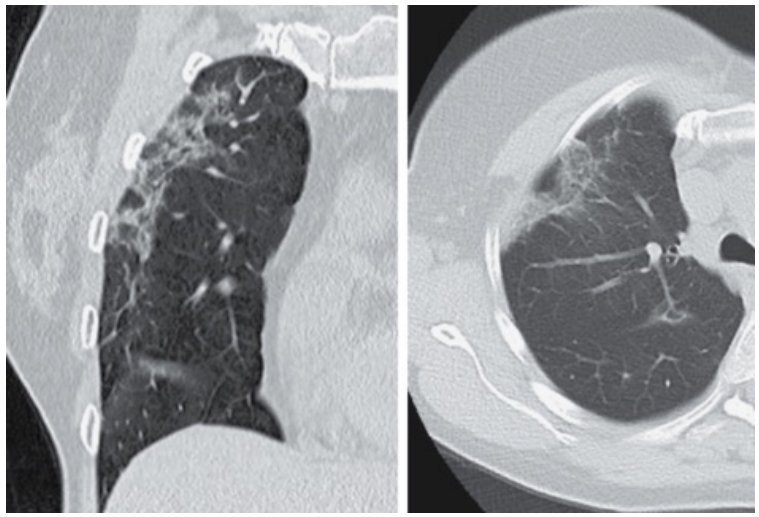
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



A 54-year-old woman with infiltrating ductal carcinoma of the right breast that had been treated with lumpectomy, locoregional radiation, and chemotherapy presented to the emergency department with a 4-week history of cough, fever, and dyspnea. On physical examination, an occasional cough was noted. Lung auscultation was normal. Computerized tomography (CT) of the chest is shown. What is the most likely diagnosis?

Drug-induced pneumonitis

Idiopathic pulmonary fibrosis

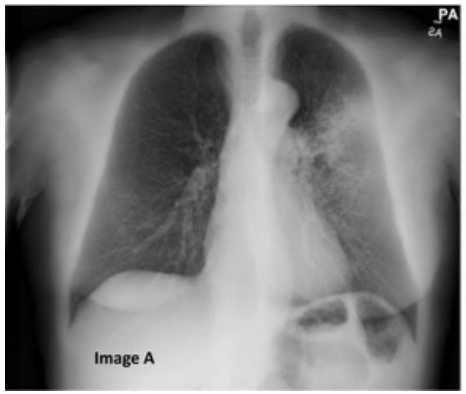
Lympahgitis carcinomatosis

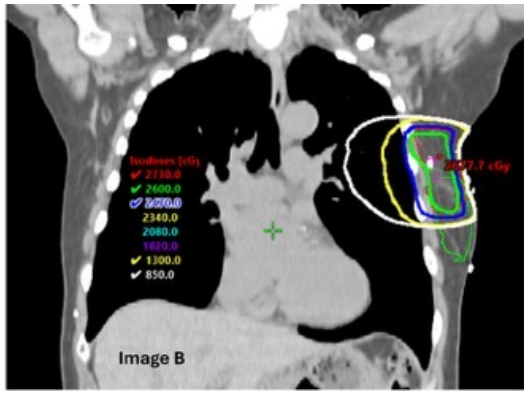
Radiation pneumonitis

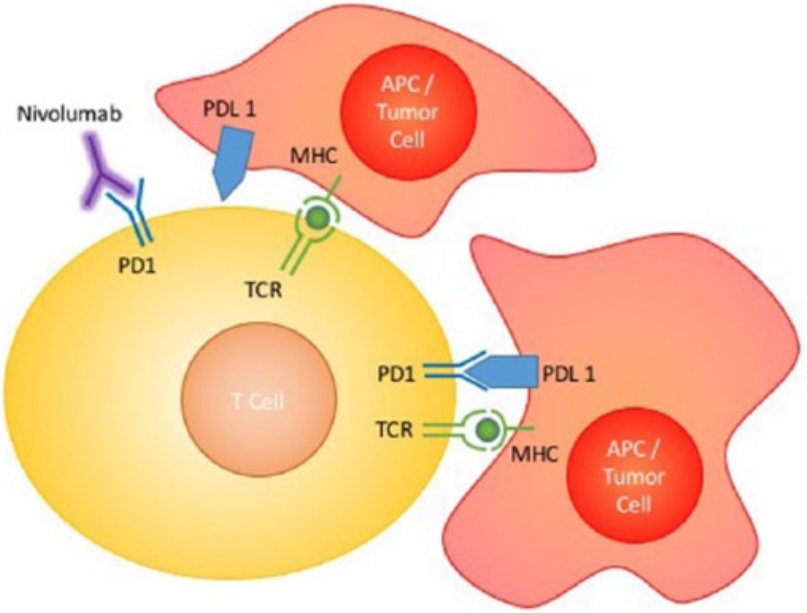
Viral pneumonia

CT of the chest showed fibrotic and ground-glass opacities in the irradiated area of the right upper lobe with volume loss and elevation of the minor fissure that corresponded to the radiotherapy field. A diagnosis of radiation pneumonitis was made. The risk of radiation pneumonitis increases with higher doses of radiation. Treatment with a prolonged taper of glucorticoids was given.

Radiation pneumonitis is an inflammatory reaction in the lungs that can occur as a side effect of radiation therapy, including treatment for breast cancer. It typically develops within a few months after radiation treatment, often between 1 and 3 months, but can occur up to 12 months afterward. While radiation pneumonitis can occur in some breast cancer patients receiving radiation, it's generally considered a relatively uncommon complication, especially with modern radiation techniques.



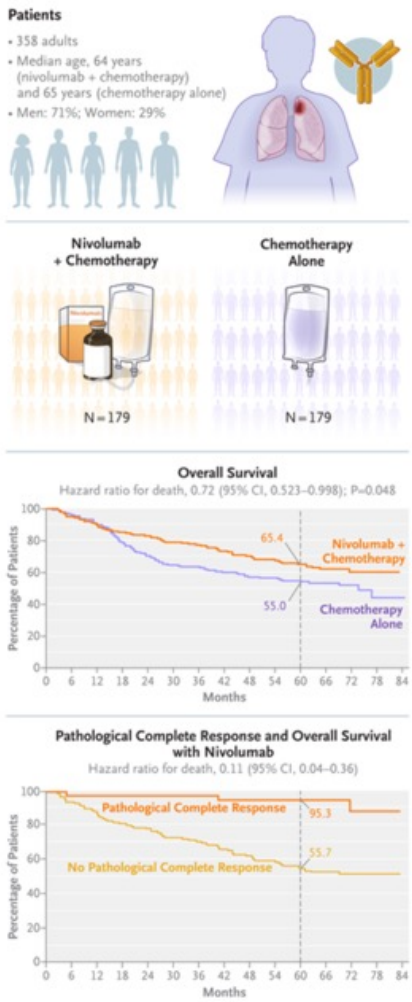



Nivolumab
PDL 1
APC / Tumor Cell
MHC
PD1
TCR
T Cell
PD1
PDL 1
TCR
MHC
APC / Tumor Cell

Overall Survival with Neoadjuvant Nivolumab plus Chemotherapy in Lung Cancer

Neoadjuvant nivolumab plus chemotherapy significantly improved pathological complete response and event-free survival in patients with resectable non–small-cell lung cancer (NSCLC) in a phase 3 trial. Data are needed on overall survival.

In this open-label, phase 3 trial, patients with stage IB to IIIA resectable NSCLC were randomly assigned to receive nivolumab plus chemotherapy or chemotherapy alone for three cycles, followed by surgery. The primary end points were event-free survival and pathological complete response. Here, we report the results of the planned analysis of overall survival.



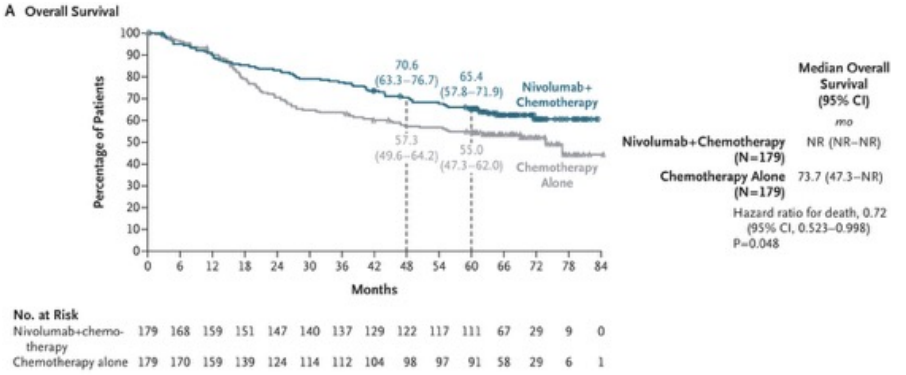
Here, we report the prespecified final analysis of overall survival according to status regarding pathological complete response and presurgery clearance of circulating tumor DNA (ctDNA). We also update results regarding event-free survival at 5 years, which provide additional insights into the role of neoadjuvant chemoimmunotherapy in resectable NSCLC.

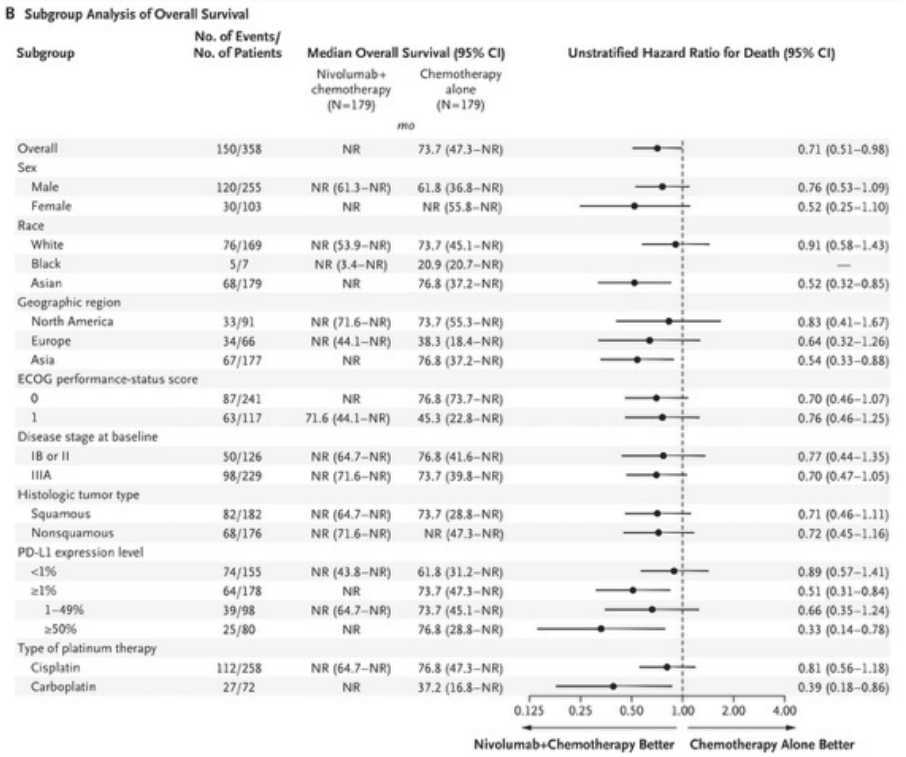
Patients

Briefly, enrolled patients had resectable stage IB to IIIA NSCLC (according to the staging criteria of the American Joint Committee on Cancer, 7th edition), an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (assessed on a 5-point scale, with higher scores indicating greater disability), no known *EGFR* mutations or *ALK* translocations, and no previous systemic anticancer treatment.

Ourcomes

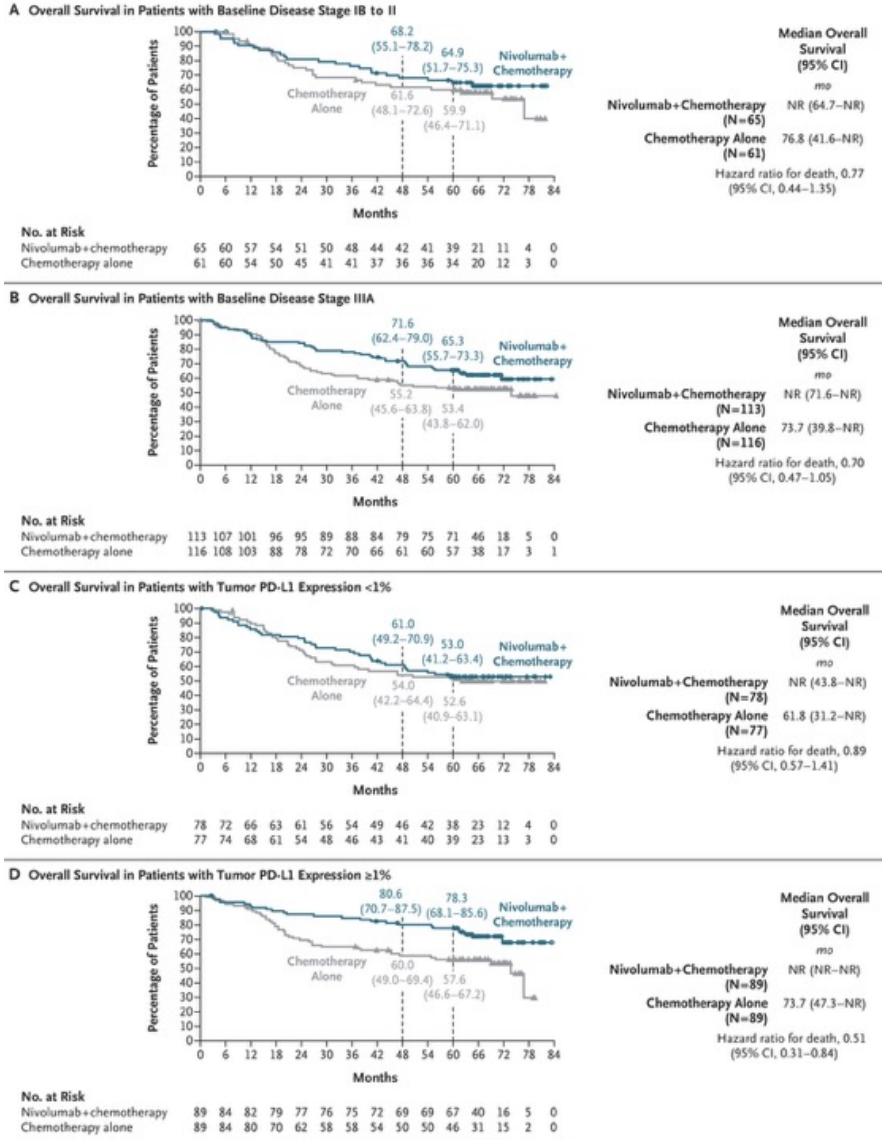
Overall survival (the time from randomization until death from any cause) was the key secondary end point. This end point was evaluated in all the patients who had undergone concurrent randomization and in prespecified subgroups, including those defined according to baseline disease stage (IB to II or IIIA), expression of tumor programmed death ligand 1 (PD-L1) (a level of <1%, ≥1%, 1 to 49%, or ≥50%), and findings on histologic analysis (squamous-cell or nonsquamous-cell cancer). Other prespecified end points included major pathological response.

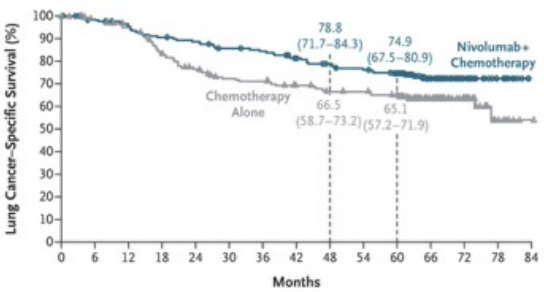




Overall Survival in All Patients and According to Prespecified Subgroups.

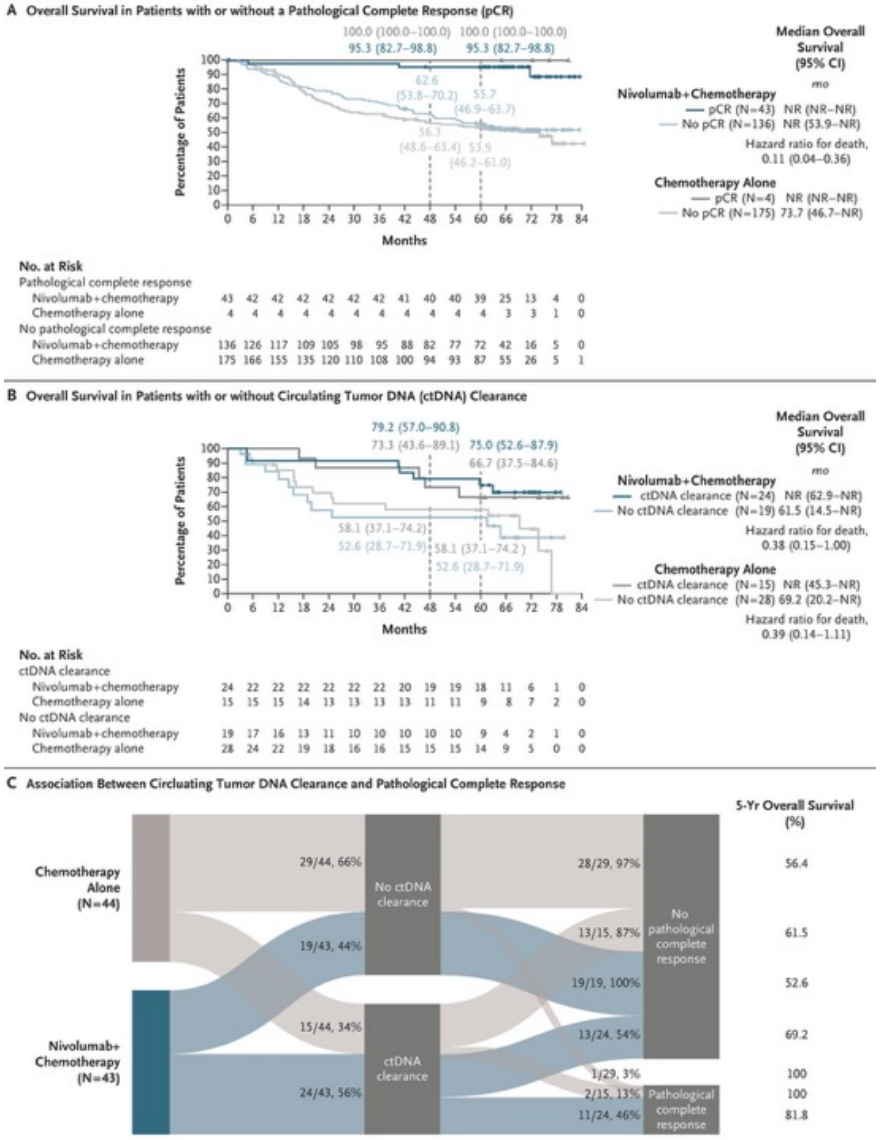
Panel A shows overall survival among the patients who underwent concurrent randomization. Open circles and open triangles indicate censored data for the nivolumab-plus-chemotherapy group and the chemotherapy-alone group, respectively. The 1-year overall survival was 89.8% (95% confidence interval [CI], 84.3 to 93.5) and 90.4% (95% CI, 85.0 to 93.9) in the two groups, respectively; the 2-year overall survival was 83.1% (95% CI, 76.7 to 87.8) and 70.5% (95% CI, 63.2 to 76.6), respectively; and the 3-year overall survival was 77.4% (95% CI, 70.5 to 82.9) and 63.7% (95% CI, 56.1 to 70.3), respectively. Panel B shows overall survival in prespecified patient subgroups. In Panel B, the confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing; all subgroup analyses were prespecified. ECOG denotes Eastern Cooperative Oncology Group, NR not reached, and PD-L1 programmed death ligand 1.





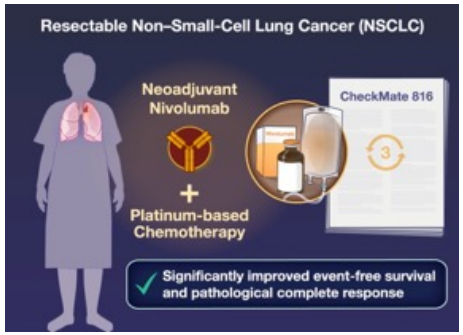
Lung Cancer–Specific Survival.

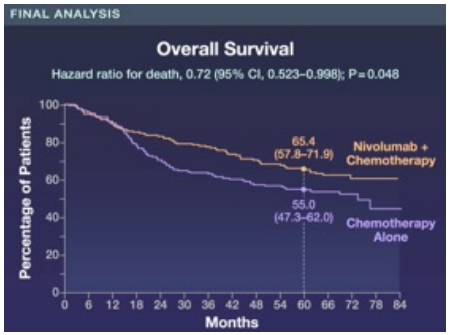
Listed are events that were determined by the investigator to be specifically related to lung cancer. Open circles and open triangles indicate censored data for patients in the nivolumab-plus-chemotherapy group and the chemotherapy-alone group, respectively. Confidence intervals were not adjusted for multiplicity.

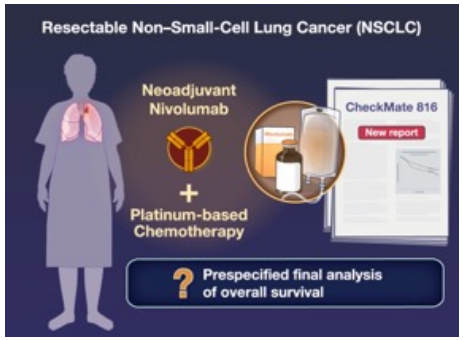


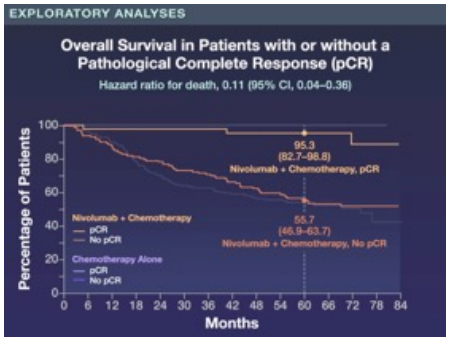
Overall Survival According to Pathological Complete Response and Clearance of Circulating Tumor DNA.

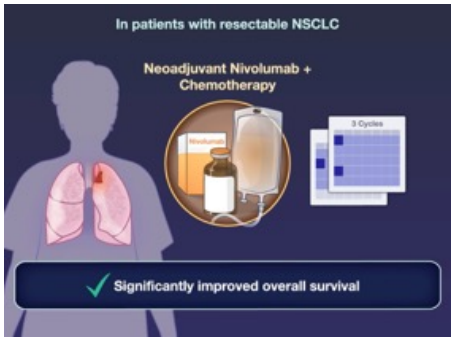
Panel A shows overall survival among the patients according to the presence or absence of pathological complete response. Panel B shows overall survival among the patients according to the presence or absence of clearance of circulating tumor DNA (ctDNA) after neoadjuvant treatment. Open circles and open triangles indicate censored data for patients in the nivolumab-plus-chemotherapy group and the chemotherapy-alone group, respectively. Panel C shows the association between ctDNA clearance from cycle 1 to cycle 3 and pathological complete response in patients with detectable ctDNA. Data for patients in China are not included in the analysis of ctDNA because of local regulations. Confidence intervals were not adjusted for multiplicity.

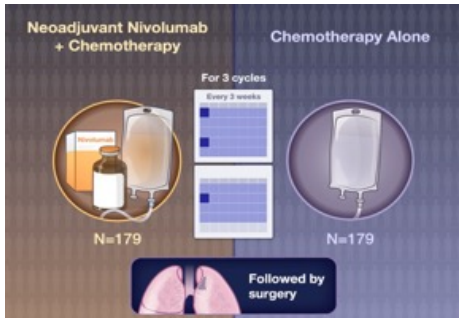

Resectable Non–Small-Cell Lung Cancer (NSCLC)
Neoadjuvant Nivolumab
+
Platinum-based Chemotherapy
CheckMate 816
3
Significantly improved event-free survival and pathological complete response

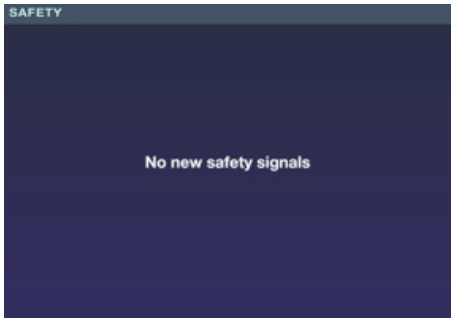

FINAL ANALYSIS
Overall Survival
Hazard ratio for death, 0.72 (95% CI, 0.523–0.998); P=0.048
Percentage of Patients
100
80
60
40
20
0
65.4
(57.8–71.9)
Nivolumab + Chemotherapy
55.0
(47.3–62.0)
Chemotherapy Alone
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Months


Resectable Non–Small-Cell Lung Cancer (NSCLC)
Neoadjuvant Nivolumab
+
Platinum-based Chemotherapy
CheckMate 816
New report
Prespecified final analysis of overall survival

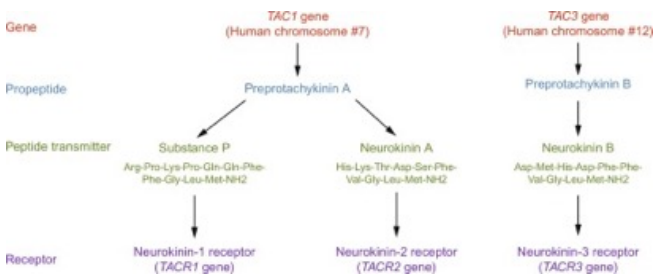

EXPLORATORY ANALYSES
Overall Survival in Patients with or without a Pathological Complete Response (pCR)
Hazard ratio for death, 0.11 (95% CI, 0.04–0.36)
Percentage of Patients
100
80
60
40
20
0
95.3
(82.7–98.8)
Nivolumab + Chemotherapy, pCR
Nivolumab + Chemotherapy
pCR
No pCR
55.7
(46.9–63.7)
Nivolumab + Chemotherapy, No pCR
Chemotherapy Alone
pCR
No pCR
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Months

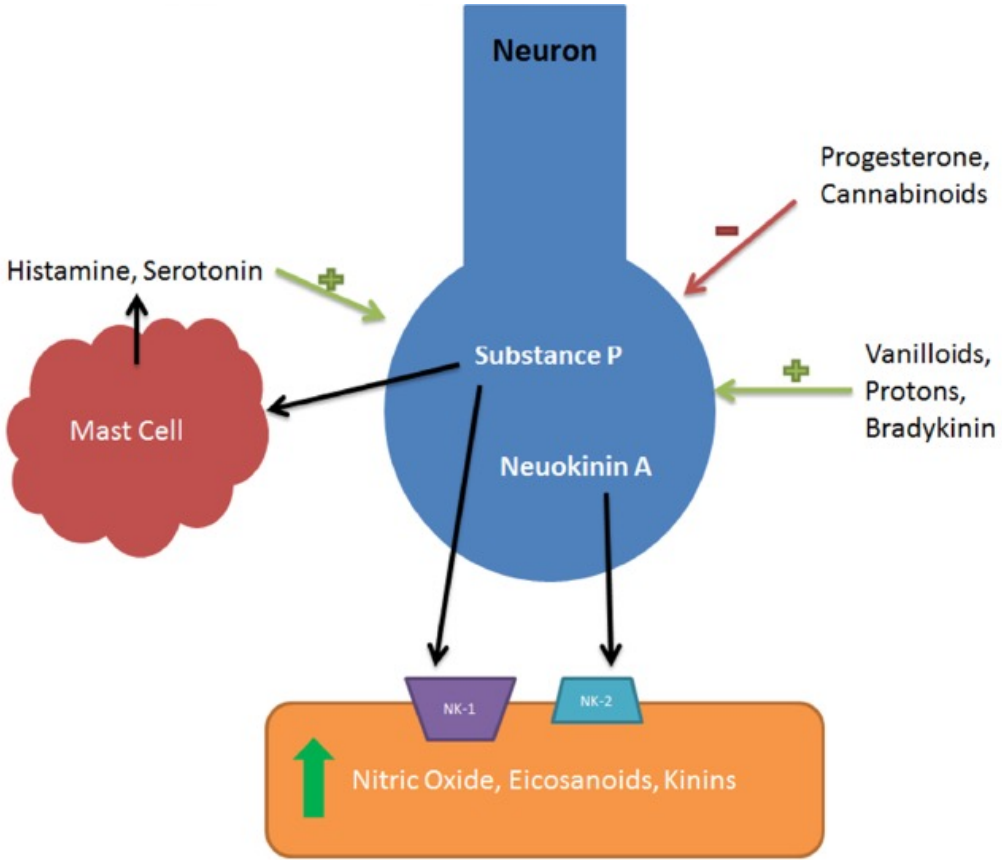

In patients with resectable NSCLC
Neoadjuvant Nivolumab + Chemotherapy
3 Cycles
Significantly improved overall survival


Neoadjuvant Nivolumab + Chemotherapy
Chemotherapy Alone
For 3 cycles
Every 3 weeks
N=179
N=179
Followed by surgery


SAFETY
No new safety signals

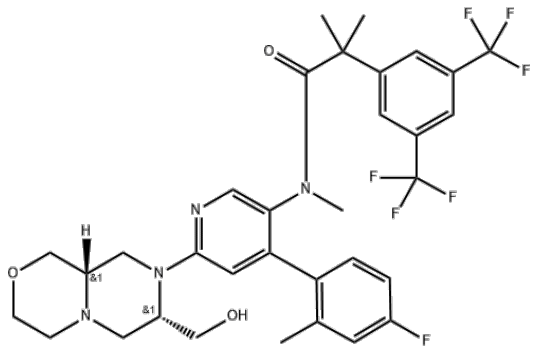
Neurokinine sind eine Gruppe von Neuropeptiden, die als Neurotransmitter und Gewebshormone fungieren und eine wichtige Rolle bei verschiedenen physiologischen Prozessen spielen. Zu den wichtigsten Neurokininen beim Menschen gehören Substanz P, Neurokinin A und Neurokinin B. Sie wirken auf Tachykininrezeptoren (NK1, NK2 und NK3) und sind an Prozessen wie Schmerzempfindung, Entzündungsreaktionen, gastrointestinalen Funktionen, Stressreaktionen und möglicherweise auch an der Entstehung psychiatrischer Erkrankungen beteiligt.





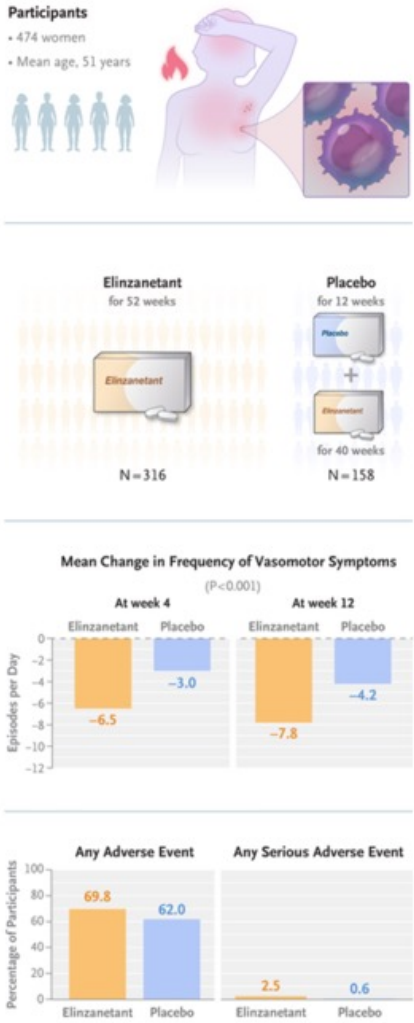
Substanz P ist ein Neuropeptid, das eine wichtige Rolle bei der Schmerzübertragung, Entzündungsreaktionen und der Regulation verschiedener physiologischer Prozesse spielt. Es handelt sich um ein Molekül aus 11 Aminosäuren, das von Nervenzellen und Immunzellen gebildet wird.

Elinzanetant ist ein experimenteller, nicht-hormoneller Wirkstoff, der zur Behandlung von vasomotorischen Symptomen (Hitzewallungen) in den Wechseljahren eingesetzt wird. Es handelt sich um einen dualen Neurokinin-1 (NK1)- und Neurokinin-3 (NK3)-Rezeptor-Antagonisten. Elinzanetant wird einmal täglich oral verabreicht.



Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer

Women receiving endocrine therapy for hormone receptor (HR)–positive breast cancer or its prevention among those at high risk for breast cancer commonly have vasomotor symptoms. Data are lacking on the effects of elinzanetant, a neurokinin-targeted therapy shown to be effective in treating vasomotor symptoms, in this population. We performed a phase 3 trial involving women 18 to 70 years of age with moderate-to-severe vasomotor symptoms associated with endocrine therapy for HR-positive breast cancer or its prevention. Women were randomly assigned in a 2:1 ratio to receive once-daily elinzanetant at a dose of 120 mg for 52 weeks or once-daily placebo for 12 weeks followed by once-daily elinzanetant at a dose of 120 mg for 40 weeks. The primary end points were the change in the mean daily frequency of moderate-to-severe vasomotor symptoms from baseline to week 4 and to week 12.



Elinzanetant is a neurokinin (NK)-targeted therapy in development for the treatment of vasomotor symptoms associated with menopause that specifically antagonizes both NK-1 and NK-3 receptors. Increasing evidence indicates that hypothalamic kisspeptin–neurokinin–dynorphin (KNDy) neurons play a role in thermoregulation. KNDy neurons express receptor–ligand systems, including NK-1 and NK-3 receptors and their respective ligands, substance P and neurokinin B. Declining estrogenic activity that results from natural menopause or endocrine therapy leads to hypertrophy and hyperactivity of KNDy neurons. The resulting hypertrophy and hyperactivity are accompanied by elevated expression of neurokinin B and substance P, which disrupts thermoregulation and results in subsequent vasomotor symptoms. NK-1 receptors may also have a role in peripheral vasodilatation and primary insomnia.

Study Design

We conducted a 52-week, phase 3, interventional, double-blind, randomized, placebo-controlled trial at 90 sites in Europe, Canada, Israel, and Kazakhstan. Institutional review board and ethics committee approval was obtained from each trial site.

Participants

We enrolled women 18 to 70 years of age who were receiving endocrine therapy (tamoxifen or aromatase inhibitors with or without GnRH analogues) for HR-positive breast cancer or its prevention among those at high risk for breast cancer and had at least 35 moderate-to-severe vasomotor symptoms per week that were associated with endocrine therapy. The trial was designed to enroll at least 40% of participants receiving tamoxifen and at least 40% receiving aromatase inhibitors.

Efficacy End Points

The primary end points were the change in the mean daily frequency of moderate-to-severe vasomotor symptoms from baseline to week 4 and to week 12. The frequency of vasomotor symptoms was measured with the use of a hot-flash daily diary similar to diaries used in other clinical trials involving participants with vasomotor symptoms.

