Proffered Papers

Breast cancer, advanced disease

643 ORAL

Letrozole (FEMARA®), a new potent, selective aromatase inhibitor (AI): Superior to another AI, aminoglutethimide (AG), in postmenopausal women with advanced breast cancer (ABC), after relapse or progression on previous anti-estrogen therapy

K. Possinger, M. Gershanovich, D. Campos, G. Romieu, H. Lurie, T. Bonaventura, H.A. Chaudri, U. Homberger, M.A Bischoff. *For the Letrole International Trial Group (AR/BC3); Universitätsklinik Charité Medizinische Klinik II, Schumannstrasse 20 Berlin, Germany*

Over 2 years, 555 pts with ABC previously treated with anti-estrogens were randomly assigned open-label od letrozole 2.5 mg (185), or 0.5 mg (192) or AG 250 mg bid with corticosteroid replacement (178). Pts had to have measurable or evaluable disease, positive or unknown ER/PgR status. Tumor response and progression were evaluated by blinded peer review applying UICC criteria to serial tumor images, obtained 3-monthly for up to 33 mos. Dominant site was visceral in 44% pts, bone in 30%. Treatment comparisons were adjusted for relevant baseline covariates using multivariate regression models.

Letrozole was superior to AG in TTP (2.5 mg, risk ratio 0.68, P = 0.004 and 0.5 mg, risk ratio 0.76, P = 0.03) and TTF (2.5 mg, risk ratio 0.66, P = 0.001 and 0.5 mg, risk ratio 0.75, P = 0.02). Letrozole 2.5 mg was superior in survival to AG (risk ratio 0.68, P = 0.02) and to letrozole 0.5 mg (risk ratio 0.72, P = 0.04). There was no significant difference in survival between letrozole 0.5 mg and AG. Overall ORR (CR+PR) was 17.8% for letrozole 2.5 mg (median duration 23.2 mos), 16.7% for 0.5 mg (median duration 20.6 mos) and 11.2% for AG (median duration 14.0 mos). Duration of clinical benefit (CR+PR+NC > 6 mos) was 23.2 mos for letrozole 2.5 mg, 17.5 mos for letrozole 0.5 mg and 12.3 mos for AG (P = 0.01).

Both doses of letrozole were well tolerated, with discontinuation because of AEs in <3%. Rash ascribed by the investigator to trial treatment occurred in 8.4% pts on AG, 2.2% on letrozole 2.5 mg (P < 0.05). No serious related AEs wee reported for letrozole 2.5 mg.

Letrozole is the first new AI to show superior antitumor efficacy to another established AI, aminoglutethimide. Letrozole 2.5 mg was superior to 0.5 mg and is the recommended dose.

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Significantly improved survival with 'arimidex' (anastrozole (A)) compared with megestrol acetate (MA) in postmenopausal women with advanced breast cancer (ABC): Updated results of two randomised trials

W. Jonat[1], A. Buzdar[2], A. Howell[3], A. Webster[4], K. Strutt[4]. *For the Arimidex International Study Group;, ; [1]Kiel, Germany; [2]Houston, USA; [3]Manchester; [4]Macclesfield, UK*

Purpose: Two randomised studies of similar design comparing 2 doses of A (1 mg and 10 mg daily) with MA (40 mg 4 times daily) in 764 postmenopausal women with ABC which had relapsed or progressed whilst on tamoxifen treatment, have recently undergone updated analyses based on mature survival data.

Methods: Data from the 2 studies were combined for a single analysis. Treatments were compared using a Cox regression model adjusting for predefined factors.

Results: Median follow-up was 31 months. 62% of patients overall had died. Significant improvement in survival was associated with A 1 mg compared with MA (hazard ratio (HR) 0.78, p = 0.02). A 1 mg resulted in a longer median survival (26.7 vs 22.5 months), and a higher 2 year survival (56.1% vs 46.3%) than MA. Analysed individually the 2 studies were consistent: each demonstrated a lower risk of death on A 1 mg than on MA (HRs 0.74, p = 0.048, and 0.85, p = 0.34). A 10 mg also demonstrated improved survival over MA (HR 0.83, p = 0.10). Response and time to progression were not significantly different between treatment arms.

Conclusion: A 1 mg results in improved survival compared with MA in postmenopausal women with ABC. There is no dose-response between the 2 doses of A, thus confirming the choice of 1 mg as the therapeutic clinical dose.

