that have previously been shown to correlate with toxicity/outcome in small patient groups receiving at least one of the FEC compounds (ABCBI/MDRI, ABCC1/MRP1, ABCC2/MRP2, ABCG2, ALDH3A1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A5, DPYD, GSTP1, MTHFR, NQ01, TYMS, XPD/ERCC2, XRCC1). Secondly we investigated previously not studied genes known to be involved in epirubicin metabolisation (UGT1A1, UGT1A6, UGT2B7).

Material and Methods: We identified 1089 breast cancer patients treated in a single centre with 3 to 6 cycles of (neo-)adjuvant FEC (fluorouracil 500, epirubicin 100, cyclophosphamide 500 mg/m^2) from 2000–2010 for whom germline DNA is available. All patients were retrospectively evaluated through electronic chart review for all related non hematological grade 3−4 events (diarrhea, mucositis, myalgia, allergy, fatigue, nausea and vomiting). For statistical evaluation, correction was made for number of planned cycles, age and body mass index using logistic regression analyses. Because of multiple testing the false discovery rate (FDR) was calculated.

Results: Grade 3−4 non hematological events occurred in 43 out of 1089 patients (4%) (diarrhea 7/43, mucositis 8/43, myalgia 2/43, allergy 1/43, fatigue 7/43, nausea and vomiting 20/43). Homozygous (CC, 10%) and heterozygous (AC, 43%) variant genotypes for rs1801131 in the MTHFR gene, compared to the wild-type (AA, 47%) were significantly associated with all related non hematological grade 3−4 events (7.0 vs 4.8 vs 2.4%, p-value 0.033, FDR 0.72).

None of the other SNP could show a significant association (more details on other SNP and subcategories of endpoints will be presented at the meeting).

Conclusions: Genetic variation in a large set of candidate genes could not predict non hematological severe toxicity. The association found in the MTHFR gene was only moderately and with a high FDR. This is by far the largest breast cancer cohort in which the impact of genetic variability on toxicity was investigated.

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Inflammatory Breast Cancer, Moroccan Study

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Background: Inflammatory breast cancer (IBC) is characterized by a particular geographic distribution, being described as more common in the region of North Africa with 5−7% incidence.

IBC present specific histological and biological characteristics compared to non-inflammatory breast cancer.

It's an aggressive form of breast cancer, with poor prognosis: 5-year overall survival reached only 20−30% with a multimodal treatment for localized disease.

Material and Methods: The authors collected the cases of IBC diagnosed and treated at the institute during four years; they analyzed the epidemiology, clinical presentation, histological characteristics, treatment, and therapeutic results.

The diagnosis of IBC was clinical according to the AJCC (American Join Cancer Committee) definition. Maximal delay for inflammatory symptoms was 6 months to eliminate locally advanced pseudo inflammatory breast cancer: T4b with inflammatory aspect.

Results: From January 2005 to December 2008, we collected 172 cases of IBC (T4d) from 3400 new cases treated at the institute, representing 5%.

The median age was 46 years and 62% of the patients were inferior to 50 years.

73% presented clinical lymph nodes involvement and 27% was initially metastatic.

SBR (Scarff Bloom Richardson) was grade 1 in only 5.8% of cases. When performed, Estrogen receptors (ER) were negative in 51%, and HER2 was positive in 59%.

After Neoadjuvant chemotherapy for localized disease, 75% of the patients presented clinical objective response (cOR); 5.6% presented pathologic complete response (pCR) on the breast according to Chevalier grading, and only 2.1% on both breast and axillary lymph nodes.

Median progression free survival (PFS) and overall survival (OS) were respectively 12.4 and 15.8 months; 3-year PFS and OS were respectively 8% and 6.1%.

Statistical study found only negative ER and initial metastasis as predictive factors for worse OS and PFS.

Conclusion: IBC is an aggressive form of breast cancer, with more pejorative criteria compared to non-inflammatory breast cancer: younger age, negative ER, positive HER2, High SBR grade, lymph nodes and metastatic diffusion. This is explaining the poor prognosis of this disease.

Maximal result can be performed by multimodal treatment (neoadjuvant chemotherapy + surgery + adjuvant irradiation +/− adjuvant chemotherapy) for localized disease.

Other active treatments must be studied and validated in the future.

