



Nichts geht mehr? Die multipel-rezidierte, multiresistente ITP

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Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker	Scientific Advisory Board	Other
Novartis	X		X		X	X	
Amgen	X				X	X	
Alexion					X		
Janssen					X		
AOP					X		
Celgene/BMS							X
Sobi	X				X		
Argenx	X						
Grifols	X				X		
AstraZeneca					X		

Definition refraktäre ITP

- 2009¹: keine Response auf Standardtherapien inklusive Splenektomie
- 2016²: keine Response auf Standardtherapien ohne Splenektomie
- 2020³: keine Response auf mind. 2 Standardtherapien (Rituximab + TPO-RA), sehr niedrige Thrombozytenwerte und Blutungszeichen
- 2022⁴: anhaltend niedrige Thrombozyten trotz Ausschöpfung aller für den Patienten zu Verfügung stehenden Therapien, unabhängig von Blutungszeichen

¹Rodeghiero Blood. 2009, ²Cuker Blood 2016, ³Miltiadous Blood 2020, Vianelli Ann Hematol. 2022

Refractory immune thrombocytopenia in adults: Towards a new definition

Donald M. Arnold¹  | Bianca Clerici^{1,2} | Ekaterina Ilicheva³ | Waleed Ghanima^{4,5,6}

- 20 ITP Experts of Cooperative ITP Study Group in September 2022 answered a web-based survey:
“95% felt that there was a need for a new definition of refractory ITP for clinical and research purposes”
 - anhaltende Thrombozytopenie < 20 Gpt/l und Blutungszeichen
 - refraktär auf Rituximab, 2 TPO-RAs und 1 Immunsuppressivum
 - nur kurzes Ansprechen (< 7 Tage) auf IVIG oder Steroid

Häufigkeit der refraktären ITP - In Abhängigkeit von der Definition

Patient group	McMaster ITP registry	Norwegian ITP registry
ITP patients in the Registry	N= 531 including primary (n=408) and secondary ITP (n=123)	N=255 including primary (n=236) and secondary ITP (n=19)
First-line therapy ^a + any second-line ^b therapy	225 (42%)	116 (45.5%)
First-line therapy + rituximab + TPO-RA	40 (7.5%)	28 (11%)
First-line therapy + rituximab + TPO-RA + splenectomy	25 (4.7%)	8 (3.1%)
First-line therapy + rituximab + TPO-RA + any immune suppressant medication ^c	30 (5.6%)	4 (1.6%)
First-line therapy + rituximab + TPO-RA + any immune suppressant medication + splenectomy	20 (3.8%)	1 (0.4%)

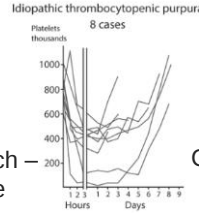
Der (multi-)refraktäre ITP Patient

- ✓ Fehldiagnose - Re-Diagnostik erforderlich (!!!)
- ✓ Medikamententoxizität (Steroid!)
- ✓ hat ein hohes Risiko für Blutungen und Infektionen
- ✓ Reduzierte Lebensqualität

Hohe
Morbidität
und
Mortalität

„The **mortality** among refractory patients (n=37) defined as unresponsive to splenectomy, RTX, 2 TPO-RAs was 14%, all patients had been hospitalized more than once, 24% had been admitted to an intensive care unit, and 40% had developed at least one infection“

