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The role of HER-2 in Breast Cancer

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I. INTRODUCTION

Human epidermal growth factor receptor type2 (HER-2) was emerged as a molecular biomarker in breast cancer, as important as the estrogen-receptor (ER). It is located on chromosome 17q21.1 and is a member of the type I growth factor receptor family. In breast cancer, HER-2 is over-expressed in 20%–30% of primary tumors. The clinical behavior of human breast cancer associated with this gene was originally demonstrated in 1987 [1]. According to the initial report, HER-2 gene amplification could independently predict the time of disease relapse and overall survival in breast cancer patients. Thus, this gene is considered as one of the prognostic factors for breast cancer [2, 3]. However, conflicting results were reported later [4, 5]. This may be partly because of differences in the methodologies used to determine HER-2 status. At present, HER-2 is not considered a definite and independent prognostic marker of breast cancer [6].

Along with estrogen receptor (ER), HER-2 is an important gene for molecular targeting treatment of breast cancer. Thus, as a predictor of the efficiency of HER-2-targeted therapy, HER-2 status is established by a number of studies. Breast cancer cases with over expression of HER-2, as determined by immunohistochemistry or gene amplification by fluorescence in situ hybridization (FISH) showed a high rate of response to HER-2-targeted therapy [6].

For the treatment of breast cancer, HER-2 is useful from 2 clinical aspects as a target of HER2 inhibitors and a predictor of the efficiency of anti-cancer agents. Inhibition of HER-2 is necessary for treating breast cancer with HER-2 over expression (HER-2 subtype). At present, molecule-targeting drugs against HER-2, such as trastuzumab and lapatinib, are successfully used on a routine clinical basis, although the long-term outcome is still unknown. Without HER-2 Inhibitors, treatment would not be possible for cancers of the HER-2 subtype.

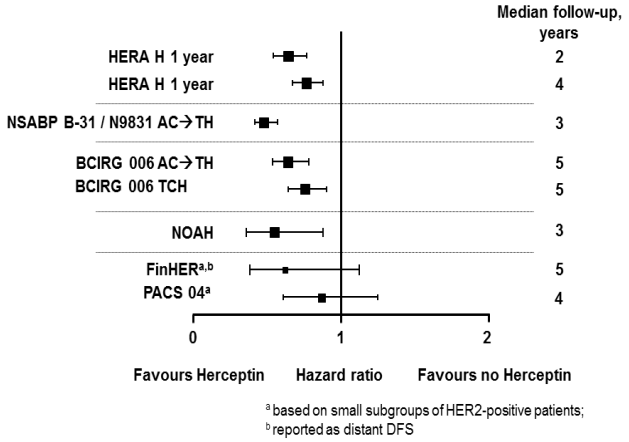

Fig. 1. Benefits of Herceptin for Disease-free Survival. Data reproduced from Gianni L et al. Abstract 25 presented at the 11th International Conference on the Primary Therapy of Early Breast Cancer, St Gallen, Switzerland, 11-14 March 2009.; Gianni L et al. Lancet 2010; 375: 377-384.; Joensuu H et al. Abstract presented at the St Gallen Primary Therapy of Early Breast Cancer 11th International Conference, St Gallen, Switzerland, 11-14 March, 2009; abs S24.; Perez EA et al. J Clin Oncol (Meeting Abstracts) 2007; 25: 6s, abs 512.; Slamon D et al. Oral presentation 62 at the 32nd SABCS, San Antonio, Texas, USA, 10-13 December 2009.; Smith IE et al. Lancet 2007; 369: 29–36.; Spielmann M et al. Breast Cancer Res Treat 2007; 106 (Suppl 1): S19.

HER-2 could also be used as a predictor of the efficiency of cytotoxic agents. ER negativity, proliferating markers, and HER-2 over expression can be used to predict the efficacy of any anti-cancer agent. Although there is no specific predictor for individual anti-cancer agents, HER-2 seems to be the most promising predictor, especially for anthracycline. Meta-analyses have revealed that the efficacy of anthracycline is confined to HER-2 subtype cancers [7-10].

Anthracycline is still a primary drug for the treatment of breast cancer, but from these findings, it seems that the use of anthracycline for the chemotherapy for breast cancer is questionable. For the treatment of HER-2 subtype breast cancers, a combination of anti-cancer agents and HER-2 inhibitors needs to be considered because HER-2 inhibitors are indispensible for this treatment. We need to determine whether anthracycline can be used as an anti-cancer agent in combination with HER-2 inhibitor.

