

GBCC 2013, Symposium 3
10th Oct, 2013
Seoul , Korea



Kumamoto University

Neoadjuvant therapy for early breast cancer in HER2 type and Luminal type tumors

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COI Disclosure Information

Hiroataka Iwase, MD, PhD

I have the following financial relationships to disclose.

Leadership position/advisory role for: none

Stockholder in: none

Patents and royalties from: none

Honoraria (lecture fee) from: AstraZeneca

Honoraria (manuscript fee) from: none

Grant/Research funding from: AstraZeneca, Chugai-Roche, Novartis,
Takeda, Taiho, Daiichi-Sankyo

Other remuneration from: none

Practice guidelines based on scientific evidence
edited by JBCS; <http://www.jbcsguideline.jp/>



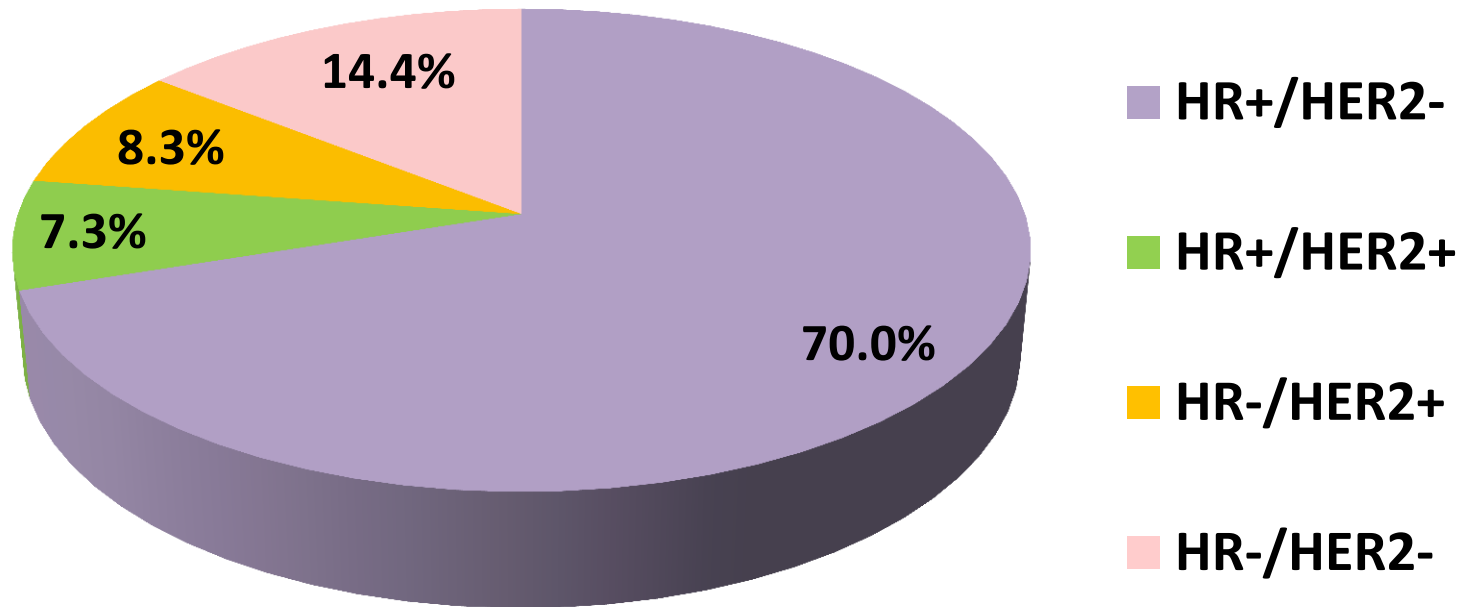
Guidelines include the latest knowledge regardless of the adaptation of public health insurance.

Discrepancy between clinical practice and new knowledge in Japan

- **Neoadjuvant anti-HER2 therapy for HER2-positive early breast cancer, e.g. lapatinib or lapatinib + trastuzumab**
- **Neoadjuvant combination endocrine therapies for premenopausal ER-positive breast cancer, e.g. LH-RH agonist + AI**
- **Platinum for triple negative metastatic breast cancer**
- **Combination of Fulvestrant with AI ····**
- **Multi-gene assay for treatment decision, e.g. OncotypeDx[®], MammaPrint[®], PAM50, etc...**
- **Genetic testing for HBOC**

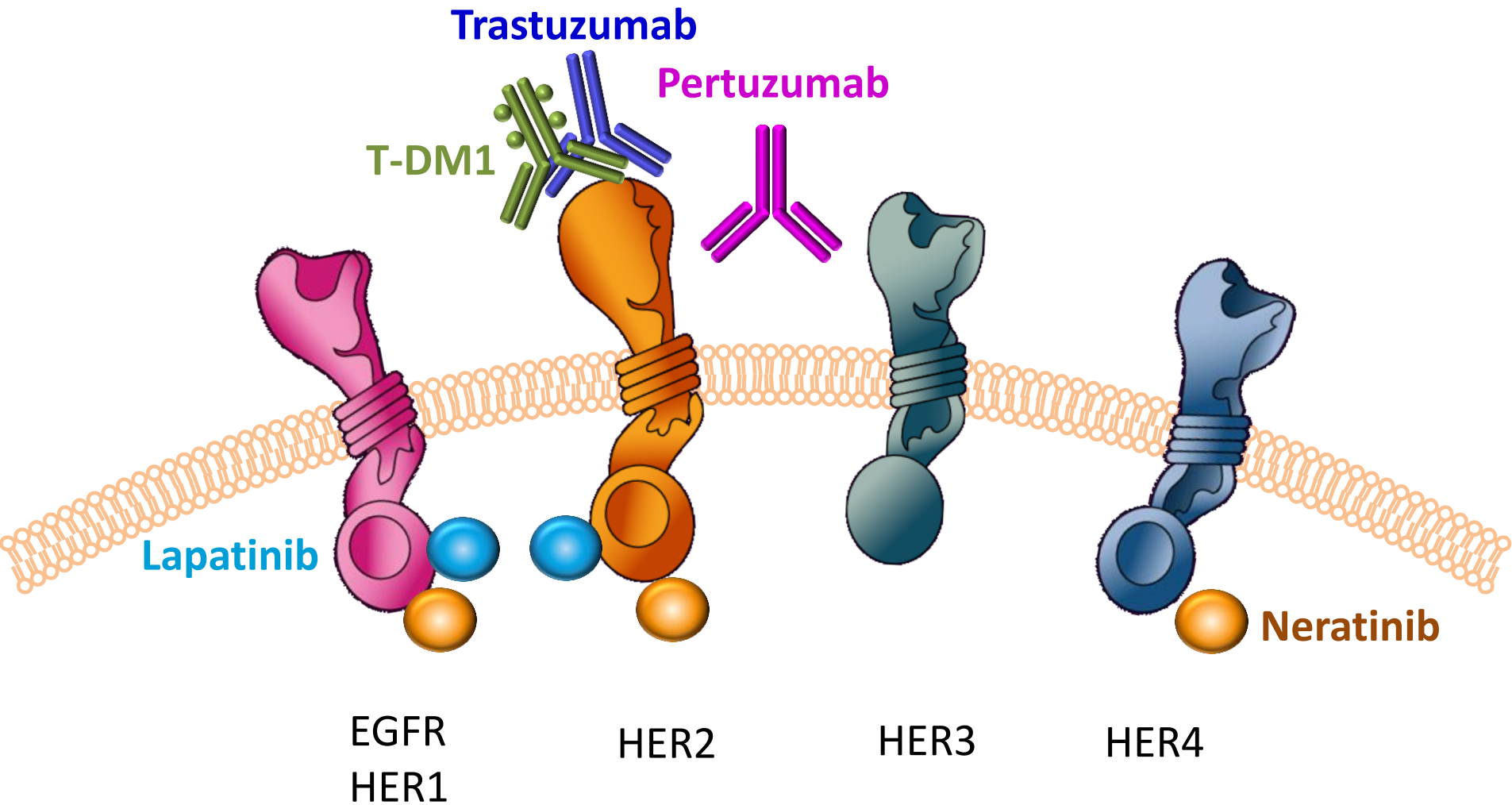
Breast cancer surveillance data reported by the Japanese Breast Cancer Society

