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40 YEAR ANNIVERSARY SAN ANTONIO BREAST CANCER SYMPOSIUM®

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Updates in the Treatment of HER2+ Disease

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Financial Disclosure

SARA A. HURVITZ, MD, FACP

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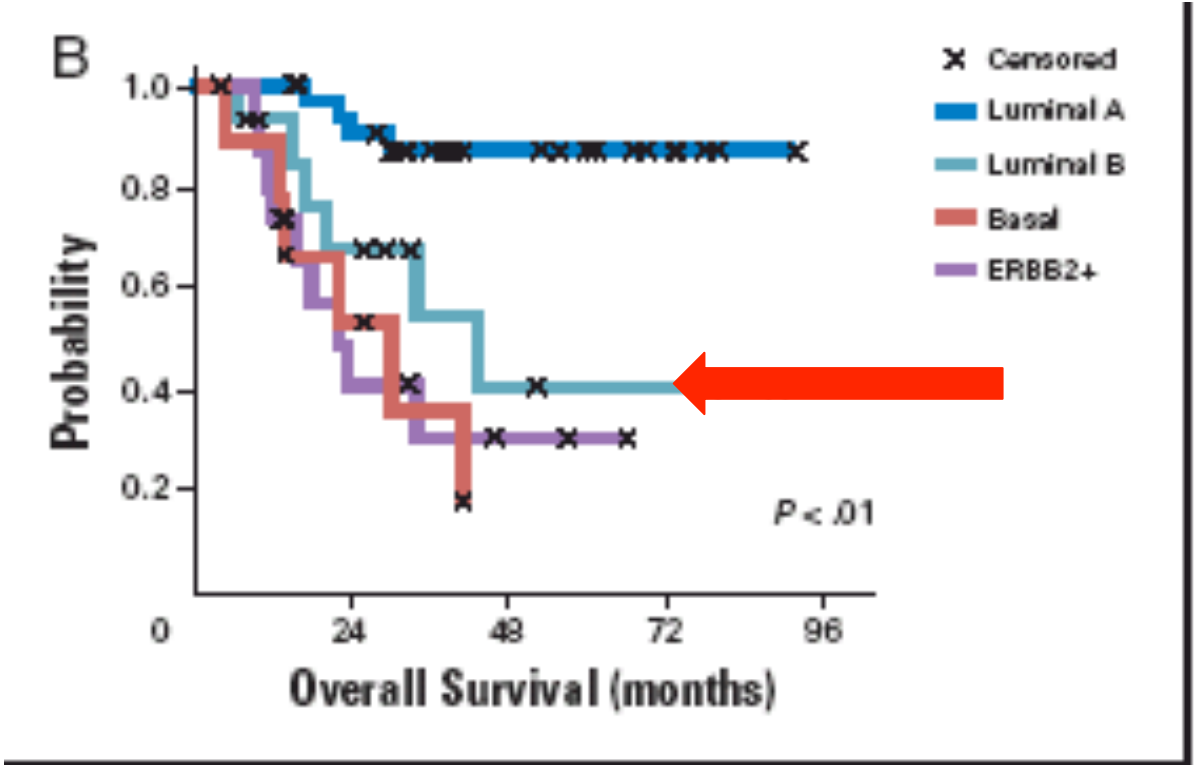
Stock/Shareholder:	**No disclosures**
Employee:	**No disclosures**

Overview

- Targeting HER2 in the absence of the target: NSABP B-47
- Ideal length of adjuvant trastuzumab: SOLD
- Can we mitigate GI tox with adjuvant neratinib: CONTROL
- Biosimilar trastuzumab: ABP-980
- Novel therapies on the horizon
  - DS-8201
  - Pyrotinib
  - Tucatinib
- What do we do on Monday morning? A paradigm for treating early and late stage disease

Trastuzumab has altered the natural history of HER2+ early stage disease

Poor Prognosis HER2+ Disease (*without* trastuzumab)



Overall Survival for HER2+ trastuzumab-treated early disease

Study	Median F/U	HER2+/+tras	HER2+/-tras	HER2 –
BCIRG 005[1]/006[2]	10 years	(1841/2149) **86%**	(870/1073) 81%	(2647/3298) **80%**
NOAH[3]	5 years	(87/117) **74%**	(74/118) 63%	(75/99) **76%**
Italian Registry[4]	4.1 years	(52/53) **98%**	(140/161) 87%	(1108/1186) **93%**
GeparQuattro[5]	5.4 years	(392/446) **88%**		(889/1049) **85%**
FinHer[6]	5 years	(12/115) **90%**	(21/116) 82%	(61/778) **92%**

1. Mackey J et al. Annals Oncol. 2016;27:1041-47. 2. Slamon DJ et al. Cancer Res. 2015;76(4 Suppl):Abstract nr S5-04. 3. Gianni L et al. Lancet Oncol. 2014;15:640-47. 4. Musolino A et al. Cancer. 2011;117:1837-46. 5. Von Minckwitz G et al. Ann Oncol. 2013;25(1):81-89.

Targeting HER2 in the *absence* of the target

NSABP B-47

San Antonio Breast Cancer Symposium, December 5-9, 2017

NSABP B-47 (NRG Oncology)
Phase III RCT Comparing Adjuvant Chemotherapy with AC→Weekly Paclitaxel or TC x 6 with or without Trastuzumab for 1 Year in High-risk, Invasive Breast Cancer Negative for HER2 by ISH and with IHC 1+ or 2+ (HER2-Low IBC)

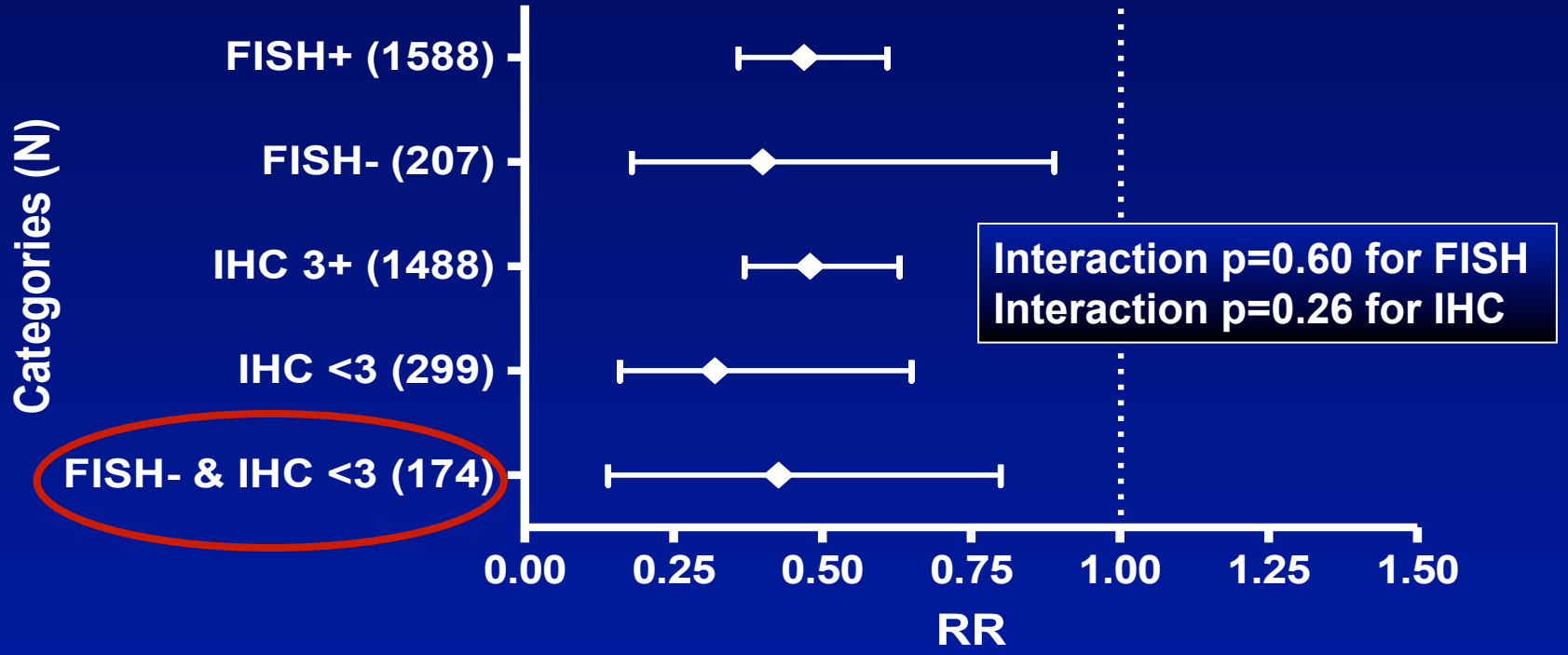
Louis Fehrenbacher, Reena S. Cecchini, Charles E. Geyer, Jr., Priya Rastogi, Joseph P. Costantino, James N. Atkins, John Crown, Jonathan Polikoff, Jean-Francois Boileau, Louise Provencher, Christopher Stokoe, Timothy D. Moore, André Robidoux, Virginia Borges, Kathy S. Albain, Sandra M. Swain, Soonmyung Paik, Eleftherios P. Mamounas, Norman Wolmark

NSABP B-31 Central HER2 Assay Result

	Central HER2 FISH negative	Central IHC negative (0-2+)	Both Negative
Before amendment (any lab)	103/529 **(19.5%)**	122/528 **(23.1%)**	87/529 **(16.4%)**
After amendment (qualified lab)	104/1266 **(8.2%)**	177/1259 **(14.1%)**	87/1266 **(6.8%)**
Total Final	207/1795 **(11.5%)**	299/1787 **(16.7%)**	**174**/1795 **(9.7%)**

GS01-2 Fehrenbacher et al

RR of ACTH/ACT for DFS (NSABP B-31)



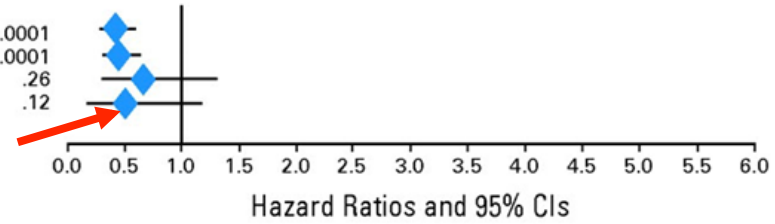
Note: RR adjusted for ER and nodal status

GS01-2 Fehrenbacher et al

N9831 Outcomes by HER2 Status

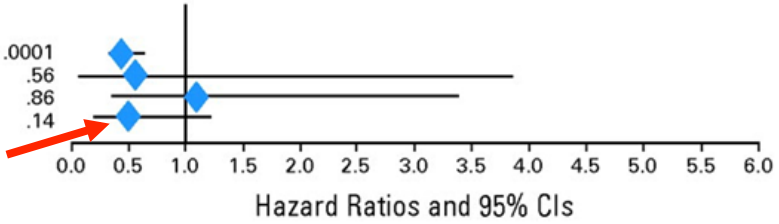
A

Subgroup	n	HR*	95% CI	*P*
IHC or FISH *HER2*/CEP17 RATIO				
IHC 3+	1,512	0.46	0.33 to 0.63	< .0001
FISH ≥ 2.0	1,639	0.49	0.36 to 0.68	< .0001
IHC 0, 1, 2+	333	0.69	0.36 to 1.32	.26
FISH < 2.0	156	0.54	0.25 to 1.17	.12



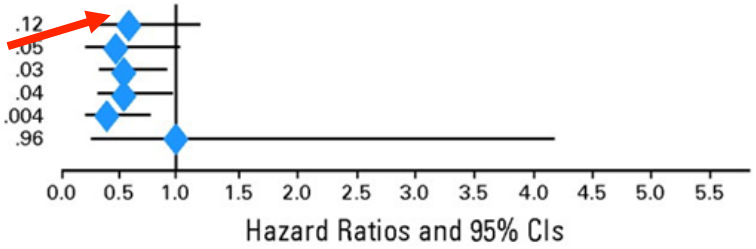
B

IHC/FISH *HER2*/CEP17 RATIO				
3+/ ≥ 2.0	1,408	0.45	0.32 to 0.63	< .0001
3+/ < 2.0	53	0.57	0.08 to 3.89	.56
0,1,2+/ ≥ 2.0	219	1.11	0.36 to 3.43	.86
0,1,2+/ < 2.0	103	0.51	0.21 to 1.23	.14



C

FISH *HER2*/CEP17 RATIO				
< 2.0	156	0.54	0.25 to 1.17	.12
2.0 - 5.0	253	0.42	0.18 to 1.01	.05
5.0 - 8.0	515	0.50	0.27 to 0.92	.03
8.0 - 11.0	473	0.51	0.27 to 0.95	.04
11.0 - 15.0	328	0.35	0.17 to 0.72	.004
≥ 15.0	70	0.96	0.21 to 4.35	.96

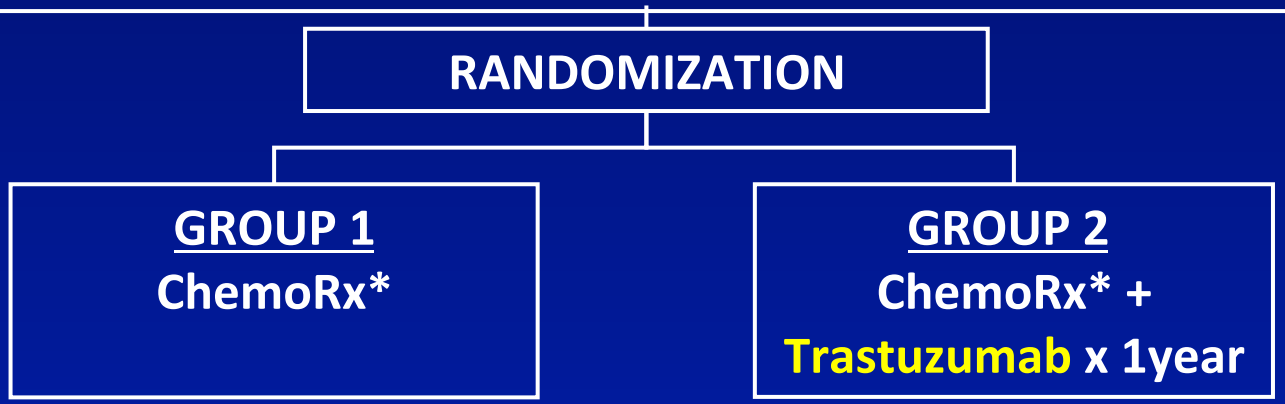


Perez EA, et al. J Clin Oncol. 2010;28:4307-15

B-47: Adjuvant Trastuzumab in HER2 Low Breast Cancer

Eligibility

- High-risk Node Negative (T2 TNBC or T2 ER positive and Grade 3 or RS ≥25)
- Node Positive with T1-3
- IHC must be 1+, or 2+
  - If 2+ then ISH must be negative for gene amplification, with ratio <2.0, and HER2 gene copy of <4 per nucleus.



