Cetuximab in combination with capecitabine and cisplatin as first-line treatment in advanced gastric cancer: Randomized controlled phase III EXPAND study

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Disclosures

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Rationale for cetuximab in advanced gastric cancer (AGC)

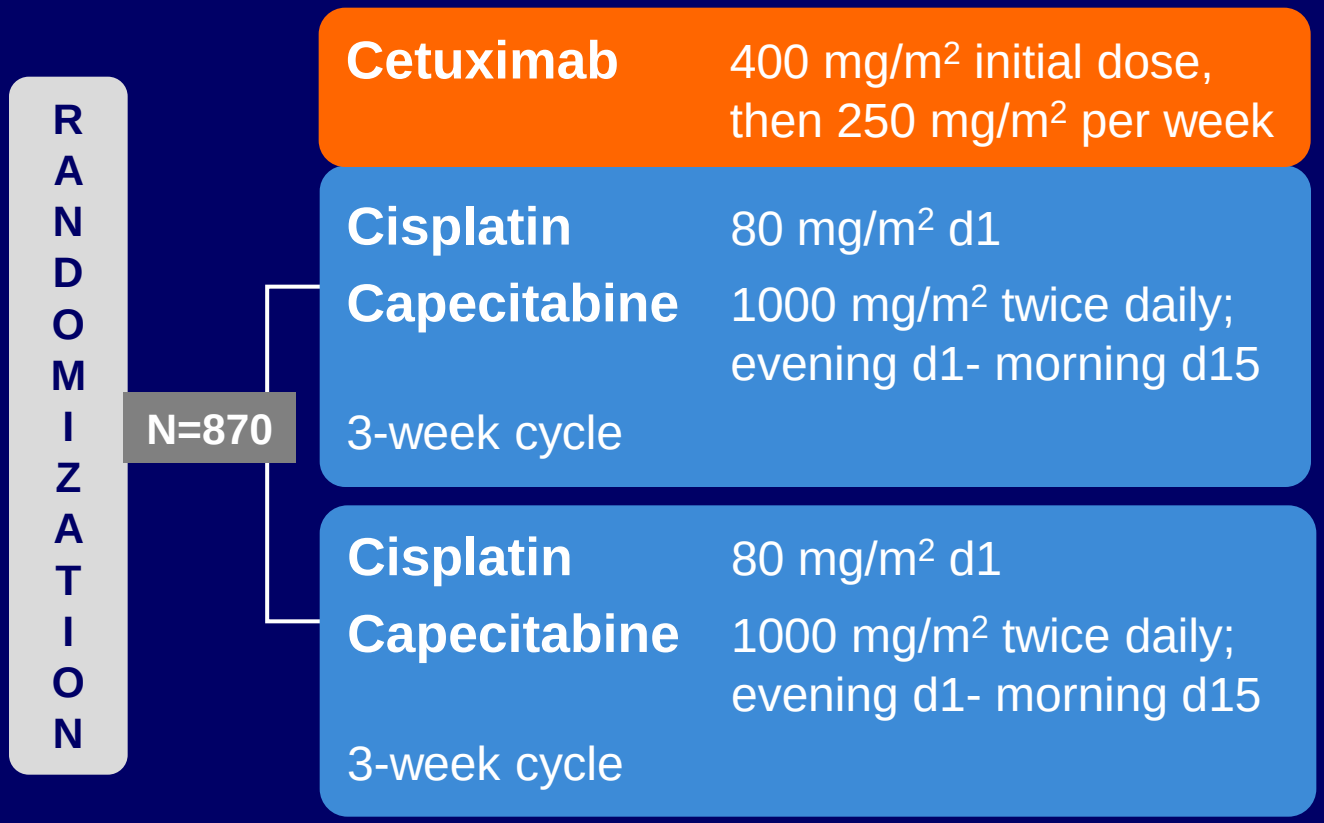
- EGFR pathway is important for tumor growth and metastasis
  - Rates of EGFR over-expression vary in AGC

