Scientific Research Publishing

Journal of Cancer Therapy, 2017, 8, 933-940
http://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Impressive Objective Response to Nab-Paclitaxel plus Trastuzumab as Fifth Line Therapy in an Elderly HER-2 Positive Breast Cancer Patient

Maria Rosaria Valerio[1], Chiara Ancona[1], Antonella Marchese[2], Vittorio Gebbia[2*]

[1]Medical Oncology Unit, Department of Oncology, University of Palermo, Palermo, Italy
[2]Medical Oncology Unit, La Maddalena Clinic for Cancer, University of Palermo, Palermo, Italy
Email: *vittorio.gebbia@gmail.com

How to cite this paper: Valerio, M.R., Ancona, C., Marchese, A. and Gebbia, V. (2017) Impressive Objective Response to Nab-Paclitaxel plus Trastuzumab as Fifth Line Therapy in an Elderly HER-2 Positive Breast Cancer Patient. *Journal of Cancer Therapy*, **8**, 933-940.
https://doi.org/10.4236/jct.2017.811082

Received: October 20, 2017
Accepted: November 13, 2017
Published: November 16, 2017

Abstract

Background: Agent targeting HER-2 pathway plus chemotherapy has represented a major progress in the management of patients with breast cancer. However, the role of late-line treatment in heavily pretreated patients is still largely unclear. In the last decade, nab-paclitaxel has shown significant activity and good toxicity profile in metastatic breast cancer. **Case Presentation**: We report the case of a 76-year-old Caucasian woman with metastatic HER-2 positive ductal infiltrating breast carcinoma treated with a combination of weekly nab-paclitaxel and trastuzumab as fifth-line therapy. She had previously received first-line paclitaxel and trastuzumab, second-line vinorelbine and trastuzumab, third-line TDM1 and fourth-line oral capecitabine and lapatinib. Clinical and radiological staging showed progression at bone, skin and soft-tissue. The patient received weekly nab-paclitaxel plus trastuzumab. Massive objective response was clinically and PET documented which lasted 8 months. Tolerance to treatment was fairly good as well as cardiac safety. **Conclusion**: To the best of our knowledge, this is the first reported case of efficacy of nab-paclitaxel in combination with trastuzumab as fifth-line of treatment in a patient with metastatic HER-2 positive breast cancer.

Keywords

Nab-Paclitaxel, Trastuzumab, HER-2, Metastasis, Breast Cancer

1. Introduction

Patients with HER-2 positive breast cancer present a very aggressive disease

marked by shorter disease-free and overall survival due in part to an increased likeness to disseminate to visceral organs and central nervous system [1]. The availability of anti-neoplastic agents targeting HER-2 has led to significant improvements in survival of these patients and to date sound clinical data support the use of trastuzumab and pertuzumab based combinations as well as TDM1 in this clinical setting [2] [3]. However a significant proportion of patients progressing after third-line TDM1 is still in a good performance status and may deserve further treatment even if no clear indications are reported in major guidelines mainly because of lack of specifically designed trials [4]. Therefore medical oncologists are often free of following their personal experience.

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) has been shown to be active and better tolerated than standard paclitaxel and is considered an optimal partner of immunological agents because its administrations do not require premedication with corticosteroids [5] [6] [7]. In this paper we report a case of a woman with metastatic breast carcinoma over-expressing HER-2 successfully treated with a combination of weekly nab-paclitaxel plus trastuzumab as fifth-line therapy.

2. Case Presentation

A 64-year-old Caucasian woman underwent radical left mastectomy and omolateral axillary lymphonodes dissection in November 2006. Pathology revealed a moderately differentiated ductal infiltrating carcinoma with two axillary nodes positive for carcinoma stage pT2, pN1b (2/10), M0. Systemic clinical and radiological evaluation was negative for distant disease. Immunohistochemistry showed positive estrogen receptors (60%) and positive progestin receptors (65%), KI-67 index of 35%, and a HER-2 score of 0. The patient was then treated with adjuvant chemotherapy with epirubicin and docetaxel from December 2006 to March 2007 followed by letrozole for 5 years. She was clinically and radiological controlled on a regular basis without signs or symptoms of progressive disease.

