2011/10/08
第9 回 浜松オンコロジーフォーラム

胃癌治療における分子標的薬剤の現状と展望

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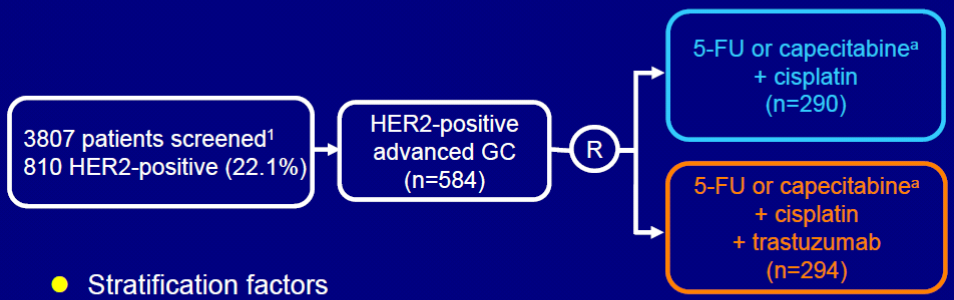
RCTs with targeting agents for metastatic gastric cancer

Line	Study	Agent tested	Control arm	Primary endpoint
First	ToGA (HER2)	trastuzumab	cape/cis	OS
	LOGiC(HER2)	lapatinib	cape/oxa	OS
	AVAGAST	bevacizumab	cape/cis	OS
	EXPAND	cetuximab	cape/cis	PFS
	REAL-3	panitumumab	epiru/cape/oxa	OS
Second	TyTAN (HER2)	lapatinib	paclitaxel	OS
	RAINBOW	ramucirumab	paclitaxel	OS
	GRANITE2	everolimus	paclitaxel	PFS
		ramucirumab	placebo	OS
Second/ third	GRANITE1	everolimus	placebo	OS

Her-2陽性胃癌について

ToGA trial design

Phase III, randomized, open-label, international, multicenter study

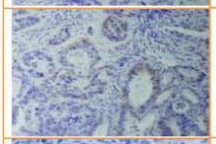
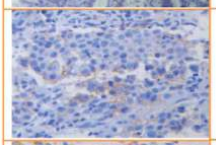
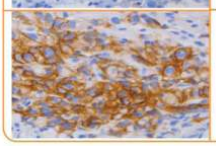


- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

[a]Chosen at investigator's discretion
GEJ, gastroesophageal junction

[1]Bang et al; Abstract 4556, ASCO 2009

HER2病理診断基準

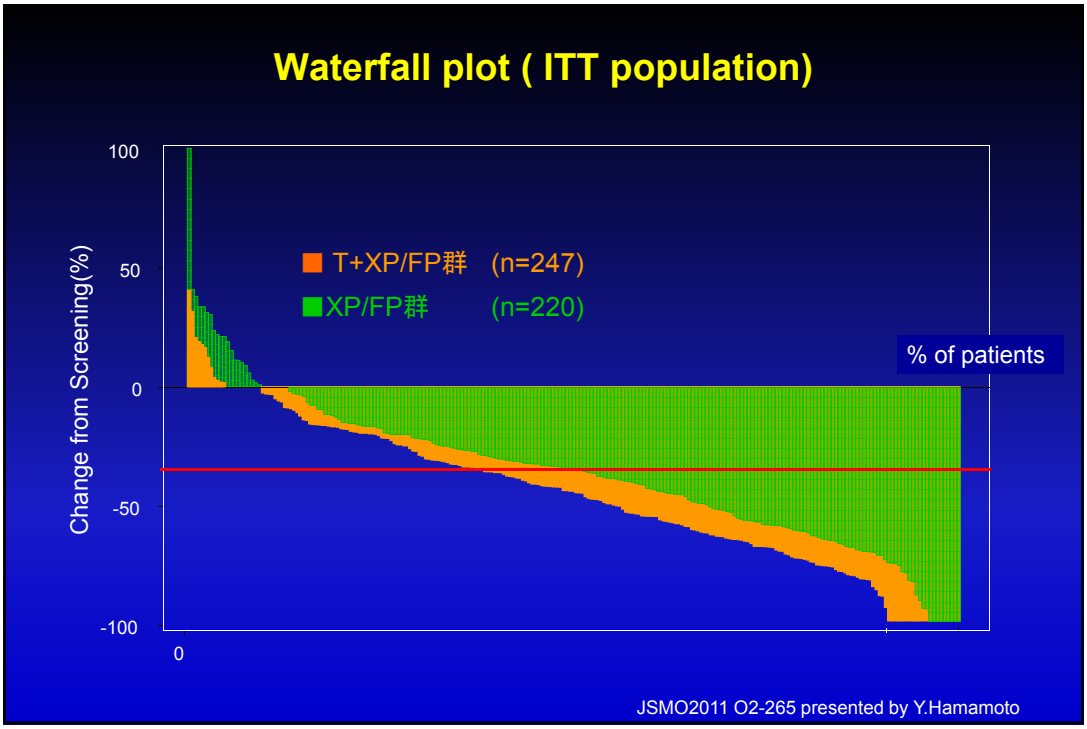
	Score	Surgical specimen–staining pattern	Biopsy specimen–staining pattern	HER2 overexpression assessment
	0	No reactivity or membranous reactivity in <10% of tumour cells	No reactivity or no membranous reactivity in any tumour cell	Negative
	1+	Faint/barely perceptible membranous reactivity in ≥10% of tumour cells; cells are reactive only in part of their membrane	Tumour cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumour cells stained	Negative
	2+	Weak-to-moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells	Tumour cell cluster with a weak-to-moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Equivocal
	3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells	Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Positive

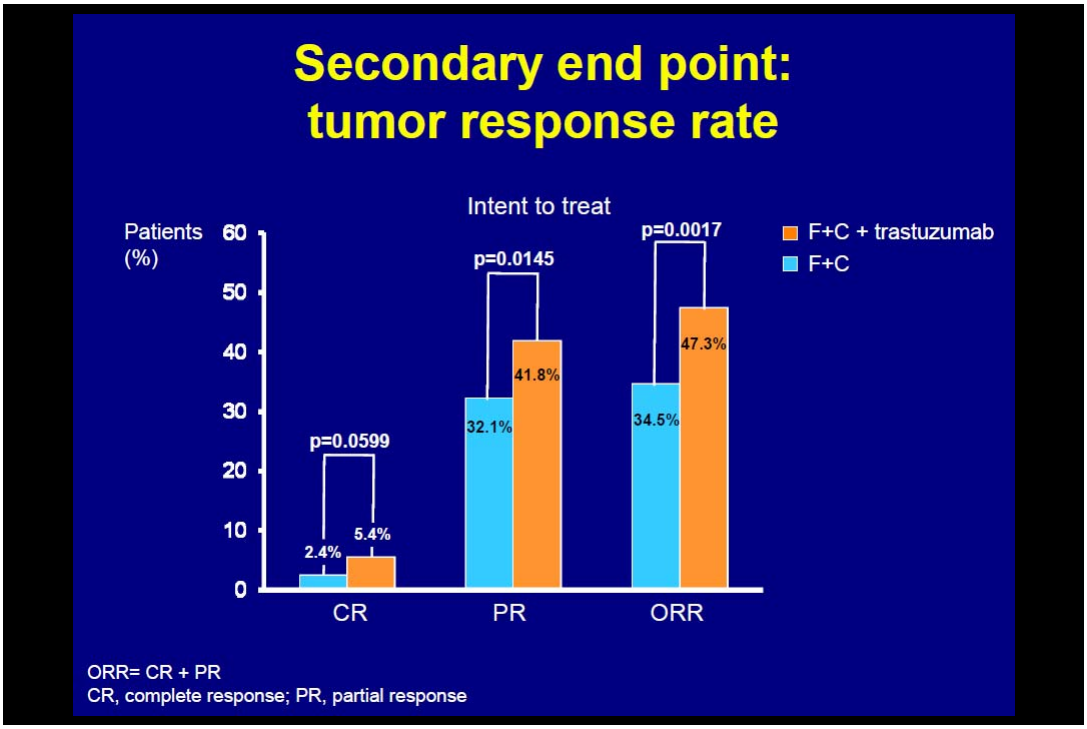
Rushoff et al. N Pathologe, 2010

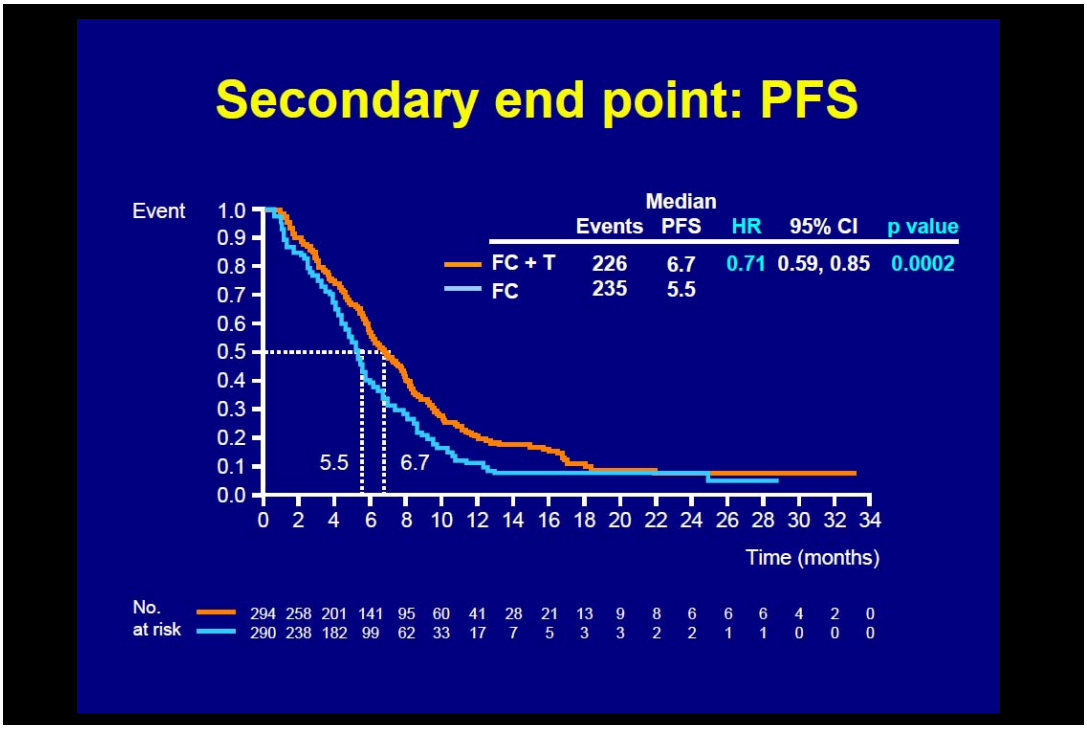
HER2病理診断基準：胃癌と乳癌での違い

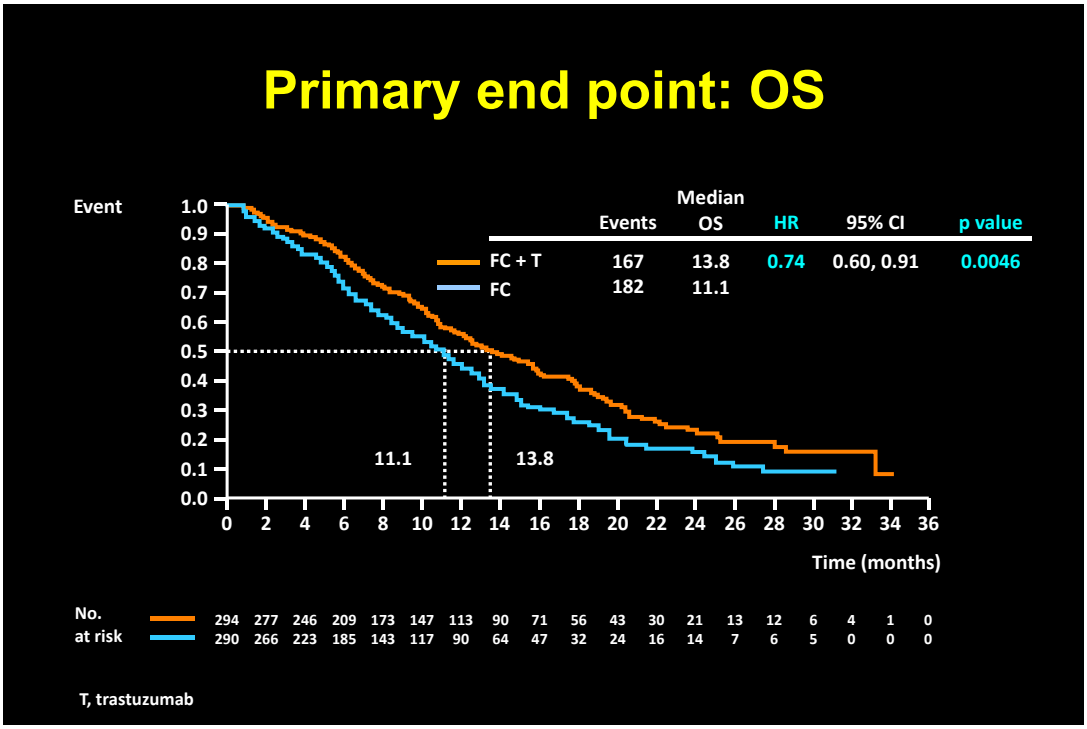
		Gastric cancer	Breast cancer
IHC scoring	Extent (Area Cut-off)	Biopsy specimens≥5 Cells Resection specimens: ≥10%	≥10% (≥30%)[a]
	Circularity	Mostly missing (often only lateral in IHC2+/3+)	A must in IHC2+/3+
(F)ISH analysis	Cell number	20 cohesive tumor cells showing highest gene count	20 cohesive tumor cells showing highest gene count
	Amplification	Ratio≥2.0	Ratio≥2.0 (≥2.2)[a]
HER2 positivity	Tumor type	About 30% of intestinal-type about 15% of mixed-type about 5% of diffuse type	15–25% of ductal type (G2/G3)
	Tumor location	About 30% at cardiac/GEJ about 15% of gastric cancer	No correlation
Patient selection	FISH vs. IHC	IHC more predictive than FISH: IHC primary FISH only if IHC2+	FISH/IHC equally predictive:

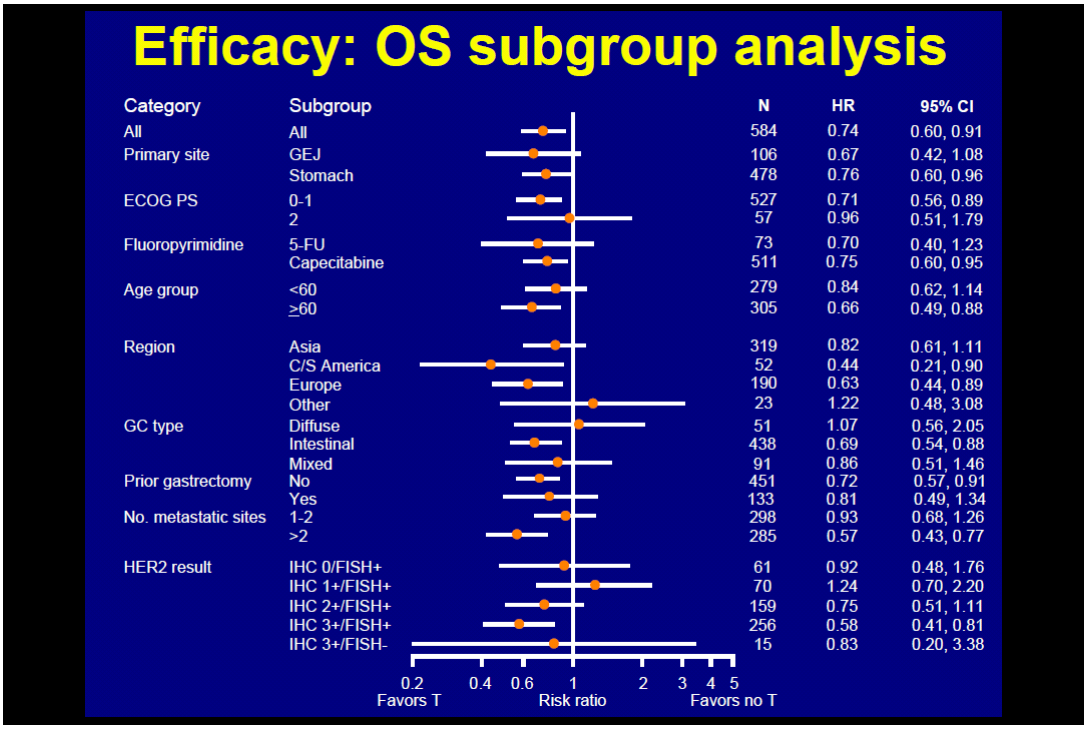
Rushoff et al.: Virchow Arch, 2010

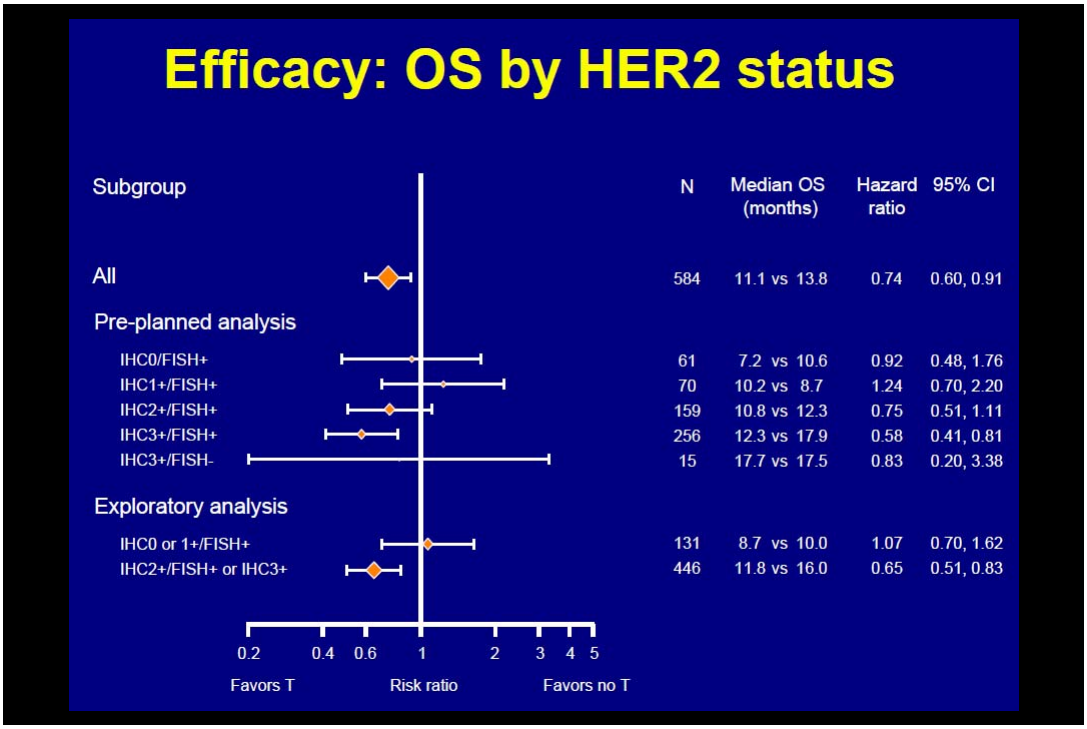

Waterfall plot (ITT population)
100
50
0
-50
-100
Change from Screening(%)
T+XP/FP群 (n=247)
XP/FP群 (n=220)
% of patients
0
JSMO2011 O2-265 presented by Y.Hamamoto


