Efficacy Results from the ToGA Trial: A Phase III Study of Trastuzumab Added to Standard Chemotherapy in First-Line HER2-Positive Advanced Gastric Cancer

Van Cutsem E et al.
Proc ASCO 2009;Abstract LBA4509.

Introduction

- Chemotherapy improved survival compared to best supportive care in patients with advanced gastric cancer (GC) and combination chemotherapy was superior to monotherapy (*JCO* 2006;24:2903).
- Roughly 22% of patients with advanced GC have HER2-positive disease (ASCO 2009;Abstract 4556).
- Anti-HER2 antibody trastuzumab is active in GC cell lines in vitro and in vivo.
- Current study objective:
  - Evaluate the addition of trastuzumab to fluoropyrimidine/cisplatin in patients with HER2-positive advanced GC.

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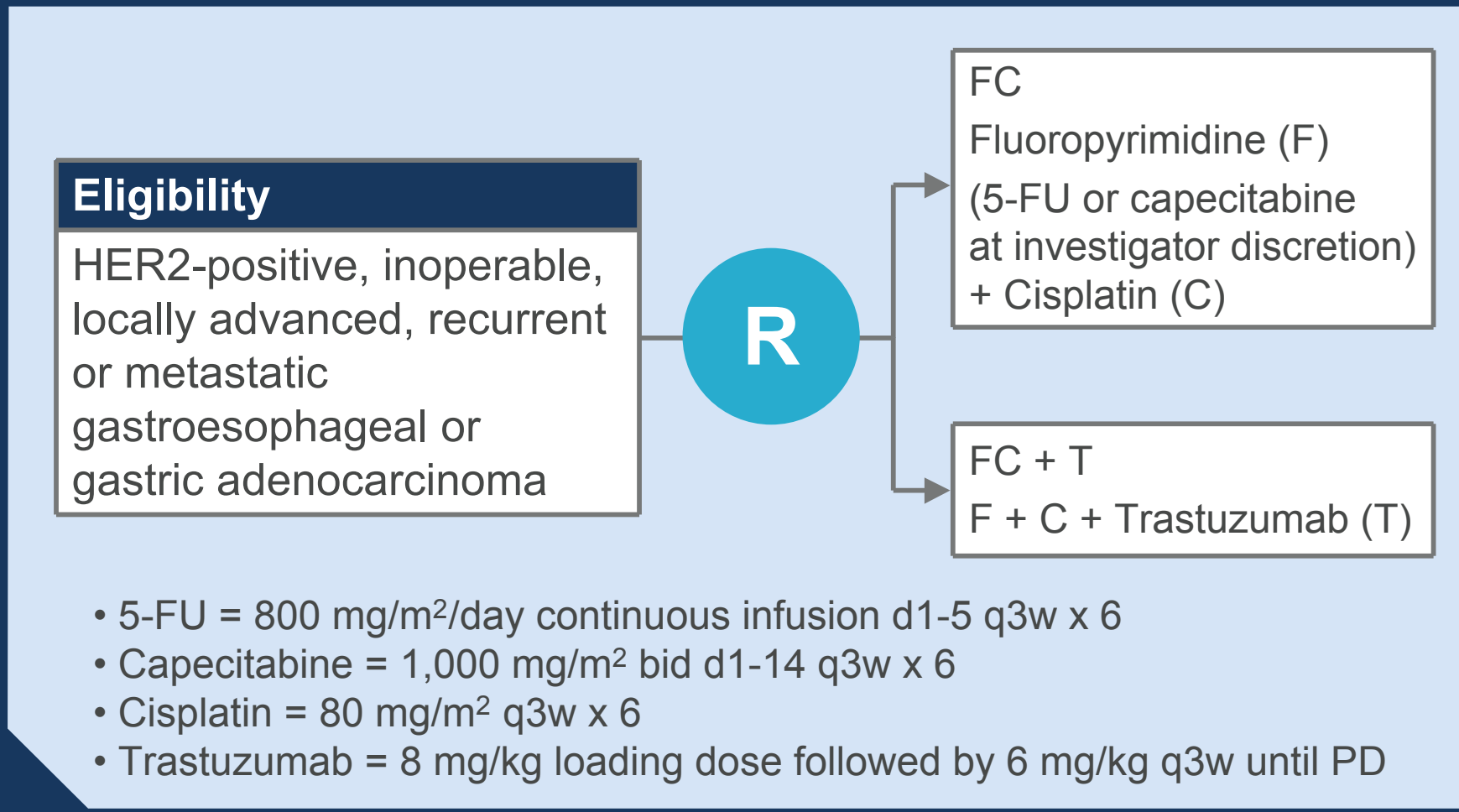
ToGA Trial Design (n = 584)



