Endpoint	Fr Schedule	Estimated absolute difference in 5-year event rates[1] (%) (95% CI)	Crude HR (95% CI)
LR relapse ST-A			
	50 Gy	-	1
	41.6 Gy	0.2 (−1.3−2.6)	1.05 (0.63−1.75)
	39 Gy	0.9 (−0.8−3.7)	1.26 (0.77−2.08)
LR relapse ST-B			
	50 Gy	-	1
	40 Gy	−0.6 (−1.7−0.9)	0.79 (0.48−1.29)
Mild/marked change in breast appearance ST-A			
	50 Gy	-	1
	41.6 Gy	2.8 (−5.0−11.5)	1.09 (0.85−1.40)
	39 Gy	−10.8 (−17.6−−2.9)	0.69 (0.52−0.91)
Mild/marked change in breast appearance ST-B			
	50 Gy	-	1
	40 Gy	−5.6 (−11.8−1.2)	0.83 (0.66−1.04)

[1]compared with 50 Gy

2027 ORAL

Predictors of increased risk of breast fibrosis at 10 years with higher radiation dose in the early breast cancer (EORTC "Boost versus no Boost" trial 22881–10882).

S. Collette[1], L. Collette[1], T. Budiharto[2], J.C. Horiot[3], P. Poortmans[4], H. Struikmans[5], W.F. Van den Bogaert[6], A. Fourquet[7], J.J. Jager[8], H. Bartelink[9]. *[1]EORTC Data Center, Statistics Department, Brussels, Belgium; [2]EORTC Data Center, Radiation Oncology Group, Brussels, Belgium; [3]Centre Georges-Francois-Leclerc, Radiotherapy Department, Dijon, France; [4]Dr. Bernard Verbeeten Instituut, Radiotherapy Department, Tilburg, The Netherlands; [5]Medisch Centrum Haaglanden – Westeinde, Radiotherapy Department, Den Haag, The Netherlands; [6]Universitair Ziekenhuis Gasthuisberg, Radiotherapy Department, Leuven, Belgium; [7]Institut Curie, Radiotherapy Department, Paris, France; [8]Maastro – Maastricht Radiation Oncology, Radiotherapy Department, Maastricht, The Netherlands; [9]The Netherlands Cancer Institute-Antoni Van Leeuwenhoekziekenhuis, Radiotherapy Department, Amsterdam, The Netherlands*

Introduction: In patients with early breast cancer undergoing microscopically complete excision followed by whole breast irradiation (WBI), the EORTC "Boost trial" showed that an extra boost dose of 16 Gy reduced the risk of local recurrence by 41% in all age groups. The absolute benefit was smaller in the older age groups where the absolute 10-year risk of failure is lowest. The boost also significantly increased the risk of moderate and severe fibrosis. We now investigate predictors of the long term risk of fibrosis, to weight the risks versus the benefits of delivering a boost.
Material and Methods: 5318 patients were randomized between a boost dose of 16 Gy and no boost dose, with a median follow-up of 10.8 years. Fibrosis was scored on a 4-point scale (none/minor/moderate/severe). Predictors of the time to first occurrence of moderate or severe fibrosis were studied by Cox regression (significance level alpha=0.01) and treatment-factor interactions by Logrank test (significance level alpha=0.05).
Results: Prognostic models were developed on a random subset of 1827 patients without boost and 1797 with a boost. On both arms, the risk of moderate or severe fibrosis significantly increased ($P < 0.01$) with increasing maximum WBI dose in the breast and with concomitant chemotherapy but was not influenced by the patient's age. In addition, only in the boost arm, the risk further increased ($P < 0.01$) if patients received adjuvant tamoxifen, had post-operative breast oedema or haematoma, but it decreased ($P < 0.01$) if WBI was given with >6 MV X-rays. The risk of fibrosis with an electron boost was lower than with other boost techniques ($P < 0.01$), but it increased with increasing electron energy ($P < 0.01$).
Conclusions: For each patient, our models allow to predict the expected risk of long term fibrosis with or without boost, based on several factors that can be assessed post-surgery (post-operative oedema or haematoma) or post-WBI (WBI dose, adjuvant treatments and, if a boost is given, boost technique and energy). The risk of fibrosis is independent of age. Our models should be especially helpful in deciding to deliver a boost in older patients for whom the absolute risk of local failure is relatively modest.

