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Pathological complete response to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastro-oesophageal junction cancer: interim results of the global, Phase 3 MATTERHORN study

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Introduction

- FLOT chemotherapy has become the perioperative standard of care in operable GC/GEJC based on the FLOT-4 trial[1,2]
- Combination of PD-1 blockade and chemotherapy is a standard therapy in first-line metastatic GC / GEJC[3–5]
- We present the pCR results from a pre-specified interim analysis from the MATTERHORN study (NCT04592913) of peri-operative durvalumab, an anti-PD-L1 antibody plus FLOT versus placebo plus FLOT in resectable GC / GEJC

FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; mDFS, median disease-free survival; mOS, median overall survival; pCR, pathological complete response; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1.

1. Al-Batran S-E, et al. *Lancet* 2019;393:1948–1957; 2. Al-Batran S-E, et al. *Lancet Oncol* 2016;17:1697–1708; 3. Bang Y-J, et al. *Gastric Cancer* 2019;22:828–837; 4. Janjigian YY, et al. *Lancet* 2021;398:27–40; 5. Sun JM, et al. *Lancet* 2021;398:759–771.

Methods

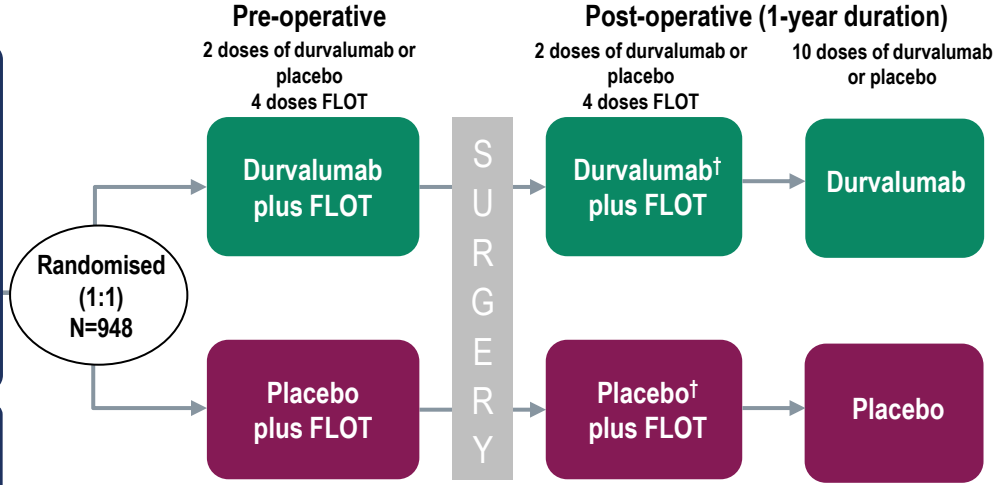
MATTERHORN is a global, Phase 3, randomised, double-blind, placebo-controlled study

Study population

- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N+ M0)
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America and South America

Stratification factors

- Geographic region: Asia versus non-Asia
- Clinical lymph node status: positive versus negative
- PD-L1 status: TAP <1% versus TAP ≥1%*



Primary objective:

- EFS

Key secondary endpoints:

- Central review of pCR‡ by modified Ryan criteria
- Overall survival

Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative) followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles

*Measured by VENTANA PD-L1 (SP263) assay. †Durvalumab or placebo monotherapy may be continued if post-operative FLOT is discontinued due to toxicity. ‡pCR was scored using modified Ryan criteria by central review.
FLOT: 5-fluorouracil 2600 mg/m^2, oxaliplatin 85 mg/m^2, docetaxel 50 mg/m^2, leucovorin 200 mg/m^2 on Days 1 and 15 Q4W, 2 doses (two cycles) pre- and post-operative; durvalumab: 1500 mg on Day 1 Q4W, 2 doses (two cycles) of durvalumab or placebo pre- and post-operative.
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastro-oesophageal junction; PD-L1, programmed cell death-ligand 1; PS, performance status; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Q2W, every 2 weeks; Q4W, every 4 weeks; TAP, tumour area positivity.

