Neue Therapien SCD - P-Selektin-Antagonisten

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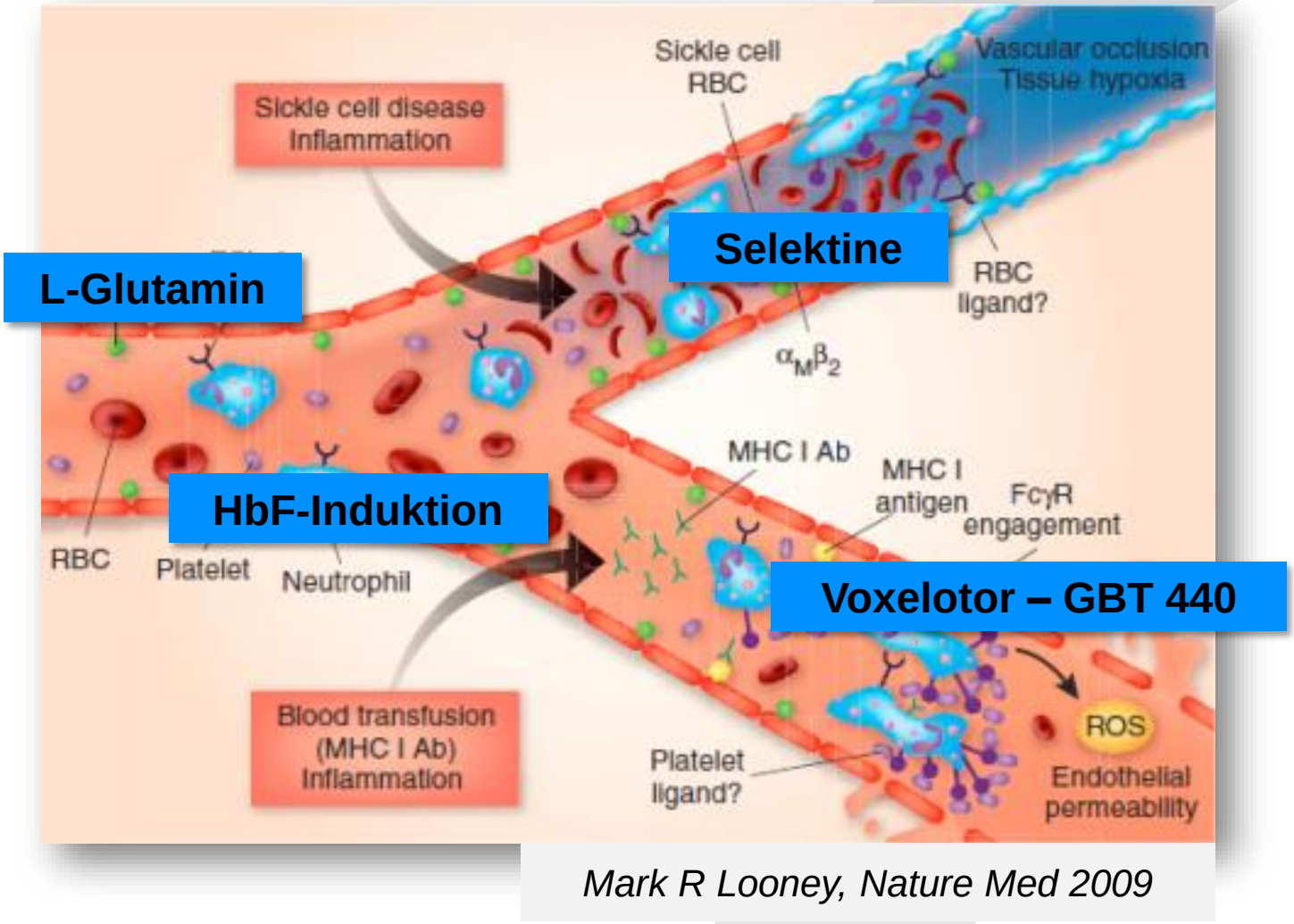
Disclosure

