

<https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club>

The weekly Clinical Journal Club by Dr. Friedrich C. Luft

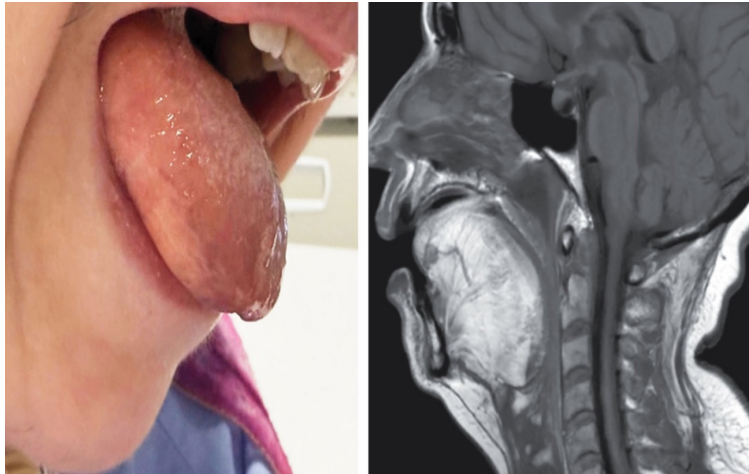
Usually every Wednesday 17:00 - 18:00



Klinische Forschung

Experimental and Clinical Research Center (ECRC) von MDC und Charité

Als gemeinsame Einrichtung von MDC und Charité fördert das Experimental and Clinical Research Center die Zusammenarbeit zwischen Grundlagenwissenschaftlern und klinischen Forschern. Hier werden neue Ansätze für Diagnose, Prävention und Therapie von Herz-Kreislauf- und Stoffwechselerkrankungen, Krebs sowie neurologischen Erkrankungen entwickelt und zeitnah am Patienten eingesetzt. Sie sind eingeladen, uns beizutreten. [Bewerben Sie sich!](#)



Physical examination of the tongue showed macroglossia. Owing to clinical suspicion of an underlying metabolic myopathy, enzymatic and genetic tests were done. Enzymatic activity of acid α -glucosidase in leukocytes was low, and genetic testing identified compound heterozygosity for pathogenic variants in GAA. A diagnosis of late-onset Pompe disease, an autosomal recessive lysosomal disorder that manifests as a skeletal myopathy, was made.

A 54-year-old woman presented with a 4-month history of progressively worsening asthenia and falls and 5 days of dyspnea. On exam, there was also head drop and mild symmetric weakness of the proximal upper and lower limbs. The creatine kinase level was 373 U per liter (reference range, 24 to 173). Magnetic resonance imaging of the head and cervical spine was notable for fatty infiltration of the tongue and paravertebral muscles. Which of the following is the most likely disease category?

Age-related sarcopenia

Cervical myelopathy

Hypercholesterolemia

Infectious myositis

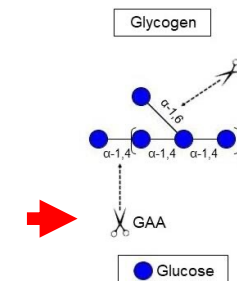
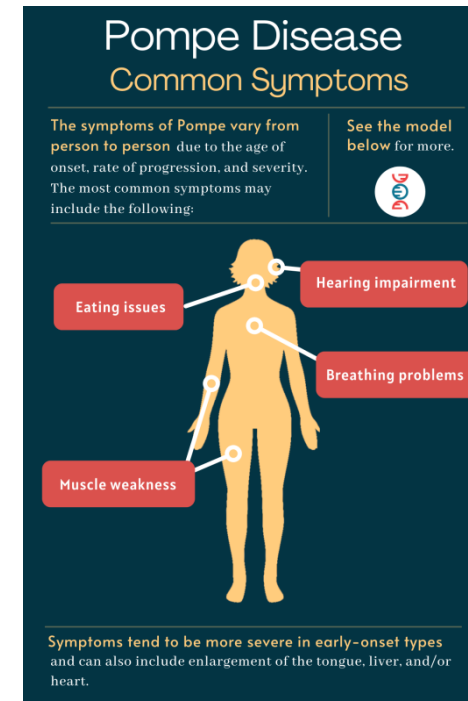


Lysosomal storage disease

Die **Late-Onset Pompe Disease (LOPD)**, auch spätsicherer oder adulter Morbus Pompe genannt, ist eine seltene, vererbte Stoffwechselkrankheit, bei der sich Zucker (Glykogen) in den Muskelzellen ansammelt.

Was ist LOPD?

- **Ursache:** Ein Mangel oder Defekt des Enzyms *saure Alpha-Glukosidase* (GAA). Das Gen dafür ist verändert.
- **Ablauf:** Der Körper kann Glykogen in den Zellbläschen (Lysosomen) nicht richtig abbauen. Dadurch schwellen die Zellen an und die Muskeln werden über die Zeit geschwächt.
- **Unterschied zur Babyform:** Im Gegensatz zur schweren infantilen Form (IOPD), die im ersten Lebensjahr auftritt, bricht LOPD erst im Jugend- oder Erwachsenenalter aus.



BCL11A ist ein Protein-codierendes Gen auf Chromosom 2, das als wichtiger Transkriptionsfaktor die Blutbildung und die Entwicklung des Gehirns steuert.

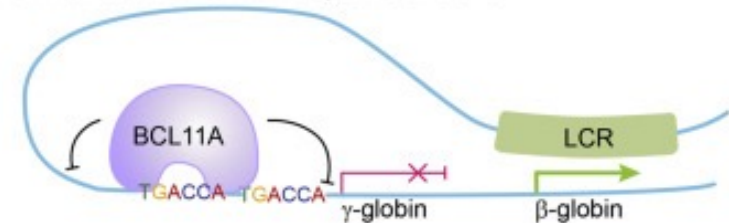
Funktion und Bedeutung

- **Hämoglobin-Schalter:** BCL11A steuert den Wechsel von fetalem Hämoglobin (HbF) zu adultem Hämoglobin (HbA) nach der Geburt, indem es die Gamma-Globin-Genexpression unterdrückt.
- **Therapeutisches Ziel:** Die gezielte Abschaltung oder Reduktion von BCL11A in Blutstammzellen reaktiviert das gesunde fetale Hämoglobin. Dies ist ein wichtiger Ansatz zur Behandlung von Sichelzellanämie und Beta-Thalassämie.
- **Entwicklungsstörungen:** Mutationen oder Deletionen im BCL11A-Gen können zu neurologischen Entwicklungsstörungen, Intelligenzminderung, Sprachverzögerungen und Autismus-Spektrum-Störungen führen.

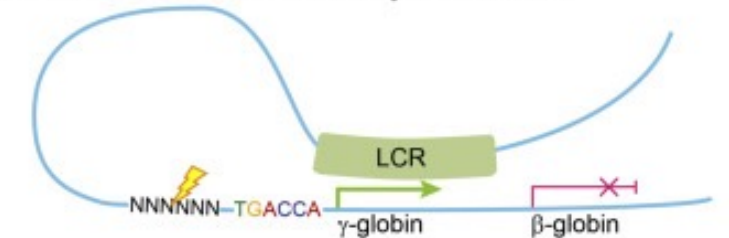
Approaches



Normal adult human erythroid cells



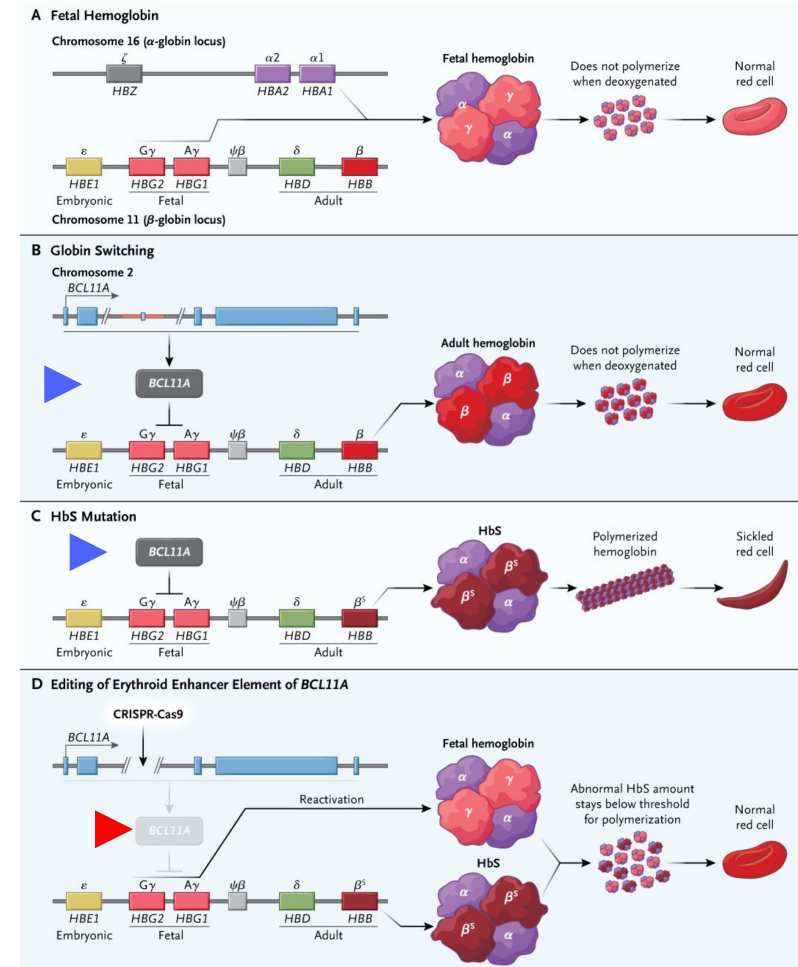
HPFH or CRISPR edited erythroid cells



Locus control region = LCR

Advancing Gene Editing for Children with Hemoglobinopathies

Sickle cell disease and β -thalassemia are highly prevalent inherited conditions associated with serious complications and a shortened life span. Transfusions in patients with severe β -thalassemia and hydroxyurea therapy in those with sickle cell disease can improve outcomes for many of these patients, yet early diagnosis, consistent access to safe blood products, and effective disease-modifying therapies are not universally available. Chronic organ injury and iron overload ultimately add to the disease burden on persons with these conditions, which affects their quality of life and longevity. Until recently, access to curative options had been limited primarily by the lack of a suitable donor for most patients. The emergence of genetic therapies (gene addition and gene editing) has added an exciting and much-needed opportunity for durable, transformational treatment.



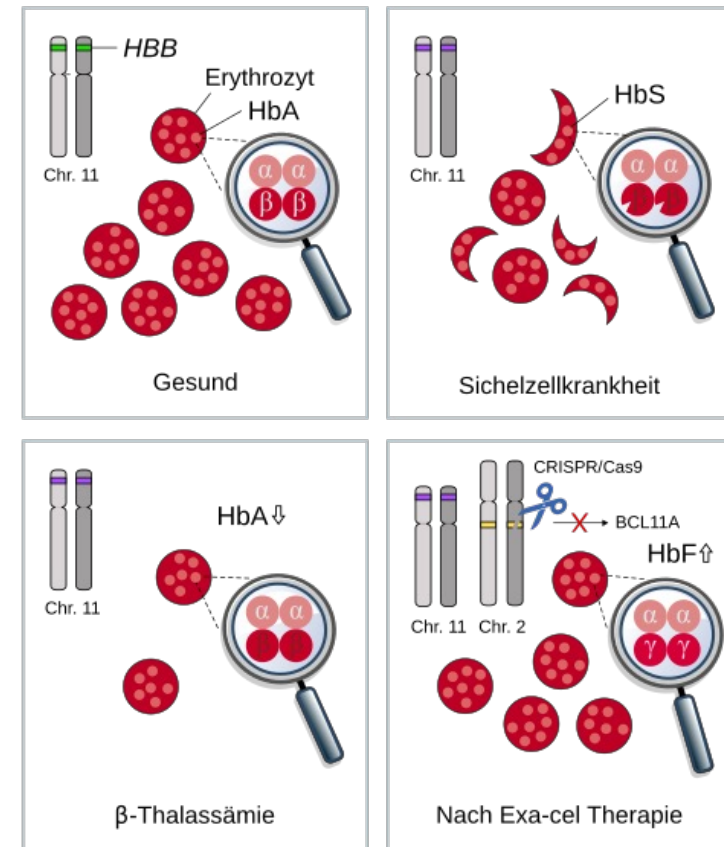
Exa-cel (Exagamglogen-autotemcel) ist die erste zugelassene Gentherapie, die auf der Gen-Schere CRISPR/Cas9 basiert.

Was ist Exa-cel?

- **Wirkungsweise:** Patienteneigene Blutstammzellen werden im Labor mit CRISPR/Cas9 so verändert, dass sie wieder fetales Hämoglobin (HbF) produzieren.
- **Technologie:** Die Gen-Schere schneidet gezielt einen Teil der DNA (im BCL11A-Gen) aus, welcher die HbF-Bildung normalerweise unterdrückt.

Behandelte Krankheiten

- **Schwere Sichelzellkrankheit (SCD):** Verringert schmerzhafte Gefäßverschlüsse.
- **Transfusionsabhängige β -Thalassämie (TDT):** Ermöglicht oft ein Leben ohne regelmäßige Bluttransfusionen.



Der Ablauf einer Behandlung mit Exa-cel (Exagamglogen-autotemcel) entspricht im Kern einer autologen Stammzelltransplantation, allerdings mit einer entscheidenden Besonderheit: Die Zellen werden vor dem Zurückgeben genetisch verändert.

Exa-cel in Children with Transfusion-Dependent β -Thalassemia or Sickle Cell Disease

Exagamglogene autotemcel (exa-cel) is a cell therapy in which autologous CD34+ hematopoietic cells are engineered through ex vivo clustered regularly interspaced short palindromic repeats–Cas9 editing of the erythroid-specific **enhancer region of *BCL11A*** to express fetal hemoglobin. In phase 3 studies involving participants 12 to 35 years of age with sickle cell disease or transfusion-dependent β -thalassemia, exa-cel eliminated vaso-occlusive crises and the need for red-cell transfusions. In two ongoing, phase 3, open-label, single-group studies, we evaluated exa-cel in children 5 to 11 years of age with transfusion-dependent β -thalassemia or sickle cell disease. Before exa-cel infusion, participants underwent myeloablative conditioning with pharmacokinetically dose-adjusted busulfan. The primary end points were **transfusion independence for at least 12 consecutive months** in children with transfusion-dependent β -thalassemia and freedom from severe vaso-occlusive crises for at least 12 consecutive months in children with sickle cell disease.

Conclusions

Exa-cel therapy resulted in transfusion independence or freedom from severe vaso-occlusive crises in participants with transfusion-dependent β -thalassemia or sickle cell disease, respectively, who were followed for at least 16 months. All the participants had grade 3 or 4 adverse events. (Funded by Vertex Pharmaceuticals and CRISPR Therapeutics.)

Transfusion-dependent β -thalassemia and sickle cell disease are severe, monogenic hemoglobinopathies caused by mutations in *HBB* — the gene encoding β -globin chains — with onset during infancy, coinciding with the switch from fetal hemoglobin to adult hemoglobin. Transfusion-dependent β -thalassemia is treated with regular, lifelong red-cell transfusions and iron chelation to control iron overload; sickle cell disease is characterized by painful vaso-occlusive crises and chronic hemolytic anemia. Both diseases can lead to progressive end-organ damage and early death. Exagamglogene autotemcel (exa-cel) is a nonviral cell therapy approved for adolescents and adults with transfusion-dependent β -thalassemia or sickle cell disease that reactivates fetal hemoglobin synthesis through ex vivo clustered regularly interspaced short palindromic repeats (CRISPR)–Cas9 gene-editing of CD34+ autologous hematopoietic stem and progenitor cells at the erythroid-specific enhancer region of *BCL11A*. In two phase 3 pivotal studies involving participants 12 to 35 years of age, exa-cel infusion resulted in **transfusion independence in 91%** of the participants with transfusion-dependent β -thalassemia and elimination of severe **vaso-occlusive crises in 97%** of the participants with sickle cell disease. We hypothesized that the benefits of exa-cel would be equivalent in younger patients.

For the manufacture of exa-cel, CD34+ hematopoietic stem and progenitor cells were mobilized with the use of granulocyte colony-stimulating factor and plerixafor in children with transfusion-dependent β -thalassemia and with plerixafor alone in children with sickle cell disease and were then collected through apheresis for up to 3 consecutive days (collection target, 15×10^6 CD34+ cells per kilogram of body weight). Exa-cel was manufactured from the autologous CD34+ cells with the use of CRISPR-Cas9 and a single-guide RNA targeting the *BCL11A* erythroid-specific enhancer region. Before receiving the exa-cel infusion, children received myeloablative conditioning with pharmacokinetically adjusted busulfan for 4 days (cumulative area under the curve [AUC] target, 82 mg·hour per liter; range, 74 to 90 mg·hour per liter). Initially, busulfan was administered either once daily or every 6 hours, but the protocol in both studies was amended to allow dose administration only every 6 hours to minimize variability in exposure. Exa-cel was infused intravenously through a central venous catheter 2 to 7 days after completion of busulfan administration.

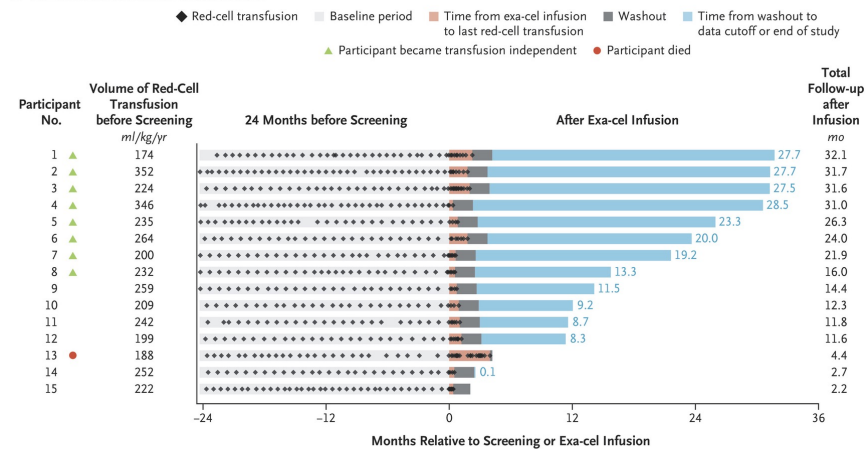
End Points

In CLIMB THAL-141, the primary end point was transfusion independence, defined by a weighted average hemoglobin level of at least 9 g per deciliter without red-cell transfusion for at least 12 consecutive months.

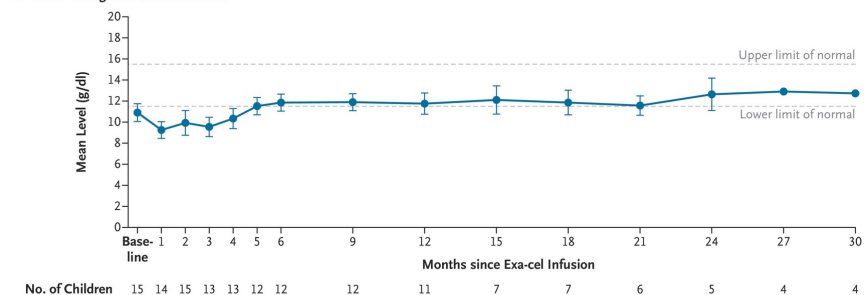
Characteristic	Transfusion-Dependent β -Thalassemia (N = 15)	Sickle Cell Disease (N = 11)
Sex — no. (%)		
Male	10 (67)	5 (45)
Female	5 (33)	6 (55)
Age at screening — yr	7.5 $\pm$ 2.2	8.5 $\pm$ 2.6
Race or ethnic group — no. (%) [†]		
White	4 (27)	1 (9)
Black	0	10 (91)
Asian	4 (27)	0
Not collected in accordance with local regulations	7 (47)	0
Other	0	0
Multiple	0	0
Genotype — no. (%)		
β^0/β^0 -like	5 (33)	—
β^0/β^0	2 (13)	—
β^0 /IVS-I-110	2 (13)	—
IVS-I-110/ IVS-I-110	1 (7)	—
Non- β^0/β^0 -like	10 (67)	—
β^+/β^+	3 (20)	—
β^+/β^0	5 (33)	—
β^S/β^+	2 (13)	—
β^S/β^S	—	11 (100)
Median annualized volume of red-cell transfusions (range) — ml/kg	232.3 (173.5–352.3)	—
Median annualized no. of red-cell transfusion episodes	13.5 (12.0–17.5)	—
Severe VOCs [‡]		
Annualized number [§]	—	3.2 $\pm$ 1.1
Annual incidence — no. (%)		
≥ 3 VOCs/yr	—	6 (55)
< 3 VOCs/yr	—	5 (45)
Total hemoglobin concentration — g/dl	10.9 $\pm$ 1.5	9.5 $\pm$ 0.8
Total fetal hemoglobin concentration		
Grams per deciliter	0.4 $\pm$ 0.3	0.9 $\pm$ 0.3
Percent	3.5 $\pm$ 2.6	9.4 $\pm$ 3.7
Spleen intact — no. (%)	14 (93)	—
Median no. of mobilization cycles (range)	1 (1–2)	2 (1–3)
Median exa-cel dose (range) — $\times 10^6$ CD34+ cells/kg	11.9 (3.9–18.8)	5.4 (3.0–8.3)

Adverse Event	Transfusion-Dependent β -Thalassemia (N = 15)	Sickle Cell Disease (N = 11)
<i>no. of participants (%)</i>		
Any grade ≥ 3 adverse event*	15 (100)	11 (100)
Febrile neutropenia	13 (87)	8 (73)
Stomatitis	9 (60)	2 (18)
Neutrophil count decreased	9 (60)	4 (36)
Platelet count decreased	8 (53)	5 (45)
Anemia	7 (47)	4 (36)
Mucosal inflammation	3 (20)	6 (55)
Thrombocytopenia	3 (20)	3 (27)
White-cell count decreased	3 (20)	0
Alanine aminotransferase level increased	2 (13)	1 (9)
Decreased appetite	2 (13)	3 (27)
Hepatic iron overload	2 (13)	0
Leukopenia	2 (13)	3 (27)
Lymphocyte count decreased	2 (13)	1 (9)
Neutropenia	2 (13)	4 (36)
Veno-occlusive liver disease	2 (13) [†]	0

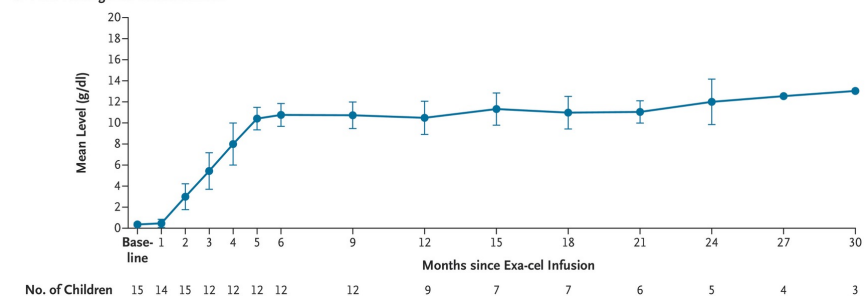
A Transfusion Status after Exa-cel Infusion



B Total Hemoglobin Concentrations

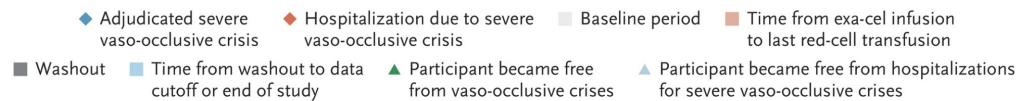


C Fetal Hemoglobin Concentrations

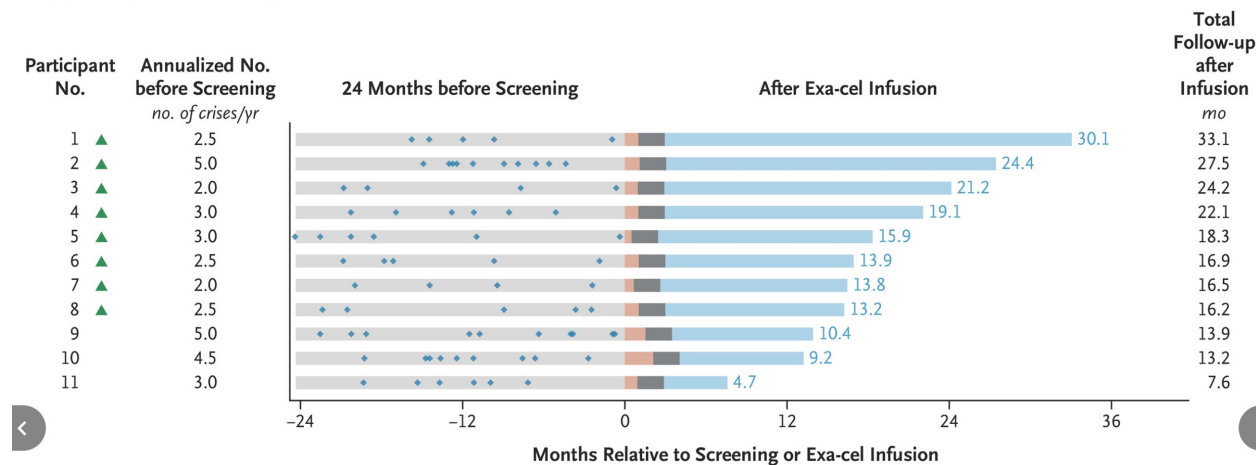


Transfusion Status and Changes in Hemoglobin and Fetal Hemoglobin Concentrations after Exa-cel Infusion in Children with Transfusion-Dependent β -Thalassemia (CLIMB THAL-141).

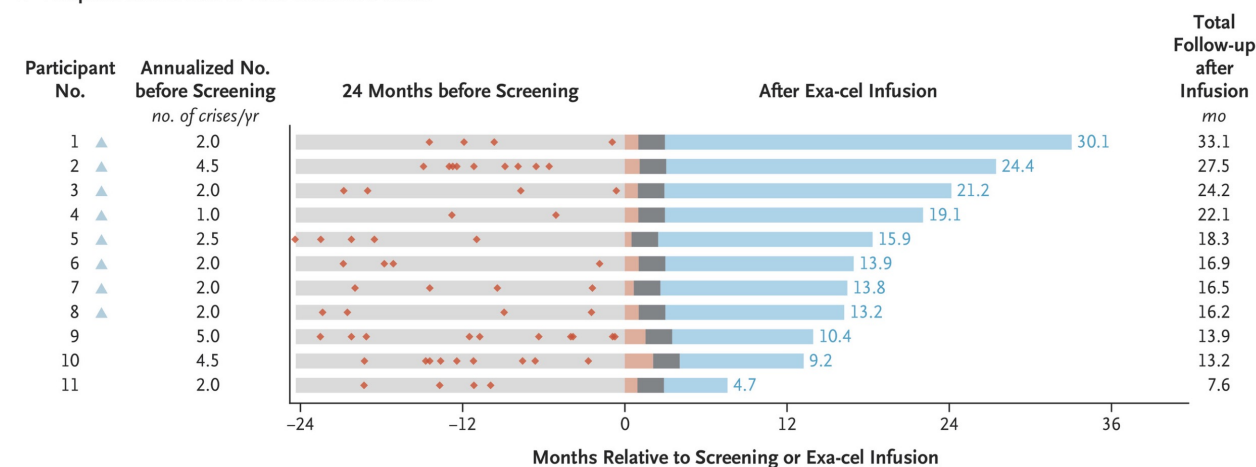
Panel A shows the transfusion status for all 15 children with transfusion-dependent β -thalassemia in the full analysis population (all the children who received an infusion of exagamglogene autotemcel [exa-cel]). The red boxes indicate time from exa-cel infusion to last adjudicated red-cell transfusion for post-transplantation support or transfusion-dependent β -thalassemia management. The dark-gray boxes indicate the 60-day washout period after the last transfusion. The blue boxes and blue numbers indicate the time without red-cell transfusions (indicated by the blue numbers) starting from the end of the washout period to the data cutoff at the interim analysis. All red-cell transfusions that occurred after administration of exa-cel were adjudicated by the independent end-point adjudication committee. Participants 1 through 8 could be evaluated for the primary end point (transfusion independence for at least 12 consecutive months) and comprised the primary efficacy population. Participant 13 had a serious adverse event of veno-occlusive liver disease that was considered by the investigator to be related to busulfan and not related to exa-cel, with subsequent multiorgan failure and pneumonia resulting in death on study day 132. Panels B and C show the mean total hemoglobin and fetal hemoglobin concentrations, respectively, according to trial visit during the follow-up period for all 15 children in the full analysis population. Dots indicate means, and I bars indicate 95% confidence intervals (shown only for time points with ≥ 5 children), which should not be used in place of hypothesis testing. The number of children evaluated at each time point is shown below the x axis. The dashed lines in Panel B indicate the upper and lower limits of the age-adjusted normal range (11.5 to 15.5 g per deciliter).



A Vaso-Occlusive Crises Status



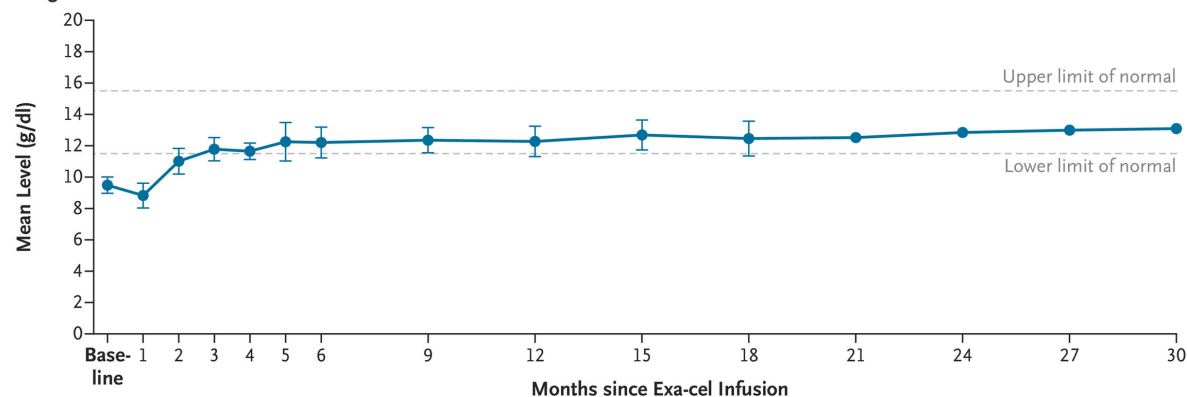
B Hospitalizations Due to Vaso-Occlusive Crises



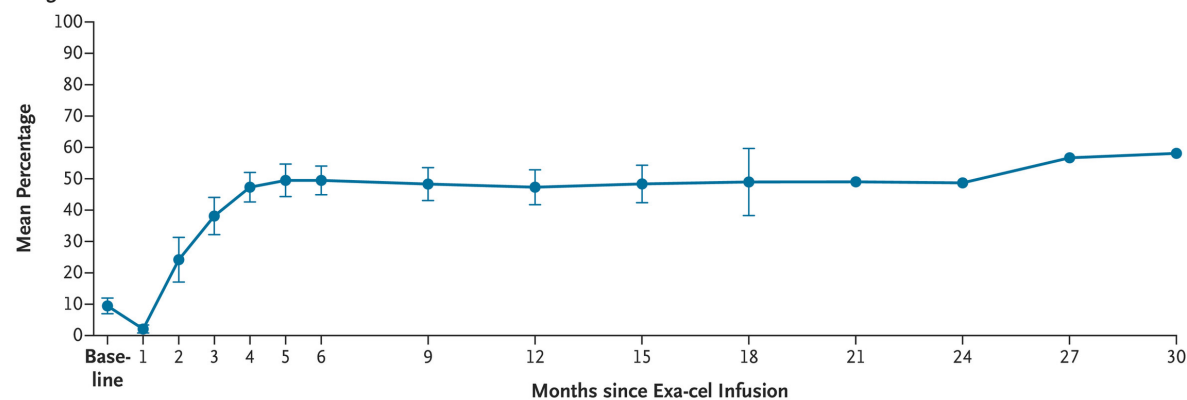
Vaso-occlusive Crises and Hospitalizations after Exa-cel Infusion in Children with Sickle Cell Disease (CLIMB SCD-151).

Shown are the vaso-occlusive crisis status (Panel A) and hospitalizations due to vaso-occlusive crises (Panel B) for all 11 children with sickle cell disease in the full analysis population. The red boxes indicate the time from exa-cel infusion to last adjudicated red-cell transfusion for post-transplantation support or sickle cell disease management. The dark-gray boxes indicate the 60-day washout period after the last transfusion. The blue boxes and blue numbers indicate the time without vaso-occlusive crises (Panel A) or the duration of freedom from hospitalizations due to vaso-occlusive crises (Panel B) from the end of the washout period to the data cutoff at the interim analysis. Participants 1 through 8 could be evaluated for the primary end point (freedom from severe vaso-occlusive crises for at least 12 consecutive months) and comprised the primary efficacy population.

A Total Hemoglobin Concentrations



B Fetal Hemoglobin Concentrations



Changes in Hemoglobin and Fetal Hemoglobin Concentrations after Exa-cel Infusion in Children with Sickle Cell Disease (CLIMB SCD-151).

Shown are the mean total hemoglobin (Panel A) and fetal hemoglobin (Panel B) concentrations according to study visit during the follow-up period for the full analysis population. Dots indicate means, and I bars indicate 95% confidence intervals (shown only for time points with ≥ 5 children), which should not be used in place of hypothesis testing. The number of children evaluated at each time point is shown below the x axis. The dashed lines in Panel A indicate the upper and lower limits of the age-adjusted normal range (11.5 to 15.5 g per deciliter).