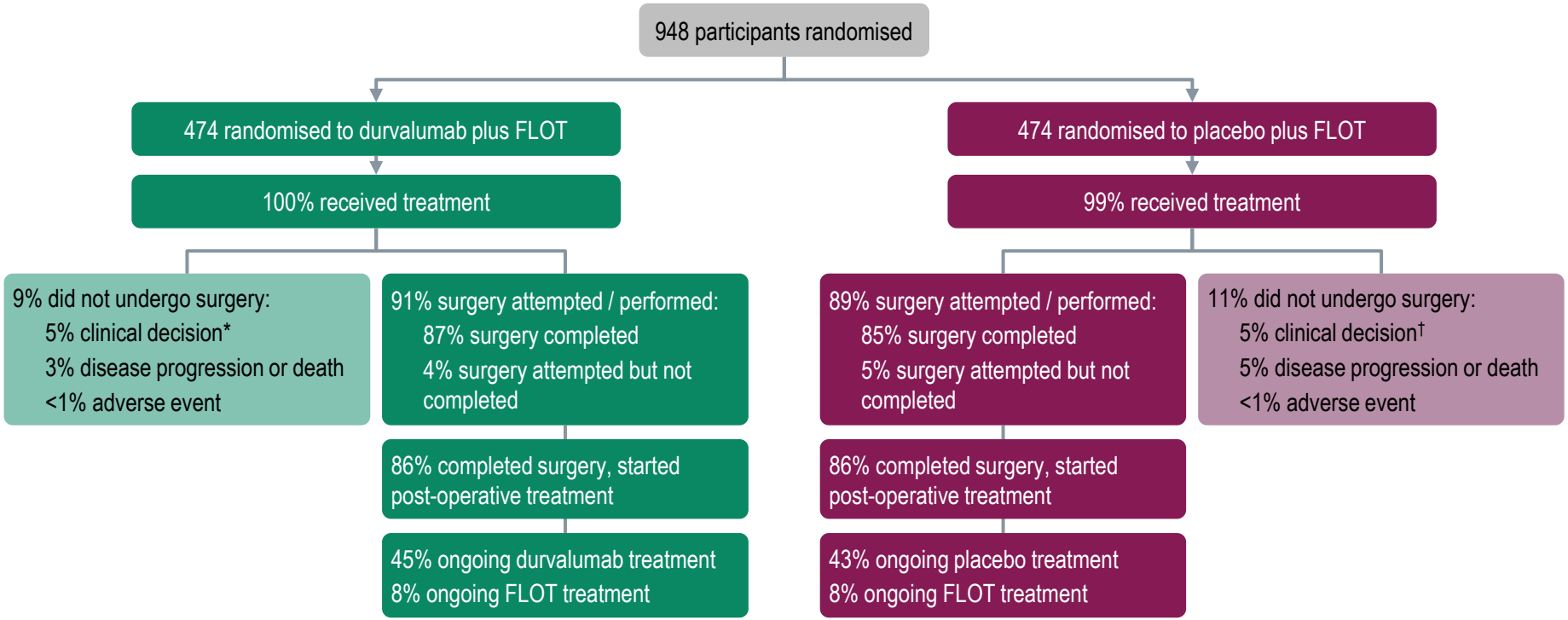
Statistical considerations

Interim analysis: pCR

- Data cut-off: 1 February 2023
- pCR was an α-controlled endpoint, with α=0.1% (two-sided) allocated to pCR
- Superiority for durvalumab plus FLOT versus placebo plus FLOT was evaluated using a stratified Cochran-Mantel-Haenszel test
- The MATTERHORN study is ongoing for the analysis of the primary objective of EFS
  - EFS will be tested with a total α=5% (two-sided) following α recycling strategy and a statistically significant pCR outcome

EFS, event-free survival; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; pCR, pathological complete response.

