopag, avatrombopag, lusutrombopag-oral

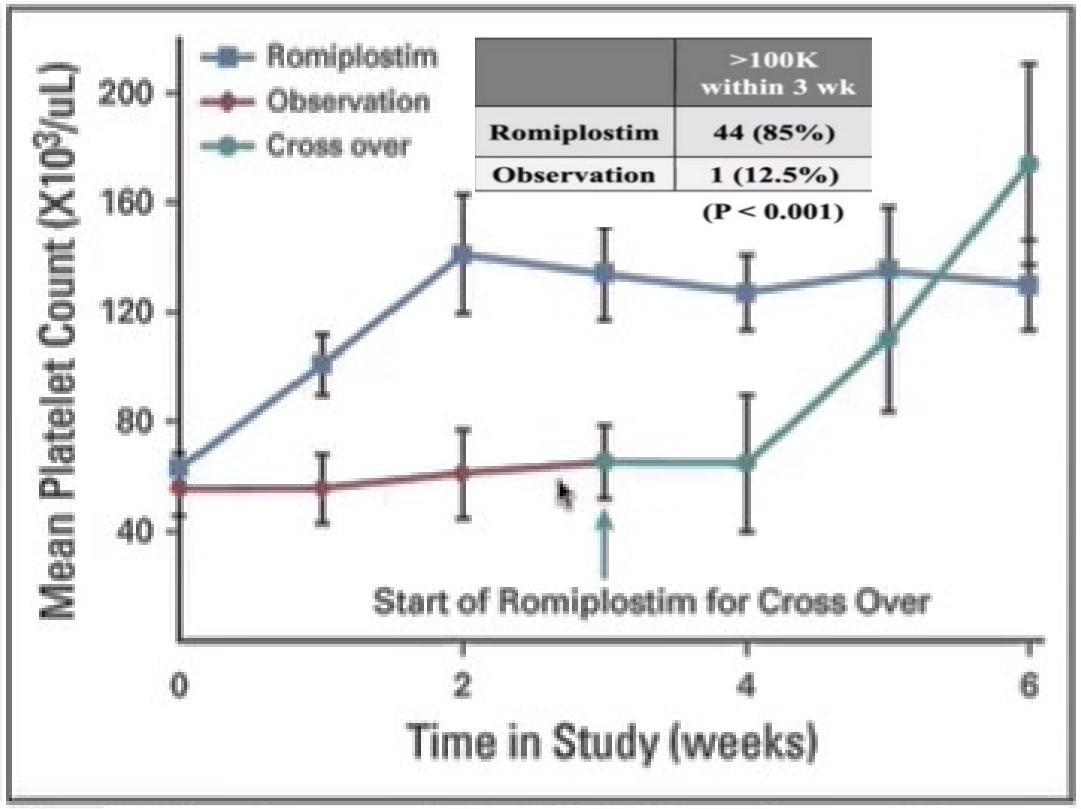


Haematologica 2019;104(6):1112-1123

Does Treatment of CIT Benefit Progression Free or Overall Survival?

Why is TPO-RA Use only an NCCN 2B Recommendation? Drive rank score=1

Phase 2 study: Romiplostim vs SOC for CIT in solid tumor malignancies



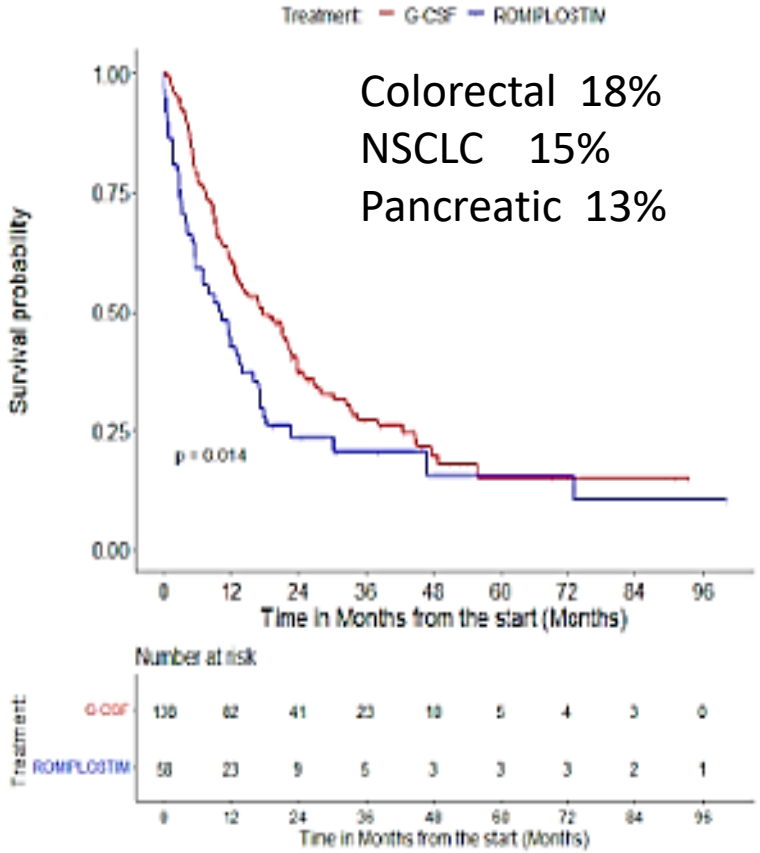
	>100K within 3 wk
Romiplostim	44 (85%)
Observation	1 (12.5%)

(P < 0.001)

Soff et al. J Clin Oncol. 2019; **37**: 2892-2898

ABS 0801: Impact of Romiplostim on Overall Survival in Chemotherapy Induced Thrombocytopenia. Wilkins CR et al.

Figure 1. Kaplan Meier Curve of median overall survival in G-CSF versus Romiplostim treated patients.



Colorectal 18%
NSCLC 15%
Pancreatic 13%

Retrospective exact-matched cohort analysis:

Mean overall survival:
Romiplostim 12 mos
G-CSF (no ROM) 21 mos

P = 0.014

ISTH Guidelines for the Treatment of Chemotherapy Induced Thrombocytopenia

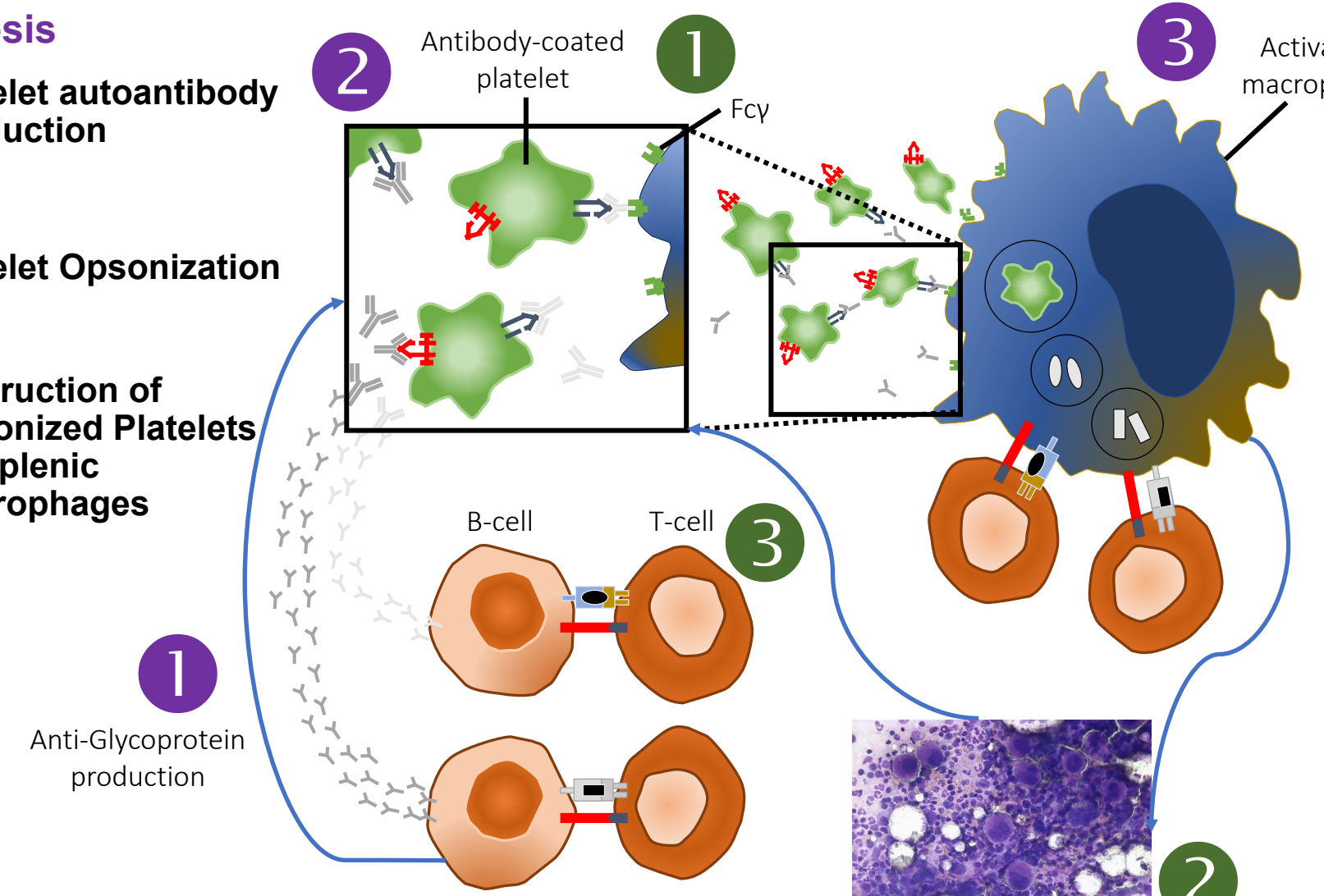
Soff G et al. JTH. 2024;22(1):53-60

- Suggest (weak recommendation) TPO-RA when inadequate platelet recovery at d1 chemo cycle to avoid dose reduction ≥ 7d delay for tx
  - Assuming ANC and hemoglobin recoveries
- TPO-RA for solid tumor malignancies where full dose chemo is expected to achieve or maintain clinically-relevant response
- Titrate TPO-RA to lowest dose to obtain platelets ≥ 100K at d1 chemo cycle
- No clinical benefit or trend toward adverse outcomes:
  - AML and/or high risk MDS
  - Autologous SCT for lymphoma or MM; inadequate data on allo-SCT
  - Inadequate data for lymphoma, low grade MDS; NOT FOR ROUTINE USE

ITP is an Autoimmune Disorder Mediated by Autoantibodies

Pathogenesis

1. **Platelet autoantibody production**
2. **Platelet Opsonization**
3. **Destruction of Opsonized Platelets by Splenic Macrophages**



Bone Marrow Image from ASH.

Treatment MOA

1. **Splenectomy, corticosteroids, IVIg, IV Anti-D, danazol, Vinca alkaloids**
2. **TPO receptor agonists, corticosteroids**
3. **Azathioprine, cyclophosphamide, cyclosporin, corticosteroids, danazol, mycophenolate mofetil**

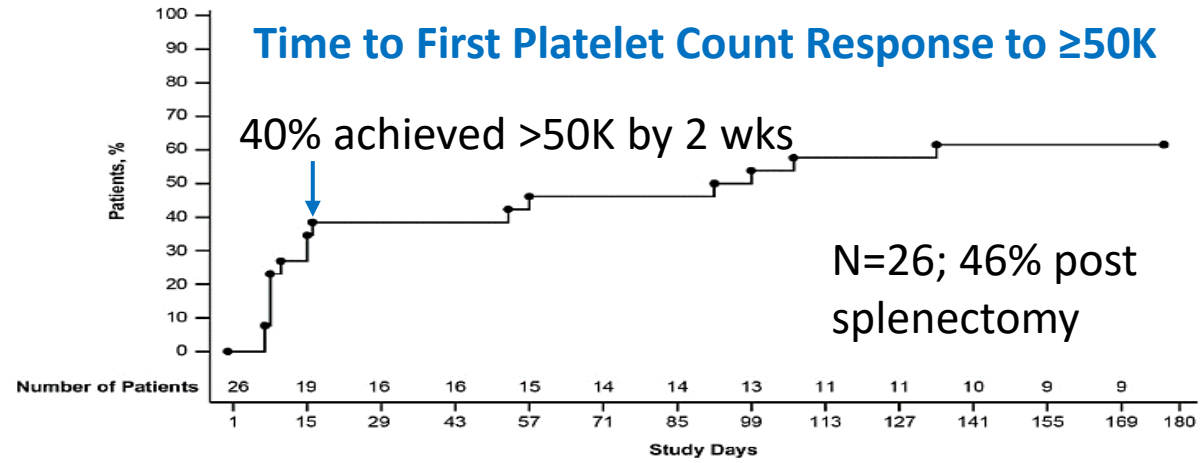
Cines DB, et al. *N Engl J Med.* 2002;346(13):995-1008.

ABS 685: Initial Report of Part B Phase ½ Efficacy and Safety Results for Oral Bruton Tyrosine Kinase Inhibitor Rilzabrutinib in Patients with Relapsed Immune Thrombocytopenia

