JBUON 2021; 26(3): 714-719
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Cardiac safety of neoadjuvant chemotherapy with epirubicin and cyclophosphamide followed by docetaxel/pertuzumab/trastuzumab for HER2-positive breast cancer patients

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Summary

Purpose: *Early-stage, HER2-positive breast cancer is increasingly treated with neoadjuvant chemotherapy (NAC). After the positive results of the Neosphere trial, the standard of care has been the combination of chemotherapy with two anti-HER2 agents, trastuzumab and pertuzumab. Many oncologists use the sequence of four cycles of anthracycline-containing regimen followed by four cycles of taxane with the two monoclonals. We report here the cardiac safety of four cycles of epirubicin with cyclophosphamide followed by four cycles of docetaxel with trastuzumab and pertuzumab, given at the neoadjuvant setting in early, HER2-positive breast cancer.*

Methods: *We retrospectively collected data from the medical records of patients treated at our clinic between 2014 and 2020.*

Results: *It total, 55 patients treated with the same regimen were identified. There were 20 estrogen receptor (ER)-negative and 35 ER-positive patients. Complete pathologic response was observed in 64.8% of the patients. After a median cardiac follow-up of 2.61 years, and a total of 283 echocardiograms, there was only one recorded asymptomatic Left Ventricular Ejection Fraction (LVEF) fall > 25% and no symptomatic left ventricular systolic dysfunction. LVEF consistently dropped during treatment, but the drop was not significant enough to necessitate treatment interruption, and improved during follow-up*

Conclusion: *Our data confirm the effectiveness and cardiac safety of the aforementioned neoadjuvant regimen.*

Key words: *breast cancer, neoadjuvant chemotherapy, human epidermal growth factor receptor-3, cardiac safety, trastuzumab, pertuzumab*

Introduction

Chemotherapy in early-stage breast cancer can be administered either before (neoadjuvant) or after (adjuvant) surgery. It has been documented that the survival benefits are equal in both cases [1]. However, neoadjuvant chemotherapy (NAC) offers several advantages to the adjuvant approach, including but not limited to the improvement of surgical outcomes, the acquisition of prognostic information based on the response to treatment, and the possibility to modify systemic treatment in case of residual disease. One of the most important prognostic factors of disease-free survival (DFS) and overall survival (OS) has been established to be pathologic complete response (pCR) after NAC, with a greater benefit in specific tumor subtypes, particularly HER2-positive and triple-negative tumors [2,3]. The indications for NAC are therefore based on the extent and biology of the tumor.

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Received: 05/12/2020; Accepted: 09/01/2021

For HER2-positive disease, the standard of care is NAC (usually containing the sequential administration of an anthracycline and a taxane) plus anti-HER2 based treatment. In the neoadjuvant setting, the NOAH trial established the superiority of trastuzumab plus chemotherapy in comparison to chemotherapy [4,5]. Subsequently, the NeoSphere [6] and Tryphaena [7] trials established the superiority of dual anti-HER2 blockade (trastuzumab+pertuzumab) in comparison to trastuzumab alone.

A potential concern with these regimens is cardiotoxicity. The cardiotoxicity of anthracyclines is well documented. The reported incidence of drug-associated left ventricular dysfunction is 3-5% for doxorubicin and 0.9-11.4% for epirubicin [8]. It is dose-dependent, and potentially irreversible [8], therefore all chemotherapy regimens conform to a maximum cumulative lifetime dose for each anthracycline. Anti-HER2 based treatment is also cardiotoxic. The cardiotoxicity of trastuzumab was first noted in the large-scale randomized trial that led to its approval in the metastatic setting, which identified a 27% incidence of cardiac dysfunction in patients receiving concomitant trastuzumab, anthracycline and cyclophosphamide, as opposed to 8% in patients not receiving trastuzumab [9]. With an increased emphasis on cardiac safety and monitoring, the four large adjuvant trials of trastuzumab (NSABP B-31, NCCTG N9831, HERA, and BCIRG-006) showed less than 4% difference in severe congestive heart failure and cardiac death between the trastuzumab and non-trastuzumab patients, but noted a higher incidence of less severe cardiac events in those receiving trastuzumab [10], a trend consistent across the neoadjuvant studies too.