(n=63,296, 2004/1/1~2009/1/7)



HR+; ER+ and/or PgR+,
HR-; ER-and PgR-

Anti-HER2 therapy and HER family



Development of anti-HER2 therapy in Japan

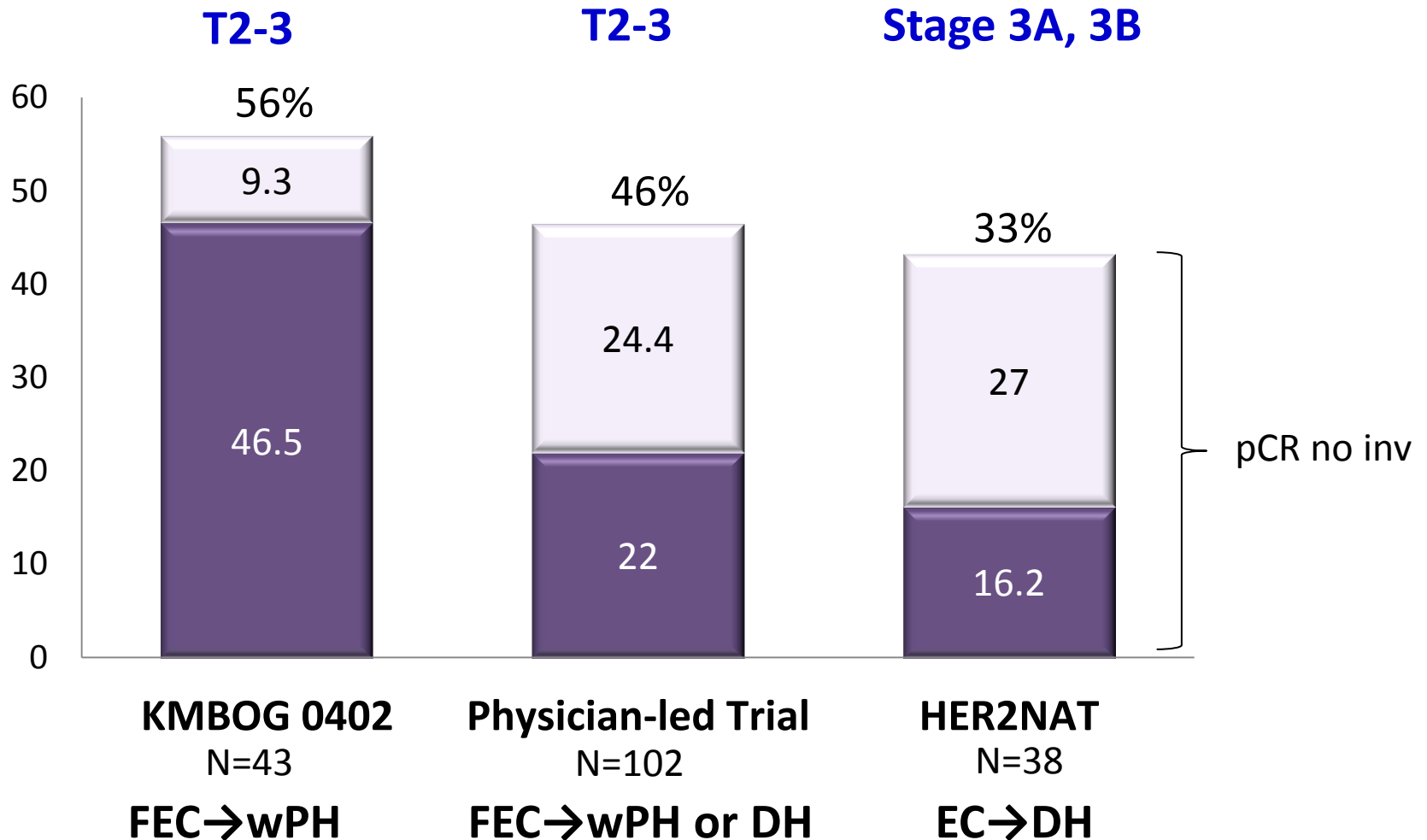
- **Trastuzumab**
 - 2001 for metastatic breast cancer (mBC)
← **Tmab + Taxan, Continue Tmab with any CT beyond PD**
 - 2008 Adjuvant setting for eBC ← **CT with Tmab (1 y)**
 - 2011 Neoadjuvant therapy for eBC ← **NOAH, MDACC**
- **Lapatinib**
 - 2009 for mBC combination with capecitabine
 - **20XX** Adjuvant setting ← **ALTTO**
 - **20XX** Neoadjuvant setting ← **neo-LaTH, neo-ALTTO**
- **Pertuzumab (Pergeta ®)**
 - 2013/07 mBC ← **Pmab + Tmab + Taxane (Any CTx)**
- **Trastuzumab emtansine, TDM-1 (Kadcyla®)**
 - 2013/09 mBC

