

Which new targets are on the horizon in gastric cancer?



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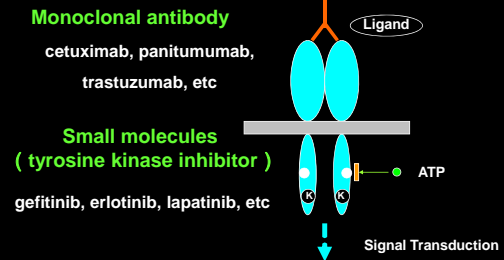
Needs for molecular targeting agents in advanced GC

- limitations of current cytotoxic combination regimens in terms of survival. (mPFS: 5-6 M)
- significant toxicities in triplet cytotoxic combinations. (consider that DCF in GC, FOFOXILI in CRC have not widely distributed.)
- toxicities of molecular targeting agents usually do not overlap those of cytotoxic agents.
- numerous successful evidences in other tumor types.

Molecular targeting agents under development for GC

agents	phase	enrollment
HER family inhibitor		
Trastuzumab (anti-HER2 Ab)	III	completed
Cetuximab (anti-EGFR Ab)	III	recruiting
Lapatinib (HER1/2 inhibitor)	III	recruiting
Panitumumab (anti-EGFR Ab)	III	recruiting
Angiogenesis inhibitor		
Bevacizumab (anti-VEGF Ab)	III	completed
Sunitinib (anti-VEGFR TKI)	I/II	recruiting
Sorafenib (anti-VEGFR TKI)	I/II	recruiting
Axitinib (anti-VEGFR TKI)	I/II	recruiting
Others		
Everolimus (mTOR inhibitor)	III	recruiting
ARQ197 (c-MET TKI)	II	planning
E 7050 (c-MET TKI)	I	recruiting
AUY922 (hsp90 inhibitor)	I	recruiting

Agents targeting to EGFR/HER family



Anti-EGFR therapy for GC: single agent

Agents	n	line	RR	M-TTP(M)	MST(M)
Gefitinib	75	Second line	0%	1.2	3.5
Erlotinib	70	First line	9%	1.8	3.5 / 5.7
Lapatinib	47	First line	7%	2.0	5.0

Rojo , et al. JCO, 2006; Dragovic, et al. JCO 2006; Iqbal S, et al; ASCO 2007

Cetuximab combinations for GC: first-line phase II

Agents	n	RR	M-PFS(M)	MST(M)
FOLFIRI+cetux	34	44 %	8	16
Iri/FU (AIO)+cetux	49	55 %	—	—
mFOLFOX6+cetux	40	50 %	5.5	9.9
FUFOX+cetux	46	65 %	7.6	9.5
XELOX+cetux	44	52 %	6.6	11.7
CDDP/doce +cetux	44	41 %	—	—

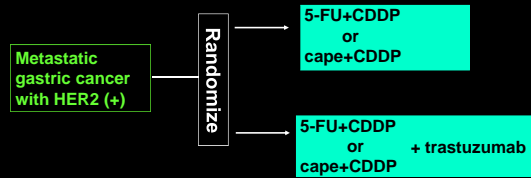
Pinto , et al. Ann Oncol, 2007; Moehler et al, ASCO-GI 2008;
Han SW, et al. ASCO-GI 2008; Lordick et al. ASCO 2007;
Kim C, et al ASCO-GI, 2009; Pinto et al. ASCO 2008

RCTs of anti-EGFR/HER2 for gastric cancer

Regimen	Target accrual	Primary End point
First line		
Cape+CDDP vs. cape+CDDP+ cetuximab	870	PFS
EOX vs. EOX + panitumumab	730	OS
*Cape+CDDP vs. cape+CDDP + trastuzumab	584	OS
*XELOX vs. XELOX + lapatinib	410	PFS
Second line		
Irinotecan vs. irinotecan + nimotuzumab (rPII)	80	RR
*W-paclitaxel vs. w-paclitaxel + lapatinib	314	OS

* Patients with HER2 (+)

ToGA study: trastuzumab global study



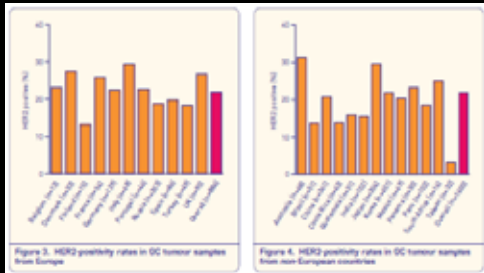
Required sample size = 584

Primary endpoint; Overall survival

Participants; 120 centers / 22 countries

Primary endpoint has met !