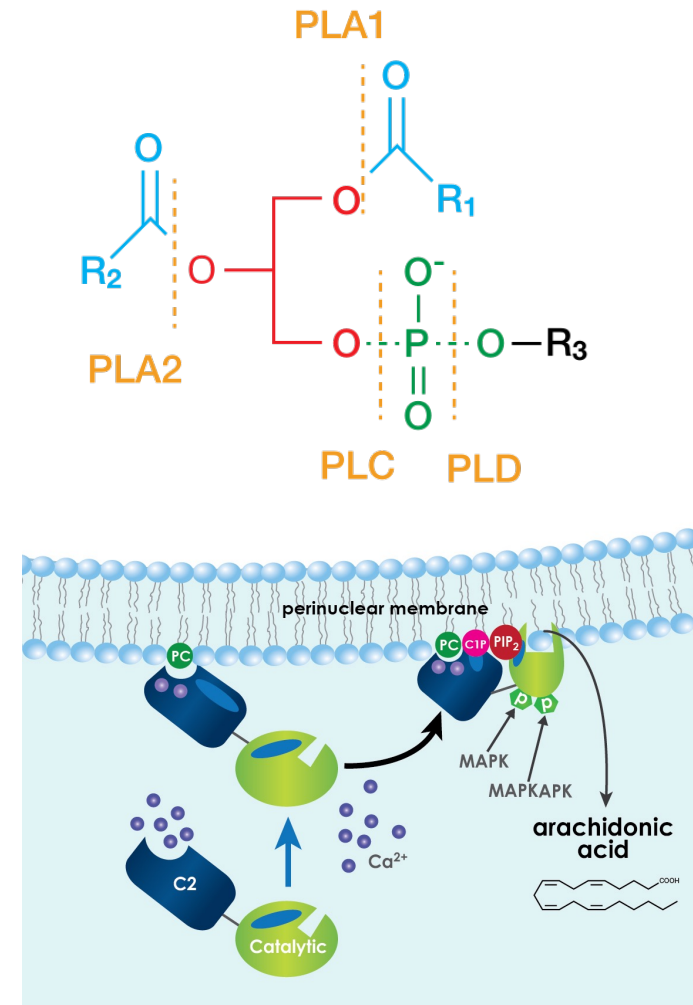
Discussion

These two ongoing phase 3 studies of exa-cel included children 5 to 11 years of age with transfusion-dependent β -thalassemia or severe sickle cell disease. Each of the eight children with transfusion-dependent β -thalassemia who could be evaluated were **transfusion independent for at least 12 consecutive months**, and each of the eight children with sickle cell disease who could be evaluated were free from vaso-occlusive crises for at least 12 consecutive months (the primary end points); the status of the remaining seven children and the remaining three children, respectively, was not evaluable. None of the children with transfusion-dependent β -thalassemia had transfusions after the 60-day washout period, and **none of the children with sickle cell disease had vaso-occlusive crises** after exa-cel infusion. The mean duration of transfusion independence and of freedom from vaso-occlusive crises was 23.4 months and 19.0 months, respectively. In both studies, increases in fetal hemoglobin concentrations resulted in mean total hemoglobin concentrations in the normal range, with pancellular fetal hemoglobin distribution.

Phospholipase A2 (PLA2) bezeichnet eine Gruppe von Enzymen, die die hydrolytische Abspaltung von Fettsäuren am C2-Atom (sn-2-Position) von Phospholipiden katalysieren.

Biologische Funktion und Bedeutung

- **Lipidstoffwechsel:** PLA2-Enzyme sind essenziell für den Abbau und Umbau von Membranphospholipiden in eukaryotischen Zellen.
- **Signaltransduktion:** Sie setzen Arachidonsäure frei, welche als Ausgangssubstrat für die Biosynthese von Entzündungsmediatoren (wie Prostaglandinen und Leukotrienen) dient.
- **Toxine:** PLA2-Isoformen sind häufig Hauptbestandteile von Schlangen-, Insekten- und Skorpiongiften, wo sie Zellmembranen zerstören.



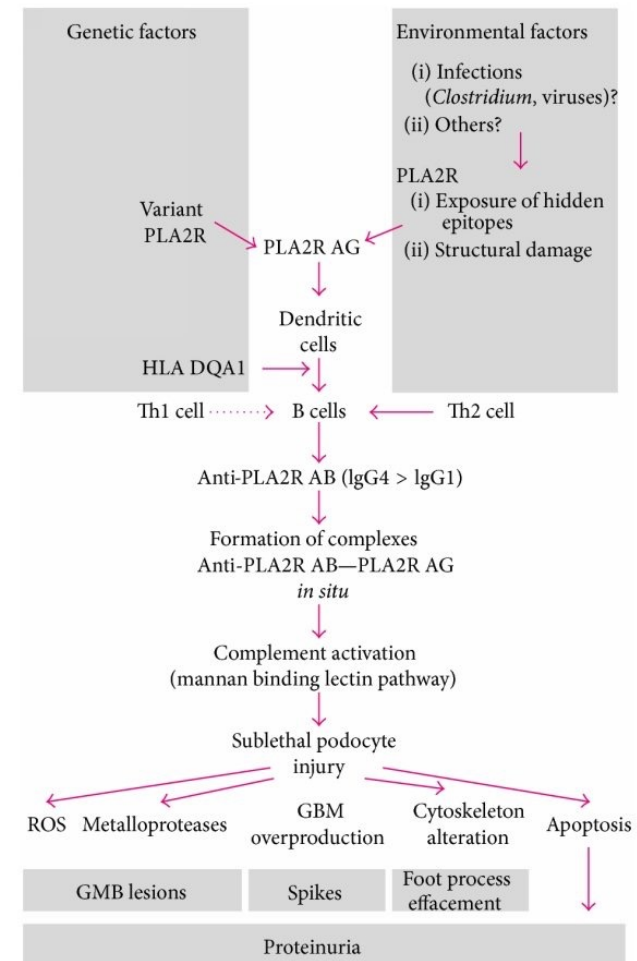
Der **Phospholipase-A2-Rezeptor (PLA2R)** ist ein Typ-1-Transmembranprotein, das vor allem in den Nieren von den Podozyten (speziellen Zellen der Nierenkörperchen) exprimiert wird.

In der Medizin spielt er eine **entscheidende Rolle als Zielstruktur (Antigen) bei Autoimmunerkrankungen der Niere.**

1. Physiologische Funktion (Im gesunden Körper)

Die genaue biologische Hauptfunktion im **gesunden Menschen ist noch nicht vollständig entschlüsselt**. Bekannt ist jedoch:

- **Regulation von Enzymen:** Er bindet verschiedene Typen des Enzyms *Phospholipase A2* und steuert deren Aktivität (positive oder negative Regulation).
- **Zellschutz & Clearance:** Er hilft dabei, diese Phospholipasen aus dem Gewebe zu entfernen (Clearance) und ist an allgemeinen regulatorischen Prozessen der Zelle beteiligt.
- **Struktur:** Er gehört zur Familie der Mannose-Rezeptoren und kann zuckerähnliche Strukturen (Lektine) binden



Die membranöse Glomerulonephritis (MGN) ist eine chronische Entzündung der Nierenkörperchen und die häufigste Ursache für ein nephrotisches Syndrom bei Erwachsenen.

Was ist die MGN?

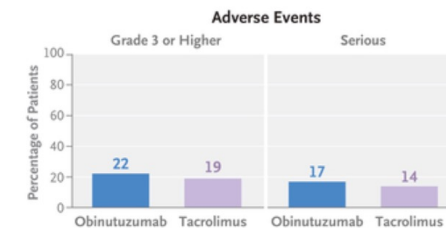
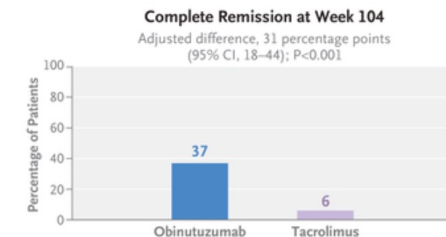
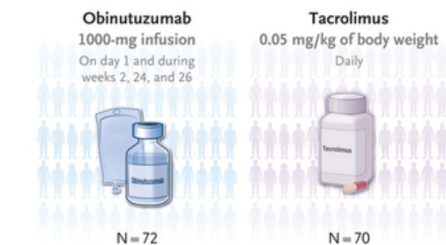
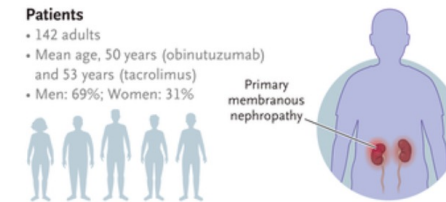
- **Krankheitsbild:** Antikörper lagern sich an den Filterstrukturen der Niere (Basalmembran) ab.
- **Folgen:** Großer Eiweißverlust über den Urin (Proteinurie), Wassereinlagerungen (Ödeme) und Fettstoffwechselstörungen.
- **Ursachen:** Meistens primär (autoimmun durch Antikörper wie Anti-PLA2R), seltener sekundär durch Infektionen, Medikamente oder andere Erkrankungen.



Obinutuzumab or Tacrolimus in Primary Membranous Nephropathy

Studies of **obinutuzumab**, a **type II anti-CD20 antibody**, have shown efficacy in the treatment of hematologic cancers and autoimmune diseases. An evaluation of the efficacy and safety of obinutuzumab in patients with primary membranous nephropathy is needed.

In a phase 3 trial, we randomly assigned adults with primary membranous nephropathy in a 1:1 ratio to receive intravenous obinutuzumab or oral tacrolimus. **The primary end point was complete remission** (defined as a urinary protein-to-creatinine ratio of 0.3 or lower and a stable estimated glomerular filtration rate [eGFR]) at week 104. Key secondary end points were complete or partial remission at week 104, complete remission at week 76, a sustained reduction in the eGFR of at least 30%, duration of complete remission, and change in the Patient-Reported Outcomes Measurement Information System Fatigue T score from baseline to week 104. Fixed-sequence hierarchical testing was performed. Safety was assessed.



Primary membranous nephropathy is the most common cause of **idiopathic nephrotic syndrome in adults without diabetes**. Approximately 70 to 80% of patients with membranous nephropathy have circulating anti-phospholipase A₂ receptor (anti-PLA2R) autoantibodies. Initial supportive management includes renin–angiotensin–aldosterone system blockade. Patients with persistent nephrotic syndrome receive immunosuppressive therapy. Treatment with glucocorticoids, cytotoxic medications, or calcineurin inhibitors is often effective but may result in substantial side effects, including hypertension, nephrotoxic effects, infertility, and infections. In the Membranous Nephropathy **Trial of Rituximab** (MENTOR) trial, the type I anti-CD20 monoclonal antibody rituximab was **superior to cyclosporine** in maintaining remission of proteinuria for up to 24 months in patients with primary membranous nephropathy. Obinutuzumab, a glycoengineered type II anti-CD20 monoclonal IgG1 antibody, has been associated with enhanced antibody-dependent cell-mediated cytotoxicity and phagocytosis, enhanced direct B-cell death, and less reliance on complement-dependent cytotoxicity as compared with type I anti-CD20 antibodies — features that result in more profound and durable B-cell depletion. We report the results of the MAJESTY trial, a phase 3, multicenter, open-label, randomized, active-comparator trial evaluating the efficacy and safety of **obinutuzumab** as compared with **tacrolimus** in patients with primary membranous nephropathy.

Trial Procedures

The trial consisted of the following periods: screening, open-label treatment, escape treatment, long-term follow-up, and safety follow-up. Patients were randomly assigned in a 1:1 ratio to receive intravenous obinutuzumab or oral tacrolimus. Obinutuzumab was administered in an intravenous infusion at a dose of 1000 mg on day 1 and during weeks 2, 24, and 26. Tacrolimus was administered orally at an initial dose of 0.05 mg per kilogram of body weight per day, which was adjusted to maintain a target trough concentration of 5 to 7 ng per milliliter through week 52 and then tapered over a period of 8 weeks. Randomization was performed centrally with the use of an interactive voice- and Web-based response system and a block design. Randomization was stratified according to geographic region (United States, Canada, and Europe vs. the rest of the world) and anti-PLA2R autoantibody level (≥ 175 U per milliliter vs. < 175 U per milliliter).

Assessment of Efficacy End Points

The primary end point was complete remission at week 104. Complete remission was defined as a 24-hour UPCR of 0.3 or lower and a stable eGFR (an eGFR $\geq 85\%$ of the baseline rate, calculated with the Chronic Kidney Disease Epidemiology Collaboration equation).

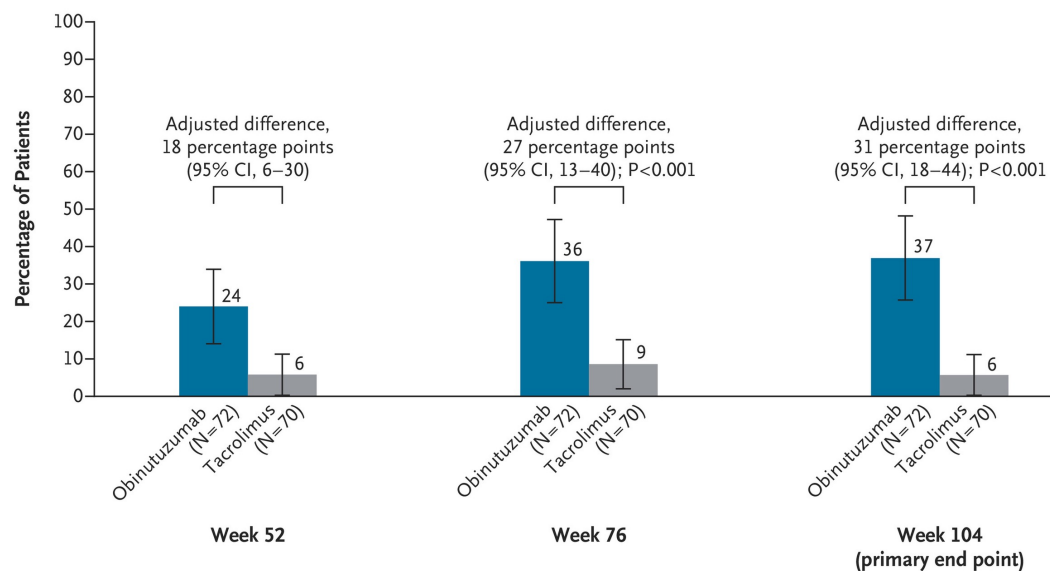
Characteristic	Obinutuzumab (N=72)	Tacrolimus (N=70)
Mean age — yr	49.9±12.0	52.6±10.0
Sex — no. (%)		
Male	54 (75)	44 (63)
Female	18 (25)	26 (37)
Hispanic or Latino ethnic group — no. (%)†	14 (19)	16 (23)
Race — no. (%)†		
White	51 (71)	49 (70)
Asian	15 (21)	20 (29)
Black	3 (4)	1 (1)
Unknown	1 (1)	0
Not reported	2 (3)	0
Geographic region — no. (%)‡		
United States, Canada, and Europe	34 (47)	34 (49)
Rest of the world	38 (53)	36 (51)
Previous use of immunosuppressive therapy — no. (%)		
Yes	20 (28)	21 (30)
No	52 (72)	49 (70)
Use of renin–angiotensin–aldosterone inhibitors — no. (%)§	69 (97)	70 (100)
Serum creatinine level — μmol/liter		
Mean	97.1±39.7	84.7±32.8
Median (range)	89.0 (38.0–236.0)	76.5 (33.0–224.0)
eGFR — ml/min/1.73 m²		
Mean	81.5±27.7	86.0±24.8
Median (range)	85.0 (24.0–145.0)	89.0 (30.0–129.0)
24-hr UPCR¶		
Mean	7.4±3.1	7.2±3.1
Median (range)	6.8 (1.4–18.0)	6.8 (2.8–18.1)
<5 — no. (%)	12 (17)	20 (29)
≥5 — no. (%)	60 (83)	50 (71)
Serum albumin level — g/liter		
Mean	28.8±5.9	28.7±5.5
Median (range)	28.0 (17.0–45.0)	28.0 (18.0–45.0)
24-hr Urinary protein level — g/day		
Mean	10.2±5.7	9.7±4.8
Median (range)	9.1 (1.7–33.8)	8.9 (2.5–24.4)
Anti-PLA2R autoantibody level‡		
Mean — U/ml	198.4±409.5	165.7±258.9
Median (range) — U/ml	73.5 (3.0–3043.8)	92.8 (29.9–1922.5)
Positive, ≥14 U/ml — no. (%)	54 (75)	57 (81)
High, ≥175 U/ml — no. (%)	23 (32)	23 (33)
Low, <175 U/ml — no. (%)	49 (68)	47 (67)
Anti-THSD7A autoantibody level — no. (%)		
Negative	56 (78)	51 (73)
Missing data	16 (22)	19 (27)

* Plus–minus values are means ±SD. The abbreviation eGFR denotes estimated glomerular filtration rate. PLA2R rhog.

Primary and Key Secondary Efficacy End Points.

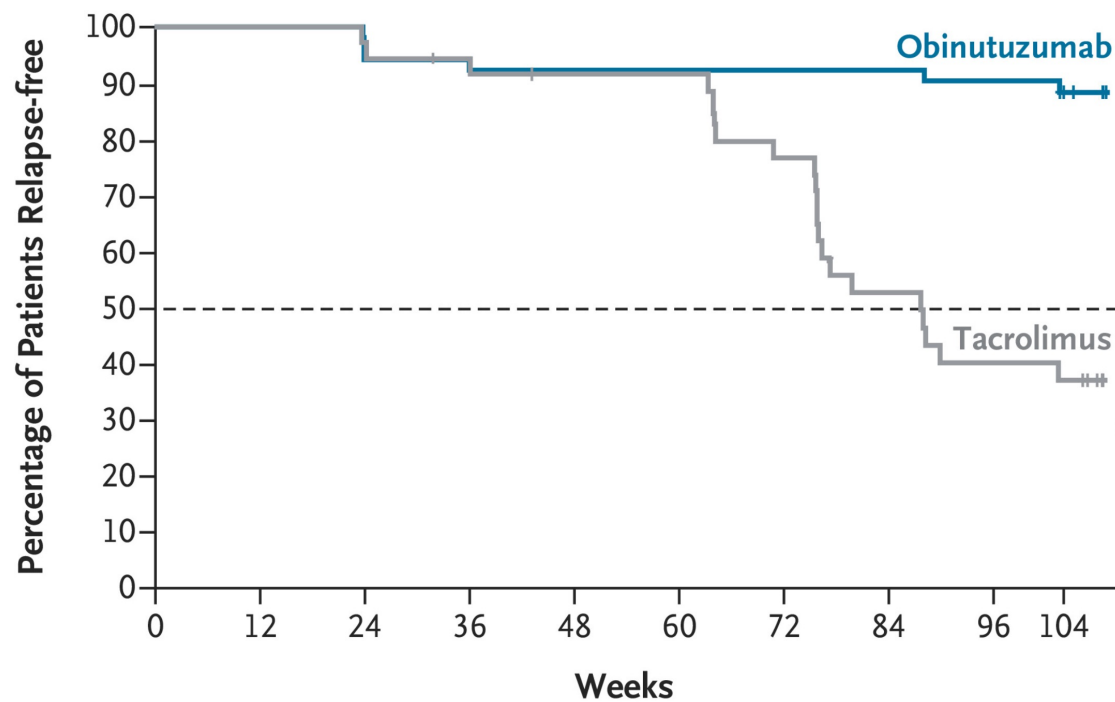
End Point	Obinutuzumab (N=72)	Tacrolimus (N=70)	Treatment Effect (95% CI)†	P Value
Primary end point				
Complete remission at wk 104‡				
No. of patients/total no. (%)	26/71 (37)	4/70 (6)	—	—
% of patients (95% CI)§	37 (26 to 48)	6 (<1 to 11)	31 (18 to 44)	<0.001
Key secondary end points				
Complete or partial remission at wk 104¶				
No. of patients/total no. (%)	36/71 (51)	9/70 (13)	—	—
% of patients (95% CI)§	51 (39 to 62)	13 (5 to 21)	38 (24 to 52)	<0.001
Complete remission at wk 76‡				
No. of patients/total no. (%)	26/72 (36)	6/70 (9)	—	—
% of patients (95% CI)	36 (25 to 47)	9 (2 to 15)	27 (13 to 40)	<0.001
Sustained reduction from baseline in the eGFR of ≥30% starting at wk 76				
No. of patients with event/total no. (%)	3/51 (6)	2/31 (6)	—	—
Median time to event — wk	NE	NE	1.10 (0.18–6.61)	0.91**
Duration of complete remission				
No. of patients assessed	38	7	—	—
Median (95% CI) — wk	104.9 (80.6 to NE)	55.3 (17.4 to 90.9)	0.62 (0.23 to 1.70)	—
Change in the PROMIS Fatigue T score from baseline to wk 104††				
No. of patients assessed	70	67	—	—
Adjusted mean	–1.4±0.9	1.7±0.9	–3.1 (–5.5 to –0.6)	—

Event	Obinutuzumab (N = 71)	Tacrolimus (N = 70)
Any adverse event		
No. of patients (%)	62 (87)	61 (87)
No. of events	323	300
No. of events per 100 patient-yr (95% CI)	274 (244 to 304)	331 (294 to 369)
Any serious adverse event		
No. of patients (%)	12 (17)	10 (14)
No. of events	13	13
No. of events per 100 patient-yr (95% CI)	11 (5 to 17)	14 (7 to 22)
Death — no. (%)†	0	0
Adverse event that led to withdrawal from the trial — no. (%)	0	1 (1)
Adverse event that led to discontinuation of the trial drug — no. (%)	2 (3)	6 (9)
Grade ≥3 adverse event — no. (%)	16 (22)	13 (19)
Infection		
No. of patients (%)	36 (51)	26 (37)
No. of events	72	52
No. of events per 100 patient-yr (95% CI)	61 (47 to 75)	57 (42 to 73)
Infections occurring in ≥5% of the patients in either trial group — no. (%)		
Coronavirus disease 2019	11 (16)	10 (14)
Upper respiratory tract infection	10 (14)	7 (10)
Influenza	5 (7)	4 (6)
Nasopharyngitis	4 (6)	1 (1)
Serious infection		
No. of patients (%)	4 (6)	4 (6)
No. of events	4	4
No. of events per 100 patient-yr (95% CI)	3 (<1 to 9)	4 (1 to 11)
Adverse event that led to death — no. (%)	0	0
Adverse event related to the trial drug — no. (%)‡	34 (48)	40 (57)
Serious adverse event related to the trial drug — no. (%)‡	7 (10)	3 (4)
Adverse events of special interest — no. (%)§		
Infusion-related reaction¶	27 (38)	—
Grade ≥3 infection	3 (4)	—
Hepatitis B virus reactivation	1 (1)	—
Progressive multifocal leukoencephalopathy	0	—
Drug-related neutropenia	3 (4)	—
Drug-related thrombocytopenia	1 (1)	—
Gastrointestinal perforation	0	—
Worsening of preexisting cardiac conditions	0	—
Hy's law criteria met	0	0
Suspected transmission of an infectious agent by the trial drug	0	0



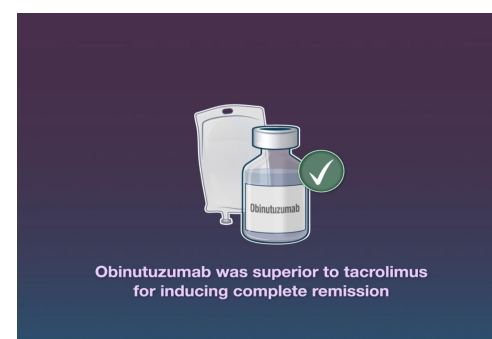
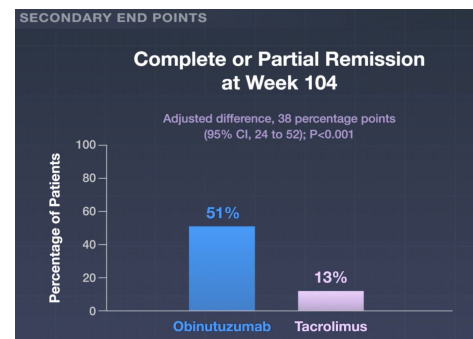
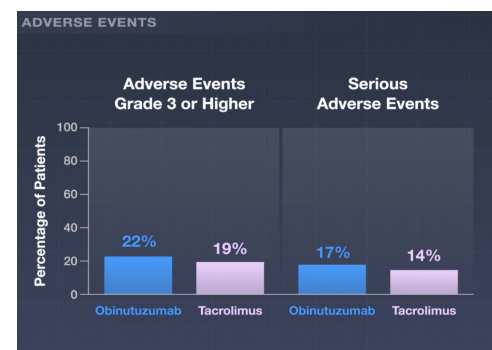
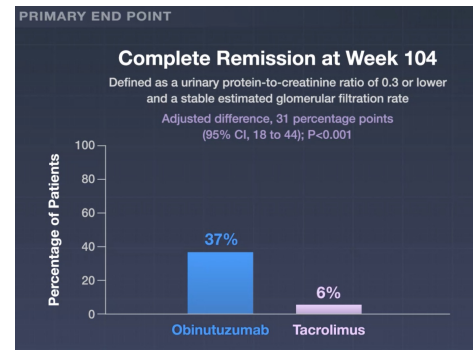
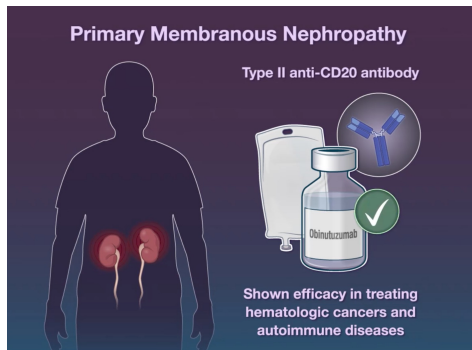
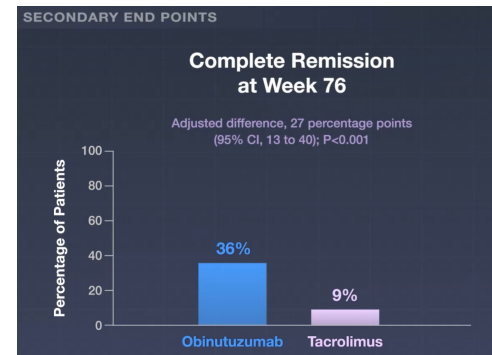
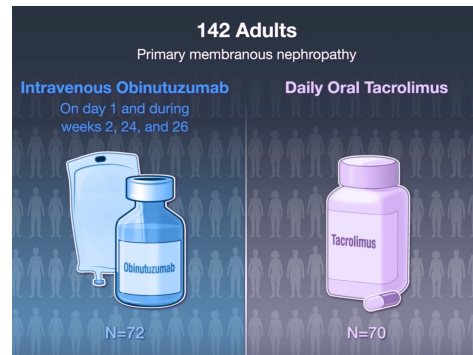
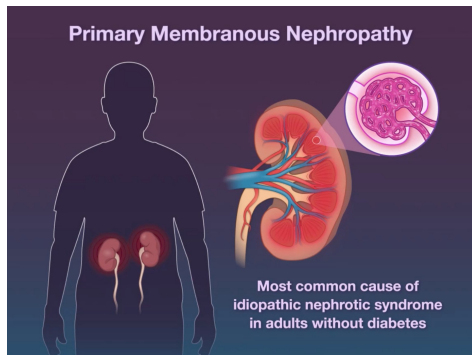
Complete Remission at Weeks 52, 76, and 104.

Shown is the percentage of patients who had complete remission at week 52, week 76, and week 104.



Relapse after Complete or Partial Remission through Week 104.

Shown is the percentage of patients who were relapse-free after complete or partial remission through week 104, which was assessed in an analysis (not controlled for type I error) of the time from randomization to the first occurrence of relapse during the open-label treatment period. Relapse was defined as the recurrence of a 24-hour urinary protein-to-creatinine ratio higher than 3.5, with an increase from the nadir of at least 50% required among patients with partial remission. The dashed line indicates the median. Tick marks indicate censored data.

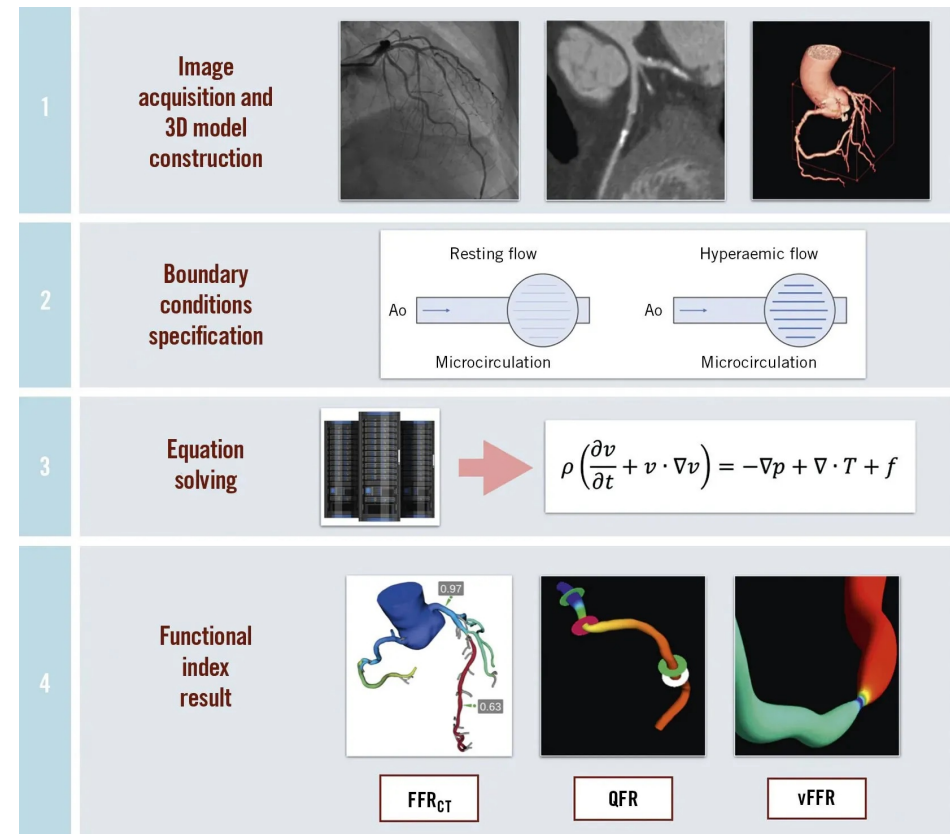


Der deutsche Begriff für *functional coronary angiography* lautet funktionelle Koronarangiografie (oder *funktionelle Koronardiagnostik*).

Während die klassische, rein anatomische Koronarangiografie lediglich die Struktur und Engstellen (Stenosen) der Herzkranzgefäße sichtbar macht, prüft die funktionelle Variante, wie stark diese Engstellen den **Blutfluss tatsächlich behindern** und ob sie eine relevante Durchblutungsstörung des Herzmuskels verursachen

Benötigte Nachrüstung für einen bestehenden Katheterplatz

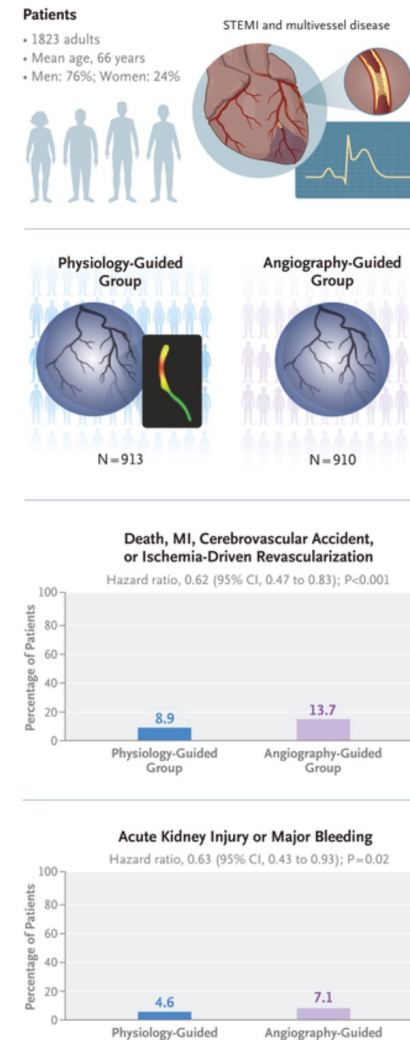
- **Hardware-Module:** Moderne Elektrophysiologie- und Hämodynamik-Messplätze im HKL verfügen meist über vorbereitete Einschübe oder Schnittstellen. Es wird lediglich eine Verbindungseinheit (ein integriertes Modul des Systemherstellers oder eine separate mobile Konsole) benötigt, um das Signal des Druckdrahtes zu verarbeiten



- **The Image:** The doctor takes standard 2D X-ray images of the coronary arteries from different angles.
- **The Software:** Advanced computer algorithms reconstruct these images into a **3D digital model** of the heart's arteries.
- **Fluid Dynamics:** The software uses computational fluid dynamics to calculate how blood flows through the mathematical model, estimating the pressure drop without physically threading a sensor across the blockage.

Complete Revascularization Guided by Functional Coronary Angiography in STEMI

Complete coronary-artery revascularization is recommended in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease, but the preferred strategy for identifying nonculprit lesions that warrant treatment remains uncertain. In this international, randomized trial, we assigned patients with STEMI and multivessel disease in whom the culprit lesion had been successfully treated to undergo complete coronary-artery revascularization guided by functional coronary angiography (physiology-guided group) or by conventional angiography (angiography-guided group). The primary outcome was a composite of death from any cause, myocardial infarction, cerebrovascular accident (stroke or transient ischemic attack), or ischemia-driven revascularization, assessed in a time-to-event analysis. The primary safety outcome was a composite of contrast-associated acute kidney injury or major bleeding.



Complete coronary-artery revascularization has become the standard of care for patients presenting with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease. However, the appropriate strategy for identifying which nonculprit lesions warrant revascularization remains uncertain. In clinical practice, decisions regarding nonculprit lesions are still largely based on angiographic assessment despite its limited ability to define lesions that are functionally important and warrant revascularization.