Meta-analysis comparison neo- adjuvant chemotherapy with or without Tmab

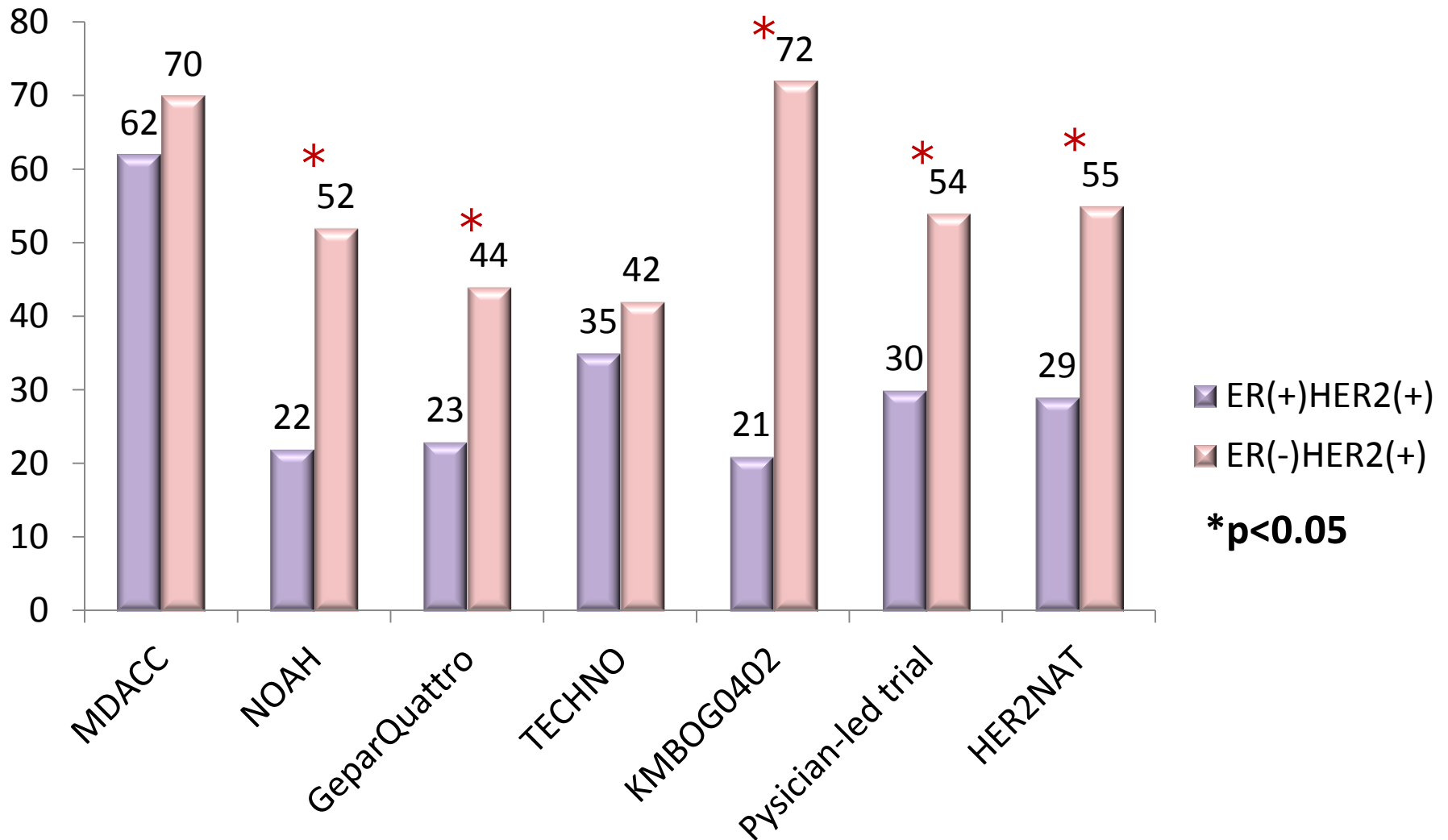
	Chemotherapy alone	Chemotherapy + Trastuzumab	Relative risk (95%CI)	P value
pCR	21 %	38 %	1.85 (1.39-2.46)	< 0.001
BCSR; breast conserving surgery rate	58 %	56 %	0.98 (0.80-1.19)	0.82
CHF	0 %	0.9 %	-	n.s.

Buzdar A 2005, H2269 2010, ABCSG24 2009, NOAH 2010, Pierga JY,2010

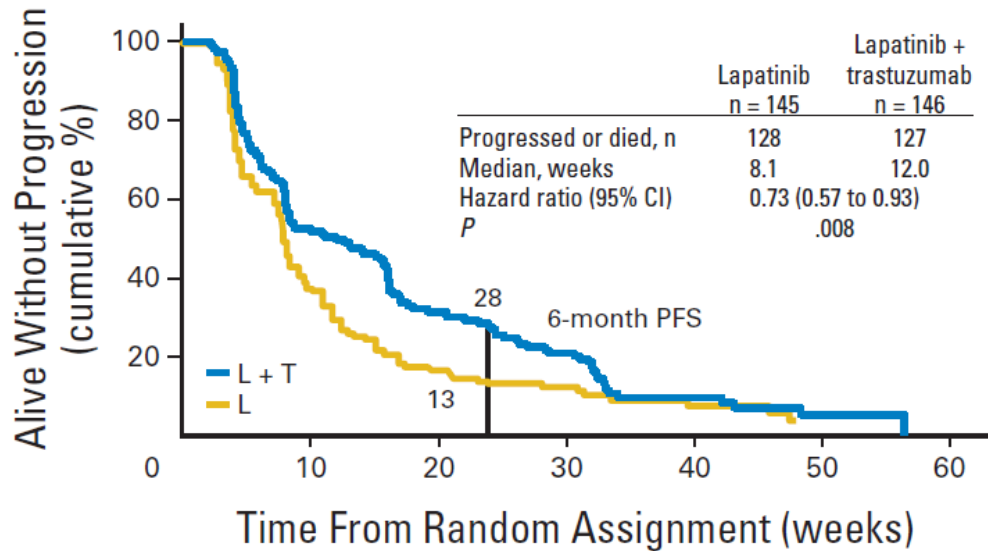
PCR rate of NACTx with Tmab for HER2-positive BC in Japanese trials



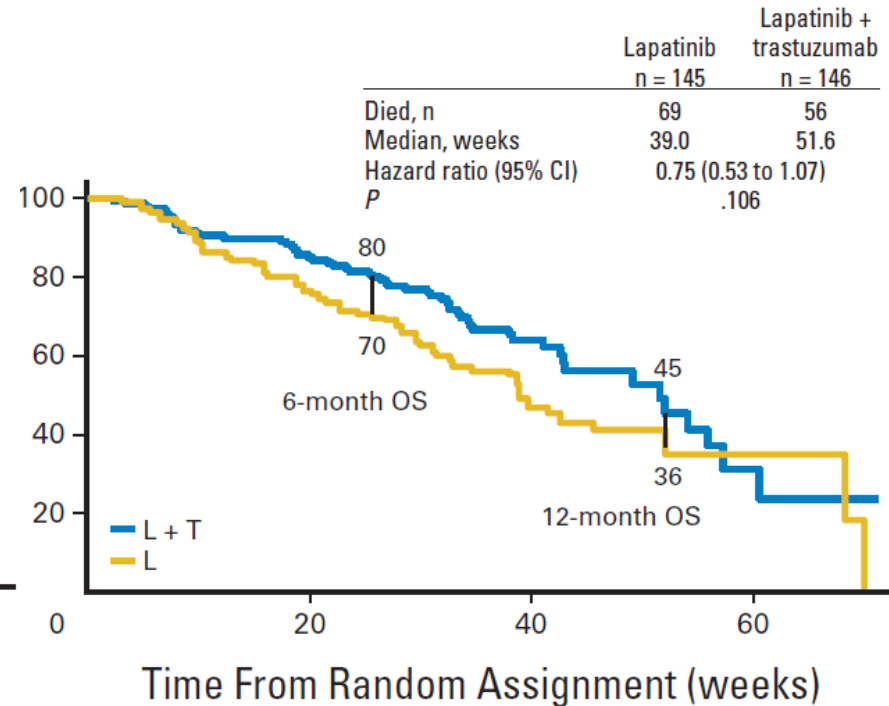
Differences of clinical complete response according to ER status



Comparison between lapatinib alone vs. combination with trastuzumab in women with HER2-positive, trastuzumab-refractory mBC



