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Proffered paper oral

# Impact of Neoadjuvant Systemic Treatment and Prior Surgery On Sentinel Lymph Node Detection – Results From the Prospective German Multiinstitutional SENTINA Trial

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**Background:** For patients with breast cancer undergoing preoperative / neoadjuvant systemic treatment (NST) the optimal timing of sentinel lymph node biopsy (SLNB) is still unclear. Evidence for both feasibility (detection rate, DR) and reliability (false negative rate, FNR) of SLNB is limited and derived only from monocentric and/or retrospective data.

**Material and Methods:** The SENTINA trial (SENTinel NeoAdjuvant) is a 4-arm prospective multicenter cohort study designed to examine the DR and FNR of a standardized SLNB-procedure in the neoadjuvant setting. In this first analysis, we present data on sentinel lymph node (SLN) detection rates in patients with breast cancer before and after NST. In SENTINA, patients were categorized into four treatment arms according to axillary staging results before and after NST. Patients with a cN0 status underwent SLNB prior to NST and were categorized as arm A and B: If the SLN was histologically negative no further axillary surgery was performed after NST (arm A), whereas in case of histologically positive SLN status, a second SLNB and AD was performed after NST (arm B). Patients with a cN1 status prior to NST underwent no axillary surgery prior to NST and were stratified as arm C and D: If patients converted to cN0 after NST, SLNB and AD were performed (arm C); patients presenting with cN1 status after NST underwent classical AD (arm D).

**Results:** 1240 patients from 104 institutions entered the trial. 804 women had clinically negative lymph nodes and received SLNB prior to NST (arm A/B). Among these, 284 patients (34.5%) had histologically involved nodes and underwent a second SLNB followed by AD after NST (B2). 436 patients, who presented initially with suspicious nodes and converted to a cN0 status after NST (arm C) received SLNB without any prior axillary surgery. The SLN detection rate was 99.1 % (798/805) in arm A/B and 81.9% (357/436) in arm C. For patients with a positive SLN in arm A/B who received a second SLNB after NST the detection rate was no more than 62.3 % (177/284). The difference between the detection rates of these three groups was highly statistically significant ( $p < 0.001$ ).

**Conclusion:** The SLN detection rate in patients with breast cancer is highly dependent on prior systemic and/or surgical treatment. The SLN detection rate in patients converting from a clinically positive to a clinically negative axilla status through NST is significantly lower compared to patients with an a priori clinically negative axilla. Both, however, are yet significantly higher compared to patients who receive prior surgery and systemic treatment before SLNB is performed.

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Proffered paper oral

# Relevance of Breast Cancer Subtypes in Response Monitoring with 18F-FDG PET/CT During Neoadjuvant Chemotherapy

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**Background:** Neoadjuvant chemotherapy (NAC) is increasingly applied in stage II and III breast cancer. Response monitoring with magnetic resonance imaging (MRI) has been shown valuable, but knowledge of the breast cancer subtype is essential for correct interpretation of response assessment. The aim of the present study was to evaluate the relevance of breast cancer subtype for <sup>18</sup>F-fluorodeoxyglucose (FDG) positron emission

tomography with computed tomography (PET/CT) markers for monitoring of therapy response during NAC.

**Methods:** Evaluation included 98 women with primary stage II or III breast cancer. FDG PET/CT scans were performed before and after six weeks of NAC using similar prone patient positioning. FDG uptake of the primary tumor was quantified using maximum standardized uptake values (SUV<sub>max</sub>). Tumors were divided into three subtypes using immunohistochemistry: human epidermal growth factor receptor 2 (HER2) positive, estrogen receptor (ER) positive/HER2 negative and triple negative. Tumor response was assessed as presence of residual tumor in the surgery specimen (no response or partial response) or absence thereof (near complete or complete response). Multivariable regression analysis and receiver operating characteristic (ROC) analyses were employed to determine significant associations.

**Results:** A (near) complete response at pathology was observed in 19 (76%) of 25 HER2 positive tumors, 7 (16%) of 45 ER positive/HER2 negative tumors and 20 (71%) of 28 triple negative tumors. In the multivariable regression analysis, (near) complete response in the surgery specimen was significantly associated with relative reduction of SUV<sub>max</sub> of the tumor between both scans and breast cancer subtype (area under the curve of the ROC curve 0.85 [95% confidence interval 0.77–0.93],  $p < 0.001$ ); no significant associations were found for FDG uptake at baseline and age. In a subgroup analysis of breast cancer subtype, a significant association was found between pathologic response and relative reduction of SUV<sub>max</sub> for ER positive/HER2 negative and triple negative tumors ( $p = 0.003$  and  $p = 0.009$ , respectively), but not for HER2 positive tumors ( $p = 0.192$ ).

