FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

September 12, 2013

sBLA 125409/51
Pertuzumab (PERJETA®)
Applicant: Genentech, Inc.

Disclaimer*: The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the pertuzumab neoadjuvant application to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.*

1. Introduction

Genentech, Inc. submitted a supplemental Biologics License Application (sBLA) to support marketing approval of Perjeta (pertuzumab) for the following indication:

"PERJETA is a HER2/neu receptor antagonist indicated for:
Neoadjuvant treatment of breast cancer, in combination with trastuzumab and docetaxel for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin."

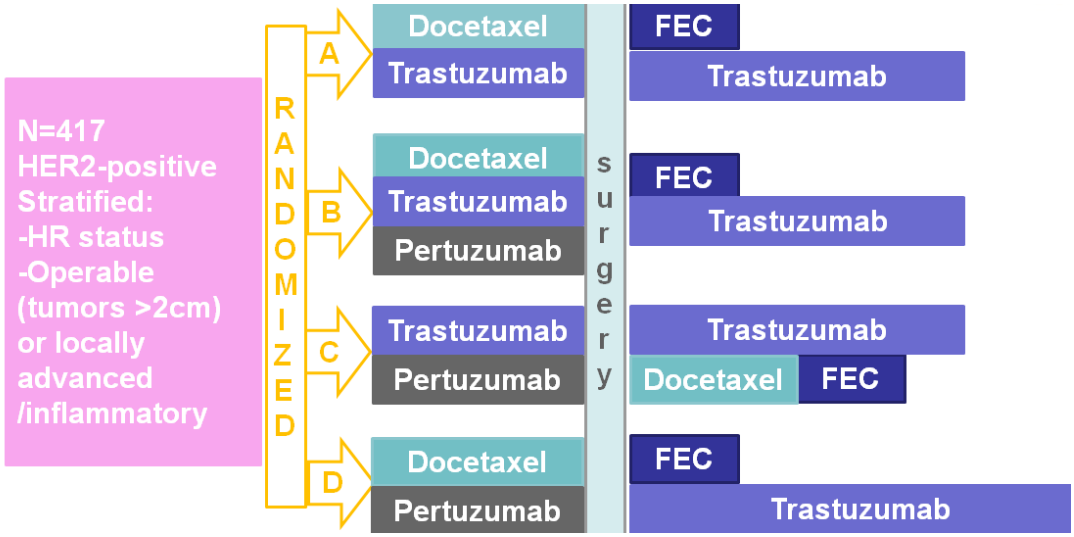
Currently there are no FDA approved agents for the neoadjuvant (preoperative) treatment of breast cancer. Since this is the first application for a neoadjuvant indication, FDA would like to have a public discussion at ODAC.

2. sBLA Summary

Pertuzumab is a monoclonal antibody that targets the extracellular domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2). Pertuzumab was approved in June 2012 and is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Main Study:
The main study supporting this efficacy supplement is NEOSPHERE (WO20697), a multicenter, randomized trial designed to evaluate four neoadjuvant regimens in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d). Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery: trastuzumab plus docetaxel, pertuzumab plus trastuzumab and docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel (Figure 1). The main comparison for this sBLA review is trastuzumab plus docetaxel (control) vs. pertuzumab plus trastuzumab and docetaxel (experimental). Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity. The primary endpoint of the study was pathological complete response (pCR) rate defined as absence of invasive cancer in the breast (ypT0/is).

Figure 1: NEOSPHERE Study Design



The NEOSPHERE study efficacy results are summarized in Table 1. Statistically significant improvements in pCR rates were observed in patients receiving pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel. The pCR rates and magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors.

Table 1: Summary of Efficacy from NEOSPHERE

Endpoint/Study Population	H + T	Ptz + H + T	Ptz + H	Ptz + T
Overall ITT	**N=107**	**N=107**	**N=107**	**N=96**
pCR[1], n (%) [95% CI][2]	23 (21.5%) [14.1, 30.5]	42 (39.3%) [30.0, 49.2]	12 (11.2%) [5.9, 18.8]	17 (17.7%) [10.7, 26.8]
p-value (with Simes corr. for CMH test)[3]		0.0063 (vs. H+T)	0.0223 (vs. H+T)	0.0018 (vs. Ptz+H+T)
Hormonal receptor-positive subgroup	**N=50**	**N=50**	**N=51[4]**	**N=46**
pCR[1], n (%) [95% CI] 2	6 (12.0%) [4.5, 24.3]	11 (22.0%) [11.5, 36.0]	1 (2.0%) [0.1, 10.5]	4 (8.7%) [2.4, 20.8]
Hormonal receptor-negative subgroup	**N=57**	**N=57**	**N=55[4]**	**N=50**
pCR[1], n (%) [95% CI] [2]	17 (29.8%) [18.4, 43.4]	31 (54.4%) [40.7, 67.6]	11 (20.0%) [10.4, 33.0]	13(26.0%) [14.6, 40.3]

