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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!](#)



A 33-year-old man with systemic lupus erythematosus presented with a 1-week history of pruritic, burning plaques. Examination showed pink, edematous plaques on the hands, elbows, knees, and feet. Laboratory testing showed elevated antinuclear and anti-double-stranded DNA antibody levels and low complement levels. Skin biopsy showed leukocytoclastic vasculitis. Treatment with oral and topical glucocorticoids was started. One week later, the lesions evolved into fixed, urticarial, annular, and targetoid plaques with rims of purpura on the thighs, chest, abdomen, and back. Which of the following is the most likely diagnosis?

Urticarial vasculitis is characterized by urticarial lesions that persist for more than 24 hours and histopathologic evidence of leukocytoclastic vasculitis. Lesions may be associated with burning, purpura, and residual hyperpigmentation. Urticarial vasculitis may occur in association with SLE, particularly when serum complement levels are low.

Chronic spontaneous urticaria

Erythema multiforme

Secondary syphilis

Subacute cutaneous lupus erythematosus

☒ Urticarial vasculitis

Die **Urtikaria-Vaskulitis** ist eine seltene, entzündliche Erkrankung der kleinen Blutgefäße in der Haut, die optisch an eine gewöhnliche Nesselsucht (Urtikaria) erinnert, aber eine echte Gefäßentzündung darstellt.

Symptome und Merkmale

Langanhaltende Quaddeln: Die Hautveränderungen oder Quaddeln bleiben im Gegensatz zur normalen Nesselsucht länger als 24 Stunden am selben Ort.

Brennen statt Juckreiz: Betroffene spüren oft eher Schmerzen oder ein Brennen als starken Juckreiz.

Verfärbungen: Nach dem Abklingen hinterlassen die Stellen häufig eine bräunliche Restpigmentierung (Hyperpigmentierung).

Zusatzzeichen: Manchmal kommen tiefe Schwellungen (Angioödeme) oder Gelenk- und Bauchschmerzen hinzu.



A 76-Year-Old Man with Dizziness and Altered Mental Status

A 76-year-old man was evaluated in the emergency department of this hospital because of dizziness and altered mental status.

On the day of the current evaluation, the patient was observed **crawling on a city sidewalk**. He appeared pale and diaphoretic. On evaluation by emergency medical services, he reported feeling **dizzy and “weird.”** A fingerstick blood glucose level was 152 mg per deciliter (8.4 mmol per liter). He was brought to the emergency department of this hospital for further evaluation.

In the emergency department, the patient could not recall recent events, but he reported shortness of breath, as well as chronic back pain and **persistent ringing in the ears**. He was unable to give additional details of his history, but he provided the name of the hospital where he routinely received care. On a phone consultation, physicians at that hospital reported that the patient had a **history of traumatic brain injury, post-traumatic stress disorder, seizure disorder, chronic back pain due to spinal stenosis, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, gastroesophageal reflux disease, and anxiety (10 diseases)**.

Prescribed medications included lisinopril and transdermal lidocaine. There were no known drug allergies. The patient had **consumed alcohol in the past** but not for 40 years. His family history was unknown.

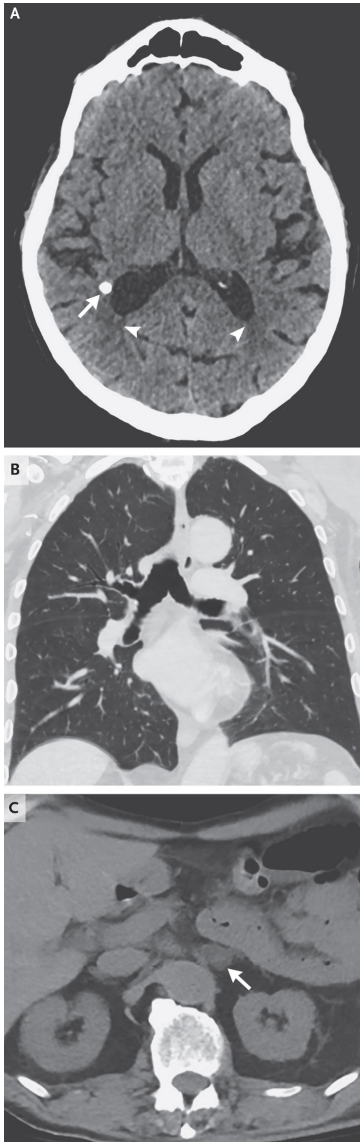
The temporal temperature was 36.6°C, the heart rate 92 beats per minute, the blood pressure **183/113 mm Hg**, the respiratory rate **27 breaths per minute**, and the oxygen saturation 99% while the patient was breathing ambient air. The patient appeared disheveled and diaphoretic. He was somnolent but awakened to verbal stimuli. He was oriented to person, place, and time but only intermittently followed commands. A small superficial skin abrasion was noted above the left eyebrow. There was mild tenderness on palpation of the midback but no other evidence of trauma. The remainder of the examination was normal.

Point-of-care ultrasonography, performed with an approach known as FAST (focused assessment with sonography for trauma), showed no abnormalities. The blood ethanol level was undetectable, and urine toxicologic testing was negative for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates. The blood levels of lipase, magnesium, and N-terminal pro-B-type natriuretic peptide were normal, as were results of liver-function tests. There was mild normocytic anemia, but the complete blood count with differential count was otherwise normal.

Variable	Reference Range, Adults†	On Presentation	16 Hr after Presentation	24 Hr after Presentation
Blood				
Sodium (mmol/liter)	135–145	140	145	143
Potassium (mmol/liter)	3.4–5.0	4.3	3.0	3.6
Chloride (mmol/liter)	98–108	106	111	111
Carbon dioxide (mmol/liter)	23–32	15	15	16
Urea nitrogen (mg/dl)	8–25	19	18	20
Creatinine (mg/dl)	0.60–1.50	1.57	1.32	1.42
Glucose (mg/dl)	70–110	142	74	74
Calcium (mg/dl)	8.5–10.5	7.8	7.3	7.7
Albumin (g/dl)	3.3–5.0	3.8	3.8	3.5
Lactate (mmol/liter)	0.5–2.0	2.1	1.1	—
High-sensitivity troponin T (ng/liter)	0–9	41	44	—
Hemoglobin (g/dl)	13.5–17.5	13.2	12.6	11.7
Hematocrit (%)	41.0–53.0	39.7	38.1	36.0
Prothrombin time (sec)	11.5–14.5	30.2	35.9	—
Prothrombin-time international normal- ized ratio	0.9–1.1	2.9	3.6	—
D-dimer (ng/ml)	<500	2075	—	—
Thyrotropin (μIU/ml)	0.40–5.00	—	0.25	—
Free thyroxine (ng/dl)	0.9–1.8	—	0.8	—
Triiodothyronine (ng/dl)	60–181	—	31	—
Iron (μg/dl)	30–160	—	40	—
Iron-binding capacity (μg/dl)	230–404	—	320	—
Ferritin (μg/liter)	10–200	—	39	—
Vitamin B ₁₂ (pg/ml)	>231	—	383	—

Variable	Reference Range, Adults†	On Presentation	16 Hr after Presentation	24 Hr after Presentation
25-Hydroxyvitamin D (ng/ml)	20–80	—	9	—
Arterial blood gas				
Fraction of inspired oxygen	—	—	—	0.21
pH	7.35–7.45	—	—	7.50
Partial pressure of carbon dioxide (mm Hg)	35–42	—	—	21
Partial pressure of oxygen (mm Hg)	80–100	—	—	68
Bicarbonate (mmol/liter)	24–30	—	—	16
Urine				
Color	Yellow	Yellow	—	—
Clarity	Clear	Clear	—	—
pH	5.0–9.0	6.0	—	—
Specific gravity	1.001–1.035	1.034	—	—
Glucose	Negative	Negative	—	—
Ketones	Negative	2+	—	—
Leukocyte esterase	Negative	Negative	—	—
Nitrite	Negative	Negative	—	—
Blood	Negative	1+	—	—
Protein	Negative	Negative	—	—
Erythrocytes (per high-power field)	0–2	10–20	—	—
Leukocytes (per high-power field)	<10	<10	—	—
Bacteria	None	None	—	—

Patient presents with a HCO₃ of 15 and an AG 19
ABGs done 24 h later.



Initial Imaging Studies.

An axial image from CT angiography of the head (Panel A), obtained before the administration of contrast material, shows nonspecific mild white-matter changes (arrowheads) and a nonspecific small right-peritrigonal calcification (arrow). A coronal image from CT angiography of the chest (Panel B), obtained after the administration of contrast material, shows **no pulmonary edema**, consolidation, or pneumothorax. An axial image from CT angiography of the abdomen (Panel C), obtained before the administration of contrast material, shows a left adrenal nodule (arrow) with an attenuation level of less than 10 Hounsfield units, a finding consistent with an **adenoma (incidentaloma)**.

Normal saline with 5% dextrose was administered intravenously. During the next 8 hours, the patient was agitated and combative. He repeatedly removed peripheral intravenous catheters and disconnected monitors. He was no longer oriented to place or time. Two doses of olanzapine were administered intravenously, and the patient slept for several hours during the night.

Sixteen hours after the patient arrived in the emergency department, the temporal temperature was 37.7°C, the heart rate 78 beats per minute, the blood pressure **160/72 mm Hg**, the respiratory rate **20 breaths per minute**, and the oxygen saturation 100% while he was breathing ambient air. The patient was observed to be breathing deeply. He was able to state his name, but his speech was otherwise nonsensical and dysarthric. He followed commands only when visual cues were given; for example, he stuck out his tongue after the examiner demonstrated the task. Motor, sensory, and reflex examinations were normal; tests of cerebellar function were not performed. The results of electroencephalography (EEG) were normal, without epileptiform abnormalities. Normal saline with potassium chloride was administered intravenously, as was lorazepam. Additional imaging studies were obtained.

The patient's mental status did not improve. Twenty-four hours after he arrived in the emergency department, he was admitted to the hospital with a working diagnosis of seizure. The temporal temperature was 37.6°C, the heart rate 77 beats per minute, the blood pressure 151/70 mm Hg, the respiratory rate 22 breaths per minute, and the oxygen saturation 98% while he was breathing ambient air. Respiratory effort appeared increased. He was somnolent, and he followed simple commands but did not open his eyes in response to sternal rub. The blood levels of creatine kinase, fibrinogen, and ammonia were normal.

What is the most likely diagnosis in this case?

Central hypothyroidism.

Herpes simplex virus encephalitis.

Hypertensive encephalopathy.

Salicylate toxicity.

Seizure disorder.

Wernicke's encephalopathy.

Differential Diagnosis

Intoxication or Withdrawal

The negative urine toxicologic testing makes intoxication from drugs that are commonly associated with substance use disorders unlikely. Although alcohol withdrawal could cause altered mental status, ethanol was not detected, and the patient reportedly had not consumed alcohol for 40 years.

Toxins and Medications

The history obtained from the patient, although limited, does not suggest potential exposure to poisons.

Central Nervous System Disorders

The absence of fever, headache, nuchal rigidity, and leukocytosis makes an infection involving the central nervous system unlikely. However, causes of viral encephalitis — such as herpes simplex virus, West Nile virus, eastern equine encephalitis virus, and Powassan virus — should be considered in this patient.

Metabolic Disorders

Both hyperthyroidism and hypothyroidism can cause altered mental status. Initial laboratory testing revealed a low thyrotropin level, as well as low free thyroxine and triiodothyronine levels.

Hypertensive Encephalopathy

This patient's initial blood pressure of **183/113 mm Hg** suggests the possibility of **hypertensive encephalopathy**.

Wernicke's Encephalopathy

Wernicke's encephalopathy is an important consideration in this patient with altered mental status. He reportedly did not drink alcohol, but he could still be at risk for Wernicke's encephalopathy in the context of malnutrition. Patients with Wernicke's encephalopathy can present with metabolic acidosis, respiratory alkalosis, and hyperventilation.

Hyperventilation and Respiratory Alkalosis

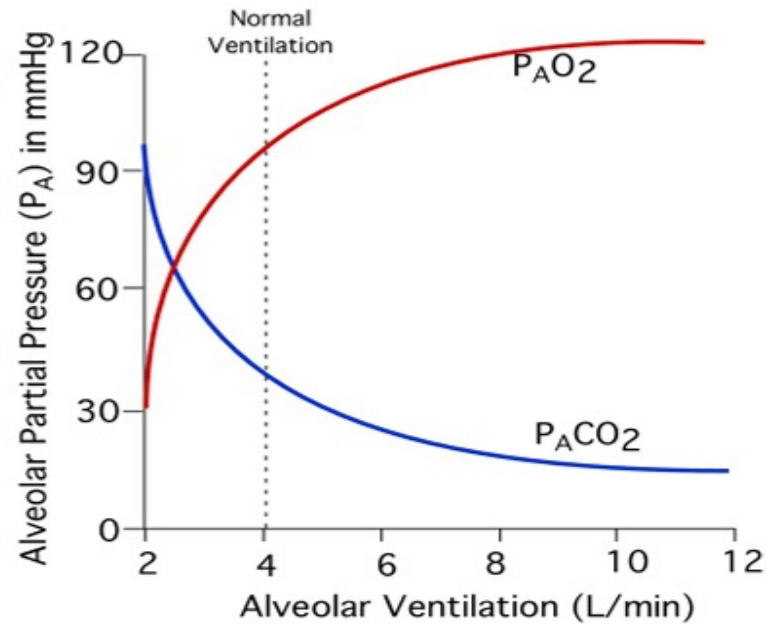
The patient initially reported dyspnea and was noted to have both deep breathing and increased work of breathing. In addition, arterial blood gas measurements were consistent with **respiratory alkalosis**, a finding that further supports the **possibility of hyperventilation**.

Anion-Gap Metabolic Acidosis

In addition to respiratory alkalosis, the patient had an **elevated anion gap** (19 mmol per liter), which indicates concurrent anion-gap metabolic acidosis. He had mild lactic acidosis and suspected malnutrition, with **2+ ketones in the urine**, but there was no evidence of diabetic ketoacidosis or severe renal failure. Anion-gap metabolic acidosis, in combination with hyperventilation with respiratory alkalosis and altered mental status, is suggestive of **salicylate toxicity**.

$$H = (24 \times PCO_2) / HCO_3$$

$$PAO_2 = 150 - PaCO_2 / 0.8$$



		24 Hr after Presentation	
		—	
Na	143	FiO ₂	0.21
K	3.6	pH	7.50
Cl	111	PCO ₂	21
HCO ₃	16	PO ₂	68
AL 16		HCO ₃	16

PAO₂ wäre 120 mm Hg,
Also die BGA ist venös

Respiratory Alkalose + AG metabolische Azidose

The diagnostic test in this case was measurement of the blood salicylate level. The patient had a salicylate level of 56 mg per deciliter (4.05 mmol per liter; reference value, <20 mg per deciliter [1.45 mmol per liter]), a finding that confirmed the diagnosis of salicylate toxicity.

Follow-up

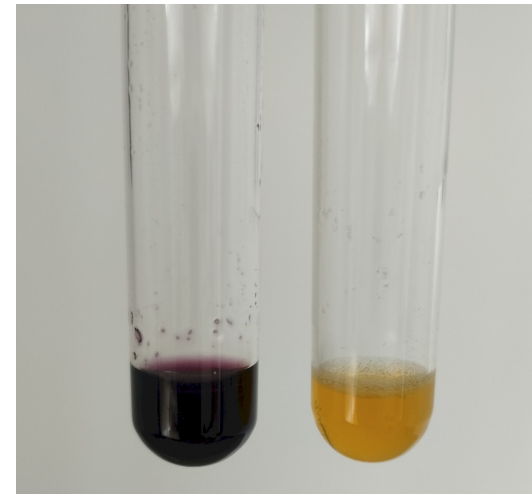
After salicylate toxicity was identified in this patient, **poison control was consulted**, and an infusion of **bicarbonate was initiated for urine alkalinization**. The nephrology service was consulted regarding possible hemodialysis if the patient's clinical condition worsened or the salicylate level increased. Serial measurement of the salicylate level was performed; the level was within the reference range in 26 hours. During the next 2 days, the patient's mental status improved, and he reported that **he had taken aspirin regularly for lower back pain and had recently increased his use** after losing access to prescribed opioids for back pain. He was discharged from the hospital with planned follow-up for adrenal and thyroid abnormalities, but 18 months later, he has had no further medical encounters in our health care system.

Final Diagnosis

Chronic salicylate toxicity. It took MGH 24 h to work up an AL 16 and a pH of 7.50.

Symptome einer ASS-Vergiftung: Die Beschwerden können zeitverzögert auftreten und steigern sich mit dem Schweregrad:

- **Leichte bis mittelschwere Vergiftung:**
 - **Ohrensausen (Tinnitus)** und geminderte Hörwahrnehmung
 - **Hyperventilation** (auffällig schnelle, tiefe Atmung)
 - Übelkeit, Erbrechen und Bauchschmerzen
 - Schwindel, Kopfschmerzen und starkes Schwitzen
- **Schwere Vergiftung:**
 - **Übersäuerung des Blutes** (metabolische Azidose)
 - Verwirrung, Ruhelosigkeit, Delirium oder Halluzinationen
 - Hohes Fieber (Hyperthermie)
 - Krampfanfälle, Bewusstlosigkeit und Koma
 - Organversagen (insbesondere Nierenversagen und Lungenödem)



Der **Nachweis von ASS (Acetylsalicylsäure) im Urin mittels Eisen(III)-chlorid** (engl. *Ferric Chloride Test*) ist ein klassischer, medizinischer Schnelltest. Er wird in der klinischen Chemie und Toxikologie genutzt, um eine **Salicylat-Ausscheidung (z. B. nach einer Aspirin-Überdosierung) qualitativ nachzuweisen**

An 80-Year-Old Woman with Pancytopenia

An 80-year-old woman was admitted to this hospital because of pancytopenia and the identification of **schistocytes on a peripheral-blood smear**.

Six weeks before admission to this hospital, nausea, vomiting, and diarrhea developed, along with chills and subjective fever. The symptoms resolved after 4 days without specific intervention, but then intermittent dysphagia with solid foods and early satiety developed. During the next 4 weeks, the patient had gradually progressive fatigue and light-headedness. The fatigue progressed to the point that she could no longer stay at work for more than a few hours; she presented to another hospital for evaluation.

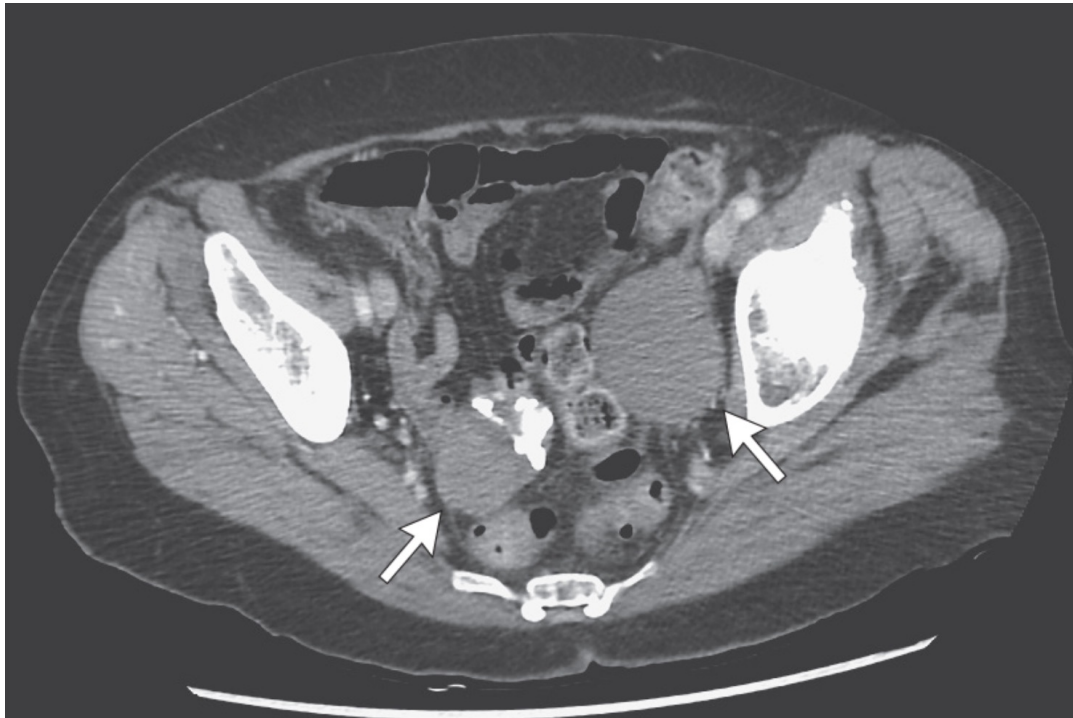
At the other hospital, the patient reported that she had ongoing **fatigue and had lost 6 kg of weight over a 5-week period**.

On examination, the temperature was 38.9°C, the weight 55.5 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 21.9. Laboratory studies revealed pancytopenia, and examination of a **peripheral-blood smear revealed schistocytes**. Blood levels of glucose and electrolytes were normal, as were the results of kidney-function and liver-function tests; other laboratory test results are shown. Imaging studies were obtained.

Variable	Reference Range, Adults, Other Hospital	4 Mo before Presentation, Other Hospital	On Presentation, Other Hospital	Day 7, Other Hospital	Day 8, Other Hospital	Reference Range, Adults, This Hospital*	On Presentation, This Hospital
Hematocrit (%)	37.0–47.0	33.7	24.8	24.8	24.3	36.0–46.0	24.8
Hemoglobin (g/dl)	12.0–16.0	10.2	8.2	7.8	7.8	12.0–16.0	7.5
White-cell count (per μ l)	4800–10,800	8100	2700	3300	3100	4500–11,000	2740
Differential count (%)							
Neutrophils	40–74	52	55	48	—	40–70	21
Lymphocytes	19–48	30	26	44	—	22–44	72
Monocytes	3–9	4	8	1	—	4–11	4
Eosinophils	0–7	2	0	0	—	0–8	1
Basophils	0–1	0	0	0	—	0–3	1
Bands	0–7	11	9	7	—	0–10	6
Platelet count (per μ l)	140,000–440,000	112,000	57,000	28,000	37,000	150,000–400,000	43,000
Mean corpuscular volume (fl)	79.0–97.0	—	79.7	85.2	85.0	80.0–100.0	87.3
Red-cell distribution width (%)	11.5–14.5	—	26	22.3	22.7	11.5–14.5	23.1
Reticulocyte count (%)	0.5–1.5	—	—	1.9	1.8	0.7–2.5	3.0
Prothrombin time (sec)	9.4–12.3	—	—	12.3	—	11.5–14.5	14.8
Prothrombin-time international normalized ratio	0.9–1.1	—	—	1.16	—	0.9–1.1	1.2
Activated partial-thromboplastin time (sec)	23.6–32.9	—	—	No clot formed	—	22.0–36.0	34.7
Fibrinogen (mg/dl)	186–458	—	—	371	—	150–400	232
D-dimer (ng/ml)	—	—	—	—	—	<500	1166
Haptoglobin (mg/dl)	30–200	—	246	280	202	30–200	113
Lactate dehydrogenase (U/liter)	84–246	—	497	453	342	110–210	326
Ferritin (μ g/liter)	8–252	—	—	1340	—	10–200	564
Bilirubin (mg/dl)†							
Total	0.2–1.0	—	1.1	1.7	1.3	0.0–1.0	0.7
Direct	0.0–0.2	—	—	0.9	0.6	0.0–0.4	0.2
Albumin (g/dl)	3.4–5.0	—	—	1.8	2.3	3.3–5.0	3.2

Red cells,
white cells,
platelets all
low

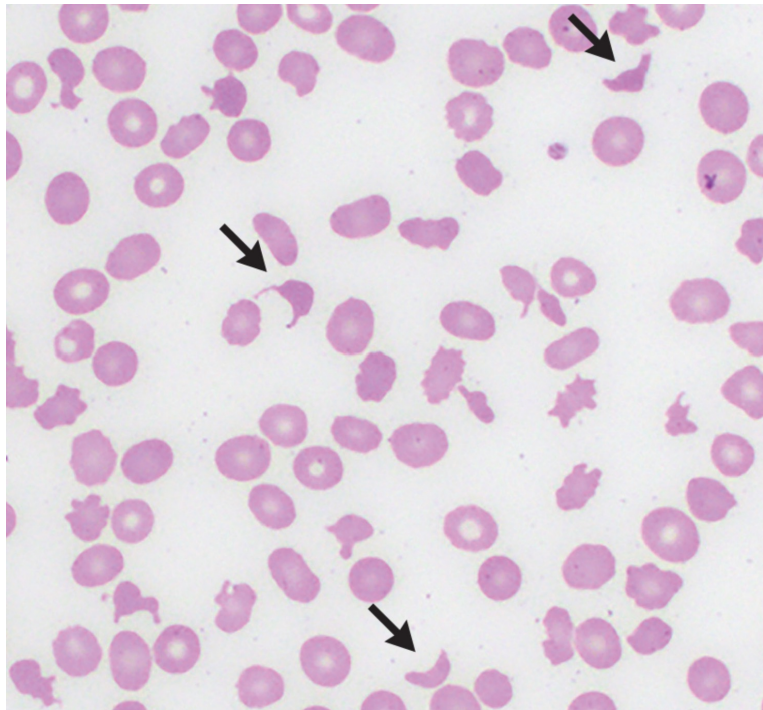
Low
reticulocytes
and normal
haptoglobin
normal ferritin



A chest radiograph was normal. Computed tomography (CT) of the abdomen and pelvis, performed after the administration of intravenous and oral contrast material, revealed a small hiatal hernia, multiple simple cysts in the right kidney, and indeterminate bilateral pelvic masses measuring 4.8 cm in diameter on the right side and 6.3 cm in diameter on the left side.

On hospital day 6, the oxygen saturation decreased to 89% while the patient was breathing ambient air and then increased to 94% when oxygen was delivered through a nasal cannula at a rate of 3 liters per minute. CT of the chest, performed after the administration of intravenous contrast material, revealed ground-glass opacities and interlobular septal thickening, findings consistent with pulmonary edema, along with bilateral pleural effusions of a small to moderate size. The administration of intravenous fluids was stopped, and one dose of intravenous furosemide was provided.

On hospital day 7, fever resolved but pancytopenia persisted. Examination of a peripheral-blood smear revealed a moderate amount of schistocytes, severe anisocytosis, large platelets, and an increased amount of bands without blasts. Direct and indirect Coombs' tests were negative, as were nucleic acid tests for babesiosis and anaplasmosis. Blood levels of electrolytes, glucose, cobalamin, folate, homocysteine, and anticardiolipin IgG and IgM were normal, as were the results of kidney-function and liver-function tests. The results of serologic tests for Epstein–Barr virus were consistent with previous infection. Flow cytometry of the peripheral blood showed phenotypically normal myeloid cells; there was an increased amount of atypical CD34+ myeloblasts, which accounted for less than 1% of leukocytes and were of unclear clinical significance.



Blood Specimen.

Wright's staining of a peripheral-blood smear shows anisopoikilocytosis with several schistocytes (arrows).

On evaluation in this hospital, the patient reported that her energy level had increased. She recalled that she had felt mildly confused at the other hospital, but the confusion had since resolved. She had had no gum bleeding or blood in the stool or urine. Other medical history included hypertension and dyslipidemia. **Surgical history included hysterectomy** at 40 years of age, with no vaginal bleeding since the procedure.

One year earlier, routine laboratory testing had revealed mild thrombocytopenia and anemia. **A bone marrow biopsy performed at that time** had revealed slightly hypercellular marrow with maturing trilineage hematopoiesis but with some erythroid abnormalities and occasional hyperchromatic megakaryocytes; cytogenetic analysis had shown a **loss of chromosomes 3 and 5 and a gain of chromosome 8 in 65% of the cells.**

On examination, the temperature was 36.8°C, the blood pressure 150/65 mm Hg, the pulse 72 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 97% while oxygen was administered through a nasal cannula at a rate of 2 liters per minute. The patient was alert and oriented, and she did not appear ill. There were no petechiae. There was no bleeding at the site of tunneled catheter placement in the right internal jugular vein. The first and second heart sounds were normal; a grade 2/6 systolic murmur was heard at the left lower sternal border. The remainder of the physical examination was normal.

The results of serum protein electrophoresis were normal. The levels of serum free kappa and lambda light chains were increased, with a normal ratio. Screening for human immunodeficiency virus infection was negative. Urinalysis showed 2+ urobilinogen, without bilirubin, blood, glucose, ketones, protein, or nitrates; the specific gravity and pH were normal. **Consultation was obtained from the gynecology service** regarding the bilateral pelvic masses noted on CT of the abdomen and pelvis. Blood levels of CA 125, CA 19-9, and carcinoembryonic antigen were normal, and **follow-up in the gynecology clinic was recommended for further evaluation after discharge.**

What is the most likely diagnosis in this case?

Anaplasmosis.

Myelodysplastic syndrome.

Myelophthisis.

Thrombotic
thrombocytopenic purpura.

Toxin exposure from
chemical cleaning agents.

Vitamin B₁₂ deficiency.

Differential Diagnosis

Thrombotic Thrombocytopenic Purpura

This patient was initially thought to have TTP, a thrombotic microangiopathy associated with a mortality as high as 90% if untreated. Patients with TTP present with severe thrombocytopenia, Coombs-negative **intravascular hemolytic anemia**, and end-organ dysfunction due to formation of platelet-rich thrombi in small vessels.

Pancytopenia

The differential diagnosis for pancytopenia is broad, and it can be helpful to break it down into categories.

Systemic Diseases

Systemic diseases that lead to increased circulating levels of inflammatory cytokines and hormones (e.g., interleukin-6, tumor necrosis factor α , and hepcidin) can cause bone marrow suppression.

Medications and Toxins

Exposure to a medication or toxin with myelosuppressive properties can lead to low blood counts.

Peripheral Destruction or Sequestration of Blood Cells

Peripheral destruction or sequestration of blood cells can lead to pancytopenia. However, **there is no clear laboratory evidence of red-cell destruction.**

Nutritional Disorders

Nutritional deficiencies can result in impaired production of blood cells. **Vitamin B₁₂ and folate** are required for DNA synthesis, and deficiency in these nutrients causes cells to arrest in the S phase (synthesis phase) of the cell cycle.

Myelophthisis

Myelophthisis is the **infiltration of bone marrow** by nonhematopoietic cells, which leads to the disruption of normal hematopoiesis or the development of bone marrow fibrosis.