Participant disposition



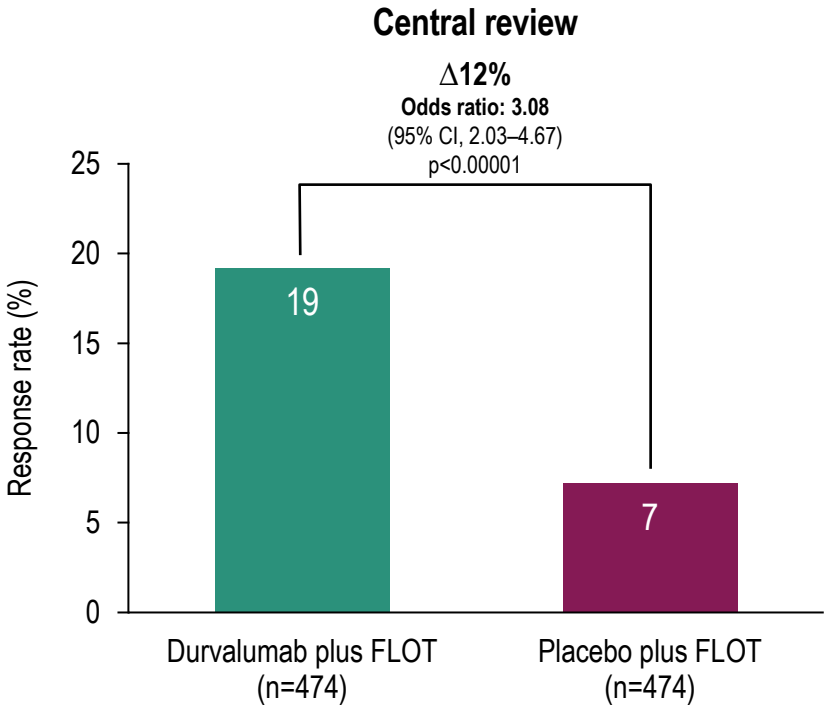
*Clinical decision included participant decision (2%), unfit for surgery (<1%), discontinuation (1%), investigator decision (<1%), or other or unspecified (1%). †Clinical decision included participant decision (2%), unfit for surgery (1%), discontinuation (1%), investigator decision (<1%) or other or unspecified (<1%). Numbers of participants ongoing treatment at data cut-off: 1 February 2023. First patient enrolled: 30 November 2020; first patient randomised: 2 December 2020, last patient randomised: 28 September 2022.
FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel.

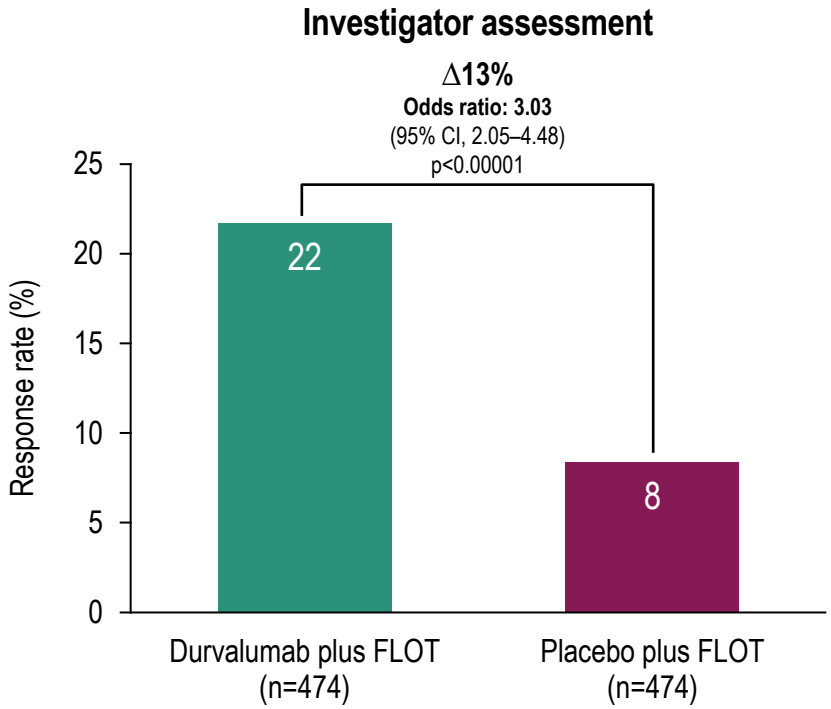
Baseline characteristics

		Durvalumab plus FLOT (n=474)	Placebo plus FLOT (n=474)
Median age, (range) years		62 (26–84)	63 (28–83)
Male, n (%)		326 (69)	356 (75)
Region of enrolment, n (%)	Asia	90 (19)	90 (19)
	Non-Asia	384 (81)	384 (81)
ECOG PS, n (%)	0	337 (71)	366 (77)
	1	137 (29)	108 (23)
Primary tumour location, n (%)	Gastric	324 (68)	316 (67)
	GEJ	150 (32)	158 (33)
Siewert status, n (%)	Type 1	44 (9)	55 (12)
	Type 2	72 (15)	68 (14)
	Type 3	34 (7)	35 (7)
Primary tumour stage, n (%)	T0–T1a	6 (1)	0
	T1b–T2	44 (9)	36 (8)
	T3	307 (65)	321 (68)
	T4a	101 (21)	103 (22)
	T4b	16 (3)	14 (3)
Clinical lymph node status,* n (%)	Positive	329 (69)	330 (70)
	Negative	145 (31)	144 (30)
PD-L1 expression status by TAP,† n (%)	<1%	48 (10)	47 (10)
	≥1%	426 (90)	427 (90)
	<5%	236 (50)	230 (49)
	≥5%	238 (50)	244 (52)
Histology type, n (%)	Intestinal	174 (37)	168 (35)
	Diffuse	104 (22)	85 (18)
	Unspecified adenocarcinoma or other	196 (41)	221 (47)

