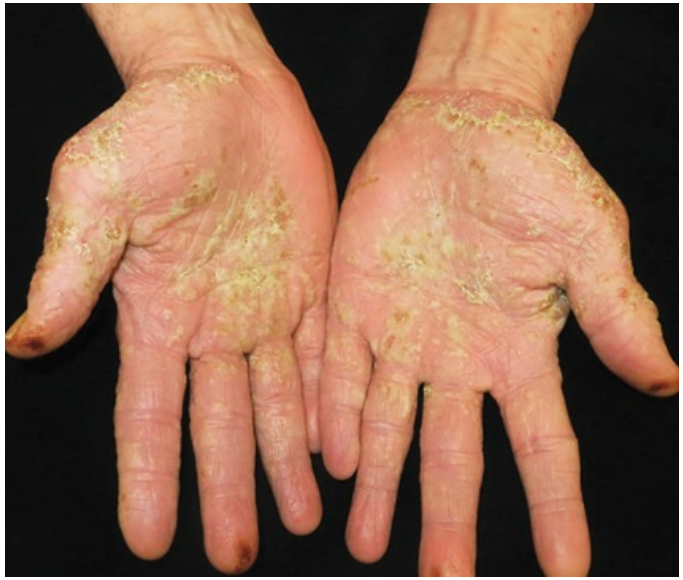
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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 diagnosis of primary palmoplantar pustulosis — a chronic inflammatory skin condition characterized by sterile pustules — was made. The condition is highly associated with cigarette smoking. Treatment with topical triamcinolone and oral cyclosporine was initiated. Smoking cessation was recommended.

A 60-year-old man with a 30-pack-year smoking history presented to the dermatology clinic for a 2-year history of a painful rash on his palms and soles. Previous treatment with various antibacterial agents had been ineffective. Laboratory studies revealed neutrophilic leukocytosis and an elevated C-reactive protein level. What is the diagnosis?

Contact dermatitis

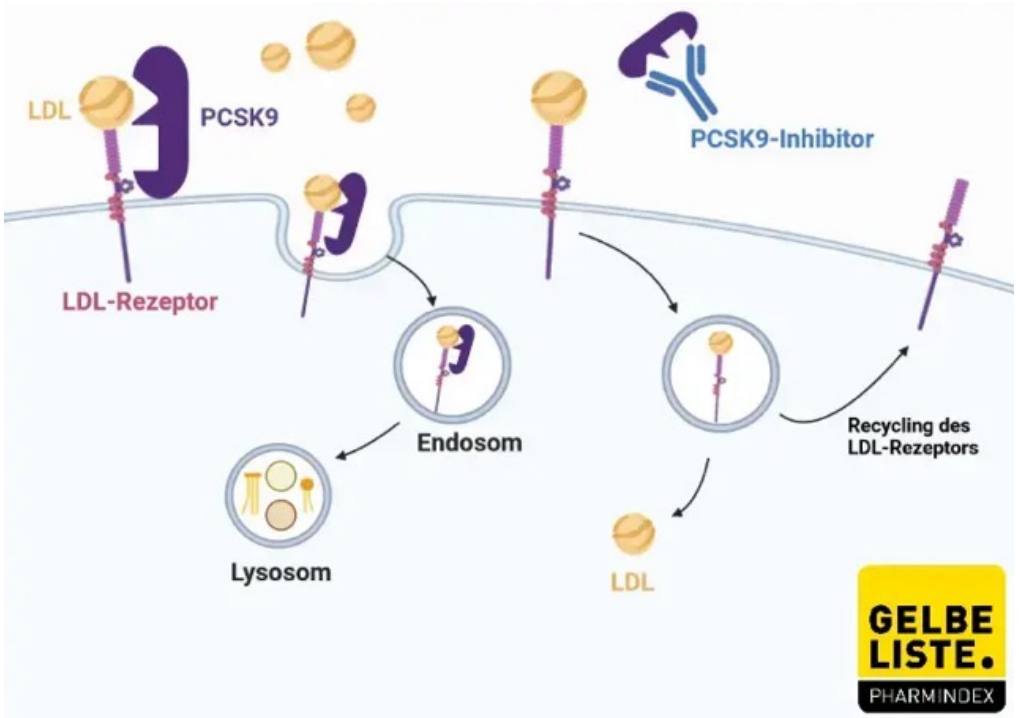
Dyshidrotic eczema

Palmoplantar plaque psoriasis

Palmoplantar pustulosis

Secondary syphilis

PCSK9 (Proprotein Convertase Subtilisin/Kexin type 9) ist ein Enzym, das in der Leber produziert wird und eine Schlüsselrolle bei der Regulation des LDL-Cholesterinspiegels spielt, indem es LDL-Rezeptoren abbaut und so die Aufnahme von LDL-Cholesterin aus dem Blut verhindert; PCSK9-Hemmer (z. B. Alirocumab (Praluent) und Evolocumab (Repatha)) sind Medikamente, meist monoklonale Antikörper, die dieses Enzym blockieren, die Anzahl der LDL-Rezeptoren erhöhen und dadurch das LDL-Cholesterin stark senken, was sie zu einer wichtigen Therapieoption für Hochrisikopatienten macht, die Statine nicht vertragen oder nicht ausreichend ansprechen.

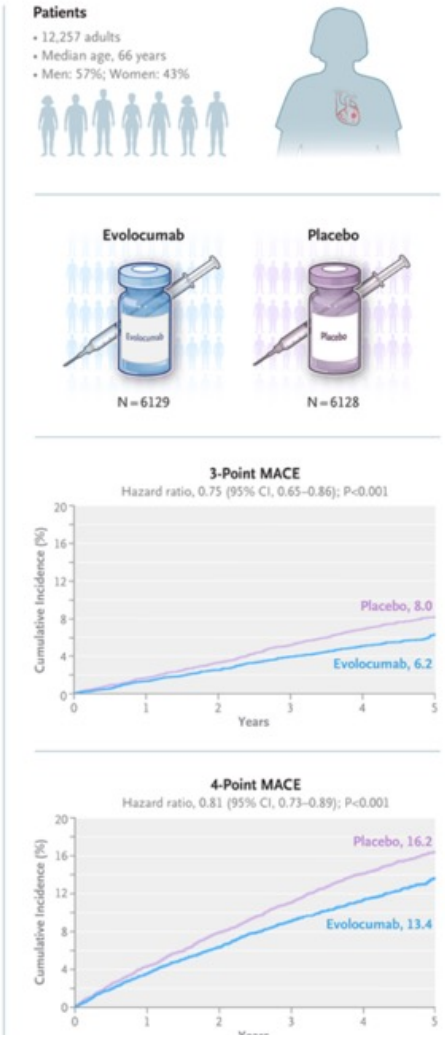


Evolocumab in Patients without a Previous Myocardial Infarction or Stroke

The proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor evolocumab reduces the risk of major adverse cardiovascular events (MACE) among patients with a previous myocardial infarction, stroke, or symptomatic peripheral artery disease. The effect of evolocumab on the risk of MACE among patients without a previous myocardial infarction or stroke is unknown.

We conducted an international, double-blind, randomized, placebo-controlled trial of evolocumab in patients with atherosclerosis or diabetes and without a previous myocardial infarction or stroke who had a low-density lipoprotein cholesterol level of at least 90 mg per deciliter. Patients were randomly assigned in a 1:1 ratio to receive evolocumab at a dose of 140 mg every 2 weeks or placebo. The two primary end points were a composite of death from coronary heart disease, myocardial infarction, or ischemic stroke (3-point MACE) and a composite of 3-point MACE or ischemia-driven arterial revascularization (4-point MACE).

(Primary prevention)



Low-density lipoprotein (LDL) cholesterol is a well-established modifiable cardiovascular risk factor. Lowering LDL cholesterol levels with proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors reduces the risk of cardiovascular events, but this treatment has been studied primarily in patients at very high risk who had a previous major atherosclerotic cardiovascular disease event, such as myocardial infarction or stroke. The effect of PCSK9 inhibition on cardiovascular events has not been well studied in populations without a previous major cardiovascular ischemic event.

The Effect of Evolocumab in Patients at High Cardiovascular Risk without Prior Myocardial Infarction or Stroke (VESALIUS-CV) trial was a dedicated cardiovascular-outcomes trial that tested whether evolocumab treatment would lead to a lower risk of a first major cardiovascular event than placebo among patients at high cardiovascular risk who had atherosclerosis or diabetes but had not had a myocardial infarction or stroke previously. The trial was designed to have a median follow-up of at least 4.5 years in order to better characterize the long-term efficacy and safety of evolocumab therapy.

Eligible patients must have been without a history of myocardial infarction or stroke and had to meet trial criteria for at least one of the following four disease categories: coronary artery disease, atherosclerotic cerebrovascular disease, peripheral artery disease, or high-risk diabetes. The category of high-risk diabetes refers to patients with diabetes that is long-standing (≥10 years' duration), is treated with daily insulin, or is complicated by microvascular disease.

Randomization

Eligible patients were randomly assigned in a 1:1 ratio to receive subcutaneous injections of evolocumab at a dose of 140 mg every 2 weeks or matching placebo. Evolocumab and placebo were supplied by the sponsor.

End Points

The two primary efficacy end points of the trial were a composite of death from coronary heart disease, myocardial infarction, or ischemic stroke (3-point major adverse cardiovascular event [MACE]) and a composite of death from coronary heart disease, myocardial infarction, ischemic stroke, or ischemia-driven arterial revascularization (4-point MACE).

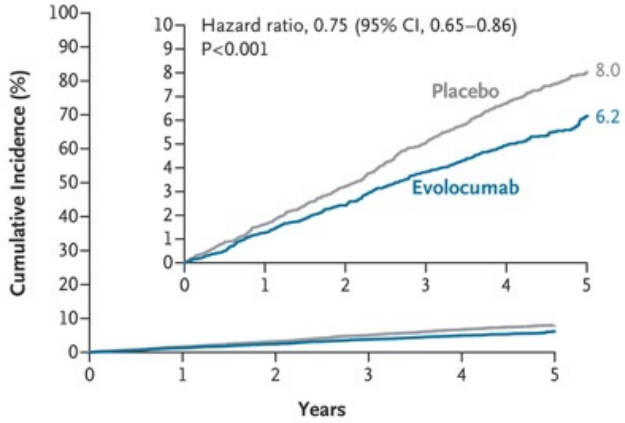
The less than optimally treated patients

Characteristic	Evolocumab (N=6129)	Placebo (N=6128)
Median age (IQR) — yr	66 (60–71)	66 (60–71)
Female sex — no. (%)	2619 (43)	2595 (42)
White race — no./total no. (%)†	5708/6128 (93)	5693/6122 (93)
Hispanic ethnic group — no./total no. (%)†	1017/6127 (17)	1016/6126 (17)
Median weight (IQR) — kg	85 (74–97)	85 (74–96)
Median body-mass index (IQR)‡	30 (27–34)	30 (27–33)
Geographic region — no. (%)		
North America	678 (11)	679 (11)
Europe	4238 (69)	4234 (69)
Asia–Pacific	320 (5)	307 (5)
Central or South America	893 (15)	908 (15)
Coexisting conditions — no. (%)		
Hypertension	5351 (87)	5319 (87)
Diabetes	3598 (59)	3524 (58)
Current smoking	1681 (27)	1715 (28)
Qualifying disease categories for inclusion — no. (%)§		
Any qualifying atherosclerosis	4092 (67)	4116 (67)
Coronary artery disease without previous myocardial infarction	2755 (45)	2771 (45)
Cerebrovascular disease without previous stroke	607 (10)	606 (10)
Peripheral artery disease	1050 (17)	1086 (18)
High-risk diabetes	3052 (50)	2950 (48)
High-risk diabetes without qualifying atherosclerosis	2009 (33)	1992 (33)
Lipid-lowering therapy — no. (%)		
Any lipid-lowering therapy	5641 (92)	5609 (92)
High-intensity lipid-lowering therapy¶	4407 (72)	4447 (73)
Any statin	5339 (87)	5304 (87)
High-intensity statin‖	4160 (68)	4165 (68)
Moderate- or low-intensity statin	1179 (19)	1139 (19)
Ezetimibe	1188 (19)	1249 (20)
Lipid values (IQR) — mg/dl**		
Low-density lipoprotein cholesterol	122 (104–149)	122 (104–149)
Non–high-density lipoprotein cholesterol	152 (130–182)	153 (130–182)
High-density lipoprotein cholesterol	47 (40–57)	47 (40–57)
Total cholesterol	201 (178–233)	202 (178–233)
Triglycerides	153 (111–216)	152 (111–220)
Apolipoprotein B	102 (89–123)	100 (88–119)
Median estimated GFR (IQR) — ml/min/1.73 m^2	79 (66–93)	78 (65–93)

Primary and Secondary End Points.

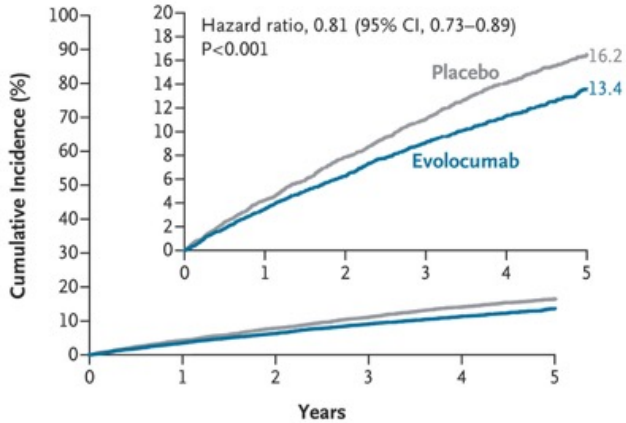
End Point	Evolocumab (N=6129)	Placebo (N=6128)	Hazard Ratio (95% CI)	P Value
	no. (5-yr Kaplan–Meier estimate, %)			
Primary end points†				
3-Point MACE	336 (6.2)	443 (8.0)	0.75 (0.65–0.86)	<0.001
4-Point MACE	747 (13.4)	907 (16.2)	0.81 (0.73–0.89)	<0.001
Secondary end points‡				
Myocardial infarction, ischemic stroke, or ischemia-driven arterial revascularization	674 (12.2)	834 (15.0)	0.79 (0.72–0.88)	<0.001
Death from coronary heart disease, myocardial infarction, or ischemia-driven arterial revascularization	664 (11.9)	819 (14.6)	0.79 (0.72–0.88)	<0.001
Death from cardiovascular causes, myocardial infarction, or ischemic stroke	374 (6.8)	503 (9.1)	0.73 (0.64–0.84)	<0.001
Death from coronary heart disease or myocardial infarction	232 (4.2)	313 (5.6)	0.73 (0.62–0.87)	<0.001
Myocardial infarction	149 (2.7)	229 (4.1)	0.64 (0.52–0.79)	<0.001
Ischemia-driven arterial revascularization	561 (10.1)	699 (12.5)	0.79 (0.70–0.88)	<0.001
Death from coronary heart disease	105 (1.9)	117 (2.1)	0.89 (0.68–1.16)	0.39
Death from cardiovascular causes	156 (2.8)	195 (3.6)	0.79 (0.64–0.98)	NA
Death from any cause	434 (7.9)	539 (9.7)	0.80 (0.70–0.91)	NA
Ischemic stroke	115 (2.3)	144 (2.7)	0.79 (0.62–1.01)	NA

A 3-Point MACE



No. at Risk						
Placebo	6128	5921	5726	5483	4176	1496
Evolocumab	6129	5948	5796	5623	4301	1560

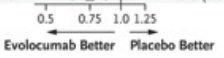
B 4-Point MACE



No. at Risk						
Placebo	6128	5770	5460	5151	3865	1368
Evolocumab	6129	5816	5575	5324	4016	1448

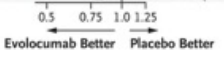
A 3-Point MACE

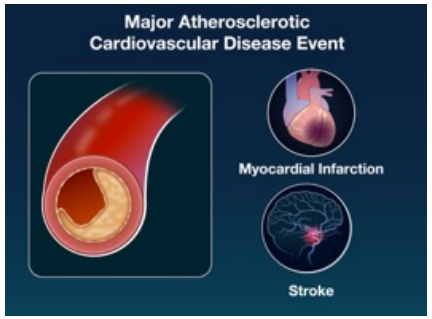
Subgroup	Evolocumab	Placebo	Hazard Ratio (95% CI)
	no. of events/no. of patients		
Overall	336/6129	443/6128	0.75 (0.65–0.86)
Age			
<65 yr	139/2657	165/2732	0.86 (0.69–1.08)
≥65 yr	197/3472	278/3396	0.68 (0.57–0.82)
Sex			
Male	226/3510	296/3533	0.75 (0.63–0.90)
Female	110/2619	147/2595	0.74 (0.58–0.95)
Geographic region			
North America	49/678	81/679	0.60 (0.42–0.85)
Europe	221/4238	282/4234	0.77 (0.65–0.92)
Other	66/1213	80/1215	0.80 (0.58–1.11)
Race			
White	306/5708	407/5693	0.74 (0.64–0.85)
Non-White	30/420	36/429	0.87 (0.53–1.41)
Qualifying disease category			
Any qualifying atherosclerosis	237/4092	307/4116	0.76 (0.65–0.91)
High-risk diabetes without qualifying atherosclerosis	99/2009	136/1992	0.71 (0.55–0.92)
LDL cholesterol at baseline			
≤104 mg/dl	80/1546	103/1547	0.77 (0.58–1.03)
>104–122 mg/dl	90/1550	111/1523	0.78 (0.59–1.04)
>122–149 mg/dl	72/1512	118/1537	0.60 (0.45–0.81)
>149 mg/dl	94/1520	111/1521	0.85 (0.65–1.12)
Statin intensity			
High	203/4160	288/4165	0.70 (0.58–0.83)
Moderate or low	71/1179	81/1139	0.81 (0.59–1.12)
None	62/790	74/824	0.88 (0.63–1.23)
Ezetimibe			
Yes	63/1188	86/1249	0.74 (0.53–1.02)
No	273/4941	357/4879	0.75 (0.64–0.87)

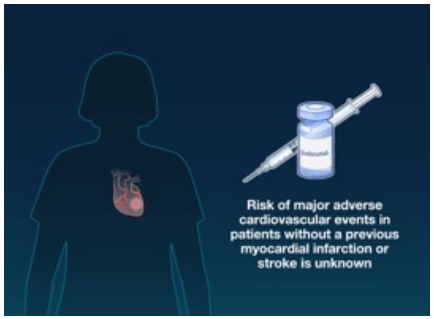


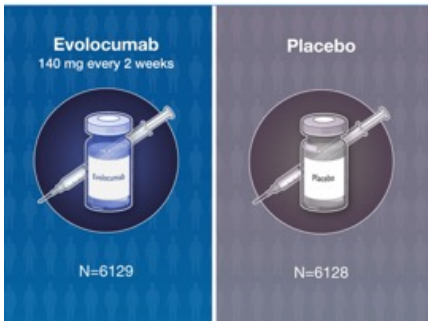
B 4-Point MACE

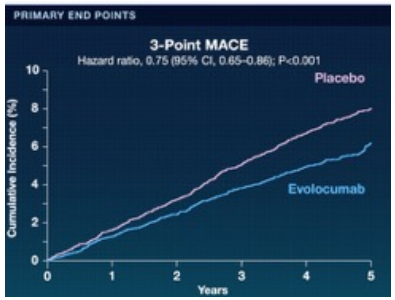
Subgroup	Evolocumab	Placebo	Hazard Ratio (95% CI)
	no. of events/no. of patients		
Overall	747/6129	907/6128	0.81 (0.73–0.89)
Age			
<65 yr	297 2657	361/2732	0.83 (0.71–0.97)
≥65 yr	450/3472	546/3396	0.79 (0.70–0.89)
Sex			
Male	510/3510	606/3533	0.83 (0.73–0.93)
Female	237/2619	301/2595	0.77 (0.65–0.92)
Geographic region			
North America	104/678	154/679	0.66 (0.52–0.85)
Europe	513/4238	603/4234	0.84 (0.74–0.94)
Other	130/1213	150/1215	0.84 (0.66–1.06)
Race			
White	684/5708	832/5693	0.80 (0.72–0.89)
Non-White	63/420	74/429	0.87 (0.62–1.22)
Qualifying disease category			
Any qualifying atherosclerosis	584/4092	687/4116	0.84 (0.75–0.94)
High-risk diabetes without qualifying atherosclerosis	163/2009	216/1992	0.74 (0.60–0.90)
LDL cholesterol at baseline			
≤104 mg/dl	188/1546	222/1547	0.83 (0.69–1.01)
>104–122 mg/dl	214/1550	237/1523	0.88 (0.73–1.05)
>122–149 mg/dl	163/1512	229/1537	0.70 (0.57–0.86)
>149 mg/dl	182/1520	219/1521	0.83 (0.68–1.01)
Statin intensity			
High	458/4160	564/4165	0.80 (0.71–0.90)
Moderate or low	159/1179	187/1139	0.79 (0.64–0.98)
None	130/790	156/824	0.87 (0.69–1.10)
Ezetimibe			
Yes	162/1188	205/1249	0.80 (0.65–0.99)
No	585/4941	702/4879	0.81 (0.73–0.90)

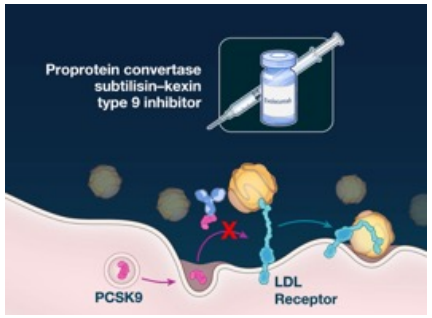


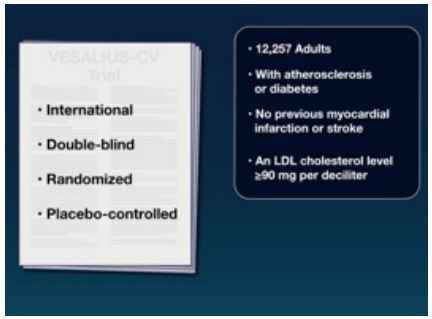

Major Atherosclerotic Cardiovascular Disease Event
Myocardial Infarction
Stroke

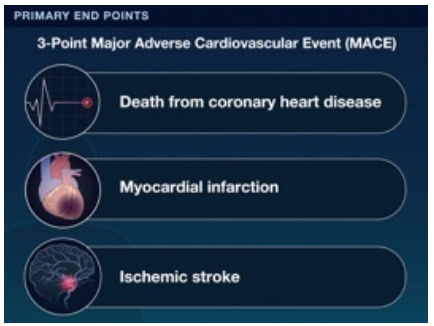

Risk of major adverse cardiovascular events in patients without a previous myocardial infarction or stroke is unknown

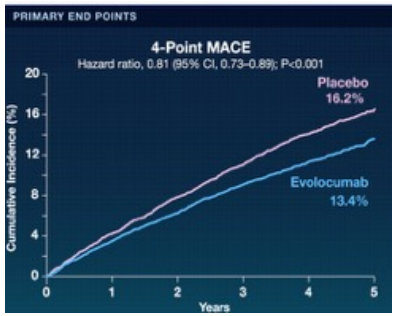

Evolocumab
140 mg every 2 weeks
Placebo
N=6129
N=6128

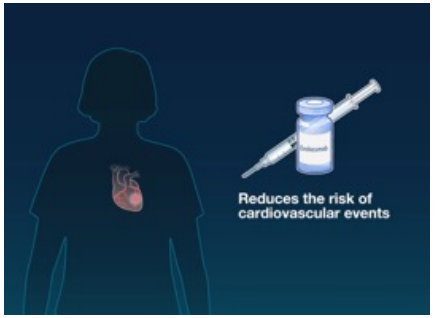

PRIMARY END POINTS
3-Point MACE
Hazard ratio, 0.75 (95% CI, 0.65–0.86); P<0.001
Placebo
Evolocumab
Cumulative Incidence (%)
Years

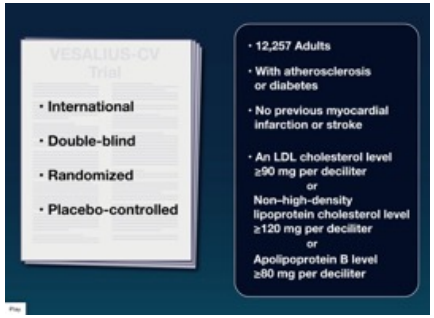

Proprotein convertase subtilisin–kexin type 9 inhibitor
PCSK9
LDL Receptor

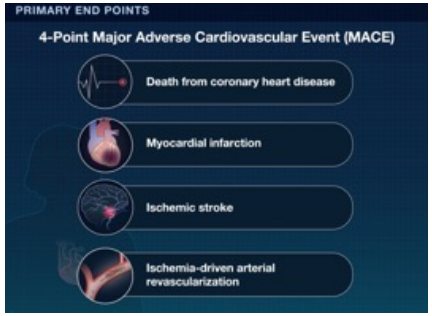

VESALIUS-CV Trial
International
Double-blind
Randomized
Placebo-controlled
12,257 Adults
With atherosclerosis or diabetes
No previous myocardial infarction or stroke
An LDL cholesterol level ≥90 mg per deciliter


PRIMARY END POINTS
3-Point Major Adverse Cardiovascular Event (MACE)
Death from coronary heart disease
Myocardial infarction
Ischemic stroke


PRIMARY END POINTS
4-Point MACE
Hazard ratio, 0.81 (95% CI, 0.73–0.89); P<0.001
Placebo
16.2%
Evolocumab
13.4%
Cumulative Incidence (%)
Years

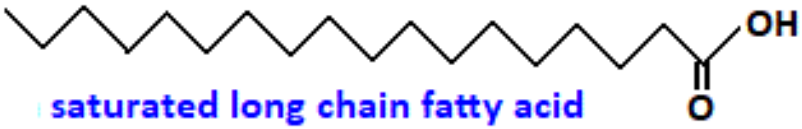

Reduces the risk of cardiovascular events


VESALIUS-CV Trial
International
Double-blind
Randomized
Placebo-controlled
12,257 Adults
With atherosclerosis or diabetes
No previous myocardial infarction or stroke
An LDL cholesterol level ≥90 mg per deciliter
or
Non-high-density lipoprotein cholesterol level ≥120 mg per deciliter
or
Apolipoprotein B level ≥80 mg per deciliter


PRIMARY END POINTS
4-Point Major Adverse Cardiovascular Event (MACE)
Death from coronary heart disease
Myocardial infarction
Ischemic stroke
Ischemia-driven arterial revascularization


Evolocumab led to a lower risk of first major cardiovascular events as compared with placebo

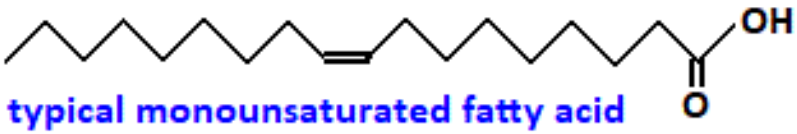
Examples of long chain saturated and unsaturated fatty acids that can be obtained from natural animal fats or vegetable oils



saturated long chain fatty acid

stearic acid

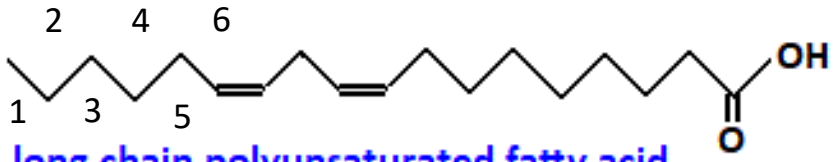
$C_{17}H_{35}COOH$



typical monounsaturated fatty acid

oleic acid (omega 9)

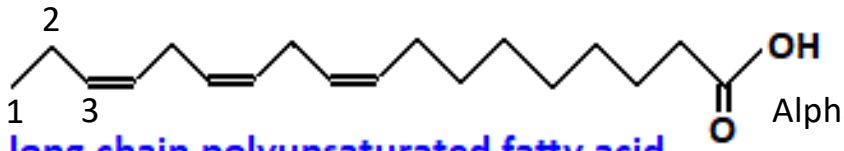
$C_{17}H_{33}COOH$



long chain polyunsaturated fatty acid

linoleic acid (omega 6) Corn oil

$C_{17}H_{31}COOH$



long chain polyunsaturated fatty acid

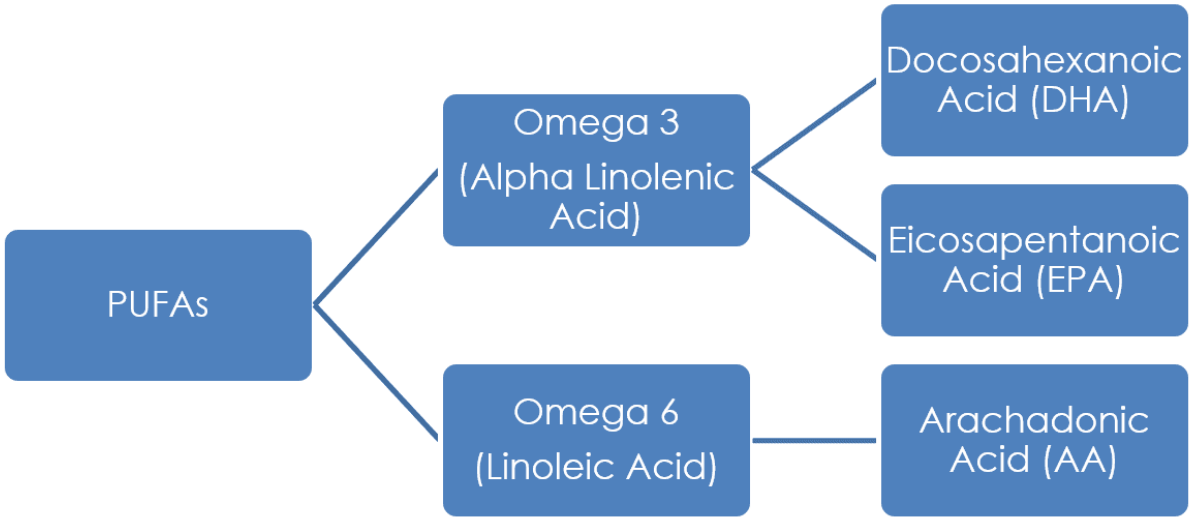
linolenic acid (omega 3) Fish oil

$C_{17}H_{29}COOH$

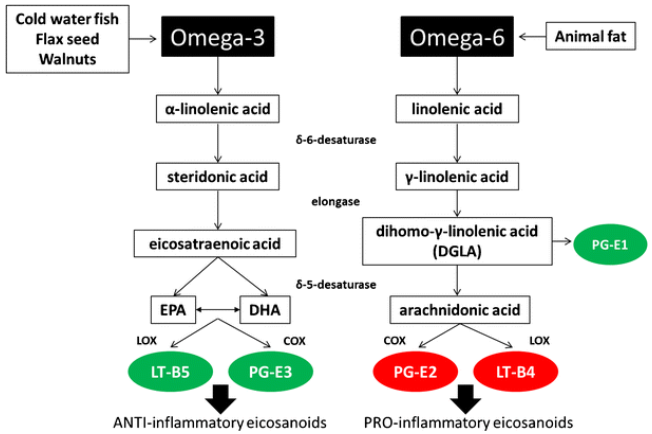
Omega Ende

Alpha Ende

- **Alpha (α) End:** This is the **carboxyl group** ($-COOH$) end of the molecule. In chemical numbering, the carboxyl carbon itself is Carbon 1, while the carbon immediately adjacent to it is designated as the **alpha carbon**.
- **Omega (ω) End:** This is the **methyl group** ($-CH_3$) end, also called the "tail". The carbon atom at the very end of the hydrocarbon chain is designated as the **omega carbon** because omega is the last letter of the Greek alphabet.

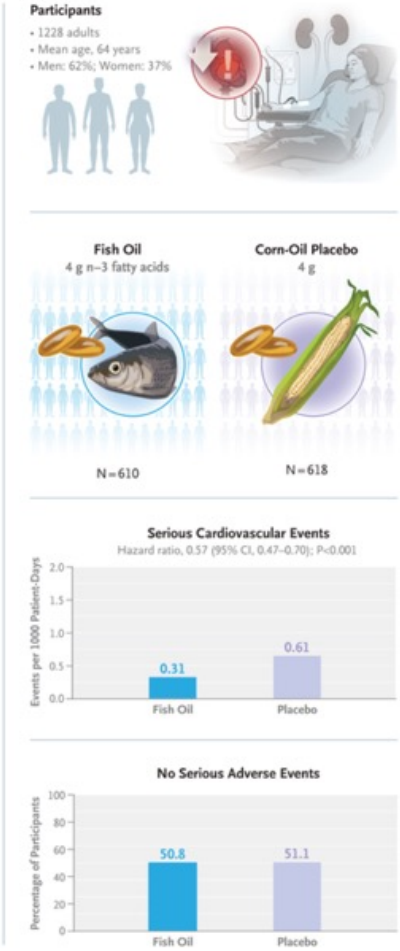


Fish are animals!



Fish-Oil Supplementation and Cardiovascular Events in Patients Receiving Hemodialysis

Cardiovascular disease is the leading cause of death in patients receiving hemodialysis, yet effective preventive therapies remain limited. Supplementation with n−3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may have cardiovascular benefits in the general population, but efficacy among patients receiving hemodialysis is uncertain. In a double-blind, randomized, placebo-controlled trial conducted at 26 sites in Canada and Australia, we assigned adult patients receiving maintenance hemodialysis to daily supplementation with fish oil (4 g of n−3 polyunsaturated fatty acids [1.6 g of EPA and 0.8 g of DHA]) or corn-oil placebo. The primary end point was a composite of all serious cardiovascular events including sudden and nonsudden cardiac death, fatal and nonfatal myocardial infarction, peripheral vascular disease leading to amputation, and fatal and nonfatal stroke. Secondary end points included extension of the primary end point to include noncardiac causes of death, the individual components of the primary end point, and a first cardiovascular event or death from any cause.



Dialysis styles, Statins, MR Blockers etc. were all (largely) negative

Globally, more than 3.8 million people currently receive kidney-replacement therapy for end-stage kidney disease; most are treated with hemodialysis. Cardiovascular disease affects more than two thirds of persons receiving hemodialysis and accounts for more than 75% of the associated deaths[3]; cardiovascular mortality is 20 times as high as that in the general population, a finding that highlights the importance of effective cardiovascular management. However, these high-risk patients receiving maintenance hemodialysis are challenged by both traditional and nontraditional cardiovascular risk factors, and there are few proven medical interventions for the prevention of cardiovascular events in this population.

The effect of n−3 polyunsaturated fatty acids in reducing the risk of cardiovascular disease was reported more than 50 years ago, yet their effects remain controversial. Recent studies have suggested that n−3 fatty acids reduce the risk of cardiovascular events in the general population and that there is an inverse relation between n−3 fatty acid blood levels and the risk of cardiovascular events. Although n−3 fatty acid blood levels are lower in patients receiving hemodialysis than in the general population, it is unclear whether oral fish-oil supplementation can reduce the risk of cardiovascular events and death in this patient population. We hypothesized that among patients treated with maintenance hemodialysis, oral supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the long-chain n−3 polyunsaturated fatty acids found in fish oil, would lead to a lower rate of cardiovascular events than placebo.

Participants

Eligible participants were 18 years of age or older, had end-stage kidney disease, were receiving hemodialysis three or four times per week, and were in clinically stable condition before enrollment. Participants who were taking n−3 fatty acid supplements at the time of randomization or had an allergy to fish, soy, corn, or any of their products were excluded.

Randomization, Interventions, and Follow-up

Participants were assigned in a 1:1 ratio to daily oral supplementation with fish oil (4 g of steam-deodorized, citrus-flavored n−3 polyunsaturated fatty acids in four 1-g capsules containing a total of 1.6 g of EPA and 0.8 g of DHA) or citrus-flavored corn-oil placebo.

End Points

The primary end point was a composite of all serious cardiovascular events including cardiovascular death (sudden and nonsudden cardiac death, fatal myocardial infarction, and fatal stroke) and nonfatal cardiovascular events (nonfatal myocardial infarction, peripheral vascular disease leading to amputation, and nonfatal stroke). Heart failure was not included, given the common noncardiac etiologic factors of fluid overload in patients receiving hemodialysis. Each serious cardiovascular event was counted (i.e., participants could contribute data on more than one event).