The cardiotoxicity of trastuzumab is thought to be reversible, unlike the cardiotoxicity of anthracyclines which until recently was considered irreversible. In the HERA trial, most patients with cardiac dysfunction recovered in fewer than 6 months [11], and at 8-years of median follow-up, 81.2% of patients with confirmed left ventricular ejection fraction (LVEF) decrease had reached recovery [12]. Similarly, in the 7-year follow-up of the NSABP B-31 trial, the majority of patients who experienced cardiac dysfunction recovered their LVEF in the normal range [13]. This led to the classification of "Type 2" cardiotoxicity with trastuzumab in contrast to "Type 1" or irreversible cardiotoxicity with anthracyclines. Recent evidence suggests that anthracycline cardiotoxicity could also recover in some cases, and so the classification has fallen out of favor given a perceived oversimplification of the underlying pathophysiology and natural history of cardiotoxicity.

The addition of pertuzumab does not seem to be associated with an increased risk of cardiac dysfunction compared to the trastuzumab plus chemotherapy combination. In the NeoSphere trial [6], no significant change was detected when pertuzumab was added to trastuzumab. Only 6 out of 417 patients in the study had a LVEF decline to less than 50%, and all but one recovered. In the Tryphaena study [7], 24 out of 225 patients experienced significant LVEF declines, and all but one recovered. This data is consistent across multiple patient groups, including the metastatic setting, as evidenced in the CLEOPATRA study [14].

The neoadjuvant chemotherapy with anti-HER2 agents pertuzumab and trastuzumab has been established as the standard of care in the majority of patients with HER2-positive early breast cancer. Cardiotoxicity remains a concern and long-term data is scarce, particularly regarding its reversibility. Valuable information can be obtained in this area from real world data of patients being followed up for an extended time period after the completion of anti-HER2 treatment.

We report the outcomes (both to cardiac toxicity and tumor responses) for 55 consecutive HER2-positive breast cancer patients that received the same regimen (as per standard of care), consisting of four cycles of epirubicin and cyclophosphamide followed by four cycles of docetaxel, trastuzumab and pertuzumab.

Methods

We retrospectively collected data from the medical records of patients treated at our clinic between 2014 and 2020. The analysis included all patients with histologically confirmed diagnosis of breast cancer and HER2 positivity as defined by ASCO/CAP guidelines [15], who were treated with NAC with four cycles of Epirubicin 90 mg/m^2 and Cyclophosphamide 600 mg/m^2 followed by four cycles of docetaxel 90mg/m^2, pertuzumab and trastuzumab. The pre-treatment core-needle biopsy also included immunohistochemical determination of estrogen and progesterone receptors, as well as Ki-67. Following the completion of NAC, all patients underwent operation. They subsequently received adjuvant radiotherapy where indicated, adjuvant hormonal treatment in case of hormone receptor positivity, and adjuvant anti-HER2 treatment. Adjuvant anti-HER2 treatment included trastuzumab with or without pertuzumab until the completion of 1 year, or trastuzumab emtansine (TDM-1) for 1 year in case of residual disease following its 2019 approval based on the results of the KATHERINE trial [16].

The primary endpoint of this study was the determination of the cardiac safety of the regimen used. Pathologic responses are presented as well. Complete pathological response (pCR) was defined (as per FDA

guidelines [17]) as no evidence of residual invasive disease in the breast or axillary lymph nodes. For the determination of cardiac safety, patients were subjected to serial cardiac monitoring via transthoracic ECHO and measurement of the LVEF, using various methods including the Simpson's biplane method considered to be the gold standard for 2D heart assessment, at the following time periods: 1) Before anthracycline chemotherapy, 2) Before taxane chemotherapy (plus pertuzumab and trastuzumab), 3) During cycles 6-10 of anti-HER2 treatment, 4) During cycles 11-14 of anti-HER2 treatment , 5) During cycles 15-18 of anti-HER2 treatment, 6) Year two follow-up, 7) Year three follow-up.

