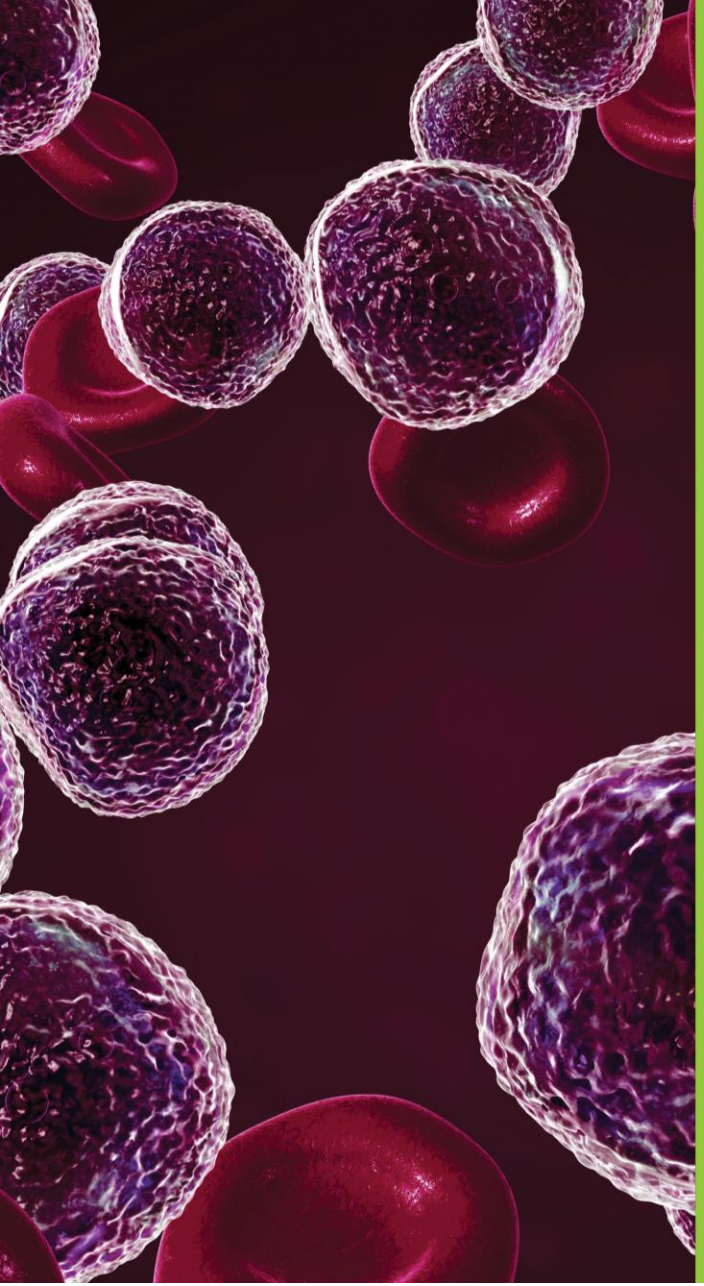

Updates in Non-Malignant Hematology

Katherine Walsh, MD, MAEd, FACP
Vanderbilt University Medical Center

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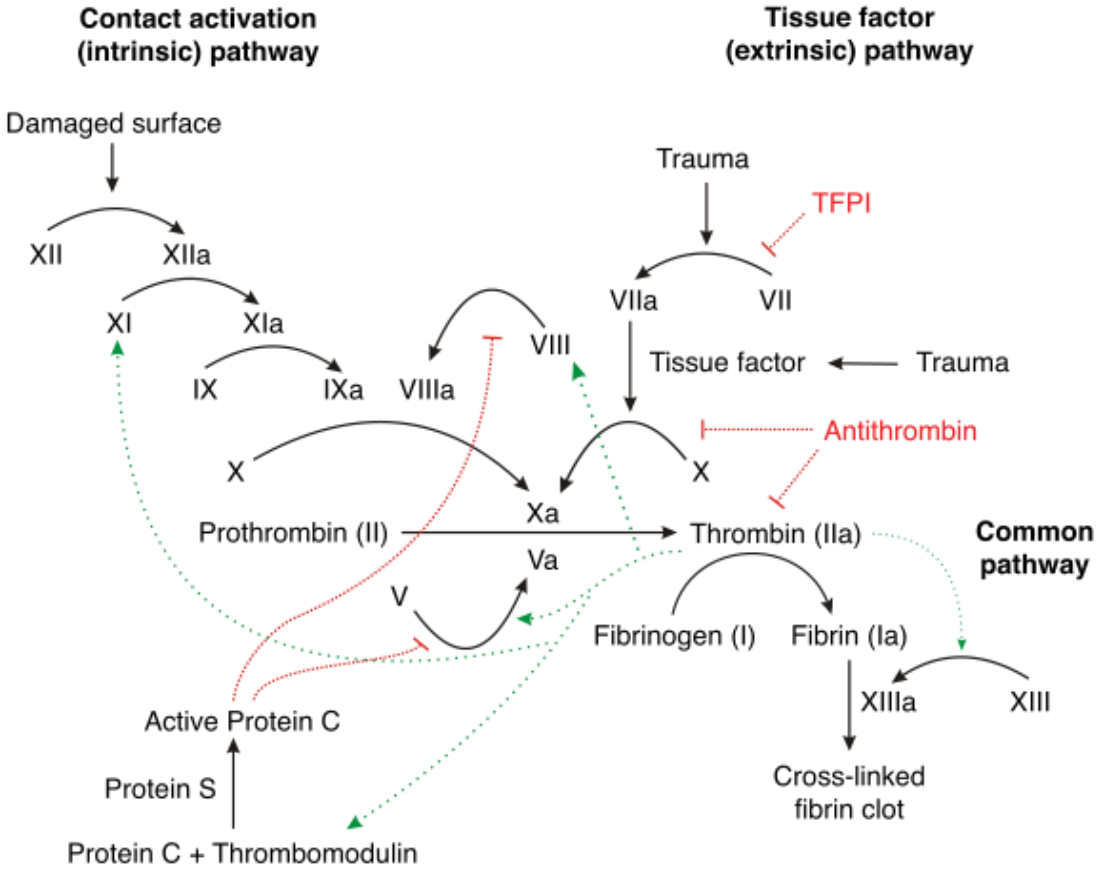
Updates in Non-Malignant Hematology Overview

