BREAST CANCER REVIEW
January 2007

BREAST CANCER - MOLECULAR BIOLOGY

S Blair and J Massague (Nat Med 2002; 8: 1076-7). Breast cancer related to misplacement of p27 from nucleus (where it inhibits cdk2/cyclin E activation) to the cytoplasm. Can be a target...

I Tolgaz et al (Cancer 2003;97:1841-8). N=341. Studied EGFR, HER2, met. Only met expression correlated with poor prognosis (HR=2.04 for survival).

K Keyomarsi et al. (NEJM 2002;347:1566-75). N=395. Increased cyclin E expression strongly correlated with survival with/without lymph node metastases. In Stage I low cyclin E expression none recurred while among 12 pts with high expression all died of breast cancer metastases. No correlation for cyclin D1 or cyclin D3. Results were similar for Stage II and III; not in Stage IV.

B Uzzan et al (Ca Res 2004;64:2941-55). Review microvessel density studies. Reporting on 43 independent sutides and using median microvessel density as a cut-off there was a correlation with OS HR=1.5 and RFS HR=1.5 when values were high.Similar resultas in negative node patients. It is a significant though weak prognostic factor...

J Holland et al (Clin Ca Res 2004;10:5647-9). MMTV related Human Mmmary tumor virus as a contributing factor in the etiology of breast cancer?. Presence of env protein in 30% occidental cancer cases, 10% oriental cases and 70% in Tunisia. Horizontal transmission.

RS Muraoka-Cook et al (Clin Ca Res 2005;11:937-43). TGF Beta activation/production contribute to tumor progression. Approaches to inhibit TGFB: ligand MoAb and small molecule KI (serine-threonine) (CAT 192 against TGFB1 and CAT 152 against TGFB2), blocking receptors. A potential risk is acceleration of preneoplastic lesions since TGFB is both a suppressor and a promoter of carcinogenesis.

K Osborne (JCO 2005;23:1616-22) ER+ Her2+ cases have a better response to aromatase inhibitors than to TMX (75% vs 30%). These patients can benefit from combination of antiER+Heerceptin therapies and delay resistance/restore resposiveness to TMX.

E Espinosa et al. (JCO 2005;23:7278-85) RT-PCR of 70 gene signature array (NEJM 2002;347:1999-2009) to validate risk. Tested in 96 patients and confirmed good and poor risk groups. Added also HER2, EGFR, PLAT and MUC-1 but found no additional value. In multivariate analysis signature profile and lymph node status were significant factors.

*639. PIK3Ca mutation found in 27.9% mets breast cancer. Conferred resistance to Taxanes and may serve to define mTOR antagonists. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185)

Combined Letrozole + Herceptine for ER+ HER2+ tumors: OR 25%, MDR 73 wks, TTP 32 wk. Suggest common resistance pathways... (Abs 596 Proc ASCO, 2005; 23)

*****J A Menendez et al (JCO 2006;24:3735-46). Heregulin activates HER3 and HER4 and subsequently these dimerize HER2. Cell that overexpress Heregulin have a very good response to CDDP, TXL and VCR given with Trastuzumab in spite of absence of HER2 expression. So certain patients without HER2 may respond to CDDP-TXL-Herceptin.**

********T Sjoblom et al (VE Velculescu) (Science 2006;314:268). 13.023 genes analysed in 11 breats cancer and 11 cloroectal cancer. Median accumulation of mutant genes per tumor close to 90. Total number in breast cancer averaged 11 mutation. Majority unknown previously and affect transcription, adhesion and invasion. Validation was performed in 24 additional cases for breast and CRC. Mutations were: 81% missense, 7% nonsense , 4% altered splicing, 8% insertion/deletion/duplications. cancer was 189 genes,**

BREAST CANCER – HEREDITARY

JEW Ashkenazim: 185 del AG, 1.05% truncate BRCA1.
188 del 11, 0.01%, termination mutation BRCA1
5382 insC, 0.11%, frameshift mutation BRCA1
6174 del T, 1.36%, BRCA2 frameshift mutation
ICELAND: 999 del 5

*Meijers-Heijboer et al (NEJM 2001;345:159-64) Bilateral prophylactic mastectomy in BRCA carriers 0/76 tumors while controls showed 8/63 tumors (4 with + ly nodes). Alterantives are first choice bilateral mastectomy and second oophorectomy+TMX+ close surveillance with MRI...

*Metanalysis fo incidence of breast cancer lifetime for women with one first degree relative with breast cancer is 5.5% and 13.3% in case of two relatives.

* NYBCSG (Science 2003;302:643). BRCA-1 risk of developing breast cancer at 70 y.o. 84%, & ovarian cancer 63%. For BRCA-2 breast 87% & ovarian 27%. Other influences are: for pts born after 1940 much higher incidence (84% at 60 yo), together with other known factors: ager of menarche, weight-diet, exercise, reproductive factors, environment...

****J Kramer et al (JCO 2005;23:8629-35). Oophorectomy reduced breast cancer incidence: 6/33 BRCA1 carriers as compared to 27/65 carriers without oophorectomy. HR =.38, very important measure…!**

*508. Studied BRCA1/BRCA2 mutations in triple negative (ER,PR,HER2) breast cancer. According to family history and age/personal history there were 3-4 expected hereditary cancers and found 9 BRCA1 (39.1%) and 8.7% BRCA2... Much higher incidence than expected. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185)

H Risch et al (JNCI 2006;98:1694-706). Kin cohort study of patients with invasive ovarian cancer found 75/977 BRCA1 and 54/977 BRCA2 (13.2%) overall mutation rate. BRCA1 was associated with excess risk of gastric, hepatobiliary, renal and testes cancer, while BRCA2 associated with pancreas and prostate cancer. Prevalence was for BRCA1: breast cancer 90% and ovarian cancer 24% at 80 yo; and for BRCA2: 41% and ovarian 8.4% at 80 yo. The presence of mutation in Ontario was 1:100, higher than expected.

BREAST CANCER – RISK FACTORS

*HRT Trial Women Health Initiative. J Hays et al (NEJM 2003;348:1839-54). N=>20.000. Estrogen + Progestin. Final analysis showed 2 serious events/100 women/year, after 5 years use, which lead to early stopping. (Serious events were: stroke, coronary, pulmonary embolism, & breast cancer). There was also a decrease in hip fracture and in colorectal cancer. No differences were observed in QOL tests and no improvement of cognition, only improvement in hot flashes (sleep disturbances).

Million women Study Col. (Lancet 2003;362:419-27). HRT increases breast cancer risk HR 1.66 and Estrogen + Progestin HR 2. HRT use for 10 y increase 5 additional breast cancers per 1000 users.

Ahlgren et al (NEJM 2004;351:1619-26). Breast cancr related risks: early menarche, height at 14 y.o, low BMI at 14 y.o.

*****L Travis et al (JNCI 2005;97:1428-37). Cumulative incidence of brest cancer after RT (40 Gy without alkylating agents) for Hodgkin kymphoma are: 35 y.o. 1.4%; 45 y.o. 11.1%; and 55 y.o. 29%. Excessive risk!…**

BREAST CANCER – PREVENTION

*Cuzick et al (Lancet 2003;361:246-300). Metanalysis of prevention with TMX or Raloxifene (N=>50.000) indicate a prevention of 48% of ER+ tumors and none in ER- tumors. Risk of endometrial cancer RR=2.4-3.4; venous thromboembolism risk RR=1.9

DL Page et al (Lancet 2003;361:125-9). Atrypical lobular hyperplasia in bx is correlated with 20% ivasive cancer at a mean interval of 14.8 y. 68% of tumors in same breast and 324% contralateral breast. Anticipaction...

*B Arun et al (Sem Oncol 2004;31:22-9). COX2 expression correlate with high risk and tumor progtression (grade, ly node mets abd >T size). AntoCOX2 (celecoxib 400 mg bid) syenrgic with exem,estane and FEC (where increased 20% OR). Promising as a preventive agent and in combinationtherapy. Usually HER2 expression correlate with COX2 expression.

P Goss et al (Clin Ca Res 2004;1072-9). Exemestane (25 mg qd x 5 y)vs placebo vs Exemestane+Celecoxib (400 mg qd x 3 y) (NCI Canada MAP3 trial) for breast cancer prevention... Waiting for results.

BJ Trock et al (JNCI 2006;98:459-71). Soy intake meta-analysis 10 studies: 8 are not supportive but were not stratified according to menopausal status.

L Gallicchio et al (Cancer 2006;106:1443-52). Use of anti.inflammatory drugs in biopsy proven beningn breast disease helped to prevent cancer OR =.46 (N 1467 women with beniongn breast disease).

Dietary fat reduction improves RFS. Womens Intervention Nutrition Study (Abst 10, Plenary, Proc ASCO, 2005; 23)

***5. Breast cancer prevention: Chemoprevention STAR trial. TMX 20mg qd vs RLX 60mg qd x 5y. N=19747, Gail>1.66% at 5 y. RR:1.02. Uterus cancer decreased 40% with RLX. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185).

