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# Behandlung der erworbenen Thrombotisch-Thrombozytopenische Purpura

TTP Patiententag

05.11.2021

Paul Brinkkötter | Klinik II für Innere Medizin, Uniklinik Köln

# Interessenskonflikte

**Vorträge, Beratertätigkeiten, Reiseunterstützung, Forschungsprojekte:**

| | |
|---|---|
| Alexion | Pfizer |
| Astellas | Sanofi Genzyme |
| Astra Zeneca | Travere Therapeutics |
| Bayer | Vifor |
| Novartis | |

# Klinischer Fall (46 Jahre, männlich)

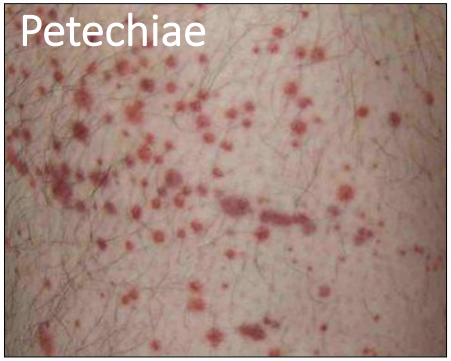
**Klinik:**

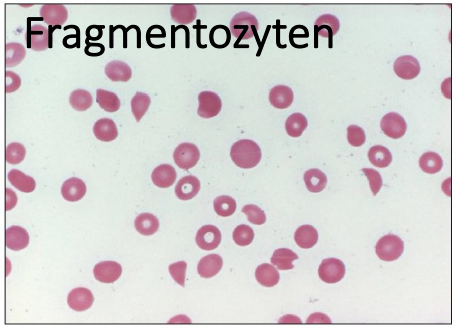
- Sklerenikterus
- Petechiale Einblutungen
- Allg. Schwäche

**Labor:**

| | |
|---|---|
| Kreatinin | 5.31 mg/dL |
| LDH | 1677 U/L |
| Haptoglobin | <0.2 g/L |
| Hämoglobin | 9.3 g/dL |
| Fragmentozyten | 6/1000 Ery |
| Thrombozyten | 3 x $10^9$/L |

**TMA**




ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aTTP, acquired thrombotic thrombocytopenic purpura; Ery, erythrocytes; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

Voelker L, et al. ADAMTS13 and VWF activities guide individualized caplacizumab treatment in patients with aTTP. Blood Adv. 2020;4(13):3093-3101.
Voelker L, et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood Adv. 2020;4(13):3085-3092



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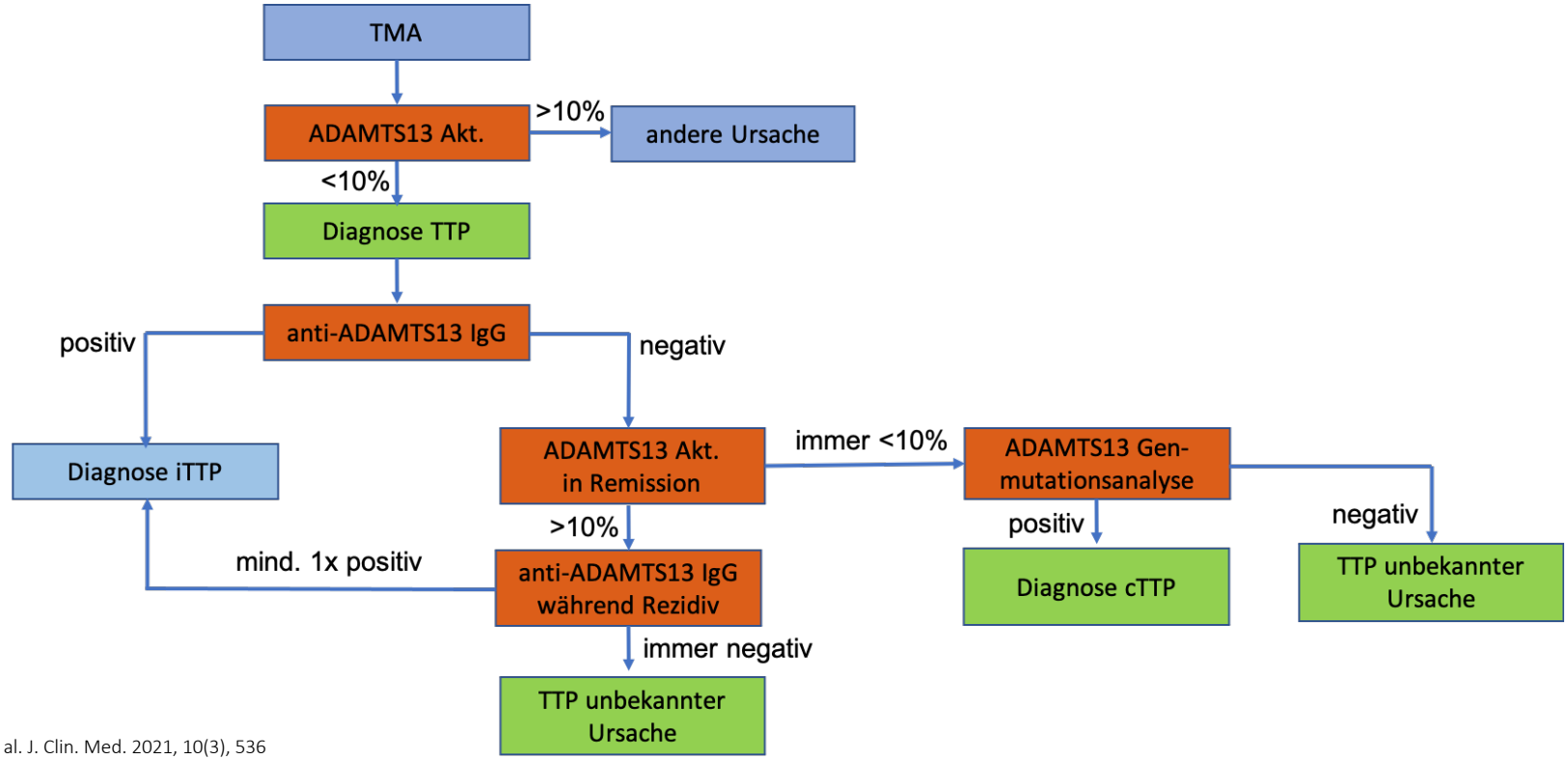
# Diagnose der TTP




