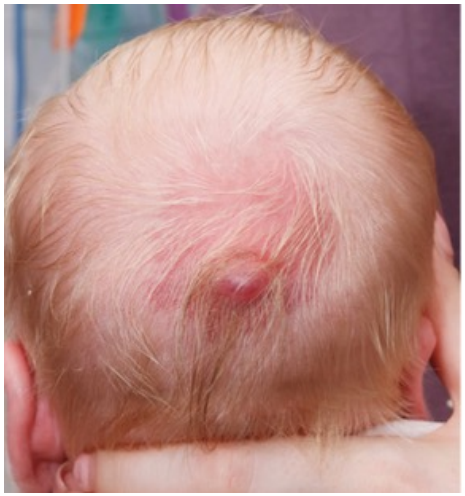
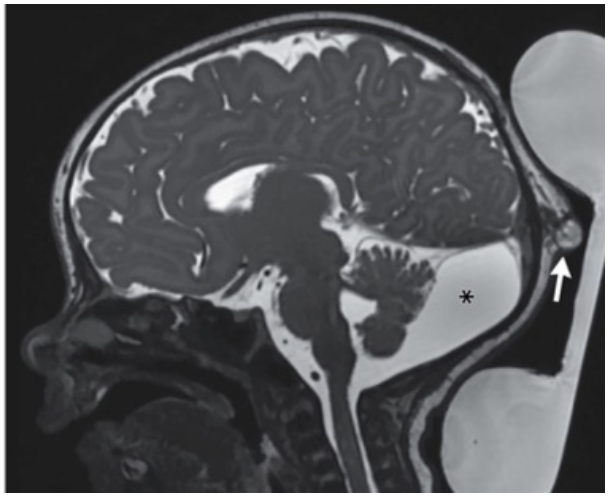
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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 5-week-old boy was brought in for evaluation of a painful lump on his scalp that had been present since birth. The otherwise healthy baby had been born at term. Ultrasonography of the lesion showed a subcutaneous structure of mixed echogenicity. Physical examination and magnetic resonance imaging of the head is shown. What is the most likely etiology of the lump?

Atretic cephalocele

Cephalohematoma

Dermoid cyst

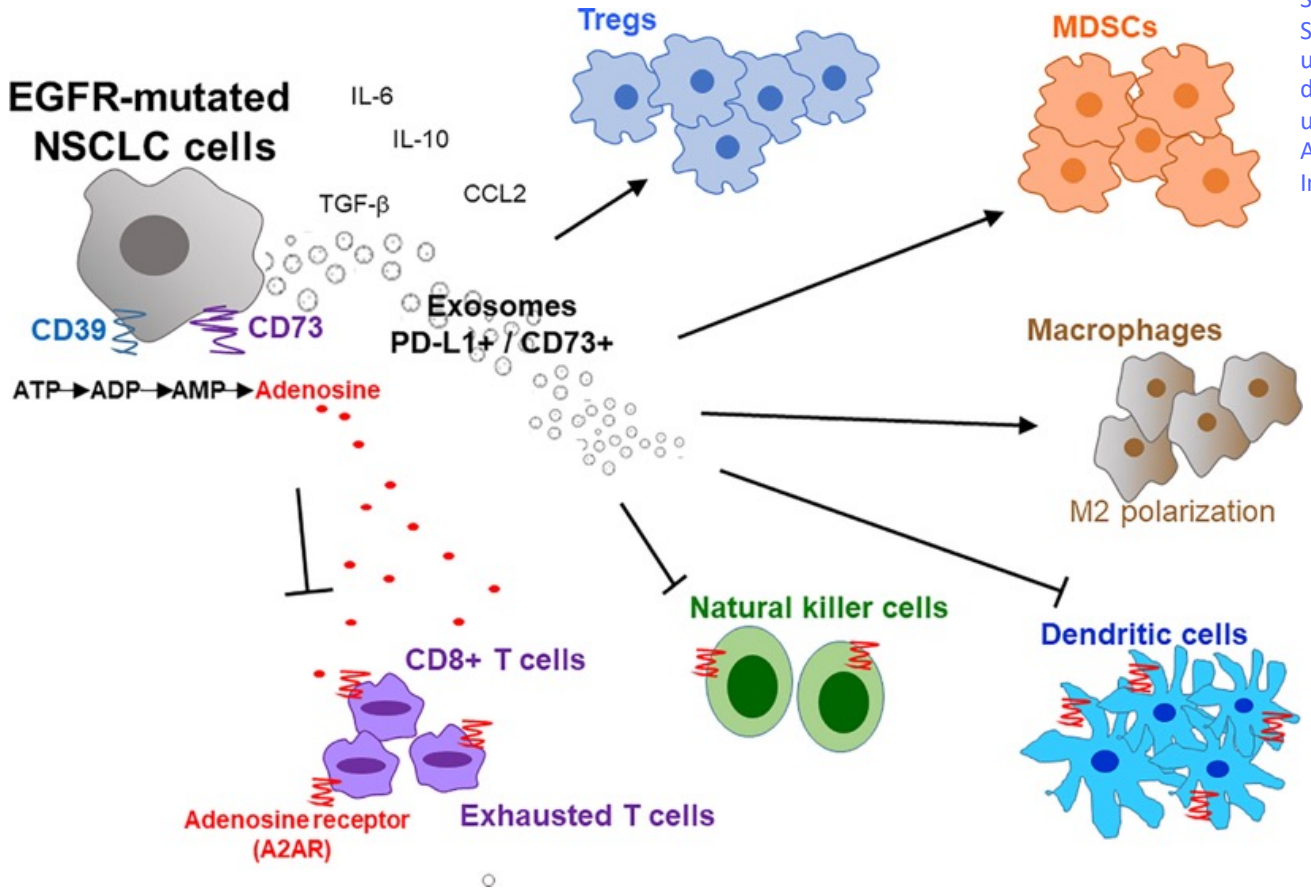
Lipoma

Meningocele

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. The ring of dark, coarse hair seen around the lesion, consistent with the “hair collar” sign, raised concern for a neural-tube defect, thus a biopsy was not performed. The MRI showed an extracranial cystic lesion with high signal intensity on T2-weighted sequences and low signal intensity on T1-weighted sequences. Blake’s pouch cyst (a cystic malformation on the posterior fossa) was also incidentally identified. Neurosurgical resection of the lesion was performed, and at 1-year follow-up, the child was developing normally.

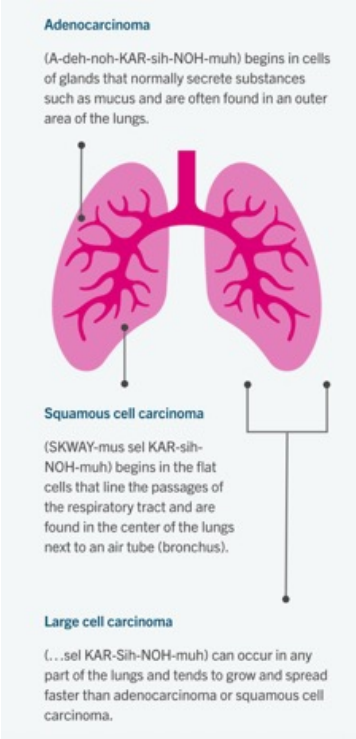
Das nicht-kleinzellige Lungenkarzinom (NSCLC) mit einer Mutation des epidermalen Wachstumsfaktorrezeptors (EGFR) stellt eine spezifische Untergruppe von Lungenkrebs dar, die im Jahr 2026 durch hochgradig personalisierte Therapieansätze gekennzeichnet ist. Etwa 10–15 % der kaukasischen und bis zu 50 % der asiatischen Patienten mit Adenokarzinomen weisen diese Treibermutation auf, die ein unkontrolliertes Zellwachstum fördert.

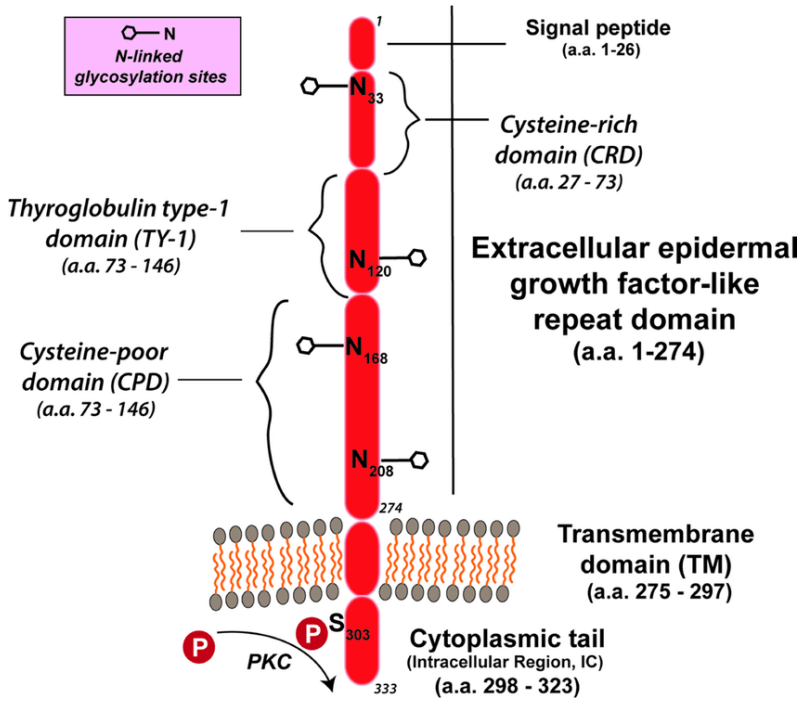
MDSC steht für Myeloid-Derived Suppressor Cells (myeloische Suppressorzellen), eine Gruppe unreifer Knochenmarkzellen, die das Immunsystem unterdrücken und bei Krankheiten wie Krebs, Autoimmunerkrankungen und Infektionen vermehrt auftreten



TROP2 ist ein transmembranes Glykoprotein, das natürlicherweise bei der Embryonalentwicklung eine Rolle spielt, in gesundem Erwachsenengewebe jedoch nur in geringem Maße vorkommt. In vielen Krebszellen wird es hingegen **überexprimiert**, was es zu einem idealen Angriffspunkt für zielgerichtete Therapien macht. Es fördert als Onkogen das Tumorwachstum, die Zellteilung und die Metastasierung.. In der modernen Onkologie des Jahres **2026** ist **TROP2** (Trophoblast Cell Surface Antigen 2) einer der bedeutendsten Biomarker und therapeutischen Zielpunkte bei der Behandlung solider Tumoren.

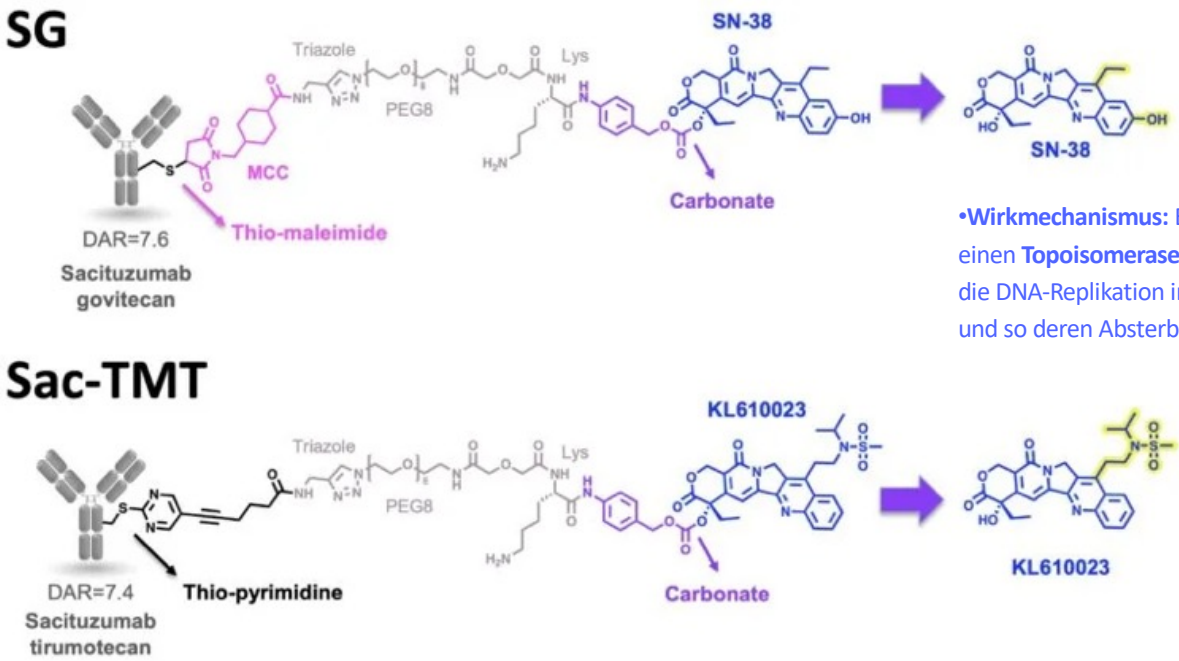
NSCLC





Sac.TMT (**Sacituzumab Tirumotecan**) ist ein neuartiger Antikörper-Wirkstoff-Konjugat (ADC) zur zielgerichteten Krebstherapie, der eine Antikörper-Komponente, die an das TROP2-Protein bindet, mit einem zytotoxischen Medikament verbindet, um Krebszellen zu bekämpfen. Es wird in klinischen Studien zur Behandlung verschiedener Krebsarten untersucht, darunter metastasierter dreifach-negativer Brustkrebs, nicht-kleinzelliger Lungenkrebs (NSCLC) und Gebärmutterhalskrebs, oft mit vielversprechenden Ergebnissen bezüglich Überlebensvorteilen gegenüber Standardtherapien.

SN-38 ist der **hochwirksame, aktive Metabolit des Krebsmedikaments Irinotecan** (CPT-11) und gehört zur Klasse der Topoisomerase-I-Inhibitoren; es ist etwa 1000-fach stärker als Irinotecan und wirkt, indem es die Zellteilung blockiert und so den Zelltod (Apoptose) in Krebszellen auslöst

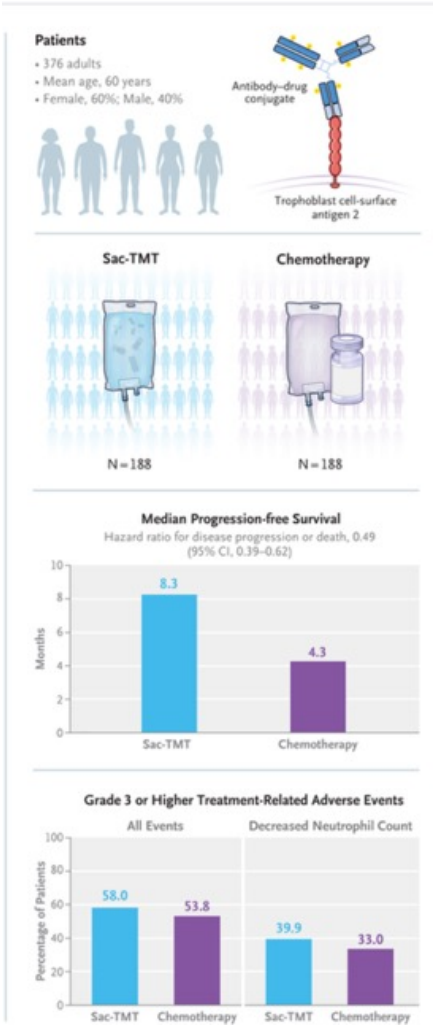


•**Wirkmechanismus:** Es handelt sich um einen **Topoisomerase-I-Inhibitor**, der die DNA-Replikation in Krebszellen stört und so deren Absterben herbeiführt.

Sacituzumab Tirumotecan in EGFR-TKI–Resistant, EGFR-Mutated Advanced NSCLC

Sacituzumab tirumotecan (sac-TMT) is an antibody–drug conjugate targeting trophoblast cell-surface antigen 2 that has shown significant survival benefits in patients with *EGFR*-mutated non–small-cell lung cancer (NSCLC) that has progressed after epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy and platinum-based chemotherapy.

In this phase 3 trial, we enrolled patients with *EGFR*-mutated locally advanced or metastatic nonsquamous NSCLC that had progressed after EGFR-TKI therapy. The patients were randomly assigned, in a 1:1 ratio, to receive sac-TMT monotherapy or pemetrexed plus platinum-based chemotherapy. The primary end point was progression-free survival as assessed by blinded independent review. Overall survival was a hierarchically tested key secondary end point. In the interim analysis of progression-free survival as assessed by blinded independent review, sac-TMT monotherapy met the prespecified criterion for significance (two-sided P<0.0001); we report here the prespecified final analysis of progression-free survival and the preplanned interim analysis of overall survival.



Epidermal growth factor receptor (*EGFR*) mutations are present in a substantial proportion of patients with non–small-cell lung cancer (NSCLC). For patients with *EGFR*-mutated advanced NSCLC who are not candidates for curative treatment or for those with metastatic disease, third-generation EGFR tyrosine kinase inhibitors (TKIs) are the standard first-line therapy. However, acquired resistance to EGFR-TKIs inevitably develops, and subsequent treatment options are limited. Platinum-based doublet chemotherapy remains a standard of care in this context, but its efficacy is modest. Recent trials have explored chemotherapy-based combination strategies incorporating ivonescimab (an anti–programmed cell death protein 1 [PD-1] and vascular endothelial growth factor bispecific antibody), sintilimab (a PD-1 inhibitor) with a bevacizumab biosimilar drug, amivantamab (an EGFR and c-Met bispecific antibody) with or without lazertinib (an EGFR inhibitor for patients with *EGFR* exon 19 deletion), and human epidermal growth factor receptor (HER) 3–directed antibody–drug conjugate. These regimens have shown improvements in progression-free survival outcomes; however, overall survival benefits remain uncertain. Thus, there remains a need for new therapies for patients with EGFR-TKI–resistant, *EGFR*-mutated NSCLC.

Sacituzumab tirumotecan (sac-TMT) is an antibody–drug conjugate targeting trophoblast cell-surface antigen 2 (Trop-2) that was developed by conjugating the antibody to a belotecan-derived topoisomerase I inhibitor.

Procedures

The patients were randomly assigned with the use of a centralized stratified block randomization system in a 1:1 ratio to receive either sac-TMT or pemetrexed plus platinum-based chemotherapy. Stratification factors included previous treatment with third-generation EGFR-TKIs (first-line use, second-line use, or no previous use) and brain metastases (presence or absence). Sac-TMT was administered intravenously at a dose of 5 mg per kilogram of body weight on day 1 and day 15 of each 28-day cycle. The chemotherapy regimen consisted of pemetrexed (500 mg per square meter of body-surface area) plus the investigator's choice of carboplatin (area under the curve of 5 mg per milliliter per minute) or cisplatin (75 mg per square meter), all administered on day 1 of each 21-day cycle for up to four cycles, followed by pemetrexed maintenance therapy.

Assessments

Tumor response and progression were evaluated by blinded independent review according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

End Points

The primary end point was progression-free survival as assessed by blinded independent review according to RECIST, version 1.1. Secondary end points included overall survival; progression-free survival as assessed by investigators; objective response (complete or partial response), disease control, and response duration (each assessed by both blinded independent review and investigators); safety; and patient-reported outcomes.

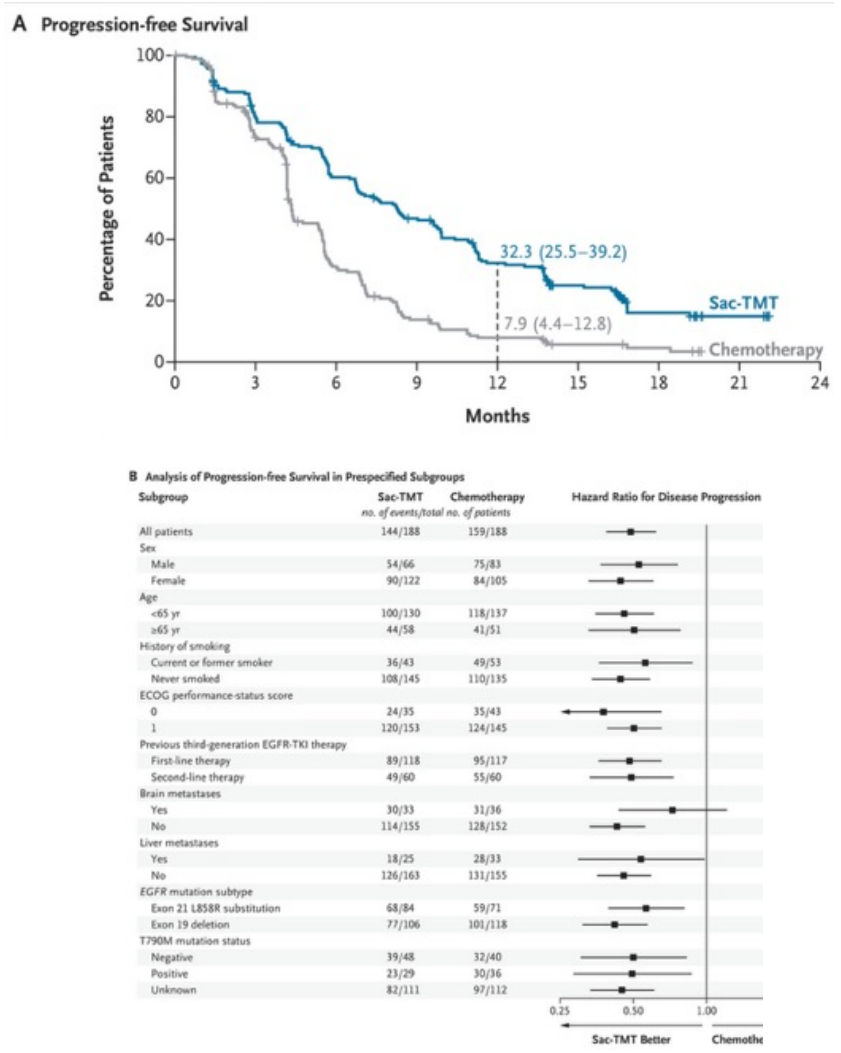
Characteristic	Sacituzumab Tirumotecan (N=188)	Chemotherapy (N=188)
Age		
Median (range) — yr	60 (31–75)	59 (33–75)
≥65 yr — no. (%)	58 (30.9)	51 (27.1)
Male sex — no. (%)	66 (35.1)	83 (44.1)
Asian race — no. (%)	188 (100.0)	188 (100.0)
Smoking history — no. (%)		
Current or former smoker	43 (22.9)	53 (28.2)
Never smoked	145 (77.1)	135 (71.8)
ECOG performance-status score — no. (%)†		
0	35 (18.6)	43 (22.9)
1	153 (81.4)	145 (77.1)
Adenocarcinoma — no. (%)	188 (100.0)	188 (100.0)
Disease stage — no. (%)‡		
IIIB or IIIC	6 (3.2)	3 (1.6)
IV	182 (96.8)	185 (98.4)
Brain metastases — no. (%)	33 (17.6)	36 (19.1)
Liver metastases — no. (%)	25 (13.3)	33 (17.6)
≥3 Metastatic sites — no. (%)	128 (68.1)	126 (67.0)
EGFR mutation subtype — no. (%)§		
Exon 21 L858R substitution	84 (44.7)	71 (37.8)
Exon 19 deletion	106 (56.4)	118 (62.8)
Other	8 (4.3)	7 (3.7)
T790M mutation status — no. (%)¶		
Negative	48 (25.5)	40 (21.3)
Positive	29 (15.4)	36 (19.1)
Unknown	111 (59.0)	112 (59.6)
Previous third-generation EGFR-TKI — no.(%)‖	178 (94.7)	178 (94.7)
First-line therapy	118 (62.8)	117 (62.2)
Second-line therapy	60 (31.9)	60 (31.9)

Efficacy End Points as Assessed by Blinded Independent Review (Intention-to-Treat Population).

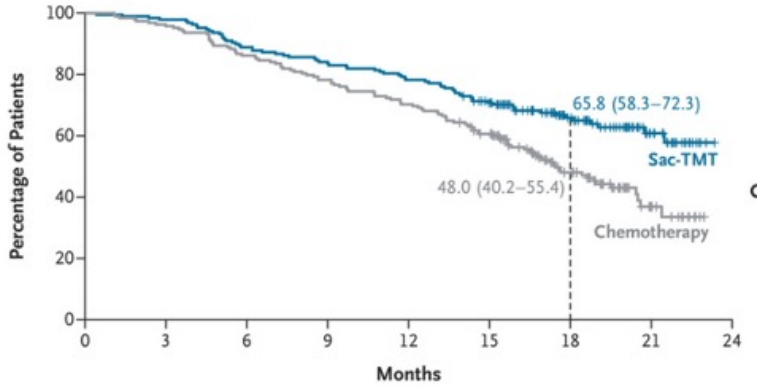
End Point	Sacituzumab Tirumotecan (N=188)	Chemotherapy (N=188)	Difference (95% CI)
Best overall response — no. (%)			
Complete response	1 (0.5)	0	
Partial response	113 (60.1)	81 (43.1)	
Stable disease	50 (26.6)	70 (37.2)	
Progressive disease	20 (10.6)	26 (13.8)	
Imaging could not be evaluated	1 (0.5)	0	
No assessment†	3 (1.6)	11 (5.9)	
Objective response — no. (% [95% CI])‡	114 (60.6 [53.3–67.7])	81 (43.1 [35.9–50.5])	17.0 (7.0 to 27.1)
Disease control — no. (% [95% CI])§	164 (87.2 [81.6–91.6])	151 (80.3 [73.9–85.7])	6.7 (–0.7 to 14.0)
Median response duration (95% CI) — mo¶	8.3 (6.2–10.0)	4.2 (3.0–4.4)	
Response duration ≥12 mo (95% CI) — %‖	36.3 (27.3–45.3)	8.1 (3.3–15.8)	

Treatment-Related Adverse Events (Safety Population).

Event	Sacituzumab Tirumotecan (N=188)		Chemotherapy (N=182)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	number of patients (percent)			
Any treatment-related adverse event	188 (100.0)	109 (58.0)	179 (98.4)	98 (53.8)
Leading to dose reduction	57 (30.3)	—	41 (22.5)	—
Leading to dose interruption	69 (36.7)	—	60 (33.0)	—
Leading to treatment discontinuation	0	—	1 (0.5)	—
Leading to death†	0	—	1 (0.5)	—
Any treatment-related serious adverse event	17 (9.0)	—	32 (17.6)	—
Treatment-related adverse event with an incidence of ≥10% in either group				
Anemia	159 (84.6)	21 (11.2)	139 (76.4)	26 (14.3)
White-cell decreased	157 (83.5)	52 (27.7)	127 (69.8)	40 (22.0)
Alopecia	157 (83.5)	0	17 (9.3)	0
Neutrophil count decreased	142 (75.5)	75 (39.9)	126 (69.2)	60 (33.0)
Stomatitis‡	121 (64.4)	9 (4.8)	9 (4.9)	0
Nausea	89 (47.3)	1 (0.5)	86 (47.3)	2 (1.1)
Anorexia	78 (41.5)	0	58 (31.9)	0
Fatigue	72 (38.3)	7 (3.7)	73 (40.1)	4 (2.2)
Weight loss	52 (27.7)	0	28 (15.4)	1 (0.5)
Thrombocytopenia	51 (27.1)	4 (2.1)	85 (46.7)	30 (16.5)
Vomiting	50 (26.6)	0	39 (21.4)	1 (0.5)
Alanine aminotransferase increased	46 (24.5)	1 (0.5)	63 (34.6)	2 (1.1)
Constipation	39 (20.7)	0	31 (17.0)	0
Aspartate aminotransferase increased	35 (18.6)	1 (0.5)	63 (34.6)	2 (1.1)
Rash	35 (18.6)	0	14 (7.7)	0
Lymphocyte count decreased	30 (16.0)	6 (3.2)	23 (12.6)	7 (3.8)
Hypoalbuminemia	23 (12.2)	0	27 (14.8)	0
γ-Glutamyltransferase increased	20 (10.6)	2 (1.1)	27 (14.8)	3 (1.6)
Hyperuricemia	20 (10.6)	0	17 (9.3)	0
Diarrhea	19 (10.1)	1 (0.5)	6 (3.3)	0
Hypokalemia	14 (7.4)	4 (2.1)	23 (12.6)	7 (3.8)

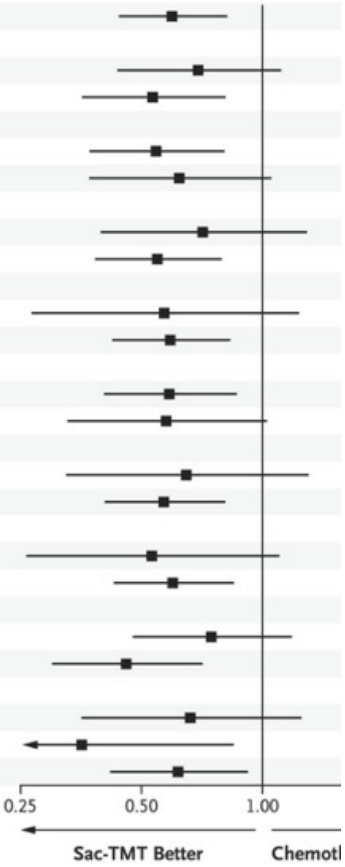


A Overall Survival



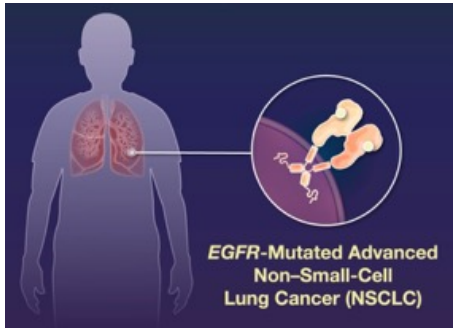
B Analysis of Overall Survival in Prespecified Subgroups

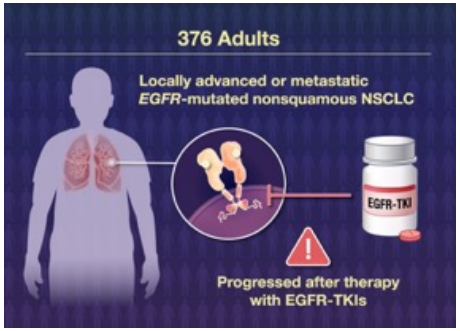
Subgroup	Sac-TMT	Chemotherapy
	no. of events/total no. of patients	
All patients	67/188	101/188
Sex		
Male	28/66	47/83
Female	39/122	54/105
Age		
<65 yr	41/130	69/137
≥65 yr	26/58	32/51
History of smoking		
Current or former smoker	18/43	29/53
Never smoked	49/145	72/135
ECOG performance-status score		
0	10/35	19/43
1	57/153	82/145
Previous third-generation EGFR-TKI therapy		
First-line therapy	44/118	67/117
Second-line therapy	20/60	29/60
Brain metastases		
Yes	13/33	21/36
No	54/155	80/152
Liver metastases		
Yes	12/25	22/33
No	55/163	79/155
EGFR mutation subtype		
Exon 21 L858R substitution	36/84	38/71
Exon 19 deletion	31/106	63/118
T790M mutation status		
Negative	18/48	21/40
Positive	7/29	20/36
Unknown	42/111	60/112

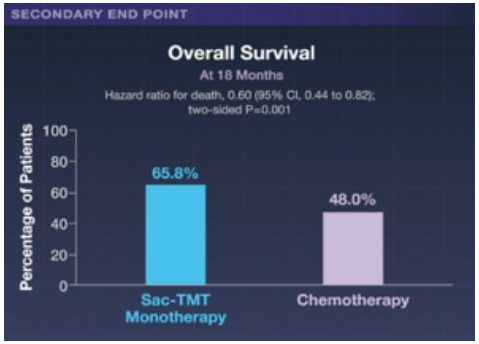


Interim Analysis of Overall Survival.

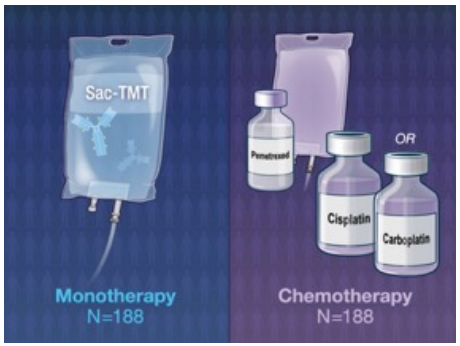
Shown are the results from the intention-to-treat population (all 376 patients who underwent randomization) as of the data-cutoff date of July 6, 2025. Panel A shows Kaplan–Meier estimates of overall survival. Panel B shows a forest plot of overall survival in prespecified subgroups. Overall survival was defined as the time from randomization to death from any cause. For Panel B, the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. NE denotes could not be estimated.

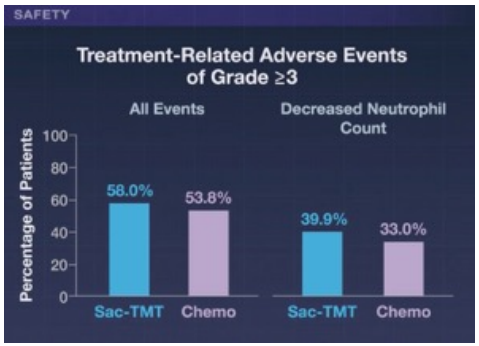

EGFR-Mutated Advanced
Non–Small-Cell
Lung Cancer (NSCLC)

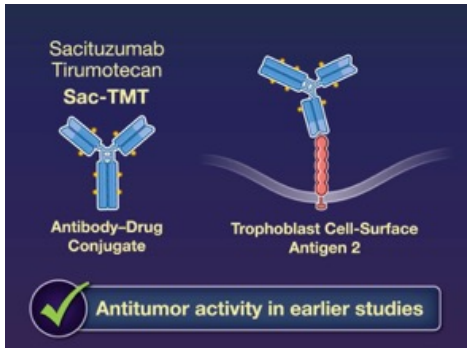

376 Adults
Locally advanced or metastatic
EGFR-mutated nonsquamous NSCLC
EGFR-TKI
Progressed after therapy
with EGFR-TKIs

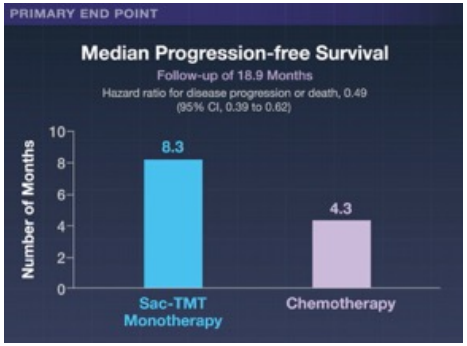

SECONDARY END POINT
Overall Survival
At 18 Months
Hazard ratio for death, 0.60 (95% CI, 0.44 to 0.82);
two-sided P=0.001
Percentage of Patients
100
80
60
40
20
0
65.8%
48.0%
Sac-TMT
Monotherapy
Chemotherapy

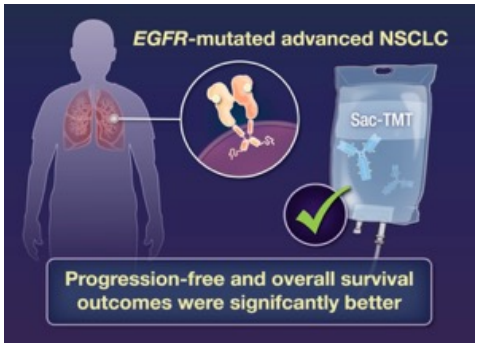

Epidermal Growth Factor Receptor
Tyrosine Kinase Inhibitors
EGFR-TKI
EGFR-Mutated Advanced
Non–Small-Cell
Lung Cancer (NSCLC)


Sac-TMT
OR
Pemetrexed
Cisplatin
Carboplatin
Monotherapy
N=188
Chemotherapy
N=188

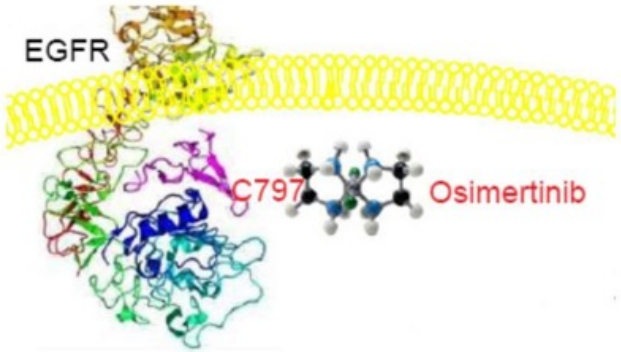

SAFETY
Treatment-Related Adverse Events
of Grade ≥3
All Events
Decreased Neutrophil
Count
Percentage of Patients
100
80
60
40
20
0
58.0%
53.8%
39.9%
33.0%
Sac-TMT
Chemo
Sac-TMT
Chemo

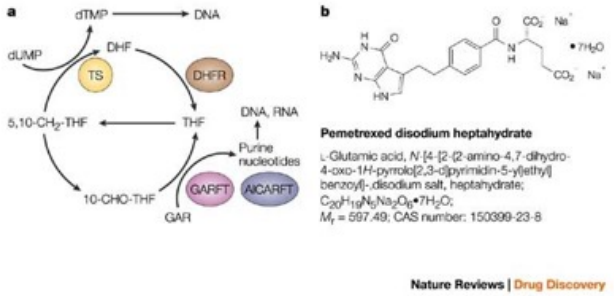

Sacituzumab
Tirumotecan
Sac-TMT
Antibody–Drug
Conjugate
Trophoblast Cell-Surface
Antigen 2
Antitumor activity in earlier studies


PRIMARY END POINT
Median Progression-free Survival
Follow-up of 18.9 Months
Hazard ratio for disease progression or death, 0.49
(95% CI, 0.39 to 0.62)
Number of Months
10
8
6
4
2
0
8.3
4.3
Sac-TMT
Monotherapy
Chemotherapy


EGFR-mutated advanced NSCLC
Sac-TMT
Progression-free and overall survival
outcomes were signifcantly better

Osimertinib ist ein zielgerichteter Krebsmedikament, ein sogenannter Tyrosinkinase-Inhibitor, zur Behandlung des nicht-kleinzelligen Lungenkarzinoms (NSCLC), das spezifische Mutationen im Epidermalen Wachstumsfaktor-Rezeptor (EGFR) aufweist (EGFRm). Es hemmt gezielt das Wachstum dieser Krebszellen und wird als Tablette eingenommen. Die Standarddosis ist 80 mg einmal täglich, aber Anpassungen sind aufgrund von Nebenwirkungen möglich.