ITP – Timeline^{1,2,3,4,5}



1950
Harrington Selbstversuch –
Autoimmune Genese

2003
Gehemmte Thrombopoese
nachgewiesen

2016
Studie DEX vs. PSL

2025
Ph3 - Ianalumab

1735
Purpura
haemorrhagica

1960-2000
Azathioprin, CSA, MMF

2009
Zulassung Romiplostim

2020
Zulassung Fostamatinib

1951
Kortisonbehandlung Case
Report

2006
Erste Rituximab Studie

2019
Zulassung Avatrombopag

2024
Ph3 - Rilzabrutinib
PH2 - Ianalumab

1916
Erste Splenektomie
durchgeführt

1980
Immunglobuline Case
Report

2010
Zulassung Etrombopag

2022
Ph3 - Efgartigimod /
Ph2 - Rilzabrutinib

1 Aktuelle Onkopedia-ITP-Leitlinie; <https://www.onkopedia.com/de/onkopedia/guidelines/immunthrombozytopenie- itp/@@guideline/html/index.html>
2 Fachinformation Nplate®; Aktueller Stand.
3 Fachinformation Revolade®; Aktueller Stand.
4 Fachinformation Doptelet®; Aktueller Stand.
5 Fachinformation Tavalles®; Aktueller Stand.

Markers of refractoriness to ITP treatments

splenectomy

- Older age
- Multiple previous lines of treatment
- Absence of previous response to corticosteroids and IVIg (debated)
- Low peak of platelet count after splenectomy
- Hepatic/mixed platelet sequestration on Indium-labeled autologous platelet study

rituximab

- Older age and male sex ? (debated)
- Chronic ITP (one study)
- Absence of previous response to corticosteroids (one registry)
- Absence of antinuclear antibodies (one study)

TPORAs

- Chronic ITP (debated)
- Previous splenectomy (debated)
- High TPO level in serum (debated)
- Complement activation (one study)

fostamatinib

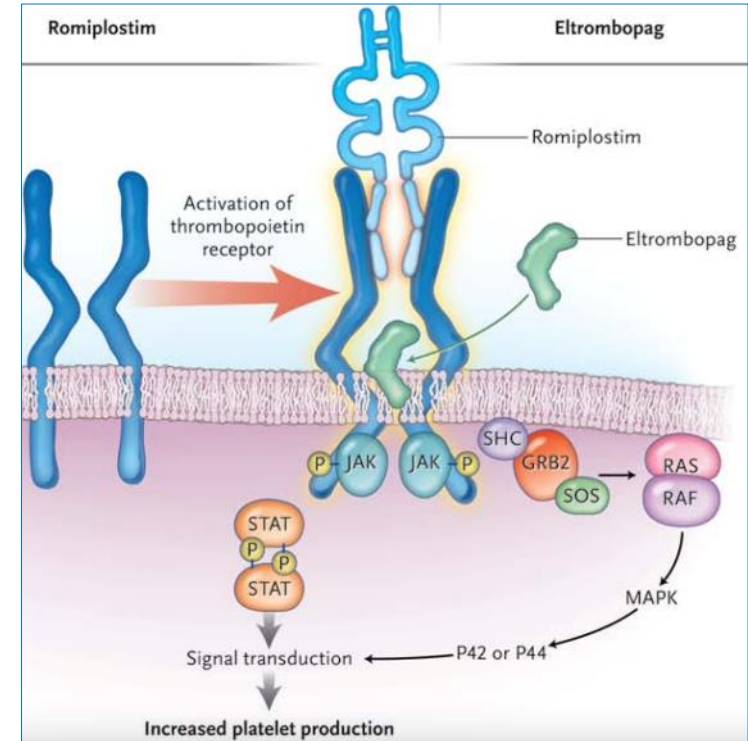
- Used as >2nd line of treatment ? (one study)

multirefractory

- Bleeding at ITP diagnosis
- Absence of response to corticosteroids (one study)
- Presence of gammopathy of unknown significance (one study)

Thrombopoietin Receptor Agonists (TPO-RAs)

- Problem der Adhärenz
 - Orale Einnahme vs s.c. Gabe
 - Wirksamkeitsreduktion durch Nahrungsmittel
- Verschiedene Ansatzpunkte am Rezeptor
 - > Keine Kreuzresistenz