Sukumar S et al. J. Clin. Med. 2021, 10(3), 536



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# Klinischer Fall (46 Jahre, männlich)

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| --- |
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| Petechiae |
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| Thrombozyten | $3 \times 10^9$/L |

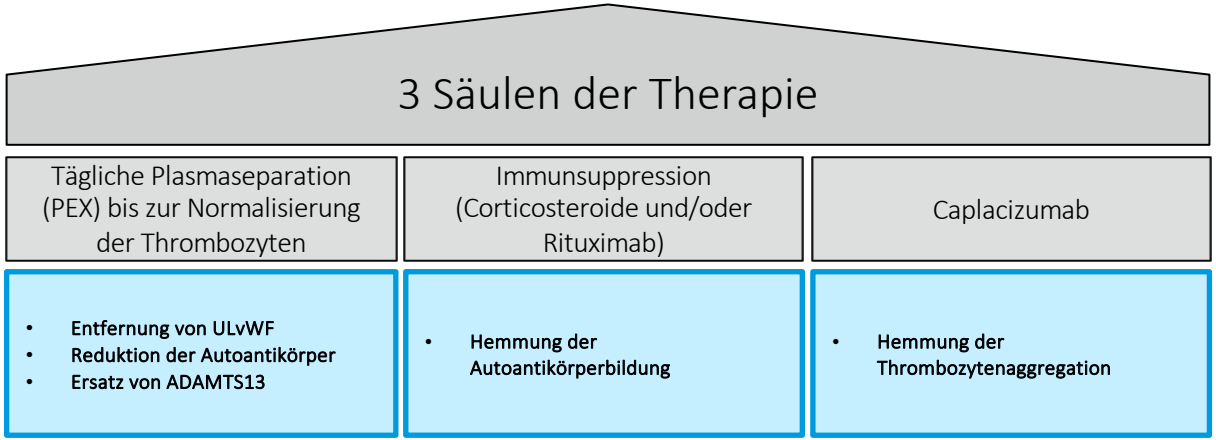
| Plasmic score | Risiko | ADAMTS13 Aktivität <10% |
| --- | --- | --- |
| **0–4** | niedrig | 4.3% |
| **5–6** | moderat | 56.8% |
| **7** | hoch | 96.2% |

Plasmic score 5

**TMA**

**TTP**
(ADAMTS13 Aktivität <0.3%)

# TTP – aktuelle Therapieoptionen




PEX: Plasmaseparation
ULvWF: Ultra-large von Willebrand Factor
ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13



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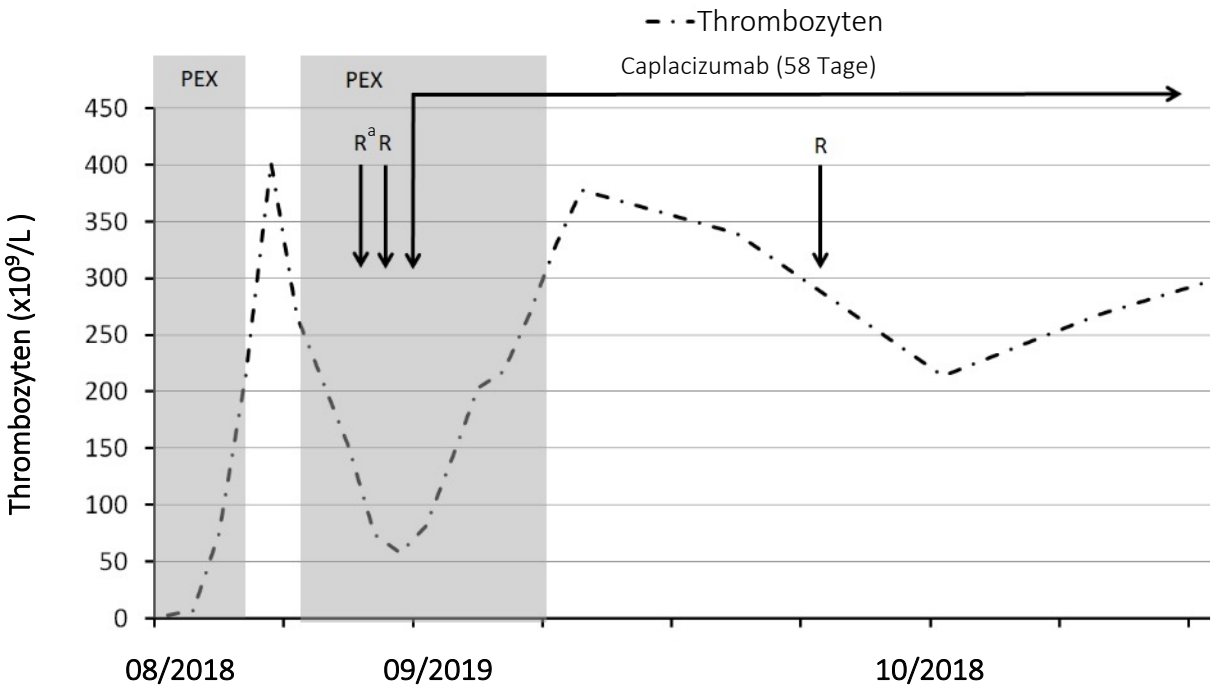
# Klinischer Fall



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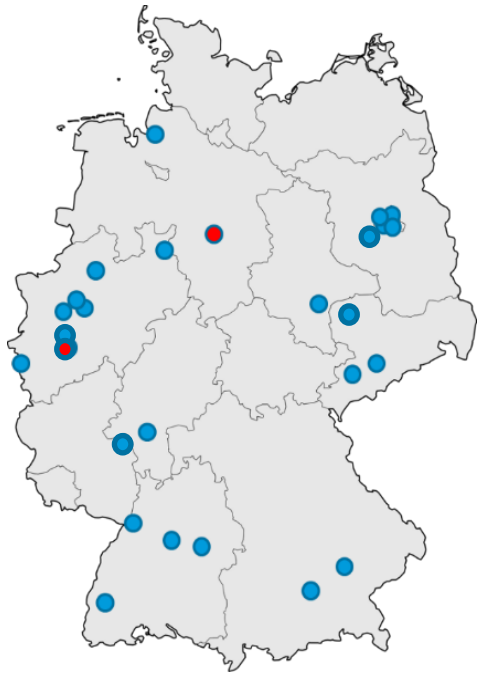
# Caplacizumab: Real-World Experience (2018–2019)

## EMA Zulassung 08/2018

## Deutschland

- Compassionate use program 09/2018
- Offizielle Markeinführung 10/2018

**Real-World Experience (12/2019: 60 Patienten)**



EMA, European Medicines Agency.



