Chugai Investigators'Meeting on
Breast Cancer in Chicago 2012

ASCO 1998－2012
から学ぶ抗HER2療法の進歩

浜松オンコロジーセンター
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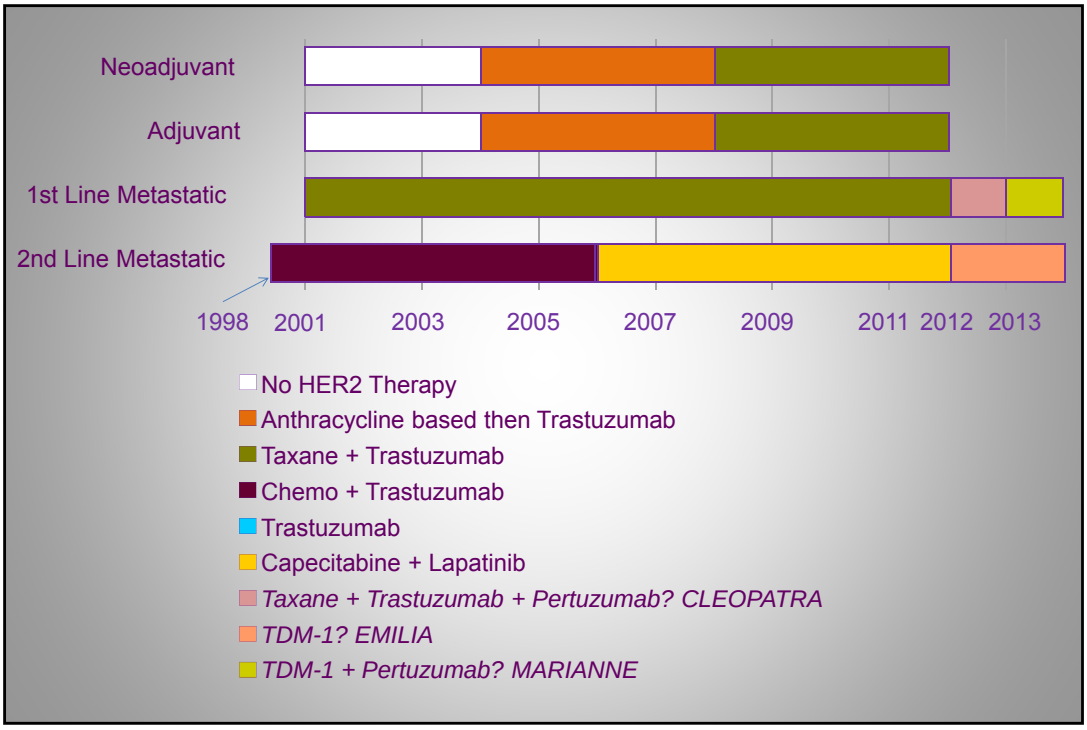
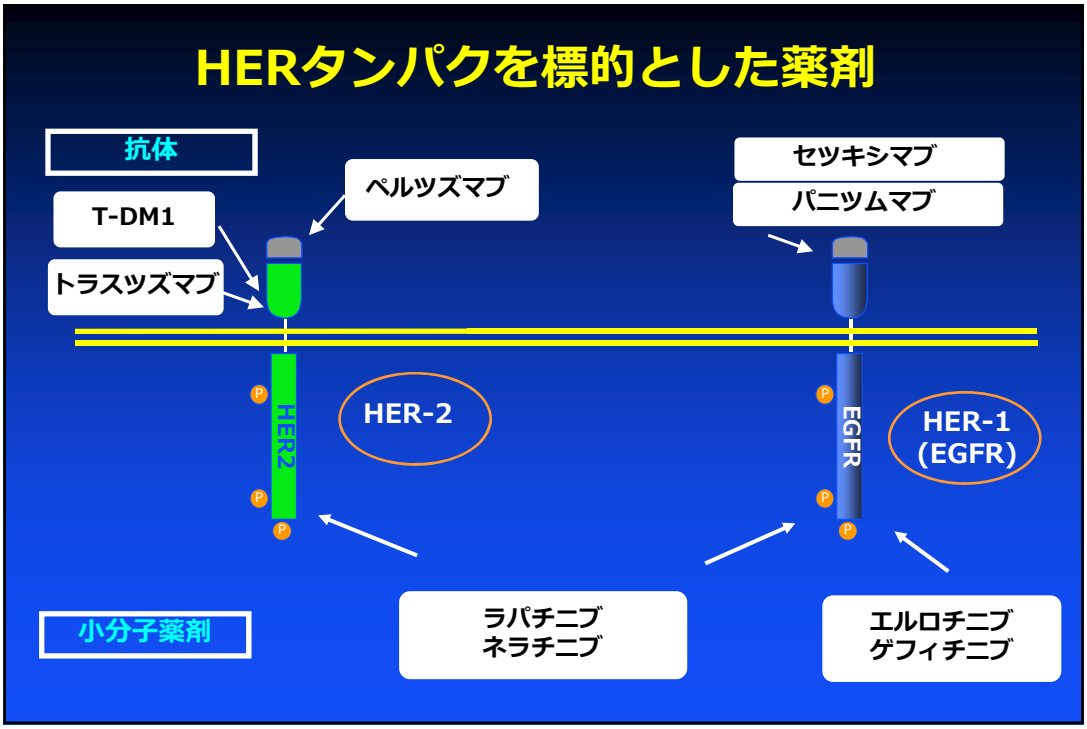
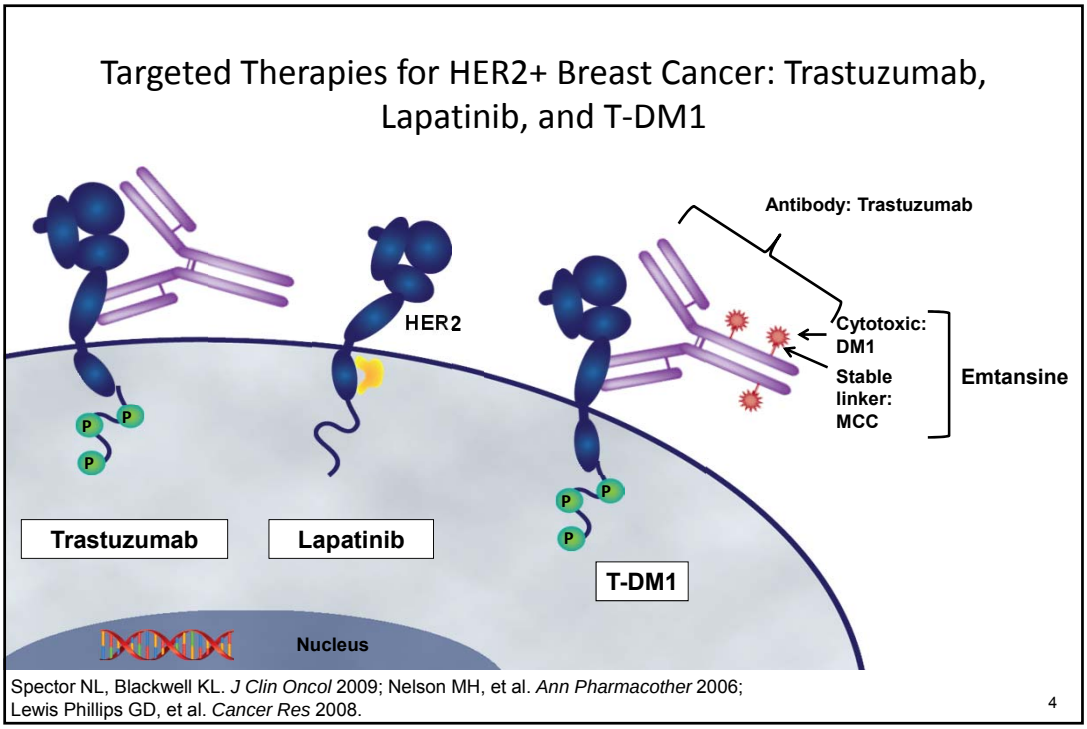
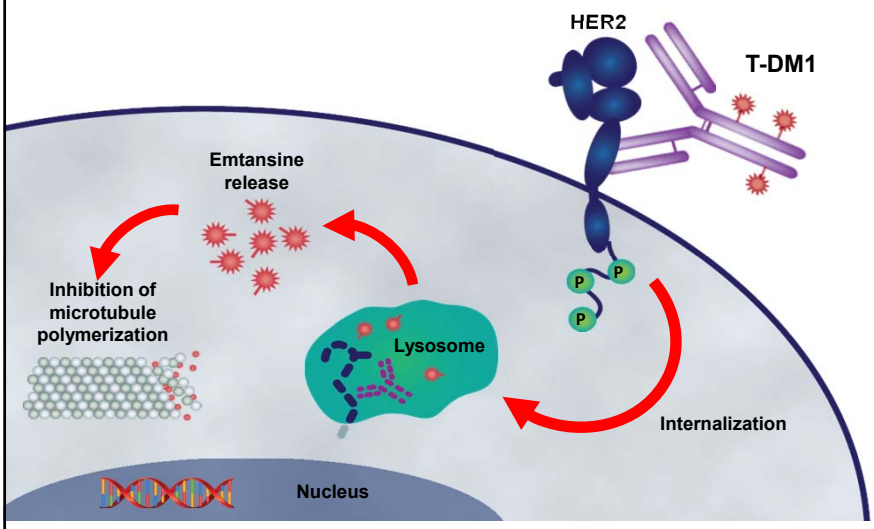
twatanab@oncoloplan.com




HERタンパクを標的とした薬剤
抗体
T-DM1
トラスツズマブ
ペルツズマブ
セツキシマブ
パニツムマブ
HER2
HER-2
EGFR
HER-1
(EGFR)
小分子薬剤
ラパチニブ
ネラチニブ
エルロチニブ
ゲフィチニブ


Targeted Therapies for HER2+ Breast Cancer: Trastuzumab, Lapatinib, and T-DM1
Antibody: Trastuzumab
HER2
Cytotoxic: DM1
Stable linker: MCC
Emtansine
Trastuzumab
Lapatinib
T-DM1
Nucleus
Spector NL, Blackwell KL. J Clin Oncol 2009; Nelson MH, et al. Ann Pharmacother 2006; Lewis Phillips GD, et al. Cancer Res 2008.
4

T-DM1: Mechanism of Action



Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

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ASCO歴史展望　抗HER2療法の巻

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Efficacy and Safety of Herceptin as a Single Agent in HER2-overexpressing Metastatic Breast Cancer

ASCO 1998 Abstract #376

M. Cobleigh, C.L. Vogel, D. Tripathy, N.J. Robert, S. Scholl, L. Fehrenbacher, V. Paton, S. Shak, G. Lieberman, D. Slamon

for Genentech, Inc and Herceptin Multinational Clinical Investigators

Phase II study of Herceptin as a Single Agent

Objectives

- **Primary**
  - Overall response rateby REC (Response Evaluation Committee)
  - Safety
- **Secondary**
  - Duration of response
  - Time to disease progression
  - Survival
  - Quality of Life

Phase II study of Herceptin as a Single Agent

Design

- Single arm, open-label
- Multicenter (54 centers), multinational
- 222 women enrolled
- Treatment
  - 4 mg/kg IV loading dose
  - 2 mg/kg weekly maintenance dose

Objective Response

Population	n	CR		PR		ORR %	95% CI
		n	%	n	%		
Response Evaluation Committee assessment							
All enrolled, intent-to-treat	222	8	4	26	12	15	11-21
All treated	213	8	4	26	12	16	11-22
Investigators' assessment							
All enrolled, intent-to-treat	222	9	4	37	17	21	16-27
All treated	213	9	4	37	17	22	16-28

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Addition of Herceptin to First Line Chemotherapy for HER2 Overexpressing Metastatic Breast Cancer Increases Clinical Benefit: A Randomized, Controlled Multinational Phase III

ASCO 1998 Abstract #377

D. Slamon, B. Leyland-Jones, S. Shak,
V. Paton, A. Bajamonde, T. Fleming,
W. Eiemann, J. Wolter, J. Baselga, L. Norton
for Genentech, Inc and Herceptin Multinational Clinical Investigators

Trastuzumab Combination with Chemotherapy

L. Norton, ASCO 1999 Abstract #483

適格例 (n =469)

- 転移性乳癌
- HER2過剰発現
- 再発後化学療法未施行
- 計測可能病変
- PS 60%以上

No adjuvant anthracyclines

Adjuvant anthracyclines

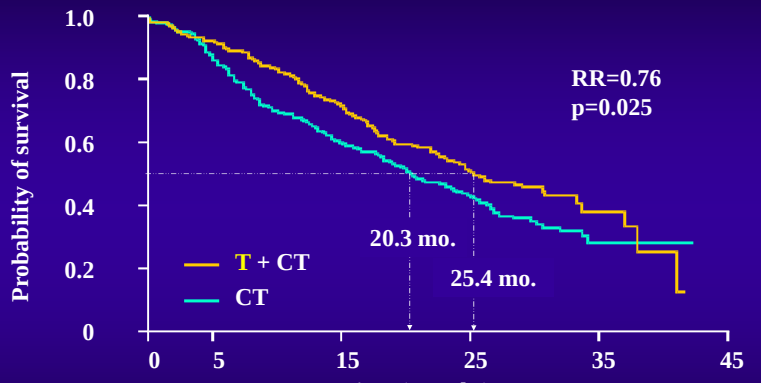
Trastuzumab + AC (n = 143)

AC (n = 138)

Trastuzumab + Taxol (n = 92)

Taxol (n = 96)

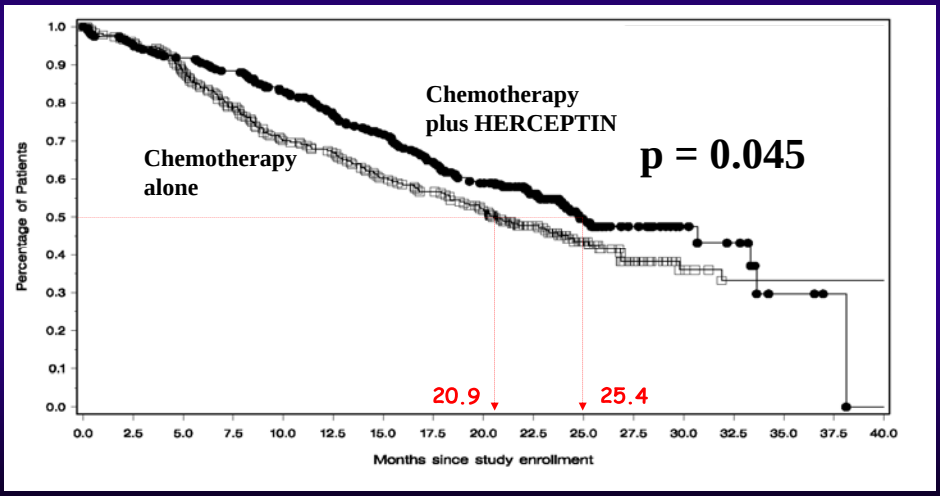
Overall survival



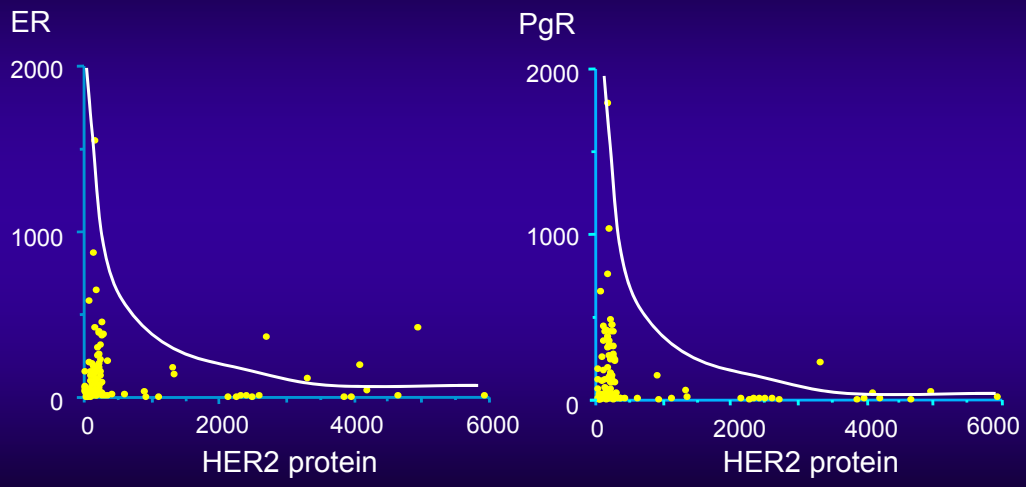
CT patients treated with Trastuzumab after disease progression 24% 62% 65%

Herceptin® Combination with Chemotherapy

Survival



Relationship between Hormone Receptors and HER2 Protein Content in Breast Cancer Tissues



Toru Watanabe, et al. 1993

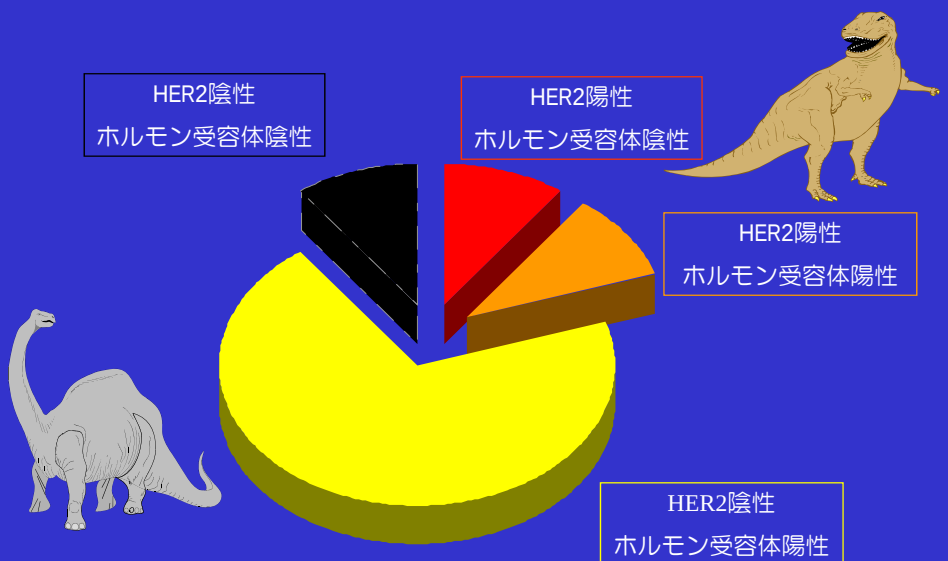
Identification of two breast cancer subtypes

type	A	B
nuclear grade	low	high
mitosis	few	many
necrosis	low	high
lymphoid infiltration	few	many
p53	negative	positive
HER2	negative	positive
ER	positive	negative
PgR	positive	negative
bcl 2	positive	negative

Identification of four breast cancer subtypes based on hormone receptors and HER2

ER and/or PgR	HER 2 -	HER 2 +
+	A	AB
-	O	B

個別化治療のための乳がんの分類



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Efficacy and Safety of Trastuzumab as a Single Agent in First-Line Treatment of HER2-Overexpressing Metastatic Breast Cancer

	Objective Response		Clinical Benefit*	
Subset	n	%	n	%
All patients, n = 111 (95% CI)	29	26 (18.0-34.3)	42	38