Dialysis patients

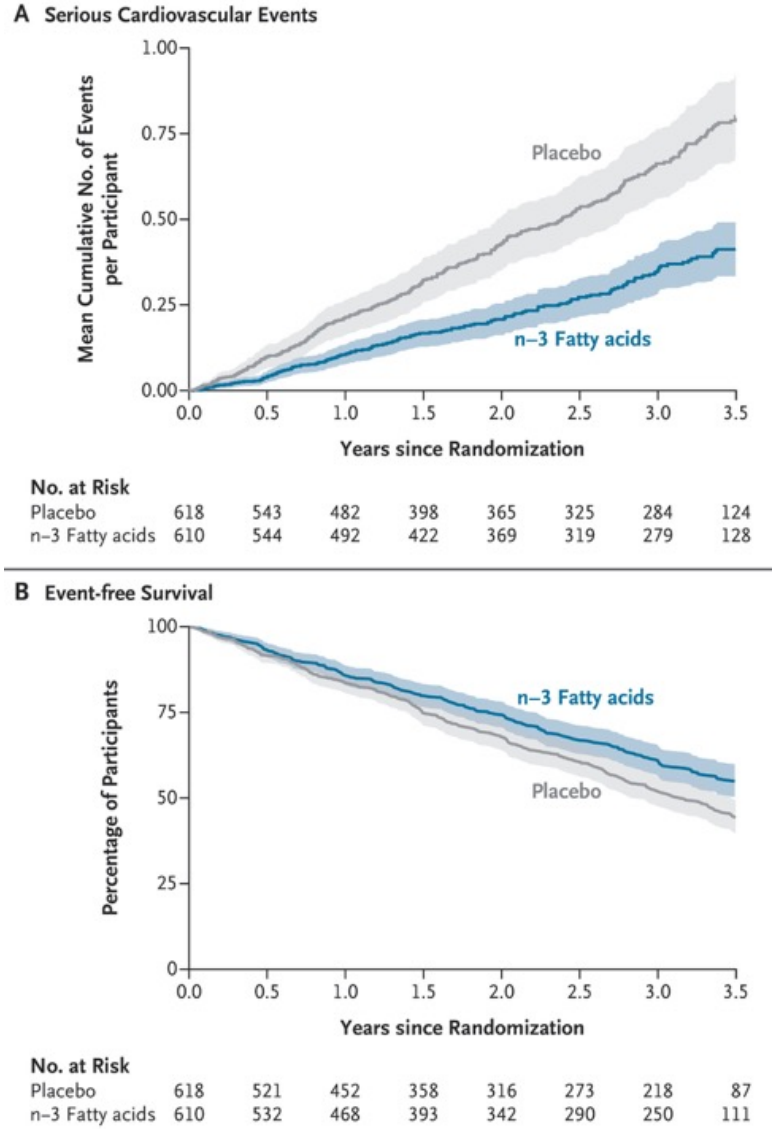
Characteristic	Fish Oil (N=610)	Placebo (N=618)
Age — yr	64.1±13.5	64.5±13.8
Male sex — no. (%)†	377 (62.2)	387 (63.1)
Body-mass index‡	27.3±6.4	27.5±6.6
Race or ethnic group — no. (%)§		
White	244 (40.0)	244 (39.5)
Asian	99 (16.2)	95 (15.4)
Southeast Asian	76 (12.5)	99 (16.0)
Black	86 (14.1)	71 (11.5)
Other	43 (7.0)	39 (6.3)
Unknown or multiple	62 (10.2)	70 (11.3)
Coexisting conditions — no. (%)		
Diabetes	342 (56.1)	330 (53.4)
Hypertension	522 (85.6)	516 (83.5)
No history of cardiovascular disease — no. (%)	392 (64.3)	402 (65.0)
Median duration of hemodialysis (IQR) — yr	2.3 (1.1–4.9)	2.6 (1.1–4.8)
Median laboratory values (IQR)		
Hemoglobin — g/liter	109 (101–118)	110 (102–118)
Sodium — mmol/liter	137 (135–139)	137 (134–139)
Potassium — mmol/liter	4.7 (4.3–5.1)	4.7 (4.3–5.1)
Bicarbonate — mmol/liter	24 (22–26)	24 (22–26)
Total cholesterol — mmol/liter	3.41 (2.79–4.20)	3.29 (2.84–4.12)
LDL cholesterol — mmol/liter	1.59 (1.15–2.24)	1.50 (1.10–2.22)
HDL cholesterol — mmol/liter	1.04 (0.83–1.29)	1.05 (0.84–1.33)
Triglycerides — mmol/liter	1.29 (0.94–1.95)	1.35 (0.92–1.97)
Medications — no. of participants (%)		
Statin	332 (54.4)	357 (57.8)
Other lipid-lowering agent	37 (6.1)	47 (7.6)
Beta-blocker	301 (49.3)	303 (49.0)
Calcium-channel blocker	277 (45.4)	251 (40.6)
Renin–angiotensin system inhibitor¶	236 (38.7)	244 (39.5)
Diuretic	172 (28.2)	169 (27.3)
Anticoagulant or antiplatelet‖	141 (23.1)	143 (23.1)

Primary and Secondary End Points.

End Point	Fish Oil		Placebo		Hazard Ratio (95% CI)†
	No. of Events	Rate *no. per 1000 patient-days*	No. of Events	Rate *no. per 1000 patient-days*	
Primary end point					
Primary end-point events among all participants	158	0.31	309	0.61	0.57 (0.47–0.70)
Primary end-point events in subgroups based on history of a cardiovascular event at baseline					
Previous cardiovascular event	81	0.43	164	0.91	0.50 (0.37–0.67)
No previous cardiovascular event	77	0.24	145	0.45	0.55 (0.40–0.76)
Secondary end points					
Primary end-point events plus noncardiac death	266	0.52	381	0.76	0.77 (0.65–0.90)
Death from any cause	175	0.34	195	0.39	0.89 (0.73–1.01)
Components of the primary end point					
Cardiac death	63	0.12	113	0.22	0.55 (0.40–0.75)
Fatal and nonfatal myocardial infarction	49	0.10	96	0.19	0.56 (0.40–0.80)
Peripheral vascular disease leading to amputation	35	0.07	66	0.13	0.57 (0.38–0.86)
Fatal and nonfatal stroke	11	0.02	34	0.07	0.37 (0.18–0.76)
First cardiovascular event or death from any cause	215	0.45	270	0.60	0.73 (0.61–0.87)

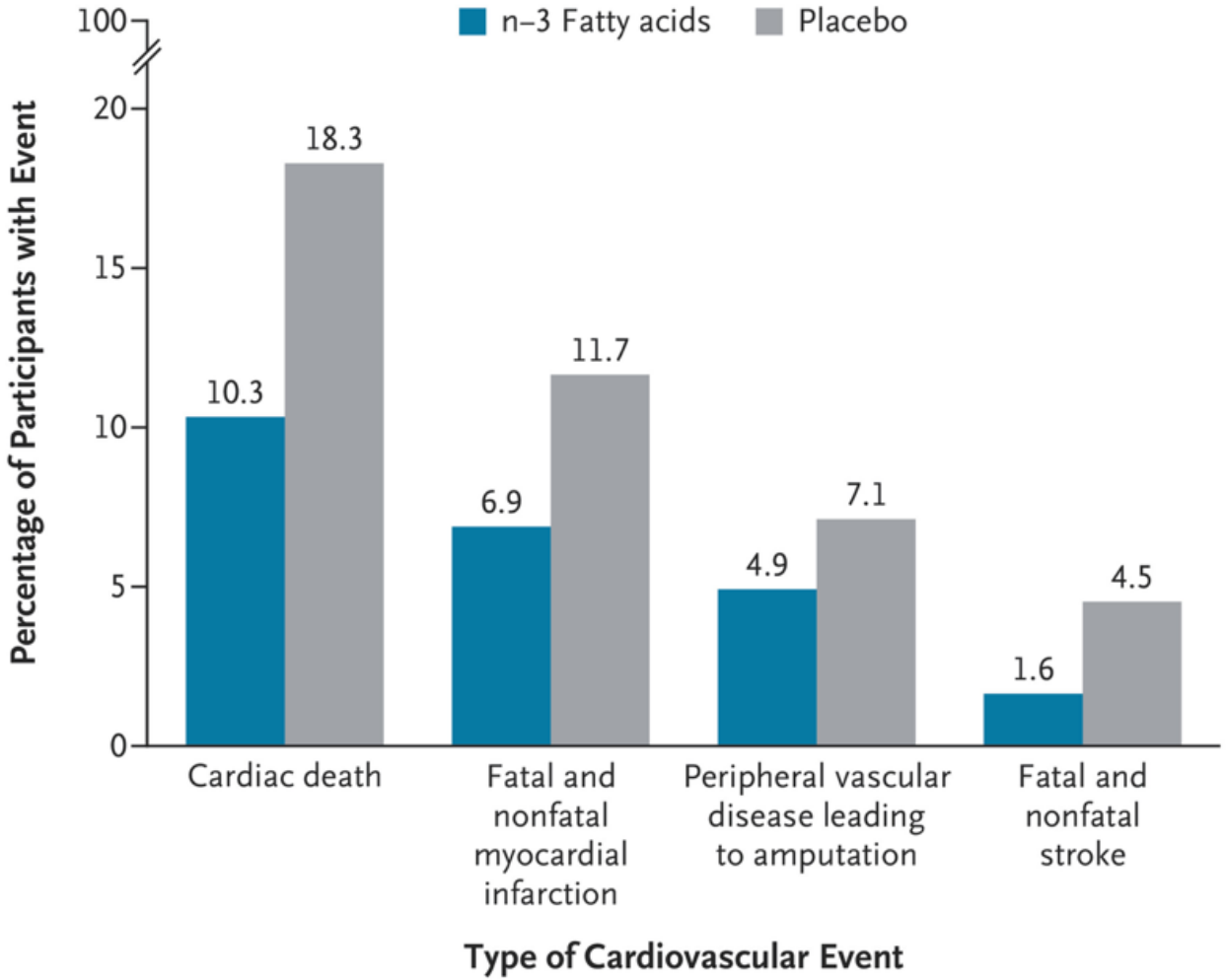
Safety and Serious Adverse Events.

Serious Adverse Event	Fish Oil (N=610)	Placebo (N=618)
	no. of participants with event (%)	
Infection	124 (20.3)	110 (17.8)
Vascular access–related event	51 (8.4)	63 (10.2)
Dialysis-related event		
Fluid overload	52 (8.5)	48 (7.8)
Other	18 (3.0)	18 (2.9)
Diabetes complication	12 (2.0)	5 (0.8)
Endocrinology-related event	16 (2.6)	21 (3.4)
Hemodynamic problem, multifactorial	39 (6.4)	41 (6.6)
Gastrointestinal tract–related event	56 (9.2)	61 (9.9)
Hematology-related event	11 (1.8)	9 (1.5)
Cancer-related event	6 (1.0)	9 (1.5)
Orthopedics-related event	36 (5.9)	34 (5.5)
Respirology-related event	31 (5.1)	23 (3.7)
General discomfort	12 (2.0)	10 (1.6)
Failure to thrive or cope	15 (2.5)	21 (3.4)
Altered level of consciousness	16 (2.6)	21 (3.4)
Neurology-related event	23 (3.8)	21 (3.4)
Surgery-related event	11 (1.8)	3 (0.5)
Overdose or intoxication	4 (0.7)	4 (0.6)
Trauma	1 (0.2)	1 (0.2)
Allergic reaction	0	1 (0.2)
Bleeding according to type		
Gastrointestinal bleeding	16 (2.6)	26 (4.2)
Cerebral bleeding	10 (1.6)	9 (1.5)
Other type of bleeding	6 (1.0)	13 (2.1)
Total	29 (4.8)	47 (7.6)
Other serious adverse event*	1 (0.2)	2 (0.3)
No serious adverse event	310 (50.8)	316 (51.1)



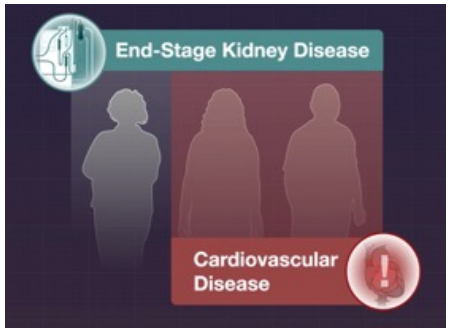
Mean Cumulative Cardiovascular Events and Event-free Survival.

Panel A shows the mean cumulative number of serious cardiovascular events per participant in each trial group. Events included cardiovascular death (sudden and nonsudden cardiac death, fatal myocardial infarction, and fatal stroke) and nonfatal cardiovascular events (nonfatal myocardial infarction, peripheral vascular disease leading to amputation, and nonfatal stroke). The shaded areas are the pointwise 95% confidence intervals. The numbers beneath the figure are the numbers of participants who were still being followed for serious cardiovascular events (i.e., the numbers still alive and who did not have censored data). Panel B shows event-free survival according to trial group. The shaded areas are the pointwise 95% confidence intervals. The numbers beneath the figure are the numbers of those at risk who were still alive, did not have censored data, and had not yet had a serious cardiovascular event.

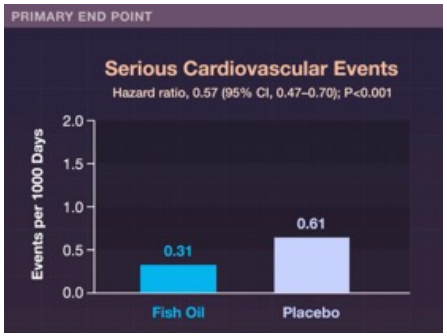


Participants with Cardiovascular Events.

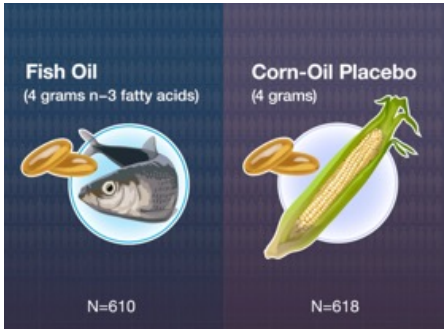
The risk differences (fish oil vs. placebo) and their associated 95% confidence intervals were −8.0 percentage points (95% CI, −12.0 to −3.9]) for cardiac death, −4.8 percentage points (95% CI, −8.2 to −1.4) for fatal and nonfatal myocardial infarction, −2.2 percentage points (95% CI, −5.0 to −0.6) for peripheral vascular disease leading to amputation, and −2.9 percentage points (95% CI, −5.0 to −0.8]) for fatal and nonfatal stroke. Note that differential follow-up was not considered in these analyses of binary events.

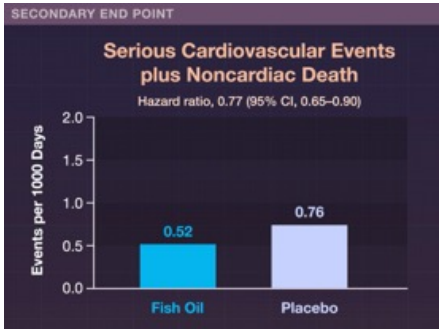

End-Stage Kidney Disease
Cardiovascular Disease

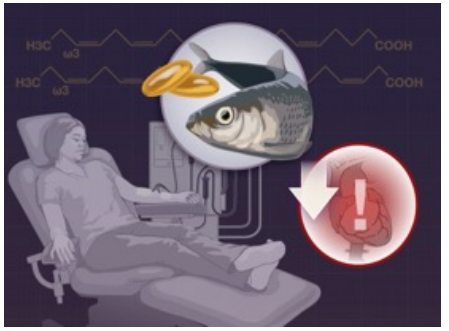

PISCES
Fish Oil


PRIMARY END POINT
Serious Cardiovascular Events
Hazard ratio, 0.57 (95% CI, 0.47–0.70); P<0.001
Events per 1000 Days
2.0
1.5
1.0
0.5
0.0
0.31
0.61
Fish Oil
Placebo


n–3 Polyunsaturated Fatty Acids

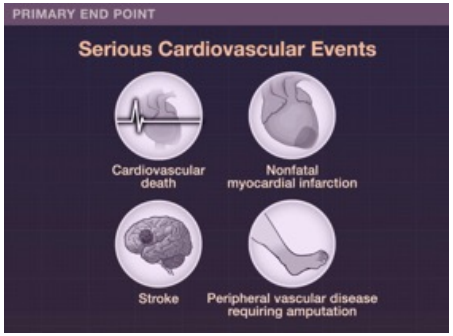

Fish Oil
(4 grams n–3 fatty acids)
Corn-Oil Placebo
(4 grams)
N=610
N=618

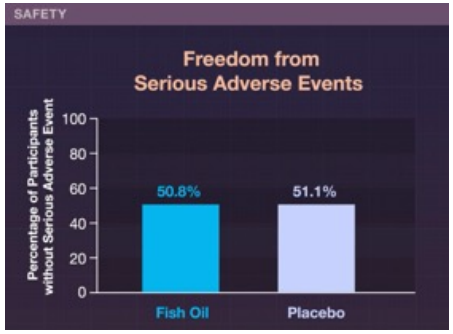

SECONDARY END POINT
Serious Cardiovascular Events
plus Noncardiac Death
Hazard ratio, 0.77 (95% CI, 0.65–0.90)
Events per 1000 Days
2.0
1.5
1.0
0.5
0.0
0.52
0.76
Fish Oil
Placebo



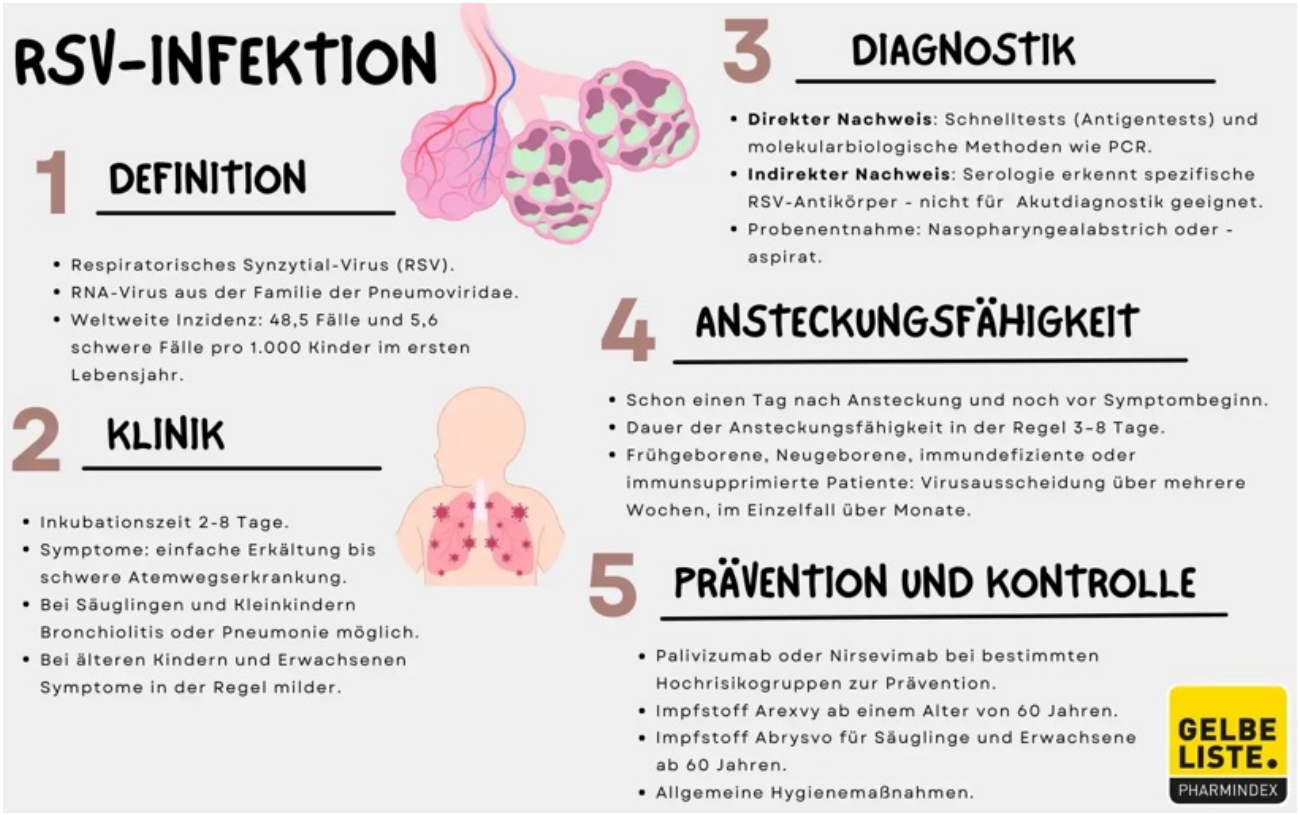
Miraculous


n–3 Polyunsaturated Fatty Acids


PRIMARY END POINT
Serious Cardiovascular Events
Cardiovascular death
Nonfatal myocardial infarction
Stroke
Peripheral vascular disease requiring amputation

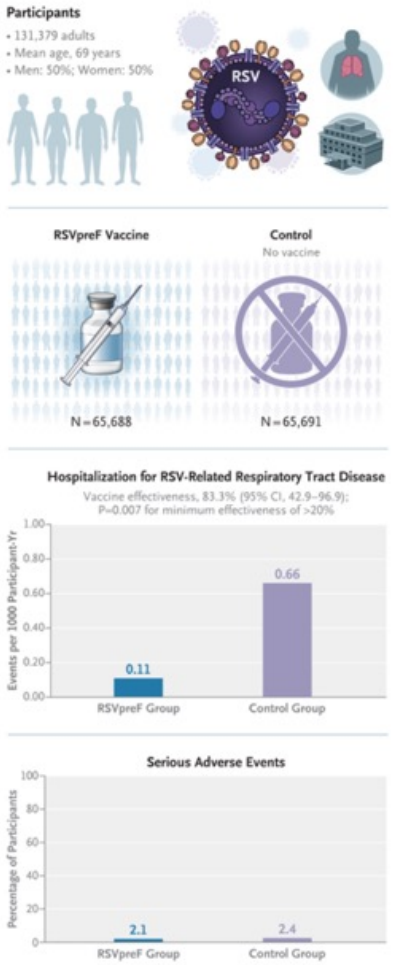

SAFETY
Freedom from
Serious Adverse Events
Percentage of Participants without Serious Adverse Event
100
80
60
40
20
0
50.8%
51.1%
Fish Oil
Placebo

RSV-Lungenentzündung ist eine schwere Atemwegserkrankung, verursacht durch das Respiratorische Synzytial-Virus (RSV), die häufig bei Säuglingen, Kleinkindern und älteren Menschen auftritt, oft mit Fieber, Husten, Atemnot und schweren Verläufen wie Bronchitis oder Lungenentzündung, die einen Krankenhausaufenthalt erfordern kann und besonders bei Risikogruppen gefährlich ist. Die Übertragung erfolgt durch Tröpfcheninfektion, und während milde Fälle einer Erkältung ähneln, können schwere Fälle Lungenentzündungen verursachen, die stationäre Behandlung nötig machen.



RSV Prefusion F Vaccine for Prevention of Hospitalization in Older Adults

Respiratory syncytial virus (RSV) can cause serious illness in older adults. The bivalent RSV prefusion F protein–based vaccine (RSVpreF) has been shown to prevent RSV-associated respiratory illness, but data from randomized trials with regard to its effect on outcomes involving hospitalization are limited. In this pragmatic, open-label trial with individual randomization, participants who were 60 years of age or older were assigned in a 1:1 ratio to receive the RSVpreF vaccine (the RSVpreF group) or no vaccine (the control group) during the 2024–2025 winter season. Baseline and outcome data were collected with the use of national registries. The primary end point was hospitalization for RSV-related respiratory tract disease. Secondary end points included hospitalization for RSV-related lower respiratory tract disease and hospitalization for respiratory tract disease from any cause. The prespecified criterion for success for the primary end point and RSV-related secondary end points was a minimum vaccine effectiveness of greater than 20%.



Respiratory syncytial virus (RSV) is a common cause of respiratory tract disease in older adults and a major cause of severe respiratory illness in both older adults and persons with underlying conditions. It is estimated that 5.2 million cases of severe RSV-related respiratory illness, 470,000 hospitalizations, and 33,000 deaths occur annually in industrialized countries.

A bivalent RSV prefusion F protein–based vaccine (RSVpreF), which contains stabilized prefusion F glycoproteins from RSV, was recently developed for adults 60 years of age or older. Phase 3 trials of RSVpreF vaccines against RSV-related lower respiratory tract disease have shown vaccine efficacy levels of 88.9%, 82.6%, and 83.7% for nonadjuvanted, adjuvanted, and mRNA-based forms, respectively. However, the trials were not designed or powered to evaluate severe outcomes such as hospitalization. Data from preliminary observational studies suggest that the RSVpreF vaccine has 73 to 90% real-world effectiveness against hospitalization for RSV-related respiratory illness, but such studies are limited by confounding factors. In addition, the effects of RSVpreF vaccination on hospitalization for respiratory disease from any cause or for cardiorespiratory disease remain unclear.

Trial Participants

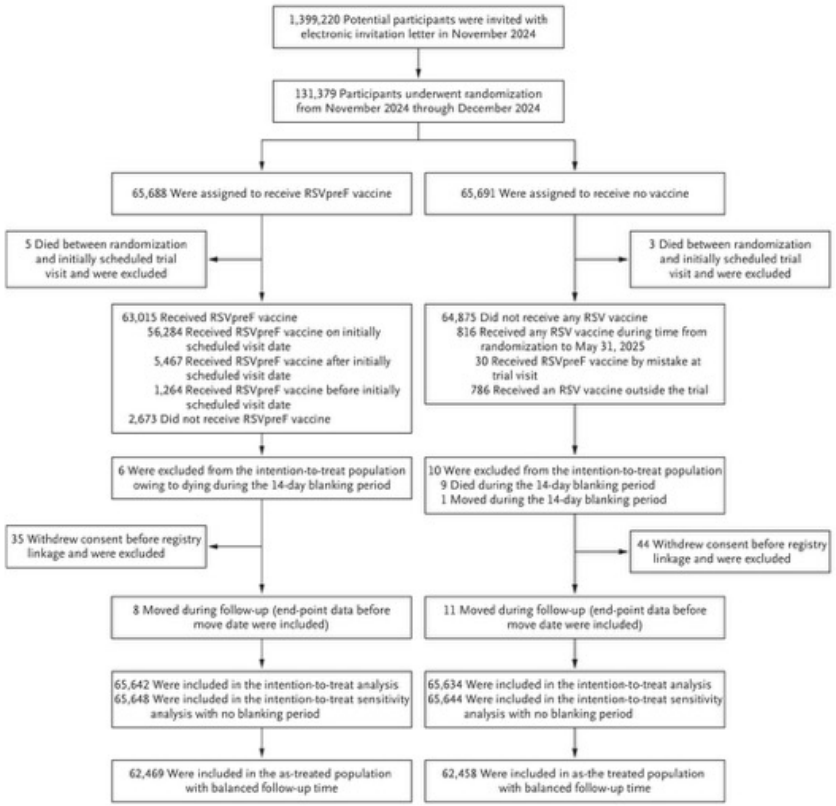
Adults who were 60 years of age or older and had a Danish civil registration number were eligible to enroll in the trial. The trial had no formal exclusion criteria but required that vaccination follow routine clinical guidelines, with assessment for contraindications (hypersensitivity to the vaccine or its components or acute illness on the day of vaccination). Since the RSVpreF vaccine was approved as a one-time dose in Denmark at the time of enrollment, participants were asked at their vaccination appointment if they had previously received the vaccine, according to routine vaccination practices. All the participants provided written informed consent that authorized access to their electronic medical records and data linkage to the national health registries.

Trial Procedures

The RSVpreF vaccine contained RSV subgroup A stabilized prefusion F antigen (60 μg) and RSV subgroup B stabilized prefusion F antigen (60 μg) and was administered as a single intramuscular injection. The control group did not receive any vaccine as part of the trial.

End Points

The primary end point was hospitalization for RSV-related respiratory tract disease, defined as hospitalization with either a primary diagnosis code of RSV infection or a primary diagnosis code of respiratory tract disease combined with RSV infection that was confirmed by a specific ICD-10 code for RSV infection as the secondary diagnosis or a positive RSV test performed within 7 days before or 2 days after admission. Key secondary end points were hospitalization for RSV-related lower respiratory tract disease and hospitalization for respiratory tract disease from any cause.



Characteristic	RSVpreF Group (N = 65,642)	Control Group (N = 65,634)
Age — yr	69.4±6.5	69.4±6.5
Age ≥75 yr — no. (%)	13,839 (21.1)	13,853 (21.1)
Male sex — no. (%)	32,931 (50.2)	33,082 (50.4)
Any chronic disease — no. (%)	27,562 (42.0)	27,554 (42.0)
Chronic lung disease — no. (%)	4,808 (7.3)	4,802 (7.3)
Chronic obstructive pulmonary disease — no. (%)	1,706 (2.6)	1,678 (2.6)
Diabetes — no. (%)	7,190 (11.0)	7,249 (11.0)
Cancer — no. (%)	7,549 (11.5)	7,547 (11.5)
Chronic cardiovascular disease — no. (%)	14,377 (21.9)	14,285 (21.8)
Ischemic heart disease — no. (%)	4,896 (7.5)	4,850 (7.4)
Heart failure — no. (%)	1,513 (2.3)	1,460 (2.2)
Atrial fibrillation — no. (%)	5,154 (7.9)	4,972 (7.6)
Cerebrovascular disease — no. (%)	2,287 (3.5)	2,386 (3.6)
Hypertension — no. (%)	9,818 (15.0)	9,904 (15.1)
Chronic kidney disease — no. (%)	6,660 (10.1)	6,704 (10.2)
Liver disease — no. (%)	960 (1.5)	1,051 (1.6)
Neurologic or neuromuscular disease — no. (%)	1,477 (2.3)	1,429 (2.2)
Rheumatic disease — no. (%)	1,511 (2.3)	1,475 (2.2)
Immunodeficiency — no. (%)	2,619 (4.0)	2,580 (3.9)
Influenza vaccination in previous season — no. (%)	52,552 (80.1)	52,381 (79.8)
Influenza vaccination in 2024–2025 season before randomization — no. (%)	53,008 (80.8)	52,818 (80.5)
Coadministration of influenza vaccine — no. (%)	113 (0.2)	0
Coadministration of Covid-19 vaccine — no. (%)	110 (0.2)	0
Previous pneumococcal vaccination — no. (%)	42,077 (64.1)	41,996 (64.0)
Previous RSV vaccination — no. (%)	61 (0.1)	66 (0.1)

Primary, Secondary, and Exploratory End Points.

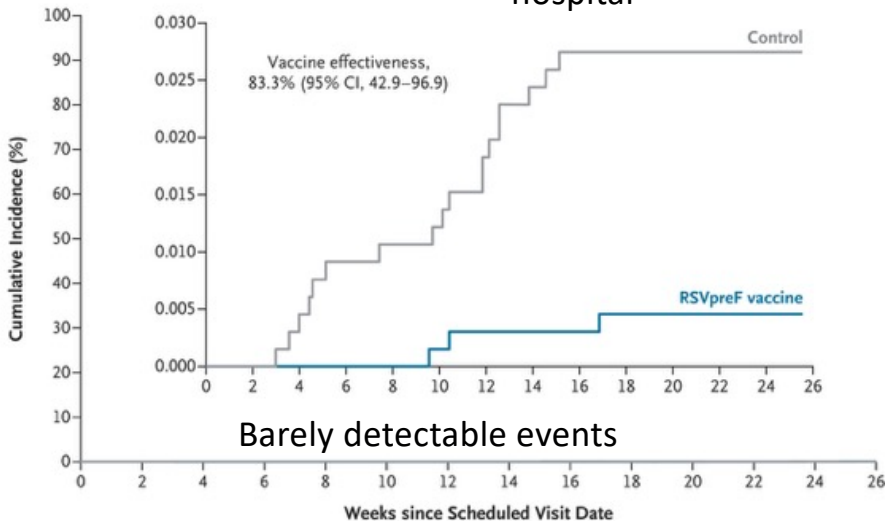
End Point	RSVpreF Group				Control Group				Absolute Rate Reduction†	Vaccine Efficacy (95% CI)	P Value‡
	Participants	Events	Total Follow-up	Incidence Rate	Participants	Events	Total Follow-up	Incidence Rate			
	no.	*no.*	*participant-yr*	*events/1000 participant-yr*	*no.*	*no.*	*participant-yr*	*events/1000 participant-yr*	*events/1000 participant-yr*	%	
Primary end point											
Hospitalization for RSV-related respiratory tract disease											
ITT population	65,642	3	27,320	0.11	65,634	18	27,330	0.66	0.55	83.3 (42.9 to 96.9)	0.007§
Age group in ITT population											
60–74 years	51,803	1	21,670	0.05	51,781	10	21,668	0.46	0.41	90.0 (29.7 to 99.8)	
≥75 years	13,839	2	5,650	0.35	13,853	8	5,662	1.41	1.06	75.0 (−25.0 to 97.4)	
As-treated population with balanced follow-up times	62,469	3	25,639	0.12	62,458	17	25,630	0.66	0.54	82.4 (39.0 to 96.7)	0.01§
Key secondary end points											
Hospitalization for RSV-related lower respiratory tract disease	65,642	1	27,321	0.04	65,634	12	27,332	0.44	0.40	91.7 (43.7 to 99.8)	0.009§
Hospitalization for respiratory tract disease from any cause	65,642	284	27,257	10.42	65,634	335	27,268	12.29	1.87	15.2 (0.5 to 27.9)	0.04¶
Additional secondary end points											
RSV-related hospitalization‖	65,642	1	27,321	0.04	65,634	8	27,333	0.29	0.25	87.5 (6.8 to 99.7)**	
Hospitalization for RSV-related cardiorespiratory disease	65,642	3	27,320	0.11	65,634	19	27,330	0.70	0.59	84.2 (46.4 to 97.0)**	
Hospitalization for cardiorespiratory disease from any cause	65,642	715	27,167	26.32	65,634	794	27,171	29.22	2.90	9.9 (0.3 to 18.7)**	
Hospitalization for lower respiratory tract disease from any cause	65,642	236	27,269	8.65	65,634	298	27,278	10.92	2.27	20.8 (5.8 to 33.6)**	
Hospitalization for any cause	65,642	3,526	26,581	132.7	65,634	3,598	26,583	135.4	2.70	2.0 (−2.7 to 6.5)**	
Death from any cause	65,642	146	27,321	5.34	65,634	120	27,335	4.39	−0.95	−21.7 (−56.1 to 5.1)**	
Prespecified exploratory RSV-related end points											
Laboratory-confirmed RSV infection (any health care setting)	65,642	19	27,316	0.70	65,634	67	27,316	2.45	1.75	71.6 (52.2 to 83.9)**	
Hospitalization for any cause plus a positive RSV test	65,642	4	27,320	0.15	65,634	20	27,329	0.73	0.58	80.0 (40.3 to 95.0)**	
Prespecified exploratory influenza-related end points											
Laboratory-confirmed influenza (any health-care setting)	65,642	251	27,257	9.21	65,634	217	27,280	7.95	−1.26	−15.8 (−39.3 to 4.0)**	
Influenza-related hospitalization‖	65,642	48	27,309	1.76	65,634	37	27,325	1.35	−0.41	−29.8 (−104.8 to 17.3)**	

Serious Adverse Events during the 6-Week Safety Surveillance Period, According to Trial Group.

