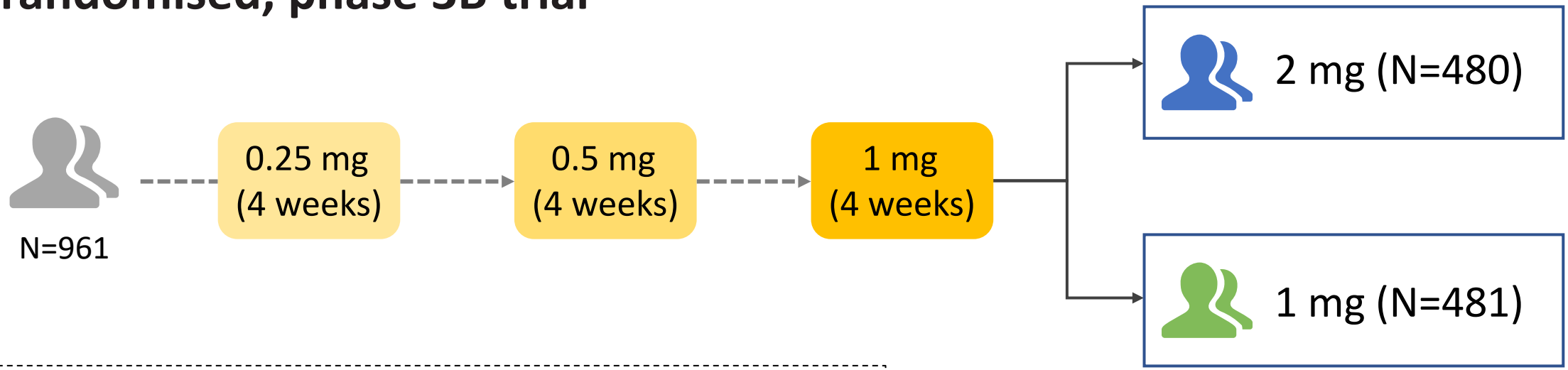
期刊報告

藥品諮詢組 張妤藥師 2021.11.4

Lancet Diabetes Endocrinol 2021; 9: 563–74

Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial



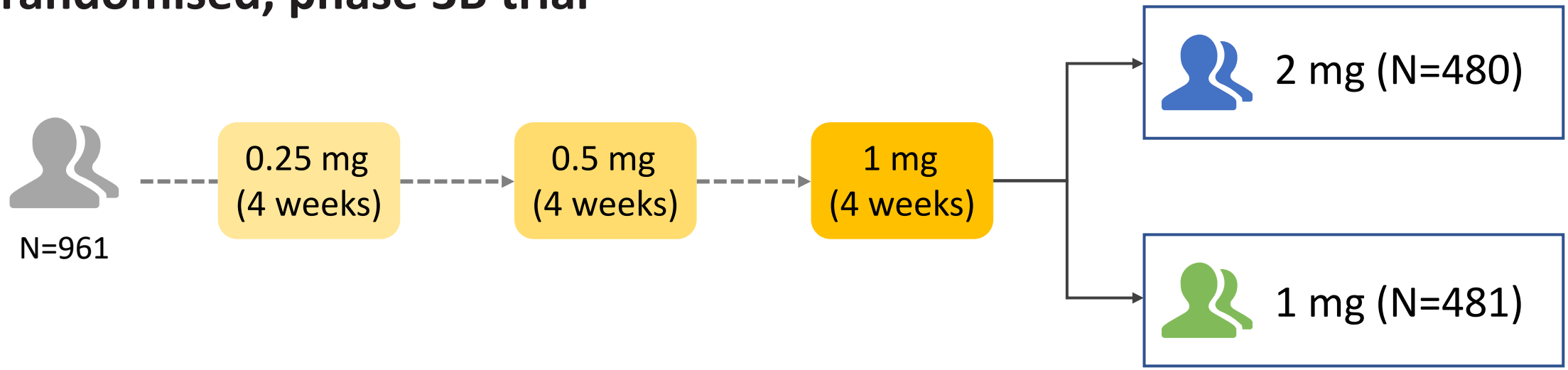
Inclusion criteria

- ✓ Age ≥18 y/o with T2DM for at least 180 days
- ✓ HbA1C 8-10%
- ✓ Metformin ≥1500 mg or maximum tolerated/effective dose alone or in combination with Sulfonylurea

Glycaemic rescue medication could be implemented from week 16 onwards in the case of persistent hyperglycaemia.

Lancet Diabetes Endocrinol 2021; 9: 563–74

Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial



- Primary outcome: Change from baseline at week 40 in HbA1c.
- Secondary outcome: Change from baseline at week 40 in bodyweight.

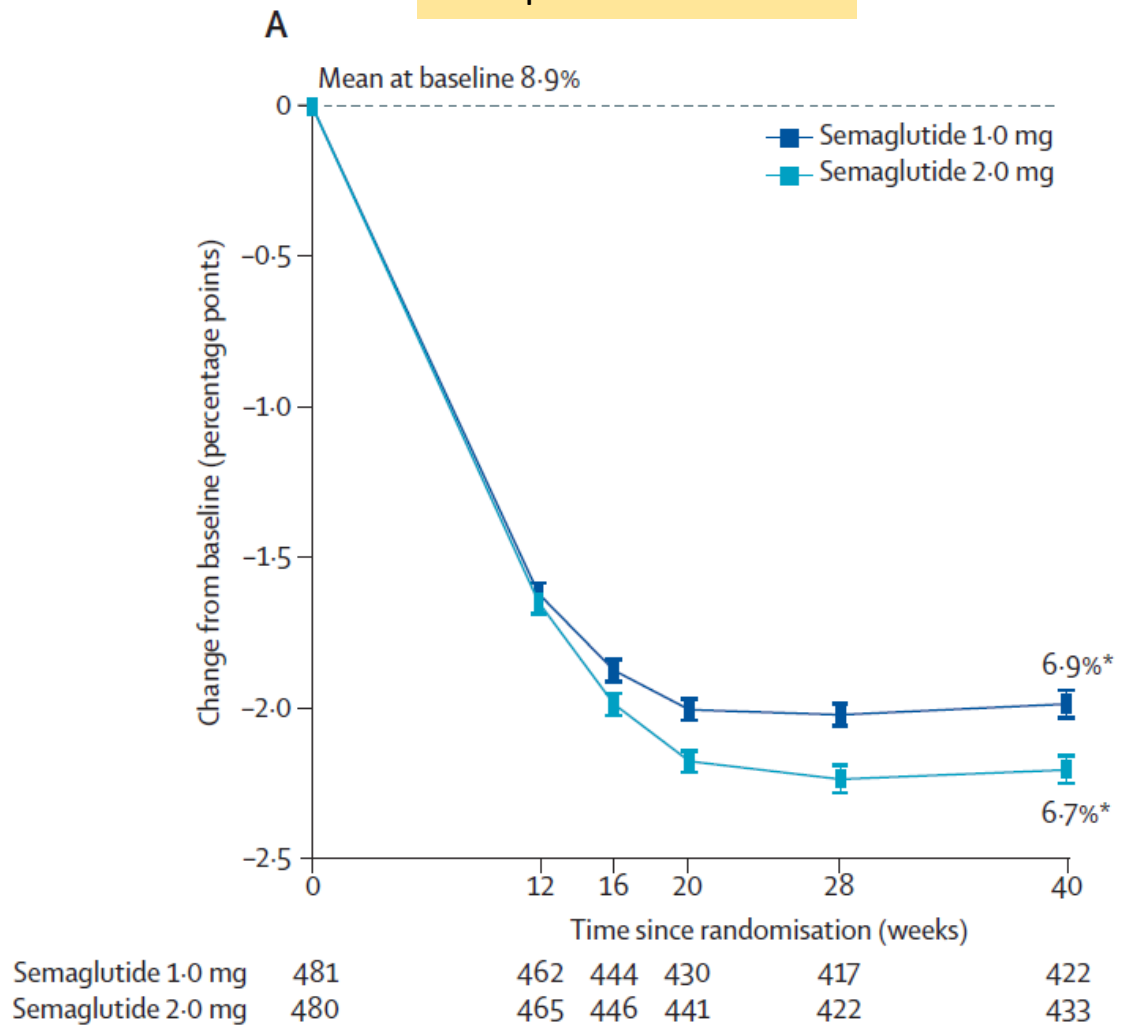
Baseline characteristics

	Semaglutide 1·0 mg (n=481)	Semaglutide 2·0 mg (n=480)	Overall (n=961)
Age, years	58·2 (9·9)	57·9 (10·0)	58·0 (10·0)
Gender			
Women	197 (41%)	201 (42%)	398 (41%)
Men	284 (59%)	279 (58%)	563 (59%)
Race			
American Indian or Alaska native	1 (<1%)	0	1 (<1%)
Asian*	36 (7%)	33 (7%)	69 (7%)
Black or African American	17 (4%)	26 (5%)	43 (4%)
White	427 (89%)	420 (88%)	847 (88%)
Other	0	1 (<1%)	1 (<1%)
Country			
Bulgaria	50 (10%)	46 (10%)	96 (10%)
Canada	11 (2%)	9 (2%)	20 (2%)
Czech Republic	8 (2%)	7 (1%)	15 (2%)
Greece	18 (4%)	19 (4%)	37 (4%)
Hungary	81 (17%)	75 (16%)	156 (16%)
Japan	25 (5%)	25 (5%)	50 (5%)
Poland	68 (14%)	68 (14%)	136 (14%)
Slovakia	40 (8%)	52 (11%)	92 (10%)
Ukraine	20 (4%)	30 (6%)	50 (5%)
USA	160 (33%)	149 (31%)	309 (32%)

	Semaglutide 1·0 mg (n=481)	Semaglutide 2·0 mg (n=480)	Overall (n=961)
Diabetes duration, years			
Mean	9·8 (6·2)	9·2 (6·2)	9·5 (6·2)
Median (IQR)	9·6 (4·9–13·4)	7·9 (4·7–12·1)	8·7 (4·8–12·8)
HbA_{1c}, %	8·8 (0·6)	8·9 (0·6)	8·9 (0·6)
HbA_{1c}, mmol/mol	73·1 (6·9)	73·4 (6·9)	73·3 (6·9)
Fasting plasma glucose, mmol/L	10·9 (2·7)	10·7 (2·8)	10·8 (2·8)
Bodyweight, kg	98·6 (24·4)	100·1 (22·6)	99·3 (23·5)
BMI, kg/m²	34·4 (7·2)	34·8 (6·8)	34·6 (7·0)
Waist circumference, cm	112·2 (16·4)	113·4 (16·4)	112·8 (16·4)
Estimated glomerular filtration rate, mL/min per 1·73 m²	93·0 (17·5)	93·9 (16·4)	93·4 (16·9)
≥90 mL/min per 1·73 m²	309 (64%)	316 (66%)	625 (65%)
60 to <90 mL/min per 1·73 m²	147 (31%)	150 (31%)	297 (31%)
30 to <60 mL/min per 1·73 m²	25 (5%)	14 (3%)	39 (4%)
Systolic blood pressure, mm Hg	134 (14)	134 (14)	134 (14)
Diastolic blood pressure, mm Hg	80 (10)	81 (9)	81 (9)
Pulse rate, beats per minute	75·4	76·4	75·9
Diabetic retinopathy	37 (8%)	50 (10%)	87 (9%)
Anti-diabetes medication at randomisation			
Metformin	481 (100%)	480 (100%)	961 (100%)
Sulfonylurea	259 (54%)	253 (53%)	512 (53%)

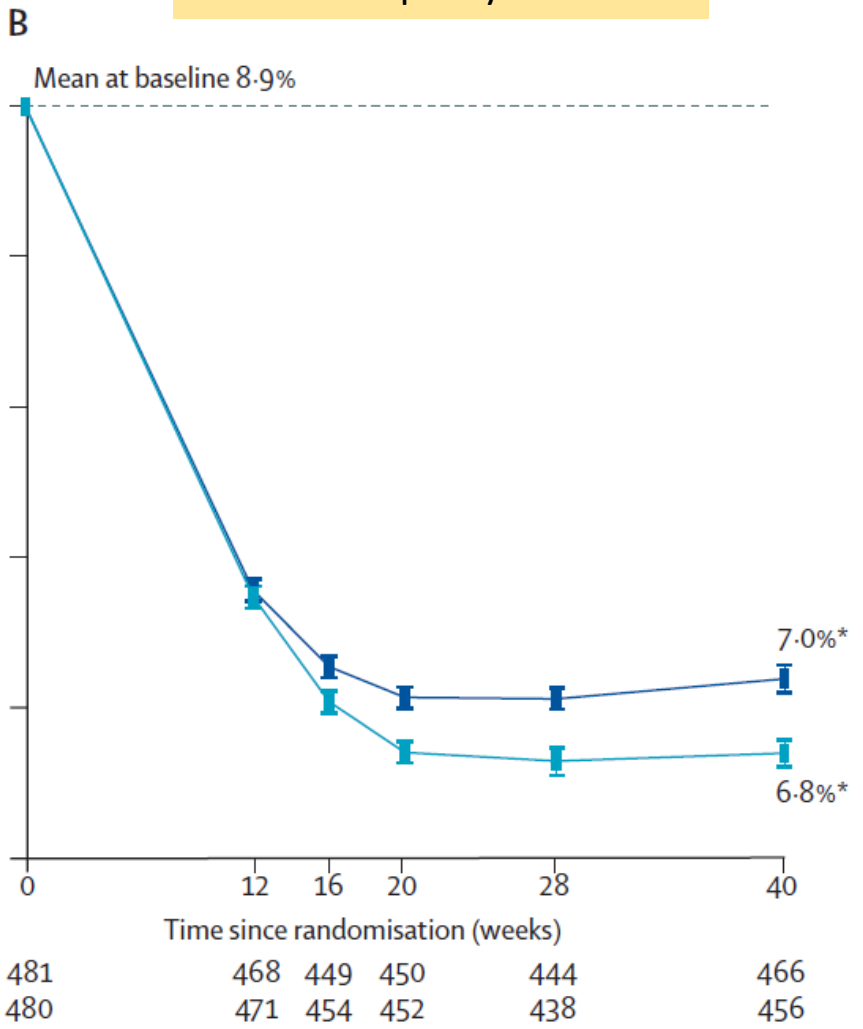
Outcomes---HbA1C

Trial product estimand



ETD –0·23 (95% CI –0·36 to –0·11); p=0·0003

Treatment policy estimand

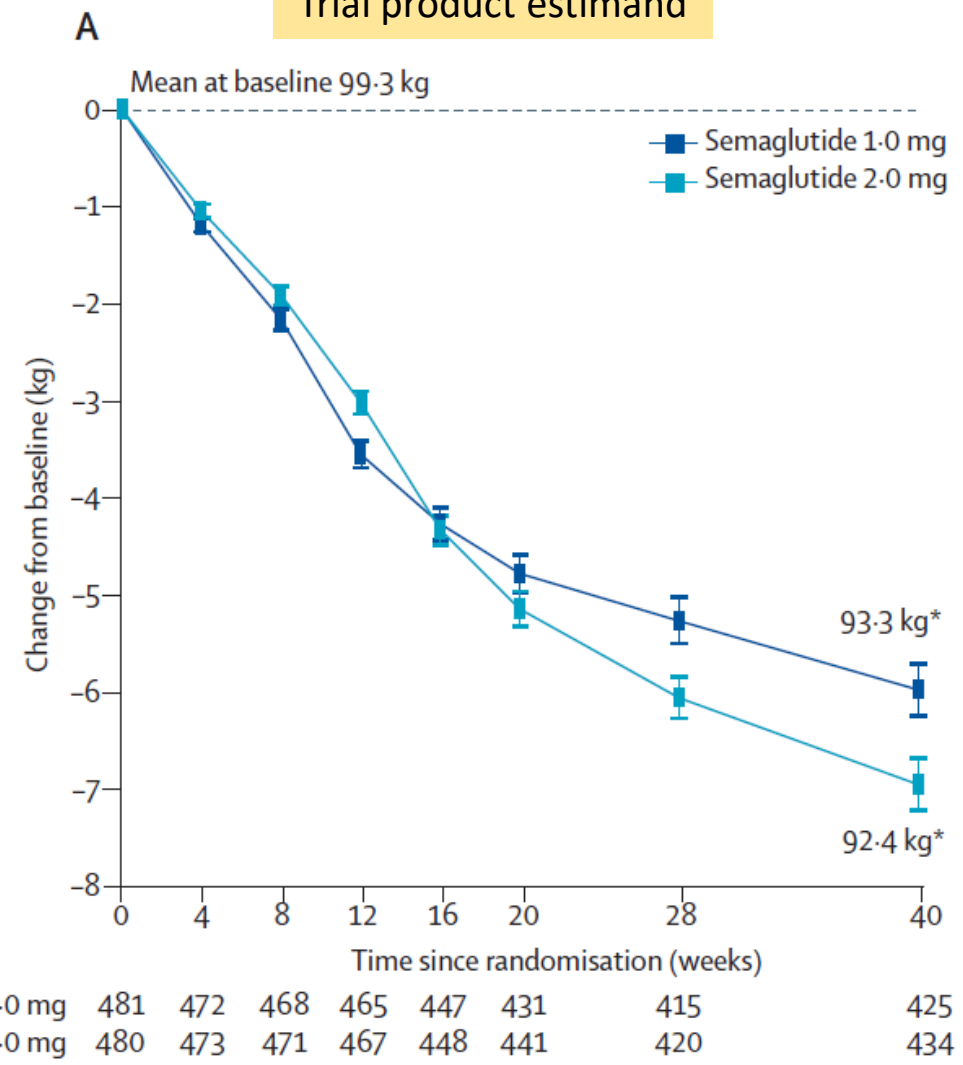


ETD –0·18 (95% CI –0·31 to –0·04); p=0·0098

ETD: estimated treatment difference

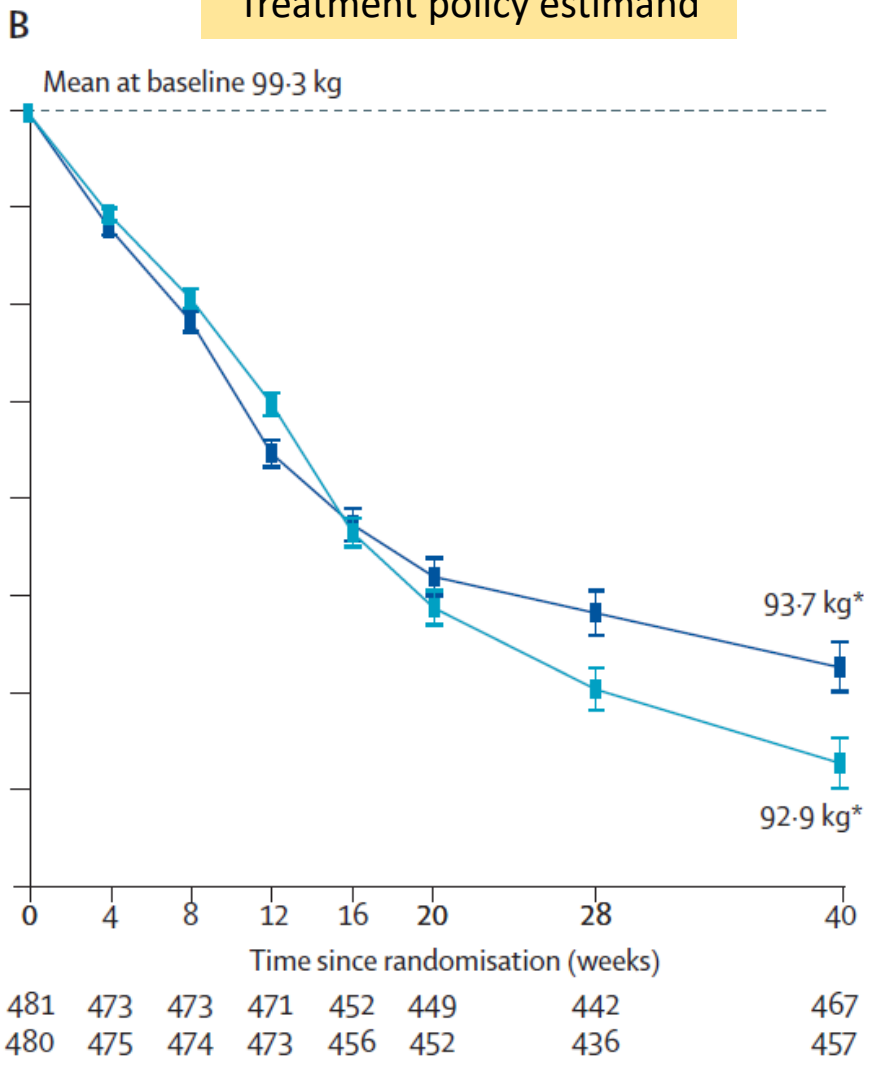
Outcomes---Bodyweight

Trial product estimand



ETD –0·93 (95% CI –1·68 to –0·18); p=0·015

Treatment policy estimand



ETD –0·77 (95% CI –1·55 to 0·01); p=0·054

ETD: estimated treatment difference

Outcomes

	Semaglutide 1·0 mg (n=481)	Semaglutide 2·0 mg (n=480)	Estimated treatment difference or OR (95% CI)	p value
Estimated mean change from baseline at week 40				
Fasting plasma glucose, mmol/L	−3·1	−3·4	−0·33 (−0·61 to −0·04)*	p=0·026
BMI, kg/m²	−2·1	−2·4	−0·30 (−0·57 to −0·04)*	p=0·026
Waist circumference, cm	−5·2	−5·8	−0·54 (−1·34 to 0·26)*	p=0·18
Participants reaching outcome at week 40				
HbA_{1c} <7·0%†	57·5	67·6	OR 1·60 (1·21 to 2·13)‡	p=0·0010
HbA_{1c} ≤6·5%§	38·5	51·7	OR 1·80 (1·36 to 2·36)‡	p<0·0001
Weight loss ≥5%	51·3	59·2	OR 1·41 (1·08 to 1·84)‡	p=0·012
Weight loss ≥10%	22·6	28·4	OR 1·40 (1·03 to 1·90)‡	p=0·031

Analyses include both observed and imputed data. ETD=estimated treatment difference. OR=odds ratio. *Once-weekly semaglutide 2·0 mg minus once-weekly semaglutide 1·0 mg. †American Diabetes Association target. ‡Estimated odds ratio of reaching outcome at week 40 with semaglutide 2·0 mg compared with semaglutide 1·0 mg. §American Association of Clinical Endocrinologists target.