As the mechanisms of breast cancer development and proliferation are being elucidated, the strategies for treating breast cancer have also changed drastically. I intend to review and discuss the influence of HER-2 on individual treatment strategies for breast cancer.

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II. TARGET OF HER-2 INHIBITORS

A monoclonal antibody directed against the extracellular domain of p185HER2 was introduced in 1989 [11]. With the use of recombinant technologies, trastuzumab, a monoclonal IgG1 class humanized murine antibody, was successfully developed as a "bench to bedside" medicine. It was initially used for patients with advanced relapsed breast cancer with over expression of HER-2, and the treatment showed significant survival benefit [12]. Since then, it has become an important therapeutic option for patients with HER-2-subtype cancer and is, at present, widely used in both adjuvant and metastatic settings [13-19] (Fig.1). Although trastuzumab is approved of as a single-agent regimen, most patients are administered other anti-cancer agents along with it.

Lapatinib is the second clinically available HER-2 inhibitor, which is a small-molecule dual inhibitor of the epidermal growth factor receptor (EGFR) and HER-2 tyrosine kinases. It was introduced in 2007, almost 10 years after the introduction of trastuzumab [20]. In combination with capecitabine, it is effective for the treatment of metastatic, HER-2-positive breast cancer after the standard treatment [21] (Fig.2). Since the combination of lapatinib and capecitabine improved survival in breast-cancer patients, they are, at present, used in combination. Although there are several ongoing phase III trials in adjuvant settings for lapatinib alone and in combination with other anti-cancer agents, efficacy data have not yet been published [22,23] (Fig.3).

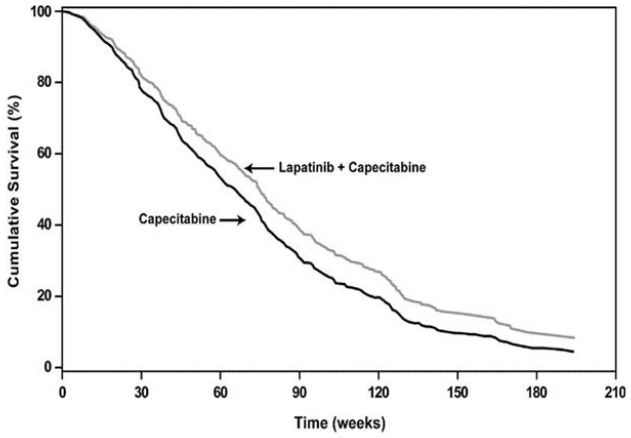

Fig. 2. Kaplan–Meier estimates of overall survival curves of lapatinib + capecitabine and capecitabine alone. The adjusted hazard ratio of 0.81 (95% CI, 0.65–1.00; p = .051) represents a 19% lower risk for death for patients treated with lapatinib plus capecitabine than for those treated with capecitabine alone. The adjusted survival curves considering these main treatment effects show that the survival benefit was maintained over time in the combination arm. Data reproduced from Cameron D et al. The Oncologist 2010.

Given the proven efficacy of trastuzumab and lapatinib for the treatment of HER-2-positive breast cancer, accurate and reliable methods to determine HER-2 status have become an important issue to avoid misclassification of HER-2-positive breast cancers as HER-2 negative. If this treatment is administered on the basis of such misclassification, patients will have to unnecessarily bear the cost of the treatment and the potential adverse effects of these drugs. Further refinement of HER-2 diagnostic tests, and development of efficient and resistant biomarkers, and toxicity predictors of HER-2 inhibitors are required.