Herceptin® and Paclitaxel Every Three Weeks for Metastatic Breast Cancer

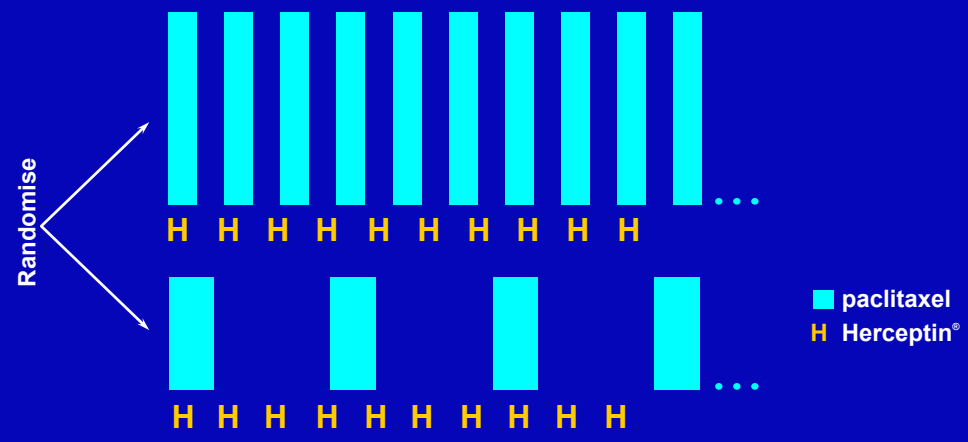
Pharmacokinetics
Safety
Tolerability

Gelmon K, et al. ASCO 2001, page 69a, Abstract 271

mayo 23

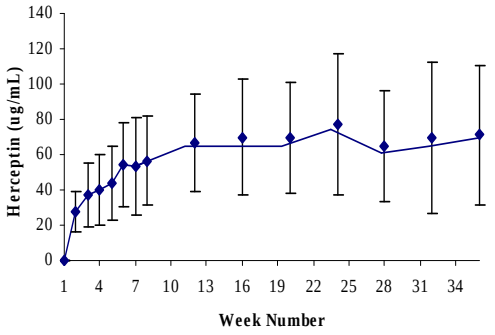
Modification of CALGB 9840 – dose-dense versus standard paclitaxel

HER2-positive patients

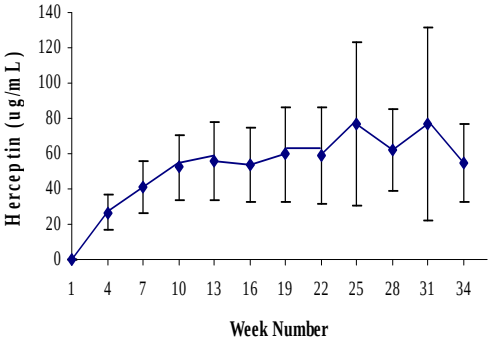


Trough Levels - Weekly vs q3w

Weekly Administration



Q-3 Weekly Administration



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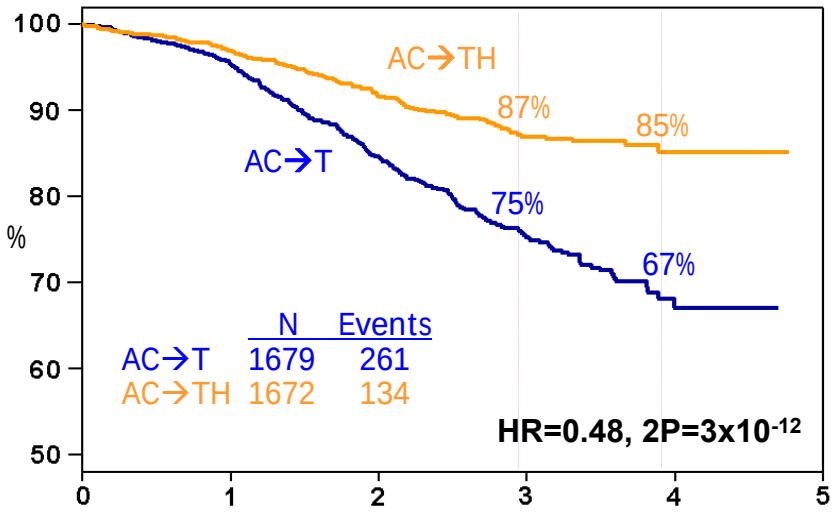
Doxorubicin and Cyclophosphamide
Followed by Paclitaxel
with or without Trastuzumab
as Adjuvant Therapy for Patients with
HER-2 Positive Operable Breast Cancer

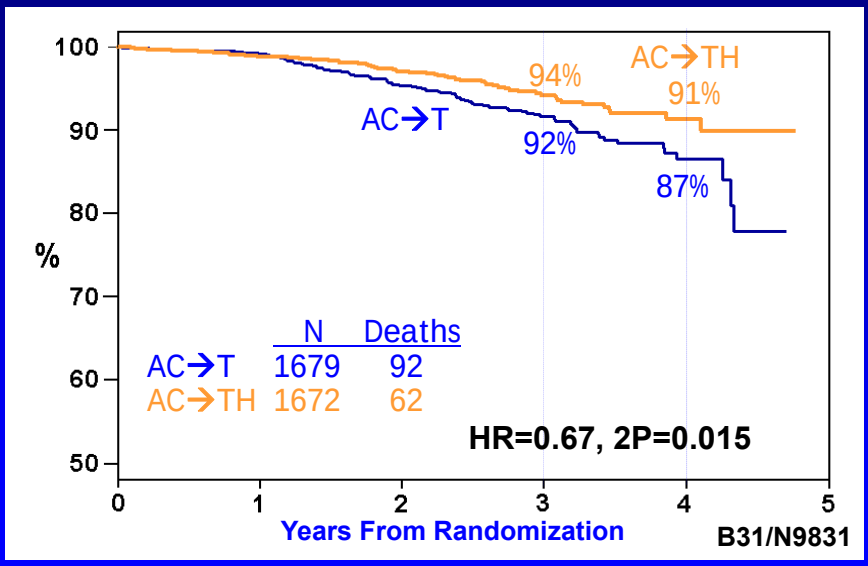
Combined Analysis of
NSABP-B31/NCCTG-N9831

Romand EH et al.

Disease-Free Survival



B-31/N9831 Survival



ASCO, Scientific Session, May 16, 2005

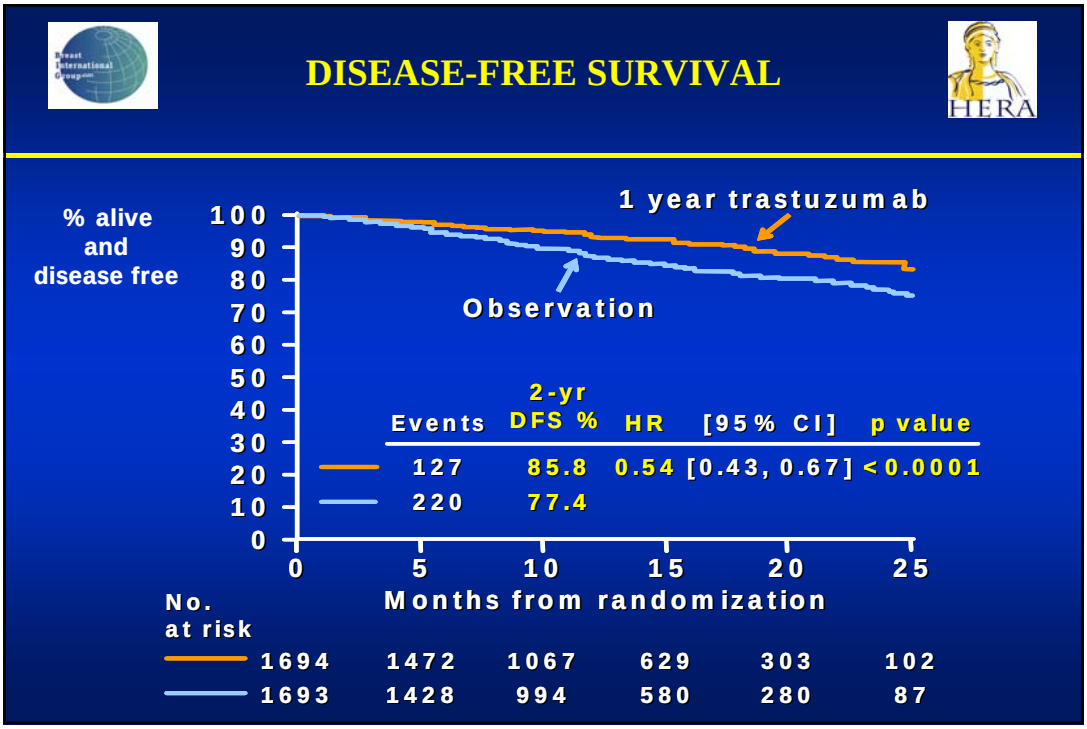
FIRST RESULTS OF THE HERA TRIAL

A randomized three-arm multi-centre comparison of:

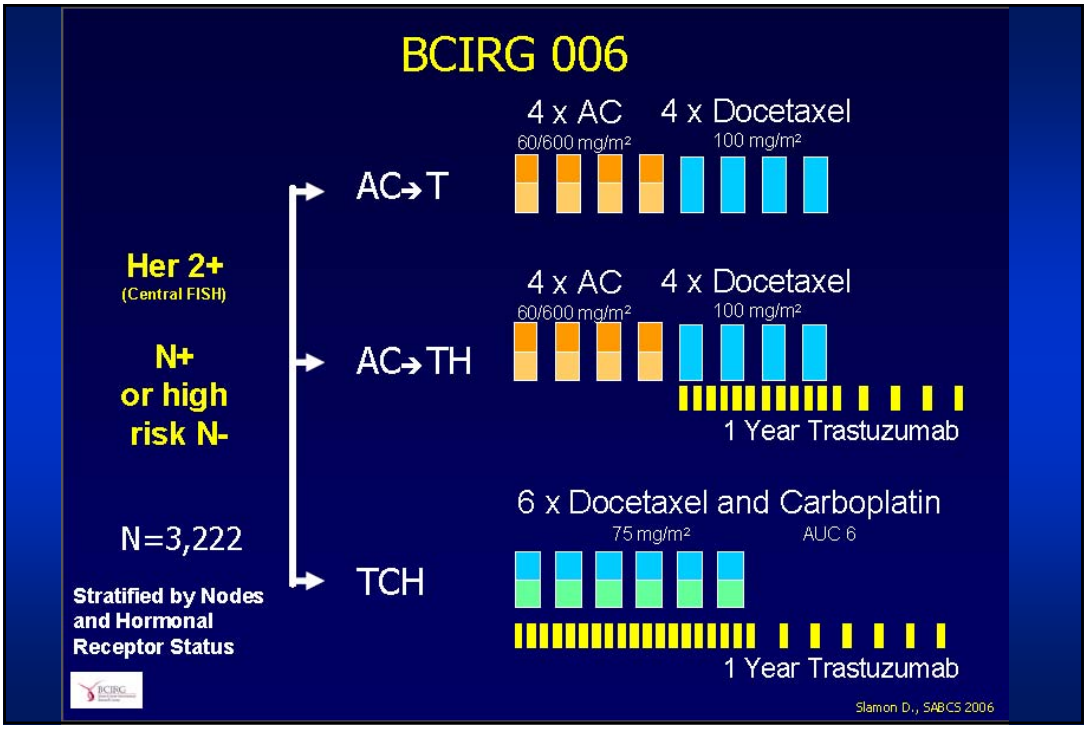
- 1 year Herceptin®
- 2 years Herceptin®
- or no Herceptin®

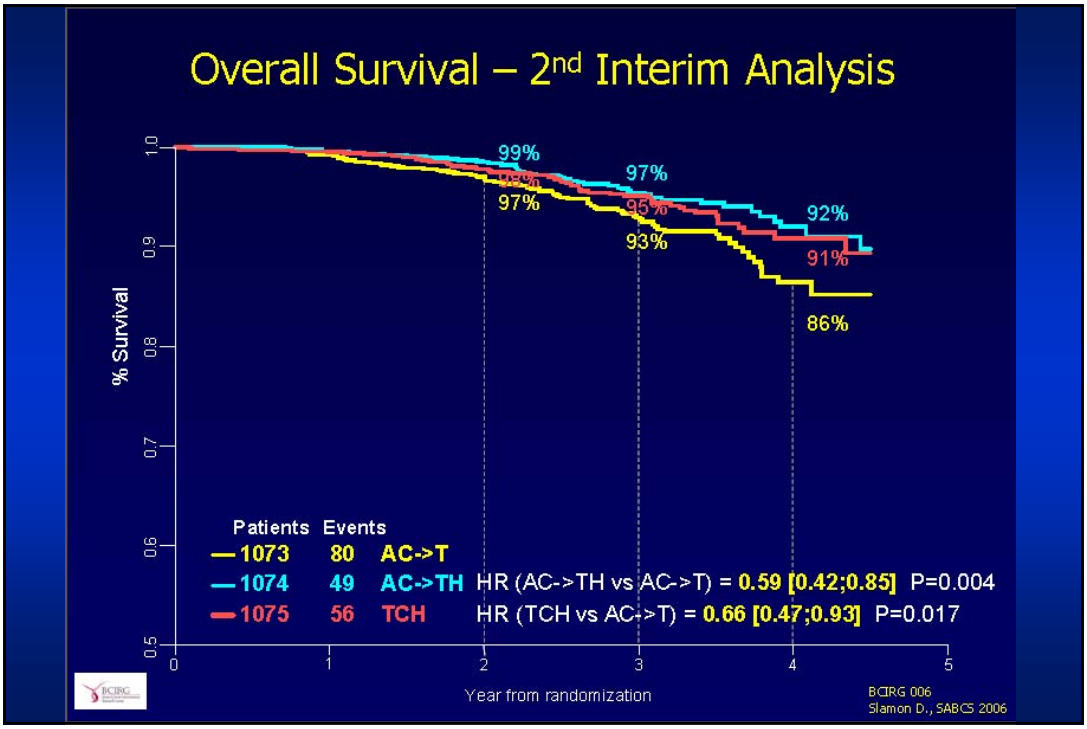
in women with HER-2 positive primary breast cancer who have completed adjuvant chemotherapy

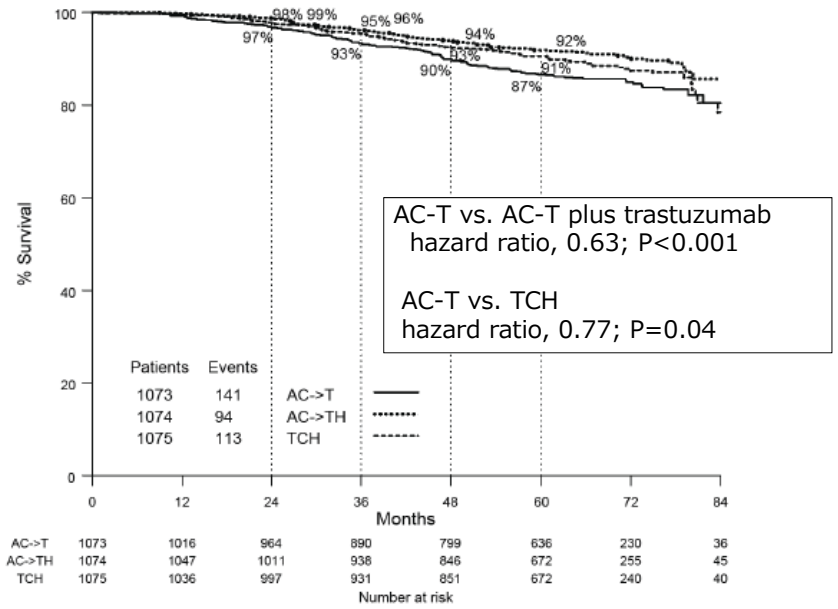
Martine J. Piccart-Gebhart, MD, PhD on behalf of:
The Breast International Group (BIG), NON-BIG participating groups, Independent sites, F. Hoffmann – La Roche Ltd.


DISEASE-FREE SURVIVAL
HERA
% alive and disease free
100
90
80
70
60
50
40
30
20
10
0
1 year trastuzumab
Observation
Events
2-yr DFS %
HR
[95% CI]
p value
127
85.8
0.54
[0.43, 0.67]
< 0.0001
220
77.4
0
5
10
15
20
25
Months from randomization
No. at risk
1694 1472 1067 629 303 102
1693 1428 994 580 280 87


BCIRG
Breast Cancer International Research Group
Phase III Trial Comparing
AC-T with AC-TH and with TCH
in the Adjuvant Treatment of
HER2 positive Early Breast Cancer Patients:
Second Interim Efficacy Analysis
Slamon D, Eiermann W, Robert N, Pienkowski T,
Martin M, Pawlicki M, Chan A, Smylie M, Liu M,
Falkson C, Pinter T, Fornander T, Shiftan T, Valero V,
Von Minckwitz G, Mackey J, Tabah-Fisch I, Buyse M,
Lindsay MA, Riva A, Bee V, Pegram M, Press M,
Crown J, on behalf of the BCIRG 006 Investigators.
Study sponsored by Sanofi-Aventis
Support from Genentech


BCIRG 006
4 x AC
60/600 mg/m²
4 x Docetaxel
100 mg/m²
AC→T
Her 2+
(Central FISH)
N+
or high
risk N-
4 x AC
60/600 mg/m²
4 x Docetaxel
100 mg/m²
AC→TH
1 Year Trastuzumab
6 x Docetaxel and Carboplatin
75 mg/m²
AUC 6
N=3,222
TCH
Stratified by Nodes
and Hormonal
Receptor Status
1 Year Trastuzumab
Slamon D., SABCS 2006


Overall Survival – 2nd Interim Analysis
% Survival
1.0
0.9
0.8
0.7
0.6
0.5
99%
97%
97%
95%
93%
92%
91%
86%
Patients Events
1073 80 AC->T
1074 49 AC->TH HR (AC->TH vs AC->T) = 0.59 [0.42;0.85] P=0.004
1075 56 TCH HR (TCH vs AC->T) = 0.66 [0.47;0.93] P=0.017
0
1
2
3
4
5
Year from randomization
BCIRG 006
Slamon D., SABCS 2006



Slamon D, et al *N Engl J Med* **365:** 1273-1283, 2011.