In August 2012 physical examination revealed the occurrence of rapidly evolving cutaneous lesions on the anterior left thoracic wall close to the previous mastectomy scar, which were biopsied. Pathological and immunohistochemical examination showed metastases of ductal infiltrating carcinoma with no expression of estrogen and progestin receptors, KI-67 index of 60%, and HER-2 3+. Extensive staging showed a mass in the contralateral breast and a positive axillary node, which was considered a second primary breast cancer. Mammography showed a solid infiltrative lesion in the upper-inner quadrant of 30 mm diameter, with irregular margins and multiple micro-calcification clusters. Since pertuzumab was not yet available in the country the patient was treated with systemic paclitaxel and trastuzumab only. After 6 months paclitaxel was stopped and the patients was treated with single-agent trastuzumab. In May 2013 at progression of disease she received second-line treatment with weekly vinorelbine

and trastuzumab. In November 2014 cancer progressed both at the cutaneous lesions and the occurrence of metastatic lymphonodes. The patient was then treated with third-line TDM-1 with no signs of progression until February 2016. Fourth-line treatment consisted of oral capecitabine plus lapatinib with required careful involvement of a familiar caregiver to avoid poor treatment adherence and prompt diagnosis and treatment of potential toxicity. Oral treatment was started in March 2016 and continued until august 2016 when reevaluation of disease showed a massive clinical and PET-documented metastatic involvement of bone, nodes, skin, pectoral muscle and contralateral breast (Figure 1 and Figure 2). She also complained of asthenia and significant itching and moderate pain at cutaneous lesions. After informed consent and approval by the regulatory committee of the hospital due to the lack of registration of nab-paclitaxel in this setting the patient—now aged 76 but in excellent clinical conditions—was offered to receive a fifth-line treatment with weekly nab-paclitaxel 100 mg/m^2 weekly for three consecutive weeks followed by a week off and trastuzumab 2 mg/kg accordingly to previous report [8]. A new biopsy showed a HER-2 positive score 3+, ductal infiltrating carcinoma with negative hormone receptor

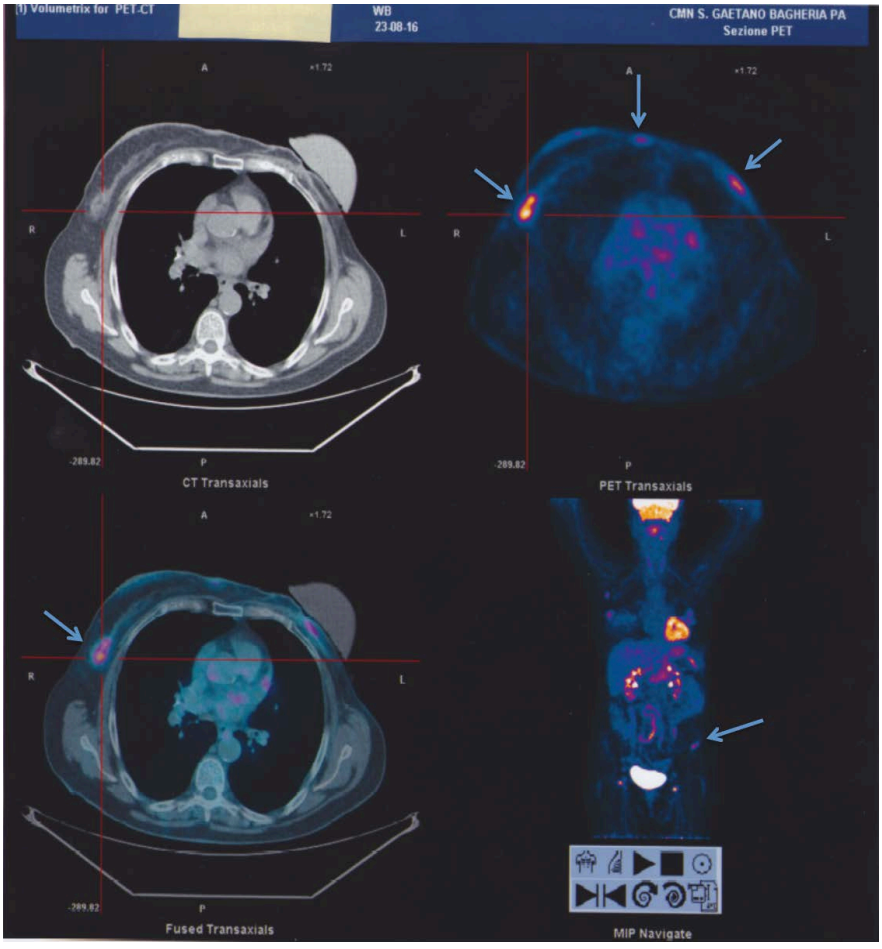

Figure 1. Basal PET scan before starting weekly nab-paclitaxel plus trastuzumab. Arrows point sites of disease.