Event	RSVpreF Group (N=63,045)	Control Group (N=68,326)
	no. of patients (%)	
Any serious adverse event	1341 (2.1)	1669 (2.4)
Any cardiovascular serious adverse event	224 (0.4)	286 (0.4)
Any respiratory serious adverse event	116 (0.2)	113 (0.2)
Any gastrointestinal serious adverse event	136 (0.2)	171 (0.3)
Any neurologic serious adverse event	41 (0.1)	40 (0.1)
Any cancer-related serious adverse event	61 (0.1)	85 (0.1)
Any infection-related serious adverse event	40 (0.1)	57 (0.1)
Any injury-related serious adverse event	156 (0.2)	205 (0.3)
Fatal serious adverse event	17 (<0.1)	33 (<0.1)
Any serious adverse reaction†	5 (<0.1)	NA
Bell's palsy	1 (<0.1)	3 (<0.1)
Pericarditis	2 (<0.1)	2 (<0.1)

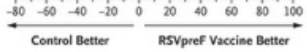
(3%)

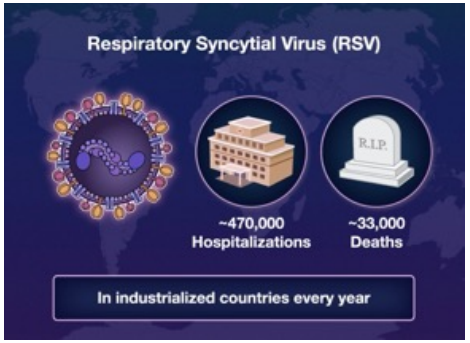
But marked protection from hospital



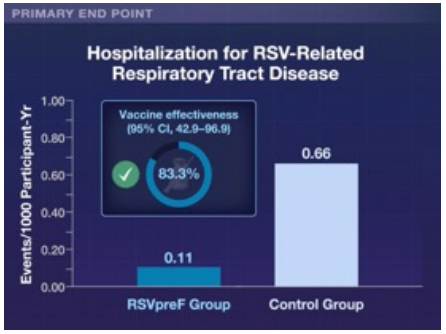
Barely detectable events

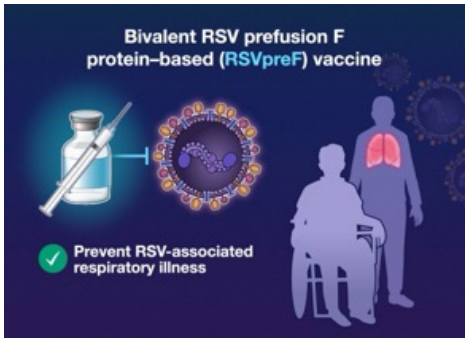
Subgroup	RSVpreF Vaccine	Control	Vaccine Effectiveness (95% CI)
	no. of events/total no. of participants		
Overall	3/65,642	18/65,634	83.3 (42.9 to 96.9)
Age			
60–74 yr	1/51,803	10/51,781	90.0 (29.7 to 99.8)
≥75 yr	2/13,839	8/13,853	75.0 (–25.0 to 97.4)
<Median	0/32,890	4/32,751	—
≥Median	3/32,752	14/32,883	78.5 (23.6 to 96.1)
Sex			
Male	2/32,931	9/33,082	77.7 (–6.8 to 97.7)
Female	1/32,711	9/32,552	88.9 (19.4 to 99.8)
Presence of at least 1 chronic disease			
No	0/38,080	5/38,080	—
Yes	3/27,562	13/27,554	76.9 (16.0 to 95.8)
Chronic lung disease			
No	3/60,834	13/60,832	76.9 (16.1 to 95.8)
Yes	0/4808	5/4802	—
Cardiovascular disease			
No	1/51,265	11/51,349	90.9 (37.6 to 99.8)
Yes	2/14,377	7/14,285	71.6 (–51.1 to 97.1)
Diabetes mellitus			
No	2/58,452	17/58,385	88.2 (50.4 to 98.7)
Yes	1/7190	1/7249	—
Cancer			
No	2/58,093	12/58,087	83.3 (25.2 to 98.2)
Yes	1/7549	6/7547	83.3 (–37.4 to 99.6)
Chronic kidney disease			
No	1/58,982	12/58,930	91.7 (43.7 to 99.8)
Yes	2/6660	6/6704	66.4 (–85.2 to 96.7)
Immunosuppression			
No	1/63,023	13/63,054	92.3 (48.8 to 99.8)
Yes	2/2619	5/2580	60.5 (–147.3 to 96.1)
Influenza vaccination in same season			
No	0/12,634	1/12,816	—
Yes	3/53,008	17/52,818	82.4 (38.8 to 96.7)
Previous pneumococcal vaccination			
No	0/23,565	3/23,638	—
Yes	3/42,077	15/41,996	80.0 (29.2 to 96.3)

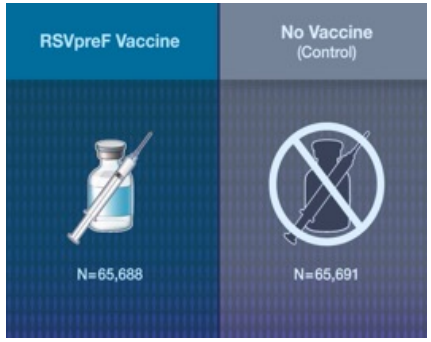


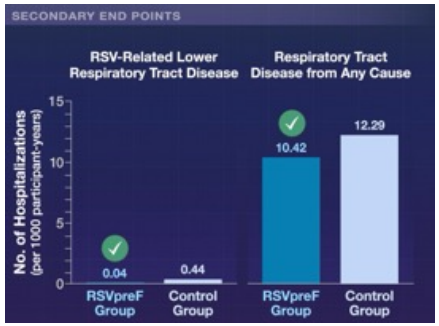

Respiratory Syncytial Virus (RSV)
R.I.P.
~470,000
Hospitalizations
~33,000
Deaths
In industrialized countries every year

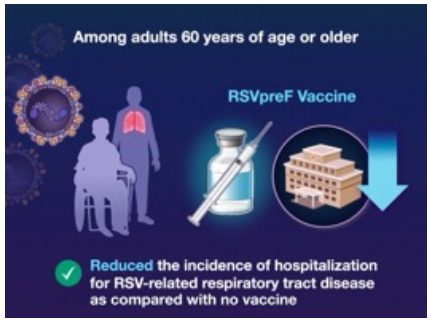

DAN-RSV Trial
Prevent
hospitalizations
in older adults?

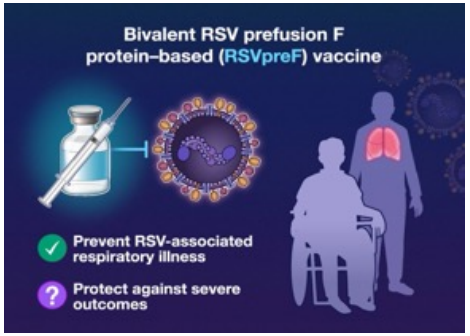

PRIMARY END POINT
Hospitalization for RSV-Related
Respiratory Tract Disease
Vaccine effectiveness
(95% CI, 42.9–96.9)
83.3%
Events/1000 Participant-Yr
1.00
0.80
0.60
0.40
0.20
0.00
0.11
0.66
RSVpreF Group
Control Group

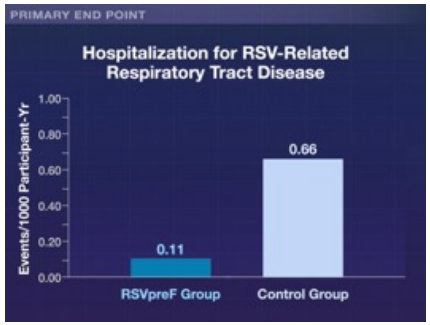

Bivalent RSV prefusion F
protein–based (RSVpreF) vaccine
Prevent RSV-associated
respiratory illness

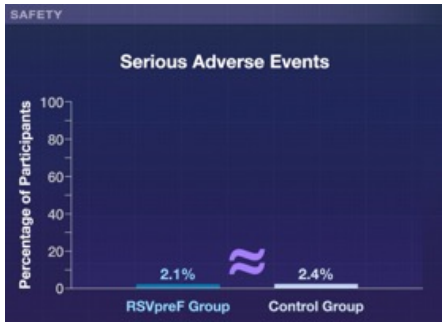

RSVpreF Vaccine
No Vaccine
(Control)
N=65,688
N=65,691


SECONDARY END POINTS
RSV-Related Lower
Respiratory Tract Disease
Respiratory Tract
Disease from Any Cause
No. of Hospitalizations
(per 1000 participant-years)
15
10
5
0
0.04
0.44
10.42
12.29
RSVpreF
Group
Control
Group
RSVpreF
Group
Control
Group


Among adults 60 years of age or older
RSVpreF Vaccine
Reduced the incidence of hospitalization
for RSV-related respiratory tract disease
as compared with no vaccine


Bivalent RSV prefusion F
protein–based (RSVpreF) vaccine
Prevent RSV-associated
respiratory illness
Protect against severe
outcomes

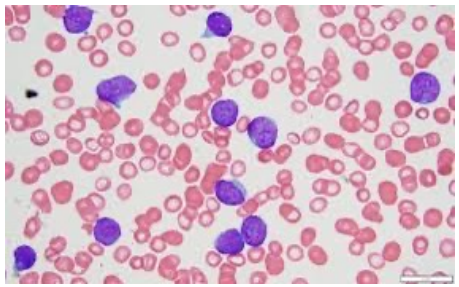

PRIMARY END POINT
Hospitalization for RSV-Related
Respiratory Tract Disease
Events/1000 Participant-Yr
1.00
0.80
0.60
0.40
0.20
0.00
0.11
0.66
RSVpreF Group
Control Group

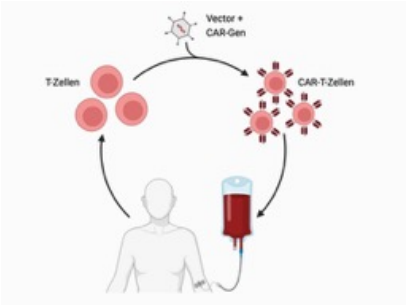

SAFETY
Serious Adverse Events
Percentage of Participants
100
80
60
40
20
0
2.1%
≈
2.4%
RSVpreF Group
Control Group

T-Zell-Leukämien sind eine Gruppe seltener und oft aggressiver bösartiger Erkrankungen des Immunsystems, die von den **T-Lymphozyten** (einer Art weißer Blutkörperchen) ausgehen.

Wichtige Formen

- **T-ALL (T-Zell-akute lymphatische Leukämie):** Eine sehr aggressive Form, die vor allem Kinder und junge Erwachsene betrifft.
- **T-PLL (T-Zell-Prolymphozytenleukämie):** Eine seltene, schnell fortschreitende Form, die meist ältere Erwachsene (ca. 65 Jahre) betrifft.
- **Adulte T-Zell-Leukämie (ATL):** Eine durch das HTLV-1-Virus verursachte Form, die oft mit Hautveränderungen einhergeht.
- **LGL-Leukämie (Large Granular Lymphocyte):** Eine meist chronische und langsamer verlaufende Form.





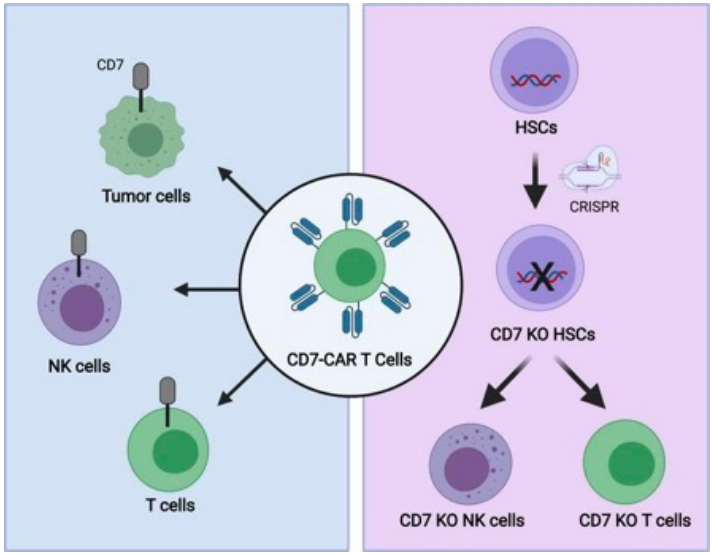
CD7 (Cluster of Differentiation 7) ist ein Oberflächenprotein, das primär in der Diagnose und Forschung von T-Zell-Erkrankungen eine zentrale Rolle spielt.

Biologische Bedeutung und Funktion

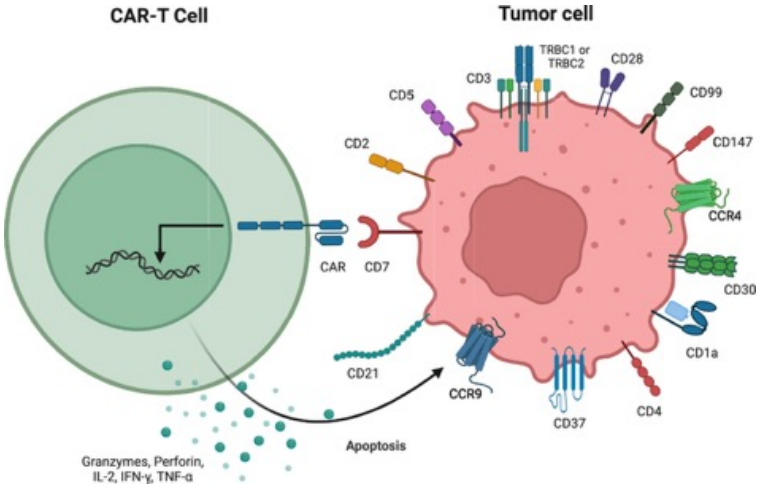
•**Zellmarker:** Es ist eines der frühesten Antigene, das während der Entwicklung von T-Zellen und Natürlichen Killerzellen (NK-Zellen) auftritt und über die gesamte Differenzierung hinweg exprimiert bleibt.

•**Struktur:** CD7 ist ein Transmembran-Glykoprotein der Immunglobulin-Superfamilie mit einer Masse von etwa 40 kDa (beim Menschen kodiert auf Chromosom 17).

•**Immunfunktion:** Die genaue Funktion ist noch Gegenstand der Forschung.



T cells against T cells



Universal Base-Edited CAR7 T Cells for T-Cell Acute Lymphoblastic Leukemia

CD7 is an attractive target for chimeric antigen receptor (CAR) T-cell therapy in relapsed or refractory T-cell acute lymphoblastic leukemia (ALL). Supportive results of first-in-human studies of base-edited anti-CD7 CAR (BE-CAR7) T cells with triple C→T deamination-mediated knockouts of TCRαβ, CD52, and CD7 have been reported previously.

Methods

In a phase 1 study, we administered BE-CAR7 T cells to children (≤16 years of age) with relapsed or refractory T-cell ALL after they had undergone lymphodepletion with fludarabine, cyclophosphamide, and alemtuzumab. Adults with compassionate-use access arrangements were also eligible. Patients who had remission by day 28 after the BE-CAR7 T-cell infusion proceeded to allogeneic hematopoietic stem-cell transplantation. The primary outcome was safety. Secondary outcomes included duration of remission, disease-free survival, and overall survival.

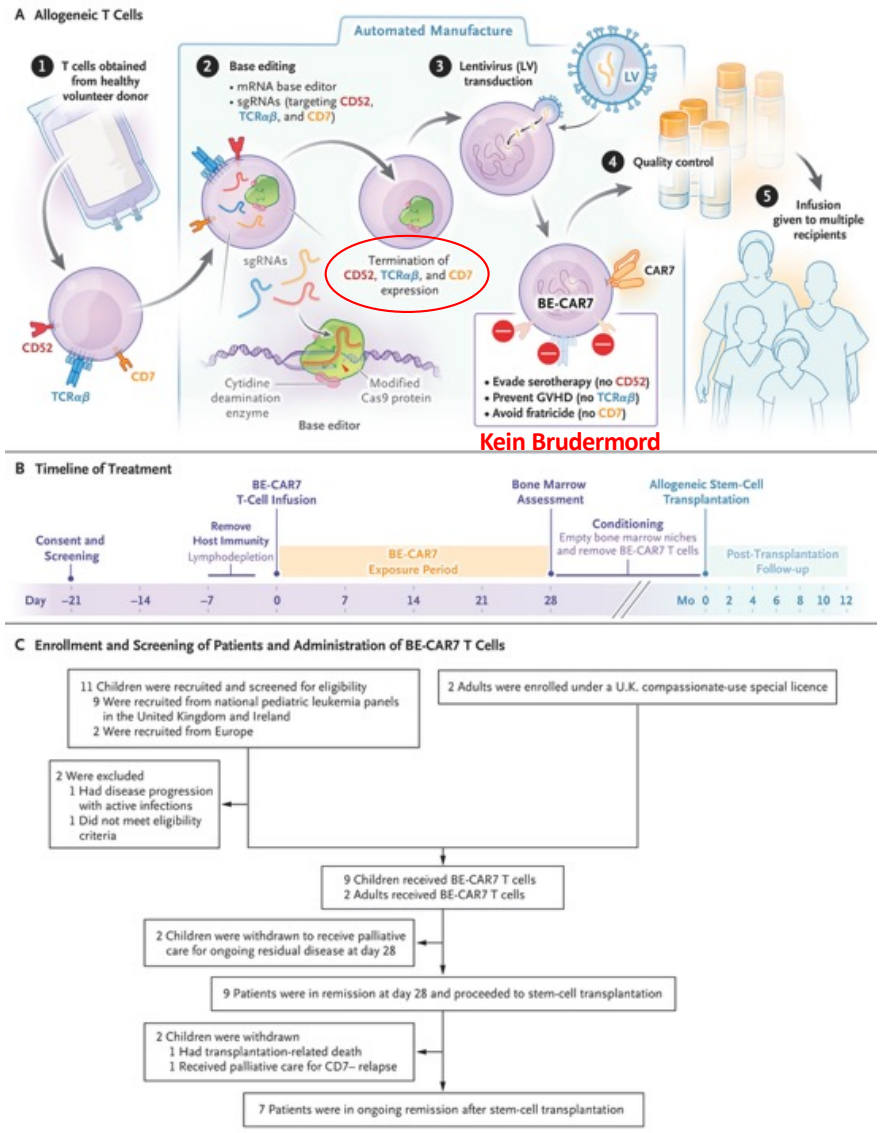
Conclusions

Universal BE-CAR7 T cells induced leukemic remission in patients with relapsed or refractory T-cell ALL, thus allowing successful allogeneic hematopoietic stem-cell transplantation in most of the patients. (Funded by the Medical Research Council and others; ISRCTN Registry number, ISRCTN15323014.)

A number of chimeric antigen receptor (CAR) T-cell strategies targeting suitable antigens in T-cell ALL have been proposed, and CD7 has emerged as one of the most compelling targets because, even though it is present on normal lymphocytes and hematopoietic precursors, expression is consistently high and stable in T-cell ALL blast populations. Fratricide effects between cells that are engineered to express anti-CD7 CARs have been addressed through the use of CD7− T-cell subsets or by coexpression of protein-expression blockers to sequester and prevent CD7 expression at the cell surface. Clinical-phase testing with the use of such approaches is under way in the context of autologous and matched allogeneic donors. Alternatively, genome editing has been applied to disrupt CD7 expression and has been combined with simultaneous disruption of T-cell receptor gene expression for the production of universal donor CAR T cells devoid of TCRαβ.

Previously, base editing (cytidine deamination guided by clustered regularly interspaced short palindromic repeats [CRISPR]) has been applied to introduce premature stop codons or modify critical splice sites for TCRαβ, CD7, and additional multiplexed knockout effects and has been combined with lentiviral transduction of T cells with an anti-CD7 CAR. Advantages of base editing over nuclease editing include minimizing karyotype aberrations or chromosomal translocations, as has been previously reported for transcription activator–like effector nucleases (TALENs) and CRISPR-Cas9 nuclease–mediated products. We previously reported results from a first-in-human study of base-edited anti-CD7 CAR (BE-CAR7) T cells that were infused in order to secure deep molecular remissions of refractory T-cell ALL before allogeneic stem-cell transplantation.

„Off the shelf“



Production of Universal Base-Edited CAR7 T Cells and the Enrollment, Screening, and Treatment of Patients.

Base editing by means of clustered regularly interspaced short palindromic repeats (CRISPR)–guided cytidine deamination was used for multiplexed editing ahead of lentiviral transduction with an anti-CD7 chimeric antigen receptor (CAR7) of T cells obtained from a healthy volunteer donor with the use of a largely automated process on a CliniMacs Prodigy device (Panel A). Precise C→T conversions introduced premature stop codons or disrupted splice sites at high efficiency after off-device electroporation. Removal of cell-surface CD7 prevented fratricide, and CD52– cells evaded alemtuzumab. After expansion, residual TCRαβ T cells were depleted by magnetic-bead selection to prevent graft-versus-host disease (GVHD). Finally, cells were cryopreserved in dose-banded aliquots and submitted for quality-control assessments. The term mRNA denotes messenger RNA, and sgRNA single-guide RNA. Patients provided written informed consent and underwent screening approximately 2 weeks before lymphodepletion, which comprised fludarabine, cyclophosphamide, and alemtuzumab (Panel B). Infusion of base-edited CAR7 (BE-CAR7) T cells was undertaken on day 0, and patients were treated in the hospital until bone marrow assessments on day 28. Patients who were in remission (target minimal residual disease [MRD], $<10^{-4}$) proceeded to allogeneic stem-cell transplantation after a conditioning step to remove BE-CAR7 T cells and clear bone marrow niches. Study monitoring continued for 12 months after stem-cell transplantation, before patients were enrolled into a long-term follow-up study. Panel C shows the process of enrollment, screening, and treatment of the patients in the study. National Health Service (NHS)–eligible pediatric patients in the United Kingdom and Ireland were considered for enrollment at national leukemia panels. Referrals were eligible for care from the U.K. NHS, including under S2 reciprocal care arrangements with Europe. Two adults received the investigational therapy under special license arrangements for compassionate use and were treated according to the same protocol.

Methods

Base-Edited CAR7 T Cells

The design, manufacture, characterization, and release of BE-CAR7 T-cell banks has been described previously. All doses of the investigational product were contained in vials that had been generated from the same registry donor (Anthony Nolan Stem Cell Registry); the investigational product was generated in a single campaign (Good Manufacturing Practices [GMP] 3) in which 59% of the CD45+ cells expressed CAR7, with 3.6 vector copies per cell and residual TCRαβ expression of 0.1%, and cells were more than 99% CD7− and more than 98% CD52−.

Treatment Schedule

In this phase 1 study, we enrolled children 6 months to 16 years of age with relapsed or refractory CD7+ T-cell ALL that was quantifiable in bone marrow ($>10^{-4}$ on flow cytometry or polymerase-chain-reaction [PCR] assay). Patients underwent lymphodepletion with fludarabine (150 mg per square meter of body-surface area), cyclophosphamide (120 mg per kilogram of body weight in patients ≤16 years of age or 1500 mg per square meter in those >16 years of age), and alemtuzumab (1 mg per kilogram). Lymphodepletion was followed by infusion within an allowed range of 0.2×10^6 to 2.0×10^6 BE-CAR7 T cells per kilogram (with a maximum dose of 5×10^4 TCRαβ+ T cells per kilogram, in order to limit the risk of GVHD).

Outcomes

The primary outcome was safety. Secondary outcomes included the frequency and duration of remission, disease-free survival, and overall survival.

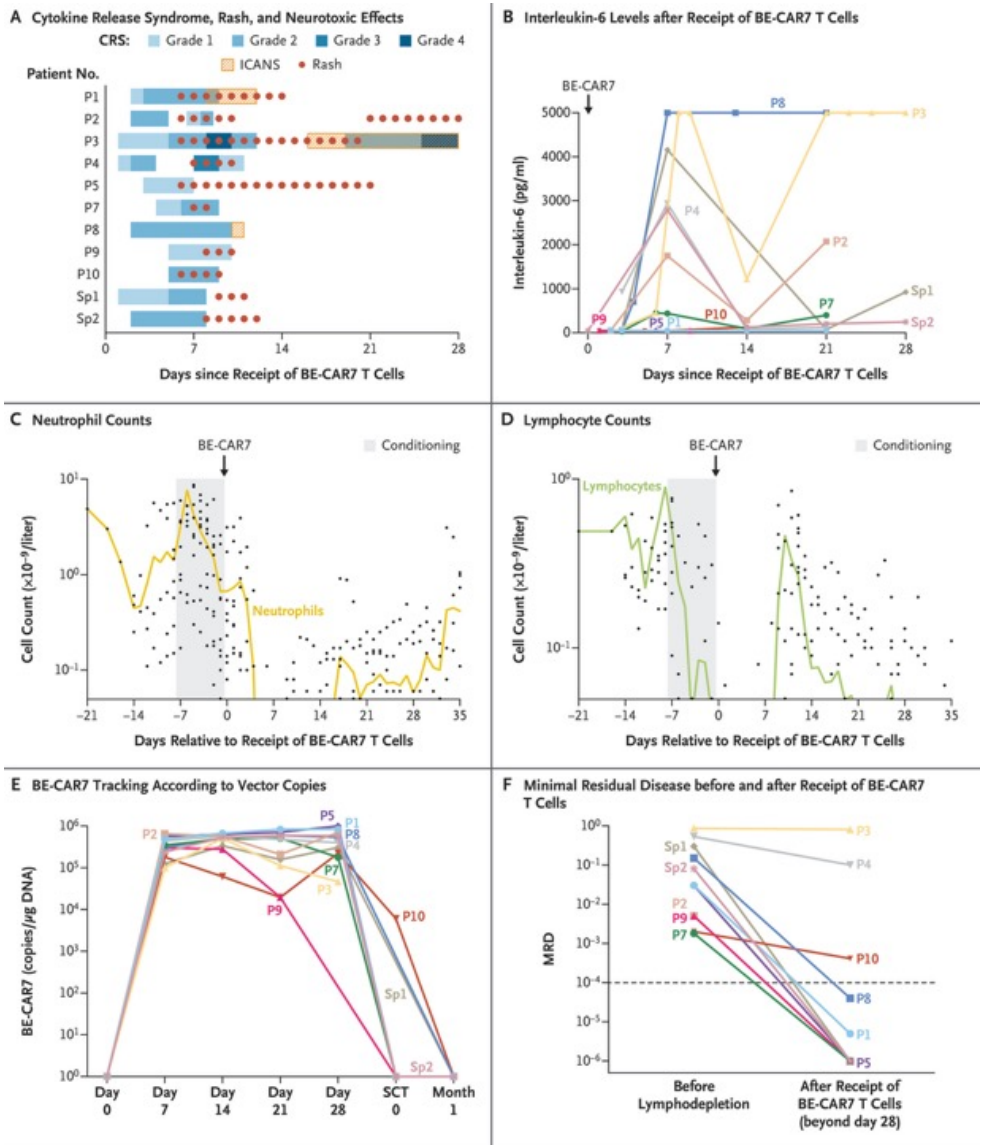
Characteristics of the Patients, Study Interventions, and Outcomes.

Variable	Patient No.										
	P1	P2	P3	P4	P5	P7	P8	P9	P10	Sp1	Sp2
Diagnosis	T-cell ALL	MPAL	T-cell ALL	T-cell ALL	ETP	ETP	N-ETP	T-cell ALL	T-cell ALL	T-cell ALL	T-cell ALL
Previous SCT	Yes	Yes	No	No	No	No	No	No	No	No	Yes
Blasts (%)	9.0	0.5	86.9	53.0	3.0	0.2	15.6	0.5	0.02	63.1	8.4
Cell dose ($\times 10^4$/kg)	0.7	0.9	1.0	0.8	0.8	0.8	0.7	0.9	0.8	0.8	0.9
Viral reactivations	BK, CMV, EBV, HHV6	ADV, BK, CMV, EBV, HHV6	BK	ADV, HHV6	ADV, BK	ADV, BK, EBV, HHV6	ADV, BK, HHV6	ADV, HHV6	ADV, RSV	ADV, BK, CMV, EBV	ADV, BK, EBV
Bone marrow at day 28											
On flow cytometry	Hypocellular	Hypocellular	Neg	Hypocellular	Neg	Neg	Neg	Hypocellular	Neg	Hypocellular	Neg
MRD on PCR assay	$<10^{-4}$	$<10^{-4}$	$>10^{-2}$	$>10^{-2}$	ANA	ANA	$<10^{-4}$	$<10^{-4}$	4×10^{-4}	ANA	$<10^{-4}$
Allogeneic SCT donor†	10/10 MUD	10/10 MUD	NA	NA	9/10 MMUD	9/10 UCB	8/10 UCB	10/10 UCB	Haplo	10/10 MUD	10/10 MUD
Chemotherapy	F: 160 mg/m² C: 120 mg/kg	F: 120 mg/m² C: 120 mg/kg	NA	NA	E: 60 mg/kg	F: 150 mg/m² T: 42 g/m²	E: 60 mg/kg	E: 60 mg/kg	E: 60 mg/kg R: 200 mg/m²	C: 120 mg/kg	F: 150 mg/m² M: 140 mg/m²
ATG	Yes	Yes	NA	NA	Yes	No	Yes	No	Yes	No	Yes
Radiotherapy dose (Gy)	2	2	NA	NA	12	4	12	8	12	13	NA
Outcome‡	Complete remission	Complete remission	Death	Death	Death	Complete remission	CD7– relapse	Complete remission	Complete remission	Complete remission	Complete remission

Summary of Adverse Events, According to the Maximum Grade of Severity.

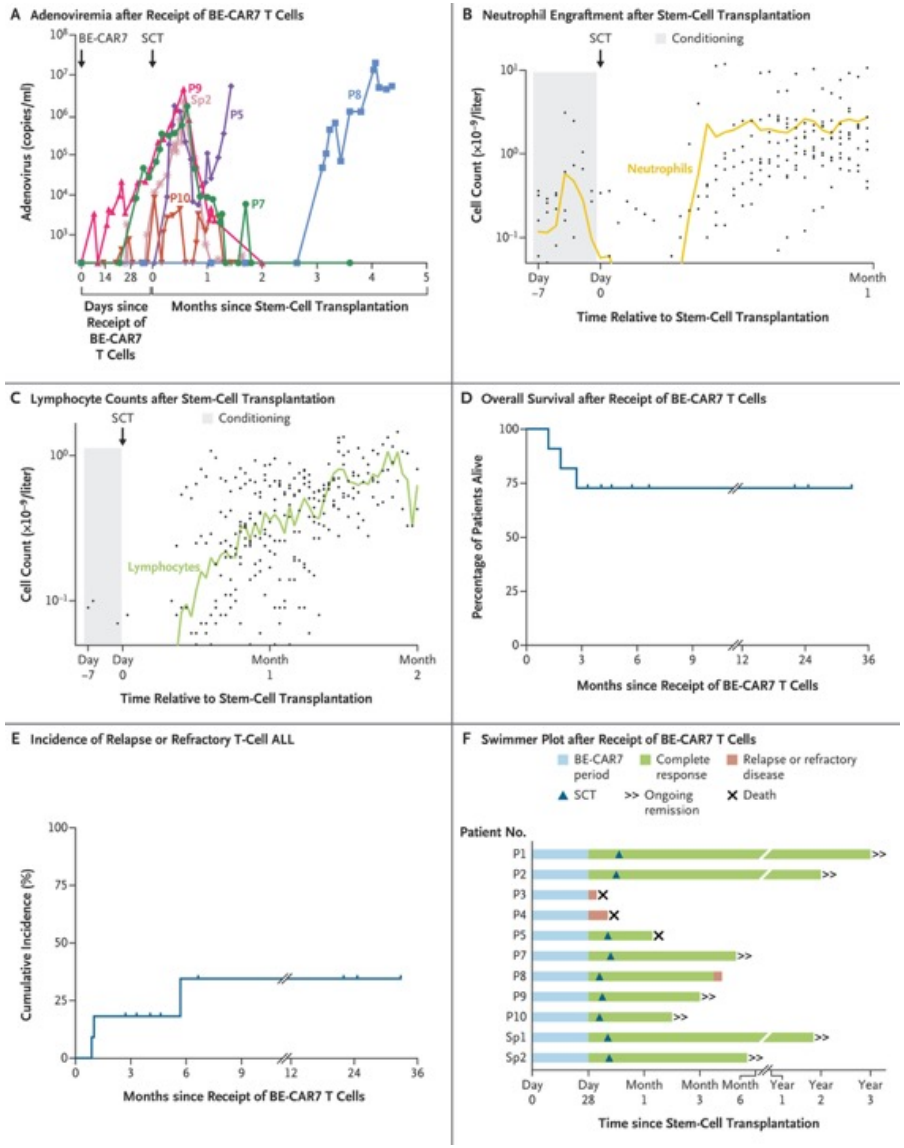
Cytokine release syndrome

Event	Patient No.										
	P1	P2	P3	P4	P5	P7	P8	P9	P10	Sp1	Sp2
	maximum grade of severity										
CRS	2	2	4	3	1	2	2	1	2	2	2
ICANS	1	—	1	—	—	—	1	—	—	—	—
Rash	1	3	1	2	2	2		2	2	1	2
Immune effector cell–associated hemotoxic effect	4	4	4	4	4	4	4	4	4	4	4
Viremia	3	2	1	1	2	2	—	2	2	3	1
Bacteremia	4	—	—	—	—	—	3	—	—	3	3
Aspergillosis	—	—	5	3†	—	—	—	—	—	—	—
Liver-function abnormality	—	1	3	1	—	2	3	—	2	—	—
Renal or electrolyte abnormality	1	1	3	1	—	2	3	—	3	—	—
Coagulopathy	1	—	3	1	—	—	4	—	1	2	—
Other adverse event of grade 3 or 4	—	—	4‡	—	3§	—	—	—	—	—	—



CAR T-Cell–Mediated Complications, Biomarkers, Vector Copy Numbers, and Remissions.

Patients P1 through P5 and P7 through P10 were children, 5 to 15 years of age. Patients Sp1 and Sp2 were adults (38 and 27 years of age, respectively) who received therapy under special license arrangements for compassionate use. Major toxic effects, including cytokine release syndrome (CRS), rash, and immune cell–associated neurotoxicity syndrome (ICANS), occurred in all the patients during the investigational period from the time of the BE-CAR7 infusion to day 28 (Panel A). CRS was of grade 1, 2, or 3 in all the patients, with one patient also having grade 4 CRS. All the patients except one had transient rash, which either resolved spontaneously or after the use of glucocorticoids. Serum levels of interleukin-6, a biomarker of CRS, became elevated within 7 to 14 days after the administration of BE-CAR7 T cells (Panel B). Neutropenia followed lymphodepletion (from day −7 onward) and, in most patients, continued beyond day 28 (Panel C). Lymphopenia after the receipt of chemotherapy and BE-CAR7 T cells was expected and continued beyond day 28 in all patients (Panel D). In Panels C and D, the graphed line represents the mean of individual samples (dots) obtained at the time points marked. Shading indicates the conditioning period between lymphodepletion and the administration of BE-CAR7 T cells. Quantification of the vector copy number by digital droplet polymerase-chain-reaction (PCR) assay confirmed that BE-CAR7 T cells were circulating even during lymphopenia until allogeneic stem-cell transplantation (SCT), after which no further signals were detected (Panel E). All the patients who received the investigational therapy had complete morphologic remission, and all but three had remission with MRD of less than 10^{-4} according to flow cytometry or PCR assay (Panel F) and were thus eligible for allogeneic stem-cell transplantation.



Viral Reactivations and Survival Analyses.

Viral reactivations were frequent during the investigational and transplantation-related lymphopenic periods. Adenovirus reactivations were detected in blood from approximately day 14 after the administration of BE-CAR7 T cells and were managed with antiviral therapy until post-transplantation reconstitution, with protracted complications in Patients P5, P8, and Sp2 (Panel A). The kinetics of neutrophil and lymphocyte recovery (Panels B and C, respectively) were as expected after allogeneic stem-cell transplantation, with no evidence of persistence or effect from the BE-CAR7 T cells. In Panels B and C, the graphed line represents the mean of individual samples (dots) obtained at the time points marked, and shading indicates the conditioning period before transplantation. Overall survival was assessed among all the patients who received the investigational therapy (Panel D), and the cumulative incidence of leukemia progression or relapse over time was also assessed (Panel E). In Panels D and E, tick marks indicate censored data. ALL denotes acute lymphoblastic leukemia. A swimmer plot (Panel F) summarizes data on the status of all the patients during BE-CAR7 therapy and after stem-cell transplantation (triangle), with the first patient (Patient P1) remaining disease-free at 36 months.

Discussion

We described previously how C→T base-editing was applied to generate BE-CAR7 T cells with triple knockouts for experimental therapy against T-cell ALL in three children who had been enrolled into a first-in-class clinical trial. Two of those patients, both of whom had had a relapse after previous allogeneic stem-cell transplantation, are in ongoing, long-term remission. The initial experience provided evidence of the potential medical applications of base editing. Here, we report data on the primary outcome of safety and on secondary efficacy outcomes in the pediatric study cohort with additional data from two adult patients who were treated according to the same protocol under compassionate access arrangements.

The study design and strategy aimed to maximize the likelihood of successful outcomes even in a phase 1 study, with the use of stringent inclusion criteria stipulating complete CD7 coverage across the entire blast population and with the exclusion of patients with preexisting anti-HLA antibodies directed against the product. Although two different donor banks had been established before the study was initiated, the study to date has drawn only on a single donor for all the patients who received a dose of the investigational therapy; this situation may have contributed to the consistency of responses encountered across the cohort.

In this phase 1 study, we found that universal BE-CAR7 T cells induced antileukemic responses in all the patients with relapsed or refractory CD7+ T-cell ALL who received the treatment, which enabled 9 patients to undergo allogeneic hematopoietic stem-cell transplantation in deep remission. Limitations included CD7 antigen loss and risks of viral-related complications.

Functional Dyspepsia

Summary

Functional dyspepsia is a common but serious medical syndrome that can induce weight loss and food aversion and may be associated with increased risks of hospitalization and death. It probably comprises several different and as yet incompletely characterized disorders. Patients with local mucosal microinflammation driven by an aberrant Th2 response may represent an important subgroup. There is overlap with other gastrointestinal syndromes, particularly irritable bowel syndrome and gastroesophageal reflux disease, and patients with overlap have more severe symptoms. There is no approved drug for functional dyspepsia. Treatment is empirical and directed at symptoms and consists of acid suppressants and low-dose tricyclic antidepressants (and other neuromodulators) along with appropriate nutritional and psychological support.