**Conclusion:** Knowledge of the breast cancer subtype appears relevant for the assessment of response to NAC with FDG PET/CT. Response monitoring with FDG PET/CT may predict a pathological response adequately in ER positive/HER2 negative and triple negative tumors, but seems less accurate in HER2 positive tumors. The reasons for these differences need to be elucidated in further investigations.

Wednesday, 21 March 2012

15:45–17:15

## CLINICAL SCIENCE SYMPOSIUM

## Resistance to Hormonal Therapy

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Invited

## Overview of Mechanism of Resistance in Hormonal Therapy

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The estrogen receptor (ER) is a key regulator of breast cancer (BC) biology and is expressed in almost 75% of breast cancers. Targeting ER has been the focus of endocrine treatment strategies developed during the last decades. ER selective modulators or downregulators (i.e. tamoxifen or fulvestrant), and inhibitors of estrogen synthesis (i.e. aromatase inhibitors) are among the most successful targeted agents ever developed for cancer. Due to their excellent activity and tolerability, these agents have significantly improved the management of ER positive disease. However, at least 25% of patients in the adjuvant setting and all patients in the advanced setting develop resistance to hormonal therapy after a variable period of time. Therefore, endocrine resistance accounts for a large fraction of therapeutic failures in BC each year resulting in millions of deaths worldwide.

Biological mechanisms of endocrine resistance seem to often rely on altered ER pathway function rather than reduced ER levels. As the complex ER biology can be physiologically modulated by a number of signalling pathways, deregulation of such pathways has been historically recognized as a major driver of endocrine resistance. The paradigm of such interaction is hyper activation of the Epidermal Growth Factor Receptor family members EGFR and HER2 that have been shown to modulate ER phosphorylation and activation, co-factors recruitment and, ultimately, response to endocrine treatment. Other relevant pathways such as the IGF1R, PI3K/Akt, p44/42 MAPK and stress activated protein kinases (JNK and p38 MAPK) have been associated to endocrine resistance by means of their crosstalk with ER and, possibly, by inducing a shift in ER function towards cooperation with other transcription factors such as AP-1. Recent clinical data showed for the first time that modulation of such pathways in combination with endocrine therapy can improve patient outcomes. From a prospective standpoint, these data serve to clinically validate the concept that complete ER blockade is achieved by targeting not only ER but also its relevant signalling partners. As new biologic information on ER activity translates into innovative therapeutic approaches, a number of signalling inhibitors are in pre-clinical and clinical development for this subset of patients. Due to the clinical importance of this issue, scientific

improvements in this area will certainly be major contributions to the fight against BC.

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Invited

# Modulation of Resistance to Biological Agents

Abstract not received.

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Invited

# Modulation of Resistance to Hormonal Agents

Abstract not received.

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Proffered paper oral

# Everolimus (Rad001) as Treatment in Breast Cancer Patients with Bone Metastases Only – First Results of the Multi-centre, Placebo-controlled, Randomized Discontinuation Phase II RADAR Study

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**Background:** RAD001 is an orally bioavailable rapamycin ester analogue, which acts by selectively inhibiting mTOR (mammalian target of rapamycin). mTOR is a key player in down stream signaling of different pathways. In vitro, RAD001 stops formation and activity of osteoclasts. Therefore, treating advanced breast cancer with progressive bone metastases with RAD001 seems to be reasonable.

**Patients and Methods:** We evaluated RAD001 in a placebo-controlled, phase II, randomized discontinuation study in breast cancer patients (pts) with bone metastases only. Pts were eligible if they had HER2-negative, hormone-receptor (HR)-positive or -negative disease, with a maximum of 2 previous lines of endocrine therapy (ET) and 1 previous line of chemotherapy (CT). All pts received zoledronate and pts with HR-positive disease could receive (ET). All pts started with RAD001 during a run-in phase of 8 weeks. Pts with stable disease were randomized to RAD001 or placebo; pts with response continued with RAD001 and pts with progression went off study. Primary outcome was time to progression (TTP) in pts being stable on 8 weeks of RAD001. Main secondary objectives were response rate after 8 weeks, TTP in pts with a response after 8 weeks of RAD001, overall clinical benefit, safety and toxicity of RAD001. It was assumed that placebo would obtain a median TTP of 8 weeks which would then be increased by to 16 weeks (hazard rate of 2), thus requiring 76 randomized pts. It was expected that 70% of all pts would have stable disease after the run-in phase. Overall, 110 pts were planned for enrollment. Due to slow recruitment and a dysbalance between pts randomized and discontinued, study recruitment stopped in December 2012.

