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End-of-study analysis from JACOB: a phase III study of pertuzumab (P) + trastuzumab (H) and chemotherapy (CT) in HER2-positive metastatic gastric or gastro-oesophageal junction cancer (mGC/GEJC)

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Disclosure information

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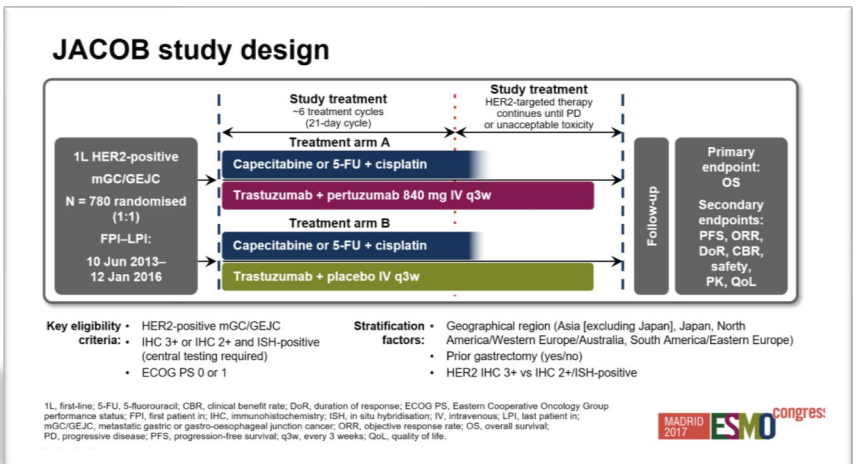
Background

- The addition of H to CT significantly improved OS in patients with previously untreated, HER2-positive locally advanced or metastatic GC/GEJC[1]
- In studies in patients with HER2-positive early and metastatic BC, the addition of P to H + CT significantly improved outcomes[2–4]
- There may be differences in the biology of HER2-positive BC and GC/GEJC, e.g. HER2 heterogeneity is more common in GC[5]
- JACOB assessed the efficacy and safety of P + H + CT in patients with previously untreated HER2-positive metastatic GC/GEJC[6]
  - Primary analyses were previously reported and showed that OS was not significantly improved with the addition of P to H + CT (median follow-up: >24.4 mo*)[6]
- Here, we present the results of the end-of-study descriptive analyses (median follow-up: >44.4 mo†)

* Median follow-up: P + H + CT = 24.4 mo; PLA + H + CT = 25.0 mo. † Median follow-up: P + H + CT = 46.1 mo; PLA + H + CT = 44.4 mo.
BC, breast cancer; CT, chemotherapy; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; H, trastuzumab; mo, months; OS, overall survival; P, pertuzumab; PLA, placebo.
1. Bang YJ & Van Cutsem E, *et al. Lancet* 2010; **376:**687–97; 2. Baselga J, *et al. N Engl J Med* 2012; **366:**109–19; 3. Swain SM, *et al. N Engl J Med* 2015; **372:**724–34;
4. von Minckwitz G, *et al. N Engl J Med* 2017; **377:**122–31; 5. Rueschoff J, *et al. Mod Pathol* 2012; **25:**637–50; 6. Tabernero J, et al. *Lancet Oncol* 2018; **19:** 30481–9.

JACOB: Phase III study in 1L, HER2-positive mGC/GEJC
Primary analysis



Statistical considerations	
Target HR	0.77 (502 OS events for 80% power at two-sided alpha 0.05)
Median OS	Placebo arm: 15.0 mo; Pertuzumab arm: 19.3 mo
Minimum detectable difference	HR = 0.836

One interim efficacy analysis at ~70% information fraction*

A hierarchical testing procedure was implemented for the analysis of OS, PFS and ORR

* Interim efficacy analysis boundary was determined by applying the Lan-DeMets method and an O'Brien-Fleming alpha-spending function. Interim analysis OS: HR = 0.77 (95% CI 0.63, 0.96; P-value = 0.017); this result missed the interim analysis stopping boundary of 0.0157. Primary analyses were presented at the ESMO 2017 Congress (data cut-off: 9 December 2016).

