

Benign Hematology: Clotting, Bleeding and More

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Disclosures

- Research- Bayer, NovoNordisk, Octapharma, Genentech/Roche, Sangamo, Takeda
- Advisory Boards- Argenx, Bayer, BioMarin, CSL-Behring, Freeline, Genentech/Roche, Grifols, NovoNordisk, Octapharma, Pfizer, Takeda, Principia, Rigel, Spark
- DSMB- NIH, Dimension, Revo, Octapharma
- Stock- Not applicable
- Employment – Not applicable
- Speakers' Bureau – Not applicable

Topics

- Advances in Immune Thrombocytopenic Purpura (ITP)
- ITP and COVID-19
- COVID-19 and coagulation
- Cancer and Thrombosis
- Hemophilia and Gene therapy
- New reversal strategy for direct acting oral anticoagulants (DOACs)

Treatment of Newly Diagnosed ITP

ASH 2019

Suggests treatment instead of observation for platelet count <30K

“...may be a subset of patients for whom observation may be appropriate”

Suggests hospital admission over outpatient management for platelet count <20K *at diagnosis*

International Consensus Report (ICR) 2019

Suggests treatment instead of observation for platelet count <20K

Patient considerations weigh heavily in treatment decisions

Suggests hospital admission over outpatient management for platelet count <20K *at diagnosis*

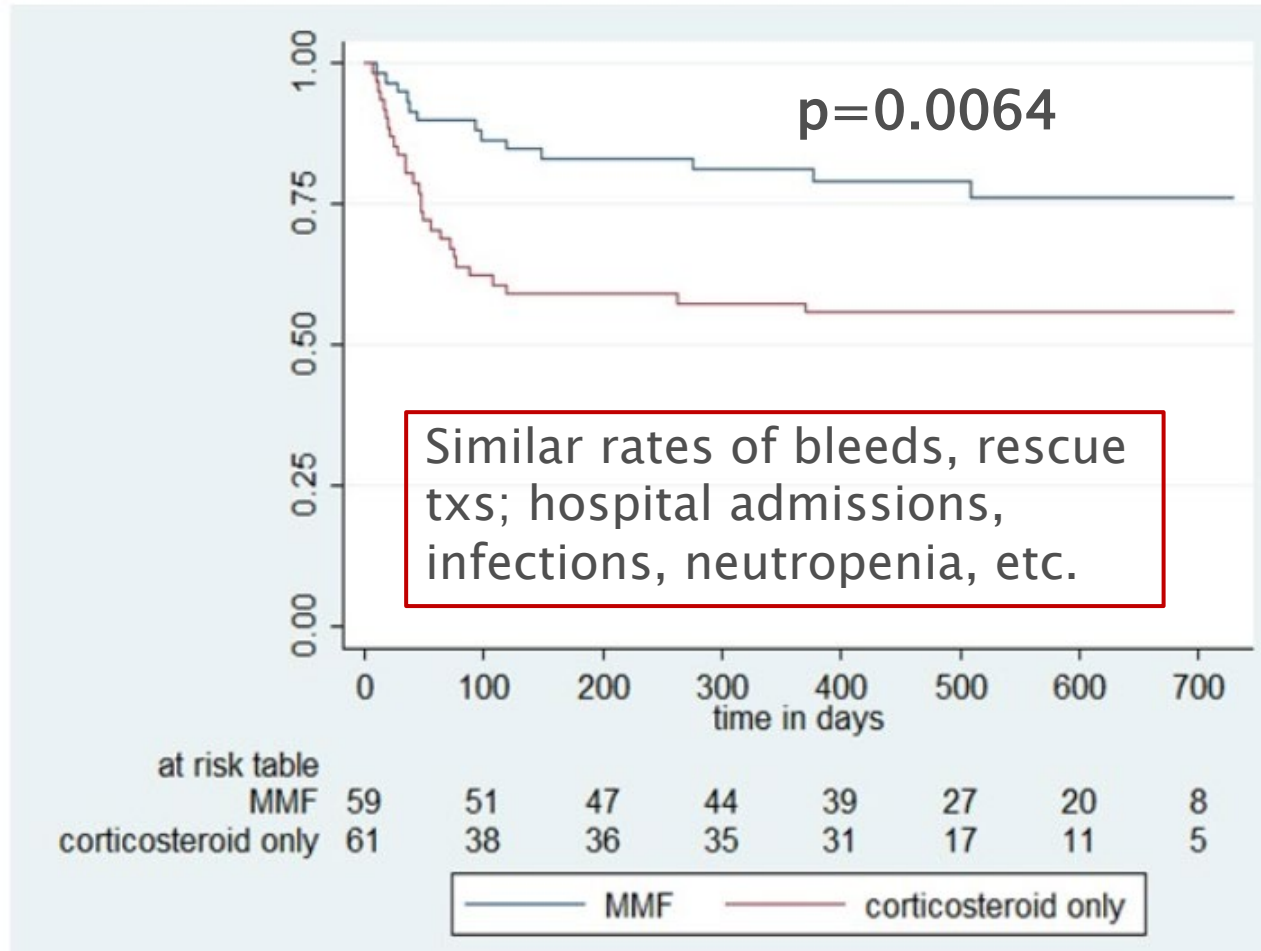
Both highlight patients >60 are a high risk group more likely to experience major bleeding

Upfront Management

- No reliable way to predict response to therapy in advance
- Both guidelines recommend corticosteroids as the front-line treatment of choice for newly diagnosed ITP
- Goal: decrease risk of bleeding, NOT normalize platelet count
- Balance risk of side effects, likelihood of benefit, cost, route of administration, insurance, patient preferences and values
- **Both guidelines place value on avoidance of prolonged courses (>2-3 weeks with taper) of corticosteroids given side effects**
- Consider transition to second line therapy

A Multicentre Randomised Trial of First Line Treatment Pathways for Newly Diagnosed Immune Thrombocytopenia: Standard Steroid Treatment Versus Combined Steroid and Mycophenolate. the Flight Trial

Figure 1: Kaplan Meier graph showing the proportion of patients without treatment failure



First randomized trial using MMF to treat ITP; good efficacy and tolerability, even with the inclusion of elderly patients (27.5% were >70 years, 15.8% >75 years)

Corticosteroid only: 1 mg/kg/d prednisolone x 4d; 40 mg/d x 2 wk; 20 mg/d x 2 wk; 10 mg/d x 2 wk; 5 mg/d x 2 wks; 5 mg qod x 2 wk; then stop
 MMF: 500 mg bid x 2 wk; 750 mg bid x 2 wks; 1g bid x 2 wk for 6 mos, if tolerated; if CR, taper to lowest dose to maintain plts >100K;