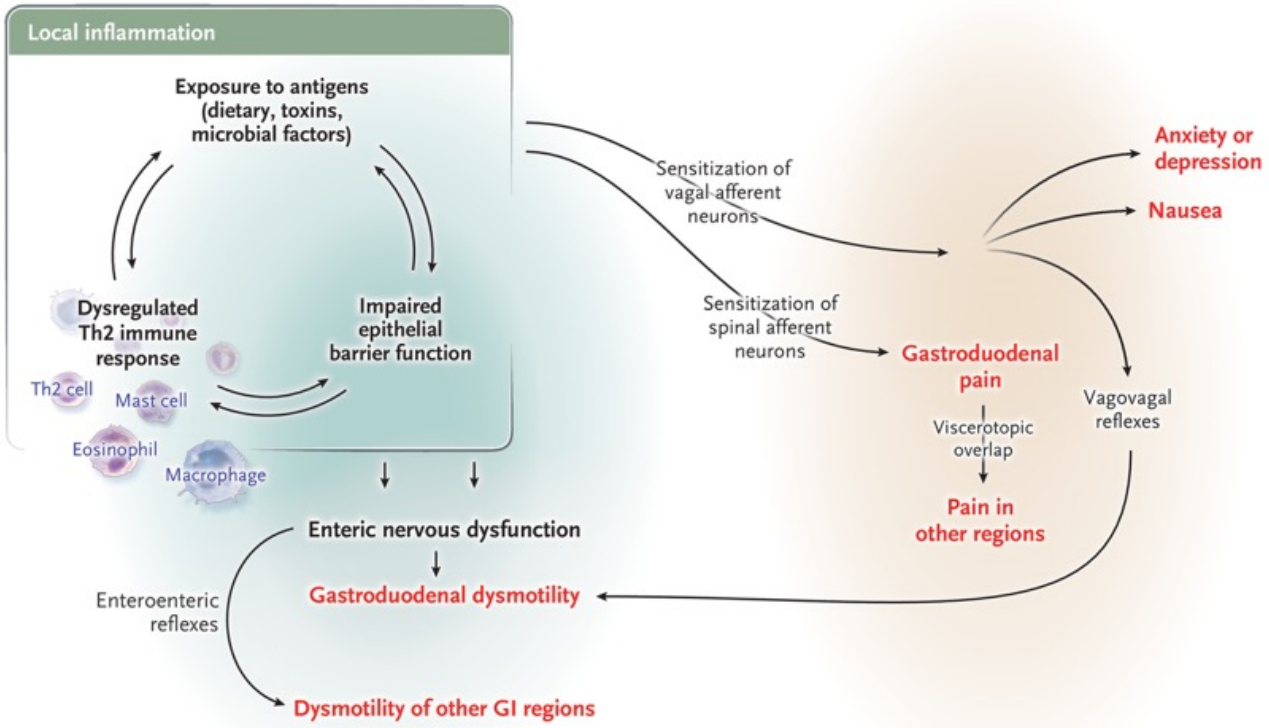
Auf Deutsch bedeutet Dyspepsie **Verdauungsstörung** oder **„Fehlverdauung“**, ein Sammelbegriff für Beschwerden im Oberbauch wie Schmerzen, Druckgefühl, Völlegefühl, Übelkeit oder frühe Sättigung, die oft ohne eine klare organische Ursache auftreten und dann als **funktionelle Dyspepsie** oder **Reizmagen** bezeichnet werden.

A 33-year-old woman presents with a 3-year history of epigastric burning pain, nausea, and early satiety after meals. She is increasingly anxious because endoscopy and imaging have not found any underlying cause, and she has not had a response to omeprazole or over-the-counter medications. How would you further evaluate and treat this patient?

KEY POINTS

Functional Dyspepsia

- Functional dyspepsia is a common but serious medical syndrome that can induce weight loss and food aversion and may be associated with increased risks of hospitalization and death.
- The syndrome probably comprises several different and as yet incompletely characterized disorders; local microinflammation driven by an aberrant response by type 2 helper T cells may represent an important subset of cases.
- Functional dyspepsia can overlap with other gastrointestinal syndromes, particularly irritable bowel syndrome and gastroesophageal reflux disorder, and persons with such overlap have more severe symptoms.
- There is no approved drug therapy; treatment is empirical and directed at symptoms, consisting of acid suppressants and low-dose tricyclic antidepressants (and other neuromodulators), along with appropriate nutritional and psychological support.



Proposed Pathophysiological Model of Functional Dyspepsia.

Local gastroduodenal inflammation triggered by luminal antigens leads to a dysregulated immune response by type 2 helper T (Th2) cells and activation of eosinophils, mast cells, and macrophages. The resulting impairment of the epithelial barrier function may further facilitate antigen penetration and perpetuate the microinflammation. These changes drive enteric nervous dysfunction, leading to dysmotility of the gastroduodenal region and other regions of the gut. The changes also result in the sensitization of vagal and spinal afferent pathways, leading to pain felt in the epigastrium (as well as other regions of the gut), nausea, and changes in affect. This conceptual model is probably applicable only to a subgroup of patients with functional dyspepsia rather than all persons who meet symptomatic criteria for this disorder. GI denotes gastrointestinal.

Differential Diagnosis of Symptoms Associated with Functional Dyspepsia.

Symptoms and Other Potential Causes	Relevant Symptoms	Tests to Rule Out Other Causes
Early satiety (fullness)		
Gastric cancer	Unexplained weight loss; chronic untreated *Heliobacter pylori* infection; age >60 yr; risk factors related to geographic location, ethnic group, and others	Upper endoscopy
Gastroparesis	Recurrent or frequent vomiting or severe nausea	Gastric emptying test
Epigastric pain		
Peptic ulcer	*H. pylori* infection, use of nonsteroidal antiinflammatory medication	Upper endoscopy
Gallstone disease	Crescendo–decrescendo episodic pain lasting ≥30 min, often severe	Ultrasound of the gallbladder and bile ducts
Anterior cutaneous nerve entrapment syndrome or chronic abdominal-wall pain	Point tenderness	Carnett's sign (pressure on the point of tenderness before and after the patient tenses the abdominal wall reveals increased tenderness on tensing)
Chronic pancreatitis	Risk factors (e.g., alcohol use, genetic predisposition), steatorrhea	Pancreatic imaging
Epigastric burning		
Gastroesophageal reflux	Heartburn, regurgitation	Upper endoscopy, pH testing
Bloating		
Celiac disease	Family history, diarrhea, unexplained iron deficiency	Celiac serologic testing
Small intestinal bacterial overgrowth	Long-term use of proton-pump inhibitor, dysmotility of the small intestines	Breath test, duodenal aspirate for bacteria, empirical treatment with antibiotics

Clinical Features Prompting Further Evaluation.

- Evidence of gastrointestinal bleeding (e.g., hematemesis, melena, and bright-red blood from the rectum)
- New-onset symptoms in patients 60 years of age or older (in the United States)
- Iron-deficiency anemia
- Unexplained weight loss (>10% of body weight)
- Progressive dysphagia or odynophagia
- Persistent vomiting
- Long-term use of aspirin or nonsteroidal antiinflammatory drugs
- Strong family history of gastrointestinal cancer (especially esophagogastric)
- History of upper gastrointestinal cancer
- Lymphadenopathy or abdominal mass

Treatments to Consider in Functional Dyspepsia.

Drug Class	Pathophysiological Target	Examples	Relative Strength of Evidence
Acid suppressants	Acid-induced reflexes triggered by enteric and sensory neurons	Proton-pump inhibitor, H2RA	Symptom abatement with standard dose of PPI: relative risk of no improvement, 0.86 (95% CI, 0.78 to 0.95)[27] Symptom abatement with H2RA: relative risk of no improvement, 0.81 (95% CI, 0.73 to 0.90)[28]
Neuromodulators	Increased or aberrant signaling by afferent neurons to the CNS	Tricyclic antidepressants, duloxetine, mirtazapine, pregabalin, gabapentin	Symptom abatement with low-dose tricyclic antidepressant: relative risk of no improvement, 0.75 (95% CI, 0.62 to 0.90)[27] No placebo-controlled trials of duloxetine; not as efficacious as nortriptyline for functional dyspepsia symptoms but better with regard to anxiety, depression, and quality of life[30] Pregabalin: relative risk of no improvement with pregabalin, 0.53 (95% CI, 0.29 to 0.96)[31]
Motility agents†	Delayed gastric emptying, decreased gastric accommodation	Metoclopramide, domperidone, prucalopride, buspirone	Controlled trials of metoclopramide, domperidone, and prucalopride are lacking; buspirone (three small trials of 4-wk duration) led to nonsignificant improvement in functional dyspepsia and gastroparesis symptoms vs. placebo (standardized mean difference, −0.14; 95% CI, −0.44 to 0.17; P=0.39); with regard to individual symptoms, buspirone reduced only the severity of bloating more than placebo[32]
Th2 response modulators	Eosinophil and mast-cell activation	Montelukast, mast-cell antagonists (H1RA, H2RA, ketotifen)	Evidence limited to children only[32]; no evidence for mast-cell antagonists
Agents affecting the microbiota	Dysbiosis	*Bacillus coagulans* and *B. subtilis* combination, rifaximin	Limited evidence: single trials, small numbers, and short-term results
Over-the-counter remedies	Miscellaneous	Peppermint-oil preparations	Limited evidence: few trials, small numbers, and short-term results

Treatments to Consider in Functional Dyspepsia.

Group	*H. pylori* Testing	Prompt EGD	PPIs	Tricyclic Antidepressant Agents	Prokinetic Agents	Psychological Therapy	Complementary or Alternative Medicine
ACG and CAG[42]	Test all patients and treat	Patients >60 yr of age or who have symptoms that arouse concern	First-line therapy	Second-line therapy	Third-line therapy	In the case of failure of medical treatment	Not recommended
UEG and ESNM[49]	Test all patients and treat	Mandatory for diagnosis but can be deferred in primary care in absence of alarm features	Endorsed	No consensus	No consensus	No consensus	No consensus
BSG[27]	Test all patients and treat	Reserved for patients with risk factors	First-line therapy	Second-line therapy	Recommended drugs not available in the United States	In the case of failure of medical treatment or for other considerations (e.g., weight loss)	No statement

Treatment Approach in Patients with Refractory Symptoms of Functional Dyspepsia.

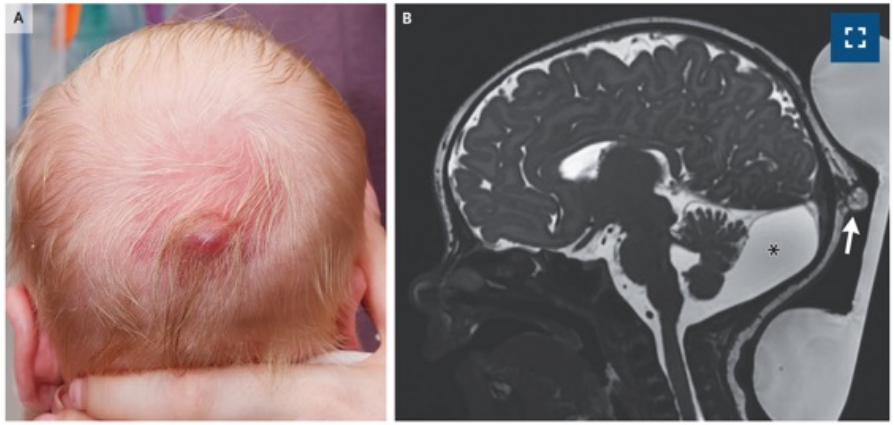
Treatable conditions to consider
Small intestinal bacterial overgrowth
Suspect with IBS-like symptoms and prominent gas, bloating particularly with long-standing use of proton-pump inhibitors
Consider appropriate testing, treatment for small intestinal bacterial overgrowth, or both
Food-driven immune responses
Consider if patient has strong history of atopy, prominent eosinophils on mucosal biopsy, or evidence of mast-cell activation
Autoimmune or autoinflammatory disease
Consider if patient has history of known autoimmune syndromes (hypothyroidism, sicca symptoms, etc.) particularly with autonomic symptoms or joint hypermobility
Treatment of symptoms
Pain
Low-dose naltrexone
Milnacipran or levomilnacipran
Zonisamide or lacosamide
Valproate
Lamotrigine
Oxcarbazepine or carbamazepine
Quetiapine
Food-driven immune response
Elimination diet
H1RA and H2RA combinations
Ketotifen
Montelukast
Nausea
Antihistamines — promethazine, diphenhydramine
Anticholinergics — meclizine, scopolamine
NK1 receptor antagonists — aprepitant
Cannabinoids — dronabinol
Zonisamide or lacosamide
Antipsychotics — prochlorperazine, haloperidol, quetiapine, olanzapine
Autoimmune or inflammatory disease — work with rheumatologist to consider appropriate immunomodulator therapy
Supportive treatments
Cognitive behavioral therapy, hypnotherapy, and others
Control of anxiety and depression, if present
Transcutaneous vagal-nerve stimulation

Conclusions and Recommendations

We would prescribe low-dose amitriptyline, nortriptyline, or imipramine (e.g., at a dose of 10 mg taken at night and adjusted to a range of 25 to 50 mg), with ondansetron (at a dose of 4 mg as needed) prescribed for nausea. If the patient does not have a response and pain remains prominent, we would recommend a trial of pregabalin (up to 50 mg taken three times daily for 4 to 6 weeks); an alternative would be duloxetine (at a dose of 30 to 60 mg daily). If nausea is bothersome, especially if associated with weight loss, we would prescribe mirtazapine, often beginning at very low doses (e.g., 3.75 to 7.5 mg taken at night) and increasing in weekly increments to a range of 30 to 45 mg a day. Patients taking this drug must be cautioned about the potential for excessive weight gain.

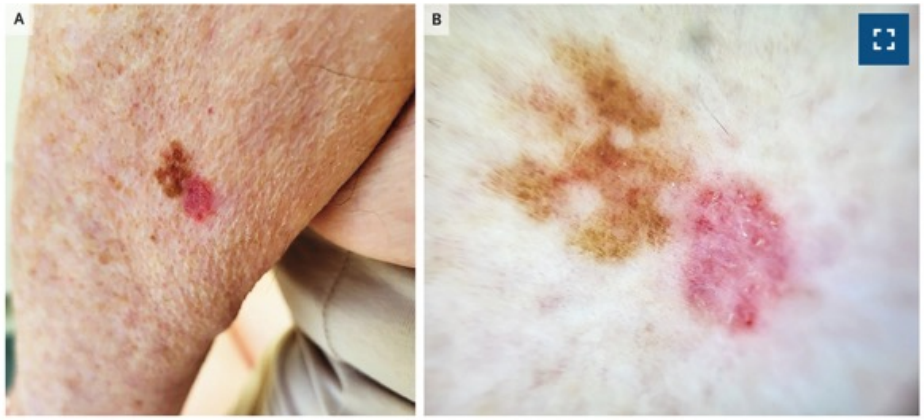
In patients who have refractory symptoms, we recommend further diagnostic testing and therapeutic interventions that assume a neuropathic origin of the symptoms but are entirely empirical, may have clinically significant adverse effects, and are best delivered in the setting of an integrated and experienced multidisciplinary care clinic. In a survey, nearly half of patients with functional dyspepsia would accept an effective therapy even when the trade-off was a 13% risk of sudden death. Nevertheless, patients must be informed partners in these trial-and-error approaches, and clinical trials are needed to guide best practice and to develop new and more effective treatments.

Atretic Cephalocele



A 5-week-old boy was brought to the hospital with a painful lump on his scalp that had been present since birth. The otherwise healthy baby had been born at term. His mother had taken folate supplementation during pregnancy. On physical examination, a tense, nonpulsatile, 1.3-cm round mass was noted on the occiput (Panel A). The lesion transmitted light on transillumination. It was surrounded by a ring of dark, coarse hair, consistent with the "hair collar" sign seen with neural-tube defects. The rest of the examination was normal. Owing to concern about a neural-tube defect, a biopsy was not performed. Ultrasonography of the lesion showed a subcutaneous structure of mixed echogenicity. Subsequent magnetic resonance imaging of the head revealed an extracranial cystic lesion with high signal intensity on T2-weighted sequences (Panel B, arrow) and low signal intensity on T1-weighted sequences. Blake's pouch cyst (a cystic malformation on the posterior fossa) was also incidentally identified (Panel B, asterisk). A diagnosis of atretic cephalocele was made. Cephaloceles are herniations of cranial contents through a defect in the skull. They are described as atretic when they do not contain neural tissue. Six weeks after presentation, neurosurgical resection of the lesion was performed. At 1-year follow-up, the child was developing normally.

Collision Lesion



An 80-year-old woman presented to the plastic surgery clinic with a 6-month history of a skin lesion on the posterior aspect of her left upper arm. Physical examination revealed a brown lesion with irregular borders adjacent to a second, pink lesion with well-defined borders and superficial scaling (Panel A). On dermoscopy, the first lesion had a homogeneous brown color with eccentric hyperpigmented asymmetric globules representative of unevenly distributed nests of melanocytes along the dermoepidermal junction. The pink lesion had telangiectatic vessels and multiple small erosions (Panel B). On histopathological examination of an excisional biopsy specimen, the first lesion was identified as a melanoma in situ and the second lesion as a superficial basal-cell carcinoma. A diagnosis of a collision lesion of melanoma in situ and basal-cell carcinoma was made. A collision lesion is formed when two or more unique tumors with distinct boundaries occur in the same anatomical location. Collision lesions pose a diagnostic challenge because the clinical appearance of one lesion may mask or distract from the other lesion, resulting in misdiagnosis. A wide local excision was performed with clear margins. At follow-up 1 year after the procedure, no evidence of recurrence was found.

Case 1-2026: A 50-Year-Old Woman with Fever and Abdominal Pain

A 50-year-old woman was admitted to this hospital because of fever and abdominal pain after she had returned from a trip to rural Brazil.

The patient was born and raised in Brazil and immigrated to Boston in early adulthood. In the weeks leading up to the current presentation, she traveled to a remote area in northeastern Brazil. Four days before the current presentation, after she had returned to Massachusetts, fatigue developed. The next day, she had several episodes of watery diarrhea that were accompanied by nausea and mild diffuse abdominal discomfort. Her symptoms lasted for 3 days, and her weight decreased by 3 kg. Dyspnea and lethargy developed, and she presented to the emergency department of this hospital.

In the emergency department, the patient answered questions only intermittently owing to malaise; additional history was obtained from her husband. In the days before the current presentation, the patient had noted chills, malaise, headache, and pain in the knees and legs. She had not noted rash, jaundice, pruritus, chest pain, cough, eye or ear pain or dysfunction, hematochezia, melena, dysuria, or hematuria.

The patient had a history of schistosomiasis that had occurred during childhood and had been complicated by noncirrhotic portal hypertension, esophageal varices, splenomegaly, chronic thrombocytopenia, and chronic leukopenia. Other medical history included gastroesophageal reflux disease, iron deficiency anemia, hypothyroidism, and allergic rhinitis.

Approximately 10 years before the current presentation, ultrasonography of the liver reportedly revealed coarse echogenicity that was consistent with fatty infiltration. Evaluation for a cause of liver disease was unrevealing, and a liver biopsy showed features of nodular regenerative hyperplasia but no clinically significant fibrosis. Six years before the current presentation, liver elastography showed a liver stiffness of 18.4 kPa (reference range, 2 to 7), a finding consistent with F4 fibrosis (liver stiffness, >14 kPa). The levels of thyrotropin and alpha-fetoprotein were normal; other laboratory test results obtained at that time are shown in Table 1. Four years before the current presentation, liver ultrasonography reportedly revealed morphologic features in the liver that were consistent with cirrhosis, as well as gallbladder wall thickening and splenomegaly, with the spleen measuring 16 cm in the greatest dimension (reference value, ≤12). Esophagogastroduodenoscopy procedures performed 30 months and 2 months before the current presentation reportedly showed grade II esophageal varices (2 to 3 mm in diameter and mildly tortuous or straight).

Medications included levothyroxine, cetirizine, ergocalciferol, resveratrol, and a multivitamin. Propranolol had caused fatigue, and there was a history of adverse reactions to medications containing sulfa. The patient had received vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hepatitis A and B viruses, and pneumococcus.

Variable	Reference Range, Other Hospital	6 Yr before Current Presentation, Other Hospital	Reference Range, Adults, This Hospital†	On Current Presentation, This Hospital	On Arrival in ICU, This Hospital
Blood					
Hemoglobin (g/dl)	11.5–16.4	13.0	12.0–16.0	12.3	12.1
Hematocrit (%)	36.0–48.0	39.2	36.0–46.0	37.2	37.8
White-cell count (per μl)	4000–10,900	2160	4500–11,000	2150	22,850
Differential count (per μl)					
Neutrophils	1920–7600	1430	1800–7700	1750	19,130
Lymphocytes	720–4100	520	1000–4800	230	550
Monocytes	160–1100	140	200–1200	20	750
Eosinophils	0–500	60	0–900	0	180
Bands (%)	—	—	0–10	13.4	14.6
Peripheral-blood smear	—	—	No abnormal forms present	Plasma cells, metamyelocytes, and polychromatic red cells present	Metamyelocytes, vacuolated white cells, burr cells, and polychromatic red cells present
Platelet count (per μl)	150,000–450,000	56,000	150,000–400,000	37,000	29,000
Sodium (mmol/liter)	136–145	141	135–145	138	137
Potassium (mmol/liter)	3.4–5.0	3.8	3.4–5.0	4.0	3.8
Chloride (mmol/liter)	98–107	105	98–108	104	102
Carbon dioxide (mmol/liter)	22–31	26	23–32	20	10
Urea nitrogen (mg/dl)	6–23	16	8–25	21	24
Creatinine (mg/dl)	0.50–1.20	0.49	0.60–1.50	0.97	1.33
Glucose (mg/dl)	70–115	125	70–110	91	21
Calcium (mg/dl)	8.6–10.7	8.9	8.5–10.5	8.4	7.7
Magnesium (mg/dl)	—	—	1.7–2.4	1.6	1.8
Lactate (mmol/liter)	—	—	0.5–2.0	4.7	13.2
Total protein (g/dl)	6.0–8.0	7.1	6.0–8.3	6.1	5.1
Albumin (g/dl)	3.5–5.2	3.8	3.3–5.0	3.6	3.1
Alanine aminotransferase (U/liter)	10–50	125	7–33	76	102
Aspartate aminotransferase (U/liter)	10–50	101	9–32	64	131
Alkaline phosphatase (U/liter)	40–130	229	45–115	242	396
Total bilirubin (mg/dl)	0.0–1.0	0.9	0.0–1.0	2.2	5.7
Direct bilirubin (mg/dl)	—	—	0.0–0.4	1.2	4.4
Fibrinogen (mg/dl)	—	—	200–400	159	79
Prothrombin time (sec)	11.8–15.2	14.8	10.0–13.0	20.9	27.8
International normalized ratio	0.9–1.1	1.2	0.9–1.1	1.9	2.5
Partial-thromboplastin time (sec)	—	—	24.0–37.5	54.1	79.7
D-dimer (ng/ml)	—	—	<500	—	>7650
Haptoglobin (mg/dl)	—	—	30–200	—	20
Lactate dehydrogenase (U/liter)	—	—	110–210	—	277
Venous pH	—	—	7.30–7.40	—	7.15
Urine					
Color	—	—	Yellow	—	Orange
Clarity	—	—	Clear	—	Turbid
pH	—	—	5.0–9.0	—	6.0
Specific gravity	—	—	1.001–1.035	—	1.020
Glucose	—	—	Negative	—	Negative
Ketones	—	—	Negative	—	Trace
Leukocyte esterase	—	—	Negative	—	1+
Nitrite	—	—	Negative	—	Negative
Blood	—	—	Negative	—	3+
Protein	—	—	Negative	—	2+
Erythrocytes (per high-power field)	—	—	0–2	—	20–50
Leukocytes (per high-power field)	—	—	<10	—	>100
Bacteria	—	—	None	—	1+

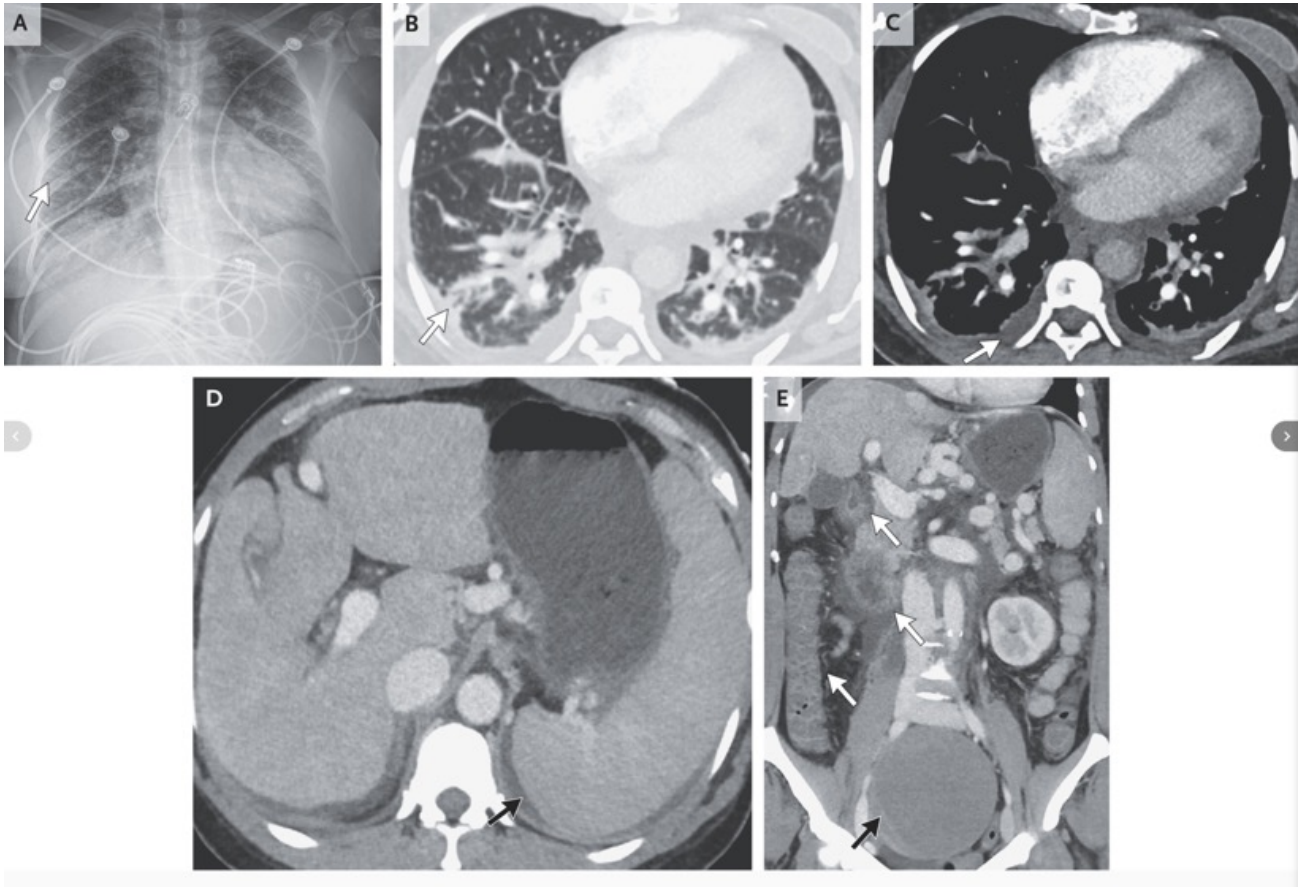
The patient lived in a suburb of Boston with her family, and she worked in the service industry, where she was often exposed to dust. She did not use alcohol, tobacco, or other substances. She had no history of travel other than the recent trip to Brazil. During the trip, she had been bitten by multiple mosquitoes while spending time at a beach in a region where cases of dengue fever and chikungunya virus infection were known to have occurred. She had not taken malaria prophylaxis. She had no known sick contacts. Information on other environmental, animal, and food exposures was not available. One of her brothers had died in his fourth decade of life from chronic liver disease attributed to alcohol use. Two other brothers had a history of hematemesis, one of whom had had schistosomiasis and had undergone splenectomy.

On examination, the temporal temperature was 38.4°C, the heart rate 105 beats per minute, the blood pressure 76/44 mm Hg, the respiratory rate 32 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. She appeared lethargic and unwell, with diaphoretic pale skin and labored rapid breathing. Petechiae of the posterior palate were present. The abdomen was slightly distended and diffusely tender; the tenderness was most notable in the right upper quadrant and suprapubic area. Murphy's sign was absent, and the spleen tip was palpable. No costovertebral tenderness was noted. Trace edema of the legs was present, but there was no rash. The remainder of the examination was normal.

Blood cultures were obtained.

During the patient's first hour in the emergency department, 1 liter of lactated Ringer's solution and vancomycin, ceftriaxone, and azithromycin were administered intravenously, and the blood pressure rose to 90/54 mm Hg. Electrocardiography showed sinus tachycardia and borderline-low QRS voltage in the precordial leads. A rapid malaria antigen test was negative.

Piperacillin–tazobactam was administered intravenously. During the next 2 hours, despite the administration of an additional 2 liters of intravenous crystalloid fluid, the blood pressure decreased to 73/41 mm Hg; treatment with a continuous infusion of norepinephrine was started at a rate of 6 µg per minute.



Radiograph and CT Images.

An upright chest radiograph (Panel A) and axial images from contrast-enhanced CT of the chest (Panels B and C) show diffuse interstitial and airspace opacities in both lungs (Panels A and B, arrows) and small pleural effusions (Panel C, arrow). An axial image from non–contrast-enhanced CT of the abdomen and pelvis (Panel D) and a coronal reconstruction image (Panel E) show morphologic features in the liver that are consistent with cirrhosis; large portosystemic collaterals, including gastroesophageal varices; splenomegaly (Panel D, arrow); a 12.2-cm exophytic uterine mass (Panel E, black arrow); distal gastric, duodenal, and diffuse colorectal wall thickening (Panel E, white arrows); and small-volume ascites and diffuse mesenteric and retroperitoneal edema.

Differential Diagnosis

This 50-year-old woman with a history of portal hypertension and liver disease had fatigue, diarrhea, leg pain, headache, and chills after returning from a trip to remote northeastern Brazil. Refractory shock ensued, with disseminated intravascular coagulation (DIC), capillary leak, and marked leukocytosis with a left shift. In working toward the most likely diagnosis in this patient's case, I will focus on the distinctive feature of rapid deterioration with refractory septic shock and DIC, while considering her preexisting diseases and recent travel.

Host Factors

The patient had acquired schistosomiasis as a child in Brazil. The infection had been complicated by portal hypertension and hypersplenism, which can cause chronic leukopenia and thrombocytopenia. Although schistosomiasis can cause presinusoidal liver disease, the patient later had imaging findings that were consistent with fatty liver disease, fibrosis, and possible cirrhosis; these features were not confirmed on biopsy. Cirrhosis leads to several important functional immunologic defects, including hypocomplementemia, increased gut translocation of bacteria, and portosystemic shunting.

Bacterial Infections

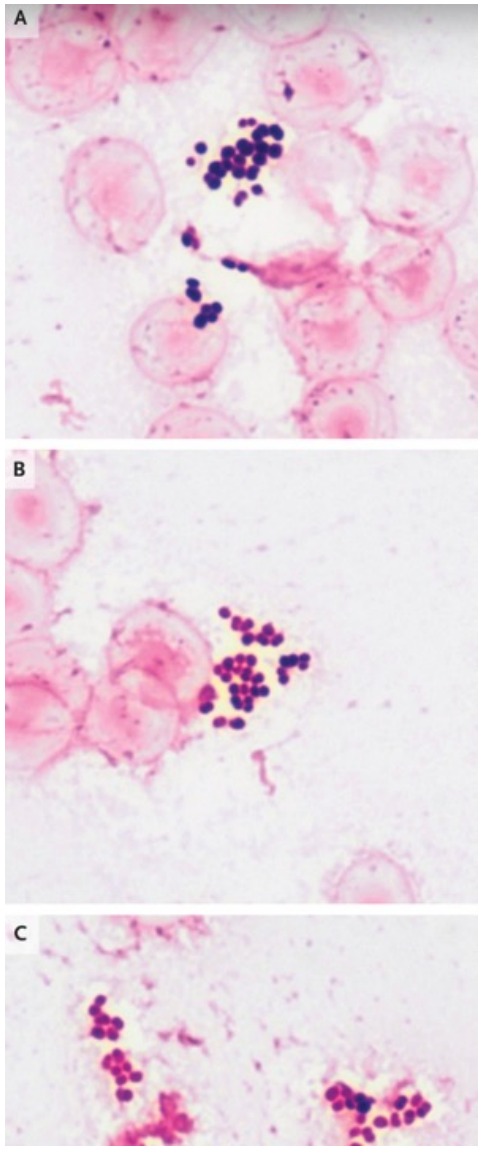
Enteric fever due to *Salmonella enterica* serovar Typhi infection is the underlying cause in many cases of severe illness that occur after travel to Brazil, but the rapid progression of disease that was seen in this patient would be unusual with this diagnosis. In addition, the patient had no evidence of relative bradycardia, no skin findings that were consistent with rose spots, and no imaging findings such as intestinal perforation that would be suggestive of the disease (presumed gm - sepsis).

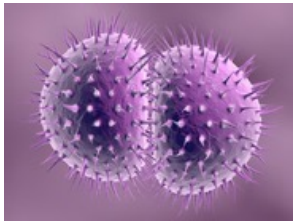
Diagnostic Testing

The diagnostic test in this case was a blood culture. Bacterial growth was detected in the aerobic bottle after 21 hours of incubation. Gram's staining was performed on the positive blood-culture broth, and the bacteria initially appeared to be gram-positive cocci in clusters. The broth was subcultured on agar plates for organism identification and susceptibility testing. Examination of the blood agar plate after 10 hours of incubation revealed small, gray, glistening colonies. Organism identification performed with matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry showed findings consistent with *N. meningitidis*.

Autopsy

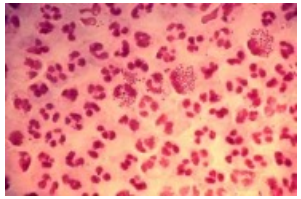
An autopsy was performed.





Blood-Culture Specimens.

On initial Gram's staining of broth from the positive blood-culture bottle (Panel A), the bacteria appear to be gram-positive cocci in clusters. On repeat Gram's staining of broth from the same blood-culture bottle with progressively increased decolorization time (Panels B and C), removal of the crystal violet–iodine complex is shown, and the bacteria appear to be gram-negative diplococci. Images are courtesy of Emily Williams.



