第7回たちてんwebかんふぁ
14 May 2009

症例呈示
～HER2陽性乳癌の治療戦略～

浜松オンコロジーセンター
乳腺科 田原 梨絵

～前医での初期治療～

【症例】51歳 閉経後
【術前診断】右cT2N0M0 stageⅡA
【手術】2000/2/28 右乳房全摘術+腋窩手術
【病理】IDC(solid-tub) t 不明 n0
NG3 ER- PgR- HER2(3+) ly+ v-
【術後治療】
2000/4 UFT(N-SAS-BC 01)→薬剤性肝障害
2000/11 AC
→発熱、倦怠感、食欲不振にて2サイクルで中止
以降、経過観察のみ

～前医での再発治療～

【再発診断】2002年3月右鎖骨上リンパ節転移
【DFI】2年
【再発治療】
2002/4　PTX
2002/5　Herceptin→infusion reaction出現にて中止
→PTX単独治療にてCR
2003/4　右鎖骨上放射線照射（50Gy）
→右鎖骨下リンパ節転移が出現
2003/9　PTX再開＋high dose TOR→肝機能障害にてTOR中止
2004/5　Herceptin再導入→infusion reaction出現し中止
→腫瘍マーカー上昇
2004/12　CPT-11→PD
2005/3　DTX 1 回のみ施行
2005/3　右鎖骨下　放射線照射（40Gy）
2005/5　右鎖骨上リンパ節腫大
→***当院セカンドオピニオンへ***

～当院での治療方針～

- ハーセプチンによるinfusion reaction
- いろいろな薬剤による肝機能障害

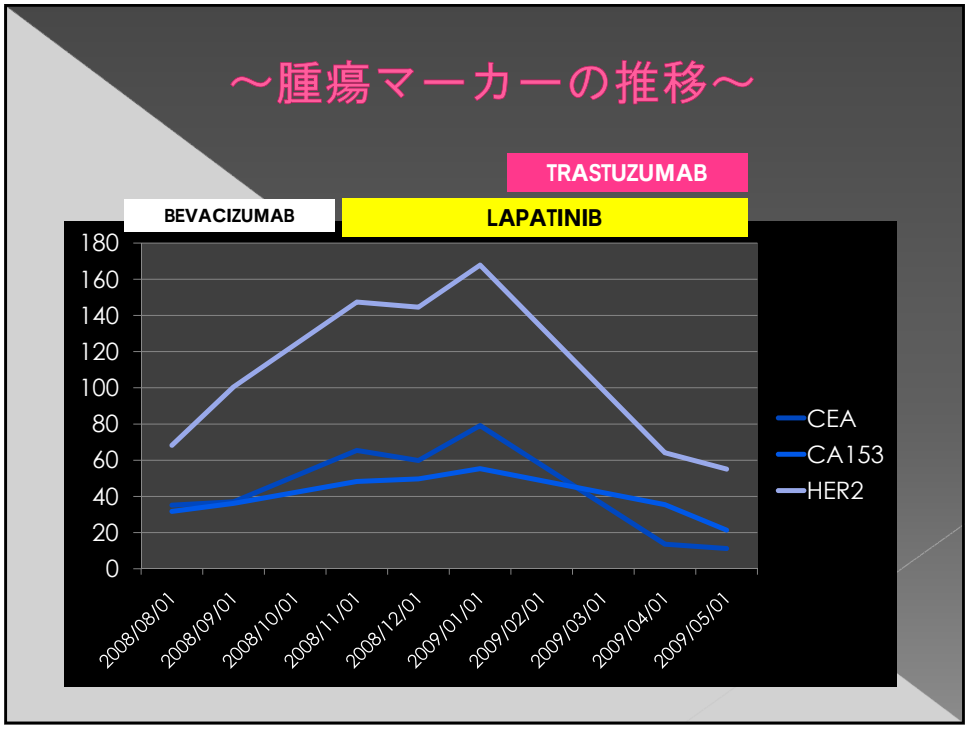
どうにか工夫してハーセプチン治療を開始したい！
2005/8
前投薬（デカドロン16mg）使用にて施行
→発熱が出現したが完遂できた