To avoid bias, the echocardiographic measurements of each individual were performed by the same cardiologist with offline measurements in every different period. All data were collected from June to September, 2020 (database lock). According to the methodological features of an observational non-interventional study, all analyses were descriptive, and the results presented should be interpreted as such. All statistical analyses were performed using GraphPad Prism 8.0.1 software.

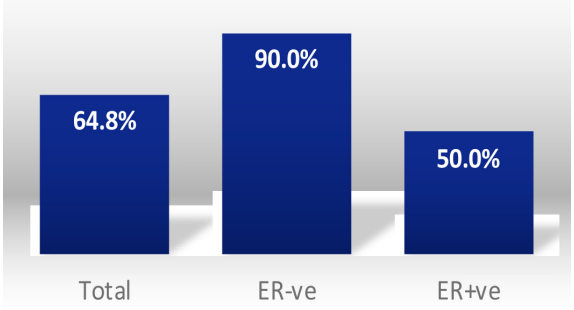

Figure 1. Pathologic complete response rate according to tumor subtype.

Results

A total of 55 patients were included in the analysis. Twenty were estrogen receptor (ER)-negative and 35 were ER-positive. The age of the patients ranged between 31 and 74 years (median age at diagnosis 50 years). All patients had pre-treatment core-needle biopsy with immunohistochemical determination of at least ER and PR, HER2 and Ki67. We included all patients for whom we had full histology reports from the final surgery on the day of the database lock.

Four patients were receiving treatment for type 2 diabetes at the time of diagnosis, 13 were on anti-hypertensive medication and 14 on antilipidemics. There were 33 never-smokers, 10 that had discontinued smoking more than one year before diagnosis and 12 current smokers. Median body mass index [BMI, calculated as BMI= Body weight (Kgs) / Height (m)2] was 26.45 (17.75-52.08).

The surgical processes have already been described elsewhere [18]. From the cohort of 55 patients, 54 were available for response. Table 1 and Figure 1 summarize the response data and the population subgroups. Complete pathologic response (pCR) was observed in 64.8% of patients.

Table 1. Complete pathological response (pCR) according to histology, hormonal receptors, Ki67 and genetic profile

Factors	*n*	*pCR (%)*	*x^2 OR p?*
Histology			
IDC	54	35/53 (66.0%)	
ILC	1	0/1 (0%)	
Hormonal receptors			
Positive	35	17/34 (50%)	
Negative	20	18/20 (90%)	p=0.003
Grade			
Grade 1-2	15	11/15 (73.3%)	
Grade 3	40	26/39 (66.7%)	p=0.637
Ki67 (%)			
<40	27	13/27 (48.1)	
40-100	27	20/26 (76.9)	p=0.031
Unknown	1	1 (100)	
Genetic profile			
Unchecked	32	17/31 (54.8%)	
Checked	23	18/23 (78.3%)	p=0.075
• Wild-type (%)	18	14/18 (77.8)	
• Any pathogenic mutation (%)	5	4/5 (80)	p=0.915
Total (%)	55	35/54 (64.8%)	