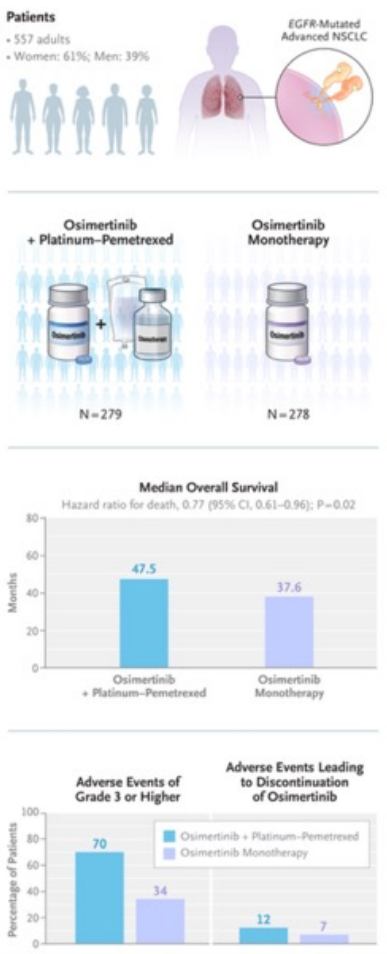




Pemetrexed ist ein Zytostatikum (Chemotherapie-Medikament), ein Antifolat-Wirkstoff, der das Wachstum von Krebszellen hemmt, indem er wichtige Enzyme blockiert, die für die Zellteilung nötig sind, vor allem bei Lungenkrebs (NSCLC) und Pleuramesotheliom, oft in Kombination mit Cisplatin. Es wirkt, indem es Folsäure nachahmt und so den Aufbau von DNA/RNA stört, wodurch das Wachstum der schnell wachsenden Krebszellen gebremst wird. Pemetrexed wird als intravenöse Infusion verabreicht und erfordert begleitende Vitamine zur Reduzierung von Nebenwirkungen.

Survival with Osimertinib plus Chemotherapy in EGFR-Mutated Advanced NSCLC

The primary analysis of this trial showed that first-line treatment with osimertinib plus chemotherapy with a platinum-based agent and pemetrexed led to significantly longer progression-free survival than osimertinib monotherapy among patients with epidermal growth factor receptor (*EGFR*)–mutated advanced non–small-cell lung cancer (NSCLC). Results from the planned final analysis of overall survival are needed. In this phase 3, international, open-label trial, we randomly assigned in a 1:1 ratio patients with *EGFR*-mutated (exon 19 deletion or L858R mutation) advanced NSCLC who had not previously received treatment for advanced disease to receive either osimertinib (80 mg once daily) plus chemotherapy with pemetrexed (500 mg per square meter of body-surface area) and a platinum-based agent (cisplatin [75 mg per square meter] or carboplatin [pharmacologically guided dose]) or osimertinib monotherapy (80 mg once daily). The key secondary end point was overall survival.



Osimertinib is a third-generation, irreversible, central nervous system (CNS)–active epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) that potently and selectively inhibits both EGFR-TKI–sensitizing and *EGFR* p.Thr790Met (T790M) resistance mutations. On the basis of findings from the phase 3, international FLAURA trial, osimertinib monotherapy is a preferred first-line treatment for patients with *EGFR*-mutated advanced non–small-cell lung cancer (NSCLC).

Findings from previous randomized trials showed prolonged progression-free survival and overall survival with the combination of gefitinib (a first-generation EGFR-TKI) and chemotherapy with a platinum-based agent and pemetrexed, as compared with gefitinib alone.The phase 3, international, open-label, randomized FLAURA2 trial evaluated the combination of osimertinib and chemotherapy with a platinum-based agent and pemetrexed as first-line treatment for patients with *EGFR*-mutated advanced NSCLC. In the primary analysis (data cutoff, April 3, 2023), this combination therapy led to significantly longer investigator-assessed progression-free survival than osimertinib monotherapy (hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.49 to 0.79; $P<0.001$), and the progression-free survival benefit with osimertinib plus platinum–pemetrexed was consistent across prespecified subgroups. Furthermore, the safety profile of osimertinib plus platinum–pemetrexed was consistent with the established profiles of the individual agents.

Patients

In brief, patients were eligible for inclusion in the trial if they were 18 years of age or older (or ≥20 years of age in Japan) and had locally advanced or metastatic nonsquamous NSCLC with local or central confirmation of an *EGFR* mutation (exon 19 deletion or L858R mutation).

Trial Design and Treatment

Patients were randomly assigned in a 1:1 ratio to receive either osimertinib plus platinum–pemetrexed or osimertinib monotherapy. Combination therapy consisted of osimertinib (80 mg) administered orally once daily plus chemotherapy with pemetrexed (500 mg per square meter of body-surface area) and a platinum-based agent (the investigator's choice of either cisplatin [75 mg per square meter] or carboplatin.

End Points and Assessments

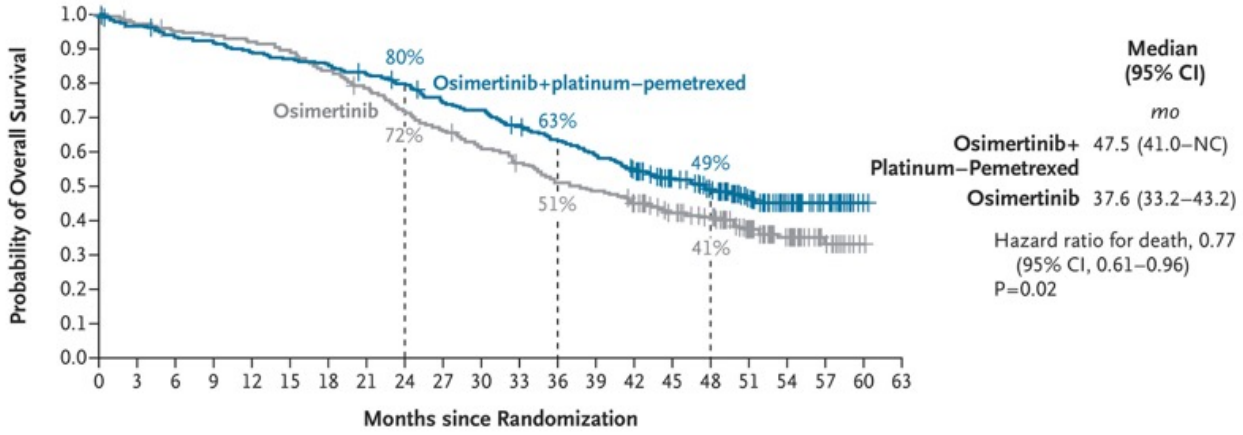
The primary end point was progression-free survival on the basis of investigator assessment with RECIST, version 1.1; the results of the primary analysis have been reported previously. The key secondary end point was overall survival, which was defined as the time from randomization until death from any cause.

Summary of Adverse Events.

Event	Primary Analysis (data cutoff, April 3, 2023)		Final Analysis of Overall Survival (data cutoff, June 12, 2025)	
	Osimertinib+ Platinum–Pemetrexed (N=276)	Osimertinib (N=275)	Osimertinib+ Platinum–Pemetrexed (N=276)	Osimertinib (N=275)
	number of patients (percent)			
Adverse event of any cause	276 (100)	268 (97)	276 (100)	269 (98)
Grade ≥3 adverse event	176 (64)	75 (27)	193 (70)	94 (34)
Adverse event leading to death	18 (7)	8 (3)	22 (8)	10 (4)
Serious adverse event	104 (38)	53 (19)	126 (46)	75 (27)
Adverse event leading to discontinuation of treatment				
Discontinuation of any trial treatment	132 (48)	17 (6)	150 (54)	20 (7)
Discontinuation of osimertinib	30 (11)	17 (6)	34 (12)	20 (7)
Discontinuation of carboplatin or cisplatin†	46 (17)	—	46 (17)	—
Discontinuation of pemetrexed	119 (43)	—	137 (50)	—
Adverse event considered by the investigator to be possibly causally related to any trial treatment	269 (97)	241 (88)	269 (97)	242 (88)
Grade ≥3 adverse event	146 (53)	29 (11)	152 (55)	35 (13)
Adverse event leading to death	5 (2)	1 (<1)	5 (2)	2 (1)
Serious adverse event	52 (19)	15 (5)	56 (20)	18 (7)

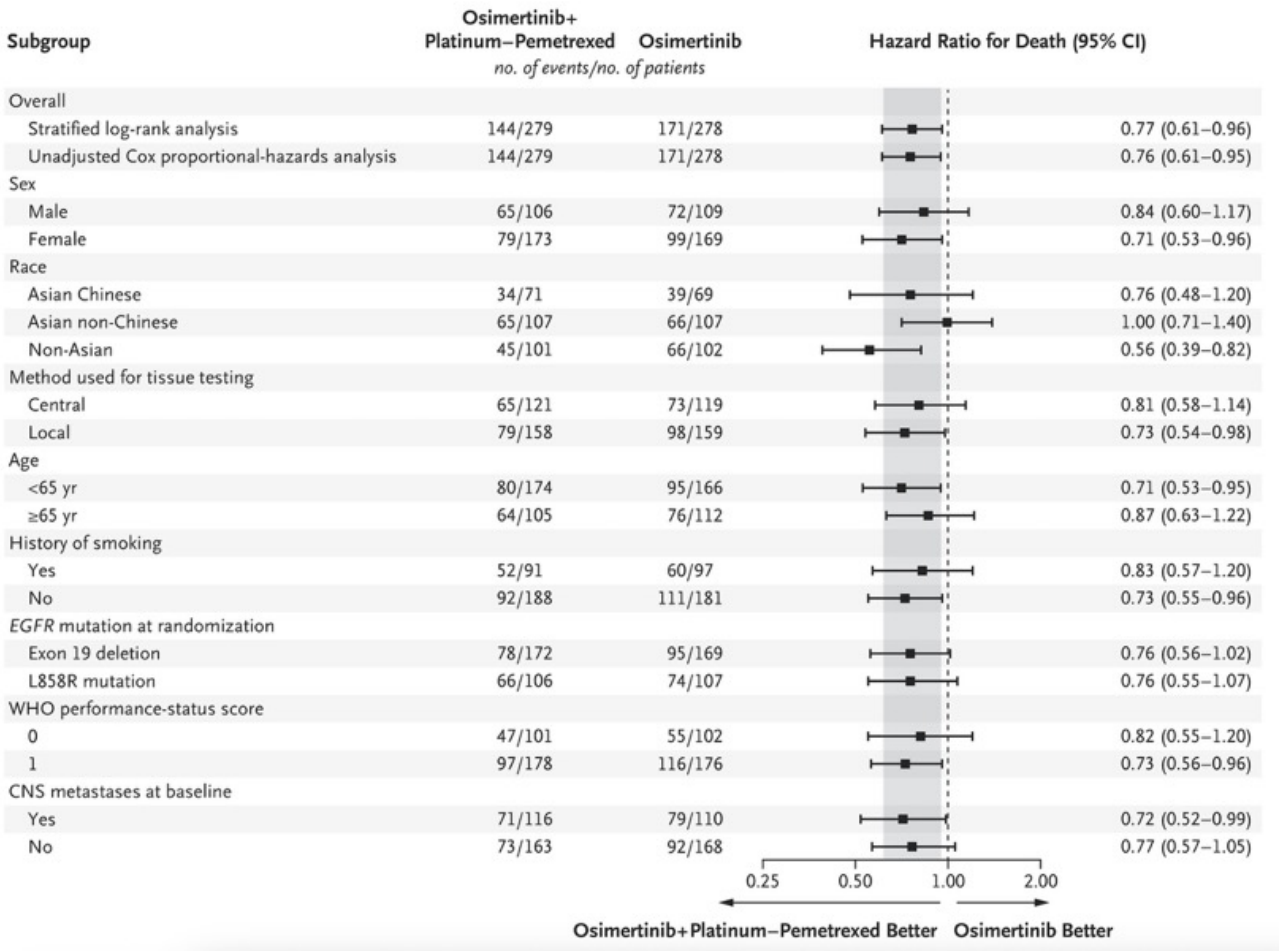
Most Common Adverse Events.

Event	Osimertinib + Platinum–Pemetrexed (N=276)					Osimertinib (N=275)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)					*number of patients (percent)*				
Anemia	132 (48)	28 (10)	48 (17)	56 (20)	0	31 (11)	19 (7)	8 (3)	4 (1)	0
Diarrhea	129 (47)	84 (30)	36 (13)	9 (3)	0	116 (42)	93 (34)	22 (8)	1 (<1)	0
Nausea	120 (43)	80 (29)	36 (13)	4 (1)	0	32 (12)	26 (9)	6 (2)	0	0
Decreased appetite	90 (33)	51 (18)	30 (11)	9 (3)	0	31 (11)	21 (8)	7 (3)	3 (1)	0
Constipation	89 (32)	65 (24)	23 (8)	1 (<1)	0	31 (11)	25 (9)	6 (2)	0	0
Rash	81 (29)	56 (20)	23 (8)	2 (1)	0	61 (22)	48 (17)	13 (5)	0	0
Fatigue	81 (29)	44 (16)	29 (11)	8 (3)	0	30 (11)	27 (10)	2 (1)	1 (<1)	0
Vomiting	79 (29)	55 (20)	21 (8)	3 (1)	0	20 (7)	15 (5)	4 (1)	1 (<1)	0
Covid-19†	73 (26)	27 (10)	42 (15)	3 (1)	0	47 (17)	22 (8)	25 (9)	0	0
Stomatitis	71 (26)	42 (15)	28 (10)	1 (<1)	0	51 (19)	31 (11)	19 (7)	1 (<1)	0
Paronychia	70 (25)	29 (11)	39 (14)	2 (1)	0	75 (27)	36 (13)	38 (14)	1 (<1)	0
Neutropenia	68 (25)	4 (1)	27 (10)	30 (11)	7 (3)	11 (4)	4 (1)	5 (2)	2 (1)	0
Neutrophil count decreased	65 (24)	6 (2)	27 (10)	25 (9)	7 (3)	18 (7)	7 (3)	9 (3)	2 (1)	0
ALT level increased	58 (21)	36 (13)	17 (6)	5 (2)	0	23 (8)	17 (6)	4 (1)	2 (1)	0
Dry skin	54 (20)	46 (17)	8 (3)	0	0	68 (25)	64 (23)	4 (1)	0	0
Platelet count decreased	53 (19)	20 (7)	12 (4)	18 (7)	3 (1)	22 (8)	19 (7)	3 (1)	0	0
Thrombocytopenia	51 (18)	19 (7)	13 (5)	16 (6)	3 (1)	13 (5)	7 (3)	3 (1)	3 (1)	0
Blood creatinine level increased	50 (18)	35 (13)	15 (5)	0	0	16 (6)	11 (4)	5 (2)	0	0
AST level increased	50 (18)	43 (16)	6 (2)	1 (<1)	0	15 (5)	12 (4)	0	3 (1)	0
White-cell count decreased	46 (17)	9 (3)	28 (10)	8 (3)	1 (<1)	20 (7)	9 (3)	10 (4)	1 (<1)	0
Peripheral edema	44 (16)	34 (12)	10 (4)	0	0	16 (6)	13 (5)	3 (1)	0	0
Cough	43 (16)	32 (12)	11 (4)	0	0	38 (14)	24 (9)	14 (5)	0	0



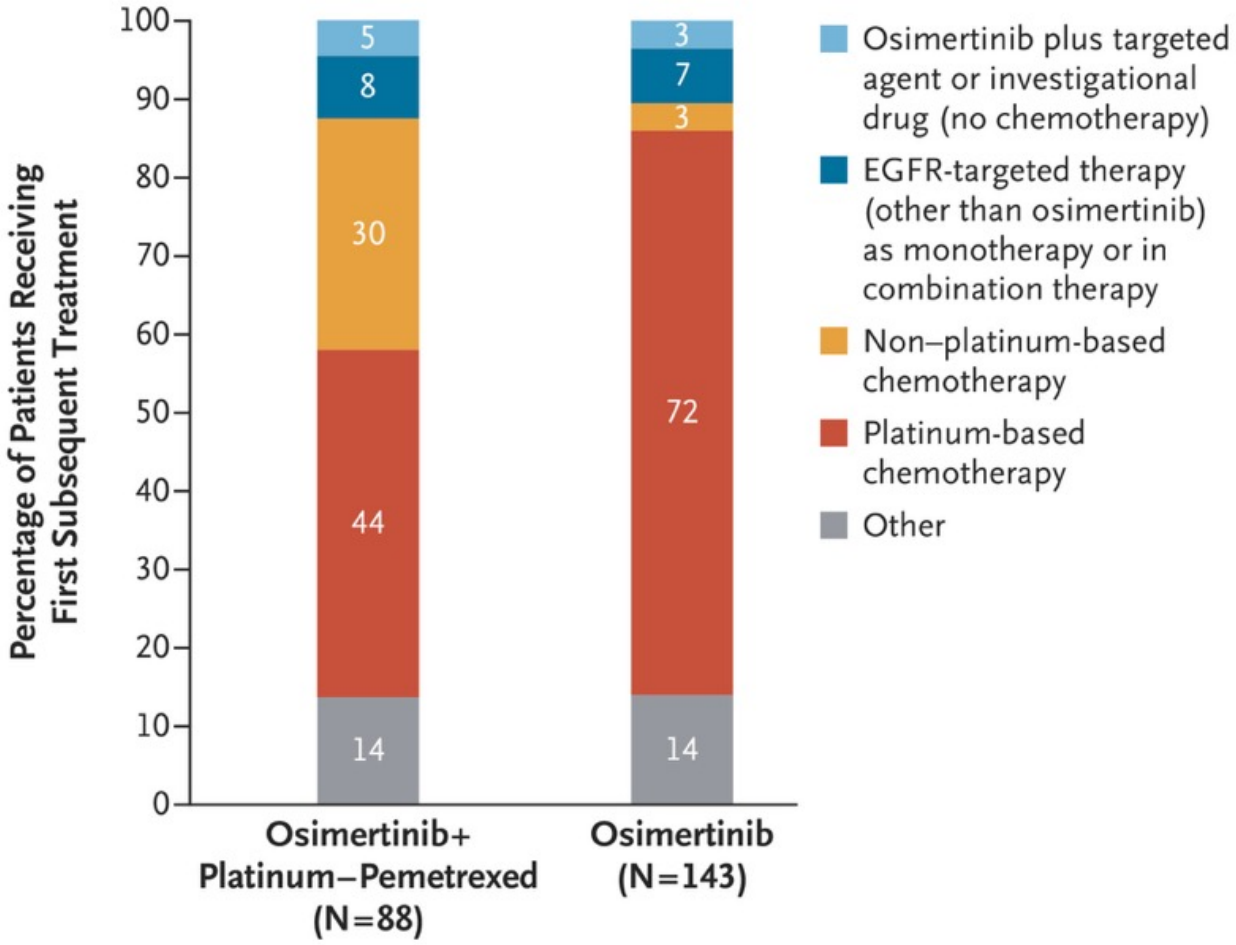
Overall Survival.

Kaplan–Meier estimates of overall survival in the full analysis set are shown. Tick marks indicate censored data; patients who had not died at the time of the analysis had their data censored at the last recorded known survival date. Dashed lines indicate the 24-month, 36-month, and 48-month landmark estimates. The median duration of follow-up among patients with censored data was 51.2 months (range, 0.2 to 60.4) in the osimertinib plus platinum–pemetrexed group and 51.3 months (range, 0.1 to 60.1) in the osimertinib monotherapy group; the median duration of follow-up among all the patients, regardless of censoring, was 42.6 months (range, 0.1 to 60.4) and 35.7 months (range, 0.1 to 60.1), respectively. NC denotes not calculable.



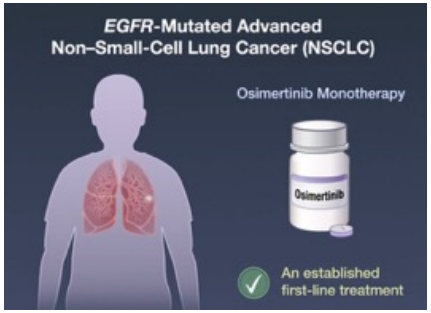
Subgroup Analysis of Overall Survival.

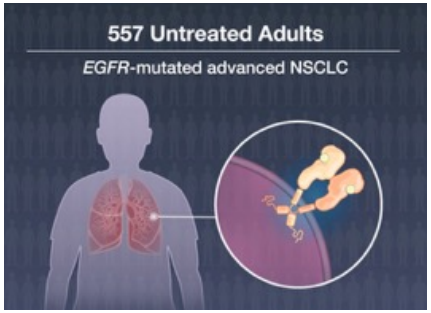
A forest plot of overall survival in prespecified subgroups is shown. A hazard ratio of less than 1 indicates a lower risk of death with osimertinib plus platinum–pemetrexed than with osimertinib monotherapy. The Cox proportional-hazards model included the randomized trial treatment, the subgroup covariate of interest, and the treatment according to subgroup interaction. Race was reported by the patient; options were given on a drop-down list at randomization. *EGFR* is the gene that encodes the epidermal growth factor receptor. Patients with co-occurrence of an exon 19 deletion and a L858R mutation were included in the subgroup for exon 19 deletion. World Health Organization (WHO) performance-status scores range from 0 to 5, with higher scores indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry out all predisease activities without restrictions, and a score of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work. Central nervous system (CNS) metastases status at baseline was based on investigator assessment of data in the electronic case-report form regarding the CNS lesion site at baseline, medical history, surgical history, or history of radiotherapy for CNS metastases. The shaded area indicates the 95% confidence interval for the overall hazard ratio for death among all the patients. In the subgroup analysis, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

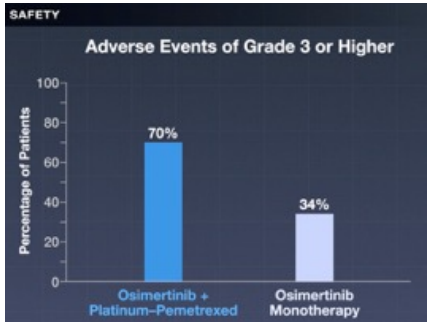


Summary of First Subsequent Treatments Received.

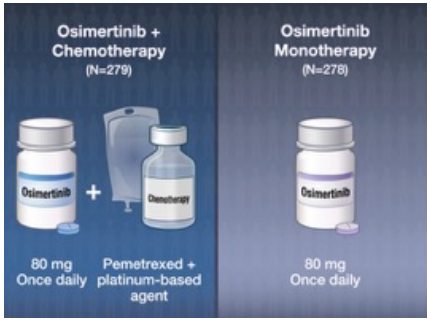
Bar plots of the first subsequent treatments received among patients who had discontinued first-line treatment with osimertinib owing to disease progression are shown. Subsequent treatments were chosen by the investigator. Trial treatment that was continued beyond disease progression was considered to be first-line treatment and is not included here. The "other" category included antibody–drug conjugates, immunotherapies (programmed death 1 and programmed death ligand 1 inhibitors), other investigational anticancer therapies, antiangiogenic therapies (vascular endothelial growth factor [VEGF] and VEGF receptor inhibitors), catequentinib hydrochloride, savolitinib, and unspecified herbal and traditional anticancer medicines. One patient in the osimertinib plus platinum–pemetrexed group and eight patients in the osimertinib monotherapy group received osimertinib in combination with platinum-based doublet chemotherapy as the first subsequent treatment. EGFR denotes epidermal growth factor receptor.

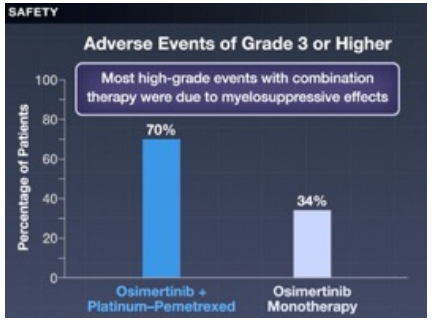

EGFR-Mutated Advanced
Non–Small-Cell Lung Cancer (NSCLC)
Osimertinib Monotherapy
Osimertinib
An established
first-line treatment


557 Untreated Adults
EGFR-mutated advanced NSCLC


SAFETY
Adverse Events of Grade 3 or Higher
Percentage of Patients
100
80
60
40
20
0
70%
34%
Osimertinib +
Platinum–Pemetrexed
Osimertinib
Monotherapy

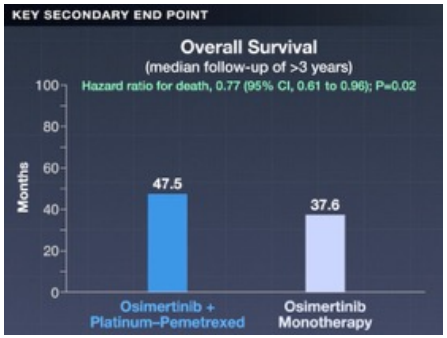

Prolonged progression-free survival
Osimertinib
Chemotherapy
FLAURA2 Trial
Platinum–pemetrexed
chemotherapy

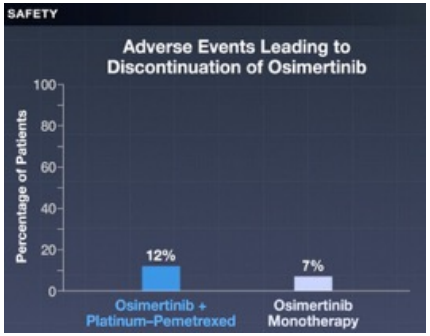

Osimertinib +
Chemotherapy
(N=279)
Osimertinib
Monotherapy
(N=278)
Osimertinib
Chemotherapy
80 mg
Once daily
Pemetrexed +
platinum-based
agent
Osimertinib
80 mg
Once daily


SAFETY
Adverse Events of Grade 3 or Higher
Most high-grade events with combination
therapy were due to myelosuppressive effects
Percentage of Patients
100
80
60
40
20
0
70%
34%
Osimertinib +
Platinum–Pemetrexed
Osimertinib
Monotherapy

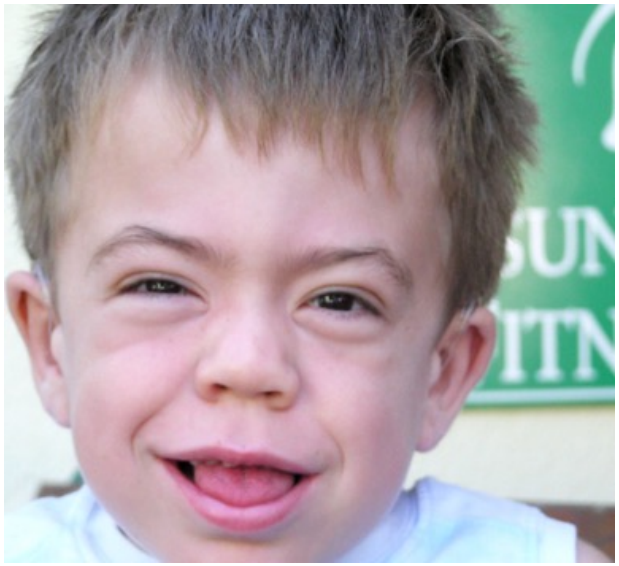

Osimertinib + Platinum–Pemetrexed
Osimertinib
Chemotherapy
Significantly longer overall survival
An increased risk of reversible
high-grade adverse events

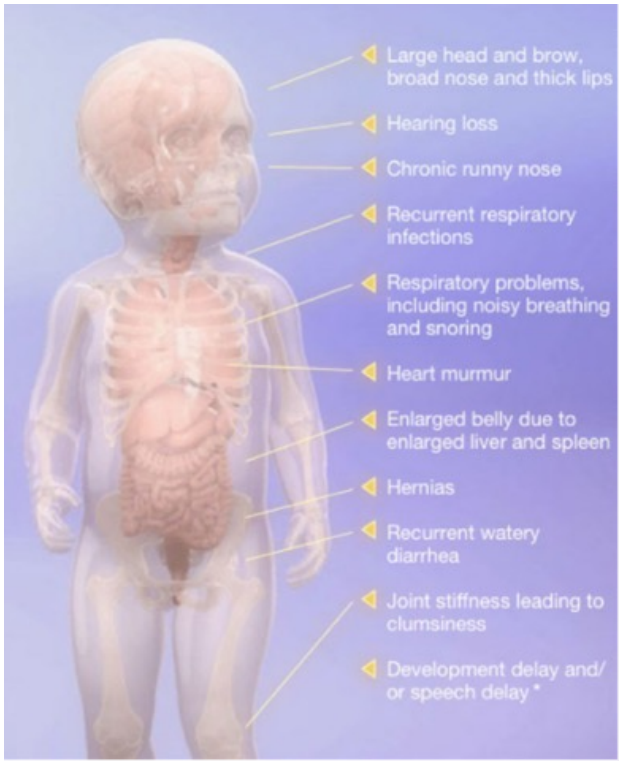

Clarify longer-term outcomes
Osimertinib
Chemotherapy
FLAURA2 Trial
Overall
Survival
Platinum–pemetrexed
chemotherapy


KEY SECONDARY END POINT
Overall Survival
(median follow-up of >3 years)
Hazard ratio for death, 0.77 (95% CI, 0.61 to 0.96); P=0.02
Months
100
80
60
40
20
0
47.5
37.6
Osimertinib +
Platinum–Pemetrexed
Osimertinib
Monotherapy

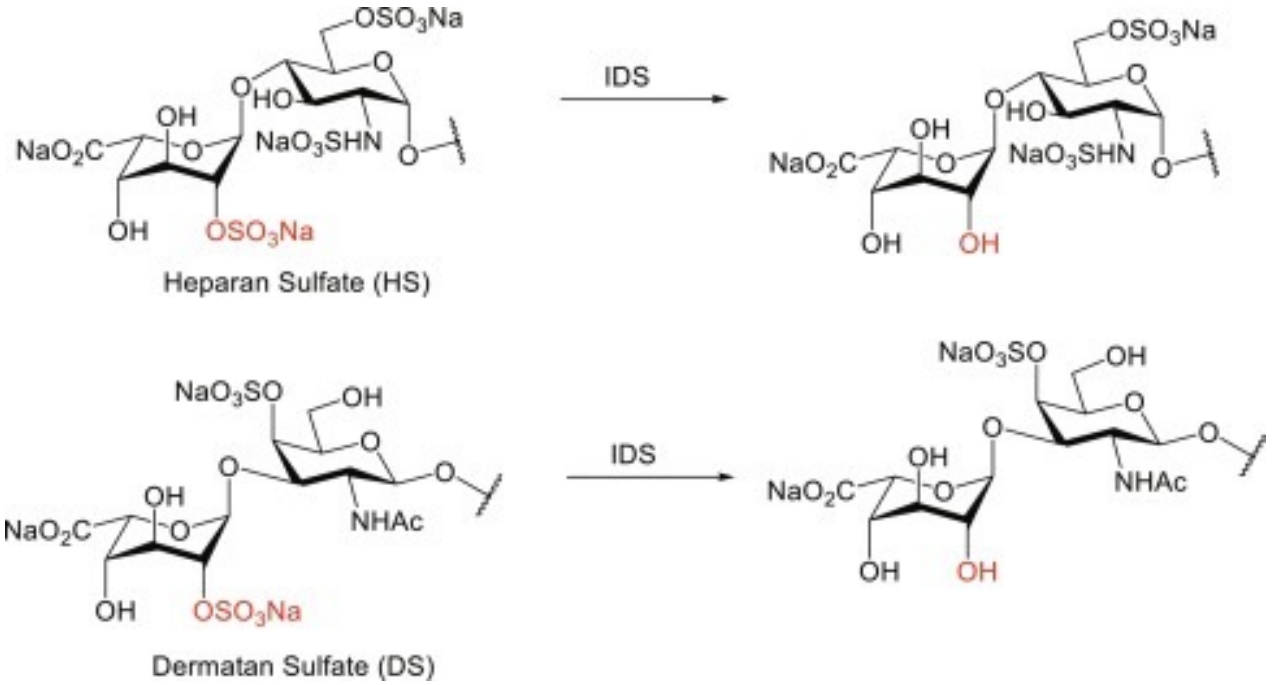

SAFETY
Adverse Events Leading to
Discontinuation of Osimertinib
Percentage of Patients
100
80
60
40
20
0
12%
7%
Osimertinib +
Platinum–Pemetrexed
Osimertinib
Monotherapy

Mucopolysaccharidose Typ II (MPS II), auch bekannt als Hunter-Syndrom, ist eine seltene, genetisch bedingte Stoffwechselstörung, bei der dem Körper ein Enzym (Iduronat-2-Sulfatase) fehlt, um spezielle Zucker (Glykosaminoglykane) abzubauen, was zu deren Anreicherung und Schädigung von Organen, Geweben und dem Gehirn führt, primär bei Jungen auftritt und von mild bis schwer reichen kann, mit Symptomen wie vergrößerter Leber/Milz, Herzproblemen, Atemwegsschwierigkeiten, Skelettdeformitäten und geistiger Beeinträchtigung.

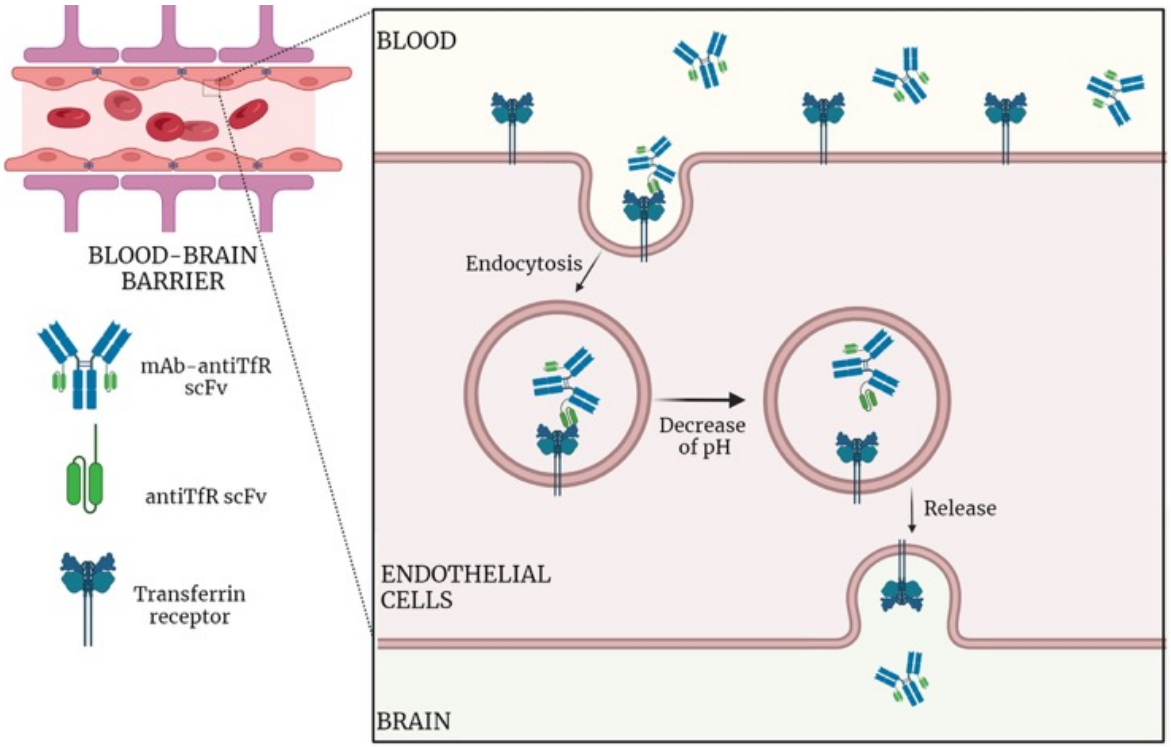




Iduronate-2-sulfatase (IDS) is a Ca2+-dependent enzyme belonging to the family of sulfatases that catalyzes the hydrolysis of sulphurylated glycosaminoglycans (GAGs), like dermatan and heparan sulphate. Its deficiency or modification leads to the accumulation of GAGs in the human body and to the occurrence of severe conditions, such as Hunter disease, or Mucopolysaccharidosis type II.



The transferrin receptor (TfR) is crucial in the brain, primarily for transporting iron into the brain via the blood-brain barrier (BBB) by binding to iron-laden transferrin, making it a key target for delivering drugs and therapies across the BBB to treat neurological conditions like Alzheimer's disease (AD). Researchers use anti-TfR antibodies to shuttle therapeutics into the brain, with studies showing that optimized antibody design, considering affinity and valency, significantly impacts delivery efficiency, though its role in AD progression and aging is still being explored.



An Intravenous Brain-Penetrant Enzyme Therapy for Mucopolysaccharidosis II

Background

Tividenofusp alfa, comprising iduronate-2-sulfatase fused to an engineered transferrin receptor–binding Fc domain, has been developed to treat neurologic and peripheral manifestations of mucopolysaccharidosis type II (MPS II), a rare lysosomal disorder causing progressive multisystem and neurologic decline.