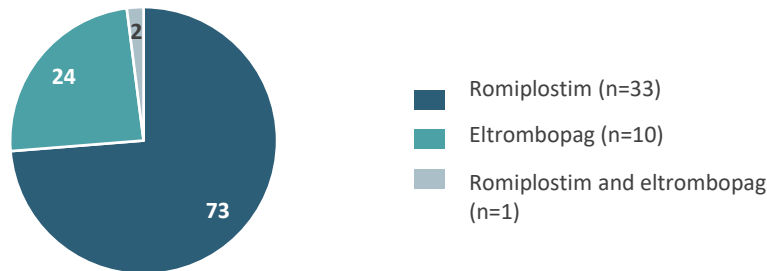


Imbach P et Crowther M. *N Engl J Med* 2011;365:734-41.

Adults with immune thrombocytopenia who switched to avatrombopag following prior treatment with eltrombopag or romiplostim: A multicentre US study

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Susie Lee⁵ | Matthew Wojdyla⁶ | Michael Vredenburg⁶ | Adam Cuker⁷

Type of treatment patients switched from prior to avatrombopag treatment (% of group; N=44)



N=44 patients with cITP
median (range) age of 61
52% female
mean ITP duration of **8.3 years**

Switched due to:

52%

23/44 patients

convenience



32%

14/44 patients

lack of effectiveness



16%

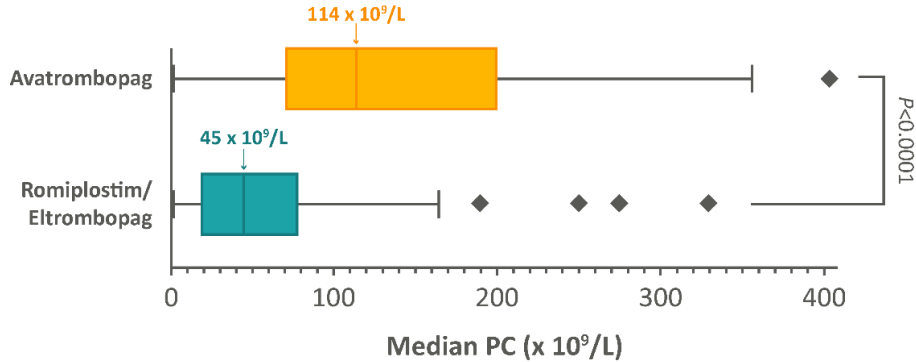
7/44 patients

adverse events

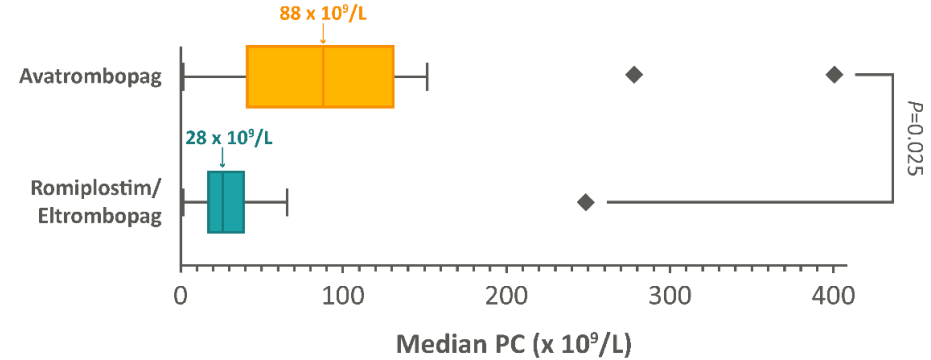


Platelet response after switching to avatrombopag from romiplostim or eltrombopag

Median Platelets, all patients (N=44)



Median Platelets, patients who switched due to ineffectiveness of romiplostim/eltrombopag (n=14)





POSTER 2596. AVATROMBOPAG PLUS FOSTAMATINIB# COMBINATION EFFICACY AND SAFETY IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA

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INTRODUCTION

Avatrombopag (AVA) is a **thrombopoietin receptor agonist (TPO-RA)**, approved for the treatment of immune thrombocytopenia (ITP), as second line in subjects with chronic ITP unresponsive to other treatments. At day 8, 65% patients present a **response** and global response rate of AVA is 69% with a mean duration of 12.4 weeks in its pivotal study¹.