Functional coronary angiography is now available and enables an assessment of coronary physiology directly from angiographic images, including both fractional flow reserve (FFR) estimates and pullback analysis, without the need for pressure wires or hyperemic agents. In patients with chronic coronary syndromes and intermediate lesions, this approach has been shown to be noninferior to wire-based FFR and superior to angiography-guided decision making. However, evidence regarding the role of functional coronary angiography in the treatment of patients with STEMI and multivessel coronary artery disease remains limited. We conducted the international, randomized Functional Coronary Angiography to Indicate and Guide Revascularization in STEMI Patients with Multivessel Disease (AIR-STEMI) trial to evaluate whether a strategy of complete coronary-artery revascularization guided by functional coronary angiography is superior to one guided by conventional angiography in patients with STEMI and multivessel disease.

Patients

Patients were eligible if they were hospitalized with a STEMI, had undergone successful percutaneous coronary intervention (PCI) of the culprit lesion, and had multivessel coronary artery disease with at least one lesion in a nonculprit coronary artery with a reference vessel diameter of at least 2.5 mm and an angiographically estimated diameter stenosis of 50 to 99%. Key exclusion criteria were the inability to identify a clear culprit lesion, presence of a nonculprit lesion in the left main coronary artery, planned or previous surgical revascularization, and life expectancy of less than 1 year.

Treatments and Follow-up

Patients in the physiology-guided group underwent functional coronary angiography assessment of all nonculprit lesions with an angiographically estimated diameter stenosis of 50% or greater. Functional coronary angiography consisted of an estimation of the distal FFR value in the nonculprit vessel; lesions with an FFR value of 0.80 or less were considered to be functionally important and were treated with PCI in accordance with a virtual-PCI plan that was based on the FFR pullback curve. Analyses were performed at a central core laboratory with the use of angiography-derived FFR software, including Murray law–based quantitative flow ratio (AngioPlus Core, Pulse Medical Imaging Technology) and vessel FFR (CAAS vFFR, Pie Medical Imaging). PCI of lesions with negative functional assessment (value, >0.80) was considered to be a protocol violation. Patients in the angiography-guided group underwent PCI of all nonculprit lesions with an angiographically estimated diameter stenosis of 50% or greater.

Outcomes

The primary outcome was a composite of death from any cause, myocardial infarction, cerebrovascular accident (stroke or transient ischemic attack), or ischemia-driven revascularization, assessed in a time-to-event analysis.

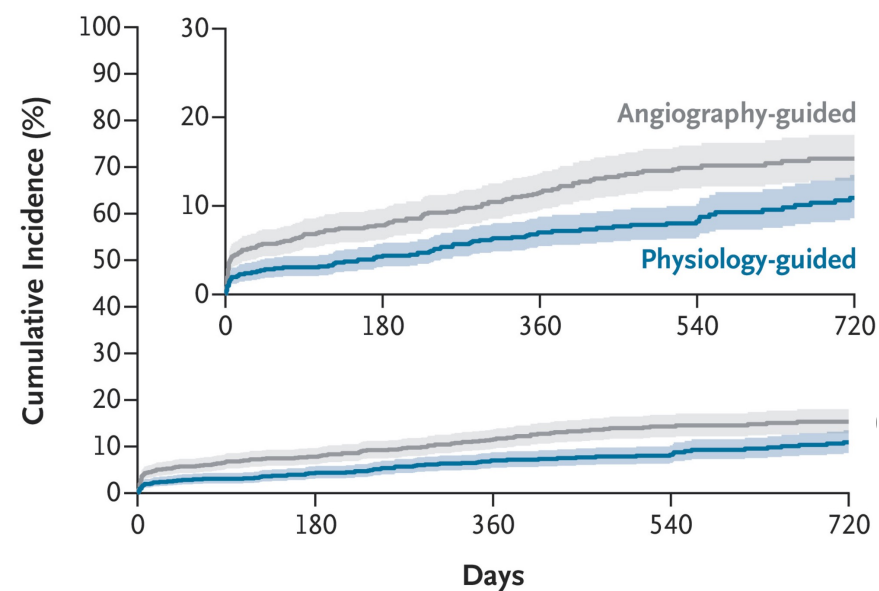
Characteristic	Physiology-Guided Revascularization (N=913)	Angiography-Guided Revascularization (N=910)
Median age (IQR) — yr	67 (58–76)	66 (57–75)
Female sex — no. (%)	223 (24.4)	208 (22.9)
Coexisting conditions — no. (%)		
Hypertension	638 (69.9)	614 (67.5)
Dyslipidemia	482 (52.8)	504 (55.4)
Diabetes	195 (21.4)	205 (22.5)
Current smoker — no. (%)	292 (32.0)	278 (30.5)
Previous myocardial infarction — no. (%)	87 (9.5)	98 (10.8)
Previous PCI — no. (%)	96 (10.5)	105 (11.5)
Previous cerebrovascular accident — no. (%)†	33 (3.6)	38 (4.2)
Chronic kidney disease — no. (%)	116 (12.7)	127 (14.0)
Peripheral artery disease — no. (%)	100 (11.0)	106 (11.6)
Clinical presentation — no. (%)		
Cardiac arrest	34 (3.7)	32 (3.5)
Killip class ≥2‡	192 (21.0)	171 (18.8)
Laboratory data		
Median hemoglobin (IQR) — g/dl	13.7 (12.5–14.9)	13.9 (12.8–15.0)
Median creatinine clearance (IQR) — ml/min	85.2 (69.5–100.4)	83.0 (67.2–98.8)
Median left ventricular ejection fraction (IQR) — %	50.0 (45.0–55.0)	50.0 (44.0–56.0)
Length of hospital stay (IQR) — days	5.0 (3.5–6.5)	5.5 (4.0–6.0)
Medication at discharge — no. (%)		
Aspirin	890 (97.5)	874 (96.0)
Clopidogrel	201 (22.0)	195 (21.4)
Ticagrelor	623 (68.2)	609 (66.9)
Prasugrel	82 (9.0)	94 (10.3)
Oral anticoagulation	86 (9.4)	85 (9.3)
ACE inhibitor or ARB	790 (86.5)	772 (84.8)
Beta-blocker	698 (76.5)	685 (75.3)
Statin	882 (96.6)	878 (96.5)
Ezetimibe	522 (57.2)	525 (57.7)
Bempedoic acid	12 (1.3)	18 (2.0)
PCSK9 inhibitor	17 (1.9)	14 (1.5)

Procedural Data.

Variable	Physiology-Guided Revascularization (N=913)	Angiography-Guided Revascularization (N=910)
Procedures		
Total — no.	1332	1590
Index procedures — no.	913	910
With PCI of nonculprit vessels — no./total no. (%)	115/913 (12.6)	197/910 (21.6)
Staged procedures — no.	419	680
With PCI of nonculprit vessels — no./total no. (%)	397/419 (94.7)	674/680 (99.1)
Median no. of days from index procedure to staged procedure (IQR)	3.0 (2.0–4.0)	2.0 (0–4.0)
Radial-artery access — no./total no. (%)	1291/1332 (96.9)	1539/1590 (96.8)
Median volume of contrast medium used (IQR) — ml	180.0 (117.5–242.5)	223.0 (158.0–288.0)
Culprit vessel — no. (%)		
Left main coronary artery	29 (3.2)	22 (2.4)
Left anterior descending artery	341 (37.3)	351 (38.6)
Circumflex artery	219 (24.0)	206 (22.6)
Right coronary artery	324 (35.5)	331 (36.4)
Nonculprit vessel		
Total no.	1147	1128
Location — no./total no. (%)		
Left anterior descending artery	479/1147 (41.8)	473/1128 (41.9)
Circumflex artery	352/1147 (30.7)	342/1128 (30.3)
Right coronary artery	316/1147 (27.6)	313/1128 (27.7)
Reference-vessel diameter (IQR) — mm	3.0 (2.7–3.3)	3.0 (2.7–3.3)
Median percent diameter stenosis (IQR)	80.0 (72.5–87.5)	79.0 (72.0–86.0)
Percent diameter stenosis — no./total no. of vessels (%)		
50–69%	266/1147 (23.2)	224/1128 (19.9)
70–89%	675/1147 (58.8)	711/1128 (63.0)
90–99%	206/1147 (18.0)	182/1128 (16.1)
Median lesion length (IQR) — mm	23.0 (15.0)	23.0 (16.0)
Physiological assessment — no./total of nonculprit vessels		
Angiography-derived fractional flow reserve	1132/1147	NA
Wire-based fractional flow reserve	15/1147	NA
Fractional flow reserve (IQR)	0.80 (0.70–0.90)	NA
Functionally important nonculprit vessel — no./total no. (%)	590/1147 (51.4)	NA
Nonculprit vessel treated with PCI — no./total no. (%)	596/1147 (52.0)	1071/1128 (94.9)

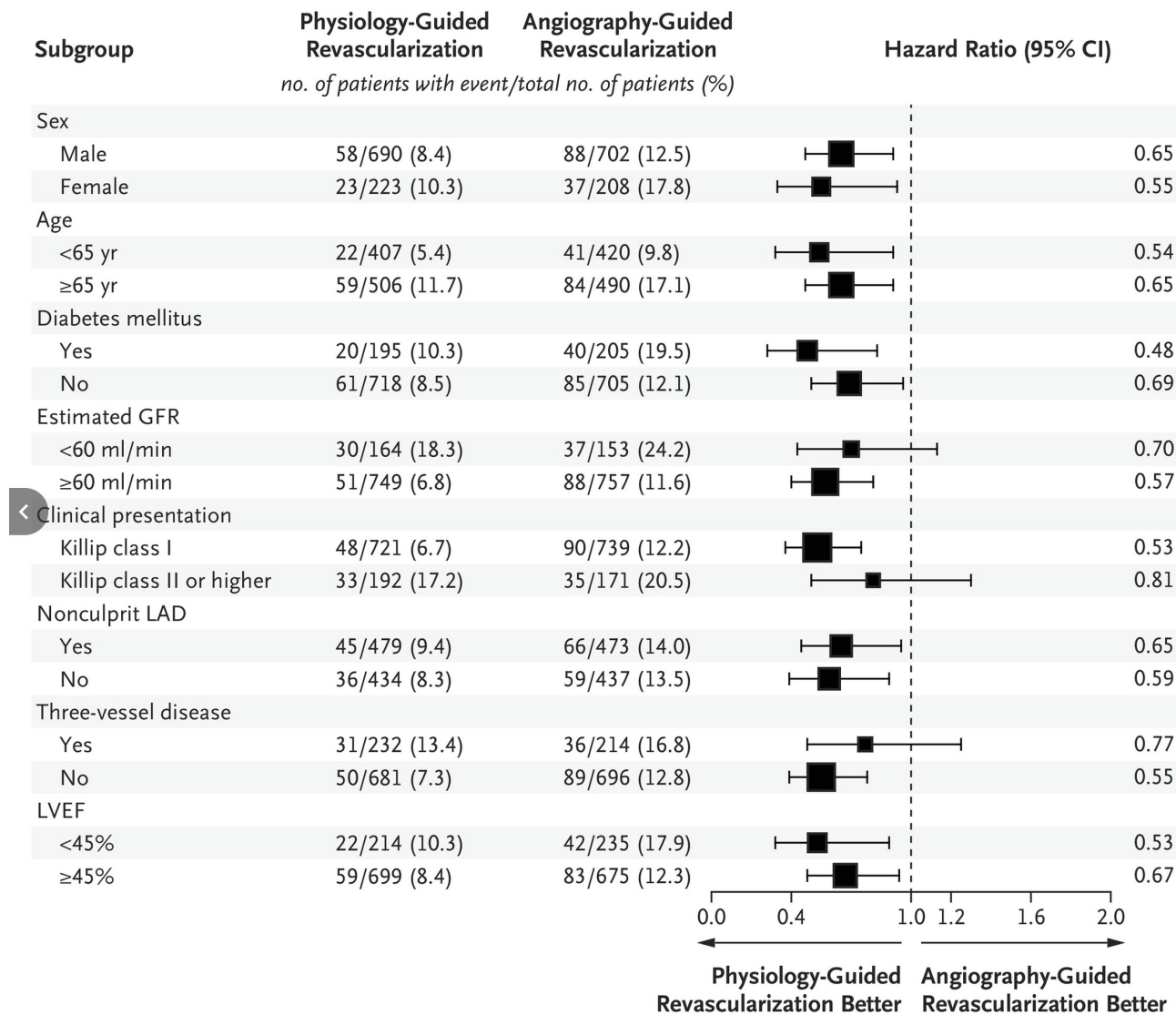
Efficacy and Safety Outcomes.

Outcome	Physiology-Guided Revascularization (N=913)	Angiography-Guided Revascularization (N=910)	Hazard Ratio (95% CI) [§]	P Value
	<i>no. of patients (%)</i>			
Primary outcome†	81 (8.9)	125 (13.7)	0.62 (0.47–0.83)	<0.001
Secondary outcomes				
Cardiovascular death or myocardial infarction	52 (5.7)	96 (10.5)	0.52 (0.37–0.73)	
Death				
Cardiovascular death	36 (3.9)	46 (5.1)	0.77 (0.50–1.20)	
Cardiovascular death	20 (2.2)	31 (3.4)	0.64 (0.36–1.12)	
Noncardiovascular death	16 (1.8)	15 (1.6)	1.07 (0.53–2.17)	
Myocardial infarction	35 (3.8)	73 (8.0)	0.47 (0.31–0.70)	
Procedure-related	15 (1.6)	33 (3.6)	0.45 (0.24–0.83)	
Spontaneous	21 (2.3)	45 (4.9)	0.46 (0.27–0.77)	
Ischemic stroke	3 (0.3)	4 (0.4)	0.75 (0.17–3.35)	
Ischemia-driven coronary revascularization	29 (3.2)	47 (5.2)	0.61 (0.38–0.97)	
Other outcomes				
Stent thrombosis	6 (0.7)	11 (1.2)	0.54 (0.20–1.47)	
Definite	6 (0.7)	10 (1.1)	0.60 (0.22–1.65)	
Probable	0	1 (0.1)	—	
Safety outcomes				
Composite of contrast-associated acute kidney injury or BARC stage 3, 4, or 5‡	42 (4.6)	65 (7.1)	0.63 (0.43–0.93)	0.02
Contrast-associated acute kidney injury	20 (2.2)	36 (4.0)	0.55 (0.32–0.94)	
BARC stage 3, 4, or 5	23 (2.5)	33 (3.6)	0.69 (0.41–1.18)	



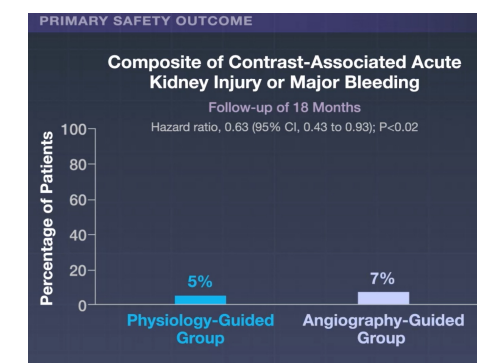
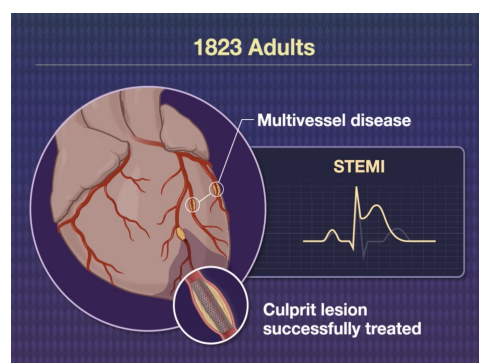
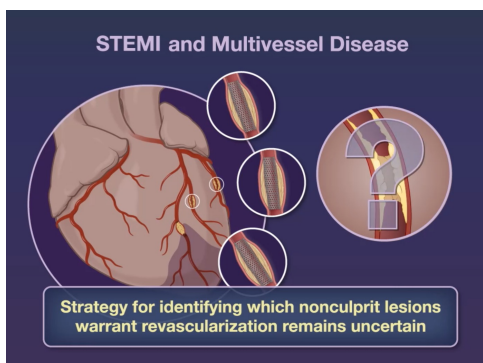
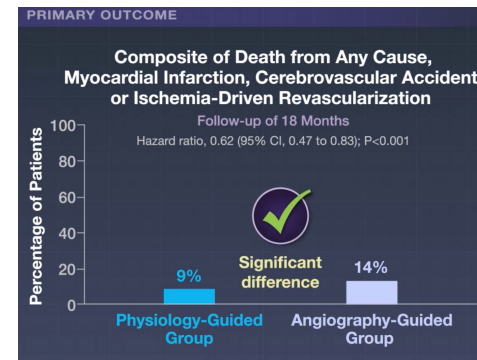
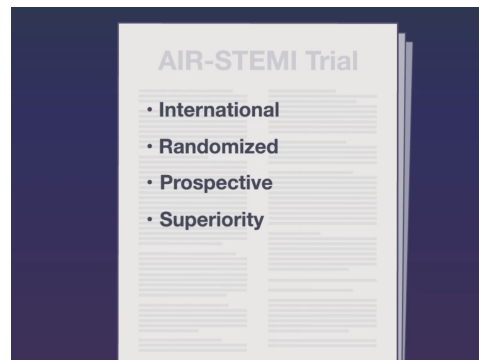
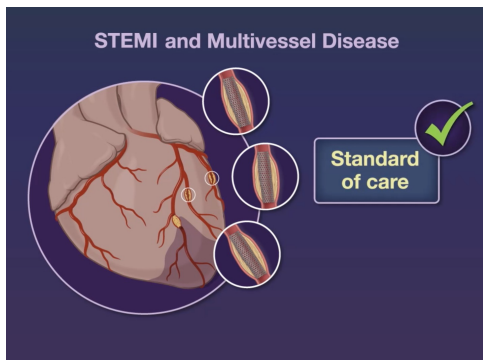
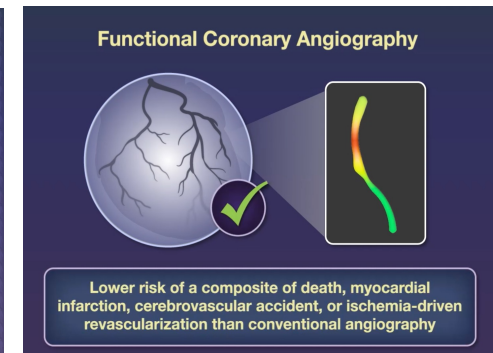
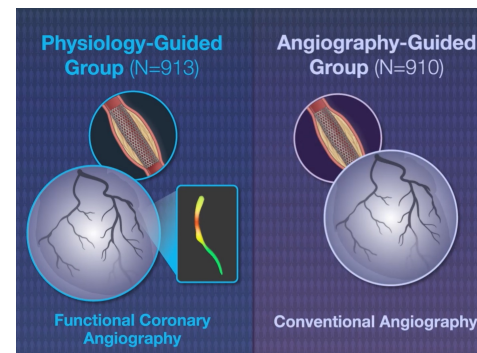
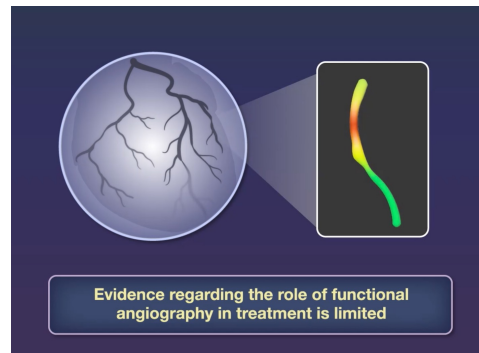
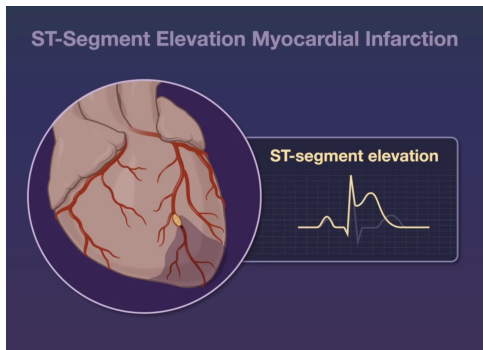
Primary-Outcome Events after Revascularization.

Patients were randomly assigned to undergo physiology-guided revascularization or angiography-guided revascularization.



Subgroup Analysis of the Primary Outcome.

The sizes of the squares are proportional to the number of patients in each subgroup. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to evaluate treatment effects. The estimated glomerular filtration rate (GFR) was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula. LAD denotes left anterior descending coronary artery, and LVEF left ventricular ejection fraction.



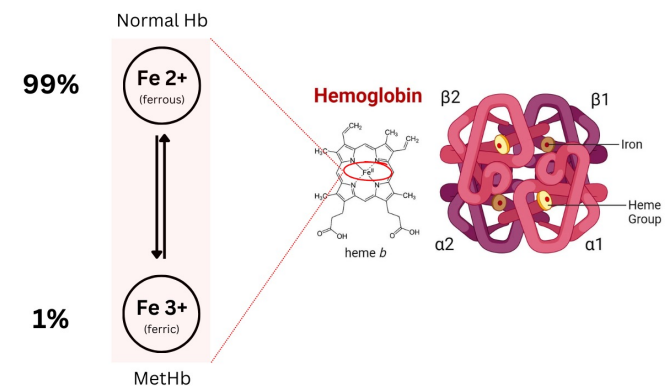
Eine **Methämoglobinämie** ist eine Bluterkrankung, bei der das Eisen im Hämoglobin von der doppelwertigen (Fe^{2+}) in die dreiwertige (Fe^{3+}) Form oxidiert ist, wodurch es **funktionsunfähig für den Sauerstofftransport** wird.

Ursachen und Formen

- **Angeborene Form (kongenital):** Beruht meist auf einem genetischen Mangel des Enzyms *NADH-Cytochrom-b5-Reduktase* oder dem Vorkommen struktureller Hämoglobinvarianten (HbM).
- **Erworbene Form (acquired):** Die weitaus häufigere Form entsteht akut durch den Kontakt mit oxidierenden Chemikalien oder Medikamenten.
- **Auslösende Substanzen:** Dazu gehören **Lokalanästhetika** wie *Benzocain* und *Prilocain*, Medikamente wie ***Dapson* oder *Sulfonamide***, sowie **Nitrite/Nitrate** in Lebensmitteln oder verunreinigtem Brunnenwasser (besonders gefährlich für Säuglinge).



Hemoglobin and Methemoglobin





Measurement report

16.02.17 09:10

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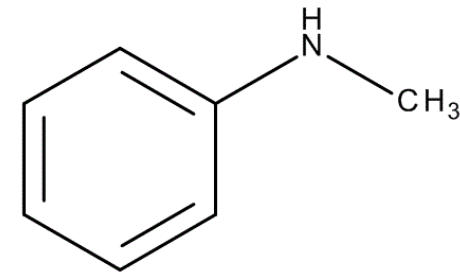
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Operator ID : DR.ABG

CCU Local District Hospital

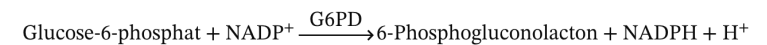
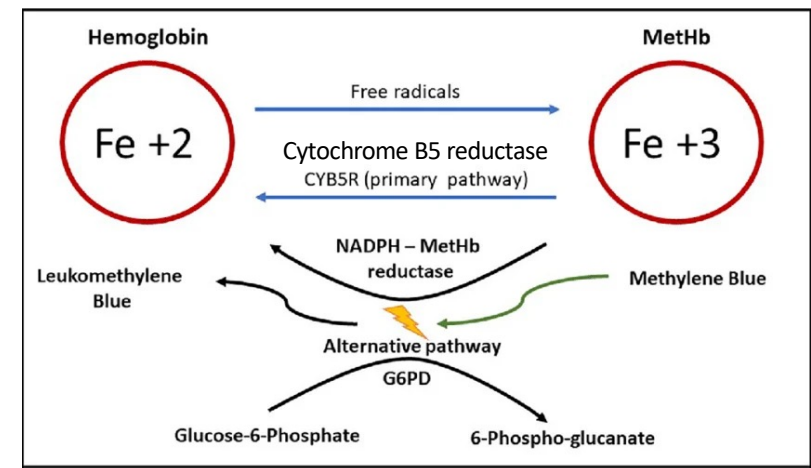
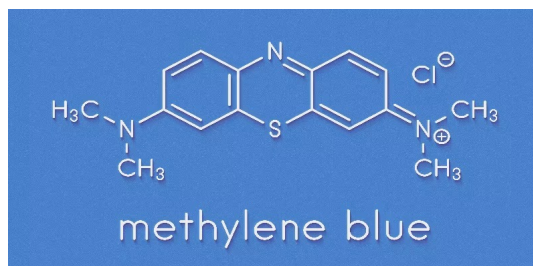
Pat. ID	047328	
Patient Name	Mr. White	
Date of birth	03.05.72	
Remark	Room Air	
FIO ₂	0.21	
Temperature	37.0 °C	
pH	7.390	[7.350 – 7.450]
pCO ₂	4.99 kPa	[4.67 – 6.00]
pO ₂	12.25 kPa	[10.67 – 13.33]
cHCO ₃ ⁻	24.0 mmol/L	[22 – 26]
BE	0.7 mmol/L	[-2.0 – +2.0]
Na ⁺	140.0 mmol/L	[135.0 – 148.0]
K ⁺	3.90 mmol/L	[3.50 – 4.50]
Cl ⁻	100.0 mmol/L	[98.0 – 107.0]
Ca ²⁺	1.200 mmol/L	[1.120 – 1.320]
Hct	40.0 %	[35.0 – 50.0]
tHb	130.0 g/L	[120.0 – 150.0]
COHb	1.0 %	[0.5 – 2.5]
O ₂ Hb	97.0 %	[95.0 – 99.0]
MetHb	1.0 %	[0.4 – 1.5]
SO ₂	99.0 %	[75.0 – 99.0]
Glu	4.0 mmol/L	[3.3 – 6.1]
Lac	1.0 mmol/L	[0.4 – 2.2]

N-Methylanilin (auch *N-Monomethylanilin* oder *NMA*) ist eine organisch-chemische Verbindung aus der Gruppe der sekundären aromatischen Amine. Es besitzt die Summenformel **C₇H₉N** (Strukturformel: C₆H₅NHCH₃) und ist ein Derivat des Anilins, bei dem ein Wasserstoffatom der Aminogruppe durch eine Methylgruppe substituiert wurde.



1. Wirkungsmechanismus

- **Oxidation des Eisens:** Das Hämoglobin (Hb) in den roten Blutkörperchen enthält zweiwertiges Eisen (Fe²⁺), das für den Sauerstofftransport verantwortlich ist. N-Methylanilin (bzw. dessen Abbauprodukte) führt zu einer Oxidation dieses Eisens in die dreiwertige Form (Fe³⁺).



Outbreak of Severe Methemoglobinemia during Maritime Migration

Migrants crossing the Central Mediterranean sea route travel in overcrowded vessels, where fuel may leak and contaminate seawater accumulating on the vessel floor, resulting in prolonged dermal **exposure and fuel-related skin injuries**. Since March 2024, clusters of cases of severe acquired **methemoglobinemia** with no apparent cause have been identified by clinicians in Lampedusa at disembarkation among migrants arriving in Italy.

We conducted a coordinated clinical and toxicologic investigation to characterize these cases and identify the underlying cause. Biologic samples were obtained from a subset of patients and analyzed for methemoglobin-inducing agents. A fuel sample from a vessel associated with one of the case clusters was also analyzed.

Conclusions

This investigation identified **dermal absorption of the gasoline additive N-methylaniline** from fuel-contaminated seawater as the likely cause of recurrent, life-threatening methemoglobinemia associated with maritime migration. These findings underscore the importance of methylene blue availability and frontline diagnostic capacity in settings where similar exposure conditions may occur.

The Central Mediterranean sea route, connecting primarily Libya and Tunisia with southern Italy, is one of the major maritime migration routes to Europe and has been associated with the largest number of reported migrant deaths and disappearances worldwide. Migrants commonly spend many hours or even days in overcrowded, unseaworthy vessels, where fuel may leak and contaminate seawater accumulating on the floor of the boat, resulting in prolonged dermal contact. Acute conditions, including hydrocarbon inhalation and fuel burns, have been described in this setting. However, reports of severe acquired methemoglobinemia, an uncommon but potentially life-threatening condition, have been lacking in the context of maritime migration.

Beginning in **March 2024, clinicians in Lampedusa**, Italy, a primary point of arrival along the Central Mediterranean route, identified clusters of migrants presenting at disembarkation with severe methemoglobinemia. The recurrence of these cases suggested a shared exposure in this context. We conducted a coordinated clinical and toxicologic investigation to characterize these cases and identify the underlying cause.

Case Identification

Cases were first identified in March 2024 during routine clinical evaluation of migrants at disembarkation in the emergency health care facility in Lampedusa, Italy. Elevated methemoglobin levels were incidentally detected on arterial blood gas analysis with CO-oximetry (a multiwavelength test that measures abnormal types of hemoglobin in the blood, including carboxyhemoglobin and methemoglobin), prompting consultation with the Pavia Poison Control Center (PPCC), a national referral center for clinical toxicology. These early cases served as sentinel events, initiating a coordinated investigation through the PPCC. As additional cases were identified, a recurring clinical pattern was recognized, and targeted assessment was progressively incorporated into triage at disembarkation and subsequent evaluation. The cases included in this investigation were identified between March 2024 and December 2025 from toxicologic consultation requests to the PPCC. Requests originated primarily from clinicians at the emergency health care facility in Lampedusa and from referral hospitals in Sicily, with a small number from other points of arrival. Migrants who had an elevated methemoglobin level detected at the initial evaluation after disembarkation were included in the study. Cases were grouped according to the date of disembarkation to assess temporal clustering.

Clinical Management

Clinical coordination among the PPCC, clinicians in Lampedusa, and referral hospitals was established to support case identification and management. The health care facility in Lampedusa faced considerable logistic and resource constraints, including limited laboratory capacity, lack of access to blood transfusion, and reliance on a single helicopter for transfer to referral hospitals in Sicily. Accordingly, a standardized management protocol that was based on methemoglobin levels, the presence of anemia, and clinical severity was implemented in Lampedusa to guide treatment and prioritize transfers. Methylene blue (a treatment for methemoglobinemia), which had been initially unavailable in Lampedusa, was subsequently stocked on site.

Toxicologic Investigation

The PPCC coordinated the obtaining of biologic samples from a subset of patients to identify potential causative agents. Samples were obtained at referral hospitals 6 to 48 hours after disembarkation. Timing and collection depended on logistic feasibility.

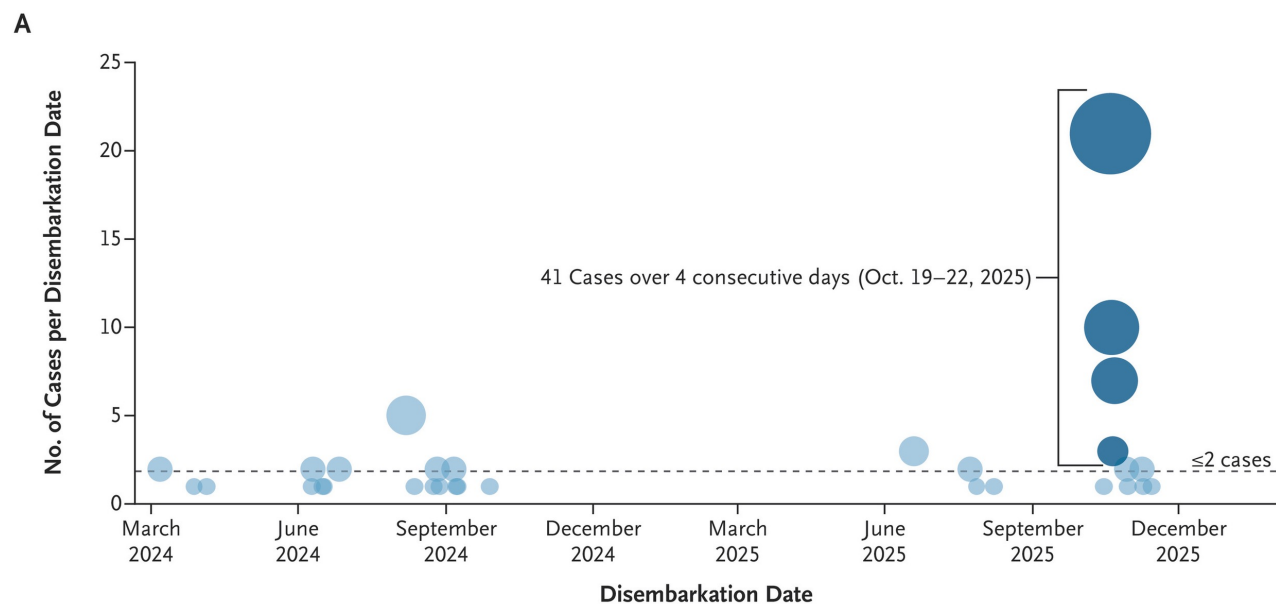
Clinical and Demographic Characteristics

Characteristic	Patients (N=82)
Male sex — no. (%)†	74 (90)
Age — yr‡	
Median (IQR)	22.5 (19.5–28.0)
Range	15–47
Region of origin — no. (%)	
South Asia	27 (33)
Sub-Saharan Africa	15 (18)
Middle East	9 (11)
North Africa	8 (10)
Unknown	23 (28)
Clinical presentation at first evaluation — no./total no. (%)	
Dyspnea	22/68 (32)
Altered mental status	19/68 (28)
Evidence of fuel exposure — no. (%)§	51 (62)
▶ Methemoglobin level at first measurement¶	
Median (IQR) — %	44.6 (32.0–55.7)
Range — %	3.6–68.0
▶ ≥25% — no. (%)	68 (83)
▶ ≥50% — no./total no. (%)	34/79 (43)
Treatment	
Methylene blue	
≥1 Dose — no. (%)	74 (90)
Multiple doses — no./total no. (%)	41/66 (62)
Ascorbic acid — no. (%)	34 (41)
N-acetylcysteine — no. (%)	39 (48)
Blood transfusion among patients with hemolytic anemia — no./total no. (%)**	26/26 (100)
Laboratory findings — no./total no. (%)††	
Hemolytic anemia‡‡	38/51 (75)
▶ G6PD deficiency§§	16/44 (36)
Complications and outcomes††	
Splenic rupture — no./total no. (%)	4/30 (13)
Death — no. (%)	2 (2)

Detection and Concentrations of N-Methylaniline, Aniline, and Their Metabolites in Biologic Samples from 39 Patients.

