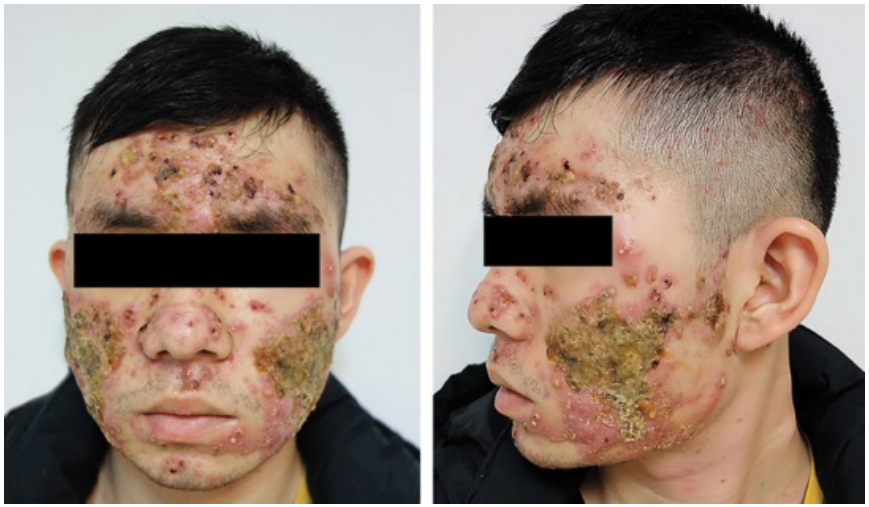
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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 19-year-old man with a history of mild acne vulgaris presented with a 10-day history of rapidly worsening acne, along with fever, muscle aches, and knee pain. His temperature was 38.5°C. On physical examination, diffuse papulonodular and pustular lesions with areas of overlying crusting were noted across the forehead, nose, cheeks, and chin. There were similar lesions on the neck, shoulders, chest, back, and thighs. Laboratory studies were notable for neutrophilic leukocytosis and an elevated erythrocyte sedimentation rate and C-reactive protein level. A culture of a skin swab grew only Cutibacterium acnes. Histopathological examination of a skin-biopsy specimen taken from behind the left ear showed suppurative folliculitis with adjacent dermal edema. What is the most likely diagnosis?

Acne fulminans

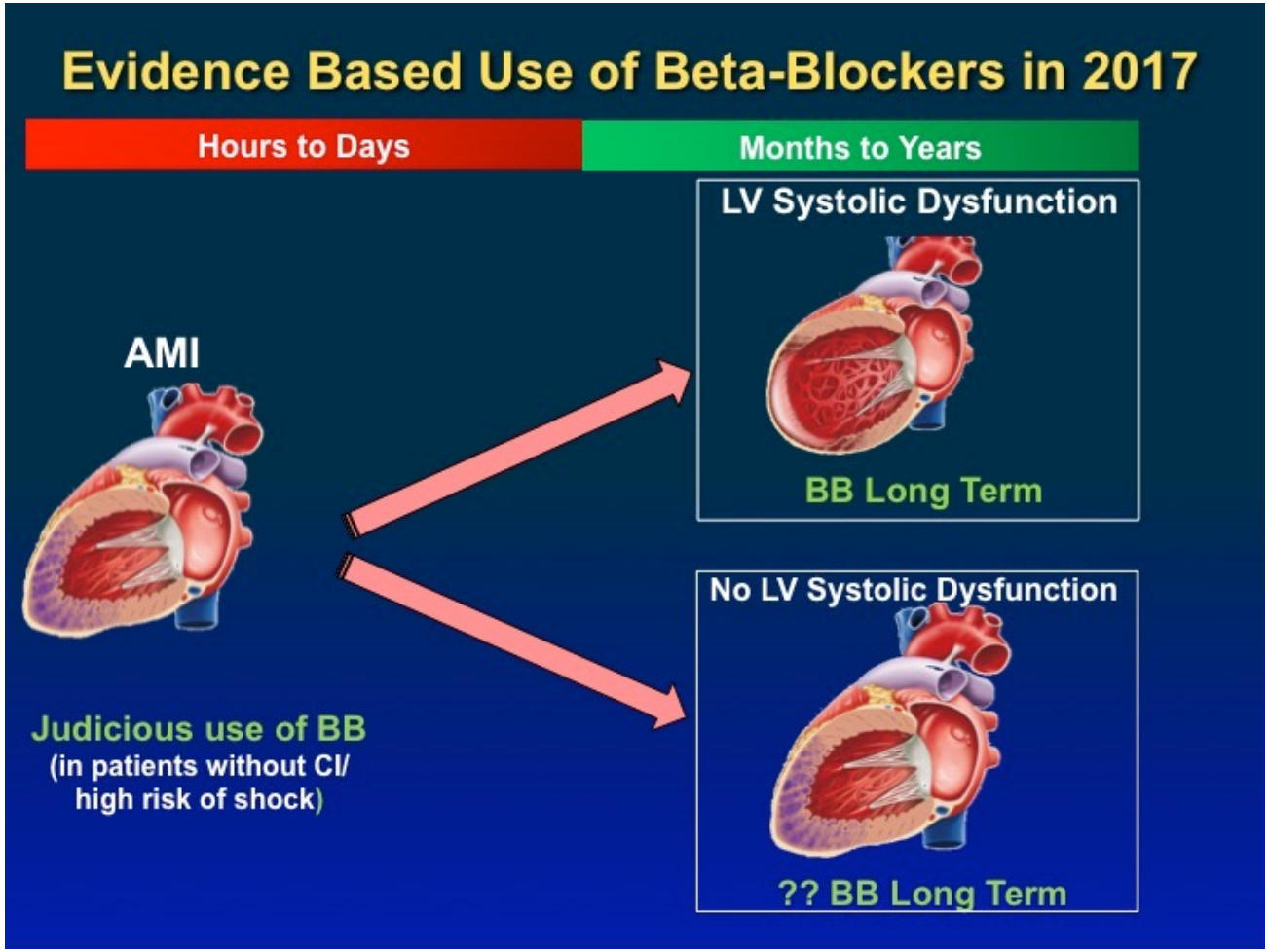
Acute febrile neutrophilic dermatosis

Hidradenitis suppurativa

Pustular psoriasis

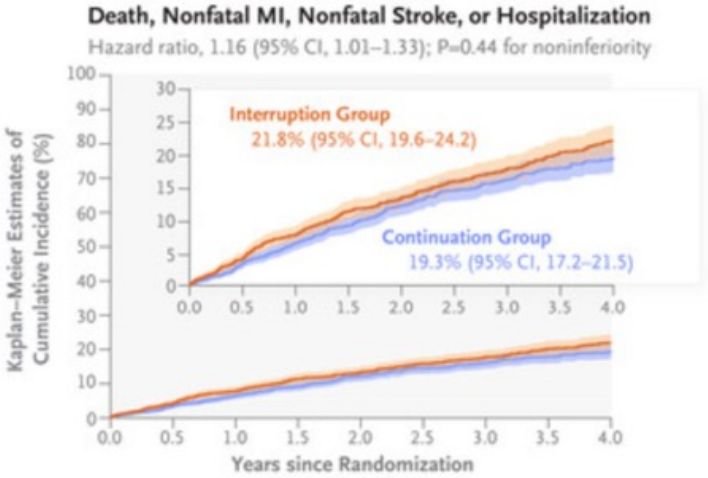
Rosacea fulminans

Acne fulminans is an acute, severe variant of inflammatory acne and may be associated with systemic symptoms, such as fever, myalgias, arthralgias, and even osteolytic bone lesions. The condition may be induced by isotretinoin therapy or occur spontaneously, as in this case. Treatment may include oral glucocorticoids, isotretinoin, and topical antimicrobial agents.


Evidence Based Use of Beta-Blockers in 2017
Hours to Days
Months to Years
AMI
LV Systolic Dysfunction
BB Long Term
No LV Systolic Dysfunction
?? BB Long Term
Judicious use of BB
(in patients without CI/
high risk of shock)

Beta-Blocker Interruption or Continuation after Myocardial Infarction

The appropriate duration of treatment with beta-blocker drugs after a myocardial infarction is unknown. Data are needed on the safety and efficacy of the interruption of long-term beta-blocker treatment to reduce side effects and improve quality of life in patients with a history of uncomplicated myocardial infarction. In a multicenter, open label, randomized, noninferiority trial conducted at 49 sites in France, we randomly assigned patients with a history of myocardial infarction, in a 1:1 ratio, to interruption or continuation of beta-blocker treatment. All the patients had a left ventricular ejection fraction of at least 40% while receiving long-term beta-blocker treatment and had no history of a cardiovascular event in the previous 6 months. The primary end point was a composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reasons at the longest follow-up (minimum, 1 year), according to an analysis of noninferiority (defined as a between-group difference of <3 percentage points for the upper boundary of the two-sided 95% confidence interval). The main secondary end point was the change in quality of life as measured by the European Quality of Life–5 Dimensions questionnaire.



Interruption of beta-blockers did not appear to improve quality of life.

The benefit of beta-blocker therapy in patients with myocardial infarction is derived from trials carried out before the modern era of myocardial reperfusion and pharmacotherapy. Early coronary reperfusion therapy has led to a sharp decrease in the risks of heart failure and death after myocardial infarction and has led to questions about the add-on benefits of lifelong beta-blocker treatment in patients with a preserved left ventricular ejection fraction and no other primary indication for beta-blocker therapy. Contemporary large nationwide registries have often suggested an absence of long-term benefit of beta-blocker therapy in such patients, although data have been inconsistent. Results from a randomized trial have been lacking to evaluate late discontinuation of beta-blockers in the absence of chronic heart failure or left ventricular dysfunction.

We conducted the ABYSS (Assessment of Beta-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hospitalization) trial to evaluate beta-blocker continuation or interruption among patients with a history of myocardial infarction who had a left ventricular ejection fraction of at least 40%. We hypothesized that beta-blocker interruption would be clinically safe and that the patients' quality of life would improve.

Trial Population

Patients were eligible for enrollment if they had a history of myocardial infarction at least 6 months before enrollment and were being treated with a beta-blocker, regardless of the agent or the dose. Key exclusion criteria were chronic heart failure or a reduced left ventricular ejection fraction (<40%), any cardiac event during the 6 months before enrollment, or any other primary indication for beta-blocker therapy, such as arrythmia, migraine, or uncontrolled hypertension.

Intervention and Management

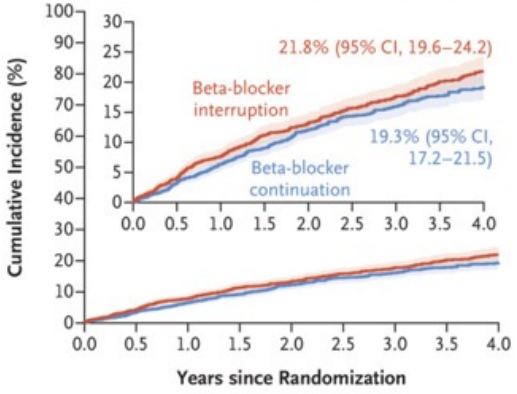
Patients were randomly assigned in a 1:1 ratio to a strategy of either interruption or continuation of beta-blocker therapy with the same agent at the same dose.

Characteristic	Beta-Blocker Interruption (N=1846)	Beta-Blocker Continuation (N=1852)
Demographic and cardiovascular risk		
Age — yr	63.5±11.2	63.5±10.9
Male sex — no. (%)	1530 (82.9)	1531 (82.7)
Median body-mass index (IQR)†	26.3 (23.9–29.4)	26.5 (24.1–29.6)
Current smoker — no. (%)	385 (20.9)	342 (18.5)
Hypertension — no. (%)	786 (42.6)	805 (43.5)
Diabetes — no. (%)	372 (20.2)	375 (20.2)
Dyslipidemia — no. (%)	948 (51.4)	994 (53.7)
Medical history		
ST-segment elevation myocardial infarction — no. (%)	1168 (63.3)	1162 (62.7)
Non–ST-segment elevation myocardial infarction — no. (%)	678 (36.7)	690 (37.3)
Median time from index myocardial infarction to randomization (IQR) — yr	2.9 (1.2–6.2)	2.8 (1.1–6.6)
Multivessel disease — no. (%)	955 (51.7)	979 (52.9)
Revascularization for index myocardial infarction — no./total no. (%)	1755/1846 (95.1)	1757/1852 (94.9)
Completeness‡	1601/1753 (91.2)	1619/1755 (92.1)
Percutaneous coronary intervention	1709/1755 (97.4)	1693/1757 (96.4)
Fibrinolysis	29/1755 (1.7)	46/1757 (2.6)
Coronary-artery bypass grafting	62/1755 (3.5)	83/1757 (4.7)
Peripheral vascular disease — no. (%)	104 (5.6)	83 (4.5)
Stroke or transient ischemic attack — no. (%)	56 (3.0)	67 (3.6)
Episode of heart failure — no. (%)§	34 (1.8)	26 (1.4)
Arrhythmia — no. (%)	7 (0.4)	5 (0.3)
Health status		
Left ventricular ejection fraction		
Median (IQR) — %	60 (52–60)	60 (52–60)
Patients with value of 40 to 50% — no. (%)	430 (23.3)	435 (23.5)
Residual angina — no. (%)	21 (1.1)	30 (1.6)
Median blood pressure (IQR) — mm Hg		
Systolic	132 (121–144)	131 (121–144)
Diastolic	77 (70–83)	77 (70–83)
Median resting heart rate (IQR) — beats/min	63 (57–71)	63 (57–71)

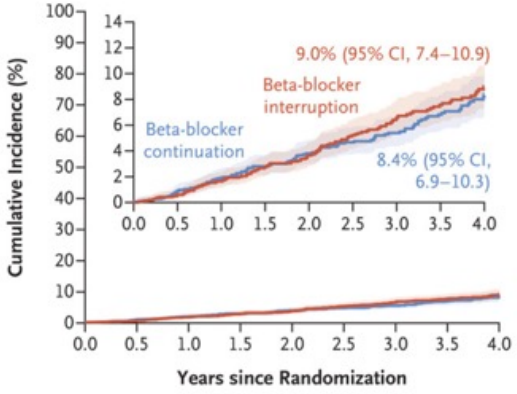
Primary and Secondary End Points

End Point	Beta-Blocker Interruption (N=1846)	Beta-Blocker Continuation (N=1852)	Risk Difference (95% CI)*	Hazard Ratio (95% CI)*	P Value†
Primary end point					
Composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reason — no./total no. (%)	432/1812 (23.8)	384/1821 (21.1)	2.8 (<0.1 to 5.5)	1.16 (1.01 to 1.33)	0.44
Secondary end points					
Composite of death, myocardial infarction, or stroke — no. (%)	132 (7.2)	126 (6.8)	0.4 (−1.3 to 2.0)	1.05 (0.82 to 1.34)	
Composite of death, myocardial infarction, stroke, or hospitalization for heart failure — no. (%)	155 (8.4)	141 (7.6)	0.8 (−1.0 to 2.5)	1.11 (0.88 to 1.39)	
Death — no. (%)	76 (4.1)	74 (4.0)			
Cardiovascular cause	28 (1.5)	21 (1.1)			
Noncardiovascular cause	44 (2.4)	48 (2.6)			
Undetermined cause	4 (0.2)	5 (0.3)			
Myocardial infarction — no. (%)	46 (2.5)	44 (2.4)			
Type 1: spontaneous	36 (2.0)	32 (1.7)			
Type 2: related to ischemic imbalance	1 (0.1)	0 (0.0)			
Type 4a: related to percutaneous coronary intervention	2 (0.1)	1 (0.1)			
Type 4b: related to stent thrombosis	8 (0.4)	11 (0.6)			
Stroke — no. (%)	18 (1.0)	19 (1.0)			
Ischemic	14 (0.8)	14 (0.8)			
Hemorrhagic	1 (0.1)	1 (0.1)			
Transient ischemic attack	3 (0.2)	4 (0.2)			
Hospitalization for cardiovascular reason — no. (%)	349 (18.9)	307 (16.6)			
Coronary-related reason	263 (14.2)	221 (11.9)			
Angina or ischemia	67 (3.6)	55 (3.0)			
Angiography	146 (7.9)	117 (6.3)			
Percutaneous coronary intervention	90 (4.9)	84 (4.5)			
Coronary-artery bypass grafting	4 (0.2)	4 (0.2)			
Heart failure	34 (1.8)	23 (1.2)			
Tachycardia					
Supraventricular	28 (1.5)	28 (1.5)			
Ventricular	6 (0.3)	7 (0.4)			
Syncope or dizziness	28 (1.5)	25 (1.3)			
Invasive procedure aside from pacemaker implantation	31 (1.7)	24 (1.3)			
Pacemaker or equivalent implantation	11 (0.6)	11 (0.6)			
Conduction disorder	2 (0.1)	2 (0.1)			
High blood pressure	5 (0.3)	3 (0.2)			
Peripheral artery disease or limb ischemia	34 (1.8)	23 (1.2)			
Aortic dissection or aneurysm	4 (0.2)	8 (0.4)			
Valvular reason	4 (0.2)	4 (0.2)			
Bleeding event	18 (1.0)	15 (0.8)			
Other cardiovascular event	18 (1.0)	11 (0.6)			

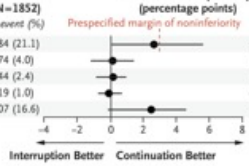
A Death, Myocardial Infarction, Stroke, or Hospitalization for Cardiovascular Cause (primary cardiovascular composite end point)



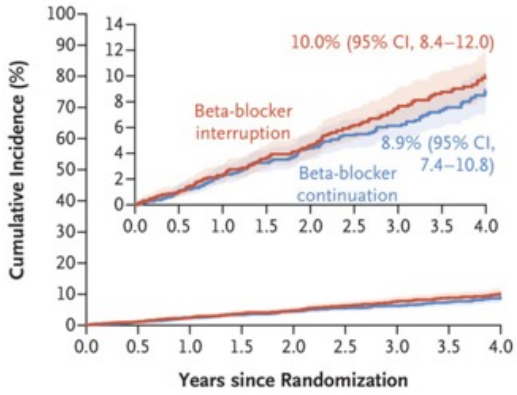
B Death, Myocardial Infarction, or Stroke



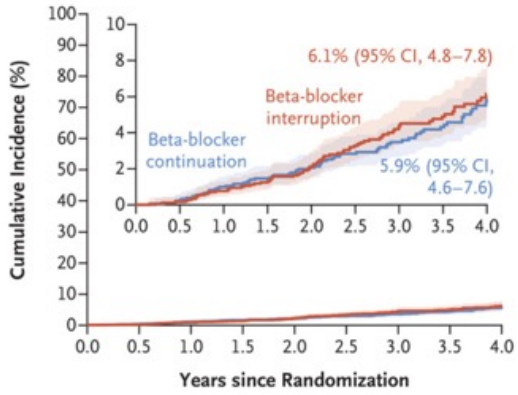
End Point	Beta-Blocker Interruption (N=1846)	Beta-Blocker Continuation (N=1852)	Risk Difference (95% CI) (percentage points)
	no. of patients with event (%)		Prespecified margin of noninferiority
Primary end point	432 (23.8)	384 (21.1)	2.8 (<0.1 to 5.5)
Death	76 (4.1)	74 (4.0)	0.1 (−1.2 to 1.4)
Myocardial infarction	46 (2.5)	44 (2.4)	0.1 (−0.9 to 1.1)
Stroke	18 (1.0)	19 (1.0)	−0.1 (−0.7 to 0.6)
Hospitalization for cardiovascular reason	349 (18.9)	307 (16.6)	2.3 (−0.1 to 4.8)



C Death, Myocardial Infarction, Stroke, or Hospitalization for Heart Failure

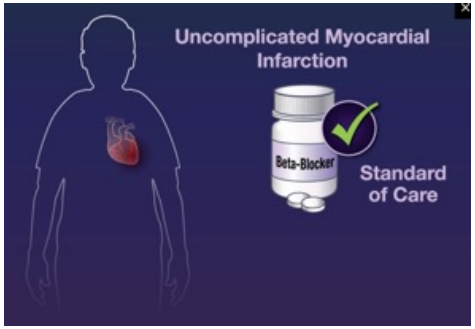


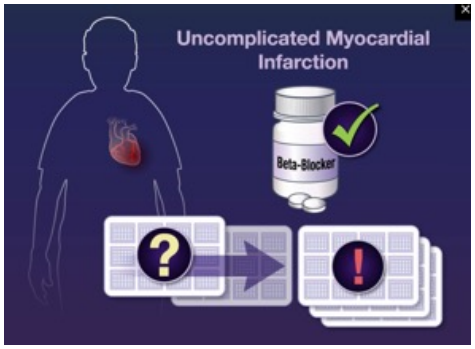
D Death from Any Cause



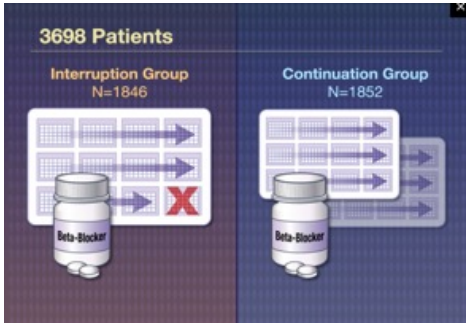
Scores on European Quality of Life–5 Dimensions (EQ-5D) Questionnaire.

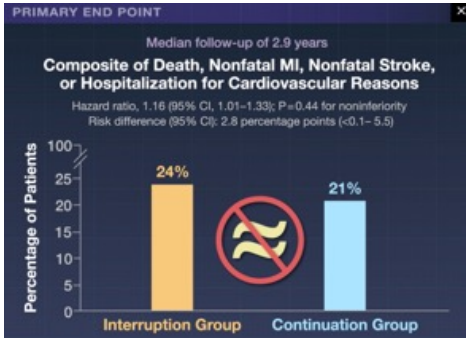
Variable	Beta-Blocker Interruption (N=1846)	Beta-Blocker Continuation (N=1852)	Difference (95% CI)
EQ-5D score at baseline			
No. of patients with data	1804	1821	
Mean score	0.866±0.181	0.866±0.182	
Median score (IQR)	0.910 (0.817–1.000)	0.910 (0.817–1.000)	
Peak EQ-5D score at 6 or 12 mo			
No. of patients with data	1674	1657	
Mean score	0.901±0.168	0.897±0.176	
Median score (IQR)	1.000 (0.872–1.000)	1.000 (0.872–1.000)	
Absolute change in EQ-5D score from baseline to last follow-up			
No. of patients with data	1639	1631	
Mean difference	0.033±0.150	0.032±0.164	0.002 (–0.008 to 0.012)†
Median difference (IQR)	0.000 (0.000–0.090)	0.000 (0.000–0.090)	


Uncomplicated Myocardial Infarction
Beta-Blocker
Standard of Care


Uncomplicated Myocardial Infarction
Beta-Blocker

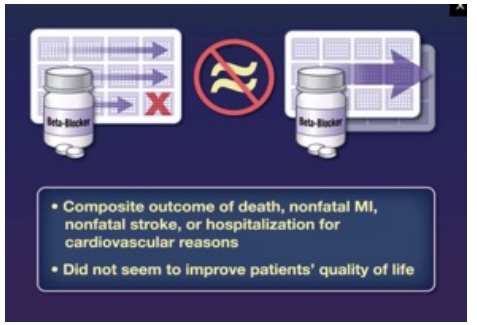

Trial
Beta-Blocker
• Safe
• Improve quality of life


3698 Patients
Interruption Group
N=1846
Continuation Group
N=1852
Beta-Blocker
Beta-Blocker

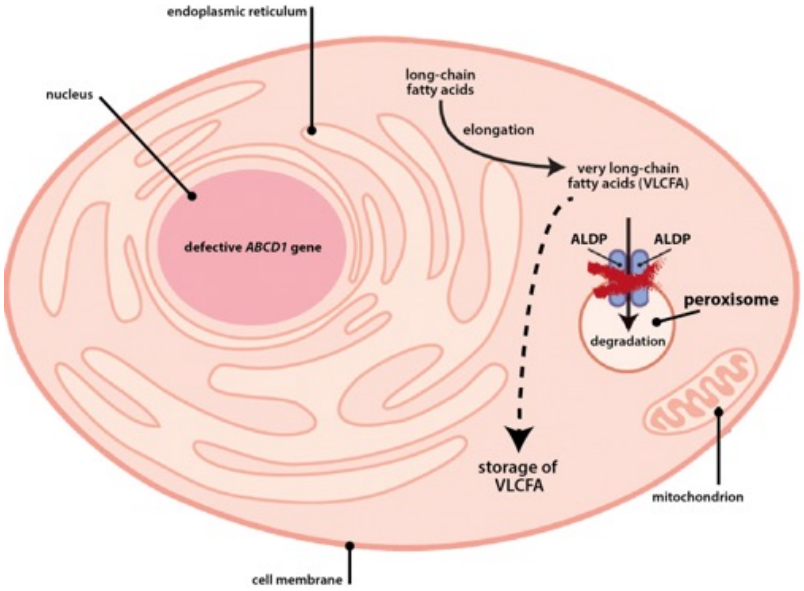

PRIMARY END POINT
Median follow-up of 2.9 years
Composite of Death, Nonfatal MI, Nonfatal Stroke, or Hospitalization for Cardiovascular Reasons
Hazard ratio, 1.16 (95% CI, 1.01–1.33); P=0.44 for noninferiority
Risk difference (95% CI): 2.8 percentage points (<0.1– 5.5)
Percentage of Patients
100
25
20
15
10
5
0
24%
21%
Interruption Group
Continuation Group

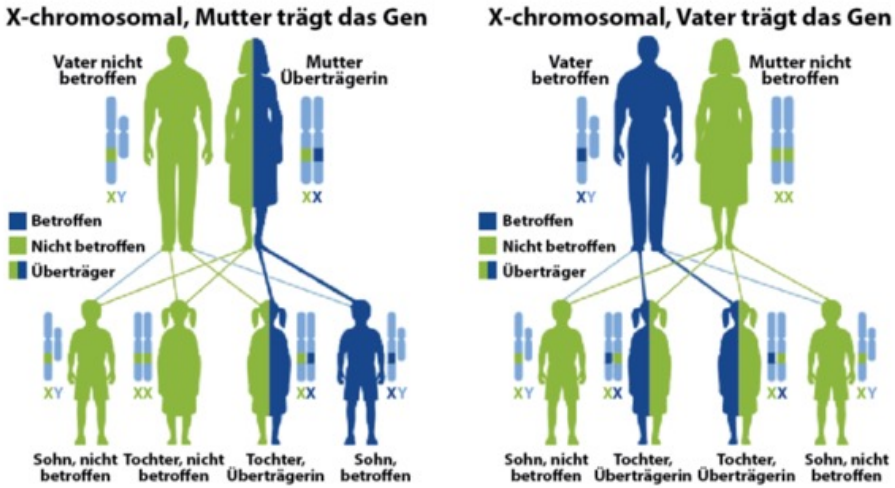

SECONDARY END POINT
Absolute Change in Quality of Life
Score range, 0 to 1; higher score indicates better health status; minimal clinically important difference, 0.05 points
Mean Absolute Change
0.05
0.04
0.03
0.02
0.01
0
0.033
0.032
Difference, 0.002
(95% CI, –0.008 to 0.012)
Interruption Group
Continuation Group


Beta-Blocker
Beta-Blocker
• Composite outcome of death, nonfatal MI, nonfatal stroke, or hospitalization for cardiovascular reasons


Beta-Blocker
Beta-Blocker
• Composite outcome of death, nonfatal MI, nonfatal stroke, or hospitalization for cardiovascular reasons
• Did not seem to improve patients' quality of life

Die Adrenoleukodystrophie (ALD) ist eine ernste fortschreitende genetische Krankheit, die die Nebennieren, das Rückenmark und die weiße Substanz des Nervensystems schädigt. Sie wurde erstmals 1923 erkannt und anfangs Schilder-Krankheit oder sudanophilie Leukodystrophie genannt. Im Jahre 1970 wurde die Bezeichnung Adrenoleukodystrophie geprägt. „Adreno“ bezieht sich auf die Nebennieren (glandulae adrenales); “leuko” auf die weiße Substanz des Gehirns, und „Dystrophie“ bedeutet Störung von Wachstum oder Entwicklung.

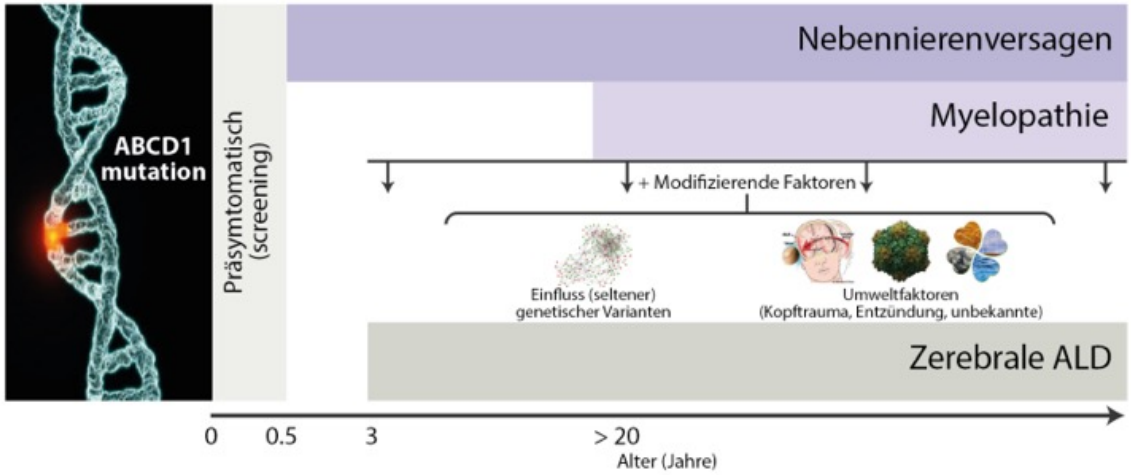


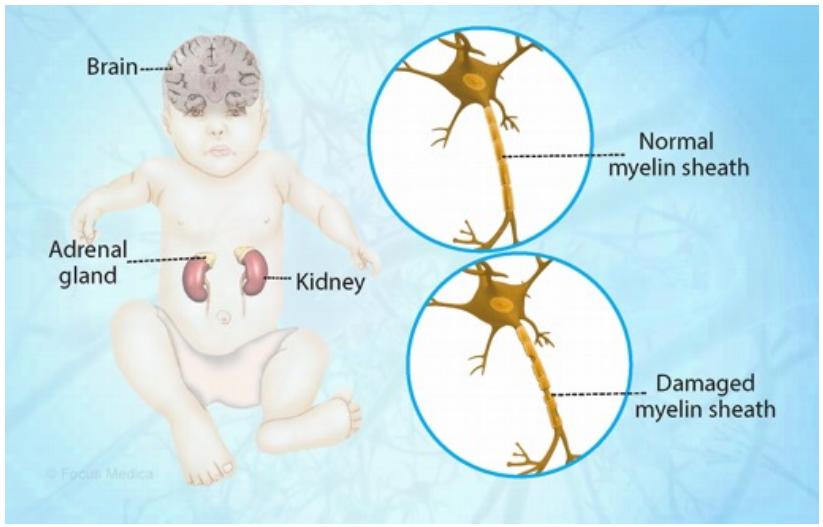


Das ABCD1–Gen ist auf dem X-Chromosom an Genlokus Xq28 kodiert.