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# Caplacizumab: Real-World Experience (2018–2019)

REGULAR ARTICLE

blood advances

## Real-world data confirms the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura

Linus A. Völker,[1,2,*] Jessica Kaufeld,[3,*] Wolfgang Miesbach,[4] Sebastian Brähler,[1,2] Martin Reinhardt,[3] Lucas Kühne,[1,2] Anja Mühlfeld,[5] Adrian Schreiber,[6,7] Jens Gaedeke,[6,7] Markus Tölle,[8] Wolfram J. Jabs,[9] Fedai Özcan,[10] Silke Markau,[11] Matthias Girndt,[11] Frederic Bauer,[12,13] Timm H. Westhoff,[12,13] Helmut Felten,[14] Martin Hausberg,[14] Marcus Brand,[15] Jens Gerth,[16] Markus Bieringer,[17] Martin Bommer,[18] Stefan Zschiedrich,[19] Johanna Schneider,[19] Saban Elitok,[20] Andreas Gawlik,[20] Anja Gäckler,[21] Andreas Kribben,[21] Vedat Schwenger,[22] Ulf Schoenermarck,[23] Maximilian Roeder,[24] Jörg Radermacher,[25,26] Jörn Bramstedt,[27] Anke Morgner,[28] Regina Herbst,[28] Ana Harth,[29] Sebastian Potthoff,[30] Charis von Auer,[31] Ralph Wendt,[32] Hildegard Christ,[33] Paul T. Brinkkoetter,[1,2,†] and Jan Menne[3,†]

blood advances

## ADAMTS13 and vWF activities guide individualized caplacizumab treatment in patients with aTTP

Linus A. Völker,[1,2,*] Jessica Kaufeld,[3,*] Wolfgang Miesbach,[4] Sebastian Brähler,[1,2] Martin Reinhardt,[3] Lucas Kühne,[1,2] Anja Mühlfeld,[5] Adrian Schreiber,[6] Jens Gaedeke,[6] Markus Tölle,[7] Wolfram J. Jabs,[8] Fedai Özcan,[9] Silke Markau,[10] Matthias Girndt,[10] Frederic Bauer,[11] Timm H. Westhoff,[11] Helmut Felten,[12] Martin Hausberg,[12] Marcus Brand,[13] Jens Gerth,[14] Markus Bieringer,[15] Martin Bommer,[16] Stefan Zschiedrich,[17] Johanna Schneider,[17] Saban Elitok,[18] Andreas Gawlik,[18] Anja Gäckler,[19] Andreas Kribben,[19] Vedat Schwenger,[20] Ulf Schoenermarck,[21] Maximilian Roeder,[22] Jörg Radermacher,[23] Jörn Bramstedt,[24] Anke Morgner,[25] Regina Herbst,[25] Ana Harth,[26] Sebastian Potthoff,[27] Charis von Auer,[28] Ralph Wendt,[29] Hildegard Christ,[30] Paul T. Brinkkoetter,[1,2,†] and Jan Menne[3,†]

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# Caplacizumab: Real-World Experience (2020)



Dutt T, et al. Real-world evidence of caplacizumab use in the management of acute TTP. Blood. 2020 Nov 4:blood.2020007599. doi: 10.1182/blood.2020007599. Online ahead of print.
Coppo P, et al. A regimen with caplacizumab, immunosuppression and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. Blood. 2020 Nov 4:blood.2020008021. doi: 10.1182/blood.2020008021. Online ahead of print..v



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# Caplacizumab: Real-World Experience (Stand 2021)

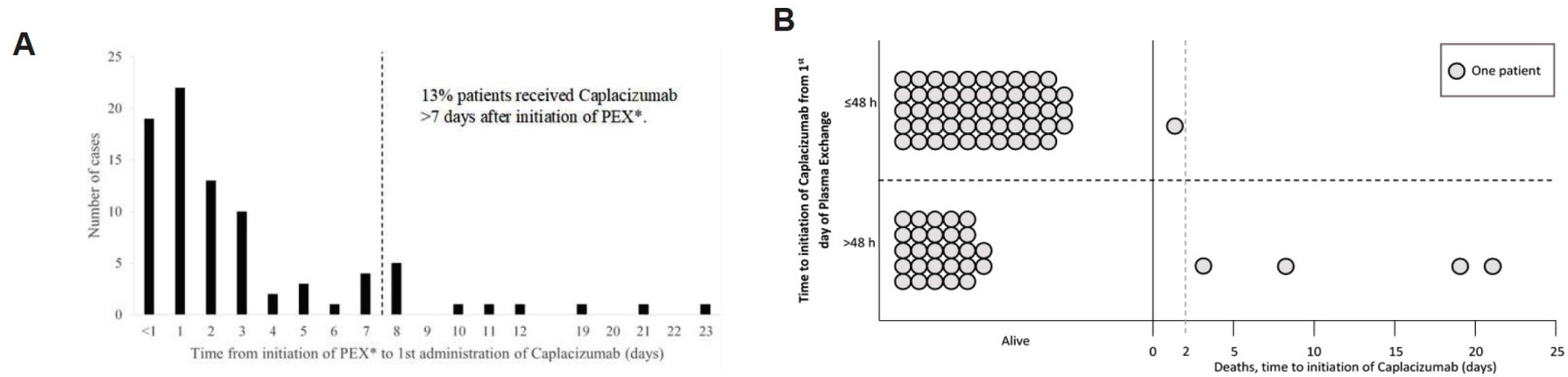
| | Deutschland[1] | GB[2] | Frankreich[3] | Phase II/III (Titan/ Hercules)[4,5] |
|---|---|---|---|---|
| **Patienten (n)** | 60 | 85 | 90 | 108 |
| **Beginn Caplacizumab (median)** | | | | |
| nach Diagnose iTTP | 3 (0-27) | - | - | - |
| nach Beginn PEX | - | 2 (1-3) | 0 (0-4) | - |
| **Thrombozyten > 150 Tsd. (Tagen)** | 3 (1-13) | 3 (2-4) | 5 (4-6) | 2.75 (2.65-2.87) |
| Exazerbationen | 3.3% | 2.3% | 3.4% | 5.6% |
| Todesfälle | 1.7% | 5.8% | 1.1% | 0 (1 während Nachbeobachtung) |

