Sickle Cell Disease and Clotting Disorders of the Blood

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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

What is gene therapy?

- Introduction of genes into existing cells to **prevent or cure** a wide variety of diseases

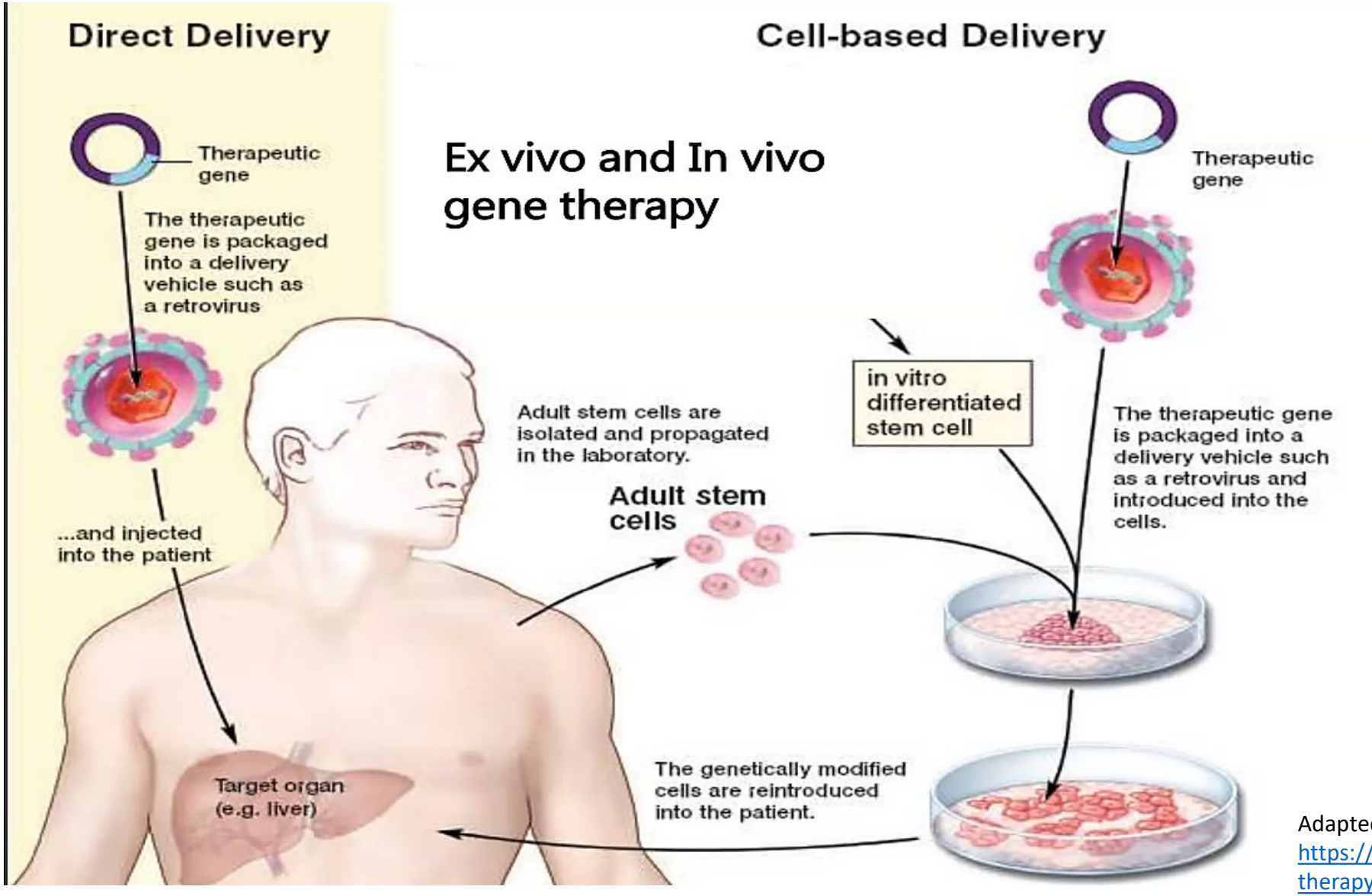
- Technique for **correcting missing or defective genes** responsible for disease development, e.g. gene replacement or gene augmentation

- Technique to **inactivate or "knock out"** a mutated gene that is functioning improperly, e.g. targeted inhibition of gene expression

- The therapeutic gene can be introduced into a **somatic cell or a germ cell**

    - Somatic cell therapy (hepatocyte, bone marrow stem cell, blood cells, muscle, etc.) will not be inherited by later generations
    - Germ cell therapy involves ova or sperm and is heritable
    - For safety, ethical, and technical reasons, germ cell gene therapy is not currently being used

Techniques for gene transfer in gene therapy



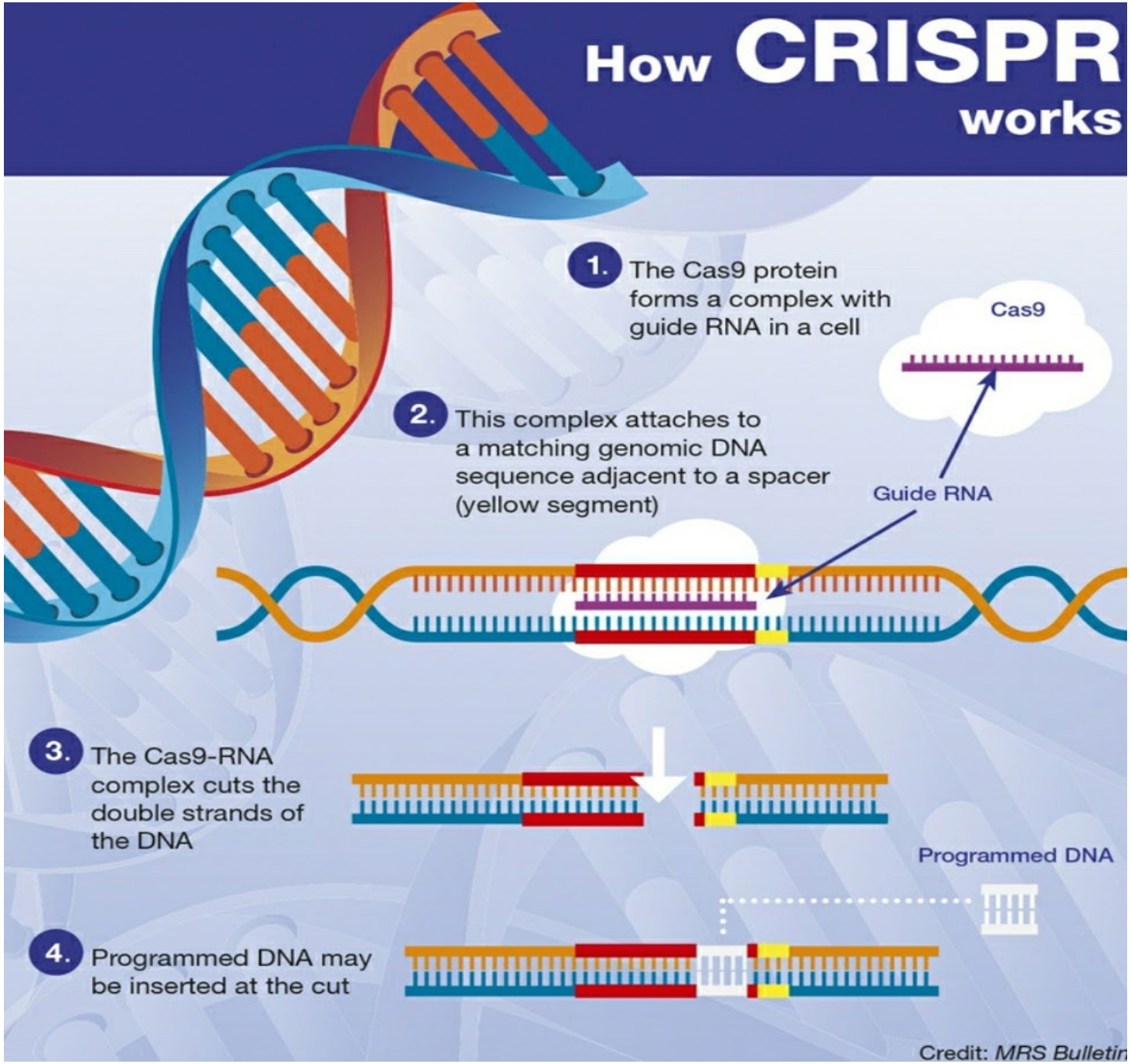
Viral Vectors

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



Gene Editing

- Clustered, regularly interspaced, short palindromic repeats or **CRISPR-Cas9**
- **Highly engineered Zinc finger nucleases**

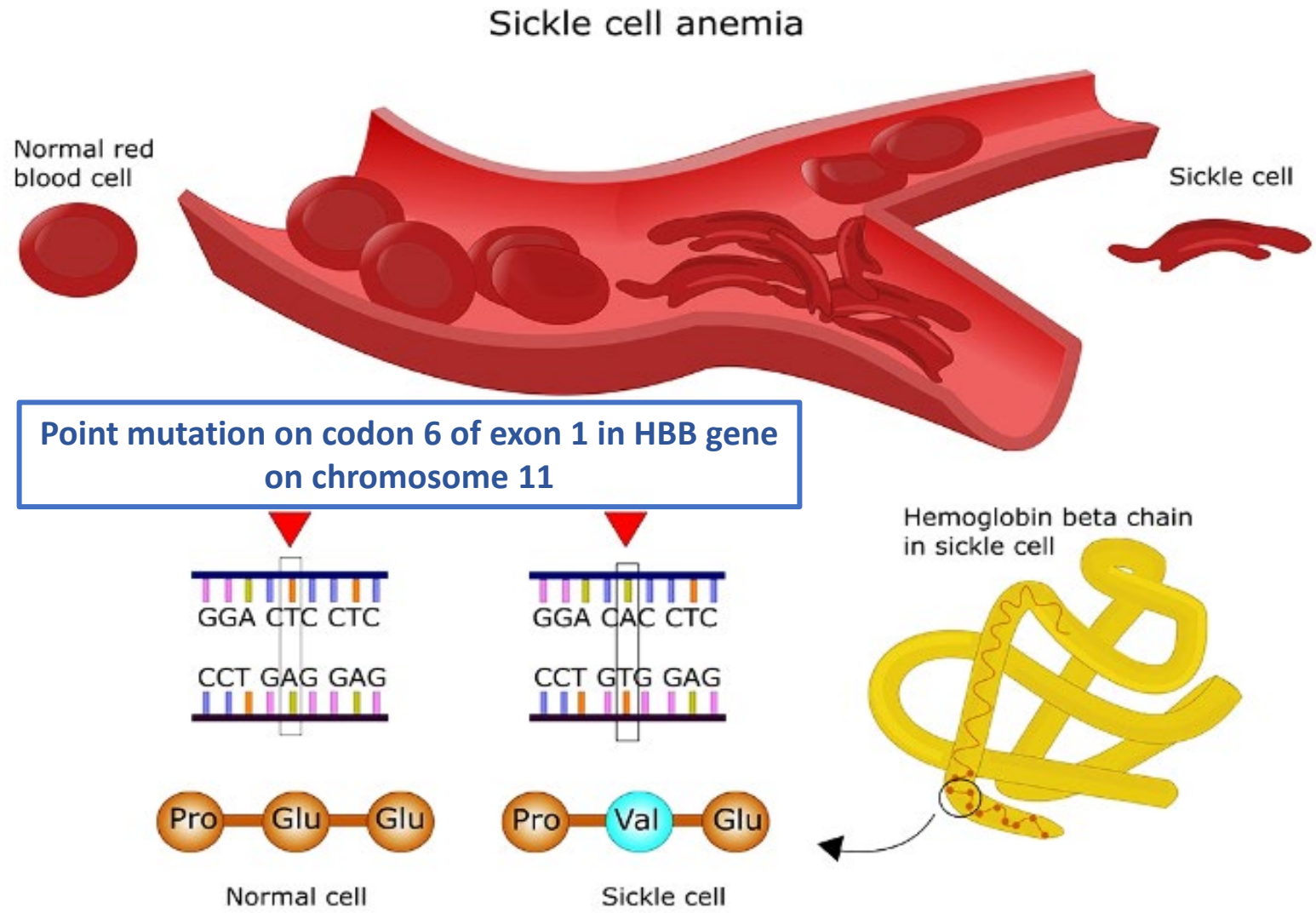
Cut and Paste technology used for the purpose of altering genetic expression or changing the genome