*Stratification factor data. †Measured by VENTANA PD-L1 (SP263) assay.
ECOG, Eastern Cooperative Oncology Group; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastro-oesophageal junction; PD-L1, programmed cell death ligand-1; PS, performance status.

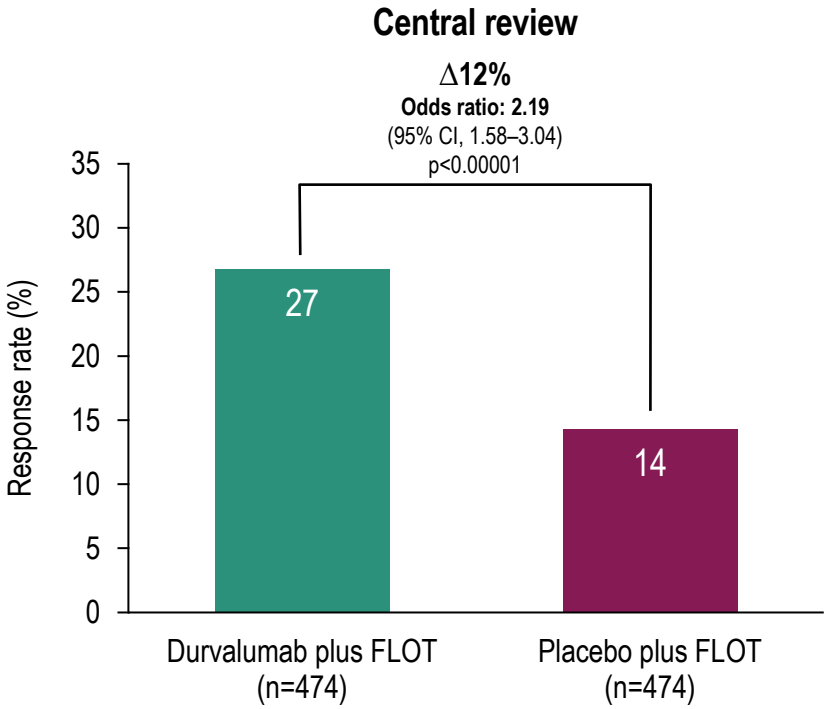
Pathological complete response





Participants achieve pCR if there is no residual viable tumour cells found at primary tumour and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central (or local) assessment. Central review of pCR was scored using modified Ryan criteria which assess both the primary tumour and lymph nodes.
CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; pCR, pathological complete response.

