7LBA LATE BREAKING ABSTRACT

A 5-fraction regimen of adjuvant radiotherapy for women with early breast cancer: first analysis of the randomised UK FAST trial (ISRCTN62488883, CRUKE/04/015)

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Background: Hypofractionated breast radiotherapy (RT) based on 13 or 15 fractions was shown by the START trial to be as safe and effective as 50 Gy in 2.0 Gy fractions (Fr). This trial evaluates hypofractionation further, testing 5 Fr of 5.7 Gy and 6.0 Gy whole breast RT against 25 Fr of 2.0 Gy (FAST trial ISRCTN62488883, sponsor The Institute of Cancer Research).
Methods: Inclusion criteria: age >50 years, invasive carcinoma, breast conservation surgery, pathological tumour <3 cm, clear margins, pathologically node negative. Exclusion criteria: cytotoxic chemotherapy, lymphatic RT, breast boost. Patients were randomised to 50 Gy in 25 Fr (2.0 Gy) or to 28.5 Gy (5.7 Gy) or 30 Gy (6.0 Gy) in 5 once-weekly fractions. 3D dosimetry (95–107%) was required for all patients. Patients had photographs of both breasts pre-RT and at 2 & 5 years, with annual clinical assessments of adverse effects and local tumour control. Primary endpoint was 2-year change in breast appearance assessed by comparison with baseline photographs scored on a 3-point scale (none, mild or marked). Clinical assessments of adverse effects were scored on a 4-point scale (none, mild, moderate or marked). Comparisons used c^2 trend test for photographs and survival analyses of clinical assessments of adverse effects (year 2 onwards).
Results: 915 patients were recruited from October 2004-March 2007. Mean age = 62.7 years; ductal histology = 71%; tumour grade 1+2 = 88%; endocrine therapy = 89%. Median follow up was 28.3 months. Only 17 patients (5.2%) developed moist desquamation (12 in 50 Gy, 3 in 30 Gy, 2 in 28.5 Gy) out of 327 with RTOG skin toxicity data available. 686 patients had 2-year photographic assessments, with mild and marked change in breast appearance in 18.8% and 1.7% after 50 Gy, 24.1% and 9.1% after 30 Gy, and 20.0% and 4.0% after 28.5 Gy. Risk ratios for mild and marked change for 30 Gy vs. 50 Gy were 1.39 (95% CI 0.98–1.97) and 5.55 (1.94–15.84), $p < 0.001$; and for 28.5 Gy vs. 50 Gy were 1.09 (0.75–1.58) and 2.33 (0.73–7.42), $p = 0.22$. Any clinically-assessed moderate/marked adverse effects in the breast were increased for 30 Gy compared with 50 Gy (hazard ratio, HR 2.12, 95% CI 1.34–3.36, $p = 0.001$), but similar for 28.5 Gy (HR 1.02, 95% CI 0.60–1.73, $p = 0.94$). To date, 2 local tumour relapses have been recorded.
Conclusions: 28.5 Gy in 5 Fr in 5 weeks of whole breast RT appears as safe in terms of adverse effects (assessed clinically and by photograph) as a standard 25-fraction schedule at this stage in follow up.

1LBA LATE BREAKING ABSTRACT

Impact of regional hyperthermia (RHT) on response to neo-adjuvant chemotherapy and survival of patients with high-risk soft-tissue sarcoma (HR-STS): Results of the randomized EORTC-ESHO intergroup trial (NCI-00003052)