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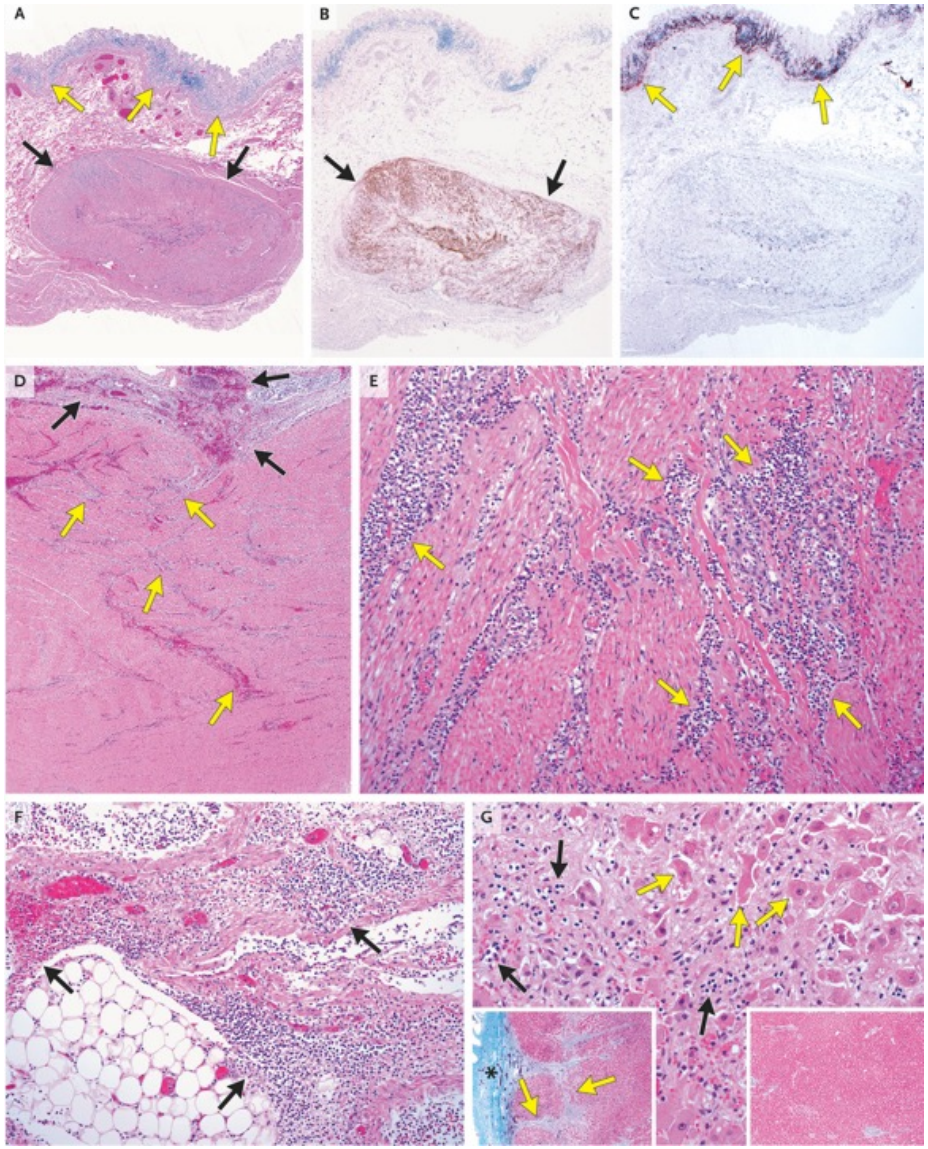
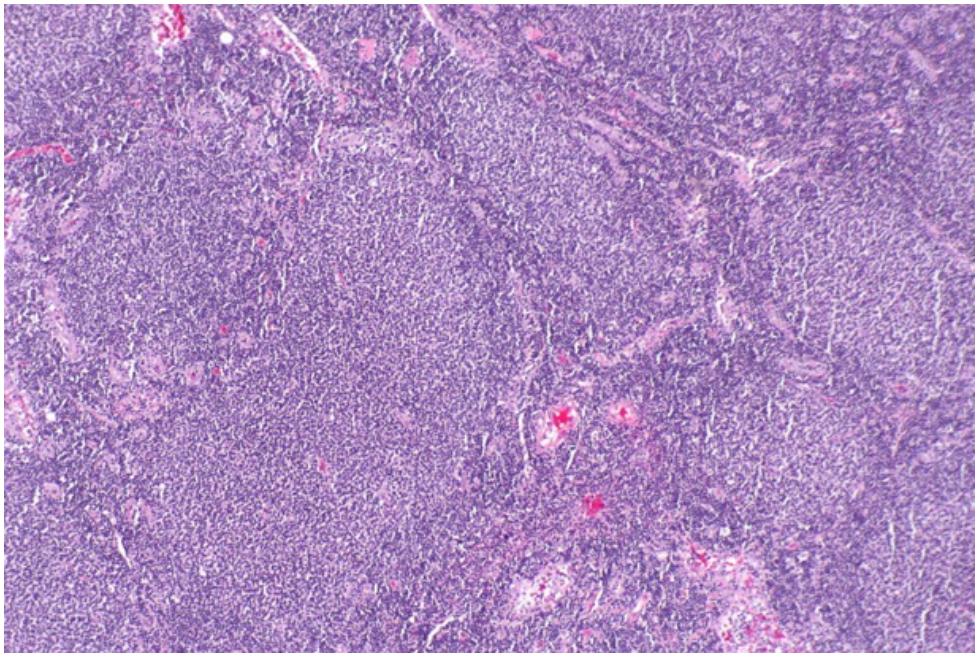


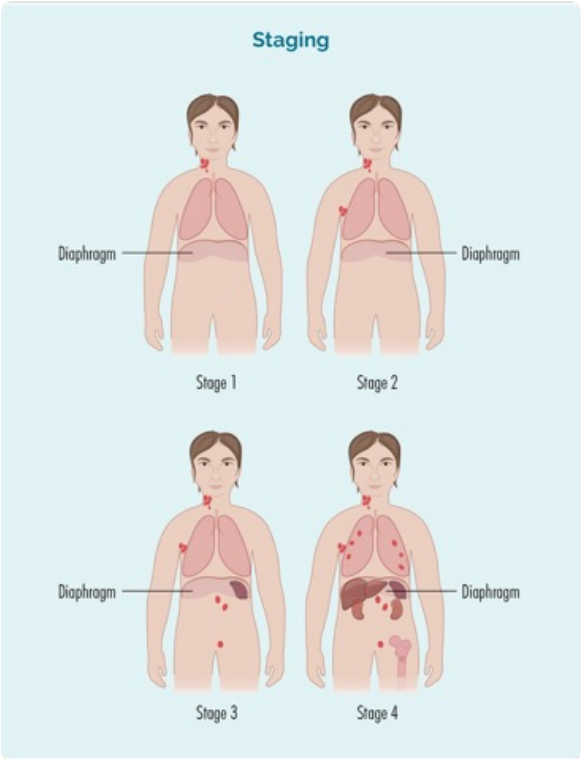
Autopsy Specimens.

Hematoxylin and eosin staining of a section of the body of the stomach (Panel A) shows a mass in the submucosa (black arrows) and chronic inflammation in the mucosa (yellow arrows). Immunohistochemical staining for CD117 (Panel B) is positive in tumor cells (in brown; arrows), a finding that indicates a gastrointestinal stromal tumor. Immunohistochemical staining for CD3 (Panel C) shows numerous T lymphocytes in the mucosa (in brown; arrows). Hematoxylin and eosin staining of a section of the pylorus of the stomach (Panels D and E) shows hemorrhage and inflammation in the submucosa (black arrows) and muscularis propria (yellow arrows). The mucosa was intact with focal acute inflammation (not shown). Hematoxylin and eosin staining of a section of perigastric adipose tissue (Panel F) shows extension of the acute inflammation (arrows). Hematoxylin and eosin staining of a section of the subcapsular portion of the liver (Panel G) shows hepatocyte loss (in the center) with remaining hepatocytes (yellow arrows) and chronic inflammation (black arrows). Trichrome staining of the liver (Panel G, insets) shows capsular fibrosis (left inset, asterisk) and focal bridging fibrosis (left inset, arrows) in the subcapsular regions but no substantial fibrosis in the rest of the liver (right inset).

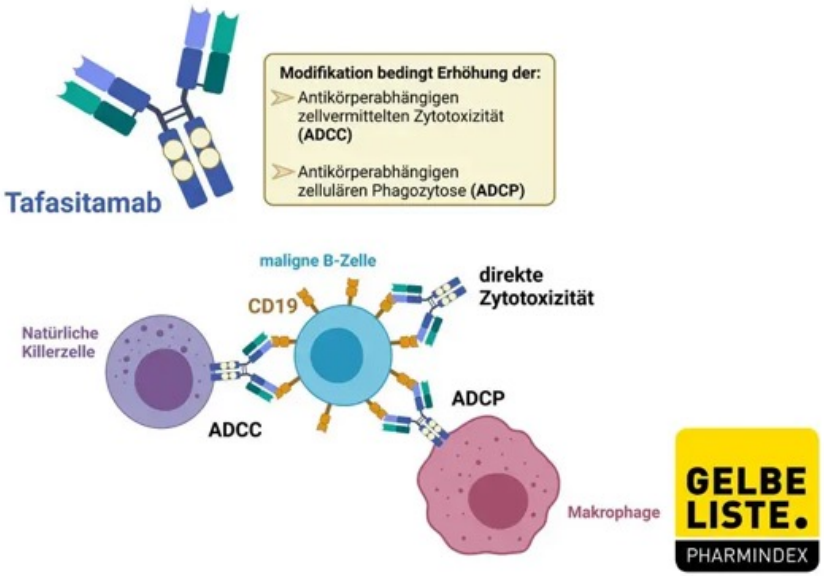
Follicular lymphoma (FL) is a slow-growing (indolent) blood cancer and the second most common type of non-Hodgkin lymphoma, affecting B-lymphocytes (white blood cells) that form abnormal clusters, or "follicles," in lymph nodes and other tissues. While not typically curable, it's often manageable, with symptoms like painless swollen lymph nodes, fatigue, and night sweats. Diagnosis involves biopsies and imaging, while treatments range from active surveillance to chemotherapy, immunotherapy, and targeted therapies, with recurrence being common but treatable.



The most common type of non-Hodgkin lymphoma (NHL) is **Diffuse Large B-Cell Lymphoma (DLBCL)**



Tafasitamab ist ein humanisierter monoklonaler Antikörper, der gezielt das Protein CD19 auf B-Zellen angreift und zur Behandlung von bestimmten Formen des Blutkrebses, insbesondere rezidiviertem oder refraktärem diffusem großzelligem B-Zell-Lymphom (DLBCL), eingesetzt wird, meist in Kombination mit dem Medikament Lenalidomid. Er wirkt, indem er die Abwehrzellen des Körpers aktiviert, um die Krebszellen zu zerstören, und ist eine wichtige Chemotherapie-freie Option für Patienten, die nicht für eine [[autologe Stammzelltransplantation]] in Frage kommen.



Lenaldomid zielt auf bestimmte Proteine (z.B. Ikaros und Aiolos, kodiert durch IKZF1 und IKZF3), die für das Überleben von B-Zellen wichtig sind, was den programmierten Zelltod (Apoptose) auslöst.

IKZF1 (Ikaros Family Zinc Finger 1) ist ein Gen, das den Transkriptionsfaktor Ikaros kodiert, der eine entscheidende Rolle bei der Entwicklung des lymphatischen Systems, der Blutbildung (Hämatopoese) und der Immunfunktion spielt

Tafasitamab, lenalidomide, and rituximab in relapsed or refractory follicular lymphoma (inMIND): a global, phase 3, randomised controlled trial

Summary

Background Follicular lymphoma is characterised by episodes of remission and relapse, with patients requiring multiple lines of therapy. Lenalidomide plus rituximab is a commonly used immunotherapy combination in patients with relapsed or refractory follicular lymphoma. We aimed to assess the efficacy and safety of adding tafasitamab, a CD19-targeted Fc-enhanced monoclonal antibody, to lenalidomide and rituximab in this setting.

Methods This phase 3, double-blind, randomised, placebo-controlled trial (inMIND) was done in 210 centres (including community-based haematology clinics, major hospitals, and academic institutions) in North America, Europe, and the Asia–Pacific region. Adults with relapsed or refractory follicular lymphoma, who had received at least one previous line of systemic therapy, were eligible for enrolment and randomly assigned (1:1) to receive treatment with up to 12 cycles (28-day cycle length) of tafasitamab (12 mg/kg by intravenous infusion on days 1, 8, 15, and 22 of cycles 1–3 and days 1 and 15 of cycles 4–12) or placebo, both with lenalidomide (20 mg/day orally on days 1–21 of cycles 1–12) and rituximab (375 mg/m^2 by intravenous infusion on days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2–5). Treatment assignment was achieved via an interactive voice or web response system; patients, investigators, and the funder were masked until the primary analysis. Study endpoints were investigator assessed unless otherwise specified. The primary endpoint was progression-free survival in the intention-to-treat population of all randomised patients; safety was assessed in all randomised patients who received at least one dose of study drug. The trial is registered with ClinicalTrials.gov (NCT04680052) and EUDRA-CT (2020–004407–13) and is active but no longer enrolling.

Findings Between April 16, 2021, and Aug 10, 2023, a total of 817 patients were assessed for eligibility; 548 patients with relapsed or refractory follicular lymphoma were enrolled and randomly assigned to treatment with either tafasitamab (n=273) or placebo (n=275). 299 (55%) of all randomised patients were male and 249 (45%) were female. The addition of tafasitamab to lenalidomide and rituximab resulted in significantly lower risk of progression, relapse, or death versus placebo (median progression-free survival by investigator 22·4 months [95% CI 19·2 to not evaluable] in the tafasitamab group *vs* 13·9 months [11·5–16·4] in the placebo group; hazard ratio 0·43 [95% CI 0·32–0·58]; p<0·0001) in the planned primary analysis. Improvement in progression-free survival was confirmed by independent review committee. Adverse events were reported in 272 (99%) of 274 patients in the tafasitamab group and 270 (99%) of 272 patients in the placebo group. Most common adverse events occurring in either the tafasitamab group or placebo group were neutropenia (133 [49%] *vs* 123 [45%]) and diarrhoea (103 [38%] *vs* 77 [28%]). There were no deaths due to treatment-related adverse events in the tafasitamab group; two (1%) patients had fatal adverse events related to treatment in the placebo group.

Interpretation The addition of tafasitamab to lenalidomide and rituximab resulted in a statistically significant and clinically meaningful improvement in progression-free survival, with an acceptable safety profile in patients with relapsed or refractory follicular lymphoma. This combination represents a potential new standard-of-care treatment.

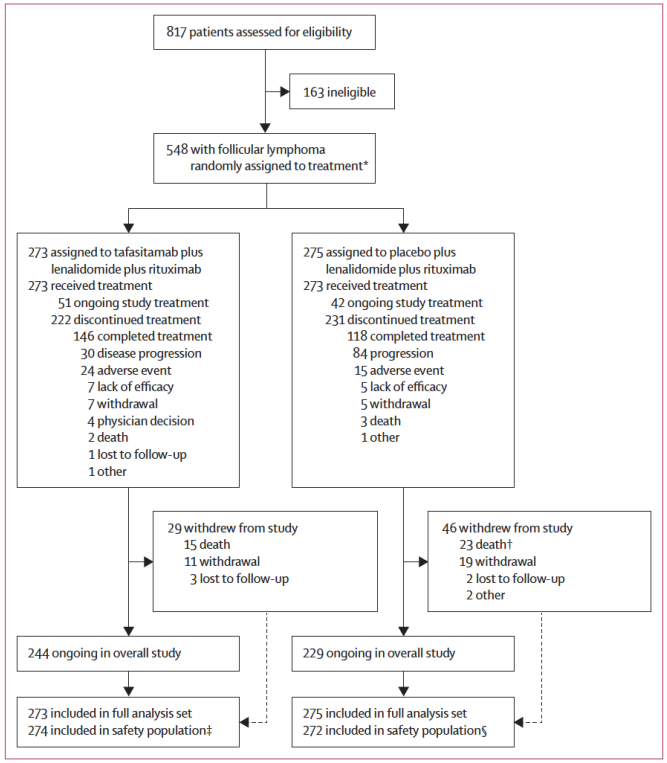


Figure 1: **Patient disposition**
Data are presented for the intention-to-treat population (full analysis set) and safety populations as of the data cutoff date of Feb 23, 2024. *106 patients had marginal zone lymphoma (not described in this report). †Death for one patient was reported but not recorded in the end-of-study form. ‡One patient randomly assigned to the placebo plus lenalidomide and rituximab group is included in the tafasitamab plus lenalidomide and rituximab safety population because the patient erroneously received tafasitamab. §Three patients randomly assigned to the placebo plus lenalidomide and rituximab group are not included in the safety population because they erroneously received tafasitamab (n=1) or did not receive any study treatment due to confirmation of rituximab hypersensitivity (n=1), and withdrawal by patient (n=1).

	Tafasitamab plus lenalidomide plus rituximab (n=273)	Placebo plus lenalidomide plus rituximab (n=275)	Total (N=548)
Age, years	64·0 (36–88)	64·0 (31–85)	64·0 (31–88)
≥65 years	136 (50%)	136 (50%)	272 (50%)
≥75 years	54 (20%)	54 (20%)	108 (20%)
Sex			
Male	150 (55%)	149 (54%)	299 (55%)
Female	123 (45%)	126 (46%)	249 (45%)
Ethnicity			
Hispanic or Latino	31 (11%)	24 (9%)	55 (10%)
Not Hispanic or Latino	228 (84%)	226 (82%)	454 (83%)
Not reported	11 (4%)	23 (8%)	34 (6%)
Unknown	3 (1%)	2 (1%)	5 (1%)
Race			
White	219 (80%)	219 (80%)	438 (80%)
Black or African American	1 (<1%)	0	1 (<1%)
Asian	40 (15%)	42 (15%)	82 (15%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Pacific Islander	0	0	0
Not reported	11 (4%)	10 (4%)	21 (4%)
Other	2 (1%)	4 (2%)	6 (1%)
ECOG PS at enrolment			
0	181 (66%)	192 (70%)	373 (68%)
1	85 (31%)	75 (27%)	160 (29%)
2	7 (3%)	8 (3%)	15 (3%)
Bone marrow involvement			
Yes	88 (32%)	91 (33%)	179 (33%)
No	169 (62%)	162 (59%)	331 (60%)
Unknown	3 (1%)	13 (5%)	16 (3%)
Missing	13 (5%)	9 (3%)	22 (4%)
Ann Arbor stage at enrolment			
I/II	52 (19%)	50 (18%)	102 (19%)
III/IV	221 (81%)	225 (82%)	446 (81%)
Met GELF criteria at enrolment	222 (81%)	232 (84%)	454 (83%)
Follicular lymphoma grade			
1/2	203 (74%)	203 (74%)	406 (74%)
3A	67 (25%)	71 (26%)	138 (25%)
B symptoms	63 (23%)	67 (24%)	130 (24%)
FLIPI score at enrolment			
0–1	57 (21%)	57 (21%)	114 (21%)
2	79 (29%)	67 (24%)	146 (27%)
3–5	137 (50%)	150 (55%)	287 (52%)
Missing	0	1 (<1%)	1 (<1%)
Number of previous lines of therapy	1 (1–7)	1 (1–10)	1 (1–10)
1	147 (54%)	153 (56%)	300 (55%)
2	66 (24%)	71 (26%)	137 (25%)
3	39 (14%)	30 (11%)	69 (13%)
≥4	21 (8%)	21 (8%)	42 (8%)

(Table 1 continues on next page)

	Tafasitamab plus lenalidomide plus rituximab (n=273)	Placebo plus lenalidomide plus rituximab (n=275)	Total (N=548)
(Continued from previous page)			
Previous systemic anticancer treatment regimens			
Anthracyclines	161 (59%)	167 (61%)	328 (60%)
Anti-CD20 plus CHOP	151 (55%)	161 (59%)	312 (57%)
Bendamustine alone or in combination	114 (42%)	101 (37%)	215 (39%)
Anti-CD20 monotherapy	54 (20%)	51 (19%)	105 (19%)
Anti-CD20 monotherapy as only previous treatment	26 (10%)	19 (7%)	45 (8%)
Anti-CD20 plus CVP	30 (11%)	43 (16%)	73 (13%)
Chemotherapy plus ASCT	19 (7%)	23 (8%)	42 (8%)
Relapsed or refractory status to last therapy			
Relapsed	148 (54%)	164 (60%)	312 (57%)
Refractory	112 (41%)	97 (35%)	209 (38%)
Undetermined	13 (5%)	14 (5%)	27 (5%)
Refractory to previous anti-CD20	118 (43%)	115 (42%)	233 (43%)
POD24 positive	85 (31%)	88 (32%)	173 (32%)
Time since last antilymphoma therapy			
≤2 years	147 (54%)	157 (57%)	304 (56%)
>2 years	126 (46%)	118 (43%)	244 (45%)
Time since initial follicular lymphoma diagnosis, years	5·2 (0–34)	5·5 (1–33)	5·3 (0–34)
Follicular lymphoma diagnosis confirmed by central pathology	256 (94%)	251 (91%)	507 (93%)

Data are n (%) or median (range). ASCT=autologous stem cell transplantation. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. CVP=cyclophosphamide, vincristine, and prednisone. ECOG PS=Eastern Cooperative Oncology Group performance status. FLIPI=Follicular Lymphoma International Prognostic Index. GELF=Groupe d'Etude des lymphomes Folliculaires. POD24=progression of disease within 24 months of initial diagnosis.

Table 1: **Baseline patient characteristics (intention-to-treat population)**

Progression free interval

Duration of response

Survival

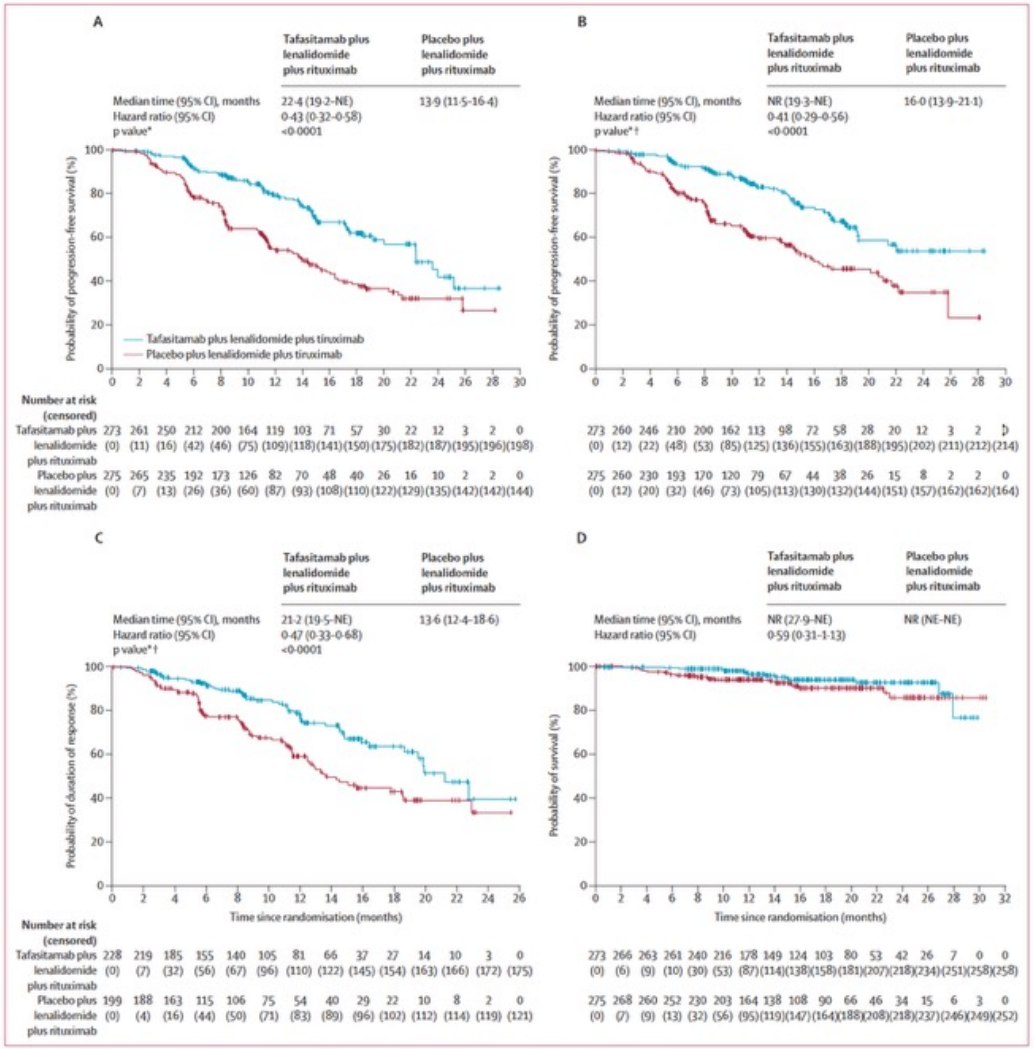


Figure 2: Progression-free survival (A, B), duration of response (C), and overall survival (D) (intention-to-treat population)
(A) Kaplan-Meier analysis of progression-free survival as assessed by the investigator. (B) Kaplan-Meier analysis of progression-free survival as assessed by independent review committee, who were masked to treatment assignment. (C) Duration of response in patients who had an overall response (partial or complete response; 228 of 273 patients in the tafasitamab group vs 199 of 275 patients in the placebo group). (D) Overall survival. Tick marks indicate censored data. NE=not evaluable. NR=not reached. *Stratified log-rank test with an overall two-sided significance level of 5%. †Nominal p value.

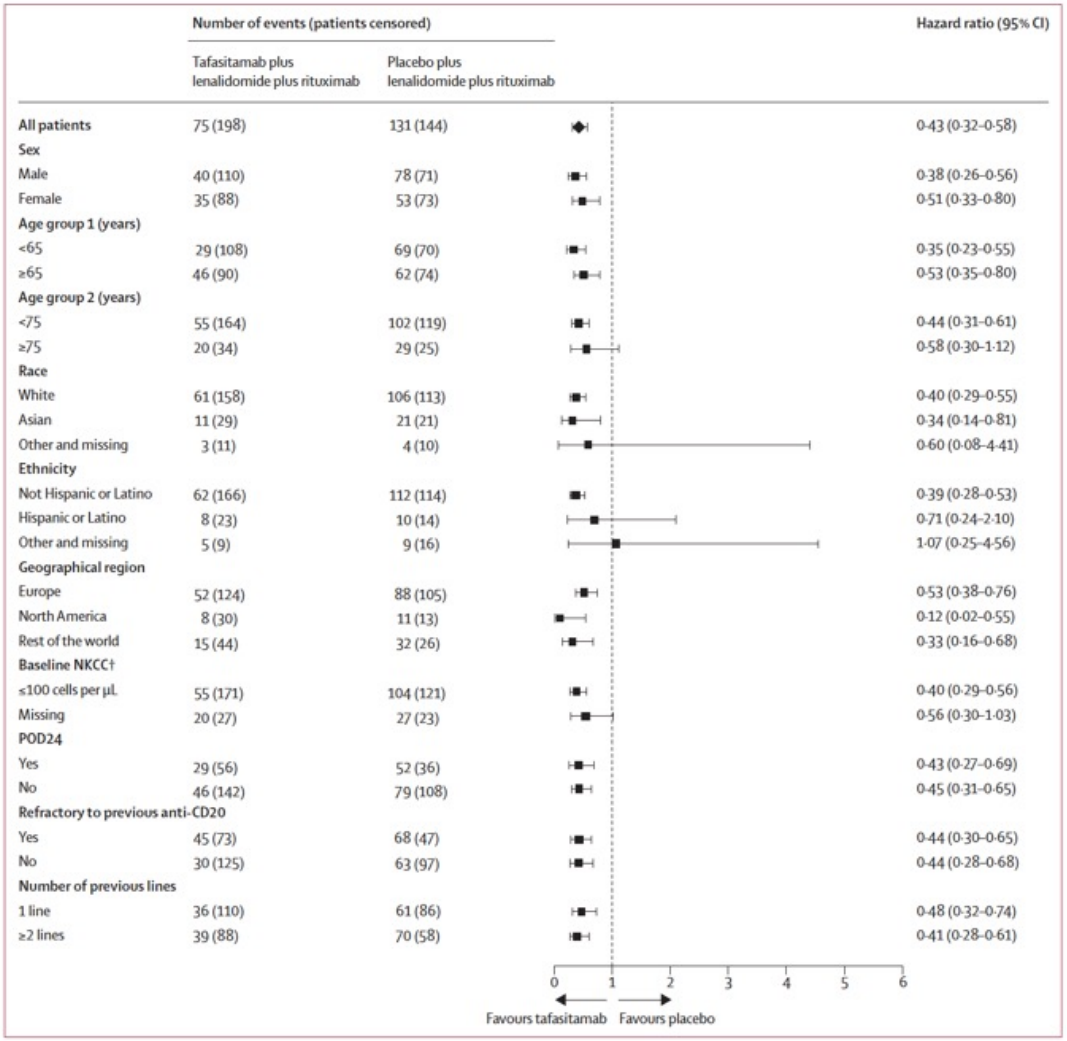


Figure 3: **Forest plot of hazard ratios for progression-free survival (intention-to-treat population)***
NKCC=natural killer cell count. POD24=progression of disease within 24 months of initial diagnosis. *Subgroup analyses are based on stratification factor. †No patient had baseline NKCC >100 cells per µL.

	Tafasitamab plus lenalidomide plus rituximab	Placebo plus lenalidomide plus rituximab
Overall response rate (intention-to-treat population)		
Patients	273	275
Best response*		
Complete response	124 (45%)	94 (34%)
Partial response	104 (38%)	105 (38%)
Stable disease	28 (10%)	46 (17%)
Progressive disease	7 (3%)	20 (7%)
Not evaluable	2 (1%)	0
Not done	8 (3%)	10 (4%)
Complete response (radiographic)†	141 (52%)	110 (40%)
Overall response rate‡, % (95% CI)§	84% (78·6–87·7)	72% (66·7–77·6)
Odds ratio¶||| (95% CI)§	2·0 (1·30–3·02)	..
Nominal p value||	0·0014	..
PET-CR (FDG-avid population)		
Patients with FDG-avid positive PET scan at baseline	251	254
Patients with post-baseline PET assessments**	201/251 (80%)	205/254 (81%)
Best metabolic response based on PET		
Complete metabolic response (PET-CR)	124 (49%)	101 (40%)
Partial metabolic response	37 (15%)	39 (15%)
No metabolic response/stable disease	19 (8%)	12 (5%)
Progressive metabolic disease	19 (8%)	51 (20%)
PET after confirmed progressive disease or new anti-lymphoma treatment initiation	2 (1%)	2 (1%)
Not done	50 (20%)	49 (19%)
PET-CR††, % (95% CI)§	49% (43·1–55·8)	40% (33·7–46·1)
Odds ratio¶||| (95% CI)§	1·5 (1·04–2·13)	..
p value||	0·029	..

Data are n (%) or n/N (%) unless otherwise specified. CR=complete response. FDG=fluorodeoxyglucose. *Per Lugano 2014 criteria. †Complete response (radiographic) included patients with positive baseline bone marrow morphological involvement without confirmed morphological complete response (bone marrow not done or not evaluable) after radiographic complete response. ‡Overall response rate was defined as the proportion of patients who achieved a complete or partial response as determined per Lugano classification at any time during the study but before the first progressive disease and before or at the start of a new antilymphoma treatment. §Calculated using Clopper–Pearson method. ¶The strata information was based on the data obtained from the interactive response technology used for randomisation. ||By stratified Cochran–Mantel–Haenszel. **Percentages are calculated based on patients with a positive PET scan at baseline, defined as having a Deauville score of 4 or 5 at baseline. ††The PET-CR rate is defined as the proportion of patients who achieved complete metabolic response at any time after start of treatment as per Lugano criteria in patients with FDG-avid disease at baseline by PET-CR results only. Patients with no post-baseline assessment by PET, or who did not achieve a complete metabolic response, were not considered PET-CR responders.

Table 2: **Best overall response (intention-to-treat population) and PET-CR (FDG-avid population) as assessed by the investigator**

	Tafasitamab plus lenalidomide plus rituximab (n=274*)		Placebo plus lenalidomide plus rituximab (n=272†)		Total (N=546)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Any adverse event	268 (98%)	195 (71%)	263 (97%)	189 (69%)	531 (97%)	384 (70%)
Diarrhoea	103 (38%)	2 (1%)	77 (28%)	5 (2%)	180 (33%)	7 (1%)
Constipation	79 (29%)	2 (1%)	67 (25%)	0	146 (27%)	2 (<1%)
Neutropenia	78 (29%)	109 (40%)	59 (22%)	102 (38%)	137 (25%)	211 (39%)
COVID-19	76 (28%)	16 (6%)	60 (22%)	6 (2%)	136 (25%)	22 (4%)
Rash	60 (22%)	3 (1%)	58 (21%)	1 (<1%)	118 (22%)	4 (1%)
Fatigue	57 (21%)	5 (2%)	43 (16%)	0	100 (18%)	5 (1%)
Cough	52 (19%)	0	47 (17%)	0	99 (18%)	0
Muscle spasms	49 (18%)	0	49 (18%)	0	98 (18%)	0
Pyrexia	50 (18%)	4 (1%)	40 (15%)	6 (2%)	90 (16%)	10 (2%)
Nausea	48 (18%)	1 (<1%)	37 (14%)	1 (<1%)	85 (16%)	2 (<1%)
Infusion-related reaction	42 (15%)	2 (1%)	40 (15%)	1 (<1%)	82 (15%)	3 (1%)
Pruritus	44 (16%)	1 (<1%)	28 (10%)	0	72 (13%)	1 (<1%)
Thrombocytopenia	32 (12%)	17 (6%)	36 (13%)	20 (7%)	68 (12%)	37 (7%)
Anaemia	31 (11%)	12 (4%)	32 (12%)	16 (6%)	63 (12%)	28 (5%)
Asthenia	36 (13%)	3 (1%)	27 (10%)	2 (1%)	63 (12%)	5 (1%)
Oedema peripheral	20 (7%)	0	35 (13%)	3 (1%)	55 (10%)	3 (1%)
Upper respiratory tract infection	25 (9%)	1 (<1%)	29 (11%)	0	54 (10%)	1 (<1%)
Hypokalaemia	22 (8%)	4 (1%)	30 (11%)	3 (1%)	52 (10%)	7 (1%)
Decreased appetite	27 (10%)	0	23 (8%)	2 (1%)	50 (9%)	2 (<1%)
Back pain	31 (11%)	0	15 (6%)	0	46 (8%)	0
Abdominal pain	20 (7%)	0	25 (9%)	5 (2%)	45 (8%)	5 (1%)
Headache	27 (10%)	1 (<1%)	18 (7%)	0	45 (8%)	1 (<1%)
Respiratory tract infection	18 (7%)	2 (1%)	24 (9%)	1 (<1%)	42 (8%)	3 (1%)
Dizziness	21 (8%)	0	19 (7%)	0	40 (7%)	0
Arthralgia	19 (7%)	0	21 (8%)	0	40 (7%)	0
Dyspnoea	18 (7%)	1 (<1%)	21 (8%)	5 (2%)	39 (7%)	6 (1%)
Insomnia	21 (8%)	0	17 (6%)	0	38 (7%)	0
Nasopharyngitis	17 (6%)	0	20 (7%)	0	37 (7%)	0
Increased alanine aminotransferase	18 (7%)	2 (1%)	18 (7%)	2 (1%)	36 (7%)	4 (1%)
Oropharyngeal pain	24 (9%)	1 (<1%)	10 (4%)	0	34 (6%)	1 (<1%)
Urinary tract infection	18 (7%)	2 (1%)	15 (6%)	3 (1%)	33 (6%)	5 (1%)
Rash maculopapular	18 (7%)	3 (1%)	14 (5%)	1 (<1%)	32 (6%)	4 (1%)
Vomiting	19 (7%)	0	12 (4%)	2 (1%)	31 (6%)	2 (<1%)
Pneumonia	17 (6%)	23 (8%)	13 (5%)	14 (5%)	30 (5%)	37 (7%)
Decreased neutrophils	17 (6%)	16 (6%)	12 (4%)	18 (7%)	29 (5%)	34 (6%)
Pain in extremity	21 (8%)	0	7 (3%)	0	28 (5%)	0
Myalgia	15 (6%)	0	13 (5%)	1 (<1%)	28 (5%)	1 (<1%)
Decreased weight	13 (5%)	0	14 (5%)	0	27 (5%)	0
Chills	13 (5%)	0	13 (5%)	0	26 (5%)	0
Dyspepsia	14 (5%)	0	12 (4%)	0	26 (5%)	0
Increased aspartate aminotransferase	13 (5%)	1 (<1%)	13 (5%)	0	26 (5%)	1 (<1%)
Decreased white blood cell count	13 (5%)	5 (2%)	12 (4%)	3 (1%)	25 (5%)	8 (1%)
Rhinorrhoea	14 (5%)	0	10 (4%)	0	24 (4%)	0
Influenza	15 (6%)	0	8 (3%)	1 (<1%)	23 (4%)	1 (<1%)
Hypomagnesaemia	13 (5%)	1 (<1%)	8 (3%)	0	21 (4%)	1 (<1%)
Paraesthesia	13 (5%)	0	9 (3%)	0	22 (4%)	0
Neuropathy peripheral	13 (5%)	0	6 (2%)	0	19 (3%)	0
Hyperglycaemia	7 (3%)	4 (1%)	7 (3%)	1 (<1%)	14 (3%)	5 (1%)

(Table 3 continues on next page)

	Tafasitamab plus lenalidomide plus rituximab (n=274*)		Placebo plus lenalidomide plus rituximab (n=272†)		Total (N=546)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
(Continued from previous page)						
Hypertension	6 (2%)	1 (<1%)	7 (3%)	4 (1%)	13 (2%)	5 (1%)
Pulmonary embolism	2 (1%)	4 (1%)	1 (<1%)	3 (1%)	3 (1%)	7 (1%)
COVID-19 pneumonia	3 (1%)	13 (5%)	0	3 (1%)	3 (1%)	16 (3%)
Acute kidney injury	1 (<1%)	8 (3%)	1 (<1%)	6 (2%)	2 (<1%)	14 (3%)
Febrile neutropenia	0	12 (4%)	1 (<1%)	6 (2%)	1 (<1%)	18 (3%)
Syncope	0	4 (1%)	0	2 (1%)	0	6 (1%)

Data are n (%); patients were counted once under each MedDRA preferred term, for grade 1–2 and for grade 3–4 adverse events. Cutoffs were based on clinical relevance to assess the safety profile of the treatments. MedDRA=Medical Dictionary for Regulatory Activities. *One patient randomly assigned to the placebo plus lenalidomide and rituximab group is included in the tafasitamab plus lenalidomide and rituximab safety population because the patient erroneously received tafasitamab. †Three patients randomly assigned to the placebo plus lenalidomide and rituximab group are not included in the safety population because they erroneously received tafasitamab (n=1) or did not receive any study treatment due to confirmation of rituximab hypersensitivity (n=1), and withdrawal by patient (n=1).