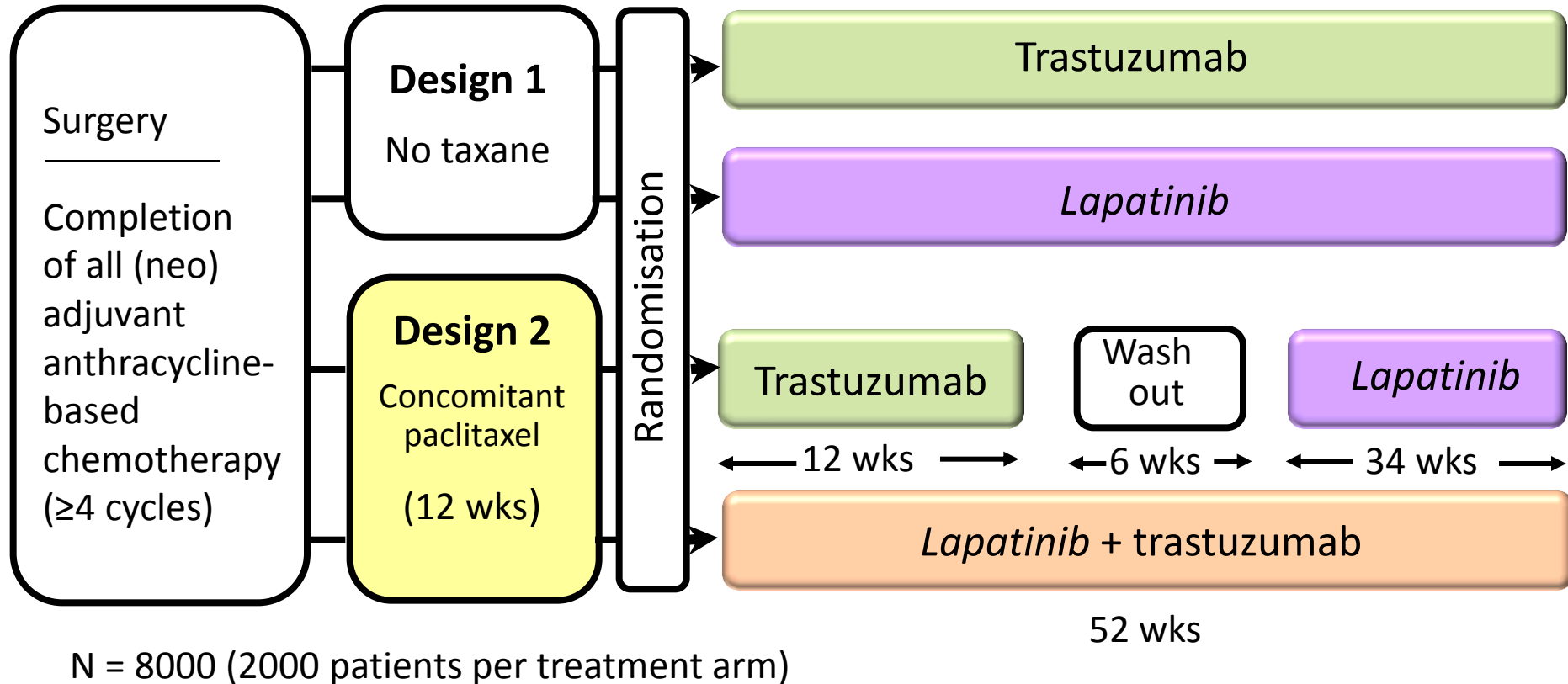
PFS (hazard ratio [HR] 0.73; 95% CI, 0.57 to 0.93; $P=0.008$)



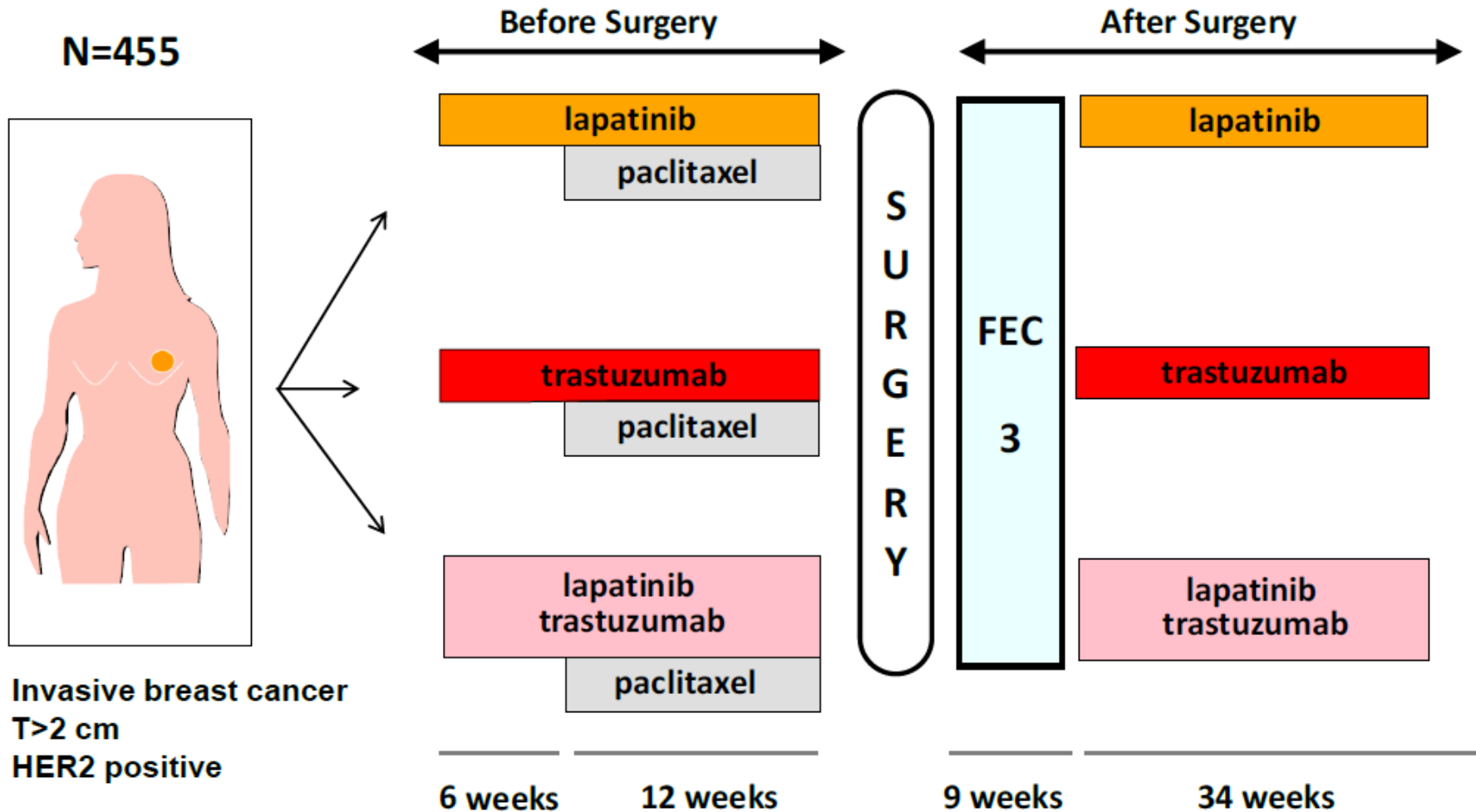
OS (hazard ratio [HR] 0.75; 95% CI, 0.53 to 1.07; $P=0.106$)