Analyte and Matrix	Detected in Patient	Median Concentration (IQR) or Range†
	no./total no. (%)	
N-methylaniline		
Urine	26/37 (70)	5008 (2033–10,500)
Blood	14/38 (37)	504 (285–2025)
N-methyl-p-aminophenol		
Urine	36/37 (97)	137,328 (68,930–528,596)
Blood	1/38 (3)	9500
Aniline		
Urine	17/37 (46)	1475 (370–2339)
Blood	3/38 (8)	740–2979
p-Aminophenol		
Urine	18/37 (49)	6699 (3775–10,181)
Blood	0/38	—

Severe methemoglobinemia can be associated with spontaneous splenic rupture. While historically distinct, recent clinical evidence—notably a landmark **September 2026 study** published in the *New England Journal of Medicine* ([NEJM](#))—has firmly established a link between the two conditions.



Temporal Distribution of Methemoglobinemia Cases and Associated Cutaneous Findings.

Panel A shows the temporal distribution of methemoglobinemia cases according to disembarkation date between March 2024 and December 2025. The size of the circle is proportional to the number of cases identified on each date. Most dates were associated with one or a few cases (light blue circles), whereas a marked temporal cluster occurred over a period of 4 consecutive days (October 19–22, 2025), which accounted for 41 cases (dark blue circles). Smaller temporal groupings were observed at other time points. Panels B, C, and D show fuel-related cutaneous burns at presentation in affected patients. Cutaneous burns compatible with prolonged contact with fuel–seawater mixtures predominantly involved the gluteal region (Panels B and C) and lower limbs — areas that are most frequently in contact with contaminated seawater during maritime crossings. Migrants are often seated in the lower compartments of overcrowded vessels and may remain partially immersed for prolonged periods. More-extensive involvement, including dorsal lesions (Panel D), was observed in some patients.



Discussion

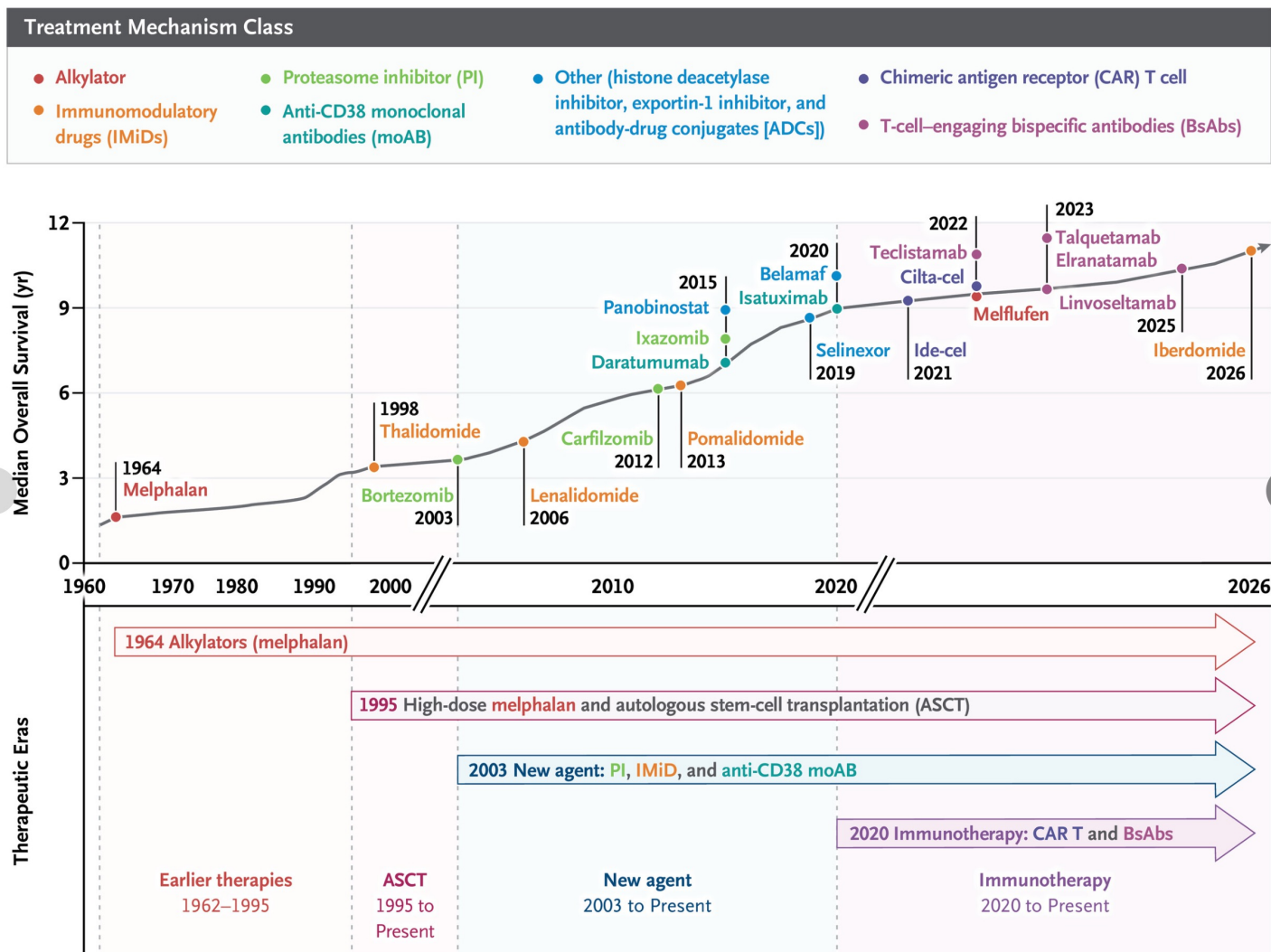
This investigation identified ***N*-methylaniline exposure** as the likely cause of severe methemoglobinemia in migrants rescued along the Central Mediterranean sea route. The repeated occurrence of severe methemoglobinemia at initial evaluation after disembarkation, with temporal clustering and the involvement of migrants from diverse geographic origins, suggested a shared exposure during maritime transit. No apparent cause of methemoglobinemia emerged from the initial clinical evaluation. Fuel exposure was the only consistent finding; however, gasoline is not known to cause methemoglobinemia, a factor that prompted further investigation.

These findings identify a cause of **severe, recurrent methemoglobinemia** in migrants along the Central Mediterranean sea route, which was attributable to dermal absorption of *N*-methylaniline from fuel-contaminated seawater during maritime transit. The resulting severe methemoglobinemia is frequently life-threatening, and prompt recognition and treatment with methylene blue are critical, even in resource-limited reception settings where this antidote may not be routinely available. Ensuring the availability of methylene blue and frontline diagnostic capacity, including pulse CO-oximetry and **rapid point-of-care G6PD testing**, is essential to improve outcomes in prehospital and maritime rescue settings where similar exposure conditions may occur.

Treatment Decisions in Multiple Myeloma

Summary

Revolutions in transplantation and targeted and immune therapies have transformed multiple myeloma from a disease with an associated survival of a few years into one for which functional cure is an emerging goal. This abundance of effective therapies has created clinical complexity. Here we provide a practical framework, anchored in trial evidence and informed by emerging biologic discoveries, for the navigation of treatment decisions across the disease spectrum. We outline how cytogenetic and genomic risk stratification, functional fitness, and measurable residual disease status individualize therapy in newly diagnosed disease, in which quadruplet induction therapy is now standard and the role of autologous transplantation is being reevaluated. Regarding relapse, we address the sequencing of B-cell maturation antigen–directed chimeric antigen receptor (CAR) T cells, bispecific antibodies, and antibody–drug conjugates, emphasizing T-cell fitness and multiantigen targeting to counter exhaustion and antigen escape. We also consider early interception in high-risk smoldering myeloma. Throughout, we underscore that enrollment of patients in clinical trials should be considered in order to ensure continued progress.



Belamaf denotes belantamab mafodotin, cilta-cel denotes ciltacabtagene autoleucel, and ide-cell denotes idecabtagene vicleucel.

Navigating Treatment Decisions in Newly Diagnosed and Relapsed Multiple Myeloma

- Risk stratification — cytogenetic and genomic profiling (with the use of International Myeloma Society–International Myeloma Working Group 2025 Consensus Genomic Staging criteria), functional fitness, and measurable residual disease (MRD) — anchors individualized therapy; double-hit disease (the presence of two or more high-risk cytogenetic abnormalities) warrants intensification regardless of MRD status.
- Quadruplet induction (combinations of anti-CD38 antibody, proteasome inhibitor, immunomodulatory drug, and dexamethasone) is now standard therapy for both transplant-eligible and fit, transplant-ineligible patients.
- Autologous transplantation remains a frontline option, but the necessity of the procedure is being reevaluated; patients at standard risk for relapse who have deep MRD-negative responses to quadruplet induction may reasonably defer the procedure.

- Maintenance therapy should be risk-adapted: intensified, prolonged, and often doublet therapy for patients with high-risk disease versus therapy of potentially finite duration for patients at standard risk for relapse who have sustained MRD negativity.
- At relapse, B-cell maturation antigen (BCMA)–directed chimeric antigen receptor (CAR) T cells and bispecific antibody combinations are transformative; the use of CAR T-cell therapy early and targeting of an alternate myeloma antigen at progression counters T-cell exhaustion and antigen escape.
- Clinical-trial enrollment should be considered at every decision point, because some promising strategies remain available only at the trial stage (e.g., in vivo and allogeneic CAR T-cell therapy, trispecific-antibody therapy, cereblon E3 ligase modulators, vaccines, new targeted therapies, and the use of intensified interception in smoldering myeloma).

Risk Stratification — the Foundation of Individualized Therapy

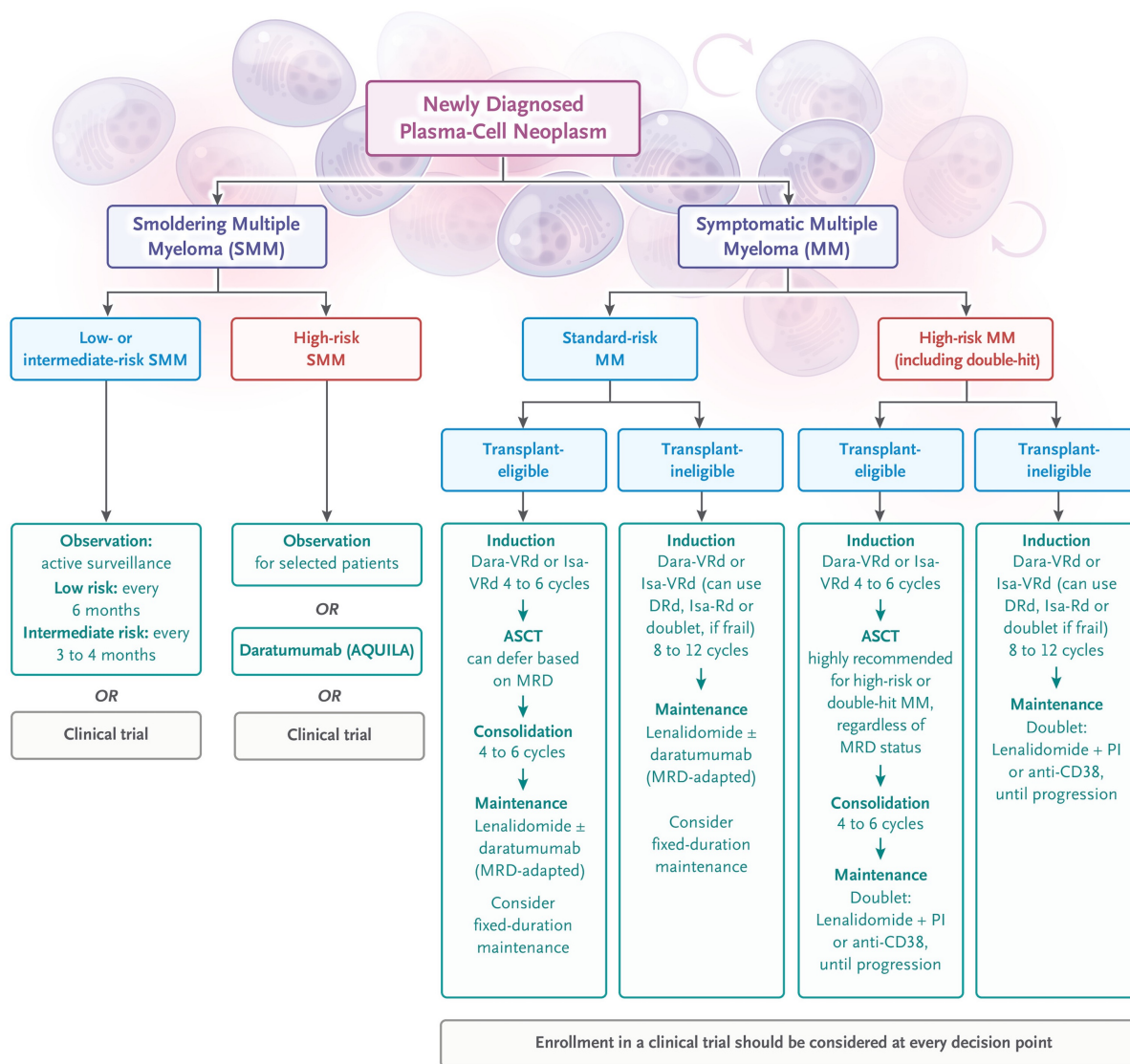
Treatment decisions begin with assessment of the biologic characteristics of the disease. Multiple myeloma is not one disease but a collection of genetically distinct entities with divergent natural histories and treatment sensitivities. The International Myeloma Society (IMS)–International Myeloma Working Group (IMWG) 2025 Consensus Genomic Staging defines high-risk disease as the presence of a del(17p) or *TP53* mutation or both ($\geq 20\%$ of clonal plasma cells); biallelic del(1p); t(4;14), t(14;16), or t(14;20) with 1q gain or amplification or del(1p); or 1q gain or amplification with del(1p). Double-hit myeloma (characterized by two or more high-risk cytogenetic features) carries the poorest prognosis, and intensified therapy (including ASCT regardless of MRD status) and doublet maintenance are recommended. This risk-adapted framework represents expert consensus rather than a strategy that has been prospectively proven to be superior.

Newly Diagnosed Myeloma

First Decision — Transplantation Eligibility

The initial consideration in the treatment of a patient with newly diagnosed multiple myeloma is whether the patient is eligible to undergo transplantation. On the basis of functional assessment, patients can undergo ASCT safely well into the eighth decade of life. Because four-drug combinations are now primary therapy for patients who are eligible for transplantation and for fit patients who are transplantation-ineligible, the decision regarding transplantation need not be finalized at diagnosis and can be deferred until the response to induction is known.

For transplantation-eligible patients, ASCT remains a frontline option, but in the era of four-drug induction and immunotherapy, its role is increasingly being reevaluated.

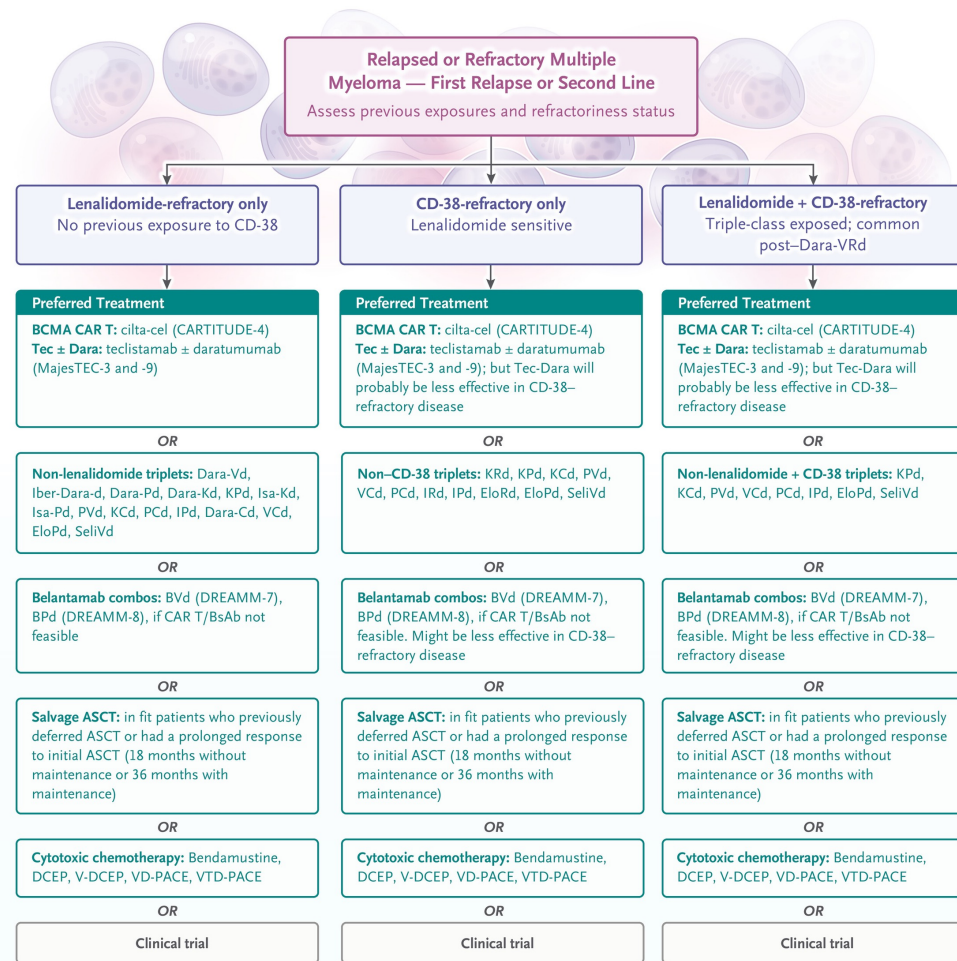


Treatment Algorithm for Newly Diagnosed Plasma-Cell Neoplasms.

Risk (standard and high) is stratified according to International Myeloma Society–International Myeloma Working Group 2025 Consensus Genomic Staging criteria. High risk is defined as the presence of any of the following: del(17p) and TP53 mutations; biallelic deletion(1p); t(4;14), t(14;16), or t(14;20) plus gain or amplification of 1q or del(1p); or gain or amplification of 1q plus del(1p). Double-hit myeloma is disease in which at least two qualifying high-risk cytogenetic features are present. Deferral of ASCT in standard-risk patients in whom there has been a first complete response should be a shared decision, with recognition that the longest reported period of progression-free survival still incorporates transplantation and that deferral may entail a potentially shorter first remission. Amp denotes amplification, D dexamethasone, dara daratumumab, del deletion, Isa isatuximab, MRD measurable residual disease, R lenalidomide, t translocation, and V bortezomib.

Algorithm Showing Second-Line Treatment in Relapsed or Refractory Multiple Myeloma at First Relapse.

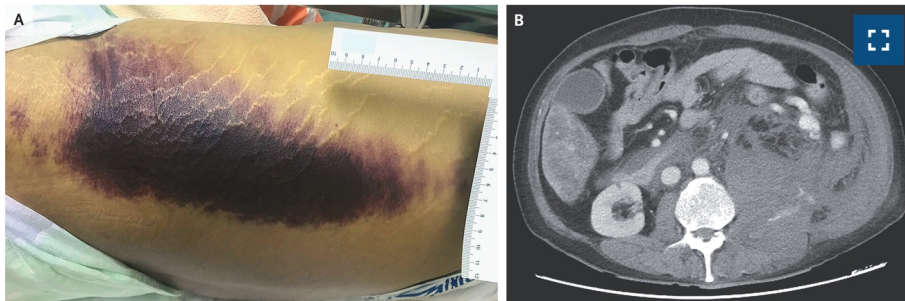
Shown are key principles for treatment. BCMA CAR T-cell therapy is preferred over bispecific-antibody therapy when both are accessible, according to guidance from the International Myeloma Working Group Immunotherapy Committee. Earlier lines of therapy are associated with superior immune fitness and better outcomes with CAR T-cell therapy, so CAR T-cell therapy should not be reserved as a last resort. Available evidence favors sequencing CAR T-cell therapy before bispecific antibodies, with better outcomes reported for bispecific-antibody salvage after CAR T-cell relapse than for CAR T-cell therapy after previous bispecific-antibody exposure. Venetoclax-based regimens should be considered for t(11;14)–positive relapsed or refractory multiple myeloma regardless of treatment approach. Lenalidomide-based regimens are less preferable if clinically significant renal disease is present. Bortezomib-based regimens are less preferable if clinically significant heart disease or uncontrolled hypertension is present. Doublet therapy should be considered rather than triplet therapy in frail patients. Clinical trials should be offered at every relapse and is the only access point for the most transformative emerging platforms (e.g., in vivo CAR T-cell therapy, trispecific T-cell engagers, CELMoDs, next-generation immunotherapies). B denotes belantamab mafodotin; BCMA B-cell maturation antigen; Cd cyclophosphamide and dexamethasone; ciltacel ciltacabtagene autoleucel; DCEP dexamethasone, cyclophosphamide, etoposide, and cisplatin; Elo elotuzumab; I isatuximab; K carfilzomib; P pomalidomide; PACE cisplatin, doxorubicin, cyclophosphamide, and etoposide; Pd pomalidomide and dexamethasone; Rd lenalidomide and dexamethasone; Seli selinexor; tec teclistamab; and Vd bortezomib and dexamethasone.



Conclusions

Modern management of multiple myeloma calls for a systematic approach: accurate risk stratification, evidence-based induction and transplantation decisions, MRD-guided maintenance tailored to risk, and early, strategic deployment of T-cell–redirecting therapies at relapse. Several principles should guide decision making. Quadruplet induction is now standard. ASCT remains an important frontline option for eligible patients, although its role is being reevaluated in the era of quadruplet, CAR T-cell, and bispecific antibody-based induction approaches. Fixed-duration maintenance may suffice for patients at standard risk for progression without upfront ASCT, whereas patients at high risk are candidates for intensified, prolonged maintenance. At relapse, BCMA-directed CAR T-cell therapy and bispecific antibody combinations are both effective and preferred. Multiantigen targeting can address antigen escape. The biologic principles of treatment (T-cell fitness and immune remodeling) is beginning to inform therapy selection.

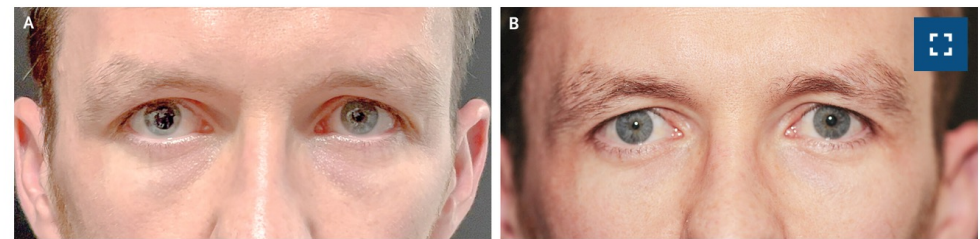
Grey Turner's Sign



A 46-year-old man with cirrhosis presented to the emergency department with a 1-week history of left flank pain. He reported no recent trauma, medical procedures, or use of anticoagulant or antiplatelet medications. His heart rate was 128 beats per minute, and his blood pressure was 64/37 mm Hg. Physical examination was notable for a large ecchymosis on the left flank — a finding known as Grey Turner's sign — that was tender to palpation (Panel A; ruler branding has been masked). Grey Turner's sign may be seen in cases of intraabdominal or retroperitoneal bleeding. Although this finding is classically associated with pancreatitis, it may occur in other conditions, and abdominal imaging is required to identify the underlying cause. Laboratory studies were notable for anemia, severe thrombocytopenia, and metabolic values that yielded a Model for End-Stage Liver Disease score of 26, which indicates advanced liver disease with a substantial risk of death in the short term. Point-of-care ultrasonography of the abdomen showed no intraabdominal free fluid. Computed tomography of the abdomen with administration of contrast material showed active extravasation of the contrast material into the left psoas muscle and retroperitoneal space (Panel B, axial view). A diagnosis of spontaneous retroperitoneal hemorrhage due to coagulopathy of liver disease was made. Transarterial angioembolization of the bleeding vessel was performed, and the bleeding was controlled. After a 3-week hospital stay, the patient was discharged home.

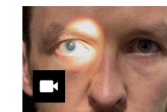
Adie Tonic Pupil

(differentiate from Argyl-Robertson pupil)



A 36-year-old man presented to the ophthalmology emergency department with a 1-week history of asymptomatic anisocoria. Physical examination revealed that the right pupil was dilated (Panel A) and constricted minimally to light and the left pupil constricted briskly to light ([Video 1A](#)). With accommodation, both pupils constricted and the right pupil sustained constriction. Visual acuity, extraocular movements, and deep-tendon reflexes were normal. Administration of dilute pilocarpine (0.125% concentration) to both eyes resulted in more constriction of the right pupil than the left pupil (Panel B), a finding that indicated denervation hypersensitivity in the right eye. The glycated hemoglobin level was normal. A diagnosis of Adie tonic pupil was made. Adie tonic pupil is an idiopathic pupillary disorder that is caused by postganglionic parasympathetic denervation of the iris sphincter. It results in light–near dissociation, tonic constriction with accommodation, and cholinergic hypersensitivity in the denervated pupillary muscle. On slit-lamp examination, segmental vermiform movements of the iris due to uneven denervation and partial reinnervation of the iris sphincter muscle were seen ([Video 1B](#), right eye). Reassurance regarding the benign nature of the diagnosis was provided. At a 3-week follow-up visit, the anisocoria remained.

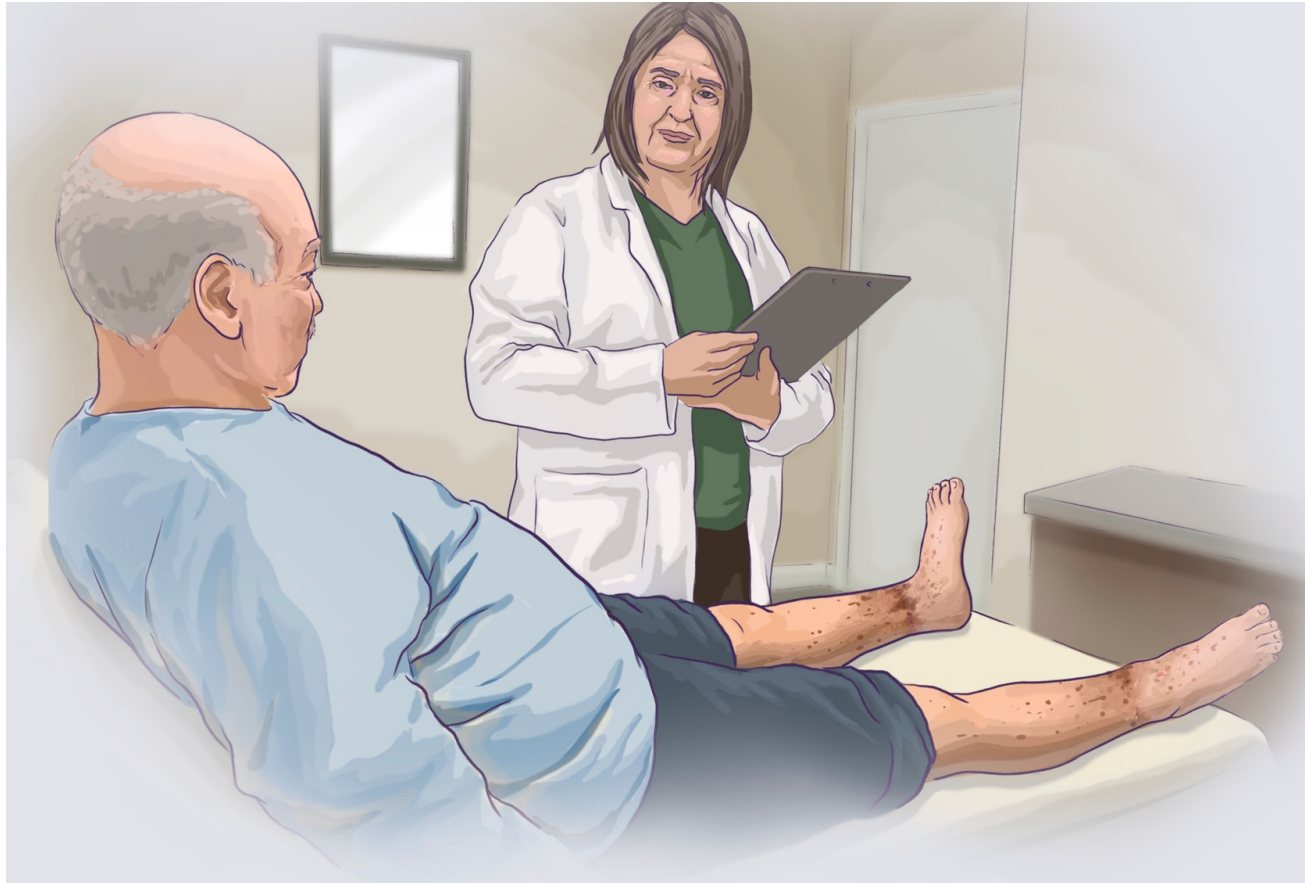
VIDEOS



Adie Tonic Pupil 0m 21s

A Rash and Red Urine

A Case from Brigham and Women's Hospital



Case Presentation

A 73-year-old man with a history of heart failure presented to the emergency department with a rash, weight gain, dyspnea, and new-onset visible hematuria.

Three weeks before the current presentation, the patient noticed a new rash on his legs and feet and was evaluated in the dermatology clinic. Biopsy of purpuric lesions of the legs and feet revealed leukocytoclastic vasculitis. Direct immunofluorescence staining was positive for IgA. He was advised to start with a trial of conservative treatment that included rest, compression stockings, and topical fluocinonide 0.05% ointment, with the plan to consider oral prednisone therapy if the rash worsened.

One week before the current presentation, he presented to his primary care physician with edema of the legs and feet with an unchanged rash and dyspnea on exertion, and he reported a weight gain of 5 kg over a period of 2 weeks. He reported no abdominal pain, arthralgias, fevers, or headaches. He was admitted to the hospital for treatment of presumed worsening acute decompensated heart failure and was then transferred home with hospital support services for ongoing intravenous diuresis.

One day before the current presentation, new-onset visible hematuria developed and the patient was found to have an elevated serum creatinine level. He was transferred to our hospital the next day.

Patient History

Medical History

Atrial fibrillation
Heart failure with mid-range ejection fraction (ejection fraction, 45%), New York Heart Association Class II
Hyperlipidemia
Hypertension
Iron-deficiency anemia
Nephrolithiasis

Surgical History

Emergency pancreatoduodenectomy for ruptured aneurism of the superior mesenteric artery with pancreatic injury (2 years before the current presentation)
Ventral hernia repair (1 year before the current presentation)

Allergies

Chlorhexidine (rash)

Medications

Aspirin, 81 mg daily
Atorvastatin, 80 mg daily
Carvedilol, 12.5 mg twice daily
Ferrous sulfate, 325 mg every other day
Furosemide (oral), 40 mg daily
Lisinopril, 10 mg daily
Rivaroxaban, 20 mg daily
Spironolactone, 25 mg daily

Social History

Retired chemist
Reports occasional alcohol consumption
Reports no history of cigarette smoking
Reports no illicit drug use

Family History

Mother with Parkinson's disease
Father with myocardial infarction

Not a diagnosis



Warum
so wenig
Eisen?

Physical Examination

Vital signs

Heart rate, 86 beats per minute

Blood pressure, 142/96 mm Hg

Temperature, 36.4°C

Oxygen saturation, 98% while the patient was breathing ambient air

Body-mass index, 26.8

General appearance

Lying propped up in bed

Comfortable-appearing

Head, eyes, ears, nose, and throat

Mucous membranes moist

No lymphadenopathy

Heart

Normal rate and irregularly irregular rhythm

No murmurs, rubs, or gallops

Jugular venous pressure elevated, at 10 cm of water

Lungs

No increased work of breathing

Clear on auscultation

No rales, rhonchi, or wheezes

Abdomen

Normal bowel sounds

Soft, nontender on palpation, and nondistended

No costovertebral angle tenderness

No shifting dullness

Arms and legs

Warm and well perfused

2+ radial and dorsalis pedis pulses

1+ edema of the legs and feet, worse on the left side

No erythema, swelling, tenderness, or gross deformity of the elbows, wrists, knees, or ankles

Skin

Scattered petechiae and purpuric macules on the ankles and distal legs



Purpuric lesions of the legs and feet.

Purpura Schönlein-Henoch

Benannt ist sie nach den deutschen Ärzten Johann Lukas Schönlein (1793–1864), der die „Peliosis rheumatica“ 1837 beschrieb, und Eduard Heinrich Henoch (1820–1910). Die Purpura Schönlein-Henoch wurde in der Chapel-Hill-Konferenz 2012 in IgA-Vaskulitis umbenannt.

Laboratory Evaluation

Basic Metabolic Panel and Complete Blood Count

Variable*	Result	Normal Range	Flag
Sodium (mmol/liter)	137	136–145	–
Potassium (mmol/liter)	3.8	3.5–5.2	–
Chloride (mmol/liter)	100	95–106	–
Carbon dioxide (mmol/liter)	25	20–31	–
Urea nitrogen (mg/dl)	33	9–23	High
Creatinine (mg/dl)	2.81	0.50–1.30	High
Estimated glomerular filtration rate (ml/min/1.73 m ²)	23	>60	Low
Glucose (mg/dl)	105	74–106	–
White-cell count (per mm ³)	4750	4000–10,000	–
Red-cell count (per mm ³)	2.97	4.50–5.90	Low
Hemoglobin (g/dl)	7.8	13.5–17.5	Low
Hematocrit (%)	25.1	41.0–53.0	Low
Mean corpuscular volume (fl)	84.5	80.0–100.0	–
Mean corpuscular hemoglobin (pg)	26.3	27.0–31.0	Low
Mean corpuscular hemoglobin concentration (g/dl)	31.1	32.0–36.0	Low
Platelet count (per mm ³)	231,000	150,000–450,000	–
Red-cell distribution width (%)	16.9	11.5–14.5	High

*The baseline creatinine level was 1.0 mg per deciliter; 1 week before admission, the creatinine level was near baseline, at 1.2 mg per deciliter. The baseline hemoglobin level was 8.0 g per deciliter.