Hormonal therapy and radiation as indicated. Chemotherapy by MD Choice:

*AC→WP: Doxorubicin 60mg/m2 and Cyclophosphamide 600mg/m2 q2 or 3 wks x 4 followed by qwk paclitaxel x 12

or TC: Docetaxel 75mg/m2 + Cyclophosphamide 600mg/m2 q3wk x 6

GS01-2 Fehrenbacher et al

B-47: Study Population

Primary Endpoint: iDFS

Accrual from Jan 2011 to Feb 2015	50 months
Median follow-up time (months)	46.1 months
Number randomized	3,270
Number without follow-up	63 (1.9%)

B-47: Patient Characteristics

Characteristic	Cohorts	ChemoRx	ChemoRx + Trast
Age at entry (yrs)	≤49 ≥50	41.1% 58.9%	41.9% 58.1%
Race	White Black Other	84.0% 8.8% 7.2%	82.6% 10.7% 6.8%
Number of positive nodes	Negative 1 – 3 4 or more	21.5% 52.4% 26.1%	18.4% 53.0% 28.6%
ER/PgR status	Both Negative ER and/or PgR Positive	17.2% 82.8%	17.3% 82.7%
Intended chemotherapy	AC→WP TC	55.8% 44.2%	55.9% 44.1%
IHC Score	1+ 2+	56.2% 43.8%	57.7% 42.3%

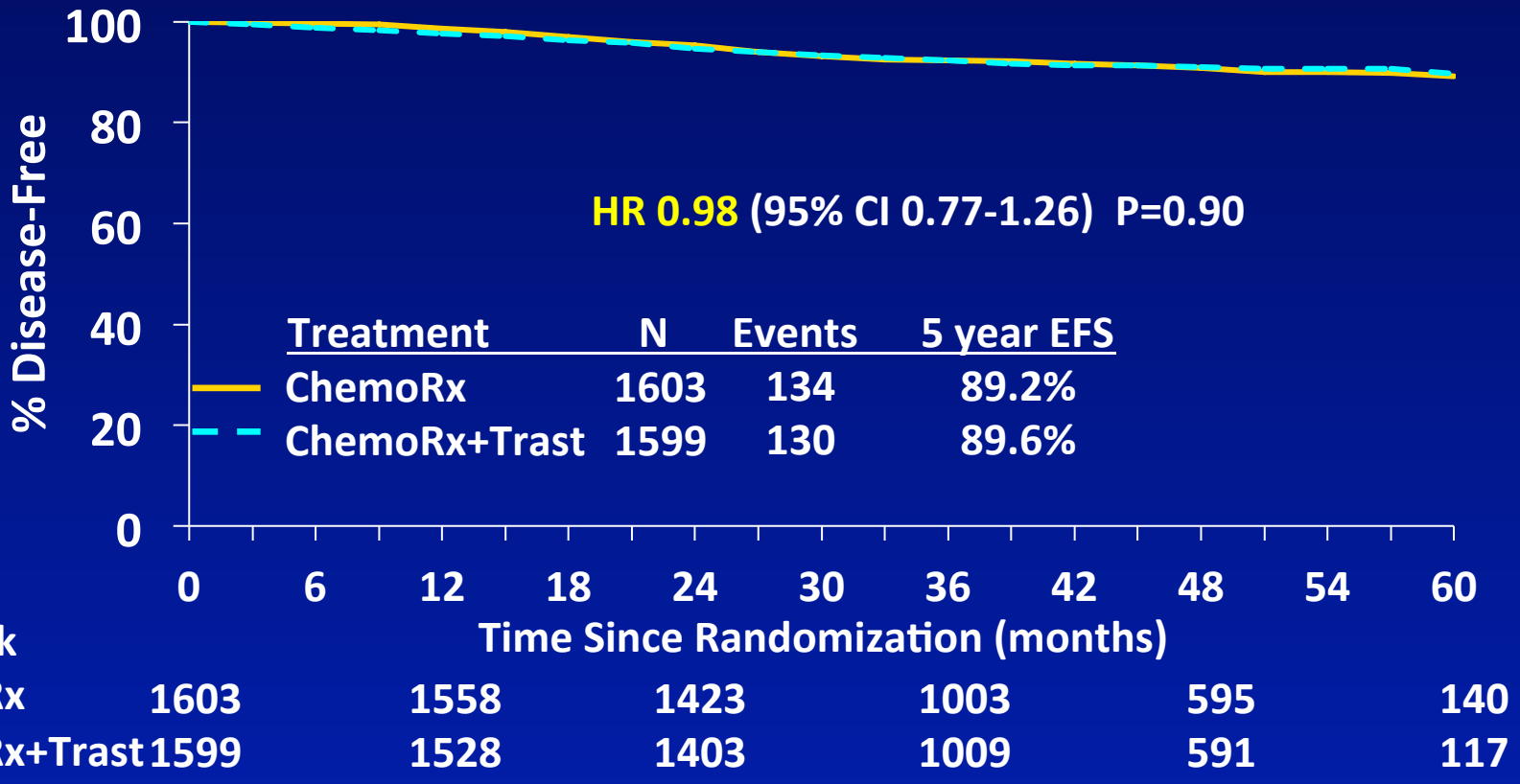
B-47 Severe Toxicities of Interest

Toxicity	ChemoRx	ChemoRx + Trast
Grade 3 CHF	1 (0.1%)	8 (0.5%)
Grade 3 LV Dysfunction	4 (0.2%)	28 (1.7%)
Grade 4, 5 Sepsis	4 (0.2%)	9 (0.6%)
Grade 3, 4 Febrile Neutropenia	66 (4.1%)	74 (4.6%)
Any Grade 4 SAE	66 (4.1%)	75 (4.6%)
Death on Therapy	3 (0.2%)	7 (0.4%)

One CHF death Chemorx(AC-WP+Trast),

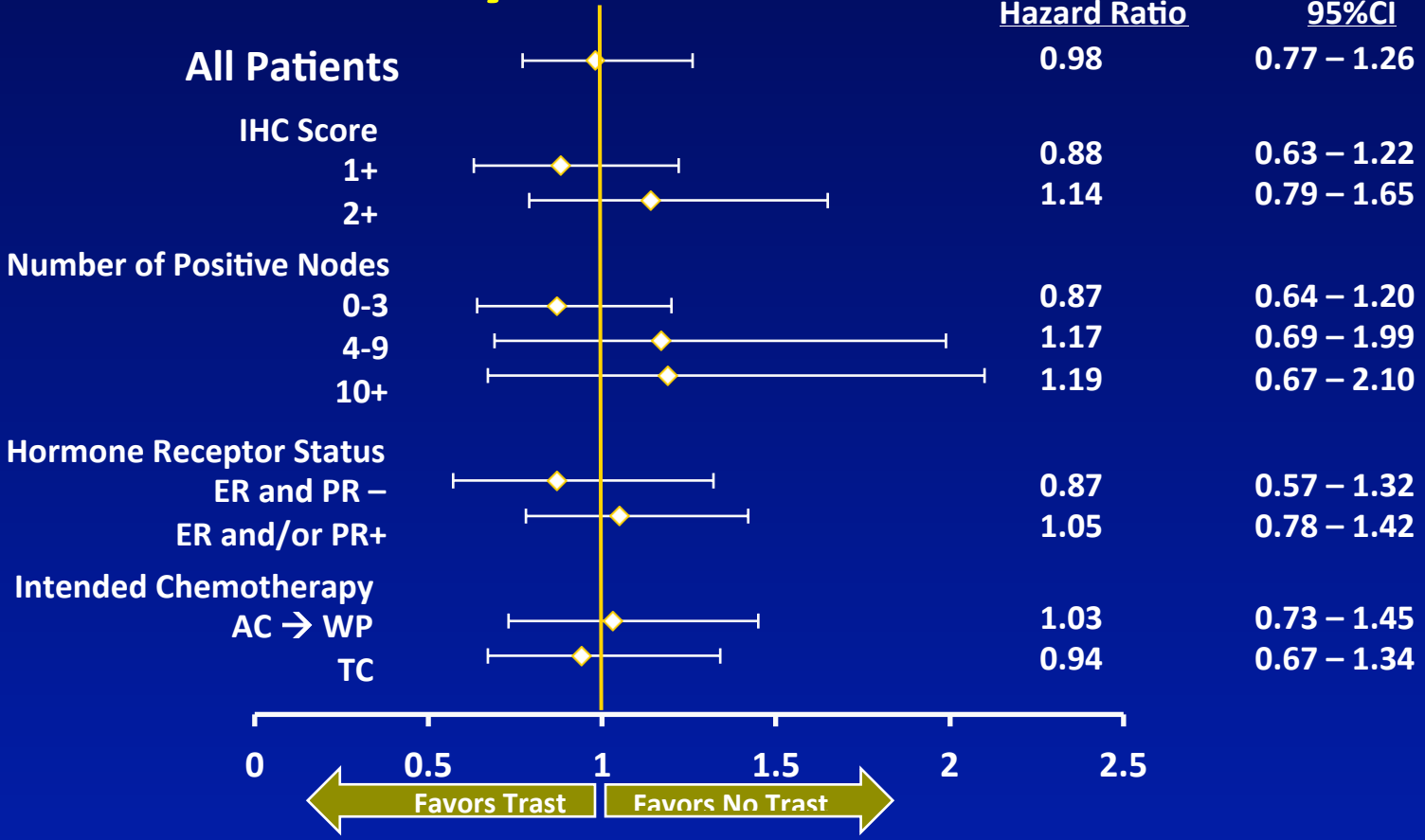
GS01-2 Fehrenbacher et al

B-47: Invasive Disease-Free Survival

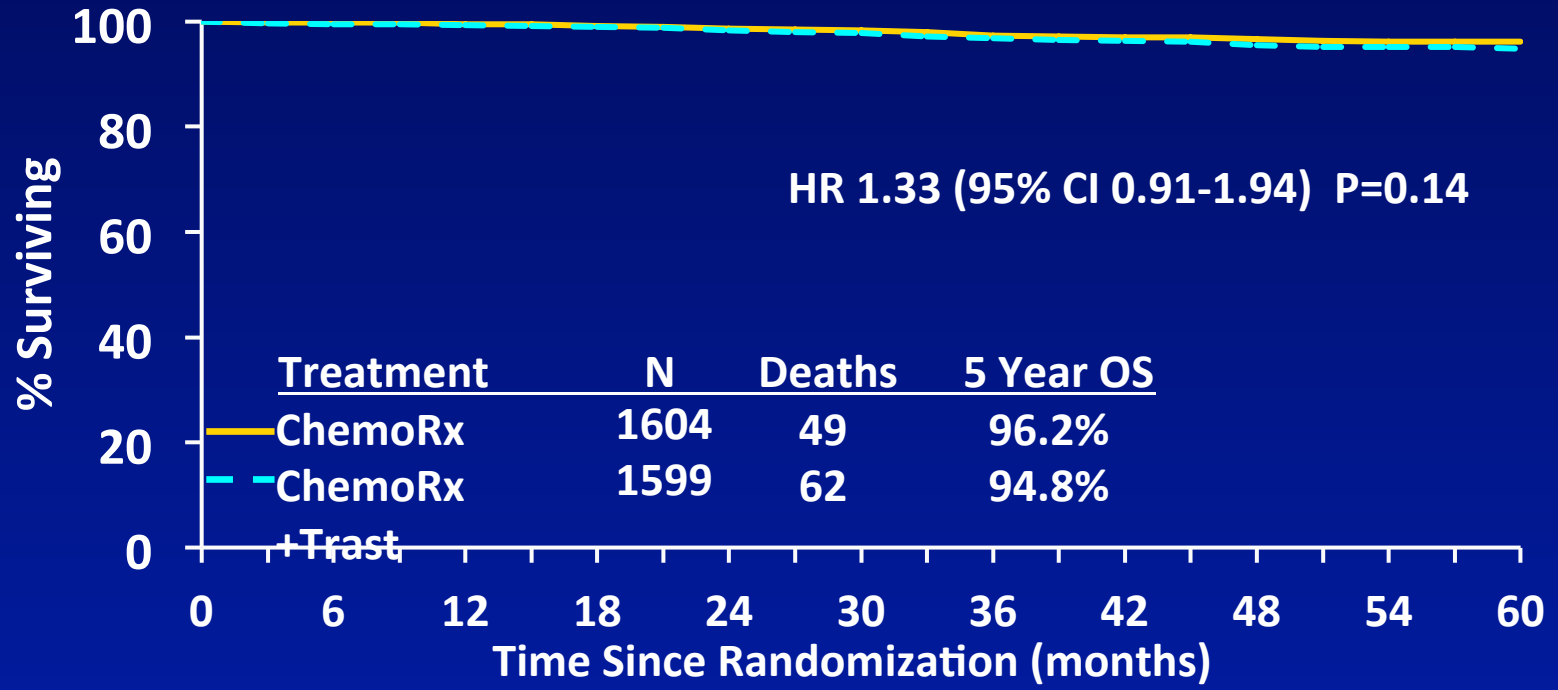


No. at Risk						
ChemoRx	1603	1558	1423	1003	595	140
ChemoRx+Trast	1599	1528	1403	1009	591	117

B-47: IDFS by Stratification Variables



B-47: Overall Survival



No. at Risk

ChemoRx	1604	1577	1507	1099	703	169
ChemoRx+Trast	1599	1563	1497	1113	683	149

Conclusions

- The benefit of trastuzumab in central tested HER2-low patients identified retrospectively from 2 major adjuvant trials that used local testing for eligibility are not readily explained and not confirmed in this study

- There is NO benefit with trastuzumab therapy in patients with FISH ratios <2.0 and IHC staining intensity of 1+ or 2+

Ideal length of adjuvant trastuzumab: Is there still a question?