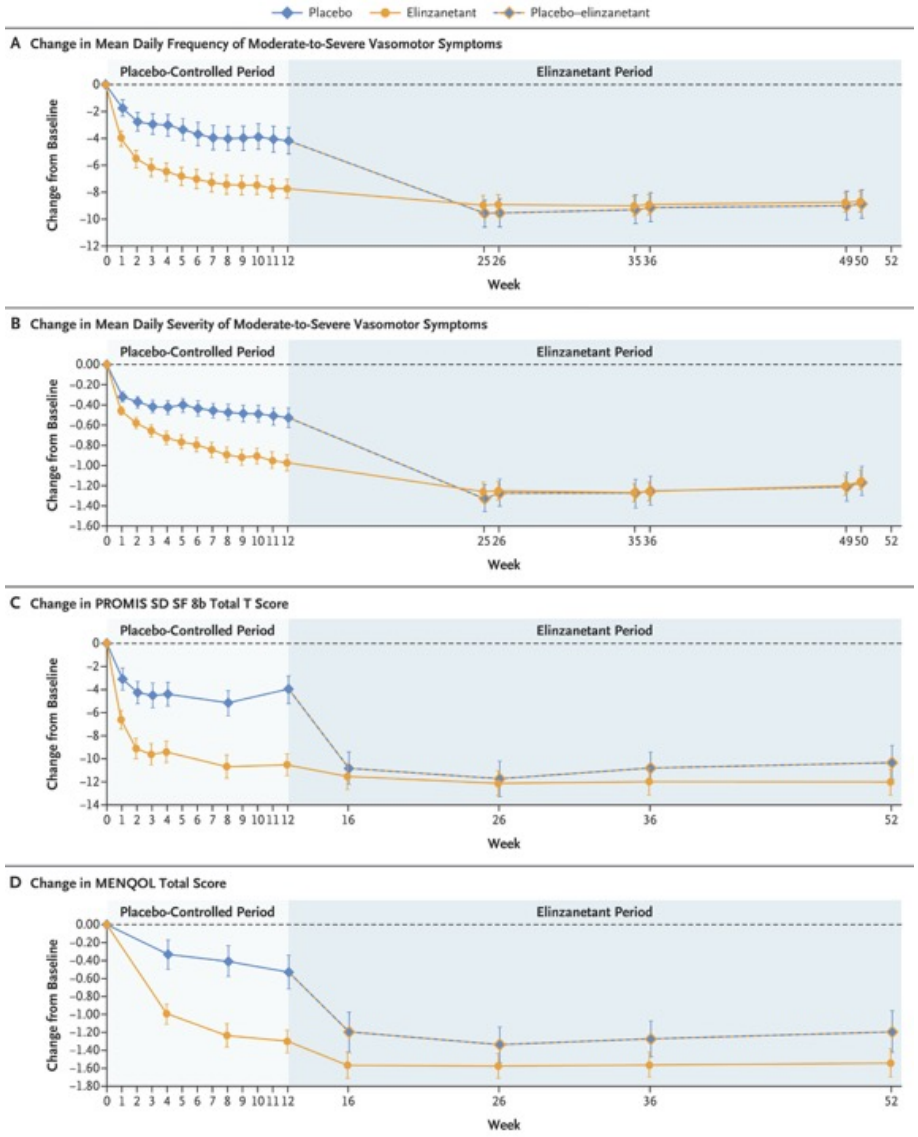
Characteristic	Elinzanetant (N=316)	Placebo (N=158)
Race or ethnic group — no. (%)†		
White	278 (88.0)	140 (88.6)
Black	6 (1.9)	1 (0.6)
Asian	1 (0.3)	1 (0.6)
American Indian or Alaska Native	2 (0.6)	1 (0.6)
Hispanic or Latino	7 (2.2)	5 (3.2)
Not reported	29 (9.2)	15 (9.5)
Age — yr	50.8±7.5	51.5±6.7
Body-mass index‡	26.1±4.6	26.8±4.7
Smoking history — no. (%)		
Never	201 (63.6)	108 (68.4)
Former	71 (22.5)	33 (20.9)
Current	44 (13.9)	17 (10.8)
Cancer status — no. (%)		
Current breast cancer	315 (99.7)	158 (100.0)
High risk for breast cancer	1 (0.3)	0
Stage at initial diagnosis — no. (%)		
Stage 0	8 (2.5)	8 (5.1)
Stage I	159 (50.3)	71 (44.9)
Stage II	127 (40.2)	67 (42.4)
Stage III	21 (6.6)	12 (7.6)
Not applicable§	1 (0.3)	0
Histologic findings — no. (%)		
Infiltrating ductal carcinoma not otherwise specified	219 (69.3)	97 (61.4)
Lobular carcinoma not otherwise specified	37 (11.7)	25 (15.8)
Ductal carcinoma in situ, solid type	19 (6.0)	9 (5.7)
Other	41 (13.0)	27 (17.1)
Type of endocrine treatment — no. (%)		
Tamoxifen	175 (55.4)	90 (57.0)
Aromatase inhibitors	141 (44.6)	68 (43.0)
Median duration of endocrine therapy (range) — mo	20.4 (0.0–97.2)	18.0 (1.2–116.4)

Summary of Adverse Events That Occurred during the 52-Week Treatment

Adverse Event	Weeks 1–12		Weeks 13–26		Weeks 27–52
	Elinzanetant (N=315)	Placebo (N=158)	Elinzanetant (N=294)	Placebo–Elinzanetant (N=150)†	Elinzanetant (N=409)
	number of participants (percent)				
At least one	220 (69.8)	98 (62.0)	154 (52.4)	81 (54.0)	217 (53.1)
At least one severe	13 (4.1)	4 (2.5)	7 (2.4)	7 (4.7)	16 (3.9)
At least one that led to discontinuation of trial drug	23 (7.3)	4 (2.5)	4 (1.4)	6 (4.0)	3 (0.7)
At least one serious	8 (2.5)	1 (0.6)	8 (2.7)	4 (2.7)	18 (4.4)
Occurred in at least 5% of participants in any trial group					
Headache	30 (9.5)	20 (12.7)	13 (4.4)	7 (4.7)	11 (2.7)
Arthralgia	20 (6.3)	10 (6.3)	19 (6.5)	6 (4.0)	15 (3.7)
Fatigue	30 (9.5)	8 (5.1)	7 (2.4)	5 (3.3)	3 (0.7)
Somnolence	34 (10.8)	6 (3.8)	4 (1.4)	5 (3.3)	1 (0.2)
Diarrhea	16 (5.1)	3 (1.9)	6 (2.0)	4 (2.7)	7 (1.7)
Nausea	19 (6.0)	10 (6.3)	6 (2.0)	5 (3.3)	3 (0.7)

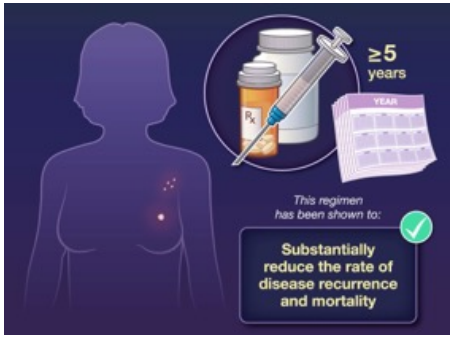
Pharmacokinetics

Endocrine therapy did not appear to have an effect on the pharmacokinetics of elinzanetant. No clinically relevant changes from baseline in the pharmacokinetics of tamoxifen (and its metabolites) or anastrozole were observed in the elinzanetant group.

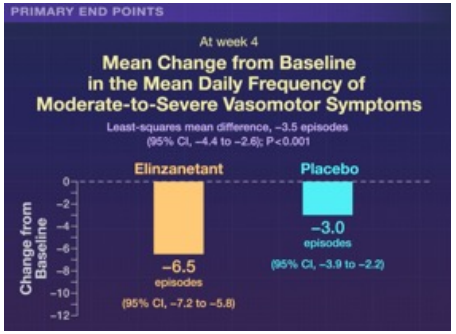


Change over Time in Frequency and Severity of Vasomotor Symptoms and Patient-Reported Outcome Measures.

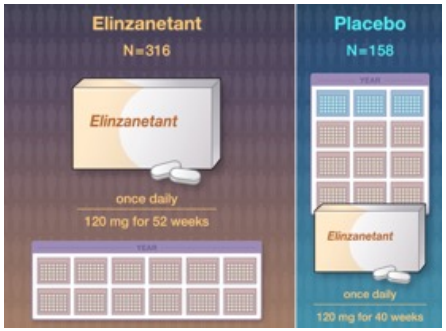
Shown is the mean change from baseline in the mean daily frequency of moderate-to-severe vasomotor symptoms (Panel A), the mean daily severity of vasomotor symptoms (Panel B), Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form (PROMIS SD SF) 8b total T score (scores range from 28.9 to 76.5, with higher scores indicating more severe sleep disturbances) (Panel C), and the Menopause-Specific Quality of Life (MENQOL) questionnaire score (scores range from 1 to 8, with higher scores indicating more impaired menopause-related quality of life) (Panel D) in the full analysis population (all participants who underwent randomization). The mean daily severity of vasomotor symptoms was calculated by multiplying the number of mild episodes a participant had in a day by 1, the number of moderate episodes by 2, the number of severe episodes by 3, and then dividing the sum of these values by the total number of episodes the participant had that day. The mean daily value was set to 0 if the participant had no episodes that day. Additional details are provided in the Supplementary Methods. A decrease in the PROMIS SD SF 8b total T score and in the MENQOL total score indicates a decrease in sleep disturbances and an improvement in menopause-related quality of life, respectively. Participants in the placebo–elinzanetant group received placebo for 12 weeks followed by elinzanetant for 40 weeks. Confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

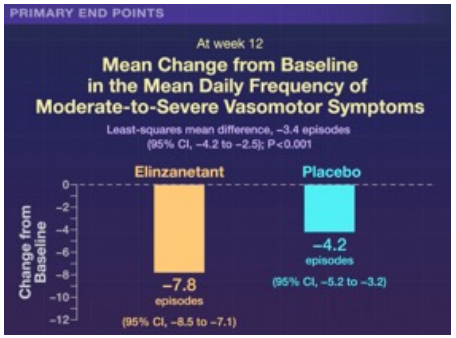

≥5 years
YEAR
This regimen has been shown to:
Substantially reduce the rate of disease recurrence and mortality

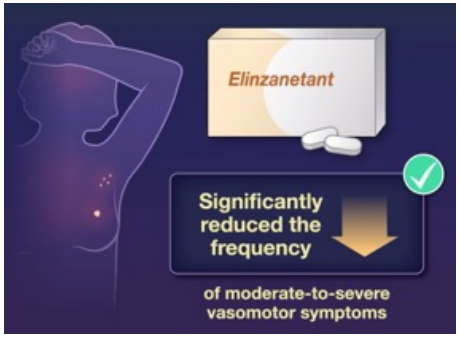

Efficacy and Safety
Elinzanetant
Treating symptoms associated with endocrine therapy
Hormone receptor–positive breast cancer

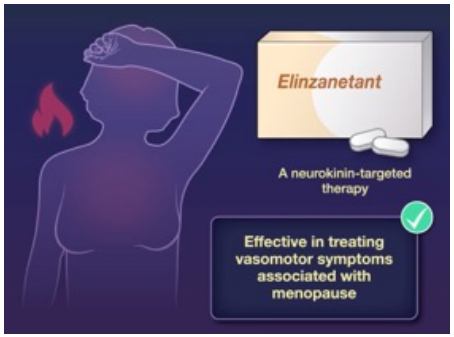

PRIMARY END POINTS
At week 4
Mean Change from Baseline in the Mean Daily Frequency of Moderate-to-Severe Vasomotor Symptoms
Least-squares mean difference, −3.5 episodes
(95% CI, −4.4 to −2.6); P<0.001
Elinzanetant
Placebo
Change from Baseline
0
−2
−4
−6
−8
−10
−12
−6.5
episodes
(95% CI, −7.2 to −5.8)
−3.0
episodes
(95% CI, −3.9 to −2.2)

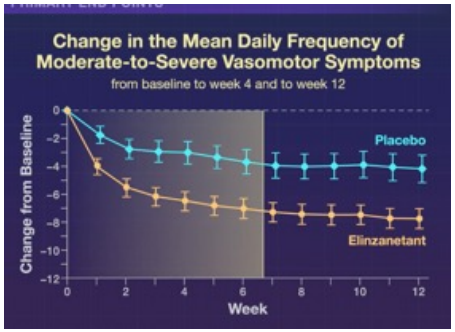

Vasomotor symptoms
(hot flashes)
• Common adverse reactions to endocrine therapy
• Can negatively affect quality of life
• Lead to nonadherence

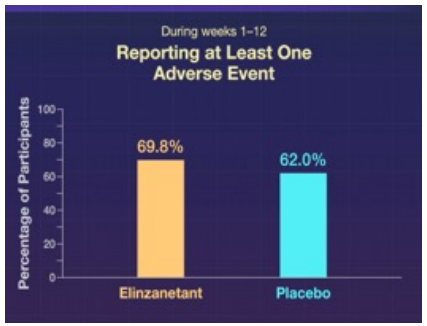

Elinzanetant
N=316
Elinzanetant
once daily
120 mg for 52 weeks
YEAR
Placebo
N=158
YEAR
Elinzanetant
once daily
120 mg for 40 weeks


PRIMARY END POINTS
At week 12
Mean Change from Baseline in the Mean Daily Frequency of Moderate-to-Severe Vasomotor Symptoms
Least-squares mean difference, −3.4 episodes
(95% CI, −4.2 to −2.5); P<0.001
Elinzanetant
Placebo
Change from Baseline
0
−2
−4
−6
−8
−10
−12
−7.8
episodes
(95% CI, −8.5 to −7.1)
−4.2
episodes
(95% CI, −5.2 to −3.2)

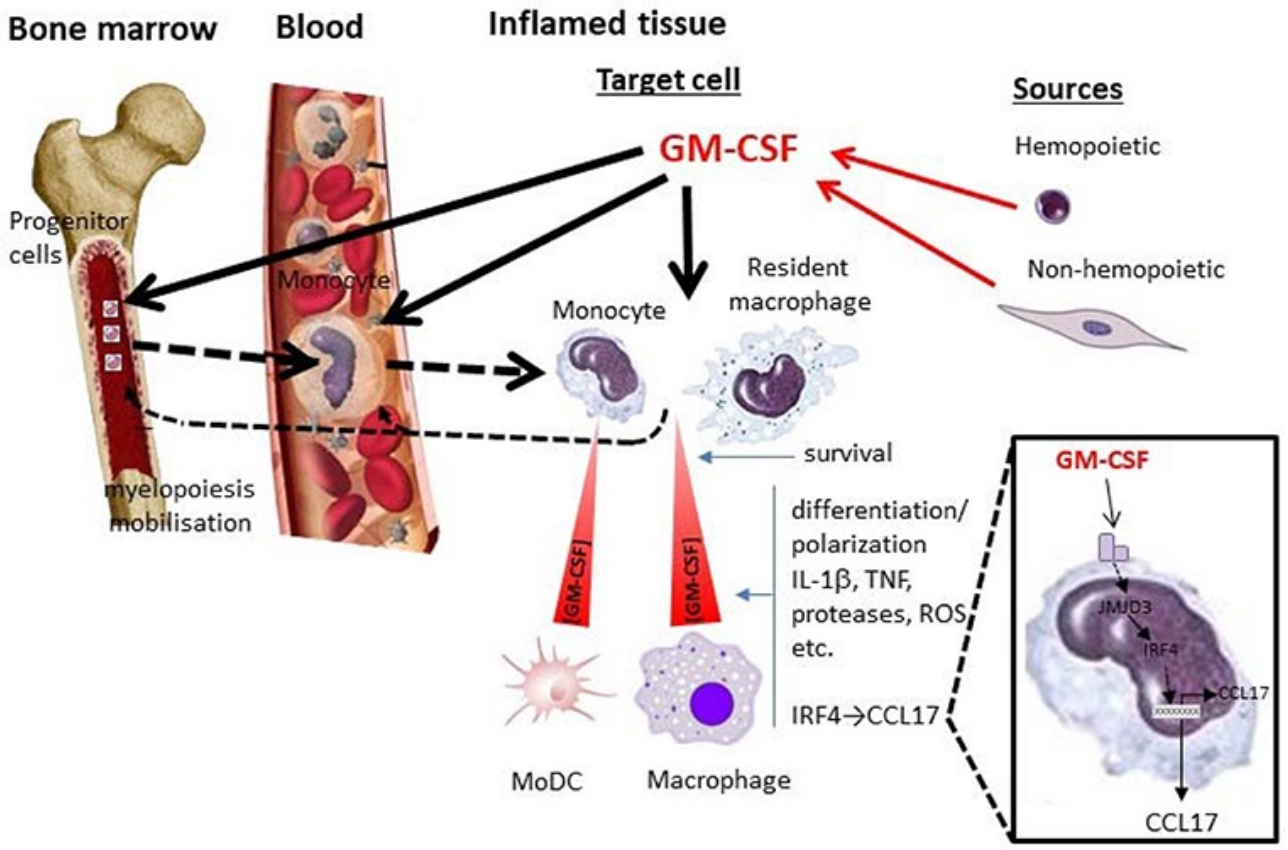

Elinzanetant
Significantly reduced the frequency
of moderate-to-severe vasomotor symptoms


Elinzanetant
A neurokinin-targeted therapy
Effective in treating vasomotor symptoms associated with menopause

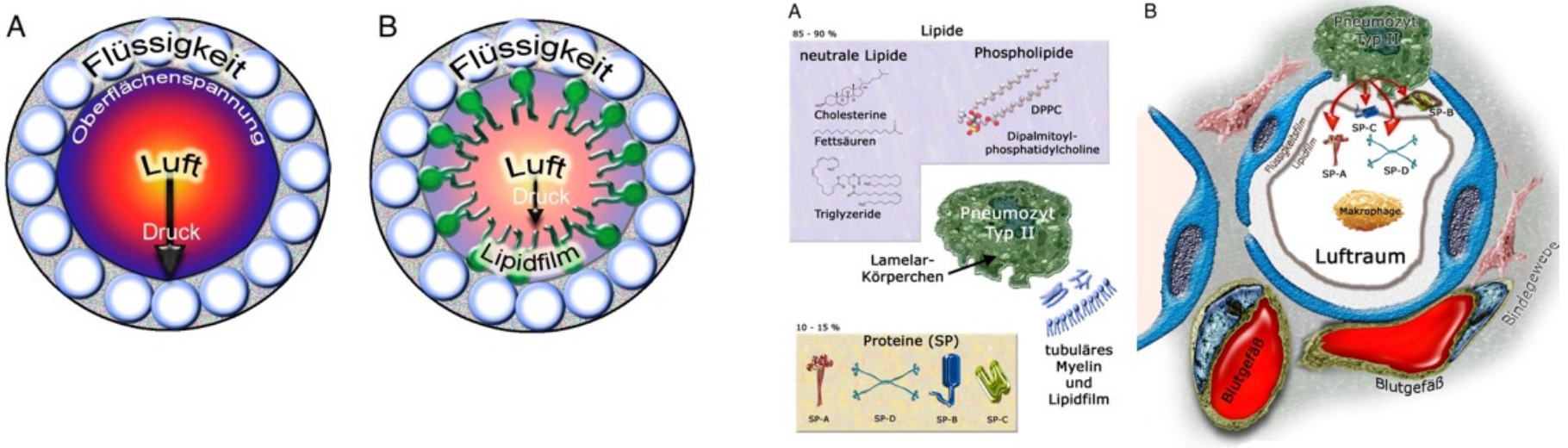

Change in the Mean Daily Frequency of Moderate-to-Severe Vasomotor Symptoms
from baseline to week 4 and to week 12
Change from Baseline
0
−2
−4
−6
−8
−10
−12
Placebo
Elinzanetant
0
2
4
6
8
10
12
Week


During weeks 1–12
Reporting at Least One Adverse Event
Percentage of Participants
100
80
60
40
20
0
69.8%
62.0%
Elinzanetant
Placebo

GM-CSF steht für Granulozyten-Makrophagen-Kolonie-stimulierender Faktor (Granulocyte-Macrophage Colony-Stimulating Factor). Es ist ein Zytokin, das von verschiedenen Zellen des Immunsystems und Endothelzellen produziert wird und die Bildung von weißen Blutkörperchen, insbesondere Granulozyten und Makrophagen, stimuliert. GM-CSF wird auch als Kolonie-stimulierender Faktor 2 (CSF2) bezeichnet.



Surfactant ist eine oberflächenaktive Substanz, die in der Lunge produziert wird und hauptsächlich aus Lipiden und Proteinen besteht. Es senkt die Oberflächenspannung in den Lungenbläschen (Alveolen) und verhindert so, dass diese beim Ausatmen zusammenfallen. Ein Mangel an Surfactant kann bei Frühgeborenen zu Atemnotsyndrom (RDS) führen.



GM-CSF in Autoimmune Pulmonary Alveolar Proteinosis

Primary PAP. Caused by disruption of granulocyte–macrophage colony-stimulating factor (GM-CSF) signaling and can be divided into the following types:

Autoimmune PAP, caused by GM-CSF autoantibodies

Hereditary PAP, caused by variants in genes encoding the GM-CSF receptor subunit alpha (*CSF2RA*) or cytokine receptor common subunit beta (*CSF2RB*); the median age of onset is typically in early childhood (3–6 years)

Secondary PAP. Caused by reduced function or numbers of alveolar macrophages as a result of the following diseases or disorders:

Hematologic disorders such as myelodysplastic syndrome and myeloid leukemias; because of epidemiology of these underlying primary disorders, such patients are typically older (median, 50–60 years of age)

Cancers

Immune deficiency syndromes

Chronic inflammatory syndromes

Chronic infections

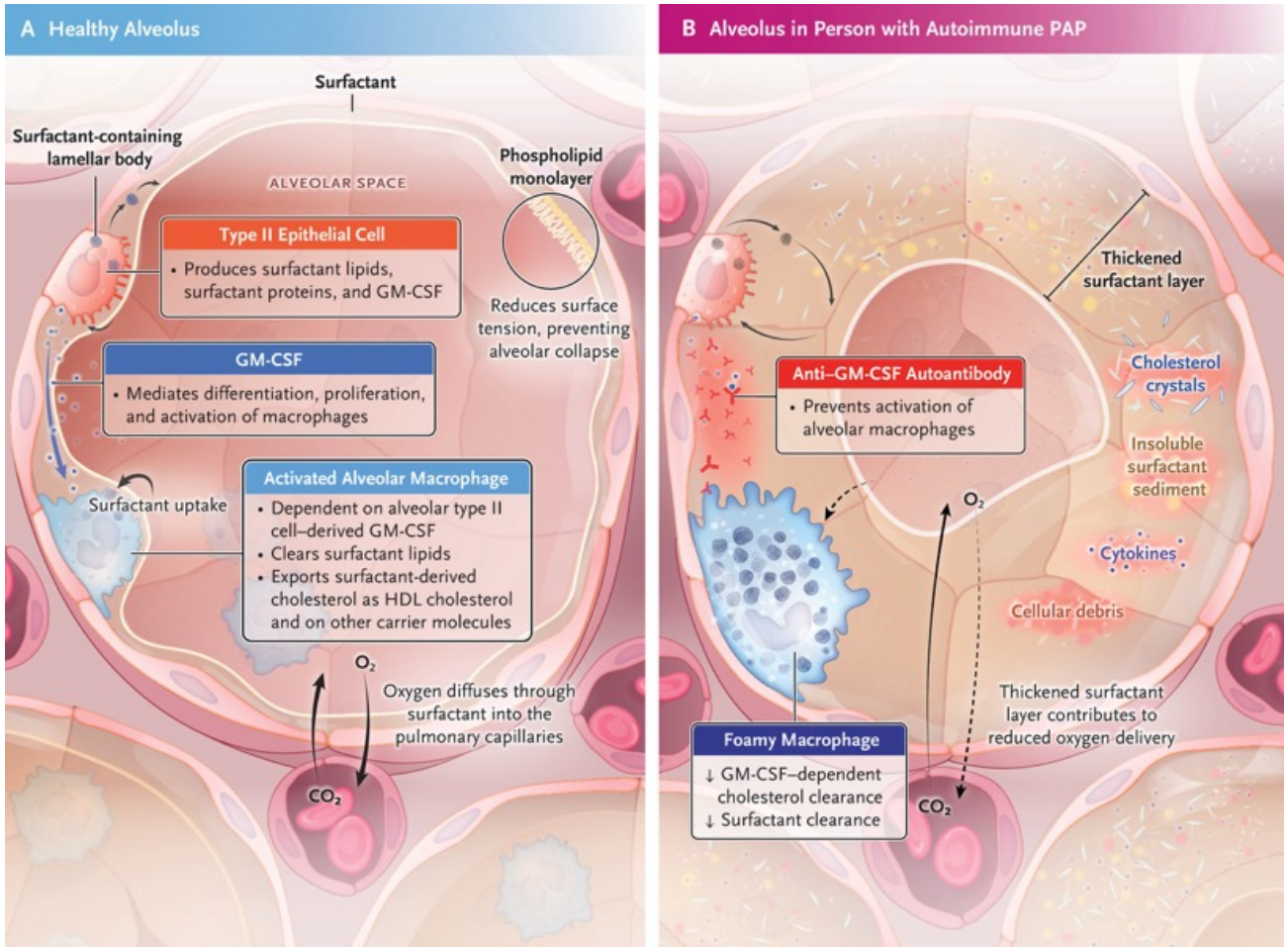
Toxic inhalation syndromes, caused by environmental toxins, dusts, or other particulate materials; acute silicoproteinosis has historically been the most common, but with improving industrial hygiene regulations, the incidence is decreasing

Congenital PAP. Caused by surfactant production disorders with onset soon after birth, which result from the following genetic changes:

Variants causing deficiency in any of the surfactant proteins

Variants causing deficiency in the lipid transporter ATP-binding cassette subfamily A member 3 (ABCA3)

Variants affecting lung development



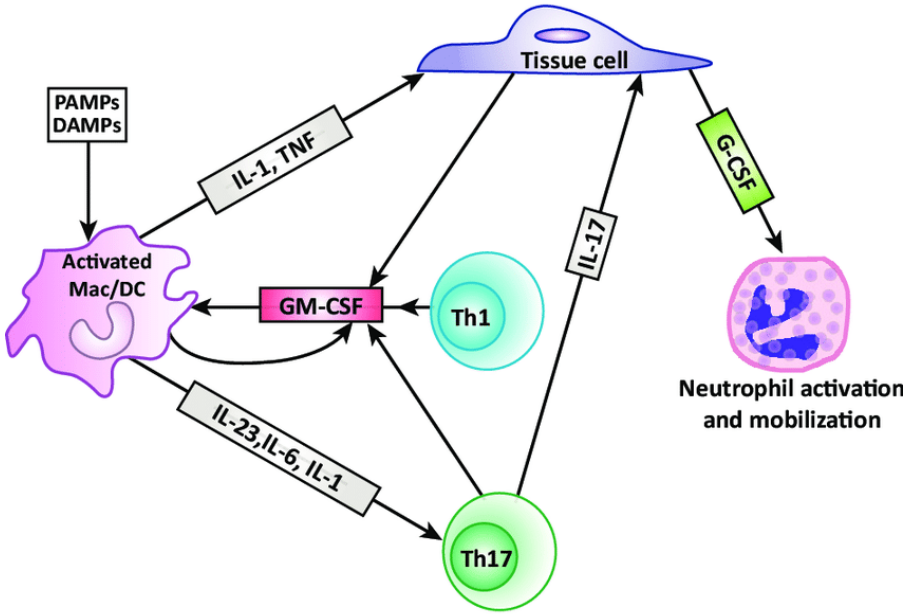
The Alveolus and Autoimmune Pulmonary Alveolar Proteinosis (PAP).

In a healthy person, the alveolar structure and function are maintained by the normal physiological surfactant layer, which is sufficiently thick (approximately one to three molecules) to reduce surface tension in order to prevent alveolar collapse but thin enough to allow adequate diffusion of oxygen and carbon dioxide across the alveolar wall (Panel A). Homeostasis is strictly maintained by the balanced secretion of surfactant lipids and proteins by alveolar type II epithelial cells and clearance by type II cells and a local population of highly specialized alveolar macrophages, the differentiation and function of which require the local actions of granulocyte–macrophage colony-stimulating factor (GM-CSF) to enable the ingestion of surfactant and export of the derived cholesterol byproducts normally. In autoimmune PAP, endogenous autoantibodies bind and block GM-CSF from acting on the cognate receptors on alveolar macrophages (Panel B). The resulting functional impairment of the alveolar macrophages prevents the export of surfactant-derived cholesterol, which accumulates within vacuoles in the cytoplasm and leads to the characteristic foamy-appearing cells seen on lavage cytologic examination. Gradually, the diseased alveoli fill with accumulated insoluble surfactant sediment, debris from dead cells, cholesterol crystals, and inflammatory cytokines. The thickened surfactant layer and surfactant-filled alveoli lead to impaired oxygen transfer, which results in systemic hypoxemia, dyspnea, and progressive respiratory failure. HDL denotes high-density lipoprotein.

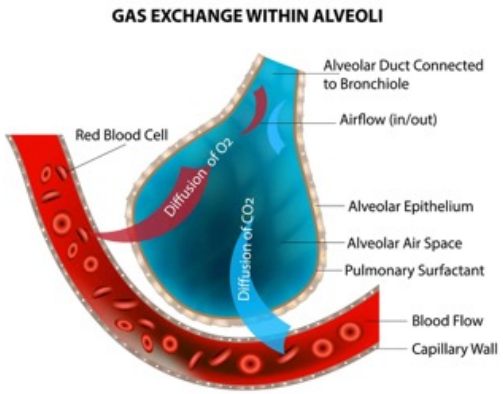
Key Concepts

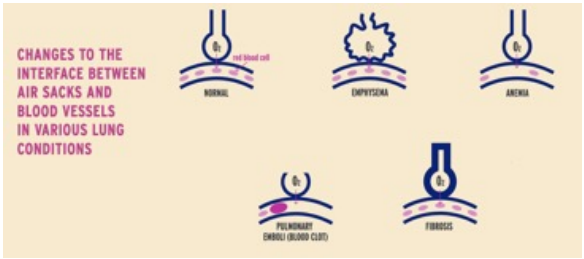
Granulocyte–macrophage colony-stimulating factor (GM-CSF)	A cytokine and a soluble mediator of cell growth secreted by a wide variety of cell types. Such mediators were defined with the laboratory tool of colony growth of hematopoietic cells in semisolid agar to identify "colony-stimulating factors" (CSFs). GM-CSF stimulates myeloid progenitor cells in the bone marrow to proliferate and differentiate into granulocytes and macrophages. These functions link GM-CSF to the normal inflammatory response. Its overexpression is implicated in the sustained inflammatory elements of some diseases such as rheumatoid arthritis. The systemic pharmacologic administration of recombinant GM-CSF leads to a dose-dependent peripheral-blood neutrophilia, monocytosis, and eosinophilia.
Macrophage	A type of immune cell that plays a crucial role in the immune system by digesting cellular debris and pathogens. Macrophages originate from monocytes in the blood and confer innate immunity, which is typically the body's first line of defense against foreign antigens. In addition, they mediate wound healing and tissue repair by releasing growth factors and antiinflammatory cytokines. Macrophages can be found within many organs, including the liver, brain, bones, and lungs, as well as in the blood, particularly at sites of infection.
Surfactant	A complex mixture consisting of 80% highly polar phospholipids (such as saturated phosphatidyl choline), 10% neutral lipids (such as free cholesterol), and 10% specific surfactant proteins. The major surfactant proteins are A, B, and D. The presence and normal function of surfactant are critical for normal pulmonary function and the prevention of alveolar collapse during respiration by creating a continuous thin lining that reduces surface tension and protects against microorganisms.

Bei Molgramostim handelt es sich um den rekombinanten Granulozyten-Makrophagen-Kolonie-stimulierenden Faktor (GM-CSF). Von dem Glykoprotein ist bereits bekannt, dass es Schädigungen des Lungengewebes abwenden kann. Es spielt eine wichtige Rolle bei der Abwehr von Bakterien und Viren in der Lunge.



DLCO steht für die Diffusionskapazität der Lunge für Kohlenmonoxid (engl. diffusing capacity of the lung for carbon monoxide). Es ist ein Maß dafür, wie gut Gase, insbesondere Sauerstoff und Kohlendioxid, zwischen den Lungenbläschen (Alveolen) und dem Blutkreislauf austauschen können. Ein DLCO-Test ist ein wichtiger Bestandteil der Lungenfunktionsprüfung und kann helfen, Lungenerkrankungen zu diagnostizieren und ihren Schweregrad zu beurteilen.

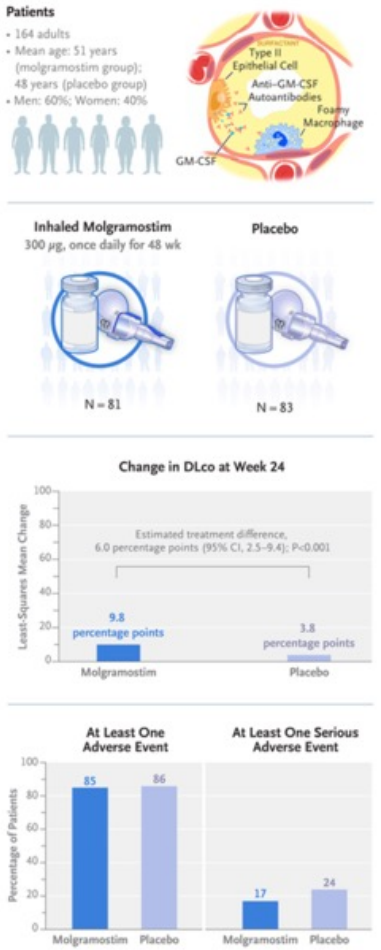




Phase 3 Trial of Inhaled Molgramostim in Autoimmune Pulmonary Alveolar Proteinosis

Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare disease characterized by progressive surfactant accumulation and hypoxemia caused by autoantibodies against granulocyte–macrophage colony-stimulating factor (GM-CSF), which alveolar macrophages require to clear surfactant. Molgramostim is a formulation of inhaled recombinant human GM-CSF, but its efficacy and safety in patients with aPAP have not been studied sufficiently.

In this phase 3, double-blind, placebo-controlled trial, we randomly assigned patients with aPAP to receive molgramostim at a dose of 300 µg or placebo once daily for 48 weeks. The primary end point was the change from baseline to week 24 in the diffusing capacity of the lungs for carbon monoxide (DLCO), which was adjusted for hemoglobin concentration and expressed as a percentage of the predicted value. Secondary end points adjusted for multiplicity were the change from baseline in DLCO at 48 weeks and the change from baseline in the St. George's Respiratory Questionnaire total (SGRQ-T) and activity (SGRQ-A) scores (scores range from 0 to 100, with lower scores indicating better quality of life) and in exercise capacity at 24 and 48 weeks.



Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare disease characterized by accumulation of surfactant within alveoli, which results in progressive dyspnea, hypoxemia, decreased exercise capacity, and reduced quality of life. Of all PAP cases, 90% are aPAP, which has a prevalence of 6 to 27 per million in the general population. Pathogenesis is driven by autoantibodies that neutralize granulocyte–macrophage colony-stimulating factor (GM-CSF), which alveolar macrophages require to clear surfactant. High-titer GM-CSF autoantibodies are the basis of an accurate diagnostic test with a sensitivity and specificity of 100%. The natural history of aPAP is variable due to differences in the rate of surfactant accumulation; serious infections, pulmonary fibrosis, or both develop in some patients, and aPAP can lead to death. Currently, aPAP is treated with whole-lung lavage, a procedure that involves hospitalization, intubation, and mechanical ventilation, in which excess surfactant is partially removed by being physically washed out of the lungs; however, whole-lung lavage does not correct the pathophysiologic defect or prevent surfactant accumulation.

Recently published European Respiratory Society guidelines recommend inhaled GM-CSF as therapy for symptomatic patients with confirmed aPAP. Here, we report results from the IMPALA-2 trial, which evaluated the efficacy and safety of inhaled molgramostim, a recombinant human GM-CSF produced in *Escherichia coli*.

Patients

Eligible patients were at least 18 years of age and had received a diagnosis of aPAP on the basis of an elevated serum GM-CSF autoantibody concentration and compatible findings from computed tomography (CT) of the chest, lung biopsy, or cytologic analysis of bronchoalveolar-lavage fluid. Patients were required to have a diffusing capacity of the lungs for carbon monoxide (DLco) of no more than 70% of the predicted value after adjustment for hemoglobin concentration, a change in DLco of less than 15 percentage points during the 6-week screening period, and a resting peripheral-blood oxyhemoglobin saturation (SpO_2) of more than 85% after breathing ambient air for 15 minutes.

Trial Design and Treatments

The trial comprised an initial 6-week screening period, a 48-week double-blind intervention period, and an ongoing open-label treatment period offered to patients who completed the double-blind intervention period. Data from the open-label treatment period are not reported. Patients were assigned in a 1:1 ratio to receive once-daily inhaled molgramostim at a dose of 300 µg or matching placebo.