- Hemophilia
- ITP
- Thrombosis

Hemophilia Updates

- Fitusiran:
  - subQ siRNA agent that targets antithrombin
  - Normalizes thrombin formation
  - Re-balances hemostasis
- ATLAS-INH
  - Hemophilia WITH inhibitors
- ATLAS-A/B
  - Hemophilia withOUT inhibitors



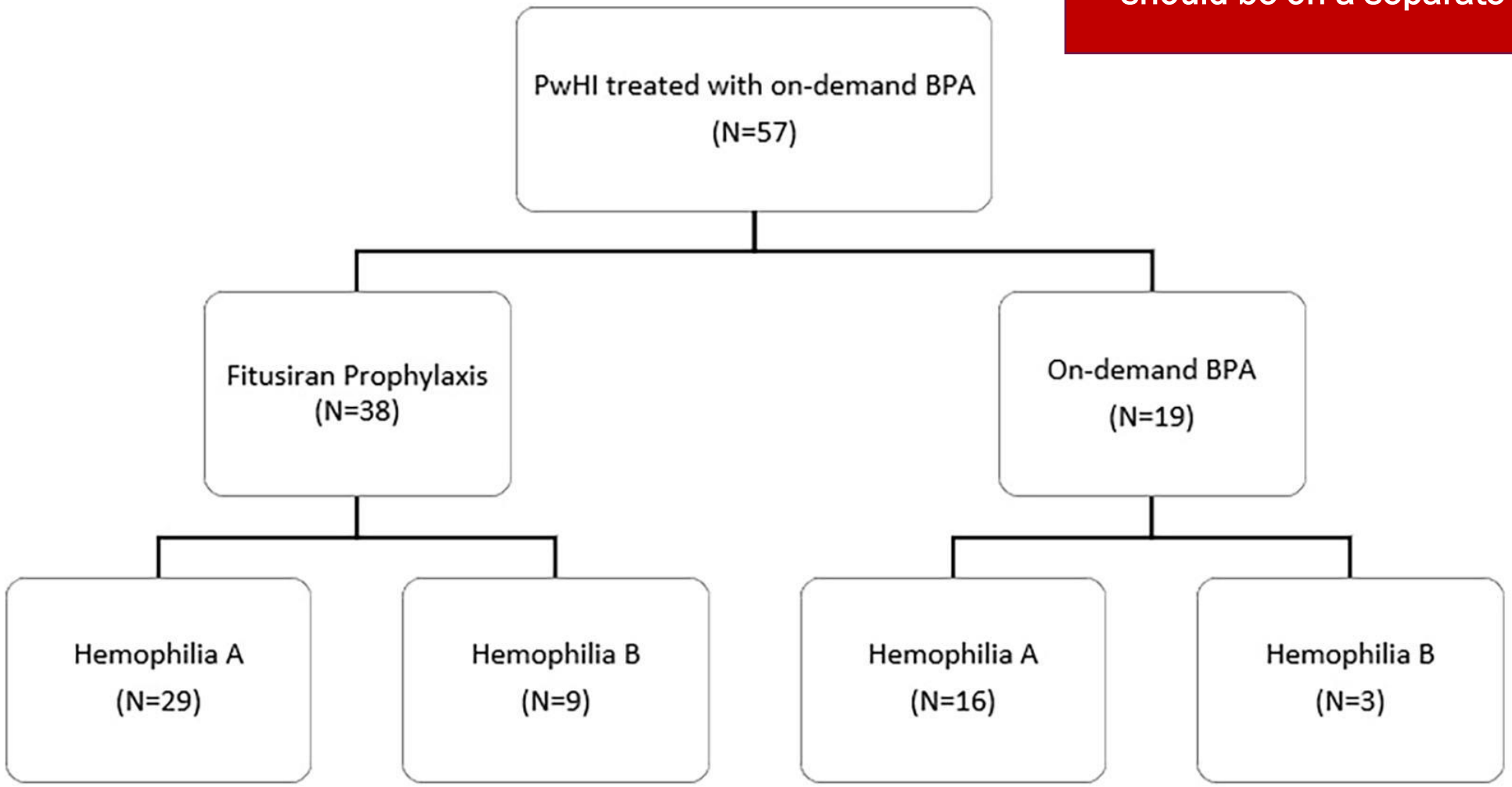
https://en.wikipedia.org/wiki/Antithrombin

Efficacy and Safety of Fitusiran Prophylaxis, an siRNA Therapeutic, in a Multicenter Phase 3 Study (ATLAS-INH) in People with Hemophilia A or B, with Inhibitors (PwHI)

Guy Young, MD, Alok Srivastava, MD, FRACP, FRCPA, FRCP, Kaan Kavakli, MD, PhD, Cecil Ross, MBBS, MD, Jameela Sathar, MD, Huyen Tran, MD, PhD, Runhui Wu, MD, PhD, Jing Sun, MD, Stacey Poloskey, MD, Zhiying Qui, PhD, Salim Kichou, MD, Shauna Andersson, MD, PhD, Baisong Mei, MD, PhD and Savita Rangarajan, MBBS, MD, FRCP, FRCPath

Please confirm if Table 1 below should be on a separate slide.

