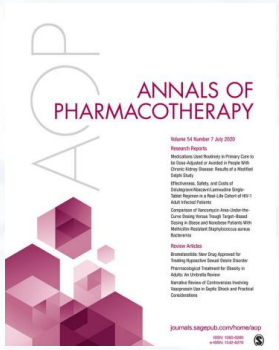
期刊報告



2021.09.23

藥物諮詢組　鄒芸軒藥師

Metronomic capecitabine as adjuvant therapy in locoregionally advanced nasopharyngeal carcinoma: a multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial

Volume 398, Issue 10297, 24–30 July 2021, Pages 303-313

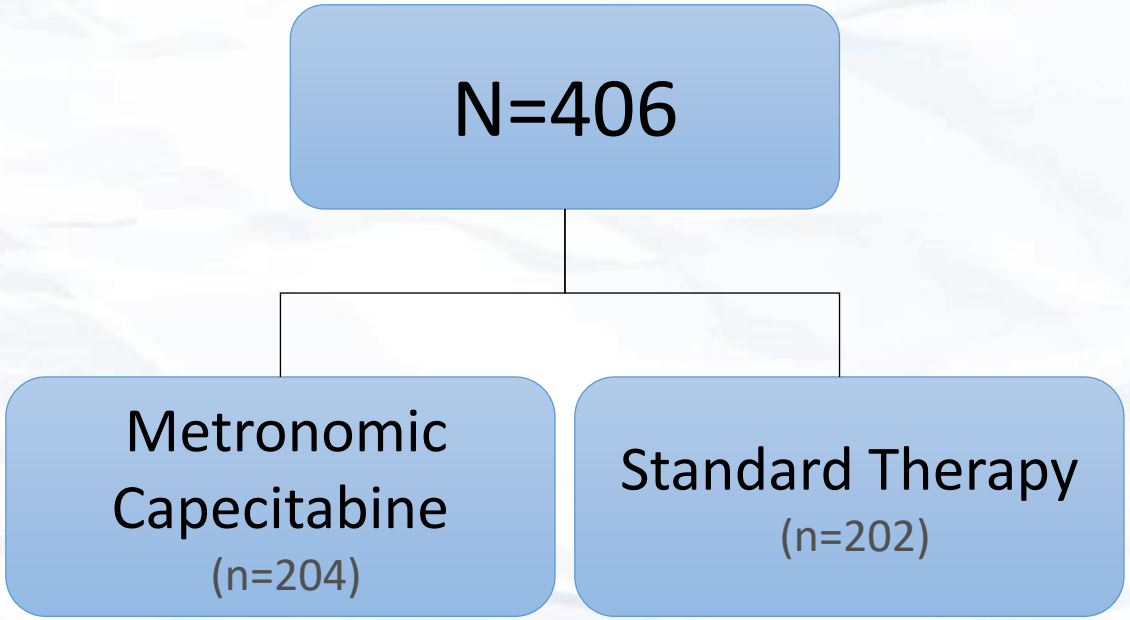
- Design: multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial

Inclusion Criteria

- aged 18–65 years, at 14 hospitals in China
- nasopharyngeal carcinoma stage III–IVA, excluding T3–4N0 and T3N1 disease
- complete the recommended standard of care

Exclusion Criteria

- Did not complete the recommended concurrent chemoradiotherapy or induction chemotherapy
- receiving previous radiotherapy or chemotherapy before
- receiving surgery, biotherapy, or immunotherapy
- a history of cancer
- an illness that would interfere with the ability to take oral medication
- a severe coexisting illness
- being pregnant or lactating



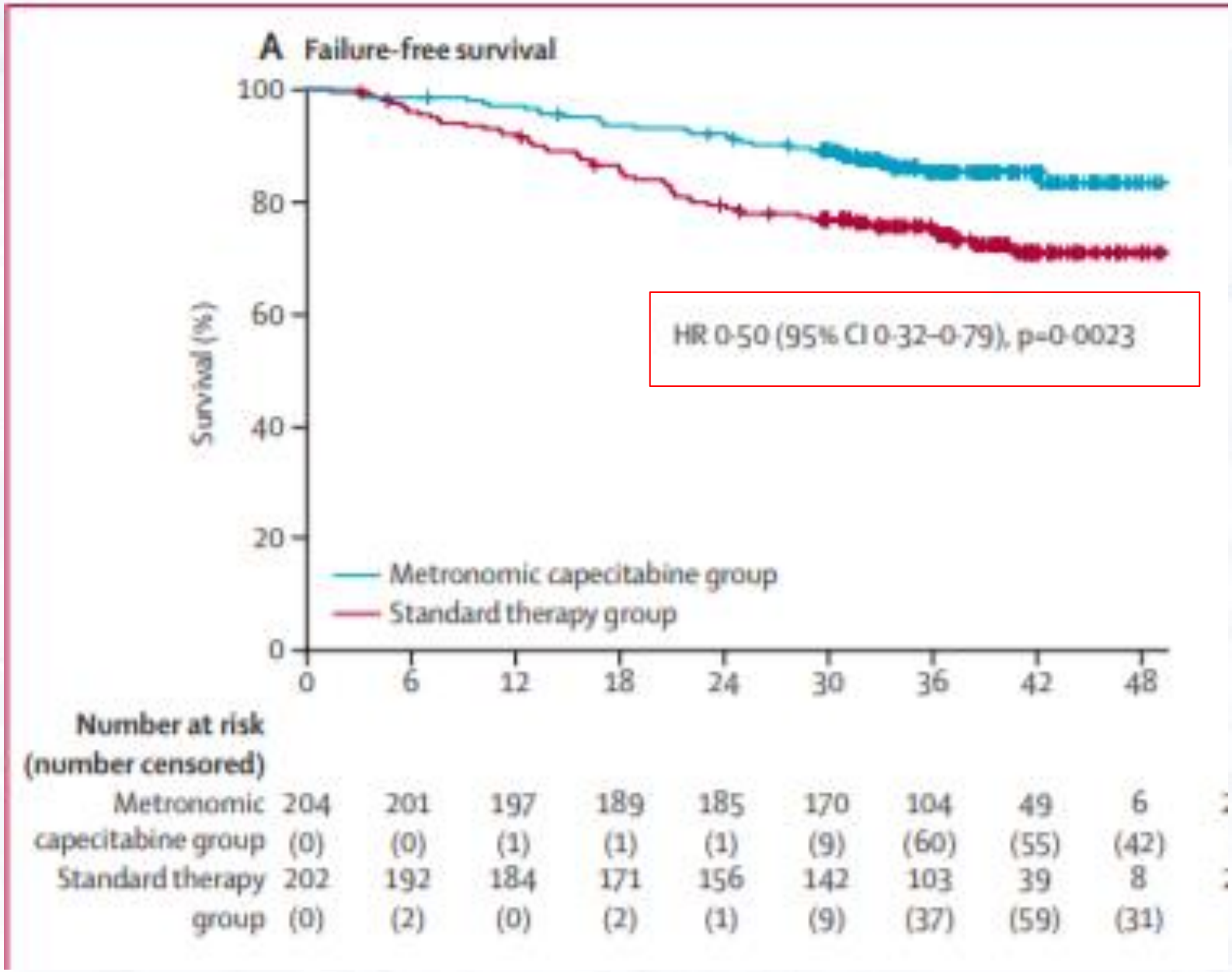
Primary endpoint:
Failure-free survival at 3 years, defined as the time from randomisation to disease recurrence or death due to any cause.

Baseline characteristics

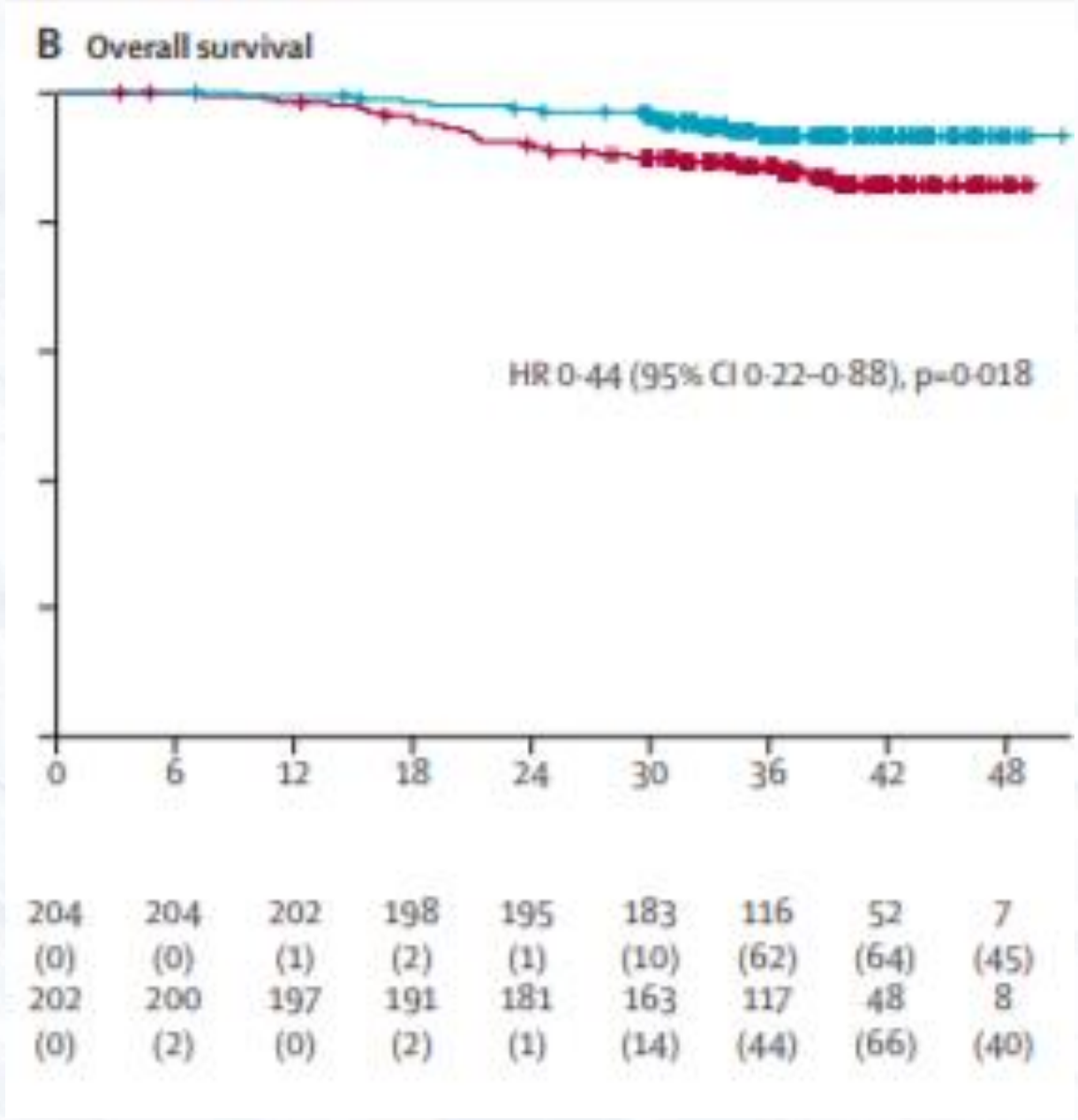
	Metronomic capecitabine group (n=204)	Standard therapy group (n=202)
Age, years		
Median	45 (38–53)	46 (38–53)
Range	22–65	18–65
Sex		
Male	161 (79%)	150 (74%)
Female	43 (21%)	52 (26%)
ECOG performance status*		
0	109 (53%)	115 (57%)
1	95 (47%)	87 (43%)
Tumour category†		
T1	5 (2%)	6 (3%)
T2	27 (13%)	31 (15%)
T3	83 (41%)	77 (38%)
T4	89 (44%)	88 (44%)
Node category†		
N1	39 (19%)	35 (17%)
N2	105 (51%)	113 (56%)
N3	60 (29%)	54 (27%)

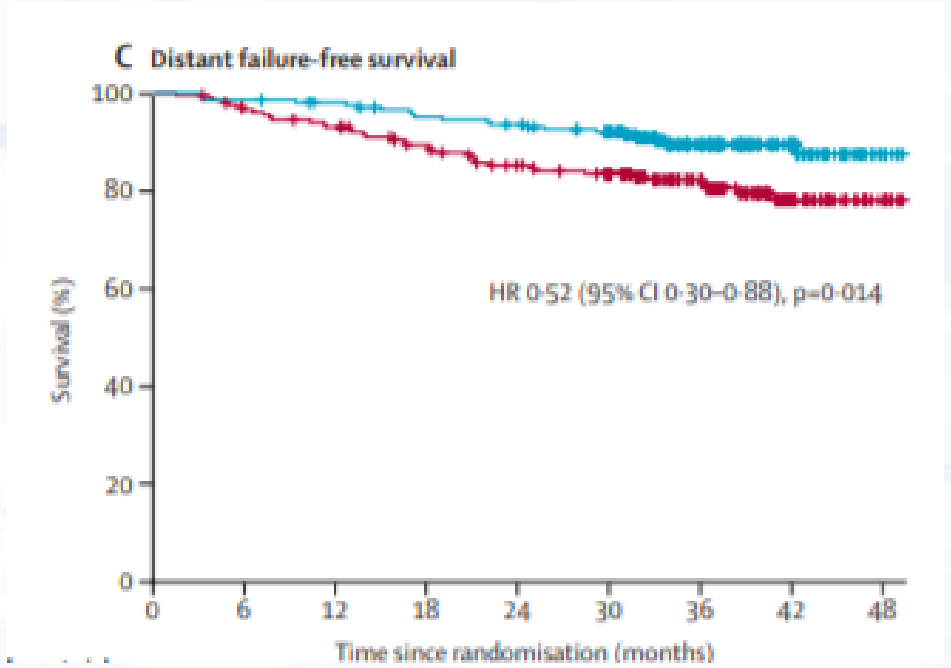
	Metronomic capecitabine group (n=204)	Standard therapy group (n=202)
Disease stage†		
III	69 (34%)	73 (36%)
IVA	135 (66%)	129 (64%)
Induction chemotherapy		
Yes	158 (77%)	158 (78%)
No	46 (23%)	44 (22%)
Induction chemotherapy regimens		
Docetaxel and cisplatin	113/158 (72%)	120/158 (76%)
Docetaxel, cisplatin, and fluorouracil	35/158 (22%)	28/158 (18%)
Gemcitabine and cisplatin	10/158 (6%)	10/158 (6%)
Number of cycles of induction chemotherapy		
2	45/158 (28%)	46/158 (29%)
3	113/158 (72%)	112/158 (71%)
Administration of concurrent cisplatin		
Once every 3 weeks	196 (96%)	193 (96%)
Weekly	8 (4%)	9 (4%)