6. Breast prevention: Ca 1 g + Vit D 400 IU D3 suppl for 7 y. N=36282 (Womens Health Initiative, in addition 57% were randomized to HRT vs Placebo). Results: No reduction in breast cancer. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185)

L Herrington et al (JCO 2005;23:4275-86) Contralateral mastectomy decreased breast cancer mortality from 2.7% to 0.5%.

Statins reduce breast cancer risk 51% incidence (Abst 514 Proc ASCO, 2005; 23)

K Chan et al (Sem Oncol 2006;33:642-6) Chemoprevention of breast cancer proposed in HR>1.7, that is age >45 yo, strong family hx, prior atypical hyperplasia, BRCA 1-2 carrier status and prior breast cancer.

TR Milanese et al (JNCI 2006;98:1600-7). Age related lobular involution starts after 40 yo and correlates inversely with parity. It was studied in 9000 women of the Mayo Clinic Benign Breast Diagbnostic Cohort and found no involutuion 18%, partial involution in 59% and complete involution in 22%. Cancer risk HR was 7.79, 4.06 and 1.4 respectively. Can the induction of involution be a new target?.

BREAST CANCER – SCREENING

M Kriege et al Screening Study Group (NEJM 2004;351:427-37). N=1909 with familial/genetic traits. Breast examination (sensitivity 17.9, specificity 98.1), mammography 33.3 and 95; MRI 79.5% and 89.8%. New golden standard.

N Hylton (JCO 2005;23:1678-84). MRI advantage in breast cancer screning is due to the MRIO early enhancement of contrast filled vessels in tumors (benign proliferative dx , in situ ca and invasive ca). Microcalcificactions difficult to see. MRI as a screenig technique detects 1-4% tumors in fiorst round, 50% unseen by mammography and up to 10% in high risk patients. Very good in staging (size correlation, multicentricity and DCI) or assessment of neoadjuvant therapy. Disadvantages: Cost, complementary need of mammography, difficulties in performing bx based on MRI images.

C Lehman et al (Cancer 2005;103:1898-905). N=390, contraletral screening. Mammography vs MRI. MRI found 6% new cancers unseen or unpalpable & 5% more benign pathology biopsies.

L Tabar et al (Cancer 2004;101:1745-59). Review mammography findings: Tumors 1-1.4 cm, stellate, oval, powdery with crushed stone-like and casating calcificatyions. Only casting calcifications correlated with prognosis: increase ly no mets (OR 3.29), poorer histological grade (OR 7.04), and higher death rate (OR 9.19).

E Pisano et al (NEJM 2005;353:1773-83). Film mammography vs digital mammography have similar diagnostic accuracy though in premenopausal (<50 y.o.) digital is better due to dense breast parenchyma.

CK Kuhl et al. (JCO 2005;23:8469-76). Mammography + US insufficient for early diagnosis of cancer in increased familial risk patients. MRI provides haigher sensitivity at more favorable stage. In 529 asymptomatic patients mammography sensitivity 33%, US sensitivity 40% and both 49%, MRI sensitivity 91%.

C Perlet et al (Cancer 2006;106:982-90). MRI vacuum assisted breast biopsy proved very accurate diagnostic procedure (96%). In 538 patients 21 unsuccessful and repeat biopsy; 96% successful (27% malignant, 3% ductal hyperplasia and 70% benign). NO false negatives.

BREAST CANCER – PROGNOSTIC FACTORS

M Cristofanilli et al (NEJM 2004;351:781-91). Number of circulating breast cancer tumor cells (cytokeratin+) below or above 5/7.5 mL had prognostic impact: initially MPFS 2.7 vs 7 mo and MOS 10.1 vs >18 mo; at first Fup after Chx MPFS 2.1 vs 7 mo nad MOS 8.2 vs >18 mo. Eaerly predictor of response...

*P Manders et al (Cancer 2004;101:486-94). UPA (x=0.46), PAI-1 (x=1.43) and uPA:PAI-1 (x=0.046 ng/mg protein). N=576 pts untreated. The results > median values related to worst prognosis (RFS and OS) in ly no negative patients. Thuis occur in about 50% of patients regardless of RE, grade and size).

*S Paik et al (NEJM 2004;351:2817-26). RT-PCR 21 genes in parafin embedded tumor tissue (NSABBP-B14, TMX adjuvant, ly no negative). Porcessed 668 samples. Low risk 51% (10 y recurrence 6.8%), intermediate risk 22% (10 y recurrence 14.3%) and high risk 27% (10 y recurrence 30.5%). Validated techniques.

***JP Buak et al (JCO 2005;5993-6001). Mitotic index in ly no negative breast cancer (MAI). Selected cut off at <10 or >10. HR 4.42. (N=516 with a Mfup 118 mo, all <55 yo). Metatases occurred in 24.6%; 10 y OS 22% difference.**

***S Braun et al (NEJM 2005;353:793-802). Pooled analysis of 9 studies of BM micrometastases in Stage I & II, MFup 5.2 y, N=4703. Micrometas present in 30.6% and correlated with higher grade and ly no+, ER-. Mortality HR 2.15. 10 y DFS HR=2. Poor prognosis.**

**534. UPA/PAI predict survival... ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

10503. Adjuvant ChX can be spared using tumor tissue determination of UPA/PAI in 30% of patients. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185.

N Xemidis et al (JCO 2006;24:3756-62). CK 19+ cells in peripheral blood (measured by real time PCR) in patients with negative lymph node mets present in 36/167 (21.6%). Correlated with Her 2 ++/+++. Impoirtant factor of survival: 60 vs 100%, DFS 4% vs 90%.

S Paik et al (JCO 2006;24:3726-34). 21 gene recurrence score (RS) assay in NSABP-B20 trial (TMX vs TMX+ChX) in N=661. High RS (>31) indicated benefit for ChX RR 0.26 and 10 y Distant Recurrence Ratio decreased 27.6%. Low RS (<18) RR 1.31 for ChX and 10 y DRR –1.1% (no benefit). It may lead to avoid ChX in small lymph node negative tumor patients.

M Buyse et al (JNCI 2006;98:1183-92). 70 gene prognostic signature (cell cycle, invasion, metastasis and angiogenesis genes) validation study in node negative patients. N=307. Time for distant mets HR 2.32, OS HR 2.79. In high risk group (N=191) 10 y OS 69% and in low risk group (N=111) 10 y OS 89%. Provides independent prognostic information, better than clinical, and can help to avoid chemotherapy in low risk patients.
INTRINSIC SUBTYPE CLASSIFIER: 306 gene expression profile to identify 5 tumor types (Luminal A & B, Basal like, HER2+ and Normal breasts like cancer types.
ONCOTYPE DX (commercialized). 21 gene ER+ distinguished low intermediate and high risk recurrence for ChX recommendation
MAMMAPRINT (commercialized). 70 gene cell invasion and metastases for early breast cancer ChX recommendation
WOUND RESPONSE SIGNATURE: 512 GENES OF MIGRATION, REMODELLING, BLOOD VESSEL GROWTH. Predict poor survival.
TWO GENE: ER+ reuqiring ChX. Predict less well.

J O´Shaughnessy et al (NEJM 2006;355:615-17). Current MINDACT and TAILORX use the 70 gene prognostic profile and the 21 gene recurrence score to define which ER- node- patienst benefit from ChX and asvoid treating the rest (30-50%).

Ch Fang et al (NEJM 2006;355:560-9). N=2295 samples. Applied 5 gene profile tests: Intrinsic subtypes (basal, luminal A, luminal B, HER2 +ER- and normal); 70 gene profile; 21 gene RS; 2 gene ratio (less precise); and Wound response signature. Large overlapping classification results of poor risk patients was identified.

P Urban et al (JCO 2006;24:4245-53). UPA mRNA (quantitative PCR technology) in erbB2+ tumors had a prognostic impact for MFS (HR 4.3). erbB2+ uPA- had similar outcome than erbB2- tumors. ErbB2- is 60%; erbB2-uPA+ is 20%, erbB2+uPA+ is 10% and erbB2+uPA- is 20%.

Y Ishii et al (JNCI 2006;98:1238-47). High Cyclin D1 correlates with low STAT3. Induces apoptosis. It might be a marker of Bortezomib response...

KR Hess (G Hortobagyi) et al (JCO 2006;24:4236-44). N=131. Stage I-III breast cancer. Array with 30 probe oligonucleotide microarrays of FNAB samples. Developing kit 82 patients and assessed in 51 independent validation cases. Pathologic CR 26%. Predictive sensitivity 92% (better than clinical 61%). Negative prediction value 96% (vs 86% clinically). Identified correctly 12/13 pCR and 27/28 residual tumor patients...

W Woodward et al (Yago Nieto). (JCO 2006;24:2910-6). Nodal ratio review, cut off ratio at 0.8. Better predictor than absolute count. An intergroup study on going...