SOLD

Trials Exploring Shorter Duration Trastuzumab

Trial	Duration	Chemotherapy	Start	Accrual	Status/Results
PHARE	6 vs 12 mos	Investigator Choice (~90% anthracycline-based)	5/2006	3384	Published 2013[1] Non-inferiority not reached, cardiac tox better with shorter
Hellenic Oncology	6 vs 12 mos	ddFEC/D	10/2004	481	Published 2015[2] Non-inferiority not reached
Short-HER	9 wks vs 1 year	A=T vs T+FEC	12/2007	1253	Reported ASCO 2017[3] Non-inferiority not reached, cardiac tox better with shorter
SOLD	9 wks vs 1 year	T+FEC	1/2008	2168	Reported SABCS 2017
Persephone	6 vs 12 mos	Investigator Choice	10/2007	2500	Cardiac outcomes published 2016[4]; awaiting DFS analysis

1. Pivot X et al. Lancet Oncol 2013;14:741-8. 2. Mavroudis D et al. Ann Oncol 2015;26:1333-40 3. Conte PF et al. J Clin Oncol 2017;35(15s):Abs 501. 4. Earl HM et al. Br J Cancer 2016;115:1462-70.

FBCG

San Antonio Breast Cancer Symposium – December 5-9, 2017

BIG
Breast International Group

A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer

The Synergism Or Long Duration (SOLD) trial

H Joensuu, J Fraser, H Wildiers, R Huovinen, P Auvinen, M Utriainen, P Nyandoto, KK Villman, P Halonen, H Granstam-Björneklett, L Lundgren, T Turpeenniemi-Hujanen, J Yachnin, D Ritchie, T Huttunen, R Paridaens, P Canney, VJ Harvey, PL Kellokumpu-Lehtinen, H Lindman

SOLD Hypothesis

- Administration of trastuzumab concomitantly with a taxane for a brief time period is not inferior in terms of DFS as compared with the standard treatment*, and may be less cardiotoxic

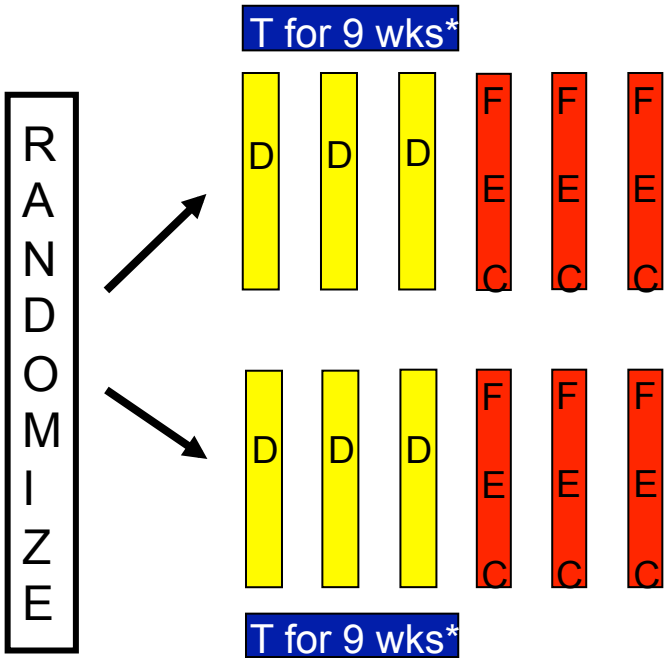
*Standard:
Chemotherapy plus 12 months of anti-HER2-directed treatment ± endocrine therapy

SOLD design

Docetaxel (D)
80/100 mg/m^2
iv 3-wkly

$F_{600}E_{75}C_{600}$
iv 3-wkly

Trastuzumab
(T)



*Wkly iv,
or 3-wkly either iv or sc

In both groups:

- Locoregional RT given according to the institutional practice
- Endocrine therapy for a minimum of 5 yrs when cancer ER/PR +ve

T to complete 1 year of administration**

**14 times 3-weekly, either iv or sc

GS3-04 Joensuu et al

Key Baseline Characteristics

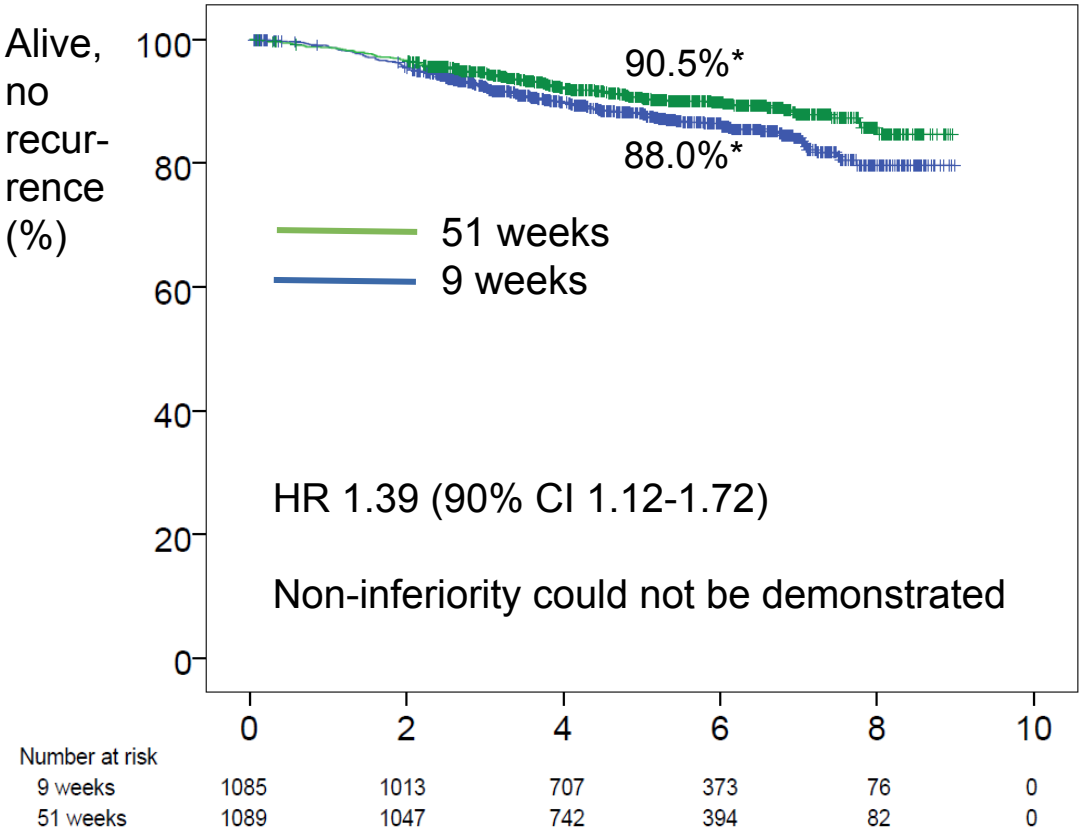
Characteristic	9-week group (n=1,085)	1-year group (n=1,089)
Median age (range) – years (range)	56 (23-82)	56 (27-79)
Premenopausal	33 %	33 %
Breast tumor diameter		
≤10 mm	12 %	14 %
11-21 mm	44 %	42 %
21-50 mm	41 %	42 %
>50 mm	3 %	3 %
Axillary lymph nodes with cancer		
0	60 %	60 %
1-3	30 %	29 %
>3	11 %	11 %
Ductal histological type	92 %	92 %
Estrogen receptor-positive	66 %	66 %
Progesterone receptor-positive	46 %	47 %

DFS Events (ITT) (Median f/u 5.2 years)

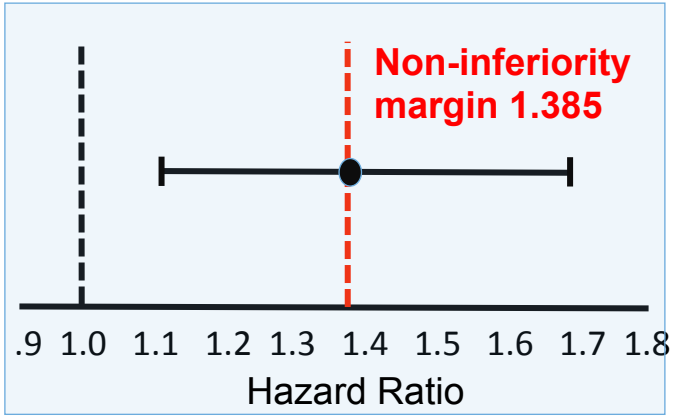
Event	9-wk group (n=1,085) n (%)	1-yr group (n=1,089) n (%)	
Any recurrence or death	140 (13)	105 (10)	
Distant recurrence	73 (7)	61 (6)	
Locoregional recurrence	17 (2)	13 (1)	
Contralateral BC	15 (1)	7 (1)	
Second cancer	27 (3)	24 (2)	
Death without cancer	14 (1)	5	
(0)			

DFS = Disease-free survival
ITT = Intention-to-treat

Disease-free Survival

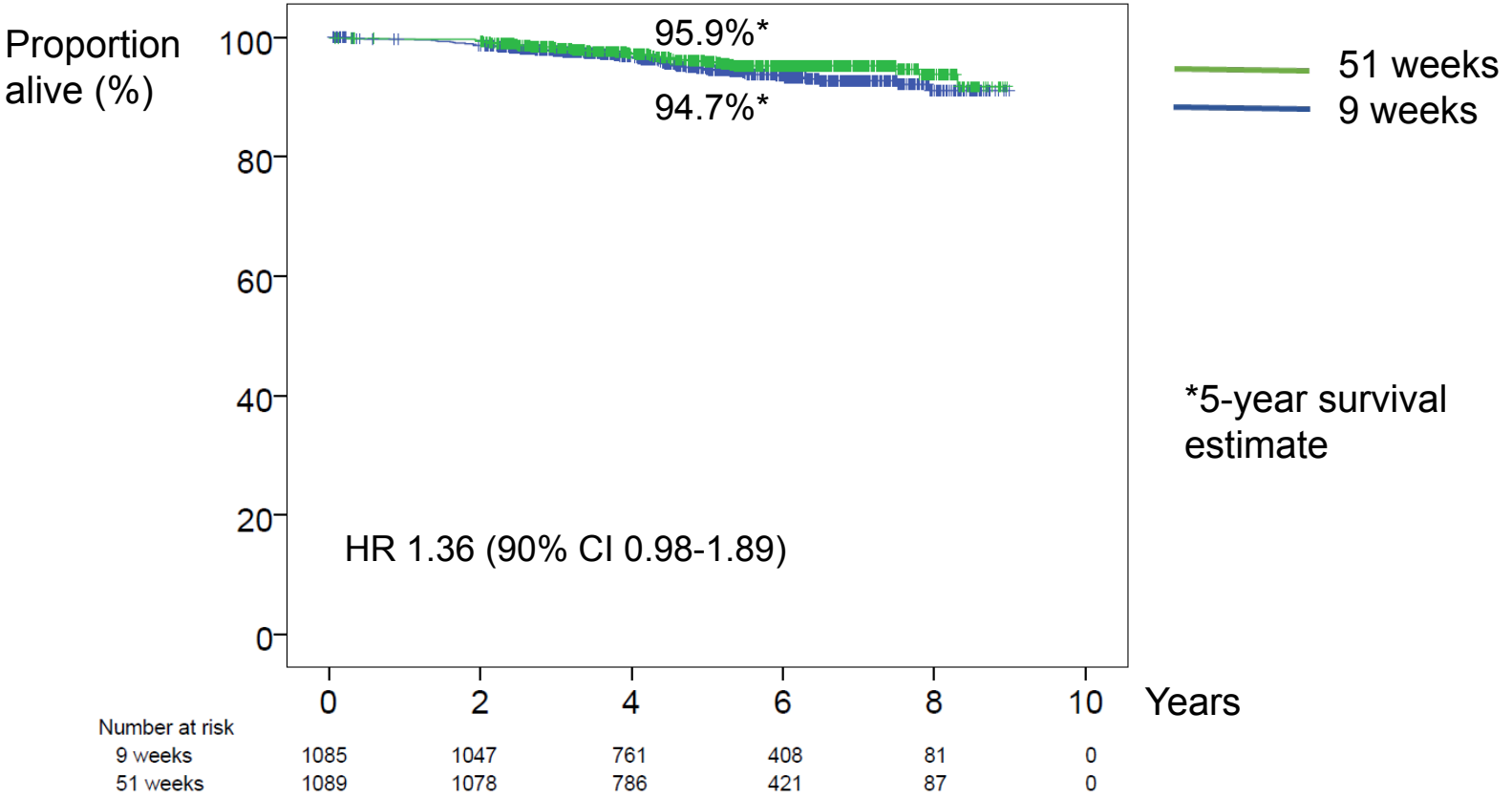


*5-year DFS estimate



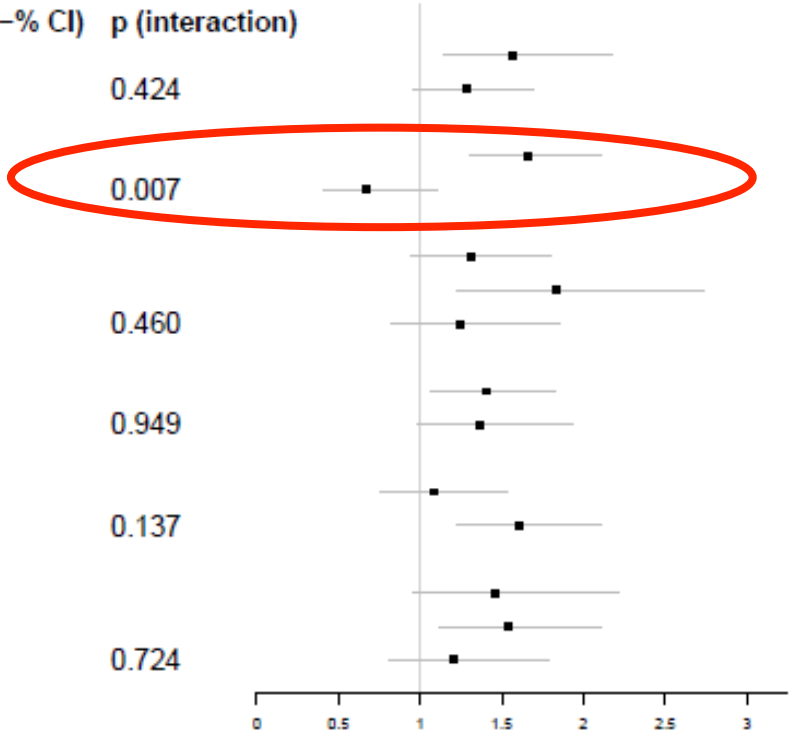
Overall Survival

GS3-04 Joensuu et al



Predefined sSubgroup Analyses for DFS

Subgroup		Hazard Ratio (90−% CI)	p (interaction)
ER status	Negative	1.57 (1.14−2.17)	
	Positive	1.28 (0.96−1.69)	0.424
Docetaxel dose	80 mg/m2	1.66 (1.30−2.11)	
	100 mg/m2	0.67 (0.41−1.10)	0.007
Nodes with cancer	0	1.31 (0.95−1.80)	
	1−3	1.83 (1.22−2.74)	
	3+	1.24 (0.82−1.85)	0.460
Centre accrual	< 100 patients	1.40 (1.06−1.83)	
	=> 100 patients	1.37 (0.98−1.93)	0.949
Age	< 50 yrs	1.08 (0.76−1.53)	
	>= 50 yrs	1.61 (1.23−2.11)	0.137
Stage	I	1.46 (0.96−2.22)	
	II	1.54 (1.12−2.11)	
	III	1.21 (0.81−1.79)	0.724



