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Safety data from a phase II trial of weekly nab-paclitaxel in combination with bevacizumab as first-line treatment in metastatic breast cancer

M. Danso[1], J. Blum[2], N. Robert[3], L. Krekow[4], R. Rotche[5], D. Smith[6], P. Richards[7], T. Anderson[8], D. Richards[9], J. O'Shaughnessy[10]. *[1]Cancer Centers of Florida, Hem/Onc, Winter Park, USA; [2]Texas Oncology PA, Onc, Dallas, USA; [3]Fairfax Northern VA, Hem/Onc, Fairfax, USA; [4]Texas Oncology PA, Onc, Bedford, USA; [5]Blue Ridge Cancer Care, Hem/Onc, Christiansburg, USA; [6]Northern Cancer Specialists, Onc, Vancouver, USA; [7]Onc and Hem Assoc of Southwest VA, Onc/Hem, Salem, USA; [8]Mid Cities Oncology, Onc, Belford, USA; [9]Tyler Cancer Center, Onc, Tyler, USA; [10]Baylor Sammons Cancer Center Texas Oncology PA, Onc, Dallas, USA*

Background: In a clinical trial of 722 patients (pts) with locally recurrent metastatic breast cancer (MBC) solvent-based paclitaxel 90 mg/m^2 was administered intravenously (IV) over 1 hr weekly for 3 weeks followed by a week of rest (q3/4w) alone or in combination with bevacizumab 10 mg/kg every 2 weeks (q2w) [Miller et al., ASCO 2005]. As compared with single agent, the combination had a greater median progression-free survival (PFS; 11.4 vs. 6.11, $p < 0.0001$) and overall response rate (ORR; 30% vs. 14%, $p < 0.0001$). The purpose of the current study is to evaluate the safety of 130-nanometer albumin bound (nab-) paclitaxel in combination with bevacizumab in MBC.

Methods: In this multicenter, open-label study in the US Oncology Research Network, HER-2 negative pts with MBC, receiving first line chemotherapy were given weekly nab-paclitaxel 125 mg/m^2 IV infused over 30 minutes on days 1, 8, and 15, and bevacizumab 10 mg/kg on days 1 and 15 of a 28-day cycle. HER-2 negative pts with measurable adenocarcinoma of the breast with ECOG PS 0−2 were included.

Results: 49 women were enrolled from 19 October 2005 to 26 October 2007 with 41 pts treated (mean age, 59 years; mean # cycles, 4.0). 93% of pts had visceral disease, 59% had prior chemotherapy, 41% had anthracycline, 12% had docetaxel and 12% had paclitaxel in the adjuvant setting. Grade 3, 4 hematologic adverse events were neutropenia (30%, 16%) and anemia (8%, 3%). The most common non-hematologic grade 3, 4 adverse event was sensory neuropathy (10%, 2%).

Conclusions: Results on this preliminary analysis shows that nab-paclitaxel in combination with bevacizumab has an acceptable safety profile with no unanticipated toxicities. Updated safety data will be presented.

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Steroid aromatase inhibitors in metastatic breast cancer after disease progression to nonsteroid inhibitors-efficacy?

J. Pesic[1], D. Donat[1], S. Tesanovic[1], J. Trifunovic[1], T. Pesic[2], D.D. Donat[3], L.J. Muzikravic[4]. *[1]Institute of Oncology, Clinic for Internal Oncology, Sremska Kamenica, Serbia; [2]Clinical Center Novi Sad, Clinic for internal medicine, Novi Sad, Serbia; [3]Medical Faculty Novi Sad, Postgraduet study, Novi Sad, Serbia; [4]Institute of oncology, Clinic for internal oncology, Sremska Kamenica, Serbia*

Background: Aromatase inhibitors are standard treatment for steroid dependent breast cancer.The aim of the paper was to present the efficacy of steroid aromatase inhibitor (exemestane) used in the tretment of breast cancer patients with disease progression to nonsteroid aromatase inhibitors, such as letrozole and anastrozole.