Table 2: **Supportive secondary outcomes, trial product estimand**

Adverse effects

	Semaglutide 1·0 mg (n=480)			Semaglutide 2·0 mg (n=479)		
	n (%)	Events	Events per 100 patient-years of exposure	n (%)	Events	Events per 100 patient-years of exposure
Treatment-emergent adverse events	251 (52%)	828	201·4	272 (57%)	775	189·1
Severity						
Mild	199 (41%)	575	139·8	215 (45%)	552	134·7
Moderate	111 (23%)	216	52·5	108 (23%)	194	47·3
Severe	26 (5%)	37	9·0	19 (4%)	29	7·1
Serious	25 (5%)	40	9·7	21 (4%)	29	7·1
Deaths*	1 (<1%)	1	0·2	2 (<1%)	2	0·5
Treatment-emergent adverse events leading to premature treatment discontinuation						
Overall	22 (5%)	22	5·4	21 (4%)	21	5·1
Gastrointestinal adverse events	13 (3%)	13	3·2	16 (3%)	16	3·9
Gastrointestinal adverse events						
Overall	148 (31%)	353	85·8	163 (34%)	346	84·4
Mild	121 (25%)	250	60·8	134 (28%)	247	60·3
Moderate	54 (11%)	92	22·4	47 (10%)	79	19·3
Severe	8 (2%)	11	2·7	12 (3%)	20	4·9

	Semaglutide 1·0 mg (n=480)			Semaglutide 2·0 mg (n=479)		
	n (%)	Events	Events per 100 patient-years of exposure	n (%)	Events	Events per 100 patient-years of exposure
Treatment-emergent adverse events in >5% in any treatment group by preferred term						
Nausea	70 (15%)	99	24·1	69 (14%)	98	23·9
Diarrhoea	42 (9%)	83	20·2	45 (9%)	51	12·4
Vomiting	32 (7%)	41	10·0	37 (8%)	55	13·4
Dyspepsia	25 (5%)	26	6·3	16 (3%)	17	1·0
Decreased appetite	18 (4%)	18	4·4	29 (6%)	29	1·0
Hypoglycaemia†						
Level 1	54 (11%)	133	32·3	41 (9%)	82	20·0
Level 2	18 (4%)	24	5·8	12 (3%)	19	4·6
Level 3	1 (<1%)‡	1	0·2	2 (<1%)§	2	0·5

Occurred after premature treatment discontinuation during the 7-week safety follow-up while receiving treatment with insulin.

Adverse effects

	Semaglutide 1·0 mg (n=480)			Semaglutide 2·0 mg (n=479)		
	n (%)	Events	Events per 100 patient-years of exposure	n (%)	Events	Events per 100 patient-years of exposure
Treatment-emergent adverse events	251 (52%)	828	201·4	272 (57%)	775	189·1
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Moderate	111 (23%)	216	52·5	108 (23%)	194	47·3
Severe	26 (5%)	37	9·0	19 (4%)	29	7·1
Serious	25 (5%)	40	9·7	21 (4%)	29	7·1
Deaths*	1 (<1%)	1	0·2	2 (<1%)	2	0·5
Treatment-emergent adverse events leading to premature treatment discontinuation						
Overall	22 (5%)	22	5·4	21 (4%)	21	5·1
Gastrointestinal adverse events	13 (3%)	13	3·2	16 (3%)	16	3·9
Gastrointestinal adverse events						
Overall	148 (31%)	353	85·8	163 (34%)	346	84·4
Mild	121 (25%)	250	60·8	134 (28%)	247	60·3
Moderate	54 (11%)	92	22·4	47 (10%)	79	19·3
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	n (%)	Events	Events per 100 patient-years of exposure	n (%)	Events	Events per 100 patient-years of exposure
Treatment-emergent adverse events in >5% in any treatment group by preferred term						
Nausea	70 (15%)	99	24·1	69 (14%)	98	23·9
Diarrhoea	42 (9%)	83	20·2	45 (9%)	51	12·4
Vomiting	32 (7%)	41	10·0	37 (8%)	55	13·4
Dyspepsia	25 (5%)	26	6·3	16 (3%)	17	1·0
Decreased appetite	18 (4%)	18	4·4	29 (6%)	29	1·0
Hypoglycaemia†						
Level 1	54 (11%)	133	32·3	41 (9%)	82	20·0
Level 2	18 (4%)	24	5·8	12 (3%)	19	4·6
Level 3	1 (<1%)‡	1	0·2	2 (<1%)§	2	0·5

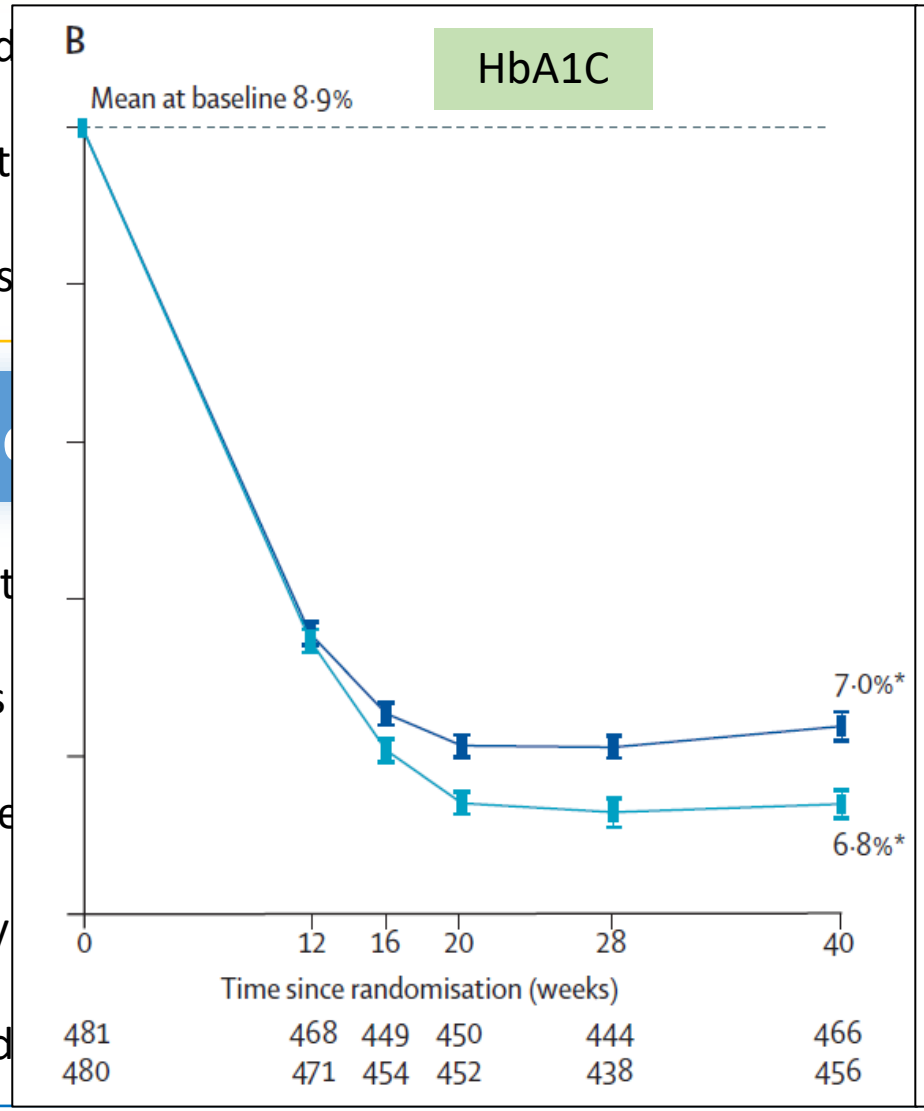
- In combination with a sulfonylurea
- Occurred during the 7-week safety follow-up while receiving treatment with a sulfonylurea.

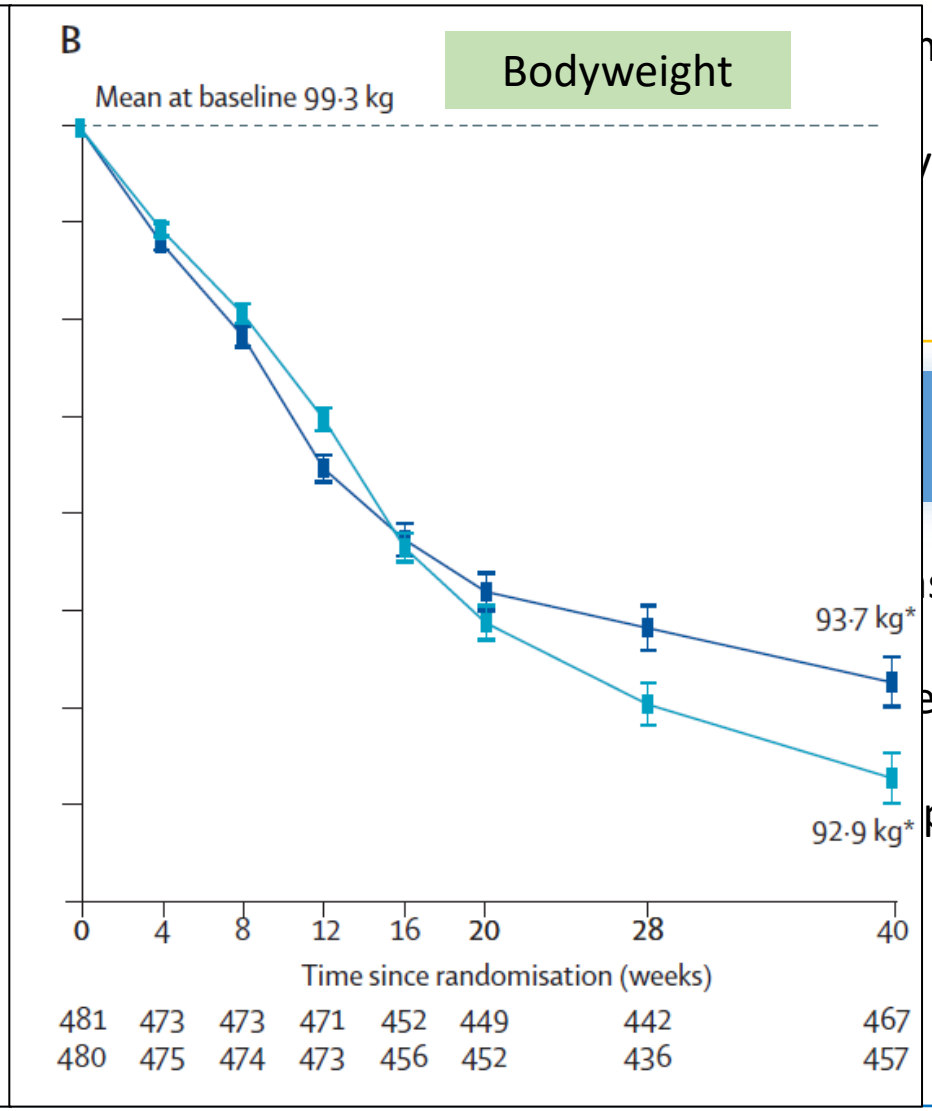
Conclusion

- Semaglutid … more participant … weight for both doses …

Limitati…

- Although it … s mean HbA1c reductions … een explored.
- The trial de … practice, in which only … of semaglutid …





THE LANCET

Lancet Diabetes Endocrinol 2021; 9: 595–605

Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial

Saxenda® (Liraglutide 18mg/3ml/pen)

適應症：

用於體重控制，做為低熱量飲食及增加體能活動外之輔助療法，適用對象為成人病人且初始身體質量指數 (BMI) 為：

- ≥30 kg/m² ，或
- ≥27 kg/m²至<30 kg/m²，且病人至少有一項體重相關共病，例如第二型糖尿病、高血壓或血脂異常。

以每天3.0 mg治療12週後，若病人初始體重並未減輕至少5%，應停止善纖達治療。

Lancet Diabetes Endocrinol 2021; 9: 595–605

Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial

2017.7.20-2020.2.21 in the USA

N=185

- 500 kcal deficient diet
- 150 min/week physical activity (x 2 weeks)

Liraglutide 3 mg SC QD (N=92)

(x 40 weeks)

Placebo (N=93)

Inclusion criteria

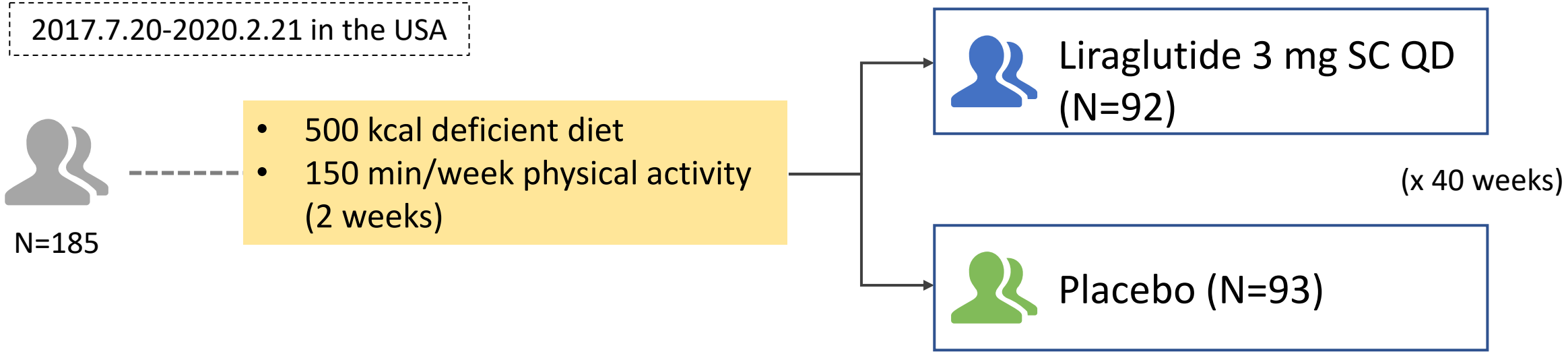
- ✓ Age ≥35 y/o with BMI ≥27 kg/m2 with metabolic syndrome
- ✓ Free from type 1 or type 2 diabetes
- ✓ Be able to undergo a neck-to-knee MRI scan for body fat assessment

- The dose was titrated up on a weekly basis by 0·6 mg increments to a target dose of 3·0 mg.
- Participants unable to tolerate an initial dose increase were allowed to wait an additional week before re-attempting dose titration.

Lancet Diabetes Endocrinol 2021; 9: 595–605

Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial

2017.7.20-2020.2.21 in the USA



- Primary outcome: Investigating the efficacy of liraglutide compared to placebo in reducing VAT.
- Secondary outcome: Changes in abdominal subcutaneous adipose tissue volume, total fat tissue volume, fat-free tissue volume, lower body adipose tissue volume, and hepatic fat content were all measured by MRI.

