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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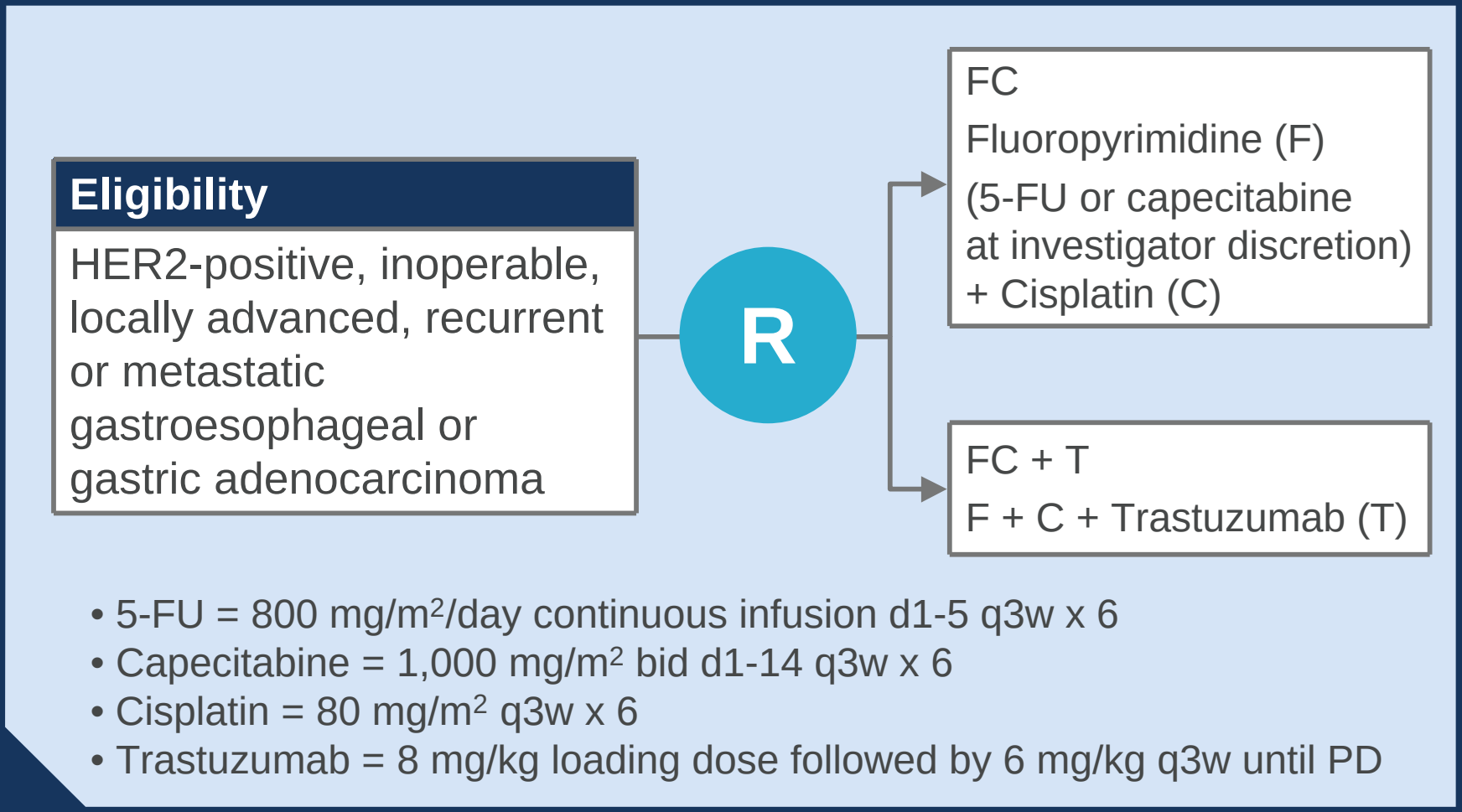
ToGA Trial Design (n = 584)