Methods

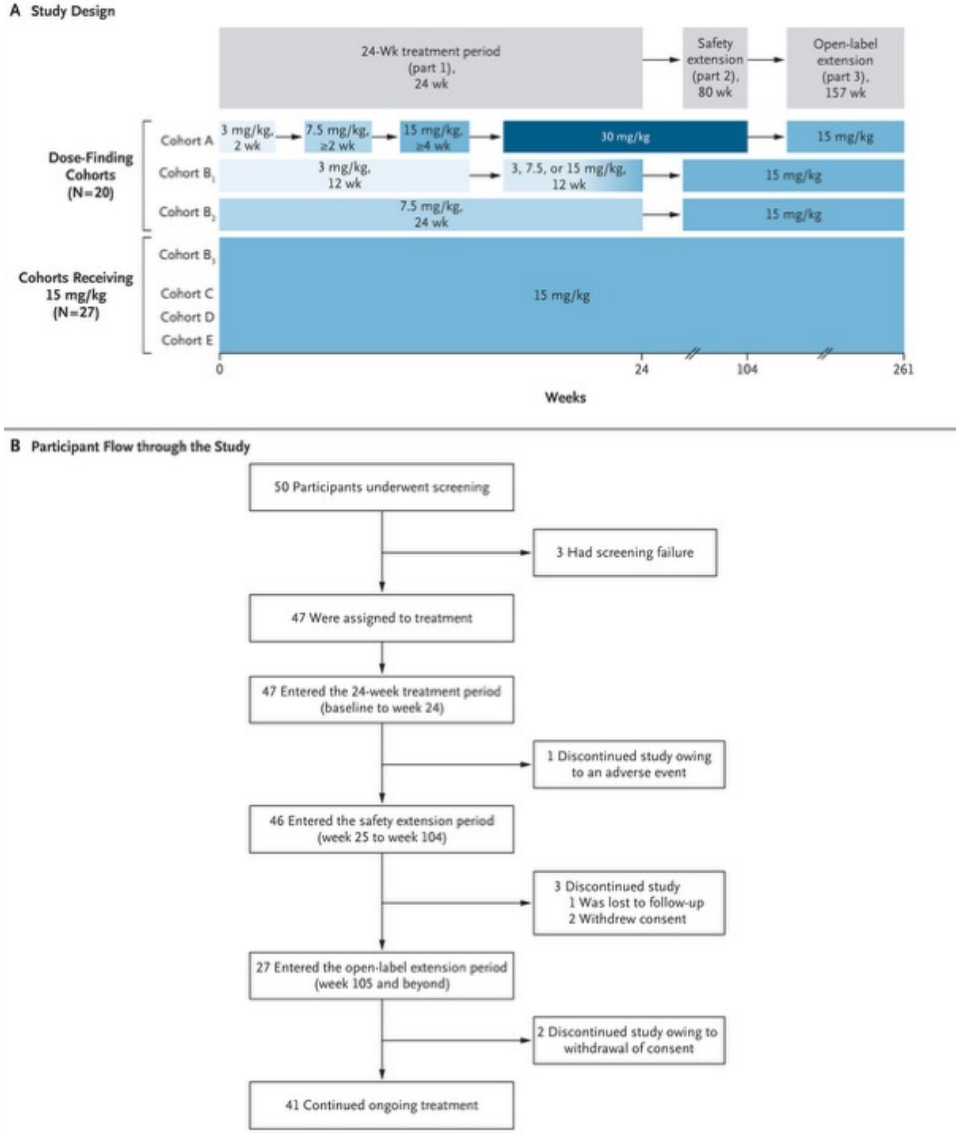
We conducted a phase 1–2, open-label study in which male participants up to 18 years of age with MPS II received weekly intravenous tividenofusp alfa for 24 weeks, followed by an 80-week safety extension and a 157-week open-label extension. The primary objective was to evaluate the safety of tividenofusp alfa. Secondary objectives were to evaluate central nervous system and peripheral effects as assessed by cerebrospinal fluid (CSF) and urinary heparan sulfate levels, adaptive behavior (as assessed with the Vineland Adaptive Behavior Scales), and liver volume.

Conclusions

In participants with MPS II, tividenofusp alfa treatment was commonly associated with adverse events. Heparan sulfate, the primary substrate that accumulates in the CSF and urine in persons with MPS II, appeared to decrease to levels within the range of unaffected children. A randomized trial is ongoing to further evaluate these effects.

Mucopolysaccharidosis type II (MPS II; the Hunter syndrome; Online Mendelian Inheritance in Man number, 309900) is a progressive X-linked lysosomal disease caused by deficient iduronate-2-sulfatase activity, leading to organ dysfunction and premature death, with an incidence of 1 per 100,000 to 170,000 live births. Disease progression results from the accumulation of glycosaminoglycans (GAGs), leading to lysosomal dysfunction and neuronal injury as evidenced by elevated levels of neurofilament light chain (NfL), a biomarker of neurodegeneration. Approximately two thirds of patients with MPS II go on to have neuronopathic MPS II, characterized by progressive neurocognitive decline beginning at approximately 2 to 4 years of age. This decline is not addressed by standard enzyme-replacement therapy (ERT), which does not cross the blood–brain barrier. Brain accumulation of heparan sulfate, a hallmark of neuronopathic MPS II, can be indirectly assessed through its levels in cerebrospinal fluid (CSF).

Tividenofusp alfa is a novel ERT fusion protein comprising an engineered transferrin receptor (TfR)–binding Fc domain and iduronate-2-sulfatase enzyme. Tividenofusp alfa binds to abundantly expressed TfR at the blood–brain barrier and in tissues, enabling broad tissue distribution through tailored TfR binding affinity and mannose-6-phosphate receptor binding, to address both central nervous system (CNS) and somatic manifestations of MPS II.



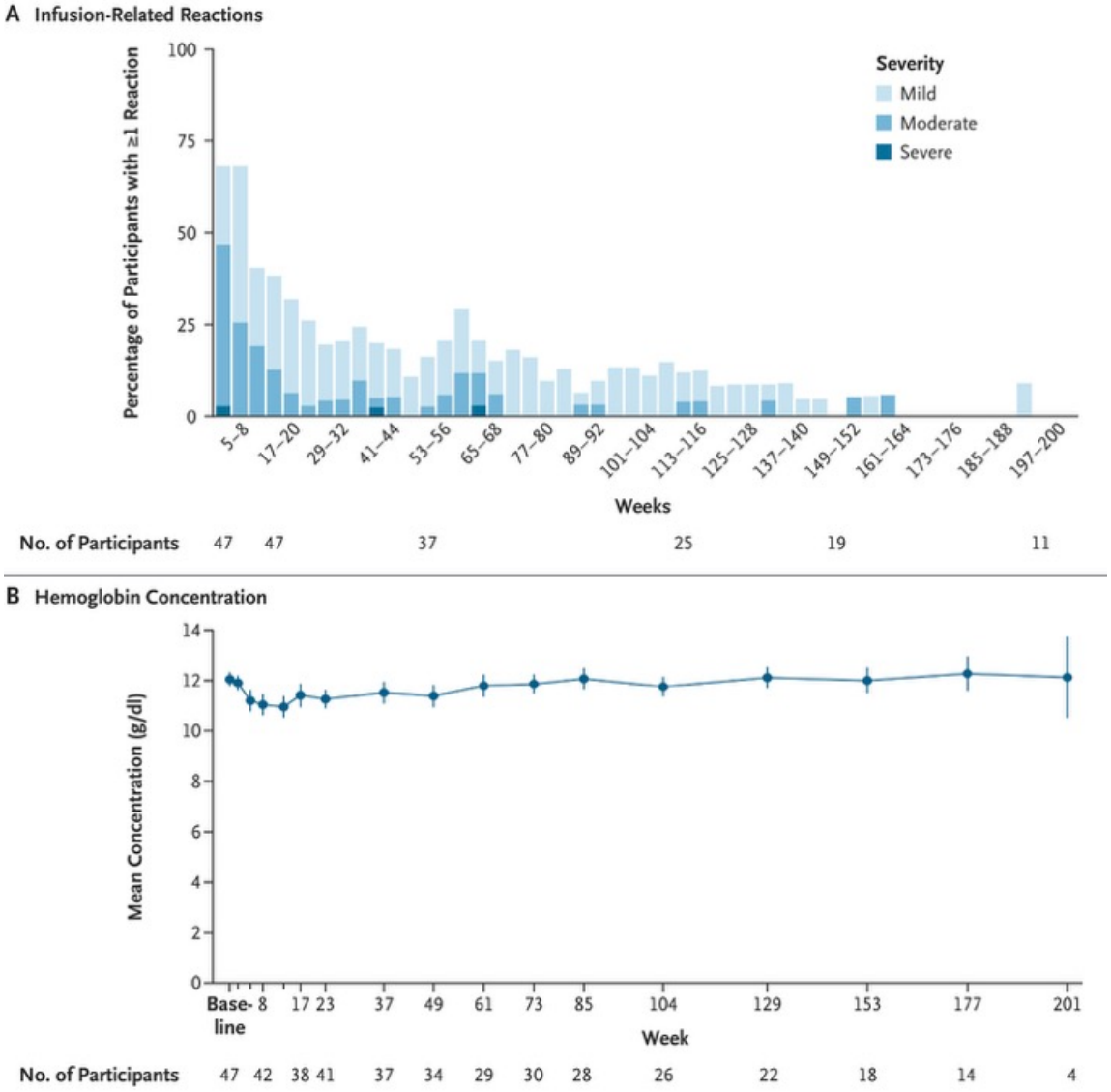
Study Design and Participant Flow through the Study.

In Panel A, the doses shown are for weekly intravenous infusions of tividenofusp alfa. According to the study protocol, doses could be modified on the basis of emerging data. Within-participant dose escalation was performed as indicated in cohorts A, B_1, and B_2 to explore safety of increasing doses (cohort A) and to support dose finding (cohort B). The choice of escalated dose from week 12 in cohort B_1 was based on investigator discretion. In Panel B, reasons for screening failure were withdrawal of consent, the developmental quotient at screening, and lack of preexisting liver enlargement (1 participant each). Six participants discontinued participation in the study: one owing to an infusion-related reaction, four as a result of withdrawal of consent, and one owing to loss to follow-up.

Characteristic	All Participants (N=47)
Median age (range) — yr	5 (0.3–13)
Age group — no. (%)	
<4 yr	14 (30)
≥4 yr	33 (70)
Sex — no. (%)	
Male	47 (100)
Female	0
Race — no. (%)†	
White	27 (57)
Not reported or unknown	8 (17)
Asian	4 (9)
Black	4 (9)
More than one race	3 (6)
Other	1 (2)
Ethnic group — no. (%)†	
Not Hispanic or Latino	38 (81)
Hispanic or Latino	7 (15)
Not reported	2 (4)
MPS II phenotype — no. (%)	
Neuronopathic	44 (94)
Non-neuronopathic	3 (6)
Developmental quotient‡	
No. of participants evaluated	46
Mean	55±29
Type of genetic variant — no. (%)	
Missense or synonymous	22 (47)
Large deletion, rearrangement, stop, frameshift, or splice	25 (53)
ERT category — no. (%)§	
Had not previously received ERT	15 (32)
Had previously received ERT	32 (68)
Age at initiation of ERT¶	
No. of participants evaluated	33
Median (range) — yr	3 (0.3–10)
Duration of previous ERT¶	
No. of participants evaluated	33
Median (range) — mo	26 (1–135)
Status with respect to antidrug antibodies — no. (%)	
Positive	24 (51)
Negative	23 (49)

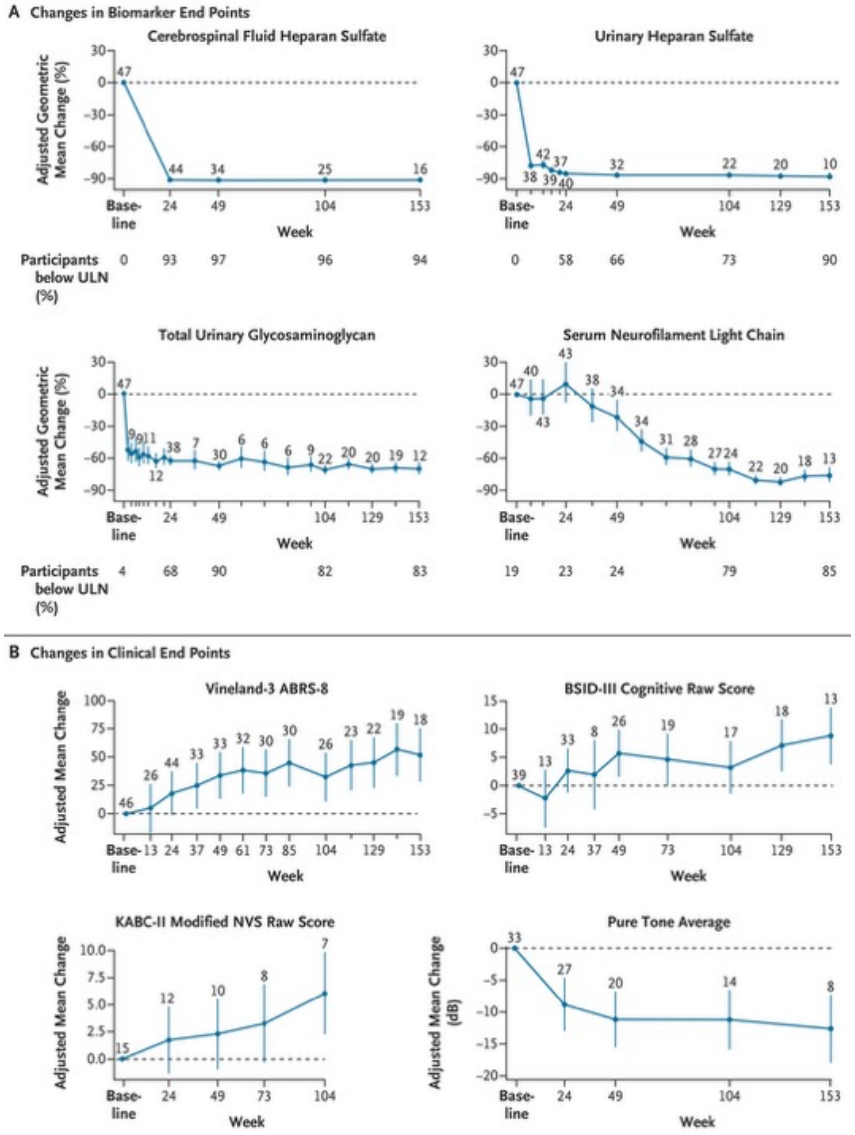
Summary of Adverse Events (Safety Analysis Population).

Event	Part 1: 24-Week Treatment Period (N=47)	Part 2: 80-Week Safety Extension (N=46)	Part 3: 157-Week Open-Label Extension (N=27)	All Periods (N=47)
	number of participants (percent)			
Adverse event†	47 (100)	41 (89)	25 (93)	47 (100)
Mild	8 (17)	3 (7)	8 (30)	2 (4)
Moderate	35 (74)	30 (65)	15 (56)	32 (68)
Severe	4 (9)	8 (17)	2 (7)	13 (28)
Serious adverse event‡	6 (13)	11 (24)	4 (15)	18 (38)
Treatment-related serious adverse event§	3 (6)	0	0	3 (6)
Adverse events of special interest¶				
Infusion-related reaction	27 (57)	15 (33)	4 (15)	29 (62)
Anemia	11 (23)	2 (4)	1 (4)	11 (23)
Adverse event leading to discontinuation of study participation	1 (2)	0	0	1 (2)
Adverse event leading to dose reduction	22 (47)	11 (24)	4 (15)	27 (57)
Adverse event leading to dose interruption	34 (72)	37 (80)	15 (56)	43 (91)
Most frequent adverse events				
Infusion-related reaction	39 (83)	26 (57)	11 (41)	41 (87)
Upper respiratory tract infection	11 (23)	20 (43)	8 (30)	28 (60)
Pyrexia	11 (23)	17 (37)	6 (22)	26 (55)
Cough	8 (17)	14 (30)	6 (22)	22 (47)
Vomiting	14 (30)	10 (22)	6 (22)	20 (43)
Diarrhea	9 (19)	10 (22)	4 (15)	19 (40)
Rash	10 (21)	8 (17)	6 (22)	19 (40)
Anemia	18 (38)	3 (7)	2 (7)	18 (38)
Covid-19	6 (13)	13 (28)	2 (7)	18 (38)
Rhinorrhea	9 (19)	8 (17)	4 (15)	18 (38)



Infusion-Related Reactions and Hemoglobin Levels over Time (Safety Analysis Population).

Panel A shows the percentage of participants who had at least one infusion-related reaction during each 4-week interval of treatment with tividenofusp alfa, categorized according to severity. Percentages were calculated as the number of participants who had at least one infusion-related reaction during a given interval divided by the number of participants who received tividenofusp alfa in that interval (a maximum of one infusion-related reaction per participant per interval was counted, with the highest severity recorded). Infusion-related reactions spanning multiple intervals were attributed to the interval of onset. Panel B shows the mean hemoglobin concentrations from baseline through week 201. A transient mean decrease was observed early in treatment, with mean levels stabilizing and remaining near baseline thereafter. The 95% confidence intervals (error bars) were not adjusted for multiplicity and should not be used as a substitute for formal hypothesis testing.



Change from Baseline in Key Biomarkers and Selected Exploratory Clinical End Points (Full Analysis Population).

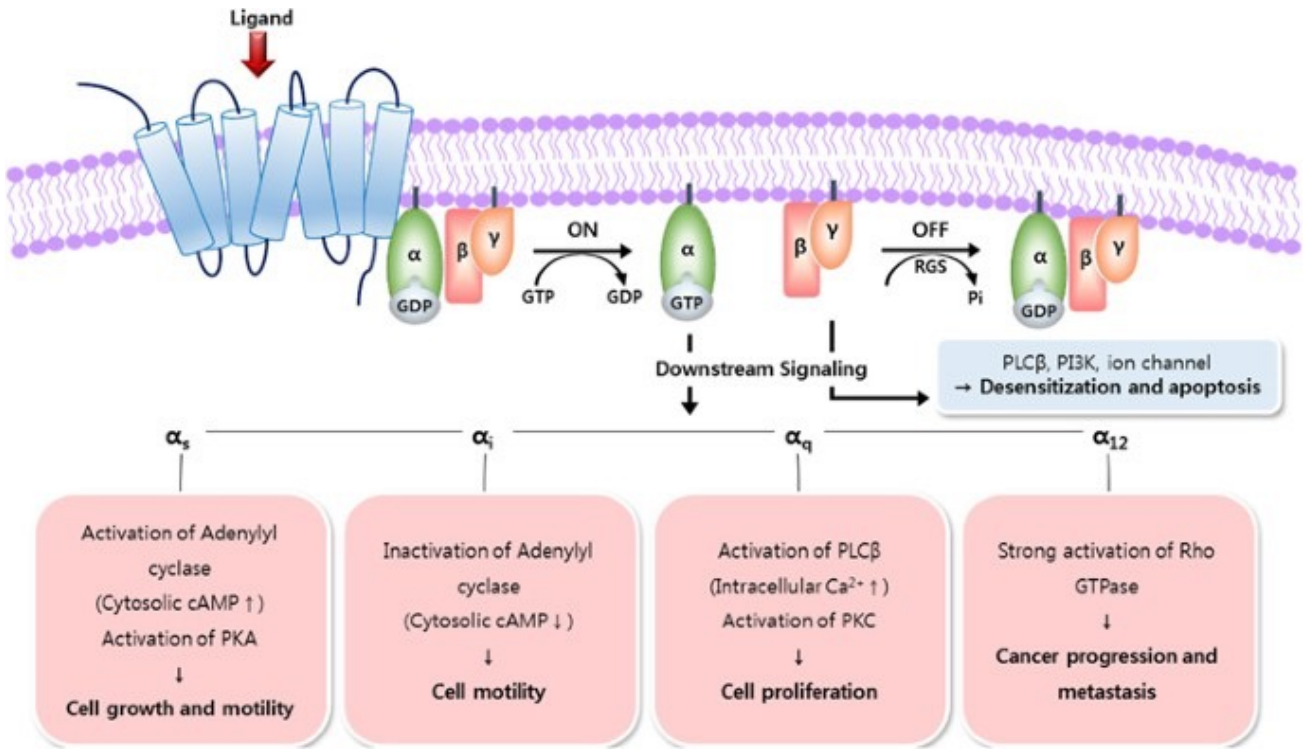
Numbers on data points are the numbers of participants assessed at that visit. Differences in visit frequency are due to different protocol-defined schedules of assessment. The 95% confidence intervals (error bars) were reported on the basis of model least-squares means without adjustment for multiplicity and should not be used as a substitute for hypothesis testing. Only protocol-planned visits that are consistent across all cohorts with the number of observations equal to or greater than five at the time of data extraction for this analysis are included in the mixed model for repeated measures (MMRM) analyses. Panel A shows adjusted geometric mean changes from baseline with 95% confidence intervals derived with the use of an MMRM that included the baseline biomarker concentration, visit, age group at treatment initiation (<4 vs. ≥4 years), type of genetic variant (missense or synonymous vs. other), and enzyme-replacement therapy (ERT) category (urinary heparan sulfate and total urinary glycosaminoglycan levels only) as fixed effects. For urinary heparan sulfate level, data are shown for the following time points: baseline and weeks 7, 13, 17, 21, 24, 49, 104, 129, and 153. For total urinary glycosaminoglycan level, data are shown for the following time points: baseline and weeks 2, 4, 6, 8, 10, 13, 17, 21, 24, 37, 49, 61, 73, 85, 97, 104, 117, 129, 141, and 153. For serum neurofilament light-chain level, data are shown for the following time points: baseline and weeks 7, 13, 24, 37, 49, 61, 73, 85, 97, 104, 117, 129, 141, and 153. ULN denotes upper limit of the normal range. Panel B shows adjusted mean changes from baseline with 95% confidence intervals derived with the use of an MMRM that included the baseline score, visit, age group at treatment initiation (<4 vs. ≥4 years), type of genetic variant (missense or synonymous vs. other), and ERT category (pure tone average only) as fixed effects. Values for the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3), eight-subdomain Adaptive Behavior Raw Score composite (ABRS-8) range from 0 to 664, with higher scores indicating better adaptive behavior. For the Vineland-3 ABRS-8, data are shown for the following time points: baseline and weeks 13, 24, 37, 49, 61, 73, 85, 104, 117, 129, 141, and 153. Values for the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), cognitive raw score range from 0 to 91, with higher scores indicating better cognitive function. Values for the Kaufman Assessment Battery for Children, Second Edition (KABC-II), modified nonverbal scale (NVS) raw score range from 0 to 52, with higher scores indicating better nonverbal cognitive abilities

Discussion

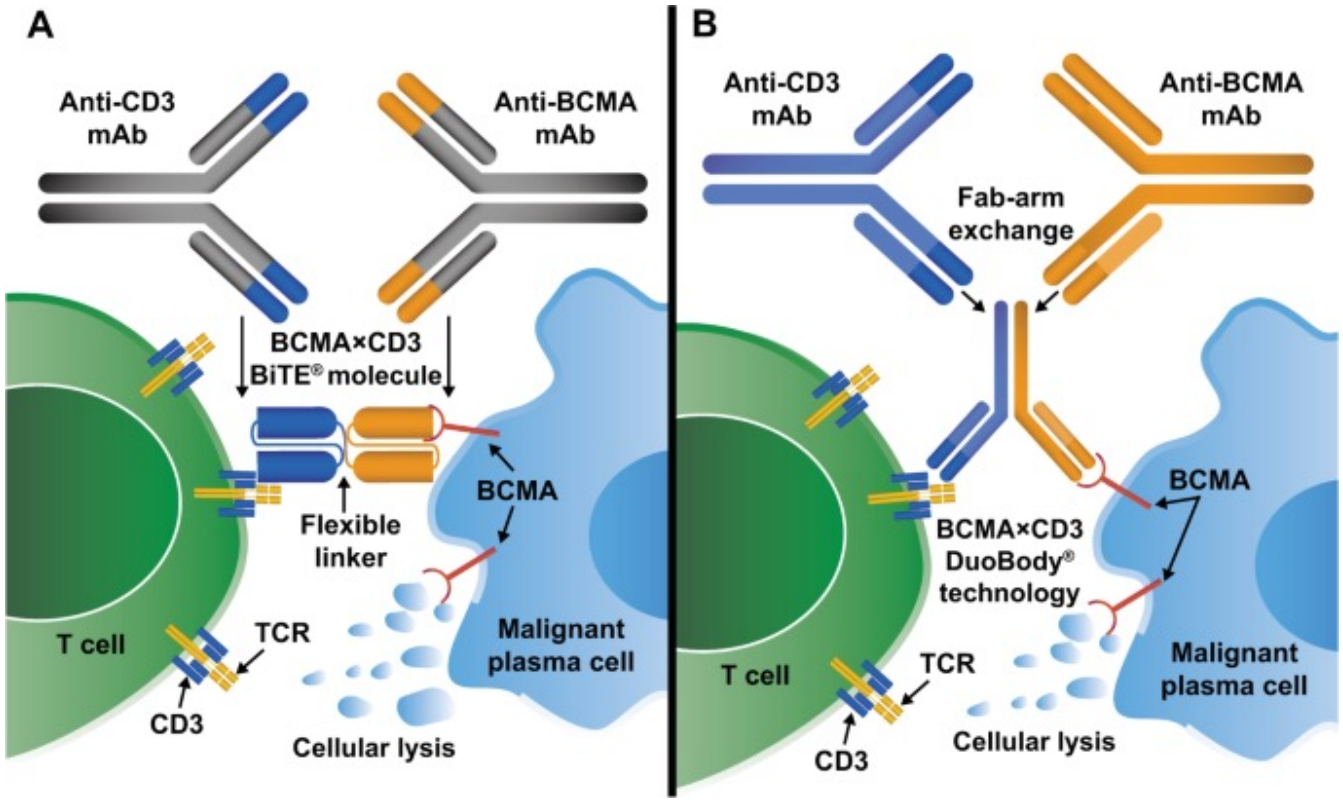
This phase 1–2, open-label study with safety extension evaluated the safety of tividenofusp alfa in 47 children with MPS II who had somatic disease and, typically, neurodevelopmental impairment. Common adverse events in participants treated with tividenofusp alfa included infusion-related reactions, respiratory infection, pyrexia, and anemia. All study participants had adverse events, with infusion-related reactions being the most common. Infusion-related reactions, including hypersensitivity events such as anaphylaxis, are a known risk of ERTs, including standard-of-care idursulfase for MPS II. In this study, most participants had at least one moderate adverse event (including infusion-related reactions); these events were clinically manageable with standard supportive care. The incidence and severity of infusion-related reactions decreased over time. Most participants maintained weekly infusions throughout their respective study period, with a median treatment duration of more than 2 years. Given the TfR-mediated mechanism of tividenofusp alfa, anemia was a prespecified adverse event of special interest. The hemoglobin level is not routinely monitored in pediatric populations with MPS II, and this study may be the first to systematically characterize anemia in this context. At baseline, 19% of the participants had anemia of grade 1 or higher. Decreases in the hemoglobin level were observed early with tividenofusp alfa treatment but generally returned to baseline values, were clinically manageable, and did not result in discontinuation of study participation. Causes of anemia are probably multifactorial, including nutritional deficiencies, frequent phlebotomy early in the study, and possible immune effects such as the formation of antidrug antibodies.

Anti-GPRC5D therapy targets the G protein-coupled receptor family C group 5 member D (GPRC5D), a protein highly expressed on multiple myeloma (MM) cells but minimally on most normal tissues, making it a promising target for treating this blood cancer. Treatments involve specially engineered cells, like CAR T-cells, or antibodies that recognize GPRC5D on cancer cells, leading to their destruction, showing high response rates in relapsed/refractory MM patients, even those previously treated with other therapies like anti-BCMA treatments.

Talquetamab



Das **B-Zell-Reifungsantigen** (BCMA), auch bekannt als **CD269** oder TNFRSF17, ist ein Protein, das fast ausschließlich auf der Oberfläche von reifen B-Lymphozyten und Plasmazellen vorkommt. Da es auf bösartigen Plasmazellen beim **Multiplen Myelom** massiv übererprimiert wird, aber auf gesundem Gewebe kaum vorhanden ist, gilt es im Jahr 2026 als einer der wichtigsten therapeutischen Angriffspunkte in der Hämato-Onkologie.



Dual Targeting of Extramedullary Myeloma with Talquetamab and Teclistamab

Background

Patients with plasmacytomas that are noncontiguous with bone marrow (true extramedullary myeloma) are at high risk for disease progression or relapse. Phase 1 of the RedirecTT-1 study showed promising efficacy with dual-antigen targeting of myeloma with talquetamab (anti–G protein–coupled receptor family C group 5 member D) plus teclistamab (anti–B-cell maturation antigen) in patients with triple-class–exposed relapsed or refractory multiple myeloma, including those with true extramedullary myeloma.

Methods

In this phase 2 study, we investigated talquetamab plus teclistamab exclusively in patients with drug-resistant, true extramedullary myeloma. The primary end point was overall response, evaluated with the use of functional imaging. Secondary end points included the duration of response, progression-free survival, overall survival, and safety.

Conclusions

Most patients with drug-resistant, true extramedullary myeloma had a response with talquetamab plus teclistamab. The incidence of adverse events of grade 3 or above was high and was consistent with previous observations for each agent as monotherapy.

Plasmacytomas exhibit high genomic and microenvironmental complexity, including heterogeneous G protein–coupled receptor family C group 5 member D (GPRC5D) and B-cell maturation antigen (BCMA) expression. Talquetamab (anti-GPRC5D) and teclistamab (anti-BCMA) are first-in-class bispecific antibodies approved as monotherapies for relapsed or refractory myeloma in patients with previous exposure to a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody (triple-class exposure). In the RedirecTT-1 phase 1 study, the recommended phase 2 regimen of talquetamab plus teclistamab elicited a response in 80% of the patients, with a complete response or a stringent complete response in 52%; the probability of a 12-month duration of response was 91%. The observed safety profile was consistent with that of each agent alone in patients with relapsed or refractory myeloma. In a subgroup of patients with true extramedullary myeloma, a response occurred in 61% and the probability of a 12-month duration of response was 82%. These data suggest that dual targeting of GPRC5D and BCMA with talquetamab and teclistamab may lead to a response in a higher percentage of patients, with greater depth and durability of the response, than targeting either antigen alone. Here, we report the results of the RedirecTT-1 phase 2 study of talquetamab plus teclistamab in patients with true extramedullary myeloma.

Methods

Study Design and Patients

We conducted a multicenter, nonrandomized, open-label, phase 1b–2 study of talquetamab plus teclistamab in patients with relapsed or refractory multiple myeloma. In the phase 2 cohort, patients had true extramedullary myeloma, defined by at least one nonradiated, bone-independent, soft-tissue plasmacytoma (≥2 cm in the greatest dimension) confirmed by central review of whole-body positron-emission tomography and computed tomography (PET-CT) scans; magnetic resonance imaging (MRI) was permitted as an alternative to PET-CT with sponsor approval.

Study Treatment

Patients received talquetamab subcutaneously at a dose of 0.8 mg per kilogram of body weight plus teclistamab at a dose of 3.0 mg per kilogram every other week in 28-day cycles, after a dose step-up period. Step-up doses were adapted from approved schedules used with each drug as monotherapy. Patients could switch to monthly doses of talquetamab and teclistamab after completing four cycles and having a very good partial response or better or after completing six cycles irrespective of the depth of response, according to investigator discretion. Patients received study treatment until unacceptable side effects developed, consent was withdrawn, disease progression was confirmed, death occurred, or the investigator or sponsor made the decision to discontinue treatment.

End Points and Assessments

The phase 2 primary end point was overall response (defined as a partial response or better), assessed by an independent review committee with the use of IMWG 2016 criteria.

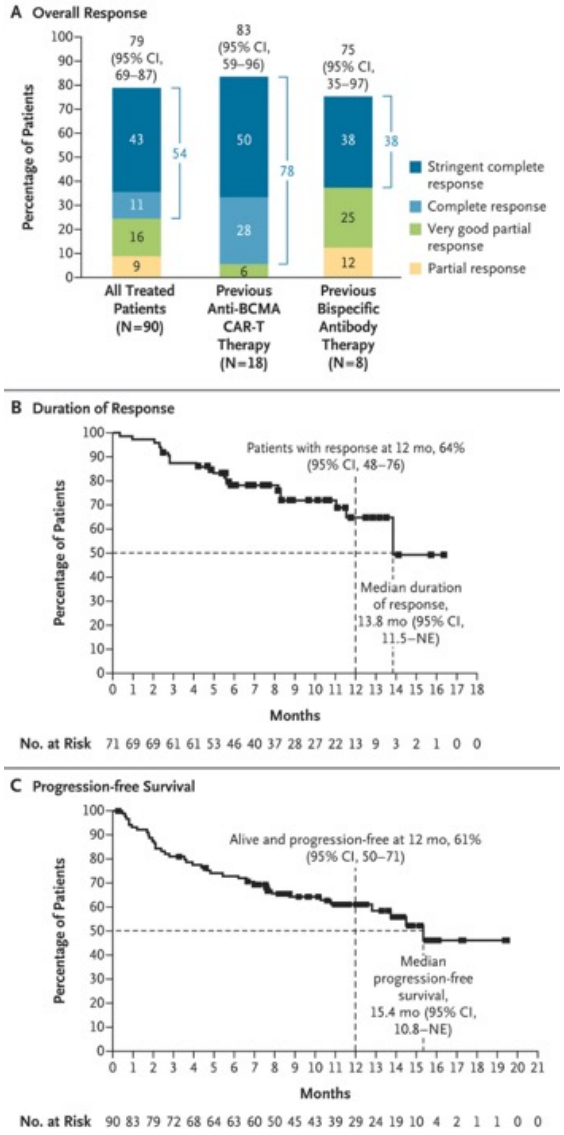
Characteristic	All Patients (N=90)
Bone marrow plasma cells ≥60% — no./total no. (%)†	10/86 (12)
At least 1 true extramedullary plasmacytoma — no. (%)‡§	90 (100)
Extramedullary plasmacytomas‡	
Median no. (range)	2 (1–7)
Distribution — no. (%)	
1	38 (42)
2–3	29 (32)
≥4	23 (26)
Extramedullary myeloma tumor volume — no. (%)	
<25 cm^2	49 (54)
25–50 cm^2	19 (21)
>50 cm^2	22 (24)
High cytogenetic risk — no./total no. (%)¶	14/65 (22)
Measurable disease — no. (%)‖	
Nonsecretory	4 (4)
Oligosecretory	31 (34)
Median time since diagnosis (range) — yr**	4.7 (0.7–21.4)
Previous lines of treatment	
Median no. (range)	4 (1–10)
Distribution — no. (%)	
≤3	39 (43)
>3	51 (57)

Hematologic and Nonhematologic Adverse Events, Excluding Infections.

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	90 (100)	68 (76)
Hematologic events		
Neutropenia	65 (72)	56 (62)
Anemia	46 (51)	28 (31)
Thrombocytopenia	34 (38)	23 (26)
Nonhematologic events		
Oral adverse event†	78 (87)	4 (4)
Cytokine release syndrome	70 (78)	0
Nonrash skin-related adverse event‡	62 (69)	0
Nail-related adverse event§	50 (56)	0
Weight decrease	48 (53)	10 (11)
Dry mouth	40 (44)	0
Cough	33 (37)	0
Diarrhea	30 (33)	3 (3)
Pyrexia¶	28 (31)	1 (1)
Hypokalemia	27 (30)	7 (8)
Fatigue	27 (30)	3 (3)
Nausea¶	27 (30)	0

Most Common Infections.

Infection	Any Grade	Grade 3 or 4	Grade 5†
	number of patients (percent)		
Any infection	71 (79)	28 (31)	0
Upper respiratory tract infection	22 (24)	3 (3)	0
Covid-19	20 (22)	5 (6)	1 (1)‡
Pneumonia	16 (18)	4 (4)	1 (1)
Urinary tract infection	12 (13)	3 (3)	0
Viral upper respiratory tract infection	9 (10)	2 (2)	0
Oral candidiasis	6 (7)	0	0
Sinusitis	5 (6)	2 (2)	0



Discussion

This phase 2 study prospectively assessed response by central radiology review, with FDG PET-CT imaging graded according to the Deauville scale and IMPETUS criteria. Talquetamab plus teclistamab led to an overall response of 79% (54% of the patients had a complete response or better), and 64% of the patients with a response had a response duration of at least 12 months. The study population included patients with nonsecretory or oligosecretory disease; such patients have historically been excluded from most clinical studies because of restrictive eligibility criteria. Our findings offer valuable data for treatment in a population that is both clinically challenging and underrepresented in existing clinical studies. The definition of true extramedullary myeloma in our study is aligned with the emerging consensus that the diagnosis should include only soft-tissue plasmacytomas that are noncontiguous with bone.

At 12 months, progression-free survival was 61% and overall survival was 74%, results that compare favorably with durability and survival outcomes observed with other approved T-cell–redirecting therapies. Approximately three quarters of the patients had grade 3 or 4 adverse events, a finding that is consistent with the known safety profile of each agent alone, yet only 6% of the patients discontinued treatment with one or both agents because of a nonfatal adverse event. Adverse events resulted in death in 10 patients, 5 of whom died from infections. Among patients with a response, the response was maintained after a switch to a monthly dosing schedule.

REVIEW ARTICLE

Cardiogenic Shock

Summary

Cardiogenic shock is characterized by depression of cardiac function that leads to low blood pressure, coronary ischemia, and further decreased cardiac contractility resulting in tissue hypoxemia. The condition is associated with high early mortality, approaching 50%, which is largely influenced by the underlying etiologic factors. In infarct-related cardiogenic shock, rapid restoration of coronary blood flow substantially reduces mortality. Mechanical circulatory support devices offer hemodynamic stabilization and improved outcomes in carefully selected patients, although optimal patient selection and timing of initiation of mechanical circulatory support remain areas of active investigation. Although there have been advances in coronary revascularization techniques and mechanical circulatory support devices, overall survival in cardiogenic shock has improved only modestly. Therefore, future research should focus on refining treatment algorithms, optimizing device use, and developing new strategies to address the high mortality associated with cardiogenic shock.