Aplastic Anemia

Aplastic anemia is a general term that refers to an “empty bone marrow,” which can be caused by autoimmune diseases, toxins, infections, or inherited bone marrow failure syndromes. It is characterized by hypocellular bone marrow, with an absence of early myeloid forms. Although cytogenetic aberrations can be found with both congenital and acquired forms of aplastic anemia, only a few genes are typically affected, and the breadth of molecular mutations is less extensive than the **long list of driver mutations characteristic of myelodysplastic syndrome (MDS)**.

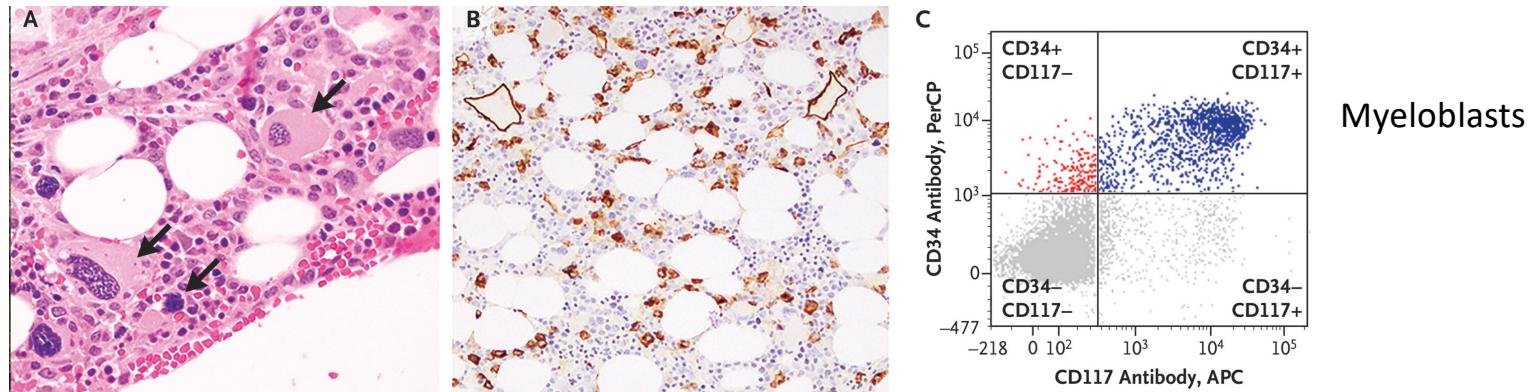
Do the results of this patient’s previous bone marrow biopsy, performed 1 year before this presentation, help in evaluating the possibility of aplastic anemia? The bone marrow was not hypocellular; in fact, it was **hyperplastic and had evidence of dysplasia and multiple cytogenetic abnormalities**.

Myelodysplastic Syndrome

MDS is a primary myeloid neoplasm characterized by peripheral-blood cytopenias, dysplasia of the bone marrow, clonal proliferation of hematopoietic stem cells, recurrent acquired molecular abnormalities, and a risk of transformation to acute leukemia. The importance of recurrent molecular driver mutations in the pathogenesis of MDS has become increasingly recognized. These clonal signatures are important for risk stratification, and they can also help to guide clinical care (e.g., predicting the response to targeted therapy). This patient's previous bone marrow biopsy, performed 1 year earlier, most likely provided evidence of MDS, and her current presentation probably reflects disease evolution manifested by worsening cytopenias. A bone marrow biopsy should be performed to definitively rule out progression of MDS or transformation to acute leukemia.

Schistocytes

Would a diagnosis of MDS explain the schistocytes that were identified on this patient's peripheral-blood smear? Schistocytes are typically associated with microangiopathic destruction, which is characteristic of TTP, complement-mediated hemolytic–uremic syndrome, and disseminated intravascular coagulation. However, the **finding of schistocytes on a peripheral-blood smear is not specific.**



Bone Marrow Specimens.

Hematoxylin and eosin staining of a core biopsy specimen of the bone marrow (Panel A) shows abnormal megakaryocytes, including small hypolobated forms as well as larger forms with hyperchromatic nuclei (arrows). CD34 immunostaining of the specimen (Panel B) shows an increased amount of **positive myeloblasts** in the bone marrow. A plot showing the results of flow cytometry of the bone marrow with respect to the **expression of CD34 and CD117** (Panel C) indicates an increased amount of **CD34+ CD117+ myeloblasts (in blue)**. Flow cytometry was performed with the antigen conjugates peridinin chlorophyll protein complex (PerCP) and allophycocyanin (APC). The overall morphologic, immunophenotypic, cytogenetic, and molecular findings are consistent with a **myeloid neoplasm** best classified as myelodysplastic syndrome with excess blasts 2 (MDS-EB2).

Discussion of Management

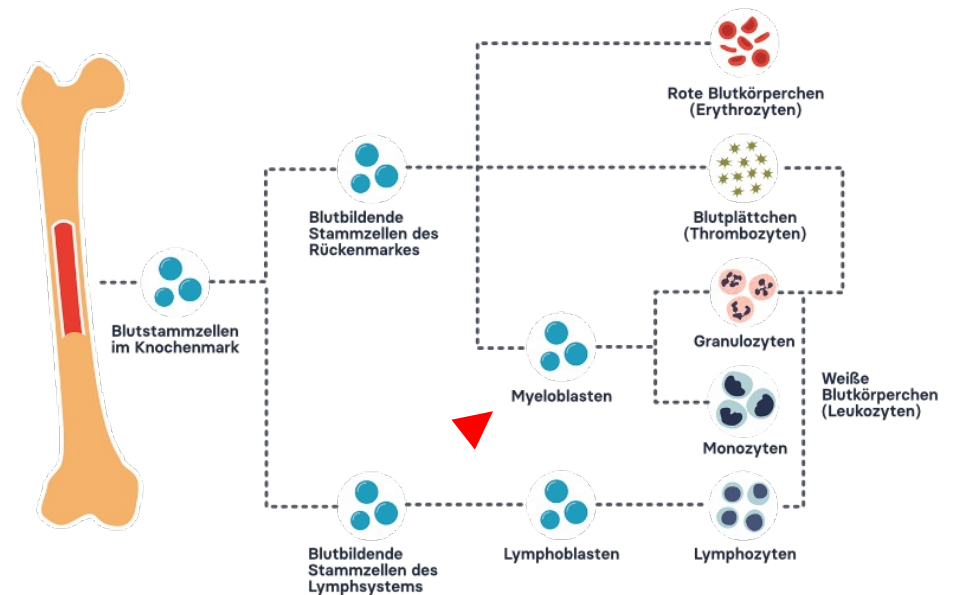
The patient was discharged from this hospital, and her care was resumed locally, at the hospital where she had presented initially. Her score on the Revised International Prognostic Score System (IPSS-R) was 7.5 (reference range, 0 to 4.0), which is considered high risk and is associated with a median overall survival of 0.8 years. Although no curative therapies could be offered, the patient elected to proceed with standard-of-care palliative therapy with **intravenous azacitidine, an inhibitor of DNA methylation**. After three cycles of therapy, the patient's blood counts improved, with resolution of neutropenia, and no blood transfusions were needed. A peripheral-blood smear continued to show a few schistocytes.

After 6 months of treatment, progressive pancytopenia developed, and blood transfusions were then provided. A repeat bone marrow biopsy revealed disease progression; the core biopsy specimen showed 15% blasts, an increase from the 10% blasts seen on the previous core biopsy specimen. Treatment with intravenous azacitidine was continued.

Das **Myelodysplastische Syndrom (MDS)** ist eine Erkrankung des blutbildenden Knochenmarks, bei der genetisch veränderte Stammzellen nicht mehr genügend gesunde und reife Blutzellen bilden können.

Krankheitsbild und Ursachen

- Bei MDS produzieren die Stammzellen im Knochenmark fehlerhafte, unreife Vorläuferzellen (Blasten).
- Es entsteht ein Mangel an reifen Blutzellen (Zytopenie) im Blut.
- Die Erkrankung tritt meist im höheren Lebensalter auf (der Altersgipfel liegt bei über 75 Jahren).
- In einigen Fällen kann MDS in eine akute myeloische Leukämie (AML) übergehen.



Beim Myelodysplastischen Syndrom (MDS) ist **SF3B1** die am häufigsten betroffene spezifische Genmutation, dicht gefolgt von Mutationen in den Genen **TET2** und **ASXL1**.

TET2 reguliert die epigenetische Genaktivität (DNA-Methylierung).

A 29-Month-Old Boy with Seizure and Hypocalcemia

A 29-month-old boy was transferred to this hospital because of a seizure and hypocalcemia. Approximately 2 months before the current evaluation, the patient had a febrile seizure. After the seizure, his mother reported that his “waddling” gait had become more pronounced. Two weeks before the current evaluation, the patient was seen in the orthopedic clinic at another hospital. On examination, the cover-up test — in which the distal lower leg is covered and the alignment of the proximal lower leg is compared with that of the upper leg — was negative, a finding consistent with physiologic bowing of the leg. There was a pes planus (flatfoot) deformity that resolved when the patient was not bearing weight on the foot, and there was an external (positive) foot progression angle with ambulation.

On the morning of the current evaluation, the patient’s mother noticed that the child was grunting while sleeping, with his eyes rolled upward and his arms stiffened and flexed. Emergency medical services were called. Vital signs, mental status, and findings on physical examination were reportedly normal. Laboratory evaluation was notable for a blood calcium level of 5.0 mg per deciliter (1.25 mmol per liter; reference range, 8.5 to 10.5 mg per deciliter [2.12 to 2.62 mmol per liter]). Intravenous calcium gluconate was administered. The patient was transferred to the emergency department of this hospital, arriving approximately 18 hours after a presumed seizure.

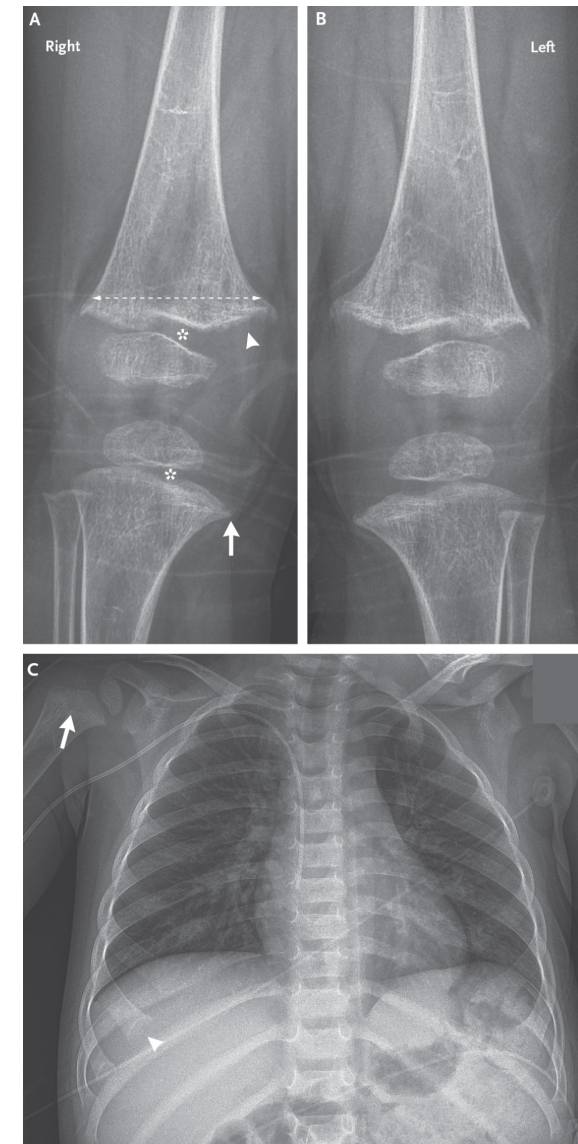
The patient had been delivered at full term and had reportedly met developmental milestones for his age. His medical history was notable for **atopic dermatitis**, which had been diagnosed when he was 9 weeks of age, as well as **multiple environmental and food allergies**. One year earlier, an allergist had revealed elevated levels on **IgE tests** specific to food allergens (milk, cashews, pistachios, egg whites, almonds, soybeans, chickpeas, green peas, lentils, peanuts, and sesame seeds) and environmental allergens (dogs, cats, and dust mites), although the patient later underwent food challenges to peanuts, legumes, almonds, and sesame seeds in an allergy clinic and had no symptoms. There were no known drug allergies. The patient had received diphenhydramine, hydroxyzine, epinephrine, and topical betamethasone as needed. **He had not received any routine childhood vaccinations because of his parents' refusal.**

Variable	Reference Range, Age-Adjusted [†]	On Admission, This Hospital
Blood		
Sodium (mmol/liter)	135–145	140
Potassium (mmol/liter)	3.4–5.0	4.1
Chloride (mmol/liter)	98–108	104
Carbon dioxide (mmol/liter)	23–32	20
Anion gap (mmol/liter)	3–17	16
Urea nitrogen (mg/dl)	5–20	17
Creatinine (mg/dl)	0.30–1.00	0.25
Glucose (mg/dl)	70–110	106
Calcium (mg/dl)	8.5–10.5	▶ 5.6
Ionized calcium (mmol/liter)	1.14–1.30	▶ 0.88
Magnesium (mg/dl)	1.7–2.4	1.9
Phosphorus (mg/dl)	4.5–5.5	4.3
Alkaline phosphatase (U/liter)	142–335	▶ 673
Parathyroid hormone (pg/ml)	10–60	▶ 177
Urine		
Creatinine (mg/dl)	Not defined	46
Calcium (mg/dl)	Not defined	▶ 19.7
Phosphate (mg/dl)	Not defined	47.8

The patient lived with his mother, father, two older siblings, and dog in New England. Although the **mother was a vegetarian**, she occasionally included chicken in the patient's "natural" and organic diet. The patient's mother had **obsessive-compulsive disorder** and anxiety, and his father had oral allergy syndrome and a history of varus knee deformity in childhood. The **patient's two siblings had atopic dermatitis, environmental allergies, and food allergies**. There was no family history of seizure.

Imaging Studies.

Anteroposterior radiographs of the knees obtained during the current admission (Panels A and B) show generalized demineralization. The metaphyses throughout both knees show flaring (dashed arrow) and **fraying and cupping** (arrowhead). There is beaking of the medial aspect of the proximal tibial metaphyses (arrow). The radiolucent **physees are widened** (asterisks). (Abnormalities are marked on the image of the right knee only.) An anteroposterior radiograph of the chest obtained during a previous admission (Panel C) shows subtle **flaring and cupping** of the right proximal humeral metaphysis (arrow) and mild flaring of the anterior ends of the ribs (arrowhead).



Radiographs of the knees showed several abnormalities that affected the knees symmetrically. The bones were diffusely radiolucent with thinned cortices; these features suggest **generalized demineralization**. No acute or healing fracture was detected. The **metaphyses** of the distal femur and the proximal tibia had a **widened, flared contour** bilaterally; in addition, the medial aspect of the **proximal tibial metaphysis** showed a **beaked (pointed) contour bilaterally**. The zone of provisional calcification — the area located between the metaphysis and the **radiolucent primary growth plate** (physis), where chondrocytes are responsible for longitudinal growth of long bones — **was frayed in appearance, with focal areas of cupping (concavity)**. The radiolucent physes were **abnormally widened** in the distal femur and the proximal tibia bilaterally.

What is the most likely diagnosis in this case?

Autoimmune polyglandular syndrome type 1.

Chronic kidney disease.

22q11.2 deletion syndrome (DiGeorge syndrome).

Pseudohypoparathyroidism.

Tumor lysis syndrome.

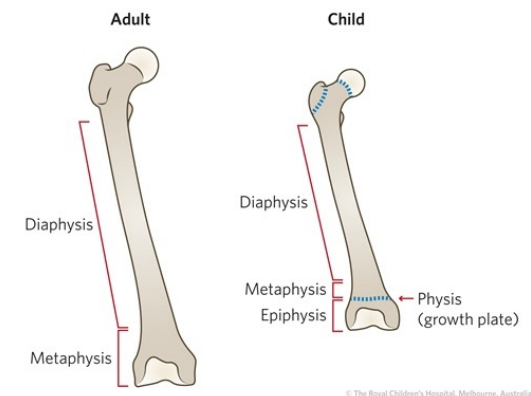
Vitamin D deficiency.

The **radiographic hallmarks of active childhood rickets** include a classic triad of metaphyseal changes—**fraying, cupping, and splaying**—alongside **widening of the growth plates (physes)** due to defective bone mineralization. These findings are most pronounced in rapidly growing areas, such as the **wrists, knees, and anterior rib ends**.

Because rickets results from a failure to mineralize newly formed osteoid and cartilage, the skeletal alterations can be categorized by the specific regions affected.

Physeal Widening: The growth plate (physis) becomes abnormally thick and elongated because unmineralized cartilage cells continue to pile up without transforming into bone.

Loss of the Zone of Provisional Calcification: The dense, sharp, white line normally seen at the junction between the growth plate and the metaphysis becomes indistinct, fuzzy, or completely disappears.



Differential Diagnosis

Hypocalcemia

The differential diagnosis of hypocalcemia can be divided into causes associated with elevated parathyroid hormone (PTH) levels and causes associated with depressed PTH levels. PTH secretion regulates the calcium level and is stimulated by a low blood calcium level. PTH acts on bones by triggering the release of calcium and phosphate and acts on the kidneys by triggering the resorption of calcium and excretion of phosphate. It also triggers renal production of 1,25-dihydroxyvitamin D, which increases intestinal calcium and phosphate absorption. As the blood calcium level rises, PTH production is suppressed. Thus, the appropriate homeostatic response to hypocalcemia is secondary hyperparathyroidism due to compensatory responses of the calcium–PTH–vitamin D axis.

Hypocalcemia and a Low PTH Level

Causes of hypocalcemia in the context of hypoparathyroidism can be divided into congenital and acquired causes. Congenital causes primarily include genetic disorders that result in abnormal PTH synthesis, such as **familial isolated hypoparathyroidism, 22q11.2 deletion syndrome (DiGeorge syndrome), or certain mitochondrial disorders.** In this patient, the **PTH level was elevated**, so these causes of hypocalcemia can be ruled out.

Hypocalcemia and a High PTH Level

Causes of hypocalcemia in the context of hyperparathyroidism can be divided into those associated with **PTH resistance**, those associated with calcium loss, and those associated with poor calcium intake or absorption.

Vitamin D Deficiency

Vitamin D deficiency can be divided into **genetic, prenatal or perinatal**, and childhood causes. Genetic disorders that alter the metabolism of vitamin D include **deficiencies in enzymes (25-hydroxylase or 1 α -hydroxylase)** and **defects in the vitamin D receptor**, which cause vitamin D resistance; however, these disorders seem unlikely, given their **absence in the family history**.

Diagnosis

Vitamin D deficiency due to poor nutrition associated with food allergies and avoidance.

Pathological Discussion

The **diagnostic test result in this case was the markedly low 25-hydroxyvitamin D level** of 4 ng per milliliter (10 nmol per liter; age-adjusted normal range, 20 to 80 ng per milliliter [50 to 200 nmol per liter]). Vitamin D deficiency can account for each laboratory abnormality summarized.

Diagnostic Testing.

Variable	Reference Range, Age-Adjusted†	On Admission	Hospital Day 7	Hospital Day 12
Calcium (mg/dl)	8.5–10.5	5.6↓	9.0	9.9
Ionized calcium (mmol/liter)	1.14–1.30	0.88↓	1.20	1.27
Phosphorus (mg/dl)	4.5–5.5	4.3↓	4.6	4.9
Alkaline phosphatase (U/liter)	142–335	673↑	566↑	429↑
Parathyroid hormone, intact (pg/ml)	10–60	177↑	135↑	94↑
25-Hydroxyvitamin D (ng/ml)	20–80	4↓	10↓	15↓
1,25-Dihydroxyvitamin D (pg/ml)	24–86	16↓	316↑	—

Treatment Doses of Vitamin D.

Age	Daily Treatment Dose, 90 Days	Single Treatment Dose	Daily Maintenance Dose
<i>international units</i>			
<3 mo	2000	NA	400
3 to 12 mo	2000	50,000	400
>12 mo to 12 yr	3000–6000	150,000	600
>12 yr	6000	300,000	600

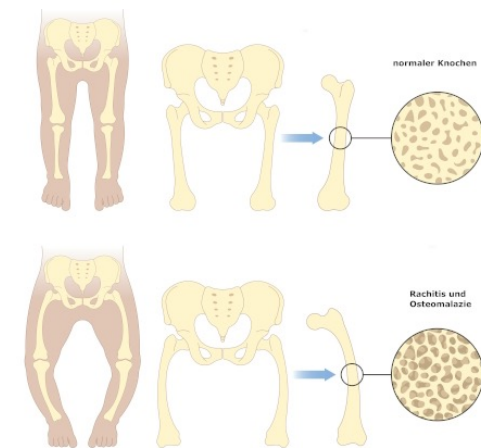
In a 2015 case-finding survey of Canadian pediatricians, risk factors for nutritional rickets included demographic characteristics (recent immigration), physiological features (skin melanin content, food allergies, feeding challenges associated with prematurity, developmental delay, and maternal vitamin D deficiency), and aspects of diet (lack of vitamin D supplementation and dietary restrictions) and behavior (lack of sun exposure). Of note, this patient had three of these risk factors (food allergies, lack of vitamin D supplementation, and dietary restrictions).

Follow-up

Intravenous calcium gluconate was administered until the ionized calcium level was more than 1 mmol per liter, and the patient also received oral calcium supplements. We had difficulty maintaining the ionized calcium level at more than 1 mmol per liter for sustained durations, so a **continuous calcium infusion** was administered for 7 days. For his underlying diagnosis of vitamin D deficiency, he was given **vitamin D** at a dose of 50,000 IU on day 1, followed by 1000 IU per day, as well as elemental calcium at a dose of 300 mg three times per day. The patient was ultimately discharged while receiving calcium carbonate and vitamin D. **At the time of discharge, the calcium level was 9.4 mg per deciliter (2.35 mmol per liter)**, the ionized calcium level 1.25 mmol per liter, the alkaline phosphatase level 429 U per liter, and the PTH level 94 pg per milliliter. At his most recent visit to the endocrine clinic, he was doing well and his laboratory values had normalized. At 3 years 11 months of age, his height was in the 19th percentile and his weight was in the 69th percentile. He had passing results on food challenges for several allergens that were performed in the office, **but his intake of milk, eggs, and multiple tree nuts continues to be restricted.**

Eine **chronische Hypokalziämie** (dauerhaft erniedrigter Kalziumspiegel im Blutserum unter **2,20 mmol/l**) entwickelt sich meist schleichend. Im Gegensatz zur akuten Form, die sich oft durch plötzliche Muskelkrämpfe (Tetanie) äußert, zeigt sich die chronische Variante durch vielfältige, oft unauffällige Langzeitsymptome und Organschäden. Eine chronische Unterversorgung resultiert meist aus Störungen der hormonellen Regulation (Parathormon und Vitamin D) oder Aufnahme Problemen:

- **Hypoparathyreoidismus:** Eine Unterfunktion der Nebenschilddrüsen – meist unabsichtlich nach Schilddrüsenoperationen entstanden –, wodurch zu wenig Parathormon (PTH) gebildet wird.
- **Chronischer Vitamin-D-Mangel:** Ohne ausreichend Vitamin D kann der Darm nicht genug Kalzium aus der Nahrung aufnehmen.
- **Chronische Niereninsuffizienz:** Die Nieren verlieren die Fähigkeit, Vitamin D in seine aktive Form umzuwandeln, und scheiden zudem vermehrt Kalzium aus.
- **Malabsorptionssyndrome:** Erkrankungen wie Zöliakie oder Morbus Crohn, die die Nährstoffaufnahme im Darm stören.
- **Chronischer Magnesiummangel:** Ein niedriger Magnesiumspiegel blockiert sowohl die Freisetzung als auch die Wirkung von Parathormon



Matrix ist da, wird aber nicht mineralisiert.

A 72-Year-Old Woman with Altered Mental Status and Acidemia

A 72-year-old woman was evaluated at this hospital because of altered mental status.

Five years before the current admission, the patient underwent transurethral resection of a 4-cm papillary transitional-cell carcinoma of the bladder (grade 3 of 3) that had invaded the muscularis propria. She received local radiation therapy, as well as chemotherapy with fluorouracil and mitomycin C. Cytologic examination of the urine performed 3 months before the current admission reportedly showed findings that were suggestive of urothelial cancer. Two weeks before the current admission, the patient had hematuria with clots, accompanied by dysuria and flank pain. She received a course of oral ciprofloxacin. Four days before the current admission, cystoscopy revealed evidence of mild radiation cystitis, blood clots, and a new 1.5-cm tumor on the left lateral bladder wall. Results of an analysis of a urine specimen obtained by catheterization are shown; cytologic examination revealed high-grade urothelial carcinoma. Bladder fulguration was scheduled.

On the second day after cystoscopy (2 days before the current admission), the patient noted an unintentional weight gain of 2.5 kg during the preceding 2 days. On the third day after cystoscopy, the patient's cardiologist recommended that she add a second daily dose of torsemide and spironolactone to her current regimen. Results of laboratory testing of blood obtained by a home health aide are shown.

Variable	Reference Range, Adults†	At Cystoscopy, 4 Days before Current Admission	2 Days before Current Admission	In Emergency Department	On Admission to ICU	Morning of Second Day in ICU	Afternoon of Second Day in ICU
Urine							
Color	Yellow	—	—	—	Brown	—	Yellow
Clarity	Clear	—	—	—	Turbid	—	Turbid
pH	5.0–9.0	5.0	—	—	5.0	—	5.0
Specific gravity	1.001–1.035	1.010	—	—	1.011	—	1.009
Glucose	Negative	Trace	—	—	3+	—	1+
Ketones	Negative	Negative	—	—	Negative	—	1+
Leukocyte esterase	Negative	Negative	—	—	2+	—	1+
Nitrite	Negative	Negative	—	—	Negative	—	Negative
Blood	Negative	3+	—	—	3+	—	3+
Protein	Negative	2+	—	—	1+	—	Negative
Red cells (per high-power field)	0–2	—	—	—	>100	—	>100
White cells (per high-power field)	<10	—	—	—	<10	—	10–20
Bacteria	None	—	—	—	1+	—	1+
Blood							
Hemoglobin (g/dl)	12.0–16.0	—	10.1	8.9	8.5	8.8	—
Hematocrit (%)	36.0–46.0	—	34.0	30.0	29.1	29.9	—
White-cell count (per μ l)	4500–11,000	—	9620	12,210	12,690	13,150	—
Platelet count (per μ l)	150,000–400,000	—	290,000	248,000	264,000	271,000	—
Sodium (mmol/liter)	135–145	—	137	136	139	139	143
Potassium (mmol/liter)	3.4–5.0	—	4.4	4.7	4.5	4.3	4.0
Chloride (mmol/liter)	98–108	—	90	92	96	94	94
Carbon dioxide (mmol/liter)	23–32	—	33	30	27	22	17
Urea nitrogen (mg/dl)	8–25	—	63	90	89	90	93
Creatinine (mg/dl)	0.60–1.50	—	1.81	3.16	3.18	3.10	3.17
Glucose (mg/dl)	70–110	—	214	203	184	177	230
Anion gap (mmol/liter)‡	3–17	—	14	14	16	23	32
Phosphorus (mg/dl)	2.6–4.5	—	—	—	7.5	7.4	—
Lactate (mmol/liter)	0.5–2.2	—	—	0.7	0.9	0.6	1.1
High-sensitivity troponin T (ng/liter)	0–9	—	—	117	122	—	—
N-terminal pro-B-type natriuretic peptide (pg/ml)	<900	—	—	8812	—	—	—
Venous blood pH	7.30–7.40	—	—	7.16	—	—	—
Serum osmolality (mOsm/kg)	280–296	—	—	—	—	—	349
Arterial blood gases							
Fraction of inspired oxygen	—	—	—	—	0.40	0.40	0.40
pH	7.35–7.45	—	—	—	7.19	7.18	7.17
Partial pressure of carbon dioxide (mm Hg)	35–42	—	—	—	87	74	68
Partial pressure of oxygen (mm Hg)	80–100	—	—	—	81	89	84

CPAP patient
Chronic
respiratory
acidosis,
compensated.

Baseline HCO_3^- 33

Chronic PaCO_2
(probably) >55

Na 143, K 4.0,
Cl 94, HCO_3^- 17

AL 32

pH 7.17
 PaCO_2 68

$\text{H} = (24 \times 68) / 17$
 $= 96$

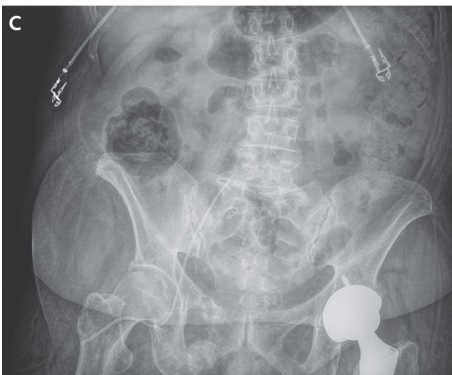
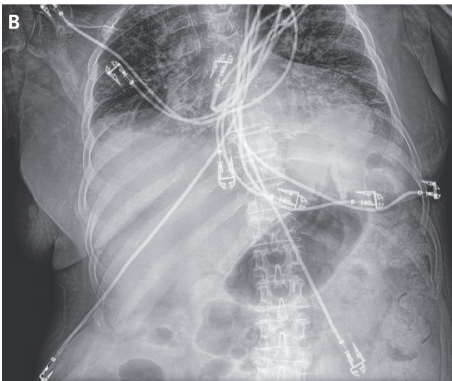
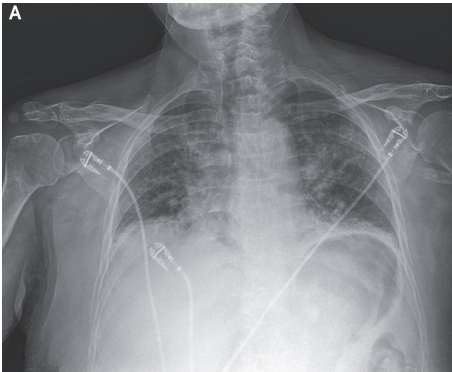
The patient's medical history included asthma and recurrent bronchitis, restrictive lung disease, obstructive sleep apnea, precapillary and postcapillary pulmonary hypertension with right ventricular dysfunction, heart failure with preserved ejection fraction, coronary artery disease, right bundle-branch block, stage 3a chronic kidney disease (baseline creatinine level, 1.3 mg per deciliter [115 mmol per liter]; reference range, 0.6 to 1.5 mg per deciliter [53 to 133 mmol per liter]), hyperlipidemia, hypertension, type 2 diabetes mellitus, gout, gastroesophageal reflux disease, appendectomy, iron-deficiency anemia, osteoarthritis resulting in right total hip replacement and knee arthroscopy, osteoporosis with lumbar compression and previous hip fracture, fibromyalgia, depression, and anxiety (>15 diseases). Medications included oral aspirin, armodafinil, allopurinol, colchicine, dapagliflozin, metformin, melatonin, metoprolol, montelukast, extended-release morphine sulfate, pantoprazole, pravastatin, sertraline, spironolactone, torsemide, and as-needed lorazepam and immediate-release morphine sulfate. The patient also received inhaled fluticasone–salmeterol and mometasone, as-needed supplemental oxygen, and albuterol and ipratropium nebulizers as needed (>20 meds). Cefuroxime, celecoxib, and oxycodone had caused urticaria.