End Points and Assessments

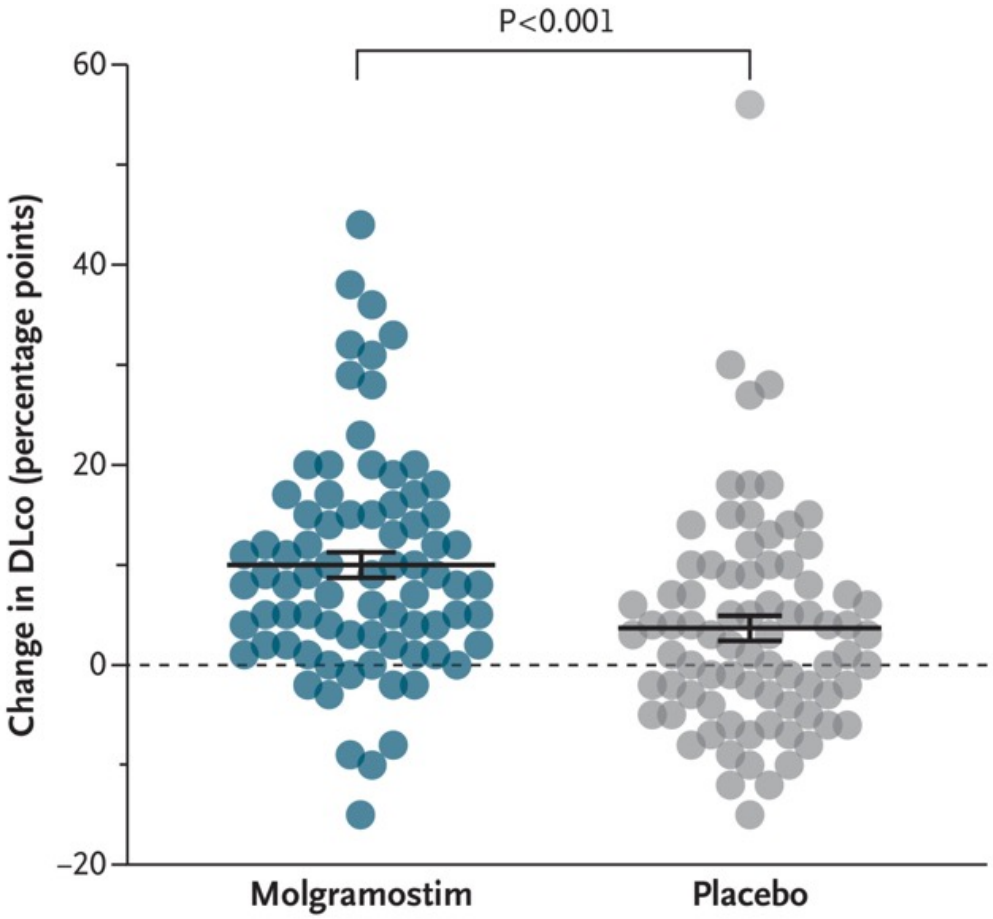
The primary end point, the change from baseline in DLco at week 24, was chosen because DLco is a standardized measure of gas transfer that is widely used in clinical practice. In addition, changes in DLco correlate with changes in the severity of aPAP (i.e., the extent of surfactant accumulation) and predict indications for whole-lung lavage.

Demographic and Clinical Characteristics of the Patients at Baseline.

Characteristic	Molgramostim (N=81)	Placebo (N=83)
Age — yr	50.8±13.0	48.4±12.7
Female sex — no. (%)	37 (46)	29 (35)
Pulmonary gas transfer		
DLco — %†	52.6±11.7	52.6±10.4
A-aDo_2 — mm Hg	27.7±16.4	26.5±19.2
Median disease severity score (range)‡	2 (1–5)	2 (1–5)
Respiratory health–related quality of life		
SGRQ-T score§	39.5±19.2	41.2±18.1
SGRQ-A score¶	54.6±25.6	57.8±22.4
Exercise capacity — MET‖	7.1±2.2	7.2±2.1
Median ground-glass opacity score (range)**	10.5 (3.0–14.0)	10.3 (2.0–15.0)
Previous whole-lung lavage therapy		
Any previous use — no. of patients (%)	41 (51)	50 (60)
No. of previous procedures/patient††	4.2±4.1	4.7±5.0
Median time since last procedure (range) — mo††	15.9 (2.8–283.8)	10.9 (3.1–244.9)
Any previous GM-CSF therapy — no. of patients (%)	20 (25)	12 (14)
Median serum GM-CSF antibody titer (range)‡‡	262,144 (32,768–16,777,216)	262,144 (4096–16,777,216)

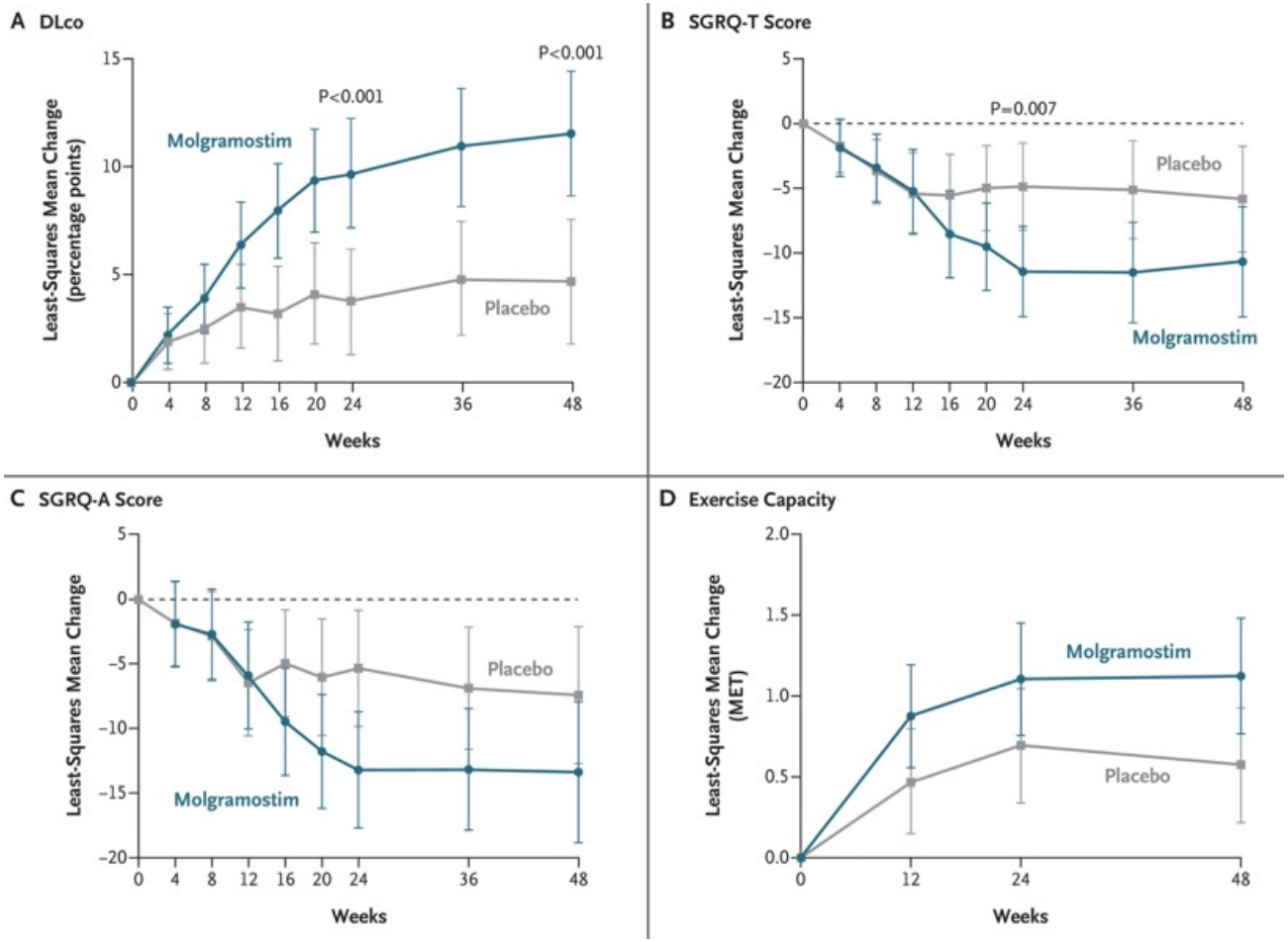
Primary and Secondary End Points Included in the Hierarchical Testing Procedure.

End Point	Molgramostim (N=81)	Placebo (N=83)	Estimated Treatment Difference	P Value
Primary end point				
Change in DLco, baseline to wk 24 (95% CI) — percentage points†	9.8 (7.3 to 12.3)	3.8 (1.4 to 6.3)	6.0 (2.5 to 9.4)	<0.001
Secondary end points				
Change in DLco, baseline to wk 48 (95% CI) — percentage points†	11.6 (8.7 to 14.5)	4.7 (1.8 to 7.6)	6.9 (2.9 to 10.9)	<0.001
Change from baseline to wk 24				
SGRQ-T score (95% CI)‡	−11.5 (−15.0 to −8.0)	−4.9 (−8.3 to −1.5)	−6.6 (−11.4 to −1.8)	0.007
SGRQ-A score (95% CI)	−13.0 (−17.6 to −8.5)	−5.2 (−9.8 to −0.7)	−7.8 (−14.1 to −1.5)	NS
Exercise capacity (95% CI) — MET§	1.1 (0.8 to 1.5)	0.7 (0.3 to 1.1)	0.4 (−0.1 to 0.9)	
Change from baseline to wk 48				
SGRQ-T score (95% CI)‡	−10.7 (−15.0 to −6.4)	−5.9 (−10.0 to −1.7)	−4.9 (−10.8 to 1.0)	
SGRQ-A score (95% CI)	−13.4 (−18.9 to −7.9)	−7.4 (−12.7 to −2.1)	−6.0 (−13.6 to 1.6)	
Exercise capacity (95% CI) — MET§	1.1 (0.8 to 1.5)	0.6 (0.2 to 0.9)	0.6 (0.1 to 1.0)	



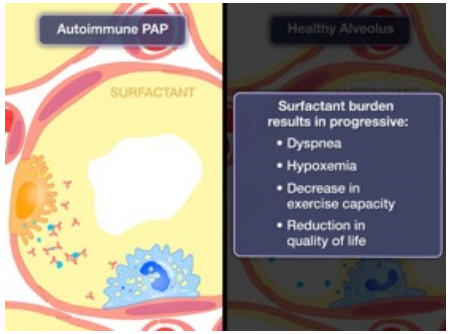
Change in DLco from Baseline to Week 24 (Primary End Point).

Shown is the change from baseline in the diffusing capacity of the lungs for carbon monoxide (DLco), adjusted for hemoglobin concentration and expressed as a percentage of the predicted value, at week 24 in the molgramostim group (77 patients) and the placebo group (81 patients), with no imputation for missing data. Each circle represents the observed result for 1 patient. The horizontal lines represent arithmetic means, and the vertical bars standard errors. The dashed line indicates no change from baseline. The P value is based on an analysis in which missing data were replaced with the use of multiple imputation.

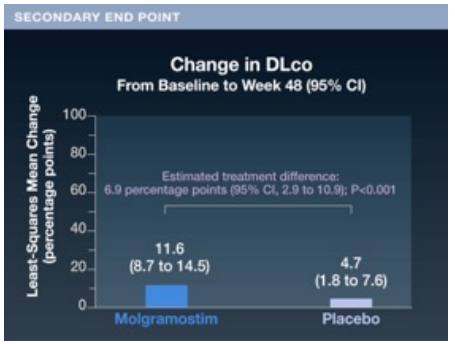


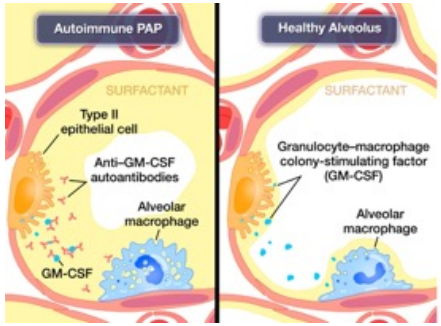
Change over Time in Measures of Pulmonary Gas Transfer, Respiratory Health–Related Quality of Life, and Exercise Capacity.

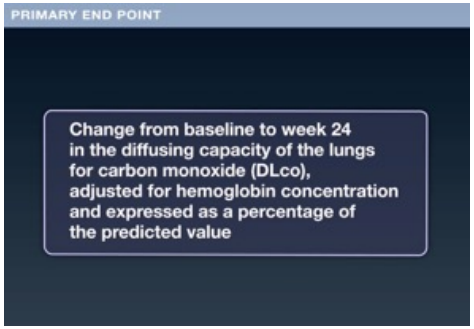
Shown is the least-squares mean change from baseline in DLco (Panel A), the St. George's Respiratory Questionnaire total (SGRQ-T) (Panel B) and activity (SGRQ-A) (Panel C) scores, and exercise capacity (expressed as the peak metabolic equivalent of oxygen consumption [MET] at maximal exercise effort) (Panel D) over the 48-week double-blind intervention period for all the patients who underwent randomization (81 in the molgramostim group and 83 in the placebo group). A change in DLco of 10 percentage points is the minimal clinically important difference in patients with pulmonary fibrosis.[33] The minimal clinically important difference in aPAP has not been established. SGRQ-T and SGRQ-A scores each range from 0 to 100, with higher scores indicating more severe effects on respiratory health–related quality of life; a 4-point change in the SGRQ-T score is considered to be the minimal clinically important difference in chronic obstructive pulmonary disease.[34] Exercise capacity was assessed with the use of an exercise treadmill test conducted according to a conservative protocol involving 31 stages (at 30 seconds per stage) of ramp up with minimal adjustments in treadmill speed and grade from one stage to the next. Values range from 2.3 MET (stage 1) to 9.8 MET (stage 31). In cardiovascular disease, a change of at least 0.5 MET is considered to be a quality indicator for patients participating in cardiac rehabilitation.[40,41] I bars indicate 95% confidence intervals.

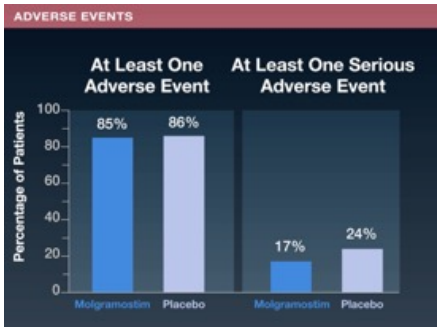

Autoimmune PAP
Healthy Alveolus
SURFACTANT
Surfactant burden results in progressive:
• Dyspnea
• Hypoxemia
• Decrease in exercise capacity
• Reduction in quality of life

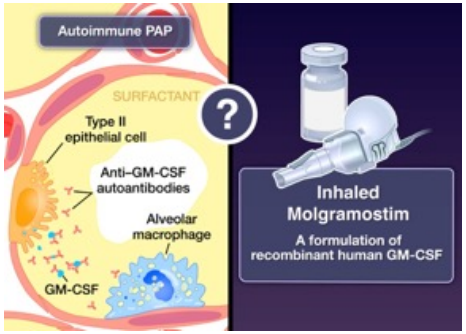

164 Adults
Inhaled Molgramostim (300 µg)
Once daily, 48 weeks
N=81
Placebo
Once daily, 48 weeks
N=83

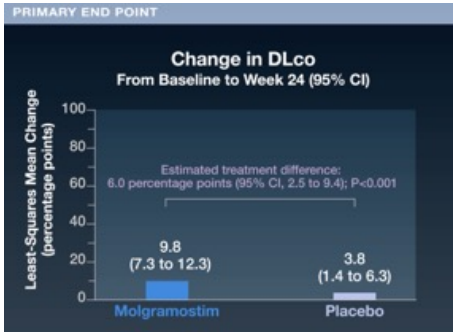

SECONDARY END POINT
Change in DLco
From Baseline to Week 48 (95% CI)
Least-Squares Mean Change (percentage points)
Estimated treatment difference:
6.9 percentage points (95% CI, 2.9 to 10.9); P<0.001
11.6 (8.7 to 14.5)
4.7 (1.8 to 7.6)
Molgramostim
Placebo


Autoimmune PAP
Healthy Alveolus
SURFACTANT
Type II epithelial cell
Anti–GM-CSF autoantibodies
Alveolar macrophage
GM-CSF
Granulocyte–macrophage colony-stimulating factor (GM-CSF)


PRIMARY END POINT
Change from baseline to week 24 in the diffusing capacity of the lungs for carbon monoxide (DLco), adjusted for hemoglobin concentration and expressed as a percentage of the predicted value

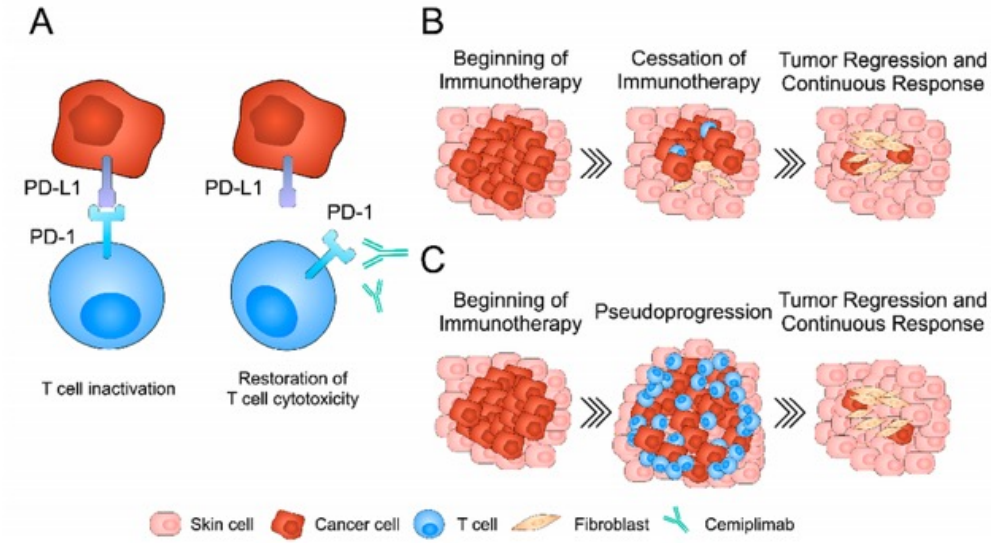

ADVERSE EVENTS
At Least One Adverse Event
At Least One Serious Adverse Event
Percentage of Patients
85%
86%
17%
24%
Molgramostim
Placebo


Autoimmune PAP
SURFACTANT
Type II epithelial cell
Anti–GM-CSF autoantibodies
Alveolar macrophage
GM-CSF
Inhaled Molgramostim
A formulation of recombinant human GM-CSF


PRIMARY END POINT
Change in DLco
From Baseline to Week 24 (95% CI)
Least-Squares Mean Change (percentage points)
Estimated treatment difference:
6.0 percentage points (95% CI, 2.5 to 9.4); P<0.001
9.8 (7.3 to 12.3)
3.8 (1.4 to 6.3)
Molgramostim
Placebo


In patients with autoimmune PAP:
Daily treatment with inhaled molgramostim led to greater improvement in pulmonary gas transfer over 24 weeks than placebo

Der Antikörper Cemiplimab gehört zur pharmakologischen Klasse der Immunonkologika und wird angewendet zur Behandlung des metastasierten und lokal fortgeschrittenen kutanem Plattenepithelkarzinom. Das Medikament ist gegen den Immun-Checkpoint-Rezeptor PD-1 gerichtet und verstärkt die T-Zell-Antwort.

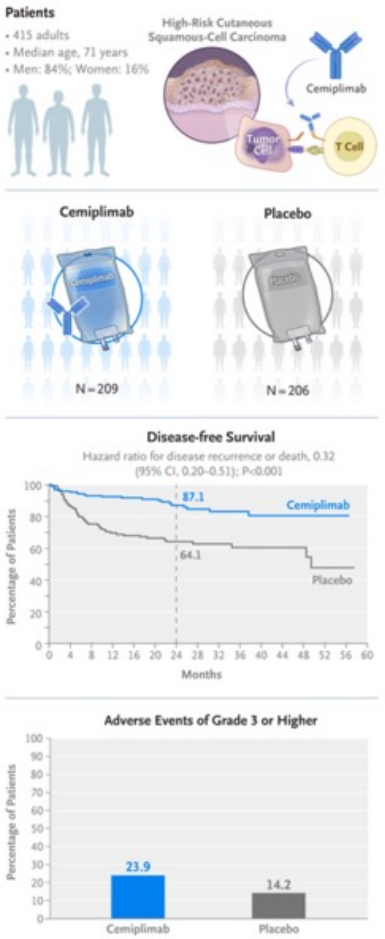


Cemiplimab und Nivolumab sind beides Immun-Checkpoint-Inhibitoren, die auf denselben Immun-Checkpoint-Rezeptor, PD-1, abzielen, um die Immunreaktion gegen Krebs zu stärken. Der Hauptunterschied liegt in ihrem spezifischen Zulassungsprofil: Nivolumab (Opdivo) wurde früher zugelassen und ist für eine breitere Palette von Krebsarten indiziert, während Cemiplimab (Libtayo) als neuer gilt und spezifische Indikationen hat, wie kutanes Plattenepithelkarzinom.

Adjuvant Cemiplimab or Placebo in High-Risk Cutaneous Squamous-Cell Carcinoma

Patients who have cutaneous squamous-cell carcinoma with high-risk features are at risk for recurrence after definitive local therapy. The benefit of systemic adjuvant therapy options has not been well established in clinical trials.

In a phase 3, randomized trial, we enrolled patients with local or regional cutaneous squamous-cell carcinoma, after surgical resection and postoperative radiotherapy, at high risk for recurrence owing to nodal features (extracapsular extension with largest node ≥20 mm in diameter or at least three involved nodes) or nonnodal features (in-transit metastases, T4 lesion [with bone invasion], perineural invasion, or locally recurrent tumor with ≥1 additional risk feature). Patients were assigned in a 1:1 ratio to receive adjuvant cemiplimab (350 mg) or placebo, administered intravenously every 3 weeks for 12 weeks, followed by a dose increase to 700 mg administered every 6 weeks for up to 36 weeks (≤48 weeks total). The primary end point was disease-free survival. Secondary end points included freedom from locoregional recurrence, freedom from distant recurrence, and safety.



A subset of patients with cutaneous squamous-cell carcinoma have disease recurrence, either locoregional or distant, after undergoing surgery and receiving adjuvant radiotherapy. A randomized, phase 3 trial (Postoperative Skin Trial/Trans-Tasman Radiation Oncology Group [POST/TROG] 05.01) showed no additional benefit of carboplatin administered concurrently with adjuvant radiotherapy, as compared with radiotherapy alone, in patients at elevated risk for recurrence of cutaneous squamous-cell carcinoma. However, that trial helped to identify patient subpopulations at the highest risk for recurrence.

Cemiplimab, a programmed death 1 (PD-1)–targeting antibody, is approved for the treatment of locally advanced (i.e., not suitable for resection) or metastatic cutaneous squamous-cell carcinoma, with a response occurring in 47% of patients and an estimated median duration of response of 41 months (range, 2 to 55).

Patients

We recruited patients from 107 sites across 16 countries. Eligible patients were 18 years of age or older with local or regional cutaneous squamous-cell carcinoma and had completed both curative-intent surgery, with macroscopic gross resection of all disease, and postoperative radiotherapy (or concurrent chemoradiotherapy) at a biologically equivalent dose of at least 50 Gy within 2 to 10 weeks before randomization.

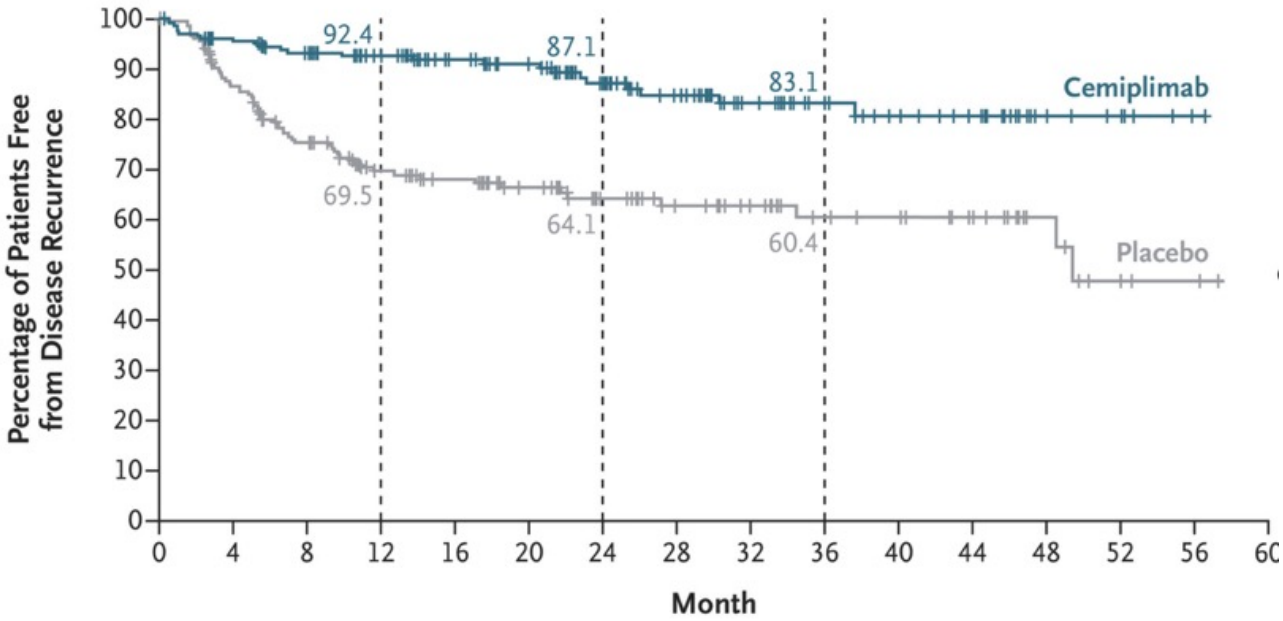
End Points and Assessments

The primary end point was disease-free survival, defined as the time from randomization to the first documented disease recurrence.

Characteristic	Cemiplimab (N=209)	Placebo (N=206)
Age		
Median (range) — yr	71 (33–87)	70.5 (36–95)
≥65 yr — no. (%)	153 (73.2)	141 (68.4)
Male sex — no. (%)	174 (83.3)	174 (84.5)
Race — no. (%)†		
Asian	5 (2.4)	8 (3.9)
White	189 (90.4)	189 (91.7)
Other	1 (0.5)	1 (0.5)
Unknown or not reported	14 (6.7)	8 (3.9)
Geographic region — no. (%)		
North America	37 (17.7)	31 (15.0)
Australia or New Zealand	90 (43.1)	90 (43.7)
Rest of the world	82 (39.2)	85 (41.3)
ECOG performance-status score — no. (%)‡		
0	133 (63.6)	131 (63.6)
1	76 (36.4)	75 (36.4)
Anatomical region of resected high-risk tumor — no. (%)		
Head and neck	166 (79.4)	177 (85.9)
Non–head and neck	43 (20.6)	29 (14.1)
High-risk category — no. (%)§		
Nodal	125 (59.8)	117 (56.8)
Nonnodal	84 (40.2)	89 (43.2)
High-risk criteria — no. (%)¶		
Nodal disease with extracapsular extension and ≥1 lymph node ≥20 mm in diameter	105 (50.2)	96 (46.6)
Nodal disease with ≥3 nodes positive on surgical pathology report, regardless of extracapsular extension	33 (15.8)	37 (18.0)
In-transit metastases	20 (9.6)	21 (10.2)
T4 lesion	17 (8.1)	16 (7.8)
Perineural invasion	32 (15.3)	32 (15.5)
Recurrent high-risk cutaneous squamous-cell carcinoma with ≥1 additional feature	55 (26.3)	50 (24.3)
≥N2b disease associated with the recurrent lesion	17 (8.1)	13 (6.3)
≥T3 lesion	37 (17.7)	29 (14.1)
Poorly differentiated histologic findings and diameter of recurrent lesion ≥20 mm	16 (7.7)	13 (6.3)
PD-L1 tumor proportion score — no. (%)		
≥1%	155 (74.2)	154 (74.8)
<1%	42 (20.1)	43 (20.9)
Indeterminate	12 (5.7)	9 (4.4)

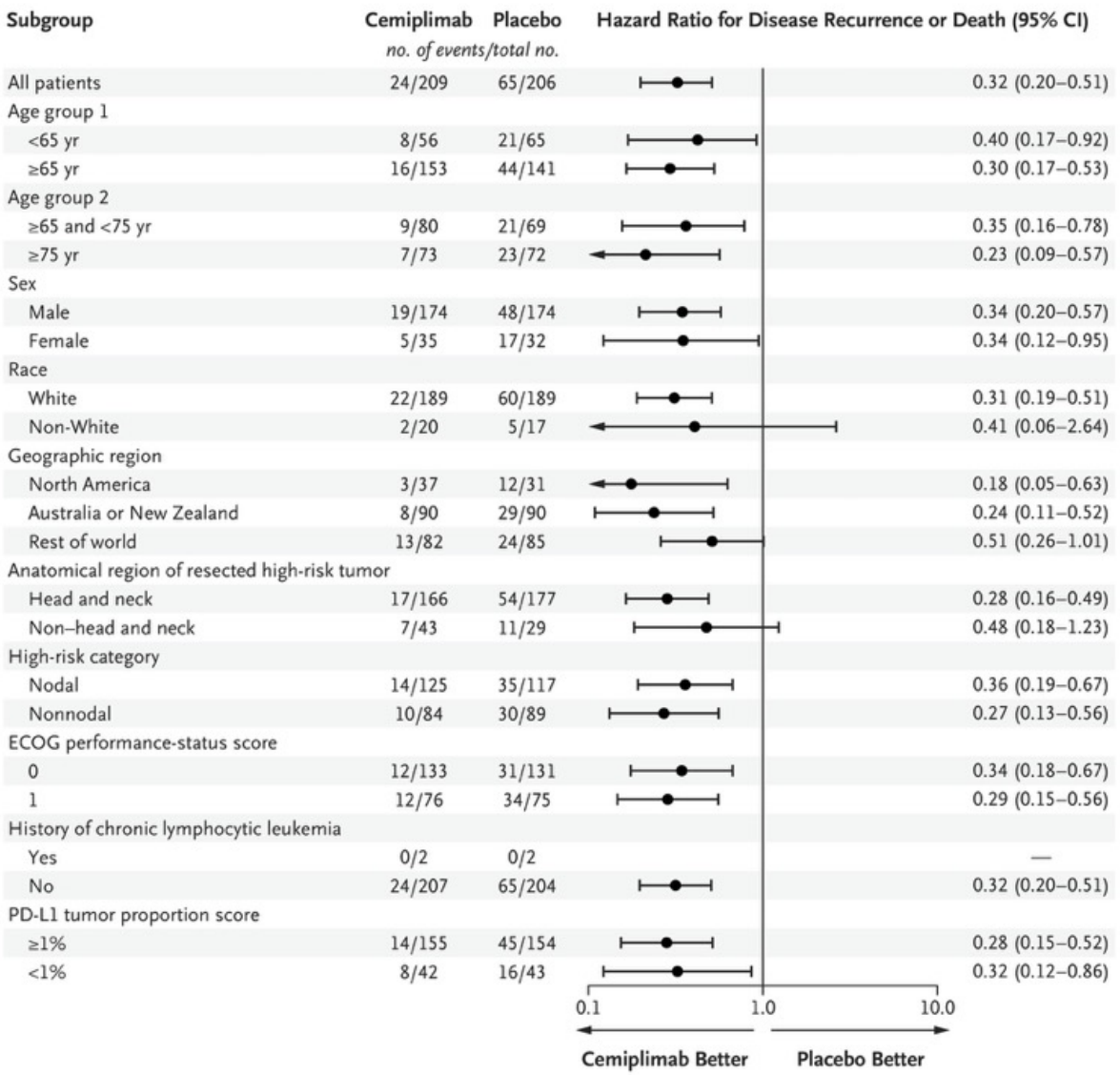
Adverse Events during Treatment Period, According to Grade.

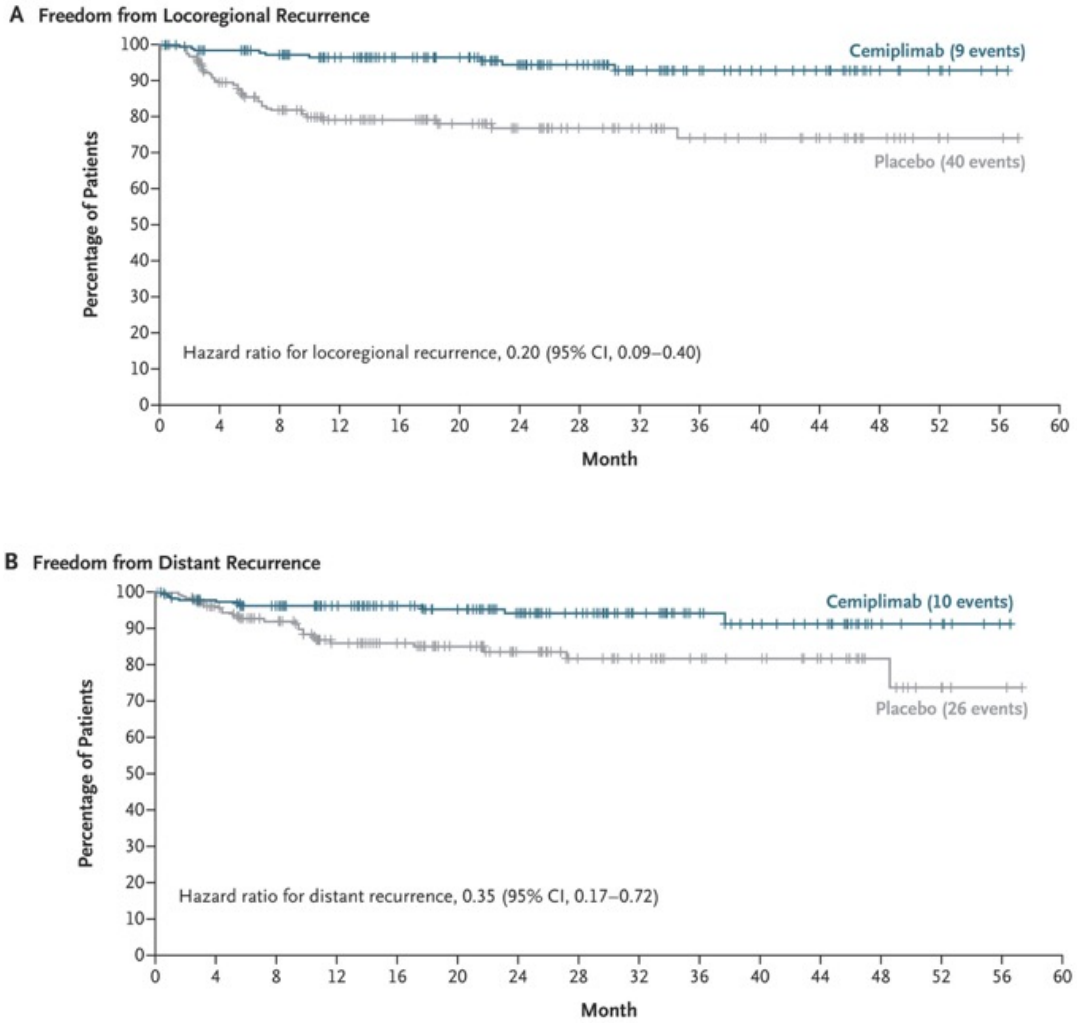
Event	Cemiplimab (N=205)		Placebo (N=204)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients with event (percent)			
Any adverse event	187 (91.2)	49 (23.9)	182 (89.2)	29 (14.2)
Serious adverse event	36 (17.6)	31 (15.1)	19 (9.3)	14 (6.9)
Adverse event leading to discontinuation of cemiplimab or placebo	20 (9.8)	16 (7.8)	3 (1.5)	2 (1.0)
Adverse event leading to death†	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)
Adverse events in ≥10% of the patients in either group‡				
Fatigue	45 (22.0)	1 (0.5)	44 (21.6)	0
Pruritus	33 (16.1)	1 (0.5)	25 (12.3)	0
Rash	33 (16.1)	1 (0.5)	18 (8.8)	0
Diarrhea	32 (15.6)	3 (1.5)	38 (18.6)	0
Arthralgia	26 (12.7)	0	25 (12.3)	0
Hypothyroidism	24 (11.7)	1 (0.5)	6 (2.9)	0
Maculopapular rash	23 (11.2)	0	12 (5.9)	0
Bowen's disease	16 (7.8)	1 (0.5)	21 (10.3)	2 (1.0)



Disease-free Survival.

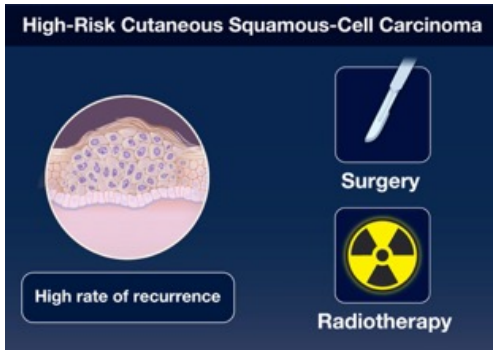
Analyses of disease-free survival were based on the Kaplan–Meier method, with stratification according to high-risk tumor (head and neck vs. non–head and neck) and geographic region (North America vs. Australia or New Zealand vs. the rest of the world). The threshold for significance was set to 0.00455 on the basis of the O'Brien–Fleming alpha spending function. The P value was based on a stratified proportional-hazards model. Second primary cutaneous squamous-cell carcinoma tumors were not included as events in the primary end-point analysis of disease-free survival. Tick marks indicate censored data. NE denotes could not be evaluated, and NR not reached.