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A Phase III Randomized, Open-Label, International Study Comparing Lapatinib and Capecitabine vs. Capecitabine in Women with Refractory Advanced or Metastatic Breast Cancer (EGF100151)

C.E. Geyer, D. Cameron, D. Lindquist, S. Chan, T. Pienkowski, C.G. Romieu, A. Jagiello-Gruszfeld, J. Crown, B. Kaufman, A. Chan, J.K. Forster

Allegheny General Hospital, Pittsburgh, PA; Western General Hospital, Edinburgh, UK; US Oncolgy Research Network, Houston,TX; Nottingham City Hospital, Nottingham, UK; Cancer Center, Warsaw, Poland; CRCC Val d'Aurelle Paul Lamarque, Montpellier, France; ZOZ MSWiA, Olsztyn, Poland; St. Vincent's University Hospital, Dublin, Ireland; Sheba Medical Center, Tel Hashomer, Israel; Mount Medical Centre, Perth, Australia; GlaxoSmithKline, Greenford, UK

Study Design

- Progressive, HER2+ MBC or LABC
- Previously treated with anthracycline, taxane and trastuzumab*
- No prior capecitabine

Stratification:
- Disease sites
- Stage of disease

RANDOMIZE

N=528

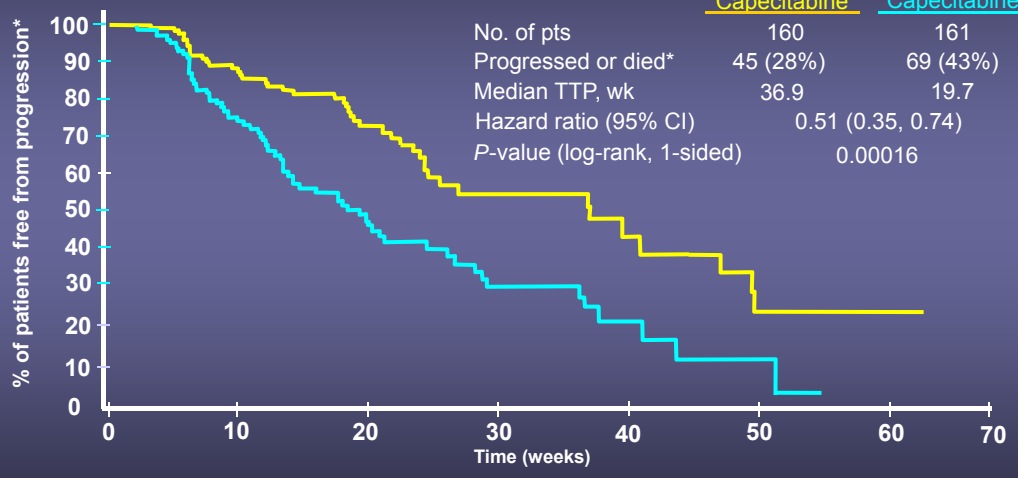
→ Lapatinib 1250 mg po qd continuously + Capecitabine 2000 mg/m^2/d po days 1-14 q 3 wk

→ Capecitabine 2500 mg/m^2/d po days 1-14 q 3 wk

Patients on treatment until progression or unacceptable toxicity, then followed for survival

*Trastuzumab must have been administered for metastatic disease

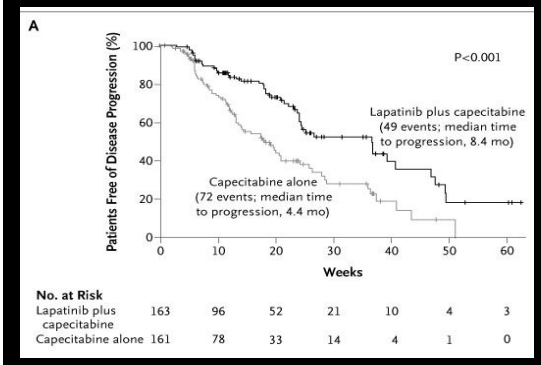
Time to Progession – ITT Population



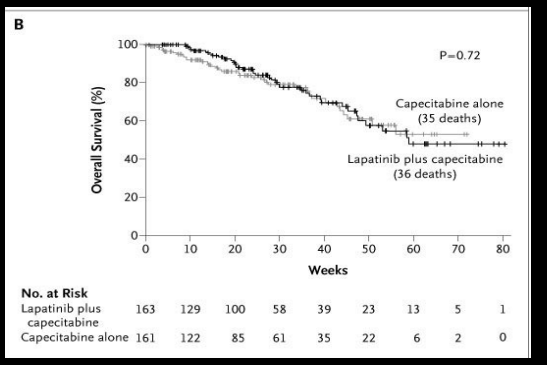
	Lapatinib + Capecitabine	Capecitabine
No. of pts	160	161
Progressed or died*	45 (28%)	69 (43%)
Median TTP, wk	36.9	19.7
Hazard ratio (95% CI)	0.51 (0.35, 0.74)	
P-value (log-rank, 1-sided)	0.00016	

*** Censors 4 patients who died due to causes other than breast cancer**

Disease Progression free Survival



Overall Survival



Geyer CE et al. N Engl J Med 2006;355:2733-2743

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Randomized Controlled Trial Comparing Taxane-Based Chemotherapy with Lapatinib or Trastuzumab as First-Line Therapy for Women with HER2+ Metastatic Breast Cancer:

Interim Analysis of NCIC CTG MA.31/ GSK EGF 108919

K Gelmon, F Boyle, B Kaufman, D Huntsman, A Manikhas, A Di Leo, M Martin, L Schwartzberg, S Dent, S Ellard, K Tonkin, Y Nagarwala, K Pritchard, T Whelan, D Nomikos, JA Chapman, W Parulekar

ClinicalTrials.gov: NCT00667251

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

gsk

Study Objectives

- Primary
  - To compare the Progression Free Survival (PFS) of taxane therapy plus lapatinib to taxane therapy plus trastuzumab
- Secondary:
  - Overall survival
  - Adverse events
  - Incidence of CNS metastases (first progression) and time to CNS metastases
  - Objective response rate (ORR), Clinical Benefit response rate(CB), time to response and duration of response
  - QOL
  - Correlative studies

NCIC CTG
NCIC GEC

Statistical Design - 1

- Primary endpoint is PFS:
  - Time from randomization to progression by RECIST 1.0 or death from any cause
  - Primary analysis is by ITT
  - Secondary analysis is centrally-confirmed HER2+
  - Sensitivity analyses to account for asymmetric follow-up
  - If non-inferiority demonstrated: test for superiority

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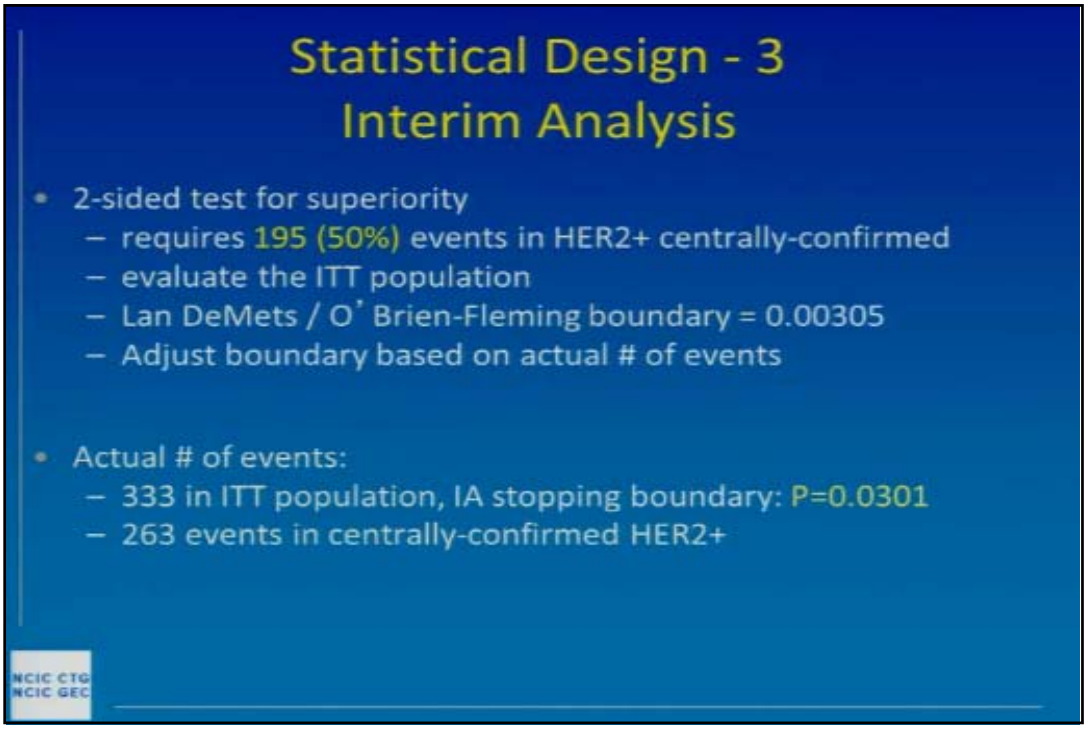
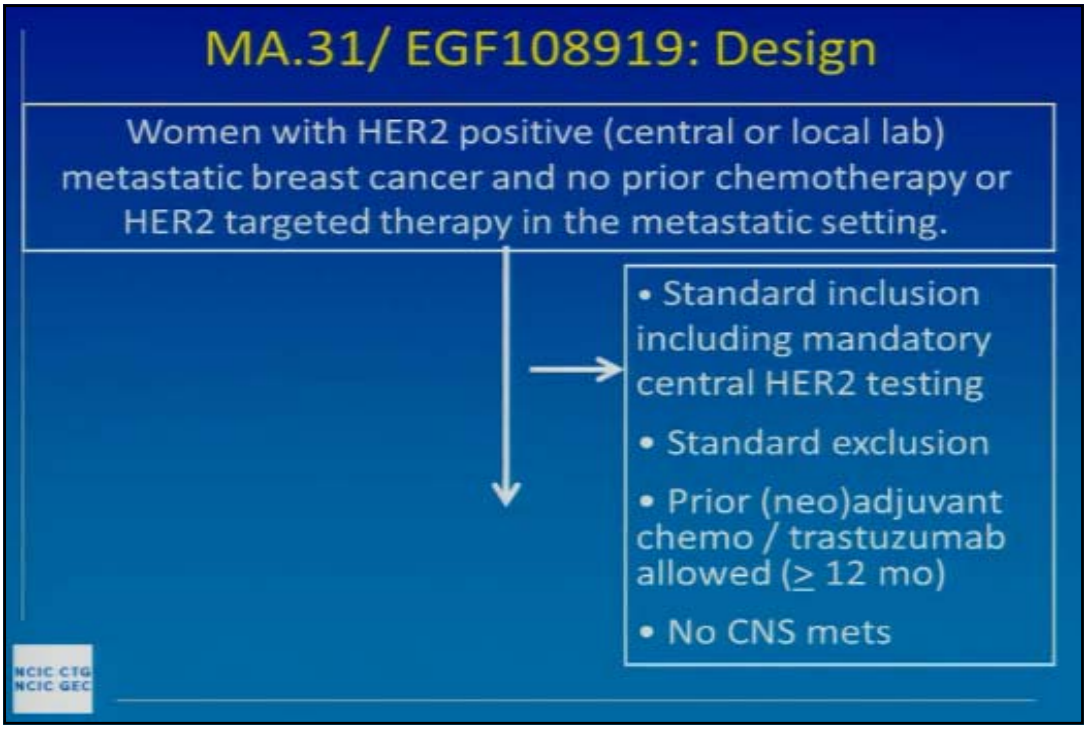
NCIC GEC

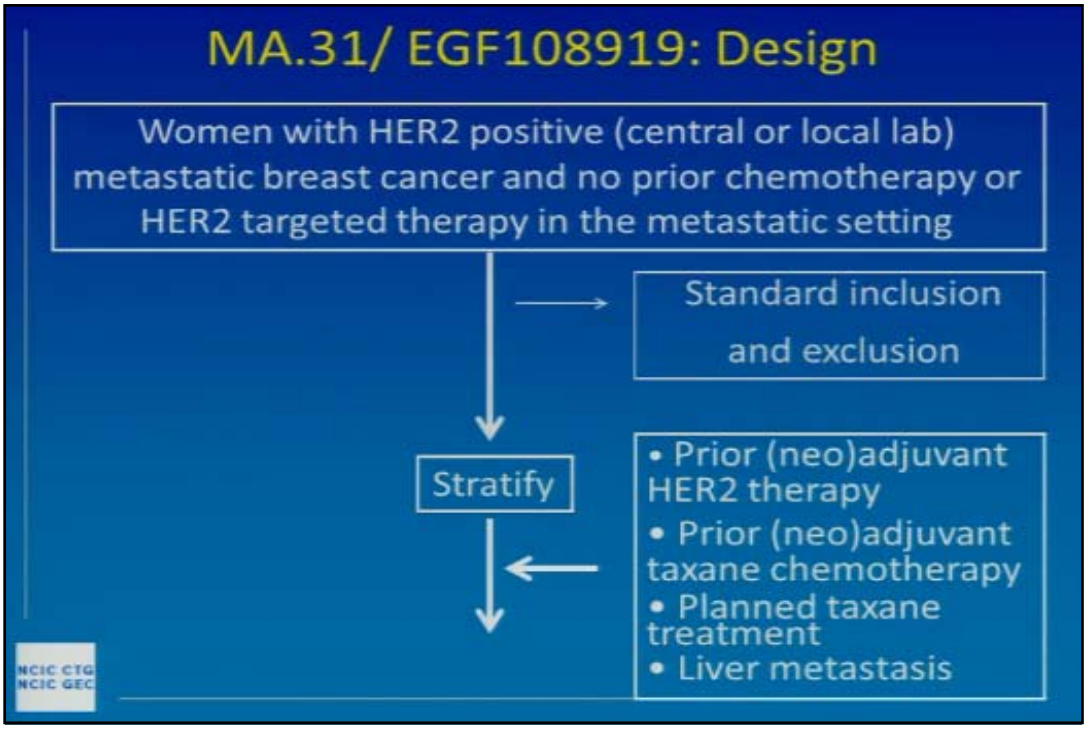
Statistical Design - 2

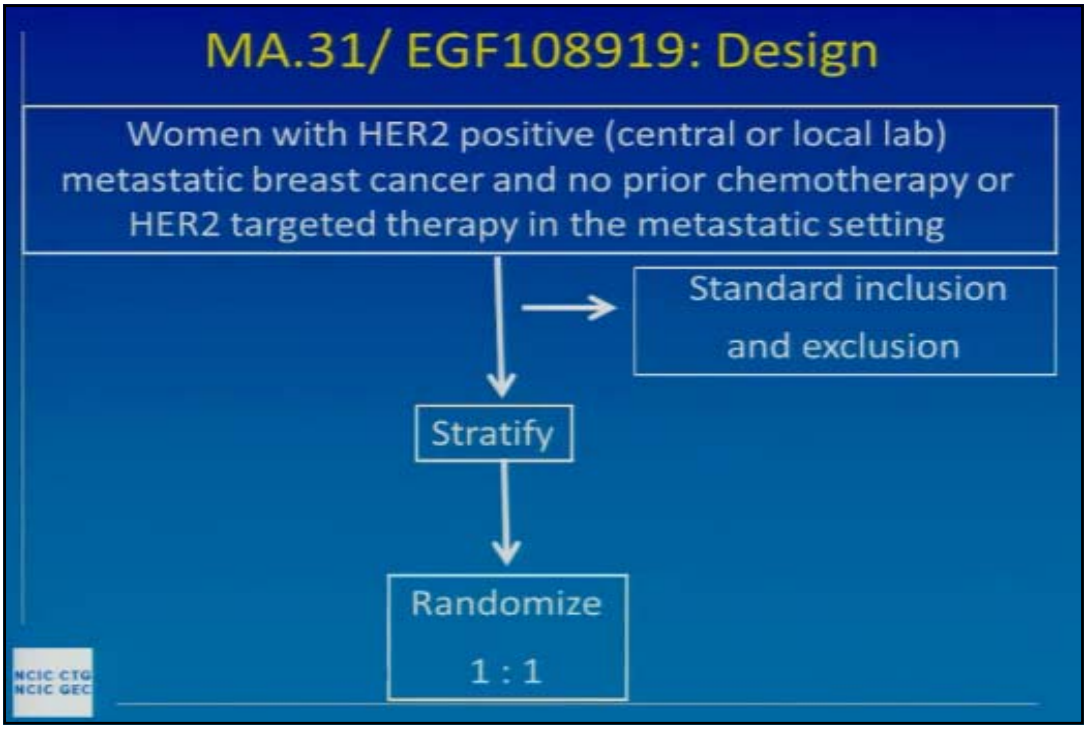
- Non-inferiority margin: HR<1.25 for LTAX/L vs TTAX/T
- 1 sided alpha = 2.5%; beta = 90%
- 390 events required
- Accrue over 2 years
- Follow-up 1 year
- NCIC CTG holds, manages and analyzes the database

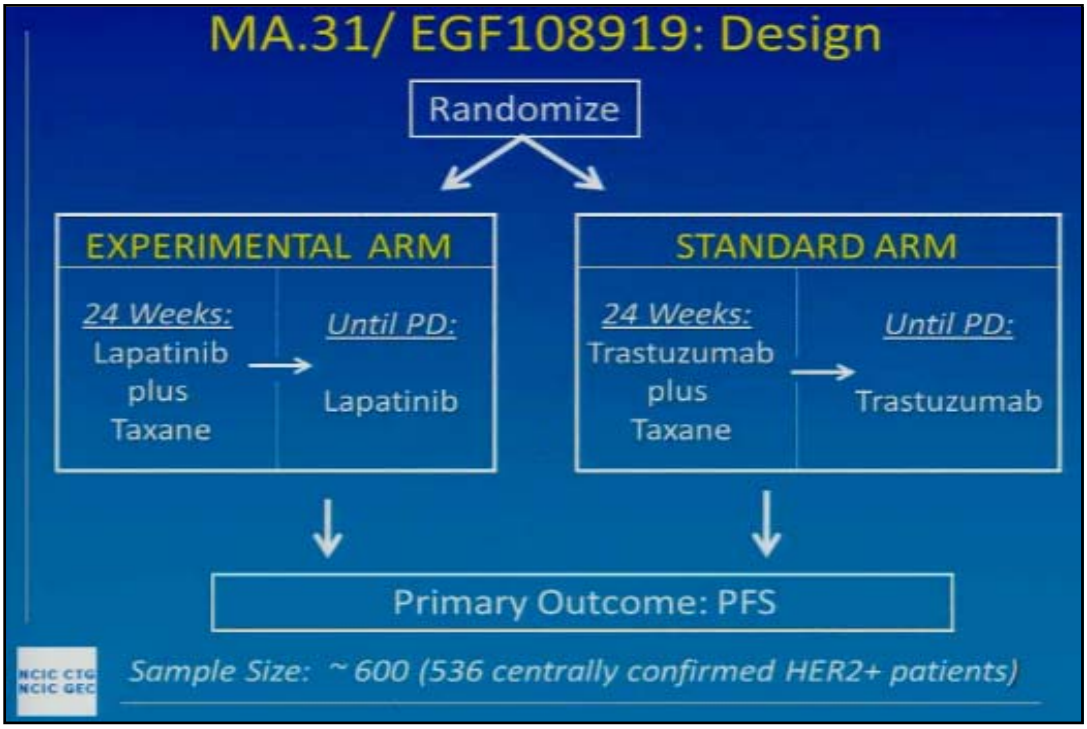
NCIC CTG
NCIC GEC

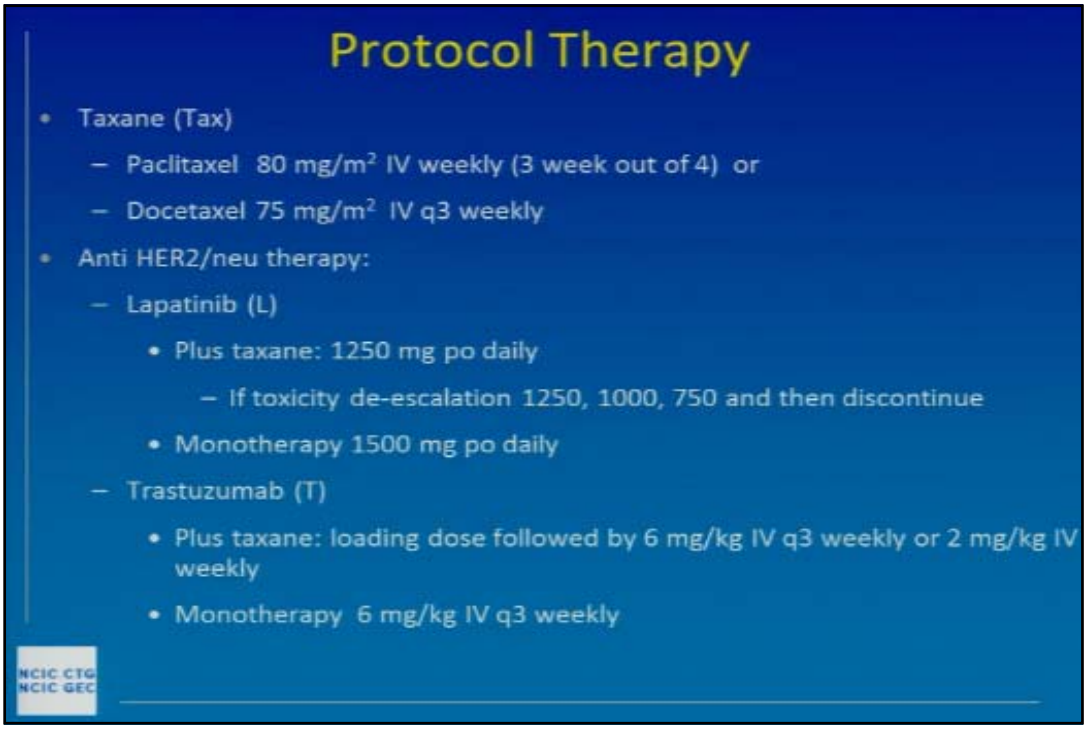

Statistical Design - 3
Interim Analysis
• 2-sided test for superiority
– requires 195 (50%) events in HER2+ centrally-confirmed
– evaluate the ITT population
– Lan DeMets / O' Brien-Fleming boundary = 0.00305
– Adjust boundary based on actual # of events
• Actual # of events:
– 333 in ITT population, IA stopping boundary: P=0.0301
– 263 events in centrally-confirmed HER2+
NCIC CTG
NCIC GEC