Fewer tx failures: MMF+CS vs CS: 22% vs 44%, aHR=0.41 [0.21, 0.80], p=0.0064

When secondary ITP was excluded: aHR 0.37 [0.19, 0.71] p=0.0029

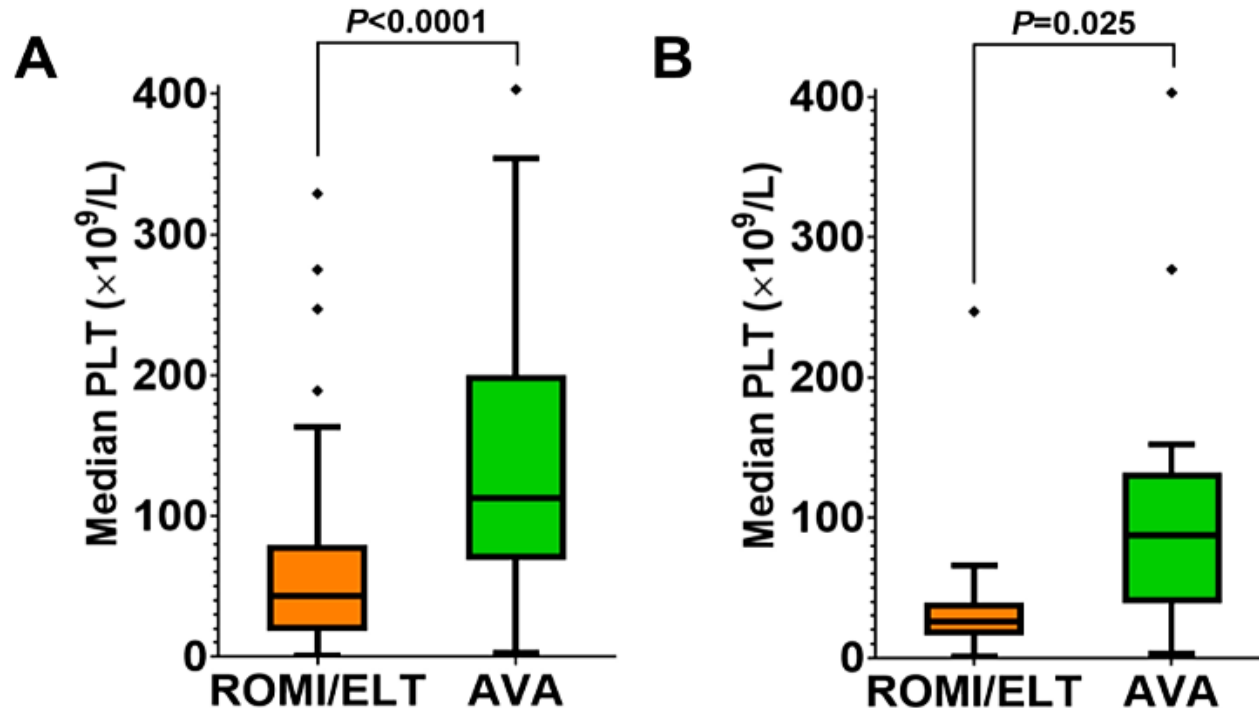
Second-line Therapies

Class/therapy	Agents	
Splenectomy		
Anti-CD20 antibody	Rituximab	
TPO-RAs	Eltrombopag, romiplostim, avatrombopag	
Syk inhibition	Fostamatinib	
Immunosuppressants	Azathioprine, MMF, danazol, cyclosporine, cyclophosphamide, vinca alkaloids, dapsone	
Investigational	FcRn inhibition	Rozanolixizumab, efgartigmod
	BTK inhibitor	PRN1008
	Hypomethylation	Low-dose decitabine

- No head-to-head trials exist comparing one second line therapy to another
- Limited clinical predictors and/or molecular biomarkers to guide treatment decisions

Are the TPO-RA agents interchangeable?

Rates of platelet response following switch to avatrombopag in the absence of rescue therapy (counts were disqualified if <8 weeks from receipt of rescue corticosteroids or <4 weeks from IVIG).

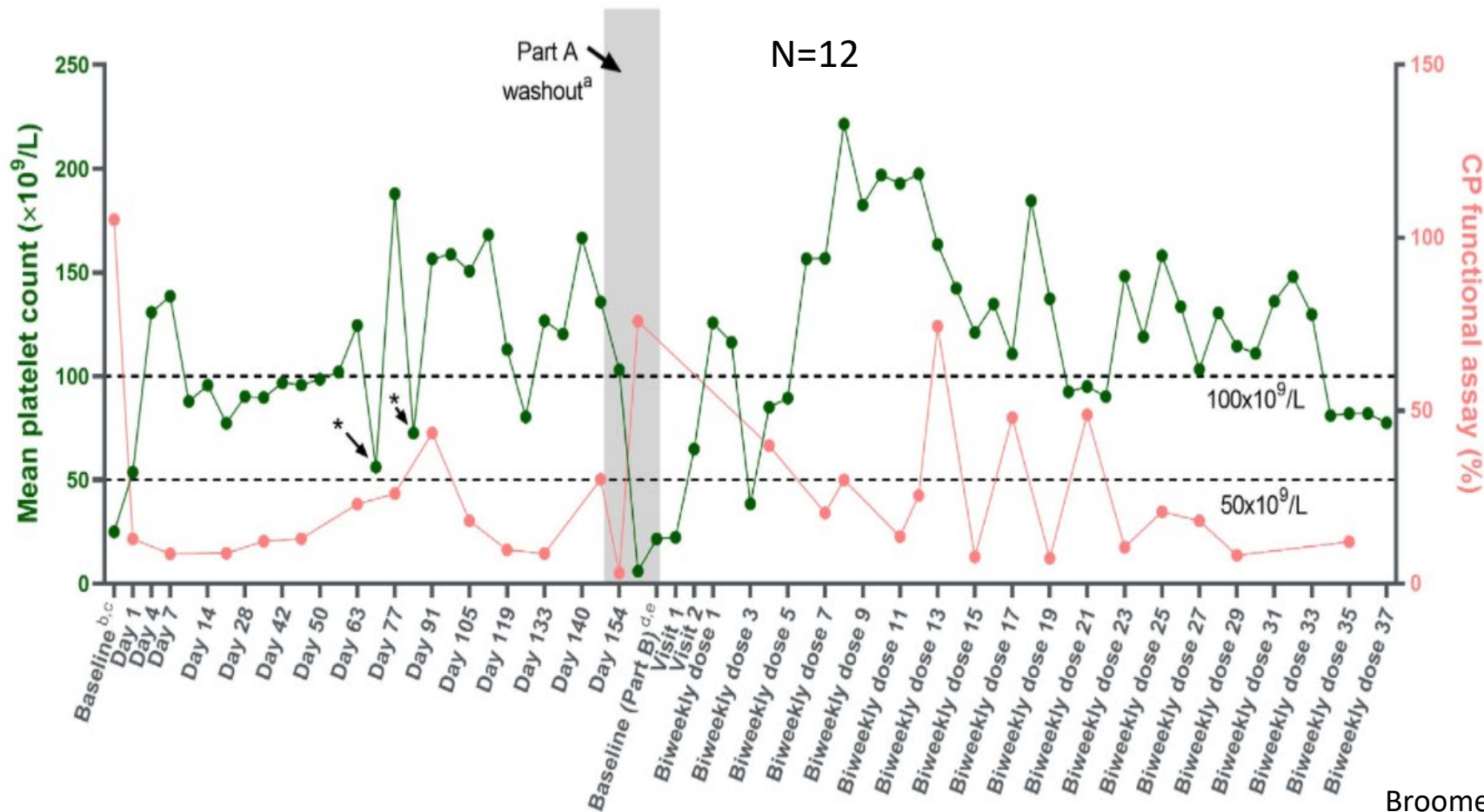


Conclusions: In a heavily-pretreated chronic ITP population, Avatrombopag (AVA) was effective following therapy with romiplostim (ROM) or Eltrombopag (ELT), with high response rates even in patients with inadequate response to a prior TPO-RA

Median platelet counts for each patient prior to switch (during treatment with romiplostim or eltrombopag) vs. following the switch to avatrombopag. For each patient, the median platelet count is the median of the most recent 3 platelet counts measured while receiving that agent. (A) All patients ($N=45$). (B) Patients switched due to ineffectiveness of romiplostim or eltrombopag ($N=14$). One patient with median Plt $585 \times 10^9/L$ on avatrombopag omitted from both graphs to preserve graph resolution.

