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%),

diarrhoea (5% vs 5%), dyspnoea (4% vs 5%), neutropaenia (3% vs 5%), mucositis (4% vs 1%), and others less frequently. The no. of pts discontinuing treatment due to adverse events in the CAP+PL arm was 9 (8%) and in the CAP+SOR arm was 15 (13.4%). The most common reasons for discontinuation (CAP+PL vs CAP+SOR) include HFSR (2 vs 8) and diarrhoea (3 vs 1).
Conclusions: In this randomised double-blind phase 2 trial, the oral combination of CAP+SOR demonstrated significant improvement in PFS in pts with locally adv or met BC. The regimen was tolerable and exhibited a clinically manageable toxicity profile. No new or unexpected side effects were observed with this combination. These results represent the first randomised study to demonstrate the efficacy of SOR in the treatment of adv BC.

4LBA LATE BREAKING ABSTRACT

Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated vs conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC)

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Background: Accelerated radiotherapy counteracts repopulation of tumor cells during treatment and may significantly improve local control and survival in patients with locally advanced NSCLC (CHART-trial, Saunders 1997). Nevertheless local failure rates $\geqslant$80% call for radiation dose escalation, using conformal techniques. We report here the final results of the CHARTWEL trial (CHART weekend less).
Patients and Methods: Between 1997 and 2005 406 pts. with NSCLC were randomized by 15 centres in Germany, Poland and Czech Republic. Inclusion criteria: UICC stage (I: 10%, II: 6%, IIIA:38% IIIB:46%), WHO performance 0−1. Randomization was stratified according to stage, histology, neoadjuvant chemotherapy (CTx; no = 300/yes = 106) and center. All patients were treated with 3D RT using a linear accelerator to 60 Gy/40 f/2.5 w (CHARTWEL) or 66 Gy/33 f/6.5 w (CF). The trial was carried out within the Arbeitsgemeinschaft Radioonkologie (trial # ARO 97-1) of the Deutschen Krebsgesellschaft and sponsored by the Deutsche Krebshilfe.
Results: Intent-to-treat analysis did not reveal significant differences of overall survival (primary endpoint) at 2, 3 and 5 yrs after CHARTWEL (31%, 22% and 11%) vs CF (32%, 18% and 7%; HR 0.92, 95% CI 0.75–1.13, p = 0.43). Also local tumor control rates (LC; HR 0.86; 0.68–1.09; p = 0.22) and distant metastasis rates (HR 1.06; 0.78–1.44; p = 0.71) did not significantly differ between the arms. Acute dysphagia was more pronounced after CHARTWEL. Pneumonitis determined by imaging was increased after CHARTWEL, without clinical differences. Exploratory analysis revealed a significant trend for improved LC after CHARTWEL vs CF with increasing UICC, T or N stage (p = 0.006–0.025) and after CTx (HR 0.48, 0.26–0.89, p = 0.019).
Conclusions: OS and LC were not significantly different after CHARTWEL and CF in the overall trial population. The impact of higher total dose in CF on LC was compensated by the shorter overall treatment time in CHARTWEL. This confirms a time factor of fractionated radiotherapy in NSCLC, and cautions treatment prolongation. The efficacy of CHARTWEL vs CF was higher in advanced stages and after CTx. From this we hypothesize that CHARTWEL after neoadjuvant CTx is a promising avenue to intensify treatment of locally advanced NSCLC which may overcome current limitations by toxicity of simultaneous radiochemotherapy.

5LBA LATE BREAKING ABSTRACT

First efficacy findings from a randomized phase III trial of capecitabine + oxaliplatin vs. bolus 5-FU/LV for stage III colon cancer (NO16968/XELOXA study)

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Background: Adjuvant capecitabine is at least equivalent to bolus i.v. 5-FU/LV in disease-free survival (DFS) and overall survival (OS) in stage III colon cancer [Twelves et al. NEJM 2005; ASCO GI 2008]. Phase III clinical trials in 1st- and 2nd-line metastatic colorectal cancer have shown that capecitabine + oxaliplatin (XELOX) is as effective and safe as oxaliplatin + infusional 5-FU/LV [Cassidy et al. JCO 2008; Rothenberg et al, Ann Oncol 2008; Ducreux et al. ASCO 2007; Diaz-Rubio et al. JCO 2007; Porschen et al. JCO 2007]. NO16968 was designed to compare the efficacy and safety of XELOX with bolus i.v. 5-FU/LV (the standard regimen at study start) for stage III colon cancer. In a planned safety analysis, XELOX had an acceptable safety profile in this setting [Schmoll et al. JCO 2007].
Materials and Methods: Patients were randomized to receive either XELOX (capecitabine 1000 mg/m^2 orally bid d1−14 + oxaliplatin 130 mg/m^2 i.v. d1, q3w for 8 cycles) or bolus i.v. 5-FU/LV according to the Mayo Clinic (LV 20 mg/m^2 + 5-FU 425 mg/m^2 d1−5, q4w for 6 cycles) or Roswell Park (LV 500 mg/m^2 + 5-FU 500 mg/m^2 d1, w1−6 in 8w cycles $\times$4) regimens, as both had shown nearly identical efficacy in a prior trial [Haller et al. JCO 2005]. Each participating center's preferred 5-FU/LV regimen was selected at study start and used in all patients treated at that center.
Results: 1886 patients were recruited and randomized between April 2003 and October 2004. Of these, 1864 were evaluable in the previously reported safety analysis. After a median follow-up of 57 months, 1886 patients are evaluable for the primary study endpoint, DFS, which was significantly superior for XELOX at 3 and 4 years.

	3-year DFS	4-year DFS
XELOX	71.0%	68.4%
5-FU/LV	67.0%	62.3%
	HR 0.80, p = 0.0045	

Conclusions: XELOX is superior to i.v. bolus 5-FU/LV in DFS as adjuvant treatment for stage III colon cancer. The results with XELOX in the adjuvant setting confirm the benefits shown with oxaliplatin plus 5-FU combinations in stage III patients enrolled in the MOSAIC (FOLFOX vs. LV5FU2) and NSABP C-07 (5-FU/LV vs. FLOX) trials, and may provide a potential additional option for patients with stage III disease. OS data are currently immature; follow-up is ongoing, and updates will be reported when available.

6LBA LATE BREAKING ABSTRACT

Addition of cetuximab to oxaliplatin-based combination chemotherapy (CT) in patients with KRAS wild-type advanced colorectal cancer (ACRC): a randomised superiority trial (MRC COIN)

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Background: Cetuximab (C) has proven efficacy in *KRAS* wild-type (wt) advanced colorectal cancer (ACRC). One of the two questions posed by the COIN trial (ISRCTN27286448) was whether the addition of cetuximab to continuous oxaliplatin-based chemotherapy (CT) improves overall survival