HER2 positive rate in TOGA trial

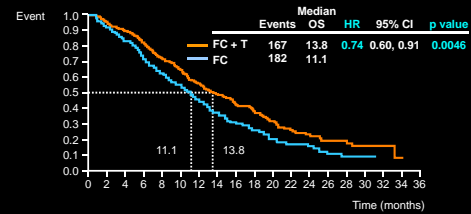


Europe: 21.7% in total

Non-Europe: 21.7% in total

Kang et al. ASCO-GI 2008

Primary endpoint: OS



No. at risk

FC + T: 294 277 246 209 173 147 113 90 71 56 43 30 21 13 12 6 4 1 0

FC: 290 266 223 165 143 117 90 64 47 32 24 16 14 7 6 5 0 0 0

T, trastuzumab

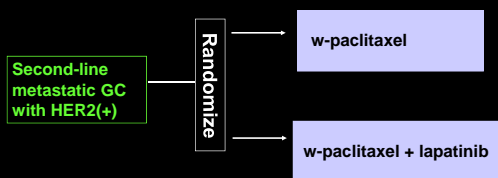
Van Cutsem, et al. ASCO, 2009

Pre-planned subgroup analysis according to FISH and IHC results: needs for optimal selection?

	n	Chemo mOS	Chemo+T mOS	HR death (95% CI)
FISH+/IHC0	61	7.2	10.6	0.92 (0.48-1.76)
FISH+/IHC1+	70	10.2	8.7	1.24 (0.71-2.20)
FISH+/IHC2+	159	10.8	12.3	0.75 (0.51-1.11)
FISH+/IHC3+	256	12.3	17.9	0.58 (0.41-0.81)
FISH-/IHC3+	15	17.7	17.5	0.83 (0.20-3.38)

Cunningham D, ASCO, 2009

A randomized trial of lapatinib for GC; TYTAN trial



Primary endpoint; OS

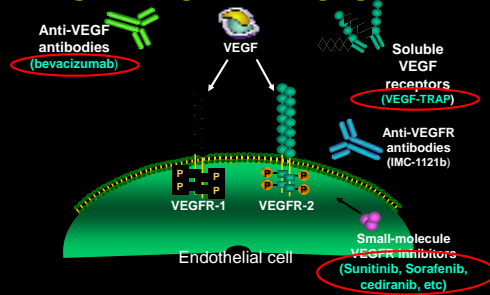
Sample size: 314

Participants: mainly Asian countries

EGFR/HER2-targeted agent: summary of clinical studies

- activity of single agent seemed very modest
- Cetuximab combined with cytotoxic regimen may be beneficial and are now under investigation in RCTs
- trastuzumab showed significant survival prolongation in HER2 positive patients that will change standard of care in advanced gastric cancer
- lapatinib combined with XELOX in first-line and with paclitaxel in second line are now being evaluated in RCTs

Agents targeted to angiogenesis

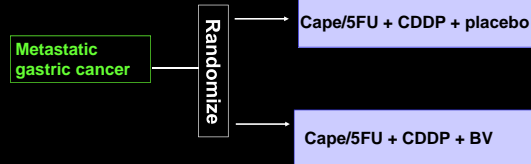


Bevacizumab combinations for GC: first-line phase II

Agents	n	RR	M-PFS(M)	MST(M)
CDDP/CPT+BV	47	65%	8.3	12.3
Doc/CDDP/CPT+BV	26	68%	—	—
FOLFOX6+BV	16	63%	7	8.9
mDCF+BV	45	67%	12	16.2

Shah, et al. JCO, 2006; Enzinger et al, ASCO-GI 2008;
Cohenuram, et al. ASCO-GI 2008; Jhaver et al, ASCO-GI 2009

Global registration study of bevacizumab for gastric cancer: AVAGAST study



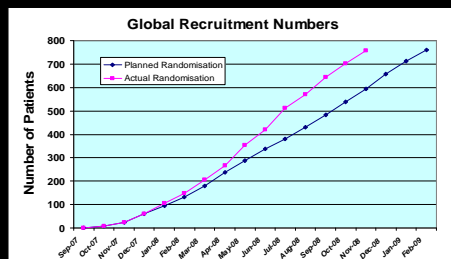
Required sample size = 760

Primary endpoint; Overall survival

Participants;