On examination, the patient appeared frail and somnolent and was in mild respiratory distress. The temporal temperature was 36.3°C, the heart rate 73 beats per minute, the blood pressure 102/54 mm Hg, the respiratory rate 25 breaths per minute, and the oxygen saturation 96% while she was receiving supplemental oxygen through a nasal cannula at a rate of 4 liters per minute. The weight was 76.0 kg (as compared with 72.3 kg measured 3 weeks earlier); the height was 152 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 32.9. During the interview, she required frequent redirection, offered brief answers, and followed simple commands. Strength in the arms and legs was symmetric. The lung sounds were diminished in the anterior lung fields, with decreased respiratory efforts and bibasilar crackles. On auscultation, a grade 2/6 systolic murmur was present at the base. There was mild, diffuse abdominal tenderness and 2+ edema in both legs, with mildly diminished pulses that were symmetric. The remainder of the examination was normal. The patient received intravenous vancomycin, ceftriaxone, and metronidazole. Bilevel positive airway pressure was initiated. Norepinephrine and bumetanide were administered intravenously.

Four hours after the patient arrived in the emergency department, she was admitted to the intensive care unit (ICU). The temporal temperature was 36.7°C, the heart rate 69 beats per minute, the blood pressure 91/55 mm Hg while she was receiving intravenous norepinephrine, the respiratory rate 20 breaths per minute, and the oxygen saturation 93% while she was receiving bilevel positive airway pressure (inspiratory pressure, 12 cm of water; positive end-expiratory pressure, 5 cm of water; fraction of inspired oxygen, 0.40).

Blood levels of acetaminophen, ethanol, and salicylates were undetectable, and urine toxicology screening was negative. Other laboratory test results are shown. A radial arterial catheter and a femoral central venous catheter were placed; measurements of central venous pressure ranged from 8 to 12 cm of water. Bedside cardiac ultrasonography reportedly showed that the left ventricular cavity was small but was functioning normally and that the right ventricle was dilated and hypokinetic.

In the morning of the second day in the ICU, the patient was somnolent. The norepinephrine dose was increased from 5 µg per minute to 14 µg per minute, and vasopressin was started. Overnight, the urine output was recorded at approximately 100 to 150 ml per kilogram per hour, with a net fluid balance of -373 ml from the previous day. Intravenous chlorothiazide and calcium gluconate were administered. The glycated hemoglobin level was 7.5% (reference range, 4.3 to 5.6); the levels of thyrotropin, cortisol, aspartate aminotransferase, and alanine aminotransferase were normal. (Patient developed metabolic acidosis with AL 32 while in the ICU.)



Abdominal and pelvic radiographs showed nondilated bowel loops, a partially healed fracture of the right pubic ramus, and evidence of previous left total hip arthroplasty. In the afternoon of the second day in the ICU, the patient reported diffuse myalgias, and intravenous bumetanide was changed to intravenous furosemide. Over the course of the first 12 hours of the second day, the urine output was 1895 ml, with a total fluid balance of -884 ml. Diagnostic and management decisions were made.

What is the most likely diagnosis in this case?

Chronic acetaminophen use causing elevated level of 5-oxoproline.

Ethylene glycol ingestion.

Euglycemic diabetic ketoacidosis.

Salicylate toxicity.

Type A lactic acidosis.

Type B lactic acidosis.

Differential Diagnosis

This 72-year-old woman with bladder cancer, right heart failure, stage 3a chronic kidney disease, and type 2 diabetes mellitus who had been taking metformin and dapagliflozin presented with altered mental status and a possible urinary tract infection. She was in shock, for which she received vasopressors, and had evidence of organ dysfunction, including delirium, acute-on-chronic kidney failure, hypercapnic and hypoxemic respiratory failure, heart failure, and persistent acidemia. The possible causes of her shock include sepsis (possible urinary tract infection), cardiac dysfunction (peripheral and pulmonary edema), and intravascular hypovolemia (fasting perioperative state, probable reduced oral intake since surgery, and increased doses of diuretics).

The anion gap increased from 14 mmol per liter (reference range, 3 to 17) to 32 mmol per liter — a change of 18 mmol per liter. This increase exceeds the decrease in the bicarbonate level from 30 mmol per liter to 17 mmol per liter (reference range, 23 to 32) — a change of 13 mmol per liter — and most likely indicates renal compensation for the respiratory acidosis. **The patient had high anion-gap metabolic acidosis**, but no apparent non-anion-gap metabolic acidosis was present. In formulating a differential diagnosis, the patient's case centers around the root cause of the key feature — high anion-gap metabolic acidosis.

Approximately 35% of the anion gap is now recognized to originate from Krebs cycle intermediates, which are involved in amino acid, glucose, and triglyceride metabolism. The acronym GOLD MARK provides a useful framework for developing a differential diagnosis for high anion-gap metabolic acidosis in this patient.

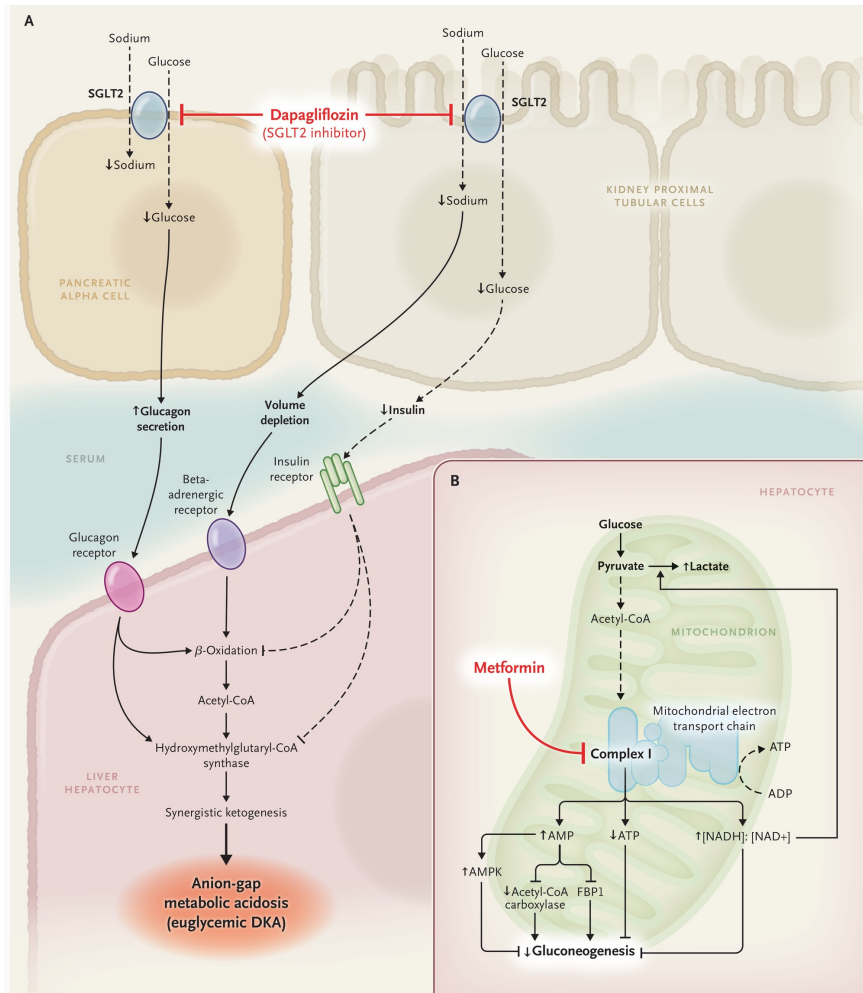
Cause	Description	Considerations in This Patient	Recommendations in This Patient
G: Glycols	Ethylene glycol and propylene glycol toxicity, typically arising from ingestions	No known ingestion history, and a higher osmolar gap would be expected	Consider measuring blood glycol level
O: 5-Oxoproline	Increased blood level in some patients who use acetaminophen on a long-term basis, typically in the context of renal insufficiency and undernourishment	No report of acetaminophen use, and acetaminophen level undetectable	Consider measuring blood 5-oxoproline level
L: L-Lactate	Elevated level resulting from either type A lactic acidosis (due to reduced tissue oxygenation) or type B lactic acidosis (due to underlying metabolic conditions in the absence of inadequate tissue oxygenation; can be associated with metformin use)	Shock present (associated with type A lactic acidosis), and metformin use reported (associated with type B lactic acidosis), but lactate level not elevated	Monitor blood lactate level; consider measuring metformin level and temporarily discontinuing metformin use
D: D-Lactate	Isomer of L-lactate; elevated level (which can cause D-lactic acidosis) arising in association with short-bowel syndrome, with metabolism of propylene glycol, and occasionally in association with diabetic ketoacidosis	Unlikely	—
M: Methanol	Methanol toxicity	No known ingestion history, and a higher osmolar gap would be expected	Consider measuring blood methanol level
A: Aspirin	Salicylate toxicity	Aspirin use reported, but salicylate not detected on toxicology testing	Temporarily discontinue aspirin use
R: Renal failure	Accumulation of organic acids and ammonium due to impaired urinary acidification	Patient's high anion-gap metabolic acidosis too high to be explained by renal insufficiency alone	Continue to monitor and treat acute-on-chronic kidney failure
 K: Ketoacidosis	Accumulation of ketones due to diabetes, starvation, or alcohol use	Euglycemic diabetic ketoacidosis strongly suspected	Evaluate and treat for euglycemic diabetic ketoacidosis; temporarily discontinue use of sodium-glucose cotransporter 2 inhibitor

Ketoacidosis

This patient most likely has ketoacidosis, which could be due to either diabetes or starvation. Ketoacidosis involves a decrease in intracellular glucose, which leads to a **shift in metabolism toward the production of fatty acids**, including the ketones acetoacetate and β -hydroxybutyrate, as vital organ fuel. The use of **sodium–glucose cotransporter 2 (SGLT2) inhibitors in persons with diabetes can trigger euglycemic diabetic ketoacidosis** in the context of certain stressors such as infection or surgical procedures, which this patient had. SGLT2 inhibitors reduce glucose reabsorption in the proximal tubules of the kidneys, which results in a reduction in the blood glucose level; this reduction in the glucose level leads to decreases in insulin response and intracellular glucose levels, thus propagating euglycemic diabetic ketoacidosis. These medications also enhance glycosuria, which contributes to dehydration. Several features of this patient's presentation support the **diagnosis of dapagliflozin-induced euglycemic diabetic ketoacidosis**. The presence of 3+ glucose on urinalysis, despite a normal blood glucose level, fits with SGLT2 inhibitor–associated glycosuria. Urinary glucose can be used by some bacteria as a nutrient, which confers a risk of infection. In addition, the pharmacologic effects of dapagliflozin last 2 to 3 days (even as long as 9 days) after discontinuation, given its **half-life of 12.9 hours**, which contributes to the persistence of euglycemic diabetic ketoacidosis, even after the medication is stopped.

Effects of Dapagliflozin and Metformin on Cellular Metabolism.

As shown in Panel A, inhibition of SLC5A2, also known as sodium–glucose cotransporter 2 (SGLT2), by dapagliflozin in the proximal tubules of the kidneys induces glucosuria and reductions in the blood glucose level and sodium delivery. SGLT2 inhibitors also directly increase glucagon secretion by pancreatic alpha cells. This dual effect leads to a higher blood glucagon level, a lower insulin level, and volume depletion due to diuresis. During periods of organismal stress, these hormonal effects induce a synergistic suppression of hepatic glucose use. Instead, they promote ketogenesis through the increase in lipid β -oxidation and ketogenic enzyme hydroxymethylglutaryl-CoA synthase. Unchecked ketogenesis induces metabolic acidosis through accumulation of acetoacetate and β -hydroxybutyrate without the presence of marked hyperglycemia, a condition known as “euglycemic diabetic ketoacidosis (DKA).” As shown in Panel B, one of the actions of metformin is to inhibit complex I of the mitochondrial electron transport chain, which induces elevations in the cellular ratio of NADH to NAD⁺ and reduces pyruvate use in the citric acid cycle. This, in turn, leads to a higher rate of conversion of pyruvate to lactate by lactate dehydrogenase, which, if uncontrolled, induces lactic acidosis. AMPK denotes AMP-activated protein kinase, CoA coenzyme A, and FBP1 fructose-1,6-bisphosphatase 1.



Diagnostic Testing

The diagnostic test in this case was measurement of the **blood β -hydroxybutyrate level**, which was **9.1 mmol per liter** (reference value, <0.4). β -Hydroxybutyrate is quantitated by an enzymatic method with the use of β -hydroxybutyrate dehydrogenase on an automated chemistry analyzer. In contrast, the urine dipstick test for ketones is semiquantitative; it involves a test strip on which sodium nitroprusside reacts with acetoacetate to form a purple complex. The analytical sensitivity for acetoacetate is 5 mg per deciliter (0.5 mmol per liter). The test strip does not react with β -hydroxybutyrate, but its reactivity with acetone is approximately 10% of that with acetoacetate. Ketogenesis involves the reduction of acetoacetate to β -hydroxybutyrate by β -hydroxybutyrate dehydrogenase with the use of NADH cofactor; alternatively, acetoacetate can undergo spontaneous decarboxylation to acetone, a minor ketone component. **The ratio of β -hydroxybutyrate to acetoacetate**, the two primary ketone bodies in circulation, is dependent on the redox potential (**i.e., the ratio of the reduced form of NADH to the oxidized form of NADH**) in hepatocellular mitochondria.

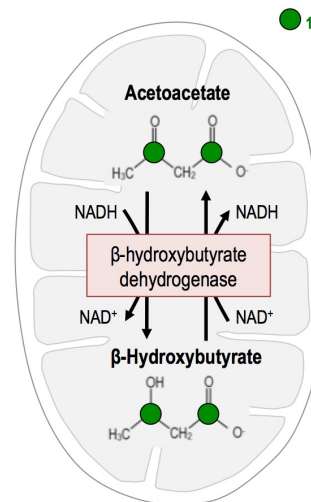
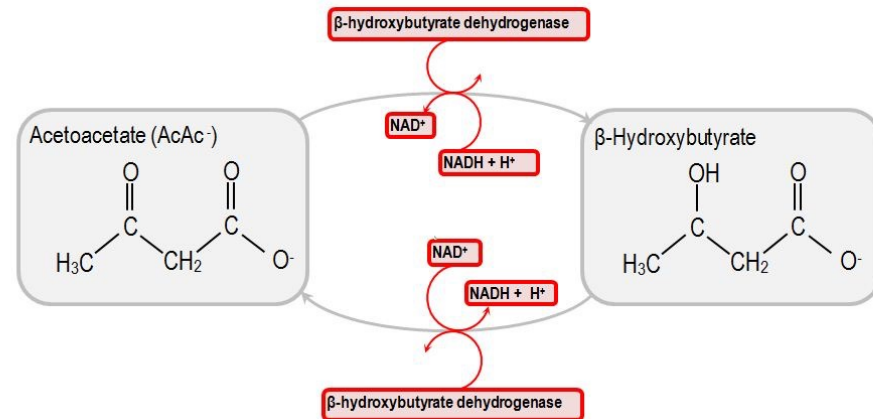
Follow-up

In the 9 hours after intravenous insulin therapy was started, the anion gap decreased by more than half, and the arterial pH and bicarbonate levels normalized. Renal function returned to baseline levels. Treatment with metformin and the SGLT2 inhibitor was discontinued indefinitely, and repaglinide was started. Eight weeks later, the patient underwent transurethral resection of the bladder tumor, which was uneventful.

Das Verhältnis von **Beta-Hydroxybutyrat (β -HB)** zu **Acetoacetat (AcAc)** ist ein zentraler medizinischer Indikator, der den **metabolischen Status und den mitochondrialen Redox-Zustand (NADH/NAD^+ -Verhältnis)** in den Zellen widerspiegelt. Im gesunden Zustand liegt das normale Verhältnis im Blut bei etwa **1:1 bis 3:1** zugunsten von Beta-Hydroxybutyrat.

Die biochemische Reaktion: Das Enzym *Beta-Hydroxybutyrat-Dehydrogenase* wandelt Acetoacetat unter Verbrauch von NADH in Beta-Hydroxybutyrat um.

Der Redox-Marker: Da diese Reaktion reversibel und direkt an das mitochondriale NADH/NAD^+ -Verhältnis gekoppelt ist, zeigt eine Verschiebung des Ketonkörper-Verhältnisses an, wie viel "Reduktionsäquivalente" (Energie) in den Mitochondrien vorhanden sind.



Bei einer ausgeprägten **Ketoazidose verschiebt sich das Verhältnis** zwischen Beta-Hydroxybutyrat (β -HB) und Acetoacetat (AcAc) massiv **zugunsten von Beta-Hydroxybutyrat**.

Während das physiologische Normalverhältnis im Blut etwa bei **1:1 bis 2:1** liegt, kann es sich bei einer diabetischen oder alkoholischen Ketoazidose auf Werte von **3:1 bis hin zu 10:1** erhöhen.

A 22-Year-Old Man with Pain and Erythema of the Left Hand

A 22-year-old man was admitted to this hospital because of **pain and rapidly spreading erythema of the left hand**. The patient had been well until the day of admission, when he awoke with pain and swelling of the left hand that involved the distal interphalangeal joint of the second finger and the proximal interphalangeal joint of the fourth finger. Over a period of several hours, the pain progressed and bullae began to form. He began to have **pain with movement of the second and fourth fingers, and the bullae turned dark purple**; these changes prompted the patient to present to the emergency department of this hospital. In the emergency department, the patient reported pain of the left hand that worsened with movement of the second and fourth fingers. There was no lethargy, fatigue, headache, dyspnea, cough, or pain elsewhere. The patient had no notable medical history and **had been well before the day of presentation**.

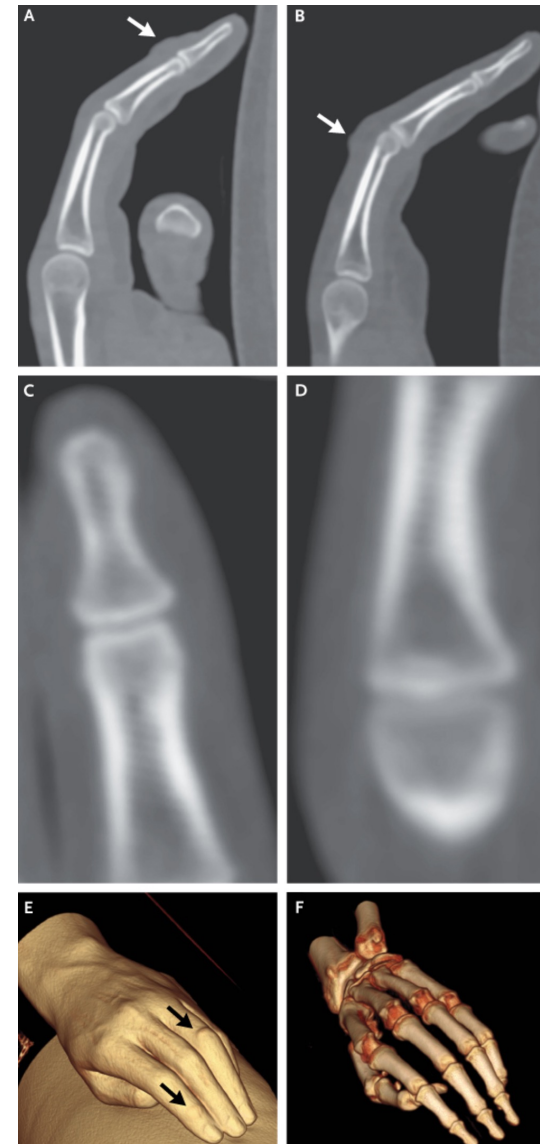


On examination, the patient appeared well. The temperature was 38.6°C, the blood pressure 126/63 mm Hg, the heart rate 101 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. There were two violaceous, tender bullae on the dorsal aspect of the left hand — one on the distal interphalangeal joint of the second finger and one on the proximal interphalangeal joint of the fourth finger, each measuring 7 mm by 3 mm. In addition, there was nontender, streaking erythema spreading across the dorsal aspect of the left hand, the volar aspect of the left forearm, and the medial aspect of the left upper arm into the axilla. There was no axillary lymphadenopathy.

On further examination of the left arm, the **soft-tissue compartments were soft and compressible**, without evidence of crepitus. Finger flexion and extension were intact but limited by pain and swelling in the second and fourth fingers. Results of motor and sensory examinations were normal. The hand was warm. The radial pulse was palpable, and the capillary refill was brisk. The remainder of the overall physical examination was unremarkable. **A blood specimen was obtained for culture**, a complete blood count, and a metabolic panel. Initial laboratory test results are shown.

Variable	Reference Range, Adults†	On Presentation
Hemoglobin (g/dl)	12.0–16.0	14.8
Hematocrit (%)	41.0–53.0	45.5
White-cell count (per μ l)	4500–11,000	10,520
Differential count (per μ l)		
Neutrophils	1800–7700	8650
Immature granulocytes	0–100	30
Lymphocytes	1000–4800	990
Eosinophils	0–900	30
Basophils	0–300	30
Monocytes	200–1200	790
Platelet count (per μ l)	150,000–450,000	254,000
Sodium (mmol/liter)	135–145	139
Potassium (mmol/liter)	3.4–5.0	3.7
Chloride (mmol/liter)	98–108	102
Carbon dioxide (mmol/liter)	23–32	23
Creatinine (mg/dl)	0.60–1.50	0.97
Urea nitrogen (mg/dl)	8–25	19
Aspartate aminotransferase (U/liter)	9–32	8
Alanine aminotransferase (U/liter)	7–33	12
Alkaline phosphatase (U/liter)	30–100	40
Total bilirubin (mg/dl)	0.0–1.0	0.5
International normalized ratio	0.9–1.1	1.2
Prothrombin time (sec)	11.5–14.5	15.0
Partial-thromboplastin time (sec)	22.0–36.0	31.3
C-reactive protein (mg/liter)	<8.0	4.1
Erythrocyte sedimentation rate (mm/hr)	0–13	2
Lactic acid (mmol/liter)	0.5–2.0	1.2

Computed tomography (CT) of the left hand and arm, performed after the administration of intravenous contrast material, revealed focal soft-tissue swelling overlying the distal interphalangeal joint of the second finger and the proximal interphalangeal joint of the fourth finger on the dorsal aspect of the left hand. There was no evidence of osseous erosion, periosteal reaction, fracture, joint effusion, fluid collection, or subcutaneous air. The left forearm had a normal appearance on imaging. While the patient was in the emergency department, additional history was obtained. The patient was not taking any medications and had no known allergies to medications. He had recently graduated from college and was seeking employment. He lived with his parents in a suburban area of New England. There was no history of recent travel or sick contacts. He rarely drank alcohol and did not smoke cigarettes or use illicit drugs. There was no notable family history.



The patient had recently begun practicing taxidermy (Präparatoren) as a new hobby. Four days before presentation, he received a frozen deer hide from a friend, which he began to prepare for tanning. When he first received the deer hide, he scraped the skin and fur to remove numerous ticks. On the day before presentation, he kneaded the hide with his hands and massaged into it a mixture of deer brain and tap water that had been prepared the day before and left to stand overnight. While the patient was working with the animal hide, he did not wear protective clothing or gloves. His mother had assisted in part of the process but remained well. Intravenous fluid, ceftriaxone, and vancomycin were administered, and the patient was admitted to the hospital. Consultants from the orthopedic hand service, dermatology, and infectious diseases evaluated the patient.

What is the most likely diagnosis in this case?

Cellulitis due to infection with *Streptococcus pyogenes*.

Contagious ecthyma due to infection with orf virus.

Cutaneous anthrax due to infection with *Bacillus anthracis*.

Erysipeloid due to infection with *Erysipelothrix rhusiopathiae*.

Plague due to infection with *Yersinia pestis*.

Ulceroglandular tularemia due to infection with *Francisella tularensis*.

Differential Diagnosis

Skin and Soft-Tissue Infections

Beta-hemolytic streptococcus, especially group A streptococcus (*Streptococcus pyogenes*), is the most common cause of cellulitis, and blistering and lymphangitis may occur. *Staphylococcus aureus* can cause cellulitis, but a purulent infection of the skin and soft tissue usually develops.

Plague

Could this patient have an infection with *Yersinia pestis*, known as the plague? This infection has multiple possible routes of transmission, including handling of infected animal tissue.

Transmission by this route can result in bubonic or septicemic plague.

Brucellosis

Brucellosis can be caused by multiple species of brucella. *Brucella abortus* is well described in deer, posing a risk of infection in hunters. Brucellosis can develop after skin contact with infected animal tissue. The usual incubation period is 2 to 4 weeks, but it is possible for the disease to manifest in 5 days.

Tularemia

Tularemia is caused by the bacterium *Francisella tularensis*. Like the plague, tularemia has multiple possible routes of transmission, including contact with infected animal tissue. *F. tularensis* has been described in deer, but infection in humans is usually associated with contact with other animals.

Orf

Orf, also known as contagious ecthyma, should be considered in this patient. The **orf virus** is in the parapoxvirus genus. Humans are infected after contact with animals directly or with contaminated equipment. Although most cases result from contact with sheep or goats, the virus has been **found in deer**, and transmission to a human from a deer carcass has been described.

Anthrax

A diagnosis of cutaneous anthrax, which is caused by *Bacillus anthracis*, fits with several features of this case, particularly the deer-hide exposure.⁷ Of the several types of anthrax, cutaneous anthrax is the most common and least lethal. Infection usually results from handling of infected animal products. **A hallmark of cutaneous anthrax is that it is painless; this patient had marked and progressive pain. Thus, we should continue to look for a diagnosis that is consistent with all the features of this case.**

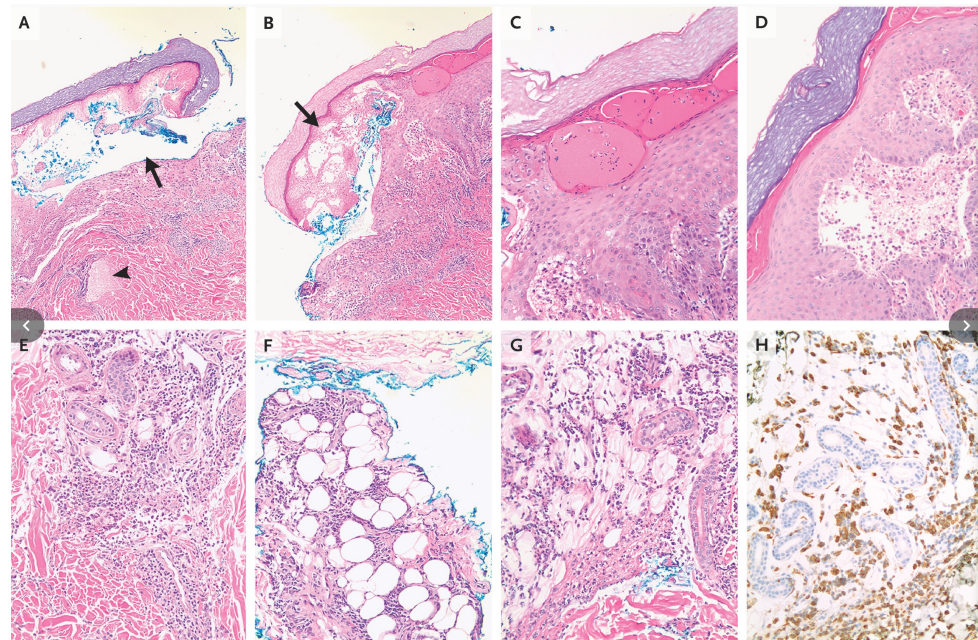
Erysipelothrix rhusiopathiae Infection

Erysipelothrix rhusiopathiae can infect humans after animal exposure. When the infection occurs in humans, the most common presentation is a localized cutaneous disease known as erysipeloid. When the infection occurs in pigs, it can cause a disease known as swine erysipelas, which is characterized by fever, arthritis, and skin abnormalities. The terminology is confusing because human erysipelas is a superficial cellulitis that is usually caused by group A streptococcus.

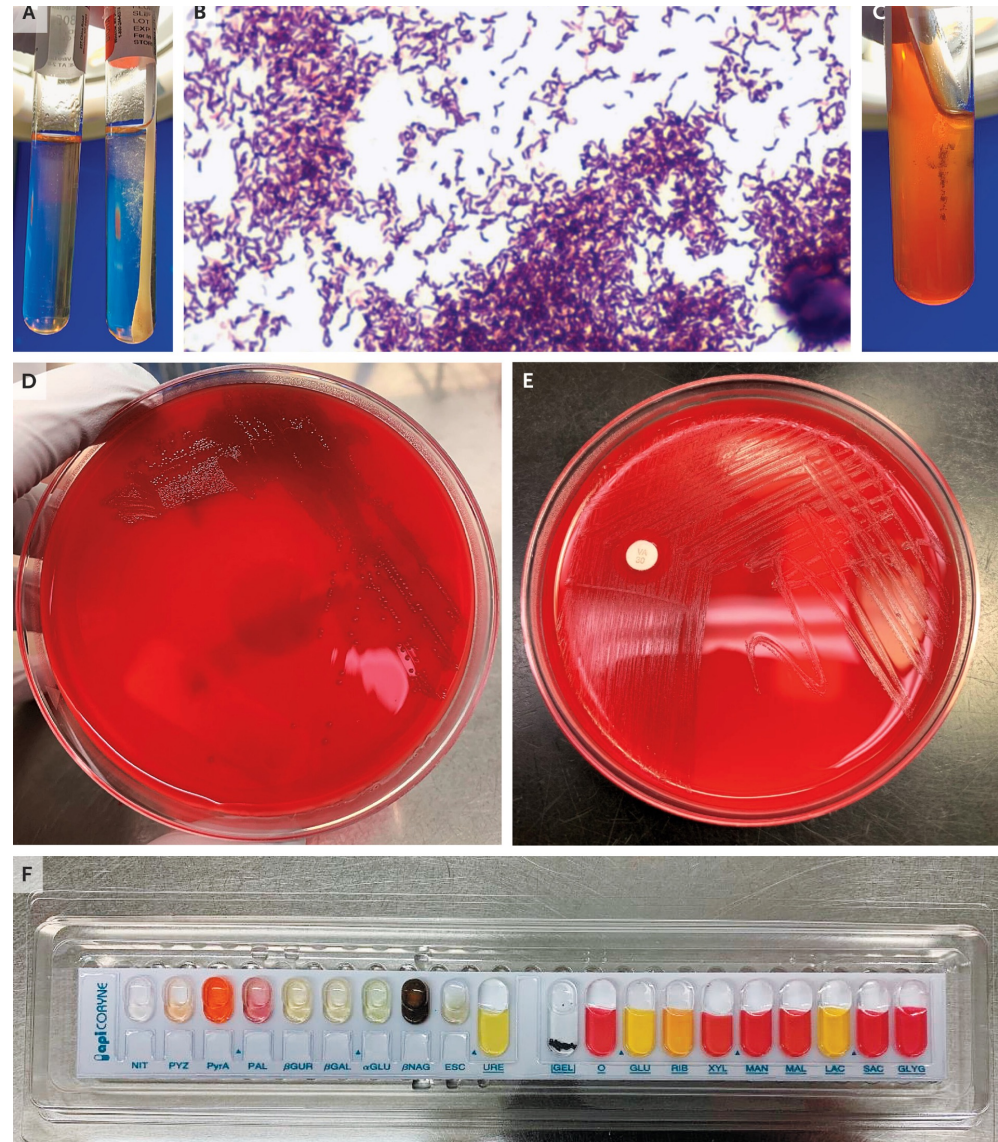
Pathological Discussion

Two superficial swabs and a punch-biopsy specimen from the dorsal surface of the left index and ring fingers were obtained 1 day after the onset of symptoms and were submitted for routine microbiologic cultures; the biopsy specimen was also submitted for pathological evaluation. Because the initial clinical differential diagnosis included cutaneous anthrax, all specimens were handled inside a biosafety cabinet in accordance with recommendations from the Centers for Disease Control and Prevention.