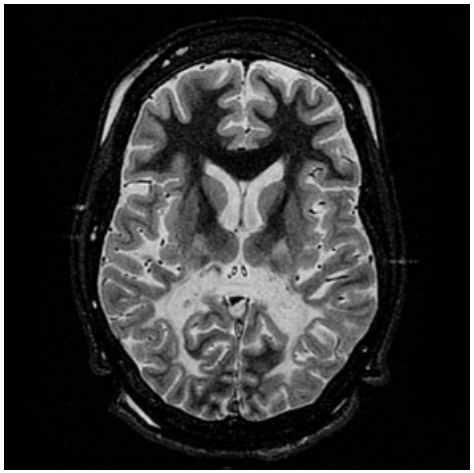
Das **Adrenoleukodystrophie-Protein**, kurz **ALDP**, ist ein ATP-abhängiges Transportprotein für sehr langkettige Fettsäuren (VLCFAs). Es befördert die Fettsäuren vom Zytosol ins Lumen des Peroxisoms und spielt somit eine wichtige Rolle beim Fettsäurestoffwechsel. ALDP zählt zu den ATPasen der AAA-Familie.

Die ALD ist eine erbliche Stoffwechselkrankheit, bei der ein Fehler in einem spezifischen Enzymsystem zur Anhäufung von sehr langkettigen Fettsäuren (Very Long Chain Fatty Acids, VLCFA) in allen Geweben des Körpers führt. Diese besonderen Fettsäuren (VLCFA) schädigen Zellen und Gewebe. Aus noch ungeklärten Gründen sind vor allem das Gehirn, das Rückenmark, die Hoden und die Nebennieren betroffen. Im Zentralnervensystem führt die Anhäufung der VLCFA schließlich zur Zerstörung der Markscheiden (des Myelins), welche die Nervenfasern umgeben und zu entsprechenden neurologischen Störungen. Die VLCFA schädigen auch die Zellen der Nebennieren und verursachen dadurch die Addison-Krankheit (Nebennierenversagen).





Die therapeutischen Möglichkeiten beschränken sich hauptsächlich darauf, die Symptome der Erkrankung zu lindern. So werden Medikamente gegen spastische Muskelkrämpfe verabreicht, ebenso wie Steroidhormone gegen die neurologischen Begleiterscheinungen. Interferon und Lovastatin bewirken nur selten eine Unterdrückung der entzündlichen Prozesse im Gehirn. Zur Erhöhung der Peroxisomenzahl wird die Gabe von 4-Phenylbutyrat erwogen.

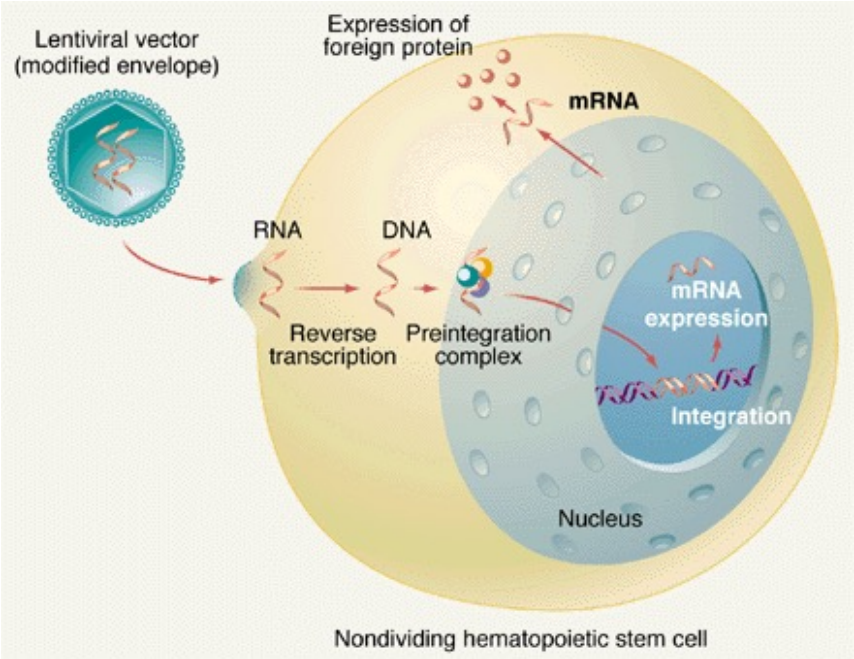


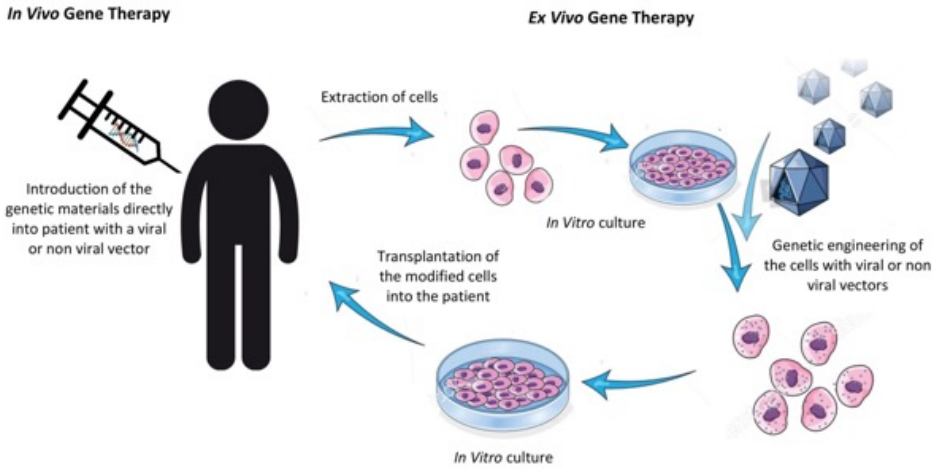
Die einzige kurative Therapie ist die Knochenmarktransplantation, die besonders effektiv ist, wenn sie bei der zerebralen Form in frühen Stadien der Neurodegeneration oder präsymptomatisch erfolgt. Der Mechanismus ist bisher nicht verstanden, es wird aber ein Austausch der myeloischen Zellen durch solche des Spenders vermutet, zu denen möglicherweise auch die Mikroglia des zentralen Nervensystems gehören. Bei HLA-identischen Spendern und frühzeitiger Stammzelltransplantation sind die langfristigen Ergebnisse gut.

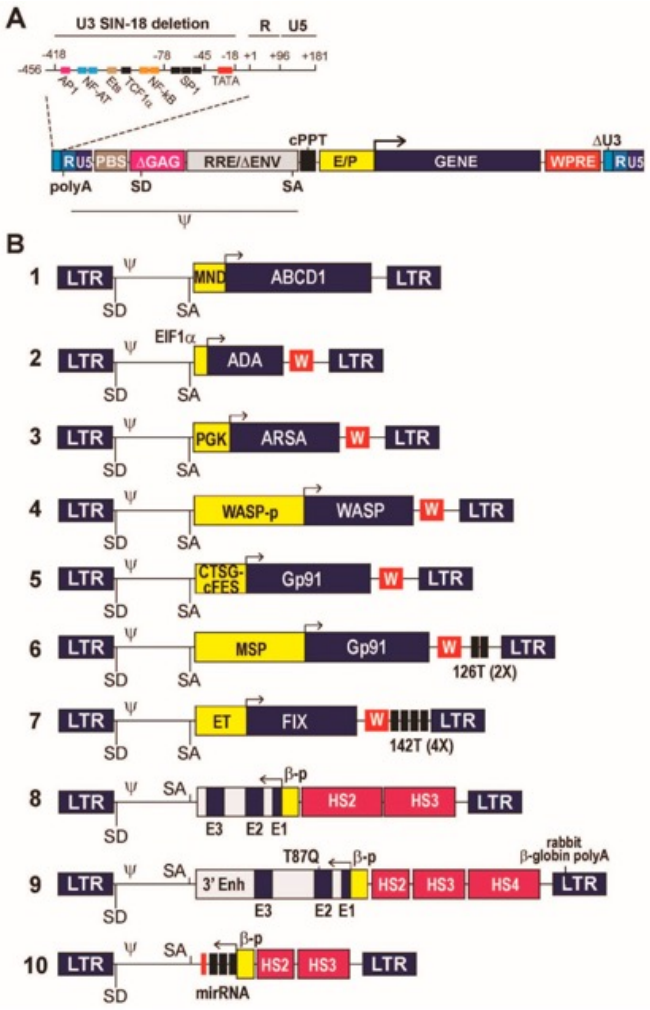
Gentherapie:

Voraussichtlich wird in nicht zu ferner Zukunft die Transplantation von autologen hämatopoetischen Zellen (vom Patienten selbst stammende Knochenmarkzellen), die mittels eines lentiviralen Vektors genetisch korrigiert wurden und dem Patienten wieder infundiert werden, eine zusätzliche therapeutische Option sein. Diese Einschätzung beruht auf den berichteten höchst ermutigenden Ergebnissen bei den ersten beiden so behandelten Patienten.

Lentiviral vectors are the most frequently used tool to stably transfer and express genes in the context of gene therapy for monogenic diseases. The vast majority of clinical applications involves an ex vivo modality whereby lentiviral vectors are used to transduce autologous somatic cells, obtained from patients and re-delivered to patients after transduction. Examples are hematopoietic stem cells used in gene therapy for hematological or neurometabolic diseases or T cells for immunotherapy of cancer. We review the design and use of lentiviral vectors in gene therapy of monogenic diseases, with a focus on controlling gene expression by transcriptional or post-transcriptional mechanisms in the context of vectors that have already entered a clinical development phase.







Schematic representation of HIV-1-derived lentiviral vectors (LVs) used in clinical applications of gene therapy for monogenic diseases. (A) A prototype, third-generation LV provirus, featuring a disabling (SIN) deletion of the enhancer/promoter sequences in the U3 region of the long terminal repeat (LTR) up to position -18 from the viral transcription start site. The enlarged portion of the LTR shows the original arrangement of the transcription factor binding sites and TATA box in the HIV-1 U3 region, deleted in the LV LTR. The poly(A) signal-containing R and the U5 regions of the LTR are retained. PBS, primer binding site; ΔGAG, deleted, non-coding portion of the GAG gene containing the D1 major HIV-1 splice donor (SD) site (CTG/GTGAGTAC); RRE, Rev-responsive element; ΔENV, deleted portion of the ENV gene containing the A7 HIV-1 splice acceptor (SA) site (TCGTTTCAG/A); cPPT, central polypurine tract; E/P, enhancer/promoter component of the expression cassette (the arrow represents the transcription start site); WPRE, woodchuck hepatitis virus post-transcriptional regulatory element; Ψ, extended packaging signal. (B) 1 to 10, schematic composition of the LVs described in the text. MND, modified enhancer/promoter of the murine myeloproliferative sarcoma virus; ABCD1, ATP-binding cassette, subfamily D, member 1 cDNA; EF1α, short promoter of the elongation factor 1α gene; ADA, Adenosine deaminase cDNA; W, WPRE; PGK, phosphoglycero kinase gene promoter; ARSA, arylsulfatase cDNA; WASPp, 1.6-kb extended Wiskott-Aldrich protein gene promoter; WASP, Wiskott-Aldrich protein cDNA; CTSG-cFES, hybrid promoter containing cFES regulatory regions and CTSG promoter. GP91, Gp91phox cDNA; MSP, myeloid-specific promoter; 126T (2×) tandem repeat of the miR-126 binding site; ET, liver-specific transthyretin promoter/enhancer; FIX, coagulation factor IX cDNA; 142T (4×) tetrameric repeat of the miR-142 binding site; E3, E2, E1, exons 3, 2 and 1 of the human β-globin gene; βp, human β-globin gene promoter; HS2, HS3, HS4, hypersensitive site 2, 3 and 4 regions of the β-globin locus-control region; 3’ Enh, 3’ enhancer of the human β-globin gene. T87Q, codon substitution causing a tryptophan to glutamine amino acid substitution at position 87 of the β-globin protein; miRNA, gene encoding a shRNA/miR hybrid small nuclear RNA targeting the BCL11A transcription factor mRNA.

Lentiviral Gene Therapy for Cerebral Adrenoleukodystrophy

Cerebral adrenoleukodystrophy is a severe form of X-linked adrenoleukodystrophy characterized by white-matter disease, loss of neurologic function, and early death. Elivaldogene autotemcel (eli-cel) gene therapy, which consists of autologous CD34+ cells transduced with Lenti-D lentiviral vector containing *ABCD1* complementary DNA, is being tested in persons with cerebral adrenoleukodystrophy.

In a phase 2–3 study, we evaluated the efficacy and safety of eli-cel therapy in boys with early-stage cerebral adrenoleukodystrophy and evidence of active inflammation on magnetic resonance imaging (MRI). The primary efficacy end point was survival without any of six major functional disabilities at month 24. The secondary end points included overall survival at month 24 and the change from baseline to month 24 in the total neurologic function score.

Conclusions

At a median follow-up of 6 years after lentiviral gene therapy, most patients with early cerebral adrenoleukodystrophy and MRI abnormalities had no major functional disabilities. However, insertional oncogenesis is an ongoing risk associated with the integration of viral vectors.

Adrenoleukodystrophy is an X-linked metabolic disease caused by pathogenic variants in *ABCD1* that lead to a deficiency in peroxisomal transporter ATP-binding cassette domain 1 (ABCD1 or adrenoleukodystrophy protein) and the accumulation of saturated very-long-chain fatty acids. Cerebral adrenoleukodystrophy develops in approximately 35% of affected boys before adulthood. Progressive white-matter inflammation and demyelination lead to the loss of cognitive and neurologic function, and early death ensues. Magnetic resonance imaging (MRI) of the head with gadolinium enhancement is useful in diagnosing cerebral disease before the onset of clinical symptoms.

Allogeneic hematopoietic stem-cell transplantation (HSCT) is the standard of care for cerebral adrenoleukodystrophy and can stabilize the disease and preserve function if it is performed at an early stage when demyelination is limited.

Autologous hematopoietic stem-cell gene therapy may provide an alternative treatment without many of the risks associated with allogeneic HSCT. Clinical data from small numbers of patients with early-stage cerebral adrenoleukodystrophy suggested that the use of lentiviral vectors containing *ABCD1* complementary DNA stabilized disease, but long-term follow-up in a larger patient population is lacking. We report the results of a completed initial 24-month study, a phase 2–3, multicenter, open-label study involving patients who received elivaldogene autotemcel (eli-cel) gene therapy transduced with Lenti-D lentiviral vector and who are participating in an ongoing long-term follow-up study.

Trial Design and Eligibility

The 24-month study and the ongoing 13-year follow-up study were designed to assess the safety and efficacy of eli-cel gene therapy in boys 17 years of age or younger who had cerebral adrenoleukodystrophy at enrollment.

Cell Collection and Eli-cel Infusion

CD34+ cells, obtained from patients by apheresis after mobilization with granulocyte colony-stimulating factor (G-CSF) with or without the hematopoietic stem-cell mobilizing agent plerixafor, were transduced with Lenti-D lentiviral vector under validated standard operating procedures, in accordance with Good Manufacturing Practice, to produce the patient-specific eli-cel drug product.

Clinical, Imaging, and Laboratory Assessments

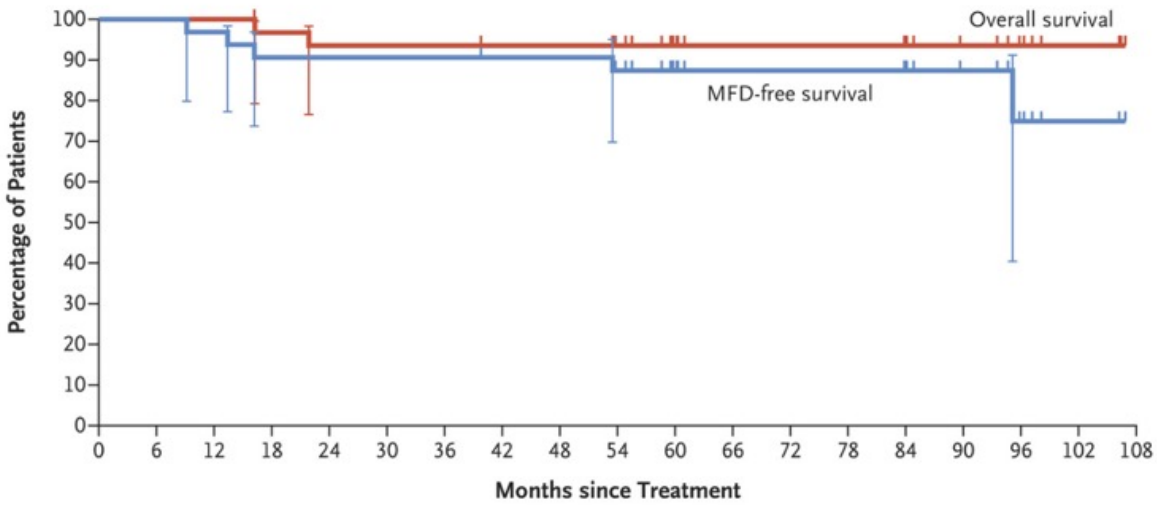
Patients were monitored for successful engraftment, which was defined by specific neutrophil and platelet counts. The primary efficacy end point was survival without any of the six major functional disabilities at month 24. The primary safety end point was acute (grade II or higher) or chronic GVHD by month 24.

Patient, Disease, and Transplantation Characteristics at Baseline.

Characteristic	Value (N = 32)
Patients	
Median age (range) — yr	6 (3–13)
Median duration of follow-up (range) — mo	60.2 (13.4–106.9)
Median Loes score (range)*	2 (1–9)
Median neurologic function score (range)†	0 (0–1)
Median time from enrollment to eli-cel infusion (range) — days	67 (58–89)
Mobilization, apheresis, and conditioning	
Median dose of granulocyte colony-stimulating factor (range) — μg/kg/day	10.0 (8.9–12.5)
Median dose of plerixafor (range) — mg/kg/day‡	0.24 (0.24–0.24)
Median no. of aphereses per mobilization cycle (range)	2 (1–4)
Median no. of mobilization cycles per patient (range)	1 (1–1)
Median estimated average area under the curve of busulfan (range) — μmol × min/liter/day§	4717.5 (4039–5041)
Median total dose of cyclophosphamide (range) — mg/kg	199.2 (150.6–212.9)
Eli-cel drug product	
Median vector copy number (range) — copies/diploid genome	1.2 (0.5–2.7)
Median lentiviral vector positive cells (range) — %	45 (19–67)
Median eli-cel dose (range) — CD34+ cells/kg	11.4 (5.0–20.1)

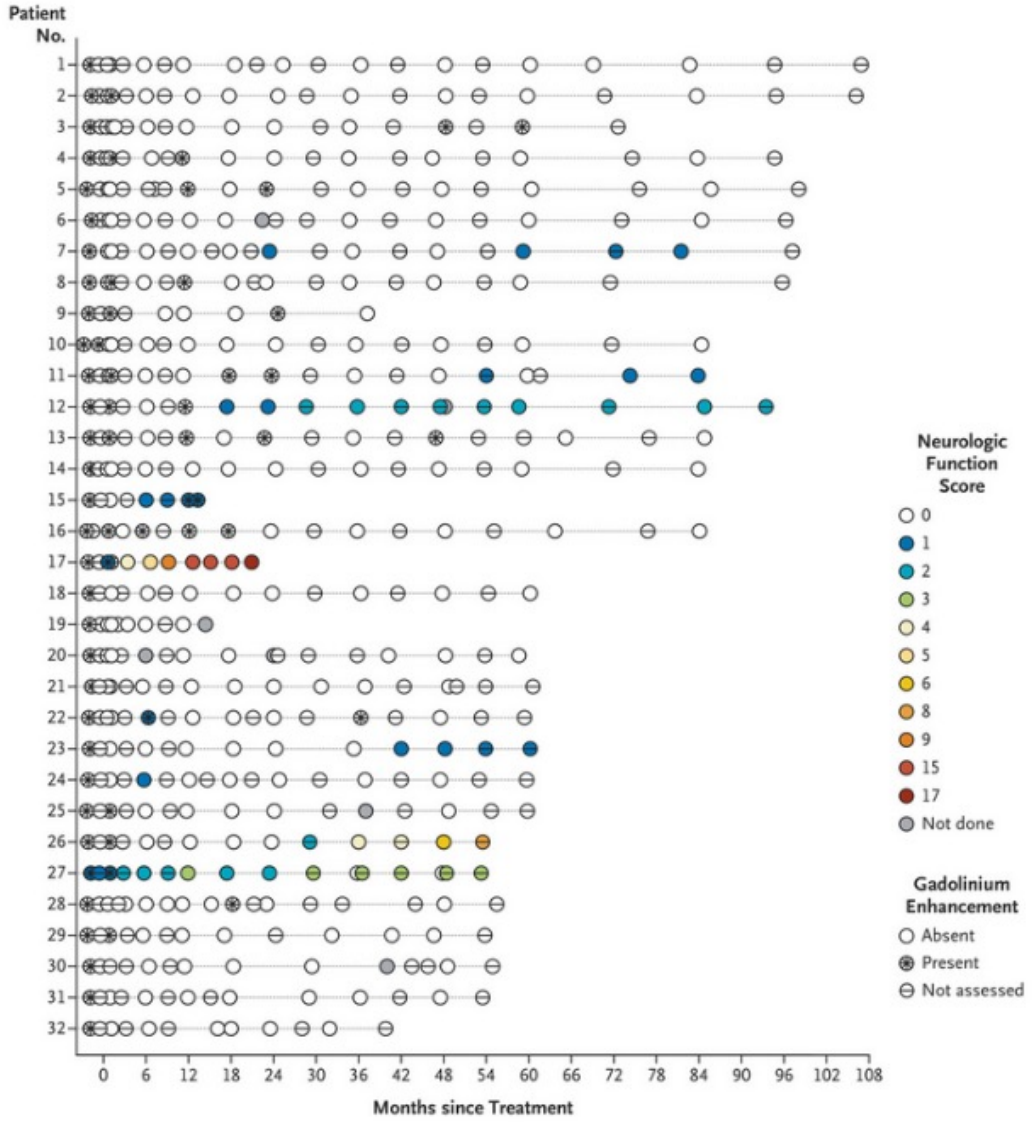
Incidence and Timing of Adverse Events.

Events	2-Yr Study (N=32)				13-Yr Follow-up Study (N=29)
	Mobilization to before Conditioning	Conditioning to before Neutrophil Engraftment	Neutrophil Engraftment through Month 12	After Month 12 through Month 24*	After Month 24 through Most Recent Assessment
	number of patients (percent)				
At least one adverse event	27 (84)	32 (100)	27 (84)	9 (28)	10 (34)
At least one adverse event attributed to mobilization or apheresis	15 (47)	0	0	0	0
At least one adverse event attributed to conditioning†	0	32 (100)	20 (62)	0	0
At least one adverse event attributed to eli-cel	0	2 (6)	1 (3)	0	1 (3)
Vomiting	0	2 (6)	0	0	0
Viral cystitis	0	0	1 (3)	0	0
Myelodysplastic syndrome	0	0	0	0	1 (3)
At least one serious adverse event‡	1 (3)	8 (25)	12 (38)	4 (12)	7 (24)
Blood and lymphatic system disorders	0	8 (25)	0	0	1 (3)
Cardiac disorders	0	0	0	1 (3)‡	0
Eye disorders	0	0	0	0	1 (3)
Gastrointestinal disorders	0	1 (3)	1 (3)	1 (3)	0
General disorders and administration site conditions	0	0	6 (19)	0	3 (10)
Hepatobiliary disorders	0	0	0	1 (3)	0
Infections and infestations	1 (3)	0	5 (16)	2 (6)	1 (3)
Injury, poisoning, and procedural complications	0	0	2 (6)	0	0
Metabolism and nutrition disorders	0	0	1 (3)	0	0
Musculoskeletal and connective-tissue disorders	0	0	0	1 (3)	0
Benign, malignant, or unspecified neoplasms	0	0	0	0	1 (3)
Nervous system disorders§	0	1 (3)	1 (3)	2 (6)	5 (17)
Psychiatric disorders	0	0	0	0	1 (3)
Renal and urinary disorders	0	0	0	1 (3)	0
Respiratory, thoracic, and mediastinal disorders	0	0	0	1 (3)	0



Kaplan–Meier Analyses of Overall Survival and Survival Free of Major Functional Disabilities.

Survival free of major functional disabilities (MFDs) was defined as survival without receipt of allogeneic hematopoietic stem-cell transplantation and free of the following six MFDs: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement. Data from patients who withdrew from the study and whose final outcome was unknown were censored at the time they withdrew from the study. Twenty-six patients are MFD-free and remain in long-term follow-up. One patient died of transplantation-related causes after withdrawal from the study after undergoing allogeneic hematopoietic stem-cell transplantation, which had been performed owing to disease progression detected by radiography; this death is included in the Kaplan–Meier estimate. I bars indicate 95% confidence intervals; the widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing.



Individual Patient Results for Gadolinium Enhancement Status and Neurologic Function Score Over Time (Secondary End Points).

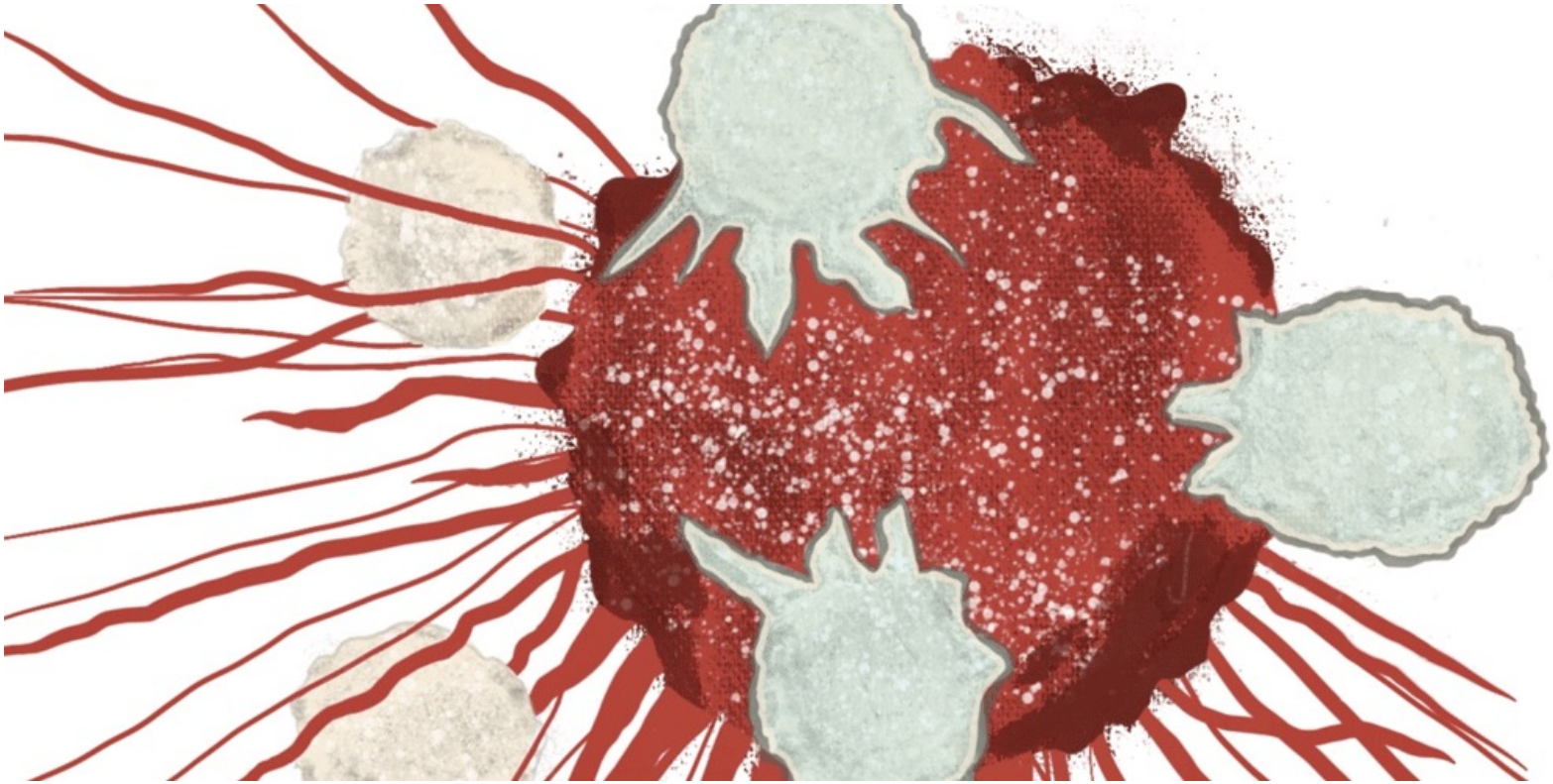
The neurologic function score ranges from 0 to 25, with higher scores indicating more severe deficits.

Discussion

This study of gene therapy with autologous genetically modified hematopoietic stem cells showed the possibility of lengthening disability-free survival in patients with cerebral adrenoleukodystrophy. The current analyses extend interim results published in the *Journal* to the full study population (32 patients), in which 26 of the 32 patients (Kaplan–Meier estimate, 75%) remain in the study and have been free of major functional disabilities for a median duration of 60.6 months, with a maximum duration of follow-up of 8.9 years in two patients. The incidence of serious adverse events related to eli-cel was low. During the long-term follow-up period, 5 patients had new onset of seizures, and 4 of these 5 patients had evidence of worsening Loes scores. At month 48, overall survival was 94% and survival free of major functional disabilities was 91%. The rates that have been published with respect to allogeneic HSCT in patients with similar clinical status at baseline are 77.8% for 4-year overall survival and 63.2% for the percentage of patients with no major functional disabilities. However, comparative inferences cannot be drawn since these populations were not directly compared.

As expected with autologous therapy, GVHD did not occur, and although conditioning-related serious infections occurred, they did not result in death. These findings contrast with what has been shown to occur with allogeneic HSCT during the peritransplantation period in which serious infections (in up to 29% of patients), acute GVHD in the first 100 days (in 18 to 31% of patients), and graft failure (in up to 24% of patients with grafts from unrelated donors) can contribute to transplantation-related mortality, which remains high at 8 to 15% in persons with cerebral adrenoleukodystrophy. The duration of hospitalization for patients undergoing transplantation was shorter with eli-cel (median, 29 days [range, 15 to 54]) than with allogeneic HSCT (51 days [range, 25 to 240] as reported in 59 patients in a contemporaneous study).

Historically, lentiviral vectors included strong viral promoters which had a side effect of insertional mutagenesis, nuclear DNA mutations that affect the function of a gene. These strong viral promotors were shown to be the main cause of cancer formation.



Hematologic Cancer after Gene Therapy for Cerebral Adrenoleukodystrophy

Gene therapy with elivaldogene autotemcel (eli-cel) consisting of autologous CD34+ cells transduced with lentiviral vector containing *ABCD1* complementary DNA (Lenti-D) has shown efficacy in clinical studies for the treatment of cerebral adrenoleukodystrophy. However, the risk of oncogenesis with eli-cel is unclear. We performed integration-site analysis, genetic studies, flow cytometry, and morphologic studies in peripheral-blood and bone marrow samples from patients who received eli-cel therapy in two completed phase 2–3 studies (ALD-102 and ALD-104) and an ongoing follow-up study (LTF-304) involving the patients in both ALD-102 and ALD-104.

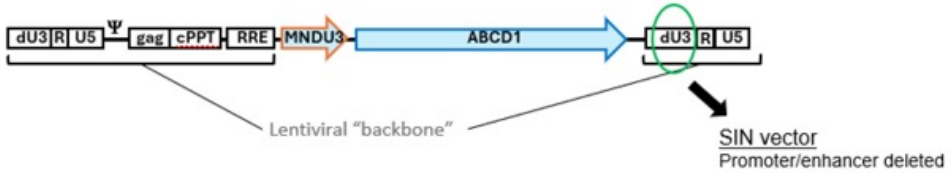
Conclusions

Hematologic cancer developed in a subgroup of patients who were treated with eli-cel; the cases are associated with clonal vector insertions within oncogenes and clonal evolution with acquisition of somatic genetic defects.