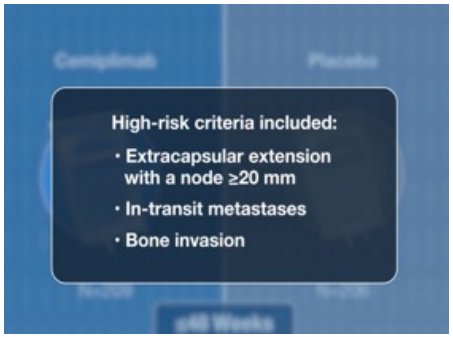

Subgroup
Cemiplimab
Placebo
Hazard Ratio for Disease Recurrence or Death (95% CI)
no. of events/total no.
All patients 24/209 65/206 0.32 (0.20–0.51)
Age group 1
<65 yr 8/56 21/65 0.40 (0.17–0.92)
≥65 yr 16/153 44/141 0.30 (0.17–0.53)
Age group 2
≥65 and <75 yr 9/80 21/69 0.35 (0.16–0.78)
≥75 yr 7/73 23/72 0.23 (0.09–0.57)
Sex
Male 19/174 48/174 0.34 (0.20–0.57)
Female 5/35 17/32 0.34 (0.12–0.95)
Race
White 22/189 60/189 0.31 (0.19–0.51)
Non-White 2/20 5/17 0.41 (0.06–2.64)
Geographic region
North America 3/37 12/31 0.18 (0.05–0.63)
Australia or New Zealand 8/90 29/90 0.24 (0.11–0.52)
Rest of world 13/82 24/85 0.51 (0.26–1.01)
Anatomical region of resected high-risk tumor
Head and neck 17/166 54/177 0.28 (0.16–0.49)
Non–head and neck 7/43 11/29 0.48 (0.18–1.23)
High-risk category
Nodal 14/125 35/117 0.36 (0.19–0.67)
Nonnodal 10/84 30/89 0.27 (0.13–0.56)
ECOG performance-status score
0 12/133 31/131 0.34 (0.18–0.67)
1 12/76 34/75 0.29 (0.15–0.56)
History of chronic lymphocytic leukemia
Yes 0/2 0/2 —
No 24/207 65/204 0.32 (0.20–0.51)
PD-L1 tumor proportion score
≥1% 14/155 45/154 0.28 (0.15–0.52)
<1% 8/42 16/43 0.32 (0.12–0.86)
0.1
1.0
10.0
Cemiplimab Better
Placebo Better

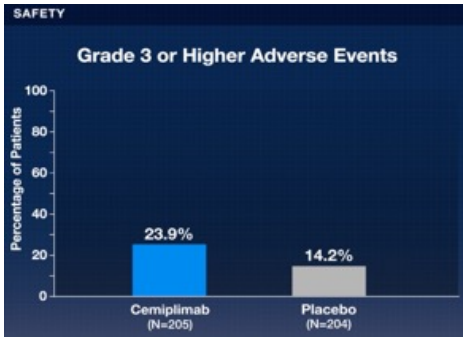


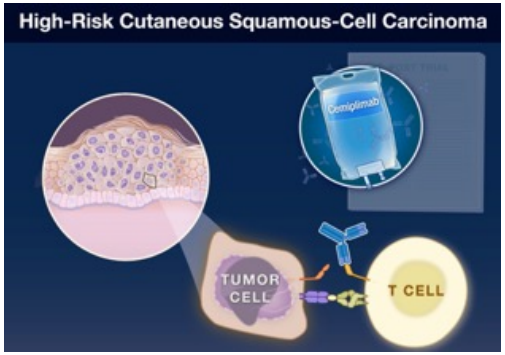
Freedom from Locoregional Recurrence and Freedom from Distant Recurrence.

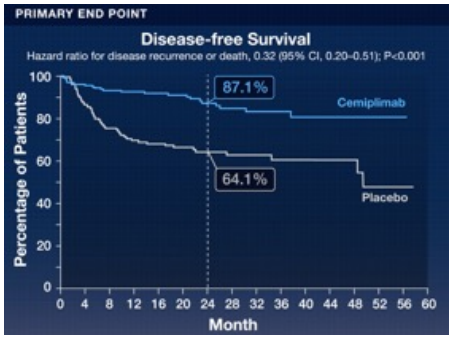
Analyses of locoregional recurrence (Panel A) and distant recurrence (Panel B) were based on the Kaplan–Meier method, with stratification according to high-risk tumor (head and neck vs. non–head and neck) and geographic region (North America vs. Australia or New Zealand vs. the rest of the world). Hazard ratios were based on stratified proportional-hazards models. Tick marks indicate censored data.


High-Risk Cutaneous Squamous-Cell Carcinoma
Surgery
Radiotherapy
High rate of recurrence


High-risk criteria included:
• Extracapsular extension with a node ≥20 mm
• In-transit metastases
• Bone invasion

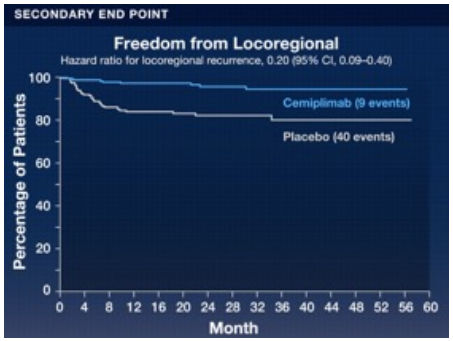

SAFETY
Grade 3 or Higher Adverse Events
Percentage of Patients
100
80
60
40
20
0
23.9%
14.2%
Cemiplimab (N=205)
Placebo (N=204)


High-Risk Cutaneous Squamous-Cell Carcinoma
Cemiplimab
TUMOR CELL
T CELL


PRIMARY END POINT
Disease-free Survival
Hazard ratio for disease recurrence or death, 0.32 (95% CI, 0.20–0.51); P<0.001
Percentage of Patients
100
80
60
40
20
0
87.1%
Cemiplimab
64.1%
Placebo
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
Month


Cemiplimab
Cemiplimab significantly improved disease-free survival


Cemiplimab
Placebo
Cemiplimab
Placebo
N=209
N=206
≤48 Weeks


SECONDARY END POINT
Freedom from Locoregional
Hazard ratio for locoregional recurrence, 0.20 (95% CI, 0.09–0.40)
Percentage of Patients
100
80
60
40
20
0
Cemiplimab (9 events)
Placebo (40 events)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
Month

ChatGPT

Tipps, um das volle Potenzial von ChatGPT auszuschöpfen

Um das volle Potenzial von ChatGPT auszuschöpfen, ist es wichtig, die besten Praktiken und Strategien zu kennen, die Ihnen dabei helfen, effektivere Ergebnisse zu erzielen. Hier geben wir Ihnen ein paar Tipps und Ratschläge, um das volle Potenzial von ChatGPT zu nutzen und Ihre Produktivität in verschiedenen Bereichen zu steigern.

Stellen Sie klare und präzise Fragen

ChatGPT kann nur so gut antworten, wie die Fragen, die Sie stellen. Stellen Sie deshalb klare und präzise Fragen, damit ChatGPT Ihnen die bestmögliche Antwort geben kann.

Vermeiden Sie unnötige Informationen

Je klarer und präziser Ihre Frage ist, desto besser wird ChatGPT in der Lage sein, Ihnen zu antworten. Vermeiden Sie unnötige Informationen und umschreiben Sie Ihre Frage nicht unnötig. Stellen Sie stattdessen eine direkte und klare Frage.

Seien Sie geduldig und experimentieren Sie

ChatGPT ist ein lernendes System und seine Fähigkeiten verbessern sich ständig. Wenn Sie eine bestimmte Frage oder Anfrage haben und ChatGPT nicht in der Lage ist, Ihnen eine zufriedenstellende Antwort zu geben, versuchen Sie es mit anderen Formulierungen oder verschiedenen Fragetypen. Seien Sie geduldig und experimentieren Sie, um das Beste aus ChatGPT herauszuholen. Je öfter Sie ChatGPT verwenden, desto besser wird es Sie verstehen und Ihnen helfen können.

Trennen Sie verschiedene Anfragen klar voneinander

Wenn Sie ChatGPT verschiedene Anfragen stellen, wie z.B. um eine Zusammenfassung, eine Übersetzung oder einen Code zu erstellen, stellen Sie sicher, dass Sie diese klar voneinander trennen. Verwenden Sie dafür unterschiedliche Satzzeichen wie Doppelpunkte, Gänsefüßchen oder Aufzählungszeichen, um Ihre Anfragen zu kennzeichnen und die Arbeit von ChatGPT zu erleichtern. Beispiel: Bitte diesen Text Zusammenfassung: TEXT oder Bitte folgendes in Englisch übersetzen: TEXT

Nutzen Sie die Möglichkeiten von ChatGPT

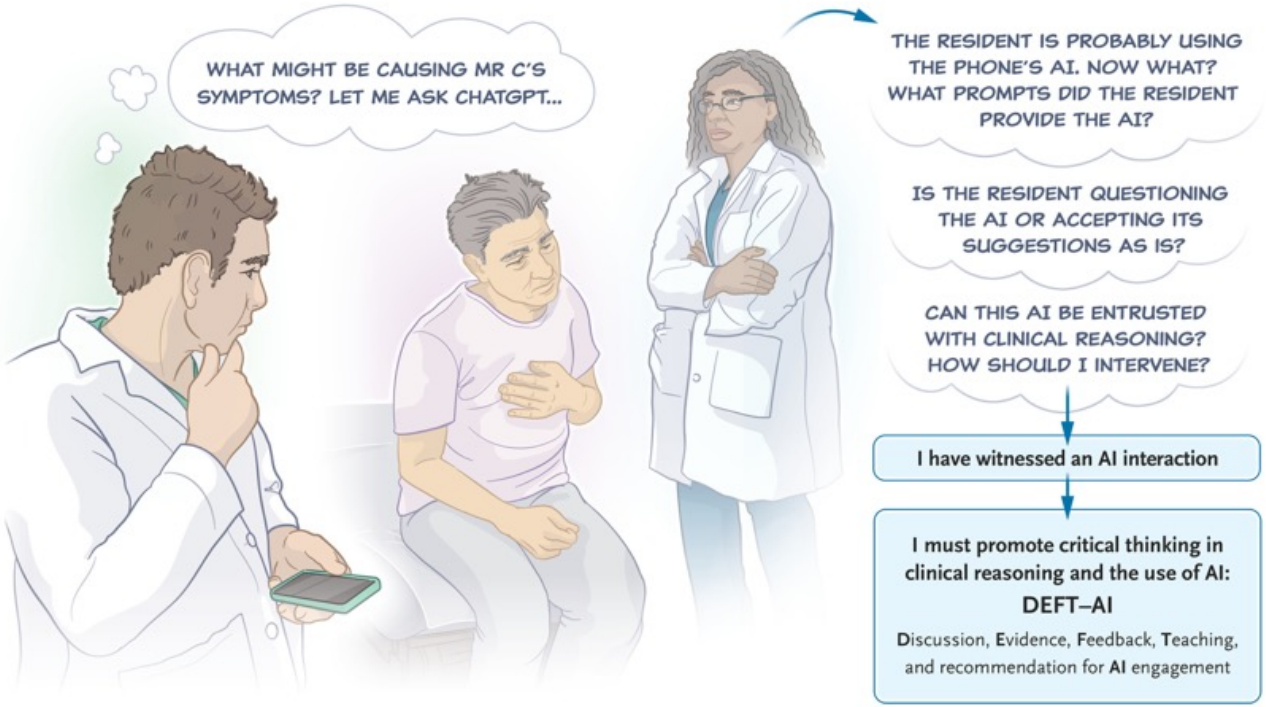
ChatGPT kann nicht nur Fragen beantworten, sondern auch Wissen vermitteln, Witze machen oder einfach nur eine interessante Unterhaltung bieten. Nutzen Sie die verschiedenen Anwendungsmöglichkeiten von ChatGPT, um das Beste aus ihm herauszuholen.

Educational Strategies for Clinical Supervision of Artificial Intelligence Use

Human–computer interactions have been occurring for decades, but recent technological developments in medical artificial intelligence (AI) have resulted in more effective and potentially more dangerous interactions. Although the hype around AI resonates with previous technological revolutions, such as the development of the Internet and the electronic health record, the appearance of large language models (LLMs) seems different. LLMs can simulate knowledge generation and clinical reasoning with humanlike fluency, which gives them the appearance of agency and independent information processing. Therefore, AI has the capacity to fundamentally alter medical learning and practice. As in other professions, the use of AI in medical training could result in professionals who are highly efficient yet less capable of independent problem solving and critical evaluation than their pre-AI counterparts.

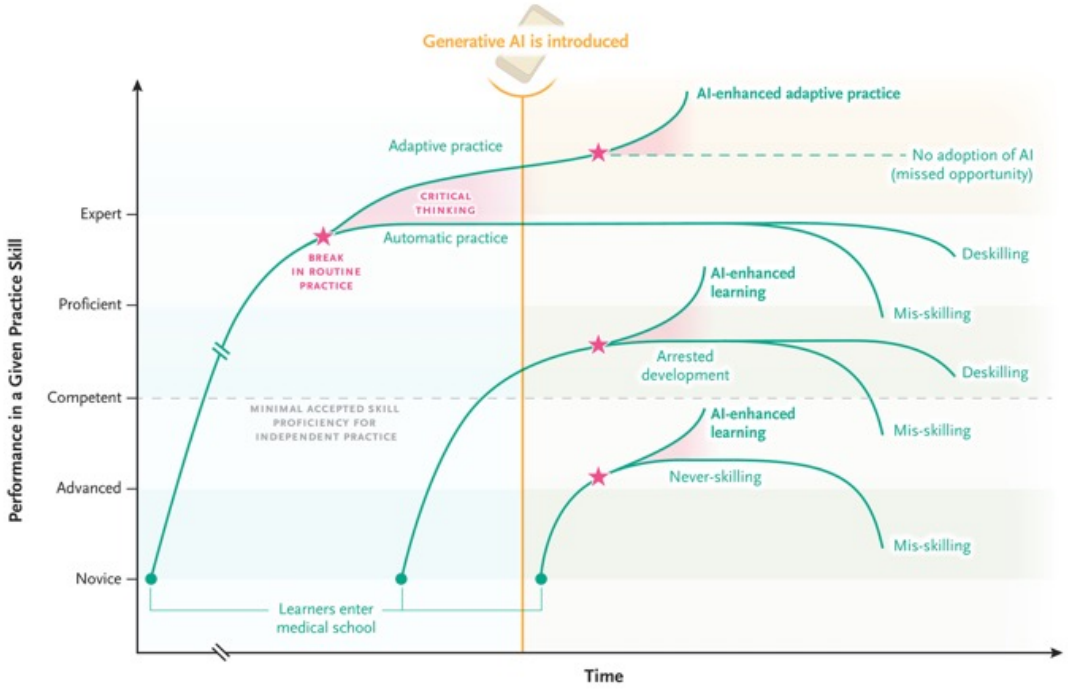
Educational Strategies for Clinical Supervision of Artificial Intelligence Use

- Use of artificial intelligence (AI) for the development of expert practice presents unprecedented opportunities but also poses risks, such as “deskilling,” “never-skilling,” and “mis-skilling.”
- Clinical supervisors may be less experienced with AI than learners are. Faculty development should embrace shared learning environments that allow coexploration of AI capabilities and limitations.
- Adaptive practice — shifting between efficiency and innovation — is foundational in AI-enabled learning. Critical thinking supports this shift and must be taught and modeled.
- AI interactions lead to moments when clinicians receive outputs they cannot fully retrace, which prompts a leap of faith. Pausing to recognize these moments is essential for critical thinking.
- DEFT-AI (diagnosis, evidence, feedback, teaching, and recommendation for AI use) is a structured framework to promote critical thinking and AI literacy during learner–AI interactions.
- Two AI use behaviors emerge: cyborg (tight intertwining of user and AI for each task) and centaur (division of tasks between user and AI, with critical oversight). Adaptive AI practice requires the ability to shift between these behaviors according to the complexity of the task and the risk involved.



An Educator Witnessing a Learner's Use of Artificial Intelligence (AI).

An educator, acting as a clinical preceptor, observes a resident who is using a large language model chatbot to assist with a differential diagnosis. The educator recognizes the inherent challenge of trusting an AI tool that may not be fully reliable. This moment of AI interaction prompts the educator to intervene in what could be a high-risk scenario for both the learner and the patient. By stepping in, the educator creates an opportunity to make critical thinking a scaffold and to foster deeper engagement with clinical reasoning and the responsible use of AI — an approach encapsulated in DEFT-AI (diagnosis, evidence, feedback, teaching, and recommendation for AI use).

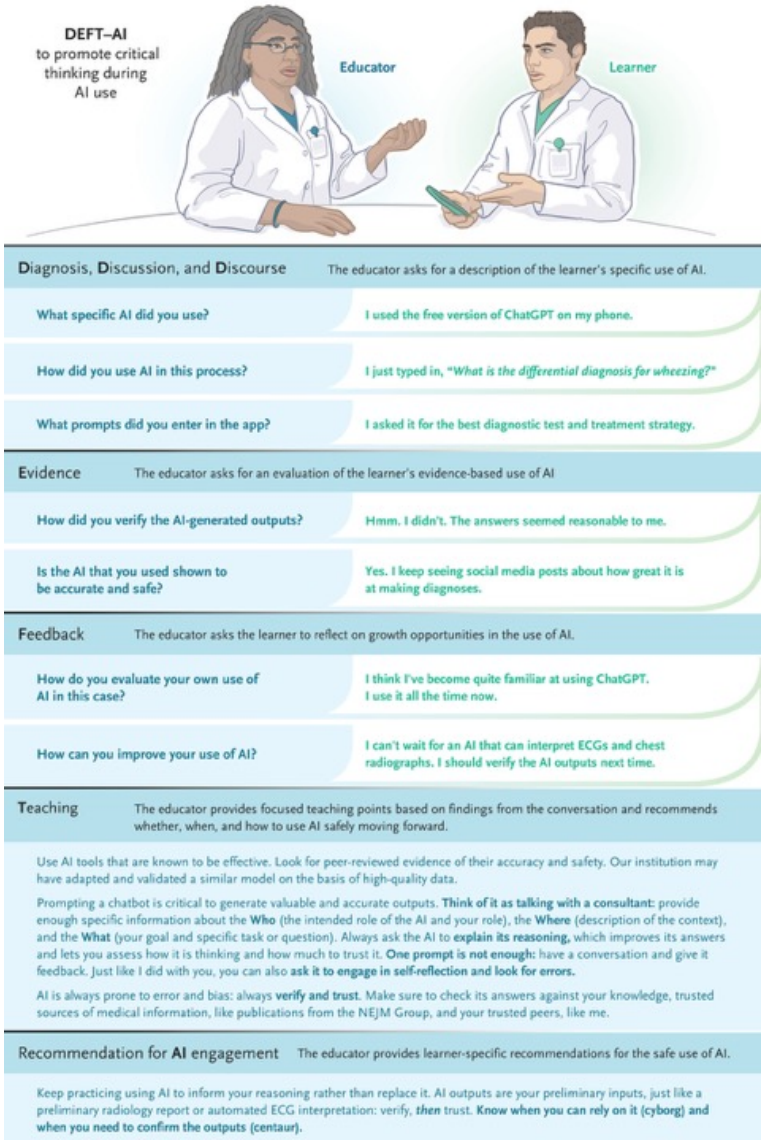


Deskilling is the process by which skilled labor within an industry or economy is eliminated by the introduction of technologies operated by semi- or unskilled workers.

Mis-skilling is a poor fit between an individual's capabilities and the requirements of the job, or a shortage of the right skills within an organization's Management Information Systems (MIS) department.

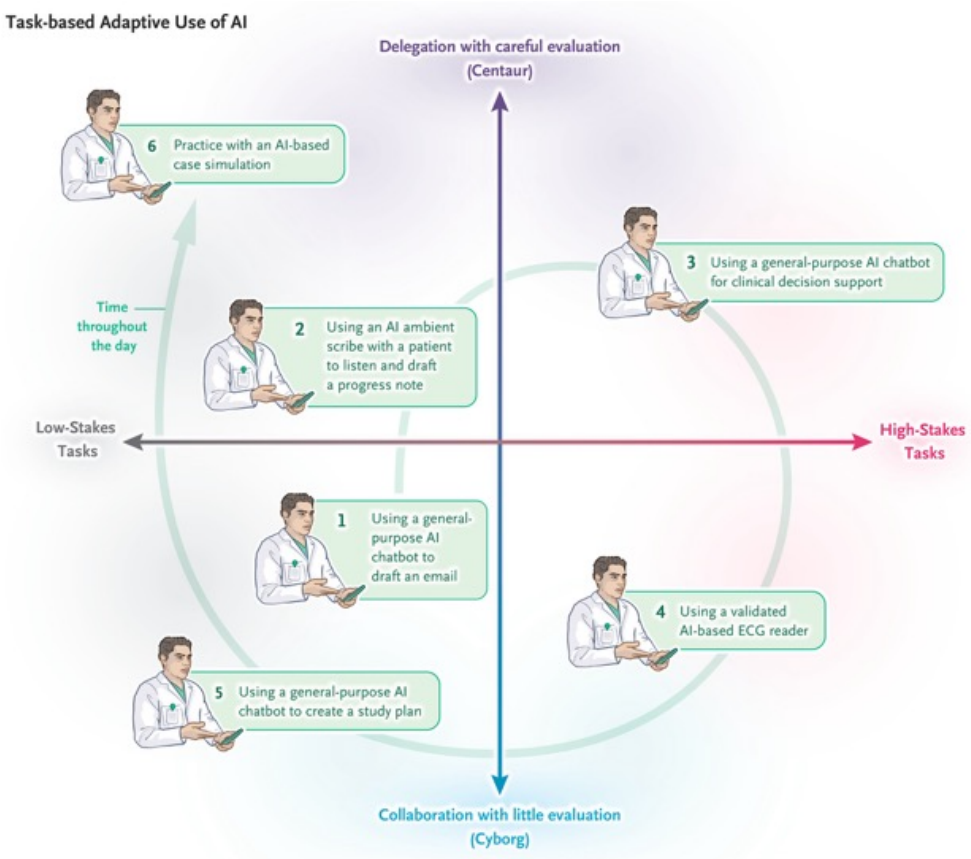
Development of Adaptive Practice and the Effects of AI.

Through practice and critical thinking, learners develop the ability to shift to innovative, adaptive practice in response to a break in routine, automatic practice (star). As they progress and enter clinical practice, the use of AI introduces both risks and opportunities. Cognitive off-loading onto AI can lead to overdependence on AI and "deskilling," whereas blind reliance on AI may result in "mis-skilling," with AI errors going unchallenged. If introduced too early, AI may prevent learners from acquiring essential skills ("never-skilling"). Conversely, judicious use of AI can enhance practice and learning by emphasizing the need for critical thinking and fostering effective human–AI collaboration.



Use of DEFT-AI to Promote Critical Thinking during an AI Interaction.

After recognizing an AI interaction, the educator engages the learner in a structured educational moment to discuss the interaction, evaluate it, provide feedback, and teach clinical reasoning, as well as the use of AI. The discussion encompasses the learner's clinical reasoning process and approach to using AI, including the prompts used. The educator probes the learner for the use of supporting and opposing evidence to evaluate the learner's clinical and AI knowledge. This process helps determine whether the learner used AI to replace clinical reasoning or to inform it and offers a window into the learner's AI literacy. The educator then guides the learner in reflecting on growth opportunities and encourages critical thinking about AI interactions and clinical reasoning. Finally, the educator provides focused teaching on using AI effectively, selecting the right tools, and refining prompts. The learner is encouraged to adapt the use of AI to the task, switching between reliance on AI output (cyborg strategy) and confirmation of AI output (centaur strategy). Table S2 provides an expanded version of DEFT-AI.



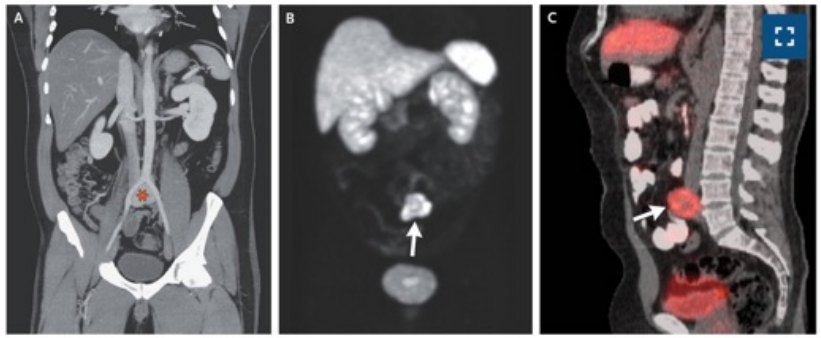
Task-Based Adaptive Use of AI.

AI engagement behaviors should vary moment to moment, adapting to the type of task and its associated risk. The degree of human–AI integration can range from strategic delegation (centaur) to tight collaboration (cyborg). Centaur strategies are appropriate when human judgment must lead, particularly in high-stakes tasks or in situations in which the AI tool has not been validated for the specific intended use. With a centaur mindset, the clinician carefully delegates to AI and always evaluates the output. Cyborg strategies may enhance efficiency for low-risk, creative, or well-validated tasks. Adaptive AI use involves shifting between these modes on the basis of skill, task, and context.

Verify and Trust

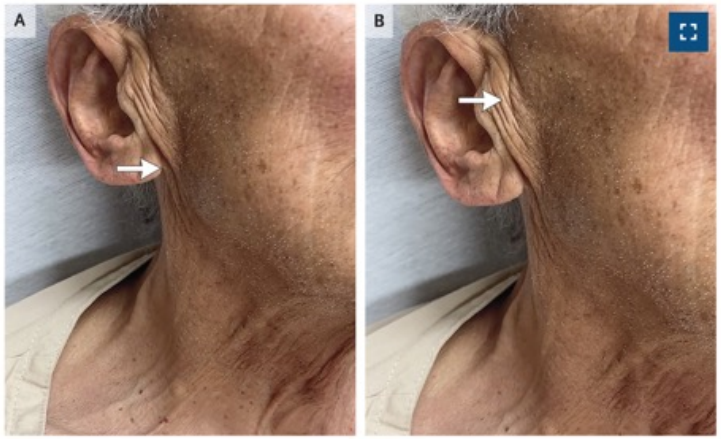
Despite the technical advancements of AI tools, their use still requires leaps of faith with careful consideration; the need for verification is at the heart of AI interactions. As medical learners increasingly use these tools, often as an integral part of their patient evaluations, medical educators must face the reality that AI interactions are here to stay. Although critical thinking is the bulwark against the deskilling, never-skilling, and mis-skilling that can arise from an overreliance on AI, the opportunity to promote critical thinking as a scaffold can accelerate the development of adaptive practice skills and concurrently improve the AI literacy of both learners and educators. DEFT-AI provides a structured and common-sense approach to promote critical thinking during learner–AI interactions and underscores the importance of establishing the validity of an AI output as part of the AI use process. The onus lies with educators to inculcate in their trainees the conviction that verification is key to AI use. To do this effectively will require curricular redesign, with close collaboration among AI developers, health care systems, and educational programs, in order to promote AI competencies among learners and educators. We must also include systematic assessment of learner–AI interactions in the educational settings in which they occur. Without governance structures, rigorous validation frameworks, and ongoing monitoring, the risk of AI-driven errors and biases may outweigh the benefits of AI technologies, which may thus jeopardize medical education rather than improve it. Ultimately, fostering a “verify and trust” paradigm is crucial for ensuring that AI is a beneficial augmentation of human expertise.

Paraganglioma in the Organ of Zuckerkandl



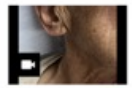
A 39-year-old man with no known medical history presented to the emergency department with a 1-day history of lower abdominal pain. The blood pressure was 203/132 mm Hg. A physical examination was notable for suprapubic tenderness. Computed tomography of the abdomen revealed a retroperitoneal mass below the aortic bifurcation (Panel A, asterisk). Owing to concern about a catecholamine-secreting tumor, plasma metanephrine levels were checked. The metanephrine level was 60 pg per milliliter (reference range, 0 to 88), and the normetanephrine level was 2330 pg per milliliter (reference range, 0 to 210). Subsequent positron-emission tomography–computed tomography (PET-CT) with gallium-68–dotatate revealed uptake in the mass (Panel B, arrow, maximum intensity projection image; Panel C, arrow, fused PET-CT image), which indicated dense overexpression of somatostatin receptors. Physiologic uptake was seen in other organs, and excreted tracer was noted in the bladder. Surgical resection of the tumor was performed. Histopathological analysis of a tumor specimen showed focal large and irregular cell nests. Immunohistochemical staining was positive for chromogranin, synaptophysin, GATA3, and S100. A diagnosis of a paraganglioma in the organ of Zuckerkandl — a collection of paraganglia found along the abdominal aorta — was made. The patient recovered well, and the plasma normetanephrine level was normal at a 2-week postoperative follow-up visit. He did not return for further care, so genetic testing was not performed.

Abdominojugular Reflux Test



A 79-year-old man with heart failure with reduced ejection fraction and atrial fibrillation presented to the emergency department with a 2-week history of shortness of breath. On physical examination, there was an irregular heart rhythm, crackles in both lungs, and pitting edema in both legs up to the mid-thigh. The jugular venous pressure was estimated to be 17 cm of water (arrow, Panel A) (normal value, <4 cm of water). The abdominojugular reflux test was performed by applying firm, sustained pressure to the center of the abdomen. There was a sustained increase in jugular venous pressure of more than 3 cm of water for more than 10 seconds while pressure was applied (Panel B, arrow; see video), which indicated a positive test. (A transient increase in jugular venous pressure that returned to baseline in 10 seconds or less while abdominal pressure was applied would have indicated a negative test.) A positive abdominojugular reflux test indicates that the right ventricle is unable to compensate for the increased venous return caused by the compression of the mesenteric venous system. It is seen in any condition that impairs right ventricular filling or contraction, including biventricular heart failure (as in this case), constrictive pericarditis, restrictive cardiomyopathy, and pulmonary hypertension. After treatment with diuresis led to the loss of 9 kg (20 lbs) of body weight, the patient's condition improved.

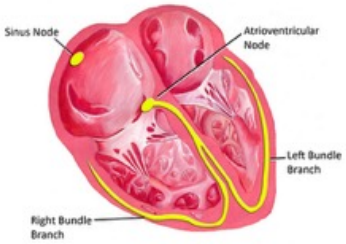
VIDEO

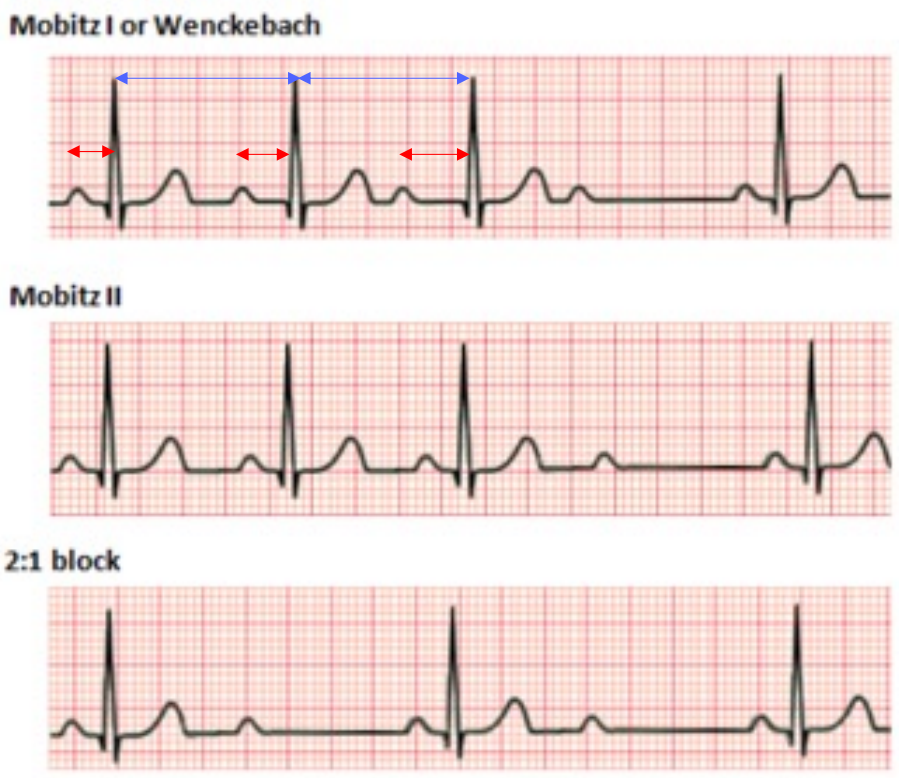


Abdominojugular Reflux Test

0m 30s

Der Mobitz-I-Herzblock (Wenckebach) ist durch eine fortschreitende Verlängerung der PQ-Zeit bis zu einer blockierten Vorhofaktion gekennzeichnet, was meist eine gute Prognose hat und selten eine Behandlung erfordert, während der Mobitz-II-Herzblock durch plötzlich ausbleibende Vorhofaktionen bei gleichbleibenden PQ-Zeiten charakterisiert ist, eine schlechtere Prognose hat und fast immer eine Schrittmacherimplantation erfordert.





Case 24-2025: A 32-Year-Old Woman with Fatigue and Myalgias

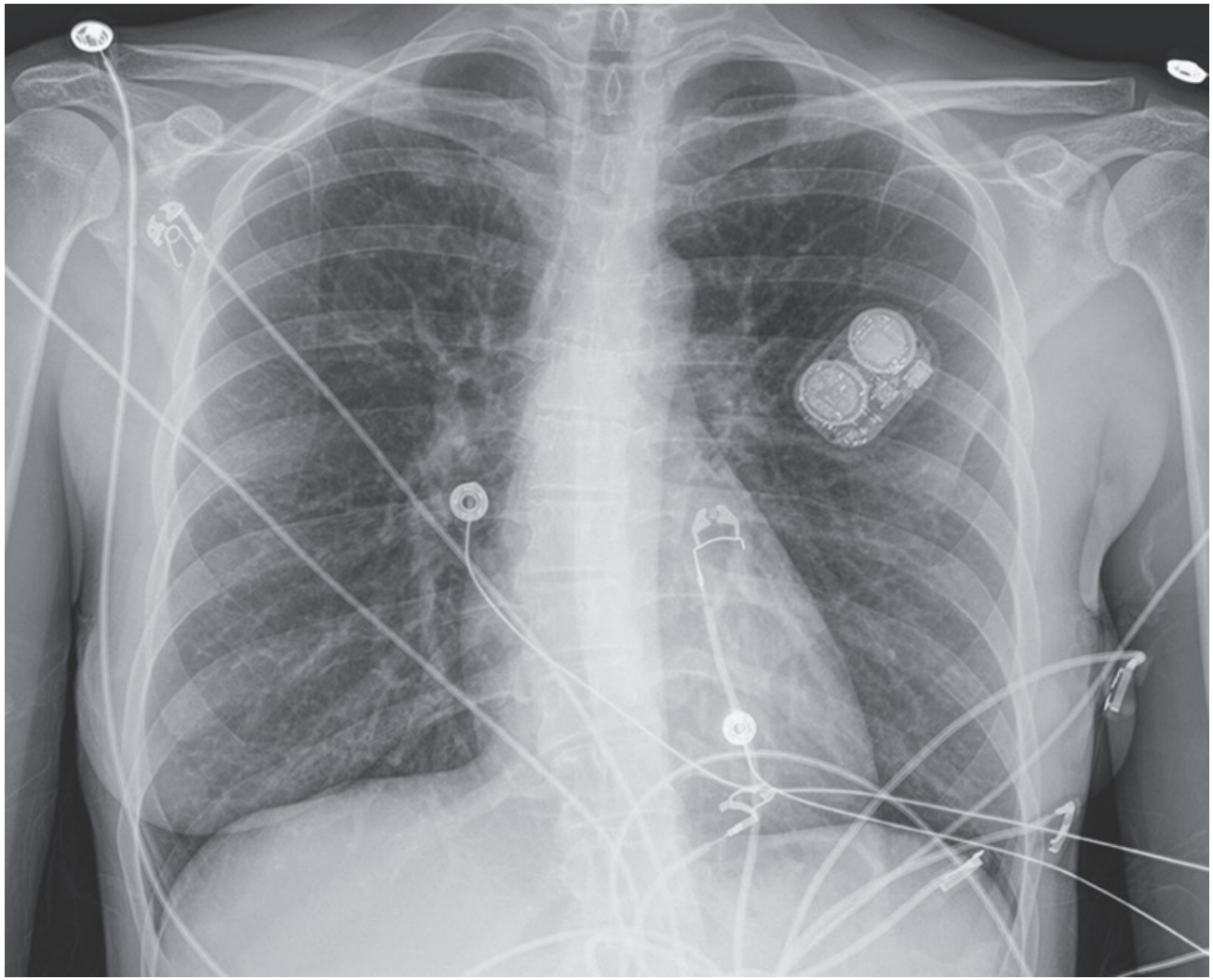
Two and a half years before the current presentation, the patient had fatigue, headache, myalgias, and "brain fog" after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Evaluation of these symptoms included consultations with neurology, immunology, and rheumatology specialists at another hospital. The blood levels of electrolytes, thyrotropin, alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, C-reactive protein, and ferritin were normal, as were the complete blood count and differential count and the results of tests of kidney function. Serologic tests for cytomegalovirus, Epstein–Barr virus, ehrlichia species, anaplasma species, and *Borrelia burgdorferi* were reportedly negative. The results of magnetic resonance imaging of the head were reportedly normal.