BREAST CANCER – PREVENTION

C Fabian et al (Clin Ca Res 2004;10:5403-17). Arzoxifene (3rd generation ERM with absence of uterine agonist activity and a higher ER affuinity as compared with Raloxifene). Randomized study with doses 10 mg, 20 mg or 50 mg qdvs control in T1, T2 & in situ. At the operation time decrease in proliferative index and in ER. Selected for chemoprevention study...

*M Kalidas et al (JNCI 2004;96:1731). N=7700. Raloxifene CORE trial randomizing RX 60 mg qd (reduction of bone fractures 35-47%), vs 120 mg qd vs placebo. Final results demonstrated a reduction

ion breast cancer incidence 72% at 4y. Reduction of breast cancer overall 59% and ER cancer 66%. Continued CORE trial for 4 additional years.

P Goss et al (Clin Ca Res 2004;10:72-9). COX2 expression corelates with high risk and tumor progression (grade, ly node mets and T size). Anti-COX 2 synergic with exemestane and FEC (where showed a 20% increase in OR rate). HER2 expression correlate with COX2 expression. Trial MAP-3 from NCI-Cabada compare Exemestanbe vs placebo vs Exemestane 25 mg qd x 5 y + Celecoxib 400 mg qd x 3 y… Waiting eagerly for the results…

*L Herrington et al (JCO 2005;23:4275-86). Contralateral prophylactic mastectomy decreases breast cancer mortality: contralateral breast cancer 0.5% (untreated 2.7%)

PREVENTION TRIALS

- ATLAS: Adj TMX 5 vs 10 y (N=20.000 pre-post meno with breast cancer).
- ATTOM (Adj TMX Treatment Offers More).N=20.000 pre-post with breast cancer with adj TMX 2 y vs 7 y
- IBIS2 (Interntl Breast Cancer Interventrion Study) N=16.000 with high risk breast cancer. Randomized Anastrazole vs Placebo
- STAR (Study of TMX and Raloxifene). N=22.000 post meno high risk. TMX 20 mg vs RXF 60 both x 5y.
- CORE (Continuing Outcomes Relevant to Evista). N=4.000, previously on MORE (Multiple Outcomes on RFN Evaluation Trial) of RXF vs Placebo x 4 additional years) (M Kalidas et al, JNCI 2004;96;1711, Breast cancer reduction 59% and ER+ brest cancer 66%).
- RUTH (Raloxifene Use in the Heart). N=10.000, at risk of coronary Dx. RFX vs Placebo.

J Hays et al (HRT Trial Women Health Initiative) (NEJM 2005;348:1839-54). N>20.000. Eastrogen + Progestin. Stopped because of mexcess risk for coronary, stroke, pulmonary embolism and breast cancer, and a decrease in hip fracture and colon cancer. Final analysis 2 serious events/100 women/year/ after 5 y use. NO differences in QOL tests, only hot flashes and sleep disturbances, without improvement in cognition.

BJ Trock et al (JNCI 2006;98:459-71). Soy intake meta-analysis in 8/10 not supportive, but there was no stratification according to menopausal status. Risk reduction stronger OR 0.70 as compared to postmenopausal OR 0.77
L Gallicchio et al (Cancer 2006;106:1443-52). Use of antinflammatory drugs in biopsy proven beningn breast disease helped to prevent cancer . OR 0.46 (in N= 1467 women with biopsy of benign breast diagnosis). BREAST CANCER – IN SITU

E Fisher et al (Cancer 2004;100:238-44). Natural history od lobular ca in situ, Mfup 12 y. N=180 treated with local excission and surveillance. Ipsolat recurrence 14.4%, contralat recurrence 7.8%. 5%of the recurrences were invasive, the rest were again lobular ca in situ. Mortality 2%.

G Leonard and S Swain (JNCI 2004;96:906-20). Review diuctal ca insitu. Axillary ly no mets present in 1.4% DCIS and 5.1% DCIS with microinvasion. Dx by MRI 95% (mammography only 74%). Risk factors: famuily history, previous breast cancer, older age at first pregnancy, estrogen therapy. When left untreated, the risk of inasive greast cancer is 20-75% at 2-30 y Fup. ER+ 64%, PR+ 57%, HER2+ <20%. Recommended therapy: Lumpectomy + RT+TMX (when RE/RP+).

BREAST CANCER – LOCAL THERAPY

U Veronesi et al (NEJM 2003;349<.546-53). N=536, T<2cm. Randomized study comparing SNB + total axillary dissection vs SNB+ Total axillary dissection only when ly no was +. Demonstrated accuracy and sfe technique. SNB sensitivity 91.2% and specificty 100%.

*A Ring et al, Royal Marsden, (JCO 2003;21:4540-5). N=136 in cCR after neoadjuvant Chx. Randomized to surgery (5y DFS 74%, 10 y DFS 60%) or RT (76% and 70%). 5y local recurrence was 21% with surgery and 10% with RT!...

V Vinh-Hung et al. (JNCI 2004;96:115-21). Metanalysis of conservative surgery +/- RT in 15 trials, >9400 pts. RR mortality without RT 1.086. That is a 8.6% mortality excess due to risk of recurrence...

T Pawlik et al MDACC, (Cancer 2004;100:490-8). Accelerated partial breast irradiation (APBI). Feasinbility sutdy with 443 pts treated with conservative surgery. Only 25% had a resected volume of <75 cc (size of the FDA approved balloon catheter based APBI. There is a new catheter of 125 cc recently approved and untested.

***G Viale, ESO Milan, (Cancer 2005;103:492-500). Peritumoral vascular invasion present in 29% of early breast cancer. SNB + in T>23cm 74% when vascular invasion present. In cases withour vascular invasion, and T< 1cm, positivity iof SNB was only 9.5%.**

V Gebski et al. (JNCI 2006;98:26-38). Metanalysis of 38 trials of RT with adequate bilogical doses and fields, N=13.199 patients. OS gain 2.9% absolute gain at 5 y and 6.4% at 10 y.

R Mansel et al (JNCI 2006;98:599-609). Randomized trial (N=1031) os SLN bx and axillary dissection. Lymphedema risk o.37 and sensory loss 0.37. Better QOL and RX of choice.

F Peintinger et al MDACC (Cancer 2006;107:1248-54). Neoadjuvant Chx operated patients with greast conserving surgery (N=109). Local recurrence 2.7%, 5y LRR free survival 98.1%. sequential mastectomy was adequate for recurrences also.

M Intra et al (ESO HSJ Nov 2006). Complte eaxillary dissection reduced from 54% to 23% and SLNBx increased from 46% to 77% in period 2000-2005.

G Paganelli et al (ESO HSJ Nov 2006). Intraoperative avidine injection followed by radiolabelled biotin postoperative radiotherapy in the breast. RT to index quadrant 5 Gy GBq (roughly 20 Gy) when giving 3.7 GBq 90-Y-biotin in 100 ml

BREAST CANCER – METASTASES

M Van der Sangen et al (Vancer 2003;98:11-7). Isolated supraclavicular recurrence (N=42). Interval from surgery 2.5 y. Tereated with surgery, Chx and RTx CR 83%. Local recurrence 34%. 5yOS 38% and 5 y distant DFS 22%.

D Bonchardy et al (Cancer 2004;100:28-35). Lung mets resection results in N=125, age x=53, resected 1-16, me 1, size 2 cm. 5 y OS 45%, 10 y OS 30%.

10555. Gammaknife for CNS breast metastases: 75 patients/162 lesions. MPFS 5.3 mo, MOS 8.1 mo, 2yPFS 9.6% and 2 yOS 18%. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

10581. Hepatic artery chemotherapy with anthra and taxanes: 60% OR, MDR 5.4 mo, MOS 13 mo. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

10626. Intra-arterial TXL for hepatic metastases 3/7 PR, MDR 5-9 mo. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

166-Holmium-DOTMP for single bone metastases. Doses 870-2065 mCi (use BMT for doses>1cGy/hour). Performed a localization test with 30 mCi to assess for skeletal uptake. Out of 6 pts, 2>5yPFS. MTTP 10 mo. (Abst 569 Proc ASCO, 2005; 23)

O Bruland et al (Clin Ca Res 2006;12:6250s-6s). Ra 223 obtained through generator from Actinium 227 (Act 227/ Thalium227) half life 11.4 d Decays to stable Lead (Pb207). It is alfa emitter (more toxic for tumor cells) but very well tolerated. Indicated in bone metastases. Dose estimates with 125 kBq/kg (prostate and breast cancer).

BREAST CANCER – NEOADJUVANT THERAPY

*Nabholtz JM et al (ASCO 2002; 36abst. TXT75+ADM50+CPA500 vs F500A50C500 x 6 showed benefit for TAC DFS 82% vs 74% in >3 + ly no (33 MFup).