- RWE Daten bestätigen die Ergebnisse der Phase II/III Studien
- GB/D Kohorten sind retrospektive Beobachtungsstudien
- F Kohorte war eine prospektive Studie (French triple regime)

1. Voelker L, et al. Blood Adv. (2020), 2. Dutt T, et al. Blood. (2020), 3. Coppo P, et al. Blood. (2020), 4. Peyvandi F et al. N Engl J Med (2016)
5. Scully M, et al. N Engl J Med. (2019)

# Caplacizumab: Großbritannien (Dutt et al. Blood 2020)

Figure 1




Dutt T, et al. Real-world evidence of caplacizumab use in the management of acute TTP. Blood. 2020 Nov 4:blood.2020007599. doi: 10.1182/blood.2020007599. Online ahead of print.



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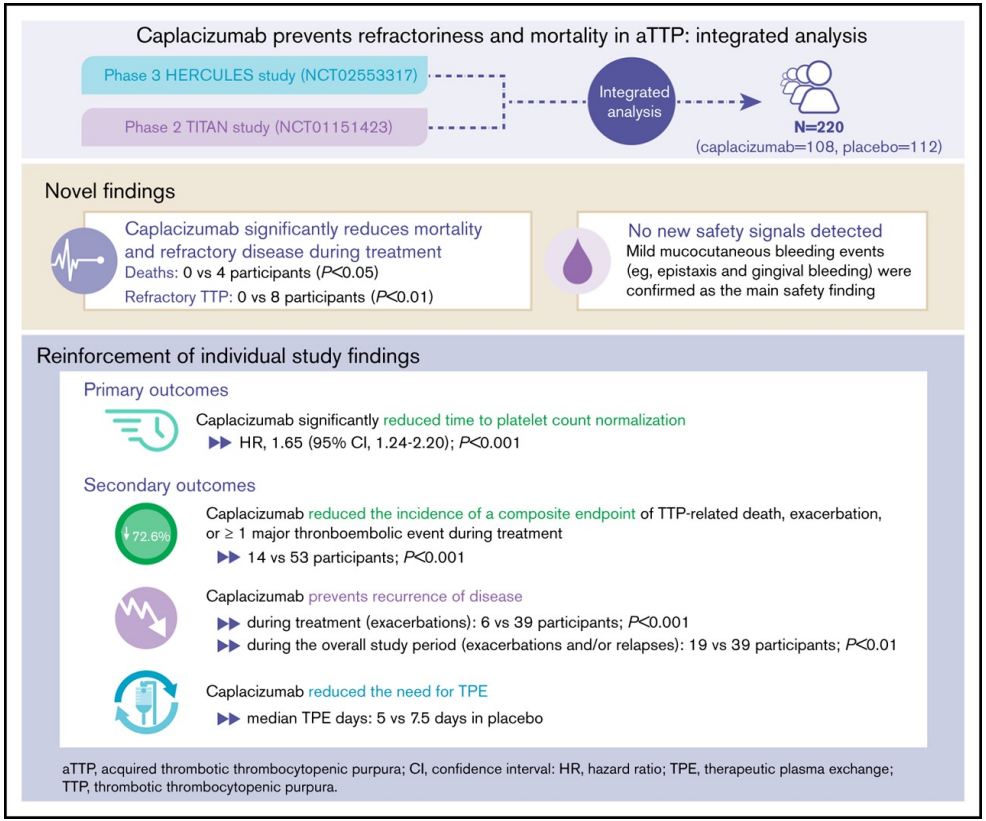
# Kombinierte Analyse der Phase II / III Studien (Titan/Hercules)




Peyvandi F et al. Blood Adv (2021)



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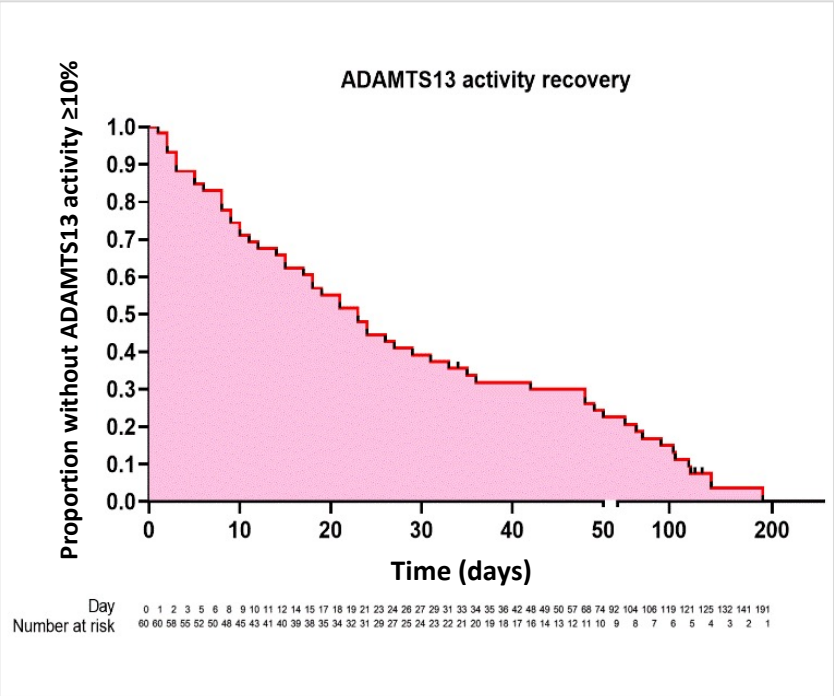
# Caplacizumab: Real-World Experience (Deutschland)




| Characteristic | German cohort 2018/2019 |
|---|---|
| **Median time until ADAMTS13 activity >10%, days after last PEX, days** | 21 |
| **ADAMTS13 activity >10% prior to day 30 after PEX, %** | 58.3 |

*From Völker L, et al. Blood Adv. 2020;4(13):3093-3101. Used with permission from The American Society of Hematology.*

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PEX, plasma exchange. [a]ADAMTS13 activity at the end of the post-PEX treatment period (including possible treatment extensions).