To express *ABCD1* complementary DNA (cDNA), the elivaldogene autotemcel (eli-cel) gene therapy, which contains autologous CD34+ cells transduced with Lenti-D lentiviral vector, uses a virally derived synthetic regulatory element that includes the U3 segment of the myeloproliferative sarcoma virus long terminal repeat with the negative control region deleted and the DL587 endogenous retrovirus primer binding site substituted (MNDU3).

Supplemental Figure S1: Schematic of the integrated lenti-D LVV.

Ψ Packaging symbol; RRE, Rev responsive element; cPPT, central polypurine tract.



Adrenoleukodystrophy is an X-linked metabolic disease caused by mutations in the *ABCD1* gene that lead to a deficiency in encoding peroxisomal transporter ATP-binding cassette domain 1 (adrenoleukodystrophy protein) and the buildup of very-long-chain fatty acids in tissue and plasma. Cerebral adrenoleukodystrophy develops in approximately 35% of affected boys before adulthood and results in progressive destruction of white matter, loss of cognitive and neurologic function, and early death if untreated.

Cerebral adrenoleukodystrophy is caused by germline pathogenic variants in the *ABCD1* peroxisomal transporter, which results in the toxic accumulation of very-long-chain fatty acids, progressive loss of white matter, and deteriorating neurologic function.

We evaluated eli-cel in two completed clinical studies (ALD-102 and ALD-104), with ongoing long-term follow-up in one integrated study (LTF-304) involving the patients in both the ALD-102 and the ALD-104 study.

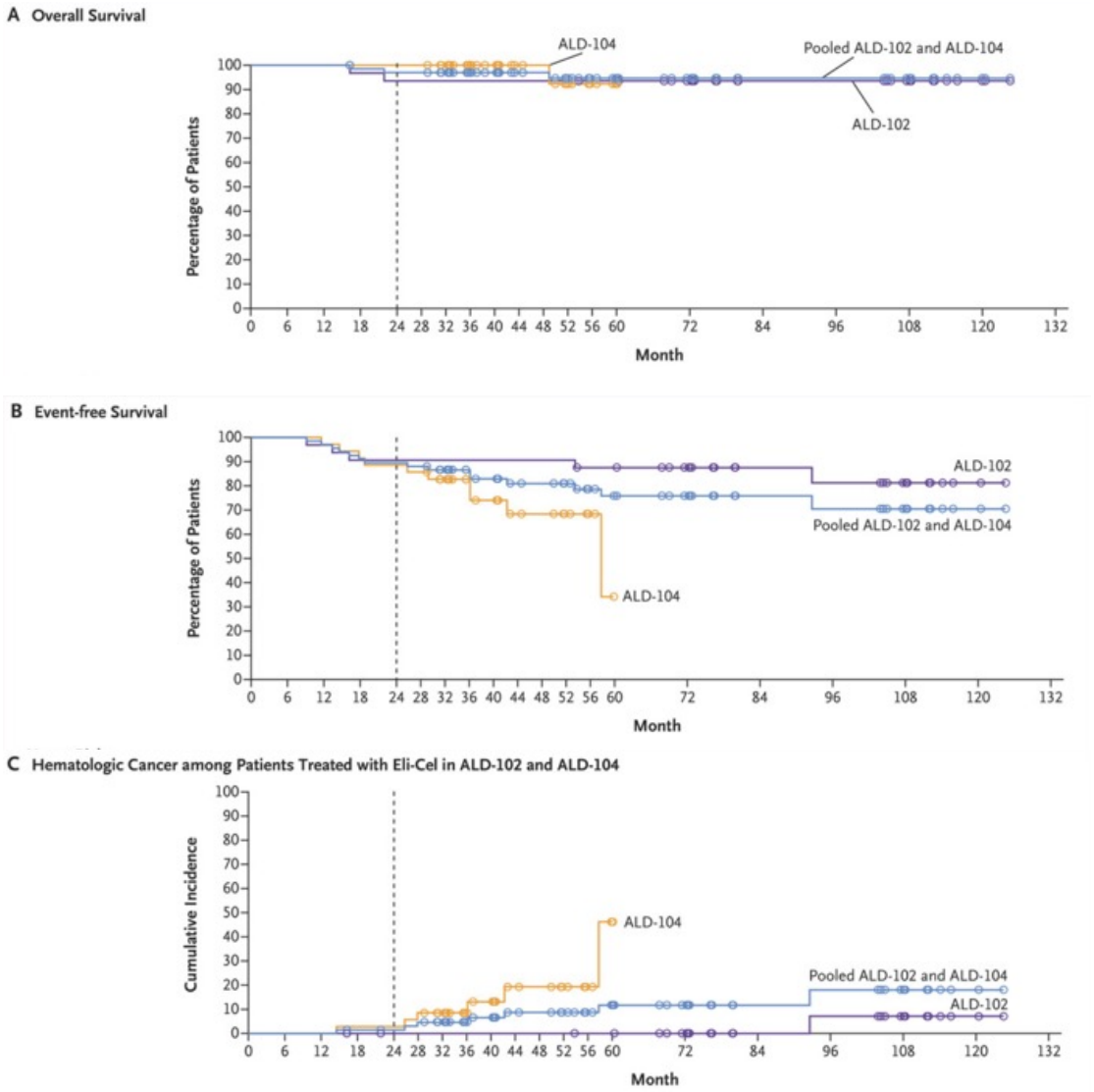
Although the integration of lentiviral vectors has proved to be safe in previous clinical studies of gene therapy, two reports have described clonal expansions related to lentiviral vector insertions associated with abnormal splicing events. We comprehensively characterize the clinicopathological and genetic features of seven cases of hematologic cancer (as of April 25, 2024) in patients who received eli-cel (one patient in the ALD-102 study and six patients in the ALD-104 study).

Patients

A total of 67 patients received eli-cel infusion during the completed studies (32 patients in the ALD-102 study and 35 patients in the ALD-104 study). As of April 25, 2024, the probability of event-free survival (survival without major functional disabilities, hematologic cancer, or rescue-cell administration or allogeneic hematopoietic stem-cell transplantation) at 4 years was 81.0% (95% confidence interval [CI], 68.8 to 88.8).

Selected Baseline and Treatment Characteristics of Presented Patients.

Characteristic	Patient 3	Patient 46	Patient 36	Patient 44	Patient 54	Patient 33	Patient 61	Patients without Hematologic Cancer (N=60)
				Value				*Median (range)*
Age at eli-cel infusion — yr	5	11	13	10	9	6	7	6 (4–14)
History of blood disease	No	No	No	No	No	No	No	
Baseline blood count†								
Hemoglobin — g/dl	11.7	13.7	12.8	14.9	13.1	12.8	10.2	13.5 (10.5–15.7)
White cells — $\times 10^{-9}$/liter	6.9	4.7	3.2	7.29	4.8	8	6	6.7 (3.5–15.7)
Platelets — $\times 10^{-9}$/liter	347	245	405	336	165	243	157	303 (191–492)
Mobilization regimen	G-CSF	G-CSF and plerixafor	G-CSF and plerixafor	G-CSF and plerixafor	G-CSF and plerixafor	G-CSF and plerixafor	G-CSF and plerixafor	
Conditioning regimen	Busulfan–cyclophosphamide	Busulfan–fludarabine	Busulfan–fludarabine	Busulfan–fludarabine	Busulfan–fludarabine	Busulfan–fludarabine	Busulfan–fludarabine	
Estimated average area under the plasma busulfan concentration–time curve per day — min×μmol/liter	4729	4995	5586	5282	5473	5640	5160	4970 (3478–5695)
VCN in drug product — c/dg	1.6	1.3	1.8	1.2	1.4	3.1	1.1	1.2 (0.5–2.7)
Total cells in drug product — $\times 10^{-6}$/kg of body weight	6	5.7	12.1	15.1	9.6	22.8	7.7	12.0 (5.0–38.2)
Lentiviral vector cells in drug product — %	62	ND	70	45	60	84	41	47 (19–74)
Platelet engraftment — days after drug infusion	37	106	104	24	21	34	58	29 (14–108)
Neutrophil engraftment — days after drug infusion	37	14	12	12	15	13	17	13 (11–41)

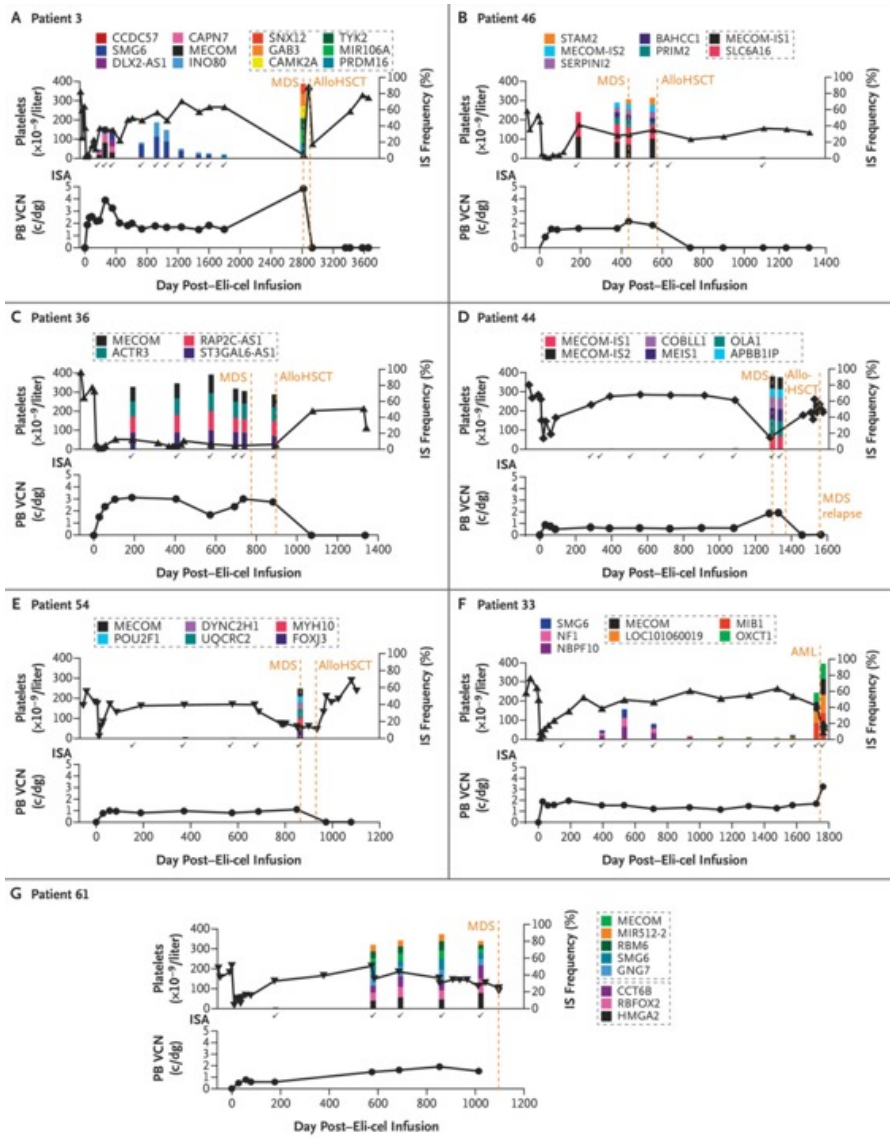


Overall Survival, Event-free Survival, and Hematologic Cancer.

Shown are Kaplan–Meier curves for overall survival (Panel A), event-free survival (Panel B), and hematologic cancer (Panel C) in patients treated with eli-cel. Purple lines represent the ALD-102 study, orange lines represent the ALD-104 study, and blue lines represent pooled date from the ALD-102 and ALD-104 studies. The ongoing long-term follow-up study (LTF-304) involving patients from both the ALD-102 and ALD-104 studies began after month 24 (dashed line). Results for cumulative incidence curves of hematologic cancer were consistent when death and allogeneic hematopoietic stem-cell transplantation (HSCT) for progression or patient withdrawal were included as competing events. Exposure-adjusted incidence rate per 100 person-years was calculated as 100 times the number of events divided by the total person-years of follow-up. For patients who received a diagnosis of hematologic cancer or who underwent allogeneic HSCT, the follow-up time is up to the earliest time the diagnosis was received or when the patient underwent allogeneic HSCT. The data shown are as of April 25, 2024.

Bone Marrow Findings and Hematologic Cancer Diagnosis and Treatment.

Characteristic	Patient 3	Patient 46	Patient 36	Patient 44	Patient 54	Patient 33	Patient 61
Bone marrow findings							
Bone marrow cell morphologic characteristics	Mo 92: Mild hypocellularity (60%) Increased myeloid–erythroid ratio and left-shifted myeloid maturation Blasts, 15% Trilineage dysplasia present including abundant micromegakaryocytes	Mo 12: Moderate hypocellularity (40–50%); <10% Atypical megakaryocytes† Blasts, <5% Mo 14 and 18: 15% Hypocellularity with progressive megakaryocytic dysplasia including micromegakaryocytes	Mo 26: Normocellularity (80%), with trilineage hematopoietic maturation Dysplastic megakaryocytes Blasts, 1%	Mo 42: Mild hypocellularity (50–60%) with dysplastic megakaryocytes Myeloblasts, 8%, showing abnormal coexpression of CD7	Mo 28: Myelodysplasia with 18% blasts	Mo 57: AML with myelomonocytic features 48–65% blasts Normocellular bone marrow (80–90%)	Mo 36: Diminished cellularity Presence of a group of myeloid blast cells (7%), including a blast cell with an Auer body consistent with myeloid MDS
Chromosome and karyotype analysis	Normal	Presumed germline aberration at chromosome 14	Normal	Normal	Monosomy 7, 80%	Normal	NA
MDS FISH	Normal	Normal	Normal	Normal	NA	Normal	NA
Targeted deep sequencing with RHP	Somatic mutations in *KRAS* c.35G>C (p.G12A) at 14% VAF, and *NRAS* c.35G>A (p.G12D) at 3% VAF and *JAK2* c.2696T>C (p.I899T), VUS at 48% VAF	Germline VUS in *CDKN2A* c.168C>G (p.S56R) at a VAF of 41%	No somatic mutations in the genes screened	Pathogenic *WT1* c.1142C>A (p.S381*) at 39% VAF and a VUS in *CDKN2B* c.34G>A (p.G12S) at 38% VAF	Mutation in *RUNX1*	Somatic mutation in *KRAS* c.35G>A(p.G12) at 14.6% VAF (206x consensus coverage)	Mutation in *RUNX1* c.496 C>G (p.R166G) at 8.7% VAF (922x consensus frequency)
Diagnosis and treatment of hematologic cancer							
Age at diagnosis — yr	12	12	15	13	11	11	10
Diagnosis	MDS-EB	MDS-ULD	MDS-ULD	MDS-EB	MDS-EB	AML	MDS
Time of diagnosis — mo since eli-cel infusion	92	14	26	42	28	57	36
Pretransplantation therapy	Cytoreductive therapy	NA	NA	Cytoreductive therapy	Cytoreductive therapy	Cytoreductive therapy and chemotherapy	NA
Transplantation therapy	Myeloablative conditioning and allogeneic HSCT	Myeloablative conditioning and allogeneic HSCT	Myeloablative conditioning and allogeneic HSCT	Myeloablative conditioning and allogeneic HSCT	Myeloablative conditioning and allogeneic HSCT	NA	NA
Donor type	Unrelated mismatch cord donor	Parent haplotransplant	Parent haplotransplant	Sibling haplotransplant	Parent haplotransplant	NA	NA
Relative time of allo-HSCT — mo	95	19	29	45	31	NA	NA
Relative time of post–allogeneic HSCT bone marrow investigation — mo	96	21	31	52§	33	NA	NA
Post–allogeneic HSCT bone marrow findings	100% donor cells; morphologic, immunophenotypic, and molecular remission	100% donor cells; flow cytometry, FISH, and karyotype, normal; no mutations detected with RHP	100% donor cells; flow cytometry and morphologic analyses, normal	>97% donor cells,§ trace recipient; morphologic analyses, normal; cytogenetics, normal; MRD, negative	100% donor cells	NA	NA
Current status	Mo 120: alive, free of MFD, MDS resolved	Mo 43: alive, free of MFD, MDS resolved	Mo 49: died from GVHD	Mo 52: alive, free of MFD, MDS relapsed (MRD, negative at last follow-up)§	Mo 37: alive, MDS resolved	Mo 61: alive, free of MFD, AML unresolved	Mo 37: alive, MDS unresolved

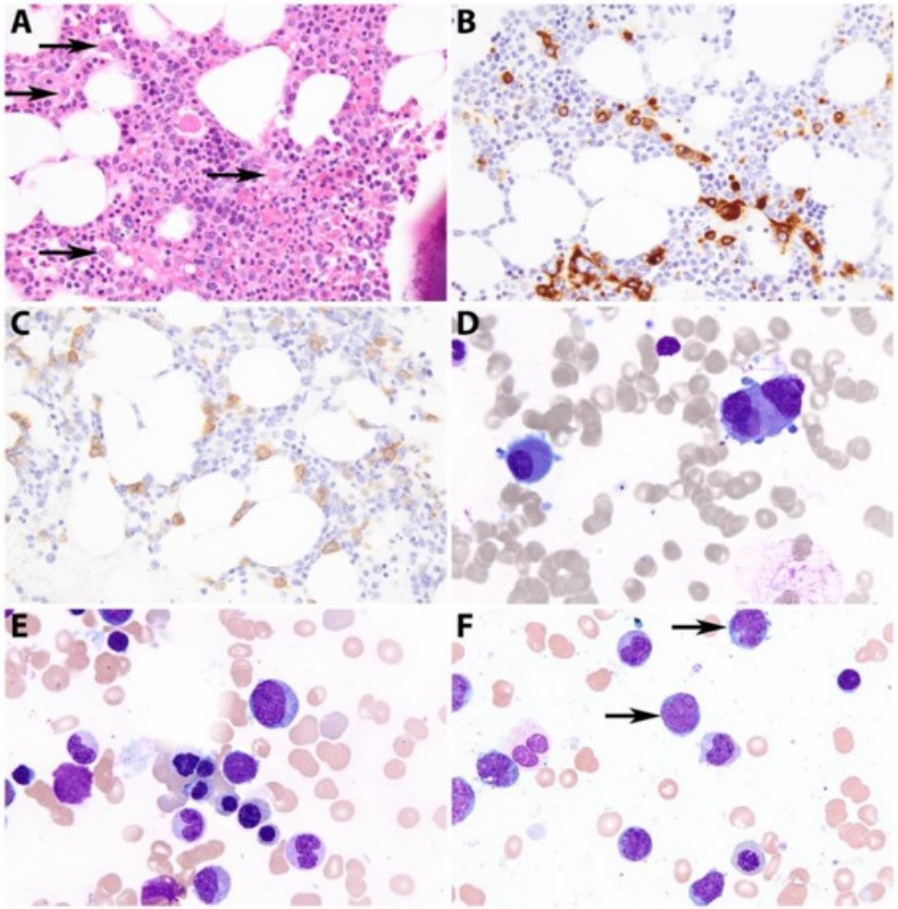


Integration-Site (IS) Analysis, Platelet Counts, and Peripheral-Blood Vector Copy Number Over Time for Individual Patients.

Shown are the results (as of April 25, 2024) for Patients 3, 46, 36, 44, 54, 33, and 61. Check marks indicate the timing of the IS analysis (ISA), which was performed on peripheral-blood samples. ISs from different time points that are located within five base pairs are considered the same IS. The plot shows all ISs that occur with a relative frequency of 10% or more at any time point or any two or more ISs in a clone with a relative frequency of 5% or more at any time point. Multiple ISs in the same clone were defined as multiple ISs with a relative frequency within 20% of each other. Genes in gray dashed boxes represent genes within the same clone. The limit of quantification for IS analysis was a relative frequency of 5%. The MECOM gene involved was 3+168905559 for Patient 3, 3+169089800 (MECOM-IS1) and 3-168929610 (MECOM-IS2) for Patient 46, 3+168881163 for Patient 36, 3+169034816 (MECOM-IS1) and 3−168952545 (MECOM-IS2) for Patient 44, 3-168884077 for Patient 54, 3+169089416 for Patient 33, and 3-168890747 for Patient 61. AlloHSCT denotes allogeneic hematopoietic stem-cell transplantation, MDS myelodysplastic syndrome, PB peripheral blood, and VCN vector copy number.

Supplemental Figure S2: Histopathologic features of MDS occurring post-gene therapy for CALD in Patient 44.

A) Bone marrow core biopsy findings include frequent small dysplastic megakaryocytes and micromegakaryocytes (arrows). B) CD61 immunohistochemical stain shows that megakaryocytes are increased and overtly dysplastic including frequent micromegakaryocytes. C) CD34 immunohistochemical stain shows an increase in CD34+ blasts making up approximately 15% of total cellularity overall. D) Aspirate smear showing dysplastic small megakaryocytes with hypolobated/simplified nuclei and separated nuclear lobes. E) Aspirate smear showing dyserythropoiesis including erythroid precursors with irregular nuclear contours. F) Aspirate smear findings included increased blasts (arrows). [A: H&E stain, 200x original magnification. B-C: 200x original magnification. D-F: Wright-Giemsa stain, 1000x original magnification.]



Results of Integration-Site Analysis.

Characteristic	Patients with Hematologic Cancer (N=7)	Patients without Hematologic Cancer (N=60)	All Patients (N=67)
Median highest total no. of unique mappable integration sites within each patient across all visits (range)	9748 (2548–14,796)	6732 (582–15,683)	6973 (583–15,683)
Median highest relative frequency of any unique mappable integration site within each patient across all visits (range)	25 (18–34)	11 (0–55)	14 (0–55)
Persistent oligoclonality at any time — no. (%)†			
Yes	6 (86)	23 (38)	29 (43)
No	1 (14)	37 (62)	38 (57)
Current persistent oligoclonality — no./total no. (%)‡			
Yes	5/6 (83)	15/23 (65)	20/29 (69)
No	1/6 (17)	8/23 (35)	9/29 (31)
Current oligoclonality — no. (%)§			
Yes	7 (100)	21 (35)	28 (42)
No	0	39 (65)	39 (58)
Persistent integration site in a known oncogene at any time — no. (%)¶			
Yes	6 (86)	16 (27)	22 (33)
No	1 (14)	44 (73)	45 (67)
Current persistent integration site in a known oncogene — no./total no. (%)‖			
Yes	5/6 (83)	13/16 (81)	18/22 (82)
No	1/6 (17)	3/16 (19)	4/22 (18)
Current integration site in a known oncogene — no. (%)**			
Yes	7 (100)	16 (27)	23 (34)
No	0	44 (73)	44 (66)

Discussion

As of April 25, 2024, among the 67 patients treated with eli-cel, 7 patients (10%) have received a diagnosis of hematologic cancer (338 person-years of total follow-up; incidence rate, 2.1 per 100 person-years; 95% CI, 0.8 to 4.2). Hematologic cancer was diagnosed in 1 of 32 patients (3%) treated in the ALD-102 study with 222 person-years of follow-up (incidence rate, 0.5 per 100 person-years; 95% CI, 0 to 2.5) and in 6 of 35 patients (17%) in the ALD-104 study with 116 person-years of follow-up (incidence rate, 5.2 per 100 person-years; 95% CI, 1.9 to 10.9).

We hypothesize that the specific features of Lenti-D vector design, such as the presence of enhancer sequences, overexpression of the transgene *ABCD1* (which may affect the ability of cells to engraft in the administered product), aspects of the conditioning regimen for eli-cel, or G-CSF use, play a role in mediating insertional oncogenesis. The way these factors individually, in combination, or with other unidentified variables interact with one another to lead to genotoxicity is unclear. However, we believe that our results should inform future studies of gene therapy regarding the choice of promoter used when designing lentiviral vectors. In addition, expression of the transgene should be high enough to arrest disease progression but also be lineage-restricted, if possible, and low enough to reduce the likelihood of genotoxicity and genomic instability. Our results suggest that patients who are considering lentiviral vector gene therapy should continue to be educated on the risk of hematologic cancer and, if treated, monitored closely. Finally, for patients treated with eli-cel, one intervention to reduce the risk of cancer may be to consider the use of busulfan–cyclophosphamide as the preparative regimen instead of busulfan–fludarabine.

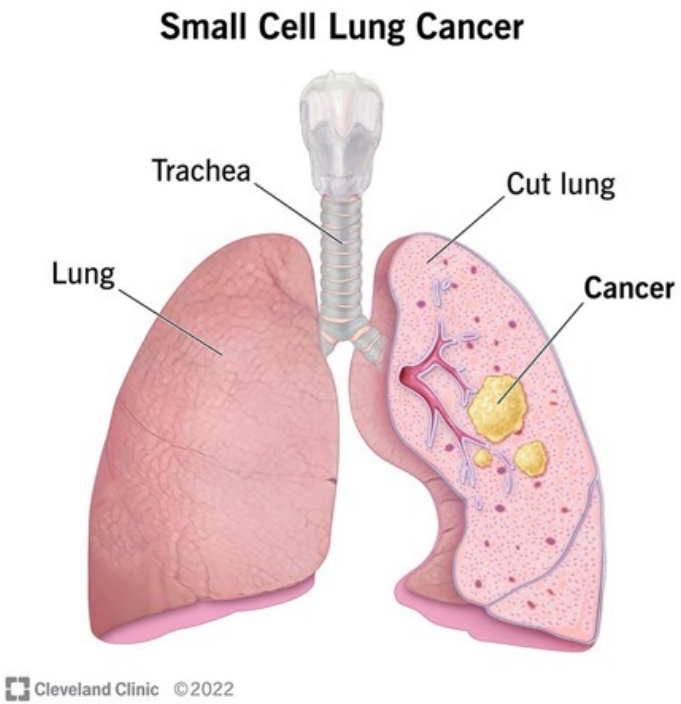
Weighing the Risks of Lentiviral Gene Therapy for Cerebral Adrenoleukodystrophy

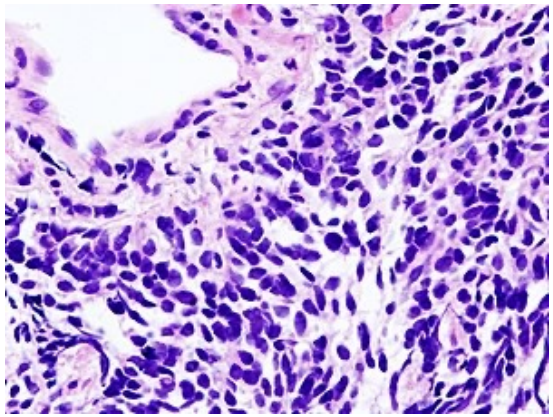
More than 30 years ago, the first transplantation with autologous hematopoietic stem cells modified with integrated murine retroviral vectors carrying potentially therapeutic genes was performed in patients with serious human disorders. The past decade has been marked by an acceleration in the publication of data from clinical trials and in regulatory approvals for therapies that use viral gene addition to treat hemoglobinopathies, immunodeficiencies, and metabolic neurologic disorders such as cerebral adrenoleukodystrophy. After the induction of numerous hematologic cancers linked to activation or dysregulation of nearby oncogenes by viral promoter–enhancers contained within the retroviral vector among patients enrolled in early clinical trials, the field shifted to the use of lentiviral vectors, which have an integration pattern that was predicted to be safer and that had lowered the risk of genotoxic hematologic cancers in animal models.

First, the high risk appears to be closely related to the inclusion of the strong viral MND promoter (an engineered, artificial promoter comprising both the U3 region of a Moloney modified murine leukemia retrovirus with long-terminal repeats and an enhancer from the myeloproliferative sarcoma virus) in the lentivirus, with no cases of hematologic cancer linked to insertional genotoxicity from lentiviral vectors in at least 250 other patients who received hematopoietic stem-cell therapies with other lentiviruses and equivalent patient-years of observation.

I fear that additional cases of hematologic cancer might arise over time in patients with cerebral adrenoleukodystrophy who received lentiviral gene therapy with this vector, given the long latency of at least the current cases and the finding of oligoclonal expansions in a substantial fraction of the other patients who received this therapy. These troubling events raise the bar for offering eli-cel autologous gene therapy for cerebral adrenoleukodystrophy.

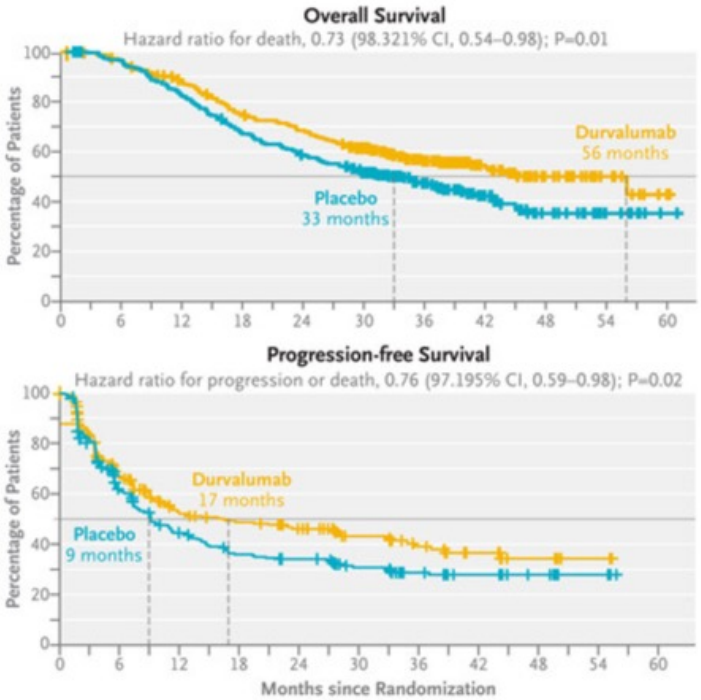
Als kleinzelliges Bronchialkarzinom, kurz SCLC, bezeichnet man ein Bronchialkarzinom, das bei mikroskopischer Betrachtung aus kleinen Zellen (APUD-Zellen) besteht. Etwa 15-20 % aller Bronchialkarzinome sind kleinzellige BC.[1] Der wichtigste bekannte Risikofaktor für die Entstehung ist das Rauchen.
Das Karzinom ist meist zentral in der Lunge lokalisiert. Durch lymphogene und hämatogene Metastasierung kommt es frühzeitig zu einer Tumoraussaat in Gehirn, Knochen, Leber und Nebennierenrinde.





Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer

Adjuvant therapy with durvalumab (PD-L1), with or without tremelimumab, may have efficacy in patients with limited-stage small-cell lung cancer who do not have disease progression after standard concurrent platinum-based chemoradiotherapy. In a phase 3, double-blind, randomized, placebo-controlled trial, we assigned patients to receive durvalumab at a dose of 1500 mg, durvalumab (1500 mg) plus tremelimumab at a dose of 75 mg (four doses only), or placebo every 4 weeks for up to 24 months. Randomization was stratified according to disease stage (I or II vs. III) and receipt of prophylactic cranial irradiation (yes vs. no). Results of the first planned interim analysis of the two primary end points of overall survival and progression-free survival (assessed on the basis of blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1) with durvalumab as compared with placebo (data cutoff date, January 15, 2024) are reported; results in the durvalumab–tremelimumab group remain blinded.