- 5-FU = 800 mg/m^2/day continuous infusion d1-5 q3w x 6
- Capecitabine = 1,000 mg/m^2 bid d1-14 q3w x 6
- Cisplatin = 80 mg/m^2 q3w x 6
- Trastuzumab = 8 mg/kg loading dose followed by 6 mg/kg q3w until PD

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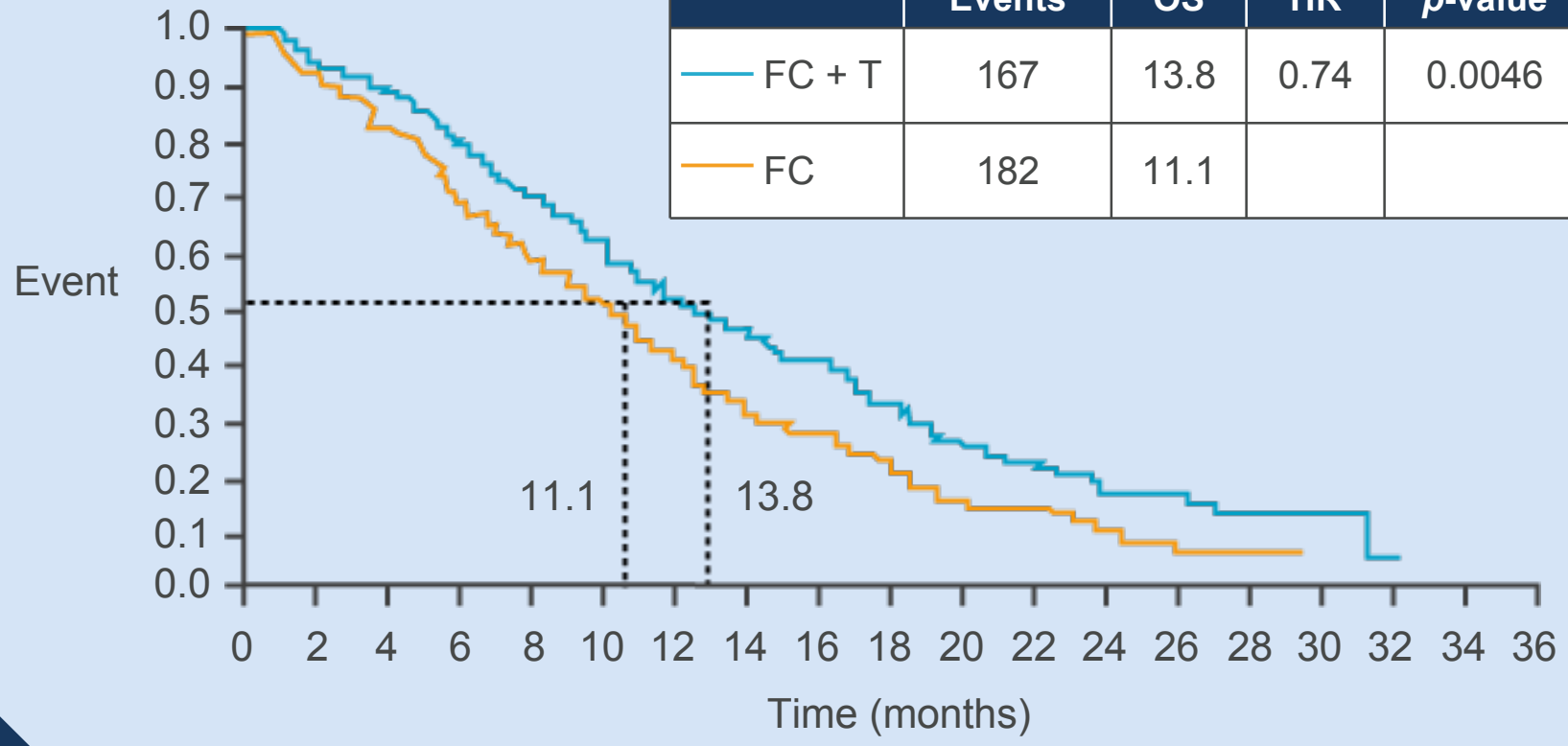
Primary Endpoint: Overall Survival (OS)