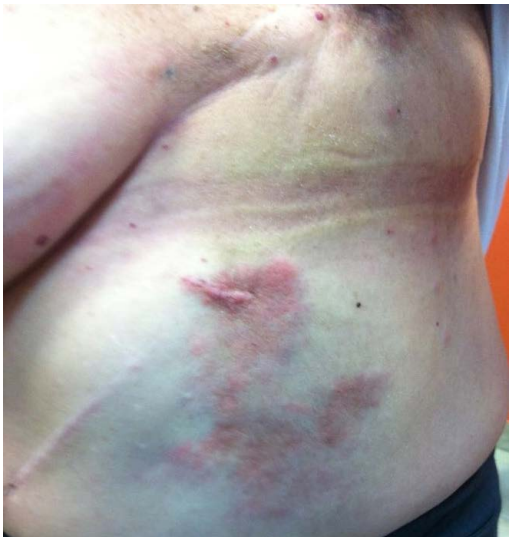

Figure 2. Cutaneous metastatic lesions at basal.

expression. Hemocromocytometric analysis, serum chemistry test as well as cardiological evaluation comprising echocardiogram and evaluation of LVEF were within the normal limits. A bone-health treatment was also started after odontoiatric evaluation with subcutaneous denosumab every 4 weeks with vitamin D and calcium supplementation. In December 2016 a massive PET-documented response was observed at most of sites of disease (**Figure 3**). Also physical examination showed almost complete regression of cutaneous lesions (**Figure 4**) and the patient reported disappearance of cutaneous itching and pain. Tolerance to treatment was fairly good. Major toxicities were grade 1 - 2 anemia and leukopenia. Alopecia and grade-1 neurotoxicity were already present and related to previous treatments and the latter did not worsen during nab-paclitaxel therapy. In March 2017 cancer progressed with the appearance of new metastatic lesions and patient was treated with gemcitabine and trastuzumab for three months without any benefit. Overall the patient has a time-to-progression of 8 months with a good quality of life and is still alive at the time of this report. The patient had given her informed consent permission to be published.

3. Discussion

Sequential chemotherapy plus HER-2 blocking agents represent the treatment backbone of metastatic HER-2 positive breast cancer patients [9]. Taxanes are themost active cytotoxic drugs for the treatment of such patients and have been extensivelyinvestigated in the treatment of HER-2 positive breast cancer. More recent studies have shown that nab-paclitaxel may be safely and effectively administered to all patients forwhom the treatment choice is a taxane even if in a rechallenge strategy [5] [6] [7]. However the role of late-line treatment in this clinical setting is still partially unclear [9] [10]. Infact the benefit of treatment after pertuzumab/trastuzumab and TDM1-based lines in HER-2 positive patients are uncertain since generally the probability of response to treatment declines