～当院での治療経過～

2005/8　Her（２回目まで前投薬使用）
→腫瘍マーカー上昇
2006/4　Her+VNR　→腫瘍マーカーは低下したが
副作用出現にて３コース後にHer単独へ
2006/6　Her　→腫瘍マーカー上昇、鎖骨下リンパ節腫大
2006/10　Her+VNR　→前回と同様の副作用出現
2007/1　Her単独　→鎖骨上下リンパ節増大
2007/4　GEM　→腫瘍マーカー上昇
2007/6　Her＋Xeloda　→腫瘍マーカー上昇
2008/2　CMF 1クール　→腫瘍マーカー上昇
2008/4　Her　→腫瘍マーカー上昇
2008/7　AVASTIN　→多発肺転移出現
2008/11　Lapatinib　→腫瘍マーカー上昇
2009/2　Lapatinib + Her

～Lapatinib～

2008/11/20　ラパチニブ１日３錠内服開始
→皮疹の出現あり、下痢は認めず
2009/2/13　ハーセプチン併用開始、１日５錠へ増量
2009/2/14　発熱・悪寒にて連携病院へ入院
2009/2/21　激しい下痢(Grade3)が出現
2009/2/28　ラパチニブ中止
2009/3/3　下痢が止まる
2009/3/10　ラパチニブ１日３錠内服再開
その後はラパチニブ１日３錠内服、下痢が出現したら中止、下痢が改善したら内服再開という方針へ
→最終的に
３～４日内服→下痢→３～４日休薬→下痢改善→内服再開
というサイクルで内服を継続した




A Randomized Study of Lapatinib (Tykerb/Tyverb®) in Combination with Trastuzumab versus Lapatinib Monotherapy in Heavily Pretreated HER2+ Metastatic Breast Cancer Patients Progressing on Trastuzumab Therapy

J. O'Shaughnessy[1], K. Blackwell[2], H. Burstein[3], AM. Storniolo[4], G. Sledge[4], S. Vukelja[5] J. Baselga[6], M. Koehler[7], S. Laabs[7], A. Florance[7], D. Roychowdhury[7]

[1]Baylor Sammons Cancer Center, [5]Texas Oncology, PA, US Oncology, Dallas, TX; [2]Duke University Medical Center, Durham, NC; [3]Dana-Farber Cancer Institute, Boston, MA; [4]I.U. Simon Cancer Center, Indianapolis, IN; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]Medicine Development Center Oncology, GlaxoSmithKline, Collegeville, PA