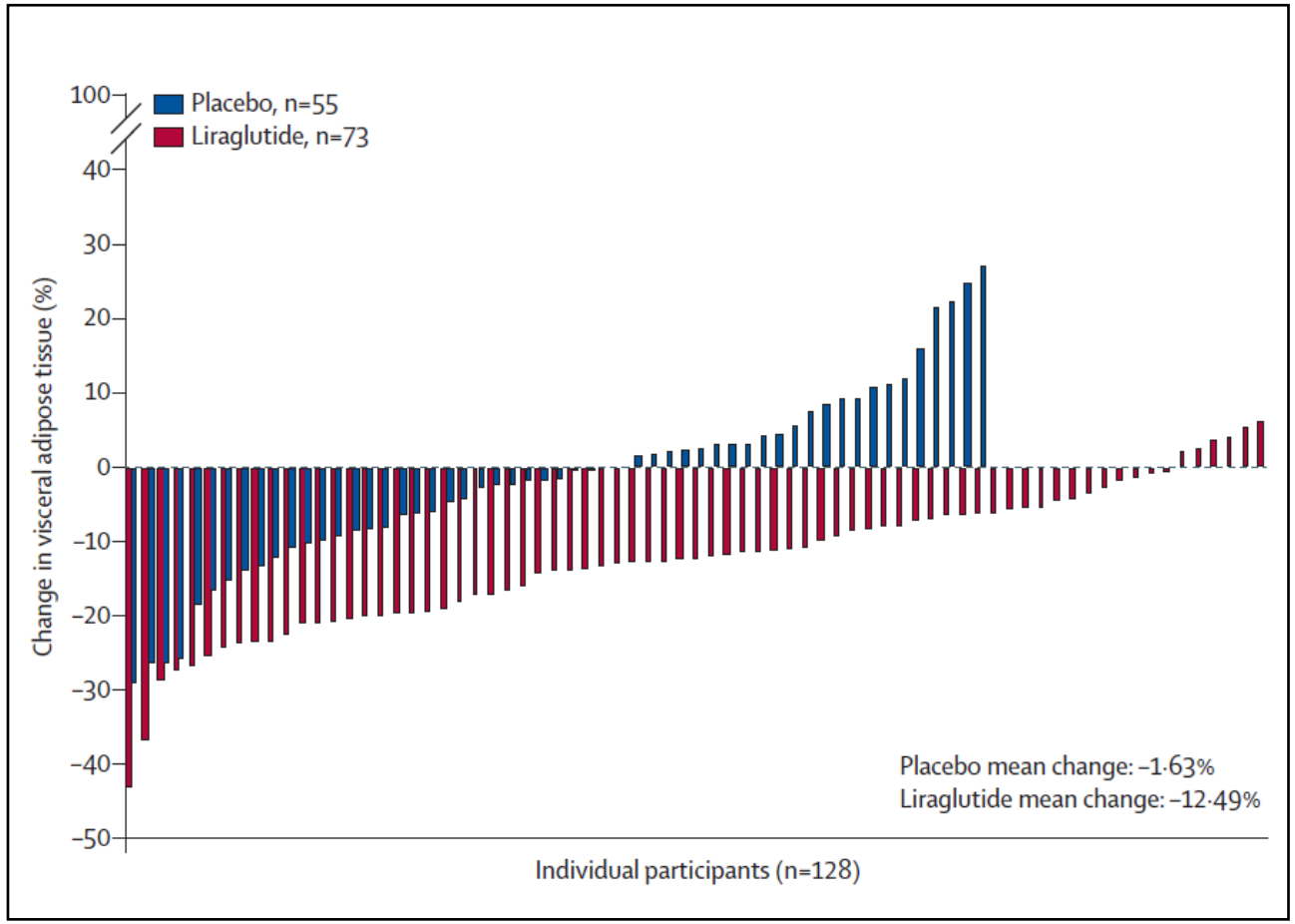
Baseline characteristics

	Placebo (n=55)	Liraglutide (n=73)
Age, years	50·9 (8·8)	49·6 (9·8)
Female	51 (93%)	67 (92%)
Male	4 (7%)	7 (8%)
Race		
White	35 (64%)	43 (59%)
Black	19 (35%)	28 (38%)
Other	1 (2%)	2 (3%)
Ethnicity		
Hispanic	12 (22%)	18 (25%)
On-treatment time, weeks	36·1 (8·2)	36·2 (8·6)
Systolic blood pressure, mm Hg	125·8 (13·9)	130·3 (14·9)
Diastolic blood pressure, mm Hg	78·5 (8·3)	80·9 (7·8)
Weight, kg	102·3 (17·9)	101·0 (17·9)
Height, m	1·6 (0·1)	1·6 (0·1)
BMI, kg/m²	38·1 (6·1)	37·2 (6·0)
Waist circumference, cm	104·8 (10·6)	105·5 (12·2)
Hip circumference, cm	122·1 (13·0)	119·8 (11·6)
Baseline, kcal/day	2196 (189)	2177 (195)

	Placebo (n=55)	Liraglutide (n=73)
Medical history		
Hypertension,	20 (36%)	30 (41%)
Hyperlipidaemia	16 (29%)	15 (20%)
Prediabetes	3 (5%)	2 (3%)
Lab Values		
Fasting blood glucose, mg/dL	99·1 (14·4)	100·6 (12·9)
Fasting insulin, mIU/L	18·0 (17)	16·3 (10·8)
HOMA-IR	4·85 (7·01)	4·22 (3·56)
Triglycerides, mg/dL	118·3 (50·6)	109·4 (49·7)
HDL-C, mg/dL	54·6 (11·8)	58·6 (11·9)
C-reactive protein, mg/L	7·8 (6·8)	8·0 (4·3)
NT-proBNP, pg/mL	63·2 (44·7)	59·6 (44·1)
Body fat–composition		
Total body adipose tissue, L	40·9 (9·8)	39·6 (8·9)
Visceral adipose tissue, L	4·5 (1·7)	4·5 (2·1)
Abdominal subcutaneous adipose tissue, L	16·2 (4·2)	15·6 (4·3)
Lower body adipose tissue, L	15·6 (5·0)	14·7 (4·3)
Liver fat	6·1% (6·1)	7·6% (7·9)
Total body lean tissue, L	21·5 (3·5)	21·6 (3·8)

Outcomes

	Placebo (n=55)	Liraglutide (n=73)	Estimated treatment difference for liraglutide *vs* placebo (95% CI)	p value
Primary outcome				
Visceral adipose tissue change	−1·63% (12·3%)	−12·49% (9·3%)	−10·86% (−6·97 to −14·75)	<0·0001
Secondary outcomes				
Percentage changes				
Weight	−1·19% (4·68)	−6·59% (4·80)	−5·40% (−3·74 to −7·01)	<0·0001
BMI	−1·08% (4·88)	−6·53% (4·84)	−5·45% (−3·75 to −7·15)	<0·0001
Waist circumference	−4·16% (6·06)	−6·90% (6·43)	−2·74% (−0·56 to −4·92)	0·021
Total body adipose tissue	−0·95% (7·80)	−9·59% (7·15)	−8·64% (−6·00 to −11·27)	<0·0001
Abdominal subcutaneous adipose tissue	−0·77% (8·40)	−9·87% (8·23)	−9·10% (−6·18 to −12·01)	<0·0001
Lower body adipose tissue	−1·29% (8·57)	−9·95% (7·61)	−8·66% (−5·80 to −11·52)	<0·0001
Liver fat	20·63% (104·92)	−12·37% (61·43)	−33·00% (−1·90 to −64·10)	0·025
Total body lean tissue	−0·90% (3·66)	−2·47% (4·04)	−1·57% (−0·23 to −2·91)	0·029
Total body fat/total body lean tissue	0·01% (7·83)	−7·23% (7·25)	−7·24% (−4·58 to −9·89)	<0·0001



Outcomes

	Placebo (n=55)	Liraglutide (n=73)	Estimated treatment difference for liraglutide *vs* placebo (95% CI)	p value
Percentage changes				
Fasting blood glucose	0·83%	−5·62%	−6·45% (−2·15 to −10·75)	0·0048
Fasting insulin	7·73%	20·58%	12·85% (−9·48 to 35·18)	0·41
HOMA-IR	11·85%	15·35%	3·5% (−21·02 to 28·02)	0·88
Triglyceride: HDL-C ratio	−2·18%	−2·1%	0·08% (-10·25 to −10·41)	0·99
C-reactive protein	19·02%	−19·91%	−38·93% (−17·45 to −60·41)	0·038
NT-proBNP	20·47%	12·1%	−8·37% (−36·02 to 19·28)	0·38

	Placebo (n=55)	Liraglutide (n=73)	Estimated treatment difference for liraglutide *vs* placebo (95% CI)	p value
Absolute changes				
Fasting blood glucose, mg/dL	−0·22	−6·49	−6·27 (−1·82 to −10·72)	0·0061
Fasting insulin mIU/L	−1·48	0·75	2·23 (−1·74 to 6·20)	0·47
HOMA-IR	−0·69	−0·15	0·54 (−1·02 to 2·10)	0·98
Triglyceride: HDL-C ratio	−0·16	−0·02	0·14 (−0·12 to 0·40)	0·58
C-reactive protein, mg/L	−0·64	−2·18	−1·54 (−3·35 to 0·28)	0·031
NT-proBNP, pg/mL	1·44	−8·10	9·54 (−25·13 to 6·05)	0·32

Adverse effects

	Liraglutide (n=92)	Placebo (n=93)
Gastrointestinal related	43 (47%)	12 (13%)
Constipation	13 (14%)	5 (5%)
Nausea–vomiting	13 (14%)	3 (3%)
Gastrointestinal upset–dyspepsia	11 (12%)	3 (3%)
Diarrhoea–flatulence	6 (7%)	1 (1%)
Upper respiratory tract infection–pharyngitis	10 (11%)	14 (15%)
Injection site reaction	7 (8%)	8 (9%)
Headache	5 (5%)	5 (5%)
Joint pain	5 (5%)	3 (3%)
Insomnia	2 (2%)	0
Dizziness	3 (3%)	0
Fever	0	2 (2%)
Other	9 (10%)	12 (13%)
Hepatic cyst	3 (3%)	2 (2%)

Conclusion

- Liraglutide at a once-daily dose of 3·0 mg, when used as an adjunct to a reduced-calorie diet and increased physical activity, significantly lowered visceral fat and ectopic fat over a median 36 weeks on treatment compared with a placebo in a population of adults with overweight and obesity at high cardiovascular disease risk.

Limitation

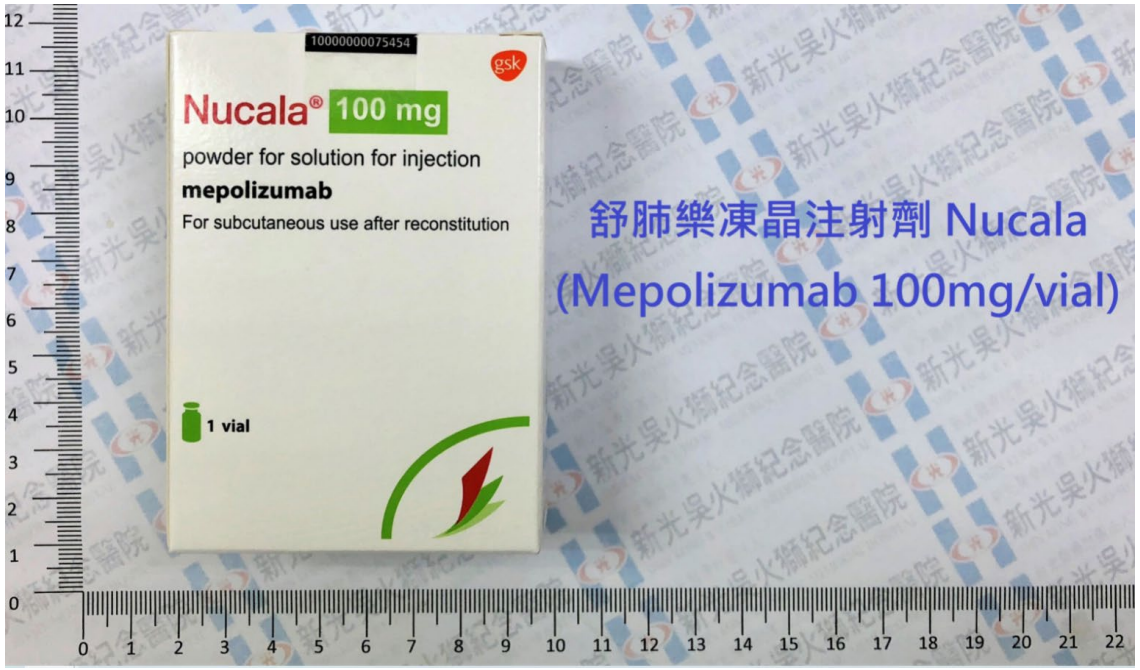
- Among randomly assigned participants, there was a 31% rate of attrition (ie, participants who left the trial early and did not obtain follow-up imaging assessment).
- Our study was not designed to ascertain prospective cardiovascular events and, thus, cannot quantify exact cardiovascular risk, nor are we able to evaluate the effects of liraglutide on cardiovascular risk through its effects on visceral adipose tissue.

THE LANCET

Lancet Respir Med 2021;9: 1141–53

Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial

Nucala (Mepolizumab 100 mg/vial)



適應症：

1. 嚴重氣喘之維持治療：表現型為嗜伊紅性白血球的嚴重氣喘且控制不良(severe refractory eosinophilic asthma)之6歲以上病人之附加維持治療。
   - ✓ ≥12 y/o: 100 mg SC Q4W
   - ✓ 6-11 y/o: 40 mg SC Q4W
2. 嗜伊紅性肉芽腫併多發性血管炎：治療嗜伊紅性肉芽腫併多發性血管炎[eosinophilic granulomatosis with polyangiitis (EGPA)]之成人病人。
   - ✓ Adult: 300 mg SC Q4W

Lancet Respir Med 2021;9: 1141–53

Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial

2017.5.25-2018.12.12 in 11 countries

N=407

- ≥35 y/o, having at least one nasal surgery in the past 10 years.
- Maintenance therapy with intranasal spray.
- Displayed ≥2 different symptoms for at least 12 weeks.

Mepolizumab 100 mg SC Q4W (N=206)

Placebo (N=201)

(x 52 weeks)

Primary endpoints:

- Change from baseline in total endoscopic nasal polyp score at week 52.
- Change from baseline in mean nasal obstruction VAS score during weeks 49-52.

Standard of care

- Daily mometasone furoate intranasal spray
- Saline nasal irrigation
- Courses of systemic corticosteroid or antibiotics

Baseline characteristics

	Placebo (n=201)	Mepolizumab (n=206)
Age, years	48·9 (12·5)	48·6 (13·6)
Female	76 (38%)	67 (33%)
Male	125 (62%)	139 (67%)
Race		
White and European	183 (91%)	190 (92%)
East Asian	7 (3%)	6 (3%)
Black and African American	4 (2%)	5 (2%)
Arabic and North African	4 (2%)	2 (1%)
Central and South Asian	1 (1%)	2 (1%)
South East Asian	1 (1%)	1 (1%)
Multiple	1 (1%)	0
Ethnicity		
Hispanic or Latino	29 (14%)	24 (12%)
Not Hispanic and not Latino	172 (86%)	182 (88%)
Body-mass index, kg/m²		
Median	27·2 (24·6–30·5)	27·4 (24·4–30·3)
Mean	28·2 (5·5)	28·2 (5·3)
Duration of nasal polyps, years		
Median	10·0 (5·3–16·0)	9·0 (5·0–15·3)
Mean	11·5 (8·3)	11·4 (8·5)
Previous nasal surgery		
0	0	0
≥1	201 (100%)	206 (100%)
≥2	120 (60%)	98 (48%)
≥3	73 (36%)	51 (25%)
≥4	38 (19%)	24 (12%)
≥5	26 (13%)	11 (5%)

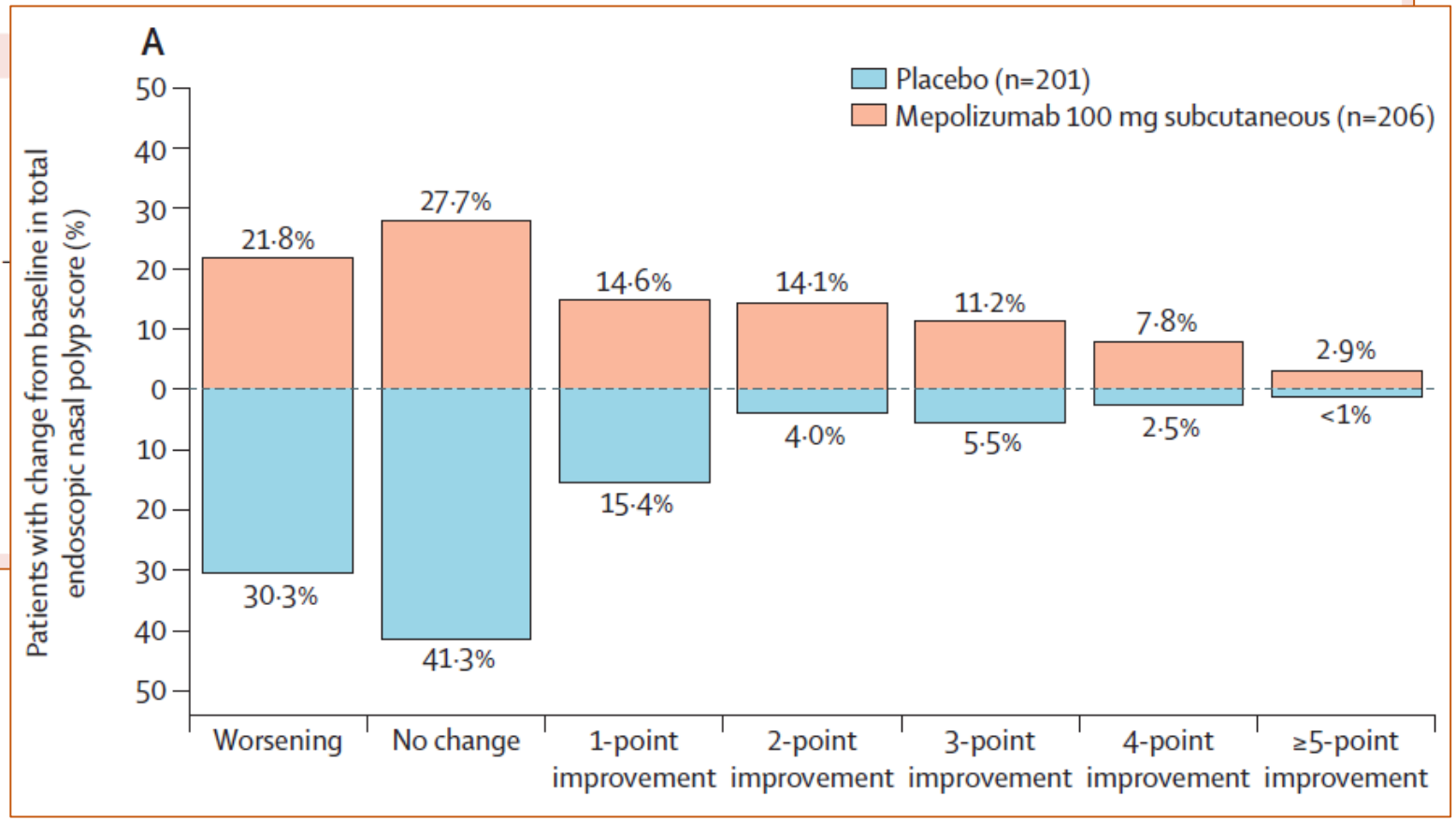
	Placebo (n=201)	Mepolizumab (n=206)
(Continued from previous column)		
Total endoscopic score (scale 0–8)		
Median	6·0 (5·0–6·0)	5·0 (5·0–6·0)
Mean	5·6 (1·4)	5·4 (1·2)
Nasal obstruction VAS score (scale 0–10)†		
Median	9·1 (8·5–9·7)	9·0 (8·3–9·6)
Mean	9·0 (0·8)	8·9 (0·8)
Overall symptom VAS score (scale 0–10)†		
Median	9·2 (8·7–9·8)	9·1 (8·4–9·7)
Mean	9·1 (0·7)	9·0 (0·8)
Nasal symptom composite‡ score (scale 0–10)†		
Median	9·2 (8·6–9·6)	9·1 (8·5–9·6)
Mean	9·0 (0·8)	9·0 (0·8)
Loss of smell VAS score (scale 0–10)†		
Median	10·0 (9·6–10·0)	10·0 (9·6–10·0)
Mean	9·7 (0·6)	9·6 (0·8)
SNOT-22 total score†		
Median	64·0 (51·0–77·0)	64·0 (50·0–77·0)
Mean	64·4 (19·0)	63·7 (17·6)
Patients with asthma	149 (74%)	140 (68%)
Patients with aspirin-exacerbated respiratory disease	63 (31%)	45 (22%)
Blood eosinophil count, cells per µL§	400 (0·91)	390 (0·88)

Total nasal endoscopic polyp score	
0	No polyps
1	Polyps confined to the middle meatus
2	Multiple polyps occupying the middle meatus
3	Polyps extending beyond middle meatus
4	Polyps completely obstructing the nasal cavity

How troublesome are your symptoms of rhinosinusitis?

