after primary chemotherapy (group 3), both from study 9302. Characteristics of patients in-group 1, 2 and 3 were respectively: median age 47, 46 and 45 years old. Median pathological affected lymph nodes 16 (10–12:40%; 13–15:19%; 16–19:21%; >19:20%), 7 (4–9:72%; 9:28%), and 6 (0–3:40%; 4–9:37%; 9:23%). Estrogen receptors were positive in 42%, 59% and 30% respectively in-groups 1, 2 and 3. Histological grade was in-group 1: GI 6%, GII 30%, and GIII 50%, unknown 14%. In group 2: GI 0%, GII 54%, GIII 30%, unknown 16% and in group 3: GI 3%, GII 33%, GIII 17%, unknown 47%. Median follow up was 33 months (19–61), 30 months (19–52) and 30 months (19–52) respectively in each group. Three year disease-free survival (DFS) is 65% (CI 61–69), 90% (CI 84–96) and 43% (CI 33–53). Three year overall survival is 79% (CI 74–84), 94% (CI 89–99) and 81% (CI 73–89). There were 3 treatment-related deaths (1.2%). In comparison with the group historical results achieved with standard adjuvant chemotherapy, HDC with STAMP V and stem cell transplant support may increase DFS and OS in patients with high-risk breast cancer with 10 or more N+ and 4 or more locally advanced tumors after primary chemotherapy. However, it does not provide any advantage in patients with inflammatory breast cancer. New Studies: patients with metastatic breast cancer not candidate for study 9303 or if the center decided to stop the inclusion in that protocol since January 1998 the EBDIS study from Ireland were accepted as SOLTI protocol with number 9703.

The Group decided also to joint the European Study for high-close in Small Cell Lung Cancer and one study for Ovarian Carcinoma was also pending for approval.

For the near future the Group will develop studies in other tumors and areas as the biologic treatment of Breast Cancer and other tumors.

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High dose chemotherapy in the adjuvant setting for high risk breast cancer patients – Results from a randomized study

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525 high risk, e.g. ≥8 positive axillary nodes or ≥5 positive nodes and receptor negativity and high S-phase, breast cancer patients were randomised during the study period March 1, 1994 to March 4, 1998, between tailored and dose escalated FEC versus conventional FEC followed by autologous peripheral blood stem cell supported high dose therapy with CTC_b. Patients in both arms received loco-regional radiotherapy followed by tamoxifen at 20 mg/day for 5 years. In order to avoid stage migration we applied very similar staging criteria compared with our previous studies. The inclusion figures have been compared with our population based cancer registries, and we thus conclude our study population to be very representative for this high risk group of patients. All analyses were performed according to the intention to treat principle.

At a median follow-up of 23.7 months we have 66 relapses in the tailored FEC arm and 92 in the high dose arm with CTB_b. This difference is not statistically significant according to the Whitehead model.

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Randomized studies of high-dose chemotherapy in high-risk breast cancer in The Netherlands

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High-dose chemotherapy is frequently employed in the adjuvant treatment of high-risk breast cancer, but its role in this setting has not been established. We have published a randomized study of 81 patients with infraclaviculair node-positive breast cancer, which did not show any survival advantage for high-dose therapy (Rodenhuis S et al, Lancet 1998; 352: 515). Although the morbidity in this study was acceptable and there were no toxic deaths, a previously unreported long-term toxicity was identified: Neuropsychological sequelae were more often seen in the high-dose arm than in the standard arm (Van Dam et al, JNCI 1998; 90: 210). Early results of larger randomized studies are becoming available. The largest randomized study, that of the Netherlands Working Party for High-dose Therapy in Solid Tumors, had randomized 860 patients with 4 or more tumor-positive axillary lymph nodes in April 1999, and will close in June 199, when >880 patients have been accrued. This study has the statistical power to detect a 10% survival advantage for high-dose therapy.

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Review of North American high dose trials

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Four North American randomized trials of high dose therapy in high-risk primary and metastatic breast cancer are published in at least abstract form, and two are ongoing.

Adjuvant: The CALGB Intergroup study of Peters et al, compared high vs. intermediate dose CBP after a CAF induction in 783 randomized patients. (Proc ASCO 1999;18:1a) Although low dose CBP is not a standard regimen, scientifically, the design is a pure comparison between high and low dose CBP. This BCNU containing regimen had a 7.4% mortality, which varied with the experience of the transplant center and increased with patient age. With a median of 3.6 years of follow-up, at the time of presentation at ASCO, there was a trend for improved PFS for high dose chemotherapy, but no difference in survival. PFS is at 70% and therefore only 1/3 of the predicted relapses have occurred.

An MD Anderson Hospital study, closed for lack of accrual with 78 patients, showed no advantage for high dose chemotherapy. (Proc ASCO 1998;17:12) Transplant mortality was 1/39 (2.5%)

Metastatic: The Philadelphia Intergroup study, the number of patients randomized is 199, 36% of the 535 patients entered. (Proc ASCO 1999;18:1a) An additional 18% of the randomized patients were ineligible or did not receive their assigned treatment. Responders to 4 to 6 cycles of CAF or CMF chemotherapy were randomized to high dose CTCb versus continued CMF until progression or for up to 2 years. Disease free and overall survival are similar. Mortality on the BMT arm was 1%.

In a Duke CR study, 98 patients who attained a CR were randomized between a BMT immediately vs. at the time of relapse. Disease free survival was significantly improved for the immediate BMT group, but survival favored the group getting delayed BMT. (Proc ASCO 1996;15:121)

Because of the very different designs and follow-ups, any conclusions remain controversial.

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Oesophageal cancer – Who benifits from neoadjuvant therapy

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Surgery remains the mainstay of therapy in patients with potentially resectable stages with both squamous cell and adenocarcinomas of the esophagus provided a compete resection (R0) can be accomplished. However the vast majority of patients present with locally advanced stages. To increase the rate of complete resections neoadjuvant (preoperative) therapy (chemotherapy [CTx]or simultaneous or sequential radiochemotherapy [RTx/CTx]) have been introduced into the multimodal treatment since more than 20 years. Preoperative CTx, mainly on the basis of cisplatinum/5-FU has shown to be feasible and does not increase the rate of postoperative morbidity or postoperative mortality. However there was no significant increase in the rate of complete resections consistently observed. Preoperative RTx/CTx increases the response rate and inproves local tumour control, but is associated with substantial perioperative morbidity and mortality. Because of these conflicting datas the role of neoadjuvant therapy and the treatment of patients with primary resectable tumour stages remains controversial.

A potential benefit appears to be limited to a subgroup of patients responding either clinically or pathologically to neoadjuvant therapy. On the contrary non responding patients have a disappointing prognosis even after a complete resection. The answer to the question whether patients who respond to neoadjuvant therapy have biologically more favorable tumours than non-responders may be obtained by investigations of molecular markers (e.g. cyclin D1, p53, c-erb-B2, p16 etc.) on pretherapeutic biopsies. Tumour thymidylate synthase (TS) levels appear to be predictive of both response to neoadjuvant therapy and survival. TS expression may help to stratify patients for 5-FU containing neoadjuvant chemotherapy regimens.

However due to tumour cell heterogeinity the predictive value of investigations performed on biopsies may be limited.

Positron emission tomography (PET) offers another method for response prediction. According to our preliminnary results the lack of a decrease in FDG uptake after 2 courses of preoperative CTx (day 15) identifies non responding patients with sufficient probability. Therefore research must focus on modalities with high accuracy that allow pretherapeutic identification of those patients who will or will not respond to neoadjuvant therapy.