1L, first-line; 5-FU, 5-fluorouracil; CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FPI, first patient in; GEJC, gastro-oesophageal junction cancer; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridisation; IV, intravenous; LPI, last patient in; mGC, metastatic gastric cancer; mo, months; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; q3w, every 3 weeks; QoL, quality of life.

Tabernero J, et al. *Ann Oncol* 2017; **28:** suppl. 5; Tabernero J, et al. *Lancet Oncol* 2018; **19:** 30481–9.

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Baseline patient demographics and disease characteristics

Primary analysis

ITT population	P + H + CT n = 388	PLA + H + CT n = 392
Sex, %		
Male	294 (76%)	323 (82%)
Female	94 (24%)	69 (18%)
Age, years		
Median (IQR)	62.0 (54·5–69)	61.0 (54–68%)
Geographic region		
Asia (excluding Japan)	143 (37%)	146 (37%)
Japan	40 (10%)	40 (10%)
North America, western Europe, Australia	133 (34%)	133 (34%)
South America, eastern Europe	72 (19%)	73 (19%)
Measurability, %		
Measurable disease	351 (91%)	352 (90%)
Non-measurable evaluable disease only	37 (10%)	40 (10%)
Number of metastatic sites, %*		
1–2	305 (79%)	303 (78%)
>2	83 (21%)	88 (23%)

ITT population	P + H + CT n = 388	PLA + H + CT n = 392
Histological subtypes (Lauren classification), %		
Diffuse	18 (5%)	21 (5%)
Intestinal	353 (91%)	350 (89%)
Other†	17 (4%)	21 (5%)
Primary site, %		
Gastro-oesophageal junction	110 (28%)	98 (25%)
Stomach	278 (72%)	294 (75%)
ECOG performance status, %*		
0	162 (42%)	162 (41%)
1	226 (58%)	229 (59%)
HER2 status, %		
IHC 2+ and in situ hybridisation-positive	129 (33%)	130 (33%)
IHC 3+	259 (67%)	262 (67%)
Previous gastrectomy		
Yes	105 (27%)	102 (26%)
No	283 (73%)	290 (74%)

* n = 391 in the PLA + H + CT arm. † Mixed or indeterminable. Data are n (%), unless otherwise specified. CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; H, trastuzumab; IHC, immunohistochemistry; IQR, interquartile range; ITT, intention-to-treat; P, pertuzumab; PLA, placebo. Tabernero J, *et al. Ann Oncol* 2017; **28:** suppl. 5; Tabernero J, *et al. Lancet Oncol* 2018; **19:** 30481–9. Reprinted from *The Lancet Oncology*, 19 (10), Josep Tabernero, Paulo M Hoff, Lin Shen, Atsushi Ohtsu, Manish A Shah, Karen Cheng, Chunyan Song, Haiyan Wu, Jennifer Eng-Wong, Katherine Kim, Yoon-Koo Kang. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study, 1372–84, Copyright (2018), with permission from Elsevier.

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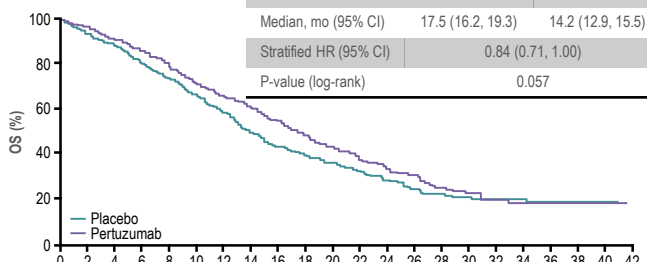
Efficacy results (ITT population)

Primary analysis

Primary endpoint: OS*

ITT population	P + H + CT (n = 388)	PLA + H + CT (n = 392)
Events, n	242	262
Median, mo (95% CI)	17.5 (16.2, 19.3)	14.2 (12.9, 15.5)
Stratified HR (95% CI)	0.84 (0.71, 1.00)	
P-value (log-rank)	0.057	



Number at risk (number censored)

P + H + CT	388	363 (10)	342 (34)	323 (12)	297 (14)	266 (15)	243 (17)	209 (35)	175 (49)	149 (56)	114 (75)	92 (86)	67 (100)	54 (108)	36 (117)	27 (123)	16 (131)	10 (136)	6 (140)	4 (142)	3 (242)
PLA + H + CT	392	359 (9)	339 (11)	306 (13)	279 (15)	252 (15)	221 (16)	175 (31)	143 (42)	118 (54)	95 (69)	76 (78)	60 (86)	47 (91)	38 (96)	31 (101)	23 (108)	14 (117)	7 (123)	4 (126)	2 (128)

