

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

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

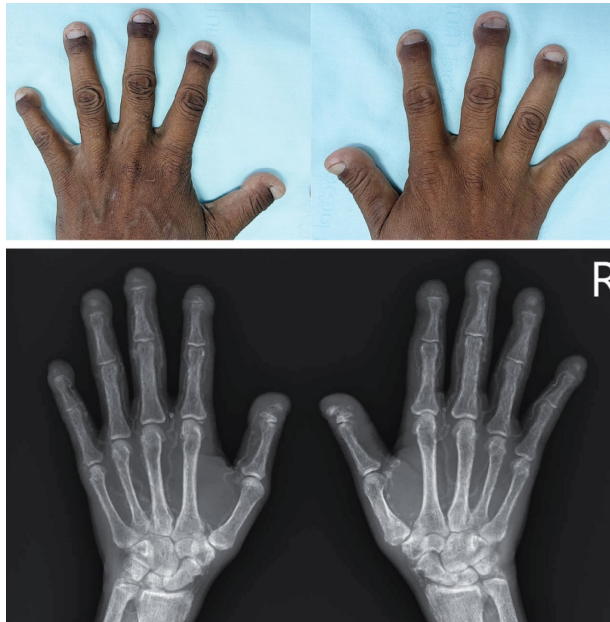
Usually every Wednesday 17:00 - 18:00



Klinische Forschung

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

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



Radiographs of the hands showed resorption of the terminal tufts of all the phalanges, a finding consistent with acro-osteolysis. Acro-osteolysis is associated with several conditions, including systemic sclerosis, Raynaud's phenomenon, exposure to vinyl chloride, and thermal injury. In this case, renal osteodystrophy and tertiary hyperparathyroidism in the context of end-stage kidney disease were identified as the underlying causes.

A 46-year-old man with chronic kidney disease presented with a 2-year history of painless shortening and rounding of the fingertips. Ten years earlier, he had received a diagnosis of chronic kidney disease due to obstructive nephropathy from nephrolithiasis. Since then, he had been intermittently lost to follow-up. On physical examination, all the fingertips were short, broad, and bulbous, with a pseudoclubbing appearance. The toes had similar but less severe changes. What do the findings on the exam and imaging represent?



Acro-osteolysis

Arthritis mutilans

Clubbing (Trommelschlägelfinger)

Hypertrophic osteoarthropathy

Sclerodactyly

Als Akroosteolyse bezeichnet man den krankhaften Abbau und Schwund von Knochengewebe an den Endgliedern der Finger und Zehen. Sie ist kein eigenständiges Krankheitsbild, sondern ein Symptom, das bei verschiedenen rheumatischen, genetischen oder durch Umwelteinflüsse ausgelösten Grunderkrankungen im Körper auftritt. **Häufige Ursachen:**

- **Kollagenosen:** Besonders die systemische Sklerodermie und das Raynaud-Syndrom führen durch Durchblutungsstörungen oft zu diesem Knochenschwund.
- **Endokrine Störungen:** Ein Hyperparathyreoidismus (Überfunktion der Nebenschilddrüse) stört den Calciumhaushalt.
- **Äußere Einwirkungen:** Schwere Verbrennungen, Erfrierungen oder Verletzungen der Finger und Zehen.
- **Giftstoffe:** Längerer Kontakt mit Vinylchlorid (früher oft bei der Arbeit in der Plastikindustrie).
- **Genetische Syndrome:** Seltene erbliche Erkrankungen wie das Hajdu-Cheney-Syndrom.



Helfen Schleimlöser auf ITS?

Guide on Intensive Care Unit or High Dependency Care Unit (ICU/HD)



“
My uncle met with an accident and was seriously injured. He was warded in the ICU for comprehensive care. He had tubes and drains put onto him.

We were very worried and concerned by his condition. We wanted to be with him at all times to do whatever we could to help him.

What is the Intensive Care Unit?

The Intensive Care Unit (ICU) is a specialised section of the hospital that provides comprehensive and continuous care for persons who are critically ill and who can benefit from treatment.

Our Intensive Care team consists of doctors, nurses, pharmacists, respiratory therapists, dietitians and physiotherapists.

Our nurses will orientate patients and their families to be familiar with the ICU environment.

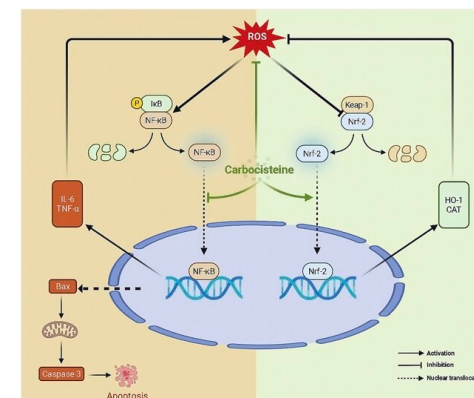
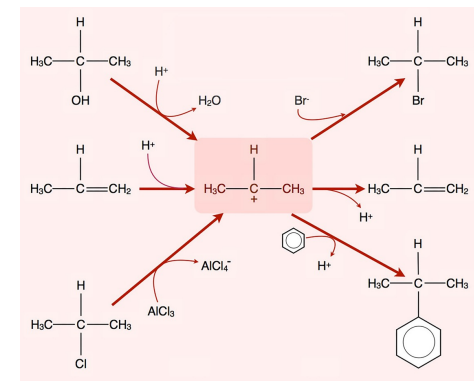
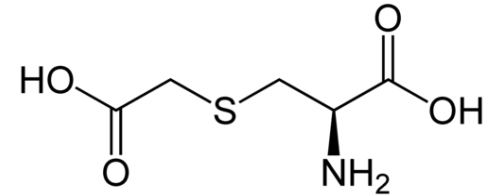


Stimmt das alles?

Carbocystein (auch Carbocistein) ist ein schleimlösender Arzneistoff aus der Gruppe der Mukolytika, der bei Atemwegserkrankungen mit zähem Schleim wie Bronchitis oder COPD eingesetzt wird, um den abhusbaren Schleim zu verflüssigen. **Wirkung und Anwendung:**

- **Schleimlösung:** Macht zähes Bronchialsekret dünnflüssiger.
- **Einsatzgebiete:** Akuter Husten, Bronchitis und chronische Atemwegserkrankungen (COPD).
- **Eigenschaften:** Wirkt neben der Verflüssigung auch entzündungshemmend und antioxidativ.

Der Wirkstoff hemmt die sogenannten Becherzellen in der Bronchialschleimhaut. Dadurch verändert sich die Zusammensetzung des Sekrets: Der Körper produziert weniger von dem zähen, dicken Schleim und stattdessen mehr dünnflüssige Flüssigkeit. Durch diese veränderte Konsistenz kann der Schleim leichter durch die Flimmerhärchen abtransportiert und abgehustet werden.

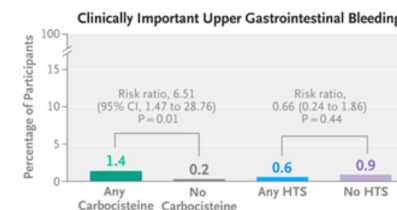
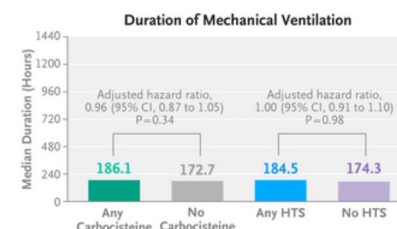
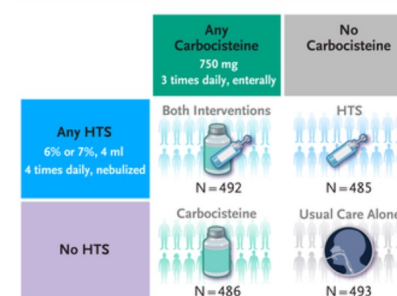
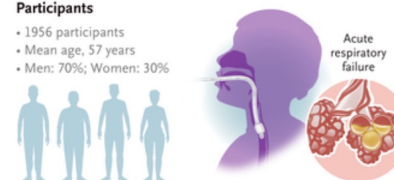


Carbocisteine or Hypertonic Saline for Acute Respiratory Failure

Mucoactive agents are widely used in patients with acute respiratory failure despite limited evidence of their effectiveness or safety. We conducted a multicenter, open-label, randomized trial with a 2-by-2 factorial design that involved critically ill, mechanically ventilated participants 16 years of age or older with acute respiratory failure and difficult-to-clear secretions. All participants received usual care along with carbocisteine (750 mg three times daily enterally), 6% or 7% nebulized hypertonic saline (HTS) (4 ml four times daily), both interventions, or usual care alone for up to 28 days. The primary outcome was duration of mechanical ventilation (from randomization to first successful unassisted breathing). The primary comparisons were between any carbocisteine and no carbocisteine and between any HTS and no HTS, with each comparison comprising two treatment groups.

Participants

- 1956 participants
- Mean age, 57 years
- Men: 70%; Women: 30%



Acute respiratory failure is the most common cause of patient admission to an intensive care unit (ICU). Invasive mechanical ventilation confers a predisposition to retained airway secretions secondary to disrupted mucociliary clearance and altered secretion properties (e.g., volume and rheologic properties). To address this, mucoactive agents are often used in patients with difficult-to-clear secretions. International data show that **mucoactive agents have been used in more than 80% of ICUs** and in **approximately 20 to 30% of patients receiving invasive mechanical ventilation**, with carbocisteine (a mucoregulator) and hypertonic saline (an expectorant) being the most commonly used mucoactive agent. A systematic review from 2020 concluded that the available evidence for use of mucoactive agents in patients with acute respiratory failure was limited. No data were available to support or refute the use of carbocisteine, and findings for hypertonic saline were inconsistent and of low quality. Therefore, we conducted a trial to evaluate the clinical effectiveness of carbocisteine and hypertonic saline in combination with usual care, as compared with usual care alone, in patients 16 years of age or older with acute respiratory failure.

Methods

Trial Design and Oversight

The MARCH (Mucoactives in Acute Respiratory Failure: Carbocisteine and Hypertonic Saline) trial was a phase 3, open-label, randomized trial with a 2-by-2 factorial design that involved critically ill participants with acute respiratory failure.

Participants

Eligible participants were 16 years of age or older, were receiving invasive mechanical ventilation for acute respiratory failure, and had difficult-to-clear secretions as determined according to clinician judgment. Key exclusion criteria were routine mucoactive use for preexisting chronic respiratory conditions, mucoactive treatment that had commenced more than 24 hours before trial enrollment, and known adverse reaction to either carbocisteine or hypertonic saline.

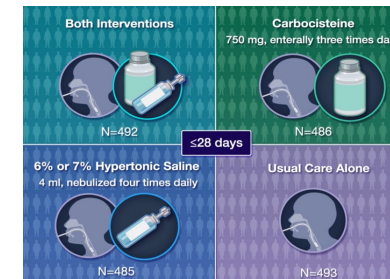
Interventions

All the participants received usual care and were also randomly assigned to receive carbocisteine alone (750 mg three times daily, administered enterally for up to 28 days), nebulized 6% or 7% hypertonic saline alone (4 ml four times daily for up to 28 days), [a combination of carbocisteine and hypertonic saline, or usual care alone.](#)

Outcomes

The primary outcome was the duration of mechanical ventilation, which was defined as the time (in hours) from randomization to first successful unassisted breathing (with unassisted breathing being maintained for 48 hours) or death.

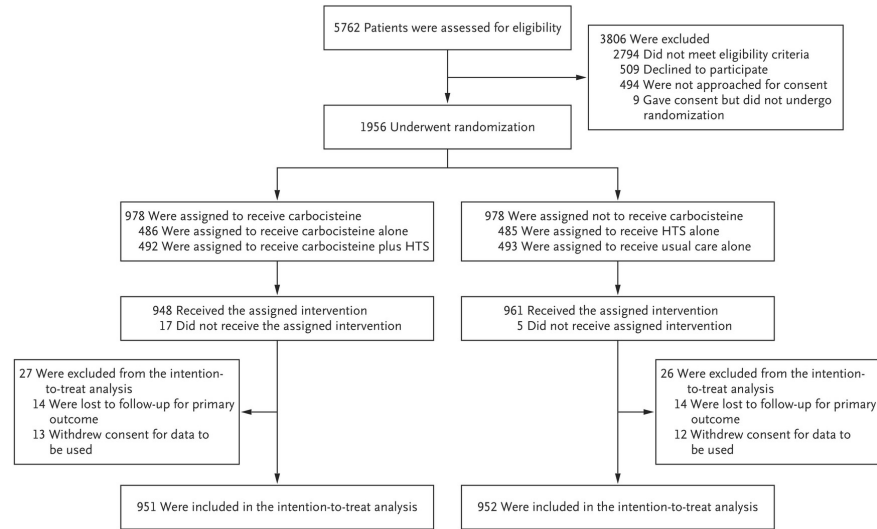
Characteristic	Any Carbocisteine (N=965)	No Carbocisteine (N=966)	Any HTS (N=967)	S (N=964)
Age — yr	56.7±15.4	57.5±14.5	56.6±15.1	57.7±14.8
Sex — no. (%)				
Male	667 (69.1)	682 (70.6)	678 (70.1)	671 (69.6)
Female	298 (30.9)	284 (29.4)	289 (29.9)	293 (30.4)
Race — no. (%)†				
White	832 (86.2)	837 (86.6)	831 (85.9)	838 (86.9)
Black	19 (2.0)	26 (2.7)	23 (2.4)	22 (2.3)
Asian	29 (3.0)	28 (2.9)	26 (2.7)	31 (3.2)
Unknown	83 (8.6)	71 (7.3)	83 (8.6)	71 (7.4)
Other	2 (0.2)	4 (0.4)	4 (0.4)	2 (0.2)
Functional Comorbidity Index‡	1.6±1.4	1.6±1.4	1.6±1.4	1.6±1.4
ICU admission diagnostic category — no. (%)§				
Respiratory system	290 (30.1)	261 (27.0)	284 (29.4)	267 (27.7)
Central nervous system	148 (15.3)	191 (19.8)	158 (16.3)	181 (18.8)
Cardiovascular system	165 (17.1)	153 (15.8)	149 (15.4)	169 (17.5)
Chronic respiratory condition	198 (20.5)	212 (21.9)	217 (22.4)	193 (20.0)
Neurologic diagnosis	240 (24.9)	256 (26.5)	242 (25.0)	254 (26.3)
Currently receiving antibiotics to treat a pulmonary infection	689 (71.4)	693 (71.7)	686 (70.9)	696 (72.2)
Presence of ARDS	202 (20.9)	204 (21.1)	206 (21.3)	200 (20.7)
APACHE II score¶				
Mean — points	17.2±6.8	17.0±6.3	17.2±6.6	17.0±6.5
Participants with available data — no.	964	966	967	963
SOFA score				
Mean — points	9.3±3.6	9.4±3.5	9.4±3.6	9.3±3.5
Participants with available data — no.	789	800	793	793
Tidal volume				
Mean — ml	470.6±150.8	466.2±146.5	467.7±149.7	469.1±147.7
Participants with available data — no.	952	952	954	950
Total respiratory rate				
Mean rate — breaths/min	20.7±5.9	20.8±5.9	20.7±5.9	20.8±5.9
Participants with available data — no.	961	963	965	959
PEEP				
Mean — cm of water	8.2±2.7	8.3±2.8	8.3±2.8	8.2±2.7
Participants with available data — no.	956	954	957	953
Pao ₂ /Fio ₂ ratio				
Mean — mm Hg	221.1±87.5	224.0±97.8	224.6±96.1	220.4±89.3
Participants with available data — no.	953	957	957	953
Paco ₂				
Mean — kPa	5.8±1.3	5.8±1.4	5.8±1.4	5.8±1.3
Participants with available data — no.	954	956	958	952
pH				
Mean	7.40±0.08	7.40±0.08	7.41±0.08	7.40±0.08
Participants with available data — no.	953	960	960	953
Type of humidification — no./total no. (%)				
Heated humidification	694/886 (78.3)	687/907 (75.7)	698/899 (77.6)	683/894 (76.4)
Heat moisture exchange	189/886 (21.3)	214/907 (23.6)	199/899 (22.1)	204/894 (22.8)
Other	3/886 (0.3)	6/907 (0.7)	2/899 (0.2)	7/894 (0.8)



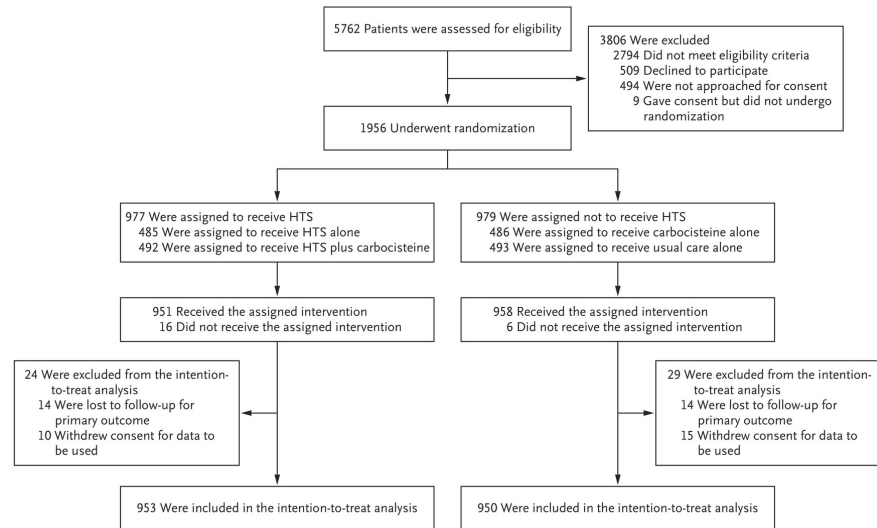
Primary and Secondary Outcomes.

Outcome	Any Carbocisteine	No Carbocisteine	Difference, Any Carbocisteine vs. No Carbocisteine (95% CI)	Any HTS	No HTS	Difference, Any HTS vs. No HTS (95% CI)
Primary outcome: duration of mechanical ventilation						
Median duration (95% CI) — hr†	186.1 (168.3 to 196.6)	172.7 (165.2 to 190.4)	0.96 (0.87 to 1.05)‡	184.5 (165.6 to 194.1)	174.3 (166.9 to 192.7)	1.00 (0.91 to 1.10)§
No. of participants with available data	951	952		953	950	
Secondary outcomes¶ 						
Time to the first successful extubation**						
Median duration (95% CI) — hr†	352.4 (283.1 to 428.2)	356.9 (287.3 to 448.6)	1.03 (0.92 to 1.15)	403.0 (308.7 to 455.2)	321.5 (262.8 to 402.9)	1.00 (0.89 to 1.11)
No. of participants with available data	955	953		958	950	
Reintubation — no./total no. (%)††	50/965 (5.2)	49/966 (5.1)	1.02 (0.70 to 1.50)	56/967 (5.8)	43/964 (4.5)	1.30 (0.88 to 1.91)
Receipt of respiratory physiotherapy — no./total no. (%)††‡‡	955/965 (99.0)	951/966 (98.5)	1.01 (1.00 to 1.02)	953/967 (98.6)	953/964 (98.9)	1.00 (0.91 to 1.10)
Frequency of respiratory physiotherapy‡‡‡§§						
Median no. of sessions (95% CI)	8.0 (7.7 to 9.0)	8.0 (8.0 to 9.0)	-0.17 (-1.07 to 0.72)	8.0 (7.0 to 9.0)	8.0 (8.0 to 9.0)	0.04 (-0.86 to 0.94)
No. of participants with available data	955	951		953	953	
Duration of antibiotic use §§						
Median no. of days (95% CI)	9.0 (8.0 to 9.0)	8.0 (8.0 to 9.0)	-0.68 (-1.77 to 0.41)	9.0 (8.0 to 9.0)	8.0 (8.0 to 9.0)	-0.21 (-1.31 to 0.88)
No. of participants with available data	749	758		746	761	
Duration of ICU stay¶¶§§						
Median no. of days (95% CI)	14.0 (13.0 to 15.0)	14.0 (13.0 to 15.0)	1.01 (0.92 to 1.11)	14.0 (13.0 to 15.0)	14.0 (13.0 to 15.0)	1.04 (0.95 to 1.14)
No. of participants with available data	951	949		955	945	
Duration of hospital stay¶¶§§						
Median no. of days (95% CI)	29.0 (27.0 to 31.0)	27.0 (25.0 to 29.0)	1.03 (0.91 to 1.17)	29.0 (26.0 to 31.0)	28.0 (26.0 to 30.0)	1.04 (0.94 to 1.14)
No. of participants with available data	929	922		928	923	
Death from any cause — no./total no. (%)††						
By day 28	220/965 (22.8)	229/966 (23.7)	0.96 (0.82 to 1.13)	216/967 (22.3)	233/964 (24.2)	0.92 (0.79 to 1.09)
By day 60	245/965 (25.4)	269/966 (27.9)	0.91 (0.79 to 1.06)	248/967 (25.7)	266/964 (27.6)	0.93 (0.80 to 1.08)
By month 6	276/965 (28.6)	292/966 (30.2)	0.95 (0.82 to 1.09)	281/967 (29.1)	287/964 (29.8)	0.98 (0.85 to 1.12)

A Any Carbocisteine vs. No Carbocisteine

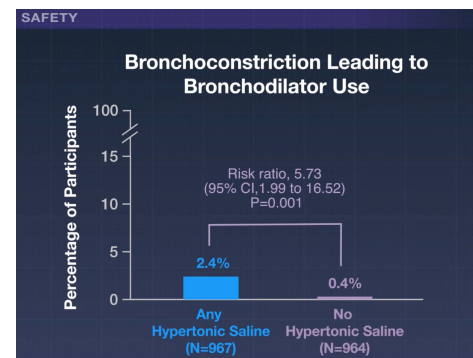
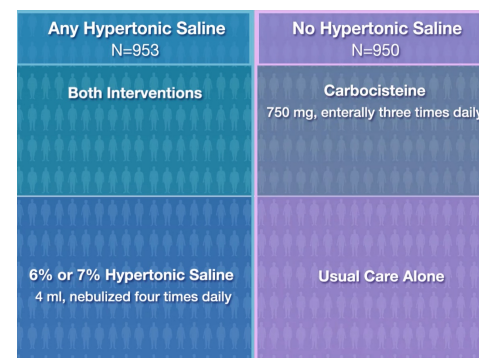
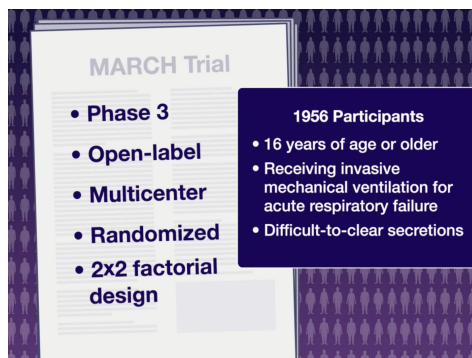
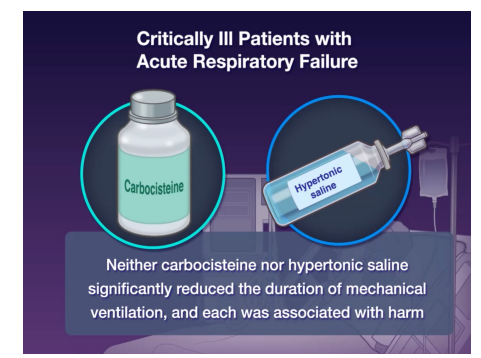
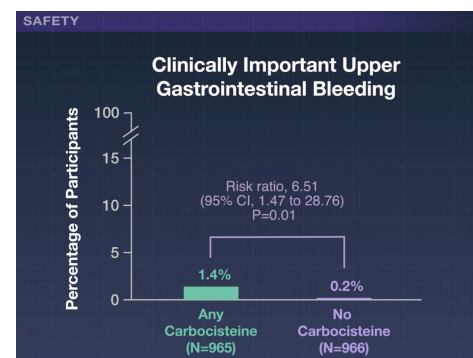
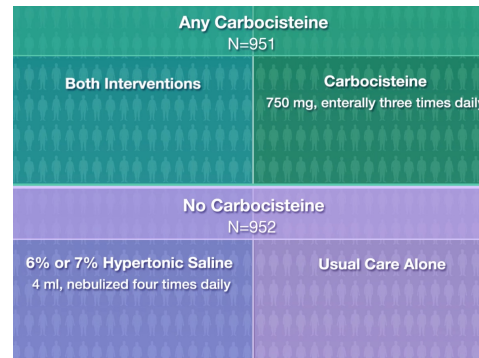
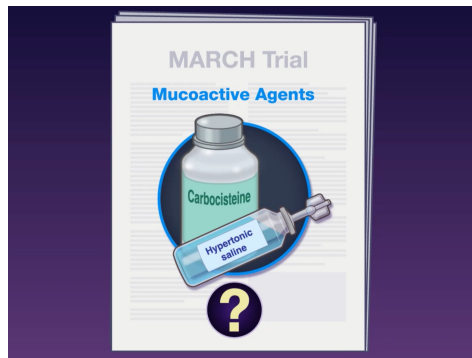
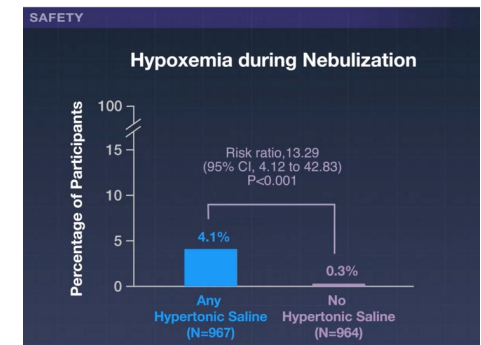
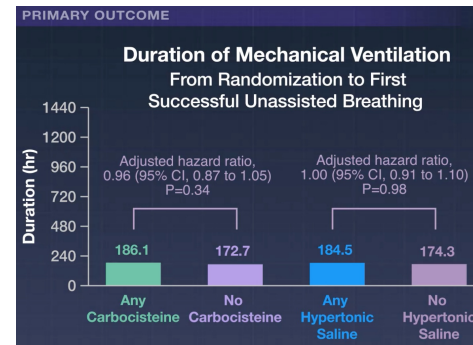
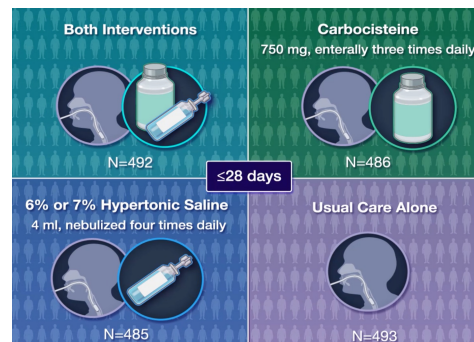
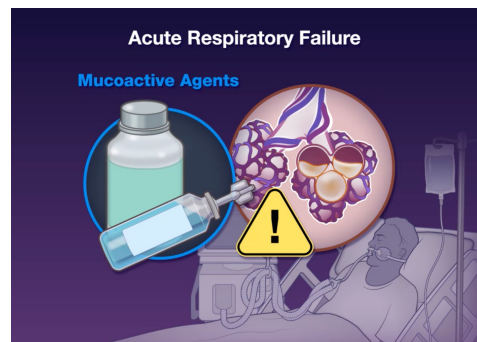


B Any HTS vs. No HTS



Safety Outcomes.

Outcome	Treatment and Comparison Groups				Risk Ratio [95% CI]	P Value§
Clinically important upper GI bleeding due to peptic ulceration confirmed on upper GI endoscopy	Carbocisteine Alone	HTS Alone	Combination	Usual Care Alone		
No. of participants with event/ total no. (%)	7/479 (1.5)	0/481	6/486 (1.2)	2/485 (0.4)		
	Any Carbocisteine	No Carbocisteine	Any HTS	No HTS		
No. of participants with event/ total no. (%)	13/965 (1.4)	2/966 (0.2)	6/967 (0.6)	9/964 (0.9)		
Any carbocisteine vs. no carbocisteine					6.51 (1.47 to 28.76)	0.01
Any HTS vs. no HTS					0.66 (0.24 to 1.86)	0.44
Bronchoconstriction leading to nebulized bronchodilator use	Carbocisteine Alone	HTS Alone	Combination	Usual Care Alone		
No. of participants with event/ total no. (%)	2/479 (0.4)	12/481 (2.5)	11/486 (2.3)	2/485 (0.4)		
	Any Carbocisteine	No Carbocisteine	Any HTS	No HTS		
No. of participants with event/ total no. (%)	13/965 (1.4)	14/966 (1.5)	23/967 (2.4)	4/964 (0.4)		
Any carbocisteine vs. no carbocisteine					0.93 (0.44 to 2.00)	0.85
Any HTS vs. no HTS					5.73 (1.99 to 16.52)	0.001
Ventilator or circuit dysfunction with respiratory deterioration	Carbocisteine Alone	HTS Alone	Combination	Usual Care Alone		
No. of participants with event/ total no. (%)	2/479 (0.4)	6/481 (1.2)	6/486 (1.2)	4/485 (0.8)		
	Any Carbocisteine	No Carbocisteine	Any HTS	No HTS		
No. of participants with event/ total no. (%)	8/965 (0.8)	10/966 (1.0)	12/967 (1.2)	6/964 (0.6)		
Any carbocisteine vs. no carbocisteine					0.80 (0.32 to 2.02)	0.64
Any HTS vs. no HTS					1.99 (0.75 to 5.29)	0.17
Hypoxemia during nebulization	Carbocisteine Alone	HTS Alone	Combination	Usual Care Alone		
No. of participants with event/ total no. (%)	1/479 (0.2)	20/481 (4.2)	20/486 (4.1)	2/485 (0.4)		
	Any Carbocisteine	No Carbocisteine	Any HTS	No HTS		
No. of participants with event/ total no. (%)	21/965 (2.2)	22/966 (2.3)	40/967 (4.1)	3/964 (0.3)		
Any carbocisteine vs. no carbocisteine					0.96 (0.53 to 1.73)	0.88
Any HTS vs. no HTS					13.29 (4.12 to 42.83)	<0.001



50 years of „slime loosening“ all useless and harmful

Der medizinische Fachbegriff „**Wheezing**“ bezeichnet ein **pfeifendes, Giemen oder keuchendes Atemgeräusch** bei Kindern, das meistens beim **Ausatmen** auftritt. Es entsteht, wenn die tieferen Atemwege (die Bronchien) verengt oder blockiert sind. Bei Kleinkindern und Babys ist dieses Symptom extrem häufig: **Etwa 30 bis 40 Prozent aller Kinder** erleben bis zu ihrem 6. Lebensjahr mindestens eine solche Episode. Da die Atemwege bei kleinen Kindern noch sehr eng sind, führen Schwellungen dort viel schneller zu Geräuschen. **Mögliche Ursachen**

- **Virusinfektionen:** Häufig ausgelöst durch einfache Erkältungsviren oder das RS-Virus (RSV). Man spricht dann von einem *infektassoziierten Wheezing*.
- **Asthma bronchiale:** Wheezing kann ein Vorläufer oder Symptom von frühkindlichem Asthma sein, besonders wenn es wiederholt und ohne Infekt auftritt.
- **Allergien:** Überempfindlichkeiten (z.B. gegen Pollen oder Hausstaubmilben) können die Bronchien verengen.
- **Verschluckte Fremdkörper:** Wenn ein Kind plötzlich ohne vorherige Erkältung zu pfeifen beginnt, besteht immer die Gefahr, dass ein kleiner Gegenstand oder Essensteilchen in die Atemwege gelangt ist

ALLERGIEN UND ASTHMA BEI KINDERN

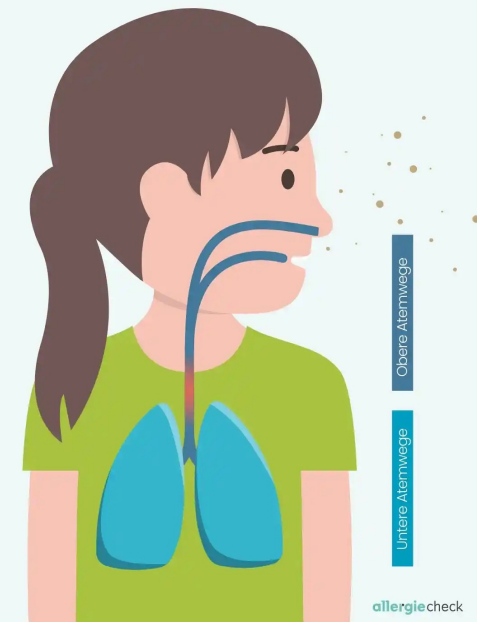
Allergieauslöser wie Hausstaubmilben und Pollen können Entzündungen in der Nase verursachen, die bis in die Lungen herunterwandern können.

ALLERGIE- SYMPTOME

- Verstopfte oder laufende Nase
- Juckende Nase
- Niesen

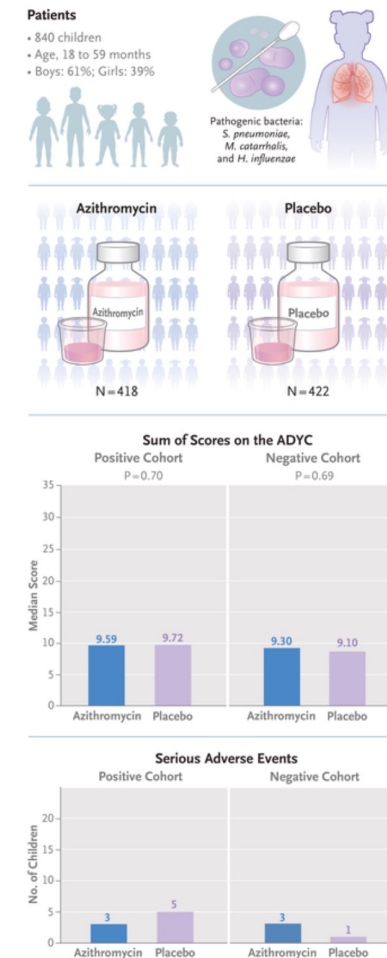
ASTHMA- SYMPTOME

- Husten und pfeifende Atmung (Giemen)
- Atembeschwerden
- Engegefühl in der Brust



Azithromycin for Preschoolers with Wheezing in the Emergency Department

Wheezing illnesses are a leading cause of hospitalization for preschool-age children and are frequently treated with antibiotics. Observational studies have shown more frequent isolation of three pathogenic bacteria (*Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*) from nasopharyngeal samples from children with recurrent episodes of wheezing than from those without such illnesses. In this multicenter trial, we randomly assigned patients 18 to 59 months of age who presented to an emergency department with a moderate-to-severe episode of wheezing to receive azithromycin once daily at a dose of 12 mg per kilogram of body weight or matching placebo for 5 days. The primary outcome was the sum of scores on the Asthma Flare-up Diary for Young Children (ADYC) over 5 days. Primary-outcome scores could range from 5 to 35, with higher scores indicating more severe wheezing-related symptoms. Efficacy was assessed separately in patients who tested positive for pathogenic bacteria (the positive cohort) and in those who tested negative (the negative cohort). Secondary outcomes were length of stay in the emergency department, length of hospital stay, and return emergency department visits or hospitalizations within 72 hours. Bacterial clearance and antimicrobial resistance were measured at follow-up visits 1 to 3 weeks after randomization.