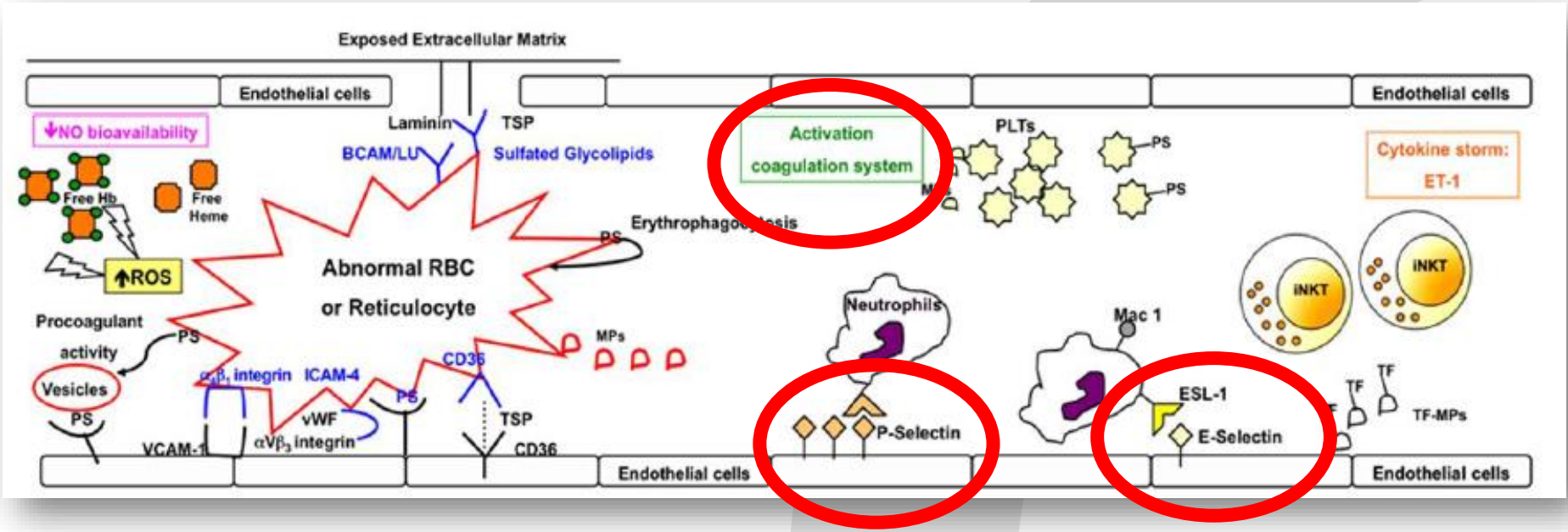
Bestehender Beratervertrag und Reisekostenerstattung 2018 durch Novartis Pharma

Therapieansätze



Mark R Looney, Nature Med 2009

Endothel und Selektine



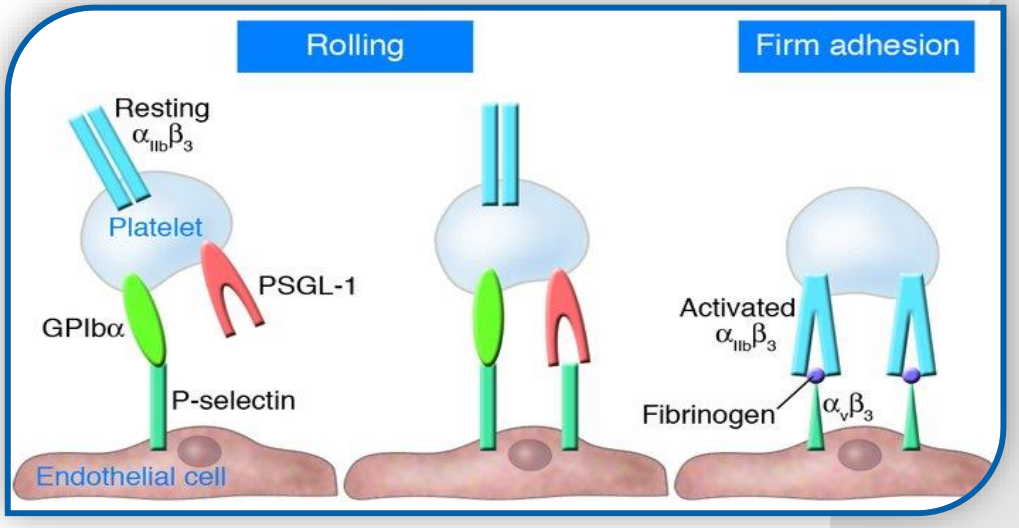
Heparine-Tinzaparin

SEG101 P-Selektin-Inhibitor

GMI-1070 Rivipansel

Matte et al, Medi J Hematol Inf Dis, 2019

P-Selektin ist ein Zelladhäsionsmolekül



Vermittelt das “rolling” und Anhaften von Blutzellen am aktivierten Endothel[1]