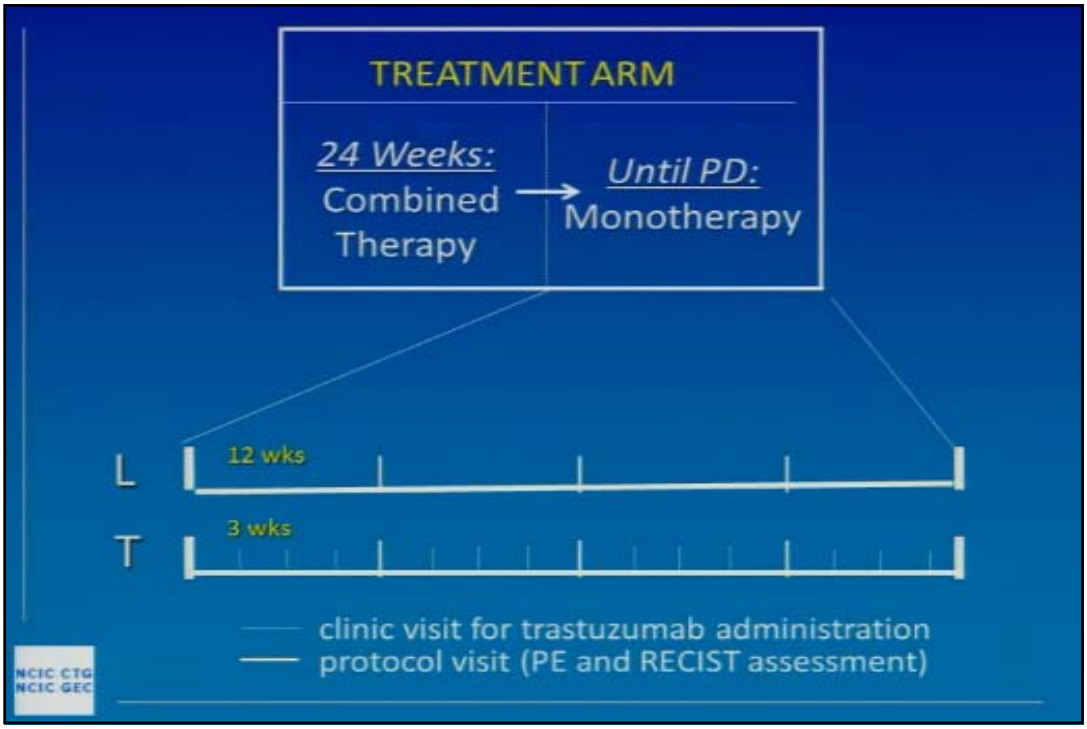

MA.31/ EGF108919: Design
Women with HER2 positive (central or local lab) metastatic breast cancer and no prior chemotherapy or HER2 targeted therapy in the metastatic setting.
• Standard inclusion including mandatory central HER2 testing
• Standard exclusion
• Prior (neo)adjuvant chemo / trastuzumab allowed (≥ 12 mo)
• No CNS mets
NCIC CTG
NCIC GEC


MA.31/ EGF108919: Design
Women with HER2 positive (central or local lab) metastatic breast cancer and no prior chemotherapy or HER2 targeted therapy in the metastatic setting
Standard inclusion and exclusion
Stratify
• Prior (neo)adjuvant HER2 therapy
• Prior (neo)adjuvant taxane chemotherapy
• Planned taxane treatment
• Liver metastasis
NCIC CTG
NCIC GEC


MA.31/ EGF108919: Design
Women with HER2 positive (central or local lab) metastatic breast cancer and no prior chemotherapy or HER2 targeted therapy in the metastatic setting
Standard inclusion and exclusion
Stratify
Randomize
1 : 1
NCIC CTG
NCIC GEC


MA.31/ EGF108919: Design
Randomize
EXPERIMENTAL ARM
24 Weeks: Lapatinib plus Taxane
Until PD: Lapatinib
STANDARD ARM
24 Weeks: Trastuzumab plus Taxane
Until PD: Trastuzumab
Primary Outcome: PFS
NCIC CTG NCIC GEC
Sample Size: ~600 (536 centrally confirmed HER2+ patients)


Protocol Therapy
Taxane (Tax)
Paclitaxel 80 mg/m² IV weekly (3 week out of 4) or
Docetaxel 75 mg/m² IV q3 weekly
Anti HER2/neu therapy:
Lapatinib (L)
Plus taxane: 1250 mg po daily
If toxicity de-escalation 1250, 1000, 750 and then discontinue
Monotherapy 1500 mg po daily
Trastuzumab (T)
Plus taxane: loading dose followed by 6 mg/kg IV q3 weekly or 2 mg/kg IV weekly
Monotherapy 6 mg/kg IV q3 weekly
NCIC CTG NCIC GEC


TREATMENT ARM
24 Weeks:
Combined Therapy
Until PD:
Monotherapy
L
12 wks
T
3 wks
clinic visit for trastuzumab administration
protocol visit (PE and RECIST assessment)
NCIC CTG
NCIC GEC


Study Conduct
UK-65
Ukraine-8
Poland-19
Russia-101
Canada-75
The Netherlands-14
Germany-66
Belgium-9
USA-23
France-10
Israel-31
Korea-36
Japan-42
Spain-38
Italy-13
Mexico-9
India-8
Taiwan-22
Thailand-21
Australia-30
Argentina-12
Median follow-up: 13.6 months
(12.9 months on lapatinib arm; 14 months on trastuzumab arm)
NCIC CTG
NCIC GEC

Acknowledgements

We would like to thank all the patients and their families who participated on this trial, as well as the following investigators:

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- Anthony Landis
- Michael McLaughlin
- Manuel Modiano
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MA.31 Flow Diagram

652 patients randomized in Dec 7, 2011

636 patients randomized Nov 7, 2011 (ITT)

318 LTAX/L	318 TTAX/T
266 Centrally confirmed Her2/neu status	259 Centrally confirmed Her2/neu Status
5 did not receive protocol therapy	1 did not receive protocol therapy
42 without PFS assessment	36 without PFS assessment
318 in ITT PFS analysis 313 in safety analysis	318 in ITT PFS analysis 317 in safety analysis

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Baseline Characteristics

	LTAX/L (n=318)	TTAX/T (n=318)
Age –median *(range)*	55.4 (27-87)	54.1 (29-84)
ECOG 0/1	96%	97%
Prior (Neo) adjuvant anti HER2/neu therapy	18%	18%
Prior (Neo) adjuvant taxane therapy	21%	22%
Metastatic breast cancer at primary diagnosis	42%	43%
Liver metastases	46%	46%
Planned 3 weekly docetaxel treatment	55%	55%
Planned weekly paclitaxel treatment	45%	45%

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* ER/PR tested centrally

Results of Interim Analysis

- DSMC Review:
  - ITT PFS: HR = 1.38; P = 0.006
- DSMC recommendation was accepted according to NCIC CTG policies
- Repeat analysis using more conservative censoring:
  - ITT PFS: HR = 1.33; P = 0.01

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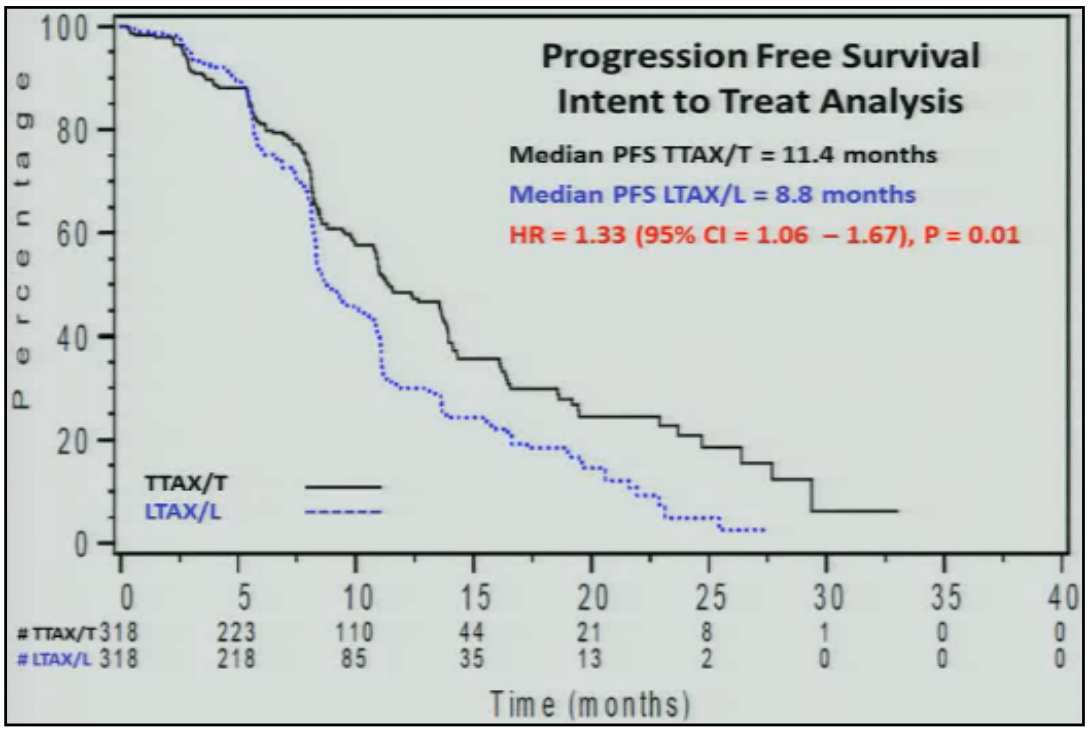
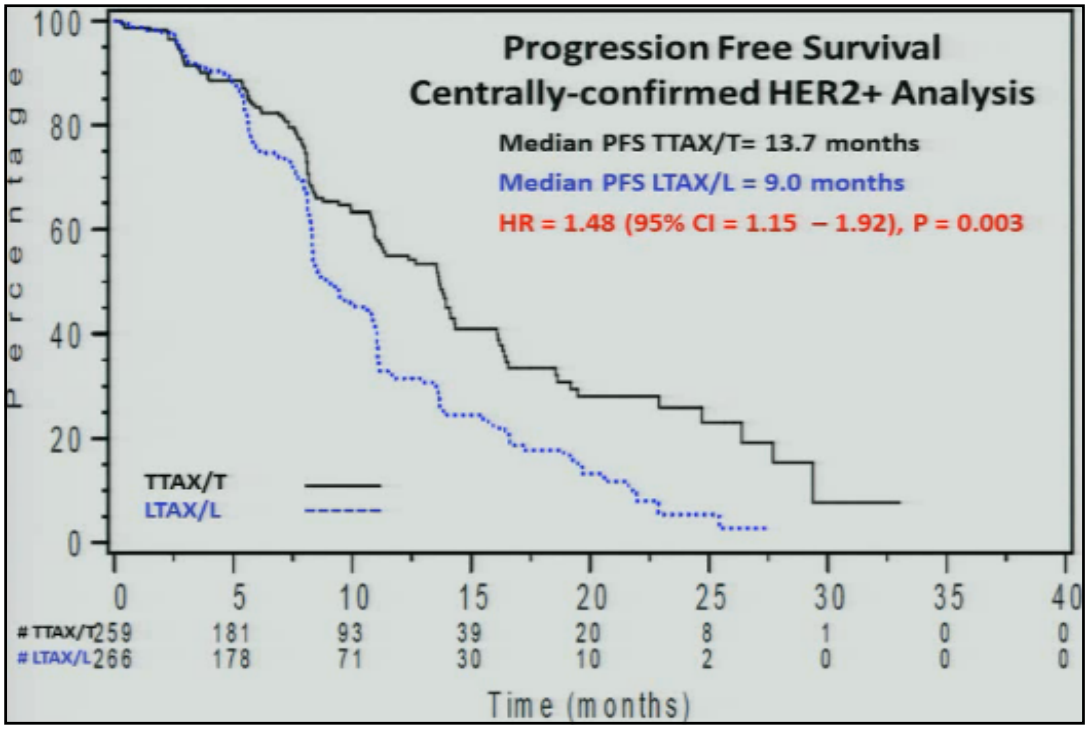
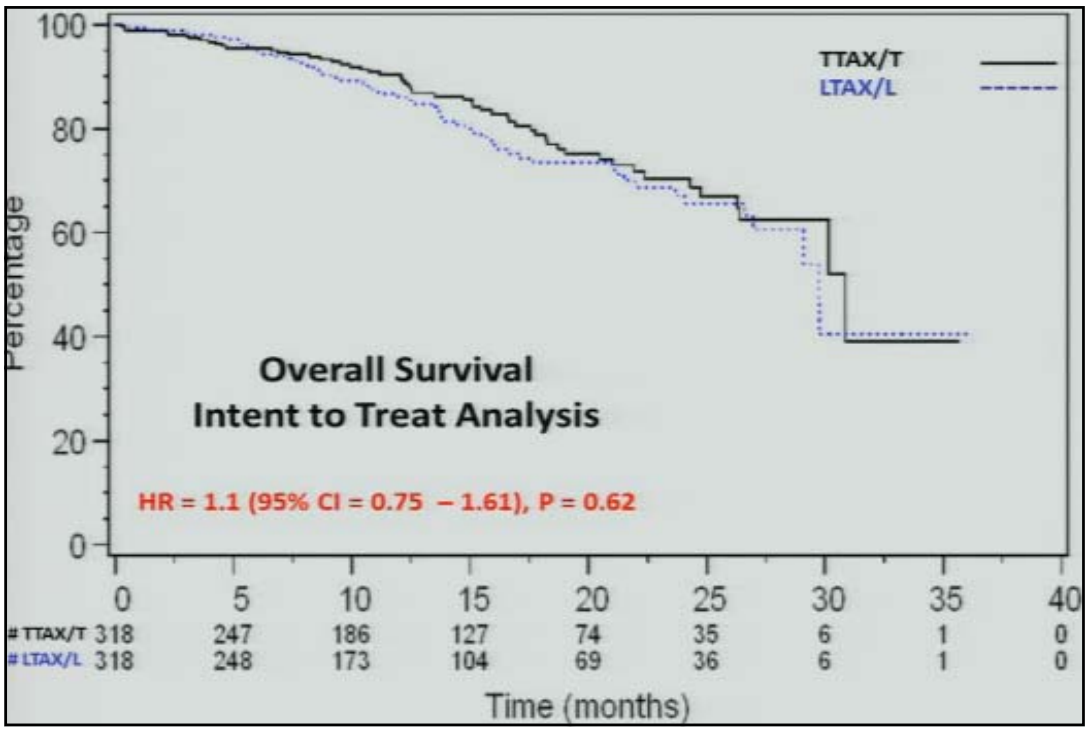
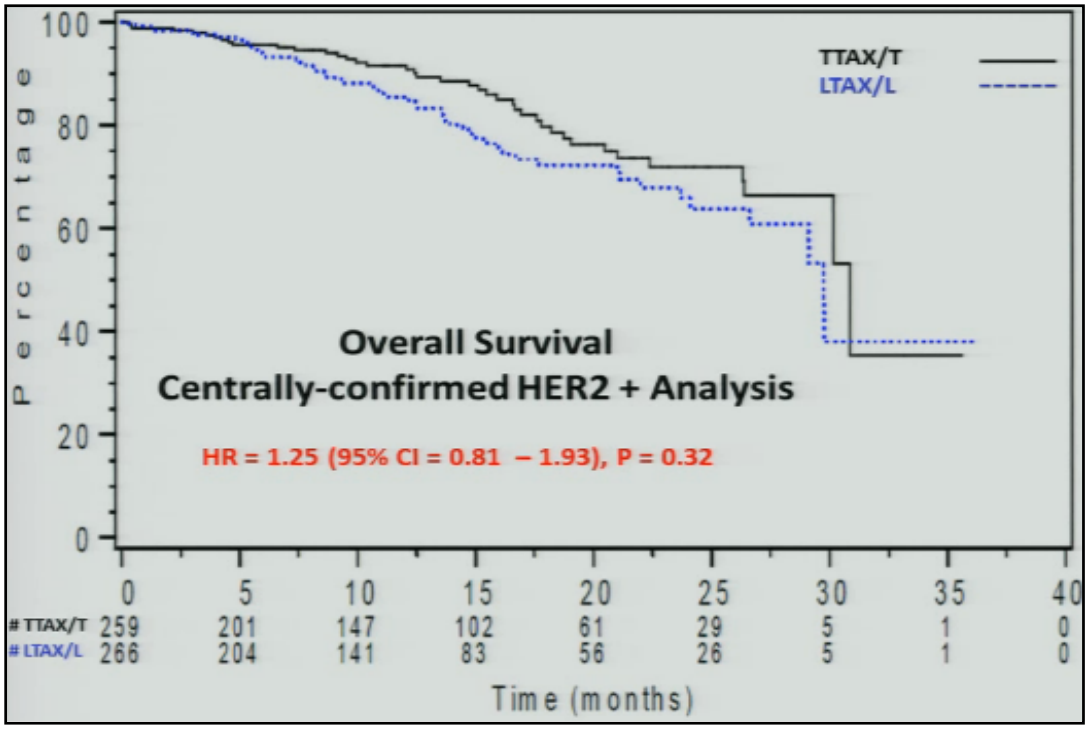
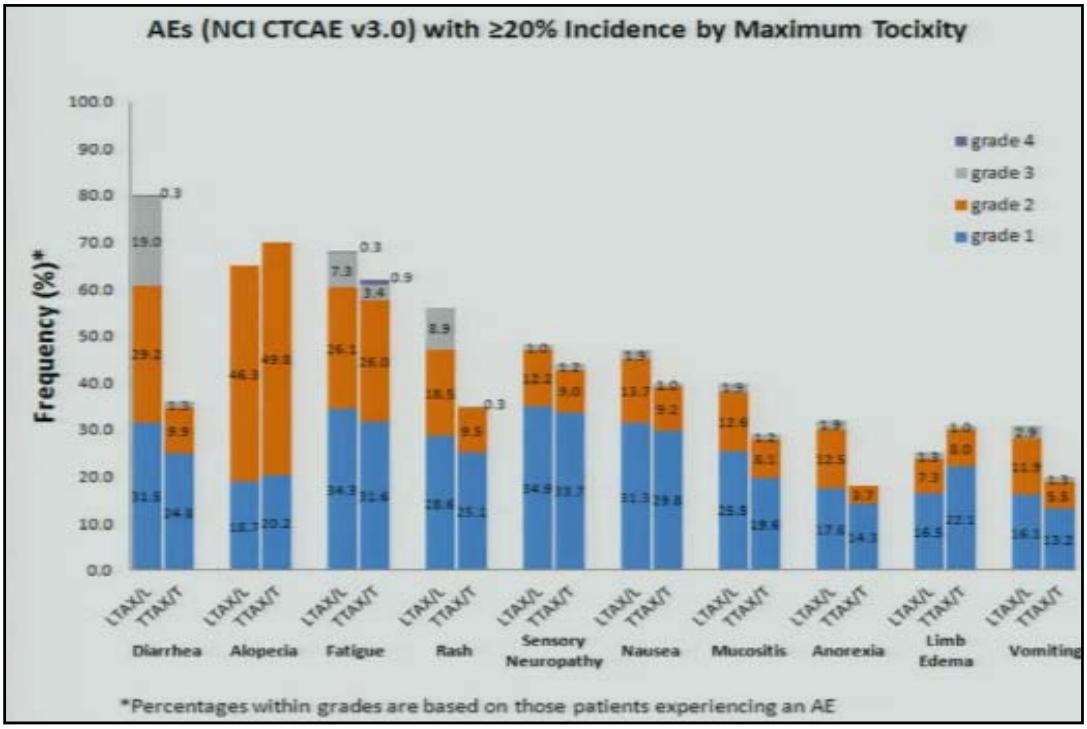