Asia (Japan, Korea, China etc), US/SA, EU (Belgium, France, Germany, etc)

Accrual status: AVAGAST



770 patients has been recruited in one year

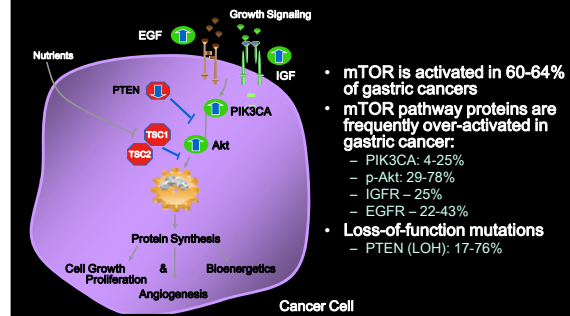
Other angiogenesis inhibitors under development in GC

Agents	MOA	Comb. regimen	phase
Sunitinib	Multi-target TKI	S-1+CDDP 5FU+CDDP	I / II
Sorafenib	Multi-target TKI	S-1+CDDP Cape+CDDP	I / II
Axitinib	Multi-target TKI	Cape+CDDP	I / II

Angiogenesis inhibitor: summary of clinical studies

- bevacizumab combinations seemed promising in phase II studies
- accrual to AVAGAST phase III trial has been completed without significant safety issues
- other agents such as, sorafenib, sunitinib, and axitinib are under investigations in early studies

mTOR Pathway Activation in Gastric Cancer



Phase II study of everolimus in metastatic gastric cancer in Japan – Results

Prior chemotherapy (N=53):

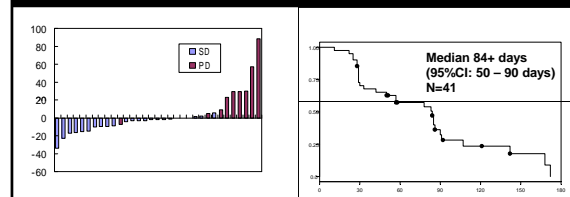
	One prior regimen pts	Two prior regimens pts		Total
		First-line	Second-line	
FUs* alone	11	12	3	26
FUs* + CDDP**	13	12	4	29
FUs* + CPT	0	0	1	1
FUs* + PTX	2	1	0	3
CPT + CDDP	0	1	3	4
MTX+S-FU	1	0	0	1
CPT alone	0	0	6	6
PTX alone***	0	0	9	9
Total	27	28	28	

*Including S-FU derivatives (S-1, capecitabine, etc)
 Including oxaliplatin, *including NK105

Muro K, et al: ASCO 2008

Efficacy Results

everolimus (RAD001) single agent phase II



DCR = 54.7%

M-PFS = 2.7M

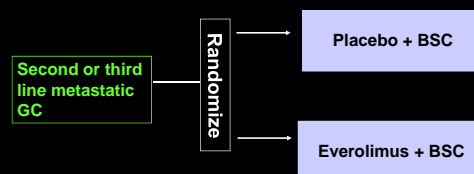
Muro K, et al: ASCO 2008

OS and PFS in second-line trials in advanced GC

Source, n	Regimen(s)	mOS (mo)	mPFS (mo)
This study, 2009 n=53	RAD001	10.1	2.7
Hironaka 2009* n=38	Paclitaxel	5.0	2.1†
Jo 2007* n=154	Docetaxel	7.2	2.9†
Lee 2007 n=32	Paclitaxel + cisplatin	9.1	2.9†
Oh 2007* n=48	FOLFOX	8.0	3.0†
Park 2008 n=43	Mitomycin + S-1	8.0	3.4
Beak 2005 n=32	Irinotecan + cisplatin	6.1	3.8†
Takizuchi 2008 n=35	Paclitaxel + doxorubicin	10.7	4.0

*Retrospective reporting of medical records at the Saitama Cancer Center, Saitama, Japan, September 2002 to September 2004
 †Retrospective reporting of medical records at the Asean Medical Center, South Korea, December 2000 to March 2006
 ‡Population was 29.2% third-line
 †Time to progression

