Arrival Date: 23.11.2022 | Published Date: 30.04.2023 | Vol: 8, Issue: 2 | pp: 431-436 | Doi Number: http://doi.org/10.5281/zenodo.7931256

EFFICACY OF TRASTUZUMAB EMTANSINE THERAPY IN SEQUANTIAL TREATMENT IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

HER2-POZİTİF METASTATİK MEME KANSERİ OLAN HASTALARDA SIRALI TEDAVİDE TRASTUZUMAB EMTANSİN TEDAVİSİNİN ETKİNLİĞİ

Serdar ATA [1], Burcu ARSLAN BENLİ [1], Oğuzhan KESER [1], Ahmet Ziya BAYHAN [1], Hakan DEMİR [1], Ömer DEMİROĞLU [1], Ali Alper SOLMAZ [1], Timuçin ÇİL [1], Berna BOZKURT DUMAN [1]

[1] Department of Medical Oncology, University of Health Sciences, Adana City Training and Research Hospital, Adana, Turkey.

ABSTRACT

Aim: The aim of this study was to evaluate the efficacy of Lapatinib, trastuzumab emtansine (T-DM1) treatment after pertuzumab in patients with HER2-positive metastatic breast cancer.

Materials and Methods: The study included HER2-positive breast cancer patients who were followed up and treated in Adana City Training and Research Hospital. Totally 1840 patients with a diagnosis of breast cancer in the hospital management system were evaluated, 670 patients who were determined to be metastatic were evaluated for eligibility. Thirty-one patients who received pertuzumab before T-DM1 treatment, while 34 patients who received T-DM1 before pertuzumab were included.

Results: Of the 65 female patients included in the study, 59 had ductal adenocarcinoma (90.8%) and 6 had lobular adenocarcinoma (9.2%). Seventeen patients (26.2%) had bone metastases, 20 patients (30.7%) had visceral metastases, and 28 patients (43.1%) had bone and visceral metastases together. Overall survival (OS) was 23.8±3 months in those who did not receive pertuzumab before T-DM1 in the metastatic setting, while it was similar in those who received pertuzumab with 22.4±2.9 months (p=0.969). Progression-free survival (PFS) was 9.1±1.3 months in those who did not receive pertuzumab before T-DM1 in the metastatic setting, while it was significantly lower in patients who received pertuzumab with 4.9±0.8 months (p=0.005). The comparison of initiation of T-DM1 after pertuzumab as second-line therapy in the metastatic setting and its use in later therapeutic lines revealed no difference in PFS and OS (p=0.628 and p=0.706, respectively).

Conclusion: Pertuzumab should be preferred primarily because it is more effective in metastatic HER2-positive breast cancer. Despite the significant decrease in PFS of patients using T-DM1 after pertuzumab, there was no decrease in OS; therefore the earlier T-DM1 therapy is initiated following pertuzumab, the more effective it is.

Keywords: Breast cancer, HER-2, Pertuzumab, Trastuzumab emtansine.

ÖZET

Giriş: Bu çalışma HER2 pozitif metastatic meme kanseri olan hastalarda pertuzumab sonrası T-DM1 tedavisinin etkinliğini değerlendirmeyi amaçlamıştır**.**

Materyel ve Metod: Adana Eğitim ve Araştırma Hastanesi'nde takip edilen HER2-pozitif metastatik meme kanseri olan hastalar çalışmaya alındı. Hastane yönetim sisteminde meme kanseri tanısı alan toplam 1840 hasta değerlendirildi, metastatik olduğu belirlenen 670 hasta uygunluk açısından değerlendirildi. T-DM1 tedavisi öncesi pertuzumab alan 31 hasta ile pertuzumab öncesi T-DM1 alan 34 hasta çalışmaya dahil edildi.