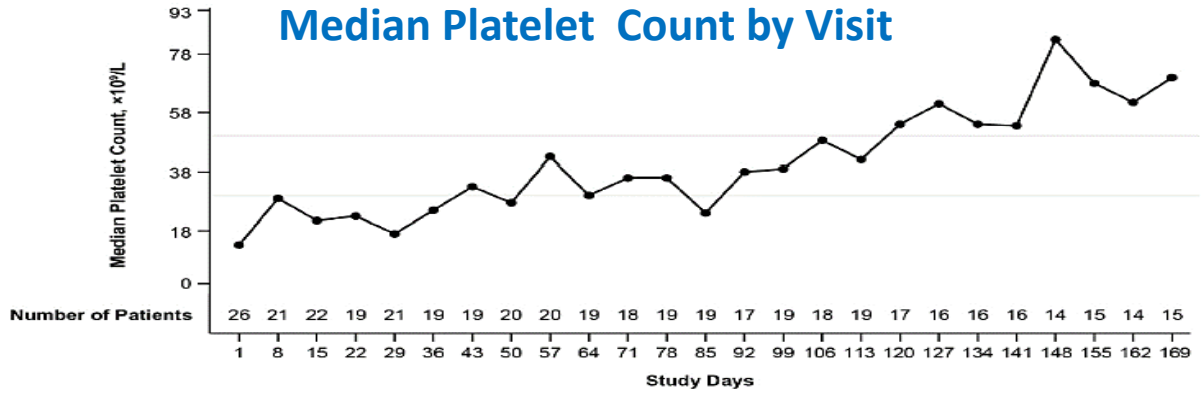
Cooper N

drive rank 1

A



B

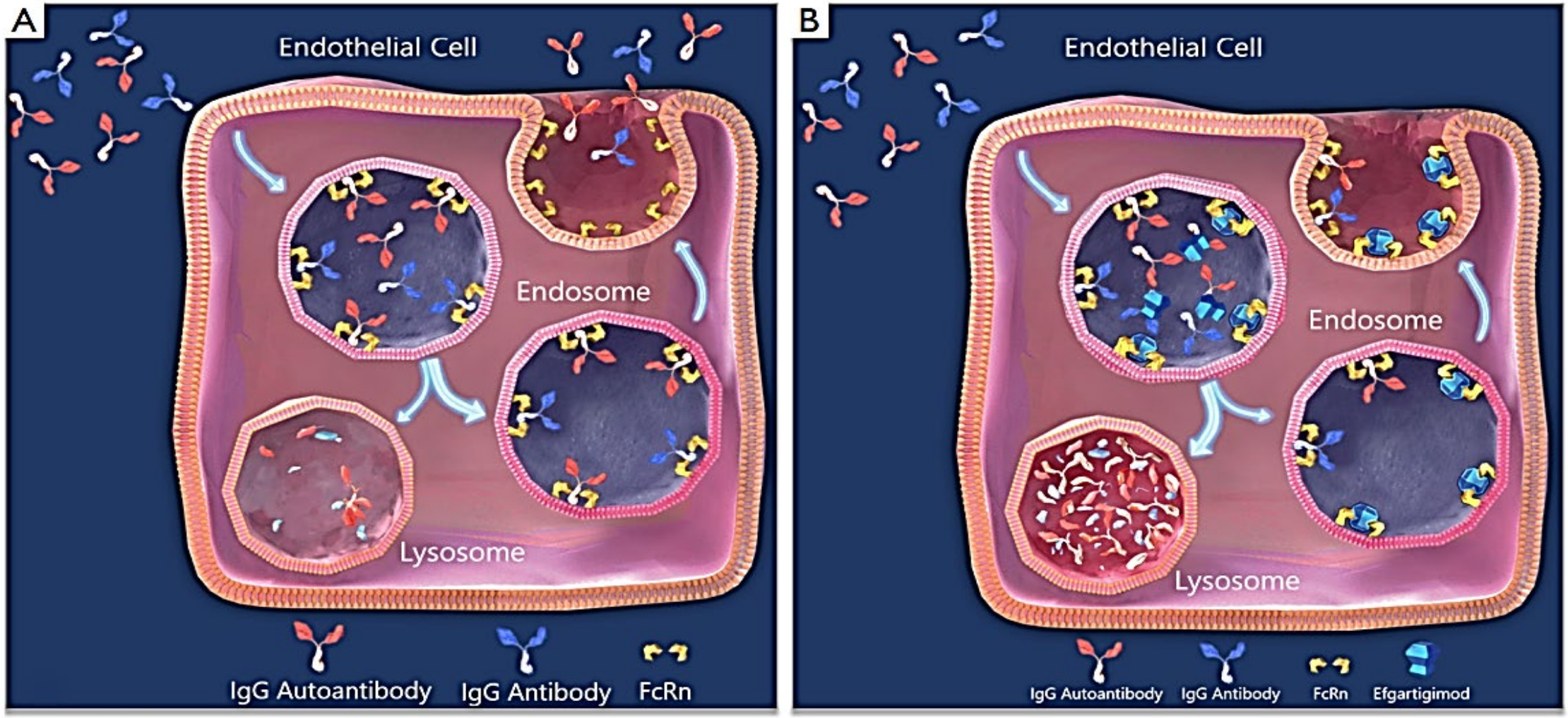


Bruton Tyrosine Kinase Inhibitors in ITP

- Inhibit B-cell activation
- Interrupt antibody-coated phagocytosis by FcR in spleen and liver
- Induce sustained anti-inflammatory effects

Mode of Action for FcRn Receptor Antagonists in ITP

Efgartigimod= Engineered human IgG1 antibody Fc fragment without Fab region
Rozanolixizumab = Humanized high affinity anti-FcRn IgG4 mAb with Fab region



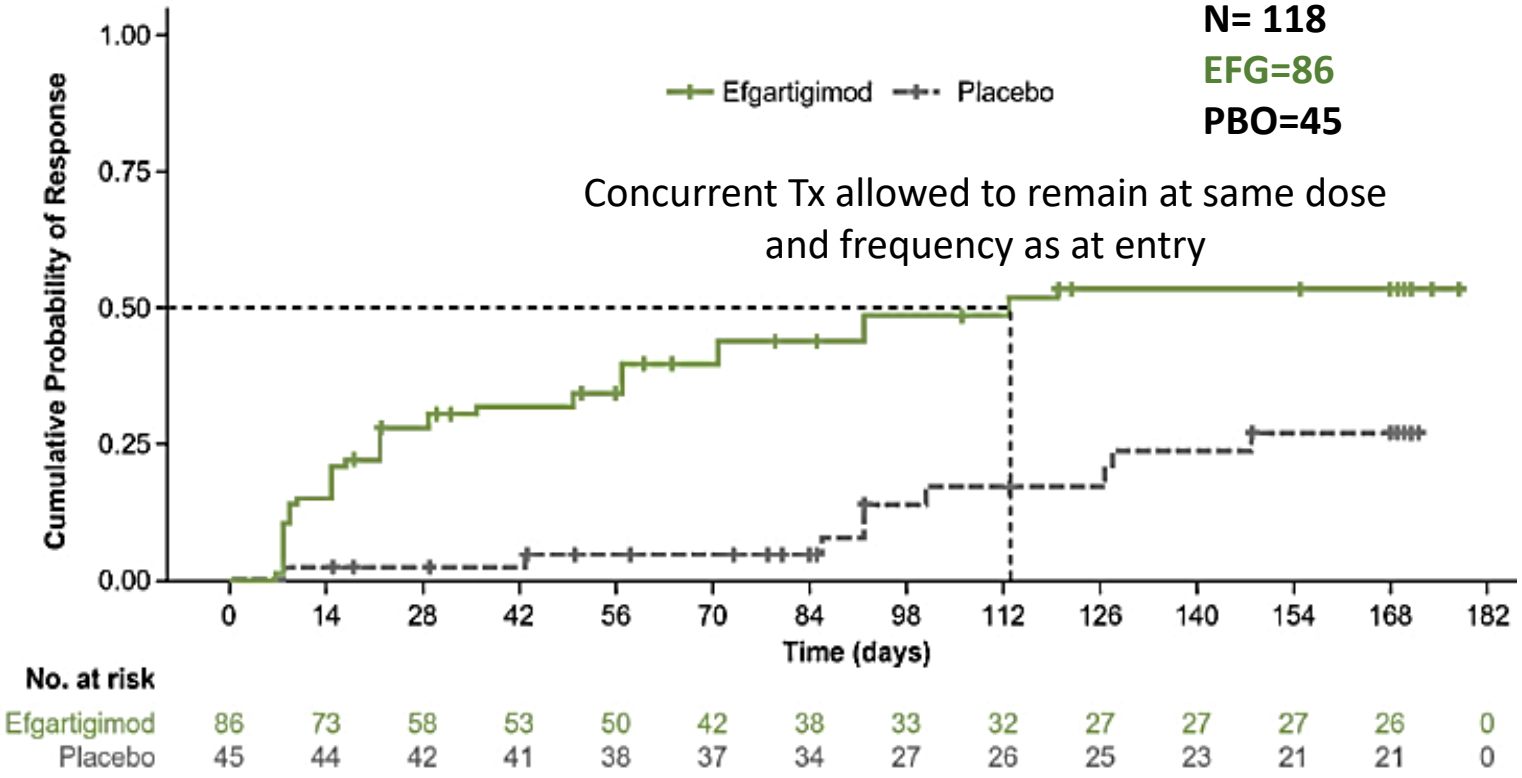
Adapted from Newland AC, McDonald V. FcRn antagonists in ITP. Ann Blood 2021;6:6