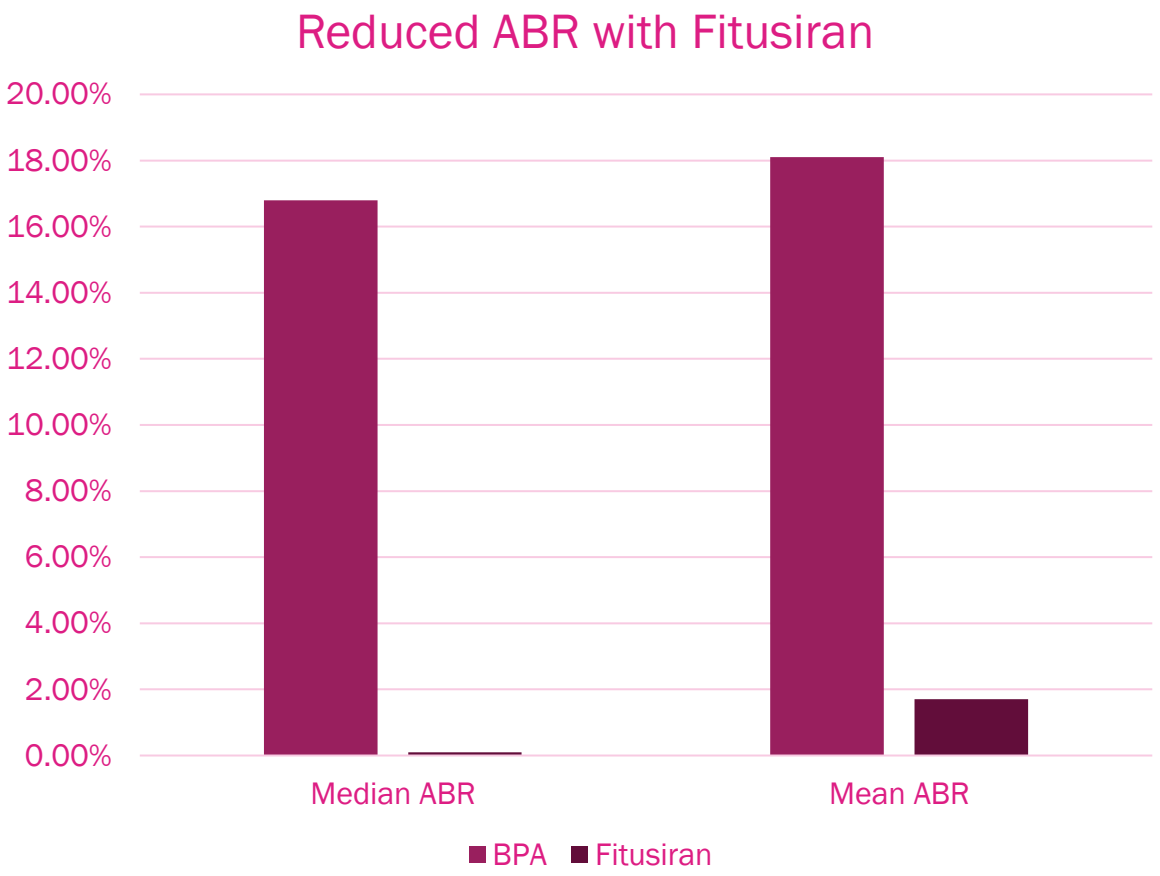
Figure 1: Study participant disposition



At the primary endpoint (9 months), eligible participants transitioned to the long-term study to receive ongoing fitusiran or to initiate fitusiran for those who were randomized to the on-demand arm.

ATLAS-INH: Results

- Endpoints:
  - Primary: Annualized Bleeding Rate (ABR)
  - Secondary Spontaneous ABR, Joint ABR, QOL
- Results:
  - Statistically significant outcomes in favor of fitusiran for all endpoints
  - % of pts with NO bleeds that required treatment:
    - 65.8% (fitusiran) vs 5.3% (OD)
  - Safety:
    - Mild-mod elevation in AST or ALT
    - 1 suspected spinal vessel thrombosis related to fitusiran (stopped study)



ATLAS-INH: Conclusions

- “Once-monthly 80 mg fitusiran prophylaxis resulted in significantly lower rate of bleeding events among people with hemophilia A or B with inhibitors, and it improved HR-QoL”
- “Reported TEAEs in the fitusiran prophylaxis arm were generally consistent with previously identified risks of fitusiran or what is anticipated in an adult and adolescent population with severe hemophilia A or B”
- Next Step: Ongoing study of reduced dose and dose frequency of fitusiran

Fitusiran, an Investigational siRNA Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: First Results from a Phase 3 Study to Evaluate Efficacy and Safety in People with Hemophilia a or B without Inhibitors (ATLAS-A/B)

Alok Srivastava, MD, FRACP, FRCPA, FRCP, Savita Rangarajan, MBBS, MD, FRCP, FRCPath, Kaan Kavakli, MD, PhD, Robert Klamroth, MD, Gili Kenet, MD, Liane Khoo, MD, MBBS, PhD, FRACP, FRCPA, Chur-Woo You, MD, PhD, Weiqun Xu, MD, PhD, Niel Malan, MD, Laurent Frenzel, MD, PhD Catherine N. Bagot, MD, FRCPath, MBBS, Oleksandra Stasyshyn, MD, PhD, Chia-Yau Chang, MD, Stacey Poloskey, MD, Shauna Andersson, MD, PhD, Zhiying Qiu, PhD, Baisong Mei, MD, PhD and Steven W. Pipe, MD

ATLAS-A/B

- Study Population: Men ≥ 12 years old without inhibitors
- Study Duration: 9 months
- Study Design:

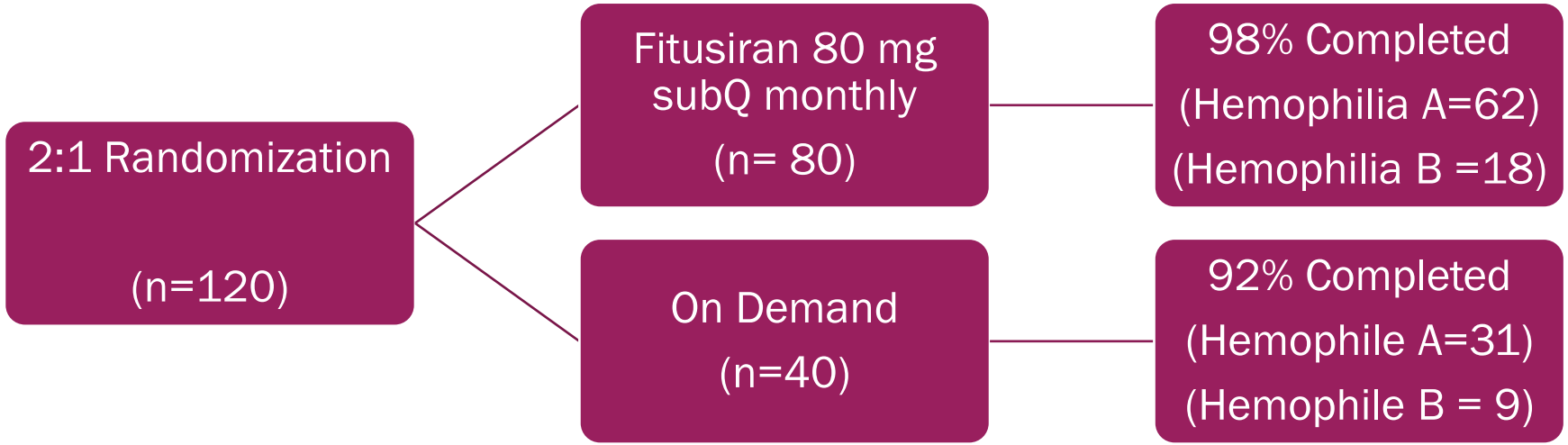


Table: Bleeding events in the ATLAS-A/B study (efficacy period)

	Fitusiran 80 mg Prophylaxis (N=79)	Factor Concentrates On-demand (N=40)	P-value*
Any treated bleeding event			
Estimated ABR (95% CI)	3.1 (2.3, 4.3)	31.0 (21.1, 45.5)	<0.0001
% ABR reduction (95% CI)	89.9 (84.1, 93.6)		
Observed ABR Median (IQR)	0.0 (0.0; 3.4)	21.8 (8.4; 41.0)	
Observed ABR Mean (SD)	3.1 (5.1)	29.6 (26.0)	
Participants with zero treated bleeds, n (%)	40 (50.6)	2 (5.0)	
Treated spontaneous bleeds			
Estimated ABR (95% CI)	1.8 (1.2, 2.7)	22.0 (14.2, 34.3)	<0.0001
% ABR reduction (95% CI)	91.7 (85.9, 95.1)		
Observed ABR Median (IQR)	0.0 (0.0; 1.7)	16.1 (3.4; 27.6)	
Observed ABR Mean (SD)	1.8 (3.6)	21.7 (23.0)	
Participants with zero treated bleeds, n (%)	50 (63.3)	5 (12.5)	
Treated joint bleeds			
Estimated ABR (95% CI)	2.3 (1.6, 3.3)	23.4 (15.4, 35.7)	<0.0001
% ABR reduction (95% CI)	90.3 (83.9, 94.1)		
Observed ABR Median (IQR)	0.0 (0.0; 3.4)	15.9 (4.2; 33.5)	
Observed ABR Mean (SD)	2.2 (4.0)	22.2 (21.2)	
Participants with zero treated bleeds, n (%)	46 (58.2)	5 (12.5)	

*P-value from a negative binomial regression model with treatment arm, randomization strata of number of bleeds in the 6 months prior to study (≤10, > 10) and randomization strata of hemophilia type (A vs. B) as fixed effects, and the logarithm of the duration that each patient spends in the efficacy period matching the bleeding episode being analyzed as an offset variable (p-value versus null hypothesis of ratio = 1). ABR, annualized bleeding rate; CI, confidence interval; IQR, interquartile range; SD, standard deviation.