Small-cell lung cancer is an aggressive cancer that accounts for approximately 15% of all lung tumors. Approximately one third of patients who receive a diagnosis of small-cell lung cancer present with limited-stage disease, for which longest survival is achieved with concurrent thoracic chemoradiotherapy with the use of platinum–etoposide and early thoracic radiotherapy, followed by prophylactic cranial irradiation when indicated. However, most patients have a disease relapse within 2 years after starting treatment, and overall survival at 5 years ranges from 29 to 34%. No advances in systemic treatments for limited-stage small-cell lung cancer have been made in the past three decades. Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that binds to programmed death ligand 1 (PD-L1), blocking its interaction with programmed death 1 (PD-1) and CD80 on activated T cells.

Methods

Patients

Eligible patients had histologically or cytologically documented limited-stage small-cell lung cancer (stage I, II, or III [patients with stage I or II disease had to have medically inoperable disease], assessed according to the *AJCC Cancer Staging Manual*, 8th edition, or the *Staging Manual in Thoracic Oncology* of the International Association for the Study of Lung Cancer) and had not had progression after the receipt of definitive concurrent chemoradiotherapy.

End Points and Assessments

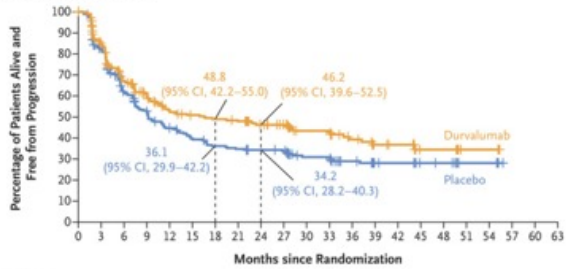
The two primary end points were overall survival and progression-free survival in a comparison of the durvalumab group with the placebo group.

Characteristic	Durvalumab (N=264)	Placebo (N=266)
Median age (range) — yr	62 (28–84)	62 (28–79)
Male sex — no. (%)	178 (67.4)	188 (70.7)
Race — no. (%)†		
White	130 (49.2)	137 (51.5)
Asian	131 (49.6)	121 (45.5)
Black	1 (0.4)	3 (1.1)
Other	2 (0.8)	5 (1.9)
Geographic region — no. (%)‡		
Asia	129 (48.9)	120 (45.1)
Europe	94 (35.6)	112 (42.1)
North or South America	41 (15.5)	34 (12.8)
WHO performance-status score — no. (%)§		
0	132 (50.0)	126 (47.4)
1	132 (50.0)	140 (52.6)
Former or current smoker — no. (%)	241 (91.3)	240 (90.2)
Tumor–node–metastasis stage at diagnosis — no. (%)¶		
I or II	33 (12.5)	34 (12.8)
III	231 (87.5)	232 (87.2)
Previous concurrent chemoradiotherapy — no. (%)		
Chemotherapy regimen in first cycle		
Cisplatin–etoposide	173 (65.5)	178 (66.9)
Carboplatin–etoposide	91 (34.5)	88 (33.1)
Radiotherapy fractionation schedule		
Once daily	195 (73.9)	187 (70.3)
Twice daily	69 (26.1)	79 (29.7)
Best response		
Complete response	31 (11.7)	34 (12.8)
Partial response	191 (72.3)	200 (75.2)
Stable disease	42 (15.9)	32 (12.0)
Time from end of previous concurrent chemoradiotherapy to randomization — no. (%)		
<14 days	32 (12.1)	32 (12.0)
14 to <28 days	79 (29.9)	80 (30.1)
≥28 days	153 (58.0)	154 (57.9)
Receipt of prophylactic cranial irradiation before randomization — no. (%)¶	142 (53.8)	143 (53.8)

Objective Responses (Intention-to-Treat Population).

End Point	Durvalumab (N=264)	Placebo (N=266)
Objective response		
No. of patients who could be evaluated†	175	169
No. of patients with a response	53	54
Percentage of patients with a response (95% CI)	30.3 (23.6–37.7)	32.0 (25.0–39.6)
Best objective response — no./total no. (%)‡		
Complete response	5/175 (2.9)	4/169 (2.4)
Partial response	48/175 (27.4)	50/169 (29.6)
Stable disease for ≥7 wk	94/175 (53.7)	76/169 (45.0)
Progressive disease	24/175 (13.7)	33/169 (19.5)
Could not be evaluated§	4/175 (2.3)	6/169 (3.6)
Duration of response		
No. of patients with a response	53	54
Disease progression or death — no./total no. (%)	22/53 (42)	23/54 (43)
Censored data — no./total no. (%)	31/53 (58)	31/54 (57)
Median duration of response (95% CI) — mo¶	33.0 (22.4–NR)	27.7 (9.6–NR)
Ongoing response at 12 mo (95% CI) — %¶	74 (59–84)	60 (44–73)
Ongoing response at 18 mo (95% CI) — %¶	71 (57–82)	55 (39–68)

A Progression-free Survival



	No. of Events/ Total No. (%)	Median Progression-free Survival (95% CI)
		mo
Durvalumab	139/264 (52.7)	16.6 (10.2–28.2)
Placebo	169/266 (63.5)	9.2 (7.4–12.9)

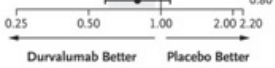
Stratified hazard ratio for disease progression or death, 0.76 (99.816% CI, 0.53–1.08) (97.195% CI, 0.59–0.98) P=0.02

No. at Risk

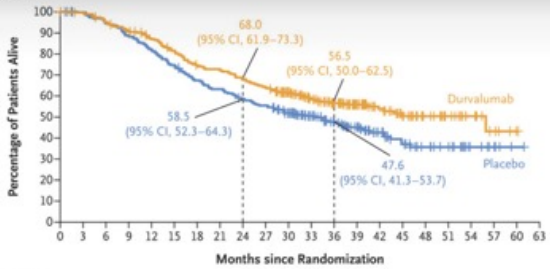
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

B Subgroup Analysis of Progression-free Survival

Subgroup	Durvalumab *no. of events/total no. (%)*	Placebo *no. of events/total no. (%)*	Hazard Ratio for Disease Progression or Death (95% CI)
All patients, intention-to-treat analysis	139/264 (52.7)	169/266 (63.5)	0.76 (0.61–0.95)
Age at randomization			
<65 yr	83/160 (51.9)	98/162 (60.5)	0.77 (0.58–1.03)
≥65 yr	56/104 (53.8)	71/104 (68.3)	0.77 (0.54–1.10)
Sex			
Male	96/178 (53.9)	120/188 (63.8)	0.80 (0.61–1.04)
Female	43/86 (50)	49/78 (63)	0.71 (0.47–1.08)
Race			
White	65/130 (50.0)	90/137 (65.7)	0.68 (0.49–0.93)
Asian	72/131 (55.0)	75/121 (62.0)	0.91 (0.66–1.26)
Geographic region			
Asia	70/129 (54.3)	73/120 (60.8)	0.91 (0.65–1.26)
Europe	46/94 (49)	75/112 (67.0)	0.60 (0.41–0.86)
North America or South America	23/41 (56)	21/34 (62)	0.88 (0.49–1.61)
WHO performance-status score at screening			
0	60/133 (45.1)	82/131 (62.6)	0.64 (0.46–0.90)
1	79/131 (60.3)	87/135 (64.4)	0.91 (0.67–1.24)
Smoking status			
Current or former smoker	129/241 (53.5)	154/240 (64.2)	0.78 (0.62–0.99)
Nonsmoker	10/23 (43)	15/26 (58)	0.62 (0.27–1.37)
Tumor–node–metastasis stage			
I or II	14/33 (42)	19/34 (56)	0.71 (0.35–1.42)
III	125/231 (54.1)	150/232 (64.7)	0.77 (0.61–0.98)
Previous chemotherapy			
Carboplatin–etoposide	44/91 (48)	57/88 (65)	0.61 (0.41–0.90)
Cisplatin–etoposide	95/173 (54.9)	112/178 (62.9)	0.86 (0.65–1.13)
Previous radiotherapy schedule			
Once daily	108/195 (55.4)	122/187 (65.2)	0.77 (0.60–1.00)
Twice daily	31/69 (45)	47/79 (59)	0.72 (0.45–1.13)
Best response to concurrent CRT			
Complete response	15/31 (48)	18/34 (53)	1.00 (0.50–1.99)
Partial response	106/191 (55.5)	130/200 (65.0)	0.81 (0.62–1.04)
Stable disease	18/42 (43)	21/32 (66)	0.50 (0.26–0.94)
Time from end of concurrent CRT to randomization			
<14 days	18/32 (56)	27/32 (84)	0.45 (0.24–0.83)
14 to <28 days	43/79 (54)	50/80 (62)	0.89 (0.59–1.34)
≥28 days	78/153 (51.0)	92/154 (59.7)	0.79 (0.58–1.07)
Receipt of prophylactic cranial irradiation			
Yes	65/142 (45.8)	84/143 (58.7)	0.73 (0.53–1.01)
No	74/122 (60.7)	85/123 (69.1)	0.80 (0.59–1.09)



A Overall Survival



	No. of Deaths/ Total No. (%)	Median Overall Survival (95% CI)
		mo
Durvalumab	115/264 (43.6)	55.9 (37.3–NR)
Placebo	146/266 (54.9)	33.4 (25.5–39.9)

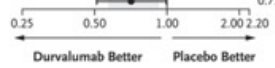
Stratified hazard ratio for death, 0.73 (98.321% CI, 0.54–0.98) P=0.01

No. at Risk

Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

B Subgroup Analysis of Overall Survival

Subgroup	Durvalumab *no. of deaths/total no. of patients (%)*	Placebo *no. of deaths/total no. of patients (%)*	Hazard Ratio for Death (95% CI)
All patients, intention-to-treat analysis	115/264 (43.6)	146/266 (54.9)	0.73 (0.57–0.93)
Age at randomization			
<65 yr	69/160 (43.1)	83/162 (51.2)	0.76 (0.55–1.04)
≥65 yr	46/104 (44.2)	63/104 (60.6)	0.70 (0.48–1.02)
Sex			
Male	79/178 (44.4)	108/188 (57.4)	0.70 (0.52–0.93)
Female	36/86 (42)	38/78 (49)	0.83 (0.52–1.31)
Race			
White	60/130 (46.2)	77/137 (56.2)	0.75 (0.53–1.05)
Asian	53/131 (40.5)	64/121 (52.9)	0.72 (0.50–1.04)
Geographic region			
Asia	51/129 (39.5)	62/120 (51.7)	0.72 (0.50–1.04)
Europe	41/94 (44)	64/112 (57.1)	0.67 (0.45–0.98)
North America or South America	23/41 (56)	20/34 (59)	0.98 (0.54–1.80)
WHO performance-status score at screening			
0	48/133 (36.1)	74/131 (56.5)	0.55 (0.38–0.79)
1	67/131 (51.1)	72/135 (53.3)	0.94 (0.67–1.31)
Smoking status			
Current or former smoker	108/241 (44.8)	138/240 (57.5)	0.72 (0.56–0.92)
Nonsmoker	7/23 (30)	8/26 (31)	NC
Tumor–node–metastasis stage			
I or II	11/33 (33)	12/34 (35)	0.92 (0.40–2.11)
III	104/231 (45.0)	134/232 (57.8)	0.71 (0.55–0.91)
Previous chemotherapy			
Carboplatin–etoposide	31/91 (34)	46/88 (52)	0.56 (0.35–0.89)
Cisplatin–etoposide	84/173 (48.6)	100/178 (56.2)	0.82 (0.61–1.10)
Previous radiotherapy schedule			
Once daily	92/195 (47.2)	107/187 (57.2)	0.72 (0.55–0.95)
Twice daily	23/69 (33)	39/79 (49)	0.68 (0.40–1.14)
Best response to concurrent CRT			
Complete response	12/31 (39)	15/34 (44)	0.90 (0.41–1.92)
Partial response	88/191 (46.1)	116/200 (58.0)	0.76 (0.57–1.00)
Stable disease	15/42 (36)	15/32 (47)	0.54 (0.25–1.13)
Time from end of concurrent CRT to randomization			
<14 days	14/32 (44)	24/32 (75)	0.47 (0.24–0.91)
14 to <28 days	37/79 (47)	51/80 (64)	0.59 (0.38–0.90)
≥28 days	64/153 (41.8)	71/154 (46.1)	0.90 (0.64–1.27)
Receipt of prophylactic cranial irradiation			
Yes	53/142 (37.3)	67/143 (46.9)	0.75 (0.52–1.07)
No	62/122 (50.8)	79/123 (64.2)	0.71 (0.51–0.99)

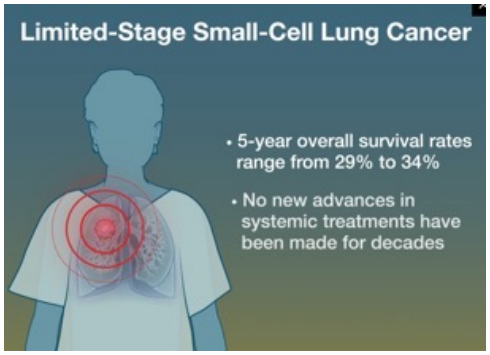


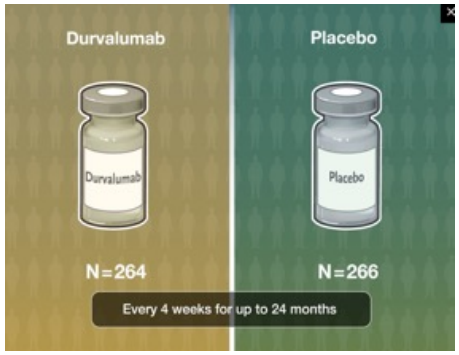
Discussion

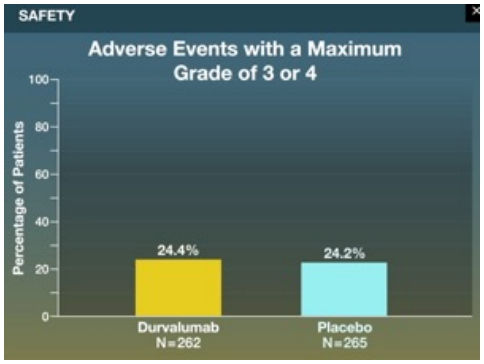
Systemic treatment for limited-stage small-cell lung cancer has not advanced in the past three decades. Early improvements in survival among patients with limited-stage small-cell lung cancer occurred after the adoption of concurrent platinum-based chemoradiotherapy and early thoracic radiotherapy in patients who were fit enough to undergo this treatment. However, poor long-term outcomes led to the exploration of alternative radiotherapy schedules and systemic therapy. Twice-daily thoracic radiotherapy was initially hailed as a treatment advance, but a meta-analysis showed that overall survival and the incidence of toxic effects were similar to those seen with once-daily radiotherapy among patients with limited-stage small-cell lung cancer. Previous trials of adjuvant and maintenance systemic therapy also did not show significant improvements in outcomes in patients with limited-stage small-cell lung cancer. In our trial, the first planned interim analysis showed that, among patients with limited-stage small-cell lung cancer who had not had disease progression after definitive concurrent chemoradiotherapy, the use of adjuvant durvalumab therapy resulted in significant improvements, as compared with placebo, in the two primary end points of overall survival and progression-free survival.

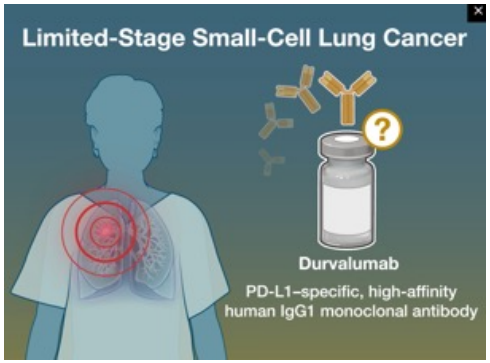
Adverse Events (Safety Population).

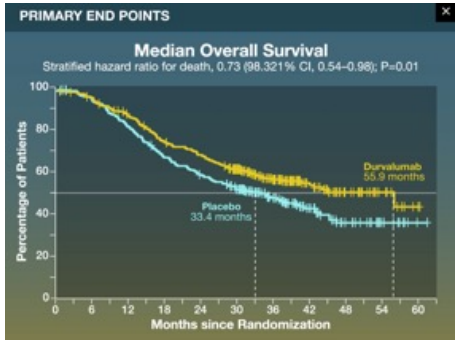
Event	Durvalumab (N=262)†		Placebo (N=265)	
	Any Grade	Grade 3 or 4‡	Any Grade	Grade 3 or 4‡
	number of patients (percent)			
Any adverse event of any cause	247 (94.3)	64 (24.4)	234 (88.3)	64 (24.2)
Any serious adverse event, including events with outcome of death	78 (29.8)	—	64 (24.2)	—
Any adverse event with outcome of death§	7 (2.7)	—	5 (1.9)	—
Any event leading to discontinuation of durvalumab or placebo	43 (16.4)	—	28 (10.6)	—
Any event leading to dose interruption	91 (34.7)	—	76 (28.7)	—
Any immune-mediated adverse event¶	84 (32.1)	14 (5.3)	27 (10.2)	4 (1.5)
Common adverse events occurring at any grade in ≥10% or at a maximum severity of grade 3 or 4 in ≥1% of patients in either group				
Radiation pneumonitis	60 (22.9)	3 (1.1)	62 (23.4)	5 (1.9)
Decreased appetite	44 (16.8)	0	34 (12.8)	0
Hypothyroidism	42 (16.0)	0	10 (3.8)	0
Cough	40 (15.3)	0	32 (12.1)	0
Pruritus	34 (13.0)	0	19 (7.2)	0
Nausea	33 (12.6)	0	29 (10.9)	0
Dizziness	32 (12.2)	0	20 (7.5)	0
Fatigue	32 (12.2)	1 (0.4)	34 (12.8)	4 (1.5)
Diarrhea	29 (11.1)	5 (1.9)	22 (8.3)	0
Pneumonia	29 (11.1)	7 (2.7)	20 (7.5)	9 (3.4)
Pneumonitis	28 (10.7)	3 (1.1)	16 (6.0)	2 (0.8)
Rash	28 (10.7)	1 (0.4)	16 (6.0)	0
Constipation	27 (10.3)	0	26 (9.8)	0
Hyperthyroidism	27 (10.3)	0	4 (1.5)	0
Headache	24 (9.2)	1 (0.4)	35 (13.2)	0
Anemia	23 (8.8)	3 (1.1)	16 (6.0)	3 (1.1)
Arthralgia	18 (6.9)	0	29 (10.9)	1 (0.4)
Hyperglycemia	11 (4.2)	3 (1.1)	10 (3.8)	0
Hypertension	9 (3.4)	3 (1.1)	4 (1.5)	0
Lipase increased	8 (3.1)	5 (1.9)	7 (2.6)	4 (1.5)
Amylase increased	7 (2.7)	3 (1.1)	3 (1.1)	0
Chronic obstructive pulmonary disease	6 (2.3)	1 (0.4)	7 (2.6)	4 (1.5)
Pulmonary embolism	6 (2.3)	5 (1.9)	4 (1.5)	3 (1.1)
Pneumonitis or radiation pneumonitis‖	100 (38.2)**	8 (3.1)	80 (30.2)	7 (2.6)
Pneumonitis or radiation pneumonitis leading to discontinuation of durvalumab or placebo	23 (8.8)	—	8 (3.0)	—

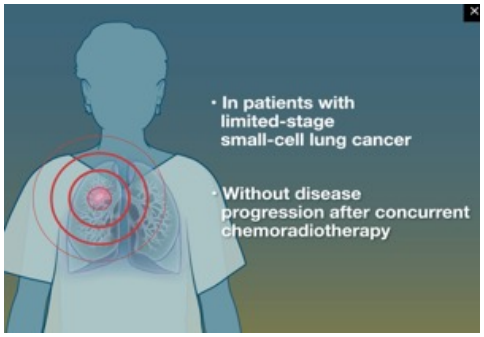

Limited-Stage Small-Cell Lung Cancer
• 5-year overall survival rates range from 29% to 34%
• No new advances in systemic treatments have been made for decades

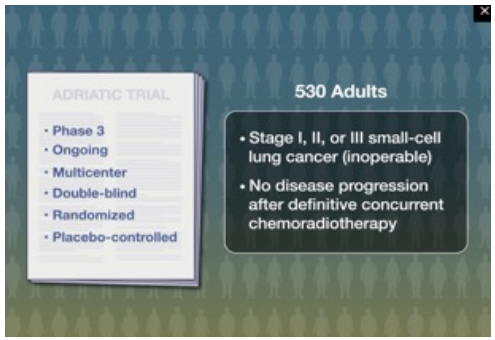

Durvalumab
Placebo
Durvalumab
Placebo
N=264
N=266
Every 4 weeks for up to 24 months

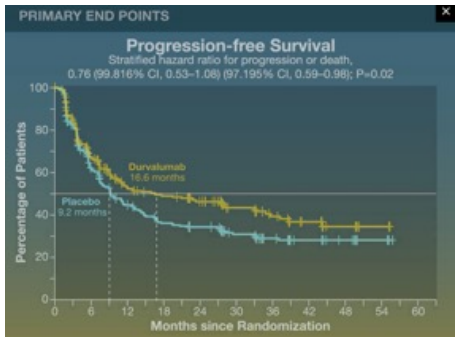

SAFETY
Adverse Events with a Maximum Grade of 3 or 4
Percentage of Patients
100
80
60
40
20
0
24.4%
24.2%
Durvalumab N=262
Placebo N=265


Limited-Stage Small-Cell Lung Cancer
Durvalumab
PD-L1–specific, high-affinity human IgG1 monoclonal antibody


PRIMARY END POINTS
Median Overall Survival
Stratified hazard ratio for death, 0.73 (98.321% CI, 0.54–0.98); P=0.01
Percentage of Patients
Durvalumab 55.9 months
Placebo 33.4 months
Months since Randomization


• In patients with limited-stage small-cell lung cancer
• Without disease progression after concurrent chemoradiotherapy


ADRIATIC TRIAL
• Phase 3
• Ongoing
• Multicenter
• Double-blind
• Randomized
• Placebo-controlled
530 Adults
• Stage I, II, or III small-cell lung cancer (inoperable)
• No disease progression after definitive concurrent chemoradiotherapy


PRIMARY END POINTS
Progression-free Survival
Stratified hazard ratio for progression or death, 0.76 (99.816% CI, 0.53–1.08) (97.195% CI, 0.59–0.98); P=0.02
Percentage of Patients
Durvalumab 16.6 months
Placebo 9.2 months
Months since Randomization


Durvalumab
Adjuvant therapy with durvalumab significantly improved overall survival and progression-free survival

REVIEW ARTICLE

Hairy-Cell Leukemia

Because of its unique morphologic and clinical features, hairy-cell leukemia (HCL) has been recognized as a distinct entity since 1958. At that time, because of the lack of immunologic markers, the term “leukemic reticuloendotheliosis” was coined. The name “hairy-cell leukemia” was proposed in 1966 by Schrek and Donnelly, on the basis of cytoplasmic projections observed in the leukemic cells in peripheral blood from two patients. The cell of origin of HCL has been a matter of debate for many years, with most studies favoring a monocytic derivation of leukemic cells because they can phagocytose latex particles. The B-cell origin of HCL was definitively established through the demonstration of clonal rearrangement of immunoglobulin genes and was then confirmed by the expression of B-cell markers.

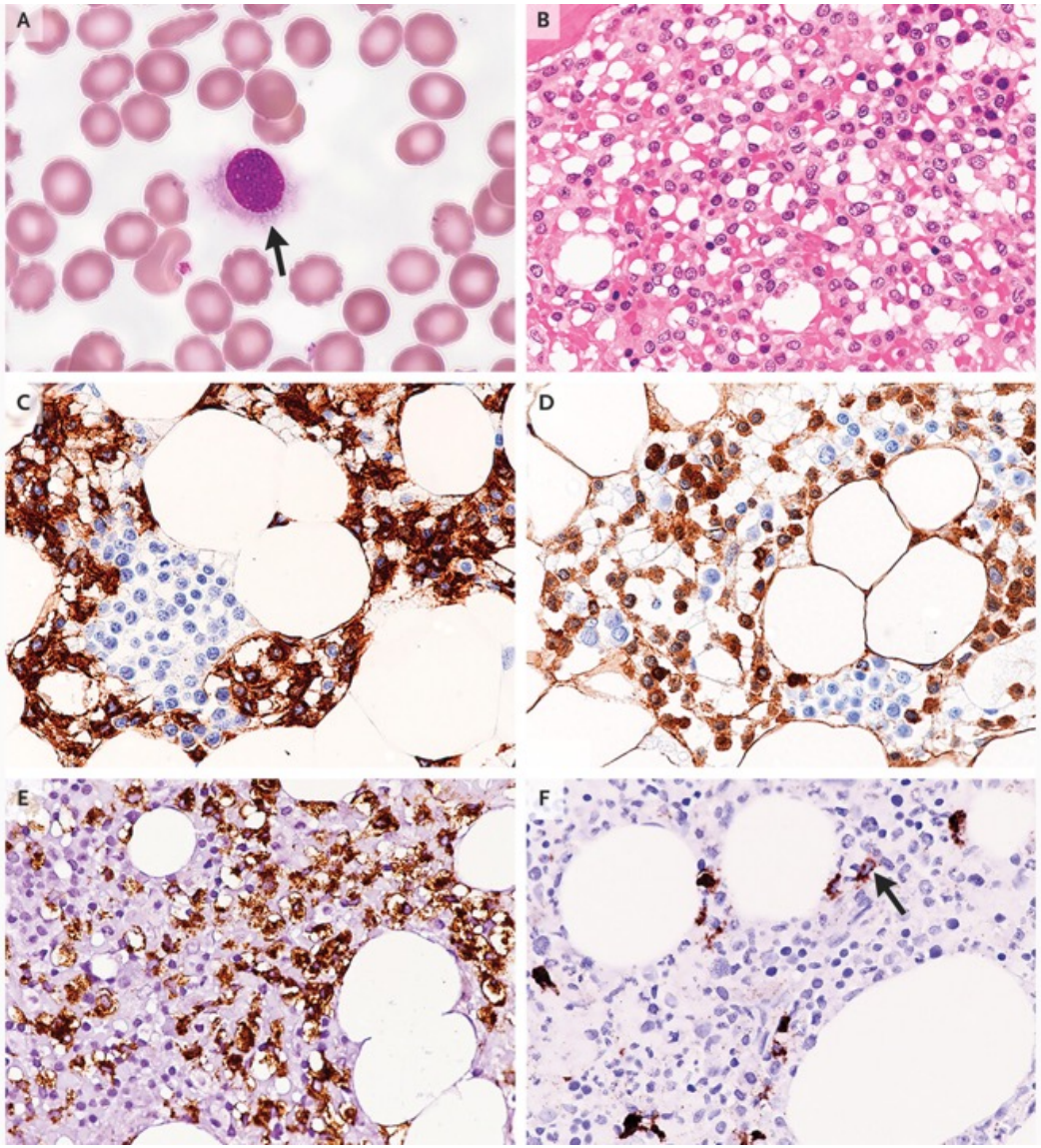
HAIRY-CELL LEUKEMIA

- Hairy-cell leukemia (HCL) is a rare, indolent neoplasm of mature B cells with hairlike surface projections that circulate in the blood and preferentially infiltrate the bone marrow and spleen.
- The clinical picture is characterized by male predominance, onset in adulthood with cytopenias and splenomegaly, a remitting–relapsing pattern of response to sequential treatments, and an almost normal life expectancy with current therapies.

- The BRAF V600E kinase-activating mutation is the genetic cause of HCL in at least 95% of cases and shapes key disease traits, including the peculiar morphologic features.
- Testing for the BRAF V600E mutation or protein and for HCL-specific immunophenotypic markers (including annexin A1) allows for the differential diagnosis of diseases that mimic HCL (e.g., HCL variant and splenic marginal-zone lymphoma), which require distinct clinical management.
- Myelotoxic chemotherapy with cladribine or pentostatin, alone or combined with the anti-CD20 monoclonal antibody rituximab, is a highly effective standard care for patients with HCL.
- Chemotherapy-free strategies based on BRAF inhibitors (e.g., vemurafenib or dabrafenib) are increasingly used in patients with relapsed or refractory HCL and in those with active infections and are being explored in a front-line context as an alternative to chemotherapy.

Pathologic Features and Immunophenotype

HCL is characterized by involvement of the bone marrow, spleen, and peripheral blood with mature, small-to-intermediate-size B cells that have ample cytoplasm, an oval or cleaved nucleus, and homogeneous chromatin without prominent nucleoli. The leukemic cells have thin, circumferential surface projections, which are best visualized in peripheral-blood smears and which account for the vivid name of the disease.



Pathological and Immunophenotypic Features of Hairy-Cell Leukemia.

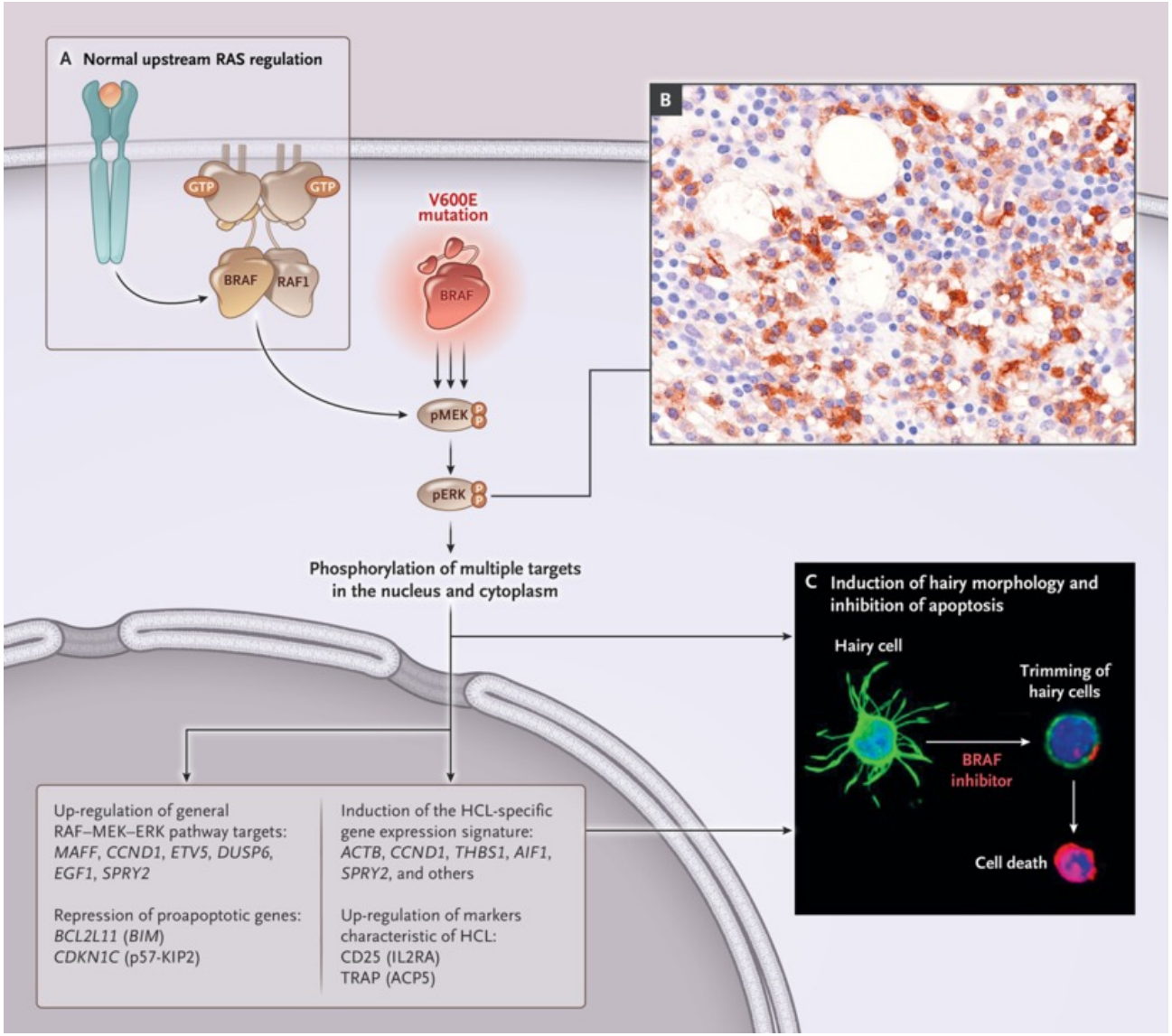
Panel A shows a circulating leukemic hairy cell (arrow) in a peripheral-blood smear (May–Grünwald–Giemsa stain). Panel B shows diffuse infiltration by leukemic hairy cells with a fried-egg appearance in a bone marrow–biopsy specimen (hematoxylin and eosin stain). The bone marrow–biopsy specimen in Panel C shows leukemic hairy cells that express the CD20 antigen (immunoperoxidase stain). Panel D shows leukemic hairy cells that are positive for annexin A1 in a bone marrow–biopsy specimen (immunoperoxidase stain). Leukemic hairy cells strongly express the BRAF V600E mutant protein. Many BRAF V600E–positive cells are present at diagnosis, as shown in the bone marrow–biopsy specimen in Panel E (immunoperoxidase stain). In a bone marrow–biopsy specimen obtained after therapy, shown in Panel F, rare BRAF V600E–positive cells are detectable (immunoperoxidase stain).