2028 ORAL

Concomitant versus sequential chemo-radiotherapy for early breast cancer: meta-analysis of randomized clinical trials (RCTs)

P. Carlini, E. Bria, P. Pinnarò, P. Papaldo, C. Nisticò, F. Ambesi-Impiombato, G. Arcangeli, E. Terzoli, F. Cognetti, D. Giannarelli. *Regina Elena Institute, Medical Oncology, Rome, Italy*

Background: Adjuvant chemotherapy (CT) and radiotherapy (RT) are considered complementary standard treatment for patients undergone surgery for early breast cancer. A number of RCTs have investigated if the concomitant approach of both treatments improved outcomes over sequential. It has been suggested that the sequence of these two treatments may affect patient outcome. A delay in initiating radiotherapy was found to increase the risk of local recurrence and also have a detrimental effect on survival. Conversely, a delay in the administration of systemic chemotherapy while radiotherapy is delivered could allow the proliferation of micro-metastatic disease. A meta-analysis comparing the concomitant over the sequential strategy has been planned.
Methods: A literature-based meta-analysis was accomplished, and event-based relative risk ratios (RRs) with 95% confidence interval (CI) were derived. A fixed- (FEM) and a random-effect (REM) model according to the inverse variance and heterogeneity test were applied as well. Absolute difference (AD) and the Number of patients Needed to Treat (NNT) were calculated. Primary end-points were: disease-free survival (DFS) and overall survival (OS); secondary end-points were: breast cancer recurrence- (BCR), nodal recurrence- (NR), distant recurrence- (DR) and controlateral breast cancer- (Con BC) rates.
Results: Five RCTs were gathered (2430 patients); one RCT did not report the DFS result. Results are depicted in the table.

	End-Point	Pts (#RCTs)	RR (95% CI)	p	Het. (p)
Primary	DFS	1783 (4)	0.98 (0.84, 1.16)	0.87	0.52
	OS	2430 (5)	0.99 (0.94, 1.06)	0.94	0.90
Secondary	BCR	2430 (5)	0.66 (0.46, 0.94)	0.025	0.56
	NR	2186 (4)	1.05 (0.77, 1.43)	0.73	0.25
	DR	2430 (5)	1.03 (0.85, 1.24)	0.72	0.22
	Con BC	1539 (3)	0.83 (0.43, 1.46)	0.52	0.65

BCR was significantly less with concomitant CT+RT, with a AD of 1.93%, which translates into 52 NNT.

Conclusions: Concomitant chemo-radiotherapy after surgery for early breast cancer does not improve both DFS and OS over sequential. Nevertheless, a significant less rate of breast recurrences are present with concomitant approach. The choice of such approach should be weighted with the type of chemotherapy (i.e. anthracyclines, which do not allow such strategy), toxicity and scheduling issues.

2029 ORAL

Breast-conserving surgery with or without radiotherapy in women with ductal carcinoma in situ: a meta-analysis of randomized trials

G. Viani, S.J.E. Eduardo Jose Stefano, A.S.L. Sergio Luis Afonso, F.L.I. Ligia Issa De Fendi. *Faculdade de Medicina de Marilia, Radiation Oncology, Marilia, Brazil*

Background: To investigate whether Radiation therapy (RT) should follow breast conserving surgery in women with ductal carcinoma in situ from breast cancer (DCIS) with objective of decreased mortality, invasive or non invasive ipsilateral recurrence, distant metastases and contralateral breast cancer rates. We have done a meta-analysis of these results to give a more balanced view of the total evidence and to increase statistical precision.
Materials and Methods: A meta-analysis of randomized controlled trials (RCT) was performed comparing RT treatment for DCIS of breast cancer to observation. The MEDLINE, EMBASE, CANCERLIT, Cochrane Library databases, Trial registers, bibliographic databases, and recent issues of relevant journals were searched. Relevant reports were reviewed by two reviewers independetly and the references from these reports were searched for additional trials.
Results: The reviewers identified four large RCTs, yielding 3665 patients. Pooled results from this four randomized trials of adjuvant radiotherapy showed a significant reduction of invasive and DCIS ipsilateral breast cancer with odds ratio (OR) of 0.40 (95% CI 0.33−0.60, $p < 0.00001$) and 0.40 (95% CI 0.31−0.53, $p < 0.00001$), respectively. There was not difference in distant metastases (OR = 1.04, 95% CI 0.57−1.91, $p = 0.38$) and death rates (OR = 1.08, 95% CI 0.65−1.78, $p = 0.45$) between the two arms. There were more contralateral breast cancer after adjuvant RT (66/1711, 3.85%) versus observation (49/1954, 2.5%). The likelihood

of contralateral breast cancer was 1.53-fold higher (95% CI 1.05−2.24, p = 0.03) in radiotherapy arms.
Conclusion: Radiation therapy should follow lumpectomy in women with localized, mammographically detected DCIS. Our findings in 3665 patients strongly confirm that radiotherapy substantially reduces invasive and DCIS ipsilateral breast cancer recurrence risk after breast-conserving surgery. No data are currently available to identify a subgroup of women with the kind of DCIS who did not need to be treated with radiation therapy.