Lower respiratory illnesses that present with wheezing are a major cause of respiratory distress and health care utilization in early life. Azithromycin has both antiinflammatory and antibacterial effects, and its potential role in treating wheezing illnesses in preschool-age children could be attributable to one or both of these properties. None of the studies described above assessed efficacy in association with nasopharyngeal bacterial colonization, which may help to elucidate the mechanism of action of azithromycin in the treatment of wheezing illnesses.

Given that up to **one fourth of wheezing episodes** among preschoolers are treated with **antibiotics**, we conducted the Azithromycin Therapy in Preschoolers with a Severe Wheezing Episode Diagnosed at the Emergency Department (AZ-SWED) trial to evaluate whether a **5-day course** of azithromycin decreases the severity of illness in young children presenting to the emergency department with wheezing, with separate analyses according to the **presence** or **absence** of nasopharyngeal colonization with *S. pneumoniae*, *M. catarrhalis*, or *H. influenzae*.

Methods

Trial Design and Oversight

We conducted this randomized, placebo-controlled, clinical trial at eight pediatric emergency departments in the United States that are affiliated with the Pediatric Emergency Care Applied Research Network.

Patients

The target population was children 18 to 59 months of age who presented to the emergency department with a moderate-to-severe episode of expiratory wheezing (as ascertained by emergency department care providers). Children were assessed according to the Pediatric Respiratory Assessment Measure (PRAM) by trained care providers (e.g., physicians, nurse practitioners, and nurses) as soon as possible after arrival in the emergency department, and assessments were periodically updated. PRAM scores range from 0 to 12, with higher scores indicating greater severity of the acute wheezing episode. Children were eligible for the trial if they had a PRAM score of 4 or higher, which indicates moderate-to-severe symptoms, at any time during the visit to the emergency department.

Randomization, Interventions, and Procedures

Patients were randomly assigned to receive one dose (12 mg per kilogram of body weight) of azithromycin or placebo orally each day for 5 days.

Outcome Measures

The primary outcome was the sum of scores on the [Asthma Flare-up Diary for Young Children \(ADYC\)](#) over the 5 days after randomization, as reported by caregivers. The ADYC is a previously validated Web-based measure with 17 questions, each of which is scored on a scale from 1 to 7.

Demographic and Clinical Characteristics of the Patients at Baseline.

Characteristic	Positive Cohort			Negative Cohort		
	Azithromycin (N=257)	Placebo (N=264)	Overall (N=521)	Azithromycin (N=158)	Placebo (N=154)	Overall (N=312)
Demographic characteristics						
Male sex — no./total no. (%)	155/257 (60.3)	164/263 (62.4)	319/520 (61.3)	102/158 (64.6)	91/154 (59.1)	193/312 (61.9)
Age group — no. (%)						
18 to <24 mo	44 (17.1)	59 (22.3)	103 (19.8)	18 (11.4)	21 (13.6)	39 (12.5)
24 to <36 mo	102 (39.7)	91 (34.5)	193 (37.0)	40 (25.3)	44 (28.6)	84 (26.9)
36 to <48 mo	69 (26.8)	66 (25.0)	135 (25.9)	54 (34.2)	51 (33.1)	105 (33.7)
48 to <60 mo	42 (16.3)	48 (18.2)	90 (17.3)	46 (29.1)	38 (24.7)	84 (26.9)
Race or ethnic group — no. (%)†						
American Indian or Alaska Native	0	1 (0.4)	1 (0.2)	2 (1.3)	0	2 (0.6)
Asian	6 (2.3)	3 (1.1)	9 (1.7)	1 (0.6)	2 (1.3)	3 (1.0)
Black or African American	109 (42.4)	124 (47.0)	233 (44.7)	84 (53.2)	80 (51.9)	164 (52.6)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.2)	1 (0.6)	0	1 (0.3)
White	96 (37.4)	91 (34.5)	187 (35.9)	46 (29.1)	47 (30.5)	93 (29.8)
Multiracial	13 (5.1)	12 (4.5)	25 (4.8)	9 (5.7)	8 (5.2)	17 (5.4)
Unknown	32 (12.5)	33 (12.5)	65 (12.5)	15 (9.5)	17 (11.0)	32 (10.3)
Hispanic or Latino ethnic group — no. (%)†						
Yes	49 (19.1)	53 (20.1)	102 (19.6)	28 (17.7)	35 (22.7)	63 (20.2)
No	201 (78.2)	206 (78.0)	407 (78.1)	129 (81.6)	116 (75.3)	245 (78.5)
Unknown or not reported	7 (2.7)	5 (1.9)	12 (2.3)	1 (0.6)	3 (1.9)	4 (1.3)
Clinical characteristics						
Admitted to the hospital — no./total no. (%)‡	123/257 (47.9)	138/263 (52.5)	261/520 (50.2)	77/158 (48.7)	78/154 (50.6)	155/312 (49.7)
Received other antibiotics in emergency department — no./total no. (%)	4/257 (1.6)	3/263 (1.1)	7/520 (1.3)	3/158 (1.9)	2/154 (1.3)	5/312 (1.6)
PRAM score for eligibility§						
Mean	6.0±1.78	6.2±1.81	6.1±1.80	6.5±1.91	6.6±1.97	6.5±1.94
Category — no. (%)						
4–7	202 (78.6)	205 (77.7)	407 (78.1)	116 (73.4)	114 (74.0)	230 (73.7)
8–12	55 (21.4)	59 (22.3)	114 (21.9)	42 (26.6)	40 (26.0)	82 (26.3)
Fever — no./total no. (%)¶	32/256 (12.5)	50/262 (19.1)	82/518 (15.8)	13/157 (8.3)	17/153 (11.1)	30/310 (9.7)

PRAM score for eligibility§						
Mean	6.0±1.78	6.2±1.81	6.1±1.80	6.5±1.91	6.6±1.97	6.5±1.94
Category — no. (%)						
4–7	202 (78.6)	205 (77.7)	407 (78.1)	116 (73.4)	114 (74.0)	230 (73.7)
8–12	55 (21.4)	59 (22.3)	114 (21.9)	42 (26.6)	40 (26.0)	82 (26.3)
Fever — no./total no. (%)¶	32/256 (12.5)	50/262 (19.1)	82/518 (15.8)	13/157 (8.3)	17/153 (11.1)	30/310 (9.7)
Primary care visits for wheezing in past year — no./total no. (%)						
0	74/237 (31.2)	77/242 (31.8)	151/479 (31.5)	47/146 (32.2)	41/143 (28.7)	88/289 (30.4)
1	36/237 (15.2)	50/242 (20.7)	86/479 (18.0)	23/146 (15.8)	43/143 (30.1)	66/289 (22.8)
>1	127/237 (53.6)	115/242 (47.5)	242/479 (50.5)	76/146 (52.1)	59/143 (41.3)	135/289 (46.7)
Emergency department or urgent care visits for wheezing in past year — no./total no. (%)						
0	68/243 (28.0)	70/248 (28.2)	138/491 (28.1)	38/145 (26.2)	38/145 (26.2)	76/290 (26.2)
1	59/243 (24.3)	54/248 (21.8)	113/491 (23.0)	34/145 (23.4)	48/145 (33.1)	82/290 (28.3)
>1	116/243 (47.7)	124/248 (50.0)	240/491 (48.9)	73/145 (50.3)	59/145 (40.7)	132/290 (45.5)
Wheezing-related hospitalizations in past year — no./total no. (%)						
0	144/241 (59.8)	157/248 (63.3)	301/489 (61.6)	93/147 (63.3)	93/144 (64.6)	186/291 (63.9)
1	59/241 (24.5)	48/248 (19.4)	107/489 (21.9)	31/147 (21.1)	30/144 (20.8)	61/291 (21.0)
>1	38/241 (15.8)	43/248 (17.3)	81/489 (16.6)	23/147 (15.6)	21/144 (14.6)	44/291 (15.1)
Antibiotics taken in past year — no./total no. (%)	86/231 (37.2)	73/239 (30.5)	159/470 (33.8)	44/135 (32.6)	47/135 (34.8)	91/270 (33.7)
Inhaled glucocorticoids taken in past year — no./total no. (%)	99/232 (42.7)	84/241 (34.9)	183/473 (38.7)	57/140 (40.7)	58/140 (41.4)	115/280 (41.1)
Oral glucocorticoids taken in past year — no./total no. (%)	126/234 (53.8)	125/241 (51.9)	251/475 (52.8)	89/147 (60.5)	72/142 (50.7)	161/289 (55.7)
Positivity of nasopharyngeal swab sample — no. (%)						
Human rhinovirus	176 (68.5)	203 (76.9)	379 (72.7)	116 (73.4)	109 (70.8)	225 (72.1)
Human respiratory syncytial virus	27 (10.5)	33 (12.5)	60 (11.5)	10 (6.3)	7 (4.5)	17 (5.4)
Bocavirus	19 (7.4)	11 (4.2)	30 (5.8)	5 (3.2)	3 (1.9)	8 (2.6)
Human metapneumovirus	16 (6.2)	6 (2.3)	22 (4.2)	4 (2.5)	5 (3.2)	9 (2.9)
Human parainfluenza virus	8 (3.1)	9 (3.4)	17 (3.3)	3 (1.9)	4 (2.6)	7 (2.2)
Any combination of viruses	19 (7.4)	20 (7.6)	39 (7.5)	10 (6.3)	7 (4.5)	17 (5.4)
Negative for all tested viruses — no. (%)	37 (14.4)	23 (8.7)	60 (11.5)	26 (16.5)	30 (19.5)	56 (17.9)

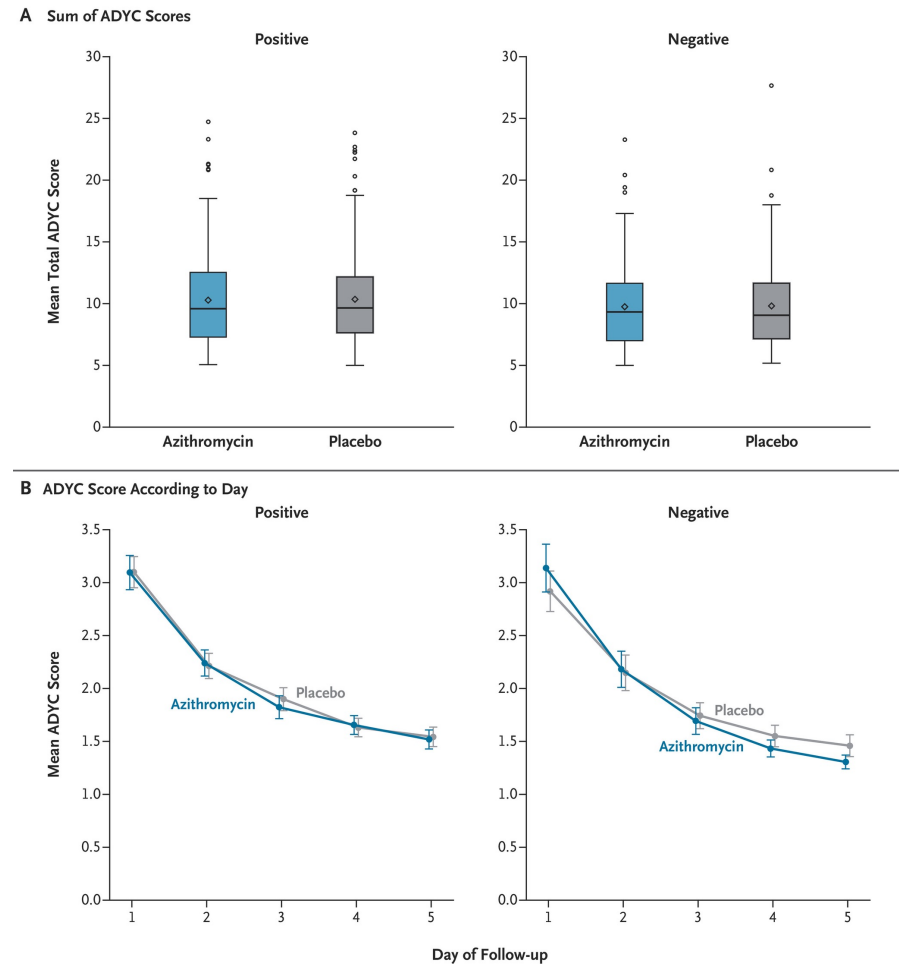
No differences across the groups

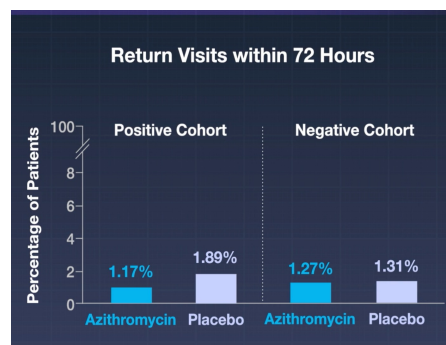
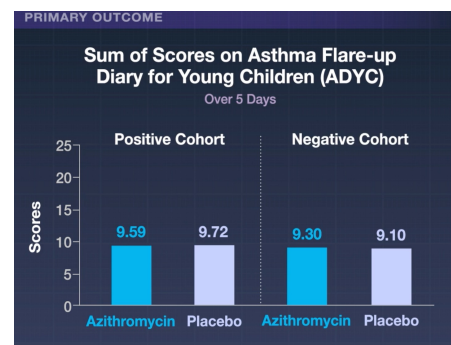
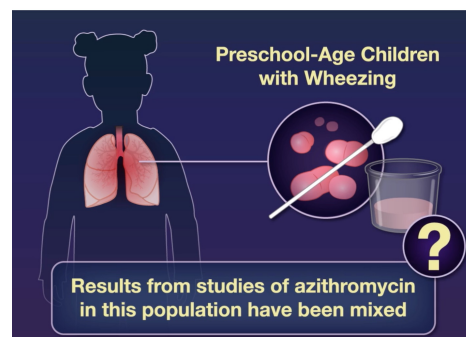
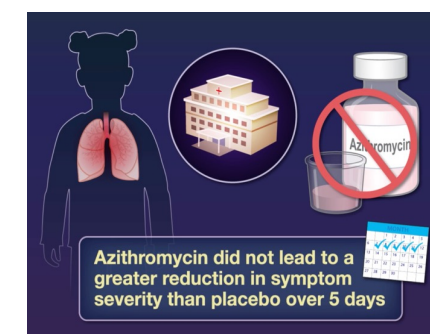
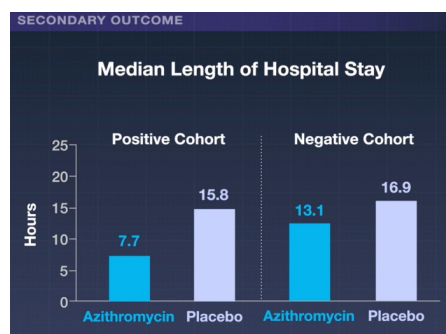
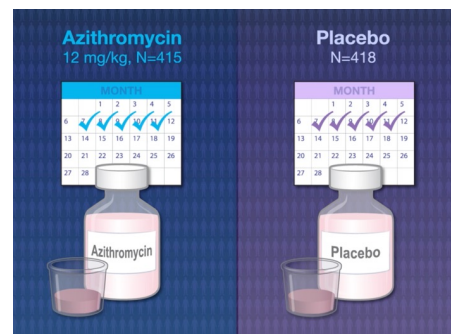
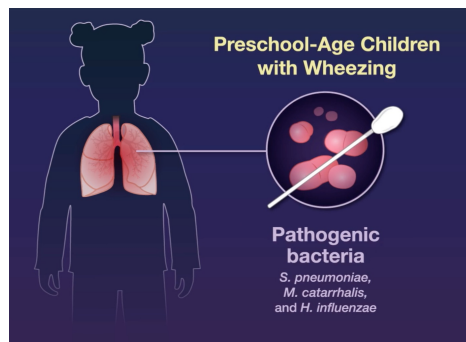
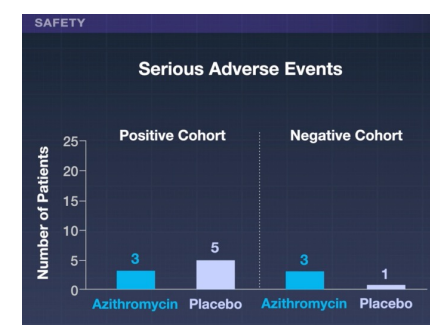
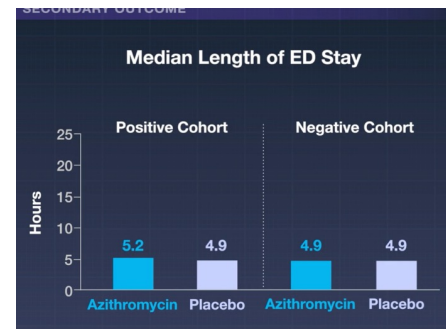
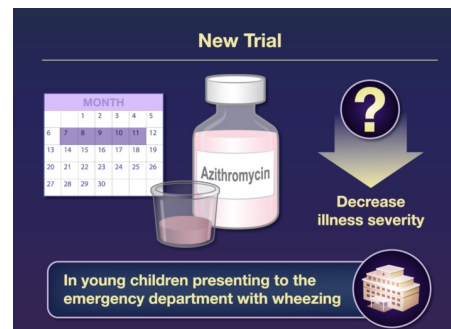
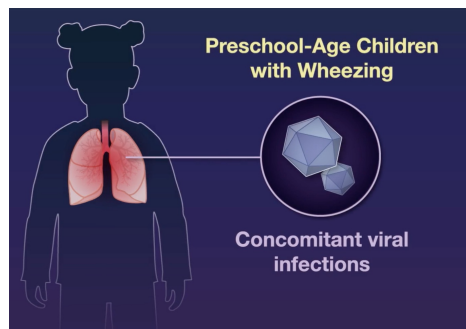
Primary and Secondary Outcomes.

Outcome	Positive Cohort			Negative Cohort		
	Azithromycin (N=257)	Placebo (N=264)	Difference in Means or Risk Ratio (97.5% CI)†	Azithromycin (N=158)	Placebo (N=154)	Difference in Means or Risk Ratio (97.5% CI)†
Primary outcome						
Sum of scores on ADYC‡						
Median (IQR)	9.59 (7.29 to 12.60)	9.72 (7.66 to 12.17)	—	9.30 (6.97 to 11.62)	9.10 (7.19 to 11.45)	—
Mean	10.34±3.82	10.39±3.69	-0.05 (-0.80 to 0.69)§	9.76±3.40	9.83±3.41	-0.07 (-0.95 to 0.81)¶
Secondary outcomes						
Length of stay in emergency department — hr						
Median (IQR)	5.2 (4.1 to 6.8)	4.9 (3.9 to 7.0)	—	4.9 (3.9 to 6.2)	4.9 (3.8 to 6.4)	—
Mean	6.0±3.4	6.0±3.9	-0.0 (-0.7 to 0.7)	5.7±3.8	6.5±7.5	-0.7 (-2.2 to 0.8)
Hospital length of stay — hr						
Median (IQR)	7.7 (4.5 to 28.4)	15.8 (4.3 to 29.6)	—	13.1 (4.3 to 29.5)	16.9 (4.3 to 29.5)	—
Mean	20.0±20.5	20.8±21.1	-0.8 (-4.9 to 3.3)	20.8±23.3	20.9±20.7	-0.1 (-5.8 to 5.5)
Return visit to emergency department or hospitalization — no. (%)**	3/256 (1.17)	5/264 (1.89)	0.6 (0.1 to 3.1)	2/158 (1.27)	2/153 (1.31)	0.9 (0.1 to 8.4)

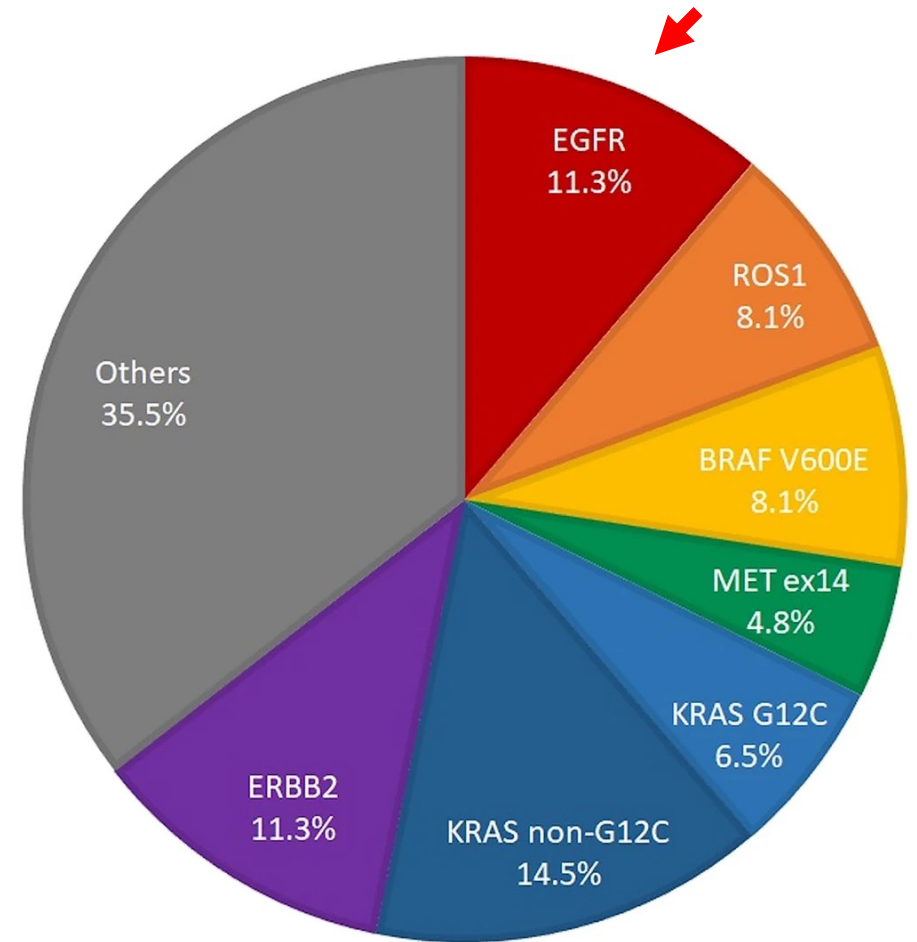
Distribution of Sums of Scores on the Asthma Flare-up Diary for Young Children (ADYC) and ADYC Scores According to Day.

Shown are the sums of scores on the ADYC (Panel A) and the mean daily scores (Panel B) in the positive and negative cohorts over the 5 days after randomization, as reported by caregivers. The ADYC comprises 17 questions, each of which is scored on a scale from 1 to 7, with higher scores indicating more severe wheezing-related symptoms. Daily ADYC scores were calculated as the average score per question, and the five daily scores were added to determine the total score (the primary outcome). The range of possible primary-outcome values was 5 to 35. In Panel A, the horizontal lines within the boxes indicate the medians; the circles within the boxes indicate the means; the bottom and top of the boxes indicate the 25th and 75th percentiles, respectively; and the I bars indicate the lowest and highest values within 1.5 times the interquartile range. Individual data points above the bars indicate outliers beyond this threshold. In Panel B, I bars indicate 95% confidence intervals.





NSCLC and Mutations

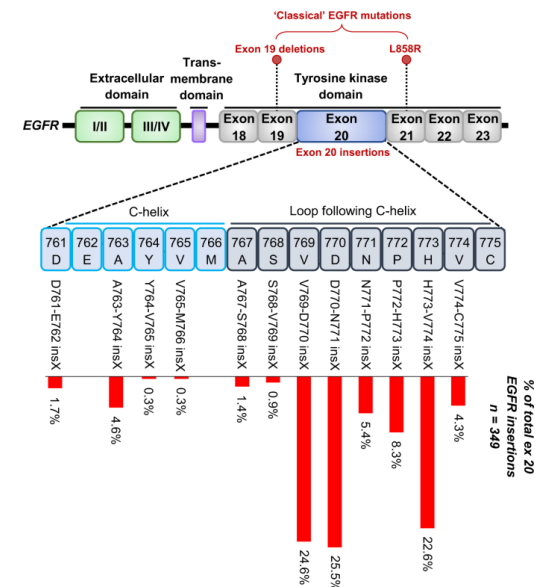


Eine **EGFR-Mutation** beim nicht-kleinzelligen Lungenkarzinom (NSCLC) ist eine genetische Veränderung des Wachstumsfaktor-Rezeptors, die unkontrolliertes Tumorwachstum antreibt. Sie tritt bei **etwa 10–15 % der Patienten in Deutschland auf**, besonders häufig bei Nichtrauchern und Adenokarzinomen. Der Nachweis ermöglicht eine hochwirksame, maßgeschneiderte Tablettentherapie.

Grundlagen und Häufigkeit

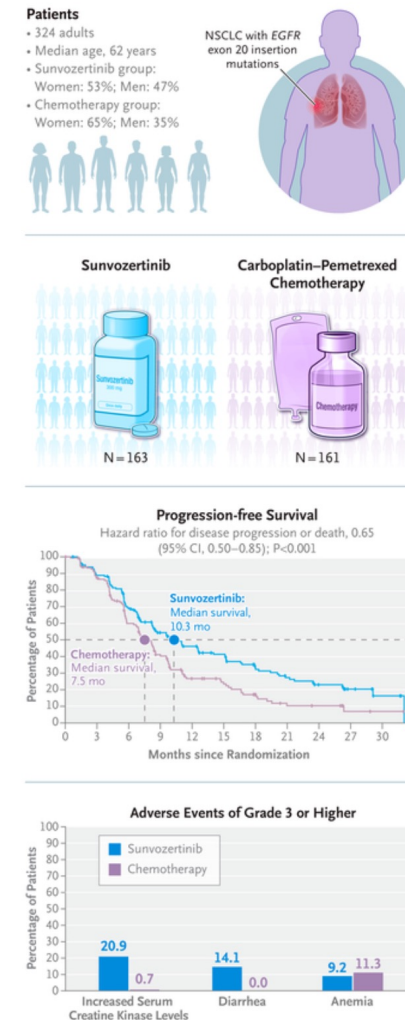
- **Biologische Rolle:** Der veränderte Rezeptor sendet ständige Wachstumssignale an die Krebszelle.
- **Häufigste Typen:** Rund 85–90 % der Mutationen sind Exon-19-Deletionen oder die Punktmutation L858R.
- **Patientengruppe:** Betroffen sind oft Personen ohne Raucherhistorie oder mit nur geringem Tabakkonsum

Eine **EGFR-Exon-20-Insertionsmutation** (EGFRex20ins) ist eine seltene, spezifische Untergruppe von Treibermutationen beim nicht-kleinzelligen Lungenkarzinom (NSCLC), die etwa **4 bis 10 % aller EGFR-Mutationen ausmacht**. Im Gegensatz zu klassischen EGFR-Mutationen sprechen diese Tumoren meist **nicht auf herkömmliche Tyrosinkinase-Inhibitoren (TKIs) an**.



First-Line Sunvozertinib in NSCLC with EGFR Exon 20 Insertion Mutations

Sunvozertinib received accelerated approval for use in later lines of therapy for patients with advanced non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations. Data are needed on the efficacy and safety of sunvozertinib as a first-line treatment for NSCLC. In this phase 3, international trial, we randomly assigned, in a 1:1 ratio, patients with advanced nonsquamous NSCLC with *EGFR* exon 20 insertions to receive sunvozertinib or chemotherapy (carboplatin–pemetrexed). The primary end point was progression-free survival as assessed by blinded independent central review. Crossover to the sunvozertinib group was allowed after disease progression was confirmed. Secondary end points included overall survival, investigator-assessed progression-free survival, objective response (complete or partial response), change in tumor size, and duration of response.



Epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations occur in 2 to 3% of cases of non–small-cell lung cancer (NSCLC) and in up to 12% of cases of *EGFR*-mutated NSCLC. *EGFR* exon 20 insertions are highly heterogeneous, with over 100 subtypes, clustered in near-loop, far-loop, and helical regions. The insertional mutations at *EGFR* exon 20 induce a rigid conformation of the kinase-active site and form steric hindrance, an effect that results in a smaller drug-binding pocket and limits effective binding of conventional first- to third-generation *EGFR* tyrosine kinase inhibitors (TKIs).

Sunvozertinib is specifically designed to target *EGFR* exon 20 insertions, as well as sensitizing and uncommon mutations, and it has shown antitumor activity across a broad spectrum of *EGFR* exon 20 insertion subtypes to overcome the heterogeneous effects of these mutations.

We conducted the phase 3, international, randomized WU-KONG28 trial to evaluate the antitumor efficacy and safety of sunvozertinib as compared with platinum-based chemotherapy as first-line treatment in patients with advanced NSCLC with *EGFR* exon 20 insertions. Here, we report the primary results of the trial.

Methods

Patients

Eligible patients were 18 years of age or older, had a diagnosis of histologically or cytologically confirmed nonsquamous NSCLC, and had received no previous systemic anticancer therapy (e.g., chemotherapy or EGFR-TKIs) for locally advanced (stage IIIB or IIIC according to the eighth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer) or metastatic (stage IV) NSCLC with *EGFR* exon 20 insertions.

Trial Design and Treatment

Eligible patients were randomly assigned in a 1:1 ratio to receive sunvozertinib or chemotherapy in 3-week cycles, stratified according to brain metastasis status at baseline (yes or no).

In the sunvozertinib group, patients received treatment until disease progression or other discontinuation criteria were met as defined in the protocol. The dose of oral sunvozertinib was 300 mg once daily. In the chemotherapy group, patients received carboplatin–pemetrexed for up to 4 or 6 cycles, at the discretion of the investigator, followed by pemetrexed maintenance therapy until disease progression or other discontinuation criteria were met. Carboplatin was administered at a target area under the plasma concentration-time curve of 5, and pemetrexed at a dose of 500 mg per square meter of body-surface area, by intravenous infusion every 3 weeks, along with adequate supplementation with folic acid and vitamin B12.

End Points

The primary end point was progression-free survival, defined as the time from randomization until disease progression (as assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or death from any cause. The key secondary end point was overall survival, defined as the time from randomization until death from any cause.