Genetic Features

The clonal immunoglobulin gene rearrangements of HCL are somatically mutated and class-switched in the majority of cases, which indicates an origin from a peripheral antigen-experienced B cell. HCL has a distinct transcriptional profile, at both the messenger RNA and microRNA levels, that is similar to the profile of post–germinal center memory B cells but with altered expression of chemokine and adhesion receptors. These gene-expression profiling studies have also provided molecular insights into some of the biologic properties of HCL, including the morphologic features, the bone marrow fibrosis induced by leukemic cells, and the pattern of leukemic-cell dissemination to certain anatomical sites.

The *BRAF* V600E kinase-activating mutation is the clonal genetic event underlying the pathogenesis of at least 95% of all HCL cases across the entire clinical spectrum of this disease, and the mutation is stable at relapse, even decades after the onset of HCL. The *BRAF* oncogene (located at the 7q34 cytoband) encodes a serine–threonine kinase of the RAF family and is a key component of the RAS–RAF–MEK–ERK signaling pathway.

Feature	HCL	HCL Variant†	SMZL	SDRPL
Clinical features				
Splenomegaly with little or no lymphadenopathy	Yes	Yes	Yes	Yes
Marked male predominance	Yes	No	No	No
Pancytopenia	Frequent	Infrequent	Infrequent	Infrequent
Monocytopenia	Yes	No	No	No
Leukocytosis	Infrequent	Frequent	Frequent	Frequent
Dry or hemodiluted marrow aspirate	Frequent	No	No	No
Response to purine analogue monotherapy	Very good	Poor	Poor	Poor
Features of leukemic lymphocytes on blood smears				
Nucleus	Oval or indented	Round or oval	Round	Round or oval
Nucleolus	Absent or small	Prominent	Absent or small	Absent or small
Cytoplasm	Abundant, clear	Abundant, clear or basophilic	Basophilic	Basophilic
Cell-surface projections	Thin, circumferential	Variably reported	Short, polar	Thick, polar
Immunophenotype				
CD20	Positive	Positive	Positive	Positive
CD5	Usually negative	Negative	Usually negative	Negative
CD23	Usually negative	Negative	Negative	Negative
CD10	Usually negative	Negative	Negative	Negative
CD103	Positive	Usually positive	Usually negative	Usually negative
CD11c	Positive	Usually positive	Variably reported	Variably reported
CD25	Positive	Negative	Positive in a minority of cases	Negative
CD123	Positive	Negative	Negative	Negative
Annexin A1	Positive	Negative	Negative	Negative
BRAF V600E protein	Positive	Negative	Negative	Negative
Genetic lesions				
BRAF V600E mutation	Present	Absent	Absent	Absent
7q Deletion	Present in a minority of cases	Present in a minority of cases	Present in a minority of cases	Present in a minority of cases
MAP2K1 mutations	Absent	Present in a minority of cases	Absent	Absent
KLF2 mutations	Present in a minority of cases	Absent	Present in a minority of cases	Absent
CDKN1B mutations	Present in a minority of cases	Absent	Absent	Absent
KMT2C mutations	Present in a minority of cases	Present in a minority of cases	Absent	Absent
NOTCH2 mutations	Absent	Absent	Present in a minority of cases	Absent
Alterations in NF-κB pathway genes‡	Absent	Absent	Present in a minority of cases	Absent
CCND3 mutations	Absent	Present in a minority of cases	Present in a minority of cases	Present in a minority of cases
U2AF1 mutations	Absent	Present in a minority of cases	Absent	Absent
BCOR mutations or deletions	Absent	Absent	Absent	Present in a minority of cases
TP53 mutations or deletions	Absent	Present in a minority of cases	Present in a minority of cases	Absent

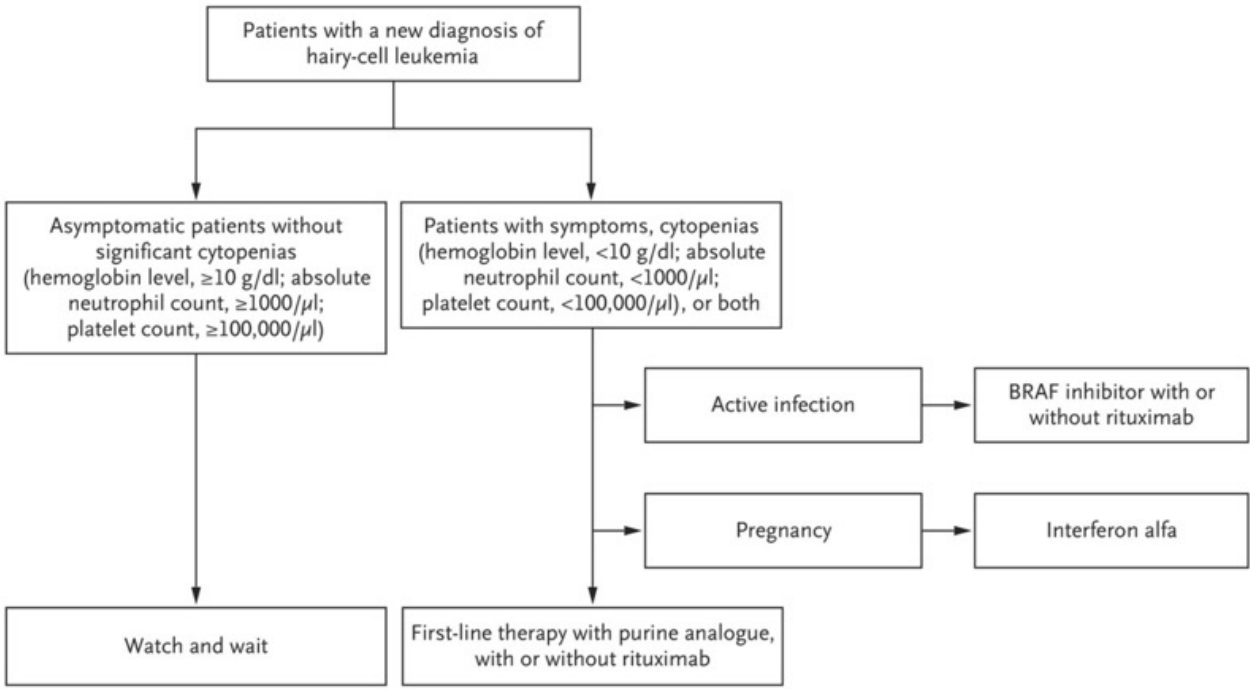


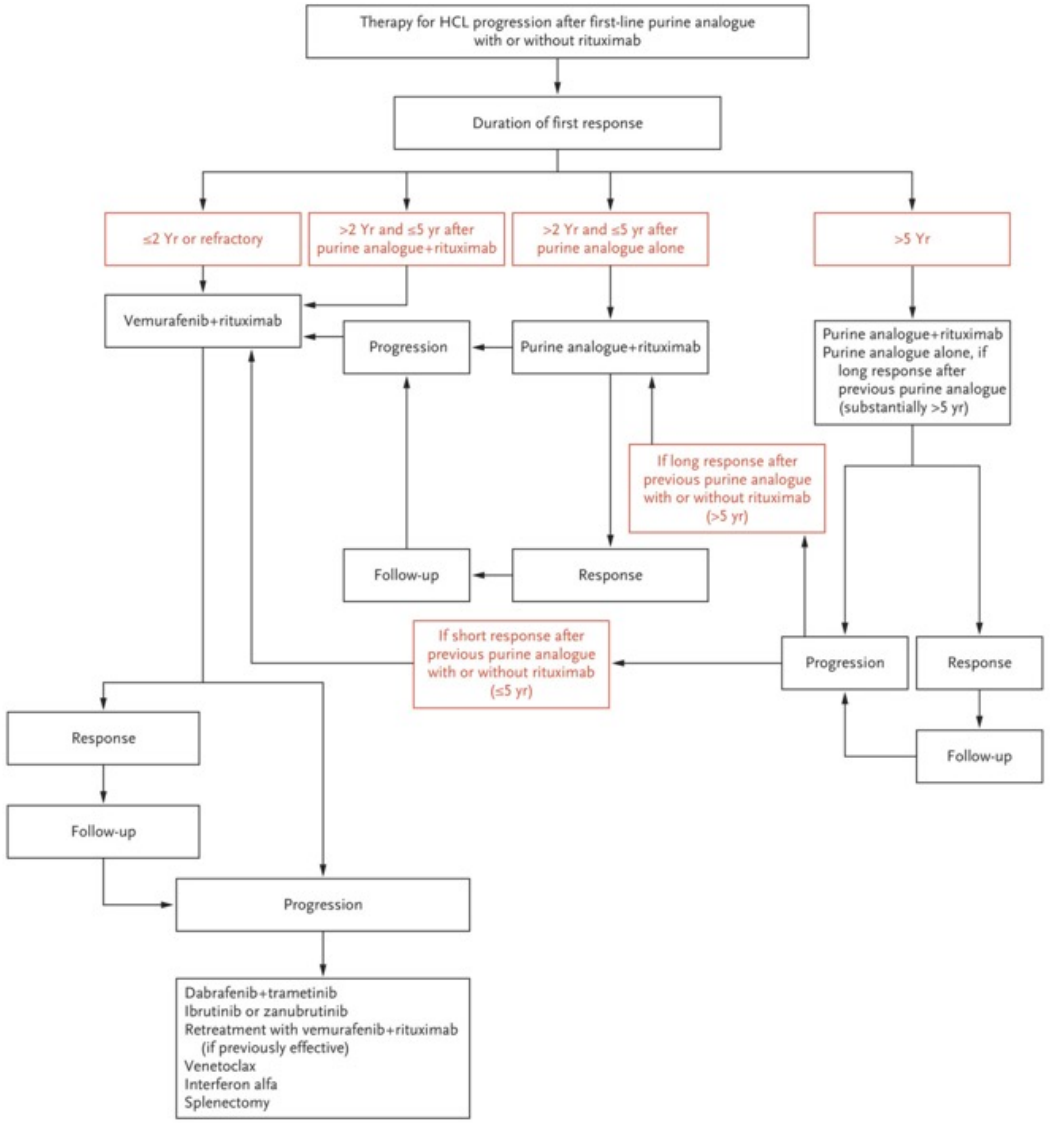
Pathogenesis of Hairy-Cell Leukemia (HCL).

The V600E missense mutation in the cytosolic serine–threonine kinase BRAF leads to its constitutive activation (independently of upstream regulation by RAS at the plasma membrane, as shown in Inset A) and, hence, to downstream phosphorylation of the MEK kinases (pMEK), which in turn phosphorylate the ERK kinases (pERK); Inset B shows pERK expression by HCL cells in a bone marrow–biopsy section (immunoperoxidase stain). Subsequent pERK-mediated phosphorylation of numerous targets in the nucleus and the cytoplasm generally promotes survival, proliferation, growth, and motility. At the molecular level, among the genes transcriptionally up-regulated by the RAF–MEK–ERK signaling pathway in HCL, there are not only those commonly up-regulated in most cell types but also some that are characteristic markers of HCL (i.e., CD25 and TRAP), as well as the whole expression signature that distinguishes HCL from normal mature B-cell subsets and mature B-cell neoplasms. At the cellular level, aberrant pathway activity in HCL induces the characteristic hairy projections of the leukemic cells and inhibits apoptosis; Inset C shows a confocal immunofluorescence image of a primary HCL cell exposed in vitro to the BRAF inhibitor vemurafenib, which first trims the hairy projections (rich in F-actin and thus labeled in green by the cytoskeleton marker phalloidin) and then induces apoptosis, as indicated by the red staining for the apoptotic marker annexin V. (The blue stain is nuclear dye DRAQ5.) This figure was adapted from Lim et al.[37]

First-Line Therapy

"Watch and wait" is the preferred strategy for the approximately 10 to 20% of patients who present without clinically significant cytopenias related to HCL (i.e., those with a hemoglobin level of ≥10 g per deciliter, an absolute neutrophil count of ≥1000 per microliter, and a platelet count of ≥100,000 per microliter) and without symptomatic organomegaly, recurrent infections, and constitutional symptoms.





Therapy for Refractory or Relapsed HCL.

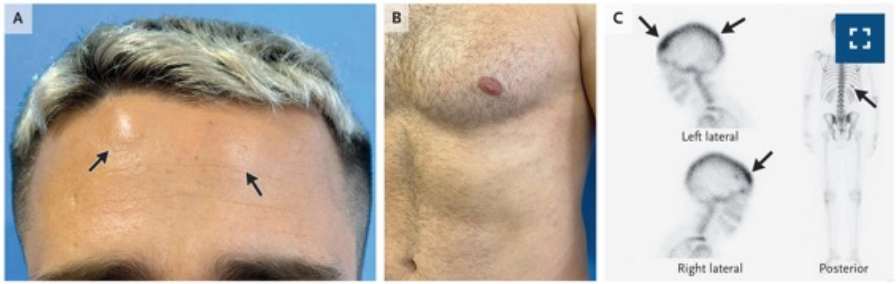
Shown is a possible algorithm for the treatment of HCL that does not respond to, or that relapses after, first-line chemotherapy. Each red box shows the proposed duration of a response to the previous therapy as the basis for choosing the subsequent treatment. Not shown in this algorithm are other considerations that should be factored into this choice; for example, for patients who have had previous severe toxic effects from chemotherapy or who are currently ineligible for chemotherapy, vemurafenib plus rituximab could be considered regardless of the duration of response after the preceding chemotherapy treatment. Purine analogues include cladribine or pentostatin; fludarabine and bendamustine have also been effective when combined with rituximab in patients with relapsed or refractory HCL.

Future Directions

Next-generation BRAF inhibitors that can also counteract adaptive and genetic reinduction of ERK signaling through CRAF are being developed for the treatment of BRAF-mutated solid cancers and may also be valuable in treating HCL.

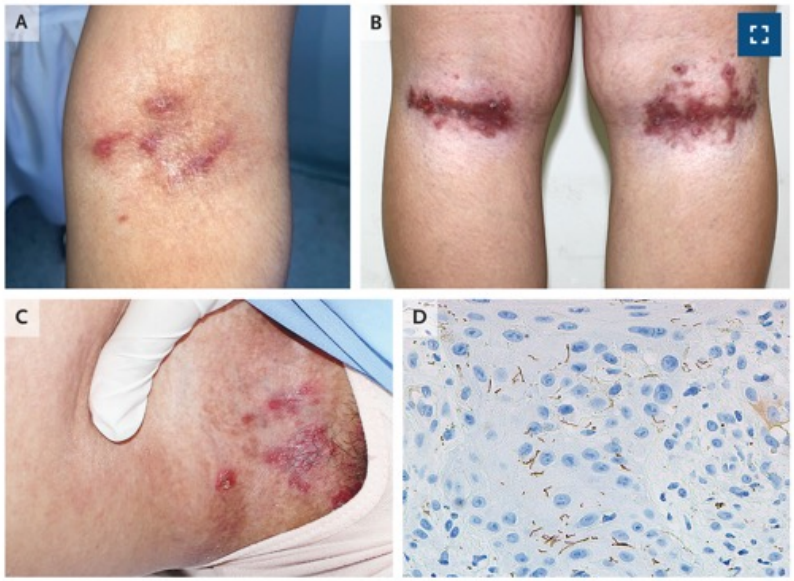
The attractive efficacy and safety profile of vemurafenib plus rituximab in refractory or relapsed HCL offers promise for a chemotherapy-free front-line treatment as an alternative to purine analogues. The effectiveness of BRAF inhibition plus anti-CD20 immunotherapy as first-line treatment has been confirmed in a phase 2, single-group trial of vemurafenib and obinutuzumab, with 90% of patients having an MRD-negative complete response and no relapse at a median follow-up of almost 3 years. A phase 2 randomized trial (EudraCT number, 2021-001864-12) is evaluating whether front-line treatment with vemurafenib plus rituximab is less toxic and not less active than the chemotherapy-based standard care. Whether the duration of a response after treatment with vemurafenib plus rituximab will be similar to that with chemotherapy (alone or followed by rituximab in the case of MRD persistence in the blood) will also be investigated.

Secondary Syphilis with Osteitis



A 32-year-old man with well-controlled human immunodeficiency virus infection presented to the emergency department with a 1-month history of painful bumps on his forehead. Six months before presentation, testing for syphilis had been negative. In the 3 months before presentation, he had had condomless sex with four male partners. Physical examination was notable for two firm, tender nodules on the forehead (Panel A, arrows). A macular rash was seen on the torso (Panel B). A computed tomographic scan of the head showed two frontal, subgaleal lesions with lytic bone involvement. A bone scan with technetium-99m–labeled methylene diphosphonate showed uptake in the two frontal lesions, the occiput, and the scapula and 11th rib on the right side (Panel C, arrows). A rapid plasma reagin (RPR) titer was 1:32, and a *Treponema pallidum* particle agglutination assay was positive. Owing to concern about possible cancer, a bone biopsy was planned. However, the bone lesions and rash rapidly abated after one dose of penicillin G benzathine and completely resolved by the third dose. A final diagnosis of secondary syphilis with osteitis was made. Although secondary syphilis is treated with a single dose of penicillin, three doses were given in this case owing to therapeutic uncertainty regarding the osteitis. A repeat bone scan that was performed 6 months after the completion of treatment was normal, and a repeat RPR titer was 1:1.

Intertriginous Rash in Secondary Syphilis



A 25-year-old woman with systemic lupus erythematosus (SLE) presented to the dermatology clinic with a 3-month history of a rash on her arms, legs, and groin. She had been having condomless sexual intercourse with one male partner during the year preceding presentation. During the 9 months before presentation, she had been taking hydroxychloroquine at a dose of 200 mg daily and prednisolone at a dose of 15 to 40 mg daily to control her SLE. Physical examination was notable for erosive, violaceous plaques in the antecubital fossae (Panel A, left arm), popliteal fossae (Panel B), and inguinal regions (Panel C, right groin). There were also scaly erythematous patches on both palms. A *Treponema pallidum* hemagglutination assay was positive, and the rapid plasma reagin (RPR) titer was 1:128. Immunohistochemical staining of a skin-biopsy sample of the right inguinal crease was positive for *T. pallidum* (Panel D). A diagnosis of secondary syphilis with an intertriginous rash was made. In patients with immunosuppression, the rash of secondary syphilis can be highly variable and atypical. Treatment with benzathine penicillin G and counseling on safe-sex practices were given. The rash had abated by 1 month after treatment, and the RPR titer had decreased to 1:16 by 6 months after treatment.

Case 31-2024: A 37-Year-Old Man with Fever, Myalgia, Jaundice, and Respiratory Failure

A 37-year-old man was admitted to this hospital because of fever, myalgia, jaundice, and hypoxemia.

The patient had been healthy until 9 days before this admission, when malaise, fatigue, and generalized weakness developed. The symptoms were severe, and he slept almost all day and night. Seven days before this admission, the patient had an oral temperature of 39.4°C, and headache developed, as well as achiness and stiffness in the arms, shoulders, knees, and legs. He was not able to eat a full meal because of decreased appetite and nausea. He did not have abdominal pain, vomiting, or diarrhea.

Five days before this admission, the fever and headache abated; however, the achiness increased, and the patient noticed that his urine was dark yellow. Three days before this admission, the patient sought evaluation in the urgent care clinic of another hospital. Testing was negative for severe acute respiratory syndrome coronavirus 2, respiratory syncytial virus, and influenza virus types A and B. He was instructed to get adequate rest and hydration. Two days before this admission, the symptoms had not abated, and the patient returned to the urgent care clinic. On examination, new yellow discoloration of the skin and eyes was observed, and he was instructed to go to the emergency department of the other hospital.

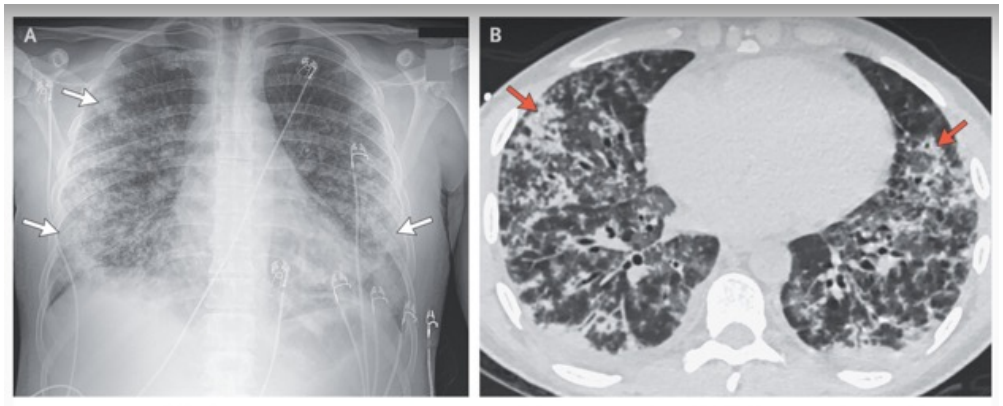
On evaluation, the temporal temperature was 36.8°C, the blood pressure 106/70 mm Hg, the pulse 109 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The white-cell count was 17,900 per microliter (reference range, 4500 to 11,000), the platelet count 34,000 per microliter (reference range, 150,000 to 400,000), and the hemoglobin level 15.7 g per deciliter (reference range, 13.0 to 17.0). The creatinine level was 3.0 mg per deciliter (265 µmol per liter; reference range, 0.6 to 1.4 mg per deciliter [53 to 124 µmol per liter]), the total bilirubin level 15.9 mg per deciliter (272 µmol per liter; reference range, 0.0 to 1.2 mg per deciliter [0 to 21 µmol per liter]), and the direct bilirubin level more than 10.0 mg per deciliter (171 µmol per liter; reference range, 0.0 to 0.5 mg per deciliter [0 to 9 µmol per liter]).

Variable	Reference Range, Other Hospital	2 Days before Current Admission, Other Hospital	Reference Range, This Hospital†	On Current Admission, This Hospital
Blood				
White-cell count (per µl)	4500–11,000	17,900	4500–11,000	21,700
Differential count (per µl)				
Neutrophils	1500–7800	16,100	1800–7700	15,190
Lymphocytes	1000–4800	500	1000–4800	2410
Monocytes	0–800	1000	200–1200	200
Immature granulocytes	0–90	140	—	—
Hemoglobin (g/dl)	13.0–17.0	15.7	13.5–17.5	10.2
Hematocrit (%)	37.5–50.0	45.2	41.0–53.0	27.6
Platelet count (per µl)	150,000–400,000	34,000	150,000–450,000	67,000
Sodium (mmol/liter)	137–146	129	135–145	124
Potassium (mmol/liter)	3.5–5.3	3.4	3.4–5.0	3.3
Chloride (mmol/liter)	98–107	92	98–108	86
Carbon dioxide (mmol/liter)	23–32	24	23–32	20
Urea nitrogen (mg/dl)	5–25	48	8–25	59
Creatinine (mg/dl)	0.6–1.4	3.0	0.60–1.50	3.36
Glucose (mg/dl)	70–100	117	70–110	81
Magnesium (mg/dl)	—	—	1.7–2.4	1.5
Lactate dehydrogenase (U/liter)	—	—	110–210	298
Haptoglobin (mg/dl)	—	—	30–200	292
Lactic acid (mmol/liter)	0.5–2.0	1.0	0.5–2.0	1.9
Total bilirubin (mg/dl)	0.0–1.2	15.9	0.0–1.0	26.1
Direct bilirubin (mg/dl)	0.0–0.5	>10.0	0.0–0.4	26.1
Aspartate aminotransferase (U/liter)	15–41	50	10–40	44
Alanine aminotransferase (U/liter)	14–63	38	10–55	41
Alkaline phosphatase (U/liter)	40–129	103	45–115	106
Total protein (g/dl)	6.4–8.3	6.2	6.8–8.3	4.9
Albumin (g/dl)	4.0–5.0	3.3	3.3–5.0	2.5
D-Dimer (ng/ml)	0–500	1640	0–500	3486
Fibrinogen (mg/dl)	187–446	>840	150–400	474
Prothrombin time (sec)	—	11.1	11.5–14.5	16.7
International normalized ratio for prothrombin time	—	1.0	0.9–1.1	1.4
Activated partial-thromboplastin time (sec)	—	28.5	22.0–36.6	32.3
Urine				
Bilirubin	Negative	Large	Negative	2+
Urobilinogen	Negative	Trace	Negative	Negative
Blood	Negative	Moderate	Negative	Negative
Glucose	Negative	Positive (250 mg/dl)	Negative	Negative
Ketones	Negative	Trace	Negative	Negative
Leukocyte esterase	Negative	Trace	Negative	Negative
Nitrites	Negative	Negative	Negative	Negative
Protein	Negative	Positive (300 mg/dl)	Negative	Negative
pH	5.0–8.0	6.5	5.0–9.0	5.5
Specific gravity	1.005–1.030	1.011	1.001–1.035	1.005
Red cells (per high-power field)	0–2	3–5	—	—
White cells (per high-power field)	0–5	6–10	—	—

During the subsequent 2 days, the patient received intravenous fluids. On the third hospital day, the blood pressure decreased to 71/60 mm Hg, and the oxygen saturation had also decreased. The creatinine level increased to 3.8 mg per deciliter (336 µmol per liter), the hemoglobin level decreased to 10.3 g per deciliter, and the total bilirubin level increased to 20.9 mg per deciliter (357 µmol per liter). Supplemental oxygen was administered through a nasal cannula, and boluses of intravenous fluids were given. The patient was transferred to this hospital for further treatment.

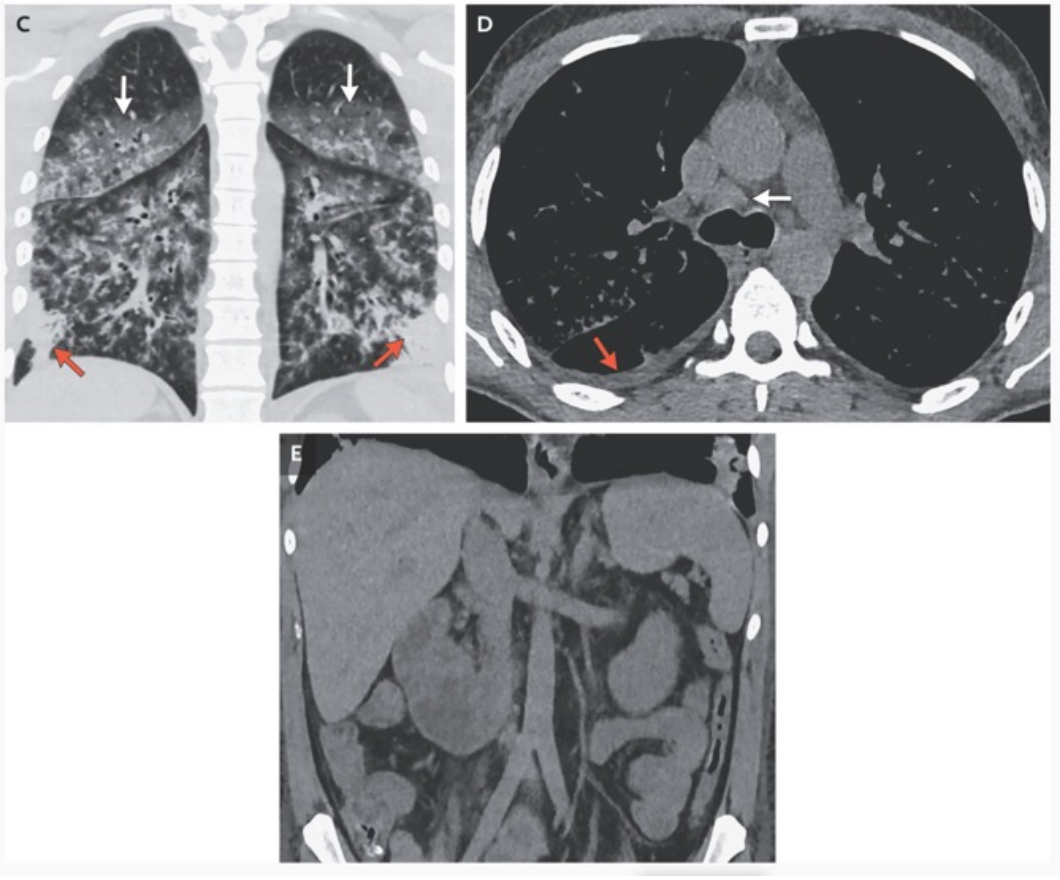
The patient worked in an office, and he took daily walks with his dog through the woods and along a river; he recalled receiving multiple insect bites during these walks. He reported no recent travel. He had smoked one pack of cigarettes per day for 16 years and used marijuana daily. He consumed two alcoholic drinks at a time, a few times per week, and he did not use illicit drugs.

On examination, the temporal temperature was 36.3°C, the blood pressure 100/56 mm Hg, the pulse 103 beats per minute, the respiratory rate 42 breaths per minute, and the oxygen saturation 91% while the patient was receiving supplemental oxygen through a nasal cannula at a rate of 4 liters per minute. He was alert and oriented but appeared ill. He had increased work of breathing, with the use of accessory muscles of respiration; diffuse rales were heard in both lungs. There was no abdominal tenderness, hepatosplenomegaly, asterixis, or leg swelling. Marked scleral icterus and jaundiced skin were present, but he had no conjunctival suffusion, rash, or ulcers.



Imaging Studies of the Chest, Abdomen, and Pelvis. A chest radiograph (Panel A) shows bilateral, predominantly peripheral, patchy airspace opacities (arrows) in both lungs. CT images of the chest, abdomen, and pelvis were obtained without the administration of intravenous contrast material.

Radiography of the chest revealed bilateral, predominantly peripheral, patchy opacities. Ultrasonography of the abdomen showed hyperechogenic and prominent portal triads with a “starry sky” appearance; there was no biliary ductal dilatation or hydronephrosis. Computed tomography (CT) of the chest, abdomen, and pelvis, performed without the administration of intravenous contrast material, revealed multifocal consolidative and ground-glass opacities with tree-in-bud nodularity in both lungs, as well as small pleural effusions and enlarged mediastinal and hilar lymph nodes. No hepatic lesions, biliary ductal dilatation, or hepatosplenomegaly were noted.