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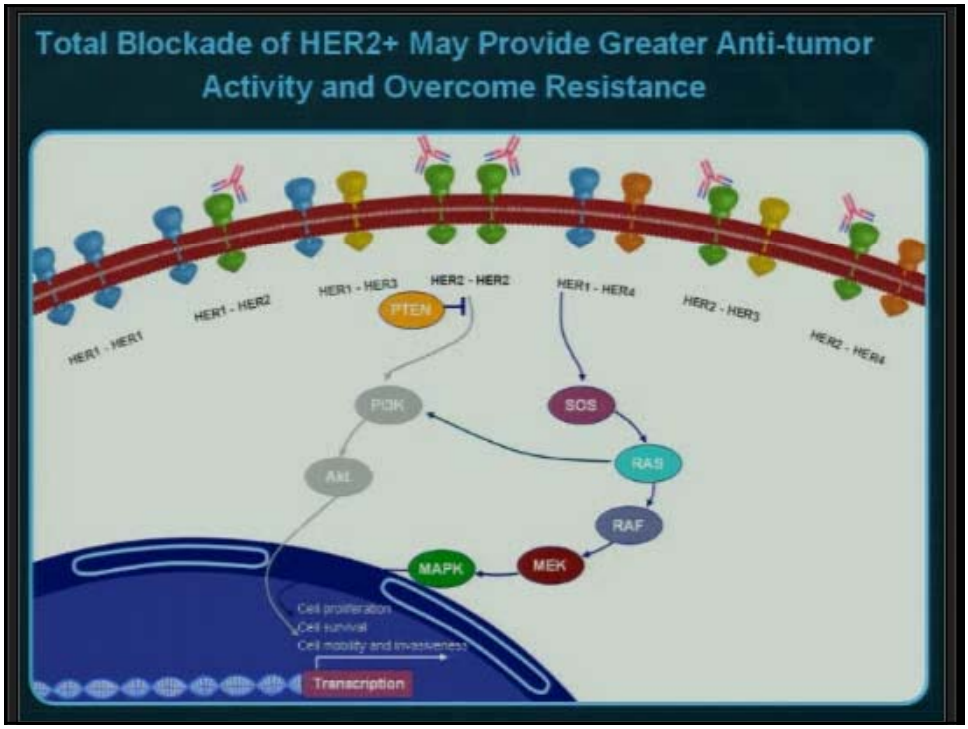
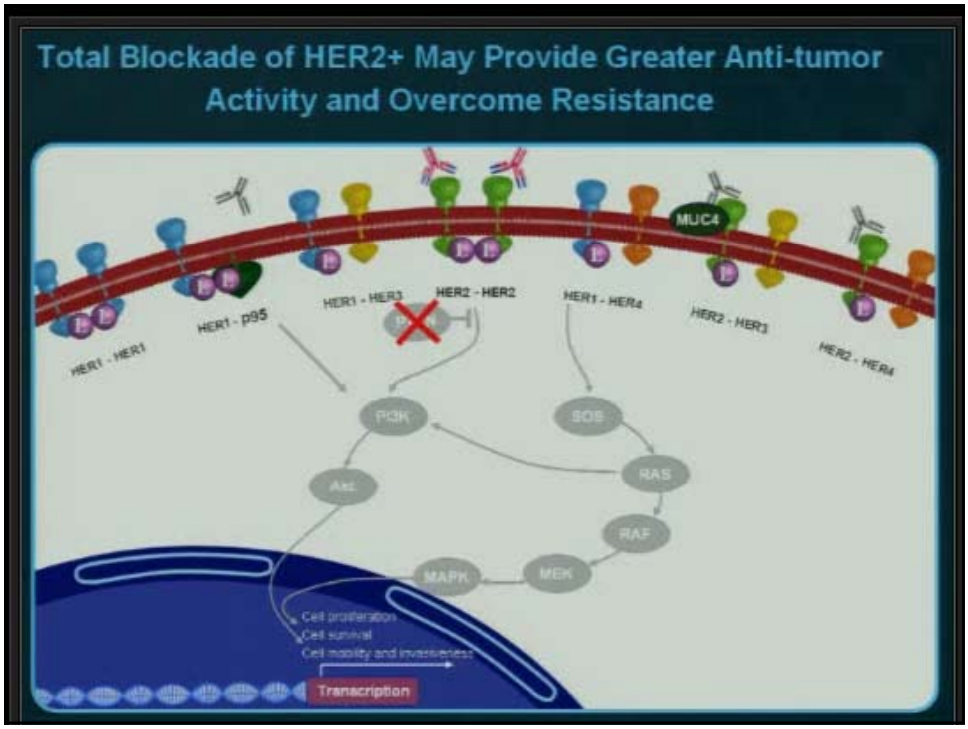
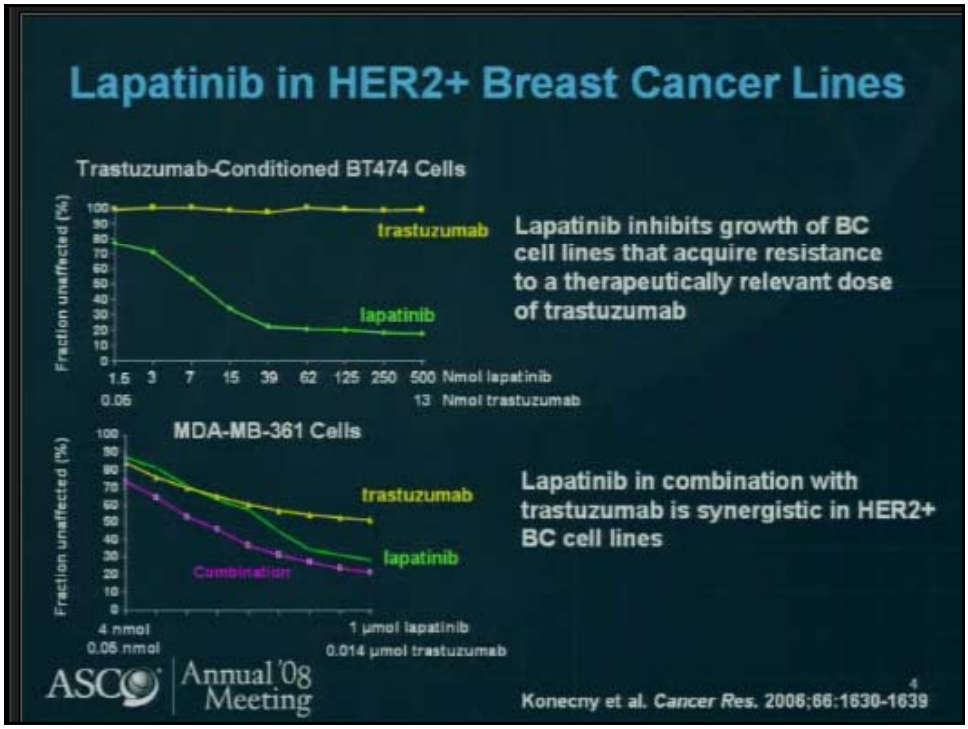