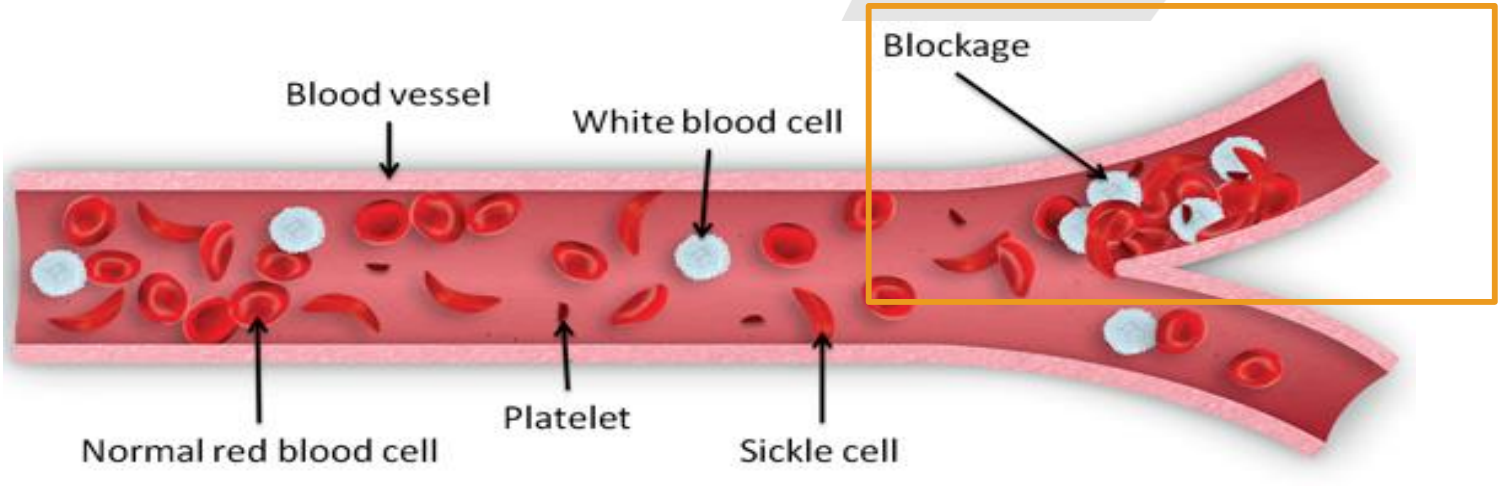
Interaktion von P-Selektin und seinen Liganden trägt zur Spezifität von Interaktionen zwischen Endothelzellen, Thrombozyten und Leukozyten im Rahmen von Inflammation, Koagulation und Atherosklerose[2]

Gesunde Erythrozyten binden kaum an P-Selektin und adhärieren deshalb nicht signifikant am Endothel[2]

1. Wagner DD & Frenette PS. *Blood* 2008;111:5271–5281; 2. Matsui NM *et al. Blood* 2001;98:1955–1962; Figure: Gawaz M *et al. J Clin Invest* 2005;115:3378–3384

P-Selektin und VOC Entwicklung

Aktiviertes P-Selektin bindet an Leukozyten PSGL-1 Rezeptor und PSGL-1-like Rezeptor auf **Sichelzellen**