Combined complete and near-complete pathological response

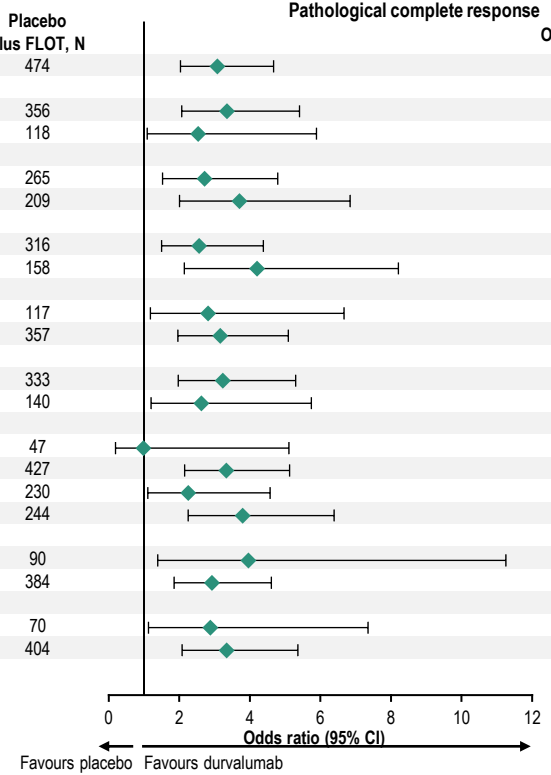


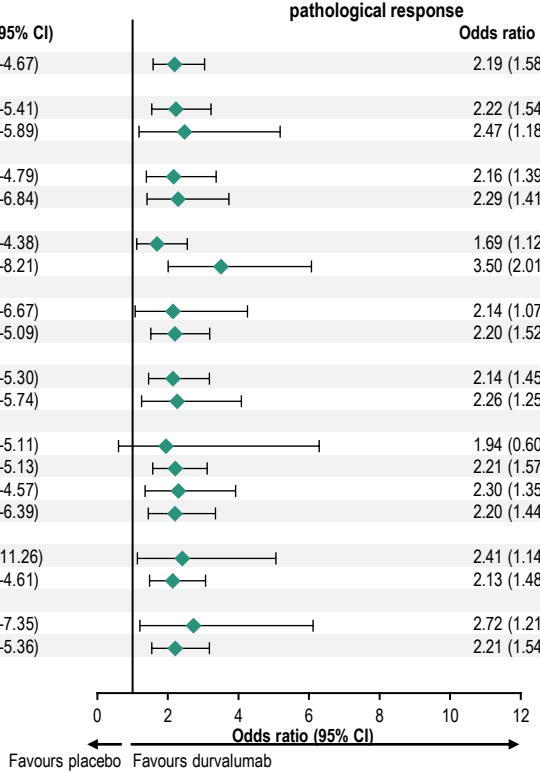
Near-complete pathological response = single or rare small groups of cancer cells at time of resection per modified Ryan criteria

Participants achieve pCR if there is no residual viable tumour cells found at primary tumour and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central (or local) assessment. Central review of pCR was scored using modified Ryan criteria.
CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; pCR, pathological complete response.

Pathological response subgroup analysis (central review)