- Cetuximab
  - Chimeric IgG1 monoclonal antibody targeting EGFR
  - Mediates antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Effective and safe in mCRC and SCCHN
  - Promising results in phase II studies in AGC[1-3]

EGFR, epidermal growth factor receptor;
mCRC, metastatic colorectal cancer;
SCCHN, squamous cell carcinoma of the head and neck

[1]Lordick F, et al. Br J Cancer 2010;102:500-5
[2]Moehler M, et al. Ann Oncol 2011;22:1358-66
[3]Pinto C, et al. Br J Cancer 2009;101:1261-68

Study design



Study treatment until:

- Radiographically documented PD
- Unacceptable toxicity
- Withdrawal of consent

- Stratified by: disease status, prior esophago-/gastrectomy, prior (neo-) adjuvant chemo (radio) therapy

PD, progressive disease

Endpoints and statistical assumptions

- **Primary endpoint**: PFS assessed by independent review
- **Secondary endpoints**: OS, ORR, safety, QoL, biomarkers
- **Statistical assumptions**
  - 631 events required to detect HR=0.8 with 80% power and α=0.05 for:
    - PFS (median PFS improvement from 5.6 to 7 months)
    - OS (median OS improvement from 10 to 12.5 months)
  - Required sample size: 870 patients
- Protocol amended to make final analysis at 631 PFS events or 31 March 2012 (whichever occurred first)
  - Due to lower than expected PFS event rate

HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life

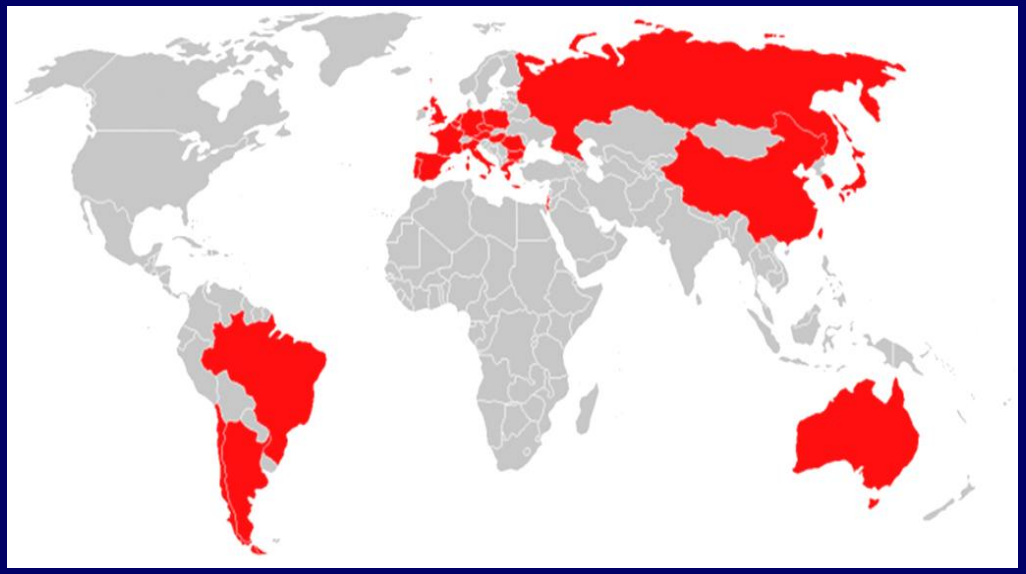
Main eligibility criteria

- Adenocarcinoma of the stomach or GEJ
- Measurable disease according to RECIST (version 1)
- Unresectable advanced (M0) or metastatic (M1) disease
- Adequate hematological and organ function and ECOG PS <2
- No previous chemotherapy for advanced disease
- No previous adjuvant chemotherapy within 1 year and <300 mg/m^2 cisplatin administered
- No prior treatment with anti-EGFR and/or VEGF(R) targeting agents
- No clinically relevant cardiac disease (CAD, CHF, cardiomyopathy, MI within 1 year or high risk of uncontrolled arrhythmia)