Cardiac safety

- Less cardiac toxicity was observed in the 9-week group

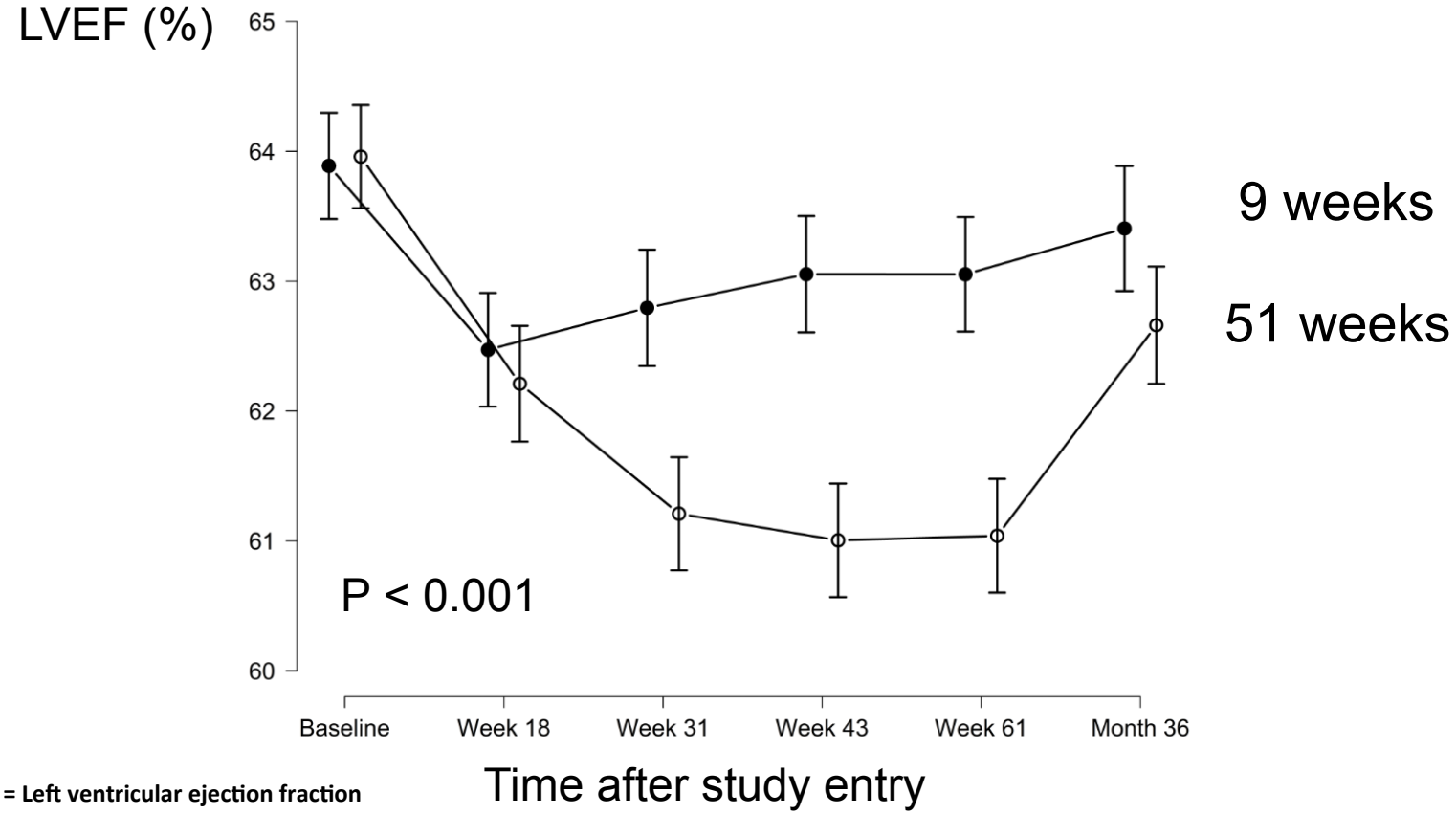
Event	9-week group n (%)	1-year group n (%)
Any protocol-defined cardiac adverse event*	22 (2.0)	42 (3.9)*
Congestive heart failure	21 (1.9)	36 (3.3)**

*P = 0.012

**P = 0.046

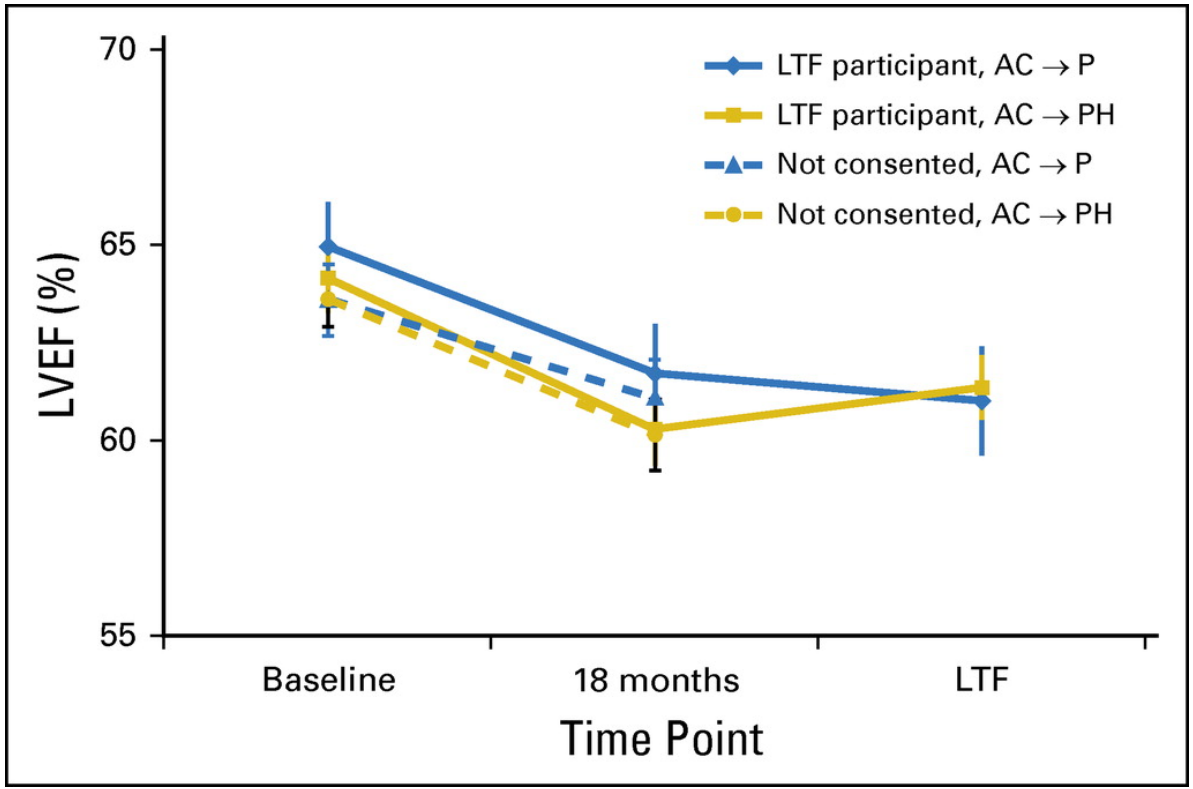
*Any Gr. 3 or 4 cardiac event; symptomatic cardiac failure; cardiac failure requiring medical management; LVEF decrease >10 percentage points and to a value <50%; LVEF decrease to <45% from any baseline value

Mean LVEF stratified by the treatment group



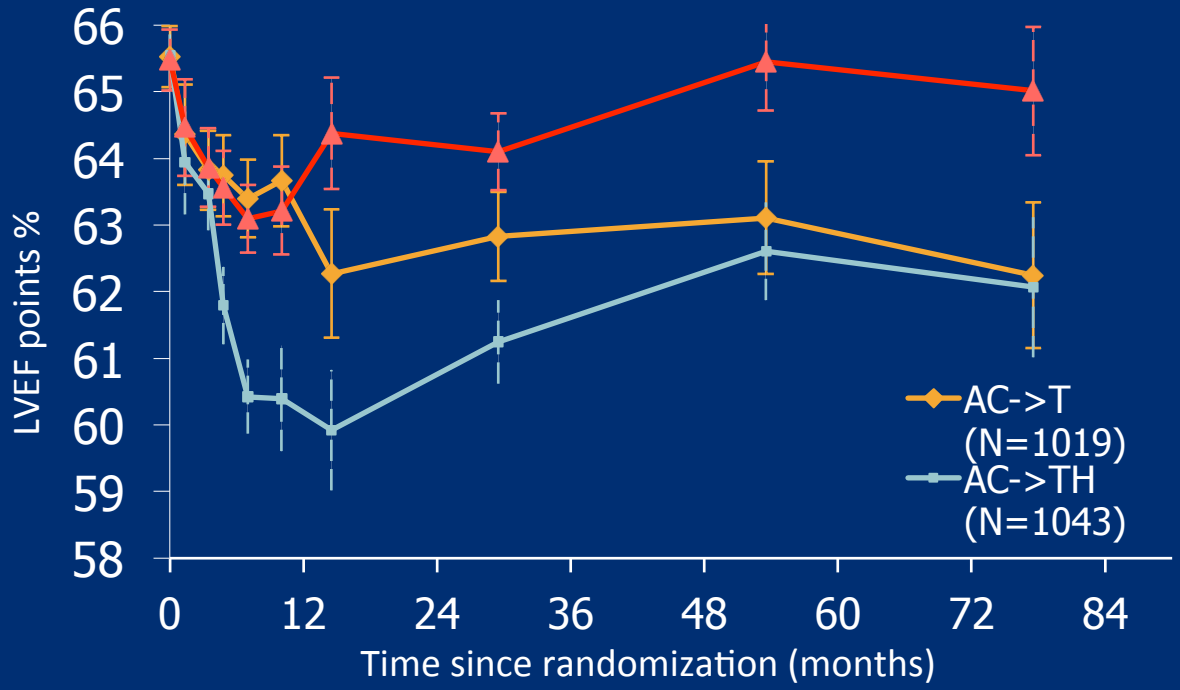
LVEF = Left ventricular ejection fraction

NSABP B-31 Mean LVEF over time



Ganz P et al. J Clin Oncol 2017;35(35):3942–3948

BCIRG 006: Non-anthracycline regimen safest for the heart
Mean LVEF - All Observations



Slamon D et al. Ca Research 2015;76: Abstr S5-04

Conclusions

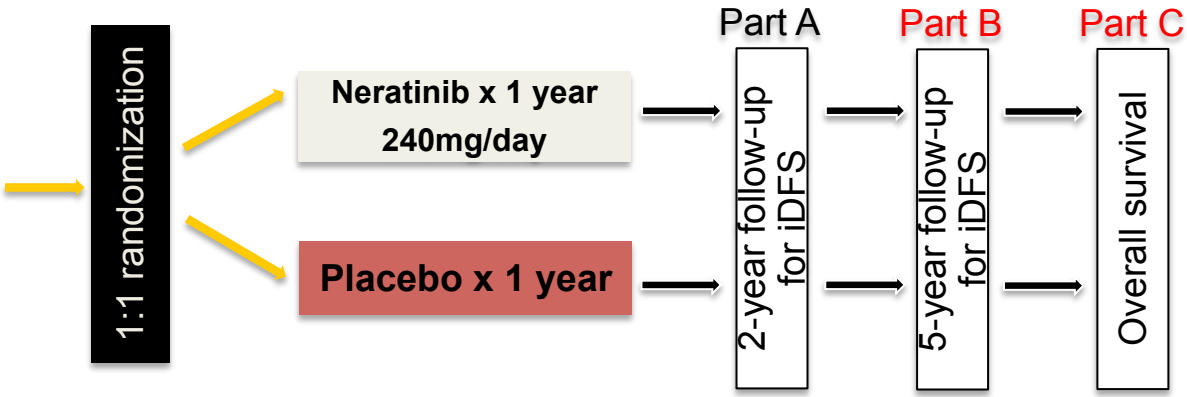
- Non-inferiority of 9-weeks of adjuvant trastuzumab plus chemotherapy could not be demonstrated as compared to 1-year of trastuzumab plus chemotherapy in terms of DFS
- Patients treated with the 9-week duration had fewer cardiac events and had the LVEF better maintained
  - *All patients received anthracycline-based therapy, which increases rates of cardiac toxicity*
- Chemotherapy plus 1-year of anti-HER2 therapy should remain the standard