Bulgular: Çalışmaya dahil edilen 65 kadın hastanın 59'unda duktal adenokarsinom (%90,8), 6'sında lobüler adenokarsinom (%9,2) vardı. On yedi hastada (%26,2) kemik metastazı, 20 hastada (%30,7) visseral metastaz ve 28 hastada (%43,1) kemik ve visseral metastaz birlikte mevcuttu. Genel sağkalım (OS), metastatik aşamada T-DM1 öncesi pertuzumab almayanlarda 23,8±3 ay iken, pertuzumab alanlarda 22,4±2,9 ay ile benzerdi (p=0,969). Progresyonsuz sağkalım (PFS) metastatik aşamada T-DM1 öncesi pertuzumab almayanlarda 9,1±1,3 ay iken, pertuzumab alan hastalarda 4,9±0,8 ay ile anlamlı olarak daha düşüktü (p=0,005). Metastatik aşamada ikinci basamak tedavi olarak pertuzumab sonrası T-DM1 başlanması ile daha sonraki tedavi basamaklarında kullanımının karşılaştırılmasında PFS ve OS'de fark saptanmadı (sırasıyla p=0.628 ve p=0.706).

Sonuç: Pertuzumab, metastatik HER2-pozitif meme kanserinde daha etkili olduğu için öncelikle tercih edilmelidir. Pertuzumab sonrası T-DM1 kullanan hastalarda PFS'de anlamlı düşüş olmasına rağmen OS'de azalma olmadı; bu nedenle pertuzumabın ardından T-DM1 tedavisi ne kadar erken başlatılırsa o kadar etkili olur.

Anahtar Kelimeler: HER-2, Meme kanseri, Pertuzumab, Trastuzumab emtansine

Sorumlu Yazar / Corresponding Author: Serdar Ata, MD, Department of Medical Oncology, University of Health Sciences, Adana City Training and Research Hospital, Adana, Turkey. **E-mail:** drserdarata@gmail.com

Bu makaleye atıf yapmak için / Cite this article: Ata S, Arslan Benli B, Keser O, Bayhan AZ, Demir H, Demiroğlu Ö, Solmaz AA, Çil T, Duman BB. (2023). Efficacy of Trastuzumab Emtansine Therapy in Sequantial Treatment in Patients with HER2-Positive Metastatic Breast Cancer. *Gevher Nesibe Journal of Medical & Health Sciences*, 8(2), 431-436. http://doi.org/10.5281/zenodo.7931256

INTRODUCTION

Breast cancer is the most common cancer in women, according to the cancer data of the World Health Organization (Sung et al., 2021). Amplification of human epidermal growth factor receptor 2 (HER2) gene occurs in approximately 20% of patients, (Slamon et al., 1987, 1989) and these patients have a worse prognosis than those without HER2 amplification (Sjögren et al., 1998; Sorlie et al., 2001). HER2 oncogene encodes a transmembrane (HER-2) oncogene encodes a transmembrane tyrosine kinase receptor that has evolved as a major classifier of invasive breast cancer and target of therapy for the disease .Trastuzumab is the first drug approved by the FDA for the treatment of this patient group. Lapatinib, trastuzumab emtansine (T-DM1), and pertuzumab were later approved for use in patients with progressive metastatic breast cancer following trastuzumab therapy.

T-DM1 is a conjugate comprised of the monoclonal antibody trastuzumab and the cytotoxic drug emtansine. Its use for the treatment of metastatic HER2-positive breast cancer was approved by the United States Food and Drug Administration (FDA) in February 20132.

Later, the CLEOPATRA phase 3 study demonstrated efficacy of pertuzumab in metastatic HER2-positive breast cancer. With the subsequent NEOSPHERE and TRYPHANE studies, it has been included in neoadjuvant therapy.

This study aimed to evaluate the efficacy of T-DM1 after pertuzumab in HER2-positive patients with metastatic breast cancer.

MATERIALS AND METHODS

In this study, patients who were followed up and treated with a diagnosis of metastatic breast cancer in Adana Training and Research Hospital Medical Oncology Clinic between 1 January 2017 and 1 January 2022 were screened retrospectively. The treatments received by patients who underwent radiological biopsy of potential site of primary tumor or its metastasis and were pathologically diagnosed with breast cancer were screened from archive files. Totally 1840 patients with a diagnosis of breast cancer in the hospital management system were evaluated, 670 patients who were determined to be metastatic were evaluated for eligibility. The previous treatments of 70 patients who received T-DM1 therapy were analyzed. Three patients who received T-DM1 as adjuvant therapy and 2 patients who received pertuzumab therapy in the neoadjuvant setting were excluded from the study, thus 65 patients were included in the study. These patients were divided into two groups; 31 of these patients received pertuzumab treatment before T-DM1 treatment, while 34 of them received T-DM1 treatment before pertuzumab treatment in the metastatic setting. All of the patients with a c-erbB2 score of 2+ immunohistochemically were HER2-positive by FISH. This study was designed according to Helsinki declaration and was started after Ethics approval (Number: 21.10.2021/1619).