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Relevance of Primary Systemic Chemotherapy in &;ldquo;Luminal A" Breast Cancer

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Background: Since the concept of intrinsic subtypes based on gene profiles was introduced, treatment strategies for breast cancer have changed. However, patients and doctors often encounter difficulties choosing appropriate treatments because of uncertain subtype definitions. Luminal A (LumA) tumours are good targets for endocrine therapy while responses to chemotherapy are poor. Thus, there is now controversy as to whether to give primary systemic chemotherapy (PSC) to LumA patients. We investigated the effect of PSC in LumA to identify factors possibly predicting a good response to this treatment.

Methods and Patients: We studied 220 patients who received PSC during the 2006 through 2008 period at our institution. These patients were given CEF (epirubicin: 75–100 mg/m^2, 4 cycles) followed by taxane (paclitaxel: 80 mg/m^2, weekly, 12 treatments; or docetaxel: 75 mg/m^2, tri-weekly, 4 cycles). Chemotherapeutic effects were determined by pathologists using the General Rules for Clinical and Pathological Recording of Breast Cancer of the Japanese Breast Cancer Society. Among Her2 negative luminal tumours, we judged disease to be luminal B (LumB) if tumour grade or the Ki67 index (>30%) was high. Eighty-seven LumA tumours, among 220, were specifically examined for tumour characteristics and biomarkers. We also evaluated the expressions of proteins regulating tumour proliferation, such as FOXM1, by immunohistochemistry (IHC).

Results: As to the subtype proportions; LumA: 40%, LumB: 19%, Her2: 24%, triple negative: 18%. The overall pCR rate was 17%. The pCR rate in LumA was only **7%** while LumB, Her2 and triple negative tumours had rates of 13, 29 and 23%, respectively. We found no specific difference between pCR and non-pCR among LumA cases in age, tumour structure, grade, ER, or PR. However, when two LumA groups, good and poor responders to PSC, were compared, there were significantly more PR-negative tumours among those showing good responses. The 46% of LumA that are PR-negative constitute a good response group while only 25% of PR-positive LumA responded to chemotherapy. As for IHC results, LumA with low FOXM1 expression showed a better response to PSC.

Conclusion: PR-negative tumours had better responses to PSC. Further investigations are needed to reveal which LumA patients are likely to benefit from PSC, which would increase possibilities for breast conserving surgery.

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Primary Systemic Therapy for Hormone-sensitive Breast Cancer − in View of Ki-67 Labeling Index

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Background: Chemotherapy effect for hormone-sensitive breast cancer is controvertible, while high proliferation as measured by Ki-67 is one of the factors arguing for the inclusion of chemotherapy. We reviewed results of primary systemic therapy (PST) for our hormone-sensitive breast cancer patients to examine the correlation between PST effect and Ki-67 labeling index.

Material and Methods: Among 117 primary breast cancer patients, who underwent PST in our hospital between 2009–2011, We studied with 61cases, which were hormone receptor positive (ER⩾10% andPgR⩾10%) and negative Her2 status. We classified them into 3 groups; Ki-67 low (<15%), moderate (⩾15%, <30%), and high (⩾30%), and reviewed their PST effect categorically.

Results: 35 patients received neoadjuvant chemotherapy while 26 patients underwent neoadjuvant endocrine therapy. Clinical response rate for neoadjuvant chemotherapy group was; Ki-67 low: 87.5% (7/8), moderate: 81.8% (9/11), high: 93.7% (15/16). 3 cases with high Ki-67 achieved pathological complete response, but no cases with low or moderate Ki-67. In neoadjuvant endocrine therapy group, on the other hand, clinical response rate was; Ki-67 low: 36.4% (4/11), moderate: 62.5% (5/8), high; 14.3% (1/7). 1 case with moderate Ki-67 and 1 case with high Ki-67 developed progressive disease. Pathological complete response was achieved in only 1 case with low Ki-67.

Conclusions: Our results indicate that hormone-sensitive breast cancer with high Ki-67 tends to be more responsive to chemotherapy, but less to endocrine therapy, which may support St. Gallen Consensus 2011; neoadjuvant chemotherapy is less useful in the Luminal A subtype, while is considered for Luminal B disease.