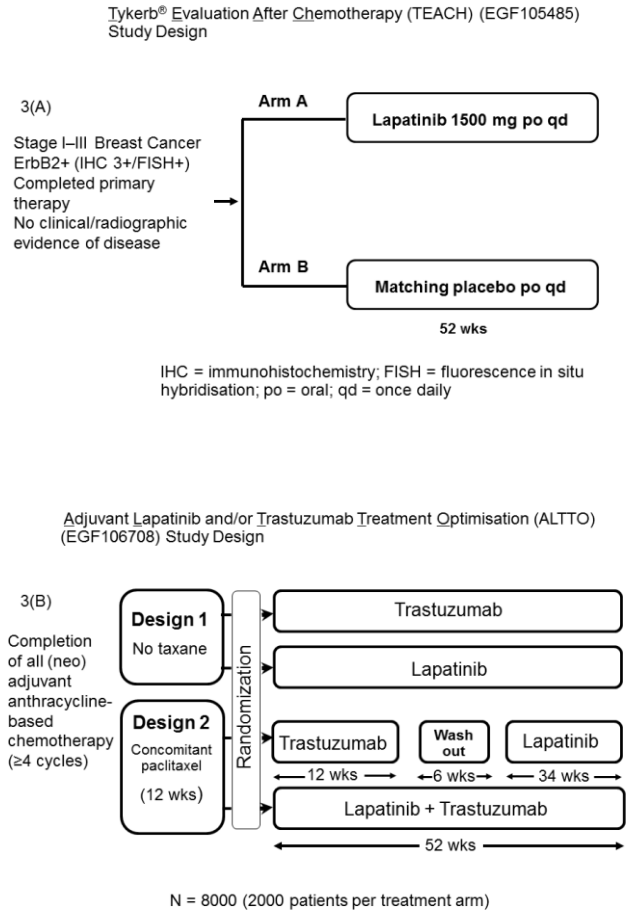

Fig. 3 (A) Tykerb® Evaluation After Chemotherapy (TEACH) (EGF105485) study design: use of lapatinib in adjuvant setting. Key inclusion criteria for the TEACH study include initial diagnosis of confirmed breast cancer Stage I–III, ErbB2-positive (IHC 3+ or FISH+), completed primary therapy and no clinical/radiographical evidence of disease. Patients will be randomised to receive either lapatinib 1500 mg orally once daily or placebo for 52 weeks.

(B) Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) (EGF106708) Study Design: use of lapatinib in adjuvant setting1. Design 1 of this randomised, multicentre, Phase III study will compare the efficacy of lapatinib alone, versus trastuzumab alone, versus trastuzumab followed by lapatinib, or versus lapatinib plus trastuzumab, as adjuvant treatment. Design 2 is similar except that all patients will also receive concurrent paclitaxel for the first 12 weeks after randomisation. This pioneering collaborative group study is one of the largest adjuvant breast cancers studies to date (planned enrolment of 8000 patients) and the first truly global collaborative study. ALTTO will also provide the most comprehensive translational research to date, aimed towards identifying those patients most likely to respond to lapatinib treatment..

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III. PREDICTORS OF ANTI-CANCER AGENTS

Recent meta-analyses of published data have suggested that anthracycline-containing regimens are more beneficial than nonanthracycline-containing regimens in patients with HER-2 over expression [7-10] (Fig.4). This is partly because HER-2 is located in the same amplicon of chromosome 17 as the topoisomerase IIa gene (TOP2A), which is a target gene of anthracyclines (Fig.5) [24]. As compared to the amplification of the HER2 gene, amplification or deletion of the TOP2A gene in breast cancers is postulated to be more closely associated with responsiveness to anthracycline-containing chemotherapy [25-27]. However, it remains unclear that HER-2 and/or TOP2A amplification/alteration are ready for routine clinical use in selecting anthracycline-containing chemotherapy.

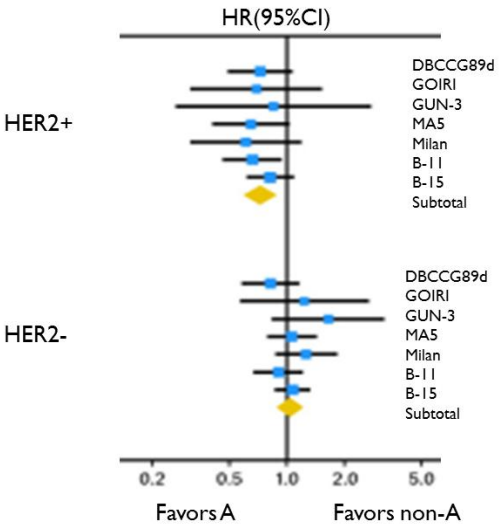

Fig 4. Meta-analysis of hazard ratios in trials comparing anthracycline- vs non-anthracycline-based regimens by HER-2 status: Overall survivals. Seven studies provided sufficient information to be included in a meta-analysis of overall survival (OS)s. In this meta-analysis, there was a significant treatment benefit for anthracycline-based regimens in patients with HER2-positive cancer for OS (HR = 0.73; 95% CI, 0.62 to 0.86) but there was no significant benefit in patients with HER2-negative cancers (OS HR = 1.03). Data reproduced from Pritchard KI et al. JCO 2008.