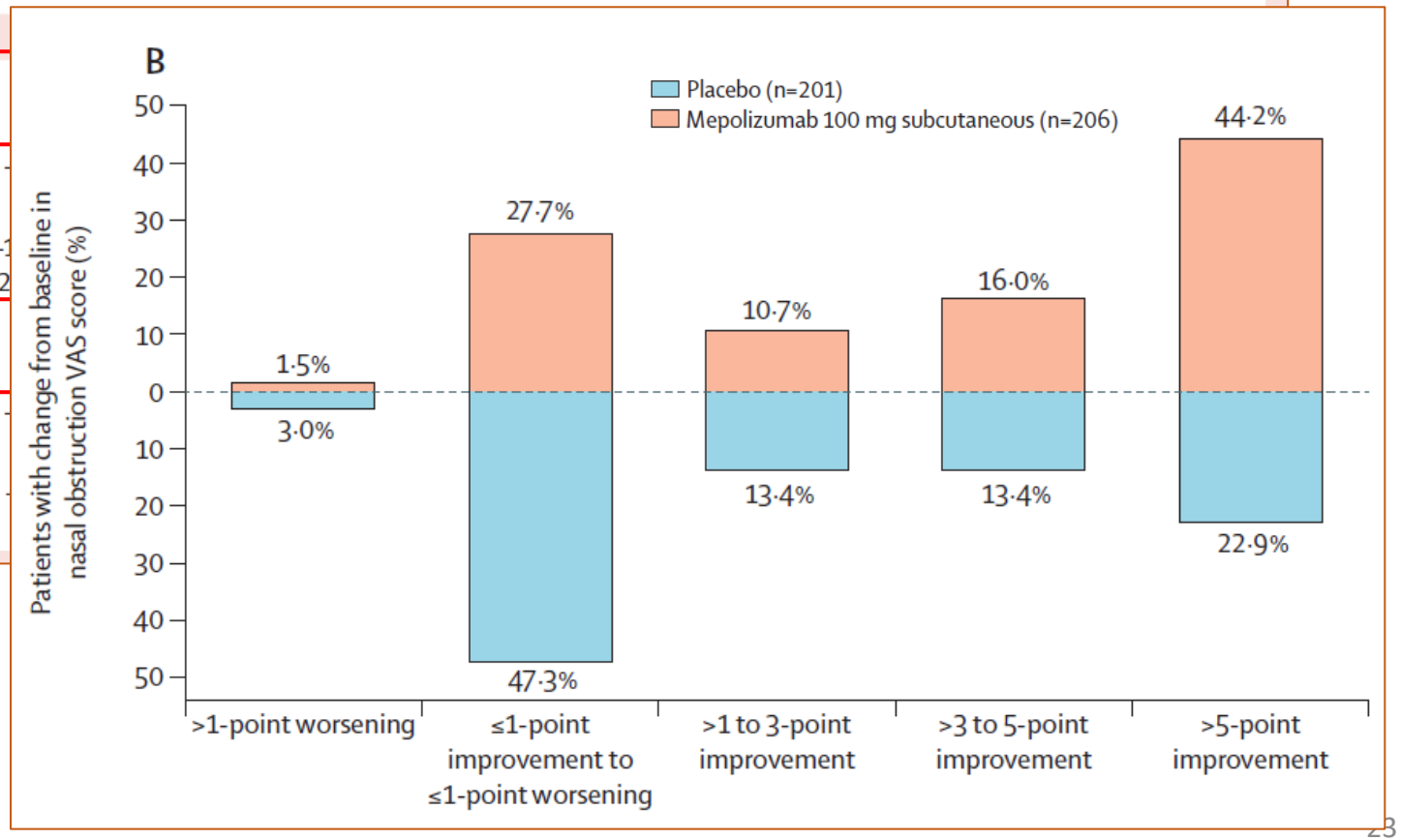
Outcomes

	Placebo (n=201)			Mepolizumab (n=206)			Treatment effect (95% CI); p value
	Median change from baseline	Mean (SD) change from baseline	Proportion of patients, n (%)	Median change from baseline	Mean (SD) change from baseline	Proportion of patients, n (%)	
Coprimary endpoints							
Change from baseline in total endoscopic nasal polyp score at week 52*	0·00	−0·1 (1·46)	..	−1·00	−0·9 (1·90)	..	−0·73 (−1·11 to −0·34)†; p<0·0001‡
Change from baseline in nasal obstruction VAS score during weeks 49–52*	−0·82	−2·5 (3·15)	..	−4·41	−4·2 (3·42)	..	−3·14 (−4·09 to −2·18)†; p<0·0001‡
Secondary endpoints							
Proportion of patients having nasal surgery up to week 52 (time-to-first nasal surgery)							
Change from baseline in overall symptom VAS score during weeks 49–52*							
Change from baseline in SNOT-22 total score at week 52*							
Proportion of patients requiring systemic corticosteroids (≥1 course) for nasal polyps until week 52							
Change from baseline in composite** VAS score during weeks 49–52*							
Change from baseline in loss of smell VAS symptom score during weeks 49–52*							



Outcomes

	Placebo (n=201)			Mepolizumab (n=206)			Treatment effect (95% CI); p value
	Median change from baseline	Mean (SD) change from baseline	Proportion of patients, n (%)	Median change from baseline	Mean (SD) change from baseline	Proportion of patients, n (%)	
Coprimary endpoints							
Change from baseline in total endoscopic nasal polyp score at week 52*	0·00	−0·1 (1·46)	..	−1·00	−0·9 (1·90)	..	−0·73 (−1·11 to −0·34)†; p<0·0001‡
Change from baseline in nasal obstruction VAS score during weeks 49–52*	−0·82	−2·5 (3·15)	..	−4·41	−4·2 (3·42)	..	−3·14 (−4·09 to −2·18)†; p<0·0001‡
Secondary endpoints							
Proportion of patients having nasal surgery up to week 52 (time-to-first nasal surgery)	..						
Change from baseline in overall symptom VAS score during weeks 49–52*	−0·90						
Change from baseline in SNOT-22 total score at week 52*	−14·00						
Proportion of patients requiring systemic corticosteroids (≥1 course) for nasal polyps until week 52	..						
Change from baseline in composite** VAS score during weeks 49–52*	−0·89						
Change from baseline in loss of smell VAS symptom score during weeks 49–52*	0·00						



Adverse effects

	Placebo (n=201)	Mepolizumab (n=206)
All adverse events		
Any on-treatment event	168 (84%)	169 (82%)
Treatment-related event	19 (9%)	30 (15%)
Leading to treatment discontinuation	4 (2%)	4 (2%)
Leading to study withdrawal	1 (1%)	0
Serious adverse events		
Any on-treatment event	13 (6%)	12 (6%)
Treatment-related event*	1 (1%)	0
Resulting in death†	1 (1%)	0
Systemic or local injection-site reactions		
Systemic reaction	1 (1%)	2 (1%)
Local injection-site reaction	2 (1%)	5 (2%)
Anaphylaxis	0	0

	Placebo (n=201)	Mepolizumab (n=206)
Most common adverse events‡		
Nasopharyngitis	46 (23%)	52 (25%)
Headache	44 (22%)	37 (18%)
Epistaxis	18 (9%)	17 (8%)
Sinusitis	22 (11%)	10 (5%)
Back pain	14 (7%)	15 (7%)
Acute sinusitis	13 (6%)	13 (6%)
Oropharyngeal pain	10 (5%)	16 (8%)
Upper respiratory tract infection	14 (7%)	12 (6%)
Nasal polyps	16 (8%)	8 (4%)
Bronchitis	13 (6%)	10 (5%)
Asthma	18 (9%)	4 (2%)
Cough	13 (6%)	7 (3%)
Arthralgia	5 (2%)	13 (6%)
Otitis media	10 (5%)	5 (2%)

Conclusion

- This phase 3 study showed the efficacy of mepolizumab with an acceptable safety profile in adults with severe chronic rhinosinusitis with nasal polyps.

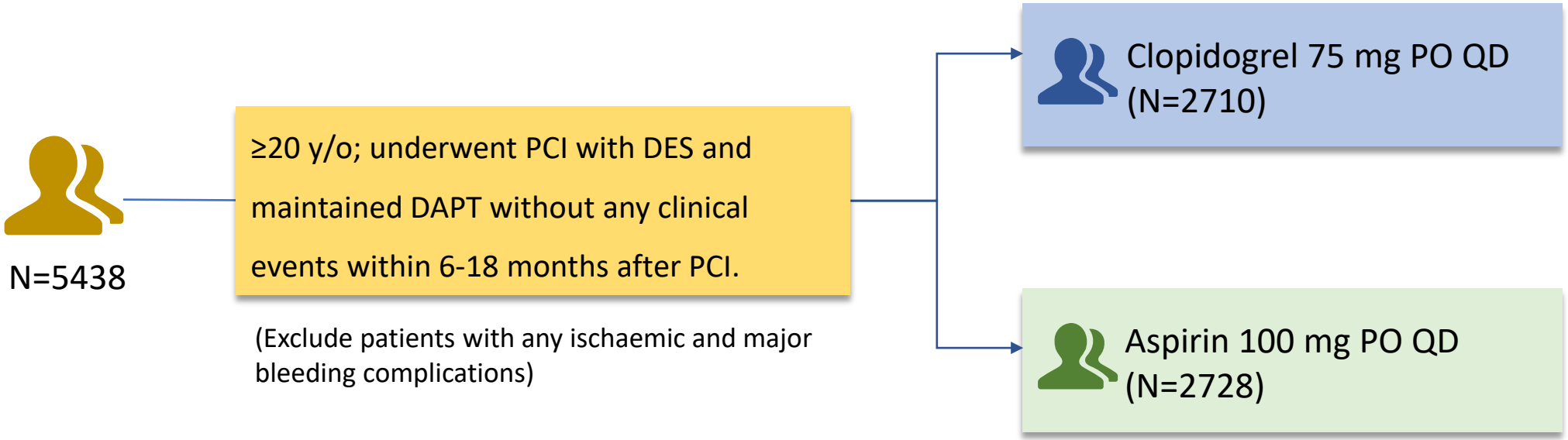
Limitation

- Nasal polyp size determination can be subjective in routine clinical practice. Therefore, to counteract this potential bias, SYNAPSE used independent centrally masked reviewers to score the nasal polyp size and minimise any subjectivity and variability of this assessment.
- If a patient met the criteria for surgery during the study, the decision to prescribe another course of systemic corticosteroids or proceed to surgery was decided by the physician, who would have been influenced by many subjective factors beyond treatment failure, including surgeon preference, patient desire, and comorbidities.

Lancet 2021; 397: 2487–96

Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial

2014.03.26-2018.05.29 in South Korea



Primary endpoint:

All-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding complications during the 24-months follow-up period.

Baseline characteristics

	Clopidogrel (n=2710)	Aspirin (n=2728)
Age, years	63·5 (10·7)	63·4 (10·7)
Sex		
Female	695 (25·6%)	689 (25·3%)
Male	2015 (74·4%)	2039 (74·7%)
Diabetes*	925 (34·1%)	935 (34·3%)
Insulin-dependent diabetes	55 (2·0%)	62 (2·3%)
Hypertension	1664 (61·4%)	1674 (61·4%)
Dyslipidaemia	1884 (69·5%)	1883 (69·0%)
Current smoker	545 (20·1%)	581 (21·3%)
Chronic kidney disease	356 (13·1%)	337 (12·4%)
Previous myocardial infarction	437 (16·1%)	435 (15·9%)
Previous cerebrovascular accident	120 (4·4%)	133 (4·9%)
Clinical indication of PCI		
Silent ischaemia	58 (2·1%)	70 (2·6%)
Stable angina	688 (25·4%)	701 (25·7%)
Unstable angina	975 (36·0%)	959 (35·2%)
NSTEMI	526 (19·4%)	528 (19·4%)
STEMI	463 (17·1%)	470 (17·2%)

	Clopidogrel (n=2710)	Aspirin (n=2728)
(Continued from previous column)		
DAPT at the randomisation		
Aspirin plus clopidogrel	2218 (81·8%)	2212 (81·1%)
Aspirin plus ticagrelor	266 (9·8%)	268 (9·8%)
Aspirin plus prasugrel	212 (7·8%)	235 (8·6%)
Aspirin plus clopidogrel plus cilostazol	14 (0·5%)	13 (0·5%)
Angiographic data per patient		
Extent of CAD		
One-vessel disease	1367 (50·4%)	1376 (50·4%)
Two-vessel disease	855 (31·5%)	844 (30·9%)
Three-vessel disease	488 (18·0%)	507 (18·6%)
Left main disease	142 (5·2%)	130 (4·8%)
PCI for bifurcation lesion	285 (10·5%)	295 (10·8%)
Two-stenting for bifurcation PCI	46 (1·7%)	42 (1·5%)
PCI for CTO lesion	257 (9·5%)	254 (9·3%)
Number of treated lesions†	1·3 (0·6)	1·3 (0·6)
Mean diameter of implanted stents, mm	3·1 (0·4)	3·1 (0·4)
Minimum diameter of implanted stents, mm	3·0 (0·5)	3·0 (0·5)

Outcomes

	Clopidogrel (n=2710)	Aspirin (n=2728)	Hazard ratio (95% CI)*	p value
Primary composite endpoint†	152 (5·7%)	207 (7·7%)	0·73 (0·59–0·90)	0·003
Thrombotic composite endpoint‡	99 (3·7%)	146 (5·5%)	0·68 (0·52–0·87)	0·003
Any bleeding (BARC type ≥2)§	61 (2·3%)	87 (3·3%)	0·70 (0·51–0·98)	0·036
All-cause death¶	51 (1·9%)	36 (1·3%)	1·43 (0·93–2·19)	0·101
Cardiac death	19 (0·7%)	14 (0·5%)	1·37 (0·69–2·73)	0·374
Non-cardiac death	32 (1·2%)	22 (0·8%)	1·47 (0·85–2·52)	0·167
Non-fatal myocardial infarction	18 (0·7%)	28 (1·0%)	0·65 (0·36–1·17)	0·150
Stroke	18 (0·7%)	43 (1·6%)	0·42 (0·24–0·73)	0·002
Ischaemic stroke	14 (0·5%)	26 (1·0%)	0·54 (0·28–1·04)	0·064
Haemorrhagic stroke	4 (0·2%)	17 (0·6%)	0·24 (0·08–0·70)	0·010
Readmission due to ACS	66 (2·5%)	109 (4·1%)	0·61 (0·45–0·82)	0·001
Major bleeding (BARC type ≥3)	33 (1·2%)	53 (2·0%)	0·63 (0·41–0·97)	0·035
Any revascularisation	56 (2·1%)	69 (2·6%)	0·82 (0·57–1·16)	0·261
Target lesion revascularisation	24 (0·9%)	36 (1·4%)	0·67 (0·40–1·12)	0·130
Target vessel revascularisation	37 (1·4%)	48 (1·8%)	0·78 (0·50–1·19)	0·245
Definite or probable stent thrombosis	10 (0·4%)	16 (0·6%)	0·63 (0·29–1·39)	0·251
Any minor gastrointestinal complications	272 (10·2%)	320 (11·9%)	0·85 (0·72–1·00)	0·048

24-months follow-up period:

- All-cause death
- Non-fatal myocardial infarction
- Stroke
- Readmission due to acute coronary syndrome
- Major bleeding

Conclusion

- Compared with aspirin, clopidogrel monotherapy was associated with a lower risk of the composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding during the 24-month follow-up period.

Limitation

- The comparison between clopidogrel and aspirin for the secondary endpoints was not adjusted for multiple testing and, therefore, we cannot make any definitive conclusions regarding the secondary endpoints.
- Phenotypic and genetic testing for clopidogrel was not done and the study population was east Asian patients, which might limit the generalisability of the study.
- Follow-up duration of 24 months might be too short to give a concrete conclusion.

Lancet Diabetes Endocrinol 2021; 9: 586–94

Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial

2020.04.22-2021.01.01 in the USA, the UK, Canada, Mexico, Brazil, India, Argentina

N=1250

- ≥18 y/o; hospitalized with laboratory confirmed of suspected SARS-CoV-2 infection no more than 4 days.
- At least one cardiometabolic risk factor: hypertension, T2DM, CAD, HF, eGFR 25-60 ml/min per 1.73 m2

Dapagliflozin 10 mg PO QD (N=625)

Placebo (N=625)

(x 30 days)

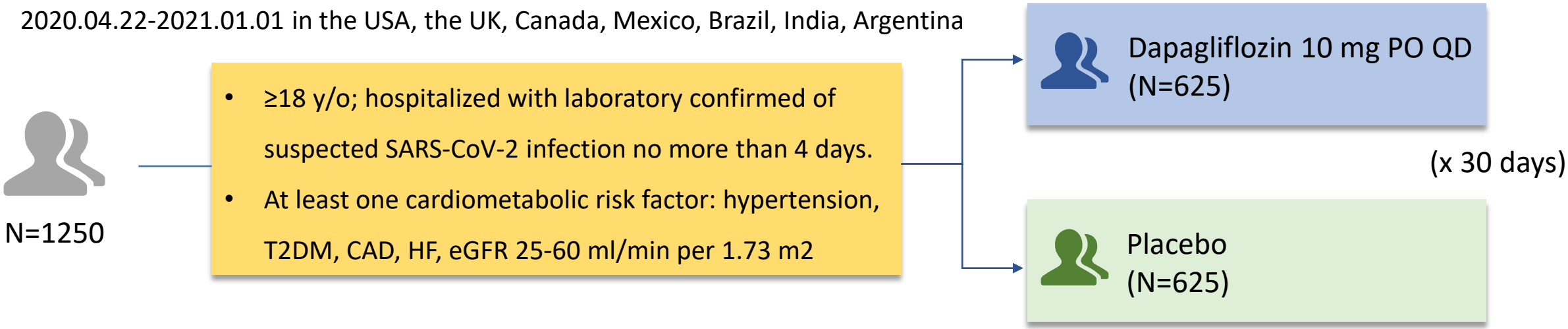
Exclusion criteria

- ✓ Critical illness (need for mechanical ventilation, acute kidney failure, need for vasopressor support)
- ✓ eGFR <25 ml/min per 1.73 m2
- ✓ T1DM and history of diabetic ketoacidosis
- ✓ Current treatment with any SGLT2i

Lancet Diabetes Endocrinol 2021; 9: 586–94

Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial

2020.04.22-2021.01.01 in the USA, the UK, Canada, Mexico, Brazil, India, Argentina



- Primary outcome of prevention: Composite of time to new or worsened respiratory, cardiovascular, or kidney organ dysfunction during the index hospitalization, or death from any cause at any time during the 30 day treatment period.
- Primary outcome of recovery: A hierarchical composite that ranked patients into categories using the severity and timing of events experienced during the 30 day treatment period.