During the next 2 years, the patient received acupuncture therapy and used herbal supplements, which helped to alleviate her symptoms. Five weeks before the current presentation, the patient was reinfected with SARS-CoV-2. After 5 days, symptoms associated with acute SARS-CoV-2 infection abated and she returned to her usual state of health.

Nine days before the current presentation, the patient began to have neck tightness and pain after lifting heavy objects. The pain radiated to the head and scapulae. Six days before the current presentation, she was evaluated by her primary care physician, who was affiliated with the other hospital. Examination was reportedly normal. Treatment with ibuprofen, magnesium, acupuncture, and massage were recommended.

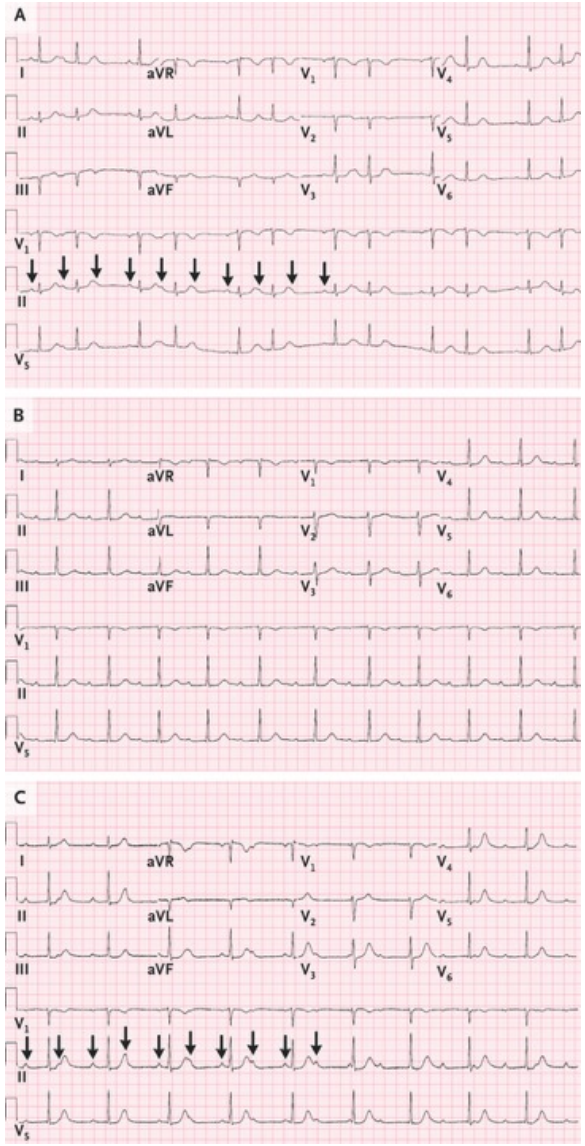
The neck pain did not abate. Three days before the current presentation, the pain began to radiate down the right arm, and severe fatigue developed. The patient presented to the emergency department of a second hospital for evaluation. On examination, the temporal temperature was 36.8°C, the heart rate 50 beats per minute, and the blood pressure 109/55 mm Hg. She had full range of motion in the neck and tenderness on palpation of the right side of the upper neck and the right side of the upper back. A radiograph of the cervical spine was reportedly normal. Treatment with intravenous ketorolac, oral methocarbamol, and transdermal lidocaine was administered, and a tapering dose of oral methylprednisolone was prescribed.

During the next 2 days, the back and neck pain resolved. However, the fatigue worsened and myalgias developed. The patient had palpitations and an irregular pulse, as well as waxing and waning lower chest pain that she described as tightness. The chest pain was both pleuritic and positional in nature, and she rated the pain at 5 on a scale of 0 to 10 (with 10 indicating the most severe pain). She presented to the emergency department of a third hospital for evaluation.



Chest Radiograph.

A single-view frontal image obtained with a portable device shows no evidence of pneumonia or pulmonary edema and no pleural effusion. The heart size is normal. An implantable loop recorder projects over the left hemithorax. Electrocardiographic leads can also be seen.



Electrocardiograms.

An electrocardiogram (ECG) obtained on presentation (Panel A) shows Mobitz type I second-degree atrioventricular block, along with first-degree atrioventricular block with a PR interval of 240 msec. The QRS complexes associated with Mobitz type I block appear in a regularly irregular — or "grouped beating" — cadence. An ECG obtained on hospital day 1 (Panel B) shows sinus rhythm with first-degree atrioventricular block with a PR interval of 350 msec. An ECG obtained on hospital day 2 (Panel C) shows sinus rhythm with complete atrioventricular block and junctional escape rhythm. Arrows in Panels A and C indicate P waves.

Differential Diagnosis

This young woman who lives in a rural area began to have neck and arm pain and fatigue after recovering from infection with SARS-CoV-2. She then began to have pleuritic and positional chest pain, palpitations and an irregular pulse, dyspnea on exertion, and myalgias, and the blood level of d-dimer was elevated. At the current presentation, the patient had Mobitz type I second-degree atrioventricular block and an elevated blood level of NT-proBNP. In working toward the most likely diagnosis, I will consider cardiac and pulmonary conditions that could account for these findings.

Complications of Infection with SARS-CoV-2

The patient's remote and recent infections with SARS-CoV-2 warrant evaluation for possible long-term consequences of coronavirus disease 2019 (Covid-19) such as carditis or multisystem inflammatory syndrome, a condition that is similar to Kawasaki's disease.

Pulmonary Embolism

Pulmonary embolism was appropriately considered in this patient who had presented with dyspnea on exertion, pleuritic chest pain, and an elevated blood level of d-dimer. Recent infection with SARS-CoV-2 is associated with thrombotic events in some patients.

Acute Coronary Syndrome

The development of atherosclerotic coronary vascular disease would be unusual in a person of this patient's age. However, this patient had a family history that may have increased her risk of heart disease, and she had a history of exposure to tobacco, vaping, and marijuana.

Infection

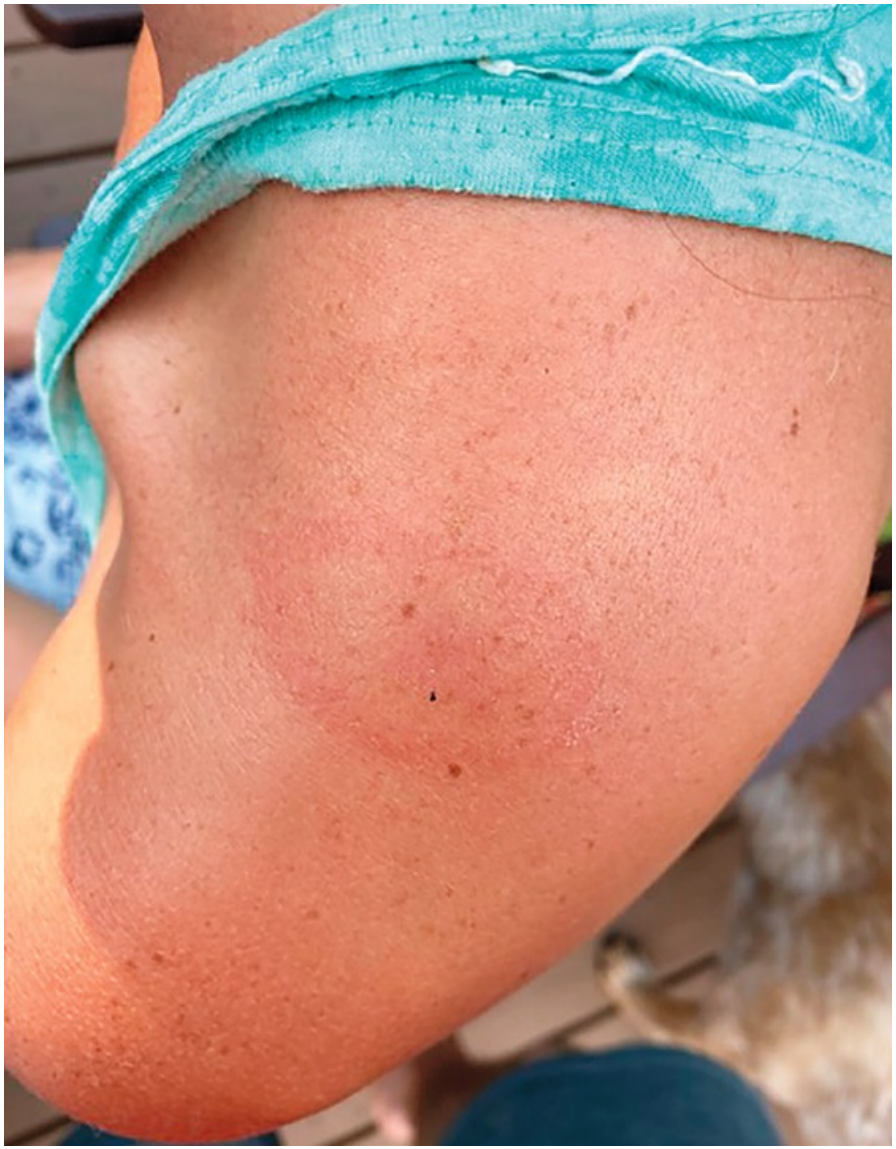
The patient's nonspecific prodromal symptoms of myalgia and headache, followed by pleuritic chest pain and atrioventricular block, may be suggestive of an infectious process culminating in myocarditis.

Lyme Carditis

Early consideration of Lyme carditis in a patient with atrioventricular block is extremely important, since conduction abnormalities can advance rapidly to third-degree atrioventricular block and may begin to abate within hours after the administration of antibiotic agents. This patient did not report having had a tick bite, but she lives in a wooded area of New England and spends time outdoors — factors that increase the likelihood that she had been exposed to ticks infected with *B. burgdorferi*, the causative agent of Lyme disease in the United States.

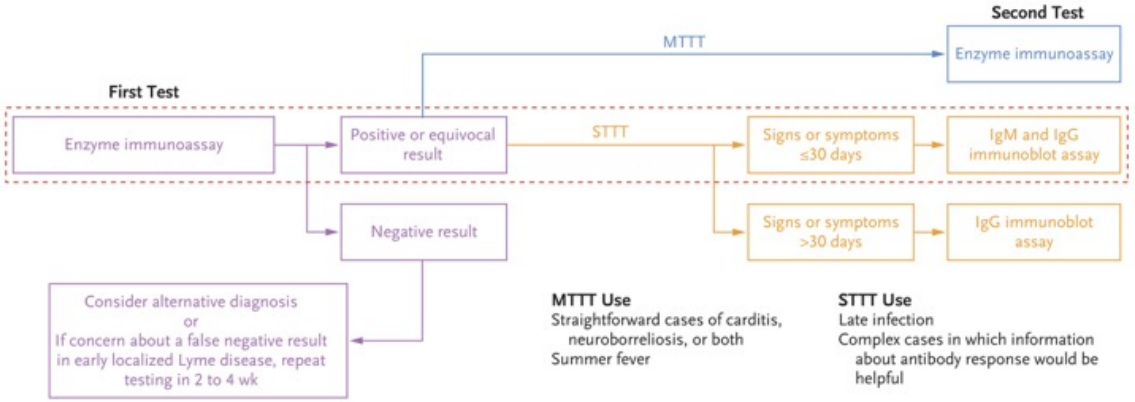
The Patient

On my third day in the hospital, my friend (who is a nurse) reminded me to show a picture I had taken with my phone of a rash I had 3 weeks before this hospitalization. The rash in the picture was on my arm, but at the time, I had similar rashes all over my body.



Photograph of Previous Rash.

A photograph taken by the patient 3 weeks before the current presentation shows an erythematous, circular, macular rash on the left arm. Note that the small black mark inside the rash was present on the original photograph and is considered by the treating clinicians to be an artifact.



Two-Tiered Testing Algorithms for Diagnosis of Lyme Disease.

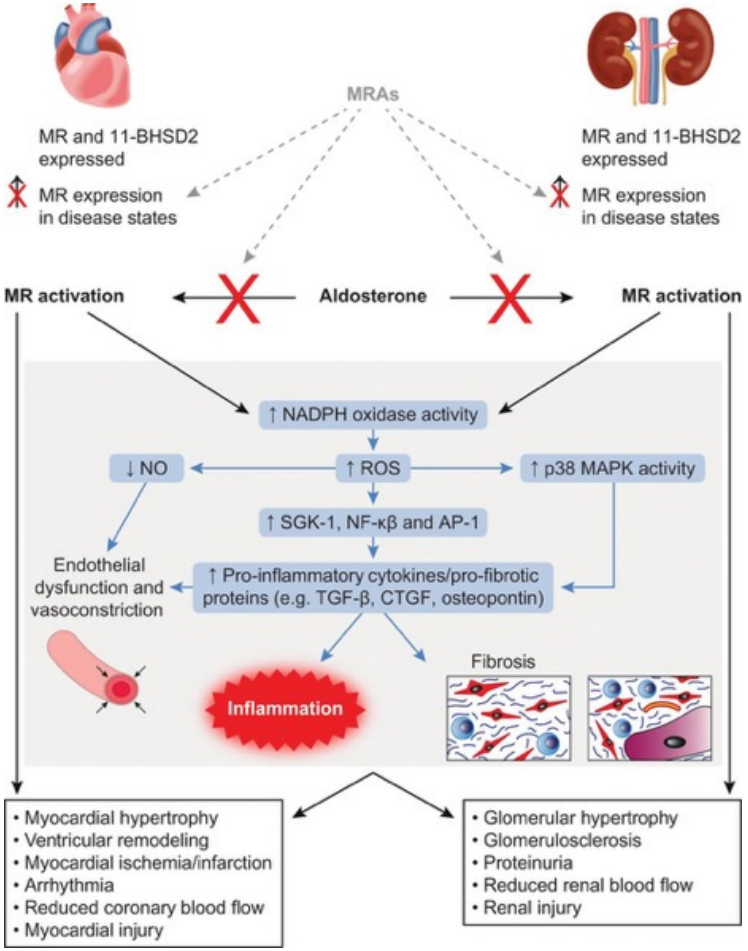
The steps in purple show components of the algorithm shared by both standard two-tiered testing (STTT) and modified two-tiered testing (MTTT). The steps in orange show components of the algorithm specific to STTT. The steps in blue show components of the algorithm specific to MTTT. The red dashed outline shows the STTT algorithm that was used for this patient, which included an enzyme immunoassay followed by an immunoblot assay; the patient had had signs or symptoms for 30 days or less when the algorithm was used to make the diagnosis. MTTT includes the use of only enzyme immunoassays that have been approved by the Food and Drug Administration. For STTT, an immunofluorescence assay can also be used as the first-tier test.

Follow-up

The patient's PR interval decreased, and she was discharged home on hospital day 4 with instructions to complete a 3-week course of oral doxycycline. The patient was seen in the cardiology clinic 2 weeks after discharge. She continued to have fatigue but had resumed participation in low-intensity exercise. The first-degree atrioventricular delay that had been seen on ECG resolved within 2 weeks after onset. During the next few months, her functional status slowly improved, and she was able to return to her previous activity level.

THE LANCET

Non-renal mineralocorticoid receptor (MR) effects include the promotion of inflammation, fibrosis, hypertrophy, and oxidative stress in the heart, vasculature, adipose tissue, and even the brain. Overactivation of MR in these tissues contributes to organ injury in conditions like heart failure and chronic kidney disease. While the kidney is the primary regulator of fluid and electrolytes via the MR, its widespread presence in other organs allows for diverse, pathological effects independent of, or alongside, its traditional role.



Safety and efficacy of steroidal mineralocorticoid receptor antagonists in patients with kidney failure requiring dialysis: a systematic review and meta-analysis of randomised controlled trials

Summary

Background Mineralocorticoid receptor antagonists can prevent cardiovascular events in patients with heart failure and non-severe chronic kidney disease, but their effects in patients with kidney failure requiring dialysis are uncertain. We aimed to assess the efficacy and safety of mineralocorticoid receptor antagonists in this patient population.

Methods In this systematic review and meta-analysis, we updated our previous systematic review by searching MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature for randomised controlled trials published between database inception and March 18, 2025. Trials comparing a mineralocorticoid receptor antagonist with placebo or standard of care in adults (aged ≥18 years) receiving maintenance dialysis were eligible. Studies that did not report an outcome of interest (cardiovascular mortality, heart failure hospitalisation, all-cause mortality, all-cause hospitalisation, hyperkalaemia, gynaecomastia or breast pain, or hypotension) were excluded. Two reviewers independently identified studies, extracted data, and assessed the risk of bias using the Cochrane risk-of-bias tool. The main outcome was cardiovascular mortality assessed using the empirical Bayes random-effects models, stratified by risk-of-bias. The protocol is registered with PROSPERO (CRD420251008119).

Findings 19 trials of steroidal mineralocorticoid receptor antagonists including 4675 participants met eligibility criteria. Effect estimates differed trials with low and high risk of bias. In four trials with a low risk of bias (n=3562), 264 cardiovascular deaths occurred in 1785 patients in the mineralocorticoid receptor antagonist group compared with 276 of 1777 patients in the control group (odds ratio 0·98 [95% CI 0·80–1·20]; I^2=0·0%; τ^2=0·0; moderate certainty) resulting in an absolute risk reduction of 1 fewer event per 1000 patients per year (95% CI 14 fewer to 11 more).

Interpretation Our findings suggest that steroidal mineralocorticoid receptor antagonists have little to no effect on cardiovascular mortality in patients requiring dialysis. There is insufficient information on the effects of steroidal mineralocorticoid receptor antagonists in subgroups of patients requiring dialysis and no information on non-steroidal mineralocorticoid receptor antagonists. Future trials would need to consider the likelihood of only smaller effects or effects limited to patients or events with pathophysiology that is more clearly driven by aldosterone in their design.

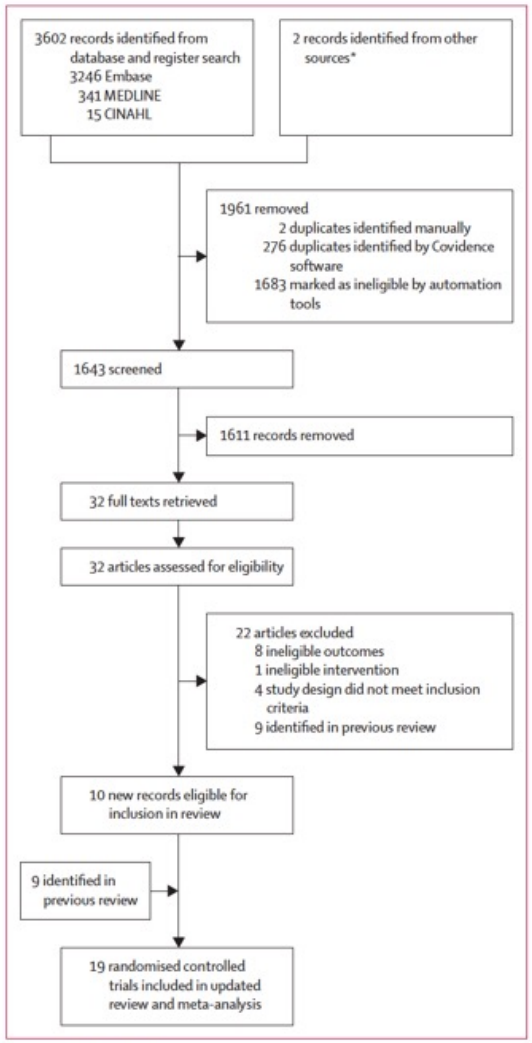


Figure 1: Study selection
CINAHL=Cumulative Index to Nursing and Allied Health Literature database.
*ALCHEMIST[14] and ACHIEVE[15] trials.

	Design	Mineralocorticoid receptor antagonist	Regimen*	Control	Patients, n	Female n (%)	Male n (%)	Age, years (mean [SD])	Heart failure n (%)	Dialysis type	Length of follow-up
Gross et al (2005)[21]	Crossover	Spironolactone	50 mg twice daily	Placebo	8	5 (62·5%)	3 (37·5%)	53 (10)	Not reported	Haemodialysis	4 weeks
Taheri et al (2009)[22]	Parallel	Spironolactone	25 mg after haemodialysis	Placebo	Intervention n=8; control n=8	Intervention 3 (37·5%); control 2 (25%)	Intervention 5 (62·5%); control 6 (75·0%)	Intervention 59·5 (6·5); control 56·8 (9·3)	Intervention 8 (100%); control 8 (100%)	Haemodialysis	6 months
Vukusich et al (2010)[23]	Parallel	Spironolactone	50 mg three times weekly after haemodialysis	Placebo	Intervention n=33; control n=33	Intervention 10 (33·3%); control 9 (39%)	Intervention 20 (66·7%); control 14 (61·0%)	Intervention 60·1 (5·2); control 55·6 (3·6)	Not reported	Haemodialysis	24 months
Taheri et al (2012)[24]	Parallel	Spironolactone	25 mg every other day	Placebo	Intervention n=9; control n=9	Intervention 4 (44·4%); control 4 (44·4%)	Intervention 5 (55·6%); control 5 (55·6%)	Intervention 50·7 (17·4); control 57·2 (13·1)	Intervention 9 (100%); control 9 (100%)	Peritoneal dialysis	6 months
Ito et al (2014)[25]	Parallel	Spironolactone or eplerenone	Spironolactone 25 mg daily or eplerenone 50 mg daily	NA	Intervention n=78; control n=80	Intervention 23 (29·5%); control 22 (27·5%)	Intervention 55 (70·5%); control 58 (72·5%)	Intervention 57·4 (12·3); control 55·6 (14·4)	Not reported	Peritoneal dialysis	24 months
Matsumoto et al (2014)[26]	Parallel	Spironolactone	25 mg daily	NA	Intervention n=157; control n=152	Intervention 44 (28%); control 62 (40·8%)	Intervention 113 (72·0%); control 90 (59·2%)	Intervention 67·4 (12·3); control 67·7 (11·2)	Not reported	Haemodialysis	36 months
Ni et al (2014)[27]	Parallel	Spironolactone	25–50 mg daily	Placebo	Intervention n=40; control n=36	Intervention 16 (40%); control 15 (41·7%)	Intervention 24 (60·0%); control 21 (58·3%)	Intervention 55·7 (12·3); control 54·9 (14·2)	Not reported	Haemodialysis and peritoneal dialysis	12 weeks
Feriman-De-Stefano et al (2015)[28]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=10; control n=9	Intervention 4 (50%); control unclear	Intervention 4 (50·0%); control unclear	Unclear reporting	Not reported	Haemodialysis	6 months
Walsh et al (2015)[29]	Parallel	Eplerenone	50 mg daily	Placebo	Intervention n=77; control n=77	Intervention 30 (39%); control 28 (36·4%)	Intervention 47 (61·0%); control 49 (63·6%)	Intervention 62·1 (14·6); control 63·1 (13·7)	Intervention 8 (10·4%) control 6 (7·8%)	Haemodialysis	13 weeks
Yongsiri et al (2015)[30]	Crossover	Spironolactone	25 mg daily	Placebo	20	12 (60%)	8 (40·0%)	52·4 (12·4)	Not reported	Peritoneal dialysis	4 weeks
Lin et al (2016)[31]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=125; control n=128	Intervention 52 (41·6%); control 48 (37·5%)	Intervention 73 (58·4%); control 80 (62·5%)	Intervention 70·3 (10·9); control 70·6 (8·4)	Intervention 0 (0·0%); control 0 (0·0%)	Haemodialysis and peritoneal dialysis	24 months
Charytan et al (2019)[32]	Parallel	Spironolactone	12·5, 25, or 50 mg daily	Placebo	Intervention n=78; control n=51	Intervention 25 (32·1%); control 19 (37·3%)	Intervention 53 (67·9%); control 32 (62·7%)	Intervention 54·6 (12·5); control 56·8 (11·5)	Intervention 13 (14·1%); control 10 (19·6%)	Haemodialysis	36 weeks

(Table 1 continues on next page)

	Design	Mineralocorticoid receptor antagonist	Regimen*	Control	Patients, n	Female n (%)	Male n (%)	Age, years (mean [SD] or median [IQR])	Heart failure n (%)	Dialysis type	Length of follow-up
(Continued from previous page)											
Gueiros et al (2019)[33]	Parallel	Spironolactone	25 mg daily	NA	Intervention n=16; control n=17	Intervention 4 (57·1%); control 4 (44·4%)	Intervention 3 (42·9%); control 5 (55·6%)	Intervention 69·7 (8·9); control 61·3 (8·6)	Not reported	Peritoneal dialysis	12 months
Hammer et al (2019)[34]	Parallel	Spironolactone	50 mg daily	Placebo	Intervention n=50; control n=47	Intervention 10 (20·0%); control 12 (25·5%)	Intervention 40 (80·0%); control 35 (74·5%)	Intervention 60·6 (13·1); control 59·9 (13·4)	Intervention 3 (6%); control 1 (2%)	Haemodialysis	40 weeks
Ziaee et al (2019)[35]	Parallel	Spironolactone	25 mg after haemodialysis	NA	Intervention n=24; control n=24	Intervention 10 (45·5%); control 8 (38·1%)	Intervention 12 (54·5%); control 13 (61·9%)	Intervention 69·2 (13·5); control 67·5 (10)	Not reported	Haemodialysis	9 months
Thanaponsatorn et al (2022)[36]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=20; control n=20	Intervention 6 (35·3%); control 6 (35·3%)	Intervention 11 (64·7%); control 11 (64·7%)	Intervention 46 (15·9); control 54·7 (11·9)	Not reported	Peritoneal dialysis	6 months
Walsh et al (2025)[15]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=1269; control n=1275	Intervention 466 (37·0%); control 465 (36·4%)	Intervention 794 (63·0%); control 810 (63·5%)	Intervention 61·5 (11); control 62·1 (11)	Intervention 155 (12·3%); control 135 (10·6%)	Haemodialysis and peritoneal dialysis	Median 1·8 years
Rossignol et al (2025)[24]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=320; control n=324	Intervention 110 (34·4%); control 90 (27·8%)	Intervention 210 (65·6%); control 234 (72·2%)	Intervention 71·1 (64·3–77·4);† control 71·5 (63·2–79·0)†	Intervention 37 (11·6%); control 37 (11·4%)	Haemodialysis	Median 32·6 months
Vongchaiudomchoke et al (2025)[37]	Crossover	Spironolactone	50 mg before haemodialysis	Placebo	49	19 (39%)	30 (61·0%)	54 (14)	Not reported	Haemodialysis	24 weeks

NA=not applicable. *Route of administration was oral for all study drugs. †Median (IQR).

Table 1: Characteristics of included trials

	All studies			Studies with a low risk of bias			Studies with a high risk of bias		
	Participants, n	OR (95% CI)	I^2	Participants, n	OR (95% CI)	I^2	Participants, n	OR (95% CI)	I^2
Cardiovascular mortality	4349	0·73 (0·46–1·16)	42·7	3562	0·98 (0·80–1·20)	2·9	787	0·33 (0·17–0·67)	0·0
Heart failure hospitalisations	3182	0·70 (0·30–1·65)	71·1	3182	0·70 (0·30–1·65)	71·1	..	..	..
All-cause mortality	4503	0·73 (0·53–1·01)	34·1	3602	0·97 (0·84–1·12)	0·0	901	0·40 (0·25–0·65)	0·0
All hospitalisations	2538	0·96 (0·87–1·06)	NA	2538	0·96 (0·87–1·06)	NA	..	..	..
Hyperkalaemia (≥6·0 mmol/L)	1104	1·07 (0·82–1·40)	0·0	927	1·06 (0·81–1·38)	0·0	177	2·54 (0·26–24·6)	0·0
Hyperkalaemia (≥6·5 mmol/L)	2918	1·50 (1·11–2·03)	0·0	2918	1·50 (1·11–2·03)	0·0	..	..	..
Gynaecomastia or breast pain	4292	3·66 (2·02–6·62)	0·0	3448	3·02 (1·57–5·81)	0·0	844	8·69 (2·17–34·8)	0·0
Hypotension	3012	1·04 (0·61–1·78)	0·0	2821	0·99 (0·54–1·83)	0·0	191	1·22 (0·39–3·78)	0·0

OR=odds ratio. NA=not applicable.

Table 2: **Pooled clinical outcomes in trials of mineralocorticoid receptor antagonists (*vs* control) in patients receiving dialysis**

Studies, n	Certainty assessment				Risk of outcome	Summary effect		
	Risk of bias	Inconsistency	Indirectness	Imprecision	Control group	Odds ratio (95% CI)	Absolute difference in number of events per 1000 patients (95% CI)	Certainty
Cardiovascular death								
5	No concerns	Not serious	Not serious	Serious	6·0%*	0·98 (0·80 to 1·20)	−1 (−14 to 11)	Moderate
Heart failure hospitalisation								
2	No concerns	Serious	Not serious	Serious	6·6%	0·70 (0·30 to 1·65)	−19 (−45 to 38)	Low
All-cause death								
6	No concerns	Not serious	Not serious	Serious	12·0%*	0·97 (0·84 to 1·21)	−3 (−17 to 22)	Moderate
All-cause hospitalisation								
1	No concerns	Not applicable	Not serious	Not serious	58·0%	0·97 (0·83 to 1·14)	−7 (−46 to 32)	Moderate
Hyperkalaemia (≥6·5 mmol/L)								
4	No concerns	Not serious	Serious	Not serious	5·0%†	1·50 (1·11 to 2·03)	23 (5 to 47)	Moderate
Gynaecomastia or breast pain								
10	Some concerns	Not serious	Not serious	Not serious	0·5%	3·66 (1·82 to 7·36)	13 (4 to 31)	Moderate
Hypotension								
5	Some concerns	Not serious	Serious	Serious	2·0%	1·04 (0·61 to 1·78)	1 (15 to −8)	Low

All included studies were randomised controlled trials. Risk of each outcome was based on the aggregate control group risk, with the exception of cardiovascular and all-cause death, which were estimated as annual risks from epidemiological data. *Estimated annual risk. †Due to heterogeneity in control event rates, an annual rate of 5·0% was assumed; however, this value should be considered uncertain.

Table 3: Summary of findings according to the Grading of Recommendations Assessment, Development and Evaluation approach, by outcome

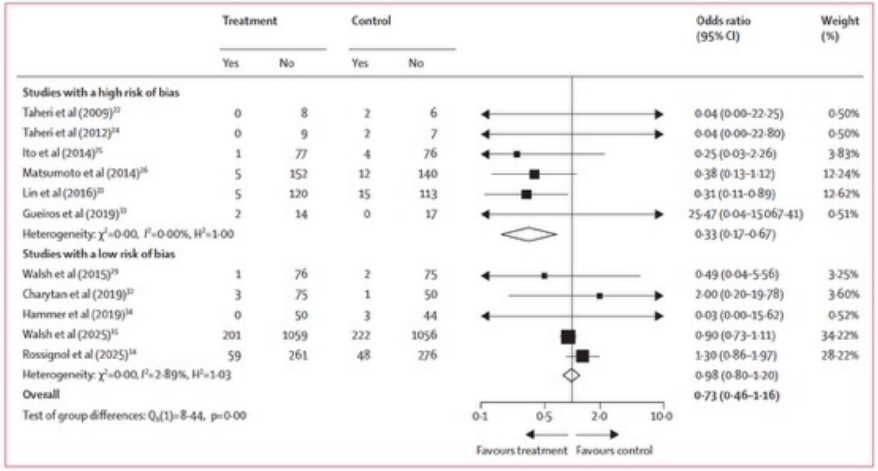


Figure 2: Effect of mineralocorticoid receptor antagonists on cardiovascular mortality in patients with kidney failure receiving maintenance dialysis
The empirical Bayes random-effects model was used. Yes=number of individuals with an event. No=number of individuals without an event.

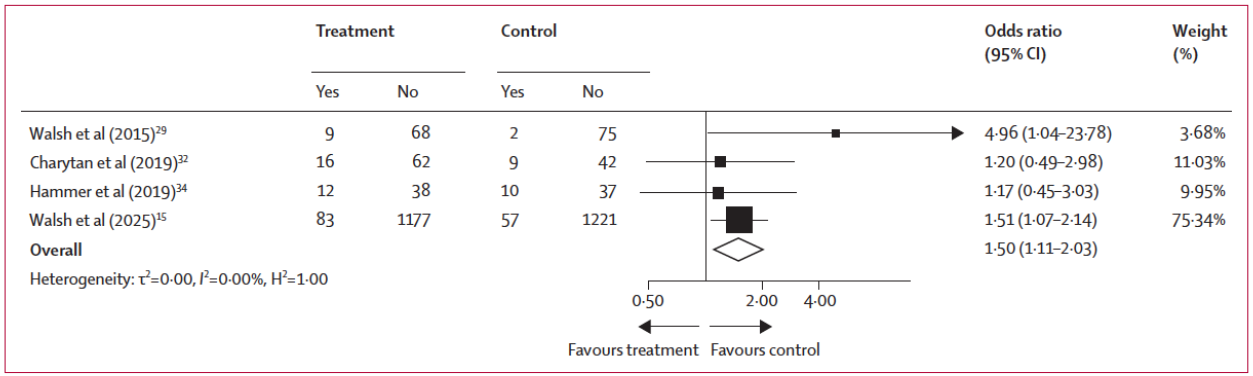


Figure 3: Effect of mineralocorticoid receptor antagonists on hyperkalaemia in patients with kidney failure receiving maintenance dialysis
The empirical Bayes random-effects model was used. Hyperkalaemia was defined as a serum potassium concentration of ≥6·5 mmol/L in patients with kidney failure receiving maintenance dialysis. Yes=number of individuals with an event. No=number of individuals without an event.

Research in context

Evidence before this study

Previous meta-analyses of randomised controlled trials suggested a large benefit of mineralocorticoid receptor antagonists, primarily spironolactone, on cardiovascular death (relative risk [RR] 0·34 [95% CI 0·15–0·75]) and all-cause death (0·40 [0·23–0·69]) and a variable increase in the risk of hyperkalaemia (3·05 [1·21–7·70]) in individuals receiving maintenance dialysis. These meta-analyses were limited by a small number of events and a reliance on trials at high risk of bias. Current guidelines recommend the use of non-steroidal mineralocorticoid receptor antagonists in patients with diabetes and chronic kidney disease at risk of progression of chronic kidney disease and steroidal mineralocorticoid receptor antagonists for those with resistant hypertension and chronic kidney disease not receiving dialysis, but no recommendations exist regarding their use in patients with kidney failure receiving dialysis.

Added value of this study

This updated meta-analysis includes ten additional randomised controlled trials, including two recently completed randomised controlled trials at low risk of bias, substantially increasing the number of patients and events to base inferences on.

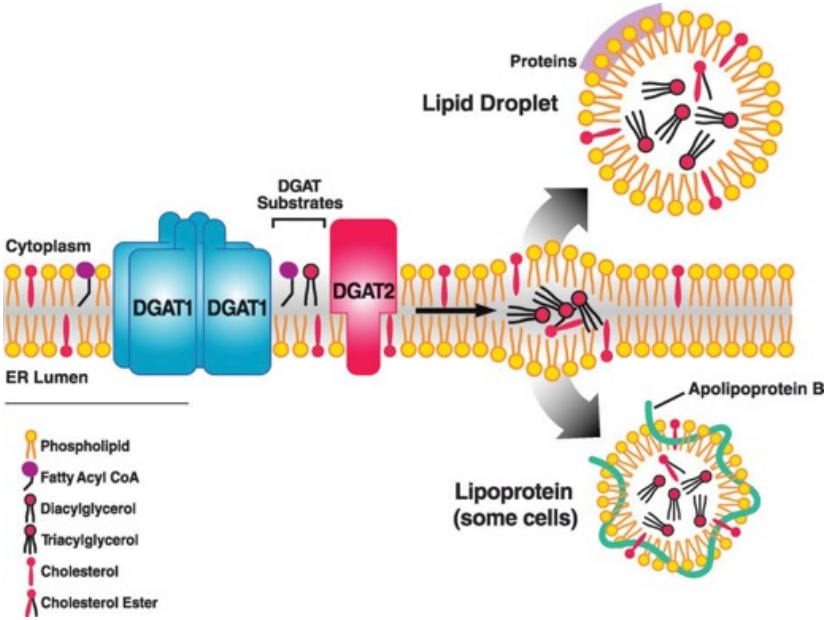
Our findings suggest that steroidal mineralocorticoid receptor antagonists, predominantly spironolactone, have little to no effect of on cardiovascular death in these patients.