Total Blockade of HER2+ May Provide Greater Anti-tumor Activity and Overcome Resistance
HER1 - HER1
HER1 - HER2
HER1 - HER3
HER2 - HER2
PTEN
HER1 - HER4
HER2 - HER3
HER2 - HER4
PI3K
SOS
RAS
AKT
RAF
MEK
MAPK
Cell proliferation
Cell survival
Cell mobility and invasiveness
Transcription


Total Blockade of HER2+ May Provide Greater Anti-tumor Activity and Overcome Resistance
MUC4
HER1 - HER1
HER1 - p95
HER1 - HER3
HER2 - HER2
HER1 - HER4
HER2 - HER3
HER2 - HER4
PI3K
SOS
RAS
Akt
RAF
MEK
MAPK
Cell proliferation
Cell survival
Cell mobility and invasiveness
Transcription


Lapatinib in HER2+ Breast Cancer Lines
Trastuzumab-Conditioned BT474 Cells
Fraction unaffected (%)
trastuzumab
lapatinib
1.5 3 7 15 39 62 125 250 500 Nmol lapatinib
0.05 13 Nmol trastuzumab
Lapatinib inhibits growth of BC cell lines that acquire resistance to a therapeutically relevant dose of trastuzumab
MDA-MB-361 Cells
Fraction unaffected (%)
trastuzumab
lapatinib
Combination
4 nmol 1 µmol lapatinib
0.05 nmol 0.014 µmol trastuzumab
Lapatinib in combination with trastuzumab is synergistic in HER2+ BC cell lines
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Konecny et al. Cancer Res. 2006;66:1630-1639

Lapatinib has Monotherapy Activity in Metastatic Breast Cancer

Population	Response	Reference
1st-Line Trastuzumab Naïve	ORR ≈ 24% RR* ≈ 28%	Gomez et al, *JCO* 2008 Slamon et al, ASCO 2008
Trastuzumab Pretreated (IBC)	ORR ≈ 40%	Johnston et al, *JCO* 2008
Heavily Pretreated HER2+ MBC	ORR ≈ 2-24%	Blackwell et al, ASCO 2005 Iwata et al, SABCS 2006

*12 wk response rate includes confirmed and unconfirmed responses

- Single-agent activity supports the use of lapatinib as a comparator
- Trastuzumab monotherapy in patients whose tumors recently progressed on trastuzumab is not feasible in clinical studies

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Phase III Study to Test if Total HER2+ Blockade Improves Clinical Outcome

Key Inclusion
- HER2+(FISH+/ IHC3+) MBC
- Progression on
  - Anthracycline
  - Taxane
  - Trastuzumab
- Progression on most recent trastuzumab regimen

Stratification Factors
- Visceral Disease
- Hormone Receptor

RANDOMIZATION

Lapatinib 1500 mg/day PO
N=148

Crossover if PD after 4wk therapy (N=73)

Lapatinib 1000 mg/day PO
Trastuzumab 4→2 mg/kg IV qw
N=148

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Study conducted and funded by GlaxoSmithKline