	Median			
	Events	OS	HR	*p*-value
FC + T	167	13.8	0.74	0.0046
FC	182	11.1		



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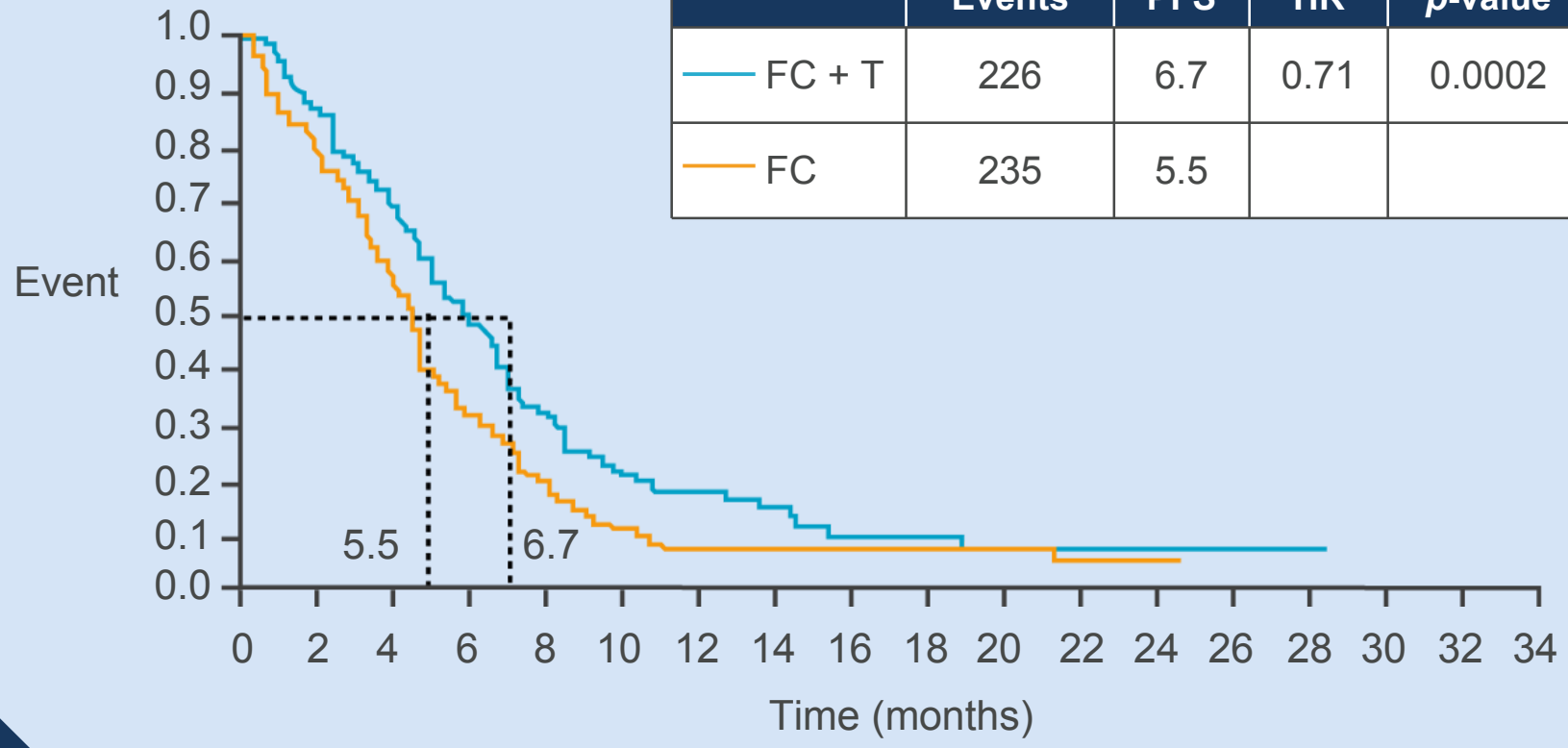
Secondary Endpoint: Progression-Free Survival (PFS)

	Median			
	Events	PFS	HR	*p*-value
FC + T	226	6.7	0.71	0.0002
FC	235	5.5		



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Cardiac Adverse Events (AEs)

	FC (n = 290)		FC + T (n = 294)	
	All	**Grade 3/4**	**All**	**Grade 3/4**
Total cardiac AEs	6%	3%	6%	1%
Cardiac failure	<1%	<1%	<1%	<1%
Asymptomatic LVEF decline				
<50%	1.1%		5.9%	
<50% and by ≥10%	1.1%		4.6%	
Cardiac AEs leading to death	<1%		<1%	
Cardiac AEs related to treatment	<1%		<1%	

Van Cutsem E et al. *Proc ASCO* 2009;Abstract LBA4509.