**M Citron et al CALGB 9741 (JCO 2003;21:1431-9). N=2005. Randomized study to ADM 60 mg/m2 x 4 then TXL 175 mg/m2 then CPA 600 mg/m2 x 4 q 3 (1000 neutrophils, 25% dose reduction if toxic) vs ADMx4 then TXL x 4 then CPA x4 q 2 wk (+GCSF 5 ug/kg/d x 7 d, d3-d10), VS AC x 4 then TXL x 4 q 3 vs AC x 4, then TXL x 4 q 2 (+GCSF) & afterwards RT and TMX. Rwesults indicated dose dense DFS 0.74 and OS 0.69, 4 yDFS 82% anmd standard 4yDFS 75%. Overall lowere nuimber of events, less than wexpected, no toxic death rate. Both in ER+ (19% reduction) and ER – (32% reduction of risk). New standard!

V Dieras et al (JCO 2004;22:4958-65). Randomized study T2-3 N0-1 to ADM 60mg/m2 + TXL 200 mg/m2 q 3 x 4 then surgery (pCR 16%, breast conservation 58%, OR 89% and PFS at 31 mo Fup for pCR 91%) vs ADM same + CPA 600 mg/m2 q 3 x 4 then surgery (pCR 10%, Breast conservation 45%, OR 70% and 31 mo PFS for pCR 70%).

P Lebowitz et al (Clin Ca Res 2004;10:6764-9). Stage 2-3. TXT 75 mg/m2 + Xel 937,5 mg/m2 bid d 2-15 x 4. OR 90%, CR 31%, pCR 10%.

***S Mohsin et al (JCO 2005;23:2460-8). Neoadjuvant Herceptin wkly x 3 induced 23% OR & decrease less than PR in 20% in priimary breast cancer. Apoptosis increased from 3.5% to 4.7% (35% above baseline) suggesting a mechanism of synergy with chemotherapy.**

***GV Minckwitz et al (JCO 2005;23:2676-85). N=913, T2-3, N0-2, randomized to ADM 50-TXT 75 +GCSF q 2 wk x 4 (pCR 7%, OR 78.6%, btreast conservation 58.1%) vs ADM 60 + CPA 600 x 4 then TXT 100 q 3 x 4 (pCR 14.3%, OR 85%, Breast conservation 63.4%).**

***L Carey et al JNCI 2005;97:1137-42). N=132. 5y DFS correlates with stage after surgery following neadjuvant chemtyherapy: Stage 0= 95%, I=84%, II=72% and III=47%.**

*** A Buzdar et al (JCO 2005;23:3676-85). N=42, HER2+, planned 164 pts. Neoadjuvant TXLx4 then CEFx4 (pCR 21%), vs Same+ Herceptin wkly x 24 wk (pCR41%) NO congestive heart failure observed.**

****M Citron et al (L Norton, CALGB, JCO 2003;21:1431-9). N=2005 Randomized to A 60 x 4 then T 175/3h x 4 then C 600 x 4, all q 3 wk or t AC x4 the T x 4 q 3 or same q 2 (+GCSF), and then RT/TMX. Dose dense: DFS 0.74, OS 0.69 and 4 yDFS 82% vs standard 4yDFS 75%. New standard. NO toxic deaths.**

Neoadjuvant AT-CMF vs A-CMF better pT0 (23%) & freedom from progresion HR 0.65 (Abst 513, Proc ASCO, 2005; 23)

**LBA 537. Neoadjuvant AC+TXL wkly (80 mg/m2/wk x 12) vs AC wkly+ then TXL wkly (G Ellis, Proc ASCO 2000) (ADM wkly 24 mg/m2 + CPA 60 mg/m2 /d po x 15 weeks + GCSF 5 ug/kg/d x 6-7 wks). N=269. HR 1.98 for OR with less toxicity. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

Neoadjuvant in Her2+ tumors: (N=31) TXT 60 mg/m2+ NVB 45 mg/m2+ Herceptine q2 wk x6 (GCSF & quinolones) pCR 45% & pT1a 65%, OR 88%. Very high pathological complete and microscopic response...(Abst 591 Proc ASCO, 2005; 23)

M Kaufmann et al (JCO 2006;24:1940-9). Updated results of neadjuvant systemic therapy, consensus of Sept 2004 meeting: Purpose to improve surgical options, to obtain information on response and to obtain long term disesase free survival. Xcandidates all that require adjuvant therapy. DOUBTS IN t1-t2 BECAUSE OF n UNCERTAINTY. Regimes based of Anthracyclines and TXns added benefit on DFS & CR rate (not on OS). Duratin at least 4 mo, to increase the chance of pCR up to 20% (with TXns).

***** M C Green et al (JCO 2005;23:5983-92). N=258. Randomized wkly TXL 80 mg/m2 x 12 (pCR 28.2% and breast conserving 61/127, less neurotoxicity and better tolerance) or TXL 150-225 mg/m2 q 3 wk x 3 (pCR 15.7% and breast conservation 48/131) before FAC x 4. Quite clear…**

L Gianni et al (Clin Ca Res 2005;11:8715-21). N=1355. Randomized to surgery followed by ADM x 4 -> CMF x 4 adjuvant or ADM+TXL x 4 -> CMF x 4 (breast sparing 34%) or neoadjuvant ADM+TXL x 4 -> CMF x 4 -> surgery (OR 78%, CR breast 23% and axilla 20%, CR only related to ER/PR negative patients, and breast sparing 65%)

J Hurley et al (JCO 2006;24:1831-8). HER2- or inflammatory breast cancer. Neoadjuvant TXL 70 mg/m2 + CDDP 70 mg/m2 + Herceptin wkly x 4 and then q 2 wk up to 12 wk-> surgery-> Adj ADM+CPA+RT+/- TMX. PCR 23% in T and 17% breast and axilla. HER2* 23%. M F up 43 mo. Pathiol CR: 4 y PFS 81%, 4y OS 86%.(In pCR breast and axilla 4 y PFS 100%). In no pCR 4 y PFS 76% and 4 y OS 83%.

JA Sparano et al (JCO 2006;24:3013-8). Neoadjuvant TIPIFARNIB (FTASE inhibitor) 100-300 mg/buid x 6-14 d + DOX 60 mg/m2 + CPA 600 mg/m2 d 1 x 4. Recommended dose TIPIFARNIB 200 mg bid d 2-7. Pathological CR 7/21 (33%). Inhibition of Ftase >50% in 5/5 tested patients. Increase in pCR?.

BREAST CANCER – ADJUVANT THERAPY

P Goss et al (NEJM 2003;349:1793-802). N=5187, Mfup 2.4 y. After 5 y TMX Randomized to Letrozole (recurrences 75, 4 yDFS 93%, deaths 31, myalgia, osteoporosis, hot flashes and arthritis) or Placebo (recurrences 132, 4yDFS 87%, 42 deaths). Improvement of DFS.

HERCEPTIN TRIALS (Sem Oncol 2003;30:54-64)

- ECOG (E2198) Ly no +. Randomized 234 pts. TXLx4+HERx10 then Acx4 vs same + HER x 52. **Satellite ASCO symposium 2005: On going, 4yDFS 85% vs 67%; 2YDFS 85.5% vs 77.4%**.
- NSABP (B31) (N=2.700) Date expected 2005. Randomized ACx4 then TXLx4 vs same + HER x52. **Satellite ASCO symposium 2005: Mfup 2 y: Recurrence 8%**
- NCCTG (N9831) Ly no +. Date expected in 2005. Randomized TXL wklyx 12 vs TXL same then HER x 52 vs TXL wkly + HER wkly x 12 then HER x 52. **Satellite ASCO symposium 2005: Mfup 1.5 y: Recurrence 15%.**
- BCIRG (006) (N=3.150) Europe & USA expected 2004. Ly no +, high risk. Randomized Acx4 then TXTx4 vs TXT same + HER wklyx 12 then HER q 3wk x 13 vs TXL-CDDP/CBDCA x 6 + HER q 2 wk x 18 then HER q 3 wk x 11.
- BIG-01-01 (HERA) (N=3.190). Europe expected 2006. Any ly no, prior CHx or neoadj & RT randomized to then No HER vs HER q 3 x 1 y vs HER q 3 x 2 y. FED French (N=2.600). Ly no +. First Randomization to CEF vs EPI+TXT and then second randomization HER q 2 wkx 1y vs observation.

HORMONETHERAPY ADJUVANT TRIALS
ATAC (MRC) (Lancet 2002;359:2131-9). Randomized TMX x 5 y vs Anastrazole x 5 y vs TMX+Anastrazole x 5. DFS 0.8, Contralateral breast cancer 0.5. Mfup 47 mo.
(J)MA.17 North Amer Intergroup. (NEJM 2003;349:1793-802). 5 y TMX & then Placebo vs Letroozole . DFS HR 0.57 (6% difference).