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Taxol (T) versus doxorubicin (D) as first-line chemotherapy (CT) in advanced breast cancer (ABC): An EORTC randomized study with crossover

R. Paridaens, P. Bruning, J. Klijn, T. Gamucci, L. Biganzoli, A. Van Vreckem, G. Hoctin Boes, D. Curran, M. Piccart. *On behalf of EORTC-IDBBC/ECSG participating centres; U.Z. Gasthuisberg, Afdeling Gezwelziekten, Herestraat 49 3000 Leuven, Belgium*

Three-hundred-thirty-one anthracycline-naive patients (pts) with ABC have been randomized to receive either T 200 mg/m^2 over 3 h or D 75 mg/m^2 q 3 weeks. Pts who progressed within 7 courses of first-line CT were crossed to the alternative drug, while the crossover was optional for later progression (PD). Data regarding pt characteristics and toxicity have already been given (Sem Oncol 23 suppl 11: 11–15, 1996). Dose-reductions in pts receiving first-line T or D were needed in 10% and 28% of pts, respectively. Regarding second-line T or D, dose was reduced in 14% and 22% of pts, respectively. The overall response rate for first-line CT, according to an intent to treat analysis is 36%; 28% of pts had stable disease. So far, among 76 pts crossed to D and 51 to T, 106 have completed second-line CT. Considering only pts who did mandatory crossover (T and D resistant pts), the tumor response rate is as follow:

No. of evaluable pts	CR + PR%	NC%	PD%
55	36	44	20

Updated data regarding response rates, time to progression and quality of life (assessed by Rotterdam Symptom Checklist and EORTC QLQ-C30) by treatment arm will be presented.

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Mitoxantrone (N) vs. 5-fluorouracil/epirubicin/ cyclophosphamide (FEC) as first line therapy in high-risk metastatic breast cancer

G. von Minckwitz[1], E. Heidemann[2], R. Souchon[3], H. Samonigg[4], W.D. Hirschmann[5], H. Bodenstein[6], A. Schindler[7], M. Schulze[8], H. Clemens[9], M. König[10], A. Schari[11], J.Th. Fischer[12], M. Kaufmann[1]. *[1]Univ. Frauenklinik Frankfurt; [2]Diakonissenkrankenhaus Stuttgart (KH), Stuttgart; [3]KH-Hagen; [4]Univ. Klinik Graz; [5]Städt. Kliniken Kassel; [6]KH Minden; [7]Univ. Frauenklinik Essen; [8]KH Zittau; [9]Univ. Frauenklinik Tübingen; [10]Med Univ. Klinik Tübingen; [11]Univ. Frauenklinik Köln; [12]Städt. Kliniken Karlsruhe, Germany*

Purpose: To evaluate the effectivity and tolerability of a mono- (N) versus a polychemotherapy (FEC) patients (P) with high-risk metastatic breast cancer (HRBC).

Patients and Method: From 7/92 to 8/96 248 P with HRBC (≤35 years, visceral involvement, DFI ≤ 18 months) were prospectively randomised for line 1st line therapy. By now 224 P are evaluable for toxicity and 171 for effectivity. 110 P received F = 500 mg/m^2, E = 50 mg/m^2, C = 500 mg/m^2 every 3 weeks and 114 P N = 12 mg/m^2 every 3 weeks until progression.

Results: An interim analysis revealed that thin there was no significant difference in response rates (CR + PR) between the FEC and the N. Time to progression was identical in both groups. N showed a more extensive myelotoxicity, however nausea & vomiting and hairloss were less

frequent. Quality of life was significantly better according to the modified Brunner-Score in N compared to the FEC group.

Conclusion: As to the preliminary results the mono-compared to the poly-chemotherapy regimen didn't appear to show a difference in efficacy but a significantly better tolerability.

The study is on going.

The study was supported by Wyeth-Lederle.

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Prospective randomized study of mitoxantrone (M) and vinorelbine (V) vs fluorouracil (F), epirubicin (E) or adriamycin (A) and cyclophosphamide (C) in patients with advanced breast cancer (ABC)

F. Turpin[1], D. Serin, G. Ganem, G. Calais, P. Maillart, P. Colin, G. Prévost, P. Romestaing, J.D. Tigaut, P. Clavère, M. Namer. *[1]Centre René Huguenin, Saint-Cloud, France*

Background: A woman with ABC has a life expectancy of 18–24 months under treatment and the key point thus remains quality of life. Side-effects most feared by women are alopecia, nausea/vomiting.