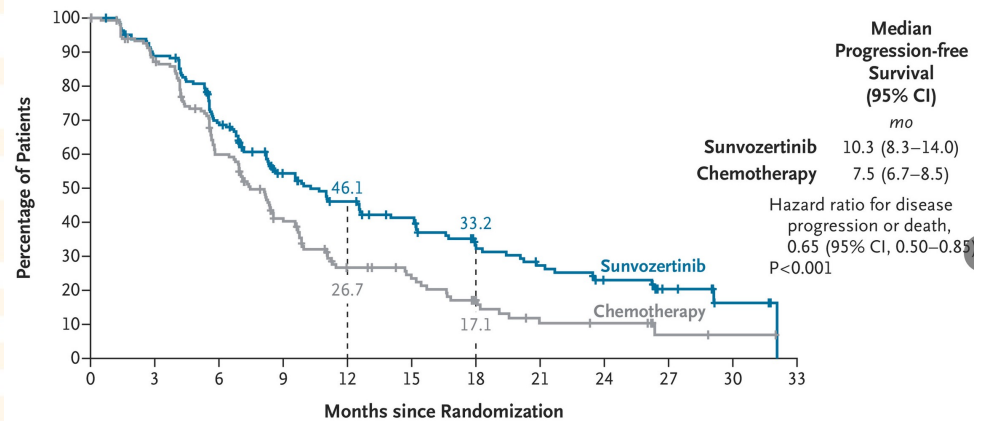
Characteristic	Sunvozertinib (N=163)	Chemotherapy (N=161)
Age		
Median (range) — yr	62 (27–87)	62 (28–85)
Distribution — no. (%)		
<65 yr	89 (54.6)	93 (57.8)
≥65 yr	74 (45.4)	68 (42.2)
Sex — no. (%)		
Male	76 (46.6)	56 (34.8)
Female	87 (53.4)	105 (65.2)
Race — no. (%)†		
Asian	102 (62.6)	102 (63.4)
Non-Asian	61 (37.4)	59 (36.6)
Geographic region — no. (%)		
North America or European Union‡	50 (30.7)	52 (32.3)
Other§	113 (69.3)	109 (67.7)
History of smoking — no. (%)		
Yes	62 (38)	54 (33.5)
No	101 (62)	107 (66.5)
ECOG performance-status score — no. (%)¶		
0	46 (28.2)	43 (26.7)
≥1	117 (71.8)	118 (73.3)
Baseline brain metastasis — no. (%)		
Yes	21 (12.9)	20 (12.4)
No	142 (87.1)	141 (87.6)
Number of organs involved — no. (%)		
1 to 3	92 (56.4)	106 (65.8)
>3	71 (43.6)	55 (34.2)
EGFR exon 20 insertion subtype — no. (%)		
769_ASV	51 (31.3)	52 (32.3)
770_SVD	21 (12.9)	32 (19.9)
Other	83 (50.9)	69 (42.9)
Unknown	8 (4.9)	8 (5.0)
EGFR exon 20 insertion region — no. (%)		
Near loop	111 (68.1)	109 (67.7)
Far loop	41 (25.2)	43 (26.7)
C-helix	3 (1.8)	1 (0.6)
Unknown	8 (4.9)	8 (5.0)
Histologic type — no. (%)		
Adenocarcinoma subtype	160 (98.2)	158 (98.1)
Other	3 (1.8)	3 (1.9)

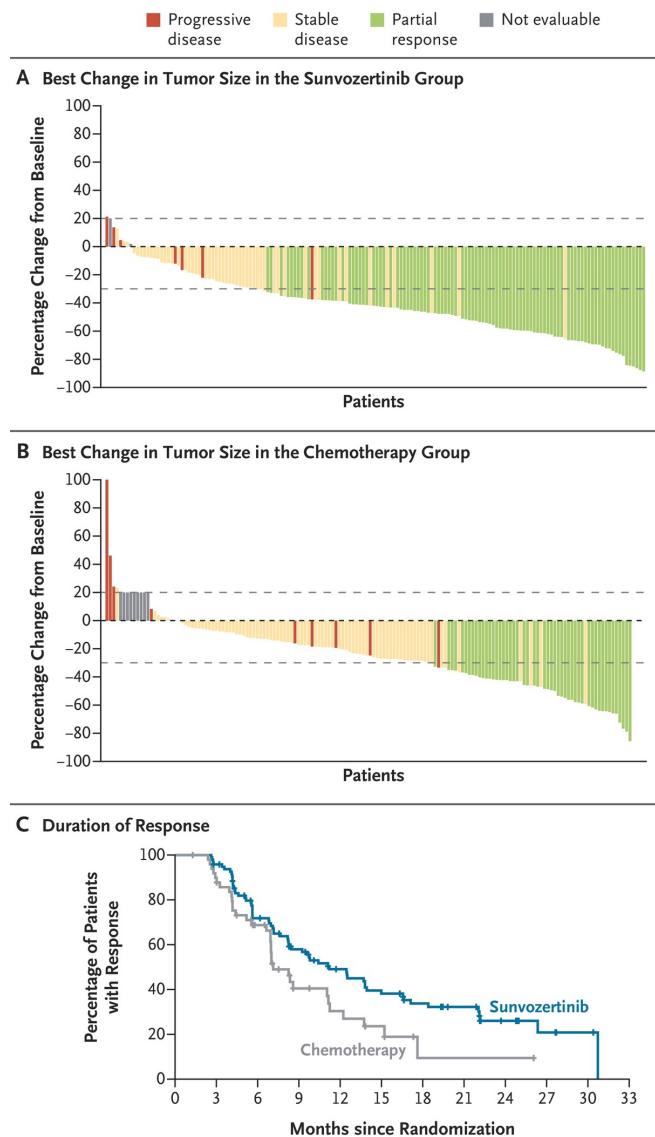
Key Efficacy End Points

End Point	Sunvozertinib (N=163)	Chemotherapy (N=161)	Treatment Effect (95% CI)†	P Value
Progression-free survival‡				
Median (95% CI) — mo	10.3 (8.3–14.0)	7.5 (6.7–8.5)	0.65 (0.50–0.85)	<0.001
Percentage of patients (95% CI)				
At 12 mo	46.1 (37.9–53.9)	26.7 (19.3–34.6)	NA	NA
At 18 mo	33.2 (25.3–41.3)	17.1 (10.7–24.7)	NA	NA
At 24 mo	23.0 (15.8–31.0)	10.3 (5.1–17.6)	NA	NA
Objective response‡				
Percentage of patients (95% CI)	58.9 (50.9–66.5)	31.1 (24.0–38.8)	3.2 (2.0–5.0)	NA
Duration of response				
Median (95% CI) — mo	11.2 (8.2–13.9)	7.1 (6.9–11.1)	NA	NA
Overall survival				
Median (95% CI) — mo	29.8 (21.8–NE)	28.8 (20.7–NE)	0.99 (0.70–1.40)	0.48
Percentage of patients (95% CI)				
At 18 mo	65.5 (56.9–72.9)	67.2 (58.4–74.5)	NA	NA
At 24 mo	57.4 (48.3–65.4)	56.2 (46.9–64.5)	NA	NA
At 30 mo	50.0 (39.4–59.6)	49.1 (39.4–58.1)	NA	NA

Adversity

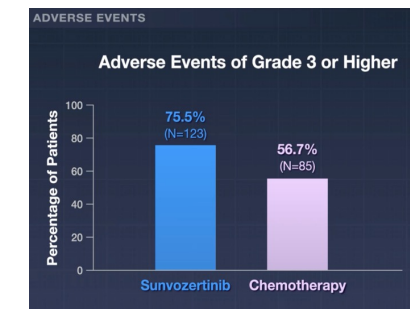
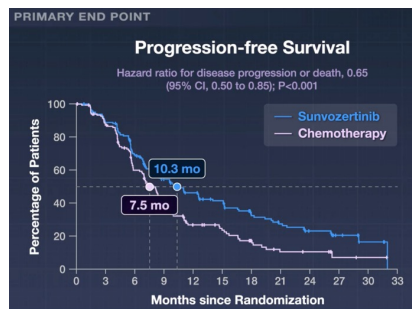
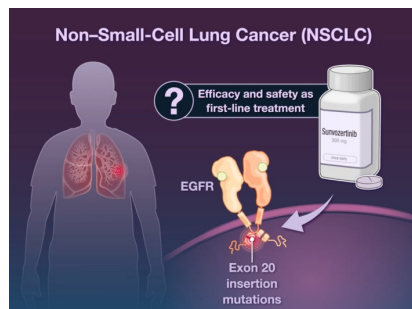
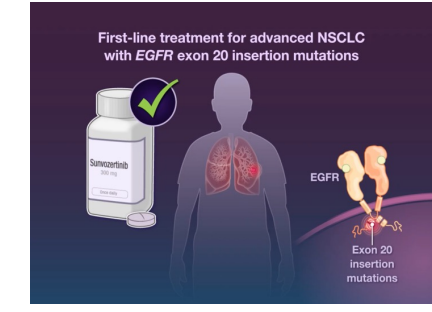
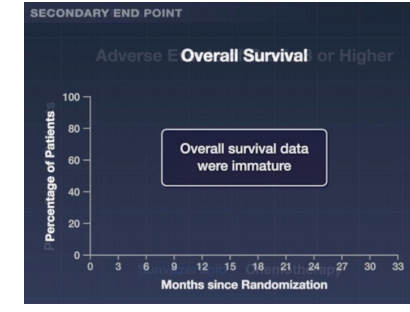
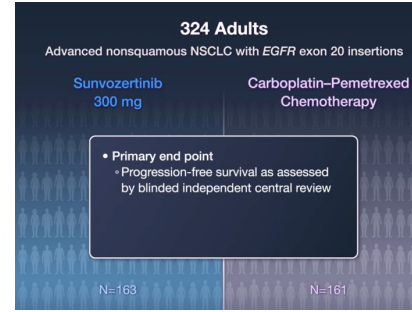
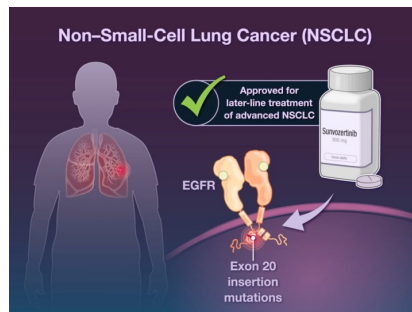
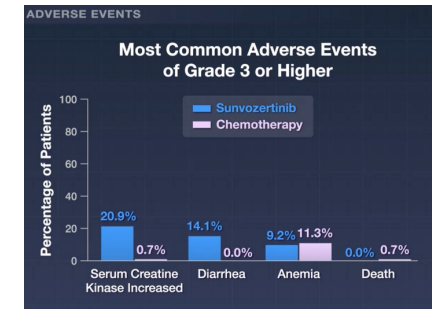
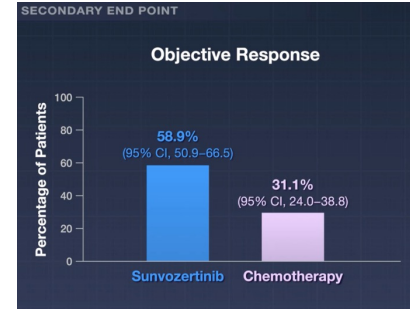
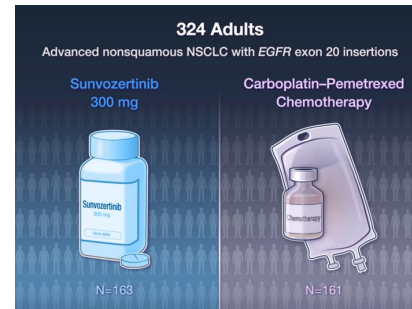
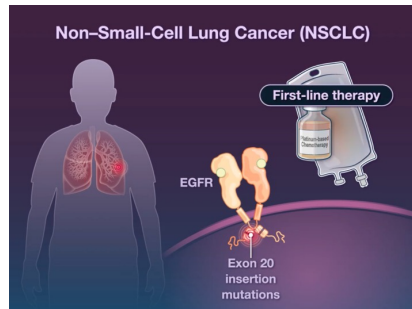
	Sunvozertinib (N = 163)		Chemotherapy (N = 150)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
<i>number of patients (percent)</i>				
Any adverse event	163 (100.0)	123 (75.5)	149 (99.3)	85 (56.7)
Any treatment-related adverse event	163 (100.0)	100 (61.3)	146 (97.3)	74 (49.3)
Any serious adverse event	74 (45.4)	NA	40 (26.7)	NA
Any treatment-related serious adverse event	30 (18.4)	NA	19 (12.7)	NA
Any adverse event leading to drug interruption	95 (58.3)	NA	56 (37.3)	NA
Any treatment-related adverse event leading to drug interruption	74 (45.4)	NA	41 (27.3)	NA
Any adverse event leading to dose reduction	68 (41.7)	NA	40 (26.7)	NA
Any treatment-related adverse event leading to dose reduction	66 (40.5)	NA	36 (24.0)	NA
Any adverse event leading to drug discontinuation	19 (11.7)	NA	18 (12.0)	NA
Any treatment-related adverse event leading to drug discontinuation	12 (7.4)	NA	17 (11.3)	NA
Any adverse event with fatal outcome	7 (4.3)	NA	2 (1.3)	NA
Any treatment-related adverse event with fatal outcome	0	NA	1 (0.7)	NA
Adverse events that emerged during treatment and were reported in ≥20% of patients in either group				
Diarrhea	142 (87.1)	23 (14.1)	25 (16.7)	0
Serum creatine kinase increased	95 (58.3)	34 (20.9)	6 (4.0)	1 (0.7)
Anemia	93 (57.1)	15 (9.2)	94 (62.7)	17 (11.3)
Rash	86 (52.8)	1 (0.6)	10 (6.7)	0
Paronychia	79 (48.5)	6 (3.7)	1 (0.7)	0
Weight decreased	71 (43.6)	6 (3.7)	17 (11.3)	1 (0.7)
Decreased appetite	63 (38.7)	3 (1.8)	42 (28.0)	2 (1.3)
Serum creatinine increased	55 (33.7)	1 (0.6)	14 (9.3)	0
Nausea	46 (28.2)	3 (1.8)	69 (46.0)	2 (1.3)
Vomiting	46 (28.2)	3 (1.8)	36 (24.0)	3 (2.0)
Hypokalemia	41 (25.2)	6 (3.7)	11 (7.3)	1 (0.7)
Amylase increased	38 (23.3)	2 (1.2)	17 (11.3)	0
Lipase increased	38 (23.3)	9 (5.5)	11 (7.3)	2 (1.3)
Aspartate aminotransferase increased	36 (22.1)	4 (2.5)	56 (37.3)	1 (0.7)
Mouth ulceration	33 (20.2)	2 (1.2)	5 (3.3)	0
Alanine aminotransferase increased	29 (17.8)	3 (1.8)	52 (34.7)	2 (1.3)
Fatigue	25 (15.3)	2 (1.2)	30 (20.0)	4 (2.7)
Neutrophil count decreased	24 (14.7)	4 (2.5)	68 (45.3)	28 (18.7)
White-cell count decreased	20 (12.3)	1 (0.6)	59 (39.3)	10 (6.7)
Constipation	18 (11.0)	1 (0.6)	38 (25.3)	0
Platelet count decreased	15 (9.2)	4 (2.5)	33 (22.0)	10 (6.7)





Best Response and Duration of Response.

Shown are waterfall plots of the best percentage change from baseline in tumor size as assessed by blinded independent central review among patients in the sunvozertinib group (Panel A) and among those in the chemotherapy group (Panel B). A total of 158 patients with measurable target lesions (determined by blinded independent central review) were included in the sunvozertinib group, and 154 were included in the chemotherapy group. Also shown are Kaplan–Meier estimates of duration of response as assessed by blinded independent central review (Panel C) in the efficacy population.



Ozempic-Faces: Abnehmspritze führt immer öfter zum Schönheitschirurgen statt in die Ernährungstherapie



Vor

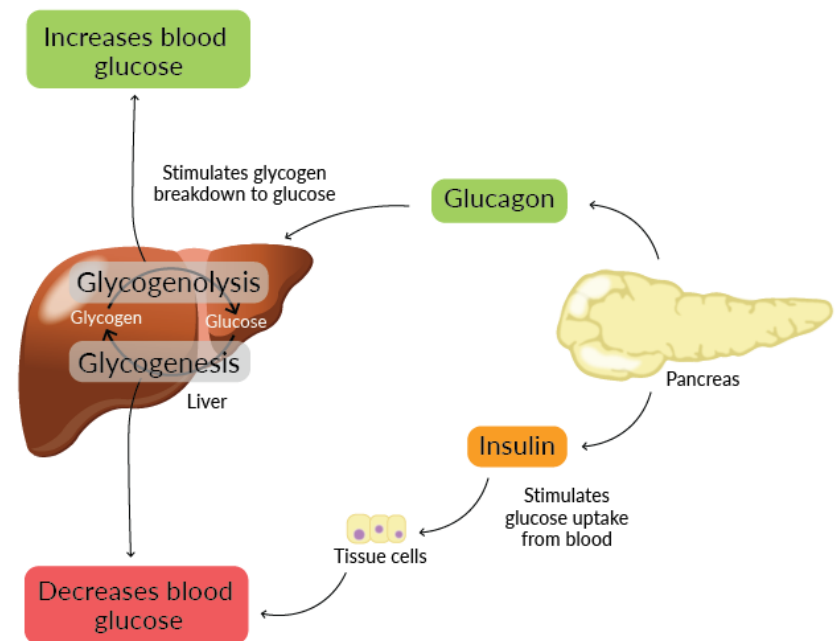
Nach

Wie die Deutsche Gesellschaft für Ästhetisch-Plastische Chirurgie (DGÄPC) berichtet, fragen immer mehr Patienten

Straffungsoperationen nach. Der Grund: Eine häufige Folge des schnellen Gewichtsverlustes ist eine hängende Haut. Ein Problem, für dessen Behebung die plastische Chirurgie zuständig ist, die nun ganz enorm vom Abnehm-Hype profitiert. In einer Umfrage der DGÄPC gaben mehr als 30 % der Mitglieder an, dass sich vermehrt Patienten nach erfolgreichem Gewichtsverlust durch eine Abnehmspritze einer sogenannten „liftingchirurgischen Operation“ unterziehen. Der starke Gewichtsverlust wiederum führt dazu, dass sich gerade bei Menschen mit schwachem Bindegewebe überschüssiges Gewebe nicht von allein wieder zurückbildet.

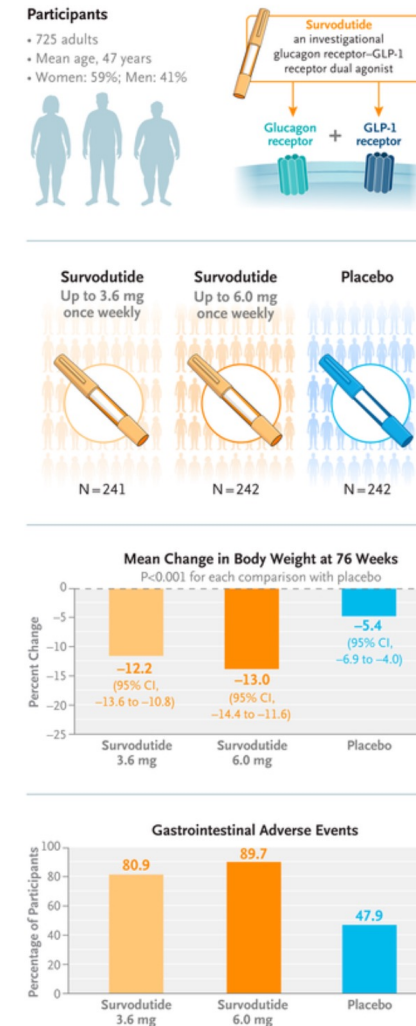
Die Kombination aus GLP-1-Rezeptor- und Glukagonrezeptor-Agonisten (GLP-1/Glukagon-Dualagonisten) zielt darauf ab, die **Gewichtsabnahme** und den **Energieumsatz** im Vergleich zu reinen GLP-1-Wirkstoffen deutlich zu verstärken

- **GLP-1-Komponente:** Dämpft den Appetit im Gehirn, fördert das Sättigungsgefühl und verzögert die Magenentleerung, was die Kalorienaufnahme senkt. Zudem stimuliert sie die Insulinausschüttung.
- **Glukagon-Komponente:** Erhöht normalerweise den Blutzucker, steigert aber in pharmakologischer Dosis den Energieumsatz (Kalorienverbrennung), fördert die Fettverbrennung (Lipolyse) und den Abbau von Leberfett.
- **Sollwert-Verschiebung:** Glukagon treibt den Energieverbrauch nach oben, während GLP-1 den starken, kompensatorischen Hunger dämpft, der bei erhöhtem Kalorienverbrauch normalerweise auftreten würde.
- **Blutzuckerkontrolle:** Die blutzuckererhöhende Eigenschaft von Glukagon wird durch die blutzuckersenkende und insulinotrope Wirkung von GLP-1 ausgeglichen, wodurch das Risiko für eine Hyperglykämie minimiert wird.



Survodutide Once Weekly for the Treatment of Adults with Obesity

Although medications with glucagon-like peptide-1 (GLP-1) receptor agonist activity have transformed the management of obesity and shown substantial cardiometabolic benefits, unmet needs remain. Suvrodutide, an investigational glucagon receptor–GLP-1 receptor dual agonist, led to substantial weight reduction in a phase 2 trial involving adults with obesity without diabetes. In this phase 3, double-blind trial, we randomly assigned adults with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher, or 27 or higher with at least one obesity-related complication (excluding diabetes), in a 1:1:1 ratio to receive once-weekly suvrodutide administered subcutaneously at a dose adjusted up to 3.6 mg or 6.0 mg or placebo, in addition to counseling for lifestyle modification. The two primary end points were **the percent change in body weight and a reduction in body weight of at least 5% from baseline to week 76**. The primary efficacy analysis was conducted according to the treatment-regimen estimand, which incorporates the effects of any early discontinuation of suvrodutide or placebo, the use of protocol-prohibited obesity medications, and a prolonged dose-escalation period.



Obesity is a chronic neurometabolic disease characterized by excess overall or ectopic adipose tissue; it can lead to serious health complications, reduced quality of life, and an increased risk of death. Obesity affects approximately 1 billion adults worldwide, a fact that highlights a pressing need for more effective therapies.

Medications with glucagon-like peptide-1 (GLP-1) receptor agonist activity — particularly the GLP-1 receptor agonist semaglutide and the GLP-1 receptor–glucose-dependent insulinotropic polypeptide receptor dual agonist tirzepatide — are associated with substantial health gains. However, heterogeneity in responses with current medications suggests that compounds with complementary mechanisms that may expand treatment options for managing the disease, addressing metabolic dysfunction beyond weight loss, and ameliorating complications would be useful.

Oxyntomodulin, an endogenous incretin-related peptide hormone, stimulates the glucagon receptor and the GLP-1 receptor; agonism of both is hypothesized to confer additional benefits owing to the physiological effects of glucagon, a peptide hormone that reduces appetite and induces lipolysis, in addition to its glycemic effects.

Synthetic unimolecular peptide **dual agonists of the glucagon and GLP-1 receptors** with enhanced receptor activation capacity and extended half-lives have been developed, including survodutide and mazdutide (which was approved in 2025 in China).

Methods

Trial Design

We conducted this 76-week, phase 3, double-blind, randomized, placebo-controlled trial at 116 clinical sites across 14 countries.

Participants

Eligible persons were at least 18 years of age, with a BMI of 30 or higher — or 27 or higher with at least one obesity-related complication (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or metabolic dysfunction–associated steatohepatitis [MASH]) — and at least one previous participant-reported unsuccessful dietary effort to lose weight.

Randomization and Treatment

Participants were randomly assigned in a 1:1:1 ratio to receive survodutide at a dose adjusted up to 3.6 mg, survodutide at a dose adjusted up to 6.0 mg, or placebo, administered subcutaneously once weekly.

End Points

The two primary end points were the percent change in body weight and a reduction in body weight of at least 5% from baseline to week 76, in accordance with Food and Drug Administration (FDA) and European Medicines Agency guidance for the development of obesity medications.

Patients

End Point	Survodutide, 3.6 mg (N = 241)	Survodutide, 6.0 mg (N = 242)	Placebo (N = 242)
Primary end points			
Mean change in body weight (95% CI) — %	−12.2 (−13.6 to −10.8)	−13.0 (−14.4 to −11.6)	−5.4 (−6.9 to −4.0)
Difference vs. placebo (95% CI) — percentage points	−6.8 (−8.8 to −4.8)†	−7.5 (−9.6 to −5.5)†	
Weight reduction of ≥5% — % of participants	72.6	71.9	46.3
Odds ratio, survodutide vs. placebo (95% CI)	3.1 (2.0 to 4.7)†	3.0 (2.0 to 4.4)†	—
Key secondary end points			
Weight reduction of ≥10% — % of participants	55.2	56.6	26.0
Odds ratio, survodutide vs. placebo (95% CI)	3.6 (2.4 to 5.5)†	3.9 (2.5 to 5.8)†	—
Weight reduction of ≥15% — % of participants	35.7	45.9	12.0
Odds ratio, survodutide vs. placebo (95% CI)	4.1 (2.5 to 6.8)†	6.3 (3.8 to 10.5)†	—
Weight reduction of ≥20% — % of participants	24.9	28.5	6.6
Odds ratio, survodutide vs. placebo (95% CI)	5.0 (2.6 to 9.3)†	6.0 (3.2 to 11.2)†	—
Mean change in body weight — kg	−13.1	−14.1	−5.9
Difference vs. placebo (95% CI)	−7.2 (−9.4 to −5.0)†	−8.1 (−10.3 to −5.9)†	—
Mean change in waist circumference — cm	−10.5	−11.5	−5.4
Difference vs. placebo (95% CI)	−5.2 (−7.1 to −3.2)†	−6.1 (−8.0 to −4.1)†	—
Mean change in systolic blood pressure — mm Hg	−6.7	−5.4	−5.9
Difference vs. placebo (95% CI)	−0.7 (−3.0 to 1.6)‡	0.6 (−1.7 to 2.9)‡	—
Mean change in EB PRO total score — points§	−7.8	−8.1	−7.3
Difference vs. placebo (95% CI)	−0.5 (−2.2 to 1.3)	−0.9 (−2.6 to 0.9)	—
Mean change in EB PRO Capacity to Resist domain score — points§	−4.2	−4.3	−3.8
Difference vs. placebo (95% CI)	−0.4 (−1.3 to 0.6)	−0.5 (−1.4 to 0.5)	—

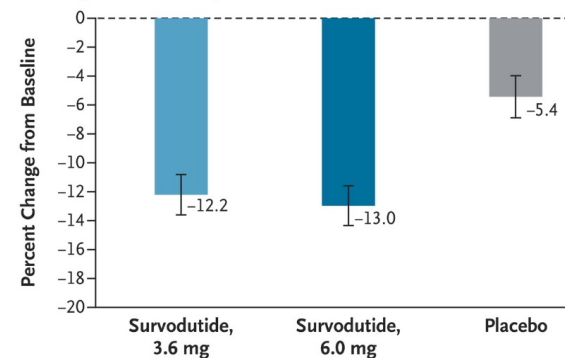
Endpoints

End Point	Survodutide, 3.6 mg (N = 241)	Survodutide, 6.0 mg (N = 242)	Placebo (N = 242)
Secondary end points for the treatment-regimen estimand			
Mean change in BMI (95% CI)	−4.6 (−5.2 to −4.1)	−5.0 (−5.6 to −4.5)	−2.1 (−2.7 to −1.5)
Mean change in diastolic blood pressure (95% CI) — mm Hg	−4.1 (−5.1 to −3.0)	−3.6 (−4.6 to −2.6)	−3.4 (−4.5 to −2.3)
Mean change in glycated hemoglobin level (95% CI) — percentage points	−0.2 (−0.2 to −0.1)	−0.2 (−0.2 to −0.1)	0.0 (−0.1 to 0.1)
Mean change in fasting plasma glucose level (95% CI) — mg/dl	−7.4 (−8.9 to −6.0)	−6.0 (−7.3 to −4.7)	−1.2 (−2.8 to 0.4)
Mean change in fasting plasma insulin level (95% CI) — %†	−28.4 (−34.3 to −22.1)	−29.2 (−34.6 to −23.3)	−8.6 (−16.4 to −0.04)
Mean changes in lipid levels (95% CI) — %†			
Total cholesterol	−7.6 (−9.7 to −5.5)	−8.4 (−10.3 to −6.5)	−4.5 (−6.8 to −2.2)
HDL cholesterol	1.4 (−0.7 to 3.6)	3.1 (1.0 to 5.2)	0.2 (−2.0 to 2.5)
LDL cholesterol	−8.8 (−11.7 to −5.8)	−9.0 (−11.8 to −6.2)	−5.7 (−9.0 to −2.4)
VLDL cholesterol	−24.6 (−28.9 to −19.9)	−30.1 (−33.9 to −26.0)	−10.6 (−16.0 to −4.8)
Triglycerides	−22.7 (−26.9 to −18.2)	−27.7 (−31.4 to −23.8)	−8.8 (−14.0 to −3.3)
Free fatty acids	−12.2 (−18.1 to −5.9)	−13.1 (−18.5 to −7.4)	−9.5 (−16.0 to −2.6)
Mean changes in liver markers (95% CI) — %†			
Alanine aminotransferase	−16.3 (−21.3 to −11.1)	−13.0 (−17.9 to −7.8)	−14.5 (−20.0 to −8.8)
Aspartate aminotransferase	−7.1 (−11.0 to −3.1)	−5.9 (−9.7 to −2.0)	−6.2 (−10.5 to −1.8)
Further end points‡			
Mean change in Fibrosis-4 index score (95% CI)§	0.10 (0.05 to 0.14)	0.05 (0.01 to 0.10)	0.05 (0.01 to 0.09)
Mean change in uric acid level (95% CI) — μmol/liter	−53.0 (−61.6 to −44.5)	−73.8 (−82.2 to −65.3)	−8.6 (−17.2 to −0.03)
Secondary end points for the substudy of body composition¶			
Mean change in total fat volume (95% CI)			
Absolute change — liters	−9.7 (−12.2 to −7.2)	−10.9 (−13.5 to −8.4)	−4.1 (−6.6 to −1.6)
Relative change — %	−22.9 (−28.7 to −17.0)	−27.8 (−33.8 to −21.9)	−9.5 (−15.3 to −3.6)
Mean change in lean body volume (95% CI)			
Absolute change — liters	−1.9 (−2.5 to −1.4)	−2.7 (−3.2 to −2.1)	−0.8 (−1.4 to −0.3)
Relative change — %	−7.2 (−9.3 to −5.2)	−9.8 (−11.8 to −7.7)	−2.9 (−5.0 to −0.9)
Lean loss ratio — %	11.1	11.3	12.8
Mean change in visceral fat volume (95% CI)			
Absolute change — liters	−1.6 (−2.1 to −1.2)	−1.9 (−2.5 to −1.4)	−0.7 (−1.2 to −0.2)
Relative change — %	−29.8 (−38.4 to −21.1)	−34.0 (−43.0 to −25.0)	−11.8 (−20.5 to −3.0)
Mean change in subcutaneous fat volume (95% CI)			
Absolute change — liters	−7.2 (−9.1 to −5.4)	−8.0 (−9.8 to −6.1)	−3.2 (−5.0 to −1.3)
Relative change — %	−23.0 (−28.9 to −17.2)	−28.1 (−34.0 to −22.3)	−9.8 (−15.6 to −4.0)
Mean relative change in liver-fat content (95% CI) — %	−46.0 (−66.5 to −25.5)	−63.1 (−83.6 to −42.6)	−24.5 (−44.8 to −4.2)

Adversity

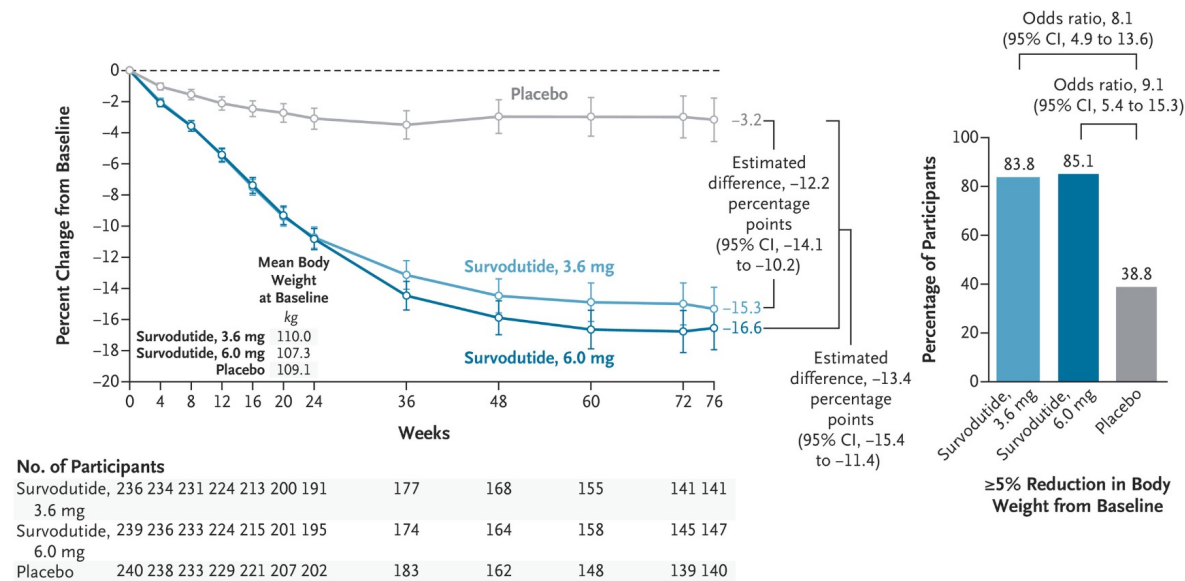
Event	Survodutide, 3.6 mg (N = 241)	Survodutide, 6.0 mg (N = 242)	Placebo (N = 242)
<i>number of participants (percent)</i>			
Any adverse event	232 (96.3)	236 (97.5)	208 (86.0)
Any serious adverse event	20 (8.3)	20 (8.3)	15 (6.2)
Any fatal adverse event	0	0	0
Adverse event leading to trial discontinuation	6 (2.5)	4 (1.7)	2 (0.8)
Adverse event leading to discontinuation of survodutide or placebo	57 (23.7)	60 (24.8)	13 (5.4)
Gastrointestinal adverse event	43 (17.8)	49 (20.2)	7 (2.9)
Adverse events occurring in ≥10% of the participants in any trial group†			
Nausea	147 (61.0)	157 (64.9)	42 (17.4)
Vomiting	98 (40.7)	108 (44.6)	15 (6.2)
Diarrhea	77 (32.0)	96 (39.7)	45 (18.6)
Constipation	75 (31.1)	79 (32.6)	30 (12.4)
Fatigue	45 (18.7)	36 (14.9)	21 (8.7)
Upper respiratory tract infection	40 (16.6)	31 (12.8)	29 (12.0)
Nasopharyngitis	31 (12.9)	27 (11.2)	33 (13.6)
Eructation	30 (12.4)	18 (7.4)	3 (1.2)
Dyspepsia	29 (12.0)	28 (11.6)	10 (4.1)
Decreased appetite	28 (11.6)	43 (17.8)	19 (7.9)
Gastroesophageal reflux disease	28 (11.6)	35 (14.5)	9 (3.7)
Headache	25 (10.4)	32 (13.2)	20 (8.3)
Dizziness	13 (5.4)	32 (13.2)	17 (7.0)
Events related to specific safety topics of interest			
Gastrointestinal disorder‡	195 (80.9)	217 (89.7)	116 (47.9)
Liver-related event§	13 (5.4)	10 (4.1)	14 (5.8)
Cholelithiasis†	3 (1.2)	5 (2.1)	1 (0.4)
Cholecystitis†	2 (0.8)	1 (0.4)	0
Hypersensitivity§	19 (7.9)	18 (7.4)	18 (7.4)
Acute kidney injury†	1 (0.4)¶	1 (0.4)¶	0
Hypotension, including syncopal events§	5 (2.1)	18 (7.4)	4 (1.7)
Syncope†	5 (2.1)	4 (1.7)	2 (0.8)
Hypoglycemia§	3 (1.2)	2 (0.8)	1 (0.4)
Hyperglycemia§	2 (0.8)	4 (1.7)	14 (5.8)
Suicidal ideation or behavior§	1 (0.4)	0	0
Major depressive disorder§	8 (3.3)	6 (2.5)	12 (5.0)
Dysesthesia§	9 (3.7)	6 (2.5)	2 (0.8)
Adjudication-confirmed events			
SP-MACE**	0	0	1 (0.4)
Asymptomatic pancreatic hyperenzymemia	6 (2.5)	4 (1.7)	3 (1.2)

A Overall Change in Body Weight (treatment-regimen estimand)



Panel A shows the percent change in body weight from baseline to week 76, derived from an analysis-of-covariance model, for the treatment-regimen estimand, which incorporates the effects of any early discontinuation of survodutide or placebo, the use of protocol-prohibited obesity medications, and a prolonged dose-escalation period.