The specific location of the genetic codes that need to be changed, or "edited", is identified on the DNA strand, and then, using the Cas9 or ZNF protein, which acts like a pair of scissors, that location is cut off from the strand. **A DNA strand, when broken, has a natural tendency to repair itself.**

Supply the desired sequence of genetic codes that **binds itself with the broken DNA strand**

Urnov, F., *Nat Rev Genet* **11**, 636–646 (2010). https://doi.org/10.1038/nrg2842

Sickle Cell Anemia: Pathophysiology, Genetics, and Epidemiology



Adapted from: https://aleteia.org/2017/03/06/gene-therapy-cures-teen-with-sickle-cell-disease; downloaded 2/6/2023

- SCD affects approximately 100,000 Americans
- SCD occurs among about 1 out of every 365 Black or African-American births
- SCD occurs among about 1 out of every 16,300 Hispanic-American births
- About 1 in 13 Black or African-American babies is born with sickle cell trait (SCT)
- 300,000 births per year worldwide with SCD

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention; May 2, 2022; https://www.cdc.gov/ncbddd/sicklecell/data.html

ABS 11: Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease: Updated Clinical Results and Investigations into Two Cases of Anemia from Group C of the Phase 1/2 HGB-206 Study

Walters MC et al.

Drive Rank Score=5

- LentiGlobin vector for **ex vivo SCD gene therapy**
- Autologous transplantation of hematopoietic stem and progenitor cells (HSPCs) transduced with the BB305 lentiviral vector encoding a modified β-globin gene → anti-sickling HbA^{T87Q}
- The ongoing phase 1/2 HGB-206 study is the largest clinical trial of GT in SCD to date

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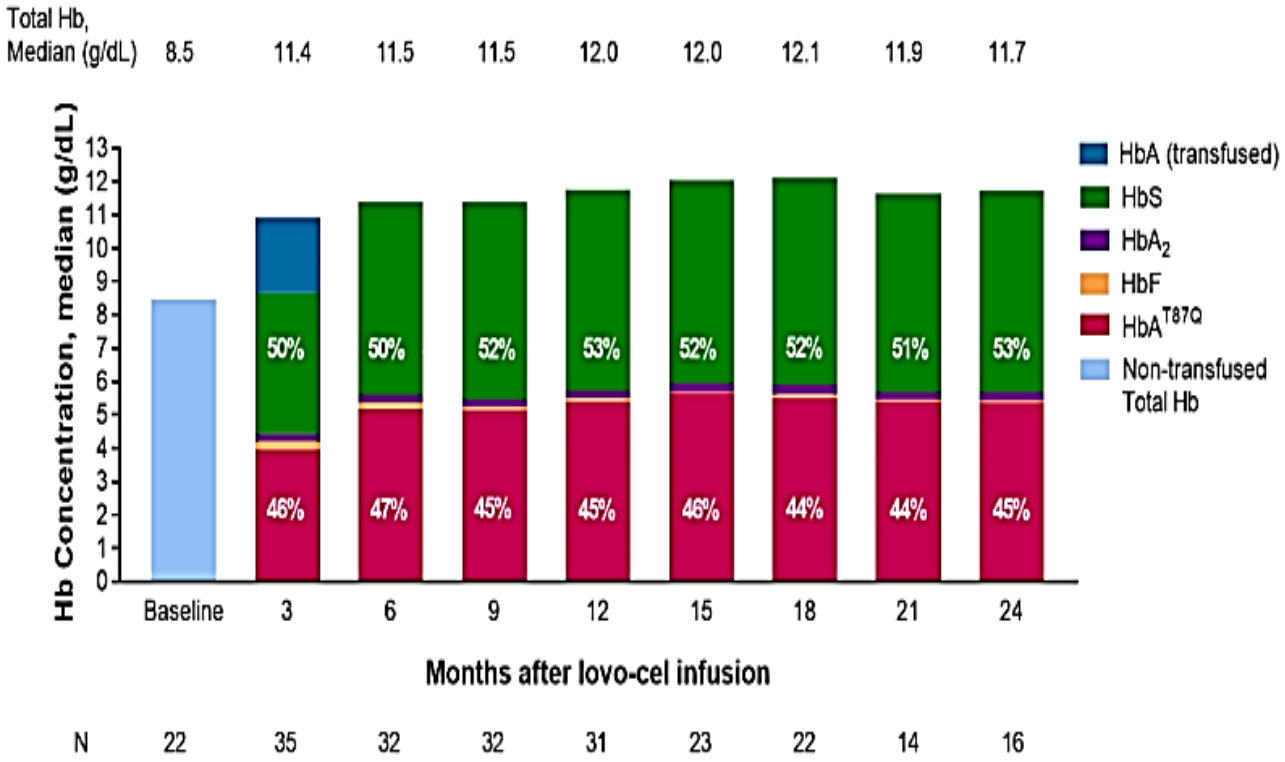
- 35 Pts (≥12–≤50 yrs of age) with SCD and recurrent severe vaso-occlusive episodes underwent plerixafor mobilization and apheresis followed by myeloablative busulfan conditioning and lovo-cel infusion
- Median follow-up = 20.9 months; (min–max: 8.5–28.5).
- Median HbA^{T87Q} levels of ≥5 g/dL during this period
- 28/29 pts had a complete resolution of severe VOEs; no severe VOEs reported during long-term follow up
- Key hemolysis markers approached normal levels
- 15 pts (43%) had ≥1 serious adverse event; most frequent were abdominal pain, drug withdrawal syndrome (opiate), nausea, vomiting, and dehydration (6% each). **No cases of veno-occlusive liver disease, graft failure, replication-competent lentivirus, vector-mediated insertional oncogenesis, or hematologic malignancies were observed**
- 2 pts with refractory anemia despite marrow evidence of adequate HbA^{T87Q} production; MDS changes in marrows; low level trisomy 8; NGS negative

ABS 11: Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease: Updated Clinical Results and Investigations into Two Cases of Anemia from Group C of the Phase 1/2 HGB-206 Study

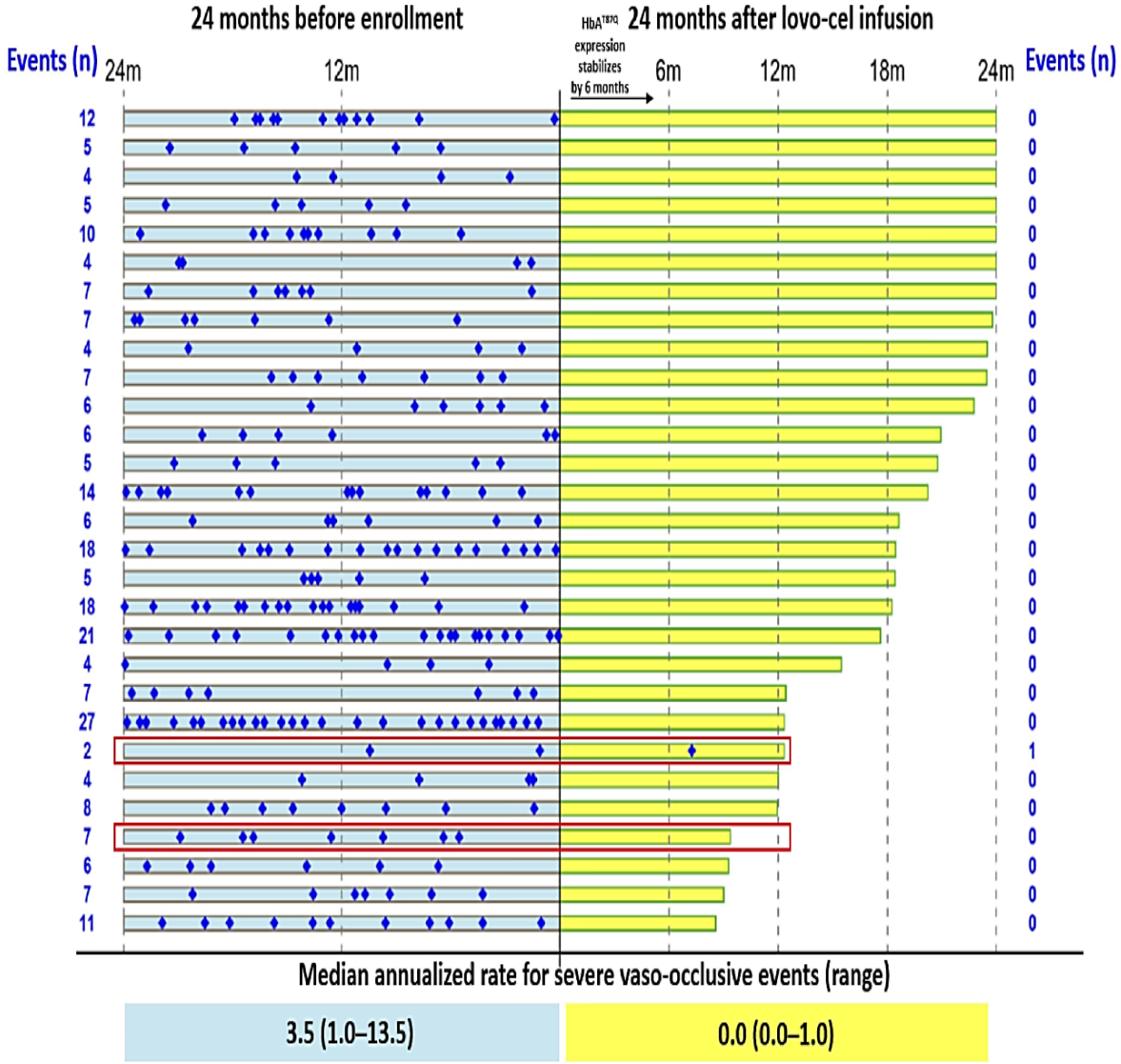
Walters MC et al.

Figure 1A. Total Hb and Fractions in Group C of the HGB-206 Study



Data is reported as of July 2021 data cut. Percentages represent the median Hb fraction as a percentage of non-transfused total Hb; the baseline was an average of two qualified non-transfused total Hb values (measured in g/dL) during the 24 months before study enrollment.

Figure 1B. Severe Vaso-Occlusive Events in Group C of the HGB-206 study



ABS 786: Treatment of Individuals with Severe Sickle Cell Disease with OTQ923, an Autologous, *Ex Vivo*, CRISPR/Cas9-Edited, CD34+ Hematopoietic Stem and Progenitor Cell Product, Leads to Durable Engraftment and Fetal Hemoglobin Induction

Sharma A et al.