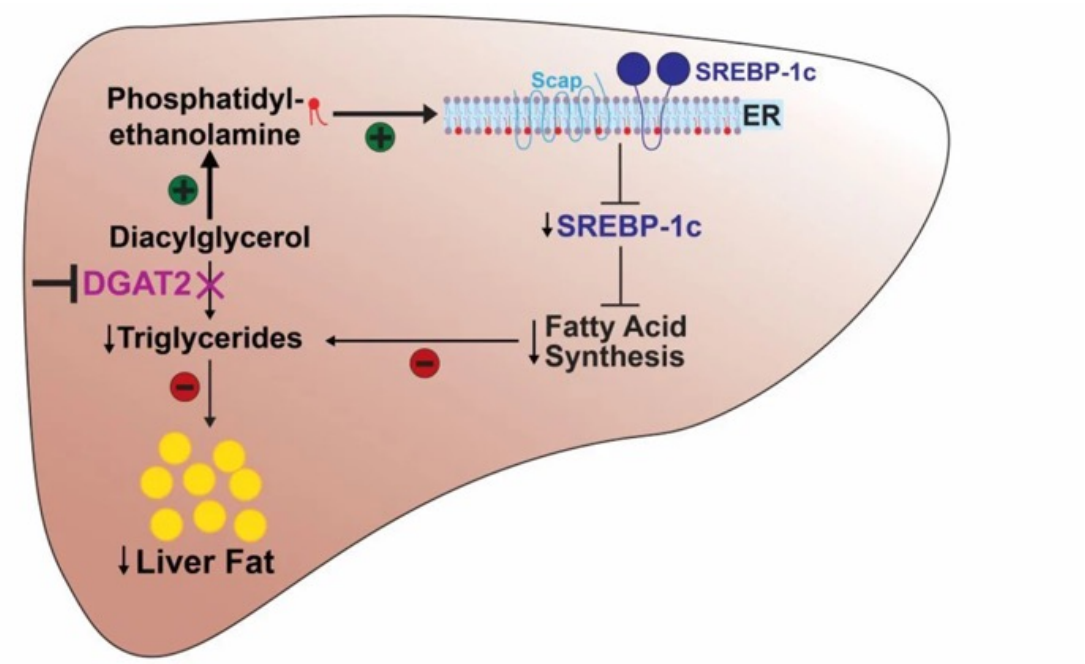
We identified an increase in the risk of hyperkalaemia (defined as a serum potassium concentration ≥6·5 mmol/L) and gynaecomastia or mastodynia, but the absolute risks of these were low in the included randomised controlled trials.

Implications of all the available evidence

The available evidence does not support the use of mineralocorticoid receptor antagonists to reduce the risk of cardiovascular death in patients with kidney failure receiving maintenance dialysis.

DGAT2 ist die Abkürzung für Diacylglycerol-O-Acyltransferase 2, ein Enzym, das eine Schlüsselrolle bei der Synthese von Triglyceriden (Speicherfett) spielt, indem es den letzten Schritt der Triglyceridbildung durchführt. Es ist wichtig für die Speicherung von Fetten in Lipidtröpfchen und hat Bedeutung für Krankheiten wie die nichtalkoholische Fettlebererkrankung (NAFLD).





Antisense oligonucleotide DGAT-2 inhibitor, ION224, for metabolic dysfunction-associated steatohepatitis (ION224-CS2): results of a 51-week, multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

Summary

Background ION224, a liver-directed antisense inhibitor of diacylglycerol O-acyltransferase 2 (DGAT2), suppresses de novo lipogenesis, an important metabolic pathway associated with lipotoxicity and the underlying inflammation, hepatocellular injury, and fibrosis in metabolic dysfunction-associated steatohepatitis (MASH). This study aimed to prospectively assess the safety and efficacy of ION224 in patients with MASH and fibrosis.

Methods ION224-CS2 was an adaptive, two-part, multicentre, randomised, double-blind, placebo-controlled, phase 2 trial conducted at 43 clinical sites in the USA and Puerto Rico in patients aged 18–75 years with biopsy-confirmed MASH and fibrosis (stages F1, F2, and F3) and baseline liver steatosis ≥10%. In part 1, participants were randomly assigned (1:1:1) to subcutaneous injections of ION224 60 mg, 90 mg, or 120 mg, or placebo, once per month. In part 2, participants were randomly assigned (2:1) to ION224 90 mg and 120 mg or placebo after a pre-specified interim analysis of safety and efficacy (liver steatosis). The primary endpoint was ≥2-point reduction in Non-Alcoholic Fatty Liver Disease Activity Score Activity Score (NAS) with ≥1-point improvement in hepatocellular ballooning or lobular inflammation, and without worsening of fibrosis at week 51. The primary analysis was in a predefined per-protocol set that included patients who received at least ten of 13 doses of the study drug without missing three consecutive doses and completed the final liver biopsy at the end of treatment. ION224-CS2 was registered at ClinicalTrials.gov (NCT04932512) and is closed.

Findings Between June 8, 2021, and Dec 27, 2022, 160 participants were randomly assigned to receive ION224 60 mg (n=23), 90 mg (n=45), or 120 mg (n=46), or placebo (n=46), of whom 123 were included in the per-protocol set. The primary endpoint was met in 18 (46%) of 39 participants in the 90-mg group (predicted risk 46·2% [95% CI 30·5–61·8]; risk difference 27·4% [95% CI 6·7–48·1], p=0·0094) and 20 (59%) of 34 in the 120-mg group (58·8% [42·3–75·4]; 40·1% [18·7– 61·4], p=0·0002) compared with six (19%) of 32 in the placebo group (predicted risk 18·7% [95% CI 5·2–32·3]). ION224 was safe and well tolerated. Adverse events were reported in 107 (94%) of participants treated with ION224 and 41 (89%) of 46 participants treated with placebo. There were no deaths and no treatment-related serious adverse events.

Interpretation This study provides the first clinical evidence that antisense-mediated inhibition of DGAT2 with ION224 could be a safe and efficacious strategy for the treatment of MASH. The observed histological improvements were independent of changes in bodyweight, suggesting potential to combine with other therapies such as GLP-1 based treatments.

Funding Ionis Pharmaceuticals.

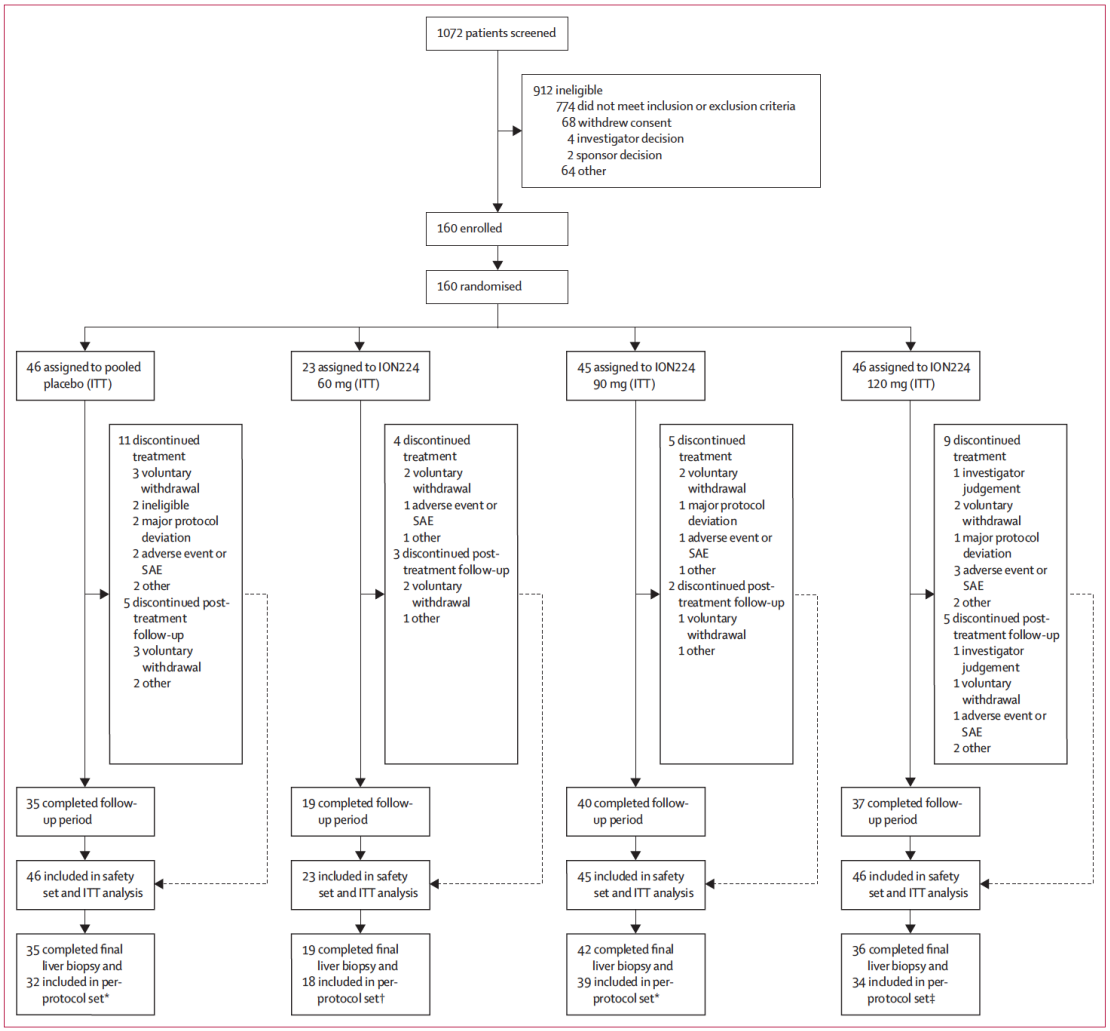


Figure 1: **Trial profile**
ITT=intention-to-treat. SAE=serious adverse event. *Three patients were excluded from the per-protocol set; two deviated from the protocol because of antidiabetic-related medications and one had a final liver biopsy ≥12 weeks from last dose. †One patient was excluded from the per-protocol set due to having a final liver biopsy ≥12 weeks from last dose. ‡Two patients were excluded from the per-protocol set; one had unevaluable liver biopsy and one had a final liver biopsy ≥12 weeks from last dose.

	Pooled placebo (n=46)	60-mg group (n=23)	90-mg group (n=45)	120-mg group (n=46)
Age, years				
Mean (SD)	54 (12)	53 (10)	54 (13)	52 (10)
Median (IQR)	56 (46–63)	53 (48–62)	58 (46–64)	54 (45–59)
Sex				
Female	36 (78%)	18 (78%)	28 (62%)	32 (70%)
Male	10 (22%)	5 (22%)	17 (38%)	14 (30%)
Ethnicity				
Hispanic or Latino	14 (30%)	10 (43%)	26 (58%)	20 (43%)
Not Hispanic or Latino	32 (70%)	13 (57%)	19 (42%)	26 (57%)
Race				
White	42 (91%)	21 (91%)	39 (87%)	43 (93%)
Black	1 (2%)	1 (4%)	1 (2%)	2 (4%)
Asian	1 (2%)	1 (4%)	2 (4%)	1 (2%)
American Indian or Alaskan Native	0	0	1 (2%)	0
Other	2 (4%)	0	2 (4%)	0
Bodyweight, kg				
Mean (SD)	106·1 (23·6)	104·9 (18·3)	99·3 (20·8)	106·0 (21·5)
Median (IQR)	100·5 (88·5–115·1)	104·0 (94·9–115·2)	96·5 (84·5–113·5)	102·3 (90·2–123·3)
BMI, kg/m²				
Mean (SD)	39·1 (8·2)	37·9 (5·8)	36·6 (6·7)	37·7 (6·7)
Median (IQR)	37·2 (33·1–43·6)	37·7 (33·4–43·3)	34·7 (31·1–41·5)	38·2 (33·7–41·1)
Healthy (18·5–24·9 kg/m²)	0	1 (4%)	0	0
Overweight (25–29·9 kg/m²)	2 (4%)	1 (4%)	8 (18%)	6 (13%)
Obese (≥30 kg/m²)	44 (96%)	21 (91%)	37 (82%)	40 (87%)
Liver fat content*	21·9% (7·6)	21·6% (7·7)	23·5% (7·9)	22·3% (6·8)
NAS: eligibility screening read†	6 (3–7)	5 (4–7)	5 (4–7)	6 (4–8)
Liver fibrosis stage: eligibility screening read‡				
F1	3 (7%)	1 (4%)	3 (7%)	3 (7%)
F2	17 (37%)	11 (48%)	20 (44%)	17 (37%)
F3	26 (57%)	11 (48%)	22 (49%)	26 (57%)
Alanine aminotransferase, U/L	58 (34)	57 (34)	58 (42)	59 (32)
>1·5 × ULN	11 (24%)	6 (26%)	9 (20%)	9 (20%)
Aspartate aminotransferase, U/L	43 (25)	43 (34)	37 (22)	40 (17)
>1·5 × ULN	7 (15%)	3 (13%)	5 (11%)	5 (11%)
Bilirubin, mg/dL	0·48 (0·14)	0·47 (0·13)	0·53 (0·25)	0·54 (0·23)
Gamma glutamyl transferase, U/L	69 (60)	53 (40)	59 (66)	63 (53)
Total cholesterol, mg/dL	192·7 (45·7)	175·8 (45·6)	176·8 (41·8)	185·2 (40·1)
LDL cholesterol, mg/dL	108·9 (39·2)	98·7 (41·9)	101·1 (40·3)	103·7 (35·1)
HDL cholesterol, mg/dL	45·3 (10·2)	41·7 (14·1)	45·0 (12·2)	44·6 (10·1)
Triglycerides, mg/dL	200·4 (104·5)	177·5 (64·6)	152·9 (60·1)	183·8 (72·2)
Liver stiffness, kPa§	13·7 (8·61)	12·6 (6·1)	11·3 (4·0)	12·3 (5·4)
Enhanced Liver Fibrosis test score¶	9·7 (0·9)	9·7 (0·9)	9·7 (0·7)	9·8 (0·9)

(Table 1 continues on next page)

	Pooled placebo (n=46)	60-mg group (n=23)	90-mg group (n=45)	120-mg group (n=46)
(Continued from previous page)				
HbA_{1c}	6·5% (1·0)	6·3% (0·8)	6·6% (1·4)	6·9% (1·3)
≤5·6%	10 (22%)	5 (22%)	8 (18%)	8 (17%)
5·7–6·4%	15 (33%)	9 (39%)	20 (44%)	13 (28%)
≥6·5%	21 (46%)	9 (39%)	17 (38%)	25 (54%)
Type 2 diabetes	26 (57%)	11 (48%)	19 (42%)	25 (54%)
Hypertension	30 (65%)	14 (61%)	26 (58%)	26 (57%)
Dyslipidaemia	36 (78%)	13 (57%)	27 (60%)	26 (57%)
Baseline statin use	18 (39%)	6 (26%)	18 (40%)	13 (28%)
Baseline GLP-1 receptor agonist use	8 (17%)	2 (9%)	5 (11%)	7 (15%)
Baseline SGLT-2 inhibitor use	1 (2%)	3 (13%)	3 (7%)	2 (4%)

Data are n (%), mean (SD), or median (IQR), unless otherwise specified. Percentages might not total 100 because of rounding. HbA_{1c}=glycated haemoglobin. NAS=Non-Alcoholic Fatty Liver Disease Activity Score. ULN=upper limit of normal. *Liver fat content was measured using MRI-derived proton density fat fraction. †NAS is the unweighted sum of scores for steatosis (scale 0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2) and ranges from 0 to 8 on the basis of the non-alcoholic steatohepatitis (NASH) Clinical Research Network scoring system. Higher scores indicate more severe disease. Data are median (range). ‡The fibrosis stages according to the NASH Clinical Research Network are as follows: F0, no fibrosis; F1, mild (perisinusoidal or periportal) fibrosis; F2, moderate (perisinusoidal and portal or periportal) fibrosis; F3 severe (bridging) fibrosis; and F4, cirrhosis.[26] §Liver stiffness was assessed by means of vibration-controlled transient elastography (FibroScan). Higher values indicate more severe fibrosis. Advanced fibrosis is considered unlikely if the value is below 8 kPa and likely if the value is 12 kPa or higher. ¶The Enhanced Liver Fibrosis test consists of a panel of three serum biomarkers associated with matrix turnover: hyaluronic acid, tissue inhibitor of metalloproteinase 1, and procollagen type III N-terminal peptide. Advanced fibrosis is considered unlikely if the value is below 7·7 and likely if the value is 9·8 or higher. A score of 9·8 or higher indicates an increased risk of progression to cirrhosis and liver-related clinical events.

Table 1: **Baseline demographic and clinical characteristics**

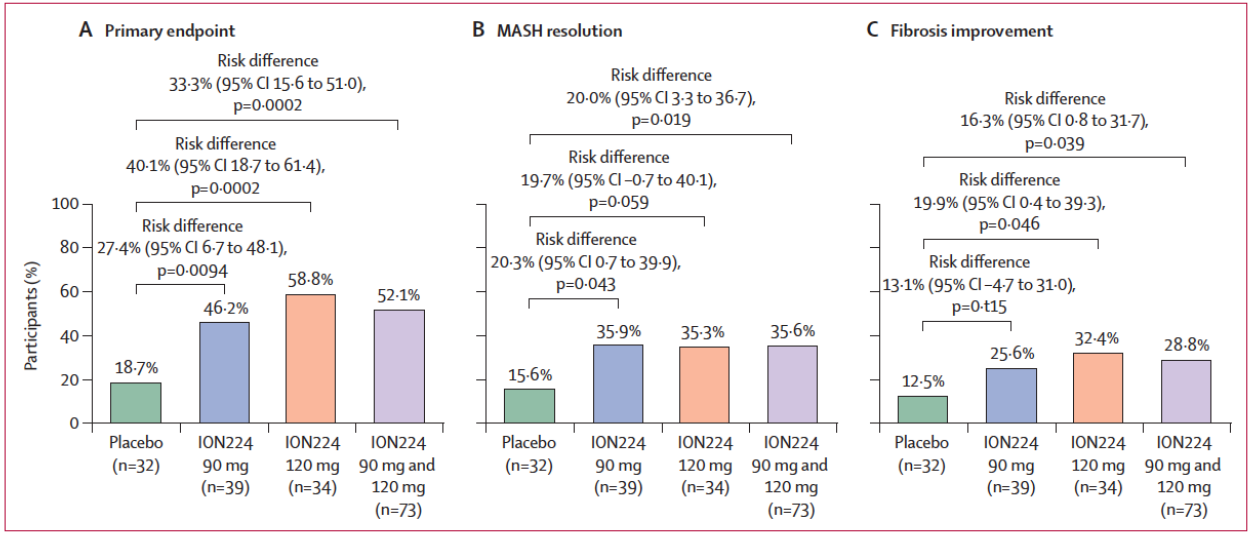


Figure 2: **Primary and key secondary biopsy endpoints in the pre-specified per-protocol set**
(A) The proportion of participants with at least a 2-point reduction in NAS, at least a 1-point improvement in hepatocellular ballooning or lobular inflammation, and without worsening in fibrosis stage at week 51 (primary endpoint). (B) Proportion of participants with MASH resolution without worsening fibrosis at week 51. MASH resolution was defined as a score of 0–1 for lobular inflammation and a score of 0 for hepatocellular ballooning. (C) Proportion of participants with fibrosis improvement (ie, reduction of ≥1 stage in fibrosis) without worsening steatohepatitis by Non-Alcoholic Fatty Liver Disease Activity Score Activity score at week 51. Predicted risks, risk differences, 95% CIs, and p values for the risk differences in percentage between each ION224 group and pooled placebo group were estimated using a binomial regression model with an identity link. The proportions displayed in the bar plot represent the predicted rates. MASH=metabolic dysfunction associated steatohepatitis. NAS=Non-Alcoholic Fatty Liver Disease Activity Score Activity Score.

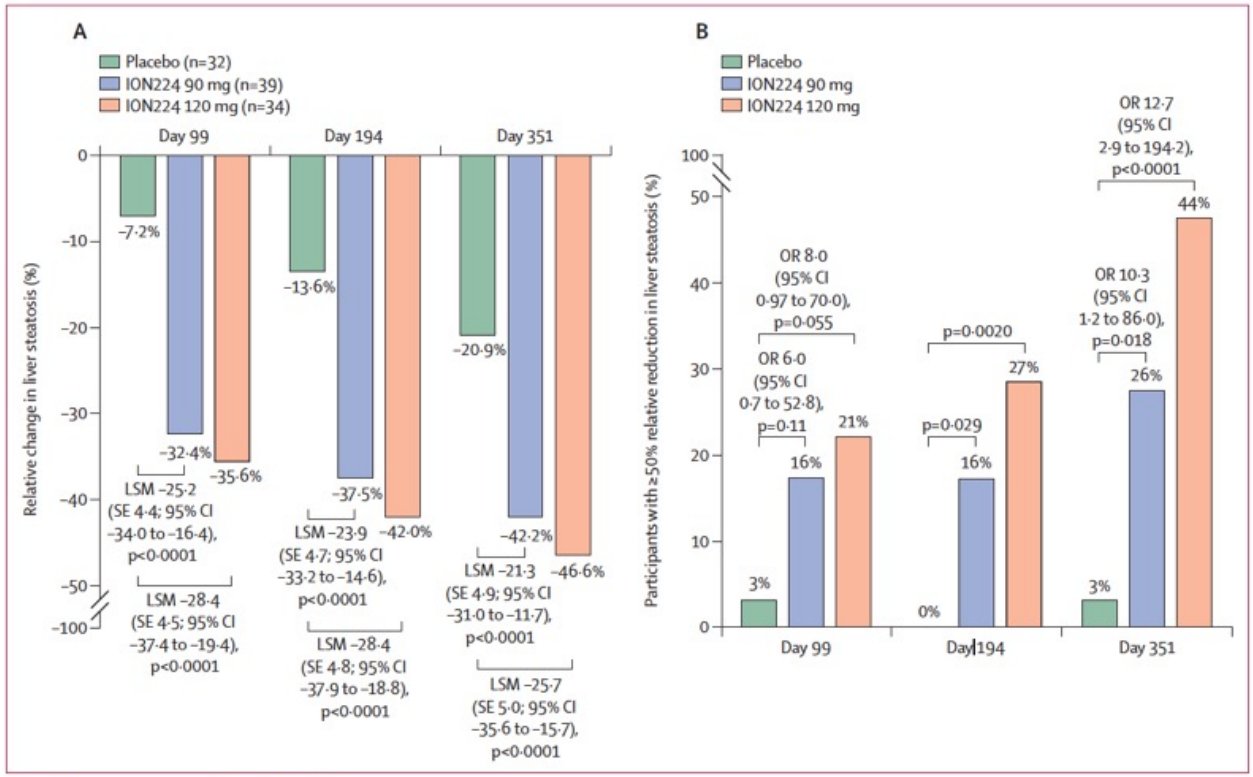


Figure 3: **Liver steatosis evaluated by MRI-PDFF over time**

(A) The key secondary endpoint of relative reduction in liver steatosis from baseline over time as evaluated by MRI-PDFF. Baseline was defined as the last non-missing measurement taken before the first administration of study drug. p values were obtained using the mixed-effect model with repeated measures. (B) Post-hoc analysis of the proportion of participants with ≥50% relative reduction in liver steatosis from baseline. p values were determined using the Chi square test or Fisher's exact test if the expected cell counts were less than 5 in either group. The denominator for percentage calculation is the number of participants in each treatment group with non-missing MRI-PDFF results (31 in the placebo group; 39 in the 90-mg group, 34 in the 120-mg group). For Day 194, the odds ratio and 95% CIs could not be estimated because the number of participants with ≥50% relative reduction in liver steatosis was 0 in the placebo group. Data are from the prespecified per-protocol set. LSM=least squares mean. MRI-PDFF=MRI-derived proton density fat fraction. OR=odds ratio.

	Placebo (n=46)		60-mg group (n=23)		90-mg group (n=45)		120-mg group (n=46)		Overall (n=160)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any adverse event	41 (89%)	249	21 (91%)	103	43 (96%)	270	43 (93%)	261	148 (93%)	883
Mild	13 (28%)	159	6 (26%)	58	16 (36%)	174	12 (26%)	172	47 (29%)	563
Moderate	24 (52%)	85	14 (61%)	44	26 (58%)	94	28 (61%)	86	92 (58%)	309
Severe	4 (9%)	5	1 (4%)	1	1 (2%)	2	3 (7%)	3	9 (6%)	11
Any serious adverse event*	4 (9%)	4	2 (9%)	2	1 (2%)	3	4 (9%)	4	11 (7%)	13
Adverse events leading to discontinuation	2 (4%)	2	1 (4%)	1	1 (2%)	1	3 (7%)	5	7 (4%)	9
≥1 TEAE with an incidence rate >5%	31 (67%)	104	18 (78%)	36	35 (78%)	110	37 (80%)	118	121 (76%)	368
COVID-19	8 (17%)	10	7 (30%)	7	12 (27%)	12	11 (24%)	11	38 (24%)	40
Urinary tract infection	8 (17%)	16	2 (9%)	4	8 (18%)	11	11 (24%)	17	29 (18%)	48
Upper respiratory tract infection	2 (4%)	2	3 (13%)	3	5 (11%)	5	10 (22%)	12	20 (13%)	22
Sinusitis	5 (11%)	10	1 (4%)	1	6 (13%)	6	5 (11%)	5	17 (11%)	22
Influenza	3 (7%)	3	1 (4%)	1	3 (7%)	3	2 (4%)	2	9 (6%)	9
Nausea	9 (20%)	10	2 (9%)	2	6 (13%)	9	8 (17%)	8	25 (16%)	29
Abdominal pain upper	2 (4%)	3	2 (9%)	2	4 (9%)	12	3 (7%)	3	11 (7%)	20
Diarrhoea	9 (20%)	10	2 (9%)	2	5 (11%)	7	2 (4%)	2	18 (11%)	21
Vomiting	4 (9%)	4	0	0	5 (11%)	6	1 (2%)	2	10 (6%)	12
Arthralgia	2 (4%)	4	2 (9%)	2	3 (7%)	3	9 (20%)	10	16 (10%)	19
Back pain	4 (9%)	4	2 (9%)	2	7 (16%)	7	5 (11%)	5	18 (11%)	18
Injection site erythema	0	0	1 (4%)	3	1 (2%)	1	7 (15%)	13	9 (6%)	17
Injection site pain	2 (4%)	3	1 (4%)	1	2 (4%)	4	5 (11%)	7	10 (6%)	15
Headache	5 (11%)	5	3 (13%)	3	5 (11%)	7	4 (9%)	4	17 (11%)	19
Procedural pain	3 (7%)	4	2 (9%)	2	6 (13%)	6	2 (4%)	2	13 (8%)	14
Hypertension	3 (7%)	3	1 (4%)	1	5 (11%)	5	4 (9%)	4	13 (8%)	13
Diabetes	2 (4%)	2	0	0	2 (4%)	3	5 (11%)	5	9 (6%)	10

TEAE=treatment-emergent adverse event. *No serious adverse events were deemed by the investigator to be drug-related and there was no trend in the type of serious adverse event.

Table 2: **Treatment-emergent adverse events in the safety set**

Research in context

Evidence before this study

Metabolic dysfunction-associated steatohepatitis (MASH), the severe form of metabolic dysfunction-associated steatotic liver disease, is a growing global health concern, affecting an estimated 5% of the global population. The condition is characterised by excess accumulation of liver fat, hepatic inflammation, cellular injury, and fibrosis, which can progress to cirrhosis and liver-related mortality. Despite ongoing efforts to develop pharmacological treatments, only one drug, resmetirom, has received approval from the US Food and Drug Administration.

One potential therapeutic approach is to inhibit de novo lipogenesis, thereby reducing the progression of inflammation and fibrosis in MASH. Diacylglycerol O-acyltransferase 2 (DGAT2) is a rate-limiting enzyme in triglyceride synthesis. We previously demonstrated antisense-mediated DGAT2 inhibition as a potential therapeutic approach in a 13-week study in patients with type 2 diabetes and liver steatosis, in whom treatment with an unconjugated DGAT2 antisense oligonucleotide significantly (clinically and statistically) reduced hepatic steatosis. These findings provided a strong rationale for further investigation of DGAT2 inhibition as a targeted therapy for MASH and fibrosis.

We searched PubMed from database inception to April 21, 2025, for articles published in English on DGAT2 inhibition in MASH. We used the following search terms without any further restrictions: ("DGAT2 inhibition" [All Fields] AND "NASH" [All Fields] OR "DGAT2 inhibition" [All Fields] AND "MASH" [All Fields]). The search yielded 38 articles. No biopsy-anchored randomised trials were found.

Added value of this study

This multicentre, randomised, placebo-controlled trial evaluated ION224, a ligand-conjugated antisense oligonucleotide inhibitor of DGAT2, in patients with biopsy-confirmed MASH and liver fibrosis. Subcutaneous ION224 once per month for 1 year resulted in significant histological improvements, including resolution of MASH and improved fibrosis, and the effects were maintained in participants with advanced fibrosis (stage F3). ION224 was well tolerated, with no treatment-related serious adverse events or adverse effects on lipid profiles, including no hypertriglyceridemia—an issue observed with other investigational therapies targeting de novo lipogenesis. These findings support DGAT2 inhibition via a liver-directed antisense oligonucleotide as a promising therapeutic strategy for MASH.

Implications of all the available evidence

This study provides the first clinical evidence that antisense-mediated inhibition of DGAT2 leads to MASH resolution and fibrosis improvement without worsening of hepatic function or hyperlipidaemia and without any changes in bodyweight. These results validate liver-targeted DGAT2 inhibition as a potential new treatment approach for MASH and support further clinical development of ION224 for MASH as single-agent and combination therapy.

Community mental health care is a system for promoting mental well-being, preventing mental illness, and supporting people with mental health conditions within their local communities, rather than in traditional psychiatric hospitals. It utilizes a network of services, often including multidisciplinary teams like Community Mental Health Teams (CMHTs), to provide accessible, recovery-oriented, and evidence-based care, such as medication management, therapy, case management, and crisis intervention.

Building community capacity in mental health care with the Strong Minds–Strong Communities programme: a randomised controlled trial in the USA

Summary

Background Provider shortages and lack of culturally responsive care limit mental health services in reaching multicultural populations worldwide. We examined the effectiveness of a psychoeducational intervention aimed at building community capacity to address depression and anxiety among racial, ethnic, and linguistic minoritised adults.

Methods Strong Minds–Strong Communities (SM–SC) was a 6-month, multicentre, longitudinal, randomised trial done in 37 community-based organisations and clinics in two US sites (Massachusetts and North Carolina). Adults aged 18 years and older speaking English, Spanish, Mandarin, or Cantonese, with moderate to severe depression or anxiety symptoms assessed using the Computerized Adaptive Test for Mental Health (CAT-MH), were eligible for inclusion. Participants were randomly assigned (1:1) to a psychoeducational intervention provided by community health workers or a usual care condition, which constituted receiving a US National Institutes of Health booklet about anxiety and depression. Both conditions included referrals for social determinants of health needs. Randomisation was stratified by site using computer-generated blocks of size 2. Investigators and participants were not masked to treatment allocation, but outcome assessors were. Primary outcomes were changes from baseline at months 6 and 12 in self-reported depression and anxiety symptoms using the Hopkins Symptom Checklist-25 (HSCL-25), level of functioning using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2·0), and perceived quality of care using the Global Evaluation of Care domain of the Perceptions of Care Outpatient Survey (PoC-OP) in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT04092777, and has been completed.

Findings From Sept 4, 2019, to March 3, 2023, 5265 potential participants were approached for study inclusion. 2681 were excluded and 2584 were assessed for eligibility. A further 1417 were excluded, and 1167 were deemed eligible for study inclusion. 1044 participants were randomly assigned, 524 to the SM–SC intervention and 520 to the usual care group. The mean age of participants was 42·6 years (SD 13·3) and 875 (83·8%) were female, 165 (15·8%) were male, and four (0·4%) were other. Between baseline and 6 months, intervention participants reported greater improvements in depression and anxiety symptoms (standardised effect size, 0·39 [95% CI 0·27–0·52]), functioning (standardised effect size, 0·28 [0·16–0·39]), and perceived quality of care (standardised effect size, 0·47 [0·31–0·62]). These greater improvements in depression and anxiety symptoms, functioning, and perceived quality of care attenuated but remained significant 6 months post-intervention (standardised effect sizes of 0·28 [95% CI 0·16–0·40] for depression and anxiety, 0·21 [0·08–0·33]) for functioning, and 0·33 [0·16 –0·50] for perceived quality of care).

Interpretation The intervention shows that a culturally adapted intervention can improve depression and anxiety symptoms in Black, Latino, and Asian populations and provides an alternative to mental health care shortages by building community capacity.

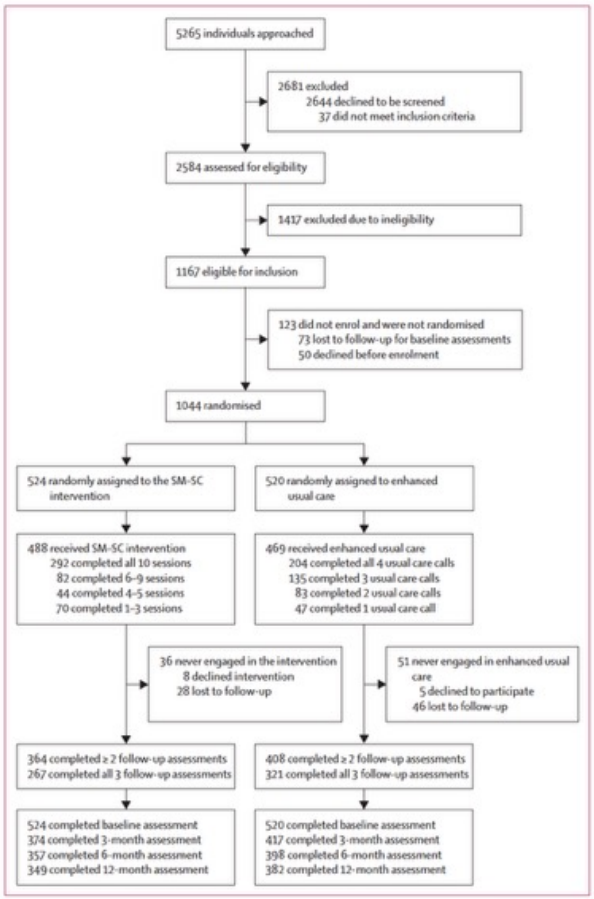


Figure 1: **Trial profile**
SM-SC=Strong Minds-Strong Communities.