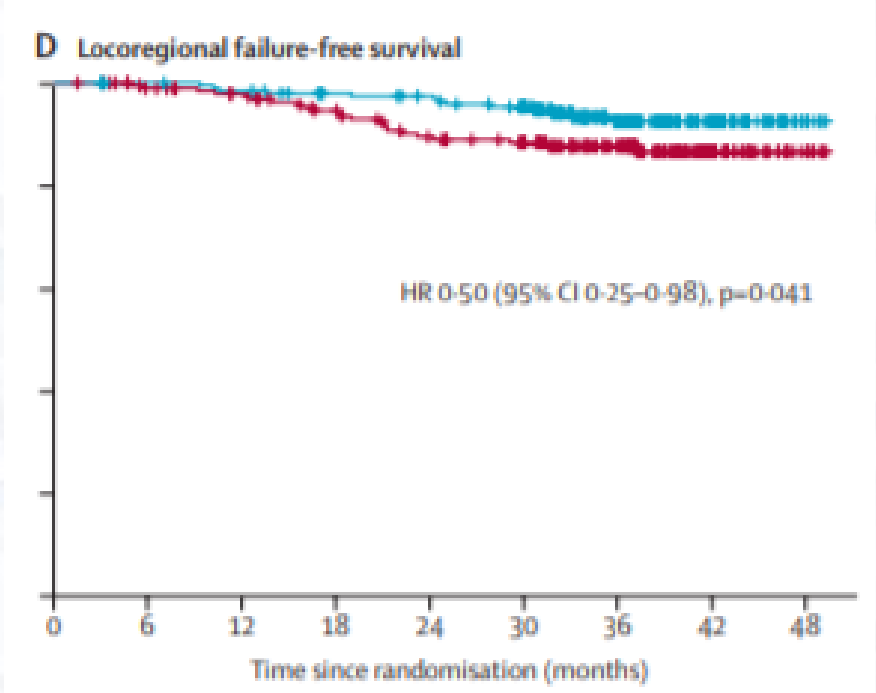
Primary Outcomes

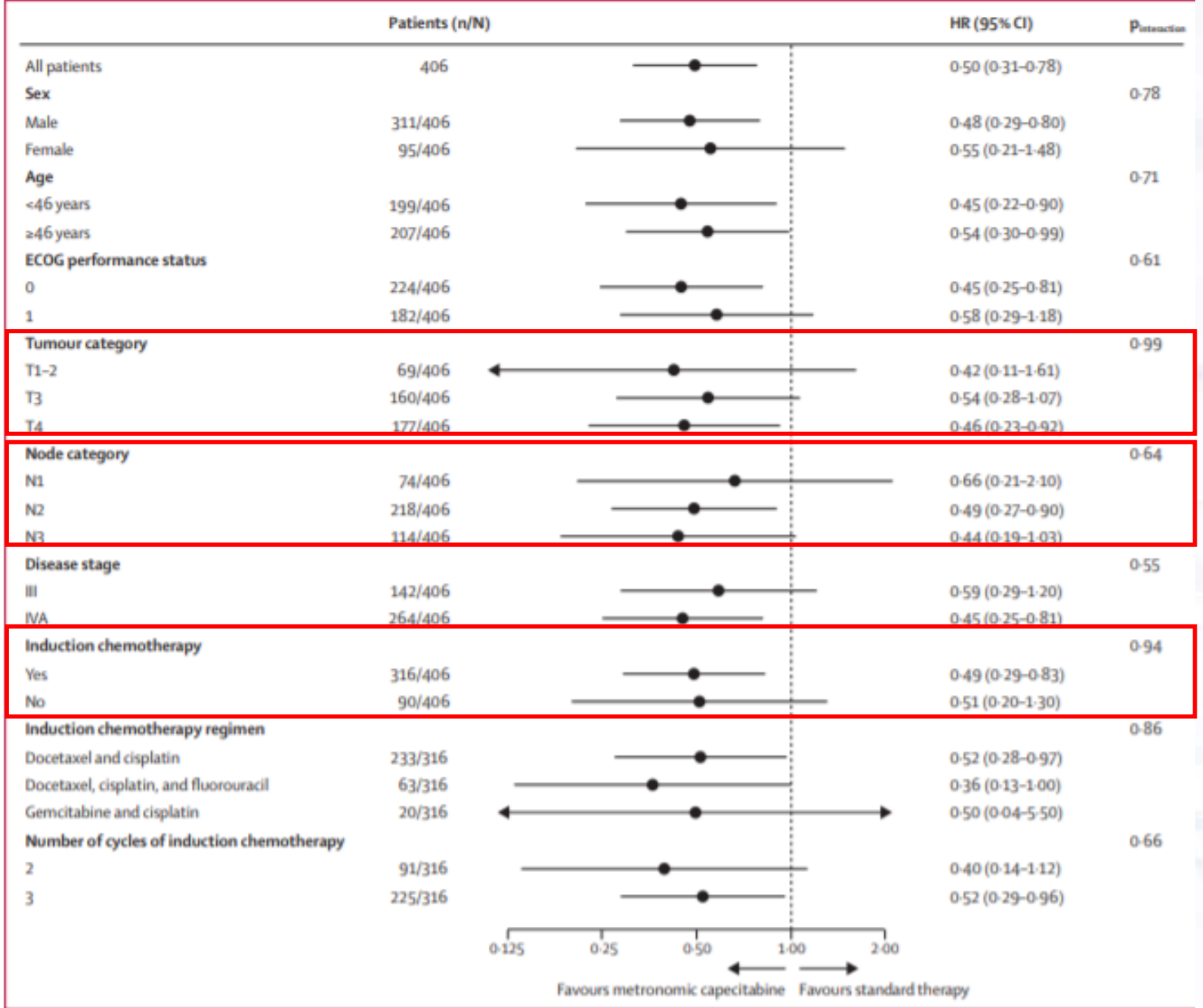


Secondary outcomes








Patients (n/N)
HR (95% CI)
$p_{interaction}$
All patients 406 0·50 (0·31–0·78)
Sex 0·78
Male 311/406 0·48 (0·29–0·80)
Female 95/406 0·55 (0·21–1·48)
Age 0·71
<46 years 199/406 0·45 (0·22–0·90)
≥46 years 207/406 0·54 (0·30–0·99)
ECOG performance status 0·61
0 224/406 0·45 (0·25–0·81)
1 182/406 0·58 (0·29–1·18)
Tumour category 0·99
T1–2 69/406 0·42 (0·11–1·61)
T3 160/406 0·54 (0·28–1·07)
T4 177/406 0·46 (0·23–0·92)
Node category 0·64
N1 74/406 0·66 (0·21–2·10)
N2 218/406 0·49 (0·27–0·90)
N3 114/406 0·44 (0·19–1·03)
Disease stage 0·55
III 142/406 0·59 (0·29–1·20)
IVA 264/406 0·45 (0·25–0·81)
Induction chemotherapy 0·94
Yes 316/406 0·49 (0·29–0·83)
No 90/406 0·51 (0·20–1·30)
Induction chemotherapy regimen 0·86
Docetaxel and cisplatin 233/316 0·52 (0·28–0·97)
Docetaxel, cisplatin, and fluorouracil 63/316 0·36 (0·13–1·00)
Gemcitabine and cisplatin 20/316 0·50 (0·04–5·50)
Number of cycles of induction chemotherapy 0·66
2 91/316 0·40 (0·14–1·12)
3 225/316 0·52 (0·29–0·96)
0·125
0·25
0·50
1·00
2·00
Favours metronomic capecitabine
Favours standard therapy

Safety

	Metronomic capecitabine group (n=201)			Standard therapy group (n=200)		
	Any grade	Grade 1 or 2	Grade 3 or 4	Any grade	Grade 1 or 2	Grade 3 or 4
Any adverse event	182 (91%)	147 (73%)	35 (17%)	112 (56%)	101 (51%)	11 (6%)
Haematological adverse event						
Leukopenia	54 (27%)	48 (24%)	6 (3%)	39 (20%)	33 (17%)	6 (3%)
Neutropenia	37 (18%)	30 (15%)	7 (3%)*	25 (13%)	20 (10%)	5 (3%)
Anaemia	71 (35%)	70 (35%)	1 (<1%)	51 (26%)	49 (25%)	2 (1%)
Thrombocytopenia	24 (12%)	23 (11%)	1 (<1%)	19 (10%)	19 (10%)	0
Non-haematological adverse event						
Hand-foot syndrome	117 (58%)	99 (49%)	18 (9%)	0	0	0
Fatigue	55 (27%)	54 (27%)	1 (<1%)	36 (18%)	36 (18%)	0
Nausea	44 (22%)	42 (21%)	2 (1%)	21 (11%)	21 (11%)	0
Sensory neuropathy	37 (18%)	34 (17%)	3 (1%)	16 (8%)	14 (7%)	2 (1%)
Anorexia	36 (18%)	36 (18%)	0	18 (9%)	18 (9%)	0
Weight loss	27 (13%)	30 (15%)	0	13 (7%)	13 (7%)	0
Vomiting	26 (13%)	25 (12%)	1 (<1%)	14 (7%)	14 (7%)	0
Elevated ALT or AST concentrations	23 (11%)	23 (11%)	0	15 (8%)	15 (8%)	0
Mucositis or stomatitis	21 (10%)	20 (10%)	1 (<1%)	9 (5%)	9 (5%)	0
Diarrhoea	19 (9%)	18 (9%)	1 (<1%)	4 (2%)	4 (2%)	0

Data are treatment-related adverse events reported in at least 10% of patients, or grade 3 or higher treatment-related adverse events in the metronomic capecitabine group, according to the maximum Common Terminology Criteria for Adverse Events grade. The safety analysis population included all patients who had started the treatment that they had been randomly assigned. Some patients had more than one adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Grade 4 neutropenia occurred in one (<1%) patient in the metronomic capecitabine group. No other grade 4 or 5 adverse events were reported.

Table 2: **Adverse events in the safety analysis population**

Conclusion

- addition of metronomic capecitabine significantly improved failure-free survival in patients with high-risk locoregionally advanced nasopharyngeal carcinoma

limitation

- open-label
- The study was done in an endemic region (China)
- Different induction chemotherapy regimens and cycles

Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

Volume 398, Issue 10302, 28 August–3 September 2021, Pages 759-771

1.14 子宮內膜癌

與lenvatinib併用適用於曾經接受過全身性治療後疾病惡化，且不適合根治手術或放射治療的不具有高微衛星不穩定性(microsatellite instability-high, MSI-H)或錯誤配對修復功能不足(mismatch repair deficient, dMMR)之晚期子宮內膜癌病人。

此適應症係依據腫瘤整體反應率及反應持續時間加速核准*[參見臨床研究(12.14)]*，此適應症仍須執行確認性試驗以證明其臨床效益。

1.15 食道癌

與含鉑及fluoropyrimidine之化學療法併用，做為局部晚期無法切除或轉移性食道癌或胃食道接合部癌病人的第一線治療藥物。

治療患有復發性局部晚期或轉移性食道鱗狀細胞癌，經確效之試驗檢測出腫瘤有PD-L1表現(綜合陽性分數[CPS]≥10)，且先前曾接受一種(含)以上全身性治療，於治療時或治療後發生疾病惡化的病人。

1.16 三陰性乳癌(Triple Negative Breast Cancer)

與化學療法併用，治療局部復發性無法切除或轉移性之三陰性乳癌(TNBC)，且經確效之試驗檢測出腫瘤有PD-L1表現(綜合陽性分數[CPS]≥10)病人*[參見用法用量(2.1)]*。

此適應症係依據無惡化存活期結果(Progression-free survival)加速核准*[參見臨床研究(12.16)]*，此適應症仍須執行確認性試驗以證明其臨床效益。

1.17 高腫瘤突變負荷量(Tumor Mutational Burden-High; TMB-H)癌症

治療患有無法切除或轉移性、經確效之試驗檢測出高腫瘤突變負荷量(TMB H) [≥10 mutations/megabase (mut/Mb)]、於先前治療後出現惡化現象且無任何其他適當替代治療選擇之實體腫瘤的成人病人。

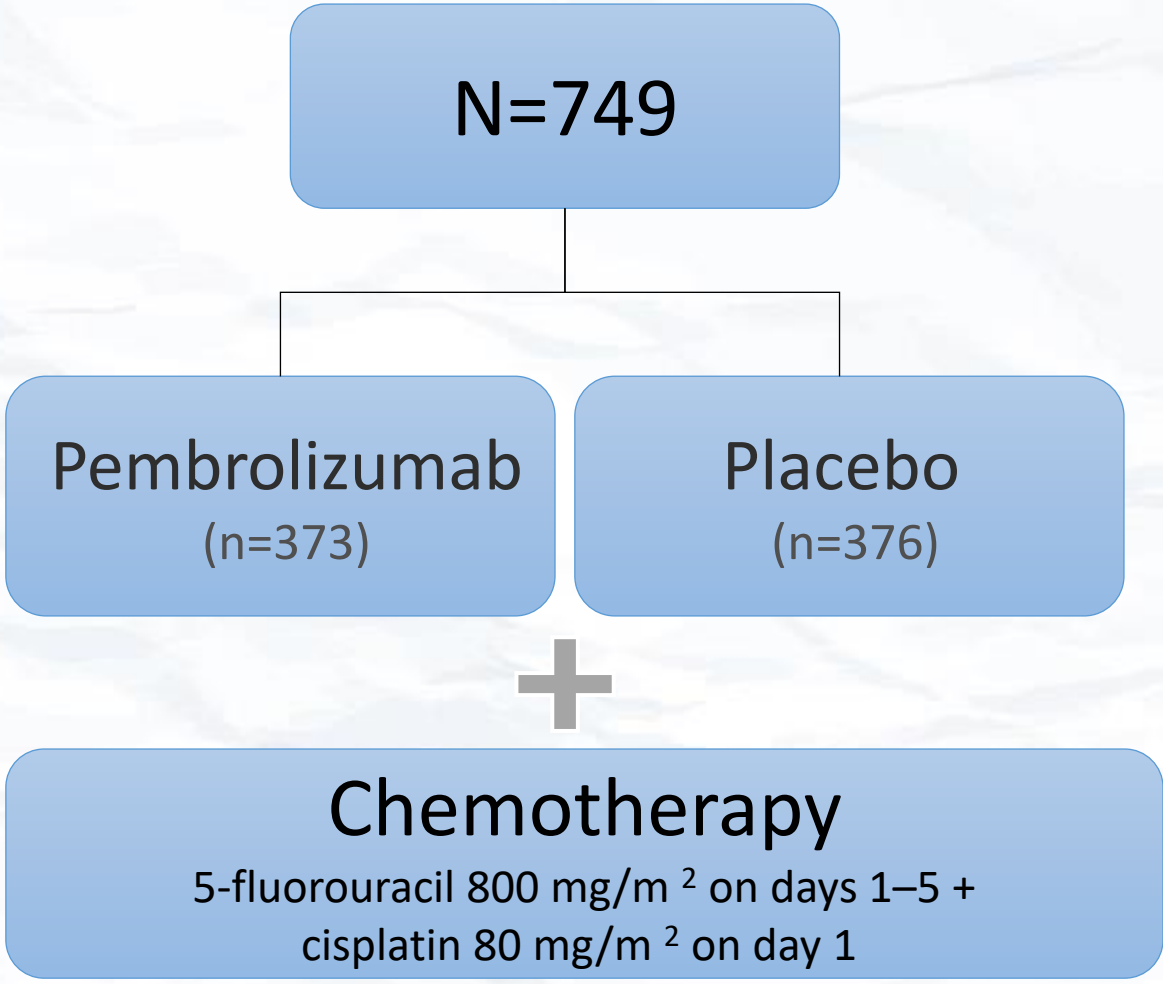
此適應症係依據腫瘤整體反應率及反應持續時間加速核准[參見*臨床研究(12.17)*]，此適應症仍須執行確認性試驗以證明其臨床效益。

Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

Volume 398, Issue 10302, 28 August–3 September 2021, Pages 759-771

- Design: randomised, placebo-controlled, double-blind, phase 3 study

Inclusion Criteria
• July 25, 2017-June 3, 2019 in 26 countries • Adult (≥18 y/o) patients with previously untreated, locally advanced, unresectable or metastatic oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer
Exclusion Criteria
• resectable or potentially curable with radiation therapy • previous therapy • EGFR(+) • CNS metastases or carcinomatous meningitis or both • autoimmune disease that had required systemic treatment

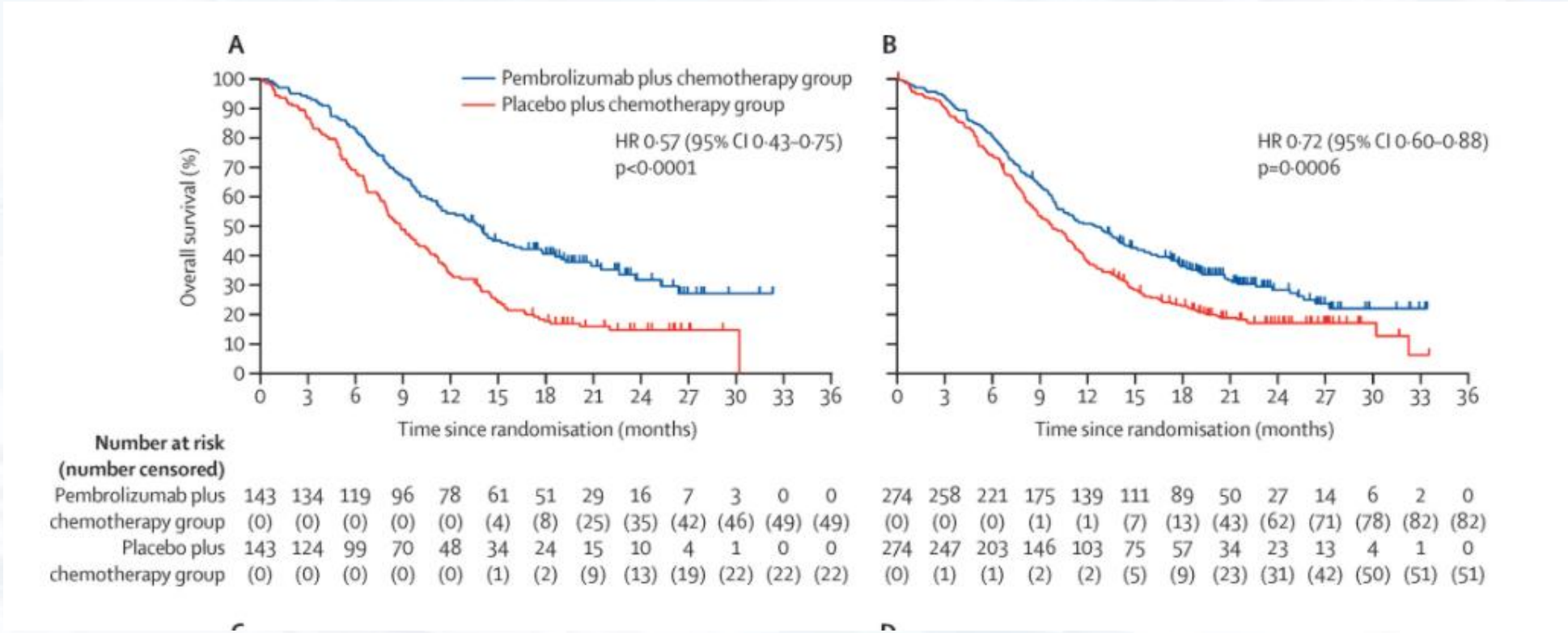


Baseline characteristics

	Pembrolizumab plus chemotherapy group (n=373)	Placebo plus chemotherapy group (n=376)
Age, years		
Median (range)	64 (28–94)	62 (27–89)
≥65	172 (46%)	150 (40%)
Sex		
Female	67 (18%)	57 (15%)
Male	306 (82%)	319 (85%)
Asia region*	196 (53%)	197 (52%)
Race		
Asian	201 (54%)	199 (53%)
White	139 (37%)	139 (37%)
Missing	14 (4%)	15 (4%)
Native American	9 (2%)	12 (3%)
African American	5 (1%)	2 (1%)
Other†	5 (1%)	9 (2%)
ECOG performance status		
0	149 (40%)	150 (40%)
1	223 (60%)	225 (60%)
2	1 (<1%)	1 (<1%)