ATLAS-A/B: Conclusions

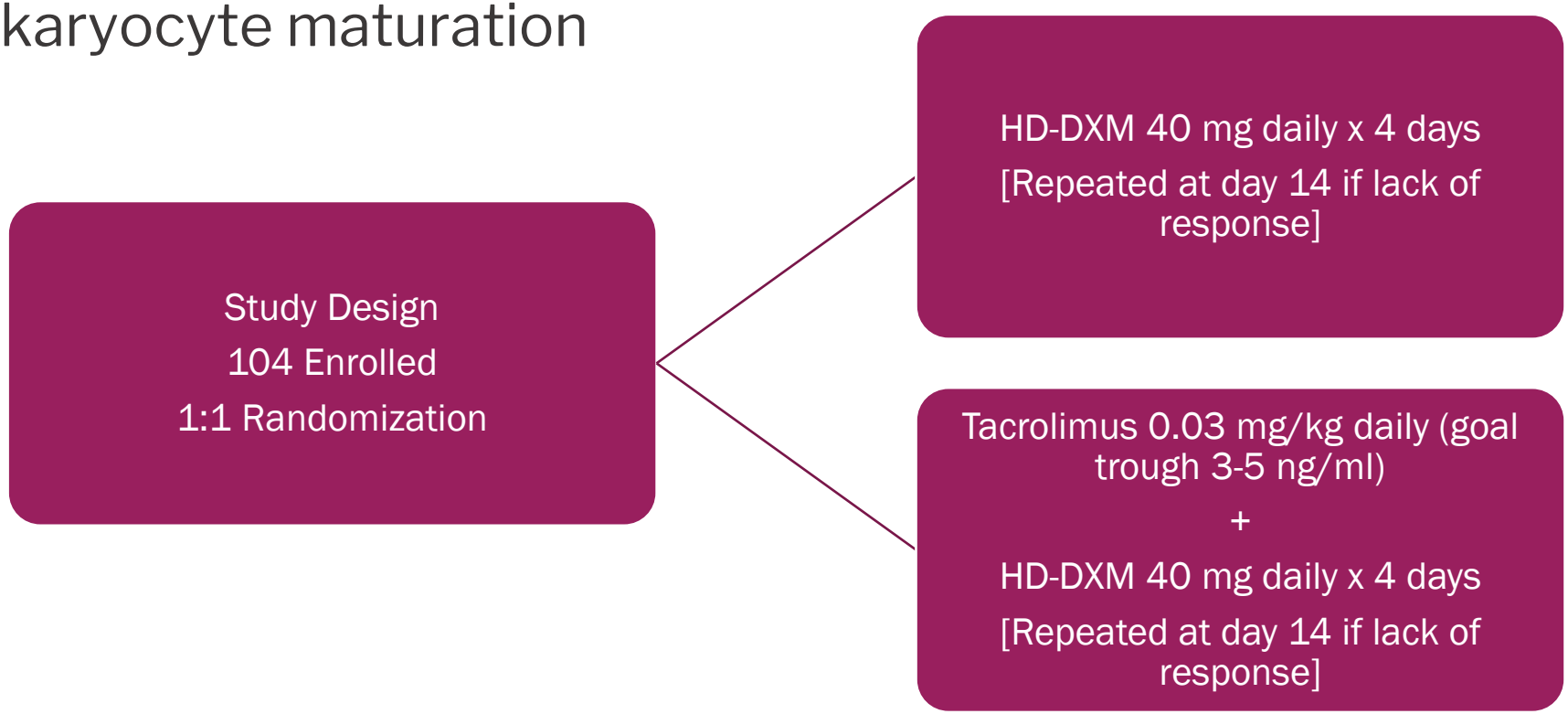
- Safety:
  - “Reported TEAEs in the fitusiran prophylaxis arm were generally consistent with previously identified risks of fitusiran or what is anticipated in an adult and adolescent population with severe hemophilia A or B”
    - Two patients stopped fitusiran due to cholecystitis and increased ALT, none due to thrombotic events
- Efficacy:
  - “Fitusiran prophylaxis resulted in a significant reduction in ABR in people with severe hemophilia A or B without inhibitors. This reduction in bleeding was associated with a meaningful improvement in quality of life”
    - Ongoing studies are investigating reduced dose and frequency of fitusiran

Tacrolimus Plus High-Dose Dexamethasone Versus High-Dose Dexamethasone Alone As First-Line Treatment for Adult Immune Thrombocytopenia: The Phase 2, Open Label, Randomized Trial (TARGET 020)

Zhuo-Yu An, Ye-Jun Wu, Yun He, Xiao-Lu Zhu, Hong-Xia Shi, Chen-Cong Wang, Hao Jiang, MD, Jin Lu, MD, Qian Jiang, MD, Qiu-Sha Huang, Hai-Xia Fu, Feng-Rong Wang, Xiao-Dong Mo, Yu Wang, Xiang-Yu Zhao, Yuan-Yuan Zhang, Wei Han, Huan Chen, Yao Chen, Chen-Hua Yan, Jing-Zhi Wang, Ting-Ting Han, Yu-Hong Chen, Yi-Fei Cheng, Ying-Jun Chang, Lan-Ping Xu, Kai-Yan Liu, Xiao-Jun Huang and Xiaohui Zhang

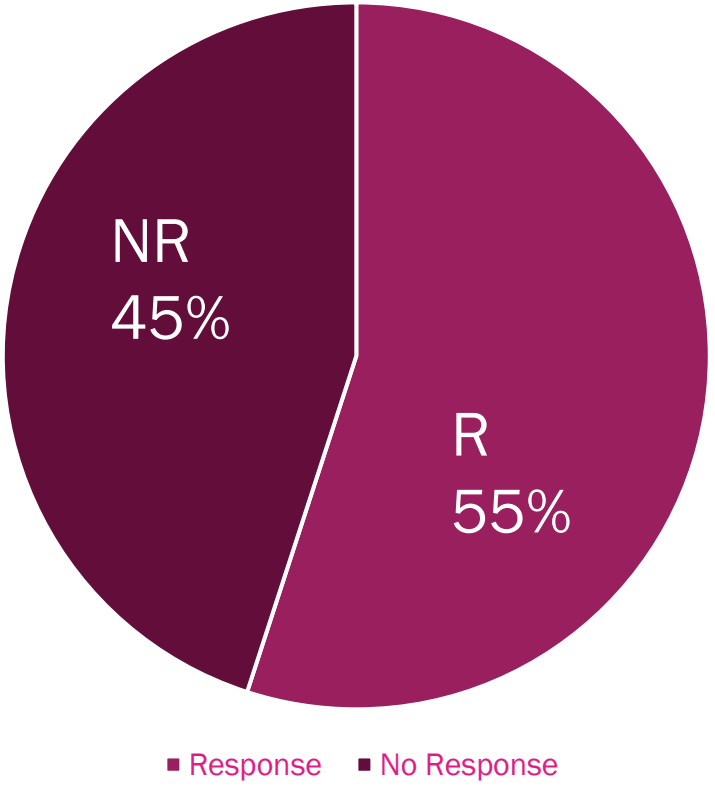
TARGET 020: "Dual-target" Strategy

- High dose dexamethasone (HD-DXM): Inhibits abnormal B cell activity to reduce the increase in platelet destruction
- Tacrolimus: Inhibits hyperactivated T cells to reduce impairment in megakaryocyte maturation

