



Neoadjuvant pertuzumab, T-DM1, weekly paclitaxel and possible anthracyclines in HER2 positive early breast cancer treatment—questions from the KRISTINE study

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For over a decade, the standard of care for early breast cancer that overexpresses human epidermal growth factor 2 (HER2) has been cytotoxic chemotherapy in combination with HER2 targeted agents. Randomised phase III trials showed that the addition of trastuzumab, a humanised monoclonal antibody that targets the transmembrane domain of HER2, to (mostly) anthracycline-taxane-based chemotherapy improved overall survival (OS) with a small increase in cardiotoxicity (1). More recently, research has focused on the modification of these regimens to incorporate other anti-HER2 therapies with proven activity in advanced breast cancer such as pertuzumab (P), a monoclonal antibody with a slightly different binding site from trastuzumab, which inhibits heterodimerisation. When added to neoadjuvant chemotherapy, pertuzumab increased the rate of pathological complete response (pCR) (2,3). This additional efficacy of combination HER2 targeted therapy has led researchers to question whether traditional cytotoxic chemotherapy might be omitted in the management of early stage HER2 positive breast cancer. The KRISTINE study aimed to answer this question by comparing taxane-based combination treatment with targeted therapy alone (4).

The neoadjuvant KRISTINE study was a phase III, multi-centre, randomised trial that compared the pCR rate in HER2 positive tumours after neoadjuvant treatment with docetaxel, carboplatin, trastuzumab and pertuzumab (TCHP) versus ado-trastuzumab emtansine (T-DM1/K) plus pertuzumab (P) (4). This trial was powered to detect

a 15% increase in the locally determined pCR rate (the primary endpoint) from 60% (TCHP) to 75% (KP) at a two-sided α level of 5%. In total, 444 patients were randomised and stratified according to hormone receptor status, stage at diagnosis (stage IIA–IIIA versus stage IIIB–C) and geographical location. The population recruited was well matched with a preponderance of patients with earlier stage (IIA–IIIA =83% in each arm) and hormone receptor positive tumours (62% in each arm). Overall, there was an 11.3% (95% CI, -2.0 to -20.5) absolute difference in the pCR rate observed between the two treatment arms: 55.7% (TCHP) versus 44.4% (KP), $P=0.016$. As might have been predicted this difference was larger for patients with hormone receptor negative tumours (-19.0%; 95% CI, -4.6 to -33.3). As also expected, toxicities were lower in the KP arm: fewer patients (KP: 88%) had any adverse events compared with those receiving TCHP (99%). The most common grade 3–4 adverse events in the TCHP group were neutropenia (25% *vs.* <1%), diarrhoea (15% *vs.* <1%) and febrile neutropenia (15% *vs.* 0). No deaths were reported during neoadjuvant treatment. Congestive heart failure (CHF) occurred in 1% patients who received TCHP, compared to no patients in the KP arm. In addition, quality of life analyses showed a marginally prolonged time to decline in health-related quality of life in favour of the KP combination.

There was a strong rationale for the design of the KRISTINE study. T-DM1 and pertuzumab were