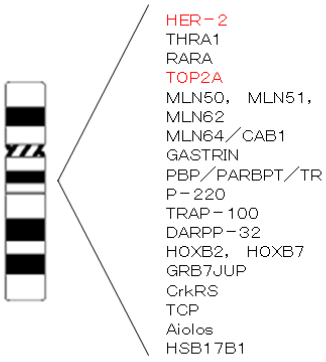

Fig 5. From one target gene to multiple target genes. HER-2 amplicon has been reported to have other relevant genes co-amplified (or deleted) at human chromosome locus 17q12–q21. These genes could have significant impact on the biological phenotype of the tumor when amplified (or deleted) together with HER-2 including topoisomerase IIα. Data reproduced from Jarvinen TA, Liu ET. Breast Cancer Res Treat. 2003.

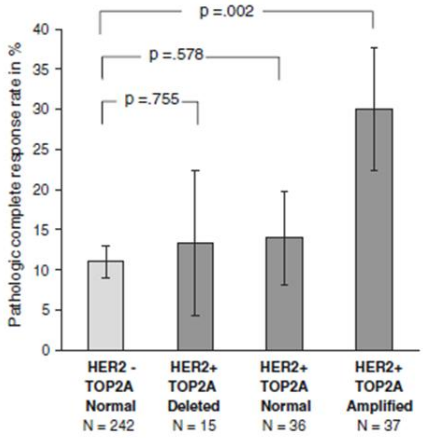

Fig 6. Pathologic complete response rates and disease-free survival. HER2 amplification was associated with a significantly higher pathologic complete response (pCR) rate only when TOP2A was co-amplified (30% vs. 11%, P = 0.002) but not when deleted (13% vs. 11%, P = 0.755) or normal (14% vs. 11%, P = 0.578) compared to HER2 non-amplified tumors. Data reproduced from Konecny GE et al. Breast Cancer Res Treat 2010.

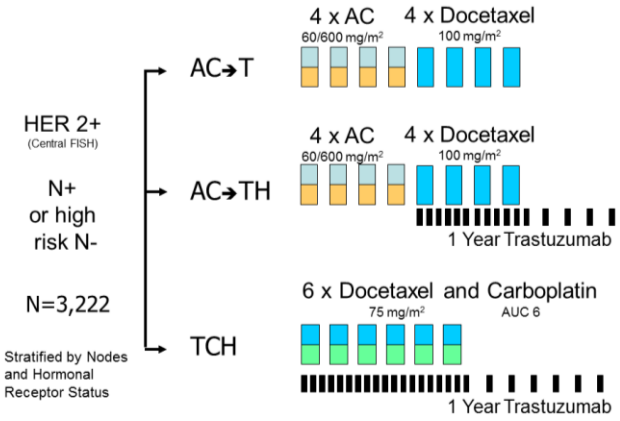

Fig. 7. BCIRG 006 Trial Design.

Accurate and reproducible measurement remain crucial [28].

Recently, a comprehensive study with the reliable FISH assay was performed to examine the association between the response of HER-2 and TOP2A to anthracycline (Fig.6) [29]. HER-2 amplification was found in 27% of 350 breast cancer patients. Among them, TOP2A amplification was found in 46%, and TOP2A deletions in 18%. TOP2A gene alterations were not found in HER-2 non-amplified cases. HER-2 amplification was associated with a significantly higher pathologic complete response (pCR) rate only when TOP2A was co-amplified, but not when it was deleted or expressed at normal levels, as compared to HER-2 non-amplified tumors. In multivariate analysis, TOP2A amplification, but not HER-2 amplification, was associated with a significantly higher pCR rate.

The BCIRG 006 Trial included the validation of TOP2A gene amplification as a predictor of anthracycline benefit in a trastuzumab-based adjuvant treatment setting (Fig.7) [18]. However, it is not confirmed that TOP2A amplification testing is reliable as an indicator for anthracyclines in the treatment of HER-2–positive breast cancer.