Hematoxylin and eosin staining of a punch-biopsy specimen of skin from the dorsal surface of the left fourth digit shows bullae formation (Panel A, arrow), lymphatic dilatation (Panel A, arrowhead), and epidermal necrosis (Panel B, arrow). At higher magnification, the epidermis shows intraepidermal microvesicles (Panel C) and underlying subepidermal edema with early bullae formation (Panel D). There is a dermal periadnexal and perivascular cellular infiltrate (Panel E) that extends into the adipose tissue of the hypodermis (Panel F). The infiltrate has focal areas of necrosis with associated dermal edema, and it is predominantly lymphohistiocytic, with occasional neutrophils (Panel G). Immunohistochemical staining shows abundant cells expressing CD68, a marker of histiocytic origin (Panel H, in brown).



Panel A shows bacterial growth on day 2 throughout the medium but primarily in the top and middle parts of the tube (right tube), a classic feature of facultative anaerobic bacteria. In **Panel B, Gram's staining of the colonies shows gram-positive, rod-shaped bacteria with nonsporulating, nonbranching, filamentous features.** Panel C shows that the organism produced hydrogen sulfide after inoculation into a triple sugar iron agar slant tube. The production of hydrogen sulfide is indicated by the presence of ferrous sulfide (shown as a black precipitate), which is produced when ferrous ammonium sulfate (present in the triple sugar iron agar) reacts with hydrogen sulfide gas. Panel D shows that the organism developed small alpha-hemolytic colonies after subculture and overnight incubation on routine sheep-blood agar. **Panel E shows bacterial colonies abutting a 30- μ g vancomycin disk, a finding that indicates antimicrobial resistance.** In Panel F, a biochemical test panel confirms that the pathogen is *Erysipelothrix rhusiopathiae*.



Akute Handinfektionen sind medizinische Notfälle, die unbehandelt rasch zu schweren Gewebeschäden, Funktionseinschränkungen oder einer lebensgefährlichen Sepsis (Blutvergiftung) führen können. Aufgrund der engen anatomischen Verhältnisse an der Hand mit Sehnenscheiden, Gelenkkapseln und Geweberäumen können sich bakterielle Erreger (meist *Staphylococcus aureus* oder Streptokokkengruppen) extrem schnell ausbreiten. Jede akute, fortschreitende Entzündung an der Hand gehört **umgehend in fachärztliche, idealerweise handchirurgische Behandlung.**

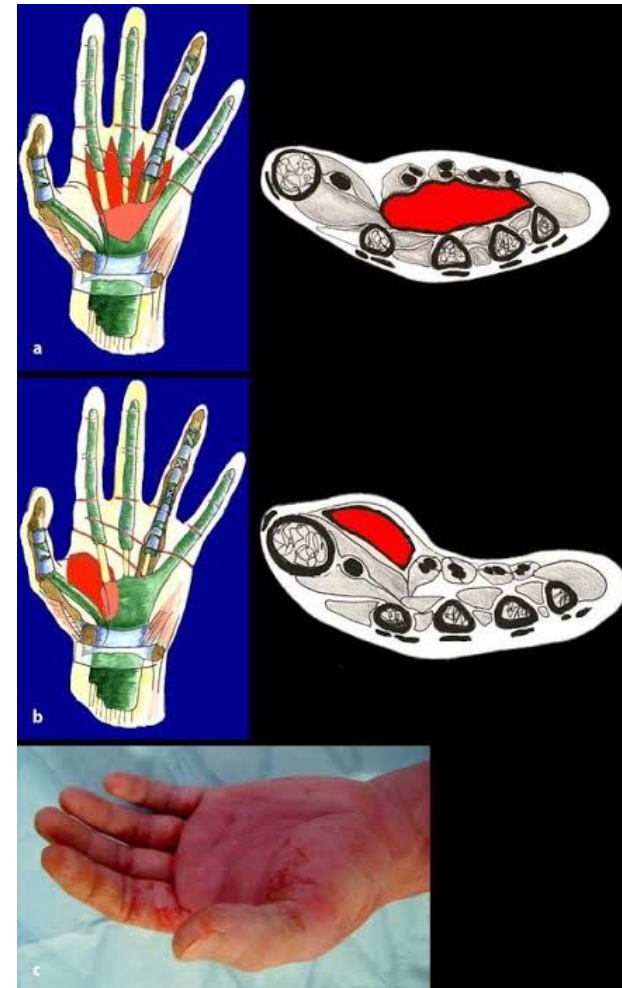
Starke, oft pochende Schmerzen (verstärken sich meist nachts oder beim Tieflagen der Hand)

Deutliche Schwellung und Rötung (oft auch am Handrücken, selbst wenn die Wunde in der Hohlhand liegt)

Eingeschränkte Beweglichkeit oder extreme Schmerzen bei der passiven Streckung eines Fingers

Überwärmung des betroffenen Bereichs

Sichtbare Eiteransammlungen unter der Haut oder am Nagelbett



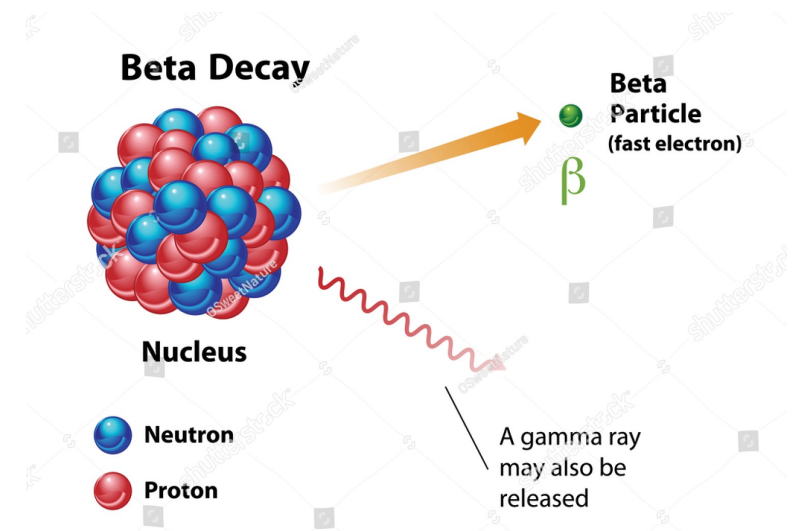
Der **Betazerfall** (engl. *beta decay*) ist eine Art von radioaktivem Zerfall, bei dem ein instabiler Atomkern seine Zusammensetzung ändert, um einen stabileren Zustand zu erreichen.

1. Beta-Minus-Zerfall (β^-)

- **Der Prozess:** Ein **Neutron** im Kern wandelt sich in ein **Proton** um.
- **Die Teilchen:** Dabei entstehen ein schnelles **Elektron** (das als Betateilchen ausgeschleudert wird) und ein **Elektron-Antineutrino**.
- **Die Folge:** Da ein Neutron mehr zum Proton wird, erhöht sich die Ordnungszahl des Atoms um 1. Das Element verändert sich (es wandelt sich in ein Nachbarelement im Periodensystem um).

2. Beta-Plus-Zerfall (β^+)

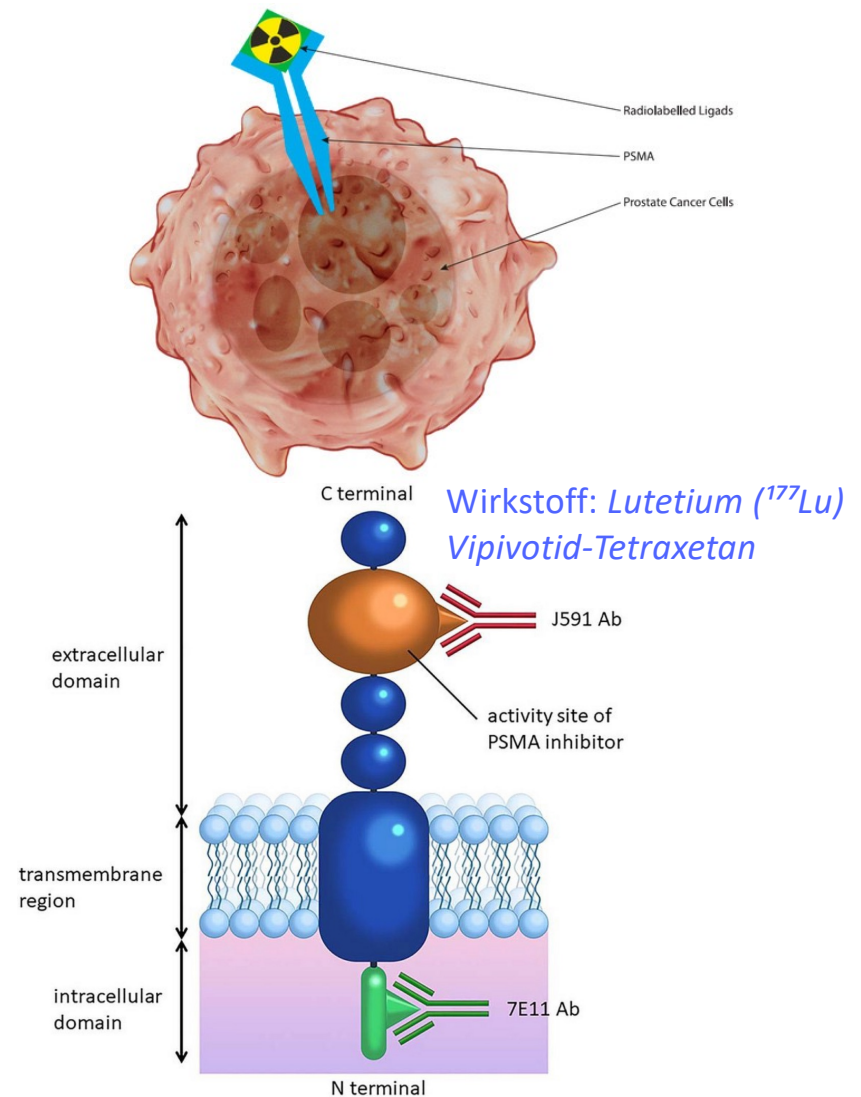
- **Der Prozess:** Ein **Proton** im Kern wandelt sich in ein **Neutron** um.
- **Die Teilchen:** Dabei entstehen ein **Positron** (der Antimaterie-Partner des Elektrons, positiv geladen) und ein **Neutrino**.
- **Die Folge:** Die Ordnungszahl verringert sich um 1, weil das Atom ein Proton verliert.



Das **Prostata-spezifische Membranantigen (PSMA)** auf Deutsch bedeutet **Prostata-spezifisches Membranantigen** (oft auch als Protein auf der Zellmembran bezeichnet).

Was ist PSMA?

- **Definition:** Ein Eiweiß (Glykoprotein), das auf der Oberfläche von Zellen sitzt.
- **Vorkommen:** Es kommt auf gesunden Prostatazellen vor, ist jedoch auf **Prostatakrebszellen** (Prostatakarzinomzellen) oft massiv erhöht.
- **Funktion:** Es dient im Körper als Enzym (eine Carboxypeptidase).



[¹⁷⁷Lu]Lu-PSMA-617 in patients with PSMA-positive metastatic androgen pathway modulator-naïve/sensitive prostate cancer (PSMAddition): a phase 3 randomised, controlled trial

Prostate-specific
membrane
antigen PSMA

Androgen
receptor
pathway
inhibitor
ARPI

¹⁷⁷Lutetium is
LuLu

Androgen
deprivation
therapy
ADT

Can LuLu help
help ADT plus
ARPI?

Summary

Background A contemporary standard of care for patients with metastatic androgen pathway modulator-naïve/sensitive (APMN/S) prostate cancer (also known as metastatic hormone-sensitive prostate cancer) is androgen deprivation therapy (ADT) plus an androgen receptor pathway inhibitor (ARPI) until progression. PSMAddition aimed to evaluate the efficacy and safety of [¹⁷⁷Lu]Lu-PSMA-617 (¹⁷⁷Lu-PSMA-617) combined with ADT plus ARPI in prostate-specific membrane antigen (PSMA)-positive metastatic APMN/S prostate cancer.

Methods PSMAddition is an ongoing, randomised, controlled, phase 3 superiority trial conducted at 169 sites across 20 countries, including hospitals, medical centres, and specialist cancer centres. Eligible male patients had treatment-naïve or minimally treated metastatic APMN/S prostate cancer diagnosed by CT, MRI, or bone scan and one or more PSMA-positive metastatic lesion on centrally read baseline [⁶⁸Ga]Ga-PSMA-11 PET. Patients were randomly assigned 1:1 to open-label, intravenous ¹⁷⁷Lu-PSMA-617 (7·4 GBq [200 mCi] ±10% every 6 weeks for up to six cycles) with ADT plus ARPI (¹⁷⁷Lu-PSMA-617 arm) or ADT plus ARPI (control arm). ADT and ARPI were investigator-chosen according to local authorisation and administered per local product labelling. Control arm patients with centrally confirmed radiographic progression could cross over to ¹⁷⁷Lu-PSMA-617. The primary endpoint was radiographic progression-free survival (centrally assessed per Prostate Cancer Clinical Trials Working Group 3-modified RECIST 1.1 or death); secondary endpoints included safety and tolerability. We report the second interim analysis of radiographic progression-free survival in the intention-to-treat population (all randomly assigned participants; data cutoff Jan 13, 2025). Safety was assessed in all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT04720157, and is ongoing.

Findings From June 15, 2021, to July 25, 2023, 1529 patients were screened and 1144 were randomly assigned (n=572 per arm; 1144 [100%] male, 572 [50%] with de novo metastatic APMN/S prostate cancer, 779 [68%] with high-volume disease; median age 68.0 years [IQR 62.0–73.0]). Baseline characteristics were balanced between arms. At second interim analysis for radiographic progression-free survival (median time from randomisation to data cutoff 23.6 months [IQR 20.3–29.2]; median radiographic progression-free survival follow-up time 19.6 months [IQR 14.0–24.1]), 139 (24%) of 572 participants in the ¹⁷⁷Lu-PSMA-617 arm and 172 (30%) of 572 participants in the control arm had radiographic disease progression or death. Radiographic progression-free survival was significantly improved in the ¹⁷⁷Lu-PSMA-617 arm versus the control arm, with a 28% reduction in the relative risk of radiographic progression or death (HR 0.72 [95% CI 0.58–0.90]; p=0.0021; median radiographic progression-free survival not reached in either arm). The primary endpoint was thus met. Grade 3 or worse adverse events occurred in 286 (51%) of 564 patients in the ¹⁷⁷Lu-PSMA-617 arm and 243 (43%) of 565 patients in the control arm. Serious adverse events occurred in 180 (32%) of 564 patients in the ¹⁷⁷Lu-PSMA-617 arm and 162 (29%) of 565 in the control arm; of which 17 (3%) in the ¹⁷⁷Lu-PSMA-617 arm were ¹⁷⁷Lu-PSMA-617-related. The most common adverse event was dry mouth, in 258 (46%) patients in the ¹⁷⁷Lu-PSMA-617 arm and 21 (4%) patients in the control arm; all were grade 1 or 2 and none were serious. Other common adverse events with higher incidence in the ¹⁷⁷Lu-PSMA-617 arm included cytopenias and gastrointestinal disturbances.

Interpretation Combining ¹⁷⁷Lu-PSMA-617 with ADT plus ARPI prolonged radiographic progression-free survival in patients with PSMA-positive metastatic APMN/S prostate cancer. Although adverse events were more frequent, there were no unexpected safety findings associated with the drug combination. Therefore, combining ¹⁷⁷Lu-PSMA-617 with ADT plus ARPI might be a new treatment option in metastatic APMN/S prostate cancer.

Funding Novartis.

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is highly expressed on prostate cancer cells in both APMN/S and APMR metastatic prostate cancer, with some variation in expression levels among patients, across disease stage, and with treatment exposure.^{13–17} [¹⁷⁷Lu]Lu-PSMA-617 (¹⁷⁷Lu-PSMA-617; also known as lutetium (¹⁷⁷Lu) vipivotide tetraxetan), is a PSMA-targeted radioligand therapy that selectively delivers β -particle radiation to PSMA-positive cells and the surrounding tumour microenvironment. In two pivotal phase 3 trials, VISION and PSMAfore, ¹⁷⁷Lu-PSMA-617 significantly improved radiographic progression-free survival and was well tolerated with a favourable benefit–risk profile.^{18–20} Both studies used a treatment regimen of ¹⁷⁷Lu-PSMA-617 7.4 GBq (200 mCi) every 6 weeks for up to six cycles, depending on tolerability and disease progression.^{18–20} ¹⁷⁷Lu-PSMA-617 was also associated with delayed time to worsening in patient-reported health-related quality of life (HRQoL) and pain, and time to symptomatic skeletal events.^{21,22} On the basis of these findings, the US Food and Drug Administration (FDA) approved ¹⁷⁷Lu-PSMA-617 for treatment of PSMA-positive metastatic APMR prostate cancer in patients previously treated with ARPI in both the post-taxane and taxane-naïve settings.^{23,24}

Combining ¹⁷⁷Lu-PSMA-617 with hormonal therapy could enhance efficacy by increasing anti-tumour effects and improving activity against heterogeneous tumours in both APMN/S and APMR metastatic prostate cancer.^{25–31} The phase 3 PSMAAddition study was designed to compare the efficacy and safety of ¹⁷⁷Lu-PSMA-617 combined with ADT plus ARPI versus ADT plus ARPI in patients with treatment-naïve or minimally treated PSMA-positive metastatic APMN/S prostate cancer, using a similar six-cycle ¹⁷⁷Lu-PSMA-617 regimen as was established in the metastatic APMR prostate cancer setting. Here, we report preplanned interim analyses of the primary endpoint of radiographic progression-free survival, the key secondary endpoint of overall survival, safety and tolerability, and other secondary endpoints in PSMAAddition.

	¹⁷⁷ Lu-PSMA-617 with ADT plus ARPI (n=572)	ADT plus ARPI (n=572)	Overall (n=1144)
Age, years	68.0 (62.0–73.0)	68.0 (63.0–73.0)	68.0 (62.0–73.0)
≥70 years	246 (43%)	246 (43%)	492 (43%)
<70 years	326 (57%)	326 (57%)	652 (57%)
Race			
American Indian or Alaska Native	1 (<1%)	2 (<1%)	3 (<1%)
Asian	101 (18%)	118 (21%)	219 (19%)
Black or African American	26 (5%)	29 (5%)	55 (5%)
Native Hawaiian or Other Pacific Islander	0	1 (<1%)	1 (<1%)
White	356 (62%)	345 (60%)	701 (61%)
Unknown	88 (15%)	77 (13%)	165 (14%)
ECOG performance status			
0	397 (69%)	407 (71%)	804 (70%)
1	174 (30%)	155 (27%)	329 (29%)
2	1 (<1%)	7 (1%)	8 (1%)
Metastatic sites			
Soft tissue	342 (60%)	338 (59%)	680 (59%)
Bone	522 (91%)	521 (91%)	1043 (91%)
Non-nodal soft tissue*			
Lung	66 (12%)	83 (15%)	149 (13%)
Liver	11 (2%)	21 (4%)	32 (3%)
Lung or liver	72 (13%)	95 (17%)	167 (15%)
Adrenal	7 (1%)	5 (1%)	12 (1%)
Central nervous system	1 (<1%)	0	1 (<1%)
Lymph nodes†	202 (35%)	192 (34%)	394 (34%)
None	1 (<1%)	2 (<1%)	3 (<1%)
Missing	2 (<1%)	1 (<1%)	3 (<1%)
Metastatic androgen pathway modulator-naïve/sensitive prostate cancer			
De novo‡§	298 (52%)	274 (48%)	572 (50%)
Recurrent¶	249 (44%)	274 (48%)	523 (46%)

(Table 1 continues on next page)

	¹⁷⁷ Lu-PSMA-617 with ADT plus ARPI (n=572)	ADT plus ARPI (n=572)	Overall (n=1144)
(Continued from previous page)			
PSA concentration, ng/mL	12.06 (3.16–53.24)	11.64 (2.83–44.15)	11.91 (3.01–50.34)
eGFR category			
Normal	214 (37%)	206 (36%)	420 (37%)
Mild impairment	308 (54%)	303 (53%)	611 (53%)
Moderate impairment	45 (8%)	52 (9%)	97 (8%)
LDH concentration, IU/L	181 (158–207)	178 (159–203)	179 (158–206)
Gleason score			
<8 (grade group 1–3)	152 (27%)	134 (23%)	286 (25%)
≥8 (grade group 4–5)	389 (68%)	406 (71%)	795 (69%)
Tumour volume			
High	389 (68%)	390 (68%)	779 (68%)
Low	183 (32%)	182 (32%)	365 (32%)
Planned or previous prostatectomy or definitive radiotherapy to primary prostate tumour**			
Yes	156 (27%)	155 (27%)	311 (27%)
No	416 (73%)	417 (73%)	833 (73%)
FACT-P			
Total score	123.0 (110.0–135.0)	122.0 (109.0–132.0)	123.0 (109.0–134.0)
Questionnaire completed††	511 (89%)	483 (84%)	994 (87%)
EQ-5D-5L			
Utility score	0.8 (0.8–1.0)	0.8 (0.7–1.0)	0.8 (0.8–1.0)
Questionnaire completed††	512 (90%)	487 (85%)	999 (87%)
BPI-SF			
Pain intensity score	1.0 (0.0–2.8)	1.3 (0.0–2.8)	1.0 (0.0–2.8)
Questionnaire completed††	509 (89%)	481 (84%)	990 (87%)

Data are median (IQR) or n (%). All participants were male (sex was defaulted to male in the clinical database). ADT=androgen deprivation therapy. AJCC=American Joint Committee on Cancer. ARPI=androgen receptor pathway inhibitor. BPI-SF=Brief Pain Inventory–Short Form. ECOG=Eastern Cooperative Oncology Group. eGFR=estimated glomerular filtration rate. EQ-5D-5L=the European Quality of Life 5-Dimensions 5-Levels. FACT-P=Functional Assessment of Cancer Therapy–Prostate. LDH=lactate dehydrogenase. PSA=prostate-specific antigen. Race was recorded according to the US Office of Management and Budget categories, if permitted to be collected by local law. *Excludes reported other visceral sites; other is defined as any metastatic site other than soft tissue, bone, lung, liver, skin, adrenal gland, central nervous system, and lymph nodes and is recorded on the case report form as malignant ascites, pancreas, spleen, or as a free-text entry; 351 patients (31%) were recorded as other (¹⁷⁷Lu-PSMA-617 arm: 176 [31%]; control arm 175 [31%]). †Pelvic and/or extra-pelvic lymph node metastasis. ‡Stage IVb at initial diagnosis (AJCC Cancer Staging Manual 8th edition).³⁵ §62 of 572 received previous treatment. ¶1225 of 523 received previous treatment. ||Per CHAARTED study³² criteria using conventional imaging. **Stratification factor as reported by investigator; does not include any other type of local treatment to primary prostate tumour. ††Questionnaire compliance based on first study visit; completion defined as questionnaire completed and score calculable.

Table 1: Baseline demographics and disease characteristics

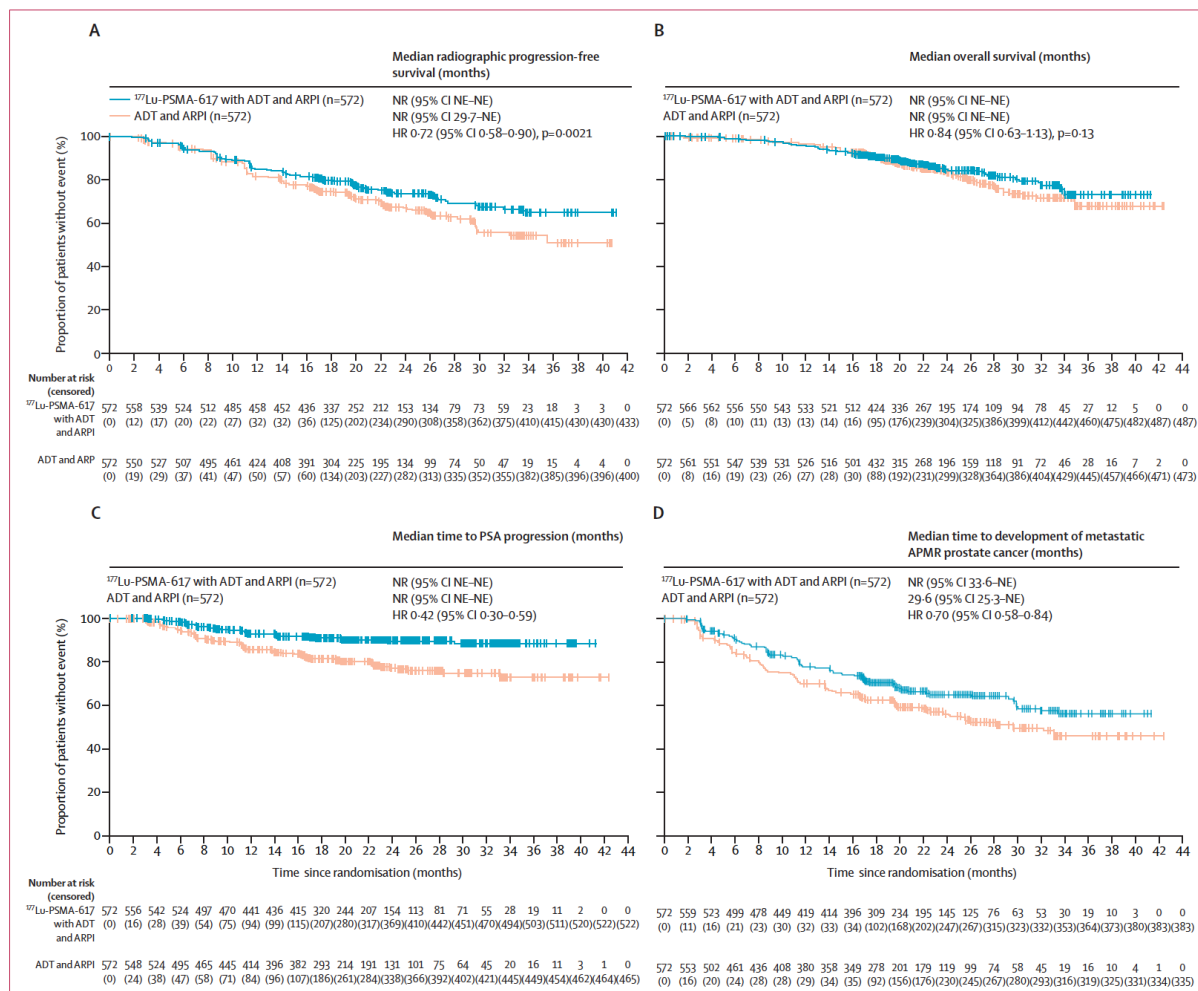


Figure 2: Radiographic progression-free survival, overall survival, time to PSA progression, and time to metastatic APMR prostate cancer

(A) Radiographic progression-free survival (primary endpoint). Significance threshold at second interim analysis (Jan 13, 2025) of radiographic progression-free survival p=0.0092 (one-sided; stratified log-rank test); information fraction, 74.4%. (B) Overall survival (key secondary endpoint). Significance threshold at first interim analysis (Jan 13, 2025) of overall survival: 0.0011 (one-sided; stratified log-rank test); information fraction, 47.3%. (C) Time to PSA progression (secondary endpoint); not analysed inferentially. (D) Time to development of metastatic APMR prostate cancer (secondary endpoint); not analysed inferentially. A breakdown of event types in the primary and key secondary endpoints is provided in the appendix (p 25). ADT=androgen deprivation therapy. APMR=androgen pathway modulator-resistant. ARPI=androgen receptor pathway inhibitor. HR=hazard ratio. NE=not estimable. NR=not reached. PSA=prostate-specific antigen.