	Total sample (n=1044)	Control group (n=520)	SM–SC intervention group (n=524)
Survey language			
English	371 (35·5%)	197 (37·9%)	174 (33·2%)
Spanish	559 (53·5%)	269 (51·7%)	290 (55·3%)
Mandarin	72 (6·9%)	32 (6·2%)	40 (7·6%)
Cantonese	42 (4·0%)	22 (4·2%)	20 (3·8%)
Study location			
North Carolina	522 (50·0%)	261 (50·2%)	261 (49·8%)
Massachusetts	522 (50·0%)	259 (49·8%)	263 (50·2%)
Age, years	42·6 (13·3)	42·8 (13·4)	42·4 (13·2)
Gender			
Male	165 (15·8%)	88 (16·9%)	77 (14·7%)
Female	875 (83·8%)	429 (82·5%)	446 (85·1%)
Other	4 (0·4%)	3 (0·6%)	1 (0·2%)
Race and ethnicity			
Non-Latino White	92 (8·8%)	46 (8·8%)	46 (8·8%)
Non-Latino Black	149 (14·3%)	80 (15·4%)	69 (13·2%)
American Indian	3 (0·3%)	1 (0·2%)	2 (0·4%)
Non-Latino Asian	137 (13·1%)	68 (13·1%)	69 (13·2%)
Latino	654 (62·6%)	322 (61·9%)	332 (63·4%)
Mixed	7 (0·7%)	3 (0·6%)	4 (0·8%)
Other	2 (0·2%)	0	2 (0·4%)
Birthplace			
Born outside of the USA	704 (67·4%)	341 (65·6%)	363 (69·3%)
Born in the USA	340 (32·6%)	179 (34·4%)	161 (30·7%)
Education			
Less than high school	401 (38·4%)	194 (37·3%)	207 (39·5%)
High school and above	640 (61·3%)	326 (62·7%)	314 (59·9%)
Missing	3 (0·3%)	0	3 (0·6%)

(Table continues on next column)

	Total sample (n=1044)	Control group (n=520)	SM–SC intervention group (n=524)
(Continued from previous column)			
Marital status			
Married or cohabitating	565 (54·1%)	280 (53·8%)	285 (54·4%)
Widowed, divorced, or separated	219 (21·0%)	109 (21·0%)	110 (21·0%)
Never married	257 (24·6%)	130 (25·0%)	127 (24·2%)
Missing	3 (0·3%)	1 (0·2%)	2 (0·4%)
Insurance status			
Uninsured	354 (33·9%)	167 (32·1%)	187 (35·7%)
Insured	683 (65·4%)	349 (67·1%)	334 (63·7%)
Missing	7 (0·7%)	4 (0·8%)	3 (0·6%)
Primary outcomes			
Psychological distress, (HSCL-25)	2·1 (0·5)	2·1 (0·5)	2·1 (0·5)
Functioning (WHODAS 2.0)	23·5 (8·8)	23·3 (8·6)	23·8 (8·9)
Perceptions of Care (PoC-OP)	NA	NA	NA
Secondary outcomes			
CAT-MH-Depression	57·3 (12·6)	56·8 (12·5)	57·9 (12·8)
CAT-MH-Anxiety	51·8 (17·7)	51·2 (17·9)	52·3 (17·5)

Data are n (%) or mean SD. SM–SC=Strong Minds–Strong Communities. HSCL-25=Hopkins Symptom Checklist-25. WHODAS 2.0=World Health Organization Disability Assessment Schedule 2.0. PoC-OP=Global Evaluation of Care domain of the Perceptions of Care Outpatient Survey. CAT-MH=Computerized Adaptive Test for Mental Health. NA=not available at baseline.

Table: **Baseline characteristics**

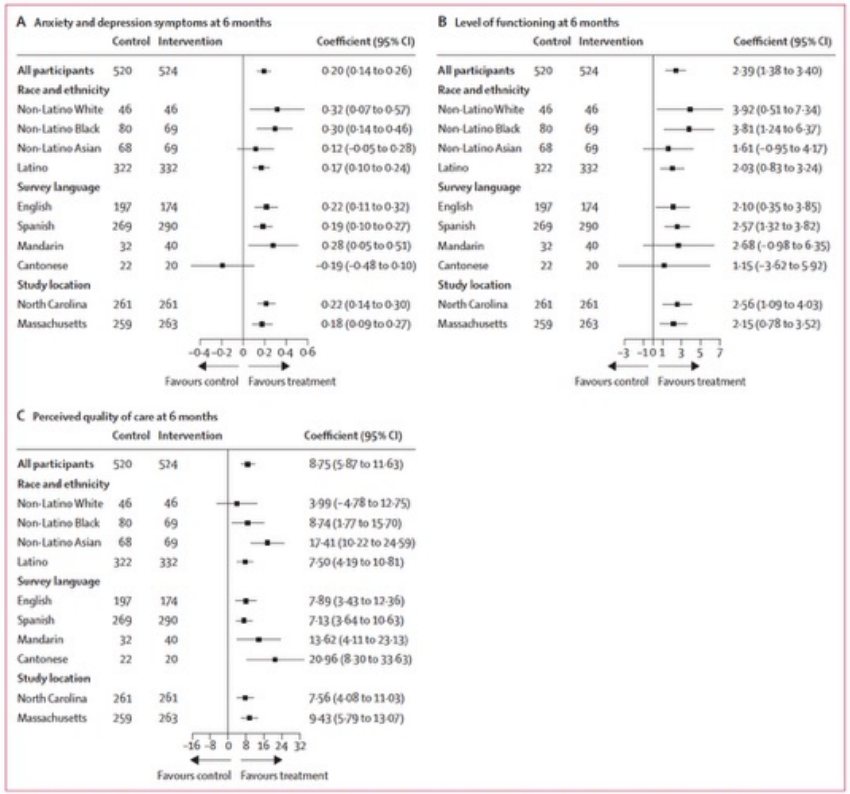


Figure 2: **Depression and anxiety symptoms (A), level of functioning (B), and perceived quality of care (C) at the 6-month primary endpoint**
Data are presented for both treatment groups and for prespecified subgroup analyses.

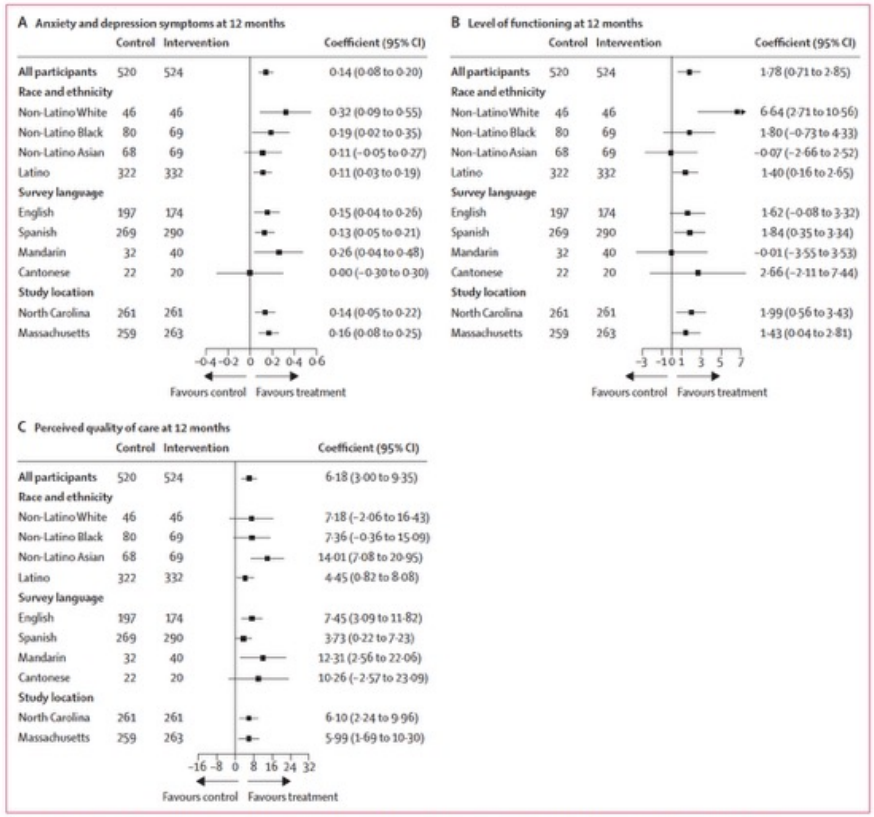


Figure 3: **Depression and anxiety symptoms (A), level of functioning (B), and perceived quality of care (C) at the 12-month primary endpoint**
Data are presented for both treatment groups and for prespecified subgroup analyses.

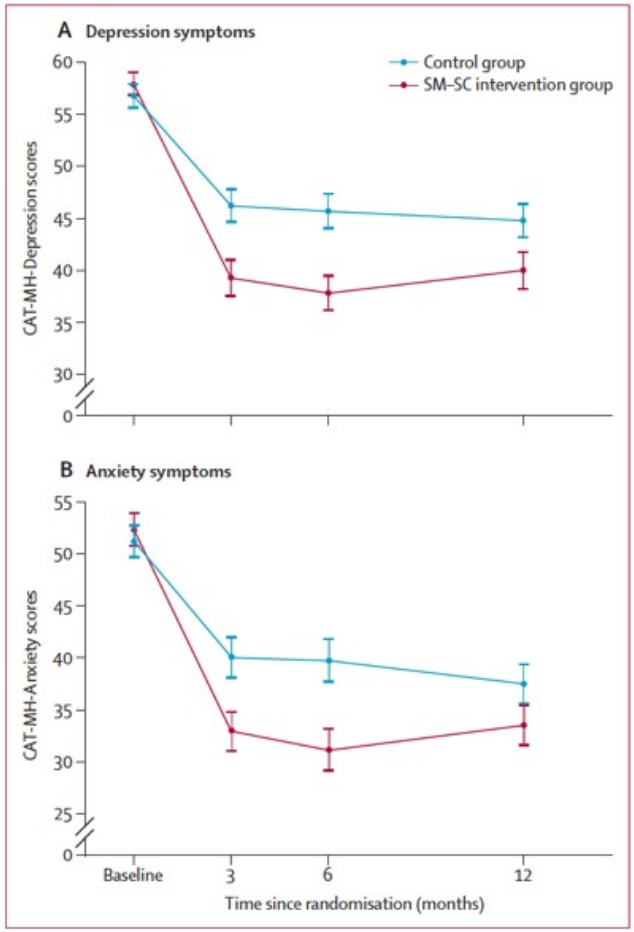


Figure 4: **Depression and anxiety symptom CAT-MH scores up to 12 months**
CAT-MH=Computerized Adaptive Test for Mental Health. SM–SC=Strong Minds–Strong Communities.

Research in context

Evidence before this study

Substantial disparities in mental health care exist for racial, ethnic, and linguistic minoritised populations, who are less likely to start and remain in treatment and receive quality care. There is considerable empirical support for brief, manualised, and scalable skill-based interventions delivered by licensed clinicians or experts to reduce symptoms of depression or anxiety in adults. However, few providers that can offer culturally and linguistically responsive evidence-based mental health care, and a shortage of trained providers can exacerbate mental health service disparities for diverse communities. Community health workers with expertise in engaging with diverse communities and who might themselves have community connections have been successful in increasing mental health access for minoritised populations.

We systematically searched PsychInfo and Web of Science for evidence of brief, scalable, or community health worker-led mental health interventions using the terms (("psychosocial intervention") OR ("mental health intervention")) AND ("community health worker") OR ("brief") OR ("scalable") without date or country restrictions. Only articles published in English were included. We found evidence for multiple brief community health worker-led mental health interventions for racial and ethnic minoritised groups, older adults, and individuals with disabilities. One was a problem-solving mental health intervention for low-income adolescents in India. Another was a combined behavioural activation and social learning intervention for older Latinx adults with anxiety and depression. A final example was a parenting and nutrition intervention that also had secondary effects on maternal depressive symptoms in Tanzania. Most of these studies only utilised participants from one specific racial or ethnic minoritised group. We could not find any randomised controlled trials that were administered in more than two languages or that utilised social determinants of health referrals as a control condition. We also did not find any randomised controlled trials that assessed whether mental health outcomes could vary as a function of the participant's language, race, or ethnicity.

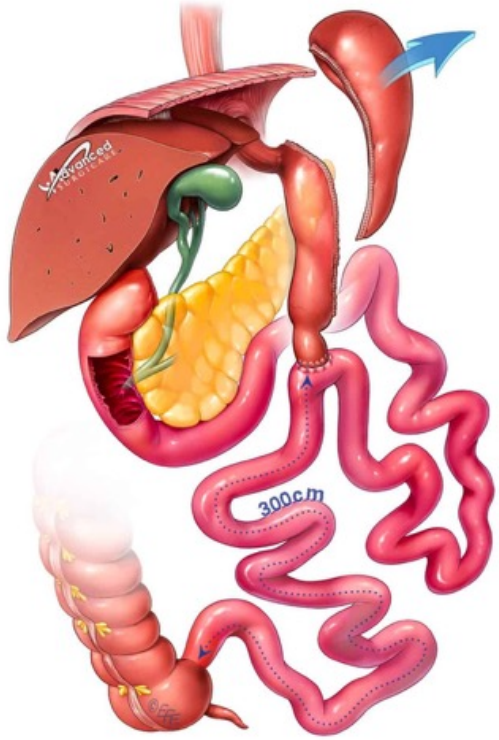
Added value of this study

This study adds to growing the evidence base as an intervention that is culturally responsive, linguistically appropriate, and delivered by community health workers with clinical supervision. We evaluated the intervention's effectiveness in varied practices with different populations in diverse languages. Our study enabled the community engagement and organisational readiness necessary to build capacity to tackle mental health worker shortages. As such, the intervention provides an alternative for reducing mental health symptoms and improving functioning for minoritised populations. Our study builds off previous interventions designed to reduce mental health disparities of minoritised older adults. This study demonstrates the effectiveness of a new, standardised community health worker-led mental health intervention, delivered in English, Spanish, Mandarin, and Cantonese for racial, ethnic, and linguistic minoritised populations. Participants in both treatment and control conditions received referrals to address social determinants of health needs, and thus the culturally adapted, linguistically appropriate intervention was compared with a meaningful usual care condition. We found that participants assigned to the intervention reported a significant reduction in depression and anxiety symptoms and greater improvements in the level of functioning and perceived quality of care when compared with those assigned to usual care with social determinants of health referrals.

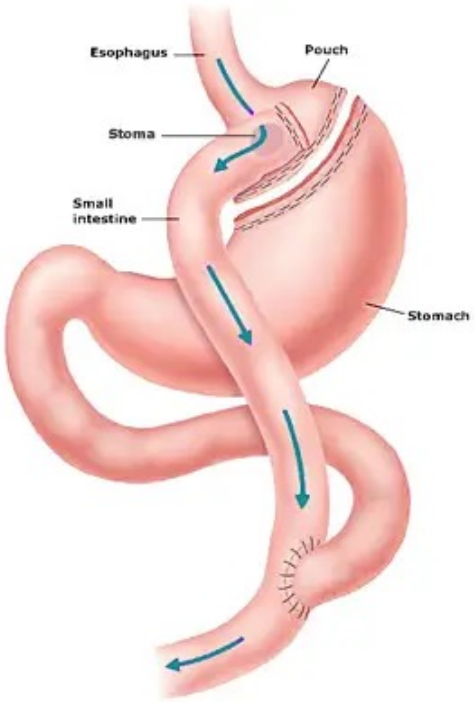
Implications of all the available evidence

The Strong Minds–Strong Communities intervention demonstrates significant potential in mitigating racial and ethnic disparities in mental health care through the role of community experts to fill gaps in mental health services. Although racial and ethnic disparities in mental health stem from multiple factors (both at the individual and structural level), a lack of language-matched mental health services can perpetuate disparities. Multiple studies have suggested that not being able to deliver services in the dominant language of the client can decrease the quality of mental health services and discourage racial and ethnic minoritised populations from initiating and engaging in treatment. Our findings support the inclusion of community health worker-led, linguistically appropriate interventions in mental health care. Future research should examine how investment in this model can address a range of practice and health-care system challenges.

SADI-S steht für Single Anastomosis Duodeno-Ileal Bypass with Sleeve Gastrectomy. Es ist eine bariatrische Operation, die sowohl eine Schlauchmagenbildung (Sleeve Gastrectomy) als auch eine Bypass-Anlage (Duodeno-Ileal Bypass) kombiniert, um Gewichtsverlust und die Verbesserung von Stoffwechselerkrankungen wie Typ-2-Diabetes zu erreichen.



Der Roux-Y-Magenbypass, kurz RYGB, stellt nach der Schlauchgastrektomie das zweithäufigste Verfahren der bariatrischen Chirurgie in Deutschland dar. Es wird sowohl als restriktives als auch malabsorptives Verfahren eingestuft.



Efficacy and safety of single-anastomosis duodeno-ileal bypass with sleeve gastrectomy versus Roux-en-Y gastric bypass in France (SADISLEEVE): results of a randomised, open-label, superiority trial at 2 years of follow-up

Summary

Background Since 2007, single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) has been proposed as an alternative to Roux-en-Y gastric bypass (RYGB) in the treatment of obesity. We conducted a multicentre randomised trial, with the hypothesis that SADI-S could be more effective than RYGB at 2-year follow-up.

Methods This multicentre, open-label, individually randomised superiority trial was conducted in France; patients were recruited from 22 bariatric institutions, mostly public academic hospitals. Key inclusion criteria were patients with a BMI ≥40 kg/m² or ≥35 kg/m² with obesity-related comorbidities (type 2 diabetes, hypertension, dyslipidaemia, sleep apnoea, or osteoarthrosis), and a candidate for SADI-S or RYGB gastric bypass as a primary surgery or after a sleeve gastrectomy. Main key exclusions included previous bariatric surgery (other than sleeve gastrectomy), inflammatory bowel disease, type 1 diabetes, and untreated *Helicobacter pylori* infection. Participants were randomly assigned (1:1) to SADI-S or RYGB, stratified by centre, failure of sleeve gastrectomy, and presence of type 2 diabetes. The primary endpoint was percentage excess weight loss (%EWL) at 2 years (%EWL=[(weight at 2 years−initial weight)/(initial weight−ideal weight)]×100). The study is registered with ClinicalTrials.gov, NCT03610256 and is completed.

Findings Between Nov 8, 2018, and Sept 29, 2021, a total of 381 patients were randomly assigned (intention-to-treat population) and included in the primary analysis (SADI-S: 190, RYGB: 191). Mean age was 44·4 years (SD 10·64), mean BMI was 46·2 kg/m² (6·40), 265 (70%) were female, and 79 (21%) had a primary sleeve gastrectomy. 43 (12%) of 370 participants were lost to follow-up. At 2 years, the mean %EWL was statistically significantly higher in the SADI-S group compared with the RYGB group (–76·0% [SD 26·7] *vs* –68·1% [28·7], confirming the superiority of SADI-S (mean difference –6·72% [95% CI –12·64 to –0·80], p=0·026). The primary outcome was missing for 78 (20%) of 381 participants, with 46 (59%) of 78 participants in the SADI-S group and 32 (41%) of 78 in the RYGB group, p=0·09. The number of serious adverse events related to the surgical technique in the safety population, including all operated patients, was 40 in the SADI-S group including three anastomotic leaks and eight severe diarrhoea compared with 35 in the RYGB group including five internal hernia and five severe abdominal pain cases of which two required diagnostic laparoscopy.

Interpretation SADI-S showed superior weight loss compared with RYGB at 2 years, with a similar safety profile.

Funding French Ministry of Health (Direction Générale de l'offre de Soin – DGOS).

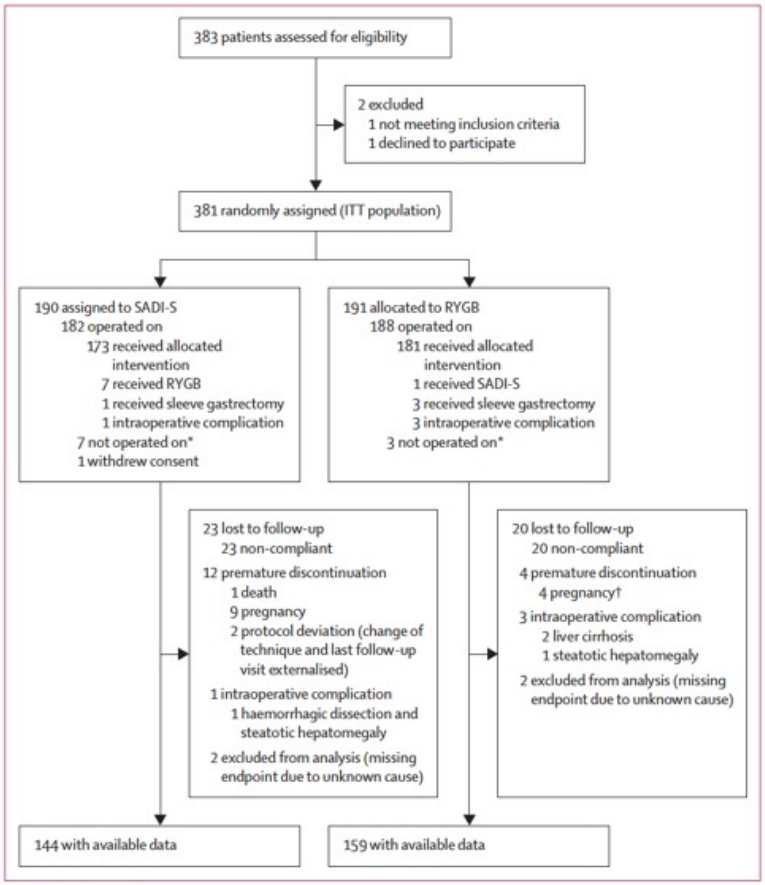


Figure 1: **Trial profile**

ITT=intention to treat. RYGB=Roux-en-Y gastric bypass. SADI-S=single anastomosis duodeno-ileal bypass with sleeve gastrectomy. *In the SADI-S group, seven patients allocated to surgery were not operated on for the following reasons: one was lost to follow-up before surgery, three withdrew their consent, one was under legal protection, one had to undergo surgery for a multinodular goitre, and one was deemed unfit for surgery due to continued smoking. In the RYGB group, three patients were not operated on for the following reasons: one was lost to follow-up before surgery, one withdrew consent, and one refused to undergo surgery. †Four pregnancies, and one pregnancy declared after month 21, but since the patient's weight had been measured at month 20 (within the predefined 2-year assessment window) this measurement was considered valid and included in the primary endpoint analysis.

	SADI-S group (n=190)	RYGB group (n=191)
Mean age, years (SD)	44·0 (10·5); n=189	44·8 (10·8); n=191
Missing data	1	0
Sex		
Male n (%)	57/189 (30%)	58/191 (30%)
Female, n (%)	132/189 (70%)	133/191 (70%)
Missing data	1	0
Mean weight, kg (SD)	130·6 (23·6); n=189	128·4 (22·6); n=191
Missing data	1	0
Mean BMI, kg/m² (SD)	46·1 (6·4); n=189	46·3 (6·4); n=191
Missing data	1	0
BMI ≥50 kg/m²	46/189 (24%)	53/191 (28%)
Missing data	1	0
Mean HbA_{1c}, % (SD)	6·2 (1·4); n=179	6·1 (1·2); n=182
Missing data	11	9
Mean fasting glycaemia, mmol/l (SD)	6·3 (2·5); n=177	6·2 (2·3); n=181
Missing data	13	10
Type 2 diabetes	59/189 (31%)	60/191 (31%)
Missing data	1	0
Mean HbA_{1c}, % (SD)	7·4 (1·8); n=57	7·2 (1·5); n=58
Missing data	2	2
Mean fasting glycaemia, mmol/l (SD)	7·9 (3·0); n=57	7·9 (3·4); n=57
Missing data	2	3
Mean duration of diabetes, years (SD)*	7·7 (7·3); n=53	5·7 (5·3); n=55
Missing data	6	5
On diabetes treatment	53/59 (90%)	52/60 (87%)
Missing data	0	0
On oral antidiabetic agents	51/53 (96%)	50/52 (96%)
Missing data	6	8
On GLP-1 agonist	24/53 (45%)	22/52 (42%)
Missing data	6	8
On insulin†	19/53 (36%)	14/52 (27%)
Missing data	6	8
Arterial hypertension	82/189 (43%)	86/191 (45%)
Missing data	1	0
Dyslipidaemia	69/189 (37%)	63/191 (33%)
Missing data	1	0
Arthrosis	55/189 (29%)	69/191 (36%)
Missing data	1	0
Sleep apnoea	127/189 (67%)	135/191 (71%)
Missing data	1	0
Primary sleeve gastrectomy	38/189 (20%)	41/191 (21%)
Missing data	1	0

Data are for the intention-to-treat population. Data are n or n/N (%) unless otherwise stated. SADI-S=single anastomosis duodeno-ileal bypass with sleeve gastrectomy. RYGB=Roux-en-Y gastric bypass. Post-hoc analysis comparing SADI-S with RYGB regarding mean duration of diabetes and patients on insulin, respectively: *p=0·11, †p=0·44.

Table 1: **Baseline characteristics**

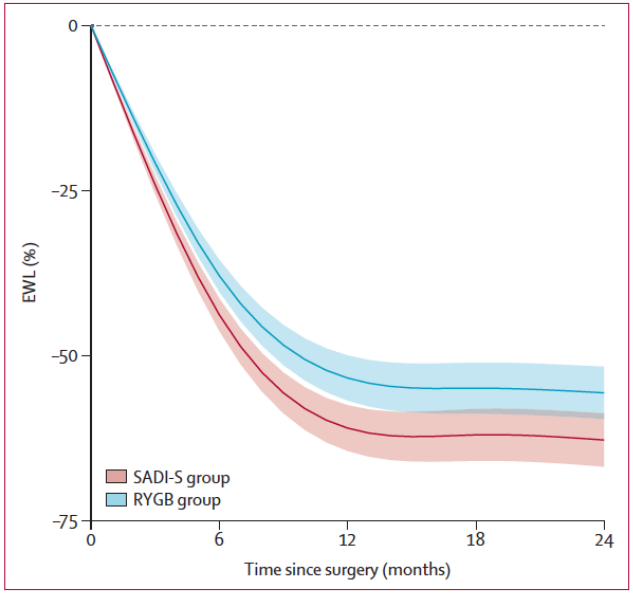


Figure 2: **Predicted trajectories of %EWL in the ITT population**
Curves are mean population-level predictions of %EWL as a function of time, from the linear mixed-effects model used for the sensitivity analysis without stratification variables (type 2 diabetes and history of sleeve). EWL=excess weight loss. ITT=intention to treat. RYGB=Roux-en-Y gastric bypass. SADI-S=single anastomosis duodeno-ileal bypass with sleeve gastrectomy.

	Mean %EWL (SD)		Primary analysis (regression model at 24 months with imputation)		Sensitivity analysis (linear mixed-effects model)		Complete-case analysis (regression model at 24 months)	
	RYGB	SADI-S	Adjusted absolute difference (95% CI)	p	Adjusted absolute difference (95% CI)	p	Adjusted absolute difference (95% CI)	p
ITT	−68·09 (28·70); n=191	−76·00 (26·65); n=190	−6·71 (−12·64 to −0·80)	0·026	−7·18 (−12·80 to −1·57)	0·012	−7·56 (−13·06 to −2·06)	0·0072
PP	−67·74 (28·48); n=184	−76·55 (25·95); n=163	−7·39 (−13·25 to −1·54)	0·014	−8·65 (14·25 to −3·05)	0·0026	..	..

Models were adjusted for minimisation factors (type 2 diabetes status and history of sleeve gastrectomy) and random intercept for study centre. Missing data were handled using multiple imputation by chained equations. Sensitivity analyses included complete-case and longitudinal mixed-effects regression models. Missing data for the primary outcome: 78 participants (21%), 45 (58%) in the SADI-S group and 33 (42%) in the RYGB group. EWL=excess weight loss. ITT=intention to treat. PP=per protocol. RYGB=Roux-en-Y gastric bypass. SADI-S=single anastomosis duodeno-ileal bypass with sleeve gastrectomy.

Table 2: **Primary and sensitivity analyses of the mean difference %EWL between SADI-S and RYGB**

	SADI-S group		RYGB group		p
	Baseline	2 years	Baseline	2 years	
Type 2 diabetes					
Patients on medication for diabetes, n (%)	53/59 (90%)	21/59 (36%)	52/60 (87%)	18/60 (30%)	0·52
Missing	0	0	0	0	..
Patients on oral antidiabetic agents, n (%)	51/53 (96%)	17/59 (29%)	50/52 (96%)	16/60 (27%)	0·79
Missing	6	0	8	0	..
Patients on GLP-1 agonist, n (%)	24/53 (45%)	3/59 (5·0%)	22/52 (42%)	4/60 (7%)	0·71
Missing	6	0	8	0	..
Patients on insulin, n (%)	19/53 (36%)	9/59 (15%)	14/52 (27%)	8/60 (13%)	0·76
Missing	6	0	8	0	..
Mean HbA_{1c}	n=57	n=46	n=58	n=41	..
% (SD)	7·4 (1·8)	5·9 (1·3)	7·2 (1·5)	5·8 (1·0)	0·23
mmol/mol (SD)	57·15 (19·10)	40·63 (14·05)	54·94 (16·35)	40·37 (10·64)	..
Missing	2	13	2	19	..
Remission, n (%)	..	30/53 (57%)	..	32/52 (62%)	0·61
Missing	..	6	..	8	..
Hypertension					
Remission, n (%)	..	28/82 (34%)	..	26/86 (30%)	0·59
Dyslipidaemia					
Remission, n (%)	..	43/69 (62%)	..	31/63 (49%)	0·13

RYGB=Roux-en-Y gastric bypass. SADI-S=single anastomosis duodeno-ileal bypass with sleeve gastrectomy.

Table 3: **Changes in type 2 diabetes parameters, hypertension, and dyslipidaemia at baseline and 2 years of follow-up**

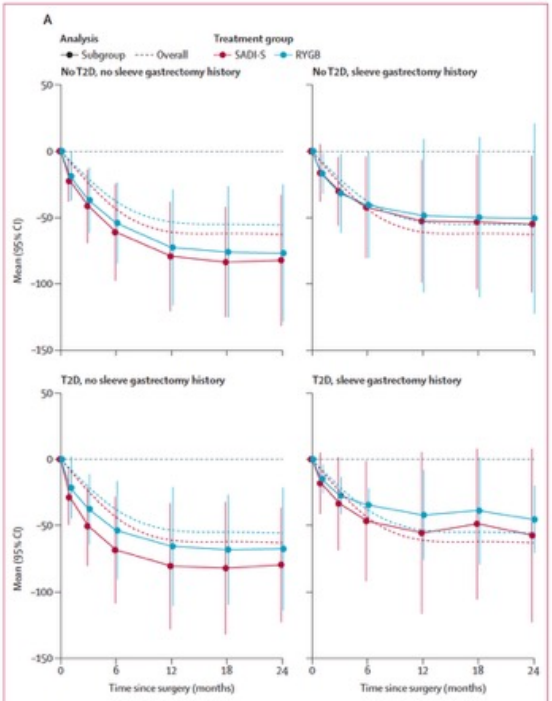
	SADI-S Group (n=190)	RYGB Group (n=191)	p value
Patients with early surgical complications <30 days, n (%)	10/190 (6%)	3/191 (2%)	0·042
Duodeno-ileal anastomotic leaks	3 (2%)	0	–
Gastro-jejunal anastomotic leaks	0	1 (1%)	–
Acute anastomotic ulcer	1 (1%)	0	–
Intraperitoneal collection	2 (1%)	1 (1%)	–
Wall abscess	2 (1%)	1 (1%)	–
Wall haematoma	3 (2%)	1 (1%)	–
Patients with late surgical complications >30 days, n (%)	3/179 (2%)	18/184 (10%)	0·0009
Internal hernia	0	5 (3%)	–
Bowel occlusion	0	4 (2%)	–
Acute anastomotic ulcer	1 (1%)	4 (2%)	–
Incisional hernia	2 (1%)	4 (2%)	–
Vomiting and food intolerance	0	2 (1%)	–
Patients with early medical complications <30 days, n (%)	48/177 (27%)	48/183 (26%)	0·85
Vomiting	18/177(10%)	12/183(7%)	–
Abdominal pain	15/177 (9%)	9/183 (5%)	–
Diarrhoea	21/177 (12%)	9/183 (5%)	–
Constipation	3 (2%)	5 (3%)	–
Symptomatic vitamin deficiency	0	1 (1%)	–
Pulmonary embolism	1 (1%)	0	–
Pneumonia	0	1 (1%)	–
Respiratory distress	0	1 (1%)	–
Cardiovascular event	0	2 (1%)	–
Anorexia	1 (1%)	0	–
Early dumping syndrome	8 (4%)	19 (10%)	–
Late dumping syndrome	2 (1%)	4 (2%)	–
Patients with late medical complications >30 days, n (%)	76/179 (43%)	91/184 (50%)	0·18
Vomiting	17 (9%)	25 (13%)	–
Abdominal pain	15 (8%)	26 (14%)	–
Diarrhoea	41 (22%)	12 (6%)	–
Constipation	7 (4%)	9 (5%)	–
Food intolerance	3 (2%)	3 (2%)	–
Protein deficiency	9 (5%)	4 (2%)	–
Symptomatic vitamin deficiency	15 (8%)	12 (6%)	–
Phlebitis	0	0	–
Pulmonary embolism	0	0	–
Pneumonia	0	0	–
Respiratory distress	0	0	–
Cardiovascular event	0	2 (1%)	–
Dysphagia	1 (1%)	2 (1%)	–
Early dumping syndrome	0	2 (1%)	–
Late dumping syndrome	1 (1%)	2 (1%)	–
Kidney stones (at least once during follow-up)	10/190 (5%)	8/191 (4%)	0·62
Surgical treatment for kidney stones	3 (2%)	2 (1%)	–
Clinical GERD at 2 years	27/144 (19%)	12/159 (8%)	0·004
PPI use in GERD patients	26/141 (18%)	11/155 (7%)	–
Early dumping syndrome (clinical symptoms) at 2 years	6/131 (5%)	16/140 (11%)	0·039
Sigstad score ≥7 at 2 years	6/164 (4%)	13/164 (8%)	0·095

(Table 4 continues on next page)

	SADI-S Group (n=190)	RYGB Group (n=191)	p value
(Continued from previous page)			
Overall complications of grade ≥3 (Dindo-Clavien classification)	13/98 (13%)	21/113 (19%)	0·295
Reoperation (early)	4/57 (7%)	3/51 (6%)	0·81
Mean hospital stay (days)	4·8 (SD 7·47)	2·8 (SD 2·85)	<0·001
30-day readmission rate	3 (2%)	5 (3%)	0·49

EWL=excess weight loss. GERD=gastroesophageal reflux disease. PPI=proton pump inhibitor. RYGB=Roux-en-Y gastric bypass. SADI-S=single anastomosis duodeno-ileal bypass with sleeve gastrectomy.

Table 4: Comparison of early and late complications between SADI-S and RYGB at 2-year follow-up



B

Estimate	Subgroup	Coefficient	CI	p value
Changes in % EWL in the SADI-S group compared with RYBG, function of stratification criteria	No sleeve history, no T2D	−4·56	−12·96 to 3·84	0·2861
	Sleeve history, no T2D	−5·69	−20·42 to 9·04	0·4479
	No sleeve history, T2D	−11·75	−22·71 to −0·79	0·0357
	Sleeve history, T2D	−6·70	−32·65 to 19·25	0·6118

Research in context

Evidence before this study

We searched PubMed, Embase, and Cochrane Library for articles published from Jan 1, 2007, to Jan 31, 2024, without language restrictions, using the search terms "SADI-S" OR "Single Anastomosis Duodenal Switch" OR "Single Anastomosis Duodeno-Ileal Bypass" OR "Biliopancreatic Diversion with Duodenal Switch" AND "Roux-en-Y Gastric Bypass" AND "Bariatric Surgery" AND "randomized trial". Single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) is a relatively new procedure, described in 2007, designed to simplify biliopancreatic diversion with duodenal switch (BPD-DS), which is the most effective bariatric and metabolic procedure. SADI-S was proposed as a less complex alternative with the potential to achieve greater weight loss than Roux-en-Y gastric bypass (RYGB), a long-established and validated standard in bariatric surgery. We identified no published randomised controlled trials comparing SADI-S with RYGB. Available evidence is limited to retrospective series and small prospective cohorts, with heterogeneity in surgical techniques and follow-up duration. Observational data suggest that SADI-S provides excellent weight loss (with percentage excess weight loss ranging from 67% to 114% at 2 years) and high type 2 diabetes remission rates exceeding 80% in some studies, but with adverse effects of nutritional deficiencies and diarrhoea. However, the quality of this evidence is low, with risks of selection bias and few long-term nutritional assessment.

Added value of this study

SADI-S is a recently adopted bariatric–metabolic technique that has gained increasing international attention but, until now, lacked high-quality comparative evidence. SADISLEEVE is the first multicentre randomised controlled trial comparing SADI-S with RYGB, the current reference standard in bariatric and metabolic surgery. Unlike earlier studies that focused on highly malabsorptive techniques such as BPD-DS in patients with class IV obesity, this trial was designed to reflect current clinical practice, including standard bariatric candidates as well as revisional cases after sleeve gastrectomy—a growing population given that sleeve now represents 60% of bariatric procedures with 20–30% resulting in suboptimal clinical response or recurrent weight gain. This study provides evidence that SADI-S, when performed with appropriate technical standardisation (common channel length of at least 250 cm) and structured nutritional follow-up, achieves greater weight loss than RYGB without increasing nutritional risk (ie, protein and vitamin deficiencies), and with comparable metabolic outcomes.