Warum hat er Eisenmangel-Anämie?

Urinalysis

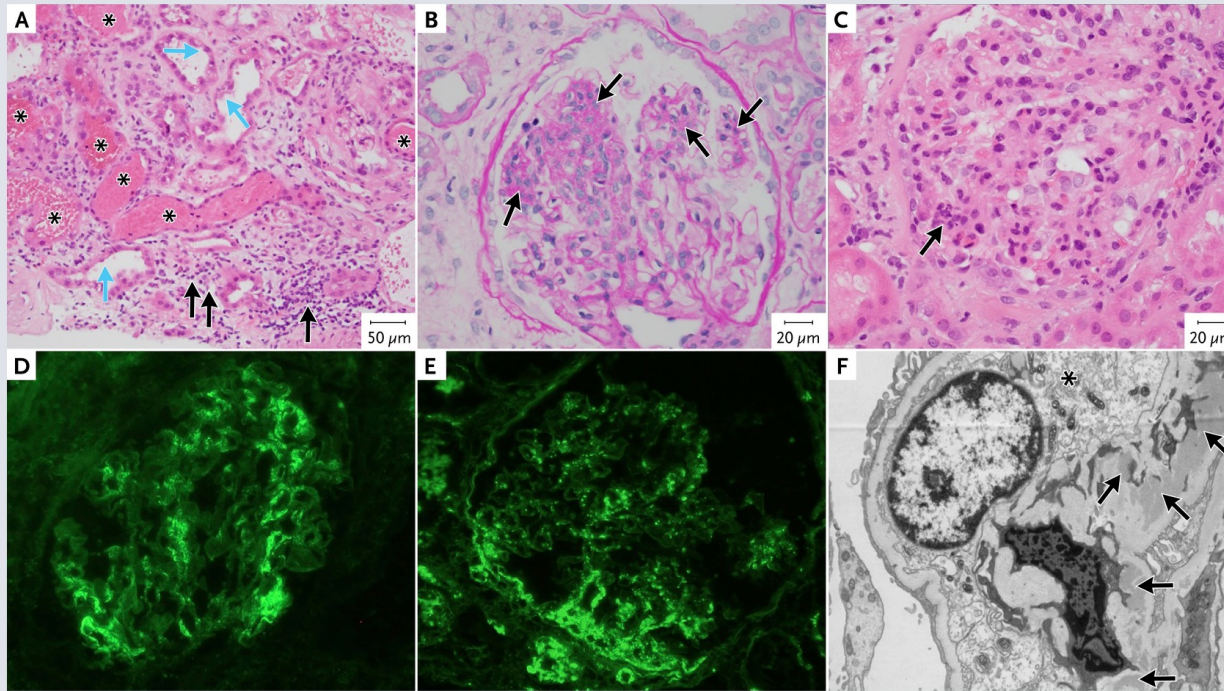
Variable*	Result	Normal Range	Flag
Bilirubin	Negative	Negative	–
Blood	3+	Negative	High
Glucose	Negative	Negative	–
Ketones	Negative	Negative	–
Leukocyte esterase	Trace	Negative	High
Nitrites	Negative	Negative	–
pH	6.0	4.5–8.0	–
Protein	2+	Negative	High
Specific gravity	1.015	1.003–1.035	–
Urobilinogen	Negative	Negative	–
Red cells (per high-power field)	182	Negative	High
White cells (per high-power field)	17	Negative	High
Bacteria (per high-power field)	1+	Negative	High
Urine creatinine (mg/dl)	74.8	–	–
Urine microalbumin (mg/dl)	48.6	0.0–2.0	High
Urine protein (mg/dl)	101.0	0.0–15.0	High
Urine microalbumin-to-creatinine ratio (mg per g)	649.7	0.0–30.0	High

*Previous urinalyses were only notable for 1+ protein.

Additional Testing

Variable*	Result	Normal Range	Flag
N-terminal pro-B-type natriuretic peptide (pg/ml)	33,438	<900	High
Erythrocyte sedimentation rate (mm/hr)	43.4	0.0–20.0	High
Albumin (g/dl)	3.1	3.5–5.2	Low
C-reactive protein (mg/liter)	37.0	0.0–8.0	High
C3 (mg/dl)	91	90–180	–
C4 (mg/dl)	14	10–40	–
Antineutrophil cytoplasmic antibodies	Negative	Negative	–
Rheumatoid factor (IU/ml)	<13	<13	–
Cryoglobulin (g/liter)	Negative	Negative	–
Serum protein electrophoresis	Normal	Normal	–
Antinuclear antibody	Negative	Negative	–

*The baseline N-terminal pro-B-type natriuretic peptide level was approximately 3000.



In Panel A, hematoxylin and eosin staining (magnification $\times 200$) reveals acute injury with flattened epithelial lining (blue arrows) associated with red-cell casts (asterisks) and acute interstitial inflammation (black arrows). Periodic acid–Schiff staining of a glomerulus ($\times 400$) reveals mesangial hypercellularity (Panel B, arrows). Hematoxylin and eosin staining of a glomerulus ($\times 400$) reveals glomerulitis with endocapillary hypercellularity (Panel C, arrow) typical of active glomerulonephritis. In Panels D and E, immunofluorescence studies on frozen tissue show mesangial deposits dominant for IgA along with C3 mesangial reactivity. In Panel F, electron microscopy reveals mesangial electron dense deposit (arrows) along with endothelial swelling (asterisk).

Pathological Analysis

The patient's creatinine level continued to rise rapidly, up to 3.4 mg per deciliter on hospital day 2, and the decision was made to perform a kidney biopsy to establish a definitive diagnosis.

Examination of the kidney-biopsy specimen with light microscopy revealed segmental endocapillary proliferation in one glomerulus, one active cellular crescent (7%), and two glomeruli with fibrocellular crescents. There was moderate interstitial inflammation with severe acute tubular injury, along with numerous red-cell casts that were attributed to the active glomerulonephritis. Moderate chronic changes were noted, with 11 of 25 glomeruli (44%) showing global sclerosis and with interstitial fibrosis and tubular atrophy (IFTA) in 20% of the renal cortex, along with moderate arterial and arteriolar sclerosis. Immunofluorescence studies revealed mesangial deposits of IgA, C3, and IgM.

The MEST-C score (which is based on five histopathologic indicators: mesangial hypercellularity [M], endocapillary hypercellularity [E], segmental glomerulosclerosis [S], tubular atrophy or interstitial fibrosis [T], and the presence of crescents [C]) was M1, E1, S1, T0, C1.

The patient's rapid decline in kidney function (>50% decline in the glomerular filtration rate within a period of 3 months), along with active glomerular inflammation, supported a clinical syndrome of rapidly progressive glomerulonephritis.

Given the IgA-dominant glomerulonephritis and the accompanying vasculitic rash, a diagnosis of IgA vasculitis with nephritis and rapidly progressive glomerulonephritis was made.

What Would You Do?

Which one of the following is the most appropriate initial treatment option for IgA vasculitis with nephritis and rapidly progressive glomerulonephritis?

Select a strategy to see whether it is an appropriate choice and to learn about the probable outcome. You will be able to return to the list of choices to review the probable consequences of each choice.

- ☐ A Initiate immunosuppressive therapy with intravenous glucocorticoids
- ☐ B Initiate plasmapheresis
- ☐ C Initiate RAAS inhibition with an ACE inhibitor or an ARB
- ☐ D Initiate dialysis

☒ A Initiate immunosuppressive therapy with intravenous glucocorticoids



☐ B Initiate plasmapheresis



☐ C Initiate RAAS inhibition with an ACE inhibitor or an ARB



☐ D Initiate dialysis



IgA Vasculitis with Nephritis

LEARNING MODULE

Overview

IgA vasculitis is a systemic small-vessel vasculitis characterized by the deposition of IgA-dominant immune complexes. Although it most often manifests in adolescence, it can occur at any age.

The clinical spectrum of IgA vasculitis ranges from disease that is limited to the skin to systemic involvement that most commonly affects the gastrointestinal tract, joints, and kidneys. A classic presentation is an adolescent with a recent upper respiratory tract infection who has a purpuric rash, with or without associated arthralgias, abdominal pain, or hematuria.

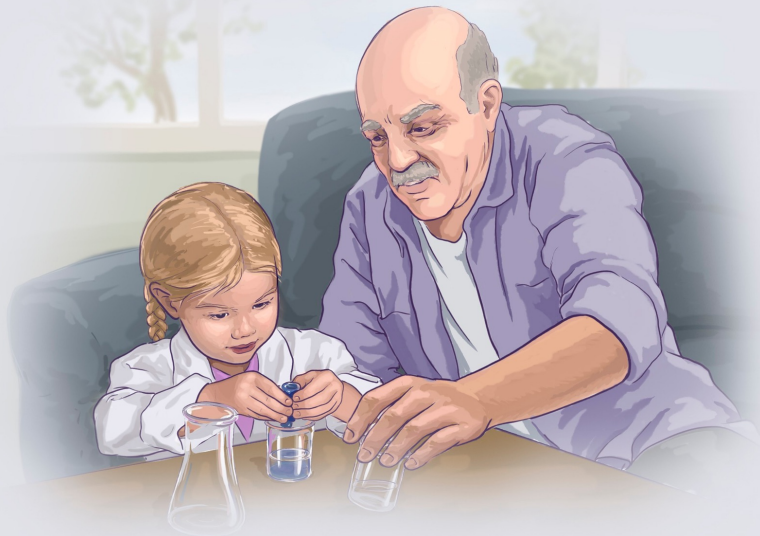
In children, IgA vasculitis is often self-limited, whereas in adults, it often follows a progressive or relapsing course. Given the relative rarity of IgA vasculitis in adults, evaluation for secondary causes, including underlying cancer, should be considered, particularly in cases with prolonged or treatment-refractory disease. Kidney involvement occurs in 20 to 80% of cases and is referred to as **IgA vasculitis with nephritis**. Adults are at higher risk for progression to advanced kidney disease, particularly in the context of urinary protein levels higher than 1 gram per day, hypertension, or high-risk histologic features, all of which correlate with a faster decline in the glomerular filtration rate.

Diagnosis is confirmed by the presence of IgA-predominant mesangial deposition and mesangial proliferation on kidney biopsy. Importantly, **IgA vasculitis with nephritis** is indistinguishable from **IgA nephropathy** — a primary glomerulonephritis without systemic manifestations — on biopsy. Historically, IgA vasculitis with nephritis and IgA nephropathy have been considered to be two clinical manifestations of the same disease; however, growing evidence suggests that the two may differ in the degree of glomerular inflammation and may respond differently to certain treatments.

Patient Outcome

The patient received intravenous methylprednisolone at a dose of 125 mg per day, followed by oral prednisone at a dose of 60 mg per day, along with omeprazole and trimethoprim-sulfamethoxazole for gastric ulcer and pneumocystis prophylaxis, respectively. His kidney function initially worsened, with the serum creatinine level peaking at 5.32 mg per deciliter before decreasing to 3.5 mg per deciliter by the time of discharge 1 week later.

In addition to high-dose glucocorticoid therapy, he received two doses of rituximab. After discharge, he established care with a nephrologist and received treatment with tapering doses of a glucocorticoid over a period of 5 weeks. At 3 months after discharge, the rash on his legs and feet had resolved and his kidney function had continued to slowly improve with decreasing levels of urinary protein and creatinine (creatinine level, 1.8 mg per deciliter; glomerular filtration rate, 40 ml per min per 1.73 m²). He was also given an ACE inhibitor and an SGLT2 inhibitor for long-term kidney protection.

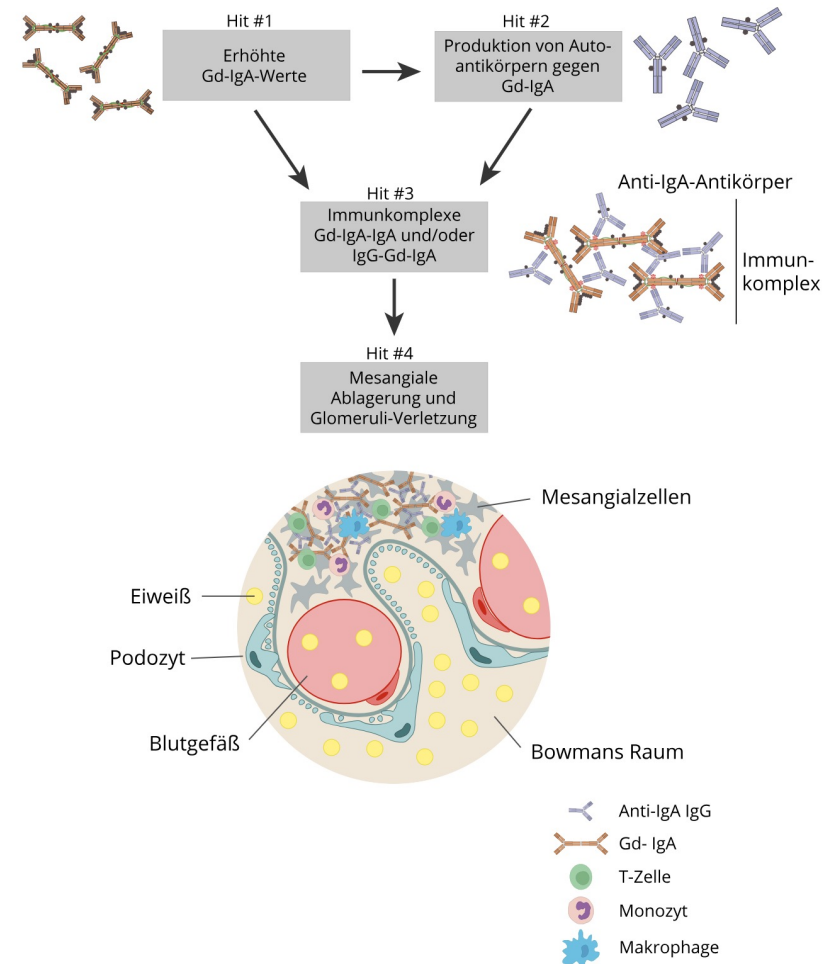
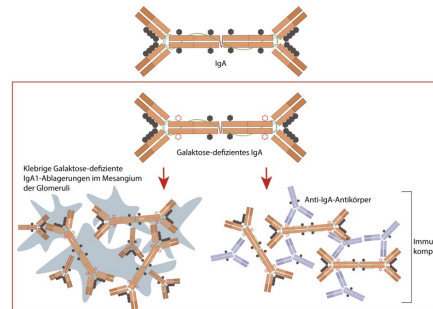


Teaching Points

- IgA vasculitis with nephritis commonly manifests in adolescents but can occur at any age.
- Diagnosis of IgA vasculitis with nephritis and IgA nephropathy is confirmed by kidney biopsy. Either diagnosis may occur with rapidly progressive glomerulonephritis, defined as a decline in the glomerular filtration rate exceeding 50% within a period of 3 months.
- High-dose intravenous glucocorticoids are the first line of treatment for IgA vasculitis with nephritis for suppression of inflammation and preservation of kidney function. Early initiation of glucocorticoid therapy is associated with improved outcomes. Rituximab or cyclophosphamide may be added in selected cases on the basis of treatment response and clinicopathologic features.
- Long-term management of IgA vasculitis with nephritis includes RAAS inhibition, SGLT2 inhibition, blood-pressure control, and lifestyle measures (e.g., sodium restriction, weight reduction, and lipid-lowering therapy), but immunosuppression is the urgent priority in patients who also have rapidly progressive glomerulonephritis.

Entstehungsmechanismus (Pathogenese)

- **Fehlerhafte Antikörper:** Der Körper bildet eine veränderte Form des Immunglobulins A1 (Gd-IgA1), bei der ein Zuckerbaustein (Galaktose) fehlt.
- **Immunkomplexe:** Gegen diese fehlerhaften IgA-Moleküle bildet das Immunsystem fälschlicherweise Autoantikörper (IgG). Sie verbinden sich zu sogenannten Immunkomplexen.
- **Ablagerung in den Nieren:** Diese Komplexe wandern durch den Blutkreislauf und lagern sich in den Filtereinheiten der Nieren (den Glomeruli bzw. im Mesangium) ab.
- **Entzündung und Schädigung:** Die Ablagerungen aktivieren das Komplementsystem (Teil der Immunabwehr) und führen zu einer Entzündung, die das Nierengewebe langfristig schädigen kann.



Die moderne Behandlung der IgA-Nephropathie hat sich in den letzten Jahren stark von rein unspezifischen Blutdrucksenkern hin zu gezielten, ursachenbezogenen Therapien entwickelt.

Neue zielgerichtete Medikamente

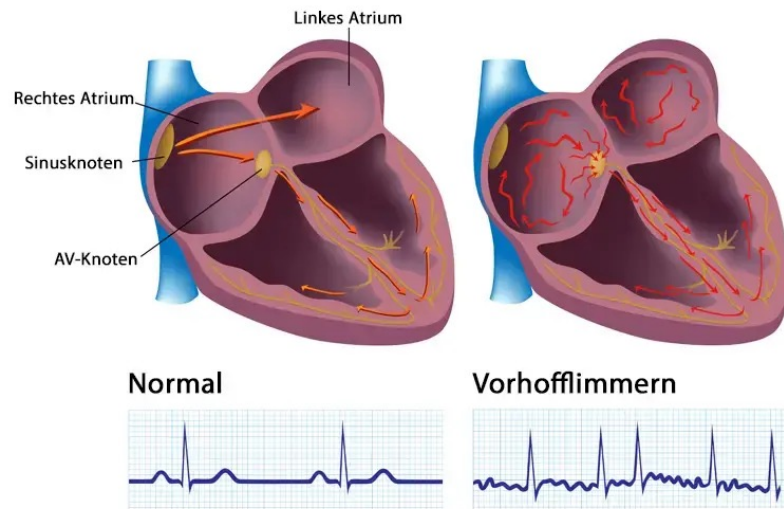
- **Nefecon (Kinpeygo®):** Hierbei handelt es sich um eine spezielle, **magensaftresistente Zubereitung des Kortikosteroids Budesonid**. Es setzt den Wirkstoff gezielt im Dünndarm (an den sogenannten Peyerschen Plaques) frei, wo die fehlerhafte Produktion der IgA1-Antikörper ihren Ursprung hat. Dadurch wird die Nierenfunktion geschont, während das Risiko schwerer Nebenwirkungen im Vergleich zu herkömmlichen, systemischen Kortisonen stark sinkt.
- **Sparsentan (Filspari®):** Ein **dualer Rezeptorantagonist**, der gleichzeitig den Endothelin- und den Angiotensin-II-Rezeptor blockiert. Diese doppelte Schutzwirkung senkt den Druck in den Nierenkörperchen effektiv und verringert die Eiweißausscheidung (Proteinurie) im Urin deutlich.
- **Weitere Ansätze in klinischen Studien:** Neue Substanzen wie *Atacicept* oder *Sibeprenlimab* greifen noch tiefer in das Immunsystem ein, indem sie spezifisch die **Zytokine BAFF und APRIL** hemmen, welche für die Bildung der krankheitsauslösenden Antikörper verantwortlich sind.

THE LANCET

Symptomatisches Vorhofflimmern ist eine spürbare, unregelmäßige und oft zu schnelle Herzrhythmusstörung, die sofortige ärztliche Abklärung erfordert.

Typische Symptome

- **Herzstolpern oder Palpitationen:** Das Gefühl von unregelmäßigem Schlagen oder flattern im Brustkorb.
- **Herzrasen:** Ein stark beschleunigter Puls, oft über 100 Schläge pro Minute.
- **Luftnot:** Kurzatmigkeit bereits bei leichten körperlichen Anstrengungen.
- **Leistungsabfall:** Allgemeine Schwäche und geminderte Belastbarkeit.
- **Schwindel:** Plötzliches Benommenheitsgefühl oder Schwarzvorausgen



Catheter ablation for symptomatic atrial fibrillation (PVI-SHAM-AF): a randomised, double-blind, sham-controlled, multicentre trial

Summary

Background Guidelines recommend catheter ablation for symptom relief in patients with atrial fibrillation. The aim of this trial was to ascertain whether catheter ablation improves atrial fibrillation-related quality of life more than a sham procedure.

Methods PVI-SHAM-AF was a double-blind, multicentre, randomised trial conducted at nine study sites in Germany and Poland. Patients aged 18 years or older with symptomatic paroxysmal or persistent atrial fibrillation were randomly assigned in a 2:1 ratio to catheter ablation or a sham procedure using an automated online randomisation system with variable block sizes, stratified by trial site. The primary endpoint was the between-group difference in change from baseline to 6 months in the Atrial Fibrillation Effect on the Quality-of-life Questionnaire (AFEQT) summary score. The prespecified primary analysis was done in the intention-to-treat population and included all randomly assigned patients, with missing data handled by multiple imputation. This trial is registered with ClinicalTrials.gov (NCT05119231) and 12-month follow-up is ongoing.

Findings Between Nov 12, 2021, and Nov 3, 2025, 1199 patients were invited to participate in the study and 262 patients consented and were randomly assigned: 173 patients to catheter ablation and 89 to sham. The median age was 67 years (IQR 62–73); 134 (51%) were female and 128 (49%) were male. Median follow-up was 184 days (IQR 181–191). At 6 months, the mean AFEQT summary score had increased from 61·3 (SD 20·1) to 81·1 (16·6) in the catheter ablation group and from 59·2 (19·0) to 74·9 (19·5) in the sham control group. The Hodges–Lehmann estimate of the between-group difference in change was 2·6 (95% CI –2·7 to 8·0; $p=0·36$). One death occurred in each group; neither was considered related to the study procedure. Serious adverse events adjudicated as related or possibly related to the study procedure occurred in ten unique patients: six patients in the catheter ablation group and four patients in the sham control group. One of these was an ischaemic stroke occurred in the sham control group.

Interpretation Catheter ablation did not demonstrate superiority over a sham procedure for improving atrial fibrillation-related quality of life at 6 months.

Funding Helios Gesundheit (Förderung Leipziger Herzmedizin).

Der [AFEQT-Score](#) (Atrial Fibrillation Effect on Quality-of-Life) ist ein validierter, patienten-berichteter Fragebogen zur Messung der gesundheitsbezogenen Lebensqualität von Patienten mit Vorhofflimmern

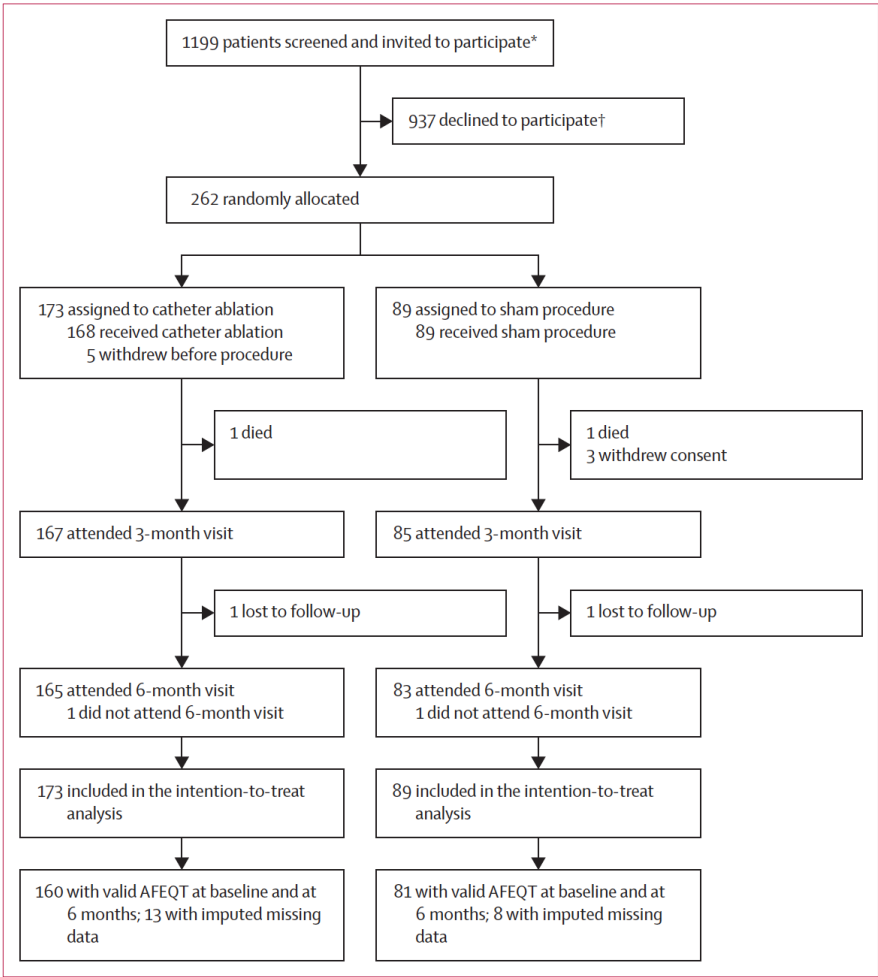


Figure 1: Trial profile

Missing primary outcome data were handled by multiple imputation in the intention-to-treat analysis. AFEQT=Atrial Fibrillation Effect on the Quality-of-life Questionnaire. *All patients invited to participate met eligibility criteria. †Among those who declined participation, 434 (46%) were female and 503 (54%) were male, and median age was 67 years (IQR 61–74); no further clinical or demographic details were recorded.

	Catheter ablation (n=173)	Sham control (n=89)
Age, years	67 (62–73)	69 (63–73)
Sex		
Female	78/173 (45%)	56/89 (63%)
Male	95/173 (55%)	33/89 (37%)
BMI, kg/m ²	29 (26–33)	30 (27–34)
Type of atrial fibrillation		
Paroxysmal	79/173 (46%)	49/89 (55%)
Persistent	94/173 (54%)	40/89 (45%)
Time since first atrial fibrillation diagnosis, years	1.3 (0.4–4.0)	1.4 (0.4–4.1)
EHRA score*		
1	8/172 (5%)	3/89 (3%)
2	121/172 (70%)	59/89 (66%)
3	41/172 (24%)	24/89 (27%)
4	2/172 (1%)	3/89 (3%)
Baseline AFEQT score	61 (46–77)†	61 (44–75)
Hypertension	156/173 (90%)	79/89 (89%)
Diabetes of any type	39/173 (23%)	24/88 (27%)
Coronary artery disease	34/172 (20%)	11/87 (13%)
Heart failure	23/173 (13%)	15/88 (17%)
Stroke	10/173 (6%)	1/88 (1%)
CHA2DS2-VASc risk score‡		
1	32/173 (18%)	12/89 (13%)
2	48/173 (28%)	22/89 (25%)
3	44/173 (25%)	32/89 (36%)
4–6	49/173 (28%)	23/89 (26%)
Left atrial volume, mL	88 (39)	85 (36)
Left atrial volume index, mL/m ²	42 (18)	42 (17)
Left ventricular ejection fraction, %	60% (7)	60% (8)
Estimated glomerular filtration rate, mL/min per 1.73 m ²	90 (84–95)	89 (84–95)
NT-proBNP, ng/mL	393 (182–907)	345 (184–813)
History of cardioversion		
Paroxysmal atrial fibrillation	16/67 (24%)	14/45 (31%)
Persistent atrial fibrillation	78/90 (87%)	33/38 (87%)
History of antiarrhythmic drugs		
Class I	21/173 (12%)	17/89 (19%)
Class II	152/173 (88%)	79/89 (89%)
Class III	31/173 (18%)	17/89 (19%)
Anticoagulation	170/173 (98%)	85/89 (96%)

Data are n (%), n/N (%), median (IQR), or mean (SD). The number of available data points is shown in the appendix 1 (p 13). AFEQT=Atrial Fibrillation Effect on the Quality-of-life Questionnaire. EHRA=European Heart Rhythm Association. NT-proBNP=N-terminal pro-B-type natriuretic peptide. *EHRA score is based on the severity of symptoms of atrial fibrillation and the associated limitations on physical activity. Classes range from I (patient does not notice atrial fibrillation) to IV (normal daily activity must be discontinued entirely during atrial fibrillation). Eight patients in the ablation group and three patients in the sham group were classified as EHRA I on inclusion; study sites classified patients who were in sinus rhythm upon inclusion as EHRA I as they did not have current atrial fibrillation, but had AFEQT scores as low as 49. †Six values missing. ‡The CHA₂DS₂-VASc is a clinical score that estimates the risk of stroke among patients with atrial fibrillation; values range from 0 to 9, with higher scores indicating a higher risk of stroke.

Table 1: Baseline demographic and clinical characteristics

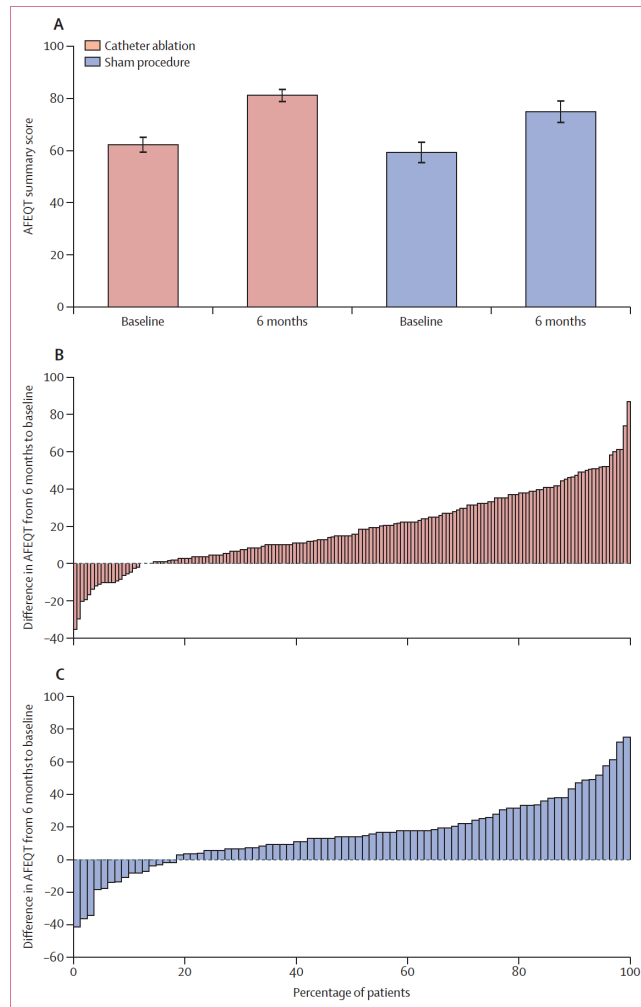


Figure 2: AFEQT summary scores and changes from baseline to 6 months
Mean AFEQT summary score at baseline and after 6 months in the catheter ablation and sham control groups (A). Error bars show 95% CIs. Waterfall plots show the change in AFEQT summary score from baseline to 6 months for individual patients in the catheter ablation group (B) and sham control group (C). The Hodges-Lehmann estimate of the between-group difference in change was 2.6 points (95% CI -2.7 to 8.0; $p=0.36$). AFEQT=Atrial Fibrillation Effect on the Quality-of-life Questionnaire.

	Catheter ablation, mean (SD)	Sham control, mean (SD)	Treatment effect (95% CI)*
AFEQT summary score (primary endpoint)	19.0 (20.5)	15.6 (21.7)	2.6 (-2.7 to 8.0)
AFEQT subscales			
Symptoms	19.0 (25.8)	13.8 (23.6)	5.5 (0.4 to 10.6)
Daily activities	20.6 (27.2)	17.9 (28.1)	6.0 (0.2 to 11.7)
Treatment concerns	16.1 (20.6)	14.2 (22.9)	3.8 (-0.9 to 8.4)
Treatment satisfaction	19.5 (26.0)	8.8 (26.3)	7.8 (2.0 to 13.6)
SF-36			
Physical functioning	6.8 (16.7)	7.9 (21.1)	1.1 (-3.3 to 5.5)
Role (physical)	16.7 (40.0)	19.9 (41.6)	3.1 (-6.1 to 12.3)
Bodily pain	5.8 (25.9)	6.2 (30.0)	1.7 (-4.2 to 7.6)
General health perceptions	3.3 (15.7)	1.1 (16.6)	2.2 (-1.6 to 5.9)
Vitality	7.7 (17.2)	6.3 (18.9)	2.6 (-1.5 to 6.6)
Social functioning	7.8 (22.9)	5.0 (22.6)	2.9 (-2.1 to 7.9)
Role (emotional)	5.5 (45.6)	7.7 (38.0)	2.5 (-6.8 to 11.7)
Mental health	4.7 (15.9)	1.9 (16.5)	3.6 (0.0 to 7.1)
Physical composite score	3.4 (7.2)	3.9 (9.1)	0.4 (-1.5 to 2.4)
Mental composite score	2.3 (9.9)	1.0 (8.8)	1.8 (-0.4 to 3.9)
EQ-5D-3L			
Index score (TTO method)	-0.012 (0.154)	-0.024 (0.204)	0.014 (-0.024 to 0.052)
Visual scale	8.7 (18.4)	5.9 (19.4)	3.8 (-0.2 to 7.8)

Data in the second and third columns are observed mean changes (SD) taken directly from the raw data. AFEQT=Atrial Fibrillation Effect on the Quality-of-life Questionnaire. SF36=Medical outcomes Study 36-Item Short-Form Health Survey. TTO=time trade-off. *The primary treatment effect is the Hodges-Lehmann estimate from the prespecified intention-to-treat analysis of all 262 randomly assigned patients, with missing values handled by multiple imputation. Other treatment effects are mixed-model estimates with 95% CIs. Because these are adjusted values, they need not agree with the differences in the mean changes from the second and third columns. The mixed-model analyses included data from 258 (98%) of 262 randomly assigned patients: 169 (98%) of 173 in the catheter ablation group and 89 (100%) of 89 in the sham control group. Note that columns two and three comprise estimates from patients who provided data at baseline and the 6-month follow-up (ie, 241 patients). Five patients did not receive the study procedure. Four of them did not answer the AFEQT, SF-36, or EQ-5D-3L questionnaires at any point in time, whereas one did. The remaining 258 patients are included in each of the mixed models.