KEY POINTS

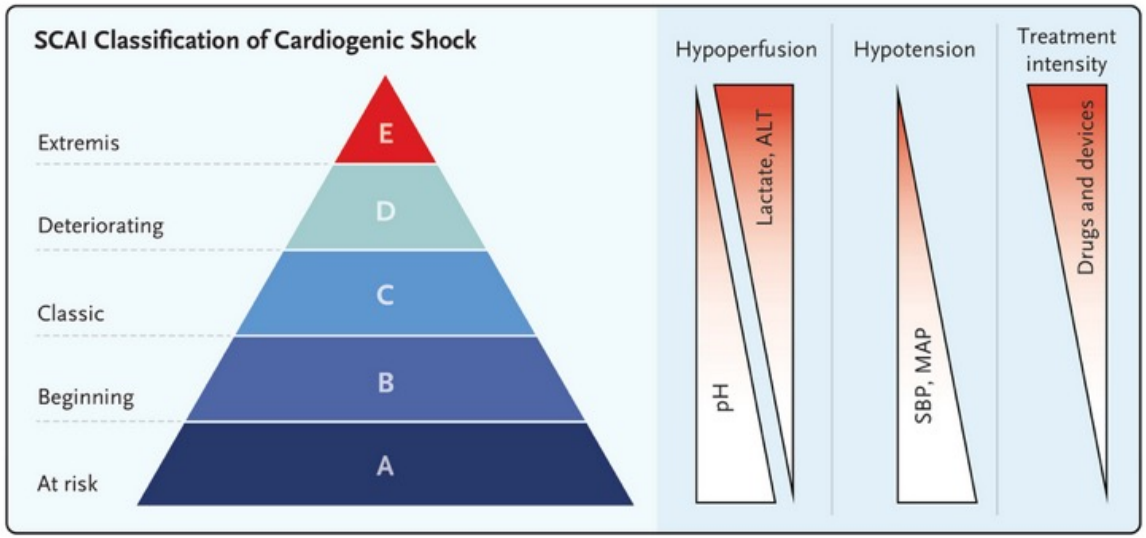
Cardiogenic Shock

- Cardiogenic shock is associated with early mortality approaching 50%, depending on the underlying cause.
- Immediate revascularization in infarct-related cardiogenic shock reduces mortality.
- In patients with multivessel coronary artery disease, current evidence indicates that only the culprit lesion should be revascularized in the acute setting.
- Mechanical circulatory support decreases mortality in selected patient groups.
- Further research is urgently needed to address the high mortality associated with cardiogenic shock.

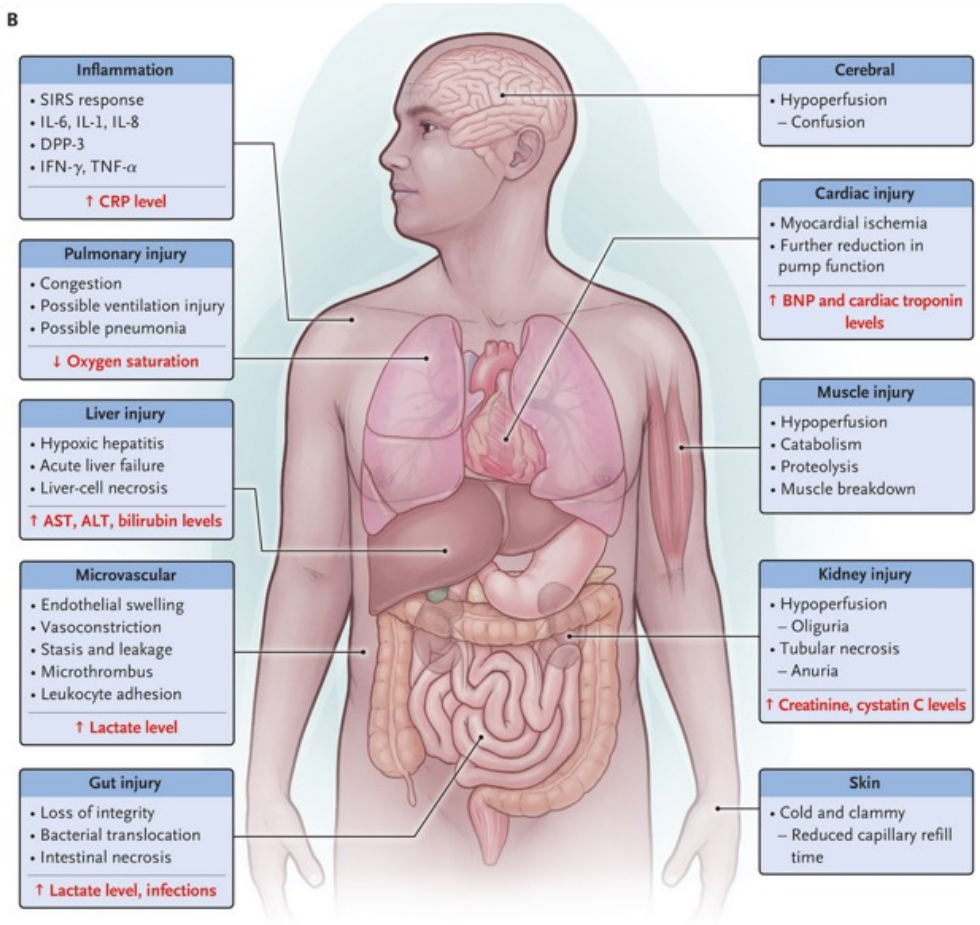
Definitions of Cardiogenic Shock in Major Randomized Trials.

SHOCK[5]	TRIUMPH[6]	IABP-SHOCK II[7]	CULPRIT-SHOCK[8]	ECLS-SHOCK[4]	DanGer Shock[9]
One of the following: AMI with SBP <90 mm Hg for ≥30 min Support to maintain SBP ≥90 mm Hg Plus both of the following: End-organ hypoperfusion (urine output <30 ml/hr) or cool extremities Heart rate >60 beats/min Hemodynamic criteria†: Cardiac index of ≤2.2 liters/min/m² Plus pulmonary capillary wedge pressure ≥15 mm Hg	AMI with patency of infarct-related artery spontaneously or after PCI Refractory cardiogenic shock >1 hr after PCI with SBP <100 mm Hg despite vasopressors (dopamine ≥7 μg/kg/min or norepinephrine or epinephrine ≥0.15 μg/kg/min) End-organ hypoperfusion Clinical or hemodynamic criteria for elevated left ventricular filling pressure LVEF <40%	One of the following: AMI with SBP <90 mm Hg for ≥30 min Catecholamines required to maintain SBP >90 mm Hg Plus clinical pulmonary congestion Plus impaired end-organ perfusion with at least one of the following criteria: Altered mental status Cold, clammy skin and extremities Urine output <30 ml/hr Lactate level >2.0 mmol/liter	AMI with planned early revascularization by PCI Multivessel coronary artery disease defined as >70% stenosis in at least two major vessels (≥2 mm diameter) with identifiable culprit lesion One of the following: SBP <90 mm Hg for >30 min Use of catecholamines required to maintain SBP >90 mm Hg Pulmonary congestion Impaired organ perfusion with at least one of the following criteria: Altered mental status Cold, clammy skin and extremities Urine output <30 ml/hr Lactate level >2.0 mmol/liter	MI with planned early revascularization with PCI or CABG One of the following: SBP <90 mm Hg for >30 min Catecholamine therapy required to maintain SBP >90 mm Hg Impaired organ perfusion with at least one of the following criteria: Altered mental status Cold, clammy skin and extremities Urine output <30 ml/hr Lactate level >3.0 mmol/liter	STEMI <36 hr before randomization Cardiogenic shock with: SBP <100 mm Hg or use of vasopressors to maintain SBP >100 mm Hg Lactate level >2.5 mmol/liter or SVO_2 <55% LVEF <45%

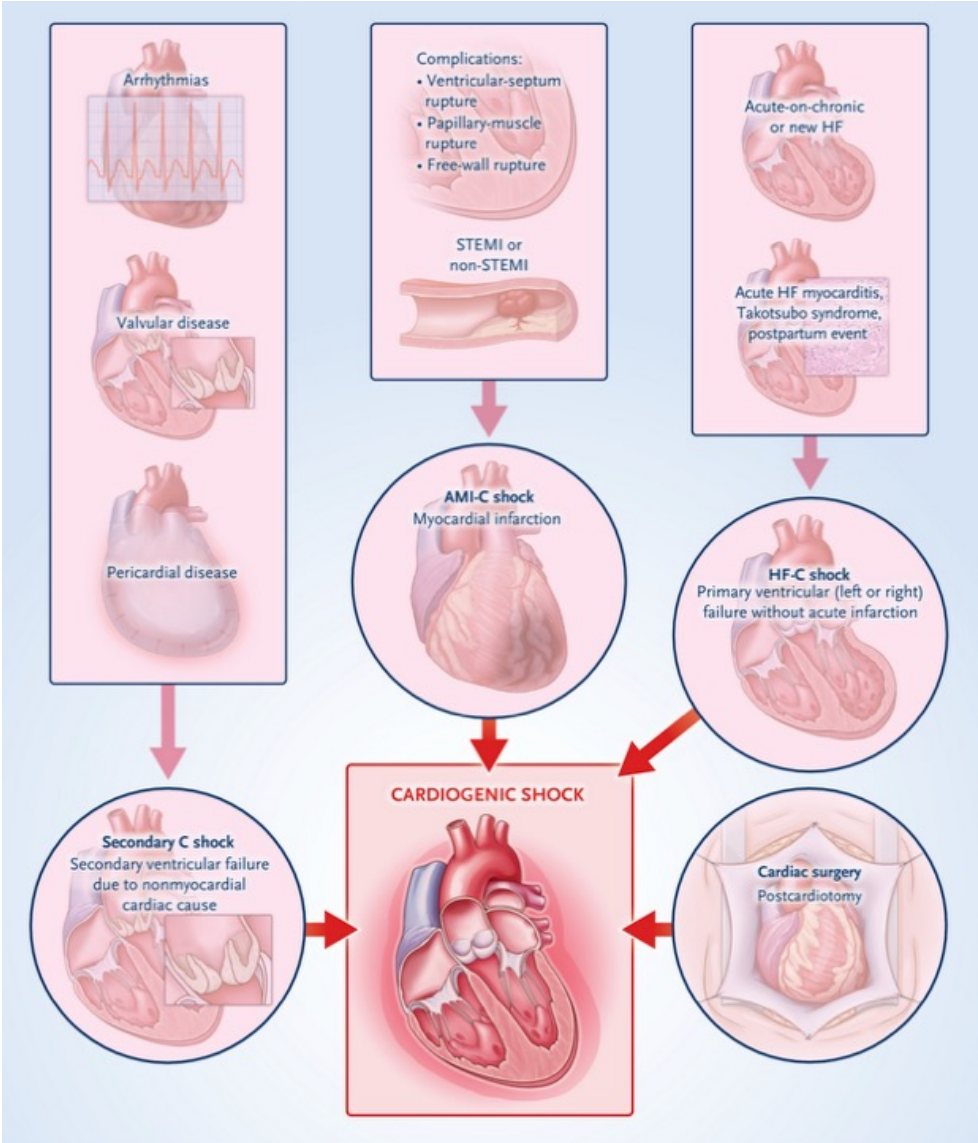
A



Organ Involvement and Staging of Cardiogenic Shock. Panel A shows the cardiogenic shock staging system recommended by the Society for Cardiovascular Angiography and Interventions (SCAI) and the associated degree of hypoperfusion and hypotension and degree of treatment intensity. Stage A denotes risk for cardiogenic shock development but no current presence of signs or symptoms of shock and a lactate level of up to 2 mmol per liter.

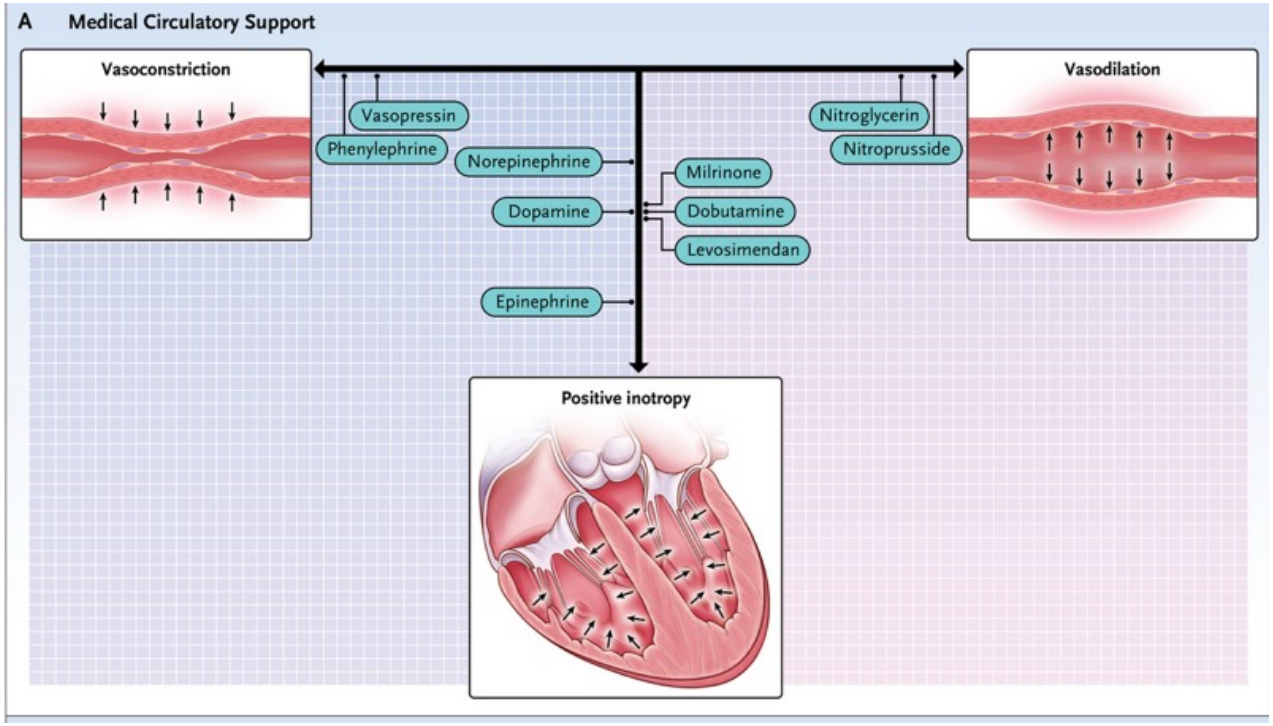


Stage B denotes beginning cardiogenic shock with clinical evidence of relative hypotension or tachycardia without hypoperfusion and a lactate level of up to 2 mmol per liter. Stage C denotes classic cardiogenic shock with a lactate level greater than 2 mmol per liter, cardiac index of less than 2.2 liters per minute per square meter of body-surface area and pulmonary capillary wedge pressure over 15 mm Hg. Stage D denotes deteriorating cardiogenic shock with a rising lactate level or a lactate level that is consistently higher than 2 mmol per liter and hemodynamic signs that lead to escalating doses of vasopressors or the addition of mechanical circulatory support. Stage E denotes extreme cardiogenic shock with a lactate level greater than 8 mmol per liter and hemodynamically profound hypotension despite maximal hemodynamic support. (Panel A is adapted from the SCAI SHOCK Classification pyramid.) Panel B shows multisystem organ involvement in cardiogenic shock with associated clinical signs and laboratory markers. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, BNP brain natriuretic peptide, CRP C-reactive protein, DPP-3 dipeptidyl peptidase 3, IFN-γ interferon-γ, IL interleukin, MAP mean arterial blood pressure, SBP systolic blood pressure, SIRS systemic inflammatory response syndrome, and TNF-α tumor necrosis factor α.

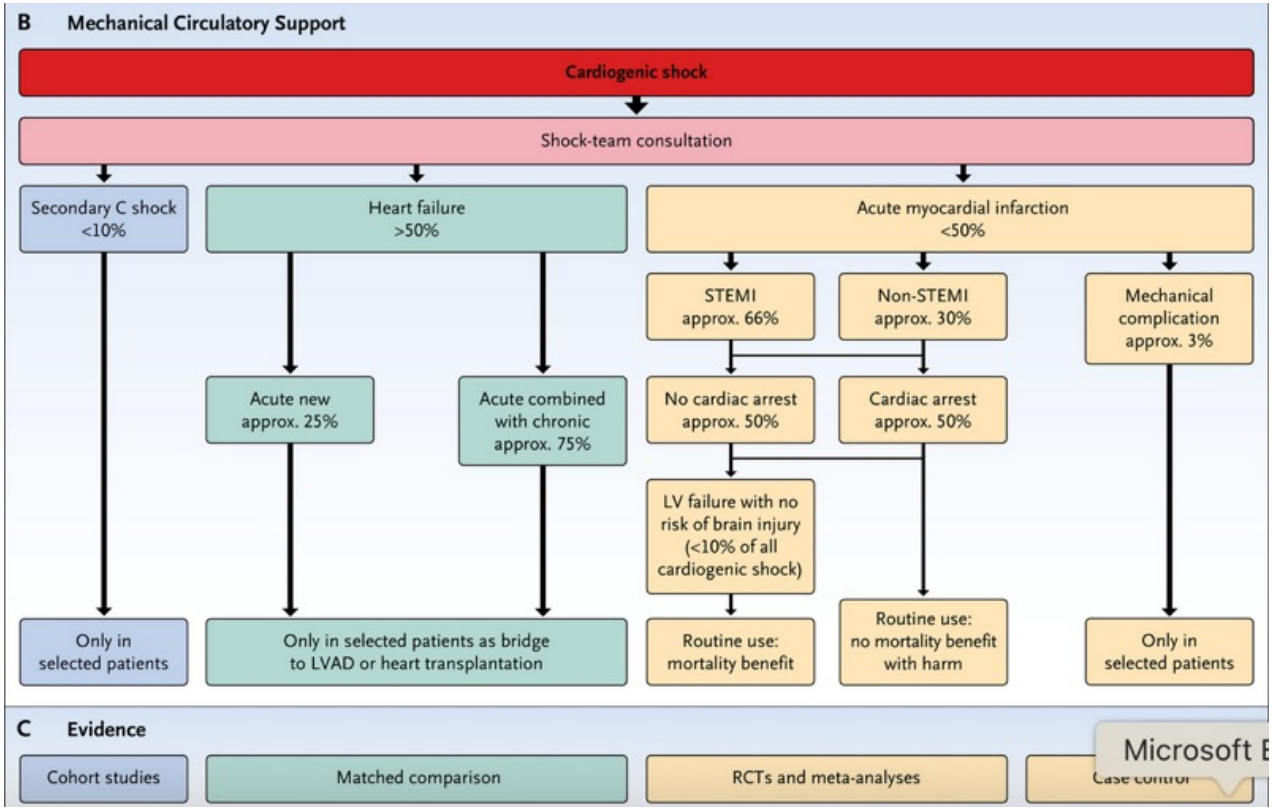


Causes of Cardiogenic Shock.

AMI-C shock denotes acute myocardial infarction–related cardiogenic shock, C shock cardiogenic shock, HF heart failure, HF-C shock heart failure–related cardiogenic shock, and STEMI ST-segment elevation myocardial infarction.



Medical and Mechanical Circulatory Support.
Panel A shows the hemodynamic effects of vasoactive drugs, such as vasopressors and inodilators on vasoconstriction, vasodilation, and inotropy.



Panel B shows possible indications for mechanical circulatory support with respect to different causes of cardiogenic shock based on current evidence. No risk of hypoxic brain injury relates to the DanGer Shock trial criteria. LV denotes left ventricular, LVAD left ventricular assist device, and RCT randomized, controlled trial.

Pharmacologic Management of Cardiogenic Shock

Fluid Management

In patients who have central hypovolemia without congestion and in whom hemodynamics improve after a leg-raise test, administration of crystalloid solutions may improve hemodynamics. Intravenous loop diuretics may reduce fluid retention and pulmonary edema in cases of volume overload. Avoiding hypovolemia is crucial, and fluid management should be based on pathophysiological considerations and may differ on the basis of right ventricular–dominant or left ventricular–dominant failure.

Inotropes and Inodilators

Contractility can be enhanced by inotrope therapy, although the effect of these agents on outcomes is not well established. The first-line choice of an inotrope lacks a clear consensus and the selection of inotropes for treating patients in cardiogenic shock varies widely.

Vasopressors

In a randomized comparison of 1679 patients with diverse causes of shock, treatment with dopamine was associated with substantially more arrhythmic events than treatment with norepinephrine but with no difference in mortality.

Mechanical Circulatory Support Devices

Temporary percutaneous mechanical circulatory support can stabilize hemodynamics and enhance end-organ perfusion in cardiogenic shock.

Intraaortic Balloon Pump

Owing to its ease of insertion, cost, and favorable adverse-event profile, the intraaortic balloon pump (IABP) is still widely used.

Venoarterial Extracorporeal Membrane Oxygenation

Venoarterial ECMO, which delivers flow support of up to 6 liters per minute, can provide full respiratory and circulatory assistance for the right and left ventricles.

Microaxial Flow Pumps

Microaxial flow pumps provide a peak flow of approximately 4.3 liters per minute with a percutaneously placed catheter and are used to treat cardiogenic shock with predominant left ventricular dysfunction. Microaxial flow pumps have been investigated in few randomized trials involving patients with cardiogenic shock and in large-scale propensity-matched studies including more than 100,000 patients; the studies consistently have shown no survival benefit and higher complication rates.

Left Atrial-to-Femoral Arterial Devices

The TandemHeart mechanical circulatory support device, which directs flow from the left atrium to a femoral artery, is rarely used in clinical practice as compared with venoarterial ECMO or microaxial flow pumps.

General Reflections on Mechanical Circulatory Support

Patient selection for temporary mechanical circulatory support in cardiogenic shock is key to identifying a possible benefit with regard to clinical outcomes. The use of mechanical circulatory support varies and is influenced by expert opinions, practitioner experience, and health care reimbursement, among other factors.

Treatment of Causes of Cardiogenic Shock

Revascularization in Acute Myocardial Infarction

The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial did not show a reduction in 30-day mortality with early revascularization as compared with initial medical stabilization. However, longer-term results showed reduced mortality (by up to 6 years) with early revascularization. Therefore, early revascularization is highly recommended in society guidelines. Multiple registries have shown that a delay in revascularization in the clinical setting of cardiogenic shock is associated with worse clinical outcomes, a finding that has led to a call for more efforts to reduce the time from first medical contact to balloon inflation (door-to-balloon time) in this patient population.

Mechanical and Valvular Complications and Access-Site Considerations

Mechanical complications after acute myocardial infarction, such as papillary muscle rupture or ventricular septal-wall and free-wall rupture or defects, are rare and of decreasing incidence; however, if these occur, the prognosis is dismal. Therefore, surgical or percutaneous correction is required for survival.[2]

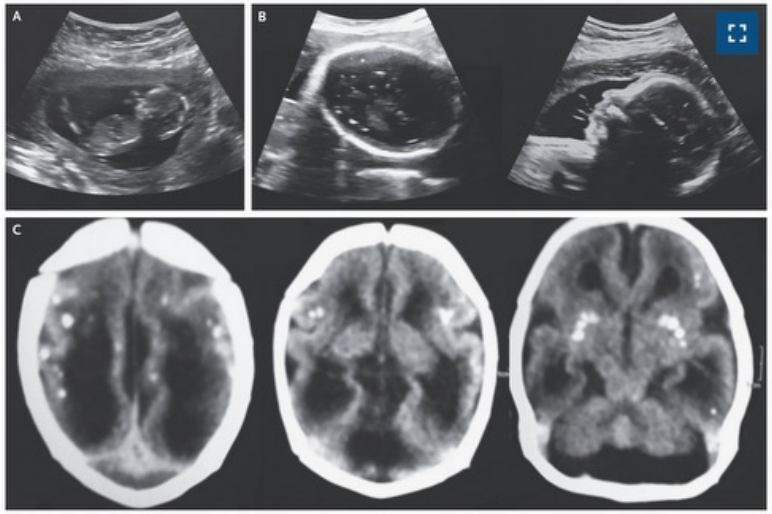
Ongoing (Still Recruiting or Completed but Not Published) Randomized Trials in Cardiogenic Shock.

Trial and ClincalTrials.gov No.	Type of Cardiogenic Shock	Experimental Intervention	Control	Sample Size	Primary End Point	Remarks
Mechanical circulatory support						
ECMO-RRT (NCT02870946)	AMI and HF	VA-ECMO plus RRT	VA-ECMO only	362	Mortality at 30 days	
HEMO-ECMO (NCT03729765)	AMI and HF	VA-ECMO plus hemoperfusion	VA-ECMO	60	Change in IL-6 level at 3 days	
ANCHOR (NCT04184635)	AMI	VA-ECMO plus IABP	Best medical therapy	400	Mortality or VA-ECMO at 30 days	
UNLOAD-ECMO (NCT05577195)	AMI and HF	VA-ECMO plus Impella CP	VA-ECMO	198	Mortality at 30 days	Lactate level >5 mmol/liter for inclusion
ULYSS (NCT05366452)	AMI	Impella CP	Best medical therapy	204	Either composite of all-cause death, ECMO, LVAD, or heart transplantation at 30 days	
RECOVER IV (NCT05506449)	AMI	Impella CP	Best medical therapy including IABP	558	Mortality at 30 days	Stopped early for safety
ICONE (NCT05699005)	AMI and HF	Individualized transfusion during VA-ECMO	Conventional transfusion during VA-ECMO	138	Total number of PRBCs transfused during support, adjusted for VA-ECMO duration	
REMAP ECMO (NCT05913622)	AMI and HF	VA-ECMO plus IABP	VA-ECMO	430	Successful weaning from VA-ECMO at 30 days	Bayesian analysis, adaptive design
Transcatheter interventions						
MINOS (NCT05298124)	AMI and HF	M-TEER	Best medical therapy	144	Composite of in-hospital death from any cause, cardiac transplantation, implantation of durable LVAD, or discharge with palliative inotropic therapy	Mitral regurgitation grade 3+ or 4+
RESCUE-SHOCK (NCT05527717)	AMI	Immediate multivessel PCI with VA-ECMO	Culprit-lesion only PCI with VA-ECMO	560	Composite of death from any cause, LVAD, or heart transplantation at 90 days	
Inotropes, vasopressors, and hemodynamic agents						
LevoHeartShock (NCT04020263)	AMI and HF	Levosimendan	Placebo	610	Composite of death from any cause, VA-ECMO, or dialysis at 30 days	
CAPITAL DOREMI-2 (NCT05267886)	AMI and HF	Dobutamine or milrinone	Placebo	346	Composite of in-hospital death from any cause and the occurrence of any of the following ≤12 hr after start of intervention: • Sustained hypotension (MAP ≤55 mm Hg) or sustained use of high-dose vasopressors • Lactate level >3.5 mmol/liter at 6 hr or thereafter • Need for MCS • Atrial or ventricular arrhythmia leading to emergent electrical cardioversion • Cardiac arrest	SCAI shock C or D
NorShock (NCT05168462)	AMI	MAP ≥55 mm Hg	MAP ≥65 mm Hg	776	Composite of death from any cause and severe renal failure leading to renal replacement therapy	
PACCS (NCT05485376)	HF	PAC	No PAC	400	In-hospital mortality	Lactate level >2 mmol/liter
Systemic approaches and antiplatelet agents						
DAPT-SHOCK (NCT03551964)	AMI	Cangrelor plus DAPT with ticagrelor	DAPT with ticagrelor	605	Laboratory end point, platelet reactivity index; clinical end point, MACE	Primary laboratory end point met; primary clinical end point not met
DOBERMANN (NCT05350592)	AMI preshock	Tocilizumab or dobutamine (or both)	Placebo		Pro–B-type natriuretic peptide plasma concentration <48 hr	2×2 factorial design; patients with preshock, no overt cardiogenic shock; double-blind
COCCOA (NCT03773822) — Completed	AMI and HF	Combination of hydrocortisone and fludrocortisone	Placebo	380	Free of corticosteroid therapy at day 7	

Future Perspectives

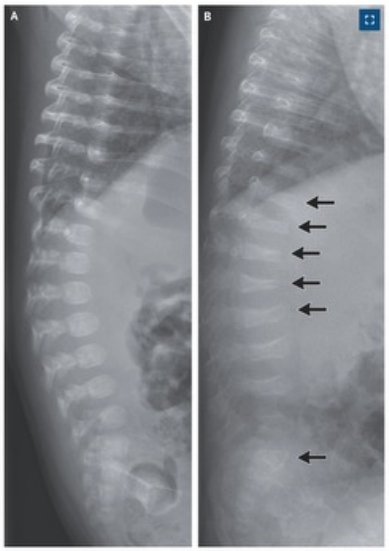
In general, randomized trials in cardiogenic shock are difficult to perform, and only a few trials have enrolled a sufficient number of patients to be adequately powered to detect differences in outcomes. The diversity of cardiogenic-shock phenotypes complicates patient selection for trials, potentially causing variability in treatment responses, and may also explain neutral trial results. Therefore, advanced phenotyping of patients with cardiogenic shock to understand who might benefit from specific targeted therapeutic strategies should be taken into account in trial design. Ethical considerations, owing to the acuity and severity of the condition, present another issue that challenges informed-consent processes. Despite challenges associated with clinical trials in cardiogenic shock, it has been repeatedly shown that such trials can be performed successfully. International activities are therefore required to build large shock-research networks to answer the multiple open questions regarding treatment.

Congenital Zika Syndrome



A 6-month-old baby boy was referred to a pediatric neurology clinic in Brazil for evaluation of developmental delay. At 12 weeks' gestation, prenatal ultrasonography had shown a normally developing head (Panel A). At the beginning of the second trimester, which was during the 2015–2016 Zika virus epidemic, the baby's mother had had a rash and tested positive for Zika virus. Prenatal ultrasonography at 29 weeks' gestation had shown microcephaly and calcifications in the brain parenchyma (Panel B; left, axial view; and right, sagittal view). When the baby was born at term, he had microcephaly and a positive serum IgM test for Zika virus. Severe developmental delay and epilepsy subsequently developed. Computed tomography of the head at 1 month of age had revealed lissencephaly and multiple intracranial calcifications in the subcortical region and basal ganglia (Panel C shows different levels of calcifications; left and center, axial view; and right, coronal view). At the current presentation, physical examination was notable for a lack of head support, eye contact, and vocalization. Diffuse hypertonia and hyperreflexia signs were also seen. A diagnosis of probable congenital Zika syndrome was made on the basis of the exposure history, clinical and radiographic findings, and negative prenatal maternal testing for other infections that cause congenital neurologic conditions. Physical, occupational, and speech therapy was recommended.

Osteogenesis Imperfecta



A 17-day-old boy was referred to a pediatric skeletal disorders clinic for evaluation of suspected osteogenesis imperfecta. Prenatal ultrasonography at 23 weeks' gestation had shown shortened and deformed long bones with possible femoral fractures. There was no family history of skeletal disorders. On physical examination, macrocephaly, blue sclerae, and bowing and shortening of the legs were noted. Radiographs of the spine showed slightly increased translucency of the vertebrae but no deformities or loss of height (Panel A, lateral view). During the subsequent 2.5 months, new fractures of the humeri and femurs occurred. A repeat radiograph of the spine at 3.5 months of age showed profound loss of vertebral bone mass, as well as vertebral compression fractures (Panel B, arrows, lateral view). Genetic testing identified a missense mutation in *COL1A1*, the gene that — along with *COL1A2* — encodes type I collagen. A diagnosis of osteogenesis imperfecta type III was made. In cases of severe osteogenesis imperfecta, vertebral compressions may occur in infants before the development of the gravitational stress of sitting or standing. Quarterly treatment with intravenous bisphosphonates was started when the child was 5 months old. At 8 months after the first infusion, only one new fracture had occurred.

Closing the Gap

A 31-year-old woman presented to the emergency department in October with a 10-day history of fever, sinus pressure, cough, nausea, and vomiting. Her husband and 1-year-old child, who attends day care, had similar symptoms.

In the preceding 5-month period, unlike her family members, she had had night sweats, fatigue, an unintentional 4.5-kg (10-lb) weight loss, and three episodes of coughing, nasal congestion, sinus pressure, nausea, and vomiting. Her sinonasal symptoms had been diagnosed as upper respiratory tract infections and had resolved with decongestants and cough suppressants.

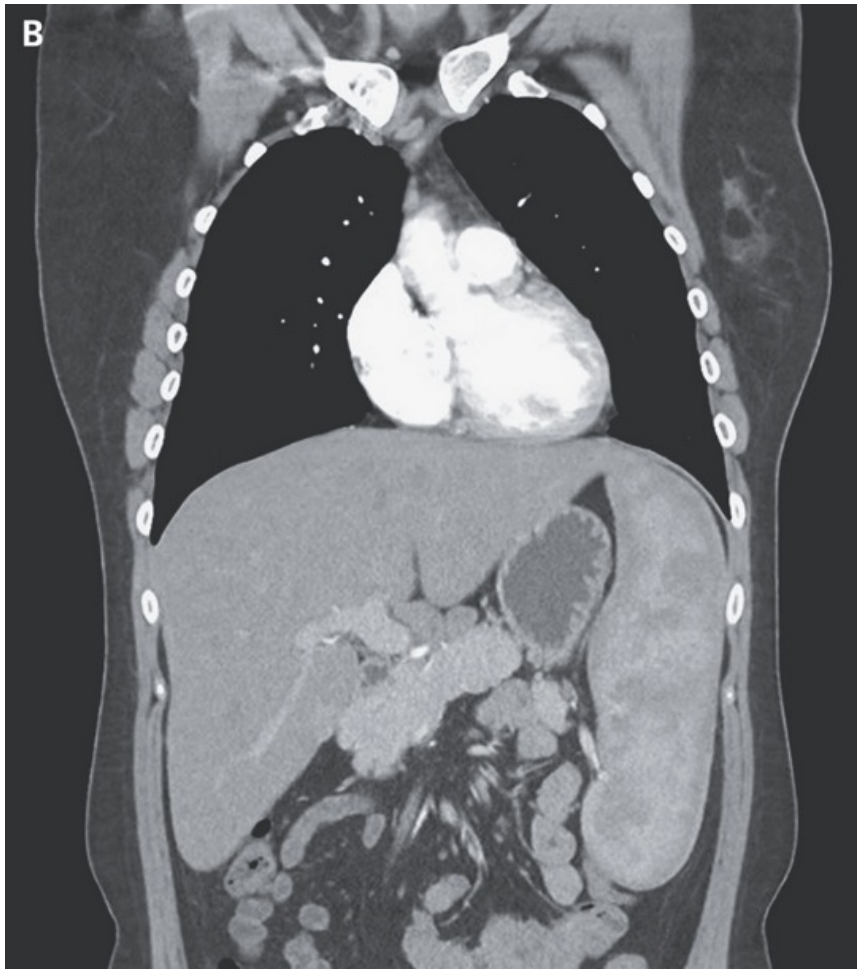
The patient was born in Florida and had lived in Baltimore most of her life. One week before her current illness, she had traveled to Chicago, where, at a petting zoo, she had direct contact with cows and sheep. She had not otherwise traveled in the preceding year. She owned two dogs and one cat and had no known bites, scratches, tick bites, or rodent exposure. She owned potted plants and did not garden. She worked in an office and reported drinking two alcoholic drinks weekly; she reported never having used tobacco or nonprescribed drugs. She noted no sexual partners other than her husband, took no medications, and had never been homeless or incarcerated.

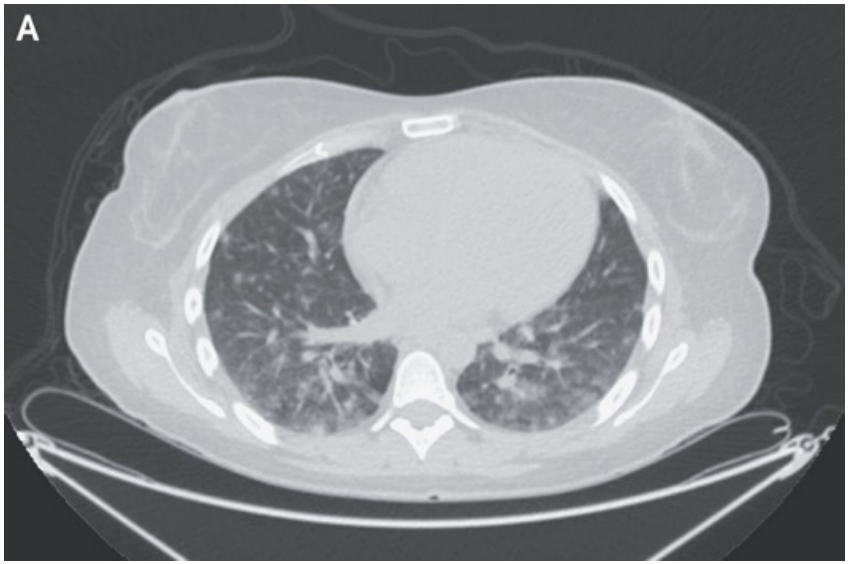
At 14 years of age, she had been treated for immune thrombocytopenia with intravenous immune globulin, and the condition had not recurred. She was otherwise healthy as a child and adolescent.

Her blood pressure was 120/68 mm Hg, heart rate 122 beats per minute, respiratory rate 16 breaths per minute, oxygen saturation 100% while she was breathing ambient air, and oral temperature 39.5°C (103.1°F). The body-mass index (the weight in kilograms divided by the square of the height in meters) was 22.5. Frontal and maxillary sinuses were tender to palpation. Dentition was intact; the oropharynx was pink without tonsillar enlargement, erythema, or exudate. Smooth, nontender cervical lymph nodes measuring approximately 2 cm in diameter were palpable. Lung fields were clear to auscultation. There was nontender hepatomegaly measuring 5 cm below the costal margin in the midclavicular line, and the spleen tip was palpable. The remainder of the physical examination was unremarkable.