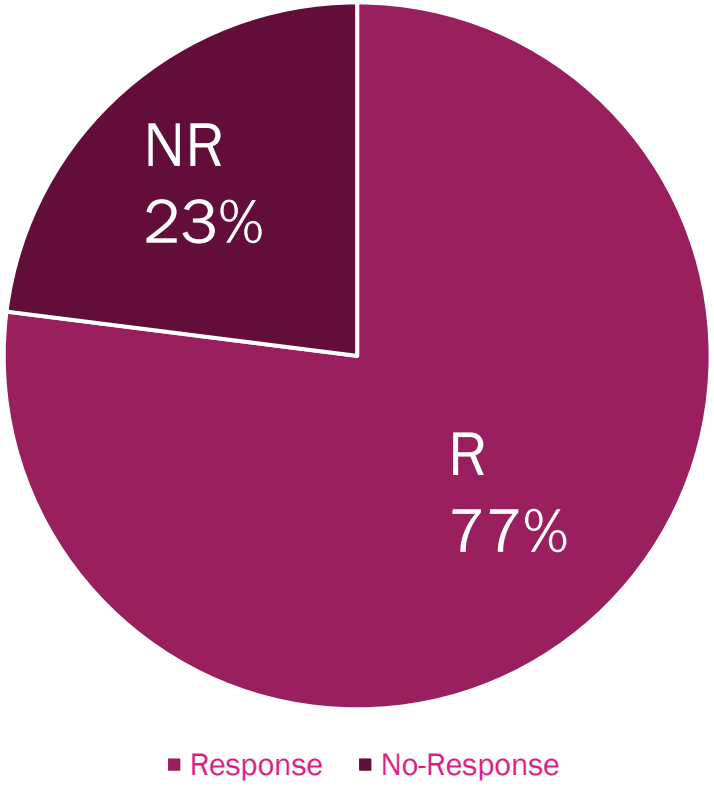


TARGET 020: Tacrolimus for ITP

HD-DXM Alone at 14 days



Tacro + HD-DXM at 14 days



Results:
At 6 months: SR for Tacro+HD-DXM was 64.5% versus 41% for HD-DXM alone
All AE were grade 1 or 2 and there were no treatment related deaths

TARGET 020: Tacrolimus for ITP

- CONCLUSIONS:
  - The combination of low-dose tacrolimus plus high-dose dexamethasone is an effective first line therapy for ITP, providing a sustained prolonged response
  - The combination is safe compared to the HD-DXM control arm
  - The combination could be a promising first line treatment to achieve long-term response.

Updated Phase I/II Safety and Efficacy Results for Oral Bruton Tyrosine Kinase Inhibitor Rilzabrutinib in Patients with Relapsed/Refractory Immune Thrombocytopenia

David J. Kuter, MD, DPhil, Nikolay Tzvetkov, MD, Merlin Efraim, MD, Zane Kaplan, PhD, Jiří Mayer, Prof, MD, Philip Y Choi, BSc, MBBS, PhD, A.J. Gerard Jansen, MD, PhD, Vickie McDonald, Ross Baker, Robert J. Bird, FRACP, FRCP, FRCPA, MBBS, MRCP, Mamta Garg, MD, FRCP, FRCPath, Jaromir Gumulec, MD, Milan Kostal, MD, Terry Gernsheimer, Waleed Ghanima, Olga Bandman, MD, Puneet Arora, Regan Burns, Mengjie Yao, Ahmed Daak, Timothee Sourdille, MD, Fareha Iqbal, Dolca Thomas, MD, Ann Neale and Nichola Cooper, MD

BTK Inhibition for ITP: Rilzabrutinib

- Background:
  - BTK inhibitors interfere with phagocytosis by macrophages and B cell antibody production
  - No prior clinical trial had investigated BTK inhibition in ITP

- Study Design:
  - Open label, dose finding study requiring platelet <30K on two occasions
  - Concurrent treatment with steroids and TPO agonist allowed
  - Primary endpoint: 2+ consecutive platelet counts of 50K or more AND increased by more than 20K without the need for rescue medication in the preceding 4 weeks
  - Patients who met the primary endpoint went on to an open label continuation study

- Population Enrolled:
  - Relapsed/refectory ITP with history of response to one prior line of therapy
  - Age 18-80 years old
  - Median time since ITP diagnosis was 6 years
  - Median of 4 prior therapies

BTK Inhibition for ITP: Rilzabrutinib

- Major effect seen at the 400 mg PO BID dose level (n=45)
  - 18 patients (40%) met the primary endpoint
  - 16 of the 18 reached clinically significant platelet count of 50K or more within the first 8 weeks
- Long term continuation study (LTE)
  - N=16 met primary endpoint
  - At start of LTE, median platelet was 87
  - Median treatment duration: 478 days
  - 90% maintained primary endpoint
  - 100% maintained platelet count >30

Primary Efficacy Responders (n=18)	Median # of weeks of study	Duration of response (median # of weeks)
30K or greater	20.5	95%
30K or greater with 20K or more increase above baseline	18	86%
50K or greater	14	72%

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BTK Inhibition for ITP: Rilzabrutinib

- Summary: “This is the first clinical trial to assess the role of BTK inhibition in chronic ITP treatment”
- Key Take Away: “In patients with heavily pretreated ITP, rilzabrutinib 400 mg BID was well-tolerated and had durable, clinically significant platelet responses that were consistent across subgroups and with extended treatment in LTE.”
- Next Step: randomized phase III LUNA 3 trial is ongoing to assess the degree and duration of response in ITP