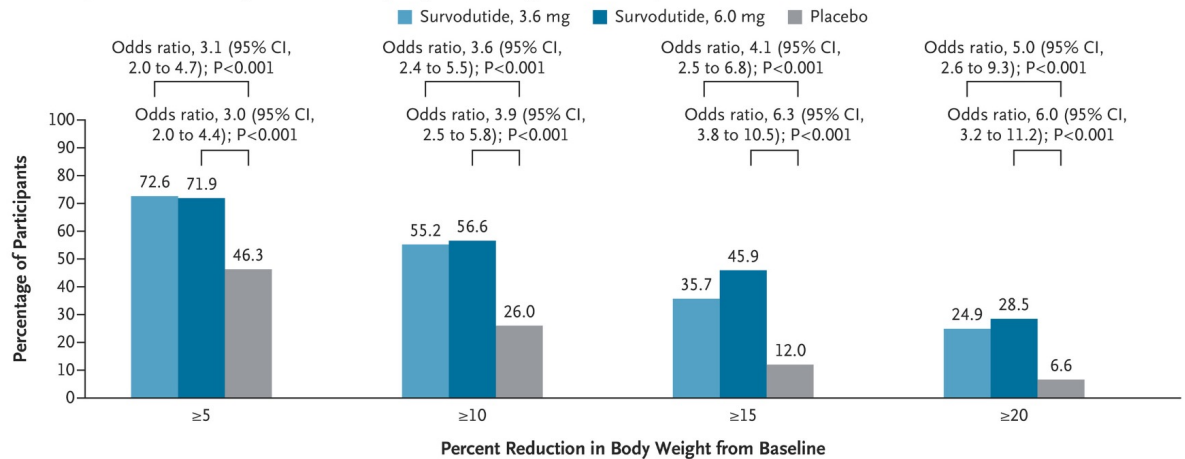
B Change in Body Weight by Week and Percentage of Participants with ≥5% Weight Reduction at Week 76 (efficacy estimand)

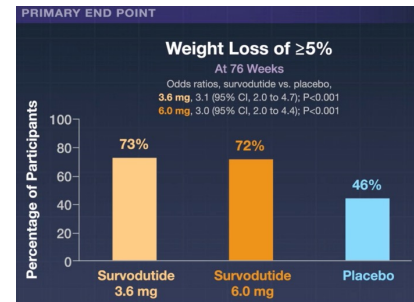
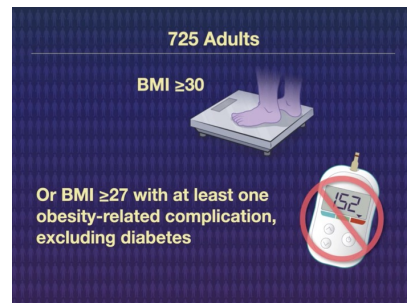
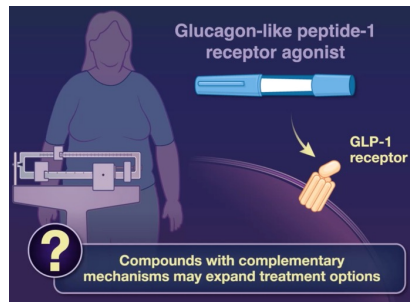
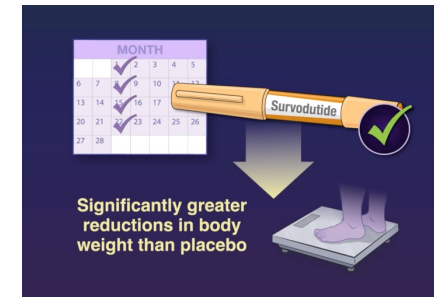
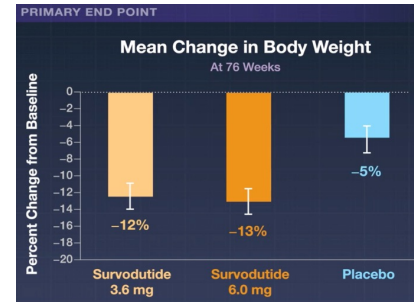
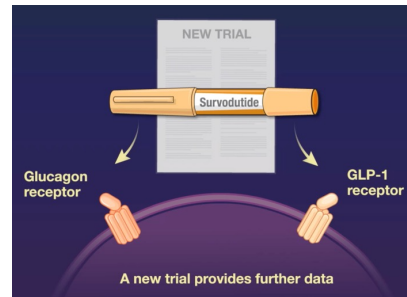
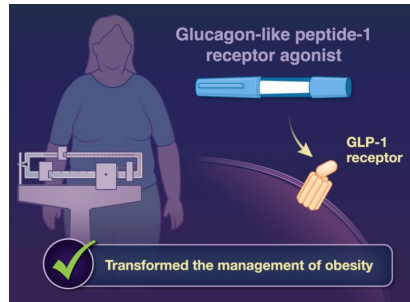


Effects of Survodutide on Body Weight.

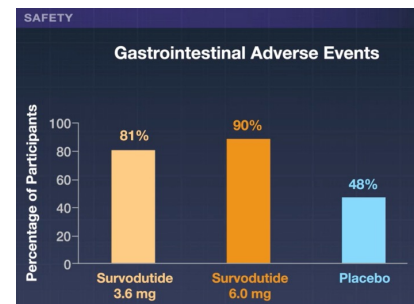
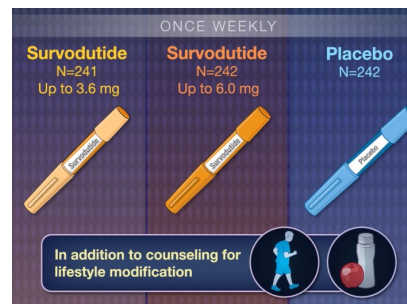
Panel B shows the percent change in body weight according to the number of weeks since randomization, derived from an analysis with a mixed model for repeated measures, and the percentage of participants who had weight reduction of at least 5% from baseline to week 76, both for the efficacy estimand, which represents the hypothetical treatment effect if all the participants had adhered to the assigned trial regimen and had not received prohibited therapy for obesity and which incorporates the effects of any prolonged dose-escalation phase. I bars in Panels A and B indicate 95% confidence intervals. The widths of the confidence intervals in Panel B have not been adjusted for multiplicity and should not be used for hypothesis testing. Panel C shows the percentages of participants who had weight reduction of at least 5%, at least 10%, at least 15%, or at least 20% from baseline to week 76 for the treatment-regimen estimand.

C Participants Who Met Weight-Reduction Targets (treatment-regimen estimand)





Excellent weight loss with „the usual“ side effects



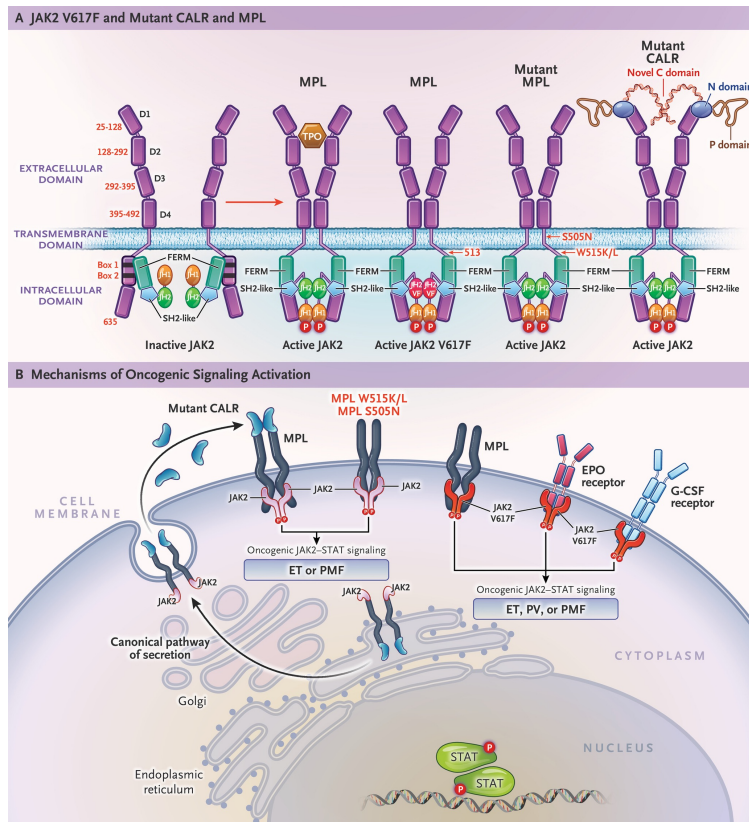
Myeloproliferative Neoplasms

Summary

Classic myeloproliferative neoplasms, including essential thrombocythemia, polycythemia vera, and primary myelofibrosis, are chronic, clonal hematopoietic stem-cell disorders. These disorders are driven by gain-of-function **mutations in the genes Janus kinase 2 (JAK2), calreticulin (CALR), or the thrombopoietin receptor (MPL) that activate cytokine signaling.** These mutations arise decades before clinical disease develops and confer a clonal advantage that is further shaped by comutations in epigenetic, splicing, or signaling genes. Inflammation enhances clonal dominance, favoring the development of myelofibrosis and thrombotic complications. Disease evolution may culminate in secondary acute myeloid leukemia, which has a poor prognosis. Current therapies primarily aim to control symptoms, thrombosis, and splenomegaly, but they have limited disease-modifying effects, except for pegylated interferon alfa and JAK2 inhibitors in some patients. **Emerging therapies that selectively target mutant CALR and JAK2 V617F** using immunotherapy and selective inhibitors could be a breakthrough in the treatment of persons with myeloproliferative neoplasms, with the expectation of achieving durable disease modification and potentially clonal eradication.

Representation of the Main Structures and Functions of the Myeloproliferative Neoplasm Driver Mutations.

Panel A shows a schematic representation of Janus kinase 2 (JAK2) in its inactive state on the thrombopoietin receptor (MPL) and in the active conformation induced by the *MPL* mutations or calreticulin (*CALR*) mutations. JAK2 comprises four domains: FERM, SH2-like, JH2 (pseudokinase), and JH1 (kinase). Mutant *CALR* generates a new positively charged C-terminal tail and lacks the KDEL motif and therefore confers abnormal protein properties. The N domain interacts with immature N-glycans on the extracellular domain of MPL, which is favored by the new C terminal. A fragment located in the first part of the new C terminal interacts with acidic patches of the MPL N terminal, inducing a stable interaction. MPL consists of two extracellular cytokine receptor-like modules, each of which is composed of two fibronectin type III-like domains (D1–D2 and D3–D4), a transmembrane domain, and an intracellular domain. At the basal state, MPL is expressed as a monomer at the cell surface. Binding of thrombopoietin (TPO) to the first cytokine receptor-like module induces MPL dimerization and conformational changes that activate JAK2. *MPL* mutations within the transmembrane and juxtamembrane regions promote spontaneous dimerization and constitutive activation of the receptor. VF denotes JAK2 V617F. Panel B shows the mechanisms of oncogenic signaling activation. Mutant *CALR* binds to MPL monomers in the endoplasmic reticulum and travels through the canonical secretory pathway to the cell surface. At the plasma membrane, mutant *CALR* dimerizes, thereby inducing MPL dimerization and constitutive activation of the JAK2–signal transducer and activator of transcription (STAT) pathway, as well as additional signaling cascades such as RAS–mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)–AKT. *MPL* mutations within the transmembrane and juxtamembrane regions similarly promote spontaneous dimerization and constitutive receptor activation. The JAK2 V617F mutation enables JAK2 to autophosphorylate, which drives constitutive activation of not only MPL but also other type I cytokine receptors such as the erythropoietin (EPO) receptor and granulocyte colony-stimulating factor (G-CSF) receptor, together with their downstream signaling pathways. Consequently, mutant *CALR* and *MPL* are restricted to megakaryocytic neoplasms (essential thrombocythemia [ET] and primary myelofibrosis [PMF]), whereas JAK2 V617F is found across all three myeloproliferative neoplasm subtypes (ET, polycythemia vera [PV], and PMF).



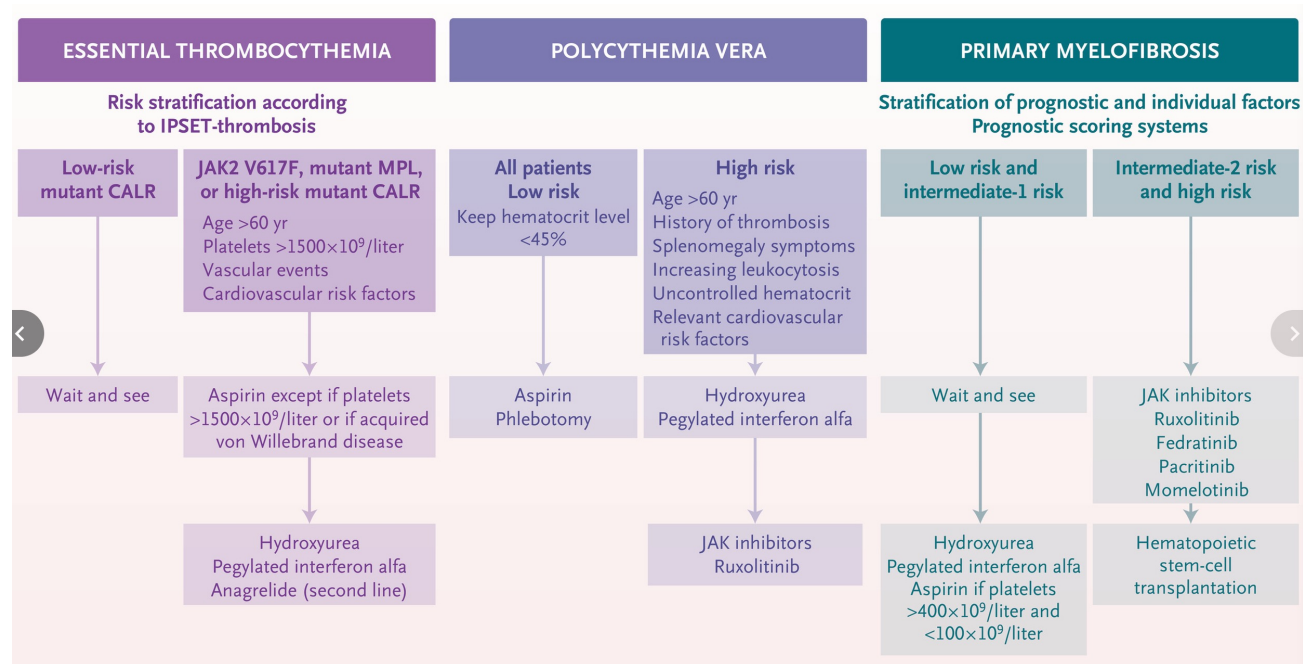
Myeloproliferative Neoplasms

- Classic myeloproliferative neoplasms (essential thrombocythemia, polycythemia vera, and primary myelofibrosis) are clonal stem-cell disorders driven by Janus kinase 2 (JAK2), calreticulin (CALR), or the thrombopoietin receptor (MPL) mutations that arise decades before the development of clinical disease and that dysregulate cytokine signaling.
- Disease progression results in megakaryocyte dysplasia, granulocyte hyperplasia, splenomegaly, fibrosis, and anemia, particularly in primary myelofibrosis.
- A progressive increase in JAK2–STAT (signal transducer and activator of transcription) signaling and inflammatory cytokines drives systemic symptoms and may culminate in leukemic transformation.
- Current therapies primarily control symptoms and disease-related complications rather than eradicating the malignant clone.
- New targeted therapies against JAK2 V617F and immunotherapeutic strategies targeting mutant CALR aim to achieve true disease modification.
- Early acquisition of driver mutations creates opportunities for early intervention but raises challenges related to clonal evolution, resistance, and competing clones.

Disease Type and Affected Pathways and Molecules	Essential Thrombocythemia	Polycythemia Vera	Post-ET or Post-PV MF or PMF	Secondary AML
Signaling Genes				
Myeloproliferative Neoplasm Drivers				
JAK2 V617F				
JAK2 exon 12				
MPL W515 and others				
CALR type 1-like				
CALR type 2-like				
Other drivers				
SH2B3				
KRAS and NRAS				
CBL				
PTPN11				
KIT				
BRAF				
NF1				
PPM1D				
Epigenetic Regulators				
DNA Methylation Regulators				
TET2				
DNMT3A				
IDH1 and IDH2				
Chromatin Modifiers				
EZH2				
ASXL1				
Spliceosome Genes				
SF3B1				
U2AF1				
ZRSF2				
SRSF2				
Transcription Factors				
RUNX1				
ETV6				
CUX1				
TP53				
NFE2				
Cytogenetic Abnormalities				
Chromosome 1 abnormalities				
inv(3)				
del(5q) or -5				
-7 or del(7q)				
+8				
+9 or inv(9)				
del(12p)				
del(13q)				
del(17q)				
del(20q)				
+21				

Drivers and Associated Comutations in the Three Disorders of Myeloproliferative Neoplasm.

Progression of myeloproliferative neoplasms is driven by acquisition of additional somatic alterations beyond the myeloproliferative neoplasm driver mutation (*JAK2*, *MPL*, or *CALR*). Secondary mutations affecting signaling, epigenetic regulation, splicing, and transcriptional pathways, together with cytogenetic abnormalities, increase in frequency during myelofibrosis progression and leukemic transformation and are associated with adverse outcomes. Dark colors denote the mutation is present in more than 5% of cases, and light colors denote the mutation is present in less than 5% of cases. MF denotes myelofibrosis.



Myeloproliferative Neoplasm Treatments According to Disease and Vascular and Prognostic Risks.

The therapeutic algorithms presented here are adapted from international consensus guidelines for myeloproliferative neoplasms, including European LeukemiaNet, National Comprehensive Cancer Network, European Hematology Association, American Society of Hematology, and International Working Group-Myeloproliferative Neoplasms Research and Treatment recommendations, as well as established prognostic models such as the International Prognostic Score for Thrombosis in Essential Thrombocythemia, Dynamic International Prognostic Scoring System, and Mutation-Enhanced International Prognostic System. The algorithms are not universally accepted and may vary among countries depending on the authorization of the different drugs.

Selective Therapies for JAK2 V617F and Mutant CALR Myeloproliferative Neoplasm and Other Promising Therapeutic Strategies.

Mutation and Therapy	Description	In Vitro Activities	In Vitro Biologic Effects	In Vivo Effects	Clinical Trial Status	ClinicalTrials.gov No.
JAK2 V617F						
AJ1-11095	Type II inhibitor Stabilizes the inactive conformation of JAK2	Higher selectivity for JAK2 than for JAK1, JAK3, and TYK2	Overcomes JAK-STAT persistence in SET2 cell lines	Hematologic, molecular, and clinical responses in pre-clinical JAK2 V617F knock-in mouse models	Ongoing, phase 1 trial of JAK-resistant myelofibrosis	NCT06343809
Flonolitinib	Allosteric inhibitor Binds both JH2 and JH1 of JAK2	JAK, FLT3, and CDK6 inhibitor	Targets JAK2 V617F in cell lines and primary cells in patient	Targets JAK2 V617F in vivo in BMT mouse models and cell-derived xenograft models Decreases symptoms, splenomegaly, hepatomegaly, and fibrosis and improves survival	Phase 1–2 involving patients with myelofibrosis with spleen response or improved symptom response Phase 2 ongoing Approved in China	NCT05153334
INCB160058	Allosteric inhibitor JH2 binding	Selectivity for JAK2 Minimal activity against JAK1, JAK3, TYK2, and other kinases	Efficacy and specificity for JAK2 V617F over JAK2 wild type in cell lines and primary patient cells	Efficacy for JAK2 V617F in vivo in PDX	Ongoing, phase 1	NCT06311591
Mutant CALR						
INCA033989	Fully human IgG1 monoclonal antibody against N terminal of mutant CALR	Selective for mutant CALR	Efficacy and selectivity on mutant CALR cells in vitro in cell lines and in primary patient cells Induction of apoptosis and cell-cycle arrest	Efficacy in <i>Calr</i> 52-bp deletion and <i>Calr</i> -5-bp insertion in knock-in mouse models Normalization of platelet counts and megakaryocyte hyperplasia Selective activity on <i>Calr</i> -mutated cells	Both trials are ongoing Rapid and sustained normalization of platelets and molecular response in approximately 90% of patients with essential thrombocythemia at first data-cut-off date Spleen, symptom, anemia, and molecular responses in patients with myelofibrosis Limited toxic effects	NCT06034002 and NCT05936359
JNJ-88549968	Human bispecific IgG antibody against both mutant CALR and CD3 T-cell-redirecting antibody	Selective for mutant CALR	Efficacy and selectivity by inducing T-cell cytotoxicity in mutant CALR cells in vitro, on cell lines, and in primary patient cells	Antitumor activities in 2 models of PDX carrying CALR52-bp deletion	Ongoing	NCT06150152

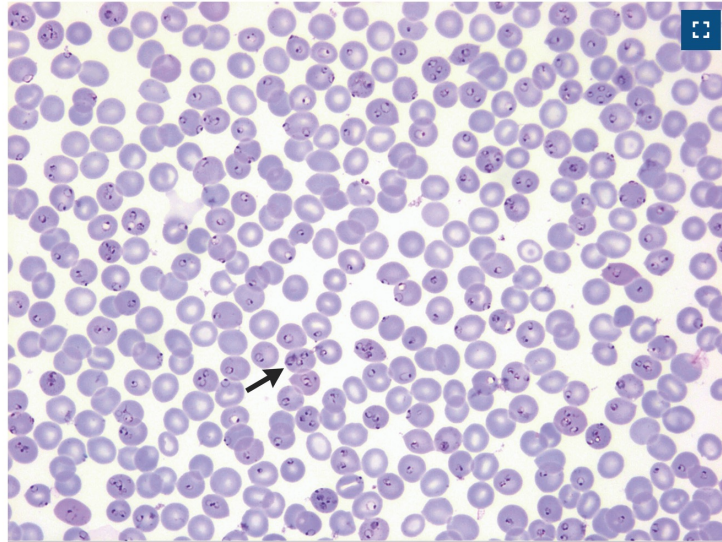
Treatments or Combination Therapies with Clinical Efficacy, Evidence of Fibrosis Reduction, and Improved Variant Allele Frequency in Phase 3 Trials.

Target	Compound	Clinical Trials	Diseases	Outcomes	ClinicalTrials.gov No.
Telomerase	Imetelstat (9.4 mg/kg) vs. best available therapy	Phase 3, open-label, randomized IMPactMF trial	Myelofibrosis refractory to JAK inhibitor or unacceptable side effects from JAK inhibitor	Ongoing, phase 2 — improved SVR35 and TSS50 scores, acceptable safety profile, and reduced the level of marrow fibrosis and variant allele frequency at 24 wk with 4.7 vs. 9.4 mg/kg	NCT04576156
MDM2	Navtemadlin (KRT-232) vs. best available therapy	Phase 3, open-label, randomized BOREAS trial	Relapsed myelofibrosis or myelofibrosis refractory to JAK inhibitor	Improvement in SVR35 and TSS50 scores and sign of reduced level of marrow fibrosis and variant allele frequency at 24 wk	NCT03662126
XPO1	Selinexor plus ruxolitinib vs. placebo plus ruxolitinib	Phase 3, double-blind, randomized, placebo-controlled SENTRY trial	Intermediate- or high-risk myelofibrosis not previously treated with JAK inhibitor	Ongoing, phase 1 — improvement in SVR35 and TSS50 scores at 24 wk	NCT04562389
BCL2 and BCL-xL	Navitoclax plus ruxolitinib vs. placebo plus ruxolitinib	Phase 3, double-blind, placebo-controlled TRANSFORM-1 trial	Myelofibrosis not previously treated with JAK inhibitor	Nonsignificant improvement in SVR35 (proportion of patients with an end-point event was twice as high with navitoclax plus ruxolitinib as with placebo plus ruxolitinib) and TSS50 scores	NCT04472598
BET inhibitor	Pelabresib plus ruxolitinib vs. placebo plus ruxolitinib	Phase 3, double-blind, placebo-controlled MANIFEST-2 trial	Myelofibrosis not previously treated with JAK inhibitor	Increased SVR35 and TSS50 scores and sign of decreased level of marrow fibrosis and anemia at 24 wk with pelabresib plus ruxolitinib vs. placebo plus ruxolitinib	NCT04603499
LSD1 inhibitor	Bomedemstat	Phase 3, open-label, extension study	Essential thrombocythemia or polycythemia vera previously treated with bomedemstat	Ongoing, phase 2 — improvement in SVR35 and TSS50 scores, normalization of platelet levels, reduction of variant allele frequency	NCT06351631
LSD1 inhibitor	Bomedemstat	Phase 3, double-blind, randomized, active comparator-controlled Shorespan-007 trial	Essential thrombocythemia not previously treated with cytoreductive therapy	Ongoing	NCT06456346

Conclusions

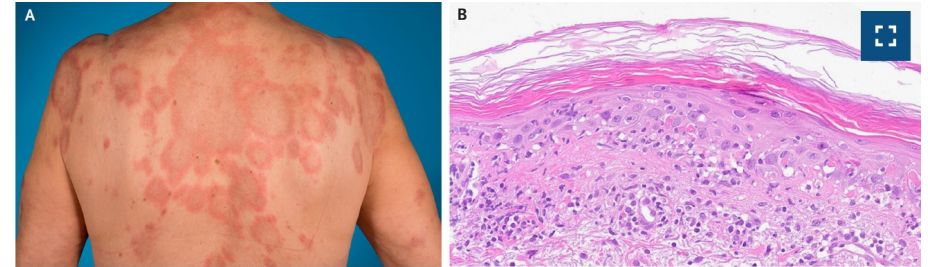
Twenty years after the discovery of *JAK2 V617F*, the pathophysiological features of myeloproliferative neoplasms are beginning to be better understood. However, the precise mechanisms of heterogeneity in *JAK2 V617F* myeloproliferative neoplasm remain unclear. One hypothesis under investigation is that the disease originates from specific HSC subtypes (with distinct lineage bias) and that the interaction of these subtypes with the microenvironment influences disease development. A significant recent finding is the long latency period between the acquisition of the myeloproliferative neoplasm driver mutation, particularly *JAK2 V617F*, and onset of clinical disease, which offers a potential window for early therapeutic intervention before additional mutations accumulate or complications arise. In recent years, new molecules and strategies have been developed to target the myeloproliferative neoplasm drivers, with notable progress for therapies targeting CALR mutants. However, further advances are needed for therapies **targeting *JAK2 V617F* and *MPL* mutants**. These therapies hold promise for keeping the disease latent or even eradicating it entirely. However, they raise important questions regarding the manner in which additional mutations may affect efficacy, the stage at which the disease remains dependent on the driver mutation or clonal fitness, and the potential risk of unmasking other non–myeloproliferative neoplasm driver–mutated HSCs. As with other cancers, if these new therapies are to substantially affect myeloproliferative neoplasm clonal disease, early intervention will be crucial to prevent disease progression and the emergence of therapy resistance.

Severe *Plasmodium falciparum* Malaria



An 82-year-old man was brought to the emergency department after being “found down.” One week earlier, he had returned from a 1-month visit to Chad, his country of birth, and had started having weakness. His body temperature was 37.4°C, and his blood pressure was 88/47 mm Hg. The physical examination was notable for confusion. Laboratory studies showed a hemoglobin level of 12 g per deciliter (reference range, 13.5 to 17), an elevated lactate dehydrogenase level, thrombocytopenia, metabolic acidosis, and acute kidney injury. A peripheral-blood smear showed ring-form trophozoites within erythrocytes and an estimated parasitemia level (expressed as a percentage of erythrocytes) of 50.7% (May–Grünwald Giemsa staining). Some erythrocytes had multiple ring forms (arrow) — a finding highly characteristic of infection with *Plasmodium falciparum*. Polymerase-chain-reaction testing of the blood was positive for *P. falciparum*. On the basis of the presence of several criteria — including impaired consciousness, acidosis, renal impairment, and a parasitemia level of greater than 10% — a diagnosis of severe *P. falciparum* malaria was made. Treatment with intravenous artesunate was initiated and then changed to oral artemisinin-based therapy on hospital day 7, when the parasitemia level was less than 0.5%. On hospital day 8, the hemoglobin level decreased to 5.6 g per deciliter; the decrease was attributed to delayed hemolysis from intravenous artesunate. The patient was discharged home on hospital day 23 in good condition.

Drug-Induced Subacute Cutaneous Lupus Erythematosus

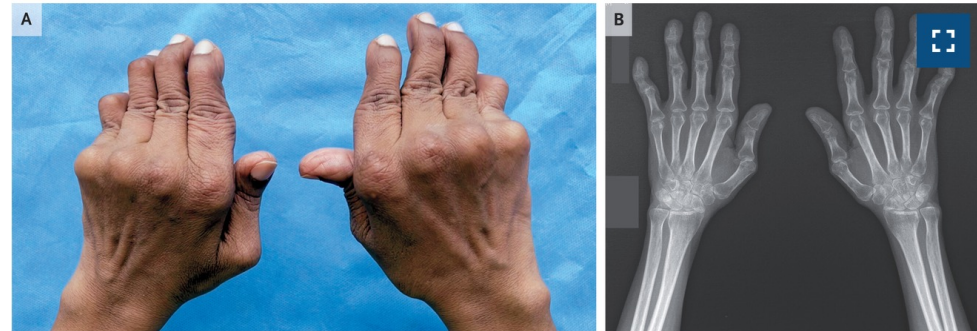


A 73-year-old woman with rheumatoid arthritis presented to the dermatology clinic with burning skin lesions that had emerged on her torso several months earlier. She had taken etanercept for 15 years before the rash started and had been taking pantoprazole for 10 months before the current presentation. Physical examination showed annular polycyclic lesions with indurated, erythematous borders and central clearing on the upper back and arms (Panel A). A quantitative antinuclear antibody test performed with indirect immunofluorescence was positive, and the anti-Ro antibody level was greater than 240 U per milliliter (reference value, <7). Histopathological analysis of a skin-biopsy sample from the patient's back showed vacuolar interface dermatitis with apoptotic keratinocytes (Panel B, hematoxylin and eosin staining), and Alcian blue staining showed dermal mucin. A diagnosis of drug-induced subacute cutaneous lupus erythematosus was made. Lesions in subacute cutaneous lupus erythematosus have annular and papulosquamous morphologic features and anti-Ro positivity in most cases. A thorough medication history is necessary to differentiate drug-induced from idiopathic subacute cutaneous lupus erythematosus. Culprit medications include thiazides, anti-tumor necrosis factor agents, and proton-pump inhibitors — the last of which was considered to be the trigger in this case. Cessation of the offending drug typically leads to resolution of the rash. Pantoprazole was discontinued, and treatment with hydroxychloroquine and topical clobetasol was started. The rash abated after 4 months and had not recurred 1 year after discontinuation of hydroxychloroquine and topical clobetasol.

Jaccoud's Arthropathy

Die **Jaccoud-Arthropathie** (auch *Jaccoud-Arthritis*) ist eine **chronische, deformierende Gelenkerkrankung**, die vor allem die Hände betrifft. Das wichtigste Merkmal ist, dass die Fehlstellungen der Finger zwar optisch stark einer schweren rheumatoiden Arthritis ähneln, im Röntgenbild jedoch **keine Zerstörung der Knochen** (Gelenkerosionen) zu sehen ist.

Ursprünglich wurde die Erkrankung nach dem französischen Arzt Sigismond Jaccoud benannt, der sie als seltene Spätfolge nach wiederholten Schüben von **Rheumatischem Fieber** beschrieb. Heute tritt sie jedoch weitaus häufiger als Begleiterscheinung des **Systemischen Lupus erythematoses (SLE)** oder anderer Autoimmunerkrankungen auf.



A 30-year-old woman presented to the rheumatology clinic with a 2-year history of pain, swelling, and morning stiffness in the wrists, knuckles, and fingers. During the 6 months before presentation, she had received treatment with methotrexate for possible rheumatoid arthritis, but her symptoms had not abated. Physical

examination was notable for swan-neck deformities and slight ulnar deviations of fingers two through five and Z-shaped deformities of the thumbs on both hands when the fingers were extended (Panel A). When the hands were clenched into fists or pressed against the table, the joint deformities largely resolved ([Video](#)) — a finding consistent with Jaccoud's arthropathy. Jaccoud's arthropathy is a chronic, deforming arthropathy that results from laxity of the ligaments and tendons around joints rather than destruction of bone and cartilage. The deformities are reducible with pressure, and radiography typically does not show bony erosions. Jaccoud's arthropathy mimics rheumatoid arthritis and is most often associated with systemic lupus erythematosus (SLE). Radiography of the hands showed juxtaarticular osteopenia but no bony erosions (Panel B; labeling has been masked). On the basis of further history taking and serologic testing, a final diagnosis of Jaccoud's arthropathy with underlying SLE was made. Treatment with hydroxychloroquine, prednisolone, and a higher dose of methotrexate was initiated. At the 4-month follow-up, the patient's joint pain had abated but the deformities persisted.

VIDEO



Resolution of the Joint
Deformities 0m 14s



Case 24-2026: A 74-Year-Old Man with Dyspnea, Proximal Muscle Weakness, and Hypoxemia

The patient had been in his usual state of health, with hypertension and dyslipidemia, until 7 months before the current presentation, when intermittent binocular diplopia developed. Evaluation by an ophthalmologist affiliated with this hospital revealed ptosis in the right eye and fluctuating strabismus that was not associated with a cranial nerve abnormality. Testing for **acetylcholine receptor antibodies was positive**, and computed tomography (CT) of the chest showed a normal thymus. Treatment with **pyridostigmine** was started for presumed ocular myasthenia gravis, and the patient was referred to the neurology clinic affiliated with this hospital.

Five months before the current presentation, the patient was evaluated in the neurology clinic. The **ocular symptoms persisted**. Diarrhea had developed after the start of treatment with pyridostigmine, which was subsequently stopped. Treatment with **prednisone was started**. The diarrhea resolved, but the ocular symptoms persisted, and the dose of prednisone was increased gradually over the course of the next 2 months.