Long-Term Safety and Efficacy of Sutimlimab in Patients with Chronic Immune Thrombocytopenia

Figure 1. Mean platelet counts ($\times 10^9/L$) and CP activity over time in patients receiving sutimlimab



INHIBITION OF CLASSICAL COMPLEMENT PATHWAY (CP)

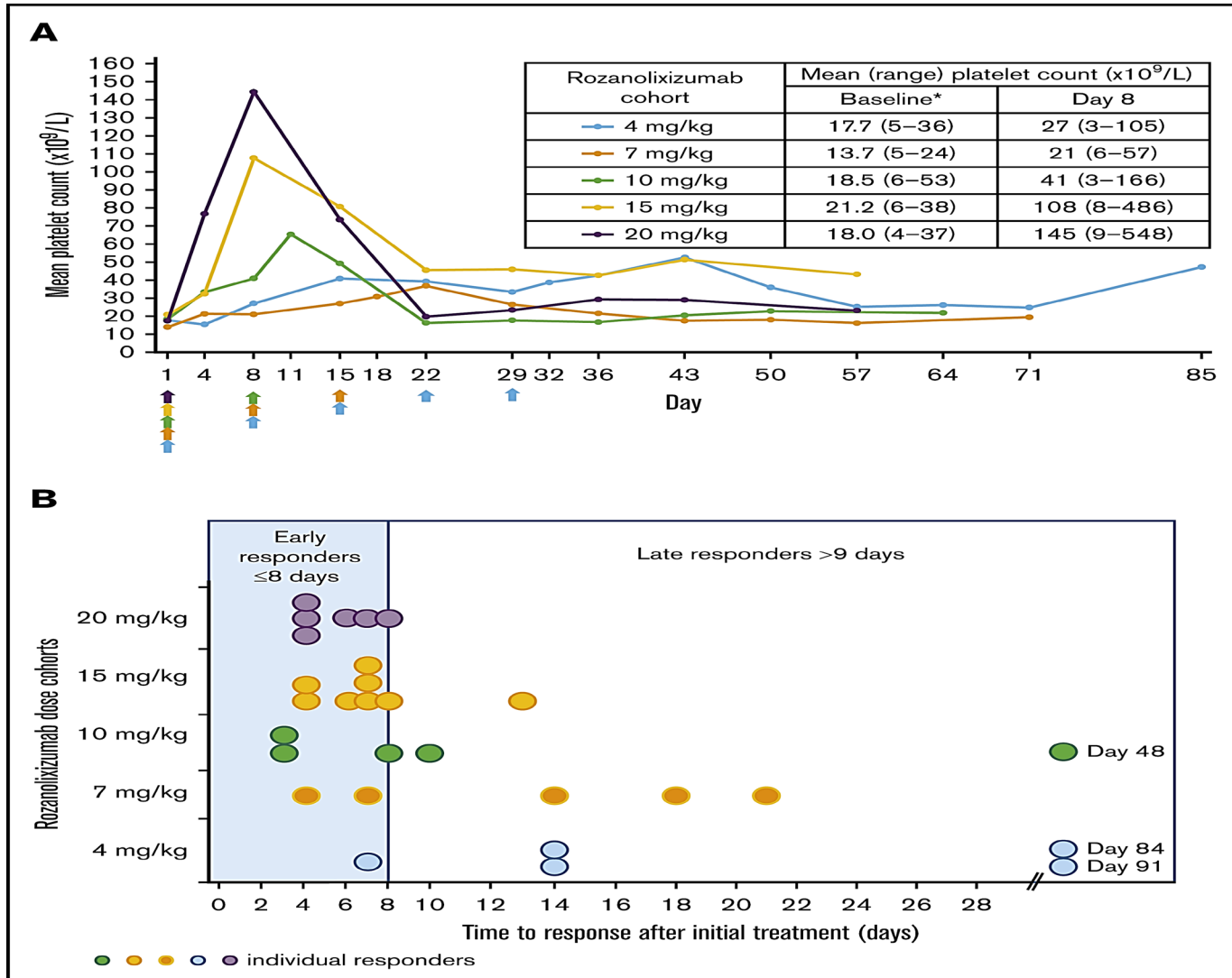
With humanized monoclonal AB selectively blocks activation of the CP by binding to C1s

Eight patients insufficiently responded to rituximab and 9 had insufficient response to TPO-RAs

Plt responses correlate with changes in CP activity, consistent with CP inhibition.

> 1 pathophysiologic etiology for heterogeneity of ITP

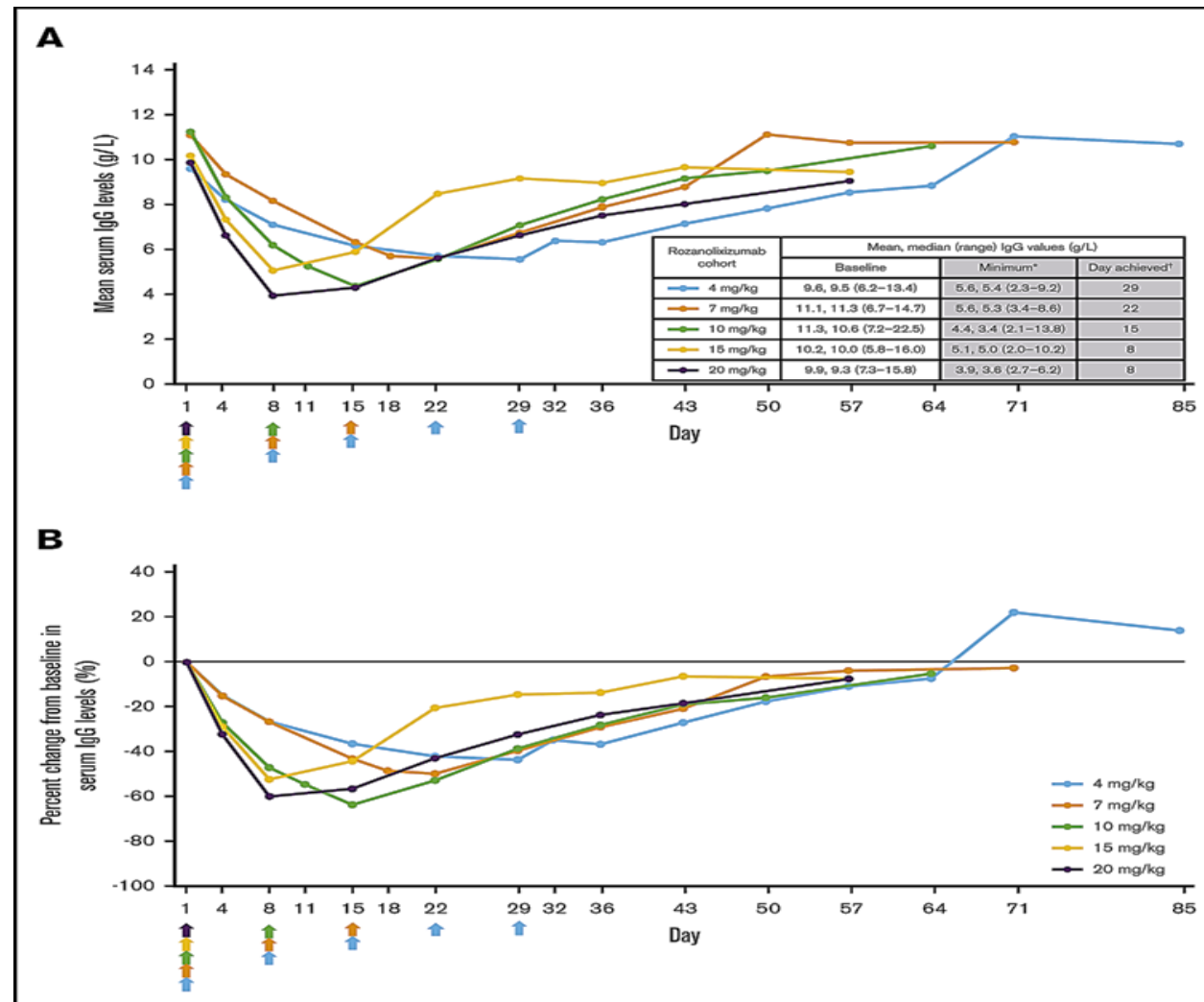
Phase 2 multiple-dose study of an FcRn inhibitor, rozanolixizumab, in patients with primary immune thrombocytopenia