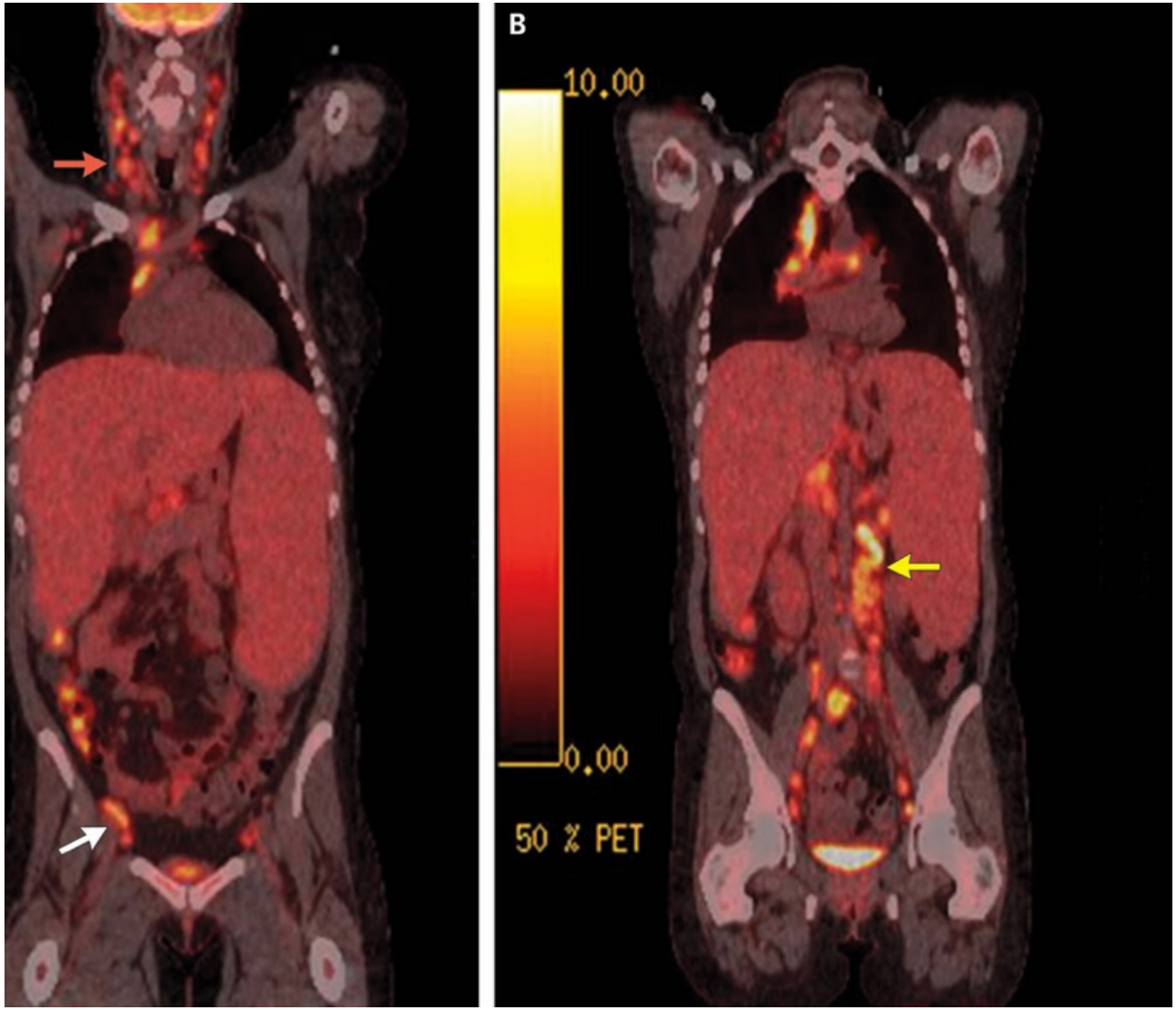
The white-cell count was 2200 per cubic millimeter, with 62% neutrophils, 23% lymphocytes, 13% monocytes, and 0.4% eosinophils. The absolute neutrophil count was 1380 cells per cubic millimeter. The hemoglobin level was 10.7 g per deciliter, mean corpuscular volume 71.7 fl, and platelet count 88,000 per cubic millimeter. The absolute reticulocyte count was 16,700 per cubic millimeter (reference range, 24,100 to 87,700), and immature platelet fraction 8.2% (reference range, 0.1 to 6.3). The haptoglobin level was 187 mg per deciliter (reference range, 32 to 197), ferritin level 104 ng per milliliter (reference range, 30 to 400), and lactate dehydrogenase level 299 U per liter (reference range, 122 to 220).

A peripheral-blood smear showed microcytic, hypochromic anemia, occasional pencil cells (rod-shaped red cells), lymphopenia, and thrombocytopenia. The aspartate aminotransferase level was 87 U per liter (reference range, 0 to 31), alanine aminotransferase level 79 U per liter (reference range, 0 to 31), alkaline phosphatase level 328 U per liter (reference range, 30 to 120), and total bilirubin level 0.8 mg per deciliter (13.7 µmol per liter) (reference value, <1.2 mg per deciliter [20.5 µmol per liter]). The total protein level was 5.5 g per deciliter (reference range, 6.0 to 8.2), and the albumin level 4.0 g per deciliter (reference range, 3.5 to 5.3). The erythrocyte sedimentation rate was 11 mm per hour (reference range, 4 to 25). The C-reactive protein level was 4.5 mg per deciliter (reference value, <0.5). Urinalysis was negative for leukocytes and red cells and showed trace protein.
Serum immunoglobulin levels were decreased, with an IgG level of 336 mg per deciliter (reference range, 610 to 1616), an IgA level of 17 mg per deciliter (reference range, 61 to 348), and an IgM level of 28 mg per deciliter (reference range, 35 to 242). Contrasted computed tomography of the sinuses, chest, abdomen, and pelvis revealed bilateral frontal and maxillary sinusitis, numerous scattered irregular pulmonary nodules of varying sizes with lower lung predominance (Figure 1A), several subcentimeter hyperdense liver nodules, liver enlargement measuring 20 cm in the craniocaudal dimension (reference value, <13 cm) (Figure 1B), splenomegaly measuring 20.5 cm (reference value, <13), and diffuse intrathoracic and intraabdominal lymphadenopathy (many nodes >2 cm).

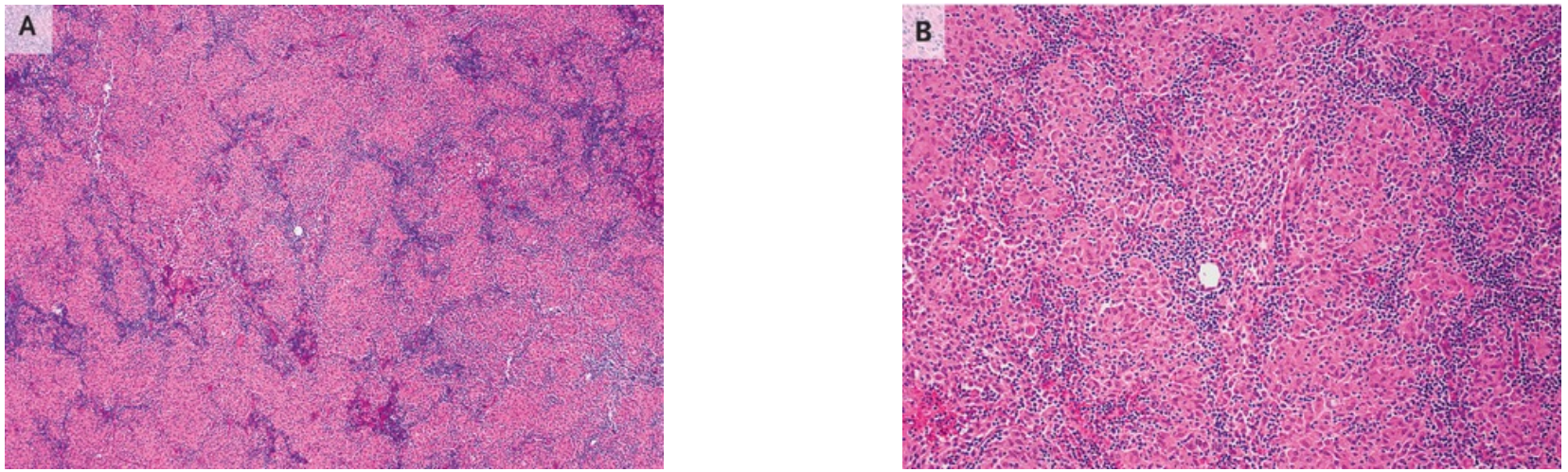




Imaging Studies of the Chest.
An axial computed tomographic scan of the chest shows bilateral pulmonary nodules of varying size in the perilymphatic and peribronchovascular distribution (Panel A); a coronal view shows hepatomegaly and splenomegaly (Panel B).



Imaging Studies from the Skull Base to Mid-Thigh.
A coronal positron-emission tomographic–computed tomographic scan shows bulky, ^{18}F-fluorodeoxyglucose–avid lymphadenopathy in the cervical (red arrow) and inguinal (white arrow) chains (Panel A), as well as the periaortic and retroperitoneal chains (Panel B, yellow arrow).



Histologic Examination of an Excisional Biopsy Sample of the Right Supraclavicular Lymph Node.

Hematoxylin and eosin staining showed effaced lymph-node architecture by nonnecrotizing granulomatous inflammation (Panel A); the granulomas were small, compact, and comprised epithelioid histiocytes (Panel B, higher magnification). The histologic images were provided by Caroline Early, M.D.

Commentary

This 31-year-old woman presented with recurrent episodes of fever, sinusitis, cough, nausea, and vomiting, with associated night sweats and unintentional weight loss. She was found to have pancytopenia, hepatosplenomegaly, pulmonary and hepatic nodules, and nonnecrotizing granulomatous inflammation. Extensive evaluation for infectious and malignant causes was unrevealing. Ultimately, the additional combination of hypogammaglobulinemia and impaired vaccine response led to a diagnosis of CVID.

CVID is a group of primary immune disorders with impaired antibody production characterized by low serum immunoglobulin levels and inadequate antibody response to vaccines and infections. CVID is the most common symptomatic primary immunodeficiency, with a reported incidence of approximately 1 in 20,000 persons. CVID affects both sexes equally and can manifest at any age. Most diagnoses occur between 20 and 40 years of age. The average delay to diagnosis is 6 to 7 years from the onset of cardinal symptoms.

One hallmark of CVID is frequent sinopulmonary or enteric infections, often with encapsulated bacteria. However, only a third of patients with CVID have infections as the sole manifestation, whereas one or more autoimmune, inflammatory, or malignant complications may develop in the rest. These complications include immune thrombocytopenia (as seen in our patient), autoimmune hemolytic anemia, nonnecrotizing granulomatous inflammation, noninfectious pulmonary and gastrointestinal disease, benign lymphoproliferation, and malignant conditions (especially lymphoma). Infectious complications tend to occur early in the disease course, whereas malignant conditions are most often late complications. Autoimmune complications may occur at any time.

The pathogenesis of autoimmunity and granulomatous inflammation in CVID is poorly defined. Current research suggests an intrinsic immunologic defect leading to dysregulation of cellular immunity, in addition to impaired humoral immunity. Along with impaired B-cell function, many patients with CVID have systemic immune activation, especially persistent T-cell activation or serum cytokine elevation.

Intimate partner violence refers to behaviour within an intimate relationship that causes physical, sexual or psychological harm, including acts of physical aggression, sexual coercion, psychological abuse and controlling behaviours.

Intimate Partner Violence vs. Domestic Violence

Intimate Partner Violence

Intimate Partner Violence includes any behaviors that one intimate partner (current or former) uses over another to establish power and control. These can include physical or sexual violence, but they do not always; they can be financial, emotional/psychological, cultural, spiritual, reproductive, or other controlling behaviors.

Domestic Violence

1) For **YWCA Spokane,** we utilize the term domestic violence to refer to any situation where one partner in an intimate relationship tries to maintain power and control over the other person.
2) **Legally,** Domestic Violence applies to any two parties in the same household who commit crimes of physical harm, bodily injury, or assault; creating a fear that physical harm, bodily injury, pushing, shoving, slapping, punching, kicking, or assault will happen soon; sexual assault; or stalking.

Child Survivors of Intimate Partner DV

Children are often accidentally or incidentally impacted by a parent experiencing Intimate Partner Domestic Violence. Our child advocate and therapist work with children whose primary issues/concerns stem from witnessing their parent go through Intimate Partner Domestic Violence.

Child Survivors of Domestic Violence

If the prominent concern is sexual assault and/or child maltreatment (particularly physical abuse), YWCA Spokane will refer these cases to Lutheran Community Services or Partners with Families and Children for support services. Depending on the nature and severity of the abuse, may also be a mandated report to Child Protective Services.

Please do not hesitate to call our Intimate Partner Domestic Violence Support Services at 509-789-9297 to see if our agency is right for your case, to make an appointment, or to simply speak to someone if you need support.

Disease burden attributable to intimate partner violence against females and sexual violence against children in 204 countries and territories, 1990–2023: a systematic analysis for the Global Burden of Disease Study 2023

Summary

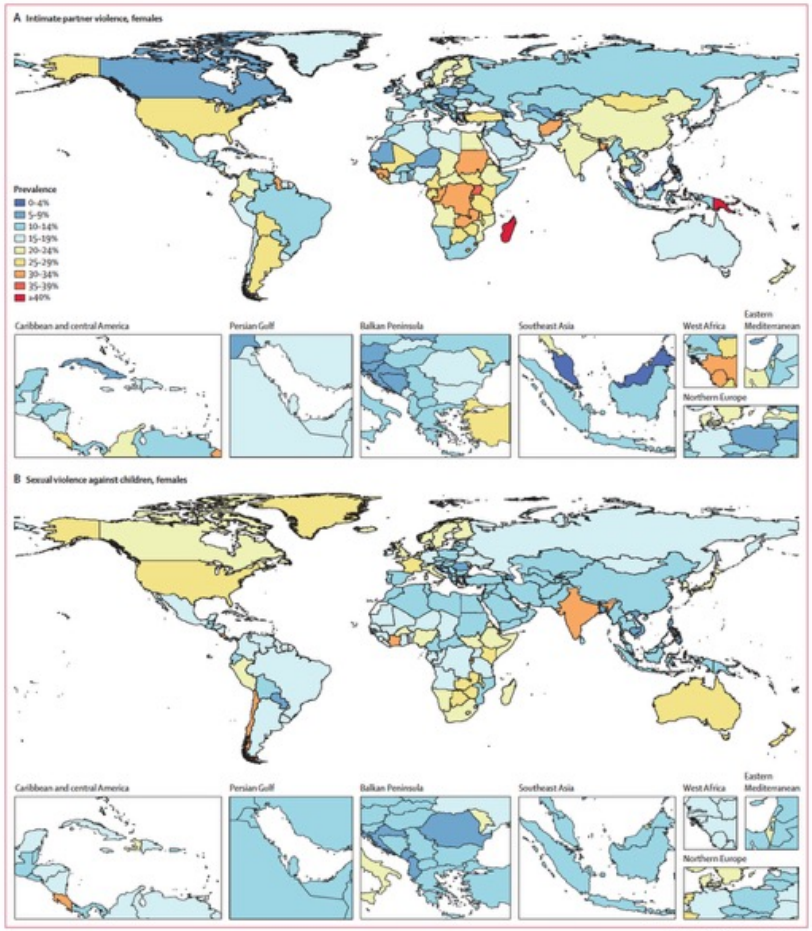
Background Violence against women and against children are human rights violations with lasting harms to survivors and societies at large. Intimate partner violence (IPV) and sexual violence against children (SVAC) are two major forms of such abuse. Despite their wide-reaching effects on individual and community health, these risk factors have not been adequately prioritised as key drivers of global health burden. Comprehensive x§and reliable estimates of the comparative health burden of IPV and SVAC are urgently needed to inform investments in prevention and support for survivors at both national and global levels.

Methods We estimated the prevalence and attributable burden of IPV among females and SVAC among males and females for 204 countries and territories, by age and sex, from 1990 to 2023, as part of the Global Burden of Diseases, Injuries, and Risk Factors Study 2023. We searched several global databases for data on self-reported exposure to IPV and SVAC and undertook a systematic review to identify the health outcomes associated with each of these risk factors. We modelled IPV and SVAC prevalence using spatiotemporal Gaussian process regression, applying data adjustments to account for measurement heterogeneity. We employed burden-of-proof methodology to estimate relative risks for outcomes associated with IPV and SVAC. These estimates informed the calculation of population attributable fractions, which were then used to quantify disability-adjusted life-years (DALYs) attributable to each risk factor.

Findings Globally, in 2023, we estimated that 608 million (95% uncertainty interval 518–724) females aged 15 years and older had ever been exposed to IPV, and 1·01 billion (0·764–1·48) individuals aged 15 years and older had experienced sexual violence during childhood. 18·5 million (8·74–30·0) DALYs were attributed to IPV among females and 32·2 million (16·4–52·5) DALYs were attributed to SVAC among males and females in 2023. IPV and SVAC were among the top contributors to the global disease burden in 2023, particularly among females aged 15–49 years, ranking as the fourth and fifth leading risk factors, respectively, for DALYs in this group. Among the eight health outcomes found to be associated with IPV, anxiety disorders and major depressive disorder were the leading causes of IPV-attributed DALYs, accounting for 5·43 million (–1·25 to 14·6) and 3·96 million (1·71 to 6·92) DALYs in 2023, respectively. SVAC was associated with 14 health outcomes, including mental health disorder, substance use disorder, and chronic and infectious disease outcomes. Self-harm and schizophrenia were the leading causes of SVAC-attributed burden, with SVAC accounting for 6·71 million (2·00 to 12·7) DALYs due to self-harm and 4·15 million (–1·92 to 13·1) DALYs due to schizophrenia in 2023.

Interpretation IPV and SVAC are substantial contributors to global health burden, and their health consequences span a variety of individual health outcomes. Importantly, mental health disorders account for the greatest share of disease burden among survivors. Investing in prevention of these avoidable risk factors has the potential to avert millions of DALYs and considerable premature mortality each year. Our findings represent strong evidence for global and national leaders to elevate IPV and SVAC among public health priorities. Sustained investments are needed to prevent IPV and SVAC and to implement interventions focused on supporting the complex social and health needs of survivors.

Funding Gates Foundation.



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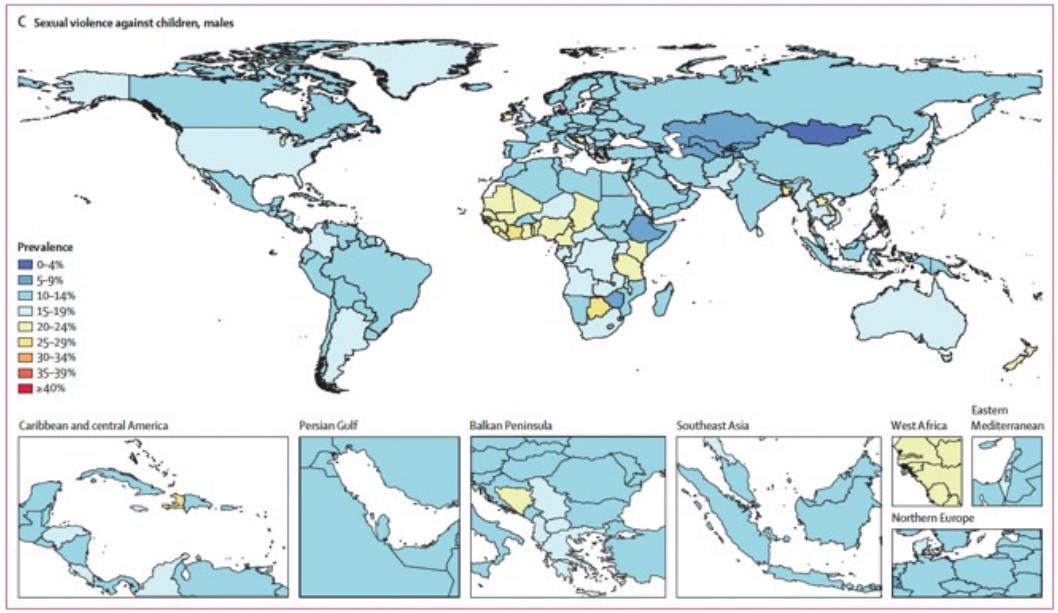


Figure 1: **Age-standardised prevalence of intimate partner among females aged 15 years and older (A) and sexual violence against children among females (B) and males (C), in 2023**
Exposure to sexual violence against children was estimated for females and males aged 15 years or older retrospectively reporting on sexual violence experienced during childhood (before age 18 years).

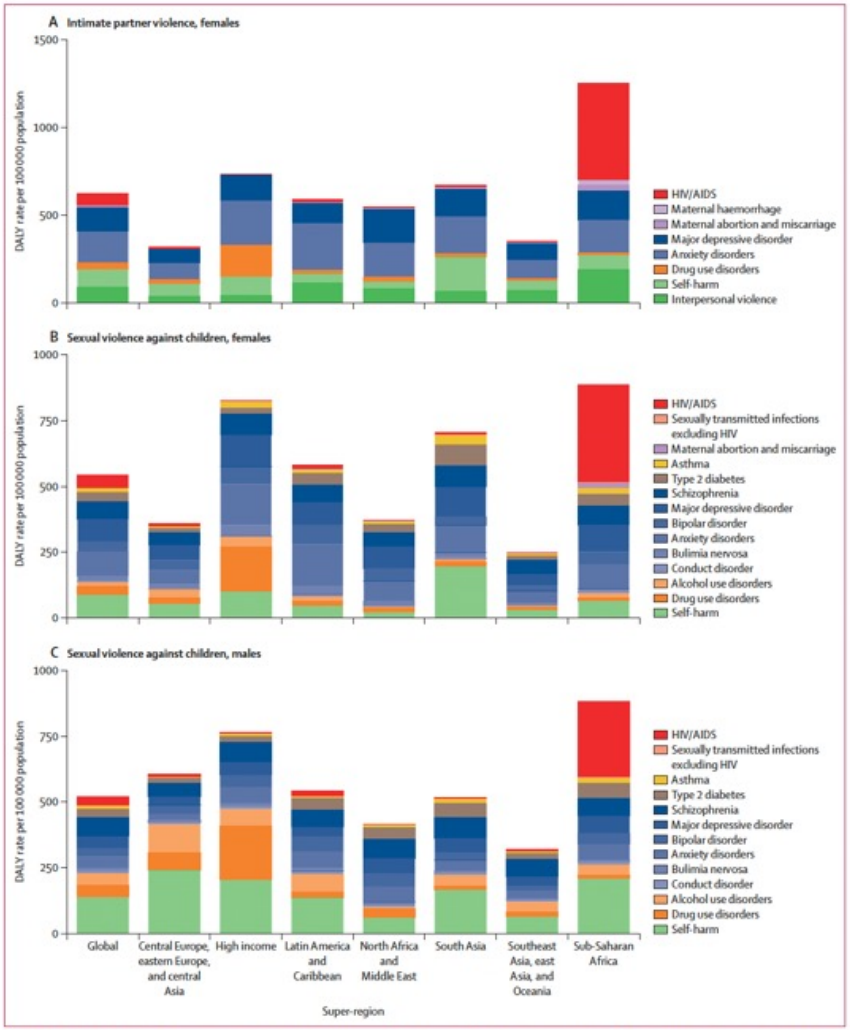
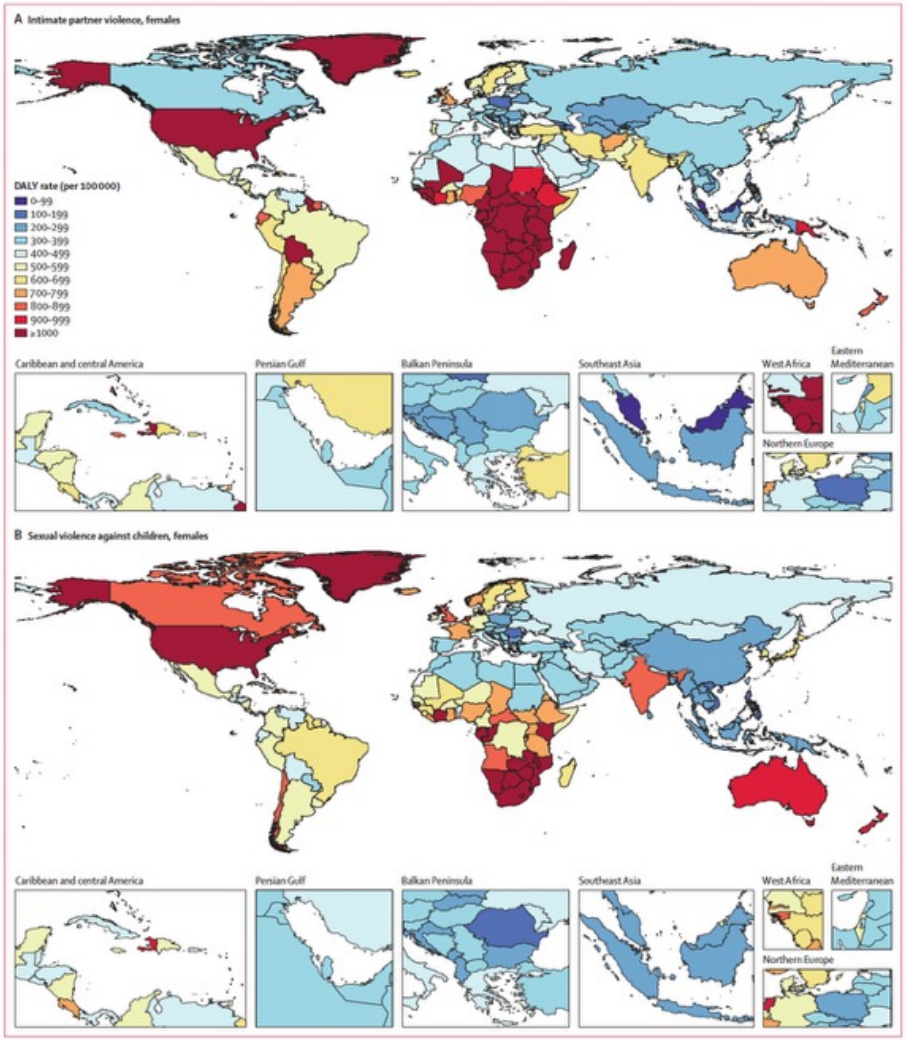


Figure 2: Age-standardised rates of cause-specific DALYs attributable to intimate partner violence among females (A) and to sexual violence against children among females (B) and males (C) aged 15 years and older, globally and by super-region, 2023

Bar heights represent all-cause DALY rates attributed to the respective risk factor and among the respective population globally and in each of the seven GBD super-regions. Colours indicate cause groupings, while shading within each colour category denotes specific Level 3 causes in the GBD cause hierarchy. DALY=disability-adjusted life-year. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.



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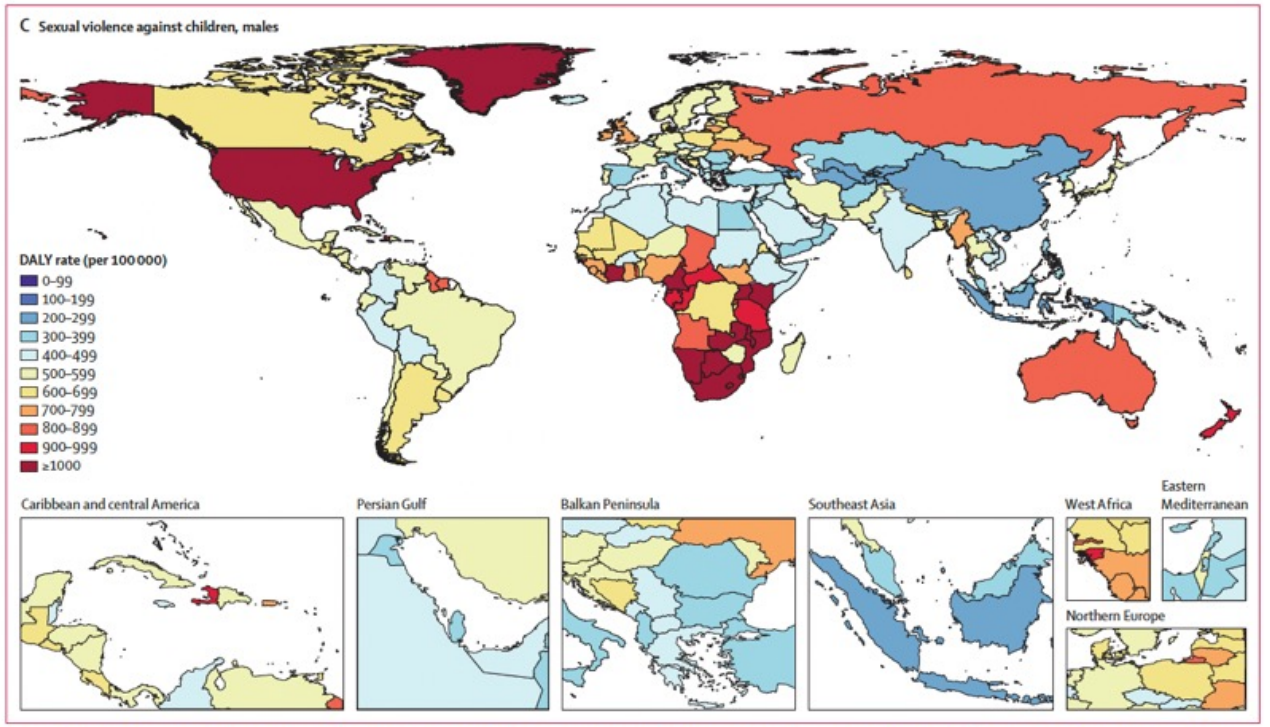


Figure 3: **Age-standardised DALY rates attributable to intimate partner violence among females (A) and to sexual violence against children among females (B) and males (C) aged 15 years and older, 2023**

DALY rates are presented per 100 000 people. DALY=disability-adjusted life-year.

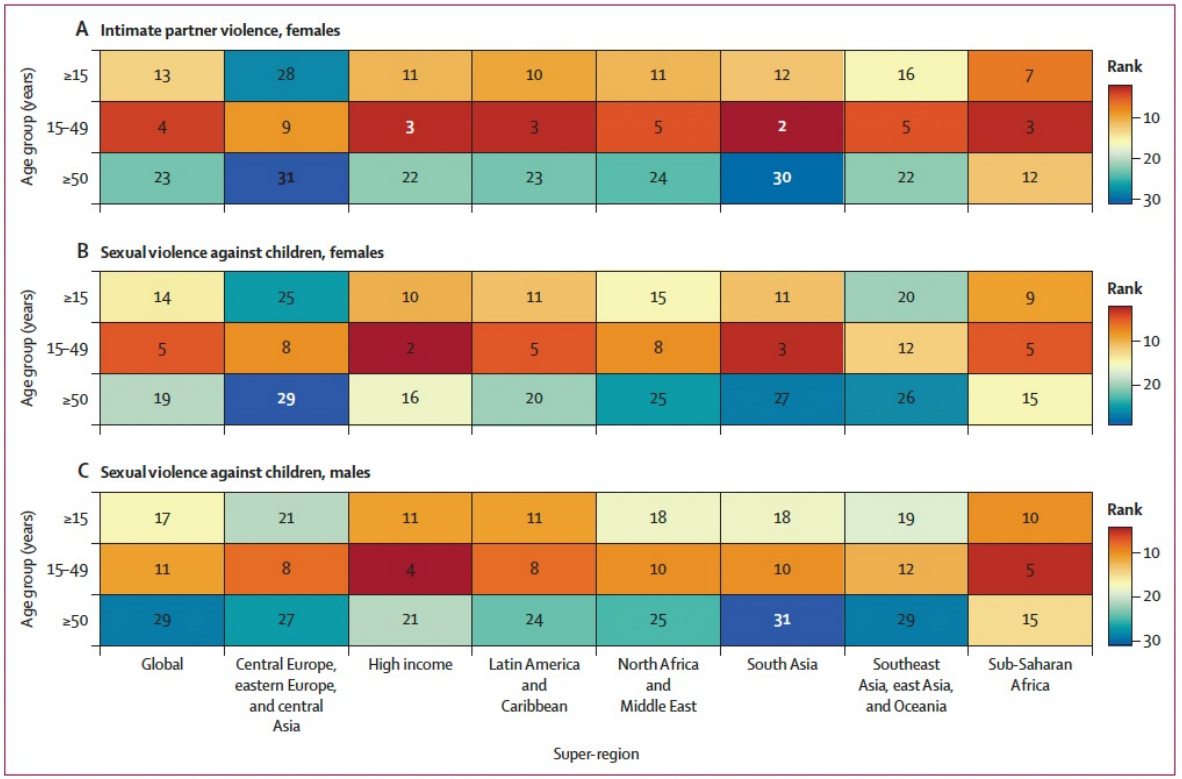


Figure 4: **Rankings of DALY counts attributable to intimate partner violence among females (A) and to sexual violence against children among females (B) and males (C), compared with other Level 3 risk factors included in GBD 2023, globally and by super-region**

Rows display DALY count rankings for all individuals aged 15 years and older, as well as for specific age strata. Columns show rankings globally and across each of the seven GBD super-regions. Numbers within each cell indicate the ranking of the respective risk factor among GBD Level 3 risk factors (see full list in appendix 1 section 8) within each population group and geographical region in 2023. Cell colours represent the relative rankings, ranging from red (lower ranking, higher DALYs) to blue (higher ranking, lower DALYs). Detailed risk factor rankings for ages 15 years and older and 15–49 years are available in appendix 2 (figures S3–S6). DALY=disability-adjusted life-year. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

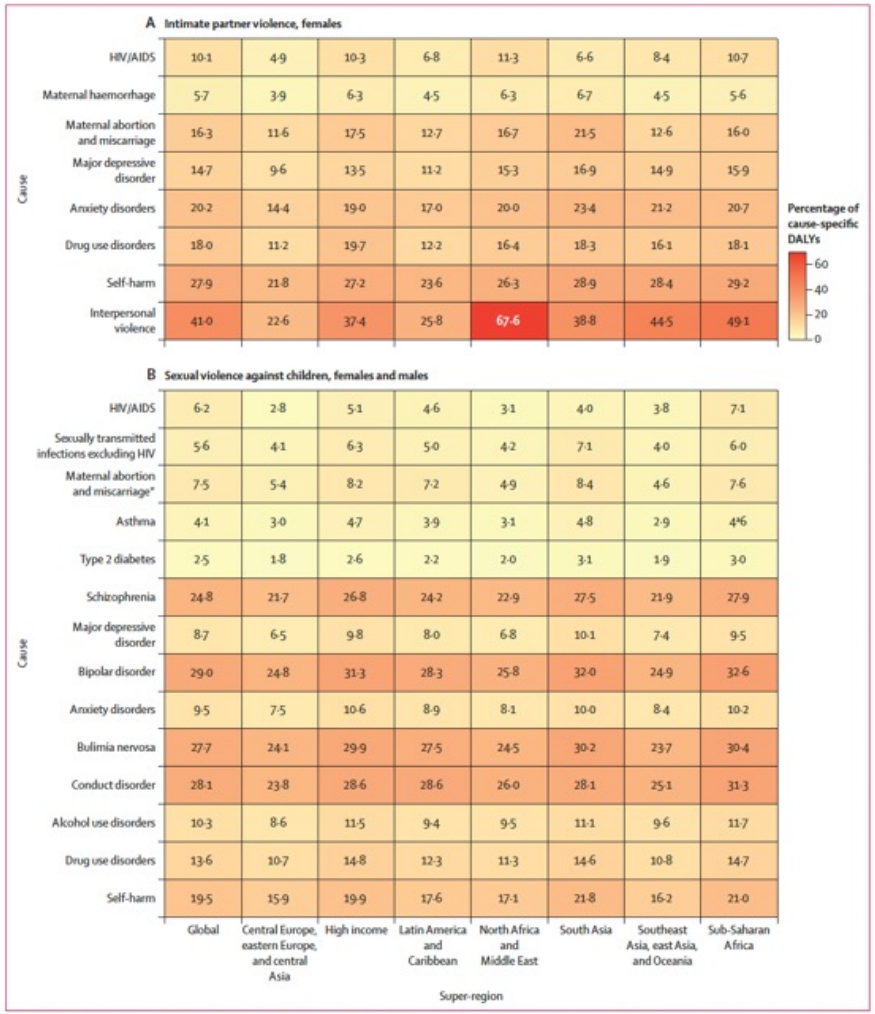


Figure 5: **Percentage of cause-specific health burden attributable to intimate partner violence among females (A) and to sexual violence against children among females and males combined (B) aged 15 years and older, globally and by super-region, 2023**

Percentages represent the proportion of cause-specific DALYs among individuals aged 15 years and older attributed to intimate partner violence or sexual violence against children globally or within a specific super-region. Numbers within each cell are estimated mean percentages, while cell colours represent the relative level of the mean percentage, ranging from yellow (lower percentage) to red (higher percentage). Causes are presented at Level 3 of the GBD cause hierarchy. DALY=disability-adjusted life-year. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. *Female-specific condition.

Research in context

Evidence before this study

Numerous individual and meta-analytic studies have assessed the magnitude of intimate partner violence (IPV) and sexual violence against children (SVAC), providing essential insights into their global prevalence. WHO estimates that 27% of ever-partnered women aged 15–49 years have experienced physical or sexual IPV, while UNICEF estimates that 1 in 5 girls and women and 1 in 7 boys and men alive today have been subjected to sexual violence as children. Country-level prevalence estimates, however, remain limited by data scarcity. Furthermore, the health effects of IPV and SVAC have been mostly analysed at the individual level, with several meta-analyses finding a link between these exposures and various health outcomes. Most recently, a comprehensive systematic review and meta-analysis effort spanning data from 1970 to 2023, which used robust relative risk estimation techniques, found highly significant and consistent associations between IPV and SVAC and a wide range of adverse outcomes, including mental health conditions, physical injuries, and HIV. However, there is a notable lack of timely and detailed research on the overall population-level health effects. Previous analyses from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) have connected IPV and SVAC with a limited number of outcomes, thereby underestimating their full health burden.

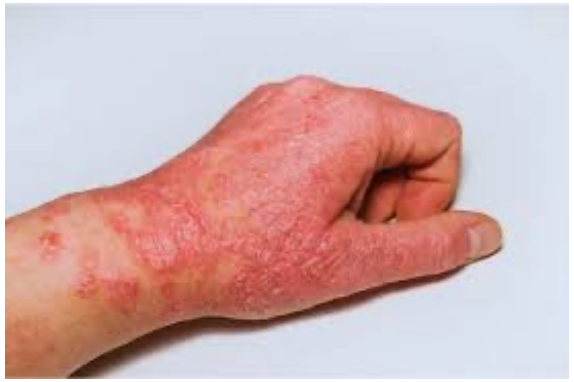
Added value of this study

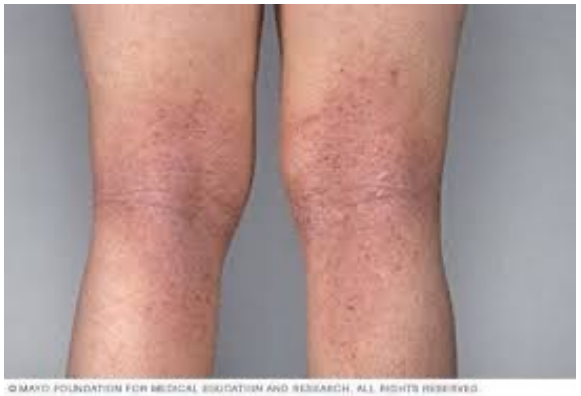
We provide comprehensive and timely estimates of the disease burden attributable to IPV and SVAC for 204 locations. This study updates and expands previous estimates produced as part of GBD by incorporating several methodological improvements, including updated data sources, solutions to differential reporting challenges, and a systematic evaluation of new risk-outcome associations. Specifically, compared with the previous GBD cycle (GBD 2021), we incorporated 195 new sources of data to refine IPV prevalence estimates and an additional 211 sources to enhance SVAC prevalence estimates, thereby strengthening the data foundation of our analyses. We also introduced substantive methodological advances in our SVAC exposure estimation process. In particular, we revised the definition of SVAC—extending the age range of exposure from before 15 years to before 18 years—to align with international classifications of violence against children. To address a persistent challenge in violence research, we also adjusted our SVAC estimates for differential reporting across survey modes. In addition, our systematic reviews and meta-analyses enabled the assessment of a greater number of long-term health outcomes linked to IPV and SVAC, expanding upon those included in previous GBD rounds. Risk-outcome pairs were added in GBD 2023 based on data-driven determination of a risk-outcome association. For IPV, we included five additional causes of health burden, for a total of eight health outcomes. Similarly, for SVAC, the number of associated health outcomes increased from two in GBD 2021 to 14 in GBD 2023. Together, these improvements address some of the major limitations of estimating the disease burden attributable to SVAC and IPV in earlier GBD iterations and enhance our understanding of the magnitude of the health effects associated with these risks.