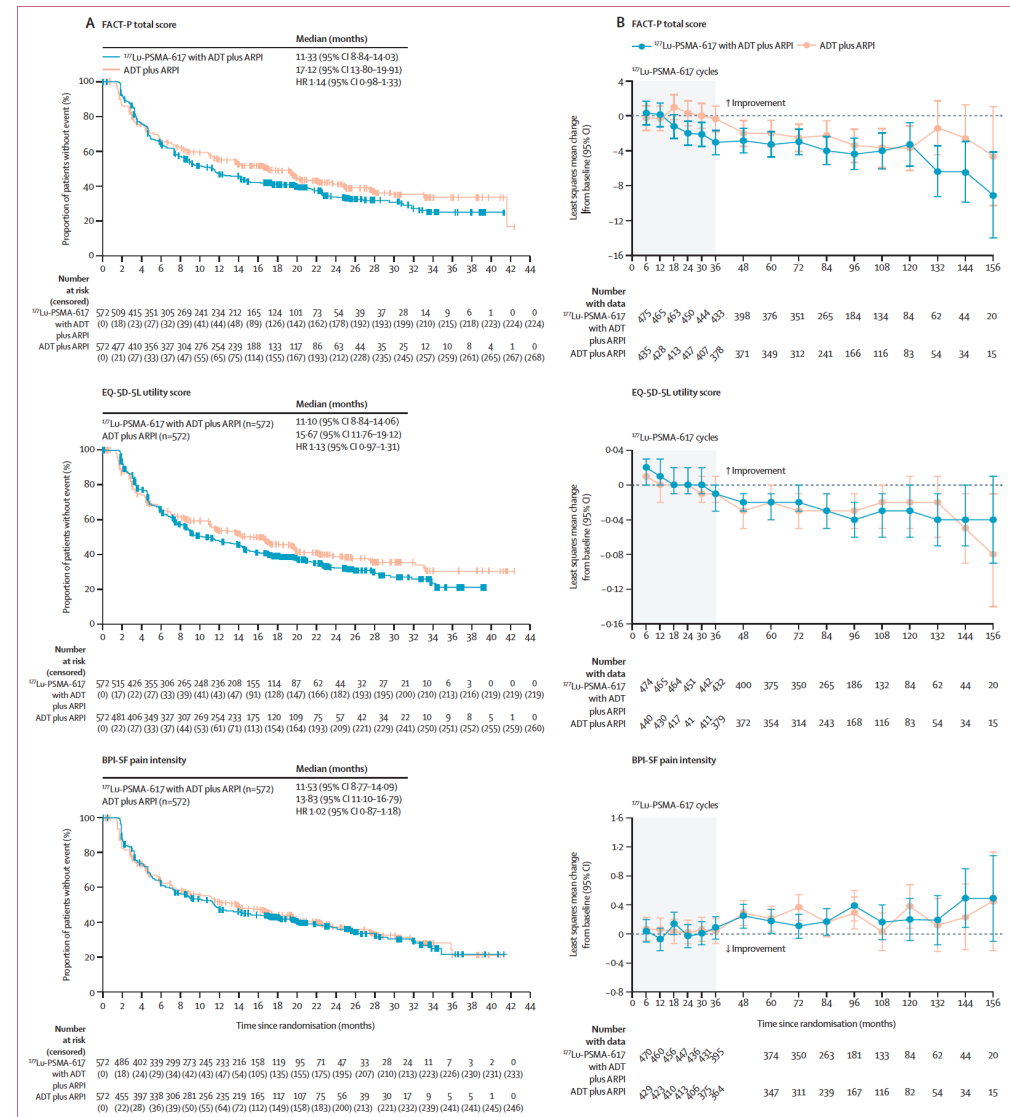
	177Lu-PSMA-617 with ADT plus ARPI (n=564)		ADT plus ARPI (n=565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with adverse event				
Any	555 (98%)	286 (51%)	546 (97%)	243 (43%)
Related to any study treatment	504 (89%)	128 (23%)	394 (70%)	69 (12%)
177Lu-PSMA-617-related	441 (78%)	78 (14%)	..	..
ADT-related or ARPI-related	418 (74%)	81 (14%)	394 (70%)	69 (12%)
Serious	180 (32%)	150 (27%)	162 (29%)	129 (23%)
Related to any study treatment	39 (7%)	31 (5%)	14 (2%)	12 (2%)
177Lu-PSMA-617-related	17 (3%)	13 (2%)	..	..
ADT-related or ARPI-related	27 (5%)	22 (4%)	14 (2%)	12 (2%)
Leading to death	15 (3%)	15 (3%)	14 (2%)	14 (2%)
Treatment-related	0	0	0	0
Leading to discontinuation of any study treatment	91 (16%)	46 (8%)	51 (9%)	23 (4%)
Leading to 177Lu-PSMA-617 discontinuation*	45 (8%)	28 (5%)	..	..
Dose reduction†	22 (4%)	13 (2%)	..	..
Dose delay‡	68 (12%)	27 (5%)	..	..
Occurring in ≥10% of patients in the 177Lu-PSMA-617 with ADT plus ARPI arm				
Dry mouth§	258 (46%)	0	21 (4%)	0
Fatigue	196 (35%)	6 (1%)	158 (28%)	6 (1%)
Nausea¶	193 (34%)	1 (<1%)	53 (9%)	0
Hot flush	164 (29%)	0	205 (36%)	0
Anaemia	153 (27%)	28 (5%)	75 (13%)	15 (3%)
Arthralgia	111 (20%)	5 (1%)	130 (23%)	9 (2%)
Back pain	101 (18%)	8 (1%)	110 (19%)	16 (3%)
Constipation	101 (18%)	0	91 (16%)	0
Asthenia	92 (16%)	2 (<1%)	73 (13%)	5 (1%)
Decreased appetite	81 (14%)	5 (1%)	37 (7%)	1 (<1%)
Vomiting	78 (14%)	4 (1%)	21 (4%)	0
COVID-19	76 (13%)	5 (1%)	60 (11%)	2 (<1%)
Hypertension	76 (13%)	34 (6%)	95 (17%)	35 (6%)
Diarrhoea**	69 (12%)	1 (<1%)	56 (10%)	0
Headache	69 (12%)	0	51 (9%)	2 (<1%)
ALT increased	68 (12%)	19 (3%)	73 (13%)	14 (2%)
Dysgeusia	67 (12%)	0	23 (4%)	0
White blood cell count decreased	63 (11%)	12 (2%)	18 (3%)	3 (1%)
AST increased	61 (11%)	10 (2%)	65 (12%)	11 (2%)
Lymphocyte count decreased	60 (11%)	28 (5%)	21 (4%)	7 (1%)

Data are n (%). ADT=androgen deprivation therapy. ALT=alanine aminotransferase. ARPI=androgen receptor pathway inhibitor. AST=aspartate aminotransferase. *Listed in the appendix (p 30). †Listed in the appendix (p 31). ‡Listed in the appendix (p 32). §Dry mouth: grade 1 in 231 patients (41%) and grade 2 in 27 patients (5%) in the 177Lu-PSMA-617 with ADT plus ARPI arm; grade 1 in 19 patients (3%) and grade 2 in two patients (<1%) in the ADT plus ARPI arm. ¶Nausea: grade 1 in 156 patients (28%) and grade 2 in 36 patients (6%) in the 177Lu-PSMA-617 with ADT plus ARPI arm; grade 1 in 39 patients (7%) and grade 2 in 14 patients (2%) in the ADT plus ARPI arm. ||Vomiting: grade 1 in 47 patients (8%) and grade 2 in 27 patients (5%) in the 177Lu-PSMA-617 with ADT plus ARPI arm; grade 1 in 13 patients (2%) and grade 2 in eight patients (1%) in the ADT plus ARPI arm. **Diarrhoea: grade 1 in 52 patients (9%) and grade 2 in 16 patients (3%) in the 177Lu-PSMA-617 with ADT plus ARPI arm; grade 1 in 43 patients (8%) and grade 2 in 13 patients (2%) in the ADT plus ARPI arm.

Table 2: Adverse events

Figure 3: Time to worsening and longitudinal assessment of health-related quality of life and pain

(A) Time to worsening in FACT-P total score (composite time to worsening, defined as time from randomisation to the first occurrence of >10 point decrease from baseline, or clinical disease progression, or death). EQ-5D-5L utility score (composite time to worsening, defined as time from randomisation to the first occurrence of 0.08 point decrease from baseline, or clinical disease progression, or death) and BPI-SF pain intensity (composite time to worsening, defined as time from randomisation to the first occurrence of $\geq 30\%$ or ≥ 2 point increase from baseline, or clinical disease progression, or death). (B) Longitudinal mixed model repeated measures analysis of change from baseline in FACT-P total score, EQ-5D-5L utility score, and BPI-SF pain intensity. Shaded region represents time on ^{177}Lu -PSMA-617 treatment. ADT=androgen deprivation therapy. BPI-SF=Brief Pain Inventory-Short Form. EQ-5D-5L=the European Quality of Life 5-Dimensions 5-Levels. FACT-P=Functional Assessment of Cancer Therapy-Prostate. HR=hazard ratio.



Research in context

Evidence before this study

[¹⁷⁷Lu]Lu-PSMA-617 (¹⁷⁷Lu-PSMA-617) is a prostate-specific membrane antigen (PSMA)-targeted radioligand therapy for the treatment of prostate cancer. To assess evidence from clinical trials of ¹⁷⁷Lu-PSMA-617 in patients with metastatic androgen modulator-naïve/sensitive (APMN/S) prostate cancer (also known as metastatic hormone-sensitive prostate cancer), we used the terms “(metastatic hormone-sensitive prostate cancer) AND (lutetium OR radioligand) AND randomised NOT review[pt]” to search PubMed for English-language publications from the past 10 years to Nov 1, 2025. No previous phase 3 trials of radioligand therapy in metastatic APMN/S prostate cancer were identified. We identified two completed and published randomised controlled phase 2 trials of ¹⁷⁷Lu-PSMA-617. Both trials had primary endpoints based on PSA changes, and therefore neither was fit for regulatory drug approval. In the CONSOLIDATE study in patients with synchronous high-volume metastatic APMN/S prostate cancer and residual disease after chemohormonal treatment, prostate-specific antigen (PSA) nadir concentrations below 0.2 ng/mL were more frequent with ¹⁷⁷Lu-PSMA-617 than placebo (risk ratio 4.5 [95% CI 1.2–17.4]; p=0.008) with no grade 3–4 toxicity. In the UpFrontPSMA study in patients with de novo high-volume metastatic APMN/S prostate cancer receiving androgen deprivation therapy (ADT), undetectable PSA concentrations were more frequent with ¹⁷⁷Lu-PSMA-617 followed by docetaxel versus docetaxel alone (odds ratio 3.88, 95% CI 1.61–9.38; p=0.002), without increased toxicity.

Added value of this study

PSMAAddition is the first phase 3 trial of any targeted radionuclide therapy in patients with metastatic APMN/S prostate cancer. These findings complement those of two previous phase 3 trials in patients with metastatic androgen pathway modulator-resistant (APMR) prostate cancer (also known as metastatic castration-resistant prostate cancer), which led to regulatory recognition in some countries, where it is now standard of care. PSMAAddition extends evidence for the therapeutic benefit of PSMA-targeted radioligand therapy from metastatic APMR to APMN/S prostate cancer. This study addresses whether radioligand therapy can be integrated into the contemporary standard of care of ADT plus an androgen receptor pathway inhibitor (ARPI), informing treatment intensification strategies in earlier disease.

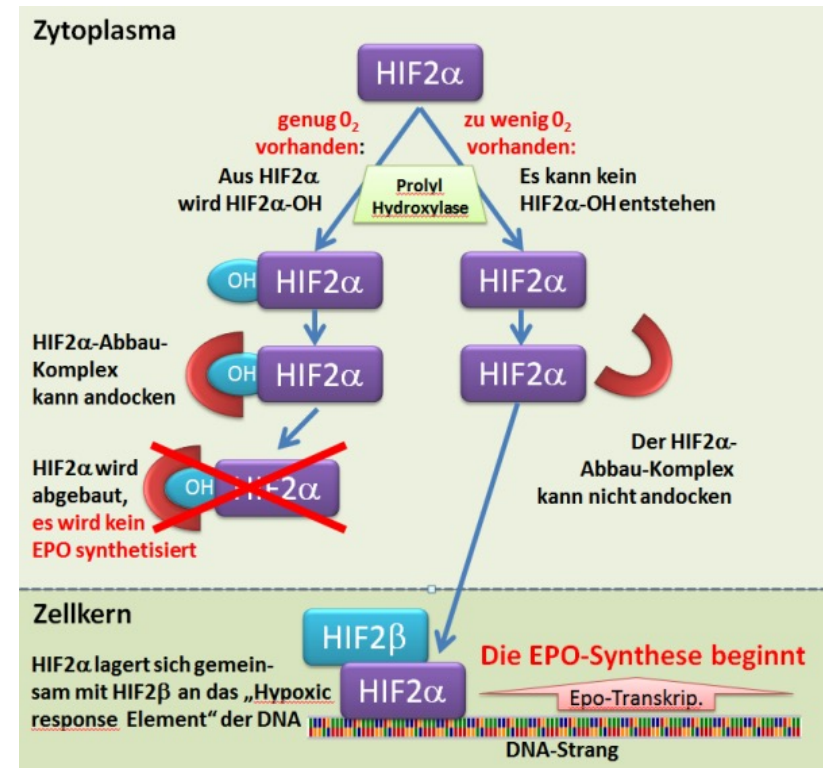
Implications of all the available evidence

The results of PSMAAddition provide evidence for the benefit of combining ¹⁷⁷Lu-PSMA-617 with ADT and ARPI in patients with PSMA-positive metastatic APMN/S prostate cancer who are appropriate for treatment with ADT plus ARPI. Together with existing phase 3 evidence from metastatic APMR prostate cancer, these findings support the use of PSMA-targeted radioligand therapy earlier in the disease course and establish ¹⁷⁷Lu-PSMA-617 plus ADT and ARPI as a potential new standard-of-care treatment option in this setting.

HIF-2 α steht für **Hypoxie-induzierter Faktor 2-alpha** (englisch: *Hypoxia-inducible factor 2-alpha*). Es handelt sich dabei um ein lebenswichtiges Eiweiß (einen sogenannten Transkriptionsfaktor), das die **Antwort des Körpers auf Sauerstoffmangel (Hypoxie) steuert**.

Das Gen, das für dieses Protein codiert, heißt offiziell **EPAS1** (*Endothelial PAS domain protein 1*). Für die Erforschung dieses Sauerstoff-Messsystems in unseren Zellen gab es im Jahr 2019 den **Nobelpreis für Medizin**.

- **Bei genug Sauerstoff (Normoxie):** Der Körper braucht das Protein gerade nicht. Es wird durch Sauerstoff-aktivierte Enzyme (PHDs) markiert und im zellulären "Mülleimer" (Proteasom) sofort wieder abgebaut.
- **Bei Sauerstoffmangel (Hypoxie):** Die Abbau-Enzyme können ohne Sauerstoff nicht arbeiten. HIF-2 α bleibt stabil, wandert in den Zellkern und schaltet dort gezielt Gene an, um das Überleben der Zelle zu sichern.



Belzutifan ist ein moderner, antineoplastischer Arzneistoff zur **Behandlung bestimmter Krebserkrankungen und Tumoren**. Es ist das erste Medikament einer neuen Wirkstoffklasse, den sogenannten **HIF-2 α -Inhibitoren** (Inhibitoren des Hypoxie-induzierbaren Faktors 2 alpha).

Das Medikament wird als Monotherapie (Einzeltherapie) bei Erwachsenen in zwei wesentlichen Bereichen eingesetzt:

- **Fortgeschrittenes klarzelliges Nierenzellkarzinom (RCC):** Für Patienten mit fortgeschrittenem Nierenkrebs, deren Erkrankung nach mindestens zwei vorherigen Therapien (darunter eine Immuntherapie mit einem PD-[L]1-Inhibitor und zielgerichtete VEGF-Therapien) weiter fortgeschritten ist.
- **Von-Hippel-Lindau-Syndrom (VHL):** Für Patienten mit dieser seltenen genetischen Erkrankung, die aufgrund dessen an Nierenzellkarzinomen, Hämangioblastomen im Zentralnervensystem oder neuroendokrinen Tumoren der Bauchspeicheldrüse (pNET) leiden, wenn rein lokale Behandlungen (wie Operationen) nicht infrage kommen.

Lenvatinib ist ein zielgerichteter **Tyrosinkinase-Inhibitor**, der das Wachstum von Krebszellen und die Bildung neuer Blutgefäße im Tumor hemmt.

Anwendung und Wirkung

- **Einsatzgebiete:** Wird unter anderem bei Schilddrüsenkarzinomen, Leberzellkrebs (hepatozelluläres Karzinom) und Gebärmutterhals- bzw. Endometriumkarzinomen (oft in Kombination mit Pembrolizumab) eingesetzt.
- **Wirkweise:** Blockiert bestimmte Rezeptoren (wie VEGF und FGFR) auf der Zelloberfläche, um die Blutversorgung des Tumors zu stoppen.

Belzutifan plus lenvatinib versus cabozantinib in patients with previously treated advanced renal cell carcinoma (LITESPARK-011): an open-label, randomised, controlled, phase 3 trial

Summary

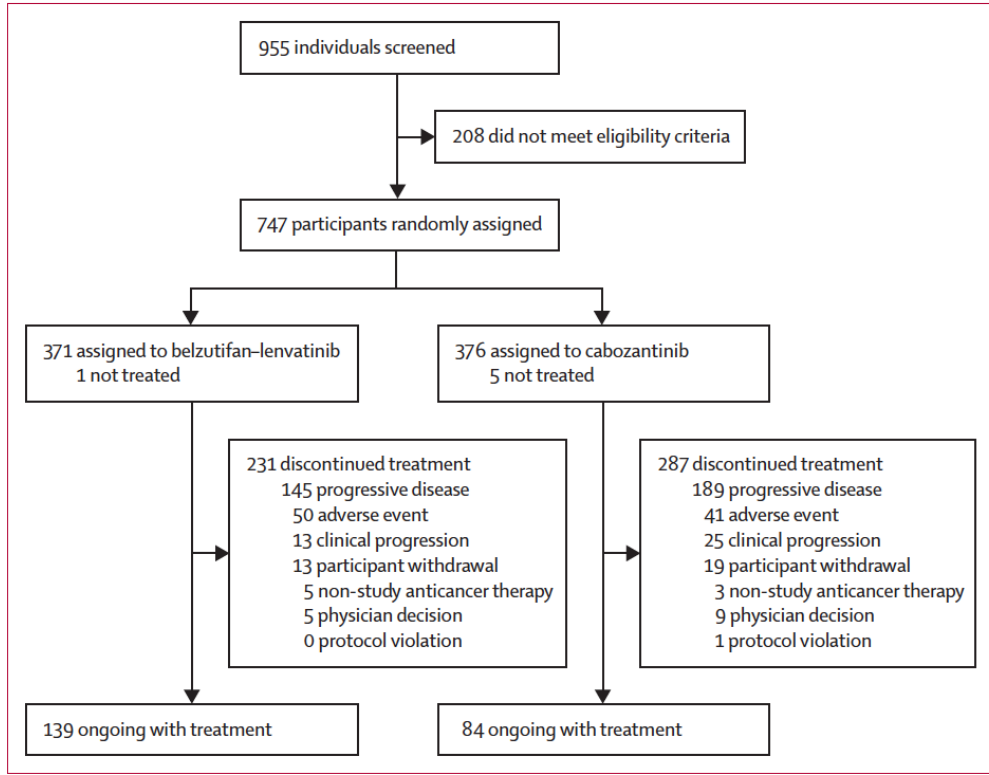
Background The identification of a clear standard of care for patients with advanced clear-cell renal cell carcinoma following anti-PD-1 or anti-PD-L1 therapy warrants study as an unmet need. We aimed to investigate belzutifan plus lenvatinib versus cabozantinib in participants with clear-cell renal cell carcinoma previously treated with immune checkpoint inhibitors.

Methods LITESPARK-011 is a phase 3, open-label, randomised, active-controlled study conducted at 184 medical centres in 25 countries in Asia, Australia, Europe, North America, and South America. Participants were aged 18 years or older with advanced unresectable, locally advanced or metastatic stage IV clear-cell renal cell carcinoma, with disease progression following anti-PD-1 or anti-PD-L1 therapy with or without previous VEGFR-tyrosine-kinase inhibitors. Participants were randomly assigned (1:1) to receive 120 mg belzutifan plus 20 mg lenvatinib (belzutifan–lenvatinib) or 60 mg cabozantinib orally once daily until disease progression or unacceptable adverse events occurred. Randomisation was done using a web-based interactive response system (block size four) and stratified by International Metastatic Renal-Cell Carcinoma Database Consortium prognostic score (0 vs 1–2 vs 3–6), line of previous immunotherapy (adjuvant, neoadjuvant-adjuvant, or first-line vs second-line), and geographical region (North America vs western Europe vs rest of the world). The dual primary endpoints were progression-free survival by masked independent central review and overall survival, assessed in all randomly assigned participants. Safety was assessed in all randomly assigned participants who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT04586231, and has completed participant recruitment and is ongoing with treatment and follow-up.

Findings Between March 5, 2021, and Sept 1, 2023, 955 individuals were screened for eligibility, 747 of whom were randomly assigned to belzutifan–lenvatinib (n=371) or cabozantinib (n=376). 565 (76%) participants were male and 182 (24%) were female; 651 (87%) were White (table 1). At second interim analysis (data cutoff April 9, 2025; median follow-up 29·0 months [IQR 23·7–34·9]), progression-free survival was significantly longer in the belzutifan–lenvatinib group compared with the cabozantinib group (median 14·8 months [95% CI 11·2–16·6] vs 10·7 months [9·2–11·1]; hazard ratio [HR] 0·70 [95% CI 0·59–0·84]; one-sided p<0·0001). Overall survival was not significantly different between the groups (median 34·9 months [95% CI 27·5–not reached] vs 27·6 months [24·0–31·4]; HR 0·85 [95% CI 0·68–1·05]; one-sided p=0·061). Grade 3 or worse treatment-emergent adverse events occurred in 311 (84%) of 370 participants in the belzutifan–lenvatinib group and 307 (83%) of 371 participants in the cabozantinib group, most commonly hypertension in both groups (114 [31%] participants in the belzutifan–lenvatinib group and 107 [29%] in the cabozantinib group). Treatment-related adverse events led to two deaths in the belzutifan–lenvatinib group and one death in the cabozantinib group.

Interpretation Belzutifan–lenvatinib represents a novel and efficacious treatment option. Although overall survival was not significantly different between the groups, belzutifan–lenvatinib might be a new standard of care for patients with advanced clear-cell renal cell carcinoma with disease progression after previous anti-PD-1 or anti-PD-L1 therapy. The safety profile of belzutifan–lenvatinib was consistent with those of the individual drugs.

Funding Merck Sharp & Dohme, a subsidiary of Merck & Co.

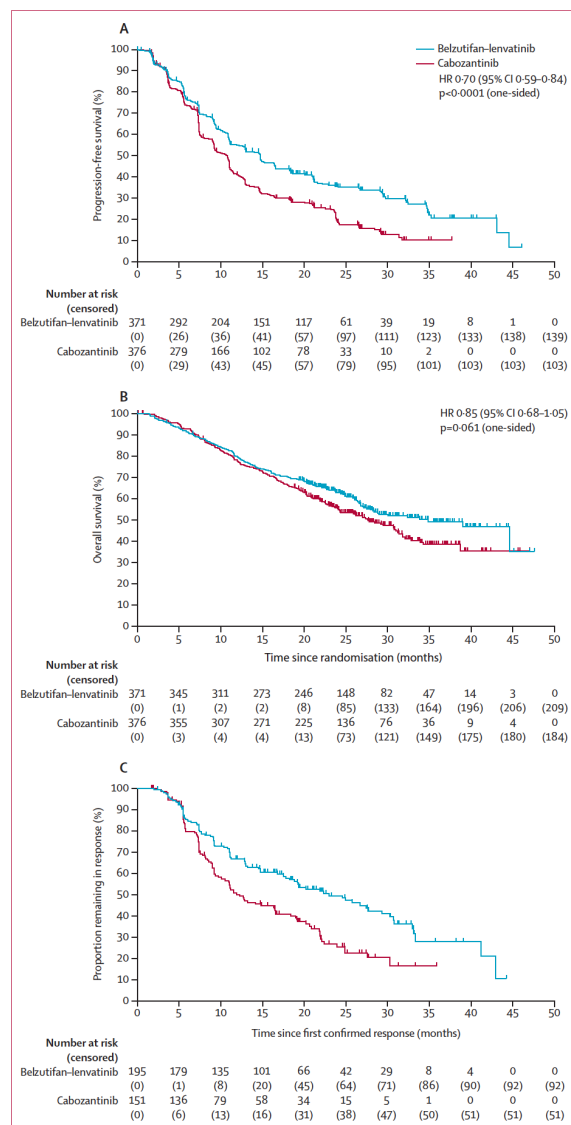


	Belzutifan-lenvatinib group (n=371)	Cabozantinib group (n=376)
Age		
Median, years	63.0 (55.0-70.0)	62.5 (55.0- 68.0)
≥65 years	162 (44%)	152 (40%)
Sex		
Male	273 (74%)	292 (78%)
Female	98 (26%)	84 (22%)
Race*		
American Indian or Alaska Native	7 (2%)	5 (1%)
Asian	29 (8%)	38 (10%)
Black or African American	1 (<1%)	2 (1%)
Multiple	2 (1%)	6 (2%)
White	330 (89%)	321 (85%)
Missing	2 (1%)	4 (1%)
Geographical region*		
North America	64 (17%)	63 (17%)
Western Europe	221 (60%)	216 (57%)
Rest of the world	86 (23%)	97 (26%)
Karnofsky performance status score†		
90 or 100	276 (74%)	277 (74%)
70 or 80	95 (26%)	99 (26%)
IMDC prognostic risk categories*		
Favourable, score 0	84 (23%)	95 (25%)
Intermediate, score 1-2	226 (61%)	215 (57%)
Poor, score 3-6	61 (16%)	66 (18%)
Sarcomatoid features		
Present	29 (8%)	27 (7%)
Absent	250 (67%)	230 (61%)
Unknown	92 (25%)	119 (32%)
Number of previous therapies*		
Adjuvant only	15 (4%)	18 (5%)
1	252 (68%)	251 (67%)
2	100 (27%)	107 (28%)
3	4 (1%)	0
Number of previous VEGFR-tyrosine-kinase inhibitors*		
0	158 (43%)	165 (44%)
1	203 (55%)	205 (55%)
2	10 (3%)	6 (2%)
Previous nephrectomy	231 (62%)	233 (62%)
Presence of lung metastases	235 (63%)	247 (66%)
Presence of bone metastases	148 (40%)	153 (41%)

Data are median (IQR) or n (%). Sex and race were self-reported. IMDC=International Metastatic Renal-Cell Carcinoma Database Consortium. *IMDC risk categories, number of previous lines of therapy, and geographical region based on electronic case report form collected at study entry. †Karnofsky performance status score assessed on a scale from 0 to 100, with lower scores indicating greater disability; a score of 100 indicates no restrictions on activity, and a score of 70 indicates participant is able to care for self but unable to carry on normal activities or do active work.

Table 1: Participant demographics and clinical characteristics at baseline

Figure 2: Progression-free survival, overall survival, and duration of response
 (A) Non-parametric Kapan–Meier estimates of progression-free survival by masked independent central review per RECIST 1.1 at the second interim analysis. Censored data at the last timepoint the participant was known to be alive and without disease progression are indicated with tick marks. (B) Non-parametric Kapan–Meier estimates of overall survival at the second interim analysis. Censored data at the last timepoint the participant was known to be alive are indicated with tick marks. (C) Non-parametric Kapan–Meier estimates of duration of response at the second interim analysis in participants in the intention-to-treat population who had a confirmed partial or complete response by masked independent central review per RECIST 1.1. HR=hazard ratio. RECIST 1.1=Response Evaluation Criteria in Solid Tumours version 1.1.



	Belzutifan–Lenvatinib group (n=371)	Cabozantinib group (n=376)
Objective response rate (95% CI)	53% (47–58)	40% (35–45)
Median duration of response, months (95% CI)	23.0 (18.3–29.3)	12.3 (9.7–16.6)
Median time to response, months (IQR)	2.0 (1.9–3.9)	1.9 (1.8–3.7)
Best overall response		
Complete response	20 (5%)	4 (1%)
Partial response	175 (47%)	147 (39%)
Stable disease*	143 (39%)	186 (49%)
Progressive disease	21 (6%)	22 (6%)
No evidence of disease	1 (<1%)	2 (1%)
Not evaluable†	3 (1%)	5 (1%)
No assessment‡	8 (2%)	10 (3%)

Data are % (95% CI), median (95% CI), median (IQR), or n (%).
 RECIST 1.1=Response Evaluation Criteria in Solid Tumours version 1.1. *Includes participants with stable disease and non-complete response or non-progressive disease. †Includes participants with insufficient data for assessment of response per RECIST 1.1. ‡Includes participants without post-baseline assessment by the data cutoff date.

Table 2: Best objective response assessed by masked independent central review per RECIST 1.1 at second interim analysis, intention-to-treat population

	Belzutifan–lenvatinib group (n=370)		Cabozantinib group (n=371)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Any adverse event	369 (>99%)	311 (84%)	369 (99%)	307 (83%)
Anaemia	256 (69%)	70 (19%)	95 (26%)	27 (7%)
Hypertension	218 (59%)	114 (31%)	210 (57%)	107 (29%)
Diarrhoea	195 (53%)	29 (8%)	260 (70%)	39 (11%)
Fatigue	167 (45%)	33 (9%)	151 (41%)	16 (4%)
Nausea	150 (41%)	14 (4%)	143 (39%)	4 (1%)
Decreased appetite	145 (39%)	10 (3%)	150 (40%)	13 (4%)
Proteinuria	136 (37%)	34 (9%)	72 (19%)	12 (3%)
Hypothyroidism	132 (36%)	1 (<1%)	104 (28%)	0
Vomiting	116 (31%)	3 (1%)	60 (16%)	3 (1%)
Arthralgia	107 (29%)	9 (2%)	62 (17%)	7 (2%)
Asthenia	105 (28%)	28 (8%)	75 (20%)	17 (5%)
Weight decreased	104 (28%)	16 (4%)	109 (29%)	22 (6%)
Constipation	97 (26%)	3 (1%)	84 (23%)	0
Headache	82 (22%)	0	46 (12%)	0
Aspartate aminotransferase increased	78 (21%)	10 (3%)	125 (34%)	14 (4%)
Palmar–plantar erythrodysaesthesia syndrome	76 (21%)	4 (1%)	190 (51%)	30 (8%)
Alanine aminotransferase increased	70 (19%)	14 (4%)	115 (31%)	21 (6%)
Stomatitis	52 (14%)	6 (2%)	104 (28%)	12 (3%)
Dysgeusia	46 (12%)	0	103 (28%)	3 (1%)

Data are n (%). *Any grade adverse events that occurred in at least 20% of any participants who received at least one dose of study treatment (as-treated population) are reported, along with the frequency of grade 3–5 adverse events. Adverse events were reported from randomisation up to 30 days after treatment cessation (or up to 90 days for serious adverse events). Events are presented in decreasing order of frequency in the belzutifan–lenvatinib column. Participants may have had more than one event.

