failure would still occur. This has raised the need for new drugs or combination regimen in the treatment of metastatic breast cancer (MBC). Unfortunately, based on limited data in the oncology literature, several agents including vinorelbine, capecitabine, ixabepilone and pegylated liposomal doxorubicin had only minimal antitumor activity (response rates ranged 10−20 %) in patients with MBC who progressed on first-line taxane-based treatment. There are limited published data demonstrating favorable response in MBC after the failure of taxane-based treatment or rechallenging with anthracyclines which were previously used in the adjuvant setting. Pegylated liposomal doxorubicin (Lipo-Dox®) is a non-toxic alternative agent to doxorubicin. The aim of this study is to evaluate the efficacy and safety of pegylated liposomal doxorubicin combination as second line treatment in patients with MBC who failed previous taxane-based treatment.

Material and Methods: From Aug. 2005 to Jul. 2010, 43 patients with MBC who progressed after prior treatment with taxane-containing regimen were recruited in this prospective, multicenter, single-arm, phase II trial. Treatment with pegylated liposomal doxorubicin 40 mg/m^2, cyclophosphamide 500 mg/m^2 and 5-Fluorouracil 500 mg/m^2 were delivered every 3 weeks until disease progression or the appearance of intolerance toxicity. The primary endpoint of this study is objective response rate and the secondary objectives are to evaluate progression free survival (PFS), duration of response, overall survival (OS) and safety profiles.

Result: Forty-three patients were included in the analysis. The median age was 52.5 years (36–67.5) and ECOG performance status was 0−2. 77.8% of patients had visceral metastases and 55.6 % of patients had equal or more than three metastatic lesions. An objective tumor response was observed in 18 patients (41.9%), stable disease in 18 patients (41.9 %) and the clinical benefit rate (objective response rate plus stable disease greater than 6months) in 26 patients (60.47%). The median progression free survival (PFS) and overall survival (OS) were 8.2 and 36.6 months, respectively. The majority of adverse event were mild to moderate. Grade 3/4 neutropenia and leucopenia were observed 14% and 9% by cycles. 12% patients had grade 2−3 mucositis, but only 7% patients experienced grade 2/3 hand and foot skin reaction by cycles.

Conclusion: The pegylated liposomal doxorubicin, cyclophosphamide and 5-fluorouracil combination regimen showed promising response rate and manageable side effects. The regimen could considered to be a treatment option for patients with MBC who failed previous taxane-based treatment.

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Oral Vinorelbin (osVNR) − An Observational Study on Practical Matter in Three Italian Oncology Centers

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Background: osVNR is more expensive than iv VNR but according to several Authors it is much less time consuming for Patients (Pts), Nurses (drug preparation and administration) and Oncologists (Taylor, Proc NCRI 2005, Abs 435), preferred by Patients (Lju JCO 1997; Catania, BRCT 2005) and, actually, more cost/effective (Lelay, 2002, Mantovani 2005). Several variables as type of Institution (public or private), geographical situation and site of blood drowing could modify the final evaluation of osVNR in clinical practice.

Patients and Methods: we measured time spent by Pts and accompaniyng person (when applicable) for transfers, waiting and treatement, time of Nurses and Oncologists, toxicities (evaluated both by Oncologist and Pts) and overall Pts 's feeling in 287 osVNR administrations (60 mgs/sqm dd 1,8−21 in 75.3%; metronomic 80 mgs/sqm dd 1,3 and 5/week qq 4 weks, in 24.7%) (169 cycles in Trieste and 87 in Brindisi public Hospitals, 31 in Catania Humanitas private Hospital) in 44 metastatic breast cancer Pts.

Results: 80% of Pts had an accompaniyng person in all Centers. The ratio access/cycle is similar in public Institutions (0.94), higher in the private one (1.2). Similarly the time of Oncologist, 16 min/cycle versus 31. Blood drowing was done at home/near-home in 83.4% of cases in Catania, 63.2% in Brindisi and 16,6% in Trieste. Overall dosing mistakes were reported in 32.3% of cycles (16.7% Trieste; 43.8 Brindisi; 33.4 Catania). No difference between Centers in Nurse 's time (13 min) was recorded. Pts transfer time is similar in Trieste and Catania (50 min) vs 136 min in Brindisi. G3 toxicity rate was 0% with metronomic dosing and 30% with the classic one, viceversa toxicity G1/2 was higher (92,9% vs 73%), mainly nausea and diarrhoea. The overall toxicity was 70.5% for G1/2 and 18.2% for G3.