Secondary end point:
tumor response rate
Intent to treat
Patients (%)
60
50
40
30
20
10
0
p=0.0599
2.4%
5.4%
p=0.0145
32.1%
41.8%
p=0.0017
34.5%
47.3%
F+C + trastuzumab
F+C
CR
PR
ORR
ORR= CR + PR
CR, complete response; PR, partial response

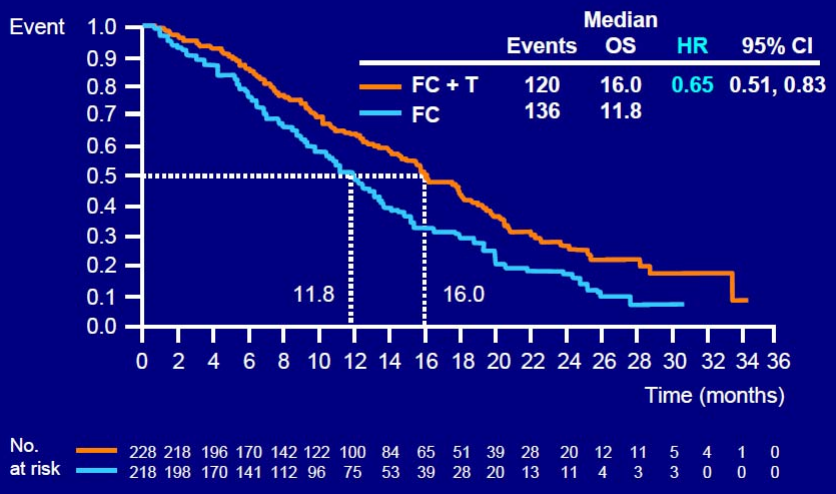

Secondary end point: PFS
Event
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
5.5
6.7
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34
Time (months)
Median
Events PFS HR 95% CI p value
FC + T 226 6.7 0.71 0.59, 0.85 0.0002
FC 235 5.5
No. at risk
294 258 201 141 95 60 41 28 21 13 9 8 6 6 6 4 2 0
290 238 182 99 62 33 17 7 5 3 3 2 2 1 1 0 0 0


Primary end point: OS
Event
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
11.1
13.8
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Time (months)
Median
Events OS HR 95% CI p value
FC + T 167 13.8 0.74 0.60, 0.91 0.0046
FC 182 11.1
No. at risk
294 277 246 209 173 147 113 90 71 56 43 30 21 13 12 6 4 1 0
290 266 223 185 143 117 90 64 47 32 24 16 14 7 6 5 0 0 0
T, trastuzumab


Efficacy: OS subgroup analysis
Category
Subgroup
N
HR
95% CI
All
All
584
0.74
0.60, 0.91
Primary site
GEJ
106
0.67
0.42, 1.08
Stomach
478
0.76
0.60, 0.96
ECOG PS
0-1
527
0.71
0.56, 0.89
2
57
0.96
0.51, 1.79
Fluoropyrimidine
5-FU
73
0.70
0.40, 1.23
Capecitabine
511
0.75
0.60, 0.95
Age group
<60
279
0.84
0.62, 1.14
≥60
305
0.66
0.49, 0.88
Region
Asia
319
0.82
0.61, 1.11
C/S America
52
0.44
0.21, 0.90
Europe
190
0.63
0.44, 0.89
Other
23
1.22
0.48, 3.08
GC type
Diffuse
51
1.07
0.56, 2.05
Intestinal
438
0.69
0.54, 0.88
Mixed
91
0.86
0.51, 1.46
Prior gastrectomy
No
451
0.72
0.57, 0.91
Yes
133
0.81
0.49, 1.34
No. metastatic sites
1-2
298
0.93
0.68, 1.26
>2
285
0.57
0.43, 0.77
HER2 result
IHC 0/FISH+
61
0.92
0.48, 1.76
IHC 1+/FISH+
70
1.24
0.70, 2.20
IHC 2+/FISH+
159
0.75
0.51, 1.11
IHC 3+/FISH+
256
0.58
0.41, 0.81
IHC 3+/FISH-
15
0.83
0.20, 3.38
0.2
0.4
0.6
1
2
3
4
5
Favors T
Risk ratio
Favors no T


Efficacy: OS by HER2 status
Subgroup
N
Median OS (months)
Hazard ratio
95% CI
All
584
11.1 vs 13.8
0.74
0.60, 0.91
Pre-planned analysis
IHC0/FISH+
61
7.2 vs 10.6
0.92
0.48, 1.76
IHC1+/FISH+
70
10.2 vs 8.7
1.24
0.70, 2.20
IHC2+/FISH+
159
10.8 vs 12.3
0.75
0.51, 1.11
IHC3+/FISH+
256
12.3 vs 17.9
0.58
0.41, 0.81
IHC3+/FISH-
15
17.7 vs 17.5
0.83
0.20, 3.38
Exploratory analysis
IHC0 or 1+/FISH+
131
8.7 vs 10.0
1.07
0.70, 1.62
IHC2+/FISH+ or IHC3+
446
11.8 vs 16.0
0.65
0.51, 0.83
0.2
0.4
0.6
1
2
3
4
5
Favors T
Risk ratio
Favors no T

OS in IHC2+/FISH+ or IHC3+
(exploratory analysis)



Safety: non-hematological AEs

AE, %	F+C n=290		F+C + trastuzumab n=294	
	All	Grade 3/4	All	Grade 3/4
Nausea	63	7	67	7
Vomiting	46	8	50	6
Fatigue	28	2	35	4
Diarrhea	28	4	37	9
Constipation	32	2	26	<1
Asthenia	18	3	19	4
Stomatitis	15	2	24	<1
Weight decrease	14	2	23	2
Abdominal pain	14	1	16	1

AEs occurring in >10% of patients

【ガイドライン委員会のコメント（案）】

1）本試験の結果、HER2陽性胃癌（切除不能な進行再発の胃癌・食道胃接合部癌）に対して
トラスツズマブを含む化学療法が新たな標準治療となることが示された。
また、本試験では3,665例がIHCまたはFISHによるHER2スクリーニングを受け、810例（22.1%）
がHER2陽性(IHC3+またはFISH陽性）と判定されている。
今後は、化学療法選択前にHER2検査を実施することが推奨される。
(註：2011年4月時点ではIHCとFISH検査を同月に検査することは保険で認められていない）

2）本試験では**HER2陽性の定義をIHC3+またはFISH+**とした。
なお、サブセット解析の結果、IHC3+または、IHC2+かつFISH+のHER2高発現群
(446例、76.4%）で生存期間の延長がより明確に示された。（16.0ヶ月/11.8ヶ月、ハザード比0.65
（0.51-0.83））

3）本試験では重篤な循環器疾患が除外されたこともありトラスツズマブ群で特に目立った有害事象
の増加は認められなかった。しかし、乳癌でのトラスツズマブ使用経験から治療前や治療中およ
び治療後の**心機能等への留意が必要である。**

4）本試験の試験群のレジメンは**カペシタビン (or 5-FU) ＋シスプラチンとトラスツズマブの併用であ
り、HER2陽性胃癌に対してはこのレジメンが推奨される。**
本邦の進行胃癌に対する標準治療である**S-1＋シスプラチンとトラスツズマブの併用に関しては
有効性ならびに毒性等のプロファイルは不明であり、今後の臨床研究の課題である。**

Evaluation of the appropriate use of trastuzumab in treatment for advanced or metastatic HER2-positive gastric cancer

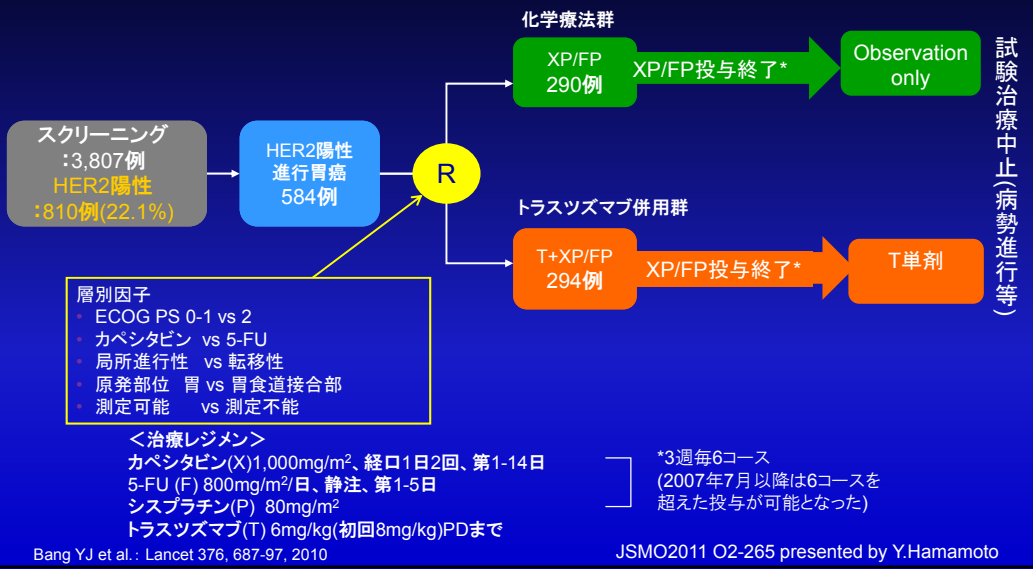
Yasuo Hamamoto

On behalf of the ToGA investigators

16　　JSMO2011 O2-265 presented by Y.Hamamoto

Background : ToGA trial

- 多国籍多施設共同ランダム化非盲検第Ⅲ相試験



＜治療レジメン＞
カペシタビン(X)1,000mg/m²、経口1日2回、第1-14日
5-FU (F) 800mg/m²/日、静注、第1-5日
シスプラチン(P) 80mg/m²
トラスツズマブ(T) 6mg/kg(初回8mg/kg)PDまで

*3週毎6コース
(2007年7月以降は6コースを超えた投与が可能となった)

Bang YJ et al.: Lancet 376, 687-97, 2010

JSMO2011 O2-265 presented by Y.Hamamoto

対象と方法

方法

- ToGA試験において、各症例の薬剤治療歴を抽出し、薬剤の組み合わせとその投与期間を集計した
  - Observation only期間の定義

  - T単剤投与期間の定義

対象

- ToGA ITT population (n=584)

JSMO2011 O2-265 presented by Y.Hamamoto

T単剤投与症例と、Observation only症例の治療選択状況とその理由

<T単剤またはObservation onlyとなった理由>

例数(%)	XP/FP群 Observation onlyとなった症例 (n=97)	T+XP/FP群 T単剤投与が行われた症例(n=159)
化学療法6サイクルの投与完遂	78 (80%)	131 (82%)
その他	19 (20%)	28 (18%)

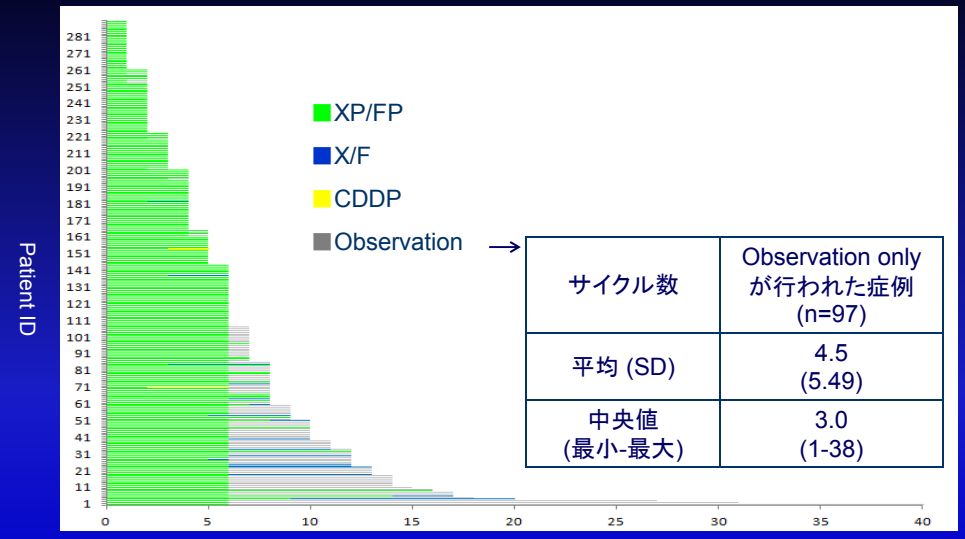
<T単剤またはObservation onlyが終了した理由>

例数(%)	XP/FP群 Observation onlyとなった症例 (n=97)	T+XP/FP群 T単剤投与が行われた症例(n=159)
効果不十分	73 (75%)	115 (72%)
治療継続拒否	4 (3%)	9 (6%)
有害事象	9 (9%)	5 (3%)
その他	3 (1%)	2 (1%)
治療継続中*	8 (8%)	28 (18%)

*データカットオフ時に試験治療を継続していた症例

JSMO2011 O2-265 presented by Y.Hamamoto

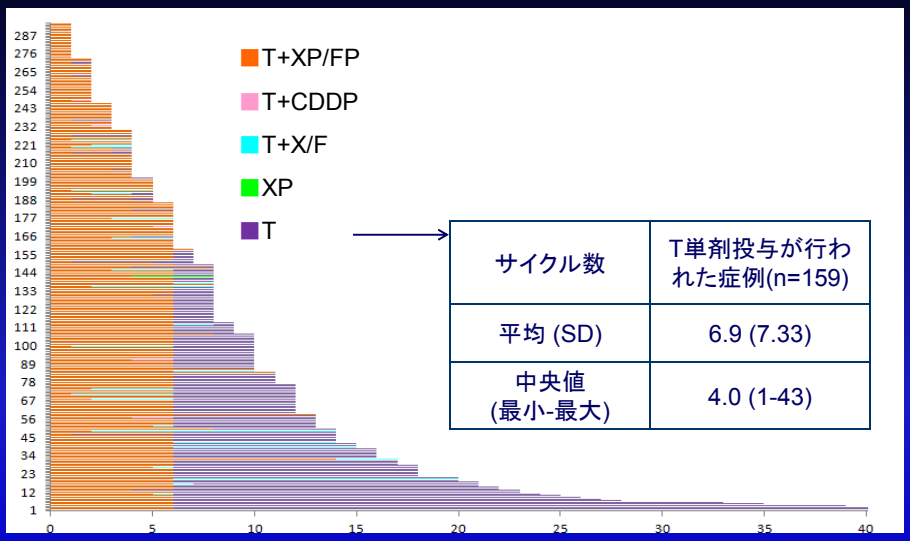
XP/FP群における各症例の投与薬剤組み合わせ別サイクル数(n=290)



サイクル数	Observation only が行われた症例 (n=97)
平均 (SD)	4.5 (5.49)
中央値 (最小-最大)	3.0 (1-38)

JSMO2011 O2-265 presented by Y.Hamamoto

T+XP/FP群における 各症例の投与薬剤組み合わせ別サイクル数(n=294)



サイクル数	T単剤投与が行われた症例(n=159)
平均 (SD)	6.9 (7.33)
中央値 (最小-最大)	4.0 (1-43)

JSMO2011 O2-265 presented by Y.Hamamoto

T単剤期間とObservation only期間

	XP/FP群 Observation onlyが行われた症例(n=97)	T+XP/FP群 T単剤投与が行われた症例(n=159)
平均（日） (SD)	78.8 (112.46)	129.3 (160.68)
中央値（日） (最小-最大)	39.0 (1-796)	70.0 (1-882)

JSMO2011 O2-265 presented by Y.Hamamoto

On-going lapatinib trials for HER2 gastric cancer

Lapatinib is the standard for patients with mBC who has a prior history of trastuzumab.

1st line

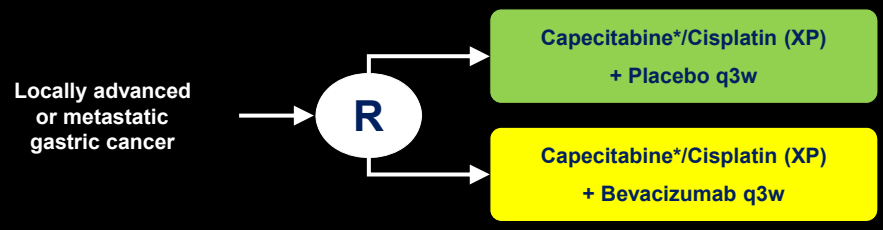
LOGiC Global Trial; *CapeOX +/- Lapatinib*
PE: OS, n=533

2nd line

TyTAN Asian Trial; *weekly PTX +/- Lapatinib*
PE: OS, n=260

➢*Very important to establish disease entity of HER2 positive GC and to follow breast story*

AVAGAST: A Randomized Double-Blind Placebo- Controlled Phase III Study



Stratification factors:

1. Geographic region
2. Fluoropirimidine backbone
3. Disease status

*5-FU also allowed if cape contraindicated

Cape 1000 mg/m^2 oral bid, d1–14, 1-week rest

Cisplatin 80 mg/m^2 d1

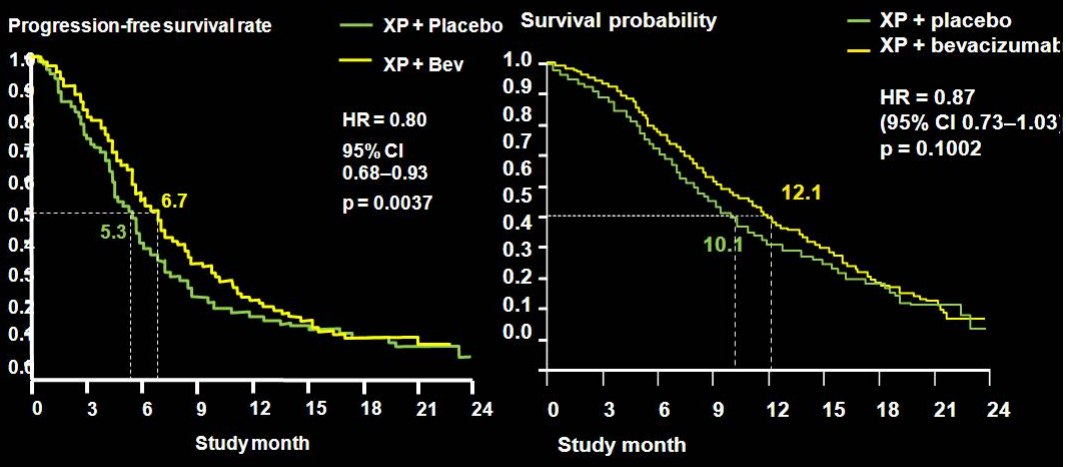
Bevacizumab 7.5 mg/kg d1

Maximum of 6 cycles of cisplatin

Cape and bevacizumab/placebo until PD

Starting dose of bev/placebo: 30 minutes, subsequent doses: 15 minutes

PFS and OS: AVAGAST

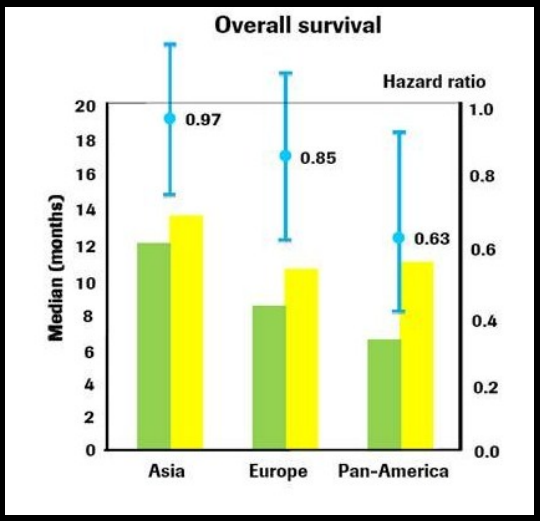


Kang YK et al. ASCO, 2010

5 Lesson from AVAGAST trial

- Regional difference cannot be ignored.
- Median survival time in developed countries is around one year.
- Thus, it is very difficult to show survival benefit in the 1st line setting for all gastric cancers;
  > 2M difference is necessary to get a hazard ratio of 0.8 (11 vs 14M).
- Bevacizumab has no killing activity by itself.
- Because gastric cancers are very heterogeneous;
  There may be specific types of gastric cancer to some molecular target agents.
  → Enriched population selected by bio-marker, like Herceptin.
- Single target such as Bevacizumab may not be sufficient;
  Multiple target TKI ? Or Combination of molecular target agents ??