Patients treatment response and progression were adjudicated by comparing conventional imaging reports in the hospital management system based on RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1. The treatment response and progression of those followed up with positron emission tomography/computed tomography (PET-CT) were determined by evaluating result reports.

STATISTICS

SPSS (Statistical Package for the Social Sciences) version 23.0 software package was used for statistical analysis of the data. Categorical measures were summarized as numbers and percentages and continuous measures as mean, deviation, and minimum-maximum. Normality distribution was checked using the Shapiro-Wilk test. The Mann-Whitney U test was used to compared non-normally distributed groups. The sensitivity and specificity of RDW/MPV (red cell distribution width/mean platelet volume) and NLR (neutrophil to lymphocyte ratio) values were calculated based on the T-DM1 treatment timing variable of the patients included in the study, and the cut-off value was determined by examining the area under the ROC curve. Kaplan-Meier and log-rank tests were used to analyze the survival and recurrence results of the patients. The level of statistical significance was set at 0.05 for all tests.

RESULTS

Of the 65 female patients included in the study, 59 had ductal adenocarcinoma (90.8%) and 6 had lobular adenocarcinoma (9.2%). The mean age of the patients was 57.1±12.8 years. Seventeen patients had only bone metastasis (26.2%), 20 patients had only visceral metastasis (30.7%), while 28 patients (43.1%) had concurrent bone and visceral metastases. Forty-eight (73.8%) of the patients were estrogen receptor-positive and 29 (44.6%) were progesterone receptor-positive. Estrogen receptor was positive in 28 (96.5%) of 29 patients who were progesterone receptor-positive. Eight (12.3%) patients had a c-erbB2 score of 2+, while 57 (87.7%) patients had a c-erbB2 score of 3+. Of the patients included in the study, 39 (60%) died. The clinical characteristics of the patients are shown in Table 1.

Table 1. Clinical characteristics of patients

	Patients receiving T-DM1 before pertuzumab	**Patients receiving T-DM1 after pertuzumab**
Number of patients n(%)	34(52.3%)	31(47.7%)
Histological type n(%)		
Ductal	31(52.5%)	28(47.5%)
Lobular	3(50%)	3(50%)
Visceral metastasis n(%)		
Yes	26(76.4%)	22(70.9%)
No	8(23.6%)	9(29.1%)
ER n(%)		
Positive	26(54.1%)	22(45.9%)
Negative	8(47%)	9(53%)
PR n(%)		
Positive	15(51.7%)	14(48.3%)
Negative	19(52.7%)	17(47.3%)
C-erbB2 Positivity n(%)		
2+	1(14.2%)	6(85.8%)
3+	33(56.8%)	25(43.2%)
Progression during T-DM1 treatment		
Yes	18(52.9%)	18(58.0%)
No	16(47.1%)	13(52.0%)

*T-DM1: trastuzumab emtansine, ER: estrogen receptor, PR:progesterone receptor

Overall survival (OS) was 23.8±3 months in those who did not receive pertuzumab before T-DM1 in the metastatic setting, while it was similar in those who received pertuzumab with 22.4±2.9 months (p=0.969) (Figure 1). Progression-free survival (PFS) was 9.1±1.3 months in those who did not receive pertuzumab before T-DM1 in the metastatic setting, while it was significantly lower in patients who received pertuzumab with 4.9±0.8 months (p=0.005) (Figure 2).