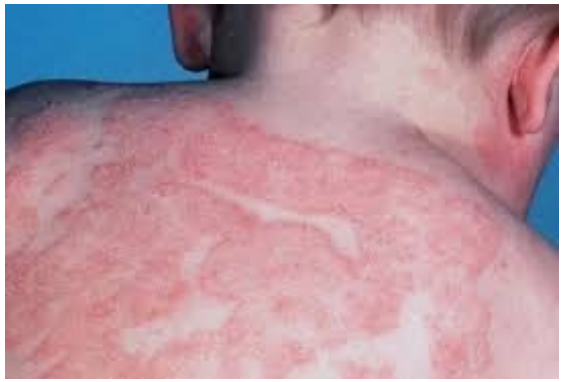
Implications of all the available evidence

Quantifying the disease burden attributable to IPV and SVAC is essential for enabling timely and effective interventions. Moreover, by leveraging the GBD comparative framework, we position IPV and SVAC alongside other major health threats, moving beyond viewing them solely as social or criminal concerns. Our results indicate that these risks contribute to a range of fatal and non-fatal outcomes and affect populations worldwide, regardless of their development status, and are particularly detrimental to young and middle-aged individuals. Given that coordinated responses can mitigate these risks, it is imperative to implement comprehensive prevention strategies to reduce the occurrence of IPV and SVAC, alongside multipronged support systems to address the complex recovery and healing needs of survivors. We strongly advocate integrating both prevention measures and survivor support into broader public health initiatives that also address mental health disorders, substance misuse, suicide, homicide, and HIV. Prioritising these risks in the global health agenda is essential for promoting global sustainability and protecting future generations. In addition, it should be acknowledged that our understanding of the scope of this problem continues to be limited by data sparsity on all forms of violence, including less studied forms, such as emotional, economic and reproductive abuse, and IPV against males. There is a continued need for further data collection and modelling efforts to more fully capture the true health impacts of violence against women and children.

Atopische Dermatitis (auch **Neurodermitis** genannt) ist eine chronisch-entzündliche, nicht ansteckende Hauterkrankung, die durch schubweise auftretende Ekzeme, trockene Haut und intensiven Juckreiz gekennzeichnet ist. Sie zählt zu den häufigsten Hauterkrankungen weltweit und betrifft in Industrieländern etwa 10–20 % der Kinder und 2–10 % der Erwachsenen.





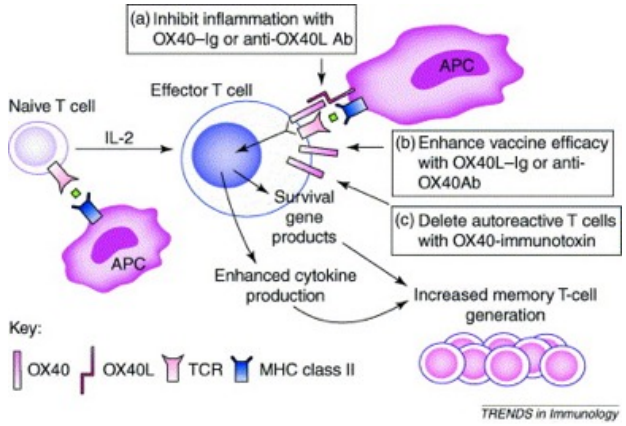


Der **OX40-Rezeptor** (auch bekannt als **CD134** oder **TNFRSF4**) ist ein kostimulierender Immun-Checkpoint-Rezeptor aus der Tumor-Nekrose-Faktor-Rezeptor-Superfamilie (TNFRSF). Er spielt im Jahr 2026 eine zentrale Rolle in der Entwicklung neuer Therapien für **Autoimmunerkrankungen** und in der **Onkologie**.

Biologische Funktion

OX40 wird nicht dauerhaft, sondern erst **24 bis 72 Stunden nach einer Aktivierung** auf der Oberfläche von T-Zellen (insbesondere CD4+ Helferzellen und CD8+ Killerzellen) exprimiert.

- **Aktivierung:** Die Bindung an seinen Liganden (**OX40L**) fördert das Überleben, die Vermehrung und die Zytokinproduktion von T-Zellen.
- **Gedächtnisbildung:** OX40 ist entscheidend für die Bildung von langlebigen Gedächtnis-T-Zellen, was für die langfristige Immunität (oder Chronizität von Entzündungen) wichtig ist.
- **Regulation:** Die Aktivierung von OX40 kann die unterdrückende Wirkung von regulatorischen T-Zellen (Tregs) abschwächen.



Efficacy and safety of rocatinlimab for the treatment of moderate-to-severe atopic dermatitis in ROCKET-IGNITE and ROCKET-HORIZON: two global, double-blind, placebo-controlled, randomised phase 3 clinical trials

Summary

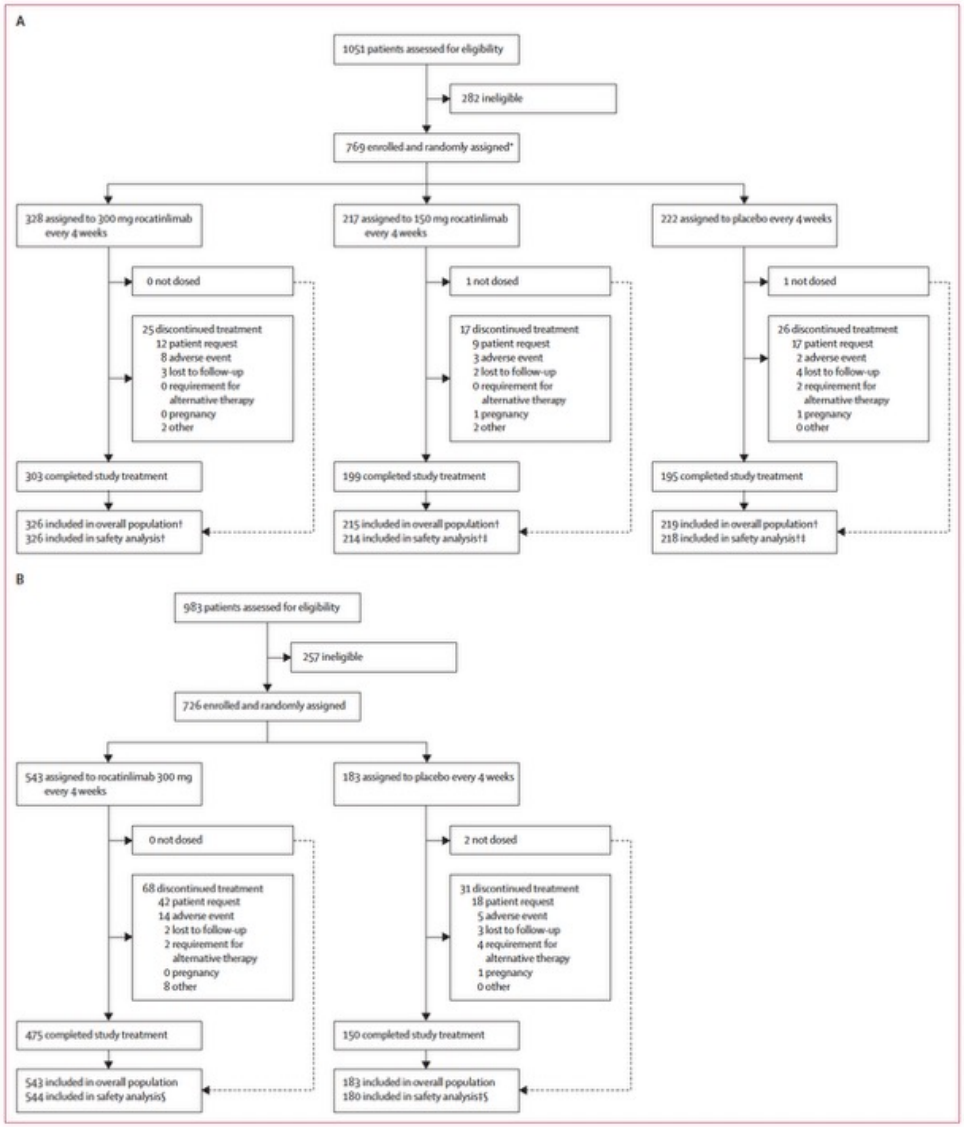
Background Rocatinlimab is a T cell rebalancing therapy that inhibits and reduces the number of pathogenic T cells by targeting the OX40 receptor expressed on the surface of activated T cells. Two global phase 3 studies were performed to assess the efficacy and safety of rocatinlimab for the treatment of moderate-to-severe atopic dermatitis in adults.

Methods ROCKET-IGNITE (IGNITE) and ROCKET-HORIZON (HORIZON) were 24-week randomised, double-blind, placebo-controlled phase 3 trials conducted in 19 countries each. Eligible patients were 18 years and older with confirmed atopic dermatitis (American Academy of Dermatology Consensus Criteria) diagnosed 1 year or longer before study entry with moderate-to-severe disease activity, defined by an Eczema Area and Severity Index (EASI) score of 16 and over, validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD) score of 3 (moderate) or 4 (severe), and affected body surface area of 10% and above. In IGNITE, patients were randomly allocated in a 3:2:2 ratio to receive subcutaneous 300 mg rocatinlimab, 150 mg rocatinlimab, or placebo; in HORIZON, patients were randomised 3:1 to receive subcutaneous 300 mg rocatinlimab or placebo. Randomisation was stratified by baseline disease severity (vIGA-AD score of 3 *vs* 4) and geographical region (Japan *vs* non-Japan Asian countries *vs* rest of world). Across both trials, 24-week treatment was administered at weeks 0, 2, and 4 and then every 4 weeks thereafter with the last dose at week 20. The coprimary endpoints for both trials were EASI-75 response (≥75% improvement in EASI score from baseline) at week 24 and vIGA-AD score of 0 or 1 (defined as a score of 0 [clear skin] or 1 [almost clear skin], representing a ≥2-point improvement from baseline) at week 24. Rescue therapy use, including topical therapy, phototherapy, and systemic therapy, was permitted from day 1; all patients who received rescue therapy were considered non-responders for all visits after the first use of rescue therapy but could generally continue study treatment unless prohibited per protocol. Efficacy analyses were conducted in all randomised patients; safety analyses were conducted in all patients who received one or more dose of study treatment, with patients grouped according to actual treatment received. The trials were registered at ClinicalTrials.gov: ROCKET-IGNITE (NCT05398445) and ROCKET-HORIZON (NCT05651711).

Findings Between May 31, 2022, and June 12, 2024, 769 patients were randomised in IGNITE (two patients were enrolled under an earlier protocol before study re-design and excluded from the analysis; after the protocol update, 328 were included in the 300 mg rocatinlimab group; 217 in the 150 mg rocatinlimab group; and 222 in the placebo group) and between Dec 14, 2022, and Dec 12, 2023, 726 patients were randomised in HORIZON (543 in 300 mg rocatinlimab and 183 in placebo). Both trials met their coprimary endpoints. Rocatinlimab treatment resulted in statistically significant improvements in EASI-75 response in comparison with placebo at week 24 in IGNITE (138 [42%] of 326 patients on 300 mg rocatinlimab; 78 [36%] of 215 on 150 mg rocatinlimab; and 28 [13%] of 219 on placebo; percentage difference *vs* placebo: 300 mg rocatinlimab 29·5% [95% CI 22·3–36·1], p<0·001 and 150 mg rocatinlimab 23·4% [15·4–30·9], p<0·001) and HORIZON (rocatinlimab, 178 [33%] of 543 *vs* placebo, 25 [14%] of 183; percentage difference 19·1% [95% CI 12·4–25·2], p<0·001). Statistically significant improvements with rocatinlimab treatment in comparison with placebo were also observed at week 24 for vIGA-AD score of 0 or 1 response in IGNITE (77 [24%] of 326 patients on 300 mg rocatinlimab; 41 [19%] of 215 patients on 150 mg rocatinlimab; and 19 [9%] of 219 patients on placebo; percentage difference *vs* placebo 14·9% [95% CI 8·8–20·6], p<0·001 for 300 mg rocatinlimab and 10·3% [3·8–16·6], p=0·002 for 150 mg rocatinlimab) and HORIZON (105 [19%] of 543 for 300 mg rocatinlimab *vs* 12 [7%] of 183 for placebo; percentage difference 12·8% [95% CI 7·6–17·3], p<0·001). The incidences of treatment-emergent adverse events were generally similar across rocatinlimab and placebo treatment groups in IGNITE and HORIZON. The most frequently reported adverse events in patients receiving rocatinlimab (defined as occurring in ≥4% of patients in any rocatinlimab treatment group and at a rate ≥2 times that of placebo) included pyrexia (105 [12%] of 870 for 300 mg rocatinlimab and 26 [12%] of 214 for 150 mg rocatinlimab), chills (48 [6%] of 870 and five [2%] of 214 for the 300 mg and 150 mg doses, respectively), and aphthous ulcers (38 [4%] of 870 and six [3%] of 214, respectively). Most events of pyrexia and chills were considered injection-related reactions; events were generally mild or moderate in severity and primarily occurred after the first dose. Serious adverse events were reported in 2% to 5% of patients in the rocatinlimab groups and 4% to 6% of patients in the placebo groups. No deaths were reported.

Interpretation Rocatinlimab treatment resulted in statistically significant and clinically meaningful improvements across clinical endpoints, including the coprimary endpoints of EASI-75 response and vIGA-AD score of 0 or 1, in comparison with placebo and had a clinically acceptable safety profile in adult patients with moderate-to-severe atopic dermatitis.

Funding Amgen and Kyowa Kirin.



	ROCKET-IGNITE			ROCKET-HORIZON	
	Rocatinlimab 300 mg (n=326)	Rocatinlimab 150 mg (n=215)	Placebo (n=219)	Rocatinlimab 300 mg (n=543)	Placebo (n=183)
Age, years	38·5 (15·4)	36·6 (13·9)	37·1 (14·0)	37·8 (14·6)	40·4 (15·6)
Sex					
Male	194 (60%)	131 (61%)	122 (56%)	295 (54%)	102 (56%)
Female	132 (40%)	84 (39%)	97 (44%)	248 (46%)	81 (44%)
Weight, kg	74·4 (17·3)	79·0 (19·4)	76·3 (18·6)	76·8 (18·4)	79·8 (20·4)
Race					
White	196 (60%)	127 (59%)	128 (58%)	325 (60%)	107 (58%)
Asian	113 (35%)	70 (33%)	73 (33%)	161 (30%)	61 (33%)
Black	12 (4%)	11 (5%)	10 (5%)	19 (3%)	10 (5%)
Other	5 (2%)	7 (3%)	8 (4%)	38 (7%)	5 (3%)
Region					
North America	77 (24%)	53 (25%)	47 (21%)	191 (35%)	70 (38%)
Asia	93 (29%)	60 (28%)	64 (29%)	108 (20%)	37 (20%)
Europe	131 (40%)	89 (41%)	92 (42%)	190 (35%)	63 (34%)
Other	25 (8%)	13 (6%)	16 (7%)	54 (10%)	13 (7%)
Age at atopic dermatitis disease onset, years	15·9 (19·9)	14·6 (18·2)	15·6 (17·9)	13·2 (17·8)	14·9 (18·6)
Duration since onset of atopic dermatitis, years	22·6 (16·0)	22·0 (14·6)	21·5 (14·9)	24·6 (15·4)	25·4 (16·3)
vIGA-AD score*					
3 (moderate)	206 (63%)	137 (64%)	143 (65%)	336 (62%)	112 (61%)
4 (severe)	119 (37%)	78 (36%)	76 (35%)	207 (38%)	71 (39%)
Missing†	1 (<1%)	0	0	..	..
EASI total score‡	29·2 (11·4)	29·3 (11·0)	28·1 (10·1)	28·5 (10·9)	28·6 (11·1)
≤21 (moderate)	98 (30%)	56 (26%)	69 (32%)	159 (29%)	57 (31%)
>21 (severe and very severe)	227 (70%)	159 (74%)	150 (69%)	384 (71%)	126 (69%)
BSA of atopic dermatitis involvement§	44·7 (22·3)	45·0 (21·1)	42·1 (19·6)	44·1 (22·1)	44·0 (22·5)
WP-NRS score¶	7·2 (1·6)	7·2 (1·7)	7·1 (1·8)	7·2 (1·8)	7·2 (1·9)
DLQI‖	13·3 (6·7)	14·1 (7·0)	13·5 (6·2)	13·6 (7·0)	13·9 (7·0)
Previous use of systemic therapy for atopic dermatitis	183 (56%)	129 (60%)	136 (62%)	342 (63%)	116 (63%)
Previous failure** of systemic therapy for atopic dermatitis	134 (41%)	100 (47%)	99 (45%)	281 (52%)	97 (53%)
Previous use of an immunosuppressant for atopic dermatitis	80 (25%)	31 (14%)	52 (24%)	143 (26%)	52 (28%)
Previous use of biologic or systemic JAK inhibitor for atopic dermatitis	69 (21%)	40 (19%)	48 (22%)	130 (24%)	30 (16%)
Previous failure** of biologic or systemic JAK inhibitor for atopic dermatitis	37 (11%)	26 (12%)	22 (10%)	88 (16%)	15 (8%)
Number of previous failures** of biologic or systemic JAK inhibitor for atopic dermatitis					
1	29 (9%)	18 (8%)	14 (6%)	53 (10%)	11 (6%)
2	6 (2%)	4 (2%)	7 (3%)	25 (5%)	2 (1%)
3+	2 (1%)	4 (2%)	1 (<1%)	10 (2%)	2 (1%)

Data are n (%) or mean (SD). Percentages do not always add to 100% because of rounding. BSA=body surface area. DLQI=Dermatology Life Quality Index. EASI=Eczema Area and Severity Index. IGA=Investigator Global Assessment. JAK=Janus kinase. vIGA-AD=validated Investigator Global Assessment for atopic dermatitis. WP-NRS=Worst Pruritus Numeric Rating Scale. *vIGA-AD scores range from 0 (clear skin) to 4 (severe disease); to be eligible for enrolment, patients were required to have an IGA score of ≥3. †Assessments for eligibility were evaluated after the patient was randomly allocated. ‡The EASI assesses four atopic dermatitis signs (erythema, papulation or oedema, excoriation, and lichenification) over four body areas (head and neck; upper limbs; trunk; and lower limbs); the composite score ranges from 0 to 72, with higher values indicating greater severity or extent of disease. §BSA is assessed for each part of the body and is reported as a percentage of all major body sections combined. ¶WP-NRS is a single-item questionnaire that evaluates worst severity of itch with a score ranging from 0 (no itch) to 10 (worst itch imaginable); mean score was based on a weekly mean score for the week prior to the assessment timepoint. ‖The DLQI is a ten-item questionnaire with a composite score rating impact on quality of life, with each item rated with a score from 0 (not at all) to 3 (very much). Total scores range from 0 to 30, and lower scores indicate better health-related quality of life. **Previous failure is defined as failure to achieve and maintain remission or a low disease activity state (comparable to an IGA score of 0 [clear] to 2 [mild]) or IGA greater than 2 or less than 50% improvement of eczema lesions or inadequate control of impactful lesions (highly visible areas or those important for function) or inadequate control of any of or a combination from pruritus, sleep disturbance, atopic dermatitis skin pain, or insufficient improvement on atopic dermatitis-related Quality of Life (eg, effect on daily activities and work) after treatment at the labelled or appropriate dose per local guidelines, with sufficient treatment duration (ie, approximately 16 weeks for approved biologics or JAK inhibitors for atopic dermatitis).

Table 1: Baseline demographic and disease characteristics in ROCKET-IGNITE and ROCKET-HORIZON overall populations

	ROCKET-IGNITE			ROCKET-HORIZON	
	Rocatinlimab 300 mg (n=326)	Rocatinlimab 150 mg (n=215)	Placebo (n=219)	Rocatinlimab 300 mg (n=543)	Placebo (n=183)
Coprimary endpoints					
EASI-75 response* at week 24	138 (42%)	78 (36%)	28 (13%)	178 (33%)	25 (14%)
Treatment difference	29·5% (22·3–36·1)	23·4% (15·4–30·9)	–	19·1% (12·4–25·2)	–
p value vs placebo	p<0·001	p<0·001	–	p<0·001	–
vIGA-AD score of 0 or 1 response† at week 24	77 (24%)	41 (19%)	19 (9%)	105 (19%)	12 (7%)
Treatment difference	14·9% (8·8–20·6)	10·3% (3·8–16·6)	–	12·8% (7·6–17·3)	–
p value vs placebo	p<0·001	p=0·002	–	p<0·001	–
Key secondary endpoints					
EASI-75 response* at week 16	125 (38%)	69 (32%)	30 (14%)	159 (29%)	23 (13%)
Treatment difference	24·6% (17·4–31·2)	18·2% (10·4–25·8)	–	16·8% (10·3–22·6)	–
p value vs placebo	p<0·001	p<0·001	–	p<0·001	–
EASI-90 response‡ at week 24	89 (27%)	53 (25%)	16 (7%)	108 (20%)	9 (5%)
Treatment difference	19·9% (13·8–25·6)	17·2% (10·3–23·8)	–	15·0% (10·0–19·2)	–
p value vs placebo	p<0·001	p<0·001	–	p<0·001	–
vIGA-AD score of 0 or 1 response† at week 16	56 (17%)	27 (13%)	12 (5%)	69 (13%)	5 (3%)
Treatment difference	11·7% (6·4–16·6)	7·1% (1·7–12·3)	–	10·0% (6·0–13·3)	–
p value vs placebo	p<0·001	p=0·009	–	p<0·001	–
rIGA score of 0 or 1 response§ at week 24	74 (23%)	35 (16%)	18 (8%)	89 (16%)	9 (5%)
Treatment difference	14·4% (8·4–20·0)	8·0% (1·8–14·0)	–	11·5% (6·7–15·5)	–
p value vs placebo	p<0·001	p=0·010	–	p<0·001	–
FASS clear at week 24¶‖	64/270 (24%)	45/181 (25%)	16/174 (9%)	84/468 (18%)	9/153 (6%)
Treatment difference	14·5% (7·6–20·8)	15·4% (7·7–22·8)	–	12·1 (6·6–16·8)	–
p value vs placebo	p<0·001	p<0·001	–	p<0·001	–
HASS clear at week 24¶‖	56/241 (23%)	30/153 (20%)	10/151 (7%)	65/405 (16%)	6/141 (4%)
Treatment difference	16·7% (9·8–23·0)	12·7% (5·1–19·9)	–	11·7% (6·3–16·1)	–
p value vs placebo	p<0·001	p<0·001	–	p<0·001	–
WP-NRS score reduction ≥4 at week 16**††	72/306 (24%)	45/205 (22%)	16/203 (8%)	110/505 (22%)	18/162 (11%)
Treatment difference	15·4% (9·1–21·1)	13·7% (6·8–20·3)	–	10·5% (4·1–16·1)	–
p value vs placebo	p<0·001	p<0·001	–	p=0·003	–
WP-NRS score reduction ≥4 at week 24**††	87/306 (28%)	54/205 (26%)	18/203 (9%)	121/505 (24%)	17/162 (10%)
Treatment difference	19·2% (12·6–25·3)	17·1% (9·8–24·1)	–	13·4% (7·0–19·0)	–
p value vs placebo	p<0·001	p<0·001	–	p<0·001	–
SP-NRS score reduction ≥4 at week 24**††	74/241 (31%)	49/169 (29%)	13/158 (8%)	109/418 (26%)	14/138 (10%)
Treatment difference	21·7% (14·1–28·7)	20·2% (12·0–28·0)	–	15·8% (8·8–21·9)	–
p value vs placebo	p<0·001	p<0·001	–	p<0·001	–
DLQI score reduction ≥4 at week 24††‡‡	163/297 (55%)	105/199 (53%)	49/204 (24%)	228/496 (46%)	43/171 (25%)
Treatment difference	31·0% (22·8–38·7)	28·2% (19·1–36·9)	–	20·8% (12·6–28·3)	–
p value vs placebo	p<0·001	p<0·001	–	p<0·001	–

Data are n (%) or adjusted percentage difference (95% CI) versus placebo; p values are also shown. Mantel-Haenszel common risk difference and 95% Klingenberg confidence interval, and the p value obtained from a Cochran-Mantel-Haenszel test were adjusted for the stratification factors of baseline disease severity and geographical region. AD=atopic dermatitis. DLQI=Dermatology Life Quality Index. EASI=Eczema Area and Severity Index. FASS=facial AD severity score. HASS=hand AD severity score. rIGA=revised Investigator's Global Assessment. SP-NRS=Skin Pain Numeric Rating Scale (weekly mean score). vIGA-AD=validated Investigator's Global Assessment for Atopic Dermatitis. WP-NRS=Worst Pruritus Numeric Rating Scale (weekly mean score). *EASI-75 response was defined as at least 75% reduction from baseline in EASI total score from baseline. †vIGA-AD score of 0 or 1 response was defined as a score of 0 (clear) or 1 (almost clear) with a 2-point reduction from baseline. ‡EASI-90 response was defined as at least 90% reduction from baseline in EASI total score from baseline. §rIGA score of 0 or 1 response was defined as achieving vIGA-AD 1 response with the presence of only barely perceptible erythema or vIGA-AD 0 response and a 2-point reduction from baseline. ¶HASS and FASS are instruments that rate the overall severity of hand and facial AD based on a four-category scale ranging from clear (0) to severe (4). ‖Numbers of patients evaluable for the corresponding endpoint requiring presence of hand or facial AD at baseline, respectively. **WP-NRS and SP-NRS are single-item questionnaires that evaluate worst severity of itch and AD skin pain with a score ranging from 0 (none or no impact) to 10 (worst or worst impact); mean score was based on a weekly mean score for the week prior to the assessment timepoint. ††Numbers of patients evaluable for the corresponding endpoint requiring baseline score ≥4. ‡‡The DLQI is a ten-item questionnaire with a composite score rating impact on quality of life, with each item rated with a score of 0 (not at all) to 3 (very much). Total scores range from 0 to 30, and lower scores indicate better health-related quality of life.

Table 2: Summary of key efficacy endpoints in ROCKET-IGNITE and ROCKET-HORIZON, primary analysis, overall populations

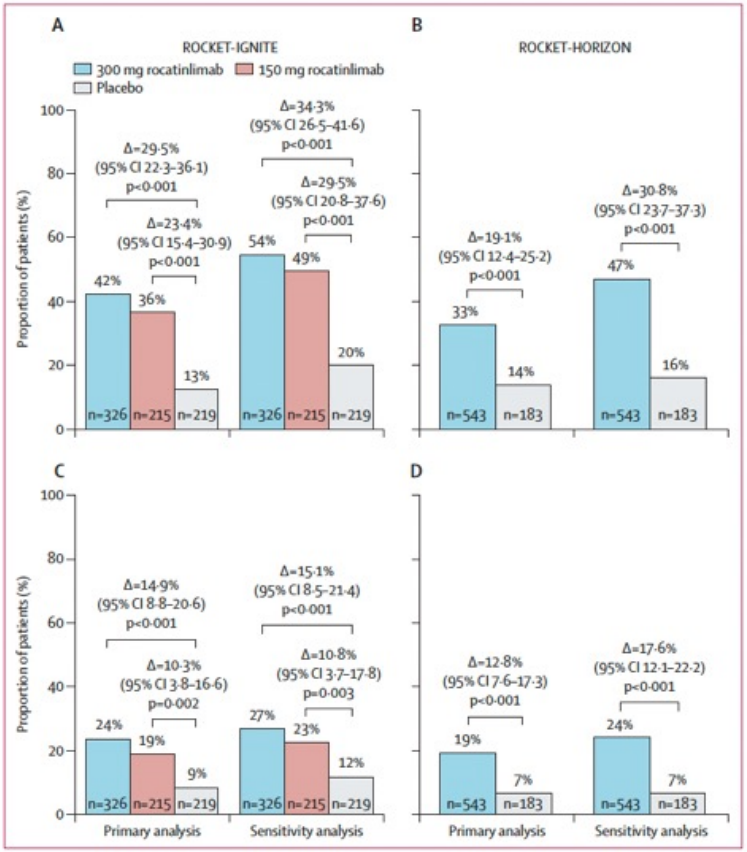


***Figure 2*: Coprimary endpoints in ROCKET-IGNITE and ROCKET-HORIZON—primary and sensitivity analyses**
EASI-75 response* at week 24 in ROCKET-IGNITE (A) and ROCKET-HORIZON (B); vIGA-AD score of 0 or 1† at week 24 in ROCKET-IGNITE (C) and ROCKET-HORIZON (D). Adjusted effect sizes (percentage difference with 95% Klingenberg CIs) and p values versus the placebo obtained from a Cochran–Mantel–Haenszel test adjusting for the random allocation stratification variables. In the primary analysis, patients who used rescue therapy were classified as non-responders at all subsequent visits after the initiation of rescue therapy. In the sensitivity analysis, results are reported for all patients based on observed data regardless of rescue therapy use. Non-responder imputation was used for the remaining missing data after rescue therapy and treatment discontinuation events were handled in both the primary and sensitivity analyses. EASI=Eczema Area and Severity Index. vIGA-AD=validated Investigator's Global Assessment for Atopic Dermatitis. *EASI-75 response was defined as at least 75% reduction from baseline in EASI total score from baseline. †vIGA-AD score of 0 or 1 was defined as a score of 0 (clear) or 1 (almost clear) with 2-point or greater reduction from baseline.

	ROCKET-IGNITE			ROCKET-HORIZON	
	Rocatinlimab 300 mg (n=326)	Rocatinlimab 150 mg (n=214)*	Placebo (n=218)*	Rocatinlimab 300 mg (n=544)†	Placebo (n=180)*
At least one treatment-emergent adverse event	226 (69%)	151 (71%)	151 (69%)	371 (68%)	114 (63%)
Treatment-emergent adverse events according to maximum severity‡					
Mild	112 (34%)	72 (34%)	56 (26%)	154 (28%)	29 (16%)
Moderate	99 (30%)	71 (33%)	78 (36%)	198 (36%)	70 (39%)
Severe	15 (5%)	8 (4%)	17 (8%)	19 (3%)	15 (8%)
At least one treatment-emergent serious adverse event	15 (5%)	6 (3%)	12 (6%)	10 (2%)	8 (4%)
Death	0	0	0	0	0
At least one treatment-emergent adverse event leading to discontinuation of study treatment	8 (2%)	3 (1%)	2 (1%)	14 (3%)	5 (3%)
Serious	2 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	2 (1%)
Non-serious	6 (2%)	2 (1%)	1 (<1%)	13 (2%)	3 (2%)
Treatment-emergent adverse events reported in ≥4% of patients treated with rocatinlimab by preferred term					
Pyrexia	49 (15%)	26 (12%)	10 (5%)	56 (10%)	2 (1%)
Atopic dermatitis	33 (10%)	27 (13%)	56 (26%)	104 (19%)	48 (27%)
Nasopharyngitis	30 (9%)	26 (12%)	19 (9%)	48 (9%)	21 (12%)
Headache	29 (9%)	17 (8%)	10 (5%)	39 (7%)	7 (4%)
Upper respiratory tract infection	17 (5%)	8 (4%)	9 (4%)	34 (6%)	6 (3%)
Aphthous ulcer	16 (5%)	6 (3%)	2 (1%)	22 (4%)	1 (1%)
Chills	15 (5%)	5 (2%)	4 (2%)	33 (6%)	2 (1%)
Influenza	13 (4%)	8 (4%)	6 (3%)	18 (3%)	3 (2%)
COVID-19	7 (2%)	11 (5%)	10 (5%)	22 (4%)	2 (1%)
Fatigue	6 (2%)	14 (7%)	8 (4%)	··§	··§

Data are number of patients (%). Adverse events were coded using Medical Dictionary for Regulatory Activities version 27·0. Data are presented from the safety population that included patients who received at least one dose of study treatment. *One patient each in the IGNITE rocatinlimab 150 mg group and the IGNITE placebo group and two patients in the HORIZON placebo group did not receive any study treatment and were excluded from the safety analyses. †One patient in the HORIZON placebo group received one dose of rocatinlimab at week 8 in error and thus was included in the HORIZON rocatinlimab 300 mg group for safety analyses. ‡If patients experienced multiple occurrences of the same event, the patients were counted once for the event with maximum severity. §Data not reported to prevent potential unblinding of patients who remain in the long-term extension study.

Table 3: **Summary of treatment-emergent adverse events in the ROCKET-IGNITE and ROCKET-HORIZON safety populations**

Research in context

Evidence before this study

The OX40 signalling pathway plays a key role in driving and sustaining T cell-mediated inflammation in atopic dermatitis. The pathway is currently being explored as an important therapeutic target, with several molecules employing different mechanisms in development. The OX40 receptor (OX40R) is a costimulatory molecule that is transiently expressed on activated effector and memory T cells. Targeting OX40R in atopic dermatitis represents a novel therapeutic approach, as currently approved biologic therapies for the treatment of moderate-to-severe disease focus on disrupting T helper 2 (Th2)-mediated inflammation, while leaving other inflammatory cytokines known to drive atopic dermatitis pathogenesis unaddressed. Targeting Th2-mediated inflammation alone does not address T memory cells, which are responsible for driving disease chronicity. Rocatinlimab binds to OX40R to inhibit and reduce pathogenic OX40R+ effector and memory T cells in atopic dermatitis. We searched PubMed from database inception to July 8, 2025, with the search terms "([KHK4083] OR [AMG 451] OR [rocatinlimab]) AND atopic dermatitis)". No language or article type restrictions were used. No phase 3 trial results were identified; one phase 1, single-centre, open-label study of KHK4083 (rocatinlimab) in Japanese patients with moderate-to-severe atopic dermatitis (NCT03096223), and one phase 2, randomised, double-blind, placebo-controlled trial that evaluated the safety and efficacy of rocatinlimab every 4 weeks (150 mg or 600 mg) or every 2 weeks (300 mg or 600 mg) in adult patients with atopic dermatitis (NCT03703102) were found. Results from the phase 2 study showed that rocatinlimab improved atopic dermatitis signs and symptoms across clinical efficacy endpoints and patient-reported outcomes in comparison with placebo treatment.

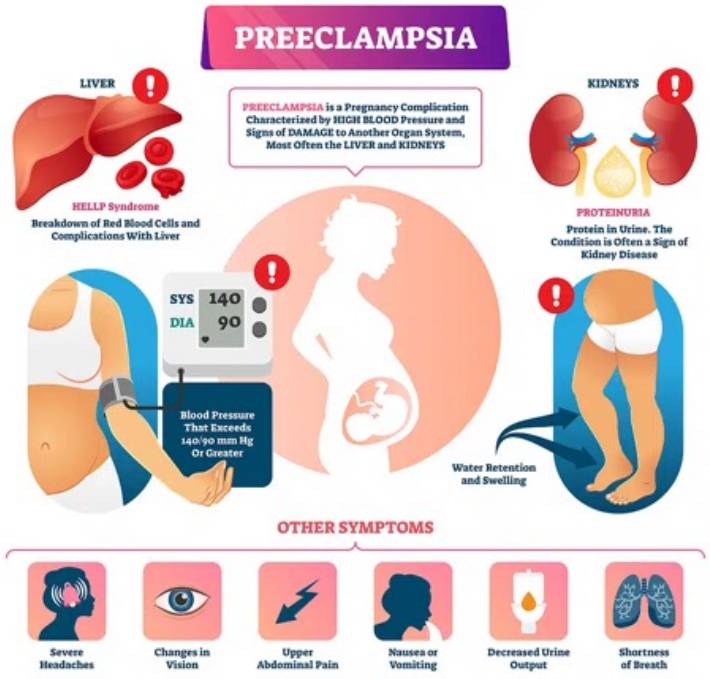
Added value of this study

The ROCKET-IGNITE and ROCKET-HORIZON trials were the first phase 3, double-blind, placebo-controlled, randomised clinical trials to examine a therapeutic targeting the OX40 signalling pathway and specifically evaluated rocatinlimab monotherapy for the treatment of moderate-to-severe atopic dermatitis. The trials included a substantive percentage of patients who had previously not responded to systemic treatment for atopic dermatitis, reflecting real-world populations and allowing for the evaluation of rocatinlimab in patients with harder-to-treat disease. Rescue therapy use was permitted from day 1, and clinical efficacy was assessed at week 24. All primary and key secondary efficacy endpoints were met in both trials, with rocatinlimab every 4 weeks resulting in statistically greater improvements in atopic dermatitis signs and symptoms in comparison with placebo for both the 300 mg and 150 mg doses. Responses showed continual improvement through week 24, suggesting the potential for additional improvement with continued treatment, which may be particularly meaningful given the chronic nature of atopic dermatitis. Exploratory analyses supported the selective reduction of OX40R+ CD4+ T cells while generally preserving overall CD4+ T cell populations. Safety evaluations found that rocatinlimab treatment was associated with injection-related reactions of fever and chills in a minority of patients (≤15%); these events were generally mild or moderate in severity and predominately occurred after the first dose only.