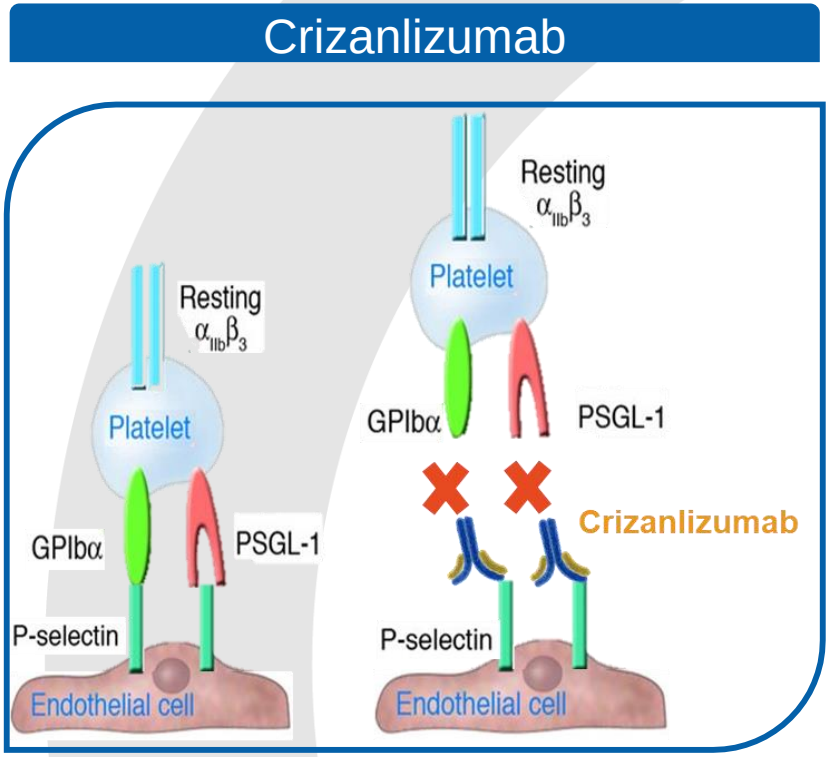
Zell–Zell-Interaktionen resultieren in Formation eines vasookklusiven Clots
→Schmerz,Hämolyse, Organschädigung und Mortalität[1]

1. Manwani D & Frenette PS. *Blood* 2013;122:3892–3898

VOC, vaso-occlusive crisis; PSGL-1, P-selectin glycoprotein ligand-1

Crizanlizumab: Ein high-affinity P-Selektin Inhibitor

- Humanisierter Antikörper, der P-Selektin spezifisch und mit hoher Affinität bindet[1]
- Bindung an Rezeptoren wird verhindert → Prävention VOCs, Verbesserung des Blutflusses[2–4]
- Langzeitanwendung vielversprechend und angestrebt



1. Ataga KI *et al. N Engl J Med* 2017;376:429–439; 2. Embury SH *et al. Blood* 2004;104:3378–3385; 3. Matsui NM *et al. Blood* 2001;98:1955–1962; 4. Kutlar A *et al. Am J Hematol* 2012;87:536–539

SUSTAIN Studie

SUSTAIN: A Multicenter, Randomized, Placebo-Controlled, Double-Blind, 12-Month Study to Assess Safety and Efficacy of SelG1 with or without Hydroxyurea Therapy in Sickle Cell Disease Patients with Sickle Cell-Related Pain Crises

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

K.I. Ataga, A. Kutlar, J. Kanter, D. Liles, R. Cancado, J. Friedrisch, T.H. Guthrie, J. Knight-Madden, O.A. Alvarez, V.R. Gordeuk, S. Gualandro, M.P. Colella, W.R. Smith, S.A. Rollins, J.W. Stocker, and R.P. Rother

Kenneth I. Ataga et al. Blood 2016;128:1

blood

SUSTAIN Studiendesign

- Phase 2, Multi-Center Studie
- 198 Patienten (HbSS, HbS/b-Thal, HbSC)
- 2-10 Schmerzkrisen jährlich
- Mit Hydroxycarbamid-Therapie und ohne
- Drei Gruppen:

  high-dose (5mg/kg, 67 Patienten), low-dose Crizanlizumab (2,5mg/kg, 66 Patienten), Placebo (65 Patienten)
- 52 Wochen
- Primäre Endpunkte:

  Rate an vaso-okklusiven Schmerzkrisen, die medizinische Versorgung benötigten

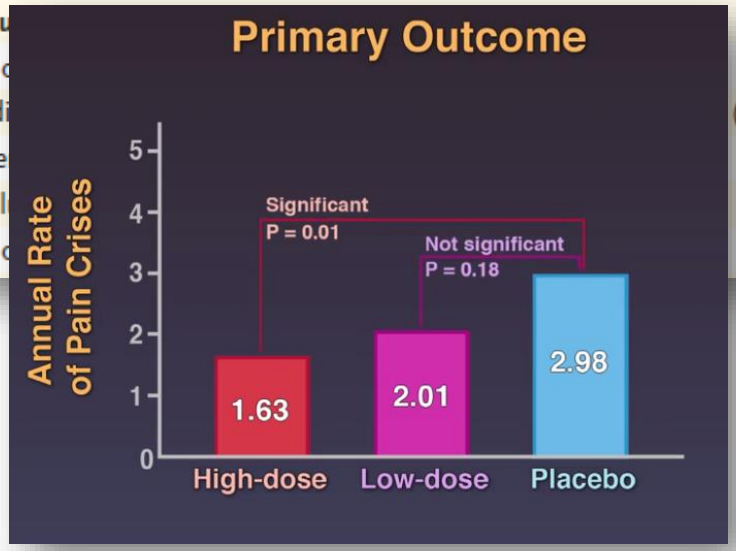
  Andere Krisen: akutes Thoraxsyndrom, Milzsequestration, Priapismus

Ataga et al. , NEJM, 2017

SUSTAIN Ergebnisse

Table 2. Annual Rates of Sickle Cell–Related Pain Crises.*

Variable	High-Dose Crizanlizumab	Low-Dose Crizanlizumab	Placebo
Primary end point: annual rate of crises in the intention-to-treat population			
No. of patients	67	66	65
Median rate of crises per year (IQR)	1.63 (0.00–3.97)	2.01 (1.00–3.98)	2.98 (1.25–5.87)
Difference from placebo — %	−45.3	−32.6	—
P value	0.01	0.18	—
No. of patients with crisis rate of zero at end of trial	24	12	11
Annu			
No.	40	44	41
Medi	(0.00–3.42)	2.00 (1.00–3.02)	2.18 (1.96–4.96)
Diffe	−52.3	−8.3	—
P val	0.02	0.13	—
No.	15	7	5