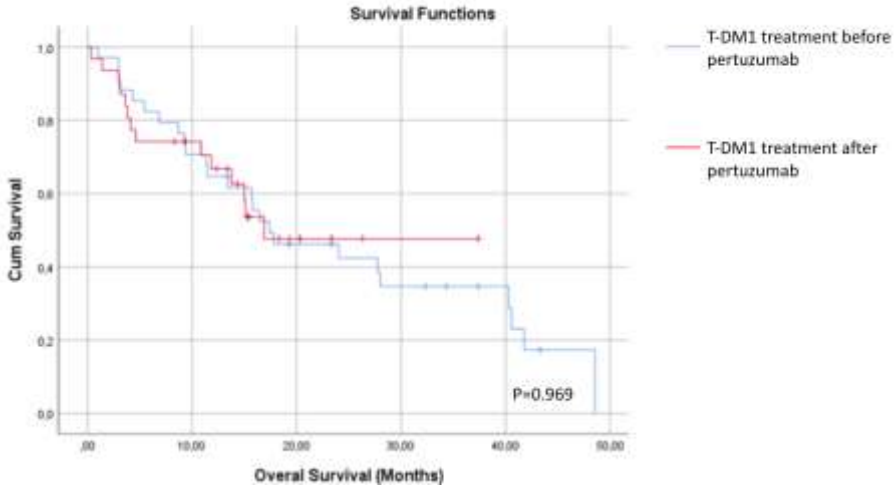

Figure 1. OS relative to T-DM1

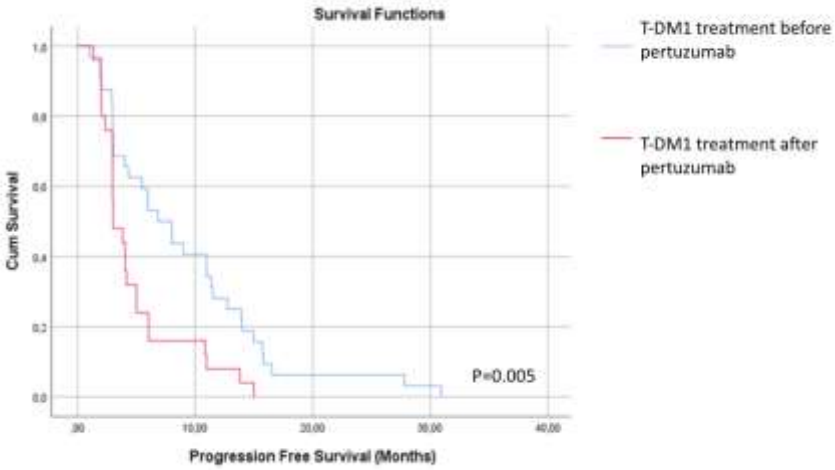

Figure 2. PFS relative to T-DM1

The comparison of initiation of T-DM1 therapy after pertuzumab as second-line therapy in the metastatic setting and its use in later therapeutic lines revealed no difference in PFS and OS (p=0.628 and p=0.706, respectively). The comparison of the patients who used T-DM1 after trastuzumab in the metastatic setting with those who used T-DM1 immediately after pertuzumab showed no difference in PFS and OS (p=0.083 and p=0.199, respectively). Among the patients who used T-DM1 after pertuzumab, OS was statistically significantly shorter in those with visceral metastasis (p=0.033); however, the decrease in PFS was not significant (p=0.192). Among the patients who used T-DM1 without pertuzumab, PFS was shorter in those with bone metastasis than in those without bone metastasis (p=0.003), while OS value was similar in patients with visceral or bone metastasis (p=0.688).

DISCUSSION

As known, pertuzumab should be preferred primarily because it is more effective in metastatic HER2-positive breast cancer. Previously T-DM1 was used because of its efficacy is more than capasitabine-lapatib. On the other hand after pertuzumab started to be used, it found a place for itself in later steps. However, we found that the PFS value was statistically shortened by T-DM1 after pertuzumab treatment compared to patients using T-DM1 first, but this treatment has no effect on OS.

With the discovery of new drugs for patients with metastatic breast cancer, there has been a significant improvement in OS. Since there are many drug treatments available in these patients, the question of which of these drugs would be more effective has gained importance. Although there are currently multiple drugs with which HER2-positive patients can be treated, the answer to the question of which order to use these drugs is more effective in patients with breast cancer is still being sought.

