*JMS 2020;3(3):116-124*
*UDC:618.19-006.6-085.277*

# DUAL HER2 BLOCKADE WITH TRASTUZUMAB AND PERTUZUMAB IN HER2-POSITIVE BREAST CANCER: SINGLE CENTER REAL WORLD DATA

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**Abstract**

Agents targeting the human epidermal growth factor receptor 2 (HER2) have improved outcomes of advanced HER2-positive breast cancer with durable responses. We evaluated therapy with trastuzumab and pertuzumab in early and metastatic HER2-positive breast cancer patients. In this paper we discuss the practicalities of treating patients with this combination with a particular focus on treatment in the single center setting.

We retrospectively identifed patients on adjuvant and frst-line anti-HER2 therapy at The University Clinic of Radiotherapy and Oncology Skopje for at least 1 year from 2019 to 2020. Demographics, treatments and adverse events were recorded.

The combination of pertuzumab–trastuzumab has established efficacy in patients with HER2-positive advanced/metastatic breast cancer. Management of treatment related side-effects such as diarrhea, febrile neutropenia and neuropathy typically include dose reduction or switching taxane. Specific patients with poorer tolerance of chemotherapy such may require particular management strategies.

The roles of trastuzumab and pertuzumab are now very well established in the frst-line setting; identifying predictors of long-term response to these would be important in selecting which patients might beneft from entry into future clinical trials assessing the long-term beneft of these newer agents in addition.

***Keywords:*** Breast cancer, HER2 positive, Trastuzumab, Pertuzumab.

## Introduction

Breast cancer is the most commonly diagnosed cancer in women in North Macedonia. In the 10-year report "Cancer in the Republic of North Macedonia, 2010-2019" prepared by the Institute of Public Health (IPH)and using the data contained in the Cancer Registry, there are 7378 number of new cases of breast cancer, 24.52% of the cancers in females of all ages [1].

Approximately one in five women have HER2-positive cancer, a more aggressive form of breast cancer with a relatively poor prognosis [2].

Although initial presentation with metastatic disease is rare (< 6% of patients), approximately 30% of patients initially diagnosed with earlier stage breast cancer will eventually develop metastatic disease [3].

The development of targeted biological therapies for women with HER2-positive metastatic breast cancers has improved progression-free survival (PFS), overall survival(OS) and overall response rate (ORR) compared with traditional chemotherapy, especially in the first-line setting.

The development of HER2-targeted therapy in the firstline setting; specifically trastuzumab, internationally, significantly extended survival beyond previously used chemotherapy regimens [2,4-7].

More recently, pertuzumab was developed, and it has been trialed in combination with trastuzumab and chemotherapy for women with HER2- positive metastatic breast cancer [8].

This combination of pertuzumab with trastuzumab and docetaxel has shown significant improvements in ORRs, PFS and OS in women with HER2-positive metastatic breast cancer.

The adjuvant treatment with trastuzumab became available in North Macedonia in 2006. In addition, pertuzumab was registered by the The Macedonian Agency for Medicines and Medical Devices (MALMED) in 2013 and at the moment the drug is not on positive list of reimbursed medicines. Since 2019 it is on Conditional Budget approved by the Ministry of Health for a period of 2 years instead.

Pertuzumab is indicated in combination with trastuzumab and chemotherapy (docetaxel,paclitaxel, capecitabine or hormone therapy drugs (anastrozole, letrozole, exemestane, tamoxifen, fulvestrant, GnRH agonists) for the treatment of early and metastatic HER2-positive breast cancer.

As a result of these highly effective anti-HER2 agents, patients with HER2-positive metastatic breast cancer are now surviving longer.

## CLINICAL EFFICACY AND SAFETY OF DUAL HER2 BLOCKADE WITH TRASTUZUMAB AND PERTUZUMAB

The combination of pertuzumab (or placebo)– trastuzumab–docetaxel in the metastatic or locally advanced HER2-positive setting has been tested in several clinical trials. In the CLEOPATRA study, statistically significant improvement in PFS was reported (18.5 months in pertuzumab group compared to 12.4 months in the control group; hazard ratio (HR) for progression 0.62; 95% CI, 0.51–0.75; P < 0.001) [8].