	Neoadjuvant chemotherapy			Neoadjuvant endocrine therapy		
	low Ki-67 (n = 8)	moderate Ki-67 (n = 11)	high Ki-67 (n = 16)	low Ki-67 (n = 11)	moderate Ki-67 (n = 8)	high Ki-67 (n = 7)
Clinical Response*						
CR	0 (0.0%)	1 (9.1%)	3 (18.7%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
PR	7 (87.5%)	8 (72.7%)	12 (75.0%)	4 (36.4%)	5 (62.5%)	0 (0.0%)
SD	1 (12.5%)	2 (18.2%)	1 (6.3%)	7 (63.6%)	2 (25.0%)	5 (71.4%)
PD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (14.3%)
Pathological Response**						
Grade 0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (12.5%)	0 (0.0%)
Grade 1a	0 (0.0%)	1 (9.1%)	4 (25.0%)	5 (45.5%)	2 (25.0%)	4 (57.1%)
Grade 1b	7 (87.5%)	6 (54.5%)	5 (31.3%)	4 (36.4%)	5 (62.5%)	3 (42.9%)
Grade 2	1 (12.5%)	4 (36.4%)	4 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 3	0 (0.0%)	0 (0.0%)	3 (18.8%)	1 (9.1%)	0 (0.0%)	0 (0.0%)

*Clinical Response evaluated by RECIST; CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

**Pathological Response evaluated by response criteria of Japanese Breast Cancer Society; Grade 0: no response, Grade 1: slight response (Grade 1a: mild response, Grade 1b: moderate response), Grade 2: marked response, Grade 3: complete response.

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Significantly Higher Pathologic Complete Response Rate with Weekly Compared with Three-weekly Paclitaxel and Carboplatin Plus Trastuzumab Neoadjuvant Therapy − Results of a Randomized Trial in Human Epidermal Growth Factor Receptor 2-positive Breast Cancer

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Background: Paclitaxel works synergistically with trastuzumab in HER2 positive breast cancer. But few trials have studied the combination of a paclitaxel-containing regimen and trastuzumab in the neoadjuvant setting. We conducted a phase III randomized trial to compare the efficacy and safety of weekly and 3-weekly paclitaxel (P) and carboplatin (C) plus trastuzumab (H) for the neoadjuvant treatment of HER2 positive breast cancer.

Material and Methods: 38 patients (pts) with stage IIB to IIIC disease and HER2 positive (IHC3+ and/or FISH+) were randomized to receive neoadjuvant treatment with four cycles of weekly PCH (P: 80 mg/m^2, C: AUC=2, d1, 8, 15, q4w and H: 2 mg/kg every week with loading dose of 4 mg/kg), or 3-weekly PCH (P: 175 mg/m^2, C: AUC=6, q3w and H: 6 mg/kg every 3 weeks with loading dose of 8 mg/kg). Primary endpoint was pathological complete response (pCR) rate. Secondary endpoints included response rate, lymph node downstage rate, disease free survival (DFS) and safety.

Results: 19 pts were treated in each arm and pretreatment characteristics were similar in the two groups. All pts completed the 4 planned cycles of neoadjuvant treatment and received mastectomy or breast conserving surgery. The overall combined pCR rate was 60.5% (73.7% in weekly group and 47.4% in 3-weekly group, p = 0.091, Fisher's test). Subgroup analysis indicated a higher pCR rate in the weekly PCH group (10/14; 71.4%) than in the 3-weekly PCH group (3/12, 25%) for luminal B type patients (p = 0.047). Axillary lymph node downstage rates were similar in each group. No cardiac side effects was found in either group. If we add 15 cases preliminary weekly PCH neoadjuvant therapy data into the analysis, the pCR rate of combined weekly PCH group is 76.5% (26/34), which is significantly higher than that of 3-weekly group (p = 0.018). In luminal B subgroup analysis, weekly PCH maintains its superior efficacy over 3-weekly PCH (70.8% vs. 25%, P = 0.014).

Conclusion: Neoadjuvant treatment with a weekly PCH regimen achieved higher pCR rates compared with a 3-weekly PCH regimen for HER2 positive, especially luminal B type, breast cancer, with good cardiac safety profile and without exposure to anthracyclines. Preliminary results are encouraging and further cases are needed to be enrolled to confirmed the statistically significant differences between the groups.