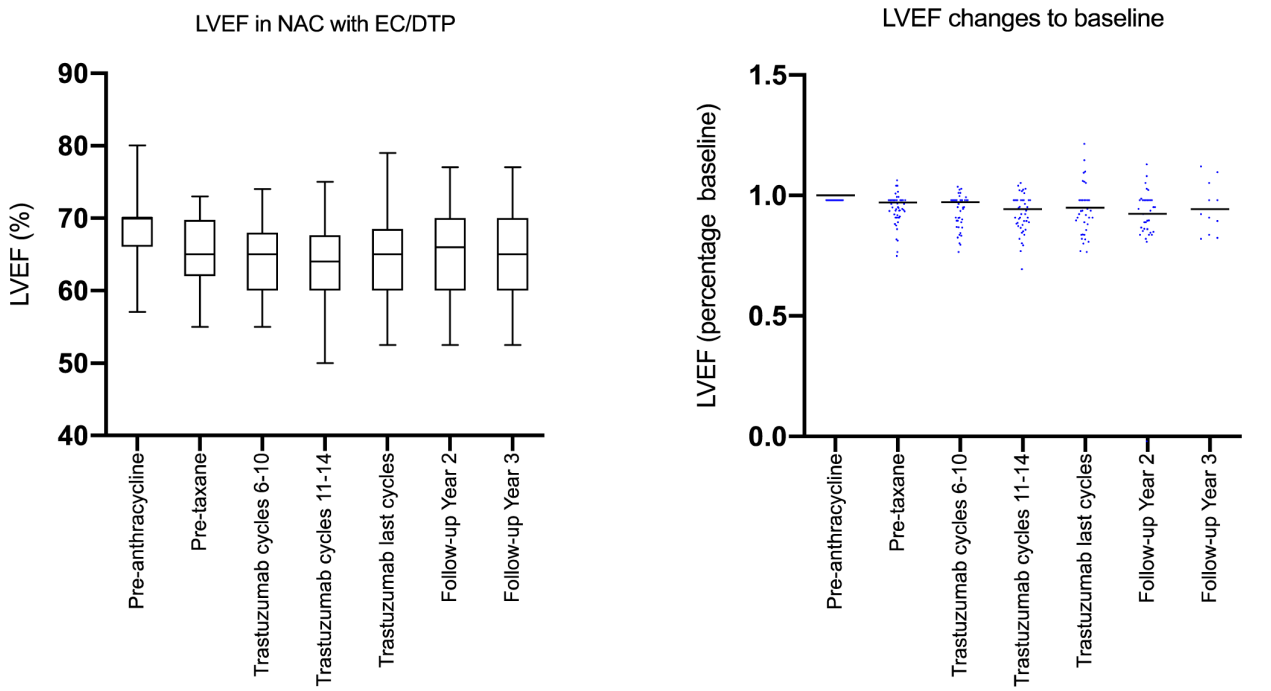

Figure 2. Left ventricular ejection fraction (LVEF) percentage changes over time. No statistically significant changes from baseline were observed.

The rate of pCR was higher in ER-negative (90%) than in ER-positive patients (50%), a difference which was statistically significant (p=0.003). The rate of pCR was also higher in patients with Ki67>40% (76.9%) than patients with Ki67<40% (48.1%) (p=0.031). From the 19 patients that had residual disease, 10 received post-neoadjuvant treatment with TDM-1.

Cardiac safety results are presented in Figure 2. A total of 283 echocardiograms were performed, with a median cardiological follow-up of 2.61 years. LVEF consistently dropped during treatment, but the drop was not significant enough to necessitate treatment interruption, and consistently improved during follow-up. There was only one recorded asymptomatic LVEF fall > 25% (from 70% to 50%) in a patient with coexisting hyperlipidemia and hypertension, and one patient needed to have a coronary angiogram during follow-up, which was normal. LVEF drop and recovery did not differ between obese and non-obese patients, smokers and non-smokers or patients with hyperlipidemia, diabetes or hypertension.

Discussion

This study was designed to assess the cardiac safety and efficacy of NAC in patients treated with four cycles of anthracycline and cyclophosphamide followed by four cycles of docetaxel, pertuzumab and trastuzumab. It is important to note that these patients were not preselected or part of a clinical trial, but patients being treated in the clinic on an everyday basis.