The median OS was 56.5 months compared to 40.8 months (HR 0.68; 95% CI, 0.56–0.84; P < 0.001) [9]. This represents a considerable gain (approximately 16 months) in OS for patients administered pertuzumab as part of their treatment for HER2-positive breast cancer. Furthermore, the authors noted that the estimate of OS is conservative, as the effect of treatment crossover was not taken into account [9].

This pivotal study shifted treatment practice from trastuzumab plus a taxane, to the new first-line international standard regimen of pertuzumab–trastuzumab–taxane[10].

However, concerns of toxicity in combination with docetaxel and the HER2 doublet (pertuzumab–trastuzumab) led to clinical trials that explored combination with paclitaxel [11].

The primary purpose of the study by Dang et al was to determine whether weekly paclitaxel was feasible in combination with pertuzumab and trastuzumab in women with firstor second-line HER2-positive metastatic breast cancer. The authors reported PFS of 86% at six months, similar to that observed in the CLEOPATRA study, suggesting paclitaxel is a suitable alternative taxane in this setting [11].

Other anti-HER2 therapy regimens are also of research interest, and these have been assessed in the MARIANNE study [12]. In this study, the combination of trastuzumab + docetaxel was compared with trastuzumab–emtansine (T–DM1) alone or pertuzumab + T–DM1. The study met one of its primary endpoints (non-inferiority compared to trastuzumab + docetaxel), but did not meet superiority. Of note, however, the T–DM1-containing regimens (including pertuzumab + T–DM1) were associated with significantly better health-related quality of life and tolerability compared to the trastuzumab + docetaxel arm [12].

The incidence of alopecia, diarrhea, peripheral neuropathy, peripheral edema and neutropenia was less in T–DM1 containing arms, whereas nausea, headache, epistaxis, pyrexia, vomiting and chills were greater[12]. Based on these pivotal studies, clinicians have recommended the use of dual anti-HER2 blockade pertuzumab and trastuzumab in combination with taxane chemotherapy in the first-line setting as the new international standard of care.

Our University Clinic of Radiotherapy and Oncology Skopje participated in both the CLEOPATRA study and the MARIANNE study with Prof. Snezhana Smichkoska as country principal investigator.

## PRACTICAL CONSIDERATIONS IN THE FIRST-LINE SETTING

Pertuzumab in combination with trastuzumab and a taxane is recommended in the first-line setting, based on the evidence presented in the CLEOPATRA study [9].

The CLEOPATRA study has reported good efficacy in combination with docetaxel[9]. Other taxanes (paclitaxel and nab-paclitaxel) have been used in clinical practice in combination with trastuzumab. [13,14].

Having a choice of taxane allows modification of taxane for safety reasons.

In North Macedonia, available taxanes include docetaxel and paclitaxel. Although paclitaxel has less convenient dosing, it is preferred by many clinicians due to a more favorable safety profile; that is, lower rates of febrile neutropenia and mucositis, with similar rates of diarrhea when compared to docetaxel. In our experience, docetaxel use is limited by the severity and frequency of febrile neutropenia. Diarrhea with HER2 doublet plus taxanes is a clinically important side effect that must be monitored.

Administration of docetaxel should continue for between six to eight cycles in line with CLEOPATRA, as tolerated, after which the recommendation would be to cease docetaxel administration. Administration beyond eight cycles is associated with significant hematologic toxicity, and should be avoided. Based on the limited available evidence in combination with pertuzumab and trastuzumab, weekly paclitaxel is a possible alternative to a docetaxel-containing regimen [11].

Paclitaxel has also shown good efficacy and tolerability when combined with trastuzumab alone [15]. Paclitaxel can be ceased after 6 months, or when maximal response has been achieved or before neuropathy (which is more common with paclitaxel) becomes too severe[15].

Administration of pertuzumab and trastuzumab should continue until disease progression, or

unacceptable tolerability.