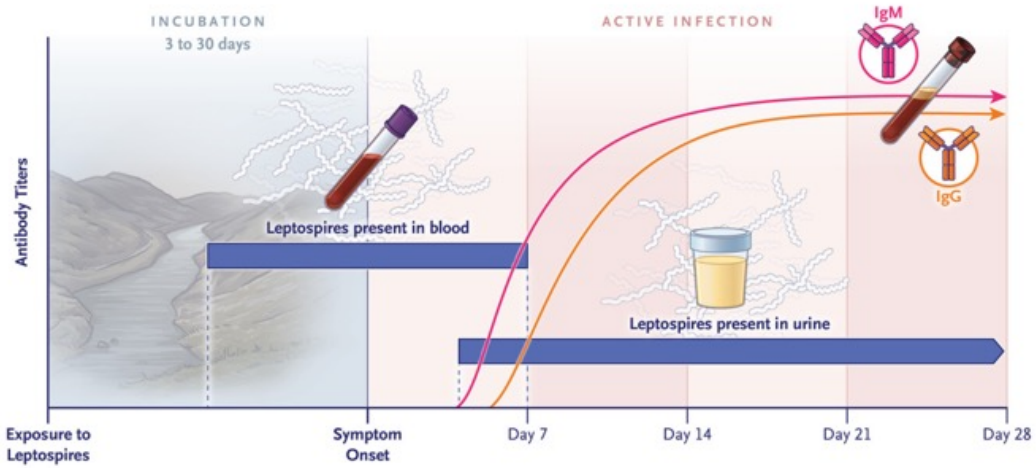


Differential Diagnosis

Dr. William C. Hillmann: This previously healthy 37-year-old man presented with an acute, nonspecific febrile syndrome with prominent fatigue, malaise, and myalgia, which was complicated by hypoxic respiratory failure and multiple laboratory abnormalities, including leukocytosis, acute kidney failure, and conjugated hyperbilirubinemia.

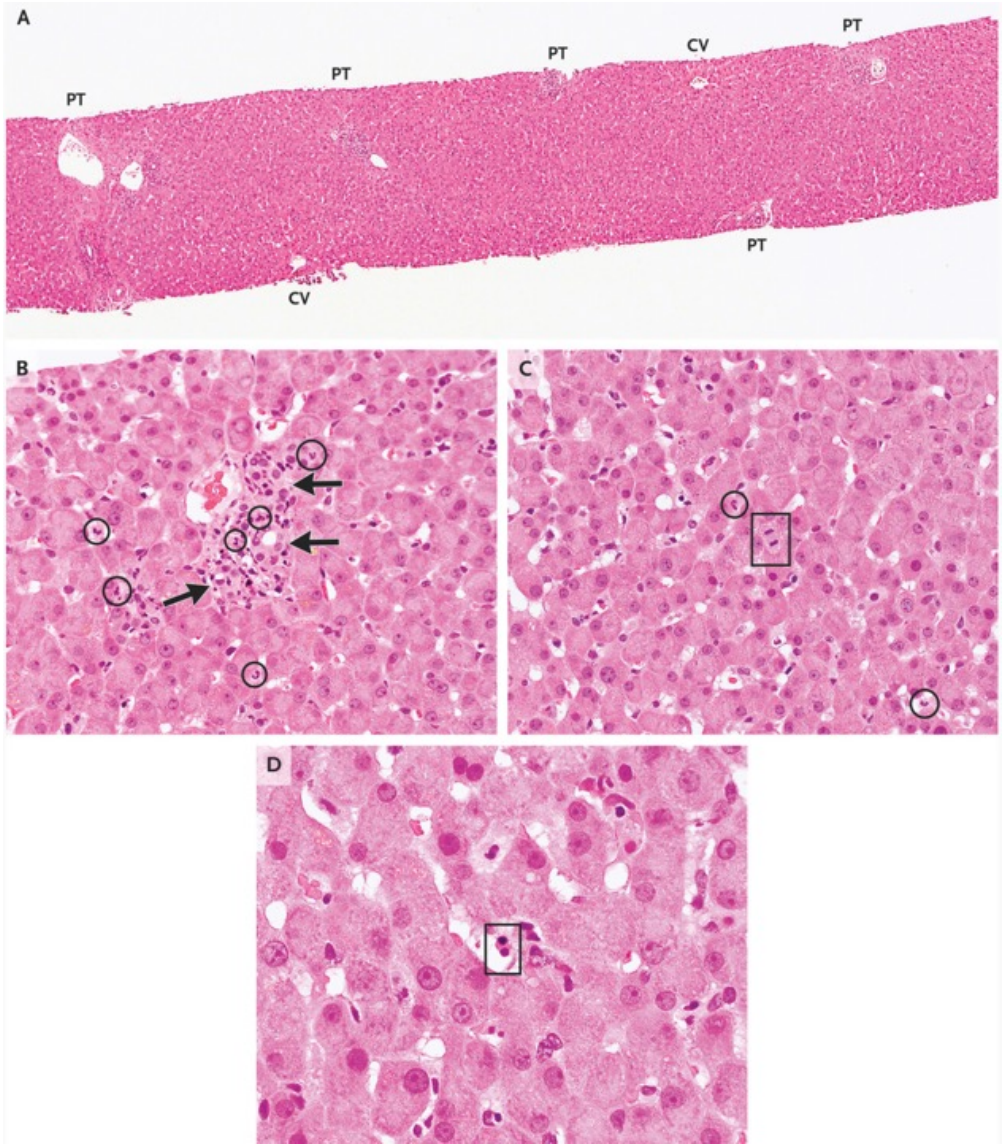
Leptospirosis

Leptospirosis is a zoonotic spirochetal infection that is most prevalent in tropical environments. Humans can acquire leptospirosis through contact with urine from infected mammals (often rats) or through exposure to a freshwater environment contaminated with the urine. Although leptospirosis is relatively uncommon in New England, this patient regularly walked his dog by a river, and it is possible that swimming in the river or having water splash onto a mucous membrane could account for his exposure. We do not know whether his dog had received the leptospirosis vaccine, which is commonly administered to dogs in this region.



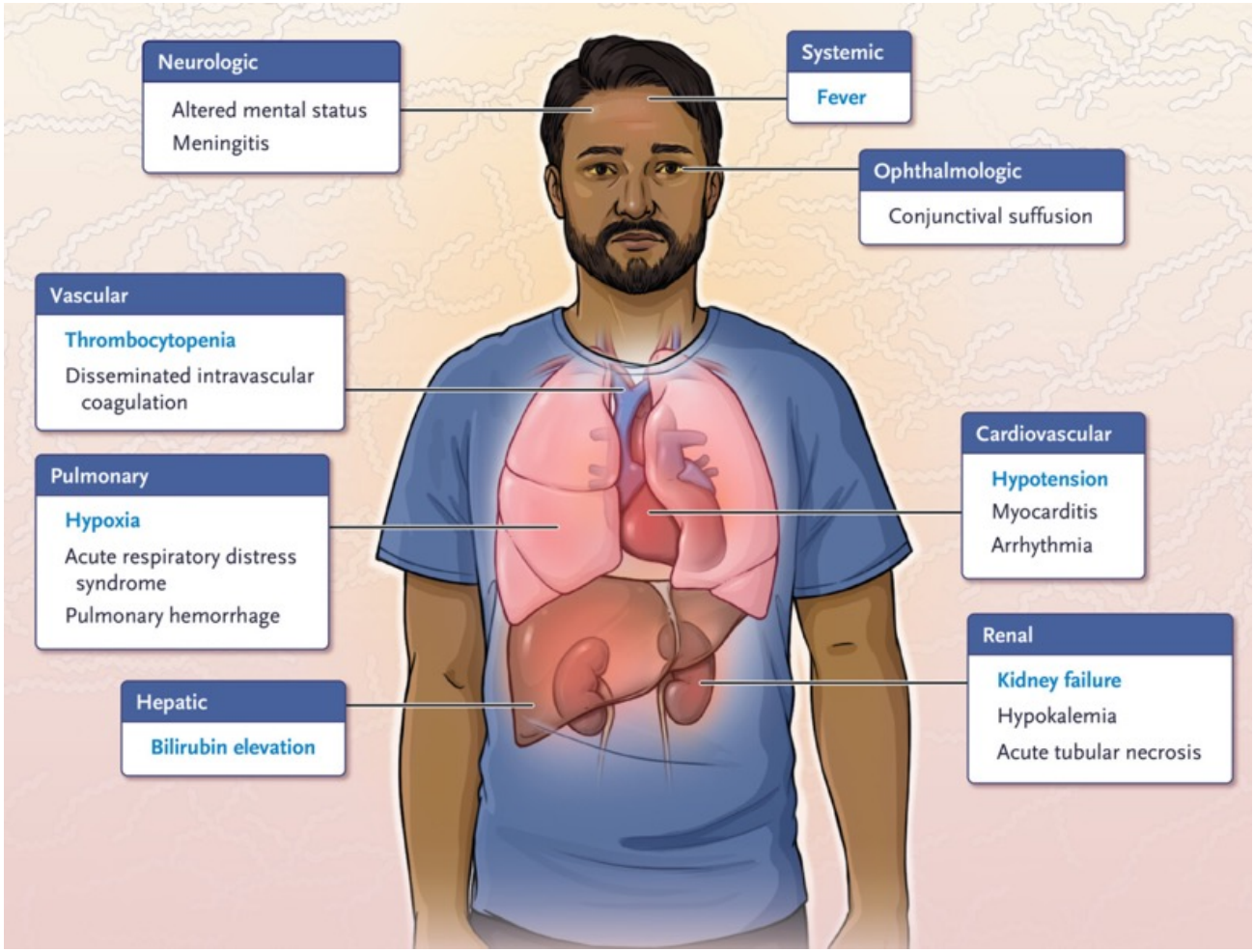
Phases of Leptospirosis and Diagnostic Testing.

The diagnosis of leptospirosis can be made through direct detection of the organism, which can be done with various methods, or through detection of antibodies to leptospires. In the first week after the onset of symptoms, leptospires are present in the blood, and nucleic acid amplification testing (NAAT) of whole blood is recommended.



Biopsy Specimen of the Liver.

A percutaneous, nonfocal liver biopsy was performed. Hematoxylin and eosin staining of the biopsy specimen (Panel A) shows a smooth contour and normal lobular architecture, including portal tracts (PT) and central veins (CV). Higher magnification of a portal tract (Panel B) shows mixed inflammation, including neutrophils (circles) and mononuclear cells, along with nonspecific, reactive changes in the bile ducts (arrows). Higher magnification of lobules (Panels C and D) shows circulating neutrophils with left-shifted band forms (circles), scattered mitotic figures (Panel C, rectangle), and nucleated red cells (Panel D, rectangle).



Clinical Manifestations of Leptospirosis.

Leptospirosis can manifest with a wide array of possible clinical signs and symptoms. The features present in this patient (shown in blue) include fever, thrombocytopenia, hypoxia, hypotension, kidney failure, and a markedly elevated bilirubin level.

In most cases, patients recover without the use of antimicrobial therapy. When this patient presented to the hospital, the probability of leptospirosis was high enough that we initiated empirical doxycycline therapy while awaiting the results of diagnostic testing.

Follow-up

Treatment with doxycycline was continued while the results of tests for leptospirosis were pending. The use of empirical vancomycin and cefepime therapy was discontinued once cultures of the blood had been negative for 48 hours. On the fifth hospital day, the white-cell count peaked at 54,950 per microliter, and the direct bilirubin level peaked at 39.0 mg per deciliter (667 µmol per liter); the creatinine level had improved and was 1.59 mg per deciliter (141 µmol per liter). The hypoxia, which could have been related to pulmonary hemorrhage, resolved; the acute kidney failure, which was attributed to acute tubular necrosis, abated. On the eighth hospital day, the white-cell count decreased to 18,870 per microliter, the direct bilirubin level to 26.1 mg per deciliter (369 µmol per liter), and the creatinine level to 1.4 mg per deciliter (124 µmol per liter). The patient was discharged home.

At home, the patient completed a 14-day course of doxycycline. The color of the skin, urine, and stool gradually returned to normal, and the malaise and fatigue were slow to abate. One month after discharge, the acute kidney failure had resolved; 2 months after discharge, the hyperbilirubinemia had resolved. Now, 11 months after discharge, the patient still struggles to cope with the mental health effects of the medical trauma related to his critical illness and hospitalization.

Final Diagnosis

Icteric leptospirosis.

Reductions in recurrence in women with early breast cancer entering clinical trials between 1990 and 2009: a pooled analysis of 155 746 women in 151 trials

Summary

Background Distant recurrence in women with oestrogen receptor-positive early breast cancer persists at a constant rate for more than 20 years after diagnosis, with little equivalent data for oestrogen receptor-negative breast cancer. Using the database of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) we investigated rates of distant breast-cancer recurrence in oestrogen receptor-positive and oestrogen receptor-negative tumours and trends in outcomes over time.

Methods In this pooled analysis of randomised controlled trial data, patients in the EBCTCG database of more than 650 000 women in trials of treatment for early-stage breast cancer were screened for eligibility. Women were eligible if they were enrolled between 1990 and 2009 and newly diagnosed with oestrogen receptor-positive breast cancer and scheduled for at least 5 years of endocrine therapy, or oestrogen receptor-negative disease, and if they were younger than 75 years at diagnosis, had a tumour diameter of 50 mm or less, and fewer than ten positive axillary lymph nodes, and no evidence of distant metastases at entry. Trial of neoadjuvant therapy, or those in which adjuvant therapy was unclear, and women with oestrogen receptor-negative, progesterone receptor-positive disease, or those for whom outcome or baseline data were missing were excluded. The primary outcome was time to first distant recurrence as defined by each trial, ignoring any locoregional recurrence or contralateral breast cancer. 10-year risks of distant recurrence by period of diagnosis were compared using Cox regression adjusted for patient and tumour characteristics, trial, and assigned treatment.

Findings Of the 652 258 women with early breast cancer in the EBCTCG database on Jan 17, 2023, patient-level data were available from 151 randomised trials that included 155 746 women. Rates of distant tumour recurrence improved similarly in women with oestrogen receptor-positive and oestrogen receptor-negative tumours. 80·5% of the improvement for oestrogen receptor-positive disease and 89·8% of the improvement for eostrogen receptor-negative disease was explained by changes in patient and tumour characteristics and improved treatments, but remained significant ($p<0·0001$). More recently diagnosed patients were more likely to have node-negative disease. 10-year distant recurrence risks during 1990–99 versus 2000–09 were as follows: for node-negative disease, 10·1% versus 7·3% for oestrogen receptor-positive disease and 18·3% versus 11·9% for oestrogen receptor-negative disease; for disease with one to three positive nodes, 19·9% versus 14·7% for oestrogen receptor-positive disease and 31·9% versus 22·1% for oestrogen receptor-negative disease; and for disease with four to nine positive nodes, 39·6% versus 28·5% for oestrogen receptor-positive disease and 47·8% versus 36·5% for oestrogen receptor-negative disease. After adjustment for therapy, rates were reduced by 25% (oestrogen receptor-positive disease) and 19% (oestrogen receptor-negative disease) after 2000 versus the 1990s, with similar improvements observed in oestrogen receptor-positive disease beyond 5 years.

Interpretation Most of the improvement in trial outcomes is explained by a greater proportion of women with lower-risk disease entering trials and improved adjuvant treatment. After adjustment, women diagnosed since 2000 have about a fifth lower rate of distant recurrence than the 1990s. Long-term risks of distant recurrence for oestrogen receptor-positive disease remain, but are about a tenth lower now than in our previous report.

	Oestrogen receptor-positive disease				Oestrogen receptor-negative disease			
	Overall (N=114 811)	1990–99 (N=29 080)	2000–04 (N=45 495)	2005–09 (N=40 236)	Overall (N=40 935)	1990–99 (N=15 295)	2000–04 (N=16 180)	2005–09 (N=8830)
Age at diagnosis								
<35 years	3036 (2·6%)	640 (2·2%)	1318 (2·9%)	1078 (2·7%)	2520 (6·2%)	1113 (7·0%)	958 (5·9%)	449 (5·1%)
35–44 years	17 962 (15·6%)	3560 (12·2%)	7351 (16·2%)	7051 (17·5%)	9769 (23·9%)	4044 (25·4%)	3787 (23·4%)	1938 (22·0%)
45–54 years	35 997 (31·4%)	8408 (28·9%)	14 712 (32·3%)	12 877 (32·0%)	13 898 (34·0%)	5210 (32·7%)	5866 (36·3%)	2822 (32·0%)
55–64 years	37 214 (32·4%)	10 024 (34·5%)	14 665 (32·2%)	12 525 (31·1%)	10 857 (26·5%)	3903 (24·5%)	4291 (26·5%)	2663 (30·2%)
65–74 years	20 602 (17·9%)	6448 (22·2%)	7449 (16·4%)	6705 (16·7%)	3891 (9·5%)	1655 (10·4%)	1278 (7·9%)	958 (10·9%)
Mean difference per decade	..		−0·17 (−0·18 to −0·16); p<0·0001		..		0·09 (0·07 to 0·11); p<0·0001	
Tumour diameter, mm								
1–10 (T1a–b)	20 100 (17·5%)	3568 (12·3%)	7917 (17·4%)	8615 (21·4%)	4135 (10·1%)	1582 (9·9%)	1842 (11·4%)	711 (8·1%)
11–20 (T1c)	47 433 (41·3%)	12 874 (44·3%)	18 534 (40·7%)	16 025 (39·8%)	15 028 (36·7%)	5924 (37·2%)	5569 (34·4%)	3535 (40·0%)
21–30 (T2)	29 766 (25·9%)	8290 (28·5%)	11 685 (25·7%)	9791 (24·3%)	13 074 (31·9%)	4916 (30·9%)	5153 (31·9%)	3005 (34·0%)
31–50 (T2)	17 512 (15·3%)	4348 (15·0%)	7359 (16·2%)	5805 (14·4%)	8698 (21·3%)	3503 (22·0%)	3616 (22·4%)	1579 (17·9%)
Odds ratio per category by time period	..		0·86 (0·85 to 0·88); p<0·0001		..		0·97 (0·95 to 1·00); p=0·024	
Axillary nodal status								
Zero positive nodes	49 735 (43·3%)	10 673 (36·7%)	17 465 (38·4%)	21 597 (53·7%)	17 784 (43·4%)	6841 (43·0%)	6025 (37·2%)	4918 (55·7%)
One to three positive nodes	46 412 (40·4%)	12 285 (42·3%)	19 328 (42·5%)	14 799 (36·8%)	14 967 (36·6%)	5329 (33·5%)	6570 (0·6%)	3068 (34·8%)
Four to nine positive nodes	18 664 (16·3%)	6122 (21·1%)	8702 (19·1%)	3840 (9·5%)	8184 (20·0%)	3755 (23·6%)	3585 (22·2%)	844 (9·6%)
Odds ratio per category by time period	..		0·68 (0·67 to 0·69); p<0·0001		..		0·77 (0·75 to 0·79); p<0·0001	
Tumour grade (differentiation)								
Low (well differentiated)	14 000 (12·2%)	3625 (12·5%)	5923 (13·0%)	4452 (11·1%)	661 (1·6%)	391 (2·5%)	207 (1·3%)	63 (0·7%)
Moderate	46 903 (40·9%)	10 924 (37·6%)	19 207 (42·2%)	16 772 (41·7%)	6257 (15·3%)	2707 (17·0%)	2540 (15·7%)	1010 (11·4%)
High (poorly differentiated)	25 947 (22·6%)	5694 (19·6%)	11 885 (26·1%)	8368 (20·8%)	23 257 (56·8%)	6930 (43·5%)	10 474 (64·7%)	5853 (66·3%)
Unknown grade	27 961 (24·4%)	8837 (30·4%)	8480 (18·6%)	10 644 (26·5%)	10 760 (26·3%)	5897 (37·0%)	2959 (18·3%)	1904 (21·6%)
Odds ratio per category by time period*	..		1·05 (1·03 to 1·06); p<0·0001		..		1·71 (1·66 to 1·75); p<0·0001	
Progesterone receptor status (oestrogen-receptor positive)								
Oestrogen receptor-positive, progesterone-poor disease	18 255 (15·9%)	5253 (18·1%)	7892 (17·4%)	5110 (12·7%)	..	..	..	..
Oestrogen receptor-positive, progesterone-positive disease	96 556 (84·1%)	23 827 (81·9%)	37 603 (82·6%)	35 126 (87·3%)	..	..	..	..
Odds ratio by time period	..		1·19 (1·16 to 1·21); p<0·0001		..	..	..	..
HER2 overexpression								
HER2 negative	52 341 (45·6%)	6320 (21·7%)	21 060 (46·3%)	24 961 (62·0%)	13 179 (32·2%)	2009 (12·6%)	5888 (36·4%)	5282 (59·8%)
HER2 positive	13 018 (11·3%)	1189 (4·1%)	8723 (19·2%)	3106 (7·7%)	8945 (21·9%)	929 (5·8%)	6652 (41·1%)	1364 (15·5%)
HER2 unknown	49 452 (43·1%)	21 571 (74·2%)	15 712 (34·5%)	12 169 (30·2%)	18 811 (46·0%)	12 987 (81·6%)	3640 (22·5%)	2184 (24·7%)
Odds ratio for HER2 testing by time period	..		2·46 (2·42 to 2·50); p<0·0001		..		4·77 (4·61 to 4·94); p<0·0001	
p value for HER2 positivity by period	..		p<0·0001		..		p<0·0001	

(Table 1 continues on next page)

	Oestrogen receptor-positive disease				Oestrogen receptor-negative disease			
	Overall (N=114 811)	1990–99 (N=29 080)	2000–04 (N=45 495)	2005–09 (N=40 236)	Overall (N=40 935)	1990–99 (N=15 295)	2000–04 (N=16 180)	2005–09 (N=8830)
(Continued from previous page)								
Original breast surgery								
Breast conserving	64 919 (56·5%)	13 992 (48·1%)	24 415 (53·7%)	26 512 (65·9%)	21 014 (51·3%)	7324 (46·0%)	8148 (50·4%)	5542 (62·8%)
Mastectomy	47 184 (41·1%)	13 903 (47·8%)	19 959 (43·9%)	13 322 (33·1%)	18 326 (44·8%)	7930 (49·8%)	7346 (45·4%)	3050 (34·5%)
Unknown	2708 (2·4%)	1185 (4·1%)	1121 (2·5%)	402 (1·0%)	1595 (3·9%)	671 (4·2%)	686 (4·2%)	238 (2·7%)
Odds ratio per category by time period*	..		0·71 (0·70 to 0·71); p<0·0001		..		0·73 (0·71 to 0·75); p<0·0001	
Chemotherapy scheduled								
Yes	75 414 (65·7%)	17 329 (59·6%)	30 910 (67·9%)	27 175 (67·5%)	37 518 (91·7%)	13 265 (83·3%)	15 473 (95·6%)	8780 (99·4%)
Non-anthracycline, non-taxane chemotherapy	9361 (8·2%)	1845 (6·3%)	3244 (7·1%)	4272 (10·6%)	6181 (15·1%)	3672 (23·1%)	2056 (12·7%)	453 (5·1%)
Anthracycline	22 513 (19·6%)	10 200 (35·1%)	6881 (15·1%)	5432 (13·5%)	12 964 (31·7%)	7257 (45·6%)	2879 (17·8%)	2828 (32·0%)
Taxane	3197 (2·8%)	332 (1·1%)	976 (2·2%)	1889 (4·7%)	1908 (4·7%)	128 (0·8%)	1029 (6·4%)	751 (8·5%)
Anthracycline + taxane	40 343 (35·1%)	4952 (17·0%)	19 809 (43·5%)	15 582 (38·7%)	16 465 (40·2%)	2208 (13·9%)	9509 (58·8%)	4748 (53·8%)
No	39 397 (34·3%)	11 751 (40·4%)	14 585 (32·1%)	13 061 (32·5%)	3417 (8·3%)	2660 (16·7%)	707 (4·4%)	50 (0·6%)
Odds ratio for chemotherapy by time period	..		1·18 (1·16 to 1·20); p<0·0001		..		4·82 (4·48 to 5·18); p<0·0001	
Odds ratio for anthracycline by time period	..		0·99 (0·97 to 1·00); p=0·059		..		2·08 (2·02 to 2·15); p<0·0001	
Odds ratio for taxane by time period	..		1·62 (1·60 to 1·65); p<0·0001		..		3·22 (3·12 to 3·32); p<0·0001	
Trastuzumab scheduled in HER2-positive disease								
Yes	6139 (46·6%)	0	4380 (49·6%)	1759 (55·5%)	4672 (51·9%)	0	3812 (56·8%)	860 (63·1%)
No	7048 (53·4%)	1189 (100%)	4448 (50·4%)	1411 (44·5%)	4329 (48·1%)	929 (100%)	2896 (43·2%)	504 (37·0%)
Odds ratio between 2000–04 and 2005–09	..		1·27 (1·17 to 1·37); p<0·0001		..		1·30 (1·15 to 1·46); p<0·0001	
Aromatase inhibitors given (oestrogen receptor-positive disease)								
Yes	47 165 (41·1%)	4250 (14·6%)	17 332 (38·1%)	25 583 (63·6%)	..	..	..	..
No	67 646 (58·9%)	24 830 (85·4%)	28 163 (61·9%)	14 653 (36·4%)	..	..	..	..
Odds ratio by time period	..		2·84 (2·76 to 2·92); p<0·0001		..	..	..	..
Duration of endocrine therapy (oestrogen receptor-positive disease)								
5 years	96 686 (84·2%)	29 080 (100%)	41 655 (91·6%)	25 951 (64·5%)	..	..	..	..
>5 years	18 125 (15·8%)	0	3840 (8·4%)	14 285 (35·5%)	..	..	..	..
Odds ratio between 2000–04 and 2005–09	..		5·97 (5·74 to 6·21); p<0·0001		..	..	..	..

Odds ratios and p values are for comparisons between all time periods. *Excluding unknown.

Table 1: **Characteristics of 114 811 women with oestrogen receptor-positive disease scheduled to receive 5 years or more of endocrine therapy and 40 935 women with oestrogen receptor-negative disease**

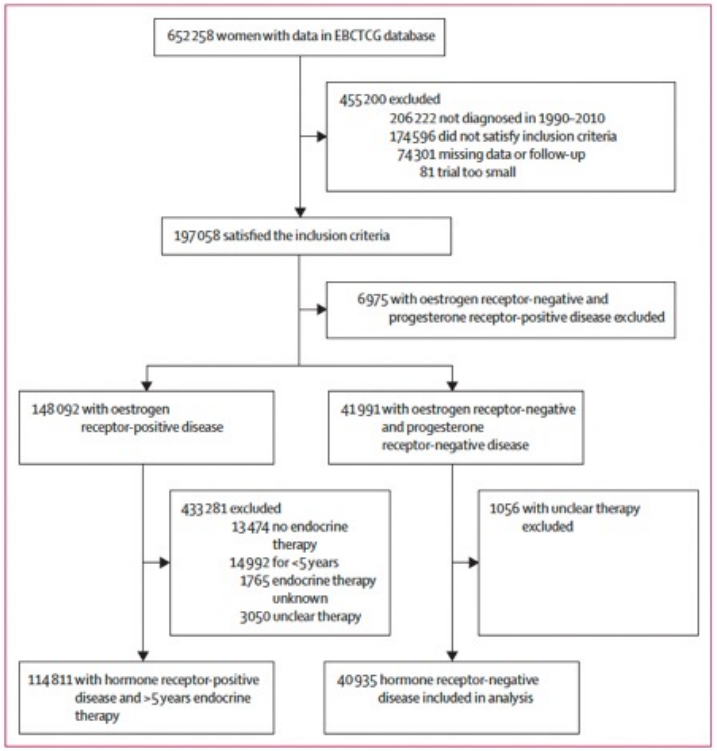
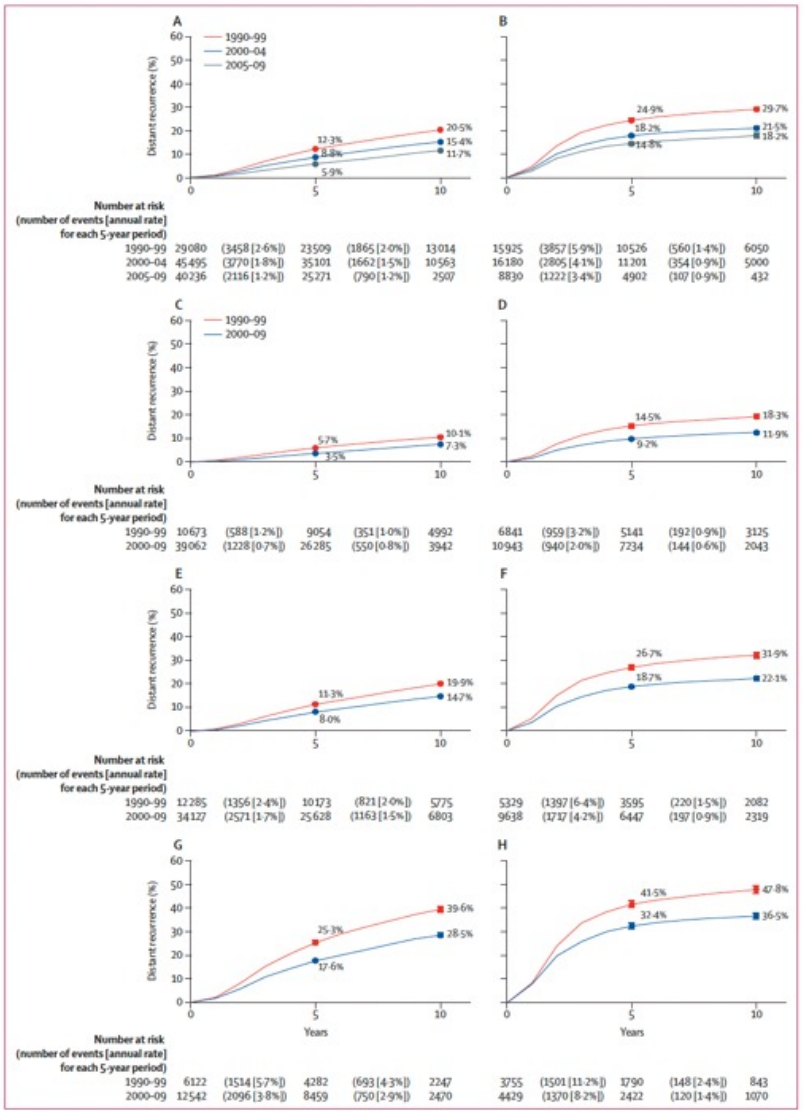


Figure 1: **Selection of patients for the analysis of trends in outcome over time**
Patients were required to be younger than 75 years, with a tumour diameter of less than 50 mm, with fewer than ten positive nodes, and no known distant metastases at entry. EBCTCG=Early Breast Cancer Trialists' Collaborative Group.

Figure 2: **Risk of distant recurrence by period of enrolment**
Risk of distant recurrence in patients with oestrogen receptor-positive disease (A); oestrogen receptor-negative disease (B); node-negative, oestrogen receptor-positive disease (C); node-negative, oestrogen receptor-negative disease (D); one-to-three positive nodes and oestrogen receptor-positive disease (E); one-to-three positive nodes and oestrogen receptor-negative disease (F); four-to-nine positive nodes and oestrogen receptor-positive disease (G); four-to-nine positive nodes and oestrogen receptor-negative disease (H). pinteraction<0·0001 between oestrogen receptor-positive and oestrogen receptor-negative disease (A, B). (C–H) Periods 2000–04 and 2005–09 combined to reflect the similarity of outcomes in those periods (for graphs for three time periods see appendix pp 37–38).