Drive Rank Score=5

- BCL11A is a transcription factor that binds to *HBG1/HBG2* promoters and produces a γ-to-β globin switch
- Inhibiting BCL11A reverses the switch and induces HbF expression in adult RBCs.
- OTQ923 is an autologous, *ex vivo*, CRISPR/Cas9-edited, CD34+ cellular product with targeted disruption of the *HBG1/HBG2* promoters on chromosome 11.
- Results in HbF induction and phenotypically consistent with HPFH

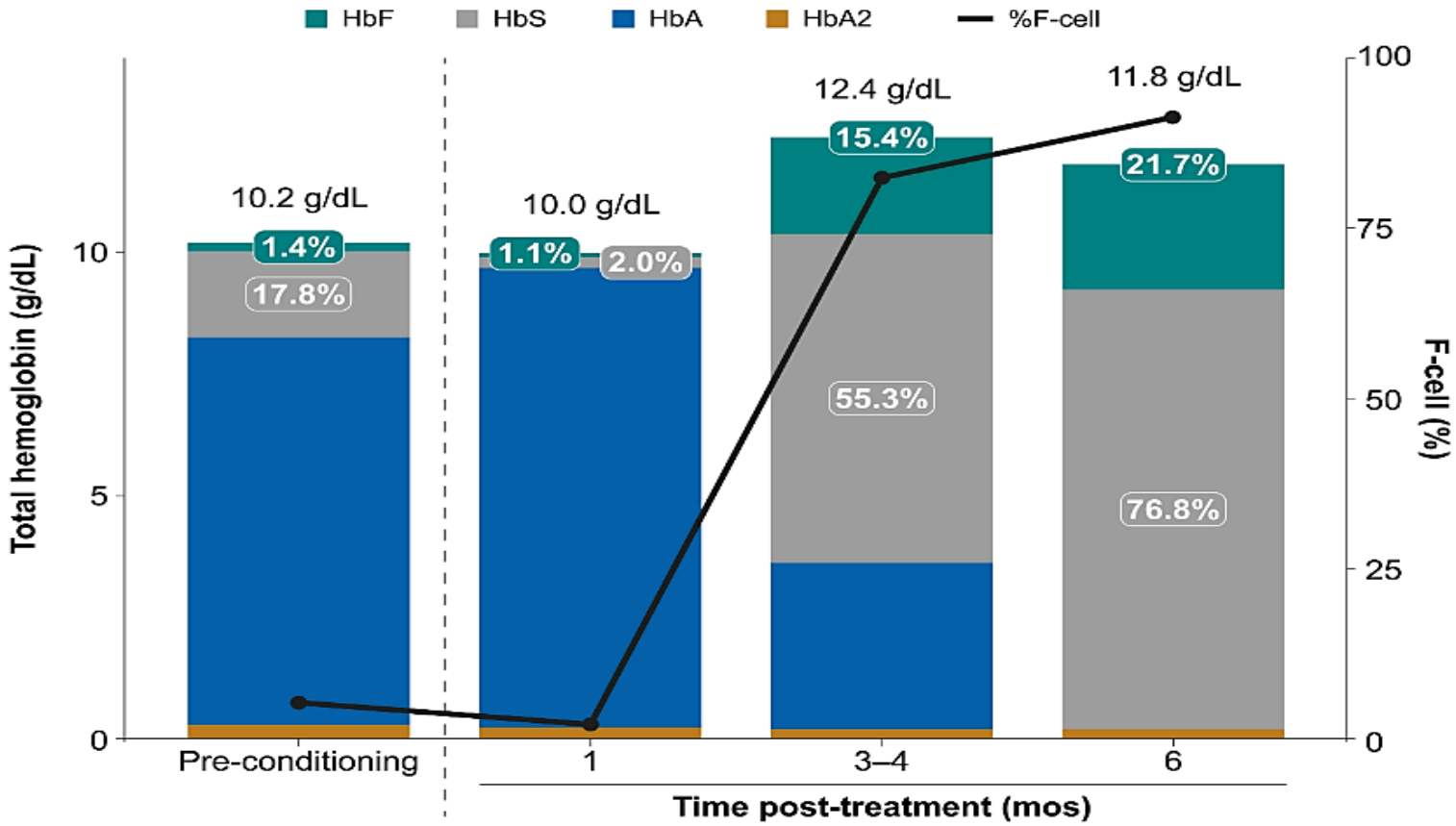
- 2 pts with severe SCD received altered CD34+ HPSCs after plerixafor mobilization, apheresis, and busulfan myeloablation

ABS 786: Treatment of Individuals with Severe Sickle Cell Disease with OTQ923, an Autologous, *Ex Vivo*, CRISPR/Cas9-Edited, CD34+ Hematopoietic Stem and Progenitor Cell Product, Leads to Durable Engraftment and Fetal Hemoglobin Induction

Sharma A et al.

Drive Rank Score=5

Figure 1A: Induction of fetal hemoglobin in Participant 1.



Pt 1 showed 22.1% HbF at 9 mos after infusion

Pt 2 had achieved an HbF level of 15.9% at 3 mos post infusion

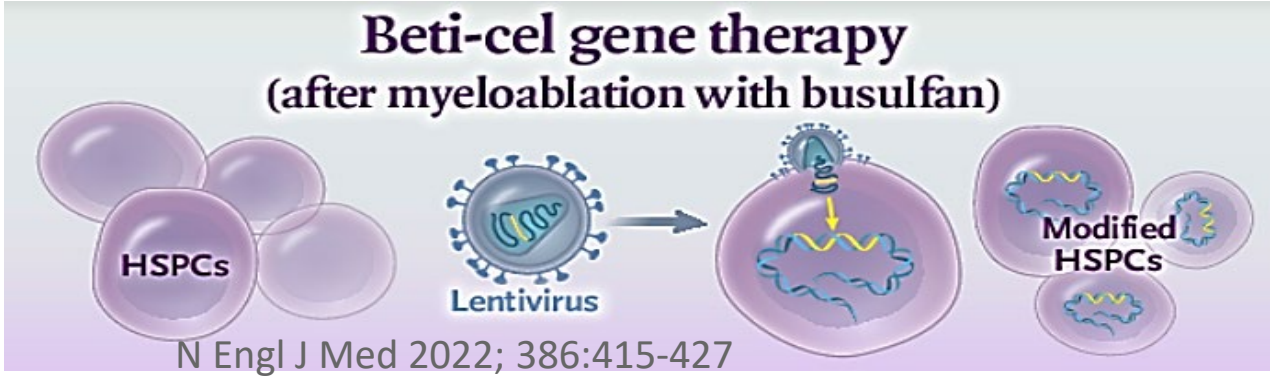
Induction of HbF **was pancellular,** with an F-cell percentage around 91% at 6 mos after infusion

Neither participant had any SCD-related VOEs after infusion of the cellular product.

ABS 2348: Long Term Outcomes of 63 Patients with Transfusion-Dependent β-Thalassemia (TDT) Followed up to 7 Years Post-Treatment with betibeglogene autotemcel (beti-cel) Gene Therapy and Exploratory Analysis of Predictors of Successful Treatment Outcomes in Phase 3 Trials

Walters MC et al. **Drive Rank Score=5**

- Beti-cel *ex vivo* gene therapy adds functional modified *HBB* gene, $\beta^{A\text{-}T87Q}$, to autologous CD34+ HSPCs via transduction with lentiviral vector, thereby reversing the genetic cause of Transfusion-Dependent β-Thalassemia
- 63 pts with TDT received beti-cel; followed for median of 41.4 (9.0–87.5) months
- Median time to neutrophil & platelet engraftment: 23 (13–39) and 45 (19–191) days
- 18% (11/63) pts experienced ≥1 AE considered related or possibly related to beti-cel:
  - abdominal pain (5/63 [8%])
  - thrombocytopenia (3/63 [5%])
  - Both resolved beyond 2 yrs post-infusion
  - Veno-occlusive liver disease in 11% (7/63);
  - Resolved after appropriate treatment.



N Engl J Med 2022; 386:415-427

- No malignancies, insertional oncogenesis, or vector-derived replication competent lentivirus
- **The safety of the beti-cel treatment regimen largely reflected the known side effects of hematopoietic stem cell collection and the busulfan conditioning regimen**

ABS 2348: Long Term Outcomes of 63 Patients with Transfusion-Dependent β-Thalassemia (TDT) Followed up to 7 Years Post-Treatment with betibeglogene autotemcel (beti-cel) Gene Therapy and Exploratory Analysis of Predictors of Successful Treatment Outcomes in Phase 3 Trials

Walters MC et al.