T=docetaxel, Ptz=pertuzumab, H=trastuzumab, CI=Confidence Interval

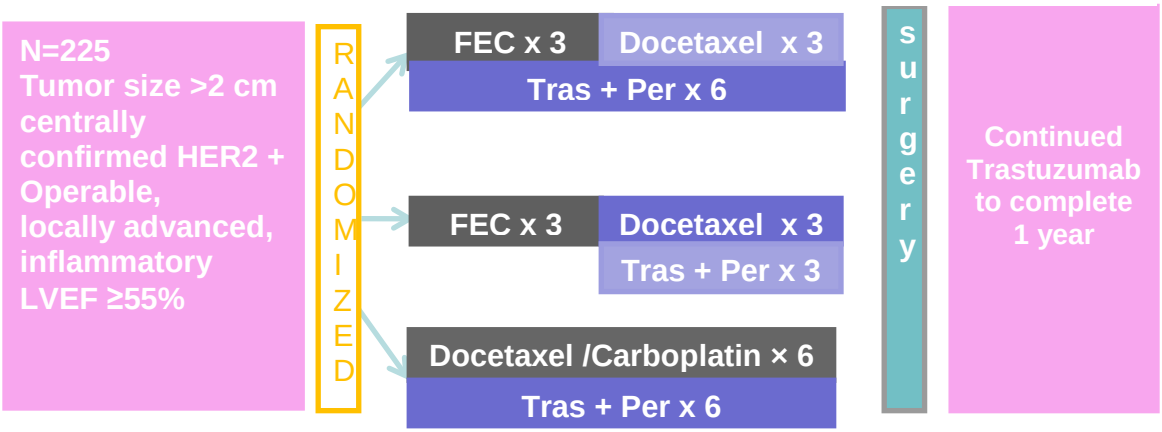
[1] ypT0/isypN0, [2] 95% CI for one sample binomial using Pearson-Clopper method. [3] p-value from Cochran-Mantel-Haenszel (CMH) test, with Simes multiplicity adjustment

[4] One patient had unknown hormonal receptor status. The patient did not achieve a pCR.

Supportive Studies:
Genentech submitted two additional studies to support this sBLA application.

TRYPHAENA (BO22280) is a randomized Phase 2 study conducted in 225 patients with HER2-positive, locally advanced, operable, or inflammatory (T2-4d) breast cancer (Figure 2). Patients were randomized to receive 1 of 3 neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with pertuzumab and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with pertuzumab, or 6 cycles of TCH in combination with pertuzumab. The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study. Secondary endpoints were pCR rate in the breast (ypT0/is), DFS, PFS, and OS.

Figure 2: TRYPHAENA Study Design



Higher pCR rates were observed in the 3 pertuzumab treatment arms compared to the NEOSPHERE study possibly due to the incorporation of the anthracycline regimen preoperatively. The results were consistent using the two pCR definitions (ypT0/is and ypT0/isypN0) (Table 2). Similar to the NEOSPHERE study results, the pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors (46.2% to 50.0% and 65.0% to 83.8% respectively).