Material: We included 34 patients that received steroid aromatase inhibitors after disease progression to nonsteroid aromatase inhibitors. All patients were treated at our Institute during the period from June 2006 to june 2007. Average age of the patients was 59 years (range: 40−78 years), with ECOG status 0 to 2. Disease involment of one organ was registered in 24 (70.5%) patientsand two or more organs involment was found in 10 (29.4%) patients. Metastatic disease in all patients was treated with nonsteroid aromatase inhibitors: 14 (41.1%) patients received letrozole and 20 (58.8%) were given anastrozole.

Results: Out of 34 treated patients 4 (11.7%) had CR, 7 (20.5%) responded with PR, SD was found in 12 (35.2%) patients, while PD was found in 11 (32, 3%) patients.RR (PR+CR) was evidenced in 11 (32.3%) patients and tumor control rate (TCR) in 23 (67.6%) patients. Better TCR was achieved in patients with nonvisceral metastases: 13 (38.2%) patients compared with 10 (29.4%) patients with visceral metastases, but thedifference did not reached statistical significance. Side effects were mild (grade 1 and 2) expressed mostly as menopausal discomforts, muskulosceletal pain and gastroinetstinal distress.

Conclusion: Although a small number of patients was studied, the achieved RR and TCR responses are indicative for the application of steroid aromatase inhibitors in the treatment of metastatic breast cancer after failure of nonsteroidal aromatase inhibitors. Toxic effects were mild. We did not observed any difference in RR in the patients group previously treated with letrozole and anastrozole.

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A phase II study of, Docetaxel (T), Doxorubicin (A) and Cyclophosphamide (C)-TAC, in metastatic breast cancer – experience on 139 cases from Bangladesh

A.B.M.F. Karim[1], A.M.M. Shariful Alam[2], P.S. Akhtar[2], P.A. Banu[3], M.A. Hai[4], M.S. Reza[5], Q. Chowdhury[2], E. Hoque[2], T.U. Ahmed[6]. *[1]Salahuddin Hospital, Oncology, Dhaka, Bangladesh; [2]National Institute of Cancer Research & Hospital, Oncology, Dhaka, Bangladesh; [3]Delta Medical Centre, Oncology Unit, Dhaka, Bangladesh; [4]Bangladesh Cancer Society and welfare Home, Radiation Oncology, Dhaka, Bangladesh; [5]Ahsania Mission cancer Hospital, Oncology, Dhaka, Bangladesh; [6]Bangladesh Medical College & Hospital, Medical Oncology, Dhaka, Bangladesh*

Background: TAC has shown significant anti-tumour activity in operable node positive breast cancer. We conducted a prospective study to evaluate the effect of this regimen in metastatic breast cancer.

Materials and Methods: One hundred and thirty-nine patients with metastatic breast cancer were included in this study between January 2001 and December 2003. Median age was 55.5 year (range 45−66). The sites of metastasis were liver, lung, bone, lymph nodes and skin. 15.1% (21 pts) had more than 2 metastatic sites. Chemotherapy with TAC – Docetaxel 60−75 mg/m^2, Doxorubicin 50 mg/m^2, Cyclophosphamide 500 mg/m^2, all on day-1 were administered at 3 weeks interval. Growth factor support with lenograstim was prophylactically given to all patients for 3−5 days following chemotherapy.

Results: Total number of evaluable patients was 136. Two patients died due to other complications and one withdrew consent. Performance status ranged from ECOG 1−3. The overall response rate was 67%, of which 13.6% (10) had complete responses. Overall survival was mean 23.8 (9.2−32.6) months. Neutropenia was the commonest toxicity occurring in 13 pts (17.6%) with febrile neutropenia in 6 (8.16%) of cases. There were no grade 4 toxicities. Grade 3 toxicities were limited to neutropenia in 6 pts (8.16%), nausea in 8 (10.88%), diarrhea in 5 (6.8%), vomiting in 12 (16.3%), stomatitis in 5 (6.8%) and allergic reaction in 2 (2.72%) of pts. No cardiac or neuro-toxicity was observed.