Ataga et al. , NEJM, 2017

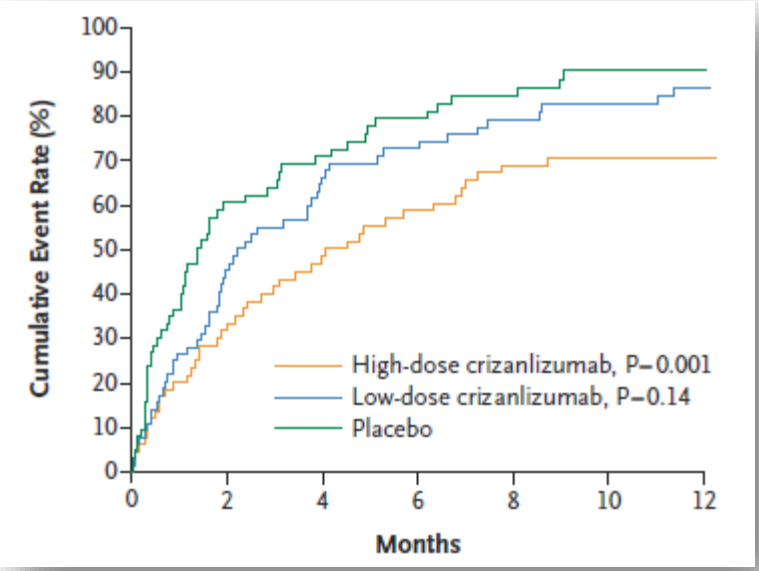
SUSTAIN Ergebnisse

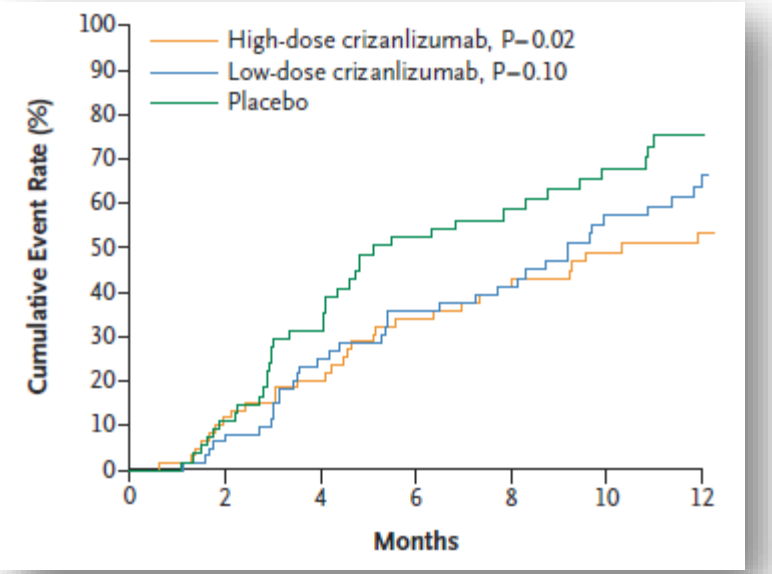
Variable	High-Dose Crizanlizumab	Low-Dose Crizanlizumab	Placebo
Subgroup analyses in the intention-to-treat population			
According to concomitant hydroxyurea use			
Use			
No. of patients	42	41	40
Median rate of crises per year (IQR)	2.43 (0.00–4.01)	2.00 (1.00–3.93)	3.58 (1.13–6.23)
Difference from placebo — %	–32.1	–44.1	
No use			
No. of patients	25	25	25
Median rate of crises per year (IQR)	1.00 (0.00–2.00)	2.16 (1.89–3.98)	2.00 (1.63–3.90)
Difference from placebo — %	–50.0	8.0	—
According to no. of crises in previous 12 mo			
2–4 crises			
No. of patients	42	41	41
Median rate of crises per year (IQR)	1.14 (0.00–3.96)	2.00 (1.00–3.02)	2.00 (1.00–3.90)
Difference from placebo — %	–43.0	0.0	—
5–10 crises			
No. of patients	25	25	24
Median rate of crises per year (IQR)	1.97 (0.00–3.98)	3.02 (2.00–5.19)	5.32 (2.01–11.05)
Difference from placebo — %	–63.0	–43.2	—

Gleiches Outcome auch für Sichelzellsubtypen

Ataga et al. , NEJM, 2017

SUSTAIN Ergebnisse





Ataga et al. , NEJM, 2017

Die Zeit zum ersten und auch die Zeit
zwischen erstem und zweitem Event ist unter Crizanlizumab deutlich verlängert

SUSTAIN Ergebnisse

Table 1. Results from SUSTAIN Multicenter Study of SelG1 (5.0 mg/kg) in Patients with Sickle Cell Disease: ITT Population

Event	SelG1 (n=67)	Placebo (n=65)	Change	P-value
Median annual rate of pain crises	1.6	3.0	-47%	0.010
Median time to first pain crisis (months)	4.1	1.4	+2.9x	0.001
Median time to second pain crisis (months)	10.3	5.1	+2.0x	0.022
Median annual rate of uncomplicated pain crises	1.1	2.9	-62%	0.015
Median annual rate of acute chest syndrome	0.0	0.0	-	0.780
Median annual rate of days hospitalized	4.0	6.9	-42%	0.450

Kenneth I. Ataga et al. Blood 2016

SUSTAIN Ergebnisse

Keine Auswirkungen auf Hämolyse oder baseline Hämoglobin

Measures of Hemolysis

To investigate whether crizanlizumab had an effect on hemolytic variables in patients with sickle cell disease, changes in hemoglobin, lactate dehydrogenase, number of reticulocytes, haptoglobin, and indirect bilirubin were assessed during the study. No significant differences were observed in any of these variables between patients receiving crizanlizumab and those receiving placebo (data not shown).