- OS was not significantly improved with the addition of P (vs placebo) to H + CT
- 16% reduction in risk of death and 3.3 mo increase in median OS

Secondary endpoints	P + H + CT (n = 388)	PLA + H + CT (n = 392)
Events, n	311	324
Median PFS, mo (95% CI)	8.5 (8.2, 9.7)	7.2 (6.4, 8.2)
HR (95% CI)	0.73 (0.62, 0.86)	
Baseline measurable disease	n = 351	n = 352
ORR, % (CR + PR)	56.7	48.3
Difference, % (95% CI)	8.4 (0.9–15.9)	
Median DoR, mo (95% CI)	n = 199 10.2 (8.4, 10.7)	n = 170 8.4 (6.8, 8.7)

PFS

- 27% reduction in risk of progression or death

ORR

- 8.4% improvement in ORR

Due to hierarchical testing, statistical significance could not be concluded

* Median follow-up: P + H + CT = 24.4 mo; PLA + H + CT = 25.0 mo. Clinical cut-off: 9 December 2016. ITT population: all randomised patients. CI, confidence interval; CR, complete response; CT, chemotherapy; DoR, duration of response; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; mo, months; ORR, objective response rate; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PLA, placebo; PR, partial response. Tabernero J, et al. *Ann Oncol* 2017; **28:** suppl. 5; Tabernero J, et al. *Lancet Oncol* 2018; **19:** 30481–9. OS and PFS results reprinted from *The Lancet Oncology*, 19 (10), Josep Tabernero, Paulo M Hoff, Lin Shen, Atsushi Ohtsu, Manish A Shah, Karen Cheng, Chunyan Song, Haiyan Wu, Jennifer Eng-Wong, Katherine Kim, Yoon-Koo Kang. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study, 1372–84, Copyright (2018), with permission from Elsevier.

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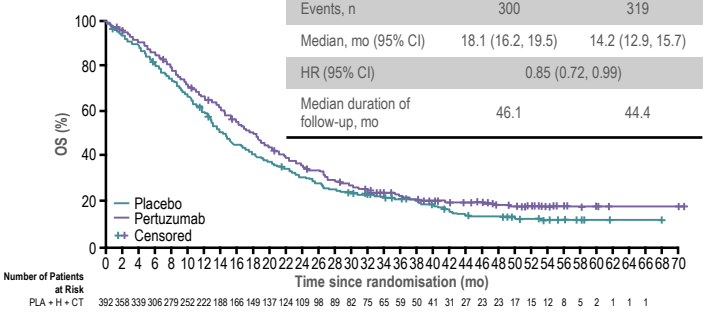
Efficacy results
End-of-study analysis

Primary endpoint: OS

ITT population	P + H + CT (n = 388)	PLA + H + CT (n = 392)
Events, n	300	319
Median, mo (95% CI)	18.1 (16.2, 19.5)	14.2 (12.9, 15.7)
HR (95% CI)	0.85 (0.72, 0.99)	
Median duration of follow-up, mo	46.1	44.4



Secondary endpoints	P + H + CT (n = 388)	PLA + H + CT (n = 392)
Events, n	342	353
Median PFS, mo (95% CI)*	8.5 (8.3, 9.7)	7.2 (6.4, 8.2)
Stratified HR (95% CI)	0.73 (0.62, 0.85)	
Baseline measurable disease	n = 351	n = 352
ORR, % (CR + PR)	57.0	48.6
Median DoR, mo (95% CI)	n = 203 10.2 (8.5, 12.0)	n = 175 8.4 (6.8, 9.1)

- Addition of P to H + CT (vs PLA) resulted in a 15% reduction in risk of death and a 3.9 mo increase in median OS (this analysis was descriptive)
- A numerically higher percentage of patients achieved an objective response (median DoR was 1.8 mo longer in the pertuzumab vs placebo arm)

* Median duration of PFS follow up: P + H + CT = 50.4 mo; PLA + H + CT = 47.4 mo.
Database lock: 24 Jan 2020. All analyses are descriptive.
CI, confidence interval; CR, complete response; CT, chemotherapy; DoR, duration of response; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; mo, months; ORR, objective response rate; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PLA, placebo; PR, partial response.