Table 2: Summary of Efficacy from TRYPHAENA

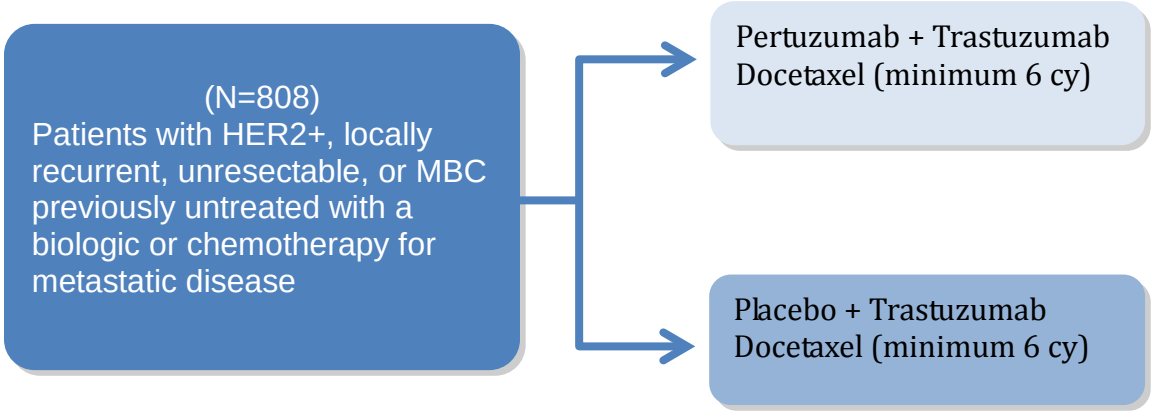
	FEC x 3→T x 3 Ptz + H x 6	FEC x 3→T x 3 + Ptz+H x 3	TCH x 6 + Ptz x 6
	N= 73	**N= 75**	**N= 77**
pCR[1], n (%) **95% CI**	45 (61.6%) [49.5, 72.8]	43 (57.3%) [45.4, 68.7]	51 (66.2%) [54.6, 76.6]
pCR[2] , n (%) **95% CI**	41 (56.2%) [44.1, 67.8]	41 (54.7%) [42.7, 66.2]	49 (63.6%) [51.9, 74.3]

FEC=5-fluorouracil, epirubicin, cyclophosphamide, T= docetaxel, Ptz= Pertuzumab, H= trastuzumab, TCH=docetaxel, carboplatin, trastuzumab , CI=Confidence Interval

[1] ypT0/is, [2] ypT0/isypN0, 95% CI for one sample binomial using Pearson-Clopper method.

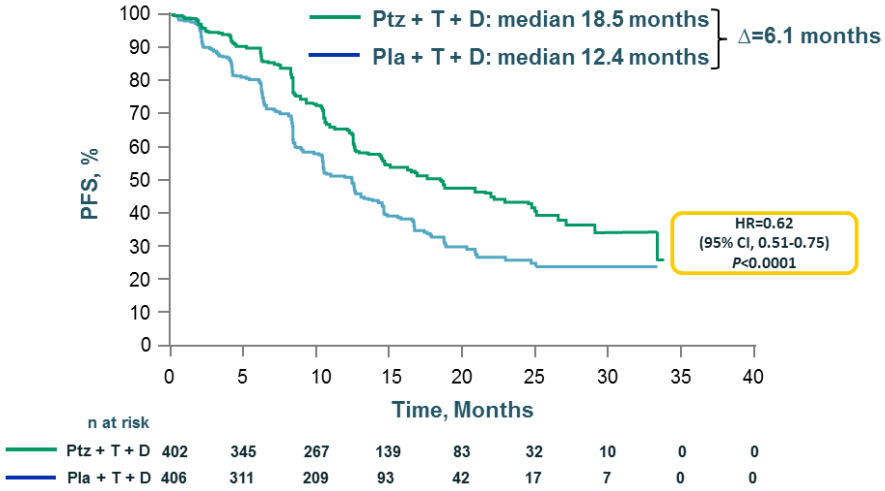
CLEOPATRA (Wo20698/TOC4129g) is a randomized, double-blind, placebo-controlled, multicenter trial in patients with HER2-positive metastatic breast cancer. The trial enrolled 808 patients who were randomly allocated (1:1) to receive pertuzumab in combination with trastuzumab and docetaxel (n=402) or placebo in combination with trastuzumab and docetaxel (n=406) (Figure 3).