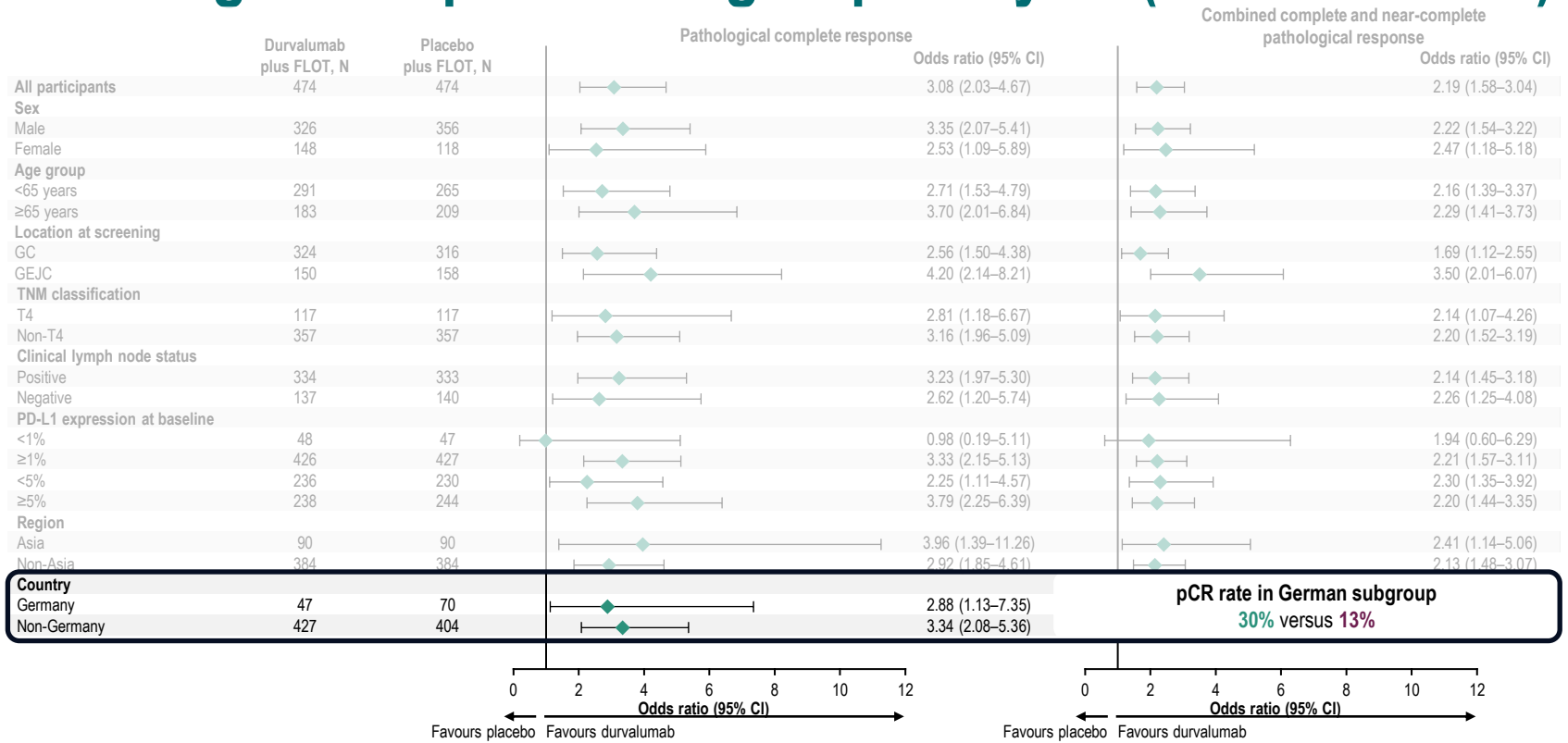
	Durvalumab plus FLOT, N	Placebo plus FLOT, N	Pathological complete response: Odds ratio (95% CI)	Combined complete and near-complete pathological response: Odds ratio (95% CI)
All participants	474	474	3.08 (2.03–4.67)	2.19 (1.58–3.04)
Sex				
Male	326	356	3.35 (2.07–5.41)	2.22 (1.54–3.22)
Female	148	118	2.53 (1.09–5.89)	2.47 (1.18–5.18)
Age group				
<65 years	291	265	2.71 (1.53–4.79)	2.16 (1.39–3.37)
≥65 years	183	209	3.70 (2.01–6.84)	2.29 (1.41–3.73)
Location at screening				
GC	324	316	2.56 (1.50–4.38)	1.69 (1.12–2.55)
GEJC	150	158	4.20 (2.14–8.21)	3.50 (2.01–6.07)
TNM classification				
T4	117	117	2.81 (1.18–6.67)	2.14 (1.07–4.26)
Non-T4	357	357	3.16 (1.96–5.09)	2.20 (1.52–3.19)
Clinical lymph node status				
Positive	334	333	3.23 (1.97–5.30)	2.14 (1.45–3.18)
Negative	137	140	2.62 (1.20–5.74)	2.26 (1.25–4.08)
PD-L1 expression at baseline				
<1%	48	47	0.98 (0.19–5.11)	1.94 (0.60–6.29)
≥1%	426	427	3.33 (2.15–5.13)	2.21 (1.57–3.11)
<5%	236	230	2.25 (1.11–4.57)	2.30 (1.35–3.92)
≥5%	238	244	3.79 (2.25–6.39)	2.20 (1.44–3.35)
Region				
Asia	90	90	3.96 (1.39–11.26)	2.41 (1.14–5.06)
Non-Asia	384	384	2.92 (1.85–4.61)	2.13 (1.48–3.07)
Country				
Germany	47	70	2.88 (1.13–7.35)	2.72 (1.21–6.12)
Non-Germany	427	404	3.34 (2.08–5.36)	2.21 (1.54–3.18)





Participants achieve pCR if there is no residual viable tumour cells found at primary tumour and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central (or local) assessment. Central review of pCR was scored using modified Ryan criteria.
CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand-1.

Pathological response subgroup analysis (central review)



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CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand-1.

Surgery and margin free resection

		Durvalumab plus FLOT (n=474)		Placebo plus FLOT (n=474)
Participants with attempted surgery, n (%)		430 (91)		422 (89)
Participants with completed surgery, n (%)		411 (87)		399 (84)
Participants with surgery attempted but not completed, n (%)		19 (4)		23 (5)
Surgery performed				
	n; % (95% CI)	411; 87 (83.3–89.6)		399; 84 (80.6–87.4)
	OR (95% CI)		1.23 (0.85–1.76)	
R0 resection in participants with attempted surgery				
	n; % (95% CI)	369; 86 (82.2–89.0)		362; 86 (82.1–89.0)
	OR (95% CI)		1.00 (0.68–1.48)	
Participants who did not undergo surgery, n (%)		44 (9)		52 (11)
Type of surgery, n (%)	Distal gastrectomy	39 (8)		38 (8)
	Subtotal gastrectomy	80 (17)		73 (15)
	Total gastrectomy	169 (36)		165 (35)
	Gastroesophagectomy	128 (27)		127 (27)
	Missing	14 (3)		19 (4)
Type of lymphadenectomy, n (%)	D1	49 (10)		35 (7)
	D2	357 (75)		359 (76)
	D3	6 (1)		5 (1)
	Missing	62 (13)		75 (16)

CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; OR, odds ratio.