synergistic in preclinical studies, have different mechanisms of action and non-overlapping toxicity profiles (5). Both have independently demonstrated remarkable activity in patients with advanced disease (5). T-DM1 was shown to be non-inferior to trastuzumab plus a taxane in the phase III MARIANNE study for patients with advanced HER2 positive breast cancer but with a favourable toxicity profile (6). In the phase II TRYPHAENA study a pCR rate (ypT0/is) of 66.2% was seen for TCHP (3). Overall, the KRISTINE study adds important information about whether traditional chemotherapy can be omitted and replaced by the rapidly improving HER2-directed therapies available. The study has a number of strengths. It was well balanced between the treatment arms and would likely represent the majority of patients in a real-world scenario presenting for consideration of neoadjuvant chemotherapy; median age, 49–50, ~60% hormone sensitive, predominantly stage IIA–IIIA (83%) and ECOG performance status =0 (94–96%). The study was adequately powered and well stratified, with patients participating from a range of geographical locations (Asia, Europe, USA and Canada). Tumours were centrally tested for HER2 status. pCR (ypT0N0 or ypTisN0) rates, the primary endpoint, was clearly defined. Sensibly and accurately, the investigators predicted that side-effects would be lower with the KP arm than in the TCHP arm and allows us to question the risk: benefit ratio of our therapies with regard to the toxicities of cytotoxic chemotherapy. The efficacy of neo-adjuvant treatment seen in the KRISTINE study is consistent with data from other trials (Table 1). These results collectively establish HER2 positive breast cancer as probably the most sensitive to preoperative therapy. The magnitude of this effect is both substantial and beyond what we could have dreamed of just a few years ago. In addition, these studies have also shown that a substantial proportion of patients (perhaps up to half) can obtain a pCR without any traditional chemotherapy (2,4,7,8). For example, the I-SPY 2 platform had previously ‘graduated’ the combination of KP based on an estimated pCR rate of 52% with responses in both the hormone receptor positive and hormone receptor negative population (8).

Despite this tremendous progress in the development of anti-HER2 therapies, significant questions remain. Although the pCR rate in KRISTINE without traditional chemotherapy was impressive (44%), this was still inferior to the combination of two anti-HER2 therapies with standard cytotoxics (55.7%, $P=0.016$.) In fact, the study failed to either demonstrate equivalence for the two

approaches or to meet the ambitious a priori estimates of pCR (60% vs. 75%). It is also interesting to note that there was no report of a central pathological review for assessment or confirmation of pCR, which is a potential weakness given challenges with this definition and the fact that pCR was the primary endpoint. Definitions of pCR have varied across trials, complicating comparisons. Some studies included residual *in situ* disease (ypTis) in the definition of pCR, while others only included no residual disease (ypT0). Nonetheless, the pCR rate for the 4 drugs combination (TCHP) in KRISTINE is one of the highest ever seen in breast cancer. It could also be argued that pertuzumab may not be needed if giving preoperative T-DM1. In the MARIANNE trial, the addition of pertuzumab to T-DM1 did not appear to improve disease control in advanced breast cancer [response rate (RR): 64.2% vs. 59.7%; PFS: 15.2 vs. 14.1 months, KP vs. K alone respectively, none statistically significant] (6). In the ADAPT trial the pCR rate for T-DM1 alone was 41% (ypTis included, 32.5% ypT0 only), which compares favourably to the pCR rate seen in KRISTINE with KP (44.4%). It is unknown whether a similar pCR rate might have been seen with T-DM1 alone (without pertuzumab) in the KRISTINE trial.

A more critical question is whether pCR is truly a worthwhile study endpoint in HER2 positive breast cancer. Interest in pCR was focused when it was established that patients who achieve a pCR with traditional chemotherapy and trastuzumab had better survival than those with lesser response (9). Reasonably, it was hoped that pCR could be a surrogate for OS and that drug development could shift from the postoperative to the preoperative setting. The advantages of this approach are that by focussing on *in vivo* assessment of tumour response the size of the trial could be minimised, conserving precious resources (patients and financial), while at the same time, facilitating the development of tissue and blood-based biomarkers. However, the results of preoperative clinical trials have often failed to live up to this promise. An improvement in pCR rates led to the accelerated FDA approval in September 2013 of pertuzumab in the preoperative setting with trastuzumab and chemotherapy (2). As previously seen in other trials, patients in the NEOSPHERE study (all groups combined) who achieved a pCR had longer PFS compared with patients who did not (85% vs. 76%, respectively; HR =0.54; 95% CI, 0.29–1.00). Critically however, although the use of pertuzumab led to a significant and clinically meaningful increase in pCR, this did not translate into any meaningful improvement in OS with longer follow up (10).