Drive Rank Score=5

Figure 1A. Transfusion Status in Phase 3 Patients

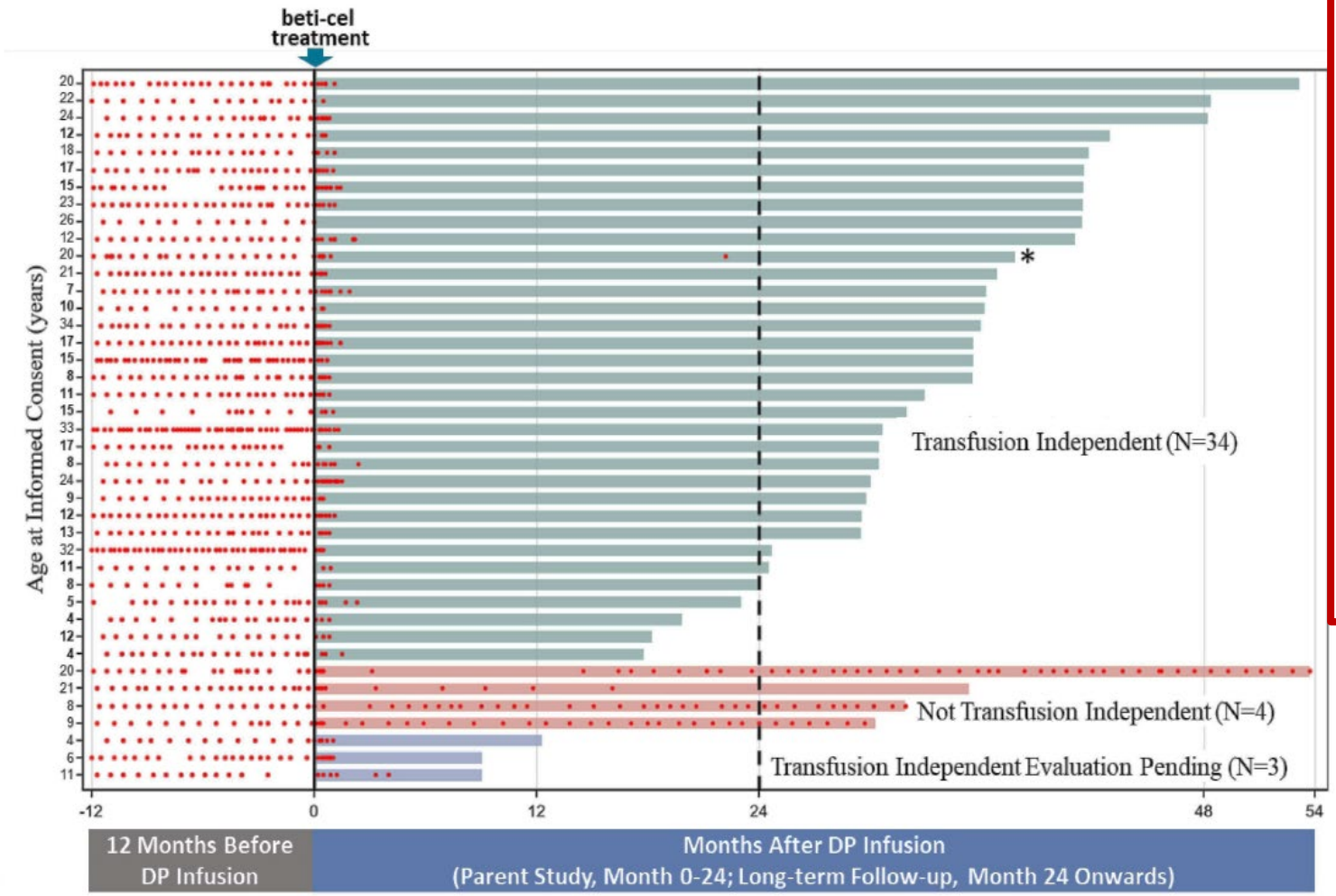
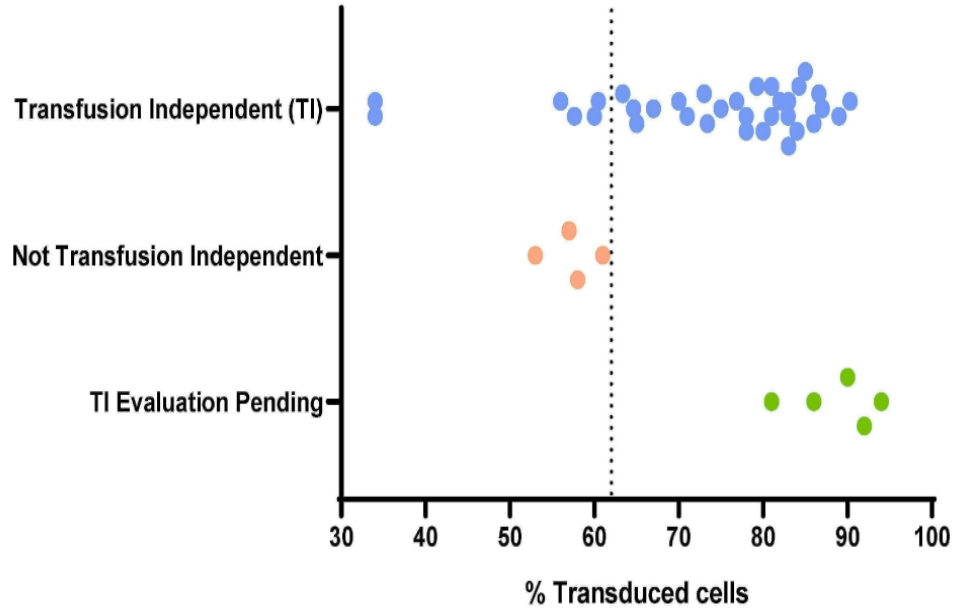


Figure 1B. Patients in Phase 3 who Achieved TI had Higher % Transduced Cells in Drug Product



Multivariate analysis demonstrated that Drug Product transduction efficiency was the most predictive attribute of transfusion independence (TI)

Exa-cel Is a Cell Therapy That Uses Non-Viral, *Ex Vivo* CRISPR/Cas9-Mediated Editing of *BCL11A* to Increase HbF Levels[1] (Exagamglogene Autotemcel)

- Naturally occurring genetic polymorphisms in *BCL11A* are associated with elevated HbF and decreased severity of TDT and SCD[2-4]
- BCL11A suppresses expression of γ-globin and thus HbF
- Editing of *Bcl11a* reactivates γ-globin expression and formation of HbF (α2γ2) in mouse models[4]
- Exa-cel is produced using non-viral, *ex vivo* editing of the erythroid-specific enhancer region of *BCL11A* in CD34+ HSPCs and reduces erythroid-specific expression of BCL11A
- Infusion of exa-cel leads to an increase in HbF levels in erythroid cells *in vivo*

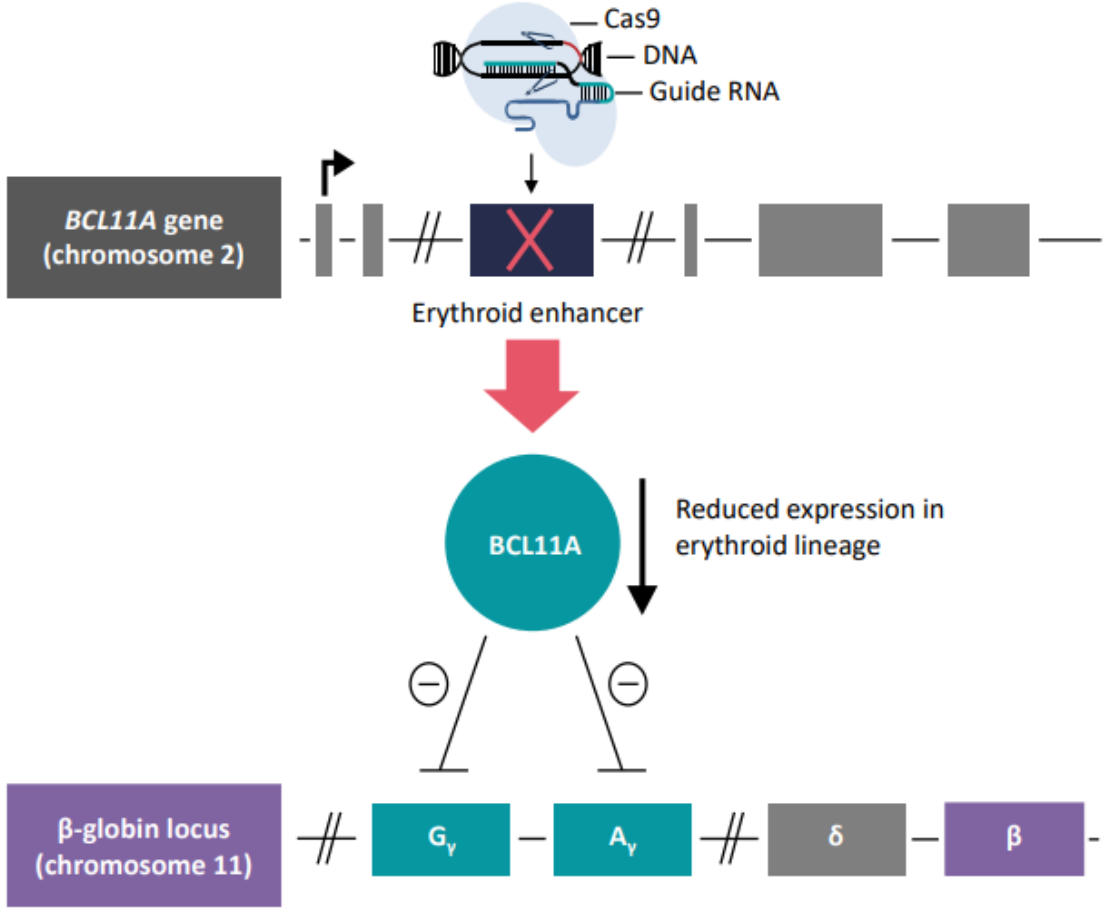


Figure modified from Canver, et al.[1]

BCL11A, B-cell lymphoma/leukemia 11A; CRISPR, clustered regularly interspaced short palindromic repeats; DNA, deoxyribonucleic acid; HbF, fetal hemoglobin; HSPC, hematopoietic stem and progenitor cell; RNA, ribonucleic acid; SCD, sickle cell disease; TDT, transfusion dependent β-thalassemia.

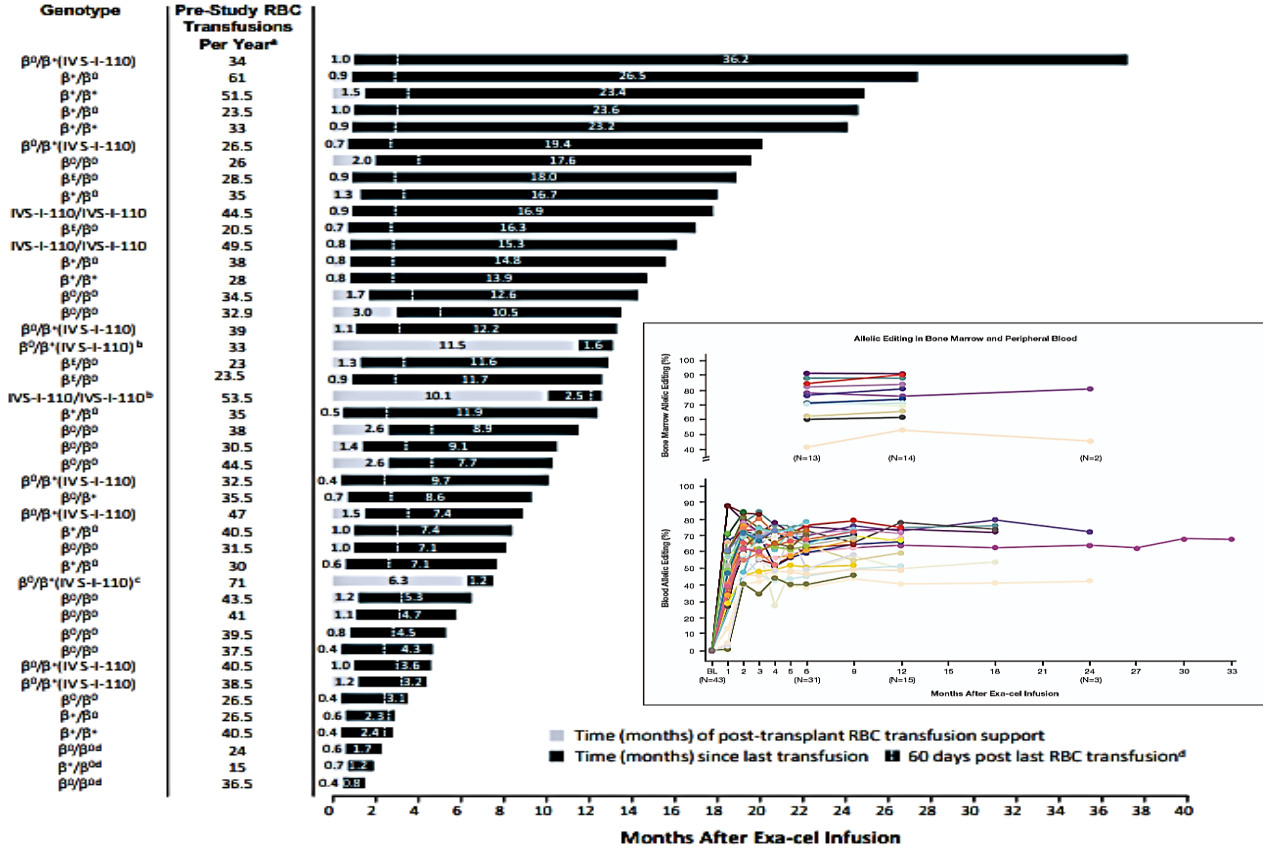
1. Canver MC, et al. *Blood*. 2016;127:2536-2545; 2. Murray N, et al. *Br J Haematol*. 1988;69:89-92; 3. Bank A. *Blood*. 2006;107:435-443; 4. Bauer DE, et al. *Science*. 2013;342:253-257.

Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia *Blood* (2022) 140 (Supplement 1): 4899–4901.

Locatelli F et al **Drive Rank Score=5**

Forty-Two of 44 Patients With TDT Treated With Exa-cel Are Transfusion-Free

- Time (months) of post-transplant RBC transfusion support is indicated by the light blue bar and time (months) since last transfusion is indicated by the dark blue bar
- 42 of 44 patients stopped RBC transfusions (duration from 0.8 to 36.2 months)
- Two patients had not yet stopped transfusions but have 75% and 89% reductions in transfusion volume



Hb, hemoglobin; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia.

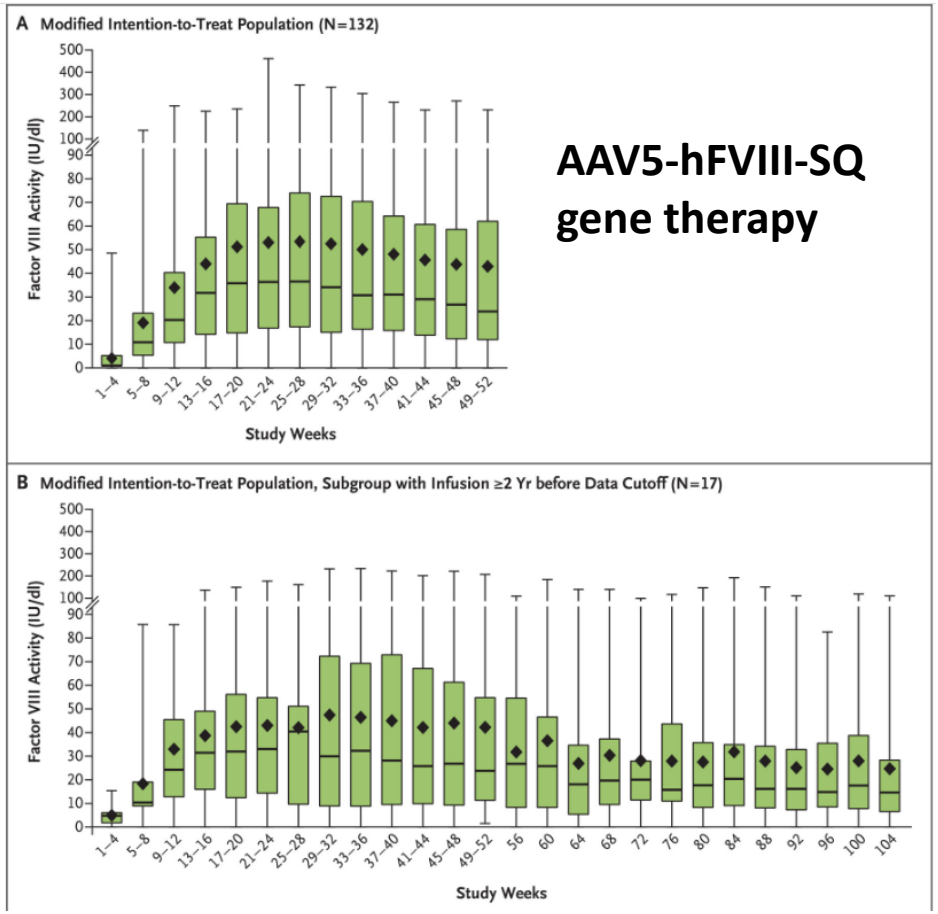
Each row in the figure on the right represents an individual patient.

[a]Number of transfusion units annualized over 2 years; [b]Received RBC transfusions at or after data cut; [c]Patient stopped transfusions after data cut; [d]Patients are evaluable for elimination of transfusions starting 60 days after their last transfusion.

In vivo Liver directed AAV gene therapy in hemophilia A and B

drive rank score=1

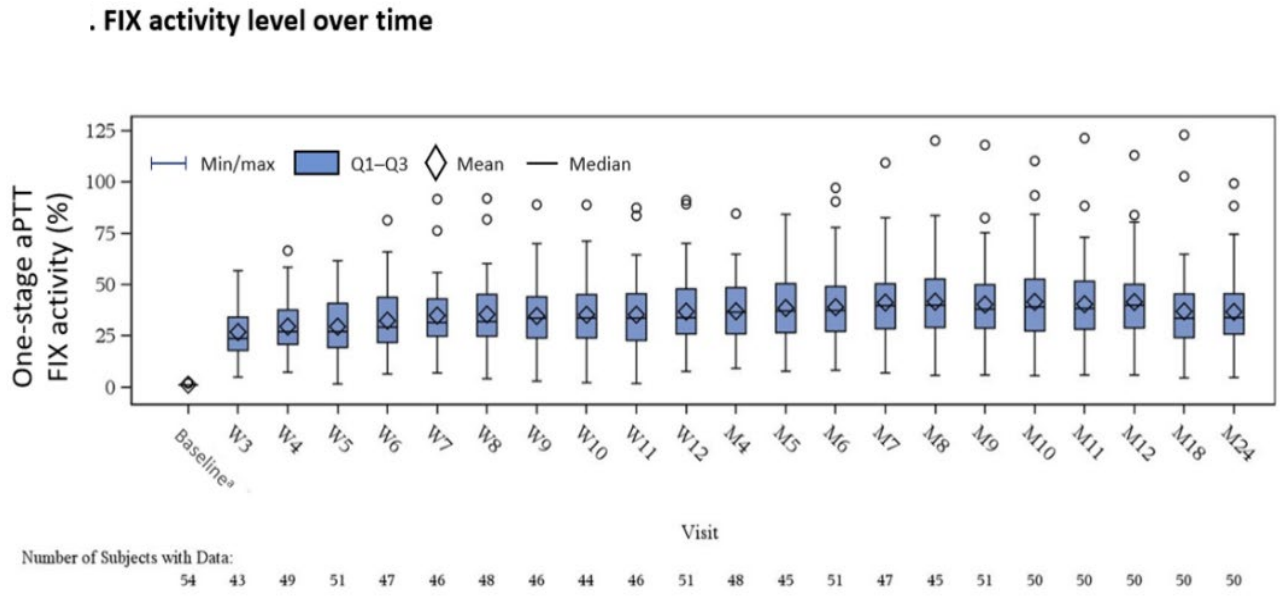
Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A



AAV5-hFVIII-SQ gene therapy

Ozelo, MC et al. N Engl J Med 2022; 386:1013-1025

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



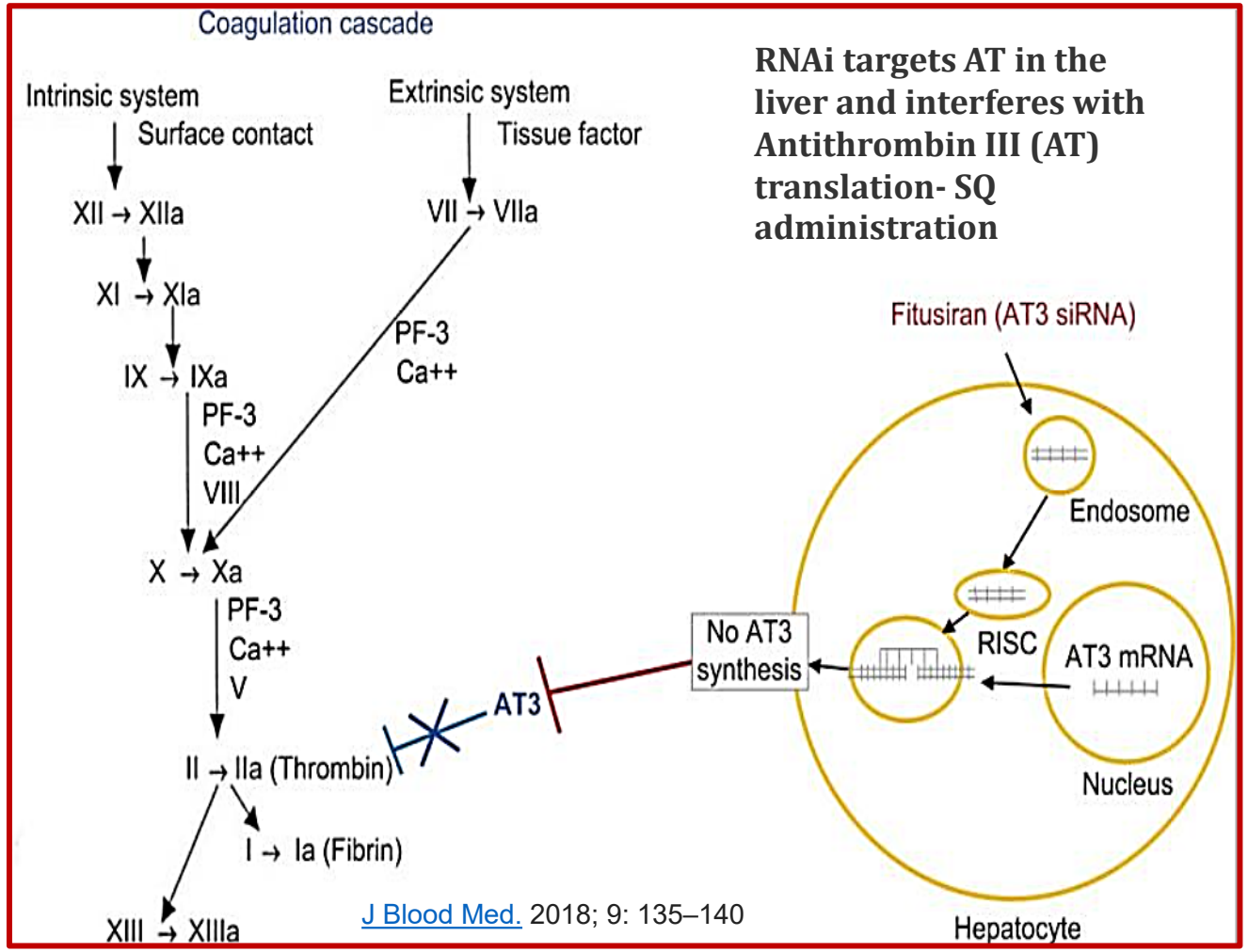
AAV5 vector, containing a codon-optimized, highly active factor IX (FIX) Padua R338L transgene

ABS 2141: ASH 2022, Pipe SW et al.