## PRACTICAL CONSIDERATIONS FOR ADMINISTRATION

In the CLEOPATRA study, initial doses of pertuzumab and trastuzumab were separated (pertuzumab given day 1 of cycle 1, and trastuzumab on day 2, cycle 1). This allowed clinicians to identify the agent responsible for any infusion-related reactions. Practically, this is not how pertuzumab is administered within Macedonian chemotherapy centers, where all three agents (pertuzumab, trastuzumab and the taxane) are successfully administered on the same day. According to the product label, docetaxel must be administered after the monoclonal antibodies, but may be administered on the same day following suitable observation periods in line with safety data from clinical trials [10].

Time required for administration of pertuzumab–trastuzumab–taxane combination Both pertuzumab and trastuzumab require postinfusion observation, due to the possibility of infusion reactions. Observation periods of 30–60 min are recommended following each infusion. The initial infusion of the pertuzumab–trastuzumab–taxane combination takes approximately 5.5 h, including observation time. Subsequent infusions may be reduced to approximately 3 h.

## TOXICITY MANAGEMENT

The most clinically important side-effects are febrile neutropenia, rash and diarrhea. The specific management of important pertuzumab side-effects is discussed later.

### *Diarrhea*

Pertuzumab–trastuzumab–taxane combinations are associated with increased rates of diarrhea compared to trastuzumab–taxane combinations alone[8].

Thus, the addition of pertuzumab may impact the tolerated dose intensity of chemotherapy. Generally, diarrhea decreases after cessation of chemotherapy. However, intermittent episodes of diarrhea may persist with the anti-HER2 doublet therapy. The mechanism of action of pertuzumab-induced diarrhea is thought to be via its obstruction of HER2 heterodimerization with epidermal growth factor receptor (EGFR), with an adverse events profile usually associated with EGFR antagonists, including secretory diarrhea[16].

This differs from the chemotherapy-induced diarrhea which is secondary to mucositis of the gastrointestinal tract [17].

Providing loperamide to patients at the time of clinic visit ensures that patients have access to treatment in the case of diarrhea. Our expert panel advise patients to take loperamide as per preferred institutional or international guidelines[18].Patients should contact their hospital or treatment center if they have more than three loose bowel motions despite loperamide use. Patients with severe diarrhea (defined as an increase of seven or more stools per day over baseline, or incontinence) should present to the hospital for further treatment, or hospitalization, as necessary. Oral antibiotics may be added for diarrhea that does not resolve within 24 h of commencing loperamide, and where fecal culture suggests infectious diarrhea [18].

### *Rash*

Rash is a significant side-effect of pertuzumab treatment, occurring in approximately 20–35% of patients receiving concomitant docetaxel, and approximately 12% of patients following cessation of docetaxel. [8,19,20].

There is currently no clinical trial evidence to guide treatment of the rash from pertuzumab[20].The rash associated with pertuzumab is typically milder and occurs less frequently than the rash observed with EGFR inhibitors[20].; however, it appears histologically similar to that observed with the EGFR inhibitors[19].The incidence of rash in the CLEOPATRA study was 33.7% (all grades, pertuzumab arm), [20]. 24.6% in the Drucker meta-analysis,20 compared to the 70–88% reported in studies of EGFR inhibitors. [21,22].

The principles of prevention and treatment of the papulopustular rash associated with EGFR inhibitors may be appropriate for patients experiencing pertuzumab-related rash. Strategies for the prevention and treatment of the rash associated with EGFR inhibitors have included topical emollients, antibiotics and steroid creams, avoidance of sun exposure and use of sunscreens[23].Systemic steroids and antibiotics (doxycycline or minocycline) have been recommended in some cases[23].The severity of rash associated with pertuzumab generally does not warrant prophylactic antibiotics. [20,23].

*Skin and nail infections*

An increased incidence of dermatological infectious complications has been observed in patients treated with pertuzumab–trastuzumab–taxane combinations. These infections include folliculitis of the scalp, abdomen or buttocks, abscesses and cellutitis. Severe paronychia has also been observed [19].

*Febrile neutropenia*

Febrile neutropenia affects approximately 10% of patients prescribed pertuzumab–trastuzumab–taxane combinations. The reason for the difference is unclear[24].