Table 1 A cross trial comparison of NeoSPHERE, TRYPHAENA, ADAPT and KRISTINE trials with regards to pathological complete response (pCR) rates

Therapy combinations	NeoSPHERE	TRYPHAENA	ADAPT	KRISTINE
Combination chemotherapy + combination anti-HER2 therapy	–	Docetaxel, carboplatin, trastuzumab + pertuzumab (TCHP); 66.2%	–	Docetaxel, carboplatin, trastuzumab + pertuzumab (TCHP); 55.7%
	–	5-fluorouracil, epirubicin, cyclophosphamide (FEC), trastuzumab + pertuzumab (FEC-HP); 61.6%	–	–
Single agent chemotherapy + combination anti-HER2 therapy	Docetaxel, trastuzumab + pertuzumab (THP); 45.8%	–	Paclitaxel, trastuzumab + pertuzumab (wPacliHP); 90.5%*	–
Combination anti-HER2 therapy alone	Trastuzumab + pertuzumab (HP); 16.8%	–	Trastuzumab + pertuzumab (HP); 36.3%*	Trastuzumab emtansine (T-DM1) + pertuzumab (KP); 44.4%

*, ypTis included.

Furthermore, the adjuvant APHINITY trial suggested a small benefit in invasive disease free survival for dual anti-HER2 therapy with pertuzumab, but as yet failed to confirm any large benefit in OS (11). A similar pattern of improved pCR without an improvement in OS was seen with lapatinib in the NEOALTTO and ALTTO trials respectively (5,12). For patients with early stage cancer the ultimate aim for systemic therapy is to increase the chance of cure compared with locoregional therapy alone. As such, OS remains the gold standard for drug development in this setting.

Although TCHP can be considered a “standard arm” in any clinical trial, the optimal chemotherapy backbone with dual anti-HER2 therapy is yet to be established. The BCIRG 007 trial showed no benefit for the addition of carboplatin to docetaxel and trastuzumab in patients with advanced HER2 positive breast cancer (13), raising questions about its utility, while taxanes have been the mainstay of treatment (5). The BCIRG 006 study was the only randomised phase III study of adjuvant trastuzumab which examined both an anthracycline-taxane-trastuzumab combination (AC-TH) and a non-anthracycline-taxane-trastuzumab combination (TCH) (14). Although there was no statistically significant difference between the trastuzumab containing arms up to 10 years, it is worth noting that this study was not powered to compare the 2 approaches (15). In fact, there was a small numerical (statistically insignificant) difference in favour of the anthracycline regimen seen at every time point on this study (DFS: 84% vs. 81% at 5 years, and a hazard ratio (HR) for

OS of 0.64 vs. 0.76 at 10 years).

Many of these studies examining dual anti-HER2 therapy have provided very little evidence (one way or another) about the optimum role for anthracyclines. In NeoSPHERE all patients received three adjuvant cycles of FEC (5-fluorouracil at 600 mg/m², epirubicin at 90 mg/m² and cyclophosphamide at 600 mg/m²). In the APHINITY study almost 80% patients received an anthracycline (11). An additional nuance is that these studies were designed before dose-dense AC was shown to be superior to the same treatment every 3 weeks (16). Subsequently, it has been shown that trastuzumab could safely be incorporated into dense-dense anthracycline-taxane regimens without an apparent increase in cardiotoxicity (17). Furthermore, many studies examining combination anti-HER2 therapy have used docetaxel at 75 mg/m² including the KRISTINE study. The ECOG E1199 study showed that when added to anthracycline-based chemotherapy the most active taxanes were either docetaxel 100 mg/m² ×4 once every 3 weeks or paclitaxel 80 mg/m² ×12 weekly (18). Many investigators are concerned about the toxicity of docetaxel 100 mg/m² leading to the widespread use of weekly paclitaxel as the standard taxane. Tolaney *et al.* adopted this approach and demonstrated excellent outcomes for weekly paclitaxel with trastuzumab in low risk HER2 positive breast cancer (19). The ADAPT study was focused on assessing early responders in hormone receptor negative disease and identified a pCR rate of 89% (ypTis included) with paclitaxel, trastuzumab and pertuzumab (wPacliHP) (20). In

a retrospective study, Singh *et al.* demonstrated very high pCR rates of 72% (ypTis included, 53% ypTis excluded) after dose-dense doxorubicin and cyclophosphamide followed by paclitaxel, trastuzumab and pertuzumab (21). Ongoing studies in the adjuvant setting may help to further address the question regarding the optimal chemotherapy backbone with anti-HER2 therapy.