Gene silencing strategies for hematologic diseases

Fitusiran for Hemophilia A and B with and without inhibitors

Drive Rank Score=1

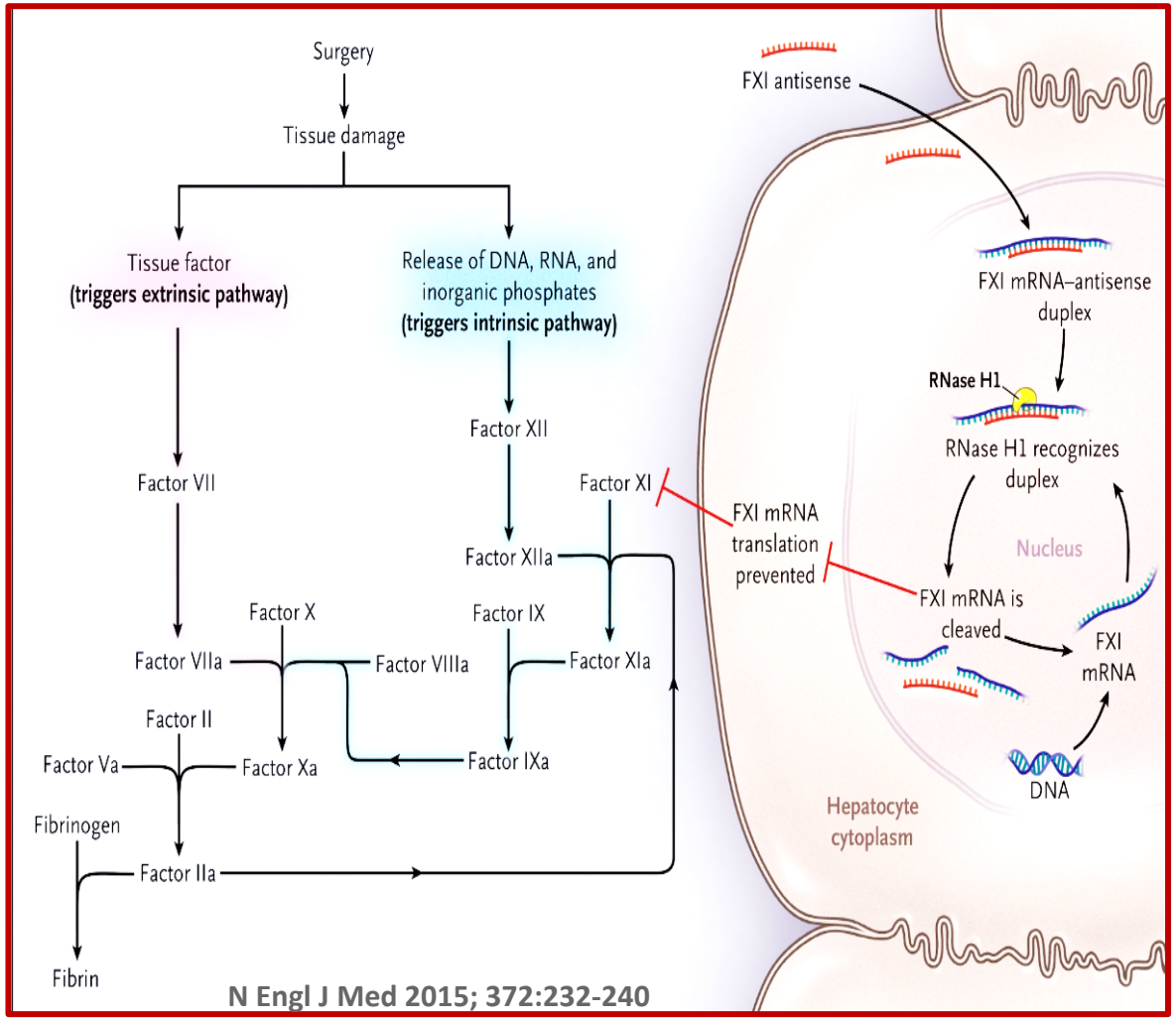


J Blood Med. 2018; 9: 135–140

Abbreviations: AT, antithrombin; mRNA, messenger RNA; RiSC, RNA-induced silencing complex; RNAi, RNA interference.

Factor XI Antisense Oligonucleotide for VTE prophylaxis for total knee arthroscopy

Drive Rank Score=1

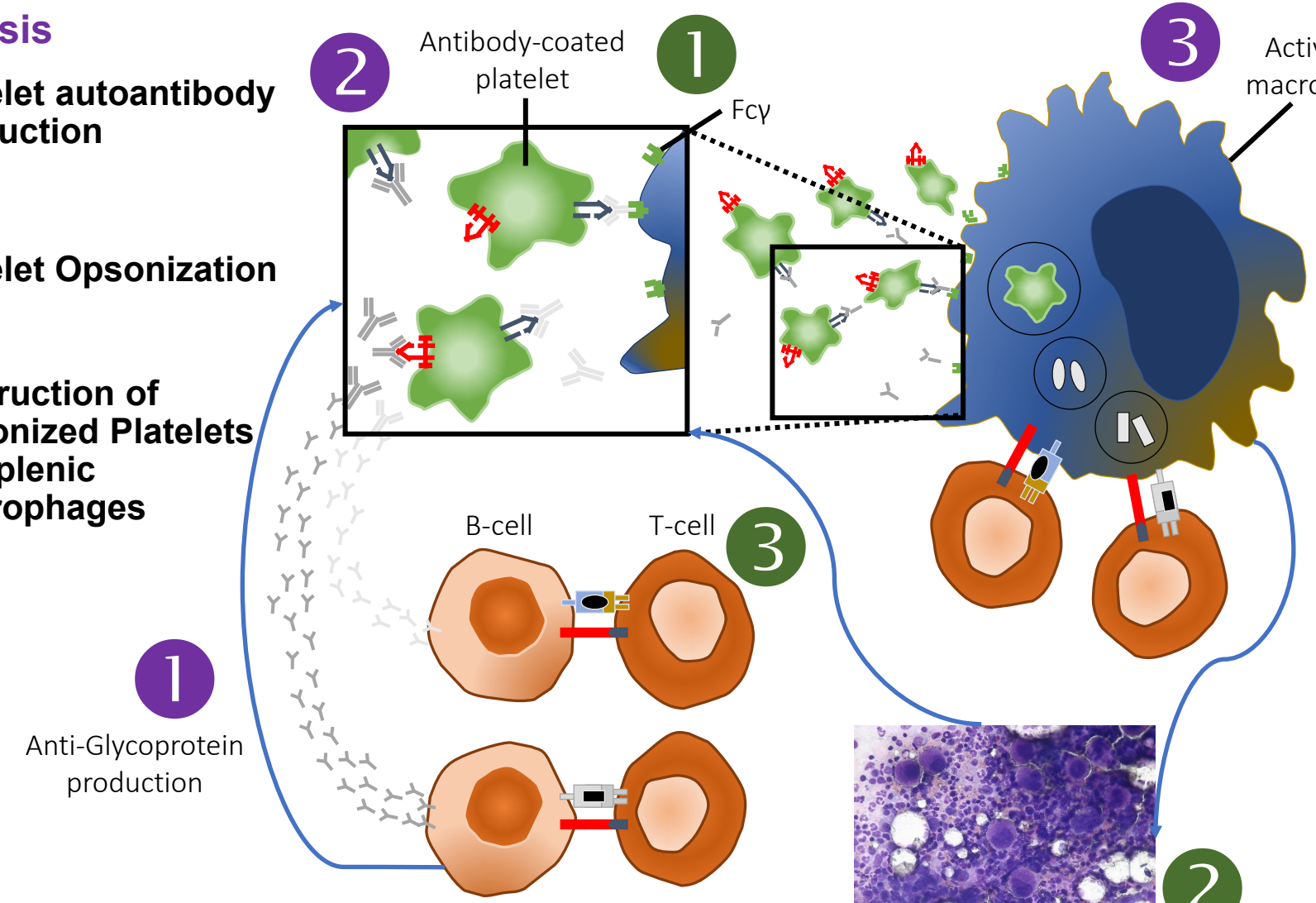


N Engl J Med 2015; 372:232-240

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.

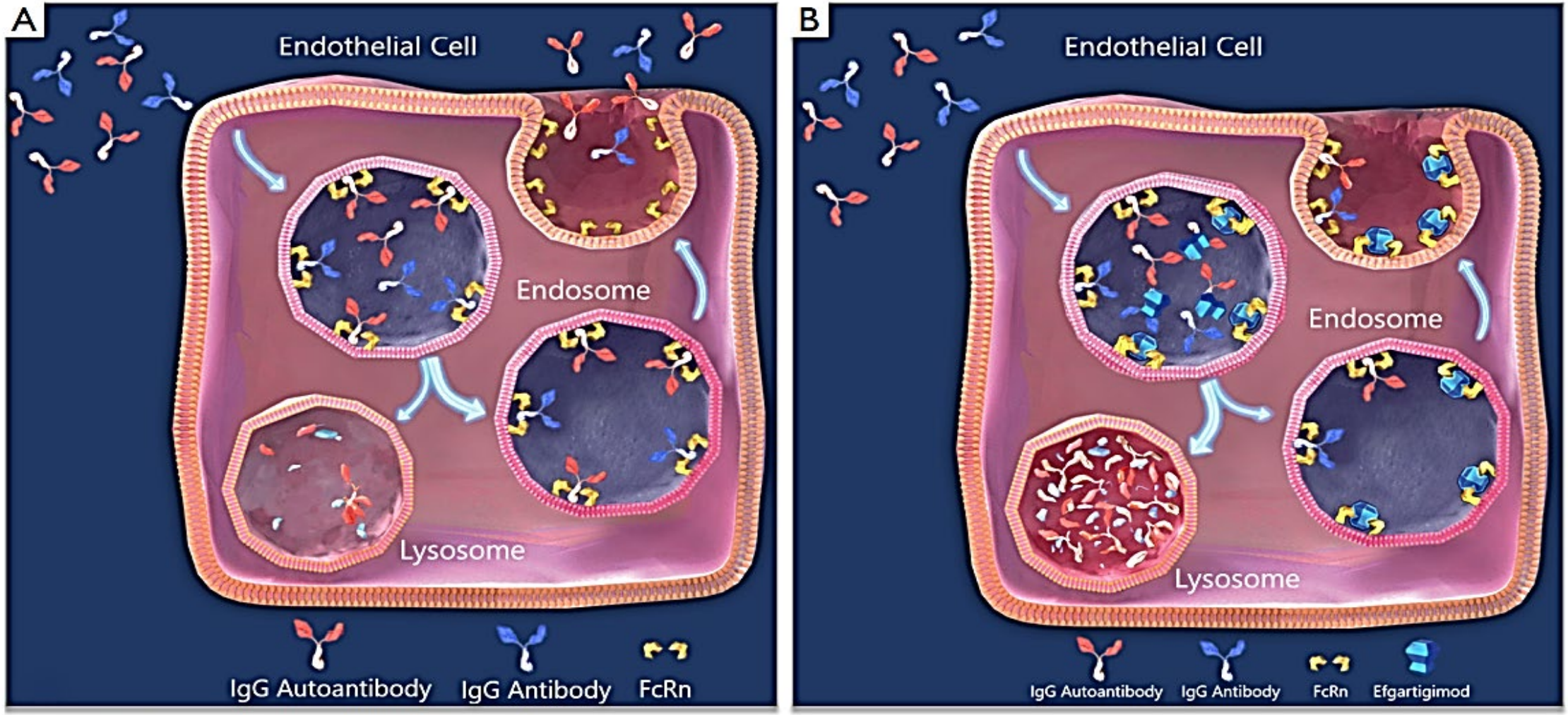
Treatment MOA

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.