Combination of TPO-RA plus immunosuppressive or immunomodulatory drugs could optimize treatment results in ITP, addressing different pathophysiological pathways². The most widely used immunomodulatory drugs in these circumstances are steroids, azathioprine and mycophenolate. **Fostamatinib (FOS)** is a splenic tyrosine kinase (SYK) inhibitor. FOS blocks the cascade of signals mediated by SYK after the activation of FcγRs, reducing macrophage activity, proliferation of B lymphocytes and production of antibodies³.

AIM

We present the experience in the **combined use of AVA with fostamatinib** in **non-responders to this TPO-RA**, an experience not reported to date.

RESULTS

In the period of time evaluated, **a total of 55 patients received treatment with AVA** in both Centers. The Norwegian data was acquired from the Norwegian ITP registry. In **16 of 55 patients**

(29%), there was no response after 2 or more weeks with AVA 280 mg weekly. **In 6 of these patients, FOS was combined with AVA** at a dose of 280mg weekly. Table 1. describes the characteristics of the 6 patients treated with the combination. Median time from initiation of AVA to combination with FOS was 14 days (Range: 14-21 days). **The overall response of the combination was 100% (1 R, 5 CR).**

Median time to R was 25 days (Range: 3-42 days) and to CR 31 days (Range: 4-153 days). Table 2 describes the characteristics of each patient's response. With a median follow-up from the start to last follow up of treatment in combination was 212 days (Range: 45-313 days), no relapse has been identified. Tapering of AVA and/or FOS was attempted in 5 patients by reducing the dose of FOS in 1 patient and the dose of AVA in 4. In patients 1 and 4, AVA was stopped, but this resulted in drop in the platelets counts. CR was achieved after reintroduction of AVA in combination.

With regard to toxicity, in the 6 patients treated with the combination AVA plus FOS, only two adverse events were described, both of them non-serious. One case of headache encountered with the use of AVA, before the initiation of FOS. The other event, was WHO grade 2 liver toxicity attributed to AVA. **Hypertransaminasemia** was resolved after the interruption of **avatrombopag** for 6 days and reduction of AVA from 140mg to 60mg weekly.

Table 1. Patients Characteristics

Patient	Sex	Age (years)	Phase of ITP	Lines of treatment before AVA	Treated with TPO-RA before AVA	Treated with EIT	Treated with RCM
1	Women	22	Chronic	4	No	No	No
2	Man	28	Persistent	5	Yes	No	Yes, R***
3	Women	24	Chronic	4	Yes	Yes, R	Yes, CR*
4	Man	66	Chronic	4	Yes	No	Yes, CR**
5	Man	58	Chronic	5	Yes	No	Yes, R***
6	Man	45	Chronic	5	Yes	Yes	Yes, R***

Patient	Initial weekly dose of FOS* (mg)	Type of Response	Time from combination to platelets >30x10 ⁹ /L (days)	Time from combination to platelets >50x10 ⁹ /L (days)	Follow up since combination start (days)	Last weekly dose of FOS (mg)	Last weekly dose of AVA (mg)	Platelet count in last visit (x10 ⁹ /L)
1	1400	CR	3	5	45	1400	60	383
2	2100	CR	42	112	313	2100	280	145
3	1400	CR	4	4	232	1400	60	160
4	2100	CR	24	31	159	700	60	102
5	2100	R	26	NCR	277	2100	280	44
6	2100	CR	32	153	192	2100	140	129