EXACT Internatl Ca Coll Group. (IES Trial). (NEJM 2004;350:1081-92). Randomized 5 y TMX vs 2-3 y TMX then 2-3 y Exemestane DFS 4.7% improvement. Mfup 30.6 mo.
NSABP –B33. Randomized 5 y TMX and the 2 y Exemestane vs 2 y Placebo.
TEAM TRIAL (Multinational). Randomized TMX vs Exemestane
ARNO trial (German Austrian Group). TMX x 5 y vs TMX x 2 the Anastrazole x 3
Z/ZO FAST. Randomized Zometa q 6 mo + Femara x 5 y vs Femara x 5 y.

IBCSG (JNCI 2003;95:1833-46). N=1063 premenopausal women, ly no -, Mfup 7 y. Randomized CMF (5yDFS er- 84%, and ER+ 81%), vs Goserelin x 24 mo (73% and 81% respectively), vs CMF then Goserelin (88% and 81% respectively) vs no adjuvant (discontinued with only 42 pts). Adj chx requiered in ER- and sequential better in ER+.

***F Herbst et al (NNBC-3 Europe) St Gallen Conference 26.Jan 2005. Node negative patients. Excluded patients with UPA <1ng/mg and PAI-1 <8.2 ng/m2, which represent 30% of the patients. Grade 1 + low UPA/PAI-1, 8% and Grade 2 + low UPA/PAI-1, 22% no adjuvant chemotherapy. Grade 2 + high UPA/PAI-1, 30%, and Grade 3, 37%, randomized to FEC 100 x 6 vs FEC 100 x 3 then TXT 100 x 3.**

***Noguchi et al, Metanalysis of Japanese Trials (JCO 2005;23:2172-84). 6 randomized trials comparing TMX vs UFT 300 mg/d x 2 y vs TMX+UFT vs control groups indicated advantage for UFT similar to TMX and further benefit for the combination. OS not significant. Propose UFT instead of CA for eldewrly postmeno, huigh risk pts, combinaed with UFT.**

***M Martin et al BC Internatl Res Group (NEJM 2005;352:2302-13). (N=1.491). Axillary +. Randomized TAC (75-50-500) 5yDFS 75%. 5yOS 87%, Hematol toxic 65% vs FAC (500-50-500) 5yDFS 68%, 5yOS 81% and hematol toxic 49%.**

****J Ingle (Clin Ca Res 2005;11:900-5). Aromatase inhibitors > TMX in ER+PR- &/or HER2+. No trials have yet adressed adjuvant therapy according to receptor status. Very difficult the obtention of study blocks from adjuvant ongoing studies (i.e ATAC trial).**

K Pritchard et al (NEJM 2006;354:2103-11). Analysed published results for MA-5 trial according to HER2 status and found RFS 0.52, OS 0.65 when HER2+ and RFS 0.91, OS 1.06 when HER2-. Anthracyclines better in HER2+ tumors (MA-5 compared CEF vs CMF).

*****E Romond et al (NSABBP-B31 & NCCTG-N9831) (NEJM 2005;353:1673-84). B31 was a randomized AC->TXL q 3 vs AC->TXL+Herceptin x 1y; N9831 was a randomized study AC->TXL wkly vs AC->TXL wkly+ Herceptin x 1y vs AC-> TXL+ Herceptin-> Herceptin x 1y. Combined control arm 261 events and Herceptin 133 events (HR 0.48, leading to an early stop), 3 y OS improved 12%, 3 y heart toxicity 2.9 to 4.1%. Major advance in therapy.**

*******Piccart-Gehhart et al (HERA trial) (NEJM 2005;353:1659-72). N=5081, NA or Adj Chx randomized to Observation; 1 y Herceptin or 2 y Herceptin. HR 0.43 and 8.4 improvement in RFS. Herceptin 2 y benefit 6%.**

M Venturini et al (JNCI 2005;97:1724-33). N=1214, Mfup 10.4 y. Randomized study comparing FEC q 3 wk vs FEC q 2 wk + GCSF. HR death 0.87, HR recurrence 0.88. No AML/MDS found. Not so clear results as in CALGB study, due to TXns?.

H Joensun et al (NEJM 2006;354:809-20). N=1010, ly no+ & high risk ly no-. Randomized to TXTx 3 -> CEF x 3 (3 y RFS 91%) or NVB x 3 -> CEF x 3 (3 y RFS 86%). Herceptin in HER2* vs no (3 y RFS 89 vs 78%).

E Brian et al (Cancer 2006;106:2337-44). Pooled analysis of Phase III trials of TXns adjuvant trials in N=15.598. Overall DFS RR 0.86; DFS ly no+ RR 0.84; OS RR 0.87 and OS ly no+ 0.84. Absolute DFS benefit 3.3-4.6%, OS 2-2.8%. Definite favorable effect, TXT better.

S Jones et al (JCO 2006;24:5381-7). N=1016, stage I-III. Randomized AC (5 y DFS 80%, 5 y OS 87%) vs TC 75/600 (5 y DFS 86%, 5y OS 90%, better).

B Eilertsen et al (JCO 2006;24:4956-62). Premenopausal ER+, ly no+ or T>5cm. N=762, Mfup 8.5 y. Randomized ovarian ablation c RT or CMF q 3 x 9 (HR DFS 0.99, HR OS 1.11). No differences.

C Poole et al (NEJM 2006;355:1851-62). Added studies NEAT and BR9601 comparing EPI x 4 -> CMF x 4 vs CMF x 6-8. 2 y RFS 91 vs 85%, 5 y RFS 76 vs 69% and 5 y OS 82 vs 75% favoring EPI induction->CMF, HR 0.69. No influence found for nodes, grade, ER, vasc invasion or ER.

*****I E Smith et al (JCO 2006;24:2444-7). Use of adjuvant AI in amenorrheic after ChX supporting menopausal status. AI reduce estradiol and increase feedback loop LH/FSH release which promote ovarian function return. Found in one center 45 women, median age 47 yo, and 27% had a return of ovarian function (even one pregnancy). Recommend therefore close monitoring and applying AIs together with ovarian suppression 8surgical/RT/LHRH analogs), otherwise give TMX!.**

511. ATAC Anastrazole randomized trial demonstrated bone loss related to anastrazole therapy. TMX more weight gain also. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

LBA 519. Adjuvant N+ breast cancer. N=2887. Randomized Ax4+CMFx3 vs ACx4+CMFx3 vs Ax3+TXTx3_CMFx3 vs ATXTx4+CMFx3. M F up 62.2 mo. EFS HR 0.79 TXT vs no TXT (borderline significance), otherwise no differences. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

LBA 520. Adjuvant N+ breast cancer. N=972. Randomized EPIx4+CMFx4 vs EPIx4+TXTx4+CMFx4. EFS HR 0.79, borderline significance. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

*LBA 527. Adjuvant TMXx2-3y_Exemestane x2 vs TMX x5. N=4740. DFS HR 0.73, no differences in OS. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

LBA 528 Adjuvant postmenopausal TMX x 5 vs Letr x 5 vs TMX x 2+Let x3 vs Let x 2+TMX x 3..... ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

Adjuvant AT vs AC in node+ & high risk node- pts. DFS better for AT HR 1.21 in RE- pts; 4 yDFS 82% AT and 79% AC. (Abst 512, Proc ASCO, 2005; 23)

***569. Metanalysis of adjuvant breast cancer. CMF po vs CMF iv (HR 0.76 better for po). CMF po vs CAF/CEF HR 0.88 in favor of Anthracyclines. Combination od Anthracyclines_CMF po benefit combination (HR 0.70). ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

BREAST CANCER – HORMONE THERAPY

A Howell (Clin Ca Res 2001;7:4402-10)
Selective estrogen receptor modulators (SERMs): Estrogens (Stylbestrol 15 mg/d, Ethhinylestradiol); Triphenylethylenes (Tamoxifen, Toremifen, GW5638); Fixed ring (Raloxifene, EM652, Arzoxifene); & Estradiol analogues (Fulvestrant, SR16234, ZK191703).
Aromatase inhibitors: Steroidal (Formestane, Exemestane); Non steroidal (Anastrazole, Letrozole).
Remaining Questions: Cycling agents to increase responses: LHRH, then AI, then Estrogen HD, then stop, then SERM, etc
Increase response: Fulvestrant vs TMX
Prolong response: Changing Hx q 3-6 mo before the appearance of resistance.

*I Cohen et al (Cancer 2002;94:3101-6). Endometrial thickening in postmenopausal women with TMX. Transvaginal US in 328: 55 (16.8%) had progression of thickened endometrium at the second evaluation at 6 months interval from start of TMX and 2/55 had carcinoma + 21 polyps + and 1 hyperplasia with atypia (52% pathologic). Another 46 (14%) had no change from previuos evaluation (14%) and 10/46 had polyps (30%). The rest were normal <5 mm (postmenopausal values). In total, 30% of pts with TMX have > 5 mm.

*L Norton: Start with Exemestane to reduce ER and then give SERM which modulates it. Works better with low ER load!