Pts toxicity evaluation was excellent in 74.5% of cases with classic dosing and 99% with the metronomic one. Overall more than 90% Pts appreciated the higher autonomy level.

Conclusions: osVNR is safe and very appreciated in metastatic breast cancer Pts. Our experience confirm that the oral route is time sparing both for Pts and Institutions. There is little difference between public and private institutions. Under an overall point of view of Pts, Families and Oncology Centers this is an important added value wich strongly reduces the pure cost for drug. There is margin of improvement working on logistics for blood drowing and further reducing the number of accesses.

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Final Results of a Phase II Study of the Combination of Oral Vinorelbine (NVBo), Capecitabine (X) and Trastuzumab (H) in HER2-positive Metastatic Breast Cancer (MBC)

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Background: Chemotherapy (CT) plus trastuzumab (H) is the standard first-line treatment for HER2-positive MBC. H plus vinorelbine regimen is among the most active and well-tolerated options in this setting. The all-oral CT combination of NVBo and X has shown activity and good tolerability in MBC. In this abstract, we report the final results of an international phase II trial evaluating NVBo + X + H in HER2-positive MBC.

Material and Methods: Main eligibility criteria included: HER2-positive disease (3+ IHC or FISH+), measurable metastatic disease previously untreated by CT, Karnofsky PS $\geqslant$70. Study treatment (until progression): NVBo was given as a 80 mg/m^2 dose (following a first cycle at 60 mg/m^2) D1 & D8 every 3 weeks, X at 1000 (750 if $\geqslant$65 y) mg/m^2/bid D1−D14 every 3 weeks, H at 4 mg/kg on D1 (loading dose) then 2 mg/kg i.v. weekly starting on D8.

Results: Main patient (pt) characteristics in the full population (n = 50): median age: 53.5 years (18% $\geqslant$65); prior (neo)adjuvant CT 54%; visceral involvement 82%; >2 metastatic sites 34%; median number of cycles: 10 (range:1−81); 72% of pts received more than 6 cycles, 58% more than 8 cycles and 32% more than 16 cycles; median number of NVBo administrations: 20 (range:1–161); median number of H administrations: 30 (range:1–251); median relative dose intensity: NVBo 76%, X 78%, H 96%; G3/4 adverse events per pt: neutropenia 71%, hand-foot syndrome 20%, diarrhoea 16%, vomiting 12%, asthenia 8%, febrile neutropenia 8% (0.5% of cycles), infection 6%, LVEF decline 4%, alopecia (grade 2) 14%. Efficacy (n = 44 evaluable pts): objective response rate (RECIST) 77% (95% CI [62−89]), CR 21%, PR 57%, SD 18%, PD 5%, disease control (CR+PR+SD $\geqslant$6 months) 93% (95% CI [81−99]); median duration of response was 13.3 months (95% CI [9.8–15.7]). Median progression-free survival was 12.8 months (95% CI [10.8–16.9]) and median overall survival was 47.0 months (95% CI [30.5–64.3]). 3 pts are still receiving full study treatment.

Conclusions: The oral regimen of NVBo and X combined with H has shown high anti-tumoral efficacy in pts. with HER2-positive MBC. Toxicity profile was acceptable, with, in particular, a very low rate of alopecia. Full treatment could be maintained until progression of the disease in the majority of pts.

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Tartrate-resistant Acid Phosphatase and C-terminal Telopeptide of Type I Collagen as Serum Tumor Markers in Women with Bone Metastases From Breast Cancer

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Background: Breast cancer (BC) remains one of the first leading causes of death in women over the age 50. Bone is the first site of distant metastases in patients with BC. Bone lysis induced by cancer cells invading the bone and promoting degradation of mineral matrix, together with the production of PTH-like peptides represent the mechanisms of cancer-induced hypercalcemia. Bone metastases (BMs) are a frequent complications in BC. They are usually detected by whole body bone scintigraphy, which unfortunately presents low sensitivity and specificity, visualizing areas of increased osteoblastic activity. In patients with BMs a number of urinary and serum markers are altered. Tartrate-resistant acid phosphatase (TRACP5b), specifically derived from osteoclasts, is a promising marker of bone resorption. Moreover, increased concentrations of carboxy-terminal telopeptide of type I collagen (ICTP), a cross-linked

product of collagen I degradation, have been observed in patients with BMs. The aim of this preliminary study was to evaluate the usefulness of TRACP5b, ICTP and bone alkaline phosphatase (BAP) in patients with BMs from BC.

