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.
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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