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Background: We reported preliminary results at ASCO 2007 (J Clin Oncol 25:abstr. 10009) that RHT improves the outcome in patients (pts) with localized, advanced HR-STS who were treated with neo-adjuvant chemotherapy. An update for primary and secondary endpoints has been performed including analysis of therapy-induced responses and survival prolongation as reported in our previous phase 2 study in an non-overlapping patient population with retroperitoneal and visceral HR-STS (Wendtner et al. J Clin Oncol 2002;22:3156−64).
Methods: Pts with HR-STS (⩾5 cm, FNCLCC grade 2/3, deep and extra-compartmental) were randomized to receive EIA (etoposide 250 mg/m^2, ifosfamide 6 g/m^2, adriamycin 50 mg/m^2, 4 cycles every 3 weeks) alone or EIA combined with RHT prior and after local therapy (surgery and radiotherapy). The primary endpoint was local progression-free survival (LPFS). Based on a sample size of 340 pts, the trial had 80% power to detect 34% risk reduction (Hazard ratio = 0.66) with a median LPFS improvement from 30 mo to 43 mo (stratified log-rank test). Secondary endpoint included objective response rates (ORR), time to progression (TTP), disease-free survival (DFS), and overall survival (OS).
Results: Between July 97 and November 2006, 341 pts were randomized and eligible for intent-to-treat analysis (ITT). By December 1, 2008, after median follow-up of 34 mo 217 events (63.6%) have occurred for DFS and 153 events (44.9%) for OS. The analysis confirmed the significant superiority of EIA + RHT in regard to LPFS (Hazard ratio = 0.58; CI 95 = 0.41–0.83, P = 0.003), median DFS (EIA + RHT: 32 mo; EIA: 18 mo; P = 0.011) and TTP (P = 0.006). In the ITT population improvement in OS was not significant (P = 0.43). EIA induction therapy increased ORR from 12.7% to 28.8% by the addition of RHT (P = 0.002). Among 269 pts (78.9% of the ITT population) who completed the initial 4 cycles for their assigned induction therapy (per-protocol-induction population), OS was significantly improved in the EIA + RHT group (Hazard ratio for death = 0.66; P = 0.038).
Conclusion: This is the first – and the only completed – randomized study on neo-adjuvant chemotherapy in HR-STS showing that the addition of RHT significantly improves ORR, TTP, LPFS, and DFS. The results on improvement in OS could validate the prespecified analysis of an earlier phase 2 study.
Supported by Deutsche Krebshilfe and Helmholtz Association (VH-VI-140), Clinical Hyperthermia and Related Technology

2LBA LATE BREAKING ABSTRACT

Denosumab versus zoledronic acid for the treatment of breast cancer patients with bone metastases: results of a randomized phase 3 study

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Bone metastases (BM) from breast cancer induce local bone destruction by increasing osteoclast activity, resulting in skeletal complications. The fully human monoclonal antibody denosumab inhibits RANKL, a key mediator of osteoclast activity. In this double-blind study (Clinicaltrials.gov NCT00321464; sponsored by Amgen Inc and Daiichi Sankyo Co, Ltd), we compared the effects of denosumab versus zoledronic acid (ZA) for the incidence of skeletal-related events (SREs) in patients with breast cancer metastatic to bone.
Eligible patients with BM were randomized to receive either subcutaneous (SC) denosumab 120 mg and intravenous (IV) placebo (N = 1026), or SC placebo and IV ZA 4 mg adjusted for creatinine clearance (N = 1020) every 4 weeks (Q4W). Patients who received prior bisphosphonate (BP) therapy for BM were excluded; prior oral BP for osteoporosis was permitted, but was required to be discontinued before study initiation. All patients were strongly recommended to take calcium (⩾500 mg) and vitamin D (⩾400 IU) supplements. The primary endpoint was time to first on-study SRE (predefined as pathologic fracture, radiation or surgery to bone, or spinal cord compression).
Denosumab significantly delayed the time to first on-study SRE compared with ZA (hazard ratio [HR] 0.82; 95% CI: 0.71, 0.95; $P = 0.01$) in this 34-month study. The median time to first on-study SRE was not reached for denosumab and therefore could not be estimated. The median time to first on-study SRE was 806 days for ZA. Denosumab also significantly delayed the time to first and subsequent on-study SRE (multiple event analysis) compared with ZA (HR 0.77; 95% CI: 0.66, 0.89; $P = 0.001$). Rates of adverse events (AEs; 96% denosumab, 97% ZA), infectious AEs (46% denosumab, 49% ZA), serious AEs (44% denosumab, 46% ZA), and infectious serious AEs (7% denosumab, 8% ZA) were similar for both treatment arms. Osteonecrosis of the jaw occurred infrequently (20 [2.0%] denosumab, 14 [1.4%] ZA; $P = 0.39$). AEs potentially associated with renal

toxicity occurred in 4.9% of the denosumab arm and in 8.5% of the ZA arm. Overall survival (HR 0.95; 95% CI: 0.81, 1.11; $P = 0.50$) and time to cancer progression (HR 0.99; 95% CI: 0.89, 1.11; $P = 0.90$) were balanced between treatment arms.
Denosumab was superior to ZA in delaying or preventing SREs. The incidence of AEs and serious AEs was consistent with what has been previously reported for these two agents. This study continues as an open-label study with denosumab.