Ceiling effect of Bevacizumab?



- MST of placebo arm in Asia is longer than those of bevacizumab arm in other regions
- HRs in each region seem to be correlated with the results of placebo arms

Survival Post-Progression

Trial	Region	Regimen	mPFS	MST	MST - PFS
AVAGAST trial	Asia	XP	5.6	12.1	6.5
		XP+Bev	6.7	13.9	7.2
	Europe	XP	4.4	8.6	4.2
		XP+Bev	6.7	11.1	4.4
	Pan-America	XP	4.4	6.8	2.4
		XP+Bev	5.9	11.5	5.9
FLAGS trial	Non-Asia	5-FU+CDDP	5.5	7.9	2.4
		S-1+CDDP	4.8	8.6	3.8
SPIRITS	Japan	S-1	4.0	11.0	7.0
		S-1+CDDP	6.0	13.0	7.0
JCOG9912	Japan	CPT-11+CDDP	4.8	1.23	7.5
START	Japan/Korea	S-1+TXT	5.4	13.0	7.6

5 Lesson from AVAGAST trial

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  > 2M difference is necessary to get a hazard ratio of 0.8 (11 vs 14M).
- Bevacizumab has no killing activity by itself.
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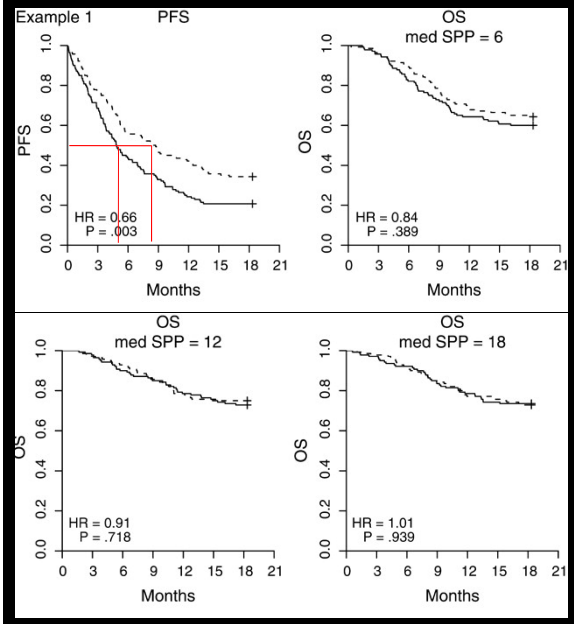
  Multiple target TKI ? Or Combination of molecular target agents ??

Simulations of PFS and OS by survival post-progression(SPP)



- OS is too high a bar when median SPP is long
- The timing at data cut-off in AVAGAST might be too early for Asian population (= immature for Asia/Japan)

Broglio K R , Berry D A JNCI J Natl Cancer Inst 2009;101:1642-1649

Study Treatments

- Stratified for PS & #prior therapy
- SLC regimen determined by investigators
- SLC continued until progression, toxicities, or withdrawal

RANDOMIZATION

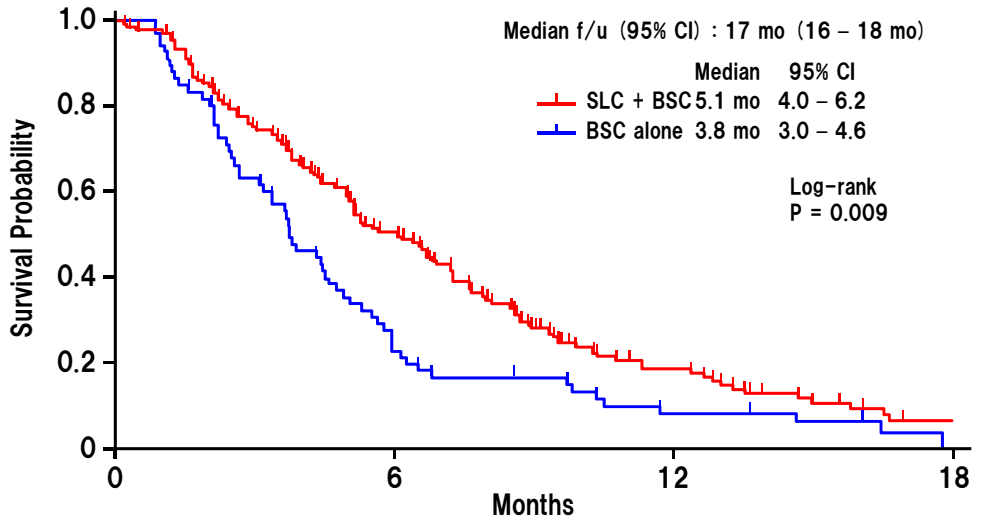
2 → Docetaxel 60 mg/m² q3wks or Irinotecan 150 mg/m² q2wks

1 → BSC alone

- Strict QC measures for BSC
- Standard BSC regimen *a priori* defined
- BSC patients could exit BSC at any time
- All patients treated & followed up in same way

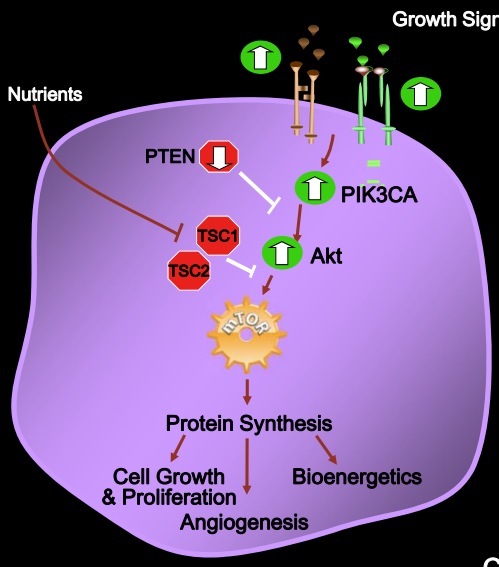
2011 ASCO Annual Meeting #4004

Overall Survival

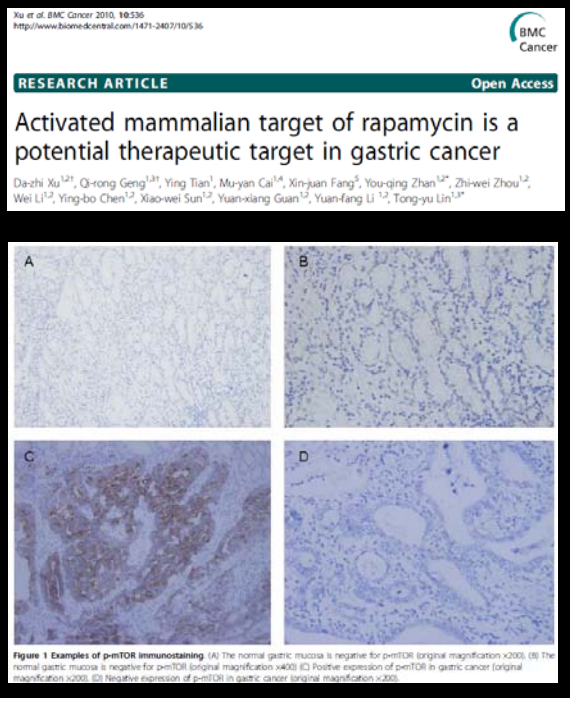


2011 ASCO Annual Meeting #4004

mTOR Pathway Activation in Gastric Cancer



- **mTOR is activated in 60-64% of gastric cancers**
- **mTOR pathway proteins are frequently over-activated in gastric cancer:**
  - PIK3CA: 4-25%
  - p-Akt: 29-78%
  - IGFR – 25%
  - EGFR – 22-43%
- **Loss-of-function mutations**
  - PTEN (LOH): 17-76%



Xu et al. BMC Cancer 2010, 10:536
http://www.biomedcentral.com/1471-2407/10/536

BMC Cancer

RESEARCH ARTICLE Open Access

Activated mammalian target of rapamycin is a potential therapeutic target in gastric cancer

Da-zhi Xu[1,2†], Qi-rong Geng[1,3†], Ying Tian[1], Mu-yan Cai[1,4], Xin-juan Fang[5], You-qing Zhan[1,2*], Zhi-wei Zhou[1,2], Wei Li[1,2], Ying-bo Chen[1,2], Xiao-wei Sun[1,2], Yuan-xiang Guan[1,2], Yuan-fang Li[1,2], Tong-yu Lin[1,3*]

Figure 1 Examples of p-mTOR immunostaining. (A) The normal gastric mucosa is negative for p-mTOR (original magnification ×200). (B) The normal gastric mucosa is negative for p-mTOR (original magnification ×400). (C) Positive expression of p-mTOR in gastric cancer (original magnification ×200). (D) Negative expression of p-mTOR in gastric cancer (original magnification ×200).

Table 1 Clinicopathologic correlation of p-mTOR expression in gastric cancer

Factors	All patients	No. of patients (%)		P
	N = 181 (%)	mTOR negative	mTOR positive	
Age(y)				.256
< 60	95(52.5)	50(56.8)	45(48.4)	
≥60	86(47.5)	38(43.2)	48(51.6)	
Sex				.926
Male	129(71.3)	63(71.6)	66(71.0)	
Female	52(28.7)	25(28.4)	27(29.0)	
Site				.053
Upper	77(42.5)	33(37.5)	44(47.3)	
Middle	28(15.5)	10(11.4)	18(19.4)	
lower	74(40.9)	43(48.9)	31(33.3)	
Diffuse	2(1.1)	2(2.3)	0(0.0)	
Tumor size				.172
≤ 4 cm	63(34.8)	35(40.0)	28(30.1)	
> 4 cm	118(65.2)	53(60.0)	65(69.9)	
Borrmann type				.398
Early stage	7(3.9)	6(6.8)	1(1.1)	
I	4(2.2)	2(2.3)	2(2.1)	
II	65(35.9)	31(35.2)	34(36.6)	
III	101(55.8)	47(53.4)	54(58.1)	
IV	4(2.2)	2(2.3)	2(2.1)	
grading				.999
1	4(2.2)	2(2.3)	2(2.1)	
2	55(30.4)	27(30.7)	28(30.1)	
3	116(64.1)	56(63.6)	60(64.5)	
4	6(3.3)	3(3.4)	3(3.3)	
Pathologic T classification				.168
T1	17(9.4)	12(13.6)	5(5.4)	
T2	35(19.3)	18(20.5)	17(18.3)	
T3	119(65.7)	55(62.5)	64(68.8)	
T4	10(5.5)	3(3.4)	7(7.5)	
Pathologic N status				.008
N negative	44(24.3)	29(33.0)	15(16.1)	
N positive	137(75.7)	59(67.0)	78(83.9)	
Pathologic stage (pTNM)				.026
I	26(14.4)	17(19.3)	9(9.7)	
II	47(26.0)	28(31.8)	19(20.4)	
III	100(55.2)	41(46.5)	59(63.4)	
IV	8(4.4)	2(2.3)	6(6.5)	

mTOR expression is a worse prognostic factor in gastric cancer patients after R0 resection

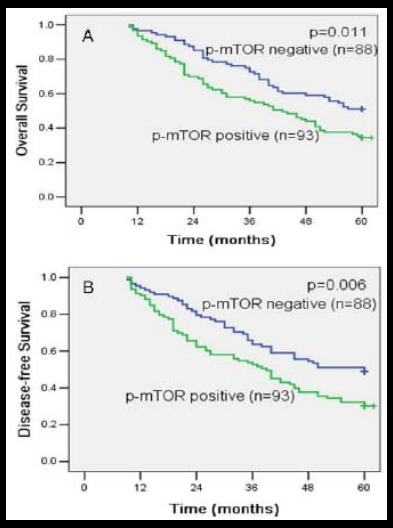
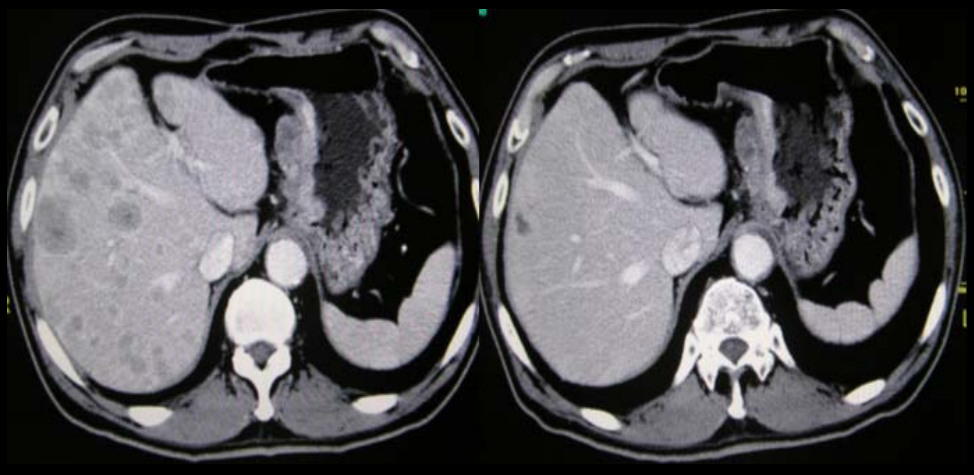


Table 3 Multivariable cox regression analysis of disease-free and overall survivals

		Disease-free suivival			Overall survival		
Factors	No.	HR	95%CI	p	HR	95%CI	p
p-mTOR				0.059			0.070
Negative	88	1.00			1.00		
Positive	93	1.452	0.986-2.138		1.443	0.970-2.147	
Infiltrating depth				0.018			0.046
pT1	17	1.00			1.00		
pT2	35	1.050	0.366-3.016	0.928	1.078	0.375-3.101	0.889
pT3	119	2.251	0.867-5.845	0.096	2.146	0.823-5.595	0.118
pT4	10	2.926	0.920-9.305	0.069	2.616	2.616-8.580	0.113
Lymph node status				0.018			0.038
Negative	44	1.00			1.00		
Positive	137	1.981	1.981-3.488		1.828	1.034-3.233	

Xu D et al. BMC Cancer, 2010

Remarkable response in pt with mGC everolimus phase I (NCCHE)

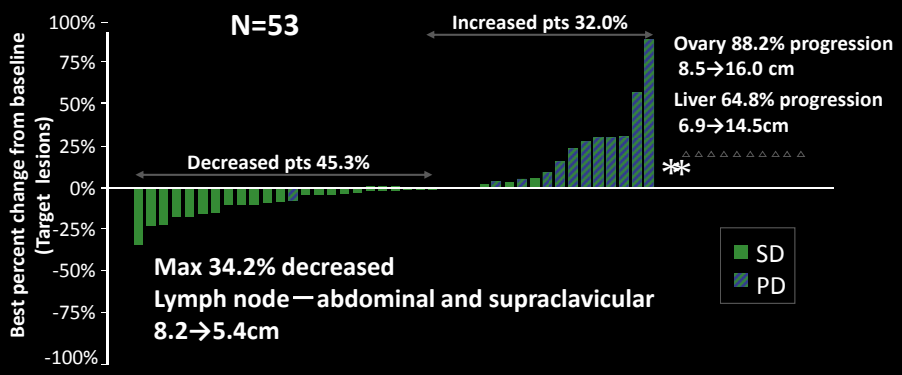


09-Jun-2006
Baseline

04-Aug-2006
2 months after everolimus

Everolimus phase 2 for second or third line AGC

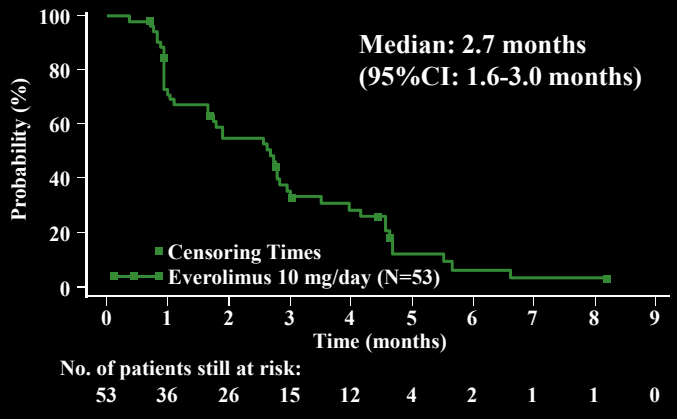
Decrease in Tumor Size from Baseline (Central Review)



DCR= 54.7% (40.4 – 68.4) (29/53)