Progression Free Survival
Intent to Treat Analysis
Median PFS TTAX/T = 11.4 months
Median PFS LTAX/L = 8.8 months
HR = 1.33 (95% CI = 1.06 – 1.67), P = 0.01
TTAX/T
LTAX/L
Percentage
100
80
60
40
20
0
0 5 10 15 20 25 30 35 40
TTAX/T 318 223 110 44 21 8 1 0 0
LTAX/L 318 218 85 35 13 2 0 0 0
Time (months)


Progression Free Survival
Centrally-confirmed HER2+ Analysis
Median PFS TTAX/T= 13.7 months
Median PFS LTAX/L = 9.0 months
HR = 1.48 (95% CI = 1.15 – 1.92), P = 0.003
TTAX/T
LTAX/L
Percentage
100
80
60
40
20
0
0 5 10 15 20 25 30 35 40
TTAX/T 259 181 93 39 20 8 1 0 0
LTAX/L 266 178 71 30 10 2 0 0 0
Time (months)


TTAX/T
LTAX/L
Percentage
Overall Survival
Intent to Treat Analysis
HR = 1.1 (95% CI = 0.75 – 1.61), P = 0.62
# TTAX/T 318 247 186 127 74 35 6 1 0
# LTAX/L 318 248 173 104 69 36 6 1 0
Time (months)


TTAX/T
LTAX/L
Percentage
Overall Survival
Centrally-confirmed HER2 + Analysis
HR = 1.25 (95% CI = 0.81 – 1.93), P = 0.32
# TTAX/T 259 201 147 102 61 29 5 1 0
# LTAX/L 266 204 141 83 56 26 5 1 0
Time (months)



Serious Adverse Events

LTAX/L (Total SAE reports = 136)			TTAX/T (Total SAE reports = 78)		
EVENT	Total Number*	Number post amendment **	EVENT	Total Number*	Number post amendment **
Diarrhea	32	25	Diarrhea	5	3
Febrile Neutropenia	17	7	Febrile Neutropenia	7	6

** Included as one of the adverse event terms within a single SAE report*

*** Protocol Amendment after first 189 patients were randomized mandated primary GCSF prophylaxis for patients on docetaxel and lapatinib*

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Conclusions

- In this study comparing LTAX/L to TTAX/T, the PFS was statistically significantly better in the trastuzumab arm with a HR of 1.33 and a 2.6 month difference (median PFS) in the ITT population and a HR of 1.48 with a 4.7 month difference (median PFS) in the centrally confirmed HER2 + population.
- The toxicity pattern of the two arms was different with more rash and diarrhea in the lapatinib containing arm and a higher incidence of decrease in LVEF from baseline in the trastuzumab arm.

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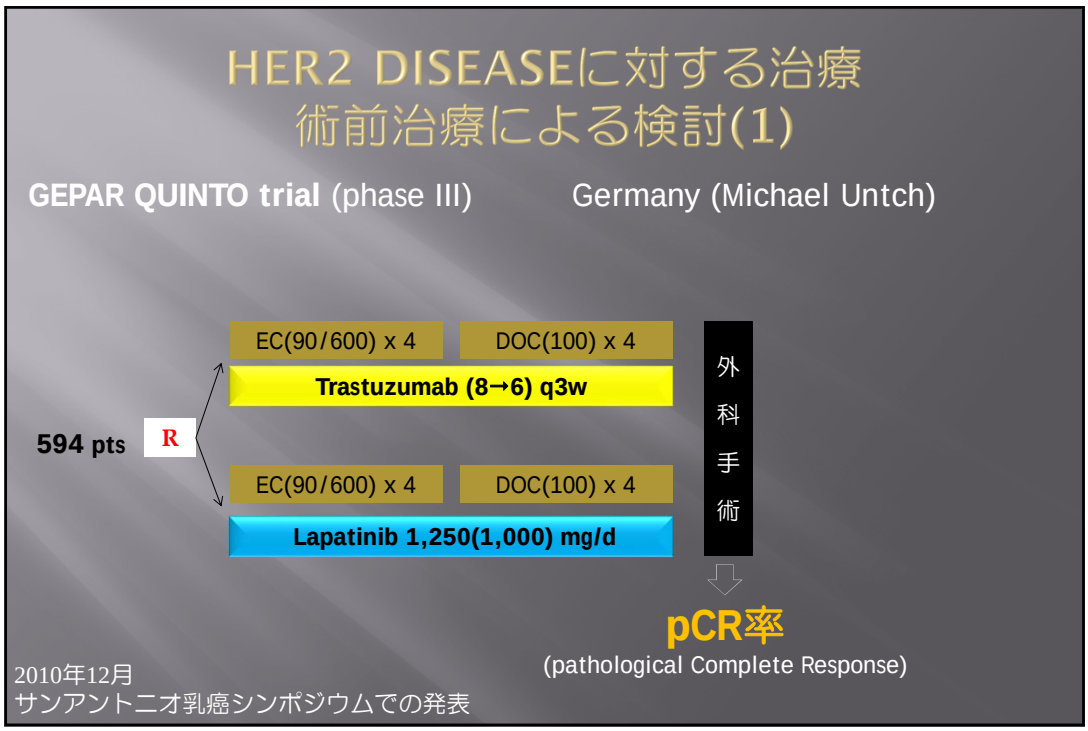
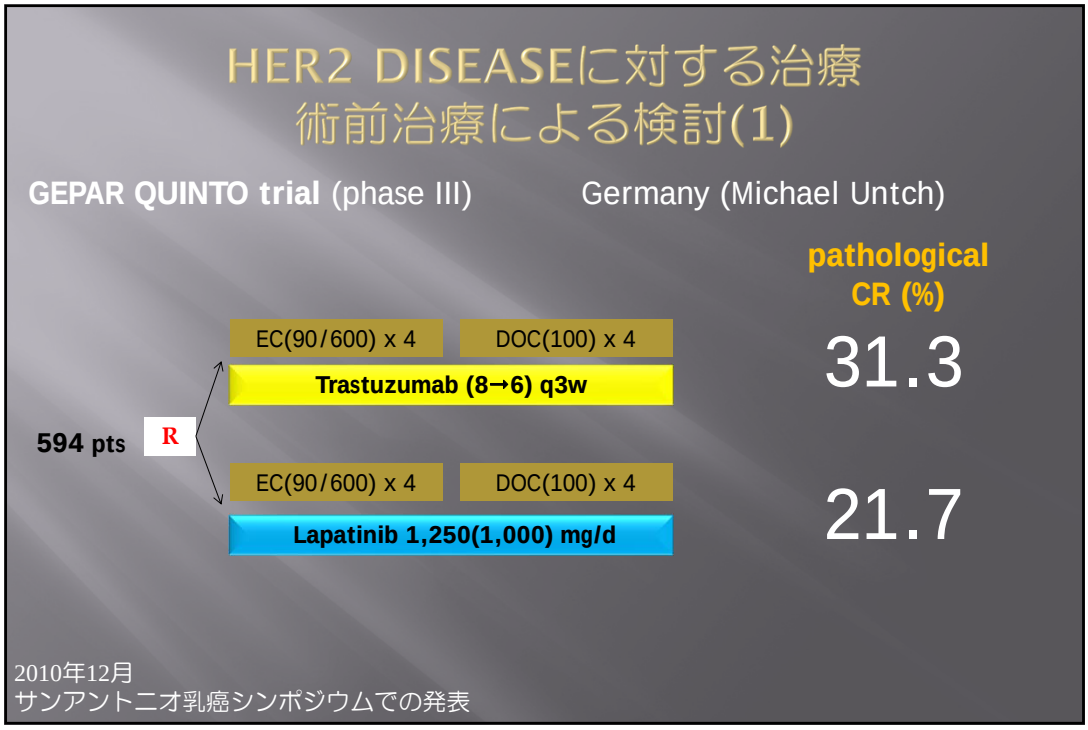
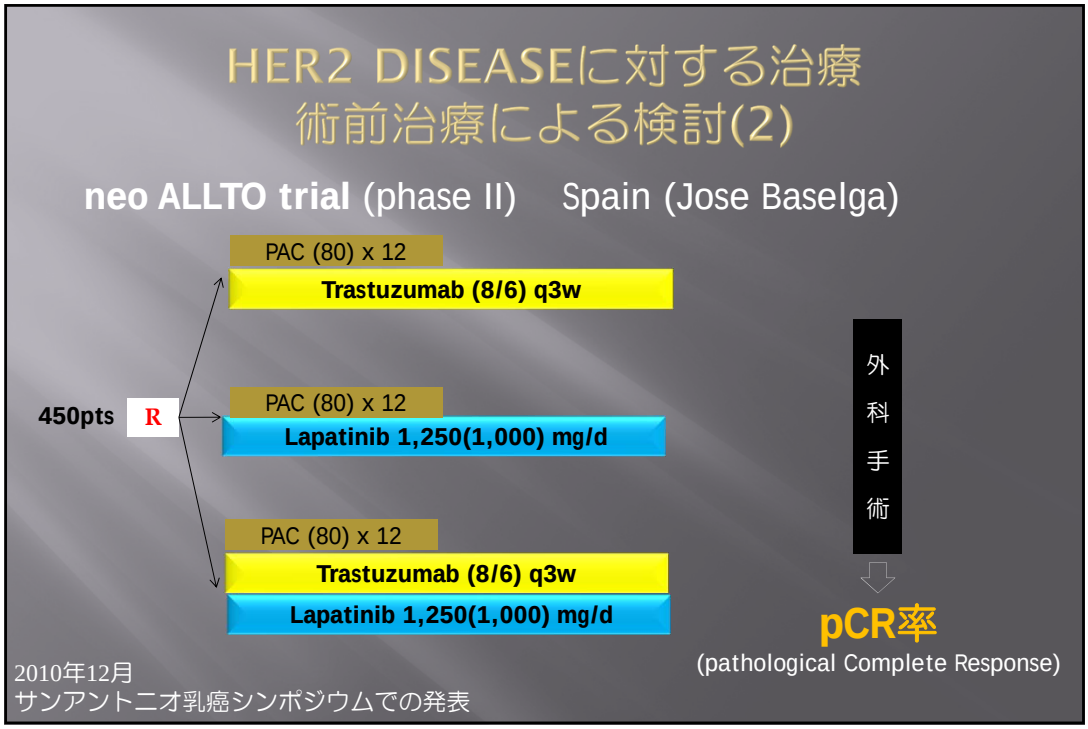
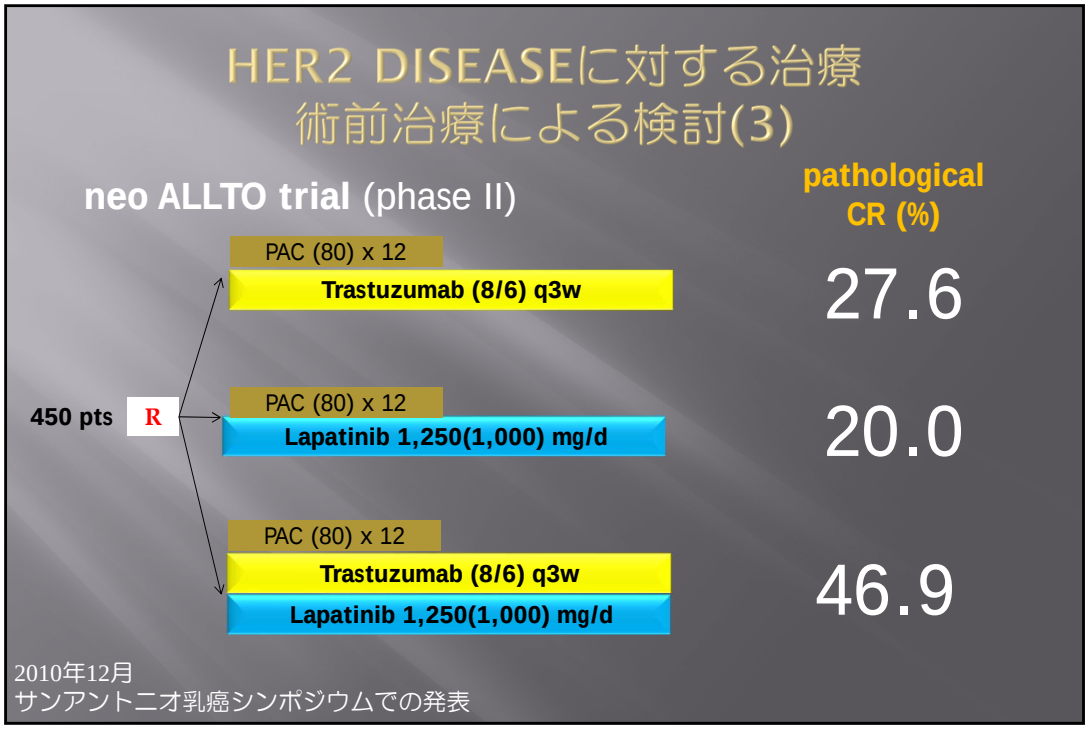
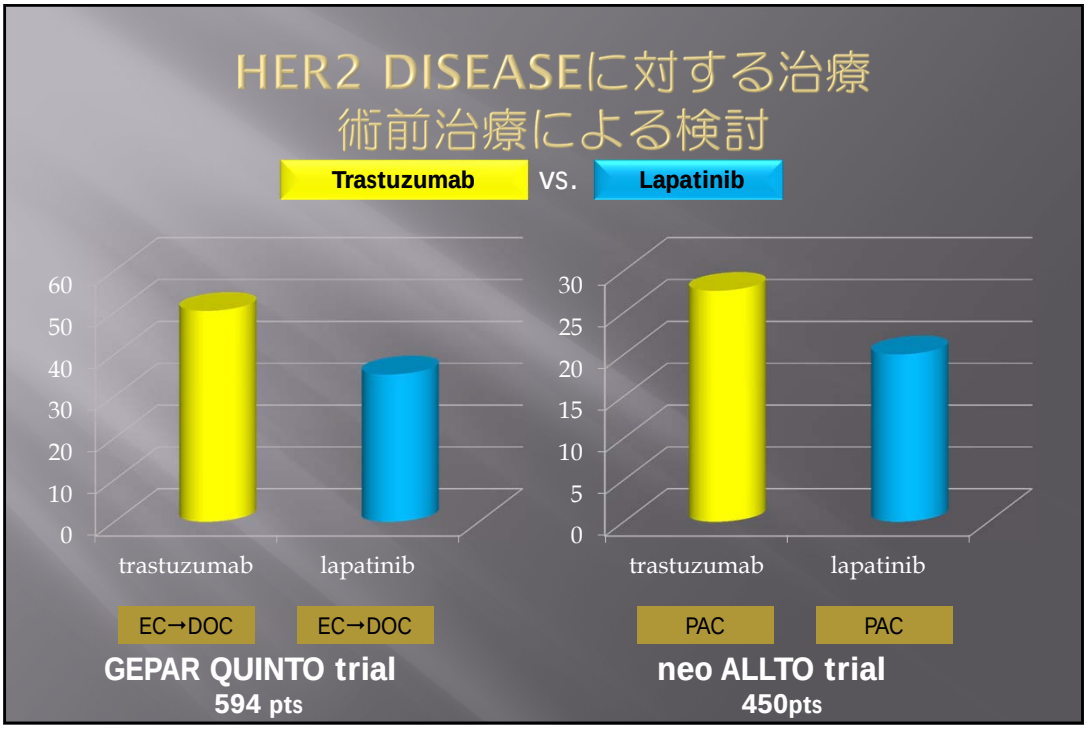

HER2 DISEASEに対する治療
術前治療による検討(1)
GEPAR QUINTO trial (phase III)
Germany (Michael Untch)
EC(90/600) x 4
DOC(100) x 4
Trastuzumab (8→6) q3w
594 pts
R
EC(90/600) x 4
DOC(100) x 4
Lapatinib 1,250(1,000) mg/d
外科手術
pCR率
(pathological Complete Response)
2010年12月
サンアントニオ乳癌シンポジウムでの発表