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 3: Efficacy and Safety of Intravenous Efgartigimod in Adults with Primary Immune Thrombocytopenia: Results of a Phase 3, Multicenter, Double-Blinded, Placebo-Controlled, Randomized Clinical Trial (ADVANCE IV)

Broome CM et al

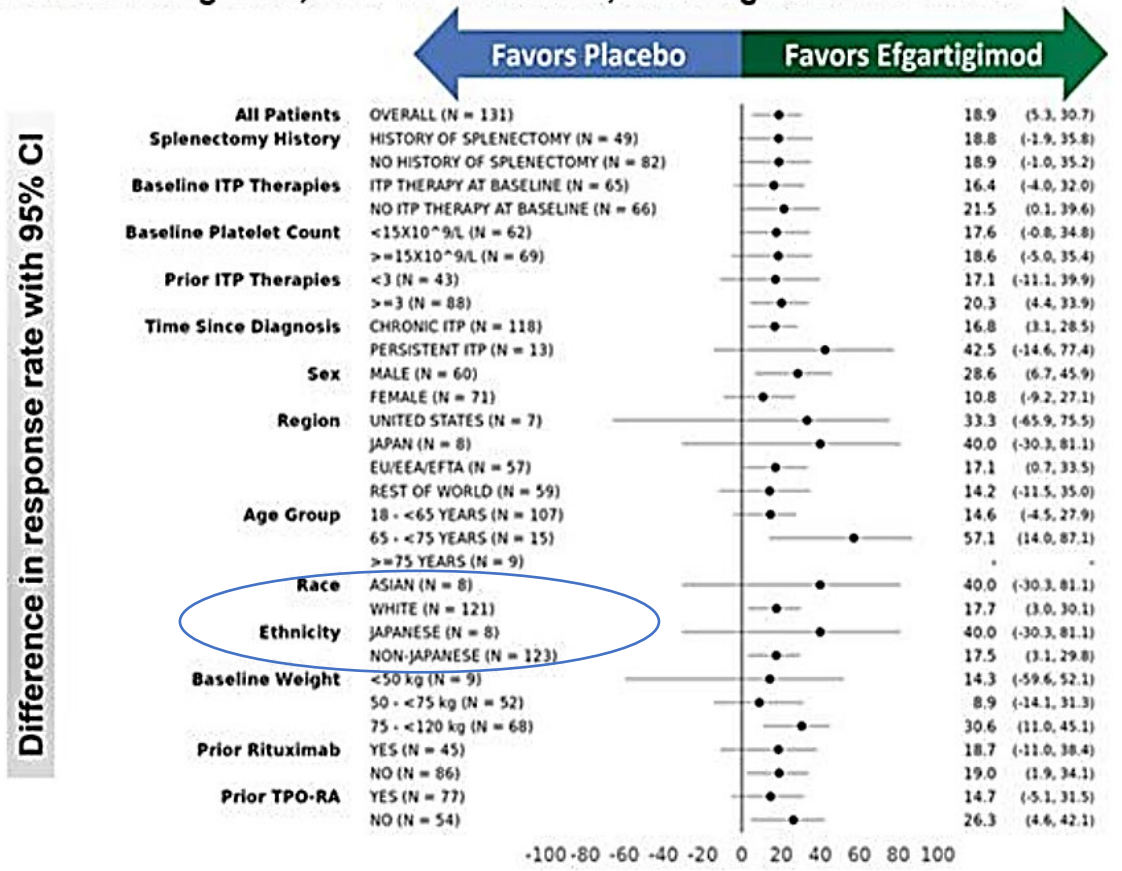
Drive Rank score = 1

Table 1: Overview of Primary and Key Secondary Endpoints

Endpoint	Population	Efgartigimod	Placebo	*P*-value
Primary endpoint				
Sustained platelet count response	Chronic	17/78 (21.8%)	2/40 (5.0%)	.0316*
Key Secondary endpoints				
Extent of disease control[a]	Chronic	6.1 (7.66), 2.0 (0.0, 11.0)	1.5 (3.23), 0.0 (0.0, 1.0)	.0009*
Sustained platelet count response	Overall	22/86 (25.6%)	3/45 (6.7%)	.0108*
Incidence of WHO bleeding events[b]	Overall	6.2 (6.39), 4.0 (1.0, 10.0)	8.3 (8.01), 5.0 (2.0, 14.0)	.8287
Durable sustained platelet count response	Overall	19/86 (22.1%)	3/45 (6.7%)	.0265

[a]Number of cumulative weeks – mean (SD), median (Q1, Q3); [b]Number of visits with WHO ≥ 1 – mean (SD), median (Q1, Q3)
*Significant at overall 5% level. These endpoints were statistically tested in a fixed sequence to maintain an overall statistical significance level or alpha-value of 5%.
Q1, first quartile; Q3, third quartile; WHO, World Health Organization.

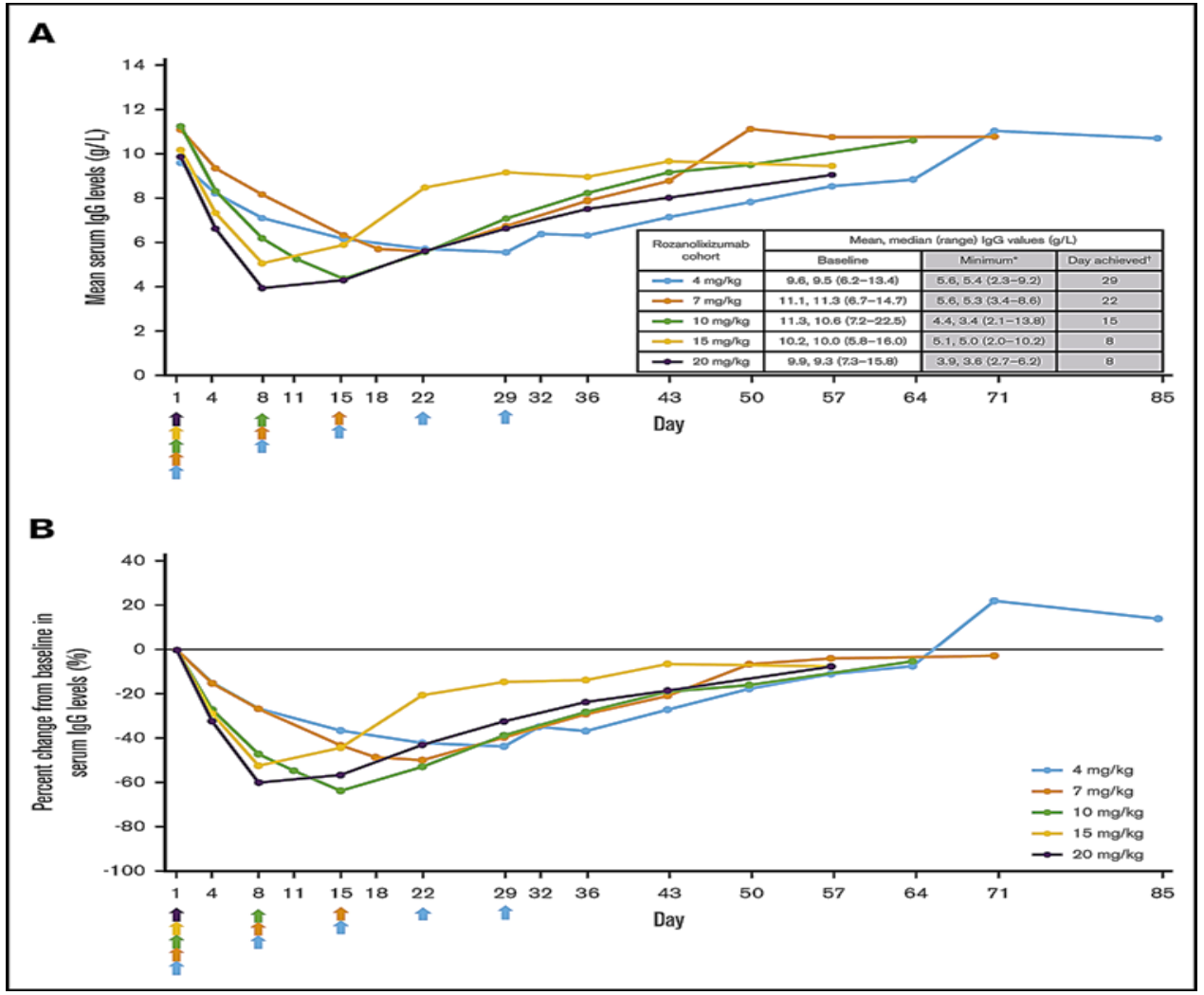
Figure 1: Participants With ITP Responded Regardless of Age, Sex, Severity, Time Since Diagnosis, Prior ITP Treatment, or Background Medication



EEA, European Economic Area; EFTA, European Free Trade Association; EU, European Union; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