Table 2: Primary and secondary outcomes, change from baseline to 6 months, in the intention-to-treat population

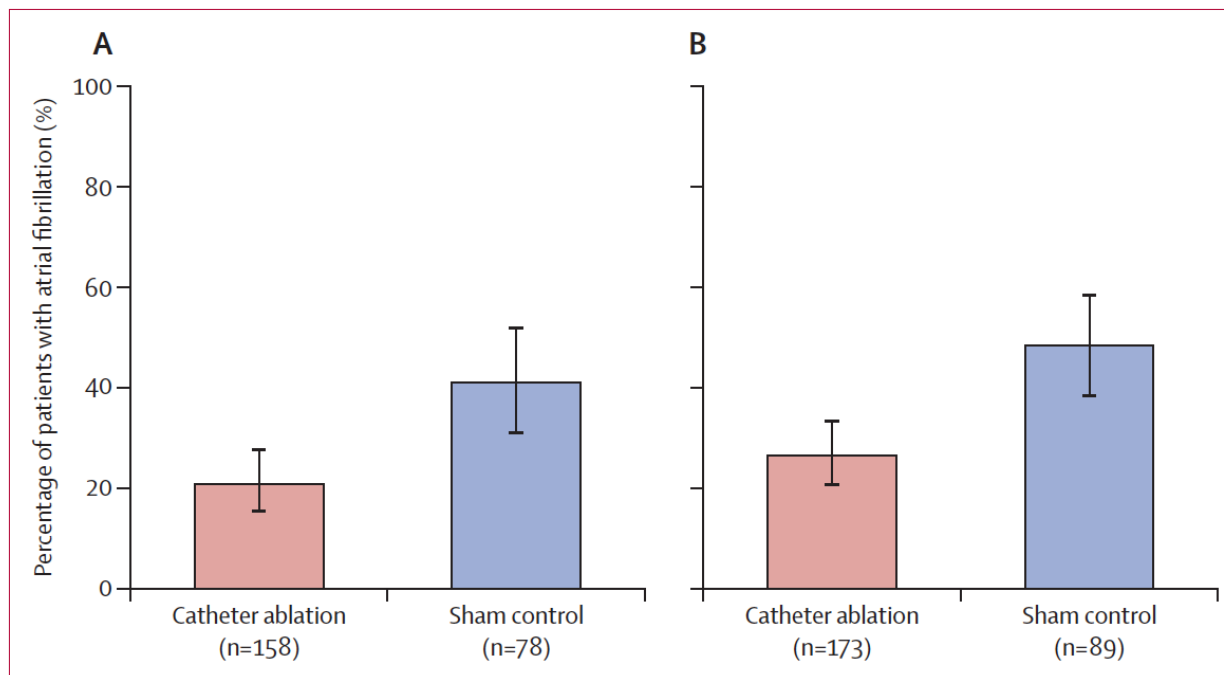


Figure 3: Atrial fibrillation outcomes at 6 months

Atrial fibrillation was detected during 7-day Holter ECG monitoring in 33 (21%) of 158 patients in the catheter ablation group and 32 (41%) of 78 in the sham procedure group; the adjusted between-group difference was -20.1 percentage points (95% CI -32.6 to -7.7; A). In a post-hoc analysis, clinically detected atrial fibrillation recurrence or atrial fibrillation detected during 7-day Holter monitoring occurred in 46 (27%) of 173 randomly assigned patients in the catheter ablation group and 43 (48%) of 89 in the sham procedure group; the adjusted between-group difference was -21.7 percentage points (95% CI -33.6 to -9.4; B). This includes all randomly assigned patients; patients without analysable 6-month Holter ECGs were counted as not having atrial fibrillation. Error bars show 95% CIs.

	Catheter ablation (n=168)		Sham control (n=89)	
	Number of SAEs	Number of SAEs of severe grade or worse	Number of SAEs	Number of SAEs of severe grade or worse
Possibly or probably related to both the trial procedure and atrial fibrillation				
Total	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Cardiac disorders				
Sinus node dysfunction	1	1	0	0
Nervous system disorders				
Embolic cerebral infarction	0	0	1	1
Possibly or probably related to the trial procedure but not to atrial fibrillation				
Total	5 (3%)	1 (1%)	3 (3%)	0
Injury, poisoning, and procedural complications				
Post-procedural haematoma	0	0	1	0
Post-procedural haemorrhage	1	0	0	0
Vascular pseudoaneurysm	0	0	1	0
Vascular disorders				
Haematoma	1	0	1	0
Haemorrhage	1	0	0	0
Cardiac disorders				
Dressler's syndrome	1	1	0	0
General disorders and administration site conditions				
Puncture site haemorrhage	1	0	0	0
Possibly or probably related to atrial fibrillation, but not the trial procedure				
Total	3 (2%)	1 (1%)	3 (3%)	0
Cardiac disorders				
Cardiac failure	3	1	0	0
Psychiatric disorders				
Alcoholism	0	0	2	0
Infections and infestations				
COVID-19	0	0	1	0
Related to neither the trial procedure nor atrial fibrillation				
Total	31 (18%)	9 (5%)	12 (13%)	3 (3%)
Infections and infestations				
Bronchitis	1	0	0	0
Cystitis	0	0	1	0
Infection	1	0	0	0
Pneumonia	1	0	0	0
Pulmonary sepsis	1	1	0	0
Pyelonephritis	0	0	1	0
Injury, poisoning, and procedural complications				
Alcohol poisoning	0	0	1	0
Clavicle fracture	0	0	1	0
Fall	1	0	0	0
Post procedural haematoma	1	0	0	0
Scapula fracture	0	0	1	0
Subdural haematoma	0	0	1	1
General disorders and administration site conditions				
Pain	2	0	0	0
Hernia	1	1	0	0
Oedema mucosal	1	0	0	0

(Table 3 continues on next page)

	Catheter ablation (n=168)		Sham control (n=89)	
	Number of SAEs	Number of SAEs of severe grade or worse	Number of SAEs	Number of SAEs of severe grade or worse
(Continued from previous page)				
Surgical and medical procedures				
Angioplasty	1	0	0	0
Hip arthroplasty	1	0	0	0
Hip surgery	1	1	0	0
Thrombectomy	1	0	0	0
Cardiac disorders				
Coronary artery disease	1	0	1	0
Angina unstable	1	0	0	0
Musculoskeletal and connective tissue disorders				
Haemarthrosis	1	0	0	0
Osteoarthritis	1	0	0	0
Spinal instability	1	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)				
Plasma cell myeloma	0	0	1	1
Prostate cancer	1	1	0	0
Small intestine carcinoma	1	1	0	0
Gastrointestinal disorders				
Ileus	1	1	0	0
Inguinal hernia	1	0	0	0
Metabolism and nutrition disorders				
Hypokalaemia	1	0	0	0
Type 2 diabetes mellitus	1	0	0	0
Nervous system disorders				
Intracranial mass	0	0	1	1
Intraventricular haemorrhage	1	1	0	0
Psychiatric disorders				
Schizophrenia	0	0	1	0
Suicide attempt	1	1	0	0
Ear and labyrinth disorders				
Vertigo positional	1	0	0	0
Endocrine disorders				
Toxic nodular goitre	1	0	0	0
Hepatobiliary disorders				
Cholecystitis	1	1	0	0
Immune system disorders				
Sarcoidosis	1	0	0	0
Respiratory, thoracic, and mediastinal disorders				
Chronic obstructive pulmonary disease	0	0	1	0
Vascular disorders				
Peripheral arterial occlusive disease	0	0	1	0
SAEs were classified according to causal relationship to the trial procedure, atrial fibrillation, or both according to independent adjudicators. Events were classified using the Medical Dictionary for Regulatory Activities. Atrial fibrillation and flutter classified as serious adverse events are listed in the appendix 1 (p 21). SAE=serious adverse event.				
Table 3: SAEs in the safety population				

Research in context

Evidence before this study

We searched PubMed from database inception to July 22, 2026, for randomised trials comparing atrial fibrillation ablation with a sham procedure, using the terms “atrial fibrillation AND ablation” OR “pulmonary vein isolation AND sham OR placebo” and no language restrictions. We excluded feasibility studies involving 20 or fewer patients. We identified only two sham-controlled trials, SHAM-PVI, involving 126 patients, and PFA-SHAM, involving 60 patients. Both trials reported greater improvement in atrial fibrillation-related quality of life with catheter ablation than with a sham procedure. However, the trials were small and differed in patient selection, ablation method, masking, endpoint hierarchy, and rhythm-monitoring methods. Formal risk of bias assessment was not performed as results were too disparate to be appropriate for pooling.

Added value of this study

PVI-SHAM-AF assessed the incremental effect of catheter ablation versus a sham procedure to improve quality of life in patients with symptomatic paroxysmal or persistent atrial fibrillation. Catheter ablation did not significantly improve

the prespecified AFEQT primary endpoint at 6 months compared with the sham procedure, despite reducing atrial fibrillation recurrence and burden. These findings differ from the quality-of-life results of SHAM-PVI and PFA-SHAM and extend the sham-controlled evidence to a broader study population in which several catheter ablation methods were permitted.

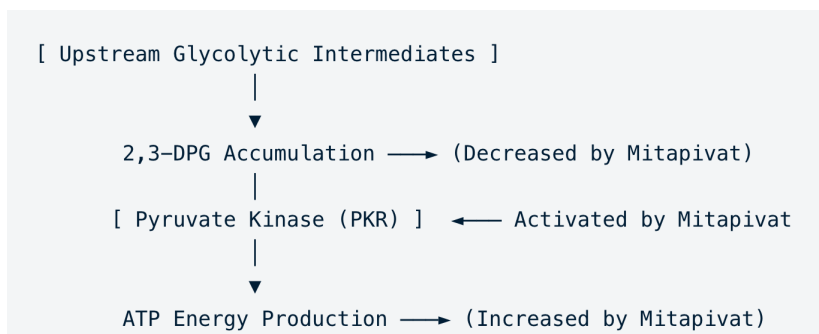
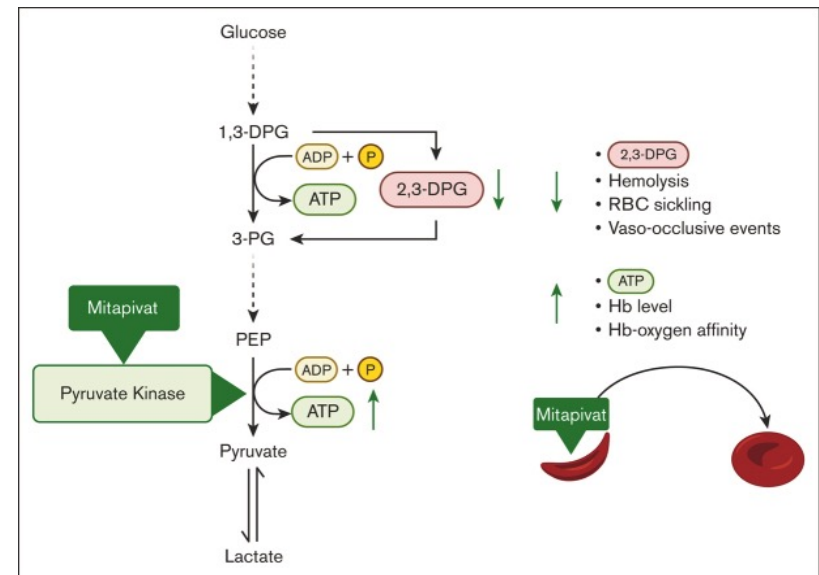
Implications of all the available evidence

The available sham-controlled trials consistently show that catheter ablation reduces atrial fibrillation recurrence or burden, but their findings for patient-reported quality of life are discordant. Clinical counselling of patients with atrial fibrillation should integrate sham-controlled data with the broader evidence base and distinguish objective rhythm-control benefits from patient-reported quality-of-life effects. Further research should clarify which patients derive additional symptomatic benefit from ablation and whether differences in baseline symptom burden, ablation method, rhythm monitoring, sham procedures, and follow-up management explain the variation between trials.

Mitapivat ist ein moderner, oral verabreichter Arzneistoff zur Behandlung bestimmter Formen der hämolytischen Anämie.

Rote Blutkörperchen (Erythrozyten) besitzen keine Mitochondrien und sind zur Energiegewinnung zu **100 % auf die anaerobe Glykolyse angewiesen**. Das Enzym *Pyruvatkinase* (spezifisch die Isoform PKR in Erythrozyten) katalysiert den letzten, entscheidenden Schritt der Glykolyse: die Umwandlung von Phosphoenolpyruvat (PEP) zu Pyruvat, bei der **ATP (Energie) generiert wird**.

- **Allosterische Bindung:** Mitapivat bindet an eine spezifische allosterische Bindungsstelle des PKR-Enzyms (eine andere Stelle als der körpereigene Aktivator Fructose-1,6-bisphosphat / FBP).
- **Stabilisierung des Tetramers:** Es stabilisiert die aktive, tetramere (vierteilige) Struktur des Enzyms. Dadurch wird die Affinität des Enzyms zu seinem Substrat (PEP) massiv erhöht.
- **Aktivierung von Mutanten:** Das Besondere ist, dass Mitapivat sowohl die gesunde Wildtyp-Form als auch **viele verschiedene mutierte Formen des Enzyms reaktivieren und stabilisieren** kann.



Mitapivat
stimulates
pyruvate
kinase

Can mitapivat
reduce
transfusions in
thalassemia?

Efficacy and safety of mitapivat in adults with transfusion-dependent α -thalassaemia or β -thalassaemia (ENERGIZE-T): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

Summary

Background The absence of disease-modifying therapies for patients with α -thalassaemia and oral disease-modifying therapies for patients with β -thalassaemia has been a substantial unmet need in these patients. We assessed the efficacy and safety of mitapivat, an oral allosteric activator of pyruvate kinase, in adults with transfusion-dependent thalassaemia.

Methods ENERGIZE-T is a global, double-blind, randomised, placebo-controlled, phase 3 trial, conducted across 19 countries in North America, Europe, Asia-Pacific, South America, and the Middle East. Patients aged 18 years or older with transfusion-dependent α -thalassaemia or β -thalassaemia were randomly allocated (2:1) with a central interactive response technology system, stratified by geographical region and thalassaemia genotype, to receive 100 mg mitapivat or placebo orally twice a day for 48 weeks. The primary endpoint was transfusion reduction response (TRR), defined as a reduction of at least 50% in transfused red blood cell units with a reduction of at least two units in any consecutive 12-week period until week 48 compared with baseline. Efficacy was analysed in the full analysis set, comprising all randomly allocated patients. Type, severity, and relationship of adverse events and serious adverse events were assessed in patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov (NCT04770779) and is active but not recruiting.

Findings Between Nov 30, 2021 and May 2, 2023, 305 patients were screened, of whom 258 were randomly allocated (median age 33.5 years [IQR 27.0–44.0]; 136 [53%] female and 122 [47%] male participants). Of 258 patients allocated, 238 (92%) completed the double-blind treatment period. All patients were required to have a safety follow-up approximately 4 weeks after the final dose of study drug, regardless of completion of the double-blind period or continuation into the open-label extension period. In the full analysis set, TRRs occurred in 52 (30%) of 171 patients in the mitapivat group and 11 (13%) of 87 in the placebo group (adjusted difference 18 percentage points [95% CI 8–27]; two-sided $p=0.0003$). The safety analysis set comprised 172 patients in the mitapivat group (including one patient allocated to the placebo group who received one dose of mitapivat in error) and 85 in the placebo group. Adverse events were reported in 155 (90%) patients treated with mitapivat and 71 (84%) treated with placebo; the most common events with mitapivat were headache, upper respiratory tract infection, initial insomnia, diarrhoea, and fatigue. Serious adverse events were reported in 19 (11%) patients treated with mitapivat and 13 (15%) treated with placebo. Ten (6%) patients who received mitapivat and one (1%) who received placebo discontinued study treatment due to adverse events. No deaths were reported.

Interpretation Mitapivat significantly reduced the transfusion burden and was generally well tolerated, showing a favourable benefit–risk profile. These findings support mitapivat as the first oral disease-modifying therapy for adults with transfusion-dependent α -thalassaemia or β -thalassaemia, providing a new treatment option to reduce transfusion burden in this patient population.

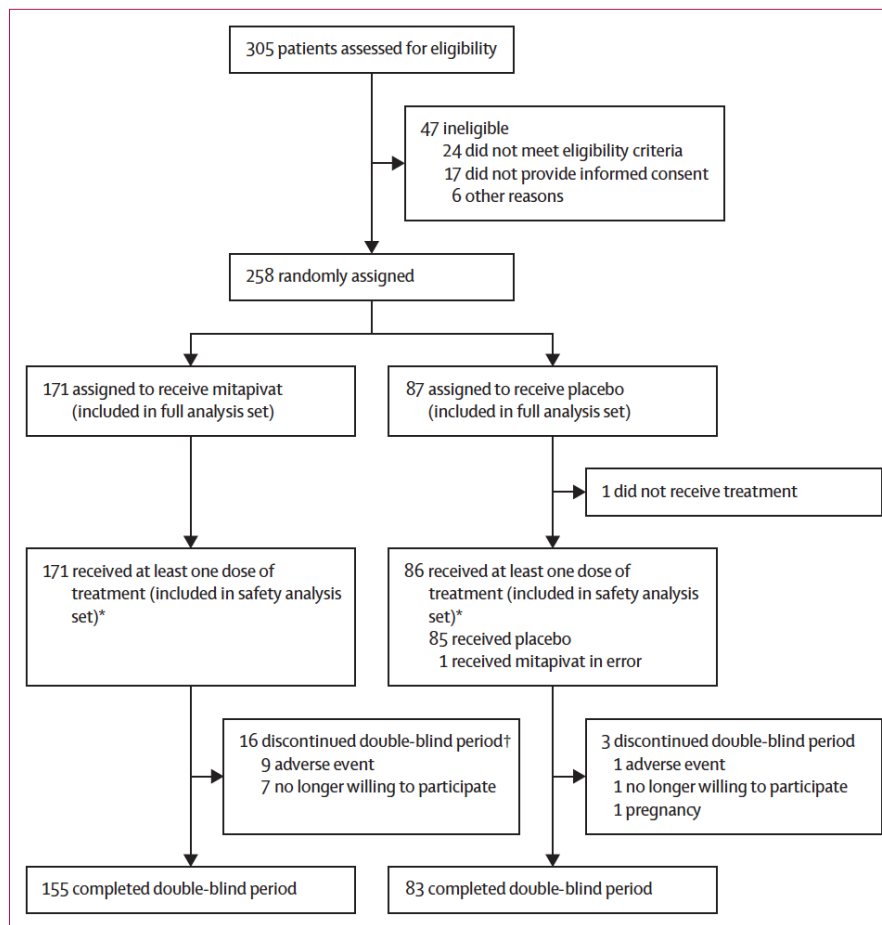


Figure 1: Trial profile

*The safety analysis set for mitapivat (n=172) comprised all patients who received at least one dose of mitapivat, including one participant randomly allocated to placebo who mistakenly received a dose of mitapivat in the double-blind period; the safety analysis set for placebo (n=85) comprised all patients who received at least one dose of placebo, excluding the patient who mistakenly received one dose of mitapivat. †One patient discontinued study treatment due to an adverse event (not included in figure) and later discontinued from the double-blind period because they were no longer willing to participate.

	Mitapivat group (n=171)	Placebo group (n=87)
Age, years		
Median (IQR)	33 (27–45)	34 (26–43)
Range	18–67	20–53
Sex		
Female	93 (54%)	43 (49%)
Male	78 (46%)	44 (51%)
Race		
White	99 (58%)	56 (64%)
Asian	56 (33%)	22 (25%)
Black or African American	1 (1%)	1 (1%)
Multiracial	2 (1%)	0
Unknown	7 (4%)	3 (3%)
Not reported	6 (4%)	5 (6%)
Ethnicity		
Hispanic or Latino	5 (3%)	3 (3%)
Not Hispanic or Latino	158 (92%)	79 (91%)
Not reported	8 (5%)	5 (6%)
Thalassaemia genotype		
Non-β ⁰ β ⁰	96 (56%)	48 (55%)
β ⁰ β ⁰	75 (44%)	39 (45%)
24-week transfusion burden*		
≤12 red blood cell units	54 (32%)	21 (24%)
>12 red blood cell units	117 (68%)	66 (76%)
Pretransfusion haemoglobin threshold, g/dL†		
Mean (SD)	8.9 (1.2)	8.8 (1.1)
Median (IQR)	9.0 (8.1–9.6)	8.9 (8.0–9.7)
Range	5.1–11.8	5.1–10.9
Splenectomy status‡		
No	79 (46%)	38 (44%)
Yes	92 (54%)	49 (56%)
Receipt of iron chelation within 1 year before randomisation‡		
No	6 (4%)	0
Yes	165 (96%)	87 (100%)
Hydroxyurea use§		
No	164 (96%)	84 (97%)
Yes	7 (4%)	3 (3%)
Mean ferritin concentration, µg/L¶	2020.0 (2290.9), n=161	1928.7 (1862.1), n=83
Mean hepatic iron by MRI, mg/g¶	5.7 (4.9), n=133	5.7 (4.7), n=74

Data are median (IQR), n (%), or mean (SD), except where otherwise specified.
 *24-week baseline transfusion burden is the total number of red blood cell units transfused during the 24-week period (168 days) before the reference date (ie, the start of study treatment, if received, or the randomisation date otherwise).
 †Defined as the mean of all documented pretransfusion haemoglobin concentration values recorded for the red blood cell transfusions administered during the 24-week period before randomisation. ‡As recorded in thalassaemia disease history electronic case report forms. §Patients treated with hydroxyurea were required to be on a stable dose for at least 16 weeks before randomisation. ¶Baseline was defined as the last assessment before the last red blood cell transfusion before randomisation.

Table 1: Baseline demographics, disease characteristics, and laboratory values of patients in the full analysis set

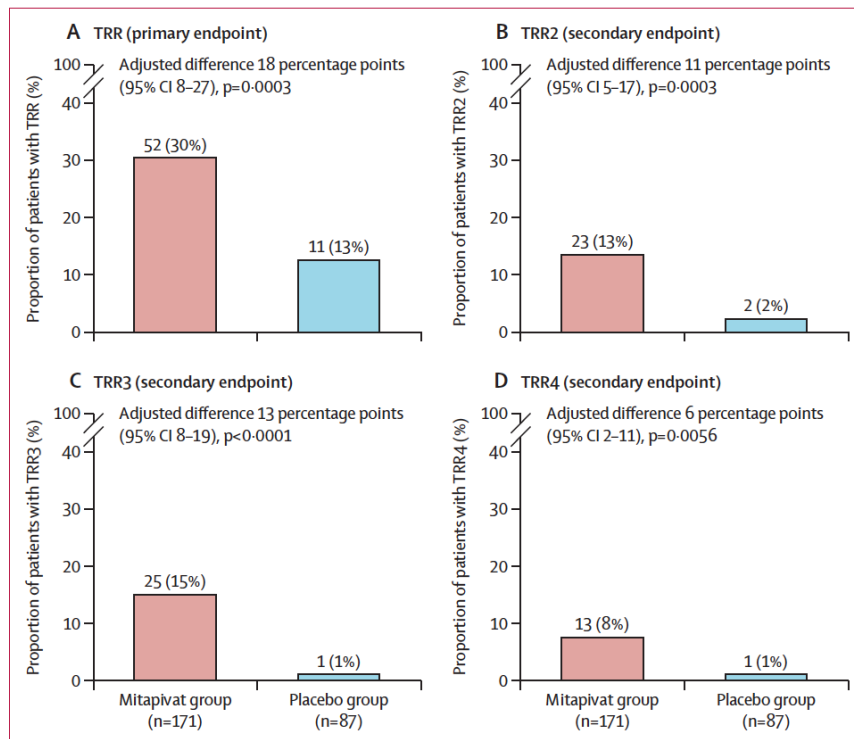


Figure 2: Primary and secondary TRR endpoints

(A) TRR, defined as reduction of at least 50% in transfused red blood cell units with a reduction of at least two units of transfused red blood cells in any consecutive 12-week period until week 48 compared with baseline; patients withdrawn from the study before week 12 (day 85) were considered non-responders. (B) TRR2, defined as at least a 50% reduction in transfused red blood cell units in any consecutive 24-week period until week 48 compared with baseline; patients withdrawn from the study before week 24 (day 169) were considered non-responders. (C) TRR3, defined as at least a 33% reduction in transfused red blood cell units between week 13 and week 48 compared with baseline; patients withdrawn from the study before week 48 were considered non-responders. (D) TRR4, defined as at least a 50% reduction in transfused red blood cell units between week 13 and week 48 compared with baseline; patients withdrawn from the study before week 48 were considered non-responders. For TRR, baseline transfusion burden was standardised to 12 weeks (24-week baseline transfusion burden $\times 12 / 24$). For TRR2, 24-week baseline transfusion burden was defined as the total number of red blood cell units transfused during the 24-week period (168 days) before the reference date (ie, the start of study treatment, if received, or the randomisation date otherwise). For TRR3 and TRR4, baseline transfusion burden was standardised to 36 weeks (24-week baseline transfusion burden $\times 36 / 24$). TRR=transfusion response rate.

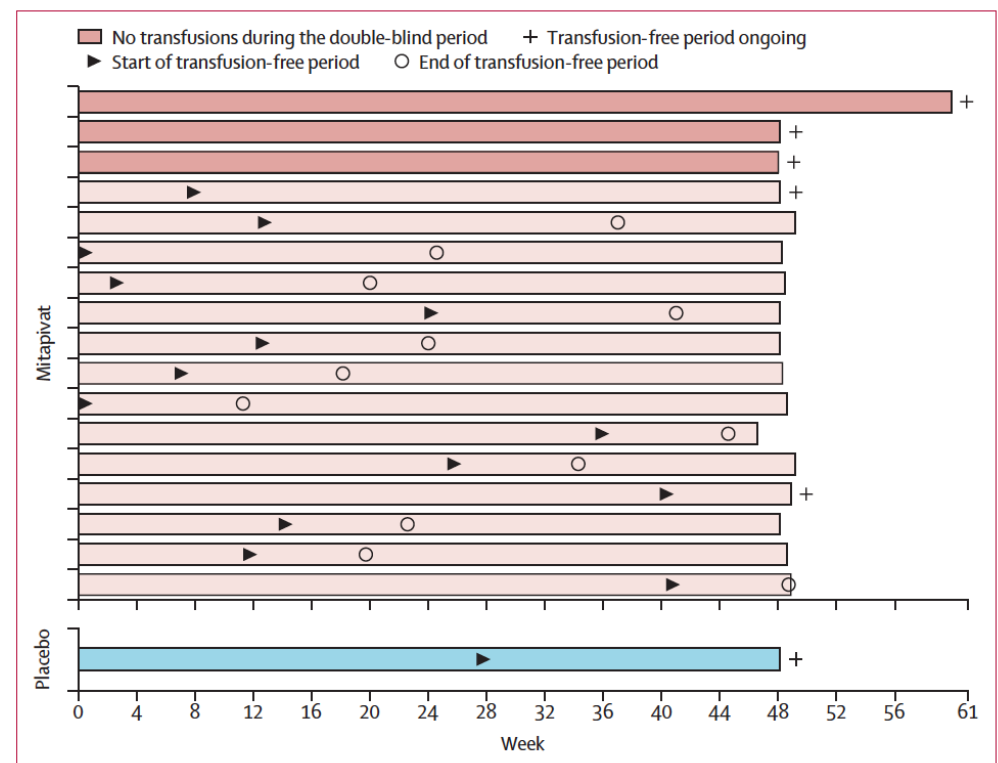


Figure 3: Swimlane plot for duration of transfusion independence for patients who had transfusion independence

Bars are ordered by longest duration of transfusion-free period. Transfusion independence was defined as being transfusion free for at least 8 consecutive weeks until week 48 in the double-blind period. For patients who had transfusion independence, duration of transfusion independence was the number of weeks in the longest transfusion-free period starting on or after the reference date (ie, the start of study treatment, if received, or the randomisation date otherwise), until week 48 in the double-blind period. A transfusion-free period was considered to start on the day after a red blood cell transfusion and end the day before the next red blood cell transfusion. For patients who did not receive any red blood cell transfusions, the start of the transfusion-free period was the reference date. For patients who either did not receive any red blood cell transfusions or received a red blood cell transfusion and no subsequent red blood cell transfusions, the end of the transfusion-free period was censored at the end of the double-blind treatment period.

	Mitapivat group (n=172)	Placebo group (n=85)
Any adverse event	155 (90%)	71 (84%)
Grade ≥3	32 (19%)	12 (14%)
Treatment-related adverse events	65 (38%)	16 (19%)
Grade ≥3	13 (8%)*	1 (1%)†
Serious adverse events	19 (11%)‡	13 (15%)§
Serious treatment-related adverse events	4 (2%)¶	1 (1%)
Adverse events leading to discontinuation of study drug**	10 (6%)††	1 (1%)‡‡
Adverse events leading to dose reduction	20 (12%)	2 (2%)
Adverse events leading to interruption of study drug	13 (8%)	5 (6%)
Adverse events leading to death	0	0
Most frequently reported adverse events of any grade§§		
Headache		
Any grade	46 (27%)	10 (12%)
Grade ≥3	0	0
Upper respiratory tract infection		
Any grade	27 (16%)	14 (16%)
Grade ≥3	0	0
Initial insomnia		
Any grade	24 (14%)	4 (5%)
Grade ≥3	3 (2%)	0
Diarrhoea		
Any grade	19 (11%)	7 (8%)
Grade ≥3	0	0
Fatigue		
Any grade	18 (10%)	2 (2%)
Grade ≥3	0	0

Data are n (%) of patients with at least one event. Adverse events were collected throughout the study and classified using Common Terminology Criteria for Adverse Events (version 4.03). *Events of insomnia (n=3); concurrent increased alanine aminotransferase and increased aspartate aminotransferase (n=2); abdominal distention, increased alanine aminotransferase, hypertransaminasaemia, increased blood pressure, lower respiratory tract infection, supraventricular arrhythmia, supraventricular tachycardia, and renal mass (all n=1). †Increased blood creatine phosphokinase. ‡Gastroenteritis (n=2); pneumonia, COVID-19 pneumonia, cellulitis, dengue fever, influenza, lower respiratory tract infection, hypersplenism, mesenteric lymphadenitis, pancytopenia, cholecystitis, acute cholecystitis, supraventricular arrhythmia, supraventricular tachycardia, radius fracture, proctitis, asthenia, hepatic cancer, dizziness, renal mass, and ruptured ovarian cyst (all n=1). §Pneumonia (n=2); viral infection, splenic haematoma, cholecystitis, acute cholecystitis, acute cholangitis, arrhythmia, left ventricular dysfunction, infusion-related reaction, cataract, increased blood creatine phosphokinase, limb deformity, spontaneous abortion, and pulmonary hypertension (all n=1). ¶Lower respiratory tract infection, renal mass, supraventricular arrhythmia, supraventricular tachycardia. ||Increased blood creatine phosphokinase. **Discontinuation due to an adverse event could be made at the discretion of the investigator, the patient, or a combination of both. ††Diarrhoea, oral paraesthesia, concurrent anxiety and insomnia, initial insomnia, supraventricular tachycardia, fatigue, hypertransaminasaemia, hepatitis C, hepatic cancer, and renal mass (all n=1). ‡‡Increased creatine phosphokinase. §§Occurring in ≥10% of either treatment group, summarised in order of decreasing frequency of patients with events based on the frequencies observed in any grade for the mitapivat group.

Table 2: Adverse events in the safety analysis set

Research in context

Evidence before this study

Patients with transfusion-dependent thalassaemia require lifelong regular red blood cell transfusions to maintain haemoglobin concentrations and suppress ineffective erythropoiesis. Regular transfusions are associated with health complications and substantial patient burden. We searched PubMed for publications in English, from database inception to Oct 31, 2021, on clinical trials (phase 1–3) in adults, and guidelines on drug treatments for thalassaemia, using the terms “alpha-thalassemia” [Title] OR “beta-thalassemia” [Title] OR “thalassemia” [Title] AND “treatment” [Title/Abstract]. Studies focusing only on non-transfusion-dependent thalassaemia were excluded. 18 publications were identified, of which one was excluded since it did not meet the search criteria for transfusion-dependent thalassaemia. The relevant trials covered a range of pharmacological interventions in patients with thalassaemia, including managing iron overload with iron chelators (eg, deferasirox), transforming growth factor-β ligand modulators, and disease-modifying agents (including subcutaneous luspatercept, which was approved for transfusion-dependent β-thalassaemia in the USA in 2019 and for transfusion-dependent and non-transfusion-dependent β-thalassaemia in Europe in 2020 and 2023, respectively). At the time of the literature search, a few gene therapy approaches had been evaluated in β-thalassaemia, including betibeglogene autotemcel, which was later approved. However,

as of the search date, there were no disease-modifying therapies approved for α-thalassaemia, and there are no oral disease-modifying therapies approved for β-thalassaemia.