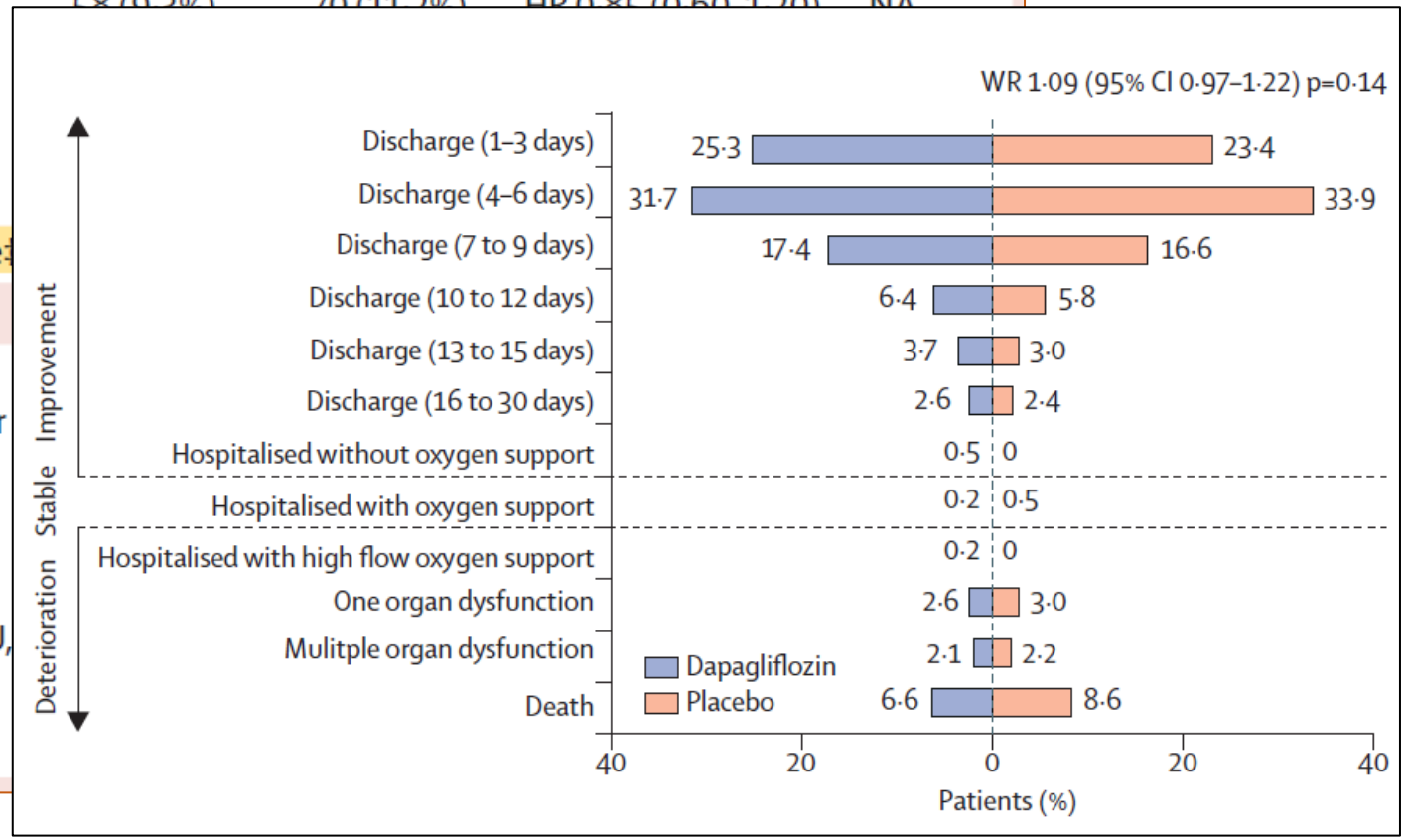
Baseline characteristics

	Dapagliflozin (n=625)	Placebo (n=625)	Total (N=1250)
Mean age, years	61·0 (13·4)	61·8 (13·5)	61·4 (13·5)
Sex, female	260 (41·6%)	273 (43·7%)	533 (42·6%)
Mean BMI, kg/m²	30·6 (6·2)	30·9 (6·4)	30·7 (6·3)
Race*			
White	452 (72·6%)	459 (74·3%)	911 (73·4%)
Black	85 (13·6%)	84 (13·6%)	169 (13·6%)
Asian	35 (5·6%)	29 (4·7%)	64 (5·2%)
Native Hawaiian or other Pacific Islander	1 (0·2%)	0	1 (0·1%)
American Indian or Alaska Native	7 (1·1%)	10 (1·6%)	17 (1·4%)
Other	43 (6·9%)	36 (5·8%)	79 (6·4%)
Ethnicity*			
Hispanic or Latino	394 (63·4%)	362 (58·5%)	756 (61·0%)
Not Hispanic or Latino	166 (26·7%)	177 (28·6%)	343 (27·7%)
Not reported or unknown	61 (9·8%)	80 (12·8%)	141 (11·3%)
Inclusion risk factors			
Type 2 diabetes	312 (49·9%)	324 (51·8%)	636 (50·9%)
Heart failure	44 (7·0%)	46 (7·4%)	90 (7·2%)
Hypertension	526 (84·2%)	534 (85·4%)	1060 (84·8%)
Atherosclerotic cardiovascular disease	93 (14·9%)	106 (17·0%)	199 (15·9%)
Chronic kidney disease, eGFR 25–60 mL/min per 1·73 m²	38 (6·1%)	44 (7·0%)	82 (6·6%)
Patients with two or more inclusion risk factors	292 (46·7%)	319 (51·0%)	611 (48·9%)

	Dapagliflozin (n=625)	Placebo (n=625)	Total (N=1250)
(Continued from previous column)			
Laboratory values at baseline			
eGFR, mL/min per 1·73 m²	84·1 (25.0)	83·4 (24·6)	83·8 (24·8)
SARS-CoV-2-test result at baseline			
Positive	584 (93·4%)	575 (92·0%)	1159 (92·7%)
Negative	30 (4·8%)	35 (5·6%)	65 (5·2%)
Test results not known	11 (1·8%)	15 (2·4%)	26 (2·1%)
Medication at baseline			
ACE inhibitor or ARB	225 (36·0%)	219 (35·0%)	444 (35·5%)
β-blocker	93 (14·9%)	98 (15·7%)	191 (15·3%)
Calcium blocker	84 (13·4%)	88 (14·1%)	172 (13·8%)
Loop-diuretic	49 (7·8%)	63 (10·1%)	112 (9·0%)
Statin	122 (19·5%)	144 (23·0%)	266 (21·3%)
Anti-coagulant	527 (84·3%)	527 (84·3%)	1054 (84·3%)
Glucose-lowering medication at baseline			
Biguanide	82 (13·1%)	75 (12·0%)	157 (12·6%)
Sulfonylurea	24 (3·8%)	22 (3·5%)	46 (3·7%)
DPP-4 inhibitor	17 (2·7%)	11 (1·8%)	28 (2·2%)
GLP-1 receptor agonist	6 (1·0%)	8 (1·3%)	14 (1·1%)
Insulin	223 (35·7%)	221 (35·4%)	444 (35·5%)
Concomitant COVID-19 medication at baseline			
Remdesivir	114 (18·2%)	111 (17·8%)	225 (18·0%)
Systemic corticosteroids	176 (28·2%)	179 (28·6%)	355 (28·4%)
Dexamethasone	133 (21·3%)	136 (21·8%)	269 (21·5%)
Other systemic glucocorticoid	50 (8·0%)	55 (8·8%)	105 (8·4%)

Outcomes

	Dapagliflozin (n=625)	Placebo (n=625)	HR, RR, or WR (95% CI)*	p value
Primary outcomes				
Prevention composite outcome	70 (11·2%)	86 (13·8%)	HR 0·80 (0·58–1·10)	0·17
New or worsening organ dysfunction	64 (10·2%)	80 (12·8%)	HR 0·80 (0·57–1·11)	NA
Respiratory decompensation				
Cardiovascular decompensation				
Kidney decompensation				
Death from any cause†				
Hierarchical composite recovery outcome‡				
Secondary outcomes				
Composite of acute kidney injury, initiation of renal-replacement therapy, or death from any cause				
Total number of days alive and free from mechanical ventilation§				
Total number of days alive, not in the ICU, and free from mechanical ventilation¶				
Hospital discharge				



Outcomes

	Dapagliflozin (n=625)	Placebo (n=625)	HR, RR, or WR (95% CI)*	p value
Primary outcomes				
Prevention composite outcome	70 (11·2%)	86 (13·8%)	HR 0·80 (0·58–1·10)	0·17
New or worsening organ dysfunction	64 (10·2%)	80 (12·8%)	HR 0·80 (0·57–1·11)	NA
Respiratory decompensation	58 (9·3%)	70 (11·2%)	HR 0·85 (0·60–1·20)	NA
Cardiovascular decompensation	47 (7·5%)	58 (9·3%)	HR 0·81 (0·55–1·19)	NA
Kidney decompensation	24 (3·8%)	35 (5·6%)	HR 0·65 (0·38–1·10)	NA

Table S1. Results of the sensitivity analyses for the primary outcome of prevention

	Dapagliflozin, n/N	Placebo, n/N	Hazard ratio (95% CI)	P-interaction
Overall	70/625	86/625	0·80 (0·58, 1·10)	
Only those with a positive SARS-CoV-2 test	65/590	79/584	0·81 (0·58, 1·12)	
Did receive remdesivir	5/114	12/111	0·45 (0·16, 1·31)	0·25
Did not receive remdesivir	65/511	74/514	0·86 (0·61, 1·20)	
Did receive systemic corticosteroids	20/176	29/179	0·66 (0·37, 1·17)	0·48
Did not receive systemic corticosteroids	50/449	57/446	0·86 (0·59, 1·26)	

Adverse effects

	Dapagliflozin (n=613)	Placebo (n=616)
Any serious adverse event, including death	65 (10·6%)	82 (13·3%)
Adverse event with the outcome of death	32 (5·2%)	48 (7·8%)
Discontinuation due to adverse event	44 (7·2%)	55 (8·9%)
Adverse events of interest		
Acute kidney injury	21 (3·4%)	34 (5·5%)
Diabetic ketoacidosis	2 (0·3%)	0

Data are n (%). Data show the number and proportion of patients with the listed outcome with an onset date on or after the date of the first dose and up to and including 2 days after the last dose of the study medication.

Table 3: Safety outcomes in the safety population

Conclusion

- In patients with cardiometabolic risk factors hospitalized with COVID-19, treatment with dapagliflozin did not result in a statistically significant risk reduction in organ dysfunction or death, or improvement in clinical recovery, but was well tolerated.

Limitation

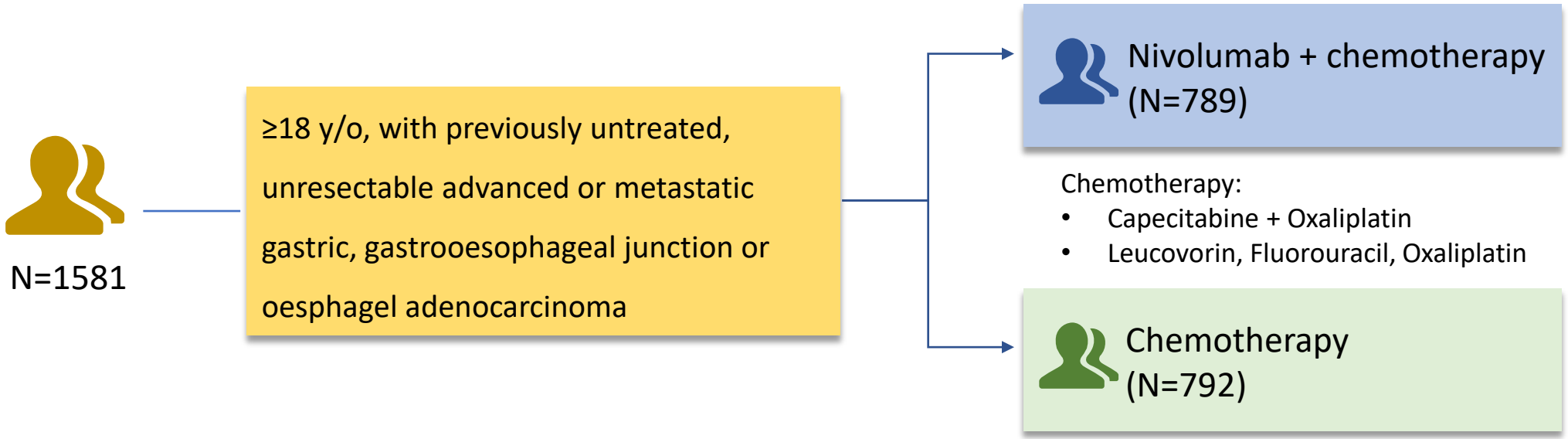
- The rates of organ dysfunction and death were lower than initially anticipated due to improvement in standard of care for treatment of COVID-19. Consequently, the accrued number of events would not allow detection of statistically significant treatment effects with a HR exceeding 0.72.
- The specific eligibility criteria might limit generalizability.

THE LANCET

Lancet 2021; 398: 27–40

First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastrooesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

2017.03.27-2019.04.24 in Asia, Australia, Europe, North America and South America



Primary endpoint: Overall survival or progression-free survival in patients with PD-L1 CPS of five or more.

CPS: combined positive score

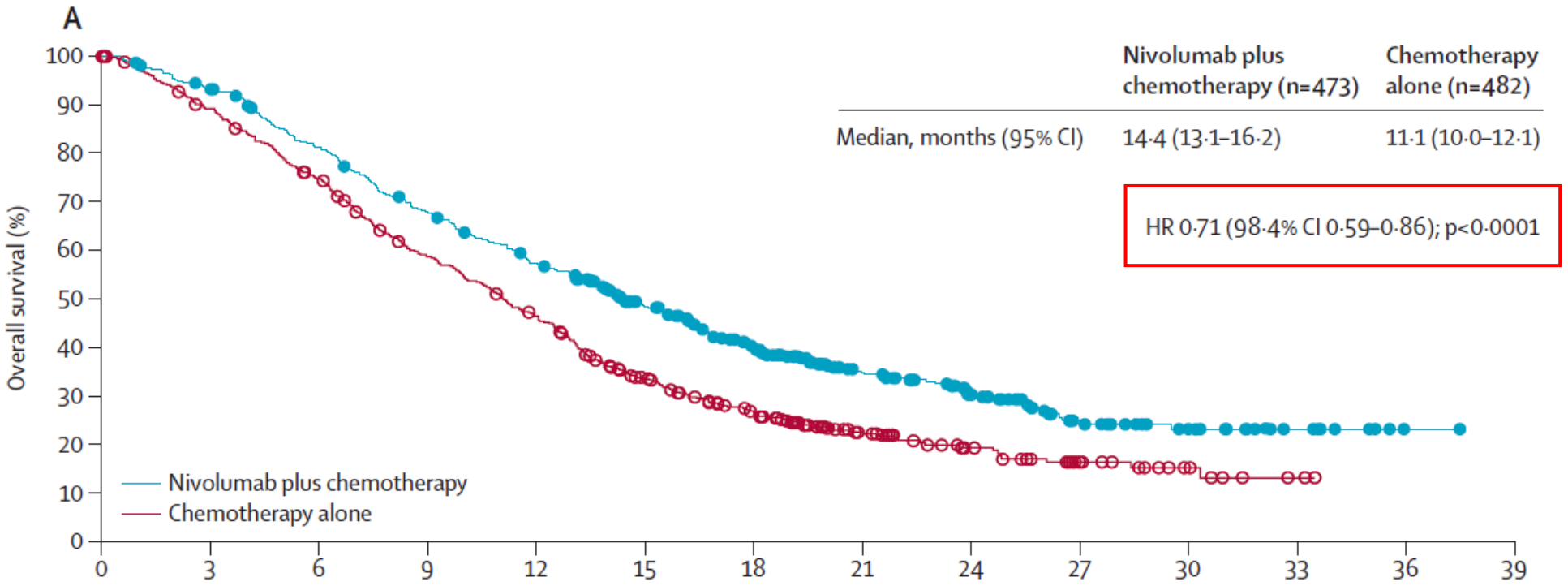
Baseline characteristics

	Patients with a PD-L1 CPS of five or more		All randomly assigned patients	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
Median age, years	63 (54–69)	62 (54–68)	62 (54–69)	61 (53–68)
<65	266 (56%)	286 (59%)	473 (60%)	488 (62%)
≥65	207 (44%)	196 (41%)	316 (40%)	304 (38%)
Sex				
Men	331 (70%)	349 (72%)	540 (68%)	560 (71%)
Women	142 (30%)	133 (28%)	249 (32%)	232 (29%)
Race				
Asian	119 (25%)	117 (24%)	186 (24%)	189 (24%)
White	328 (69%)	327 (68%)	556 (70%)	541 (68%)
American Indian or Alaska Native	10 (2%)	10 (2%)	12 (2%)	14 (2%)
Black or African American	2 (<1%)	7 (1%)	7 (1%)	11 (1%)
Other	14 (3%)	21 (4%)	28 (4%)	36 (5%)
Not reported	0	0	0	1 (<1%)
Region				
Asia	117 (25%)	111 (23%)	178 (23%)	178 (22%)
USA and Canada	67 (14%)	70 (15%)	131 (17%)	132 (17%)
Rest of world	289 (61%)	301 (62%)	480 (61%)	482 (61%)
ECOG performance status*				
0	194 (41%)	203 (42%)	326 (41%)	336 (42%)
1	279 (59%)	278 (58%)	462 (59%)	452 (57%)
2	0	0	1 (<1%)	3 (<1%)
Not reported	0	1 (<1%)	0	1 (<1%)

	Patients with a PD-L1 CPS of five or more		All randomly assigned patients	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
(Continued from previous page)				
Site of metastases				
Liver	191 (40%)	217 (45%)	301 (38%)	314 (40%)
Peritoneum	101 (21%)	96 (20%)	188 (24%)	188 (24%)
CNS	1 (<1%)	0	1 (<1%)	0
Signet ring cell carcinoma‡				
Yes	72 (15%)	69 (14%)	145 (18%)	136 (17%)
No	401 (85%)	413 (86%)	644 (82%)	656 (83%)
Lauren classification				
Intestinal type	171 (36%)	176 (37%)	272 (34%)	267 (34%)
Diffuse type	137 (29%)	141 (29%)	254 (32%)	273 (34%)
Mixed	37 (8%)	30 (6%)	58 (7%)	48 (6%)
Unknown	128 (27%)	135 (28%)	205 (26%)	204 (26%)
Microsatellite instability status				
Microsatellite stable	423 (89%)	423 (88%)	695 (88%)	682 (86%)
Microsatellite instability-high	18 (4%)	16 (3%)	23 (3%)	21 (3%)
Not reported or invalid	32 (7%)	43 (9%)	71 (9%)	89 (11%)
Chemotherapy regimen§				
FOLFOX	237/468 (51%)	242/465 (52%)	422/782 (54%)	406/767 (53%)
XELOX	231/468 (49%)	223/465 (48%)	360/782 (46%)	361/767 (47%)

Outcome---overall survival

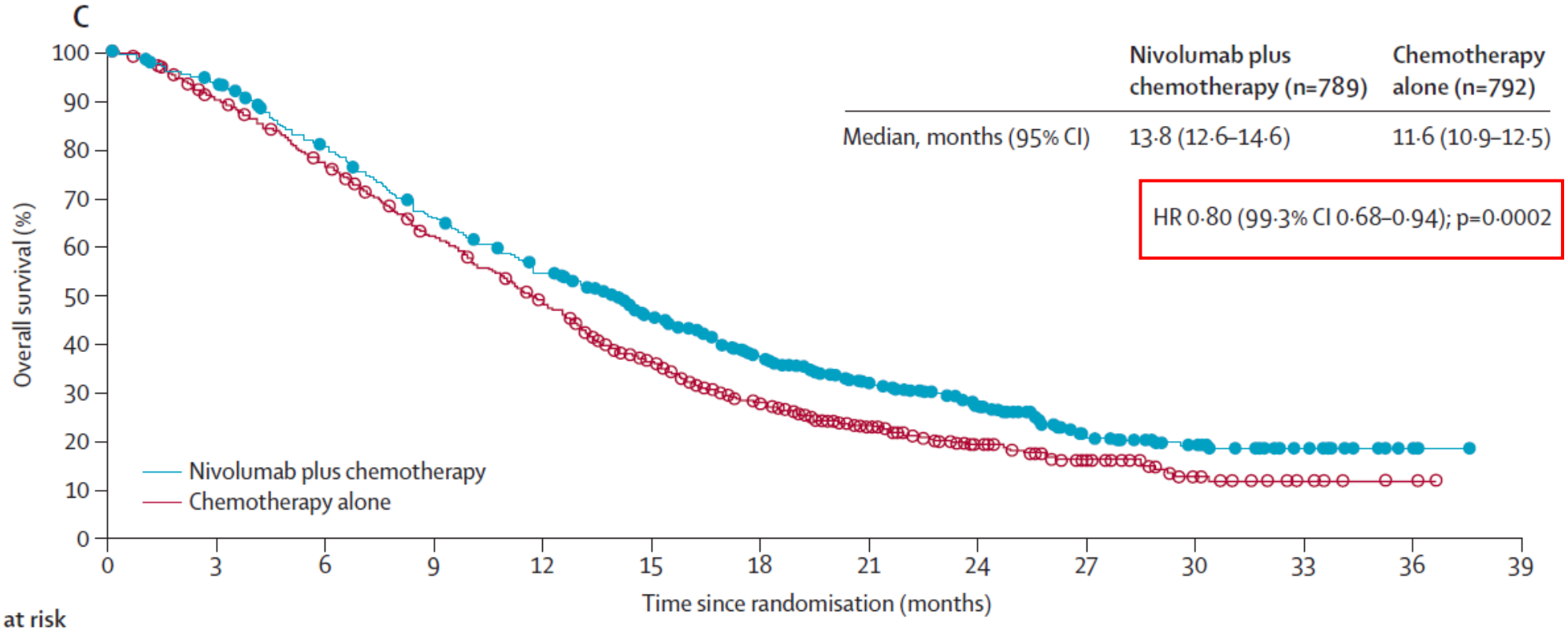
PD-L1 CPS of five or more



Number at risk (number censored)														
Nivolumab plus chemotherapy	473 (0)	438 (3)	377 (9)	313 (11)	261 (14)	198 (39)	149 (55)	96 (91)	65 (110)	33 (133)	22 (142)	9 (155)	1 (163)	0 (164)
Chemotherapy alone	482 (0)	421 (10)	350 (13)	271 (19)	211 (21)	138 (37)	98 (50)	56 (78)	34 (93)	19 (103)	8 (113)	2 (118)	0 (120)	0 (120)