Figure 3: CLEOPATRA Study Design



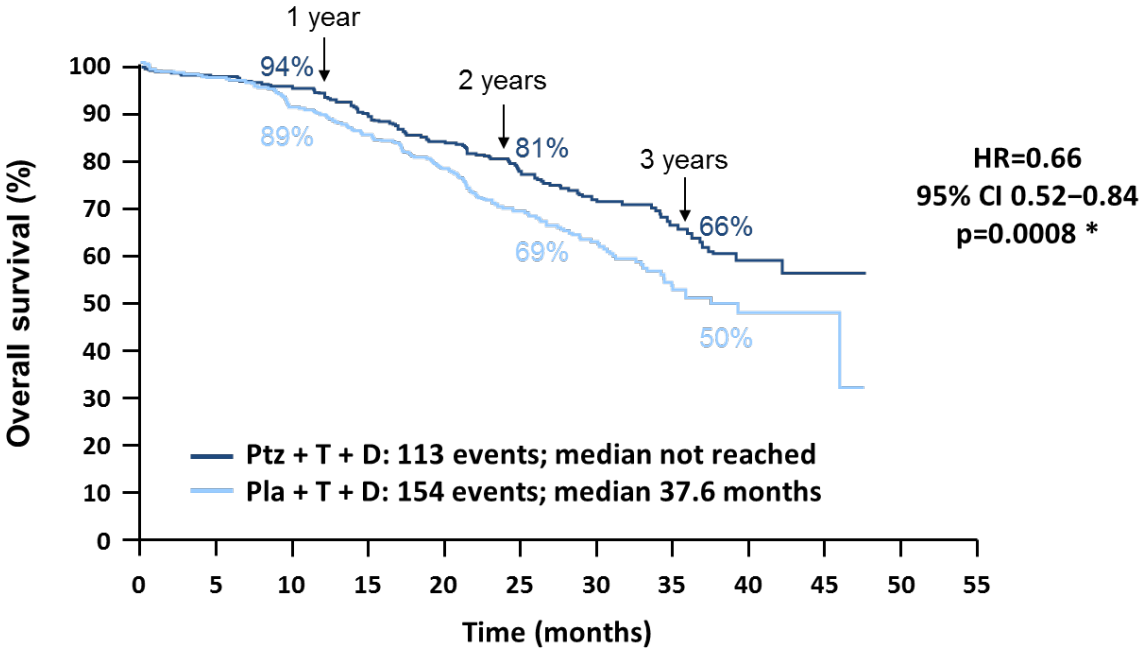
The basis of the initial approval was a statistically and clinically significant 6.1 month improvement in progression-free survival (PFS) in patients receiving pertuzumab compared to those receiving placebo [HR 0.62 (95% CI: 0.51, 0.75; p< 0.0001, log-rank test)] (Figure 4). The median PFS was 18.5 and 12.4 months for patients on the pertuzumab and placebo arms, respectively. At the time of PFS analysis, a planned interim analysis for overall survival (OS) was performed. The first interim OS analysis showed a trend towards improved survival with pertuzumab [HR 0.64 (95% CI: 0.47, 0.88), p=0.0053]. At the second interim analysis, the stopping boundary for statistical significance (p<0.0138) was crossed. Thus, the pertuzumab treatment arm demonstrated superiority in overall survival [HR=0.66, 95% CI (0.52, 0.84) p=0.0008]（Figure 5）.

Figure 4: Kaplan-Meier Curve of IRF-Assessed PFS for CLEOPATRA



Baselga J. et al, NEJM 2012

Figure 5: Kaplan-Meier Curve of Overall Survival for CLEOPATRA



* Boundary for statistical significance: p≤0.0138

Swain SM et al, Lancet Oncology 2013

3. Neoadjuvant Breast Cancer Treatment Background

New agents to treat breast cancer have historically been approved first in the metastatic setting, with approval for use in early-stage breast cancer following many years later based upon the results of large randomized adjuvant trials with prolonged follow-up. Neoadjuvant trials, in which systemic therapy is delivered prior to definitive breast cancer surgery, permit rapid assessment of drug efficacy and could expedite development and approval of treatments for early-breast cancer.

Despite advances in systemic therapy of breast cancer, there remains a need to expedite drug development and approval of highly effective therapies for patients with high-risk early-stage breast cancer. To improve the current drug development paradigm and to expedite approvals of treatments for early-stage breast cancer, the FDA is planning to open a regulatory pathway for approval of agents in the neoadjuvant breast cancer setting.

To learn about the endpoint that could support approval in neoadjuvant breast cancer, the FDA established an international working group known as Collaborative Trials in Neoadjuvant Breast Cancer (CTneoBC). Using primary source data from nearly 12,000 patients enrolled in neoadjuvant randomized controlled trials with pCR clearly defined and at least 5 years of follow-up available, FDA performed a meta-analysis to assess the relationship between pCR and long-term outcome [Cortazar et al. 2012]. In addition, the FDA published a Draft Guidance for Industry, outlining a pathway for future neoadjuvant breast cancer trials intending to use pathological complete response (pCR) to support accelerated approval. These issues were also extensively discussed on March 22, 2013, at the "Innovations in Breast Cancer Drug Development – Neoadjuvant Breast Cancer Workshop". Detailed background information is available via the following links:

- http://www.fda.gov/Drugs/NewsEvents/ucm339396.htm.
- Draft Guidance for Industry - Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval [PDF]
- TM Prowell and R Pazdur. Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer. N Eng J Med. 2012 Jun 28;366(26):2438-41
- P Cortazar, L Zhang et al. Meta-analysis results from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC). Cancer Research: December 15, 2012; Volume 72, Issue 24, Supplement 3

4. Issues

FDA would like the ODAC members to consider the following issues with this application:

a. Neoadjuvant trials require less time to assess the endpoint of pCR and differences in pCR can be detected with a smaller sample size than is required to detect differences in DFS/OS in post-operative adjuvant trials. However, conducting trials in the neoadjuvant setting early in drug development leads to a concern that patients with a curable disease may be exposed to unknown rare and late toxicities. Therefore, for a given application, the advantages of the neoadjuvant accelerated approval pathway should outweigh these concerns. The current sBLA for Perjeta® has supportive efficacy and safety data from the CLEOPATRA Phase 3 trial in the metastatic setting, which included a significant improvement in overall survival and an acceptable toxicity profile.

b. Pathological complete response has been proposed as a surrogate endpoint for predicting long-term clinical benefit in endpoints such as disease-free survival (DFS), event-free survival (EFS) and overall survival (OS). Among the 11,955 patients in the CTNeoBC meta-analysis, individual patients who attained a pCR were found to have improved EFS and OS. This association of pCR with EFS and OS is greater in patients with aggressive tumor subtypes (HER2–positive and triple-negative tumors) compared to less aggressive tumor subtypes. However, this meta-analysis found that while pCR has clear prognostic value for individual patients, an association between pCR and long-term outcome could not be confirmed at a trial level. The meta-analysis was unable to demonstrate that pCR is an established surrogate for EFS or OS, possibly because of the small improvements in pCR rates in most of the trials. However, FDA believes that with larger improvements in pCR rates with more effective treatments, pCR is a surrogate endpoint that is reasonably likely to predict clinical benefit and plans to open a regulatory pathway for accelerated approval of neoadjuvant treatments.

   An accelerated approval is subject to a postmarketing requirement to study the drug further to confirm clinical benefit. Since there is uncertainty regarding the ultimate long-term efficacy and safety of drugs approved under this pathway, long-term follow-up with confirmation of clinical benefit will be needed. As noted above, this regulatory approach has some benefits and risks. The potential benefits include allowing the use of an unestablished surrogate endpoint that can be assessed earlier than EFS or OS to permit earlier approval of highly effective agents for patients with an unmet medical need. The risks include approving an agent that ultimately does not demonstrate clinical benefit and, in the interim, exposing patients to the toxicity of therapy. We recognize that this is a trade-off

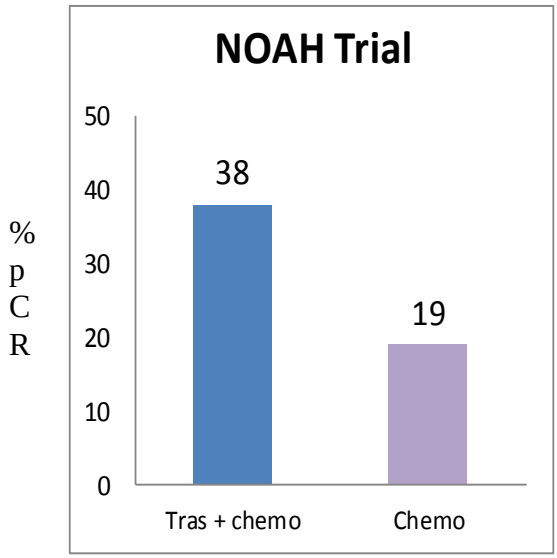
to provide earlier availability of promising anti-cancer agents. To justify the risks of this pathway, enrollment to neoadjuvant trials intended to support accelerated approval should be restricted to patients with high-risk early breast cancer.

In this case, the HER2-positive early breast cancer population is considered to be at sufficient risk of relapse to qualify for this regulatory pathway. The regulatory risks of this new pathway are reduced in this application because we already have strong supportive evidence of efficacy in the metastatic setting and a well characterized toxicity profile.