- 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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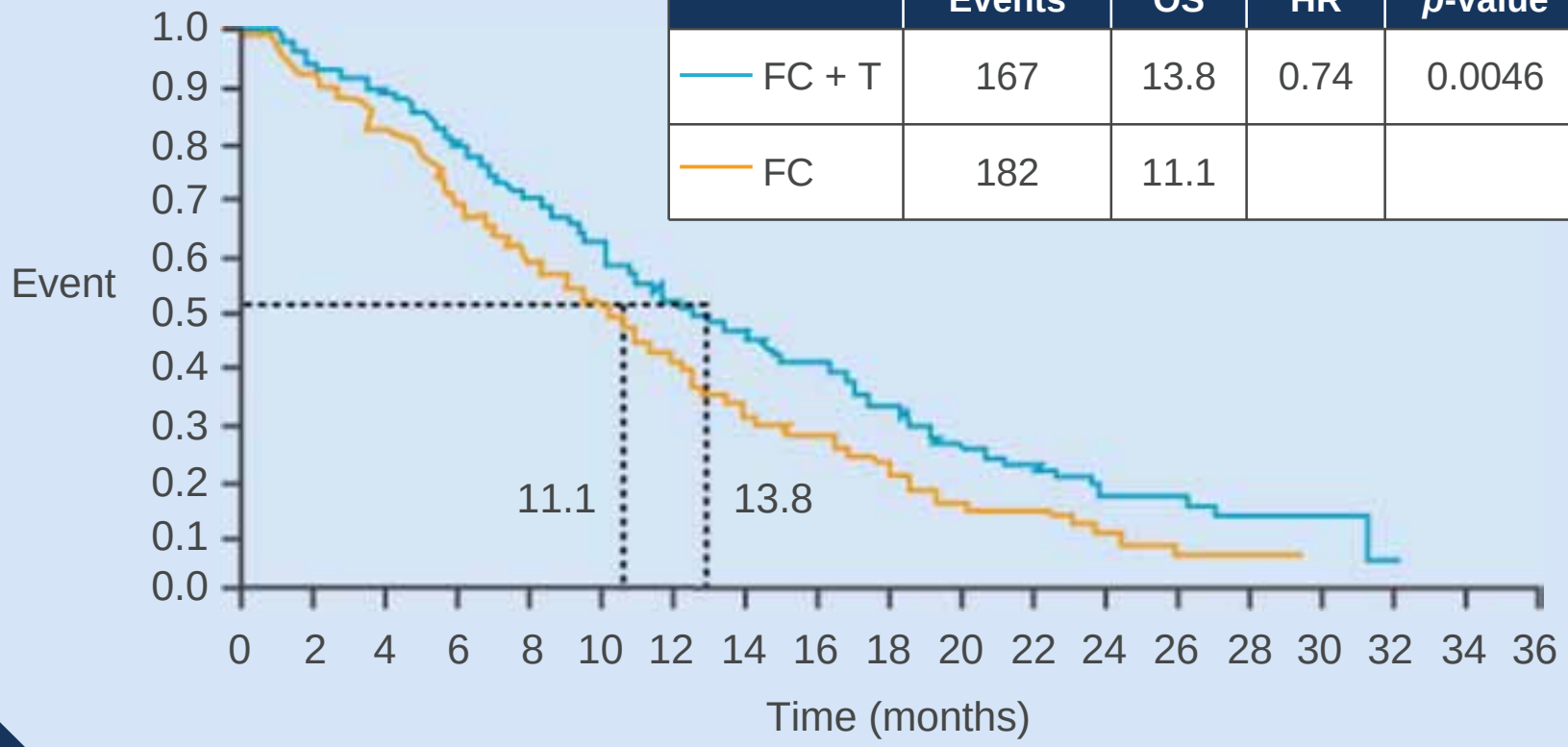
Primary Endpoint: Overall Survival (OS)