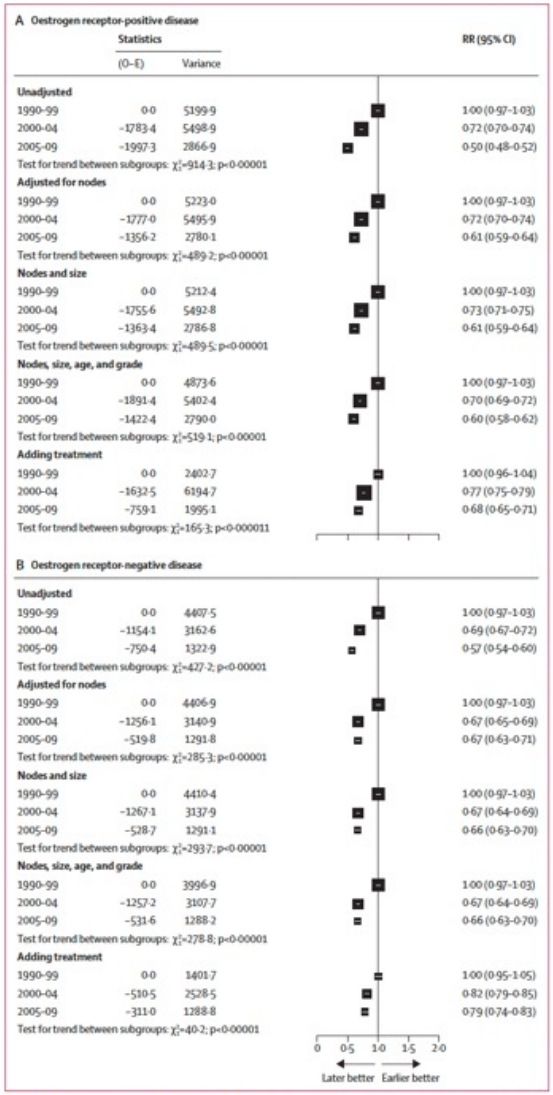
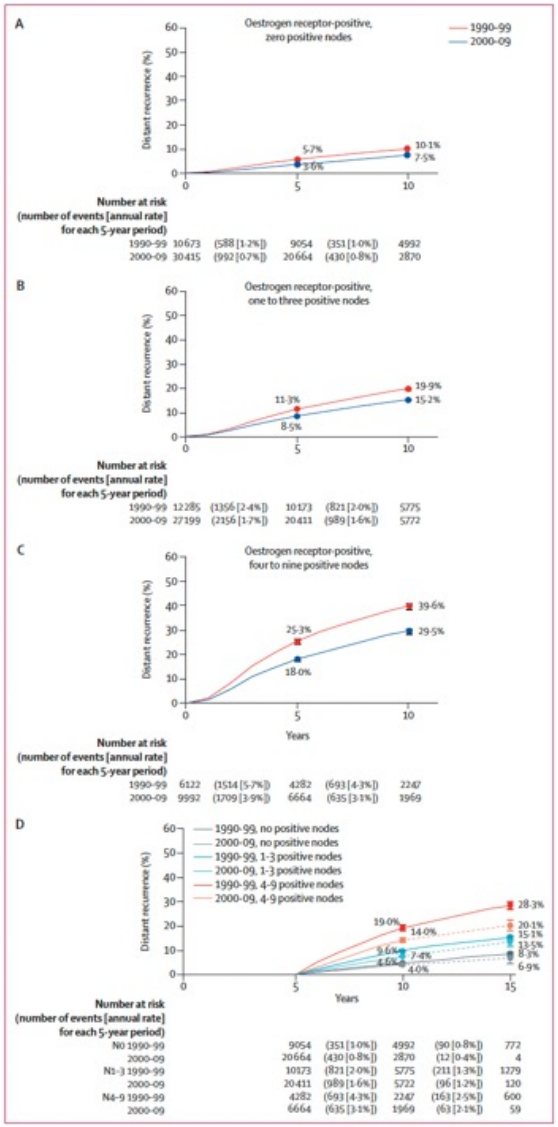


Figure 3: Association between year of diagnosis and rate ratio for distant recurrence during years 0–9 from enrolment, adjusted successively for tumour, patient characteristics, and treatment

Figure 4: **Distant recurrence by nodal status for women with oestrogen-receptor-positive disease with 5 years of scheduled endocrine therapy**
(A) Years 0–9 from diagnosis, node-negative disease. (B) Years 0–9 from diagnosis, one to three positive nodes. (C) Years 0–9 from diagnosis, four to nine positive nodes; (D) Recurrence after year 5 for women who were alive and recurrence free at 5 years split by period of diagnosis and nodal status; data beyond 10 years is smoothed for patients diagnosed after 2000 (dotted lines).

	Oestrogen receptor-positive disease	Oestrogen receptor-negative disease
Unadjusted	940·65	433·05
Univariate adjustment		
Nodes alone	481·25 (48·8)	282·45 (34·8)
Size alone	831·41 (11·6)	426·80 (1·4)
Grade alone	942·70 (-0·2)	420·11 (3·0)
Age alone	1037·28 (-10·3)	422·61 (2·4)
Bivariate adjustment		
Nodes and size	482·40 (48·7)	290·73 (32·9)
Nodes and grade	508·80 (45·9)	274·76 (36·6)
Nodes and age	503·37 (46·5)	276·01 (36·3)
Size and grade	833·15 (11·4)	426·86 (1·4)
Size and age	892·38 (5·1)	419·88 (3·0)
Grade and age	1007·64 (-7·1)	429·52 (0·8)
Adjustment for patient and tumour characteristics		
Nodes, size, grade, and age	510·18 (45·8)	276·00 (36·3)
Addition of treatment variables		
Including chemotherapy	316·14 (66·4)	59·90 (86·2)
Including chemotherapy and biological treatment	278·78 (70·4)	44·17 (89·8)
Including chemotherapy, biological treatment, and hormonal treatment (oestrogen receptor-positive disease)	182·98 (80·5)	..
Deviance associated with period of enrolment (percentage reduction from unadjusted analyses)		

Table 2: **Effect of successive adjustment on deviance associated with period of enrolment in Cox regression analyses**



Research in context

Evidence before this study

Reports by us and others have demonstrated that the risk of recurrence in women with hormone receptor-positive early breast cancer persists for at least two decades after diagnosis. However, these data were derived from trials conducted over many decades, and a recent analysis of a nationwide dataset suggested that outcomes for patients with early breast cancer have improved over time. Thus, estimates of recurrence on the basis of older datasets for women with early breast cancer, regardless of hormone receptor status, might not be relevant in today's practice. There is similarly a scarcity of information on women with hormone receptor-negative breast cancer, both in terms of outcomes and the extent to which they have improved over time. In both groups there is a need to understand the pattern of recurrence and whether the rates, or timing of recurrence, have changed with the advent of more modern therapies.

Added value of this study

Trial outcomes have improved over time in both hormone receptor-positive and hormone receptor-negative cancers. Most (80–90%) of this improvement can be explained by a combination of two factors: greater recruitment of women at lower risk in modern trials; and improved adjuvant therapies. Compared with 1990–99, in similar patients, adjusted for therapy, the rate of distant recurrence is reduced by approximately a quarter for oestrogen receptor-positive breast cancer and a fifth for oestrogen receptor-negative breast cancer. Although the risk of distant recurrence is lower in recent, compared to past eras, the risk of late recurrence is still present for patients with hormone receptor-positive breast cancer. By contrast, although risk of recurrence is lower for modern compared to older eras in hormone receptor-negative breast cancer, most of the recurrences in such patients continue to occur in the first 5 years after diagnosis.

Implications of all the available evidence

Estimates of recurrence rates can be used both by patients and their doctors in deciding on a course of therapy, in terms of balancing benefits and harms of therapies, and especially regarding whether to persist with endocrine therapy beyond 5 years in hormone receptor-positive disease, as well as in the design of future clinical trials. It is important to use up-to-date data and incorporate patient risk factors rather than simply estimating recurrence rates using overall results from older trials that reflect neither disease heterogeneity nor current case mix and outcomes.

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5-year vaccine protection following a single dose of Vi-tetanus toxoid conjugate vaccine in Bangladeshi children (TyVOID): a cluster randomised trial

Summary

Background WHO currently recommends a single dose of typhoid conjugate vaccine (TCV) in high-burden countries based on 2-year vaccine efficacy data from large randomised controlled trials. Given the decay of immunogenicity, the protection beyond 2 years is unknown. We therefore extended the follow-up of the TyVAC trial in Bangladesh to assess waning of vaccine protection to 5 years after vaccination.

Methods We conducted a cluster randomised controlled trial (TyVAC; ISRCTN11643110) in Dhaka, Bangladesh, between 2018 and 2021. Children aged 9 months to 15 years were invited to receive a single dose of TCV or Japanese encephalitis vaccine between April 15, 2018, and November 16, 2019, based on the randomisation of their clusters of residence. Children who received the Japanese encephalitis vaccine were invited to receive TCV at the final visit between Jan 6, and Aug 31, 2021, according to the protocol. This follow-on study extended the follow-up of the original trial until Aug 14, 2023. The primary endpoint of this study was to compare the incidence of blood culture-confirmed typhoid between children who received TCV in 2018–19 (the previous-TCV group) and those who received the vaccine in 2021 (the recent-TCV group), to evaluate the relative decline in vaccine protection. We also did a nested study using the test-negative design comparing the recent-TCV and previous-TCV groups with unvaccinated individuals, as well as an immunogenicity study in a subset of 1500 children.

Findings Compared with the recent-TCV group, the previous-TCV group had an increased risk of typhoid fever between 2021–23, with an adjusted incidence rate ratio of 3·10 (95% CI 1·53 to 6·29; p<0·0001), indicating a decline in the protection of a single-dose of TCV 3–5 years after vaccination. The extrapolated vaccine effectiveness in years 3–5 was 50% (95% CI –13 to 78), and was validated using the test-negative design analysis, with a vaccine effectiveness of 84% (74 to 90) in the recent-TCV group and 55% (36 to 68) in the previous-TCV group, compared with unvaccinated individuals. Anti-Vi-IgG responses declined over the study period. The highest rate of decay was seen in children vaccinated at younger than 2 years in the original trial. The inverse correlation between age and the decay of antibodies was also seen in the subgroup analysis of vaccine effectiveness, where the youngest age group (<7 years at fever visits) exhibited the fastest waning, with vaccine effectiveness dropping to 24% (95% CI –29 to 55) at 3–5 years after vaccination.

Interpretation A decline in the protection conferred by a single-dose TCV was observed 3–5 years after vaccination, with the greatest decline in protection and immune responses observed in children vaccinated at younger ages. A booster dose of TCV around school entry age might be needed for children vaccinated while younger than 2 years to sustain protection against typhoid fever during the school years when the risk is the highest.

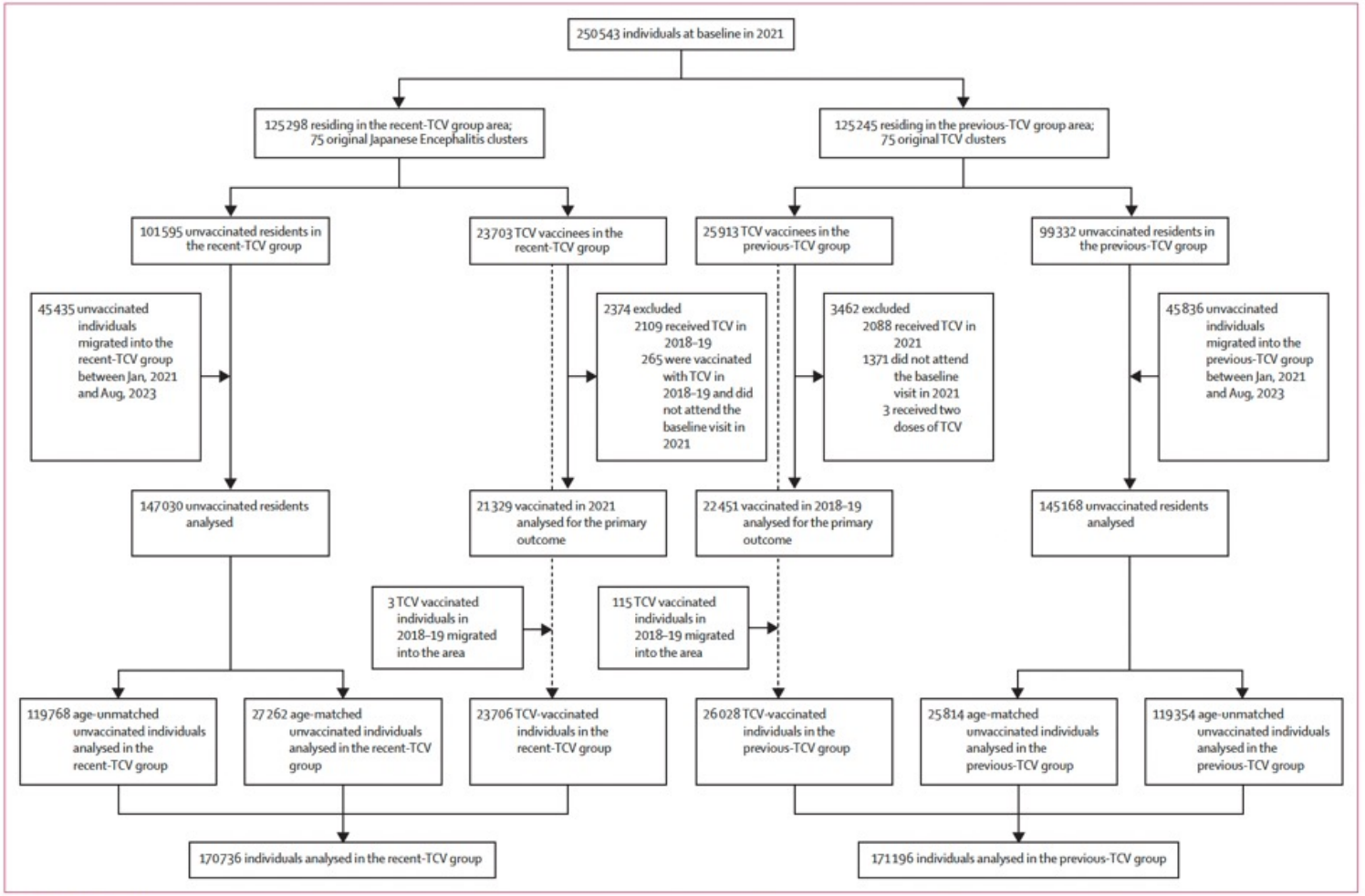


Figure 1: **Trial profile**

Age-matched unvaccinated individuals are residents of the study areas who did not receive TCV and were age-eligible (9 months to <16 years) for vaccination during the original trial vaccination campaigns.

	Recent-TCV group	Previous-TCV group	Adjusted IRR (95% CI)	p value
Vaccine recipients	(n=21 329)	(n=22 451)	3·10 (1·53–6·29)	0·0008*
Number of blood-culture-confirmed typhoid fever/person-years	14/44 848	45/46 404	..	..
Incidence rate per 100 000 person-years (95% CI)	31 (17–52)	97 (71–130)	..	..
Age-matched unvaccinated individuals	(n=27 262)	(n=25 814)	0·99 (0·61–1·59)	0·97
Number of blood-culture-confirmed typhoid fever/person-years	66/42 313	58/39 844	..	..
Incidence rate per 100 000 person-years (95% CI)	156 (121–198)	146 (111–188)	..	..
Age-unmatched unvaccinated individuals	(n=119 768)	(n=119 354)	1·18 (0·78–1·80)	0·43
Number of blood-culture-confirmed typhoid fever/person-years	59/210 825	66/209 875	..	..
Incidence rate per 100 000 person-years (95% CI)	28 (21–36)	31 (24–40)	..	..
Residents	(n=170 736)	(n=171 196)	1·32 (0·95–1·83)	0·095
Number of blood-culture-confirmed typhoid fever/person-years†	142/302 621	180/302 716	..	..
Incidence rate per 100 000 person-years (95% CI)	47 (40–55)	59 (51–69)	..	..

IRR is adjusted for design variables (the number of children aged 9 months to <16 years and ward and distance of cluster to the nearest health facility), covariates (age at TyVOID baseline and gender), and random effect (cluster). Age-matched individuals were age-eligible (9 months to <16 years) for vaccination during the original trial vaccination campaigns. Age-unmatched individuals were age-ineligible for vaccination during the original trial vaccination campaigns. IRR=incidence rate ratio. *One-sided p value. †The discrepancy between the number of typhoid fever cases in all residents and the sum of typhoid fever in vaccinated and unvaccinated individuals is because some who received TCV were excluded in the analysis of vaccinated individuals but included in the all residents analysis.

Table 1: **Incidence of blood culture-confirmed typhoid fever**

	Test-negatives for typhoid	Test-positives for typhoid	Adjusted OR (95% CI)	Vaccine effectiveness (95% CI)	p value
Test negative defined as no growth in blood culture	n=2212	n=198	..	..	..
Unvaccinated individuals	726 (33%)	125 (63%)	1 (ref)	..	..
Previous-TCV group	717 (32%)	54 (27%)	0·45 (0·32–0·63)	55% (36–68)	<0·0001
Recent-TCV group	769 (35%)	19 (10%)	0·16 (0·10–0·26)	84% (74–90)	<0·0001
Test-negative defined as positive for *Salmonella enterica* serotype Paratyphi	n=91	n=198	..	..	..
Unvaccinated individuals	32 (35%)	125 (63%)	1 (ref)	..	..
Previous-TCV group	30 (33%)	54 (27%)	0·46 (0·24–0·87)	54% (13–76)	0·018
Recent-TCV group	29 (32%)	19 (10%)	0·18 (0·08–0·37)	83% (63–92)	<0·0001

Data are n (%), unless otherwise specified. The previous-TCV group were vaccinated with TCV in 2018–19. The recent-TCV group were vaccinated with TCV in 2021. The OR and vaccine effectiveness are adjusted for gender, age at fever visit, fever clinics, timing of fever visit (by quarters, ie, 2021Q1–2023Q3), distance of the cluster of residence to the nearest health facility, and geographical ward. OR=odds ratio.

Table 2: **TCV vaccine effectiveness by the test negative design**

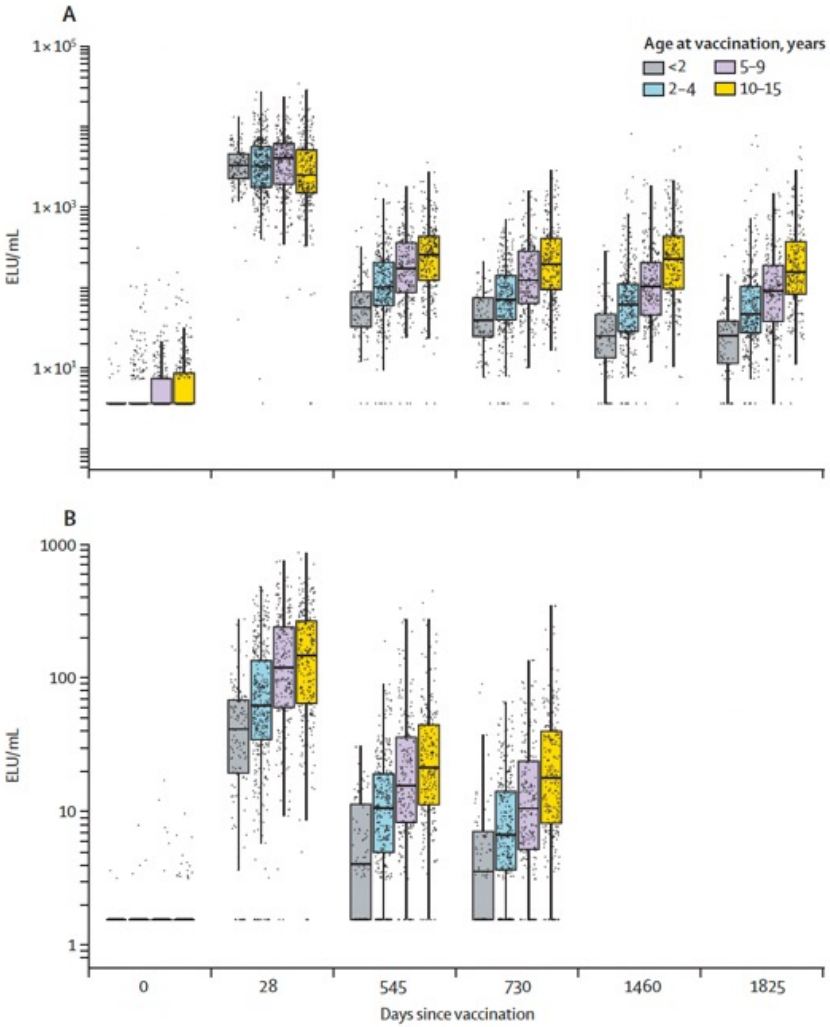


Figure 2: **Kinetics of antibody responses**
(A) Anti-Vi IgG. (B) Anti-Vi IgA.

	Test-negatives for typhoid (specimens with no growth in blood culture)	Test-positives for typhoid	Adjusted OR (95% CI)	Vaccine effectiveness (95% CI)	p value
<7 years					
Unvaccinated individuals	382 (38%)	48 (59%)	1 (ref)	..	..
Previous-TCV group	310 (30%)	28 (35%)	0·86 (0·45 to 1·29)	24% (–29 to 55)	0·31
Recent-TCV group	326 (32%)	5 (6%)	0·15 (0·06 to 0·40)	85% (60 to 94)	0·0001
7–9 years					
Unvaccinated individuals	111 (25%)	23 (56%)	1 (ref)	..	..
Previous-TCV group	158 (35%)	13 (32%)	0·41 (0·19 to 0·88)	59% (12 to 81)	0·023
Recent-TCV group	180 (40%)	5 (12%)	0·13 (0·05 to 0·38)	87% (62 to 95)	0·0001
10–14 years					
Unvaccinated individuals	122 (26%)	26 (60%)	1 (ref)	..	..
Previous-TCV group	162 (35%)	9 (21%)	0·26 (0·11 to 0·59)	74% (41 to 89)	0·0012
Recent-TCV group	180 (39%)	8 (19%)	0·20 (0·08 to 0·46)	80% (54 to 92)	0·0002
15–19 years					
Unvaccinated individuals	107 (39%)	27 (84%)	1 (ref)	..	..
Previous-TCV group	85 (31%)	4 (13%)	0·15 (0·05 to 0·49)	85% (51 to 95)	0·0014
Recent-TCV group	81 (30%)	1 (3%)	0·04 (0·01 to 0·33)	96% (67 to 99)	0·0024

The previous-TCV group were vaccinated with TCV in 2018–19. The recent-TCV group were vaccinated with TCV in 2021. The OR and vaccine effectiveness are adjusted for gender, age at fever visit, fever clinics, timing of fever visit (by quarters, ie, 2021Q1–2023Q3), distance of the cluster of residence to the nearest health facility, and geographical ward. OR=odds ratio.

Table 3: **TCV vaccine effectiveness across age groups at fever visit by test-negative design**

Research in context

Evidence before this study

Several next-generation typhoid vaccines, based on the Vi polysaccharide conjugated to a carrier protein, have been developed, with the first (Vi conjugated to tetanus toxoid) achieving WHO prequalification in 2017. To review previous studies of the efficacy of typhoid conjugate vaccine (TCV), we used the terms ("typhoid conjugate vaccine" OR "Vi-conjugate vaccine") AND ("efficacy" OR "protection") with searching filters for clinical trials, randomised controlled trials, or systematic reviews, published between Jan 1, 2018, and April 3, 2024, with no language restrictions. We identified 25 research articles in PubMed, 47 in the Cochrane Central Register of Controlled Trials, and 33 in Google Scholar. Three randomised clinical trials evaluating the efficacy of TCV in children in Malawi, Nepal, and Bangladesh were identified. The trials of a single dose of TCV reported high vaccine efficacy within 2 years in all countries (81% at 18–24 months in Malawi, 79% at 24 months in Nepal, and 85% at 18 months in Bangladesh). Data on the protection beyond 2 years is sparse, with only the TCV trial conducted in Malawi reporting the vaccine efficacy after a median follow-up period of 4·3 years. The study found no clear waning in vaccine efficacy with a cumulative vaccine efficacy of 78·3% (95% CI 66·3–86·1).

Added value of this study

We extended the follow-up of our original cluster randomised controlled trial conducted in Bangladesh to assess the protection in years 3–5 following a single dose of TCV in children aged 9 months to 15 years at vaccination. Children who received the Japanese encephalitis vaccine in the original cluster randomised controlled trial between 2018–19 were immunised with TCV in 2021. We observed a three-fold rise in the incidence of typhoid fever in the previous-TCV group (ie, vaccination in 2018–19) compared with the recent-TCV group (ie, vaccination in 2021), suggesting a decline in vaccine effectiveness approximately 3–5 years after vaccination with a single dose of TCV. We estimated the vaccine effectiveness to be 50% (95% CI −13 to 78) at 3–5 years following vaccination, based on the 2-year vaccine effectiveness of TCV in the original cluster randomised controlled trial and the adjusted incidence rate ratio between the previous-TCV and recent-TCV groups in this study. In addition, we found that the decline in vaccine effectiveness correlated with the age at vaccination, with children vaccinated while younger than 2 years exhibiting the most significant waning (from 85% to 24%). The age trend of vaccine effectiveness decline was found to be consistent with the trend of anti-Vi IgG decay among different age groups with children vaccinated at younger ages having a faster decay.

Implications of all the available evidence

Our findings showed a decline in the protection conferred by a single dose of TCV 3–5 years after vaccination. The results from our study suggest that a booster dose around school entry age for children vaccinated while younger than 2 years might be needed to sustain TCV protection throughout the school years when the highest risk of typhoid fever is experienced.

Postpartale Stimmungskrisen beschreiben psychische Zustände oder Störungen, die in einem zeitlichen Zusammenhang mit dem Wochenbett auftreten. Die Bandbreite der im Wochenbett auftretenden affektiven Zustände reicht von einer leichten Traurigkeit über Depressionen bis hin zu schweren psychotischen Erkrankungen.

Efficacy of a culturally adapted, cognitive behavioural therapy-based intervention for postnatal depression in British south Asian women (ROSHNI-2): a multicentre, randomised controlled trial

Summary

Background Postnatal depression necessitates timely and effective interventions to mitigate adverse maternal and child outcomes in the short term and over the life course. British south Asian women with depression are often underserved and undertreated due to stigma, language barriers, and cultural barriers. This trial aimed to test the clinical efficacy of a culturally adapted, group cognitive behavioural therapy (CBT)-based intervention, the Positive Health Programme (PHP), delivered by non-specialist health workers for postnatal depression in British south Asian women.

Methods This study was a randomised controlled trial, with culturally adapted recruitment and an internal pilot, comparing the PHP (intervention group) with treatment as usual (control group) in British south Asian women with postnatal depression. The study was conducted at five centres across the UK. Participants were aged 16 years or older, met the DSM-5 criteria for depression, and had infants aged 0–12 months. Randomisation (1:1) was stratified by centre, with a block size of 18, and was done through an independent remote telephone service. The PHP was delivered over 12 group sessions in 4 months. The primary outcome was recovery from depression (defined as a Hamilton Depression Rating Scale [HDRS] score ≤7) at 4 months after randomisation, and an assessment was also done at 12 months. Analysis was on an intention-to-treat basis including only participants with non-missing outcome data; we used a random-effects logistic regression model including fixed covariates for study site, baseline depression severity (HDRS score), parity, and years in education and a random coefficient for therapy group. This trial is registered with the ISRCTN (ISRCTN10697380).

Findings Of the 9136 individuals approached for recruitment between Feb 8, 2017, and March 29, 2020, 4296 women were eligible for and consented to screening, among whom 732 screened positive and were randomly allocated: 368 (50%) to the PHP group and 364 (50%) to the control group. Participants were mostly of Pakistani (397 [55%] of 719 with available data), Indian (176 [24%]), or Bangladeshi ethnicity (127 [18%]), with an overall mean age of 31·4 years (SD 5·2), with their youngest infants having a mean age of 23·6 weeks (14·2). At 4 months from randomisation, the proportion of participants who showed recovery from depression on the HDRS was significantly higher in the PHP group (138 [49%] of 281) than in the control group (105 [37%] of 281; adjusted odds ratio 1·97 [95% CI 1·26–3·10]). At the 12-month follow-up, this difference was no longer significant (1·02 [95% CI 0·62–1·66]).

Interpretation In British south Asian women with postnatal depression, a culturally adapted group CBT-based intervention could aid in quicker recovery from depression compared with treatment as usual. Further research is needed to identify how to sustain the treatment effect and establish strategies for scale-up.

Panel: **Key strategies used to facilitate recruitment[21]**

Community engagement

Bilingual research assistants attended community children's centres or community venues that host children's playgroups. We worked closely and developed service level agreements with a number of third-sector organisations across our study sites. These organisations had community link workers or outreach workers who were trained in study processes to provide information about the study and raise awareness in the community. This upskilled community workers and also ensured those with established community trust and rapport could positively influence study recruitment.

The team collaborated with different organisations to host events involving families, key opinion makers from the local community, and professionals to tackle stigma and raise awareness. Previous research staff and health professionals have labelled minority ethnic community members as "hard to reach", and thus the people in those communities are wary of working with big establishments.[19]

***Chai* with ROSHNI-2**

The team arranged regular drop-in sessions open to the community. General practitioners and health visitors were also invited to meet the general members of south Asian community and encourage conversations around mental health in the postnatal period over *chai* (tea). The events were focused on normalising conversations and tackling stigma. Information about the study was given at the end of the events and anyone eligible was able to ask for more information.

Engaging with faith leaders

The team worked to liaise and engage with faith leaders from the key religions practised in this community. Faith leaders from Muslim and Hindu communities joined study advisory groups. Meetings were held with local councils of mosques and Hindu and Sikh associations. They were briefed on the importance and background of the study and asked to support by sharing information with their congregations about the study at events. Some mosques included information on ROSHNI-2 at the end of sermons during the holy month of Ramadhan and encouraged families to engage with the project.

Family engagement

There was a need for educating family members on taboo subjects such as postnatal depression and seeking support from health services in a manner that suited them. Many felt they needed to carry on as normal and not make their situation publicly known. Family members felt that if other people found out, family reputation might be affected. Some participants would not receive permission to attend the groups from extended family or their partner. The team offered to meet with the whole family to explore and discuss the content of the group sessions and the importance of the therapy sessions, not just for the mother but also for the child or children. Family were also included in the consent process to ensure that the team were being sensitive to the power dynamics within south Asian homes and facilitating participation by adapting processes.

Language

Many languages are spoken by the British south Asian population, the common ones being Urdu, Punjabi, Gujarati, Bengali, and Tamil. Each researcher is able to speak English and one of the study languages fluently. Participants are able to communicate in the language that they feel most comfortable in. All the study materials—including promotional posters, information leaflets, and study assessments—were translated into the key study languages.

Cultural competence and staff training

Staff were trained in cultural sensitivity and competence, including awareness of participants' cultural commitments and religious beliefs. Regular team discussions were held on dynamics, respect, understanding, and appropriateness of verbal and non-verbal communications. ROSHNI-2 staff researchers and also participants helped to raise awareness among non-minority ethnic health professionals of cultural differences, including by sharing positive case studies with general practitioners or health visitors.