Methods: This study compared the new combination MV (M 12 mg/m^2 D1, V 25 mg/m^2 D1 and 8 if PN > 1000/mm^3) to FAC or FEC: F 500 mg^2, A or E 50 mg^2, C500 mg/m^2, D1. Stratification was based upon prior adjuvant chemotherapy (CT). Each cycle was repeated every 21 days.

Results: 281 patients (pts) were randomized between UV MV (142) and FAC/FEC (139). 89 pts had received prior adjuvant CT (76 with anthracyclins). 82% pts had visceral metastasis and the median number of metastatic sites was 2 (1–7). Overall, 698 MV and 841 FAC/FEC cycles were given (median/pt: 5 [MV]; 6 [FAC/FEC]). The mean dose intensity (%) was respectively 95, 96, 96 for FAC/FEC and 92, 77 for MV. Hematological toxicity delayed courses in 22% (MV) and 14% (FAC/FEC) and led to withholding of V on day 8 in 29%. Febrile neutropenia requiring antibiotics occurred in 6% (MV) and 0.6% (FAC/FEC) of cycles and led to hospitalization in respectively 16% and 3% of pts (p = 0.001). Cardiac events were mostly minor: 10 in FAC/FEC and 9 in MV. Grade 3–4 nausea/vomiting occurred in 8% [MV] and 16% [FAC/FEC] of pts (p = 0.03); alopecia was more frequent with FAC/FEC (p = 0.0001). Toxicity led to one death in each group. The objective response rates (OR) were similar: 35.5% [MV], 33.3% [FAC/FEC], p equivalency = 0.014) but the OR was higher in the pts on MV with prior adjuvant CT (33% vs 13%) and in those on FAC/FEC who had not (43% vs 35%). Time to progression and overall survival were not different in the two groups but showed a similar divergence when prior adjuvant CT was taken into account.

*Study supported by Wyeth-Lederle and Pierre Fabre Oncologie (France).

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CAF vs CMF both with tamoxifen in postmenopausal patients with advanced breast cancer – A randomized study with more than 10 years follow-up from the Danish breast cancer cooperative group

M. Andersson[1], E.L. Madsen[2], M. Overgaard[3], P. Dombernowsky[5], H.T. Mouridsen[1]. *On behalf of the Danish Breast Cancer Cooperative group (DBCG); [1]Finsen Center/Rigshospitalet University Hospital; [2]Dpt. Oncology, Odense University Hospital, [3]Dpt. Oncology, Aarhus University Hospital; [4]Dpt Oncology, Herlev University Hospital, Denmark*

In the largest study ever reported comparing CMF-like regimens with CAF, postmenopausal advanced breast cancer (ABC) patients naive to chemotherapy <66 years accrued during 1980–84 and followed through 1995 received Tamoxifen daily 30 mg and cyclophosphamide 400 mg/m^2, doxorubicin 25 mg/m^2 and 5-fluorouracil 500 mg/m$_2$ (CAF) or methotrexate 40 mg/m^2 instead of A (CMF) i.v. days 1 and 8 q 4 weeks. A was substituted by M at a cumulative dose of 550 mg/m^2. Among 341 eligible patients (CAF 161, CMF 180) response rate and median time to progression was significantly in favour of CAF: 53% *vs* 36% (p = 0 002) and 11.8 months *vs* 6.5 months (p = 0.001). Duration of response was 19.5 *vs* 18.0 months, and survival 20.8 *vs* 17.4 months (ns). Treatment intensity and toxicity was equal. After 3 years 44 *vs* 38 patients were still alive. Long recurrence free interval, good status of performance, and no visceral involvement was significantly related to long survival, while treatment was not. At end of follow-up, 3 and 4 patients were still alive. Doxorubicin-containing regimens remain the first choice of chemotherapy for ABC until newer treatments have proved superior.