Most oncologists are used to treating chemotherapy-induced febrile neutropenia, typically by dose reduction of the taxane. For example, in the CLEOPATRA trial, dose reductions of docetaxel from 75 mg/m2 to a minimum of 55 mg/m2 were permitted.8 In this study, granulocytecolony stimulating factor (GCSF) was allowed to support neutrophil counts. Lower initial doses of taxane should be considered in those with hepatic failure, and those with poor performance status as these patients are at risk of developing febrile neutropenia.

The CLEOPATRA study allowed docetaxel to be increased to 100 mg/ m2 if tolerated,8 although this dose is uncommonly used in an our institutional setting.

*Infusion-related reactions*

Infusion-related reactions have been reported with both pertuzumab and trastuzumab. In the CLEOPATRA study, 13% of patients who received pertuzumab alone on day one of the first cycle reported infusion-related reactions, compared to 9.8% in the placebo only arm[14].

The majority of these reactions were mild or moderate [3].

Despite the CLEOPATRA protocol not using routine premedication, some centers anecdotally prefer to offer premedication to their patients. Premedications might include dexamethasone, chloropyramine, and famotidine. In the event of infusion-related reactions, hospitals should follow their institutional procedure. For example, if the infusion reaction is mild, the infusion can be slowed and Methylprednisolone and Ketoprofen given. If the infusion reaction is more severe, the infusion should be ceased until the patient observations have stabilized and the clinician assesses the patient as able to perhaps recommence with a premedication at a slower infusion rate. If the reaction is very severe, for example cardiac arrest or severe bronchospasm, pertuzumab should be permanently discontinued if assessed to be the source of infusion reaction.

*Cardiac events*

Pertuzumab must not be used in patients with left ventricular ejection fractions of less than 45% or in patients with symptomatic heart failure, as per the CLEOPATRA inclusion criteria, [8].

The safety of pertuzumab in patients with left ventricular ejection fractions less than 45% is not established. Reassuringly, the incidence of cardiac events does not appear to increase with the addition of pertuzumab to trastuzumab–taxane combinations compared to trastuzumab–docetaxel alone. [8]. Regular cardiac monitoring (at three-monthly intervals) using echocardiography or multigated acquisition is recommended to monitor left ventricular ejection fraction.

THE USE OF PERTUZUMAB IN SPECIFIC PATIENT POPULATIONS

Increased toxicities are observed in certain populations with pertuzumab–trastuzumab–taxane combination and are typically managed by dose reduction of the taxane. There is no evidence supporting dose reductions of pertuzumab or trastuzumab.

*Patients with hepatic impairment*

Patients with hepatic dysfunction are of particular concern with regards to diarrhea associated with docetaxel, particularly given docetaxel has a high hepatic clearance. These patients should receive their taxane at a reduced dose, if clinically appropriate. The eviQ guidelines recommend dose reduction of docetaxel by 25% for minimal impairment, 50% for mild impairment (total bilirubin 1–1.5 times the upper limit of normal, or aspartate aminotransferase above the upper limit of normal) and to omit docetaxel completely for moderate or severe hepatic dysfunction (total bilirubin more than 1.5 times the upper limit of normal).

*Elderly patients*

Treating older patients with pertuzumab, trastuzumab and docetaxel can present significant challenges. In particular, they experienced more diarrhea, fatigue, asthenia, decreased appetite, vomiting and dygeusia than younger patients in CLEOPATRA[25].

Cardiac status should be carefully monitored, although in the CLEOPATRA study, there was no statistically significant association between age and the development of asymptomatic or symptomatic left ventricular systolic dysfunction.25 Some elderly patients experience significant toxicity from six to eight cycles of chemotherapy [25].A reduction in the number of cycles, or the dose of the taxane should be considered, and there should be careful assessment of the patient's comorbidities and performance status at all stages of treatment. Weekly paclitaxel might also be considered, as it is generally appears well tolerated by elderly patients.

*Patients with central nervous system metastases*

Patients with central nervous system metastases were not eligible for the CLEOPATRA study[8]. Based on the limited available evidence, patients with brain metastases should have their brain metastases treated first with the appropriate local therapy [26].