In adjuvant setting, ALTTO study is ongoing

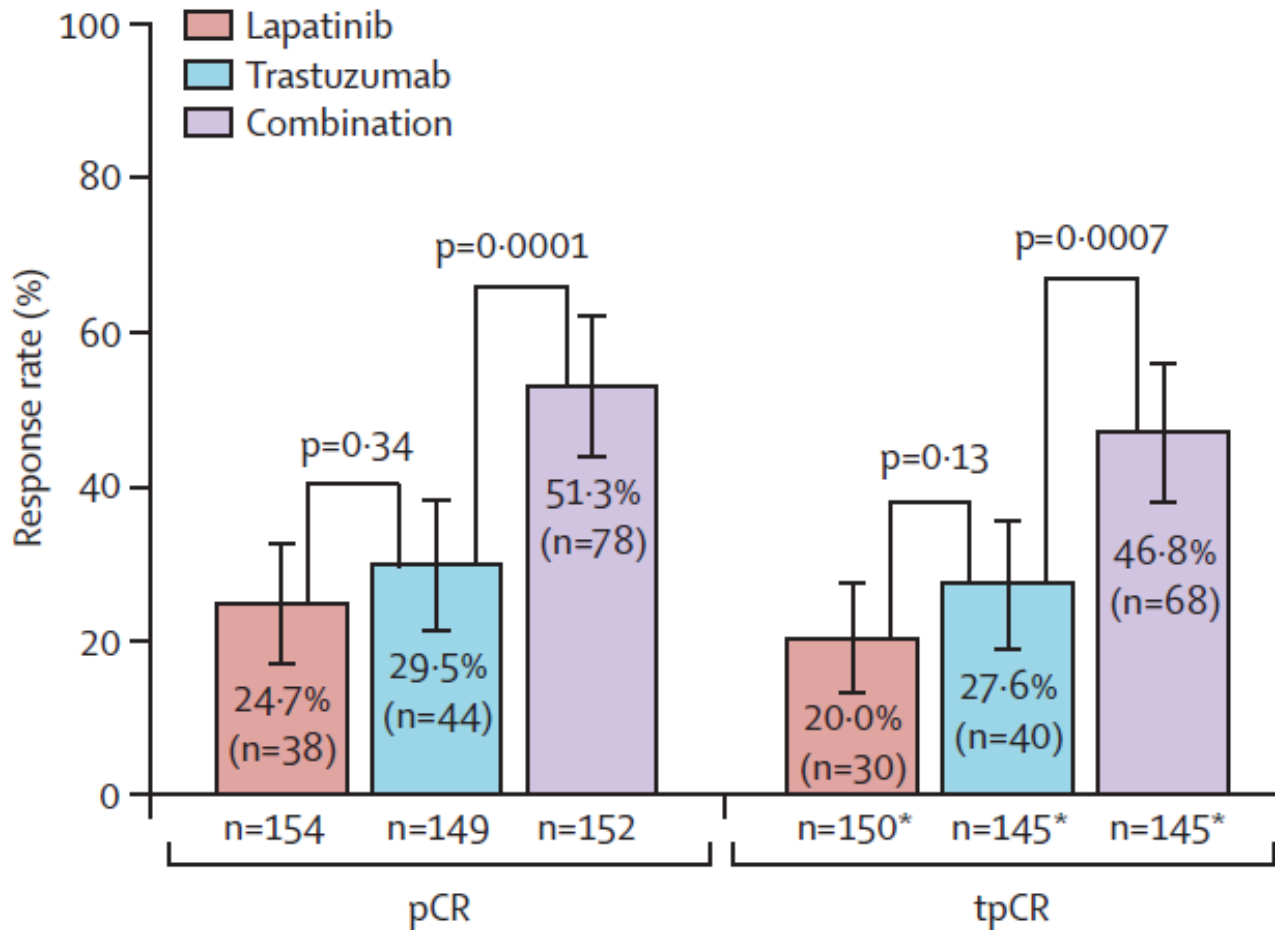
(Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation)



NeoALTTO; Study design



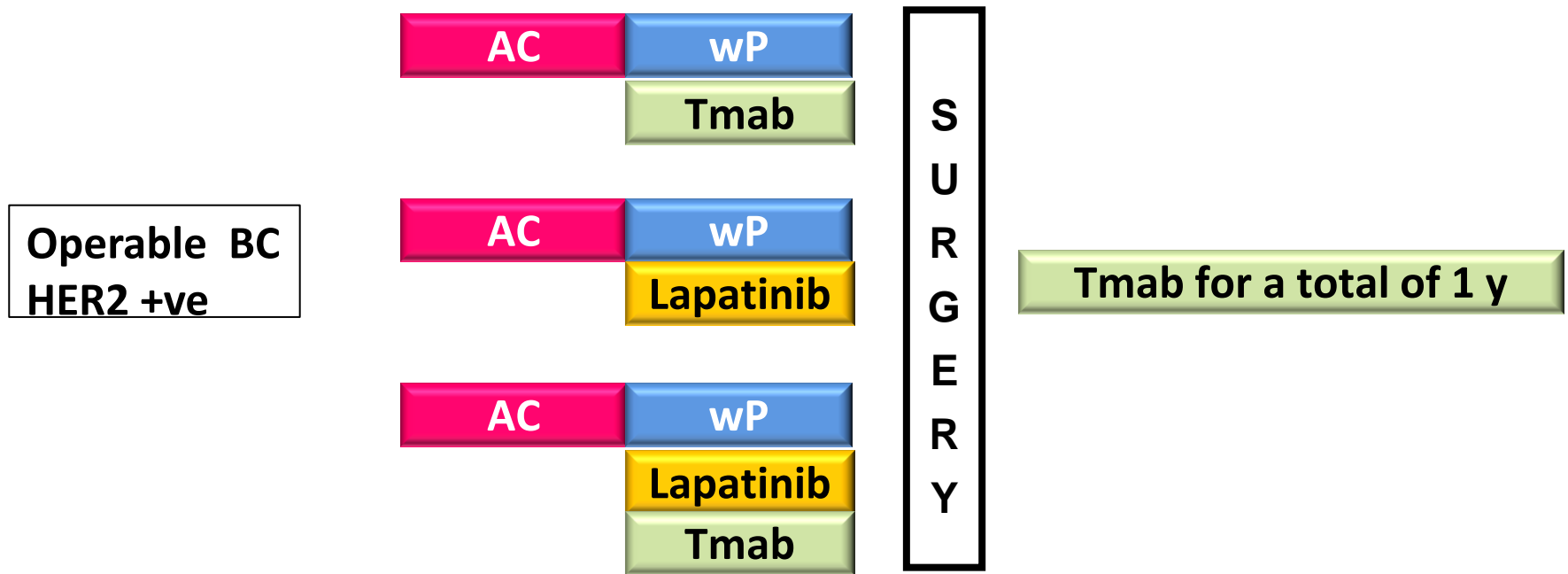
Efficacy; pCR (no invasive cancer in the breast), tpCR (no invasive cancer in the breast and no Ax) rates



Dual inhibition of HER2 might be a valid approach to treatment of HER2-positive breast cancer in the neoadjuvant setting.