Völker L, et al. *Blood Adv.* 2020;4(13):3093-3101.



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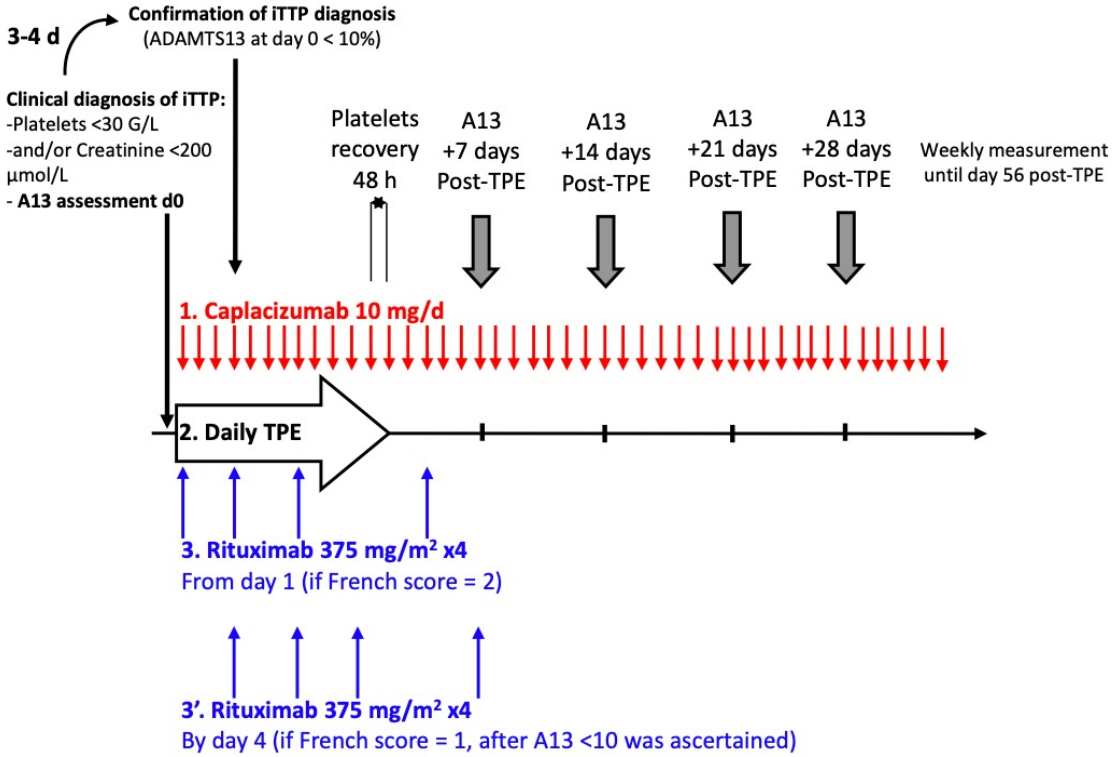
# Caplacizumab: Frankreich (Coppo et al. Blood 2020)




Coppo P, et al. A regimen with caplacizumab, immunosuppression and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. Blood. 2020 Nov 4:blood.2020008021. doi: 10.1182/blood.2020008021. Online ahead of print..



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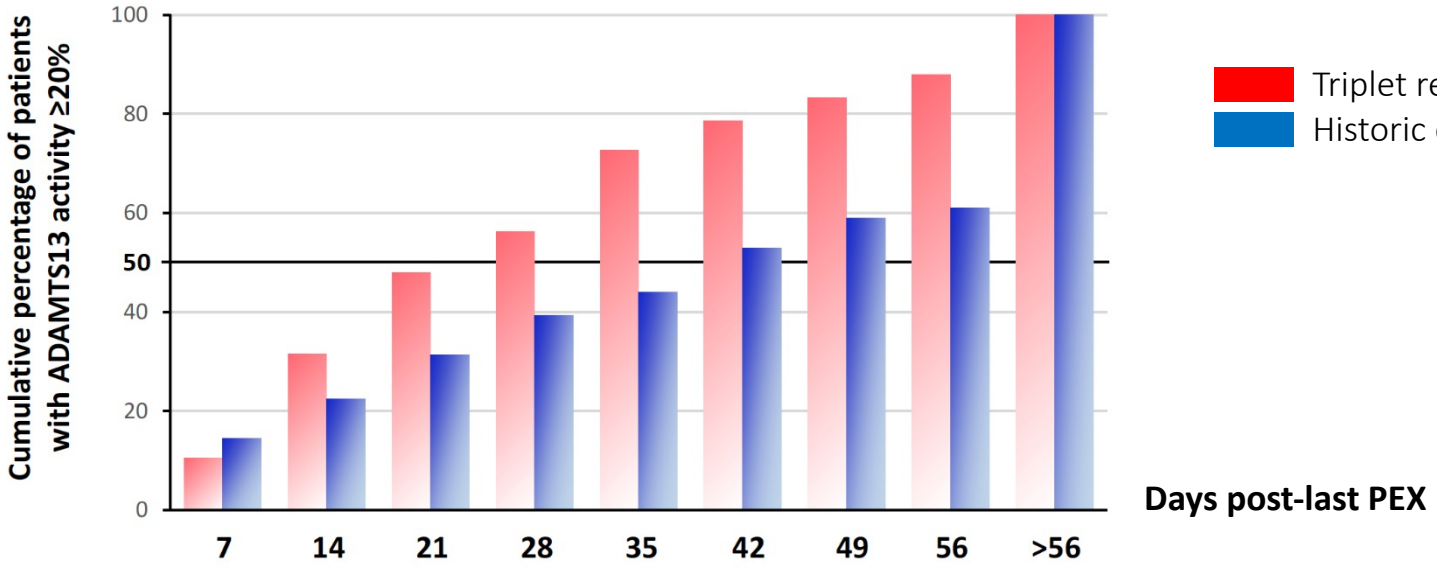
# Caplacizumab: Real-World Experience (Frankreich)




*From Coppo P, et al. Blood. 2021;137(6):733-742. Used with permission from The American Society of Hematology.*

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PEX, plasma exchange. [a]Triplet regimen comprised daily PEX, immunosuppression with corticosteroids and rituximab, and caplacizumab. [b]Historical cohort was managed with the standard regimen (ie, daily PEX and steroids in association with salvage rituximab in patients experiencing refractoriness or an exacerbation).