Approximately 14% of patients in the pertuzumab–trastuzumab arm of the CLEOPATRA study developed central nervous system (CNS) metastases as their first site of disease progression [27].

The efficacy of pertuzumab combinations in treating CNS disease is unknown. Treatment options that have demonstrated some brain-specific benefit in clinical trials include capecitabine/lapatinib, the continued use of trastuzumab, ado-trastuzumab emtansine, neratinib, and the experimental agent tucatinib (ONT-380). Preferred option among them is ado-trastuzumab emtansine, based on a subset of the large EMILIA trial that achieved a doubling in overall survival. An exploratory analysis of the single-arm - KAMILLA study also found a median time to disease progression in the brain of 11.3 months with ado-trastuzumab emtansine. We would consider capecitabine/lapatinib for central nervous system disease only in those patients who we are not able to control with local measures. Further research is needed in this area.

*Patients who relapse within 12 months of adjuvant treatment*

Patients have different sensitivities to anti-HER2 agents, depending on whether they present with de novo metastases and thus have not received trastuzumab or they developed metastatic disease after adjuvant trastuzumab. In the latter group, patients with a trastuzumab-free interval of 1 year or longer seem to be more sensitive to anti-HER2 therapies than those whose disease progressed within 1 year. Patients who had progressed on or within 12 months of their adjuvant treatment were excluded in the CLEOPATRA study[8]. Therefore, there is no evidence for treatment of this patient subset with pertuzumab. Improved PFS has been reported in a subset of patients treated with T–DM1 in the EMILIA study as compared to lapatinib and capecitabine [28].The ASCO guidelines recommend T–DM1 for this specific patient population [10].

BEYOND PROGRESSION

Once a patient has progressed following treatment with pertuzumab–trastuzumab–taxane, T–DM1 or a combination of lapatinib and capecitabine may be considered.10

Patients and methods: single center real world data

We retrospectively identifed 35 patients on adjuvant and frst-line anti-HER2 therapy at The University Clinic of Radiotherapy and Oncology Skopje from January 2019 to July 2020 (Data Cut Off). In these selected patients, 17 patients received trastuzumab plus pertuzumab in adjuvant setting and 18 patients received trastuzumab plus pertuzumab in metastatic setting.

The criteria for the treatment of patients with HER2-positive early breast cancer (EBC) at high risk of recurrence regarding tumour and nodal stage and cardiac function were the same as in pivotal (neo) adjuvant trials: tumours larger then 2 cm if node negative disease, any tumour size if node positive disease, performance status zero or one, no serious concomitant cardiac diseases and treatment with adjuvant chemotherapy or hormone therapy.[9–11] Pertuzumab was indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease

Data were collected from patient's records. Cardiac monitoring, including an assessment of the left ventricular ejection fraction, was performed every 3 months during treatment. Hematologic and liver-function tests were checked repeatedly during each cycle of chemotherapy. The main objective of this project was to evaluate the outcome of our real life patient population.

The baseline characteristics of the patients, tumours and primary treatments in adjuvant and metastatic setting are presented in Table 1 and Table 2 respectively.

**Table 1**.Patients age group receiving (neo) adjuvant Trastuzumab plus Pertuzumab

| **Patients age (yr)** | **n ( % )** |
|---|---|
| 25 – 30 | 1 (5.88) |
| 35 – 40 | 1 (5.88) |
| 40 – 45 | 3 (17.65) |
| 45 – 50 | 1 (5.88) |
| 50 – 55 | 3 (17.65) |
| 55 – 60 | 5 (29.41) |
| 65 – 70 | 2 (11.76) |
| >70 | 1 (5.88) |

| **Delivery of therapy (neoadjuvant vs adjuvant)** | **n ( % )** |
|---|---|
| Neoadjuvant therapy | 2 (11.8) |
| Adjuvant therapy | 15 (88.2) |

| **Lymph node involvement** | **n ( % )** |
|---|---|
| Negative | 6 (35.29) |
| Positive | 9 (52.95) |
| N/A (neo-adj pts) | 2 (11.76) |