The first anti-HER2 antibody-drug conjugate developed was trastuzumab, followed by T-DM1 and pertuzumab. After the CLEOPATRA study (Swain et al., 2015) demonstrated the efficacy of pertuzumab in patients with metastatic breast cancer, it has been used in earlier settings of breast cancer treatment before T-DM1. After that, the setting to use T-DM1 and its efficacy have been brought into question.

On the other hand, the efficacy of T-DM1 was demonstrated for the first time by the EMILIA study (Verma et al., 2012) and it granted FDA approval. In the EMILIA study, 61% of patients used T-DM1 as second-line therapy for metastatic disease, achieving a PFS of 9.6 months. In this study, very few patients received pertuzumab therapy before T-DM1. The results of our study revealed a PFS of 9.1 months in those who did not receive pertuzumab before T-DM1, similar to the EMILIA study, while PFS was significantly lower in those who were treated with pertuzumab before T-DM1 with 4.9 months. This shows that the efficacy of T-DM1 decreased after pertuzumab. Since patients with progression after pertuzumab will not have enough HER2 receptors on the cell surface, it has been suggested that its efficacy is worse in patients given consecutive T-DM1 in later therapeutic lines than in those who received T-DM1 after other treatments.(Arribas et al., 2011; Capelan et al., 2013; Hudis, 2007).

In our study, PFS was 4.95 months in patients who received T-DM1 immediately after pertuzumab, while it was similar in those who received other treatments and then received T-DM1 with 4.45 months (p= 0.628). Contrary to these studies, the result of our study showed no worsening in PFS; therefore, we are of the opinion that preferring the more effective T-DM1 therapy instead of capecitabine-lapatinib after pertuzumab will be beneficial for the patients.

The earlier the T-DM1 therapy is given in the metastatic setting after pertuzumab, the more effective it is, with shorter PFS as a result of its use in the progressive setting. The study by Michel L. et al. (Michel et al., 2020) reported that PFS was 7.7 months in those who received T-DM1 as second-line therapy in the metastatic setting, 3.4 months in those who received T-DM1 as third-line therapy, and 2.7 months in those who received T-DM1 as fourth-line therapy or higher. Although PFS and OS values in our study were higher in patients who received T-DM1 as first-line therapy after pertuzumab for metastatic breast cancer compared to those who received T-DM1 as next-line therapy and in patients who did not receive pertuzumab and received T-DM1 after trastuzumab in the metastatic setting compared to those who received T-DM1 as next-line therapy, there was no statistically significant difference. We believe that this is due to the small sample size of our study. Moreover, in the same study (Michel et al., 2020), OS value was not reached in patients who received T-DM1 as second-line therapy in the metastatic setting, while OS was 18.3 months in those who received T-DM1 as third-line therapy and 9.1 in those who received T-DM1 as fourth-line therapy or higher. In our study, OS was 26.0 months patients who did not receive pertuzumab in the metastatic setting and received T-DM1 after trastuzumab in the metastatic setting, 18.6 months in those who received T-DM1 as second-line therapy or higher (p=0.199), and 22.6 months in those who received T-DM1 in later therapeutic lines (p=0.681). Numerically, the OS value was higher in both groups of patients who used T-DM1 in the early setting, but it was not statistically significant. We are of the opinion that this is due to the small number of patients in the subgrouping.

A retrospective Italian study of 250 patients by Vici P. et al.(Vici et al., 2017) investigated the efficacy of T-DM1. While 39 of the patients had previously used pertuzumab, PFS was found to be 3 months in patients who used T-DM1 as second-line therapy after pertuzumab in the metastatic setting. In MARIANNE phase-3 trial, patients with metastatic breast cancer was evaluated. The PFS was 14.1 months in patients who received T-DM1 in metastaic setting, longer than our results. When evaluated their patients are younger and visseral metastasis ratio was lower (Perez et al, 2017).

Limitations of our study was its retrospective design, the patients' Eastern Cooperative Oncology Group (ECOG) performance status were not evaluated.

In conclusion, despite the significant decrease in PFS of patients using T-DM1 after pertuzumab, there was no decrease in OS; therefore the earlier T-DM1 therapy is initiated following pertuzumab, the more effective it is.