Three months before the current presentation, the patient presented to the neurology clinic for a follow-up evaluation. The ocular symptoms persisted despite treatment with the **higher dose of prednisone**. The white-cell count was 8970 per microliter (reference range, 4000 to 11,000), the absolute lymphocyte count 580 per microliter (reference range, 720 to 4100), and the platelet count 146,000 per microliter (reference range, 150,000 to 450,000). Treatment with **mycophenolate mofetil** was started.

Two months before the current presentation, the patient was reevaluated in the neurology clinic. The ocular symptoms had resolved. Leg swelling, weight gain, moon facies, and **oral thrush (Mundsoor)** had developed. The dose of prednisone was decreased by 10%, and treatment with nystatin suspension was started; the oral thrush resolved with treatment. After the dose of prednisone was decreased, new fatigable weakness developed in the proximal leg muscles on both sides; a diagnosis of **generalized myasthenia gravis** was considered.

Variable	Reference Range, Adults†	3 Months before Presentation	On Presentation	Hospital Day 3
Hemoglobin (g/dl)	13.5–17.5	14.1	10.5	9.6
Hematocrit (%)	41.0–53.0	41.8	31.5	27.3
White-cell count (per μ l)	4000–11,000	8970	4520	2110
Differential count (per μ l)				
Neutrophils	1920–7600	7670	3860	1890
Lymphocytes	720–4100	580	40	40
Monocytes	160–1100	450	140	70
Eosinophils	0–500	40	0	0
Basophils	0–150	40	0	0
Immature granulocytes	0–90	190	110	0
Platelet count (per μ l)	150,000–450,000	146,000	129,000	106,000
Aspartate aminotransferase (U/liter)	10–40	15	51	116
Alanine aminotransferase (U/liter)	10–55	20	59	118
Alkaline phosphatase (U/liter)	45–115	42	42	54
Total bilirubin (mg/dl)	0.0–1.0	0.5	0.5	0.6
Direct bilirubin (mg/dl)	0.0–0.3	—	0.2	0.3
Albumin (g/dl)	3.3–5.0	3.9	2.5	2.1
Total protein (g/dl)	6.0–8.3	6.2	4.4	5.8

On examination, the temporal temperature was 37.2°C, the blood pressure 112/64 mm Hg, the heart rate 111 beats per minute, the respiratory rate **22 breaths per minute**, and the oxygen **saturation 87%** while the patient was breathing ambient air. The oxygen saturation **increased to 98%** while supplemental oxygen was delivered through a nasal cannula at a **rate of 5 liters per minute**.

Five weeks before the current presentation, a tongue lesion developed. The lesion was painful, and the patient ate and drank less than usual. Treatment with mouthwash containing viscous lidocaine, diphenhydramine, magnesium hydroxide, and aluminum hydroxide was started, but his symptoms did not abate. Three weeks before the current presentation, he began to have two or three episodes of nonbloody, watery diarrhea per day.

The patient reported that he had ongoing pain related to the tongue lesion. The diarrhea had abated slightly.

Additional medical history included hypertension and dyslipidemia. Three months before the current presentation, screening tests performed in anticipation of immunosuppressive treatment had included an interferon- γ release assay for *Mycobacterium tuberculosis* and tests for hepatitis C virus antibodies, hepatitis B virus surface antigen, hepatitis B virus core antibodies, and hepatitis B virus surface antibodies, all of which had negative results.



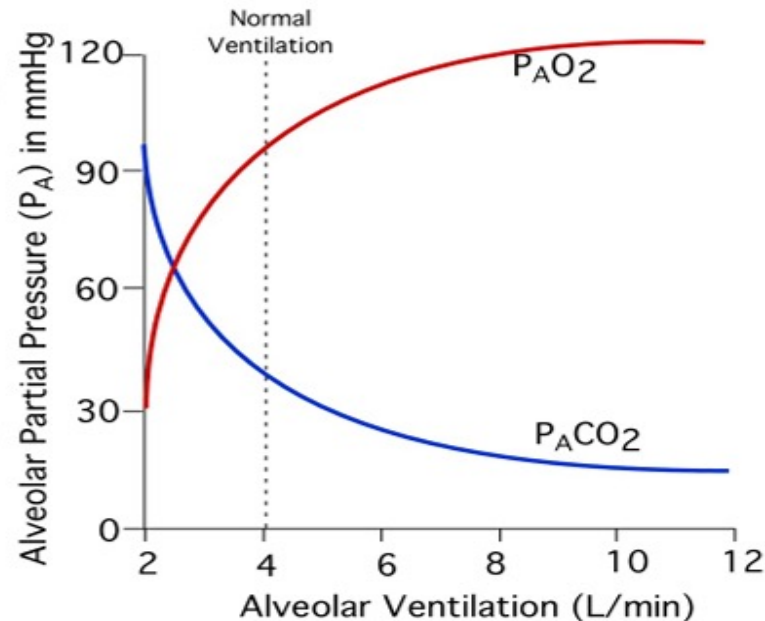
Analysis of arterial blood gas showed a pH of 7.51 (reference range, 7.35 to 7.45), a partial pressure of carbon dioxide of 29 mm Hg (reference range, 30 to 45), and a partial pressure of oxygen of 81 mm Hg (reference range, 80 to 100). Testing of a stool specimen for *Clostridioides difficile* and Shiga toxins 1 and 2 was negative.

Let us look at these blood gases a little more carefully

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

$$PAO_2 = 150 - PaCO_2/0.8$$

Alveoläre Gasformel
(Meeresebene)



Analysis of arterial blood gas showed a pH of 7.51 (reference range, 7.35 to 7.45), a partial pressure of carbon dioxide of 29 mm Hg (reference range, 30 to 45), and a partial pressure of oxygen of 81 mm Hg (reference range, 80 to 100).

Patient's PAO₂ is 114 mm Hg
Alveolar ventilation is 5 L/min.

His PaO₂ should have been 105, not 81 mm Hg. Thus, the gradient is 25 mm Hg.



The patient was admitted to this hospital. Treatment with mycophenolate mofetil was stopped, and prednisone was continued at the dose that he had been receiving as an outpatient. Intravenous immune globulin was administered daily for 3 days. He had **limited oral intake because of pain associated with the tongue lesion**. Over the course of the next 3 days, **anemia and thrombocytopenia progressed, elevated levels of alanine aminotransferase and aspartate aminotransferase were measured, and leukopenia developed.**

CT of the Chest.

CT of the chest was performed after the administration of intravenous contrast material and timed to evaluate the pulmonary arteries. An axial image in a lung window (Panel A) shows **scattered areas of interlobular septal thickening** (arrow). An axial image in a soft-tissue window (Panel B) shows heterogeneity within the atelectatic portion of the left lower lobe (white arrow) and a **small adjacent effusion** (yellow arrow). An additional axial image in a lung window (Panel C) shows **bronchial-wall thickening** (black arrow) and a 6-mm centrilobular nodule (white arrow). Note that the yellow arrow in Panel B obscures a small artifact.

Net State of Immunosuppression — A Key Organizing Principle

Infectious syndromes reflect the intersection of pathogen virulence and the host's net state of immunosuppression — a composite framework shaped by factors such as the patient's underlying disease and the mechanism, dose, and duration of immunosuppressive therapy. Glucocorticoid therapy has broad effects on innate and adaptive immunity. It impairs macrophage and neutrophil function, alters lymphocyte trafficking, decreases the number of circulating CD4+ T cells, and blunts CD8+ cytotoxic effector activity. Mycophenolate mofetil further inhibits the proliferation and function of activated T lymphocytes and B lymphocytes, impairs dendritic-cell maturation and antigen presentation, and disrupts leukocyte recruitment and adhesion.

Oral Ulcers

Reactivation of latent **herpes simplex virus (HSV) is a common cause of painful oral ulcers** in immunocompromised patients and may involve any part of the oral mucosa. Varicella–zoster virus (VZV) can cause mucosal lesions; however, a concomitant rash is usually present. **Oral ulcers associated with cytomegalovirus (CMV) or Epstein–Barr virus are uncommon and often solitary findings.**

Subacute Diarrhea

Watery diarrhea in immunocompromised patients may reflect persistent infection with common enteric pathogens; however, it may also be caused by opportunistic infections such as **CMV colitis** and disseminated fungal infection with gastrointestinal involvement.

Hypoxemia

Chest imaging in this patient showed interstitial edema with small pleural effusions, adjacent atelectasis, and findings suggestive of aspiration in the left lower lobe. There were no nodular lesions characteristic of cryptococcosis or histoplasmosis; no nodular or cavitary lesions with surrounding ground-glass opacities, which would be suggestive of angioinvasive mold infection; **no diffuse ground-glass opacities**, which would be typical of viral pneumonitis; and no granulomatous lesions or mediastinal lymphadenopathy. **In this context, hypoxemia is better explained by bulbar myasthenia**, which confers a predisposition to aspiration and atelectasis, than by community-acquired pneumonia or pneumonia caused by an opportunistic pathogen.

Cytopenias and Hepatocellular Injury

Tickborne pathogens can cause cytopenias and hepatitis. Given the patient's laboratory test results and his recent trip to Cape Cod, anaplasmosis and babesiosis, including coinfection, should be considered. Herpesviruses and disseminated fungal infections can also cause hepatitis and bone marrow suppression.

Converging on a Diagnosis

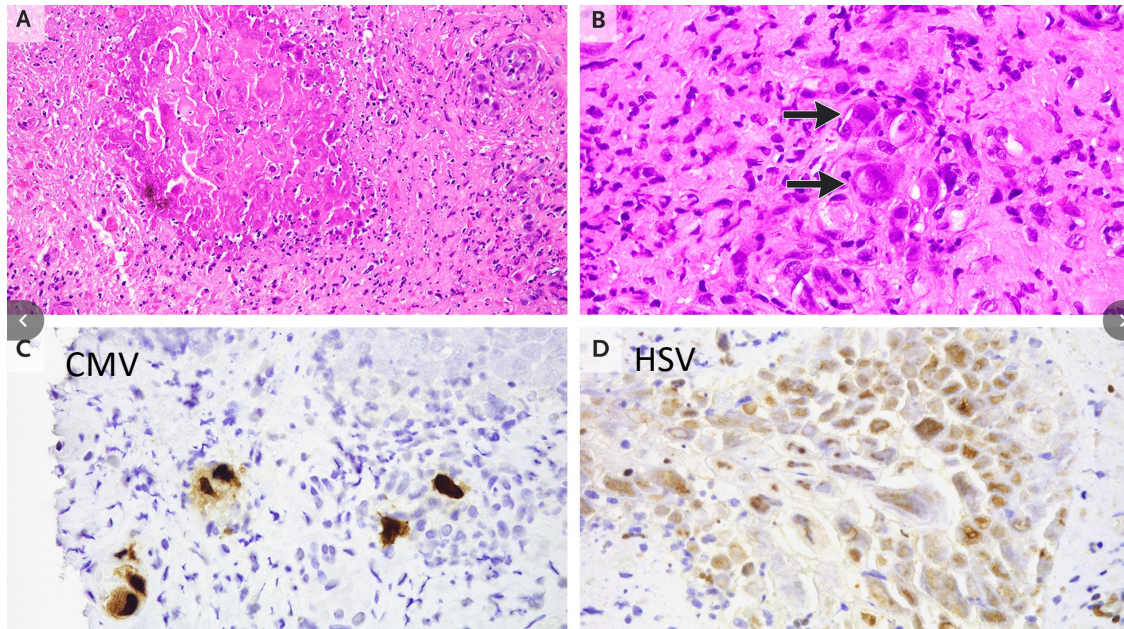
The most parsimonious diagnosis is one that explains the presence of profound T-cell lymphopenia and dysfunction, evolves as immunosuppression intensifies, and accounts for all the components of the patient's presentation.

HSV can cause a painful, necrotic tongue lesion. Although HSV alone does not readily explain progressive trilineage cytopenias and hepatitis, it could be part of a coinfection process.

Disseminated CMV infection is the most plausible explanation for all the features of this patient's syndrome. Although oral CMV ulceration is uncommon, it can occur, and such ulcers are typically deep, punched-out, and painful. Such findings reflect a vascular endothelial infection with mucosal ischemic necrosis.

Diagnostic Testing

Blood specimens were obtained to test for CMV antibodies and CMV DNA. Serologic testing was positive for CMV IgG (at a level of >10 U per milliliter) and negative for CMV IgM. This serologic pattern is consistent with previous infection rather than primary CMV infection. **CMV DNA was detected in the blood at a level of 6,270,000 IU per milliliter** (reference value, not detected). Taken together, these results indicate a high level of active CMV replication, which is **consistent with reactivation of latent CMV infection**.



Biopsy Specimen of the Tongue Lesion on Presentation.

Hematoxylin and eosin staining shows necrotic squamous epithelium (Panel A), with stromal and endothelial cells exhibiting viral cytopathic changes (Panel B, arrows).

Immunohistochemical staining for cytomegalovirus (CMV) shows strong nuclear positivity (Panel C), which confirms CMV infection. Immunohistochemical staining for herpes simplex virus (HSV) shows weak-to-moderate reactivity in necrotic squamous epithelium (Panel D), which was interpreted as a nonspecific finding; however, a concomitant HSV infection cannot be entirely ruled out.

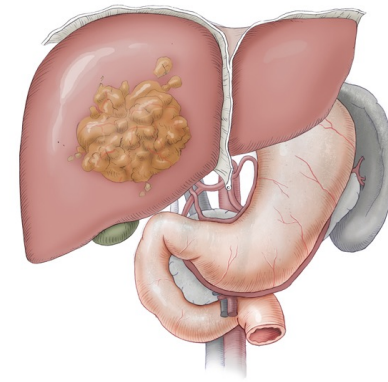
Discussion of Management

The standard induction agent for the treatment of severe disseminated CMV disease is **intravenous ganciclovir**. However, the main limitation of ganciclovir is myelosuppression, a relevant concern in this patient. This patient received **intravenous ganciclovir** and **CMV immune globulin** on hospital day 3, and treatment was transitioned to oral valganciclovir on day 14, after the CMV DNA level had decreased and clinical improvement was evident. Transition to oral therapy is appropriate after 2 to 3 weeks of intravenous therapy with a sustained viral decline, an intact gastrointestinal tract, and adequate kidney function. **Antiviral therapy was planned to be continued for at least 3 months**, provided that the patient's CMV DNA level remained undetectable. While he was receiving treatment, we were vigilant for signs or symptoms of immune reconstitution inflammatory syndrome, which did not occur.

Additional Clinical Course

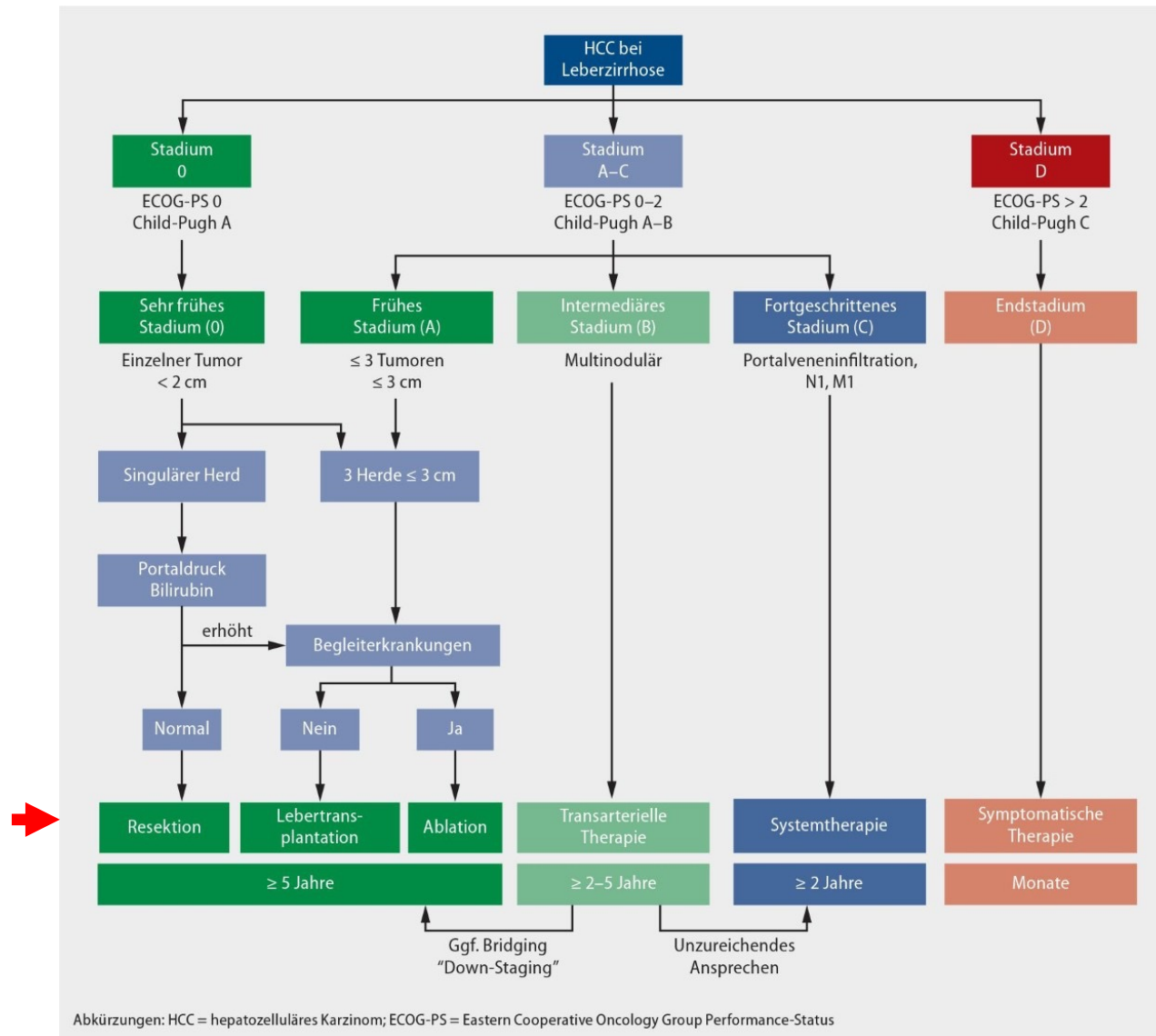
The patient continued to receive treatment with prednisone along with prophylactic sulfamethoxazole–trimethoprim; mycophenolate mofetil was not restarted. On hospital day 20, **he was discharged to a rehabilitation facility**. During a 3-week admission to the rehabilitation facility, his strength gradually increased, and when he was able to walk with a walker for up to 30 m at a time, he was discharged home.

Das **hepatozelluläre Karzinom (HCC)** – umgangssprachlich auch als **primärer Leberzellkrebs** bezeichnet – ist ein bösartiger Tumor, der direkt aus den Zellen der Leber (den Hepatozyten) entsteht. Er unterscheidet sich damit grundlegend von Lebermetastasen, die Absiedlungen anderer Krebsarten (wie Darm- oder Brustkrebs) sind. Weltweit gehört das HCC zu den **häufigsten krebsbedingten Todesursachen**, wobei in Deutschland jährlich etwa 9.000 Menschen neu erkranken und Männer dreimal häufiger betroffen sind als Frauen.

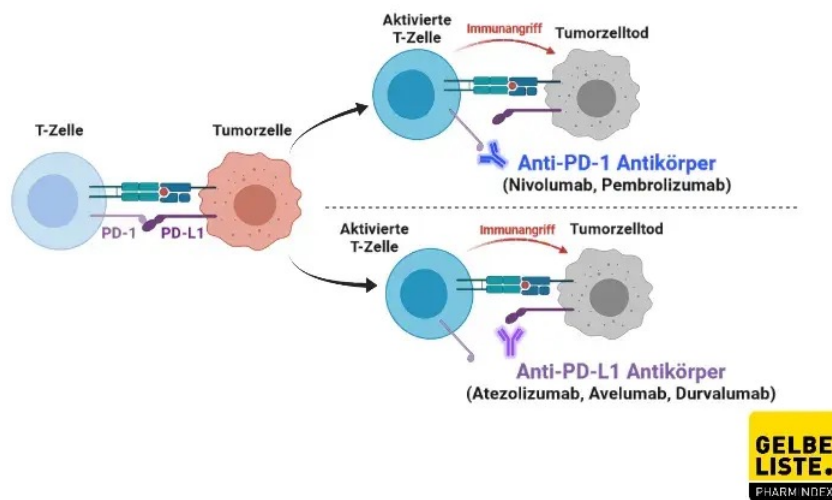


Ein HCC entwickelt sich in über 80 % der Fälle auf dem Boden einer chronisch geschädigten Leber. Zu den wichtigsten Auslösern gehören:

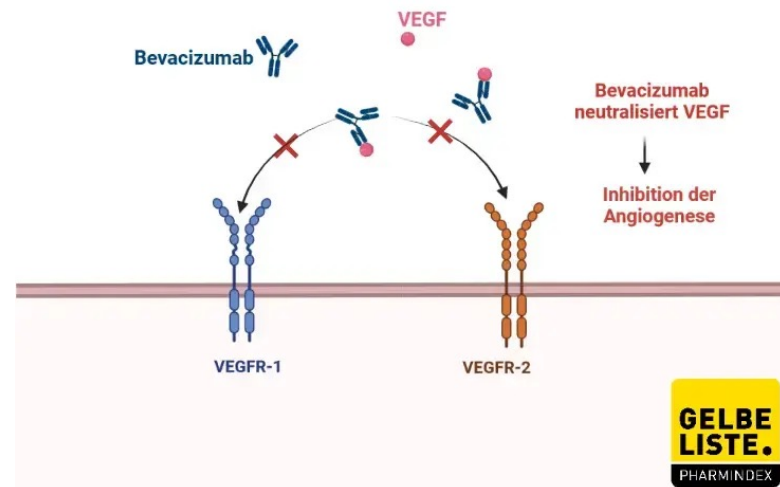
- **Leberzirrhose:** Der entzündliche Umbau von Lebergewebe in Narbengewebe ist das Hauptrisiko.
- **Chronische Virushepatitis:** Infektionen mit den Viren Hepatitis B (HBV) oder Hepatitis C (HCV).
- **Fettlebererkrankungen (NASH / MASLD):** Bedingt durch Übergewicht, Diabetes mellitus und das metabolische Syndrom gewinnen diese Ursachen stark an Bedeutung.
- **Chronischer Alkoholmissbrauch:** Ein jahrelanger hoher Alkoholkonsum schädigt die Zellen direkt.
- **Aflatoxine:** Schimmelpilzgifte in verunreinigten Nahrungsmitteln (vor allem in tropischen Regionen).



Atezolizumab ist ein **monoklonaler Antikörper** und immunonkologischer Checkpoint-Inhibitor. Er blockiert das Protein PD-L1 auf Krebs- und Immunzellen, wodurch das körpereigene Immunsystem den Tumor wieder erkennen und bekämpfen kann. Das Medikament wird als Infusion verabreicht



Bevacizumab ist ein biotechnologisch hergestellter, humanisierter **monoklonaler Antikörper**, der als Krebsmedikament (Zytostatikum/Angiogenesehemmer) eingesetzt wird. Er blockiert gezielt das Krebswachstum, indem er die Neubildung von Blutgefäßen unterdrückt, welche den Tumor mit Nährstoffen versorgen



Liver resection after atezolizumab and bevacizumab versus maintenance therapy for locally advanced hepatocellular carcinoma (TALENTOP): a multicentre, open-label, randomised, phase 3 trial

Summary

Background Resection might offer additional benefit in patients with advanced-stage hepatocellular carcinoma treated with systemic therapy. However, high-quality evidence supporting the procedure is absent. We aimed to establish whether resection can provide survival benefit in patients with advanced hepatocellular carcinoma who respond to systemic therapy.

Methods In this randomised, open-label, multicentre, phase 3 trial, we recruited treatment-naïve patients with hepatocellular carcinoma, macrovascular invasion, and no extrahepatic metastasis from 24 hospitals in China. These patients were treated in the induction phase with three cycles of intravenous atezolizumab (1200 mg every 3 weeks) plus intravenous bevacizumab (15 mg/kg bodyweight every 3 weeks) and one cycle of atezolizumab monotherapy. Patients who completed the induction phase, had a partial response or stable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and were considered feasible for resection were randomly assigned (1:1) to undergo surgical resection followed by 12 months of atezolizumab plus bevacizumab initiated 4–6 weeks after surgery (ie, the surgery group), or to maintenance atezolizumab plus bevacizumab until loss of clinical benefit or intolerable toxicity (the maintenance therapy group). Randomisation was by computer-generated sequence with permuted blocks via a central interactive web response system, stratified by tumour response and Eastern Cooperative Oncology Group performance status. Treatment administered to patients was not masked. The primary endpoint was time to treatment failure, assessed by an independent review facility and analysed by intention to treat. Time to treatment failure was defined as the time from randomisation to the first documented treatment failure (ie, local recurrence or disease progression according to RECIST 1.1, emergence of extrahepatic spread, or death). This study is registered with ClinicalTrials.gov (NCT04649489) and is ongoing.

Findings Between April 4, 2021, and July 18, 2024, a total of 489 patients were enrolled in the induction phase. Of them, 201 were randomly assigned to the surgery group (n=101; 93 male, eight female) or the maintenance therapy group (n=100; 87 male, 13 female). After a median follow-up of 18·4 months, the median time to treatment failure was 20·4 months in the surgery group and 11·8 months in the maintenance therapy group (hazard ratio 0·60, 95% CI 0·39–0·91; p=0·015). Grade 3 or 4 treatment-related adverse events occurred in 32 (39%) of 83 patients in the surgery group and 21 (21%) of 100 in the maintenance therapy group, the most common of which were increased alanine aminotransferase (seven patients [8%] in the surgery group *vs* one [1%] in the maintenance therapy group), reduced platelet count (seven [8%] *vs* three [3%]), and proteinuria (three [4%] *vs* seven [7%]). Two treatment-related deaths occurred in the surgery group due to abnormal liver function (considered related to atezolizumab) and liver failure (considered related to atezolizumab, bevacizumab, or surgery).

Interpretation In patients with advanced hepatocellular carcinoma with macrovascular invasion after systemic therapy, time to treatment failure was longer in those who had liver resection than in those who received maintenance therapy.

Funding Shanghai Roche Pharmaceuticals and Ministry of Science and Technology of China.

Patients

Eligible patients were aged 18 years or older, had histologically or radiologically confirmed hepatocellular carcinoma according to American Association for the Study of Liver Diseases criteria,¹⁵ had not received previous anti-tumour therapy, had at least one measurable lesion with macrovascular invasion and no extrahepatic spread, had a future liver remnant ratio of at least 25%, had Child–Pugh class A liver function, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Key exclusion criteria included known fibrolamellar, sarcomatoid, or mixed cholangiocarcinoma–hepatocellular carcinoma histology; severe, untreated oesophagogastric varices; clinically significant ascites; or a history of hepatic encephalopathy. Full eligibility criteria are provided in the trial protocol in appendix 2 (pp 88–92). Biological sex was self-reported by patients at enrolment, with male and female as the available options. Race and ethnicity were also self-reported by patients at enrolment. All patients provided written informed consent before enrolment.

Procedures

Tumours were assessed by contrast-enhanced CT or MRI according to RECIST version 1.1 and mRECIST after cycle 2 and on day 21 (± 7 days) of cycle 4 of the induction phase (pre-randomisation baseline), and at regular intervals thereafter. After randomisation, patients assigned to liver resection were allowed an additional assessment before surgery as a preoperative confirmation, a further assessment in the preceding 7 days of the first postoperative dose, and assessments every 9 weeks (± 7 days) thereafter. Patients assigned to continued drug therapy had a tumour assessment at week 6 (± 7 days) after randomisation and every 9 weeks (± 7 days) thereafter. All tumour assessments were completed within 7 days before dosing. All resections were done by surgeons qualified in liver resection, each holding the rank of Associate Chief Physician or above.

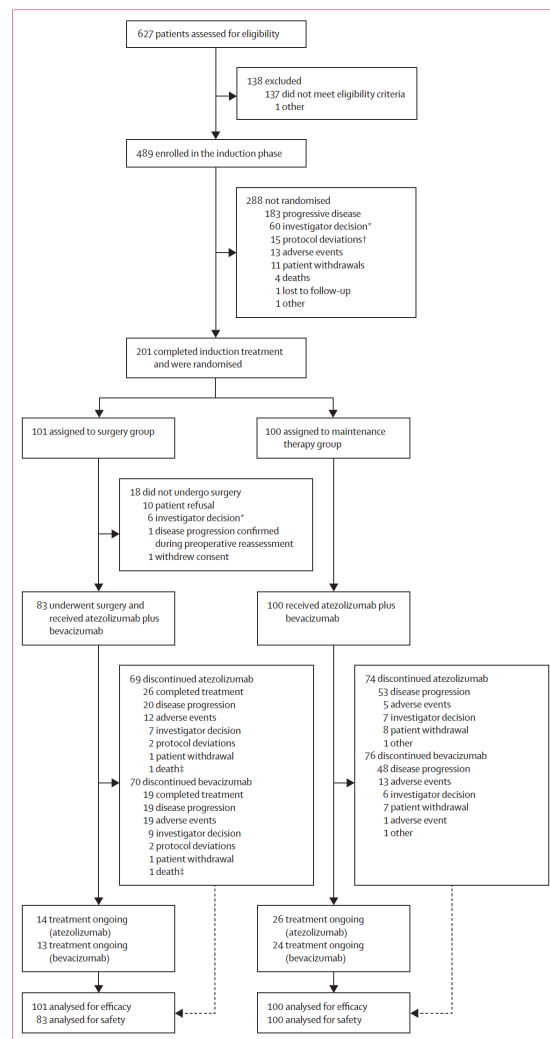


Figure 1: Trial profile

*Treatment was discontinued as this was considered most appropriate for the patient by the investigator.
†Protocol deviations included three patients who did not meet the eligibility criteria and 12 patients who did not adhere to the study protocol requirements. ‡These deaths refer to the same patient, who died of COVID-19 infection unrelated to the study treatment.

	Surgery group (N=101)	Maintenance therapy group (N=100)
Median age, years	58 (52–65)	56 (48–65)
Sex		
Male	93 (92%)	87 (87%)
Female	8 (8%)	13 (13%)
Ethnicity		
Han Chinese	96 (95%)	98 (98%)
Other	5 (5%)	2 (2%)
Aetiology		
Hepatitis B virus	91 (90%)	91 (91%)
Hepatitis C virus	3 (3%)	2 (2%)
Other	9 (9%)	9 (9%)
Portal vein classification		
Vp0	6 (6%)	7 (7%)
Vp1	5 (5%)	9 (9%)
Vp2	27 (27%)	29 (29%)
Vp3	46 (46%)	44 (44%)
Vp4	17 (17%)	11 (11%)
Hepatic vein tumour thrombosis		
Yes	17 (17%)	16 (16%)
No	84 (83%)	84 (84%)
Inferior vena cava tumour thrombus		
Yes	3 (3%)	1 (1%)
No	98 (97%)	99 (99%)
ECOG performance status score at induction phase		
0	84 (83%)	87 (87%)
1	17 (17%)	13 (13%)
ECOG performance status score at randomisation phase		
0	88 (87%)	86 (86%)
1	13 (13%)	14 (14%)
Albumin–bilirubin grade at induction phase		
1	67 (66%)	80 (80%)
2	34 (34%)	20 (20%)
3	0	0
Albumin–bilirubin grade at randomisation phase		
1	75 (74%)	81 (81%)
2	25 (25%)	19 (19%)
3	1 (1%)	0

(Table 1 continues in next column)

	Surgery group (N=101)	Maintenance therapy group (N=100)
(Continued from previous column)		
Median target lesion diameter, mm	56 (36–86)	57 (39–84)
Number of lesions (target and non-target)		
1	6 (6%)	4 (4%)
2–3	84 (83%)	82 (82%)
>3	11 (11%)	14 (14%)
AFP at induction phase		
<400 ng/mL	50 (50%)	49 (49%)
≥400 ng/mL	51 (51%)	51 (51%)
AFP at randomisation phase		
<400 ng/mL	77 (76%)	75 (75%)
≥400 ng/mL	24 (24%)	25 (25%)
Tumour treatment response		
Target lesion shrinkage ≥10%	72 (71%)	71 (71%)
No shrinkage or shrinkage <10%	29 (29%)	29 (29%)
Tumour response at randomisation phase as assessed by an IRF per RECIST version 1.1		
Complete response	0	0
Partial response	45 (45%)	42 (42%)
Stable disease	56 (55%)	57 (57%)
Progressive disease	0	1* (1%)

Data are median (IQR) or n (%). AFP=α-fetoprotein. ECOG=Eastern Cooperative Oncology Group. IRF=independent review facility. RECIST=Response Evaluation Criteria in Solid Tumors. *One patient in the maintenance therapy group was retrospectively reclassified as having progressive disease at the pre-randomisation assessment. After completion of induction phase treatment, no new lesions were identified by either the investigator or the IRF during tumour assessment, and the patient therefore proceeded to randomisation per protocol. Disease progression due to a newly detected lesion was identified after five treatment cycles. Retrospective review by both the investigator and IRF subsequently identified a previously unrecognised new lesion on the pre-randomisation imaging scans; the pre-randomisation tumour response was therefore revised to progressive disease.