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Prognostic Value of a Positive-to-negative Change in Hormonal Receptor Status Following Neoadjuvant Chemotherapy in Patients with Luminal-type Breast Cancer

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Background: This study investigated the prognostic value of positive-to-negative changes in hormonal receptor (HR) status after neoadjuvant chemotherapy in patients with luminal-type breast cancer.

Patients and Methods: Data from 224 stage II-III breast cancer patients with positive hormonal receptor (HR) status prior neoadjuvant chemotherapy (NCT) was collected, and the HR status of the residual tumors was retested after NCT. A survival analysis was performed in 214 patients with adjuvant endocrine therapy regardless of post-NCT HR status. The survival analysis also examined other clinical and pathological variables.

Results: In total, 15.2% of patients had a positive-to-negative change in HR status following NCT, and this change was observed more frequently in HER-2 positive tumors than HER-2 negative tumors (P = 0.001). Pre-NCT tumor stage (T2 *vs.* T3 *vs.* T4, P = 0.015), post-NCT node metastasis (0 *vs.* 1−3 *vs.* 4+, P = 0.006), and post-NCT HR (negative *vs.* positive, P = 0.026) were identified as independent predictive factors for DFS and significant predictors of OS (P = 0.004, P = 0.001, P < 0.001, respectively) in 214 patients who had been treated with adjuvant endocrine therapy regardless of post-NCT HR status. The 5-year DFS and OS rates were 43.5% and 59.8%, respectively, in patients with HR status conversion and 67.8% and 82.5%, respectively, in patients whose HR status remained positive (log-rank test P = 0.003 and P = 0.001). Besides, a relatively high proportion of high Ki-67 indexes were observed in tumors with HR alteration compared to tumors in which HR status remained positive (62.5% *vs.* 29.5%, P = 0.004).

Conclusion: Our results indicated that the switch of HR status after NCT is not negligible for luminal-type tumors. An HR-negative switch may lead to a poor outcome regardless of adjuvant endocrine therapy.

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The Role of Iodine-125 Seed Localization in Breast Conserving Therapy After Neo-adjuvant Chemotherapy in Breast Cancer

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Background: Neo-adjuvant chemotherapy (NAC) is increasingly used, especially in the treatment of large unifocal and multifocal breast cancer, in the framework of breast conserving therapy (BCT). Complete pathological response (CPR) is seen more often after newer chemotherapy regimes. If BCT is a surgical option, localization of the initial tumour, before initiation of NAC, is essential to guide the surgical resection. We studied the use of radioactive I-125 seeds in breast cancer patients treated with BCT following NAC. Our main objective was to analyze its value with regard to obtainment of tumour free surgical resection margins.

Material and Methods: Between January 2009 and December 2010, 85 patients were treated with NAC after I-125 seed localization. Tumours were unifocal and multifocal in 53 (63%) and 32 (38%) patients, respectively. During the chemotherapy course tumour response was monitored by magnetic resonance imaging (MRI). Definitive pathological examination was evaluated. Student t-Test and chi-square analysis were used to evaluate differences in surgical resection margins between patients with unifocal and multifocal tumours. P values of $\leqslant$ 0.05 were considered significant.

Results: After NAC, all patients underwent a lumpectomy without any secondary local excision. Nineteen patients (36%) with an unifocal tumour and 7 patients (22%) with a multifocal tumour had a CPR (p = 0.176). Overall tumour free resection margins were obtained in 78 patients of which 50 patients (94%) with unifocal tumours and 28 patients (88%) with multifocal tumours (p = 0.266). Focally involved margins were seen in 2 patients (4%) with an unifocal tumour and in 2 patients (6%) with a multifocal tumour (p = 0.273). Extensively involved margins were seen in 1 (2%) and 2 (6%) patients respectively (p = 0.291), subsequently followed in all 3 patients by a mastectomy.

Conclusions: To our experience, the I-125 radioguided lumpectomy proves to be very feasible providing an optimal per-operative three dimensional image of the tumour bed. A very high rate of microscopically complete lumpectomy was obtained in both uni- and multifocal tumours, with only 3 out of 85 patients requiring a mastectomy. Therefore, radioactive I-125 seed implantation increases the surgical opportunities for BCT following NAC, especially in the treatment of large unifocal and multifocal breast cancers.