271 ORAL

### Survival advantage of exemestane (EXE, Aromasin®) over megestrol acetate (MA) in postmenopausal women with advanced breast cancer (ABC) refractory to tamoxifen (TAM): Results of a phase III randomized double-blind study

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EXE is a new steroidal, irreversible aromatase inactivator developed for palliative and adjuvant therapy of breast cancer. In this phase III study, 769 postmenopausal TAM-refractory ABC patients (pts) were randomized to 25 mg/day EXE (366 pts) or 40 mg q.i.d. MA (403 pts). The two groups were balanced for baseline characteristics and prognostic factors: performance status, hormone receptor status, sites of disease (visceral: EXE 57%, MA 58%) and measurable disease (78% both groups). Intent-to-treat, peer-reviewed efficacy results follow below.

| Response Characteristics | EXE (N = 366) | MA (N = 403) | p |
|---|---|---|---|
| CR + PR; % (95% CI) | 15 (12–19) | 12 (9–16) | |
| Overall success; % (95% CI) | 37 (32–43) | 35 (30–40) | |
| Time-Dependent Parameters | | – median; months (95% CI) | |
| Duration of CR + PR | 17.5 (13.9–30.1) | 16.3 (11.9–19.3) | NS |
| Duration of overall success | 13.8 (11.7–16.6) | 11.3 (10.5–14.0) | 0.025 |
| Median time to progression | 4.7 (3.7–5.7) | 3.8 (3.6–5.3) | 0.037 |
| Overall survival | not reached (28.1-i) | 28.4 (22.8-i) | 0.039 |

Overall success rate (CR+ PR + NC ≥ 24 weeks), i = not yet estimable, NS – not significant

The most common (≥5%) drug-related adverse events (usually grade 1–2) were (%): EXE – hot flushes (12.6), nausea (9.2) and fatigue (7.5); MA – fatigue (10.3), increased sweating (7.5), increased appetite (5.8), nausea (5.0) and hot flushes (5.0). Grade 3–4 events (%): EXE 4.7, MA 7.5; drug-related treatment withdrawals (%): EXE 1.4, MA 2.5; drug-related deaths (%): EXE 0, MA 0.7. Weight change ≥10% pts: EXE 7.6%, MA 17.1% (p = 0.001).

**Conclusion:** EXE is a well tolerated aromatase inactivator that significantly delays tumor progression and significantly prolongs survival compared to MA in postmenopausal pts with ABC refractory to TAM.

## Breast cancer & predictive factors

272 ORAL

### Estrogen receptor-beta: A new form of estrogen receptor in breast cancer

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The female hormone, estrogen mediates its multiple effects via binding to the nuclear transcriptional factor estrogen receptor (ER). For many years the ER status of breast cancer has been used both as a predictor of response to hormone therapy and as a prognostic indicator. Recently, a new form of ER known as ER-beta, was described. The aims of this study were to investigate the distribution and possible clinical significance of this new form of ER in breast cancer. The classical ER (now known as ER-alpha) and ER-beta were measured using RT-PCR.

ER-beta expression was found in 26/51 (51%) whereas ER-alpha was present in 37/51 (73%) of primary breast cancers. No correlation was found between either the presence or level of ER-alpha or ER-beta, suggesting independent expression of the 2 receptor forms. ER-alpha (r = 0.45, p = 0.0021, n = 48) but not ER-beta levels correlated significantly with levels of ER protein as determined by ELISA (Abbott Diagnostics: ER-EIA). Furthermore, ER-alpha but not ER-beta was found more frequently in carcinomas positive for ER protein than those negative for the protein (Chi square = 12.2, p = 0.0005)

We conclude that ER-beta is expressed in approximately 50% of primary breast carcinomas and that this expression appears independent of ER-alpha. Finally, the routinely used ELISA for detecting ER appears to primarily measure the ER-alpha form.

273 ORAL

### HER2/neu as a predictive factor in breast cancer

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Oncologists are currently overwhelmed by the rapidly expanding literature on the claimed predictive or lack of predictive value of HER2/neu. We have adapted the published ASCO scale (J Clin Oncol 1996; 14: 2843) in order to use more relevant criteria for the interpretation of predictive marker studies, which can be classified as level I–V studies according to decreasing levels of evidence. Of seven studies involving 924 patients, five found the marker to be associated with hormone resistance in metastatic breast cancer (MBC). The level of evidence was II for only two studies and level I for none of them. Two published studies (levels III/V) also suggest that HER2/neu may predict for resistance to adjuvant tamoxifen in early breast cancer.

The value of HER2 in predicting response to chemotherapy (CTX) is more confusing. Of six studies in MBC with level III to V evidence, involving 712 patients, only two found that the response rate to various CTX regimens differed between HER2-positive and HER2-negative patients.

In the two large CMFP-based adjuvant studies the marker was found to predict for a relative resistance to CMF (levels II/III), while the two largest anthracycline-based adjuvant trials involving a comparison indicated that, as a group, HER2-overexpressing tumours are anthracycline responsive (level II for both).

**Conclusions:** The available studies suggest that adequately dosed anthracycline-based regimens are effective therapy for HER2-positive patients; additional level I/II studies are needed to clarify potential interactions between HER2 and hormonal therapy or CMF. The implications of these results for daily clinical practice will be discussed.

274 ORAL

### Cytokeratin (CK)-positive bone marrow micrometastases (BMM) and survival in stage I–III breast cancer

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**Purpose:** Independent data seriously questioned the use of polymorphic epithelial mucins (ie, EMA, HMFG, TAG-12) as markers for the detection of BMM. In contrast, CK has been recently established as alternative detection marker for such cells in several tumor entities. Since only limited information has been thus far available on the clinical relevance of CK⁺ BMM in breast cancer, we investigated whether the detection of such cells is correlated with early tumor recurrence and poor prognosis.

**Methods:** In a prospectively planned study, we analyzed BM specimens from 506 patients with stage I–III breast cancer and completely resected tumors (stage R0). We applied the monoclonal antibody A45-B/B3 directed against CK to detect tumor cells, and evaluated 2 × $10^6$ BM cells per patient. The median follow-up time of cancer patients time was 30 months (range, 8–68).

**Results:** CK⁺ BMM were detected in 183 (36%) of 506 breast cancer patients. This finding was significantly correlated with the diagnosis of inflammatory breast cancer (P < 0.0001), poor nuclear grading of the primary tumor (P = 0.042), and metastasis to >9 lymph nodes (P < 0.0001), but not with the overall presence of lymph node metastases (P = 0.21). At the time of follow-up, DFS and OS rates in CK⁺ BMM patients were 28% and 65%, respectively, as compared to 75% and 92% in 323 negative patients (P < 0.0001; log-rank test). Despite a short observation time, in both groups, the node-negative and node-positive patients, BMM were associated with a significantly decreased OS (P = 0.028 and P = 0.0005, respectively). In multivariate analysis, the presence of BMM, but not of lymph node metastases, was an independent prognostic parameter with a 2.51-fold increased relative risk of cancer-related death (P = 0.0028).

**Conclusions:** Immunocytochemical detection of CK⁺ BMM is a prognostic tool in stage I–III breast cancer.