Conclusions

- ToGA met its primary overall survival endpoint.
  - Trastuzumab reduced the risk of death by 26% when combined with fluoropyrimidine/cisplatin (HR = 0.74).
  - Trastuzumab prolongs median survival by nearly 3 mo in patients with HER2-positive advanced GC.
- All secondary efficacy endpoints (PFS, TTP, ORR, CBR, DoR) significantly improved with the addition of trastuzumab (data not shown).
- Addition of trastuzumab to chemotherapy was well tolerated, with no difference in the overall safety profile between treatment arms, including cardiac AEs.
- Trastuzumab in combination with chemotherapy is a new treatment option for patients with HER2-positive advanced GC.

Van Cutsem E et al. *Proc ASCO* 2009;Abstract LBA4509.

Meta-Analysis of REAL-2 and ML17032: Capecitabine and Infused 5-FU-Based Combination Chemotherapy for Advanced Oesophago-Gastric Cancer

Okines AF et al.
Ann Oncol 2009;20(9):1529-34.

Introduction

- The Phase III REAL-2[a] and ML17032[b] trials demonstrated that capecitabine (CAPE) is noninferior to 5-fluorouracil (5-FU) for overall survival (OS) and progression-free survival (PFS), respectively, in advanced esophago-gastric cancer ([a] *NEJM* 2008;358:36, [b] ASCO 2006;Abstract LBA4108).
- Both trials demonstrated that the toxicity profile of CAPE is similar to that of 5-FU within the doublet and triplet chemotherapy regimens utilized.
- <u>Current study objective:</u>
  - Conduct a meta-analysis of REAL-2 and ML17032 trials to determine whether CAPE is superior to 5-FU for survival in the treatment of advanced esophago-gastric cancer.

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

REAL-2 Trial

- Phase III REAL-2 trial (n = 1,002; two-by-two design) compared first-line CAPE- versus 5-FU-containing triplets and oxaliplatin- versus cisplatin-containing triplets in advanced esophago-gastric cancer (*NEJM* 2008;358:36).
- Trial was designed to demonstrate noninferiority for OS of CAPE- and oxaliplatin-containing regimens, as compared to 5-FU- and cisplatin-containing regimens, respectively.
  - The study met both of its primary endpoints.
- The unadjusted hazard ratio (HR) for death in the CAPE group relative to the 5-FU groups was 0.86 (95% CI 0.80-0.99).
- The unadjusted HR for death in the oxaliplatin group relative to the cisplatin group was 0.92 (95% CI 0.80-1.10).

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

ML17032 Trial

- Phase III ML17032 trial (n = 316) compared first-line cisplatin plus capecitabine (CX) versus cisplatin plus 5-FU (CF) in advanced gastric cancer (ASCO 2006;Abstract LBA4108).
- Designed to demonstrate noninferiority of CX as compared to CF for PFS.
- The study met its primary endpoint.
  - PFS = 5.6 months in the CX arm vs 5 months in the CF arm (HR = 0.81, 95% CI 0.63-1.04)
- Median OS was comparable; 10.5 months for CX arm and 9.3 months for CF arm ($p = 0.27$).
- Superiority of capecitabine was demonstrated for response rate (41% vs 29%, $p = 0.03$).

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

Multivariate Analysis: Overall Survival*

Variable	Group	n	HR (95% CI)	*p*-value
Performance status	0-1	1,175	1.87 (1.55-2.26)	0.0000
	2	138		
Age	<60 years	582	0.83 (0.73-0.94)	0.0026
	≥60 years	731		
Extent of disease	Locally advanced	273	1.64 (1.40-1.91)	0.0000
	Metastatic	1,040		

* Histopathological subtype did not have a significant effect on overall survival.

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

Multivariate Analysis: Unconfirmed Response Rate

Variable	Group	n	HR (95% CI)	*p*-value
Performance status	0-1	1,098	0.62 (0.42-0.91)	0.0140
	2	133		
Age	<60 years	549	1.32 (1.05-1.67)	0.0174
	≥60 years	682		
Gender	Female	270	1.58 (1.19-2.10)	0.0017
	Male	961		
Treatment	CAPE based	613	1.38 (1.10-1.73)	0.0057
	5-FU based	618		

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

Summary and Conclusions

- OS was superior in the patients with advanced esophago-gastric cancer treated with capecitabine combinations compared with those treated with 5-FU combinations.
- Poor performance status, age < 60 years and metastatic disease were independent predictors of poor survival.
- There was no significant difference in PFS between treatment groups on multivariate analysis (data not shown).
- Assessable patients treated with capecitabine combinations were significantly more likely to have an objective response than those treated with 5-FU combinations.
- Capecitabine may replace 5-FU in the treatment of advanced esophageal or gastric cancer.