CAD, coronary artery disease; CHF, congestive heart failure; GEJ, gastro-esophageal junction; ECOG PS, Eastern Cooperative Group Performance status; MI, myocardial infarction; VEGF(R), vascular endothelial growth factor (receptor)

Trial conduct

- From June 2008 to December 2010, 904 patients randomized
- Total of 164 sites in 25 countries worldwide
- Recruitment temporarily suspended in 2009 after 380 patients randomized, due to an imbalance in cardiac events detected by DSMB, and restarted after implementation of a cardiac monitoring programme
- Data cut-off for final analysis
  - 31 March 2012



DSMB, data safety monitoring board

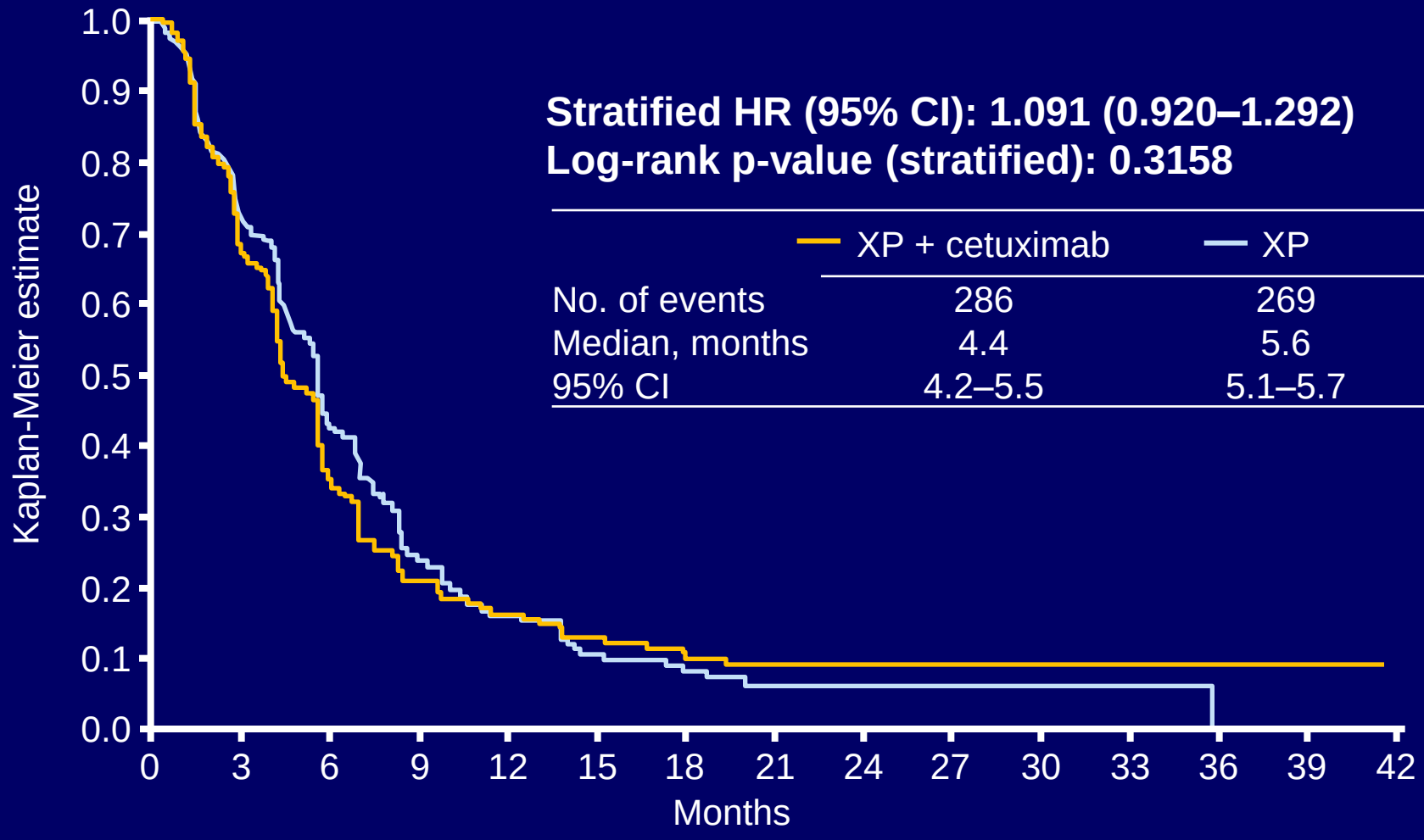
Demographics and disease characteristics