Added value of this study

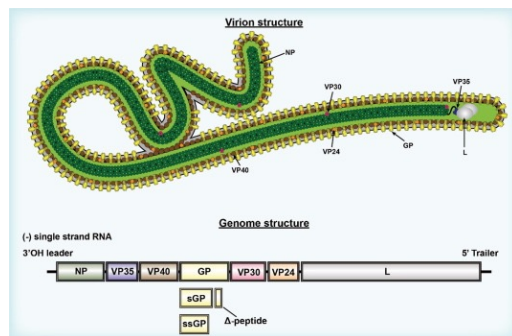
To our knowledge, ENERGIZE-T is the first randomised, phase 3 study to assess a pyruvate kinase activator (mitapivat) in adults with transfusion-dependent thalassaemia (including both α-thalassaemia and β-thalassaemia). The results of this study have established pyruvate kinase as a treatment target in patients with transfusion-dependent thalassaemia, showing significant reductions in transfusion burden in a globally representative population from 19 countries in North America, Europe, Asia-Pacific, South America, and the Middle East. Mitapivat was generally well tolerated and had a favourable benefit-risk profile. This study is also the first to show efficacy of an orally administered disease-modifying therapy in transfusion-dependent β-thalassaemia and the first to show efficacy of a disease-modifying therapy in transfusion-dependent α-thalassaemia.

Implications of all the available evidence

The findings of this global, randomised, phase 3 study support the use of mitapivat in patients with transfusion-dependent α-thalassaemia or β-thalassaemia, and offer the first oral disease-modifying therapy for this disease.

Das Bundibugyo-Ebolavirus (BDBV) ist eine von sechs bekannten Spezies innerhalb der Gattung *Orthoebolavirus* und der Erreger des hämorrhagischen Bundibugyo-Ebolafiebers. Es wurde erstmals im Jahr **2007 nach einem Ausbruch im Distrikt Bundibugyo in Uganda** wissenschaftlich identifiziert

Therapie und Impfung: Bislang gibt es **keinen speziell zugelassenen Impfstoff** und keine standardisierte antivirale Therapie gegen den Bundibugyo-Stamm. Zugelassene Impfstoffe gegen das Zaire-Ebolavirus sind hier nicht wirksam. Die Behandlung erfolgt primär supportiv (Flüssigkeits- und Elektrolytersatz). Allerdings laufen im aktuellen Ausbruchsgebiet klinische Studien (wie die PARTNERS-Studie), bei denen vielversprechende experimentelle Antikörper-Kombinationen (z. B. MBP134) und Virostatika (wie Remdesivir) getestet werden.



Hinter dem Begriff **vesicular stomatitis virus-Zaire ebola** (meist als **rVSV-ZEBOV** abgekürzt) verbirgt sich der weltweit erste hochwirksame **Impfstoff gegen das Zaire-Ebolavirus**.

Es handelt sich um einen sogenannten **Lebendimpfstoff**, der auf einem geschickten molekularbiologischen Baukastenprinzip basiert



Bundibugyo virus glycoprotein seroreactivity following recombinant vesicular stomatitis virus–Zaire Ebola virus glycoprotein vaccination in outbreak-affected populations of the Democratic Republic of the Congo: a longitudinal cohort study

Bundibugyo
BDBV

Can an
established
vaccine help?

Summary

Background There are currently no licensed vaccines for disease caused by Bundibugyo virus (BDBV). The recombinant vesicular stomatitis virus–Zaire Ebola virus glycoprotein (rVSVΔG-ZEBOV-GP) vaccine has been widely deployed during Ebola virus disease outbreaks caused by Ebola virus (EBOV). Human studies have shown cross-reactive BDBV antibody responses following licensed Ebola virus disease vaccine administration, but the durability and longitudinal kinetics of these responses in populations vaccinated during outbreaks remain unknown. We aimed to evaluate BDBV glycoprotein seroreactivity following rVSVΔG-ZEBOV-GP vaccination in two longitudinal cohorts from regions of the Democratic Republic of the Congo affected by Ebola virus disease outbreaks.

Methods This longitudinal cohort study was done in Mbandaka, Equateur Province, and Beni, North Kivu Province. Individuals aged 1 year and older who received the rVSVΔG-ZEBOV-GP vaccine under the WHO ring-vaccination protocol were eligible for enrolment. These populations were defined as: people with confirmed Ebola virus disease, contacts of people with Ebola virus disease or contacts-of-contacts, and health-care or front-line workers in areas affected by Ebola virus disease. Participants were enrolled from June 2 to July 3, 2018, in Mbandaka and from Aug 15 to 29, 2018, in Beni. Serum samples were collected from vaccine recipients and antibody reactivity was assessed using a multiplex pan-filovirus immunoassay. Both cohorts were followed up over 5 years, with seven data collection periods in each province. We evaluated longitudinal trends in EBOV and BDBV glycoprotein seroreactivity using a pan-filovirus multiplex immunoassay across follow-up visits.

Findings We analysed 5849 serum samples from 1081 participants. 715 (66%) of 1081 participants were male and 366 (34%) were female. BDBV glycoprotein seroreactivity differed substantially between study sites. At baseline, 16 (3%) of 482 participants in Mbandaka and 62 (10%) of 599 in Beni were seroreactive to BDBV glycoprotein. In Mbandaka, BDBV glycoprotein antibody reactivity remained stable through to 6 months after initial vaccination before increasing from a mean median fluorescent intensity (MFI) of 1238 (SD 1599) at 2·5 years, with 16 (5%) of 355 seroreactive, to 4845 (5881) at 3·5 years and 116 (35%) of 329 seroreactive ($p<0\cdot0001$), followed by waning at later visits. In Beni, BDBV glycoprotein antibody reactivity increased rapidly after the initial vaccination, with seroreactivity peaking at 21 days to a mean MFI of 6678 (SD 6997) with 283 (52%) of 541 participants seroreactive and at 6 months to an MFI of 6852 (6560) with 270 (54%) of 501 seroreactive. Although antibody levels decreased after 6 months, EBOV glycoprotein and BDBV glycoprotein antibody reactivity remained above baseline through to 5 years after vaccination.

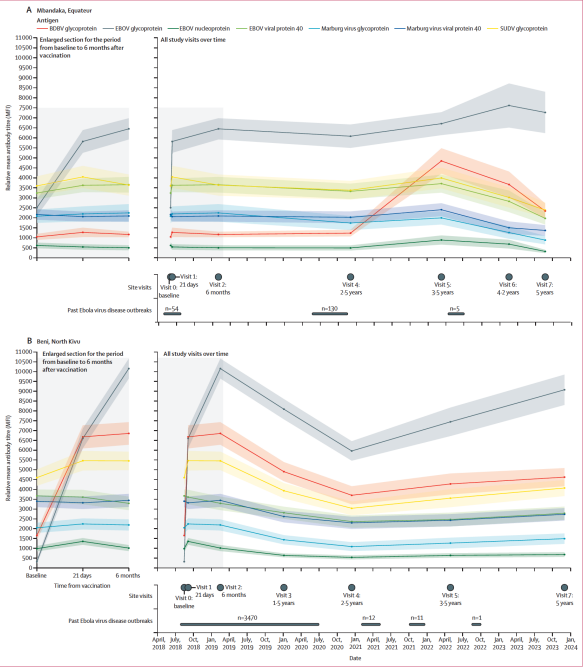
Interpretation The differing patterns of BDBV glycoprotein seroreactivity observed between Beni and Mbandaka warrant further investigation into the epidemiological and immunological factors associated with this seroreactivity, including the epidemiological significance of baseline seroreactivity observed before vaccination. To our knowledge, these findings provide the first longitudinal human data describing BDBV glycoprotein seroreactivity following licensed Ebola virus disease vaccination in populations living in regions now affected by the current outbreak of disease caused by BDBV. They add to the growing body of human evidence describing cross-reactive antibody responses following licensed Ebola virus disease vaccination and support rigorous clinical evaluation of rVSVΔG-ZEBOV-GP during the ongoing outbreak while BDBV-specific vaccines continue to be developed.

	Time from baseline	Mbandaka, Equateur	Beni, North Kivu
Baseline	..	June 2, 2018	Aug 15, 2018
Follow-up visit 1	Approximately 21 days	June 20, 2018	Sept 4, 2018
Follow-up visit 2	Approximately 6 months	Feb 5, 2019	March 22, 2019
Follow-up visit 3	Approximately 1.5 years	No visit	Jan 4, 2020
Follow-up visit 4	Approximately 2.5 years	Dec 8, 2020	Dec 14, 2020
Follow-up visit 5	Approximately 3.5 years	March 15, 2022	April 30, 2022
Follow-up visit 6	Approximately 4.2 years	Feb 22, 2023	No visit
Follow-up visit 7	Approximately 5 years	Aug 25, 2023	Dec 1, 2023

Data collection spanned on average 2 weeks from the listed start date. Visit numbers are labelled by the estimated time from baseline, subject to logistic feasibility for field visits.

Table 1: Study visit start dates

Figure 1: Detected anti-filovirus antibody MFI values after recombinant vesicular stomatitis virus–Zaire Ebola virus glycoprotein vaccination and outbreak and vaccine response timelines
 (A) Mbandaka, Equateur. (B) Beni, North Kivu. The line charts show the mean antibody MFI values to seven filovirus targets across seven study visit timepoints, with shaded areas showing 95% CIs. Enlarged charts for the period from baseline to 6 months after vaccination show further details of this period. Below the charts are the timepoints of site visits and the past Ebola virus disease outbreaks (n=number of people with Ebola virus disease). BDBV=Bundibugyo virus. EBOV=Ebola virus. MFI=median fluorescent intensity. SUDV=Sudan virus.



	Mbandaka, Equateur (n=482)	Beni, North Kivu (n=599)
Age, years		
0–5	0	0
6–18	36 (7%)	41 (7%)
19–35	152 (32%)	314 (52%)
36–55	241 (50%)	191 (32%)
56–82	53 (11%)	53 (9%)
Health zone		
Bolenge	100 (21%)	..
Mbandaka	146 (30%)	..
Wangata	236 (49%)	..
Beni	..	234 (39%)
Mangina	..	250 (42%)
Oicha	..	99 (17%)
Other	..	16 (3%)
Sex		
Male	332 (69%)	383 (64%)
Female	150 (31%)	216 (36%)
Occupational exposures*		
Health-care worker	160 (33%)	209 (35%)
Zoonotic exposure	11 (2%)	9 (2%)
Other	145 (30%)	198 (33%)
Unknown	166 (34%)	183 (31%)
Vaccination criteria†		
Close contact of person with Ebola virus disease	76 (16%)	237 (40%)
Health-care worker	154 (32%)	112 (19%)
Contact-of-contact of person with Ebola virus disease	39 (8%)	177 (30%)
Other	213 (44%)	73 (12%)
Study visit participation		
Baseline	482 (100%)	599 (100%)
21 days	467 (97%)	541 (90%)
6 months	417 (87%)	501 (84%)
1.5 years	No visit	467 (78%)
2.5 years	355 (74%)	373 (62%)
3.5 years	329 (68%)	391 (65%)
4.2 years	198 (41%)	No visit
5 years	304 (63%)	425 (71%)

Data are n (%). *Occupational exposure is derived from participant reported occupation. Participants reporting livestock farming or hunting as their primary occupation were categorised as having zoonotic occupational exposure. The other category includes all jobs without human or zoonotic risk, including vegetable farmers, fishers, teachers, merchants, technicians, students, drivers, politicians, and others. †Inclusion criteria for recombinant vesicular stomatitis virus–Zaire Ebola virus glycoprotein ring vaccination was close contacts of a person with Ebola virus disease, contacts-of-contacts, health-care workers, and in several situations other people at risk. In Mbandaka, 111 (23%) of 482 participants qualified for more than one criterion; in Beni, 275 (46%) 599 qualified for more than one criterion. In these cases, participants were sorted into the higher risk category and reported here. Our schema is: close contact is at greater risk than a health-care worker, who is at greater risk than a contact of the contact, who is at greater risk than people in other categories.

Table 2: Participant demographics

MFI = Median
fluorescence
intensity

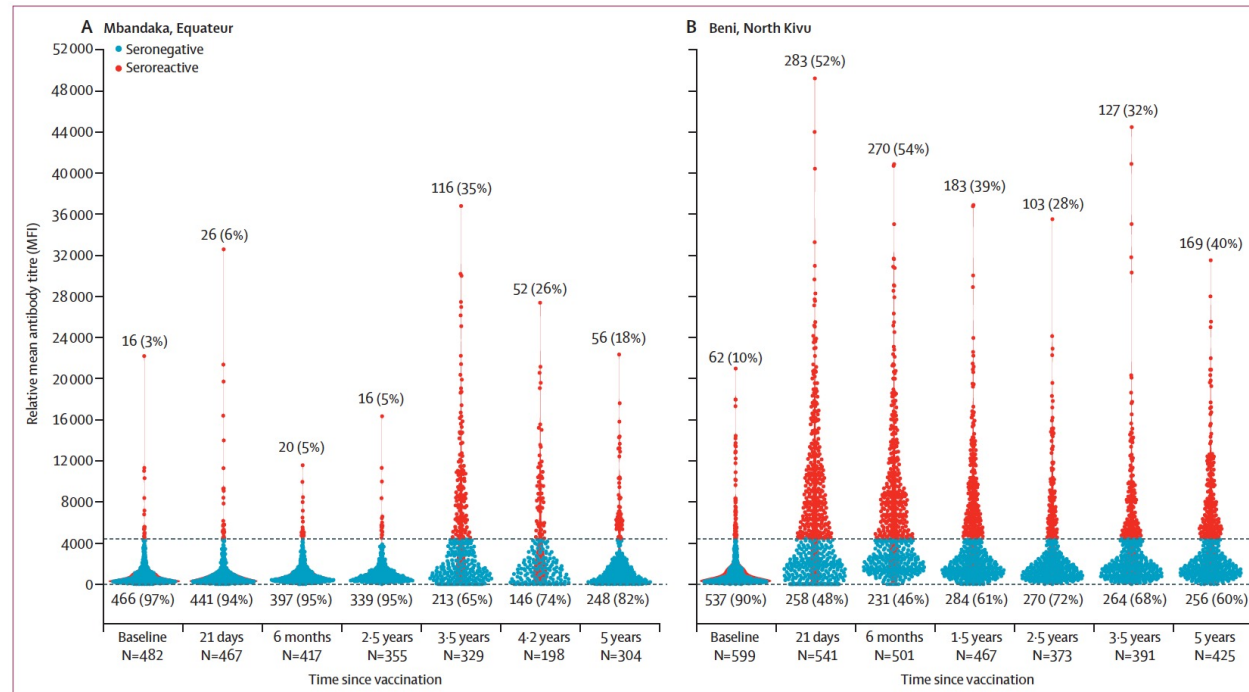


Figure 2: Detected anti-BDBV glycoprotein antibody MFI values after recombinant vesicular stomatitis virus-Zaire Ebola virus glycoprotein vaccination
The relative mean anti-BDBV glycoprotein antibody MFI values in participants in Mbandaka, Equateur, and Beni, North Kivu, over time. Red shows seroreactive specimens. Blue shows seronegative specimens. A y-intercept line at 4433 denotes the MFI minimum for seroreactivity. Counts and percentages for seroreactive and seronegative groups are plotted for each timepoint. BDBV=Bundibugyo virus. MFI=median fluorescent intensity.

Research in context

Evidence before this study

We searched PubMed and medRxiv for English-language articles published from database inception to June 25, 2026, using the terms “ERVEBO”, “rVSV-ZEBOV”, “Ebola vaccine”, “Bundibugyo virus”, “cross-reactivity”, “filovirus”, “immunogenicity”, “vaccine response”, and “durability”. Previous clinical trials and observational studies have shown robust and durable antibody responses to Ebola virus (EBOV) glycoprotein following vaccination with recombinant vesicular stomatitis virus–Zaire Ebola virus glycoprotein (rVSVΔG-ZEBOV-GP). A letter in the *New England Journal of Medicine* reported detectable cross-reactive antibody responses to Bundibugyo virus (BDBV) glycoprotein following licensed Ebola virus disease vaccination at early post-vaccination timepoints, while a separate Partnership for Research on Ebola Vaccination preprint showed persistence of EBOV glycoprotein antibody responses for 5 years after vaccination. We found no published studies evaluating the long-term longitudinal kinetics of BDBV glycoprotein seroreactivity following rVSVΔG-ZEBOV-GP vaccination in humans.

Added value of this study

To our knowledge, this study provides the first longitudinal human evaluation of BDBV glycoprotein seroreactivity following rVSVΔG-ZEBOV-GP vaccination in populations living

in regions now affected by the current outbreak of disease caused by BDBV. We analysed 5849 serum samples from 1081 participants over 5 years using a multiplex pan-filovirus immunoassay and identified distinct longitudinal patterns of BDBV glycoprotein seroreactivity between geographically separated populations. Our findings expand the limited human evidence that licensed Ebola virus disease vaccination induces cross-reactive BDBV antibody responses and provide the first longitudinal data from real-world outbreak-vaccinated populations.

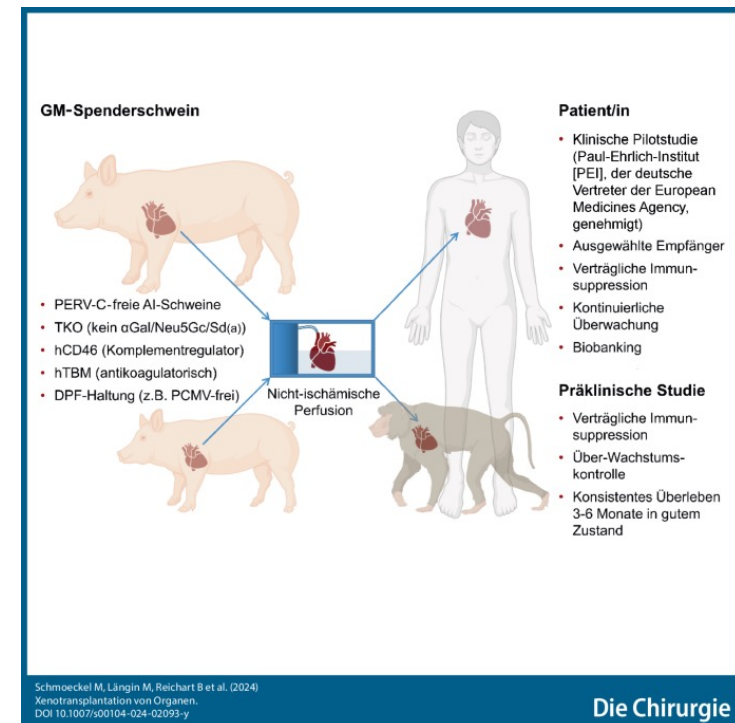
Implications of all the available evidence

Available evidence suggests that licensed Ebola virus disease vaccines induce durable antibody responses to EBOV and detectable cross-reactive antibody responses to BDBV glycoprotein in humans. Our findings extend this evidence by describing the first real-world longitudinal characterisation of BDBV glycoprotein seroreactivity in vaccinated populations living in regions previously and now affected by the current BDBV disease outbreak. These data expand the limited human evidence base available to support rigorous clinical evaluation of licensed rVSVΔG-ZEBOV-GP vaccination during the ongoing outbreak of BDBV while BDBV-specific vaccines continue to be developed and broadly protective filovirus vaccines continue to be evaluated.

Eine porcine Nieren-Xenotransplantation ist die Übertragung einer genetisch veränderten Schweineneiere auf einen Menschen.

Aktueller Meilenstein

- **Neuer Rekord:** Ärzte am Massachusetts General Hospital in Boston transplantierten einem Patienten eine genmodifizierte Schweineneiere.
- **Dauer:** Das Organ funktionierte **271 Tage (rund neun Monate)** und bewahrte den Patienten in dieser Zeit vor der Dialyse.
- **Brückenfunktion:** Nach Komplikationen und dem Versagen der Schweineneiere erhielt der Patient nach einer kurzen Dialysephase erfolgreich eine menschliche Spenderniere. Der Fall wurde im Fachjournal *The Lancet* veröffentlicht.



Porcine kidney xenotransplantation as a bridge to allotransplantation: a first-in-human study

Summary

Background Kidney xenotransplantation offers a potential solution to the organ shortage, but questions remain regarding durability, zoonotic infection risk, and whether the immunological response to the xenograft elicits sensitisation that could complicate subsequent allotransplantation. We report outcomes from a porcine kidney xenograft in a living recipient followed by human allotransplantation.

Methods A patient with end-stage kidney disease, a prolonged anticipated waiting time for deceased donor transplantation, and with no suitable living donor underwent transplantation at Massachusetts General Hospital (Boston, MA, USA) with a gene-edited porcine kidney (EGEN-2784; eGenesis [Cambridge, MA, USA]) incorporating the deletion of major glycan xenoantigens, inactivation of porcine endogenous retroviruses, and insertion of seven human transgenes. The recipient received costimulation blockade-based immunosuppression with complement inhibition. Monitoring included renal function, flow cytometric crossmatch, anti-HLA antibodies, and porcine microbial surveillance, including metagenomic sequencing. This report describes the first recipient in a planned three-patient study conducted under a US Food and Drug Administration Expanded Access Investigational New Drug application.

Findings The xenograft functioned immediately after transplantation on Jan 25, 2025, and sustained dialysis independence for 271 days. A biopsy on day 14 showed T-cell-mediated rejection, which resolved with treatment. Graft function remained stable for approximately 6 months until immunosuppression was reduced in the setting of non-zoonotic bacterial infection. Microvascular inflammation with endothelial injury subsequently emerged, progressing to thrombotic microangiopathy despite persistently negative donor-specific crossmatch, leading to graft failure and nephrectomy. Tissue analysis showed a macrophage and natural-killer-cell-predominant infiltrate with minimal T-cell involvement. No porcine pathogen transmission was detected. Anti-HLA antibodies remained unchanged. 82 days after explantation, the patient underwent human kidney allotransplantation with immediate graft function and no evidence of sensitisation during 231 days of follow-up.

Interpretation This case shows that porcine kidney xenotransplantation can provide prolonged renal support and be discontinued without clinically significant allosensitisation or zoonotic infection. Early cellular rejection resolved with treatment, whereas later graft failure was associated with microvascular injury progressing to thrombotic microangiopathy despite a negative donor-specific crossmatch, supporting the possibility that mechanisms beyond conventional antibody-mediated rejection contributed to late graft injury. Kidney xenotransplantation has the potential to provide prolonged dialysis-free support while also serving as a bridge to subsequent human allotransplantation.

Worked for about 9 months until a human donor was found.

Macrophages and NK cells were prominent.

Homograft functioned without any problems.

Porcine aspects were not involved.

Characteristics and details	
Recipient	
Age, sex	66 years, male
End-stage kidney disease cause	Type 2 diabetes
Blood group	O
Weight	90 kg
5-year transplant probability	~9% (SRTR)
5-year waiting list mortality risk	>40% (SRTR)
Expected wait time (blood group O)	>5 years
Porcine donor	
Species	Yucatan miniature pig
Total modifications	69 genomic modifications
Knockouts	GGTA1, CMAH, and B4GALNT2
Transgenes	CD46, CD55, THBD, EPCR, CD47, HMOX1, and TNFAIP3
PERV inactivation	CRISPR-Cas genome editing
Facility	Designated pathogen-free
Kidney weight	170 g
Surgical parameters	
Transplantation date	Jan 25, 2025
Cold ischaemia time	2 h 39 min
Warm ischaemia time	25 min
Duration of the surgery	2 h 15 min
Vascular anastomosis	Iliac vessels (heterotopic)
Immunosuppression	
Induction	rATG, corticosteroids, rituximab, and pegcetacoplan
Maintenance	Tegoprobart (anti-CD154), tacrolimus, MPA, and prednisone
Clinical, genomic, surgical, and immunosuppressive characteristics of the recipient and porcine donor, and details of surgical parameters and immunosuppression. The gene-edited porcine kidney (EGEN-2784) incorporated three xenoantigen knockouts, seven human transgenes, and CRISPR-Cas-mediated PERV inactivation. Immunosuppression comprised costimulation blockade-based maintenance therapy with complement inhibition at induction. MPA=mycophenolic acid. PERV=porcine endogenous retrovirus. rATG=rabbit antithymocyte globulin. SRTR=Scientific Registry of Transplant Recipients.	
Table: Xenotransplantation characteristics and details	

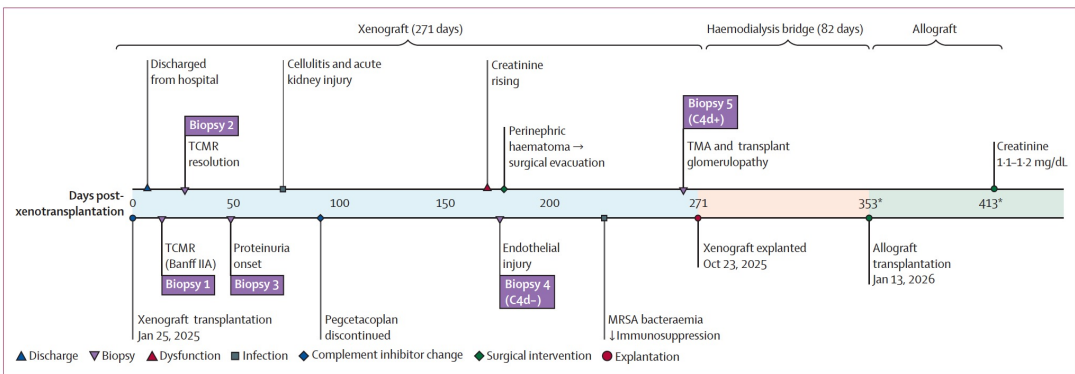


Figure 1: Clinical course
Timeline of clinical events following porcine kidney xenotransplantation in a living human recipient. The xenograft survived for 271 days (blue), followed by a haemodialysis bridge (82 days, pink), and human kidney allotransplantation (green). MRSA=meticillin-resistant *Staphylococcus aureus*. TMA=thrombotic microangiopathy. TCMR=T-cell-mediated rejection. *Days calculated from the xenograft transplantation date.

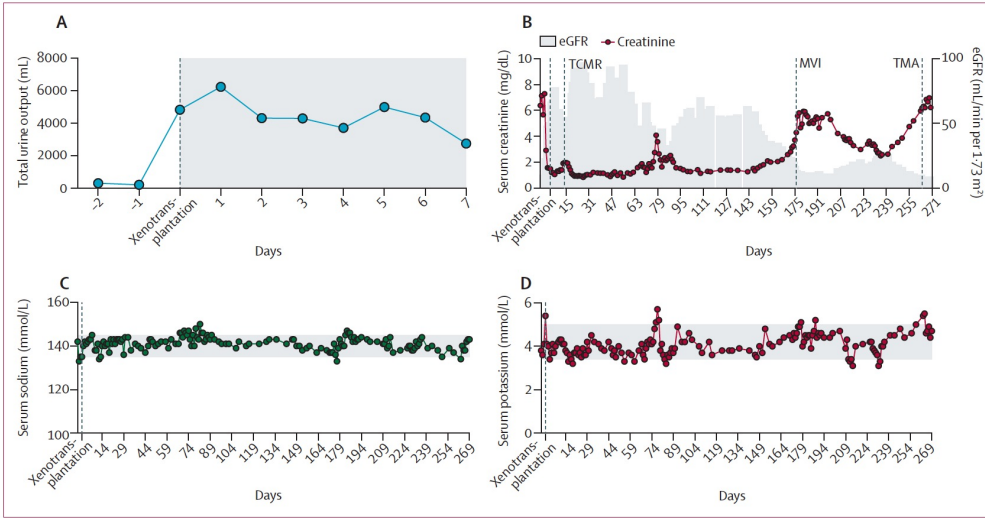


Figure 2: Longitudinal renal function and biochemical parameters before and after porcine kidney xenotransplantation
(A) Total daily urine output (mL) during the first week after xenotransplantation. (B) Serum creatinine and eGFR throughout the xenograft period. Note that scales on y axes differ between plots. Vertical dashed lines indicate for-cause kidney biopsies—key histopathological findings are annotated: day 14, Banff IIA TCMR; day 176, MVI with endothelial injury; day 264, TMA with transplant glomerulopathy. (C) Serum sodium. (D) Serum potassium. All panels share a common x-axis representing days relative to xenotransplantation (day 0). eGFR=estimated glomerular filtration rate. MVI=microvascular inflammation. TCMR=T-cell-mediated rejection. TMA=thrombotic microangiopathy.

Figure 3: Histopathological evolution of xenograft injury

(A–D) Day 14. Biopsy shows widespread mononuclear interstitial infiltrate with tubulitis (PAS, $\times 400$; A) and moderate endarteritis (arrows), diagnostic of Banff IIA TCMR (haematoxylin and eosin, $\times 400$; B). C4d immunofluorescence is present despite a negative flow cytometric crossmatch against donor cells ($\times 400$; C). Electron microscopy shows intact glomerular endothelium and podocyte foot processes ($\times 7100$; D). (E–H) Day 25. Follow-up biopsy shows resolution of TCMR with no tubulitis or endarteritis (PAS, $\times 400$; E–F). C4d staining shows weak peritubular capillary positivity ($\times 400$; G). Electron microscopy is unremarkable ($\times 3500$; H). (I–L) Day 47. Glomeruli show reactive podocytes with no tubulointerstitial or microvascular inflammation (PAS, $\times 400$; I). Arteries are unremarkable (PAS, $\times 400$; J). C4d is negative ($\times 400$; K). Electron microscopy shows podocyte injury with swelling and segmental foot process effacement ($\times 2200$) without appreciable endothelial injury (inset; L). (M–P) Day 73. Persistent reactive podocytes without evidence of rejection or endothelial injury (PAS, $\times 400$; M). Arteries and arterioles are unremarkable (PAS, $\times 400$; N). C4d is negative ($\times 400$; O). Electron microscopy shows extensive podocyte foot process effacement ($\times 7100$) with intact endothelium (inset; P). (Q–T) Day 176. Glomerulitis with endothelial injury and segmental intracapillary mononuclear cells, with evidence of early TMA; inset shows red cell fragmentation in glomerular capillaries (haematoxylin and eosin, $\times 400$; Q). Arteriolar involvement with early fibrin deposition and intimal mucoid change (arrow; haematoxylin and eosin, $\times 400$; R). C4d is negative, consistent with the absence of antibody-mediated rejection ($\times 400$; S). Electron microscopy of a glomerular capillary showing an intracapillary monocyte, swollen endothelial cell, and podocyte injury ($\times 5600$; T). (U–X) Day 264. Progressive TMA with multiple intracapillary thrombi, fibrin deposition, and red cell fragmentation in glomeruli (haematoxylin and eosin, $\times 400$; U). Similar findings in arterioles (arrow; haematoxylin and eosin, $\times 400$; V). C4d is positive in peritubular capillaries ($\times 400$; W). Electron microscopy of a glomerular capillary showing endothelial loss and intracapillary thrombi with fibrin tactoids ($\times 5600$; X). PAS=periodic acid-Schiff. TCMR=T-cell-mediated rejection. TMA=thrombotic microangiopathy.