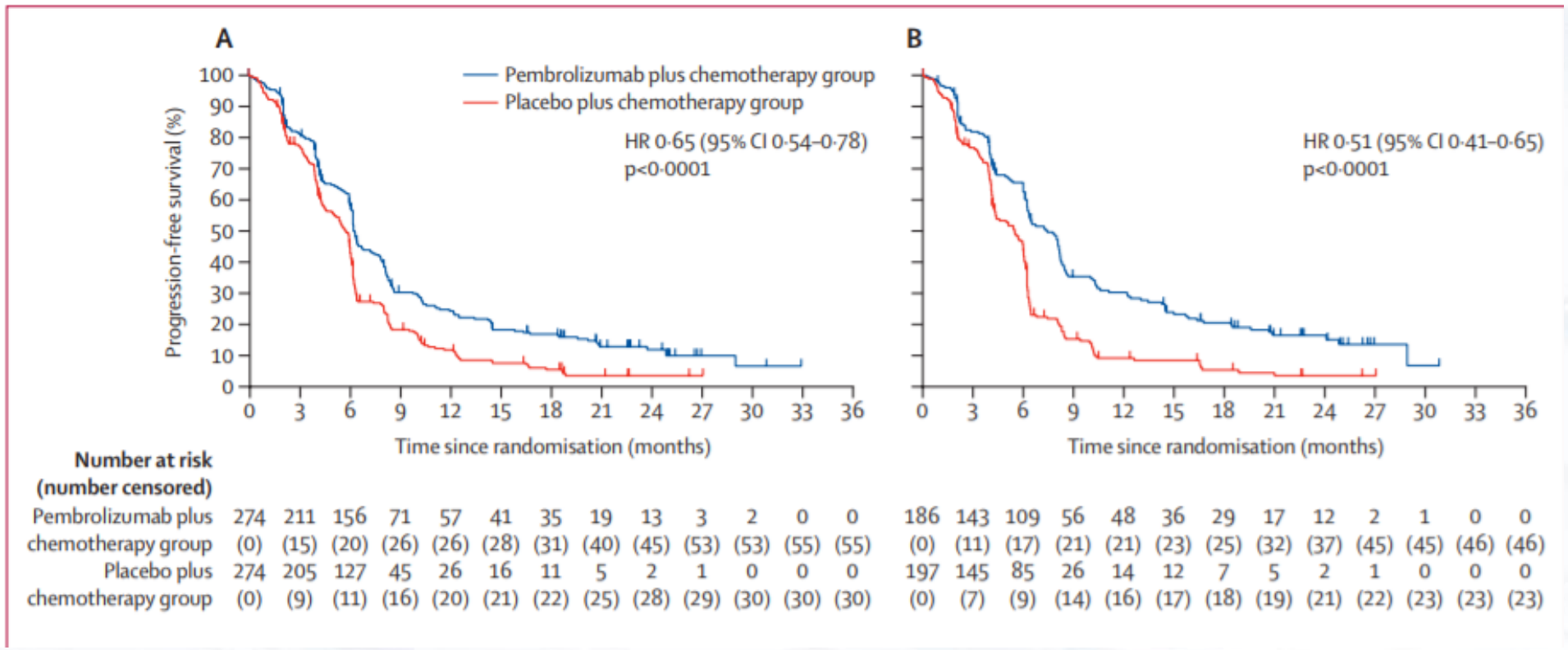
	Pembrolizumab plus chemotherapy group (n=373)	Placebo plus chemotherapy group (n=376)
Oesophageal squamous cell carcinoma	274 (73%)	274 (73%)
Adenocarcinoma	99 (27%)	102 (27%)
Oesophageal adenocarcinoma	58 (16%)	52 (14%)
Siewert type 1 gastro-oesophageal junction adenocarcinoma‡	41 (11%)	50 (13%)
Disease status		
Metastatic	344 (92%)	339 (90%)
Unresectable locally advanced	29 (8%)	37 (10%)
PD-L1 CPS ≥10	186 (50%)	197 (52%)
Oesophageal squamous cell carcinoma	143 (38%)	143 (38%)
Adenocarcinoma	43 (12%)	54 (14%)
PD-L1 CPS <10	175 (47%)	172 (46%)
Oesophageal squamous cell carcinoma	121 (32%)	126 (34%)
Adenocarcinoma	54 (14%)	46 (12%)
PD-L1 status not evaluable or missing	12 (3%)	7 (2%)

Results-Overall survival



	Pembrolizumab	**P**lacebo	**HR**
oesophageal squamous cell carcinoma, PD-L1 CPS ≥10	13.9 months	8.8 months	0.57
oesophageal squamous cell carcinoma	12.9 months	9.8 months	0.72

Results-Progression-free survival



	Pembrolizumab	Placebo	HR
oesophageal squamous cell carcinoma	6.3 months	5.8 months	0.65
PD-L1 CPS of 10 or more	7.5 months	5.5 months	0.51

Safety

	Pembrolizumab plus chemotherapy group (n=370)		Placebo plus chemotherapy group (n=370)	
	Any	Grade ≥3	Any	Grade ≥3
Any adverse event	370 (100%)	318 (86%)	368 (99%)	308 (83%)
Treatment-related adverse events*				
Nausea	233 (63%)	26 (7%)	220 (59%)	24 (6%)
Decreased appetite	145 (39%)	13 (4%)	119 (32%)	16 (4%)
Anaemia	143 (39%)	46 (12%)	162 (44%)	54 (15%)
Fatigue	135 (36%)	23 (6%)	107 (29%)	20 (5%)
Decreased neutrophil count	135 (36%)	84 (23%)	109 (29%)	62 (17%)
Vomiting	116 (30%)	23 (6%)	99 (27%)	18 (5%)
Diarrhoea	97 (26%)	12 (3%)	85 (23%)	7 (2%)
Neutropenia	96 (26%)	53 (14%)	88 (24%)	60 (16%)
Stomatitis	96 (26%)	21 (6%)	93 (25%)	14 (4%)
Decreased white blood cells	89 (24%)	32 (9%)	69 (19%)	18 (5%)
Increased blood creatinine	67 (18%)	5 (1%)	70 (19%)	1 (<1%)
Decreased platelet count	61 (16%)	7 (2%)	56 (15%)	17 (5%)
Mucosal inflammation	59 (16%)	12 (3%)	65 (18%)	13 (4%)
Leukopenia	24 (6%)	6 (2%)	28 (8%)	11 (3%)
Thrombocytopenia	25 (7%)	5 (1%)	33 (9%)	10 (3%)
Tinnitus	33 (9%)	2 (1%)	25 (7%)	0
Hyperthyroidism	19 (5%)	0	2 (1%)	0
Hypothyroidism	38 (10%)	0	22 (6%)	0
Constipation	50 (14%)	0	63 (17%)	0
Asthenia	45 (12%)	12 (3%)	35 (9%)	4 (1%)
Malaise	43 (12%)	2 (1%)	39 (11%)	4 (1%)
Increased aspartate aminotransferase	18 (5%)	3 (1%)	19 (5%)	2 (1%)
Decreased lymphocyte count	21 (6%)	7 (2%)	20 (5%)	5 (1%)
Decreased weight	43 (12%)	4 (1%)	47 (13%)	8 (2%)
Dehydration	20 (5%)	8 (2%)	16 (4%)	8 (2%)
Hypokalaemia	34 (9%)	17 (5%)	41 (11%)	19 (5%)
Hypomagnesaemia	21 (6%)	2 (1%)	14 (4%)	3 (1%)
Hyponatraemia	32 (9%)	20 (5%)	40 (11%)	20 (5%)
Dysgeusia	34 (9%)	0	32 (9%)	0
Peripheral neuropathy	32 (9%)	1 (<1%)	32 (9%)	0
Peripheral sensory neuropathy	34 (9%)	1 (<1%)	29 (8%)	1 (<1%)
Hiccups	40 (11%)	0	33 (9%)	0
Pneumonitis	20 (5%)	7 (2%)	0	0
Alopecia	51 (14%)	0	39 (11%)	0
Pruritus	23 (6%)	1 (<1%)	8 (2%)	0
Rash	29 (8%)	0	18 (5%)	1 (<1%)

(Table 2 continues on next page)

	Pembrolizumab plus chemotherapy group (n=370)		Placebo plus chemotherapy group (n=370)	
	Any	Grade ≥3	Any	Grade ≥3
(Continued from previous page)				
Adverse events of special interest†				
Hypothyroidism	40 (11%)	0	24 (6%)	0
Pneumonitis	23 (6%)	2 (1%)	2 (1%)	1 (<1%)
Hyperthyroidism	21 (6%)	1 (<1%)	3 (1%)	0
Colitis	8 (2%)	4 (1%)	6 (2%)	3 (1%)
Infusion reactions	6 (2%)	1 (<1%)	4 (1%)	0
Hepatitis	5 (1%)	5 (1%)	0	0
Adrenal insufficiency	4 (1%)	2 (1%)	2 (1%)	0
Severe skin reactions	4 (1%)	4 (1%)	2 (1%)	2 (1%)
Hypophysitis	3 (1%)	1 (<1%)	0	0
Pancreatitis	2 (1%)	0	1 (<1%)	1 (<1%)
Myositis	1 (<1%)	1 (<1%)	0	0
Nephritis	1 (<1%)	0	2 (1%)	1 (<1%)
Thyroiditis	1 (<1%)	0	0	0
Type 1 diabetes	1 (<1%)	1 (<1%)	0	0

Conclusion

- Compared with placebo, pembrolizumab plus chemotherapy significantly improved overall survival and progression-free survival
- Pembrolizumab plus chemotherapy should be considered for patients with unresectable, metastatic oesophageal cancer in the first-line setting

limitation

- Include both adenocarcinoma and squamous cell carcinoma histologies, responses might differ between these groups
- Not stratify based on PD-L1 status

Evaluating Sacubitril/Valsartan Dose Dependence on Clinical Outcomes in Patients With Heart Failure With Reduced Ejection Fraction

Annals of Pharmacotherapy 2021, Vol. 55(9) 1069–1075

- Design: retros

Inclusion Criteria
• Adult (≥18 y/ • Diagnosed wi 40%) and rec • July 2015 to D
Exclusion Criteria
• Receive sacul • Undergoing c
Coprimary outcc
• all-cause mor • 3.5 years follc

1 適應症及用法

1.1 心臟衰竭

ENTRESTO® 核准用於治療慢性心臟衰竭 (紐約心臟學會 [NYHA] 第二級至第四級) 且心室射出分率降低的患者，減少心血管死亡和心臟衰竭住院風險。

說明 : ENTRESTO® 可以和其他心臟衰竭療法併用，用於取代血管收縮素轉化酶抑制劑 (ACEI) 或血管收縮素受體阻斷劑 (ARB)。

2 用法用量

2.1 劑量

ENTRESTO® 禁止與 ACEI 併用。如欲從原本使用的 ACEI 轉換為 ENTRESTO®，兩種藥物之間須間隔 36 小時的藥物排除期 (washout period) [參閱禁忌症 (4) 及藥物交互作用 (7.1)]。

ENTRESTO® 的建議起始劑量為每日兩次 100 毫克。

依據患者耐受情況於 2 至 4 週後加倍 ENTRESTO® 劑量，達到每日兩次 200 毫克的目標維持劑量。

2.2 未服用 ACEI 或 ARB，或之前使用低劑量前述藥物患者之劑量調整

目前未服用 ACEI 或 ARB 的患者，或是之前使用低劑量前述藥物的患者，建議之起始劑量為每日兩次 50 毫克。依據患者耐受情況，每 2 至 4 週加倍 ENTRESTO® 劑量，達到每日兩次 200 毫克的目標維持劑量。

2.3 重度腎功能不全患者之劑量調整

重度腎功能不全 (eGFR < 30 mL/min/1.73 m^2) 患者之建議起始劑量，為每日兩次 50 毫克。依據患者耐受情況，每 2 至 4 週加倍 ENTRESTO® 劑量，達到每日兩次 200 毫克的目標維持劑量。

輕度或中度腎功能不全患者，不需要調整起始劑量。

2.4 肝功能不全患者之劑量調整

中度肝功能不全 (Child-Pugh B 級) 患者之建議起始劑量，為每日兩次 50 毫克。依據患者耐受情況，每 2 至 4 週加倍 ENTRESTO® 劑量，達到每日兩次 200 毫克的目標維持劑量。

輕度肝功能不全患者，不需要調整起始劑量。

不建議重度肝功能不全患者使用此藥物。

97/103
(n=205)

97/103
(n=179)

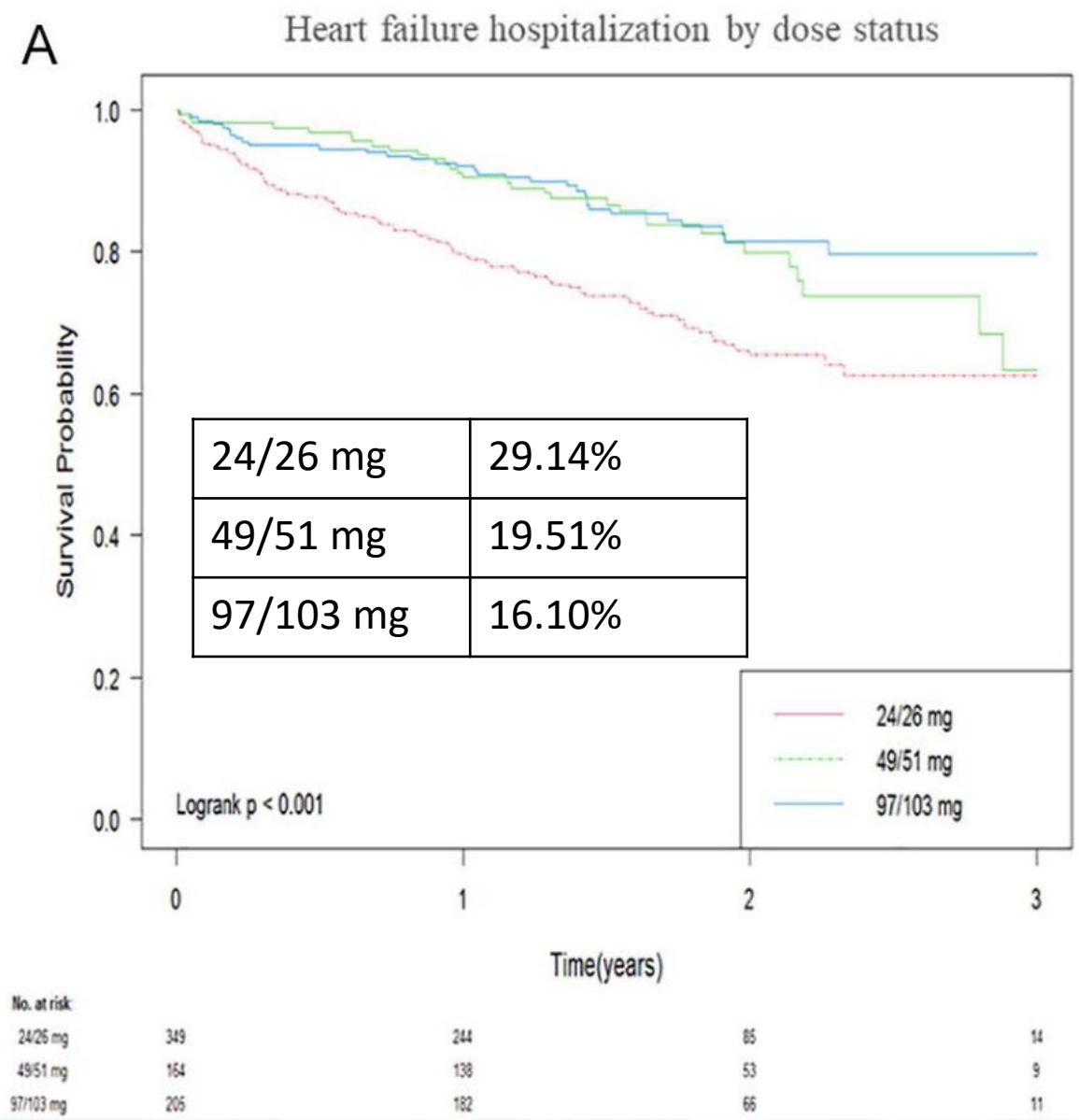
Baseline characteristics

Table 1. Baseline Characteristics in Unmatched and Propensity Score–Matched Groups.