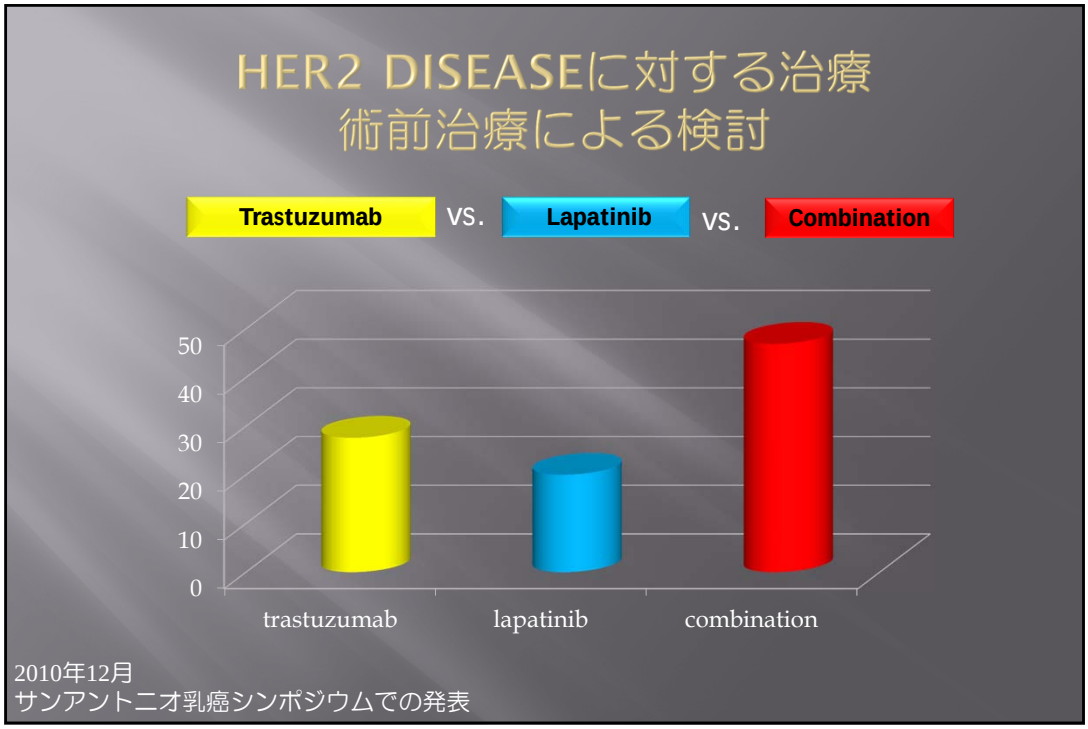

HER2 DISEASEに対する治療
術前治療による検討(1)
GEPAR QUINTO trial (phase III)
Germany (Michael Untch)
pathological
CR (%)
EC(90/600) x 4
DOC(100) x 4
Trastuzumab (8→6) q3w
31.3
594 pts
R
EC(90/600) x 4
DOC(100) x 4
Lapatinib 1,250(1,000) mg/d
21.7
2010年12月
サンアントニオ乳癌シンポジウムでの発表


HER2 DISEASEに対する治療
術前治療による検討(2)
neo ALLTO trial (phase II)　Spain (Jose Baselga)
450pts
R
PAC (80) x 12
Trastuzumab (8/6) q3w
PAC (80) x 12
Lapatinib 1,250(1,000) mg/d
PAC (80) x 12
Trastuzumab (8/6) q3w
Lapatinib 1,250(1,000) mg/d
外科手術
pCR率
(pathological Complete Response)
2010年12月
サンアントニオ乳癌シンポジウムでの発表


HER2 DISEASEに対する治療
術前治療による検討(3)
neo ALLTO trial (phase II)
pathological CR (%)
450 pts
R
PAC (80) x 12
Trastuzumab (8/6) q3w
27.6
PAC (80) x 12
Lapatinib 1,250(1,000) mg/d
20.0
PAC (80) x 12
Trastuzumab (8/6) q3w
Lapatinib 1,250(1,000) mg/d
46.9
2010年12月
サンアントニオ乳癌シンポジウムでの発表


HER2 DISEASEに対する治療
術前治療による検討
Trastuzumab
vs.
Lapatinib
60
50
40
30
20
10
0
trastuzumab
lapatinib
EC→DOC
EC→DOC
GEPAR QUINTO trial
594 pts
30
25
20
15
10
5
0
trastuzumab
lapatinib
PAC
PAC
neo ALLTO trial
450pts


でも 使いようによっては
役にたつんだぜ
悲しそうな (-_-;)
Karen Gelmon



ASCO歴史展望　抗HER2療法の巻

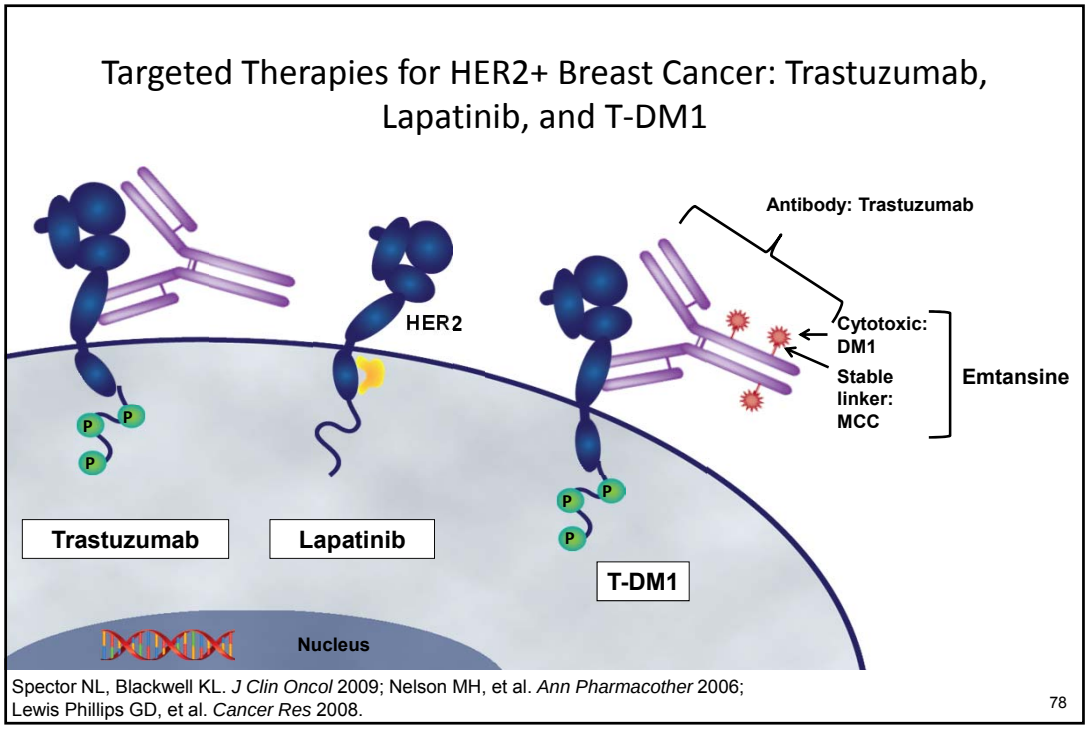
	IMPACT	Author	Publication
1998	Trastuzumab single p II MBC Second Line	Cobleigh M	JCO **17**:2639,1999
	Trastuzumab p III MBC AC/PTX ± HERCEPTIN	Slamon D	NEJM **344**:783,2001
2000	Trastuzumab single p II MBC First Line	Vogel C	JCO **20**:719, 2002
2001	Trastuzumab + Paclitaxel MBC q3w	Gelmon K	JCO **21**:3965,2003
2005	Trastuzumab adjuvant PIII NSABP-B31/NCCTG-N9831	Romand EH	NEJM **353**:1673,2005
	Trastuzumab adjuvant PIII HERA	Piccart-Gebhart MJ	NEJM **353**:1659,2005
2006	Lapatinib+ Capecitabine PIII	Geyer CE	NEJM **355**:2733,2006
2012	Trastuzumab+Taxan vs. Lapatinib+Taxan P III NCIC MA.31	Gelmon K	
	T-DM1 vs Lapatinib + Capecitabine P III	Blackwell K	

Primary Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated With Trastuzumab and a Taxane

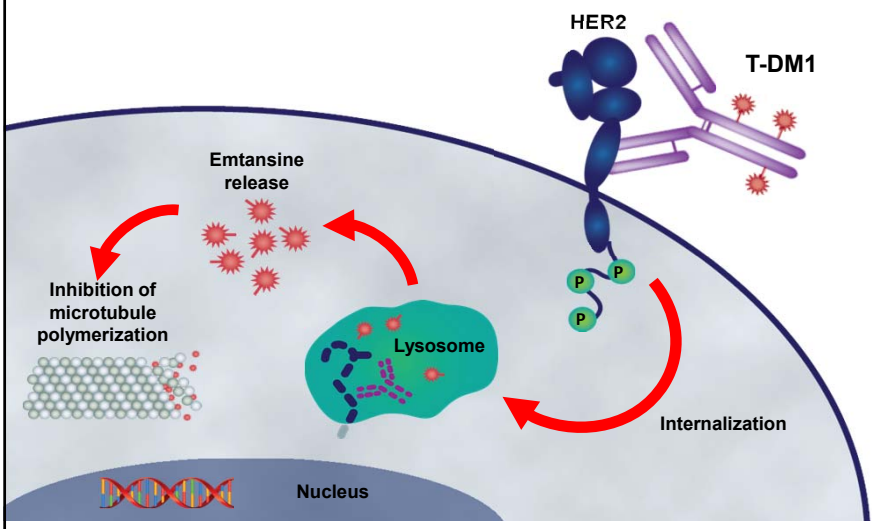
K Blackwell,[1] D Miles,[2] L Gianni,[3] IE Krop,[4] M Welslau,[5] J Baselga,[6] M Pegram,[7] D-Y Oh,[8] V Diéras,[9] S Olsen,[10] L Fang,[10], MW Lu,[10] E Guardino,[10] S Verma[11]

[1]Duke Cancer Institute, Durham, NC, USA; [2]Mount Vernon Cancer Center, Northwood, UK; [3]San Raffaele Hospital, Milan, Italy; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Medical Office Hematology, Aschaffenburg, Germany; [6]Massachusetts General Hospital, Boston, MA, USA; [7]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [8]Seoul National University College of Medicine, Seoul, Korea; [9]Institut Curie, Paris, France; [10]Genentech, Inc, South San Francisco, CA, USA; [11]Sunnybrook Odette Cancer Center, Toronto, Canada


EMILIA
Desdemona's Attendant (Othello)
Tassel Flower (*Emilia javanica*)
PRESENTED BY: LOUIS M. WEINER, MD
PRESENTED AT: ASCO Annual '12 Meeting


Targeted Therapies for HER2+ Breast Cancer: Trastuzumab, Lapatinib, and T-DM1
Antibody: Trastuzumab
HER2
Cytotoxic: DM1
Stable linker: MCC
Emtansine
P
Trastuzumab
Lapatinib
T-DM1
Nucleus
Spector NL, Blackwell KL. *J Clin Oncol* 2009; Nelson MH, et al. *Ann Pharmacother* 2006; Lewis Phillips GD, et al. *Cancer Res* 2008.
78

T-DM1: Mechanism of Action



Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

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Clinical Rationale for EMILIA

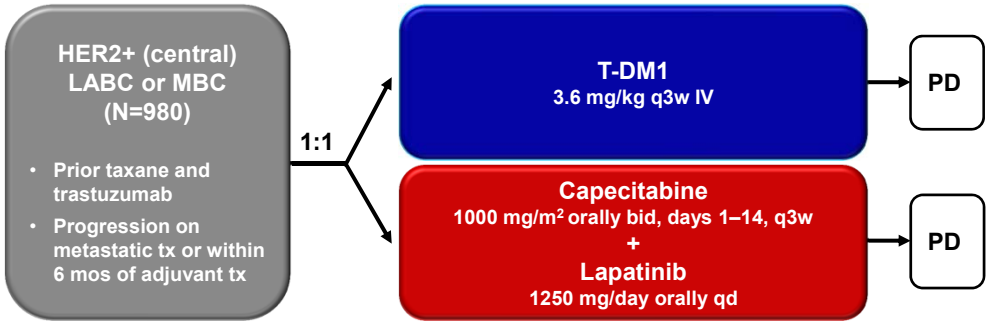
T-DM1

- Two single-arm phase 2 trials in patients who received ≥1 HER2-directed therapies for MBC
  - ORR: 25.9% (N=112)[1] and 34.5% (N=110)[2]
- Randomized phase 2 trial in patients without prior HER2-directed therapy for MBC
  - Median PFS longer with T-DM1 (n=67) vs. trastuzumab + docetaxel (n=70)
  - 14.2 vs. 9.2 months (HR=0.59; *P*=0.035)[3]

Capecitabine + Lapatinib

- Randomized phase 3 trial in patients who received prior trastuzumab
  - Median TTP longer with capecitabine + lapatinib (n=163) vs. capecitabine (n=161)
  - 8.4 vs. 4.4 months (HR=0.49; *P*<0.001)[4]

EMILIA Study Design



- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Statistical Considerations for Efficacy End Points

Hierarchical statistical analysis: performed in pre-specified sequential order

Progression-free Survival (PFS) by Independent Review

Final PFS analysis:
- Targeted number of events: 508
- 90% power to detect HR=0.75; 2-sided alpha 5%

↓

Overall Survival (OS)

Interim OS analysis:
- Efficacy stopping boundary determined using Lan-DeMets alpha spending function with O'Brien-Fleming boundary and number of death events observed

Final OS analysis:
- Targeted number of events: 632
- 80% power to detect HR=0.80; 2-sided alpha 5%

↓

Secondary End Points

Patient Disposition

	Cap + Lap	T-DM1
Randomized, n	496	495
Treated, n	488	490
On treatment at data cutoff date	125	182
Median follow-up, mos (range)	12.4 (0−35)	12.9 (0−34)

First patient in: February 23, 2009
Last patient in: October 13, 2011
Clinical data cutoff: January 14, 2012

Patient Demographics and Baseline Characteristics (1)

	Cap + Lap (n=496)	T-DM1 (n=495)
Median age, yrs (range)	53 (24–83)	53 (25–84)
Race, n (%)		
White	374 (75)	358 (72)
Asian	86 (17)	94 (19)
Black/African American	21 (4)	29 (6)
Other	10 (2)	7 (1)
Not available	5 (1)	7 (1)
World region, n (%)		
US	136 (27)	134 (27)
Western Europe	160 (32)	157 (32)
Asia	76 (15)	82 (17)
Other	124 (25)	122 (25)
ECOG PS, n (%)		
0	312 (64)	299 (61)
1	176 (36)	194 (39)

Patient Demographics and Baseline Characteristics (2)

	Cap + Lap (n=496)	T-DM1 (n=495)
Measurable disease by independent review, n (%)	389 (78)	397 (80)
Metastatic involvement, n (%)		
Visceral	335 (68)	334 (68)
Non-visceral	161 (33)	161 (33)
Metastatic sites, n (%)		
<3	307 (62)	298 (60)
≥3	175 (35)	189 (38)
Unknown	14 (3)	8 (2)
ER/PR status, n (%)		
ER+ and/or PR+	263 (53)	282 (57)
ER− and PR−	224 (45)	202 (41)
Unknown	9 (2)	11 (2)

Prior Systemic Treatment

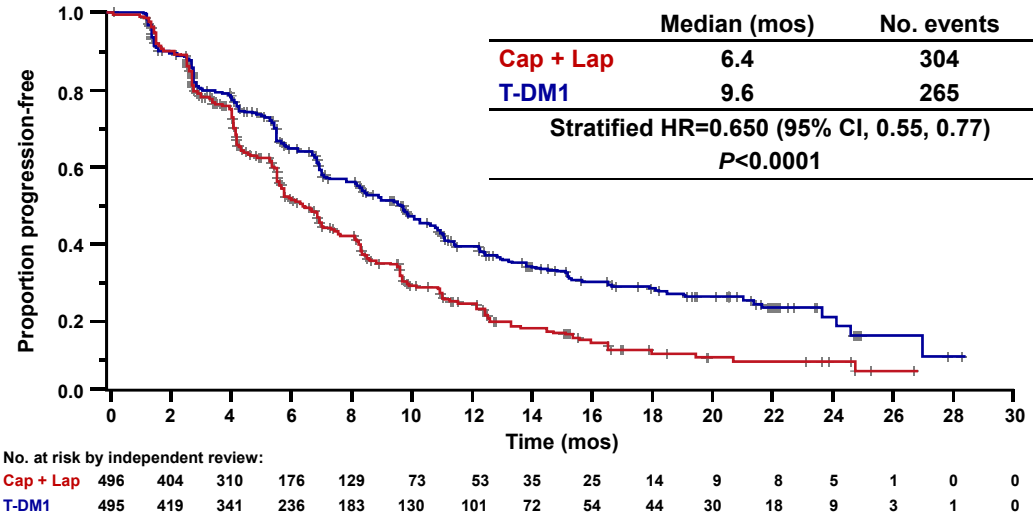
	Cap + Lap (n=496)	T-DM1 (n=495)
Prior treatment type, n (%)		
Taxanes	494 (100)	493 (100)
Anthracyclines	302 (61)	303 (61)
Endocrine agents	204 (41)	205 (41)
Prior therapy for MBC, n (%)		
Yes	438 (88)	435 (88)
No	58 (12)	60 (12)
Prior trastuzumab treatment, n (%)	495 (100)	495 (100)
EBC only	77 (16)	78 (16)
Duration of trastuzumab treatment, n (%)		
<1 yr	212 (43)	210 (42)
≥1 yr	284 (57)	285 (58)
Median time since last trastuzumab, mos (range)	1.5 (0–98)	1.5 (0–63)

Drug Exposure

	Cap (n=487)	Lap (n=488)	T-DM1 (n=490)
Median dose intensity, %	77.2	93.4	99.9
Pts with dose reduction, n (%)	260 (53.4)	133 (27.3)	80 (16.3)
T-DM1 decreased to 3.0 mg/kg, n (%)	—	—	58 (11.8)
T-DM1 decreased to 2.4 mg/kg, n (%)	—	—	22 (4.5)

Now I will present the efficacy results.