An additional question is whether 1 year of anti-HER2 therapy is needed. Patients in this study (KRISTINE) received HER2-directed therapies to complete 1 year of treatment (KP or HP for 12 postoperative cycles). Evidence for the benefit of HP to complete 1 year of treatment extends from the NEOSPHERE study where pCR rates were improved, but the lack of OS benefit and absence of randomised data to support a whole year of combination anti-HER2 therapy, means that the duration of therapy is still debatable. Although the PHARE study showed a slight statistical inferiority to 6 months of adjuvant trastuzumab in comparison to 12 months, this may well have been overcome by the addition of pertuzumab (22). If neoadjuvant TCHP is accepted as a new standard of care, the benefit of these additional adjuvant cycles should also be studied given the obvious cost implications of this treatment paradigm.

Additionally, adequate predictive biomarkers to determine who requires anthracycline-based chemotherapy, which patients will benefit from taxane-based chemotherapy alone and which patients will respond to dual HER2 blockade alone (without chemotherapy) are essential. Putative biomarkers are focussing on tumour factors such as gene copy ratios or patient factors such as age and cardiac history. Of note many patients with cardiac histories were excluded from the majority of these trials (23). The rates of cardiotoxicity seen with anthracyclines and trastuzumab when used concurrently have always been a concern, but sequential use of these agents is often considered acceptable (14,24). The addition of pertuzumab to trastuzumab inevitably raised concern for increased rates of cardiotoxicity, however despite being extensively investigated and monitored, no higher rates have been seen to date in KRISTINE (1/129 in TCHP arm and 0/223 in KP arm), consistent with other pertuzumab studies (4,25). This fact, combined with the results seen to date with dual HER2 blockade (*Table 1*), would suggest that the use of combination anti-HER2 therapy might be more important when an anthracycline is omitted from the systemic therapy regimen. The important role of the anthracyclines might also explain the lack of improvement in OS seen in many

studies, which demonstrated an apparent improvement in pCR. The use of anthracyclines might result in less financial toxicity by reserving more expensive targeted therapy such as T-DM1 and pertuzumab for patients with higher risk disease, but this could come at the price of more cardiotoxicity. Instead, a logical solution might be to utilise a taxane and dual HER2 blockade in the neoadjuvant setting and reserve anthracycline use for the adjuvant setting if a poor response is seen. Such an approach was built into the design of the KRISTINE study as it was recommended that patients who did not achieve a pCR, who had residual tumour >1 cm or residual nodal disease (> ypN0) should receive postoperative anthracycline-based chemotherapy. However, the authors of the KRISTINE study appropriately note that the trial did not include a randomisation to treatment based on differential response. Such a risk-adaptive approach is being formally explored in the KATHERINE trial, in which patients without a pCR following preoperative chemotherapy and trastuzumab were randomised to continue adjuvant trastuzumab or T-DM1. An alternative approach is being investigated in the KAITLIN study, in which patients will all receive anthracyclines and then be randomised to KP versus HP-Paclitaxel.

In summary, while the KRISTINE study will not be practice-changing, there are some interesting research questions answered and more posed by the results. TCHP improves pCR rates over KP alone but the acceptance of TCHP in the neoadjuvant setting as standard of care remains debatable with many questioning the cost: benefit of the addition of pertuzumab, the absence of an anthracycline and the choice of docetaxel (75 mg/m²) over weekly paclitaxel. Similarly, pCR is being increasingly questioned as a valid endpoint, given the lack of correlation with OS. And while there is a cohort of patients who achieve pCR without any traditional cytotoxic agent, at present systemic chemotherapy will maintain an integral role in neoadjuvant therapy as an adjunct to HER2-targeted agents. Finally, without proven predictive biomarkers to appropriately and adequately select the correct patients who will benefit the most, T-DM1 will remain an important agent for HER2 positive breast cancer in the metastatic setting but should not be utilised outside of a clinical trial in the neoadjuvant setting. Further research into predictive biomarkers in this area is essential and the results of ongoing trials like KATHERINE and KAITLIN as well as biomarker results from KRISTINE are eagerly awaited.