Rapid platelet rise is dose responsive

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?



Oral Rilzabrutinib, a Bruton Tyrosine Kinase Inhibitor, Showed Clinically Active and Durable Platelet Responses and Was Well-Tolerated in Patients with Heavily Pretreated Immune Thrombocytopenia

Table. Platelet Response in ITP Patients Initiating Rilzabrutinib 400 mg BID

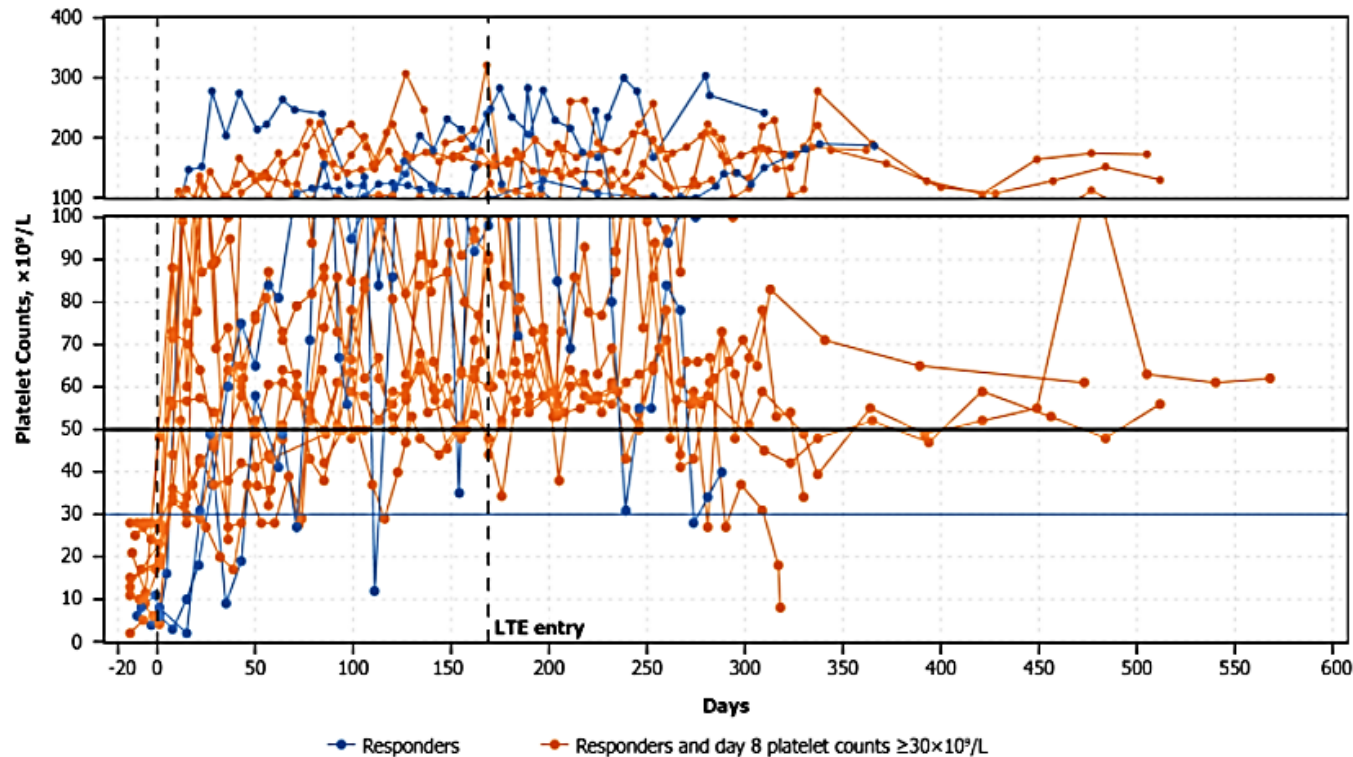


Figure. Individual platelet counts over time in LTE responding patients receiving rilzabrutinib (n = 14), including patients with day 8 platelet counts $\geq 30 \times 10^9/L$

Table. Primary Endpoint Platelet Counts for Patients Initiating Rilzabrutinib 400 mg BID Were Achieved Independent of Prior Therapy

Patients Initiating Rilzabrutinib 400 mg BID, n/n (%)	Platelet Counts	
	2 Consecutive $\geq 50 \times 10^9/L$ (primary endpoint)	
All patients	14/32 (44)	
Prior splenectomy	3/9 (33)	
Any prior therapy	Responded to Prior	No Prior Response
TPO-RA	3/11 (27)	5/13 (38)
Rituximab	2/5 (40)	2/11 (18)
Fostamatinib	2/4 (50)	1/2 (50)

Data cut-off: 05May2020. TPO-RA, thrombopoietin receptor agonist.

Kuter DJ et al. *Res Pract Thromb Haemost.* 2021; 5 (Suppl 1). <https://abstracts.isth.org/abstract/phase-i-ii-ongoing-study-of-rilzabrutinib-an-oral-bruton-tyrosine-kinase-inhibitor-in-immune-thrombocytopenia-extended-follow-up-and-long-term-analyses-with-optimal-dose/>. Accessed July 30, 2021.

ITP Secondary to COVID-19: A Comprehensive Review of Reported Cases

(as of 2/28/2021)

Demographics	
Cases	n (% of cohort)
Adult, new diagnosis	51 (81%)
Adult, relapse	7 (11.1%)
Pediatric, new diagnosis	5 (7.9%)
Pediatric, relapse	0 (0.0%)
Total	63 (100%)
Age at diagnosis (years) 53.5 ± 22	
Sex n (% of cohort)	
Male	29 (46%)
Female	30 (47.6%)
Not reported	4 (6.3%)
Comorbid conditions at time of diagnosis n (% of cohort)	
Autoimmune disease	8 (12.7%)
Cancer	5 (7.9%)
Thrombosis	4 (6.3%)
Pregnancy	2 (3.2%)

Presentation	
Bleeding symptoms	n (% of cohort)
Petechiae	20 (31.7%)
Purpura	15 (23.8%)
Epistaxis	14 (22.2%)
Gingival bleeding	12 (19%)
Ecchymoses	7 (11.1%)
Oral hemorrhagic bullae	7 (11.1%)
Hematuria	4 (6.3%)
Intracranial hemorrhage	3 (4.8%)
Venipuncture site bleeding	2 (3.2%)
Platelet count nadir (cells/ μ L)	12,600 ± 20,200
COVID-19 symptoms n (% of cohort)	
Experienced symptoms	56 (88.9%)
Symptomatic at time of diagnosis	16 (28.6%)
Post-symptomatic at time of diagnosis	8 (14.2%)
Unclear timing of symptoms and diagnosis	32 (57.1%)
Never symptomatic	5 (7.9%)
Not reported	2 (3.2%)
Time from symptom onset to diagnosis (days)	12.8 ± 8.1