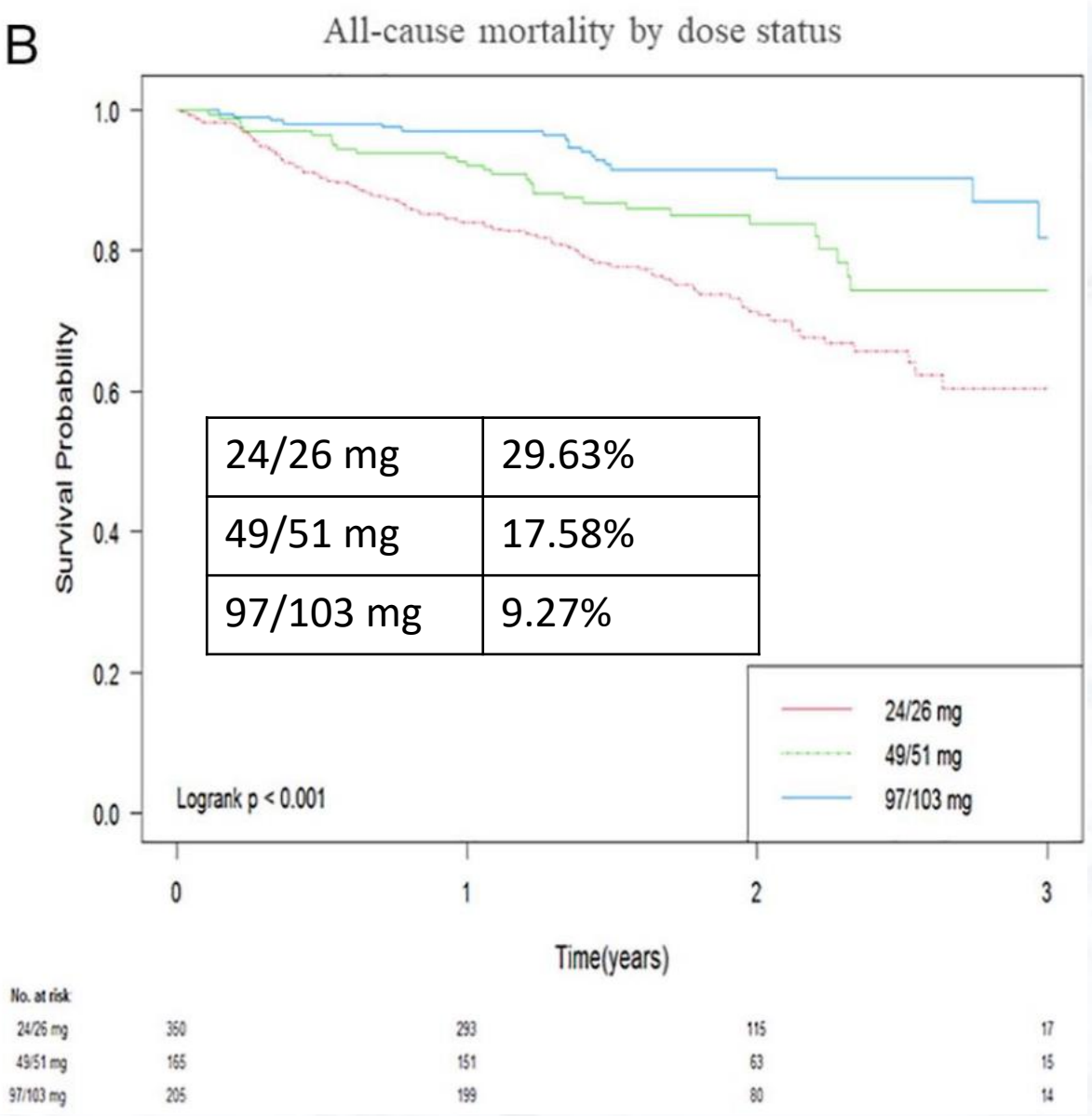
	Unmatched groups				Propensity score–matched groups			
	24/26 mg (n = 351)	49/51 mg (n = 165)	97/103 mg (n = 205)	*P* value	24/26 mg (n = 326)	49/51 mg (n = 147)	97/103 mg (n = 182)	*P* value
Age (years)	68.02 ± 12.16	64.40 ± 12.54	61.11 ± 12.57	<0.001	66.16 ± 12.34	64.83 ± 12.32	63.60 ± 12.29	0.229
Male sex (%)	66.7	72.7	70.7	0.325	68.1	72.8	72.9	0.258
Ethnicity (%)				0.859				
White	96.6	95.2	95.1					
Black	2.0	3.0	2.9					
Hispanic	0.6	0.0	0.5					
Unknown	0.9	1.8	1.5					
HTN (%)	84.0	81.8	77.6	0.162	83.4	79.8	79.4	0.261
DM (%)	53.6	50.9	47.3	0.363	52.1	49.9	48.5	0.438
SBP, mm Hg	117.63 ± 18.56	125.28 ± 18.83	123.55 ± 19.74	<0.001	120.06 ± 18.91	122.01 ± 18.13	122.16 ± 18.80	0.496
BMI (kg/m^2)				<0.001				0.189
≤24.9	21.4%	17.0%	13.7%		19.8%	20.0%	15.2%	
25-29.9	28.8%	34.5%	21.0%		27.9%	31.5%	26.0%	
≥30.0	49.9%	48.5%	65.4%		52.6%	48.5%	58.8%	
Creatinine, mg/dL	1.22 ± 0.44	1.24 ± 0.52	1.12 ± 0.36	0.014	1.20 ± 0.42	1.20 ± 0.47	1.17 ± 0.39	0.728
Potassium (mEq/L)	4.38 ± 0.73	4.34 ± 0.49	4.24 ± 0.53	0.457				
BNP, pg/mL	2144.70 ± 5208.46	1463.98 ± 2323.71	1072.34 ± 1781.50	0.012	1793.82 ± 4402.81	1523.73 ± 2449.53	1197.34 ± 1792.54	0.262
Ejection fraction (%)	26.42 ± 8.89	26.80 ± 8.29	25.53 ± 8.29	0.326	26.21 ± 8.65	26.51 ± 8.54	25.68 ± 8.45	0.700
BB (%)	91.1	88.2	86.1	0.326	93.9	94.2	92.7	0.481
Prior ACE inhibitor/ ARB (%)	65.1	76.5	73.0	0.072	79.2	85.6	83.9	0.210
MRA (%)	66.0	65.0	68.0	0.632	66.8	59.9	68.6	0.438
Loop use (%)	79.1	70.6	63.5	0.004	84.4	85.3	80.8	0.418
Digoxin (%)	15.3	15.7	14.6	0.971				

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β-blocker; BMI, body mass index; BNP, B-type natriuretic peptide; DM, diabetes mellitus; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure.

Results



24/26 mg	29.14%
49/51 mg	19.51%
97/103 mg	16.10%



24/26 mg	29.63%
49/51 mg	17.58%
97/103 mg	9.27%

Results

Table 2. Hospitalization and Mortality Before and After Propensity Matching by Sacubitril/Valsartan Dose Status.

Prematch	Sacubitril/valsartan	Hazard ratio	95% CI	*P* value
Heart failure hospitalization	24/26 vs 97/103	2.167	1.46-3.21	<0.001
	49/51 vs 97/103	1.227	0.75-2.00	0.410
	24/26 vs 49/51	1.766	1.19-2.63	0.005
All-cause mortality	24/26 vs 97/103	3.671	2.25-5.99	<0.001
	49/51 vs 97/103	1.887	1.06-3.37	0.032
	24/26 vs 49/51	1.945	1.29-2.94	0.002
Postmatch	**Sacubitril/valsartan**	**Hazard ratio**	**95% CI**	***P* value**
Heart failure hospitalization	24/26 vs 97/103	1.79	1.18-2.73	0.006
	49/51 vs 97/103	1.15	0.70-1.89	0.588
	24/26 vs 49/51	1.56	1.04-2.34	0.031
All-cause mortality	24/26 vs 97/103	2.56	1.54-4.24	<0.001
	49/51 vs 97/103	1.54	0.84-2.82	0.166
	24/26 vs 49/51	1.67	1.07-2.59	0.024

Conclusion

- 49/51- or 97/103-mg dose is associated with a lower HF hospitalization or mortality rate compared with the 24/26-mg dose group.
- No significant difference in the HF hospitalization or mortality rates between the 49/51- and 97/103-mg groups.

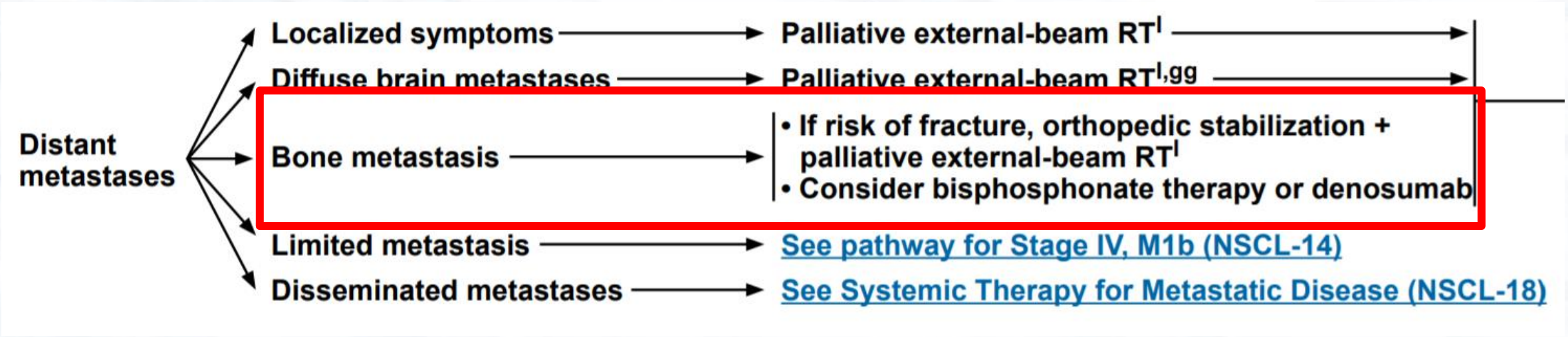
limitation

- retrospective study
- 3 dose groups based on the most frequent dose during the follow-up period
- some clinical data were limited by availability
- authors did not calculate a sample size between each dose group
- patients in the lower-dose group were numerically older

Impact of Extended-Interval Versus Standard Dosing of Zoledronic Acid on Skeletal Events in Non–Small-Cell Lung Cancer and Small-Cell Lung Cancer Patients With Bone Metastases

Annals of Pharmacotherapy 2021, Vol. 55(6) 697–704

- 目的：To determine whether the rate of SRE at 1 year in lung cancer patients with bone metastases receiving zoledronic acid Q12wk is similar to Q4wk dosing.



Impact of Extended-Interval Versus Standard Dosing of Zoledronic Acid on Skeletal Events in Non–Small-Cell Lung Cancer and Small-Cell Lung Cancer Patients With Bone Metastases

Annals of Pharmacotherapy 2021, Vol. 55(6) 697–704

- Design: single-center, retrospective cohort analysis

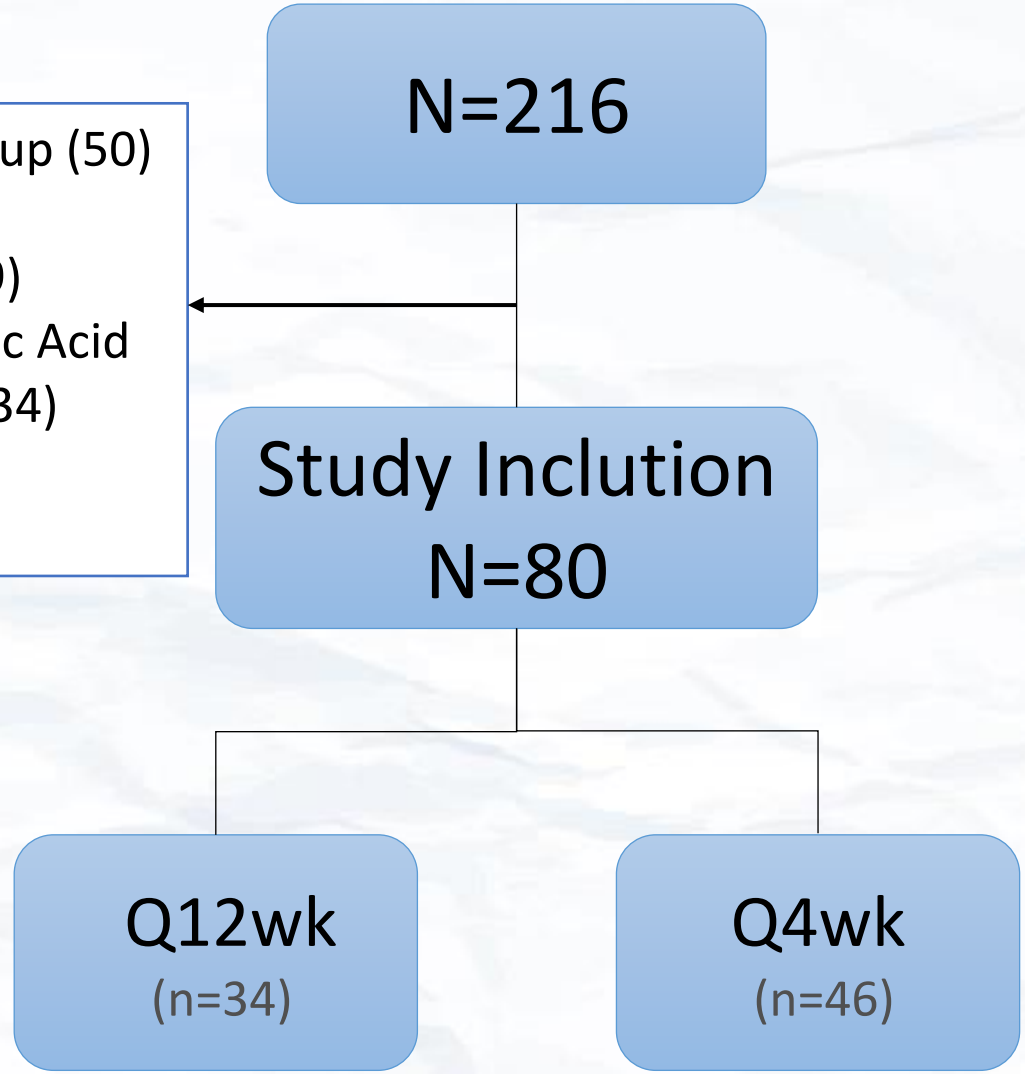
Inclusion Criteria

- Adult (≥18 y/o)
- metastatic NSCLC or SCLC with at least 1 bone metastasis
- received at least 2 doses zoledronic acid for the prevention of SREs
- January 1, 2012, and December 31, 2018

Exclusion Criteria

- incomplete medical records
- received prior IV bisphosphonates or denosumab

- Incomplete fullow-up (50)
- Received 1 dose of Zoledronic Acid (39)
- Received Zoledronic Acid of hypercalcemia (34)
- Prior bisphosphate therapy (13)



Baseline characteristics

NSCLC: n = 77, 96.3%

- bone metastases (*P* = 0.944)
- history of SRE (*P* = 0.555)
- history of oral bisphosphonate (*P* = 0.388)
- concomitant calcium (*P* = 0.159)
- vitamin D (*P* = 0.921)

- the Q12wk cohort were more treated with an EGFR inhibitor
- the Q4wk cohort were more likely to have received traditional chemotherapy

Table 1. Demographic, Baseline Disease, and Clinical Characteristics.

Baseline characteristic	Every 12 week (n = 34)	Every 4 week (n = 46)	*P* value
Age, mean (SD), years	64.2 (9.5)	62.2 (11.0)	0.387
Sex, n (%), male	15 (44.1)	18 (39.1)	0.654
Race, n (%)			
White	31 (91.2)	42 (91.3)	1.00
Asian	3 (8.8)	2 (4.3)	0.646
Black	0 (0)	2 (4.3)	0.505
BSA, mean (SD), m^2	1.82 (0.23)	1.79 (0.26)	0.560
Diagnosis, n (%)			
NSCLC	33 (97.1)	44 (95.7)	1.00
AC	29 (85.3)	41 (89.1)	0.736
SCC	4 (11.8)	3 (6.5)	0.451
SCLC	1 (2.9)	2 (4.3)	0.451
Molecular mutations, n (%)			
EGFR	14 (41.2)	5 (10.9)	0.002
ALK	2 (5.9)	1 (2.2)	0.572
PD-L1 ≥ 50%	4 (11.8)	2 (4.3)	0.393
ROS1	1 (2.9)	0 (0)	0.425
KRAS	2 (5.9)	1 (2.2)	0.572
BRAF	1 (2.9)	1 (2.2)	1.00
Median SCr (range), mg/dL	0.75 (0.5-1.32)	0.75 (0.37-1.85)	0.323
Median number of bone metastases (range)	2 (1-8)	2 (1-10)	0.944
Prior SRE, n (%)	20 (58.8)	24 (52.2)	0.555
Prior bisphosphonate use, n (%)	1 (2.9)	4 (8.7)	0.388
Alendronate	0 (0)	3 (6.5)	0.258
Ibandronate	1 (2.9)	1 (2.2)	1.00
Concomitant calcium use, n (%)	6 (17.6)	3 (6.5)	0.159
Calcium carbonate	5 (14.7)	3 (6.5)	0.275
Calcium citrate	1 (2.9)	0 (0)	0.425
Concomitant vitamin D use, n (%)	10 (29.4)	14 (30.4)	0.921
Cholecalciferol	10 (29.4)	13 (28.3)	0.910
Ergocalciferol	0 (0)	1 (2.2)	1.00
Concomitant corticosteroid use, n (%)	16 (47.1)	26 (56.5)	0.402
Median weekly prednisone dose (range), mg	120 (35-462)	184.8 (46.2-554.5)	0.146
Median duration of treatment (range), months	2.8 (1-12)	1.5 (0-9)	0.06
Antineoplastic therapy received, n (%)			
Chemotherapy	17 (50)	37 (80.4)	0.004
Immunotherapy	9 (26.5)	12 (26.1)	0.969
EGFR inhibitor	13 (38.2)	8 (17.4)	0.036
ALK inhibitor	3 (8.8)	3 (6.5)	0.695
Bevacizumab	0 (0)	7 (15.2)	0.019
Bortezomib	0 (0)	1 (2.2)	1.00