Presidential session III
Wednesday 23 September 2009, 12.30–14.30

3BA BEST ABSTRACT

Randomized MRC OV05/EORTC 55955 trial in recurrent ovarian cancer: early treatment based on increased serum CA125 alone versus delayed treatment based on conventional clinical indicators

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Background: Although CA125 often rises several months before recurrent ovarian cancer (OC) it was unknown whether early treatment (ET) based on increased CA125 alone is beneficial. In the MRC OV05/EORTC 55955 trial we investigated the benefits of ET based on increased CA125 versus delayed treatment (DT) based on clinical progression.
Methods: OC patients (pts) in CR after first-line platinum-based chemotherapy and normal CA125 were registered. Every 3 months (m) CA125 was measured and a clinical examination was performed. CA125 was blinded for the doctors and pts. The Trials Units monitored CA125. At a rise of CA125 >2× upper limit of normal, pts were randomized to ET vs. DT. Second-line therapy was according to standard local practice in both arms. Primary endpoint was OS, secondary endpoints were time to third-line therapy or death and quality of life (QoL).
Results: 1442 Pts were registered and 529 pts (265 ET, 264 DT) were randomized. Not randomized 913 pts: no relapse and normal CA 125 (29%), relapse without CA125 rise (15%), simultaneous relapse and CA125 rise (4%), death (4%), pt withdrawal (9%), other reasons (2%). Baseline characteristics were well balanced between the two arms. Median age was 61 years, 81% had FIGO stage III/IV.
Treatment: 96% ET vs. 88% DT pts received second-line therapy and 64% ET vs. 51% DT received ⩾6 cycles. Third-line therapy was administered in 67% ET vs. 54% DT, p = 0.0001. In the ET second-line therapy started median 4.8 m, and third-line median 4.7 m earlier (ET 12.5 m and DT 17.1 m, p < 0.0001). After median follow up of 57 m and a total of 370 deaths there was no difference in OS between the ET (25.7 m) and DT (27.1 m).
No improvement in QoL was observed by ET, median time of good QoL was 7.1 m for ET vs. 9.2 m for DT (p = 0.20) and time to first deterioration in global health score was 3.1 m for ET and 5.8 m for DT (p = 0.001) with significant disadvantage for fatigue 2.6 m ET vs. 6.1 m DT (p < 0.0001), role function 3.5 m ET vs. 6.0 m DT (p < 0.006) and social function 4.1 m ET vs. 8.6 m DT (p = 0.003).
Conclusions: There is no benefit from ET based on a raised serum CA125 alone. Survival in ET is the same as in DT at the cost of a shorter TFI, more chemotherapy and worse QoL.

4BA BEST ABSTRACT

A randomized phase III study comparing epirubicin, docetaxel, and capecitabine (EDC) to epirubicin and docetaxel (ED) as neoadjuvant treatment for early breast cancer – first results of the Austrian Breast and Colorectal Cancer Study Group-Trial 24 (ABCSG-24)