Okines AF et al. *Ann Oncol* 2009;20(9):1529-34.

Capecitabine/Cisplatin versus 5-Fluorouracil/Cisplatin as First-Line Therapy in Patients with Advanced Gastric Cancer: A Randomised Phase III Noninferiority Trial

Kang Y-K et al.
Ann Oncol 2009;20(4):666-73.

Introduction

- There is no globally accepted standard of care for patients with advanced gastric cancer, though combination chemotherapy is well accepted.
- The combined use of 5-fluorouracil (5FU) and cisplatin (CIS) is the standard of care in Korea and many other countries based on superior response rates compared with the use of 5FU alone (*Cancer* 1993;71:3813).
- Capecitabine (CAP) combined with CIS (CAP-CIS) has demonstrated favorable response rates in a Phase II study (*Ann Oncol* 2002;13:1893).
- Current study objective:
  - Compare the efficacy and safety of CAP-CIS versus 5FU-CIS in the first-line treatment of advanced gastric cancer.

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Phase III Open-Label Trial of CAP-CIS versus 5FU-CIS in Advanced Gastric Cancer

Accrual: 316 (Closed)

Eligibility

Patients with advanced gastric cancer (AGC)

Karnofsky PS of ≤70

No prior chemotherapy (neoadjuvant or adjuvant permitted)

No radiotherapy to target lesions

R

CIS 80 mg/m^2, d1

CAP 1,000 mg/m^2 BID, d1-14, q3wk (n = 160)

CIS 80 mg/m^2, d1

5FU 800 mg/m^2, d1-5, q3wk (n = 156)

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Survival (Per-Protocol Population)

Median Survival	CAP-CIS n = 139 (95% CI)	5FU-CIS n = 137 (95% CI)	Hazard ratio (95% CI)	*p*-value
Progression-free survival (PFS)	5.6 mo (4.9-7.3 mo)	5.0 mo (4.2-6.3 mo)	0.81* (0.63-1.04)	<0.001
Overall survival	10.5 mo (9.3-11.2 mo)	9.3 mo (7.4-10.6 mo)	0.85 (0.64-1.13)	0.008

* The upper limit of the two-sided 95% CI for the hazard ratio did not exceed the prespecified noninferiority margin of 1.25.

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Clinical Response (Per-Protocol Population)

Clinical Variable	CAP-CIS n = 139(95% CI)	5FU-CIS n = 137(95% CI)	Hazard or odds ratio (95% CI)	*p*-value
Overall response	46% (38-45%)	32% (24-41%)	1.80 (1.11-2.94)	0.02
Complete response	2%	3%	—	—
Partial response	44%	29%	—	—
Median time to response*	3.7 mo	3.8 mo	1.61 (1.10-2.35)	0.015
Median duration of response*	7.6 mo	6.2 mo	0.88 (0.56-1.36)	0.554

* Intent-to-treat population

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Select Grade 3/4 Adverse Events (Safety Population)

Toxicity	CAP-CIS n = 156	5FU-CIS n = 155
Neutropenia	25 (16%)	29 (19%)
Vomiting	11 (7%)	13 (8%)
Diarrhea	8 (5%)	7 (5%)
Hand-foot syndrome	6 (4%)	—
Leukopenia	4 (3%)	6 (4%)
Nausea	3 (2%)	4 (3%)
Stomatitis	3 (2%)	10 (6%)
Anorexia	3 (2%)	1 (<1%)

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.

Conclusions

- CAP-CIS showed significant noninferiority for PFS, compared to 5FU-CIS, in the first-line treatment of AGC.
  - PFS: 5.6 mo vs 5.0 mo ($p < 0.001$)
  - OS: 10.5 mo vs 9.3 mo ($p = 0.008$)
  - Overall response rate: 46% vs 32% ($p = 0.02$)
- CAP-CIS and 5FU-CIS had similar toxicity profiles and were well tolerated.
- CAP offers the potential for a simplified dosing schedule and avoids the inconvenience and adverse effects associated with intravenous dosing.
- These findings suggest that CAP-CIS can be used instead of 5FU-CIS as a new treatment option for patients with advanced gastric cancer.

Kang Y-K et al. *Ann Oncol* 2009;20(4):666-73.