Outcomes

Primary Outcome

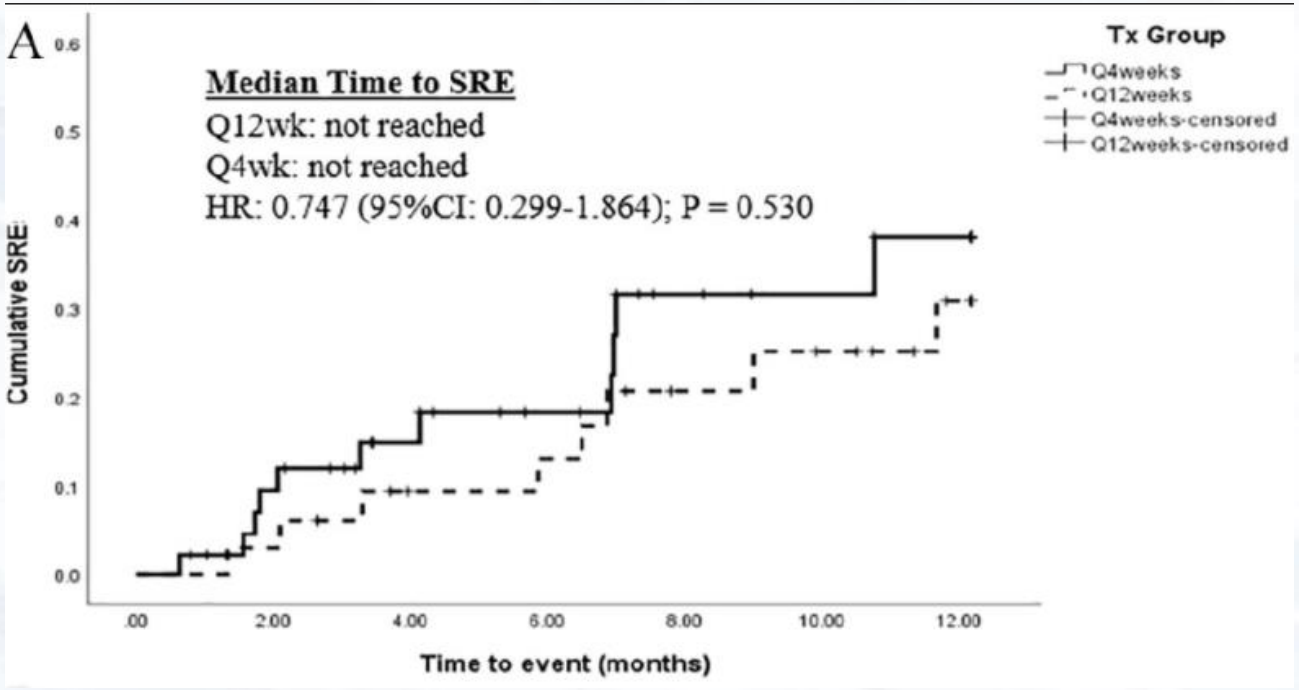
Secondary Outcome

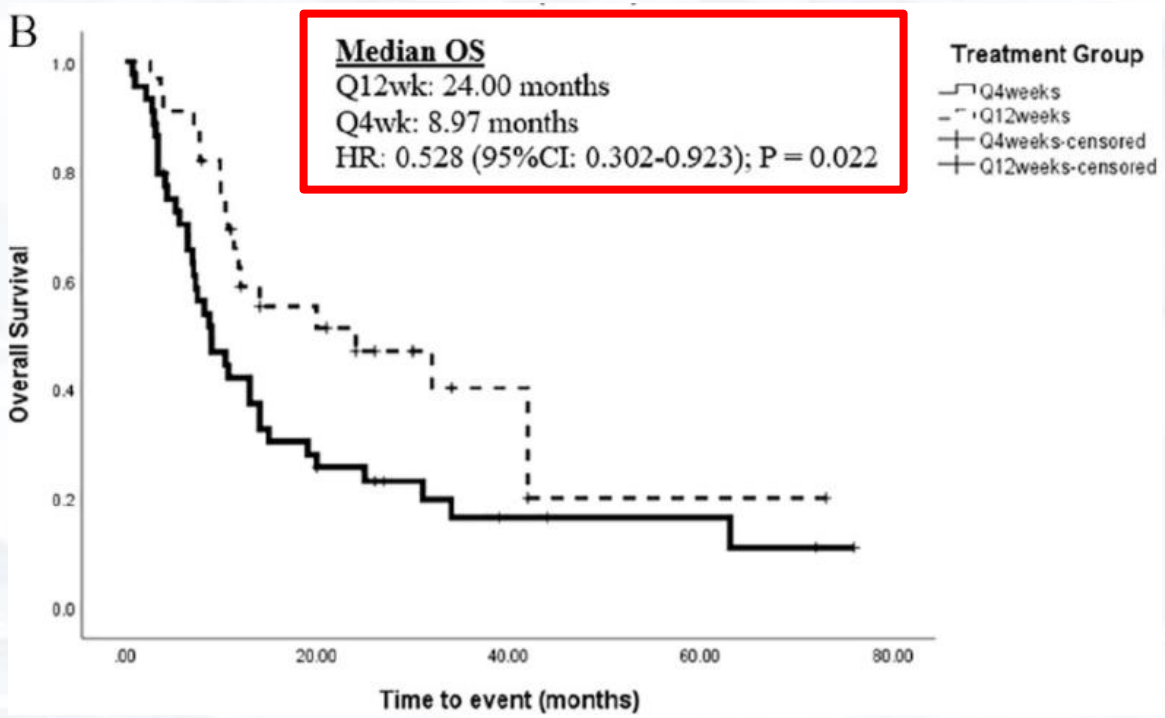
Table 2. Primary and Secondary Efficacy Outcomes and Safety Outcomes.

Outcome	Every 12 week (n = 34)	Every 4 week (n = 46)	*P* value
Incidence of SRE, n (%)	8 (23.5)	11 (23.9)	0.968 [95% CI = −0.184, +0.192]
Clinical fracture	5 (62.5)	3 (27.3)	0.275
Spinal cord compression	2 (25)	2 (18.2)	1.00
Radiation to bone	1 (12.5)	6 (54.5)	0.229
Bone surgery	0 (0)	0 (0)	
Incidence of second SRE, n (%)	2 (5.9)	1 (2.2)	0.572
Radiation to bone	1 (50)	1 (100)	1.00
Bone surgery	1 (50)	0 (0)	0.425
Mean time to SRE, months	10.6	9.9	
Median number of ZA doses (range)	3.5 (2-6)	4 (2-12)	0.161
Cumulative ZA dose, mean (SD), mg	12.65 (7.5-23.5)	16 (6.6-48)	0.138
Pain score outcomes, mean (SD)			
Pain score at 3 months	1.38 (2.22)	1.31 (2.46)	0.755
Pain score at 6 months	1.04 (2.10)	1.33 (2.44)	0.611
Pain score at 9 months	1.94 (2.95)	1.89 (3.18)	0.899
Pain score at 12 months	1.33 (2)	1.25 (2.5)	1.00
Minimum pain score	0.68 (1.51)	1.74 (2.46)	0.014
Maximum pain score	2.24 (2.97)	3.22 (2.92)	0.173
Overall pain scores	1.39 (2.35)	1.62 (2.29)	0.016
Change from baseline at 3 months	−0.59 (2.95)	0.48 (2.80)	0.510
Change from baseline at 6 months	−0.32 (2.34)	−1.06 (3.63)	0.170
Change from baseline at 9 months	0.29 (4.12)	−0.33 (2.87)	0.529
Change from baseline at 12 months	−1.33 (3.67)	−1.57 (3.05)	0.180
ONJ incidence, n (%)	0 (0)	0 (0)	—
CTCAE grade 2 kidney dysfunction, n (%)	2 (5.9)	2 (4.3)	1.00
CTCAE grade 3 hypocalcemia, n (%)	0 (0)	1 (2.2)	1.00

Abbreviations: CTCAE, common terminology criteria for adverse events; ONJ, osteonecrosis of the jaw; SRE, skeletal-related event; ZA, zoledronic acid.

Outcomes





	Median time to first SRE	Average time to first SRE	Overall survival (OS)
Q12wk	not reached	10.6 months	24.00 months
Q4wk	not reached	9.9 months	8.97 months
	P = 0.530	no difference	*P* = 0.022, [HR] = 0.528

Safety

Table 2. Primary and Secondary Efficacy Outcomes and Safety Outcomes.

Outcome	Every 12 week (n = 34)	Every 4 week (n = 46)	*P* value
Incidence of SRE, n (%)	8 (23.5)	11 (23.9)	0.968 [95% CI = −0.184, +0.192]
Clinical fracture	5 (62.5)	3 (27.3)	0.275
Spinal cord compression	2 (25)	2 (18.2)	1.00
Radiation to bone	1 (12.5)	6 (54.5)	0.229
Bone surgery	0 (0)	0 (0)	—
Incidence of second SRE, n (%)	2 (5.9)	1 (2.2)	0.572
Radiation to bone	1 (50)	1 (100)	1.00
Bone surgery	1 (50)	0 (0)	0.425
Mean time to SRE, months	10.6	9.9	
Median number of ZA doses (range)	3.5 (2-6)	4 (2-12)	0.161
Cumulative ZA dose, mean (SD), mg	12.65 (7.5-23.5)	16 (6.6-48)	0.138
Pain score outcomes, mean (SD)			
Pain score at 3 months	1.38 (2.22)	1.31 (2.46)	0.755
Pain score at 6 months	1.04 (2.10)	1.33 (2.44)	0.611
Pain score at 9 months	1.94 (2.95)	1.89 (3.18)	0.899
Pain score at 12 months	1.33 (2)	1.25 (2.5)	1.00
Minimum pain score	0.68 (1.51)	1.74 (2.46)	0.014
Maximum pain score	2.24 (2.97)	3.22 (2.92)	0.173
Overall pain scores	1.39 (2.35)	1.62 (2.29)	0.016
Change from baseline at 3 months	−0.59 (2.95)	0.48 (2.80)	0.510
Change from baseline at 6 months	−0.32 (2.34)	−1.06 (3.63)	0.170
Change from baseline at 9 months	0.29 (4.12)	−0.33 (2.87)	0.529
Change from baseline at 12 months	−1.33 (3.67)	−1.57 (3.05)	0.180
ONJ incidence, n (%)	0 (0)	0 (0)	—
CTCAE grade 2 kidney dysfunction, n (%)	2 (5.9)	2 (4.3)	1.00
CTCAE grade 3 hypocalcemia, n (%)	0 (0)	1 (2.2)	1.00

Abbreviations: CTCAE, common terminology criteria for adverse events; ONJ, osteonecrosis of the jaw; SRE, skeletal-related event; ZA, zoledronic acid.

no difference

no difference

Conclusion

- Extended-interval dosing may be safe and reasonable for patients with lung cancer with bone metastases.

limitation

- Retrospective study, small sample size, single center
- Few patients had SCLC
- Primary treatments for lung cancer differed between cohorts
- The true incidence of ONJ may be underreported

Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial

Lancet 2021; 397: 1195–203

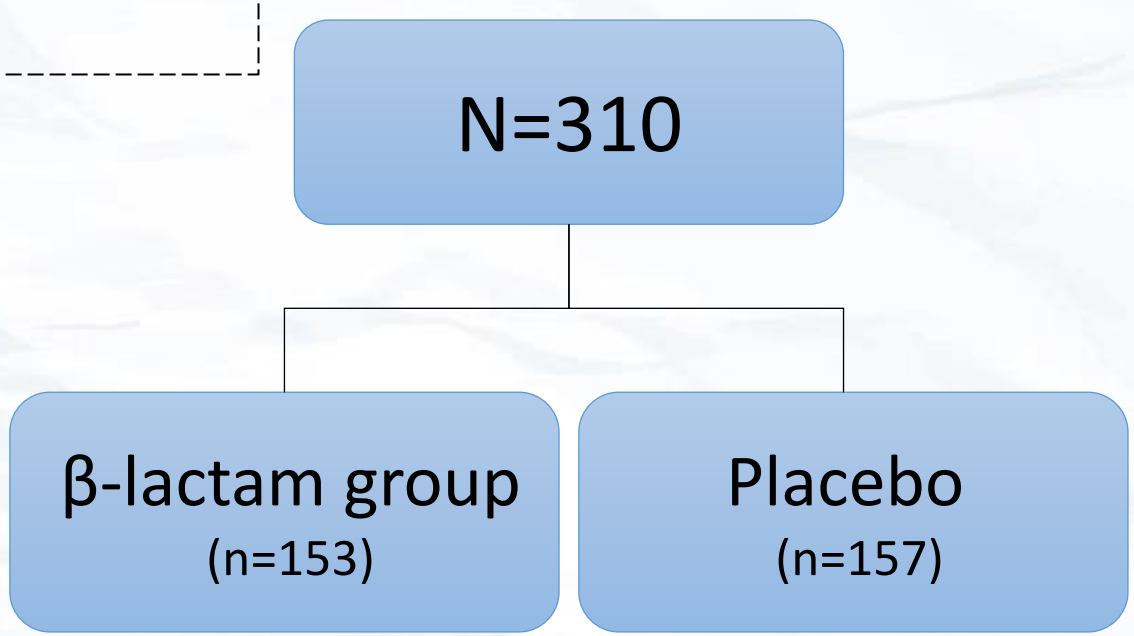
- Design: double-blind, randomised, placebo-controlled, non-inferiority trial

Inclusion Criteria

- Dec 19, 2013 - Feb 1, 2018, in 16 centres in France
- Adult (≥18 y/o)
- Moderately severe community-acquired pneumonia, treated with β-lactam monotherapy according to European guidelines, and who after 72 h of treatment had a clinical response

Exclusion Criteria

- Signs of severe or complicated community-acquired pneumonia
- Known immunosuppression
- Health-care-associated pneumonia or suspicion of aspiration pneumonia
- Any other infection necessitating concomitant antibiotic treatment



Primary outcome :
Cure 15 days after the start of antibiotic treatment with β-lactam therapy.

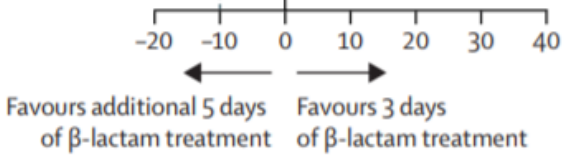
Baseline characteristics

	Placebo group (n=152)	β-lactam group (n=151)
Age, years	72·5 (54·0–85·3)	74·0 (58·0–83·0)
Sex		
Female	66 (43%)	57 (38%)
Male	86 (57%)	94 (62%)
Temperature, °C	38·8 (38·3–39·3)	38·7 (38·3–39·3)
Oxygen therapy	60 (39%)	59 (39%)
Comorbidities*	34 (22%)	39 (26%)
Liver disease	5 (3%)	2 (1%)
Heart failure	30 (20%)	33 (22%)
Cerebrovascular disease	13 (9%)	10 (7%)
Renal disease	13 (9%)	11 (7%)
Coronary insufficiency	24 (16%)	20 (13%)
Diabetes	24 (16%)	32 (21%)
Chronic obstructive pulmonary disease	31 (20%)	40 (26%)
At least two comorbidities	34 (22%)	39 (26%)
Active smoking	30 (20%)	25 (17%)
PSI score	80·5 (57·0–103)	83·0 (58·0–104)
Risk class 2 (<70)	56 (37%)	55 (36%)
Risk class 3 (71–90)	39 (26%)	34 (23%)
Risk class 4 (91–130)	45 (30%)	56 (37%)
Risk class 5 (≥131)	12 (8%)	6 (4%)
Community-acquired pneumonia score at day 0	44·4 (28·4–55·0)	46·2 (26·0–60·4)
Laboratory values at admission		
Haemoglobin, g/dL	12·8 (11·9–13·9)	13·1 (11·9–14·3)
Leucocyte, G/L	11·5 (8·05–16·0)	11·7 (8·70–15·2)
Absolute neutrophil count, G/L	9·81 (6·57–14·4)	9·68 (6·87–12·9)
Urea, mmol/L	6·70 (4·80–8·80)	5·90 (4·70–8·00)
Glucose, mmol/L	6·20 (5·40–7·00)	6·20 (5·33–7·50)
Creatinine, µmol/L	78·0 (65·0–100)	79·0 (63·0–96·0)
C-reactive protein, mg/L†	134 (59·0–234)	104 (46·8–200)
Procalcitonin, µmol/L‡	0·55 (0·20–2·23)	0·20 (0·10–0·60)
Radiological examination results		
Multilobar	30 (20%)	23 (15%)
Pleural effusion	11 (7%)	16 (11%)

Primary Outcomes

Cure on day 15

	Placebo group n of cure/total n (%)	β-lactam group n of cure/total n (%)	Risk difference (95% CI)
All patients			
Intention-to-treat analysis	117/152 (77·0%)	102/151 (67·5%)	9·42% (−0·38 to 20·04)
Per-protocol analysis	113/145 (77·9%)	100/146 (68·5%)	9·44% (−0·15 to 20·34)
Age <65 years			
Intention-to-treat analysis	48/58 (82·8%)	39/49 (79·6%)	3·17% (−10·74 to 20·96)
Per-protocol analysis	46/53 (86·8%)	39/48 (81·2%)	2·12% (−11·30 to 20·07)
Age ≥65 years			
Intention-to-treat analysis	69/94 (73·4%)	63/102 (61·8%)	11·64% (−4·05 to 24·22)
Per-protocol analysis	67/92 (72·8%)	61/98 (62·2%)	10·58% (−4·84 to 23·93)
Age ≥75 years			
Intention-to-treat analysis	51/70 (72·9%)	45/74 (60·8%)	12·05% (−5·13 to 27·27)
Per-protocol analysis	49/69 (71·0%)	43/70 (61·4%)	9·59% (−7·90 to 24·93)
PSI score <70			
Intention-to-treat analysis	46/54 (85·2%)	42/54 (77·8%)	7·41% (−7·62 to 22·75)
Per-protocol analysis	45/50 (90·0%)	42/53 (79·2%)	10·75% (−3·19 to 24·99)
PSI score ≥70			
Intention-to-treat analysis	71/98 (72·4%)	60/97 (61·9%)	10·59% (−3·74 to 23·42)
Per-protocol analysis	68/95 (71·6%)	58/93 (62·4%)	9·21% (−5·61 to 22·25)
PSI score <91			
Intention-to-treat analysis	76/95 (80·0%)	65/89 (73·0%)	6·97% (−4·73 to 20·87)
Per-protocol analysis	74/88 (84·1%)	65/87 (74·7%)	9·38% (−1·29 to 23·39)
PSI score ≥91			
Intention-to-treat analysis	41/57 (71·9%)	37/62 (59·7%)	12·25% (−6·49 to 29·94)
Per-protocol analysis	39/57 (68·4%)	35/59 (59·3%)	9·10% (−11·03 to 26·07)



Secondary Outcomes

	Placebo group	β-lactam group	Difference	p value
Cure at day 30				
ITT analysis	109/152 (72%)	109/151 (72%)	−0·47 (−11·31 to 9·98)	>0·99
Per-protocol analysis	105/141 (74%)	107/141 (76%)	−1·42 (−12·08 to 9·20)	0·89
Mortality at day 30	3/152 (2%)	2/151 (1%)	0·60 (−3·50 to 4·40)	>0·99
Patients with at least one adverse event related to treatment	22/152 (14%)	29/151 (19%)	−4·70 (−7·08 to 2·31)	0·29
Patients with at least one serious adverse event related to treatment	1/152 (1%)	1/151 (1%)	0·00 (0·00 to 0·99)	>0·99
Length of hospital stay, days,	5·00 (4·00 to 9·00)	6·00 (4·00 to 9·00)	−1·00 (−1·00 to 1·00)	0·74
Recovery time, days	15·00 (9·00 to 21·50)	15·50 (7·00 to 20·00)	−0·50 (−4·00 to 5·50)	0·33

Data are n/N (%), median (IQR) or between-group difference in percentage points, with 95% CI in parentheses. Unless otherwise stated, analyses are in the ITT population. χ^2 test was used to compare the distributions of categorical variables and Student's *t* tests to compare the distributions of quantitative continuous variables. ITT=intention-to-treat.