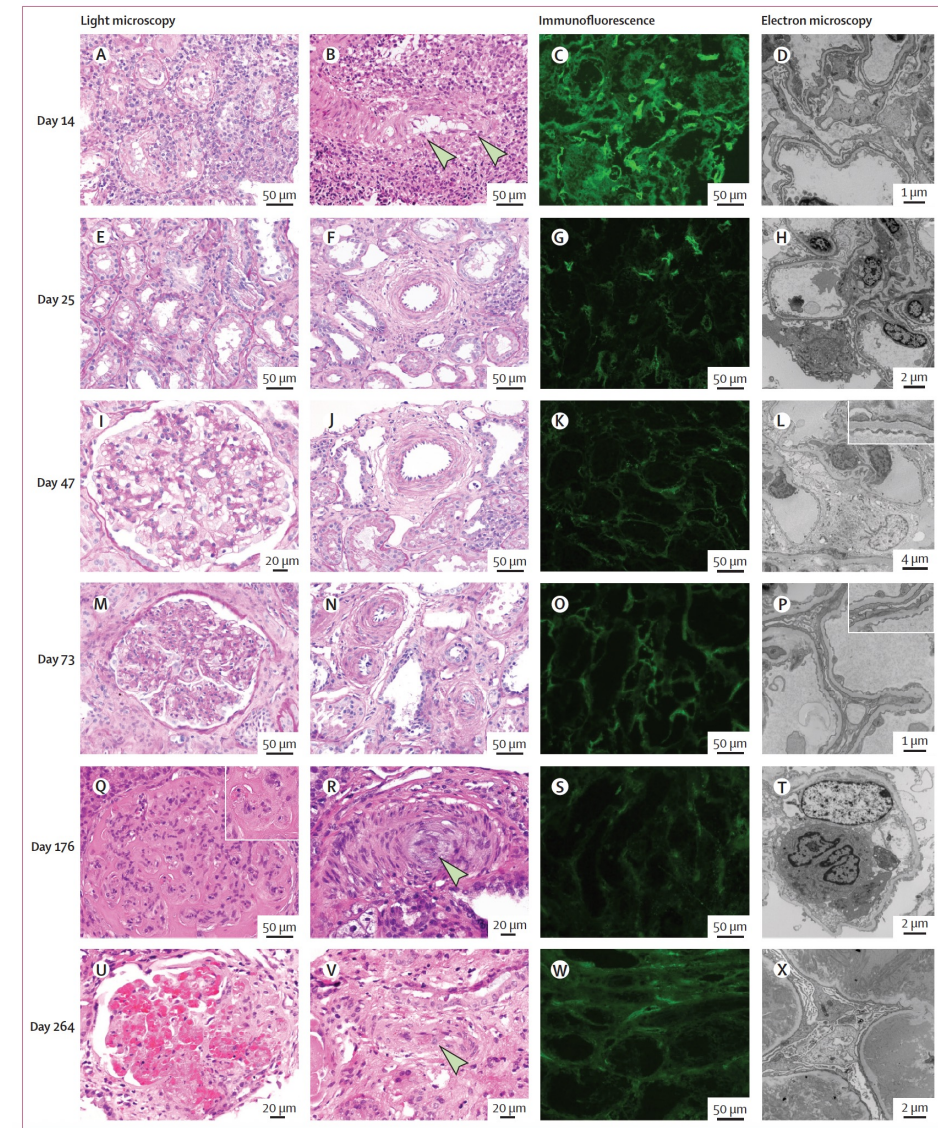
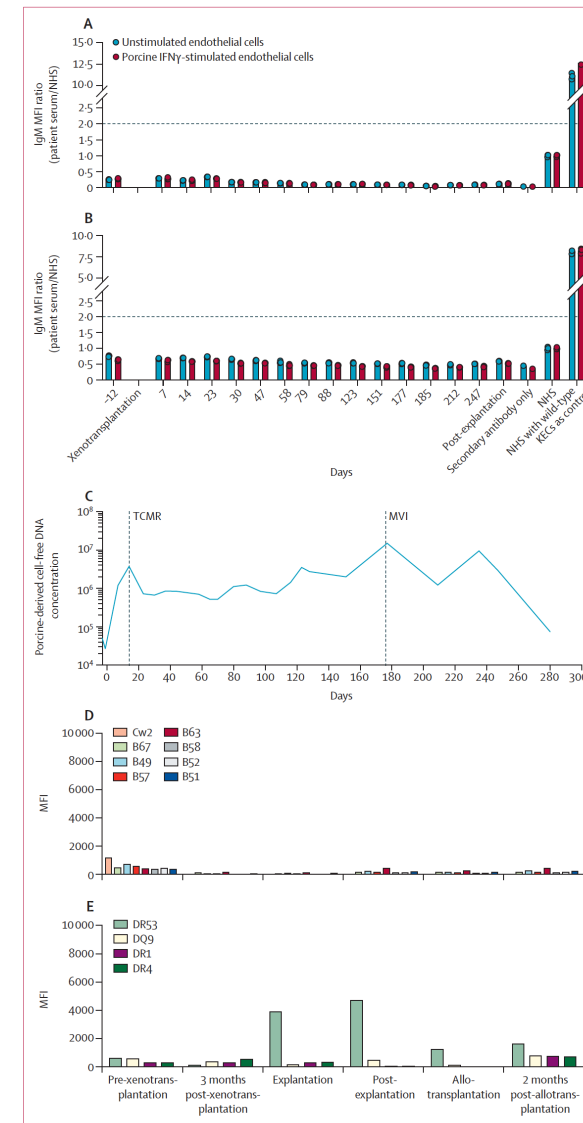


Figure 4: Immunological monitoring throughout the xenograft period and following allotransplantation

(A) FCXM showing IgM binding against donor porcine kidney endothelial cells, expressed as MFI ratio relative to pooled NHS (>100 donors) at serial timepoints in days post-xenotransplantation. (B) FCXM showing IgG binding against donor porcine kidney endothelial cells, expressed as MFI ratio relative to pooled NHS at serial timepoints in days post-xenotransplantation. Endothelial cells derived from the donor's contralateral kidney were used as target cells. The dashed horizontal line indicates the positivity threshold. Wild-type Yucatan porcine KECs were additionally tested against pooled NHS as a control. (C) Porcine-derived cell-free DNA measured serially during the xenograft period in days post-xenotransplantation; vertical dashed lines indicate biopsy-confirmed graft injury events (TCMR, day 14; microvascular inflammation with endothelial injury, day 176). (D) Anti-HLA class I antibody MFI by single-antigen bead assay, shown for specificities with peak MFI ≥ 500 . (E) Anti-HLA class II antibody MFI by single-antigen bead assay, shown for specificities with peak MFI ≥ 500 . FCXM=flow cytometric crossmatch. IFN- γ =interferon-gamma. KECs=kidney endothelial cells. MFI=mean fluorescence intensity. MPM=molecules of pig-derived cell-free DNA per μ L of plasma. MVI=microvascular inflammation. NHS=normal human serum. TCMR=T-cell-mediated rejection.



Research in context

Evidence before this study

Kidney transplantation remains the optimum therapy for end-stage kidney disease; however, organ shortage is a global challenge. Worldwide, hundreds of thousands of patients await kidney transplantation, and many die each year while on waiting lists or without access to transplantation. In the USA alone, more than 100 000 patients are currently on waiting lists. Genetically engineered porcine kidneys have emerged as a promising strategy to address this shortage. We searched PubMed on April 14, 2026, for studies published from Jan 1, 2016, to April 14, 2026, and available in English, using the terms “xenotransplantation AND kidney AND (human OR clinical)”. We included peer-reviewed original research describing porcine-to-human xenotransplantation in decedent or living recipients, with or without subsequent transition to human allotransplantation. Early studies in decedent models established technical feasibility. We reported the first porcine kidney xenotransplantation in a living human recipient in March, 2024, with survival of 52 days before death from cardiac causes unrelated to the xenograft. To our knowledge, no previous report has documented xenograft survival beyond 2 months, successful transition to human allotransplantation, or detailed mechanisms of late xenograft failure in living recipients.

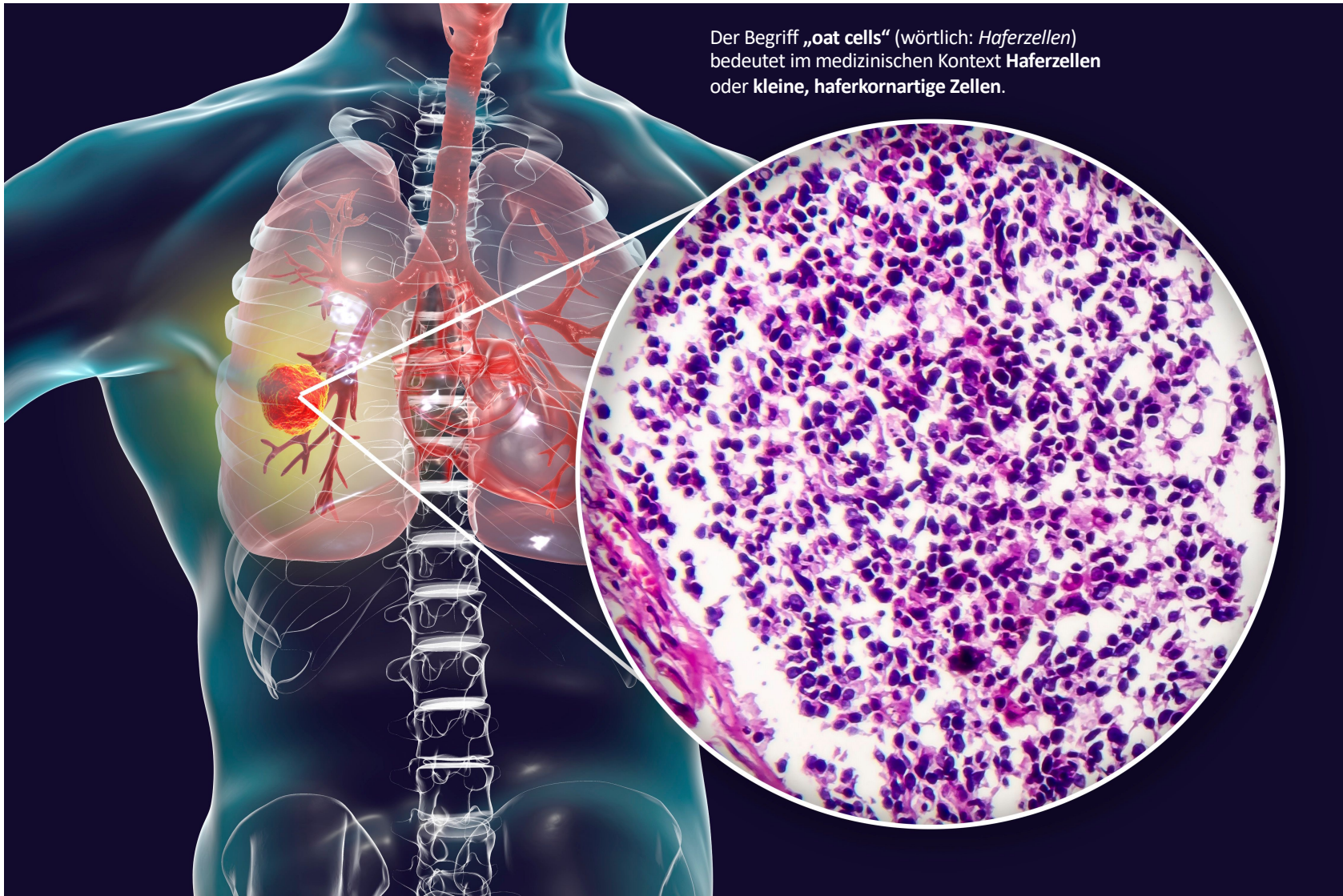
Added value of this study

In this Article, we describe, to our knowledge, the longest dialysis-free survival (9 months) following porcine kidney xenotransplantation in a living human and the first transition to human kidney allotransplantation. The allograft functioned immediately, and no allosensitisation was detected following xenograft explantation. Longitudinal immunological and pathological analyses identified a distinct phenotype of macrophage and natural-killer-cell-mediated microvascular injury leading to thrombotic microangiopathy, despite persistently negative donor-specific crossmatch. No porcine pathogen transmission was detected post-transplantation.

Implications of all the available evidence

Porcine kidney xenotransplantation can provide sustained renal function and could serve as a reversible bridge to allotransplantation without evidence of allosensitisation or zoonotic infection during follow-up. Identification of innate immune-mediated microvascular injury as a mechanism of late xenograft failure has important implications for immuno-suppressive strategies, donor genetic engineering, and monitoring in future clinical xenotransplantation studies.

Der Begriff „**oat cells**“ (wörtlich: *Haferzellen*)
bedeutet im medizinischen Kontext **Haferzellen**
oder **kleine, haferkornartige Zellen**.



The changing therapeutic landscape of small-cell lung cancer

Small-cell lung cancer (SCLC) is an exceptionally aggressive malignancy: highly proliferative, heterogeneous, and frequently metastatic at diagnosis. Although initially responsive to chemotherapy, such responses are typically transient, and recurrent disease has been largely refractory to standard cytotoxics. The past decade has been notable for major advances in our understanding of SCLC biology, and this preclinical progress is now informing multiple novel therapeutic approaches for this disease. Of particular note, defining cell-surface proteins that are uniquely or differentially expressed in SCLC has led to various targeted therapies showing substantial preliminary evidence of efficacy in patients with SCLC. Approaches in active development include T-cell engagers, antibody–drug conjugates, radioconjugates, and cell therapies, among others. In this Series paper, we summarise current standards of care, recent advances, and highlight emerging approaches showing early promise for better management of SCLC. Together, these advances are providing new hope for patients with what has been a particularly lethal disease.

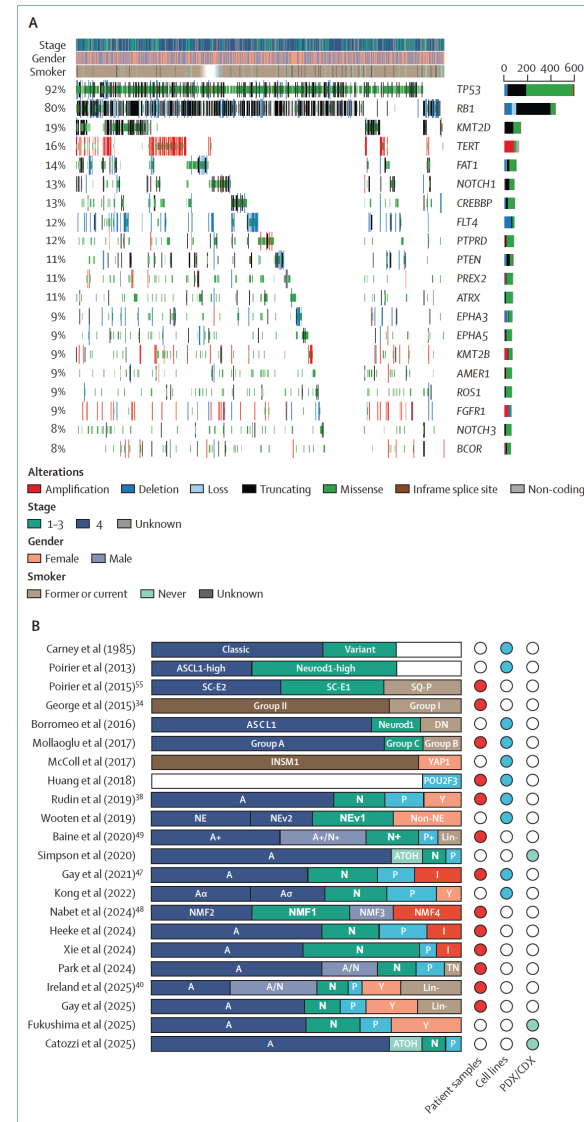
Small cell lung cancer (SCLC) originates from cells of the neuroendocrine lineage, whereas non-small cell lung cancer (NSCLC) primarily arises from bronchial or alveolar epithelial cells.

Key messages

- Next-generation T-cell engagers, antibody-drug conjugates, radioconjugates, and chimeric antigen receptor approaches are exploiting the unique small-cell lung cancer (SCLC) surfaceome with promising early efficacy
- Antibody-drug conjugates targeting DLL3, SEZ6, and B7-H3 show response rates of 40–75% in early-phase trials, with several in phase 3 evaluation
- Radioconjugate therapies are a promising emerging class in SCLC enabling combined theranostic imaging and targeted radiation delivery
- Molecular subtyping is revealing actionable subtype-specific vulnerabilities, with the first biomarker-selected trial now underway

Figure 1: Genomic and transcriptomic profiling of SCLC

(A) Common genomic alterations in SCLC. Oncoprint of the most common genomic alterations identified in 704 SCLCs profiled by MSK-IMPACT-targeted sequencing. (B) Subtype classifications. Suggested classification schemes based on histological characteristics³⁹ or gene-expression profiling.^{36,40–59} Subtypes based on the highest relative expression of *ASCL1* (SCLC-A), *NEUROD1* (SCLC-N), *POU2F3* (SCLC-P), *YAP1* (SCLC-Y), and inflamed (SCLC-I; characterised by evidence of immune-cell infiltration). SCLC=small-cell lung cancer. SC-E1=small-cell expression group 1. SC-E2=small-cell expression group 2. SQ-P=primitive squamous-like. A=SCLC-A. N=SCLC-N. P=SCLC-P. Y=SCLC-Y. NE=neuroendocrine. NEv1=neuroendocrine variant 1. NEv2=neuroendocrine variant 2. Non-NE=non-neuroendocrine. A/N=SCLC-AN. Lin-=lineage negative. PDX/CDX=patient-derived xenograft/circulating tumour-cell-derived xenograft. ATOH=cluster expressing ATOH1. I=SCLC-I. NMF=non-negative matrix factorisation. TN=triple negative.



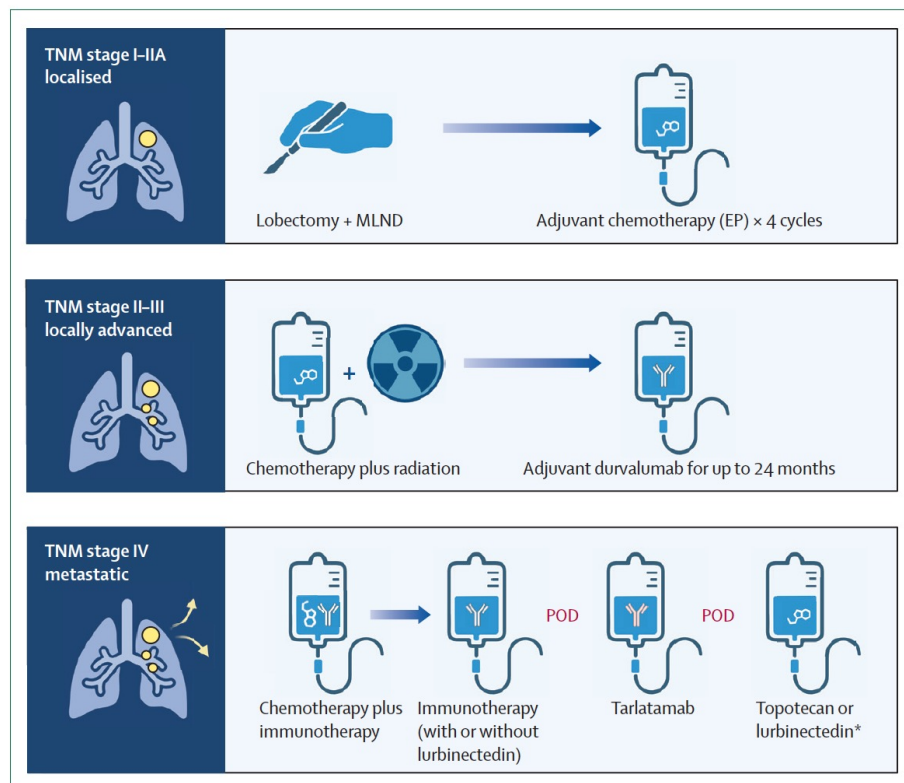


Figure 2: Small-cell lung cancer treatment by stage

TNM=tumour node metastasis. MLND=mediastinal lymph node dissection. EP=etoposide plus platinum chemotherapy. POD=progression of disease. *If not used previously.

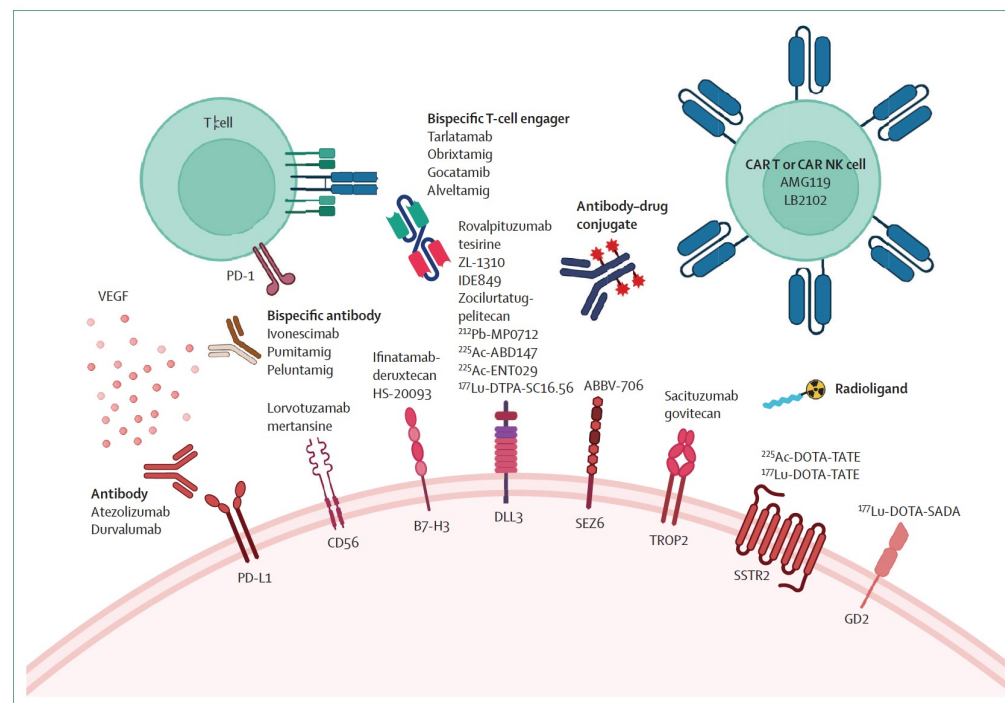


Figure 3: Exploiting the small-cell lung cancer surfaceome

Therapeutic strategies being pursued are indicated, together with corresponding targets of interest. ¹⁷⁷Lu=Lutetium-177. ²¹²Pb=Lead-212. ²²⁵Ac=Actinium-225. CAR=chimeric antigen receptor. NK=natural killer. VEGF=vascular endothelial growth factor.

	Phase	Percentage of SCLC-expressing target (%)	Therapeutic strategy in clinical development
DLL3			
NCT06780137	1/2	~80–90% ^{158–160}	T-cell engager
NCT05882058	2	~80–90% ^{158–160}	T-cell engager
NCT05652686	1/2	~80–90% ^{158–160}	Bispecific antibody
NCT07174583	1/2	~80–90% ^{158–160}	Antibody-drug conjugate
NCT07218146	3	~80–90% ^{158–160}	Antibody-drug conjugate
NCT06736418	1	~80–90% ^{158–160}	Radioconjugate
NCT07006727	1	~80–90% ^{158–160}	Radioconjugate
NCT07278479	1/2	~80–90% ^{158–160}	Radioconjugate
NCT06941480	1	~80–90% ^{158–160}	Radioconjugate
NCT05680922	1	~80–90% ^{158–160}	Chimeric antigen receptor T cell
SEZ6			
NCT07155174	2	~90% ¹⁶¹	Antibody-drug conjugate
B7H3			
NCT06954246	3	~65% ¹⁶²	Antibody-drug conjugate
NCT06203210	3	~65% ¹⁶²	Antibody-drug conjugate
NCT05280470	2	~65% ¹⁶²	Antibody-drug conjugate
TROP2			
NCT07339059	2	~20% ¹⁶³	Antibody-drug conjugate
NCT06465238	2	~20% ¹⁶³	Antibody-drug conjugate
SSTR2			
NCT05142696	1	~48% ¹⁶⁴	Radioconjugate
NCT05595460	1	~48% ¹⁶⁴	Radioconjugate
GD2			
NCT05130255	1	~39% ¹⁶⁵	Self-assembling and disassembling bispecific antibody

SCLC=small-cell lung cancer.

Table: Selected ongoing therapeutic clinical trials targeting cell-surface proteins in SCLC

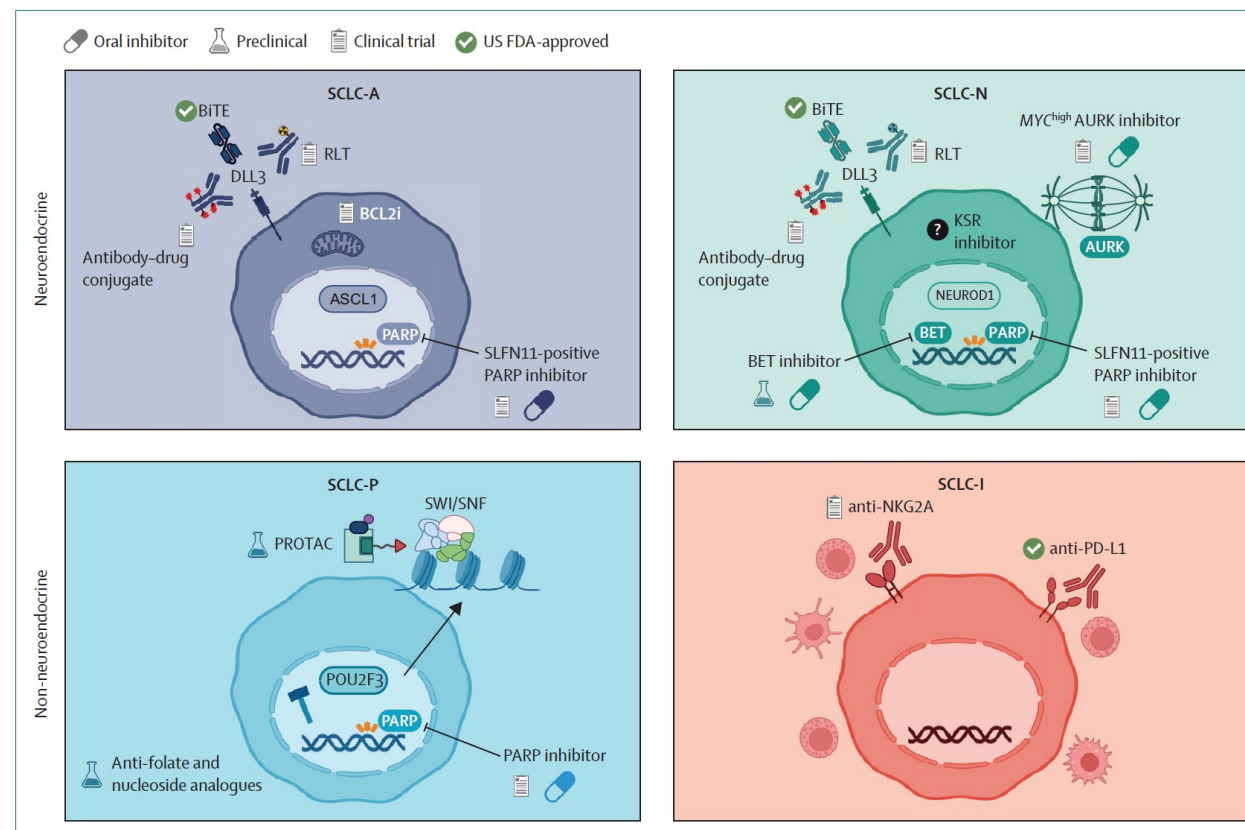


Figure 4: Putative subtype vulnerabilities

Therapeutic strategies suggested to have preferential activity based on subtype classification are shown. Subtypes based on the highest relative expression of ASCL1 (SCLC-A), NEUROD1 (SCLC-N), POU2F3 (SCLC-P), YAP1 (SCLC-Y), and inflamed (SCLC-I), which is characterised by evidence of immune-cell infiltration. BiTE=bispecific T-cell engager. US FDA=US Food and Drug Administration. RLT=radioligand therapy.

Conclusion

SCLC is a challenging disease with poor long-term survival. However, this is a particularly promising time for patients with SCLC, with recent basic and translational research efforts translating into multiple promising therapies that are beginning to show clinical impact. The past 7 years have shown more drug approvals in SCLC than in the preceding decades. Immune checkpoint blockade, although only effective in a minority of patients, has established an important milestone, providing the possibility of cure for a small number of patients with metastatic disease, and improving survival statistics in early-stage disease as well. Tarlatamab has redefined the standard of care with a new benchmark for survival in recurrent disease, and longer-term follow-up of these patients is eagerly awaited. Other T-cell engagers

offering a variety of alternative designs are showing clinical efficacy, and the best-in-class drug remains to be defined. Other particularly promising classes of agents in active clinical development for patients with SCLC include antibody–drug conjugates, bispecific antibodies, radioconjugates, and CAR T cells. These therapeutics are different in their cytotoxic mechanisms, but all take advantage of the unique surfaceome recently defined in SCLC. The best approach for such targeting, and the optimal sequencing of these therapies, remains to be seen. Through ongoing, robust, basic-science research and clinical development, these studies offer hope that SCLC will become a more manageable disease treated with rationally designed, durably effective, targeted, and biomarker-guided therapies.

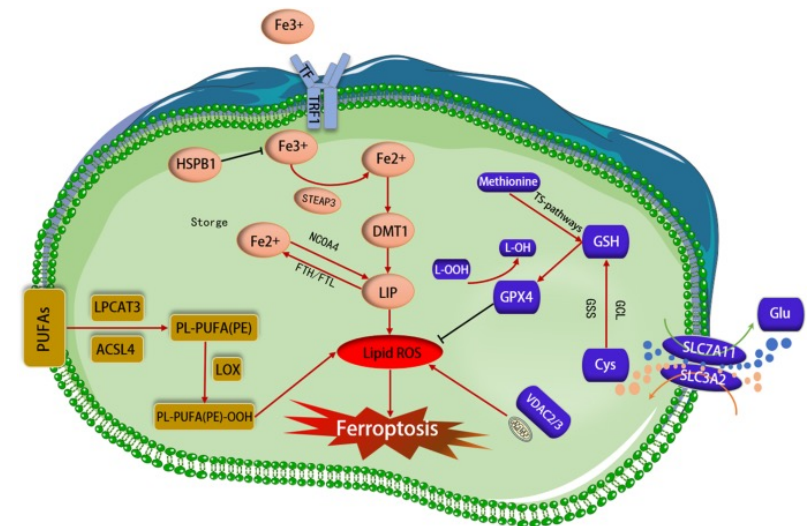
Ferroptose ist eine erst 2012 entdeckte, **eisenabhängige Form des programmierten Zelltods**, die durch die giftige Ansammlung von Lipidperoxiden in der Zellmembran ausgelöst wird.

Grundmechanismus

- **Eisenbedarf:** Freies Eisen in der Zelle treibt oxidative Prozesse an.
- **Lipidperoxidation:** Sauerstoffradikale zerstören mehrfach ungesättigte Fettsäuren in den Membranen.
- **Fehlendes Schutzsystem:** Antioxidantien wie Glutathion oder das Enzym GPX4 können die Oxidation normalerweise verhindern; bricht dieses System zusammen, stirbt die Zelle.

Medizinische Bedeutung

- **Krebstherapie:** Forscher versuchen, Krebszellen gezielt in die Ferroptose zu treiben, um resistente Tumoren abzutöten.
- **Neurodegenerative Erkrankungen:** Ein unkontrollierter Eisentod wird bei Krankheiten wie Alzheimer oder Parkinson vermutet.





Lean adipocyte oxylipin signaling restrains breast cancer through ferroptosis

INTRODUCTION: Obesity is a major risk factor for breast cancer and is associated with more aggressive disease and poorer clinical outcomes. Although obesity alters the breast tumor microenvironment, the mechanisms by which these changes influence tumor development remain poorly understood. Adipocytes are abundant in the breast and secrete metabolites and other signaling molecules that can affect neighboring epithelial and cancer cells. We investigated whether obesity-associated changes in adipocyte-derived signals regulate breast cancer progression.

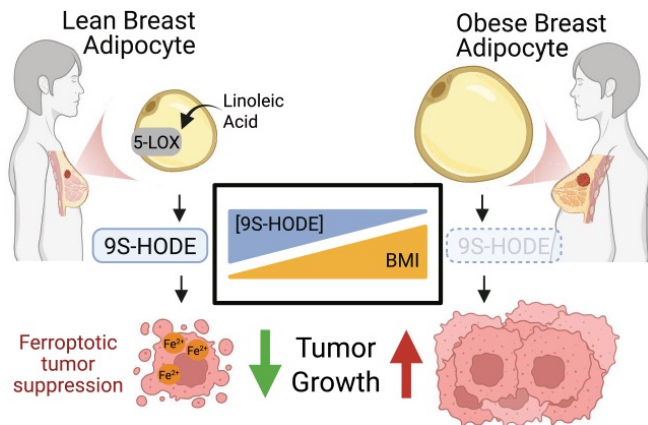
RATIONALE: Adipocytes undergo profound remodeling in obesity, including changes in lipid composition and secretion. We hypothesized that adipocytes produce lipid mediators that regulate tumor growth and contribute causally to obesity-accelerated breast cancer. To test this, we combined mouse models of obesity, primary adipocyte cultures, transcriptomics, lipidomics, and patient-derived breast cancer models to define lipid-mediated mechanisms regulating breast cancer.

RESULTS: Mouse and human breast tumors grow more rapidly in obese mice compared with lean mice. To identify the underlying mechanisms, we examined the effects of adipocyte-secreted factors from both lean and obese mice on mouse and human breast cancer models, representing different molecular subtypes. The secretome from mammary adipocytes of lean mice strongly suppressed growth, whereas secretomes from obese mice did not. The lean mammary adipocyte secretome inhibited breast cancer cell growth by inducing ferroptotic cell death, characterized by oxidative lipid damage and increased intracellular ferrous iron. Consistent with this mechanism, breast tumors from lean mice showed increased ferroptosis markers, and pharmacologic inhibition of ferroptosis selectively accelerated tumor growth in lean but not obese mice.

To identify the responsible adipocyte-derived factor, we combined several lipid depletion approaches with lipidomics. These analyses identified the oxylipin 9S-hydroxyoctadecadienoic acid (9S-HODE) as highly enriched in lean adipocyte

secretomes and lean mammary fat pads. 9S-HODE promoted lipid peroxidation, disrupted iron homeostasis, and induced ferroptosis in breast cancer cells and tumors. Closely related oxylipins, including 13S-HODE and 9R-HODE, lacked this activity. Comparatively, nontumorigenic mammary epithelial cells were resistant to 9S-HODE through diacylglycerol acyltransferase (DGAT)–dependent lipid droplet formation, which buffered lipid peroxidation stress. Inhibition of adipocyte lipoxygenase activity subsequently reduced 9S-HODE production in mammary adipocytes and accelerated tumor growth, whereas the restoration of 9S-HODE in obese mice induced ferroptosis and suppressed tumor growth. In human breast adipose tissue, 9-HODE levels were inversely correlated with body mass index, and 9S-HODE suppressed the growth of patient-derived breast cancer organoids.

The secretome from mammary adipocytes of lean mice strongly suppressed growth. These analyses identified the oxylipin 9S-hydroxyoctadecadienoic acid (9S-HODE) as highly enriched in lean adipocyte secretomes.



Mammary adipocyte-secreted 9S-HODE suppresses breast cancer. Mammary adipocytes in lean mice and individuals produce and secrete high levels of 9-HODE in a 5-lipoxygenase (5-LOX)–dependent manner. 9S-HODE suppresses tumor growth by disrupting intracellular iron homeostasis and inducing ferroptosis. In obesity, breast 9-HODE levels are reduced, thereby diminishing ferroptotic stress and, as a result, promoting accelerated breast tumor growth. BMI, body mass index.

CONCLUSION: Mammary adipocytes secrete the oxylipin 9S-HODE, which suppresses breast cancer growth through the induction of ferroptosis. Obesity disrupts this tumor-suppressive lipid signal, thereby reducing ferroptotic stress and promoting tumor progression. These findings identify the loss of adipocyte-derived 9S-HODE signaling as a mechanism linking obesity and breast cancer and support the restoration of this pathway as a potential therapeutic strategy.

ICE is arming agents with shock gloves. What are the rules?



Immigration and customs enforcement (ICE)

The weapon was supposed to give officers a safer way to use force. Now ICE is spending \$16.7 million on 6,000 pairs of electric stun gloves, built around the same promise. An officer turns on the Generated Low Output Voltage Emitters (GLOVE) by pressing a button. Once activated, the gloves deliver a painful shock when they touch bare skin.

Vulnerable people need extra safeguards. Omaha school resource officers used the gloves twice on students last school year before the district asked police to stop carrying them in schools. The manufacturer advises against use on small children, older adults and people with severe disabilities. Depending on the model, a glove delivers up to 362 volts. The user guide recommends limiting each use to 15 seconds, warning that longer exposure can increase serious health risks, including changes in blood pressure and heart rhythm that might contribute to sudden death.