Pathological staging of participants who underwent surgery

Stage	Durvalumab plus FLOT (n=430)	Placebo plus FLOT (n=422)
T0, n (%)	98 (23)	45 (11)
N0, n (%)	223 (52)	154 (37)
T-stage, n (%)		
≤T1	153 (36)	98 (23)
T2	54 (13)	46 (11)
T3	131 (30)	165 (39)
T4	48 (11)	65 (15)
M1, n (%)	4 (1)	7 (2)
Missing, n (%)	40 (9)	47 (11)

Pathological staging assessed by central review.
FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Exposure

At DCO, 45% of participants in the durvalumab plus FLOT arm and 43% in the placebo plus FLOT arm were ongoing treatment*

	Durvalumab plus FLOT (n=474)	Placebo plus FLOT (n=474)†
Number of pre-operative cycles of durvalumab or placebo plus FLOT (Day 1 and 15), n (%)		
≥1 cycle	474 (100)	470 (99)
2 cycles	462 (98)	454 (96)
Number with completed surgery, n (%)	411 (87)	397 (84)
Number of post-operative cycles of durvalumab or placebo ± FLOT (Day 1 and 15 for first 2 cycles), n (%)		
≥1 cycle	352 (74)	342 (72)
≥2 cycles	328 (69)	317 (67)
≥3 cycles	301 (64)	290 (61)
≥4 cycles	271 (57)	259 (55)
≥5 cycles	240 (51)	229 (48)
≥6 cycles	210 (44)	200 (42)
≥7 cycles	182 (38)	179 (38)
≥8 cycles	164 (35)	155 (33)
≥9 cycles	140 (30)	136 (29)
≥10 cycles	117 (25)	117 (25)
≥11 cycles	102 (22)	96 (20)
≥12 cycles	87 (18)	80 (17)

63% of participants in each arm received four post-operative doses of FLOT

*Include participants that have completed surgery but not yet received post-operative treatment. †One placebo participant received a single dose of durvalumab.
DCO, data cut-off; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Safety and tolerability

	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)
Any-grade all-causality adverse events, n (%)	470 (99)	463 (99)
Max Grade 3 / 4	326 (69)	317 (68)
Serious adverse events	210 (44)	196 (42)
Leading to death	24 (5)	19 (4)
Leading to surgery delay	15 (3)	8 (2)
Leading to discontinuation of durvalumab or placebo	34 (7)	29 (6)
Leading to discontinuation of FLOT	110 (23)	94 (20)
Any adverse event possibly related to any study treatment, n (%)	452 (95)	441 (94)
Max Grade 3/4 treatment-related adverse events	275 (58)	264 (56)
Serious treatment-related adverse events	96 (20)	75 (16)
Treatment-related adverse events leading to death	5 (1)	2 (0)
Max Grade 3 / 4 most common (≥5%†) adverse events possibly related to any study treatment, n (%)		
Neutropenia	93 (20)	96 (21)
Neutrophil count decreased	90 (19)	102 (22)
Diarrhoea	25 (5)	20 (4)
White blood cell count decreased	25 (5)	27 (6)

*One placebo patient received a single dose of durvalumab and is therefore included in the durvalumab plus FLOT group. †In at least one treatment arm.
FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Conclusions

- MATTERHORN is the first global, Phase 3, randomised, double-blind study, assessing peri-operative durvalumab plus FLOT in participants with resectable GC / GEJC
- At this pre-planned interim analysis, addition of durvalumab to peri-operative FLOT demonstrated:
  - A statistically significant and clinically relevant improvement in pCR versus placebo plus FLOT, with an absolute between-arm difference in pCR rate of 12%
  - an improvement in downstaging, with more participants achieving T0 and N0 versus placebo plus FLOT
- Adverse events incidence was similar between arms, and the observed adverse events were as expected, with no new safety concerns identified for durvalumab plus FLOT
- The MATTERHORN study is ongoing for the primary objective of EFS

FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; EFS, event-free survival; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; pCR, pathological complete response.