Conclusions: Our experience shows that TAC is a well tolerated and highly effective regimen in metastatic breast cancer. The ORR and OS are impressive for the breast cancer patients with metastatic disease. Neutropenic complication was manageable. This result should be substantiated by larger studies before adoption as a standard practice.

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Combination of trastuzumab and gemcitabine as salvage therapy in heavily pretreated patients with metastatic breast cancer

R. Bartsch[1], C. Wenzel[1], U. Pluschnig[1], G. Altorjai[1], P. Dubsky[2], R. Scheurer[1], A. Rottenfusser[3], M. Gnant[2], C.C. Zielinski[1], G.G. Steger[1]. *[1]Medical University of Vienna, First Department of Medicine and Cancer Centre, Vienna, Austria; [2]Medical University of Vienna, Department of Surgery, Vienna, Austria; [3]Medical University of Vienna, Department of Radiotherapy, Vienna, Austria*

Background: Her2+ breast cancer is associated with high recurrence rates and poor outcome. The advent of trastuzumab (T) (RhMab45D), a monoclonal humanized antibody directed against the extracellular domain of Her2 (human EGFR related 2), was a major breakthrough.

The combination of T and taxanes is the best established first-line treatment option, with vinorelbine being a possible alternative. When T however is administered in multiple lines, no standard of care exists. We initiated this study to evaluate the potential activity of the combination of T and gemcitabine (G) in patients (pts) pre-treated with T, anthracyclines, taxanes and/or vinorelbine, and capecitabine.

Patients and Methods: Pts received G at a dose of 1250 mg/m^2 on days 1+8, every 21 days. T was administered in three-week cycles. Re-evaluation of tumour status was performed with CT-scans every three cycles. Clinical benefit rate (CBR; CR+PR+SD $\geqslant$6 months[m]) was defined as primary endpoint.

Based on previous data, a 50% CBR was considered to indicate clinical activity, and a CBR < 25% was considered unacceptable. The targeted accrual for this study was set at 26 evaluable pts. If $\geqslant$11 patients experienced clinical benefit, a sample size of 26 pts provides statistical power of 80% to reject the null hypothesis that the CBR is <25% with an α of 0.05.

Results: 29 consecutive pts were included as eligible. As of July 2007, all are evaluable for toxicity, and 26 for response. Earlier therapies consisted of T (100%), anthracyclines (100%), vinorelbine+T (93%), docetaxel+T (62%), and capecitabine+T (69%). 19% experienced PR, and SD $\geqslant$ 6 months was observed in further 27%, resulting in a CBR of 46%. Time to progression (TTP) was median 3 m, range (r) 1−10, 95% CI 1.89−4.11, and overall survival 17 m, r 4−31+, 95% CI 14.68−19.36. CBR and TTP were superior in the 2nd-line setting.

Neutropenia (21%), thrombocytopenia (14%), and nausea (3%) were the only treatment-related adverse events that occurred with grade 3 or 4 intensity. Four pts (14%) developed brain metastases while on therapy.

Conclusions: While CBR was low when compared to T-based first-line therapy, it is higher than what might be expected from G alone in a similar setting. In a trial of G after anthracycline and taxane failure, 26% of pts had SD for $\leqslant$4 m, and no case of PR was observed. Together with the favourable toxicity profile, the regimen appears to be a safe and potentially effective therapy option in a heavily pre-treated population.