Can we mitigate GI tox with adjuvant neratinib:

CONTROL

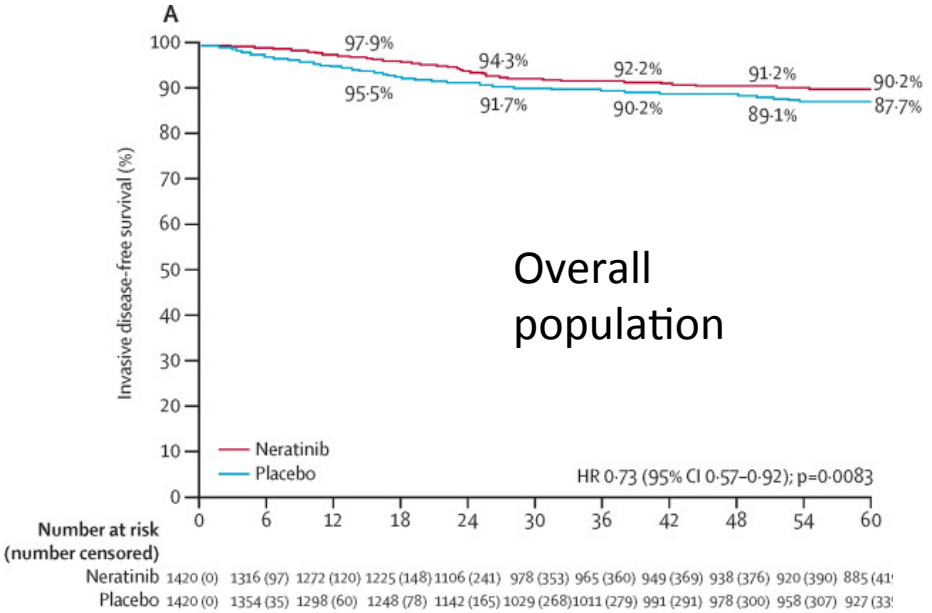
ExteNET Study Design

- HER2+ breast cancer (local)
- Prior adjuvant trastuzumab & chemotherapy
- Trastuzumab completed <14m previously
- Lymph node + or residual invasive disease after neoadjuvant therapy
- ER/PR + or –

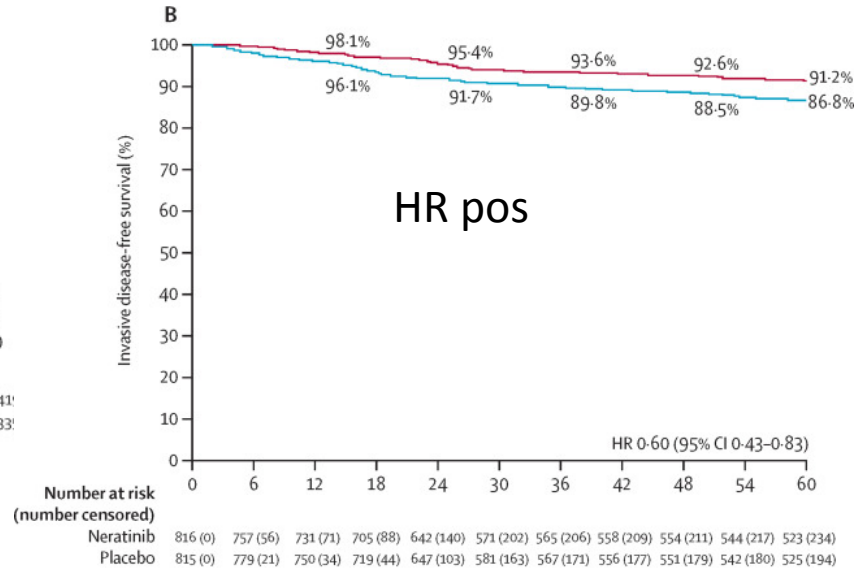


Chan et al, Lancet Oncol Volume 17, Issue 3, 2016, 367–377

ExteNET: Exploratory 5-Year iDFS



Overall population



HR pos

Holmes MM et al. Lancet Oncol 2017 Dec;18(12): 1688–1700

Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients with HER2+ early-stage breast cancer: the CONTROL trial

Sara Hurvitz,[1] Arlene Chan,[2] Nicholas Iannotti,[3] Emad Ibrahim,[4] Jo Chien,[5] Nancy Chan,[6] Andrew Kellum,[7] Vincent Hansen,[8] Gavin Marx,[9] S. DiSean Kendall,[10] Mary Wilkinson,[11] Aurelio Castrellon,[12] Rolando Ruiz,[13] Pearl Fang,[13] Daniel Hunt,[13] Susan Moran,[13] Elizabeth Olek,[13] Carlos H. Barcenas,[14] Hope S. Rugo[5]

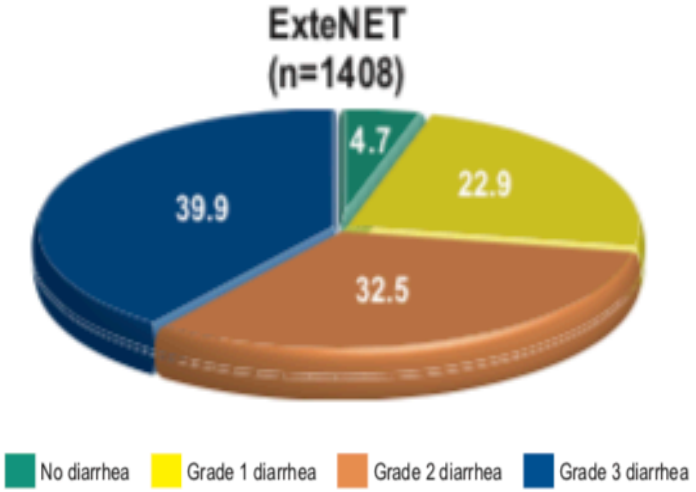
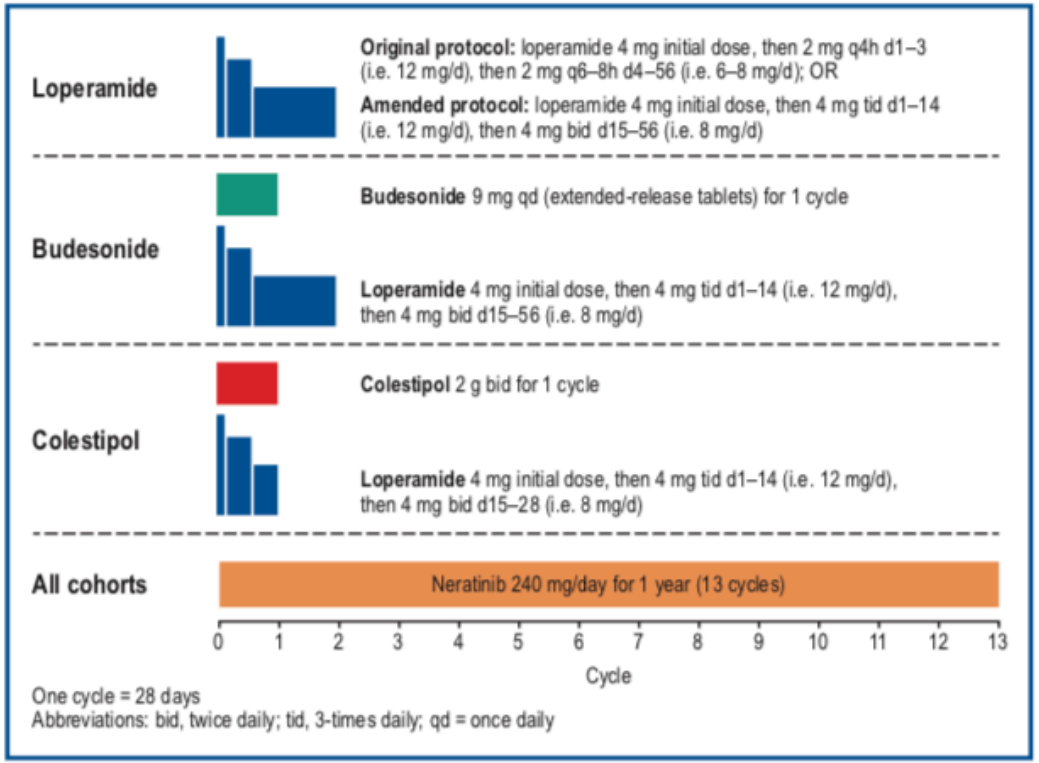


Figure 1. Treatment schedules by cohort



P3-14-01

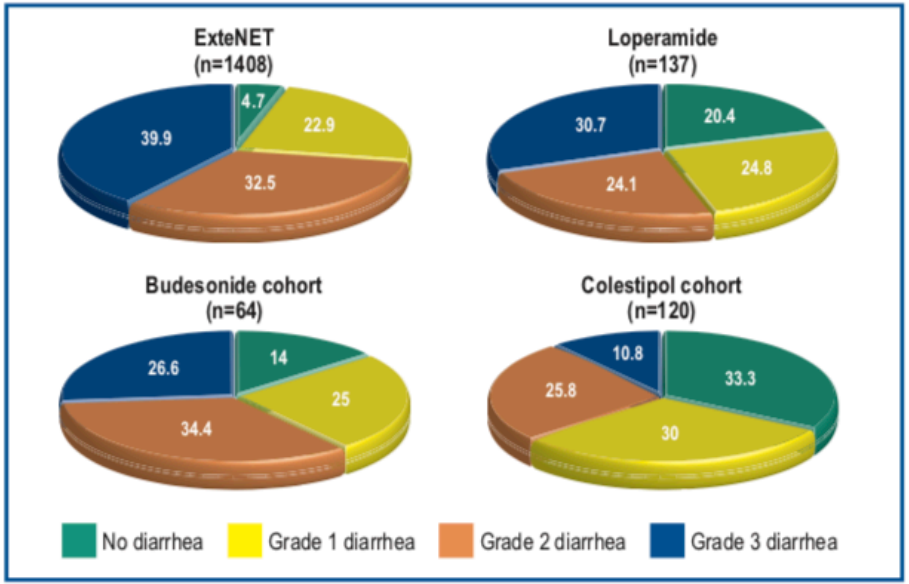
CONTROL: RESULTS

Table 2. Characteristics of treatment-emergent diarrhea (Safety population)

Study	CONTROL			ExteNET[a]
Variable	Loperamide (n=137)	Loperamide + budesonide (n=64)	Loperamide + colestipol (n=120)	Loperamide prn (n=1408)
Median cumulative duration, days				
Grade ≥2	5.0	6.0	3.5	10.0
Grade ≥3[a]	3.0	2.0	3.0	5.0[a]
Median diarrhea episodes/patient				
Any grade	2	9	2.5	8
Grade ≥2	2	3	1	3
Grade ≥3[a]	1	1	1	2
Action taken, %				
Dose hold	15.3	18.8	9.2	33.9
Dose reduction	7.3	3.1	4.2	26.4
Discontinuation	20.4	10.9	1.7	16.8
Hospitalization	1.5	0	0	1.4

[a]One grade 4 event reported in ExteNET.

Figure 2. Worst grade of treatment-emergent diarrhea (Safety population)



CONTROL

Table 3. Most common grade 3 treatment-emergent adverse events (CONTROL)

Grade 3 events, %	Loperamide cohort (n=137)	Budesonide cohort (n=64)	Colestipol cohort (n=120)
Diarrhea	30.7	26.6	10.8
Fatigue	3.6	7.8	1.7
Vomiting	1.5	3.1	1.7
ALT increased	0	3.1	0.8
Abdominal pain	1.5	1.6	0.8
Decreased appetite	1.5	1.6	0.8
Neoplasms benign, malignant and unspecified	0.7	1.6	0

NR = not reported

Trastuzumab biosimilar in the neoadjuvant setting

AMG-980

OFFICIAL best of SABCS

San Francisco, CA
United States
January 27, 2018

Safety results from a randomized, double-blind, phase 3 study of ABP 980 compared with trastuzumab in patients with breast cancer

Kolberg H-C, Demetriou GS, Zhang N, Tomasevic Z, Hanes V.