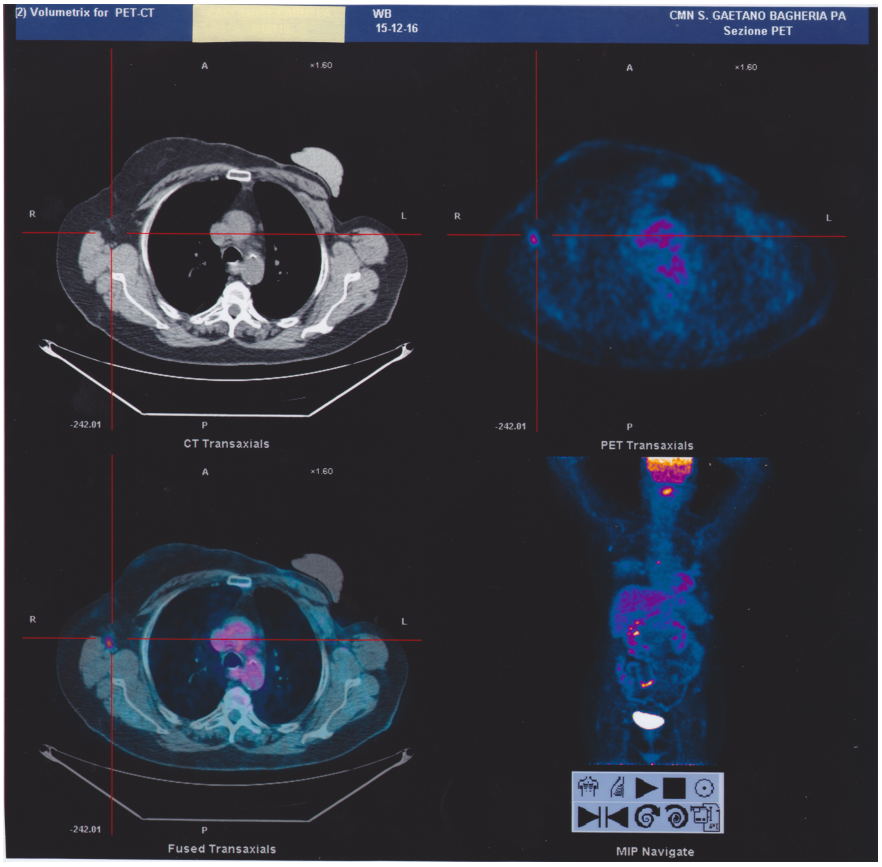

Figure 3. PET scan at first re-evaluation showing partial regression of metastatic sites after three cycles of weekly nab-paclitaxel plus trastzumab.

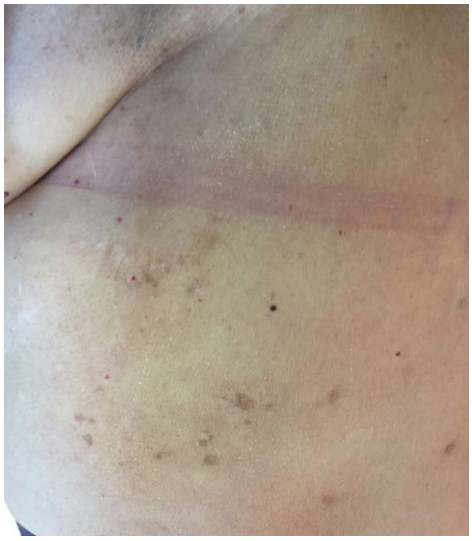

Figure 4. Complete disappearance of cutaneous lesions.

with each line of treatment [11]. This case-report depicts the impressive activity of nab-paclitaxel plus trastuzumab in a heavily pretreated woman with HER-2-positive metastatic breast cancer. Objective response at all sites of disease and its

duration were impressive especially if we consider the late-line setting and pre-treated with taxanes and improvement in cancer-related symptoms. Tolerability was also good with minor hematological side effects. These data are intriguing because the exact role of late line treatments in this clinical setting is largely unclear.

To date only few studies of nab-paclitaxel plus HER-2 blocking agent are reported in medical literature. A preliminary safety and efficacy trial of first-line pertuzumab and trastuzumab plus nab-paclitaxel or paclitaxel or docetaxel has recently reported that tolerance to treatment is superior in <65 years old patients as compared to older ones and that nab-paclitaxel is associated to lesser toxicity than other taxanes [12]. Two small-sized trials were carried out in the neo-adjuvant setting. A phase II trial including 19 her-2-positive patients treated with neo-adjuvant nab-paclitaxel and sequential anthracycline-based therapy plus trastuzumab. Pathological complete response was 58% with a good toxicity profile being grade 3/4 febrile neutropenia (7%) and grade 2/3 neuropathy (16%) the most frequent side effects [13]. Another phase II trial included 28 patients locally advanced, HER2-positive breast cancer treated with a combination of nab-paclitaxel 100 mg/m^2 with carboplatin, trastuzumab and bevacizumab [14]. Pathological complete responses were confirmed in 54% of the patients.