Management		
Treatment	n	Rate of Complete Response
Steroids, IVIG, TPO-RA	4	100.0%
IVIG, TPO-RA	6	83.3%
Steroids	13	77.0%
Steroids, IVIG	20	56.0%
IVIG	13	53.8%
Regimen including TPO-RA	10	90.0%
Regimen including steroids	37	70.2%
Regimen including IVIG	44	63.6%
Complications of therapy n % of cohort		
Thrombocytosis	1	1.6%
Acute heart failure secondary to volume overload	1	1.6%
Hyperglycemia	1	1.6%
Constitutional symptoms	1	1.6%

Outcomes	
Outcomes	n (% of cohort)
Response	
Complete	41 (65%)
Partial	20 (32.7%)
Major bleeding	7 (11.1%)
Mortality	
Due to complications of ITP	1 (1.6%)
Due to complications of COVID-19	1 (1.6%)
Level of care n (% of cohort)	
Inpatient	39 (61.9%)
ICU	8 (12.7%)
Outpatient	2 (3.2%)
Not specified	17 (27%)

Table 1. Patient demographics and clinical presentations.

Incidence of and Risk Factors for Venous Thromboembolism (VTE) Among Hospitalized Patients with Cancer and COVID-19: Report from the COVID-19 and Cancer Consortium (CCC19) Registry

- VTE risk in patients with both cancer and COVID-19 infection remains unknown
- The COVID-19 and Cancer Consortium: an international retrospective cohort study to investigate the clinical course and complications of COVID-19 among adults with active or previous history of cancer
- The overall incidence of in hospital VTE and PE was 9.3% and 5.2%, respectively. Corresponding estimates were 13.4% and 7.9% among the ICU subgroup

- Non-ICU/not on anti-cancer therapy: 4.5% VTE incidence
- Either ICU or recent anti-cancer therapy: 11.0% VTE
- ICU/recent anti-cancer therapy: 16.7% VTE

Incidence of and Risk Factors for Venous Thromboembolism Among Hospitalized Patients with Cancer and COVID-19: Report from the COVID-19 and Cancer Consortium (CCC19) Registry

Table 1. VTE incidence and risk factors among hospitalized patients with cancer and COVID-19

	Overall (N)	Number of VTE (%)	OR (95% CI)	Number of PE (%)	OR (95% CI)
All hospitalized patients	1629	152 (9.3%)		85 (5.2%)	
ICU admission					
No	947	62 (6.5%)	Reference	33 (3.5%)	Reference
Yes	530	71 (13.4%)	2.21 (1.54-3.17)	42 (7.9%)	2.44 (1.53-3.92)
<i>Unknown or missing</i>	152	19		10	
Recent anti-cancer therapy within last 3 months					
No	836	55 (6.6%)	Reference	28 (3.3%)	Reference
Yes	641	83 (12.9%)	2.11 (1.48-3.03)	49 (7.6%)	2.35 (1.48-3.8)
<i>Unknown or missing</i>	152	14		8	
Cancer status					
Remission/no evidence of disease	718	43 (6.0%)	Reference	24 (3.3%)	Reference
Active, stable/responding	412	38 (9.2%)	1.59 (1.01-2.51)	22 (5.3%)	1.71 (0.95-3.07)
Active, progressing	244	36 (14.8%)	2.72 (1.69-4.34)	18 (7.4%)	2.44 (1.3-4.53)
<i>Unknown or missing</i>	255	35		21	
Cancer subtype VTE risk group					
low-risk VTE malignancy*	674	55 (8.2%)	Reference	35 (5.2%)	Reference
High-risk VTE malignancy*	380	48 (12.6%)	1.63 (1.08-2.45)	25 (6.6%)	1.3 (0.76-2.18)
Very high-risk VTE malignancy*	47	9 (19.1%)	2.67 (1.16-5.58)	5 (10.6%)	2.15 (0.71-5.34)
Other solid tumor malignancy	283	21 (7.4%)	0.9 (0.52-1.5)	9 (3.2%)	0.58 (0.26-1.18)
Other hematologic malignancy	245	19 (7.8%)	0.95 (0.54-1.6)	11 (4.5%)	0.83 (0.4-1.61)
Pre-admission anticoagulant use					
No	1202	110 (9.2%)	Reference	68 (5.7%)	Reference
Yes	306	24 (7.8%)	0.84 (0.52-1.32)	8 (2.6%)	0.43 (0.19-0.86)
<i>Unknown or missing</i>	121	18		9	
Pre-admission antiplatelet use					
No	977	100 (10.2%)	Reference	57 (5.8%)	Reference
Yes	530	35 (6.6%)	0.62 (0.41-0.92)	20 (3.8%)	0.61 (0.36-1.01)
<i>Unknown or missing</i>	122	17		8	

* Low-risk: breast, prostate, colorectal, head and neck

* High-risk: lung, ovarian, kidney, bladder, testicular, lymphoma

* Very high-risk: pancreas, stomach, esophageal

** Multivariable adjustment was not performed in the present analysis

Thromboembolic Outcomes of Hospitalized COVID-19 Patients in the 90-Day Post-Discharge Period: Early Data from the Northwell CORE-19 Registry

Prospective Study

Table 1: Population characteristics and post-discharge outcomes

Population characteristics (N = 4100)	
Age (Mean (SD))	61.0 (17.0)
Male (N (%))	2243 (54.7)
Post-discharge outcomes N (%)	
Rehospitalization	527 (12.85)
Venous thromboembolism	99 (2.41)
Deep vein thrombosis	46 (1.12)
Pulmonary embolism	40 (0.98)
Superficial vein thrombosis	8 (0.20)
Splanchnic vein thrombosis	1 (0.02)
Other vein thrombosis	4 (0.10)
Arterial thromboembolism	45 (1.10)
Stroke	14 (0.34)
Myocardial Infarction	15 (0.37)
Major adverse limb event	11 (0.27)
Systemic Embolism	5 (0.12)
Major Bleeding	66 (1.61)
All-Cause Mortality	176 (4.29)

- Stipulated the use of post-discharge low-molecular weight heparin, direct oral anticoagulants, or baby aspirin in hospitalized COVID-19 patients with high thrombotic risk features.
- All-cause mortality rate=4.29%
- Overall thromboembolic rate =3.51%
 - 2.41% VTE/1.10% ATE
- Major bleeding rate=1.61%
- Rehospitalization rate=12.85%
- Of patients with either DVT or PE post-discharge: 13.43% died
- Importance of post-discharge surveillance and extended thromboprophylaxis