ABS 689: Time to Achieve Platelet Count Response after Intravenous Efgartigimod in Adults with Primary immune Thrombocytopenia: A Phase 3 Multicenter, Double-blinded, Placebo-controlled, Randomized Clinical Trial (Advance IV)

Broome CM et al

Drive Rank score = 0

Figure: Time to Achieve Platelet Count Response (2 Consecutive Platelet Counts of ≥50×10⁹/L): Kaplan-Meier Curves in the Overall Population (Full Analysis Set)



N= 118

EFG=86

PBO=45

Concurrent Tx allowed to remain at same dose and frequency as at entry

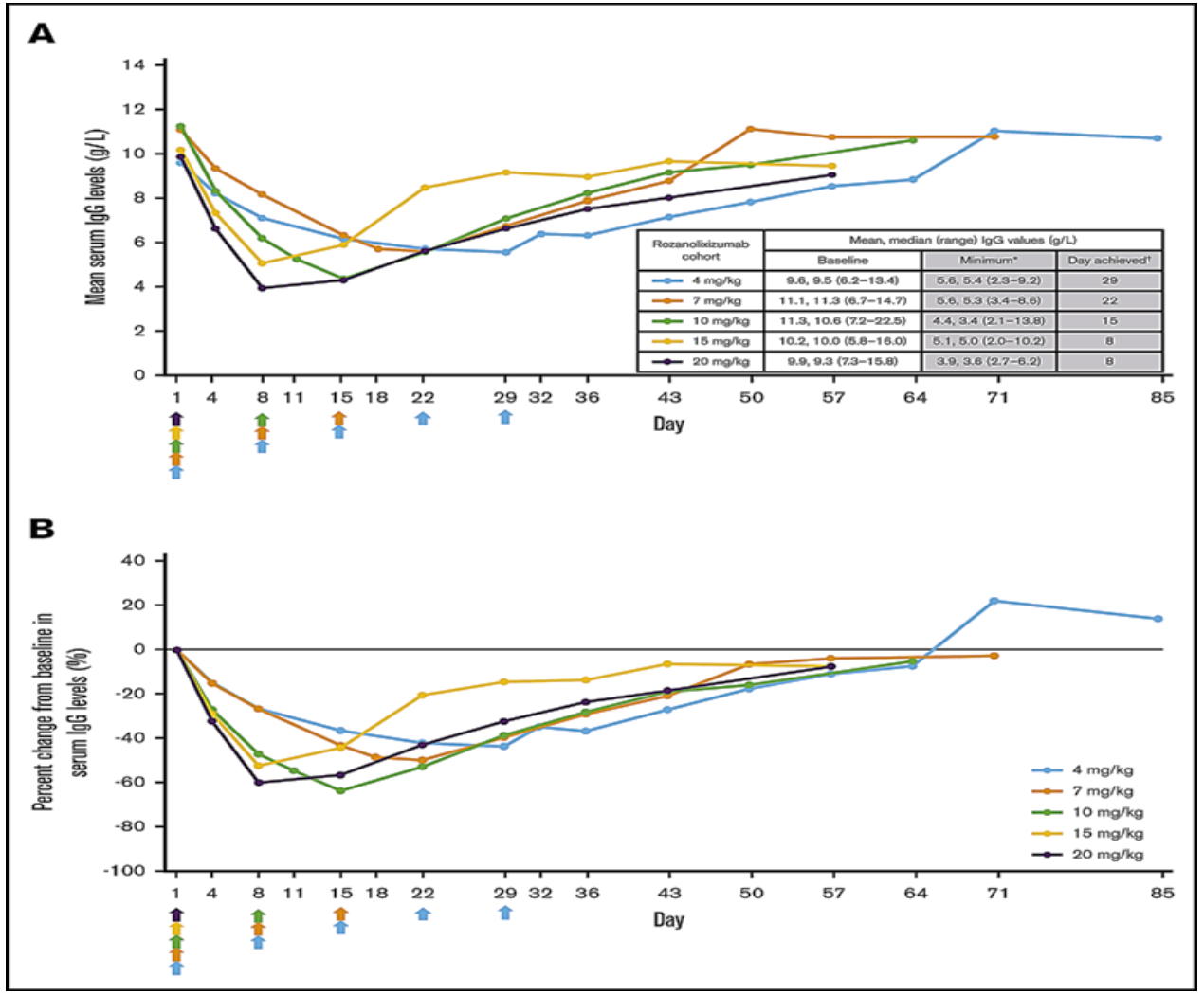
Dashed black line denotes 50% response in the EFG arm.
EFG, efgartigimod.

Response rate (%)	Time to a single PLT ≥30×10⁹/L		Time to a single PLT ≥50×10⁹/L		Time to 2 PLT ≥50×10⁹/L	
	EFG (N=86)	PBO (N=45)	EFG (N=86)	PBO (N=45)	EFG (N=86)	PBO (N=45)
Day 42	57.4	35.8	41.5	11.4	31.8	2.2
Day 84	75.0	43.3	57.0	16.6	44.0	4.6
Day 126	81.0	47.1	68.8	36.5	53.5	17.0
Day 168	85.2	51.1	72.2	47.0	53.3	27.0

(11/28/2023): ADVANCE-SC did not meet primary endpoint

Phase 2 multiple-dose study of an FcRn inhibitor, rozanolixizumab, in patients with primary immune thrombocytopenia

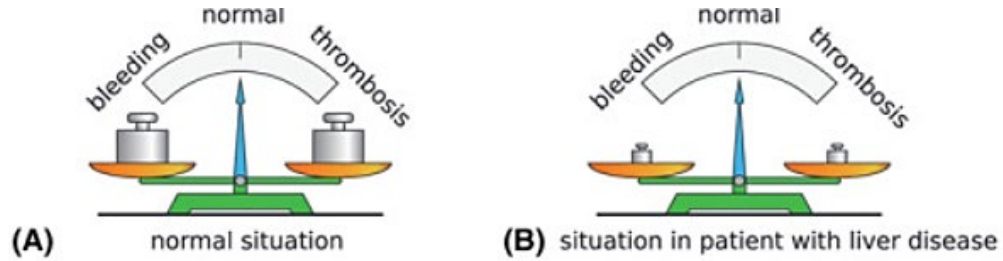
Long recovery period for IgG levels: What are the implications?