Two other studies evaluated efficacy and safety of nab-paclitaxel plus trastuzumab as first line-treatment. A phase II trial on 22 patients with c-erb-2 positive breast cancer patients treated nab-paclitaxel 125 mg/m^2/week plus trastuzumab 4 mg → 2 mg/kg/week as first line therapy reported an overall response rate of 52%. The most commonly observed toxicities were pain, fatigue and sensory neuropathy [15]. A combination of nab-paclitaxel 100 mg/m^2/w plus carboplatin AUC6 + trastuzumab 4 mg → 2 mg/kg/week was tested as first line in a phase II trial comprising 32 patients with an overall response rate of 62% (95% CI: 46% - 79%) and a progression-free survival of 16.6 months (95% CI: 7.5 - 26.5 months). grade 4 toxicities was low [16]. Neutropenia was only foundin 10% of patients and febrile neutropenia in 1 patient.

4. Conclusion

In summary, to the best of our knowledge, this is the first reported case of efficacy of nab-paclitaxel in combination with trastuzumab as fifth-line of treatment in a patient with metastatic HER-2 positive breast cancer. The impressive response achieved in this patient may suggest further prospective studies to explore the role of nab-paclitaxel in this challenging clinical setting.

Statement of Ethics

This is a retrospective case report and IRB approval was not needed. Off label use of nab-paclitaxel was obtained befor treatment.

Disclosure Statement

The authors have nothing to disclose.

References

[1] Blows, F.M., Driver, K.E., Schmidt, M.K., Broeks, A., van Leeuwen, F.E., Wesseling, J., *et al.* (2010) Subtyping of Breast Cancer by Immunohistochemistry to Investigate a Relationship between Subtypeand Short and Long Term Survival: A Collaborative Analysis of Data for 10,159 Cases from 12 Studies. *PLoS Medicine*, **7**, e1000279.

[2] Baselga, J., Cortés, J., Kim, S.B., Im, S.A., Hegg, R., Im, Y.H., Roman, L., Pedrini, J.L., Pienkowski, T., Knott, A., Clark, E., Benyunes, M.C., Ross, G. and Swain, S.M. for the CLEOPATRA Study Group (2012) Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *New England Journal of Medicine*, **366**, 109-119. https://doi.org/10.1056/NEJMoa1113216

[3] Verma, S., Miles, D., Gianni, L., Krop, I.E., Welslau, M., Baselga, J., Pegram, M., Oh, D.Y., Diéras, V., Guardino, E., Fang, L., Lu, M.W., Olsen, S., Blackwell, K., for the EMILIA Study Group (2012) Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. *New England Journal of Medicine*, **367**, 1783-1791. https://doi.org/10.1056/NEJMoa1209124

[4] Montemurro, F., Donadio, M., Clavarezza, M., Redana, S., Jacomuzzi, M.E., Valabrega, G., *et al.* (2006) Outcome of Patients with HER2-Positive Advanced Breast Cancer Progressing during Trastuzumab Based Therapy. *Oncologist*, **11**, 318-324. https://doi.org/10.1634/theoncologist.11-4-318

[5] Gradishar, W.J., Tjulandin, S., Davidson, N., Shaw, H., Desai, N., Bhar, P. *et al.* (2005) Phase III Trial of Nanoparticle Albumin-Boundpaclitaxel Compared with Polyethylated Castor Oil-Based Paclitaxelin Women with Breast Cancer. *Journal of Clinical Oncology*, **23**, 7794-7803. https://doi.org/10.1200/JCO.2005.04.937

[6] Gradishar, W.J., Krasnojon, D., Cheporov, S., Makhson, A.N., Manikhas, G.M., Clawson, A., *et al.* (2009) Significantly Longer Progression-Free Survival with Nab-Paclitaxel Compared with Docetaxel as First-Line Therapy for Metastatic Breast Cancer. *Journal of Clinical Oncology*, **27**, 3611-3619. https://doi.org/10.1200/JCO.2008.18.5397

[7] Rugo, H.S., Barry, W.T., Moreno-Aspitia, A., Lyss, A.P., Cirrincione, C., Leung, E., Mayer, E.L., Naughton, M., Toppmeyer, D., Carey, L.A., Perez, E.A., Hudis, C. and Winer, E.P. (2015) Randomized Phase III Trial of Paclitaxel Once per Week Compared with Nanoparticle Albumin-Bound Nab-Paclitaxel Once per Week or Ixabepilone with Bevacizumab as First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). *Journal of Clinical Oncology*, **33**, 2361-2369. https://doi.org/10.1200/JCO.2014.59.5298