The regimen was well tolerated with no recorded cases of severe cardiac dysfunction, and consistent but small asymptomatic declines in LVEF which progressively recovered after completion of treatment. There was only one recorded significant decrease of LVEF >10% to 50% out of 54 patients (1.8%). This pattern of LVEF declined during treatment which then recovered to pre-treatment values is also observed in the major randomized clinical trials in different patient populations. In the neoadjuvant setting, the Tryphaena study [7] showed a mean LVEF drop below baseline during the treatment period, but no more than 7% from baseline; 24 out of 225 patients (10.6%) had a significant LVEF decrease below 50%, and all but one of them recovered their LVEF to >50% during follow-up. The Tryphaena study had 3 cohorts, only one of which (cohort B with 75 enrolled patients) included three cycles of epirubicin (in combination with 5-fluorouracil and cyclophosphamide, FEC) without targeted treatment, followed by three cycles of docetaxel, trastuzumab and pertuzumab. Cohort B is therefore closer to our schedule of treatment. Of the 75 patients randomized to cohort B, there were 15 cardiac adverse events (12 drops in LVEF 10%, 2 of which were symptomatic) [19].

On the other hand, the pivotal phase II NeoSphere trial [6] randomized patients between 4

arms in the neoadjuvant setting, with either four cycles of docetaxel with pertuzumab, four cycles of docetaxel with trastuzumab, four cycles of docetaxel, trastuzumab and pertuzumab, and a chemo-free arm with four cycles of trastuzumab and pertuzumab. In the adjuvant setting all patients received anthracyclines with the same anti-HER treatment they had received in the neoadjuvant setting. In total, mean LVEF dropped no more than 4-5% from baseline; 6 out of 417 patients (1.4%) had a LVEF decrease to less than 50%, and all but one recovered. From the 107 patients that received both monoclonals and chemotherapy (group B), 9 cases of LVEF drop were reported (8%) with one case of grade 3 dysfunction (1%) [20].

More similar to our study is cohort B of the BERENICE phase II study [21], where patients received prior to surgery 4 cycles of FEC followed by 4 cycles of docetaxel, pertuzumab and trastuzumab. This was followed by pertuzumab and trastuzumab in the adjuvant setting. Of the total 198 patients in Cohort B, they reported 4 patients with at least one LVEF decline and no NYHA class III/IV heart failure events.

Comparable results were seen in the metastatic setting in the Cleopatra trial [14], with significant LVEF decrease below 50% in 6.1% of patients, 87.5% of whom recovered, and in the adjuvant setting in the Aphinity trial [22] with a total of 18 primary cardiac events (0.7%) and 65 secondary cardiac events (2.7%) after 6 years of follow-up. This data confirms the cardiac safety of this regimen, as well as the reversibility of any potential cardiotoxicity.

In our cohort, pCR was observed in 64.8% of patients. The rates of pCR were high across all subgroups. The greater benefit was seen in two groups: 1) hormonal receptor (HR)-negative tumors, and 2) tumors with higher levels of Ki67. In patients with HR-negative tumors, our results are consistent with results from the major randomized clinical trials. In the subgroup analysis of the NOAH trial [5], the 5-year overall survival (OS) for HR-negative patients was 78% in the trastuzumab plus chemotherapy group versus 60% in the chemotherapy only group (HR=0.51), whereas for HR-positive patients the OS was 65% versus 67% respectively (HR=1.05). In the NeoSphere trial [6], the use of neoadjuvant pertuzumab, trastuzumab and docetaxel was associated with a pCR rate of 63.2% in HR-negative patients, but only 26% in HR-positive ones. In the Tryphena study [7] cohort B had a pCR rate of 54.7% and in BERENICE [21] 60.7%.

In our cohort, patients with higher levels of Ki67 were also more likely to achieve pCR (76.9% in Ki67>40% versus 48.1% in Ki67<40%, p=0.031). This could suggest a potential use of Ki67 as a predictive biomarker for patients more likely to benefit from NAC. However, the utility of Ki67 as a marker has not yet been fully elucidated in clinical practice [23,24]. To our knowledge, the randomized NAC trials did not report a subgroup analysis stratified by Ki67 to use for comparison.

Conclusion

In a retrospective study assessing real-world data, neoadjuvant chemotherapy for HER2-positive patients using epirubicin, docetaxel and the combination of trastuzumab and pertuzumab proved to be an effective and safe regimen, resulting in consistently high rates of pCR. The cardiotoxicity of the regimen was minimal and reversible where present, a pattern consistent through an extended follow-up period.