Patients and Methods: A group of 11 women (median age 68 years, range 56−72 years) with BC and radiologically confirmed isolated BMs (cases), and a group of 14 age- and stage-matched women at the time of surgery without BMs (controls) were retrospectively reviewed. All patients serial measurement of TRACP5b, ICTP, and BAP. The cut-off values considered were 3.6 U/L, 4.2 U/mL, and 68 U/mL for TRACP5b, ICTP, and BAP, respectively. The odds ratios (OR) calculation with the 95% confidence interval (95% CI), the Fisher exact probability test, and the t-Student test were used to compare variables.

Results: The mean levels of TRACP5b, ICTP, and BAP (cases *vs.* controls) were 6.2±2.8 *vs.* 3.2±1.2 (t= 3.62, p = 0.0014) U/L, 8.3±6.4 *vs.* 4.2±1.6 (t = 2.32, p = 0.029) U/mL, and 151.3±98.6 *vs.* 72.5±26.4 (t = 2.87, p = 0.0085) U/mL, respectively. The corresponding OR were 7.20 (95% CI 1.06–48.64, p = 0.043), 6.41 (95% CI 1.09–37.73, p = 0.041), and 1.60 (95% CI 0.32–7.84, p = 0.42), respectively, while the OR for TRACP5b and ICTP together was 9.77 (95% CI 1.55–61.64, p = 0.014).

Conclusion: Our preliminary study shows that in patients with BC the elevation of both TRACP5b and ICTP correspond to a 9.8-fold higher risk of having BMs.

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Metastatic Breast Cancer − a Retrospective Analysis of Abdominal/pelvic Metastasis of Breast Origin

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Background: Breast cancer is the most common neoplasm in women, accounting for approximately 32% of women's tumors, with a life time risk of 1 in 10. Metastatic breast cancer is a heterogeneous disease with distinctive histological and biological features, clinical behaviours and therapy response.

The aim of study was to analyze the combined Estrogens (ER) and Progesterone (PgR) phenotypes and the Proliferation Index (Ki-67) in primary and in corresponding abdominal/pelvic metastases to compare biological features of the tumors.

Material and Methods: 21 patients with primary invasive breast cancer and corresponding abdominal or pelvic recurrences (1999–2009) entered to the study. Metastasis were localized: 16 in ovary, 1 in cervix, 1 in endometrium and 3 in omentum. Hormonal receptors were tested on 18/21 primary breast cancer and on 20/21 metastatic samples. Ki-67 was assesed on 13/21 primary breast cancer and on 19/21 metastasis. HercepTest was performed on 18/21 metastatic samples. ER, PgR and KI-67 status was classified according European guidelines. HER−2 was evaluated according to FDA-approved scoring system.

Results. Twelve out of 18 (66.6.1%) primary evaluable cases were ER+/PgR+ and 6 (33.4%) ER−/PgR-; whereas only 3/20 of metastatic sites resulted ER+/PgR+ (15%), 5 (25%) ER−/PgR+, 3 (10%) ER+/PgR- and 9 (45%) ER−/PgR-. 4/13 (30.7%) primary breast cancer and 7/19 (36.8%) metastatic cases had an high Ki67; moreover, 14 metastases were HER−2/neu negative whereas in 4 cases HER−2 was overexpressed.

Six patients (mean FU: 64 months; 12–120 months) had follow up data: after the first event, 5 were treated with Chemotherapy and Tamoxifene, whereas 1 was treated with Radiotherapy and Tam. Receptor expression was higher in primary than in secondary lesions and receptor-negative primary tumours showed receptor-negative recurrences.