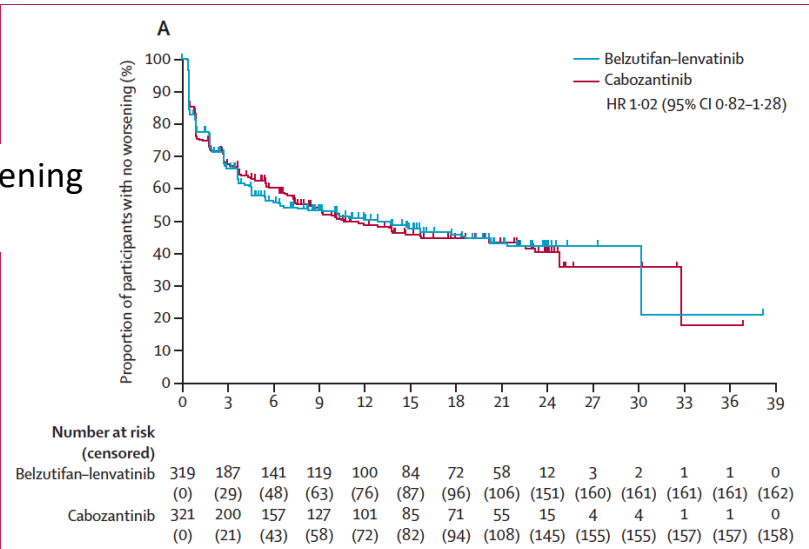
Table 3: Summary of treatment-emergent adverse events at second interim analysis, as-treated population

	Belzutifan–lenvatinib group (n=370)		Cabozantinib group (n=371)	
	Any Grade	Grade 5	Any Grade	Grade 5
Any	191 (52%)	20 (5%)	163 (44%)	12 (3%)
Hypoxia	23 (6%)	0	0	0
Pneumonia	18 (5%)	2 (1%)	14 (4%)	0
Hyponatraemia	12 (3%)	0	6 (2%)	0
Cardiac failure	10 (3%)	0	0	0
Acute kidney injury	9 (2%)	0	6 (2%)	0
Diarrhoea	9 (2%)	0	11 (3%)	0
Anaemia	8 (2%)	0	2 (1%)	0
Cholecystitis	5 (1%)	0	4 (1%)	0
Pleural effusion	5 (1%)	0	7 (2%)	0
Pneumonitis	5 (1%)	1 (<1%)	1 (<1%)	0
Influenza	4 (1%)	0	0	0
Sepsis	4 (1%)	0	3 (1%)	0
Pulmonary embolism	3 (1%)	0	9 (2%)	0
Dehydration	1 (<1%)	0	4 (1%)	0

Data are n (%). Treatment-emergent serious adverse events with incidence $\geq 1\%$ in any group are shown. As-treated population defined as all randomly assigned participants who received at least one dose of study treatment. Serious adverse events were recorded from randomisation through to 90 days after treatment discontinuation, or through to 30 days after treatment discontinuation if the participant initiated subsequent therapy. Serious adverse events considered related to study treatment were collected regardless of timing, including outside of the prespecified reporting window.

Table 4: Treatment-emergent serious adverse events, as-treated population

Worsening



No
worsening

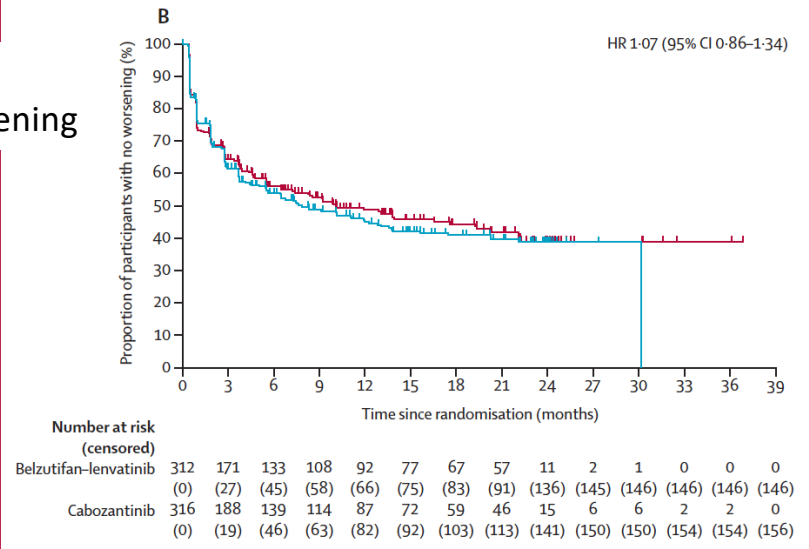


Figure 3: Time to worsening of symptoms and time to worsening of global health status and quality of life
(A) Non-parametric Kaplan–Meier estimates of the time to confirmed worsening of disease-related symptoms as assessed by FKSI-DRS score in the patient-reported outcomes analysis population at the second interim analysis. Censored data at the last available assessment (if the participant was still receiving treatment or withdrew from the trial) without worsening in FKSI-DRS score are indicated by tick marks. (B) Non-parametric Kaplan–Meier estimates of the time to confirmed worsening of global health status and quality of life as assessed by EORTC QLQ-C30 score in the patient-reported outcomes analysis population at the second interim analysis. Censored data at the last available assessment (if the participant was still receiving treatment or withdrew from the trial) without worsening in EORTC QLQ-C30 global health status and quality of life score are indicated by tick marks. HRs and 95% CIs were estimated based on a stratified Cox model. EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. FKSI-DRS=Functional Assessment of Cancer Therapy-Kidney Symptom Index: Disease Related Symptoms. HR=hazard ratio.

Research in context

Evidence before this study

We searched PubMed for clinical trials published in English between Jan 1, 2016 and Jan 1, 2026 using the search terms: “VEGF”, “vascular endothelial growth factor”, “cabozantinib”, “tivozanib”, “axitinib”, “zanzalintinib”, “lenvatinib”, “RCC”, “renal cell carcinoma”, “renal-cell carcinoma”, and “kidney cancer”, with no other restrictions or search parameters. We did not identify any randomised, phase 3 clinical trials in patients with previously treated renal cell carcinoma that showed superiority of an investigational treatment versus contemporary VEGFR-tyrosine-kinase inhibitor monotherapy as the active control. We also identified an overall paucity of randomised, phase 3 trials in patients with renal cell carcinoma previously treated specifically with anti-PD-1 or anti-PD-L1 therapy, with only three clinical trials in this population: LITESPARK-005, TiNivo-2, and CONTACT-03. We thus determined there is an unmet clinical need for novel, efficacious therapies with a manageable safety profile in this setting.

Added value of this study

To our knowledge, LITESPARK-011 is the first positive phase 3 trial in participants with advanced renal cell carcinoma

previously treated with anti-PD-1 or anti-PD-L1 agents, including participants with and without previous exposure to VEGF-targeted therapies. It is also the first randomised, phase 3 trial of a novel combination of mechanisms of action (HIF-2-alpha and VEGFR-tyrosine-kinase inhibitor) and the first phase 3 study in renal cell carcinoma to show superior efficacy versus a contemporary VEGFR-tyrosine-kinase inhibitor (cabozantinib) in any line of therapy.

Implications of all the available evidence

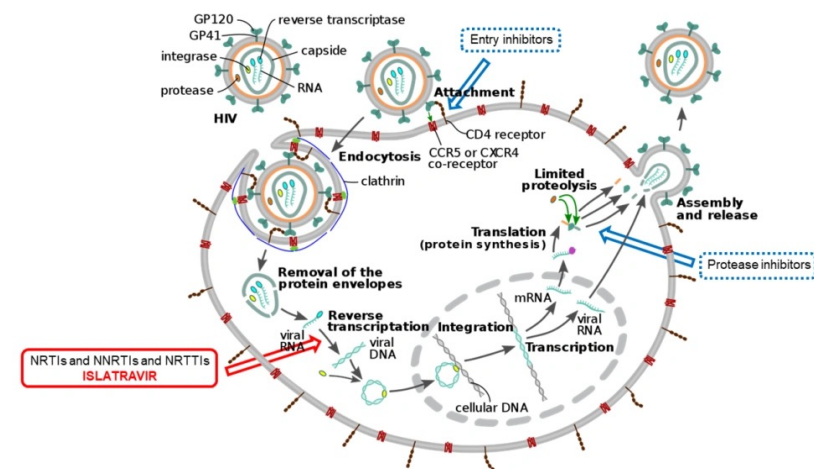
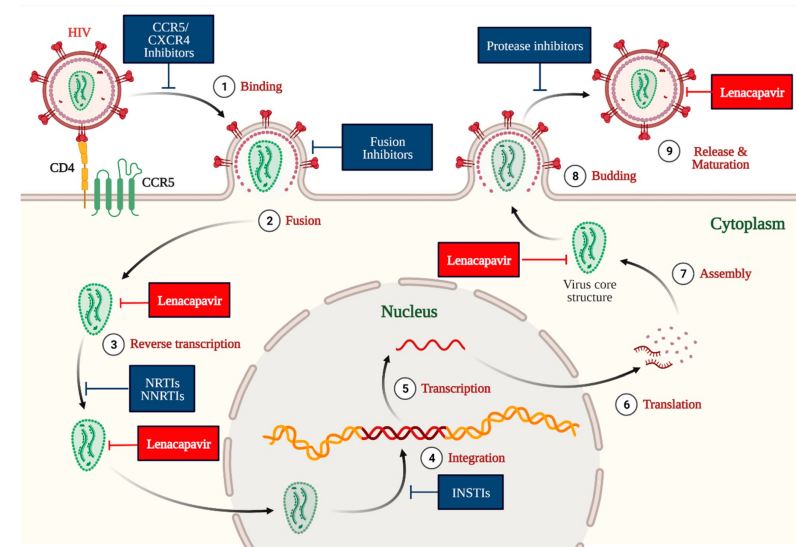
Our data establish belzutifan–lenvatinib as a potential treatment option in patients with advanced renal cell carcinoma previously treated with anti-PD-1 or anti-PD-L1 therapy, a notably difficult-to-treat patient population without an established standard of care. Furthermore, these findings help validate the mechanistic rationale for combination HIF-2-alpha and VEGFR-tyrosine-kinase inhibitor therapy, encouraging further investigation in future trials.

Die Wirkstoffkombination **Islatravir und Lenacapavir (ISL/LEN)** ist eine neuartige, vielversprechende Therapie zur Behandlung von **HIV-1-Infektionen**, die sich durch ein besonders langes Einnahmeintervall auszeichnet. Anstatt der bisher üblichen täglichen Tabletteneinnahme wird diese Kombination als **orale Single-Tablet-Regimen einmal wöchentlich** verabreicht.

Die Wirkstoffe und ihre Mechanismen

Beide Substanzen zeichnen sich durch eine sehr hohe Potenz bei niedrigen Konzentrationen und eine extrem lange Halbwertszeit im Körper aus. Sie greifen das HI-Virus an zwei völlig unterschiedlichen Stellen an:

- **Islatravir (ISL):** Der erste Vertreter einer neuen Wirkstoffklasse, den nukleosidischen **Reverse-Transkriptase-Translokations-Inhibitoren (NRTTIs)**. Er blockiert das Enzym Reverse Transkriptase auf mehrfache Weise und verhindert so hocheffektiv die Vermehrung der Virus-DNA.
- **Lenacapavir (LEN):** Ein "First-in-Class"-**Kapsidinhibitor**. Er stört die Funktion der Proteinhülle (Kapsid) des Virus in fast allen Phasen des viralen Lebenszyklus – vom Einschleusen des Erbguts in den Zellkern bis zum Zusammenbau neuer Viren.



Switch to once-weekly, single-tablet islatravir–lenacapavir from daily standard of care for HIV-1 (ISLEND-2): a multicentre, randomised, open-label, active-controlled, phase 3 non-inferiority trial

Summary

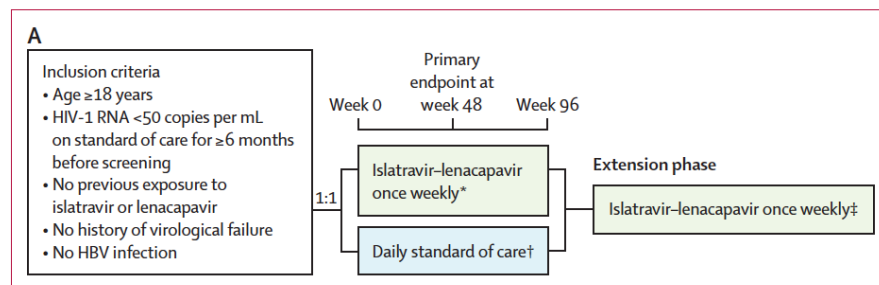
Background Antiretroviral therapies with long dosing intervals have the potential to improve virological outcomes and treatment satisfaction for people with HIV-1. We report the primary endpoint results from week 48 of ISLEND-2, a phase 3 trial evaluating the efficacy and safety of switching to once-weekly oral islatravir–lenacapavir from daily oral standard of care in virologically suppressed adults with HIV-1.

Methods This randomised, open-label, active-controlled, phase 3 non-inferiority trial was conducted at 100 sites in 14 countries and territories. Eligible participants were adults (aged ≥ 18 years) with HIV-1 who had been virologically suppressed on daily oral standard-of-care treatment for at least 6 months and had no previous virological failure. Participants were randomly assigned (1:1), using interactive response technology and stratified by geographical region, antiretroviral class, and CD4⁺ T-cell count, to switch to the once-weekly, single-tablet oral regimen of islatravir (2 mg)–lenacapavir (300 mg) or to continue daily oral standard of care for at least 96 weeks. The primary endpoint was the proportion of participants with an HIV-1 RNA viral load of 50 copies per mL or higher at week 48 (as per the US Food and Drug Administration-defined Snapshot algorithm), with a non-inferiority margin of 4%, assessed in all randomly assigned participants who received any dose of the assigned treatment. This trial is registered with ClinicalTrials.gov, NCT06630299, and is active but closed to new participants.

care. Of 626 participants, 211 (34%) were female, 193 (31%) were Black, 119 (19%) were Asian, 123 (20%) were Hispanic or Latine, and 89 (14%) were aged 65 years or older. At baseline, 552 (88%) were on a single-tablet antiretroviral regimen and 478 (76%) were receiving regimens containing integrase strand transfer inhibitors. At week 48, one (0·3%) of 314 participants in the islatravir–lenacapavir group and four (1·3%) of 312 participants in the standard-of-care group had an HIV-1 RNA viral load of 50 copies per mL or higher (difference –1·0% [95·002% CI –3·0 to 1·1]), meeting the non-inferiority criteria. Treatment-related adverse events occurred in 58 (18%) of 314 participants in the islatravir–lenacapavir group and one (<1%) of 312 participants in the standard-of-care group. Two (1%) of 314 participants in the islatravir–lenacapavir group and one (<1%) of 312 participants in the standard-of-care group discontinued the study owing to adverse events, with adverse events of grade 3 or higher occurring in 24 (8%) and 28 (9%) participants and serious adverse events in 22 (7%) and 27 (9%) participants in the islatravir–lenacapavir group and standard-of-care group, respectively. There were three deaths: one in the islatravir–lenacapavir group and two in the standard-of-care group, none of which were considered treatment-related.

Interpretation Once-weekly islatravir–lenacapavir showed non-inferior efficacy to the standard of care and was generally well tolerated. Longer-term safety data will provide further valuable insights beyond the week 48 data presented here. Islatravir–lenacapavir has potential to be the first once-weekly complete oral single-tablet regimen for HIV-1 treatment.

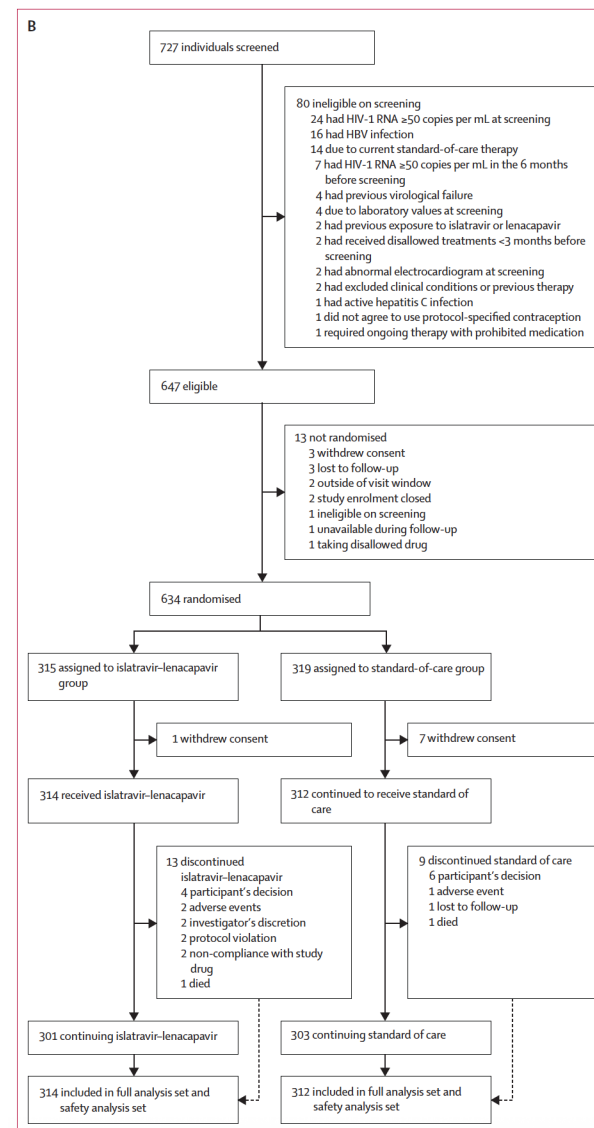
Funding Gilead Sciences and Merck Sharp & Dohme.



(Figure 1 continues on next page)

Figure 1: Trial design and profile

(A) Trial design. (B) Trial profile. HBV=hepatitis B virus. *Participants received two tablets, each containing islatravir 0.5 mg (initiation dose) and lenacapavir 300 mg (loading dose), administered orally on days 1 and 2, then one tablet containing islatravir 2 mg and lenacapavir 300 mg once weekly from day 8, without regard to food. †Participants continued guideline-recommended standard-of-care oral therapy. ‡Participants switching from standard of care to islatravir–lenacapavir in the extension phase will receive two tablets, each containing islatravir 0.5 mg (initiation dose) and lenacapavir 300 mg (loading dose), administered orally on days 1 and 2, then one tablet containing islatravir 2 mg and lenacapavir 300 mg once weekly from day 8, without regard to food.



	Islatravir–lenacapavir (n=314)	Standard of care (n=312)	Total (n=626)
Median age (IQR [range]), years	52 (42–60 [18–81])	53 (43–61 [19–83])	52 (42–60 [18–83])
≥50	180 (57%)	184 (59%)	364 (58%)
≥65	47 (15%)	42 (13%)	89 (14%)
Sex assigned at birth			
Female	105 (33%)	106 (34%)	211 (34%)
Male	209 (67%)	206 (66%)	415 (66%)
Median BMI (IQR), kg/m ²	27.0 (23.9–30.7)	26.7 (23.9–30.5)	26.9 (23.9–30.6)
Gender identity			
Cisgender man or woman	309 (98%)	308 (99%)	617 (99%)
Transgender, gender non-binary, gender non-conforming, or other	5 (2%)	4 (1%)	9 (1%)
Race			
Asian	61 (19%)	58 (19%)	119 (19%)
Black	94 (30%)	99 (32%)	193 (31%)
White	130 (41%)	134 (43%)	264 (42%)
Other*	17 (5%)	10 (3%)	27 (4%)
Not permitted†	12 (4%)	11 (4%)	23 (4%)
Ethnicity			
Hispanic or Latine	62 (20%)	61 (20%)	123 (20%)
Not Hispanic or Latine	236 (75%)	239 (77%)	475 (76%)
Not permitted†	16 (5%)	12 (4%)	28 (4%)
Geographical region			
USA	162 (52%)	162 (52%)	324 (52%)
Outside of USA	152 (48%)	150 (48%)	302 (48%)
HIV-1 RNA ≥50 copies per mL‡	4 (1%)	5 (2%)	9 (1%)
Mean CD4 ⁺ T-cell count (SD), cells per µL	795 (346.4)	761 (319.0)	778 (333.2)
Median CD4 ⁺ T-cell count (IQR), cells per µL	740 (554–987)	724 (548–925)	727 (553–966)
CD4 ⁺ T-cell count <200 cells per µL	3 (1%)	5 (2%)	8 (1%)
Median eGFR (Cockcroft–Gault; IQR), mL per min	99.0 (81.1–119.1)	94.9 (76.5–117.9)	96.7 (78.6–118.6)
Mean absolute lymphocyte count (SD), ×10 ³ cells per µL	1.99 (0.631)	1.94 (0.616)	1.96 (0.624)
History of AIDS	10 (3%)	8 (3%)	18 (3%)
Median duration of HIV-1 from diagnosis (IQR), years	16.3 (10.3–24.0)	17.2 (10.2–24.2)	17.1 (10.3–24.1)
Median duration of HIV-1 treatment (IQR), years	15.2 (9.3–21.2)	15.3 (9.3–21.9)	15.2 (9.3–21.2)
Number of antiretroviral pills per day			
1	277 (88%)	275 (88%)	552 (88%)
2	24 (8%)	29 (9%)	53 (8%)
3	12 (4%)	8 (3%)	20 (3%)
Antiretroviral medication class at baseline			
INSTI combined with one or two NRTIs	245 (78%)	233 (75%)	478 (76%)
Dolutegravir–lamivudine	88 (28%)	101 (32%)	189 (30%)
Bictegravir–emtricitabine–tenofovir alafenamide	34 (11%)	38 (12%)	72 (12%)
NNRTI combined with two NRTIs	43 (14%)	52 (17%)	95 (15%)
Protease inhibitor combined with two NRTIs	26 (8%)	27 (9%)	53 (8%)

Data are n (%) unless otherwise specified. eGFR=estimated glomerular filtration rate. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside(t)ide reverse transcriptase inhibitor. *Includes participants who selected either American Indian or Alaska Native or Other race. †In some countries, local regulators did not allow the collection of race and ethnicity information. ‡These participants had a screening HIV-1 RNA viral load of fewer than 50 copies per mL but a baseline HIV-1 RNA viral load of 50 copies per mL or higher.

Table 1: Baseline demographics and clinical characteristics of the safety analysis set

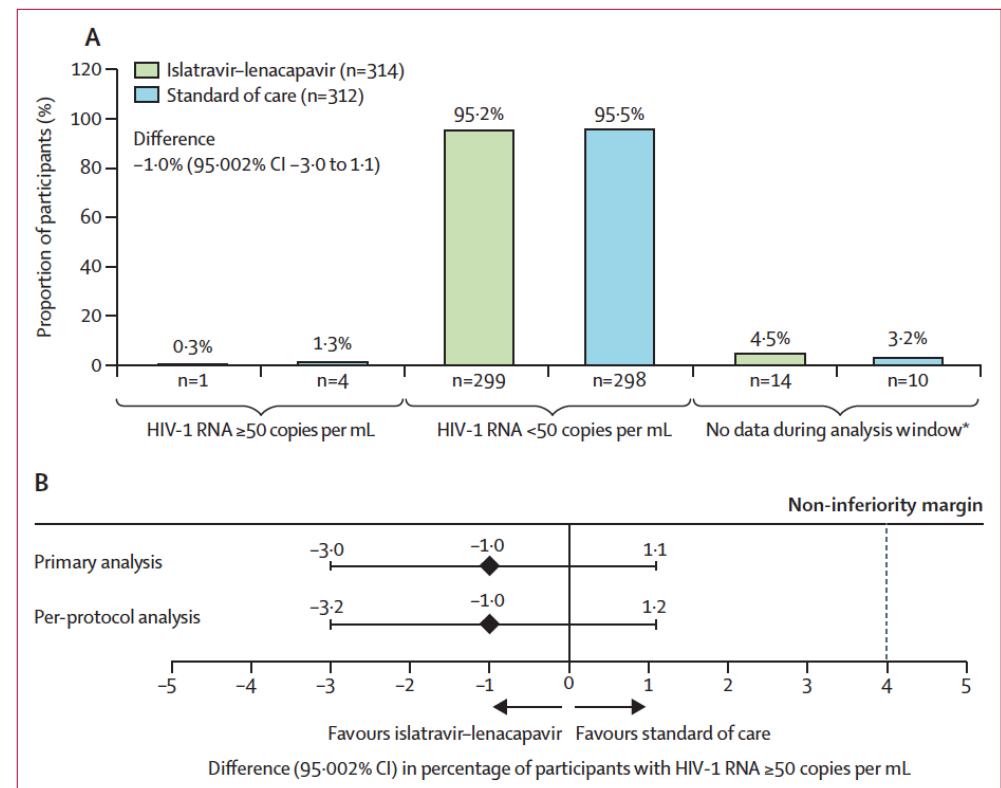


Figure 2: Efficacy outcomes at week 48

(A) Virological outcomes. (B) Non-inferiority analysis of the primary endpoint. Two-sided 95.002% CIs were constructed on the basis of stratum-adjusted Mantel–Haenszel proportion, adjusted by geographical region (USA vs outside the USA) and antiretroviral class (non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase strand transfer inhibitors). *Discontinued due to adverse events or death: islatravir–lenacapavir n=3, standard of care n=2; discontinued study due to other reasons and last available HIV-1 RNA was <50 copies per mL: islatravir–lenacapavir n=9, standard of care n=4; missing data during analysis window but still on study drug: islatravir–lenacapavir n=2, standard of care n=4. Other reasons could include discontinuation of the study drug due to investigator’s discretion, participant’s decision, loss to follow-up, non-compliance with study drug, participant never dosed with study drug, protocol violation, pregnancy, and study termination by sponsor.

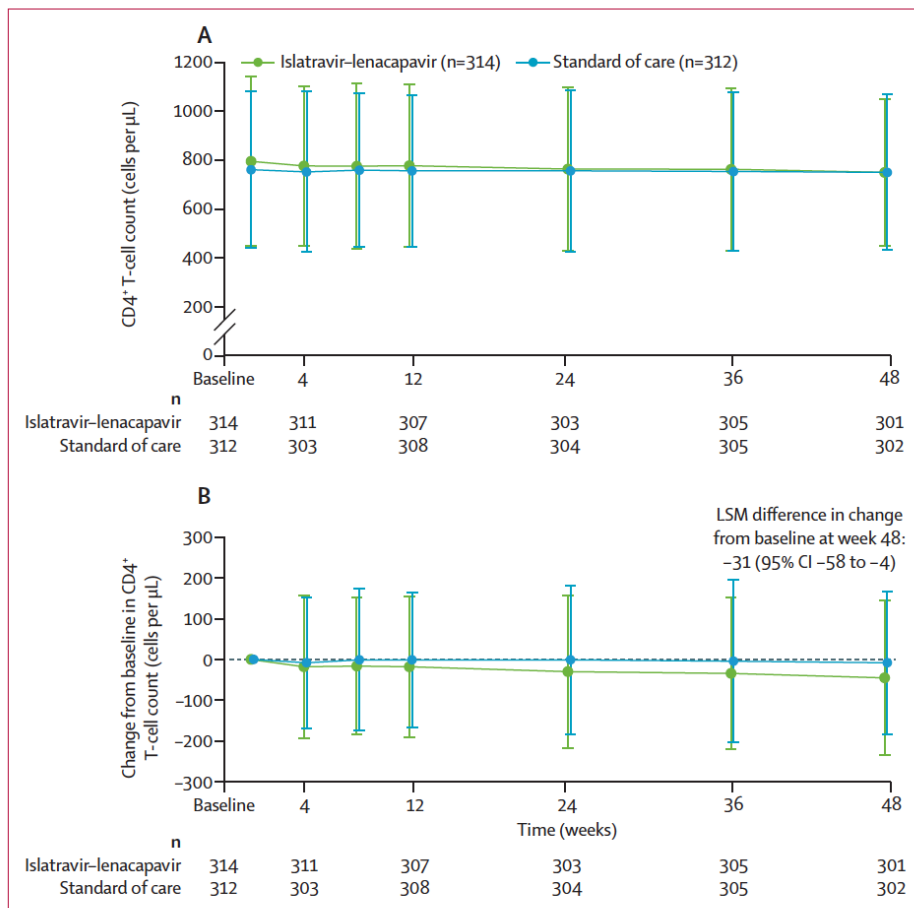


Figure 3: CD4⁺ T-cell count from baseline to week 48 in the full analysis set

(A) CD4⁺ T-cell counts. (B) Change from baseline in CD4⁺ T-cell counts. Data are mean (SD). LSM=least squares mean.

	Islatravir-lenacapavir (n=314)	Standard of care (n=312)
Adverse event, any grade	249 (79%)	241 (77%)
Adverse event of grade 3 or higher	24 (8%)	28 (9%)
Treatment-related adverse event of any grade	58 (18%)	1 (<1%)
Treatment-related adverse event of grade 3 or higher	0	0
Serious adverse event	22 (7%)	27 (9%)
Serious treatment-related adverse event	1 (<1%)†	0
Adverse event leading to discontinuation of study drugs	2 (1%)‡	1 (<1%)§
Treatment-related adverse event leading to discontinuation of study drugs	1 (<1%)¶	0
Death	1 (<1%)*	2 (1%)††
Death related to study treatment	0	0

Data are n (%). Median (IQR) exposure was 60.0 weeks (56.1–66.4) for the islatravir-lenacapavir group and 59.3 weeks (55.6–65.2) for the standard-of-care group. *Comprising adverse events beginning on or after the start date of the study drugs and up to 60 days after the permanent discontinuation of islatravir-lenacapavir, beginning on or after the day 1 visit date and up to 30 days after permanent discontinuation of standard of care, or leading to premature discontinuation of the study drugs. †A grade 2 seizure in a participant who had missed doses of antiseizure medication. The participant recovered, had no further seizures, and continued treatment with islatravir-lenacapavir. ‡Hyperbilirubinaemia (n=1), deemed related to the study drugs, and acute hepatitis B virus infection (n=1), deemed unrelated to the study drugs. §CNS lymphoma, deemed unrelated to the study drugs. ¶Hyperbilirubinaemia, deemed related to the study drugs. ||Includes any death that occurred during the study. **Road traffic accident, deemed unrelated to the study drugs. ††Pneumonia complicated by cardiogenic shock and cardiac arrest (n=1), deemed unrelated to the study drugs, and CNS lymphoma (n=1), deemed unrelated to the study drugs.