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Clinical usefulness of high-dose toremifene for patients failed by treatment with aromatase inhibitor

H. Iwase[1], Y. Yamamoto[1], T. Ohtake[2], N. Masuda[3], H. Yamashita[4], S. Saji[5], I. Kimijima[6], Y. Kasahara[7], T. Ishikawa[8], M. Sawaki[9]. *[1]Kumamoto University, Breast and Endocrine Surgery, Kumamoto, Japan; [2]Fukuashima Medical University, Surgery, Fukushima, Japan; [3]Osaka National Hospital, Surgery, Osaka, Japan; [4]Nagoya City University, Breast Surgery, Nagoya, Japan; [5]Tokyo Metropolitan Cancer and Infection diseases center Komagome Hospital, Clinical Oncology, Tokyo, Japan; [6]Northern Fukushima Medical Center, Surgery, Tokyo, Japan; [7]Fukui Saiseikai Hospital, Surgery, Tokyo, Japan; [8]Yokohama City University, Surgery, Yokohama, Japan; [9]Nagoya University, Clinical Oncology, Nagoya, Japan*

Aromatase inhibitors (AIs) have been employed as adjuvant therapy or as first or second treatment for recurrent case. However, when AI treatment fails, it is unclear what endocrine therapy is appropriate and how effective it is. Here we administered toremifene (TOR, Fareston®), a selective estrogen receptor modulator (SERM), at 120 mg/day and investigated its efficacy and safety. Of patients with recurrent or advanced breast cancer who had measurable or evaluable lesions, those who were diagnosed as having progressive disease during AI treatment and given TOR at 120 mg/day (high-dose TOR, TOR120) for endocrine therapy were selected and analyzed retrospectively in relation to the patients' medical history. Of a total of 63 cases examined, the response rate was 14.3%, clinical benefit (CB) rate was 34.9%, and median of time to failure (TTF) was 7.4 months. The last AI used was anastrozole in 20 cases and exemestane in 40 cases. The response rates to TOR120 were 15% in both groups regardless of the kind of preceding treatment drug. When TOR120 was used for secondary or tertiary treatment, the response rate was 20% (8/40), and it was 5.3% (1/20) when used as quaternary or later treatment. There was no response in five ER-negative cases, and was effective at 15.5% (9/58) in ER-positive or unknown cases. There was no difference in the rate between PgR-positive and negative cases. In cases with a HER2 score of 0, the response rate was 17.9% (5/28), while few cases showed efficacy in cases with scores of 1+ to 3+. In cases having received tamoxifen (TAM) previously, TOR120 was effective, with a response rate of 13.2% and CB of 31.6%. With regard to adverse effects, hot-flush and/or night sweating were observed in 10 cases, but all of them were categorized as Grade 1, and the treatment was rated excellent in acceptability. TOR120 was rated excellent in acceptability and high efficacy was observed when it was used up to tertiary treatment for AI failure cases. In addition, it was also considered effective for TAM failure cases.

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Treatment of advanced breast cancer with gemcitabine and vinorelbine

C. Gennatas[1], V. Michalaki[1], J. Psychogios[1], S. Gennatas[1]. *[1]University of Athens, Oncology Clinic Department of Surgery Areteion Hospital, Athens, Greece*

Background: Gemcitabine and vinorelbine are both active as single-agent therapy for metastatic breast cancer with favorable toxicity profiles. The purpose of this study was to evaluate the efficacy and safety of the combination of these agents in patients with advanced breast cancer, previously treated with anthracyclines alone or with taxanes.

Patients and Methods: A total of 96 heavily pretreated patients with metastatic breast cancer (median age 63 years, range 35−75 years) with ECOG Performance status of 0−2, entered the study. All patients had received prior adjuvant chemotherapy. Thirty-six patients had been pretreated with anthracyclines, and 8 were resistant. The combination of Gemcitabine (1000 mg/m^2) and vinorelbine (25 mg/m^2) was administered on days 1 and 8 every 3 weeks, for a total of 6 cycles.

Results: A total of 344 cycles of chemotherapy were administered (median 4 cycles per patient, range 1−9). Partial responses were observed in 34 patients (36.0%). The median duration of response was 7.5 months (range 3−11 months) and the median overall survival was 14 months. In the anthracycline pretreated population (n = 36) there were 2 partial responses (5.5%).