Coppo P, et al. *Blood.* 2021;137(6):733-742.



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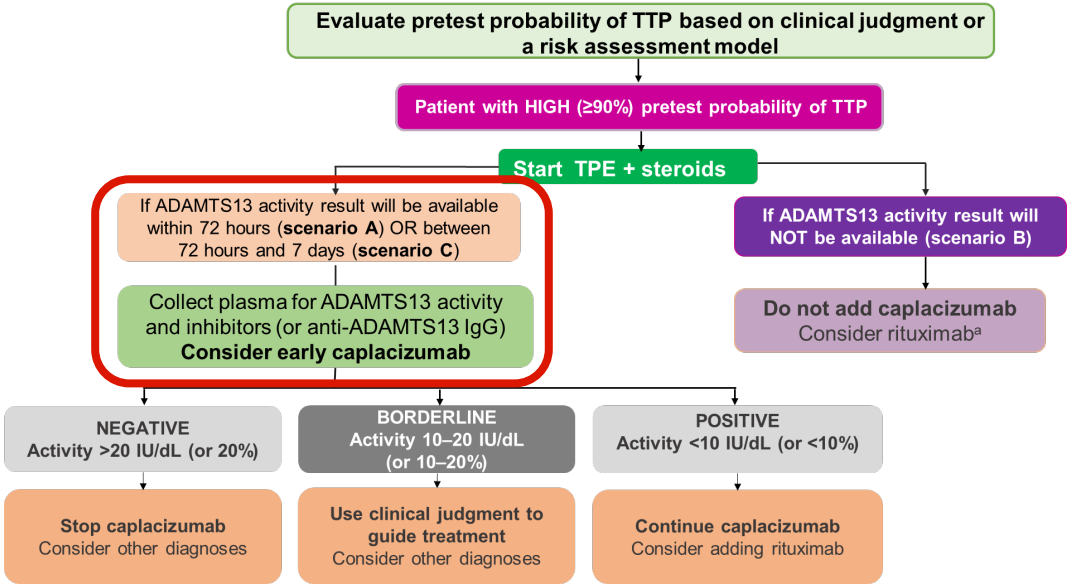
# ISTH Leitlinie zur Diagnose und Behandlung einer akuten aTTP
## Bei hoher klinischer Wahrscheinlichkeit für aTTP (≥90%)




1. Determine pretest probability of TTP using clinical judgment or a risk assessment model (PLASMIC or French score)
2. If patient has high pretest probability, begin TPE and corticosteroids
3. If timely ADAMTS13 testing is available (ideally in <72 hours; acceptable <7 days), acquire plasma samples (before initiating TPE or use of any blood product) to test for ADAMTS13 activity and inhibitor levels
4. Consider starting early caplacizumab before ADAMTS13 test results are available
5. Upon receiving ADAMTS13 test results: if positive, continue caplacizumab and consider adding rituximab; if borderline, use clinical judgment to guide treatment and consider other diagnoses; if negative, stop caplacizumab and consider other diagnoses
6. If ADAMTS13 testing is not available, do not use caplacizumab; consider rituximab

ADAMTS-13, Disintegrin und Metalloproteinase mit einem Thrombospondin-1-Motiv, Mitglied 13; aTTP, erworbene (engl. aquired) thrombotisch-thrombozytopenische Purpura; IgG, Immunoglobulin G; TPE, therapeutischer Plasma Austausch. [a]Rituximab ist nicht zugelassen zur Behandlung der TTP.
Zheng XL, et al. *J Thromb Haemost.* 17 July 2020; doi:10.1111/JTH.15006.



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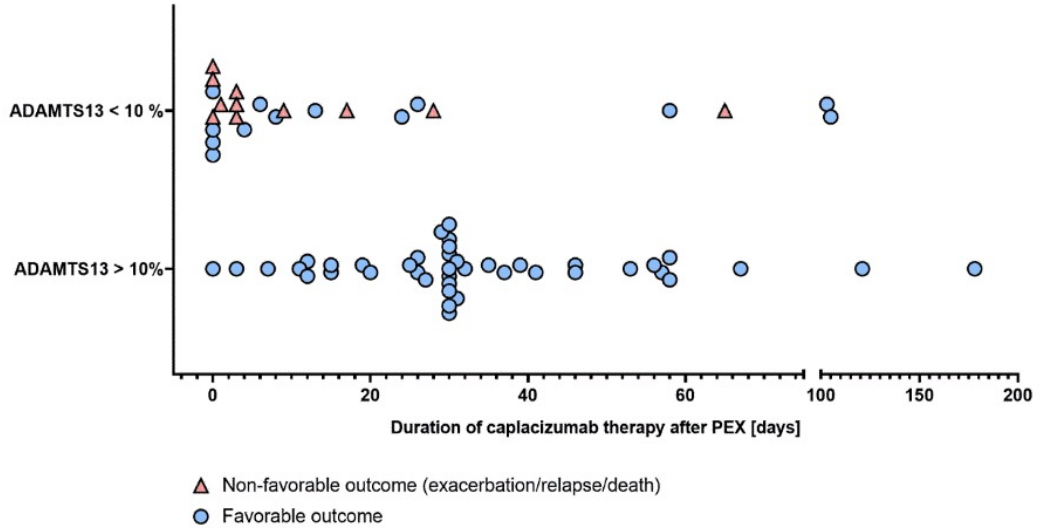
# ADAMTS13 Aktivität als Biomarker für Diagnose und Therapiesteuerung