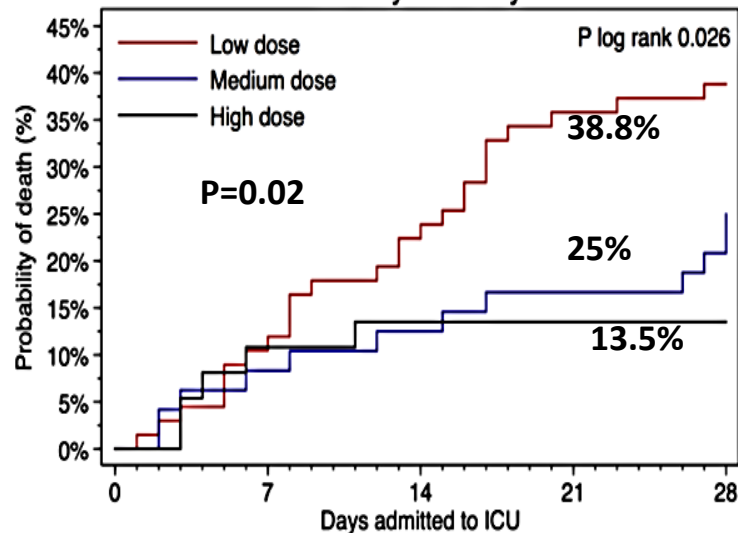
ASH Guidelines on Use of Anticoagulation in Patients with COVID-19- Updated on July 8, 2021

- ***suggest* not using anticoagulant outpatient thromboprophylaxis in patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects)**

Dosing of LMWH thromboprophylaxis and mortality in critically ill COVID-19 patients

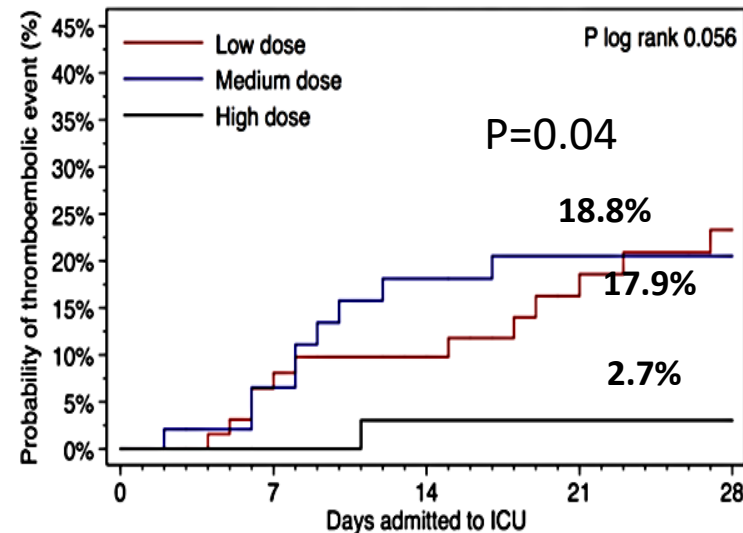
Jonmarker S et al. *Crit Care* **24**, 653 (2020). <https://doi.org/10.1186/s13054-020-03375-7>

28-day mortality



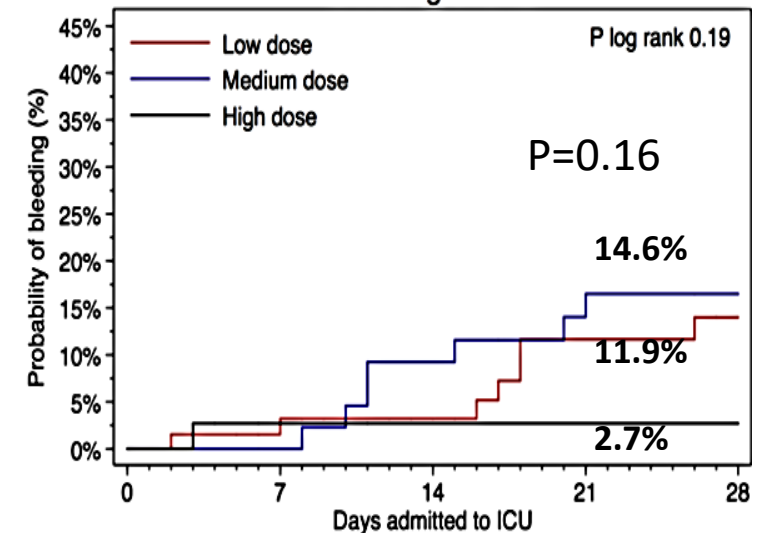
	No at risk	0	7	14	21	28
Low dose	67	60	52	43	41	
Medium dose	48	44	42	40	38	
High dose	37	33	32	32	32	

Thromboembolic events



	No at risk	0	7	14	21	28
Low dose	67	56	46	36	32	
Medium dose	48	41	35	32	30	
High dose	37	33	31	31	31	

Bleeding events



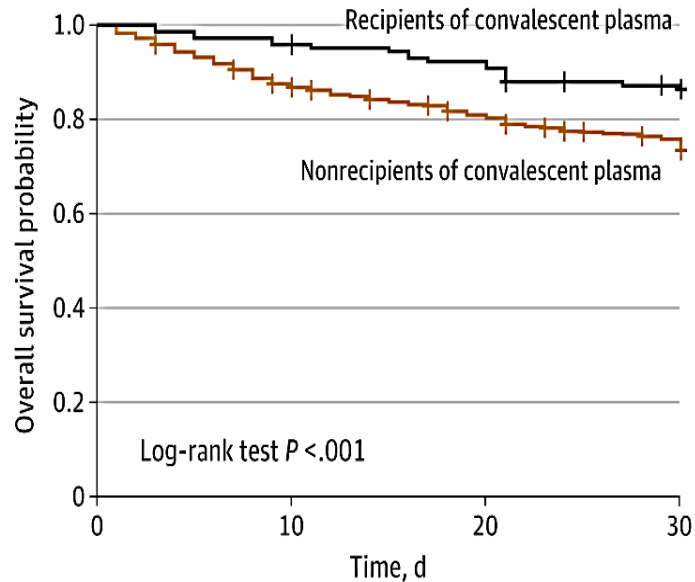
	No at risk	0	7	14	21	28
Low dose	66	59	51	38	36	
Medium dose	48	44	39	35	33	
High dose	37	32	31	31	31	

- 152 patients: 67 received low-, 48 medium-, and 37 high-dose LMWH thromboprophylaxis
- Mortality: high-dose = 13.5%; medium dose = 25.0%; low dose = 38.8%, $p = 0.02$.
- Hazard Ratio of death: High dose = 0.33 (95% confidence intervals 0.13–0.87) compared to low dose
Medium dose = 0.88 (95% confidence intervals 0.43–1.83) compared to low dose

Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19

Thompson MA et al. JAMA Oncol. Published online June 17, 2021. doi:10.1001/jamaoncol.2021.1799

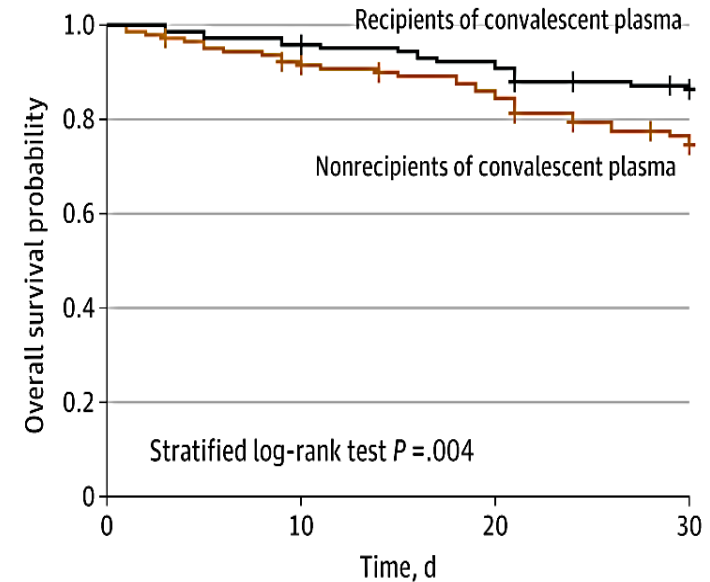
A Overall comparison



No. at risk

Nonrecipients of convalescent plasma	823	702	613	507
Recipients of convalescent plasma	143	137	129	108

B Propensity score-matched comparison



No. at risk

Nonrecipients of convalescent plasma	143	128	109	79
Recipients of convalescent plasma	143	137	129	108

Overall Survival Rates Among Recipients vs Nonrecipients of Convalescent Plasma

Biomarkers of Haemostasis and Occurrence of Venous Thromboembolism Are Associated with Disease Progression and Poor Prognosis in Patients with Pancreatic Cancer

Figure 1: Overall survival according to levels of D-dimer, PAI-1 and sP-selectin, dichotomized at the 75th percentile of distribution. PAI-1 indicates plasminogen activator inhibitor type 1; and sP-selectin soluble P-selectin.