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



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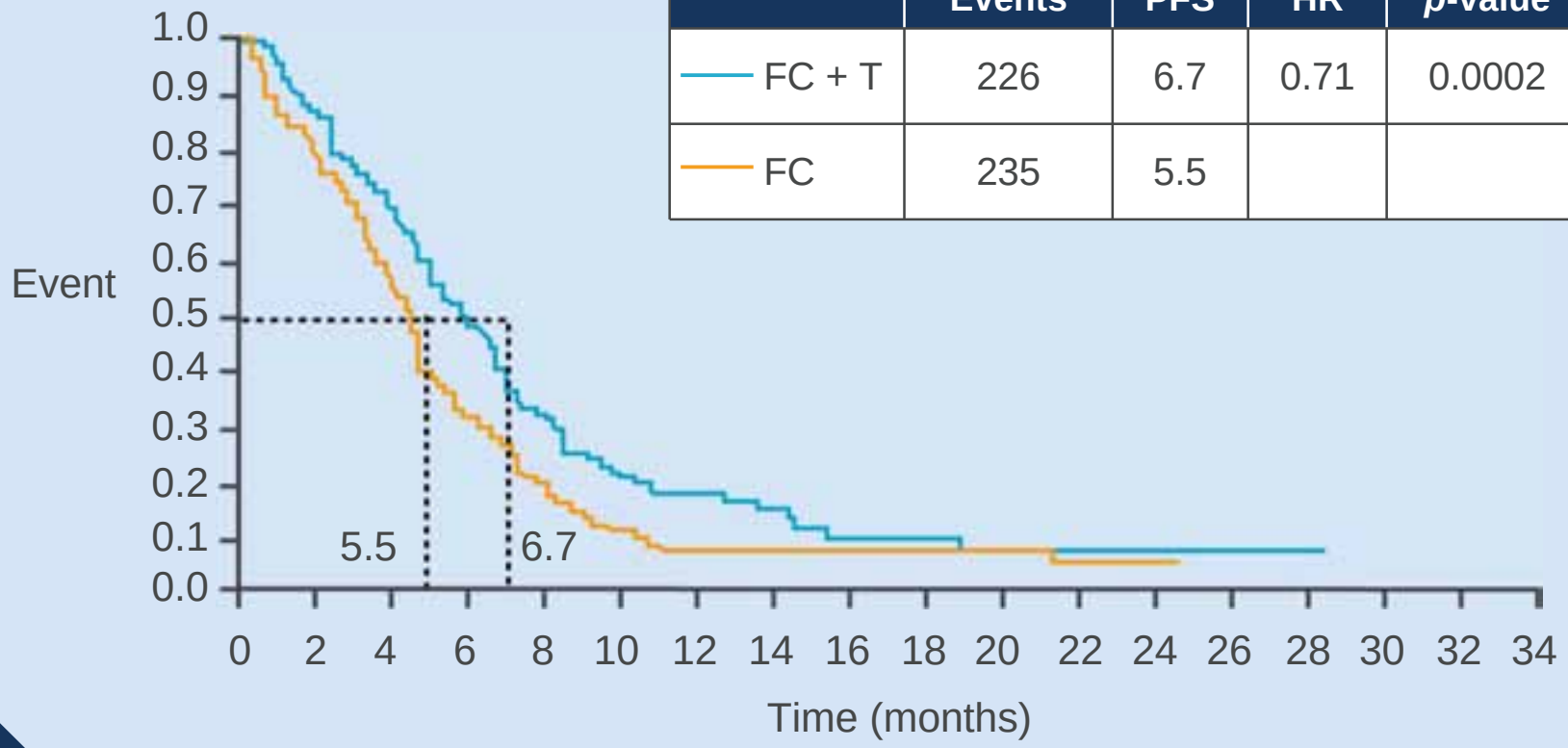
Secondary Endpoint: Progression-Free Survival (PFS)

	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.

Faculty Comments

DR ILSON: ToGA is a landmark study that validates an improvement in outcome with the use of a targeted therapy in combination with chemotherapy. The primary endpoint of overall survival was achieved, with nearly a three-month improvement, which was highly statistically significant. The secondary endpoints of progression-free survival and response rate were also improved, and trastuzumab did not add any toxicity or negatively affect quality of life. This study establishes a new standard of care in HER2-positive esophageal and gastric adenocarcinomas. Patients who overexpress HER2 should receive first-line chemotherapy/trastuzumab. The next step is to evaluate trastuzumab in the adjuvant setting, which is currently under development in RTOG-1010.

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.
- Current study objective:
  - 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.

Faculty Comments

DR ILSON: This study combines the results of two large Phase III clinical trials. The Kang study compared capecitabine/cisplatin to infusional 5-FU/cisplatin. The REAL-2 trial looked at capecitabine versus infusional 5-FU and substituted cisplatin with oxaliplatin. Both studies individually demonstrated noninferiority of capecitabine. In the pooled analysis, there appears to be a modest survival advantage for capecitabine compared to infusional 5-FU. Capecitabine is a mixed blessing in that it allows the patient to avoid a Mediport but at the cost of increased hand-foot syndrome and patient-compliance issues. In my practice, I tend to use more infusional 5-FU but with a different schedule than the Kang or REAL-2 studies. Most practitioners are tailoring 5-FU as it’s used in colorectal cancer, with a two-day infusion every two weeks.

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

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.

Faculty Comments

DR AJANI: The primary endpoint is progression-free survival, but it’s a highly underpowered study. Nobody should do a Phase III trial with 300 patients. All of the previous generations of Phase III trials in gastroesophageal cancer were small because everyone believed we could double the survival benefit. In reality, we have achieved minor advantages. Additionally, we should be targeting endpoints that the regulatory agencies expect. This study simply suggests that capecitabine may be a substitution for 5-FU as a noninferior agent without a safety advantage. Capecitabine solely offers convenience, but I use it frequently.