Conclusions. Our data revelled that loss of ER and PgR expression in abdomen and pelvic recurrent breast cancer have high incidence. Moreover, breast cancer metastases, that arise from ER and PR positive primaries, fail to respond to endocrine therapy because of the development of ER negative lesions, indeed 30% of metastatic sites evidenced a triple negative (ER, PgR, HER−2/neu) status.

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Characteristics of Molecular Breast Cancer Subtypes Among Bulgarian Women

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Breast cancer is a heterogeneous disease from a clinical as well as biological point of view. Four molecular subtypes have been identified and have to be considered when decision for treatment is made.

The purpose was to compare the molecular subtypes by clinicopathological characteristics and prognostic value for female breast cancer in Bulgaria.

Data from the Bulgarian National Cancer Registry (BNCR) about female breast cancers, diagnosed in 2005–2009 were analyzed. All patients were followed-up until 01.01.2011. Four molecular subtypes were defined on the base of immunohistochemical status of estrogen (ER), progesterone (PR) receptors and HER2, recorded in BNCR database: Luminal A (ER+, PR+/−, HER2−); Luminal B (ER+, PR+/−, HER2+); HER2 (ER−, PR−, HER2+); TNBC (ER−, PR−, HER2−). Clinicopathological characteristics of the molecular subtypes − age, stage and grade were compared, using Chi-square test, Kaplan-Meier and Cox regression methods.

There were 18450 female breast cancers, registered in BNCR database and 9303 (51.4%) of them were classified into molecular subtypes. The proportions of Luminal A, Luminal B, HER2 and TNBC were 59.0%, 20.1%, 6.8% and 14.1%; five years survival was 78.7%, 75.1%, 61.7% and 67.2% respectively. The molecular subtypes differ by age, stage and grade ($p < 0.0001$). The risk of death was lower ($p < 0.0001$) for Luminal A (with 48%) and Luminal B (with 42%), compared with TNBC, after adjusting for age, stage and grade. HER2 and TNBC showed similar prognosis ($p = 0.427$).

The comparison of molecular subtypes showed clear differences in clinicopathological characteristics. The prognosis was better for Luminal A and Luminal B types. The lack of difference in prognosis between HER2 and TNBC types can be explained with relatively recent introduction, in 2008, of adjuvant treatment with trastuzumab for Bulgarian women.

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Bone Management by Bisphosphonate in Metastatic Breast Cancer Patients

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Background: Bone is one of a common involved site of metastasis in advanced breast cancer patients. Bisphosphonate (BP), especially zoledronate (ZOL) is regarded as not only an essential key tool to reduce skeletal associated events but also improve patients' survival.

We reviewed metastatic breast cancer (MBC) cases with the aim of evaluating improvement of patients' survivals and quality of life (QoL) by BP use.

Patients and Methods: From October 2002 to September 2011, 459 patients were diagnosed as MBC. Most of patients (345/459, 75.2%) were recurrent disease, and the rest (114, 24.8%) were primary advanced disease. Receptor statuses were as follows; estrogen-receptor positive (ER+) 63.2%, HER2+ 26.6%, triple-negative 13.3%. Patients who had bone metastasis (BM) at the time of diagnosis were 37.7% of MBC patients. BP administration was considered in patient having or newly developed BM to manage her bone lesion. Concomitant chemo-, endocrine or radiotherapy was performed in practical manners. After approval of ZOL in Japan (mid 2006), all of the patients who had been already given pamdronate or incadronate, were changed to receive ZOL.

Results: Total 296 patients, 64.5% of MBC patients, including patients who were BM-free at the initial diagnosis of MBC, were diagnosed as having BM. Estrogen receptor was positive in 77.4% of patients. About one-third of the patients complained bone pain at the time of BM diagnosis. Median survival time (MST) for all MBC patients was 1376 days, and there was no difference of MST between patients BM+ or BM-. Among BM+ patients, there was no significant difference of MST between having and not having bone pain at the time of BM diagnosis. BP was administered in 218 (73.6%) of BM+ patients and improved their MST from 1315 to 1461 days compared with BP non-users including BM- patients, although, there was no statistical significance ($P = 0.0721$).

Conclusions: As De La Haba *et al* previously displayed (2010 ASCO abstr. 630) appropriate ZOL use improves BM+ patients' survival. In the same manner, our retrospective observation showed a trend of survival benefit from BP. These facts confirm bone management by ZOL is