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Footnote

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References

- Morris PG, Hudis CA. Trastuzumab-related cardiotoxicity following anthracycline-based adjuvant chemotherapy: how worried should we be? *J Clin Oncol* 2010;28:3407-10.
- Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;13:25-32.
- Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013;24:2278-84.
- Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2018;19:115-26.
- Gleeson JP, Keegan NM, Morris PG. Adding Pertuzumab to Trastuzumab and Taxanes in HER2 positive breast cancer. *Expert Opin Biol Ther* 2018;18:251-62.
- Perez EA, Barrios C, Eiermann W, et al. Trastuzumab Emtansine With or Without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2-Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study. *J Clin Oncol* 2017;35:141-8.
- Harbeck N, Gluz O, Christgen M, et al. Efficacy of 12-weeks of neoadjuvant TDM1 with or without endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer: WSG-ADAPT HER2+/HR+ phase II trial. *American Society of Clinical Oncology*; 2015.
- DeMichele AM, Moulder S, Buxton M, et al. Abstract CT042: Efficacy of T-DM1+ pertuzumab over standard therapy for HER2+ breast cancer: Results from the neoadjuvant I-SPY 2 TRIAL. New Orleans: AACR, 2016.
- von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012;30:1796-804.
- Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016;17:791-800.
- von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med* 2017;377:122-31.
- de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol* 2014;15:1137-46.
- Forbes JF, Pienkowski T, Valero V, et al. BCIRG 007: Randomized phase III trial of trastuzumab plus docetaxel with or without carboplatin first line in HER2 positive metastatic breast cancer (MBC). *J Clin Oncol* 2006;24:LBA516-LBA.
- Slamon D, Eiermann W, Robert N, et al. Adjuvant

- trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273-83.
15. Slamon DJ, Eiermann W, Robert NJ, et al. Abstract S5-04: Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer. 2016.
 16. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/ Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;21:1431-9.
 17. Morris PG, Dickler M, McArthur HL, et al. Dose-dense adjuvant Doxorubicin and cyclophosphamide is not associated with frequent short-term changes in left ventricular ejection fraction. *J Clin Oncol* 2009;27:6117-23.
 18. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 2008;358:1663-71.
 19. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* 2015;372:134-41.
 20. Nitz U, Gluz O, Christgen M, et al. Final analysis of WSG-ADAPT HER2+/HR- trial: Efficacy, safety, and predictive markers for 12-weeks of neoadjuvant dual blockade with trastuzumab + pertuzumab ± weekly paclitaxel in HER2+/HR- early breast cancer (EBC). *J Clin Oncol* 2016;34:518.
 21. Singh JC, Mamtani A, Barrio A, et al. Pathologic Complete Response with Neoadjuvant Doxorubicin and Cyclophosphamide Followed by Paclitaxel with Trastuzumab and Pertuzumab in Patients with HER2-Positive Early Stage Breast Cancer: A Single Center Experience. *Oncologist* 2017;22:139-43.
 22. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013;14:741-8.
 23. Stocker A, Hilbers ML, Gauthier C, et al. HER2/CEP17 Ratios and Clinical Outcome in HER2-Positive Early Breast Cancer Undergoing Trastuzumab-Containing Therapy. *PLoS One* 2016;11:e0159176.
 24. Morris PG, Hudis CA. Trastuzumab-Related Cardiotoxicity Following Anthracycline-Based Adjuvant Chemotherapy: How Worried Should We Be? *J Clin Oncol* 2010;28:3407-10.
 25. Sendur MA, Aksoy S, Altundag K. Cardiotoxicity of novel HER2-targeted therapies. *Curr Med Res Opin* 2013;29:1015-24.

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