NSABP B-41

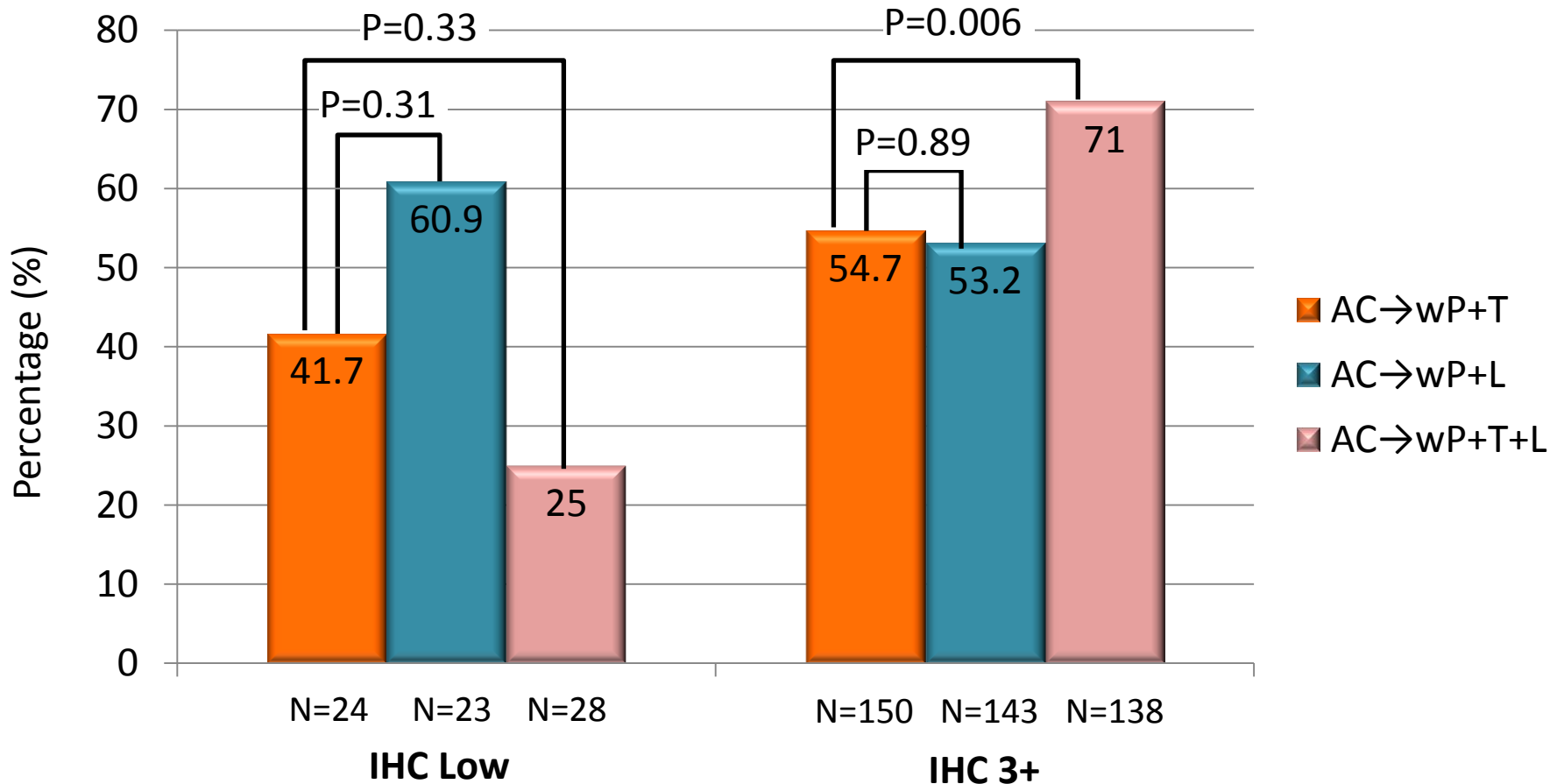
A Randomized Phase III Trial of NAT for Patients with Palpable and Operable HER2-Positive



Endpoints: pCR, cardiac events, DFS, OS, Predictor

NSABP B-41

The pCR based on HER2 overexpression



Test for interaction with IHC levels: AC→wP+T+L vs. AC→wP+T (P=0.021)

Dual blockade by lapatinib + Tmab is superior to each mono-targeting therapy.

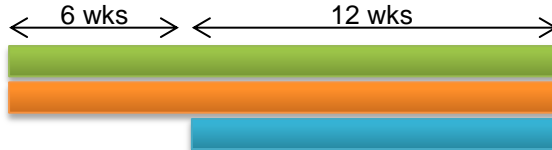
JBCRG-16 (Neo-LaTH trial)

Study design

HER2 positive
/ ER negative

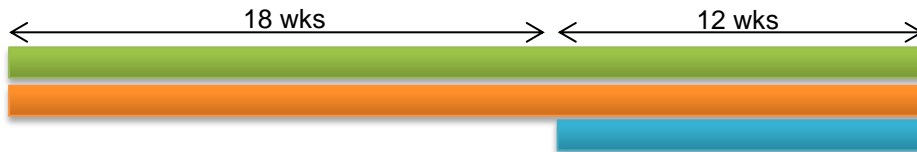
Randomization
(1:1)

Group A
(n=40)



⇒ Ope

Group B
(n=40)

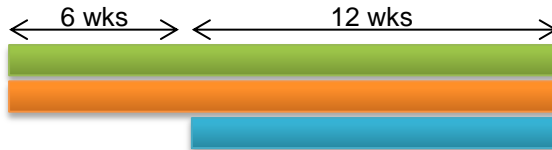


⇒ Ope

HER2 positive
/ ER positive

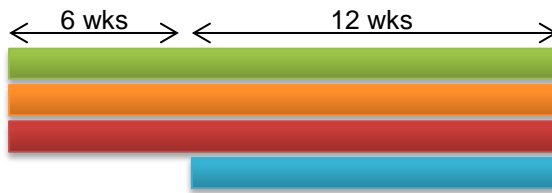
Randomization
(1:1:1)

Group C
(n=40)



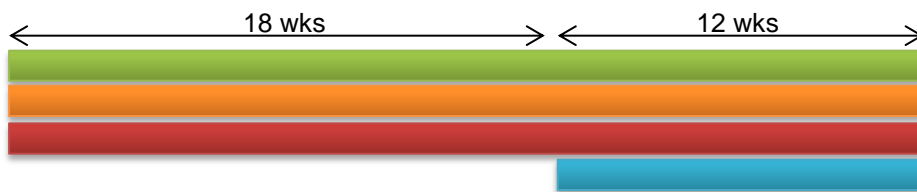
⇒ Ope

Group D
(n=40)



⇒ Ope

Group E
(n=40)



⇒ Ope

■ : lapatinib

■ : paclitaxel

■ : trastuzumab

■ : anti-hormonal therapy

Summary of anti-HER2 therapy

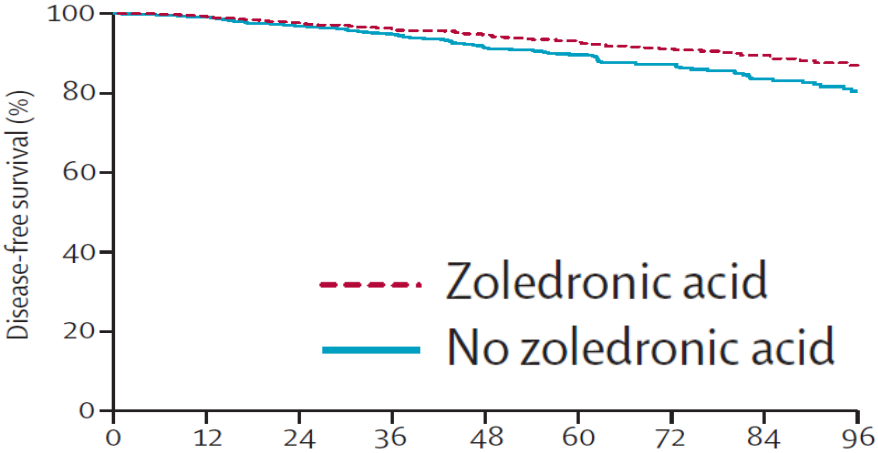
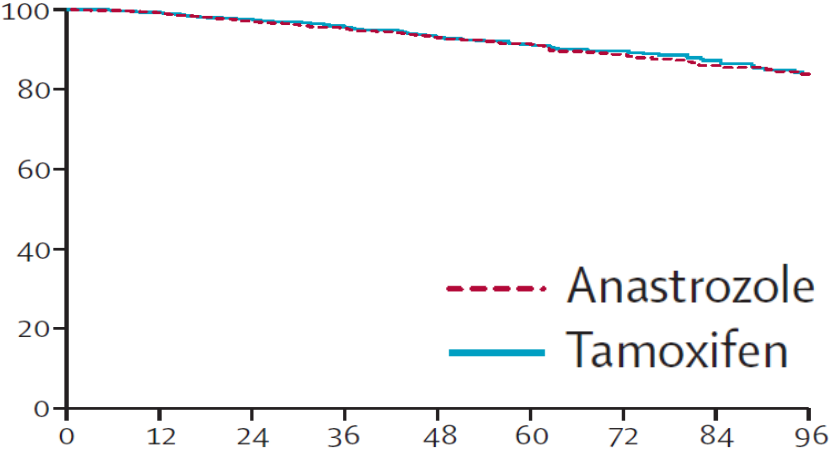
- Neoadjuvant CTx with Tmab has a high pCR rate compared to that without Tmab.
- Lapatinib + CTx may not be superior to Trastuzumab + CTx in neoadjuvant setting. In addition, dual blockade by lapatinib + Tmab can be adopted to neoadjuvant or adjuvant therapy.
- This combination trial is currently in progress by the Japanese Breast Cancer Research Group (Neo-LaTH trial) with reference to neo-ALTTO and NSABP-B41.
- Although pertuzumab and TDM1 will be soon used for metastatic breast cancer in Japan, the positioning of each anti-Her2 therapies should be discussed.