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Study EGF104900

- **Primary Endpoint:**
  - PFS in ITT population by Investigator
- **Secondary Endpoints:**
  - Overall survival; overall response rate; clinical benefit rate; duration of response; time to response; safety; quality of life
- **Patient Accrual by Region:**
  - North America (62.5%)
  - Europe (37.5%)
- **Accrual:**
  - November 17, 2005 → November 21, 2006

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Patient and Tumor Characteristics

Study Arms ITT Population	L N = 148	L+T N = 148
Median Age, Yrs. (range)	51 (29-78)	52 (26-81)
% ECOG performance status 0/1/2	47/49/4	54/41/5
Median Prior Chemotherapy Regimens	4	5
%Patients ≥ 6 Prior Regimens	28	34
Median Prior Trastuzumab Regimens for MBC	3	3
Median Time from Last Trastuzumab, days	25	27
# Patients HER2+	146	147
% ER and PgR Negative	51	51
% Visceral Disease	74	71

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Adverse Events - All Grades (% Patients)

Adverse Event (Incidence ≥10%)	Lapatinib N=146*	Lapatinib + Trastuzumab N=149
Diarrhea†	48	60
Grade 3 or 4	7	7
Rash	29	22
Nausea	28	28
Fatigue	19	21
Vomiting	18	14
Dyspnea	10	12
Anorexia	10	11
Headache	9	10
Cough	10	5

*Excludes events occurring during the crossover phase
†p=0.03; significant difference between randomized treatment arms

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Cardiac Events

	Lapatinib N=146	Lapatinib + Trastuzumab N=149
Total # patients with event[1]	5	8
- Symptomatic	1	2
Related to therapy	3	8
Resolved by data cut-off[2]	4	5
Fatal[3]	0	1

[1]Two patients had >1 occurrence
[2]Three patients recovered while remaining on treatment
[3]Cardiac failure; cause of death: pulmonary thromboembolism

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Treatment Efficacy

	L N=145	L + T N=146
Response Rate, %* (95% CI)	6.9 (3.4, 12.3)	10.3 (5.9, 16.4)
Odds Ratio (95% CI)	1.5 (0.6, 3.9) p=0.46	
Clinical Benefit Rate, %† (95% CI)	12.4 (7.5, 18.9)	24.7 (17.9, 32.5)
Odds Ratio (95% CI)	2.2 (1.2, 4.5) p=0.01	

*Confirmed CR+PR
†CR+PR+SD ≥ 6 mo

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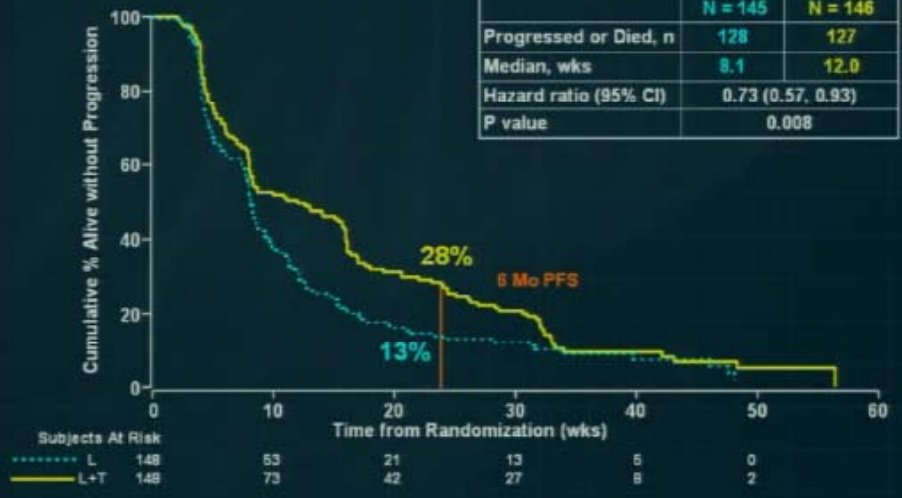
Progression-Free Survival

	L N = 145	L+T N = 146
Progressed or Died, n	128	127
Median, wks	8.1	12.0
Hazard ratio (95% CI)	0.73 (0.57, 0.93)	
P value	0.008	



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Factors Influencing PFS: Multivariate Cox Regression Analysis