Deep Vein Thrombosis after COVID-19 Vaccinations

Damon E. Houghton, MD, MS, Anand Padmanabhan, M.B.B.S., Ph.D., Aneel A. Ashrani, MD, MS, Ewa Wysokinska, MD, Rahul Chaudhary, Leslie Padrnos, MD, Rajiv K. Pruthi, M.B.B.S, Meera Sridharan, MD, PhD, Surbhi Shah, MBBS and Waldemar E. Wysokinski, MD, PhD

DVT and COVID vaccinations

- Background:
  - Thrombotic events shortly after the vaccine and in rare locations have been reported after COVID vaccinations
- Study Population:
  - Adults vaccinated across all Mayo Clinic sites from 11/1/20 to 6/1/21
    - J&J, n=16,271
    - Moderna, n=120,682
    - Pfizer, n=245,570
- Outcome:
  - Upper and lower extremity DVT and PE

Figure 1: Boxplot (median and interquartile range) of venous Duplex ultrasounds (and density) performed before and after COVID-19 vaccination by manufacturer

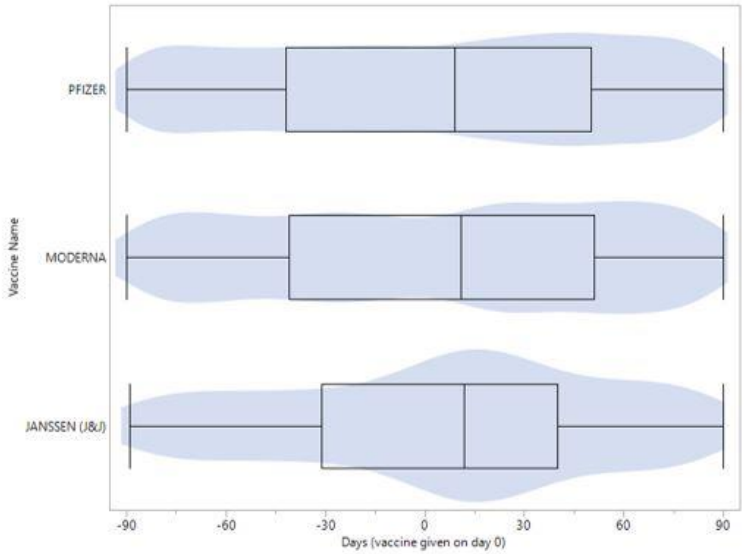


Figure 2: Probability of deep vein thrombosis per day by ultrasound in the 90 days before and after COVID-19 vaccination

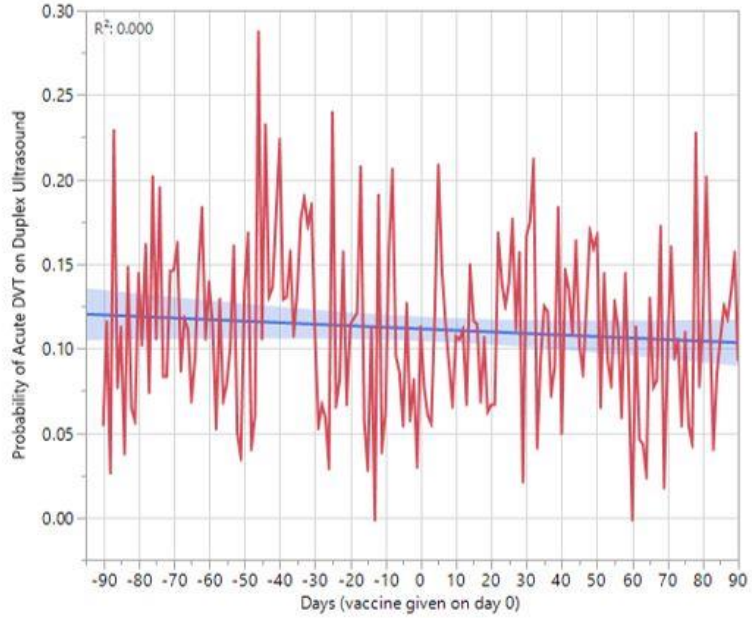


Figure 3: Time to event analysis of deep vein thrombosis after COVID-19 vaccination by vaccine manufacturer