Social media

Trained research assistants promoted the ROSHNI-2 project via social media platforms including Facebook, Twitter, and Instagram. Promotions included weekly updates and posts on the importance of maternal mental health. The pages were managed by a communications and media intern within the team in line with guidance from the National Institute for Health and Care Research on the use of social media in research. We produced short promotional animated videos, posts introducing members of the team to build trust and rapport within the community, and updates on study progress. Potential participants were able to message with questions or to express interest in participating.

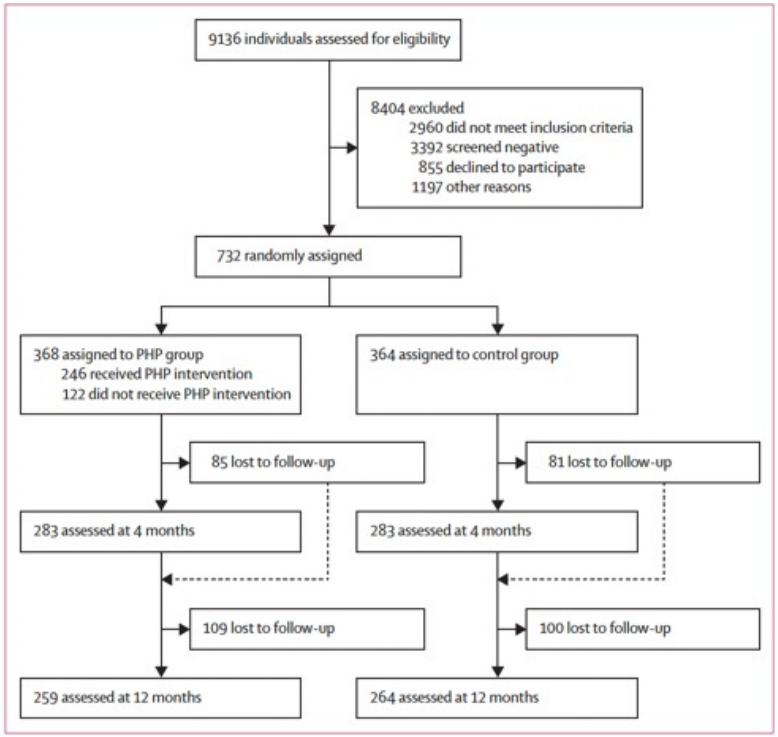


Figure 1: **Trial profile**

Numbers shown as assessed at 4 months and 12 months are those who had at least one response on the Hamilton Depression Rating Scale at that timepoint; however, the analyses included only participants with responses to at least half of the questions (see table 2 for numbers). PHP=Positive Health Programme.

	Positive Health Programme group (N=368)	Control group (N=364)
Age, years	31·3 (5·2), N=364	31·4 (5·2), N=355
Years in education	13·9 (3·6), N=300	13·7 (4·0), N=301
Years married (if married)	6·7 (4·8), N=345	7·0 (5·0), N=326
Age of youngest child, weeks	23·7 (14·1), N=307	23·6 (14·3), N=306
Number of people living in household	5·0 (1·9), N=359	5·2 (2·1), N=351
Hamilton Depression Rating Scale score	17·6 (7·3), N=367	18·0 (7·3), N=361
Ethnicity		
Indian	91/365 (25%)	85/354 (24%)
Bangladeshi	60/365 (16%)	67/354 (19%)
Pakistani	202/365 (55%)	195/354 (55%)
Other south Asian	12/365 (3%)	7/354 (2%)
English speaking		
Yes	338/363 (93%)	327/352 (93%)
No	25/363 (7%)	25/352 (7%)
Religion		
Islam	322/366 (88%)	315/357 (88%)
Hinduism	23/366 (6%)	28/357 (8%)
Christianity	2/366 (1%)	4/357 (1%)
Buddhism	3/366 (1%)	0/357
Sikhism	16/366 (4%)	9/357 (3%)
Other	0/366	1/357 (<1%)
Generational status*		
First generation	206/364 (57%)	215/353 (61%)
Second generation	120/364 (33%)	103/353 (29%)
Third generation	38/364 (10%)	35/353 (10%)
Employment status		
Full-time	42/365 (12%)	44/352 (13%)
Part-time	56/365 (15%)	43/352 (12%)
Unemployed	39/365 (11%)	43/352 (12%)
Sick	1/365 (<1%)	0/352
Housewife	197/365 (54%)	186/352 (53%)
Student	2/365 (1%)	3/352 (1%)
Other	28/365 (8%)	33/352 (9%)
Nature of employment at time of assessment		
Current employment	97/364 (27%)	93/349 (27%)
Previous employment	2/364 (1%)	2/349 (1%)
Partner employed	1/364 (<1%)	4/349 (1%)
Not applicable	264/364 (73%)	250/349 (72%)

(Table 1 continues in next column)

	Positive Health Programme group (N=368)	Control group (N=364)
(Continued from previous column)
Highest educational qualification		
Primary	12/352 (3%)	14/349 (4%)
GCSE	49/352 (14%)	68/349 (19%)
A-level	80/352 (23%)	70/349 (20%)
Undergraduate degree	121/352 (34%)	100/349 (29%)
Postgraduate degree	60/352 (17%)	59/349 (17%)
Other	30/352 (9%)	38/349 (11%)
Marital status		
Single	4/366 (1%)	7/356 (2%)
Married or cohabiting	349/366 (95%)	335/356 (94%)
Divorced or separated	13/366 (4%)	14/356 (4%)
Previously separated or widowed		
Divorced	31/330 (9%)	30/318 (9%)
Separated	15/330 (5%)	14/318 (4%)
Widowed	1/330 (<1%)	5/318 (2%)
Not applicable	283/330 (86%)	269/318 (85%)
Number of male children		
0	93/357 (26%)	103/344 (30%)
1	166/357 (46%)	158/344 (46%)
2	72/357 (20%)	64/344 (19%)
3	22/357 (6%)	14/344 (4%)
≥4	4/357 (1%)	5/344 (1%)
Number of female children		
0	107/350 (31%)	88/336 (26%)
1	143/350 (41%)	142/336 (42%)
2	70/350 (20%)	76/336 (23%)
3	25/350 (7%)	24/336 (7%)
≥4	5/350 (1%)	6/336 (2%)
Living with extended family		
Yes	111/363 (31%)	109/352 (31%)
No	252/363 (69%)	243/352 (69%)

Data are mean (SD) or n/N (%). GCSE=General Certificate of Secondary Education. A-level=General Certificate of Education Advanced Level. *Generations since a family's migration from south Asia to the UK, where "first generation" refers to those who immigrated to the UK during their lifetime, "second generation" to their children, and "third generation" to their grandchildren.

Table 1: **Baseline characteristics of study participants**

Primary outcome						
Recovery from depression (HDRS score ≤7)						
4 months						
Yes	281	138 (49%)	281	105 (37%)	1·97 (1·26 to 3·10)	0·0030
No	281	143 (51%)	281	176 (63%)	1 (ref)	..
12 months						
Yes	259	141 (54%)	261	140 (54%)	1·02 (0·62 to 1·66)	0·80
No	259	118 (46%)	261	121 (46%)	1 (ref)	..
Secondary outcomes						
Treatment response on HDRS‡						
4 months						
Yes	281	158 (56%)	279	112 (40%)	2·49 (1·38 to 4·52)	0·0026
No	281	123 (44%)	279	167 (60%)	1 (ref)	..
12 months						
Yes	259	158 (61%)	260	151 (58%)	1·07 (0·59 to 1·95)	0·82
No	259	101 (39%)	260	109 (42%)	1 (ref)	..
PHQ-9 score						
Baseline	368	15·21 (3·93)	361	15·85 (4·21)	..	..
4 months	282	7·22 (5·80)	280	9·09 (6·34)	−2·05 (−3·18 to −0·92)	<0·0001
12 months	258	6·77 (5·55)	260	7·60 (6·81)	−0·89 (−2·05 to 0·27)	0·13
GAD-7 score						
Baseline	364	11·56 (5·87)	356	11·60 (5·62)	..	..
4 months	279	6·05 (5·66)	277	7·37 (5·71)	−1·45 (−2·66 to −0·25)	0·018
12 months	256	5·95 (5·51)	259	6·40 (6·26)	−0·24 (−1·46 to 0·99)	0·71
PSCS score						
Baseline	337	63·00 (12·01)	321	62·36 (10·92)	..	..
4 months	252	69·13 (12·25)	247	67·19 (10·77)	1·76 (−0·37 to 3·89)	0·11
12 months	226	69·88 (12·32)	225	67·43 (12·61)	3·32 (1·10 to 5·54)	0·0034
Social functioning score						
Baseline	352	12·91 (9·85)	337	12·98 (9·67)	..	..
4 months	262	6·62 (7·76)	267	8·04 (8·75)	−1·57 (−3·74 to 0·59)	0·16
12 months	246	6·05 (7·98)	250	6·73 (8·77)	−0·34 (−2·51 to 1·83)	0·76
EQ-5D-3L VAS score						
Baseline	354	55·43 (19·80)	342	55·28 (20·44)	..	..
4 months	271	66·20 (21·60)	268	64·26 (21·55)	3·30 (−0·35 to 6·95)	0·077
12 months	256	68·12 (21·10)	257	65·93 (21·71)	3·48 (−0·28 to 7·23)	0·069
Satisfaction with treatment						
4 months						
Yes	260	242 (93%)	257	222 (86%)	2·72 (1·05 to 7·09)	0·040
No	260	18 (7%)	257	35 (14%)	1 (ref)	..
12 months						
Yes	252	235 (93%)	248	224 (90%)	2·03 (0·77 to 5·40)	0·16
No	252	17 (7%)	248	24 (10%)	1 (ref)	..

N values show the number of participants who answered at least half of the questions for the given scale and were included in the analysis. Binary outcomes (recovery, treatment response, and satisfaction with assessment) are presented as n (%) per group, with adjusted ORs (95% CI) for between-group comparisons. All other outcomes are presented as mean score (SD) per group, with adjusted differences (95% CI) for between-group comparisons. HDRS=Hamilton Depression Rating Scale. OR=odds ratio. PHQ-9=nine-item Patient Health Questionnaire. GAD-7=seven-item Generalized Anxiety Disorder. PSCS=Parenting Sense of Competence Scale. VAS=visual analogue scale. *Adjusted for therapist (random effect), baseline HDRS score, parity, and years in education. †Adjusted for therapist (random effect), baseline HDRS score, parity, education, and baseline value of outcome variable. ‡Defined as a ≥50% reduction in HDRS score compared with baseline.

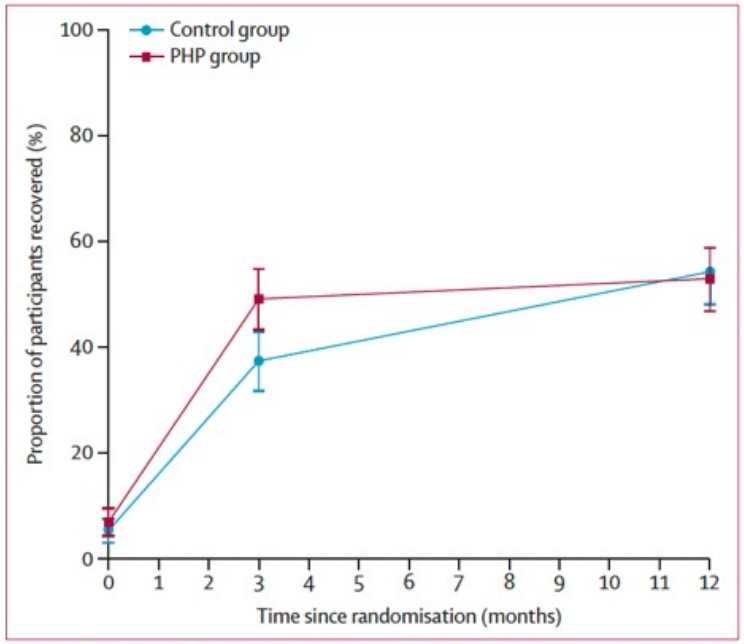


Figure 2: **Recovery from postnatal depression (primary outcome)**
Proportions of patients who had recovered from depression (defined as a score of ≤7 on the Hamilton Depression Rating Scale) at the three assessment timepoints. PHP=Positive Health Programme.

Research in context

Evidence before this study

Postnatal depression is highly prevalent worldwide, is associated with poor maternal and infant outcomes, and is a significant public health concern. The UK National Institute for Health and Care Excellence (NICE) recommends cognitive behavioural therapy (CBT) as a primary treatment for postnatal depression. Our previous systematic review and meta-analysis of 59 CBT-based interventions showed that group-based CBT interventions were effective for postnatal depression (standardised mean difference –0·67 [95% CI –0·96 to –0·38]; n=4915) in majority populations in high-income societies, even when administered by trained non-specialist health workers. It also showed a scarcity of studies on the acceptability and effectiveness of psychotherapeutic treatments for postnatal depression in women belonging to minority ethnic groups.

Added value of this study

This is the first large-scale randomised trial to test a group CBT-based intervention for postnatal depression in British south Asian women, a group that is underserved by psychological therapy services due to stigma and language and cultural barriers. Our previous exploratory work established the need for cultural adaptation of psychological therapies in the UK especially for south Asian ethnicities to improve access to care, engagement, and uptake. Based on these experiences, we developed a culturally adapted CBT-based approach, the Positive Health Programme (PHP), delivered by non-specialist health workers. Compared with treatment as usual (control), the PHP intervention was associated with a higher proportion of patients recovering from postnatal depression at 4 months after randomisation, suggesting that this intervention can aid in earlier recovery. However, no significant difference in recovery between the PHP and control groups was observed at 12 months.

Implications of all the available evidence

Minority ethnic groups are often excluded from mental health research and can be overlooked if services do not consider their cultural and social contexts. In addition to providing evidence of the feasibility and effectiveness of a culturally adapted, group CBT-based intervention for this population, the study demonstrates methodological approaches for engaging UK-based minority ethnic communities in mental health research. Outreach approaches and stakeholder and service user engagement can help to overcome some of the barriers to accessing services.

Olmesartan-induced collagenous gastritis

A 63-year-old woman presented to our department with a 6-month history of recurrent vomiting and loss of 5 kg in weight. The patient had a medical history of dyslipidaemia and hypertension; she was prescribed rosuvastatin and olmesartan. She had no history of gastrointestinal disorders, recent foreign travel, or infection with *Helicobacter pylori*.

On examination, she was generally unwell and underweight; her blood pressure was 150/88 mm Hg, pulse was 70 beats per min, oxygen saturation was 99%, and BMI was 16 kg/m^2. We found no lymphadenopathy, and abdominal examination found no masses or ascites.

Laboratory investigations showed normal complete blood count—including a typical eosinophil count; carcinoembryonic antigen, soluble interleukin-2 receptor, and antineutrophil cytoplasmic antibody tests were within normal range. Antinuclear antibody titre was 1:160 (normal value <1:40) and serum immunoglobulin E was 700 IU/mL (typical range 0–100).

An oesophagogastroduodenoscopy (OGD) showed a distended stomach with linear scars and a rough atrophic mucosa that bled easily upon contact (figure). Histopathological examination of a sample obtained by gastric biopsy showed subepithelial collagen deposition with inflammatory cell infiltration—including eosinophils (figure); the small and large intestines showed no specific findings.

At this stage, our working diagnosis included collagenous gastritis, eosinophilic gastritis, and autoimmune gastritis. And based on these working diagnoses, the patient was prescribed a proton pump inhibitor—esomeprazole 20 mg orally—which did not result in any improvement.

Further review of the medical history found that the patient had been taking olmesartan 20 mg daily for the past decade and we considered that it may have been responsible for the patient's symptoms; we therefore decided to stop it.

2 weeks later, the patient stopped vomiting and within 2 months she had gained 7 kg. A repeat OGD, 6 months post-discontinuation, showed a substantial improvement in mucosal inflammation; histopathological examination of samples obtained by biopsies, showed no evidence of residual collagen bands or significant inflammatory cell infiltration (appendix). And at 2 years after discontinuation of the olmesartan no recurrence was seen. Regarding the patient's hypertension, azelnidipine 8 mg daily was prescribed as an alternative treatment.

Collagenous gastritis is characterised by patchy subepithelial collagen bands and inflammatory cell infiltration, including eosinophils; such features can appear in other types of gastritis with similar inflammatory cell infiltration—including eosinophilic gastritis, coeliac disease, and autoimmune gastritis—necessitating a high index of suspicion to make an accurate pathological diagnosis. The precise pathogenesis of collagenous gastritis remains poorly understood and no available treatments are established owing to its rarity; associations with certain medications—including olmesartan as in our patient—have been suggested.

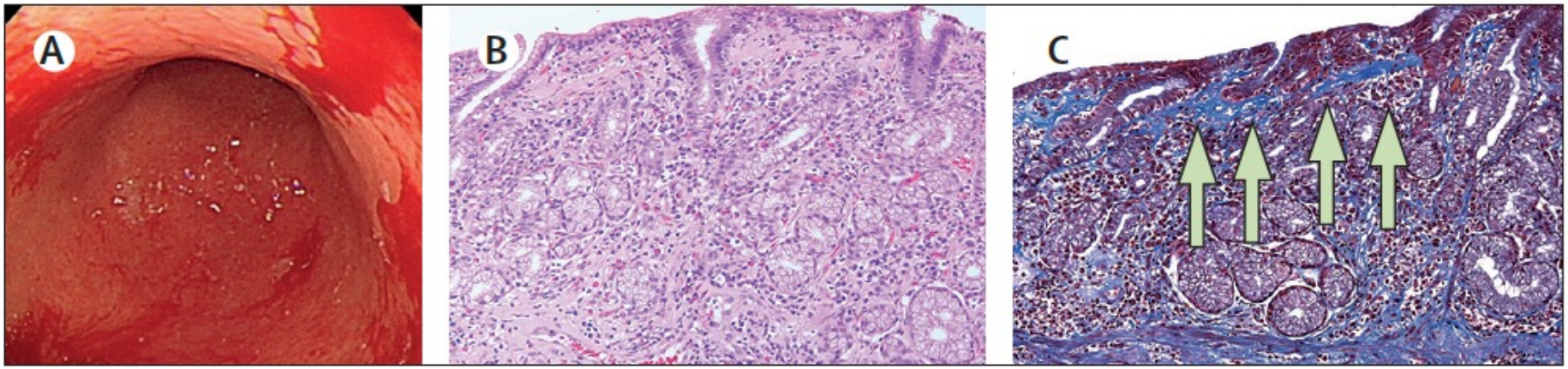


Figure: **Olmesartan-induced collagenous gastritis with inflammatory cell infiltration**
(A) Oesophagogastroduodenoscopy shows a distended stomach with linear scars on a rough, atrophic mucosa that bled easily on contact. Histopathological examination of a sample obtained from gastric biopsy shows (B) inflammatory cell infiltration, including eosinophils, and stromal fibrotic changes (haematoxylin and eosin staining). 100× magnification; and (C) markedly thickened subepithelial collagen bands (arrows; Masson's trichome staining). 100× magnification.

The *Lancet* Commission on self-harm

Panel 1: Key recommendations of the *Lancet* Commission on self-harm

Recommendations for governments

- In all countries, a whole-of-government approach should address the upstream conditions that promote self-harm. This approach should build on existing national strategies aimed narrowly at mental health and suicide to acknowledge that many other societal efforts are needed to reduce self-harm. Tackling poverty, means restriction, and the societal drivers of misery can reduce suicide rates—this evidence can usefully inform government policy in relation to self-harm.
- The punishment of people who self-harm around the world must stop; this effort must also include the decriminalisation of self-harm.
- There is an urgent need to prioritise the prevention and management of self-harm in LMICs. The banning of pesticides will lead to a reduction of pesticide-related fatal self-harm. Interventions for self-harm need to be tailored to local and cultural contexts.
- For Indigenous peoples, effective self-harm prevention strategies should prioritise self-determination and building healthy societies, thus empowering thriving cultures. Indigenous peoples should control their health services and design culturally appropriate prevention and intervention strategies. Interventions should include access to cultural healers, Elders, and Indigenous cultural activities.

Recommendations for the delivery of services

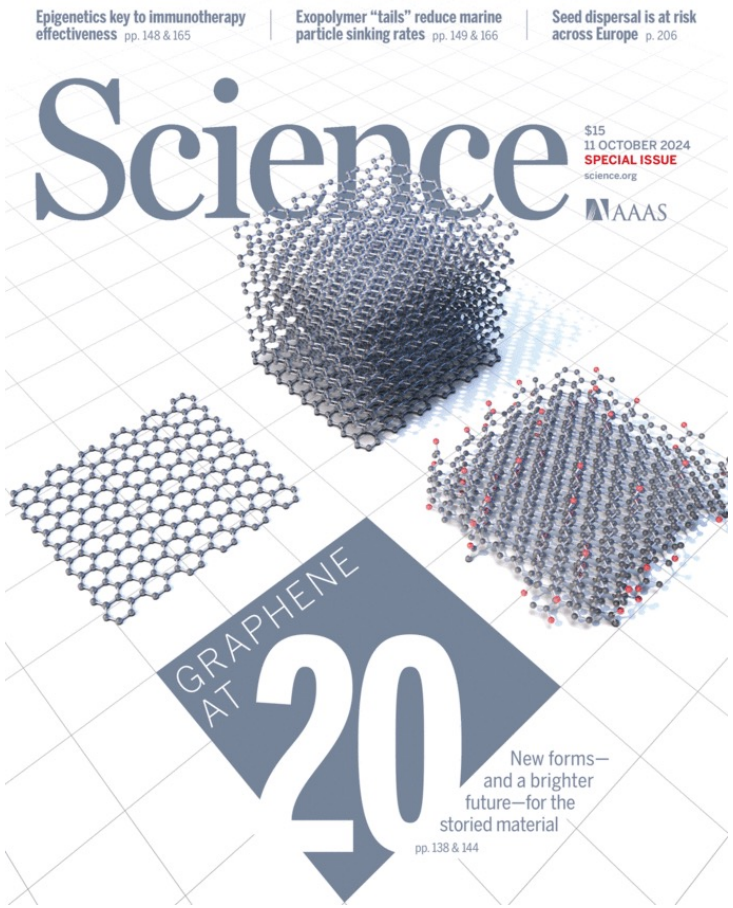
- People with lived experience of self-harm should be robustly supported to lead and participate in the design, delivery, leadership, and evaluation of care. Considering the rising rates of self-harm among young people, they should be particularly involved in the codesign of interventions.
- Better integration of services and adequate staffing capacity is needed to ensure that individuals who repeatedly self-harm receive the help they need.
- Health and social-care professionals should be trained in the compassionate assessment and management of self-harm. Ongoing supervision, staff support, and the direct involvement of people with lived experience (particularly from previously marginalised groups) should be key principles underpinning service delivery.

Recommendations for the media and wider society

- Discussion about self-harm should focus on relatable stories of survival, recovery, coping, and help seeking, with an emphasis on practical strategies. These stories should ideally be conveyed by people with lived experience. Other narratives which could have positive effects should also be carefully considered, ensuring that discussions do not lead to harm.
- The online media industry must take greater responsibility for the online safety of their users, particularly young people and other vulnerable users.

Recommendations for researchers and research funders

- International research funding should be directed towards LMICs, with priority given to areas where the burden is greatest.
- Robust and anonymised self-harm surveillance systems should be set up in all countries, to monitor trends in self-harm across the world.
- Mixed methods biopsychosocial research applying social ecological approaches to understanding self-harm should be prioritised.

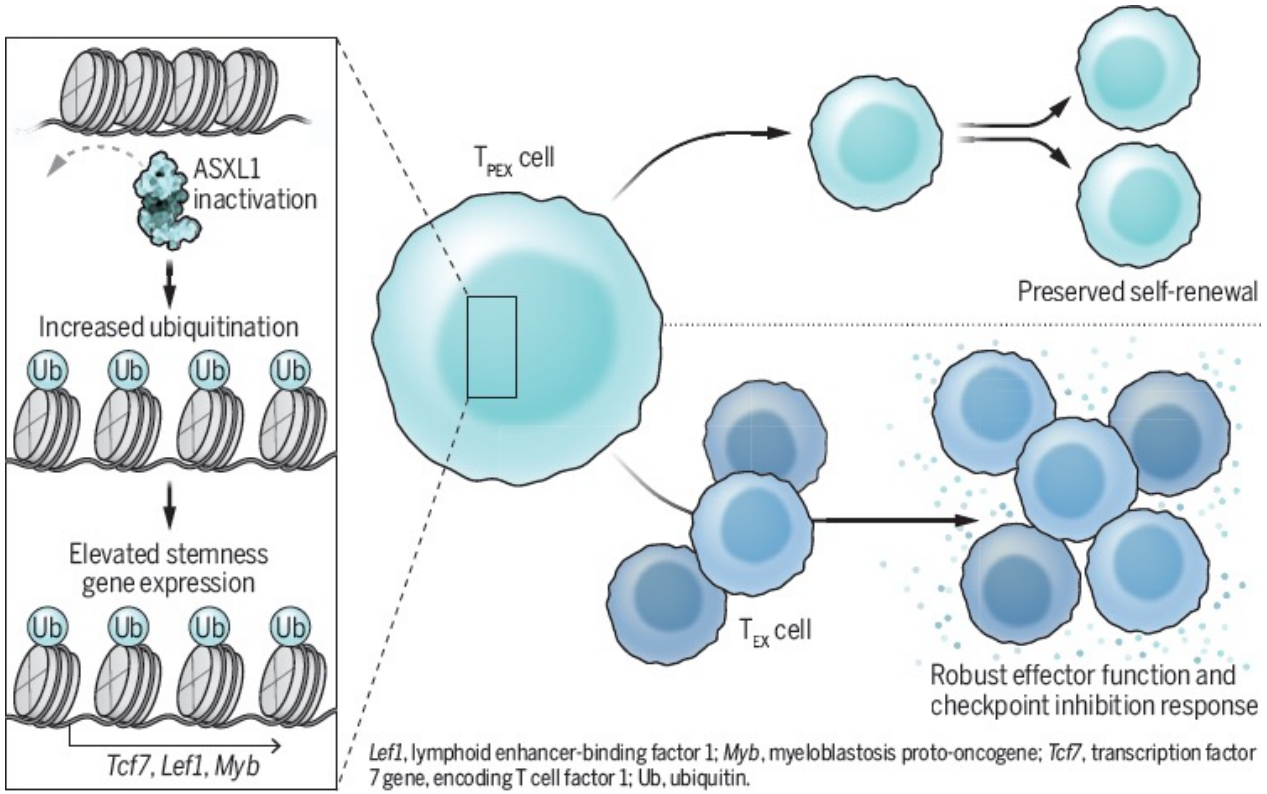


Targeting epigenetic regulators prevents T cell exhaustion

T cell exhaustion, characterized by the loss of cytokine production and sustained expression of inhibitory receptors or immune checkpoints such as programmed cell death 1 (PD-1), poses a major hurdle in cancer immunotherapies, including immune checkpoint blockade (ICB) and adoptive cell therapies. Prolonged $CD8^+$ T cell responses, such as those found in cancer and chronic infection, are maintained by so-called precursors of exhausted T (T_{PEX}) cells, which exhibit stemlike features, allowing them to undergo self-renewal while also giving rise to effector-like exhausted T (T_{EX}) cell progeny. The balance of stemness and effector differentiation determines the quality of the T cell response and makes T_{PEX} cells prime targets for therapeutic manipulation. Kang *et al.* report that deleting key epigenetic regulators can preserve ICB-responsive T_{PEX} cells during chronic antigen exposure, revealing potential targets to overcome T cell exhaustion and achieve durable therapeutic response to ICB.

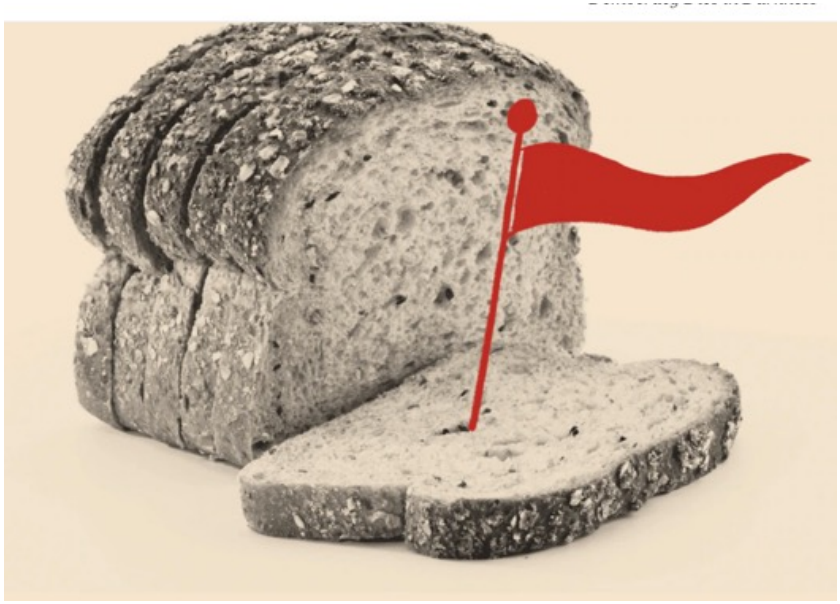
Chromatin remodeling shapes stemness in T cells

In chronic infection and cancer, $CD8^+$ T cell responses are maintained by precursors of exhausted T (T_{PEX}) cells, which exhibit stemlike features, allowing them to undergo self-renewal while also giving rise to effector-like exhausted T (T_{EX}) cell progeny. Disruption of additional sex comb-like 1 (ASXL1) leads to ubiquitination of histone 2A, which allows opening of chromatin regions in genes that promote T cell stemness and function, thus improving maintenance and response to immune checkpoint blockade.



Lef1, lymphoid enhancer-binding factor 1; *Myb*, myeloblastosis proto-oncogene; *Tcf7*, transcription factor 7 gene, encoding T cell factor 1; Ub, ubiquitin.

I’m a gastroenterologist. Here’s the surprising truth about gluten.



I get abdominal pain and brain fog when I eat gluten, but I’ve tested negative for celiac disease. Could I have gluten sensitivity? How bad is gluten really?

I have lots of patients in my gastroenterology clinic who report a sensitivity to gluten, a component of wheat, but test negative for celiac disease. In celiac disease, a common autoimmune condition that is rising worldwide, gluten triggers inflammation in the small bowel. But many people without celiac disease perceive a variety of symptoms they connect to eating gluten: bloating, diarrhea, and even brain fog, fatigue or joint aches.

While some patients do truly have a gluten-specific sensitivity, there’s a good chance it’s not actually the gluten that’s the issue. In an Italian study of nearly 400 patients complaining of symptoms related to gluten intake, the vast majority — 86 percent — did not experience any symptom improvement with a gluten-free diet.

Instead, I often advise a trial of a low FODMAP diet, particularly for those with irritable bowel syndrome. FODMAPs are a group of fermentable carbohydrates found in wheat and many other foods that are notorious for gastrointestinal distress. Examples of FODMAPs include:

- Onions and garlic
- Fruits such as apples and pears
- Lactose-containing foods like soft cheeses and milk
- Nuts such as cashews and pistachios

Das Akronym FODMAP ist die englische Abkürzung für fermentable oligo-, di-, monosaccharides and polyols. Es bezeichnet eine Gruppe von Kohlenhydraten und Zuckeralkoholen, die in vielen Nahrungsmitteln vorkommen und im Dünndarm nur schlecht resorbiert werden.

FODMAP FREE FOODS

@ibsfodmapdietitian X @fodbods


Orange


Cucumber


Potato


Carrot


Rocket/Arugular


Rhubarb


Sprouts


Parsnip


Lettuce


Japanese Pumpkin


Rice


Cheddar Cheese


Seaweed


Lactose-free milk


Olive oil


Beef


Chicken


Eggs


Fish/seafood


LF yoghurt