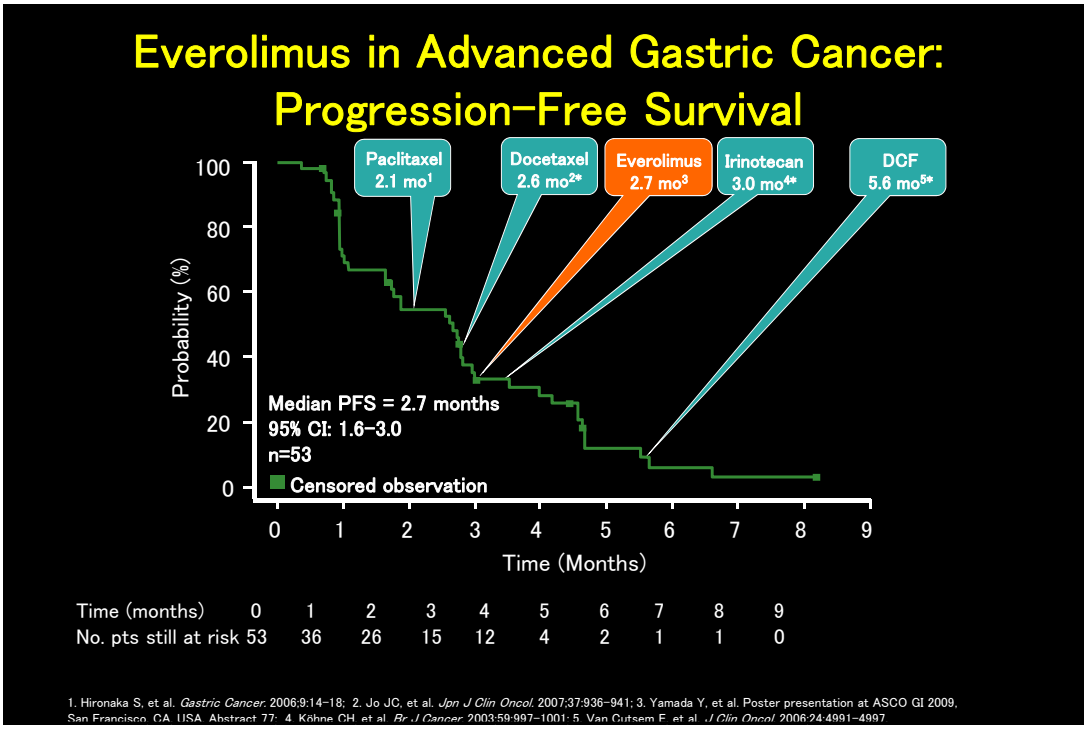
Doi T et al. J Clin Oncol 2010

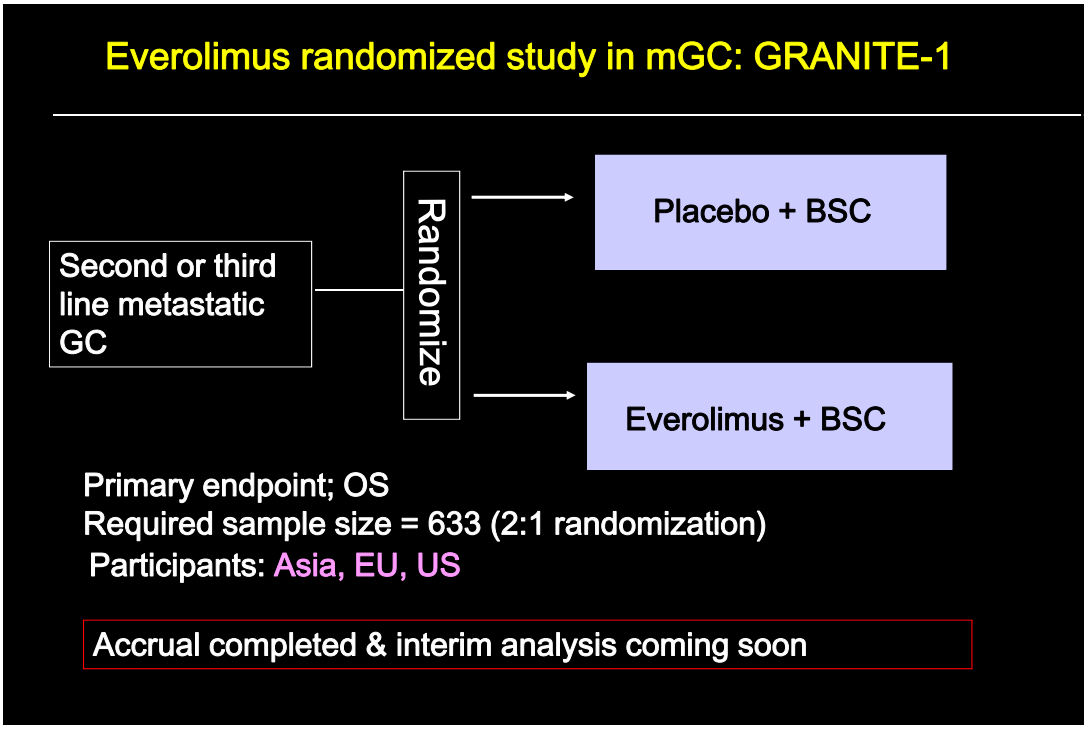
Phase II Everolimus AGC Study: Progression-Free Survival



2.6 months (95% CI, 1.0-3.0 months) for second-line subset
2.8 months (95% CI, 1.6-4.0 months) for third-line subset

1. Doi T, et al. *J Clin Oncol.* 2010;28(11):1904-1910.


Everolimus in Advanced Gastric Cancer:
Progression-Free Survival
Paclitaxel 2.1 mo[1]
Docetaxel 2.6 mo[2*]
Everolimus 2.7 mo[3]
Irinotecan 3.0 mo[4*]
DCF 5.6 mo[5*]
Probability (%)
100
80
60
40
20
0
Median PFS = 2.7 months
95% CI: 1.6-3.0
n=53
Censored observation
0 1 2 3 4 5 6 7 8 9
Time (Months)
Time (months) 0 1 2 3 4 5 6 7 8 9
No. pts still at risk 53 36 26 15 12 4 2 1 1 0
1. Hironaka S, et al. Gastric Cancer. 2006;9:14-18; 2. Jo JC, et al. Jpn J Clin Oncol. 2007;37:936-941; 3. Yamada Y, et al. Poster presentation at ASCO GI 2009,


Everolimus randomized study in mGC: GRANITE-1
Second or third line metastatic GC
Randomize
Placebo + BSC
Everolimus + BSC
Primary endpoint; OS
Required sample size = 633 (2:1 randomization)
Participants: Asia, EU, US
Accrual completed & interim analysis coming soon

On-going trials of mTOR inhibitor for gastric cancer

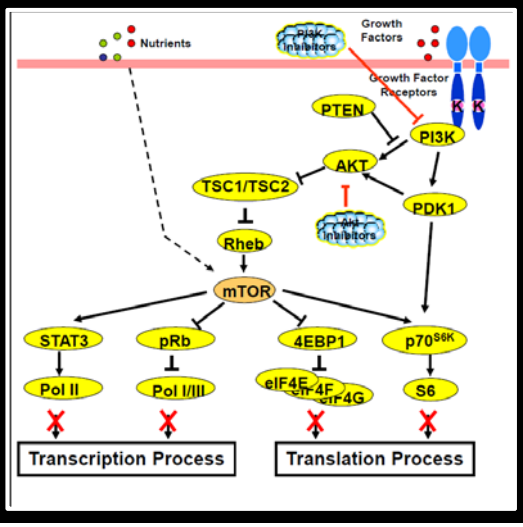
Phase	Drugs	Status
Phase III	Monotherapy vs. Best Supportive Care	Active, not recruiting
Phase III	Paclitaxel with and without Everolimus	Not yet recruiting
Phase II	Monotherapy	Completed
Phase II	Monotherapy	Active, not recruiting
Phase II	Monotherapy	Recruiting
Phase II	Combination with Cisplatin, 5-FU/LV	Recruiting
Phase I/II	Combination with Capecitabine	Recruiting
Phase I	Combination with Mitomycin C	Active, not recruiting
Phase I	Combination with XELOX	Recruiting
Phase I	Combination with Docetaxel	Recruiting
Phase I	Combination with mFOLFOX6	Not yet recruiting
Phase I	Combination with TS-1, Cisplatin	Not yet recruiting

PI3K-Akt-mTOR Pathway inhibitors

Key to achieving a response?

- 20–40% of CRCs and GCs bear alterations in one of PI3K pathway genes (i.e., PIK3CA, PTEN, PDK1, Akt2). High incidence of PIK3CA

- Compounds in clinical development:
  - PI3K inhibitors
    - GDC-0941
    - BEZ235, BGT226, BKM120
    - XL147, XL765
  - mTOR inhibitors:
    - Rapamycin (sirolimus)
    - Temsirolimus (CCI779)
    - Everolimus (RAD001)
    - Deforolimus (AP23573)
  - Dual mTORC1 and mTORC2 inhibitors
  - Akt inhibitors:
    - PBI-05204 (oleandrin)
    - MK-2206
    - GDC0068



CRC = colorectal cancer

Trastuzumab and everolimus combination in mBC

- Trastuzumab and everolimus are both active in gastric cancer *in vitro* and *in vivo*
- Trastuzumab + everolimus + paclitaxel activity in breast cancer:
  - HER2/neu overexpressing breast cancer patients resistant to trastuzumab (n=31)
  - Varied everolimus doses: 5 mg daily (n=6); 10 mg daily (n=15); 30 mg weekly (n=10)
  - RR: 83% (5 mg); 13% (10 mg); 30% (30 mg)
  - DCR: 83% (5 mg); 88% (10 mg); 80% (30 mg)

RR, response rate; DCR, disease control rate

5 Lesson from AVAGAST trial

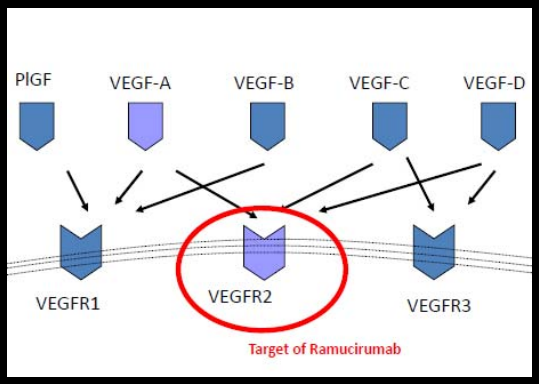
- Regional difference cannot be ignored.
- Median survival time in developed countries is around one year.
- Thus, it is very difficult to show survival benefit in the 1st line setting for all gastric cancers;
  > 2M difference is necessary to get a hazard ratio of 0.8 (11 vs 14M).
- Bevacizumab has no killing activity by itself.
- Because gastric cancers are very heterogeneous;
  There may be specific types of gastric cancer to some molecular target agents.
  → Enriched population selected by bio-marker, like Herceptin.
- Single target such as Bevacizumab may not be sufficient;
  Multiple target TKI ? Or Combination of molecular target agents ??

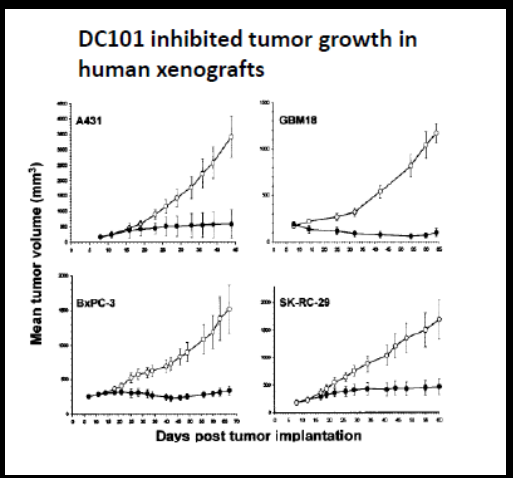
Lesson 3: Bevacizumab has no killing activity by itself

	Region	XP + Placebo Median, mo	XP + Bev Median, mo	Δ mo	Hazard Ratio	95% CI
OS	Asia	12.1	13.9	1.8	0.97	0.75–1.25
	Europe	8.6	11.1	2.5	0.85	0.63–1.14
	America	6.8	11.5	4.7	0.63	0.43–0.94
PFS	Asia	5.6	6.7	1.1	0.92	0.74–1.14
	Europe	4.4	6.9	2.5	0.71	0.54–0.93
	America	4.4	5.9	1.5	0.65	0.46–0.93
RR	Asia	45.5%	47.9%	2.4%	1.10	0.69–1.77
	Europe	28.2%	41.3%	13.1%	1.79	1.02–3.15
	America	36.4%	50.0%	13.6%	1.75	0.83–3.69

Ohtsu A, et al. WCGIC, 2010

Another angiogenesis inhibitor: ramucirumab (anti-VEGFR2 Ab)





- *VEGFR-2 appears to be the most responsible for the mitogenis and angiogenic effect of VEGF*

DC101= murine anti-VEGFR2 antibody

Response in phase I study of ramucirumab (anti-VEGFR2 Ab)

Out of 37 treated patients,

- ✓ 4 pts experienced confirmed PR
  - ◆ melanoma at 4mg/kg
  - ◆ gastric carcinoma at 4mg/kg
  - ◆ uterine leiomyosarcoma at 13 mg/mg
  - ◆ ovarian carcinoma at 16 mg/kg
- ✓ 11 pts experienced a confirmed PR or SD lasting>=24 weeks

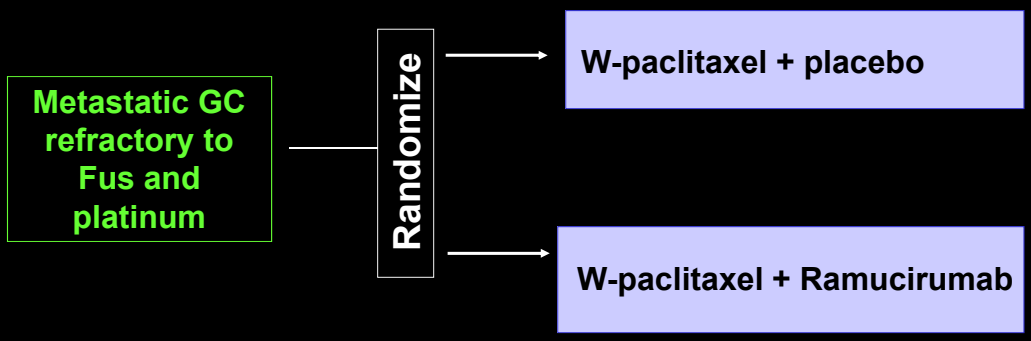
Patients with PR or SD (>=12 weeks)

Dose Level and Primary Malignancy	Best Response (≥ 12 weeks)	Duration of Response (weeks)
2 mg/kg		
Colorectal	SD	30
Breast	SD	15
Ovarian	SD	15
4 mg/kg		
Melanoma	PR	31
Gastric	PR	103
Colorectal	SD	31
6 mg/kg		
Head and neck	SD	105
Head and neck	SD	29
8 mg/kg		
Neuroendocrine (nasopharynx)	SD	151
Prostate	SD	41
Cholangiocarcinoma	SD	21
10 mg/kg		
Pancreatic	SD	37
Colorectal	SD	15*
Prostate	SD	14
Uterine leiomyosarcoma	SD	13
13 mg/kg		
Head and neck	SD	21
Uterine leiomyosarcoma	PR	70
Neuroendocrine	SD	23
16 mg/kg		
Ovarian	PR	86+*

Response rate = 15%
Disease control rate = 62%

Spratlin JL et al. J Clin Oncol 2010

Ramucirumab (anti-VEGFR2) for mGC: RAINBOW: second-line setting



Primary endpoint: Overall survival

Study rationale:

- ➢ *single agent anti-tumor activity for GC (in vitro, clinial)*
- ➢ *synergism between ramcirumab and taxane*
- ➢ *second-line setting*

5 Lesson from AVAGAST trial

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- Thus, it is very difficult to show survival benefit in the 1st line setting for all gastric cancers;
  > 2M difference is necessary to get a hazard ratio of 0.8 (11 vs 14M).
- Bevacizumab has no killing activity by itself.
- Because gastric cancers are very heterogeneous;
  There may be specific types of gastric cancer to some molecular target agents.
  → Enriched population selected by bio-marker, like Herceptin.
- Single target such as Bevacizumab may not be sufficient;
  Multiple target TKI ? Or Combination of molecular target agents ??

Blood plasma VEGF-A analysis in the AVAGAST randomized study of first-line bevacizumab + capecitabine/cisplatin in patients with advanced gastric cancer

MA Shah[1], YK Kang[2], A Ohtsu[3], L Roman[4], J Nunes[5], CP Li[6], P Delmar[7], B Langer[8], SJ Scherer[9], E Van Cutsem[10]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Asan Medical Centre, Seoul, Korea; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]Leningrad Regional Oncology Centre, St Petersburg, Russian Federation; [5]Hospital Do Cancer de Barretos, Barretos, Brazil; [6]Veterans General Hospital Cancer Center, Taipei, Taiwan; [7]F. Hoffmann-La Roche, Basel, Switzerland; [8]F. Hoffmann-La Roche, Basel, Switzerland; [9]Genentech Inc, South San Francisco, USA; [10]University Hospital Gasthuisberg, Leuven, Belgium

Samples and pVEGF-A levels

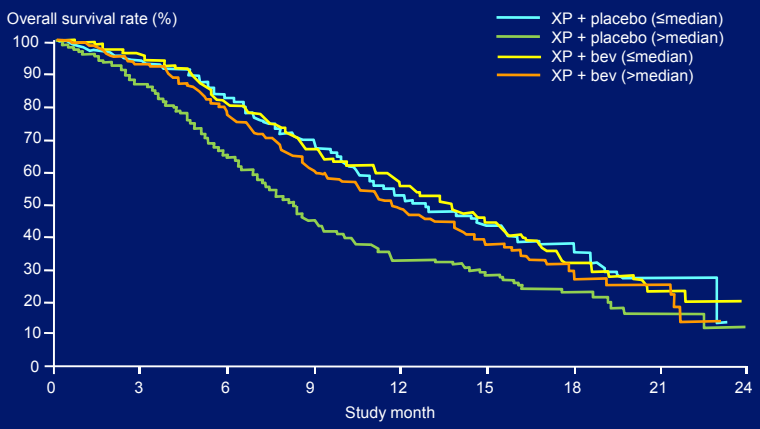
Samples

- Overall, 774 patients participated in the AVAGAST study
- Baseline pVEGF-A samples were available for 712 (92%) of these patients
- Baseline characteristics of the biomarker population were similar to the overall population

pVEGF-A

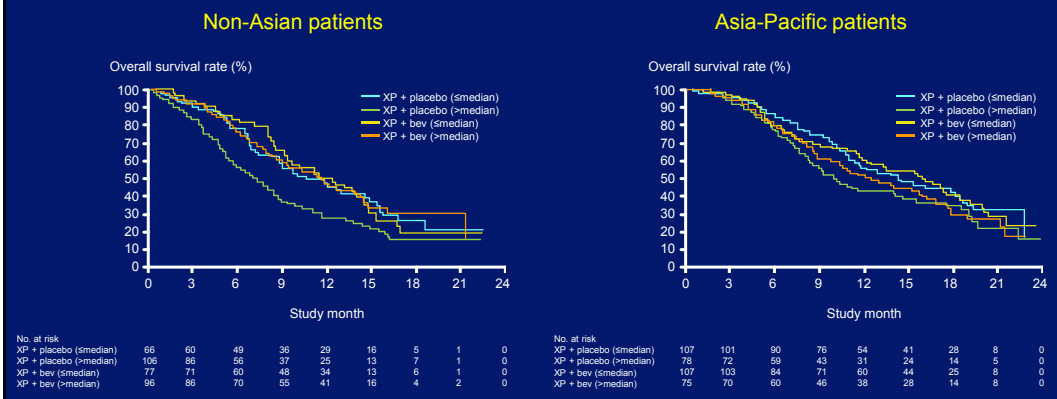
- The median plasma levels of VEGF-A at baseline was 111 ng/L (range 20–1868 ng/L) in the overall population
- Baseline pVEGF-A levels were higher in patients from non-Asian regions than in Asian patients (median 147 vs. 94 ng/L; p<0.0001; Mann-Whitney U test), and in patients with a poorer Eastern Cooperative Oncology Group performance status (p<0.0001; Mann-Whitney U test)

Kaplan-Meier estimates of overall survival by baseline pVEGF-A level and treatment group