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Background: Neoadjuvant treatment of early breast cancer aims at achieving high rates of pathological complete responses (pCR) since pCR might be a surrogate for effective eradication of micrometastatic disease leading possibly to prolonged overall survival. Capecitabine showed synergistic effects when combined with D in the palliative setting.
Materials and Methods: Primary aim of ABCSG-24 is to evaluate the influence of 6 cycles of EDC (experimental group) as compared to 6 cycles of ED (control group) in terms of the achievable rate of pCR at the time of surgery. 536 patients (268/group incl. a 5% dropout rate for 510 eligible patients) had to be accrued to the study in order to detect a difference in the rate of pCR of 16% (control group) vs. 27% (experimental group) with a power of 83% at a significance level of 0.05 (two-sided Chi-squared test). Patients with HER2 positive tumors (n = 94) where additionally randomized to receive neoadjuvant trastuzumab (T) or not. The results of the influence of neoadjuvant T in combination with EDC or ED will be available at a later time. Between 11/2004 and 11/2008 536 patients with biopsy proven operable breast cancer of any clinical T-stage (except T4d) +/− nodal involvement and without distant disease in whom neoadjuvant treatment was scheduled were stratified according to known risk factors and randomized to receive either 6 cycles of EDC every 21 days (E: 75 mg/m ^{2} i.v. and D: 75 mg/m^2 i.v. on day 1, pegfilgrastim 6 mg sq on day 2, C: 2 × 1000 mg/m^2/day for 14 days orally) or 6 cycles of ED (identical treatment regimen without C). Patients with HER2 positive tumors were also randomized to receive neoadjuvant T 8 mg/kg i.v. on day 1 followed by 6 mg/kg every 21 days or to receive no T.
Results: 512 patients are currently eligible for toxicity and efficacy. In the intention to treat analysis there was no significant difference in the incidence of serious adverse events (EDC: 26.3% vs. ED: 21.1%, p = 0.16). When capecitabine was added to ED significantly more patients had documented pCR (EDC: 61/256, 23.8% vs. ED: 39/256, 15.2%; p = 0.036) despite the fact that significantly less patients completed the scheduled 6 cycles (EDC: 75% vs. ED: 97%, p < 0.0001) mainly due to capecitabine-induced side effects.
Conclusions: Neoadjuvant EDC in early breast cancer results in a significantly higher pCR rate than ED. EDC is a feasible and safe regimen but capecitabine induced toxicity must be monitored closely.

3LBA LATE BREAKING ABSTRACT

SOLTI-0701: A double-blind, randomized phase 2b study evaluating the efficacy and safety of sorafenib (SOR) compared to placebo (PL) when administered in combination with capecitabine (CAP) in patients (pts) with locally advanced (adv) or metastatic (met) breast cancer (BC)

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Background: SOR is a potent multi-kinase inhibitor with antiangiogenic and antiproliferative activity approved for use in renal and hepatocellular cancer. To study the potential benefits of SOR in BC, we have conducted a phase 2b trial of SOR in combination with CAP for adv BC.
Methods: SOLTI-0701 was a double-blind, randomised, PL-controlled phase 2b study in pts with locally adv or met BC. Eligibility criteria included HER-2 negative tumours and <2 prior chemo regimens for adv/met BC. Pts with active brain metastasis were excluded. Pts were randomised (1:1) to receive CAP (1000 mg/m^2, orally, twice daily [BID], for 14 of every 21 days) with PL or SOR (400 mg orally BID continuously). Randomisation was stratified by visceral vs nonvisceral disease. The primary endpoint was PFS and secondary endpoints included: OS, TTP, RR, response duration, and safety. Disease assessments occurred every 6 wks for the first 24 wks of the study and then every 9 wks thereafter. A sample size of 220 pts was planned to detect the targeted HR of 0.65 (90% power and 1 sided a = 0.14). The study is registered at EudraCT (ID 2007–000290−32).
Results: Accrual was achieved over 15 mos with 229 pts enrolled (114 CAP+PL, 115 CAP+SOR). Treatment arms were balanced for age (median 55 y), ECOG (status 0, 68%), stage (IV, 91%), visceral (75%), and hormone-positive (73%). Prior chemotherapies: anthracyclines: 89%; taxanes 60%. By investigator assessment, the median PFS of CAP+PL vs CAP+SOR was 4.1 mos vs 6.4 mos; HR 0.576 (95% CI: 0.410, 0.809), $P = 0.0006$, overall RR was 31% (CAP+PL) vs 38%. OS data are pending. No treatment-related deaths in the SOR arm and 1 treatment-related death in the PL arm attributed to CAP. Toxicities of Gr 3 or 4 (CAP+PL vs CAP+SOR) included hand-foot skin reaction (HFSR) (13% vs 45%),