*Initial weekly dose of FOS (mg) was 280mg. **Response between 60-100 days. ***Response between 100-150 days. ****Response between 150-200 days. *****Response between 200-250 days. *****Response between 250-300 days. *****Response between 300-350 days. *****Response between 350-400 days. *****Response between 400-450 days. *****Response between 450-500 days. *****Response between 500-550 days. *****Response between 550-600 days. *****Response between 600-650 days. *****Response between 650-700 days. *****Response between 700-750 days. *****Response between 750-800 days. *****Response between 800-850 days. *****Response between 850-900 days. *****Response between 900-950 days. *****Response between 950-1000 days. *****Response between 1000-1050 days. *****Response between 1050-1100 days. *****Response between 1100-1150 days. *****Response between 1150-1200 days. *****Response between 1200-1250 days. *****Response between 1250-1300 days. *****Response between 1300-1350 days. 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Avatrombopag Plus Fostamatinib Combination Efficacy and Safety in Patients with ITP – Results

Efficacy

- Median time from initiation of avatrombopag to combination with FOS was 14 days (Range: 14-21 days).
- The **overall response of the combination was 100% (1 R, 5 CR)** with the **median time to R of 25 days** (Range: 3-42 days) and to CR of 31 days (Range: 4-153 days).
- With a median follow-up from the start to the last follow-up of treatment in combination of 212 days (Range: 45-313 days), **no relapse was identified**.

Safety

- In the 6 patients treated with the combination avatrombopag plus fostamatinib[#], **only two adverse events were described, both were non-serious**.
- One case of **headache** encountered with the use of avatrombopag, before the initiation of FOS.
- One **WHO grade 2 liver toxicity** attributed to avatrombopag. Hypertransaminasaemia

Patient	Initial weekly dose of FOS [#] (mg)	Type of response	Time from combination to platelets > 30x10 ⁹ /L (days)	Time from combination to platelets > 100x10 ⁹ /L (days)	Follow-up since combination start (days)	Last weekly dose of FOS [#] (mg)	Last weekly dose of AVA (mg)	Platelet count at last visit (x10 ⁹ /L)
1	1400	CR	3	5	45	1400	60	383
2	2100	CR	42	112	313	2100	280	145
3	1400	CR	4	4	232	1400	60	160
4	2100	CR	24	31	159	700	60	102
5	2100	R	26	NCR	277	2100	280	44
6	2100	CR	32	153	192	2100	140	129

Avatrombopag Plus Fostamatinib Combination Efficacy and Safety in Patients with ITP – Conclusions

Authors Conclusion

- In subjects with a lack of response to thrombopoietin analogues, the combination with immunosuppressants is an alternative to consider.
- The combination of avatrombopag and fostamatinib [#] was shown to be effective and safe, although longer series are needed to support the presented data.

My Conclusion

- Interesting therapy concept for multirefractory patients:
 - 2 weeks Avatrombopag -> combination with Fostamatinib

CASE III - 65-YEAR-OLD WOMAN

Immune thrombocytopenia, first diagnosis 12/2013

- WHO bleeding grade 0, thromb. 5 Gpt/l
- Prednisone McMillan 1mg/kg – complete remission