Marienhospital gGmbH, Klinik fur Gynakologie und Geburtshilfe, Bottrop, Germany; Charlotte Mexeke Johannesburg Academic Hospital Ward, Johannesburg Gauteng, South Africa; Amgen, Inc., Thousand Oaks, CA; Institute for Oncology and Radiology Of Serbia, Belgrade, Serbia

PD3-10

Impact of Trastuzumab Biosimilars

- Primary patent of Herceptin expired/expires:
  - July 2014 (Europe)
  - June 2019 (US).
- Significant cost reduction (~30% compared to originator)
  - Herceptin worldwide sales of ~$6.7 billion
- Increased access to the drug in low/middle income countries

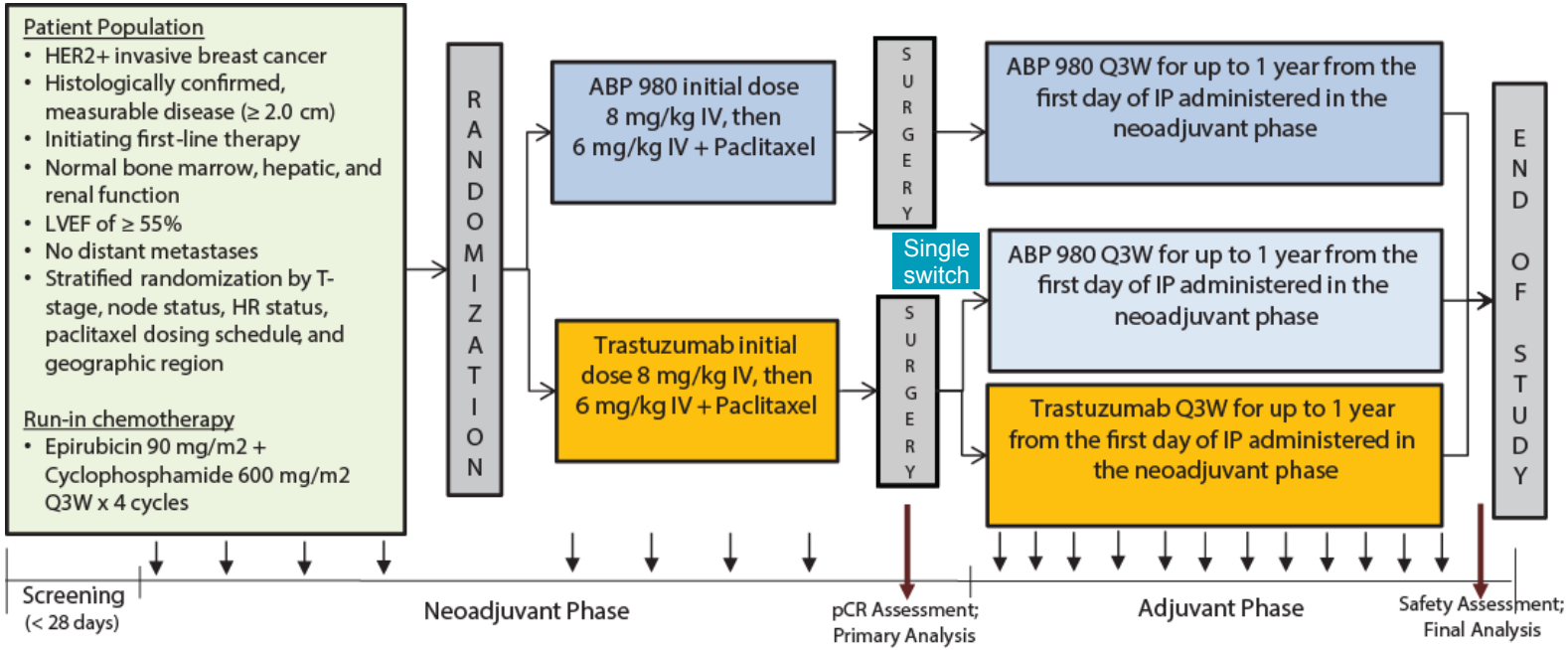
Proposed Trastuzumab Biosimilars with Positive Phase III Equivalence Studies

Company	Drug Name	Study	Primary Endpoint	N	FDA and/or EMA
Biocon/Mylan*[1]	MYL-14010	Metastatic	ORR	500	Approved
Pfizer/Hospira*[2]	PF-05280014	Metastatic	ORR	690	Submitted
Pfizer/Hospira*[3]	PF-05280014	Neoadjuvant	Drug [ ]	226	Submitted
Actavis/Amgen*[4]	ABP-890	Neoadjuvant	pCR	725	Submitted
Celltrion/Nippon Kayaku*[5]	CT-P6	Neoadjuvant	pCR	549	Submitted
Samsung Bioepis/Merck*[6]	SB3	Neoadjuvant	pCR	875	Approved

*1, Rugo et al. JAMA 2017; *2, Pegram et al. ESMO 2017; *3, Lammers et al. ESMO 2017; *4, Von Minckwitz et al. ESMO 2017; *5, Stebbing et al. Lancet Oncol 2017; *6, Pivot et al. ASCO 2017 ESMO 2017

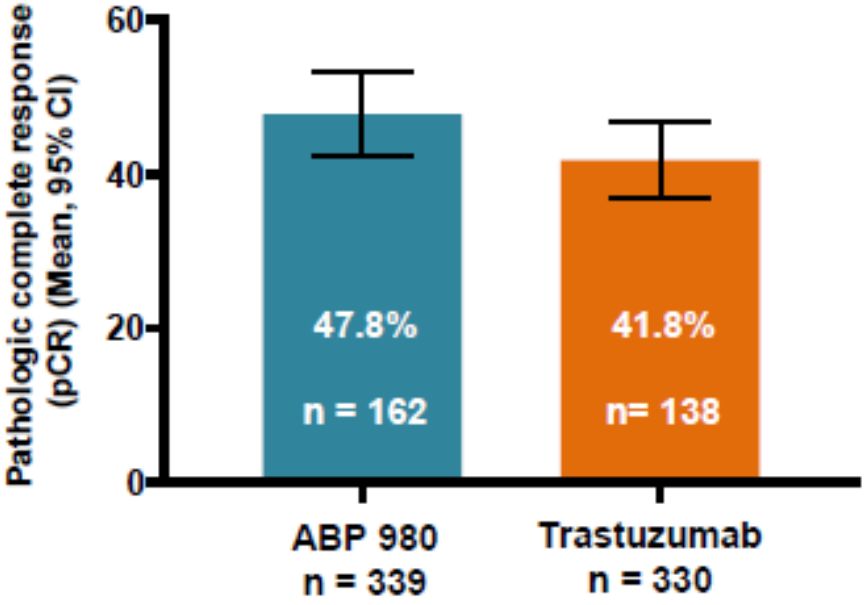
PD3-10 Kolberg et al

Efficacy and Safety of Biosimilar ABP 980 Compared With Trastuzumab in HER2+ Early Breast Cancer



Von Minckwitz et al. ESMO 2017

Efficacy and Safety of Biosimilar ABP 980 Compared With Trastuzumab in HER2+ Early Breast Cancer



*pCR is defined as ypT0N0 (DCIS allowed)

- Clinical equivalence of ABP 980 and trastuzumab in the neoadjuvant setting
- Based on central independent review, pCR rates were contained within the pre-defined statistical margins
- Safety and immunogenicity of ABP 980 comparable to those of trastuzumab
- There was no evidence of increased cardiotoxicity during the study

Von Minckwitz et al. ESMO 2017

Efficacy and Safety of Biosimilar ABP 980 Compared With Trastuzumab in HER2+ Early Breast Cancer

	980/980 (N = 349)	TRAS/TRAS (N = 171)	TRAS/980 (N = 171)
Any AE	215 (61.6)	96 (56.1)	108 (63.2)
Any grade ≥3 AE	30 (8.6)	11 (6.4)	13 (7.6)
Any fatal AE	0	0	1 (0.6)
Any serious AE	18 (5.2)	6 (3.5)	6 (3.5)
Infusion reactions	27 (7.7)	10 (5.8)	15 (8.8)
Hypersensitivity ≥G3	0	0	0
Pulmonary toxicity ≥G3	0	1 (0.6)	1 (0.6)
Cardiac failure ≥G3	0	0	1 (0.6)
LVEF decline by ≥10% and to below 50%	10/347 (2.9)	3/171 (1.8)	6/167 (3.6)
Binding antibodies	0 (0)	0 (0)	1 (0.0)
Neutralizing antibodies	0 (0)	0 (0)	0 (0)
Progression or recurrence	5.2%	5.3%	2.9%

Novel therapies on the horizon

DS-8201

OFFICIAL best of SABCS

San Francisco, CA
United States
January 27, 2018

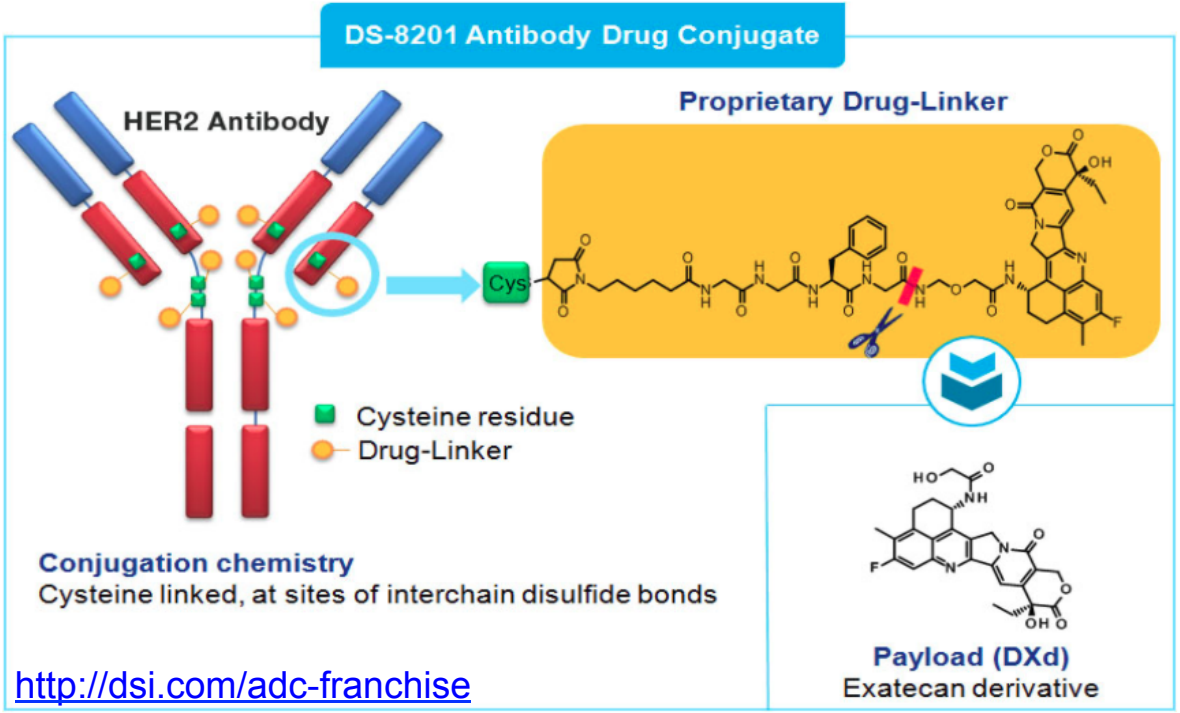
Safety and efficacy results from a phase 1 study of DS-8201a in patients with HER2 expressing breast cancers

Modi S, Tsurutani J, Takahashi S, Iwata H, Park H, Redfern CH, Doi T, Li B, Iwasa T, Taira S, Hattori M, Ma CX, Fisher JM, Naito Y, Yonemori K, Kawasaki Y, Saito K, Jikoh T, Shahidi J, Lee CC, Yver A, Tamura K.

Memorial Sloan-Kettering Cancer Center, New York, NY; Kindai University Hospital, Osakasayama, Osaka, Japan; The Cancer Institute Hospital Of Japanese Foundation for Cancer Research, Kotoku, Tokyo, Japan; Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; Washington University School Of Medicine, St Louis, MO; Sharp Memorial Hospital, San Diego, CA; National Cancer Center Hospital East, Kashiwa, Chiba, Japan; National Cancer Center Hospital, Chuoku, Tokyo, Japan; Daiichi Sankyo Co Ltd, Shinagawaku, Tokyo, Japan; Daiichi Sankyo Inc, Basking Ridge, NJ.

PD3-07

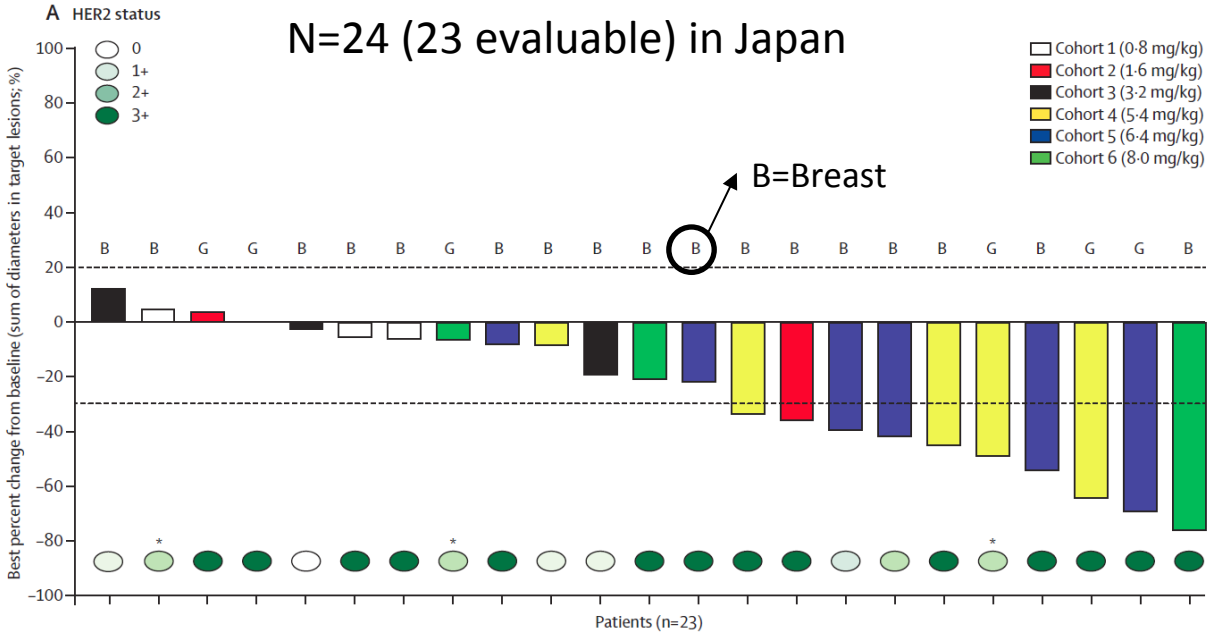
Trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody–drug conjugate



- Highly potent: Drug-to-antibody ratio = 7.8 vs 3.5 for T-DM1.
- Topoisomerase I inhibitor vs. tubulin inhibitor (T-DM1)
- Preclinically, DS-8201a has a potent bystander effect due to a highly membrane-permeable payload

Ogitani Y et al. Cancer Sci 2016
Marcoux-J et al. Protein Sci 2015

Safety, pharmacokinetics, and antitumor activity of DS-8201 in advanced breast/gastric cancer: a Phase 1 study



- No dose-limiting toxic effects or deaths.
- ORR=43% ; DCR=91%
- Responses observed at higher doses
- Antitumor activity observed in previously treated with T-DM1 or trastuzumab, and in patients with HER2-low tumors

Doi et al. Lancet Oncol 2017

Safety and efficacy results from a phase 1 study of DS-8201a in patients with HER2+ breast cancers

TABLE 3. Efficacy – Confirmed ORR, DCR, and PFS

Population	ORR, n/N (%)*	DCR, n/N (%)*	PFS (months), median (range)†
HER2-positive			
All	35/57 (61.4)	54/57 (94.7)	10.4 (1.2+, 16.8+)
HR-positive	22/39 (56.4)	36/39 (92.3)	NR (1.2+, 16.8+)
HR-negative	12/16 (75.0)	16/16 (100.0)	10.4 (1.2+, 14.1+)
Prior pertuzumab-treated	31/50 (62.0)	47/50 (94.0)	10.3 (1.2+, 16.8+)
HER2-low			
All	6/19 (31.6)	16/19 (84.2)	NR (0.5, 12.2+)
HR-positive	5/16 (31.3)	14/16 (87.5)	NR (1.2+, 12.2+)
HR-negative	0/2 (0.0)	1/2 (50.0)	7.6 (0.5, 7.6)

*Analysis set for ORR (CR+PR) and DCR (CR+PR +SD): efficacy evaluable for confirmed overall response, at least 2 postbaseline scans or progressive disease at the first scan.
†Minimum and maximum of PFS include "+" after value indicates censoring.
CR, complete response; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NR, not recorded; ORR, objective response rate; PFS, progression-free survival; SD, stable disease.