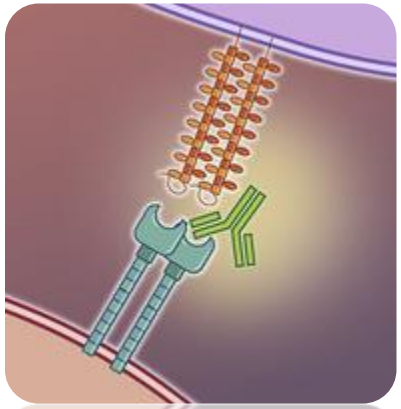
Kenneth I. Ataga et al. NEJM, 2016

SUSTAIN Adverse Events

Ataga et al. , NEJM, 2017

Crizanlizumab (SEG101) Trial

Eine offene, multizentrische Phase 2 Studie zur Dosisfindung und zur Bewertung der Sicherheit von Crizanlizumab mit oder ohne Hydroxyharnstoff/ Hydroxycarbamid Behandlung bei pädiatrischen Sichelzellpatienten mit vaso-okklusiver Krise



Novartis Pharmaceuticals

Crizanlizumab (SEG101) Trial

55 Zentren international, 3 deutsche Zentren

100 Patienten zwischen 6 Monaten und 18 Jahren

3 Gruppen: **1** 12-18 J. **2** 6 - <12 J. **3** 0,5 - <6 J.

2 Teile: **A** Dosisfindung **B** Safety

SEG101 (**Crizanlizumab**) Dosis 5.0 mg/kg i.v.

on Week 1 Day 1, Week 3 Day 1 and Day 1 of every 4-week cycle.

Einschlusskriterien

Confirmed diagnosis of sickle cell disease (SCD) (e.g. any genotype including HbSS, HbSC, HbSβ0-thalassemia, HbSβ+-thalassemia, and others) by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) performed locally.

Experienced at least 1 VOC within the preceding 12 months, as determined by medical history. Prior VOC must have resolved at least 7 days prior to the first dose in the study and should include all the following:

- the occurrence of appropriate symptoms
- either a visit to a medical facility or healthcare professional,
- receipt of oral/parenteral opioid or other non-opioid parenteral analgesia.

If receiving HU/HC or erythropoietin stimulating agent, must have been receiving the drug **for at least 6 months** prior to Screening and plan to continue taking at the same dose and schedule during the trial. Dose alterations of HU/HC during Part A are not allowed, and if this occurs, the patient will enter directly to the Part B.

Received **standard age-appropriate care for SCD**, including penicillin prophylaxis, pneumococcal immunization, and parental education

Transcranial Doppler (TCD) considered low risk within the past 6 months (for 2 to 16 years).

Ausschlusskriterien

History of **stem cell transplant**.

Received any **blood products** within 30 days of Day 1 dosing.

Participating in a **chronic transfusion program** (preplanned series of transfusions for prophylactic purposes).

Patients with **bleeding disorders**

Planning on undergoing an **exchange transfusion during the duration of the study**. Patients requiring episodic transfusion in response to worsened anemia or VOC are permitted.

Any documented history of a **stroke or intracranial hemorrhage, or an uninvestigated neurologic finding** within the past 12 months

Any **conditional TCD** within the past 12 months

Use of **therapeutic anticoagulation** (prophylactic doses permitted) or antiplatelet therapy (other than aspirin) within the 10 days prior to Week 1 Day 1 dosing

Hospitalized at Screening

Planning to **undergo a major surgical procedure** during the duration of the study

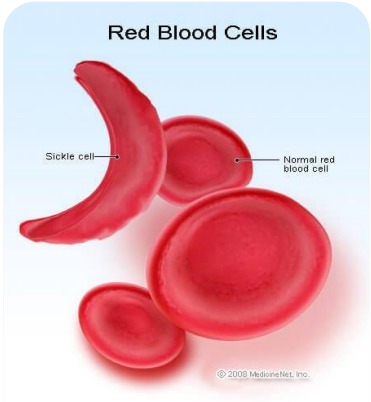
Planning to **initiate or terminate HU/HC** while on study, other than for safety reasons

Infections: including HIV, Hepatitis B/C or immune deficiency

Malignancy

Cardiac or cardiac repolarization abnormality, Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome

Primäre Endpunkte



Pharmakokinetik und Pharmakodynamik nach erster Dosis.

Confirm appropriate dosing of **crizanlizumab** in patients aged 2 to < 18 years

Pharmakokinetik und Pharmakodynamik nach fünfter Dosis.