Table 2: Safety summary of participants with any treatment-emergent adverse event*

Research in context

Evidence before this study

Treatment of HIV-1 has been transformed by the introduction of once-daily, single-tablet antiretroviral therapy (ART) regimens. However, there remains a need for additional ART regimens with longer dosing intervals to enhance convenience, adherence, and acceptability. We searched PubMed, without language restrictions, for articles reporting clinical trials or clinical studies published from database inception to June 12, 2026, using the search string “(antiretroviral AND HIV-1 AND [weekly OR long-acting] AND [oral OR injectable] AND [satisfaction OR acceptability OR preference])”. Among the 37 articles identified, 11 reported data related to the use of an intramuscular injectable regimen of cabotegravir–rilpivirine administered monthly or every 2 months. Multiple phase 3 studies of cabotegravir–rilpivirine have shown high rates of virological suppression, non-inferior to daily oral therapy. Clinical trials and real-world studies of cabotegravir–rilpivirine indicated a high level of satisfaction among people with HIV-1 with less frequent dosing, and a strong preference for injectable long-acting cabotegravir–rilpivirine compared with daily oral tablets. The reasons given for this preference included relief from the fear of disclosure, anxiety surrounding adherence and reminder of HIV status, and convenience and lifestyle-related aspects of the therapy. A phase 2 study found that the novel weekly oral combination of islatravir plus lenacapavir was well tolerated and showed a high rate of virological suppression, similar to that of bictegravir–emtricitabine–tenofovir alafenamide. In ISLEND-1, a double-blind, randomised, active-controlled, non-inferiority, phase 3 trial, the once-weekly single-tablet regimen of islatravir–

lenacapavir was non-inferior to once-daily bictegravir–emtricitabine–tenofovir alafenamide, with virological suppression occurring in a high percentage of participants.

Added value of this study

ISLEND-2 is a multinational, multicentre, randomised, open-label, active-controlled, non-inferiority, phase 3 trial evaluating the efficacy and safety of switching to once-weekly oral islatravir–lenacapavir, versus continuing daily oral standard-of-care treatment, in virologically suppressed people with HIV-1. Virological suppression with once-weekly islatravir–lenacapavir was non-inferior to that with daily standard of care at week 48, and islatravir–lenacapavir was well tolerated. The study also collected patient-reported outcomes to better understand the acceptability of changing to a once-weekly dosing schedule.

Implications of all the available evidence

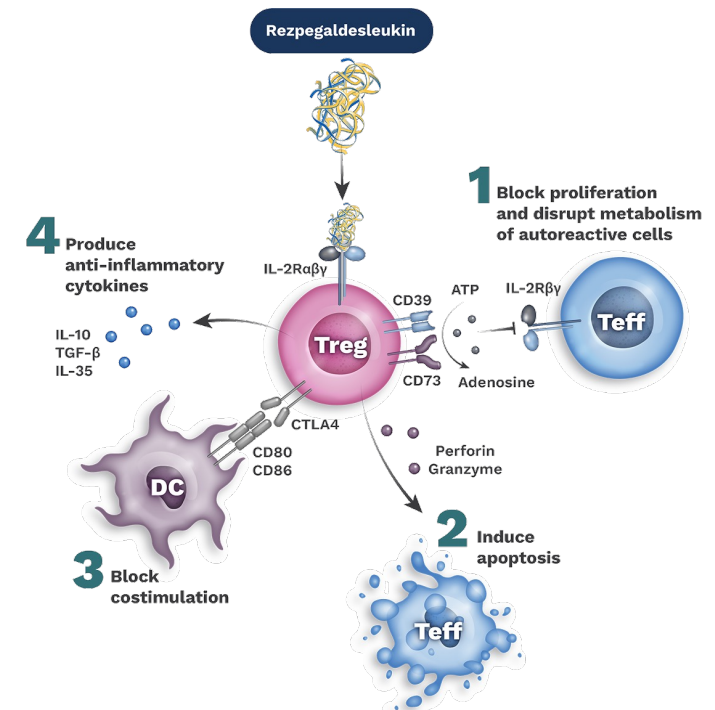
To date, long-acting ART has been restricted to injectable treatments, although there is considerable interest in long-acting oral HIV-1 treatment options. The results from the open-label ISLEND-2 trial show that islatravir–lenacapavir, a once-weekly oral treatment in development for HIV-1, is non-inferior to continuing current standard-of-care treatment and provides high levels of patient satisfaction. Alongside the results of the phase 3 companion trial ISLEND-1, which showed the non-inferiority and tolerability of islatravir–lenacapavir versus bictegravir–emtricitabine–tenofovir alafenamide, these data suggest that islatravir–lenacapavir could be the first once-weekly oral treatment for HIV-1, expanding the available therapeutic options and supporting more individualised treatment.

Rezpegaldesleukin (auch bekannt als **REZPEG** oder **NKTR-358**) ist ein neuartiger, biologischer Wirkstoff, der sich in der klinischen Entwicklung zur Behandlung verschiedener **Autoimmun- und chronisch-entzündlicher Erkrankungen** befindet.

Im Gegensatz zu den meisten bestehenden Biologika, die entzündungsfördernde Botenstoffe blockieren, verfolgt dieser Wirkstoff einen **völlig neuen Ansatz**: Er versucht, das körpereigene Immunsystem durch die **Aktivierung schützender Immunzellen wieder ins Gleichgewicht zu bringen** (it fixes the TREGs).

Der Wirkstoff ist ein sogenannter **IL-2-Rezeptor-Agonist**. Er wurde künstlich modifiziert (durch Polyethylenglykol bzw. Pegylierung), damit er im Körper stabiler bleibt und gezielt an eine bestimmte Gruppe von Zellen andockt: die **regulatorischen T-Zellen (Tregs)**.

- **Die Aufgabe der Tregs:** Diese Zellen fungieren als „Sicherheitsbremse“ des Immunsystems. Sie verhindern, dass das Immunsystem körpereigenes Gewebe oder harmlose Stoffe angreift.
- **Der Effekt von Rezpegaldesleukin:** Das Medikament kurbelt die Vermehrung und Funktion dieser regulatorischen T-Zellen massiv an. Dadurch wird die übersteigerte Immunreaktion, die bei Autoimmunerkrankungen und Ekzemen vorliegt, sanft heruntergefahren.



Rezpegaldesleukin treatment of moderate-to-severe atopic dermatitis (REZOLVE-AD): final results from the 16-week induction period of an international, double-blind, placebo-controlled, randomised phase 2b study

Summary

Background Rezpegaldesleukin is an interleukin-2 receptor agonist that selectively expands and enhances the function of regulatory T cells (Tregs), offering a novel therapeutic approach for autoimmune and inflammatory diseases such as atopic dermatitis. We aimed to compare the efficacy and safety analyses of rezpegaldesleukin with placebo in adults with moderate-to-severe atopic dermatitis naive to biological treatments.

Methods REZOLVE-AD was a phase 2b, randomised, double-blind, placebo-controlled study conducted in 107 community research centres or hospitals in ten countries (Australia, Bulgaria, Canada, Croatia, Czechia, Germany, Hungary, Poland, Spain, and the USA). Eligible patients were adults (aged 18 years or older) with confirmed atopic dermatitis (American Academy of Dermatology Consensus Criteria) diagnosed at least 12 months before enrolment, with moderate-to-severe disease activity defined by an Eczema Area and Severity Index (EASI) score of at least 16·0, validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of at least 3 (moderate), and at least 10% affected body surface area. Patients were randomly allocated (3:3:3:2) to receive subcutaneous rezpegaldesleukin 24 µg/kg or rezpegaldesleukin 18 µg/kg every 2 weeks, rezpegaldesleukin 24 µg/kg every 4 weeks, or placebo for 16 weeks during the induction period. Randomisation was done by an independent vendor using Randomisation and Trial Supply Management methodology via an interactive response system and was stratified by baseline disease severity (vIGA-AD 3 [moderate] vs 4 [severe]) and geographical region (North America vs rest of world). All patients, investigators, and those assessing outcomes were masked to treatment assignment. Outcomes for the induction period were assessed through week 16 and are included in this report. The primary endpoint was percentage change from baseline in EASI score at week 16. Efficacy and safety analyses were conducted in all randomly assigned patients exposed to study treatment, excluding those enrolled at two sites closed due to Good Clinical Practice non-compliance, both of which received notification of closure approximately 300 days before database lock. All missing data were imputed with multiple imputation. The trial was registered with ClinicalTrials.gov (NCT06136741).

Findings 398 patients were enrolled between Nov 15, 2023, and Jan 9, 2025. A total of 393 patients were analysed (104 in the rezpegaldesleukin 24 µg/kg every 2 weeks group, 106 in the rezpegaldesleukin 18 µg/kg every 2 weeks group, 110 in the rezpegaldesleukin 24 µg/kg every 4 weeks group, and 73 in the placebo group); 203 (52%) patients were female and 190 (48%) were male. All three rezpegaldesleukin groups met the primary endpoint. Rezpegaldesleukin showed dose-dependent improvements compared with placebo in mean percentage change in EASI from baseline at week 16: -61% (SE 3·8) for rezpegaldesleukin 24 µg/kg every 2 weeks, -58% (3·8) for rezpegaldesleukin 18 µg/kg every 2 weeks, and -53% (3·7) for rezpegaldesleukin 24 µg/kg every 4 weeks versus -31% (4·5) for placebo. Treatment differences versus placebo were -30 percentage points (95% CI -41·3 to -18·0; $p<0\cdot0001$) for rezpegaldesleukin 24 µg/kg every 2 weeks, -27 percentage points (-38·5 to -15·7; $p<0\cdot0001$) for rezpegaldesleukin 18 µg/kg every 2 weeks, and -22 percentage points (-33·3 to -10·3; $p=0\cdot0002$) for rezpegaldesleukin 24 µg/kg every 4 weeks. Treatment-emergent adverse events observed in at least 5% of rezpegaldesleukin-treated patients ($n=320$) and greater than placebo ($n=73$) included injection-site reaction (223 [70%] *vs* three [4%]), eosinophilia (25 [8%] *vs* two [3%]), pyrexia (20 [6%] *vs* two [3%]), headache (20 [6%] *vs* three [4%]), upper respiratory tract infections (19 [6%] *vs* four [5%]), and arthralgia (16 [5%] *vs* one [1%]). Nearly all (>99%) injection-site reactions were mild to moderate in severity and resolved. There was no evidence of an increased risk of serious or severe adverse events, and no deaths were reported during the induction period.

Interpretation Over the 16-week induction period, rezpegaldesleukin treatment resulted in significant and clinically meaningful improvements across multiple clinical endpoints, including the primary endpoint of EASI percentage change from baseline, in comparison with placebo. Rezpegaldesleukin had a clinically favourable adverse event

	Repegaldesleukin 24 µg/kg every 2 weeks (n=104)	Repegaldesleukin 18 µg/kg every 2 weeks (n=106)	Repegaldesleukin 24 µg/kg every 4 weeks (n=110)	Placebo every 2 weeks (n=73)
Primary endpoint				
EASI percentage change from baseline*	-61% (3.8)	-58% (3.8)	-53% (3.7)	-31% (4.5)
Treatment difference	-30% (-41.3 to -18.0)	-27% (-38.5 to -15.7)	-22% (-33.3 to -10.3)	..
p value	<0.0001	<0.0001	0.0002	..
Secondary endpoints				
EASI-50 response	69 (66%)	70 (66%)	60 (55%)	25 (34%)
Treatment difference†	32% (17.6 to 47.3)	32% (17.4 to 47.1)	21% (6.2 to 35.6)	..
p value	<0.0001	<0.0001	0.0086	..
EASI-75 response	43 (42%)	49 (46%)	37 (34%)	12 (17%)
Treatment difference†	26% (12.2 to 38.8)	30% (16.4 to 43.0)	17% (4.3 to 29.9)	..
p value	0.0008	0.0001	0.015	..
EASI-90 response	26 (25%)	19 (18%)	19 (17%)	7 (9%)
Treatment difference†	16% (5.4 to 27.5)	9% (-1.4 to 19.8)	8% (-1.7 to 17.7)	..
p value	0.011	0.093	0.14	..
vIGA-AD response‡§	20 (20%)	28 (26%)	21 (19%)	6 (8%)
Treatment difference†	12% (1.2 to 22.2)	18% (7.1 to 29.2)	11% (1.2 to 20.9)	..
p value	0.047	0.0054	0.053	..
Itch NRS response¶ **	40 (42%)	32 (35%)	24 (23%)	10 (16%)
Treatment difference†	27% (12.4 to 40.7)	20% (5.4 to 33.6)	7% (-5.1 to 19.8)	..
p value	0.0011	0.014	0.42	..
BSA percentage change from baseline††	-54% (4.6)	-48% (4.8)	-43% (4.4)	-17% (5.4)
Treatment difference	-37% (-51.3 to -23.1)	-30% (-44.4 to -16.5)	-25% (-39.1 to -11.8)	..
p value	<0.0001	<0.0001	0.0003	..
Data are least squares mean (SE), n (%), or adjusted percentage difference (95% CI) versus placebo. Response rates were estimated using multiple imputation. The number of responders was then calculated by multiplying the estimated response rate (using the unrounded value) by the number of participants in the analysis population and rounding to the nearest whole number. As a result, the reported responder counts and rounded responses may not always align exactly when the response rate is recalculated from the displayed responder count. BSA=body surface area. EASI=Eczema Area and Severity Index. EASI-50=reduction in EASI score by at least 50% relative to baseline score. EASI-75=reduction in EASI score by at least 75% relative to baseline score. EASI-90=reduction in EASI score by at least 90% relative to baseline score. NRS=Numerical Rating Scale. vIGA-AD=Validated Investigator Global Assessment for Atopic Dermatitis. *EASI assesses four signs of disease (erythema, oedema or papulation, excoriation, and lichenification) across four body regions (head or neck, trunk, upper and lower extremities) and extent of skin involvement in each region; scores range from 0 to 72 with higher values indicating a greater severity and extent of disease. †Mantel-Haenszel treatment differences in response rates were adjusted for stratification factors. ‡vIGA-AD describes the overall appearance of atopic dermatitis lesions at a given timepoint; scores range from 0 (clear skin) to 4 (severe disease). §vIGA-AD response was defined as a score of 0 (clear) or 1 (almost clear) and ≥2-point reduction from baseline. ¶Itch NRS describes the worst level of itch in the past 24 h; scores range from 0 (no itch) to 10 (worst itch imaginable). Patients evaluable for the corresponding endpoint requiring baseline itch NRS score ≥4 were n=95 for the repegaldesleukin 24 µg/kg every 2 weeks group, n=92 for the repegaldesleukin 18 µg/kg every 2 weeks group, n=102 for the repegaldesleukin 24 µg/kg every 4 weeks group, and n=63 for the placebo group. **Itch NRS response was defined as ≥4-point improvement from baseline in itch NRS in the subset of patients with ≥4-point itch NRS at baseline. ††BSA estimates the extent of disease or skin involvement with respect to atopic dermatitis and is expressed as a percentage of total body surface.				
Table 2: Week 16 efficacy outcomes (modified intention-to-treat population)				

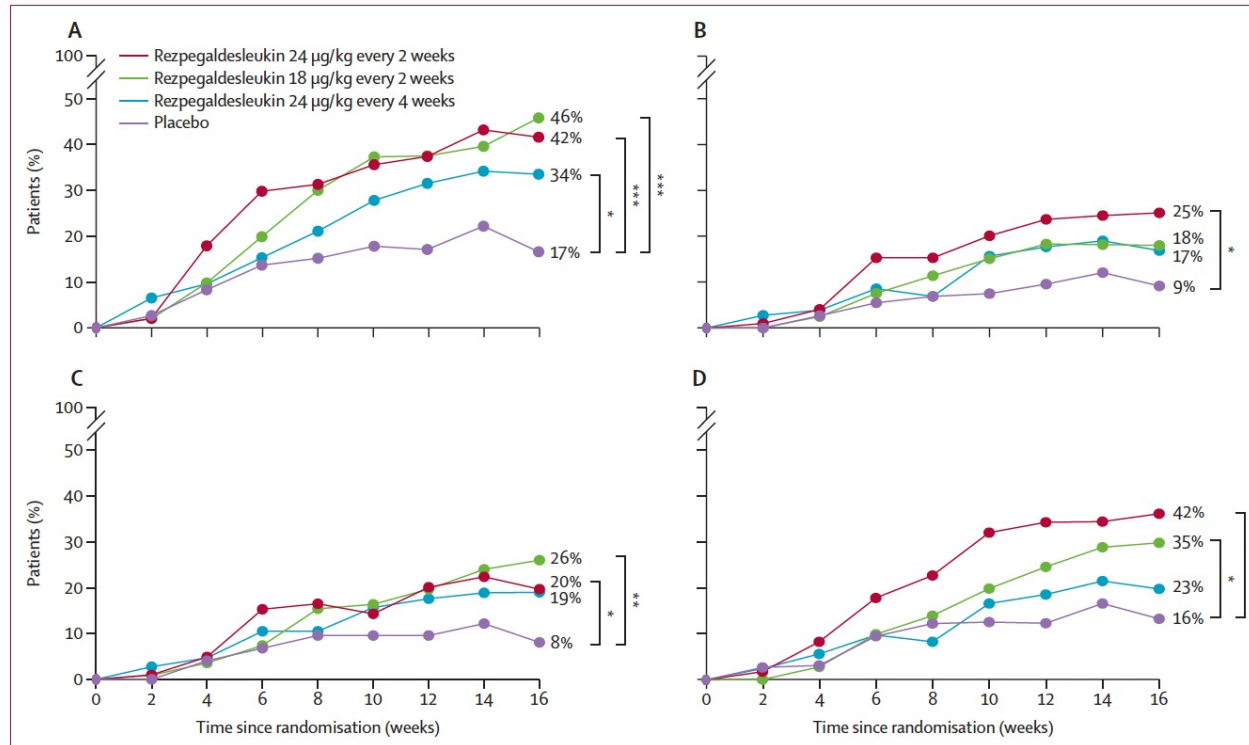


Figure 2: Responses over time for key secondary outcomes (modified intention-to-treat population)

(A) EASI-75 response. (B) EASI-90 response. (C) vIGA-AD response (defined as a score of 0 [clear] or 1 [almost clear] with a reduction from baseline of ≥ 2 points). (D) Itch NRS response (defined as a ≥ 4 -point improvement from baseline in Itch NRS [scores ranging from 0 to 10]) in patients with baseline itch NRS score ≥ 4 . For EASI-75, EASI-90, and vIGA-AD: placebo (n=73), rezpegaldesleukin 24 µg/kg every 2 weeks (n=104), rezpegaldesleukin 18 µg/kg every 2 weeks (n=106), and rezpegaldesleukin 24 µg/kg every 4 weeks (n=110). For Itch NRS: placebo (n=63), rezpegaldesleukin 24 µg/kg every 2 weeks (n=95), rezpegaldesleukin 18 µg/kg every 2 weeks (n=92), and rezpegaldesleukin 24 µg/kg every 4 weeks (n=102). EASI=Eczema Area and Severity Index (range 0–72, with higher scores indicating greater severity). EASI-75=reduction in EASI score by at least 75% relative to baseline score. EASI-90=reduction in EASI score by at least 90% relative to baseline score. NRS=Numerical Rating Scale. vIGA-AD=validated Investigator Global Assessment for Atopic Dermatitis (range from 0 to 4). *p<0.05, **p<0.01, ***p<0.001.

	Rezpegaldesleukin 24 µg/kg every 2 weeks (n=104)	Rezpegaldesleukin 18 µg/kg every 2 weeks (n=106)	Rezpegaldesleukin 24 µg/kg every 4 weeks (n=110)	Rezpegaldesleukin overall (n=320)	Placebo every 2 weeks (n=73)
At least one treatment-emergent adverse event	89 (86%)	78 (74%)	90 (82%)	257 (80%)	42 (58%)
At least one treatment-emergent adverse event (excluding injection-site reactions)	69 (66%)	60 (57%)	64 (58%)	193 (60%)	42 (58%)
At least one serious treatment-emergent adverse event	1 (1%)	4 (4%)	0	5 (2%)	0
At least one severe treatment-emergent adverse event	3 (3%)	6 (6%)	1 (1%)	10 (3%)	1 (1%)
At least one treatment-emergent adverse event leading to death	0	0	0	0	0
At least one treatment-emergent adverse event leading to discontinuation of treatment	8 (8%)	5 (5%)	5 (5%)	18 (6%)	0
Treatment-emergent adverse events reported in ≥5% of patients in any group by system organ class and preferred term					
General disorders and administration-site conditions	80 (77%)	67 (63%)	78 (71%)	225 (70%)	7 (10%)
Injection-site reaction (at least one event)	79 (76%)	66 (62%)	78 (71%)	223 (70%)	3 (4%)
Patients with ≤2 injection-site reactions	54 (52%)	68 (64%)	68 (62%)	190 (59%)	73 (100%)
Pyrexia	11 (11%)	5 (5%)	4 (4%)	20 (6%)	2 (3%)
Infections and infestations	29 (28%)	39 (37%)	32 (29%)	100 (31%)	25 (34%)
Nasopharyngitis	10 (10%)	14 (13%)	14 (13%)	38 (12%)	10 (14%)
Upper respiratory tract infection	7 (7%)	8 (8%)	4 (4%)	19 (6%)	4 (5%)
Blood and lymphatic system disorders	29 (28%)	6 (6%)	11 (10%)	46 (14%)	3 (4%)
Eosinophilia	17 (16%)	4 (4%)	4 (4%)	25 (8%)	2 (3%)
Lymphadenopathy	7 (7%)	1 (1%)	3 (3%)	11 (3%)	0
Musculoskeletal and connective tissue disorders	19 (18%)	5 (5%)	11 (10%)	35 (11%)	3 (4%)
Arthralgia	10 (10%)	2 (2%)	4 (4%)	16 (5%)	1 (1%)
Skin and subcutaneous tissue disorders	12 (12%)	10 (9%)	13 (12%)	35 (11%)	8 (11%)
Dermatitis atopic	2 (2%)	5 (5%)	6 (5%)	13 (4%)	7 (10%)
Nervous system disorders	10 (10%)	10 (9%)	9 (8%)	29 (9%)	6 (8%)
Headache	8 (8%)	6 (6%)	6 (5%)	20 (6%)	3 (4%)
Gastrointestinal disorders	8 (8%)	7 (7%)	11 (10%)	26 (8%)	3 (4%)
Respiratory, thoracic, and mediastinal disorders	6 (6%)	5 (5%)	5 (5%)	16 (5%)	1 (1%)
Investigations	6 (6%)	4 (4%)	3 (3%)	13 (4%)	1 (1%)
Data are number of patients (%). Preferred terms were coded based on the Medical Dictionary for Regulatory Activities version 26.0. The safety population comprised patients who were randomly assigned and received at least one dose of rezpegaldesleukin or placebo, excluding patients enrolled at two sites that were closed due to non-compliance with Good Clinical Practice. No serious or severe adverse events were reported at either of these sites.					
Table 3: Summary of treatment-emergent adverse events during the induction period (safety population)					

Research in context

Evidence before this study

Atopic dermatitis remains challenging to treat despite advances in systemic biological or immunosuppressive therapies targeting dysregulated pathways, including interleukin (IL)-4, IL-13, IL-31, Janus kinase, and OX40. Due to unpredictable or incomplete responses, adverse events, and chronic relapse, there remains an unmet need for efficacious and durable treatment options, with good adverse event profiles, for the management of atopic dermatitis. A disruption of the normal balance of functional regulatory T cells (Tregs) relative to conventional T cells (Tcons) is shared by many autoimmune and inflammatory diseases, including atopic dermatitis. IL-2 plays an essential role in Treg proliferation and survival, with low-dose IL-2 shown to partly rescue Treg function and provide clinical benefit in multiple autoimmune diseases. To date, more than 30 different autoimmune and inflammatory diseases have been treated with low-dose IL-2 therapy in pilot studies and clinical trials, supporting the development of therapeutic agents that restore the homeostatic balance between Tregs and Tcons. Low-dose IL-2, however, has restricted therapeutic practicality, with shortcomings including a narrow therapeutic window and short half-life, requiring frequent dosing and the potential to induce Tcons. Before the start of this study, we searched ClinicalTrials.gov and PubMed for randomised, blinded clinical trials published in English between database inception and May 15, 2023, using keywords “atopic dermatitis” and “regulatory T cells” or “interleukin-2”. Previous phase 1b studies of the IL-2 receptor agonist rezpegaldesleukin for the treatment of atopic dermatitis showed favourable data for safety and efficacy endpoints.

Added value of this study

To the best of our knowledge, this is the first report of a phase 2 clinical trial evaluating a first-in-class IL-2 receptor agonist with preferential activity for Tregs for the treatment of moderate-to-severe atopic dermatitis. The primary endpoint of mean percentage change in Eczema Area and Severity Index (EASI) at week 16 was met with all rezpegaldesleukin dosing regimens (rezpegaldesleukin 24 µg/kg every 2 weeks, rezpegaldesleukin 18 µg/kg every 2 weeks, and rezpegaldesleukin 24 µg/kg every 4 weeks). All key secondary endpoints of disease reduction were also met in the rezpegaldesleukin 24 µg/kg every 2 weeks group, including EASI reduced by at least 75% relative to baseline score, validated Investigator Global Assessment for Atopic Dermatitis score of 0 or 1, EASI reduced by at least 90% relative to baseline score, itch Numerical Rating Scale, and body surface area involvement. No new safety signals were identified.

Implications of all the available evidence

Results from the induction treatment period of this study support and extend the findings from the phase 1b study in patients with atopic dermatitis, showing a favourable adverse event profile and robust efficacy across both physician-assessed and patient-reported endpoints. The combination of consistent efficacy and absence of new safety concerns establishes a positive benefit-risk profile, particularly for patients with few treatment options or tolerability challenges with existing therapies, and supports advancement to phase 3 development. Importantly, this is the first large trial to show modulation of Tregs with clinical benefit, highlighting rezpegaldesleukin's clinical potential as a key target in the treatment paradigm for atopic dermatitis.

Pre-eclampsia

Pre-eclampsia is a multisystem disorder that arises in at least 2–4% of pregnancies and is characterised by hypertension and new-onset organ dysfunction. The pathophysiology of pre-eclampsia is diverse but mostly involves a mismatch between fetoplacental demands and uteroplacental supply, combined with a maternal predisposition to cardiometabolic disease. While our understanding of the mechanisms underlying pre-eclampsia has advanced in recent years, maternal and perinatal mortality remains high in low-income and middle-income countries (LMICs), where pre-eclampsia incidence is higher. Risk factors include maternal chronic hypertension, diabetes, obesity, and previous pre-eclampsia. Preventive strategies include structured behavioural changes focused on diet quality and moderate-intensity physical activity for women with metabolic risk factors, low-dose aspirin for women at high risk, and risk-stratified timed birth at term. To date, the only recourse for pre-eclampsia is delivery of the placenta, and many discrepancies in care remain between high-income countries and LMICs. Current efforts primarily focus on the prediction, accurate diagnosis, and prevention of pre-eclampsia.

Low-dose aspirin helps prevent preeclampsia by improving blood flow to the placenta and reducing blood vessel narrowing.

- **Blocks Thromboxane:** Low-dose aspirin targets an enzyme called COX-1 to stop platelets from making thromboxane A₂, a substance that narrows blood vessels and makes blood cells clump together.

Key messages

- Pre-eclampsia continues to contribute substantially to perinatal morbidity and mortality, disproportionately affecting populations in low-income and middle-income countries (LMICs), and racial and ethnic minority groups
- While delivery of the placenta remains the primary treatment for pre-eclampsia, advances in preventive strategies—eg, behavioural modification, aspirin use, and labour management—have improved outcomes, and calcium supplementation is no longer recommended
- Validation of biomarkers such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) remains a priority and efforts in this area may benefit from advanced analytical approaches (eg, principal component analysis and machine learning) to help characterise disease subtypes and mechanisms
- Addressing persistent research gaps requires strengthening basic science, epidemiology, social science, and clinical trial infrastructure in LMICs, with emphasis on in-country retention and analysis of biological samples and datasets
- International studies involving genetically diverse and historically under-represented populations are needed to distinguish genetic, epigenetic, metagenomic, and nutritional determinants of adverse pregnancy outcomes and their interactions across geographic settings
- Systemic health-care inequities—including limited antenatal care access, workforce shortages, inadequate training and infrastructure, and poor public awareness—should be addressed with structured patient education, postpartum surveillance, coordinated policy reform, and sustained global investment aligned with Sustainable Development Goals.

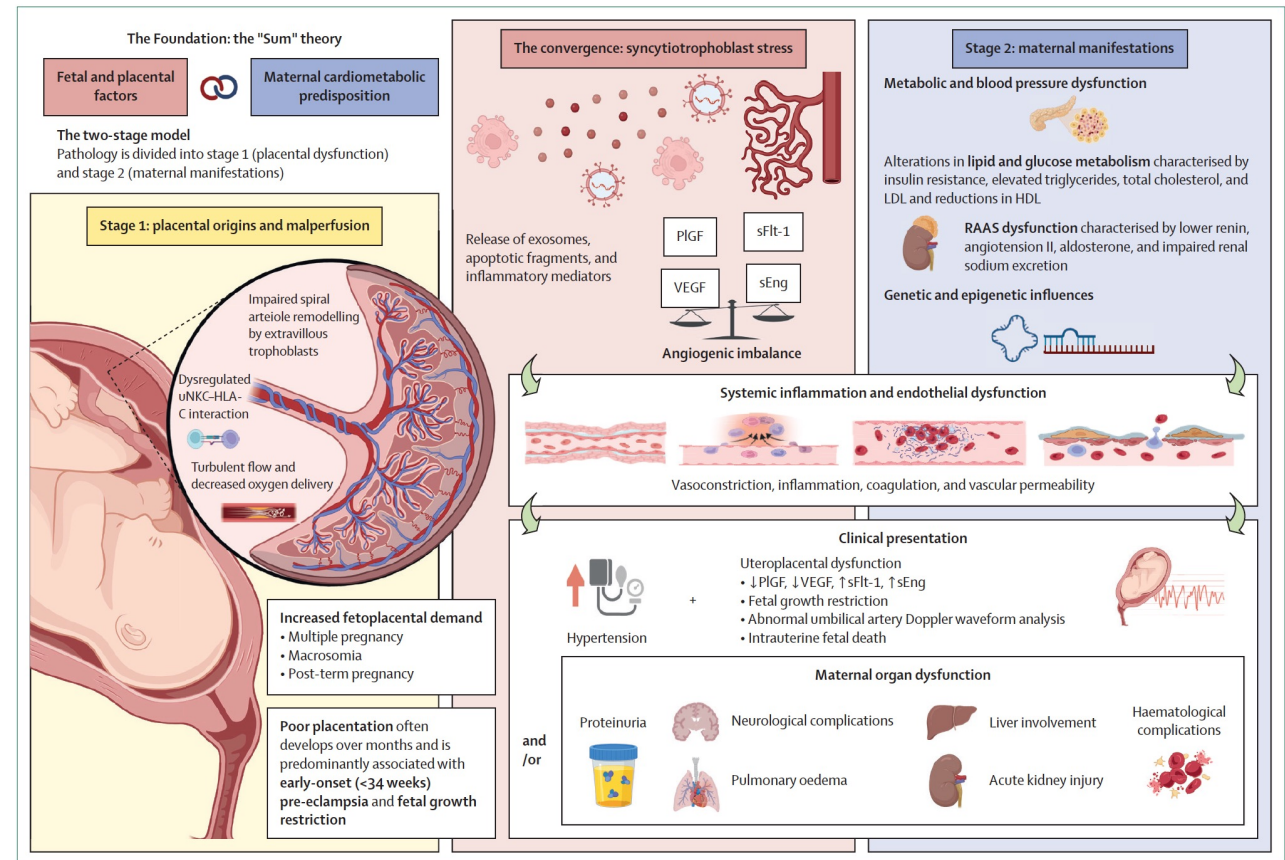


Figure 1: Pathophysiology, mechanisms, and maternal presentation of pre-eclampsia

Representation of the two-stage model with convergence in syncytiotrophoblast stress, which leads to release of placental syncytiotrophoblast stress-derived factors (eg, pro-inflammatory cytokines or placental exosomes and apoptotic fragments) and an imbalance in circulating levels of pro-angiogenic (eg, PlGF and VEGF) and anti-angiogenic factors (eg, sFlt-1 and sEng). Maternal metabolic and endothelial susceptibility will predispose a woman to disease even with less severe perturbations in fetal and placental factors. The result is systemic inflammation and endothelial dysfunction, and ultimately, the maternal and fetal characteristics of pre-eclampsia. Some women will have a mixed underlying pathway to disease. Figure created with BioRender.com. PlGF=placental growth factor. RAAS=renin-angiotensin-aldosterone system. sEng=soluble endoglin. sFlt-1=soluble fms-like tyrosine kinase-1. uNK=uterine natural killer cell. VEGF=vascular endothelial growth factor.