Genentech plans to submit efficacy and safety data from the ongoing and almost fully accrued Phase 3 study APHINITY (BO25126) that is investigating pertuzumab in the adjuvant setting, with a primary outcome measure of invasive disease-free survival (IDFS). The final analysis of IDFS from this study could permit confirmation of the clinical benefit of pertuzumab observed in the neoadjuvant setting to support conversion of accelerated approval to regular approval for the proposed indication.

c. While pCR has been proven to be informative at a patient level, indicating a more favorable prognosis for those with complete eradication of invasive tumor by preoperative therapy, the CTNeoBC meta-analysis could not establish the magnitude of improvement in pCR rates necessary to predict the superiority of one regimen over another in terms of EFS or OS. As a consequence, it is uncertain whether the 17.8% difference in pCR rates demonstrated in the NEOSPHERE study will be associated with improved long-term outcome (EFS, DFS or OS) in the confirmatory trial. In a similar patient population, the Neoadjuvant Herceptin (NOAH) Trial demonstrated that patients treated with preoperative chemotherapy plus trastuzumab had a 19% absolute difference in pCR rate compared to patients treated with the same regimen of preoperative chemotherapy alone. Addition of trastuzumab to adjuvant chemotherapy has been shown to result in a substantial improvement in DFS in 4 large adjuvant trials and OS improvement in a metastatic trial (Table 3). Whether or not a similar improvement in pCR rates (17.8%) in the NEOSPHERE trial will be accompanied by an IDFS improvement in the confirmatory trial (APHINITY) remains to be seen. However, in the CLEOPATRA trial, the use of pertuzumab in combination with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer who had not received prior anti-HER2 therapy or chemotherapy for metastatic disease, demonstrated an unprecedented improvement in median progression-free survival [HR 0.62 (95% CI: 0.51, 0.75; $p < 0.0001$, log-rank test)] and an overall survival improvement at the second interim analysis [HR = 0.66, 95% CI (0.52, 0.84) $p = 0.0008$].

Table 3: Summary of Efficacy from Trastuzumab Trials (Neoadjuvant, Adjuvant and Metastatic Breast Cancer)



Adjuvant Studies	DFS	
	HR	*p* Value
NSABP B31/NCCTG 9831 AC → TH vs AC → T	0.48	< .001
HERA Chemo → H vs obs	0.54	< .001
BCIRG 006 TCH vs AC → T	0.67	< .001
MBC Study	TTP	
	HR	*p* Value
T+ Chemo vs Chemo	0.53	< 0.0001
	OS	
	HR	*p* Value
T+ Chemo vs Chemo	0.80	.046

d. Although pCR has been the most commonly used endpoint in neoadjuvant trials, it has been variably defined, which has made interpretation of data from neoadjuvant trials challenging. The primary endpoint of the NEOSPHERE study was pCR rate in the breast (ypT0/is). In the CTNeoBC meta-analysis, we found the eradication of tumor from both the breast and lymph nodes (ypT0/isypN0) better predicted for EFS and OS compared with eradication of tumor from the breast alone (ypT0/is). Consequently, the FDA-preferred definition of pCR is the absence of invasive cancer in the breast and nodes (ypT0/isypN0). FDA analysis of the NEOSPHERE study showed statistically significant improvements in pCR rates by both the study and FDA-preferred definitions in patients receiving pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel (Table 4).

Table 4 NEOSPHERE Efficacy Results Using Two Pathological Complete Response Definitions

	pCR (ypT0/isypN0)		pCR (ypT0/is)	
	Arm A H+T	Arm B Ptz+H+T	Arm A H+T	Arm B Ptz+H+T
	N=107	N=107	N=107	N=107
pCR, n (%)	23 (21.5%)	42 (39.3%)	31 (29.0%)	49 (45.8%)
95% CI	14.1, 30.5	30.0, 49.2	20.6, 38.5	36.1, 55.7
Difference of pCR Rates	17.8% (5.7%, 29.9%)		16.8% (4.1%, 29.6%)	
p-value*	0.0063		0.0141	

T=docetaxel, Ptz=pertuzumab, H=trastuzumab
* with Simes corr. for CMH test
ypT0/isypN0 = Absence of invasive cancer in the breast and axillary nodes; DCIS allowed,
ypT0/is = Absence of invasive cancer in the breast and DCIS allowed; regardless of nodal involvement

e. Consistent improvements in pCR rates were observed across several patient subgroups including age, race, geographic region, breast cancer type (operable, locally advanced and inflammatory) and hormone-receptor status. The pCR rates and magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors. This finding is consistent with the results from several trials (CLEOPATRA, EMILIA, NEOALTTO) including the CTNeoBC meta-analysis, in which patients with HER2-positive/hormone-receptor-positive tumors do not appear to benefit to the same extent as patients with HER2-positive/hormone-receptor-negative tumors. Pre-clinical models have demonstrated continued cross-talk between the estrogen and HER2 receptors. Therefore, the therapeutic benefit of concurrent blocking of the HER2 and estrogen receptors in patients with HER2-positive/hormone-receptor-positive breast cancer to improve outcomes needs to be addressed in future trials.