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Safety overview
End-of-study analysis

- The overall safety profile was considered acceptable and comparable between arms

Safety population, n (%)	P + H + CT n = 385	PLA + H + CT n = 388
Overall safety		
AE	381 (99.0)	385 (99.2)
All-grade diarrhoea	241 (62.6)	139 (35.8)
AE with fatal outcome	27 (7.0)	31 (8.0)
Serious AE	178 (46.2)	156 (40.2)
Grade ≥3 AE	310 (80.5)	288 (74.2)
Dose modifications		
AE leading to P/PLA dose discontinuation	48 (12.5)	46 (11.9)
AE leading to P/PLA dose interruption and / or delay	110 (28.6)	94 (24.2)
Cardiac safety		
Symptomatic LVSD / heart failure	3 (0.8)	1 (0.3)
Asymptomatic LVSD / heart failure	20 (5.2)	18 (4.6)

Database snapshot lock: 24 Jan 2020. All analyses are descriptive. Safety population: all patients who received at least one dose of any study treatment.
AE, adverse event; CT, chemotherapy; H, trastuzumab; LVSD, left ventricular systolic dysfunction; P, pertuzumab; PLA, placebo.

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Post-treatment anti-cancer therapy (>1% of patients overall)

End-of-study analysis

ITT population, n (%)	P + H + CT n = 388	PLA + H + CT n = 392
Patients with >1 treatment	178 (45.9)	180 (45.9)
Overall number of treatments	484	514
Taxanes	117 (30.2)	114 (29.1)
Monoclonal antibodies	71 (18.3)	80 (20.4)
Topoisomerase inhibitors	54 (13.9)	59 (15.1)
Anti-metabolites	48 (12.4)	61 (15.6)
Platinum compounds	36 (9.3)	35 (8.9)
No coding available	27 (7.0)	29 (7.4)
Folic acid and derivatives	17 (4.4)	19 (4.8)
Anti-neoplastic agents NEC	15 (3.9)	13 (3.3)
Antineoplastic adjuncts	9 (2.3)	8 (2.0)
Tyrosine kinase inhibitors	6 (1.5)	10 (2.6)
Cytotoxic antibiotics	6 (1.5)	1 (0.3)
Herbal, homeopathic & dietary supplements	2 (0.5)	3 (0.8)
Pharmacotherapeutic class(es) not known	4 (1.0)	1 (0.3)
Immunostimulants	1 (0.3)	3 (0.8)

Database snapshot lock: 24 Jan 2020. All analyses are descriptive. Safety population: all patients who received at least one dose of any study treatment.
CT, chemotherapy; H, trastuzumab; ITT, intention-to-treat; P, pertuzumab.

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Conclusions

- JACOB did not meet its primary endpoint, but the end-of-study analysis confirmed evidence of treatment activity, with a 15% reduction in risk of death when adding P to H + CT in previously untreated patients with mGC/GEJC
  - Median OS was 18.1 months in the P + H + CT arm vs 14.2 months in the PLA + H + CT arm at >44.4 mo* (stratified HR 0.85 [95% CI 0.72, 0.99])
- The overall safety profile of P + H + CT was considered acceptable, although the incidence of all-grade diarrhoea was higher with P vs PLA
- The limited activity of P in combination with H in gastric cancer may be multi-factorial:
  - The underlying differences in HER2 expression between gastric tumours and breast tumours; gastric tumours more frequently show heterogeneity of HER2 expression[1]
  - The increased complexity of gastric tumours suggests that HER2 signalling may not be the only driver of disease progression
- The standard of care in 1L HER2-positive metastatic GC remains H plus cisplatin and oral / IV fluoropyrimidine CT

* Median follow-up: P + H + CT = 46.1 mo; PLA + H + CT = 44.4 mo.
1L, first line; CT, chemotherapy; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; H, trastuzumab; HR, hazard ratio; IV, intravenous; mGC, metastatic gastric cancer; OS, overall survival; P, pertuzumab.
1. Rueschoff J, *et al*. *Mod Pathol* 2012; **25:**637–50

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