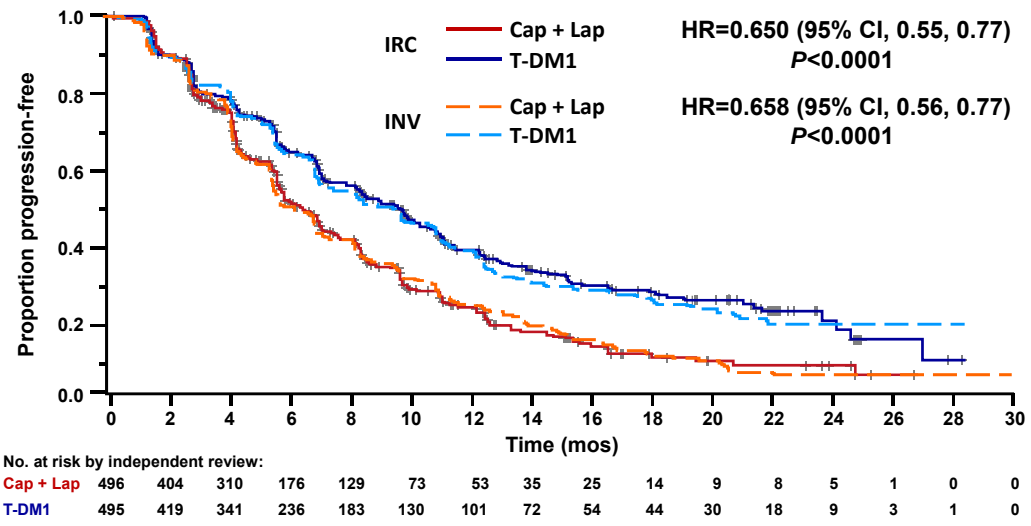
Progression-Free Survival by Independent Review



	Median (mos)	No. events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR=0.650 (95% CI, 0.55, 0.77)
P<0.0001

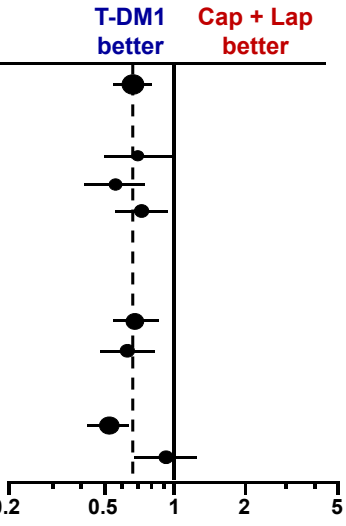
Progression-Free Survival by Independent (IRC) and Investigator (INV) Review



Progression-Free Survival Subgroup Analyses

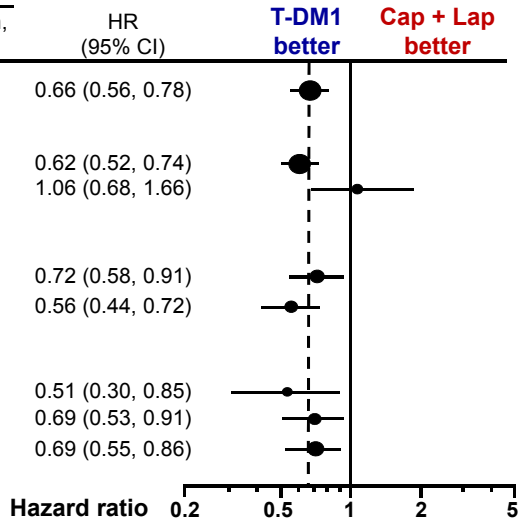
Pre-specified Stratification Factors

Baseline characteristic	Total n	Cap + Lap Median, mos	T-DM1 Median, mos	HR (95% CI)
All pts	991	6.4	9.6	0.66 (0.56, 0.78)
World region				
US	270	5.7	8.5	0.70 (0.51, 0.98)
Western Europe	317	6.4	10.9	0.56 (0.41, 0.74)
Other	404	6.9	9.6	0.73 (0.56, 0.94)
Number prior chemo regimens for MBC or unresectable LABC				
0–1	609	6.7	10.3	0.68 (0.55, 0.85)
>1	382	5.7	8.5	0.63 (0.49, 0.82)
Presence of visceral disease				
Yes	669	5.7	9.6	0.55 (0.45, 0.67)
No	322	10.2	8.5	0.96 (0.71, 1.30)



Progression-Free Survival Subgroup Analyses

Baseline characteristic	Total n	Cap + Lap Median, mos	T-DM1 Median, mos	HR (95% CI)
All pts	991	6.4	9.6	0.66 (0.56, 0.78)
Age				
<65 yrs	853	6.0	9.8	0.62 (0.52, 0.74)
≥65 yrs	138	8.1	7.0	1.06 (0.68, 1.66)
ER and PR status				
ER+ and/or PR+	545	7.1	9.0	0.72 (0.58, 0.91)
ER− and PR−	426	5.6	10.3	0.56 (0.44, 0.72)
Line of therapy[a]				
First	118	5.7	10.8	0.51 (0.30, 0.85)
Second	361	6.8	9.6	0.69 (0.53, 0.91)
Third	512	6.5	9.0	0.69 (0.55, 0.86)



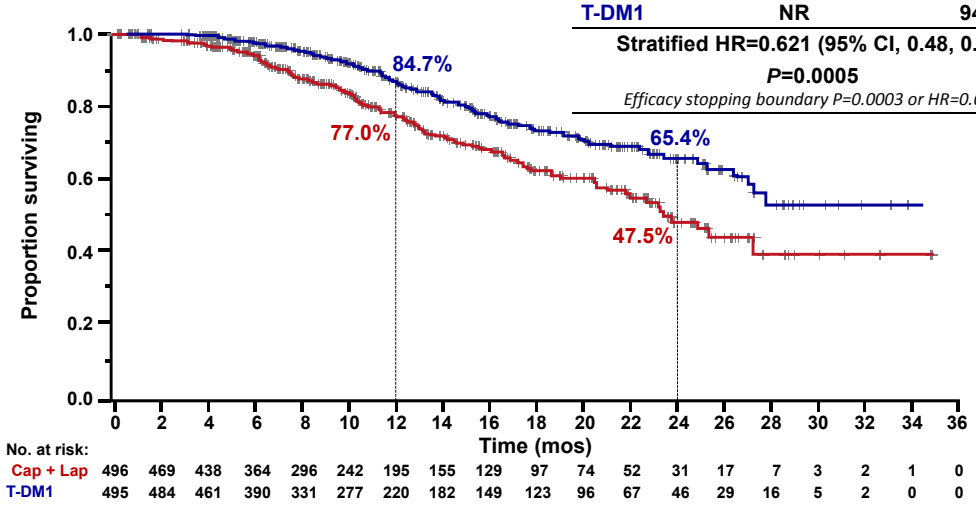
Overall Survival: Interim Analysis

	Median (mos)	No. events
Cap + Lap	23.3	129
T-DM1	NR	94

Stratified HR=0.621 (95% CI, 0.48, 0.81)

***P*=0.0005**

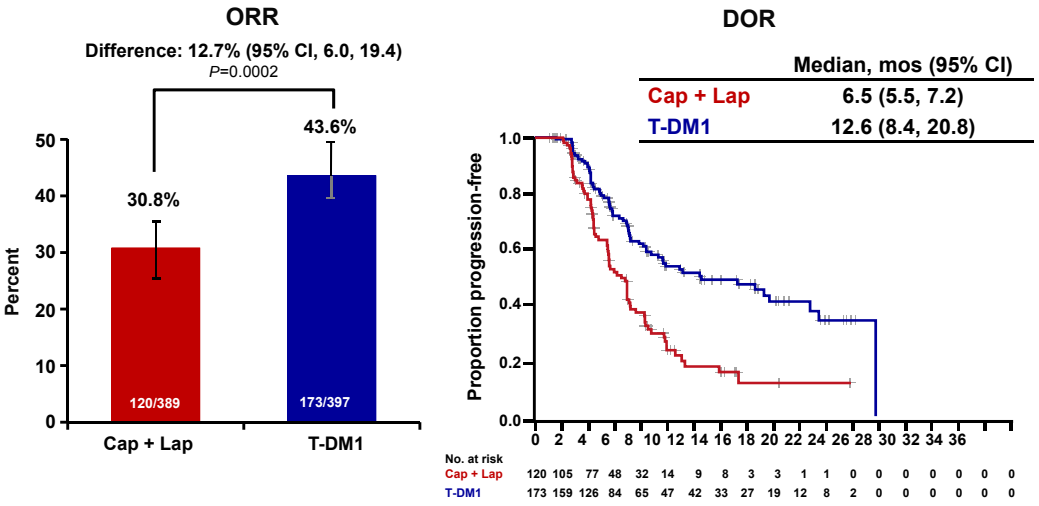
Efficacy stopping boundary P=0.0003 or HR=0.617



No. at risk:

Cap + Lap	496	469	438	364	296	242	195	155	129	97	74	52	31	17	7	3	2	1	0
T-DM1	495	484	461	390	331	277	220	182	149	123	96	67	46	29	16	5	2	0	0

Objective Response Rate (ORR) and Duration of Response (DOR) in Patients with Measurable Disease



Patient-Reported Outcomes

Time to Symptom Progression

- The FACT-Breast Trial Outcome Index[1] evaluates
  - Physical Well-Being
  - Functional Well-Being
  - Breast Cancer-Specific Symptoms
- Symptom progression defined as ≥5-point decrease from baseline

Time to symptom progression	Cap + Lap (n=445)	T-DM1 (n=450)
Median, mos	4.6	7.1
HR (95% CI)	0.80 (0.67, 0.95)	
P value	0.0121	

Overview of Adverse Events

	Cap + Lap (n=488)	T-DM1 (n=490)
All-grade AE, n (%)	477 (97.7)	470 (95.9)
Grade ≥3 AE, n (%)	278 (57.0)	200 (40.8)
AEs leading to treatment discontinuation (for any study drug), n (%)	52 (10.7)	29 (5.9)
AEs leading to death on treatment, n (%)[a]	5 (1.0)	1 (0.2)
LVEF <50% and ≥15-point decrease from baseline, %[b]	7 (1.6)	8 (1.7)

[a]Cap + Lap: CAD, multiorgan failure, coma, hydrocephalus, ARDS; T-DM1: metabolic encephalopathy.
[b]Evaluable pts: 445 (Cap + Lap); 481 (T-DM1).

Non-Hematologic Adverse Events

Grade ≥3 AEs With Incidence ≥2%

	Cap + Lap (n=488)		T-DM1 (n=490)	
Adverse Event	**All Grades, %**	**Grade ≥3, %**	**All Grades, %**	**Grade ≥3, %**
Diarrhea	79.7	**20.7**	23.3	1.6
Hand-foot syndrome	58.0	**16.4**	1.2	0.0
Vomiting	29.3	**4.5**	19.0	0.8
Hypokalemia	8.6	**4.1**	8.6	2.2
Fatigue	27.9	**3.5**	35.1	2.4
Nausea	44.7	**2.5**	39.2	0.8
Mucosal inflammation	19.1	**2.3**	6.7	0.2
Increased AST	9.4	0.8	22.4	**4.3**
Increased ALT	8.8	1.4	16.9	**2.9**

Hematologic Adverse Events

	Cap + Lap (n=488)			T-DM1 (n=490)		
Adverse Event	**All Grade, %**	**Grade 3, %**	**Grade 4, %**	**All Grade, %**	**Grade 3, %**	**Grade 4, %**
Neutropenia	8.6	**3.5**	**0.8**	5.9	1.6	0.4
Febrile neutropenia	1.0	**0.4**	**0.6**	0.0	0.0	0.0
Anemia	8.0	1.6	0.0	10.4	**2.7**	0.0
Thrombocytopenia	2.5	0.0	0.2	28.0	**10.4**	**2.4**

Conclusions

T-DM1 demonstrated improved efficacy over capecitabine + lapatinib

- **T-DM1 demonstrated a significant improvement in PFS**
  - **HR=0.650; *P*<0.0001**
- **Interim overall survival favored T-DM1 but did not cross the efficacy stopping boundary**
  - **HR=0.621; *P*=0.0005**
- **Safety and secondary efficacy end points favored T-DM1**

T-DM1 should offer an important therapeutic option in the treatment of HER2-positive metastatic breast cancer

Thanks

To all of the patients who participated in the trial and their families

To the investigators, clinicians and research staff at the 213 sites in 26 countries

EMILIA
A clinical trial of trastuzumab emtansine (T-DM1) in HER2+ MBC

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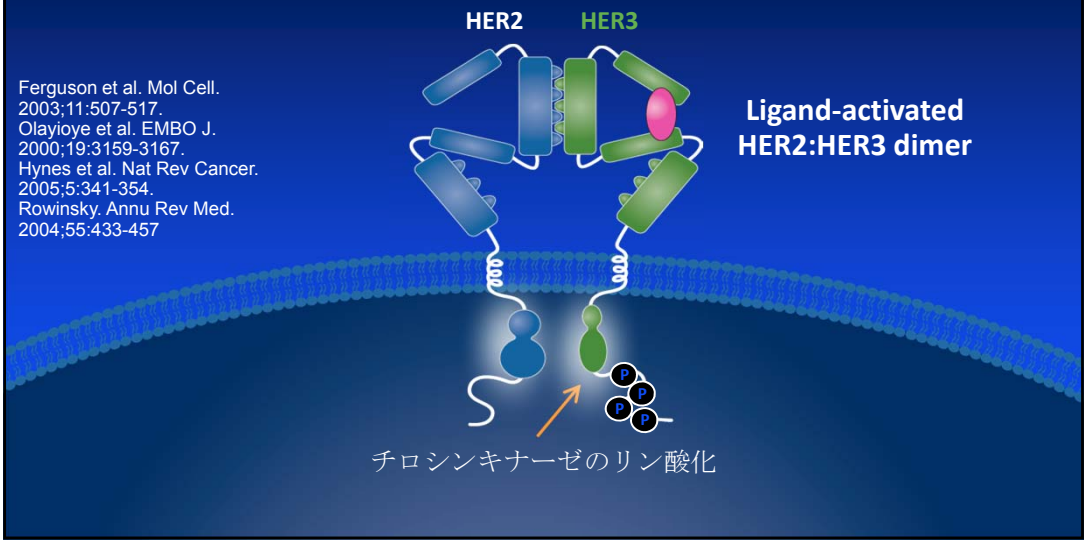
SABCS歴史展望　抗HER2療法の巻

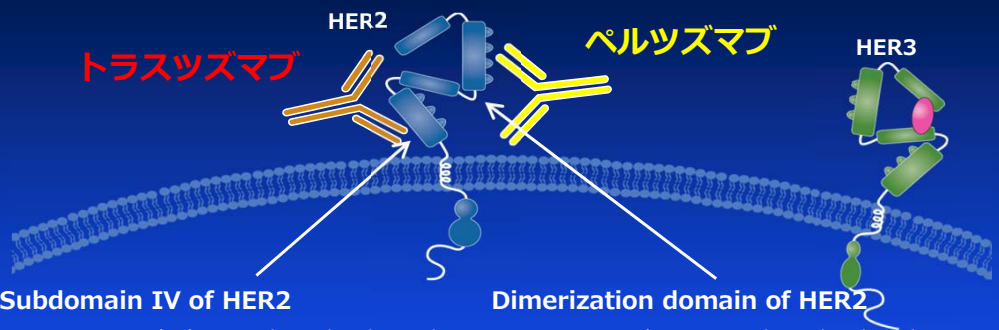
	IMPACT	Author	Publication
1998	Trastuzumab single p II MBC Second Line	Coblelgh M	JCO **17**:2639,1999
	Trastuzumab p III MBC AC/PTX ± HERCEPTIN	Slamon D	NEJM **344**:783,2001
2000	Trastuzumab single p II MBC First Line	Vogel C	JCO **20**:719, 2002
2001	Trastuzumab + Paclitaxel MBC q3w	Gelmon K	JCO **21**:3965,2003
2005	Trastuzumab adjuvant PIII NSABP-B31/NCCTG-N9831	Romand EH	NEJM **353**:1673,2005
	Trastuzumab adjuvant PIII HERA		NEJM **353**:1659,2005
2006	Lapatinib+ Capecitabine PIII	Geyer CE	NEJM **355**:2733,2006
2010	Trastuzumab vs Lapatinib vs, combination in neoadjuvant Pertuzumab vs Trastuzumab+Pertuzumab in neoajuvant	Untch M Gianni L	Lancet Oncol **13:** 135,2012 Lancet Oncol **13**: 25,2012
2011	Trastuzumab + DTX vs. Trastuzumab+Perututzumab + DTX (CLEOPATRA)	Baselga H	NEJM **366**: 109,2012
2012	Trastuzumab+Taxan vs. Lapatinib+Taxan P III NCIC MA.31	Gelmon K	
	T-DM1 vs Lapatinib + Capecitabine P III	Blackwell K	

HER2 二量体形成とシグナル伝達



Ferguson et al. Mol Cell. 2003;11:507-517.
Olayioye et al. EMBO J. 2000;19:3159-3167.
Hynes et al. Nat Rev Cancer. 2005;5:341-354.
Rowinsky. Annu Rev Med. 2004;55:433-457

トラスツズマブとペルズズマブは HER2タンパクの異なる部位に結合する



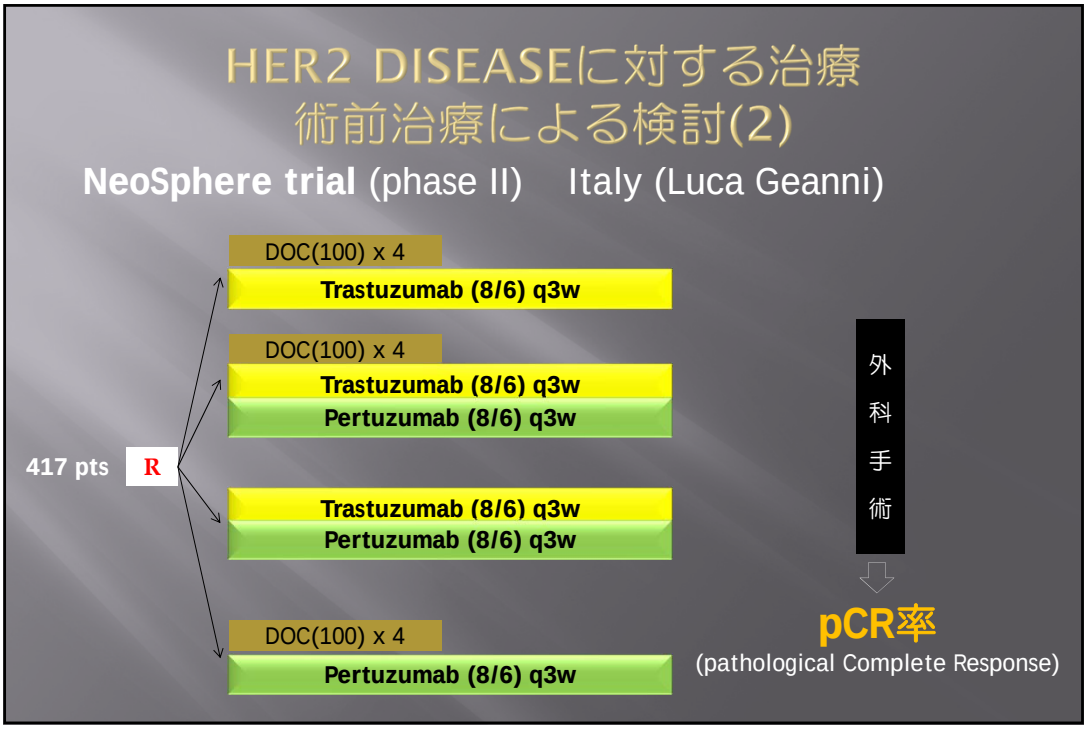
Subdomain IV of HER2

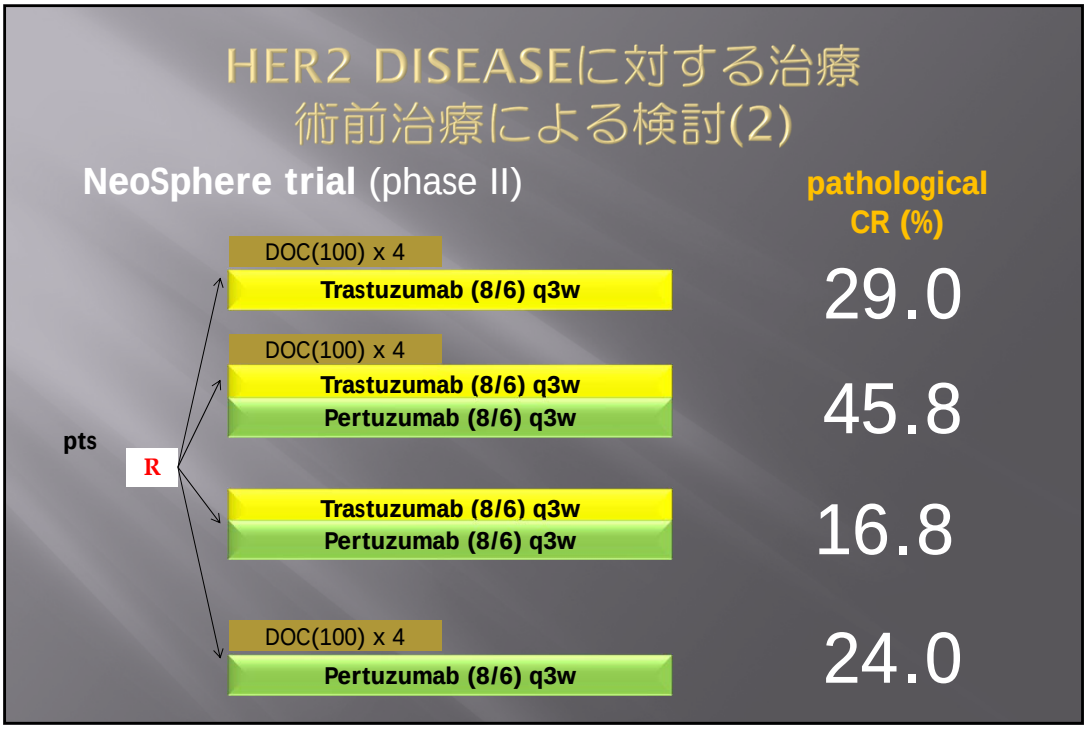
- Trastuzumab disrupts ligand-independent HER2-HER3-PI3K complex
- Trastuzumab prevents HER2 receptor shedding
- Blocks HER2 signaling and flags cells for destruction by the immune system via ADCC