Phase III study of everolimus for GC: GRANITE-1

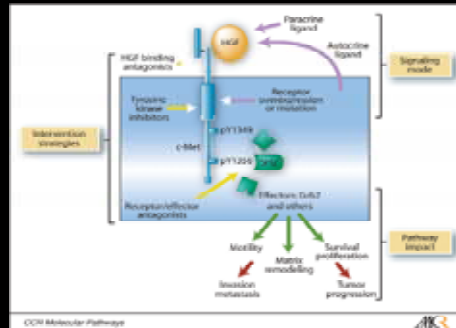


Primary endpoint: OS
 Required sample size = 633 (2:1 randomization)
 Participants: Asia, EU, US

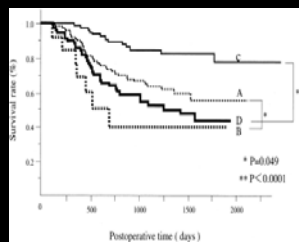
PI3K inhibitors: development status

Agent	Sponsor	Mechanism of Action	Clinical Status
LY294302	Lilly	Inhibits p110 ATP binding	Preclinical (poor solubility)
Wortmannin analogs	PHOLX	Binds p110 subunit	Preclinical
FX-866	Lilly	Inhibits p110 ATP binding	Preclinical
XL-765	Evelitis	Inhibits p110 ATP binding	Phase I
BEZ235	Novartis	Inhibits p110 ATP binding	Phase I

HGF/c-Met Signaling Pathway



C-met amplification or overexpression are markers of poor prognosis in gastric cancer



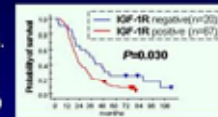
(A) Patients without c-met gene amplification (n = 115), (B) Patients with c-met gene amplification (n = 13), (C) Patients without c-met overexpression (n = 69), (D) Patients with c-met overexpression (n = 59). Significant differences were observed between A and B (P = 0.049) and C and D (P < 0.0001; log rank test).

(Nakajima et al. Cancer 85:1894 – 1902)

Rationale of IGF1R inhibitors for GC

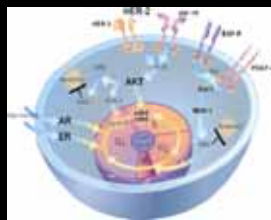
Insulin-like growth factor receptor

- ILGF1R expression in GC: 77%. Correlation with EGFR/HER2 expression, intestinal type and poor survival (Matsubara, 2007)
- 9 EC cell lines sensitive to picropodophyllin (PPI), an IGF1R TKI (Bergqvist, 2007)



Hsp90 background: The essentials

- Hsp90 is a chaperone protein which is involved in the folding of a large number of proteins (so-called client proteins)
 - In the yeast, >10% of all proteins associate with Hsp90
- In humans, > 80 client proteins are known, among them proteins that mediate cancer growth and cell survival
 - Transcription factors (e.g. estrogen receptor, androgen receptor)
 - Signaling kinases and their mutated forms (e.g. ErbB2, Akt, c-Met, Raf, EGFR, Bcr-Abl, NPM-Alk etc.)
- Abundant protein in normal cells and tumor cells
 - 1-2% of cellular protein



On-going phase I trials in NCCHE GI group (2008-2009)

Drug	Phase in Ex-Japan	
Wee1 Inhibitor	MK1726	I
PLK1 Inhibitor	MK1498	I
APOPTOSIS(TRAIL)	AMG655	II
	X	I
Epigenetic	AUY922 (hsp90)	I
	X	I
		Global phase1
C-MET Inhibitor	MK2461	I
	MK8033	I
	E7050	I
	AMG102	I
		1 st in man
HER1/HER2 Inhibitor	TAK265	I
		1 st in man
IGF1R Inhibitor	AMG479	I
	MK0646	II
	IMC-A12	II
		DDI trial
Angiogenesis inhibitor	VEGFTRAP	II
	AMG388	I
PI3K Inhibitor	X	I

Dilemma toward "personalized medicine"

- **patient selection is essential**
if targeted to 10% population = more than 7,000 pts screening
- **cost**
huge cost is required for conducting RCTs
- **validation of screening methods**
- **international collaboration is indispensable**
ethnic differences < interpatient variability

New era of targeted therapy for advanced GC

Take home messages

- trastuzumab in combination with FUs/CDDP will be a new standard of care for HER2 positive GC.
- HER2 positive population may become an independent entity as seen in breast cancer, though further studies are needed.
- agents that showed survival advantage in other tumor types, such as bevacizumab, cetuximab, lapatinib, and everolimus are being evaluated in RCTs
- other targeting agents, such as c-met, IGF-R inhibitors, hsp90 inhibitor etc. are under evaluations in early studies.