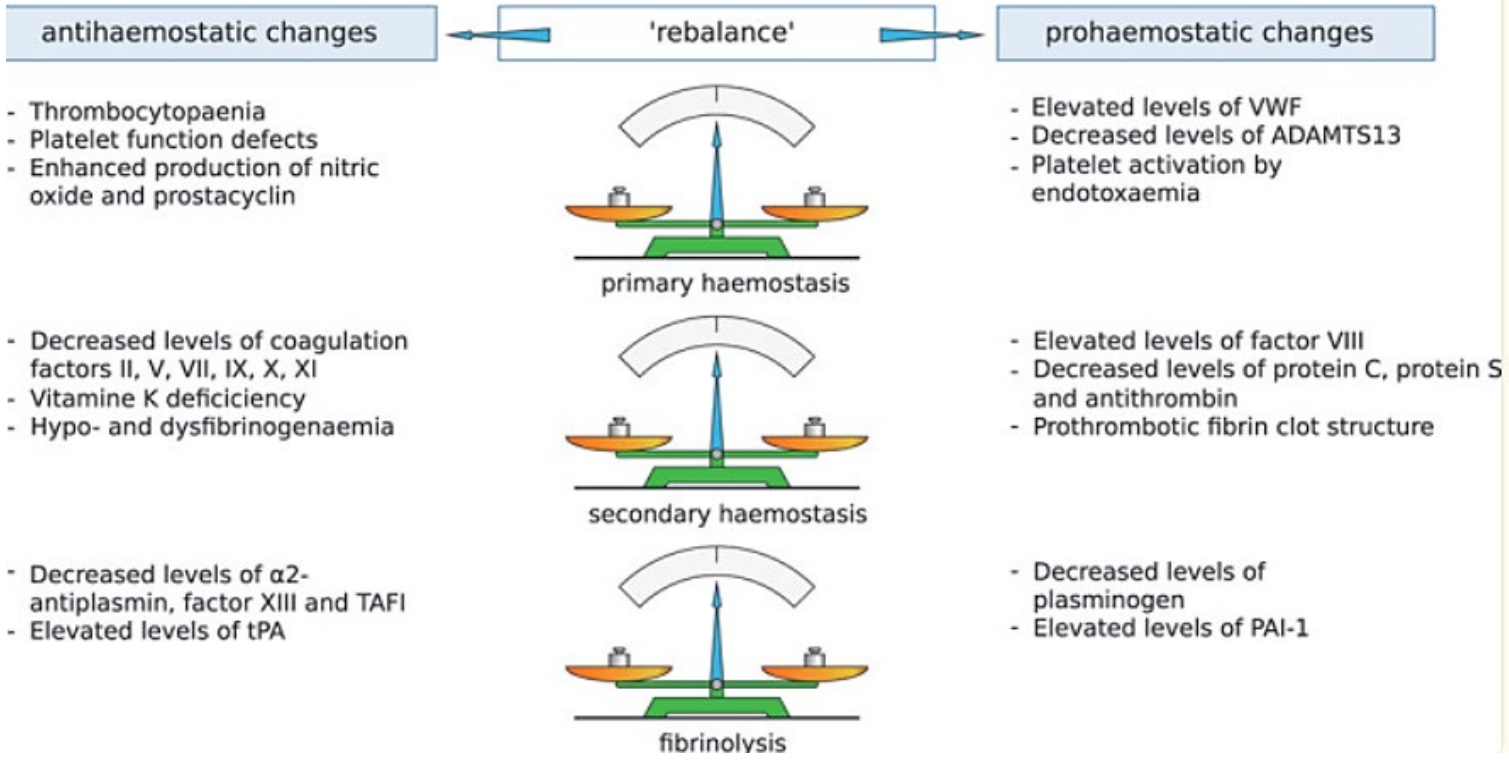


Robak T et al. Blood Adv (2020) 4 (17): 4136–4146. https://doi.org/10.1182/bloodadvances.2020002003

Hemostatic Rebalancing in Chronic Liver Disease

Hematology Am Soc Hematol Educ Program (2023) 2023 (1): 274–280





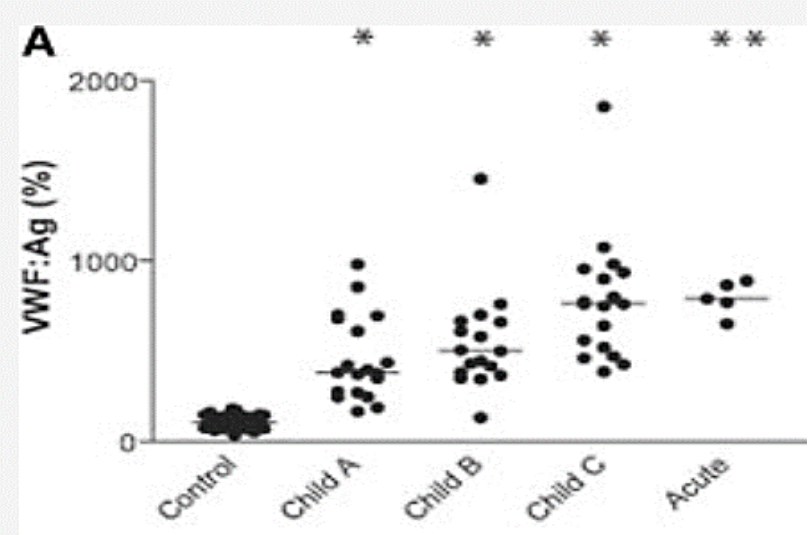
Hemostatic Testing in CLD

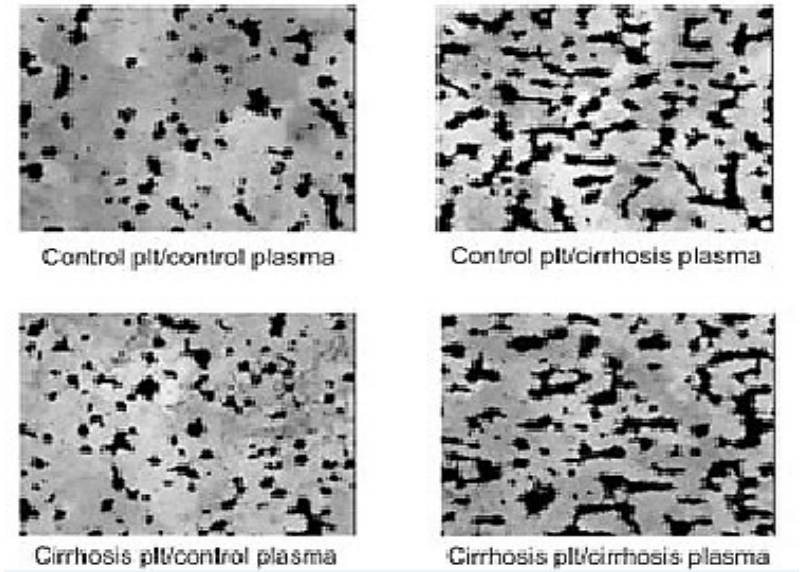
- **PT/INR does not predict procedural bleeding risk**
- **Uncertain whether procedural bleeding risk is predicted by platelet counts or fibrinogen**
- **Coag testing to predict bleeding for procedures is not advised; baseline coag testing may be helpful if bleeding occurs**
- **Coag testing indicates severity of CLD**

TGA show normal to enhanced hemostasis despite clearly abnormal conventional coag testing