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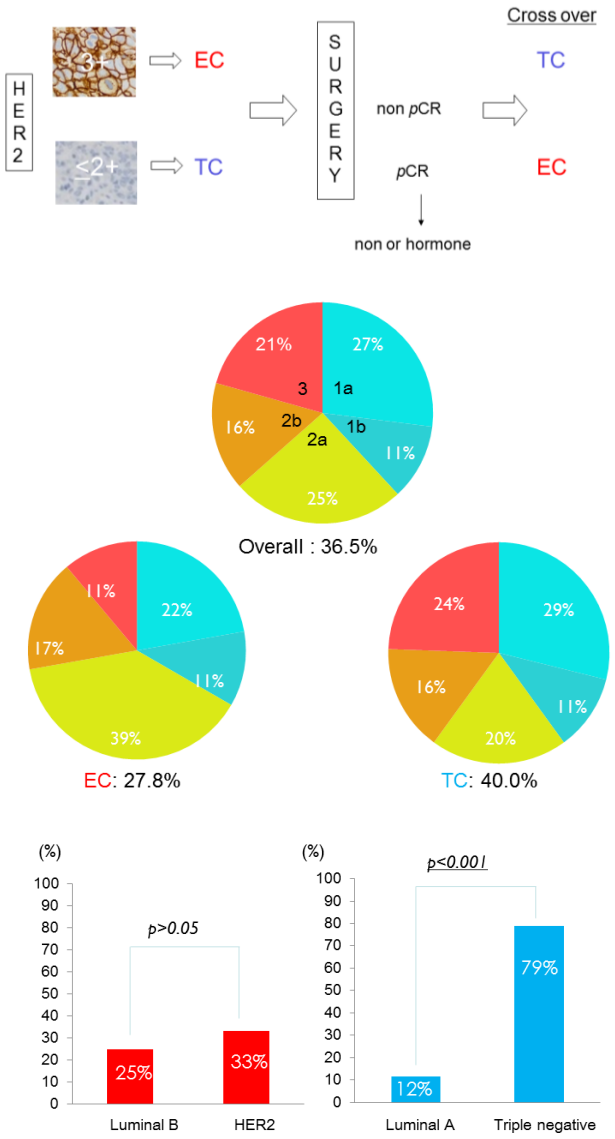

Fig 8. (A) Study Design of HER2-based Neoadjuvant Chemotherapy. Treatment plan: EC was given to patients with HER2 3+ tumors, while TC to the others. When QpCR was not achieved, cross over treatment was recommended. **(B) QpCR Rates for Overall, EC- and TC-** treated Cases. Pathological responses for overall treatment and AC or TC treatment. A QpCR was seen more frequently in the TC group than in the AC group. **(C) QpCR rates for Each Subtype**. Relationship between QpCR and histological subtypes in AC and TC regimens. Data reproduced from Ishikawa T et al. Jpn J Clin Oncol. 2010.

At present, the measurement of TOP2A gene is not standardized yet. Thus, we conducted a pilot study of the tailored treatment based on HER-2 (Fig.8A) [30]. Based on the findings; (1) the benefits of anthracyclines appear to be confined to patients with the HER-2 subtype of breast cancer [7-10]), and (2) the efficacy of the docetaxel and cyclophosphamide (TC) regimen was superior to that of the neoadjuvant doxorubicin-cyclophosphamide (AC) regimen [31, 32], patients with tumors over expressing HER-2 received 4 cycles of 60 mg/m2 anthracycline and 600 mg/m2 cyclophosphamide (AC) every 3 weeks, while those with tumors that did not over-express HER2 received 4 cycles of 75 mg/m2 docetaxel and 600 mg/m2 cyclophosphamide (TC) every 3 weeks, preoperatively. A quasi-pathological complete response (QpCR) (i.e. absence of invasive tumor or only focal residual tumor cells) was the primary endpoint with compliance and predictors for each regimen as secondary endpoints. If a QpCR was not achieved, then crossover to the alternative treatment was recommended. The QpCR rate was 36.5% (23/63) overall, 27.8% (5/18) for the AC regimen and 40.0% (18/45) for the TC regimen (Fig.8B). TC treatment induced a QpCR in most patients with triple-negative tumors (15/19) (Fig.8C). Thus, selecting neoadjuvant chemotherapy regimens on the basis of individual HER-2 status improved the efficacy of the treatment, with the TC regimen showing particular promise in the treatment of malignant tumors.

Thus, along with ER, the determination of HER-2 status independently has become an important factor in treating breast cancer patients.