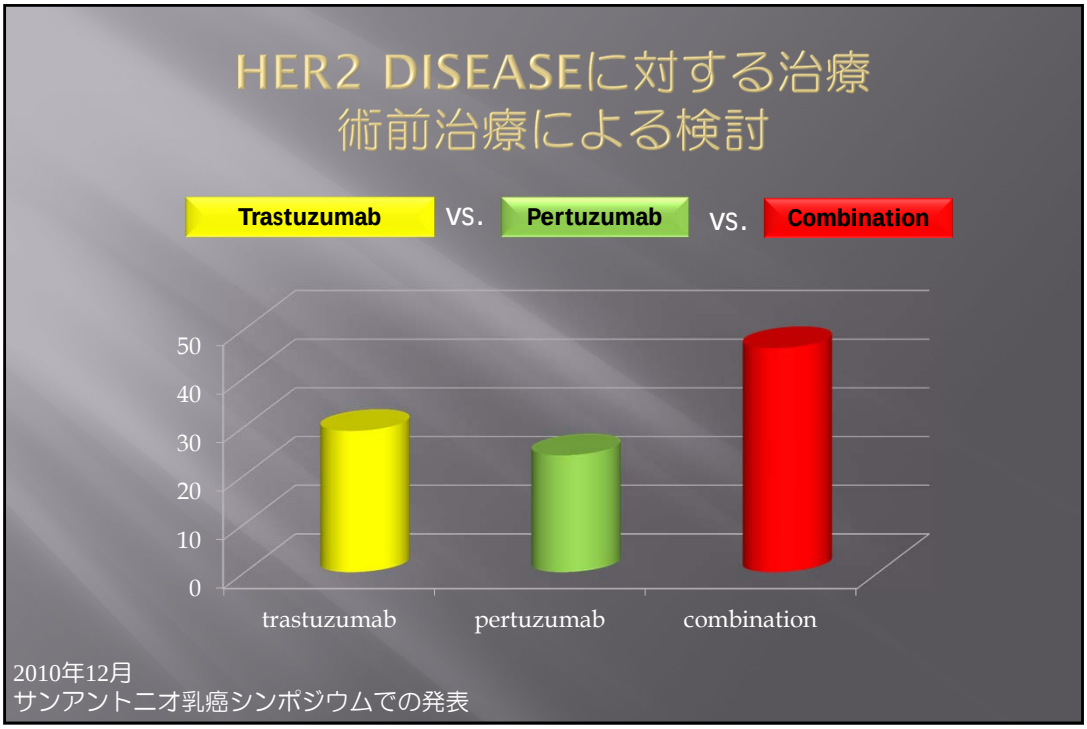
Dimerization domain of HER2

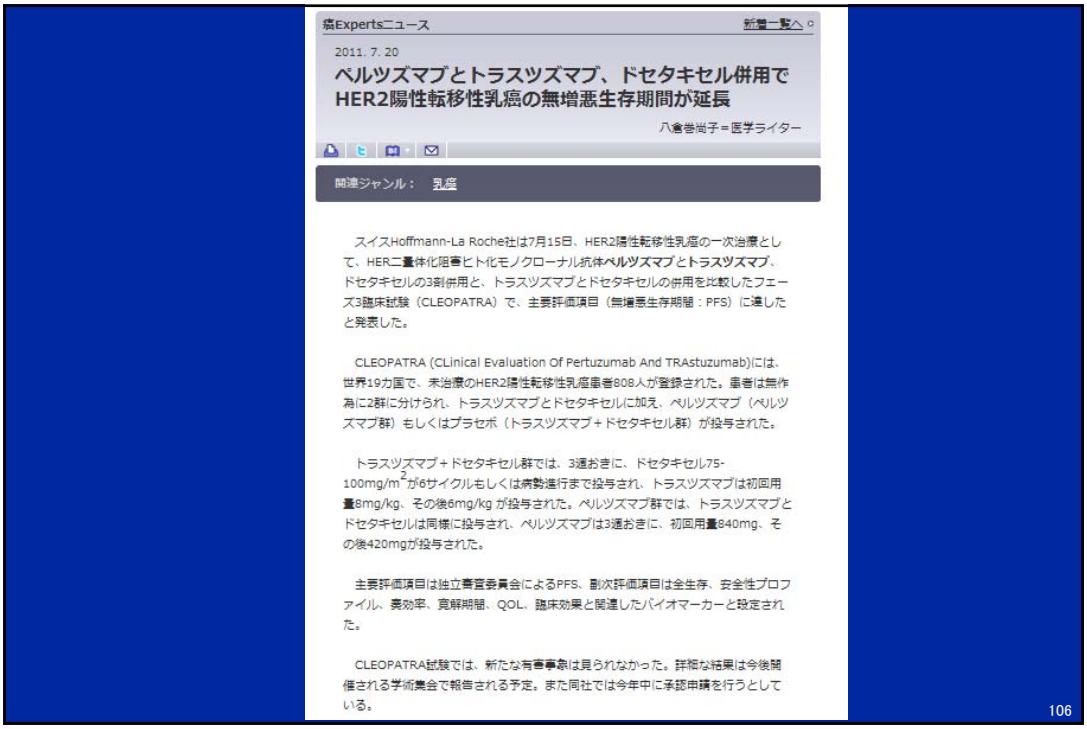
- Pertuzumab prevents ligand-induced HER2:HER3 dimerization
- Pertuzumab does not prevent HER2 receptor shedding
- Flags cells for destruction by the immune system via ADCC

Junttila et al. Cancer Cell. 2009;15:429-440; Hynes et al. Nat Rev Cancer 2005;5:341-354. Rowinsky. Annu Rev Med. 2004;55:433-457


HER2 DISEASEに対する治療
術前治療による検討(2)
NeoSphere trial (phase II)　Italy (Luca Geanni)
417 pts
R
DOC(100) x 4
Trastuzumab (8/6) q3w
DOC(100) x 4
Trastuzumab (8/6) q3w
Pertuzumab (8/6) q3w
Trastuzumab (8/6) q3w
Pertuzumab (8/6) q3w
DOC(100) x 4
Pertuzumab (8/6) q3w
外科手術
pCR率
(pathological Complete Response)


HER2 DISEASEに対する治療
術前治療による検討(2)
NeoSphere trial (phase II)
pts
R
DOC(100) x 4
Trastuzumab (8/6) q3w
DOC(100) x 4
Trastuzumab (8/6) q3w
Pertuzumab (8/6) q3w
Trastuzumab (8/6) q3w
Pertuzumab (8/6) q3w
DOC(100) x 4
Pertuzumab (8/6) q3w
pathological CR (%)
29.0
45.8
16.8
24.0


HER2 DISEASEに対する治療
術前治療による検討
Trastuzumab
vs.
Pertuzumab
vs.
Combination
50
40
30
20
10
0
trastuzumab
pertuzumab
combination
2010年12月
サンアントニオ乳癌シンポジウムでの発表


癌Expertsニュース
新着一覧へ
2011. 7. 20
ペルツズマブとトラスツズマブ、ドセタキセル併用で
HER2陽性転移性乳癌の無増悪生存期間が延長
八倉巻尚子＝医学ライター
関連ジャンル：　乳癌
スイスHoffmann-La Roche社は7月15日、HER2陽性転移性乳癌の一次治療として、HER二量体化阻害ヒト化モノクローナル抗体ペルツズマブとトラスツズマブ、ドセタキセルの3剤併用と、トラスツズマブとドセタキセルの併用を比較したフェーズ3臨床試験（CLEOPATRA）で、主要評価項目（無増悪生存期間：PFS）に達したと発表した。
CLEOPATRA (CLinical Evaluation Of Pertuzumab And TRAstuzumab)には、世界19カ国で、未治療のHER2陽性転移性乳癌患者808人が登録された。患者は無作為に2群に分けられ、トラスツズマブとドセタキセルに加え、ペルツズマブ（ペルツズマブ群）もしくはプラセボ（トラスツズマブ＋ドセタキセル群）が投与された。
トラスツズマブ＋ドセタキセル群では、3週おきに、ドセタキセル75-100mg/m2が6サイクルもしくは病勢進行まで投与され、トラスツズマブは初回用量8mg/kg、その後6mg/kg が投与された。ペルツズマブ群では、トラスツズマブとドセタキセルは同様に投与され、ペルツズマブは3週おきに、初回用量840mg、その後420mgが投与された。
主要評価項目は独立審査委員会によるPFS、副次評価項目は全生存、安全性プロファイル、奏効率、寛解期間、QOL、臨床効果と関連したバイオマーカーと設定された。
CLEOPATRA試験では、新たな有害事象は見られなかった。詳細な結果は今後開催される学術集会で報告される予定。また同社では今年中に承認申請を行うとしている。
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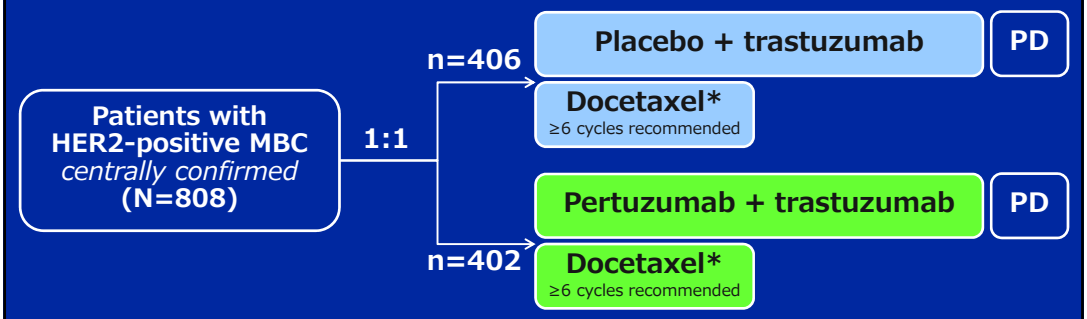
SABCS 2011

A Phase III, Randomized, Double-Blind, Placebo-Controlled Registration Trial to Evaluate the Efficacy and Safety of Placebo + Trastuzumab + Docetaxel vs. Pertuzumab + Trastuzumab + Docetaxel in Patients with Previously Untreated HER2-Positive Metastatic Breast Cancer (CLEOPATRA)

J Baselga, J Cortés, S-B Kim, S-A Im, R Hegg, Y-H Im, L Roman, J L Pedrini, T Pienkowski, A Knott, E Clark, M C. Benyunes, G Ross, and S M Swain

1. Baselga *et al. N Engl J Med* 2011

Study design



- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m², escalating to 100 mg/m² if tolerated

*<6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion

MBC, metastatic breast cancer; PD, progressive disease

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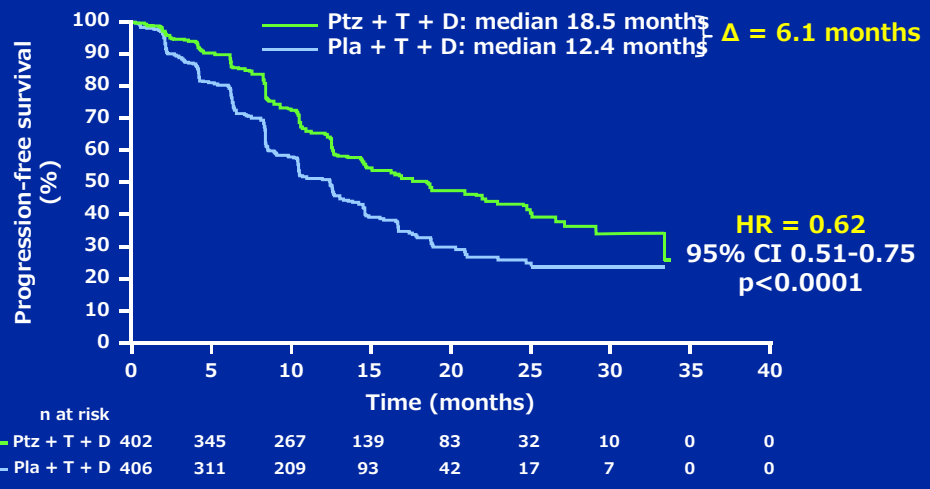
Primary endpoint: Independently assessed PFS

Median follow-up: 19.3 months



n at risk									
Ptz + T + D	402	345	267	139	83	32	10	0	0
Pla + T + D	406	311	209	93	42	17	7	0	0

D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Stratified by prior treatment status and region

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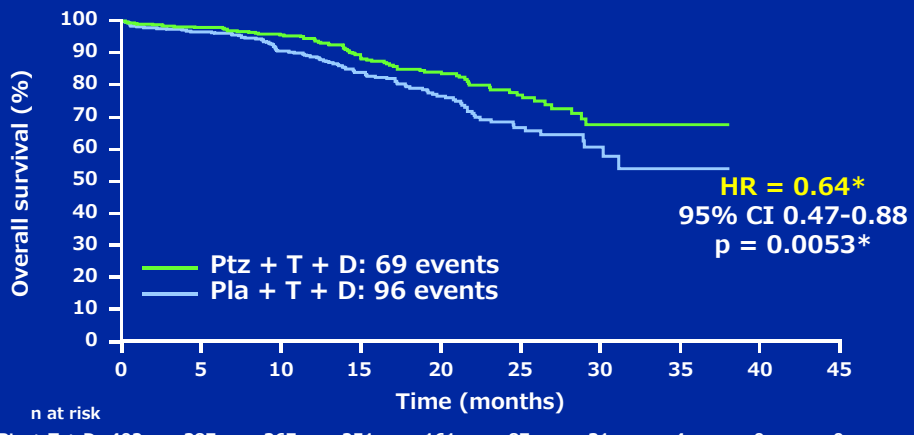
Overall survival: Pre-defined interim analysis

Median follow-up: 19.3 months, n = 165 OS events



n at risk										
Ptz + T + D	402	387	367	251	161	87	31	4	0	0
Pla + T + D	406	383	347	228	143	67	24	2	0	0

* The interim overall survival analysis did not cross the pre-specified O'Brien-Fleming stopping boundary (HR ≤0.603; p≤0.0012)

D, docetaxel; OS, overall survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

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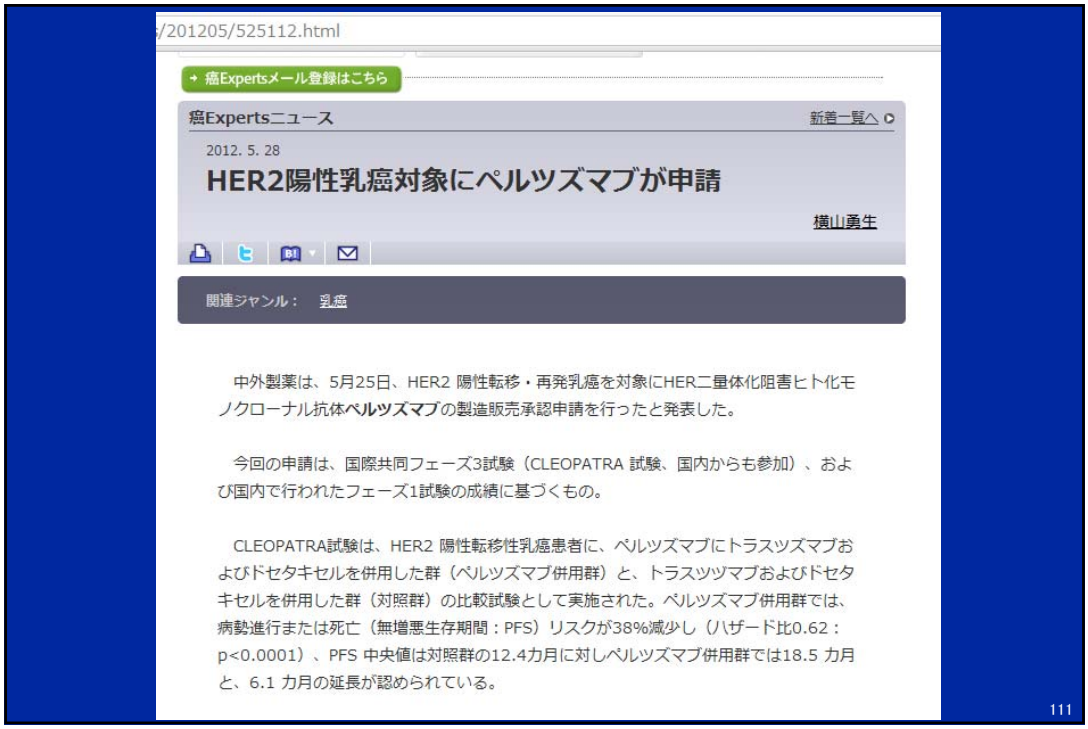
/201205/525112.html
癌Expertsメール登録はこちら
癌Expertsニュース
新着一覧へ
2012. 5. 28
HER2陽性乳癌対象にペルツズマブが申請
横山勇生
関連ジャンル：　乳癌
中外製薬は、5月25日、HER2 陽性転移・再発乳癌を対象にHER二量体化阻害ヒト化モノクローナル抗体ペルツズマブの製造販売承認申請を行ったと発表した。
今回の申請は、国際共同フェーズ3試験（CLEOPATRA 試験、国内からも参加）、および国内で行われたフェーズ1試験の成績に基づくもの。
CLEOPATRA試験は、HER2 陽性転移性乳癌患者に、ペルツズマブにトラスツズマブおよびドセタキセルを併用した群（ペルツズマブ併用群）と、トラスツズマブおよびドセタキセルを併用した群（対照群）の比較試験として実施された。ペルツズマブ併用群では、病勢進行または死亡（無増悪生存期間：PFS）リスクが38%減少し（ハザード比0.62：p<0.0001）、PFS 中央値は対照群の12.4カ月に対しペルツズマブ併用群では18.5 カ月と、6.1 カ月の延長が認められている。
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