Parameter, %	XP + cetuximab n=455	XP n=449
Male/female	75/25	74/26
Age, yrs, median (range)	60 (23–84)	59 (18–81)
≥65 yrs	31	31
ECOG PS, 0/1	52/48	51/49
Ethnic origin		
Caucasian	53	55
Asian	38	37
Other	9	8
Primary site, stomach/GEJ	83/16	83/16
Histological type (Laurén)		
Intestinal	36	33
Diffuse	17	21
Mixed	5	6
Unknown	42	40
Peritoneal metastasis, Yes/No	25/75	26/74
Disease status*, locally advanced/metastatic	4/96	3/97
Prior esophago- or gastrectomy*, Yes/No	20/80	20/80
Prior (neo-) adjuvant/ chemo (radio) therapy*, Yes/No	6/94	6/94

*Stratification factors

XP, capecitabine (Xeloda®) and cisplatin

Primary endpoint: PFS (IRC)



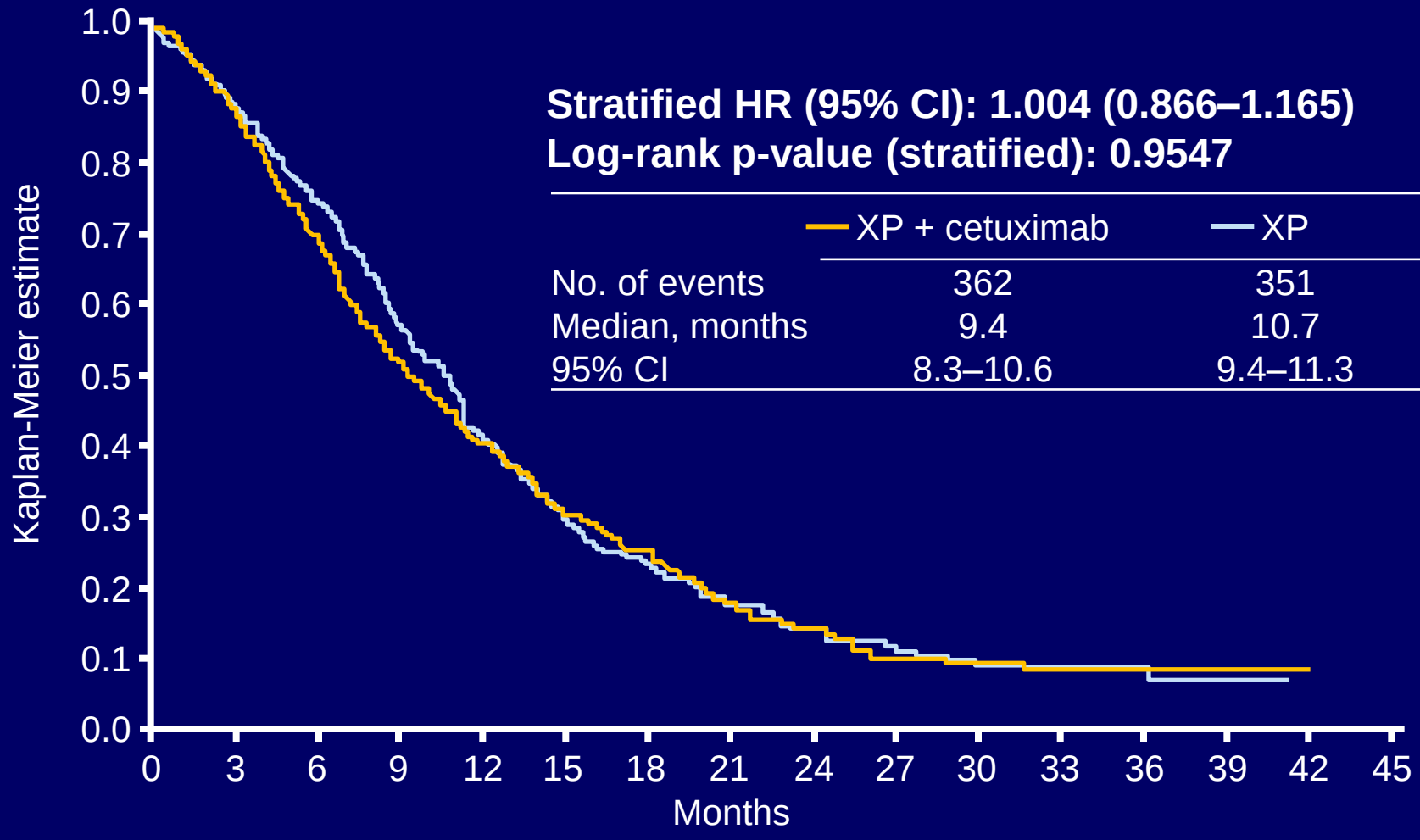
Stratified HR (95% CI): 1.091 (0.920–1.292)
Log-rank p-value (stratified): 0.3158