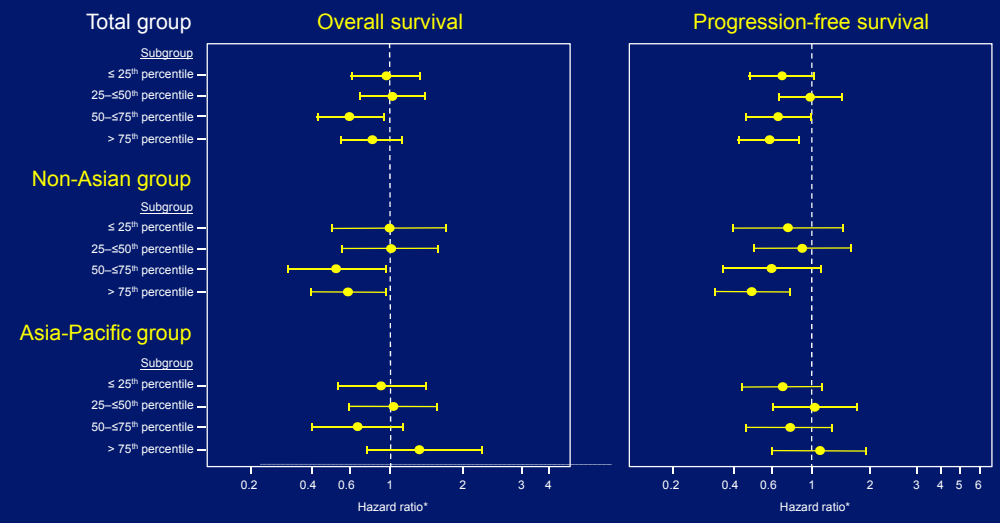


No. at risk									
XP + placebo (≤median)	173	161	139	112	83	57	33	9	0
XP + placebo (>median)	184	158	115	80	56	37	21	6	0
XP + bev (≤median)	184	174	144	119	94	57	31	9	0
XP + bev (>median)	171	156	130	101	79	44	18	10	0

Overall survival by baseline pVEGF-A level and treatment group in non-Asian / Asia-Pacific patients



pVEGF-A at baseline and OS and PFS (biomarker population, quartile analysis)



*Hazard ratio of <1 denotes benefit for bevacizumab + chemotherapy; hazard ration >1 denotes benefit for chemotherapy

Evaluation of plasma VEGF-A as a potential predictive pan-tumour biomarker for bevacizumab

Gordon C Jayson

on behalf of:

de Haas S, Delmar P, Miles DW, Shah MA, Van Cutsem E, Carmeliet P, Hegde P, Wild N, Scherer SJ

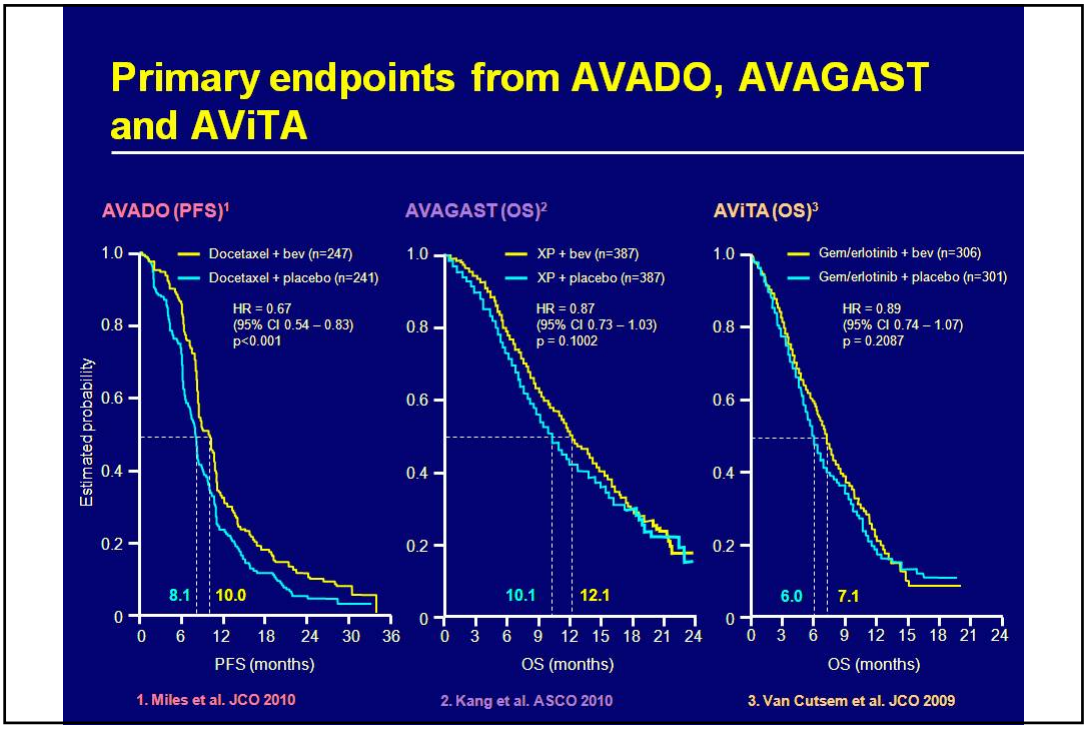
Background

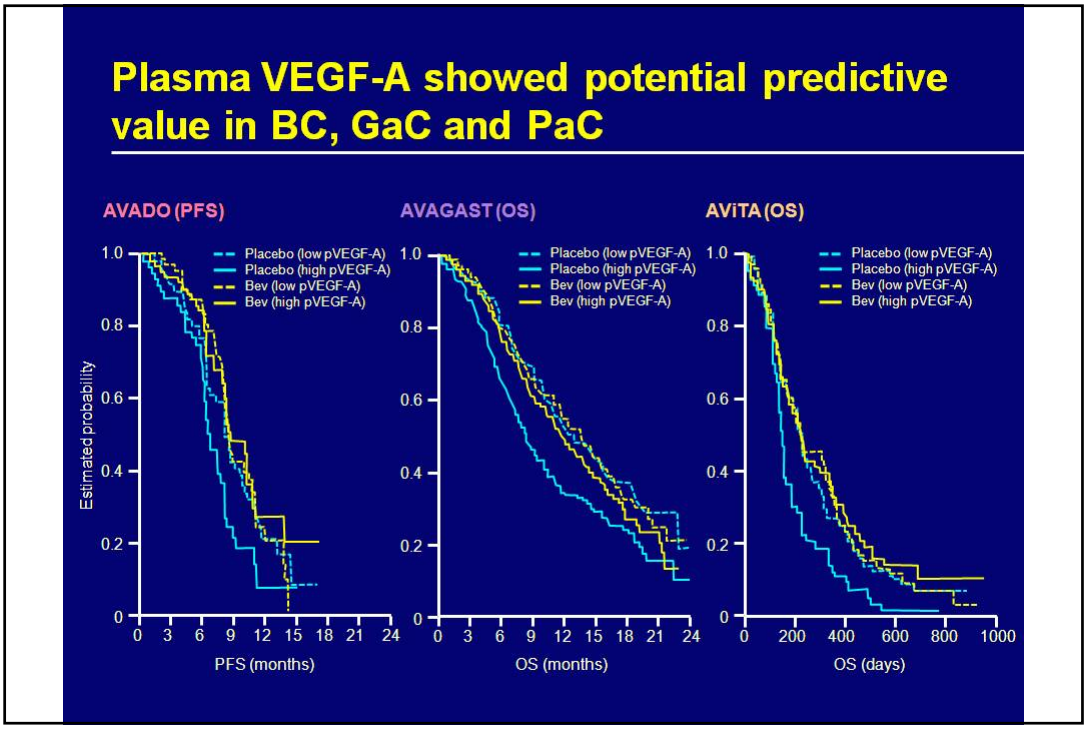
- A novel ELISA-based assay favouring shorter isoforms (VEGF-A_{121} and VEGF-A_{110}), was used to assess the predictive value of VEGF-A in 6 different bevacizumab trials

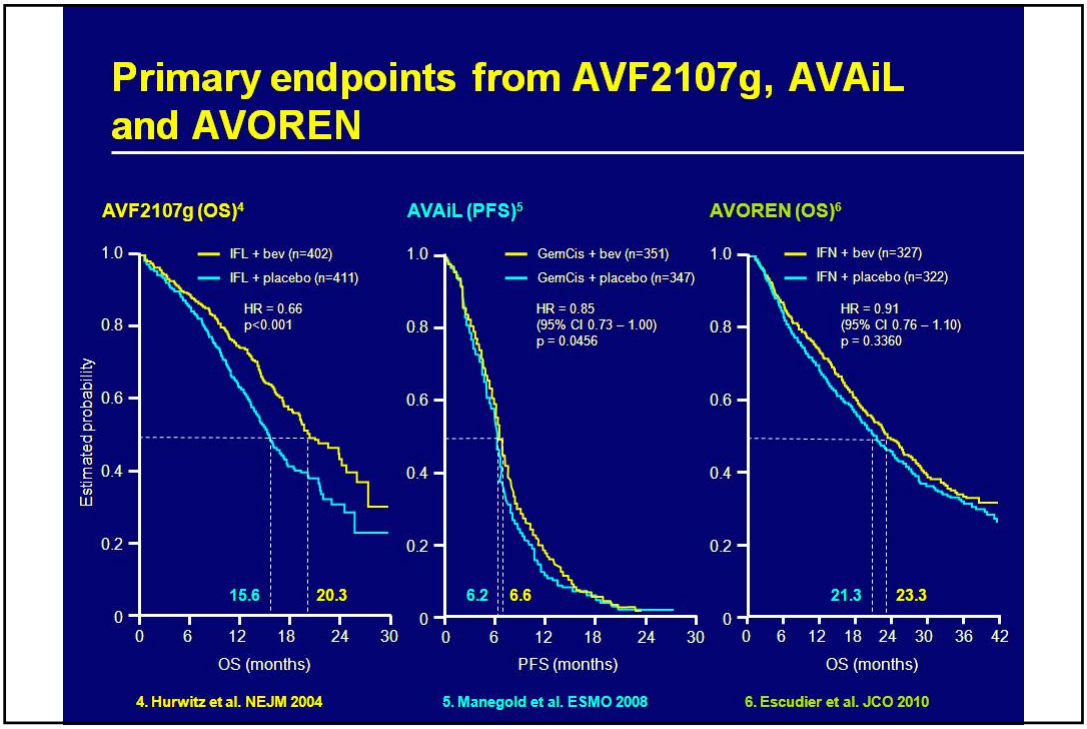
CRC	NSCLC	BC	RCC
AVF2107g[1] OS: HR=0.66 p<0.001 (n=923)	AVAiL[2] PFS: HR=0.75/0.82 p=0.003/0.03 (n=1043)	AVADO[3] PFS: HR=0.67 p=0.0002 (n=736)	AVOREN[4] PFS: HR=0.63 p=0.0001 (n=649)

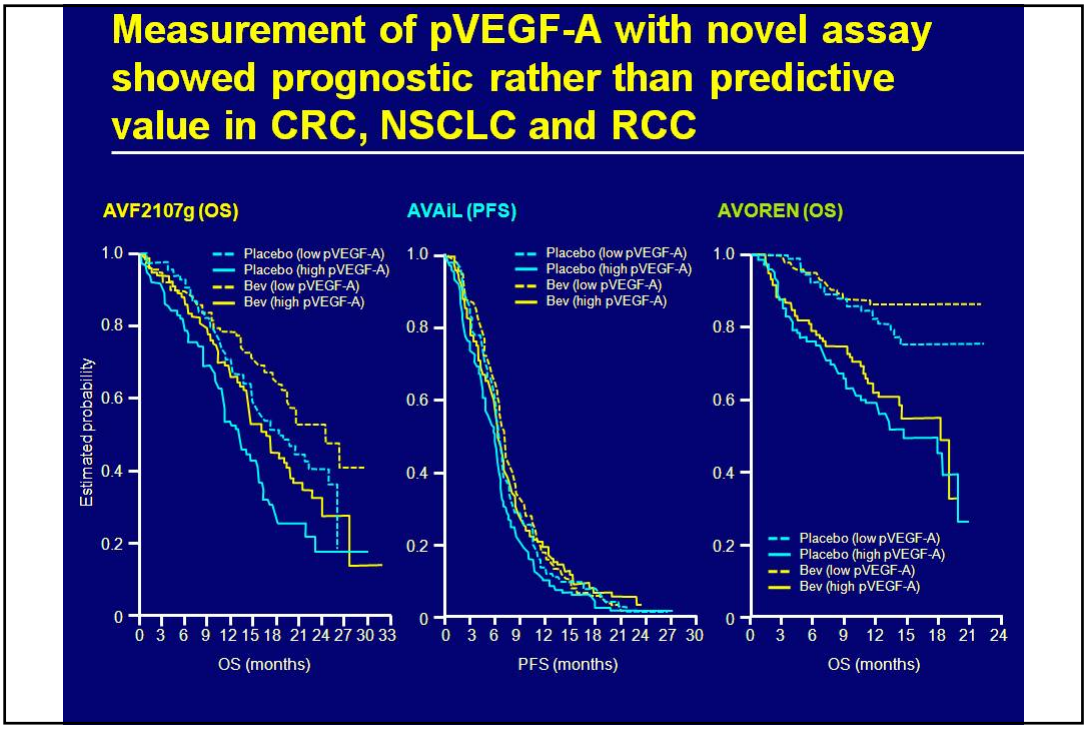
GC	PC
AVAGAST[5] OS: HR=0.87 p=0.1002 (n=774)	AViTA[6] OS: HR=0.89 p=0.2087 (n=607)

1. Hurwitz et al. NEJM 2004; 2. Reck et al. JCO 2009; 3. Miles et al. JCO 2010;
4. Escudier et al. Lancet 2007; 5. Ohtsu et al. JCO, 2011; 6. Van Cutsem et al. JCO 2009


Primary endpoints from AVADO, AVAGAST and AViTA
AVADO (PFS)1
Docetaxel + bev (n=247)
Docetaxel + placebo (n=241)
HR = 0.67
(95% CI 0.54 – 0.83)
p<0.001
8.1
10.0
PFS (months)
AVAGAST (OS)2
XP + bev (n=387)
XP + placebo (n=387)
HR = 0.87
(95% CI 0.73 – 1.03)
p = 0.1002
10.1
12.1
OS (months)
AViTA (OS)3
Gem/erlotinib + bev (n=306)
Gem/erlotinib + placebo (n=301)
HR = 0.89
(95% CI 0.74 – 1.07)
p = 0.2087
6.0
7.1
OS (months)
Estimated probability
1. Miles et al. JCO 2010
2. Kang et al. ASCO 2010
3. Van Cutsem et al. JCO 2009


Plasma VEGF-A showed potential predictive value in BC, GaC and PaC
AVADO (PFS)
AVAGAST (OS)
AViTA (OS)
Placebo (low pVEGF-A)
Placebo (high pVEGF-A)
Bev (low pVEGF-A)
Bev (high pVEGF-A)
Estimated probability
PFS (months)
OS (months)
OS (days)


Primary endpoints from AVF2107g, AVAiL and AVOREN
AVF2107g (OS)[4]
IFL + bev (n=402)
IFL + placebo (n=411)
HR = 0.66
p<0.001
15.6
20.3
Estimated probability
OS (months)
AVAiL (PFS)[5]
GemCis + bev (n=351)
GemCis + placebo (n=347)
HR = 0.85
(95% CI 0.73 – 1.00)
p = 0.0456
6.2
6.6
PFS (months)
AVOREN (OS)[6]
IFN + bev (n=327)
IFN + placebo (n=322)
HR = 0.91
(95% CI 0.76 – 1.10)
p = 0.3360
21.3
23.3
OS (months)
4. Hurwitz et al. NEJM 2004
5. Manegold et al. ESMO 2008
6. Escudier et al. JCO 2010


Measurement of pVEGF-A with novel assay showed prognostic rather than predictive value in CRC, NSCLC and RCC
AVF2107g (OS)
AVAiL (PFS)
AVOREN (OS)
Placebo (low pVEGF-A)
Placebo (high pVEGF-A)
Bev (low pVEGF-A)
Bev (high pVEGF-A)
Estimated probability
OS (months)
PFS (months)

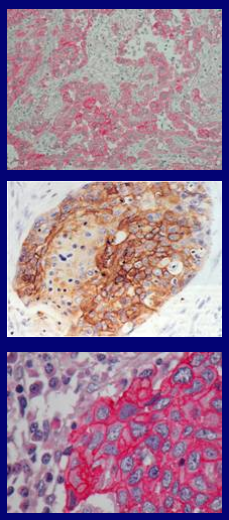
Alternative to previous slide

Overall summary of pVEGF-A data when measured with novel ELISA-based assay

		Potentially PREDICTIVE for		Potentially PROGNOSTIC for	
Tumour	Trial	PFS	OS	PFS	OS
BC	AVADO	✚	✖	✚	✚
GC	AVAGAST	✚	✚	✚	✚
PC	AViTA	✚	✚	✚	✚
CRC	AVF2107	✖	✖	✖	✚
NSCLC	AVAiL	✖	✖	✚	✚
RCC	AVOREN	✖	✖	✚	✚

EGFR Inhibitor

EGFR-expression rates in human cancers



EGFR is expressed in a variety of solid tumors

Colorectal cancer, %	72–89
Head and neck cancer, %	95–100
Lung cancer (NSCLC), %	40–80
Gastric cancer %	33-70
Breast cancer, %	14–91
Ovarian cancer, %	35–70
Renal cell cancer, %	50–90

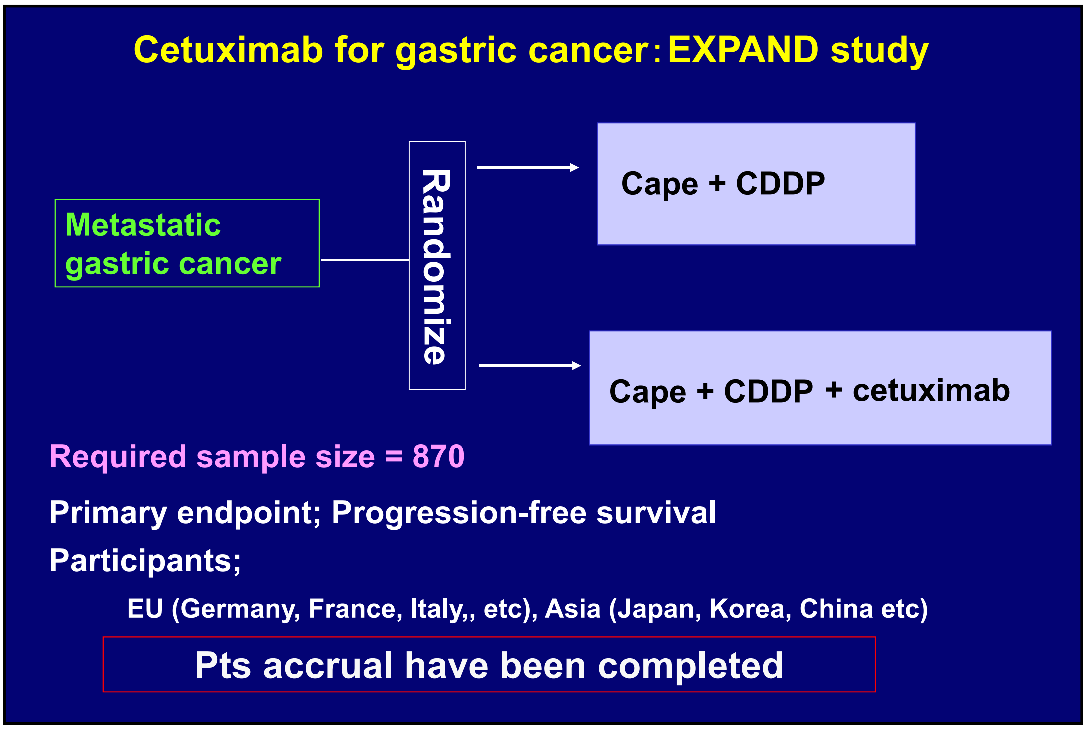
Cunningham et al. *N Engl J Med* 2004;351:337–345; Grandis et al. *Cancer* 1996;78:1284–1292; Salomon et al. *Crit Rev Oncol Hematol* 1995;19:183–232; Walker & Dearing. *Breast Cancer Res Treat* 1999;53:167–176; Folprecht et al. ASCO 2004 (Abstract #283).