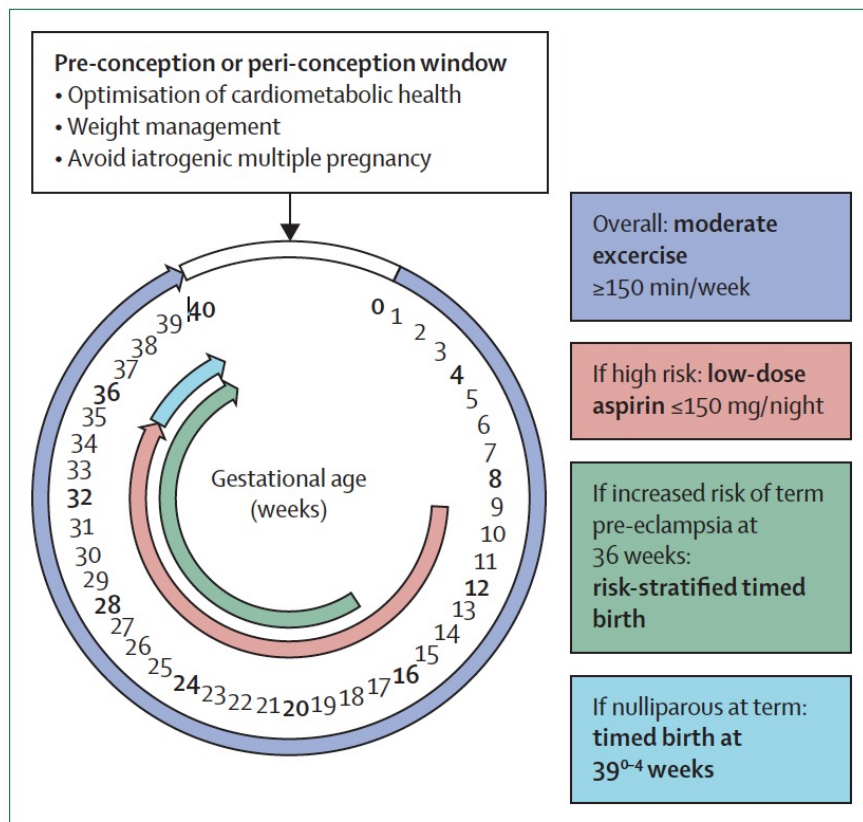


Figure 2: Prevention strategies

The pre-conception or peri-conception period is an important target window for the prevention of pre-eclampsia. Focus should be on optimisation of cardiometabolic health, weight management, and avoidance of iatrogenic multiple pregnancy when possible. Behaviour: exercise and dietary interventions are associated with improved maternal-fetal outcomes, and they are strongly recommended by international guidelines, even for women who were previously inactive. Low-dose aspirin: the most proven intervention for pre-eclampsia prevention is low-dose aspirin, offered to women at high-risk (based on first trimester screening), at a dose of 150 mg per night or lower, started before 16 weeks, and discontinued at 36 weeks (or 10 days before planned birth if earlier). Calcium: supplementation with calcium should be recommended to prevent pre-eclampsia (preterm and term) among the population with low-calcium (900 mg/day or lower) intake. Timed birth: labour induction reduces pre-eclampsia in women who are nulliparous and low risk at 39⁰⁻⁴ weeks, and among those at high risk of term pre-eclampsia, following risk-stratified timed birth. Figure created with BioRender.com.

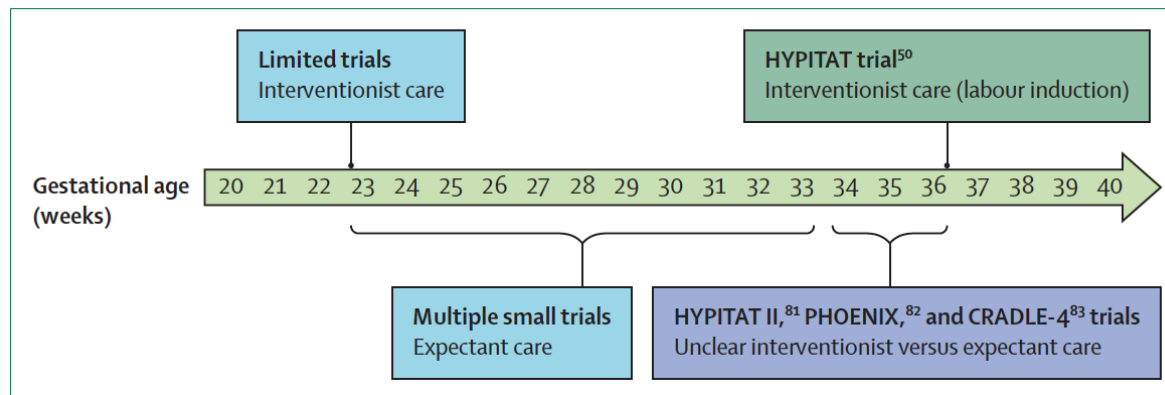


Figure 3: Timing of birth

At term gestational age, the HYPITAT trial findings suggest that interventionist (vs expectant) care, via labour induction, is associated with less maternal morbidity when antihypertensive therapy is not administered for non-severe hypertension.⁵⁰ At 34⁹ to 36⁶ weeks, optimal timing of birth is less clear. Two large definitive randomised controlled trials from high-income countries (HYPITAT II⁸¹ and PHOENIX)⁸² have shown that interventionist (vs expectant) care reduces maternal but increases neonatal morbidity. While most information about timed birth comes from high-income countries, the CRADLE-4 trial from India and Zambia⁸³ found no significant difference between interventionist and expectant care in the co-primary maternal or perinatal composite outcomes of mortality or morbidity, although interventionist care was associated with less severe hypertension and fewer stillbirths. From fetal viability until 33⁶ weeks, expectant care of pre-eclampsia is recommended. Small randomised controlled trials (six trials, n=748 pre-eclamptic pregnancies) indicate that while interventionist care is associated with fewer infants who are small-for-gestational age, they are more likely to have morbidity and stay longer in the neonatal intensive care unit, without any associated decrease in complications for mothers.⁸⁴ For pre-eclampsia complicated by severe hypertension, heavy proteinuria, or end-organ involvement, very low to low quality evidence from small randomised controlled trials (four trials, n=430) and non-randomised studies (six studies, n=455) have shown interventionist (vs expectant) care is associated with more neonatal morbidity, and does not reduce maternal risks.⁸⁵ Around peri-viability (defined based largely on resources), interventionist care is recommended,⁸⁴ because expectant care is commonly associated with maternal complications and fetal and newborn prognosis is poor.⁸⁶ Figure created with BioRender.com.

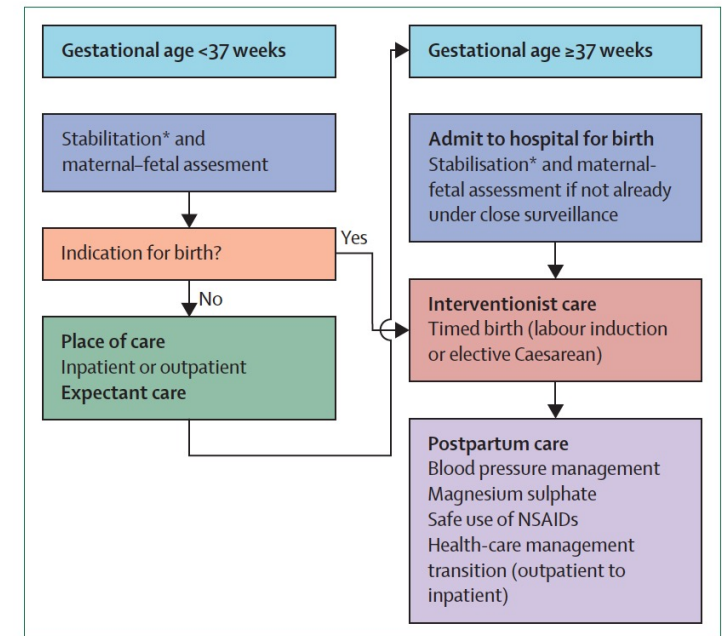


Figure 4: Management and treatment approaches

Supportive care aims to minimise adverse outcomes, and considers the place of care, maternal-fetal surveillance, blood pressure management, and magnesium sulphate. Antihypertensive therapy is part of blood pressure management and is recommended for all antenatal hypertension. Renin-angiotensin-aldosterone inhibitors are fetotoxic and contraindicated for ongoing use in pregnancy. Magnesium sulphate dose is 4 g intravenous, then infusion of 1–2 g/h for 24 hours, which can halve the risk of eclampsia occurrence or recurrence. Place of care: outpatient management can be considered where resources allow and when blood pressure is controlled, there is no end-organ involvement that requires daily, in-person assessment, and women can be relied upon to report new symptoms and can return to hospital within 30 min. NSAID=non-steroidal anti-inflammatory drug. *Antihypersensitive therapy to normalise blood pressure and consider magnesium sulphate.

Novel therapies and future directions

Emerging solutions

Therapeutic options developed for other conditions have been repurposed for pre-eclampsia prevention and treatment.¹³⁶ Immunomodulatory therapies have also been considered. Monoclonal antibodies that target complement have received particular interest.⁶⁰ Another emerging field is placental gene therapy targeting angiogenic imbalance.¹³⁷ However, there is a notable scarcity of evidence supporting the translation of these potential therapies into clinical practice. Technical challenges associated with vector delivery methods, ethical concerns, and restricted accessibility of these treatment options, particularly in LMICs, should be addressed before clinical translation.¹³⁷ These therapies are summarised in the appendix (pp 1–3).

Research gaps, challenges, and the call to action

To address research gaps, it is essential that capacity is strengthened for basic science, social science, epidemiology, and clinical trials research in LMICs. Data and biological samples stemming from research should be retained and, whenever possible, analysed in-country. Comparative studies of women of distinct genetic backgrounds living in different geographies would help to discern between genetic, epigenetic, metagenomic, and nutritional determinants of adverse pregnancy outcomes, and how they interact. There are at-risk populations that have been historically under-represented in such studies (eg, North American Indigenous Peoples and Pacific Islanders), and it should be recognised that there is greater genetic diversity in African populations than elsewhere.

Ein **Stopcodon** ist eine Abfolge von drei Nukleotiden in der mRNA, die das Ende der Proteinbiosynthese anzeigt.

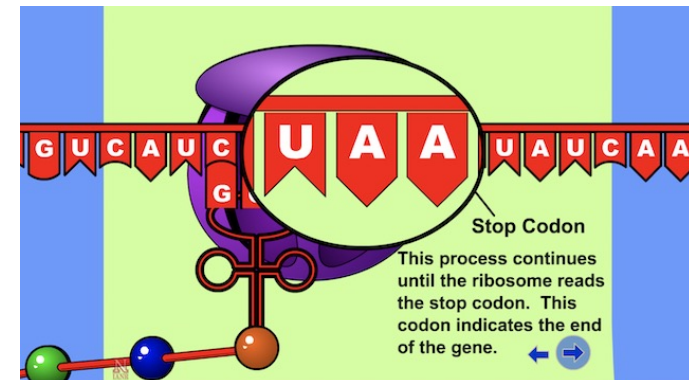
Funktion: Es signalisiert dem Ribosom, dass die Übersetzung der mRNA in ein Protein beendet ist.

- **Keine Aminosäure:** Für Stopcodons gibt es keine passenden tRNA-Moleküle, die eine Aminosäure anbringen.
- **Freisetzung:** Stattdessen binden Release-Faktoren an das Codon und lösen die fertige Aminosäurenkette ab.

Die drei normalen Stopcodons

- **UAA** (*Ochre*): Wird oft als "U are annoying" gemerkt.
- **UAG** (*Amber*): Wird oft als "U are gone" gemerkt.
- **UGA** (*Opal* oder *Umber*): Wird oft als "U go away" gemerkt.

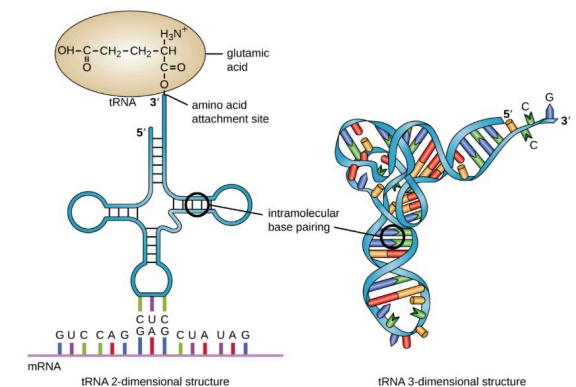
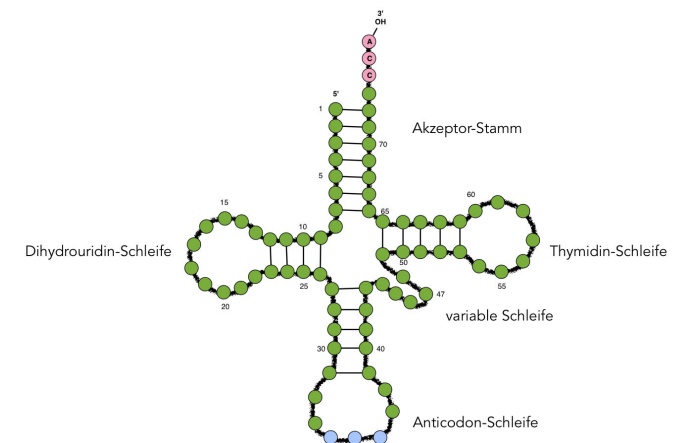
Ein anschauliches Video zur Proteinbiosynthese und den Signalen des genetischen Codes:

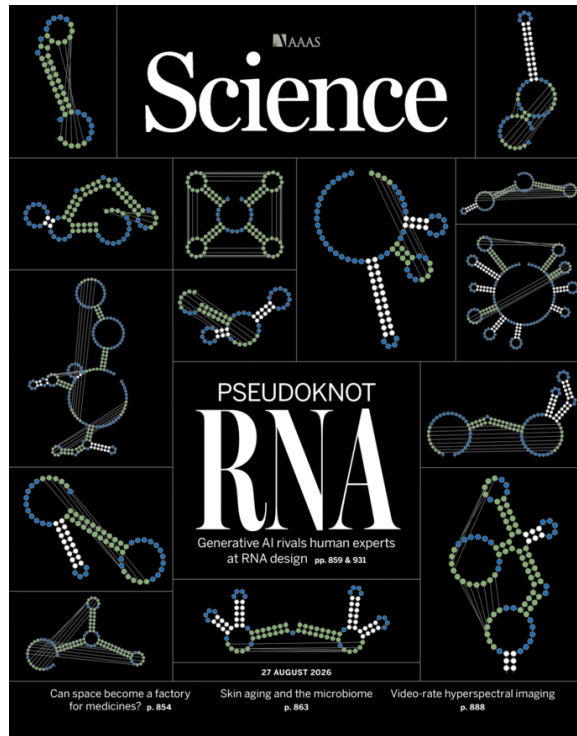


Die **tRNA** (Abkürzung für **Transfer-RNA**) ist ein kurzes **Ribonukleinsäure-Molekül** (bestehend aus ca. 73 bis 95 Nukleotiden), das als zentrales Bindeglied bei der **Proteinbiosynthese** (genauer bei der Translation am Ribosom) dient, indem es **spezifische Aminosäuren** zu den Ribosomen transportiert.

Sekundärstruktur (Kleeblattstruktur): Durch intramolekulare Basenpaarung faltet sich der Einzelstrang zu einer charakteristischen Kleeblatt-Form mit drei markanten Schleifen.

- **Tertiärstruktur (L-Form):** Im dreidimensionalen Raum nimmt die tRNA eine L-förmige Gestalt an, bei der die funktionell wichtigsten Enden möglichst weit voneinander entfernt liegen.
- **Akzeptorstamm (3'-Ende):** Tragt die konstante Basensequenz **CCA** und dient als kovalente Bindungsstelle für die spezifische Aminosäure.
- **Anticodonschleife:** Enthält ein aus drei Basen bestehendes **Anticodon**, das komplementär zum jeweiligen Codon auf der mRNA ist.
- **Weitere Schleifen:** Die **D-Schleife** (Dihydrouridin) und die **TψC-Schleife** (Thymidin-Pseudouridin-Cytidin) unterstützen die Erkennung durch Enzyme und die Bindung am Ribosom

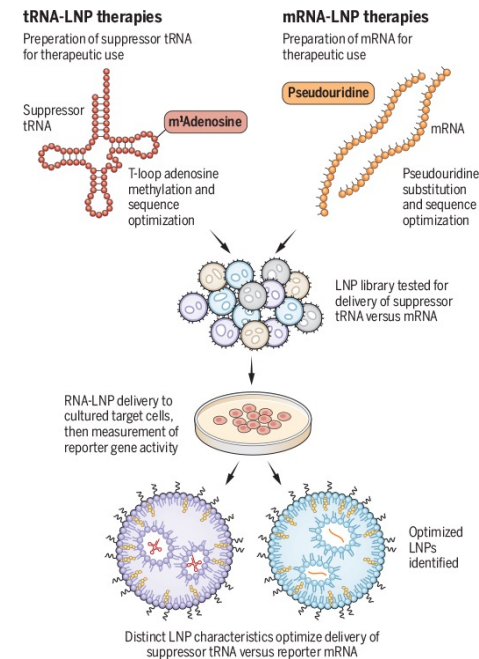




Pseudouridin (abgekürzt mit dem griechischen Buchstaben Psi, Ψ) ist ein natürlich vorkommendes, modifiziertes Nukleosid, das in allen lebenden Zellen zu finden ist. Es entsteht durch die chemische Umwandlung (Isomerisierung) des regulären RNA-Bausteins Uridin. Pseudouridin dämpft das Immunsystem.

Rethink the cargo, rethink the carrier

Chen *et al.* report reengineering tRNAs and tailoring lipid nanoparticles (LNPs) for the delivery of tRNA to enhance suppressor tRNA efficacy in animal and organoid models of cystic fibrosis. The findings are a promising step toward tRNA medicines for genetic diseases.



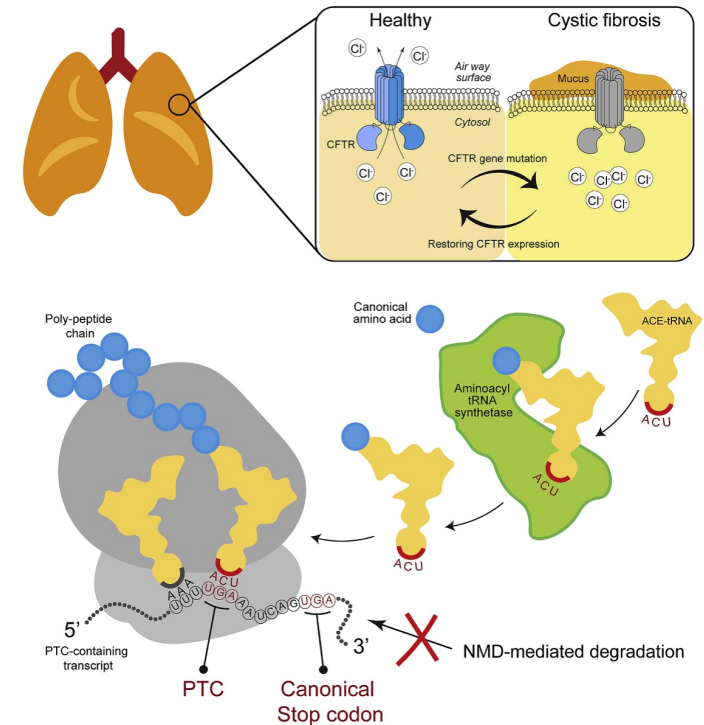
Nonviral delivery of chemically modified tRNA rescues nonsense mutations in cystic fibrosis

INTRODUCTION: Nonsense mutations introduce premature termination codons (PTCs) into messenger RNAs (mRNAs), preventing full-length protein production and accounting for ~11% of human genetic diseases. Current therapeutic strategies remain limited: Gene-editing approaches can face challenges related to delivery, immunogenicity, and off-target effects, whereas pharmacological readthrough agents have shown limited efficacy or considerable toxicity. **Suppressor transfer RNAs (sup-tRNAs), whose anticodons are engineered to read through PTCs, offer an RNA-level strategy for restoring endogenous protein synthesis without altering the genome.** This reversibility, transcript-level action, limited detectable off-target activity, and potential applicability across diseases sharing the same nonsense codon make sup-tRNAs attractive therapeutic candidates. However, their therapeutic translation has been limited by suboptimal readthrough, immune activation, short functional persistence, and inefficient delivery to disease-relevant tissues.

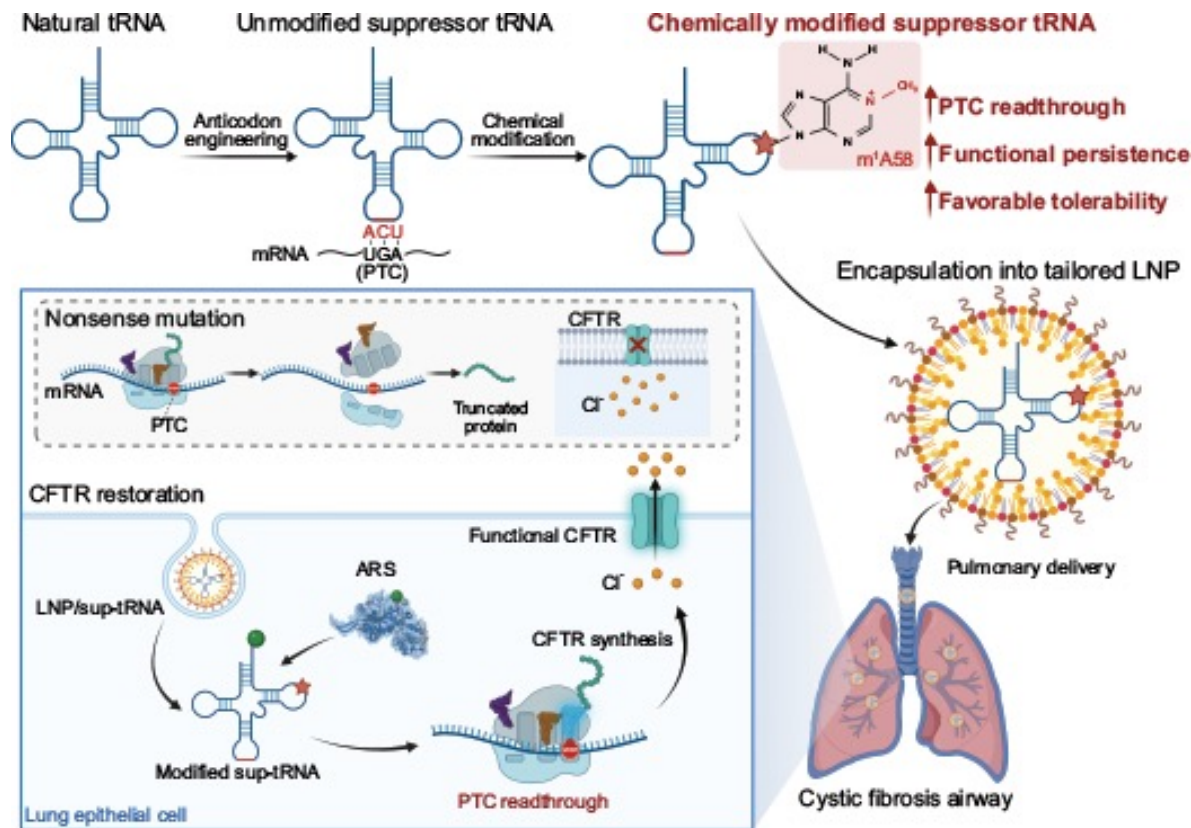
RATIONALE: RNA modifications have emerged as key regulators of RNA stability, translation, immunogenicity, and therapeutic performance. Mature endogenous tRNAs are extensively modified for shaping tRNA folding, stability, aminoacylation, decoding, and interactions with the translational machinery. We thus hypothesized that **installing defined chemical modifications into engineered sup-tRNAs could improve their activity and suitability as medicines.** In parallel, effective translation of tRNA therapeutics requires cargo-tailored delivery vehicles capable of efficiently transporting structured tRNA molecules to disease-relevant tissues. We combined site-specific tRNA engineering with a large lipid nanoparticle (LNP) screen to develop a nonviral delivery platform optimized for sup-tRNA cargo. We used cystic fibrosis (CF) as a disease model to evaluate the therapeutic efficacy of this sup-tRNA platform because nonsense mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene represent an unmet clinical need.

Suppressor-tRNAs überbrücken Stopcodons durch eine Mutation in ihrem eigenen Anticodon, wodurch sie anstelle eines Terminationsfaktors an ein Stopcodon (UAA, UAG oder UGA) binden können. Sie lesen das Stopcodon wie ein normales, protein-codierendes Codon ab und fügen eine Aminosäure in die wachsende Proteinkette ein, was als **Translational Readthrough** bezeichnet wird.

- **Die Mutation im Anticodon:** Eine normale tRNA, die für eine bestimmte Aminosäure (z. B. Tyrosin) codiert, mutiert so, dass ihr Anticodon komplementär zu einem Stopcodon wird.
- **Die biochemische Konkurrenz:** Erreicht das Ribosom bei der Translation ein Stopcodon auf der mRNA, binden dort normalerweise Proteine – die sogenannten Freisetzungsfaktoren oder **Release Factors**. Die Suppressor-tRNA steht nun in direkter Konkurrenz zu diesen Release Factors um den Platz in der A-Stelle des Ribosoms.
- **Der Einbau der Aminosäure:** Gewinnt die Suppressor-tRNA diesen biochemischen Wettbewerb, bindet sie an das Stopcodon. Das Ribosom setzt die Translation fort, lädt die mitgebrachte Aminosäure auf das Peptid und das Protein wird in voller Länge synthetisiert (anstatt vorzeitig abgebrochen zu werden)



RESULTS: We synthesized various chemically modified sup-tRNAs and systematically tested the effects of site-specific modifications. **Incorporation of N¹-methyadenosine (m¹A) at position 57 or 58 improved sup-tRNA function, increasing PTC readthrough by up to 10.6-fold for an arginine sup-tRNA.** This modification also improved aminoacylation, increased functional persistence, reduced innate immune activation, and benefited sup-tRNAs charged with different amino acids. Screening more than 1000 ionizable lipids identified TTP-3 (tRNA-tailored pulmonary delivery–3), an LNP optimized for sup-tRNA cargo. After intratracheal administration in mice, TTP-3 LNPs efficiently delivered sup-tRNAs to airway epithelial and progenitor cells and showed preliminary aerosolization compatibility. Mango II aptamer insertion enabled in vivo tracking of sup-tRNA biodistribution, revealing delivery to epithelial progenitor cells relevant to CFTR expression and airway repair. In CFTR-mutant bronchial epithelial cells, modified sup-tRNAs restored CFTR protein expression and channel activity. In a CFTR R553X mouse model, LNP–sup-tRNA treatment improved CFTR dependent swelling in intestinal organoids. In a CF patient–derived organoid model carrying a complex CFTR genotype, cotreatment with sup-tRNAs and Trikafta restored CFTR function, consistent with complementary restoration of protein production and modulator-responsive CFTR activity.



LNP delivery of chemically modified sup-tRNAs for pulmonary nonsense-mutation rescue.

Sup-tRNAs decode PTCs to overcome nonsense mutations. Chemical RNA modifications improved sup-tRNA therapy efficacy by enhancing PTC readthrough and functional persistence while reducing immune activation. A tailored LNP delivered modified sup-tRNAs to airway epithelial cells after intratracheal administration, restoring full-length CFTR production and chloride-channel function. ARS, aminoacyl-tRNA synthetase

Getting past premature termination codons (PTCs) with suppressor transfer RNAs

CONCLUSION: This work establishes a chemically modified, nonvirally delivered sup-tRNA platform for rescuing disease-causing nonsense mutations. Site-specific m¹A57/58 modification provides a chemical strategy for enhancing sup-tRNA activity, persistence, and tolerability, whereas TTP-3 LNPs illustrate the importance of cargo-specific delivery design for structured tRNA therapeutics. The aptamer-tagging approach further provides a general method for tracking tRNA biodistribution and cell type targeting in vivo. These findings provide broadly applicable engineering insights for the future development of tRNA-based medicines.

Measles' role in child's death ignites fight between RFK Jr. and Pennsylvania governor



Minutes before a news conference announcing two measles-related deaths in Pennsylvania, Gov. Josh Shapiro (D) had a heated call with the Trump administration's top health official.

Before television cameras on Tuesday, the governor accused Health Secretary Robert F. Kennedy Jr. of sowing confusion about vaccines and contributing to the return of a disease the United States eliminated more than a quarter-century ago. Shapiro said he told Kennedy that the state did not want additional help from the federal government.

The exchange has erupted into an extraordinary public feud and set off a partisan flurry of accusations over outbreaks of the highly contagious disease, which is easily prevented by a vaccine. Shapiro and Kennedy have traded lengthy barbs on social media, accusing each other of fearmongering.