| **Lymph node status** | **n ( % )** |
|---|---|
| Negative | 6 (35.29) |
| 1 – 4 | 5 (29.42) |
| >4 | 4 (23.53) |
| N/A (neo-adj pts) | 2 (11.76) |

| **Hormone receptor status** | **n ( % )** |
|---|---|
| Positive | 9 (52.94) |
| Negative | 8 (47.06) |

| **Type of adjuvant or neoadjuvant therapy** | **n ( % )** |
|---|---|
| Only Trastuzumab/Pertuzumab | 1 (5.88) |
| Anthracyclines and taxanes | 10 (58.83) |
| Anthracyclines, no taxanes | 1 (5.88) |
| Taxanes | 3 (17.65) |
| Other chemotherapy | 1 (5.88) |
| Adjuvant endocrine therapy | 1 (5.88) |

**Table 2**.Patients age group receiving Trastuzumab plus Pertuzumab in metastatic setting

| **Patients age (yr)** | **n ( % )** |
|---|---|
| 30 – 35 | 1 (5.56) |
| 35 – 40 | 2 (11.11) |
| 40 – 45 | 1 (5.56) |
| 45 – 50 | 1 (5.56) |
| 50 – 55 | 3 (16.67) |
| 55 – 60 | 2 (11.11) |
| 60 – 65 | 5 (27.78) |
| 65 – 70 | 3 (16.67) |

| **Metastatic patterns of MBC** | **n ( % )** |
|---|---|
| Bone-only | 6 (33.33) |
| Visceral-only | 12 (66.67) |

| **Hormone receptor status** | **n ( % )** |
|---|---|
| Positive | 13 (72.22) |
| Negative | 5 (27.78) |

| **Type of therapy in metastatic setting** | **n ( % )** |
|---|---|
| Only Trastuzumab/Pertuzumab | 4 (22.22) |
| Taxanes | 10 (55.55) |
| Other chemotherapy | 3 (16.67) |
| Endocrine therapy | 1 (5.55) |

Patients who begun pertuzumab and trastuzumab in the neoadjuvant setting continued to receive pertuzumab and trastuzumab, every 3 weeks, to complete 1 year (up to 18 cycles). Patients who begun treatment in the adjuvant setting received a total of 1 year (up to 18 cycles) of pertuzumab and trastuzumab-based therapy, every 3 weeks, starting on Day 1 of the first taxane-containing cycle. The average number of (neo) adjuvant Trastuzumab cycles was 8.7 ± 4.7, the minimum number being 3, and the maximum number being 18 cycles. Two out of seventeen patients completed 1-year trastuzumab with pertuzumab therapy for early breast cancer (EBC)in the study period.

Patients who begun pertuzumab and trastuzumab in the metastatic setting continued to receive pertuzumab and trastuzumab, every 3 weeks until disease recurrence or unmanageable toxicity, whichever occurred first.

The average Trasuzumab therapy for fourteen out of eighteen patients with MBC lasted 28.7 ± 23.2 months, 1 month was the shortest, and 74 months the longest treatment of the patients. Half of these patients have been receiving Trastuzumab for more than 24.5 months (median=24.5). When the pertuzumab became available for our patients in 2019 it was added to the standard first-line trastuzumab based therapy for metastatic breast cancer (MBC).

The average number of first-line trastuzumab/pertuzumab cycles was 10.8 ± 6.5, the minimum number being 1, and the maximum number being 18 cycles. For two patients the administration of Trastuzumab and Pertuzumab was delayed by more than six weeks and the treatment was restarted at the level of the initial dose of 8 mg per kilogram, which was followed by the usual maintenance dose (6 mg per kilogram every three weeks) for Trastzumab and for Pertuzumab at a initial dose of 840 mg, followed by 420 mg maintenance dose every three weeks. Two patients after relapsing on first-line trastuzumab/pertuzumab chemotherapy received second-line ado- trastuzumab–emtansine (T-DM1) therapy. No treatment interruption was recorded in both groups due to adverse events.