2030 ORAL

Efficacy of neoadjuvant trastuzumab in patients with inflammatory breast cancer: data from the NOAH (NeOAdjuvant Herceptin) Phase III trial

J. Baselga[1], V. Semiglazov[2], G.M. Manikhas[3], W. Eiermann[4], A. Lluch[5], S. Tjulandin[6], A. Feyereislova[7], B. Vanhauwere[7], P. Valagussa[8], L. Gianni[8]. *[1]Vall d'Hebron University Hospital, Barcelona, Spain; [2]NN Petrov Research Institute of Oncology, St Petersburg, Russian Federation; [3]St Petersburg City Oncology Hospital, St Petersburg, Russian Federation; [4]Frauenklinik vom Roten Kreuz, Munich, Germany; [5]Hospital Clínico Universitario de Valencia, Valencia, Spain; [6]NN Blokhin Russian Cancer Research Centre, Russian Academy of Medical Sciences, Moscow, Russian Federation; [7]F. Hoffmann-La Roche, Basel, Switzerland; [8]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background: There is currently no standard therapy for women diagnosed with HER2-positive inflammatory breast cancer (IBC), a rare and highly aggressive disease typically treated with neoadjuvant chemotherapy. Here we present data from patients (pts) with HER2-positive IBC included in the randomised Phase III NOAH (NeOAdjuvant Herceptin) trial of neoadjuvant trastuzumab (Herceptin®; H) in combination with chemotherapy.
Methods: Pts with locally advanced breast cancer at first diagnosis were recruited and assigned to 1 of 2 cohorts depending on HER2 status. All pts received neoadjuvant chemotherapy: 3 cycles of doxorubicin–paclitaxel (AT: A 60 mg/m^2, T 150 mg/m^2 q3w), 4 cycles of T (175 mg/m^2 q3w) and 3 cycles of cyclophosphamide/methotrexate/5-fluorouracil (CMF: C 600 mg/m^2, M 40 mg/m^2, F 600 mg/m^2 q4w on days 1 and 8). Pts with HER2-positive disease were randomised to receive concomitant H (8 mg/kg iv loading dose then 6 mg/kg q3w for 1 year) or chemotherapy only. The first pre-planned interim efficacy analysis evaluated the primary end point of event-free survival and secondary end points of in-breast pathological eradication (pCR), in-breast and nodal pathological eradication (tpCR), objective clinical response rate (cRR) and safety.
Results: 61/228 pts with HER2-positive disease and 14/99 with HER2-negative tumours had IBC; 31 of the pts with HER2-positive IBC received chemotherapy with H.

	HER2-negative IBC	HER2-positive IBC	
	(n = 14)	−H (n = 31)	+H (n = 31)
cRR, %	57.1	77.4	77.4
pCR, %	28.6	19.3	54.8*
tpCR, %	28.6	12.9	48.4**

*p = 0.004; **p = 0.002.

The cRR was similar with or without H in pts with HER2-positive IBC, but addition of H significantly improved the pCR and tpCR rates compared with chemotherapy alone (54.8% vs 19.3%, p = 0.004; 48.4% vs 12.9%, p = 0.002). There were no reports of left ventricular ejection fraction decreases to <45% and only 5/47 pts receiving H had absolute decreases of ⩾10%.
Conclusions: Addition of H to neoadjuvant chemotherapy more than doubled the rates of pCR and tpCR in pts with HER2-positive IBC compared with chemotherapy alone. At the low cumulative dose of administered anthracycline (total doxorubicin dose of 180 mg/m^2), the chemotherapy regimen was well tolerated with no reported symptomatic cardiac events by the time of this interim analysis.

2031 ORAL

A comparison between HER2, p53, PAI-1, angiogenesis and proliferation activity as prognostic variables in tumours from 408 patients diagnosed with early breast cancer

B. Offersen[1], K.E. Olsen[2], V. Jensen[3], R. Riisbro[4], N. Brunner[4], F.B. Sorensen[5], J. Overgaard[1]. *[1]Aarhus University Hospital, Dept. Experimental Clinical Oncology, Aarhus, Denmark; [2]Odense University Hospital, Dept. Pathol, Odense, Denmark; [3]Aarhus University Hospital, Dept. Pathol, Aalborg, Denmark; [4]Inst. Vet. Pathobiol., Faculty of Life Sciences, Copenhagen, Denmark; [5]Aarhus University Hospital, Dept. Pathol, Aarhus, Denmark*