P Loning et al.(Sem Oncol 2003;30:23-32). PK of AIs. Total body aromatization and serum estrogen leverls lower for Letrozole as compared to anastrazole, indicating more activity. Half life for anatrazole 40.6 h, Letrozole 82.2 h and Exemestane 127 h. Time to steady state 7 d, >14 d and 7 d respectively, and tiome to maximal E2 suppression 3-4 d, 2-3 d, and 7 d. TMX interacts reducing the steady state levels of Anastrazole (27%), Letrozole (38%), so better be given sequentially and not simultyaneously.

G Konesny et al (JNCI 2003;95:142-53). Studied Her2+ and ER/PR+ pts as continuous variables and found that ER/PR have reduced expression in HER2 biopsies suggesting this could be amechanism of resistance.

*S Jones (Sem Oncol 2003;30:14-20). Phase II Fulvestrant 250 mg q 4 wk show a benefit >24% in 69% TMX resitant patients, and MST is doubled as compared with hx TMX series. Phase III studies (USA 0021) Fulvestrant vs Anastrazole demonstrated 30% longer OR and 4.6% mild injection site pain; OR 18% both arms, NC 15-25 %, indicating Fulvestrant better results. And International 0020, again with >400 pts showed OR 20% vs 15% abnd siomilar NC, better for Fulvestrant. Future studies: Combuination of Fulvestrant with Ais, use Fulvestrant in premenopausal and use Fulvestrant as adjuvant therapy.

J Shon et al (JNCI 2004;96:35). TMX given in ER+ PR+ HER2+ cell lines sensitive /resistant to TMX indicated primaery resistance is due to cross-talk between receptors awith activation of AIB1, TKI, ERK1, ERK2, AKT etc. Gefitinib restored sensitivity by eliminating receptor cross-talks!...

****ER+PR- associate with HER1/HER2+ and less response to TMX, benefit from AIs.**

* C Osipo and Craig Jordan (JNCI 2003;95:1597-608). Studied cell lines MCF7E2 (estradiol estimulated) in wich Eastradiol estimulate growth and TMX/ Fulvestrant inhibited growth, and MCF7TAMLT (Tamoxifen estimulation equivalent to 5 y Rx with TMX) in which TMX estimulate growth and Estradiol induce apoptosis (estradiol ERalfa complex interact with NFkB allowing FASL/Fas apoptotic death). Important findings: When TMX induces tumor growth estradiol is required (perhaps it suppresses prosurvival Her2/NFkB inducible factors), and Fas increase, HER/neu decrease and NFkB decrease. Fulvestrant reverses estradiol effect due to regulation of ERalfa activity. It appears that TMX have three treatment phases: Initially tumor grow due to estradiol and respond to TMX or AI (estrogen withdrawal), the begining of resistance phase tumor grows witrh TMX or estradiol but responds to AIs or Fulvestrant, then with advanced resistance (after 5 y TMX) tumor grows with TMX and regress with physiological levels of estradiol but not with Ais or Fulvestrant... Can it be tried clinically?.

A Swerdlow et al, British TMX second cancwer study (JNCI 2005;97:375-84). Cohort study for endometrial cancer risk. Risk was OR=3.6, increasing with time of TMX. Risk did not decrease until 10 y after study entry. Higher mullerain/mixed mesodermal/sarcoma tumor types. Risk was equal for premeno and postmenopausal pts.

A Buzdar (Clin Ca Res 2005;11:906-8). TAS –108, a new steroidal antiestrogen with a high binding affinity for ER and active in TMX resistant cell lines. Showed agonistic activity in bone & cardiovascular systems and no effect upon the endometrium. Recommended dose 40-160 mg/d. On going Phase II and III.

J Ingle et al (JCO 2006;24:1052-6). Fulvestrant after AI/TMX. N=80. OR 14.3% + NC 20.8%, MDR 3 mo, MST 20.2 mo.

D Mauri (JNCI 2006;98:1285-91). Meta-analysis of Aids vs standard therapy for advanced breast cancer (25 trials, N=8504). RH 0.87, compared to TMX RH reduction 11%.

****** B Mory and P Goss (Clin Ca Res 2006;12:4790-3). ER pathways & mechanism of resistance. 1/ Intrinsic resistance: ERBeta, IGF-1R interaction, polymorphismof TMX genes…; 2/ Acquired resistance: TMX acting as a growth factor, upregulation of HER2/AKT pathways (mTOR inhibitor, HER/EGFR inhibitors and TKI –lapatinib, erlotinib, gefitinib or tipifarnib-), complete ER blockade (TMX+AI not better, while AI+ Fulvestrant is OK in preclinical atudies), combination of AI + TKI (so far with >12 trials not good results seen), or finally administer hich dose Estrogen to restore sensitivity…**

E Barrett-Connor et al (NEJM 2006;355:125-37). RUTH TRIAL: RXF 60 mg/d. N= 10.101 postmenopausal. Randomized to placebo. Coronary risk HR 0.95; Breast ca risk HR 0.56, Stroke 1.49, VPTE HR 1.44, Vertebral fractures HR 0.65.

*504. Cytochrome P450 2D6 phenotype +4/+4 correspond to 6.8% of the population. Patients with inhibitors (paroxetine, fluoxetine, sertraline, cimetidine, amiodarone, doxepin and ticlopidine or haloperidol) have poor DFS on TMX (HR 2.5) due to reduction in plasma levels of endoxifen, active metabolite. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

LBA 525. Mets breast cancer ER+ PR+. Atamestane+Toremifene vs Letrozol . N=865. No differences. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

552. Letrozole 2.5 mg po qd suppresses better Estradiol than Anastrazole 1 mg po qd. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

**565. Mets ER+ breast cancer (resistant to TMX or with progression <12 mo after TMX adjuvant) Randomized Celecoxib 400 mg bid + Exemestane vs Placebo + Exemestane. N=157 (continued in spite other trials closed prematurely due to cardiotoxicity). PFS 8.4 vs 4.7 mo. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

H Lane & D Lebwohl (Sem Oncol 2006;33:518-25). Rad 001 (Everolimus, 5-10 mg/d) + Letrozole 2.5 mg/d. mTOR inhibition has shown capacity to restore sensitivity to AI and enhance effect of chemotherapy. It has some sign of activity as a single agent in mets breast cancer. Efficacy trial, N=16, resistant to letrozole.OR: 1 PR and 4 NC. Toxicity mucositis 50%, fatigue 39%, headache 33%, rash 33%, anorexia 39%.

A Bottini et al (JCO 2006;24:3623-8). N=114, elderly, T2-T4 , N0-1, ER+. Randomized Letrozole 2.5 mg/d vs Letrozole + CPA 50 mg/d x 6 mo. OR 71.9% vs 87.7%. Metronomic, possible antiangiogenic effect...

BREAST CANCER –CHEMOTHERAPY

SAGA TAXANOS+GEMCITABINA
Colomer R et al (Ann Oncol 2004;15:201-6) TXL+GEM q 2 wk OR 71% & CR 26%
Fumoleau P (Sem Oncol 2003;30:15-8) TXT+GEM, OR 79% & MTTP 24 mo
Murad et al (Oncology 2003;17:26-32) TXL+GEM , OR 55% MOS 12 mo
Rinaldi et al (AJClin Oncol 2002;25:523-7) TXL+GEM ct rate,
Delfino C (Oncology 204;66:18-23) TXL+GEM, OR 67%, CR 22%, MDR 11 mo
Mavroudis D (Oncology 2004;67:250-6) TXT+GEM, OR 59%, CR 13%, MTTP 11 mo
Estevez LG et al (Sem Oncol 2004;31:31-6) Neadj TXT+GEM, OR 79%, CR 25%

J Braybrooke et al (Clin Can Res 2003;9:4682-8). CDDP 60 mg/m2 + VP civi x 5 to target steady state 1.5 ug/ml. OR 39%. Hematological toxicity >50%. OR is patients with increased Topo I expression.

L Zelek et al (JCO 2002;20:2551-8). N=64, prior DOX & TX. Phase II LOHP 130 mg/m2 d 1 + 5FU 1000 mg/m2 civi d 1-4. OR 27% (26% in prior TX and 36% in anthracycline resistant patients), MTTP 4.8 mo, MOS 11.9 mo.

J O´Shaughnessy et al (Sem Oncol 2003;30:22-6).N=38 HER2 + patients, treated with Herceptin 4 mg/m2 then 2 mg/kg wkly + GEM 1200 mg/m2 d 1 & 8. OR 32%, NC 42%, MOS 10.2 mo.

J O´Shaughnessy et al (Sem Oncol 2002;29:57-62). Alimta 500-600 mg/m2 + Vit B12 1000 ug im q 4 wk + Folic acid 400-800 mg po qd. OR 28%.

F Esteva et al (Cancer 2003;98:900-7). N=39. Exatecan mesylate 0.3-0.5 mg/m2/d x 5 q 3 wk. OR 7.7% + mR/NC 51.3%; MTTP 3 mo, MOS 14 mo. Fatigue, myalgia, paresthesia, N&V.