N=130 (76 evaluable)

- The dose levels of 5.4 and 6.4 mg/kg IV every 3 weeks were chosen for Part 2.
- Grade 3 toxicities occurred in <10% of the patients.
- Most frequent grade 3 toxicity was nausea.

FDA breakthrough therapy designation

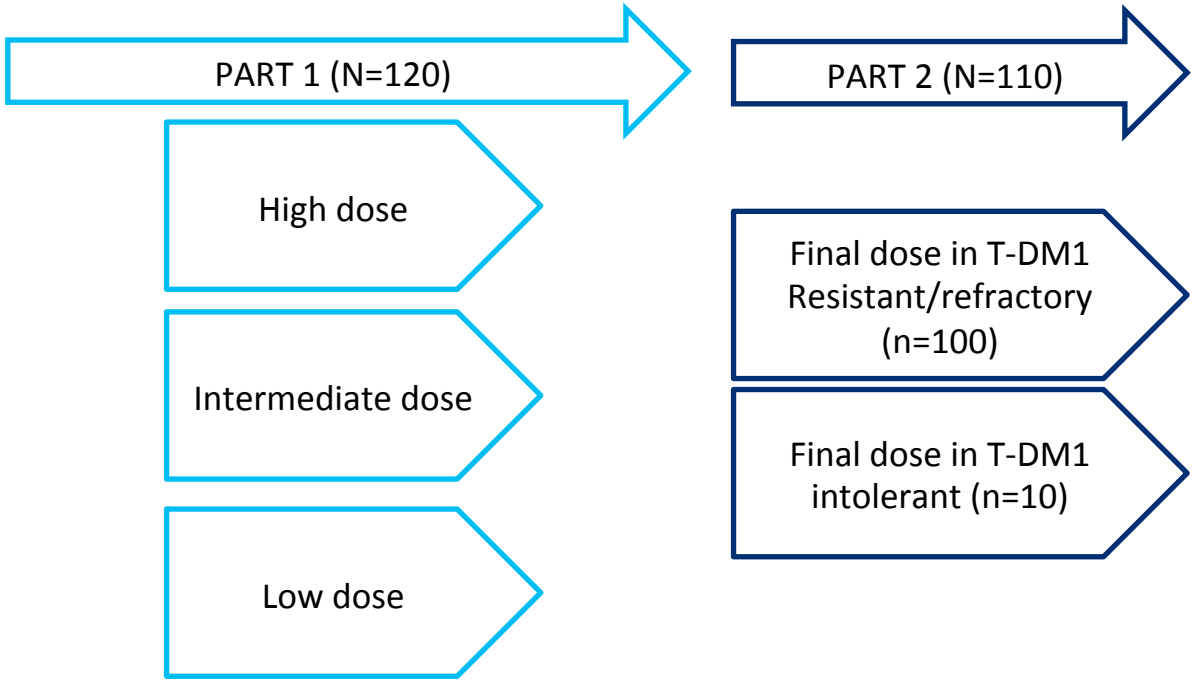
Modi et al. SABCS 2017

A Phase 2, Multicenter, Open-Label Study of DS-8201a in HER2+ Metastatic Breast Cancer Resistant/Refractory to T-DM1 (DESTINY-Breast01)

- N=230
- Primary objective: ORR

- Men or women
- Unresectable or metastatic
- HER2 positive expression
- ≥1 measurable lesion

NCT03248492



Characteristics by HER2 receptor expression

Characteristics	HER2-positive (n = 96)	HER2-low (n = 34)
Age, median (range)	55.5 (33–77)	54.5 (33–75)
ECOG performance status, n (%)		
0	50 (52.1)	20 (58.8)
1	31 (32.3)	14 (41.2)
Missing	15 (15.6)	0 (0.0)
Hormone receptor, n (%)		
Positive	58 (60.4)	27 (79.4)
Negative	25 (26.0)	5 (14.7)
Unknown	13 (13.5)	2 (5.9)
HER2 expression (IHC), n (%)*		
3+	68 (70.8)	0 (0.0)
2+	24 (25.0)	19 (55.9)
ISH positive	24 (25.0)	0 (0.0)
ISH negative	0 (0.0)	17 (50.0)
ISH equivocal	0 (0.0)	1 (2.9)
ISH missing	0 (0.0)	1 (2.9)
1+	1 (1.0)†	14 (41.2)
Missing	3 (3.1)	1 (2.9)
Number of prior cancer regimens, n (%)		
1	0 (0.0)	0 (0.0)
2	2 (2.1)	0 (0.0)
3	5 (5.2)	2 (5.9)
4	11 (11.5)	4 (11.8)
5 or more	70 (72.9)	28 (82.4)
Missing	8 (8.3)	0 (0.0)
Prior therapy, n (%)		
T-DM1‡	96 (100)	4 (11.8)
Pertuzumab	72 (75.0)	6 (17.6)

*Local laboratory testing; Herceptest Scoring Criteria (CAP/ASCO 2013)4− 3+: Uniform intense complete membrane staining in >10% of invasive tumor cells; 2+: Incomplete membrane staining that is weak to moderate in >10% of cells, or intense complete membrane staining in ≤10% of invasive tumor cells; 1+: Faint, incomplete membrane staining in >10% of invasive tumor cells; and 0: No staining is observed in invasive tumor cells or faint incomplete membrane staining in ≤10% of cells.†HER2 = −positive IHC 1+ subject: *ISH+.‡All HER2−positive subjects had previously received a trastuzumab−based regimen.ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T−DM1, trastuzumab emtansine.

Shanu Modi, et al. SABCS™2017 Abstract PD3-07

Efficacy – Confirmed ORR, DCR, and PFS

Population	ORR, n/N (%)*	DCR, n/N (%)*	PFS (months), median (range)†
HER2-positive			
All	35/57 (61.4)	54/57 (94.7)	10.4 (1.2+, 16.8+)
HR-positive	22/39 (56.4)	36/39 (92.3)	NR (1.2+, 16.8+)
HR-negative	12/16 (75.0)	16/16 (100.0)	10.4 (1.2+, 14.1+)
Prior pertuzumab-treated	31/50 (62.0)	47/50 (94.0)	10.3 (1.2+, 16.8+)
HER2-low			
All	6/19 (31.6)	16/19 (84.2)	NR (0.5, 12.2+)
HR-positive	5/16 (31.3)	14/16 (87.5)	NR (1.2+, 12.2+)
HR-negative	0/2 (0.0)	1/2 (50.0)	7.6 (0.5, 7.6)

*Analysis set for ORR (CR+PR) and DCR (CR+PR +SD): efficacy evaluable for confirmed overall response, at least 2 postbaseline scans or progressive disease at the first scan.
†Minimum and maximum of PFS include "+" after value indicates censoring.
CR, complete response; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NR, not recorded; ORR, objective response rate; PFS, progression-free survival; SD, stable disease.

Shanu Modi, et al. SABCS™2017 Abstract PD3-07

Treatment-Emergent Adverse Events, Any Grade (>20%, N = 115)

Preferred term*	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All n (%)†
Hematologic					
Anaemia	13 (11.3)	16 (13.9)	10 (8.7)	1 (0.9)	40 (34.8)
Platelet count decreased	17 (14.8)	8 (7.0)	5 (4.3)	3 (2.6)	33 (28.7)
Neutrophil count decreased	0 (0.0)	10 (8.7)	12 (10.4)	5 (4.3)	27 (23.5)
White blood cell count decreased	4 (3.5)	9 (7.8)	12 (10.4)	0 (0.0)	25 (21.7)
Aspartate aminotransferase increased	19 (16.5)	3 (2.6)	1 (0.9)	0 (0.0)	23 (20.0)
Gastrointestinal disorders					
Nausea	57 (49.6)	21 (18.3)	6 (5.2)	0 (0.0)	84 (73.0)
Decreased appetite	37 (32.2)	22 (19.1)	5 (4.3)	0 (0.0)	64 (55.7)
Vomiting	36 (31.3)	6 (5.2)	3 (2.6)	0 (0.0)	45 (39.1)
Diarrhoea	28 (24.3)	8 (7.0)	3 (2.6)	0 (0.0)	39 (33.9)
Constipation	30 (26.1)	4 (3.5)	1 (0.9)	0 (0.0)	35 (30.4)
Others					
Alopecia	40 (34.8)	6 (5.2)	0 (0.0)	0 (0.0)	46 (40.0)
Malaise	19 (16.5)	11 (9.6)	1 (0.9)	0 (0.0)	31 (27.0)
Fatigue	18 (15.7)	8 (7.0)	1 (0.9)	0 (0.0)	27 (23.5)

*Coded with MedDRA version 18.0.
†Safety analysis set of all breast cancer subjects receiving at least 1 dose at 5.4 or 6.4 mg/kg (n = 115).
MedDRA, Medical Dictionary for Regulatory Activities.

Shanu Modi, et al. SABCS™2017 Abstract PD3-07

Conclusions

- Trastuzumab deruxtecan (DS-8201a) has significant activity in subjects with HER2-positive advanced breast cancer who have received T-DM1, as well as trastuzumab with or without pertuzumab, and in heavily pretreated subjects with HER2-low breast cancer demonstrating durable responses regardless of hormone receptor status
- Trastuzumab deruxtecan (DS-8201a) was well tolerated in heavily pretreated breast cancer subjects with few grade 3 or more adverse events
- All cases of pneumonitis/lung disorders will be sent to an independent ILD adjudication committee
- Promising efficacy and safety of this ADC in HER2-expressing breast cancer warrants further investigation—pivotal phase 2 DESTINY-Breast01 study to examine efficacy and safety of DS-8201 in patients with HER2-positive unresectable and/or metastatic breast cancer who are resistant or refractory to T-DM 1 is ongoing (NCT03248492)

Novel therapies on the horizon

Pyrotinib

OFFICIAL best of SABCS NEWS

Encore Medical Education

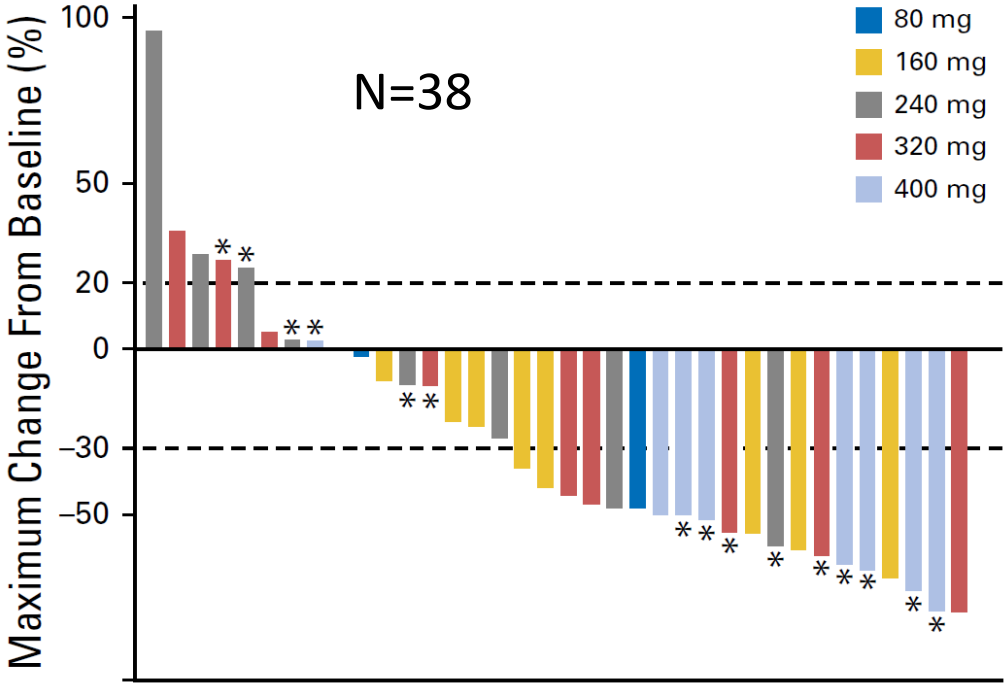
A randomized phase II trial of pyrotinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with taxanes, anthracyclines and/or trastuzumab

Xu B, Ma F, Ouyang Q, Li W, Jiang Z, Tong Z, Liu Y, Li H, Yu S, Feng J, Wang S, Hu X, Zhu X, Zou J.

Cancer Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, National Cancer Center, Beijing, China; Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School Of Medicine, Central South University, Changsha, Hunan, China; First Affiliated Hospital, Jilin University, Changchun, Jilin, China; Affiliated Hospital of Academy of Military Medical Sciences, Beijing, China; Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China; Cancer Center Of Hebei Province and The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China; Peking University Cancer Hospital & Institute, Beijing, China; Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital and Jiangsu Institute of Cancer Research, Nanjing, Jiangsu, China; Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China; Fudan University Shanghai Cancer Center, Shanghai Medical College, Fudan University, Shanghai, China; Jiangsu Hengrui Medicine Co., Ltd., Shanghai, China.