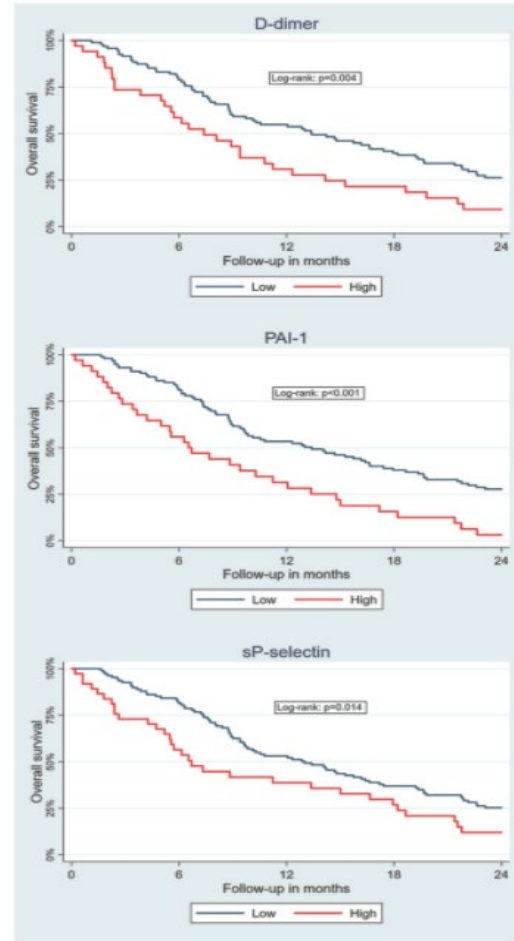
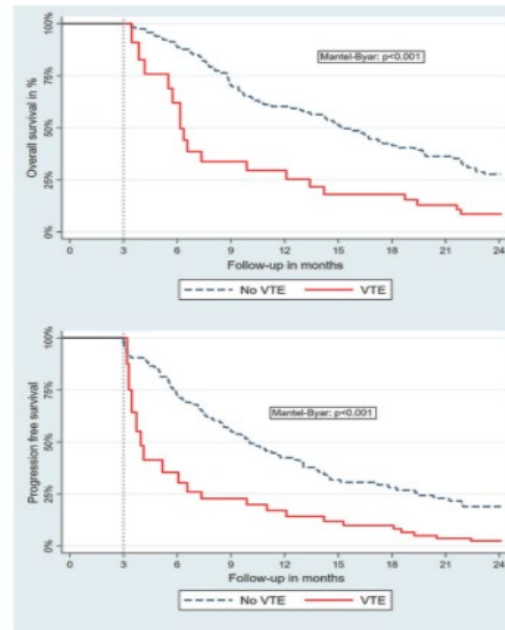
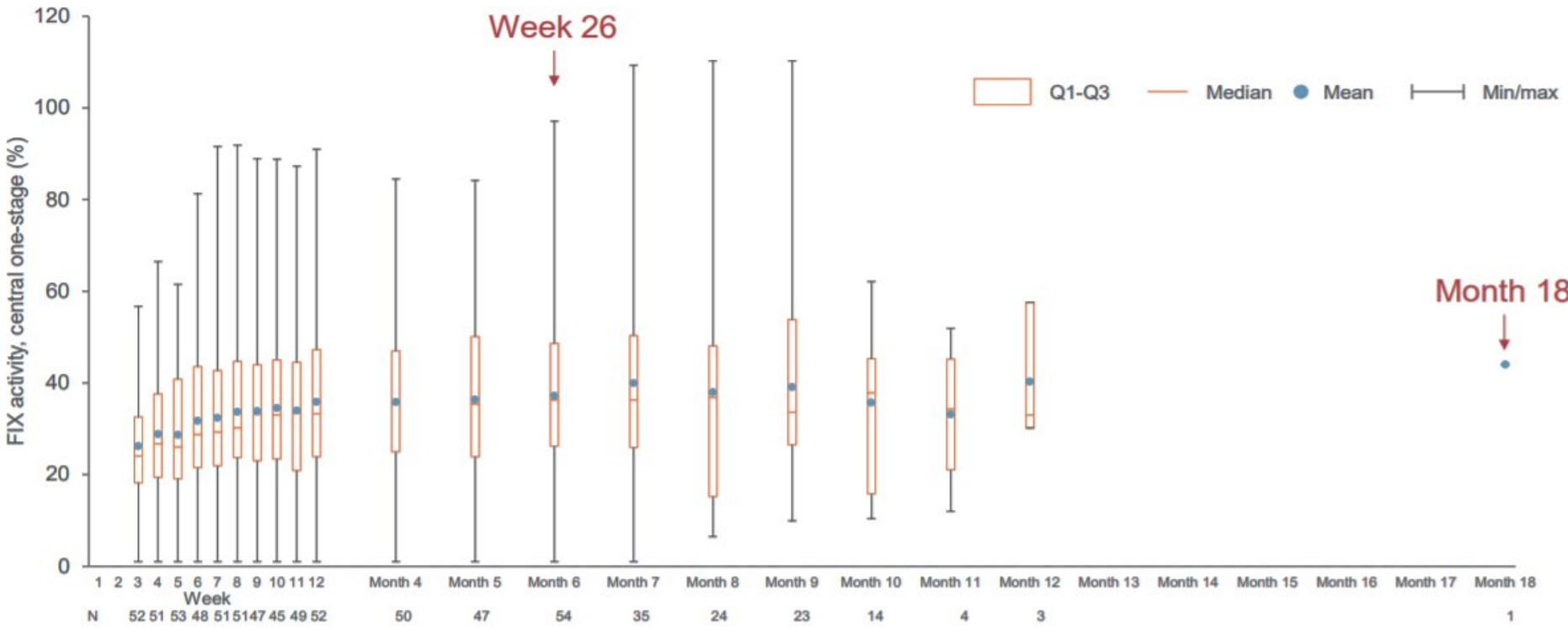


Figure 2: Landmark analysis of overall survival (OS) and progression free survival (PFS) according to the occurrence of VTE. OS indicates overall survival; PFS progression free survival, and VTE; venous thromboembolism.