Outcome---overall survival

All randomly assigned patients



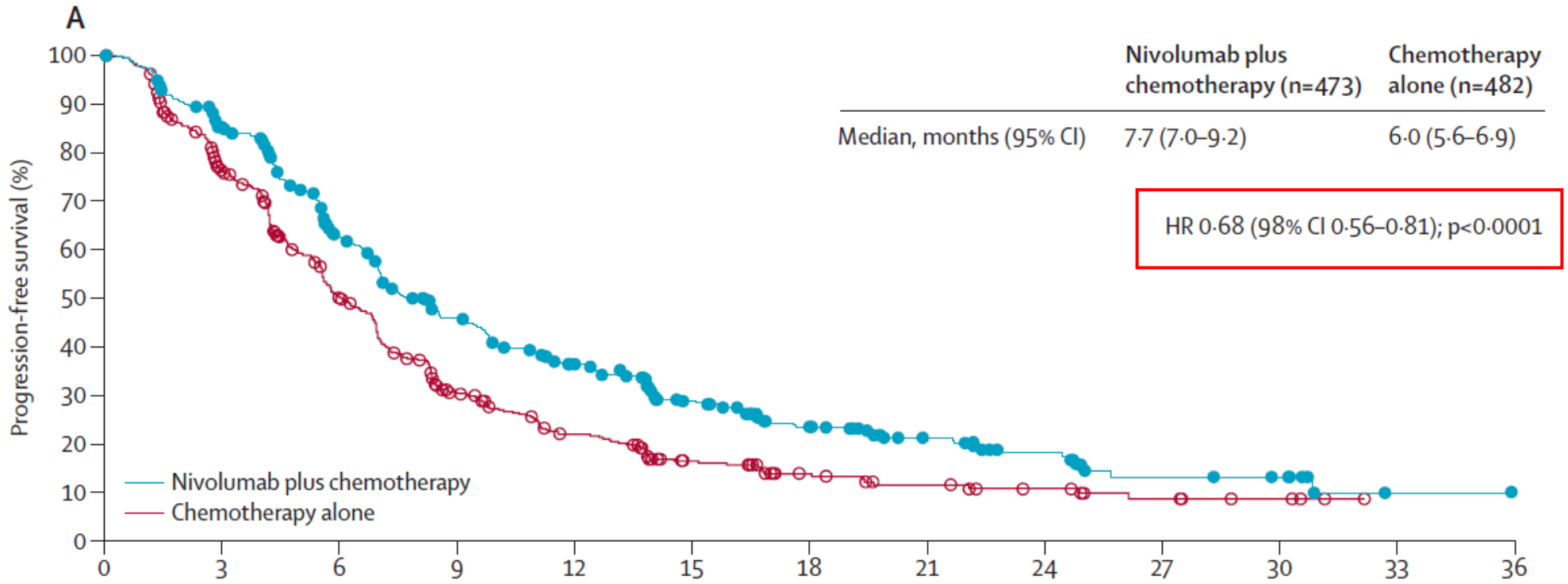
	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
Median, months (95% CI)	13·8 (12·6–14·6)	11·6 (10·9–12·5)

HR 0·80 (99·3% CI 0·68–0·94); p=0·0002

Number at risk (number censored)														
Nivolumab plus chemotherapy	789 (0)	731 (4)	621 (13)	506 (16)	420 (20)	308 (63)	226 (90)	147 (167)	100 (167)	49 (201)	34 (212)	14 (231)	2 (243)	0 (245)
Chemotherapy alone	792 (0)	697 (17)	586 (22)	469 (29)	359 (34)	239 (68)	160 (94)	94 (136)	59 (157)	35 (172)	15 (187)	7 (194)	2 (199)	0 (201)

Outcome---progression-free survival

PD-L1 CPS of five or more



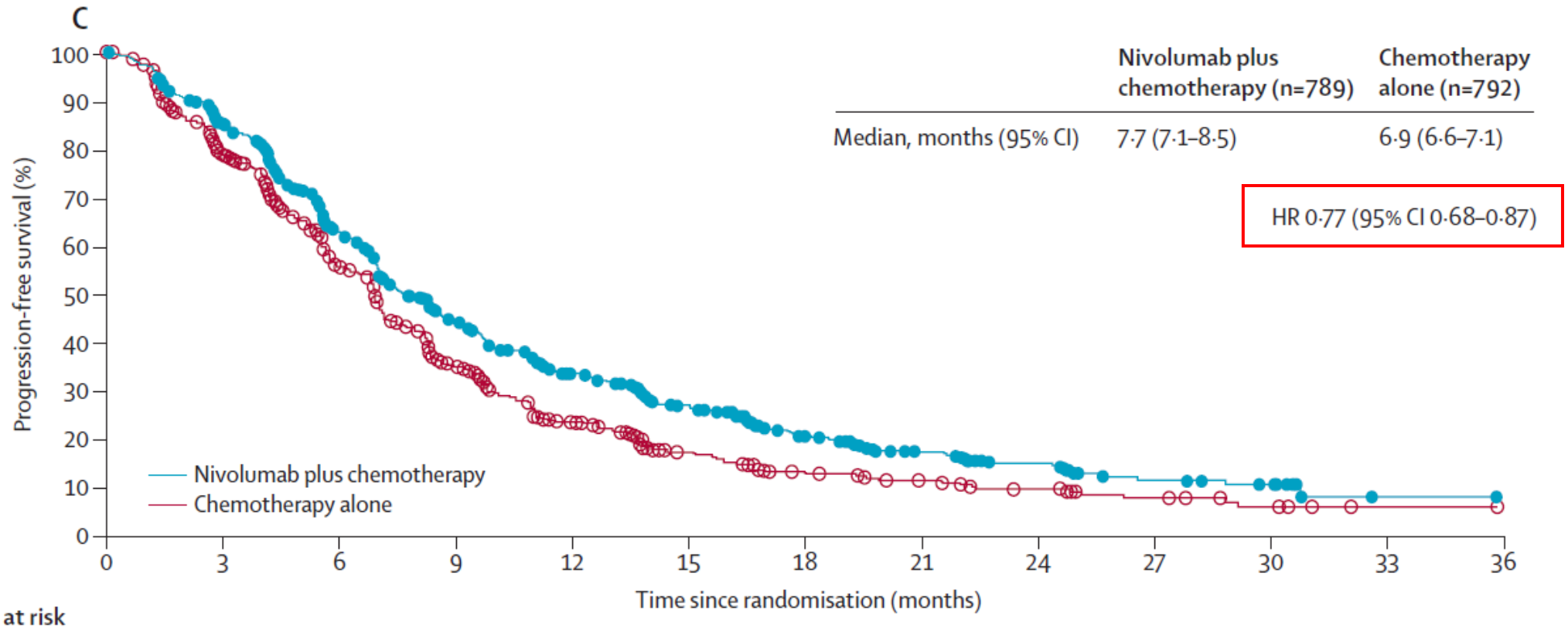
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)
Median, months (95% CI)	7·7 (7·0–9·2)	6·0 (5·6–6·9)

HR 0·68 (98% CI 0·56–0·81); p<0·0001

Number at risk (number censored)													
Nivolumab plus chemotherapy	473 (0)	384 (21)	258 (48)	181 (58)	132 (70)	89 (87)	60 (101)	39 (117)	23 (128)	10 (136)	8 (138)	1 (144)	0 (145)
Chemotherapy alone	482 (0)	325 (51)	200 (68)	109 (82)	72 (90)	41 (104)	25 (114)	18 (117)	12 (122)	7 (125)	4 (128)	0 (132)	0 (132)

Outcome---progression-free survival

All randomly assigned patients



	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
Median, months (95% CI)	7·7 (7·1–8·5)	6·9 (6·6–7·1)

HR 0·77 (95% CI 0·68–0·87)

Number at risk (number censored)													
Nivolumab plus chemotherapy	789 (0)	639 (38)	429 (84)	287 (105)	197 (125)	136 (149)	83 (173)	51 (193)	31 (207)	15 (217)	11 (220)	1 (229)	0 (230)
Chemotherapy alone	792 (0)	544 (92)	351 (133)	202 (155)	120 (173)	65 (199)	38 (211)	28 (216)	18 (222)	12 (225)	6 (229)	1 (234)	0 (235)

Adverse effects

	Nivolumab plus chemotherapy (n=782)*				Chemotherapy alone (n=767)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5†	Grade 1–2	Grade 3	Grade 4	Grade 5
All events	272 (35%)	358 (46%)	104 (13%)	4 (1%)	338 (44%)	285 (37%)	56 (7%)	0
Serious events	37 (5%)	97 (12%)	34 (4%)	4 (1%)	16 (2%)	63 (8%)	14 (2%)	0
Events leading to discontinuation	148 (19%)	109 (14%)	23 (3%)	4 (1%)	114 (15%)	58 (8%)	9 (1%)	0
Any-grade events in 10% or more of treated patients in either group								
Nausea	303 (39%)	20 (3%)	0	0	273 (36%)	19 (2%)	0	0
Diarrhoea	218 (28%)	33 (4%)	2 (<1%)	0	182 (24%)	23 (3%)	1 (<1%)	0
Peripheral neuropathy	190 (24%)	29 (4%)	2 (<1%)	0	168 (22%)	22 (3%)	0	0
Vomiting	178 (23%)	17 (2%)	0	0	142 (19%)	24 (3%)	0	0
Fatigue	172 (22%)	30 (4%)	0	0	156 (20%)	16 (2%)	1 (<1%)	0
Anaemia	156 (20%)	44 (6%)	3 (<1%)	0	150 (20%)	20 (3%)	1 (<1%)	0
Decreased appetite	143 (18%)	14 (2%)	0	0	126 (16%)	12 (2%)	1 (<1%)	0
Thrombocytopenia	138 (18%)	15 (2%)	4 (1%)	0	132 (17%)	12 (2%)	1 (<1%)	0
Platelet count decreased	136 (17%)	17 (2%)	3 (<1%)	0	96 (13%)	15 (2%)	4 (1%)	0
Peripheral sensory neuropathy	121 (15%)	16 (2%)	0	0	105 (14%)	14 (2%)	0	0
Aspartate aminotransferase increased	110 (14%)	12 (2%)	0	0	64 (8%)	5 (1%)	0	0
White blood cell count decreased	89 (11%)	20 (3%)	3 (<1%)	0	64 (8%)	12 (2%)	1 (<1%)	0
Alanine aminotransferase increased	83 (11%)	6 (1%)	0	0	45 (6%)	5 (1%)	0	0
Palmar-plantar erythrodysesthesia syndrome	83 (11%)	11 (1%)	0	0	75 (10%)	6 (1%)	0	0
Neutrophil count decreased	75 (10%)	60 (8%)	23 (3%)	0	51 (7%)	50 (7%)	17 (2%)	0
Neutropenia	73 (9%)	87 (11%)	31 (4%)	0	88 (11%)	70 (9%)	23 (3%)	0
Asthenia	66 (8%)	7 (1%)	0	0	71 (9%)	9 (1%)	1 (<1%)	0
Lipase increased	44 (6%)	34 (4%)	11 (1%)	0	18 (2%)	14 (2%)	2 (<1%)	0

Treatment-related ADR leading to discontinuation	
Nivo + chemo	36%
Chemo	24%

Treatment-related death	
Nivo + chemo	N=16
Chemo	N=4

FDA approves nivolumab in combination with chemotherapy for metastatic gastric cancer and esophageal adenocarcinoma

Resources for Information | Approved Drugs

Oncology (Cancer) / Hematologic Malignancies Approval Notifications

On April 16, 2021, the Food and Drug Administration approved nivolumab (Opdivo, Bristol-Myers Squibb Company) in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Content current as of:
04/16/2021

Regulated Product(s)
Drugs
Prescription Drugs

Adverse Drug Reaction Bulletin. 327(1): 1267-1270, Apr 2021.

Adverse effects from selected antidotes commonly used in poisonings

Paracetamol

- 10 g/time
- Hepatotoxicity

N-Acetylcysteine

- PO or IV
- Eliminate the toxic metabolite of paracetamol
- ADR: Vomiting, Anaphylactoid reaction

Iron

- Hypotension
- Metabolic acidosis
- Shock

Deferoxamine

- Chelating agent
- limit the duration of deferoxamine therapy to 24 h for maximal effect.
- ADR: Pulmonary toxicity (acute respiratory distress syndrome)

Nitrite

- Methemoglobinemia

Anticholinergic drug

- Agitated delirium, urinary retention, sinus tachycardia or hyperthermia

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Adverse effects from selected antidotes commonly used in poisonings

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- Hypotension
- Metabolic acidosis
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Deferoxamine

- Chelating agent
- limit the duration of deferoxamine therapy to 24 h for maximal effect.
- ADR: Pulmonary toxicity (acute respiratory distress syndrome)

Nitrite

- Methemoglobinemia

Methylene blue

- Extensive bluish discoloration of the plasma, skin, mucous membranes and sclera
- Serotonergic syndrome
- Methemoglobinemia

Anticholinergic drug

- Agitated delirium, urinary retention, sinus tachycardia or hyperthermia

Physostigmine

- Reversible acetylcholinesterase inhibitor
- ADR: bradycardia, fasciculations, paralysis, anxiety, tremors, seizures

Abstract

Safety and efficacy of riluzole in patients undergoing decompressive surgery for degenerative cervical myelopathy (CSM-Protect): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial

- 2012.1.31-2017.5.16 in Canada and the USA

P	• 18-80 y/o with moderate-to-severe degenerative cervical myelopathy. • Scheduled to undergo elective surgical decompression.	C	Placebo (N=153)
I	Riluzole 50 mg PO BID (N=147)	O	Chang in the mJOA score at 6 moths after surgery.

Modified Japanese Orthopaedic Association (mJOA) score

Motor dysfunction score of the upper extremity	Motor dysfunction score of the lower extremity
0—Inability to move hands	0—Complete loss of motor and sensory function
1—Inability to eat w/a spoon, but able to move hands	1—Sensory preservation w/o ability to move legs
2—Inability to button shirt, but able to eat w/a spoon	2—Able to move legs, but unable to walk
3—Able to button shirt w/great difficulty	3—Able to walk on flat floor w/a walking aid (cane or crutch)
4—Able to button shirt w/slight difficulty	4—Able to walk up and/or down stairs w/hand rail
5—No dysfunction	5—Moderate-to-significant lack of stability, but able to walk up and/or down stairs w/o hand rail
	6—Mild lack of stability but walks w/smooth reciprocation unaided/
	7—No dysfunction
Sensory dysfunction score of the upper extremities	**Sphincter dysfunction score**
0—Complete loss of hand sensation	0—Inability to micturate voluntarily
1—Severe sensory loss or pain	1—Marked difficulty w/micturition
2—Mild sensory loss	2—Mild to moderate difficulty w/micturition
3—No sensory loss	3—Normal micturition

Safety and efficacy of riluzole in patients undergoing de cervical myelopathy (CSM-Protect): a multicentre, doub randomised, phase 3 trial

- 20

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	Change from baseline	
	Riluzole (n=141)	Placebo (n=149)
Primary endpoint		
mJOA score	2·45 (2·08 to 2·82)	2·83 (2·47 to 3·19
Secondary endpoints		
Nurick grade	−1·28 (−1·49 to −1·06)	−1·15 (−1·36 to −0·
Neck Disability Index	−12·46 (−15·10 to −9·82)	−12·02 (−14·74 to −9
SF-36 Physical Component Summary	6·26 (4·53 to 7·99)	5·22 (3·82 to 6·6
EQ-5D utility score	0·10 (0·06 to 0·14)	0·11 (0·08 to 0·15
Neck pain NRS	−2·23 (−2·71 to −1·74)	−1·61 (−2·07 to −1·
Arm or shoulder pain NRS	−2·12 (−2·59 to −1·64)	−1·62 (−2·09 to −1·
ASIA motor score	3·04 (2·07 to 4·02)	3·04 (2·11 to 3·98
ASIA sensory score	7·02 (3·15 to 10·89)	6·11 (3·28 to 8·94
Grip strength	3·29 (1·87 to 4·71)	4·05 (2·58 to 5·53

Values are reported as least squares means (95% CI) of change in outcome scores from baseline to 6-month multiplicity. ASIA=American Spinal Injury Association. mJOA=modified Japanese Orthopaedic Association. N

Table 2: Primary and secondary efficacy endpoints at 6 months comparing treatment groups

	Riluzole (n=147)	Placebo (n=153)
Death	0	1 (1%)
Pseudarthrosis	3 (2%)	1 (1%)
Hardware failure	3 (2%)	2 (1%)
Worsening myelopathy	13 (9%)	21 (14%)
C5 palsy	9 (6%)	7 (5%)
Neck pain	18 (12%)	29 (19%)
Arm or shoulder pain	17 (12%)	29 (19%)
Arm paraesthesia	21 (14%)	18 (12%)
Adjacent segment degeneration	1 (1%)	0
Dural tear	3 (2%)	8 (5%)
Haematoma	3 (2%)	3 (2%)
Deep wound infection	2 (1%)	1 (1%)
Superficial wound infection	5 (3%)	3 (2%)
Dysphagia	18 (12%)	20 (13%)
Hoarseness	4 (3%)	4 (3%)
Arrhythmia	7 (5%)	1 (1%)
Venous thromboembolism	3 (2%)	1 (1%)
Elevated liver enzymes	5 (3%)	3 (2%)
Nausea	10 (7%)	13 (8%)
Dizziness	7 (5%)	6 (4%)
Diarrhoea	5 (3%)	3 (2%)
Abdominal pain	2 (1%)	4 (3%)
Pneumonia	0	2 (1%)
Serious adverse events	33 (22%)	29 (19%)

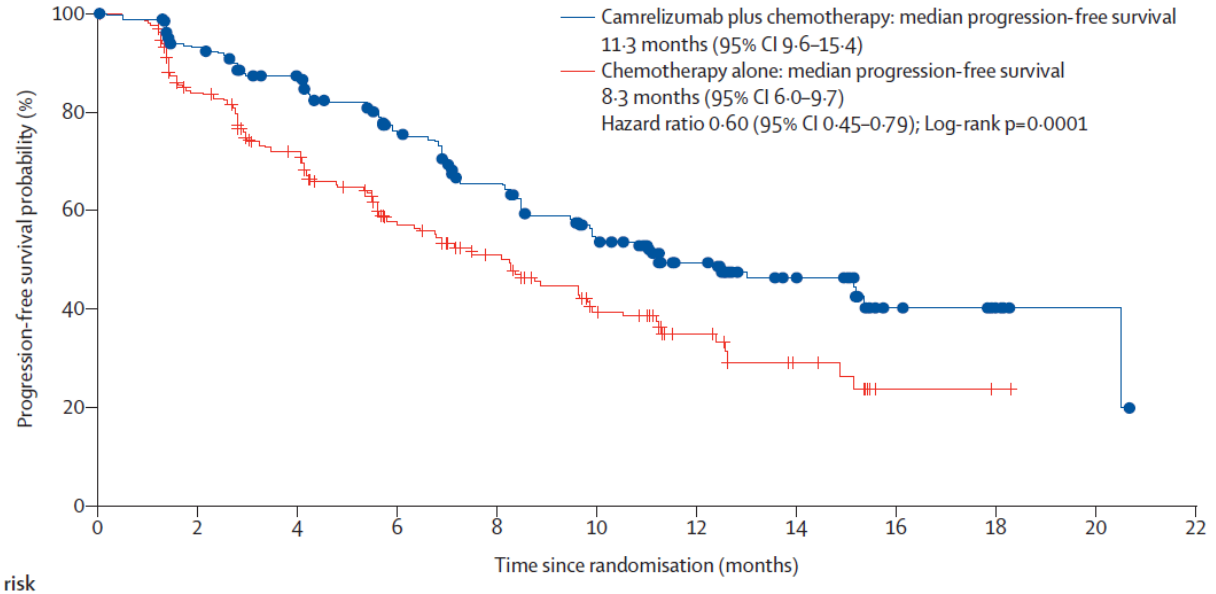
Data are n (%). Listed events are anticipated adverse events, as specified in the protocol. All adverse events were recorded, but those listed were prespecified.