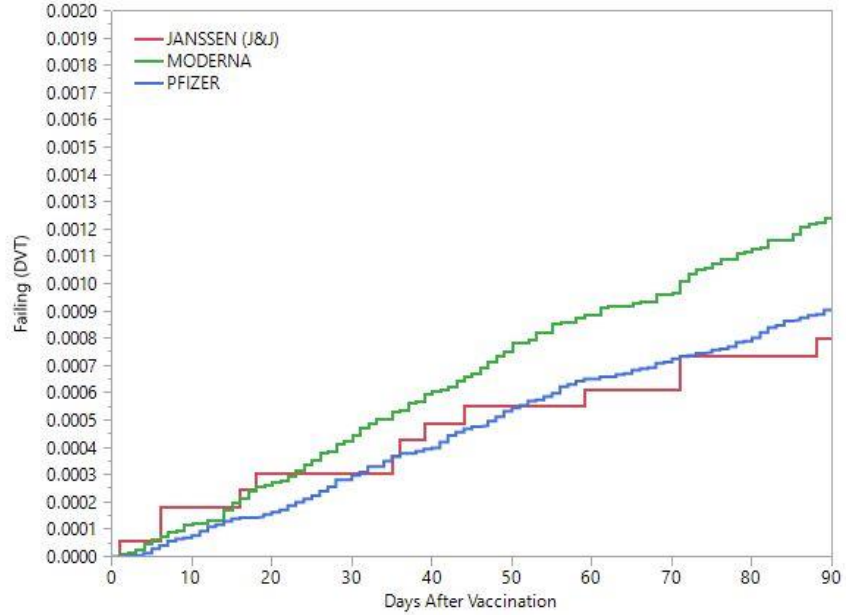
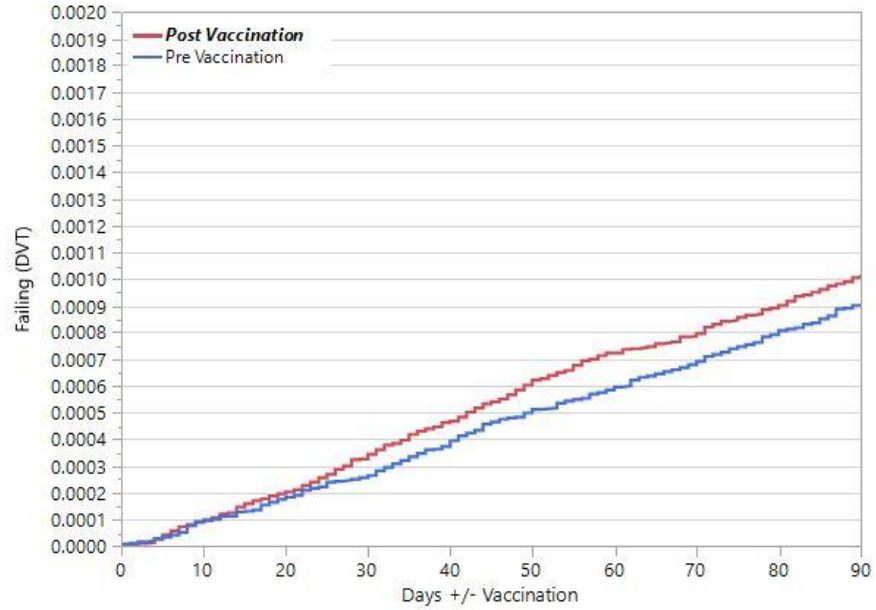


Figure 4: Time to event analysis of DVT before and after COVID-19 vaccination

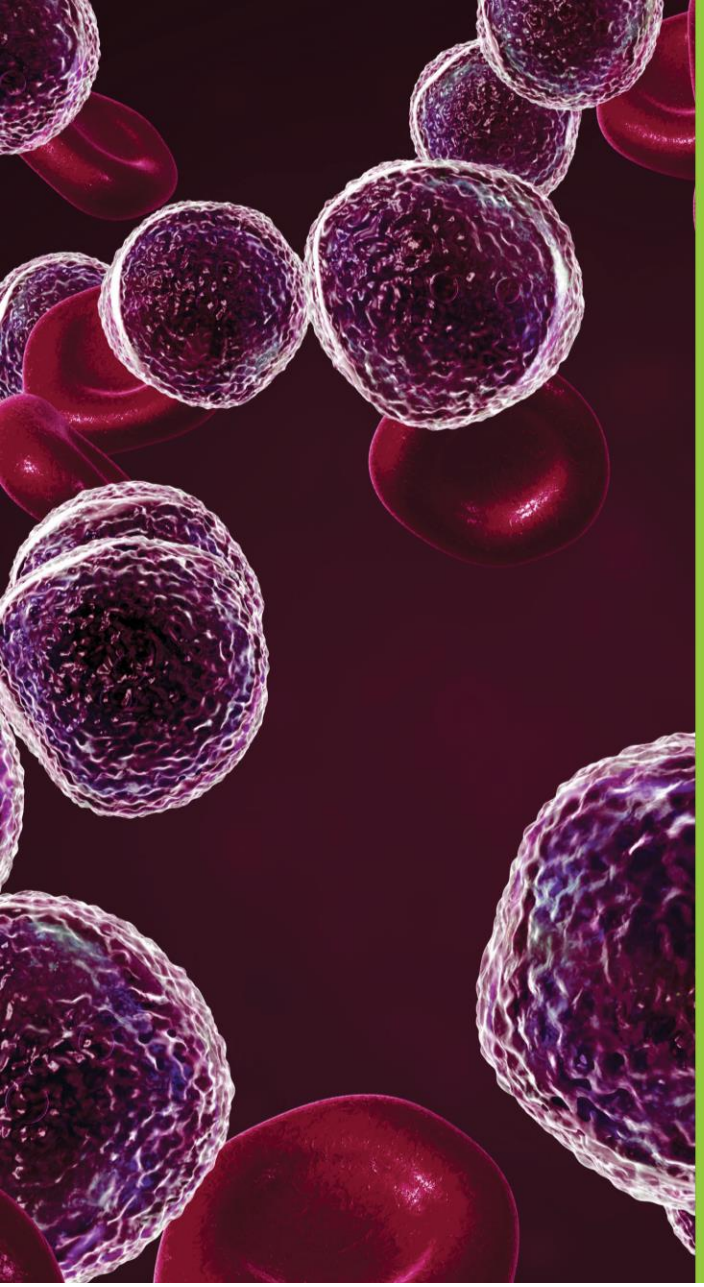


DVT after COVID vaccinations

- Conclusions
  - “Rate of thrombosis after COVID-19 vaccination are low and similar to what might be expected for population rates”
  - “Compared to baseline pre-vaccination rates, no significant increase in post vaccination risk for DVT and PE rates”
  - “We found no difference in post-vaccination DVT and PE between vaccines after adjustment”
  - “COVID-19 infection prior to vaccination was not a risk factor for post-vaccination thrombosis”

Updates in Non-Malignant Hematology Summary

- Hemophilia
  - Fitusiran prophylaxis reduced bleeding rates in patients with Hemophilia A and Hemophilia B with and without inhibitors
- ITP
  - Novel approaches of tacrolimus in combination with high-dose dexamethasone (TARGET study)) and BTK inhibition with single agent Rizalbrutinib showed improved responses in ITP
- Thrombosis
  - COVID vaccinations were not associated with increased risk for PE or DVT for the J&J, Moderna, and Pfizer vaccines



Breaker Slide

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