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Navelbine (NVB), and fractionated dose doxorubicin (DX) improves first line advanced breast cancer (ABC) chemotherapy. An overview of 3 phase II trials

J. Carmichael[1], R. Hegg[2], D. Firat[3], M. Pawlicki[4], F. Le Bras[5], P. Danel[5], F.M. Delgado[5]. *[1]Nottingham Hosp, UK; [2]ELAN, Brazil; [3]Ankara U, Turkey; [4]Oncol. Cent Krakow, Poland; [5]IRPF, France*

Aim: Anthracycline combinations represent the most powerful chemotherapeutic approach in the treatment of ABC, but their limiting toxicities are neutropenia and cardiac impairment. NVB as a single agent has demonstrated a high activity and good tolerance in ABC: 40%–60% response rate (RR). Promising results have previously been obtained with NVB 25 mg/m^2 D1 & 8 + DX 50 mg/m^2 D1 (q 3 w): 74% RR (21% CRs), mainly in visceral sites (JCO 94). This was confirmed by a significant survival advantage observed in pts with liver metastases treated with NVB + DX compared to CAF (ESMO 96). Dividing the DX dose and administering it at weekly intervals may reduce the cardiotoxicity without substantially impairing the efficacy. 3 studies were conducted with NVB + DX, both at 25 mg/m^2 D1 & 8 (q 3 w, 8 cycles) to check the efficacy, improve the tolerance and to ease outpatient administration.

Results: 120 pts were included: age 30–73y; PS 0–1: 85%; visceral involvement: 52%; adjuvant C: 18%. 668 18%.668 cycles were administered; WHO grade (G) 3–4 neutropenia: 24%; infection G 3: 6/120 pts; G 3–4 nausea/vomiting: 17 pts; G 3–4 constipation 1.5%; G 1 peripheral neuropathy: 13%; G 3 alopecia: 53.5%. No G 3–4 cardiotoxicity. The RR ranges from 70% to 77% (18–35% CRs) RR on visceral sites: 56%–86%.

Conclusion: These results confirmed that NVB + DX (25 mg/m^2 D 1 & 8) has major and reliable activity as 1st line therapy. Given its very favourable tolerance, low morbidity and absence of life threatening cardiotoxicity, out patient administration of this regimen could be recommended as 1st line treatment for ABC.

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Taxotere™ (docetaxel, D), doxorubicin (Dx) and cyclophosphamide (CTX) (TAC) in the treatment of metastatic breast cancer (MBC)

J.-M. Nabholtz, M. Smyllo, J.R. Mackey, A. Paterson, D. Noel, T. Al-Twelgerl, D. Au, E. Sansregret, F. Delorme, A. Riva. *Cross Cancer Institute, Edmonton, AB, Canada; Rhône-Poulenc Rorer, Antony, France*

Considering the promising results of combination of taxanes and anthracyclines, we conducted a phase II study of D (75 mg/m^2, 1 hour iv infusion) with Dx (60 mg/m^2, iv bolus) and CTX (500 mg/m^2, slow iv bolus) q.3 weeks (maximum 8 courses) in patients (pts) with MBC without prior anthracyclines or taxanes. Forty-five pts (238 courses delivered) were treated as follows. Characteristics: moan age: 52 years (34–70); prior adjuvant chemotherapy (CMF) 10 pts (22%); visceral metastases 29 pts (64%); bone 24 pts (53%); 3 and more sites: 18 pts (40%). Median follow-up: 7 months (3–11). Thirty-three pts are evaluable for response. The major response rate is 85% with CR: 4 pts (12%), PR 24 pts (73%), SD 5 pts (15%), PD 0 (0%), with no progression yet reported. Forty-five pts are evaluable for toxicity. Neutropenia is the main toxicity (grade 4: 78%, lasting less than 7 days), febrile neutropenia: 12.1% of courses (courses given with ciproflexacine (C): 10.8% and without C: 24%). There was no extrahematologic grade 4 toxicity, while Grade 3 occurred in 25 cycles (10.5%) (nausea/vomiting, pain, fatigue, diarrhea). Grade 3 fluid retention was seen in 1 pt (2.2%). No clinical cardiotoxicity occurred while 5 pts presented with a moderate asymptomatic and usually reversible decrease of LVEF on MUGA scan (11.1%). TAC is a well-tolerated and active regimen with no evidence of cardiac toxicity and is the base of 2 large international randomized multicentric randomized trials comparing TAC to FAC in metastatic and adjuvant setting.

651 POSTER*

Treatment of recurrent cutaneous metastatic breast cancer with tin ethyl etiopurpurin (SnET2) photodynamic therapy

T.S. Mang, R. Allison, B. Dale Wilson, V. Vongtama. *Radiation Oncology Department, Photodynamic Therapy Center Buffalo General Hospital, USA*

Introduction: Breast cancer recurrence of the chest wall following mastectomy, radiation and chemotherapy poses a therapeutic dilemma. Further intervention with any or all of these modalities is often futile and morbid. Left untreated severe pain, infection and suffering will occur. Photodynamic therapy presents as a palliative option for these individuals.