Table 3: Adverse events and safety outcomes comparing treatment groups

Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naïve patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial

- 2017.5.12-2018.6.6 in China

P	• 18-70 y/o • Confirmed stage IIIR-IV non-squamous NSCLS without EGFR and ALK alteration, had no previous systemic chemotherapy.	C	Carboplatin [AUC] 5mg/ml/min + Pemetrexed 500 mg/m2 IV on day 1 of each 3-week for 4-6 cycles Maintenance: Pemetrexed (N= 207)
I	Camrelizumab 200 mg + Carboplatin [AUC] 5mg/ml/min + Pemetrexed 500 mg/m2 IV on day 1 of each 3-week for 4-6 cycles Maintenance: Camrelizumab + Pemetrexed (N= 205)	O	Progression-free survival: • Intervention group: median 11.3 months (95% CI 9.6-15.4) • Control group: median 8.3 months (95% CI 6.0-9.7) Hazard ratio 0.60; Log-rank p=0.0001



Camrelizumab + chemotherapy:
Median 11.3 months (95% CI 9.6-15.4)

Chemotherapy alone:
Median 8.3 months (95% CI 6.0-9.7)

HR 0.60 (95% CI 0.45-0.79); Log-rank p=0.0001

Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naïve patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial

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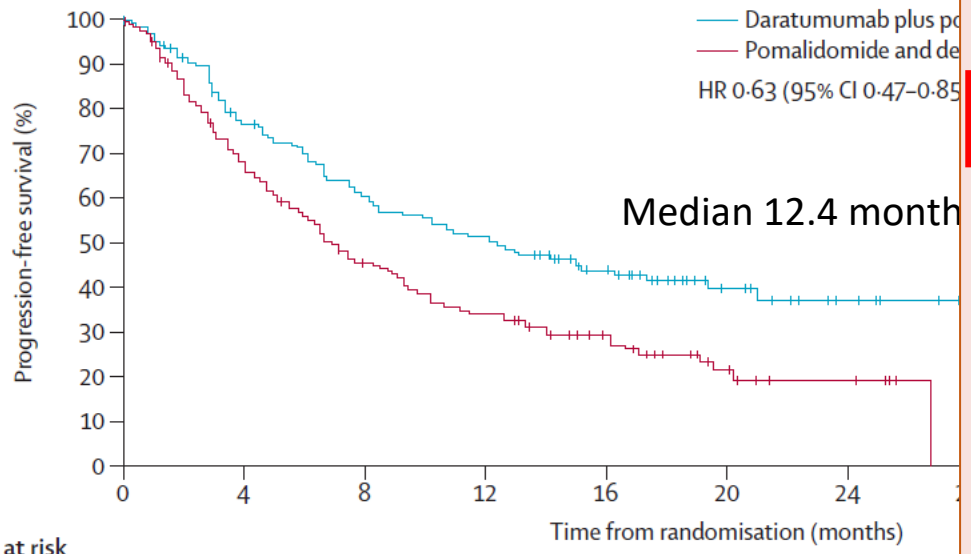
	Camrelizumab plus carboplatin and pemetrexed (n=205)		Carboplatin and pemetrexed (n=207)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Haematological toxicities				
Neutrophil count decreased	146 (71%)	78 (38%)	132 (64%)	63 (30%)
White blood cell count decreased	145 (71%)	40 (20%)	133 (64%)	30 (14%)
Anaemia	136 (66%)	38 (19%)	123 (59%)	23 (11%)
Platelet count decreased	94 (46%)	34 (17%)	79 (38%)	24 (12%)
Lymphocyte count decreased	22 (11%)	8 (4%)	21 (10%)	5 (2%)
Haemoglobin decreased	19 (9%)	3 (1%)	21 (10%)	2 (<1%)
Non-haematological toxicities				
Reactive cutaneous capillary endothelial proliferation	159 (78%)	2 (<1%)	1 (<1%)	0
Aspartate aminotransferase increased	93 (45%)	4 (2%)	68 (33%)	1 (<1%)
Alanine aminotransferase increased	88 (43%)	10 (5%)	79 (38%)	5 (2%)
Nausea	73 (36%)	2 (<1%)	61 (29%)	2 (<1%)
Asthenia	64 (31%)	7 (3%)	54 (26%)	3 (1%)
Decreased appetite	62 (30%)	5 (2%)	55 (27%)	5 (2%)
Constipation	44 (21%)	0	35 (17%)	1 (<1%)
Vomiting	42 (20%)	2 (<1%)	33 (16%)	4 (2%)
Hepatic function abnormal	41 (20%)	5 (2%)	31 (15%)	2 (<1%)
Gamma-glutamyltransferase increased	36 (18%)	6 (3%)	18 (9%)	1 (<1%)
Rash	25 (12%)	3 (1%)	11 (5%)	0
Pruritus	24 (12%)	1 (<1%)	3 (1%)	0
Blood creatinine increased	22 (11%)	1 (<1%)	10 (5%)	0
Hypothyroidism	22 (11%)	1 (<1%)	0	0
Blood bilirubin increased	21 (10%)	1 (<1%)	11 (5%)	0

	Camrelizumab plus carboplatin and pemetrexed (n=205)		Carboplatin and pemetrexed (n=207)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Serious treatment-related adverse events occurring in at least 2% of patients in either group				
Haematological toxicities				
Platelet count decreased	19 (9%)	18 (9%)	4 (2%)	4 (2%)
Bone marrow toxicity	8 (4%)	8 (4%)	1 (<1%)	1 (<1%)
White blood cell count decreased	6 (3%)	4 (2%)	4 (2%)	3 (1%)
Anaemia	5 (2%)	5 (2%)	2 (<1%)	1 (<1%)
Neutrophil count decreased	4 (2%)	3 (1%)	4 (2%)	4 (2%)
Non-haematological toxicities				
Hepatic function abnormal	8 (4%)	5 (2%)	2 (<1%)	2 (<1%)
Alanine aminotransferase increased	6 (3%)	2 (<1%)	1 (<1%)	1 (<1%)
Pneumonitis	6 (3%)	4 (2%)	2 (<1%)	1 (<1%)
Lung infection	6 (3%)	4 (2%)	0	0
Interstitial lung disease	5 (2%)	3 (1%)	0	0
Blood creatinine increased	4 (2%)	0	0	0

Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial

- 2017.06.22-2019.06.13 in 12 European countries

P	• ≥18 y/o, had relapsed or refractory multiple myeloma. • Had received at least one previous line of therapy with lenalidomide and a proteasome inhibitor.
I	① Daratumumab 1800 mg SC or 16 mg/kg IV QW-Q4W ② Pomalidomide 4 mg PO QD (days 1-21)
C	① Pomalidomide 4 mg PO QD (days 1-21) ② Dexamethasone 40 mg PO QD (days 1, 8, 15, 22) (N=153)



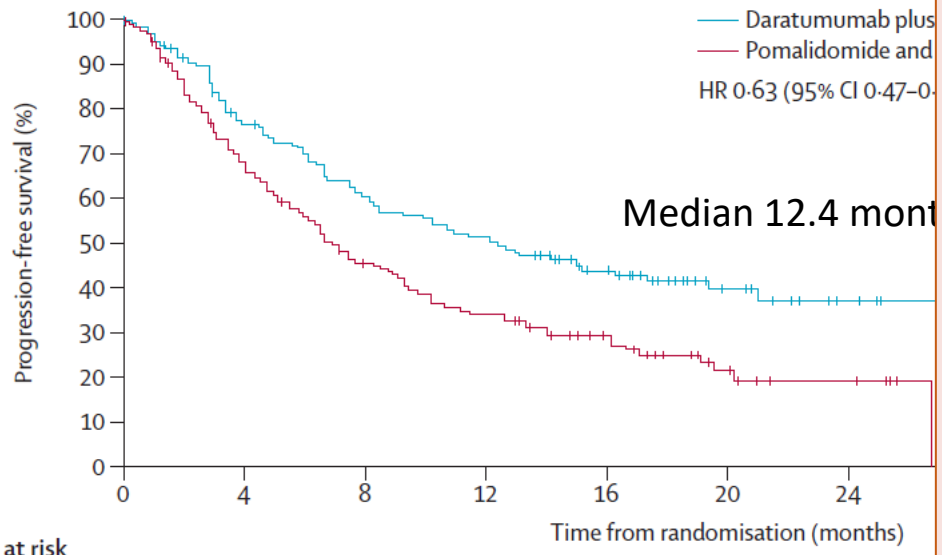
Number at risk (number censored)								
Daratumumab plus pomalidomide and dexamethasone group	151 (0)	111 (6)	87 (7)	74 (7)	48 (24)	20 (48)	8 (59)	(
Pomalidomide and dexamethasone group	153 (0)	93 (11)	61 (15)	46 (15)	27 (27)	12 (37)	5 (43)	(

	Daratumumab plus pomalidomide and dexamethasone group (n=151)	Pomalidomide and dexamethasone group (n=153)	Odds ratio (95% CI)	p value
Overall response	104 (69%; 95% CI 61–76)	71 (46%; 95% CI 38–55)	2·7 (1·7–4·4)	<0·0001‡
Best overall response				
Complete response or better	37 (25%)	6 (4%)	8·2 (3·4–20·3)	<0·0001‡
Stringent complete response§	14 (9%)	2 (1%)	..	..
Complete response	23 (15%)	4 (3%)	..	..
Very good partial response or better	77 (51%)	30 (20%)	4·3 (2·6–7·3)	<0·0001‡
Very good partial response	40 (26%)	24 (16%)	..	..
Partial response	27 (18%)	41 (27%)	..	..
Minimal response	11 (7%)	15 (10%)	..	..
Stable disease	26 (17%)	49 (32%)	..	..
Progressive disease	4 (3%)	7 (5%)	..	..
Response could not be evaluated	6 (4%)	11 (7%)	..	..
Negative status for minimal residual disease¶	13 (9%)	3 (2%)	4·7 (1·3–16·9)	0·010‖

Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial

- 2017.06.22-2019.06.13 in 12 European countries

P	• ≥18 y/o, had relapsed or refractory multiple myeloma. • Had received at least one previous line of therapy with lenalidomide and a proteasome inhibitor.
I	① Daratumumab 1800 mg SC or 16 mg/kg IV QW-Q4W ② Pomalidomide 4 mg PO QD (days 1-21)



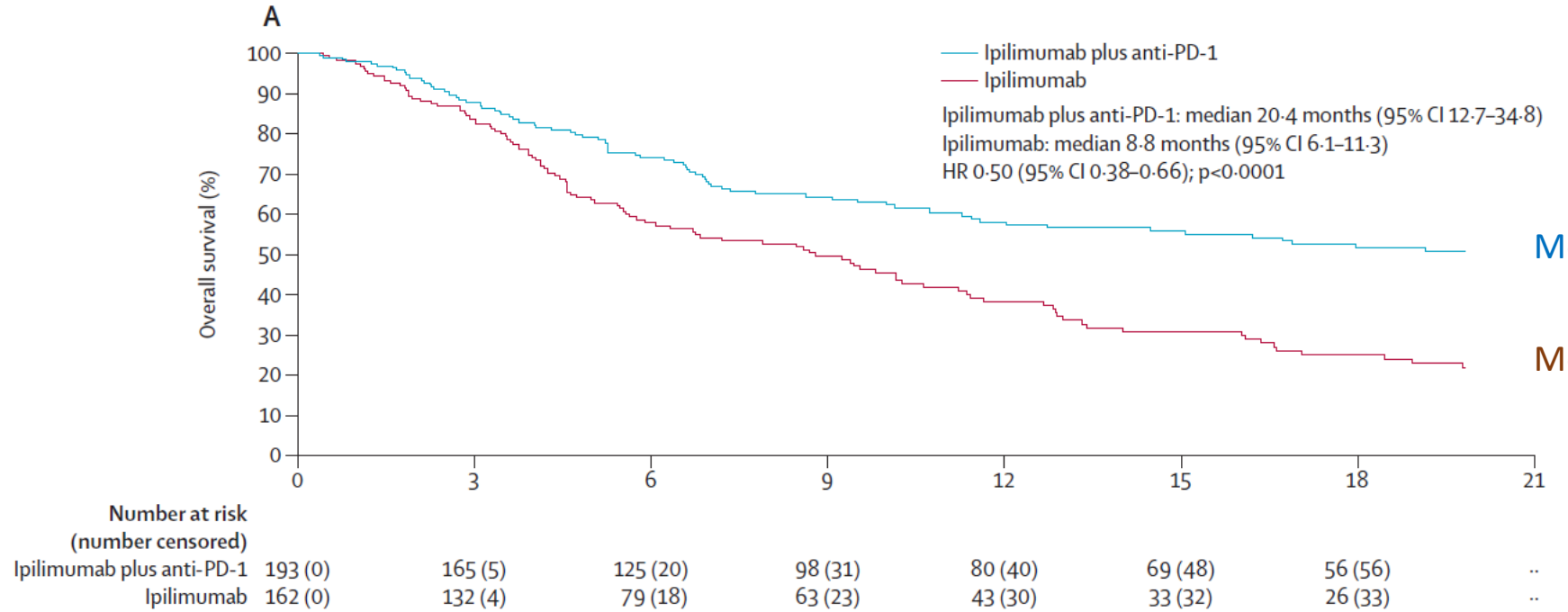
Number at risk (number censored)							
Daratumumab plus pomalidomide and dexamethasone group	151 (0)	111 (6)	87 (7)	74 (7)	48 (24)	20 (48)	8 (59)
Pomalidomide and dexamethasone group	153 (0)	93 (11)	61 (15)	46 (15)	27 (27)	12 (37)	5 (43)

	Daratumumab plus pomalidomide and dexamethasone group (n=149)			Pomalidomide and dexamethasone group (n=150)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological adverse events						
Neutropenia	4 (3%)	37 (25%)	64 (43%)	4 (3%)	49 (33%)	27 (18%)
Anaemia	30 (20%)	24 (16%)	1 (1%)	34 (23%)	31 (21%)	1 (1%)
Thrombocytopenia	22 (15%)	13 (9%)	13 (9%)	23 (15%)	19 (13%)	8 (5%)
Leukopenia	14 (9%)	16 (11%)	9 (6%)	11 (7%)	6 (4%)	1 (1%)
Lymphopenia	4 (3%)	10 (7%)	8 (5%)	7 (5%)	3 (2%)	2 (1%)
Febrile neutropenia	0	10 (7%)	3 (2%)	0	3 (2%)	1 (1%)
Non-haematological adverse events						
Infections	61 (41%)	32 (21%)	4 (3%)	48 (32%)	29 (19%)	1 (1%)
Upper respiratory tract infection	34 (23%)	0	0	21 (14%)	3 (2%)	0
Pneumonia	10 (7%)	14 (9%)	3 (2%)	8 (5%)	8 (5%)	1 (1%)
Lower respiratory tract infection	12 (8%)	14 (9%)	2 (1%)	10 (7%)	11 (7%)	2 (1%)
Fatigue	26 (17%)	12 (8%)	0	31 (21%)	7 (5%)	0
Asthenia	25 (17%)	7 (5%)	1 (1%)	23 (15%)	1 (1%)	0
Diarrhoea	25 (17%)	8 (5%)	0	20 (13%)	1 (1%)	0
Pyrexia	29 (20%)	0	0	21 (14%)	0	0
Hyperglycaemia	7 (5%)	7 (5%)	1 (1%)	12 (8%)	7 (5%)	0
Second primary malignancy	3 (2%)	NA	NA	3 (2%)	NA	NA
Any infusion-related reaction	8 (5%)	0	0	NA	NA	NA

Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study

- 2011.02.01-2020.02.06 in Australia, Europe and the USA

P	• Had received previous anti-PD-(L)1 monotherapy (nivolumab, pembrolizumab or atezolizumab) and their melanoma progressed or recurred while or after the treatment.	C	① Ipilimumab IV (N=162)
I	① Ipilimumab IV ② Anti-PD-1 (nivolumab or pembrolizumab) IV (N=193)	O	Overall survival: HR 0.50 (95% CI 0.38-0.66); p<0.0001



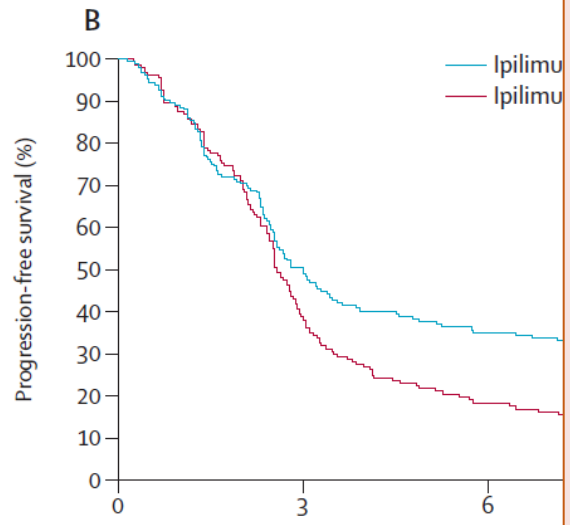
Median 20.4 months (95% CI 12.7-34.8)

Median 8.8 months (95% CI 6.1-11.3)

Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L

- 2011.02.01-2020.02.06 in Australia, E

P	• Had received previous anti-PD-(L)1 mon pembrolizumab or atezolizumab) and th progressed or recurred while or after th
I	① Ipilimumab IV ② Anti-PD-1 (nivolumab or pembrolizuma (N=193)



Number at risk (number censored)

Ipilimumab plus anti-PD-1	193 (0)	93 (2)	59 (10)
Ipilimumab	162 (0)	61 (1)	25 (6)

	Ipilimumab plus anti-PD-1 group (n=193)					Ipilimumab group (n=162)				
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 3–5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 3–5
Number of patients with at least one adverse event	102 (53%)	42 (22%)	19 (10%)	0	59 (31%)	69 (43%)	50 (31%)	4 (2%)	1 (1%)	54 (33%)
Gastrointestinal	46 (24%)	27 (14%)	19 (10%)	0	46 (24%)	27 (17%)	43 (27%)	4 (2%)	1 (1%)	48 (30%)
Diarrhoea or colitis	38 (20%)	18 (9%)	5 (3%)	0	23 (12%)	14 (9%)	30 (19%)	2 (1%)	1 (1%)	33 (20%)
Increased alanine aminotransferase or aspartate aminotransferase	15 (8%)	11 (6%)	13 (7%)	0	24 (12%)	9 (6%)	13 (8%)	2 (1%)	0	15 (9%)
Nausea or vomiting	0	0	0	0	0	4 (2%)	0	0	0	0
Increased amylase or lipase	1 (1%)	0	1 (1%)	0	1 (1%)	0	2 (1%)	0	0	2 (1%)
Skin	42 (22%)	4 (2%)	0	0	4 (2%)	27 (17%)	2 (1%)	0	0	2 (1%)
Rash or pruritus	39 (20%)	3 (2%)	0	0	3 (2%)	27 (17%)	2 (1%)	0	0	2 (1%)
Vitiligo	3 (2%)	0	0	0	0	0	0	0	0	0
Bullous pemphigoid	0	1 (1%)	0	0	1 (1%)	0	0	0	0	0
Hypophysitis, hypothyroidism, or hyperthyroidism	30 (16%)	3 (2%)	0	0	3 (2%)	9 (6%)	2 (1%)	0	0	2 (1%)
Fatigue	14 (7%)	0	0	0	0	7 (4%)	0	0	0	0
Respiratory pneumonitis	10 (5%)	2 (1%)	0	0	2 (1%)	5 (3%)	1 (1%)	0	0	1 (1%)
Arthralgia or myalgia	10 (5%)	1 (1%)	0	0	1 (1%)	10 (6%)	1 (1%)	0	0	1 (1%)
Fever	8 (4%)	2 (1%)	0	0	2 (1%)	2 (1%)	0	0	0	0
Uveitis, iritis, or blepharoconjunctivitis	5 (3%)	1 (1%)	0	0	1 (1%)	2 (1%)	1 (1%)	0	0	1 (1%)
Nephritis	6 (3%)	0	0	0	0	1 (1%)	1 (1%)	0	0	1 (1%)
Nervous system	2 (1%)	3 (2%)	0	0	3 (2%)	0	1 (1%)	0	0	1 (1%)
Headache	1 (1%)	0	0	0	0	0	0	0	0	0
Peripheral neuropathy	1 (1%)	0	0	0	0	0	0	0	0	0
Encephalitis or meningitis	0	2 (1%)	0	0	2 (1%)	0	1 (1%)	0	0	1 (1%)
Guillain-Barré Syndrome	0	1 (1%)	0	0	1 (1%)	0	0	0	0	0
Anaemia or thrombocytopenia	0	1 (1%)	0	0	1 (1%)	0	1 (1%)	0	0	1 (1%)
Myocarditis	0	0	0	0	0	0	1 (1%)	0	0	1 (1%)