- **Thromboembolic events:**

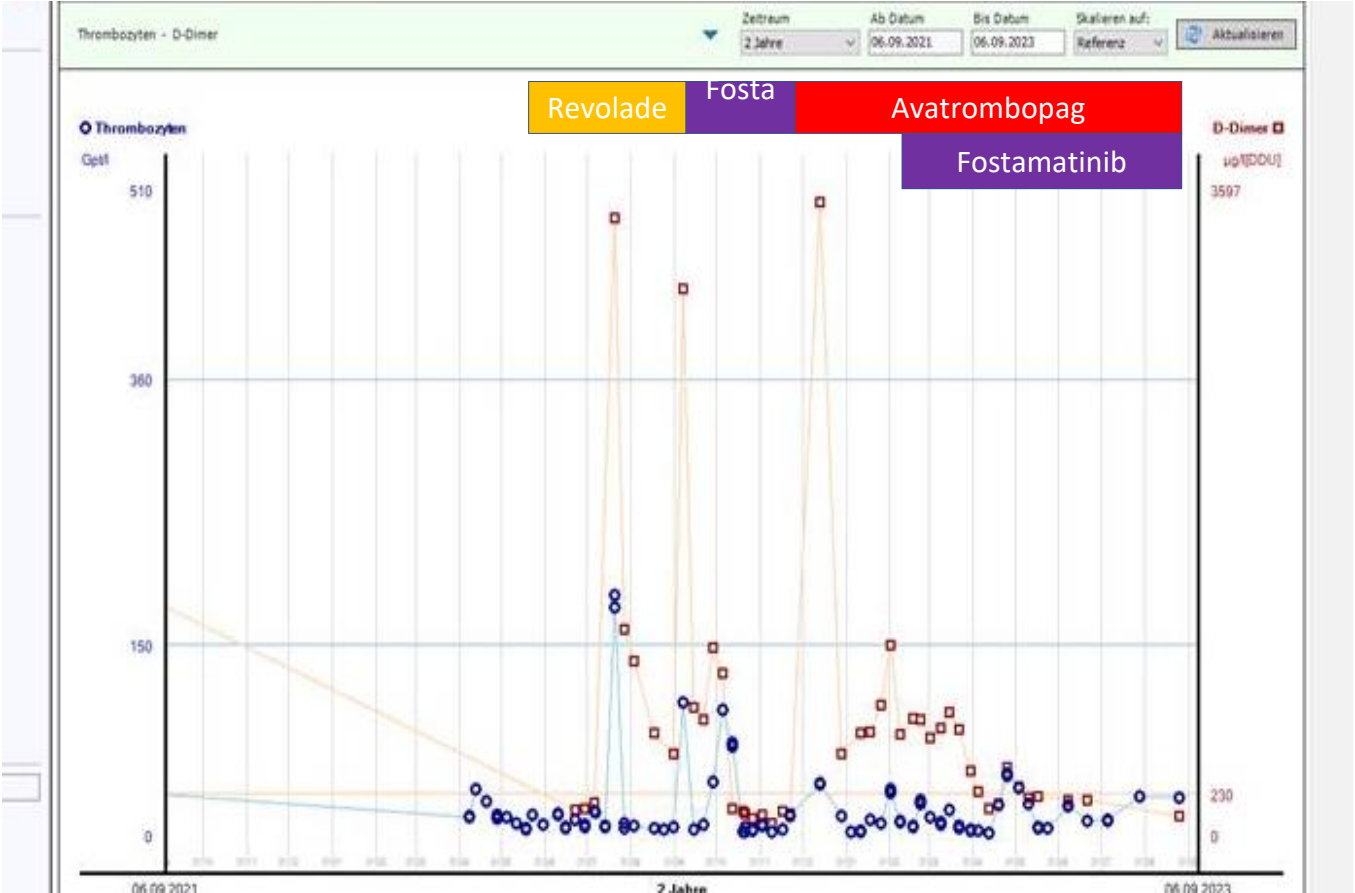
- Sinus vein thrombosis '2012
- DVT and pulmonary embolism '2015
- 2015: low molecular weight heparin -> subsequently rivaroxaban

CASE III - 65-YEAR-OLD WOMAN

- Relapse: 12/17 Thromb. 7 Gpt/l
 - start PSL 100 mg TD, Maintenance therapy alternating 5 - 40 mg
- 04/19 Influenza Infection : Thromb. 39 Gpt/l -> Prednisolone 50mg
- 02/20 Thromb. drop to 12 -> 70g Ivlg
 - no Prednisolone due to gastritis and mood disorder
- 03/20 - 04/20 4x Rituximab (weekly)
- 10/20 Splenectomy
- 04/22 Platelet drop since July 2021, Thromb.10g Gpt/l, Rivaroxaban stopped

What now?