63

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 sl. ASCO-GI 2008; Lordick et al. ASCO 2007; Kim C, et al ASCO-GI, 2009; Pinto et al. ASCO 2008


Cetuximab for gastric cancer：EXPAND study
Metastatic gastric cancer
Randomize
Cape + CDDP
Cape + CDDP + cetuximab
Required sample size = 870
Primary endpoint; Progression-free survival
Participants;
EU (Germany, France, Italy,, etc), Asia (Japan, Korea, China etc)
Pts accrual have been completed

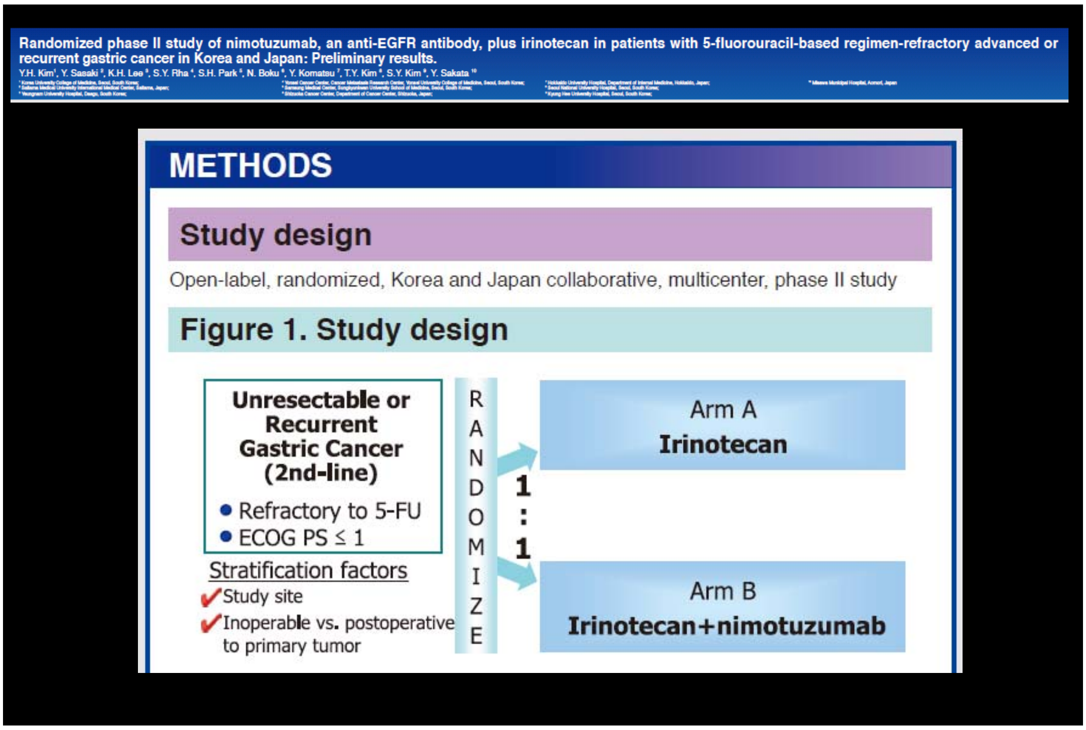
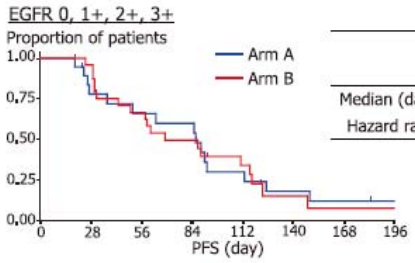

Randomized phase II study of nimotuzumab, an anti-EGFR antibody, plus irinotecan in patients with 5-fluorouracil-based regimen-refractory advanced or recurrent gastric cancer in Korea and Japan: Preliminary results.
Y.H. Kim[1], Y. Sasaki[2], K.H. Lee[3], S.Y. Rha[4], S.H. Park[5], N. Boku[6], Y. Komatsu[7], T.Y. Kim[8], S.Y. Kim[9], Y. Sakata[10]
METHODS
Study design
Open-label, randomized, Korea and Japan collaborative, multicenter, phase II study
Figure 1. Study design
Unresectable or Recurrent Gastric Cancer (2nd-line)
● Refractory to 5-FU
● ECOG PS ≤ 1
Stratification factors
✓Study site
✓Inoperable vs. postoperative to primary tumor
RANDOMIZE
1 : 1
Arm A
Irinotecan
Arm B
Irinotecan+nimotuzumab

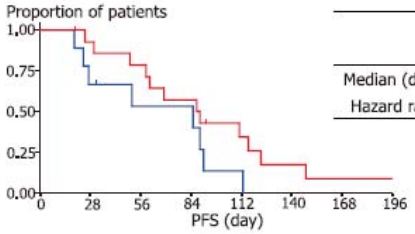
Figure 5. PFS by EGFR protein expression levels

EGFR 0, 1+, 2+, 3+



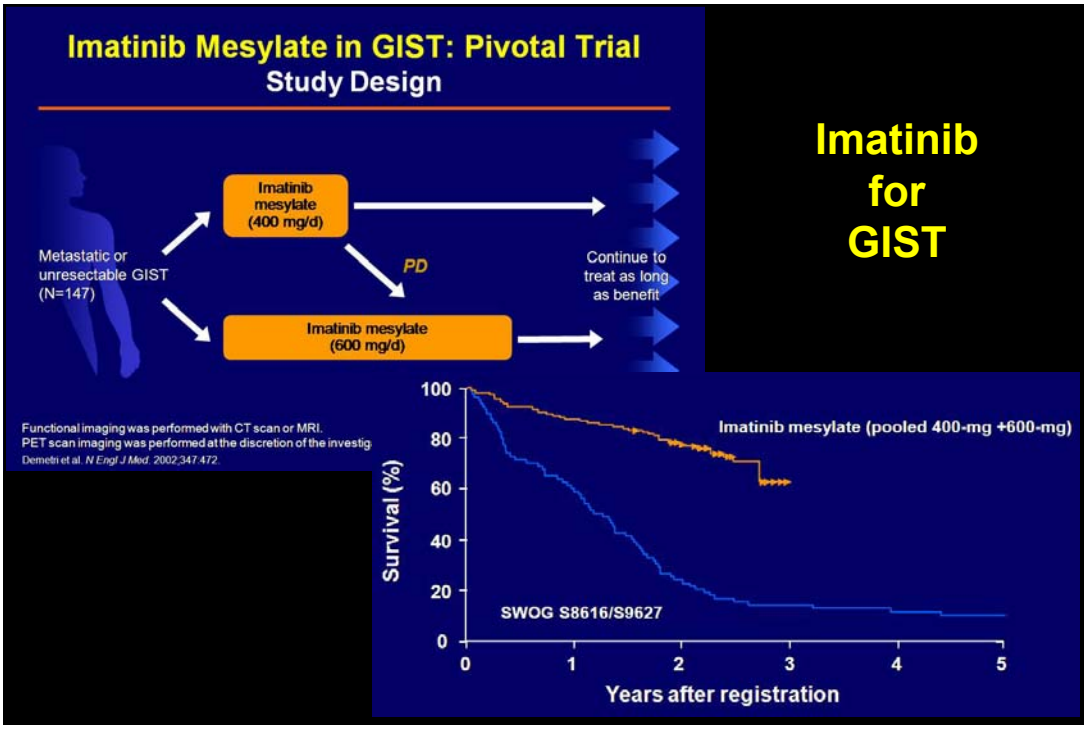
	Arm A	Arm B
	n=19	n=25
Median (days)	86.0	69.0
Hazard ratio	0.994 [0.507,1.949]	

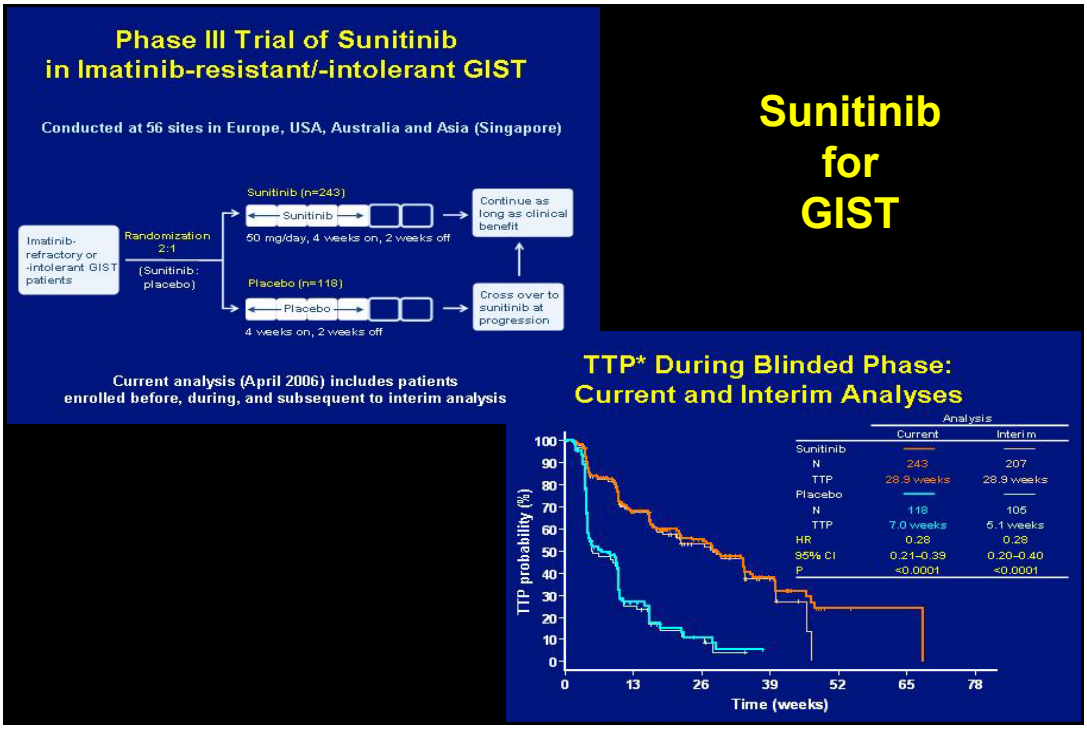
EGFR 1+, 2+, 3+

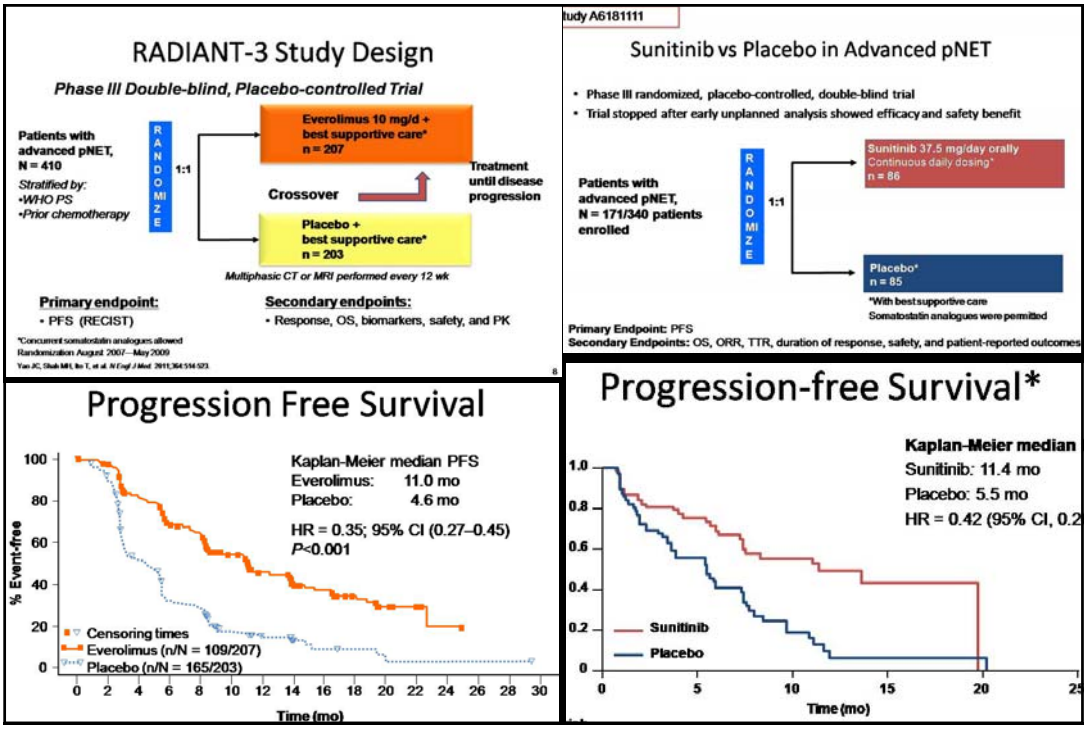


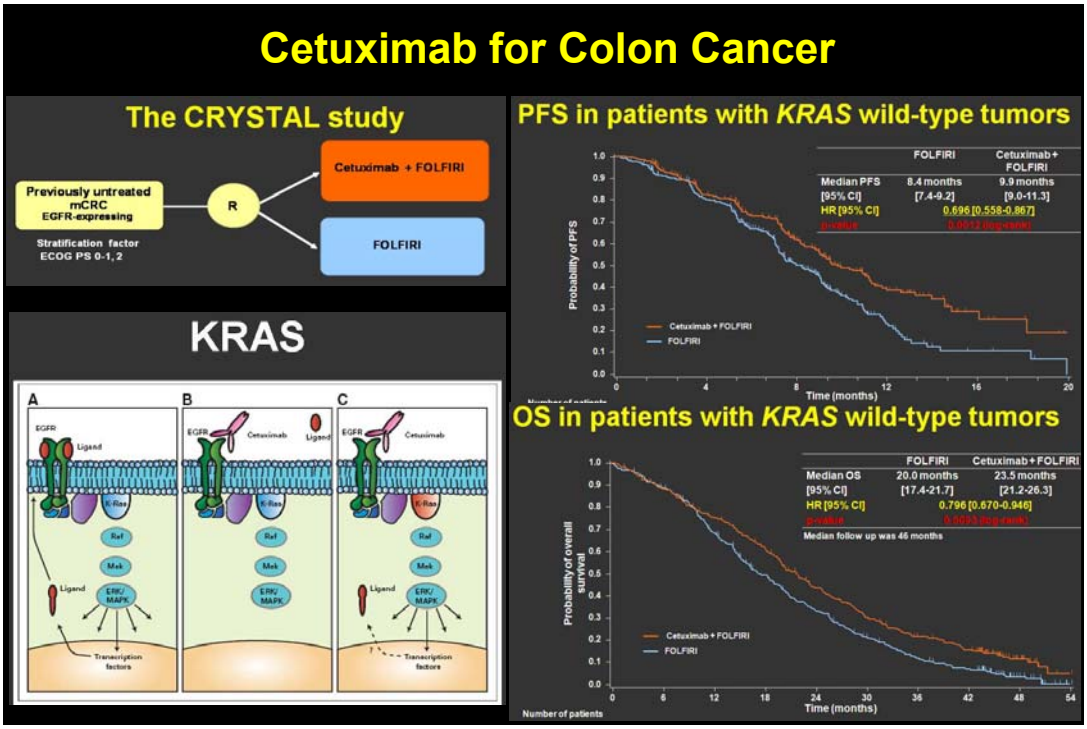
	Arm A	Arm B
	n=9	n=15
Median (days)	85.0	88.0
Hazard ratio	0.463 [0.177,1.212]	

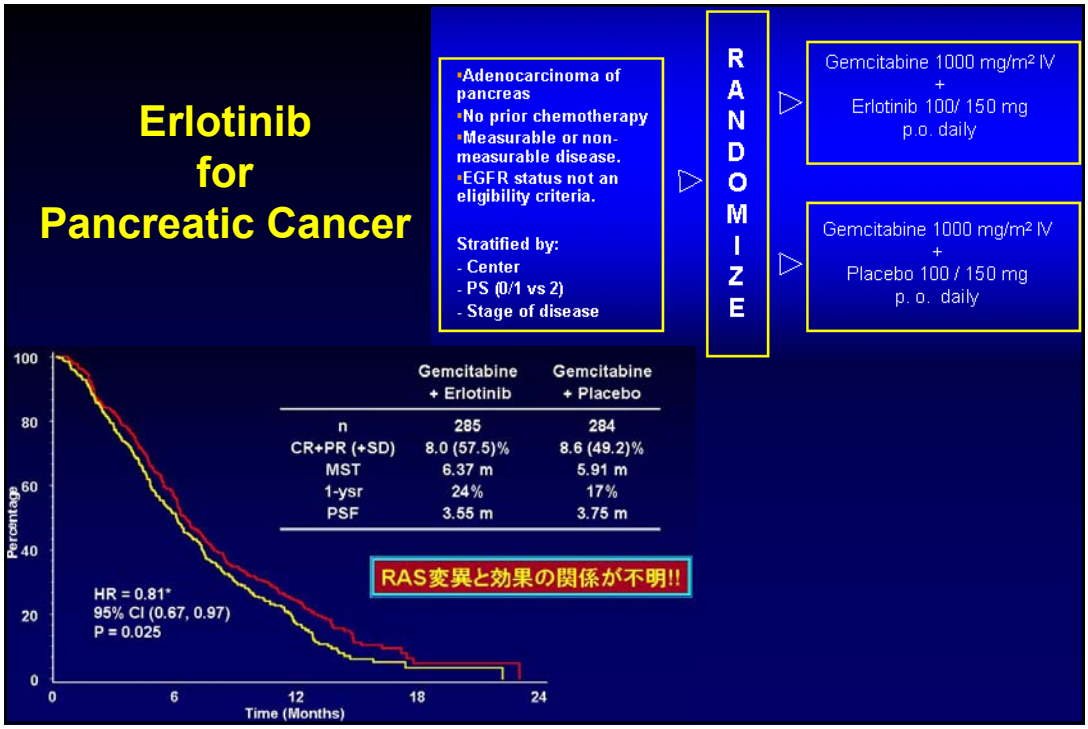
Super-responderを探せ
(個別化医療)