Table 1: Baseline characteristics of randomly assigned patients

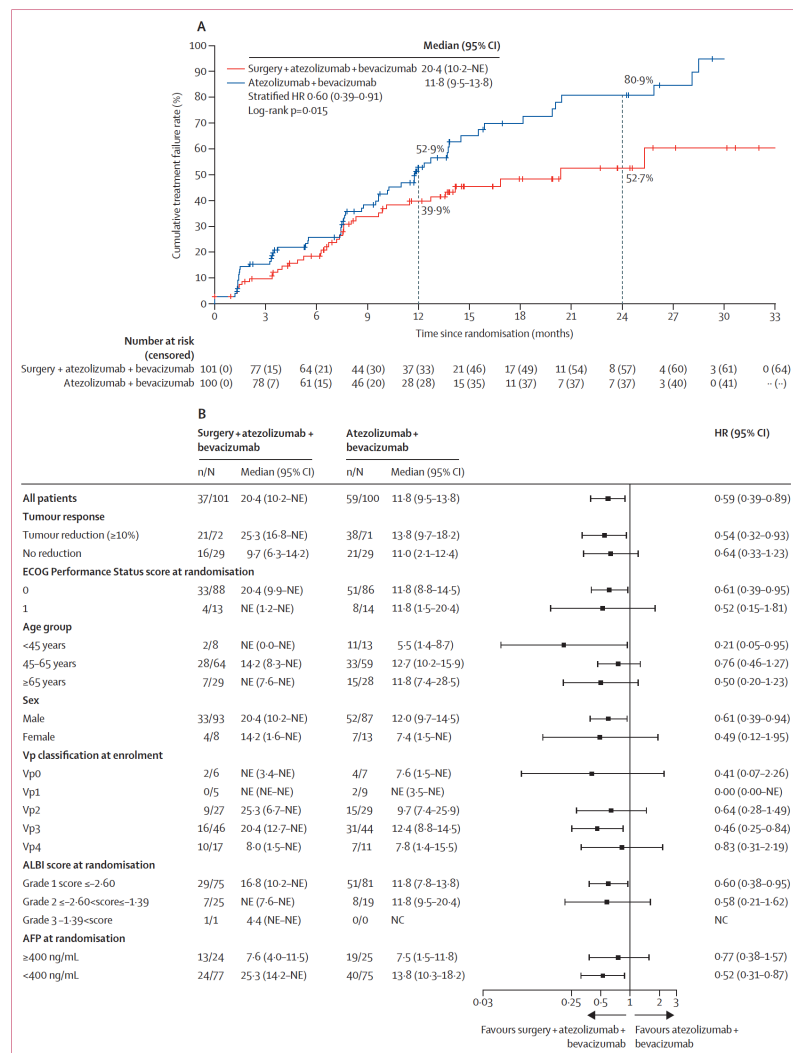


Figure 2: Time to treatment failure in randomly assigned patients, according to independent review facility assessment per Response Evaluation Criteria in Solid Tumors 1.1
(A) Kaplan-Meier estimates of time to treatment failure. (B) Time to treatment failure in key subgroups. AFP=α-fetoprotein. ALBI=albumin-bilirubin. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NC=not calculable. NE=not estimable.

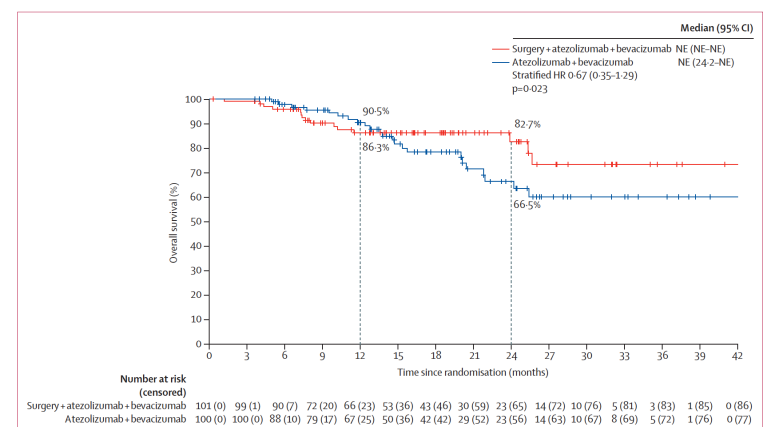


Figure 3: Kaplan-Meier analysis of overall survival in randomly assigned patients
HR=hazard ratio. NE=not estimable.

	Surgery group (N=83)	Maintenance therapy group (N=100)
Median treatment duration, cycles		
Atezolizumab	11.5 (5.0-17.0)	11.0 (5.0-17.5)
Bevacizumab	9.0 (4.0-16.0)	9.0 (5.0-17.0)
Patients with any adverse event	73 (88%)	93 (93%)
Treatment-related adverse event	66 (80%)	78 (78%)
Adverse events related to surgery	29 (35%)	-
Adverse events related to atezolizumab or bevacizumab	64 (77%)	78 (78%)
Grade 3 or 4 adverse event	41 (49%)	25 (25%)
Treatment-related grade 3 or 4 adverse event	32 (39%)	21 (21%)
Adverse events related to surgery	17 (21%)	-
Adverse events related to atezolizumab or bevacizumab	21 (25%)	21 (21%)
Serious adverse event	26 (31%)	17 (17%)
Treatment-related serious adverse event	19 (23%)	7 (7%)
Adverse events related to surgery	10 (12%)	0
Adverse events related to atezolizumab or bevacizumab	15 (18%)	7 (7%)
Deaths	3 (4%)	2 (2%)
Treatment-related deaths	2* (2%)	0
Patients discontinued any treatment due to adverse events	21 (25%)	25 (25%)
Patients discontinued and recovered after adverse events	21 (25%)	22 (22%)

Data are median (IQR) or n (%). The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. *Two treatment-related deaths occurred: abnormal liver function (n=1; suspected related to atezolizumab) and liver failure (n=1; considered related to atezolizumab, bevacizumab, or surgery).

Table 2: Summary of adverse events in randomly assigned patients

	Surgery group (N=83)				Maintenance therapy group (N=100)			
	Any grade	Grade 1-2	Grade 3-4	Death	Any grade	Grade 1-2	Grade 3-4	Death
Any treatment-related adverse events	66 (80%)	32 (39%)	32 (39%)	2 (2%)	78 (78%)	57 (57%)	21 (21%)	0
Proteinuria	31 (37%)	28 (34%)	3 (4%)	0	40 (40%)	33 (33%)	7 (7%)	0
Platelet count decreased	21 (25%)	14 (17%)	7 (8%)	0	19 (19%)	16 (16%)	3 (3%)	0
Alanine aminotransferase increased	15 (18%)	8 (10%)	7 (8%)	0	10 (10%)	9 (9%)	1 (1%)	0
White blood cell count decreased	13 (16%)	11 (13%)	2 (2%)	0	13 (13%)	12 (12%)	1 (1%)	0
Aspartate aminotransferase increased	13 (16%)	7 (8%)	6 (7%)	0	12 (12%)	12 (12%)	0	0
Blood bilirubin increased	13 (16%)	12 (15%)	1 (1%)	0	11 (11%)	10 (10%)	1 (1%)	0
Anaemia	10 (12%)	9 (11%)	1 (1%)	0	5 (5%)	4 (4%)	1 (1%)	0
Neutrophil count decreased	10 (12%)	8 (10%)	2 (2%)	0	4 (4%)	4 (4%)	0	0
Blood corticotropin increased	9 (11%)	9 (11%)	0	0	14 (14%)	14 (14%)	0	0
Hypothyroidism	9 (11%)	9 (11%)	0	0	10 (10%)	10 (10%)	0	0
Hypertension	8 (10%)	4 (5%)	4 (5%)	0	12 (12%)	10 (10%)	2 (2%)	0
Hypoalbuminaemia	8 (10%)	8 (10%)	0	0	0	0	0	0
Adrenal insufficiency	6 (7%)	6 (7%)	0	0	5 (5%)	4 (4%)	1 (1%)	0
Hypokalaemia	6 (7%)	4 (5%)	2 (2%)	0	0	0	0	0
Blood creatinine increased	5 (6%)	5 (6%)	0	0	3 (3%)	3 (3%)	0	0
Lymphocyte count decreased	5 (6%)	3 (4%)	2 (2%)	0	3 (3%)	3 (3%)	0	0
Pruritus	5 (6%)	5 (6%)	0	0	3 (3%)	3 (3%)	0	0
Pleural effusion	5 (6%)	4 (5%)	1 (1%)	0	0	0	0	0

Table 3: Treatment-related adverse events occurring in more than 5% of randomly assigned patients in either arm (safety analysis set)

Research in context

Evidence before this study

We searched PubMed from database inception to Feb 28, 2026, using the search terms "hepatocellular carcinoma", "HCC", "resection", "surgery", "PD-1 inhibitor", "PD-L1 inhibitor", "immune checkpoint inhibitors", "anti-angiogenic", "atezolizumab", and "bevacizumab", with no language restrictions, and identified no randomised controlled trials with published data similar to TALENTOP. Atezolizumab plus bevacizumab has been established as the first-line standard of care for unresectable hepatocellular carcinoma (HCC) based on the IMbrave150 trial. However, long-term survival outcomes remain unsatisfactory. Several retrospective studies have suggested that liver resection might provide additional curative opportunities and improve prognosis in patients with advanced HCC who respond to systemic therapy. The survival benefit of liver resection followed by systemic therapy compared with maintenance systemic therapy has not been prospectively evaluated, and direct head-to-head comparisons between these two treatment strategies are yet to be established.

Added value of this study

To our knowledge, TALENTOP is the first multicentre, randomised, phase 3 trial designed to assess whether liver resection can provide a time-to-treatment-failure benefit in patients with advanced HCC who respond to systemic therapy. This question represents a common clinical dilemma for surgeons and medical oncologists in the era of immunotherapy and is of paramount concern to patients and their families. The TALENTOP study showed that, compared with maintenance systemic therapy, liver resection provided a statistically significant and clinically meaningful benefit in time to treatment failure.

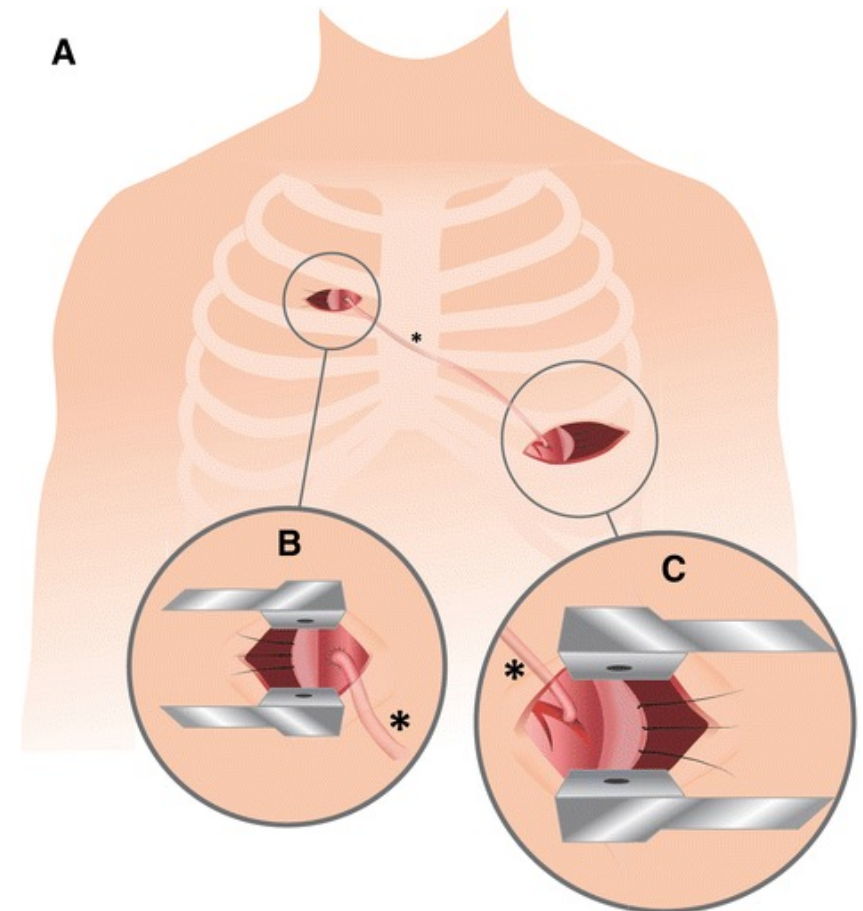
Implications of all the available evidence

The favourable risk-benefit profile for the TALENTOP regimen supports atezolizumab plus bevacizumab as an effective conversion therapy in patients with advanced HCC. Patients who have a partial response or stable disease after initial systemic therapy should undergo multidisciplinary team assessment for resectability and be considered for liver resection.

Performing coronary artery bypass grafting (**CABG**) through a small thoracotomy—instead of split-opening the breastbone via a traditional median sternotomy—is known as Minimally Invasive Coronary Artery Bypass Grafting (**MICS-CABG** or **MIDCAB**). This technique provides access to the heart through a **4- to 5-centimeter incision** made between the ribs on the left side of the chest.

Overview of Techniques

- **MIDCAB (Minimally Invasive Direct CABG):** Typically used for single-vessel disease. The surgeon uses a small left anterior thoracotomy to bypass the Left Anterior Descending (LAD) artery using the Left Internal Mammary Artery (LIMA). It is almost always performed "off-pump" on a beating heart.
- **MICS-CABG:** A more advanced evolution designed for **multivessel disease**. Using specialized instruments and video-assisted thoracoscopy, surgeons can bypass multiple blocked arteries through the same small rib incision. This can be performed off-pump or on-pump using peripheral cannulation (groin access).



Multivessel coronary artery bypass grafting via small thoracotomy versus sternotomy (MIST): an investigator-initiated, international, open-label, randomised controlled trial

Summary

Background Coronary artery bypass grafting (CABG) is a common but invasive operation traditionally performed through a median sternotomy. Minimally invasive cardiac surgery (MICS) CABG via small thoracotomy might improve postoperative recovery, but randomised evidence has been scarce. We aimed to compare patient-reported recovery after MICS CABG versus sternotomy CABG in patients with multivessel coronary artery disease and to describe clinical and safety outcomes.

Methods MIST was an investigator-initiated, international, open-label, randomised controlled trial done at seven centres (four academic hospitals and three community hospitals) in Canada, India, China, Germany, the USA, and Japan. Patients referred to participating surgeons for CABG were eligible if they were aged 18 years or older; had angiographically confirmed multivessel coronary artery disease, defined as lesions of at least 70% stenosis in at least two major epicardial vessels and at least two separate coronary artery territories (left anterior descending artery, left circumflex artery, or right coronary artery) or left main coronary stenosis of 50% or more; and were suitable for coronary surgery both with sternotomy CABG and MICS CABG. Patients who were haemodynamically compromised, had contraindications to either approach, had had previous cardiac surgery, or required concomitant procedures were excluded. Eligible patients were randomly assigned (1:1) to MICS CABG or sternotomy CABG by a central, web-based system, stratified by centre, with block sizes of four and six. The primary endpoint was patient-reported physical recovery at 1 month, assessed by the 36-item Short Form Health Survey Physical Component Summary (SF-36 PCS) score. The primary analysis was by intention to treat; safety analyses were done according to treatment received. Missing 1-month questionnaire data were handled by multiple imputation. The trial was registered with ClinicalTrials.gov (NCT03447938), and is closed to recruitment.

Findings Between Aug 24, 2018, and Nov 26, 2024, 176 patients were enrolled, 170 of whom were randomly assigned to MICS CABG (n=86) or sternotomy CABG (n=84). The median age of patients was 67·0 years (IQR 61·0–72·0), 154 (91%) patients were male, and 16 (9%) were female. At 1 month after surgery, SF-36 PCS scores were significantly higher in the MICS CABG group than in the sternotomy CABG group (mean 45·1 [SD 8·0] vs 42·2 [9·1]; mean difference 2·9 [95% CI 0·3–5·5]; p=0·031). Clinical and safety follow-up at 1 month was complete in all patients; 12-month clinical and safety follow-up was complete in all except three patients in the sternotomy CABG group. Up to 12 months after surgery, there were no deaths or strokes in either group; one major adverse cardiac or cerebrovascular event occurred in the MICS CABG group before 1 month and none in the sternotomy CABG group.

Interpretation For selected patients with multivessel coronary artery disease, MICS CABG performed by experienced teams improved patient-reported physical recovery at 1 month compared with sternotomy CABG, with no apparent safety penalty through to 12 months. These findings support consideration of MICS CABG in appropriately selected patients treated by experienced teams, and further studies of implementation, recovery pathways, and long-term outcomes.

Funding Medtronic.

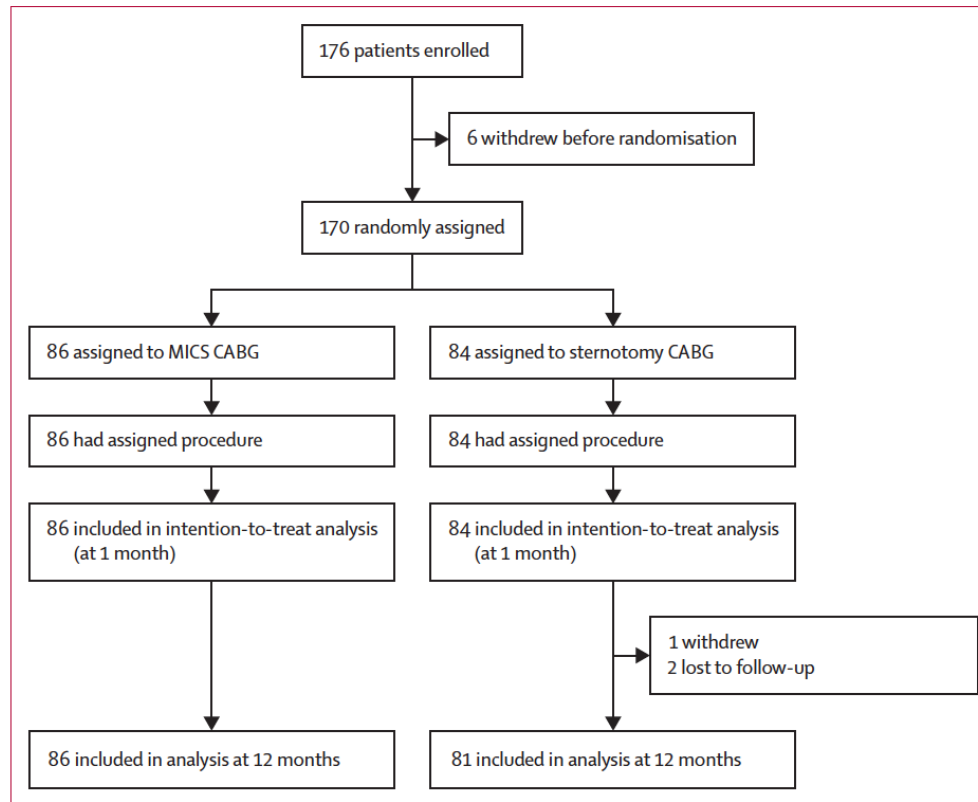


Figure 1: Trial profile

CABG=coronary artery bypass grafting. MICS CABG=minimally invasive cardiac surgery CABG.

	MICS CABG group (n=86)	Sternotomy CABG group (n=84)
Age, years	66.5 (60.0-70.0)	68.5 (62.0-74.0)
Sex*		
Male	79 (92%)	75 (89%)
Female	7 (8%)	9 (11%)
BMI, kg/m ²	26.4 (23.7-28.6)	26.8 (23.5-28.9)
Diabetes	43 (50%)	42 (50%)
Insulin-dependent	6 (14%)	7 (17%)
Non-insulin-dependent†	37 (86%)	35 (83%)
Hypertension	67 (78%)	62 (74%)
Dyslipidaemia	44 (51%)	48 (57%)
Smoking status (ever)	31 (36%)	31 (37%)
Current tobacco user	15 (48%)	7 (23%)
Former tobacco user	16 (52%)	24 (77%)
Never smoker	55 (64%)	53 (63%)
Previous myocardial infarction	29 (34%)	22 (26%)
Previous percutaneous coronary intervention	18 (21%)	14 (17%)
Congestive heart failure	7 (8%)	2 (2%)
History of transient ischaemic attack or cerebrovascular accident	6 (7%)	6 (7%)
COPD	4 (5%)	1 (1%)
Peripheral vascular disease	4 (5%)	5 (6%)
Renal failure requiring dialysis	1 (1%)	2 (2%)
Atrial fibrillation	3 (3%)	4 (5%)
LVEF <50%	13 (15%)	15 (18%)
Unstable angina	16 (19%)	24 (29%)
Urgent indication for surgery (same admission)	11 (13%)	10 (12%)
Antiplatelet agents before surgery	68 (79%)	65 (77%)
Number of diseased vessels	3.0 (3.0-3.0)	3.0 (3.0-3.0)
Diseased vessels		
Left main only	0	0
Double-vessel disease	15 (17%)	15 (18%)
Triple-vessel disease	43 (50%)	38 (45%)
Left main plus single-vessel disease	5 (6%)	5 (6%)
Left main plus double-vessel disease	11 (13%)	13 (15%)
Left main plus triple-vessel disease	12 (14%)	13 (15%)

Data are median (IQR) or n (%). CABG=coronary artery bypass grafting. COPD=chronic obstructive pulmonary disease. LVEF=left ventricular ejection fraction. MICS CABG=minimally invasive cardiac surgery CABG. *One transgender woman self-categorised as female. †Includes diet control, oral medication, or self-reported non-adherence to diet control (one patient in each group reported non-adherence to diet control).

Table 1: Baseline characteristics

	MICS CABG group (n=86)	Sternotomy CABG group (n=84)	MD, MeD, or RR (95% CI)
Time to procedure,* days	4.5 (1.0–31.0)	7.5 (2.0–29.0)	MeD –2.9 (–8.5 to 2.6)
Number of grafts	3.0 (2.0–3.0)	3.0 (2.0–3.0)	MeD 0.0 (–0.4 to 0.4)
Number of distal arterial anastomoses	2.0 (1.0–2.0)	2.0 (1.0–3.0)	MeD 0.0 (–0.4 to 0.4)
Conduits used			
LITA use	86 (100%)	84 (100%)	..
Robotic harvesting†	5 (6%)	0	..
Skeletonised	62 (72%)	54 (64%)	RR 1.12 (0.91 to 1.38)
RITA use	19 (22%)	15 (18%)	RR 1.23 (0.67 to 2.27)
Radial use	20 (23%)	23 (27%)	RR 0.85 (0.51 to 1.43)
Gastroepiploic artery use	1 (1%)	1 (1%)	RR 0.98 (0.06 to 15.36)
Multiple arterial distal anastomoses	40 (47%)	39 (46%)	RR 1.00 (0.73 to 1.38)
Arterial grafts only	22 (26%)	24 (29%)	RR 0.90 (0.55 to 1.47)
Grafts configuration			
In-situ LITA	86 (100%)	83 (99%)	..
Proximal aortic	62 (72%)	69 (82%)	RR 0.88 (0.74 to 1.04)
Y or T or I based	21 (24%)	12 (14%)	RR 1.71 (0.90 to 3.25)
Sequential LITA use	4 (5%)	3 (4%)	RR 1.30 (0.30 to 5.64)
Use of transit-time flowmetry	76 (88%)	72 (86%)	RR 1.03 (0.92 to 1.16)
Cardiopulmonary bypass			
Off-pump surgery	82 (95%)	84 (100%)	..
Time on cardiopulmonary bypass, min	103 (41– 172); n=4	..	..
Left atrial appendage exclusion	0	1 (1%)	..
Procedure duration, min	219.5 (78.4)	181.4 (54.8)	MD 38.2 (17.6 to 58.7)
Total ventilation time, h	5.2 (5.3)	11.6 (38.5)	MD –6.4 (–14.7 to –1.9)

Data are median (IQR), n (%), or mean (SD), unless otherwise specified. CABG=coronary artery bypass grafting. LITA=left internal thoracic artery. MeD=median difference. MD=mean difference. MICS CABG=minimally invasive cardiac surgery CABG. RITA=right internal thoracic artery. RR=risk ratio. *Denotes the number of days from randomisation to surgery. †Robotic internal thoracic artery harvesting was used in five patients in the MICS CABG group at two of the centres.

Table 2: Trial interventions and operative characteristics

	MICS CABG group (n=86)*	Sternotomy CABG group (n=84)*	MD, MeD, or RR (95% CI)	p value
Primary outcome				
Primary analysis				
SF-36 PCS score	45.1 (8.0)	42.2 (9.1)	MD 2.9 (0.3 to 5.5)	0.031†
Sensitivity analysis				
SF-36 PCS score adjusting for centre	..	..	MD 2.9 (0.6 to 5.2)	0.015
SF-36 PCS score adjusting for covariates‡	..	..	MD 3.1 (0.5 to 5.7)	0.020
Secondary outcomes				
Role-physical	65.6 (28.5)	55.4 (31.3)	MD 10.2 (1.1 to 19.3)	0.028
Physical functioning	70.7 (19.7)	63.8 (19.1)	MD 6.9 (1.1 to 12.8)	0.021
Bodily pain	68.4 (19.8)	63.4 (21.6)	MD 5.0 (–1.2 to 11.3)	0.11
General health	72.5 (17.2)	72.6 (18.6)	MD –0.1 (–5.5 to 5.4)	0.98
Vitality	62.6 (17.3)	62.3 (19.0)	MD 0.4 (–5.1 to 5.9)	0.89
Social functioning	78.1 (21.1)	75.4 (21.0)	MD 2.6 (–3.8 to 9.0)	0.42
Role-emotional	84.2 (21.4)	79.9 (24.2)	MD 4.3 (–2.6 to 11.3)	0.22
Mental health	79.6 (13.1)	75.5 (13.7)	MD 4.1 (–0.004 to 8.1)	0.050
Postoperative pain VAS (resting)	3.2 (1.7)	3.5 (1.7)	MD –0.4 (–0.9 to 0.2)	0.19
Postoperative pain VAS (post-physiotherapy)	3.2 (1.9)	3.4 (2.0)	MD –0.2 (–0.8 to 0.4)	0.42
Death	0	0	..	..
Major adverse cardiovascular events	1 (1%)	0	..	..
Target vessel revascularisation	1 (1%)	0	..	..
Percentage of arterial grafts per patient	54.2 (27.6)	54.7 (29.9)	MD –0.5 (–9.2 to 8.2)	0.91
Index of completeness of revascularisation	0.8 (0.3)	0.8 (0.3)	MD –0.001 (–0.084 to 0.082)	0.98
Any red blood cell transfusion, intraoperative	4/84 (5%)	13/84 (16%)	RR 0.31 (0.10 to 0.91)	0.032
Any transfusion, intraoperative	6/84 (7%)	15/84 (18%)	RR 0.40 (0.16 to 0.98)	0.045
Any red blood cell transfusion, postoperative	6/85 (7%)	15/84 (18%)	RR 0.40 (0.16 to 0.97)	0.043
Any transfusion, postoperative	8/85 (9%)	17/84 (20%)	RR 0.47 (0.21 to 1.02)	0.056
Any red blood cell transfusion	8/85 (9%)	23/84 (27%)	RR 0.34 (0.16 to 0.72)	0.0050
Any transfusion	11/85 (13%)	27/84 (32%)	RR 0.40 (0.21 to 0.76)	0.0048
Incidence of re-exploration for bleeding	1/86 (1%)	3/84 (4%)	RR 0.32 (0.03 to 3.12)	0.33
Incidence of atrial fibrillation	5/86 (6%)	6/84 (7%)	RR 0.81 (0.26 to 2.57)	0.73
Incidence of wound infection	0/86	3/84 (4%)	..	..
Length of intensive care unit stay, days	1.0 (1.0–2.0)	1.0 (1.0–2.0)	MeD 0.0 (–0.4 to 0.4)	0.42§
Length of hospital stay, days	5 (4–8)	5 (4–7)	MeD –0.0 (–1.3 to 1.3)	0.087§
EQ-5D VAS score	78.2 (16.5)	77.9 (16.4)	MD 0.3 (–4.7 to 5.3)	0.90
SAQ score	80.4 (13.3)	80.7 (10.9)	MD –0.2 (–3.9 to 3.4)	0.89
MCS score	51.9 (7.9)	51.3 (8.5)	MD 0.7 (–1.8 to 3.2)	0.60

Data are mean (SD), n/N (%), or median (IQR), except where otherwise specified. CABG=coronary artery bypass grafting. MeD=median difference. MCS=Mental Component Summary. MD=mean difference. MICS CABG=minimally invasive cardiac surgery CABG. PCS=Physical Component Summary. RR=risk ratio. SAQ=Seattle Angina Questionnaire. SF-36=36-item Short Form Health Survey. VAS=visual analogue scale. *Missing data were imputed for the quality-of-life outcomes as per the statistical analysis plan. Actual patient data available for each outcome for the MICS CABG group and the sternotomy CABG group: n=76 in the MICS CABG group and n=77 in the sternotomy CABG group for PCS; n=79 and n=77 for role-physical; n=78 and n=79 for physical functioning; n=79 and n=79 for bodily pain; n=77 and n=79 for general health; n=79 and n=79 for vitality; n=79 and n=79 for social functioning; n=79 and n=78 for role-emotional; n=79 and n=79 for mental health; n=79 and n=80 for EQ-5D VAS; n=79 and n=80 for SAQ; n=76 and n=77 for MCS; n=78 and n=74 for postoperative pain VAS (resting); and n=77 and n=73 for postoperative pain VAS (post-physiotherapy). †Sensitivity analysis comparing MICS CABG and sternotomy CABG using the Wilcoxon rank-sum test: p value 0.048. ‡Covariates: age, sex, use of cardiopulmonary bypass, number of grafts, and BMI. §Wilcoxon rank-sum test.

Table 3: Primary and secondary outcomes at 1 month after surgery

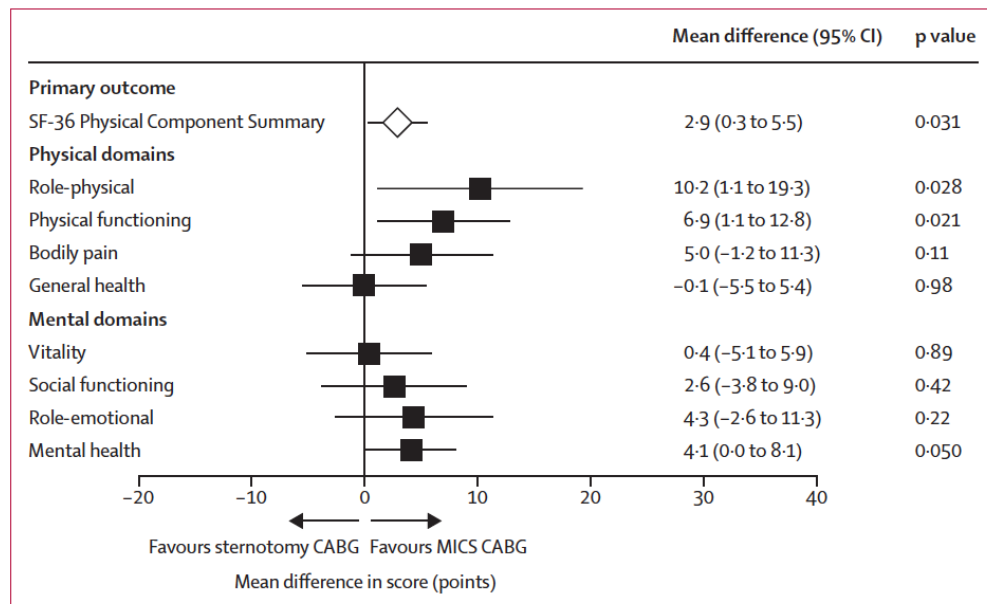


Figure 2: Primary endpoint and SF-36 domain scores at 1 month after surgery

SF-36 scores range from 0 to 100; higher scores indicate better health-related quality of life. Mean differences are MICS CABG minus sternotomy CABG. CABG=coronary artery bypass grafting. MICS CABG=minimally invasive cardiac surgery coronary artery bypass grafting. SF-36=36-item short form health survey.

	MICS CABG group (n=86)	Sternotomy CABG group (n=84)
From surgery to 1 month after surgery		
Death	0	0
MACCE (death, myocardial infarction, stroke, or target vessel revascularisation)	1/86*	0
Re-exploration for bleeding	1/86	3/84
Nosocomial infection with mesenteric ischaemia and cholecystitis	1/86	0
Deep chest wound infection	0	3/84
Haematoma evacuation	0	1/84
Acute on chronic renal failure: need for dialysis	0	1/84
From 1 month to 12 months after surgery†		
Death	0	0
MACCE (death, myocardial infarction, stroke, or target vessel revascularisation)	0	0
Hospital readmission	1/86	5/81
Haemorrhagic pericardial effusion requiring drainage	0	1/81
Repeat admissions for chest wound infection	0	1/81
Mediastinitis	0	1/81
Groin infection requiring vacuum and antibiotics	1/86	0
New renal failure requiring dialysis	0	1/81
Pyelonephritis	0	1/81

MACCE=major adverse cardiac or cerebrovascular event. CABG=coronary artery bypass grafting. MICS CABG=minimally invasive cardiac surgery CABG. *Postoperative catheterisation and re-thoracotomy for kinked graft. †Between 1 month and 12 months postoperatively, three patients in the sternotomy CABG group withdrew consent (n=1) or were lost to follow-up (n=2).

Table 4: Serious adverse events up to 12 months after surgery

Added value of this study

Although many surgical specialties have moved towards less invasive approaches, CABG largely has not. To our knowledge, the MIST trial is the first randomised controlled trial comparing MICS CABG with sternotomy CABG for multivessel coronary artery disease. Until now, the case for a less invasive, non-sternotomy approach has rested largely on single-centre series and observational registries, which are susceptible to selection and operator-experience biases. By generating randomised, multicentre evidence in a field where high-quality surgical trials remain uncommon, the trial helps clarify whether avoiding a sternotomy can improve patient-reported physical recovery at 1 month while showing no apparent reduction in procedural quality or safety through to 12 months, concerns that have tempered wider adoption of MICS CABG. It also provides randomised evidence on patient-reported recovery, an outcome of direct relevance to patients that has been less commonly used in the evaluation of surgical revascularisation. Performed by experienced teams in appropriately selected patients, the MIST trial offers recovery, procedural, and safety data that can inform the design of future trials, surgical training, and implementation research around MICS CABG.