Table 3: Most frequent grade 1–2 (≥5% in any group) and grade 3–4 (≥2% in any group) adverse events in the safety population

	Tafasitamab plus lenalidomide plus rituximab (n=274*)	Placebo plus lenalidomide plus rituximab (n=272†)	Total (N=546)
Any serious adverse event	99 (36%)	86 (32%)	185 (34%)
Pneumonia	21 (8%)	13 (5%)	34 (6%)
COVID-19	19 (7%)	7 (3%)	26 (5%)
COVID-19 pneumonia	14 (5%)	5 (2%)	19 (3%)
Acute kidney injury	8 (3%)	4 (1%)	12 (2%)
Febrile neutropenia	7 (3%)	6 (2%)	13 (2%)
Pyrexia	4 (1%)	7 (3%)	11 (2%)
Sepsis	3 (1%)	3 (1%)	6 (1%)
Neutropenia	2 (1%)	3 (1%)	5 (1%)
Abdominal pain	0	5 (2%)	5 (1%)
Diarrhoea	0	3 (1%)	3 (<1%)

Data are n (%); patients were counted once under each MedDRA preferred term. Cutoff is based on clinical relevance to assess the safety profile of the treatments. MedDRA=Medical Dictionary for Regulatory Activities. *One patient randomly assigned to the placebo plus lenalidomide and rituximab group is included in the tafasitamab plus lenalidomide and rituximab safety population because the patient erroneously received tafasitamab. †Three patients randomly assigned to the placebo plus lenalidomide and rituximab group are not included in the safety population because they erroneously received tafasitamab (n=1) or did not receive any study treatment due to confirmation of rituximab hypersensitivity (n=1), and withdrawal by patient (n=1).

Table 4: **Most frequent serious adverse events (≥1% in any group) in the safety population**

Research in context

Evidence before this study

To more fully understand the current treatment landscape and associated challenges in indolent non-Hodgkin lymphoma, we searched the PubMed database for articles published in English between Jan 1, 2020, and March 10, 2025, on the role of the tumour microenvironment as well as the impact of differences in CD20 expression in tumours on disease progression and development of treatment resistance. We used the search terms "((“non-Hodgkin lymphoma” OR “follicular lymphoma” OR “marginal zone lymphoma”) AND CD20) AND English [Language] AND (“2020/01/01”[Date - Publication]: “2025/03/10”[Date - Publication])”. Based on published reports from the search, the tumour microenvironment restricts host immune responses and treatment with anti-CD20 therapy (eg, rituximab) might reduce CD20 expression on tumour cells, contributing to resistance or relapse after monoclonal antibody therapy. Further, prognosis generally worsens with each subsequent therapy in patients with relapsed or refractory disease, highlighting the need for the development of additional treatment options that could further improve survival outcomes. Tafasitamab is an Fc-enhanced humanised monoclonal antibody that was designed to target the broadly expressed B-cell antigen CD19. In preclinical studies in models of diffuse large B-cell lymphoma and Burkitt lymphoma, antitumour activity was increased compared with respective monotherapy treatments when tafasitamab was combined with rituximab and different chemotherapeutic and non-chemotherapeutic drugs, including lenalidomide. Tafasitamab is currently approved in the USA, the EU, and other countries in combination with lenalidomide for the treatment of adult patients with relapsed or refractory, diffuse, large B-cell lymphoma who are not eligible for autologous stem cell transplantation.

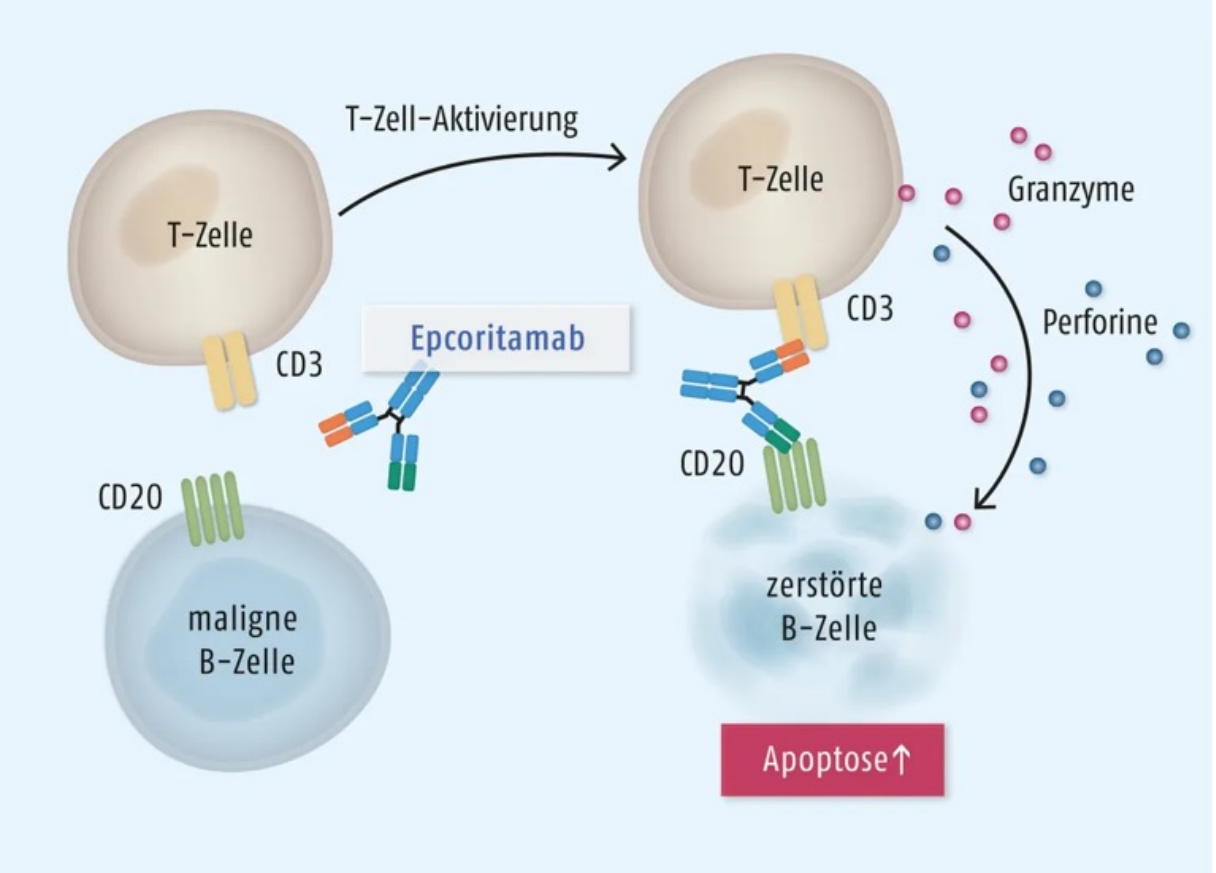
Added value of this study

In a follicular lymphoma patient population with high burden of disease, including many who were refractory to anti-CD20 monoclonal antibody therapy, tafasitamab in combination with lenalidomide and rituximab was associated with significantly longer progression-free survival compared with placebo added to lenalidomide and rituximab. This improvement was seen in all subgroups analysed (including in patients with disease progression or relapse within 24 months of initial diagnosis status, anti-CD20-refractory status, and by number of previous lines of therapy). Additionally, tafasitamab was associated with higher rates of overall response and metabolic complete response versus placebo. The safety profile of this combination was consistent with expectations and manageable for this population, and, importantly, the addition of tafasitamab did not compromise lenalidomide or rituximab delivery. To our knowledge, our study is the first to validate the approach of combining two unconjugated monoclonal antibodies (anti-CD19 with anti-CD20) in treatment of lymphoma in a large, phase 3, randomised clinical trial.

Implications of all the available evidence

CD19 represents a potential treatment target for patients with relapsed or refractory follicular lymphoma following anti-CD20 therapy. Data from our study demonstrate promising results of the addition of tafasitamab to lenalidomide and rituximab. Because this combination can be administered in the community as well as tertiary centres, these encouraging results indicate that it might become a new option for standard-of-care treatment for patients with relapsed or refractory follicular lymphoma, particularly as a second-line treatment for which few options are currently available. Future analyses will yield robust data on overall survival, as well as a more in-depth examination of quality of life in patients treated with tafasitamab. Additionally, analyses of CD19 expression in patients following treatment with tafasitamab will provide information to help guide subsequent treatment decisions.

Epcoritamab ist ein **bispezifischer CD20-gerichteter CD3-T-Zell-Engager (Fesseln)**. Er bindet gleichzeitig an das CD20-Antigen auf den bösartigen B-Zellen und an den CD3-Rezeptor auf körpereigenen T-Zellen. Dadurch werden die T-Zellen direkt an die Krebszellen herangeführt und aktiviert, um diese zu zerstören.



Epcoritamab, lenalidomide, and rituximab versus lenalidomide and rituximab for relapsed or refractory follicular lymphoma (EPCORE FL-1): a global, open-label, randomised, phase 3 trial

Summary

Background An unmet need persists for chemotherapy-free regimens that induce durable responses for relapsed or refractory follicular lymphoma. Lenalidomide and rituximab (R^2) is an accepted standard of care in this population. The EPCORE FL-1 trial aimed to evaluate the efficacy and safety of epcoritamab plus R^2 versus R^2 in participants with relapsed or refractory follicular lymphoma after at least one previous line of chemoimmunotherapy.

Methods In this multicountry, open-label, phase 3 trial, participants were randomly allocated (1:1) to fixed-duration epcoritamab plus R^2 or R^2 for up to 12 cycles. Epcoritamab was administered weekly in cycles 1–3 and every 4 weeks in cycles 4–12, lenalidomide once daily during cycles 1–12 (days 1–21), and rituximab weekly during cycle 1 and monthly in cycles 2–5. The dual primary endpoints were overall response rate and progression-free survival by independent review committee. The data reported here are from a planned interim analysis carried out after 78% of progression-free survival events had occurred. This study is registered with ClinicalTrials.gov, NCT05409066, and EudraCT, 2021–000169–34, and is ongoing (closed to recruitment).

Findings Out of 668 participants screened for eligibility across 189 academic and non-academic centres in 30 countries across Africa, Asia, Australia, Europe, North America, and South America, a total of 488 participants were randomly allocated, 243 to epcoritamab plus R² and 245 to R². The trial met its dual primary endpoints, showing superiority of epcoritamab plus R² over R² in overall response rate and progression-free survival. With a median follow-up of 14·8 months (IQR 11·4–19·0), overall response rate was 95% (95% CI 92–97) with epcoritamab plus R² versus 79% (74–84; p<0·0001) with R². Progression-free survival was longer with epcoritamab plus R² versus R² (hazard ratio 0·21 [95% CI 0·14–0·31], p<0·0001); estimated 16-month progression-free survival favoured epcoritamab plus R² (85·5% *vs* 40·2%). Grade 3 or higher adverse events were more frequent with epcoritamab plus R² (219 [90%] of 243 participants) versus R² (161 [68%] of 238 participants). Cytokine release syndrome was low grade with epcoritamab plus R² (grade 1 in 28 [21%] participants and grade 2 in seven [5%] participants) and manageable, and all events were resolved.

Interpretation Epcoritamab plus R² resulted in significantly higher response rate and longer progression-free survival versus R² among participants with follicular lymphoma who had received at least one line of therapy. Epcoritamab plus R² had more grade 3 or higher adverse events versus R². Adverse events were manageable and consistent with the established safety profiles of the individual components, with no new safety findings identified. These findings position epcoritamab plus R² as a new standard of care for second-line or subsequent treatment of follicular lymphoma.

Funding AbbVie and Genmab.

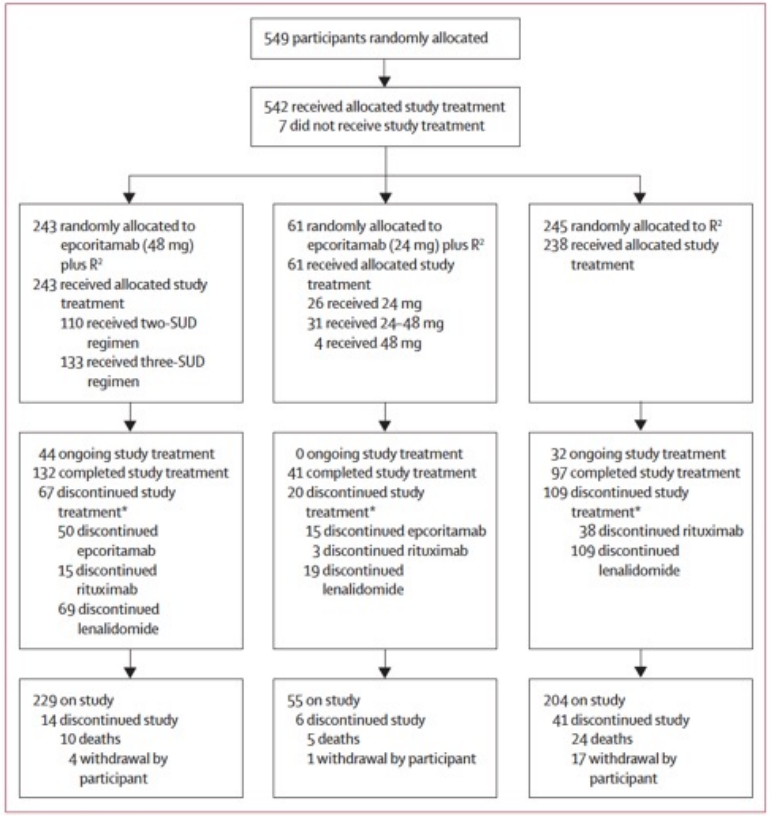


Figure 1: **Trial profile**

Participants were randomly allocated to receive epcoritamab plus R² (epcoritamab full dose 48 mg), epcoritamab plus R² (epcoritamab full dose 24 mg), or R² alone. The 24 mg epcoritamab plus R² group was closed to enrolment on the basis of the superior efficacy for the 48 mg dose that emerged in the EPCORE NHL-2 trial;[18] thus, only the 48 mg epcoritamab plus R² group and R² group data are presented here. R²=lenalidomide plus rituximab. SUD=step-up dosing. *Discontinued study treatment was defined as discontinuation of all study drugs, or discontinuation of one or more study drugs with the rest completed.

	Epcoritamab plus R² (n=243)	R² (n=245)
Age		
Median, years	60 (50-69)	63 (54-71)
<65 years	155 (64%)	139 (57%)
≥65 years	88 (36%)	106 (43%)
Sex		
Male	139 (57%)	138 (56%)
Female	104 (43%)	107 (44%)
Region		
USA or western Europe	58 (24%)	60 (24%)
Rest of world	185 (76%)	185 (76%)
Race		
American Indian or Alaska Native	0	1 (<1%)
Asian	63 (26%)	54 (22%)
Black or African American	6 (2%)	2 (1%)
White	168 (69%)	184 (75%)
Multiple	1 (<1%)	1 (<1%)
Missing	5 (2%)	3 (1%)
Eastern Cooperative Oncology Group performance status		
0	166 (68%)	170 (69%)
1	72 (30%)	68 (28%)
2	5 (2%)	7 (3%)
FLIPI score at baseline		
0-1	63 (26%)	56 (23%)
2	79 (33%)	76 (31%)
3-5	100 (41%)	113 (46%)
Unknown	1 (<1%)	0
FLIPI-2 score at baseline		
0	23 (9%)	24 (10%)
1-2	144 (59%)	118 (48%)
3-5	51 (21%)	85 (35%)
Unknown	25 (10%)	18 (7%)
Follicular lymphoma grade		
1	61 (25%)	43 (18%)
2	126 (52%)	120 (49%)
3a	52 (21%)	75 (31%)
Classic, 5th edition WHO	3 (1%)	2 (1%)
Missing	1 (<1%)	5 (2%)
Ann Arbor stage		
II	37 (15%)	44 (18%)
III	74 (30%)	68 (28%)
IV	132 (54%)	133 (54%)

(Table 1 continues in next column)

(Continued from previous column)

	Epcoritamab plus R² (n=243)	R² (n=245)
Bulky disease (≥7 cm)		
Yes	47 (19%)	61 (25%)
No	191 (79%)	176 (72%)
Missing	5 (2%)	8 (3%)
Bone marrow involvement		
Positive	70 (29%)	68 (28%)
Negative	162 (67%)	168 (69%)
Unknown	11 (5%)	9 (4%)
Time from initial diagnosis to randomisation, years	4·5 (2·4–8·2)	5·3 (2·7–9)
Number of previous lines of antilymphoma therapy		
Median	1 (1–2)	1 (1–2)
1	145 (60%)	141 (58%)
2	58 (24%)	61 (25%)
≥3	40 (16%)	43 (18%)
Previous systemic therapies		
Any antilymphoma therapy	243 (100%)	245 (100%)
Anti-CD20 antibody	243 (100%)	245 (100%)
Anti-CD20 antibody with chemotherapy	239 (98%)	240 (98%)
Immunomodulatory	9 (4%)	13 (5%)
Refractory to previous therapy		
Refractory to first-line therapy	86 (35%)	81 (33%)
Progression of disease within 24 months*	106 (44%)	93 (38%)
Double refractory disease†	91 (37%)	91 (37%)
Refractory to previous anti-CD20 antibody	104 (43%)	103 (42%)
Refractory to last line of therapy	84 (35%)	82 (33%)

Data are median (IQR) or n (%). R²=lenalidomide plus rituximab. FLIPI=Follicular Lymphoma International Prognostic Index. *Defined as progression of disease 2 years or less from the date of initiation of first-line chemoimmunotherapy. †Double refractory is refractory to previous anti-CD20 antibodies and previous alkylating agents. Refractory is defined by either or both of: best overall response to treatment as stable disease or progressive disease, or progression occurring within 6 months after completion of treatment regardless of response.

Table 1: **Participant demographic and disease characteristics at baseline (intention-to-treat population)**

	Epcoritamab plus R² (n=243)	R² (n=245)
Median follow-up, months, median (95% CI) [IQR]	14·8 (13·96–16·23) [12·0–19·3]	14·6 (13·57–15·64) [10·2–18·6]
Overall response rate, n (% [95% CI])*	231 (95% [92–97])	194 (79% [74–84])
Complete response, n (% [95% CI])*	201 (83% [77–87])	122 (50% [43–56])
Partial response	30 (12%)	72 (29%)
Stable disease	1 (<1%)	17 (7%)
Progressive disease	7 (3%)	16 (7%)
NE†	4 (2%)‡	18 (7%)‡
Duration of response		
Median, months§	NE (NE–NE)	11·5 (8·5–18·6)
12-month Kaplan–Meier estimate, %	89·2% (83·6–93·0)	48·5% (38·8–57·5)
Duration of complete response		
Median, months§	NE (NE–NE)	18·6 (11·1–NE)
12-month Kaplan–Meier estimate, %	91·2% (84·5–95·0)	56·0% (42·4–67·6)
Time to next antilymphoma treatment¶		
Median, months§	NE (NE–NE)	24·3 (18·2–NE)
16-month Kaplan–Meier estimate, %	92·8% (88·3–95·6)	64·9% (57·1–71·6)
Progression-free survival		
Median, months§	NE (NE–NE)	11·7 (11·1–15·1)
16-month Kaplan–Meier estimate, %	85·5% (79·7–89·7)	40·2% (31·8–48·4)
Time to progression		
Median, months§	NE (NE–NE)	14·8 (11·2–18·6)
Overall survival¶		
Median, months§	NE (NE–NE)	NE (NE–NE)
16-month Kaplan–Meier estimate, %	95·8% (92·0–97·8)	88·8% (83·6–92·4)
Event-free survival¶		
Median, months§	NE (NE–NE)	11·0 (9·1–12·5)

Data are n (%), median (95% CI), or Kaplan–Meier estimate % (95% CI) unless otherwise specified. R²=lenalidomide plus rituximab. NE=not evaluable. *95% CI is from the exact binomial distribution (Clopper–Pearson exact method). †Participants with no post-baseline disease assessment were also included. ‡NE: epcoritamab plus R² (n=4: 1 withdrawal, 2 deaths, 1 did not meet eligibility); R² (n=18: 8 withdrawals, 5 deaths, 3 did not meet eligibility, 1 clinical progression, 1 scan could not be read). §Based on Kaplan–Meier estimate. ¶Per investigator assessment.

Table 2: **Efficacy results according to independent review committee assessment (intention-to-treat population)**

Progression-free

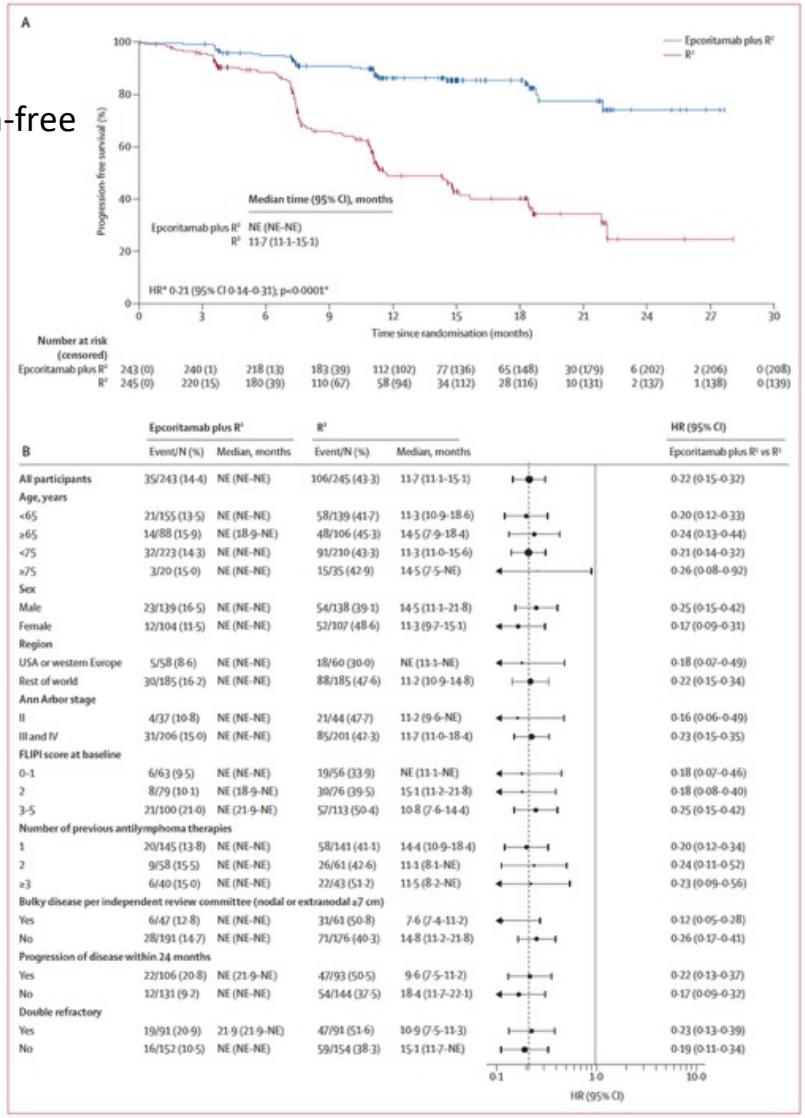


Figure 2: **Progression-free survival per independent review committee assessment in (A) the intention-to-treat population and (B) participant subgroups**
In (A), the tick marks indicate censored data. The p value is based on log-rank test. The HR is estimated using the Cox proportional hazards model. In (B), N represents the total number of participants within each category in each group. Arrows indicate that the CI is extended more than the current range. FLIPI=Follicular Lymphoma International Prognostic Index. HR=hazard ratio. NE=not evaluable. R²=lenalidomide plus rituximab. *Stratified by disease status and history.

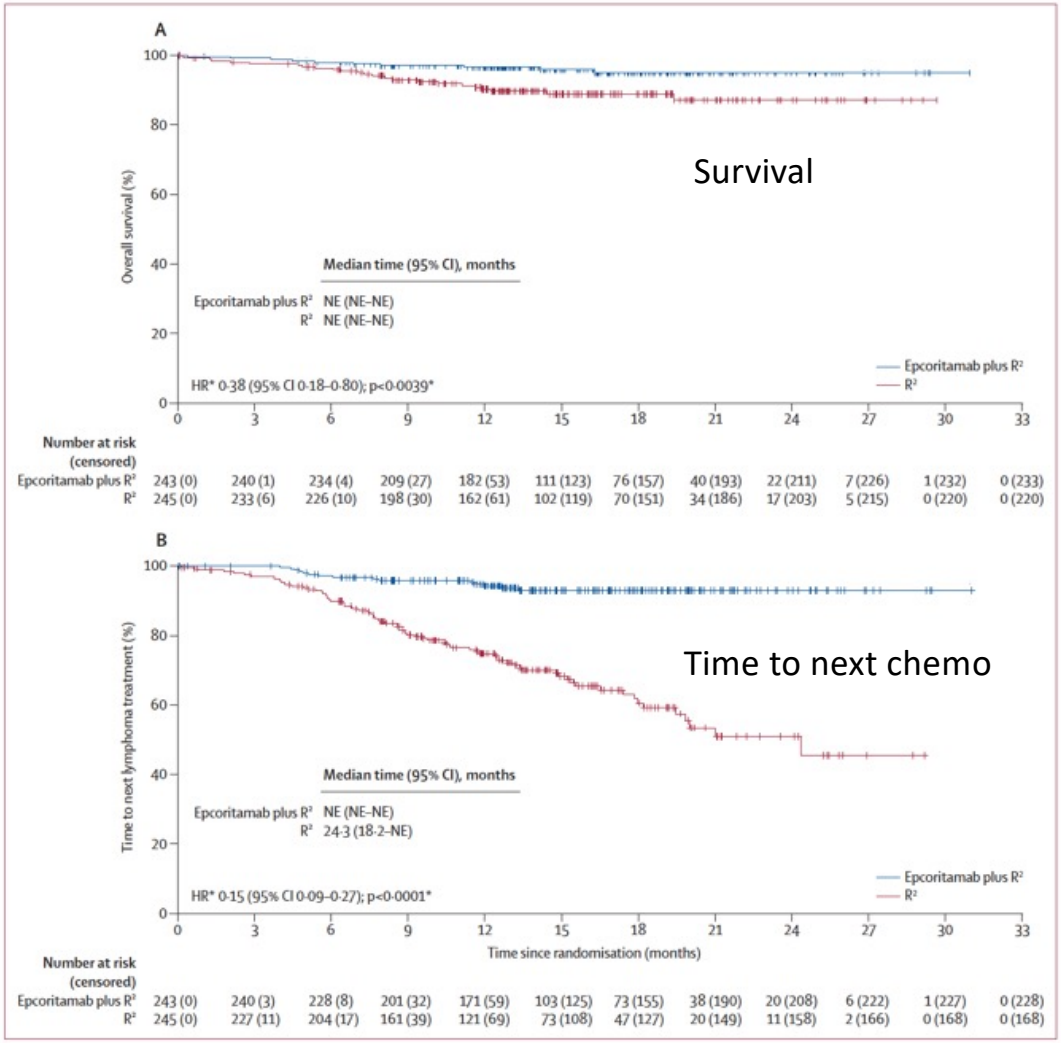


Figure 3: Overall survival (A) and time to next lymphoma treatment per investigator assessment (B)
Tick marks indicate censored data. The p value is based on log-rank test. The HR is estimated using the Cox proportional hazards model. HR=hazard ratio. NE=not evaluable. R²=lenalidomide plus rituximab. *Stratified by disease status and history.

	Epcoritamab plus R² (n=243)		R² (n=238)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	242 (>99%)	219 (90%)	235 (99%)	161 (68%)
Adverse event related to study drug	236 (97%)	203 (84%)	213 (90%)	129 (54%)
Serious adverse event	135 (56%)	..	69 (29%)	..
Adverse event leading to treatment discontinuation	46 (19%)	..	29 (12%)	..
Epcoritamab	21 (9%)	..	..	..
Rituximab	7 (3%)	..	12 (5%)	..
Lenalidomide	45 (19%)	..	29 (12%)	..
Adverse event of special interest ≥20%				
Infections*	188 (77%)	81 (33%)	125 (53%)	37 (16%)
Neutropenia	180 (74%)	167 (69%)	123 (52%)	100 (42%)
Cytokine release syndrome	85 (35%)	0	1 (<1%)	0
Anaemia	68 (28%)	19 (8%)	41 (17%)	11 (5%)
Thrombocytopenia	67 (28%)	23 (9%)	44 (18%)	15 (6%)
Pyrexia	58 (24%)	1 (<1%)	33 (14%)	3 (1%)
Rash	58 (24%)	19 (8%)	53 (22%)	9 (4%)
COVID-19	54 (22%)	7 (3%)	32 (13%)	4 (2%)

Data are n (%). The safety population consisted of all participants who received at least one dose of the study drug.
*Events were in the MedDRA system organ class "Infections and Infestations".

Table 3: Adverse events and selected events of clinical interest (safety population)

cycle 12 day 1. Comparatively, the mean difference of

Research in context

Evidence before this study

We searched PubMed and major international congresses from July 1, 2015, to July 17, 2025, for randomised clinical trials published in all languages that evaluated relapsed or refractory follicular lymphoma treatments using the search terms "follicular lymphoma" AND ("relapsed" OR "refractory") AND ("immunomodulatory" OR "lenalidomide"). From our searches, we found randomised phase 2 trials CALGB 50401 and HOVON110/Rebel and phase 3 trials AUGMENT, MAGNIFY, and inMIND. These studies supported the combination of lenalidomide and rituximab (R^2) as an internationally accepted standard for individuals with relapsed or refractory follicular lymphoma. Although R^2 offers a therapeutic option, only around half of treated patients have a complete response and most relapse, needing subsequent treatments. The additions of bendamustine in the HOVON110/Rebel trial and tafasitamab in the inMIND trial improved efficacy outcomes with no unexpected toxicities. Early-phase trials are evaluating novel agents in combination with R^2 or immunomodulatory agent lenalidomide as chemotherapy-free options for follicular lymphoma after initial therapy. We hypothesised that the addition of epcoritamab with the R^2 regimen would enhance efficacy and minimise overlapping toxicities. In preclinical studies, epcoritamab worked well in the presence of rituximab, and lenalidomide enhanced activation of immune cells. In the phase 1b/2 EPCORE NHL-2 trial (NCT04663347), fixed-duration epcoritamab plus R^2 was evaluated in patients with relapsed or refractory follicular lymphoma, yielding deep and durable responses including an overall response rate of 96%, a complete response rate of 88%, and an estimated 24-month progression-free survival of 76%. On the basis of these results, the randomised, global, open-label, phase 3 EPCORE FL-1 trial (NCT05409066) was initiated to evaluate the efficacy and safety of epcoritamab plus R^2 versus R^2 alone in individuals with relapsed or refractory follicular lymphoma.

Added value of this study

This EPCORE FL-1 trial is, to our knowledge, the first phase 3 study of a bispecific antibody combination therapy in individuals with follicular lymphoma to be reported, and showed that the combination of epcoritamab plus R^2 significantly improved response rate and reduced the risk of disease progression or death compared with R^2. Benefit was observed across all explored participant subgroups, underscoring the generalisability of these results in the broader relapsed or refractory follicular lymphoma population. Although adverse events of grade 3 or higher were more frequent with the triplet versus R^2, these were manageable and consistent with the established safety profiles of the individual components of the triplet, with no new safety findings identified.

Implications of all the available evidence

In the landscape of studies in individuals with relapsed and refractory follicular lymphoma, epcoritamab and R^2 stands as the first bispecific-based, off-the-shelf, outpatient, fixed-duration, efficacious second-line or later therapy to represent a new and improved chemotherapy-free standard of care in this population. Additionally, this regimen could be a more accessible and convenient treatment option associated with longer remission.

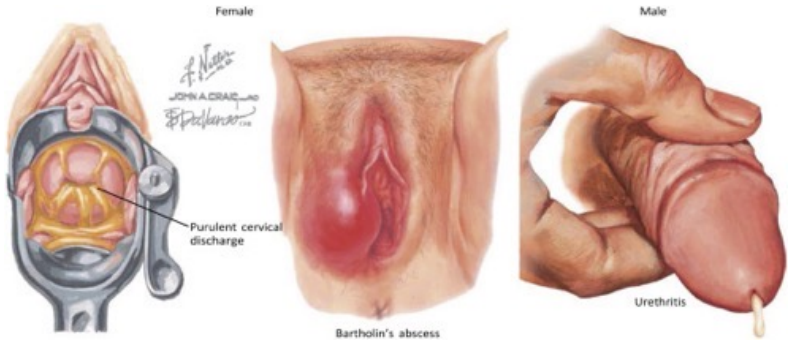
Gonorrhoe, umgangssprachlich auch **Tripper** genannt, ist eine der am häufigsten vorkommenden sexuell übertragbaren Infektionen (STI) weltweit. Sie wird durch das Bakterium *Neisseria gonorrhoeae* (Gonokokken) ausgelöst, das vor allem die Schleimhäute von Harnröhre, Gebärmutterhals, Enddarm und Rachen befällt.

Aktuelle Lage 2026

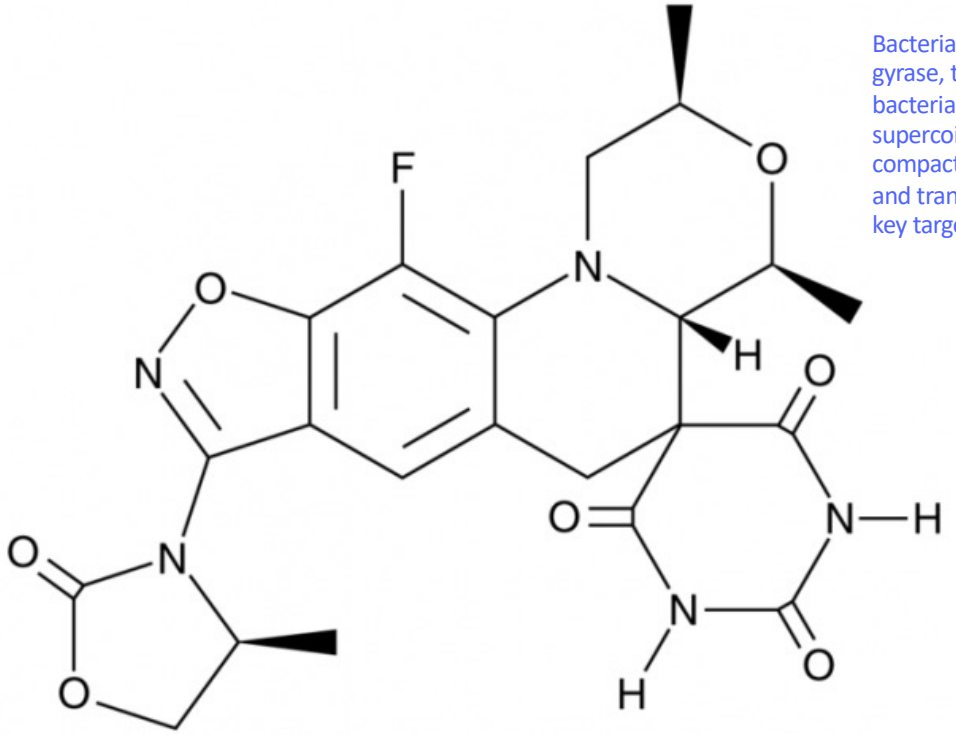
•**Steigende Fallzahlen:** In Europa und Deutschland wird ein deutlicher Anstieg der Infektionen verzeichnet. Die Melderaten bei Männern, die Sex mit Männern haben (MSM), stiegen zwischen 2014 und 2023 um fast 300 %; auch bei jungen Frauen (20–24 Jahre) verdreifachten sich die Zahlen zuletzt.

•**Resistenzproblematik:** Es treten vermehrt "Super-Gonorrhoe"-Stämme auf, die gegen gängige Antibiotika resistent sind. Im März 2025 wurden in Deutschland besorgniserregende Fälle mit Multiresistenzen gemeldet.

•**Impfung:** Seit August 2025 wird in England erstmals ein gezieltes Impfprogramm mit dem Impfstoff *4CMenB* (Bexsero) für Hochrisikogruppen angeboten, der einen gewissen Kreuzschutz gegen Gonorrhoe bietet.



Zoliflodacin (Markenname: Nuzolvence) ist ein neuartiges, einmalig oral einzunehmendes Antibiotikum, das im Dezember 2025 von der FDA für die Behandlung von unkomplizierter Gonorrhoe (Tripper) durch *Neisseria gonorrhoeae* zugelassen wurde und gegen resistente Stämme wirksam ist, indem es die bakterielle Topoisomerase Typ II hemmt und so die DNA-Synthese unterbindet. Es ist ein wichtiger Durchbruch gegen zunehmende Antibiotikaresistenzen und bietet eine Alternative zu herkömmlichen Therapien.



Bacterial topoisomerase II is essentially DNA gyrase, the specific type II topoisomerase in bacteria responsible for introducing negative supercoils into DNA, a crucial function for DNA compaction and processing during replication and transcription, making it a vital enzyme and a key target for antibiotics like fluoroquinolones.