f. The two neoadjuvant trials, NEOSPHERE (WO20697) and TRYPHAENA (BO22280), support the safety profile of pertuzumab for the treatment of women with HER2-positive early-breast cancer. The safety profile in the NEOSPHERE trial is similar to that seen in the metastatic breast cancer setting (CLEOPATRA Trial) with no new safety signals. Common side effects with pertuzumab in the

neoadjuvant setting include neutropenia, diarrhea, nausea, rash, mucosal inflammation, myalgia, fatigue, and stomatitis. In this curative intent setting, treatment was delivered as planned in the majority of patients. As seen in the metastatic breast cancer setting, increased toxicity (neutropenia) was again observed in the Asian population. This increase in toxicity appears to be due to docetaxel.

The addition of pertuzumab led to an increased incidence of all cardiac events including left ventricular dysfunction (Table 5). Discontinuation due to cardiac toxicity was low and all cases of left ventricular dysfunction in NEOSPHERE eventually recovered to LVEF $\geq$50%. All but two cases of left ventricular dysfunction in TRYPHAENA eventually recovered to LVEF >50%.

Most cases of left ventricular dysfunction in the NEOSHERE and TRYPHAENA studies were asymptomatic LVEF declines of $\geq$10% with a decrease to less than 50%. Although it appears that the cardiac safety is similar in the 3 study arms, the TRYPHAENA study is small and we believe there are insufficient safety data to support concomitant administration of an anthracycline and pertuzumab. It should be noted that cardiac events in the CLEOPATRA Trial (metastatic breast cancer) were not increased in the pertuzumab arm. An additional safety trial should be conducted to address the cardiac safety of preoperative administration of an anthracycline regimen with pertuzumab plus trastuzumab in the neoadjuvant setting.

Table 5: Cardiac Toxicity in NEOSPHERE (neoadjuvant, adjuvant and follow up periods)

	H+T	Ptz + H + T	Ptz + H	Ptz + T
NEOADJUVANT PERIOD	**N= 107**	**N= 107**	**N= 108**	**N= 94**
LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%) asymptomatic	1 (0.9%)	3 (2.8%)	0	1 (1.1%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0
ADJUVANT PERIOD	**N= 103**	**N= 102**	**N= 94**	**N= 88**
LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%) asymptomatic	1 (1.0%)	6 (6.1%)	0	5 (5.3%)
Symptomatic LV Dysfunction (CHF)	0	0	0	0
FOLLOW-UP PERIOD	**N= 97**	**N= 99**	**N= 96**	**N= 86**
LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%) asymptomatic	0	3 (3.0%)	1 (1.0%)	2 (2.3%)
Symptomatic LV Dysfunction (CHF)	0	0	0	0
TOTAL # Patients with Cardiac Event	**N= 2**	**N= 9**	**N= 2**	**N= 7**
LV Dysfunction (LVEF Decline ≥10% and drop to less than 50%) asymptomatic	2 (1.9%)	9 (8.4%)	1 (0.9%)	7 (7.4%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0

T=docetaxel, Ptz=pertuzumab, H=trastuzumab

Table 6: Cardiac Toxicity in TRYPHAENA (neoadjuvant, adjuvant and follow up periods)

	FEC x 3→T x 3 Ptz + H x 6	FEC x 3→T x 3 + Ptz+H x 3	TCH x 6 + Ptz x 6
NEOADJUVANT PERIOD	**N= 72**	**N= 75**	**N= 76**
LVEF Decline ≥10% and drop to less than 50%, asymptomatic	4 (5.6%)	1 (1.3%)	2 (2.6%)
Symptomatic LV Dysfunction (CHF)	0	2 (2.7%)	0
ADJUVANT PERIOD	**N= 68**	**N= 65**	**N= 67**
LVEF Decline ≥10% and drop to less than 50%, asymptomatic	3 (4.4%)	5 (7.7%)	2 (3.0%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (1.5%)
FOLLOW-UP PERIOD	**N= 70**	**N= 75**	**N= 74**
LVEF Decline ≥10% and drop to less than 50%, asymptomatic	1 (1.4%)	2 (2.7%)	2 (2.7%)
Symptomatic LV Dysfunction (CHF)	0	1 (1.3%)	0
TOTAL # Patients with Cardiac Event	**N= 5**	**N= 9**	**N= 6**
LVEF Decline ≥10% and drop to less than 50%, asymptomatic	5 (6.9%)	6 (8.0%)	6 (7.9%)
Symptomatic LV Dysfunction (CHF)	0	3 (4%)	1 (1.3%)