Background: The prognostic potential of HER2, p53, PAI-1 tumour tissue protein level, angiogenesis and proliferation activity (expressed by MIB-1 estimates) were investigated in tumours from 408 patients diagnosed with early breast cancer and followed >10 years. 167 patients (41%) had died from cancer.
Materials and Methods: Using immunohistochemistry tumours were stained for anti-HER2, anti-p53, anti-CD34, and anti-MIB-1, whereas PAI-1 was measured by ELISA. A HER2 score of 3+ was considered positive, and in cases of HER2 score of 2+ a FISH analysis for amplification was performed. p53 was scored in quartiles according to the density of tumour cells staining positive. Angiogenesis was evaluated by the Chalkley technique, using the hot spot approach, whereas MIB-1 estimates were based on systematic random sampling.
Results: Eighty-six tumours (21%) were HER2 positive. The distribution of p53 in classes 1 through 4 was 31, 104, 75 and 198 cases, respectively. Median PAI-1, Chalkley and MIB-1 was 0.72 ng/mg protein (range, 0−90 ng/mg protein), 5.00 (range, 2.67−12.00) and 15% (range, 1−83%), respectively. A high MIB-1 tertile was correlated with HER2 positivity (P < 0.0001), high scores of PAI-1 (P = 0.002), Chalkley count (P < 0.0001) and p53 score (P < 0.0001). None of the factors were otherwise inter-correlated. In univariate analyses with disease-specific survival (DSS) as endpoint, HER2 positivity (P < 0.0001), and increasing values of Chalkley count (P = 0.006), MIB-1 (P = 0.004) and PAI-1 level (P = 0.06) were prognostic markers. Among the 191 node-negative patients, HER2 positivity (P < 0.0001), high PAI-1 levels (P = 0.006) and postmenopausal status (P = 0.03) were associated with poor DSS. In the 217 node-positive patients, HER2 positivity (P = 0.0003), high value of MIB-1 (P = 0.02), Chalkley (P = 0.003), negative estrogen receptor (P = 0.0004) and high malignancy grade (P < 0.0001) were indicators of poor DSS. In multivariate analysis increasing number of metastatic lymph nodes (RR 2.02, 95% CI 1.67−2.44), HER2 positivity (RR 1.96, 95% CI 1.38−2.77), increasing PAI-1 (RR 1.05, 95% CI 1.02−1.07) and high malignancy grade (RR 1.28, 95% CI 1.02−1.61) showed independent prognostic value. In node-negative patients the HER2 status was an even stronger independent prognosticator with a RR 3.42, 95% CI 1.81−6.47.
Conclusion: Compared to p53, PAI-1, Chalkley counts and MIB-1, HER2 positivity was the strongest independent marker of poor prognosis, irrespective of lymph node status.

2032 ORAL

Detection of minimal residual disease (MRD) in peripheral blood of primary breast cancer patients – Translational research in the SUCCESS-Study

J. Jueckstock[1], B. Rack[1], E. Thurner-Hermanns[2], H. Forstbauer[3], K. Pantel[4], H.U. Ulmer[5], M.W. Beckmann[6], W. Lichtenegger[7], W. Janni[1], K. Friese[1]. *[1]Frauenklinik Innenstadt der LMU, Gynaecology and Obstetrics, Munich, Germany; [2]Klinikum Rosenheim, Gynaecology and Obstetrics, Rosenheim, Germany; [3]Oncologic practice Dr. Forstbauer / Dr. Ziske, Oncology, Troisdorf, Germany; [4]Department of Tumorbiology University Hamburg-Eppendorf, Oncology, Hamburg, Germany; [5]Klinikum Karlsruhe Akademisches Lehrkrankenhaus gGmbH, Gynaecology and Obstetrics, Karlsruhe, Germany; [6]Frauenklinik University of Erlangen, Gynaecology and Obstetrics, Erlangen, Germany; [7]Charité Universitaetsmedizin, Gynaecology and Obstetrics, Berlin, Germany*

Background: Patients with the detection of MRD in bone marrow are known to have an increased risk for recurrence and a poorer clinical outcome. However, peripheral blood would be the preferable compartment to monitor treatment efficacy due to increased feasibility. The translational research program of the German SUCCESS-trial was established to evaluate MRD in peripheral blood at 4 different time points during adjuvant systemic treatment of breast cancer patients.
Here first results of the detection of MRD at primary diagnosis and after adjuvant chemotherapy will be presented.
Materials and Methods: Cells were separated by Oncoquick® (greiner bio-one, Frickenhausen, Germany) followed by labelling of epithelial cells with