## Patient Outcomes




All aTTP relapses occurred in patients with ADAMTS13 activity <10% at the time of stopping caplacizumab

All aTTP relapses occurred within 15 days after stopping caplacizumab

- Mean (95% CI) was 6.9 days (3.9–9.9)

*Völker L, et al. Blood Adv. 2020;4(13):3093-3101.*



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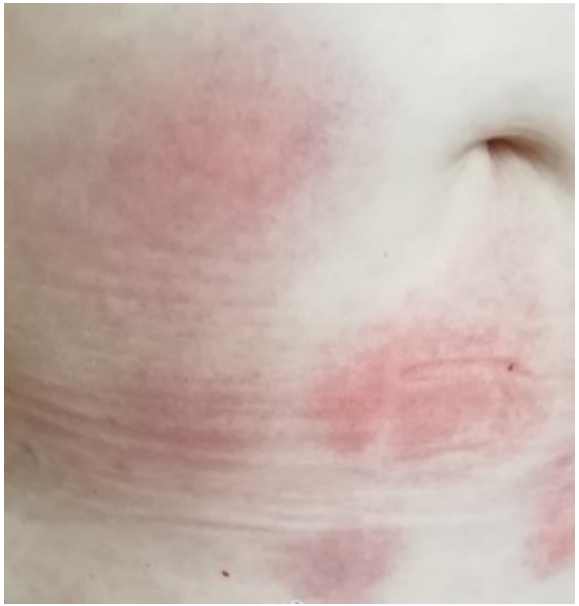
# Klinischer Fall

Tag 35: verzögerte Lokalreaktion an der Injektionsstelle mit Erythem, Pruritus und Überwärmung



Kaufeld et al. Caplacizumab: frequent local skin reaktions. Hematol. 2020 Sep 30.

# Klinischer Fall

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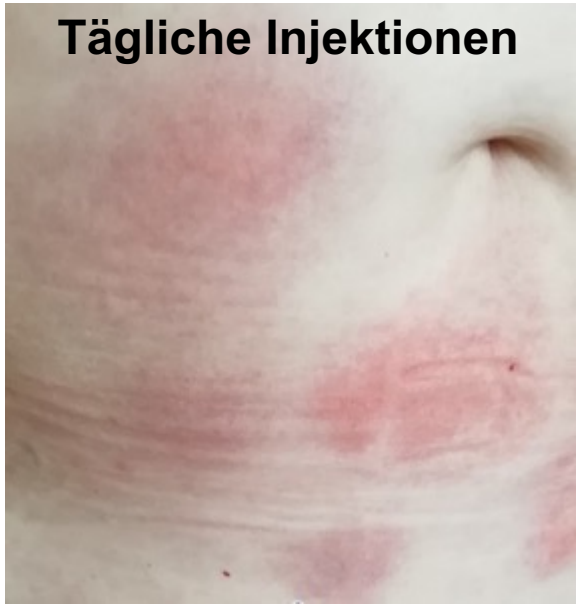


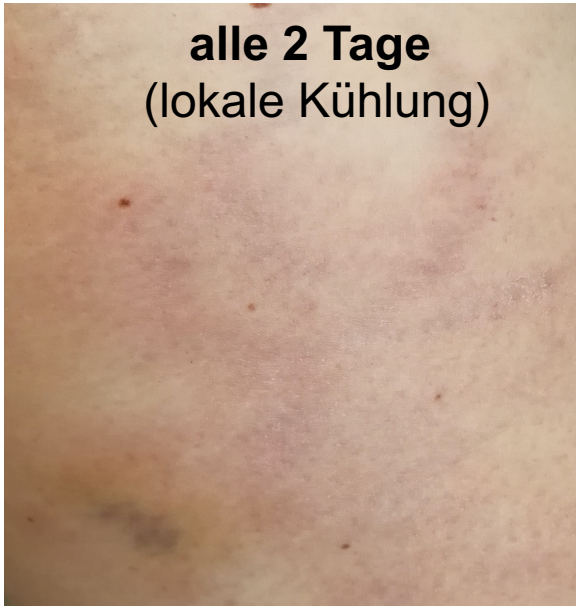


Kaufeld et al. Caplacizumab: frequent local skin reaktions. Hematol. 2020 Sep 30.



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# Klinischer Fall

| | 08/18 | 10/18 | 12/18 | 03/19 | 08/19 |
|---|---|---|---|---|---|
| ADAMTS13 Aktivität | <0.3% | <0.3% | <0.3% | 46% | 37% |

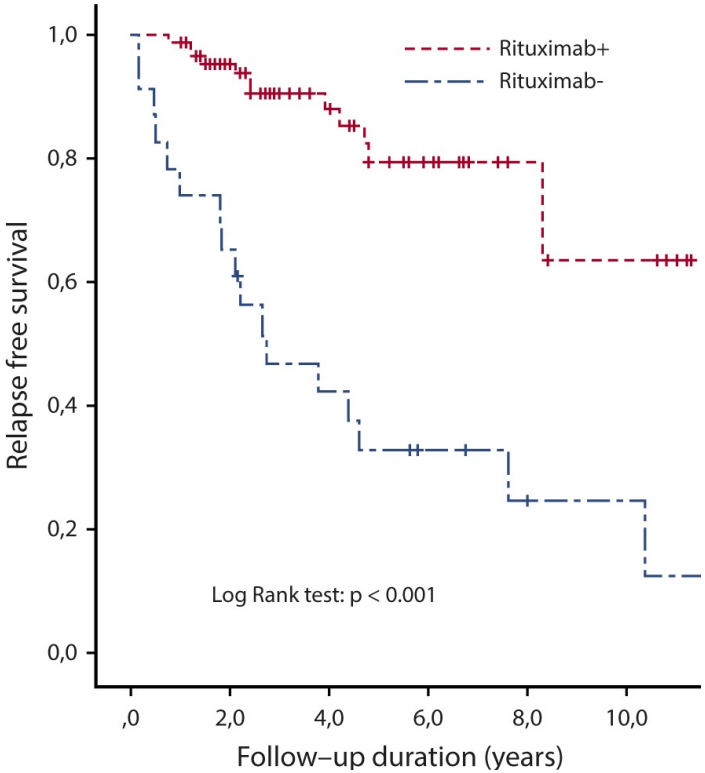
# Klinischer Fall

| | 08/18 | 10/18 | 12/18 | 03/19 | 08/19 |
|---|---|---|---|---|---|
| ADAMTS13 Aktivität | <0.3% | <0.3% | <0.3% | 46% | 37% |

| | 02/20 | 08/20 | 09/20 | 10/20 | 02/21 |
|---|---|---|---|---|---|
| ADAMTS13 Aktivität | 45% | 26% | 19% | 53% | 78% |