Implications of all the available evidence

Combining the results of this first randomised controlled trial with existing observational evidence suggests that SADI-S is a safe and effective alternative to RYGB, offering greater weight loss with an acceptable nutritional safety profile under appropriate supplementation and close follow-up. These results support SADI-S as a validated bariatric procedure, as advocated by the International Federation for the Surgery of Obesity and American Society for Metabolic and Bariatric Surgery, and justify its inclusion in the standard therapeutic armamentarium of bariatric surgeons. By showing that SADI-S can be a safe and effective option not only for patients with class IV obesity but also across a wide BMI spectrum, including both primary bariatric candidates and those with previous sleeve gastrectomy, our findings support a shift in surgical decision making. SADI-S can be considered both as a primary procedure and as a revisional option after sleeve gastrectomy, offering greater weight loss and good metabolic outcomes, particularly in patients without previous sleeve gastrectomy and with type 2 diabetes. This trial provides robust evidence to redefine the place of SADI-S in the therapeutic algorithm and contributes meaningful evidence to the ongoing evolution of obesity treatment strategies. However, long-term follow-up beyond 2 years is needed to confirm the durability of weight loss, metabolic outcomes, and safety profile.

Surgical health policy 2025–35: strengthening essential services for tomorrow's needs

Progress towards *The* Lancet *Commission on Global Surgery*'s 2030 targets has been too slow and too patchy, particularly in low-income and middle-income countries. The unmet need for surgery has continued to grow, reaching at least 160 million operations per year. Ensuring high-quality surgical care remains a crucial global challenge, with 3·5 million adults dying after surgery each year. The COVID-19 pandemic exposed the fragility of surgical services long undermined by chronic underfunding, workforce shortages, and under-resourced infrastructure. However, *The* Lancet *Commission on Global Surgery* inspired a new generation of surgeons to engage with policy, and several countries have developed national surgical plans, although most remain unfunded. Advancements in surgical data science have allowed health systems to identify priorities for improvement. Preserving this infrastructure is important, especially during periods of uncertain global health funding. The next decade requires urgent change to prevent economic instability and armed conflict from forcing surgery down the global health agenda. Reframing surgery as an essential service that saves lives, strengthens health systems, and fosters economic productivity could unlock much needed investment. Sustained progress requires integration of funding both within hospital infrastructure and across care pathways. Such holistic approaches would reinforce entire hospital systems, which are essential to national security and wellbeing.

Panel 2: Key messages

- Unmet surgical need is rising, not falling: the global unmet need for surgery has increased to 160 million procedures per year (appendix pp 8–10). Provision has not kept pace with population demands or ageing trends, particularly in low-income and middle-income countries.
- Postoperative deaths exceed major global disease burdens: an estimated 3·5 million adults die within 30 days of surgery each year (appendix pp 6–7), which is more than the total deaths attributed to HIV, malaria, and tuberculosis. Strengthening hospital infrastructure will prevent deaths by increasing the capacity to rescue patients from complications.
- Surgery strengthens health systems beyond the operating theatre: investment in surgery provides economy of scale by lifting broader hospital services, such as diagnostics, oxygen supply, energy security, and intensive care.
- Surgical expansion offers major economic returns: scaling up essential cancer surgery alone in low-income and middle-income countries could return more than international $80 billion annually in productivity gains, enabling more than 885 000 people to return to work each year. This surgical prosperity dividend is a powerful case for prioritised investment.
- Preparedness is essential, but lagging: the COVID-19 pandemic revealed how fragile surgical systems are; 28 million operations were cancelled in just 12 weeks.[3] Health systems should be better prepared for emerging risks, including global conflicts and climate events.

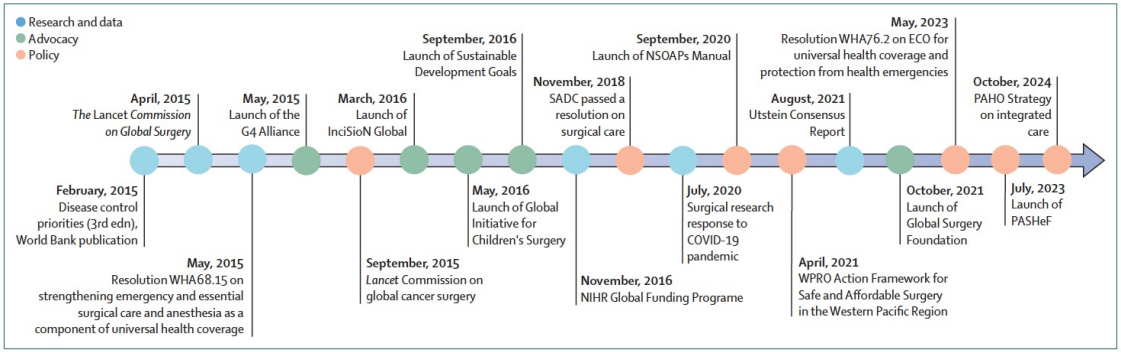


Figure 1: **Timeline of key events in global surgery**
ECO=Integrated emergency, critical, and operative Care. InciSioN=International Student Surgical Network. NIHR=National Institute for Health and Care Research. NSOAP=National Surgical, Obstetric, and Anaesthesia Plan. PAHO=Pan American Health Organization. PASHeF=Pan-African Surgical Healthcare Forum. SADC=Southern African Development Community. WHA=World Health Assembly. WPRO=World Health Organization Regional Office for the Western Pacific.

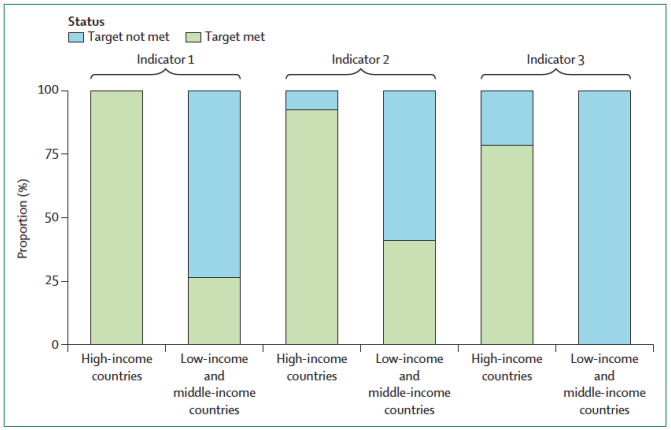


Figure 2: **Progress towards achieving *The* Lancet *Commission on Global Surgery* 2030 targets**
Our systematic review found 28 studies that reported *The* Lancet *Commission on Global Surgery* 2030 indicators: 12 with multinational data and 16 with national-level data. Country-level data were available for indicators 1–3 only. Indicator 1: access to timely essential surgery (data available for 96 countries). Indicator 2: specialist surgical workforce density (200 countries). Indicator 3: surgical volume (92 countries).

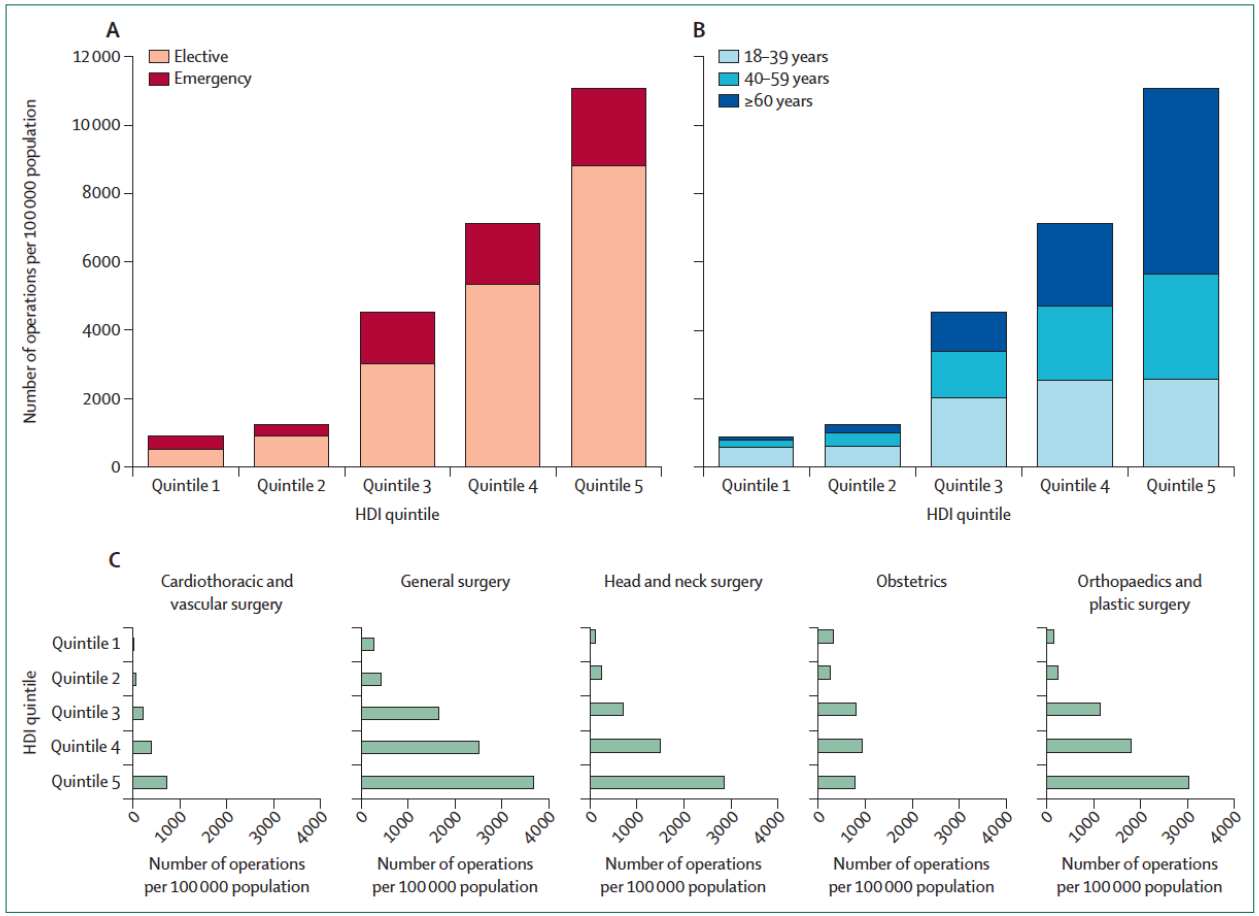


Figure 3: **Global variation in surgical case-mix**
(A) Number of operations per 100 000 population stratified by urgency of surgery. (B) Number of operations per 100 000 population stratified by age group. (C) Number of operations per 100 000 population stratified by specialty group. HDI quintile 1 is the lowest and quintile 5 is the highest. HDI=Human Development Index. Methodology is presented in the appendix (pp 6–7).

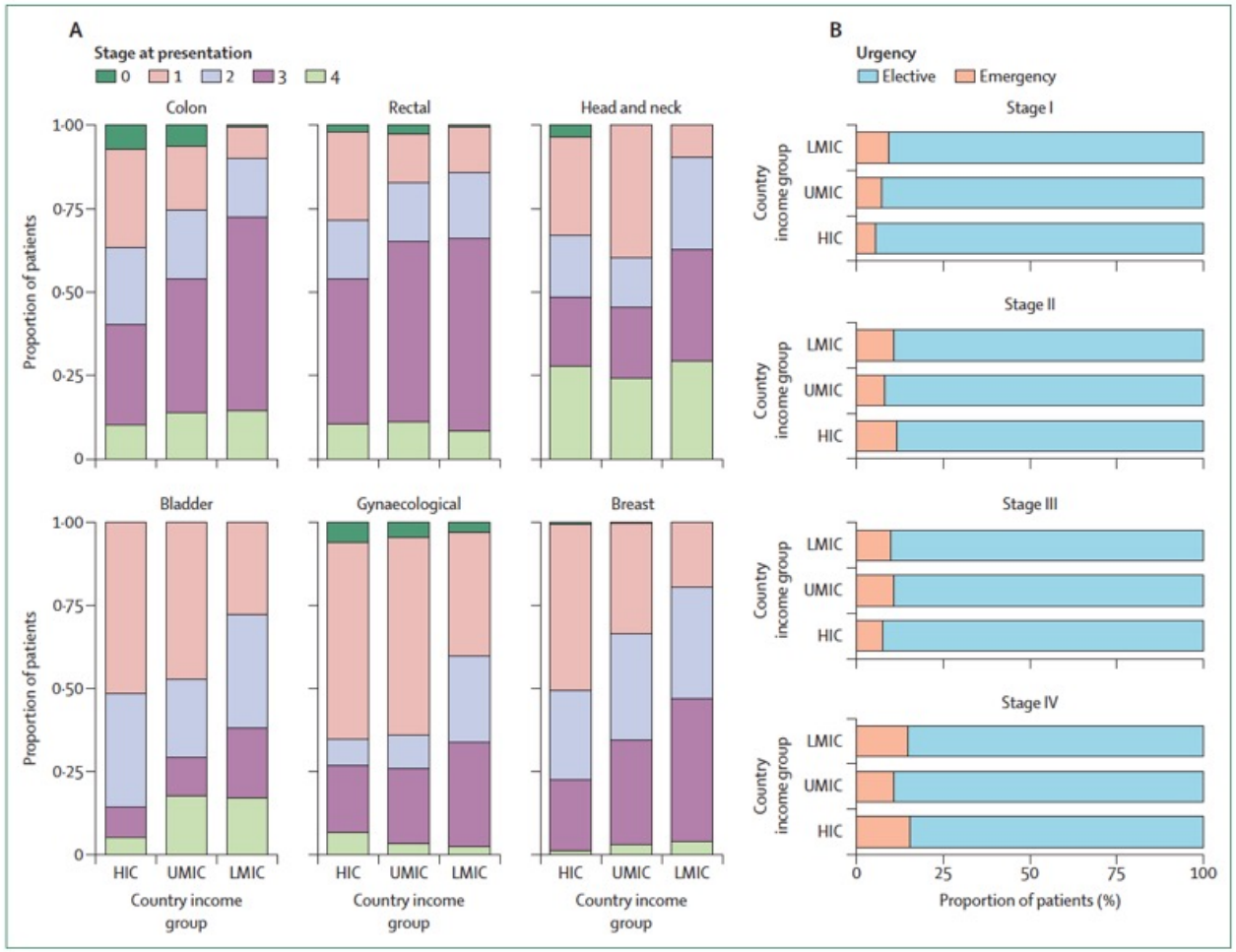


Figure 4: **Global variation in stage of presentation of solid organ cancers**
Data are from the COVIDSurg Collaborative.[22] (A) Variation in cancer stage at presentation for six common solid organ tumour types requiring surgery. (B) Global variation in urgency of colon cancer presentation by stage. LMIC=low-income and lower-middle-income country. UMIC=upper-middle-income country.

Panel 5: Research priorities for 2025–35

Research strategy

- Investment is needed to maintain the unique global surgical data infrastructure that has delivered high-quality, multi-country evidence to support better surgical care worldwide. This infrastructure will be essential for responding to new needs, including global conflicts.
- There should be a shift from channelling funding into disease-based silos to growing whole-hospital research. This shift includes identifying and disseminating learning from hospital networks that have accelerated provision of high-quality surgical care.

Research priorities

- Which interventions can reduce perioperative mortality rates?
- Which interventions can enhance postoperative recovery and reduce complications?
- Which interventions can reduce surgical site infections and antimicrobial resistance?
- How can surgery be made more cost-effective?
- What are sustainable financing strategies for achieving universal health coverage in surgical care?
- How can surgical training and workforce scaling be accelerated to meet demand?
- How can access to timely surgical care be improved?
- How can care pathways between first-referral, secondary, and tertiary hospitals be improved?
- What strategies can prevent surgical diseases and trauma?
- How can research capacity be increased in low-income and middle-income countries?

Exemplar study designs addressing these research priorities are presented in the appendix (p 33).

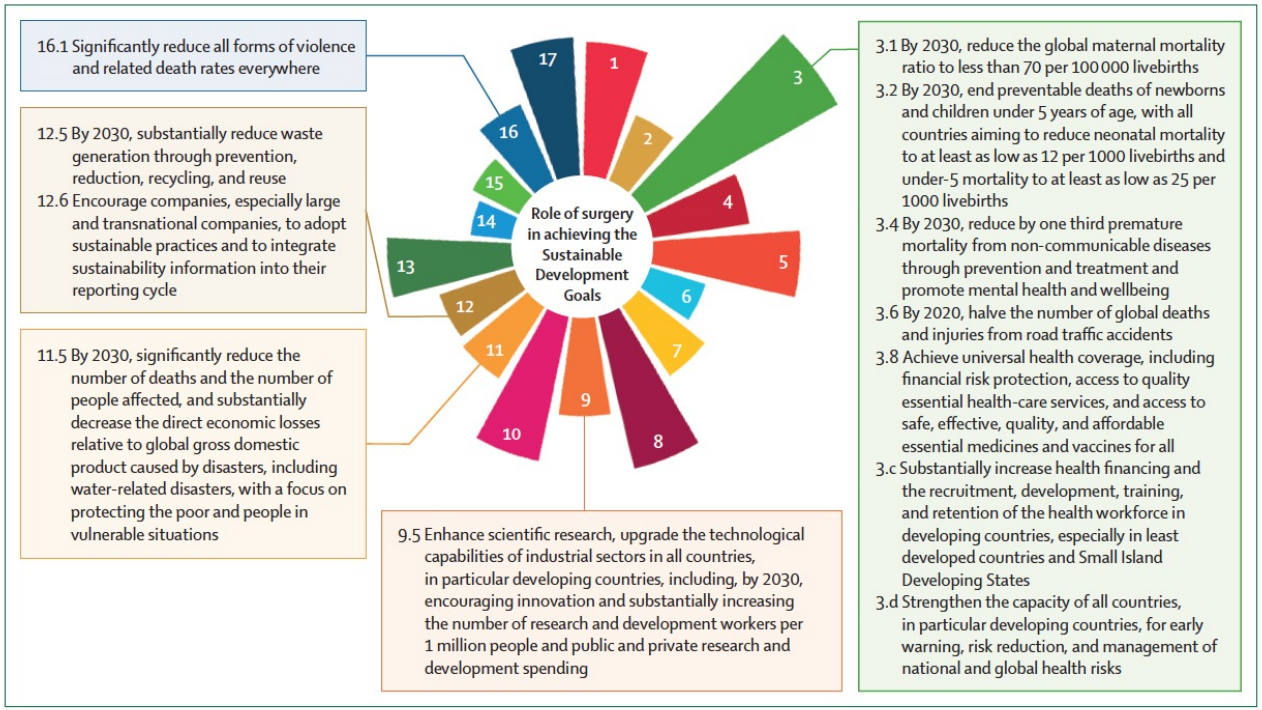


Figure 10: **Role of surgery in achieving the Sustainable Development Goals**
The height of each Sustainable Development Goal bar from the wheel is proportionate to the degree that surgery affects achieving that goal. The Sustainable Development Goal targets rated as most relevant to surgery are displayed.[161]

Conclusion

Progress towards *The* Lancet *Commission on Global Surgery* 2030 targets has been incomplete, inconsistent, and fragile. Crucial gaps remain in workforce density, surgical volume, and financial protection and, with just a few years remaining to meet targets, most countries are off track. The COVID-19 pandemic exposed the vulnerability of surgical systems, deepened existing inequities, and slowed momentum. NGOs have helped to deliver care, but without sustainable development of national surgical systems, their efforts remain a stopgap. Surgery must be embedded within wider health systems, strengthening surgical capacity through vertical investment in hospital infrastructure. It must no longer be seen as optional or too expensive; it is an essential, cost-effective service that underpins national resilience, public health, and economic productivity. The next decade must be different. Governments, funders, and global health institutions must commit to sustaining and expanding the progress in surgical data collection achieved over the past decade by establishing robust, enduring data ecosystems. These systems are essential to inform strategic investment and enhance accountability. Without such commitment, surgery risks falling even further down the global health agenda.

Panel: Action points

Amplify marginalised voices in bioethics discussions
A series of workshops and dialogues should be arranged to articulate Indigenous and other knowledges with emergent planetary health ethics.[26] Such engagements should include diverse methodologies (eg, Indigenous methods) and substantive insights into Earth-centred ethical systems and sustainable healthy living. In the south Pacific, for example, planetary health activists have engaged in Talanoa, an inclusive and respectful style of conversation and storytelling, which opens a space for Oceanic voices to transform practice and governance.[30] In Indigenous Australian settings, collaboration might involve yarning circles, truth-telling processes, and other established forms of community-led engagement.[31,32] The goal of such respectful deep listening (ie, Dadirri), and recognition of Earth-centred, country-connected Indigenous futurities, is to move towards the amplification of decolonial ethical reasoning. Such a change is conducive to an acknowledged decolonising process embedded within the advancement of bioethics while grounding it in planetary realities. Although now associated with Pasifika and other Indigenous engagement, Talanoa and yarning circles offer methods for inclusion of other currently marginalised groups, recognising their agency and thereby helping to reduce epistemic injustices and erasures in planetary health and bioethics.

Recognise the importance of intergenerational justice in public health governance
This recognition equates to giving younger generations an effective voice and power to enact changes in determining the values and scope of bioethics and public health governance.[33] The health-care system and global health organisations should listen to younger populations and address pressing issues of climate distress and planetary despair. This goal could be achieved through co-designed principles developed for women's health, community mental health, disability movements, and in community-led Indigenous health. Another possible model is the inclusion of youth representatives in health governance and advisory committees, as called for by the second *Lancet* Commission on adolescent health and wellbeing. Such processes will also re-orient bioethics more generally towards responsibilities for the health and wellbeing of future generations, who will be more severely subjected to the damage wrought by ecological disruption and degradation.[34]

Develop stronger mechanisms to link the values of environmental justice and climate justice to health equity
More effective means for factoring the structural violence of ecosystem degradation and disruption into broader bioethical reasoning should be specified and applied in health training. This goal necessitates recognition in health curricula and codes of different vulnerabilities to, and disparate agency in causing, ecosystem degradation (including climate change). The health co-benefits from just and fair sustainability transitions should be emphasised (eg, renewable energy, sustainable agrifood systems, and sustainable cities).[35,36] Although several nascent efforts aim to transform the training of health professionals, they are currently scattered and isolated, requiring national and international processes for coordination and knowledge sharing.

Develop stronger mechanisms to make multispecies justice and the preservation of biodiversity fundamental to ethical practice and regulation in biomedicine
We need to ensure that mass extinctions, land clearing, deforestation, and threats to food systems are not separated from standard bioethical reflection in curricula and regulatory codes or protocols. Strategies should be coordinated to explain and reinforce the connections between valuing and protecting the planet and all its life forms and doing the same for human health and wellbeing.[37] This goal will involve reaching out to researchers in the fields of multispecies justice and environmental humanities.

Embed planetary health ethics in global and national health governance
Promotion of planetary health ethics through institutions of global health governance and national health governance will assist in the translation of its principles into pedagogy and regulatory activities. Although engagement between different global governance agencies (eg, WHO, UNESCO, and the UN Environment Programme) has improved in the past decade, ethical reflection has rarely been involved, despite potentially aiding mediation between domains. For example, the 2005 UNESCO Universal Declaration on Bioethics and Human Rights—written without WHO input—left protection of the environment, the biosphere, and biodiversity to its last article, and the 2017 UNESCO Declaration of Ethical Principles in relation to Climate Change omits health and bioethics. Greater involvement and better translation between domains will lead to the review of influential protocols such as the World Medical Association's Declaration of Geneva, as well as national, regional, and international codes of professional ethics.[38,39]

Improve methods of communicating planetary health ethics to non-professional and non-academic groups to widen the potential effect of ethical reasoning
A truly effective, transformative ethics demands more thought on how to adapt language, methods, and communication strategies to local, national, and transnational needs. Planetary health ethics should draw more closely on the skills and strategies of health promotion and science communication.

Prioritise the assessment and reduction of the carbon footprint and general environmental damage of health-care enterprises
The ethical imperative for medical institutions not to worsen pathogenic global heating and ecosystem destruction should be enforced.[40] This goal requires sustainable health systems, with a focus on the mitigation of environmental damage they do while holding countries accountable to health-care

(Continues on next page)

Bioethics for the planet

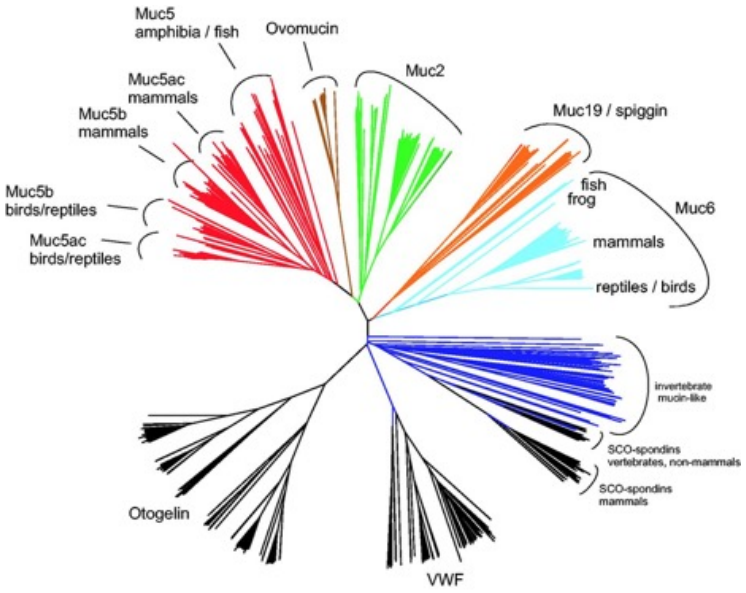
(Panel continued from previous page)

sustainability targets. Although many health-care institutions are aiming to become carbon neutral, these ad-hoc efforts should be broadened to encompass other environmental harms, and can be accelerated through focused regulation by governments and accreditation bodies.

Empower health workers and institutions to advocate for planetary health
Planetary health advocacy and political engagement should be embedded in the responsibilities of health-care professionals, and education and training should be used to amplify these professionals' obligation to the environment and non-human life forms.[28,41] This health activism attends to a rapid transition out of the carbon economy, greatly reduced per-capita consumption in high-income countries, achieving sustainable development goals, modifying food systems, combating biodiversity loss, eliminating microplastics, and reducing pollution and toxification of air, water, and land. Such a goal requires data monitoring and reporting on long-term institutional and political commitments to addressing planetary health, including the responsibilities of health and medical professional organisations, learned societies, professional accreditation bodies, and political platforms.

Summary
These action points address the pressing need to transform re-grounded bioethics into a planetary translation tool that articulates across currently separated domains of knowledge and practice. Such a transformation will aid in dismantling boundaries between health governance and environmental governance, bioethics and environmental or planetary health ethics, health-care management and health activism, social determinants of health and environmental health, and between health practice and political advocacy. Greater diversity, equity, and inclusion is required for the further development of an overarching planetary health ethics. To aid the success of this endeavour, an observatory is needed to compare and collate the successes and failures of this transformation, and to monitor and support effective implementation strategies transnationally.

MUC19 ist ein Protein-Kodierungsgen, das einen gelbildenden Mukin kodiert. Diese Mukine sind Glykoproteine, die für die Bildung von Schleim und dessen viskoelastische Eigenschaften verantwortlich sind, die Schutz und Schmierung bieten. Das MUC19-Gen spielt eine Rolle bei der Immunabwehr und ist an der Progression von Krankheiten wie Glioblastom und Entzündungen beteiligt.



Denisovans, Neanderthals gave Indigenous Americans key mucus gene

A genome sequenced from a Neanderthal jaw found in Siberia contains the same mucus gene variant found in Denisovans and many Indigenous Americans. PHOTO: THILO PARG/WIKIMEDIA COMMONS

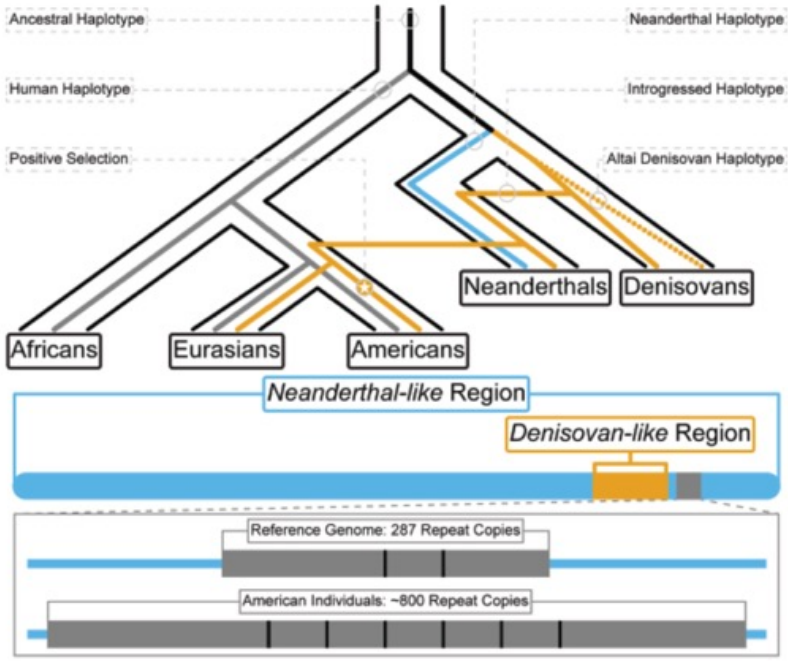
Mucus does more than simply rocket out of our noses when we sneeze. The sticky, viscous secretion that coats many organs also forms our innate immune system's first line of defense, helping trap harmful pathogens. This humble stuff varies around the world, and people Indigenous to the Americas often have a specific variant of a key mucus-producing gene known as *MUC19*. Now, scientists have tracked the winding evolutionary path this variant took from its origins in Denisovans—a mysterious ancient human ancestor—to our close cousins the Neanderthals and finally modern humans.

The *MUC19* gene: An evolutionary history of recurrent introgression and natural selection

INTRODUCTION: Modern human genomes contain a small number of archaic variants, the legacy of past interbreeding events with Neanderthals and Denisovans. Most of these variants are putatively neutral, but some archaic variants found in modern humans have been targets of positive natural selection and may have been pivotal for adapting to new environments as humans populated the world. American populations encountered a myriad of novel environments, providing the opportunity for natural selection to favor archaic variants in these new environmental contexts. Indigenous and admixed American populations have been understudied in this regard but present great potential for studying the underlying evolutionary processes of local adaptation.

RATIONALE: Previous studies identified the gene *MUC19*—which codes for a mucin involved in immunity—as a candidate for introgression from Denisovans as well as a candidate for positive natural selection in present-day Indigenous and admixed American populations. Therefore, we sought to confirm and further characterize signatures of both archaic introgression and positive selection at *MUC19*, with particular interest in modern and ancient American populations.

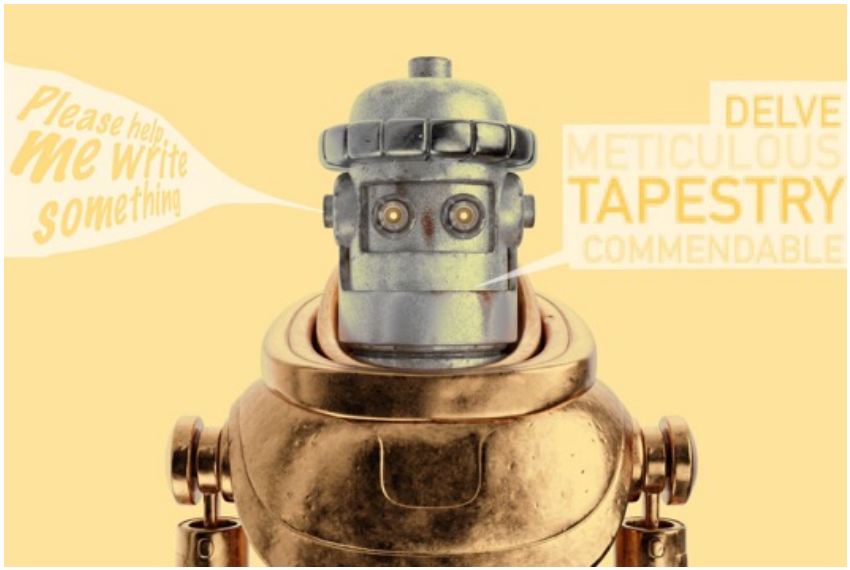
RESULTS: We identify an archaic haplotype segregating at high frequency in most admixed American populations, and among ancient genomes from 23 ancient Indigenous American individuals who predate admixture with Europeans and Africans. We conclude that the archaic haplotype has undergone positive natural selection in these populations, which is tied to their Indigenous components of ancestry. We also find that modern admixed American individuals exhibit an elevated number of variable number tandem repeats (VNTRs) at *MUC19*, which codes for the functional domain of the *MUC19* protein, where it binds to oligosaccharides to form a glycoprotein, a characteristic of the mucins. Remarkably, we find an association between the number of VNTRs and the number of introgressed haplotypes; individuals harboring introgressed haplotypes tend to have a higher number of VNTRs. In addition to the differences in VNTRs, we find that the archaic *MUC19* haplotype contains nine Denisovan-specific, nonsynonymous variants found at high frequencies in American populations. Finally, we observed that the Denisovan-specific variants are contained in a 72-kb region of the *MUC19* gene, but that region is embedded in a larger 742-kb region that contains Neanderthal-specific variants. When we studied *MUC19* in three high-coverage Neanderthal individuals, we found that the Chagyrskaya and Vindija Neanderthals carry the Denisovan-like haplotype in its heterozygous form. These two Neanderthals also carry another haplotype that is shared with the Altai Neanderthals.



The proposed evolutionary history of *MUC19*. The Denisovan-like haplotype (in orange) was first introgressed from Denisovans into Neanderthals and then introgressed into modern humans. The introgressed haplotype later experienced positive selection in populations from the Americas. The introgressed *MUC19* haplotype is composed of a 742-kb region that contains Neanderthal-specific variants (blue). Embedded within this Neanderthal-like region is a 72-kb region containing a high density of Denisovan-specific variants (orange), and an exonic variable number tandem repeat (VNTR) region (gray). The box below the 742-kb region depicts zooming into the *MUC19* VNTR region, in which admixed American individuals carry an elevated number of tandem repeat copies.

CONCLUSION: Our study identifies several aspects of the gene *MUC19* that highlight its importance for studying adaptive introgression: One of the haplotypes that span this gene in modern humans is of archaic origin, and modern humans inherited this haplotype from Neanderthals who likely inherited it from Denisovans. Then, as modern human populations expanded into the Americas, our results suggest that they experienced a massive coding VNTR expansion, which occurred on an archaic haplotype background in *MUC19*. The functional impact of the variation at this gene may help explain how mainland Indigenous Americans adapted to their environments, which remains underexplored. Our results point to a complex pattern of multiple introgression events, from Denisovans to Neanderthals and Neanderthals to modern humans, which may have later played a distinct role in the evolutionary history of Indigenous American populations.

It's happening: People are starting to talk like ChatGPT



If you use ChatGPT, Claude, Gemini or another artificial-intelligence-powered chatbot, you're probably operating under the assumption that you're both speaking the same language. You input English, it outputs English. Simple, right? Except that's a misconception: You've actually been speaking different languages.

Next, the chatbot formulates a reply, making a word-by-word prediction based on how it was trained to answer past inputs. This prediction draws on biased training data (the specific texts it learns from) and biased reinforcement learning (the feedback it receives). Ultimately, what looks like English to you is really a simulacrum of human speech.

For example, ChatGPT uses the word “delve” at higher rates than people generally do when writing or speaking English. As Florida State University researchers Tom S. Juzek and Zina B. Ward have found, this probably results from small biases and errors in the human feedback process compounding over time. Employees of AI companies checking over large language model (LLM) outputs are often low-wage workers from countries such as Nigeria and Kenya, where “delve” is used at higher rates than in American or British English.

delve = vertiefen

Now this overuse is bleeding into global culture. In the two years since ChatGPT launched in late 2022, the appearance of “delve” in academic publishing saw a tenfold increase as researchers began turning to AI for help with their papers. As scientists and writers have grown more aware of this phenomenon, they’ve taken steps to “sound less like AI.” I actually used to enjoy using the word “delve”; now I try to avoid it.

Indeed, a study reported in Scientific American last month found that people have started saying “delve” more in *spontaneous, spoken conversations*. This isn’t AI’s doing anymore; we’ve started internalizing its biases and repeating them by ourselves. I say “we” because even those in the anti-“delve” faction aren’t exempt. We might avoid using the most well-known ChatGPT giveaways, but so many words are appearing with unnatural frequency that we can’t possibly avoid them all. Are we also supposed to stop using the chatbot-overused “inquiry”? Or “surpass”? There’s too much to keep track of.

Educated people do not end sentences with prepositions!