The scheme was well tolerated. Grade 3/4 toxicity was limited to leucopenia in 4 patients (4.1%), thrombocytopenia in 2 patients (2%) and anemia in 13 patients (13.5%). No patient was hospitalized due to febrile neutropenia, and there were no treatment related deaths.

Conclusions: The combination of vinorelbine and gemcitabine is an active and manageable scheme in patients with metastatic breast cancer pre-treated with anthracycline-based schedules, or with combinations of anthracyclines and taxanes, demonstrating an acceptable toxicity profile.

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Hepatic metastases from breast carcinoma – suitability for resection?

P. Chan[1], A.S. Kaushal[1], L.K.C. Teo[1]. *[1]Tan Tock Seng Hospital, Breast Unit, Singapore*

Background: Liver metastases is found in 6–25% of patients with metastatic breast cancer. The median survival in most of these patients is 1–14 months. As mortality & morbidity of liver resections decrease over the past decade, the indications of surgery has widened for metastatic disease. Hepatic resection for liver secondaries from breast cancer has showed significant improvement in survival. The aim of this study is to determine what proportion of breast cancer patients with hepatic metastases is suitable for surgical treatment.

Methods: This is a retrospective review of 58 patients with breast cancer from January 2002 to December 2007 who have hepatic metastases. Patients were divided into whether they have extra hepatic metastases (EHM). For patients without EHM, we consider standard indications for liver resections for any liver tumour to determine suitability. The indications include number of liver lesions, albumin levels, liver reserve, fitness for operation and good respond to chemotherapy.

Results: The mean age of the patients is 57. Incidence of hepatic metastases in our centre is 5.8%. 27 (47%) patients were found to have metastases at the time of diagnosis while the rest have systemic recurrence after initial treatment. The majority of our patients (84%) have EHM which we considered as an unfavourable indication for hepatic resection. Of the 11 patients without EHM, only 1 (2%) patient was considered to have been suitable for surgery. 6 patients had low liver reserve and low serum albumin while 4 patients with normal serum albumin had diffuse hepatic involvement. The last patient with normal albumin level had 2 lesions but the disease is bilobar and she did not respond to chemotherapy and died 3 months after diagnosis.

Conclusion: Majority of breast cancer patients with hepatic metastases present either with concurrent EHM or with diffuse disease and other unfavourable factors which preclude surgical resection. Nevertheless physicians must identify the small subset of patients who are suitable for liver resection as this is likely to significantly prolong survival.

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A phase II trial of weekly docetaxel and trastuzumab in metastatic breast cancer

A. Taran[1], K. Wollschlaeger[1], B. Blümel[1], E. Kettner[2], S.D. Costa[1], J. Bischoff[1]. *[1]Universitätsfrauenklinik, Gynecology, Magdeburg, Germany; [2]Städtisches Klinikum, Gynecology, Magdeburg, Germany*

Background: Docetaxel (D) in combination with trastuzumab (T) has demonstrated significant activity in patients with HER2neu positive metastatic breast cancer (MBC). Main toxicities of this regimen include leukopenia, febrile neutropenia and infections. Weekly administration of D has been reported to have reduced haematological side effects and comparable efficacy to 3 weekly protocols. In a multicentre trial we assessed tolerability and activity of a weekly schedule of D and T.

Material and Methods: 46 women with HER2neu positive metastatic breast cancer were treated with weekly doses of D (35 mg/m^2 for 10 weeks) and T (4 mg/kg loading dose, then 2 mg/kg). Median age was 55 (34−78) years, 80% of the patients had visceral metastases. Most patients had received adjuvant chemotherapy (66 %) (anthracyclines (A) 33%, CMF 33%, A-CMF 10%, taxanes 4%), and 33% have had chemotherapy for MBC.

Results: Objective response rate was 42% (6 CRs and 12 PRs) and 38% of the patients had stable disease. Median time to progression was 6 months (95 % CI 5−9), and a 1y – survival rate of 64% was noted. Median