Trials of adjuvant and neoadjuvant endocrine therapy

Adjuvant trial	Primary analysis	Neoadjuvant Ki67 studies	Ki67 analysis
ATAC Baum et al. Lancet 2002	A > T = C n=9366	IMPACT Dowsett et al. Clin Cancer Res 2006	A > T = C n=147
BIG 1-98 Thurlimann et al. N Engl J Med 2005	L > T n=8010	P024 Ellis et al. Cancer Res 2003	L > T n=185
FACE Trial NCT00248170	A v L n=approx 4000	Murray et al. BCRT 2009	A = L
ABCESG-12 Gnant et al. N Engl J Med 2009	A = T n=1803	STAGE Lancet Oncol, 2012	A > T? n=197

A, anastrozole; C, combination; E, exemestane; L, letrozole; T, tamoxifen

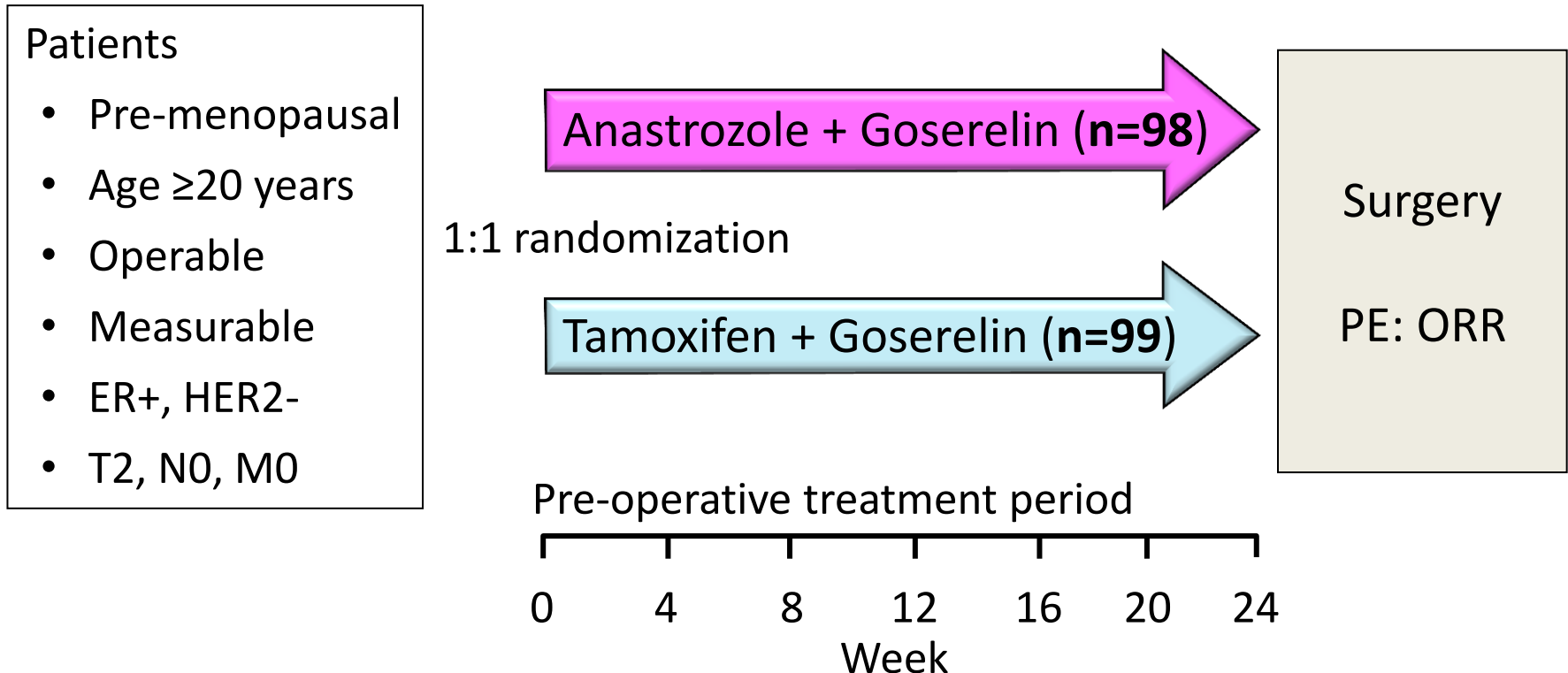
Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62month follow-up from the ABCSG-12 trial



	ANA vs TAM		Zol vs no-Zol	
	HR (95% CI)	P	HR (95% CI)	P
DFS	1.08(0.81-1.44)	0.591	0.68 (0.51-0.91)	0.009
OS	1.75 (1.08-2.83)	0.02	0.67 (0.41-1.07)	0.09

Study design of STAGE

Study of Tamoxifen or Arimidex, combined with Goserelin acetate, to compare Efficacy and safety