	Effect Tested	Hazard Ratio	P-value
Treatment	Combination Therapy vs. Monotherapy	0.72 (0.56, 0.92)	0.0095
ECOG PS	0/≥1	0.63 (0.48,0.81)	0.0005
Liver Metastasis	No/Yes	0.72 (0.56, 0.94)	0.02
# Metastatic Sites	<3/≥3	0.73 (0.56,0.95)	0.02

[1]Time from last trastuzumab, as a continuous variable, was not a significant factor

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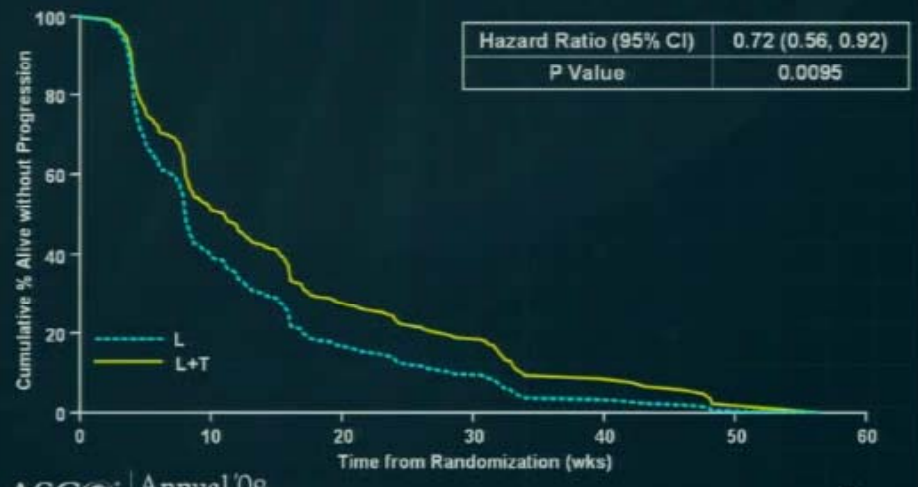
PFS Adjusted for Performance Status and Extent of Disease*



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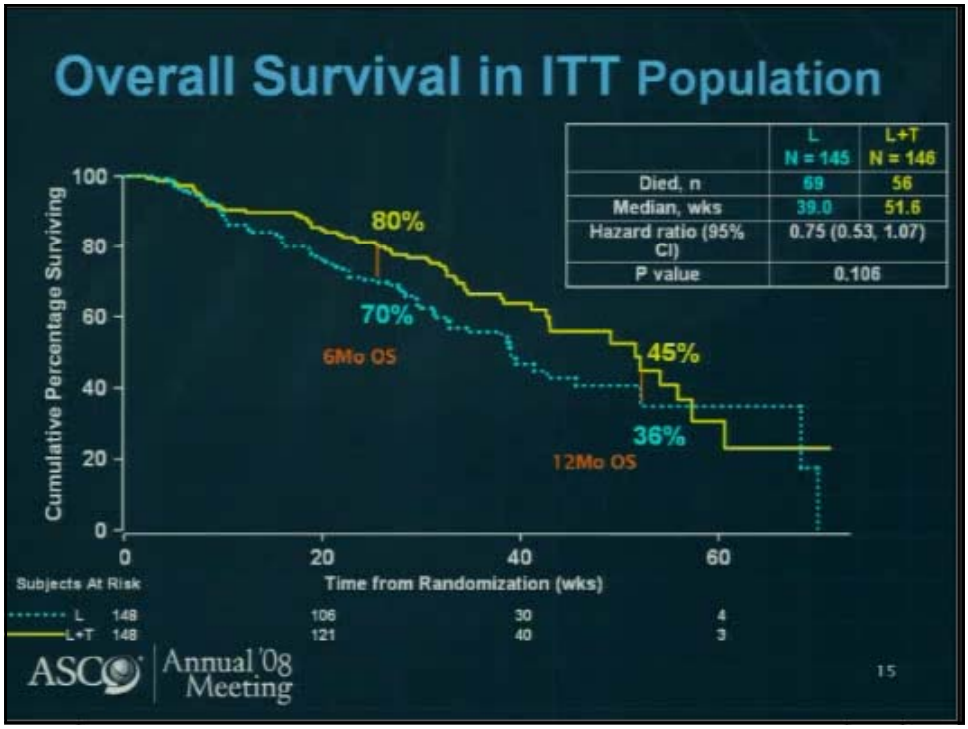
*Significant baseline covariates