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

VEXAS Syndrome: A new hematology disease

V – Vacuoles

E – E1 enzyme

X – X-linked

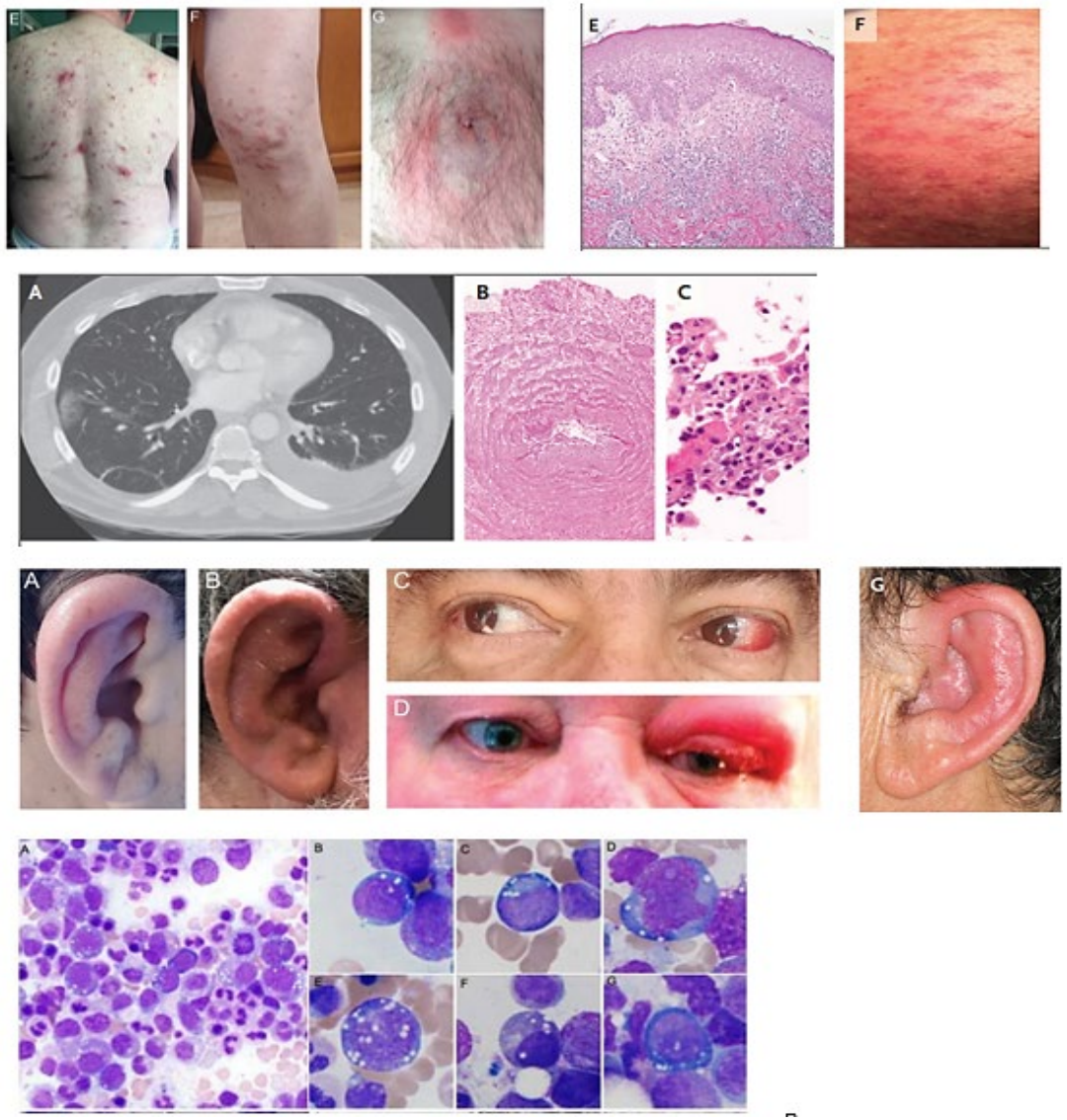
A – Autoinflammatory

S – Somatic

Demographic characteristics	
Male sex — no. (%)	25 (100)
Median age at onset (range) — yr	64 (45–80)
Died before the current study — no. (%)	10 (40)
Genetic characteristics	
Somatic *UBA1* (NM_003334.3) variant (p.Met41) — no. (%)	25 (100)
p.Met41Thr (c.122T→C)	15 (60)
p.Met41Val (c.121A→G)	5 (20)
p.Met41Leu (c.121A→C)	5 (20)
Key clinical features	
Fever — no. (%)	23 (92)
Skin involvement — no. (%)†	22 (88)
Pulmonary infiltrate — no. (%)	18 (72)
Ear and nose chondritis — no. (%)	16 (64)
Venous thromboembolism — no. (%)	11 (44)
Macrocytic anemia — no. (%)	24 (96)
Bone marrow vacuoles — no./total no. (%)	18/18 (100)
Laboratory findings	
Median C-reactive protein (IQR) — mg/liter	73 (18–128)
Median ESR (IQR) — mm/hr	97 (64–124)
Current or past treatment	
Glucocorticoids — no. (%)	25 (100)
Median no. of synthetic DMARDs (IQR)	2 (1–3)
Median no. of biologic or target synthetic DMARDs (IQR)	2 (0.5–3)
Diagnostic or classification criteria that were met — no. (%)	
Relapsing polychondritis	15 (60)
Sweet's syndrome	8 (32)
Myelodysplastic syndrome	6 (24)
Multiple myeloma or monoclonal gammopathy of undetermined significance	5 (20)
Polyarteritis nodosa	3 (12)
Giant-cell arteritis	1 (4)

Beck DB et al. N Engl J Med 2020;383:2628-38

VEXAS Syndrome



Suspect in male **patients who present in** late adulthood **with** systemic inflammatory symptoms, skin involvement, and hematologic abnormalities**, who show response to** steroids

Treatment Strategies

Steroids work but are not ideal

Allogeneic HSCT transplant is probably curative, but challenging in this specific patient population

CLINICAL TRIALS are urgently needed!

Ruxolitinib vs other, CR

1 month 67% vs 38%, p=0.13

3 months 83% vs 18%, p=0.001

6 months 87% vs 11%, p=0.002

Steroid dose reduction at 6 mos, 83.6% vs 75%

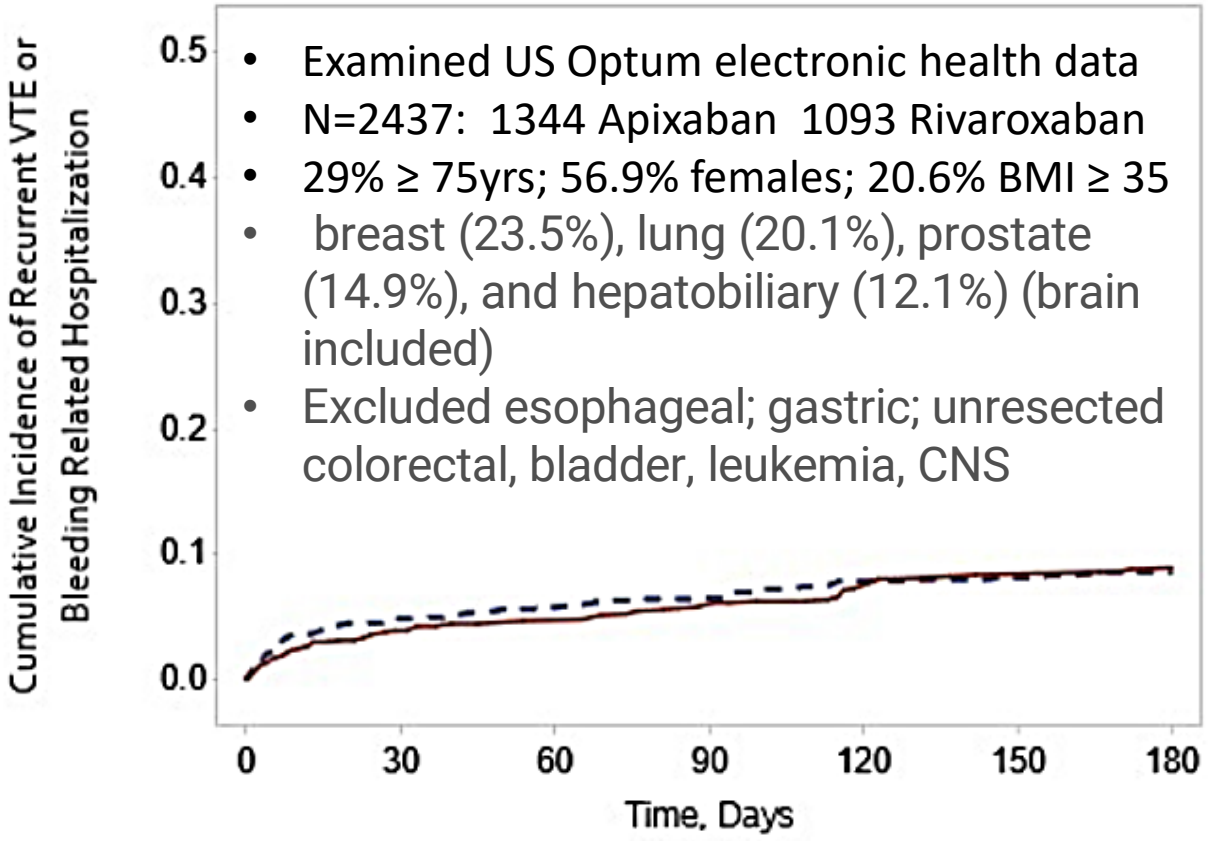
Heiblig et al. Blood.2022;25:927-31

Beck DB et al. N Engl J Med 2020;383:2628-38

ABS 522: Rivaroxaban Versus Apixaban for Treatment of Cancer-Associated Venous Thromboembolism: A Head-to-Head Analysis of the United States Cohort of the Observational Study in Cancer-Associated Thrombosis for Rivaroxaban: (H2H-OSCAR-US)

Caroti KS et al **Drive Rank Score= ?**

A



- Examined US Optum electronic health data
- N=2437: 1344 Apixaban 1093 Rivaroxaban
- 29% ≥ 75yrs; 56.9% females; 20.6% BMI ≥ 35
- breast (23.5%), lung (20.1%), prostate (14.9%), and hepatobiliary (12.1%) (brain included)
- Excluded esophageal; gastric; unresected colorectal, bladder, leukemia, CNS

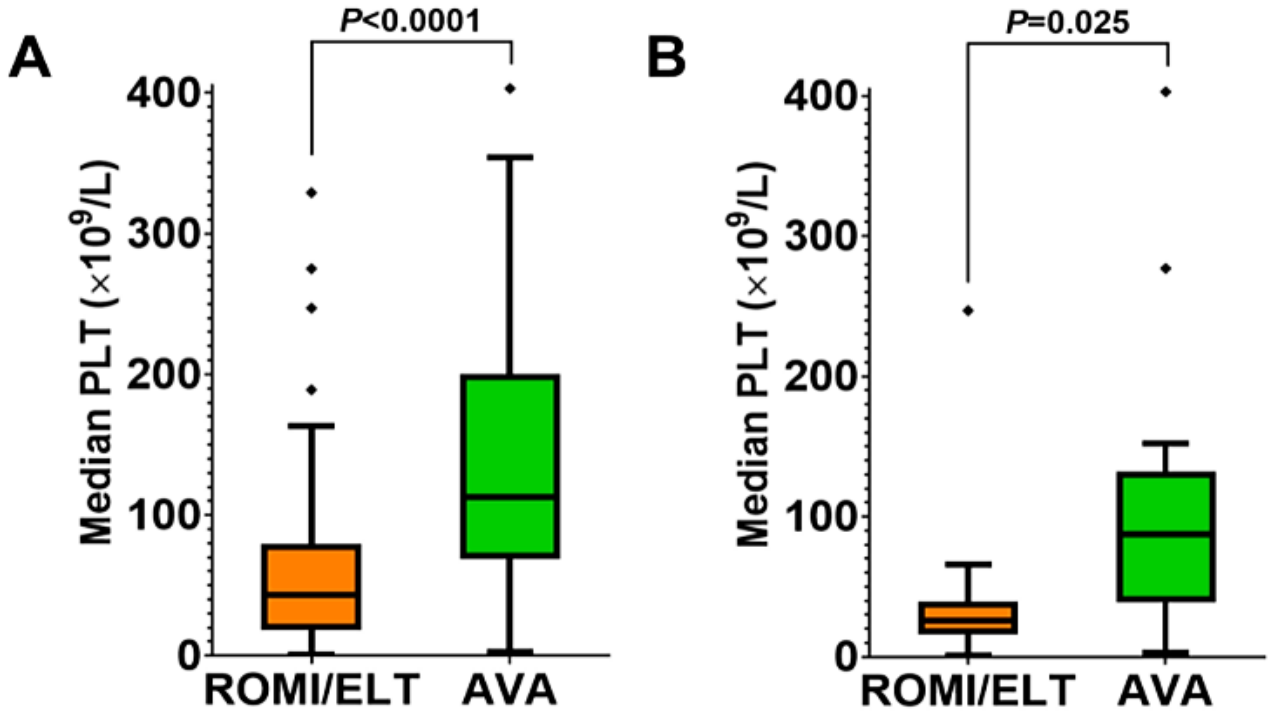
B

Outcome	Rivaroxaban N=1093 %	Apixaban N=1344 %	IPTW*-HR (95%CIs)
3 Months			
Recurrent VTE or bleeding related hospitalization	5.3	6.0	0.87 (0.60-1.27)
Recurrent VTE	3.8	4.2	0.92 (0.59-1.42)
Bleeding related hospitalization	2.4	2.3	1.05 (0.59-1.88)
Critical organ bleed	0.2	0.4	0.49 (0.09-2.59)
Recurrent VTE or critical organ bleed	3.8	4.5	0.85 (0.56-1.31)
6 Months			
Recurrent VTE or bleeding related hospitalization	7.5	7.5	1.00 (0.71-1.40)
Recurrent VTE	5.1	4.9	1.05 (0.71-1.57)
Bleeding related hospitalization	3.5	3.3	1.06 (0.63-1.79)
Critical organ bleed	0.3	0.7	0.44 (0.13-1.51)
Recurrent VTE or critical organ bleed	5.2	5.3	0.98 (0.66-1.44)

Rivaroxaban as effective and safe as apixaban, with non-inferiority demonstrated for the composite outcome of recurrent VTE or any bleeding resulting in hospitalization at 3 or 6 months.

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).



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 585×109/L on avatrombopag omitted from both graphs to preserve graph resolution.

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

Al-Samkari H et al. Res Pract Thromb Haemost. 2021; 5 (Suppl 1). https://abstracts.isth.org/abstract/switching-from-eltrombopag-or-romiplostim-to-avatrombopag-in-immune-thrombocytopenia-a-multicenter-study-of-u-s-itp-referral-centers/. Accessed July 30, 2021.