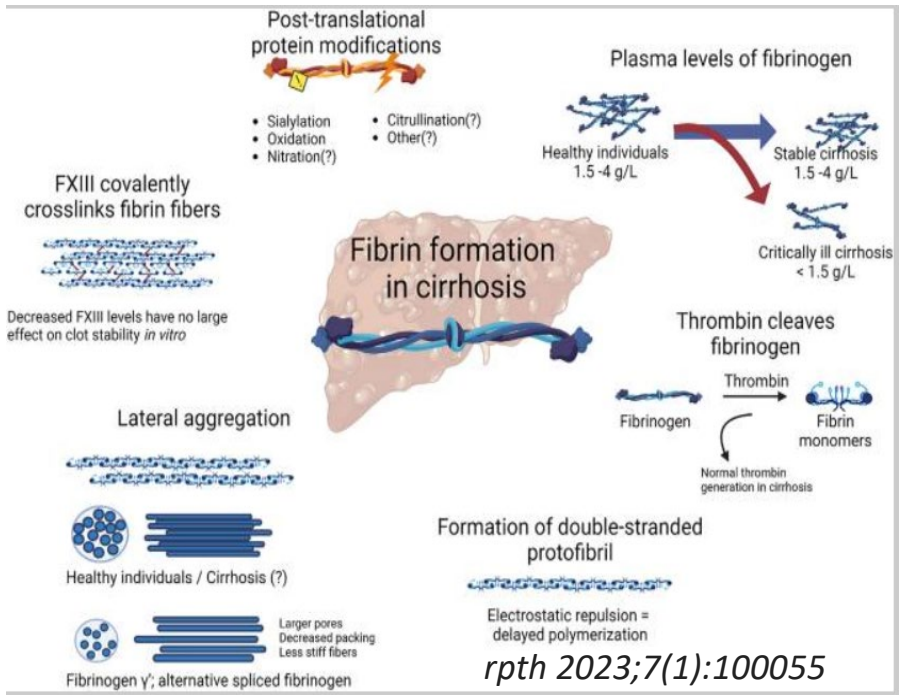
(Lisman T et al. Jhep. 2022;76:1291)

Hemostatic Rebalancing in Chronic Liver Disease

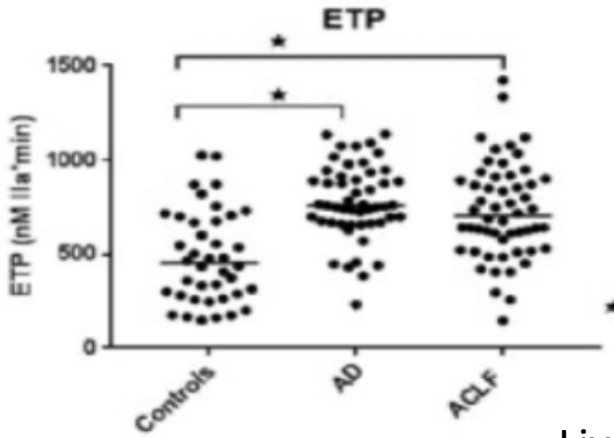




Hepatology. 2006;**44**(1):53-61



rpth 2023;7(1):100055

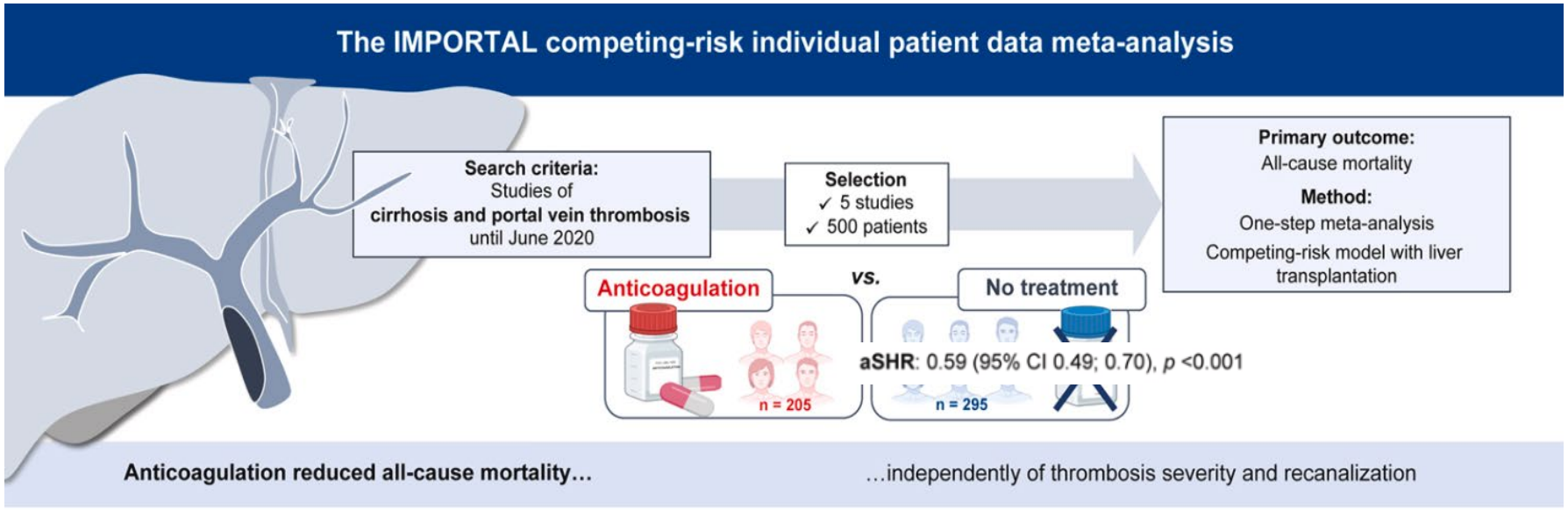


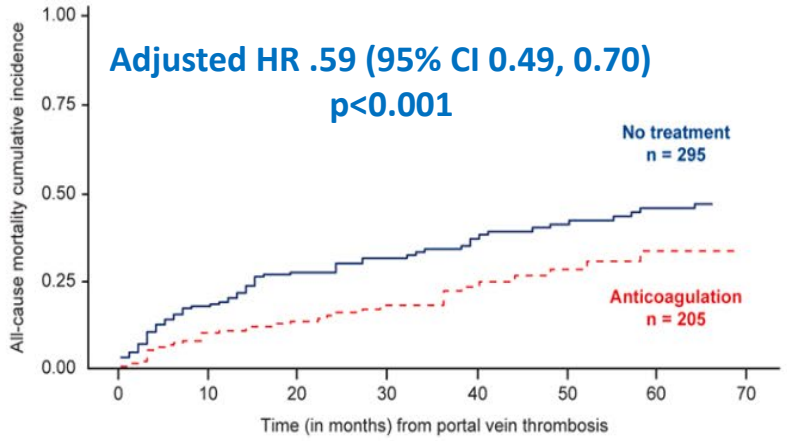
AC= Acute decompensated
ACLF= Acute on chronic

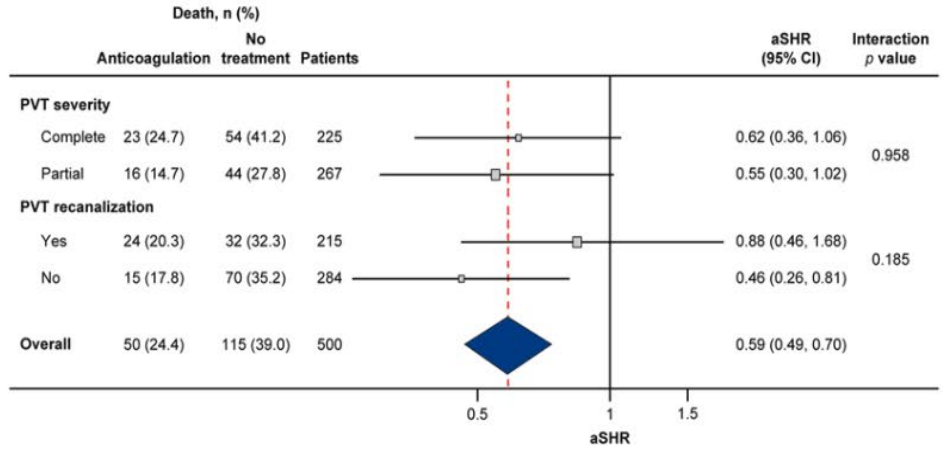
Liver Int. 2022;42(2):435)