PD3-08

Phase I Study and Biomarker Analysis of Pyrotinib, a Novel Irreversible Pan-ErbB Receptor Tyrosine Kinase Inhibitor, in HER2+ Metastatic Breast Cancer



- Dose limiting toxicity: diarrhea.
- MTD 400 mg/day
- ORR=50% ; CBR24w=61.1%
- ORR=33.3% in trastuzumab-treated
- ORR=83.3% in trastuzumab-naive

Ma et al. J Clin Oncol 2017

A randomized phase II trial of pyrotinib/capecitabine versus lapatinib/capecitabine in HER2+ metastatic breast cancer

This is an open label, multicenter, randomized phase II trial.

- HER2 positive metastatic breast cancer
- Age 18 – 70 years
- Previously treated with taxanes and anthracyclines
- With/without prior trastuzumab
- ≤2 lines of chemotherapy for advanced disease
- Previous treatment with capecitabine within 6 months is not permitted
- Brain metastasis is not permitted

RANDOMIZATION

PC: Pyrotinib (P) + Capecitabine (C)
pyrotinib 400mg, qd, d1-21, q3wks
capecitabine 1000mg/m^2, bid, d1-14, q3wks
until disease progression, intolerable toxicity or withdrawal of consent

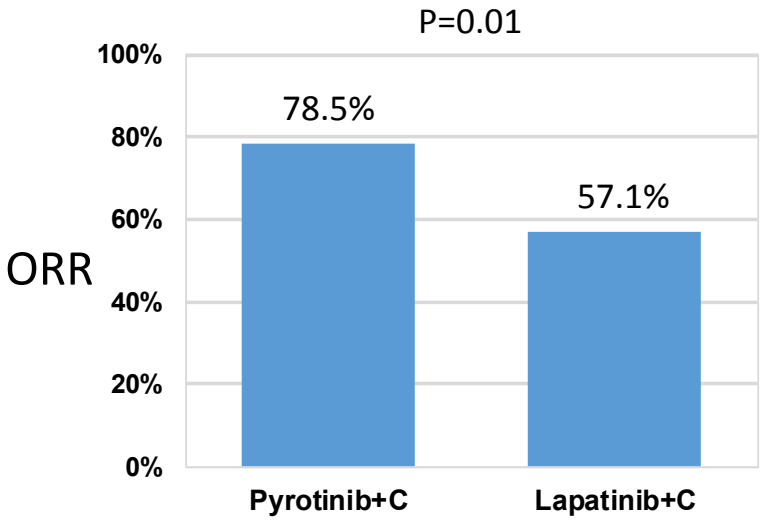
LC: Lapatinib (L) + Capecitabine (C)
Lapatinib 1250mg, qd, d1-21, q3wks
capecitabine 1000mg/m^2, bid, d1-14, q3wks
until disease progression, intolerable toxicity or withdrawal of consent

- Stratification: prior treatment with anti-HER2 monoclonal antibody (yes, no)
- Primary endpoint: overall response rate (ORR), as assessed by investigator

- Secondary endpoints:
  - Progression free survival (PFS)
  - Time to progression (TTP)
  - Duration of response (DoR)
  - Overall survival (OS)
  - Safety

Xu et al. SABCS 2017

A randomized phase II trial of pyrotinib/capecitabine versus lapatinib/capecitabine in HER2+ metastatic breast cancer



- Increased mPFS 18 vs. 7.0 months (HR=0.36 P<0.0001); irrespective of prior trastuzumab.
- Grade 3-4 toxicities higher in PC arm vs LC arm:
  - Hand-foot syndrome (24.6% vs 20.6%),
  - Diarrhea (15.4% vs 4.8%)
  - Decreased neutrophil (9.2% vs 3.2%)
  - Vomiting (4.6% vs 1.6%)
- Serious adverse events (SAEs): 7.7% vs. 6.3%.
- A Phase III trial is ongoing (NCT02973737).

Xu et al. SABCS 2017

Novel therapies on the horizon

Tucatinib

Prolonged progression-free survival (PFS) in advanced HER2+ metastatic breast cancer with or without brain metastases: A pooled analysis of tucatinib phase 1b studies

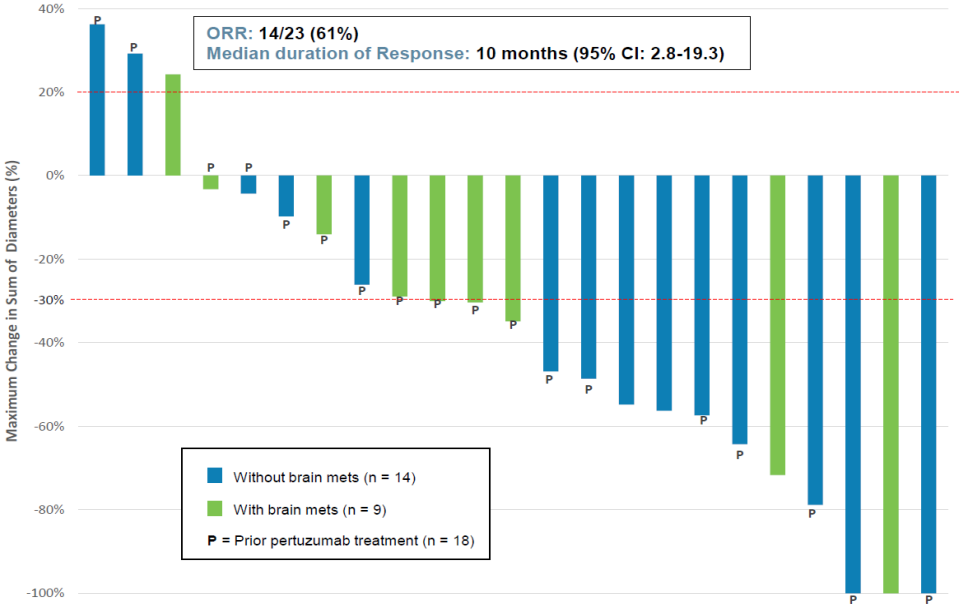
Hamilton E, Murthy R, Ferrario C, Conlin A, Krop I, Falkson C, Khan Q, Chamberlain M, Gray T, Borges V.

Sarah Cannon Research Institute, Nashville, TN; Tennessee Oncology, PLLC, Nashville, TN; The University of Texas MD Anderson Cancer Center, Houston, TX; Segal Cancer Centre - Jewish General Hospital, Montreal, QC, Canada; Providence Cancer Center, Eastside, Portland, OR; Dana-Farber Cancer Institute, Boston, MA; University of Alabama Comprehensive Cancer Center, Birmingham, AL; University of Kansas Medical Center, Westwood, KS; Cascadian Therapeutics, Inc., Seattle, WA; University of Colorado Cancer Center, Aurora, CO.

P5-20-01

A Phase 1b Study of Tucatinib (ONT-380) Combined With Capecitabine and/or Trastuzumab in HER2+ Metastatic Breast Cancer

N=23



- 300mg BID
- Encouraging anti-tumor activity seen in the triplet combination, in a heavily pre-treated population including those with brain mets
- ORR=61% ; Median PFS=7.8m
- Median DOR=10 months
- CNS ORR: 5/12 (42%)
- **Orphan drug designation by FDA for the treatment of BC brain metastases**

NCT02025192

Hamilton et al. SABCS 2016

Methods and Treatment

P5-20-01 Hamilton et al.

Methods

- Two Phase 1b studies of tucatinib, ONT-380-004 and ONT-380-005, were pooled to identify and characterize the subgroup of patients with prolonged PFS
- Prolonged PFS was defined as patients achieving twice the observed median PFS
  - Modeled after the ASCO Framework Guidelines for randomized trials
- Baseline disease characteristics and radiology findings were compared between the subgroup of patients with or without prolonged PFS

Treatment

- Study ONT-380-004: tucatinib + T-DM1 (N=50)
  - Tucatinib 300 mg PO BID
  - T-DM1 3.6 mg/kg IV once every 21 days
- Study ONT-380-005: tucatinib + capecitabine+ trastuzumab cohort (N=27)
  - Tucatinib 300 mg PO BID (all combinations)
  - Capecitabine 1000 mg/m^2 PO BID for 14 days of a 21-day cycle
  - Trastuzumab 8 mg/kg IV loading dose; 6 mg/kg IV once every 21

PFS=progression-free survival

Prolonged PFS Subgroup Results

P5-20-01 Hamilton et al.

- 77 patients were analyzed
  - 50 from the Study 004 (tucatinib + T-DM1)
  - 27 from the Study 005 (tucatinib + trastuzumab + capecitabine cohort)
- Patients received a median of 2 prior therapies including a taxane, trastuzumab, pertuzumab, T-DM1 (Study 005 only), and lapatinib
- Median PFS was
  - 8.2 months in the M TD cohort in Study 004
  - 7.8 months in the triplet cohort in Study 005
- 17 patients (22%) demonstrated PFS ≥ 17 months, operationally defined as a prolonged PFS subgroup
  - 10/50 (20%) from Study 004
  - 7/27 (26%) from Study 005

PFS=progression-free survival

Conclusions

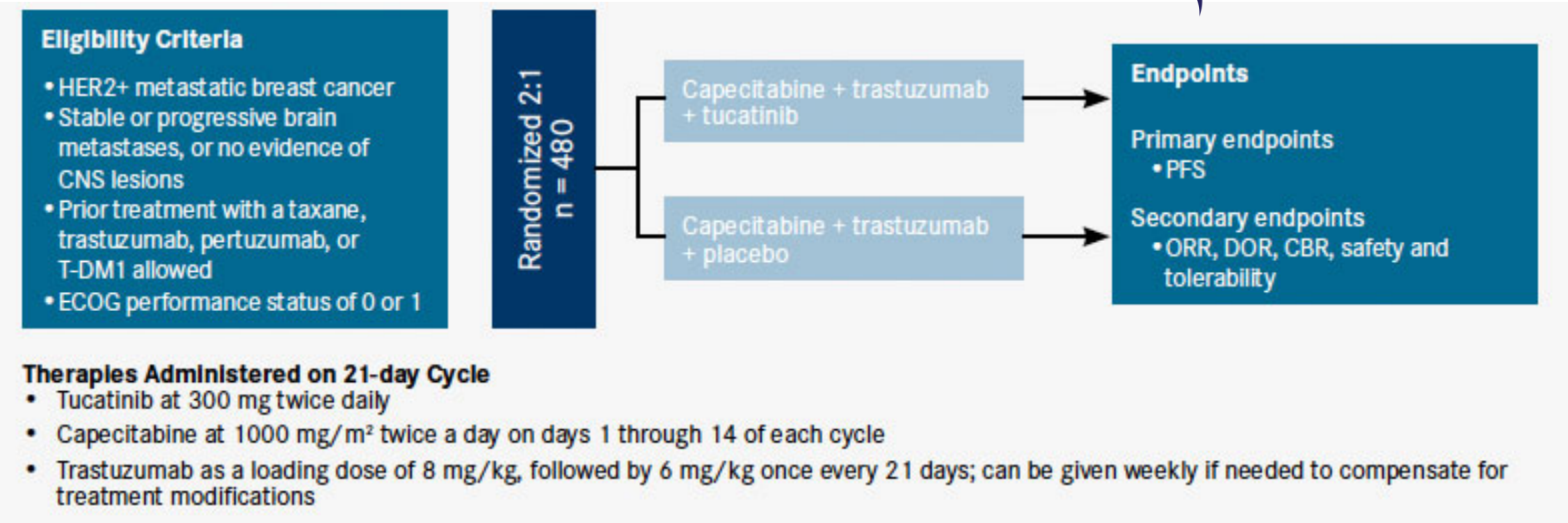
- 22% of patients treated with tucatinib in combination for late stage MBC demonstrate prolonged PFS defined as ≥ 17 months, representing a significant subgroup of patients who have extended disease control
- Patient characteristics such as hormone receptor status, presence of visceral disease, burden of disease, and age, often predictive for limited survival, were not predictive of prolonged PFS on tucatinib
- Baseline BM did not differentiate patients who achieved prolonged PFS, although the presence of BM historically has negatively impacted PFS
- Further molecular characterization of the prolonged PFS cohort may help to identify this patient group
- These data support the evaluation of tucatinib in patients with and without BM in the accruing HER2CLIMB pivotal trial

PFS=progression-free survival

Phase 2 Study of Tucatinib vs Placebo in Combination With Capecitabine & Trastuzumab in HER2+ Breast Cancer

N=480

HER2CLIMB



NCT02614794

What do we do on Monday morning?

A paradigm for treating early and late stage disease

Metastatic DIsease

- First line treatment: THP
  - Trastuzumab, Pertuzumab, Taxane (taxane 4-6 cycles then can stop, but continue HP. Add in endocrine therapy for ER+ tumors.)
- Second line treatment: T-DM1
- Treatment beyond second line:
  - Many options: lapatinib/capecitabine, lapatinib/trastuzumab, trastuzumab or lapatinib plus endocrine therapy; trastuzumab plus chemo (vinorelbine, gemcitabine, eribulin, capecitabine…)
  - Clinical trials!! Neratinib, DS-8201, Tucatinib, Pyrotinib, other…

Early Stage Disease

- Neoadjuvant therapy:
  - Chemo plus HP yields high pCR rates (TCHP, FEC-THP)
  - *Unclear how neratinib or full year pertuzumab fits in patients treated this way*
- Adjuvant therapy:
  - Trastuzumab 1 year remains standard
  - Trastuzumab concurrent with chemo *probably* better than sequential
  - Several chemo options; best studied are AC-TH, TCH (TCH less toxic)
  - De-escalation options in select pts: paclitaxel/trastuzumab; T-cy-Hx4
    - Intriguing but not yet studied in large randomized trials
  - Now available! New FDA approvals
    - 2017: Neratinib x 1 year after trastuzumab (benefit mainly in ER+. Diarrhea management needed)
    - 2018: Pertuzumab x 1 year (1.7% benefit in iDFS!)