Table 2: **Secondary outcomes**

Adverse events

The most common

	Placebo group (n=152)	β-lactam group (n=151)
Patients	22 (1)	29 (1)
Digestive disorders	17	28
Diarrhoea	13	18
Mycosis	1	1
Skin rash	0	3 (1)
Headache	2	0
Hypoxia	0	1
Clostridioides difficile infection	1	0
Hepatitis	2 (1)	1
Epistaxis	1	0
Total	24 (1)	34 (1)

Data are number of events and data in parentheses are the number of serious adverse events. One patient could present with several adverse events.

Table 3: **Adverse events and serious adverse events associated with the study treatment**

serious adverse events

Conclusion

- Among patients with community-acquired pneumonia in non-critical care wards, a strategy of discontinuation of antibiotic treatment proved to be non-inferior to 8 days of treatment.

limitation

- Cannot be extrapolated to patients who do not respond after 3 days of β-lactam therapy
- Only patients treated with β-lactam monotherapy were enrolled
- Didn’t identify a causative microorganism
- Quite wide 95% CIs in subgroup analyses

Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial

Lancet 2021; 397: 1276–92

- Design: multicentre, open-label, randomised controlled, phase 3 trial

N=643

Dolutegravir(DTG) 50mg+ emtricitabine(FTC) /tenofovir alafenamide fumarate(TAF) 200/25mg (n=217)

Dolutegravir(DTG) 50mg +emtricitabine(FTC) /tenofovir disoproxil fumarate(TDF) 200/300mg (n=215)

Efavirenz(EFV)/emtricitabine (FTC) /tenofovir disoproxil fumarate(TDF) 600/200/300mg (n=211)

Inclusion Criteria	Exclusion Criteria
• Pregnant women (aged ≥18 years) • HIV-1 infection and at 14–28 weeks' gestation • Between Jan 19, 2018, and Feb 8, 2019	• Previously taken antiretrovirals in the past • Multiple fetuses, known fetal anomaly or a history of psychiatric illness

Baseline characteristics

	Dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (n=217)	Dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (n=215)	Efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (n=211)	Total (n=643)
Age, years	26·8 (22·3–31·5)	26·0 (22·3–31·3)	26·6 (23·1–32·1)	26·6 (22·5–31·6)
Country				
Zimbabwe	82 (38%)	84 (39%)	83 (39%)	249 (39%)
South Africa	37 (17%)	37 (17%)	37 (18%)	111 (17%)
Uganda	37 (17%)	37 (17%)	36 (17%)	110 (17%)
Brazil	21 (10%)	19 (9%)	17 (8%)	57 (9%)
Botswana	16 (7%)	18 (8%)	17 (8%)	51 (8%)
Tanzania	15 (7%)	13 (6%)	15 (7%)	43 (7%)
Thailand	5 (2%)	4 (2%)	6 (3%)	15 (2%)
USA	2 (1%)	2 (1%)	0	4 (1%)
India	2 (1%)	1 (1%)	0	3 (1%)
Race				
Black	195 (90%)	196 (91%)	194 (92%)	585 (91%)
Asian	7 (3%)	5 (2%)	6 (3%)	18 (3%)
White	5 (2%)	7 (3%)	7 (3%)	19 (3%)
Other	10 (5%)	6 (3%)	4 (2%)	20 (3%)
Unknown	0	1 (1%)	0	1 (<1%)
Median gestational age at study entry, weeks	22·1 (18·4–25·0)	21·3 (18·1–25·1)	22·1 (18·3–25·6)	21·9 (18·3–25·3)
Gestational age at study entry, weeks				
14–18	58 (27%)	64 (30%)	59 (28%)	181 (28%)
19–23	93 (43%)	83 (39%)	77 (37%)	253 (39%)
24–28	66 (30%)	68 (32%)	75 (36%)	209 (33%)
HBsAg positive	3 (1%)	6 (3%)	4 (2%)	13 (2%)
Median HIV-1 RNA, $\log_{10}$ copies per mL	2·9 (2·2–3·8)	2·9 (2·1–3·6)	3·1 (2·3–3·7)	3·0 (2·2–3·7)
Median HIV-1 RNA, copies per mL	781·0 (147·0–5733·0)	715·0 (128·0–4304·0)	1357·0 (198·0–5125·0)	902·5 (152·0–5182·5)
HIV-1 RNA, copies per mL				
<50	35 (16%)	37 (17%)	27 (13%)	99 (16%)
<200	62 (29%)	66 (31%)	53 (25%)	181 (28%)

Baseline characteristics

HIV-1 RNA, copies per mL				
<50	35 (16%)	37 (17%)	27 (13%)	99 (16%)
<200	62 (29%)	66 (31%)	53 (25%)	181 (28%)
Median CD4 count, cells per µL	467 (324–624)	481 (332–642)	439 (300–616)	466 (308–624)
CD4 count, cells per µL				
<50	0	0	0	0
50–349	64 (30%)	60 (28%)	73 (35%)	197 (31%)
350–499	56 (26%)	53 (25%)	50 (24%)	159 (25%)
500–750	68 (32%)	67 (31%)	59 (28%)	194 (30%)
>750	27 (13%)	34 (16%)	26 (13%)	87 (14%)
Median weight, kg	65·0 (56·7–77·1)	63·0 (56·3–72·0)	61·4 (55·4–71·2)	63·0 (56·2–73·0)
Median body-mass index, kg/m²	25·1 (22·5–29·4)	24·5 (22·0–28·1)	24·3 (21·5–28·3)	24·7 (22·0–28·4)
Mean creatinine clearance, mL/min	192·1 (59·6)	186·6 (65·0)	182·6 (56·2)	187·2 (60·4)
Mean creatinine, mg/dL	0·49 (0·09)	0·49 (0·09)	0·49 (0·10)	0·49 (0·10)
Previously received tenofovir disoproxil fumarate or emtricitabine and tenofovir disoproxil fumarate pre-exposure prophylaxis	1 (1%)*	2 (1%)*	0	3 (1%)*

(Table 1 continues on next page)

(Continued from previous page)

Took ART during a previous pregnancy or while breastfeeding	1 (1%)*	0	1 (1%)*	2 (<1%)
Took ART during current pregnancy before enrolment	176 (81%)	180 (84%)	176 (83%)	532 (83%)
Median duration of ART, days	6 (4–10)	6 (3–8)	6 (4–9)	6 (4–9)
Efavirenz and lamivudine or emtricitabine combined with tenofovir disoproxil fumarate	166 (77%)	165 (77%)	165 (78%)	496 (77%)
Dolutegravir and emtricitabine, combined with tenofovir disoproxil fumarate or tenofovir alafenamide fumarate	7 (3%)	8 (4%)	6 (3%)	21 (3%)
Other regimen	3 (1%)	7 (3%)	5 (1%)	14 (2%)

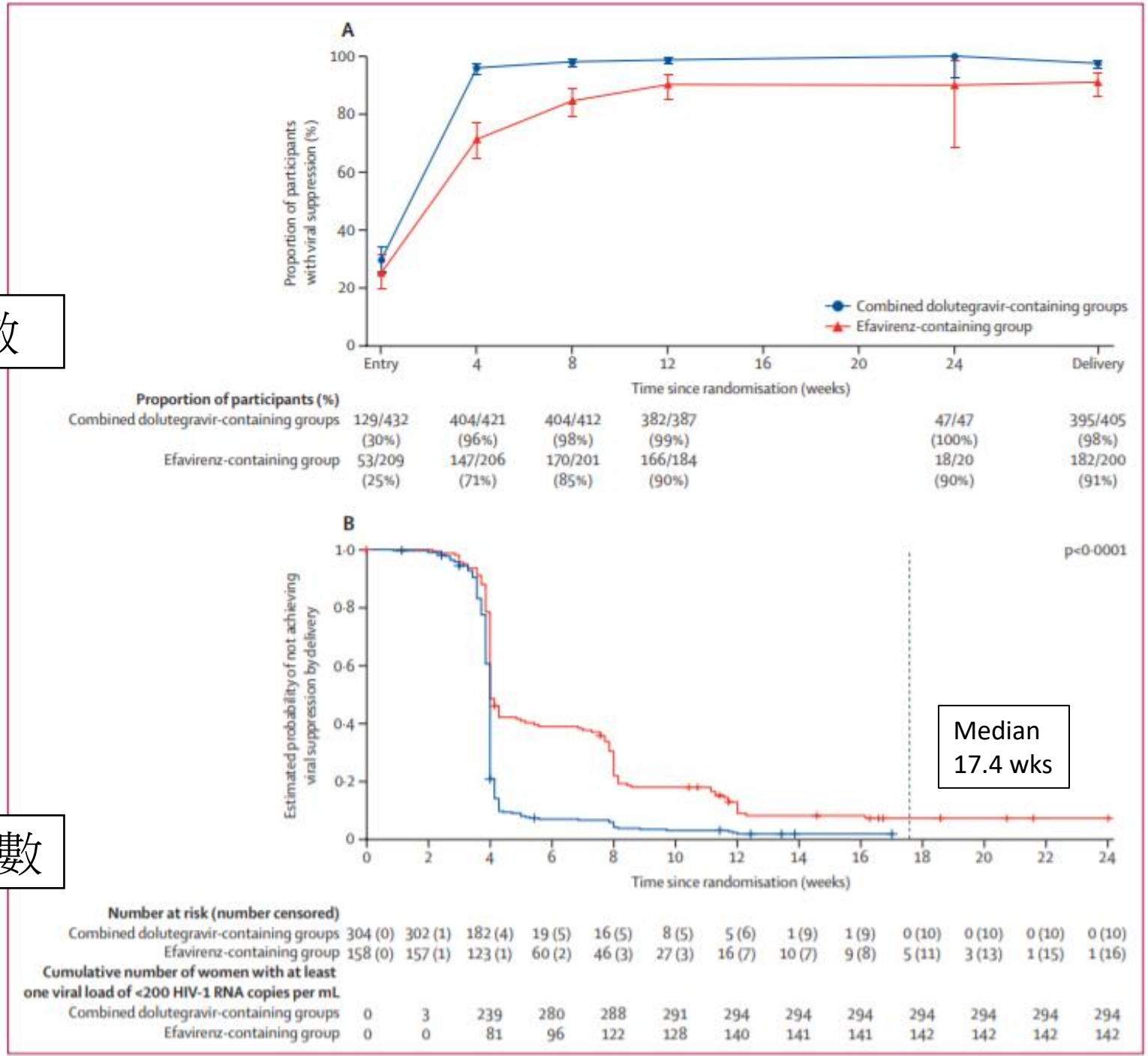
Data are median (IQR), n (%), or mean (SD). ART=antiretroviral therapy. *Participants took less than 1 week of pre-exposure prophylaxis.

***Table 1*: Baseline characteristics of participants by randomised group**

Primary Outcomes

已達到病毒抑制的孕婦人數

尚未達到病毒抑制的孕婦人數



Proportion of participants (%)							
Combined dolutegravir-containing groups	129/432 (30%)	404/421 (96%)	404/412 (98%)	382/387 (99%)		47/47 (100%)	395/405 (98%)
Efavirenz-containing group	53/209 (25%)	147/206 (71%)	170/201 (85%)	166/184 (90%)		18/20 (90%)	182/200 (91%)

Median 17.4 wks

Number at risk (number censored)													
Combined dolutegravir-containing groups	304 (0)	302 (1)	182 (4)	19 (5)	16 (5)	8 (5)	5 (6)	1 (9)	1 (9)	0 (10)	0 (10)	0 (10)	0 (10)
Efavirenz-containing group	158 (0)	157 (1)	123 (1)	60 (2)	46 (3)	27 (3)	16 (7)	10 (7)	9 (8)	5 (11)	3 (13)	1 (15)	1 (16)
Cumulative number of women with at least one viral load of <200 HIV-1 RNA copies per mL													
Combined dolutegravir-containing groups	0	3	239	280	288	291	294	294	294	294	294	294	294
Efavirenz-containing group	0	0	81	96	122	128	140	141	141	142	142	142	142

Primary Outcomes- HIV-1 RNA<200copies

	Combined dolutegravir-containing groups (n=432)	Efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (n=211)	Difference in proportions (95% CI)	p value
HIV-1 RNA <200 copies per mL				
Intention-to treat analysis	395/405 (98%)	182/200 (91%)	6·5% (2·0–10·7)	0·0052*
Per-protocol analysis	389/399 (98%)	171/187 (91%)	6·0% (1·6–10·3)	0·0077*
US FDA snapshot algorithm†	389/432 (90%)	171/211 (81%)	9·0% (3·0–15·0)	0·0032
HIV-1 RNA <50 copies per mL				
Intention-to-treat analysis	387/407 (95%)	160/201 (80%)	15·5% (9·5–21·4)	<0·0001
Per-protocol analysis	381/401 (95%)	151/188 (80%)	14·7% (8·6–20·8)	<0·0001
HIV-1 RNA <200 copies per mL stratified by HIV-1 RNA at study entry‡				
Entry HIV-1 RNA ≥200 copies per mL	275/285 (97%)	130/148 (88%)	8·7% (3·0–14·3)	0·0028
Entry HIV-1 RNA <200 copies per mL	119/119 (100%)	50/50 (100%)	0	..

Data are n/N (%), unless otherwise specified. The intention-to-treat population included all randomly assigned participants with available data on viral load at the delivery visit. Per-protocol analyses excluded viral loads from participants who switched, stopped, paused, or did not start any of the assigned antiretrovirals, or who took additional antiretrovirals before the viral load at delivery was sampled. FDA=Food and Drug Administration. *p value corrected for interim analyses. †Modified US FDA snapshot algorithm using the HIV-1 RNA concentration cutoff of less than 200 copies per mL. ‡In the intention-to-treat population.

Table 2: **Viral suppression at delivery**

Safety- maternal

	Dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (n=217)	Dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (n=215)	Efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (n=211)
Any grade 3 or higher clinical or laboratory adverse event	45 (21%)	56 (26%)	47 (22%)
Death*	1 (<1%)	0	0
Any grade 3 or higher clinical adverse event	40 (18%)	40 (19%)	38 (18%)
Infection	5 (2%)	5 (2%)	8 (4)%
Pregnancy or perinatal complication (excluding stillbirth and preterm delivery)	25 (12%)	28 (13%)	27 (13%)
Gestational hypertension	5 (2%)	5 (2%)	7 (3%)
Pre-eclampsia or eclampsia	5 (2%)	3 (1%)	1 (<1%)
Gestational diabetes	0	1 (1%)	0
Premature rupture of membranes (full-term and preterm)	5 (2%)	5 (2%)	5 (2%)
Haemorrhage (antepartum to 14 days post partum)	4 (2%)	2 (1%)	4 (2%)
Other pregnancy-related complication	8 (4%)	13 (6%)	11 (5%)
Any grade 3 or higher laboratory adverse event	9 (4%)	20 (9%)	15 (7%)
Low haemoglobin or reported anaemia	8 (4%)	17 (8%)	11 (5%)
Low creatinine clearance†	1 (<1%)	1 (<1%)	2 (1%)
High aspartate aminotransferase	0	1 (<1%)	1 (<1%)
Other maternal outcomes	..	..	..
Mean estimated creatinine clearance at delivery, mL/min‡	148·5 (51·3)	134·9 (45·8)	155·3 (48·2)
Mean creatinine concentration at delivery, mg/dL	0·64 (0·13)	0·68 (0·15)	0·57 (0·14)
Mean weekly weight gain, kg	0·378 (0·018)	0·319 (0·015)	0·291 (0·013)
Mean weekly weight gain standardised for gestational age, kg	0·371 (0·017)	0·332 (0·017)	0·289 (0·016)

Data are n (%) or mean (SD). Some participants might have had more than one grade 3 or higher event. Participants who had multiple grade 3 or higher events were only counted once within each row. Only the most frequent or relevant specific clinical events are shown. Detailed listings of grade 2 or higher adverse events are in the appendix (pp 13–16). *One participant died of sepsis approximately 2 weeks after caesarean section. †Defined as a creatinine concentration of more than 1·8 times the upper limit of normal, or an estimated creatinine clearance of less than 60 mL/min (calculated by the Cockgroft-Gault equation). ‡Calculated by the Cockgroft-Gault equation.