Zoliflodacin versus ceftriaxone plus azithromycin for treatment of uncomplicated urogenital gonorrhoea: an international, randomised, controlled, open-label, phase 3, non-inferiority clinical trial

Summary

Background Development of new treatments for gonorrhoea is a global public health priority. We aimed to evaluate the efficacy and safety of zoliflodacin versus ceftriaxone plus azithromycin in patients with uncomplicated urogenital gonorrhoea.

Methods In this phase 3, multinational, randomised, controlled, open-label, non-inferiority clinical trial, participants aged 12 years and older with clinical suspicion of uncomplicated urogenital gonorrhoea were eligible for inclusion. The trial was done in 17 outpatient clinics in Belgium, the Netherlands, South Africa, Thailand, and the USA. Participating countries with high disease prevalence were identified for participation in the study. Sites selected for participation were led by principal investigators with research experience, who were knowledgeable in HIV or sexually transmitted infections and treatment. Feasibility questionnaires and prestudy visits assessed sexually transmitted infection case management guidelines, clinical services, and resources (ie, facility, staff, proposed composition of the study team, standard sexually transmitted infection services offered at the site, assessment of laboratory capacity, research experience and ethical review of clinical trials). Eligible participants were randomly assigned (2:1) to receive a single dose of zoliflodacin 3 g (oral) or ceftriaxone 500 mg (intramuscular) plus azithromycin 1 g (oral). Treatment assignment was known to the participants and their treating clinicians; however, microbiology laboratory staff were masked and the sponsor's central study team were masked until after database lock. The primary endpoint was the proportion of patients with microbiological cure (eradication of *Neisseria gonorrhoeae*, determined by urethral or endocervical culture) at test of cure (TOC; day 6±2) in the microbiological intention-to-treat population. The primary efficacy analysis declared non-inferiority if the upper bound of the two-sided 95% CI for the treatment difference (comparator minus zoliflodacin) fell below the 12% non-inferiority margin. The trial is registered with ClinicalTrials.gov, NCT03959527, and EudraCT, 2019-000990-22.

Findings Between Nov 6, 2019, and March 16, 2023, 1011 patients were screened. 81 patients did not meet screening criteria and 930 participants were randomly assigned to zoliflodacin (n=621) or comparator (n=309). The mean participant age was 29·7 years (SD 9·4). 815 (88%) of 930 participants were assigned male at birth and 115 (12%) participants were assigned female at birth. 514 (55%) of 930 participants were Black or African American, 285 (31%) were Asian, and 113 (12%) were White. Microbiological cure rates at TOC in the microbiological intention-to-treat (urogenital) population (primary efficacy endpoint) were 460 (90·9%, 95% CI 88·1–93·3) of 506 participants for zoliflodacin and 229 (96·2%, 92·9–98·3) of 238 participants for comparator. The estimated difference between groups was 5·3% (95% CI 1·4–8·6) and the upper confidence interval limit was within the prespecified non-inferiority margin of less than 12%. Zoliflodacin was generally well tolerated and adverse events were similar between treatment groups. The most frequently reported treatment-emergent adverse events included headache (61 [10%] of 619 patients), neutropenia (42 [7%]), and leukopenia (24 [4%]) in the zoliflodacin group and injection site pain (38 [12%] of 308 patients), neutropenia (24 [8%]), and diarrhoea (22 [7%]) in the comparator group. The majority of adverse events were mild or moderate in severity. No serious adverse events were reported.

Interpretation Zoliflodacin was non-inferior to ceftriaxone plus azithromycin for the treatment of uncomplicated urogenital gonorrhoea and had a similar safety profile. These data suggest a potential role for zoliflodacin as an effective oral treatment option for uncomplicated urogenital gonorrhoea.

Funding German Federal Ministry of Research, Technology and Space, UK Department of Health and Social Care as part of the Global Antimicrobial Resistance Innovation Fund, Japan Ministry of Health, Labour and Welfare, Netherlands Ministry of Health, Welfare and Sport and Directorate-General for International Cooperation, Switzerland Federal Office of Public Health, and the Canton of Geneva, Switzerland.

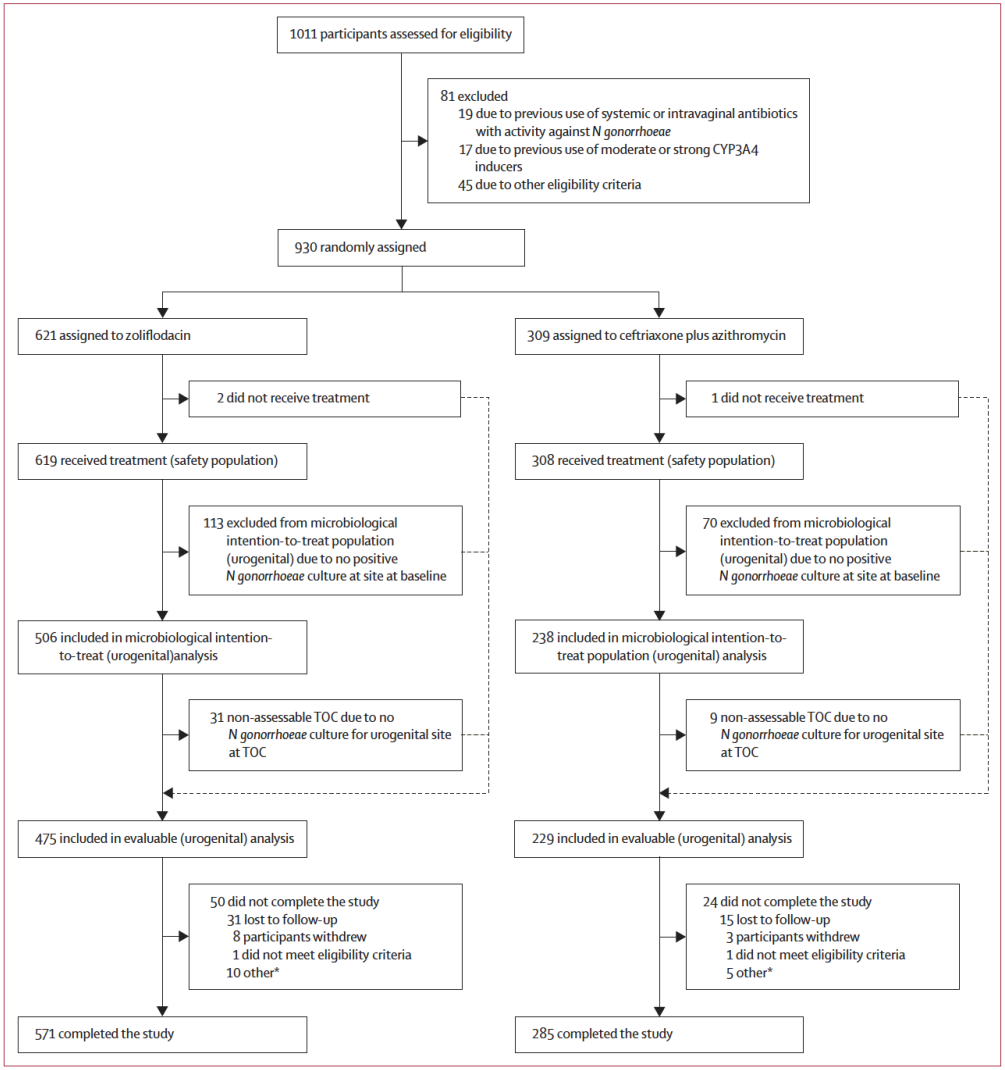


Figure 1: **Trial profile**

N gonorrhoeae=Neisseria gonorrhoeae. TOC=test-of-cure. *Participants missed or were out of window for their end-of-trial visit.

	Zoliflodacin group (n =621)	Ceftriaxone plus azithromycin (n=309)
Randomly assigned population		
Age, years		
Mean (SD)	30·0 (9·6)	29·2 (9·1)
Range	16–73	15–67
Sex assigned at birth		
Male	544 (88%)	271 (88%)
Female	77 (12%)	38 (12%)
Gender		
Male	543 (87%)	269 (87%)
Female	78 (13%)	40 (13%)
Race		
Black or African American	349 (56%)	165 (53%)
Asian	193 (31%)	92 (30%)
White	66 (11%)	47 (15%)
American Indian or Alaska Native	8 (1%)	1 (<1%)
Native Hawaiian or Other Pacific Islander	2 (<1%)	1 (<1%)
White, Asian	1 (<1%)	2 (1%)
Other	2 (<1%)	1 (<1%)
Region		
South Africa	278 (45%)	146 (47%)
Thailand	181 (29%)	89 (29%)
USA	107 (17%)	51 (17%)
Europe	55 (9%)	23 (7%)
HIV status*		
Negative	455 (73%)	234 (76%)
Positive	134 (22%)	65 (21%)
Missing	32 (5%)	10 (3%)
Fasted status†		
Fed	555 (89%)	273 (88%)
Fasted	64 (10%)	35 (11%)
Missing	2 (<1%)	1 (<1%)
Microbiological intention-to-treat population (urogenital)		
Clinical assessment (urogenital)		
Symptoms in males at birth		
Urethral discharge	446/456 (98%)	216/220 (98%)
Dysuria	392/456 (86%)	188/220 (85%)
Symptoms in females at birth		
Dysuria	17/50 (34%)	7/18 (39%)
Abnormal vaginal discharge	36/50 (72%)	11/18 (61%)
Postcoital bleeding	5/50 (10%)	0
Vaginal bleeding between periods	9/50 (18%)	1/18 (6%)
Vulvovaginal irritation	16/50 (32%)	7/18 (39%)

Data are n (%) or n/N (%), unless otherwise indicated. *HIV positive status confirmed by positive test from sample or by other evidence which included medical history or indicated previous or concomitant medication. †Fasted status: fed=food consumed ≤2 h before dosing; fasted=last meal >2 h before dosing.

Table 1: **Participant demographics and baseline characteristics**

	Zoliflodacin		Ceftriaxone plus azithromycin		Difference (95% CI)
	n/N	Proportion with microbiological cure (95% CI)	n/N	Proportion with microbiological cure (95% CI)	
Primary efficacy endpoint					
Microbiological intention-to-treat*	460/506	90·9% (88·1–93·3)	229/238	96·2% (92·9–98·3)	5·3% (1·4–8·6)
Sensitivity analysis					
Evaluable	460/475	96·8% (94·8–98·2)	229/229	100% (98·4–100)	3·2% (1·1–5·1)
Microbiological intention-to-treat including out-of-window assessments	471/506	93·1% (90·5–95·1)	231/238	97·1% (94·0–98·8)	4·0% (0·4–6·9)
Microbiological intention-to-treat excluding key protocol deviations	456/502	90·8% (88·0–93·2)	227/236	96·2% (92·9–98·2)	5·3% (1·4–8·7)
Microbiological intention-to-treat with multiple imputation					
Missing at random†	NA	NA	NA	NA	3·1% (1·3–4·8)
Missing not at random†	NA	NA	NA	NA	3·2% (1·4–5·0)
Secondary analysis					
Per-protocol‡	434/452	96·0% (93·8–97·6)	218/219	99·5% (97·5–100)	3·5% (1·0–5·8)

NA=not applicable. TOC=test of cure. *The microbiological intention-to-treat population and modified microbiological intention-to-treat population were identical, therefore the secondary analysis of the modified microbiological intention-to-treat population is not shown. †Multiple imputation analysis generated multiple instances of the dataset using a logistic regression model, and the results were pooled to produce a unique point estimate of the risk difference; cure rates in each individual treatment group were not estimated. ‡All participants in the microbiological intention-to-treat population who met all inclusion (and did not meet exclusion) criteria; complied with trial treatment; did not vomit within 30 min of administration of zoliflodacin or azithromycin; did not receive any systemic antibiotic with known activity against *Neisseria gonorrhoeae* before the TOC visit; did not receive any of the prohibited medications; abstained from sexual intercourse or used condoms for vaginal, anal, and oral sex before TOC; and returned to the trial site for the TOC visit within the specified window.

Table 2: **Microbiological cure rate at TOC at urogenital site**

	Zoliflodacin		Ceftriaxone plus azithromycin		Difference (95% CI)
	n/N	Proportion with microbiological cure (95% CI)	n/N	Proportion with microbiological cure (95% CI)	
Pharyngeal					
Microbiological intention-to-treat*	42/53	79·2% (65·9 to 89·2)	22/28	78·6% (59·0 to 91·7)	−0·7% (−20·8 to 16·3)
Evaluable	42/46	91·3% (79·2 to 97·6)	22/23	95·7% (78·1 to 99·9)	4·3% (−13·1 to 16·5)
Per-protocol†	39/46	84·8% (71·1 to 93·7)	20/23	87·0% (66·4 to 97·2)	2·2% (−18·4 to 17·7)
Rectal					
Microbiological intention-to-treat*	69/79	87·3% (78·0 to 93·8)	31/35	88·6% (73·3 to 96·8)	1·2% (−14·3 to 12·6)
Evaluable	69/72	95·8% (88·3 to 99·1)	31/31	100% (88·8 to 100)	4·2% (−7·2 to 11·5)
Per-protocol†	61/64	95·3% (86·9 to 99·0)	30/31	96·8% (83·3 to 99·9)	1·5% (−11·9 to 10·1)

TOC=test of cure. *The microbiological intention-to-treat population and modified microbiological intention-to-treat population were identical, therefore the secondary analysis of the modified microbiological intention-to-treat population is not shown. †All participants in the microbiological intention-to-treat population who met all inclusion (and did not meet exclusion) criteria; complied with trial treatment; did not vomit within 30 min of administration of zoliflodacin or azithromycin; did not receive any systemic antibiotic with known activity against *Neisseria gonorrhoeae* before the TOC visit; did not receive any of the prohibited medications; abstained from sexual intercourse or used condoms for vaginal, anal, and oral sex before TOC; and returned to the trial site for the TOC visit within the specified window.

Table 3: **Microbiological cure rate at TOC at pharyngeal and rectal sites (secondary endpoints)**

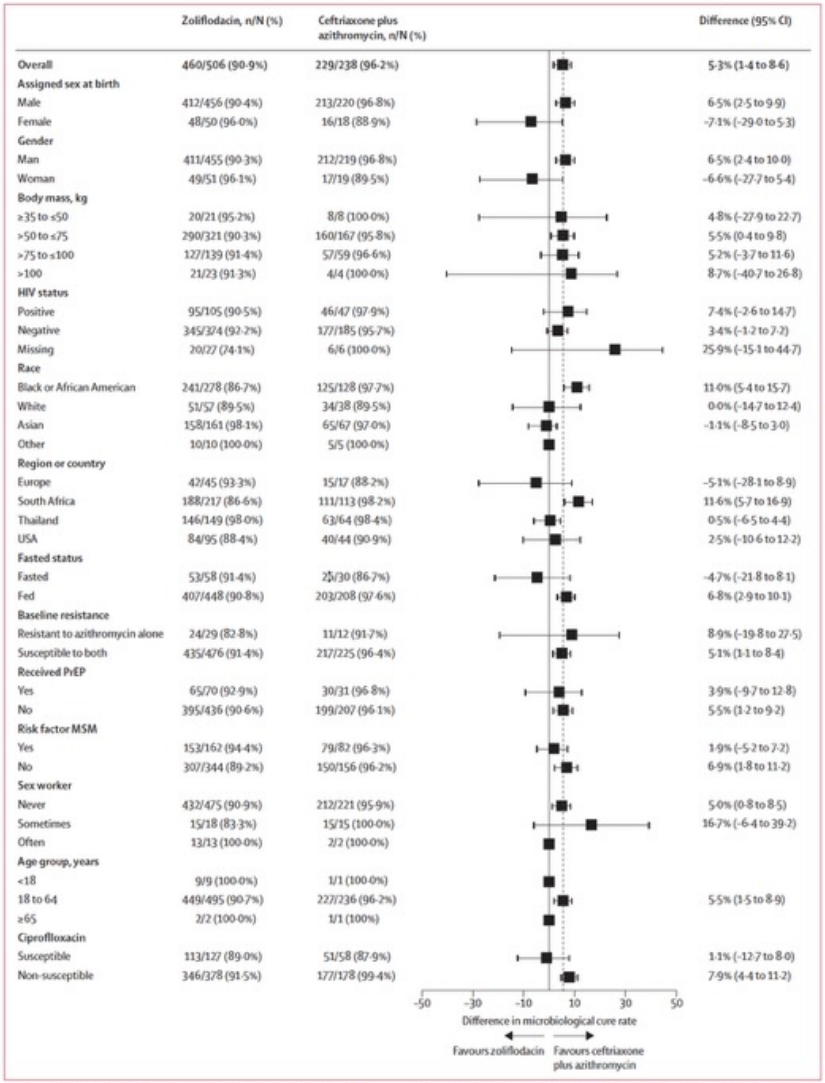


Figure 2: **Forest plot of difference in microbiological cure rate at test of cure by subgroup: microbiological intention-to-treat (urogenital) population**
The dashed vertical line indicates the overall treatment difference. MSM=men who have sex with men. PrEP=pre-exposure prophylaxis.

No difference

	Zoliflodacin group (N=619)	Ceftriaxone plus azithromycin group (N=308)
Participants with at least one treatment-emergent adverse event	286 (46%); 450	143 (46%); 257
Related treatment-emergent adverse events	117 (19%); 149	76 (25%); 113
Serious treatment-emergent adverse events	0	0
Related serious treatment-emergent adverse events	0	0
Treatment-emergent adverse events leading to treatment discontinuation	0	0
Treatment-emergent adverse events leading to death	0	0
Treatment-emergent adverse events by maximum severity		
Grade 1—mild	156 (25%); 288	82 (27%); 167
Grade 2—moderate	109 (18%); 140	43 (14%); 71
Grade 3—severe	20 (3%); 21	18 (6%); 19
Grade 4—life-threatening	1 (<1%); 1	0
Grade 5—death	0	0
Treatment-emergent adverse events by preferred term (≥3% either group)		
Headache	61 (10%); 65	14 (5%); 15
Neutropenia	42 (7%); 42	24 (8%); 24
Leukopenia	24 (4%); 24	7 (2%); 7
Neutrophil count decreased	21 (3%); 21	15 (5%); 15
Dizziness	21 (3%); 21	5 (2%); 5
Nausea	16 (3%); 16	12 (4%); 13
Diarrhoea	15 (2%); 15	22 (7%); 22
Injection site pain	5 (1%); 6	38 (12%); 38

Data are the number of participants with at least one event in each group (%); number of events.

Table 4: **Treatment-emergent adverse events in the safety population**

Research in context

Evidence before this study

Gonorrhoea represents a pressing global public health concern. In the past decade, sexually transmitted infections caused by *Neisseria gonorrhoeae* have steadily increased, with WHO estimating a global incidence of over 82 million cases per year in 2020. Effective antimicrobial treatment for gonorrhoea can help prevent transmission and long-term sequelae, but *N gonorrhoeae* has developed resistance to multiple first-line and second-line treatments. Zoliflodacin is a first-in-class spiropyrimidinetrione that inhibits bacterial DNA replication using a distinct mechanism of action and has a new target (GyrB), with potent in-vitro activity against *N gonorrhoeae* including multidrug-resistant strains. A phase 2 study found zoliflodacin efficacious in treating uncomplicated urogenital gonorrhoea, warranting further clinical investigation. This multinational, phase 3, randomised, controlled, non-inferiority clinical trial compared the efficacy and safety of a single oral dose of zoliflodacin 3 g with ceftriaxone 500 mg plus azithromycin 1 g for treatment of uncomplicated urogenital gonorrhoea. Before study conception and design, no formal literature search was undertaken, given the paucity of clinical development underway at the time. Instead, scientific advice was sought from global experts. Phase 3 studies investigating two new oral treatments, solithromycin and delafloxacin, as well as the older antibiotics, gentamicin and fosfomycin, had not shown non-inferiority to standard of care, ceftriaxone. However, ertapenem showed non-inferiority versus ceftriaxone for the treatment of anogenital *N gonorrhoeae* but had a higher frequency of adverse events and, being a broad spectrum antibiotic, concerns over stewardship and the need to reserve this antibiotic for difficult-to-treat serious bacterial infections is a limitation to its widespread use as a gonorrhoea treatment. Other than gepotidacin, which was entering phase 3 development concurrently, no new agents were identified in the development pipeline.

Added value of this study

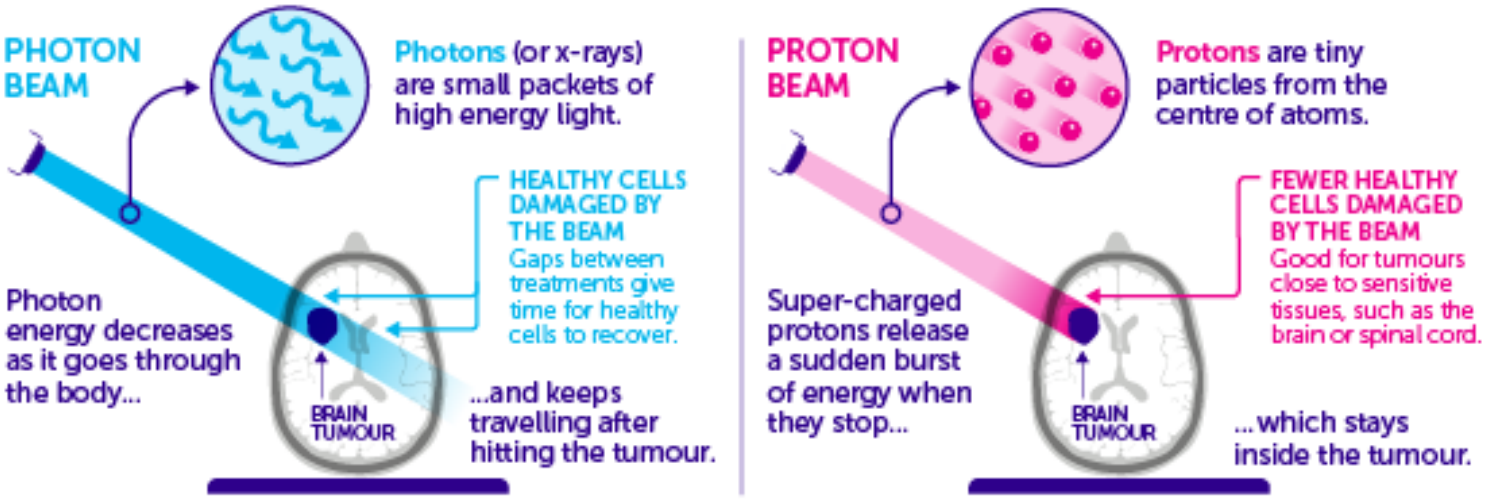
This large study was done in a highly diverse population, including regions with a high burden of gonorrhoea. Zoliflodacin showed non-inferiority to the comparator for treating uncomplicated urogenital gonorrhoea and had a similar safety profile. Analysis of microbiological cure rate at pharyngeal and rectal sites of infection showed similar efficacy outcomes between the study treatment groups.

Implications of all the available evidence

Our findings provide evidence for zoliflodacin as a potential oral treatment for uncomplicated urogenital gonorrhoea.

PHOTON AND PROTON RADIOTHERAPY WHAT'S THE DIFFERENCE?

Radiotherapy targets tumours with a beam of energy which damages DNA and kills cancer cells.



LET'S BEAT CANCER SOONER
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CANCER RESEARCH UK

Photon radiotherapy is a standard form of external beam radiation therapy that uses high-energy X-rays or gamma rays (photons) to treat cancer. As of 2026, it remains the most common and widely available form of radiation therapy globally due to its proven effectiveness and lower cost compared to newer alternatives like proton therapy.

How Photon Radiotherapy Works

- **Ionizing Radiation:** High-energy photon beams are produced by a **linear accelerator (linac)**. These beams pass through the body to reach the tumor.
- **DNA Damage:** Photons interact with atoms in cancer cells to create free radicals, which damage the cells' DNA. This prevents the cancer cells from dividing and growing, eventually leading to cell death.
- **Exit Dose:** Unlike proton therapy, which stops inside the tumor, photon beams continue through the body, delivering an "exit dose" of radiation to healthy tissues behind the tumor.

Proton radiotherapy (or proton beam therapy) is a highly precise form of radiation therapy that uses a beam of protons to target and destroy cancer cells, sparing surrounding healthy tissue more effectively than traditional X-ray radiation. Its key advantage is the ability to deliver a high dose of radiation directly to the tumor's shape and depth, releasing most of its energy within the tumor and significantly reducing damage to vital organs, making it ideal for tumors near sensitive areas like the brain, spinal cord, or in children.

How it works

- **Particle acceleration**: A machine (particle accelerator) generates a beam of high-energy protons.
- **Targeting**: The proton beam is precisely aimed at the tumor.
- **Energy release**: Protons deposit most of their energy at a specific depth (the tumor) and then stop, unlike X-rays that pass through tissue.
- **Cell destruction**: The radiation damages the DNA of cancer cells, preventing them from reproducing and eliminating the tumor.

Proton versus photon radiotherapy for patients with oropharyngeal cancer in the USA: a multicentre, randomised, open-label, non-inferiority phase 3 trial

Summary

Background Radiotherapy is an integral component of treatment for oropharyngeal cancer. Toxicity from the current state-of-the-art photon radiotherapy, intensity-modulated radiation therapy (IMRT), has prompted the search for alternative, less toxic therapies. One such alternative that might de-intensify treatment is proton therapy. In this trial, we aimed to directly compare IMRT with intensity-modulated proton therapy (IMPT), both concurrent with systemic therapy, hypothesising comparable disease control and survival and lower toxicity.

Methods This randomised, multicentre, open-label, non-inferiority, phase 3 trial was conducted in 21 sites (cancer centres or universities) in the USA. Patients (aged ≥18 years) with stage III or stage IV oropharyngeal cancer and an Eastern Cooperative Oncology Group performance status of 0–2 were recruited and randomly assigned 1:1 to receive IMPT or IMRT. All patients were treated with radiotherapy to 70 Gy in 33 fractions to the primary tumour site and cervical lymphadenopathy. The type, schedule, and dose of induction or concurrent systemic therapy were chosen locally by each institution's multidisciplinary tumour board and were consistent with international guidelines. The primary endpoint was progression-free survival and was assessed in the intention-to-treat population; safety outcomes were assessed in the per-protocol population (ie, patients who received the assigned therapy). A non-inferiority margin of 9 percentage points for progression-free survival at 3 years was used. This trial is registered with ClinicalTrials.gov (NCT01893307) and is closed to further accrual after prespecified interim analysis.

Findings From Oct 10, 2013, to May 1, 2022, 440 patients consented (median age 61 years [IQR 55–68], 399 [91%] male, 409 [93%] White); 221 were allocated to the IMPT group (with 160 [72%] receiving IMPT) and 219 to the IMRT group (136 [62%] receiving IMRT). At a median follow-up time of 3·2 years, progression-free survival rates for the IMPT group were 82·5% (95% CI 76·1–87·3) at 3 years and 81·3% (74·5–86·5) at 5 years; corresponding rates for the IMRT group were 83·0% (76·7–87·7) and 76·2% (68·0–82·6; hazard ratio [HR] 0·88 [95% CI 0·57–1·35]; p=0·005 for non-inferiority of IMPT). Overall survival rates after IMPT were 90·9% at 5 years versus 81·0% after IMRT (HR 0·58 [95% CI 0·34–0·99]; p=0·045). Treatment-related deaths occurred in nine patients; six in the IMRT group and three in the IMPT group. Deaths from disease progression occurred in 27 patients; 18 in the IMRT group and nine in the IMPT group. 5-year disease control rates for IMPT versus IMRT were similar between treatment groups (local recurrences 2·9% *vs* 5·6%, p=0·474; regional recurrences 3·4% *vs* 3·2%, p=0·860; and distant metastases 9·1% *vs* 8·9%, p=0·897). Severe lymphopenia was more common in the IMRT group (89% *vs* 76%), as were dysphagia (49% *vs* 31%), xerostomia (45% *vs* 33%), and gastrostomy tube dependence (40·2% *vs* 26·8%; p=0·018).

Interpretation IMPT showed non-inferiority to IMRT for progression-free survival, improvement in overall survival, similar disease control, and reduced high-grade toxicity relative to IMRT. Treatment-related and post-progression deaths occurred more frequently with IMRT. IMPT is a new standard-of-care treatment option for patients with oropharyngeal cancer.

Funding MD Anderson Cancer Center, Massachusetts General Hospital, National Institutes of Health, Hitachi America.

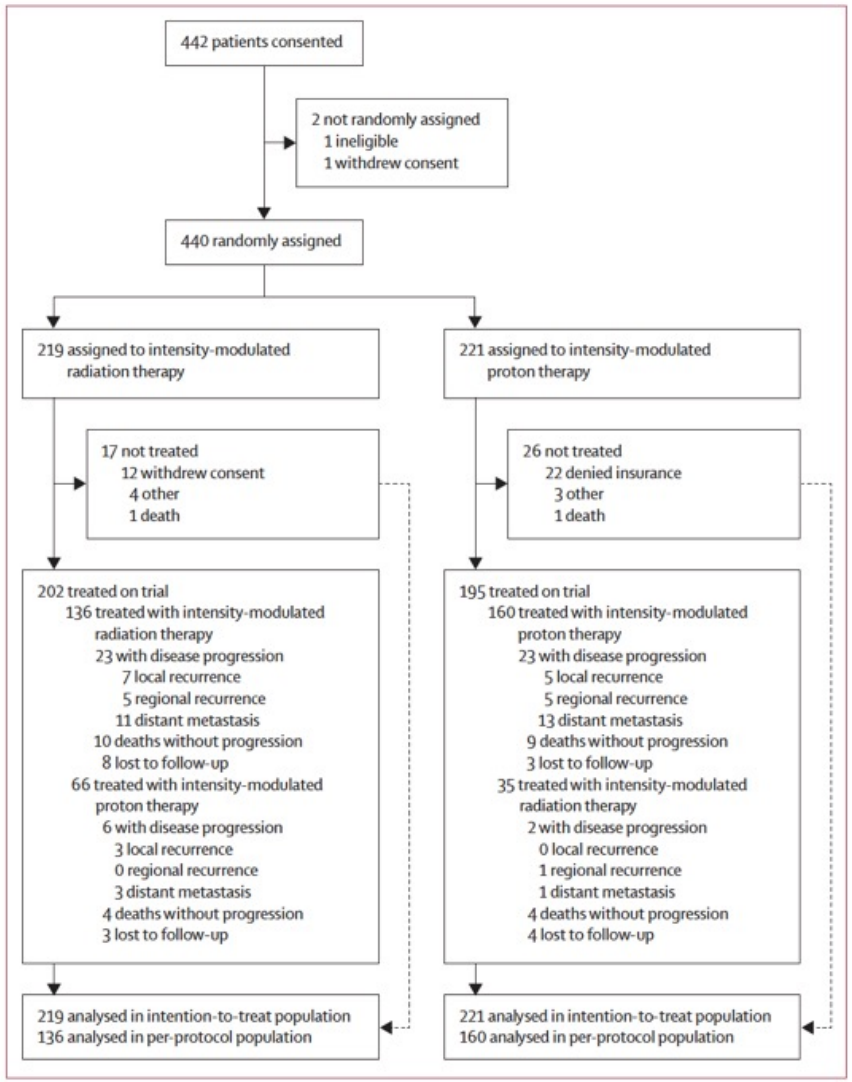


Figure 1: Trial profile

	Intensity-modulated (photon) radiation therapy	Intensity-modulated proton therapy
Age, years		
<65	134/219 (61%)	138/221 (62%)
≥65	85/219 (39%)	83/221 (38%)
Mean age, years (SD)	61·5 (9·2)	61·5 (8·6)
Median age, years (IQR)	61 (55-68)	61 (56-67)
Age range, years	34-83	33-84
Sex		
Female	18/219 (8%)	23/221 (10%)
Male	201/219 (92%)	198/221 (90%)
Race		
White	204/219 (93%)	205/221 (93%)
Black	6/219 (3%)	9/221 (4%)
Asian	1/219 (<1%)	0/221
Other	8/219 (4%)	7/221 (3%)
Ethnicity		
Hispanic or Latino	11/219 (5%)	9/221 (4%)
Not Hispanic or Latino	197/219 (90%)	194/221 (88%)
Unknown	11/219 (5%)	18/221 (8%)
Smoking status		
Never smoker	111/219 (51%)	118/221 (53%)
Current smoker	16/219 (7%)	8/221 (4%)
Quit	92/219 (42%)	95/221 (43%)
Human papillomavirus p16 status		
Positive	207/219 (95%)	211/221 (95%)
Negative	12/219 (5%)	10/221 (5%)
Induction chemotherapy		
Yes	32/219 (15%)	29/221 (13%)
No	187/219 (85%)	192/221 (87%)
Eastern Cooperative Oncology Group performance status score		
0	174/219 (79%)	161/221 (73%)
1	45/219 (21%)	58/221 (26%)
2	0/219	2/221 (1%)
Charlson Comorbidity Index		
0	75/219 (34%)	80/221 (36%)
1	59/219 (27%)	56/221 (25%)
2	41/219 (19%)	47/221 (21%)
3+	44/219 (20%)	38/221 (17%)
Oropharynx sub-site		
Tonsil	83/219 (38%)	78/221 (35%)
Base of tongue	135/219 (62%)	142/221 (64%)
Pharyngeal wall	1/219 (<1%)	1/221 (<1%)
Tumour stage*		
T1	32/219 (15%)	30/221 (14%)
T2	78/219 (36%)	85/221 (38%)
T3	51/219 (23%)	59/221 (27%)
T4a	56/219 (26%)	44/221 (20%)
T4b	2/219 (1%)	3/221 (1%)

(Table 1 continues in next column)

	Intensity-modulated (photon) radiation therapy	Intensity-modulated proton therapy
(Continued from previous column)		
Nodal stage*		
N0	13/219 (6%)	10/221 (5%)
N1	13/219 (6%)	14/221 (6%)
N2a	15/219 (7%)	8/221 (4%)
N2b	110/219 (50%)	120/221 (54%)
N2c	67/219 (31%)	62/221 (28%)
N3	1/219 (<1%)	7/221 (3%)
Clinical stage*		
Stage III	18/219 (8%)	19/221 (9%)
Stage IVA	196/219 (89%)	191/221 (86%)
Stage IVB	5/219 (2%)	11/221 (5%)
Induction chemotherapy†		
Yes	24/202 (12%)	22/195 (11%)
No	178/202 (88%)	173/195 (89%)
Concurrent therapy†		
Yes	202/202 (100%)	195/195 (100%)
No	0/202	0/202
Radiation therapy†		
Intensity-modulated radiation therapy	136/202 (67%)	35/195 (18%)
Intensity-modulated proton therapy	66/202 (33%)	160/195 (82%)
Surgery†		
Yes	19/202 (9%)	13/195 (7%)
No	183/202 (91%)	182/195 (93%)
Treatment sequence†		
Induction chemotherapy, then concurrent therapy, then surgery	3/202 (1%)	1/195 (<1%)
Induction chemotherapy, then concurrent therapy	21/202 (10%)	20/195 (10%)
Concurrent therapy, then surgery	16/202 (8%)	12/195 (6%)
Concurrent therapy	162/202 (80%)	162/195 (83%)

Data are n/N (%), unless indicated otherwise. Percentages might not total 100% due to rounding. *Per the seventh edition of the American Joint Committee on Cancer staging manual. †Data provided for all patients who were randomly allocated to treatment groups and who did not withdraw from the trial before treatment.

Table 1: Baseline characteristics

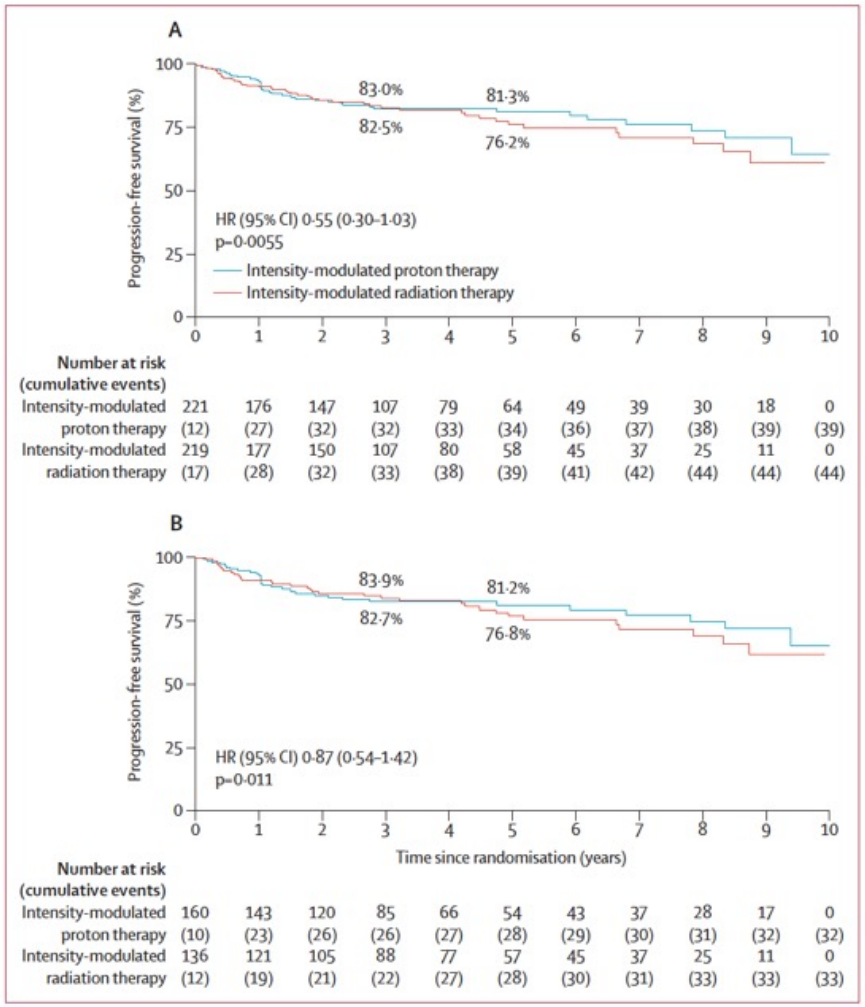


Figure 2: Progression-free survival in the intention-to-treat population (A) and the per-protocol population (B)
HR=hazard ratio.