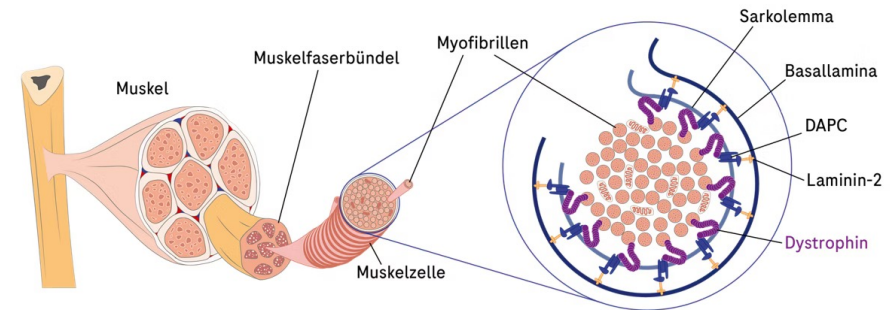
Implications of all the available evidence

For selected patients with multivessel coronary artery disease treated by experienced teams, MICS CABG improved patient-reported physical recovery at 1 month and was associated with higher physical domain scores, fewer transfusions, and shorter total ventilation time compared with sternotomy CABG, without an apparent penalty in procedural quality or 12-month safety outcomes. Clinical and safety events were infrequent, and the trial was not powered to compare clinical outcomes. Long-term follow-up of the MIST trial is ongoing and will ascertain whether early patient-centred benefits translate into durable long-term outcomes. These findings provide randomised evidence supporting the potential recovery advantages of MICS CABG in appropriately selected patients treated by experienced teams, and support further research, training, and implementation work. The relevance of these findings extends beyond the scientific community to patients and the public. The MIST trial used validated tools to evaluate patient-relevant outcomes, namely self-reported functional recovery and return to daily activities after CABG. It provides randomised evidence of improved patient-reported recovery with no apparent safety penalty through 12 months for a less invasive surgical revascularisation approach that avoids a sternotomy incision for patients with multivessel coronary artery disease. For patients, this suggests that, in appropriate circumstances and with experienced operators, multivessel bypass surgery may be achievable without a median sternotomy—an option whose role further clinical research will continue to define.

Die **Duchenne-Muskeldystrophie (DMD)** ist eine **seltene, genetisch bedingte Muskelerkrankung**, die zu einem fortschreitenden Abbau der Muskulatur führt. Sie ist die **häufigste Form der Muskeldystrophie im Kindesalter** und betrifft fast ausschließlich **Jungen** (ca. 1 von 3.500 bis 5.000 neugeborenen Knaben). Ursache ist ein Mangel des Proteins **Dystrophin**, welches für die Stabilität der Muskelzellen unverzichtbar ist. Ohne dieses Eiweiß wird Muskelgewebe nach und nach durch Fett- und Bindegewebe ersetzt.

Ursache und Vererbung

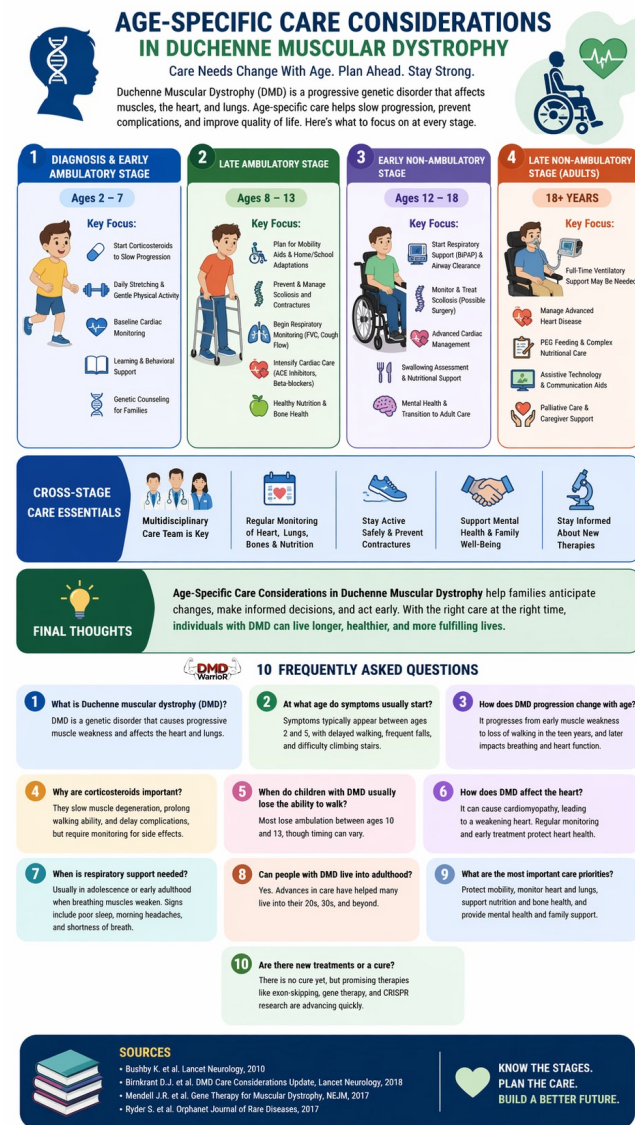
- **X-chromosomal-rezessiver Erbgang:** Da das fehlerhafte Gen auf dem X-Chromosom liegt, erkranken Jungen (die nur ein X-Chromosom besitzen). Mädchen haben meist ein zweites, gesundes X-Chromosom, das den Defekt ausgleicht; sie sind oft symptomfreie Überträgerinnen (Konduktorinnen).
- **Neumutationen:** In etwa einem Drittel der Fälle liegt keine familiäre Vererbung vor, sondern das Gen verändert sich spontan neu.



Viele Patienten mit Duchenne-Muskeldystrophie (DMD) versterben im fortgeschrittenen Krankheitsverlauf an einer Herzerkrankung. Da das fehlende Protein Dystrophin nicht nur die Skelettmuskulatur, sondern auch den Herzmuskel schädigt, kommt es häufig zu einer Kardiomyopathie oder Herzrhythmusstörungen.

Ursachen und Verlauf von Herzerkrankungen bei DMD

- **Kardiomyopathie:** Der Herzmuskel schwächt sich ab und weitet sich im Laufe der Zeit oft aus (dilatative Kardiomyopathie).
- **Fibrose:** Es kommt früh zu Narbenbildung und Bindegewebeinlagerungen im Herzgewebe.
- **Herzversagen:** Das geschwächte Herz kann den Körper nicht mehr ausreichend mit Blut versorgen, was zu einem lebensgefährlichen Pumpversagen führt

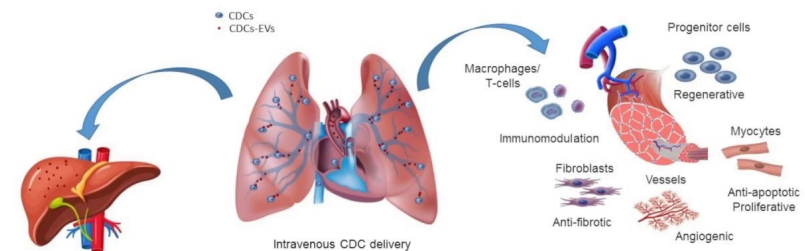


Deramioce ist eine experimentelle Zelltherapie zur Behandlung der **Duchenne-Muskeldystrophie (DMD)**, einer seltenen und fortschreitenden genetischen Erkrankung, die zu fatalem Muskelschwund führt.

Wirkmechanismus: Deramioce unterscheidet sich von klassischen Gentherapien (die fehlerhafte Gene ersetzen) durch einen regenerativen Ansatz:

- **Herkunft:** Die Therapie besteht aus allogenen Vorläuferzellen, die aus **menschlichem Spender-Herzgewebe** gewonnen werden (sogenannte *cardiosphere-derived cells* oder CDCs).
- **Funktion:** Nach der intravenösen Infusion geben diese Zellen winzige Vesikel (Exosomen) ab. Diese signalisieren den körpereigenen Immunzellen (Makrophagen), von einem entzündungsfördernden in einen **heilenden Zustand** zu wechseln.
- **Ziel:** Reduzierung von chronischen Entzündungen, Verlangsamung der Gewebevernarbung (Fibrose) und die Erhaltung der verbleibenden Muskel- und Herzfunktion.

Mechanism of Action



CDCs after administration are retained in the lungs from where they secrete exosomes and growth factors that can travel through the circulatory system and promote tissue regeneration

Deramiocele heart-derived cellular therapy in advanced Duchenne muscular dystrophy (HOPE-3): a phase 3, randomised, double-blind, placebo-controlled trial

Summary

Background Duchenne muscular dystrophy (DMD) is an X-linked genetic disease of skeletal and cardiac muscle that leads to loss of ambulation and premature death due to progressive myopathy and cardiomyopathy. Deramiocele, a heart-derived cellular therapy consisting of human allogeneic cardiosphere-derived cells, improved cardiac and skeletal muscle function in phase 1–2 studies of DMD. Our aim was to assess the efficacy and safety of deramiocele in advanced DMD and support the findings of HOPE-2.

Methods HOPE-3, a phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled study, included participants aged 10 years or older with DMD. Investigational product was infused intravenously every 3 months in outpatient settings. Skeletal and cardiac function was evaluated at 12 months. The primary endpoint was total Performance of the Upper Limb 2.0 (PUL2.0) percentage change from baseline. The trial is registered with ClinicalTrials.gov (NCT05126758).

Findings Between June 22, 2022, and May 28, 2024, 139 participants were screened, of whom 106 were randomly assigned to deramiocele (n=54) or placebo (n=52), and included in the intention-to-treat population. The primary endpoint showed significant improvements in the deramiocele group versus placebo. For total PUL2.0, least-squares mean percentage change at 12 months favoured deramiocele by 4.55% (95% CI 0.47–8.63; p=0.029). The safety profile of deramiocele was similar to that of placebo.

Interpretation Deramiocele safely slows disease progression in advanced DMD, preserving skeletal muscle function. Administered quarterly in a simple outpatient regimen, deramiocele is a promising treatment for DMD, agnostic to the precise underlying genetic lesion.

Cells were infused every three months.

Deramiocele is an investigational cellular suspension consisting of human allogeneic cardiosphere-derived cells (CDCs) originally developed to treat cardiomyopathy. CDCs survive only 1–2 weeks after transplantation but have persistent anti-inflammatory, anti-fibrotic, and immunomodulatory properties (appendix pp 3–7).¹³ While present, CDCs act by secreting paracrine factors that modulate macrophage and fibroblast function resulting in long-lasting therapeutic benefits.¹⁴ Preclinical studies revealed that CDCs improve both cardiac and skeletal muscle in models of DMD, with sustained benefits after repeated administrations.¹⁵ The discovery that CDCs work by secreting extracellular vesicles (nanosized lipid bilayer particles replete with specific bioactive RNA cargo) rationalised the systemic benefits of local cell administration and led to preclinical

Cardiosphere-derived cells (CDCs) are a specialized population of cardiac progenitor and stromal cells grown from heart tissue biopsy samples. They promote heart tissue repair and reduce scar size after a heart attack primarily by releasing healing signals and exosomes rather than by turning directly into new heart muscle.

validation of intravenous infusion as an alternative to intracardiac delivery.¹⁶ The HOPE-2 trial of deramiocele in advanced DMD—the first to use intravenous cell delivery and repeat sequential dosing of a cell therapy to treat a genetic disease—showed stabilisation of upper limb function and improved heart function relative to placebo without restriction by genotype, meeting the primary endpoint with 71% slowing of decline in mid-level PUL2.0.¹⁷ In parallel, deramiocele improved LVEF and left ventricular volumes versus placebo. A follow-up open-label extension study (HOPE-2 OLE, NCT04428476) revealed sustained benefits in upper limb and cardiac function over 3 years relative to external natural history control groups¹⁸ with no serious safety concerns over 3 years. Our aim was to assess the efficacy and safety of deramiocele in boys and young men with advanced DMD and support the findings of HOPE-2.

What paracrine factors were released by these vesicles remains a mystery.

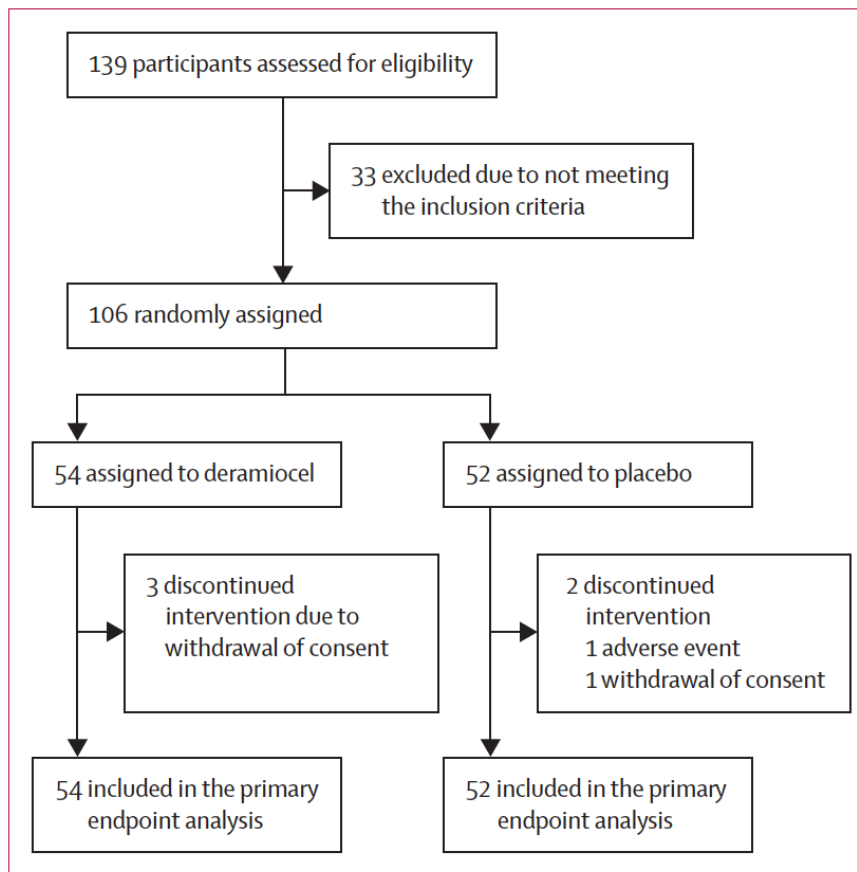


Figure 1: Trial profile

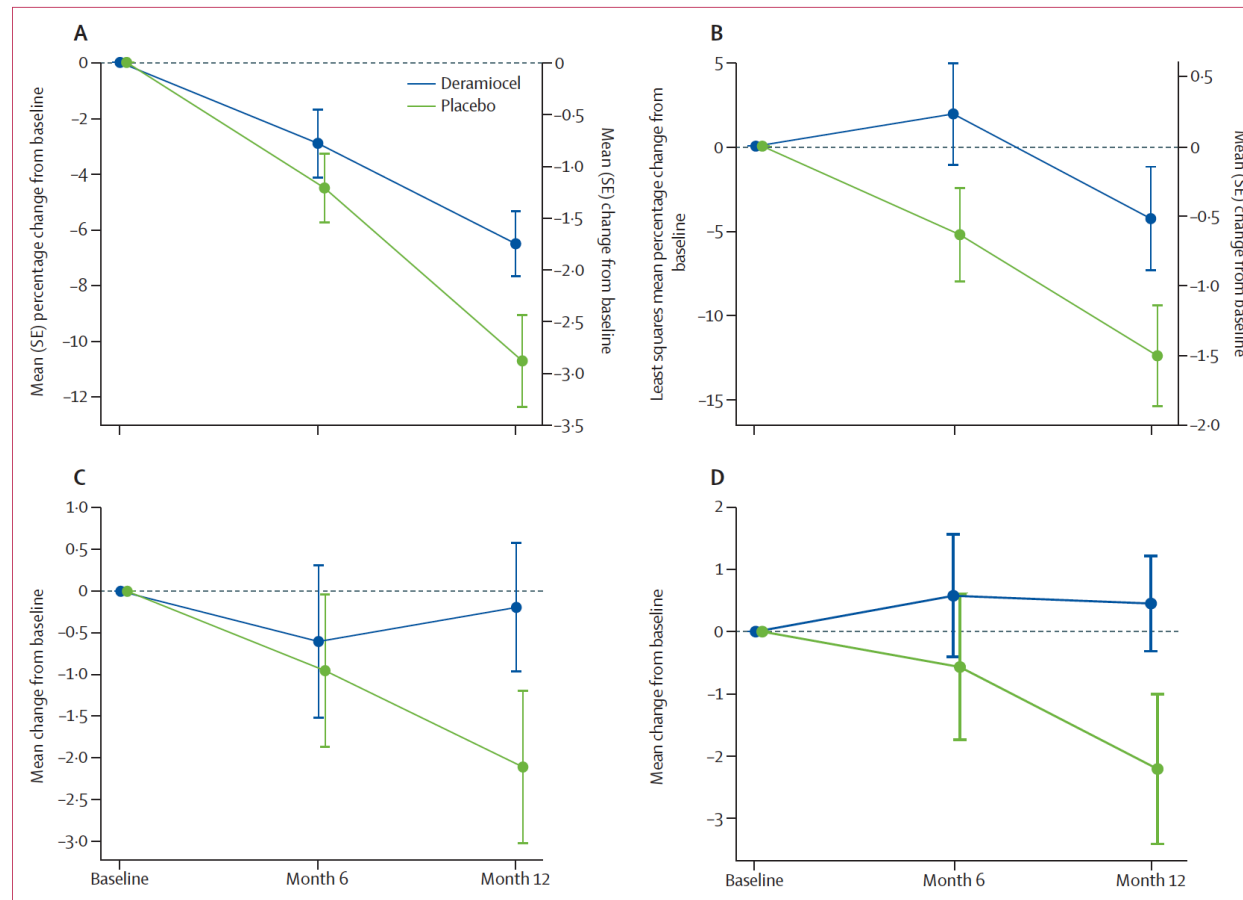
	Deramiocele (n=54)	Placebo (n=52)	Overall (n=106)
Age, years	15.0 (10–22)	14.0 (10–22)	15.0 (10–22)
Sex			
Male	54 (100%)	52 (100%)	106 (100%)
Ethnicity			
Hispanic or Latino	5 (9.3%)	6 (11.5%)	11 (10.4%)
Not Hispanic or Latino	49 (90.7%)	46 (88.5%)	95 (89.6%)
Race			
Asian	5 (9.3%)	7 (13.5%)	12 (11.3%)
Black or African American	2 (3.7%)	1 (1.9%)	3 (2.8%)
Native Hawaiian or other Pacific Islander	0	1 (1.9%)	1 (0.9%)
White	43 (79.6%)	38 (73.1%)	81 (76.4%)
Multiple	1 (1.9%)	2 (3.8%)	3 (2.8%)
Not reported	3 (5.6%)	2 (3.8%)	5 (4.7%)
Unknown	0	1 (1.9%)	1 (0.9%)
Randomisation PUL2.0 entry item score			
2, 3	25 (46.3%)	23 (44.2%)	48 (45.3%)
4, 5, 6	29 (53.7%)	29 (55.8%)	58 (54.7%)
Baseline total PUL2.0 score	27.6 (7.36)	26.5 (6.69)	27.1 (7.03)
Slow progressor indicator*	1 (1.9%)	5 (9.6%)	6 (5.7%)
Ambulatory at baseline	8 (14.8%)	8 (15.4%)	16 (15.1%)
Baseline corticosteroid use			
Prednisone	16 (29.6%)	7 (13.5%)	23 (20.7%)
Deflazacort	39 (72.2%)	43 (82.7%)	82 (77.4%)
Once daily	43 (79.6%)	39 (75.0%)	82 (77.4%)
Intermittent regimen	10 (18.5%)	12 (23.1%)	22 (20.8%)
Baseline use of genetic medication			
Exon-skipping drugs	14 (25.9%)	12 (23.1%)	26 (24.5%)
Ataluren	0	1 (1.9%)	1 (0.9%)
Microdystrophin gene replacement	1 (1.9%)	0	1 (0.9%)

Data are median (range), n (%), or mean (SD). PUL2.0=Performance of Upper Limb 2.0. *Participants with a baseline PUL2.0 entry item score of 6 (on two or three screening or baseline visits), or had documented slow progressor genotypes, were classified as positive for the Slow Progressor Indicator. The following genotypes were considered as slow progressor: exon 44 skippable mutations, exon 3–7 deletions, and other genotypes identified as slow progressor (appendix p 37).

Table 1: Demographic and disease characteristics of the intention-to-treat population

PUL 2.0 score is used to track arm and hand function over time in patients with Duchenne muscular dystrophy (DMD)

Left ventricular ejection fraction



Fiducial limits are SEM

Figure 2: Change from baseline in musculoskeletal and cardiac endpoints up to month 12

(A) PUL2.0 total score for the ITT population. (B) PUL2.0 mid-level score for the ITT population. (C) Left ventricular ejection fraction for the ITT population. (D) Left ventricular ejection fraction for the cardiomyopathy population. Each graph shows observed mean changes from baseline at baseline, month 6, and month 12 in the deramiciol (blue) and placebo (green) with accompanying standard errors (indicated by error bars). Panels (A) and (B) show the musculoskeletal measures of PUL2.0 total and mid-level scores, respectively, in the ITT population. Both panel (A) and (B) feature dual y axes, the left showing the mean observed percentage change and the right showing the observed raw mean change on the absolute scale. Panels (C) and (D) feature observed raw mean change from baseline in left ventricular ejection fraction for the ITT population and the cardiomyopathy population, respectively. PUL2.0=Performance of the Upper Limb 2.0. ITT=intention-to-treat.

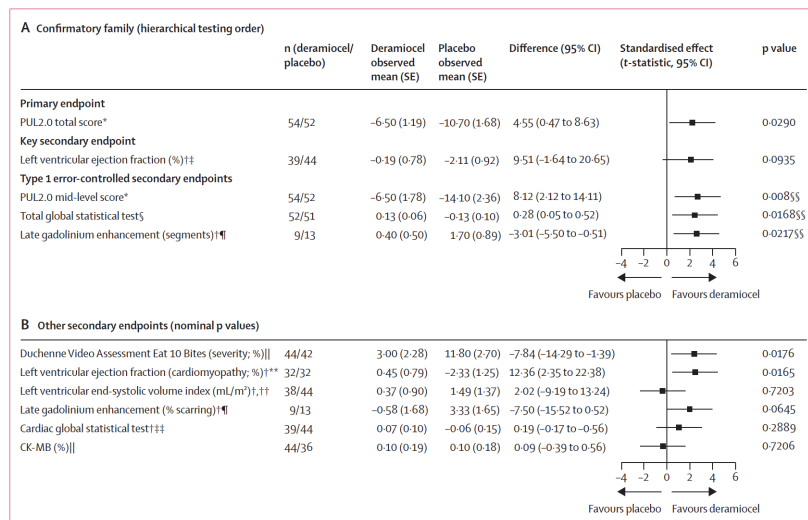


Figure 3: Forest plot of treatment effects at month 12 for the primary, key secondary, and other prespecified secondary efficacy endpoints

(A) Confirmatory family in the prespecified hierarchical (fixed-sequence) testing order that controls the family-wise type I error rate. (B) Other prespecified secondary endpoints, tested nominally. Points are standardised treatment effects, plotted so that values to the right of the reference line favour deramioce; each is the treatment difference divided by its standard error, signed towards clinical benefit, with whiskers spanning ± 1.96 . Standardisation places endpoints measured on different scales on a common axis. Tabulated treatment differences and 95% CIs are on each endpoint's analysis scale-native units for most endpoints, and the rank scale for endpoints analysed by rank ANCOVA (LVEF, LVEF [cardiomyopathy], and left ventricular end-systolic volume index). All reported p values and 95% CIs come from the prespecified covariate-adjusted models and are not adjusted for multiplicity. Analysis population and reduced CMR or cohort B subsets are indicated per endpoint by the n (deramioce/placebo) column and footnotes. LVEF=left ventricular ejection fraction. PUL2.0=Performance of the Upper Limb 2.0. ITT=intention-to-treat. LGE=late gadolinium enhancement. CK-MB=creatin kinase-myocardial band. CMR=cardiac magnetic resonance. *Treatment difference in percentage change from baseline in PUL2.0 total score and mid-level score were analysed using a prespecified mixed model with repeated measures that included treatment, cohort, pooled sites, visit, treatment-by-visit interaction, slow or non-slow progressor status, and baseline score. †Physical limitations and image quality affected the sample size of the ITT set for CMR outcomes. ‡The prespecified analysis for left ventricular ejection fraction used an ANCOVA on ranks of change from baseline at month 12, with terms for treatment group, cohort, slow progressor indicator, an indicator for screening LVEF greater than or equal to 45%, along with baseline LVEF, and age at baseline. A prespecified Hodges-Lehmann shift estimate is included to provide interpretability of the treatment difference presented in ranks. §Total global statistical test was constructed using standardised change scores at the participant level from the three endpoints of PUL2.0 total score, LVEF, and Patient Global Impression of Severity score representing the domains of feels, functions, and survives. An ANCOVA model was prespecified to produce the reported treatment difference with the model terms of treatment group, cohort, slow progressor indicator, age at baseline, and baseline value. ¶Only a subset of patients was included for tissue characterisation using LGE, reported as both the number of segments and the percentage of myocardial scarring. The model for LGE was the same as that used for LVEF. ||Duchenne Video Assessment (Eat 10 Bites severity percentage) and CK-MB were analysed using a prespecified mixed model with repeated measures with the same model terms as the PUL2.0 analysis, applied to change from baseline rather than percentage change from baseline. **Follows the same prespecified analysis for LVEF (ANCOVA on ranks), but with a subgroup of patients with documented cardiomyopathy at baseline. ††Indexed left ventricular end-systolic volume followed the same prespecified ANCOVA on ranks described for LVEF, with baseline indexed end-systolic volume substituted as the baseline covariate; the treatment difference is therefore presented on the rank scale. †††The Cardiac Global Statistical Test was constructed in the same manner as the Total Global Statistical Test, using participant-level standardised change scores from LVEF, indexed left ventricular end-systolic volume, and indexed left ventricular end-diastolic volume, and analysed with the same prespecified ANCOVA model. §§p values are nominal.

	Deramioce ^l (n=39)	Placebo (n=44)	Overall (n=83)
Age, years	16 (10-22)	14 (10-22)	15 (10-22)
Sex			
Male	39 (100%)	44 (100%)	83 (100%)
Slow progressor indicator	0	3 (6.8%)	3 (3.6%)
LVEF percentage at baseline			
Mean (SD)	54.36 (7.60)	59.62 (5.96)	57.15 (7.24)
Median (range)	55.17 (36.54-69.26)	59.54 (48.05-73.98)	57.53 (36.54-73.98)
Cardiomyopathy	32 (82.1%)	32 (72.7%)	64 (77.1%)
Baseline LVEF group			
<45%	5 (12.8%)	0	5 (6.0%)
≥45%	34 (87.2%)	44 (100%)	78 (94.0%)
Age at start of cardiac medications			
n	37	41	78
Mean (SD)	12.86 (2.95)	11.58 (2.93)	12.19 (2.99)
Median (range)	13.0 (6.3-19.3)	11.3 (5.1-17.3)	12.15 (5.1-19.3)
Baseline cardiac medication type			
Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors	37 (94.9%)	40 (90.9%)	77 (92.8%)
Beta-Adrenoceptor blockers	17 (43.6%)	17 (38.6%)	34 (41.0%)
Sodium-glucose cotransporter 2 inhibitors	3 (7.7%)	2 (4.5%)*	5 (6.0%)
Mineralocorticoid receptor antagonists	21 (53.8%)	29 (65.9%)	50 (60.2%)
No cardiac medication	2 (5.1%)	3 (6.8%)	5 (6.0%)
Ambulatory at baseline	6 (15.4%)	6 (13.6%)	12 (14.5%)
Data are median (range) or n (%), unless otherwise stated. LVEF=left ventricular ejection fraction. *SGLT2 inhibitors in the placebo group were prescribed for type 2 diabetes and not for cardiac care.			
Table 2: Demographic and disease characteristics of the cardiac-evaluable population			

	Deramioce ^l (n=53)	Placebo (n=52)	Overall (n=105)
Acute respiratory decompensation within 2 h following investigational product administration	0	0	0
Hypersensitivity reaction	22 (41.5%), 55	8 (15.4%), 18	30 (28.6%), 73
Immune sensitisation syndrome	1 (1.9%), 2	0	1 (1.0%), 2
TEAEs related to investigational product or administration procedure	44 (83.0%), 265	19 (36.5%), 51	63 (60.0%), 316
TEAEs related to investigational product	44 (83.0%), 259	16 (30.8%), 44	60 (57.1%), 303
TEAEs related to administration procedure	23 (43.4%), 54	9 (17.3%), 22	32 (30.5%), 76
TEAE severity of grade 3 or higher	1 (1.9%), 4	3 (5.8%), 3	4 (3.8%), 7
Serious TEAEs	1 (1.9%), 1	5 (9.6%), 5	6 (5.7%), 6
All-cause mortality	0	0	0
Data are n (%), E. n (%)=number and percentage of participants with adverse events. E=number of events. TEAEs=treatment-emergent adverse events.			
Table 3: Adverse events according to grade (safety population)			

	Placebo (n=52)	Deramioce ^l (n=53)	Overall (n=105)
Any treatment-emergent adverse events	43 (82.7%)	50 (94.3%)	93 (88.6%)
Infections and infestations	23 (44.2%)	22 (41.5%)	45 (42.9%)
Musculoskeletal and connective tissue disorders	15 (28.8%)	18 (34.0%)	33 (31.4%)
Injury, poisoning, and procedural complications	14 (26.9%)	14 (26.4%)	28 (26.7%)
Gastrointestinal disorders	14 (26.9%)	17 (32.1%)	31 (29.5%)
General disorders and administration site conditions	12 (23.1%)	28 (52.8%)	40 (38.1%)
Respiratory, thoracic, and mediastinal disorders	11 (21.2%)	22 (41.5%)	33 (31.4%)
Nervous system disorders	5 (9.6%)	35 (66.0%)	40 (38.1%)
Cardiac disorders	5 (9.6%)	14 (26.4%)	19 (18.1%)
Data are n (%).			
Table 4: Adverse events by Medical Dictionary for Regulatory Activities class			

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See Online for appendix

Research in context

Evidence before this study

Despite the expansion of molecular and clinical research in the four decades since the identification of the genetic basis of Duchenne muscular dystrophy (DMD), outcomes for affected boys and young men remain uniformly poor, with median life expectancy younger than 30 years. Cardiomyopathy is the most frequent cause of death. Despite treatment with guideline-directed medical therapy for heart failure, the cardiomyopathy continues to progress inexorably. Other than corticosteroids, which have limited effects on cardiomyopathy, no therapeutic intervention has been shown to slow the decline of upper limb function. Genetic therapies, while mechanistically attractive, did not provide convincing evidence of clinical benefit, particularly in DMD cardiomyopathy. A unique approach using allogeneic cardiac derived cellular therapy has been shown to deliver anti-fibrotic activity and functional benefit preclinically and in early clinical evaluation of DMD (HOPE-Duchenne; HOPE-2 trials). Deramiciel, the name of this cellular therapy product, is a suspension of allogeneic cardiosphere-derived cells administered, following pre-medication with corticosteroids and antihistamines, every 3 months by outpatient intravenous infusion. A search of the US National Library of Medicine PubMed database was done on May 24, 2026, for relevant related publications. All searches were filtered on publication date “10 years” and article type “randomized controlled trial”. The terms [“Duchenne” AND “cardiosphere cell therapy”] identified four reports of studies in the deramiciel programme (NCT03406780, NCT02485938, NCT03145298, and NCT01458405). The terms [“Duchenne” AND “stem cell therapy”] revealed no reports. Using the terms [“Duchenne” AND “PUL”] yielded two studies from the deramiciel programme: one large phase 3 study of tadalafil, which missed both primary and secondary endpoints but included Performance of Upper Limb (PUL) as exploratory (NCT01865084), and a device study in which no therapeutic benefit on PUL was identified (Netherlands Trial Register 3857). The terms [“Duchenne” AND “cardiomyopathy”] identified three reports from the deramiciel programme: one long-term open-label follow-up study to a negative randomised study of perindopril and bisoprolol as cardiomyopathy prophylaxis, a non-inferiority study of spironolactone versus eplerenone

(NCT02354352), a negative study of enalapril and metoprolol (DRKS-number 00000115; EudraCT number 2009-009871-36), and a post-hoc subgroup analysis of a randomised study of tamoxifen (NCT03354039).

Added value of this study

This multicentre, randomised, double-blind, placebo-controlled, phase 3 study recruited patients with DMD who were either late-ambulatory, defined as having a 10 m walk or run time of 10 s or greater, and thus predicted to lose significant upper limb function and ambulation within 2 years, or non-ambulatory with preserved hand-to-mouth function. All participants were treated with stable doses of corticosteroids and the majority received standard-of-care heart failure medications. At 12 months of follow up, the prespecified, type I error controlled primary endpoint was significant, supporting previous clinical evidence that deramiciel slows progression of skeletal myopathy (Performance of the Upper Limb 2.0). The key secondary endpoint of left ventricular ejection fraction (LVEF) did not reach statistical significance, although the difference favoured deramiciel. Prespecified subgroup analysis of LVEF in the population with documented cardiomyopathy at baseline did favour deramiciel with nominal significance. Two further secondary endpoints, late gadolinium enhancement, a measure of fibrofatty replacement of myocardial tissue, and a total global statistical test, showed nominal significance. Deramiciel was safe and well tolerated. This is the first phase 3 trial in advanced DMD to meet a primary efficacy endpoint.

Implications of all the available evidence

Deramiciel delays disease progression, with benefits on skeletal and cardiac muscle, in patients with advanced DMD. Delay in the progression of upper limb functional decline is likely to maintain independence and quality of life by preserving the abilities to transfer, turn, and self-feed. The observed slowing of cardiomyopathy progression in DMD is predicted to reduce mortality in this devastating paediatric genetic disease, a conjecture worth testing in future long-term registry studies. Deramiciel is the first manufactured cell therapy product shown to be efficacious in phase 3 testing for any genetic disease.



Psoriasis

Psoriasis is a common, chronic, immune-mediated skin disease affecting more than 40 million individuals worldwide. Psoriasis, along with psoriatic arthritis, are part of a broader psoriatic disease spectrum, and present with inflammatory skin and musculoskeletal manifestations driven by shared genetic, environmental, and immunological mechanisms. Skin psoriasis presents with diverse clinical phenotypes, including chronic plaque psoriasis, guttate, palmoplantar, erythrodermic, and pustular forms. Beyond cutaneous manifestations, psoriasis is associated with a substantial psychosocial burden and a wide range of comorbidities, including mental health disorders and cardio-metabolic diseases. Key psoriasis risk factors include genetic polymorphisms (most notably *HLA-C*06:02*), obesity, and environmental factors such as trauma, infections, and specific medications. Advances in understanding the key role of the IL-23–IL-17 inflammatory axis and related immunogenetic pathways have redefined psoriasis as a complex immune disorder, leading to the development of highly effective targeted biologic and small-molecule therapies that modulate cytokine signalling and intracellular pathways, offering improved disease control across cutaneous and musculoskeletal domains.