Table 3: **Maternal outcomes and grade 3 or higher adverse events from randomisation to 14 days postpartum**

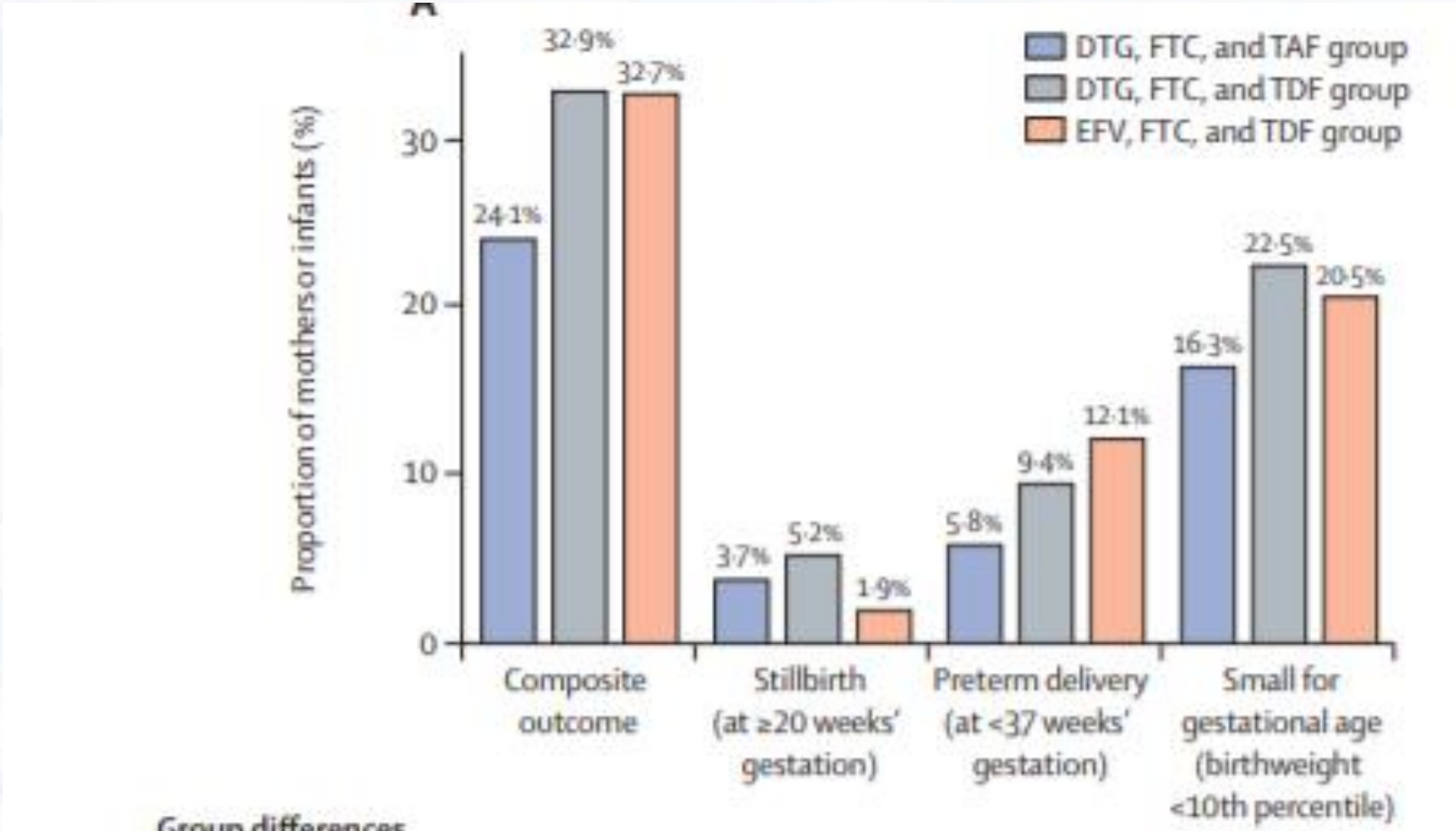
Safety-infant

	Dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (n=208)	Dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (n=202)	Efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (n=207)
Grade 3 or higher adverse events			
Any	29 (14%)	33 (16%)	43 (21%)
Infection	3 (1%)	10 (5%)	9 (4%)
Nervous system disorder*	3 (1%)	0	7 (3%)
Respiratory tract disorder	11 (5%)	6 (3%)	10 (5%)
Hypoglycaemia	4 (2%)	4 (2%)	4 (2%)
Elevated creatinine	2 (1%)	5 (3%)	4 (2%)
Elevated bilirubin	1 (<1%)	1 (<1%)	0
Other infant outcomes			
Median gestational age at birth, weeks	39·7 (38·6–40·7)	39·9 (38·7–40·7)	39·6 (38·4–40·4)
Median birthweight, g	3160 (2850–3500)	3065 (2800–3440)	3000 (2705–3325)
Low birthweight (<2500 g)	13 (6%)	19 (10%)	24 (12%)
Very low birthweight (<1500 g)	0	1 (1%)	2 (1%)
Birthweight >4 kg	8 (4%)	3 (2%)	4 (2%)
Died by age 28 days†	2 (1%)	3 (2%)	10 (5%)
Born <37 weeks	1/2 (50%)	0	3/10 (30%)
Small for gestational age	2/2 (100%)	2/3 (67%)	3/10 (30%)
Mean creatinine clearance at birth mL/min‡	52·5 (30·9)	53·3 (68·8)	49·6 (26·1)
Mean creatinine concentrations at birth, mg/dL	0·62 (1·72)	0·56 (0·31)	0·50 (0·24)

Data are n (%), median (IQR), mean (SD), or n/N (%). Some infants might have had more than one grade 3 or higher adverse event. Additional safety outcome measures from birth to age 28 days are provided in the appendix (p 25). *Two infants had hypoxic-ischaemic encephalopathy and one had a seizure in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group; and one infant had bulging fontanelle, one had hydrocephalus and intraventricular haemorrhage, and five had hypoxic-ischaemic encephalopathy in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group. †Causes of death in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group were hypoxic-ischaemic encephalopathy (n=1) and birth asphyxia (n=1); in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group were birth asphyxia (n=1), probable pneumonia (n=1), and unknown (n=1); and in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group were hypoxic-ischaemic encephalopathy (n=3), severe prematurity (n=1), neonatal sepsis (n=3), neonatal respiratory distress syndrome (n=1), fetal distress due to prolonged labour (n=1), and unknown (n=1). ‡Calculated by the Schwartz formula.

Table 4: **Infant outcomes and grade 3 or higher adverse events from birth to age 28 days**

Safety-infant



Group differences (95% CI)				
DTG, FTC, and TAF group *vs* DTG, FTC, and TDF group	−8·8% (−17·3% to −0·3%)	−1·5% (−5·4% to 2·4%)	−3·6% (−8·8% to 1·5%)	−6·2% (−13·9% to 1·5%)
DTG, FTC, and TDF group *vs* EFV, FTC, and TDF group	0·2% (−8·8% to 9·1%)	3·3% (−0·2% to 6·8%)	−2·7% (−8·7% to 3·3%)	2·0% (−6·0% to 10·0%)
DTG, FTC, and TAF group *vs* EFV, FTC, and TDF group	−8·6% (−17·1% to −0·1%)	1·8% (−1·3% to 4·9%)	−6·3% (−11·8% to −0·9%)	−4·2% (−11·7% to 3·4%)

Conclusion

- Dolutegravir-containing regimens had a significantly higher rate of viral suppression at delivery and a significantly shorter time to viral suppression
- Dolutegravir, emtricitabine, and tenofovir alafenamide fumarate had the most favourable safety profile

limitation

- open-label
- Cannot evaluate the effects of drug exposure at conception or in early pregnancy on adverse pregnancy outcomes
- excluded pregnant women with multiple gestations, known fetal anomalies, or other medical conditions

Abstract

The DIANA Study: Continued Access to Darunavir/Ritonavir (DRV/r) and Long-Term Safety Follow-Up in HIV-1-Infected Pediatric Patients Aged 3 to < 18 Years

Drug Safety volume 44, pages439–446 (2021)

- Design: open-label, single-arm, continued access study

AE incidence[a]	DRV/r BID (DELPHI) [$n = 16$]	DRV/r BID (ARIEL) [$n = 20$]	DRV/r QD (DIONE) [$n = 10$]	All patients [$N = 46$]
One or more AEs	6 (38)	5 (25)	4 (40)	15 (33)
Considered possibly related to DRV by the investigators	0	0	1 (10)	1 (2)
Most common AEs, any grade, in two or more patients overall				
Pneumonia	2 (13)	1 (5)	0	3 (7)
Gastroenteritis	1 (6)	0	1 (10)	2 (4)
Lipoatrophy	0	1 (5)	1 (10)	2 (4)
Pregnancy[b]	1 (6)	0	1 (10)	2 (4)
Asthma	0	1 (5)	1 (10)	2 (4)
One or more grade 1 or 2 AEs[b]	1 (6)	2 (10)	1 (10)	4 (9)
One or more grade 3 or 4 AEs[c]	4 (25)	3 (15)	3 (30)	10 (22)
One or more SAEs	5 (31)	4 (20)	3 (30)	12 (26)
One or more HIV-related AEs	1 (6)	2 (10)	0	3 (7)
One or more AEs for which study drug was permanently stopped	1 (6)	0	1 (10)	2 (4)

Association Between Prenatal Opioid Exposure and Neurodevelopmental Outcomes in Early Childhood: A Retrospective Cohort Study

Drug Safety volume 44, pages863–875 (2021)

- Design: re

P	• Preg • Live
I	Expose
C	Unexpo
O	Inciden

Outcome	Total number	Cases, n (%)	Crude IR (95% CI) per 100 PY	Crude HR (95% CI)	Adjusted HR (95% CI)
Primary analysis					
Unexposed	23011	1428 (6.2)	2.46 (2.34–2.59)	1	1
Exposed	1899	134 (7.1)	2.90 (2.43–3.43)	1.18 (0.99–1.41)	1.10 (0.92–1.32)
Secondary analyses					
Timing of exposure					
Unexposed	23011	1428 (6.2)	2.46 (2.34–2.59)	1	1
First trimester alone	653	47 (7.2)	2.92 (2.14–3.88)	1.18 (0.89–1.58)	1.08 (0.81–1.46)
Second trimester alone	395	30 (7.6)	3.22 (2.17–4.60)	1.32 (0.92–1.77)	1.23 (0.85–1.77)
Third trimester alone	672	42 (6.3)	2.53 (1.82–3.42)	1.02 (0.76–1.42)	1.05 (0.77–1.42)
Cumulative duration of use					
Unexposed	23011	1428 (6.2)	2.46 (2.34–2.59)	1	1
Less than 14 days	1717	116 (6.8)	2.75 (2.28–3.30)	1.12 (0.93–1.35)	1.05 (0.87–1.28)
At least 14 days	182	18 (9.9)	4.35 (2.58–6.87)	1.80 (1.13–2.87)	1.70 (1.05–2.76)
Cumulative opioid dose[a]					
Unexposed	23011	1428 (6.1)	2.46 (2.34–2.59)	1	1
Low dose (<37.5 MME)	986	60 (6.1)	2.73 (2.08–3.51)	1.11 (0.86–1.44)	1.05 (0.81–1.37)
High dose (≥37.5 MME)	913	74 (8.1)	3.05 (2.39–3.83)	1.24 (0.98–1.57)	1.22 (1.01–1.54)
Individual opioids					
Unexposed	23011	1428 (6.2)	2.46 (2.34–2.59)	1	1
Hydrocodone monotherapy	836	70 (8.4)	3.42 (2.66–4.32)	1.39 (1.09–1.77)	1.33 (1.04–1.70)
Codeine monotherapy	708	41 (5.8)	2.35 (1.68–3.18)	0.96 (0.70–1.30)	0.93 (0.68–1.28)

[a] Fetal cumulative opioid exposure was categorized by median split of the total opioid doses during pregnancy. The low and high categories correspond to 2.25–37.49 MME and 37.5–2250 MME, respectively

HR hazard ratio, *PY* person-years, *n* number, *IR* incidence rate, *MME* morphine milligram equivalent

THE LANCET

Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

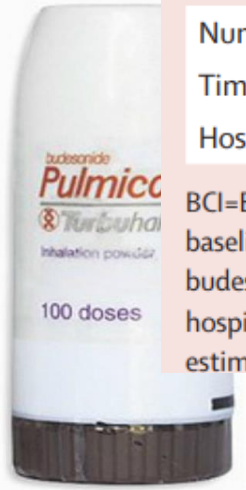
Lancet 2021; 398: 843–55

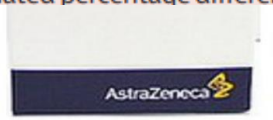
- Desi

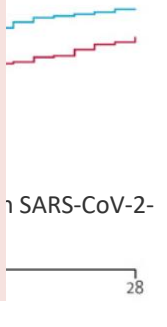
P	•
I	u
C	u
O	T

	Inhaled budesonide (95% BCI)	Usual care (95% BCI)	Estimated benefit median time to recovery or hospital admission or death rate (95% BCI)	Hazard ratio or odds ratio (95% BCI)	Probability of superiority
Primary analysis—SARS-CoV-2-positive participants					
Number of participants	787	1069	..	..	..
Time to first reported recovery, days*	11·8 (10·0 to 14·1)	14·7 (12·3 to 18·0)	2·94 (1·19 to 5·11)	1·21 (1·08 to 1·36)	>0·999
Hospital admission or death at 28 days†	6·8% (4·1 to 10·2)	8·8% (5·5 to 12·7)	2·0% (–0·2 to 4·5)	0·75 (0·55 to 1·03)	0·963
Secondary analysis—all participants					
Number of participants	990	1858	..	..	..
Time to first reported recovery, days*	10·9 (8·9 to 13·2)	13·3 (11·1 to 16·7)	2·54 (1·00 to 4·54)	1·18 (1·07 to 1·30)	>0·999
Hospital admission or death at 28 days†	5·8% (3·4 to 8·6)	7·3% (4·5 to 10·6)	1·5% (–0·3 to 3·6)	0·78 (0·57 to 1·04)	0·953
Sensitivity analysis—concurrent randomisation population					
Number of participants	787	838	..	..	..
Time to first reported recovery, days*	11·7 (9·8 to 14·2)	15·0 (12·5 to 18·3)	3·26 (1·46 to 5·43)	1·24 (1·10 to 1·39)	>0·999
Hospital admission or death at 28 days†	6·6% (3·8 to 10·1)	8·9% (5·2 to 13·1)	2·2% (0·0 to 4·9)	0·73 (0·53 to 1·00)	0·975

BCI=Bayesian credible interval. *Estimated benefit in median times to recovery are derived from a Bayesian piecewise exponential model adjusted for age and comorbidity at baseline, with 95% BCI; a positive value in estimated benefit in median time to recovery (or hazard ratio >1) corresponds to a reduction in time to recovery in days with budesonide compared with usual care; treatment superiority is declared if probability of superiority is ≥0·99 versus usual care. †Estimated absolute percentage differences in hospital admission or death were derived from a Bayesian logistic regression model adjusted for age and comorbidity at baseline, with 95% BCI; a positive value in the estimated percentage difference (or odds ratio <1) favours budesonide; treatment superiority is declared if probability of superiority is ≥0·975 versus usual care.







Cumulative number not yet recovered (recovered)

Inhaled budesonide	787 (0)	529 (272)	328 (446)	235 (526)	186 (566)
Usual care	1069 (0)	762 (341)	550 (522)	416 (637)	334 (710)

Time since randomisation (days)

Cumulative number not yet recovered (recovered)

Inhaled budesonide	787 (0)	529 (272)	328 (446)	235 (526)	186 (566)
Usual care	838 (0)	601 (262)	442 (394)	342 (483)	275 (544)

THE LANCET

Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

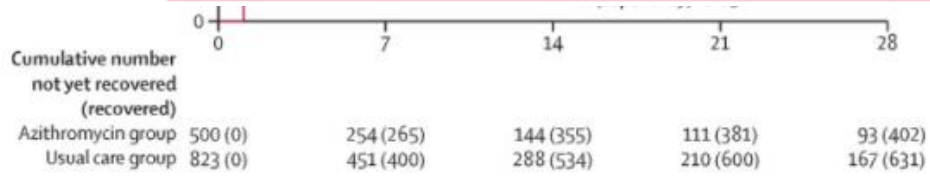
Lancet 2021; 397: 1063–74

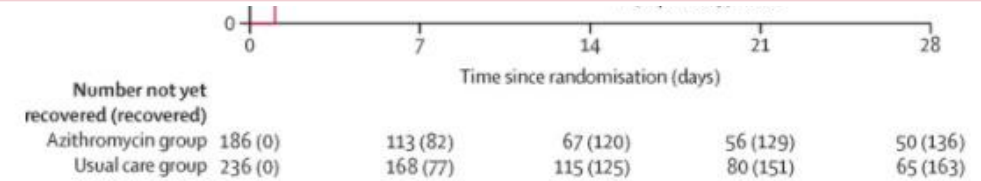
P	• ≥ 6 • Or
I	azithr
C	usual
O	time t

	Azithromycin plus usual care	Usual care alone	Estimated treatment effect (95% Bayseian credible interval)	Probability of meaningful effect	Probability of superiority
Primary outcomes (primary analysis population)					
First reported recovery	402/500 (80%)	631/823 (77%)	..	..	..
Time to first reported recovery (days)	7 (3 to 17)	8 (2 to 23)	1·08 (0·95 to 1·23)*	0·23*	0·89*
Hospitalisation or death at 28 days	16/500 (3%)	28/823 (3%)	0·3% (–1·7 to 2·2)†	0·042†	0·64†
Primary outcomes (SARS-CoV-2-positive analysis population)					
First reported recovery	136/186 (73%)	163/236 (69%)	..	..	..
Time to first reported recovery (days)	9 (4 to not reached)	13 (5 to not reached)	1·12 (0·91–1·38)*	0·47*	0·86*
Hospitalisation or death at 28 days	11/186 (6%)	17/236 (7%)	1·6% (–3·1 to 6·2)†	0·43†	0·76†

Data are n/N (%) or median (IQR). HR=hazard ratio. *Estimated HR derived from a Bayesian piecewise exponential model adjusted for age and comorbidity at baseline, with 95% Bayesian credible interval. HR >1 favours azithromycin. †Estimated absolute benefit in percentage of hospitalisation or death derived from a Bayesian logistic regression model adjusted for age and comorbidity at baseline, with 95% Bayesian credible interval. A positive value favours azithromycin.