[8] Jackischa, C., Lückb, H.J., Untchc, M., Bischoffd, J., Müllere, V., Schmidtf, M., Thillg, M. and Kiechle, M. (2012) Weekly Nab-Paclitaxel in Metastatic Breast Cancer—Summary and Results of an Expert Panel Discussion. *Breast Care*, **7**, 137-143. https://doi.org/10.1159/000338273

[9] Hurvitz, S.A., Gelmon, K.A. and Tolaney, S.M. (2017) Optimal Management of Early and Advanced HER2 Breast Cancer. *American Society of Clinical Oncology Educational Book*, **37**, 76-92. https://doi.org/10.14694/EDBK_175630

[10] Zardavas, D., Cameron, D., Krop, I. and Piccart, M. (2013) Beyond Trastuzumab and Lapatinib: New Options for HER2-Positive Breast Cancer. *American Society of Clinical Oncology Educational Book*.

[11] González-Martín, A., Alba, E., Ciruelos, E., Cortés, J., Llombart, A., Lluch, A., Andrés, R., Álvarez, I., Aramendía, J.M., de la Peña, F.A., Barnadas, A., Batista, N., Calvo, L., Galve, E., García-Palomo, A., García-Sáenz, J.Á., de la Haba, J., López, R., López-Vivanco, G., Martínez-Jáñez, N., de Dueñas, E.M., Plazaola, A., Rodríguez-

Lescure, Á., Ruiz, M., Sánchez-Rovira, P., Santaballa, A., Seguí, M.Á., Tusquets, I., Zamora, P. and Martín, M. (2016) Nab-Paclitaxel in Metastatic Breast Cancer: Defining the Best Patient Profile. *Current Cancer Drug Targets*, **16**, 415-428. https://doi.org/10.2174/1568009615666150817121731

[12] Miles, D., Schneeweiss, A., Peretz-Yablonski, T., Ciruelos, E., Puglisi, F., Easton, V., Lindegger, N., Restuccia, E. and Bachelot, T. (2017) Preliminary Safety and Efficacy of First-Line Pertuzumab Combined with Trastuzumab and Taxane Therapy in Patients ≥ 65 Years with HER2-Positive Locally Recurrent/Metastatic Breast Cancer: Subgroup Analyses of the PERUSE Study. *Proceedings of the* 2016 *San Antonio Breast Cancer Symposium*, San Antonio, 6-10 December 2016.

[13] Robidoux, A., Buzdar, A.U., Quinaux, E., Jacobs, S., Rastogi, P., Fourchotte, V., Younan, R.J., Pajon, E.R., Shalaby, I.A., Desai, A.M., Fehrenbacher, L., Geyer, C.E., Mamounas, E.P. and Wolmark, N.A. (2010) Phase II Neoadjuvant Trial of Sequential Nanoparticle Albumin-Bound Paclitaxel Followed by 5-fluorouracil/epirubicin Cyclophosphamidein Locally Advanced Breast Cancer. *Clinical Breast Cancer*, **10**, 81-86. https://doi.org/10.3816/CBC.2010.n.011

[14] Yardley, D.A., Raefsky, E., Castillo, R., Lahiry, A., Locicero, R., Thompson, D., Shastry, M., Burris, H.A. and Hainsworth, J.D. (2011) Phase II Study of Neoadjuvant Weekly Nab-Paclitaxel and Carboplatin, with Bevacizumab and Trastuzumab, as Treatment for Women with Locally Advanced HER2+ Breast Cancer. *Clinical Breast Cancer*, **11**, 297-305.

[15] Mirtsching, B., Cosgriff, T., Harker, G., Keaton, M., Chidiac, T. and Min, M. (2011) A Phase II Study of Weekly Nanoparticle Albumin-Bound Paclitaxel with or without Trastuzumab in Metastatic Breast Cancer. *Clinical Breast Cancer*, **11**, 121-128.

[16] Conlin, A.K., Seidman, A.D., Bach, A., Lake, D., Dickler, M., D'Andrea, G., Traina, T., Danso, M., Brufsky, A.M., Saleh, M., Clawson, A. and Hudis, C.A. (2010) Phase II Trial of Weekly Nanoparticle Albumin-Bound Paclitaxel with Carboplatin and Trastuzumab as Firstline Therapy for Women with HER2-Overexpressing Metastatic Breast Cancer. *Clinical Breast Cancer*, **10**, 281-287. https://doi.org/10.3816/CBC.2010.n.036