First Data from the Phase 3 HOPE-B Gene Therapy Trial: Efficacy and Safety of Etranacogene Dezaparvovec (AAV5-Padua hFIX variant; AMT-061) in Adults with Severe or Moderate-Severe Hemophilia B Treated Irrespective of Pre-Existing Anti-Capsid Neutralizing Antibodies

Overview of FIX activity^a: Beyond 26 weeks



N=54 of whom 43 responded

Mean FIX at 26 wks near normal

No immuno-suppression needed

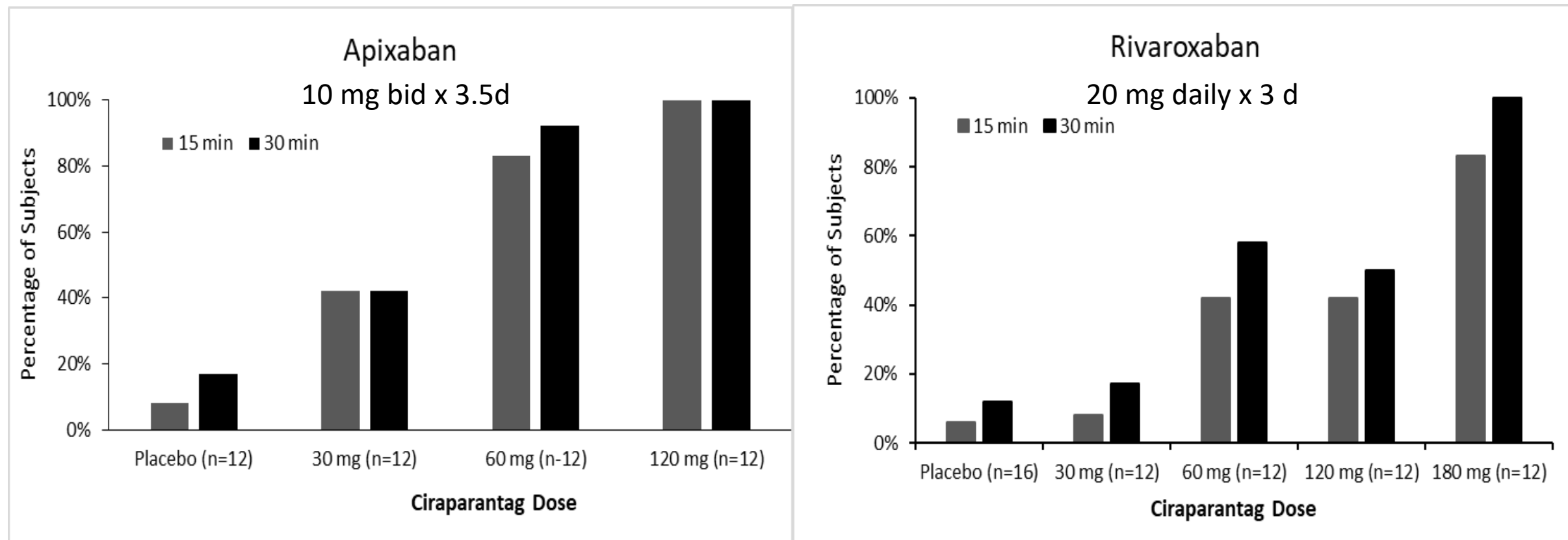
Neutralizing AAV5 Abs not excluded

Few bleeding events; no prophy FIX

^aUncontaminated central laboratory data (the visit did not occur within 10 days of exogenous FIX use). FIX levels beginning with the Week 3 assessment were used in the analysis. Subjects with 0 uncontaminated central-laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value. Baseline factor IX was imputed based on subject's historical hemophilia B severity documented on the case record form. If the patient had documented severe factor IX deficiency (FIX plasma level < 1%), their baseline factor IX activity level is imputed as 1%. If the subject had documented moderately severe factor IX deficiency (factor IX plasma level ≥1% and ≤ 2%), their baseline factor IX activity level was imputed as 2%. SD, standard deviation.

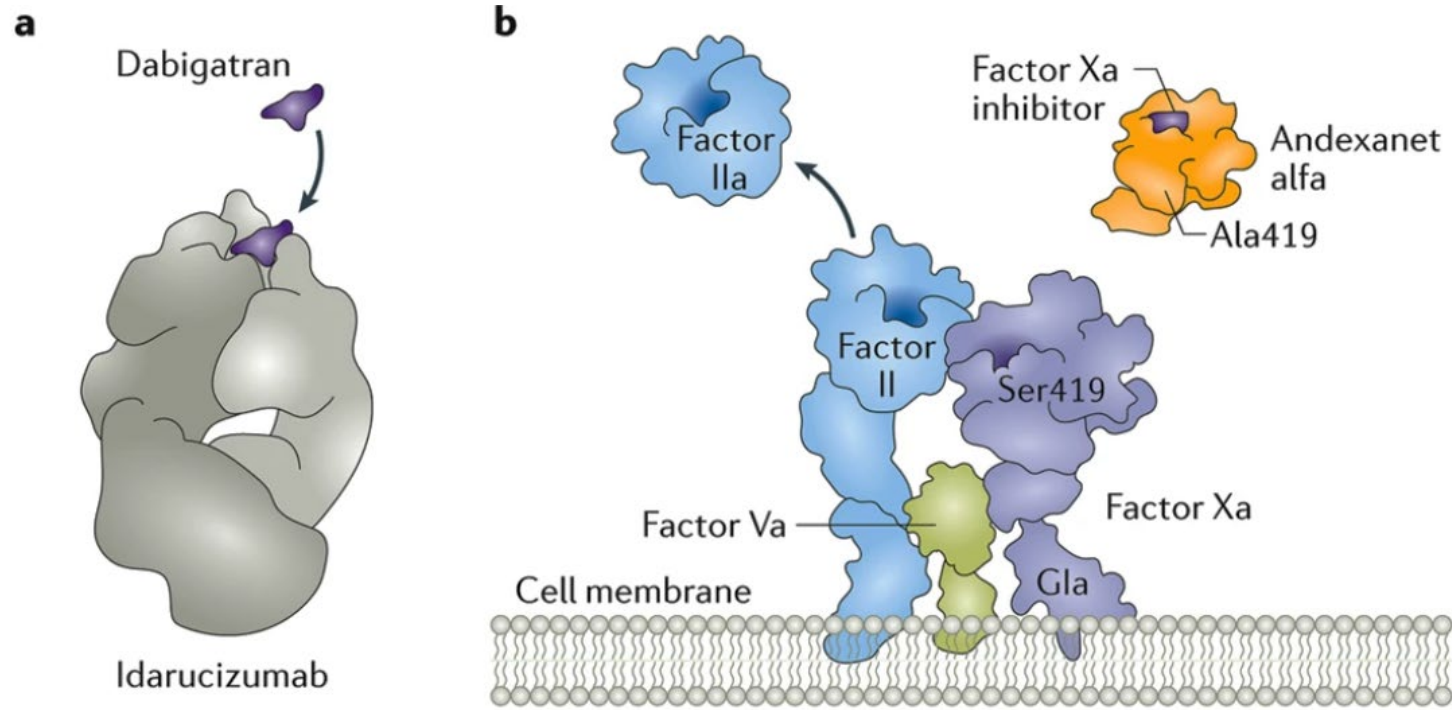
Reversal of Anticoagulation By Ciraparantag: Time to Onset and Duration of Effect

Proportion of subjects with WBCT reversed to within 10% above baseline at 15 minutes and 30 minutes after dosing



Phase II dose finding study in healthy subjects; Reversal persisted for over 24 hrs

Reversal Agents for Non-Vitamin K Antagonist Oral Anticoagulants



c

Drug	Binding sites
Apixaban	● ●
Dabigatran	● ● ● ●
Edoxaban	● ● ●
Fondaparinux	● ● ● ●
Rivaroxaban	● ● ● ●
UFH or LMWH	● ● ● ●