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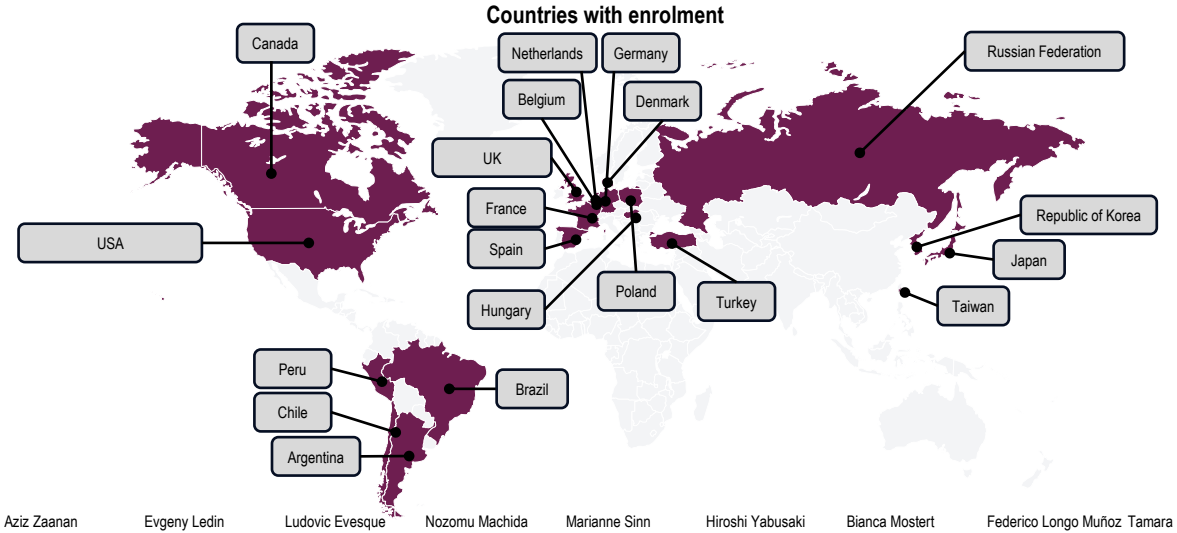

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Plain language summary

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Salah-Eddin Al-Batran

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Plain language summary

Pathological complete response to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastro-oesophageal junction cancer: interim results of the global, Phase 3 MATTERHORN study

Why did we perform this research?

- Gastric cancer / gastro-oesophageal junction cancer (GC / GEJC) are the fifth most diagnosed cancer worldwide
- FLOT is a specific combination of four medications and is a type of chemotherapy used to treat GC / GEJC. Durvalumab is a type of immunotherapy called an immune checkpoint inhibitor. In other cancers, the addition of immune checkpoint inhibitors to chemotherapy has a benefit versus chemotherapy alone
- We are currently performing the MATTERHORN study to test how well adding pre- and post-operative treatment with durvalumab to FLOT works, compared with FLOT alone, for treating GC / GEJC
- Here, we looked at whether all signs of cancer disappeared after treatment

How did we perform this research?

The amount of cancer that remains after surgery and treatment with durvalumab plus FLOT or FLOT alone was assessed. Side effects and how successful a participant's surgery was were also assessed

What were the findings of this research?

The disappearance of all signs of cancer was more common in participants treated with durvalumab plus FLOT than in those treated with FLOT alone. Surgery was similarly successful for participants treated with durvalumab plus FLOT than in those treated with FLOT alone. Side effects of durvalumab plus FLOT are manageable. The MATTERHORN study is still continuing

What are the implications of this research?

These results support the use of pre-operative treatment with durvalumab to FLOT chemotherapy for the treatment of resectable GC / GEJC

Where can I access more information?

Information about the medicines being used in this study and the people who could participate can be found here: clinicaltrials.gov/study/NCT04592913/MATTERHORN

FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer.

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Supplementary material

Enrolment by country (randomised population)

Country	Number enrolled, n (%)
Global	**948**
Germany	117 (12)
Japan	86 (9)
Spain	61 (6)
Poland	59 (6)
Brazil	54 (6)
USA	53 (6)
Republic of Korea	52 (5)
Chile	50 (5)
Turkey	50 (5)
France	49 (5)
Russian Federation	49 (5)
UK	46 (5)
Taiwan	42 (4)
Argentina	39 (4)
Peru	37 (4)
Hungary	33 (3)
Canada	29 (3)
Denmark	17 (2)
Belgium	13 (1)
Netherlands	12 (1)