E Perez et al (JCO 2004;22:2849-55). N=101, after 1-3 regimes with prior TX and anthracycline. Randomized CPT 100 mg/m2 wkly x 4 q 6 (OR 23%, MDR 4.9 mo, MOS 9.7 mo vs CPT 240 mg/m2 q 3 (OR 14%, MDR 4.2 mo MOS 8.6 mo.

***J Chang et al (JCO 2005; 23:1169-77). Pattern of resistance and incomplete response to TXT demonstrated expression of genes related to mTOR survival pathways...Should a combination of TXT and Rapamycin be tried?.**

E Brian (Cancer 2005;103:672-9). Pooled analysis of TX + Anthracyclines, with 7 trials and N=2805 indiceted benefit RR 1.21 in OR, 2.04 in CR and 1.19 in neutropenia. Only trend for OS.

K Miller et al (JCO 2005;23:792-99). N=462. Randomized Xel vs XEL+Bevacizumab OR 9.1% vs 19.8% , PFS 4.8 vs 4.1 and OS 15.1 vs 14.5 no differences...

J Low et al (JCO 2005;23:2726-34). Ixabepilone (BMS 247550, epothilone B analog) Phase II at 6 mg/m2/d x 5 q 3 in N=37. CR 3% + PR 19% + NC 35%. Nweutropenia, fatigue, diarrhea and sensory neuropathy.

M Martz et al (JCO 2005;23:4265-74). Randomized N=186 to HER+TXT vs TXT alone. OR 61% vs 34%, MOS 31.2 vs 22.7 mo, MDR 11.7 vs 5.7 mo.

SE Jones et al (JCO 2005;23:5542-57). N=449. Randomized TXT 100 mg/m2 q 3 (OR 32%, MOS 15.4 mo, and MTTP 5.7 mo) vs TXL 175 mg/m2 q 3 (OR 15%, MOS 12.7 mo, and MTTP 3.6 mo).

***N Ibrahim et al (JCO 2005;23:6019-26). ABI-007 (Albumin bound TXL). Phase II, 300 mg/m2 in 30 min iv q 3 wk. OR 48% (first line 64%). MTTP 26.6 wk, MOS 63.6 wk. No hypersensitivity, 24% hematological toxicity, 11% neuropathy.**

D Toppmeyer et al (Clin Ca Res 2002;8:670-8). Biricodar (VX710, Incel) restores P glucoprotein and MRP1 sensitivity, 120 mg/m2 in 24 h infusion q 3 wk. Study combination with TXL 80 mg/m2 (4 h after Biricodar) in patients with Progressive dx after TXl. N=37. 4 PR (11.4%). MDR 5.5 mo. Resensitization occurred... Try in TX naive patients!.

S Madhusan et al (Clin Ca Res 2004;10:6528-34). Etanercept (TNFalfa inhibitor), 25 mg biwk sq in 16 pts with progressive dx. Decrease in IL6 and CCL2 levels, only 1 NC.

***TXL 90 mg po bid wkly + CsA 10 mg/kg 30 min before TXL: OR 65%, MTTP 6.5 mo. Is this a way to overcome TXL resistance? Could it be investigated in ovarian cancer? (Abst 652 Proc ASCO, 2005; 23)

RPR109881 new taxane in taxane resistant breast cancer OR 41.9% Quite promising. Sanofi. (Abst 565 Proc ASCO, 2005; 23)

K Miller et al (JCO 2005;23:792-9). N=462. Randomized XEL 1250 mg/m2 bid x 14 + BV 15 mg/kg q 3 wk (OR 19.8%, PFS 4.8 mo, OS 15.1 mo) vs XEL alone (OR 9.1%, PFS 4.1 mo, OS 14.5 mo). No differences.

H Gomez et al (Clin Ca Res 2006;12:832-8). N=61. Alimta 500 mg/m2 10 min iv q 3 wk + FA + Vit B12. OR 31% associated to low TS expression.

LBA 516. Herceptin+TXT+CBDCA vs HERCEPTIN+TXT nodifferences. N=226. TTP 11.1 mo vs 10.4. No benefit. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

517. TXL+EPI similar to Xe+TXL (OR 41% in first line therapy). ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

532. TOP2A amplification(12%) and deletion (11.1%) had better response to EPI (OR, DFS and OS). ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

533. TOP2A del/mut in trial of CMF vs CEF demonstrated benefit for EPI. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

651 Ixabepilone 6 mg/m2 d 1-5 q 3 wk in TXN un treated breast cancer: OR 43% (23/43). MTTP 5.3 mo, MDR 5.4 mo. Median acetylated alfa tubulin was 0.2 in responders and 17.6 in non responders. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

661. CPT 100 mg/m2 + GEM d 1&8 1000 mg/m2 q 3 wk. N=51. OR 27%, benefit 36%. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

662. GIMATECAN 4 mg/m2 x 5 q wk x 2 repeated q 4 wk in Anthra-Taxan pretreated breast cancer. OR 27%. Active also in endometrial and NSCLC. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

C Dittrich (Sem Oncol 2006;33:524-8). Alimta single agent 31% OR for ChX naive and 15% previously treated. No clear dose response curve. MRD 600-900 mg/m2. ALT+DOX: OR 13/22, similar with EPI, Phase II studies; ALT + CPA OR 13/50; ALT + GEMd 1 & 8, OR 24%, MDR 5 mo, toxicity was significant; ALT 500 mg/m2 + CBDCA AUC 5 q 3 wk, OR 50% + NC 30%, MDR 7 mo, MTTP 10 mo, Phase II (JCO 2005, 23:515, Abstract, Gari et al.)

V Harvey et al (JCO 2006;24:4963-70) N=527, second line ChX or <6 mo after adjuvant ChX. Randomized study TXT 60 mg/m2, TXT 75 mg/m2 and TXT 100 mg/m2. OR 22%, 23% and 36%, Hemtologic toxicity ¾;: 76%, 83% and 93%, Febrile neutropenuia 4%, 7% and 14%.

C Dittrich et al (Clin Ca Res 2006;12:7071-8). Phase II ALT 600-2400 mg/m2 + CPA 600 mg/m2 q 3 wk in mets breast ca resistant to 2 lines ChX. MTD ALT 2499 mg/m2 + CPA 600 mg/m2. OR 24%. No curve dose effect with increasing ALT doses. Now proceweding to Phase II wuith ALT 600 vs 1800 + CPA 600.

C Geyer et al (NEJM 2006; 355:2733-43). N=274 eval, HER 2+ in Progression after Herceptin+ ADM + TXns. Randomized study LAPATINIB 1250 mg/d po + XEL 2000 mg/m2 d1-14 q 3wk. (OR 22%, TTP HR 0.49, MTTP 8.4 mo, events 49) vs XEL 2500 mg/m2 d 1-14 q 3 wk (OR 14%, MTTP 4.4 mo, Events 72). NO increase in CNS mets, no increase in toxicity.

BREAST CANCER – TARGETED THERAPY

PP Pandolfi (NEJM 2004;351:2337-8). Trastuzumab action is mediated through activation of PTEN pathway blocking AKT→ mTOR activation. When PTEN is mutated there is no response to Trastuzumab. PTEN mutation or loss occurs in 50% breast cancer patients (Nagata et al, Cancer Cell 2004;6:117-27).

A Jones et al (Sem Oncol 2004;31:29-34). Herceptin 8 mg/kg loading & then 6 mg/kg q 3 wk had similar PK, efficacy and safety as compared to the conventional schedule.

M Pegram (JNCI 2004;96:739-41). Studied Herceptin synergy with chemotherapy in 4 HER2+ breast cancer cell lines (SKBR3, BT474, MDA-MB361 & MDA-MB453) and found synergy for TXT, CBDCA, CPA & NVB and additive effect for DOX, EPI, TXL & GEM... (Combine TXT+CBDCA+HER?).

S Johnston et al (JCO 2003;21:2492-9). R11777 (FTI) Phase II 300-400 mg po bid x 21 d q 4 wk: 9/75 PR + 9/75 NC at 24 wk. MRD 300 mg continuous dosing. Intermittent dosing less hematological toxicity (mild).

S Johnston et al (Clin Ca Res 2003;):524-35). Integration of signal transduction inhibitors (STI) with endocrine therapy to overcome resistance. **TKIs**: Iressa up to DLT 800 mg/d, now on going studies in TMX resistant +/- Iressa; Tarceva 150 mg continuously; CI-1033 (panerbB inhibitor 175-200 mg qd. **FTIs** Lonafarnib, Sarasar SCH66336; R115777 (Zarnestra) Phase II in breast cancer OR 24%, now studying Zarnestra + Letrozole. **Others** RAF/MEK kinase inhibition and cell cycle inhibition.

M Cobleigh et al (Sem Oncol 2003;30:117-24). Bevacizumab Phase I-II 3-20 mg/kg iv qow. Recommended dose 10 mg/kg qow, higher doses headache, hypertension (22%). OR 9.3% (1CR+3PR). At 6 mo 16% NC. Recommend to initiate combination studies with chemotherapy.