	XP + cetuximab	XP
No. of events	286	269
Median, months	4.4	5.6
95% CI	4.2–5.5	5.1–5.7

XP + cetuximab	**455**	**233**	**94**	**44**	**30**	**20**	**14**	**8**	**4**	**4**	**3**	**3**	**1**	**1**	**0**
XP	**449**	**244**	**116**	**50**	**29**	**17**	**10**	**4**	**4**	**4**	**4**	**2**	**0**	**0**	**0**

HR, hazard ratio; IRC, independent review committee

Overall survival



Stratified HR (95% CI): 1.004 (0.866–1.165)
Log-rank p-value (stratified): 0.9547

	XP + cetuximab	XP
No. of events	362	351
Median, months	9.4	10.7
95% CI	8.3–10.6	9.4–11.3

XP + cetuximab	**455**	**382**	**298**	**224**	**171**	**129**	**91**	**51**	**27**	**16**	**14**	**12**	**5**	**2**	**1**	**0**
XP	**449**	**379**	**314**	**238**	**169**	**119**	**77**	**39**	**26**	**18**	**15**	**14**	**5**	**1**	**0**	**0**

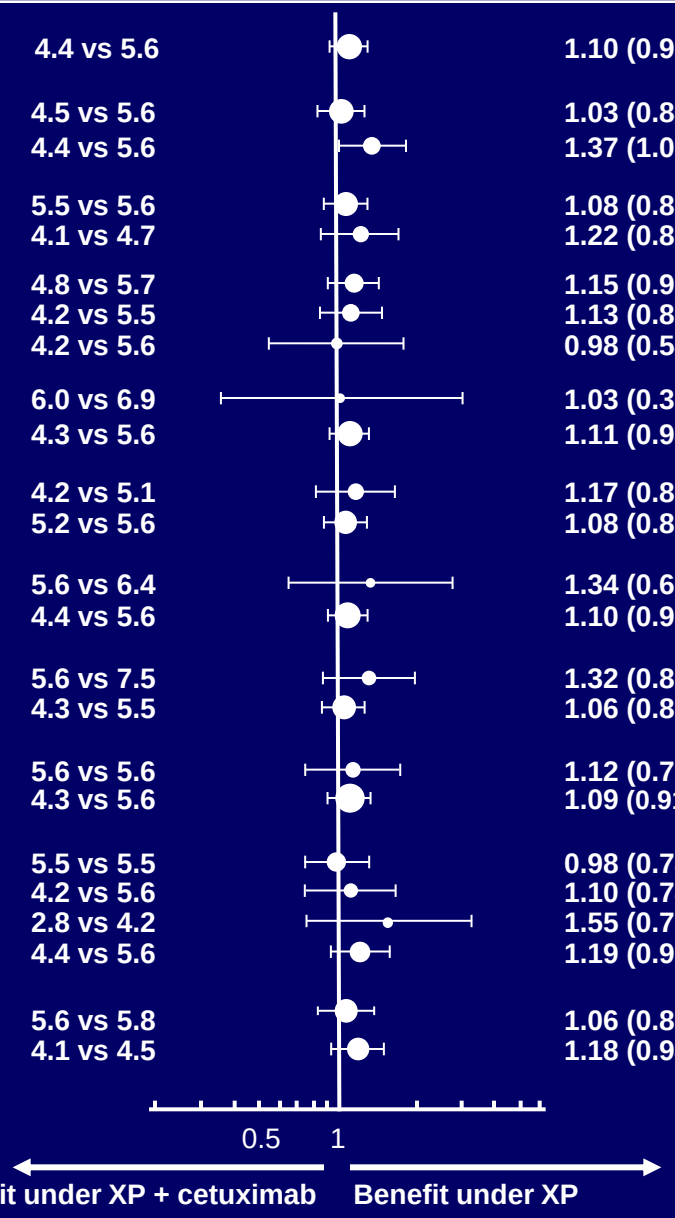
Best overall response (IRC)

Parameter, n (%)	XP + cetuximab n=455	XP n=449
Best overall response rate (CR+PR) 95% CI	136 (30) 26–34	131 (29) 25–34
Disease control rate (CR+PR+SD) 95% CI	332 (73) 69–77	317 (71) 66–75
Complete response	2 (0)	2 (0)
Partial response	134 (30)	129 (29)
Stable disease	196 (43)	186 (41)
Progressive disease	65 (14)	61 (14)
Unknown	58 (13)	71 (16)

CR, complete response; PR, partial response; SD, stable disease

PFS (IRC): subgroups