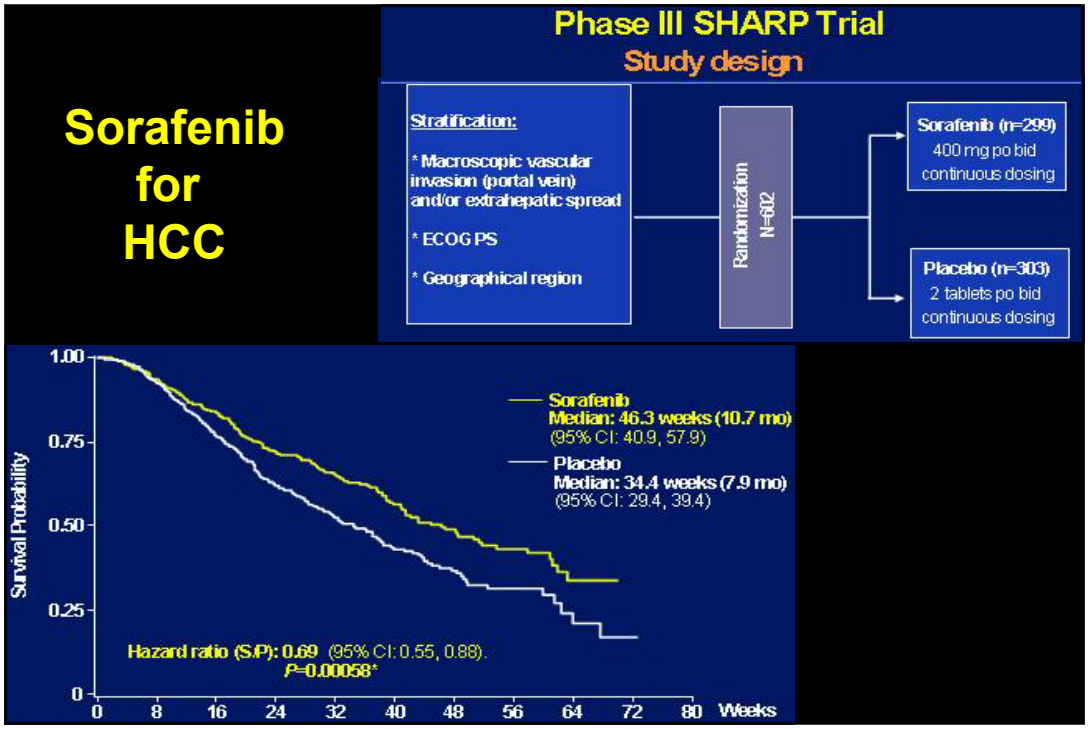

Imatinib Mesylate in GIST: Pivotal Trial
Study Design
Metastatic or unresectable GIST (N=147)
Imatinib mesylate (400 mg/d)
PD
Imatinib mesylate (600 mg/d)
Continue to treat as long as benefit
Functional imaging was performed with CT scan or MRI. PET scan imaging was performed at the discretion of the investig
Demetri et al. N Engl J Med. 2002;347:472.
Imatinib for GIST
Survival (%)
Imatinib mesylate (pooled 400-mg +600-mg)
SWOG S8616/S9627
Years after registration


Phase III Trial of Sunitinib in Imatinib-resistant/-intolerant GIST
Conducted at 56 sites in Europe, USA, Australia and Asia (Singapore)
Imatinib-refractory or -intolerant GIST patients
Randomization 2:1 (Sunitinib : placebo)
Sunitinib (n=243)
Sunitinib
50 mg/day, 4 weeks on, 2 weeks off
Placebo (n=118)
Placebo
4 weeks on, 2 weeks off
Continue as long as clinical benefit
Cross over to sunitinib at progression
Sunitinib for GIST
Current analysis (April 2006) includes patients enrolled before, during, and subsequent to interim analysis
TTP* During Blinded Phase: Current and Interim Analyses
TTP probability (%)
Time (weeks)
Analysis
Current
Interim
Sunitinib
N 243 207
TTP 28.9 weeks 28.9 weeks
Placebo
N 118 105
TTP 7.0 weeks 5.1 weeks
HR 0.28 0.28
95% CI 0.21–0.39 0.20–0.40
P <0.0001 <0.0001


RADIANT-3 Study Design
Phase III Double-blind, Placebo-controlled Trial
Patients with advanced pNET, N = 410
Stratified by:
•WHO PS
•Prior chemotherapy
RANDOMIZE
1:1
Everolimus 10 mg/d + best supportive care* n = 207
Crossover
Treatment until disease progression
Placebo + best supportive care* n = 203
Multiphasic CT or MRI performed every 12 wk
Primary endpoint:
• PFS (RECIST)
Secondary endpoints:
• Response, OS, biomarkers, safety, and PK
*Concurrent somatostatin analogues allowed
Randomization August 2007 – May 2009
Sunitinib vs Placebo in Advanced pNET
• Phase III randomized, placebo-controlled, double-blind trial
• Trial stopped after early unplanned analysis showed efficacy and safety benefit
Patients with advanced pNET, N = 171/340 patients enrolled
RANDOMIZE
1:1
Sunitinib 37.5 mg/day orally Continuous daily dosing* n = 86
Placebo* n = 85
*With best supportive care
Somatostatin analogues were permitted
Primary Endpoint: PFS
Secondary Endpoints: OS, ORR, TTR, duration of response, safety, and patient-reported outcomes
Progression Free Survival
% Event-free
Kaplan-Meier median PFS
Everolimus: 11.0 mo
Placebo: 4.6 mo
HR = 0.35; 95% CI (0.27–0.45)
P<0.001
Censoring times
Everolimus (n/N = 109/207)
Placebo (n/N = 165/203)
Time (mo)
Progression-free Survival*
Kaplan-Meier median
Sunitinib: 11.4 mo
Placebo: 5.5 mo
HR = 0.42 (95% CI, 0.2
Sunitinib
Placebo
Time (mo)


Cetuximab for Colon Cancer
The CRYSTAL study
Previously untreated mCRC EGFR-expressing
Stratification factor ECOG PS 0-1, 2
R
Cetuximab + FOLFIRI
FOLFIRI
PFS in patients with KRAS wild-type tumors
FOLFIRI
Cetuximab + FOLFIRI
Median PFS 8.4 months 9.9 months
[95% CI] [7.4-9.2] [9.0-11.3]
HR [95% CI] 0.696 [0.558-0.867]
p-value 0.0013 (log-rank)
Probability of PFS
Time (months)
KRAS
A
B
C
EGFR
Ligand
Cetuximab
K-Ras
Raf
Mek
ERK/ MAPK
Transcription factors
OS in patients with KRAS wild-type tumors
Median OS 20.0 months 23.5 months
[95% CI] [17.4-21.7] [21.2-26.3]
HR [95% CI] 0.796 [0.670-0.946]
p-value 0.0093 (log-rank)
Median follow up was 46 months
Probability of overall survival
Number of patients
Time (months)


Erlotinib
for
Pancreatic Cancer
•Adenocarcinoma of pancreas
•No prior chemotherapy
•Measurable or non-measurable disease.
•EGFR status not an eligibility criteria.
Stratified by:
- Center
- PS (0/1 vs 2)
- Stage of disease
RANDOMIZE
Gemcitabine 1000 mg/m² IV
+
Erlotinib 100/ 150 mg
p.o. daily
Gemcitabine 1000 mg/m² IV
+
Placebo 100 / 150 mg
p. o. daily
Gemcitabine + Erlotinib
Gemcitabine + Placebo
n 285 284
CR+PR (+SD) 8.0 (57.5)% 8.6 (49.2)%
MST 6.37 m 5.91 m
1-ysr 24% 17%
PSF 3.55 m 3.75 m
RAS変異と効果の関係が不明!!
Percentage
Time (Months)
HR = 0.81*
95% CI (0.67, 0.97)
P = 0.025


Sorafenib
for
HCC
Phase III SHARP Trial
Study design
Stratification:
* Macroscopic vascular invasion (portal vein) and/or extrahepatic spread
* ECOG PS
* Geographical region
Randomization N=602
Sorafenib (n=299)
400 mg po bid
continuous dosing
Placebo (n=303)
2 tablets po bid
continuous dosing
Survival Probability
Weeks
Sorafenib
Median: 46.3 weeks (10.7 mo)
(95% CI: 40.9, 57.9)
Placebo
Median: 34.4 weeks (7.9 mo)
(95% CI: 29.4, 39.4)
Hazard ratio (S/P): 0.69 (95% CI: 0.55, 0.88).
P=0.00058*

5 Lesson from AVAGAST trial

- Regional difference cannot be ignored.
- Median survival time in developed countries is around one year.
- Thus, it is very difficult to show survival benefit in the 1st line setting for all gastric cancers;
  > 2M difference is necessary to get a hazard ratio of 0.8 (11 vs 14M).
- Bevacizumab has no killing activity by itself.
- Because gastric cancers are very heterogeneous;
  There may be specific types of gastric cancer to some molecular target agents.
  → Enriched population selected by bio-marker, like Herceptin.
- Single target such as Bevacizumab may not be sufficient;
  Multiple target TKI ? Or Combination of molecular target agents ??

Lesson 5: Single target such as Bevacizumab may not be sufficient;
Multiple target TKI ? or Combination of molecular target agents ??

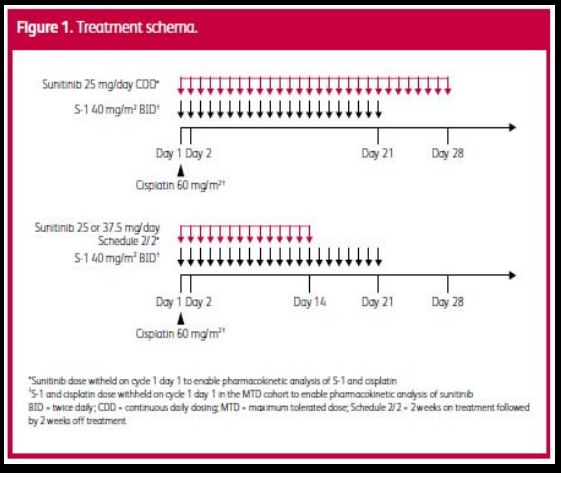
ESMO 2010

Phase I Study of Sunitinib Plus S-1 and Cisplatin in Patients with Advanced or Metastatic Gastric Cancer

K Muro,[1] Y Miyata,[2] N Machida,[3] M Li,[4] K Watanabe,[4] N Boku[2,5]

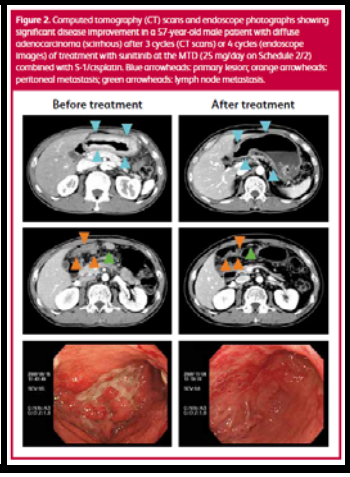
[1]Aichi Cancer Centre, Department of Clinical Oncology, Japan; [2]Saku Central Hospital, Department of Oncology, Japan; [3]Shizuoka Cancer Centre, Division of Gastrointestinal Oncology, Japan; [4]Pfizer Japan, Clinical Research, Japan; [5]St Marianna University School, Department of Clinical Oncology, Japan

Figure 1. Treatment schema.

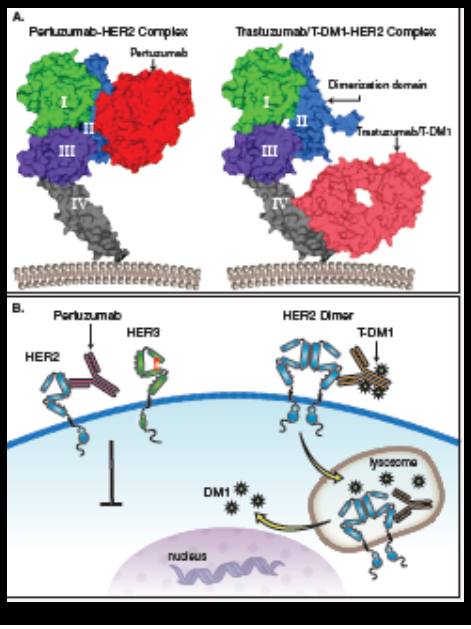


*Sunitinib dose witheld on cycle 1 day 1 to enable pharmacokinetic analysis of S-1 and cisplatin
†S-1 and cisplatin dose withheld on cycle 1 day 1 in the MTD cohort to enable pharmacokinetic analysis of sunitinib
BID = twice daily; CDD = continuous daily dosing; MTD = maximum tolerated dose; Schedule 2/2 = 2 weeks on treatment followed by 2 weeks off treatment

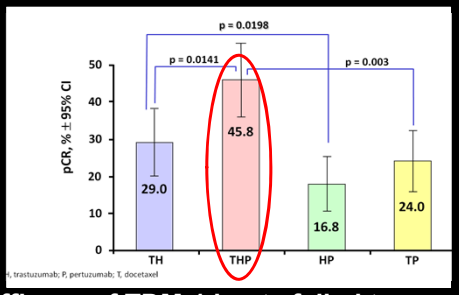
Figure 2. Computed tomography (CT) scans and endoscope photographs showing significant disease improvement in a 57-year-old male patient with diffuse adenocarcinoma (scirrhous) after 3 cycles (CT scans) or 4 cycles (endoscope images) of treatment with sunitinib at the MTD (25 mg/day on Schedule 2/2) combined with S-1/cisplatin. Blue arrowheads: primary lesion; orange arrowheads: peritoneal metastasis; green arrowheads: lymph node metastasis.



New agents for HER2: pertuzumab and TDM-1



neoadjuvant: pCR rate in taxane (T)+ herceptin(H) + pertuzumab (P)



Efficacy of TDM-1 in pts failed to taxane , trastuzumab, lapatinb, cape

Tumor Response	IRF (N=110)	Investigator (N=110)
Objective Response Rate, %	34.5	32.7
(95% CI)	(26.1–43.9)	(24.1–42.1)
CR	0	4.5
PR	34.5	28.2
SD*	44.5	50.9
PD	18.2	14.5
UE	1.8	0.9
Missing	0.9	0.9

現在の消化器領域における分子標的薬の限界：私見

消化器がんで、Addictionになっている遺伝子異常はあるのか？
著効を示す分子標的薬は開発可能か？

・肺癌においてもOncogene Addictionを起こしているのは、
喫煙歴のない“きれいな肺癌”

・”きれいながん” vs “きたないがん”
GIST > pNET > GI Cancers

・”単純な発がん” vs “多段階発がん” vs “無秩序発がん”
GIST > pNET > Pancreatic, Colorectal, HCC > Gastric

きたない胃がんには、きれいな個別化よりも、きたなく攻める？？？
分子標的治療薬も併用すれば、Cytotoxicと同じ？？？？？

ACTS-GC

Eligibility criteria:
- Histologically proven gastric carcinoma
- D≥2 lymph node dissection, R0 resection
- Stage II/III (Japanese classification)
- Negative peritoneal cytology
- Age 20-80 years
- No prior adjuvant therapy
- Adequate organ function
- Written informed consent

↓

Central Randomization (dynamic balancing)
Adjustment factors : Stage*(II, IIIA, IIIB), Institution

↓

S-1 80-120 mg/day**
4 weeks administration with 2weeks off
in each course for 12 months

Surgery only
(No further therapy)

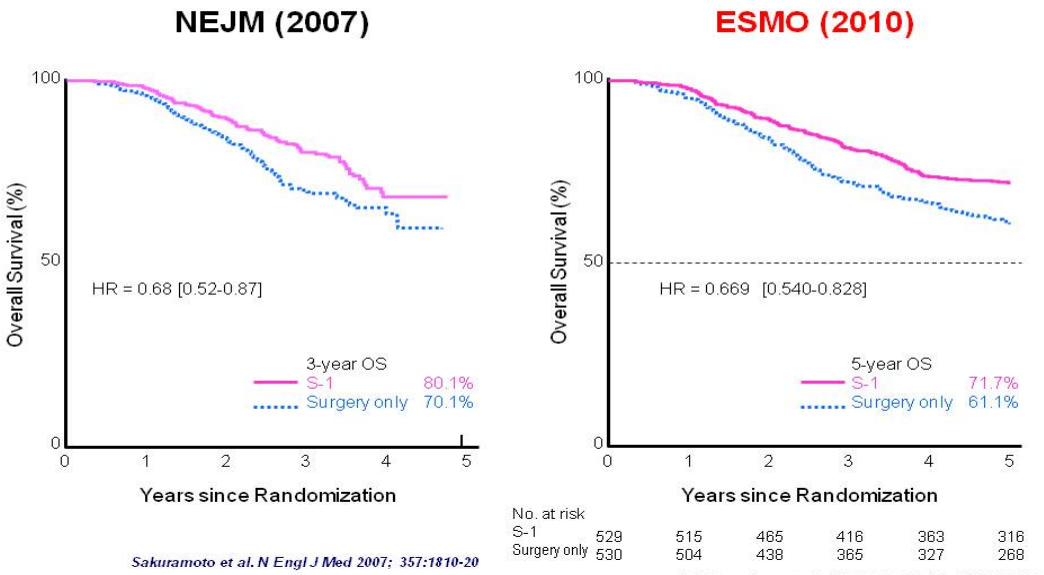
Primary endpoint:
- Overall Survival

Secondary endpoint:
- Relapse-free survival, Safety of S-1

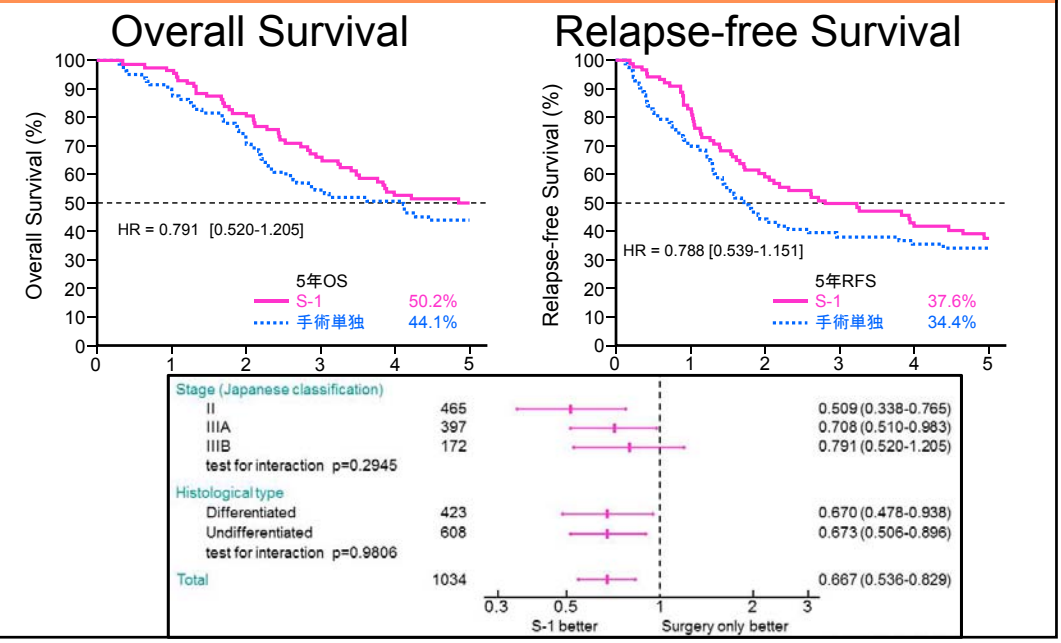
* Japanese Classification of Gastric Carcinoma, 13th ed,1999
** Body surface area (m^2)
< 1.25 m^2: 80mg/day, 1.25 - < 1.5 m^2 100mg/day,
>= 1.5 m^2 120mg/day

M Sasako et al, ESMO 2010 (#709PD)

Overall Survival



Stage IIIB in ACTS-GC trial (適格例)



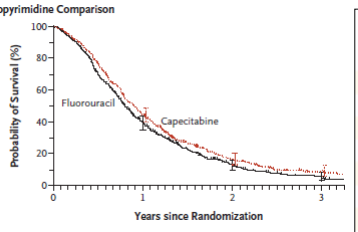
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

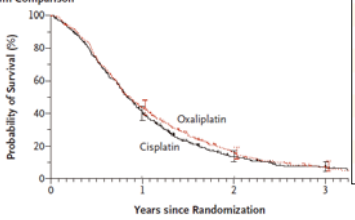
Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer

David Cunningham, M.D., F.R.C.P., Naureen Starling, M.R.C.P.,

A Fluoropyrimidine Comparison



B Platinum Comparison



Variable	ECF (N=263)	ECX (N=250)	EOF (N=245)	EOX (N=244)
Death				
No. of patients	225	213	213	199
Hazard ratio (95% CI)		0.92 (0.76–1.11)	0.96 (0.79–1.15)	0.80 (0.66–0.97)
P value		0.39	0.61	0.02
Overall survival				
Median — mo	9.9	9.9	9.3	11.2
At 1 yr — % (95% CI)	37.7 (31.8–43.6)	40.8 (34.7–46.9)	40.4 (34.2–46.5)	46.8 (40.4–52.9)
Progression-free survival				
Median — mo	6.2	6.7	6.5	7.0
Patients who had progression or died	237	231	221	213
Hazard ratio (95% CI)		0.98 (0.82–1.17)	0.97 (0.81–1.17)	0.85 (0.70–1.02)
P value		0.80	0.77	0.07
Response				
Overall — % (95% CI)†	40.7 (34.5–46.8)	46.4 (40.0–52.8)	42.4 (36.1–48.8)	47.9 (41.5–54.3)
Complete — %	4.1	4.2	2.6	3.9
Partial — %	36.6	42.2	39.8	44.0
P value		0.20	0.69	0.11

CLASSIC study design

Surgically (D2) resected Stage II, IIIA, or IIIB GC, 6 weeks prior to randomization

No prior chemotherapy or radiotherapy

n=1035

RANDOMIZATION

1:1†

n=520

8 cycles of XELOX (6 months)

Capecitabine: 1,000mg/m² bid, d1–14, q3w
Oxaliplatin: 130mg/m², d1, q3w

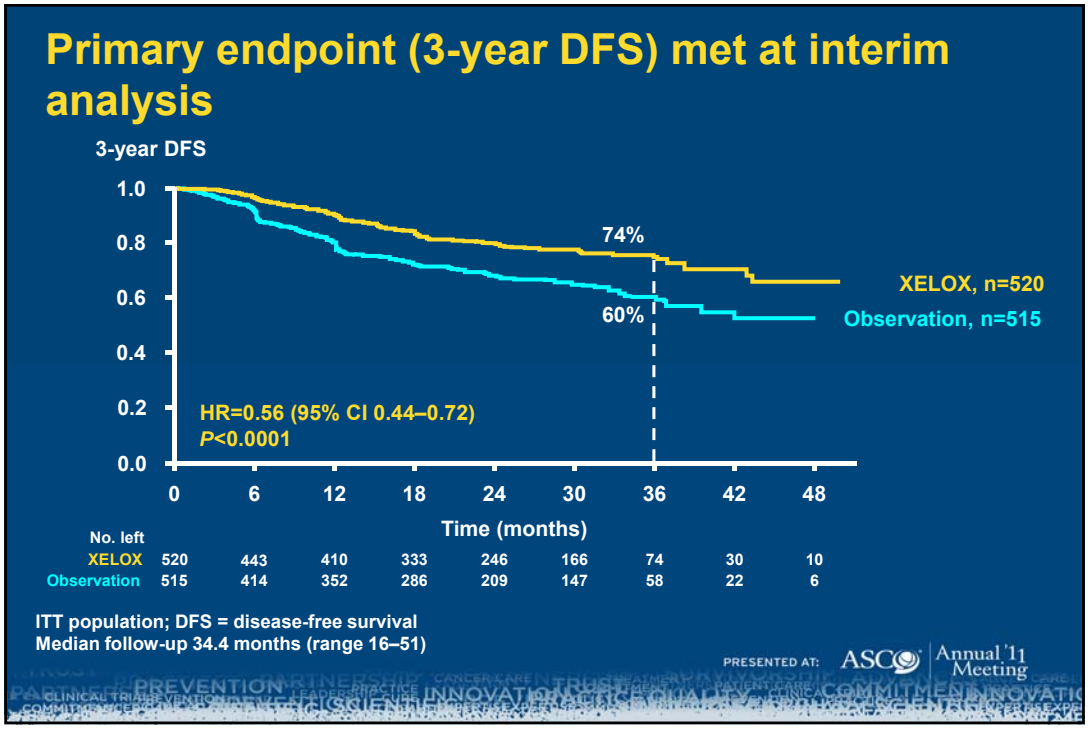
Observation: No adjuvant therapy

n=515

- Primary endpoint: 3-year DFS‡
- Secondary endpoints: overall survival and safety profile

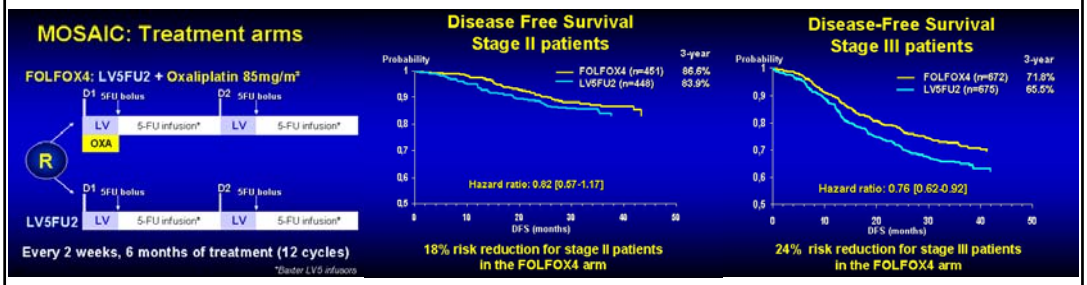
†Stratified by stage and country with age, sex, and nodal status as covariates
‡GASTRIC project: 3-year DFS and 5-year overall survival are strongly associated, Burzykowski et al. ASCO 2009

PRESENTED AT: ASCO Annual '11 Meeting

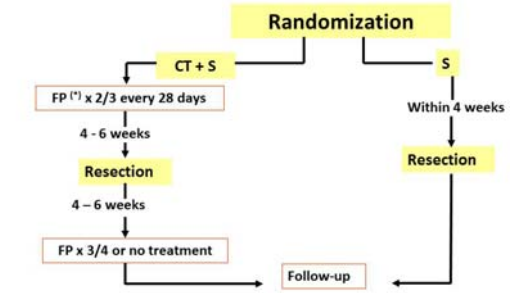


XELOXではS-1に”簡単には”勝てないですよ!!

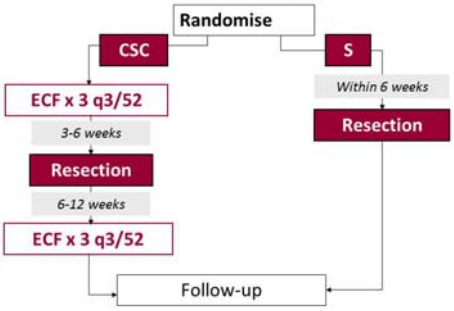
		ACTS-GC	Classic	“HR”
n		1059	1035	
観察期間		24M	34M	
DFS	All	0.62	0.58	“0.94”
	Stage II	0.55	0.55	“1.0”
	Stage IIIa	0.64	0.56	“0.88”
	Stage IIIb	0.69	0.57	“0.83”



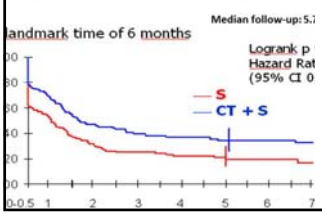
Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of the stomach and lower esophagus (ASLE): FNLCC ACCORD 07-FFCD 9703 trial



Perioperative chemotherapy in operable gastric and lower oesophageal cancer: a randomised controlled trial (the MAGIC trial, ISRCTN 93793971)

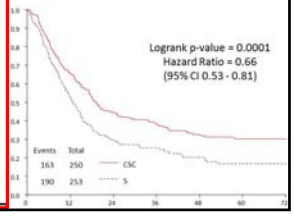


Disease Free Survival



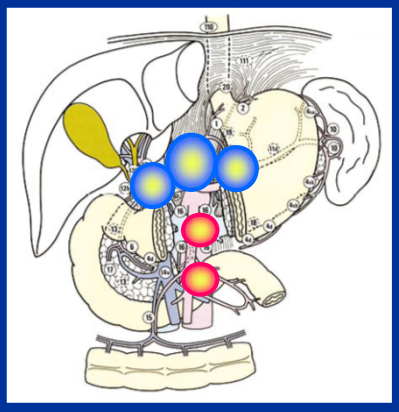
Author	Boige	Cunningham
Phase	III	III
Subjects (Stage)	Stage ≥ 2	Stage ≥ 2
Chemotherapy	FP 2-3 + 3-4	ECF 3 + 3
R0 resection rate	87 > 74	77 > 69
Completion of Post Cx(%)	37	42
3-year survival rate	- 50 > 30	40-50 > 20-30

ion-free survival*



A phase II study of preoperative chemotherapy with S-1 (S) and cisplatin (P) followed by D3 gastrectomy for gastric cancer with extensive lymph node metastasis (ELM): *-Survival results of JCOG0405*

T. Yoshikawa, K. Nakamura, A. Tsuburaya, T. Sano, J. Mizusawa, H. Katai, A. Kurita, I. Uyama, E. Nomura, M. Sasako, T



Definition of extensive lymph node metastases

Bulky N2 :
≥3cm or ≥1.5cm x ≧2

#16 :
≥1cm paraaortic

JCOG 0001

Radiological tumor response by RECIST ver 1.0 *Central review

Response	CR	PR	SD	PD	NE
N	0	33	14	4	0
% (/ 51)	0%	64.7%	27.5%	7.8%	0%

Response rate was 64.7% (95%CI; 50.1-77.6%).

Pathological response in the lymph node

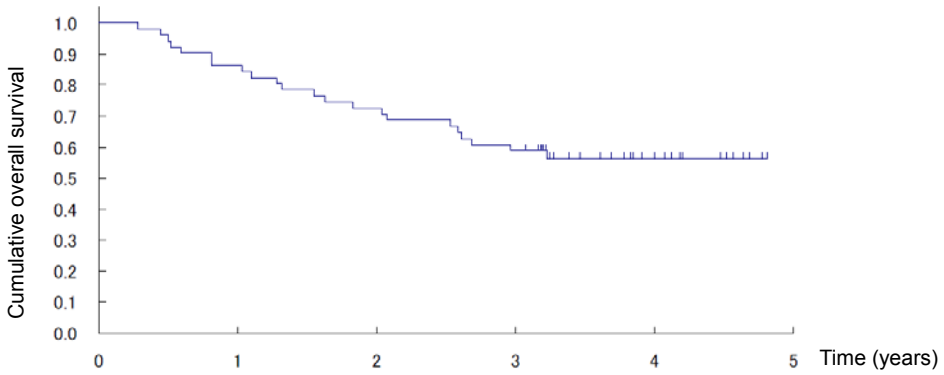
Grade*	0	1a	1b	2	3
Degeneration area	None	1/3>	1/3-2/3	>2/3	100%
n	4	17	7	11	8
% (/ 51**)	7.8%	33.3%	13.7%	21.6%	15.7%

* Grading due to the proportion of degeneration area in the primary tumor by the Japanese Classification of Gastric Carcinoma

** All eligible. Data is missing in 4 patients (3 no surgery, 1 data not available)

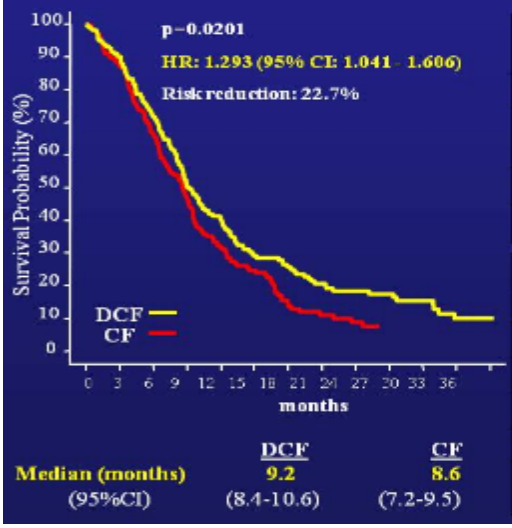
Pathological response rate of the lymph node was 51.0% (95%CI; 36.6-65.3%).

Overall survival (n=51, all eligible)



Median overall survival time; not reached
3-year overall survival ; 58.8% (95% CI, 44.1-70.9%)

DCF is Both Effective and Toxic

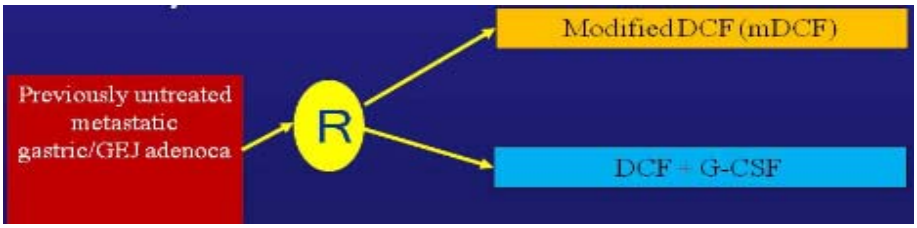


	DCF	CF
Median (months)	9.2	8.6
(95%CI)	(8.4-10.6)	(7.2-9.5)

G3-4 Attributable Toxicity

	DCF N=221	CF N=224
Neutropenia	82%	57%
Febrile neutropenia / neutropenic infection	29%	14%
Thrombocytopenia	8%	13%
Anemia	18%	26%
Nausea/Vomiting	14%	17%
Mucositis	21%	27%
Diarrhea	19%	8%
Anorexia	10%	9%
Lethargy	19%	14%
Infection	13%	7%
Deaths within 30 days	10%	8.5%

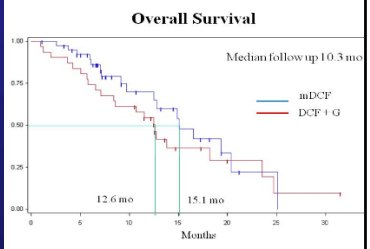
Modified DCF with bi-weekly 5-FU/LV, CDDP and DTX



MODIFIED DCF q 2 week		PARENT DCF + GCSF q 3 week	
Drug	Dose (mg/m2)	Drug	Dose (mg/m2)
Docetaxel	40	Docetaxel	75
Cisplatin	40	Cisplatin	75
Leucovorin	400	Leucovorin	-
Fluorouracil	400 IVP		
Fluorouracil	1000 IVCI/d x 2d	Fluorouracil	750 IVCI/d x 5d
GCSF	-	GCSF	Used after every cycle

mDCF is more active and feasible than original DCF

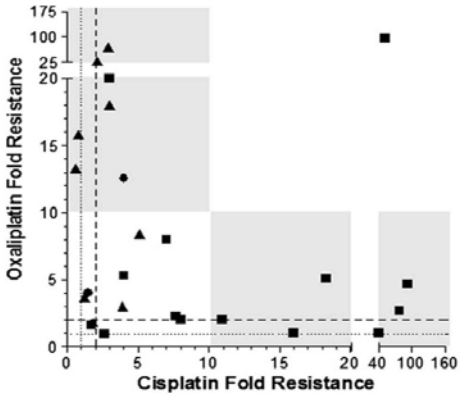
	Arm A mDCF (n=42)	Arm B DCF+GCSF (n=31)
Response Rate	52% (32-71%)	32% (16-49%)
6-month PFS(95% CI)	63% (45-76%)	48% (30-64%)
Time to Treatment Failure	8.6 mo (5.6 - 11.6 mo)	5.9 mo (3.7 – 8.6 mo)
Overall Survival (range)	15.1 mo (9.7 - 20.4 mo)	12.6 mo (7.1 - 18.2 mo)



	mDCF (n=51)			DCF + G (n=31)		
	Gr 3	Gr 4	Gr 3-4 (%)	Gr 3	Gr 4	Gr 3-4 (%)
Neutropenia	16	12	54%	11	12	74%
(Febrile Neutropenia)	(2	3	9%)	(2	3	16%)
Thrombocytopenia	1	1	4%	1	0	3%
Anemia	6	1	13%	20	0	65%

CDDPとL-OHP　同じではない

基礎実験での交差耐性

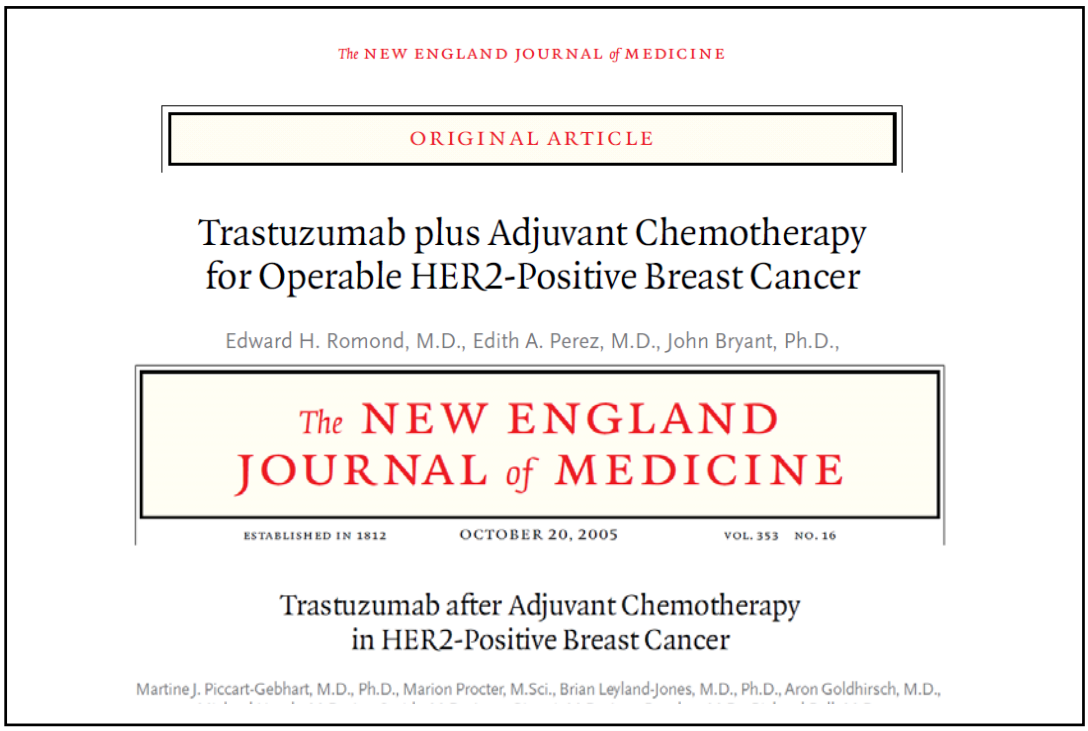


CDDP投与後のL-OHP

	Kim (2003)	Seo (2009)	Kim (2010)
L-OHP 5FU LV	q2w 85 400+2400/48h 150/48h	q2w 100 2400/48h 100/2h	q2w(FOLFOX4) 85 800+1200/48h 200/2h
N	26 Phase II	62 Retro	42 Phase II
Pre-treatment Platinum 5FU	 100% 100%	 68% 84%	 60% 91%
RR DCR	26%* (26%*) 35%	23% (25%*) 58%	21% (29%*) 55%
PFS (M) OS (M)	4.3 7.3	3.0 8.0	3.0 6.2

*CDDP耐性後に限ったRR

CDDPとOHPは、臨床的には『交差耐性はない』と考えていい
↓
効果のある症例に違いがある?



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ORIGINAL ARTICLE

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Martine J. Piccart-Gebhart, M.D., Ph.D., Marion Procter, M.Sci., Brian Leyland-Jones, M.D., Ph.D., Aron Goldhirsch, M.D.,