Declarations of interest

Loukas Kontovinis has received honoraria from IPSEN, BMS, Roche, MSD and Amgen. Athanasios Pouptsis has received honoraria from GSK. Konstantinos Papazisis has received honoraria from Novartis, Roche, GSK and MSD. The remaining authors declare no conflicts of interest.

References

1. 1Rastogi P, Anderson SJ, Bear HD et al. Preoperative chemotherapy: Updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol 2008;26:778-85. doi:10.1200/JCO.2007.15.0235
2. 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;30:1796-1804. doi:10.1200/JCO.2011.38.8595
3. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet 2014;384:164-72. doi:10.1016/S0140-6736(13)62422-8
4. Gianni L, Eiermann W, Semiglazov V et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised con-

trolled superiority trial with a parallel HER2-negative cohort. Lancet 2010;375:377-84. doi:10.1016/S0140-6736(09)61964-4

5. Gianni L, Eiermann W, Semiglazov V et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): Follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014;15:640-7. doi:10.1016/S1470-2045(14)70080-4
6. 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. doi:10.1016/S1470-2045(11)70336-9
7. 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. doi:10.1093/annonc/mdt182
8. Zamorano JL, Lancellotti P, Rodriguez Muñoz D et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. Eur Heart J 2016;37:2768-801. doi:10.1093/eurheartj/ehw211
9. Slamon D, Eiermann W, Robert N et al. Adjuvant Trastuzumab in HER2-Positive Breast Cancer. N Engl J Med 2011;365:1273-83. doi:10.1056/NEJMoa0910383
10. Telli ML, Witteles RM. Trastuzumab-related cardiac dysfunction. JNCCN J Natl Compr Cancer Netw 2011;9:243-9. doi:10.6004/jnccn.2011.0019
11. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. N Engl J Med. 2005;353:1659-72. doi:10.1056/nejmoa052306
12. Cameron D, Piccart-Gebhart MJ, Gelber RD et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet 2017;389:1195-205. doi:10.1016/S0140-6736(16)32616-2
13. Romond EH, Jeong JH, Rastogi P et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2012;30:3792-9. doi:10.1200/JCO.2011.40.0010
14. Swain SM, Baselga J, Kim S-B et al. Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer. N Engl J Med 2015;372:724-34. doi:10.1056/nejmoa1413513
15. Wolff AC, McShane LM, Hammond MEH et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med 2018;142:1364-82. doi:10.5858/arpa.2018-0902-SA
16. von Minckwitz G, Huang C-S, Mano MS et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019;380:617-28. doi:10.1056/nejmoa1814017
17. Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval | FDA. Accessed November 11, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pathological-complete-response-neoadjuvant-treatment-high-risk-early-stage-breast-cancer-use
18. Papazisis K, Liappis T, Kontovinis L, Pouptsis A, Intzes S, Natsiopoulos I. Real-world experience of neoadjuvant chemotherapy for early breast cancer patients: an observational non-interventional study in Thessaloniki, Greece. JBUON 2020;25:634-40. PMID: 32521846.
19. Schneeweiss A, Chia S, Hickish T et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. Eur J Cancer 2018;89:27-35. doi:10.1016/j.ejca.2017.10.021
20. 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. doi:10.1016/S1470-2045(16)00163-7
21. Swain SM, Ewer MS, Viale G et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): A phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol 2018;29:646-53. doi:10.1093/annonc/mdx773
22. Piccart M, Procter M, Fumagalli D et al: Interim overall survival analysis of APHINITY (BIG 4-11): A randomized, multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab vs chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. 2019 San Antonio Breast Cancer Symposium. Abstract GS1-04. Published December 11, 2019.
23. Denkert C, Budczies J, von Minckwitz G, Wienert S, Loibl S, Klauschen F. Strategies for developing Ki67 as a useful biomarker in breast cancer. Breast 2015;24:S67-S72. doi:10.1016/j.breast.2015.07.017
24. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol 2010;11:174-83. doi:10.1016/S1470-2045(09)70262-1