J Green (Cancer 2003;97:840-7). Nitrogen conatining biphosphonates (Pamidronate, Ibandronate, Zoledronic acid) inhibit function and cell survival in utmor cells through protein prenylation inhibition.

500. Serum HER2 measured by Elisa shows >20% decrease after herceptin correlated with benefit (56.5% OR and OS 898d vs 28.4% and 593d when <20% decrease). ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

*501. KOS 953 (17 AAG in cremophor) inhibitor of Hsp 90 (Hsp90 degrades Her2) 450 mg/m2, given 2 h iv after Herceptin. N=17 resistant to Herceptin: 1 PR + 3 mR+ 5 NC (MDR 5-12+ mo). On going Phase II study. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

*502. Inflammatory breast cancer. Lapatinib (inhibitor erbB1 & 2 TKI) 1500 mg/d. N=17 relapsed /refractory . Overexpressors of ErbB1/B2 OR 8/11 (72%) while non expressors 0/6. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

**503. Lapatinib 750 mg bid in N= 17 patients with CNS mets from breast cancer HER2+ on Herceptin. 2PR + 1 mR + 5 NC. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

577. BAY43-9006 (antiVEGFR2, VEGFR3 & PDGFRB) inactive in mets breast cancer (benefit OR+NC 15%). ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

BREAST CANCER – INTENSIFICATION & STEM CELL TRANSPLANTATION

Y Nieto et al (JCO2002;20:707-18). Review prognostic factors favorable for Stage IV oligometastasic breast cancer in 60 pts. MRFS 52 mo, MOS 80 mo., 5yRFS 52%, 5yOS 62%. HER2 expression and % affected ly n o (30%) were significant while number of tumor sites, number of axillary + nodes, and RT to mets sites were not significant. Score: 0 factors RFS 77%, Med RFS 80 mo; One factor RFS 41%, med RFS 28 mo; and Both factors RFS 10%, med RFS 10 mo.

D Berry et al, CALGB (JCO 2002;20:743-50). Compared the large database of 4 CALGB randomized studies using standard dose chemotherapy for metastasic breast cancer (N=1509) and IBMT Registry data (N=1188). Found no differences in overall survival at 1-4 years and a higher probability for 5y OS (23% vs 15%) favoring HD therapy (modest difference).

A Tartarone et al (BMT 2003;31:525-30). Review adjuvant HD Chx: 6/7 randomized trials showed benefit in DFS and longer interval to recurrence favouring HDChx (8 mo MDFI). NO differences observed in survival but <220 pts is the lñargest trial, and this number precludes any significancy!.

M Tallman et al (NEJM 2003;349:17-26). N=540. Adjuvant HD ChX in pts with > 10 ly no+. Randomized CAF (DOX d 1 & 8) x 6 vs CAF x6 followed by HD ChX (CPA-ThTPA-SCT) and found longer DFS, no diff in OS, reduced relapse risk. 10 y OS 60%, 10 y DFS 45%.

S Rodenhuis et al (NEJM 2003;349:7-16). N=885, Mfup 57 mo. Pts with > 4 ly no+. Randomized FEC q 3w x 5 then RT-TMX (5 yRFS 59%, 51% if >10 ly no+) vs FEC q 3 x 5 followed by HD ChX COPA-ThTPA-CBDCA (5yRFS 65% , 61% if > 10 ly no+. Benefit in Her2- tumors.

AR Zander et al (JCO 2004;22:2273-83). N=307, Mfup 3.8 y. EPI, 90 mg/m2 + CPA 600 mg/m2 q 3 w & the Randomized to CMF d 1 & 8 standard q 4 wk x 3 vs HDChX CPA-ThTPA-MTZ. HR recurrence 0.75, HR OS No differences. Better event free survival.

665. Tandem HD ChX vs Dose dense ChX. N=236, >9 ly no+. Retrospective analysis: Large benefit in young, poorly differentiated, > 2 cm, negative ER/PR, p53+ and bcl2-. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185)

Adjuvant HD therapy. N=539 pts, >4 ly nodes. ADM 80 mg/m2+TXL 200 mg/m2+CPA 3 g/m2 + GCSF x3 vs conventional x 4 then STAMP IV. No differences observed. (Abst 572 Proc ASCO, 2005; 23)

BREAST CANCER – IMMUNETHERAPY

G Peoples et al (JCO 2005;23:7536-45). E 75 (369-377, KIFGSLAFL) immunogenic peptide fro HER2/neu protein associated to GM-CSF in HLA-A2 patients: 53 treated and 29 cohort controls. Minor toxicity, all had clonal expansion of E 75 specificity, DHS not present, DFS 85.7% vaccine vs 59.8% controls at 22 mo. Recurrence rate 89% vs 21 %. Safe and possibly effective.

631. HER2 vaccine 500 ug x 5 in 14 wk. Ab response 14/15, and cytotoxic specific T cells were obtained. 2 OR in mets patients. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

P Kiewe et al (Clin Ca Res 2006;12:3085-91) Ertumaxomab (AntiHER2 + Anti CD3 + Fcgamma type I/III receptor binding (trifunctional Mo Ab) given at 10-200 ug d 1 and 13. N=15. MTD 100 ug. Fever 94%, headache 35%, lymphopenia 76%, liver enzyme alterations 47%. OR:5/15, 1 CR and 2 PR. T1H1 increased, HAMA 31%. Active.

E Mittendorf et al (Cancer 2006;106:22309-17). E75 (KIFGSLAFL, Her2 369-377) and GP2 (IISAVVGIL, Her2 654-662) both HLA-A2 restricted peptides. Both stimulated T8 and killed cell lines with HER2 target expression. Cvombined were additive. GP2 recognized 2VGP2 loaded target variants.

BREAST CANCER – QOL

T Guttuso et al (Lancet 2003;361:1703-5). Gabapentin 300 mg tid controlled nausea and vomiting from chemotherapy in 6/9 patients treated with AC.

***C Carati et al, Adelaide, South Australia (Cancer 2003;98:1114-22). Low level laser therapy for breast cancerlymphedema of the arm. Class I laser 904 nm laser beam, averages output 5 mW from heads of 0.2 cm2. Grid of 17 points separated 2 cm in axilla, treat 1 minute per point, 300 mJ/cm2 delivered at the 17 points (total 1.5 J/cm2. Results from randomized study compared to placebo showed 84% improvement!.**

R Chlebowski et al DFCI (Sem Oncol 2003;30:776-88). Estrogen deficiency management: **Active/risky**: estrogens, megestrol acetate, medroxyprogesterone. **Active without risk**: Venlafaxine 37.5-75 mg/d, Fluoxetine 20 mg/d, Paroxetine 10-20 mg/d, Gabapentine 300-900 mg/d (combine with Venlafaxine?), Clonidine 0.1 mg/d patch, Velaripride 100 mg/d, Bwellergal qd. Non active: Herbs: Evening primrose, angelia sinensis, soy, wild yam, Vit E, Exercise, Behavioural therapy.

*P Pommier et al (JCO 2004;22:1447-53). Randomized study comparing Trolamine and Calendula officinalis in radiodermitis. Benefit for calendula in acute signs grade >2 41% vs 63% incidence!.

*N Germann (Ann Oncol 2004;15:146-50). Use of anthracycline in first trimester pregnancy. N=160. Malformation 3%, Fetal death 9%, spontaneous abortion 3%, fetal complications 8% and prematurity 6%. Factors of risk: Dx of leukemia, first trimester, antharacycline dose per cycle >70 mg/m2.

*636. Internet self reporting double blind trial: SOY ISOFLAVONE 160 mg qd vs PLACEBO for hot flashes. No differences. Served to identify triggers of hot flashes and allowed better symptom control. ASCO 42ND Annual Meeting Atlanta (GA) June 2-6, 2006 (JCO suppl 24:185

JI Body et al (Clin Ca Res 2006;12:1221-8). Denosumab (Mo Ab to RANKL- ligand of NFkB) inhibits osteoclast was compared to Pamidronate showing bone resorption inhibition up to 84 d.

M McClung et al (NEJM 2006;354:821-31). N=412, low bone mineral density (lumbar spine –1.8 to –4% and hip –0.8 to –3.5%). Randomized to Denosumab 30 mg q 3 mo (improvement lumbar 3-

6.7%, hip 1.9-3.6%); Alendronate (4.6% and 2.1% respectively) and placebo (0.8% and 0.6% respectively). Similar activity.

D Grady (NEJM 2006;355:1338-47) Menopausal therapy: Paroxetine 10-20 mg (30% improvement compared to placebo), Venlafaxine 75-150 mg (34% improvement respect to palcebo), Gabapentin 300 mg tid (31% improvement respect to placebo). Vaginal cream: Estring (17 beta estradiol) 0.0075 ug/d inserted q 3 mo; Vaginal moisterizer