Subgroup	Number of patients	Median (months) XP + cetuximab vs XP	HR* (95% CI)
PFS	ITT population (n=904)	4.4 vs 5.6	1.10 (0.93–1.30)
Age	<65 (n=624)	4.5 vs 5.6	1.03 (0.84–1.26)
	≥65 (n=280)	4.4 vs 5.6	1.37 (1.01–1.86)
Gender	Male (n=673)	5.5 vs 5.6	1.08 (0.89–1.31)
	Female (n=231)	4.1 vs 4.7	1.22 (0.87–1.71)
Ethnic origin	Caucasian/white (n=490)	4.8 vs 5.7	1.15 (0.92–1.45)
	Asian (n=339)	4.2 vs 5.5	1.13 (0.86–1.48)
	Other (black) (n=75)	4.2 vs 5.6	0.98 (0.54–1.78)
Disease stage	M0 (n=28)	6.0 vs 6.9	1.03 (0.35–3.01)
	M1 (n=875)	4.3 vs 5.6	1.11 (0.94–1.32)
Peritoneal metastasis	Yes (n=229)	4.2 vs 5.1	1.17 (0.83–1.65)
	No (n=675)	5.2 vs 5.6	1.08 (0.89–1.31)
Previous (neo-)adjuvant chemo(radio) therapy	Yes (n=55)	5.6 vs 6.4	1.34 (0.65–2.79)
	No (n=849)	4.4 vs 5.6	1.10 (0.92–1.30)
Previous esophagectomy/gastrectomy	Yes (n=182)	5.6 vs 7.5	1.32 (0.88–1.97)
	No (n=722)	4.3 vs 5.5	1.06 (0.88–1.27)
Primary site	GEJ (n=144)	5.6 vs 5.6	1.12 (0.73–1.71)
	Gastric (n=747)	4.3 vs 5.6	1.09 (0.91–1.31)
Histological classification (Laurén)	Intestinal type (n=311)	5.5 vs 5.5	0.98 (0.74–1.30)
	Diffuse type (n=170)	4.2 vs 5.6	1.10 (0.74–1.65)
	Mixed (n=50)	2.8 vs 4.2	1.55 (0.75–3.22)
	NA (n=352)	4.4 vs 5.6	1.19 (0.91–1.55)
ECOG-PS	0 (n=465)	5.6 vs 5.8	1.06 (0.83–1.35)
	1 (n=438)	4.1 vs 4.5	1.18 (0.94–1.49)