Confirm appropriate dosing of **crizanlizumab** in patients aged 2 to < 18 years

Pharmakokinetik (Cmax) nach erster und fünfter Dosis [Week 1 to 15]

Confirm appropriate dosing of **crizanlizumab** in patients aged 2 to < 18 years

Pharmakokinetik pre-dose Konzentrationen [Week 3 to 19]

Confirm appropriate dosing of **crizanlizumab** in patients aged 6 months to less than 24 months of age

Häufigkeit jeglicher adverse events (AEs), um Sicherheit und Tolerabilität zu prüfen [6 months- 2 years]

Safety of **crizanlizumab** in patients aged 6 months to < 18 years

Sekundäre Endpunkte

Die Anzahl vasookklusiver Krisen (VOC)

- ohne und mit Hospitalisierung
- Art und Schwere der VOC (akutes Thoraxsyndrom, Milzsequestration, unkomplizierte Krise)

Die Anzahl und Dauer von Hospitalisierungen

Daktylitiden

Veränderungen des Baseline Hämoglobins

Adverse events (Schwere, Kausalität…)

Wachstums- und Entwicklungsdaten

Monitoring von EKG-Veränderungen

Erfassen von anti-drug-antibodies

Ausblick

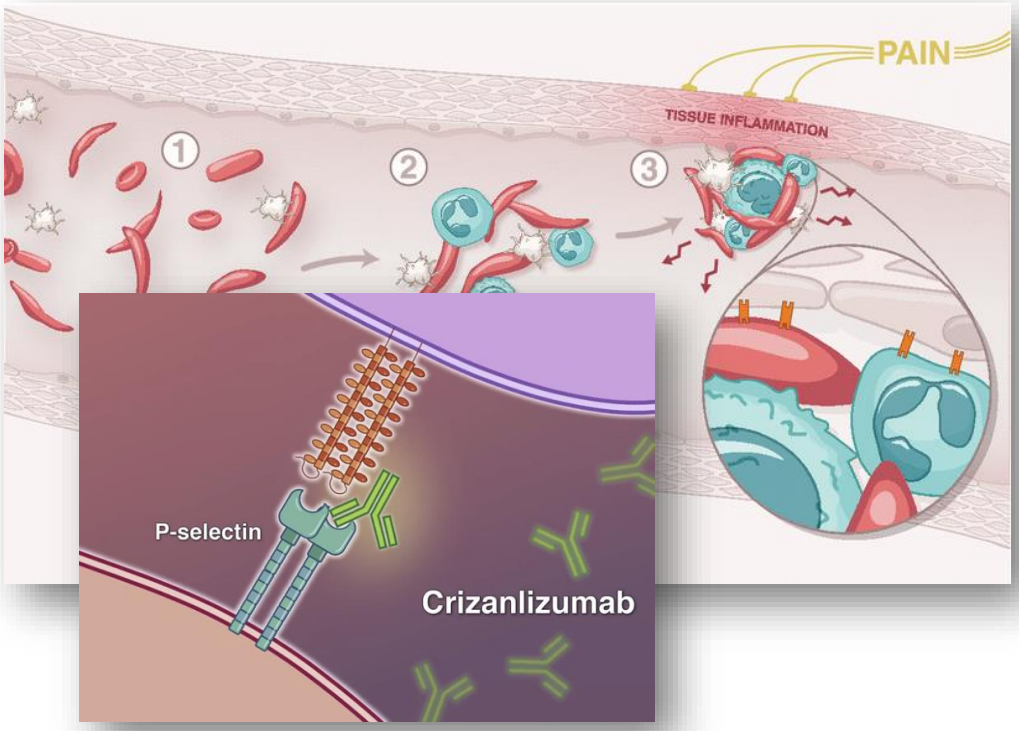
Langzeiteffekt?

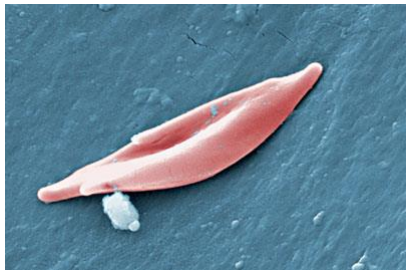
Langzeitnebenwirkungen?

Auswirkung auf Hämolyse?

Therapieadhärenz?

Bridging to HSCT?





Vielen Dank!

Kontakt

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