**Results:** From 11/06 until 12/10, 89 pts were enrolled. Median age was 59.5 years. All were HER2-negative, 93% had HR-positive disease. 15% had prior chemotherapy; 58% had prior ET for metastases. 1/3 received concomitant ET. Three pts did not start therapy, 41 discontinued during run-in phase, 32 due to progression. Six continued as responder, of whom three are still on treatment. 39 pts. with SD after the run in phase were randomized to RAD001 or placebo. Twenty-seven stopped due to progression; 9 discontinued due to AE, 4 are still on treatment.

**Conclusion:** This is the first trial recruiting pts with bone metastases only for treatment with RAD001. Overall 7/89 showed a sustained response on RAD001 + zoledronate ± ET. Final analysis will be presented at the meeting.

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Proffered paper oral

# Everolimus Added to Exemestane Reduced Bone Markers in Postmenopausal Women with Advanced Breast Cancer (ABC): the BOLERO-2 Trial

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**Background:** The BOLERO-2 study, a multinational, double-blind, placebo-controlled, phase III study comparing everolimus (EVE) in combination with exemestane (EXE) with EXE alone in postmenopausal women with estrogen receptor-positive (ER+) ABC refractory to letrozole or anastrozole, demonstrated improved response and progression-free survival (PFS) with the addition of EVE to EXE. Non-steroidal aromatase inhibitors (NSAIs) are associated with decrease in bone mineral density and increased risk of fractures. Therefore, it is important to evaluate whether new therapies in combination with NSAIs affect bone turnover. This sub-analysis evaluated the effect of EVE in combination with EXE compared with EXE alone on markers associated with bone formation and reabsorption from the BOLERO-2 study.

**Methods:** Eligible patients were treated with EXE 25 mg/d and randomized (2:1) to EVE 10 mg/d or placebo (PBO). Primary endpoint was PFS based on 457 events and median follow-up of 12.5 months. Bone turnover markers were exploratory endpoints analyzed at 6 and 12 weeks after treatment initiation. They included bone-specific alkaline phosphatase (BSAP), amino-terminal propeptide (PINP) of type I collagen, and C-terminal cross-linking telopeptide of type I collagen (CTX).

**Results:** 724 patients were randomized to receive EVE+EXE (n = 485) or EXE (n = 239). Median age was 62 years, 56% had visceral involvement, and 84% were sensitive to prior hormone therapy. At study entry, bone metastases were present in 76% of patients on EVE+EXE and 75% on EXE; 45% and 55%, respectively, used bisphosphonates at baseline. PFS per investigator assessment showed a hazard ratio (HR) of 0.44 ( $P < 1 \times 10^{-16}$ ) with a median duration of 7.4 vs 3.2 months (for EVE+EXE vs EXE alone). PFS by central assessment showed an HR of 0.36 ( $P < 1 \times 10^{-16}$ ) and a median duration of 11.0 vs 4.1 months, respectively. At 6 weeks, EVE+EXE resulted in a 24%, 56%, and 36% decrease in BSAP, PINP, and CTX compared with EXE alone during the same time interval. At 12 weeks, EVE+EXE resulted in a 19%, 68%, and 42% reduction in the presence of BSAP, PINP, and CTX compared with EXE alone. Updated results based on an additional 5 months of data (cutoff date: 08-Jul-2011) will be presented.

**Conclusion:** The combination of EVE+EXE reduced bone turnover markers compared with EXE alone during the first 12 weeks of therapy, suggesting favorable bone health clinical benefits.

Wednesday, 21 March 2012

15:45–17:15

## CLINICAL SCIENCE SYMPOSIUM

## The Axilla – A “No Go” Zone?

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Invited

## No Axillary Surgery in Breast Cancer?

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Sentinel lymph node dissection (SLND) is the standard axillary surgery for T1-T2 (\*3 cm) breast cancer (BC) patients. SLND is negative in 60 to 75% of the cases, so how can we select breast cancer patients for 'No Axillary