Anticoagulation Improves Morbidity and Survival in Splanchnic Thrombosis and Cirrhosis

drive rank score=1







Anticoagulation vs None

Liver related mortality %
9.3 20.3 p.=0.001
Liver transplantation %
12.7 8.5 p=0.129
Recanalization %
57.1 37.2 p<0.001
Stable thrombus %
28 51.8 p=0.000
Thrombus progression %
14.1 14.6 p=0.360
Total bleeding events %
19.0 15.6 p=0.315

Guerrero A et al. JHep 2023;79(1):69-78

DOACs for the treatment of cirrhosis-related splanchnic thrombosis

drive rank score N/A

Caveat: No adequately powered, prospective, randomized, controlled trials with DOACs

Authors (year)	Design	Treatment duration	Number of patients	Treatment	Recanalization	Progression /recurrence	Bleeding
De Gottardi (2016)	Retrospective	Not reported	36	30 Riva 4 Apixaban 2 Dabi	Not reported	1 (2.8%)	1 major (2.8%) 4 minor (5.6%)
Nagaoki (2018)	Retrospective	6 months	20	Edoxaban	18 (90%)	1 (5%)	3 clinically relevant (15%)
Ai (2020)	Prospective	6 months	40 (chronic PVT)	Riva Dabi	11 (28%)	3 (8%)	3 any bleeding (8%)
Naymagon (2021)	Retrospective	19 months (median)	18	Apixaban Riva Dabi	10 (56%)	1 (6%)	3 major (17%)

Hematology Am Soc Hematol Educ Program (2023) 2023 (1): 274–280

16 studies on 648 patients with any SVT treated with DOACs vs AC (Meta-analysis)

Any recanalization in 60.3% (95% CI: 41.8%-76.3%; I^2 = 84.9%; P < .001)

Full recanalization in 51.7% (95% CI: 36.0%-67.0%; I^2 = 87.4%; P < .001)

Recurrent VTE in 2.8% (95% CI: 1.4%-5.9%; I^2 = 0%; P = .787)

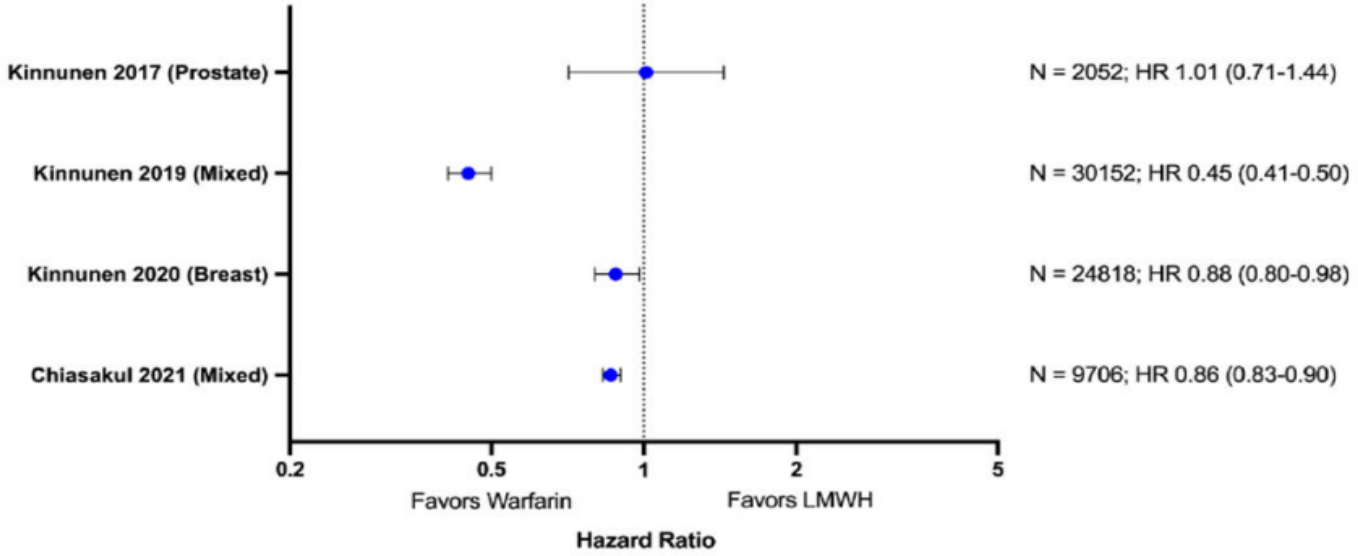
Death in 3.4% (95% CI: 1.6%-7.3%; I^2 = 13.2%; P = .318)

"Cirrhosis: associated with a higher rate of major bleeding/mortality"

Calcatera I et al.
:DOI:https://doi.org/10.1016/j.jtha.2023.10.023

ABS 138: Overall Survival of Warfarin Compared to LMWH/DOACs in Cancer-Associated Venous Thromboembolism: VA Cohort Study Ryu J

- Emerging population-based evidence suggests an association of warfarin with improved overall survival in cancer patients and possible preventive effect against certain types of cancers.
- Anti-neoplastic mechanisms of warfarin include inhibition of thrombin and Gas6 signaling.
- Implications for future research include identifying subgroups with improved outcomes.



Survival with warfarin in CA compared to other anticoagulants (mainly LMWH)

Chiasakul and Zwicker. Thromb Res. 2022;213(Suppl 1): S113–S119

Figure 1: Kaplan Meyer curve for overall survival in patients treated with warfarin (in blue) compared to patients treated with direct oral anticoagulants or low molecular weight heparin (in red) for cancer associated thrombosis.