FEC=5-fluorouracil, epirubicin, cyclophosphamide; T=docetaxel; Ptz= Pertuzumab; H=trastuzumab; TCH=docetaxel, carboplatin, trastuzumab

g. The NEOSPHERE study was designed and conducted before FDA wrote and publicly discussed the draft Guidance entitled, "Guidance for Industry – Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval". This guidance suggests a pathway to approval for neoadjuvant therapy using the accelerated approval (AA) mechanism. The final Guidance is currently in the clearance process and is expected to be publicly released this fall.

   After a thorough review of the submitted data (including review of all the pathology reports), the FDA review team believes that the totality of the data submitted, including the NEOSPHERE study results, the supportive improvement in overall survival in the CLEOPATRA (metastatic breast cancer) trial and the acceptable safety profile of pertuzumab, supports the accelerated approval of a neoadjuvant indication.

   The Agency wants to clearly state that this approach is not appropriate for all drugs. All protocols for future neoadjuvant trials conducted with regulatory intent should follow the final Guidance recommendations and include a detailed set of standard operating procedures for collection, handling, and interpretation of pathology specimens, comparable to imaging charters in oncology trials with radiographic primary endpoints.

   The draft Guidance focuses primarily on one pathway to accelerated approval for promising new molecular entities in early stages of development for breast cancer. Under this default pathway, termed the single trial model, a single large neoadjuvant randomized controlled trial powered for EFS or OS could support both accelerated approval (pCR endpoint) and, with subsequent follow-up, regular approval (EFS or OS endpoint). Alternatively, as described in the draft Guidance, accelerated approval may be granted based upon a smaller randomized controlled trial demonstrating an improvement in pCR rate. A separate large neoadjuvant or adjuvant randomized controlled trial powered to demonstrate significant improvement in DFS, EFS, or OS could serve as the confirmatory trial to support regular approval. This pathway has been termed the multiple trial model. The multiple trial model may be acceptable for agents such as pertuzumab with evidence of substantial efficacy in the metastatic setting, safety profiles that are relatively benign and well-characterized, and ongoing or fully accrued large randomized adjuvant trials such as the APHINITY trial.

h. The last issue we want to address is how to put the NEOSPHERE study results into clinical practice context. The anthracycline regimen (FEC) in the

NEOSPHERE study was given after surgery. The anthracycline regimen used in the NEOSPHERE study is not widely used in the U.S. and is not FDA-approved for use in combination with trastuzumab. As we previously pointed out, there is insufficient cardiac safety information to recommend concomitant administration of an anthracycline regimen with pertuzumab.

The main rationale for giving the anthracycline regimen after surgery in neoadjuvant trials conducted with regulatory intent is to better isolate the treatment effect of the experimental agent. As seen with the TRYPHAENA study, the combination of an anthracycline regimen (FEC), taxane and dual anti-HER2 therapy resulted in higher pCR rates (57% to 62%) compared to the NEOSPHERE study (39%), where the anthracycline regimen (FEC) was given after surgery. It is possible that higher pCR rates will translate into better clinical outcomes. However, for trials conducted with regulatory intent, it will be difficult to demonstrate a significant absolute difference in pCR rates between treatment arms when the control arm already has a high pCR rate. Therefore, the administration of anthracycline regimens following surgery may facilitate the detection of pCR differences, but may make the study results difficult to translate to the current standard of care.

Consequently, a larger study of pertuzumab delivered concurrently with epirubicin-based chemotherapy might be needed to further understand the safety and efficacy of the drug combination.

5. Summary

The NEOSPHERE study demonstrated statistically significant improvements in pCR rates in patients receiving pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel, with an acceptable safety profile. However, several questions need to be answered in future clinical trials:

- What is the optimal anthracycline regimen and should it be given preoperatively, postoperatively, concurrently or sequentially with trastuzumab/pertuzumab?
- What is the cardiac safety of concurrent or sequential preoperative anthracycline and anti-HER2 therapy?
- Are the higher pCR rates from preoperative anthracycline/anti-HER2 regimens expected to be associated with better long-term outcomes than giving the same regimen but with the anthracycline delivered after surgery?