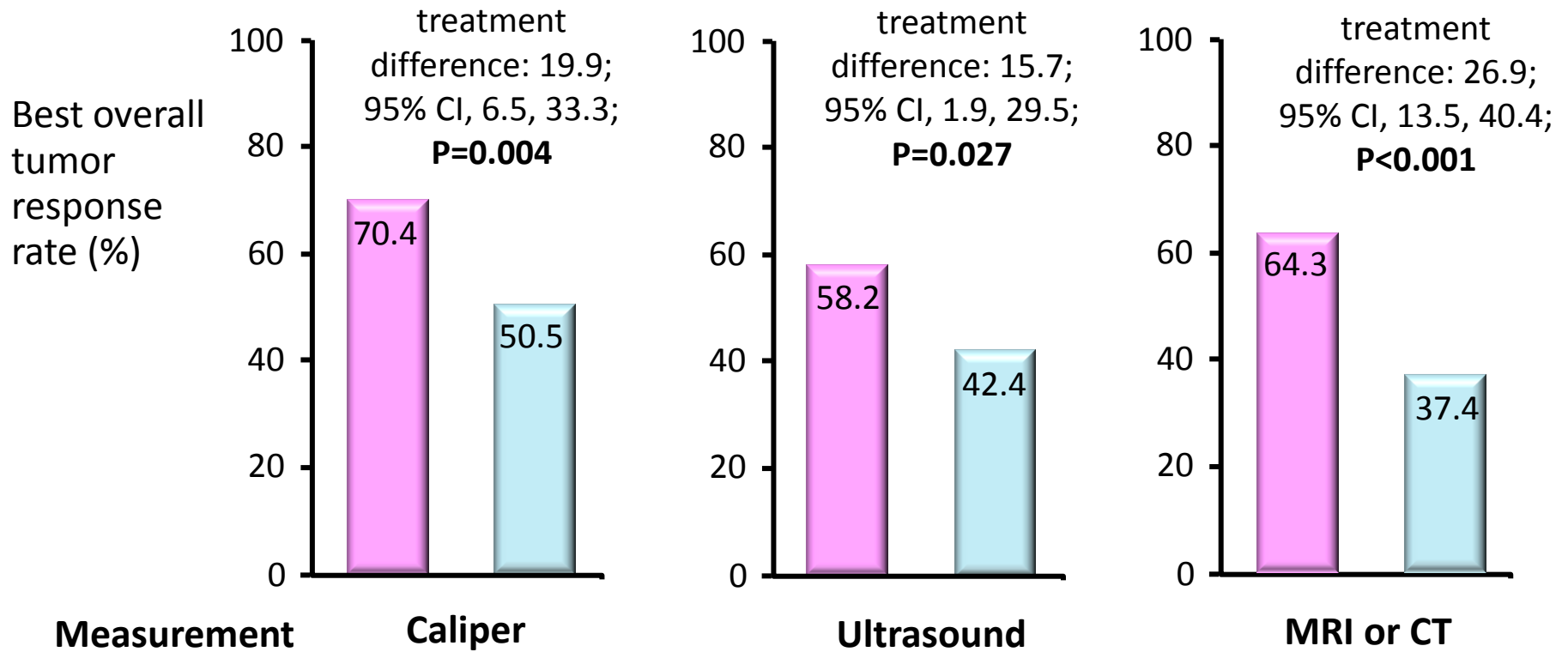


Measurement methods: caliper, ultrasound, MRI or CT

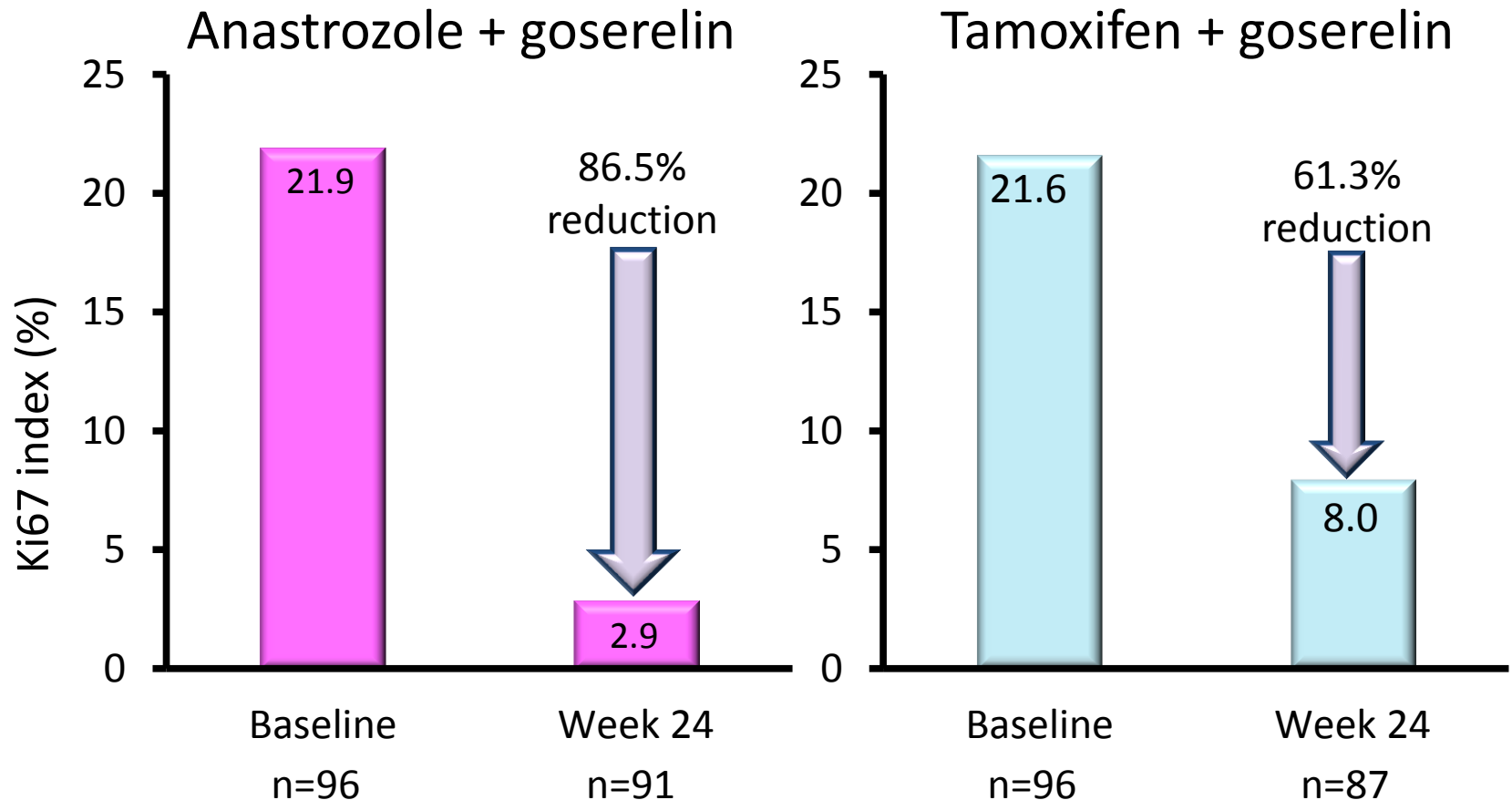
STAGE: best overall response rate

Anastrozole + goserelin (n=98)

Tamoxifen + goserelin (n=99)



Ki67 index at baseline and Week 24



Reduction ratio at Week 24 for anastrozole versus tamoxifen is 0.35 (95% CI, 0.24-0.51, $p < 0.001$). Unfortunately, we were not able to continue this trial for survival analyses considering the different results of ABCSG 12.

Potential reasons for inconsistency between STAGE and ABCSG12

- Best overall tumor response rate was significantly higher with anastrozole compared with tamoxifen in STAGE trial.
- In the STAGE study, reduction in Ki67 index was greater with anastrozole than tamoxifen in patients receiving goserelin.
- These trends are different to those in the ABCSG12 trial, possibly due to differences in baseline characteristics
 - HER2+ tumors were more frequently seen in ABCSG12
 - proportion of women with BMI >25 was lower in the STAGE study
- We already use the combination therapy of LHRH agonist with AI for ER+ Premenopausal women with advanced breast cancer in practice.

Conclusions

- Individualized therapy based on the biology of breast cancer must be developed more and more in future.
- There are lots of discrepancies between insurance based on clinical practice and the most up-to-date scientific knowledge.
 - Neoadjuvant (or adjuvant) anti-HER2 therapy for HER2-positive early breast cancer, e.g. lapatinib or lapatinib + trastuzumab
 - Neoadjuvant (or adjuvant) endocrine therapy for premenopausal ER-positive breast cancer, e.g. LH-RH agonist + AI
 - Multi-gene assay to avoid chemotherapy in luminal type
 - Genetic test for HBOCetc
- We have to share new knowledge constantly and proceed to discuss the revision of the insurance system through the breast cancer society of each country for the patients with breast cancer.

Thank you for your attention