Pathophysiology

Psoriasis is recognised as a T cell-mediated inflammatory condition in which the IL-23–IL-17 cytokine axis plays a crucial role in orchestrating the cutaneous and systemic inflammatory milieu.⁸¹

Introduction

Psoriasis is a common, chronic, immune-mediated skin disease affecting more than 40 million individuals worldwide.¹ Psoriasis along with psoriatic arthritis are part of a broader psoriatic disease spectrum, which present with inflammatory skin and musculoskeletal manifestations driven by shared genetic, environmental, and immunologic mechanisms. Skin psoriasis presents with diverse clinical phenotypes, including chronic plaque psoriasis, guttate, palmoplantar, erythrodermic, and pustular forms. Beyond cutaneous manifestations, psoriasis is associated with a substantial psychosocial burden and a wide range of comorbidities, including mental health disorders, and cardio-metabolic diseases. The aim of this Seminar is to provide an updated survey of our knowledge on psoriasis, its clinical management, and key future challenges.

variations, ranging from 30·3 per 100 000 person-years in east Asia to 321·0 per 100 000 person-years in Europe. Both prevalence and incidence rates are consistently higher in high-income regions, including Europe, North America, and Australia, while Africa and parts of Asia report the lowest rates.^{2,3} These regional variations are attributed to multiple factors, including socioeconomic development, environmental exposures, comorbidities, health-care accessibility, genetic predisposition, and varied reporting standards. Psoriasis onset typically follows a bimodal distribution, with an early peak between ages 18 to 29 years and a second onset in later decades (ie, ages 50–69 years). Psoriasis affects both sexes relatively equally, although clinical features can differ (panel 1).^{2,3} Cumulative life-course impairment captures the long-term, multidimensional burden of psoriatic disease, as comorbidities and psychological distress accumulate with time due to symptoms, stigma, and contextual factors.⁹

Panel 1: Sex and gender considerations

- While the overall prevalence of psoriasis is comparable across sexes, male patients often exhibit a greater extent of skin involvement⁴
- This discrepancy can be partly explained by the immunomodulatory effects of oestrogen,⁵ which might also account for the clinical improvement of psoriasis during pregnancy and frequent post-menopause exacerbations^{4,6}
- Women living with psoriasis consistently report a greater psychosocial effect of psoriasis on their quality of life, which might reflect the influence of gendered experiences on disease perception⁷
- In psoriatic arthritis, women are more likely to report higher levels of pain, fatigue, and physical function impairment compared with men⁸

Panel 2: Race and ethnicity considerations

- In individuals with skin of colour, plaque psoriasis erythema can appear violaceous, grey, or hyperpigmented, and scaling can be less prominent or misinterpreted
- Palmoplantar and scalp involvement is more common in patients who are Black, while pustular forms are seen more in Asian and Hispanic populations. Dyspigmentation is a major concern post-inflammation in patients with skin of colour¹¹
- Variations in morphology and distribution can delay diagnosis, underscoring the importance of clinician familiarity with psoriasis presentation across skin tones
- Diagnostic challenges are also compounded by under-representation in medical images and trials. Despite similar biological responses to treatment, people with skin of colour are less likely to receive biologics. Cultural factors (eg, hair care practices and pigmentation concerns) further affect adherence and outcomes¹²



Figure 1: Representative images of psoriasis
 Chronic plaque psoriasis on (A) dark skin and (B) light skin tones. (C) Psoriatic nail dystrophy. (D) Scalp psoriasis. (E) Palmoplantar pustulosis. (F) Inverse psoriasis.

Panel 3: Pustular psoriasis

- Generalised pustular psoriasis is a rare but potentially life-threatening disease characterised by sudden, extensive pustular eruptions, often accompanied by systemic symptoms, such as fever and malaise. Generalised pustular psoriasis can be triggered by infection, hypocalcaemia, pregnancy, or corticosteroid withdrawal, and is associated with loss-of-function mutations in *IL36RN*, gain-of-function mutations in *CARD14*, or variants in *AP1S3*, *MPO*, *SERPINA1* and *SEPRINA3*, and *BTN3A3*.²⁴⁻²⁹
- Palmoplantar pustulosis is a chronic, relapsing condition, predominantly affecting women aged 30–60 years who smoke or have smoked in the past. Palmoplantar pustulosis coexists with plaque psoriasis in 20% of cases and is more prevalent in Japan than in Western countries.^{30,31} Palmoplantar pustulosis presents with localised sterile yellow pustules confined to the palms and soles, frequently leading to major discomfort and functional impairment.^{23,32} The condition has been linked to genetic polymorphisms in *CARD14*³³ and in genes coding for the *IL-19* subfamily of cytokines.³⁴
- Acrodermatitis continua of Hallopeau primarily affects the distal digits and nail apparatus, often resulting in chronic inflammation, nail loss, and functional disability.³²

Panel 4: Key differential diagnosis of psoriasis and other skin conditions with similar morphologic features

Plaque psoriasis

- Seborrheic dermatitis
- Lichen simplex chronicus
- Squamous cell carcinoma in situ
- Cutaneous T-cell lymphoma or mycosis fungoides
- Lichen planus
- Eczematous dermatitis

Erythroderma

- Sézary syndrome
- Pityriasis rubra pilaris
- Drug reaction

Guttate psoriasis

- Small plaque parapsoriasis
- Pityriasis lichenoides chronica
- Syphilis
- Pityriasis rosea

Intertriginous psoriasis (inverse psoriasis)

- Candida
- Tinea incognito
- Seborrheic dermatitis
- Necrolytic migratory erythema
- Extramammary Paget's disease
- Bowenoid papulosis; contact dermatitis
- Langerhan's cell histiocytosis

Pustular psoriasis variants

- Acute generalised exanthematous pustulosis
- Dermatophyte infection
- Sneddon-Wilkinson disease

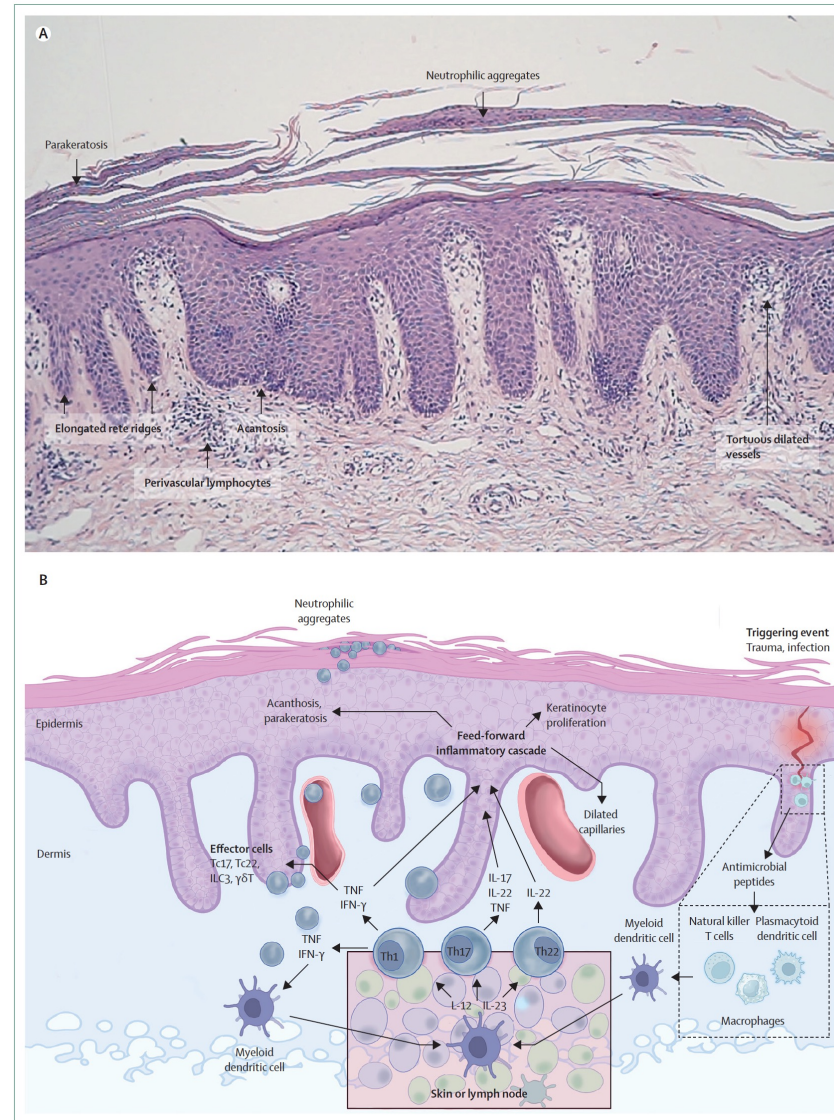


Figure 2: Pathophysiological features of psoriasis
(A) Characteristic histopathological features of plaque psoriasis. Key histological features include marked epidermal thickening (acanthosis) with characteristic rounded appearance of ridges (rete ridges), absent granular cell layer, and nuclear retention within the stratum corneum (parakeratosis). Diagnostic findings include neutrophilic aggregates within the stratum corneum forming Munro's micro-abscesses. Characteristic dermal findings include dilated, tortuous capillaries within elongated dermal papillae and prominent perivascular lymphocytic infiltrates. **(B)** Key immunopathological cells and mediators of plaque psoriasis.

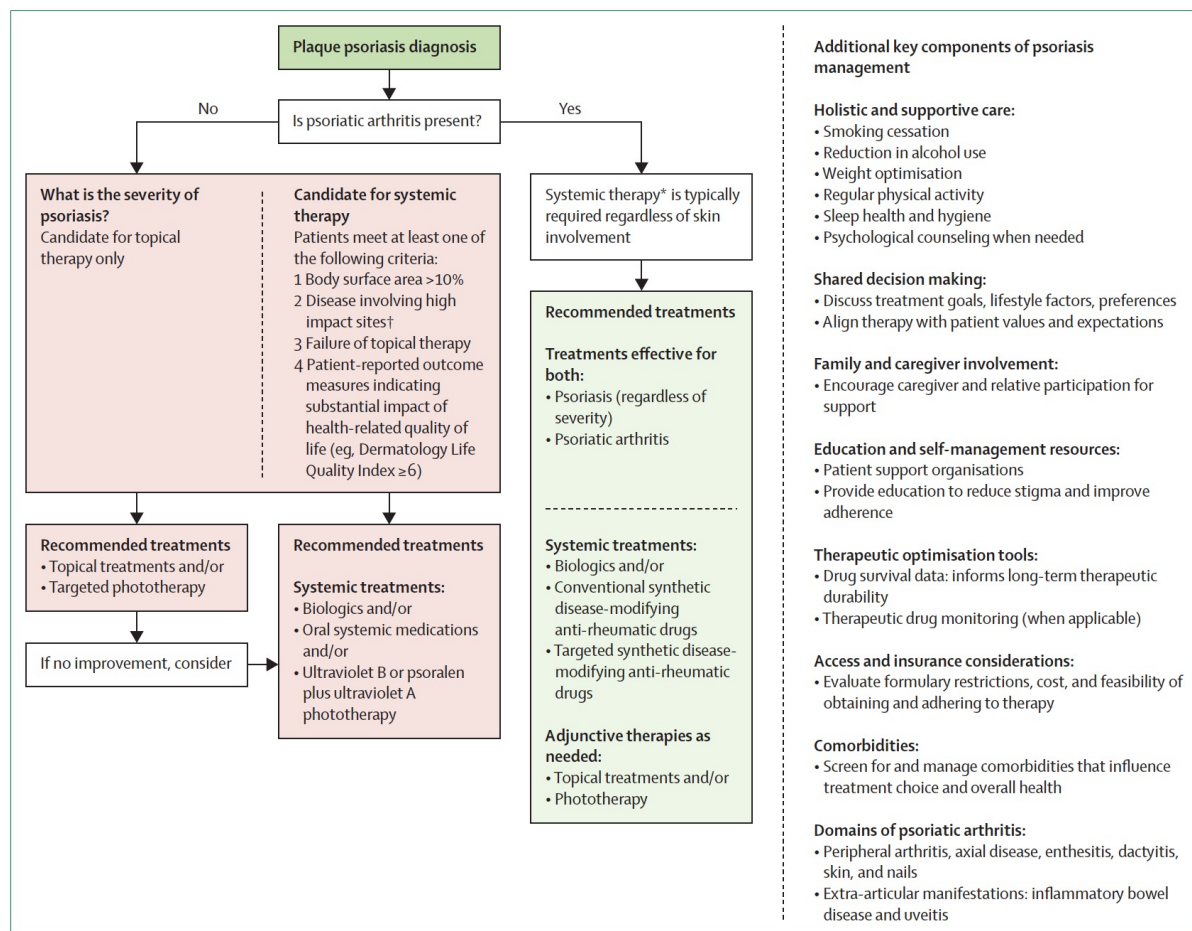


Figure 3: Treatment strategy for psoriasis

Overall treatment strategy for plaque psoriasis, adapted from Armstrong and Read,¹⁰ incorporating the International Psoriasis Council framework to define psoriasis severity and an additional criterion of a patient-reported outcome measure indicating substantial impact on health-related quality of life. *Systemic therapies include biologic and non-biologic treatments, such as phototherapy and older systemic agents. †Face, palms, soles, genitalia, scalp, or nails.

Panel 5: Recommended topical therapies for psoriasis

Scalp

- Super-potent or high-potency steroid; roflumilast 0.15–0.3%; salicylic acid 3–5%
- Recommended formulas: solutions, oils, foams, sprays, shampoos, and gels
- Other: calcipotriol or calcipotriene 0.005%*; coal tar 2–5%; tazarotene; tapinarof 1%

Intertriginous areas

- Low-potency steroid; roflumilast 0.15–0.3%; tapinarof 1%; tacrolimus 0.03%; 0.1%; pimecrolimus 1%
- Recommended formulas: ointment, cream, gel, lotion, and foam
- Other: calcipotriol or calcipotriene 0.005%*; calcitriol 3 µg

Palms, soles, or thick plaque

- Super-potent steroid; roflumilast 0.15–0.3%; tapinarof 1%
- Recommended formulas: ointment and cream
- Other: calcipotriol or calcipotriene 0.005%*; salicylic acid 3–5%; tazarotene 0.05–0.1%; liquor carbonis detergens or tar soak†; topical psoralen with ultraviolet A‡

Face

- Low-potency steroid; roflumilast 0.15–0.3%; tapinarof 1%; tacrolimus 0.03%; 0.1%; pimecrolimus 1%
- Recommended formulas: ointment, cream, lotion, gel, and foam
- Other: calcipotriol or calcipotriene 0.005%*; calcitriol 3 µg

Trunk and limbs

- High-potency or medium-potency steroid; roflumilast 0.15–0.3%; tapinarof 1%
- Recommended formulas: ointment, cream, and lotion
- Other: calcipotriol or calcipotriene 0.005%*; calcitriol 3 µg; salicylic acid 3–5%; tazarotene 0.05–0.1%

Genitals

- Low-potency steroid; roflumilast 0.15–0.3%; tapinarof 1%; tacrolimus 0.03%; 0.1%; pimecrolimus 1%
- Recommended formulas: ointment, cream, lotion, gel, and foam
- Other: calcipotriol or calcipotriene 0.005%*; calcitriol 3 µg

Management for flares

- Use corticosteroids once or twice daily for 2–4 weeks, then transition to a non-steroidal agent (eg, tapinarof, roflumilast, or calcineurin inhibitor) or weekend-only steroid use for maintenance
- Refer to a dermatologist for long-term or refractory cases

*Combination therapy note: many topical agents can be used in combination to enhance efficacy and minimise risks, such as reducing steroid exposure. A common example is calcipotriol plus bethamethasone dipropionate, available in foam, gel, and ointment formulations for multiple body areas. †A liquor carbonis detergens soak consists of immersing the affected area in a bath containing a coal tar solution. ‡Topical psoralen with ultraviolet A involves applying a psoralen medication to the affected area followed by exposure to ultraviolet A light.

	Mechanism of action	Dosing for psoriasis	Study week	PASI75 (%)	Number needed to treat vs placebo	Adverse effects and considerations	Contraindications	Indication
Methotrexate	Folic acid antagonist, dihydrofolate reductase inhibitor	15–20 mg per week plus folic acid	16	36%	6	Hepatotoxicity, gastrointestinal intolerance, pulmonary toxicity, myelosuppression, teratogenicity	Pregnancy, breastfeeding, hepatic and renal impairment, alcohol abuse, blood dyscrasias	Psoriasis plus psoriatic arthritis
Cyclosporine	Calcineurin inhibitor, suppresses IL-2 production and T-cell activation	Up to 5 mg per kg per day	8	IGA 0 or 1=65%	2	Hypertension, nephrotoxicity, metabolic effects, long-term use is discouraged	Uncontrolled hypertension, renal impairment, malignancy, serious infections	Psoriasis only
Fumarates	Nrf2 activator, anti-inflammatory and antioxidant	Up to 720 mg per day	16	37%	5	Gastrointestinal intolerance, flushing, lymphopenia; high discontinuation rate	Gastrointestinal, liver, or renal disease, lymphopenia, active infections, pregnancy	Psoriasis only
Acitretin	Oral retinoid, keratinocyte differentiation modulation	25–50 mg per day	16	47%	..	Teratogenicity, xerosis, hyperlipidaemia, hepatotoxicity	Pregnancy, breastfeeding, liver or kidney dysfunction, hyperlipidaemia, ethanol use	Psoriasis only
Apremilast	PDE4 inhibitor, increases intracellular cyclic AMP	30 mg twice daily	16	33%	4	Gastrointestinal upset, depression, weight loss, adjust dose in renal impairment	Use caution with depression or weight loss	Psoriasis plus psoriatic arthritis
Deucravacitinib	Selective TYK2 inhibitor; IL-23, IL-12, type I interferon effect blockade	6 mg once daily	16	53–58.7%	2	Nasopharyngitis, headache, acne	Avoid in severe hepatic impairment	Psoriasis only
Etanercept	TNF receptor fusion protein	50 mg twice weekly for 12 weeks, then 50 mg weekly, subcutaneously	12	49%	2	Injection site reaction, infection risk, tuberculosis reactivation	Hypersensitivity to therapeutic agent or vehicle; active serious infections, untreated latent tuberculosis, demyelinating disease, hepatitis B, uncontrolled heart failure	Psoriasis plus psoriatic arthritis
Adalimumab	Human monoclonal TNF IgG1 antibody	80 mg at week 0, 40 mg 1 week later, then 40 mg every other week, subcutaneously	16	71%	2	Same as etanercept; antidrug antibodies 6–50%	..	Psoriasis plus psoriatic arthritis
Certolizumab pegol	Pegylated humanised TNF fragment antigen-binding fragment	400 mg at weeks 0, 2, 4; 200 mg every 2 weeks, subcutaneously	16	83%	1	Same as etanercept; preferred in pregnancy and breastfeeding	..	Psoriasis plus psoriatic arthritis
Infliximab	Chimeric monoclonal TNF IgG1 antibody	5–10 mg per kg at weeks 0, 2, 6, then every 8 weeks, intravenously	10	80%	1	Same as etanercept; intravenously only; potent but not for long-term use	..	Psoriasis plus psoriatic arthritis
Secukinumab	Human monoclonal IL-17A antibody	300 mg at weeks 0, 1, 2, 3, 4, then every 4 weeks, subcutaneously	12	82%	1	Avoid in irritable bowel syndrome; infections including mucocutaneous candidiasis	Hypersensitivity to therapeutic agent or vehicle; active or history of irritable bowel syndrome, serious infections	Psoriasis plus psoriatic arthritis
Ixekizumab	Humanised monoclonal IL-17A antibody	160 mg loading dose, then 80 mg every 2 weeks to week 12, then every 4 weeks, subcutaneously	12	90%	1	Same as secukinumab; superior efficacy for scalp and nail	..	Psoriasis plus psoriatic arthritis
Brodalumab	Human monoclonal IL-17 receptor antibody	210 mg at weeks 0, 1, 2; then every 2 weeks, subcutaneously	12	86%	1	Suicidal ideation risk; discontinue if serious infection	Same as secukinumab; black box warning for suicidality	Psoriasis only
Ustekinumab	Monoclonal antibody against IL-12 or IL-23 p40	≤100 kg: 45 mg; >100 kg: 90 mg at weeks 0 and 4, then every 12 weeks, subcutaneously	12	67–76%	1–2	Discontinue if serious infection	Hypersensitivity to therapeutic agent or vehicle; active serious infections	Psoriasis plus psoriatic arthritis
Guselkumab	Human monoclonal IL-23 antibody	100 mg at weeks 0 and 4, then every 8 weeks, subcutaneously	16	PASI90=73%	1	Discontinue if serious infection	Hypersensitivity to therapeutic agent or vehicle	Psoriasis plus psoriatic arthritis

(Table continues on next page)

	Mechanism of action	Dosing for psoriasis	Study week	PASI75 (%)	Number needed to treat vs placebo	Adverse effects and considerations	Contraindications	Indication
(Continued from previous page)								
Tildrakizumab	Human monoclonal IL-23 antibody	100 mg at weeks 0 and 4, then every 12 weeks, subcutaneously	12	64%	2	..	..	Psoriasis only
Risankizumab	Human monoclonal IL-23 antibody	150 mg at weeks 0 and 4, then every 12 weeks, subcutaneously	16	PASI90=75%	1	..	..	Psoriasis plus psoriatic arthritis
Bimekizumab	Humanised monoclonal antibody against IL-17A and IL-17F	320 mg every 4 weeks for 16 weeks, then every 8 weeks, subcutaneously	16	PASI90=91%	1	Higher rates of oral candidiasis; avoid in irritable bowel syndrome; monitor for serious infections	Hypersensitivity to therapeutic agent or vehicle; active serious infections (especially candidiasis)	Psoriasis plus psoriatic arthritis
Biologic therapies for psoriasis. IGA 0 or 1=investigator's global assessment score 0 or 1. PASI75=75% or greater reduction in psoriasis area and severity index. PASI90=90% or greater reduction in PASI. PDE4=phosphodiesterase 4.								
Table: Oral systemic therapies for psoriasis								

Conclusions and future directions

Psoriasis and psoriatic arthritis are now recognised as part of a unified, broader psoriatic disease spectrum, sharing genetic, environmental, and immunological mechanisms. Advances in molecular and cellular immunology, particularly the characterisation of the IL-23–IL-17 axis, have led to transformative therapeutic innovations, improving disease control and quality of life for many patients.

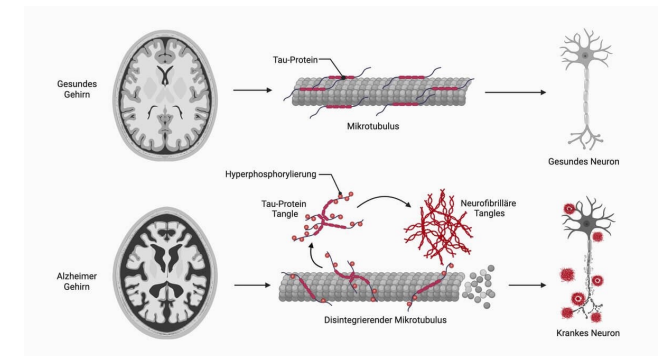
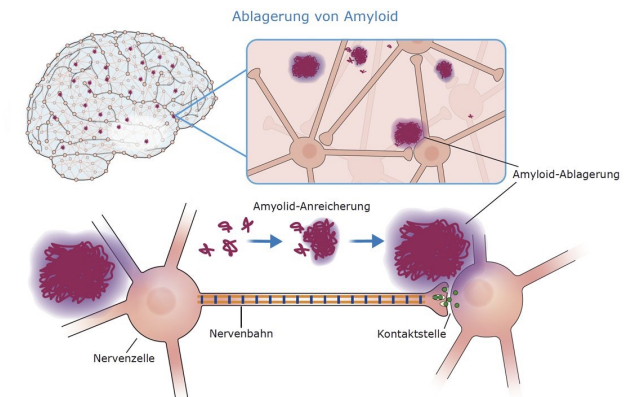
Risk of transmission of amyloid β pathology via transfused blood products

Seeded protein misfolding and aggregation are relevant to many neurodegenerative diseases. The archetype are prions: protein-only infectious agents that cause fatal neurodegenerative diseases including Creutzfeldt–Jakob disease (CJD). The recent recognition of iatrogenic amyloid β cerebral amyloid angiopathy (CAA) and Alzheimer's disease, caused by inadvertent seeding of amyloid β pathology following historical medical procedures, raises concerns that these conditions might also be transmitted via blood components and products, as was the case in rare instances for variant CJD. Recent epidemiological data showing the apparent transmission of haemorrhage risk between blood donors and recipients raise the possibility of blood-based CAA transmission. In this Viewpoint, we review the evidence for amyloid β transmission, provide an overview of relevant prion biology, and consider the circumstances under which bloodborne prion transmission has previously occurred. We discuss the implications for blood transfusion services, particularly in light of the UK Infected Blood Inquiry, and the key questions that need to be addressed to better quantify transfusion-related risk.

Eine iatrogene (durch medizinische Eingriffe verursachte) Alzheimer-Erkrankung beschreibt die **extrem seltene Hypothese**, dass Beta-Amyloid-Proteine in der Vergangenheit durch bestimmte medizinische Behandlungen von Mensch zu Mensch übertragen wurden. Heutige Standardverfahren und strikte Sterilisationsregeln **schließen ein solches Risiko im normalen Praxis- oder Klinikalltag komplett aus**.

Hintergrund und historische Fälle

- **Frühere Hormontherapien:** Die Hypothese stützt sich auf Fallstudien (u. a. im Fachjournal [Nature Medicine veröffentlicht](#)). Betroffene hatten in ihrer Kindheit (vor 1985) Extrakte von Wachstumshormonen aus Hypophysen verstorbener Menschen erhalten.
- **Prionen-Ähnlichkeit:** Diese historischen Hormonpräparate waren gelegentlich mit Krankheitserregern (wie Prionen der Creutzfeldt-Jakob-Krankheit) oder fehlgefalteten Proteinen verunreinigt.
- **Symptome:** Einige dieser Empfänger entwickelten Jahrzehnte später (im Alter zwischen 38 und 55 Jahren) frühe Anzeichen einer Demenz sowie Alzheimer-typische Biomarker im Gehirn.



Introduction

Blood transfusion is key to medical and surgical practice.¹ Transfused products include blood components (eg, red cells, platelets, and clinical plasma) and plasma-derived medicinal products (eg, coagulation factors, immunoglobulins, and albumin).² Transfusion-transmitted infections are rare but potentially catastrophic,³ and even low risks of infection can undermine public confidence. In some cases, concerns that are relevant to blood transfusion can also extend to other allogeneic substances of human origin (eg, transplanted tissues, cells, and organs). In this Viewpoint, we discuss the bloodborne transmission of protein-only pathogens, or prions, given the recent recognition of iatrogenic forms of Alzheimer's disease^{4,5} and iatrogenic amyloid β cerebral amyloid angiopathy (CAA).⁶

Conclusion

The risks of transfusion-related transmission of amyloid β pathology are currently undefined, and achieving clarity will take time. Rigorous science will help find answers, but in the meantime, public health officials and blood transfusion services are faced with difficult decisions and urgently require further data on risk and access to feasible and accurate screening assays. Patient safety needs to be the primary consideration, and the consequences of inaction should be carefully considered and justified. This approach will be essential to avoid transfusion-related amyloid β (and potentially other proteopathic seed) transmission becoming a further iatrogenic tragedy for blood transfusion services.



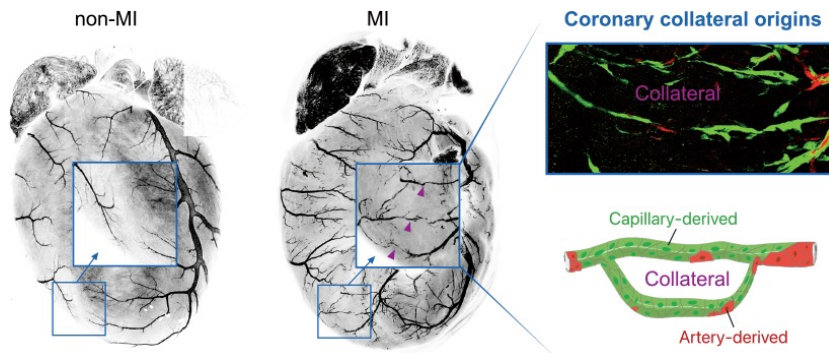
Tracing the origins of de novo coronary collateral formation in cardiac repair

INTRODUCTION: Coronary artery disease remains a leading cause of death worldwide. Acute occlusion of a coronary artery deprives downstream myocardium of oxygen and nutrients, precipitating myocardial infarction (MI). **Coronary collateral arteries, which serve as natural bypass conduits between preexisting coronary artery branches, can restore perfusion to ischemic tissue and improve clinical outcomes.** However, the cellular origin and molecular regulation of de novo collateral artery formation remain incompletely defined. Conventional lineage tracing has been constrained by imperfect marker specificity and the temporally variable nature of tamoxifen-dependent labeling.

RATIONALE: To delineate the cellular origin of coronary collaterals, we engineered complementary genetic lineage-tracing systems. We also developed tools to label capillary-derived and artery-derived vessels simultaneously within the same animal, enabling direct comparison of distinct EC sources after MI, and we interrogated the signaling pathways.

RESULTS: We identified a subset of capillary ECs that express the arterial marker Cx40, highlighting specificity limitations of conventional tracing. Across multiple independent systems, including intersectional genetics and a synthetic Notch-based method, we found that mature arterial ECs contribute modestly to new collaterals after MI. Concurrent tracing within single hearts revealed that capillary ECs constitute the primary building blocks of collateral arteries in both neonatal and adult mice, with a modest contribution from preexisting arterial ECs.

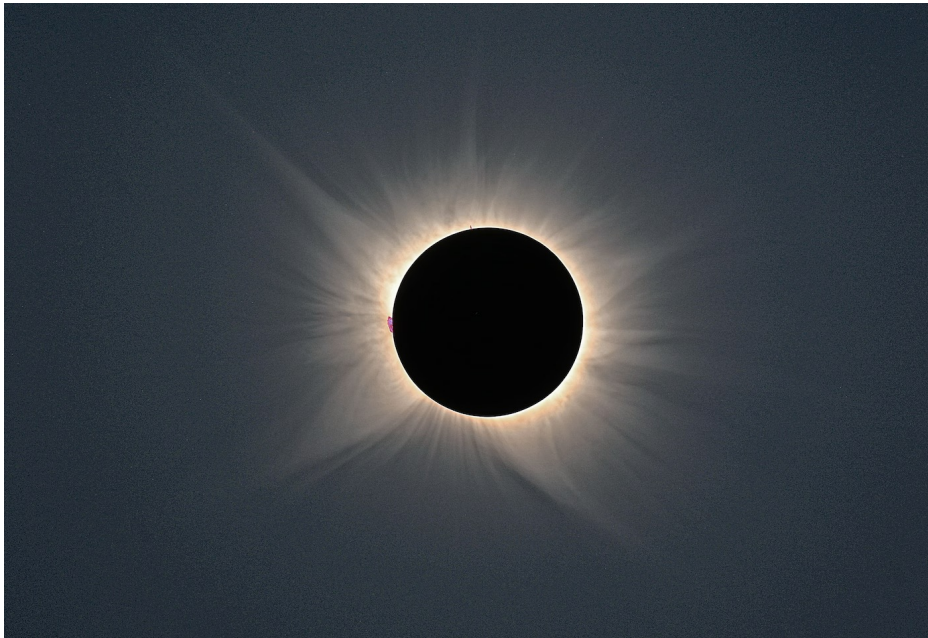
Selective ablation of capillary-derived collaterals impaired repair, increased fibrosis, and worsened cardiac function, establishing their functional necessity. To enhance collateralization, we modulated vascular endothelial growth factor (VEGF) signaling. Sustained pathway activation expanded immature arterial-like ECs but failed to improve repair. By contrast, transient delivery of *Vegfa* by using modified mRNA promoted functional collaterals, improved perfusion, reduced scarring, and enhanced cardiac function after injury. Mechanistically, VEGF-A activated the transcription factor YY1 (yin yang 1), which recruited the chromatin regulator SETD1A to promote histone H3 lysine 4 trimethylation (H3K4me3) and induce the arterial regulator *HES1* (hairy and enhancer of split-1), orchestrating capillary-to-artery conversion.



Cellular origins of coronary collateral arteries. Whole-mount imaging and schematic of neonatal mouse hearts under non-MI and MI (myocardial infarction) conditions. After injury, de novo coronary collaterals (purple arrowheads) form predominantly from capillary ECs (green) and modestly from preexisting arterial ECs (red).

CONCLUSION: De novo coronary collaterals formed after MI arise primarily through arterialization of capillaries, with a modest contribution from preexisting arteries. **We define a VEGF-A-YY1-SETD1A-HES1 epigenetic axis that orchestrates this process and demonstrate that transient VEGF stimulation can boost functional collateral formation and improve cardiac repair.** These results position capillary arterialization as a central mechanism of endogenous revascularization and present a potential therapeutic strategy for ischemic heart disease.

How I captured an image of the sun's atmosphere during a solar eclipse



I tweaked each until I was happy with the combined image — one that shows the roiling inner corona *and* the correctly resolved streamers of the outer corona. If you look closely, you can even see a few coronal loops close to the sun's surface. That's where magnetic flux pours into space and then reconnects elsewhere on the solar disk, tracing a loop.

You'll also notice a big, red flame-looking thing on the left. That's a "prominence," or a plume of rising plasma in the photosphere and chromosphere (the first and second layers of the sun's atmosphere, respectively). It's *huge* — several Earths could fit inside. The glow comes from charged, superheated hydrogen (though there's some helium in there, too). With lots of overlapping images, the red was washed out, so I re-added the prominence once the rest of the stack was done.