Rituximab

# Präemptiver Einsatz von Rituximab verhindert TTP-Episoden




Jestin ML, et al. Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. *Blood* . 2018 Nov 15;132(20):2143-2153



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# TTP – Nachsorge

- Stop PEX/Caplacizumab…
  - engmaschige Kontrolle der Thrombozyten, ADAMTS13 Aktivität (1-2-4-12 Wochen)
  CAVE: wenn ADAMTS13 <10% bei Absetzen Caplacizumab (1-2x Woche)
  - frühzeitige Gabe von Rituximab
  - Steroid-Tapering innerhalb von 1-2 Monaten
- Hohes Rezidivrisiko (30-50%), v.a. innerhalb der ersten Jahre
- Präemptive Gaben von Rituximab erwägen (ADAMTS13 Akt. <20%)
- Signifikant reduzierte Lebenserwartung
- Erhöhtes Risiko für kardio-vaskuläre Erkrankungen, Hypertonie, Depression, kognitive Defizite/dementielle Syndrome
- Assoziation von niedrig-normalen ADAMTS13 Aktivitäten mit Diabetes

# Zusammenfassung (1)

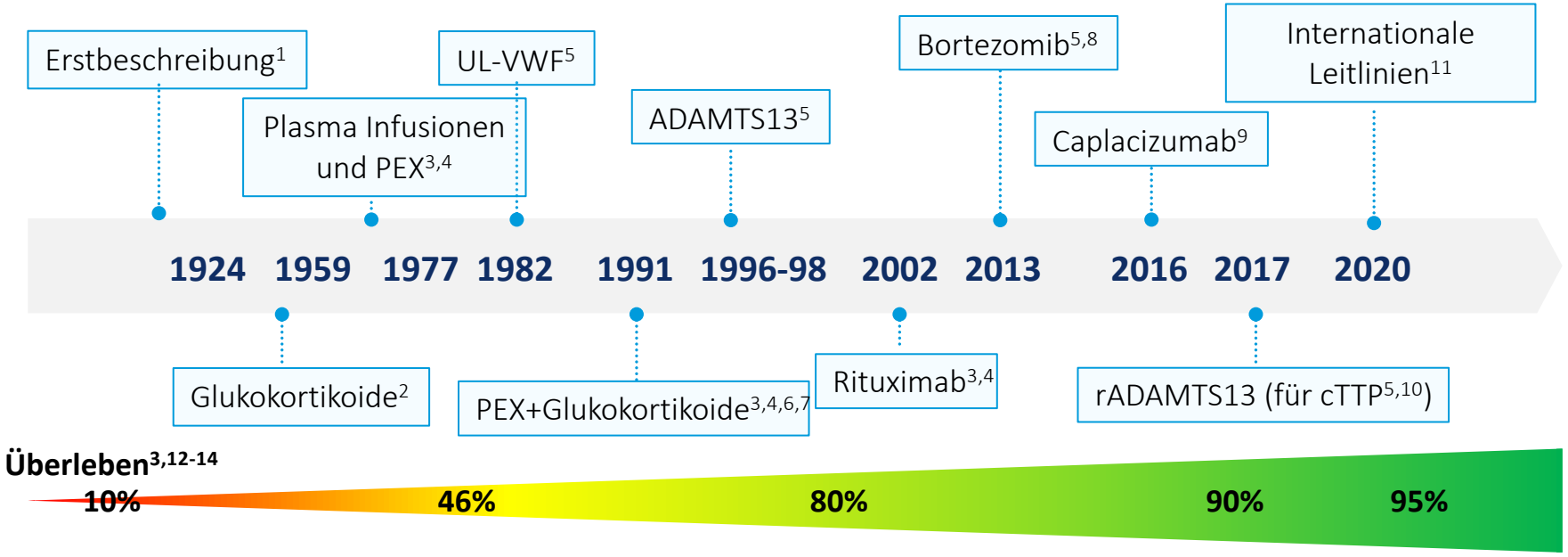
Caplacizumab
ist effektiv, deutlich schnellere Erholung der Thrombozyten

Sehr dynamisches Ansprechen der Thrombozyten

ADAMTS13 als Biomarker für Diagnose und Therapie

Präemptive Gabe von Rituximab verhindert Rezidive

# Zusammenfassung (2)




1. Moschcowitz, E. 1924; *Proc New York Path Soc* 24:21. 2. Burke HA and Hartmann RC. *AMA Arch Intern Med.* 1959;103(1):105-112. 3. George JN. *Am J Hematol.* 2012;87 Suppl 1:S88-91. 4. George JN. Blood 2021;137(6):719-720. 5. Coppo P, et al. *Res Pract Thromb Haemost.* 2018;3(1):26-37. 6. Rock GA, et al. *N Engl J Med.* 1991;325(6):393-397. 7. Bell WR, et al. *N Engl J Med.* 1991;325(6):398-403. 8. Shortt J, et al. *N Engl J Med.* 2013:368(1):90-92. 9. Peyvandi F, et al. *N Engl J Med.* 2016;374(6):511-522. 10. Scully M, et al. *Oncoscience.* 2017;4(11-12):160-161. 11. Zheng XL, et al. *J Thromb Haemost.* 2020;18(10):2496-2502. 12. Völker L, et al. *Blood Adv.* 2020;4(13):3085-3092. 13. Coppo P, et al. *Blood.* 2021;137(6):733-742. 14. Dutt T, et al. *Blood.* 137(13):1731-1740.



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# Vielen Dank!

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