CASE III - 65-YEAR-OLD WOMAN



„Klassische“ Immunsuppressiva¹

Azathioprin	Dosierung 1mg/kg/Tag -> 2mg/kg/Tag Die Therapie spricht langsam an und sollte mindestens 3–4 Monate gegeben werden. Ansprechraten 30-40%² Neutropenien sind häufig (ca. 30%)
Cyclosporin A	Ein CSA-Zielspiegel von 150–400 ng/mL wird angestrebt - 3-5 mg/kg/Tag Die Therapie spricht langsam an und sollte mindestens 2–3 Monate gegeben werden Nur Fallserien publiziert. Häufige Nebenwirkungen sind Erschöpfung, Schwäche, Niereninsuffizienz, Hypertonie, Neuropathie
Mycophenolat-Mofetil (MMF)	Zur besseren Verträglichkeit beginnt man in der Regel mit einer niedrigen Dosis und steigert dann langsam - 500mg/Tag -> 1g/Tag Ansprechraten 30-50%³ Häufig sind gastrointestinale Nebenwirkungen wie Übelkeit, Appetitlosigkeit, Durchfall, Erbrechen

¹Matzdorff et al. Oncol Res Treat 2022

²Mishra K et al. Am J Blood Res. 2021

³Abdelwahab OA et al. Clin Rheumatol. 2024

PERSPEKTIVEN IN DER BEHANDLUNG DER REFRAKTÄREN ITP

Fcn-Rezeptor-Inhibitoren

- Efgartigimod i.v.
 - Zulassung möglich, s.c. Studien negativ

BTK-Inhibitoren

- Rilzabrutinib
 - Phase 2 positiv, Phase 3 - Plenary ASH 2024

BAFF-Rezeptor Antikörper

- Ianalumab
 - 1st/2nd line - Phase III ongoing; >2nd line - ASH 2024

Komplementinhibitoren

- Sutimlimab
 - PH2 positiv - aber keine Weiterentwicklung geplant
 - Fatigue und ggf. bei C3, C4, and CH50 Mangel ??

CAR-T-Zelltherapie

- Erste pos. Heilversuche, pos. Studie China - ASH 2023



Koneczny I, Herbst R. Cells. 2019;8(7):671

Since 2022 - German ITP-Registry

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PD Dr. med. Oliver Meyer

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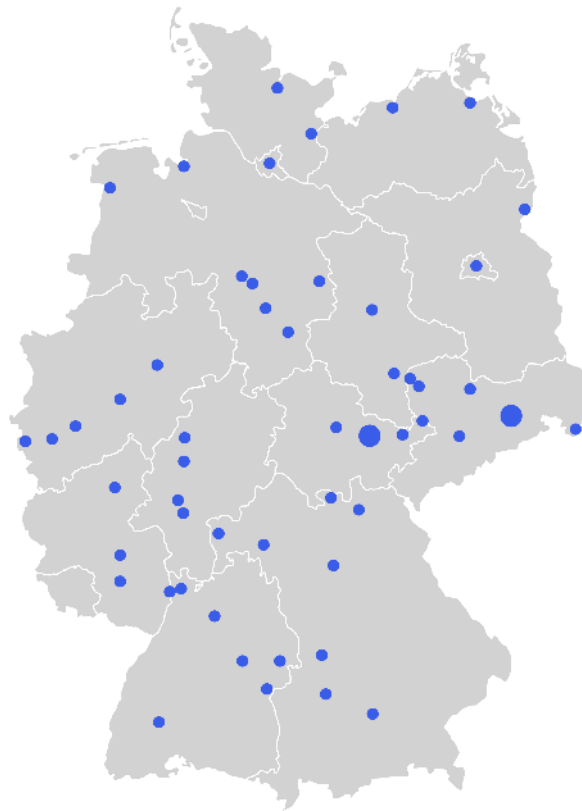
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