Table 2: **Primary outcomes**





ANNALS OF PHARMACOTHERAPY

Direct Oral Anticoagulants Versus Warfarin in the Treatment of Left Ventricular Thrombus

Annals of Pharmacotherapy 2021, Vol. 55(7) 839–845

- Design: retrospective single-center study

P	• ≥ 18 y/o, definite diagnosis of LV thrombus • Treated with either warfarin or a DOAC within 30 days of first diagnosis
I	DOAC (ie, apixaban, rivaroxaban, dabigatran, or edoxaban)
C	Warfarin
O	The composite of LV thrombus persistence, stroke, or systemic embolism

Outcome	Overall (n = 151)	Warfarin (n = 129)	DOAC (n = 22)	*P* value
Follow-up (days, IQR)	254, 98-343	271, 109-343	172.5, 56-329	0.3
Efficacy end point, n (%)	79 (52.3)	70 (54.3)	9 (40.9)	0.25
Thrombus persistence, n (%)	71 (47)	62 (48.1)	9 (40.9)	0.53
Stroke, n (%)	7 (4.6)	7 (5.4)	0 (0)	0.39
Systemic embolism, n (%)	1 (0.7)	1 (0.8)	0 (0)	1
Safety end point, n (%)	6 (4)	5 (3.9)	1 (4.5)	1
Blood transfusion, n (%)	5 (3.3)	4 (3.1)	1 (4.5)	1
Hemorrhagic stroke, n (%)	1 (0.7)	1 (0.8)	0 (0)	1
SSE, n (%)	8 (5.3)	8 (6.2)	0 (0)	0.37
Thrombus resolution, n (%)	76 (50.3)	63 (48.8)	13 (59.1)	0.37

THE LANCET

Ipa… ration-re… ised, do…

…398: 131–42

- Design:

P	• ≥ 1 • pr…
I	Ipatas…
C	Placel…
O	Radio…

	Patients, n	Median progression-free survival, months		HR for progression or death (95% CI)
		Placebo–abiraterone group	Ipatasertib–abiraterone group	
All patients	**1101**	**16·6**	**19·2**	**0·84 (0·71–0·99)**
ECOG performance status				
0	822	16·8	20·9	0·84 (0·69–1·02)
1	274	13·8	16·7	0·93 (0·67–1·28)
Age, years				
18–64	287	16·6	18·5	0·83 (0·60–1·14)
65–74	500	19·3	19·2	0·91 (0·71–1·18)
≥75	314	14·1	19·1	0·79 (0·58–1·07)
Lactate dehydrogenase level				
≤ULN	809	18·8	22·5	0·78 (0·63–0·95)
>ULN	282	11·3	12·2	1·00 (0·75–1·34)
Previous taxane-based therapy				
Yes	197	18·4	16·6	0·95 (0·63–1·41)
No	904	16·6	19·2	0·82 (0·68–0·99)
Progression factor				
PSA only	550	17·0	24·7	0·75 (0·58–0·96)
Other	551	16·5	16·4	0·93 (0·74–1·16)
Liver or lung metastases				
Yes	152	9·7	16·2	0·71 (0·47–1·06)
No	949	17·0	19·7	0·87 (0·72–1·05)
PTEN loss by immunohistochemistry				
Yes	521	16·5	18·5	0·78 (0·61–0·99)
No	580	19·1	19·7	0·90 (0·71–1·14)
PTEN loss by next-generation sequencing				
Yes	205	14·2	19·1	0·65 (0·45–0·95)
No	310	16·6	20·9	0·85 (0·62–1·18)
Unknown*	225	16·5	15·7	0·95 (0·66–1·35)

0·3 1·0 3·0

Favours ipatasertib–abiraterone Favours placebo–abiraterone

A

Progression-free survival (%)

100 80 60 40 20 0

Strati… p=0·03

Number at risk (number censored)

Placebo–abiraterone group 261 (0)

Ipatasertib–abiraterone group 260 (0)

Progression-free survival at 1 year since randomisation, % (95% CI)

63·0% (58·9–67·1)

65·3% (61·1–69·5)

27 30 33

29 (222) 5 (243)

26 (271) 2 (294)

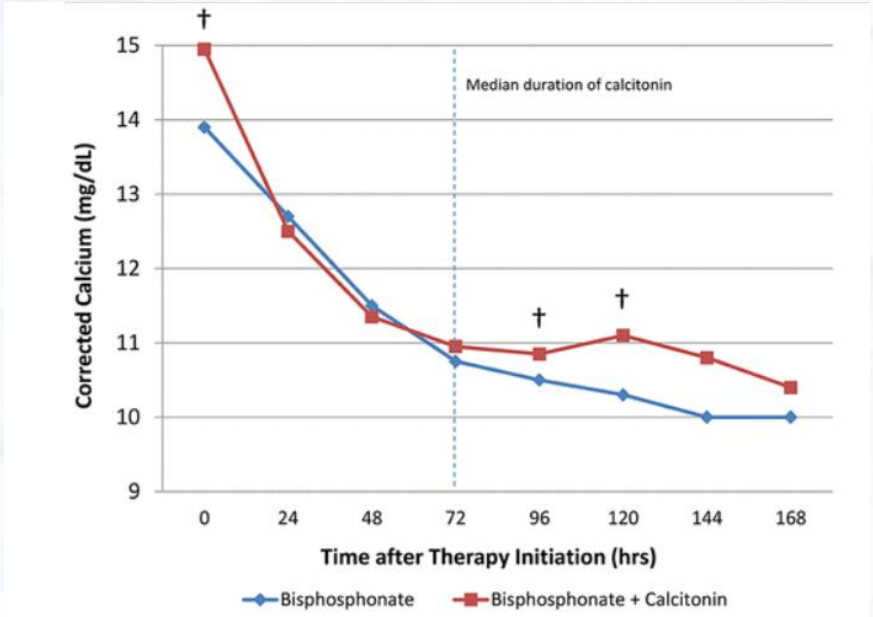
ANNALS OF PHARMACOTHERAPY

Bisphosphonate Versus Bisphosphonate and Calcitonin for the Treatment of Moderate to Severe Hypercalcemia of Malignancy

Annals of Pharmacotherapy 2021, Vol. 55(3) 277–285

- Design: retrospective, observational cohort study

P	• ≥ 18 y/o • serum calcium concentration greater than 13 mg/dL and/or ionized calcium greater than 1.50 mmol/L
I	Bisphosphonate + usual care
C	Bisphosphonate with calcitonin + usual care
O	Change in corrected serum calcium concentrations 48 hours after treatment



	Bisphosphonate (n = 94)	Bisphosphonate + Calcitonin (n = 46)	*P* value
Decrease in corrected calcium 48 hours after start of treatment (mg/dL), median [IQR]	2.4 [1.6-3.4]	3.9 [2.5-5.3]	$P < 0.001$; median difference = 1.4 (95% CI = 0.8-2.0)
Percentage decrease in corrected calcium 48 hours after start of treatment, median [IQR]	18% [12-23]	26% [17-33]	$P < 0.001$; median difference = 8% (95% CI = 4%-11%)
Incidence of normocalcemia, n (%)	69 (73)	28 (61)	0.131
Time from first therapy to normocalcemia (days), median [IQR]	2.6 [2.0-3.5]	2.5 [1.8-3.3]	0.537
Incidence of hypocalcemia, n (%)	5 (5)	1 (2)	0.388
Hospital LOS (days), mean (SD)	10.9 (8.1)	10.6 (7.3)	0.803
Inpatient mortality, n (%)	12 (12)	13 (28)	0.034
Unit at discharge, n (%)			0.861
Home	41 (50)	16 (49)	
SNF or OSH	26 (32)	12 (36)	
Hospice	15 (18)	5 (15)	

Abbreviations: IQR, interquartile range; LOS, length of stay; OSH, outside hospital; SNF, skilled nursing facility.

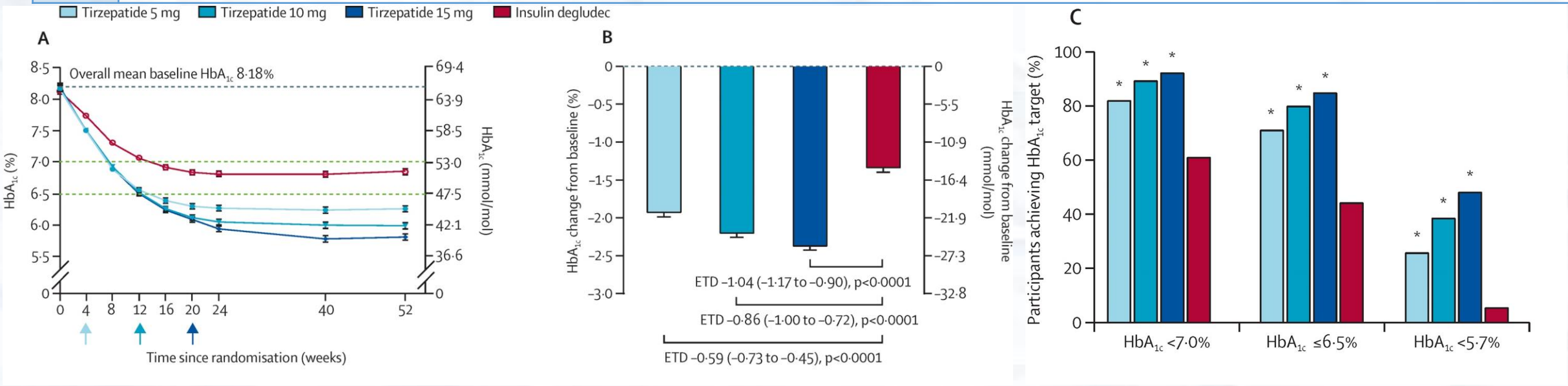
THE LANCET

Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial

Lancet 2021; 398: 131–42

- Design: open-label, parallel-group, multicentre, multinational, phase 3 study

P	• ≥ 18 y/o, HbA $_{1c}$ 7·0–10·5%, BMI ≥25 kg/m ^{2}, stable weight • insulin-naive and treated with metformin alone or in combination with an SGLT2 inhibitor for at least 3 months
I	tirzepatide 5, 10, or 15 mg SC QW
C	Titrated insulin degludec QD
O	mean change from baseline in HbA $_{1c}$ at week 52

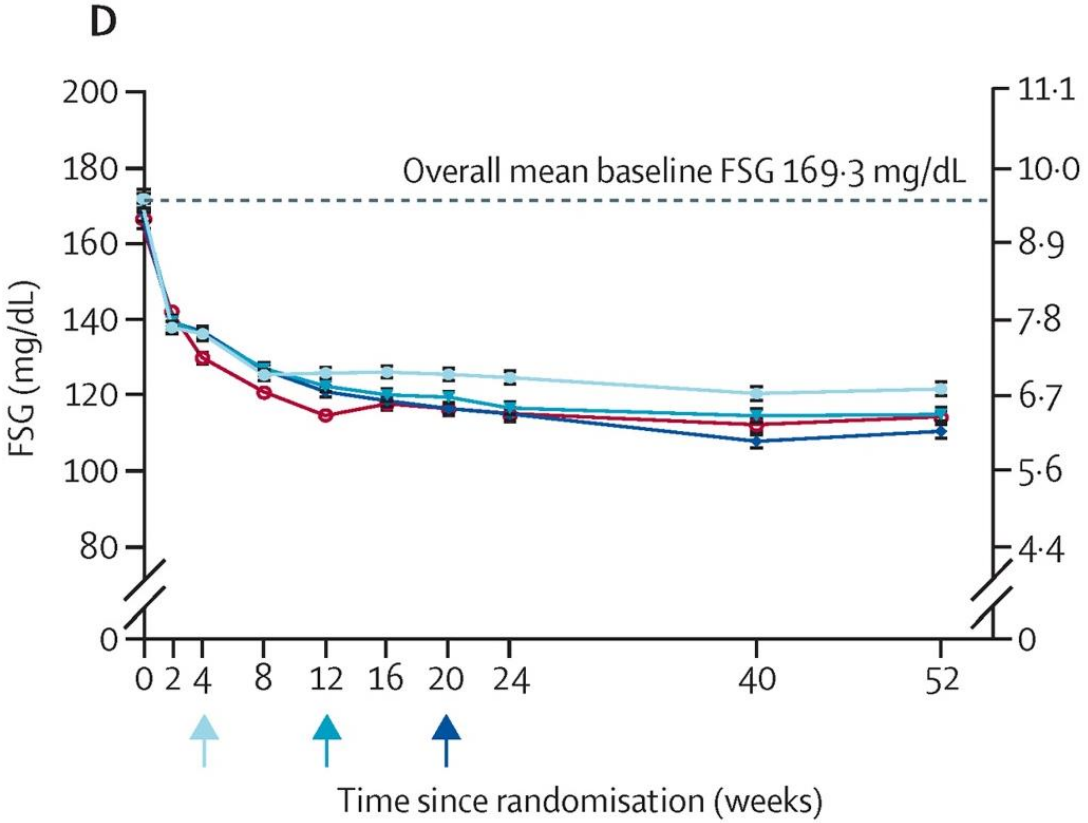


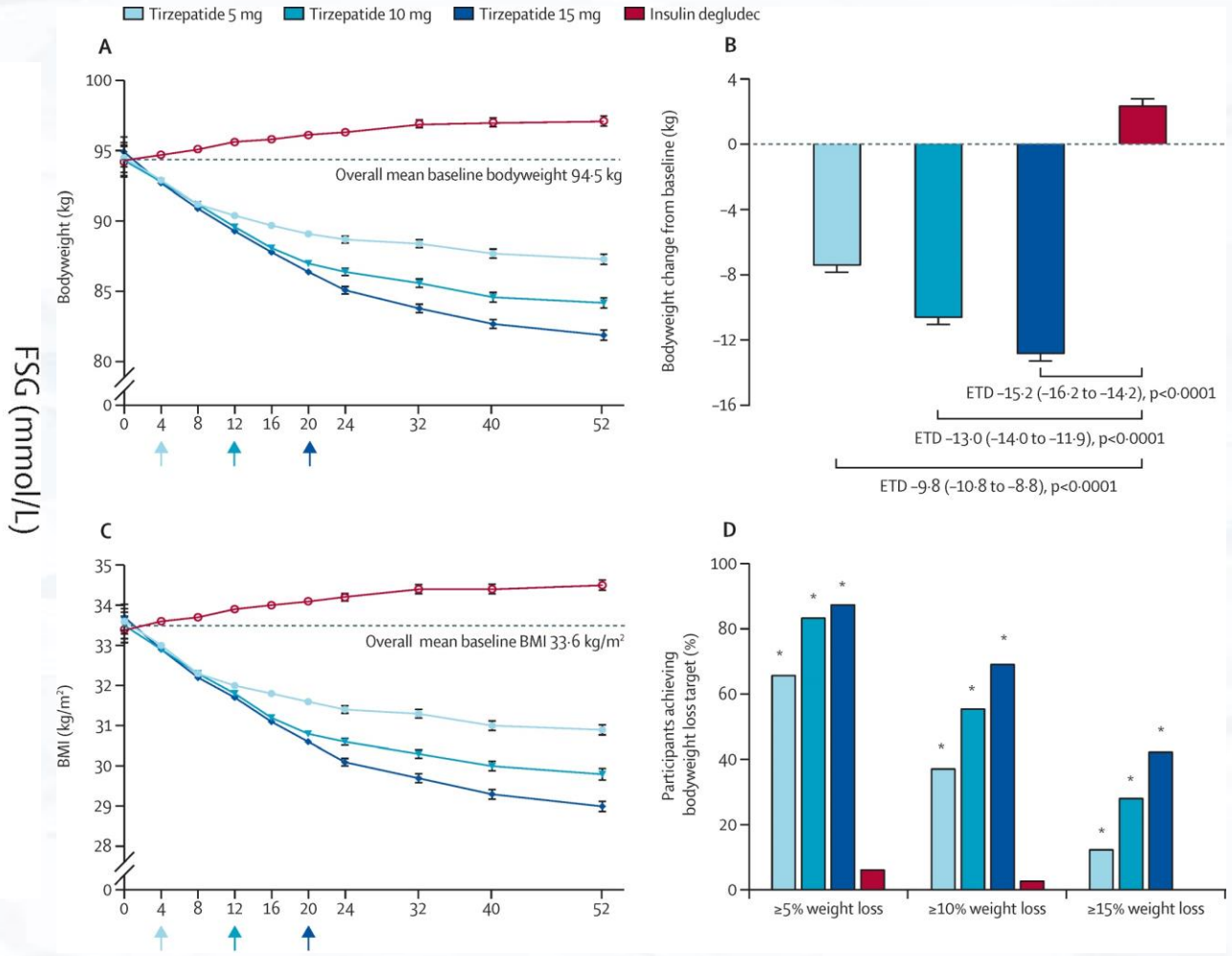
THE LANCET

Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial

Lancet 2021; 398: 131–42

Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Insulin degludec





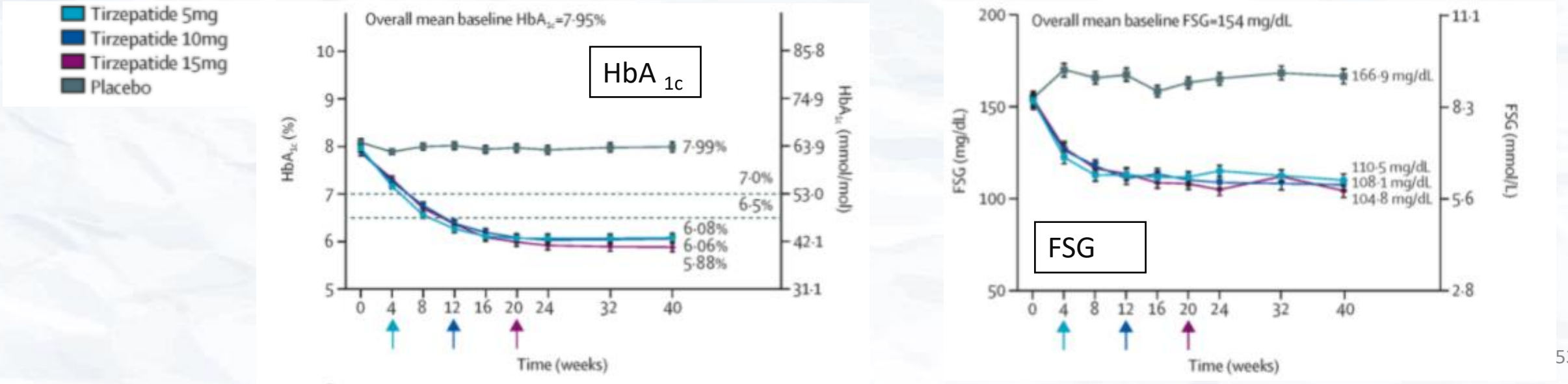
THE LANCET

Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial

Lancet 2021; 398: 143–55

- Design: 40-week, multicentre, randomised, double-blind, placebo-controlled, parallel group trial

P	• ≥ 18 y/o, Type 2 DM, HbA $_{1c}$ 7·0–9·5%, BMI ≥23 kg/m ^{2}, stable weight • naive to injectable diabetes therapy
I	tirzepatide 5, 10, or 15 mg SC QW
C	Placebo
O	mean change from baseline in HbA $_{1c}$ at week 40



Thank You