IV. OPTIMAL COMBINATIONS OF HER-2 INHIBITORS WITH ANTI-CANCER DRUGS

Because HER-2 inhibitors are indispensible for breast cancer treatment, the interaction between HER-2 inhibitors and anti-cancer agents needs to be considered for treating HER-2 subtypes of breast cancer. Preclinical data available on these combinations can be used to determine rational combinations of trastuzumab with other chemotherapeutic drugs. The interaction between trastuzumab and anti-cancer drugs in HER-2-overexpressing breast cancer cell lines was examined in one study, which showed that the anthracyclines, doxorubicin and epirubicin acted additively with trastuzumab [33] (Fig.9). A randomized clinical trial demonstrated that doxorubicin-based chemotherapy combined with trastuzumab

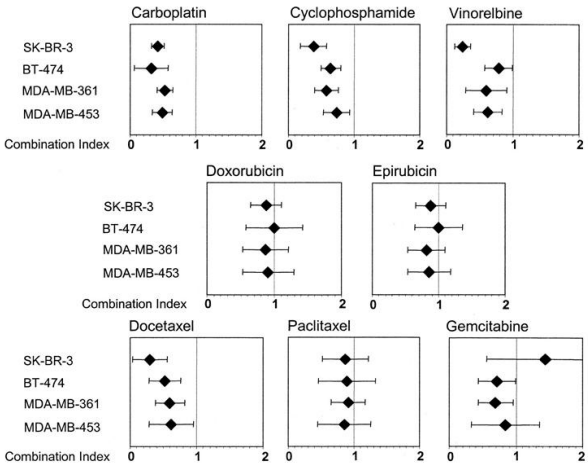

Fig 9. Mean combination index values for anticancer drug–trastuzumab combinations. Mean combination index values for chemotherapeutic drug–trastuzumab combinations in four different human breast cancer cell lines. Quantitative interactions between trastuzumab and different chemotherapeutic drugs representing six classes of cytotoxic anticancer drugs were tested and confirmed using four different HER2-overexpressing breast cancer cell lines. The synergistic reaction with trastuzumab was observed for cyclophosphamide, carboplatin and docetaxel. Data reproduced from Pegram M D et al. J Natl Cancer Inst 2004.

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showed better results than chemotherapy alone. However, cardiotoxicity was observed clinically, which was not predicted in preclinical studies. Thus, the concurrent use of anthracyclines and trastuzumab is not practical.

Synergy with trastuzumab was clear in the case of cyclophosphamide, carboplatin and docetaxel (Fig.9). As cyclophosphamide is a widely used alkylating agent, this finding may be clinically useful in that it indicates the possible efficiency of chemotherapy regimens combined with trastuzumab. More importantly, docetaxel might be the better counterpart drug than anthracycline (Fig.9,10). The combination of docetaxel and cyclophosphamide (TC) regimens has been associated with superior disease-free survival rates compared with AC regimens [31, 32]. Thus, TC in combination with trastuzumab could be a potential anti-cancer regime.

As carboplatin and docetaxel act in a highly synergistic manner, the combination of carboplatin, docetaxel, and trastuzumab was investigated using the multiple drug effect/combination index model, which demonstrated that the three-way interaction between trastuzumab, carboplatin, and docetaxel was highly synergistic [33]. Based on these preclinical data of interaction of drugs with trastuzumab, the phase III study of BCIRG006 was launched (Fig.7) [18]. Although it has not been published yet, the researchers presented an interim report, which was, by and large, consistent with their prediction.

V. SUMMARY

In summary, the discovery of HER-2 has changed the landscape of breast cancer treatment. This type of breast cancer is characterized by HER-2 gene over expression, which might be an early and crucial step in the development of the tumor. Treatment for breast cancer cannot proceed without determining HER-2 status. After the successful introduction of trastuzumab, inhibiting the expression of this gene is proved to be important for the treatment of this subtype of breast cancer. Inhibitors that target HER-2 have been actively investigated.

At present, we need to consider tailoring treatments according to the subtype of breast cancer. For non-HER-2 subtypes, we are not aware of the kind of anti-cancer agents that should be chosen. As for HER-2 subtypes, it was initially reported that S-phase-specific chemotherapeutic agents might be effective, because over expression or amplification of this gene is associated with an increased growth fraction. We are yet to decide the cytotoxic agents that should be used in combination with each HER-2 inhibitor. Anthracyclines, the most important S-phase-specific agents for breast cancer, may not be the best counterpart for HER-2 inhibitors. Taken together, breast cancer treatment may be entering an era where anthracyclines will no longer be in use.

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