**Conclusion**

The advent of targeted therapies for women with HER2-positive breast cancer has led to marked improvements in survival. Trastuzumab and pertuzumab are now very well established in the (neo) adjuvant and frst-line setting; Our results based on the treatment of real-life BC patients with more than one year of trastuzumab/pertuzumab based therapy are comparable to the results obtained in international clinical studies and indicates also that long-term anti-HER2 treatment remains safe and well tolerated in adjuvant setting.

The addition of pertuzumab was also shown to be relatively well tolerated for our patients with MBC without treatment interruption due to adverse events and continue receiving.

Further research on the dentifying predictors of long-term response to these would be important in selecting which patients might beneft from entry into future clinical trials assessing the long-term beneft of these newer agents in addition.

**References:**


1. Cancer in the Republic of North Macedonia 2010-2019, Institute of Public health of the Republic of North Macedonia
2. Smith IE. Efficacy and safety of Herceptin in women with metastatic breast cancer: results from pivotal clinical studies. Anticancer Drugs. 2001;12 Suppl 4:S3-10.
3. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist. 2005;10 Suppl 3:20-29.
4. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002;20(3):719-726.
5. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol. 1999;17(9):2639-2648.
6. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23(19):4265-4274.
7. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol. 2009;27(33):5529-5537.
8. Baselga J, Cortés J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366(2):109-119.
9. 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(8):724-734.
10. Giordano SH, Temin S, Kirshner JJ, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32(19):2078-2099.
11. Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2015;33(5):442-447.
12. 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(2):141-148.
13. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol. 2006;24(18):2786-2792.
14. Bullock K, Blackwell K. Clinical efficacy of taxane-trastuzumab combination regimens for HER-2-positive metastatic breast cancer. Oncologist. 2008;13(5):515-525.
15. Seidman AD, Fornier MN, Esteva FJ, et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene

amplification. J Clin Oncol. 2001;19(10):2587-2595.
16. Melosky B. Supportive care treatments for toxicities of anti-egfr and other targeted agents. Curr Oncol. 2012;19(Suppl 1):S59-63.
17. Gibson RJ, Keefe DMK. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. Support Care Cancer. 2006;14(9):890-900.
18. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004;22(14):2918-2926.
19. Mortimer J, Jung J, Yuan Y, et al. Skin/nail infections with the addition of pertuzumab to trastuzumab-based chemotherapy. Breast Cancer Res Treat. 2014;148(3):563-570.
20. Drucker AM, Wu S, Dang CT, Lacouture ME. Risk of rash with the anti-HER2 dimerization antibody pertuzumab: a meta-analysis. Breast Cancer Res Treat. 2012;135(2):347-354.
21. Jia Y, Lacouture ME, Su X, Wu S. Risk of skin rash associated with erlotinib in cancer patients: a meta-analysis. J Support Oncol. 2009;7(6):211-217.
22. Su X, Lacouture ME, Jia Y, Wu S. Risk of high-grade skin rash in cancer patients treated with cetuximab--an antibody against epidermal growth factor receptor: systemic review and meta-analysis. Oncology. 2009;77(2):124-133.
23. Ocvirk J, Heeger S, McCloud P, Hofheinz R-D. A review of the treatment options for skin rash induced by EGFR-targeted therapies: Evidence from randomized clinical trials and a meta-analysis. Radiol Oncol. 2013;47(2):166-175.
24. Malenfant SJ, Eckmann KR, Barnett CM. Pertuzumab: a new targeted therapy for HER2-positive metastatic breast cancer. Pharmacotherapy. 2014;34(1):60-71.
25. Miles D, Baselga J, Amadori D, et al. Treatment of older patients with HER2-positive metastatic breast cancer with pertuzumab, trastuzumab, and docetaxel: subgroup analyses from a randomized, double-blind, placebo-controlled phase III trial (Cleopatra). Breast Cancer Res Treat. 2013;142(1):89-99.
26. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32(19):2100-2108.
27. Swain SM, Baselga J, Miles D, et al. Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA. Ann Oncol. 2014;25(6):1116-1121.
28. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-1791.