Overall Survival in ITT Population
L N = 145
L+T N = 146
Died, n 69 56
Median, wks 39.0 51.6
Hazard ratio (95% CI) 0.75 (0.53, 1.07)
P value 0.106
Cumulative Percentage Surviving
100
80
60
40
20
0
80%
70%
6Mo OS
45%
36%
12Mo OS
0
20
40
60
Time from Randomization (wks)
Subjects At Risk
L 148 106 30 4
L+T 148 121 40 3
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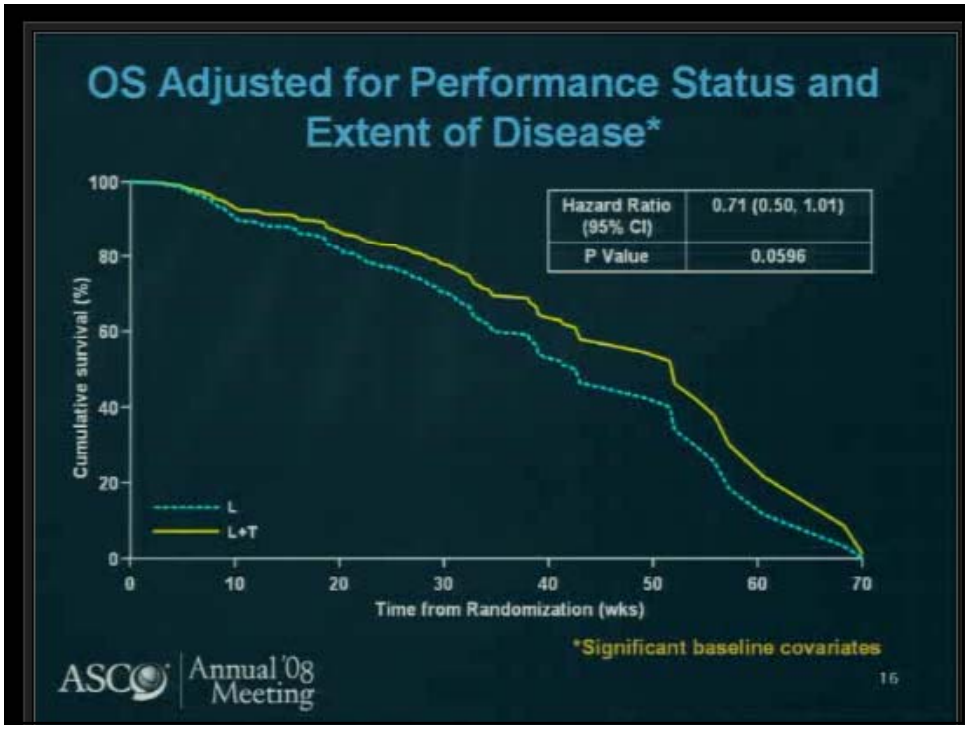
OS Adjusted for Performance Status and Extent of Disease*
Hazard Ratio (95% CI) 0.71 (0.50, 1.01)
P Value 0.0596
Cumulative survival (%)
100
80
60
40
20
0
L
L+T
0
10
20
30
40
50
60
70
Time from Randomization (wks)
*Significant baseline covariates
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Summary

- Lapatinib in combination with trastuzumab is an effective treatment for HER2+ MBC progressing on or after trastuzumab
  - Confirms preclinical synergy
- Treatment with this combination:
  - Significantly improves PFS (p=0.008)
  - Doubles clinical benefit rate (to 25%)
  - Trend in improved overall survival (p=0.106)
- Study confirms activity of single agent lapatinib (CBR 12.4%), despite several prior trastuzumab regimens
- The combination has a predictable & manageable toxicity profile

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Conclusions and Perspective

- First Phase III study confirming that more complete HER2 pathway blockade with different anti-HER2 agents improves patient outcomes
- Study met its primary endpoint: 27% reduction in risk of progression despite prior treatment with multiple trastuzumab regimens
- Findings reinforce the need to evaluate this combination in earlier MBC and support the ongoing adjuvant study (ALTTO)
- Total HER2 blockade with lapatinib and trastuzumab may provide a chemotherapy-free option for HER2+ MBC patients

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