*HR based on unstratified model

Safety: Hematological AEs

Adverse events, %	XP + cetuximab n=446		XP n=436	
	All	Grade 3/4	All	Grade 3/4
Neutropenia	44	22	55	32
Febrile neutropenia	2	2	1	1
Anemia	29	9	37	11
Leukopenia	15	4	23	6
Thrombocytopenia	18	5	21	5

AEs, adverse events

Safety: Non-hematological AEs

Adverse events, %	XP + cetuximab n=446		XP n=436	
	All	Grade 3/4	All	Grade 3/4
Nausea	62	7	62	9
Decreased appetite	50	7	46	6
Vomiting	38	7	46	8
Skin reactions*	77	13	15	0
Fatigue	43	8	37	6
Diarrhea	40	8	25	4
Hand-foot syndrome	36	7	22	2
Hypomagnesemia	30	11	14	1
Asthenia	21	5	23	6
Hypokalemia	20	13	14	9

*Composite category

Safety: Non-hematological AEs

Adverse events, %	XP + cetuximab n=446		XP n=436	
	All	Grade 3/4	All	Grade 3/4
Nausea	62	7	62	9
Decreased appetite	50	7	46	6
Vomiting	38	7	46	8
Skin reactions*	77	13	15	0
Fatigue	43	8	37	6
Diarrhea	40	8	25	4
Hand-foot syndrome	36	7	22	2
Hypomagnesemia	30	11	14	1
Asthenia	21	5	23	6
Hypokalemia	20	13	14	9

*Composite category

Safety: Cardiac AEs

Cardiac events, %	XP + cetuximab n=446		XP n=436	
	All	Grade 3/4	All	Grade 3/4
Cardiac AEs, total	13.0	6.7	9.2	4.1
Arrhythmia	7.2	1.6	4.6	0.7
Infarction/ischemia	4.7	3.2	3.4	2.1
Arrest	1.1	1.1	1.1	1.1
Congestive heart failure	0.7	0.4	0.2	0.2
Sudden death	0.2	0.2	0	0

Relative dose intensity

Treatment, %	XP + cetuximab n=446	XP n=436
Cetuximab		
80 – <90%	22	
≥90%	60	
Cisplatin		
80 – <90%	28	25
≥90%	52	44
Capecitabine		
80 – <90%	23	20
≥90%	31	28

Summary and conclusions

- No benefit from adding cetuximab to XP as first-line treatment for AGC in terms of
  - PFS (IRC)
  - OS
  - Best overall response (IRC)
- Consistent results across subgroups
- No new or unexpected safety findings but overall negative benefit/risk ratio for the experimental treatment
- Tissue is available from 97% of patients, biomarker analysis is ongoing

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