Author Contributions

Plan, design: SA, BAB, AZB, HD, ÖD, AAS, TÇ, BBD; **Material, methods and data collection:** SA, TÇ, BAB, OK, AZB, HD, AAS, TÇ, BBD; **Data analysis and comments:** SA, BAB, AZB, HD, ÖD, AAS, TÇ, BBD; **Writing and corrections:** SA, BAB, AZB, HD, ÖD, AAS, TÇ, BBD.

Conflict of interest

The authors declare that they have no conflict of interest

Funding

This study was not financially supported.

REFERENCES

Arribas, J., Baselga, J., Pedersen, K., Parra-Palau, J. L. (2011). p95HER2 and Breast Cancer: Figure 1. Cancer Research, 71(5), 1515-1519. https://doi.org/10.1158/0008-5472.CAN-10-3795

Capelan, M., Pugliano, L., De Azambuja, E., Bozovic, I., Saini, K. S., Sotiriou, C.,…Piccart-Gebhart, M. J. (2013). Pertuzumab: New hope for patients with HER2-positive breast cancer. Annals of Oncology, 24(2), 273-282. https://doi.org/10.1093/annonc/mds328

Hudis, C. A. (2007). Trastuzumab—Mechanism of Action and Use in Clinical Practice. New England Journal of Medicine, 357(1), 39-51. https://doi.org/10.1056/NEJMra043186

Michel, L. L., Hartkopf, A. D., Fasching, P. A., Kolberg, H.-C., Hadji, P., Tesch, H., …Fehm, T. N. (2020). Progression-Free Survival and Overall Survival in Patients with Advanced HER2-Positive Breast Cancer Treated with Trastuzumab Emtansine (T-DM1) after Previous Treatment with Pertuzumab. Cancers, 12(10), 3021. https://doi.org/10.3390/cancers12103021

Perez, E.A., Barrios C., Eiermann, W., Toi, M., Im, Y.H., Conte, P.,… Ellis, P.(2017). "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". Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 35(2):141-48. doi: 10.1200/JCO.2016.67.4887.

Sjögren, S., Inganäs, M., Lindgren, A., Holmberg, L., Bergh, J. (1998). Prognostic and predictive value of c-erbB-2 overexpression in primary breast cancer, alone and in combination with other prognostic markers. Journal of Clinical Oncology, 16(2), 462-469. https://doi.org/10.1200/JCO.1998.16.2.462

Slamon, D. J., Clark, G. M., Wong, S. G., Levin, W. J., Ullrich, A., McGuire, W. L. (1987). Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/ neu Oncogene. Science, 235(4785), 177-182. https://doi.org/10.1126/science.3798106

Slamon, D. J., Godolphin, W., Jones, L. A., Holt, J. A., Wong, S. G., Keith, D. E.,…Press, M. F. (1989). Studies of the HER-2/ neu Proto-Oncogene in Human Breast and Ovarian Cancer. Science, 244(4905), 707-712. https://doi.org/10.1126/science.2470152

Sorlie, T., Perou, C. M., Tibshirani, R., Aas, T., Geisler, S., Johnsen, H., …Borresen-Dale, A.-L. (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proceedings of the National Academy of Sciences, 98(19), 10869-10874. https://doi.org/10.1073/pnas.191367098

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A.,…Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians, 71(3), 209-249. https://doi.org/10.3322/caac.21660

Swain, S. M., Baselga, J., Kim, S.-B., Ro, J., Semiglazov, V., Campone, M.,…Cortés, J. (2015). Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer. New England Journal of Medicine, 372(8), 724-734. https://doi.org/10.1056/NEJMoa1413513

Verma, S., Miles, D., Gianni, L., Krop, I. E., Welslau, M., Baselga, J.,…Blackwell, K. (2012). Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. New England Journal of Medicine, 367(19), 1783-1791. https://doi.org/10.1056/NEJMoa1209124

Vici, P., Pizzuti, L., Michelotti, A., Sperduti, I., Natoli, C., Mentuccia, L., …Gamucci, T. (2017). A retrospective multicentric observational study of trastuzumab emtansine in HER2 positive metastatic breast cancer: A real-world experience. Oncotarget, 8(34), 56921-56931. https://doi.org/10.18632/oncotarget.18176