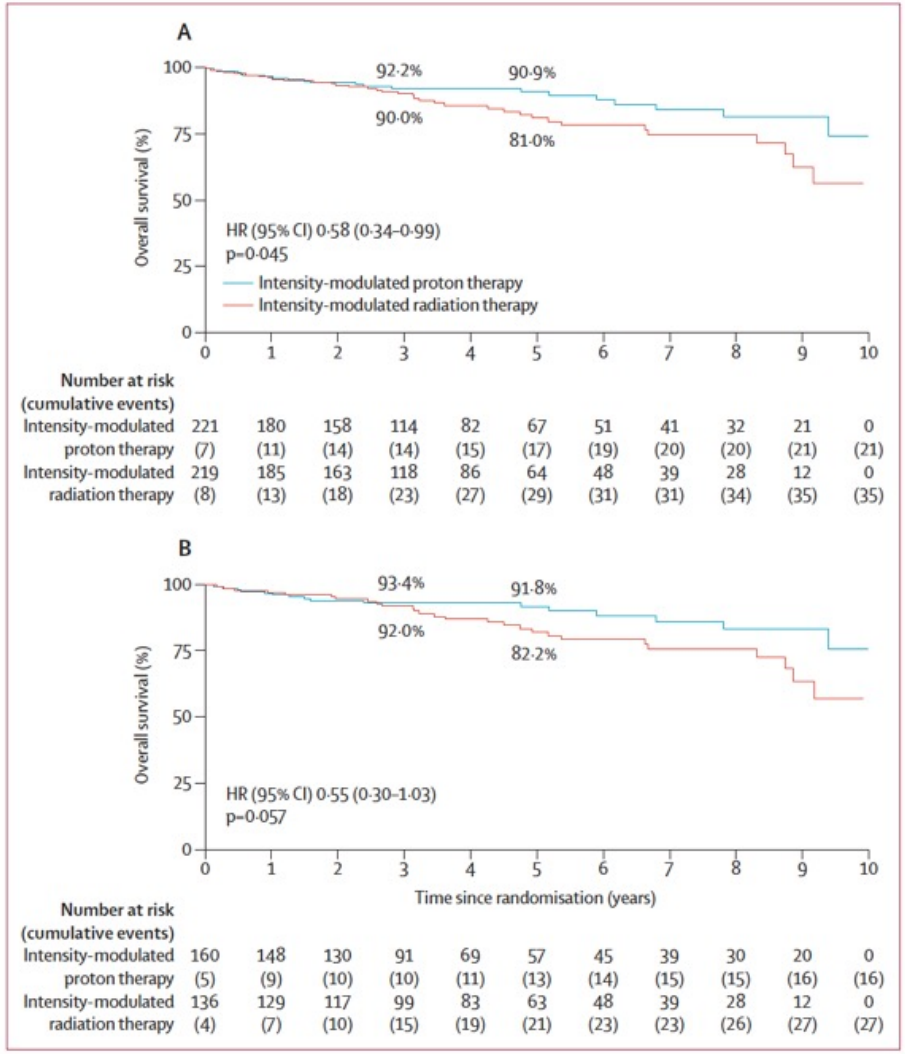


Figure 3: Overall survival in the intention-to-treat population (A) and the per-protocol population (B)
HR=hazard ratio.

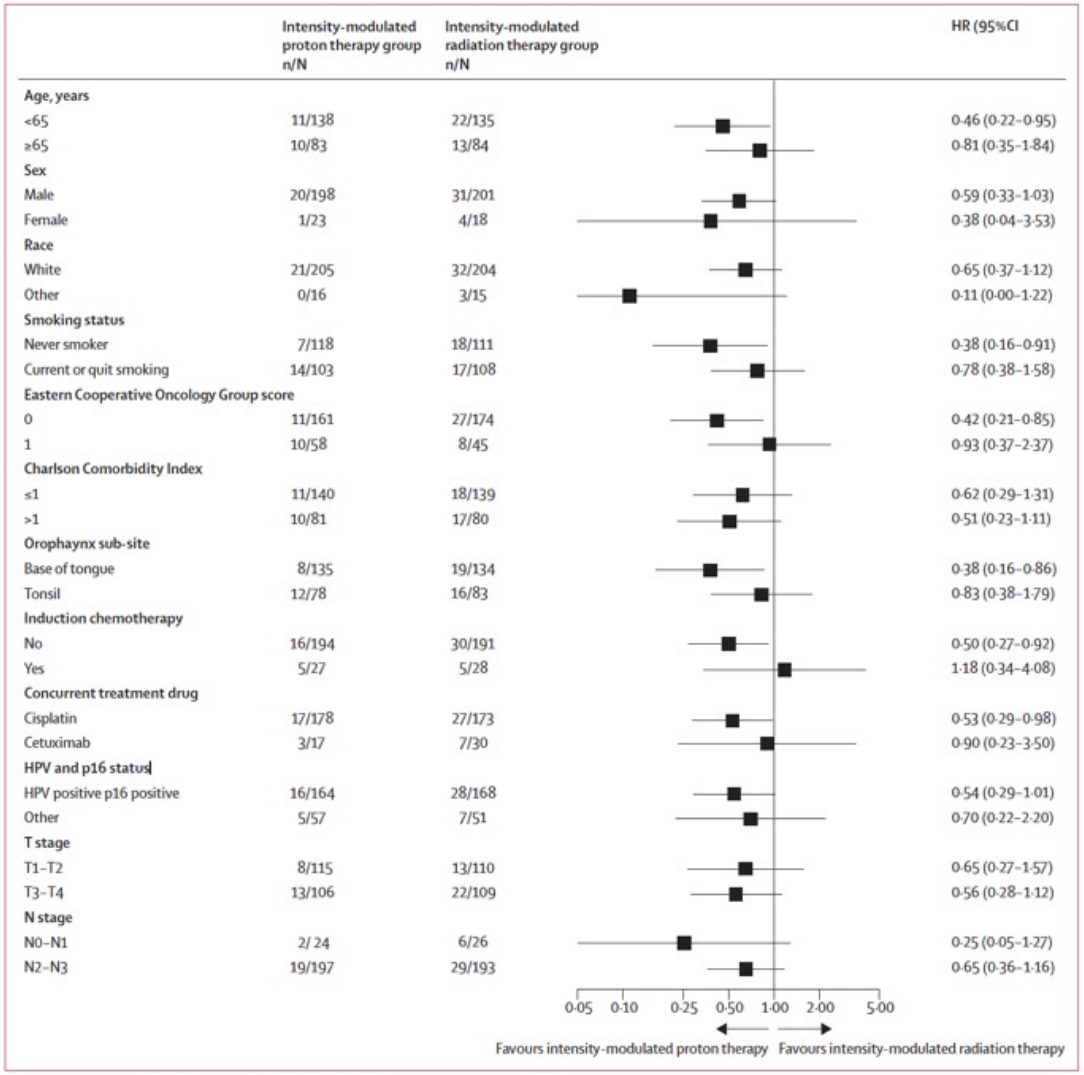


Figure 4: **Subgroup analysis of overall survival in the intention-to-treat population**
Data are number of events/number of patients at risk. HR=hazard ratio. HPV=human papillomavirus.

	Intensity-modulated (photon) radiation therapy (n=136)			Intensity-modulated proton therapy (n=160)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Lymphopenia	75 (55%)	46 (34%)	0	103 (64%)	18 (11%)	0
Oral mucositis	60 (44%)	2 (2%)	0	65 (41%)	0	0
Dysphagia	67 (49%)	0	0	54 (34%)	0	0
Oral pain	32 (24%)	0	0	39 (24%)	0	0
Weight loss	75 (55%)	0	0	74 (46%)	0	0
Dermatitis radiation	25 (18%)	0	0	39 (24%)	0	0
Nausea	19 (14%)	0	0	17 (11%)	0	0
Xerostomia (dry mouth)	61 (45%)	0	0	52 (33%)	0	0
Neutropenia	9 (7%)	4 (3%)	0	3 (2%)	1 (1%)	0
Fatigue	9 (7%)	0	0	5 (3%)	0	0
Thrombocytopenia	2 (1%)	0	0	1 (1%)	0	0
Dehydration	3 (2%)	0	0	5 (3%)	0	0
Oesophagitis	3 (2%)	0	0	5 (3%)	0	0
Vomiting	3 (2%	0	0	6 (4%)	0	0
Anaemia	2 (1%)	0	0	1 (1%)	0	0
Aspiration	1 (1%)	1 (1%)	0	0	0	0
Osteoradionecrosis	2 (1%)	0	0	1 (1%)	0	0
Suicide	0	0	2 (1%)	0	0	0

Data are n (%). Severe adverse events are defined as grade 3 or worse adverse events per the Common Toxicity Criteria Adverse Events framework. Over 95% of severe adverse events occurred during treatment or within 90 days after treatment. All patients received concurrent systemic therapy.

Table 2: **Severe adverse events in the per-protocol population**

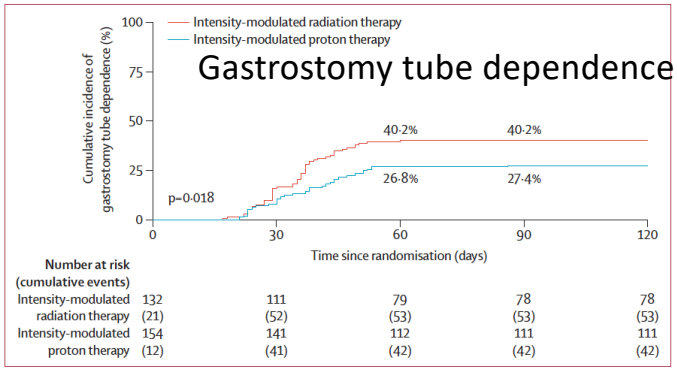


Figure 5: **Cumulative incidence of gastrostomy-tube dependence in the per-protocol population**
Patients with prophylactic gastrostomy tubes were excluded, four patients in the intensity-modulated radiation therapy group and six patients in the intensity-modulated proton therapy group.

Research in context

Evidence before this study

We identified relevant studies through searches of PubMed, ClinicalTrials.gov, and the WHO International Clinical Trial Registry Platform for open or closed randomised controlled trials from database inception to Dec 31, 2024. Search terms were "oropharyngeal carcinoma OR cancer OR neoplasm", "IMPT versus IMRT", "protons versus photons", "randomized trials", and "phase III trials". We found no published randomised controlled trials that directly compared intensity-modulated proton therapy (IMPT) with intensity-modulated radiation (photon) therapy (IMRT) for patients with oropharyngeal cancer. We found one case-controlled observational study that concluded that IMPT was associated with reduced rates of feeding tube dependency and severe weight loss compared with IMRT with similar disease outcomes. However, these data alone are insufficient to recommend IMPT over IMRT concurrent with systemic therapy for patients with advanced stage oropharyngeal cancer. There are two ongoing phase 3 head and neck trials comparing IMPT with IMRT: the TORPEdO trial in the UK (ISRCTN16424014) and the Danish Head and Neck Cancer Group 35 trial in Denmark (NCT04607694). Additionally, the ARTSCAN V phase 2 randomised controlled trial in Sweden is ongoing and comparing IMRT with IMPT for head and neck patients with tonsillar cancer (NCT03829033).

Added value of this study

To the best of our knowledge, this is the first phase 3 randomised controlled trial that compares proton versus photon radiotherapy for patients with advanced stage oropharyngeal cancer. This study shows that IMPT is non-inferior to IMRT for progression-free survival, IMPT reduces the hazard of death by 42%, and IMPT reduces high-grade toxicity relative to IMRT.

Implications of all the available evidence

This study shows that IMPT is a safe and effective treatment that de-intensifies concurrent chemoradiation strategies with IMRT. We recommend proton therapy as a new standard-of-care option for patients with head and neck oropharyngeal cancer. Although early outcomes suggest an improvement in overall survival with IMPT compared with IMRT, long-term follow-up analysis and additional phase 3 trial data will provide a robust assessment of survival outcomes in patients with oropharyngeal cancer.

Lancet Countdown on health and climate change in Africa: an international collaboration for locally led research and action

Climate change inflicts substantial economic damage on developing African nations, threatening progress towards the UN Sustainable Development Goals. There are synergies between actions needed to tackle climate change and other ongoing development priorities for Africa, including infectious disease control, facilitating clean energy access, reducing air pollution, tackling malnutrition and food insecurity, and providing universal health coverage. Action to protect human health against climate change needs to be integrated into all systems that are responsible for delivering essential services and implementing policies across all sectors that underpin the attainment of key development priorities for Africa. These systems include the Sustainable Development Goals and the African Union's 2063 Agenda for building The Africa We Want, and the ongoing negotiations and work programmes in the UN Framework Convention on Climate Change. Adequate stocktaking of and access to robust data and scientific evidence is needed to support this effort and guide priorities for policies that protect and promote health and for monitoring progress over time. In response to this need, the *Lancet* Countdown is launching a new initiative to bring together a transdisciplinary research collaboration to help build regional capacity, strengthen existing networks, generate evidence, and mobilise data across numerous domains at the climate change and health nexus in Africa.

	WHO member states that have committed to ATACH up to 2023, n (%)	HNAP developed up to 2023, n (%)	HNAP developed since 2020, n (%)	HNAP under development in 2023, n (%)
Africa	28/47 (60%)	16 (59%)	7 (26%)	2 (7%)
Americas	14/35 (40%)	9 (64%)	6 (43%)	3 (21%)
Eastern Mediterranean	14/22 (64%)	3 (23%)	1 (8%)	3 (23%)
Europe	13/53 (25%)	7 (54%)	4 (31%)	1 (8%)
South-East Asia	7/11 (64%)	5 (71%)	3 (31%)	2 (29%)
Western Pacific	7/27 (26%)	3 (43%)	2 (29%)	3 (43%)
Total	82/195 (42%)	43 (52%)	23 (28%)	14 (17%)

ATACH=Alliance for Transformative Action on Climate Change and Health. HNAP=health national adaptation plan.

Table: **Distribution of WHO member states and non-member states committed to ATACH and whether they have developed an HNAP, by WHO region**

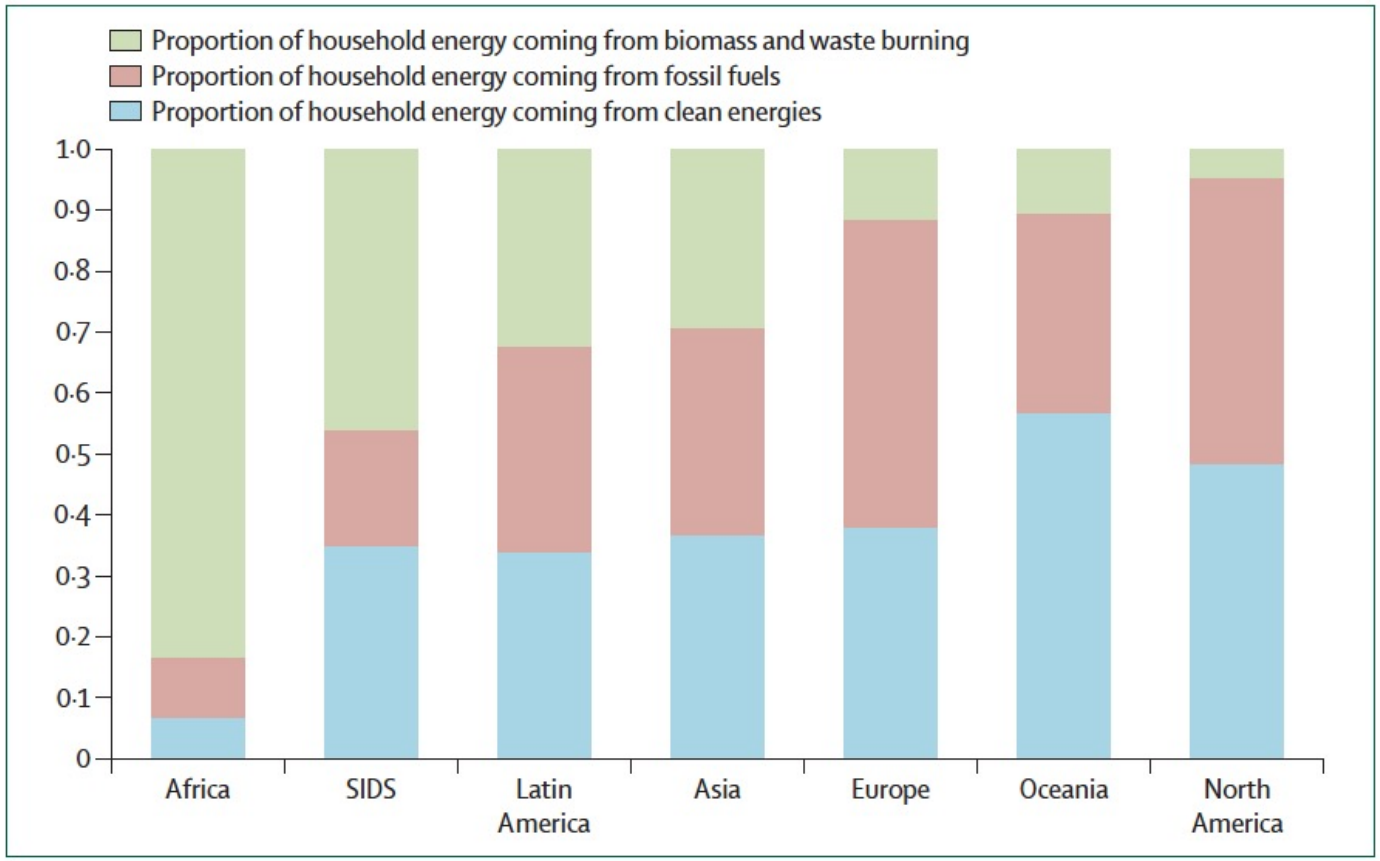


***Figure 1*: Breakdown of energy sources for household energy consumption in 2021, by *Lancet* Countdown region**

SIDS=Small Island Developing States.

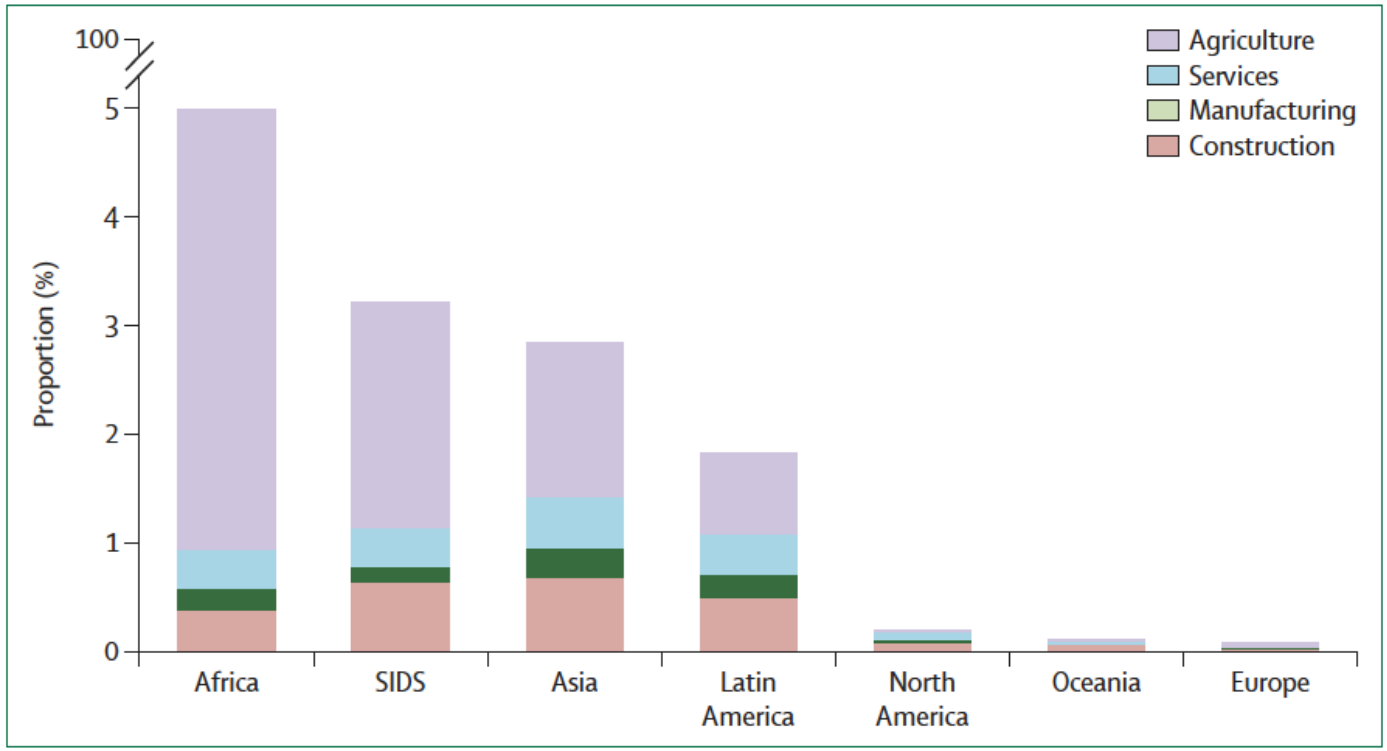


Figure 2: **Average potential loss of earnings from heat-related labour capacity reduction in 2023 as a share of gross domestic product according to sector of employment**
SIDS=Small Island Developing States.

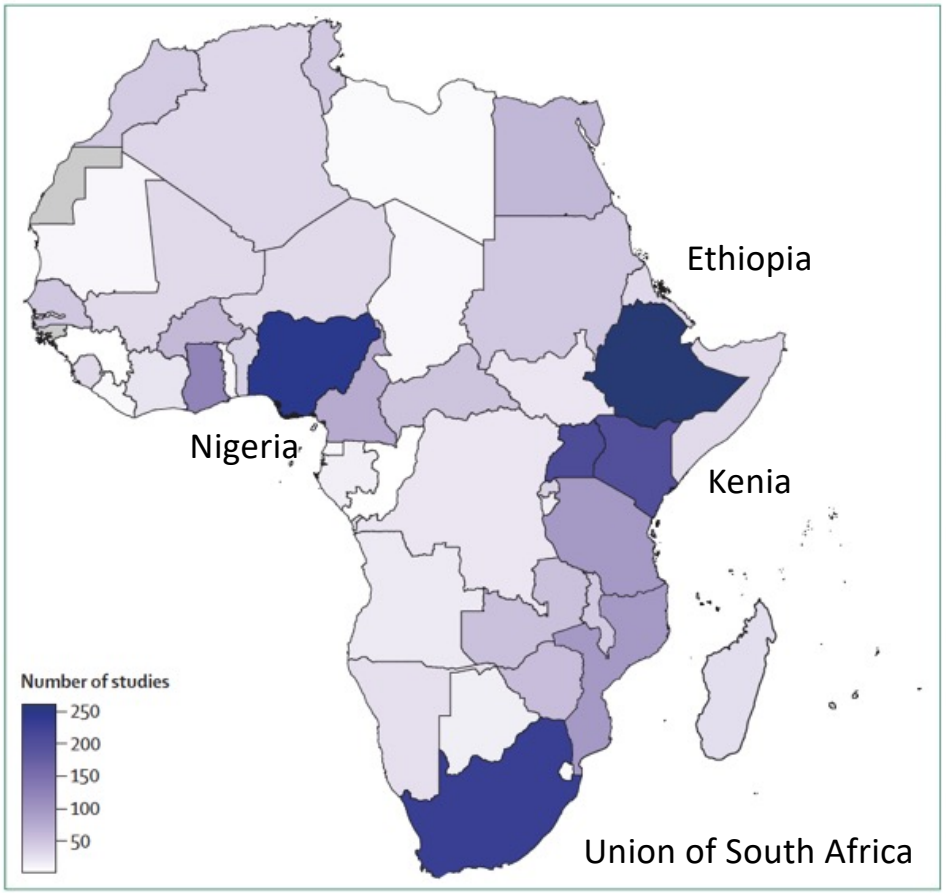


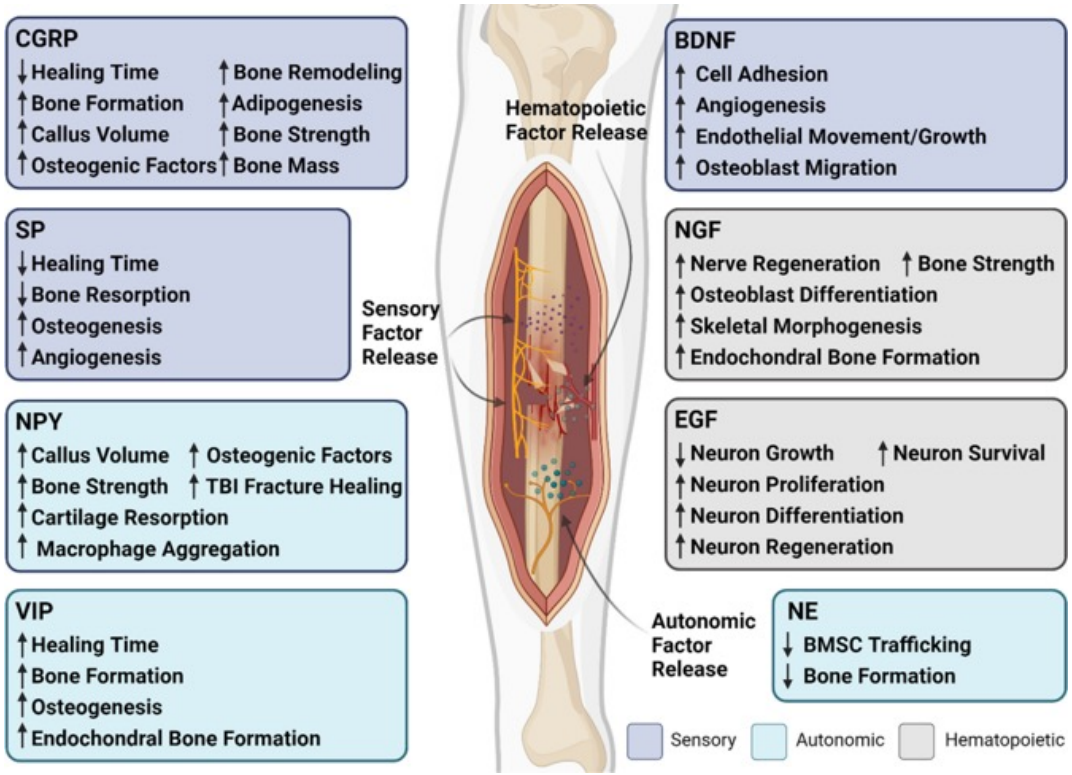
Figure 3: Scientific publications on health and climate change in Africa 1990–2023

Conclusion

The impacts of climate change on health in Africa are established and projected to increase in the future. High temperatures, drought, and extreme weather events are the most pressing threats to the wellbeing of African populations. Africa's response capacity is currently limited by and dependent on factors such as adequate access to finance, scientific evidence, new technology, and human and institutional capacity.

Given Africa's human and natural resource potential and specific vulnerability in tackling the global climate crisis and other international priorities, adaptation and mitigation efforts are paramount to safeguarding human health and wellbeing in Africa. African communities hold a wealth of knowledge from empirical lived experiences that remains untapped in addressing the growing health threats of climate change and building context-specific resilience.

Analgesics can influence bone healing, often by blocking pain signals that originate from sensory nerves crucial for repair, with NSAIDs potentially impairing healing in adults (though less so in children) and opioids like morphine weakening bone callus formation, making pain management a delicate balance between patient comfort and optimal healing, requiring careful selection of agents.



Not just a pain in the bone

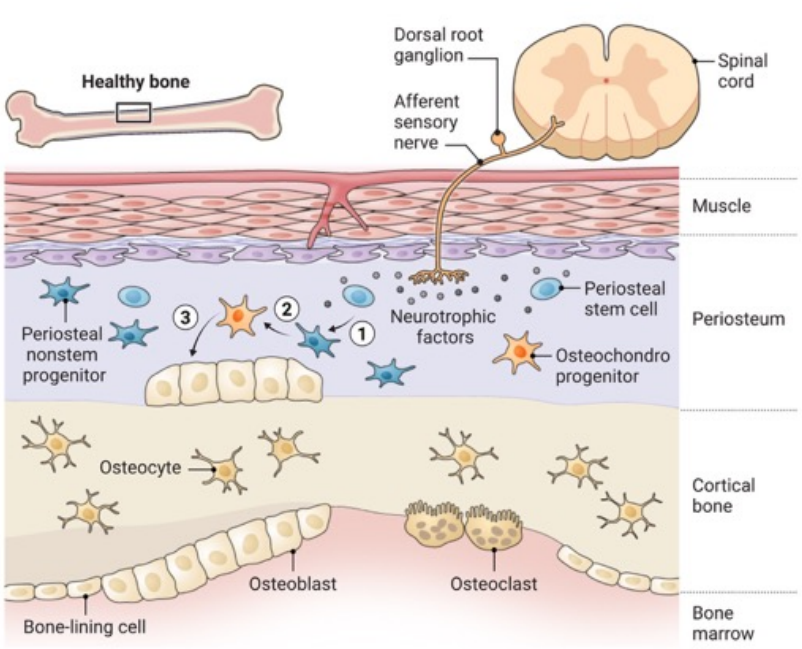
Growth factors secreted by sensory nerves promote fracture healing

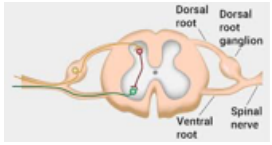
The skeleton greatly expands in size from birth to adulthood and continues to remodel throughout adult life, completely replacing itself every 10 years. But it is also able to regenerate after injury, efficiently regrowing lost bone. Bone injuries are common, with an estimated 6 million to 10 million fractures occurring each year in the United States. A lack of efficient healing can result in long-term disability, and in the geriatric population, complications from fractures are associated with increased morbidity and mortality. Because bone repair reflects the successful integration of multiple cellular and molecular processes, it is challenging to precisely define the signaling hierarchy that produces optimal healing. Xu *et al*. report an unexpected role for sensory nerves in bone healing, providing insights into communication between the nervous system and the cells responsible for bone repair.

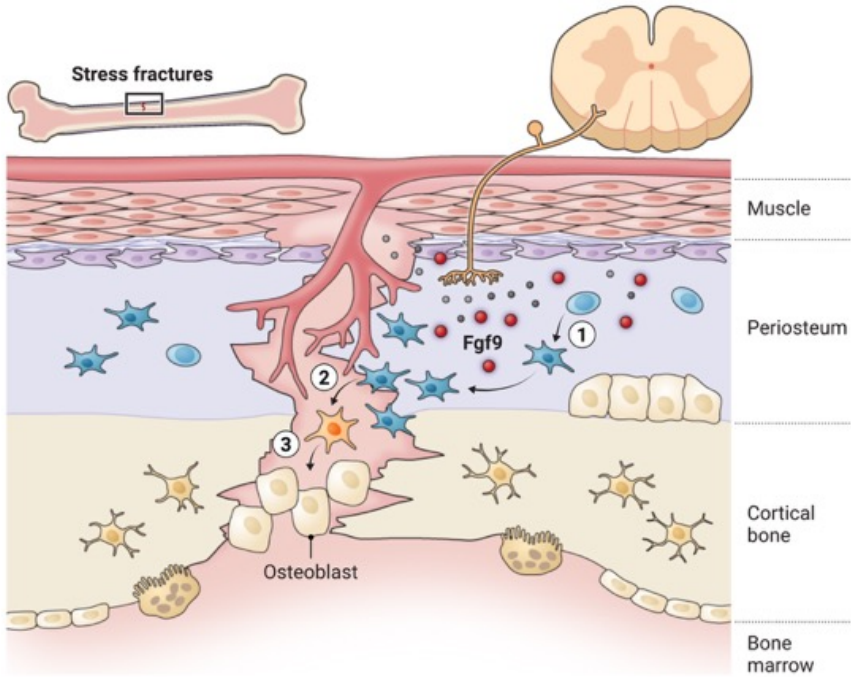
The periosteum serves as a crucial reservoir of stem and progenitor cells. Upon injury, cells resident within the periosteal niche proliferate and differentiate into the fracture callus to form chondrocytes that fill the gap created by the break. The absence of a periosteum, ablation of specific periosteal stem cell populations, or deprivation of key signaling molecules that activate periosteal stem and progenitor cells—including bone morphogenetic proteins (BMPs), Wnts, and fibroblast growth factors (FGFs)—markedly impair bone healing. The fracture callus is ultimately removed by osteoclasts, creating space for osteoblasts to lay down new bone (osteogenesis) over a time period that can last for more than 20 days in mice and several months in humans.

Sensory nerves encourage bone formation

New bone is formed as part of skeletal remodeling and growth and to repair fractures. This generation of new bone involves (**1**) the differentiation of periosteal stem cells into periosteal nonstem progenitors. (**2**) These then become osteochondro progenitors, which can (**3**) differentiate into osteoblasts that lay down bone. In the adult healthy skeleton, the periosteum is richly innervated by afferent sensory nerves originating from the dorsal root ganglia. These nerves function as pain sensors and release neurotrophic factors, which support bone formation by encouraging the differentiation of periosteal stem cells. In response to stress fractures, sensory nerve fibers release fibroblast growth factor 9 (Fgf9). This neural-derived Fgf9 is a critical mediator of neural–bone cross-talk during repair by promoting stem-cell differentiation, enhancing generation of osteoblasts, and ultimately supporting bone regeneration.

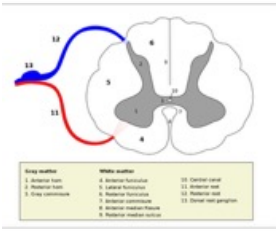






The adult skeleton is richly innervated by afferent sensory nerves that originate from the dorsal root of the spinal cord, and sensory nerve fibers located in the periosteum regulate bone remodeling and metabolism. These nerves can also communicate with bone cells during successful bone healing: interruption of innervation results in blunted vascularization, impaired skeletal stem cell differentiation, and delayed healing. Xu *et al.* performed single-cell RNA-sequencing on limb-innervating dorsal root ganglia (DRG) neurons in mice and found that gene expression dramatically changes in response to fracture. They analyzed the data using a previously developed tool that infers intercellular communication networks from single-cell RNA-sequencing data (interactome analysis). From this analysis, they deduced that DRG neurons communicate with all the major cell types present in the fracture callus, particularly with the stem and progenitor cells that are important for osteogenesis and with endothelial cells involved in vascularization. Unexpectedly, Xu e*t al*. identified neural-derived Fgf9 as a critical mediator of neural–bone cross-talk during repair. A role of Fgf9 in bone repair has been previously reported, and Xu *et al.* built on that knowledge by using mouse genetics to markedly reduce expression of Fgf9 specifically in dorsal root ganglia and sensory neurons; this showed that DRG neurons present at the fracture site secrete Fgf9, which in turn promotes bone regeneration

"Dorsal root ganglion" wird auf Deutsch als Hinterwurzelganglion oder Spinalganglion (auch Dorsalganglion, Ganglion sensorium nervi spinalis) bezeichnet.



Muscle stretch reflexes run over dorsal root ganglia

This fun hobby may reduce your dementia risk by 76 percent

What are the best ways to keep my brain sharp as I age?

There are several science-based ways to lower your risk of dementia — but one especially fun option might surprise you: dancing.

Dancing combines some of the best elements known to be associated with longevity: exercise, creativity, balance and social connection. You're investing the same time as walking or other exercise activities but may be getting much more out of it.

In fact, one study found that people who danced frequently (more than once a week) had a 76 percent lower risk of dementia than those who did so rarely.