Implications of all the available evidence

Results validate OX40R as an important therapeutic target in atopic dermatitis and support rocatinlimab monotherapy as a safe and effective treatment option for patients with moderate-to-severe disease. Additional studies are needed to further characterise the long-term efficacy, durability, and safety of rocatinlimab for the treatment of atopic dermatitis as well as to fully characterise its disease-modifying potential.

Präeklampsie ist eine ernste Schwangerschaftskomplikation, die sich typischerweise nach der 20. Schwangerschaftswoche entwickelt und durch hohen Blutdruck (Hypertonie) und Anzeichen von Organschäden, oft Eiweiß im Urin (Proteinurie), gekennzeichnet ist. Sie kann Leber, Nieren, Gehirn und Plazenta beeinträchtigen und stellt ein Risiko für Mutter und Kind dar. Symptome können unerwartete Schwellungen, Kopfschmerzen, Sehstörungen und Schmerzen im Oberbauch sein, aber auch ohne Symptome auftreten. Die Behandlung erfordert engmaschige Überwachung und kann eine frühe Entbindung zur Folge haben.



Ein Risiko für Präeklampsie von **größer als 1 zu 50 (≥ 1:50)** in der Frühschwangerschaft wird als **"hohes Risiko"** eingestuft und führt oft zu intensiverer Überwachung und präventiver Behandlung, wie z.B. Aspirin (ASS), um Frühgeburten und andere Komplikationen zu reduzieren, erklärt die Seite PMC (ncbi.nlm.nih.gov). Dieser Schwellenwert wird durch Screening-Tests ermittelt, die Risikofaktoren wie Alter, Blutdruck, Vorgeschichte und Biomarker kombinieren, und signalisiert eine deutlich höhere Wahrscheinlichkeit, dass sich die Erkrankung entwickelt, mit größeren Risiken für Mutter und Kind, wie z.B. Frühgeburtlichkeit oder Wachstumsverzögerung, erläutern die Seiten Wiley (onlinelibrary.wiley.com) und AOK (aok.de).

Bedeutung eines ≥ 1:50 Risikos-

- **Screening-Ergebnis:** Dies ist ein gängiger Grenzwert beim routinemäßigen Screening im ersten Trimester (11.-13. SSW).

Scheduled birth at term for the prevention of pre-eclampsia (PREVENT-PE): an open-label randomised controlled trial

Summary

Background In high-risk pregnancies, there is no reliable intervention to reduce term pre-eclampsia. We aimed to investigate the effect of screening for pre-eclampsia risk at 36 weeks' gestation and offering risk-stratified, planned, early-term birth.

Methods PREVENT-PE was an open-label, adaptive (planned, for sample size), randomised controlled trial, done at two maternity hospitals in the UK. We included women (aged ≥16 years) with a singleton pregnancy, live fetus without major anomalies, and ability to provide informed consent, without pre-eclampsia or participation in conflicting trials. Consenting women were randomly assigned (by a central computerised service, 1:1, in random permuted blocks of variable size, stratified by site) to the intervention group (pre-eclampsia risk assessment and, for women with a pre-eclampsia risk ≥1 in 50, risk-stratified planned early-term birth) or control group (usual care at term). The primary outcome was birth with pre-eclampsia (International Society for the Study of Hypertension in Pregnancy criteria). This trial is registered with ISRCTN, ISRCTN41632964.

Findings Of 11 280 women presenting for routine fetal ultrasound at 35^{+0} to 36^{+6} weeks' gestation between May 9, 2023, and June 7, 2024, 10 803 (95·8%) were eligible. Of 8136 women (75·3%) randomly assigned, six (0·1%) withdrew consent and 36 (0·4%) were randomly assigned in error, leaving 8094 (99·5%) in the final analyses: 4037 (49·9%) women in the intervention group and 4057 (50·1%) in the control group. 2098 (25·9%) of 8094 women self-reported non-White ethnicity and 5996 (74·1%) self-reported White ethnicity. Pre-eclampsia occurred in 158 (3·9%) of 4037 births in the intervention group and in 226 (5·6%) of 4057 in the control group (adjusted risk ratio 0·70 [95% CI 0·58–0·86]; intention-to-treat analysis with imputation). Serious adverse events did not differ between the intervention group (five [0·1%] of 4031) and control group (ten [0·2%] 4048; Fisher's exact test p=0·30).

Interpretation Planned early-term birth based on risk stratification for pre-eclampsia reduced the incidence of pre-eclampsia, without increasing emergency caesarean section or neonatal care unit admission.

Funding Fetal Medicine Foundation.

Procedures

The intervention was a strategy of pre-eclampsia risk assessment using the FMF competing-risks model. This intervention combines maternal factors (maternal age, bodyweight, height, ethnic group, method of conception, whether there is history of chronic hypertension, pre-existing diabetes, systemic lupus erythematosus, antiphospholipid syndrome, parity including previous pregnancy with pre-eclampsia [yes or no], inter-pregnancy interval in years, and family history of pre-eclampsia) with biomarkers (MAP, and serum concentrations of PlGF, and sFlt-1[10]) to estimate individual patient-specific risks of pre-eclampsia.[1,5,16,17] MAP was measured by standardised protocol, using automated devices validated for use in pregnancy and pre-eclampsia,[18] and calibrated for use at both sites by staff at NHS Medical Physics, King's College Hospital. Serum sFlt-1 and PlGF concentrations were measured using an automated device (BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany) at the Fetal Medicine Research Institute, King's College Hospital, London, according to Clinical and Laboratory Standards Institute procedures to ensure precision and accuracy, throughout the trial. The model is based on a survival-time model for the gestational age at birth with pre-eclampsia.[5] The model assumes that if the pregnancy were to continue indefinitely, all women would develop pre-eclampsia, and whether they do so or not before a specific gestational age depends on competition between birth before or after development of pre-eclampsia. A Gaussian model for gestational age at birth was chosen on the basis of model fit and interpretability. In pregnancies at low risk of pre-eclampsia, maternal factors and biomarkers serve to shift the gestational-age distribution to the right, meaning that most births will occur before pre-eclampsia develops. In pregnancies at high risk of pre-eclampsia, maternal factors and biomarkers serve to shift the gestational age distribution to the left, meaning the smaller the mean gestational age, the higher the risk for pre-eclampsia. Therefore, pre-eclampsia risk-scoring is continuous and the screen-positive rate can be adjusted to the desired population risk cutoff. The model has been externally validated[19–24] and is available online embedded in Fetal Medicine Foundation software as an app, for routine clinical use, or accessible directly through the website for one-off, individual case assessments by clinicians or researchers.

Participants with a pre-eclampsia risk of at least one in 50 were offered risk-stratified planned early term birth at 37, 38, 39, or 40 weeks' gestation. Participants with higher pre-eclampsia risk were offered birth earlier than those with a lower risk (table 1).[15] Initiation of birth was by labour induction (by local protocol) or elective caesarean (if indicated or desired by the woman), within the first 2 days of the gestational week of planned birth. Participants with a risk of pre-eclampsia below one in 50 were considered at low risk and managed as per local hospital protocols.

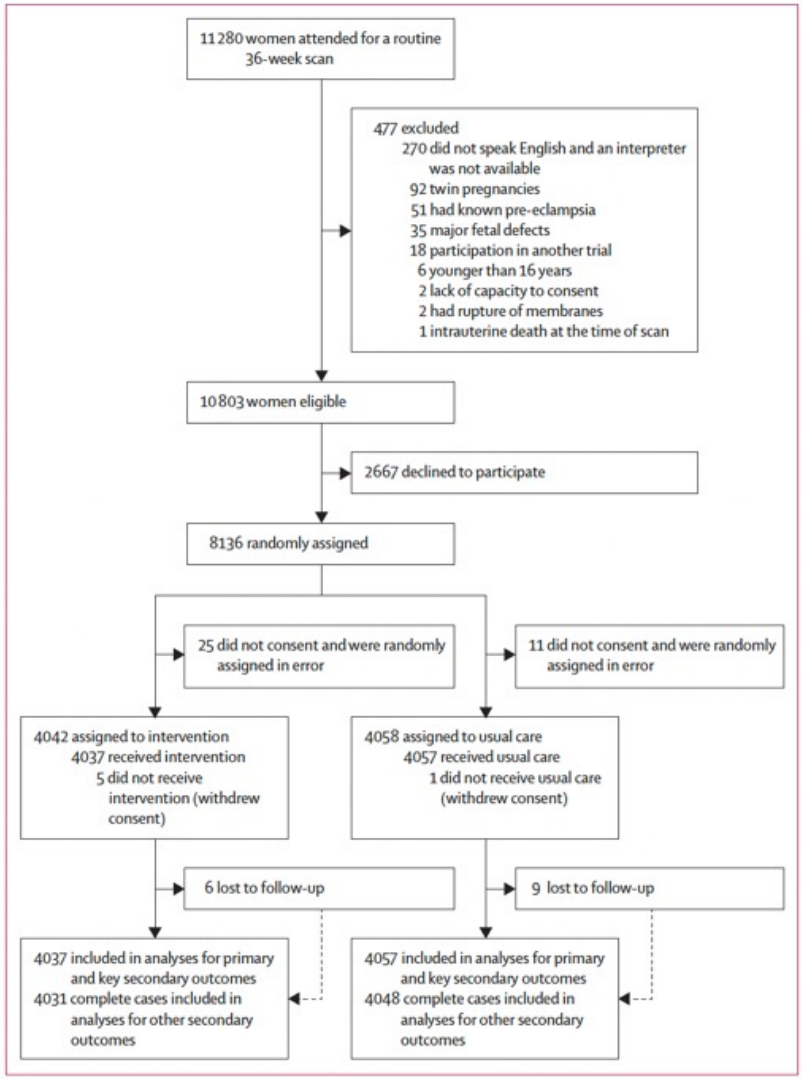


Figure: **Trial profile**

	Total trial cohort (n=8094)	Intervention group (n=4037)	Usual care group (n=4057)
Gestational age at randomisation, weeks	35·6 (35·4–35·9)	35·6 (35·4–35·9)	35·6 (35·4–35·9)
Age, years	33·2 (29·3–36·4)	33·2 (29·1–36·4)	33·1 (29·4–36·2)
Height, cm	166 (161–170)	166 (161–170)	166 (161·5–170·5)
Weight, kg	80·3 (71·6–91·4)	80·2 (71·6–91·4)	80·3 (71·5–91·5)
BMI, kg/m²	29·2 (26·1–33·1)	29·3 (26·1–33·0)	29 (26–33·1)
Self-reported ethnic group			
White	5996 (74·1)	2985 (73·9%)	3011 (74·2%)
Black	1090 (13·5%)	543 (13·5%)	547 (13·5%)
South Asian	517 (6·4%)	270 (6·7%)	247 (6·1%)
East Asian	179 (2·2%)	87 (2·2%)	92 (2·3%)
More than one	312 (3·9%)	152 (3·8%)	160 (3·9%)
Index of multiple deprivation			
1–2	1407 (17·4%)	696 (17·2%)	711 (17·5%)
3–4	2093 (25·9%)	1060 (26·3%)	1033 (25·5%)
5–6	1841 (22·7%)	917 (22·7%)	924 (22·8%)
7–8	1600 (19·8%)	802 (19·9%)	798 (19·7%)
9–10	1153 (14·2%)	562 (13·9%)	591 (14·6%)
Conception			
Spontaneous	7557 (93·4%)	3773 (93·5%)	3784 (93·3%)
Assisted by use of ovulation drugs	51 (0·6%)	22 (0·5%)	29 (0·7%)
In vitro fertilisation	486 (6·0%)	242 (6·0%)	244 (6·0%)
Cigarette smoker	221 (2·7%)	108 (2·7%)	113 (2·8%)
Mother had pre-eclampsia	302 (3·7%)	145 (3·6%)	157 (3·9%)
Medical history			
Chronic hypertension	73 (0·9%)	40 (1·0%)	33 (0·8%)
Systemic lupus erythematosus	24 (0·3%)	9 (0·2%)	15 (0·4%)
Antiphospholipid syndrome	18 (0·2%)	7 (0·2%)	11 (0·3%)
Diabetes, type 1	26 (0·3%)	17 (0·4%)	9 (0·2%)
Diabetes, type 2	40 (0·5%)	19 (0·5%)	21 (0·5%)
Obstetrical history			
Nulliparous	4023 (49·7%)	2002 (49·6%)	2021 (49·8%)
Parous without pre-eclampsia	3820 (47·2%)	1903 (47·1%)	1917 (47·3%)
Parous with pre-eclampsia	251 (3·1%)	132 (3·3%)	119 (2·9%)
Parous without small-for-gestational-age neonate	3396 (42·0%)	1690 (41·9%)	1706 (42·1%)
Parous with small-for-gestational-age neonate	675 (8·3%)	345 (8·5%)	330 (8·1%)
Interval from previous pregnancy, years	2·6 (1·6–4·4)	2·5 (1·6–4·3)	2·5 (1·6–4·5)
Gestational age at birth of previous pregnancy, weeks	39·9 (38·9–40·7)	39·8 (38·7–40·7)	40 (39–40·7)
Birthweight of previous pregnancy, g	3325 (3000–3660)	3320 (3000–3660)	3343 (3008–3686)
Screening biomarkers for pre-eclampsia, multiple of the normal median			
Mean arterial pressure	–	0·998 (0·944–1·056)	–
Placental growth factor	–	1·037 (0·561–1·805)	–
Soluble fms-like tyrosine kinase 1	–	0·972 (0·703–1·396)	–
Aspirin <16 weeks	1342 (16·6%)	710 (17·6%)	632 (15·6%)
Risk group for preterm pre-eclampsia at 11–13 weeks' gestation			
≥1 in 10	50 (0·6%)	35 (0·9%)	15 (0·4%)
1 in 50 to 1 in 10	503 (6·2%)	254 (6·3%)	249 (6·2%)
1 in 100 to 1 in 50	781 (9·7%)	401 (9·9%)	380 (9·4%)
<1 in 100	6745 (83·5%)	3341 (82·9%)	3404 (84·1%)

(Table 2 continues on next page)

	Total trial cohort (n=8094)	Intervention group (n=4037)	Usual care group (n=4057)
(Continued from previous page)			
Results of 35–36-week fetal ultrasound			
Estimated fetal weight, g	2698 (2558–2839)	2692 (2553–2835)	2702 (2560–2843)
<10th percentile	541 (6·7%)	258 (6·4%)	283 (7·0%)
>90th percentile	601 (7·4%)	281 (7·0%)	320 (7·9%)
Fetal Doppler			
Umbilical artery pulsatility index >95th percentile	102 (1·3%)	48 (1·2%)	54 (1·3%)
Middle cerebral artery pulsatility index <5th percentile	83 (1·0%)	36 (0·9%)	47 (1·2%)
Non-cephalic presentation	498 (6·2%)	257 (6·4%)	241 (5·9%)
Risk group for pre-eclampsia at 35–36 weeks' gestation			
≥1 in 2	..	65 (1·6%)	NA
1 in 3 to 1 in 5	..	100 (2·5%)	NA
1 in 6 to 1 in 20	..	318 (7·9%)	NA
1 in 21 to 1 in 50	..	402 (10·0%)	NA
<1 in 50	..	3152 (78·1%)	NA

Data are n (%) or median (IQR). NA=not applicable.

Table 2: **Characteristics of trial participants**

	Intervention group (n=4037)	Usual care group (n=4057)	Adjusted risk ratio (95% CI)	Adjusted risk difference (95% CI)	p value
Primary outcome*					
Pre-eclampsia defined by ISSHP 2021	158 (3·9)	226 (5·6)	0·70 (0·58 to 0·86)	−1·66 (−2·59 to −0·74)	0·0051
Key secondary outcomes*					
Birth by emergency caesarean section	922 (22·8)	878 (21·6)	1·06 (0·97 to 1·15)	1·2 (−0·62 to 3·01)	0·20
Neonatal care unit admission for ≥48 h	261 (6·5)	275 (6·8)	0·96 (0·81 to 1·13)	−0·37 (−1·42 to 0·68)	0·60

Data are n (%), unless otherwise indicated. ISSHP=International Society for the Study of Hypertension in Pregnancy. *Ten-fold multiple imputation was used for primary and key secondary outcomes to deal with missing data on six (0·1%) outcomes in the intervention group and nine (0·2%) outcomes in the usual care group.

Table 3: **Primary and key secondary outcomes by trial group**

	Intervention group (4031/4037 [99·9%])	Usual care group (4048/4057 [99·8%])	Adjusted risk ratio (95% CI)	Adjusted risk difference (95% CI)	p value
Maternal secondary outcomes					
Gestational hypertension defined by ISSHP 2021	188 (4·7)	157 (3·9)	1·20 (0·98 to 1·48)	0·58 (–0·25 to 1·40)	0·082
Timing of pre-eclampsia defined by ISSHP 2021*					
Antenatal onset	132 (3·3)	196 (4·8)	0·68 (0·55 to 0·84)	–1·56 (–2·42 to –0·7)	0·0004
Postnatal onset	26 (0·6)	30 (0·7)	0·87 (0·52 to 1·47)	–0·02 (–0·35 to 0·32)	0·60
Components of ISSHP 2021 definition of pre-eclampsia					
Proteinuria	95 (2·4)	141 (3·5)	0·68 (0·52 to 0·88)	–1·09 (–1·82 to –0·36)	0·0028
Maternal organ dysfunction	110 (2·7)	144 (3·6)	0·77 (0·60 to 0·98)	–0·80 (–1·56 to –0·05)	0·033
Platelet count <150 × 10⁹/L	44 (1·1)	66 (1·6)	0·67 (0·46 to 0·98)	–0·54 (–1·04 to –0·03)	0·038
Creatinine >90 µmol/L	22 (0·5)	30 (0·7)	0·74 (0·43 to 1·27)	–0·13 (–0·44 to 0·19)	0·27
Alanine or aspartate aminotransferase >40 IU/L	50 (1·2)	69 (1·7)	0·73 (0·51 to 1·04)	–0·43 (–0·92 to 0·06)	0·083
Neurological complications	33 (0·8)	44 (1·1)	0·75 (0·48 to 1·18)	–0·26 (–0·68 to 0·15)	0·22
Uteroplacental dysfunction	19 (0·5)	41 (1·0)	0·47 (0·27 to 0·80)	–0·56 (–0·93 to –0·19)	0·0057
Pre-eclampsia defined by ACOG 2019	116 (2·9)	163 (4·0)	0·72 (0·57 to 0·90)	–1·15 (–1·94 to –0·35)	0·0049
Severe features of pre-eclampsia defined by ACOG 2019	76 (1·9)	99 (2·4)	0·77 (0·57 to 1·04)	–0·56 (–1·2 to 0·07)	0·085
Severe hypertension	31 (0·8)	39 (1·0)	0·80 (0·50 to 1·28)	–0·12 (–0·48 to 0·24)	0·35
Platelet count <100 × 10⁹/L	2 (0·05)	8 (0·2)	0·25 (0·05 to 1·18)	–0·15 (–0·3 to 0·002)	0·080
Creatinine >97 µmol/L	18 (0·4)	21 (0·5)	0·86 (0·46 to 1·61)	–0·04 (–0·3 to 0·22)	0·63
Alanine or aspartate aminotransferase >67 IU/L	21 (0·5)	28 (0·7)	0·75 (0·43 to 1·32)	–0·1 (–0·42 to 0·22)	0·32
Pulmonary oedema	0	0	NA	NA	..
New-onset severe headache	27 (0·7)	39 (1·0)	0·70 (0·43 to 1·13)	–0·28 (–0·67 to 0·11)	0·15
Cerebral or visual symptoms	14 (0·3)	13 (0·3)	1·08 (0·51 to 2·30)	0·08 (–0·15 to 0·32)	0·84
Pre-eclampsia integrated estimate of risk score†	0·067 (0·048 to 0·097)	0·073 (0·053 to 0·103)	NA	NA	0·16
Severe hypertension	53 (1·3)	52 (1·3)	1·02 (0·70 to 1·50)	0·14 (–0·32 to 0·61)	0·90
Maternal admission to intensive care or high-dependency unit	65 (1·6)	78 (1·9)	0·84 (0·60 to 1·16)	–0·32 (–0·87 to 0·23)	0·28
Total number of nights in hospital†	2 (1·0 to 3·5)	2 (2 to 3)	NA	NA	0·77

(Table 4 continues on next page)

	Intervention group (4031/4037 [99·9%])	Usual care group (4048/4057 [99·8%])	Adjusted risk ratio (95% CI)	Adjusted risk difference (95% CI)	p value
(Continued from previous page)					
Fetal and newborn secondary outcomes					
Gestational age at birth, weeks†	39·4 (38·9 to 40·4)	39·6 (39·6 to 40·4)	NA	NA	0·70
<37	103 (2·6)	133 (3·3)	0·78 (0·60 to 1·00)	−0·7 (−1·43 to 0·03)	0·053
37-0-4	370 (9·2)	388 (9·6)	0·96 (0·84 to 1·1)	−0·27 (−1·51 to 0·98)	0·53
38-0-4	636 (15·8)	634 (15·7)	1·01 (0·91 to 1·11)	0·14 (−1·45 to 1·72)	0·90
39-0-4	1426 (35·4)	1367 (33·8)	1·05 (0·99 to 1·11)	1·6 (−0·47 to 3·68)	0·13
40-0-4	961 (23·8)	932 (23·0)	1·04 (0·96 to 1·12)	0·81 (−1·03 to 2·66)	0·39
≥41	535 (13·3)	594 (14·7)	0·90 (0·81 to 1·01)	−1·4 (−2·91 to 0·11)	0·068
Labour onset	..	..	..	..	0·84
Spontaneous	2136 (53·0)	2158 (53·3)	0·99 (0·95 to 1·04)	−0·32 (−2·49 to 1·86)	0·78
Induction of labour	1003 (24·9)	964 (23·8)	1·04 (0·97 to 1·13)	1·06 (−0·81 to 2·93)	0·26
No labour	892 (22·1)	926 (22·9)	0·97 (0·89 to 1·05)	−0·75 (−2·57 to 1·07)	0·42
Mode of birth					
Caesarean section	1814 (45·0)	1804 (44·6)	1·01 (0·96 to 1·06)	0·44 (−1·73 to 2·61)	0·69
Perinatal mortality	4 (0·099)	7 (0·17)	0·57 (0·17 to 1·96)	−0·07 (−0·25 to 0·09)	0·38
Stillbirth	3 (0·07)	5 (0·12)	0·60 (0·14 to 2·52)	−0·05 (−0·20 to 0·10)	0·49
Neonatal death	1 (0·02)	2 (0·05)	0·50 (0·05 to 5·52)	−0·02 (−0·13 to 0·07)	0·57
Low birthweight					
Birthweight <3rd percentile	122 (3·0)	148 (3·7)	0·83 (0·65 to 1·05)	−0·64 (−1·42 to 0·15)	0·12
Birthweight <5th percentile	219 (5·4)	238 (5·9)	0·92 (0·77 to 1·10)	−0·45 (−1·45 to 0·56)	0·39
Birthweight <10th percentile	445 (11)	457 (11·3)	0·98 (0·87 to 1·11)	−0·25 (−1·62 to 1·12)	0·72
Admission to neonatal care unit	307 (7·6)	321 (7·9)	0·96 (0·83 to 1·12)	−0·37 (−1·52 to 0·78)	0·62
Neonatal therapy	163 (4·0)	192 (4·7)	0·85 (0·70 to 1·05)	−0·64 (−1·53 to 0·24)	0·13
Intensive care unit admission	144 (3·6)	159 (3·9)	0·91 (0·73 to 1·14)	−0·22 (−1·01 to 0·58)	0·40
Ventilation with positive airway pressure or intubation	62 (1·5)	83 (2·1)	0·75 (0·54 to 1·04)	−0·47 (−0·95 to 0·01)	0·082
Neonatal morbidity	115 (2·9)	128 (3·2)	0·90 (0·70 to 1·16)	−0·38 (−1·11 to 0·34)	0·41
Intraventricular haemorrhage grade 2 or worse	0	0	..	..	..
Sepsis with confirmed bacteraemia in cultures	5 (0·12)	8 (0·20)	0·63 (0·21 to 1·91)	−0·07 (−0·26 to 0·11)	0·41
Encephalopathy requiring cooling	0	3 (0·07)	NA	..	..
Seizures	0	2 (0·05)	NA	..	..
Anaemia requiring blood transfusion	1 (0·02)	1 (0·02)	1·01 (0·06 to 16·09)	..	0·99
Respiratory distress syndrome	111 (2·8)	125 (3·1)	0·89 (0·69 to 1·15)	−0·39 (−1·10 to 0·32)	0·37
Necrotising enterocolitis requiring surgery	0	1 (0·02)	NA	..	..

Data are n (%) or median (IQR), unless otherwise indicated. ACOG= American College of Obstetricians and Gynecologists. ISSHP=International Society for the Study of Hypertension in Pregnancy. NA=not applicable. Missing values in secondary outcomes were dealt with using complete case analysis, excluding data on six (0·1%) outcomes in the intervention group and nine (0·2%) outcomes in the usual care group. See the appendix (pp 3–4) for the detailed definitions of secondary outcomes. *See appendix (p 2) for the detailed definition of pre-eclampsia. †Comparisons for the outcomes pre-eclampsia integrated estimate of risk score, gestational age at birth, and total number of nights in hospital were made using the Wilcoxon test.

Table 4: Other secondary outcomes by trial group

	Intervention group (n=4031)	Usual care group (n=4048)
Maternal admission to intensive care unit		
For severe haemolysis, elevated liver enzyme, low platelet syndrome	1 (<0·1%)	0
For cardiomyopathy	0	1 (<0·1%)
Postpartum haemorrhage (blood loss 3 L) with prolonged hospital stay ≥8 days	0	1 (<0·1%)
Postpartum haemorrhage (blood loss ≥3·5 L) with prolonged hospital stay of ≥8 days	0	1 (<0·1%)
Stillbirth	3 (0·7%)	5 (1·2%)
Neonatal death	1 (0·2%)	2 (0·5%)
Total	5 (0·1%)	10 (0·2%)

Data are n (%).

Table 5: **Serious adverse events by trial group**

Research in context

Evidence before this study

Planned birth at term might be an intervention that can reduce the incidence of pre-eclampsia, as suggested by randomised trials in both nulliparous women at low risk and those with chronic or gestational hypertension at term, as well as by large-scale observational data. We searched the Cochrane Central Register of Controlled Trials, PubMed, ClinicalTrials.gov, and the WHO Clinical Trials Registry for published or registered randomised controlled trials (from inception to Feb 19, 2025) in English that included women at increased risk of pre-eclampsia, who were randomly allocated to timed birth or expectant care at term. Search terms were "risk factors" AND "pre-eclampsia" AND timed birth ("induction" or "elective caesarean") AND "term", with the limits "human" and "randomised controlled trial". No relevant trials were identified. Most previous studies using risk stratification have focused on identifying women at high risk of preterm pre-eclampsia and offering prophylactic aspirin administration for 11–13 weeks of gestation. At term, elective induction without previous risk stratification has been shown to reduce the incidence of pre-eclampsia, but no study has assessed whether a risk-based approach to timed birth could prevent term pre-eclampsia. One risk-stratified trial assessed pravastatin from 36 weeks but found no benefit.

Added value of this study

We found that planned early-term birth based on risk stratification for term pre-eclampsia, compared with usual care, reduced the relative risk of term pre-eclampsia by 30%. Importantly, the benefit was seen without an increase in postpartum pre-eclampsia, across the components of the pre-eclampsia definition, and without a significant increase in birth by emergency caesarean or neonatal care unit treatment. The trial used the Fetal Medicine Foundation competing-risks model to assess for term pre-eclampsia risk at 36 weeks' gestation, when prediction is most accurate, by comparison with screening earlier in pregnancy. Importantly, a high proportion (75%) of eligible women chose to participate in the trial, and withdrawals and losses to follow-up were minimal, suggesting that timed birth at term was appealing to women.

Implications of all the available evidence

To our knowledge, this is the first trial to show that a personalised approach to term pre-eclampsia risk assessment to inform risk-stratified timed birth at term can reduce the incidence of disease in women, without increasing harms, including emergency caesarean birth or prolonged neonatal unit admission.

Additional analyses will examine the cost consequences of the intervention, as well as views of participants and staff involved in the trial. These analyses have the potential to inform the implementation of the intervention into guidelines and its acceptability to the intended population.

Hyperemesis gravidarum

Hyperemesis gravidarum describes nausea and vomiting in pregnancy severe enough to cause weight loss, dehydration, electrolyte imbalance, and nutritional deficiencies. The condition can render women so physically and mentally unwell that they are at increased risk of terminating a wanted pregnancy and experiencing suicidal ideation. Concerns regarding prescribing in pregnancy and inaccurate assumptions that the condition is self-limiting result in women being dismissed and having difficulty accessing appropriate care. Over the past decade, a wealth of literature has been published that gives new insights into the causes of hyperemesis gravidarum, the safety of antiemetic therapy, and short-term and long-term consequences for women with the condition and their children. This Review summarises the findings of this literature with the aim of informing decisions about the care of these women and future research priorities.

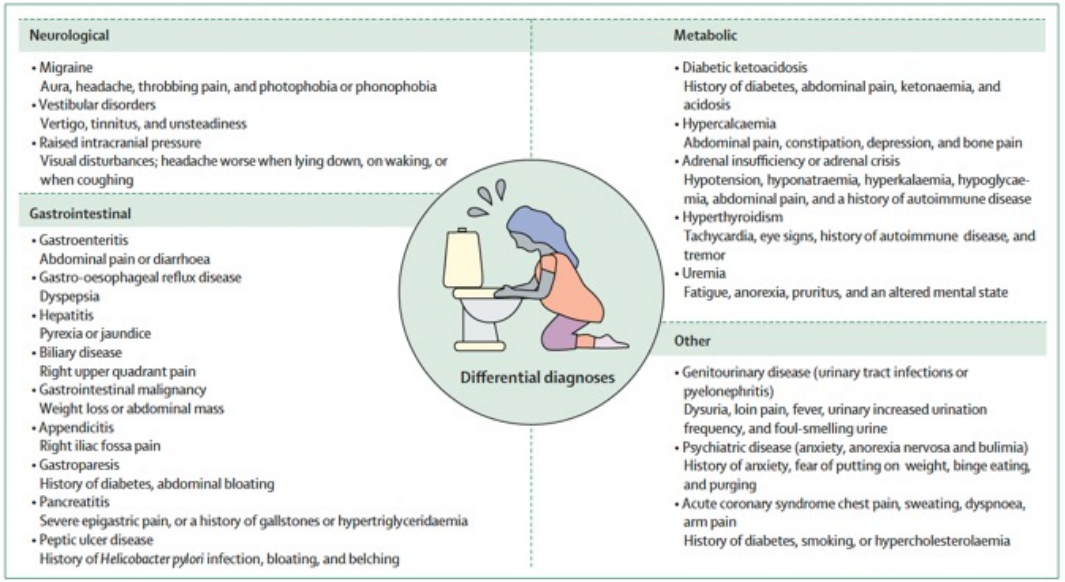


Figure 1: Differential diagnosis of nausea and vomiting in pregnancy

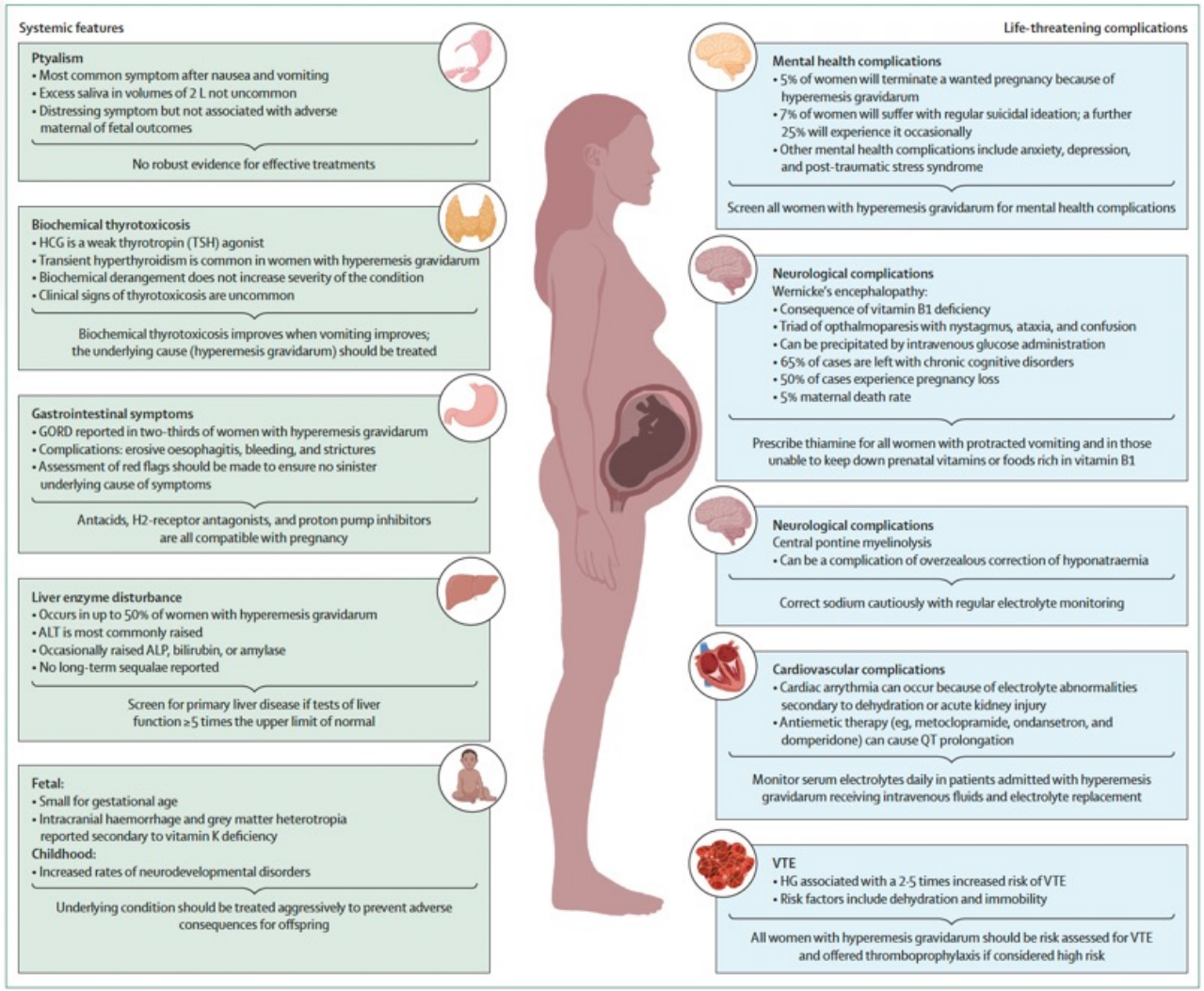


Figure 2: **Clinical features and complications of hyperemesis gravidarum**
ALP=alkaline phosphatase. ALT=alanine aminotransferase. GORD=gastro-oesophageal reflux disease. HCG=human chorionic gonadotrophin. TSH=thyroid-stimulating hormone. VTE=venous thromboembolism. Figure created with BioRender.com.

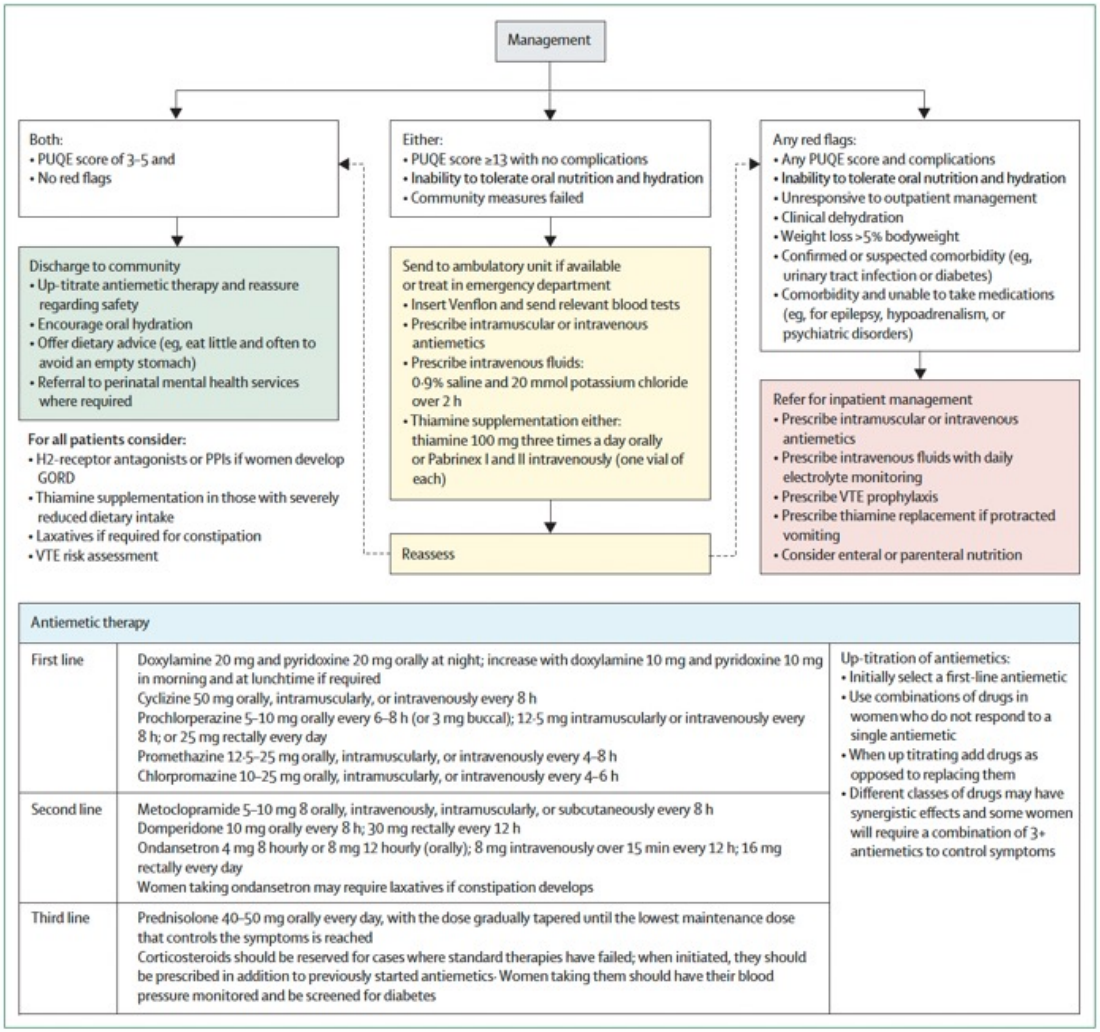


Figure 3: **Recommended management algorithm for hyperemesis gravidarum and nausea and vomiting of pregnancy**
GORD=gastro-oesophageal reflux disease. PPI=proton pump inhibitor. PUQE=pregnancy-unique quantification of emesis. VTE=venous thromboembolism. Adapted from the Royal College of Obstetricians and Gynaecologists' guideline.[65]

***Panel*: Future directions and research priorities**

Priorities for research on hyperemesis gravidarum, as defined by patients and health-care professionals, were identified through a patient–clinician James Lind Alliance partnership and include:[96]

What causes hyperemesis gravidarum?
Further studies on the causal effect of GDF15 in different populations would be important, as well as exploring other genetic predisposing factors for hyperemesis gravidarum.