Table 3: Treatment-related adverse events

Efficacy and safety of voclosporin versus placebo for lupu - blind, randomised, multicentre, placebo-controlled, phas

- 2017.04.13-2019.10.10 in North and Latin America, Europe, South

P	• Systemic lupus erythematosus with lupus nephritis (class III, IV, V). • Ineligible if eGFR ≦45 mL/min/1.73m2	C	① ②
I	① Voclosporin 23.7 mg PO BID ② Mycophenolate mofetil 1 g PO BID ③ Methylprednisolone IV QD (N=179)	O	Con OR

	Voclosporin group (n=179)	Placebo group (n=178)	OR or HR (95% CI)	p value
Primary endpoint*				
Complete renal response at 52 weeks	73 (41%)	40 (23%)	OR 2·65 (1·64–4·27)	<0·0001
Secondary endpoints				
Complete renal response at 24 weeks	58 (32%)	35 (20%)	OR 2·23 (1·34–3·72)	0·002
Partial renal response at 24 weeks	126 (70%)	89 (50%)	OR 2·43 (1·56–3·79)	<0·001
Partial renal response at 52 weeks	125 (70%)	92 (52%)	OR 2·26 (1·45–3·51)	<0·001
Time to UPCR ≤0·5 mg/mg, days	169 (141–214)	372 (295–NC)	HR 2·02 (1·51–2·70)	<0·001
Time to 50% reduction in UPCR, days	29 (29–32)	63 (57–87)	HR 2·05 (1·62–2·60)	<0·001

	Voclosporin group (n=178)	Placebo group (n=178)
Adverse event summary		
Adverse event	162 (91%)	158 (89%)
Serious adverse event	37 (21%)	38 (21%)
Serious adverse event of infections and infestations	18 (10%)	20 (11%)
Treatment-related serious adverse event	8 (4%)	8 (4%)
Adverse event leading to study drug discontinuation	20 (11%)	26 (15%)
Death*	1 (<1%)	5 (3%)
Treatment-related adverse event leading to death	0	0
Adverse events (reported ≥4% of patients)		
Infections and infestations	115 (65%)	101 (57%)
Gastrointestinal disorders	83 (47%)	61 (34%)
Investigations and infestations	60 (34%)	31 (17%)
Nervous system disorders	47 (26%)	27 (15%)
Skin and subcutaneous tissue disorders	42 (24%)	31 (17%)
Musculoskeletal and connective tissue disorders	40 (22%)	46 (26%)
Vascular disorders	38 (21%)	23 (13%)
General disorders and administration site conditions	36 (20%)	32 (18%)
Blood and lymphatic system disorders	35 (20%)	29 (16%)
Respiratory, thoracic, and mediastinal disorders	26 (15%)	17 (10%)
Renal and urinary disorders	26 (15%)	37 (21%)
Metabolism and nutritional disorders	25 (14%)	37 (21%)

Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial

- 2018.08.09 - 2019.12.20 in Asia-Pacific region, Europe, the Middle East, North America, and Oceania

P	• ≥12 y/o with moderate to severe atopic dermatitis • EASI ≥16; vIGA-AD ≥3	C	Placebo + topical corticosteroid (N=304)
I	1. Upadacitinib 15 mg + topical corticosteroid (N=300) 2. Upadacitinib 30 mg + topical corticosteroid (N=297)	O	• EASI-75 at week 16 • vIGA-AD response at week 16

	Upadacitinib 15 mg plus topical corticosteroids (n=300)	Upadacitinib 30 mg plus topical corticosteroids (n=297)	Placebo plus topical corticosteroids (n=304)
Coprimary endpoints			
EASI-75 at week 16			
Responders, n (%; 95% CI)	194 (64·6%; 59·1 to 70·0)	229 (77·1%; 72·3 to 81·9)	80 (26·4%; 21·5 to 31·4)
Adjusted percentage difference compared with placebo (95% CI)	38·1 (30·8 to 45·4); p<0·0001	50·6 (43·8 to 57·4); p<0·0001	..
vIGA-AD response at week 16*			
Responders, n (%; 95% CI)	119 (39·6%; 34·1 to 45·2)	174 (58·6%; 53·0 to 64·2)	33 (10·9%; 7·4 to 14·4)
Adjusted percentage difference compared with placebo (95% CI)	28·5 (22·1 to 34·9); p<0·0001	47·6 (41·1 to 54·0); p<0·0001	..

EASI-75: ≥75% improvement in Eczema Area and Severity Index score from baseline
vIGA-AD: validated Investigator's Global Assessment for atopic dermatitis

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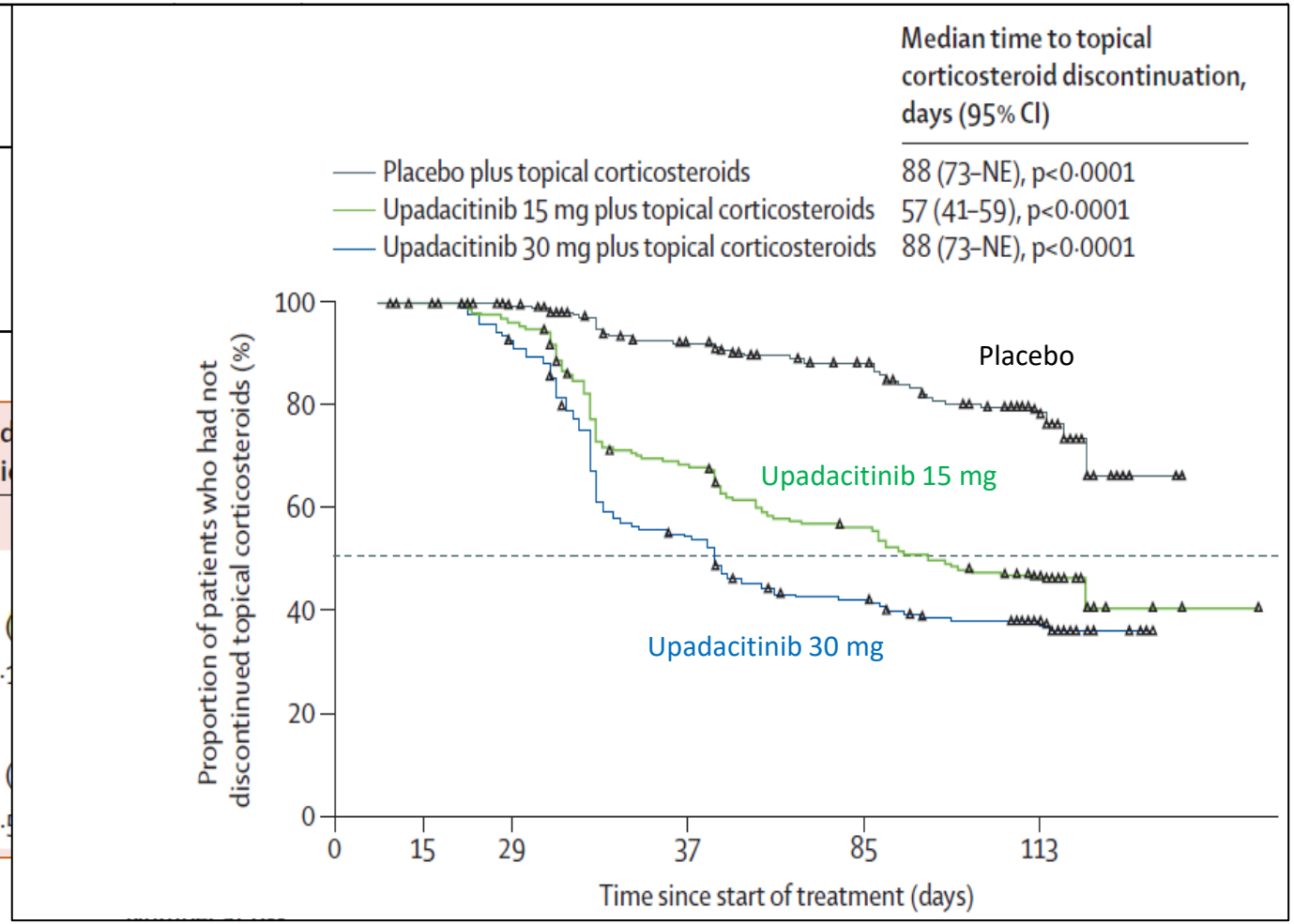
	Upac corti
Coprimary endpoints	
EASI-75 at week 16	
Responders, n (%; 95% CI)	194 (
Adjusted percentage difference compared with placebo (95% CI)	38·1
vIGA-AD response at week 16*	
Responders, n (%; 95% CI)	119 (
Adjusted percentage difference compared with placebo (95% CI)	28·5



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- 2018.08.09 - 2019.12.20 in Asia-Pacific region, Europe, the Middle East, North America, and Oceania

	Upadacitinib 15 mg plus topical corticosteroids (n=300)	Upadacitinib 30 mg plus topical corticosteroids (n=297)	Placebo plus topical corticosteroids (n=303)
Any treatment-emergent adverse event	200 (67%)	215 (72%)	190 (63%)
Serious adverse events	7 (2%)	4 (1%)	9 (3%)
Adverse events leading to discontinuation of study drug	4 (1%)	4 (1%)	7 (2%)
Deaths	0	0	0
Adverse events of special interest			
Serious infections	3 (1%)	0	3 (1%)
Opportunistic infections excluding tuberculosis and herpes zoster	3 (1%)	4 (1%)	0
Eczema herpeticum (Kaposi's varicelliform eruption)	3 (1%)	4 (1%)	0
Herpes zoster	3 (1%)	5 (2%)	3 (1%)
Active tuberculosis	0	0	0
Non-melanoma skin cancer	0	1 (<1%)	0
Malignancy (excluding non-melanoma skin cancer)	0	1 (<1%)	0
Lymphoma	0	0	0

	Upadacitinib 15 mg plus topical corticosteroids (n=300)	Upadacitinib 30 mg plus topical corticosteroids (n=297)	Placebo plus topical corticosteroids (n=303)
Hepatic disorder†	6 (2%)	3 (1%)	5 (2%)
Adjudicated gastrointestinal perforation	0	0	0
Anaemia†	0	3 (1·0)	1 (0·3)
Neutropenia†	2 (1%)	3 (1%)	0
Lymphopenia†	0	0	1 (0·3)
Creatine phosphokinase elevation†	13 (4%)	18 (6%)	7 (2%)
Renal dysfunction†	1 (<1%)	0	0
Adjudicated major adverse cardiovascular event	0	0	0
Adjudicated venous thromboembolic event	0	0	0
Most frequently reported treatment-emergent adverse events (≥5% in any treatment group)			
Acne	30 (10%)	41 (14%)	6 (2%)
Nasopharyngitis	37 (12%)	40 (13%)	34 (11%)
Upper respiratory tract infection	21 (7%)	23 (8%)	22 (7%)
Oral herpes	10 (3%)	23 (8%)	5 (2%)
Blood creatine phosphokinase elevation†	13 (4%)	18 (6%)	7 (2%)
Headache	15 (5%)	14 (5%)	15 (5%)
Atopic dermatitis	11 (4%)	2 (1%)	20 (7%)

New drug approvals

Drugs	Indication	Mechanism
Berotralstat	Prophylaxis to prevent attacks of hereditary angioedema in adults and in paediatric patients 12 years or older.	Inhibits kallikrein activity, which ultimately results in the reduction of bradykinin levels.
Inclisiran	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet.	Long-acting synthetic siRNA targeting proprotein convertase subtilsin/kexin type 9 (PCSK9) mRNA and conjugated to triantennary N-acetylgalactosamine carbohydrates (GalNAc).
Lonafarnib	Treatment of hepatitis D virus (HDV) infections, and progeria and progeroid laminopathies.	Orally active farnesyltransferase inhibitor.
Lumasiran	Primary hyperoxaluria type 1 (PH1).	Subcutaneously administered small interfering RNA (siRNA) targeting the mRNA for hydroxyacid oxidase 1 gene (HAO1; encodes glycolate oxidase).
Naxitamab	Treatment of neuroblastoma, osteosarcoma and other GD2-positive cancers.	Humanised (IgG1) anti-GD2 (hu3F8) monoclonal antibody.
Setmelanotide	Chronic weight management in patients 6 years and older with obesity caused by POMC, PCSK1 and LEPR deficiency.	Melanocortin-4 (MC4) receptor agonist.

New drug approvals

Drugs

Drugs	Indication	Mechanism
Orelabrutinib	Treatment of patients with mantle cell lymphoma or chronic lymphocytic leukaemia /small lymphocytic lymphoma, who have received at least one treatment in the past.	Second generation Bruton's tyrosine kinase inhibitor.
Tirbanibulin	For the topical treatment of actinic keratosis, and psoriasis.	Src kinase signaling inhibitor and tubulin polymerisation inhibitor.
Ansuvimab	Treatment of infection caused by Z. ebolavirus in adult and paediatric patients, including in neonates born to a mother who is RT-PCR positive for Z. ebolavirus infection.	Human monoclonal IgG1 antibody. Ansuvimab blocks binding between the Ebola virus glycoprotein and the Niemann-Pick C1 receptor.
Margetuximab	Treatment of HER2-positive breast cancer, gastric cancer and gastro-oesophageal junction cancer.	Second-generation anti-human epidermal growth factor receptor2 protein (HER2) monoclonal antibody.
Voclosporin	For use in combination with a background immunosuppressive therapy regimen for adults with active lupus nephritis.	Oral calcineurin inhibitor immunosuppressant.
Casimersen	Duchenne muscular dystrophy (DMD) in patients who have a mutation in the DMD gene that is amenable to exon 45 skipping.	Antisense oligonucleotide of the phosphorodiamidate morpholino oligomer subclass.

New drug approvals

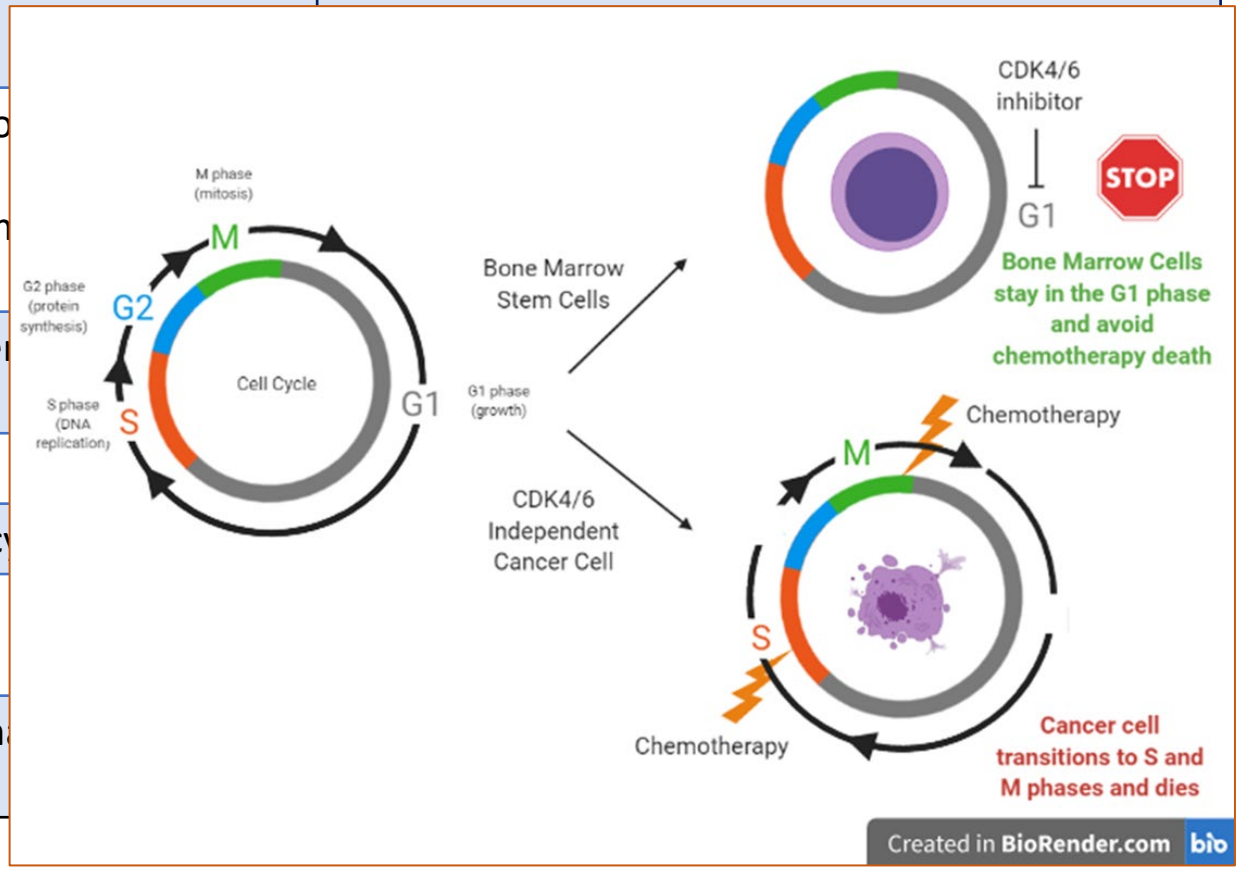
Drugs

Drugs	Indication	Mechanism
Pegcetacoplan	Treatment of adults with paroxysmal nocturnal haemoglobinuria, including those switching from C5 inhibitor therapy with eculizumab and ravulizumab.	A PEGylated pentadecapeptide binds to complement component 3 (C3) and its activation fragment C3b, controlling the cleavage of C3 and the generation of the downstream effectors of complement activation.
Olanzapine/Samidorphan	Treatment of schizophrenia and bipolar I disorder.	-Olanzapine: a generally effective second-generation antipsychotic. -Samidorphan : an antagonist at μ-opioid receptors and a partial agonist at κ- and δ-opioid receptors.
Aducanumab	Alzheimer's disease.	A human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid β.
Ibrexafungerp	Fungal infections.	Inhibition of β-1,3-D glucan synthetase.
Sotorasib	Treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC.	RAS GTPase family inhibitor.
Hetrombopag	Second-line treatment for primary immune thrombocytopenia (ITP) and severe aplastic anaemia (SAA) in adults.	Oral nonpeptide thrombopoietin receptor agonist

New drug approvals

Drugs

Drugs	Indication	Mechanism
Trilaciclib	Decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).	A small-molecule, short-acting, inhibitor of cyclin-dependent kinases (CDK) 4 and 6.
Umbralisib	Adults with relapsed or refractory marginal zo who have received ≥ 1 prior anti-CD20-based relapsed or refractory follicular lymphoma wh ≥ 3 prior lines of systemic therapy.	
Surufatinib	Treatment of solid tumours, including neuroe tumours (NETs).	
Vericiguat	Treatment of chronic heart failure.	
Fosdenopterin	Treatment of molybdenum cofactor deficienc	
Ponesimod	Treatment of multiple sclerosis (MS).	
Melphalan flufenamide	Multiple myeloma (MM) and amyloid light-ch	




NEVER
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