N=20.078
Warfarin=8383
Non-warfarin=11.696

Median OS=1204d vs 703d; HR 0.79, $p<2x10^{-16}$

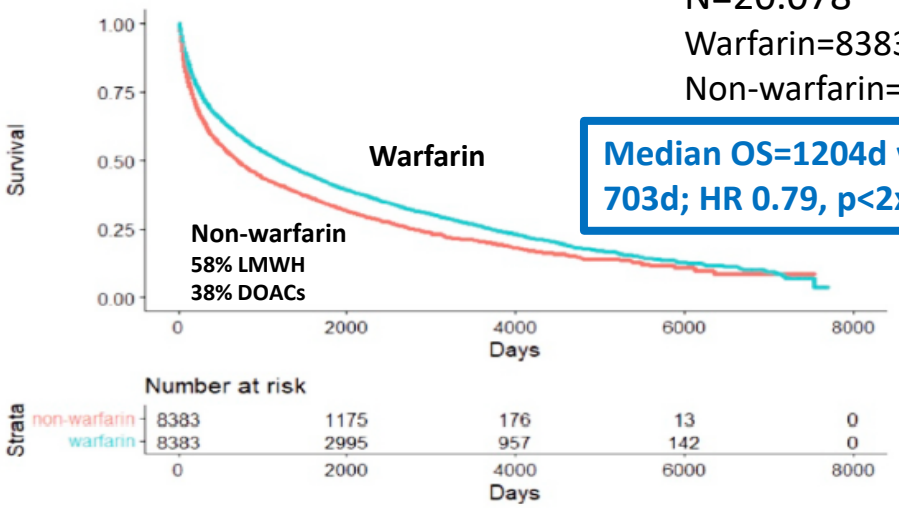
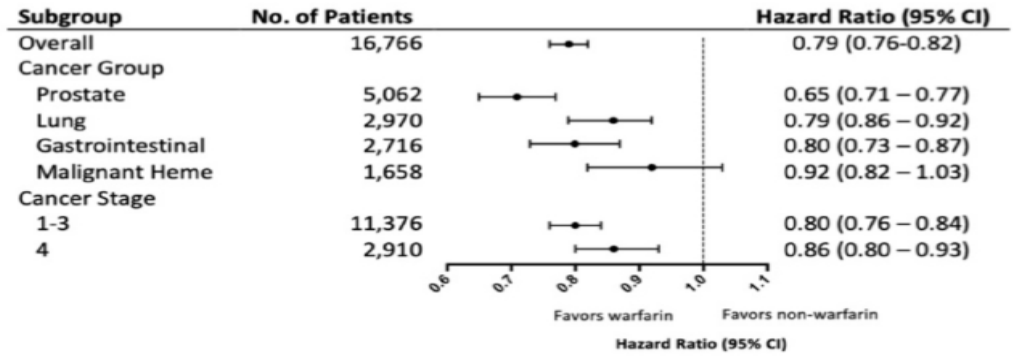
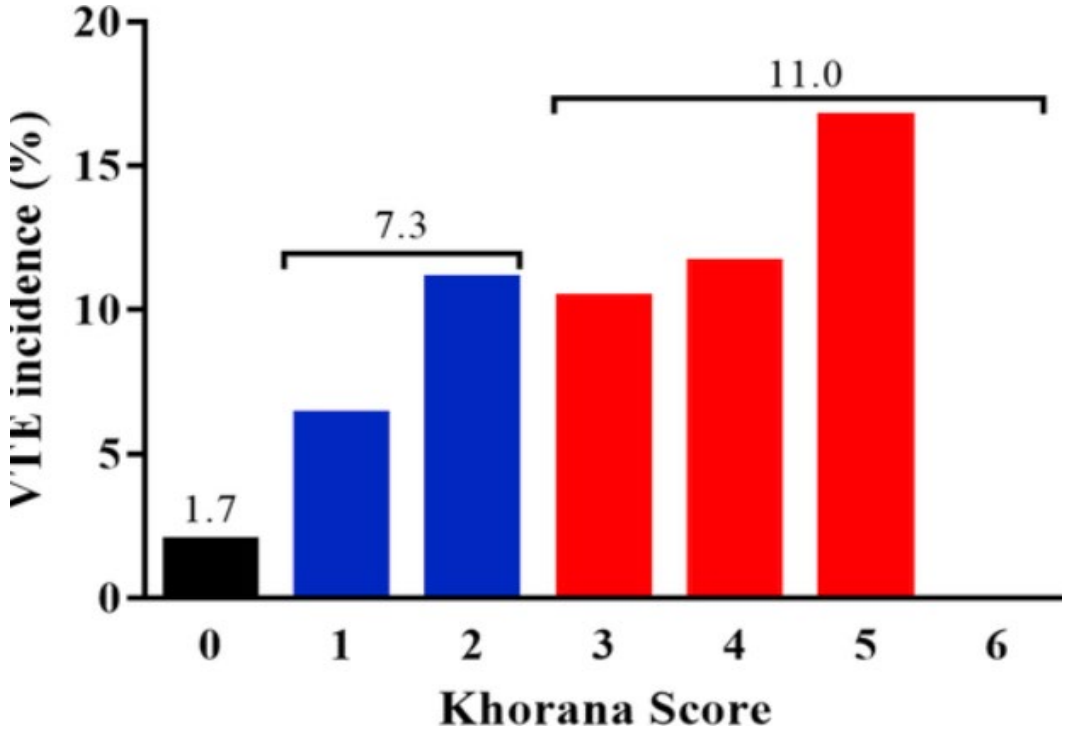


Figure 2: Subgroup analyses of overall survival. Shown is a forest plot of the subgroup analyses using Cox proportional hazards regression that included the subgroup covariate of interest



ABS 1279: Predictive Efficacy of the Khorana Score in Black Patients: Retrospective Cohort Study Akpoviroro O drive rank score=2



https://www.jacc.org/cms/asset/7ae5cec0-35da-45e8-8755-cacf1871b7de/gr4.jpg

- Studies indicate that the risk of VTE is increased in Blacks
- Original KS study did not stratify patients based on race
- Is the KS appropriately predictive of VTE in Black patients with cancer?

- Retrospective study: 233 patients; 39.9% Black
- Mean CA-to-VTE: AA-4.4 mos vs 4.3 mos in WP
- VTE Incidence at 1yr post CA dx: AA=8.4%; WP=5.8%
- **Positive Predictive Value of the KS:**

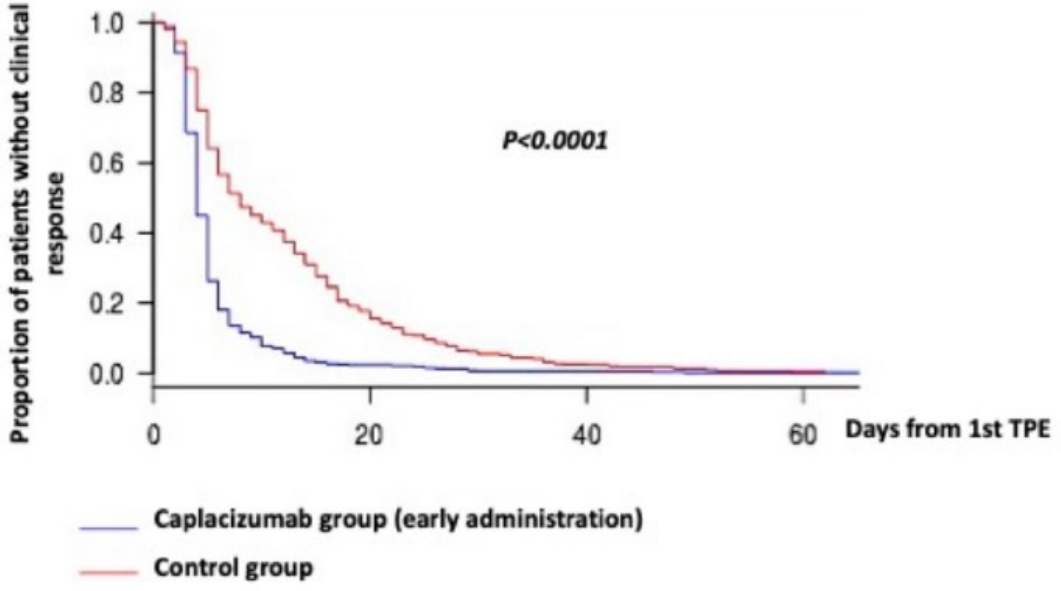
  AA: HR 13% IR 31% LR 17% **P<0.001**

  WP: HR 65% IR 54% LR 34%
- Step wise increase in PPV for KS prediction of VTE in WP; no such pattern was seen in AA.
- **KS may not be an adequate predictor of VTE in AA**

Thrombotic thrombocytopenic Purpura: New Strategies

ABS 2636: Caplacizumab frontline added to TPE and immunosuppression prevents unfavorable outcomes in iTTP: Real world experience Coppo P

Figure. Cumulative daily rate of event (clinical response)-free survival after first therapeutic plasma exchange within 3 months in patients of the caplacizumab group who received early caplacizumab administration (within 3 days following first therapeutic plasma exchange [TPE]) versus patients of the control group.



ABS 692: Recombinant ADAMTS13 for the treatment of acute events in cTTP: Results from phase 3 randomized, controlled, crossover study Scully M