Can we find a cure?
Improved understanding of the aetiology of hyperemesis gravidarum will enable the development of cures. The discovery of the hormone GDF15 as a likely contributor to aetiology, and the potential to block or modify the response to it, offers exciting opportunities to develop new therapies for hyperemesis gravidarum. Novel therapies that target GFRAL and GDF15 signalling could cure hyperemesis gravidarum in women with a genetic susceptibility related to GDF15 signalling. Future investigation of other genes implicated in the condition could provide information to develop novel therapies.

How can we most effectively manage hyperemesis gravidarum?
To date, few studies have compared the efficacy of different antiemetic therapies or combinations thereof. A personalised approach to treatment is likely to be appropriate but has not yet been the subject of research studies. Very few studies have explored the efficacy of intravenous fluids in either the inpatient or outpatient setting. Further studies are required to establish whether nutrient replacement (informed by knowledge of deficiencies in individual women) could reduce the rate of adverse maternal and fetal outcomes. In addition to physical health complications, hyperemesis gravidarum has a notable, detrimental effect on maternal mental health; further studies should also establish strategies to manage this effect.

Is hyperemesis gravidarum preventable? What are the effects of preventive treatment or early intervention on the severity and duration of the condition in subsequent pregnancies?
To date, only one small study has explored the effect of pre-emptive antiemetics on the severity of hyperemesis gravidarum; larger studies are needed, including those with different antiemetics, to validate the study's findings of beneficial effects.

What are the immediate and long-term effects of hyperemesis gravidarum on the developing fetus?
Studies to date show heterogeneous outcomes with regard to immediate effects of the condition on the developing fetus. Further studies are required to confirm these findings and to determine underlying mechanisms for both the immediate and long-term effects of hyperemesis gravidarum to improve outcomes.

Future research should also explore ethnic disparities in care for women with hyperemesis gravidarum and the cultural perception of medications in pregnancy. This research will be valuable in ensuring all women with the condition can access equitable care.

Conclusion

Hyperemesis gravidarum is a distressing, debilitating, and potentially fatal complication of pregnancy, and represents the most common reason for hospital admission in the first trimester. The condition is associated with several short-term and long-term adverse outcomes for the mother and her offspring. Women with hyperemesis gravidarum require careful monitoring of their physical and mental health to prevent its many potential complications. The condition is treated with intravenous fluid and electrolyte replacement and antiemetics, which can be used in combination and throughout pregnancy. Future directions and research priorities are summarised in the panel. Updated evidence-based guidelines exist, which, if followed by all health-care professionals, should improve the currently widespread experience of poor care by women with hyperemesis gravidarum.

Chronic kidney disease

Globally, the prevalence of chronic kidney disease is estimated to be approximately 850 million cases, with approximately 4 million individuals needing kidney replacement therapy for kidney failure. By 2050, chronic kidney disease is projected to become the fifth leading underlying cause of death worldwide. Despite its numerous causes, chronic kidney disease can be screened for, diagnosed, and staged with simple laboratory tests. Individuals with chronic kidney disease are at increased risk of kidney failure and many other health implications. Risk of premature cardiovascular disease is particularly noteworthy, as most patients with chronic kidney disease develop a disability or die from cardiovascular disease before ever progressing to kidney failure. Since 2019, large randomised trials have identified several effective treatments that both slow progressive kidney function decline and reduce cardiovascular risk, greatly expanding available treatments for chronic kidney disease. The wide range of complications associated with chronic kidney disease means that patients encounter many different specialties. Active engagement in chronic kidney disease identification and timely initiation of cost-effective interventions by all clinicians could now substantially reduce the global burden of complications of chronic kidney disease and kidney failure.

SGLT2 Inhibitoren und GLP-1 Agonisten

What was known from previous *Lancet* Seminars on chronic kidney disease?	What is new in this *Lancet* Seminar on chronic kidney disease?	What is expected in terms of ongoing trials and development?	What is needed to reduce the global burden of chronic kidney disease?
2005[2] • The global challenge of chronic kidney disease, including growing numbers of patients requiring kidney replacement therapy, was highlighted **2012**[3] • Important health implications of chronic kidney disease beyond the complication of kidney failure were described, with particular recognition of associated cardiovascular risk • Blood-pressure lowering, renin-angiotensin system inhibition, and statin-based regimens were key interventions **2017**[4] • Health-service provision to incentivise early intervention was still evolving in many countries • Inequity in access to services for chronic kidney disease disproportionally affected disadvantaged populations • Interventions targeting specific symptoms, or aimed at supporting educational or lifestyle considerations (which make a positive difference for people with chronic kidney disease), were featured **2021**[5] • The emergence of clinical cardiorenal benefits of SGLT2 inhibitors and nsMRAs from trials mainly studying chronic kidney disease with diabetes were emphasised[6-9] (as well as no effect of DDP4 inhibitors on cardiorenal outcomes[10]) • Potential lifestyle and dietary interventions were reviewed in detail • Controversy on management of specific primary causes of chronic kidney disease, including IgA nephropathy, were highlighted while trials were still ongoing	• The 2024 KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease, its first update since the first version was published in 2012[1] • Use of the kidney failure risk equation to estimate 5-year risk of need for dialysis or transplantation to improve patient counselling and referral to nephrology services when risk >5% is encouraged;[1] we propose using high risk as a method to prioritise a rapid-sequence approach to initiation of risk-modifying treatment • SGLT2 inhibition importantly reduces risk of kidney failure, heart failure hospitalisation, and other cardiovascular risk in a broad range of patients with chronic kidney disease, and, including glomerular diseases[7,11-13] • GLP-1 receptor agonists reduce the risk of kidney failure and major cardiovascular outcomes in patients with chronic kidney disease and diabetes (FLOW trial: chronic kidney disease-specific data using subcutaneous semaglutide in its anti-diabetic dose)[14,15] • Targeting the aldosterone pathway in patients with chronic kidney disease already on SGLT2 inhibition additionally reduces albuminuria,[16-18] encouraging consideration of combined use of core treatments for diabetic kidney disease • Several advances in treatment options in addition to the renin-angiotensin system and SGLT2 inhibition have shown to be effective in IgA nephropathy (eg, ERAs[19-21] and particularly immunosuppression)[22,23]	• New 2026 European Society of Cardiology guidelines on the management of cardiovascular disease in patients with chronic kidney disease in collaboration with the European Renal Association and new American Heart Association-American College of Cardiology cardio-kidney-metabolic syndrome guidelines are expected[24,25] • Chronic kidney disease trials studying nsMRAs and aldosterone synthase inhibitors in non-diabetic chronic kidney disease are ongoing;[26-28] nsMRAs are also being studied in type 1 diabetes[26] • Phase 2 trials of soluble guanylate cyclase activators in patients with diabetes and non-diabetic chronic kidney disease are ongoing[28] • More trials of immunomodulation for specific glomerular diseases are required • Definitive assessment of the clinical cardiovascular and kidney effects of an anti-inflammatory treatment with an IL-6 monoclonal antibody (ZEUS trial) is ongoing in patients with chronic kidney disease (NCT05021835)[28] • Real-time ketone monitors to facilitate the use of SGLT2 inhibitors (off label) in patients with type 1 diabetes and chronic kidney disease are needed[29] • The role of genetics in chronic kidney disease research and clinical practice is increasing[30]	• Implementation of the four core interventions for chronic kidney disease and the three extra interventions for chronic kidney disease in diabetes by all clinicians who encounter such patients is needed to reduce the global burden of chronic kidney disease and its complications • When new targets for final common pathways of chronic kidney disease progression are identified, large, simple trials of promising interventions testing effects in a wide range of patients with chronic kidney disease are preferred[31,32] (pursuing small trials of specific diseases and orphan drug designation for such interventions should be discouraged to avoid their limitations)[33] • Development of primary kidney disease-specific interventions, which are then tested in sufficiently large and long (≥2 year) trials, is required to adequately assess the safety and benefit of important GFR-based outcomes • The concept of active primary prevention of chronic kidney disease should be developed[34] and the provision of kidney replacement therapy should be expanded to implement the 2025 WHO resolution[35] and the KDIGO vision on maintenance of kidney health[34]

Figure 1: **Important progress in understanding chronic kidney disease and its management**
ESC=European Society of Cardiology. ERAs=endothelin receptor antagonists. GFR=glomerular filtration rate. GLP-1=glucagon-like peptide-1. KDIGO=Kidney Disease: Improving Global Outcomes. nsMRAs=non-steroidal mineralocorticoid receptor antagonists.

Increased risk of complications by chronic kidney disease stage relative to a healthy population

eGFR category		Persistent albuminuria category: Normal or mildly increased A1 (<30 mg/g <3 mg/mmol)		Moderately increased A2 (30-300 mg/g 3-30 mg/mmol)		Severely increased A3 (>300mg/g >30 mg/mmol)	
		Reference					
Normal or high	G1 (≥90 mL/min per 1·73 m²)	A	C	1·3	1·5	1·7	2·5
		B	D	1·5	2·4	2·6	7·2
Mildly decreased	G2 (60–89 mL/min per 1·73 m²)	0·7	0·8	1·0	1·2	1·3	1·9
		0·9	2·1	1·4	4·7	2·2	13·4
Mildly to moderately decreased	G3a (45–59 mL/min per 1·73 m²)	0·9	1·1	1·2	1·5	1·5	2·2
		1·2	6·4	1·6	11·4	2·5	28·2
Moderately to severely decreased	G3b (30–44 mL/min per 1·73 m²)	1·1	1·4	1·3	1·8	1·8	2·6
		1·5	14·8	1·8	23·3	2·8	47·7
Severely decreased	G4 (15–29 mL/min per 1·73 m²)	1·5	2·0	1·7	2·2	2·3	3·4
		2·1	40·8	2·3	51·3	3·6	84·1
Kidney failure	G5 (<15 mL/min per 1·73 m²)	2·4	3·2	2·7	3·5	3·1	4·7
		4·1	78·3	4·1	94·5	5·2	97·7

Groups of complications (n=number of outcomes)

A All-cause death (n=2·6 million) or hospitalisation (n=8·4 million)	C Cardiovascular death (n=776 000), heart failure (n=1·1 million), or atrial fibrillation (n=1·1 million)
B Atherosclerotic disease: myocardial infarction (n=451 000), stroke (n=461 000), or peripheral arterial disease (n=379 000)	D Kidney failure requiring replacement therapy (n=159 000) or acute kidney injury (n=1·4 million)

Figure 2: **KDIGO chronic kidney disease staging nomenclature and system**
Classification according to body surface area-indexed glomerular filtration rate and albuminuria categories, and associations with a selection of its complications. The numbers in each shaded box represents the hazard ratios for each category versus the reference group, after adjustment for age, sex, smoking status, systolic blood pressure, lipid measurements, anthropometry, previous disease, and medication use. Green corresponds to no chronic kidney disease, yellow corresponds to moderate risk, orange corresponds to high risk, and red corresponds to very high risk of kidney failure relative to a healthy population. Chronic kidney disease is defined as abnormalities in kidney structure or function present for a minimum of 3 months, with implications for health. Chronic kidney disease is classified on the basis of cause, glomerular filtration rate category (G1–G5), and albuminuria category (A1–A3). Plot adapted from the 2024 KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease.[1] This figure uses data from studies contributing to the Chronic Kidney Disease Prognosis Consortium: Estimated Glomerular Filtration Rate, Albuminuria, and Adverse Outcomes.[36] To formally convert albumin-to-creatinine values from mg/g to mg/mmol, division by 8·84 is required. eGFR=estimated glomerular filtration rate. Adapted with permission from the Chronic Kidney Disease Prognosis Consortium.

A

Screen for decreased eGFR <60 mL/min per 1·73 m² and increased urine albumin-to-creatinine ratio >30 mg/g
(Patients with diabetes, high blood pressure, cardiovascular disease, structural kidney abnormalities, a family history of chronic kidney disease, older age, or incidental haematuria are at risk)

Stage and confirm chronicity
Use eGFR and uACR to determine KDIGO stage (and confirm abnormalities persist), and then estimate 5-year kidney failure risk

Initiate establishing a primary cause
Assess history, family history, examination, HbA_{1c}, urine dipstick, and renal ultrasound, and consider C-reactive protein and a serological screen

Assess for cardiovascular and metabolic complications
Assess cardiovascular disease symptoms and signs, haemoglobin concentration, bone chemistry, and lipid profile

Common referral indications

Urology
- Obstructive disease
- Isolated haematuria in patients older than 40 years

Nephrology
- 5-year kidney failure risk >3–5%
- Suspected glomerular disease (eg, haematuria and albuminuria, or albuminuria not attributable to diabetes)
- Inherited kidney disease
- Anaemia of kidney disease (normocytic haemoglobin <10 g/dL)

Diabetology
- Type 1 diabetes with chronic kidney disease

Cardiology and vascular teams
- Specialist investigation and management of coronary artery disease, heart failure, atrial fibrillation, arrythmias, and peripheral arterial disease

Four core interventions to manage risk of kidney failure and cardiovascular risk (in addition to lifestyle advice)

1. **SGLT2 inhibitor**
   (not indicated for patients with type 1 diabetes or ADPKD; advise about genital infections)
2. **RAS inhibitor (ACE inhibitor or ARB)**
   (might not be indicated in patients with absence of albuminuria and blood pressure <130 mm Hg; monitor potassium)
3. **Statin-based regimen**
   (use suitable intensive regimen, eg, atorvastatin 20 mg daily, fire-and-forget appropriate for primary prevention)
4. **Blood pressure control**
   (aim for <130/80 mm Hg and <120 mm Hg systolic, when tolerated and appropriate standardised monitoring used)

Drug stewardship
- Review for nephrotoxic medication
- Adjust comedication doses for GFR
- Counsel on sick-day rules and avoidance of acute kidney injury (including resumption of treatment)

Management of complications

Symptomatic gout
- Prophylaxis with a xanthine oxidase inhibitor and acute treatment with colchicine or glucocorticoids

Hyperkalaemia
- Modify diet, improve glycaemic control, treat acidosis, review medications, and consider potassium binders

Infection
- Ensure routine vaccination (eg, against influenza, COVID-19, pneumococcus, hepatitis B, and shingles when relevant)

Type 2 diabetes: three additional interventions to manage risk of kidney failure and cardiovascular risk

1. **GLP-1 receptor agonists**
   (eg, weekly subcutaneous semaglutide at 1·0 mg per week [anti-diabetic dose])
2. **nsMRAs**
   (finerenone with potassium monitoring)
3. **Personalised intensive HbA1c target**
   (avoid metformin when eGFR <30 mL/min per 1·73 m²)

Monitor, restage, and reassess 5-year kidney failure risk at least annually

(Figure 3 continues on next page)

B

	Summarised indications for use in chronic kidney disease from US labels	Summarised 2024 KDIGO guideline update recommendation[1] and practice points (and FLOW trial details)[14]
Angiotensin-II receptor blocker (oral losartan or irbesartan)	Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension (or similar such wording)	Use is recommended in patients with chronic kidney disease and diabetes at stage A2–A3 albuminuria or in patients at stage A3 albuminuria without diabetes (limit to G1–G4); use is suggested in patients with A2 albuminuria without diabetes; consider starting people with chronic kidney disease and A1 albuminuria for specific indications (eg, to treat high blood pressure or heart failure)
SGLT2 inhibitor (oral dapagliflozin or empagliflozin 10 mg once daily)	To reduce the risk of sustained decline in eGFR, end-stage kidney disease, cardiovascular death, and hospitalisation (for heart failure*) in adults with chronic kidney disease at risk of progression	Recommend use in patients with type 2 diabetes and chronic kidney disease; in absence of diabetes, use in patients with uACR ≥200 mg/g and suggest use in patients with eGFR 20–45 mL/min per 1·73 m² when uACR <200 mg/g; generally, start when eGFR ≥20 mL/min per 1·73 m² and continue to dialysis as studies have shown continued safety and efficacy at low GFRs
Oral canagliflozin 100–300 mg daily once daily	To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalisation for heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria	
Non-steroidal mineralocorticoid receptor antagonist (Oral finerenone 10–20 mg)	To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalisation for heart failure in adult patients with chronic kidney disease associated with type 2 diabetes	Suggest use in patients with type 2 diabetes when eGFR >25 mL/min per 1·73 m², serum potassium concentration is normal, and uACR >30 mg/g despite maximum tolerated dose of RAS inhibitor
GLP-1 receptor agonist (subcutaneous semaglutide 1·0 mg weekly after 8-week titration phase)	To reduce the risk of worsening kidney disease, kidney failure, and death due to cardiovascular disease in adults with type 2 diabetes and chronic kidney disease (other indications exist for weight management with higher dosing)	Trial reported after publication of the 2024 KDIGO guideline update; FLOW trial eGFR and uACR inclusion criteria were eGFR 50–75 mL/min per 1·73 m² plus uACR 300–5000 mg/g, or eGFR 25–50 mL/min per 1·73 m² plus uACR 100–5000 mg/g[14,78]

Figure 3: **Evaluation and management of chronic kidney disease**

(A) Basic evaluation and management information for all clinicians. (B) Additional detail on four pharmacological indications for use and guideline recommendations statements for core chronic kidney disease treatments. For more details see 2024 KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease.[1] ACE=angiotensin-converting enzyme. eGFR=estimated glomerular filtration rate. GFR=glomerular filtration rate. GLP-1=glucagon-like peptide-1. HbA_{1c}=glycated haemoglobin. nsMRA=non-steroidal mineralocorticoid receptor antagonist. PAD=peripheral arterial disease. RAS=renin-angiotensin system. uACR=urine albumin-to-creatinine ratio. *Dapagliflozin indication is specifically for hospitalisation for heart failure, whereas empagliflozin is indicated to prevent all-cause hospitalisation.

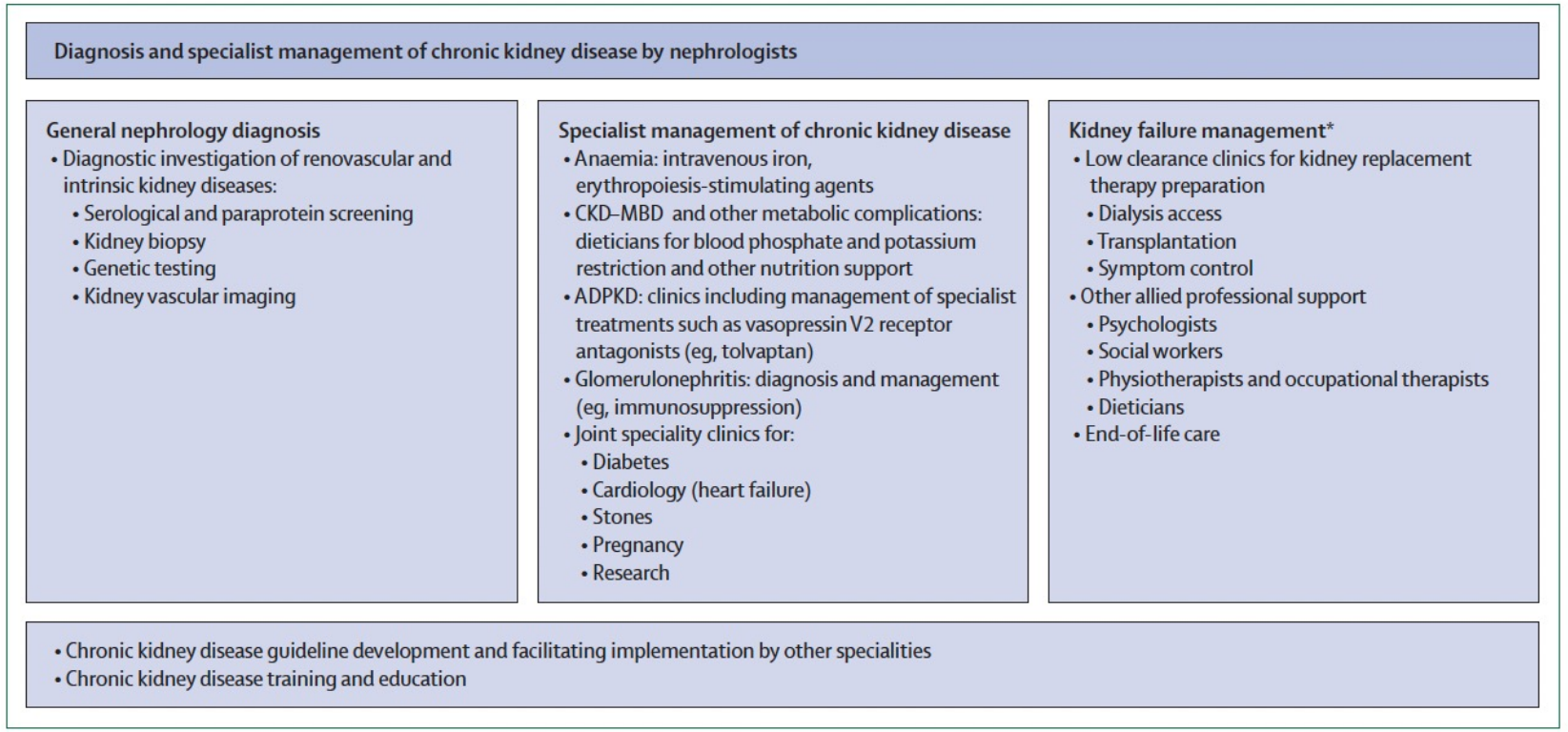


Figure 4: **Specialist nephrology management of chronic kidney disease**

For more detailed information, see Kidney Disease: Improving Global Outcomes reports, such as guidelines and conference reports covering chronic kidney disease diagnosis and management,[1] including specialist management of glomerular disease,[77] ADPKD,[81] CKD–MBD,[82,83] anaemia,[84] and other areas of practice. ADPKD=autosomal-dominant polycystic kidney disease. CKD–MBD=chronic kidney disease mineral bone disorder. ESA=erythropoiesis-stimulating agent. *Nephrologists are recommended to use 2-year kidney failure risk exceeding 40% as a trigger to begin counselling for kidney replacement therapy.

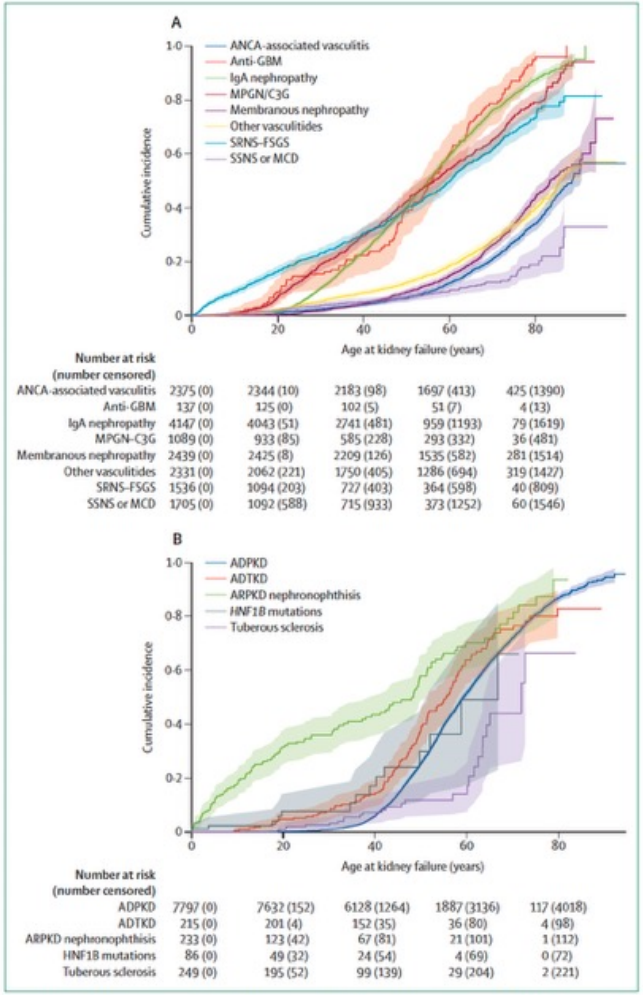


Figure 5: **Kaplan-Meier estimates of cumulative incidence of kidney failure for glomerular (A) and cystic kidney diseases (B) in the UK**

Data are censored for death. ADPKD=autosomal dominant polycystic kidney disease. ADTKD=autosomal dominant tubulointerstitial kidney disease. ANCA=antineutrophil cytoplasmic antibody. eGFR=estimated glomerular filtration rate. MPGN-C3G=membranoproliferative glomerulonephritis and C3 glomerulopathy. SRNS-FSGS=steroid resistant nephrotic syndrome, congenital nephrotic syndrome, or focal segmental glomerulosclerosis. SSNS-MCD=steroid sensitive nephrotic syndrome or minimal change disease. Reproduced from Wong et al.[39]

Conclusion

Chronic kidney disease is a condition that is generally simple to identify and stage using GFR and uACR, and is present in hundreds of millions of individuals globally. Chronic kidney disease substantially increases the risk of a wide range of cardiovascular diseases and kidney failure. Since the 2021 *Lancet* Seminar on chronic kidney disease, the effectiveness of several classes of medications that favourably modify kidney failure risk and cardiovascular risk in a broad range of people with chronic kidney disease has become evident. Guidelines highlight core evidence-based approaches, including use of SGLT2 inhibitors, RAS inhibitors, statin-based regimens, and intensive blood pressure targets. GLP-1 receptor agonists and the nsMRA finerenone should be considered in patients with chronic kidney disease and type 2 diabetes alongside lifestyle advice and personalised or suitably intensive HbA_{1c} targets. These interventions make up a new standard of care for patients with chronic kidney disease and can be implemented in many different clinical settings. If health-care services can ensure early use of cost-effective pharmacological and non-pharmacological treatments across all resource settings, the global burden of chronic kidney disease complications could be substantially alleviated.

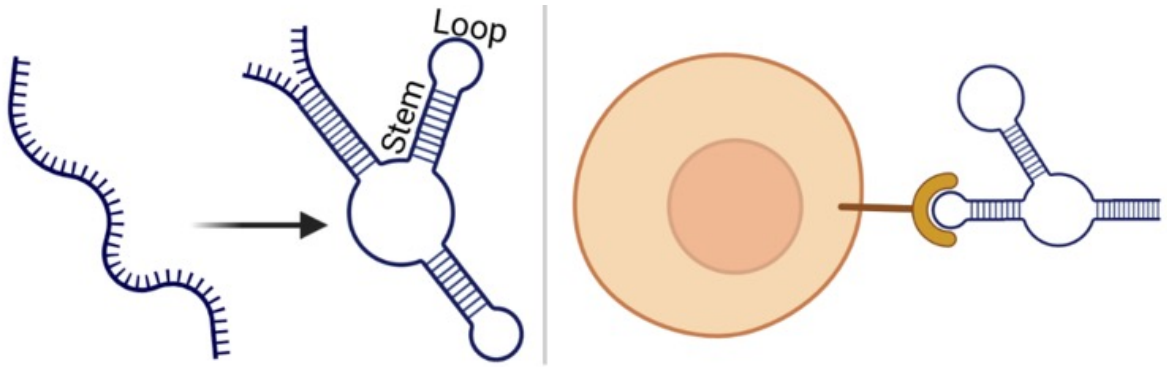
Contributors

Aptamere sind kurze, einzelsträngige Nukleinsäuren (DNA oder RNA) oder Peptide, die durch ihre spezifische räumliche 3D-Struktur an Zielmoleküle binden können. Aufgrund ihrer hohen Affinität und Spezifität werden sie oft als „chemische Antikörper“ bezeichnet.

Haupteigenschaften und Funktionen

•**Struktur:** Meist bestehen sie aus 25 bis 70 Basen. Sie falten sich in komplexe Formen, um wie ein Schlüssel ins Schloss an Proteine, Zellen oder kleine Moleküle anzudocken.

•**Herstellung:** Im Gegensatz zu Antikörpern werden sie nicht in lebenden Organismen, sondern rein synthetisch im Labor mittels des **SELEX-Verfahrens** (*Systematic Evolution of Ligands by Exponential Enrichment*) erzeugt.



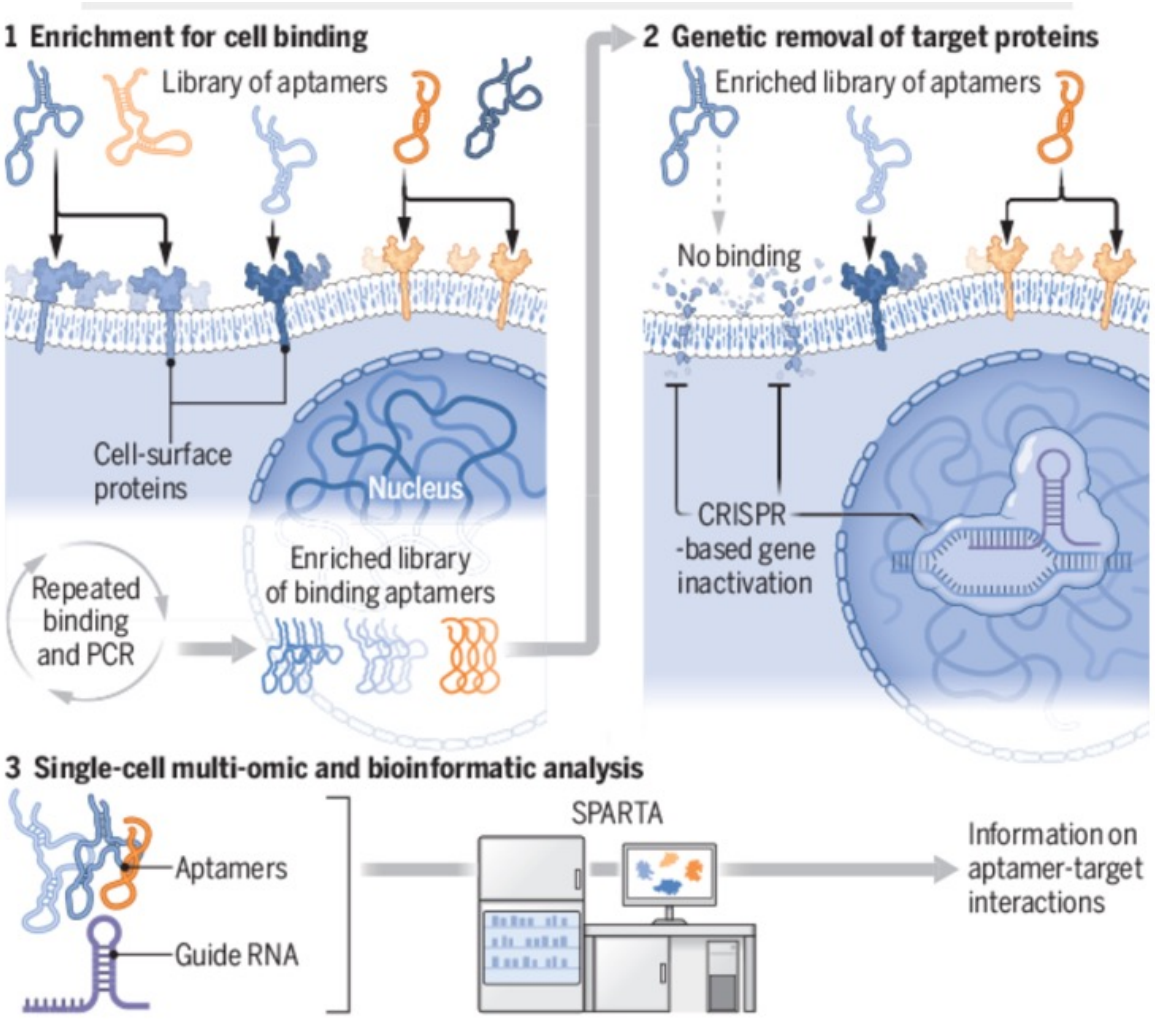
Lighting the spark of aptamer data science

Aptamers are short synthetic nucleic acids that form complex three-dimensional structures, enabling them to bind to target molecules. The binding properties of aptamers have attracted considerable interest in using them for molecular perturbations, detection of disease-related targets, and as tools in synthetic biology. Aptamers are identified through a process known as systematic evolution of ligands by exponential enrichment (SELEX). SELEX is an iterative selection method that uses large libraries of nucleic acids. During this process, the aptamer sequences within these libraries that bind to target molecules are enriched. Nevertheless, it remains a challenging task to identify the most effective, target-specific aptamers among the enriched sequences.

Luo *et al*. describe single-cell perturbation-driven aptamer recognition and kinetics sequencing (SPARK-seq), a method that combines the binding properties and sequencing capabilities of aptamers with gene inactivation studies. This approach enables the simultaneous mapping of thousands of aptamer-target interactions and the identification of aptamers that bind to low-abundance targets.

A process of elimination

Aptamers are typically identified using SELEX, which involves repeated incubation of a library of aptamers with a target (for example, a whole cell) and PCR to amplify bound sequences. In SPARK-seq, the resulting enriched library is incubated with a mixed population of cells bearing CRISPR-based inactivation of different target genes. Single-cell analysis is then used to sequence the bound aptamers and the CRISPR guide RNA present in each cell. An algorithm (SPARTA) uses this information to match families of aptamers to their targets.



PCR, polymerase chain reaction; SELEX, systematic evolution of ligands by exponential enrichment; SPARK-seq, single-cell perturbation-driven aptamer recognition and kinetics sequencing; SPARTA, single-cell perturbation-aptamer recognition and targeted aptamer-generation algorithm.

SPARK-seq: A high-throughput platform for aptamer discovery and kinetic profiling

Cell surface proteins are key disease biomarkers and therapeutic targets, yet high-throughput methods for aptamer discovery targeting these proteins in situ remain limited. We introduce single-cell perturbation-driven aptamer recognition and kinetics sequencing (SPARK-seq), a high-throughput platform integrating single-cell messenger RNA and aptamer sequencing with CRISPR-based surface protein perturbation. In a single experiment, SPARK-seq simultaneously mapped 5535 distinct aptamers to eight surface proteins, capturing interactions across more than two orders of magnitude in protein abundance and spanning diverse biophysical classes. The method discriminated closely related paralogous proteins with no detectable cross-reactivity and provided kinetic information that enabled the prioritization of aptamers with slow dissociation rates. Leveraging this kinetic diversity, we engineered variants with improved off-rate properties. SPARK-seq establishes a platform for high-efficiency discovery and rational variant design of aptamers and functional nucleic acids, unlocking possibilities in diagnostics and therapeutics.

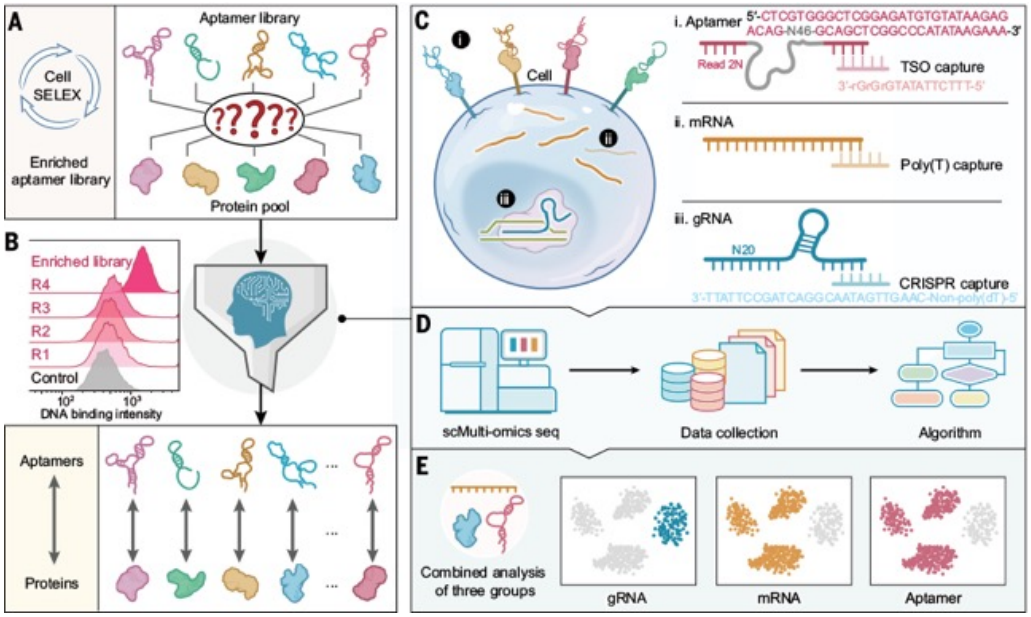


Fig. 1. SPARK-seq workflow overview. (**A**) Schematic of Cell-SELEX for enrichment of aptamers that bind native cell-surface proteins. **(B**) Flow cytometry validation of enriched library binding under physiological conditions. (**C**) Architecture of the single-cell sequencing assay. (**D**) Computational pipeline for differential analysis, integrating single-cell aptamer counts, gRNA identity, and transcriptome profiles. (**E**) Integrated single-cell readout reveals aptamer-protein interactions by correlating aptamer abundance with CRISPR perturbations and gene expression changes.

5 little habits to try every day for a healthier year

In this article

1. Brush your teeth before and after breakfast
2. Clean your ears the right way
3. Be strategic when applying deodorant
4. Make your bed
5. Wear socks to bed